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# Carbocyclization of Heterosubstituted Alkynes via the Memory of Chirality: Access to Cα-substituted Proline Derivatives

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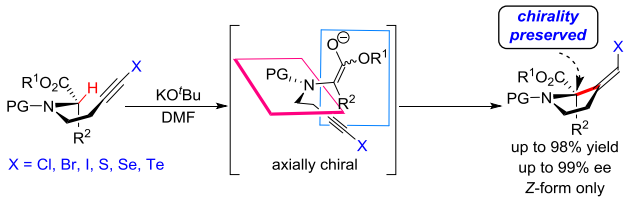


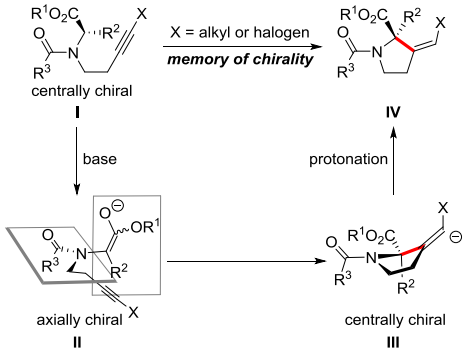

**ABSTRACT:** An efficient strategy for the asymmetric synthesis of Cα-substituted proline derivatives from acyclic α-amino acids has been established. The 5-*exo*-*dig* asymmetric cyclization of α-amino ester enolates onto heterosubstituted alkynes provided a product with excellent enantioselectivity via the memory of chirality concept. Density functional theory calculations indicated that a heteroatom is crucial for the success of the asymmetric cyclization because a more stabilized vinyl carbanion is produced. This new method has the potential to enable the rapid asymmetric construction of bioactive molecules containing the pyrrolidine skeleton.

## INTRODUCTION

In the past few decades, numerous new strategies and methodologies have been developed in the field of asymmetric synthesis. One particular concept, namely, "memory of chirality (MOC)", is distinct from the currently prevalent concepts in that the central chirality in the substrate is preserved in the reaction product via a dynamic axial chirality of transient intermediates.[1] Archetypical MOC reactions comprise the enantioselective α-functionalization of α-amino acids which is an enduring challenge in synthetic chemistry. Several types of electrophilic groups, such as alkyl halides,[2a,b] aldehydes,[2c] ketones,[2d] and electron-deficient olefins,[2e] have been shown to react with α-amino ester enolates via an MOC-based mechanism. However, alkynes have not been employed as electrophilic partners for MOC reactions. Recently, we briefly reported the transition metal-free asymmetric cyclization of α-amino ester enolates onto bromoalkynes via the MOC concept. This reaction was developed and used for the expedient total synthesis of hasubanan alkaloids.[3] In this paper, we wish to report the details of our work on the MOC heterosubstituted alkynes carbocyclization.

Many examples of alkyne carbocyclization of enolates or their equivalents are known.[4] Enolates from β-dicarbonyl-type compounds are common nucleophiles for such reactions, and this type of cyclization is regarded as a variant of the classic Conia-ene reaction.[4b] However, reports on the use of monocarbonyl enolates are very rare.[5] With this background, we investigated the feasibility of the intramolecular alkyne MOC carbocyclization of α-amino ester enolates (Scheme 1). Several issues should be addressed when employing the MOC concept for the alkyne carbocyclization of α-amino esters. In addition to the generation of axially chiral enolates **II** from the centrally chiral α-amino ester **I**, the kinetic inertness of the alkyne moiety should be overcome via appropriate electrophilic activation to allow for the facile nucleophilic attack of the chiral enolate before racemization.

**Scheme 1. Intramolecular Alkyne MOC Carbocyclization of an α-Amino Ester**

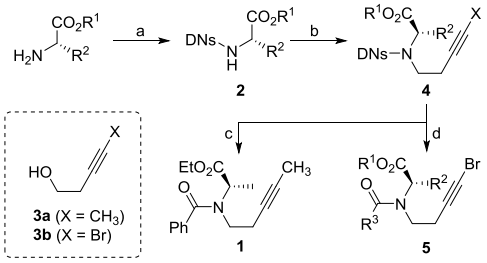



## RESULTS AND DISCUSSION

Our MOC alkyne cyclization was initially investigated with internal alkyne substrate **1**, which was accessible on scale from L-alanine ester in 3 steps without notable racemization (>99% ee), as shown in Scheme 2. The strong bases generally used for α-amino ester enolate generation, such as NaH, potassium bis(trimethylsilyl)amide (KHMDS), and LHMDS, were first examined. No reaction occurred with such bases, and the starting material was mostly recovered. To activate the alkyne moiety towards nucleophilic attack, π-Lewis acid catalysts were considered. Activated alkynes can generally be obtained by coordination to electron-deficient metals, such as Au, Pt, and Ag.[6] However, most such Lewis-acidic metals are believed to be incom-

patible with the strong base required for ester enolate generation.[7] Despite this incompatibility, the search for suitable combinations of base-alkyne activator or base-Lewis acid for internal alkyne carbocyclization was conducted. However, all attempts failed.

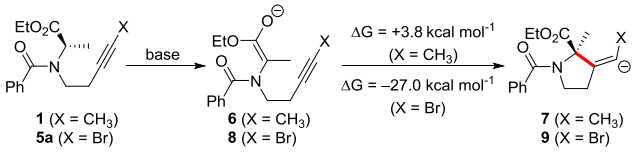
**Scheme 2. Representative Scheme for Synthesis of the MOC Substrate**[a]




[a]Reaction conditions: (a) DNsCl, TEA, DCM, 0 ℃; (b) **3**, DIAD, $PPh_3$, benzene, 25 ℃; (c) thioglycolic acid, TEA, BzCl, DCM, 25 ℃; (d) thioglycolic acid, TEA or DIPEA, acyl chloride or $Boc_2O$, DCM, 25 ℃. DNsCl = 2,4-dinitrobenzenesulfonyl chloride; DIAD = diisopropyl azodicarboxylate; TEA = triethylamine; DIPEA = *N*,*N*-diisopropylethylamine.

The envisioned carbocyclization with internal alkyne substrate **1** is an unfavorable endothermic process because the initial enolate anion will be converted to the less stable vinyl anion (Scheme 1 and 3). Our density functional theory (DFT) calculations (method: wB97XD, basis set: 6–31+G(d)) indicated that, going from *Z*-enolate **6** to α-vinyl carbanion intermediate **7**, the process is endothermic with a Gibbs free energy change at 298 K of 3.8 kcal $mol^{-1}$. Conceivably, this unfavorable thermodynamic profile could be overcome by the application of an excess of Lewis acids, such as $TiCl_4$ and $SnCl_4$, to generate stable intermediates with vinyl carbanions after carbocyclization.[8] However, according to the literature, this strategy is applicable only to substrates with β-dicarbonyl scaffolds.

**Scheme 3. Computed Gibbs Free Energy Profile**

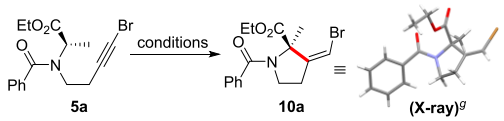



We envisioned that the carbocyclization of α-amino ester enolates with haloalkynes would be a favorable process (Scheme 3). Due to the presence of a halogen atom, haloalkynes would produce more stabilized vinyl carbanions than alkynes after nucleophilic addition. Our DFT calculations showed that carbocyclization of *Z*-enolate **8** onto bromoalkyne is thermodynamically favorable with a Gibbs free energy value of –27.0 kcal $mol^{-1}$ at 298 K.[9] The resulting vinyl halides after carbocyclization are versatile functional groups that are often employed for transition metal-catalyzed coupling reactions.[10] Thus, the use of haloalkynes in alkyne carbocyclization would be synthetically more appealing than that of terminal and internal alkyl alkynes.

The MOC carbocyclization of α-amino ester enolates with haloalkynes was performed with model substrate **5a** (Table 1), which was prepared by the same route as for the synthesis of **1**.

The reaction of **5a** with typical strong bases, such as NaH and KHMDS, failed to provide the cyclized product as in the case of internal alkyne substrate **1** (entries 1 and 2). After screening various other bases, the promising base was found to be KO$^t$Bu. When substrate **5a** was treated with powdered KO$^t$Bu at 25 ℃ in DMF, the desired product **10a** was rapidly (5 min) produced, albeit in low yield (45%) (entry 3). This reaction provided only the *Z*-isomer. The enantiomeric purity of product **10a**, as determined by chiral HPLC, was 94% ee, which indicated that MOC was well exerted during the reaction. The absolute stereochemistry of **10a**, later confirmed by X-ray crystallography and total synthesis,[3] revealed the retention of configuration at the α-carbon atom of the starting amino acid.

**Table 1. Reaction Development**[a]




| entry | base | solvent | *T* (°C) | time (h) | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | NaH | THF | 66 | 12 | - | - |
| 2 | KHMDS | THF | –78 | 30 min | - | - |
| 3 | KO$^t$Bu | DMF | 25 | 5 min | 45 | 94 |
| 4 | KO$^t$Bu | DMF | 0 | 5 min | 78 | 93 |
| 5 | KO$^t$Bu | DMF | –20 | 30 min | 72 | 90 |
| 6 | KO$^t$Bu | DMSO | 25 | 30 min | 67 | 88 |
| 7 | KO$^t$Bu | THF | 25 | 2 | 58 | 26 |
| 8 | KO$^t$Bu | DCM | 25 | 5 | 31 | 25 |
| 9 | KO$^t$Bu | $CH_3CN$ | 25 | 12 | - | - |
| 10 | NaO$^t$Bu | DMF | 0 | 1.5 | 63 | 86 |
| 11[d] | LiO$^t$Bu | DMF | 0 | 24 | 48 | 61 |
| 12[e] | KO$^t$Bu | DMF | 0 | <1 min | 68 | 97 |
| 13[f] | NaO$^t$Bu | DMF | 0 | <1 min | 55 | 92 |

[a]Reaction conditions: **5a** (0.1 mmol) and base (1.5 equiv) in solvent (0.02 M). [b]Isolated yield. [c]The ee values were determined by chiral HPLC. [d]LiO$^t$Bu (8.0 equiv) was used. [e]18-Crown-6 ether (1.5 equiv) was added. [f]15-Crown-5 ether (1.5 equiv) was added. [g]For X-ray crystallography of **10a**, see the Ref. 3 for details.

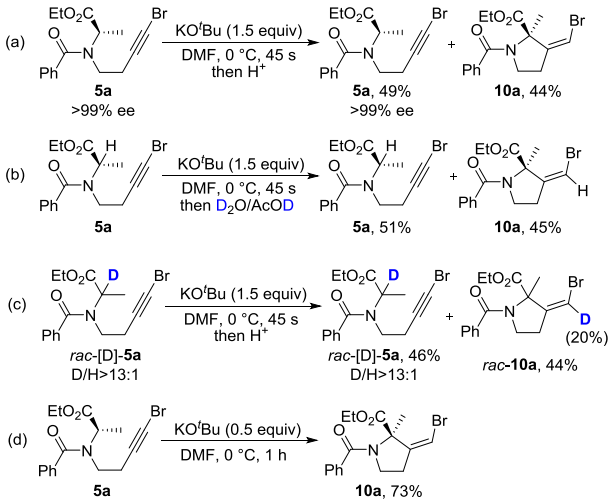
To enhance the chemical yield and degree of chirality preservation, the reaction conditions were further examined using a *tert*-butoxide base. When the temperature of the reaction in DMF was decreased to 0 ℃, the yield of **10a** greatly improved to 78% (entry 4). Nonetheless, the ee value remained unaffected. When the temperature was further lowered to –20 ℃, the reaction rate decreased, and the yield and ee slightly decreased (entry 5). DMF was the superior solvent for the reaction with respect to the enantioselectivity (entries 6–9 vs 3). The reaction in other examined solvents was slower, and the enantiomeric purity of the product was lower. The counter cation of *tert*-butoxide strongly affect the ee of the product. When NaO$^t$Bu was used as the base, the reaction rate was slower than that with KO$^t$Bu, and

the ee value of the product was lower (entries 10 vs 4). The reaction with less basic LiO$^t$Bu also provided the product. However, the reaction was substantially slower, and a large excess of base was needed to complete the reaction. The product was obtained in moderate yield (48%) and ee (61%) (entry 11).

Interesting results were obtained when a crown ether was added as an additive. In the presence of 18-crown-6 ether, the reaction with KO$^t$Bu at 0 ℃ in DMF proceeded very rapidly (<1 min) and provided the product with increased ee (97%) (entries 12 vs 4). 15-Crown-5 ether also improved the reaction rate and ee in the reaction with NaO$^t$Bu (entries 13 vs 10). These results indicated that the degree of ion pairing and the base strength of *tert*-butoxide had significant effects on the reaction rate as well as the yield and ee of the product.[11]

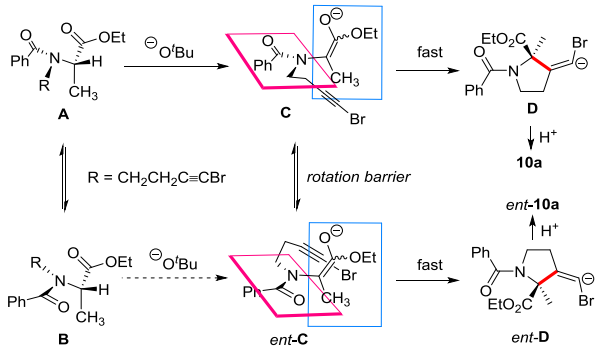
To understand this MOC reaction, we executed additional experiments. First, we analyzed the substrate remaining in the incomplete reaction mixture from the reaction of **5a** with KO$^t$Bu in DMF (Scheme 4a). The enantiomeric purity of the recovered stating material remained the same. Quenching the reaction with $D_2O$/AcOD did not lead to deuterium incorporation at the α-position of the remaining starting material or even at the vinyl position of the product (Scheme 4b). When the reaction was performed with an α-deuterated substrate, the deuterium levels in the remaining substrate were unchanged (Scheme 4c). These results suggest that any ester enolate intermediate is rapidly converted to the product before it is reprotonated. In the last case, partial incorporation of deuterium at the vinyl position of the product was observed. This result, together with the result from Scheme 4b, suggested that the HO$^t$Bu generated by the action of KO$^t$Bu on the α-proton of the substrate might be a proton source, at least partially, for the protonation of the vinyl carbanion intermediate. In fact, alkyne carbocyclization of **5a** was achieved even in the presence of subequivalent amounts of KO$^t$Bu, albeit with a longer reaction time and in slightly lower yield (Scheme 4d), which supports the above supposition of the protonation of the vinyl carbanion by HO$^t$Bu and regeneration of the *tert*-butoxide base.

**Scheme 4. Exploratory Studies to Determine the MOC Mechanism**



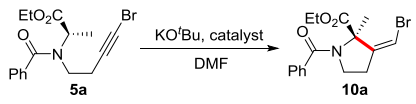

Because cyclization occurs with retention of configuration at the α-carbon, the axially chiral enolate **C** could be proposed instead of enolate *ent*-**C** as the crucial intermediate for the asymmetric MOC cyclization (Scheme 5). The formation of chiral enolate **C** could be obtained from the chiral α-amino ester by deprotonation of conformer **A,** which is one of the stable conformers of **5a**. Deprotonation of the other stable conformer **B**, where Cα-hydrogen is eclipsed with the amide group, to yield enolate *ent*-**C** would be unfavorable because of the steric interaction between *tert*-butoxide and the benzoyl group, similar to the hypothesis proposed by Kawabata.[12] Based on the results in Scheme 4 and Table 1, it was possible to conclude that the generated ester enolate **C** rapidly underwent nucleophilic addition to the bromoalkyne before it was reprotonated and racemized. Then, the resulting vinyl carbanion intermediate **D** was protonated by HO$^t$Bu to give the product **10a**.

