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Articles

Synthesis of 2,5-Disubstituted Pyrrolidines from *N*-Alkenyl and Alkynyl *N*-Benzoyloxysulfonamides Catalyzed by $(CuOTf)_2 \cdot C_6H_6$[†]

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A new synthetic method of 2,5-disubstituted pyrrolidines is developed by the cyclization of unsaturated *N*-benzoyloxysulfonamides by $(CuOTf)_2 \cdot C_6H_6$ in refluxing dichloroethane. Various *N*-4- and *N*-5-alkenyl and alkynyl *N*-benzoyloxysulfonamides are cyclized to give pyrrolidines. The cyclization proceeds *via* addition of sulfonamidoyl radicals to intramolecular unsaturated bonds or allylic hydrogen abstraction with the radical intermediates.

Key Words: Pyrrolidines, Intramolecular radical cyclization, Copper catalyst, *N*-Benzoyloxysulfonamides

Introduction

Pyrrolidines and other related azaheterocycles have attracted considerable interest due to their potential pharmacological activities,[1] and many synthetic methods have been developed.[2] Especially, intramolecular addition of nitrogen-centered radical onto unsaturated bonds is an attractive method to form five-membered azaheterocycles.[3] Although halogenated amines have been commonly employed as *N*-radical precursors, they are too unstable to be widely applied in organic synthesis.[4] Hydroxylamine derivatives are used as alternative *N*-radical precursors such as amidyl, iminyl and aminyl radicals.[5] For example, Zard has employed a cascade radical cyclization starting from *N*-benzyloxyamides to construct the core of (±)-aspidospermidine.[6] Our laboratory also reported that 1,5-naphthalenediol or copper (I) bromide catalyzed the cyclization of olefinic *O*-acetyloximes to afford dihydropyrroles *via* iminyl radicals.[7]

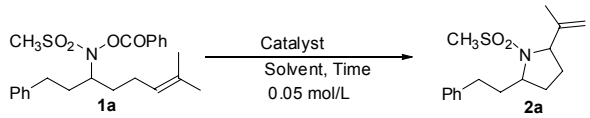
Recently, Göttlich reported that the cyclization of *N*-4-alkenyl-*N*-benzoyloxyamines was catalized by copper (I) hexafluorophosphate to afford 2-benzoyloxymethyl pyrrolidines in the presence of an equimolar amount of BF_3-etherate. The role of BF_3-etherate is explained as an activation of benzoyloxy group to facilitate the N-O bond cleavage.[8] We thought that BF_3 might coordinate to the nitrogen atom and make the one-electron reduction with Cu(I) easier. The use of *N*-benzoyloxysulfonamides instead of *N*-benzoyloxylamines might have the advantage to be reduced by Cu(I) species without the aid of BF_3-etherate. Here we report our investigation on the radical cyclization of *N*-benzoyloxysulfonamides.

Results and Discussion

Catalyst screening. As reported by our laboratory, γ, δ-unsaturated *O*-acetyloximes were converted to dihydropyrroles in the presence of a catalytic amount of 1,5-naphthalenediol or $CuBr \cdot SMe_2$ *via* radical cyclization.[9] Therefore, it was expected that *N*-benzoyloxymethanesulfonamide **1a** would also undergo radical cyclization under the above conditions. We chose *N*-benzoyloxymethanesulfonamide **1a** as a model substrate for preliminary investigations (Table 1).

In the initial experiments, the expected radical cyclization reaction did not take place at all with organic catalysts such as 1,5-naphthalenediol in dioxane at 100 °C.[10] Although the radical cyclization proceeded when **1a** was treated with an equimolar amount of $CuBr \cdot SMe_2$ in dioxane at 100 °C, the reaction proceeded very slowly and pyrrolidine **2a** was isolated after 36 h only in 20% yield together with 65% recovery of the starting material (Table 1, entry 1). Copper(I) hexafluorophosphate was not effective, and only a trace amount of pyrrolidine **2a** formed after 24 h (Table 1, entry 2). After screening various metal complexes,[11] such as TiF_3, $Ni(COD)_2$, $Cp_2Fe_2O_4$, $In(OTf)_3$, *etc.*,

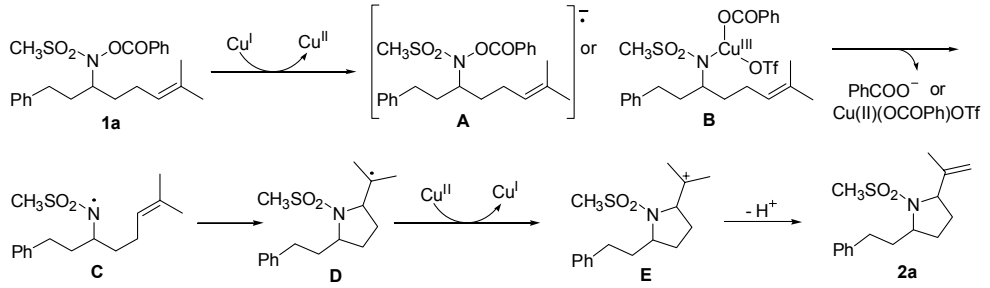
Table 1. Optimization of the synthesis of **2a** from **1a**



entry	catalyst (mol %)	solvent	temp	time	**2a** (*cis*:*trans*)
1	$CuBr \cdot SMe_2$ (100)	1,4-dioxane	100 °C	36 h	20% (1:3)
2	$CuPF_6$ (10)	toluene	110 °C	24 h	trace
3	$(CuOTf)_2 \cdot C_6H_6$ (40)	1,4-dioxane	100 °C	5 h	37% (1:2)
4	$(CuOTf)_2 \cdot C_6H_6$ (10)	toluene	110 °C	30 min	74% (1:1)
5	$(CuOTf)_2 \cdot C_6H_6$ (10)	DCE	82 °C	20 min	91% (1:1)
6	$(CuOTf)_2 \cdot C_6H_6$ (5)	DCE	82 °C	1 h	95% (1:1)

