JOC The Journal of Organic Chemistry

Note

Studies on Instructive Construction of exo-Olefin Terminated 5- and 6-Membered Nitrogen Heterocycles: SmI2-Mediated Intramolecular Cyclization of Haloalkynals

Kazunori Takahashi, Kei Fukushima, Marina Seto, Azusa Togashi, Yuichi Arai, Masayoshi Tsubuki, and Toshio Honda

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b01440 • Publication Date (Web): 25 Jul 2018

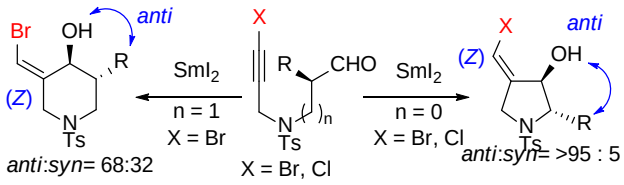
ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Studies on Instructive Construction of *exo*-Olefin Terminated 5- and 6-Membered Nitrogen Heterocycles: SmI_2-Mediated Intramolecular Cyclization of Haloalkynals

Kazunori Takahashi*, Kei Fukushima, Marina Seto, Azusa Togashi, Yuichi Arai, Masayoshi Tsubuki, Toshio Honda

Hoshi University, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan



ABSTRACT : Stereoselective construction of *exo*-olefin terminated pyrrolidine and piperidine frameworks was developed by employing SmI_2-mediated intramolecular radical cyclization of haloalkynaks. The radical cyclization affording 2,3-disubstituted pyrrolidines and piperidines proceeded in a highly stereoselective manner. On the other hand, the decreasing stereoselectivety was observed in preparation of 2,4-disubstituted pyrrolidine and 3,4-disubstituted piperidine derivatives in the cyclization.

Naturally occurring alkaloids with a wide range of interesting and important biological activities, have been recognized as promising lead molecules for the discovery of potent compounds of therapeutic agents.[1,2] Moreover, the structural diversity of these molecules has attracted extensive attention of many organic chemists, and a great deal of efforts have been made to develop new and efficient synthetic methodologies for these compounds. Since pyrrolidine and piperidine nuclei have been identified in a large class of alkaloids with diverse biological activities, we have been interested in the development of novel synthetic

strategies for constructing a pyrrolidine skeleton bearing an *exo*-bromomethylene functionality, stereoselectively, where 2,3-*trans* or *cis* disubstituted pyrrolidines with the desired stereochemistry were constructed by trivial structural manipulation of the starting materials (Figure 1).

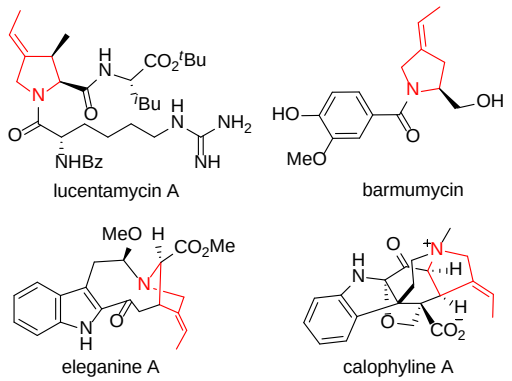
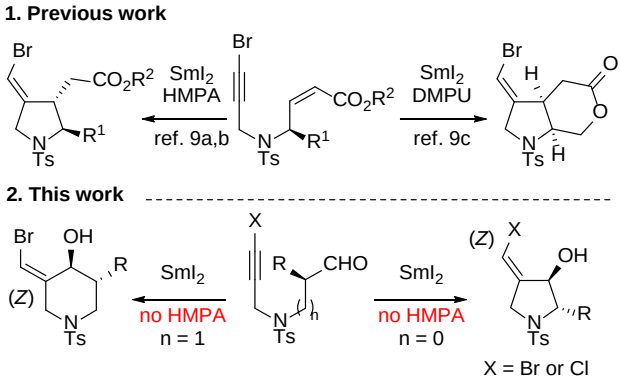


Figure 1. Structures of pyrrolidine alkaloids.

It has been well-recognized that the *exo*-halomethylene moiety plays important roles in further chemical transformations; such as transition metal-catalyzed coupling reaction[3] to introduce a variety of functionalities, stereoselective hydrogenation,[4] asymmetric epoxidation[5] and so on. Thus, exploitation of new methods for constructing an *exo*-haloolefin, stereoselectively, would be another important research subject in organic synthesis.[6]



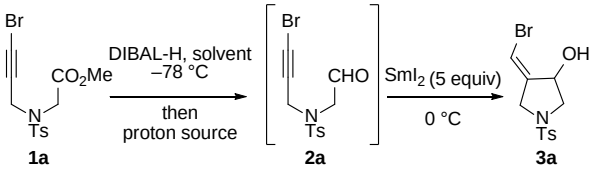
Scheme 1. SmI_2-Mediated radical cyclization.

SmI_2-Mediated intramolecular radical cyclization of alkynes with aldehydes or ketones has

already been reported to provide the corresponding *exo*-olefins. However, the stereochemistry of *exo*-olefin of the generated heterocyclic or carbocyclic compounds is usually observed as (*E*)-form with poor selectivity. Moreover, it is essential to execute this type of cyclization at low temperature to obtain the products in high diastereoselectivity.[7]

Recently, we have reported a stereoselective synthesis of 5-membered carbocyclic and heterocyclic compounds with an *exo*-olefin functionality by means of SmI_2-mediated intramolecular cyclization[8] of bromoalkynes possessing α,β-unsaturated esters in the same molecules, where the stereogenic centers of the 2,3-positions and the geometry of the *exo*-olefin could be successfully controlled (Scheme 1). As part of our ongoing work with SmI_2-mediated cyclization of alkyne derivatives[9] in connection with alkaloid synthesis, we describe herein the construction of pyrrolidine and piperidine rings with *exo*-olefin moieties by utilizing an intramolecular radical cyclization of haloalkynes with aldehydes.

Table 1. Attempted optimization of SmI_2-mediated radical cyclization.



1a **2a** **3a**

entry	solvent	proton source (equiv)	2 steps yield (%)
1[a]	CH_2Cl_2	HFIP (5)	72
2[a]	CH_2Cl_2	MeOH (5)	70
3[a]	CH_2Cl_2	^{i}PrOH (5)	73
4	toluene	HFIP (10)	33
5	toluene	^{t}BuOH (10)	54
6	toluene	MeOH (10)	69
7	toluene	^{i}PrOH (10)	73
8	toluene	^{i}PrOH (5)	57
9	toluene	^{i}PrOH (20)	67

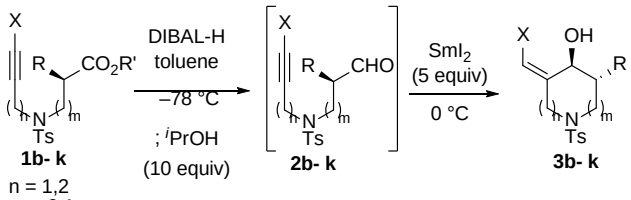
a. The reaction of **1a** with DIBAL-H/ SmI_2 was two-step synthesis. To the aldehyde **2a** in THF solution were added proton source and SmI_2.

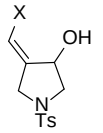
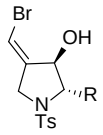
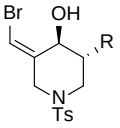
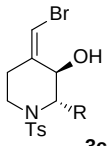
First, preparation of the key bromoalkynal **2a** and subsequent formation of a pyrrolidine ring, by two-step sequence, was investigated as follows (Table 1). Reduction of ester **1a** with DIBAL-H at –78 ºC in CH_2Cl_2 gave the crude aldehyde, which, however, was found to be unstable in SiO_2 chromatographic conditions, and **2a** could not be isolated in pure form, unfortunately. Therefore, the subsequent radical cyclization was conducted without further purification of **2a** to obtain **3a**

in reasonably good yield. Moreover, for the work-up of the reduction, we decided to treat the crude products with alcohol-based proton source, such as HFIP, MeOH, and ^{i}PrOH, since the expected aldehydes appeared to be acid-labile, even by purification with column chromatography on silica gel.

Thus, treatment of the reduction products with alcohol-based proton sources, HFIP, MeOH, and *i*PrOH, in CH_2Cl_2, and subsequent SmI_2-mediated radical cyclization afforded the desired pyrrolidine **3a** in 72, 70, and 73% yields, respectively, as the sole stereoisomer (entries 1, 2, 3). Although the above mentioned two-step synthesis of **3a** proceeded in fairly good yields, we thought that DIBAL-H reduction and subsequent radical cyclization can be carried out in a single pot for increasing the yield of **3a**. By screening of a proton source (entries 4-9) in the one-pot reaction, the use of *i*PrOH afforded the desired product **3a** in 73% yield (entry 7). The stereochemistry of the alkene moiety in **3a** was determined by analysis of its nOe spectrum. Finally, the best reaction condition for the one-pot reaction sequence was established by changing the solvent from CH_2Cl_2 to toluene. As a practical manner, treatment of chloroalkyne-ester **1b** with DIBAL-H (1.3 equiv) in toluene, followed by exposure of the crude product to SmI_2 (5 equiv) in the presence of *i*PrOH (10 equiv) afforded **3b** in 93% yield over 2 steps as the sole product with (*Z*)-configuration (Table 2). On the other hand, the reaction of iodoalkyne (1k) under the same reaction conditions as for **1b** afforded the cyclization products (***Z*-3c**) and (***E*-3c**) in 19 and 19% yields, respectively. Moreover, (*Z*)-selectivity for the resulting alkene moiety was found to decrease (*E*:*Z*= 1:1), remarkably. Due to the low yield and poor selectivity observed in the reaction of iodoalkyne, the use of bromoalkynes, as starting materials, was greatly preferable for this type of cyclization.

Table 2. Reduction of ester **1** with DIBAL-H and radical cyclization of **2**.



Product		X	R	*anti*: *syn*	yield (%)
	**3b**	Cl	R = H		93
	3c	I	R = H		38[a]
	**3d**	Br	R = CH_3	>95:5	73
	3e	Br	R = Bn	>95:5	62
	3f	Br	R = CH_2OTBS	>95:5	77
	3g	Br	R = *i*Pr	>95:5	31
	**3h**	Br	R = H		76[b]
	3i	Br	R = CH_3	68:32	73[b]
	**3j**	Br	R = H		80[b]
	3k	Br	R = CH_3	100:0	23[b]

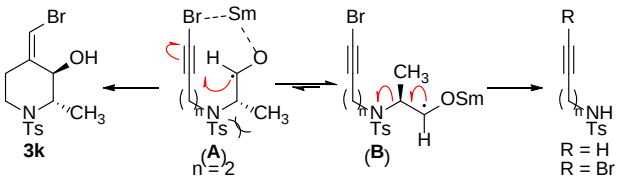
a. Isolated ***E*-3c** in 19% and ***Z*-3c** in 19% yields, respectively.

b. MeOH instead of *i*PrOH was used as a proton source.

The similar reaction for amino acid derivatives **1d**–**g** also gave 2,3-disubstituted pyrrolidines **3d**–**g** in moderate yields (62–77%). However, when this reaction was applied to bromoalkyne **1g**, the yield of the resulting pyrrolidine **3g** decreased to only 31%. The observed low yield was due to the over reduction of **1g** with DIBAL-H to the corresponding alcohol, where the radical cyclization expected for the subsequent 2nd step could not be brought about. It is worthwhile to note that a similar radical cyclization of **2f** with SmI_2 in the presence of HMPA resulted in decreasing of stereoselectivity (*anti*:*syn* = 78:22).

Next, we attempted to apply the aforementioned methodology to the preparation of piperidine derivatives as follows. When *i*PrOH was used as a proton source under the same reaction conditions as for the preparation of **3b**, the desired cyclization product **3h** could not be isolated at all, but a small amount of aldehyde **2h** was recovered. Therefore, the reaction of **1h**–**k** was carried out using MeOH instead of *i*PrOH as a proton source. The sequential reduction and SmI_2-mediated radical cyclization of **1h** and **1j** furnished the corresponding piperidines **3h** and **3j** in 76% and 80% yields, respectively. By application of this reaction to **1i** possessing a methyl

group at the α position of the formyl function, the corresponding piperidine **3i** was obtained as a diastereomeric mixture (*anti*:*syn* = 68:32) in 73% yield. The observed low selectivity might be explained by assuming that the 6-*exo*-dig mode cyclization would proceed sluggishly compared to 5-*exo*-dig mode cyclization. On the other hand, the similar reaction for compound **1k** having a methyl group between the tosylamide and formyl groups gave the piperidine derivative **3k**, 3-butynyltoluenesulfonamide and 4-bromo-3-butynyltoluenesulfonamide in 23, 7, and 45% yields, respectively (Scheme 2). Formation of bromobutynyltoluenesulfonamide and butynyltoluenesulfonamide is assumed that the transition state (**B**) seems to be preferred over the weakly chelated transition state (**A**) in terms of the steric repulsion between sulfonamide group and methyl group, and hence the C-N bond cleavage may occur prior to ring closing reaction of the bromoalkyne *via* ketyl radical.