**Scheme 5. Proposed Mechanism of MOC Cyclization of 5a**




With the successful results of the asymmetric bromoalkyne carbocyclization with KO$^t$Bu/DMF, we further optimized the reaction conditions. The results in Table 1 imply that the reaction rate is related to the ee of the product. To increase the reaction rate by increasing the electrophilicity of the bromoalkyne, alkynophilic Lewis acid catalysts were considered. As mentioned above, Lewis-acidic metals are generally incompatible with strong bases. Nonetheless, we asserted that *tert*-butoxide might be compatible with certain Lewis acids because *tert*-butoxide is not an extremely strong base.[13] We applied several transition-metal catalysts including Cu, In, Au, and Pd (Table 2).[14] To our delight, In(OTf)$_3$ was found to effectively catalyze the cyclization reaction to give **5a** in 91% yield and 98% ee (entry 2). The addition of the archetypal gold(I) phosphine complex, [AuCl(PPh$_3$)], also provided the product with an increased yield and ee. However, the reaction yield and ee value were lower than those with In(OTf)$_3$ (entries 3 vs 2).

**Table 2. Reaction Development with Transition Metal Catalysts**[a]




| entry | base | catalyst | $T$ (°C) | time (min) | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | KO$^t$Bu | CuI | 25 | 10 | 76 | 93 |
| 2 | KO$^t$Bu | In(OTf)$_3$ | 25 | 10 | 91 | 98 |

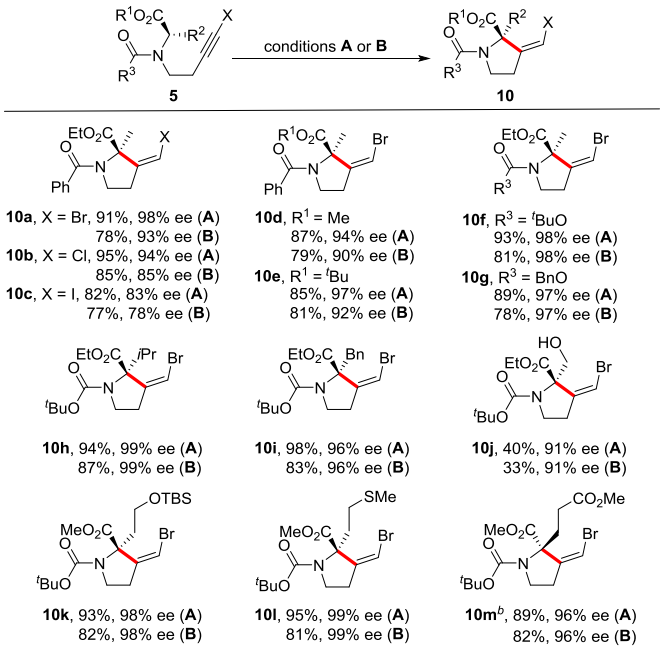
| | | | | | | |
|---|---|---|---|---|---|---|
| 3 | KO$^t$Bu | $AuCl(PPh)_3$ | 25 | 10 | 82 | 97 |
| 4 | KO$^t$Bu | $PdCl_2$ | 25 | 10 | 92 | 91 |

[a]Reaction conditions: **5a** (0.1 mmol), KO$^t$Bu (1.5 equiv), catalyst (0.1 equiv), DMF (0.02 M). [b]Isolated yields. [c]Enantiomeric excess, determined via chiral HPLC analysis.

The substrate scope is summarized in Table 3 with two optimized reaction conditions: KO$^t$Bu/DMF/$In(OTf)_3$ (condition **A**) and KO$^t$Bu/DMF (condition **B**). In general, the reaction conditions with $In(OTf)_3$ showed a higher yield and enantiomeric purity of the product. For benzoyl amide substrates (**10a**–**10e**), the ee value increased by 5% on average with $In(OTf)_3$. The overall yields with condition **A** were also improved by approximately 10% compared to condition **B**.

Initial exploration of the scope of the reaction under the identified two conditions focused on the haloalkyne moiety. Substrates possessing an iodoalkyne or chloroalkyne as the electrophilic partner underwent the reaction to provide the corresponding carbocyclization products **10b** and **10c** respectively, but the enantiomeric purity of the product was lower than that of the bromoalkyne substrate (**10b** and **10c** vs **10a**). The effects of the ester group size on the yield and ee were examined and found to be not significant (**10d** and **10e** vs **10a**). Next, the protecting group on the nitrogen was investigated. A bulky Boc group has been reported to be superior in the generation of dynamic axial chirality in amino ester enolates.[2a,15] Consistent with this finding, the substrate with a Boc group underwent the reaction to furnish the cyclized product **10f** with an excellent ee of 98%, even without $In(OTf)_3$. The substrate with the Cbz group also gave product **10g** with an excellent ee of 97% under both conditions.[16]

**Table 3. Substrate Scope of Haloalkynes**[a]

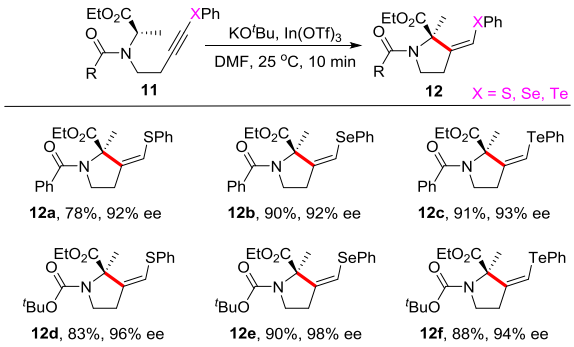



[a]Reaction condition **A**: **5** (0.1 mmol), KO$^t$Bu (1.5 equiv for **10a**–**10e**, and **10g**; 2.0 equiv for **10f**, and **10h**–**10m**), $In(OTf)_3$ (0.1 equiv), DMF (0.02 M), 25 ℃, 10 min. Reaction condition **B**: **5** (0.1 mmol), KO$^t$Bu (1.5 equiv for **10a**–**10e**, and **10g**; 2.0 equiv for **10f**, and **10h**–**10m**), DMF (0.02 M), 0 ℃, 5 min. The yields shown are isolated yields. The ee value was determined by chiral HPLC. [b]Substrate **5m** was prepared from D-glutamate.

With a Boc protecting group, α-amino esters bearing various α-alkyl groups could be cyclized to afford the Cα-substituted proline products with excellent ee (**10h**–**10m**). The influence of the α-substituent on the degree of chirality preservation and yield was not significant. However, the serine substrate **5j** gave a low yield of the product **10j** due to the β-elimination side reaction.[17]

Interestingly, the reaction conditions of KO$^t$Bu/DMF/$In(OTf)_3$ (condition **A**) were also effective for the MOC carbocyclizaion of α-amino ester enolates with chalcogen-substituted alkynes.[18] Organochalcogen compounds have attracted considerable attention for their promising potential applications in organic synthesis.[19] As shown in Table 4, all substrates with three different chalcogen atoms, sulfur, selenium, and tellurium, afforded the corresponding 5-*exo*-*dig* products with high to excellent yields and ee values under the condition **A**. Similar to bromoalkyne substrates, chalcogen-substituted alkyne substrates with a Boc group underwent the reaction to give the cyclized products **12d**–**12f** with a higher ee than the substrates with the benzoyl group.

**Table 4. Substrate Scope of Chalcogen-Substituted Alkynes**[a]




[a]Reaction conditions: **11** (0.1 mmol), KO$^t$Bu (1.5 equiv for **12a**–**12c**; 2.0 equiv for **12d**–**12f**), $In(OTf)_3$ (0.1 equiv), DMF (0.02 M). The yields shown are isolated yields. The ee value was determined by chiral HPLC.

## CONCLUSION

In conclusion, we have developed a new strategy for the asymmetric 5-*exo*-*dig* cyclization of α-amino ester enolates onto heterosubstituted alkynes via the MOC concept. The use of heteroatoms is crucial for the success of the asymmetric cyclization. This method provides access to the synthetically useful pyrrolidine skeleton of the *Z*-form heterosubstituted methylene. Notably, this reaction occurs under mild conditions and provides product with high to excellent enantioselectivity without the aid of an external chiral source. Applications of this chemistry for the synthesis of alkaloids are under investigation and will be reported in due course.

## EXPERIMENTAL SECTION

**General Information.** All of the chemicals were of reagent grade and were used as purchased. All of the reactions were performed under an inert atmosphere consisting of dry nitrogen using distilled dry solvents. The reactions were monitored by

thin layer chromatography (TLC) analysis using silica gel 60 F-254 TLC plates. The compound spots were visualized using UV light (254 nm). Flash column chromatography was carried out on silica gel (230–400 mesh). The melting points were measured by using a Büchi B-540 melting point apparatus without correction. The optical rotations were measured on a JASCO P-2000 polarimeter (Hachioji, Tokyo, Japan) using a 10 mm cell and IR spectra were acquired using an Agilent 5500a FTIR (Agilent, USA). The high-resolution mass spectra (HRMS) were recorded using fast atom bombardment (FAB) or quadrupole time-of-flight (Q-TOF). NMR spectra were obtained on a JNM-ECZ400S/L1 (JEOL, Tokyo, Japan), a Bruker AVANCE 500 (Bruker, Rheinstetten, Germany), a JEOL JNM-ECA600 (JEOL, Tokyo, Japan), or an 800-MHz Bruker Avance III HD spectrometer with a 5-mm triple resonance inverse (TCI) CryoProbe (Bruker BioSpin, Germany). HPLC was performed on an Agilent 1200 series instrument with CHIRALCEL OD-H column (0.46 × 25 cm), CHIRALPAK AD-H column (0.46 × 25 cm) and CHIRALPAK AD-3R column (0.46 × 15 cm).

**General Procedure for the Synthesis of 2.** 2,4-Dinitrobenzenesulfonyl chloride (2.86 g, 10.7 mmol, 1.10 equiv) was added to L-alanine ethyl ester hydrochloride (1.50 g, 9.76 mmol) in DCM (40 mL) at 0 ℃. Then, triethylamine (3.00 mL, 21.5 mmol, 2.20 equiv) in DCM (20 mL) was slowly added into the mixture with a syringe pump for more than 30 min. After the reaction mass was maintained between 0–20 ℃ for 5 h, the reaction was quenched with $H_2O$ (30 mL), warmed to room temperature, and extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$ and concentrated *in vacuo*. The brown residue was purified by flash column chromatography (hexane/EtOAc, 3:1) to yield **2a** (2.75 g, 7.91 mmol, 81%) as a yellow oil.

***Ethyl ((2,4-dinitrophenyl)sulfonyl)-L-alaninate (2a).*** $R_f$ = 0.40 (hexane/EtOAc, 2:1), light yellow oil; $[\alpha]_D^{20}$ = –162.8 (c = 0.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ = 8.65 (d, *J* = 2.2 Hz, 1H), 8.49 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.25 (d, *J* = 8.6 Hz, 1H), 6.18 (s, 1H), 4.22 (brs, 1H), 4.00–3.94 (m, 2H), 1.46 (d, *J* = 7.2 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 171.3, 149.6, 147.6, 139.4, 132.1, 127.1, 120.7, 61.9, 52.6, 19.2, 13.8; IR (neat, $cm^{-1}$) = 3326, 3106, 2989, 1733, 1538, 1348, 1172, 1133; HRMS (FAB): calcd for $C_{11}H_{14}N_3O_8S$: 348.0502 ($[M+H]^+$), found 348.0500.

***Methyl ((2,4-dinitrophenyl)sulfonyl)-L-alaninate (2d).*** Following the same experimental procedure of **2a** with L-alanine methyl ester hydrochloride (500 mg, 3.58 mmol), **2d** (1.02 g, 85%) was obtained as light yellow oil; $R_f$ = 0.40 (hexane/EtOAc, 2:1); $[\alpha]_D^{20}$ = –187.5 (c = 0.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ = 8.73 (d, *J* = 2.0 Hz, 1H), 8.52 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.27 (d, *J* = 8.8 Hz, 1H), 6.13 (d, *J* = 8.0 Hz, 1H), 4.30 (qd, *J* = 11.5, 5.2 Hz, 1H), 3.56 (s, 3H), 1.51 (d, *J* = 7.2 Hz, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 172.1, 149.9, 148.0, 140.2, 132.3, 127.4, 121.3, 53.1, 52.9, 19.7; IR (neat, $cm^{-1}$) = 3327, 3103, 2956, 1139, 1540, 1423, 1351, 1173, 1136; HRMS (FAB): calcd for $C_{10}H_{12}N_3O_8S$: 334.0345 ($[M+H]^+$), found 334.0346.

***tert-Butyl ((2,4-dinitrophenyl)sulfonyl)-L-alaninate (2e).*** Following the same experimental procedure of **2a** with L-alanine *tert*-butyl ester hydrochloride (500 mg, 2.75 mmol), **2e** (857 mg, 83%) was obtained as light yellow oil; $R_f$ = 0.40 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = –174.2 (c = 0.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ = 8.69 (d, *J* = 2.2 Hz, 1H), 8.49 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.26 (d, *J* = 8.6 Hz, 1H), 6.12 (d, *J* = 8.7 Hz, 1H), 4.14 (q, *J* = 5.3 Hz, 1H), 1.44 (d, *J* = 7.2 Hz, 3H), 1.26 (s, 9H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 170.5, 149.6, 147.8, 139.8, 132.1, 127.0, 120.9, 83.0, 53.3, 27.6 (3C), 19.5; IR (neat, $cm^{-1}$) = 3325, 3105, 2982, 1729, 1550, 1538, 1348, 1302, 1171, 1133, 1104; HRMS (FAB): calcd for $C_{13}H_{18}N_3O_8S$: 376.0815 ($[M+H]^+$), found 376.0816.

***Ethyl ((2,4-dinitrophenyl)sulfonyl)-L-valinate (2h).*** Following the same experimental procedure of **2a** with L-valine ethyl ester hydrochloride (500 mg, 2.75 mmol), **2h** (878 mg, 85%) was obtained as light yellow oil; $R_f$ = 0.40 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = –169.2 (c = 0.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ = 8.67 (d, *J* = 2.2 Hz, 1H), 8.49 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.23 (d, *J* = 8.6 Hz, 1H), 6.07 (s, 1H), 4.01 (d, *J* = 4.8 Hz, 1H), 3.97–3.88 (m, 2H), 2.23–2.18 (m, 1H), 1.08 (t, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 170.4, 149.7, 147.7, 139.4, 132.0, 127.1, 120.8, 62.2, 61.7, 31.2, 18.9, 17.0, 13.9; IR (neat, $cm^{-1}$) = 3322, 3106, 2970, 1732, 1537, 1348, 1172, 1137, 1021; HRMS (FAB): calcd for $C_{13}H_{18}N_3O_8S$: 376.0815 ($[M+H]^+$), found 376.0811.

***Ethyl ((2,4-dinitrophenyl)sulfonyl)-L-phenylalaninate (2i).*** Following the same experimental procedure of **2a** with L-phenylalanine ethyl ester hydrochloride (400 mg, 1.74 mmol), **2i** (597 mg, 81%) was obtained as light yellow oil; $R_f$ = 0.30 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = –63.8 (c = 0.5, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ = 8.54 (d, *J* = 2.1 Hz, 1H), 8.34 (dd, *J* = 8.6, 2.1 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.13–7.07 (m, 5H), 6.16 (d, *J* = 9.1 Hz, 1H), 4.46 (qd, *J* = 8.6, 4.6 Hz, 1H), 4.06 (q, *J* = 7.4 Hz, 2H), 3.17 (dd, *J* = 14.0, 5.0 Hz, 1H), 3.01 (dd, *J* = 14.0, 8.2 Hz, 1H), 1.16 (t, *J* = 7.2 Hz, 3H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) δ = 170.2, 149.4, 147.2, 139.3, 134.9, 131.7, 129.2 (2C), 128.5 (2C), 127.2, 127.0, 120.6, 62.0, 58.2, 38.7, 13.8; IR (neat, $cm^{-1}$) = 3336, 3105, 2986, 1736, 1538, 1349, 1170, 1029; HRMS (FAB) calcd for $C_{17}H_{18}N_3O_8S$: 424.0815 ($[M+H]^+$), found 424.0824.