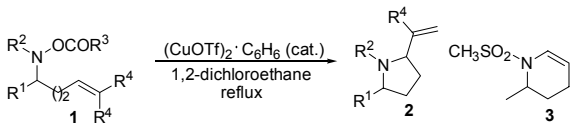
DCE = 1,2-dichloroethane $(CuOTf)_2 \cdot C_6H_6 = (CF_3SO_3Cu)_2 \cdot C_6H_6$

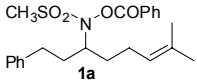
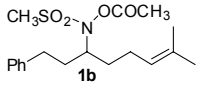
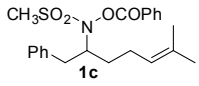
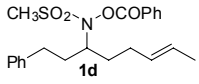
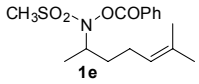
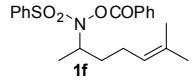
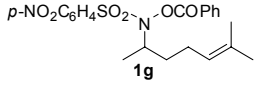
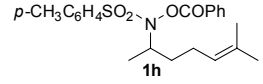
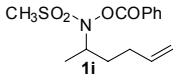
[†]This paper is dedicated to Professor Sunggak Kim on the occasion of his honorable retirement.



Scheme 1. Proposed mechanism for the cyclization of **1a**

Table 2. Cyclization of various *N*-4-alkenyl-*N*-benzoyloxysulfonamides **1**[a]



entry	substrate	Cu[I]/mol %	time/h	product (*cis*:*trans*)[b]
1		10	1	**2a** 95% (1:1)
2		10	4	**2b** 91% (6:7)
3		10	1.5	**2c** 64% (2:7)
4		10	1	**2d** 56% (1:2)
5		4	1	**2e** 84% (1:1)
6		10	4	**2f** 60% (4:5)
7		10	48	**2g** 30% (5:4)
8		15	3	**2h** 55% (4:5)
9		10	4	**3** 44%

[a]Reactions were performed under N_2 atomsphere; [b]Isolated yield.

$(CuOTf)_2{\cdot}C_6H_6$ was found to be effective, and the starting material **1a** disappeared in 5 h, yielding **2a** in 37% yield (Table 1, entry 3). In contrast, performing the reaction in toluene or 1,2-dichloroethane gave **2a** in markedly higher yields of 74% and 91%, respectively (Table 1, entry 4 and 5). The radical cyclization of **1a** proceeded smoothly when the reaction was carried out with a 5 mol % amount of $(CuOTf)_2{\cdot}C_6H_6$ in refluxing 1,2-dichloroethane to afford pyrrolidine **2a** in 95% yield. In this reaction, **2a** was obtained as a mixture of two stereoisomers with a 1:1 *cis* : *trans* ratio (Table 1, entry 6, Determination of *cis* and *trans* stereochemistry of **2a**, *vide infra*).

It was afraid that TfOH generated by the hydrolysis of $(CuOTf)_2{\cdot}C_6H_6$ acted as an acid catalyst to cause the nucleophilic substitution reaction at the nitrogen atom. Hence, **1a** was treated with a trace amount of TfOH in refluxing 1,2-dichloroethane, however the reaction did not proceed at all, and the use of an equimolar amount of TfOH made the reaction messy without formation of **2a**.

A proposed mechanism of the formation of **2a** by $(CuOTf)_2{\cdot}C_6H_6$-catalyzed reaction is depicted in Scheme 1. One-electron transfer from $(CuOTf)_2{\cdot}C_6H_6$ to **1a** or oxidative addition of **1a** occurs to generate intermediates **A** or **B**, and the resulting radical **C** cyclizes to generate alkyl radical **D**. Subsequently, the resulting copper(II) species oxidize the radical **D** to afford cation **E** with the regeneration of copper(I) complex. Finally, the elimination of a proton from intermediate **E** affords pyrrolidine **2a**.

$(CuOTf)_2{\cdot}C_6H_6$-catalyzed cyclization of *N*-4-alkenyl-*N*-benzoyloxysulfonamides. With the optimized conditions in hand, the preparations of pyrrolidines **2** from various *N*-benzoyloxyamides **1** were examined as shown in Table 2. Significant difference was not observed by replacement of benzoyloxy group to acetoxy group (entry 1 and 2), while methylsulfonyl group was found to be suitable as compared with arylsulfonyl groups, affording the product in a better yield (Table 2, entry 5, 6, 7, 8). A lower catalyst loading a 0.02 molar amount of $(CuOTf)_2{\cdot}C_6H_6$ was sufficient for the cyclization of methylsulfonyl derivative **1e** (Table 2, entry 5). Sulfonamides bearing a trisubstituted alkene moiety such as **1a** (Table 2, entry 1) gave a higher yield of the product **2a** as compared with the substrate bearing a disubstituted alkene moiety (Table 2, entry 4). Under the same conditions, **2a** was obtained in 95% yield from **1a**, whereas the yield of **2d** was 56%. The *trans* configuration of ***trans*-2d** was confirmed by X-ray crystal determination as shown in Figure 1. The significant difference of the *trans* and *cis* isomers appeared in ^{1}H NMR spectra. The 3- and 4-protons of the *trans* isomer are ob-

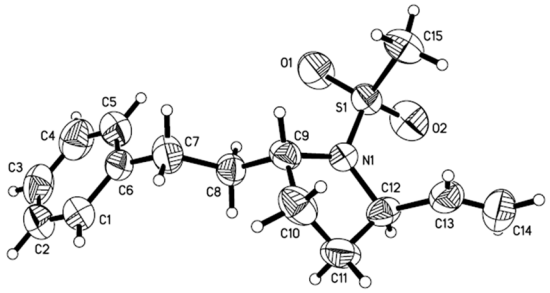


Figure 1. The molecular structure of ***trans*-2d**

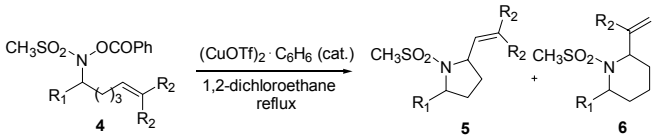
served in different regions as a double-set of multiple peaks and those of the *cis* isomer are overlapped as a single-set of multiple peaks (*vide infra*). The *trans* isomer is less polar than the *cis* isomer in thin layer chromatography.