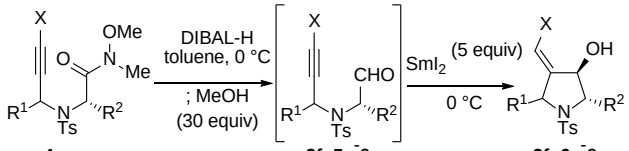


Scheme 2. Plausible reaction mechanism for C-N bond cleavage.

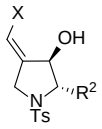
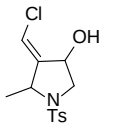
With the aim of increasing yields of cyclization products, an alternative preparation of the aldehydes via Weinreb amide **4a**–**e**,**g** was investigated, and the results were summarized in Table 3. Weinreb amide **4g**, derived from valine, was first subjected to a one-pot reaction, and the target compound **3g** was obtained in 69% yield. When the reduction of **4g** with DIBAL-H was carried out at 0 °C, the desired pyrrolidine **3g** was isolated in 36% yield after the radical cyclization. The observed low yield was probably due to the presence of a labile bromoalkyne functional group of **4g** under DIBAL-H reduction. The same reaction of chloroalkyne **4a**–**d** afforded the desired pyrrolidine derivatives **6a**–**d** in moderate yields (42–77%). By changing the proton source from MeOH to *i*PrOH for DIBAL-H reduction of **4d**, and subsequent radical cyclization of the crude aldehyde furnished a small amount of the recovered aldehyde **5d** and the cyclized pyrrolidine **6d** in 67% yield. When diastereoselective cyclization of **4e** having a methyl group at the propargylic position was attempted under the same reaction conditions, the

corresponding pyrrolidine **6e** was obtained as a diastereoisomeric mixture, in a ratio of *anti*: *syn* = 50:50, in 72% yield.

Table 3. Redical cyclization of alkynal *via* Weinreb amide **4**.

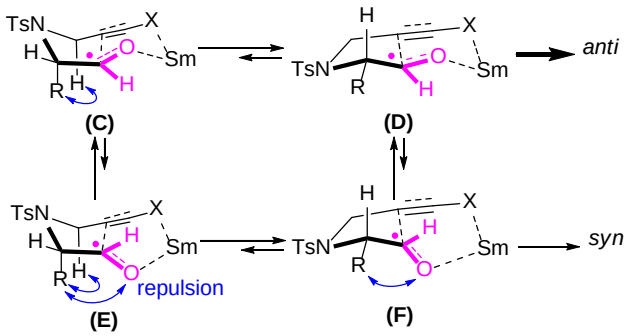


4a-g **2f, 5a-e** **3f, 6a-e**

Product		X	R	*anti*:*syn*	Yield (%)
	**3f**	Br	R^1 = H, R_2 = *i*Pr	>95:5	69[a]
	6a	Cl	R^1 = H, R_2 = CH$_3$	>95:5	58
	6b	Cl	R^1 = H, R^2 = Bn	>95:5	42
	6c	Cl	R^1 = H, R_2 = *i*Bu	>95:5	77
	6d	Cl	R^1 = H, R^2 = *i*Pr	>95:5	72
	**6e**	Cl	R^1 = CH$_3$, R^2 = H	50:50	72

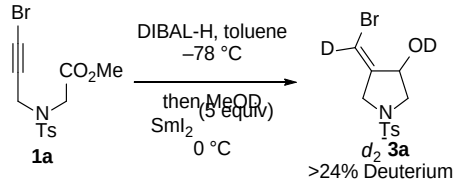
a. Reduction of **4f** with DIBAL-H was carried out at –78 °C.

The plausible reaction mechanism for radical cyclization was shown in Scheme 3. At first, treatment of aldehydes with SmI_2 would generate the corresponding ketyl radicals, where Sm^{II} or Sm^{III} might be coordinated to both oxygen and halogen atoms of alkynals to restrict the transition states, and then the radial coupling reaction could proceed to provide 2,3-*anti*- or 2,3-*syn*-disubstituted pyrrolidine derivatives (if R is alkyl group). From the examination of molecular models of conformationally capable of forming cyclic transition states (**C**–**F**), illustrated in Scheme 3, it would be reasonable to deduce that the preferred transition state for the radical reaction would be the envelope conformer (**D**) leading to 2,3-*anti* compound exclusively, since the steric repulsion between the substituent R and the carbonyl oxygen would be arisen in the transition states (**E**) and (**F**). After forming the 5-membered ring, the protonation occurred from the convex face of the molecule to give (*Z*)-alkene. On the other hand, another possible transition state (**C**) leading to 2,3-*anti* compound suffers from unfavorable 1,3-pseudodiaxial interactions between R group and the hydrogen depicted in Scheme 3.



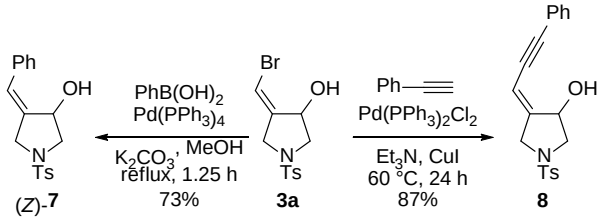
Scheme 3. Plausible reaction mechanism for radical cyclization.

Deuterium-labeling experiment of bromoalkyne **1a** was depicted in Scheme 4. DIBAL-H reduction of **1a**, followed by addition of CD_3OD gave the crude aldehyde, which on subsequent treatment with SmI_2 afforded pyrrolidine d_2-**3a**. The formation of pyrrolidine d_2-**3a** incorporating deuterium was confirmed by NMR measurement (76:24 H/D).



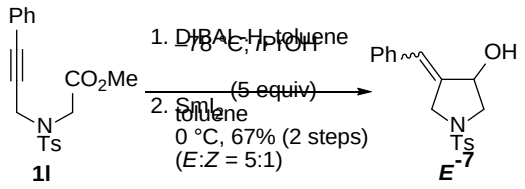
Scheme 4. Deuterium-labeling experiment.

Further functionalization of pyrrolidine derivative **3a** was then attempted by palladium-catalyzed coupling reaction as shown in Scheme 5. Suzuki-Miyaura coupling reaction of bromoalkene **3a** with phenylboronic acid successfully afforded (*Z*)-phenylalkene ***Z*-7**, stereosecifically, in 73% yield.[3b,10] In addition, Sonogashira coupling reaction of **3a** with phenylacetylene resulted in the formation of enyne **8** in 87% yield.[3c,11]



Scheme 5. Pd-Catalyzed coupling reaction of bromoalkene **3a**.

The comparative experiment was carried out by employing phenylalkyne derivative **1l** in order to prove the importance of bromo or chloro atom in haloalkynes for the observed stereocontrol of the *exo*-olefin moiety (Scheme 6). Resultantly, reduction and subsequent cyclization of **1l** as described for the preparation of **3a** from **1a** gave ***E*-** and ***Z*-7** in 56% and 11% yields, respectively (*E*:*Z* =5:1). This result supported that bromo or chloro atom of alkyne obviously contributed to both the reactivity and stereoselectivity for the radical reaction.



Scheme 6. SmI_2-Mediated cyclization of phenylalkyne **1k**.

In conclusion, we have developed SmI_2-mediated cyclization of haloalkynals leading to 5- and 6-membered heterocycles possessing an *exo*-haloolefin with (*Z*)-configuration. Particularly, the reaction of haloalkynal furnishing 2,3-disubstituted pyrrolidines was proved to proceed with high diastereoselectivity. The methodology developed here would provide an alternative efficient route to the construction of pyrrolidine and piperidine skeletons observed in a variety of naturally occurring nitrogen-heterocycles, and the synthesis of natural products along this line is under investigation.

EXPERIMENTAL SECTION

General Methods and Materials: Melting points were measured with a Yanaco MP-500P apparatus and are uncorrected. Optical rotations were measured with JASCO DIP-360 or P-2200. IR spectra were obtained using a JASCO FT/IR-4100, Shimadzu IRPrestige-21 or PerkinElmer Spectrum Two spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained on a Bruker AV III 400 (^{1}H-NMR: 400 MHz, ^{13}C-NMR: 100 MHz) or JEOL ECA-600 (^{1}H-NMR: 600 MHz, ^{13}C-NMR: 150 MHz) instrument for solutions in $CDCl_3$, and chemical shifts are reported on the δ scale using TMS as an internal standard of 0.00 for ^{1}H-NMR spectra and $CDCl_3$ as an internal standard of δ 77.00 for ^{13}C-NMR spectra, respectively. MS spectra were measured with a

JEOL-600 (EI, CI) or JMS-T100LP (ESI) spectrometer. Elemental analyses were performed on a Yanaco-MT5.

General procedure for alkylation of sulfonamide.[9a] **Methyl 3-(4-methyl-*N*-(prop-2-ynyl)-phenylsulfonamido)propanoate** (**1h'**). To a solution of *N*-tosyl-β-alanine methyl ester[12] (2.5 g, 9.3 mmol) and propargyl bromide (1.7 g, 14.3 mmol) in CH_3CN (39 mL) were added K_2CO_3 (3.8 g, 27.5 mmol) and nBu_4NI (683.0 mg, 1.9 mmol) at ambient temperature. After stirring for 3 h at 70 °C, the reaction mixture was diluted with AcOEt, and filtered through Celite. The volatile solvent was removed in vacuo. The residue was purified by column chromatography on silica gel using hexane-AcOEt-$CHCl_3$ (9:2:9, v/v) as eluent to give alkyne **1h'** (2.72 g, 99%) as a colorless solid; Mp 45–46 °C; IR ν max 3276, 1737, 1161 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.74 (2H, d, *J* = 8.3 Hz), 7.30 (2H, d, *J* = 8.3 Hz), 4.17 (2H, d, *J* = 2.5 Hz), 3.69 (3H, s), 3.49 (2H, t, *J* = 7.3 Hz), 2.71 (2H, t, *J* = 7.3 Hz), 2.43 (3H, s), 2.06 (1H, t, *J* = 2.5 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 171.6, 143.7, 135.4, 129.5 (2), 127.6 (2), 76.6, 73.8, 51.7, 42.6, 37.5, 33.6, 21.4; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{18}NO_4S$ 296.0956; Found 296.0964. Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74. Found: C, 56.87; H, 5.89; N, 4.66.

Methyl 2-methyl-3-(4-methyl-*N*-(prop-2-ynyl)phenylsulfonamido)propanoate (**1i'**). Alkylation of methyl 2-methyl-3-(4-methylphenylsulfonamido)propanoate[12] (619.3 mg, 2.29 mmol) was carried out according to the same procedure as described for **1h'** to give alkyne **1i'** (569.2 mg, 81%) as a colorless solid [eluent: hexane-AcOEt (1:1, v/v)]; Mp 76–78 °C; IR ν max 1735, 1350, 1163 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.72 (2H, d, *J* = 8.2 Hz), 7.29 (2H, d, *J* = 8.2 Hz), 4.18 (1H, dd, *J* = 18.6, 2.5 Hz), 4.10 (1H, dd, *J* = 18.6, 2.5 Hz), 3.69 (3H, s), 3.41 (1H, dd, *J* = 14.0, 7.8 Hz), 3.23 (1H, dd, *J* = 14.0, 6.9 Hz), 2.93-2.84 (1H, m), 2.42 (3H, s), 2.01 (1H, t, *J* = 2.5 Hz), 1.21 (3H, d, *J* = 7.1 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 174.9, 143.6, 135.3, 129.4 (2), 127.7 (2), 76.3, 73.9, 51.8, 49.1, 38.8, 37.5, 21.4, 14.9; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{20}NO_4S$ 310.1113; Found 310.1133. Anal. Calcd for $C_{15}H_{19}NO_4S$: C, 58.23; H, 6.19; N, 4.53. Found: C, 58.07; H, 6.18; N, 4.44.