***Ethyl O-(tert-butyldimethylsilyl)-N-((2,4-dinitrophenyl)sulfonyl)-L-serinate (2j).*** L-serine ethyl ester hydrochloride (500 mg, 2.95 mmol) in DCM (20 mL) was treated with imidazole (602 mg, 8.84 mmol, 3.00 equiv) and TBSCl (889 mg, 5.90 mmol, 2.00 equiv) at 0 ℃. The resulting mixture was allowed to warm to room temperature for 5 h, then quenched with $H_2O$ (15 mL) and extracted with DCM (2 × 20 mL). The combined organic layers were washed with brine (15 mL), dried over $Na_2SO_4$ and concentrated *in vacuo*. After the residue and 2, 4-dinitrobenzenesulfonyl chloride (786 mg, 2.95 mmol, 1.00 equiv) was redissolved into DCM (30 mL) at 0 ℃, triethylamine (827 μL, 5.90 mmol, 2.00 equiv) in DCM (15 mL) was added into the mixture slowly with syringe pump more than 15 min. After 3 h at 0 ℃ under an inert atmosphere, the reaction was quenched with $H_2O$ (20 mL), warmed to room temperature, and extracted with DCM (2 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$ and concentrated. The brown residue was purified with flash column chromatography (hexane/EtOAc, 5:1) to yield **2j** (1.12 g, 2.36 mmol, 80% for two steps) as a yellow oil. $[\alpha]_D^{20}$ = –152.9 (c = 0.5, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ = 8.73 (d, *J* = 2.3 Hz, 1H), 8.49 (dd, *J* = 8.7, 2.3 Hz, 1H), 8.23 (d, *J* = 8.7 Hz, 1H), 6.49 (d, *J* = 9.2 Hz, 1H), 4.30 (td, *J* = 9.4, 2.6 Hz,

1H), 4.13 (dd, *J* = 10.1, 2.3 Hz, 1H), 4.01–3.95 (m, 2H), 3.90 (dd, *J* = 9.8, 3.0 Hz, 1H), 1.13 (t, *J* = 7.3 Hz, 3H), 0.82 (s, 9H), 0.015 (d, *J* = 27.9 Hz, 6H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ = 169.4, 149.6, 147.8, 140.5, 131.8, 127.0, 120.9, 64.1, 62.0, 58.9, 25.5 (3C), 18.0, 14.0, –5.6, –5.9; IR (neat, $cm^{-1}$) = 3365, 3106, 2954, 2932, 2886, 2858, 1743, 1553, 1539, 1349, 1254, 1173, 1102, 1042; HRMS (FAB) calcd for $C_{17}H_{28}N_3O_9SSi$: 478.1316 ($[M+H]^+$), found 478.1320.

***Methyl O-(tert-butyldimethylsilyl)-N-((2,4-dinitrophenyl)sulfonyl)-L-homoserinate (2k).*** Following the same experimental procedure of **2j** with L-homoserine methyl ester hydrochloride (500 mg, 2.96 mmol), **2k** (1.04 g, 74%) was obtained as light yellow oil; $R_f$ = 0.30 (hexane/EtOAc, 5:1); $[\alpha]_D^{20}$ = –130.8 (c = 0.5, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ = 8.69 (d, *J* = 2.2 Hz, 1H), 8.48 (dd, *J* = 8.7, 2.2 Hz, 1H), 8.23 (d, *J* = 8.6 Hz, 1H), 4.40 (q, *J* = 3.6 Hz, 1H), 3.81–3.76 (m, 1H), 3.71–3.66 (m, 1H), 3.51 (s, 3H), 2.13–2.00 (m, 2H), 0.86 (s, 9H), 0.05 (d, *J* = 2.6 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 171.4, 149.5, 147.7, 140.1, 132.0, 126.9, 120.7, 59.4, 55.1, 52.5, 34.3, 25.8 (3C), 18.3, –5.6, –5.7; IR (neat, $cm^{-1}$) = 3325, 3107, 2955, 2931, 2885, 2858, 1744, 1539, 1349, 1171, 1100; HRMS (FAB) calcd for $C_{17}H_{28}N_3O_9SSi$: 478.1316 ($[M+H]^+$), found 478.1306.

***Methyl ((2,4-dinitrophenyl)sulfonyl)-L-methioninate (2l).*** Following the same experimental procedure of **2a** with L-methionine methyl ester hydrochloride (500 mg, 2.50 mmol), **2l** (817 mg, 83%) was obtained as light yellow oil; $R_f$ = 0.30 (hexane/EtOAc, 2:1); $[\alpha]_D^{20}$ = –169.5 (c = 0.5, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ = 8.71 (d, *J* = 2.3 Hz, 1H), 8.51 (dd, *J* = 8.6, 2.3 Hz, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 6.36 (dd, *J* = 6.8 Hz, 1H), 4.42 (d, *J* = 4.1 Hz, 1H), 3.55 (s, 3H), 2.67–2.52 (m, 2H), 2.24–2.12 (m, 1H), 2.07 (s, 3H), 2.07–2.03 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 171.3, 149.8, 147.8, 139.5, 132.2, 127.2, 121.0, 55.8, 52.9, 31.7, 29.8, 15.3; IR (neat, $cm^{-1}$) = 3310, 3103, 2920, 1738, 1538, 1348, 1166, 1102; HRMS (FAB) calcd for $C_{12}H_{16}N_3O_8S_2$: 394.0379 ($[M+H]^+$), found 394.0385.

***Dimethyl ((2,4-dinitrophenyl)sulfonyl)-D-glutamate (2m).*** Following the same experimental procedure of **2a** with D-glutamic dimethyl ester hydrochloride (500 mg, 2.36 mmol), **2m** (804 mg, 84%) was obtained as light yellow oil; $R_f$ = 0.20 (hexane/EtOAc, 2:1); $[\alpha]_D^{20}$ = +138.3 (c = 0.5, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ = 8.71 (d, *J* = 2.2 Hz, 1H), 8.49 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.25 (d, *J* = 8.6 Hz, 1H), 6.34 (d, *J* = 9.0 Hz, 1H), 4.31 (qd, *J* = 8.9, 4.5 Hz, 1H ), 3.68 (s, 3H), 3.55 (s, 3H), 2.54–2.45 (m, 2H), 2.30–2.23 (m, 1H), 2.04–1.96 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 172.9, 170.9, 149.6, 147.5, 139.2, 132.1, 127.1, 120.8, 56.0, 52.7, 51.8, 29.4, 27.4; IR (neat, $cm^{-1}$) = 3102, 3105, 2956, 1732, 1538, 1349, 1169, 1105; HRMS (FAB) calcd for $C_{13}H_{16}N_3O_{10}S$: 406.0556 ($[M+H]^+$), found 406.0563.

**General Procedure for the Synthesis of 4.** To a stirred solution of the sulfonamide **2a** (842 mg, 2.43 mmol), 4-bromo-3-butyn-1-ol[20] (539 mg, 3.64 mmol, 1.50 equiv), and $PPh_3$ (1.27 g, 4.85 mmol, 2.00 equiv) in benzene (40 mL), DIAD (1.02 mL, 4.85 mmol, 2.00 equiv) in benzene (15 mL) was added dropwise with a syringe pump for more than 10 min at room temperature under an inert atmosphere. After 1 h, the mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 4:1) to yield **4aa** (1.09 g, 2.29 mmol, 94%) as a light yellow oil.

***Ethyl N-(4-bromobut-3-yn-1-yl)-N-((2,4-dinitrophenyl)sulfonyl)-L-alaninate (4aa).*** $R_f$ = 0.40 (hexane/EtOAc, 3:1), light yellow oil; $[\alpha]_D^{20}$ = +27.4 (c = 0.5, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ = 8.49 (dd, *J* = 8.7, 2.3 Hz, 1H), 8.40 (d, *J* = 2.1 Hz, 1H), 8.30 (d, *J* = 8.7 Hz, 1H), 4.75 (q, *J* = 7.4 Hz, 1H), 4.11–3.99 (m, 2H), 3.63 (ddd, *J* = 15.5, 10.0, 5.4 Hz, 1H), 3.24 (ddd, *J* = 15.4, 9.9, 5.8 Hz, 1H), 2.73 (qd, *J* = 16.4, 5.3 Hz, 1H), 2.54 (qd, *J* = 16.5, 5.4 Hz, 1H), 1.57 (d, *J* = 7.4 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 170.8, 149.7, 148.1, 137.9, 132.7, 126.0, 119.6, 76.2, 62.0, 56.9, 45.2, 41.4, 22.3, 16.9, 14.0; IR (neat, $cm^{-1}$) = 3101, 2987, 1736, 1555, 1540, 1353, 1157; HRMS (FAB) $C_{15}H_{17}BrN_3O_8S$: 477.9920 ($[M+H]^+$), found 477.9933.

***Ethyl N-((2,4-dinitrophenyl)sulfonyl)-N-(pent-3-yn-1-yl)-L-alaninate (4ab).*** Following the same experimental procedure of **4aa** with 3-pentyn-1-ol and **2a** (260 mg, 0.75 mmol), **4ab** (294 mg, 95%) was obtained as light yellow oil; $R_f$ = 0.40 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = +29.8 (c = 0.5, $CHCl_3$); $^1H$ NMR (800 MHz, $CDCl_3$) δ = 8.46 (dd, *J* = 8.7, 2.3 Hz, 1H), 8.37 (d, *J* = 2.3 Hz, 1H), 8.26 (d, *J* = 8.7 Hz, 1H), 4.69 (q, *J* = 7.4 Hz, 1H), 4.05–3.97 (m, 2H), 3.55 (ddd, *J* = 15.5, 10.3, 5.3 Hz, 1H), 3.15 (ddd, *J* = 15.6, 10.3, 5.5 Hz, 1H), 2.58–2.54 (m, 1H), 2.42–2.37 (m, 1H), 1.69 (t, *J* = 2.7 Hz, 3H), 1.53 (d, *J* = 7.5 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (200 MHz, $CDCl_3$) δ = 170.7, 149.5, 147.9, 138.0, 132.5, 126.0, 119.5, 78.3, 74.9, 61.7, 56.7, 45.9, 21.3, 16.7, 13.8, 3.3; IR (neat, $cm^{-1}$) = 3102, 2985, 1734, 1553, 1537, 1464, 1349, 1300, 1226, 1154; HRMS (FAB) $C_{16}H_{20}N_3O_8S$: 414.0971 ($[M+H]^+$), found 414.0973.

***Ethyl N-(but-3-yn-1-yl)-N-((2,4-dinitrophenyl)sulfonyl)-L-alaninate (4ac).*** Following the same experimental procedure of **4aa** with 3-butyn-1-ol and **2a** (300 mg, 0.86 mmol), **4ac** (328 mg, 95%) was obtained as light yellow oil; $R_f$ = 0.40 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = +36.5 (c = 0.5, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ = 8.47 (dd, *J* = 8.7, 2.2 Hz, 1H), 8.38 (d, *J* = 2.2 Hz, 1H), 8.26 (d, *J* = 8.8 Hz, 1H), 4.72 (q, *J* = 7.4 Hz, 1H), 4.09–3.97 (m, 2H), 3.62 (ddd, *J* = 15.5, 10.3, 5.3 Hz, 1H), 3.22 (ddd, *J* = 15.6, 10.2, 5.6 Hz, 1H), 2.72–2.64 (m, 1H), 2.54–2.45 (m, 1H), 2.00 (t, *J* = 2.7 Hz, 1H), 1.56 (d, *J* = 7.4 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 170.8, 149.7, 148.0, 137.9, 132.7, 126.1, 119.6, 80.2, 71.0, 61.9, 56.8, 45.4, 21.1, 16.9, 14.0; IR (neat, $cm^{-1}$) = 3295, 3105, 2986, 1734, 1538, 1350, 1155; HRMS (FAB) $C_{15}H_{18}N_3O_8S$: 400.0815 ($[M+H]^+$), found 400.0806.

***Methyl N-(4-bromobut-3-yn-1-yl)-N-((2,4-dinitrophenyl)sulfonyl)-L-alaninate (4da).*** Following the same experimental procedure of **4aa** with 4-bromo-3-butyn-1-ol and **2d** (276 mg, 0.83 mmol), **4da** (364 mg, 95%) was obtained as light yellow oil; $R_f$ = 0.30 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = +13.8 (c = 0.5, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ = 8.50 (dd, *J* = 8.7, 2.2 Hz, 1H), 8.41 (d, *J* = 2.2 Hz, 1H), 8.28 (d, *J* = 8.7 Hz, 1H), 4.78 (q, *J* = 7.4 Hz, 1H), 3.67–3.59 (m, 1H), 3.62 (s, 3H), 3.24 (ddd, *J* = 15.6, 9.8, 5.8 Hz, 1H), 2.73 (qd, *J* = 16.4, 5.3 Hz, 1H), 2.54 (qd, *J* = 16.4, 5.4 Hz, 1H), 1.52 (d, *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 171.3, 149.7, 148.1, 137.9, 132.7, 126.0, 119.7, 76.2, 56.8, 52.7, 45.2, 41.5, 22.2, 16.9; IR (neat, $cm^{-1}$) = 3100, 2955, 1739, 1554, 1541, 1352, 1174, 1156, 1072; HRMS (FAB) calcd for $C_{14}H_{15}BrN_3O_8S$: 463.9763 ($[M+H]^+$), found 463.9771.

***tert-Butyl N-(4-bromobut-3-yn-1-yl)-N-((2,4-dinitrophenyl)sulfonyl)-L-alaninate (4ea).*** Following the same

experimental procedure of **4aa** with 4-bromo-3-butyn-1-ol and **2e** (143 mg, 0.38 mmol), **4ea** (173 mg, 90%) was obtained as light yellow oil; $R_f$ = 0.40 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = +6.7 (c = 0.5, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ = 8.48 (dd, *J* = 8.7, 2.2 Hz, 1H), 8.38 (d, *J* = 2.1 Hz, 1H), 8.26 (d, *J* = 8.7 Hz, 1H), 4.63 (q, *J* = 7.4 Hz, 1H), 3.63 (ddd, *J* = 15.4, 10.2, 5.2 Hz, 1H), 3.22 (ddd, *J* = 15.6, 9.9, 5.8 Hz, 1H), 2.70 (qd, *J* = 16.3, 5.3 Hz, 1H), 2.53 (qd, *J* = 16.5, 5.5 Hz, 1H), 1.52 (d, *J* = 7.4 Hz, 3H), 1.33 (s, 9H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) δ = 169.7, 149.6, 148.0, 138.1, 132.6, 126.0, 119.5, 82.8, 76.3, 57.3, 45.1, 41.3, 27.7 (3C), 22.3, 17.0; IR (neat, $cm^{-1}$) = 3102, 2980, 1729, 1554, 1537, 1364, 1349, 1301, 1245, 1072; HRMS (FAB) calcd for $C_{17}H_{21}BrN_3O_8S$: 506.0233 ([M+H]$^+$), found 506.0221.

***Ethyl N-(4-bromobut-3-yn-1-yl)-N-((2,4-dinitrophenyl)sulfonyl)-L-valinate (4ha).*** Following the same experimental procedure of **4aa** with 4-bromo-3-butyn-1-ol and **2h** (300 mg, 0.80 mmol), **4ha** (347 mg, 86%) was obtained as light yellow oil; $R_f$ = 0.50 (hexane/EtOAc, 5:1); $[\alpha]_D^{20}$ = –29.5 (c = 0.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ = 8.47 (dd, *J* = 8.7, 2.2 Hz, 1H), 8.40 (d, *J* = 2.1 Hz, 1H), 8.25 (d, *J* = 8.7 Hz, 1H), 4.13 (d, *J* = 9.8 Hz, 1H), 4.10–4.00 (m, 2H), 3.65–3.55 (m, 2H), 2.75 (ddd, *J* = 16.5, 9.8, 6.3 Hz, 1H), 2.53 (ddd, *J* = 16.2, 9.8, 6.3 Hz, 1H), 2.23–2.17 (m, 1H), 1.15 (t, *J* = 7.1 Hz, 3H), 0.99 (dd, *J* = 6.6, 3.8 Hz, 6H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 169.7, 149.7, 148.2, 137.9, 132.9, 125.8, 119.5, 76.2, 66.7, 61.5, 44.9, 41.1, 29.0, 21.7, 19.7, 19.4, 14.0; IR (neat, $cm^{-1}$) = 3103, 2972, 1732, 1554, 1538, 1365, 1349, 1167, 1146, 1108, 1022; HRMS (FAB) $C_{17}H_{21}BrN_3O_8S$: 506.0233 ([M+H]$^+$), found 506.0231.