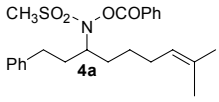
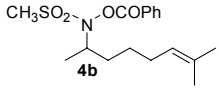
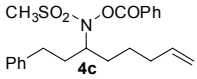
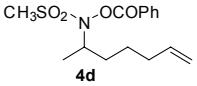
Notably, the reaction of sulfonamide **1i** which has a terminal methylene group, 6-membered cyclization product, piperidine **3**, was obtained instead of pyrrole (Table 2, entry 9). A similar piperidine formation in the cyclization was also observed by Göttlich in the $CuPF_6$-catalyzed intramolecular cyclization of olefinic *N*-chloroamines, where the rearrangement reaction pathway was proposed for the generation of piperidine deri vatives.[12]

To explore the scope of the $(CuOTf)_2{\cdot}C_6H_6$ catalyzed reaction, the cyclization of *N*-5-alkenyl sulfonamides **4** were examined expecting the formation of 2,6-disubstituted piperidines (Table 3).

Interestingly, when *N*-benzoyloxysulfonamides **4a** and **4b** which had a trisubstituted alkene moiety were subjected to the cyclization, pyrrolidines **5a** and **5b** were obtained as major products in 66% and 47% yields, respectively, whereas the expected piperidines **6a** and **6b** were isolated as minor products in 12% and 7% yields, respectively (Table 3, entry 1, 2). The *cis* isomers of pyrrolidine derivatives *cis*-**5a** and *cis*-**5b** were obtained preferentially (*vide infra*). From the terminal vinylic substrates **4c** and **4d**, only five-membered ring products **5c** and **5d** were obtained in 61% and 82% yields, respectively. (Table 3, entry 3, 4). The formation of pyrrolidine derivatives is a strong evi-

Table 3. Cyclization of *N*-benzoyloxysulfonamides **4**[a]

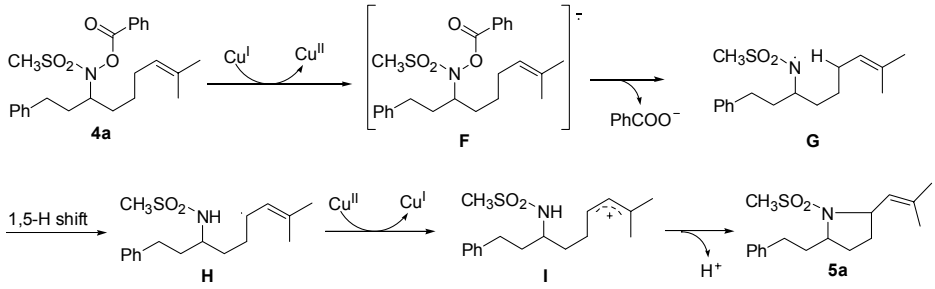


entry	substrate	Cu^I/mol %	time/h	5 (*cis*:*trans*)[b]	6[b]
1		10	2	**5a** 66% (10:1)	**6a** 12%
2		10	7	**5b** 47% (6:1)	**6b** 7%
3		20	52	**5c** 61% (3:4)	-
4		20	1	**5d** 82% (1:1)	-

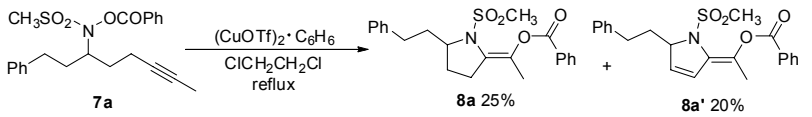
[a]Reactions were performed under N_2 atomsphere; [b]Isolated yield

dence to prove that copper(I)-catalyzed cyclization proceeds *via* aminyl radical intermediates.[13] At radical intermediate **G**, 1,5-hydrogen shift takes place to afford radical **H,** which is followed by the oxidation with Cu(II) species to give allylic cation intermediate **I** accompanying with the regeneration of copper(I). The elimination of a proton from intermediate **I** leads to the formation of C-N bond to yield product **5a** (Scheme 2).

Copper(I)-catalyzed radical cyclization of *N*-alkynyl *N*-benzoyloxysulfonamides. The above results prompted us to study the radical cyclization of *N*-benzoyloxysulfonamides **7** having an alkynyl moiety. Under the standard conditions, the radical cyclization reaction of **7a** proceeded and pyrrolidine **8a** and 2*H*-pyrrole **8a'** were obtained in low yields of 25% and 20%, res-



Scheme 2. Plausible mechanism for the cyclization of **4a**



Scheme 3. Cyclization of substrate **7a** without 1,4-cyclohexadiene

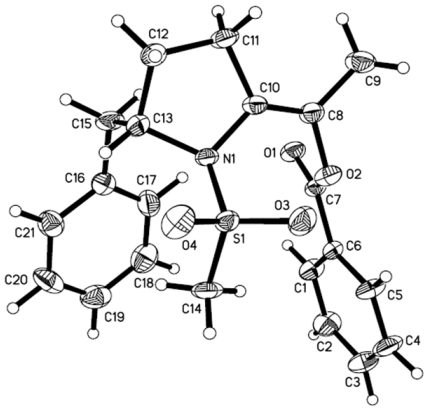
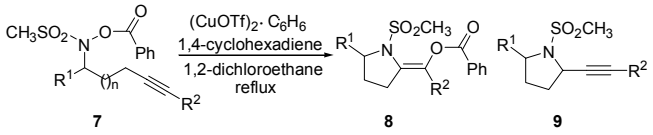
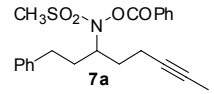
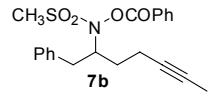
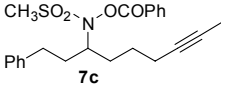
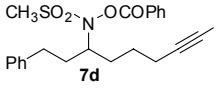


Figure 2. The molecular structure of product **8b**.