(*S*)-*N*-Methoxy-*N*-methyl-2-(4-methyl-*N*-(prop-2-ynyl)phenylsulfonamido)propanamide (**4a'**). Alkylation of (*S*)-*N*-methoxy-*N*-methyl-2-(4-methylphenylsulfonamide)propanamide[13] (3.38 g, 11.81 mmol) was carried out according to the same procedure as described for **1h'** to

give alkyne **4a'** (3.83 g, 92%) as a colorless solid [eluent: hexane-AcOEt-$CHCl_3$ (1:2:2, v/v)]; Mp 80–82 °C; $[\alpha]_D^{24}$ = –38.22 (*c* 0.9, $CHCl_3$); IR ν max 1668, 1343, 1158 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.78 (2H, d, *J* = 8.3 Hz), 7.29 (2H, d, *J* = 8.3 Hz), 5.03 (1H, q, *J* = 7.2 Hz), 4.49 (1H, dd, *J* = 17.2, 2.5 Hz), 4.39 (1H, dd, *J* = 17.2, 2.5 Hz), 3.76 (3H, s), 3.12 (3H, s), 2.42 (3H, s), 2.17 (1H, t, *J* = 2.5 Hz), 1.40 (3H, d, *J* = 7.2 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 172.2, 143.5, 136.9, 129.4 (2), 127.4 (2), 80.6, 71.9, 61.5, 50.8, 33.6, 31.8, 21.4, 16.0; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{21}N_2O_4S$ 325.1222; Found 325.1220. Anal. Calcd for $C_{15}H_{20}N_2O_4S$: C, 55.54; H, 6.21; N, 8.64. Found: C, 55.58; H, 6.27. N, 8.57.

(*S*)-*N*-Methoxy-*N*-methyl-2-(4-methyl-*N*-(prop-2-ynyl)phenylsulfonamido)-3-phenylpropanamide (**4b'**). Alkylation of (*S*)-*N*-methoxy-*N*-methyl-2-(4-methylphenylsulfonamido)-3-phenylpropanamide[14] (3.11 g, 8.57 mmol) was carried out according to the same procedure as described for **1h'** to give alkyne **4b'** (2.15 g, 63%) as a colorless oil [eluent: hexane-AcOEt-$CHCl_3$ (1:2:2, v/v)]; $[\alpha]_D^{17}$ = –55.28 (*c* 1.1, $CHCl_3$); IR ν max 1661, 1338, 1160 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.73 (2H, d, *J* = 8.1 Hz), 7.26-7.23 (5H, m), 7.15-7.13 (2H, m), 5.21 (1H, dd, *J* = 9.5, 5.3 Hz), 4.66 (1H, dd, *J* = 18.8, 2.5 Hz), 4.41 (1H, dd, *J* = 18.8, 2.5 Hz), 3.37 (3H, s), 3.28 (1H, dd, *J* = 13.3, 9.5 Hz), 3.00 (3H, s), 2.80 (1H, dd, *J* = 13.3, 5.3 Hz), 2.42 (3H, s), 2.20 (1H, t, *J* = 2.5 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 170.4, 143.5, 136.9, 136.6, 129.4 (2), 129.3 (2), 128.4 (2), 127.7 (2), 126.7, 80.3, 72.2, 61.3, 55.7, 36.6, 33.7, 31.7, 21.5; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{25}N_2O_4S$ 401.1535; Found 401.1524.

General procedure for alkylation of sulfonamide: Mitsunobu reaction.[15] Methyl 2-(*N*-(but-3-ynyl)-4-methylphenylsulfonamido)acetate (**1j'**). To a solution of *N*-tosylglycine methyl ester[9a] (249.5 mg, 1.03 mmol), 3-butyn-1-ol (86.4 mg, 1.23 mmol) and Ph_3P (557.9 mg, 2.13 mmol) in THF (4.0 mL) was added DIAD (0.4 mL, 2.03 mmol) at ambient temperature. After stirring for 5 h at the same temperature, the volatile solvent was removed in vacuo. The residue was purified by column chromatography on silica gel using hexane-AcOEt-$CHCl_3$ (19:4:19, v/v) as eluent to give alkyne **1j'** (292.9 mg, 97%) as a colorless solid; Mp 65–66 °C; IR ν max 3284, 1754, 1341, 1159 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.72 (2H, d, *J* = 8.2 Hz), 7.31 (2H, d, *J* = 8.2 Hz), 4.18 (2H, s), 3.64 (3H, s), 3.42 (2H, t, *J* = 7.2 Hz), 2.51 (2H, dt, *J* = 7.2, 2.7 Hz), 2.43 (3H, s), 1.98 (1H, t, *J* = 2.7 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 169.3, 143.6, 136.4, 129.6 (2), 127.3 (2), 81.0, 70.4, 52.2, 49.0, 47.3, 21.5, 19.2; HRMS (CI, magnetic sector) *m/z*:

$[M+H]^+$ Calcd for $C_{14}H_{18}NO_4S$ 296.0956; Found 296.0934. Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74. Found: C, 57.06; H, 5.82; N, 4.66.

(*R*)-Ethyl 2-(*N*-(but-3-ynyl)-4-methylphenylsulfonamido)propanoate (**1k'**). Alkylation of *N*-tosyl-L-alanine ethyl ester[16] (504.1 mg, 1.86 mmol) was carried out according to the same procedure as described for **1j'** to give alkyne **1k'** (257.2 mg, 43%) as a colorless oil [eluent: hexane-AcOEt (19:1, v/v)]; $[\alpha]_D^{15}$ = –44.74 (*c* 1.1, $CHCl_3$); IR ν max 3284, 1739, 1342, 1156 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.71 (2H, d, *J* = 8.3 Hz), 7.29 (2H, d, *J* = 8.3 Hz), 4.62 (1H, q, *J* = 7.1 Hz), 4.01-3.91 (2H, m), 3.46 (1H, ddd, *J* = 15.3, 10.4, 5.2 Hz), 3.30 (1H, ddd, *J* = 15.3, 10.3, 5.8 Hz), 2.72 (1H, dddd, *J* = 16.5, 10.3, 5.2, 2.7 Hz), 2.53 (1H, dddd, *J* = 16.5, 10.4, 5.8, 2.7 Hz), 2.42 (3H, s), 2.00 (1H, t, *J* = 2.7 Hz), 1.44 (3H, d, *J* = 7.4 Hz), 1.12 (3H, t, *J* = 7.1 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 171.2, 143.5, 136.5, 129.4 (2), 127.3 (2), 81.1, 70.2, 61.3, 55.4, 44.4, 21.5, 21.4, 17.0, 13.9; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{22}NO_4S$ 324.1269; Found 324.1263.

2-(*N*-(But-3-yn-2-yl)-4-methylphenylsulfonamido)-*N*-methoxy-*N*-methylacetamide (**4e'**). Alkylation of 4-methylphenylsulfonamido-*N*-methoxy-*N*-methylacetamide[17] (205.40 mg, 0.75 mmol) was carried out according to the same procedure as described for **1j'** to give alkyne **4e'** (163.50 mg, 67%) as a colorless oil [eluent: hexane-AcOEt (1:1, v/v)]; IR ν max 1686, 1340, 1157 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.88 (2H, d, *J* = 8.3 Hz), 7.31 (2H, d, *J* = 8.3 Hz), 4.68 (1H, dq, *J* = 7.1, 2.3 Hz), 4.44 (1H, d, *J* = 18.0 Hz), 4.11 (1H, d, *J* = 18.0 Hz), 3.76 (3H, s), 3.22 (3H, s), 2.43 (3H, s), 2.22 (1H, d, *J* = 2.3 Hz), 1.39 (3H, d, *J* = 7.1 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 169.6, 143.5, 136.3, 129.4 (2), 127.8 (2), 81.2, 73.0, 61.3, 45.8, 44.1, 32.5, 21.6, 21.5; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{21}N_2O_4S$ 325.1222; Found 325.1245.

General procedure for bromination of alkynes with NBS and $AgNO_3$.[9a] **Methyl 2-(*N*-(3-bromoprop-2-ynyl)-4-methylphenylsulfonamido)acetate** (**1a**). To a solution of methyl 2-(4-methyl-*N*-(prop-2-ynyl)phenylsulfonamido)acetate and *N*-(prop-2-ynyl)-*N*-tosylglycine[18] (994.7 mg, 3.5 mmol) in acetone (15 mL) were added NBS (950.0 mg, 5.3 mmol) and $AgNO_3$ (136.1 mg, 0.8 mmol) at room temperature under Ar. After stirring for 40 min at the same temperature, the reaction was quenched with sat. $NaHCO_3$ aqueous solution. The volatile solvent was removed in vacuo, and the residue was dissolved in AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and removed in vacuo. The residue was purified by column

chromatography on silica gel using hexane-AcOEt-$CHCl_3$ (9:2:9, v/v) as eluent to give bromoalkyne **1a** (1.24 g, 97%) as a colorless solid; Mp 48–50 °C; IR ν max 1753, 1162 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.72 (2H, d, *J* = 8.0 Hz), 7.32 (2H, d, *J* = 8.0 Hz), 4.27 (2H, s), 4.06 (2H, s), 3.71 (3H, s), 2.44 (3H, s); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 168.8, 144.0, 135.6, 129.6 (2), 127.4 (2), 72.7, 52.4, 47.0, 45.8, 38.6, 21.6; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{15}BrNO_4S$ 359.9905; Found 359.9893. Anal. Calcd for $C_{13}H_{14}BrNO_4S$: C, 43.35; H, 3.92.; N, 3.89. Found: C, 43.35; H, 3.92; N, 3.81.

(*S*)-Ethyl 2-(*N*-(3-bromoprop-2-ynyl)-4-methylphenylsulfonamido)propanoate (**1d**). Bromination of ethyl (2*S*)-{*N*-(prop-2-ynyl)toluenesulfonamido}propanoate[9a] (2.12 g, 5.9 mmol) was carried out according to the same procedure as described for **1a** to give alkyne **1d** (2.66 g, 99%) as a colorless oil [eluent: hexane-AcOEt-$CHCl_3$ (2:1:2, v/v)]; $[\alpha]_D^{25}$ = –26.63 (*c* 1.1, $CHCl_3$); IR ν max 1736, 1348, 1159 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.76 (2H, d, *J* = 8.3 Hz), 7.30 (2H, d, *J* = 8.3 Hz), 4.63 (1H, q, *J* = 7.3 Hz), 4.28 (1H, d, *J* = 18.7 Hz), 4.14 (1H, d, *J* = 18.7 Hz), 4.05 (2H, q, *J* = 7.2 Hz), 2.42 (3H, s), 1.44 (3H, d, *J* = 7.3 Hz), 1.16 (3H, t, *J* = 7.2 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 170.9, 143.5, 136.7, 129.3 (2), 127.4 (2), 75.2, 61.3, 54.7, 44.2, 34.8, 21.4, 16.0, 13.8; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{19}BrNO_4S$ 388.0218; Found 388.0208.

(*S*)-Methyl 2-(*N*-(3-bromoprop-2-ynyl)-4-methylphenylsulfonamido)-3-phenylpropanoate (**1e**). Bromination of methyl (2*S*)-{*N*-(prop-2-ynyl)toluenesulfonamido-3- phenyl}propanoate[9a] (182.3 mg, 0.49 mmol) was carried out according to the same procedure as described for **1a** to give bromoalkyne **1e** (219.3 mg, 99%) as a colorless oil [eluent: hexane-AcOEt (3:1, v/v)]; $[\alpha]_D^{25}$ = –41.18 (*c* 1.0, $CHCl_3$); IR ν max 1740, 1160 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.56 (2H, d, *J* = 8.4 Hz), 7.30-7.16 (7H, m), 4.82 (1H, t, *J* = 7.7 Hz), 4.28 (1H, d, *J* = 18.7 Hz), 4.22 (1H, d, *J* = 18.7 Hz), 3.55 (3H, s), 3.30 (1H, dd, *J* = 14.0, 7.7 Hz), 2.95 (1H, dd, *J* = 14.0, 7.7 Hz), 2.40 (3H, s); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 170.4, 143.5, 136.4, 136.1, 129.1 (2), 129.1 (2), 128.4 (2), 127.5 (2), 126.7, 74.9, 60.5, 52.1, 44.6, 36.2, 34.9, 21.4; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{21}BrNO_4S$ 450.0374; Found 450.0380.

(*S*)-Methyl 2-(*N*-(3-bromoprop-2-ynyl)-4-methylphenylsulfonamido)-3-(*tert*-butyldimethylsilyloxy)propanoate (**1f**). Bromination of methyl (2*S*)-3-(*tert*-butyldimethylsilyloxy)-2-{*N*-(prop-2-ynyl)toluenesulfonamido}propanoate[9a] (1.0 g,

2.35 mmol) was carried out according to the same procedure as described for **1a** to give bromoalkyne **1f** (1.16 g, 98%) as a colorless solid [eluent: hexane-AcOEt (4:1, v/v)]; Mp 110–111 °C; $[\alpha]_D^{27}$ = –0.48 (*c* 1.1, $CHCl_3$); IR ν max 1753, 1352, 1162 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.74 (2H, d, *J* = 8.3 Hz), 7.29 (2H, d, *J* = 8.3 Hz), 4.66 (1H, dd, *J* = 5.1, 3.6 Hz), 4.37 (1H, d, *J* = 18.5 Hz), 4.29 (1H, d, *J* = 18.5 Hz), 4.07 (1H, dd, *J* = 10.6, 5.1 Hz), 4.01 (1H, dd, *J* = 10.6 , 3.6 Hz), 3.63 (3H, s), 2.42 (3H, s), 0.84 (9H, s), 0.03 (3H, s), 0.01 (3H, s); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 169.4, 143.6, 136.8, 129.4 (2), 127.5 (2), 76.2, 62.8, 60.6, 52.2, 43.0, 36.4, 25.5 (3), 21.5, 18.0, –5.8, –6.0; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{31}BrNO_5SSi$ 504.0875; Found 504.0899. Anal. Calcd for $C_{20}H_{30}BrNO_5SSi$: C, 47.61; H, 5.99; N, 2.78. Found: C, 47.53; H, 5.85. N, 2.77.