***Ethyl N-(4-bromobut-3-yn-1-yl)-N-((2,4-dinitrophenyl)sulfonyl)-L-phenylalaninate (4ia).*** Following the same experimental procedure of **4aa** with 4-bromo-3-butyn-1-ol and **2i** (416 mg, 0.98 mmol), **4ia** (440 mg, 81%) was obtained as light yellow oil; $R_f$ = 0.50 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = –4.0 (c = 0.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ = 8.35 (d, *J* = 2.0 Hz, 1H), 8.33 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.27–7.20 (m, 5H), 4.92 (q, *J* = 5.2 Hz, 1H), 4.09–4.03 (m, 2H), 3.64 (ddd, *J* = 15.5, 10.0, 5.6 Hz, 1H), 3.48–3.42 (m, 2H), 3.03 (dd, *J* = 14.7, 9.1 Hz, 1H), 2.65 (qd, *J* = 16.5, 5.4 Hz, 1H), 2.45 (qd, *J* = 16.4, 5.4 Hz, 1H), 1.14 (t, *J* = 7.2 Hz, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 169.8, 149.5, 148.0, 137.7, 135.6, 132.4, 128.8 (2C), 128.7 (2C), 127.2, 125.9, 119.5, 76.3, 62.0, 61.9, 45.1, 41.3, 36.1, 21.5, 13.9; IR (neat, $cm^{-1}$) = 3102, 2984, 1737, 1555, 1368, 1352, 1167, 1107, 1021; HRMS (FAB) calcd for $C_{21}H_{21}BrN_3O_8S$: 554.0233 ([M+H]$^+$), found 554.0230.

***Ethyl N-(4-bromobut-3-yn-1-yl)-O-(tert-butyldimethylsilyl)-N-((2,4-dinitrophenyl)sulfonyl)serinate (4ja).*** Following the same experimental procedure of **4aa** with 4-bromo-3-butyn-1-ol and **2j** (639 mg, 1.34 mmol), **4ja** (699 mg, 86%) was obtained as light yellow oil; $R_f$ = 0.60 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = +47.6 (c = 0.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ = 8.49 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.38 (d, *J* = 2.0 Hz, 1H), 8.30 (d, *J* = 8.8 Hz, 1H), 4.71 (dd, *J* = 5.0, 1.8 Hz, 1H), 4.29 (dd, *J* = 11.4, 5.0 Hz, 1H), 4.17–4.08 (m, 1H), 4.03–3.95 (m, 2H), 3.68–3.53 (m, 2H), 2.80 (ddd, *J* = 16.2, 10.9, 5.5 Hz, 1H), 2.62 (ddd, *J* = 16.4, 10.9, 5.5 Hz, 1H), 1.20 (t, *J* = 7.2 Hz, 3H), 0.85 (s, 9H), 0.07 (d, *J* = 11.2 Hz, 6H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 168.9, 149.8, 148.2, 137.7, 132.8, 126.2, 119.8, 76.8, 63.8, 62.8, 62.2, 46.9, 41.1, 25.8 (3C), 22.5, 18.2, 14.2, –5.5, –5.7; IR (neat, $cm^{-1}$) = 3103, 2954, 2931, 2856, 1736, 1554, 1538, 1350, 1245, 1155, 1079, 1046; HRMS (FAB) calcd for $C_{21}H_{31}BrN_3O_9SSi$: 608.0734 ([M+H]$^+$), found 608.0744.

***Methyl N-(4-bromobut-3-yn-1-yl)-O-(tert-butyldimethylsilyl)-N-((2,4-dinitrophenyl)sulfonyl)-L-homoserinate (4ka).*** Following the same experimental procedure of **4aa** with 4-bromo-3-butyn-1-ol and **2k** (640 mg, 1.34 mmol), **4ka** (700 mg, 86%) was obtained as light yellow oil; $R_f$ = 0.50 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = +6.8 (c = 0.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ = 8.47 (dd, *J* = 8.7, 2.3 Hz, 1H), 8.40 (d, *J* = 2.1 Hz, 1H), 8.30 (d, *J* = 8.7 Hz, 1H), 4.83 (dd, *J* = 8.8, 5.3 Hz, 1H), 3.72 (q, *J* = 3.9 Hz, 2H), 3.66–3.61 (m, 1H), 3.59 (s, 3H), 3.28 (ddd, *J* = 15.6, 9.5, 6.1 Hz, 1H), 2.74 (ddd, *J* = 15.8, 10.5, 6.2 Hz, 1H), 2.53 (qd, *J* = 16.5, 9.9, 6.4 Hz, 1H), 2.31–2.23 (m, 1H), 1.96–1.87 (m, 1H), 0.87 (s, 9H), 0.05 (d, *J* = 1.4 Hz, 6H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 171.1, 149.7, 148.2, 137.6, 132.8, 125.8, 119.5, 76.3, 58.8, 58.3, 52.6, 45.9, 41.3, 33.4, 25.8 (3C), 21.9, 18.2, –5.5, –5.6; IR (neat, $cm^{-1}$) = 3105, 2954, 2931, 2858, 1741, 1555, 1539, 1351, 1253, 1170, 1149, 1104; HRMS (FAB) calcd for $C_{21}H_{31}BrN_3O_9SSi$: 608.0734 ([M+H]$^+$), found 608.0729.

***Methyl N-(4-bromobut-3-yn-1-yl)-N-((2,4-dinitrophenyl)sulfonyl)-L-methioninate (4la).*** Following the same experimental procedure of **4aa** with 4-bromo-3-butyn-1-ol and **2l** (435 mg, 1.11 mmol), **4la** (475 mg, 82%) was obtained as light yellow oil; $R_f$ = 0.60 (hexane/EtOAc, 2:1); $[\alpha]_D^{20}$ = +20.2 (c = 0.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ = 8.50 (dd, *J* = 8.7, 2.3 Hz, 1H), 8.41 (d, *J* = 2.2 Hz, 1H), 8.28 (d, *J* = 8.8 Hz, 1H), 4.80 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.66–3.59 (m, 1H), 3.60 (s, 3H), 3.26 (ddd, *J* = 15.6, 9.6, 6.0 Hz, 1H), 2.77 (ddd, *J* = 15.8, 10.5, 6.1 Hz, 1H), 2.68–2.50 (m, 3H), 2.38–2.30 (m, 1H), 2.11 (s, 3H), 2.03–1.94 (m, 1H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 170.5, 149.8, 148.1, 137.3, 132.9, 125.9, 119.6, 76.1, 60.3, 52.8, 45.8, 41.6, 30.6, 29.6, 22.0, 15.4; IR (neat, $cm^{-1}$) = 3101, 2953, 2919, 1739, 1553, 1538, 1364, 1350, 1163, 1107; HRMS (FAB) calcd for $C_{16}H_{19}BrN_3O_8S_2$: 523.9797 ([M+H]$^+$), found 523.9792.

***Dimethyl N-(4-bromobut-3-yn-1-yl)-N-((2,4-dinitrophenyl)sulfonyl)-D-glutamate (4ma).*** Following the same experimental procedure of **4aa** with 4-bromo-3-butyn-1-ol and **2m** (455 mg, 1.12 mmol), **4ma** (518 mg, 86%) was obtained as light yellow oil; $R_f$ = 0.50 (hexane/EtOAc, 2:1); $[\alpha]_D^{20}$ = –7.3 (c = 0.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ = 8.49 (dd, *J* = 8.7, 2.2 Hz, 1H), 8.40 (d, *J* = 2.1 Hz, 1H), 8.26 (d, *J* = 8.7 Hz, 1H), 4.69 (dd, *J* = 10.3, 4.5 Hz, 1H), 3.69 (s, 3H), 3.67–3.61 (m, 1H), 3.60 (s, 3H), 3.22 (ddd, *J* = 15.6, 9.4, 6.3 Hz, 1H), 2.75 (ddd, *J* = 16.2, 10.0, 5.7 Hz, 1H), 2.59–2.42 (m, 4H), 2.02–1.95 (m, 1H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 172.6, 170.2, 149.8, 148.2, 137.3, 132.9, 125.9, 119.6, 76.1, 60.8, 52.8, 52.0, 45.8, 41.6, 30.2, 25.1, 22.0; IR (neat, $cm^{-1}$) = 3102, 2954, 1737, 1554, 1540, 1368, 1353, 1166, 1108; HRMS (FAB) calcd for $C_{17}H_{19}N_3O_{10}SBr$: 535.9975 ([M+H]$^+$), found 535.9973.

**General Procedure for the Synthesis of MOC Substrates (1, 5a, 5c', and 5c–5e).** To a solution of **4aa** (273 mg, 0.57 mmol) and thioglycolic acid (79.6 μL, 1.14 mmol, 2.00 equiv) in DCM (10 mL), triethylamine (241 μL, 1.72 mmol, 3.00 equiv) in DCM (4 mL) was added dropwise at room temperature under an inert atmosphere. The reaction was stirred until judged to be

complete by TLC analysis. After quenching with sat. $NaHCO_3$ solution (10 mL), the mixture was extracted with DCM (2 × 15 mL). The crude residue was filtered with a pad of silica and Celite to yield pure secondary amine as a light yellow oil. Triethylamine (161 μL, 1.14 mmol, 2.00 equiv) and benzoyl chloride (99.7 μL, 0.86 mmol, 1.50 equiv) were added to the above secondary amine in DCM (5 mL) at 0 ℃. After 10 min, the reaction was quenched with $H_2O$ (5 mL) and extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/EtOAc, 3:1) to yield **5a** (173 mg, 0.49 mmol, 86%) as a colorless oil.

***Ethyl N-benzoyl-N-(pent-3-yn-1-yl)-L-alaninate (1).*** Following the same experimental procedure of **5a** with **4ab** (341 mg, 0.83 mmol), **1** (201 mg, 85%) was obtained as colorless oil; $R_f$ = 0.30 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = –71.1 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:1 from $^1$H NMR, $^1$H NMR (800 MHz, $CDCl_3$) δ = 7.35 (m, 5H), 4.39–4.37 (m, 1H), 4.19–4.12 (m, 2H), 3.71 (s, 0.5H), 3.38–3.35 (m, 1H), 3.15 (s, 0.5H), 2.55–2.50 (m, 1H), 2.29 (s, 1H), 1.73 (s, 1.5H), 1.67 (s, 1.5H), 1.57 (s, 1.5H), 1.40 (s, 1.5H), 1.20 (s, 3H); $^{13}$C{$^1$H} NMR (200 MHz, $CDCl_3$) δ = 172.4/171.6, 171.2, 136.2 (2C), 129.5/129.4, 128.5/128.4, 126.3 (2C), 77.9/77.2, 76.4/75.1, 61.5/61.0, 57.5/55.0, 48.4/43.2, 19.8/18.3, 15.9/14.8, 14.1, 3.3; IR (neat, $cm^{-1}$) = 2983, 2940, 1736, 1636, 1442, 1412, 1320, 1216, 1185, 1104, 1022; HRMS (FAB) calcd for $C_{17}H_{22}NO_3$: 288.1600 ($[M+H]^+$), found 288.1598.

***Ethyl N-benzoyl-N-(4-bromobut-3-yn-1-yl)-L-alaninate (5a).*** $[\alpha]_D^{20}$ = –64.1 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 2:3 from $^1$H NMR, $^1$H NMR (800 MHz, $CDCl_3$) δ = 7.39–7.36 (m, 5H), 4.44–4.41 (m, 1H), 4.22–4.15 (m, 2H), 3.75 (s, 0.5H), 3.48–3.43 (m, 0.9H), 3.22 (s, 0.6H), 2.67 (s, 1.1H), 2.39 (s, 0.9H), 1.59 (s, 1.2H), 1.43 (s, 1.8H), 1.25 (s, 3H); $^{13}$C{$^1$H} NMR (200 MHz, $CDCl_3$) δ = 172.6/171.8, 171.2, 136.0 (2C), 129.8/129.7, 128.6, 126.4 (2C), 77.7/76.4, 61.6/61.3, 57.6/55.0, 47.5/42.5, 40.9/39.8, 20.7/19.2, 16.1/14.9, 14.1; IR (neat, $cm^{-1}$) = 2984, 2938, 2344, 1736, 1639, 1219, 1075; HRMS (FAB) calcd for $C_{16}H_{19}BrNO_3$: 352.0548 ($[M+H]^+$), found 352.0542.

***Ethyl N-benzoyl-N-(4-chlorobut-3-yn-1-yl)-L-alaninate (5b).*** $AgNO_3$ (140 mg, 0.82 mmol, 0.30 equiv) and *N*-chlorosuccinimide (NCS) (734 mg, 5.50 mmol, 2.00 equiv) were added to a stirred solution of 4-(trimethylsilyl)-but-3-yn-1-yl *p*-methylbenzenesulfonate[21] (813 mg, 2.75 mmol) in $CH_3CN$ (20 mL) at 0 ℃. 5 min later, TBAF (2.90 mL, 2.89 mmol, 1.05 equiv, 1 M in THF) was added slowly. The resulting mixture was allowed to warm to room temperature and was stirred at this temperature for 12 h. After the starting material disappeared upon monitoring by TLC, the reaction was quenched with $H_2O$ (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (15 mL), dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 7:1) to yield 4-chlorobut-3-yn-1-yl 4-methylbenzenesulfonate **($S_1$)** (496 mg, 1.92 mmol, 70%) as a colorless oil. $R_f$ = 0.35 (hexane/EtOAc, 5:1); $^1$H NMR (600 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 4.05 (t, *J* = 6.9 Hz, 2H), 2.51 (t, *J* = 6.9 Hz, 2H), 2.43 (s, 3H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) δ = 145.0, 132.7, 129.9 (2C), 127.9 (2C), 67.2, 64.0, 60.0, 21.6, 19.7; IR (neat, $cm^{-1}$) = 2927, 1729, 1357, 1185, 1065; HRMS (FAB): calcd for $C_{11}H_{12}ClO_3S$: 259.0196 ($[M+H]^+$), found 259.0202.

L-alanine ethyl ester hydrochloride (0.15 g, 0.98 mmol) in $H_2O$ (10 mL) was treated with triethylamine (144 μL, 1.03 mmol, 1.05 equiv) at room temperature for 30 min. The mixture was then extracted with DCM (3 × 15 mL). The organic layers were combined, dried over $Na_2SO_4$, and concentrated *in vacuo* to afford the free amino ester. DIPEA (683 μL, 3.92 mmol, 4.00 equiv) and **$S_1$** (506 mg, 1.96 mmol, 2.00 equiv) were added to a suspension of the free amino ester in $CH_3CN$ (20 mL). After the resulting slurry was stirred at 70 ℃ for 72 h, sat. $NH_4Cl$ (10 mL) was added and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 3:1) to afford ethyl (4-chlorobut-3-yn-1-yl)alaninate **($S_2$)** (65.6 mg, 0.31 mmol, 32%) as a yellow oil. $R_f$ = 0.25 (hexane/EtOAc, 3:1); $^1$H NMR (500 MHz, $CDCl_3$) δ = 4.17 (dq, *J* = 7.1, 2.1 Hz, 2H), 3.33 (q, *J* = 7.0 Hz, 1H), 2.75 (td, *J* = 11.2, 7.0 Hz, 1H), 2.62 (td, *J* = 11.3, 6.5 Hz, 1H), 2.34 (td, *J* = 6.8, 2.1 Hz, 2H), 1.28 (q, *J* = 7.6 Hz, 3H), 1.26 (d, *J* = 7.0 Hz, 3H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) δ = 175.4, 67.4, 60.8, 58.5, 56.5, 46.2, 20.3, 19.0, 14.2; IR (neat, $cm^{-1}$) = 3325, 2979, 2241, 1731, 1185, 1155, 1069; HRMS (ESI): calcd for $C_9H_{15}ClNO_2$: 204.0786 ($[M+H]^+$), found 204.0789.