Table 4. Cyclization of various *N*-benzoyloxyamides having an alkynyl moiety[a]



7 8 9

entry	substrate	time/h	8[b]	9 (*cis*:*trans*)[b]
1		1	**8a** 56%	-
2		2	**8b** 33%	-
3		4	-	**9c** 38% (6:1)
4		5	-	**9d** 74% (6:7)

[a]Cyclization was carried out under the following conditions: $(CuOTf)_2 \cdot C_6H_6$ (5 mol %), 1,4-cyclohexadiene (1000 mol %); [b]Isolated yield.

pectively (Scheme 3).

When the reaction was performed in the presence of 10 molar amounts of 1,4-cyclohexadiene, 2*H*-pyrrole **8a'** could not be isolated and pyrrolidine **8a** was obtained in better yield of 56% (Table 4, entry 1). Substrate **7b** was transformed into pyrrolidine **8b** in 33% yield (Table 4, entry 2). The configuration of **8b** was confirmed by X-ray crystal analysis (Figure 2) as a *Z*-isomer. In addition, the cyclizations of **7c** and **7d** provided pyrrolidines **9c** and **9d** in 38% and 74% yields, respectively (Table 4, entry 3, 4).

Conclusion

In summary, $(CuOTf)_2 \cdot C_6H_6$ was found to be an effective catalyst for the cyclization of various *N*-alkenyl and alkynyl *N*-benzoyloxysulfonamides to 2,5-disubstituted pyrrolidines. The cyclization proceeds *via* sulfonamidoyl radical addition to intramolecular unsaturated bonds or allylic hydrogen abstraction with the radical intermediates.

Experimental Section

^{1}H NMR spectra were measured on Bruker Avance 300, 400 and a JEOL-AL400 spectrometers in $CDCl_3$ [using $CDCl_3$ (for ^{1}H, $\delta = 7.26$) as the internal standard]. ^{13}C NMR spectra were measured on Bruker Avance 300, 400 and a JEOL-AL400 spectrometers in $CDCl_3$ [using $CDCl_3$ (for ^{13}C, $\delta = 77.00$) as the internal standard]. IR spectra were recorded on a Shimadzu IR Prestige-21 FT-IR Spectrometer. High-resolution mass spectra were obtained with a Q-Tof Premier LC HR mass spectrometer. Melting points were uncorrected and were recorded on a Buchi B-54 melting point apparatus. Flash column chromatographs were performed using Silicycle 60 silica gel and distilled eluting solvents. 1,2-Dichloroethane ($ClCH_2CH_2Cl$) was dried by passing over a column of activated alumina (A-2, Purify) followed by a column of Q-5 scavenger (Engelhard). Toluene was obtained from an Innovative Technology PS-400-5 Solvent Purification system.

Cyclization of *N*-benzoyloxysulfonamide (1a). The experimental procedure is shown below as a typical example for the synthesis of **2a** (Table 1, entry 1). To a solution of *N*-benzoyloxysulfonamide **1a** (0.166 g, 0.4 mmol) in 10 mL of 1,2-dichloroethane was added $(CuOTf)_2 \cdot C_6H_6$ (10 mg, 0.02 mmol) at room temperature under nitrogen atmosphere. The mixture was heated to reflux for 1 h. The reaction was quenched with saturated $NaHCO_3$, and the mixture was extracted three times with ethyl acetate and the combined extracts were dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the crude product was purified by prepared thin-layer chromatography (hexane:ethyl acetate = 3:1) to afford **2a** (0.112 g, 0.38 mmol, *cis*:*trans* = 1:1) in 95% yield.

1-(Methylsulfonyl)-2-phenethyl-5-(prop-1-en-2-yl)pyrrolidine (2a). *trans*-2a: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.21-7.16 (m, 3H), 4.97 (s, 1H), 4.92 (s, 1H), 4.28 (d, 1H, $J = 8.1$ Hz), 4.02-3.95 (m, 1H), 2.87 (s, 3H), 2.65-2.60 (m, 2H), 2.50-2.40 (m, 1H), 2.32-2.18 (m, 1H), 2.15-2.04 (m, 1H), 1.88-1.67 (m, 3H, overlapped), 1.74 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 141.1, 128.4, 128.3, 126.0, 113.3, 64.2, 61.5, 41.2, 35.3, 32.9, 29.5, 28.2, 18.7; FT-IR(neat): 3020, 2399, 1454, 1331, 1215, 1149, 964, 908, 756, 667 cm^{-1}; HRMS (ESI): Found: *m/z*, 294.1528, Calcd for $C_{16}H_{24}NO_2S$ $[M+H]^+$: 294.1528. ***cis*-2a:** White solid; mp 71.5-73.5 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.21-7.17 (m, 3H), 5.10 (s, 1H), 4.92 (s, 1H), 4.23 (t, 1H, $J = 7.2$ Hz), 3.92-3.89 (m, 1H), 2.83 (s, 3H), 2.75-2.63 (m, 2H), 2.30-2.21 (m, 1H), 2.09-1.97 (m, 2H), 1.94-1.88 (m, 1H), 1.78 (s, 3H), 1.78-1.70 (m, 2H, overlapped); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 141.5, 128.4, 128.3, 126.0, 112.2, 66.0, 61.5, 38.2, 37.6, 33.0, 30.4, 30.2, 18.8; FT-IR(neat): 3019, 2399, 1454, 1337, 1215, 1153, 1049, 908, 756, 669 cm^{-1}; HRMS (ESI): Found: *m/z*, 294.1528, Calcd for $C_{16}H_{24}NO_2S$ $[M+H]^+$: 294.1528.