Methyl 3-(*N*-(3-bromoprop-2-ynyl)-4-methylphenylsulfonamido)propanoate (**1h**). Bromination of **1h'** (808.3 mg, 2.74 mmol) was carried out according to the same procedure as described for **1a** to give bromoalkyne **1h** (992.0 mg, 97%) as a colorless solid [eluent: hexane-AcOEt-$CHCl_3$ (9:2:9, v/v)]; Mp 70–72 °C; IR ν max 2216, 1737, 1348, 1161 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.73 (2H, d, *J* = 8.3 Hz), 7.33 (2H, d, *J* = 8.3 Hz), 4.17 (2H, s), 3.70 (3H, s), 3.45 (2H, t, *J* = 7.1 Hz), 2.68 (2H, t, *J* = 7.1 Hz), 2.44 (3H, s); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 171.4, 143.7, 134.9, 129.3 (2), 127.4 (2), 72.9, 51.6, 45.0, 42.7, 38.5, 33.5, 21.2; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{17}BrNO_4S$ 374.0061; Found 374.0086. Anal. Calcd for $C_{14}H_{16}BrNO_4S$: C, 44.93; H, 4.31; N, 3.74. Found: C, 44.65; H, 4.25; N, 3.69.

Methyl 3-(*N*-(3-bromoprop-2-ynyl)-4-methylphenylsulfonamido)-2-methylpropanoate (**1i**). Bromination of **1i'** (298.5 mg, 0.97 mmol) was carried out according to the same procedure as described for **1a** to give bromoalkyne **1i** (346.3 mg, 92%) as a colorless oil [eluent: hexane-AcOEt (2:1, v/v)]; IR ν max 1735, 1350, 1163 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.72 (2H, d, *J* = 8.3 Hz), 7.32 (2H, d, *J* = 8.3 Hz), 4.19 (1H, d, *J* = 18.6 Hz), 4.10 (1H, d, *J* = 18.6 Hz), 3.70 (3H, s), 3.36 (1H, dd, *J* = 14.1, 8.0 Hz), 3.19 (1H, dd, *J* = 14.1, 6.8 Hz), 2.91-2.82 (1H, m), 2.43 (3H, s), 1.22 (3H, d, *J* = 7.1 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 174.8, 143.7, 135.0, 129.4 (2), 127.6 (2), 72.8, 51.8, 49.4, 45.1, 38.9, 38.7, 21.4, 14.9; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{19}BrNO_4S$ 388.0218; Found 388.0199.

Methyl 2-(*N*-(4-bromobut-3-ynyl)-4-methylphenylsulfonamido)acetate (**1j**). Bromination of **1j'** (288.3 mg, 0.98 mmol) was carried out according to the same procedure as described for **1a**

to give bromoalkyne **1j** (363.3 mg, 99%) as a colorless solid [eluent: hexane-AcOEt (7:3, v/v)]; Mp 81–83 °C; IR ν max 1755, 1341, 1158 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.72 (2H, d, *J* = 8.3 Hz), 7.31 (2H, d, *J* = 8.3 Hz), 4.15 (2H, s), 3.65 (3H, s), 3.40 (2H, t, *J* = 7.2 Hz), 2.53 (2H, t, *J* = 7.2 Hz), 2.43 (3H, s); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 169.3, 143.7, 136.4, 129.6 (2), 127.3 (2), 76.9, 52.2, 48.9, 47.1, 40.5, 21.5, 20.4; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{17}BrNO_4S$ 374.0061; Found 374.0080. Anal. Calcd for $C_{14}H_{16}BrNO_4S$: C, 44.93; H, 4.31; N, 3.74. Found: C, 45.21; H, 4.49; N, 3.85.

(*R*)-Ethyl 2-(*N*-(4-bromobut-3-ynyl)-4-methylphenylsulfonamido)propanoate (1k). Bromination of **1k'** (247.1 mg, 0.77 mmol) was carried out according to the same procedure as described for **1a** to give bromoalkyne **1k** (283.7 mg, 92%) as a colorless oil [eluent: hexane-AcOEt (7:3, v/v)]; $[\alpha]_D^{16}$ = –42.12 (*c* 1.1, $CHCl_3$); IR ν max 1739, 1343, 1155 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.70 (2H, d, *J* = 8.2 Hz), 7.29 (2H, d, *J* = 8.2 Hz), 4.62 (1H, q, *J* = 7.3 Hz), 4.01-3.91 (2H, m), 3.45 (1H, ddd, *J* = 15.2, 10.1, 5.1 Hz), 3.45 (1H, ddd, *J* = 15.2, 9.9, 6.1 Hz), 2.73 (1H, ddd, *J* = 16.6, 9.9, 5.1 Hz), 2.57 (1H, ddd, *J* = 16.6, 10.1, 6.1 Hz), 2.42 (3H, s), 1.43 (3H, d, *J* = 7.4 Hz), 1.12 (3H, t, *J* = 7.3 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 171.2, 143.6, 136.5, 129.5 (2), 127.3 (2), 77.1, 61.3, 55.5, 44.1, 40.3, 22.5, 21.5, 17.0, 13.9; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{21}BrNO_4S$ 402.0374; Found 402.0355.

(*S*)-2-(*N*-(3-Bromoprop-2-ynyl)-4-methylphenylsulfonamido)-*N*-methoxy-*N*,3-dimethylbutanamide (4g). Bromination of **4g'** (508.9 mg, 1.44 mmol) was carried out according to the same procedure as described for **1a** to give bromoalkyne **4g** (377.0 mg, 61%) as a colorless solid [eluent: hexane-AcOEt (7:3, v/v)]; Mp 95–97 °C; $[\alpha]_D^{21}$ = –25.32 (*c* 0.9, $CHCl_3$); IR ν max 2967, 1657, 1336, 1158 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.77 (2H, d, *J* = 8.3 Hz), 7.28 (2H, d, *J* = 8.3 Hz), 4.73 (1H, d, *J* = 19.0 Hz), 4.69 (1H, d, *J* = 10.8 Hz), 4.28 (1H, d, *J* = 19.0 Hz), 3.81 (3H, s), 3.12 (3H, s), 2.42 (3H, s), 2.26-2.16 (1H, m), 0.90 (3H, d, *J* = 10.8 Hz), 0.89 (3H, d, *J* = 10.8 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 172.1, 143.5, 137.1, 129.3 (2), 127.8 (2), 76.2, 61.5, 59.1, 43.2, 34.4, 31.7, 29.3, 21.6, 20.1, 18.8; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{24}BrN_2O_4S$ 431.0639; Found 431.0652. Anal. Calcd for $C_{17}H_{23}BrN_2O_4S$: C, 47.34; H, 5.37; N, 6.49. Found: C, 47.42; H, 5.49. N, 6.49.

General procedure for chlorination of alkyne with NCS and AgOAc.[19] Methyl 2-(*N*-(3-chloroprop-2-ynyl)-4-methylphenylsulfonamido)acetate (1b). To a solution of

N-tosylglycine methyl ester (1.0 g, 3.56 mmol) in acetone (10.0 mL) were added AgOAc (735.1 mg, 4.40 mmol) and NCS (1.71 g, 12.75 mmol) at ambient temperature under Ar. After stirring for 2.5 h at reflux, the reaction was quenched with sat. $NaHCO_3$ aqueous solution. The volatile solvent was removed in vacuo, and the residue was dissolved in AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and removed under reduced pressure. The residue was purified by column chromatography on silica gel using hexane-AcOEt-$CHCl_3$ (4:2:4, v/v) as eluent to give chloroalkyne (**1b**) (890.60 mg, 80%) as a colorless oil.; IR ν max 1725, 1353, 1163 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.72 (2H, d, *J* = 8.0 Hz), 7.32 (2H, d, *J* = 8.0 Hz), 4.25 (2H, s), 4.07 (2H, s), 3.71 (3H, s), 2.44 (3H, s); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 168.8, 144.1, 135.7, 129.6 (2), 127.53(2), 64.2, 62.2, 52.4, 47.0, 37.9, 21.6; HRMS (ESI$^+$-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{13}H_{14}ClNO_4SNa$ 338.0230; Found 338.0225.

(*S*)-2-(*N*-(3-Chloroprop-2-ynyl)-4-methylphenylsulfonamido)-*N*-methoxy-*N*-methylpropanamide (**4a**). Chlorination of **4a'** (196.80 mg, 0.61 mmol) was carried out according to the same procedure as described for **1b** to give chloroalkyne **4a** (162.80 mg, 75%) as a pale yellow oil [eluent: hexane-AcOEt-$CHCl_3$ (1:2:2, v/v)]; $[\alpha]_D^{23}$ = –35.72 (*c* 1.0, $CHCl_3$); IR ν max 1670, 1159 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.76 (2H, d, *J* = 8.3 Hz), 7.30 (2H, d, *J* = 8.3 Hz), 5.06 (1H, q, *J* = 7.2 Hz), 4.49 (1H, d, *J* = 18.8 Hz), 4.40 (1H, d, *J* = 18.8 Hz), 3.78 (3H, s), 3.13 (3H, s), 2.43 (3H, s), 1.34 (3H, d, *J* = 7.2 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 171.9, 143.5, 136.9, 129.3 (2), 127.3 (2), 65.9, 61.7, 61.5, 50.5, 33.9, 31.7, 21.4, 15.8; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{20}ClN_2O_4S$ 359.0832; Found 359.0841.

(*S*)-2-(*N*-(3-Chloroprop-2-ynyl)-4-methylphenylsulfonamido)-*N*-methoxy-*N*-methyl-3-phenylpropanamide (**4b**). Chlorination of **4b'** (189.80 mg, 0.47 mmol) was carried out according to the same procedure as described for **4a** to give alkyne (**4b**) (168.00 mg, 82%) as a pale yellow oil [eluent: hexane-AcOEt (6:4, v/v)]; $[\alpha]_D^{18}$ = –57.14 (*c* 1.0, $CHCl_3$); IR ν max 1663, 1340, 1161 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.68 (2H, d, *J* = 8.1 Hz), 7.26-7.20 (5H, m), 7.15-7.12 (2H, m), 5.26 (1H, dd, *J* = 9.5, 5.7 Hz), 4.65 (1H, d, *J* = 18.8 Hz), 4.41 (1H, d, *J* = 18.8 Hz), 3.43 (3H, s), 3.24 (1H, dd, *J* = 13.2, 9.5 Hz), 3.02 (3H, s), 2.80 (1H, dd, *J* = 13.2, 5.7 Hz), 2.42 (3H, s); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 170.2, 143.5, 136.8, 136.4, 129.2 (3), 128.3 (2), 127.5 (2), 126.7, 65.6, 62.1, 61.3, 55.6, 36.3, 33.9, 31.6, 21.4; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{24}ClN_2O_4S$ 435.1145; Found 435.1155.

(*S*)-2-(*N*-(3-Chloroprop-2-ynyl)-4-methylphenylsulfonamido)-*N*-methoxy-*N*,4-dimethylpentanamide (**4c**). Chlorination of (*S*)-2-(*N*-(prop-2-ynyl)-4-methylphenylsulfonamido)-*N*-methoxy-*N*,4-dimethyl pentanamide[9a] (1.09 g, 3.09 mmol) was carried out according to the same procedure as described for **1b** to give chloroalkyne **4c** (1.14 g, 95%) as a pale yellow solid [eluent: hexane-AcOEt-$CHCl_3$ (3:1:1, v/v)]; Mp 75–76 °C; $[\alpha]_D^{19}$ = –31.55 (*c* 0.7, $CHCl_3$); IR ν max 1670, 1347, 1159 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.73 (2H, d, *J* = 8.3 Hz), 7.29 (2H, d, *J* = 8.3 Hz), 4.99-4.95 (1H, m), 4.60 (1H, d, *J* = 19.1 Hz), 4.41 (1H, d, *J* = 19.1 Hz), 3.78 (3H, s), 3.08 (3H, s), 2.42 (3H, s), 1.74-1.60 (2H, m), 1.46-1.39 (1H, m), 0.90 (3H, d, *J* = 6.6 Hz), 0.84 (3H, d, *J* = 6.5 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 172.6, 143.5, 136.3, 129.3 (2), 127.4 (2), 66.0, 61.5, 61.4, 53.1, 38.9, 34.0, 31.9, 24.6, 22.8, 21.5, 21.2; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{26}ClN_2O_4S$ 401.1302; Found 401.1287. Anal. Calcd for $C_{18}H_{25}ClN_2O_4S$: C, 53.92; H, 6.29; N, 6.99. Found: C, 53.91; H, 6.31. N, 6.90.