Triethylamine (86.0 μL, 0.64 mmol, 2.00 equiv) and benzoyl chloride (55.1 μL, 0.48 mmol, 1.50 equiv) were added to a suspension of **$S_2$** (63.5 mg, 0.32 mmol) in DCM (5 mL) at 0 ℃. After 5 min, the reaction was quenched with $H_2O$ (5 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 3:1) to yield **5b** (90.1 mg, 0.30 mmol, 93%) as a colorless oil. $R_f$ = 0.30 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = –85.4 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 2:3 from $^1$H NMR, $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.36–7.32 (m, 5H), 4.39 (m, 1H), 4.13 (m, 2H), 3.71–3.20 (m, 2H), 2.60–2.33 (m, 2H), 1.55–1.40 (m, 3H), 1.22 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 172.5/171.6, 171.1, 135.9 (2C), 129.6, 128.5, 126.2 (2C), 66.9/65.8, 61.5/61.1, 59.6/58.8, 57.5/54.9, 47.7/42.2, 19.7/18.2, 15.9/14.7, 14.0; IR (neat, $cm^{-1}$) = 2983, 2243, 1737, 1640, 1412, 1218, 1022; HRMS (FAB) calcd for $C_{16}H_{19}ClNO_3$: 308.1053 ($[M+H]^+$), found 308.1046.

***Ethyl N-benzoyl-N-(but-3-yn-1-yl)-L-alaninate (5c').*** Following the same experimental procedure of **5a** with **4ac** (420 mg, 1.05 mmol), **5c'** (247 mg, 86%) was obtained as colorless oil; $R_f$ = 0.30 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = –98.0 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:1 from $^1$H NMR, $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.25 (m, 5H), 4.31–4.24 (m, 1H), 4.03 (s, 2H), 3.64–3.13 (m, 2H), 2.52–2.27 (m, 2H), 1.91 (s, 1H), 1.47–1.32 (m, 3H), 1.12 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 172.1/171.2, 170.8, 135.7 (2C), 129.3, 128.2, 126.0 (2C), 81.3/80.0, 70.5/69.7, 61.1/60.7, 57.1/54.7, 47.6/42.3, 19.1/17.7, 15.6/14.5, 13.7; IR (neat, $cm^{-1}$) = 3262, 2983, 2940, 1733, 1633, 1412, 1319, 1216, 1103, 1021; HRMS (FAB) calcd for $C_{16}H_{20}NO_3$: 274.1443 ($[M+H]^+$), found 274.1446.

***Ethyl N-benzoyl-N-(4-iodobut-3-yn-1-yl)-L-alaninate (5c).*** AgF (12.9 mg, 0.10 mmol, 0.30 equiv) and *N*-iodosuccinimide (NIS) (91.8 mg, 0.41 mmol, 1.20 equiv) were added to a stirred solution of compound **5c'** (92.5 mg, 0.34 mmol) in $CH_3CN$ (10 mL) at room temperature. The resulting mixture was stirred for 1.5 h and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford the corresponding **5c** (119 mg, 0.30 mmol, 88%) as a colorless oil. $R_f$ = 0.32 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = –68.1 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:1 from $^1$H NMR, $^1$H NMR (500 MHz, $CDCl_3$) δ = 7.45–7.37 (m, 5H), 4.43 (m, 1H), 4.16 (m, 2H), 3.76–3.23 (m, 2H), 2.83–2.54 (m, 2H), 1.59–1.44 (m, 3H), 1.26 (s, 3H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) δ = 172.6/171.8, 171.3, 136.1, 129.8, 128.6 (2C), 126.5 (2C), 91.9/90.5, 61.7/61.3, 57.7/55.0, 47.8/42.8, 21.8/20.4, 16.1/14.9, 14.2, –3.2/–4.8; IR (neat, cm$^{-1}$) = 2939, 1735, 1268, 1415, 1219, 1022; HRMS (FAB) calcd for $C_{16}H_{19}INO_3$: 400.0410 ([M+H]$^+$), found 400.0416.

***Methyl N-benzoyl-N-(4-bromobut-3-yn-1-yl)-L-alaninate (5d).*** Following the same experimental procedure of **5a** with **4da** (387 mg, 0.84 mmol), **5d** (239 mg, 85%) was obtained as colorless oil; $R_f$ = 0.30 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = –71.9 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:1 from $^1$H NMR, $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.32–7.28 (m, 5H), 4.38–4.32 (m, 1H), 3.63 (brs, 3H), 3.63–3.16 (m, 2H), 2.59 (brs, 1H), 2.32 (brs, 1H), 1.51 (brs, 1.5H), 1.37 (s, 1.5H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 172.2, 171.4, 135.6 (2C), 129.5, 128.3, 126.1 (2C), 77.2/76.2, 57.2/54.6, 52.2, 47.3/42.2, 40.6/39.6, 20.3/18.9, 15.8/14.6; IR (neat, cm$^{-1}$) = 2245, 1737, 1631, 1409, 1319, 1219, 1022; HRMS (FAB) calcd for $C_{15}H_{17}BrNO_3$: 338.0392 ([M+H]$^+$), found 338.0396.

***tert-Butyl N-benzoyl-N-(4-bromobut-3-yn-1-yl)-L-alaninate (5e).*** Following the same experimental procedure of **5a** with **4ea** (400 mg, 0.79 mmol), **5e** (365 mg, 88%) was obtained as colorless oil; $R_f$ = 0.30 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = –76.3 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:2 from $^1$H NMR, $^1$H NMR (500 MHz, $CDCl_3$) δ = 7.39–7.35 (m, 5H), 4.32 (brs, 1H), 3.78–3.17 (m, 2H), 2.67 (brs, 1.3H), 2.39 (brs, 0.7H), 1.52–1.34 (m, 12H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) δ = 172.7, 170.3, 136.3 (2C), 129.7, 128.6 (2C), 126.4, 82.3/81.4, 77.8, 58.3/55.8, 47.6, 42.3/39.7, 28.0 (3C), 20.8/19.4, 15.9/14.8; IR (neat, cm$^{-1}$) = 2977, 2934, 1730, 1639, 1410, 1367, 1150, 1023; HRMS (FAB) calcd for $C_{18}H_{23}BrNO_3$: 380.0861 ([M+H]$^+$), found 380.0861.

**General Procedure for the Synthesis of MOC Substrates (5f, 5f', and 5h–5m).** To a solution of **4aa** (193 mg, 0.41 mmol) and thioglycolic acid (42.2 μL, 0.62 mmol, 1.50 equiv) in DCM (5 mL), *N*,*N*-diisopropylethylamine (141 μL, 0.81 mmol, 2.00 equiv) in DCM (2 mL) was added dropwise at room temperature under an inert atmosphere. After the starting material disappeared, *N*,*N*-diisopropylethylamine (141 μL, 0.81 mmol, 2.00 equiv) and $Boc_2O$ (133 mg, 0.62 mmol, 1.50 equiv) were added to the above complex at room temperature. The reaction mixture was stirred for another 12 h at room temperature before the addition of $H_2O$ (10 mL), and extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 10:1) to yield **5f** (127 mg, 0.36 mmol, 90%) as a colorless oil.

***Ethyl N-(4-bromobut-3-yn-1-yl)-N-(tert-butoxycarbonyl)-L-alaninate (5f).*** $[\alpha]_D^{20}$ = –22.2 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:1 from $^1$H NMR, $^1$H NMR (600 MHz, $CDCl_3$) δ = 4.45–4.44 (m, 0.5H), 4.14–4.07 (m, 2.5H), 3.48–3.40 (m, 1H), 3.33–3.30 (m, 0.5H), 3.21–3.18 (m, 0.5H), 2.52–2.41 (m, 2H), 1.44–1.38 (m, 12H), 1.25–1.21 (m, 3H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) δ = 172.2/172.1, 155.1/154.6, 80.6/80.5, 78.0/77.7, 61.1, 56.5/55.0, 46.1/44.8, 39.5/39.3, 28.3/28.2 (3C), 20.7/20.0, 16.1/15.5, 14.1; IR (neat, cm$^{-1}$) = 2980, 2939, 1740, 1696, 1367, 1163, 1073, 1035; HRMS (FAB) calcd for $C_{14}H_{23}BrNO_4$: 348.0810 ([M+H]$^+$), found 348.0819.

***Ethyl N-(but-3-yn-1-yl)-N-(tert-butoxycarbonyl)-L-alaninate (5f').*** Following the same experimental procedure of **5f** with **4ac** (200 mg, 0.50 mmol), **5f'** (119 mg, 88%) was obtained as colorless oil; $R_f$ = 0.20 (hexane/EtOAc, 10:1); $[\alpha]_D^{20}$ = –24.1 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:1 from $^1$H NMR, $^1$H NMR (400 MHz, $CDCl_3$) δ = 4.18–4.17 (m, 0.5H), 3.92–3.87 (m, 2.5H), 3.26–3.19 (m, 1H), 3.18–3.13 (m, 0.5H), 3.00–2.98 (m, 0.5H), 2.28–2.11 (m, 2H), 1.78 (d, *J* = 8.5 Hz, 1H), 1.21–1.15 (m, 12H), 1.03–0.99 (m, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 171.5/171.4, 154.5/154.0, 81.3/81.1, 79.8/79.7, 69.4/69.2, 60.4, 55.9/54.6, 46.0/44.8, 27.7/27.6 (3C), 19.0/18.2, 15.6/15.0, 13.6.; IR (neat, cm$^{-1}$) = 3279, 2980, 2939, 1740, 1695, 1368, 1163, 1073; HRMS (FAB) calcd for $C_{14}H_{24}NO_4$: 270.1705 ([M+H]$^+$), found 270.1704.

***Ethyl N-((benzyloxy)carbonyl)-N-(4-bromobut-3-yn-1-yl)-L-alaninate (5g).*** To a solution of **4aa** (500 mg, 1.05 mmol) and thioglycolic acid (146 μL, 2.10 mmol, 2.00 equiv) in DCM (15 mL), triethylamine (441 μL, 3.15 mmol, 3.00 equiv) in DCM (5 mL) was added dropwise at room temperature under an inert atmosphere. The reaction was stirred until judged to be complete by TLC analysis. After quenching with sat. $NaHCO_3$ solution (10 mL), the mixture was extracted with DCM (2 × 20 mL). The crude residue was filtered with a pad of silica and Celite to yield pure secondary amine as a light yellow oil. $NaHCO_3$ (176 mg, 2.10 mmol, 2.00 equiv) and benzyl chloroformate (149 μL, 1.05 mmol, 1.00 equiv) were added to the above secondary amine in $H_2O$/acetone (1:1, 6 mL) at 0 ℃. After 15 min, the reaction was quenched with $H_2O$ (5 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/EtOAc, 7:1) to yield **5g** (336 mg, 0.88 mmol, 84%) as a colorless oil. $[\alpha]_D^{20}$ = –16.1 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1.2:1 from $^1$H NMR, $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.32–7.29 (m, 5H), 5.17–5.06 (m, 2H), 4.52 (q, *J* = 7.3 Hz, 0.55H), 4.32 (q, *J* = 7.1 Hz, 0.45H), 4.13 (q, *J* = 6.9 Hz, 1.1H), 4.08–3.93 (m, 0.9H), 3.56–3.48 (m, 1H), 3.39–3.25 (m, 1H), 2.59–2.39 (m, 2H), 1.45 (d, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 1.6H), 1.12 (t, *J* = 7.0 Hz, 1.4H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 171.93/171.86, 156.0/155.6, 136.5/136.3, 128.6/128.5 (2C), 128.3 (2C), 128.1/127.9, 77.9/77.5, 67.5, 61.3, 56.0/55.8, 46.1/44.8, 40.1/39.8, 20.8/20.0, 16.2/15.6, 14.2/14.1; IR (neat, cm$^{-1}$) = 2984, 2945, 1739, 1702, 1472, 1416, 1369, 1295, 1215, 1184, 1072, 1020; HRMS (FAB) calcd for $C_{17}H_{21}BrNO_4$: 382.0654 ([M+H]$^+$), found 382.0652.

***Ethyl N-(4-bromobut-3-yn-1-yl)-N-(tert-butoxycarbonyl)-L-valinate (5h).*** Following the same experimental procedure of **5f** with **4ha** (400 mg, 0.79 mmol), **5h** (247 mg, 83%) was

obtained as colorless oil; $R_f$ = 0.40 (hexane/EtOAc, 10:1); $[\alpha]_D^{20}$ = –46.8 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:1 from $^1$H NMR, $^1$H NMR (400 MHz, $CDCl_3$) δ = 4.16–4.09 (m, 2.5H), 3.71–3.69 (m, 0.5H), 3.49–3.31 (m, 2H), 2.48–2.40 (m, 2H), 2.18 (m, 1H), 1.42–1.38 (d, 9H), 1.22 (t, *J* = 6.8 Hz, 3H), 0.94 (s, 3H), 0.85–0.84 (d, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 171.3/170.9, 155.4/154.7, 80.6/80.5, 77.7/77.6, 66.2/64.1, 60.7, 45.8/44.0, 39.3/39.1, 28.6, 28.2 (3C), 20.7/20.1/19.9, 19.24/19.16/18.9, 14.1(2C); IR (neat, cm$^{-1}$) = 2972, 2935, 2875, 1737, 1695, 1367, 1162, 1029; HRMS (FAB) calcd for $C_{16}H_{27}BrNO_4$: 376.1123 ([M+H]$^+$), found 376.1123.

***Ethyl N-(4-bromobut-3-yn-1-yl)-N-(tert-butoxycarbonyl)-L-phenylalaninate (5i).*** Following the same experimental procedure of **5f** with **4ia** (490 mg, 0.88 mmol), **5i** (284 mg, 76%) was obtained as colorless oil; $R_f$ = 0.30 (hexane/EtOAc, 10:1); $[\alpha]_D^{20}$ = –136.6 (c = 0.1, $CHCl_3$); Rotamers were observed, and the ratio was 1:1 from $^1$H NMR, $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.28–7.13 (m, 5H), 4.25–4.08 (m, 2.5H), 4.03–3.99 (m, 0.5H), 3.38–3.08 (m, 3H), 2.86–2.79 (m, 0.5H), 2.73–2.65 (m, 0.5H), 2.32–2.09 (m, 2H), 1.42 (s, 9H), 1.75 (td, *J* = 148.8, 109.0 Hz, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 171.2/171.1, 154.9/154.5, 138.2, 129.4 (2C), 128.8/128.7 (2C), 127.0/126.8, 81.1/80.7, 78.0/77.9, 63.7/62.8, 61.6/61.4, 48.2/47.6, 39.3/39.2, 36.5/35.6, 28.5 (3C), 19.9/19.3, 14.3; IR (neat, cm$^{-1}$) = 2978, 2936, 1738, 1692, 1366, 1160, 1034; HRMS (FAB) calcd for $C_{20}H_{27}BrNO_4$: 424.1123 ([M+H]$^+$), found 424.1129.

***Ethyl N-(4-bromobut-3-yn-1-yl)-N-(tert-butoxycarbonyl)-L-serinate (5j).*** Following the same experimental procedure of **5f** with **4ja** (733 mg, 1.21 mmol), then deprotect the TBS group, **5j** (373 mg, 85%) was obtained as colorless oil; $R_f$ = 0.20 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = –23.6 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:1.25 from $^1$H NMR, $^1$H NMR (400 MHz, $CDCl_3$) δ = 4.21–4.09 (brm, 3H), 4.05–3.92 (brm, 1H), 3.88–3.70 (brm, 1H), 3.58–3.42 (brm, 1H), 3.32–3.28 (brm, 1H), 2.49–2.45 (brm, 3H), 1.43 (s, 5H), 1.37 (s, 4H), 1.28–2.22 (m, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 171.1/170.5, 155.4/154.2, 81.2/81.0, 77.7/77.5, 62.8, 61.9/61.7, 61.4/61.3, 47.9/47.8, 39.6, 28.2 (3C), 20.1/19.7, 14.1; IR (neat, cm$^{-1}$) = 3447, 2977, 2934, 1736, 1692, 1459, 1416, 1367, 1162, 1037; HRMS (FAB) calcd for $C_{14}H_{23}BrNO_5$: 364.0760 ([M+H]$^+$), found 364.0753.