2-Benzyl-1-(methylsulfonyl)-5-(prop-1-en-2-yl)pyrrolidine (2c). *trans*-2c: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ

7.32-7.21 (m, 5H), 5.00 (s, 1H), 4.93 (s, 1H), 4.33 (d, 1H, J = 8.7 Hz), 4.21-4.14 (m, 1H), 3.49 (dd, 1H, J = 3.3, 12.9 Hz), 2.95 (s, 3H), 2.68-2.61 (m, 1H), 2.25-2.11 (m, 1H), 1.96-1.92 (m, 1H), 1.83-1.65 (m, 2H, overlapped), 1.73 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 138.4, 129.4, 128.5, 126.5, 112.4, 66.4, 63.2, 42.8, 37.9, 30.2, 29.5, 18.8; FT-IR(neat): 3019, 2399, 1454, 1339, 1215, 1051, 970, 906, 756, 669 cm^{-1}; HRMS (ESI): Found: *m/z*, 280.1369, Calcd for $C_{15}H_{22}NO_2S$ $[M+H]^+$: 280.1371. ***cis*-2c:** Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.22 (m, 5H), 5.11 (s, 1H), 4.94 (s, 1H), 4.28-4.24 (m, 1H), 4.12-4.08 (m, 1H), 3.34-3.30 (m, 1H), 2.77 (s, 3H), 2.70-2.64 (m, 1H), 2.05-1.97 (m, 1H), 1.96-1.88 (m, 1H), 1.81 (s, 3H), 1.81-1.71 (m, 2H, overlapped); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 138.4, 129.4, 128.5, 126.5, 112.4, 66.4, 63.2, 42.8, 38.0, 30.2, 29.5, 18.8; FT-IR (neat): 3018, 2399, 1454, 1338, 1215, 1153, 1051, 970, 908, 760, 667 cm^{-1}; HRMS (ESI): Found: *m/z*, 280.1370, Calcd for $C_{15}H_{22}NO_2S$ $[M+H]^+$: 280.1371.

1-(Methylsulfonyl)-2-phenethyl-5-vinylpyrrolidine (2d). *trans*-2d: White solid; mp 102.8-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.26 (m, 2H), 7.21-7.17 (m, 3H), 5.81-5.74 (m, 1H), 5.32 (d, 1H, J = 16.8 Hz), 5.20 (d, 1H, J = 10.8 Hz), 4.33 (t, 1H, J = 8.0 Hz), 3.79-3.74 (m, 1H), 2.84 (s, 3H), 2.70-2.55 (m, 2H), 2.43-2.35 (m, 1H), 2.27-2.19 (m, 1H), 2.16-2.06 (m, 1H), 1.90-1.71 (m, 3H, overlapped); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 136.7, 128.4, 128.3, 125.9, 117.9, 62.8, 59.9, 40.5, 36.6, 32.7, 30.3, 28.4; FT-IR(neat): 3417, 3019, 2380, 1459, 1374, 1210, 1139, 914, 758, 669 cm^{-1}; HRMS (ESI): Found: *m/z*, 280.1372, Calcd for $C_{15}H_{22}NO_2S$ $[M+H]^+$: 280.1371. ***cis*-2d:** Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.21-7.19 (m, 3H), 5.85-5.77 (m, 1H), 5.33 (d, 1H, J = 17.2 Hz), 5.16 (d, 1H, J = 10.0 Hz), 4.32-4.27 (m, 1H), 3.93-3.84 (m, 1H), 2.84 (s, 3H), 2.66 (t, 2H, J = 8.0 Hz), 2.29-2.20 (m, 1H), 2.13-2.00 (m, 2H), 1.88-1.71 (m, 3H, overlapped); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 139.1, 128.4, 128.3, 126.0, 116.1, 62.8, 61.3, 38.6, 38.3, 32.7, 31.6, 30.2; FT-IR(neat): 3447, 3019, 2380, 1459, 1380, 1338, 1148, 920, 759, 669 cm^{-1}; HRMS (ESI): Found: *m/z*, 280.1364, Calcd for $C_{15}H_{22}NO_2S$ $[M+H]^+$: 280.1371.

2-Methyl-1-(methylsulfonyl)-5-(prop-1-en-2-yl) pyrrolidine (2e). *trans*-2e: Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (s, 1H), 4.89 (s, 1H), 4.24 (d, 1H, J = 8.8 Hz), 4.15-4.09 (m, 1H), 2.86 (s, 3H), 2.32-2.22 (m, 1H), 2.20-2.10 (m, 1H), 1.74-1.67 (m, 1H), 1.72 (s, 3H), 1.59-1.54 (m, 1H), 1.33 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 112.9, 64.1, 57.3, 41.1, 31.7, 29.4, 20.9, 18.7; FT-IR (neat): 3020, 2974, 2399, 1448, 1377, 1330, 1215, 1147, 1064, 906, 756, 667 cm^{-1}; HRMS (ESI): Found: *m/z*, 204.1056, Calcd for $C_9H_{18}NO_2S$ $[M+H]^+$: 204.1058. ***cis*-2e:** Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (s, 1H), 4.90 (s, 1H), 4.21 (t, 1H, J = 6.0 Hz), 3.97-3.93 (m, 1H), 2.83 (s, 3H), 2.04-1.94 (m, 2H), 1.89-1.84 (m, 1H), 1.76 (s, 3H), 1.65-1.58 (m, 1H), 1.33 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 112.2, 66.2, 57.4, 37.9, 32.3, 30.2, 22.3, 18.9, FT-IR (neat): 3020, 2972, 2399, 1448, 1377, 1334, 1217, 1153, 1053, 904, 756, 667 cm^{-1}; HRMS (ESI): Found: *m/z*, 204.1058, Calcd for $C_9H_{18}NO_2S$ $[M+H]^+$: 204.1058.

2-Methyl-1-(phenylsulfonyl)-5-(prop-1-en-2-yl)pyrrolidine (2f). A *trans* and *cis* mixture (0.56: 0.44)**:** Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.81 (m, 2H), 7.6-7.56 (m, 0.44H), 7.53-7.49 (m, 1.56H), 7.46-7.42 (m, 1H), 5.06 (s, 0.44H), 4.89 (s, 0.44H), 4.81 (s, 0.56H), 4.73 (s, 0.56H), 4.30 (d, 0.56H, J = 8.4 Hz), 4.21-4.18 (m, 0.56H), 4.01 (t, 0.44H, J = 6.8 Hz), 3.82-3.78 (m, 0.44H), 2.26-2.06 (m, 1H), 1.80-1.41 (m, 3H), 1.77 (s, 1.32H), 1.48 (s, 1.68H), 1.37 (d, 1.32H, J = 6.4 Hz), 1.24 (d, 1.68H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 144.7, 141.8, 137.9, 132.5, 132.0, 128.9, 128.5, 127.5, 127.3, 112.9, 112.0, 66.6, 64.8, 57.7, 57.4, 31.9, 31.8, 29.8, 29.6, 22.8, 21.0, 18.6, 18.2; FT-IR (neat): 3018, 2873, 2399, 1446, 1336, 1215, 1159, 1107, 904, 756, 667, 613 cm^{-1}; HRMS (ESI): Found: *m/z*, 266.1213, Calcd for $C_{14}H_{20}NO_2S$ $[M+H]^+$: 266.1215.