(*S*)-2-(*N*-(3-Chloroprop-2-ynyl)-4-methylphenylsulfonamido)-*N*-methoxy-*N*,3-dimethylbutanamide (**4d**). Chlorination of alkyne **4f'** (103.20 mg, 0.29 mmol) was carried out according to the same procedure as described for **1b** to give chloroalkyne **4d** (107.90 mg, 95%) as a colorless solid [eluent: hexane-AcOEt-$CHCl_3$ (4:2:4, v/v)]; Mp 74–75 °C; $[\alpha]_D^{19}$ = –24.16 (*c* 1.0, $CHCl_3$); IR ν max 3484, 1337, 1155 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.77 (2H, d, *J* = 8.3 Hz), 7.28 (2H, d, *J* = 8.3 Hz), 4.71 (1H, d, *J* = 18.9 Hz), 4.69 (1H, d, *J* = 10.6 Hz), 4.25 (1H, d, *J* = 18.9 Hz), 3.81 (3H, s), 3.12 (3H, s), 2.42 (3H, s), 2.26-2.16 (1H, m), 0.92 (3H, d, *J* = 6.6 Hz), 0.89 (3H, d, *J* = 6.7 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 171.9, 143.4, 137.0, 129.1 (2), 127.5 (2), 65.5, 61.4, 61.3, 59.0, 33.5, 31.5, 29.1, 21.4, 19.9, 18.7; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{24}ClN_2O_4S$ 387.1145; Found 387.1158. Anal. Calcd for $C_{17}H_{23}ClN_2O_4S$: C, 52.77; H, 5.99; N, 7.24. Found: C, 52.65; H, 5.95. N, 7.14.

2-(*N*-(4-Chlorobut-3-yn-2-yl)-4-methylphenylsulfonamido)-*N*-methoxy-*N*-methylacetamide (**4e**). Chlorination of **4e'** (155.70 mg, 0.48 mmol) was carried out according to the same procedure as described for **1b** to give chloroalkyne **4e** (70.60 mg, 41%) as a pale yellow oil [eluent: hexane-AcOEt-$CHCl_3$ (4:3:3, v/v)]; IR ν max 1687, 1343, 1159 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.86 (2H, d, *J* = 8.3 Hz), 7.32 (2H, d, *J* = 8.3 Hz), 4.68 (1H, q, *J* = 7.1 Hz), 4.41 (1H, d, *J* = 18.0 Hz), 4.02 (1H, d, *J* = 18.0 Hz), 3.77 (3H, s), 3.22 (3H, s), 2.43 (3H, s), 1.37 (3H, d, *J* = 7.1 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 169.5, 143.6, 136.1, 129.4 (2), 127.8 (2), 66.9, 63.1,

61.3, 46.3, 44.2, 32.5, 21.5, 21.4; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{20}ClN_2O_4S$ 359.0832; Found 359.0848.

General procedure for Iodination of alkynes with NIS and $AgNO_3$.[20] **Methyl 2-(*N*-(3-iodoprop-2-ynyl)-4-methylphenylsulfonamido)acetate** (**1c**). To a solution of methyl 2-(4-methyl-*N*-(prop-2-ynyl)phenylsulfonamido)acetate and *N*-(prop-2-ynyl)-*N*-tosylglycine[18] (49.9 mg, 0.18 mmol) in acetone (1 mL) were added NIS (60.9 mg, 0.27 mmol) and $AgNO_3$ (6.40 mg, 0.04 mmol) at room temperature under Ar. After stirring for 4 h at the same temperature, the reaction was quenched with sat. $NaHCO_3$ aqueous solution. The volatile solvent was removed in vacuo, and the residue was dissolved in AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and removed in vacuo. The residue was purified by column chromatography on silica gel using hexane-AcOEt (7:3, v/v) as eluent to give iodoalkyne **1c** (71.4 mg, 99%) as a colorless solid; Mp 112.7–113.1 °C; IR ν max 1750, 1349, 1161 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.71 (2H, d, *J* = 8.2 Hz), 7.33 (2H, d, *J* = 8.2 Hz), 4.39 (2H, s), 4.07 (2H, s), 3.72 (3H, s), 2.44 (3H, s); ^{13}C-NMR (CD_3CN; 100 MHz) δ 169.8, 145.4, 136.6, 130.7 (2), 128.4 (2), 87.1, 52.9, 48.5, 40.2, 21.5, 6.30; HRMS (ESI^+-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{15}INO_4S$ 407.9766; Found 407.9738. Anal. Calcd for $C_{13}H_{14}NO_4SI$: C, 38.34; H, 3.47.; N, 3.44. Found: C, 38.44; H, 3.53; N, 3.41.

General procedure for reduction with DIBAL-H and SmI_2-mediated cyclization. (*Z*)-4-(Bromomethylene)-1-tosylpyrrolidin-3-ol (**3a**). To a solution of ester **1a** (102.5 mg, 0.28 mmol) in toluene (4.7 mL) was added dropwise DIBAL-H (1.0 M in hexane solution, 0.37 mL) at −78 °C under Ar. The reaction mixture was stirred for 20 min at −78 °C under Ar. To the reaction mixture was added *i*PrOH (0.30 mL, 2.85 mmol) at −78 °C and the whole was stirred for 10 min at 0 °C. To the reaction mixture was added dropwise SmI_2 (0.2 M in THF, 7.0 mL) at 0 °C under Ar, and the whole was stirred for 10 min at 0 °C, and treated with sat. Rochelle salt aqueous solution to stir for 1h at ambient temperature. The reaction mixture was filtered through Celite, and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane-AcOEt-$CHCl_3$ (9:2:9, v/v) as eluent to give pyrrolidine **3a** (69.0 mg, 73%) as a colorless solid; Mp 132–134 °C; IR ν max 3502, 1343, 1163 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.71 (2H, d, *J* = 8.2 Hz), 7.35 (2H, d, *J* = 8.2 Hz), 6.23 (1H,

dd, *J* = 1.8, 1.8 Hz), 4.81-4.77 (1H, m), 3.93 (1H, dd, *J* = 13.8, 1.8 Hz), 3.75 (1H, dd, *J* = 13.8, 1.8 Hz), 3.49 (1H, dd, *J* = 11.0, 5.8 Hz), 3.35 (1H, dd, *J* = 11.0, 3.3 Hz), 2.44 (3H, s), 2.31 (1H, d, *J* = 4.5 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 144.2, 143.0, 131.8, 129.8 (2), 127.9 (2), 103.7, 71.3, 55.5, 51.3, 21.5; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{15}BrNO_3S$ 331.9955; Found 331.9962. Anal. Calcd for $C_{12}H_{14}BrNO_3S$: C, 43.38; H, 4.25; N, 4.22. Found: C, 43.18; H, 4.37; N, 4.13.

(*Z*)-4-(Chloromethylene)-1-tosylpyrrolidin-3-ol (**3b**). Reduction of ester **1b** (307.7 mg, 0.94 mmol), followed by radical cyclization of the resulting aldehyde was carried out according to the same procedure as described for **3a** to give pyrroldine **3b** (259.9 mg, 93%) as a white solid. [eluent: hexane-AcOEt (6:4, v/v)]; Mp 114.2–115.4 °C; IR ν max 3373, 1340, 1165 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.73 (2H, d, *J* = 8.3 Hz), 7.37 (2H, d, *J* = 8.3 Hz), 6.14 (1H, dd, *J* = 3.8, 1.8 Hz), 4.94-4.88 (1H, m), 3.98 (1H, dd, *J* = 14.0, 1.8 Hz), 3.83 (1H, dd, *J* = 14.0, 1.8 Hz), 3.49 (1H, dd, *J* = 10.9, 5.8 Hz), 3.35 (1H, dd, *J* = 10.9, 3.1 Hz), 2.47 (3H, s), 2.27 (1H, d, *J* = 4.6 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 144.2, 140.2, 131.8, 129.8 (2), 127.9 (2), 115.3, 69.6, 55.5, 50.2, 21.5; HRMS (ESI^+-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{12}H_{14}ClNO_3SNa$ 310.0281; Found 310.0288.

(*Z*)-4-(Iodomethylene)-1-tosylpyrrolidin-3-ol (***Z*-3c**). Reduction of ester **1c** (199.7 mg, 0.491 mmol), followed by radical cyclization of the resulting aldehyde was carried out according to the same procedure as described for **3a** to give crude [eluent: hexane-AcOEt (7:3, v/v)]. Furthermore, the mixture was purified by gel permeation chromatography using $CHCl_3$ as eluent to give pyrrolidine ***Z*-3c** (34.9 mg, 19%) as colorless solid and pyrrolidine ***E*-3c** (35.3 mg, 19%) as colorless oil; Mp 147.5–148.3 °C; IR ν max 3407, 1344, 1163 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.71 (2H, d, *J* = 8.1 Hz), 7.35 (2H, d, *J* = 8.1 Hz), 6.30 (1H, dd, *J* = 1.8, 1.7 Hz), 4.63-4.57 (1H, m), 3.95 (1H, dd, *J* = 14.2, 1.7 Hz), 3.78 (1H, dd, *J* = 14.2, 1.8 Hz), 3.47 (1H, dd, *J* = 11.0, 5.6 Hz), 3.41 (1H, dd, *J* = 11.0, 3.0 Hz), 2.44 (3H, s), 2.34 (1H, d, *J* = 5.0 Hz); ^{13}C-NMR ($CDCl_3$; 150 MHz) δ 148.7, 144.2, 132.1, 129.8 (2), 128.0 (2), 75.5, 74.2, 55.4, 52.4, 21.6; HRMS (ESI^+-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{15}INO_3S$ 379.9817; Found 379.9789 Anal. Calcd for $C_{12}H_{14}INO_3S$: C, 38.01; H, 3.72; N, 3.69. Found: C, 38.21; H, 3.79; N, 3.53.

(*E*)-4-(Iodomethylene)-1-tosylpyrrolidin-3-ol (***E*-3c**). IR ν max 3417, 1343, 1162 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.74 (2H, d, *J* = 8.1 Hz), 7.37 (2H, d, *J* = 8.1 Hz), 6.49 (1H, dd, *J*

= 2.7, 1.7 Hz), 4.60-4.51 (1H, m), 3.83 (1H, dd, *J* = 15.6, 1.7 Hz), 3.74 (1H, dd, *J* = 15.6, 2.7 Hz), 3.61 (1H, dd, *J* = 10.2, 5.9 Hz), 3.23 (1H, dd, *J* = 10.2, 5.1 Hz), 2.45 (3H, s), 1.96 (1H, d, *J* = 7.8 Hz); ^{13}C-NMR ($CDCl_3$; 150 MHz) δ 150.5, 144.2, 132.2, 129.9 (2), 127.9 (2), 76.3, 72.6, 56.2, 55.1, 21.6; HRMS (ESI$^+$-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{15}INO_3S$ 379.9817; Found 379.9794.

(2*R*, 3*R*, *Z*)-4-(Bromomethylene)-2- methyl-1-tosylpyrrolidin-3-ol (**3d**). Reduction of ester **1d** (517.0 mg, 1.33 mmol), followed by radical cyclization of the corresponding aldehyde was carried out according to the same procedure as described for **3a** to give pyrrolidine **3d** (356.4 mg, 73%) as a colorless solid [eluent: hexane-AcOEt-$CHCl_3$ (9:2:9, v/v)]; Mp 101–102 °C; $[\alpha]_D^{22}$ = 27.21 (*c* 1.1, $CHCl_3$); IR ν max 3491, 1339, 1163 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.75 (2H, d, *J* = 8.3 Hz), 7.31 (2H, d, *J* = 8.3 Hz), 6.28-6.27 (1H, m), 4.44 (1H, ddd, *J* = 3.9, 2.5, 1.7 Hz), 4.03 (1H, dd, *J* = 14.3, 1.6 Hz), 3.91 (1H, ddd, *J* = 14.3, 2.5, 1.0 Hz), 3.82 (1H, dq, *J* = 6.8, 1.7 Hz), 2.42 (3H, s), 1.78 (1H, d, *J* = 3.9 Hz), 1.28 (3H, d, *J* = 6.8 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 143.8, 142.6, 134.4, 129.6 (2), 127.7 (2), 104.0, 77.7, 63.7, 50.3, 21.5, 19.6; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{17}BrNO_3S$ 346.0112; Found: 346.0132. Anal. Calcd for $C_{13}H_{16}BrNO_3S$: C, 45.10; H, 4.66; N, 4.05. Found: C, 45.03; H, 4.60. N, 3.96.