***Methyl N-(4-bromobut-3-yn-1-yl)-N-(tert-butoxycarbonyl)-O-(tert-butyldimethylsilyl)-L-homoserinate (5k).*** Following the same experimental procedure of **5f** with **4ka** (379 mg, 0.62 mmol), **5k** (235 mg, 79%) was obtained as colorless oil; $R_f$ = 0.50 (hexane/EtOAc, 5:1); $[\alpha]_D^{20}$ = –71.7 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:1.4 from $^1$H NMR, $^1$H NMR (400 MHz, $CDCl_3$) δ = 4.23–4.19 (m, 0.4H), 4.12–4.08 (m, 0.6H), 3.68–3.64 (m, 4.3H), 3.62–3.56 (m, 1.3H), 3.50–3.43 (m, 0.4H), 3.29–3.19 (m, 1H), 2.54–2.48 (m, 2H), 2.25–2.19 (m, 1H), 2.02–1.88 (m, 1H), 1.39 (d, *J* = 26.2 Hz, 9H), 0.86 (s, 9H), 0.02 (s, 6H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 172.3, 154.9/154.6, 80.6/80.4, 77.7/77.6, 59.3/59.0, 57.4/57.2, 52.0, 47.6/47.1, 39.2/39.0, 33.7/32.6, 28.3/28.2 (3C), 25.8 (3C), 20.0/19.4, 18.1, –5.5/–5.7 (2C); IR (neat, cm$^{-1}$) = 2954, 2932, 2859, 1746, 1700, 1253, 1163, 1100, 1007; HRMS (FAB) calcd for $C_{20}H_{37}BrNO_5Si$: 478.1624 ([M+H]$^+$), found 478.1620.

***Methyl N-(4-bromobut-3-yn-1-yl)-N-(tert-butoxycarbonyl)-L-methioninate (5l).*** Following the same experimental procedure of **5f** with **4la** (290 mg, 0.55 mmol), **5l** (164 mg, 75%) was obtained as colorless oil; $R_f$ = 0.50 (hexane/EtOAc, 5:1); $[\alpha]_D^{20}$ = –68.3 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:1.2 from $^1$H NMR, $^1$H NMR (400 MHz, $CDCl_3$) δ = 4.37–4.33 (m, 0.5H), 4.17–4.14 (m, 0.5H), 3.69 (s, 3H), 3.63–3.56 (m, 0.5H), 3.50–3.41 (m, 0.5H), 3.22 (td, *J* = 14.4, 7.3 Hz, 1H), 2.61–2.49 (m, 4H), 2.33–2.24 (m, 1H), 2.13–2.01 (m, 1H), 2.07 (s, 3H), 1.43 (s, 4H), 1.38 (s, 5H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 171.8, 155.1/154.6, 80.9/80.7, 77.7/77.5, 59.4/58.8, 52.2, 47.6/46.6, 39.5/39.3, 30.9, 29.7/28.9, 28.2 (3C), 20.2/19.5, 15.3; IR (neat, cm$^{-1}$) = 2976, 2953, 2919, 1743, 1696, 1367, 1160, 1041; HRMS (FAB) calcd for $C_{15}H_{25}BrNO_4S$: 394.0688 ([M+H]$^+$), found 394.0676.

***Dimethyl N-(4-bromobut-3-yn-1-yl)-N-(tert-butoxycarbonyl)-D-glutamate (5m).*** Following the same experimental procedure of **5f** with **4ma** (439 mg, 0.82 mmol), **5m** (266 mg, 80%) was obtained as colorless oil; $R_f$ = 0.40 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = +77.2 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:1 from $^1$H NMR, $^1$H NMR (800 MHz, $CDCl_3$) δ = 4.33–4.31 (m, 0.5H), 4.04 (m, 0.5H), 3.69–3.68 (d, 3H), 3.65 (s, 3H), 3.58–3.55 (m, 0.5H), 3.42–3.38 (m, 0.5H), 3.18–3.12 (m, 1H), 2.50–2.45 (m, 2H), 2.40–2.32 (m, 3H), 2.08–2.04 (m, 1H), 1.40 (d, *J* = 23.9 Hz, 9H); $^{13}$C{$^1$H} NMR (200 MHz, $CDCl_3$) δ = 173.3/173.2, 171.6/171.5, 155.2/154.5, 81.0/80.8, 77.7/77.4, 60.1/58.9, 52.2/51.7 (2C), 47.4/46.0, 39.5/39.3, 30.5/30.4, 28.24/28.16 (3C), 25.7/24.9, 20.2/19.4; IR (neat, cm$^{-1}$) = 2976, 2952, 2846, 1737, 1695, 1367, 1157, 1041; HRMS (FAB) calcd for $C_{16}H_{25}NO_6Br$: 406.0865 ([M+H]$^+$), found 406.0870.

**General Procedure for the MOC Cyclization:**

**Condition A (0.1 mmol)**: To a solution of haloalkyne substrates (**5a–5m**, 0.10 mmol) in DMF (5 mL, 0.02 M) at 25 ℃ under an $N_2$ atmosphere, $In(OTf)_3$ (0.01 mmol, 0.1 eq) and KO$^t$Bu (0.15 mmol, 1.50 equiv for **5a–5e**, and **5g** or 0.20 mmol, 2.00 equiv for **5f**, and **5h–5m**) were added. After 10 min, sat. $NH_4Cl$ (3 mL) and $H_2O$ (5 mL) were added, and the aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated by high-vacuum evaporation. The residue was purified by flash column chromatography on silica gel to afford analytically pure products **10a–10m**.

**Condition B (0.1 mmol)**: To a solution of haloalkyne substrates (**5a–5m**, 0.10 mmol) in DMF (5 mL, 0.02 M) at 0 ℃ under an $N_2$ atmosphere, KO$^t$Bu (0.15 mmol, 1.50 equiv for **5a–5e**, and **5g** or 0.20 mmol, 2.00 equiv for **5f**, and **5h–5m**) were added. After 5 min, sat. $NH_4Cl$ (3 mL) and $H_2O$ (5 mL) were added, and the aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated by high-vacuum evaporation. The residue was purified by flash column chromatography on silica gel to afford analytically pure products **10a–10m**.

**Condition A (1 mmol)**: To a solution of **5a** (381 mg, 1.09 mmol) in DMF (54 mL, 0.02 M) at 25 ℃ under an $N_2$ atmosphere, $In(OTf)_3$ (61 mg, 0.1 mmol, 0.10 equiv) and KO$^t$Bu (1.63 mmol, 183 mg, 1.50 equiv) were added. After the starting material disappeared, as judged by TLC, sat. $NH_4Cl$ (10 mL) and $H_2O$ (15 mL) were added and the complex was concentrated by high-vacuum evaporation. The white solid was redissolved in $H_2O$ (20 mL), and then the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic

phases were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 3:1) to yield **10a** (342 mg, 0.98 mmol, 90%) as a white solid.

***Ethyl (R,Z)-1-benzoyl-3-(bromomethylene)-2-methylpyrrolidine-2-carboxylate (10a).*** White solid; mp = 129–131 ℃; $[\alpha]_D^{20}$ = –156.5 (c = 0.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.44–7.35 (m, 5H), 6.14 (t, *J* = 1.9 Hz, 1H), 4.30–4.20 (m, 2H), 3.66–3.59 (m, 2H), 2.78–2.62 (m, 2H), 1.92 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 169.4, 168.8, 145.5, 136.4, 130.0, 128.3 (2C), 126.8 (2C), 98.9, 69.2, 61.4, 48.5, 34.1, 18.7, 14.2; IR (neat, cm$^{-1}$) = 3062, 2981, 1746, 1632, 1405, 1250, 1023; HRMS (FAB) calcd for $C_{16}H_{19}BrNO_3$: 352.0548 ([M+H]$^+$), found 352.0560.

***Ethyl (R,Z)-1-benzoyl-3-(chloromethylene)-2-methylpyrrolidine-2-carboxylate (10b).*** Following the general MOC procedure (condition A) with **5b** (35.1 mg, 0.11 mmol), **10b** (33.3 mg, 95%) was obtained as white solid; $R_f$ = 0.30 (hexane/EtOAc, 3:1); mp = 115–116 ℃; $[\alpha]_D^{20}$ = –225.98 (c = 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.43–7.35 (m, 5H), 6.03 (s, 1H), 4.31–4.19 (m, 2H), 3.65–3.61 (m, 2H), 2.76–2.63 (m, 2H), 1.90 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 169.7, 168.8, 142.9, 136.4, 130.0, 128.3 (2C), 126.8 (2C), 111.7, 68.5, 61.4, 48.6, 32.3, 18.7, 14.2; IR (neat, cm$^{-1}$) = 3065, 2982, 1746, 1634, 1406, 1252, 1121, 1024; HRMS (FAB) calcd for $C_{16}H_{19}ClNO_3$: 308.1053 ([M+H]$^+$), found 308.1052.

***Ethyl (R,Z)-1-benzoyl-3-(iodomethylene)-2-methylpyrrolidine-2-carboxylate (10c).*** Following the general MOC procedure (condition A) with **5c** (40 mg, 0.1 mmol), **10c** (32.8 mg, 82%) was obtained as white solid; $R_f$ = 0.30 (hexane/EtOAc, 3:1); mp = 117–119 ºC; $[\alpha]_D^{20}$ = –120.96 (c = 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.44–7.35 (m, 5H), 6.24 (t, *J* = 1.7 Hz, 1H), 4.33–4.20 (m, 2H), 3.60 (t, *J* = 7.2 Hz, 2H), 2.85–2.70 (m, 2H), 1.91 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 169.2, 168.8, 150.6, 136.4, 130.0, 128.3 (2C), 126.8 (2C), 69.9, 68.4, 61.4, 48.3, 36.4, 18.8, 14.2; IR (neat, cm$^{-1}$): 3055, 2980, 1744, 1636, 1407, 1252,1024; HRMS (FAB) calcd for $C_{16}H_{19}INO_3$: 400.0410 ([M+H]$^+$), found 400.0400.

***Methyl (R,Z)-1-benzoyl-3-(bromomethylene)-2-methylpyrrolidine-2-carboxylate (10d).*** Following the general MOC procedure (condition A) with **5d** (35 mg, 0.11 mmol), **10d** (30.5 mg, 87%) was obtained as white solid; $R_f$ = 0.30 (hexane/EtOAc, 3:1); mp = 163–165 ºC; $[\alpha]_D^{20}$ = –146.8 (c = 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.48–7.35 (m, 5H), 6.14 (t, *J* = 1.9 Hz, 1H), 3.78 (s, 3H), 3.66–3.60 (m, 2H), 2.78–2.62 (m, 2H), 1.91 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 170.2, 168.9, 145.5, 136.3, 130.0, 128.3 (2C), 126.9 (2C), 99.0, 69.1, 52.5, 48.5, 34.0, 18.8; IR (neat, cm$^{-1}$) = 3062, 2946, 2372, 1751, 1632, 1408, 1258, 1121, 1026; HRMS (FAB) calcd for $C_{15}H_{17}BrNO_3$: 338.0392 ([M+H]$^+$), found 338.0403.

***tert-Butyl (R,Z)-1-benzoyl-3-(bromomethylene)-2-methylpyrrolidine-2-carboxylate (10e).*** Following the general MOC procedure (condition A) with **5e** (39 mg, 0.1 mmol), **10e** (32.3 mg, 85%) was obtained as white solid; $R_f$ = 0.20 (hexane/EtOAc, 5:1); mp = 179–180 ºC; $[\alpha]_D^{20}$ = –130.7 (c = 0.5, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$) δ = 7.42–7.36 (m, 5H), 6.13 (t, *J* = 1.8 Hz, 1H), 3.60–3.56 (m, 2H), 2.72–2.67 (m, 1H), 2.65–2.60 (m, 1H), 1.89 (s, 3H), 1.49 (s, 9H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) δ = 168.7, 168.0, 145.9, 136.8, 129.8, 128.4 (2C), 126.6 (2C), 98.4, 81.6, 70.0, 48.6, 34.2, 28.0 (3C), 18.5; IR (neat, cm$^{-1}$) = 2974, 1743, 1636, 1446, 1405, 1367, 1252, 1169, 1123; HRMS (FAB) calcd for $C_{18}H_{23}BrNO_3$: 380.0861 ([M+H]$^+$), found 380.0859.

***1-(tert-Butyl) 2-ethyl (R,Z)-3-(bromomethylene)-2-methylpyrrolidine-1,2-dicarboxylate (10f).*** Following the general MOC procedure (condition A) with **5f** (35 mg, 0.1 mmol), **10f** (32.6 mg, 93%) was obtained as colorless oil; $R_f$ = 0.40 (hexane/EtOAc, 5:1); $[\alpha]_D^{20}$ = –32.96 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:2 from $^1$H NMR, $^1$H NMR (600 MHz, $CDCl_3$) δ = 6.05 (t, *J* = 2.1 Hz, 1H), 4.23–4.10 (m, 2H), 3.60–3.53 (m, 2H), 2.65–2.59 (m, 2H), 1.73 (s, 1H), 1.70 (s, 2H), 1.40 (s, 9H), 1.26–1.24 (m, 3H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) δ = 170.34/170.25, 153.6/153.4, 147.4/146.4, 98.1, 80.8/80.1, 68.4/67.9, 61.4/61.3, 46.2/45.8, 33.0/32.3, 28.3/28.2 (3C), 20.2/19.6, 14.1; IR (neat, cm$^{-1}$) = 3072, 2979, 2937, 2845, 1751, 1698, 1385, 1367, 1249, 1163, 1114, 1056; HRMS (FAB) calcd for $C_{14}H_{23}BrNO_4$: 348.0810 ([M+H]$^+$), found 348.0810. Because **10f** can not be fully separated after trying a few chiral columns and conditions, we transform **10f** to **10f'** for HPLC analysis.

***Ethyl (R,Z)-1-benzoyl-3-(bromomethylene)-2-methylpyrrolidine-2-carboxylate* (10f').** Trifluoroacetic acid (0.5 mL) was added to a solution of compound **10f** (16.5 mg, 0.047 mmol) in DCM (1.5 mL) and the mixture was stirred at room temperature for 30 min. The mixture was concentrated, dissolved in DCM (20 mL), washed with aq. $NaHCO_3$ and concentrated. The residue was redissolved in DCM (3 mL) and treated with triethylamine (27 μL, 0.19 mmol, 4.00 equiv) and benzoyl chloride (12 μL, 0.095 mmol, 2.00 equiv). The mixture was stirred at room temperature for 2 h, and diluted with DCM, and then, the organic phase was washed with water and concentrated. The residue was purified with flash purification by column chromatography on silica gel (hexane/EtOAc, 3:1) to afford compound **10f'** (14.7 mg, 0.042 mmol, 88%) as a white solid.

***1-Benzyl 2-ethyl (R,Z)-3-(bromomethylene)-2-methylpyrrolidine-1,2-dicarboxylate (10g).*** Following the general MOC procedure (condition A) with **5g** (39 mg, 0.1 mmol), **10g** (34.6 mg, 89%) was obtained as colorless oil; $R_f$ = 0.40 (hexane/EtOAc, 5:1); $[\alpha]_D^{20}$ = –21.56 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1.3:1 from $^1$H NMR, $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.24 (m, 5H), 6.08 (s, 1H), 5.14–5.06 (m, 2H), 4.18 (q, *J* = 7.2 Hz, 1H), 3.95–3.88 (m, 1H), 3.69–3.63 (m, 2H), 2.70–2.63 (m, 2H), 1.74 (d, *J* = 20.4 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 1.7H), 1.06 (t, *J* = 7.0 Hz, 1.3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 170.4/170.3, 154.3/154.2, 147.3/146.3, 136.8/136.2, 128.7, 128.4, 128.3, 128.2, 128.1, 98.8/98.6, 69.1/68.3, 67.6/67.1, 61.7, 46.6/46.1, 33.1/32.4, 20.5/19.6, 14.2/14.1; IR (neat, cm$^{-1}$) = 2982, 2939, 2888, 1750, 1701, 1403, 1350, 1251, 1114, 1087, 1055; HRMS (FAB) calcd for $C_{17}H_{21}BrNO_4$: 382.0654 ([M+H]$^+$), found 382.0652.