2-Methyl-1-(4-nitrophenylsulfonyl)-5-(prop-1-en-2-yl) pyrrodidine (2g). A *trans* and *cis* mixture (0.46:0.54)**:** Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, 1H, J = 8.8 Hz), 8.30 (d, 1H, J = 8.8 Hz), 8.03-7.99 (m, 2H), 5.02 (s, 0.54H), 4.91 (s, 0.54H), 4.80 (s, 0.46H), 4.76 (s, 0.46H), 4.37 (d, 0.46H, J = 8.4 Hz), 4.21 (m, 0.46 H), 4.05 (t, 0.54H, J = 6.8, 6.5 Hz), 3.89-3.85 (m, 0.54H), 2.27-2.11 (m, 1H), 1.84-1.51 (m, 3H), 1.74 (s, 1.62H), 1.44 (s, 1.38H), 1.39 (d, 1.62H, J = 6.4 Hz), 1.30 (d, 1.38H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 149.4, 147.5, 144.2, 144.1, 143.9, 128.7, 128.5, 124.2, 123.8, 113.9, 112.7, 66.9, 65.2, 58.1, 57.9, 32.0, 31.8, 29.9, 29.4, 22.6, 21.5, 18.5, 18.3; FT-IR (neat): 3018, 2875, 2399, 1450, 1336, 1215, 1159, 1037, 927, 756, 667, 613 cm^{-1}; HRMS (ESI): Found: *m/z*, 333.0893, Calcd for $C_{14}H_{18}N_2O_4SNa$ $[M+Na]^+$: 333.0885.

2-Methyl-5-(prop-1-en-2-yl)-1-tosylpyrrolidine (2h).[14] **A *trans* and *cis* mixture** (0.56:0.44)**:** Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.70 (m, 2H), 7.31 (d, 1H, J = 8.4 Hz), 7.26-7.23 (m, 1H), 5.07 (s, 0.44H), 4.89 (s, 0.44H), 4.83 (s, 0.56H), 4.75 (s, 0.56H), 4.27 (d, 0.56H, J = 8.4 Hz), 4.22-4.16 (m, 0.56H), 4.00 (t, 0.44H, J = 8.4 Hz), 3.83-3.75 (m, 0.44H), 2.43 (s, 1.32H), 2.41 (s, 1.68H), 2.25-2.07 (m, 1H), 1.77 (s, 1.68H), 1.68-1.45 (m, 3H), 1.52 (s, 1.32H), 1.37 (d, 1.32H, J = 6.4 Hz), 1.24 (d, 1.68H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 144.9, 143.1, 142.6, 138.9, 135.0, 129.5, 129.1, 127.5, 127.3, 112.7, 111.9, 66.6, 64.7, 57.6, 57.3, 31.9, 31.8, 29.8, 29.6, 22.8, 21.5, 21.4, 20.9, 18.6, 18.3; FT-IR (neat): 3196, 2968, 2378, 1456, 1336, 1115, 1028, 898, 771, 665 cm^{-1}; HRMS (ESI): Found: *m/z*, 280.1374, Calcd for $C_{15}H_{22}NO_2S$ $[M+H]^+$: 280.1371.

2-Methyl-1-(methylsulfonyl)-1,2,3,4-tetrahydropyridine (3). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (d, 1H, J = 8.4 Hz), 5.03-4.99 (m, 1H), 4.24-4.21 (m, 1H), 2.87 (s, 3H), 2.16-1.98 (m, 2H), 1.76-1.61 (m, 2H), 1.22 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.7, 107.1, 48.6, 39.0, 26.4, 18.3, 16.9; FT-IR (neat): 3024, 2931, 1359, 1338, 1261, 1215, 1163, 1001, 960, 756, 667, 644 cm^{-1}; HRMS (ESI): Found: *m/z*, 176.0747, Calcd for $C_7H_{14}NO_2S$ $[M+H]^+$: 176.0745.

2-(2-Methylprop-1-enyl)-1-(methylsulfonyl)-5-phenethyl pyrrolidine (5a). *trans*-5a: Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.21 (m, 2H), 7.19-7.15 (m, 3H), 5.12-5.08 (m, 1H), 4.66-4.61 (m, 1H), 3.71-3.66 (m, 1H), 2.89 (s, 3H), 2.86-2.58 (m, 2H), 2.38-2.34 (m, 1H), 2.23-2.10 (m, 2H), 1.88-1.81 (m, 1H), 1.80-1.74 (m, 1H), 1.74 (s, 3H), 1.73 (s, 3H), 1.63-1.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 135.9, 128.4 (overlapped), 125.9, 123.3, 59.6, 57.9, 39.8, 37.1, 32.7, 30.8, 28.6, 26.0, 18.0; FT-IR (neat): 3018, 2931, 2399, 1454, 1328, 1217, 1149, 960, 756, 667 cm^{-1}; HRMS (ESI): Found: *m/z*,

330.1508, Calcd for $C_{17}H_{25}NO_2SNa$ $[M+Na]^+$: 330.1504. ***cis*-5a:** Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.21 (m, 2H), 7.19-7.17 (m, 3H), 5.11 (d, 1H, J = 7.2 Hz), 4.53-4.49 (m, 1H), 4.02-3.97 (m, 1H), 2.95 (s, 3H), 2.89-2.62 (m, 2H), 2.17-2.06 (m, 2H), 2.04-1.93 (m, 1H), 1.86-1.69 (m, 9H, overlapped); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 134.6, 128.5, 128.3, 126.4, 126.0, 60.7, 58.8, 40.1, 38.5, 32.7, 32.5, 30.1, 25.8, 18.0; FT-IR (neat): 3018, 2935, 2399, 1496, 1454, 1377, 1325, 1215, 1145, 1058, 756, 700, 667 cm^{-1}; HRMS (ESI): Found: *m/z*, 330.1508, Calcd for $C_{17}H_{25}NO_2SNa$ $[M+Na]^+$: 330.1504.