(2*R*, 3*R*, *Z*)-2-Benzyl-4-(bromomethylene)-1-tosylpyrrolidin-3-ol (**3e**). Reduction of ester **1e** (100.0 mg, 0.22 mmol), followed by radical cyclization of the corresponding aldehyde was carried out according to the same procedure as described for **3a** to give pyrrolidine **3e** (58.1 mg, 62%) as a colorless oil [eluent: hexane-AcOEt (7:3, v/v)]; $[\alpha]_D^{24}$ = 44.49 (*c* 0.9, $CHCl_3$); IR ν max 3484, 1339, 1161, 1094 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.74 (2H, d, *J* = 8.3 Hz), 7.32-7.21 (7H, m), 6.12 (1H, br s), 4.59 (1H, br s), 4.08 (1H, dd, *J* = 9.5, 4.3 Hz), 3.93 (1H, dd, *J* = 14.2, 2.1 Hz), 3.88 (1H, dd, *J* = 14.2, 1.6 Hz), 3.07 (1H, dd, *J* = 13.7, 4.3 Hz), 2.68 (1H, dd, *J* = 13.7, 9.5 Hz), 2.40 (3H, s), 1.63 (1H, br s); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 143.8, 142.6, 136.8, 129.7 (2), 129.6 (2), 128.6 (2), 127.7 (2), 126.8, 103.8, 74.7, 69.4, 50.3, 40.5, 21.6; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{21}BrNO_3S$ 422.0425; Found 422.0404.

(2*R*, 3*R*, *Z*)-4-(Bromomethylene)-2-((*tert*-butyldimethylsilyloxy)methyl)-1-tosylpyrrolidin-3-ol (**3f**). Reduction of ester **1f** (100.2 mg, 0.20 mmol), followed by radical cyclization of the resulting aldehyde was carried out according to the same procedure as described for **3a** to give pyrrolidine **3f** (73.7 mg, 78%) as a colorless solid [eluent: hexane-AcOEt (3:2, v/v)]; Mp 103–104 °C; $[\alpha]_D^{26}$ = 29.41 (*c* 0.5, $CHCl_3$); IR ν max 3502, 2954, 1340, 1163,

1094 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.76 (2H, d, *J* = 8.3 Hz), 7.31 (2H, d, *J* = 8.3 Hz), 6.18 (1H, dd, *J* = 2.3, 1.7 Hz), 4.80 (1H, d, *J* = 3.4 Hz), 4.03 (1H, dd, *J* = 14.1, 1.7 Hz), 3.97 (1H, dd, *J* = 14.1, 2.3 Hz), 3.86 (2H, m), 3.54 (1H, dt, *J* = 8.4, 3.4 Hz), 2.42 (3H, s), 1.54 (1H, d, *J* = 3.4 Hz), 0.87 (9H, s), 0.06 (3H, s), 0.05 (3H, s); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 143.8, 143.5, 134.5, 129.6 (2), 127.7 (2), 103.0, 74.6, 69.0, 64.5, 51.3, 25.8 (3), 21.6, 18.1, –5.5, –5.6; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{31}BrNO_4SSi$ 476.0926; Found 476.0919. Anal. Calcd for $C_{19}H_{30}BrNO_4SSi$: C, 47.89; H, 6.35; N, 2.94. Found: C, 47.59; H, 6.08. N, 2.90.

(2*R*, 3*R*, *Z*)-4-(Bromomethylene)-2-isopropyl-1-tosylpyrrolidin-3-ol (**3g**). To a solution of Weinreb amide **4g** (98.0 mg, 0.23 mmol) in toluene (3.9 mL) was added dropwise DIBAL-H (1.0 M in hexane, 0.35 mL) at 0 °C under Ar. After stirring for 20 min at 0 °C under Ar, to the reaction mixture was added MeOH (0.28 mL, 6.9 mmol) at 0 °C, and the whole was stirred for 10 min at 0 °C. To the reaction mixture was added dropwise SmI_2 (0.2 M in THF, 5.8 mL) at 0 °C under Ar. After stirring for 10 min at 0 °C, the reaction was quenched with sat. Rochelle salt aqueous solution and stirred for further 1 h at ambient temperature. The reaction mixture was filtered through Celite, and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane-AcOEt (7:3, v/v) as eluent to give pyrrolidine **3g** (58.0 mg, 69%) as a colorless solid; Mp 128–130 °C; $[\alpha]_D^{18}$ = 28.25 (*c* 1.1, $CHCl_3$); IR ν max 3491, 1339, 1163 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.77 (2H, d, *J* = 8.3 Hz), 7.30 (2H, d, *J* = 8.3 Hz), 6.17 (1H, br s), 4.61 (1H, d, *J* = 3.3 Hz), 4.01 (1H, dd, *J* = 15.0, 1.6 Hz), 3.96 (1H, dd, *J* = 15.0, 1.6 Hz), 3.69 (1H, d, *J* = 6.2 Hz), 2.41 (3H, s), 1.98-1.86 (1H, m), 1.60 (1H, br s), 1.00 (3H, d, *J* = 6.9 Hz), 0.90 (3H, d, *J* = 6.8 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 144.3, 143.8, 134.5, 129.6 (2), 128.0 (2), 102.9, 73.9, 73.8, 50.9, 31.6, 21.6, 19.3, 17.9; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{21}BrNO_3S$ 374.0425; Found 374.0402. Anal. Calcd for $C_{15}H_{20}BrNO_3S$: C, 48.13; H, 5.39; N, 3.74. Found: C, 47.93; H, 5.45. N, 3.74.

(*Z*)-3-(Bromomethylene)-1-tosylpiperidin-4-ol (**3h**). Reduction of ester **1h** (111.3 mg, 0.30 mmol), followed by radical cyclization of the resulting aldehyde was carried out according to the same procedure as described for **3a** to give piperidine **3h** (78.1 mg, 76%) as a colorless oil [eluent: hexane-AcOEt-$CHCl_3$ (9:2:9, v/v)]; IR ν max 3494, 1348, 1332, 1164 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.65 (2H, d, *J* = 8.3 Hz), 7.33 (2H, d, *J* = 8.3 Hz), 6.29 (1H, d, *J* = 1.8 Hz),

4.91 (1H, br s), 4.10 (1H, dd, *J* = 12.7, 1.8 Hz), 3.64 (1H, ddd, *J* = 12.2, 4.6, 2.3 Hz), 3.30 (1H, dd, *J* = 12.7, 1.8 Hz), 2.84(1H, dt, *J* = 12.2, 3.1 Hz), 2.44 (3H, s), 1.94-1.78 (2H, m), 1.60 (1H, br s); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 143.8, 138.0, 133.1, 129.7 (2), 127.6 (2), 105.6, 64.1, 48.1, 40.6, 31.5, 21.5; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{17}BrNO_3S$ 346.0112; Found 346.0107.

(4*R, 5*R**, Z)-3-(Bromomethylene)-5-methyl-1-tosylpiperidin-4-ol** (***anti*-3i**) **(Major product).** Reduction of ester **2i** (111.3 mg, 0.28 mmol), followed by radical cyclization of the resulting aldehyde was carried out according to the same procedure as described for **3a** to give piperidine **3i** (75.0 mg, 73%, *anti*:*syn* = 68:32) as a colorless oil [eluent: hexane-AcOEt (3:2, v/v)]; IR ν max 3490, 1347, 1165 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.61 (2H, d, *J* = 8.3 Hz), 7.31 (2H, d, *J* = 8.3 Hz), 6.38 (1H, d, *J* = 1.5 Hz), 4.59 (1H, d, *J* = 2.8 Hz), 4.00 (1H, dd, *J* = 12.2, 1.5 Hz), 3.34 (1H, dd, *J* = 11.5, 1.8 Hz), 3.19 (1H, dd, *J* = 12.2, 1.6 Hz), 2.89 (1H, dd, *J* = 11.5, 2.9 Hz), 2.42 (3H, s), 2.09-2.01 (1H, m), 1.94 (1H, br s), 1.00 (3H, d, *J* = 7.1 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 143.8, 136.6, 133.1, 129.8 (2), 127.6 (2), 107.7, 69.3, 48.2, 46.3, 35.2, 21.6, 14.2; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{19}BrNO_3S$ 360.0268; Found 360.0258.

(4*S, 5*R**, *Z*)-3-(Bromomethylene)-5-methyl-1-tosylpiperidin-4-ol** (***syn*-3i**) **(Minor product).** IR ν max 3507, 1337, 1164, 1095 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.65 (2H, d, *J* = 8.2 Hz), 7.33 (2H, d, *J* = 8.2 Hz), 6.28 (1H, d, *J* = 1.4 Hz), 4.65 (1H, d, *J* = 2.1 Hz), 4.07 (1H, d, *J* = 12.6 Hz), 3.48 (1H, dd, *J* = 11.7, 1.4 Hz), 3.25 (1H, dd, *J* = 12.6, 1.5 Hz), 2.51 (1H, t, *J* = 11.7 Hz), 2.44 (3H, s), 1.93-1.84 (1H, m), 1.25 (1H, br s), 1.01 (3H, d, *J* = 6.9 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 143.8, 138.7, 133.3, 129.8 (2), 127.7 (2), 105.6, 68.4, 47.5, 46.4, 35.3, 21.6, 14.3; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{19}BrNO_3S$ 360.0268; Found 360.0256.

(*Z*)-4-(Bromomethylene)-1-tosylpiperidin-3-ol (**3j**). Reduction of ester **2j** (99.9 mg, 0.27 mmol), followed by radical cyclization of the resulting aldehyde was carried out according to the same procedure as described for **3a** to give piperidine **3j** (74.1 mg, 80%) as a colorless oil [eluent: hexane-AcOEt-$CHCl_3$ (9:2:9, v/v)]; IR ν max 3493, 1335, 1164 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.65 (2H, d, *J* = 8.0 Hz), 7.33 (2H, d, *J* = 8.0 Hz), 6.02 (1H, s), 4.86 (1H, s), 3.98-3.87 (2H, m), 2.80-2.67 (2H, m), 2.66 (1H, br s), 2.43 (3H, s), 2.31-2.24 (2H, m); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 143.9, 139.6, 132.8, 129.7 (2), 127.5 (2), 102.7, 65.4, 52.5, 46.9, 30.2, 21.5;

HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{17}BrNO_3S$ 346.0112; Found 346.0111.

(2*S*, 3*R*, *Z*)-4-(Bromomethylene)-2-methyl-1-tosylpiperidin-3-ol (**3k**). Reduction of ester **1k** (101.4 mg, 0.25 mmol), followed by radical cyclization of the resulting aldehyde was carried out according to the same procedure as described for **3a** to give piperidine **3k** (21.2 mg, 23%) as a colorless oil [eluent: hexane-AcOEt (4:1, v/v)]; $[\alpha]_D^{16}$ = 35.04 (*c* 0.4, $CHCl_3$); IR ν max 3500, 1321, 1155 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.74 (2H, d, *J* = 8.3 Hz), 7.30 (2H, d, *J* = 8.3 Hz), 6.19 (1H, d, *J* = 2.1 Hz), 4.61 (1H, br s), 4.30 (1H, dq, *J* = 7.0, 2.2 Hz), 3.82 (1H, dddd, *J* = 12.8, 5.6, 2.1, 1.1 Hz), 2.94 (1H, dt, *J* = 12.8, 3.2 Hz), 2.64 (1H, dddd, *J* = 14.5, 12.8, 5.6, 2.1 Hz), 2.55 (1H, br s), 2.42 (3H, s), 2.15 (1H, ddd, *J* = 14.5, 3.2, 1.1 Hz), 0.90 (3H, d, *J* = 6.8 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 143.5, 138.4, 137.3, 129.7 (2), 127.1 (2), 104.5, 69.9, 55.6, 40.4, 30.3, 21.5, 12.8; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{19}BrNO_3S$ 360.0268; Found 360.0298.