***1-(tert-Butyl) 2-ethyl (R,Z)-3-(bromomethylene)-2-isopropylpyrrolidine-1,2-dicarboxylate (10h).*** Following the general MOC procedure (condition A) with **5h** (38 mg, 0.1 mmol), **10h** (35.6 mg, 94%) was obtained as colorless oil; $R_f$ = 0.20 (hexane/EtOAc, 10:1); $[\alpha]_D^{20}$ = –44.3 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:1 from $^1$H NMR, $^1$H NMR (800 MHz, $CDCl_3$) δ = 6.16–6.14 (m, 1H), 4.25–4.19

(m, 1H), 4.15–4.05 (m, 1H), 3.70 (q, *J* = 9.0 Hz, 0.6H), 3.61 (q, *J* = 9.0 Hz, 0.4H), 3.56–3.49 (m, 1H), 3.06–2.99 (m, 1H), 2.67–2.63 (m, 1H), 2.61–2.56 (m, 1H), 1.42 (s, 4H), 1.40 (s, 5H), 1.23 (td, *J* = 25.8, 7.1 Hz, 3H), 1.02 (qd, *J* = 29.9, 18.0, 6.9 Hz, 6H); $^{13}C\{^1H\}$ NMR (200 MHz, $CDCl_3$) δ = 169.5, 154.0/153.7, 145.4/144.7, 99.2/99.0, 81.0/79.9, 74.2/73.9, 61.1/60.9, 47.0/46.7, 34.7/34.0, 33.1/32.9, 28.3/28.2 (3C), 19.3, 19.1/18.9, 14.1/14.0; IR (neat, $cm^{-1}$) = 2975, 2934, 2879, 1750, 1698, 1389, 1367, 1237, 1165, 1060, 1041; HRMS (FAB) calcd for $C_{16}H_{27}BrNO_4$: 376.1123 ($[M+H]^+$), found 376.1128. Because **10h** can not be fully separated after trying a few chiral columns and conditions, we transform **10h** to **10h'** for HPLC analysis.

***Ethyl (R,Z)-1-benzoyl-3-(bromomethylene)-2-isopropylpyrrolidine-2-carboxylate* (10h').** Set the reaction with **10h** (30.0 mg, 0.079 mmol) and follow the procedure of preparing **10f'**. Flash purification by column chromatography over silica gel (hexane/EtOAc, 5:1), compound **10h'** (25.2 mg, 0.066 mmol, 83%) was obtained as a white solid.

***1-(tert-Butyl) 2-ethyl (R,Z)-2-benzyl-3-(bromomethylene)pyrrolidine-1,2-dicarboxylate (10i).*** Following the general MOC procedure (condition A) with **5i** (43 mg, 0.1 mmol), **10i** (42 mg, 98%) was obtained as colorless oil; $R_f$ = 0.20 (hexane/EtOAc, 10:1); $[\alpha]_D^{20}$ = +43.26 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:1.4 from $^1H$ NMR, $^1H$ NMR (500 MHz, $CDCl_3$) δ = 7.24–7.18 (m, 3H), 7.11–7.08 (m, 2H), 6.10–6.09 (m, 1H), 4.32–4.23 (m, 1H), 4.22–4.14 (m, 1H), 3.75–3.56 (m, 2H), 3.40–3.28 (m, 1H), 3.02 (td, *J* = 9.6, 3.6 Hz, 0.6H), 2.91 (td, *J* = 9.5, 3.7 Hz, 0.4H), 2.32–2.27 (m, 1H), 1.51 (s, 5H), 1.48 (s, 4H), 1.45–1.38 (m, 1H), 1.29–1.23 (m, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 170.1/170.0, 153.7/153.4, 145.7/144.9, 137.0/136.4, 130.6/130.5 (2C), 128.1/127.9 (2C), 126.7/126.5, 99.0/98.9, 81.2/80.2, 72.6/72.2, 61.6/61.5, 46.1/46.0, 36.4/35.5, 33.2/32.3, 28.4 (3C), 14.2/14.1; IR (neat, $cm^{-1}$) = 2976, 1748, 1698, 1387, 1367, 1240, 1167, 1131, 1067, 1029; HRMS (FAB) calcd for $C_{20}H_{27}BrNO_4$: 424.1123 ($[M+H]^+$), found 424.1116.

***1-(tert-Butyl) 2-ethyl (S,Z)-3-(bromomethylene)-2-(hydroxymethyl)pyrrolidine-1,2-dicarboxylate (10j).*** Following the general MOC procedure (condition A) with **5j** (37 mg, 0.11 mmol), **10j** (14.9 mg, 40%) was obtained as colorless oil; $R_f$ = 0.30 (hexane/EtOAc, 2:1); $[\alpha]_D^{20}$ = –15.2 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:1 from $^1H$ NMR, $^1H$ NMR (500 MHz, $CDCl_3$) δ = 6.20 (s, 1H), 4.44–4.42 (brs, 0.5H), 4.29–4.16 (m, 3H), 4.10–4.08 (brs, 0.5H), 3.66–3.55 (m, 2H), 2.66–2.61 (brs, 2H), 2.35–2.30 (brs, 0.5H), 1.94 (brs, 0.5H), 1.42 (s, 9H), 1.26 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 169.4, 154.5/153.4, 144.3/143.1, 99.6/99.4, 81.5/80.9, 72.2/71.7, 62.9, 61.5, 46.7/46.6, 33.7/33.1, 28.2 (3C), 14.1; IR (neat, $cm^{-1}$) = 3482, 2979, 2931, 1744, 1698, 1393, 1367, 1252, 1169, 1148, 1036; HRMS (FAB) calcd for $C_{14}H_{23}BrNO_5$: 364.0760 ($[M+H]^+$), found 364.0756.

***1-(tert-Butyl) 2-methyl (R,Z)-3-(bromomethylene)-2-(2-((tert-butyldimethylsilyl)oxy)ethyl)pyrrolidine-1,2-dicarboxylate (10k).*** Following the general MOC procedure (condition A) with **5k** (50 mg, 0.1 mmol), **10k** (46.4 mg, 93%) was obtained as colorless oil; $R_f$ = 0.50 (hexane/EtOAc, 5:1); $[\alpha]_D^{20}$ = –25.70 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:1.8 from $^1H$ NMR, $^1H$ NMR (600 MHz, $CDCl_3$) δ = 6.05 (t, *J* = 1.9 Hz, 1H), 3.70 (s, 3H), 3.64–3.56 (m, 4H), 2.72–2.69 (m, 1H), 2.65–2.63 (m, 2.3H), 2.50–2.47 (m, 0.7H), 1.41 (s, 3H), 1.39 (s, 6H), 0.85 (s, 9H), 0.01 (s, 6H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ = 171.1/170.7, 153.7/153.4, 146.0/145.2, 98.4, 80.9/80.2, 70.4/69.9, 59.3/59.1, 52.3, 46.5/46.3, 34.7/33.8, 33.4/32.6, 28.3/28.2 (3C), 25.9 (3C), 18.2, –5.3/–5.4 (2C); IR (neat, $cm^{-1}$) = 2954, 2931, 2888, 2859, 1755, 1703, 1386, 1252, 1170, 1106, 1088; HRMS (FAB) calcd for $C_{20}H_{37}BrNO_5Si$: 478.1624 ($[M+H]^+$), found 478.1624.

***1-(tert-Butyl) 2-methyl (R,Z)-3-(bromomethylene)-2-(2-(methylthio)ethyl)pyrrolidine-1,2-dicarboxylate (10l).*** Following the general MOC procedure (condition A) with **5l** (40 mg, 0.1 mmol), **10l** (37.9 mg, 95%) was obtained as colorless oil; $R_f$ = 0.40 (hexane/EtOAc, 5:1); $[\alpha]_D^{20}$ = –7.92 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:2 from $^1H$ NMR, $^1H$ NMR (500 MHz, $CDCl_3$) δ = 6.15 (s, 1H), 3.71 (s, 3H), 3.67–3.56 (m, 2H), 2.88–2.82 (m, 1H), 2.73–2.66 (m, 1.3H), 2.60–2.54 (m, 1.7H), 2.38–2.32 (m, 2H), 2.09 (s, 3H), 1.41 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 170.6/170.3, 153.8/153.4, 144.9/144.1, 99.4, 81.2/80.5, 71.5/71.0, 52.4, 46.6/46.4, 33.7/32.9, 31.8/30.8, 28.8/28.7, 28.2 (3C), 15.6/15.5; IR (neat, $cm^{-1}$) = 2976, 2917, 1751, 1696, 1434, 1381, 1367, 1248, 1221, 1163, 1129, 1082, 1010; HRMS (FAB) calcd for $C_{15}H_{25}BrNO_4S$: 394.0688 ($[M+H]^+$), found 394.0680.

***1-(tert-Butyl) 2-methyl (S,Z)-3-(bromomethylene)-2-(3-methoxy-3-oxopropyl)pyrrolidine-1,2-dicarboxylate (10m).*** Following the general MOC procedure (condition A) with **5m** (41 mg, 0.1 mmol), **10m** (36.5 mg, 89%) was obtained as colorless oil; $R_f$ = 0.40 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = +19.3 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:2 from $^1H$ NMR, $^1H$ NMR (800 MHz, $CDCl_3$) δ = 6.16 (s, 1H), 3.71 (s, 3H), 3.64 (s, 3H), 3.62–3.54 (m, 2H), 2.83 (td, *J* = 17.9, 7.5 Hz, 1H), 2.78–2.57 (m, 3H), 2.28–2.22 (m, 2H), 1.41 (s, 9H); $^{13}C\{^1H\}$ NMR (200 MHz, $CDCl_3$) δ = 173.4/173.3, 170.6/170.4, 154.0/153.4, 144.8/143.9, 99.7, 81.3/80.6, 71.3/70.8, 52.4, 51.8/51.6, 46.7/46.4, 33.6/32.8, 29.6/29.3, 28.3/28.2 (3C), 27.4/26.7; IR (neat, $cm^{-1}$) = 2976, 2951, 2889, 1735, 1696, 1435, 1366, 1230, 1051, 1019; HRMS (FAB) calcd for $C_{16}H_{25}NO_6Br$: 406.0865 ($[M+H]^+$), found 406.0864. Because **10m** can not be fully separated after trying a few chiral columns and conditions, we transform **10m** to **10m'** for HPLC analysis.

***Methyl (S,Z)-1-benzoyl-3-(bromomethylene)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2-carboxylate* (10m').** Set the reaction with **10m** (20.0 mg, 0.049 mmol) and follow the procedure of preparing **10f'**. Flash purification by column chromatography over silica gel (hexane/EtOAc, 2:1), compound **10m'** (17.0 mg, 0.042 mmol, 85%) was obtained as a white solid.

**General Procedure for the Preparation of 11a–11c.** A mixture of alkyne **5c'** (98 mg, 0.36 mmol), diphenyl disulfide (51.1 mg, 0.23 mmol, 0.65 equiv), CuI (3.5 mg, 0.018 mmol, 0.05 equiv) and $K_2CO_3$ (99.4 mg, 0.72 mmol, 2.00 equiv) in dried DMSO (7.2 mL, 0.05 M) was stirred at room temperature for 2 days. After quenching with 10% $NaHCO_3$ solution (4 mL), the mixture was extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/EtOAc, 3:1) to yield **11a** (106 mg, 0.28 mmol, 77%) as a colorless oil.

***Ethyl N-benzoyl-N-(4-(phenylthio)but-3-yn-1-yl)-L-alaninate (11a).*** $R_f$ = 0.30 (hexane/EtOAc, 3:1), colorless oil; $[\alpha]_D^{20}$ = –54.1 (c = 0.5, $CHCl_3$); Rotamers were observed, and

the ratio was 2:3 from $^1$H NMR, $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.16 (m, 10H), 4.44 (brs, 1H), 4.10 (brs, 2H), 3.84 (brs, 0.6H), 3.53 (brs, 0.8H), 3.30 (brs, 0.6H), 2.93 (brs, 1.2H), 2.65 (brs, 0.8H), 1.61 (brs, 1.2H), 1.45 (brs, 1.8H), 1.25 (brs, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 172.9/172.0, 171.5, 136.3 (2C), 133.3/132.8, 130.0, 129.3 (2C), 128.8 (2C), 126.6 (2C), 126.2 (2C), 97.2/95.4, 68.3/67.0, 61.9/61.5, 57.9/55.2, 48.1/43.1, 21.6/20.0, 16.3/15.2, 14.4; IR (neat, cm$^{-1}$) = 3058, 2982, 2938, 1735, 1635, 1579, 1440, 1411, 1320, 1215, 1185, 1104, 1073, 1022; HRMS (FAB) calcd for $C_{22}H_{24}NO_3S$: 382.1477 ([M+H]$^+$), found 382.1469.

***Ethyl N-benzoyl-N-(4-(phenylselanyl)but-3-yn-1-yl)-L-alaninate (11b).*** Following the same experimental procedure of **11a** with diphenyl diselenide and **5c'** (67.4 mg, 0.25 mmol), **11b** (75.5 mg, 71%) was obtained as colorless oil; $R_f$ = 0.30 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = –43.8 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:1 from $^1$H NMR, $^1$H NMR (800 MHz, $CDCl_3$) δ = 7.51–7.22 (m, 10H), 4.44 (brs, 1H), 4.16 (brs, 2H), 3.82 (brs, 0.5H), 3.52 (brs, 1H), 3.28 (brs, 0.5H), 2.93 (brs, 1H), 2.65 (brs, 1H), 1.61 (brs, 1.5H), 1.44 (brs, 1.5H), 1.25 (brs, 3H); $^{13}$C{$^1$H} NMR (200 MHz, $CDCl_3$) δ = 172.7/171.8, 171.3, 136.1 (2C), 129.8/129.6, 129.5 (3C), 129.1/128.9, 128.7, 127.1/126.9, 126.5 (3C), 101.5/99.8, 61.6/61.3, 59.9, 57.7/55.1, 48.0/42.9, 21.6/20.1, 16.1/15.0, 14.2; IR (neat, cm$^{-1}$) = 3057, 2982, 2938, 1736, 1639, 1439, 1320, 1218, 1854, 1104, 1072, 1044, 1021; HRMS (FAB) calcd for $C_{22}H_{24}NO_3Se$: 430.0921 ([M+H]$^+$), found 430.0913.

***Ethyl N-benzoyl-N-(4-(phenyltellanyl)but-3-yn-1-yl)-L-alaninate (11c).*** Following the same experimental procedure of **11a** with diphenyl ditelluride and **5c'** (48.5 mg, 0.18 mmol), **11c** (65.7 mg, 77%) was obtained as colorless oil; $R_f$ = 0.25 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = –51.7 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:1 from $^1$H NMR, $^1$H NMR (800 MHz, $CDCl_3$) δ = 7.67–7.23 (m, 10H), 4.44 (brs, 1H), 4.22–4.15 (brs, 2H), 3.81–3.25 (m, 2H), 3.05– 2.38 (m, 2H), 1.59 (brs, 1.4H), 1.43 (brs, 1.6H), 1.25 (brs, 3H); $^{13}$C{$^1$H} NMR (200 MHz, $CDCl_3$) δ = 172.6/171.7, 171.3, 136.1 (2C), 135.4/135.2, 129.7 (3C), 128.6 (2C), 128.0/127.8, 126.4 (3C), 81.7/80.4, 70.6/69.8, 61.6/61.2, 57.7/55.1, 48.3/47.7/43.2/42.7, 22.1/20.6, 16.1/15.0, 14.1; IR (neat, cm$^{-1}$) = 3054, 2982, 2938, 1735, 1635, 1434, 1412, 1368, 1322, 1218, 1104, 1019; HRMS (FAB) calcd for $C_{22}H_{24}NO_3Te$: 480.0818 ([M+H]$^+$), found 480.0824.

**General Procedure for the Preparation of 11d–11f.** A mixture of alkyne **5f'** (133 mg, 0.49 mmol), diphenyl disulfide (70.1 mg, 0.32 mmol, 0.65 equiv), CuI (4.7 mg, 0.025 mmol, 0.05 equiv) and $K_2CO_3$ (136 mg, 0.99 mmol, 2.00 equiv) in dried DMSO (9.9 mL, 0.05 M) was stirred at room temperature for 2 days. After quenching with 10% $NaHCO_3$ solution (5 mL), the mixture was extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/EtOAc, 7:1) to yield **11d** (177 mg, 0.47 mmol, 95%) as a colorless oil.