1-(Methylsulfonyl)-2-phenethyl-6-(prop-1-en-2-yl)piperidine (6a). Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.21 (m, 2H), 7.19-7.17 (m, 3H), 4.80 (s, 1H), 4.72 (s, 1H), 3.90-3.83 (m, 1H), 3.75-3.68 (m, 1H), 2.80 (s, 3H), 2.70-2.66 (m, 2H), 2.64-2.60 (m, 1H), 2.26-2.19 (m, 1H), 2.18-2.09 (m, 1H), 2.05-1.96 (m, 1H), 1.95-1.87 (m, 1H), 1.84-1.69 (m, 6H, overlapped); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 141.5, 128.4, 128.3, 125.9, 113.0, 61.4, 59.9, 45.7, 38.6, 35.8, 32.5, 30.2, 29.5, 22.5; FT-IR (neat): 3018, 2939, 2399, 1519, 1336, 1215, 1151, 1045, 756, 669 cm^{-1}; HRMS (ESI): Found: *m/z*, 330.1507, Calcd for $C_{17}H_{25}NO_2SNa$ $[M+Na]^+$: 330.1504.

2-Methyl-5-(2-methylprop-1-enyl)-1-(methylsulfonyl)-pyrrolidine (5b). ***cis*-5b:** Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.10 (d, 1H, J = 9.2 Hz), 4.50-4.44 (m, 1H), 4.07-3.99 (m, 1H), 2.81 (s, 3H), 2.08-1.97 (m, 2H), 1.71-1.60 (m, 8H, overlapped), 1.27 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6, 126.5, 58.8, 56.5, 40.6, 32.5, 32.4, 25.8, 22.8, 17.9; FT-IR (neat): 3020, 2399, 1446, 1377, 1323, 1215, 1145, 1058, 756, 667 cm^{-1}; HRMS (ESI): Found: *m/z*, 218.1210, Calcd for $C_{10}H_{20}NO_2S$ $[M+H]^+$: 218.1215.

1-(Methylsulfonyl)-2-phenethyl-5-vinylpyrrolidine (5c). ***trans*-5c:** White solid; mp 102.8-104 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.26 (m, 2H), 7.21-7.17 (m, 3H), 5.81-5.74 (m, 1H), 5.32 (d, 1H, J = 16.8 Hz), 5.20 (d, 1H, J = 10.8 Hz), 4.33 (t, 1H, J = 8.0 Hz), 3.79-3.74 (m, 1H), 2.84 (s, 3H), 2.70-2.55 (m, 2H), 2.43-2.35 (m, 1H), 2.27-2.19 (m, 1H), 2.16-2.06 (m, 1H), 1.90-1.71 (m, 3H, overlapped); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 136.7, 128.4, 128.3, 125.9, 117.9, 62.8, 59.9, 40.5, 36.6, 32.7, 30.3, 28.4; FT-IR(neat): 3417, 3019, 2380, 1459, 1374, 1210, 1139, 914, 758, 669 cm^{-1}; HRMS (ESI): Found: *m/z*, 280.1372, Calcd for $C_{15}H_{22}NO_2S$ $[M+H]^+$: 280.1371. ***cis*-5c:** Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.21-7.19 (m, 3H), 5.85-5.77 (m, 1H), 5.33 (d, 1H, J = 17.2 Hz), 5.16 (d, 1H, J = 10.0 Hz), 4.32-4.27 (m, 1H), 3.93-3.84 (m, 1H), 2.84 (s, 3H), 2.66 (t, 2H, J = 8.0 Hz), 2.29-2.20 (m, 1H), 2.13-2.00 (m, 2H), 1.88-1.71 (m, 3H, overlapped); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 139.1, 128.4, 128.3, 126.0, 116.1, 62.8, 61.3, 38.6, 38.3, 32.7, 31.6, 30.2; FT-IR(neat): 3447, 3019, 2380, 1459, 1380, 1338, 1148, 920, 759, 669 cm^{-1}; HRMS (ESI): Found: *m/z*, 280.1364, Calcd for $C_{15}H_{22}NO_2S$ $[M+H]^+$: 280.1371.

2-Methyl-1-(methylsulfonyl)-5-vinylpyrrolidine (5d). ***trans*-5d:** Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82-5.73 (m, 1H), 5.28 (d, 1H, J = 16.8 Hz), 5.17 (d, 1H, J = 10 Hz), 4.33-4.29 (m, 1H), 3.98-3.91 (m, 1H), 2.86 (s, 3H), 2.32-2.12 (m, 2H), 1.73-1.69 (m, 1H), 1.64-1.60 (m, 1H), 1.32 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 117.4, 62.5, 56.0, 40.6, 31.5, 30.1, 22.2; FT-IR (neat): 3020, 2972, 1463, 1377, 1330, 1215, 1151, 1064, 962, 756, 667 cm^{-1}; HRMS (ESI): Found: *m/z*, 190.0897, Calcd for $C_8H_{16}NO_2S$ $[M+H]^+$: 190.0902. ***cis*-5d:** White solid; mp 55.5-56.8 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85-5.76 (m, 1H), 5.32 (d, 1H, J = 16.8 Hz), 5.16 (d, 1H, J = 10 Hz), 4.31-4.27 (m, 1H), 3.98-3.92 (m, 1H), 2.85 (s, 3H), 2.09-2.00 (m, 2H), 1.86-1.78 (m, 1H), 1.68-1.61 (m, 1H), 1.34 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 116.1, 63.0, 57.2, 39.0, 32.4, 31.5, 22.6; FT-IR (neat): 3018, 2399, 1519, 1423, 1336, 1215, 1153, 1045, 929, 756, 669 cm^{-1}; HRMS (ESI): Found: *m/z*, 190.0899, Calcd for $C_8H_{16}NO_2S$ $[M+H]^+$: 190.0902.