(2*R*, 3*R*, *Z*)-4-(Chloromethylene)-2-methyl-1-tosylpyrrolidin-3-ol (**6a**). To a solution of amide **4a** (160.00 mg, 0.45 mmol) in toluene (7.4 mL) was added dropwise DIBAL-H (1.0M in hexane, 0.54 mL) at 0 °C under Ar. After stirring for 20 min at 0 °C under Ar, to the reaction mixture was added MeOH (0.54 mL, 13.38 mmol) at 0 °C, and the whole was stirred for 10 min at 0 °C. To the reaction mixture was added dropwise SmI_2 (0.2M in THF, 11.15 mL) at 0 °C under Ar. After stirring for 10 min at 0 °C, the reaction was quenched with sat. Rochelle salt aqueous solution and the resulting mixture were stirred for 1 h at room temperature. The reaction mixture was filtered through Celite, and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane-AcOEt-$CHCl_3$ (3:1:1, v/v) as eluent to give pyrrolidine **6a** (78.20 mg, 58%) as a colorless oil; $[\alpha]_D^{18}$ = 35.97 (*c* 0.8, $CHCl_3$); IR ν max 3481, 1338, 1155, 1093 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.74 (2H, d, *J* = 8.3 Hz), 7.31 (2H, d, *J* = 8.3 Hz), 6.16 (1H, br s), 4.51 (1H, br s), 4.04 (1H, d, *J* = 14.1 Hz), 3.96 (1H, d, *J* = 14.1 Hz), 3.81 (1H, q, *J* = 6.8 Hz), 2.42 (3H, s), 1.70 (1H, d, J = 4.0 Hz), 1.26 (3H, d, *J* = 6.8 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 143.7, 139.6, 134.3, 129.6 (2), 127.7 (2), 115.7, 75.6, 63.9, 49.3, 21.5, 19.5; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{17}ClNO_3S$ 302.0617; Found 302.0625.

(2*R*, 3*R*, *Z*)-2-Benzyl-4-(chloromethylene)-1-tosylpyrrolidin-3-ol (**6b**). Reduction of amide

4b (152.40 mg, 0.35 mmol), followed by radical cyclization of the resulting aldehyde was carried out according to the same procedure as described for **6a** to give pyrrolidine **6b** (53.50 mg, 40%) as a colorless oil [eluent: hexane-AcOEt-$CHCl_3$ (4:3:3, v/v)]; $[\alpha]_D^{24}$ = 52.11 (*c* 0.5, $CHCl_3$); IR ν max 3485, 1338, 1156, 1093 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.75 (2H, d, *J* = 8.3 Hz), 7.32-7.21 (7H, m), 6.01 (1H, br s), 4.67 (1H, d, *J* = 4.0 Hz), 4.07 (1H, dd, *J* = 9.4, 4.3 Hz), 4.00 (1H, dd, *J* = 14.3, 2.3 Hz), 3.93 (1H, dd, *J* = 14.3, 1.6 Hz), 3.08 (1H, dd, *J* = 13.7, 4.3 Hz), 2.68 (1H, dd, *J* = 13.7, 9.4 Hz), 2.41 (3H, s), 1.45 (1H, d, *J* = 4.0 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 143.7, 139.5, 136.7, 134.5, 129.6 (2), 129.5 (2), 128.5 (2), 127.6 (2), 126.7, 115.3, 72.5, 69.4, 49.3, 40.4, 21.5; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{21}ClNO_3S$ 378.0930; Found 378.0915.

(2*S*, 3*R*, *Z*)-4-(Chloromethylene)-2-isobutyl-1-tosylpyrrolidin-3-ol (**6c**). Reduction of amide **4c** (52.70 mg, 0.13 mmol), followed by radical cyclization of the resulting aldehyde was carried out according to the same procedure as described for **6a** to give pyrrolidine **6c** (34.8 mg, 77%) as a colorless solid [eluent: hexane-AcOEt-$CHCl_3$ (3:1:1, v/v)]; Mp 88–89 °C; $[\alpha]_D^{19}$ = 30.87 (*c* 1.0, $CHCl_3$); IR ν max 1337, 1156, 1093 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.77 (2H, d, *J* = 8.3 Hz), 7.31 (2H, d, *J* = 8.3 Hz), 6.13 (1H, br s), 4.56 (1H, d, *J* = 4.8 Hz), 4.08 (1H, dd, *J* = 15.1, 2.3 Hz), 3.96 (1H, dd, *J* = 15.1, 1.7 Hz), 3.92 (1H, t, *J* = 7.6 Hz), 2.42 (3H, s), 1.79-1.69 (1H, m), 1.66 (1H, d, *J* = 4.8 Hz), 1.42 (1H, ddd, *J* = 14.1, 7.6, 7.6 Hz), 1.22 (1H, ddd, *J* = 14.1, 7.6, 6.9 Hz), 0.96 (3H, d, *J* = 7.6 Hz), 0.94 (3H, d, *J* = 6.9 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 143.7, 140.5, 134.7, 129.5 (2), 127.8 (2), 115.5, 74.2, 66.8, 48.8, 42.3, 24.8, 22.6, 22.4, 21.5; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{23}ClNO_3S$ 344.1087; Found 344.1061. Anal. Calcd for $C_{16}H_{22}ClNO_3S$: C, 55.89; H, 6.45; N, 4.07. Found: C, 55.86; H, 6.56. N, 4.02.

(2*R*, 3*R*, *Z*)-4-(Chloromethylene)-2-isopropyl-1-tosylpyrrolidin-3-ol (**6d**). Reduction of amide **4d** (81.7 mg, 0.21 mmol), followed by radical cyclization of the resulting aldehyde was carried out according to the same procedure as described for **6a** to give pyrrolidine **6d** (50.0 mg, 72%) as a colorless solid [eluent: hexane-AcOEt-$CHCl_3$ (2:1:1, v/v)]; Mp 114–115 °C; $[\alpha]_D^{19}$ = 52.90 (*c* 0.4, $CHCl_3$); IR ν max 3484, 1337, 1155 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.77 (2H, d, *J* = 8.3 Hz), 7.31 (2H, d, *J* = 8.3 Hz), 6.06 (1H, dd, *J* = 2.4, 1.7 Hz), 4.69 (1H, d, *J* = 4.2 Hz), 4.07 (1H, dd, *J* = 14.9, 2.4 Hz), 4.00 (1H, dd, *J* = 14.9, 1.7 Hz), 3.68 (1H, d, *J* = 6.2 Hz), 2.42 (3H, s), 1.98-1.86 (1H, m), 1.51 (1H, d, *J* = 4.0 Hz), 1.01 (3H, d, *J* = 6.9 Hz), 0.90 (3H, d, *J* = 6.8

Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 143.7, 141.3, 134.4, 129.5 (2), 128.0 (2), 114.6, 74.0, 71.7, 50.0, 31.5, 21.5, 19.3, 17.8; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{21}ClNO_3S$ 330.0930; Found 330.0937. Anal. Calcd for $C_{15}H_{20}ClNO_3S$: C, 54.62; H, 6.11; N, 4.25. Found: C, 54.52; H, 6.12. N, 4.18.

(3*R, 5*R**, *Z*)-4-(Chloromethylene)-5-methyl-1-tosyl pyrrolidin-3-ol** (***anti*-6e**) **and (3*S**, 5*R**, Z)-4- (chloromethylene)-5-methyl-1-tosylpyrrolidin-3-ol** (***syn*-6e**). Reduction of amide **4e** (66.70 mg, 0.19 mmol), followed by radical cyclization of the resulting aldehyde was carried out according to the same procedure as described for **6a** to give pyrrolidine **6e** (40.5 mg, 72%, *anti* : *syn* = 1:1) as a colorless oil [eluent: hexane-AcOEt-$CHCl_3$ (4:3:3, v/v)]; IR ν max 3503, 1341, 1161 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.76 (1H, d, *J* = 8.3 Hz), 7.69 (1H, d, *J* = 8.3 Hz), 7.32 (1H, d, *J* = 8.3 Hz), 7.31 (1H, d, *J* = 8.3 Hz), 6.04 (0.5H, dd, *J* = 2.1, 1.5 Hz), 6.03 (0.5H, dd, *J* = 1.6, 1.6 Hz), 4.90-4.87 (0.5H, m), 4.72 (0.5H, dddd, *J* = 6.1, 4.5, 2.9, 1.5 Hz), 4.33-4.27 (0.5H, m), 4.18 (0.5H, dq, *J* = 6.5, 1.5 Hz), 3.65 (0.5H, dd, *J* = 12.6, 5.0 Hz), 3.56 (0.5H, dd, *J* = 11.7, 2.9 Hz), 3.51 (0.5H, dd, *J* = 12.6, 2.2 Hz), 3.45 (0.5H, dd, *J* = 11.7, 6.1 Hz), 2.44 (1.5H, s), 2.43 (1.5H, s), 2.18 (0.5H, d, *J* = 4.0 Hz), 1.84 (0.5H, d, *J* = 4.5 Hz), 1.54 (1.5H, d, *J* = 7.3 Hz), 1.43 (1.5H, d, *J* = 6.5 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 146.8, 146.3, 144.0, 143.8, 134.3, 133.3, 129.8 (2), 129.6 (2), 127.7 (2), 127.6 (2), 115.8, 115.5, 69.5, 68.8, 58.5, 57.1, 55.1, 54.6, 23.8 (2), 21.5, 21.4; HRMS (CI, magnetic sector) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{17}ClNO_3S$ 302.0617; Found 302.0620.

(*Z*)-4-Benzylidene-1-tosylpyrrolidin-3-ol (***Z*-7**). To a flask were added bromoalkene **3a** (21.6 mg, 65.1 μmol), phenylboronic acid (24.3 mg, 0.199 mmol), K_2CO_3 (28.1 mg, 0.204 mmol), and $Pd(PPh_3)_4$ (23.4 mg, 20.2 μmol). After the flask was flashed with Ar, MeOH (1 mL) was added to the reaction mixture at ambient temperature. After stirring for 1.25 h at reflux, the reaction mixture was diluted with AcOEt, and washed with 1M NaOH aqueous solution. The aqueous layer was further extracted with AcOEt (×2). The combined organic layer was washed with brine, and volatile solvent was removed in vacuo. The residue was purified by column chromatography on silica gel using hexane-AcOEt (7:3, v/v) as eluent to give benzylidene **7** (15.6 mg, 73%) as a yellow solid. Mp 125.5–126.1 °C; IR ν max 3497, 1342, 1164 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.75 (2H, d, *J* = 8.3 Hz), 7.43 (2H, d, *J* = 7.3 Hz), 7.35 (2H, d, *J* = 8.3 Hz), 7.33 (2H, d, *J* = 8.3 Hz), 7.27 (1H, t, *J* = 7.3 Hz), 6.48 (1H, s), 4.73 (1H, dd, *J* = 7.5, 4.4 Hz), 4.28 (1H, d, *J* = 14.4

Hz), 3.76 (1H, d, *J* = 14.4 Hz) 3.64 (1H, d, *J* = 10.9 Hz), 3.15 (1H, dd, *J* = 10.9, 4.4 Hz), 2.44 (3H, s), 2.23 (1H, d, *J* = 7.5 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 144.0, 137.9, 135.4, 132.2, 129.8 (2), 128.6 (2), 128.5 (2), 128.0 (2), 127.9, 127.6, 69.6, 57.4, 51.9, 21.6; HRMS (ESI$^+$-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{19}NO_3SNa$ 352.0983; Found: 352.0993. Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.37; H, 5.85; N, 4.13.

(*Z*)-4-(3-Phenylprop-2-yn-1-ylidene)-1-tosylpyrrolidin-3-ol (**8**). To a solution of bromoalkene **3a** (30 mg, 0.09 mmol) and phenylacetylene (19.8 μL, 0.181 mmol) in degassed Et_3N (4 mL) were added $Pd(PPh_3)_2Cl_2$ (14.04 mg, 0.02 mmol) and CuI (7.6 mg, 0.04 mmol) at ambient temperature under Ar. After stirring for 24 h at 60 °C, the reaction mixture was cooled to room temperature. The volatile solvent was removed in vacuo, and the residue was treated with sat. NH_4Cl aqueous solution. The mixture was extracted with AcOEt, and the extract was dried over Na_2SO_4, and removed to leave a residue, which was purified by column chromatography on silica gel using hexane-AcOEt-$CHCl_3$ (17:6:17) as eluent to give phenylalkyne **8** (27.9 mg, 87%) as a pale yellow solid. Mp 159.2–160.8 °C; IR ν max 3450, 1345, 1159 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.72 (2H, d, *J* = 8.2 Hz), 7.41-7.39 (2H, m), 7.35 (2H, d, *J* = 8.0 Hz), 7.33-7.31 (3H, m), 5.78 (1H, dd, *J* = 4.0, 2.0 Hz), 4.99-4.96 (1H, m), 4.03 (1H, ddd, *J* = 15.4, 4.0, 2.0 Hz), 3.93 (1H, dd , *J* = 15.4, 2.0 Hz), 3.55 (1H, dd, *J* = 10.4, 6.0 Hz), 3.29 (1H, dd, *J* = 10.4, 4.0 Hz), 2.52 (1H, d, *J* = 3.6 Hz), 2.44 (3H, s); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 151.4, 144.2, 132.2, 131.6 (2), 130.0 (2), 129.0, 128.6 (2), 128.1 (2), 122.4, 106.0, 96.4, 84.1, 70.8, 55.3, 51.4, 21.7; HRMS (ESI$^+$-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{19}NO_3SNa$: 376.09833; Found: 376.0983. Anal. Calcd for $C_{20}H_{19}NO_3S$: C, 67.97; H, 5.42; N, 3.96. Found: C, 67.76; H, 5.52; N, 3.84.