***Ethyl N-(tert-butoxycarbonyl)-N-(4-(phenylthio)but-3-yn-1-yl)-L-alaninate (11d).*** $R_f$ = 0.4 (hexane/EtOAc, 5:1), colorless oil; $[\alpha]_D^{20}$ = –23.6 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:1 from $^1$H NMR, $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.16 (m, 5H), 4.51–4.48 (m, 0.5H), 4.17–4.08 (m, 2.5H), 3.61–3.23 (m, 2H), 2.78–2.40 (m, 2H), 1.46–1.40 (brs, 12H), 1.26–1.21 (m, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 172.5/172.3, 155.4/154.9, 133.4/133.3, 130.0, 129.3 (2C), 126.5/126.4, 126.1 (2C), 80.8/80.7, 69.8/69.7/66.9/66.7, 61.3, 56.6/55.2, 46.6/45.3, 28.5 (3C), 21.6/20.8/19.7/19.0, 16.3/15.8, 14.4; IR (neat, cm$^{-1}$) = 2979, 2936, 1740, 1696, 1472, 1367, 1214, 1162, 1100, 1073, 1024; HRMS (ESI) calcd for $C_{20}H_{27}NNaO_4S$: 400.1553 ([M+Na]$^+$), found 400.1541.

***Ethyl N-(tert-butoxycarbonyl)-N-(4-(phenylselanyl)but-3-yn-1-yl)-L-alaninate (11e).*** Following the same experimental procedure of **11d** with diphenyl diselenide and **5f'** (136 mg, 0.80 mmol), **11e** (297 mg, 87%) was obtained as colorless oil; $R_f$ = 0.4 (hexane/EtOAc, 5:1); $[\alpha]_D^{20}$ = –14.6 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:1 from $^1$H NMR, $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.48–7.19 (m, 5H), 4.50–4.44 (m, 0.5H), 4.16–4.08 (m, 2.5H), 3.57–3.32 (m, 2H), 2.79–2.63 (m, 2H), 1.45–1.39 (m, 12H), 1.25–1.21 (m, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 172.5/172.3, 155.4/154.8, 129.6 (2C), 129.0 (3C), 127.1, 101.9/101.6, 80.8/80.7, 61.3, 59.8/59.6, 56.6/55.2, 46.7/45.4, 28.5 (3C), 21.8/20.1, 16.3/15.8, 14.3; IR (neat, cm$^{-1}$) = 2976, 2934, 1738, 1693, 1577, 1476, 1365, 1297, 1250, 1214, 1160, 1100, 1070, 1021; HRMS (FAB) calcd for $C_{20}H_{28}NO_4Se$: 426.1184 ([M+H]$^+$), found 426.1179.

***Ethyl N-(tert-butoxycarbonyl)-N-(4-(phenyltellanyl)but-3-yn-1-yl)-L-alaninate (11f).*** Following the same experimental procedure of **11d** with diphenyl ditelluride and **5f'** (142.7 mg, 0.53 mmol), **11f** (241 mg, 96%) was obtained as colorless oil; $R_f$ = 0.4 (hexane/EtOAc, 5:1); $[\alpha]_D^{20}$ = –14.8 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:1 from $^1$H NMR, $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.64–7.62 (m, 2H), 7.24–7.19 (m, 3H), 4.68–4.42 (m, 0.5H), 4.14–4.06 (m, 2.5H), 3.54–3.22 (m, 2H), 2.88–2.77 (m, 2H), 1.44–1.38 (m, 12H), 1.24–1.19 (m, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ = 172.2/172.0, 155.1/154.5, 135.0 (2C), 129.5 (3C), 127.7, 113.0/112.6, 80.4/80.3, 61.9, 56.4/55.0, 46.8/45.5, 37.1/36.9, 28.3/28.2 (3C), 22.0/21.4, 16.1/15.5, 14.1; IR (neat, cm$^{-1}$) = 2979, 2937, 1739, 1695, 1473, 1367, 1297, 1251, 1215, 1162, 1101, 1071, 1034, 1019; HRMS (FAB) calcd for $C_{20}H_{27}NO_4Te$: 475.1002 ([M]$^+$), found 475.1016.

**General Procedure for the MOC Cyclization of Chalcogen-substituted Alkynes.** To a solution of chalcogen-substituted alkyne substrates (**11a–11f**, 0.10 mmol) in DMF (5 mL, 0.02 M) at 25 ℃ under an $N_2$ atmosphere, $In(OTf)_3$ (0.01 mmol, 0.1 eq) and KO$^t$Bu (0.15 mmol, 1.50 equiv for **11a–11c**, 0.20 mmol, 2.00 equiv for **11d–11f**) were added. After 10 min, sat. $NH_4Cl$ (3 mL) and $H_2O$ (5 mL) were added, and the aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated by high-vacuum evaporation. The residue was purified by flash column chromatography on silica gel to afford analytically pure products **12a–12f**.

***Ethyl (R,Z)-1-benzoyl-2-methyl-3-((phenylthio)methylene)pyrrolidine-2-carboxylate (12a).*** Following the general MOC procedure with **11a** (39 mg, 0.1 mmol), **12a** (30.4 mg, 78%) was obtained as colorless oil; $R_f$ = 0.25 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = –198.3 (c = 0.5, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ = 7.46–7.45 (m, 2H), 7.42–7.37 (m, 3H), 7.34–7.32 (m, 2H), 7.30–7.28 (m, 2H), 7.23–7.20 (m, 1H), 6.22 (t, *J* = 1.9 Hz, 1H), 4.30–4.20 (m, 2H), 3.66–3.62 (m, 2H), 2.85–2.80 (m, 1H), 2.71–2.66 (m, 1H), 1.98 (s, 3H), 1.29 (t, *J* =

7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ = 170.2, 168.8, 141.5, 136.6, 136.1, 129.9, 129.5 (2C), 129.1 (2C), 128.3 (2C), 126.84 (2C), 126.82, 118.4, 68.5, 61.4, 48.6, 34.1, 18.7, 14.2; IR (neat, $cm^{-1}$): 3065, 2981, 2935, 1737, 1634, 1443, 1406, 1250, 1121, 1162, 1118, 1024; HRMS (FAB) calcd for $C_{22}H_{24}NO_3S$: 382.1477 ($[M+H]^+$), found 382.1476.

***Ethyl (R,Z)-1-benzoyl-2-methyl-3-((phenylselanyl)methylene)pyrrolidine-2-carboxylate (12b).*** Following the general MOC procedure with **11b** (43 mg, 0.1 mmol), **12b** (38.6 mg, 90%) was obtained as colorless oil; $R_f$ = 0.30 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = –188.2 (c = 0.5, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ = 7.50–7.49 (m, 2H), 7.46–7.45 (m, 3H), 7.40–7.36 (m, 3H), 7.30–7.24 (m, 3H), 6.44 (s, 1H), 4.32–4.22 (m, 2H), 3.64–3.61 (m, 2H), 2.80–2.75 (m, 1H), 2.68–2.62 (m, 1H), 1.96 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 170.0, 168.9, 141.8, 136.6, 132.6 (2C), 131.6, 129.9, 129.3 (2C), 128.3 (2C), 127.5, 126.8 (2C), 115.5, 68.8, 61.5, 48.6, 35.0, 18.3, 14.3; IR (neat, $cm^{-1}$): 3056, 2980, 2934, 1732, 1633, 1577, 1404, 1252, 1216, 1163, 1119, 1022; HRMS (FAB) calcd for $C_{22}H_{24}NO_3Se$: 430.0921 ($[M+H]^+$), found 430.0934.

***Ethyl (R,Z)-1-benzoyl-2-methyl-3-((phenyltellanyl)methylene)pyrrolidine-2-carboxylate (12c).*** Following the general MOC procedure with **11c** (48 mg, 0.1 mmol), **12c** (43.7 mg, 91%) was obtained as colorless oil; $R_f$ = 0.30 (hexane/EtOAc, 3:1); $[\alpha]_D^{20}$ = –188.9 (c = 0.5, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ = 7.76–7.75 (m, 2H), 7.45–7.40 (m, 2H), 7.39–7.36 (m, 3H), 7.32–7.29 (m, 1H), 7.25–7.22 (m, 2H), 6.68 (s, 1H), 4.32–4.22 (m, 2H), 3.61–3.58 (m, 2H), 2.83–2.73 (m, 2H), 1.88 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 170.1, 169.2, 146.3, 138.3 (2C), 136.7, 129.9, 129.4 (2C), 128.3 (2C), 128.1, 126.8 (2C), 116.1, 98.9, 69.0, 61.6, 48.5, 36.3, 17.8, 14.4; IR (neat, $cm^{-1}$): 3053, 2979, 2933, 1725, 1632, 1574, 1401, 1252, 1164, 1121, 1018; HRMS (FAB) calcd for $C_{22}H_{24}NO_3Te$: 480.0818 ($[M+H]^+$), found 480.0824. Because **12c** can not be fully separated after trying a few chiral columns and conditions, we transform **12c** to **12c'** for HPLC analysis.

***Ethyl (R,Z)-1-benzoyl-3-(4-hydroxybut-2-yn-1-ylidene)-2-methylpyrrolidine-2-carboxylate* (12c').** To a two-necked 15 mL round-bottomed flask under an $N_2$ atmosphere containing $PdCl_2$ (1.61 mg, 0.009 mmol, 0.20 equiv), CuI (1.67 mg, 0.009 mmol, 0.20 equiv) and dry methanol (3 mL) was added *Z*-vinylic tellurides **12c** (21.1 mg, 0.044 mmol). After stirring the mixture for 15 min at room temperature, propargyl alcohol (5.2 μL, 0.18 mmol, 4.00 equiv) and triethylamine (18.1 μL, 0.26 mmol, 6.00 equiv) were added. The reaction was stirred at room temperature for 24 h. After this time the solid part was filtered under vacuum and the filtrate was treated with sat. $NH_4Cl$ (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 1:1) to yield **12c'** (7.3 mg, 0.023 mmol, 53%) as a colorless oil. $R_f$ = 0.20 (hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ –259.8 (c = 0.5, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$) δ = 7.42–7.37 (m, 5H), 5.54 (t, *J* = 2.1 Hz, 1H), 4.40–4.32 (m, 2H), 4.29–4.26 (m, 1H), 4.22–4.17 (m, 1H), 3.62 (t, *J* = 7.1 Hz, 2H), 2.80–2.70 (m, 2H), 1.92 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); $^{13}C\{1H\}$ NMR (150 MHz, $CDCl_3$) δ = 170.3, 168.9, 153.9, 136.4, 130.0, 128.4 (2C), 126.7 (2C), 103.2, 95.3, 81.1, 68.9, 61.6, 51.7, 48.2, 33.1, 19.3, 14.2; IR (neat, $cm^{-1}$) = 3383, 2981, 2901, 1727, 1621, 1408, 1252, 1226, 1160, 1118, 1022; HRMS (FAB) calcd for $C_{19}H_{22}NO_4$: 328.1549 ($[M+H]^+$), found 328.1536.

***1-(tert-Butyl) 2-ethyl (R,Z)-2-methyl-3-((phenylthio)methylene)pyrrolidine-1,2-dicarboxylate (12d).*** Following the general MOC procedure with **11d** (38 mg, 0.1 mmol), **12d** (31.5 mg, 83%) was obtained as colorless oil; $R_f$ = 0.30 (hexane/EtOAc, 5:1); $[\alpha]_D^{20}$ = –188.9 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:2 from $^1H$ NMR, $^1H$ NMR (600 MHz, $CDCl_3$) δ = 7.29–7.28 (m, 4H), 7.20–7.19 (m, 1H), 6.13 (t, *J* = 1.8 Hz, 1H), 4.22–4.08 (m, 2H), 3.67–3.52 (m, 2H), 2.72–2.68 (m, 2H), 1.78 (s, 1H), 1.74 (s, 2H), 1.43 (s, 3H), 1.42 (s, 6H), 1.25–1.21 (m, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ = 171.14/171.07, 153.7/153.6, 144.2/143.4, 136.3/136.1, 129.2 (3C), 129.03/128.99, 126.7/126.6, 117.0, 80.6/79.9, 67.6/67.2, 61.3/61.2, 46.01/46.00, 33.0/32.3, 28.4/28.3 (3C), 20.6/20.0, 14.1; IR (neat, $cm^{-1}$): 2976, 2932, 1743, 1696, 1582, 1477, 1386, 1366, 1251, 1163, 1113, 1089, 1055, 1024; HRMS (FAB) calcd for $C_{20}H_{28}NO_4S$: 378.1739 ($[M+H]^+$), found 378.1730.

***1-(tert-Butyl) 2-ethyl (R,Z)-2-methyl-3-((phenylselanyl)methylene)pyrrolidine-1,2-dicarboxylate (12e).*** Following the general MOC procedure with **11e** (43 mg, 0.1 mmol), **12e** (38.6 mg, 90%) was obtained as colorless oil; $R_f$ = 0.40 (hexane/EtOAc, 5:1); $[\alpha]_D^{20}$ = –45.6 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:2 from $^1H$ NMR, $^1H$ NMR (400 MHz, $CDCl_3$) δ = 7.47–7.45 (m, 2H), 7.27–7.24 (m, 3H), 6.35 (t, *J* = 1.8 Hz, 1H), 4.24–4.10 (m, 2H), 3.67–3.44 (m, 2H), 2.68–2.64 (m, 2H), 1.78 (s, 1H), 1.73 (s, 2H), 1.44 (s, 3H), 1.41 (s, 6H), 1.29–1.23 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 171.3, 154.1/153.8, 144.3/143.4, 132.6 (2C), 131.9/131.8, 129.5 (2C), 127.7/127.5, 114.6/114.4, 80.8/80.1, 68.2/67.8, 61.6/61.5, 46.3/45.8, 34.2/33.5, 28.6/28.5 (3C), 20.2/19.6, 14.4; IR (neat, $cm^{-1}$): 2975, 2933, 1736, 1695, 1578, 1476, 1383, 1365, 1251, 1163, 1112, 1085, 1053, 1021; HRMS (FAB) calcd for $C_{20}H_{28}NO_4Se$: 426.1184 ($[M+H]^+$), found 426.1174.

***1-(tert-Butyl) 2-ethyl (R,Z)-2-methyl-3-((phenyltellanyl)methylene)pyrrolidine-1,2-dicarboxylate (12f).*** Following the general MOC procedure with **11f** (47 mg, 0.1 mmol), **12f** (41.4 mg, 88%) was obtained as colorless oil; $R_f$ = 0.50 (hexane/EtOAc, 5:1); $[\alpha]_D^{20}$ = –48.5 (c = 0.5, $CHCl_3$); Rotamers were observed, and the ratio was 1:2 from $^1H$ NMR, $^1H$ NMR (400 MHz, $CDCl_3$) δ = 7.74–7.72 (m, 2H), 7.31–7.28 (m, 1H), 7.24–7.20 (m, 2H), 6.57 (s, 1H), 4.27–4.21 (m, 1H), 4.17–4.10 (m, 1H), 3.58–3.47 (m, 2H), 2.76–2.70 (m, 2H), 1.72 (s, 1H), 1.67 (s, 2H), 1.44 (s, 3H), 1.41 (s, 6H), 1.29–1.23 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 171.4/171.2, 154.1/153.7, 148.1/147.3, 138.2 (2C), 129.4/129.3 (2C), 128.06/127.97, 116.4/116.2, 98.2/98.0, 80.5/79.8, 68.3/67.8, 61.6/61.5, 46.0/45.5, 35.4/34.7, 28.4/28.3 (3C), 19.4/18.7, 14.31/14.26; IR (neat, $cm^{-1}$): 2975, 2933, 1729, 1695, 1574, 1475, 1382, 1365, 1252, 1164, 1112, 1078, 1050, 1018; HRMS (FAB) calcd for $C_{20}H_{27}NO_4Te$: 475.1002 ($[M]^+$), found 475.0996. Because **12f** can not be fully separated after trying a few chiral columns and conditions, we transform **12f** to **12f'** for HPLC analysis.

***1-(tert-Butyl) 2-ethyl (R,Z)-3-(4-hydroxybut-2-yn-1-ylidene)-2-methylpyrrolidine-1,2-dicarboxylate* (12f').** Set the

reaction with **12f** (16.7 mg, 0.035 mmol) and follow the procedure of preparing **12c'**. Flash purification by column chromatography over silica gel (hexane/EtOAc, 2:1), compound **12f'** (5.1 mg, 0.016 mmol, 45%) was obtained as a colorless oil.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

DFT calculation details, chiral HPLC data for compound **10** and **12**, copies of the $^{1}H$ and $^{13}C$ NMR spectra for all new products. (PDF)

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### Notes

The authors declare no competing financial interest.

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