(*Z*)-1-(1-(Methylsulfonyl)-5-phenethylpyrrolidin-2-ylidene) ethyl benzoate (8a). Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, 2H, J = 8.0 Hz), 7.58 (t, 1H, J = 7.2 Hz), 7.46 (t, 2H, J = 7.6 Hz), 7.30-7.12 (m, 5H), 4.26-4.20 (m, 1H), 2.84 (s, 3H), 2.69-2.53 (m, 4H), 2.09 (s, 3H), 2.21-2.04 (m, 1H, overlapped), 1.98-1.89 (m, 1H), 1.72-1.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 141.5, 136.6, 133.4, 130.0, 129.6, 128.6, 128.4, 128.3, 126.3, 125.9, 62.9, 40.3, 37.4, 32.6, 28.7, 27.3, 17.5; FT-IR(neat): 3417, 2927, 2254, 1730, 1452, 1346, 1273, 1151, 964, 731, 709 cm^{-1}; HRMS (ESI): Found: *m/z*, 422.1404, Calcd for $C_{22}H_{25}NO_4SNa$ $[M+Na]^+$: 422.1402.

(*Z*)-1-(5-Benzyl-1-(methylsulfonyl)pyrrolidin-2-ylidene) ethyl benzoate (8b). Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, 2H, J = 6.4 Hz), 7.63-7.60 (m, 1H), 7.49 (t, 2H, J = 6.0 Hz), 7.20-7.10 (m, 5H), 4.49-4.44 (m, 1H), 2.71-2.64 (m, 4H, overlapped), 2.12 (s, 3H), 2.17-2.09 (m, 1H, overlapped), 2.03 (s, 3H), 1.83-1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 138.7, 135.6, 133.5, 130.0, 129.65, 129.59, 128.6, 128.3, 126.5, 126.0, 65.4, 41.0, 40.7, 29.0, 27.3, 17.2; FT-IR (neat): 3426, 3055, 2307, 1728, 1420, 1327, 1265, 1150, 1110, 895, 741 cm^{-1} HRMS (ESI): Found: *m/z*, 386.1424, Calcd for $C_{21}H_{24}NO_4S$ $[M+H]^+$: 386.1426.

1-(Methylsulfonyl)-2-phenethyl-5-(prop-1-ynyl)pyrrolidine (9c). ***trans*-9c:** Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H), 7.20-7.18 (m, 3H), 4.58 (d, 1H, J = 6.8 Hz), 3.63-3.58 (m, 1H), 3.00 (s, 3H), 2.72-2.61 (m, 1H), 2.60-2.55 (m, 1H), 2.37-2.27 (m, 2H), 2.20-2.11 (m, 1H), 1.97-1.88 (m, 2H), 1.83-1.71 (m, 1H, overlapped), 1.82 (d, 3H, J = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 128.4, 128.3, 125.9, 81.3, 77.5, 58.9, 51.9, 37.3, 37.0, 32.4, 31.6, 29.4, 3.5; FT-IR(neat): 3393, 2920, 1602, 1338, 1211, 1151, 1070, 960, 760, 665 cm^{-1}; HRMS (ESI): Found: *m/z*, 292.1375, Calcd for $C_{16}H_{22}NO_2S$ $[M+H]^+$: 292.1371. ***cis*-9c:** Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.22-7.18 (m, 3H), 4.54 (s, 1H), 4.01-3.95 (m, 1H), 2.97 (s, 3H), 2.69-2.64 (m, 2H), 2.30-2.21 (m, 1H), 2.18-2.03 (m, 3H, overlapped), 1.96-1.87 (m, 1H), 1.82 (d, 3H, J = 2.0 Hz), 1.86-1.75 (m, 1H, overlapped); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 128.4, 128.3, 126.0, 80.0, 78.6, 60.5, 51.0, 41.2, 37.7, 33.4, 32.4, 30.6, 3.6; FT-IR(neat): 3454, 2924, 1338, 1149, 1069, 953, 760, 665 cm^{-1}; HRMS (ESI): Found: *m/z*, 292.1370, Calcd for $C_{16}H_{22}NO_2S$ $[M+H]^+$: 292.1371.

1-(Methylsulfonyl)-2-phenethyl-5-(phenylethynyl)pyrrolidine (9d). ***trans*-9d:** Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.17 (m, 10H), 4.84 (d, 1H, J = 6.8 Hz), 3.68 (t, 1H, J = 9.6 Hz), 3.05 (s, 3H), 2.75-2.68 (m, 1H), 2.64-2.56 (m, 1H), 2.47-2.34 (m, 2H), 2.34-2.23 (m, 1H), 2.13-2.08 (m, 1H), 2.00-1.95 (m, 1H), 1.86-1.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 131.5, 128.7, 128.43, 128.40, 128.3, 125.9,

122.0, 87.3, 85.3, 59.0, 52.2, 37.4, 37.0, 32.4, 31.6, 29.6; FT-IR(neat): 3395, 2928, 1612, 1338, 1211, 1151, 1068, 960, 760, 665 cm^{-1}; HRMS (ESI): Found: *m/z*, 354.1523, Calcd for $C_{21}H_{24}NO_2S$ $[M+H]^+$: 354.1528. ***cis*-9d:** Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.18 (m, 10H), 4.84-4.81 (m, 1H), 4.11-4.05 (m, 1H), 3.04 (s, 3H), 2.73-2.66 (m, 2H), 2.36-2.16 (m, 4H, overlapped), 2.06-1.98 (m, 1H), 1.93-1.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 131.6, 128.54, 128.46, 128.34, 128.28, 126.0, 122.4, 88.5, 84.1, 60.7, 51.2, 41.7, 37.7, 33.3, 32.4, 30.7; FT-IR(neat): 3458, 2926, 1340 1149, 1069, 953, 760, 665 cm^{-1}; HRMS (ESI): Found: *m/z*, 354.1522, Calcd for $C_{21}H_{24}NO_2S$ $[M+H]^+$: 354.1528.

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Supporting Information. Supporting Information is available on request from the correspondence author, Koichi Narasaka, FAX: +65-6791- 1961, E-mail: narasaka@ntu.edu.sg

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