Methyl 2-(4-methyl-*N*-(3-phenylprop-2-ynyl)phenylsulfonamido)acetate[21] (**1l**)**.** To a solution of *N*-tosylglycine methyl ester[9a] (599.2 mg, 2.47 mmol), 3-phenyl-2-propyn-1-ol (310.1 mg, 2.35 mmol), and Ph_3P (646.1 mg, 2.47 mmol) in THF (11.0 mL) was added DIAD (0.69 mL, 3.52 mmol) at ambient temperature. After stirring for 2 h at the same temperature, the volatile solvent was removed in vacuo. The residue was purified by column chromatography on silica gel using hexane-AcOEt-$CHCl_3$ (19:2:19, v/v) as eluent to give alkyne **1l** (691 mg, 82%) as a colorless solid. Mp 68.4–69.9 °C; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.77 (2H, d, *J* = 8.4 Hz), 7.33-7.23 (5H, m), 7.15-7.12 (2H, m), 4.48 (2H, s), 4.16 (2H, s), 3.72 (3H, s), 2.37 (3H, s); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 168.8, 143.8, 135.8, 131.4 (2), 129.5 (2), 128.5, 128.1 (2), 127.5

(2), 121.8, 86.0, 81.2, 52.2, 46.9, 38.3, 21.3.

(*E*)-4-Benzylidene-1-tosylpyrrolidin-3-ol (***E*-7**). Reduction of ester **8** (99.2 mg, 0.28 mmol), followed by radical cyclization of the resulting aldehyde was carried out according to the same procedure as described for **3a** to give pyrrolidine ***Z*-7** (9.8 mg, 11%) as a colorless solid [eluent: hexane-AcOEt (65:35, v/v)] and ***E*-7** (51.5 mg, 56%) as a colorless solid [eluent: hexane-AcOEt (65:35, v/v)]; Mp 124.0–124.8 °C; IR ν max 3498, 1341, 1165 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 7.74 (2H, d, *J* = 8.0 Hz), 7.42-7.28 (5H, m), 7.18 (2H, d, *J* = 7.5 Hz), 6.60 (1H, s), 4.70 (1H, d, *J* = 7.0 Hz), 4.24 (1H, d, *J* = 15.1 Hz), 4.13 (1H, d, *J* = 15.1 Hz), 3.49 (1H, d, *J* = 10.2 Hz), 3.19 (1H, d, *J* = 10.2 Hz), 2.42 (3H, s), 1.89 (1H, d, *J* = 7.0 Hz); ^{13}C-NMR ($CDCl_3$; 100 MHz) δ 143.9, 138.4, 135.6, 132.6, 129.8 (2), 128.7 (2), 128.4 (2), 127.8, 127.8 (2), 126.0, 73.5, 54.3, 49.5, 21.5; HRMS (ESI$^+$-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{19}NO_3SNa$ 352.0983; Found: 352.0967. Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.58; H, 5.89; N, 4.20.

ASSOCIATED CONTENT

AUTOHOR INFORMATION

Corresponding Author

E-mail:takakazu@hoshi.ac.jp

ORCID

Kazunori Takahashi: 0000-0001-5418-0586

Notes

The authors declare no competing financial interest.

Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

ACKNOWLEDGMENTS

The authors thank Prof. M. Ihara and Dr. H. Yokoe is gratefully acknowledged for helpful

discussions. We also thank Dr. H. Kasai for determination of MS. This work was supported in part by Grant-in-Aid for Young Scientists (B) (No. 25860013) to K.T. from JSPS.

REFERENCES

(1) Szychowski, J.; Truchon, J. -F.; Bennani, Y. L. Natural Products in Medicine: Transformational Outcome of Synthetic Chemistry. *J. Med. Chem.* **2014**, *57*, 9292−9308.

(2) Newman, D. J.; Cragg, G. M. Natural Products as Sources of New Drugs from 1981 to 2014. *J. Nat. Prod.* **2016**, *79*, 629−661.

(3) (a) Martin, L. D.; Stille, J. K. Palladium-Catalyzed Carbonylation of Vinyl Halides: A Route to the Synthesis of α-Methylene Lactones. *J. Org. Chem.* **1982**, *47*, 3630−3633. (b) Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-organometallics as Reaction Partners. *Chem. Rev.* **2011**, *111*, 1417−1492. (c) Chinchilla, R.; Nájera, C. Recent Advances in Sonogashira reactions. *Chem. Soc. Rev.* **2011**, *40*, 5084−5121.

(4) (a) Stork, G.; Kahne, D. E. Stereocontrol in Homogeneous Catalytic Hydrogenation via Hydroxyl Group Coordination. *J. Am. Chem. Soc.* **1983**, *105*, 1072−1073. (b) Crabtree, R. H.; Davis, M. W. Directing Effects in Homogeneous Hydrogenation with [Ir(cod)(PCy_3)(py)]PF_6. *J. Org. Chem.* **1986**, *51*, 2655−2661.

(5) (a) Katsuki, T.; Martin, V. S. Asymmetric Epoxidation of Allylic Alcohols: The Katsuki-Sharpless Epoxidation Reaction. *Org. React.* **1995**, *48*, 1−299. (b) Wang, C.; Yamamoto, H. Tungsten-Catalyzed Asymmetric Epoxidation of Allylic and Homoallylic Alcohols with Hydrogen Peroxide. *J. Am. Chem. Soc.* **2014**, *136*, 1222−1225.

(6) For reviews on transition-metal-catalyzed cyclization of alkynals, see: (a) Tanaka, K.; Tajima, Y. Transition-Metal-Catalyzed Cyclization of Alkynals via Oxametallacycle Intermediates. *Eur. J. Org. Chem.* **2012**, 3715−3725. For recent literature on metal-catalyzed cyclization of alkynals, see: (b) Shinde, M. P.; Wang, X.; Kang, E. J.; Jang, H.−Y. Platinum-Catalyzed Hydrogenative Cyclization of Yne-Enones, Yne-Aldehydes, and Yne-Dienes. *Eur. J. Org. Chem.* **2009**, *35*, 6091−6094. (c) Haynes, M. T., II; Liu, P.; Baxter, R. D.; Nett, A. J.; Houk, K. N.; Montgomery, J. Dimer Involvement and Origin of Crossover in Nickel-Catalyzed Aldehyde-Alkyne Reductive Couplings. *J. Am. Chem. Soc.* **2014**, *136*, 17495−17504. (d) Serpier,

F.; Flamme, B.; Brayer, J. –L.; Folléas, B.; Darses, S. Chiral Pyrrolidines and Piperidines from Enantioselective Rhodium-Catalyzed Cascade Arylative Cyclization. *Org. Lett.* **2015**, *17*, 1720−1723.

(7) SmI_2-mediated cyclization of alkynes and carbonyl compounds, see: (a) Shim, S. C.; Hwang, J. T. Intramolecular reductive cyclization of aldehydes and ketones with alkynes promoted by Samarium(II) iodide. *Tetrahedron Lett.* **1990**, *31*, 4765–4768. (b) Baldwin, J. E.; Turner, S. C. M.; Moloney, M. G. The synthesis of substituted pyrrolidines by a samarium (II) iodide mediated ring closure. *Tetrahedron Lett.* **1992**, *33*, 1517–1520. (c) Baldwin, J. E.; Turner, S. C.; Moloney, M. G. The synthesis of substituted pyrrolidines by a samarium (II) iodide mediated ring closure. Part 2. *Tetrahedron* **1994**, *50*, 9425–9438.

(8) For recent reviews of SmI_2-promoted reaction, see: (a) Rudkin, I. M.; Miller, L. C.; Procter, D. J. Samarium enolates and their application in organic synthesis. *Organomet. Chem.* **2008**, *34*, 19−45. (b) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 7140−7165. (c) Procter, D. J.; Flowers, R. A. II. Skrydstrup T. *Organic Synthesis Using Samarium Diiodide: A Practical Guide*; Royal Society of Chemistry Publishing: UK, 2010; p 204.

(9) (a) Takahashi, K.; Honda, T. Diastereoselective Syntheses of Functionalized Five-Membered Carbocycles and Heterocycles by a SmI_2-Promoted Intramolecular Coupling of Bromoalkynes and α,β-Unsaturated Esters. *Org. Lett.* **2010**, *12*, 3026–3029. (b) Takahashi, K.; Arai, Y.; Honda, T. The formal synthesis of (+)-15-deoxy-$\Delta^{12,14}$-prostaglandin J_2: Controlling *exo*-olefin geometry via SmI_2-mediated cyclization. *Tetrahedron Lett.* **2017**, *58*, 4048–4050. (c) Takahashi, K.; Fukushima, K.; Tsubuki, M.; Honda, T. The formal synthesis of lucentamycin A: Construction of *cis*-2,3-disubstituted pyrrolidine core by application of SmI_2-DMPU system. *Tetrahedron Lett.* **2018**, *59*, 1435–1437 and references cited therein.

(10) K. Suzuki, Cross-Coupling Reactions Of Organoboranes: An Easy Way To Construct C-C Bonds (Nobel Lecture). *Angew. Chem. Int. Ed.* **2011**, *50*, 6722−6737.

(11) Guo, R.; Li, K-G.; Gong, L-U. Catalytic cascade hydroalkoxylation/isomerization/[4+2] cycloaddition using enyne alcohols as latent dienes or dienophiles. *Org. Biomol. Chem.* **2013**, *11*, 6707−6712.

(12) Gobeaux, B.; Ghosez, L. Intramolecular [2+2] Cycloadditions of Keteniminium Salts Derived from α- and β-Amino Acids. A Route to Azabicyclic Ketones. *Heterocycles*, **1989**, *28*,

29–32.

(13) Unthank, M. G.; Tavassoli, B.; Aggarwal, V. K. Epoxy-Annulations by Reactions of α-Amido Ketones with Vinyl Sulfonium Salts. Reagent versus Substrate Control and Kinetic Resolution. *Org. Lett*. **2008**, *10*, 1501–1504.

(14) Niu, T.; Wang, K.-H.; Huang, D.; Xu, C.; Su, Y.; Hu, Y.; Fu, Y. One-Pot Transition-Metal-Free Synthesis of Weinreb Amides Directly from Carboxylic Acids. *Synthesis* **2014**, 320–330.

(15) Campolo, D.; Gaudel-Siri, A.; Mondal, S.; Siri, D.; Besson, E.; Vanthuyne, N.; Nechab, M.; M.; Bertrand M. P. Mechanistic Investigation of Enediyne-Connected Amino Ester Rearrangement. Theoretical Rationale for the Exclusive Preference for 1,6- or 1,5-Hydrogen Atom Transfer Depending on the Substrate. A Potential Route to Chiral Naphthoazepines. *J. Org. Chem*. **2012**, *77*, 2773–2783.

(16) Zhang, S.; Arvidsson, P. I. Facile Synthesis of *N*-protected Amino Acid Esters Assisted by Microwave Irradiation. *Int. J. Pept. Res. Ther.* **2008**, *14*, 219–222.

(17) Raghuram, T.; Vijaysaradhi, S.; Singh, I.; Singh, J. Convenient Conversion of Acid to Weinreb's Amide. *Synth. Commun*. **1999**, *29*, 3215–3219.

(18) González-Rodríguez, C.; Suárez, J. R.; Varela, J. A.; Saá, C. Nucleophilic Addition of Amines to Ruthenium Carbenes: *ortho*-(Alkynyloxy)benzylamine Cyclizations towards 1,3-Benzoxazines. *Angew. Chem. Int. Ed.* **2015**, *54*, 2724–2728.

(19) Nicolai, S.; Sedigh-Zadeh, R.; Waser, J. Pd(0)-Catalyzed Alkene Oxy- and Aminoalkynylation with Aliphatic Bromoacetylenes. *J. Org. Chem.* **2013**, *78*, 3783–3801.

(20) Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. A Novel Entry to 17α-Bromo- and 17α-Iodoethynyl Steroids. *Angew. Chem. Int. Ed.* **1984**, *23*, 727–729.

(21) Wessig, P.; Müller, G.; Pick, C.; Matthes, A. The Photo-Dehydro-Diels-Alder (PDDA) Reaction - A Powerful Method for the Preparation of Biaryls. *Synthesis* **2007**, 464–477.