Synthetic methods of pyrrolidines from N-hydroxysulfonamides by using bis[copper(I) trifluoromethanesulfonate]-benzene complex as a redox catalyst

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TRIFLUOROMETHANESULFONATE]-BENZENE
COMPLEX AS A REDOX CATALYST**

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2012

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List of Abbreviations

δ	chemical shift (ppm)
$^{\circ}\text{C}$	degree centigrade
Ac	acetyl
AIBN	2,2'-azo <i>bisisobutyronitrile</i>
Ar	aryl (substituted aromatic ring)
Bn	benzyl
Boc	<i>t</i> -butoxycarbonyl
Bu	butyl
br	broad singlet
calcd	calculated
cat.	catalytic
cm^{-1}	wave number
d	doublet
dd	doublet of doublets
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl azodicarboxylate
DMF	<i>N,N</i> -dimethylformamide
EDG	electron donating group
EIHRMS	Electron Ionization High Resolution Mass Spectrometry
eq/equiv	equivalent
ESIHRMS	Electrospray Ionization High Resolution Mass Spectrometry
Et	ethyl
EWG	electron withdrawing group

Hz	hertz
<i>i</i> -Pr	isopropyl
IR	infrared spectroscopy
<i>J</i>	coupling constants
M	concentration (mol/L)
M ⁺	parent ion peak (mass spectrum)
m	multiplet
Me	methyl
mg	milligram
MHz	megahertz
mmol	millimole
mp	melting point
Ms	methanesulfonyl
NMR	nuclear magnetic resonance
q	quartet
rt	room temperature
s	singlet
t	triplet
TBDPS	<i>tert</i> -butyldiphenylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine

TMS

trimethylsilyl

Ts

p-toluenesulfonyl

Abstract

The synthesis of azaheterocycles which are an important class of natural products and pharmacologically active compounds has been investigated for a long time and many methodologies were reported. Radical reactions were also applied to the synthesis of azaheterocycles but not very widely. In this thesis, the author describes the development of catalytic methods to synthesize 2,5-disubstituted pyrrolidines from *N*-alkenyl, alkynyl and alkyl *N*-benzoyloxysulfonamides by using $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ as a redox catalyst. These reactions involve sulfonamidyl radicals as the key intermediates, which are generated by one electron reduction of *N*-benzoyloxysulfonamides. Thus generated sulfonamidyl radicals successively follow the two kinds of steps; 1) addition to intramolecular unsaturated bond or 2) 1,5- hydrogen abstraction.

Firstly, addition of sulfonamidyl radicals to intramolecular unsaturated bond was studied, and after the screening of redox catalysts, $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ was found to act as an efficient catalyst as shown in eq 1 and 2. From *N*-4-alkenyl-*N*-benzoyloxysulfonamides **1**, 2,5-disubstituted pyrrolidines **2** were obtained (equation 1), and acetylenic sulfonamides **3** were also converted to pyrrolidines **4** under the same reaction conditions (equation 2).

It was expected that 6-membered products could be formed by the cyclization of *N*-5-

alkenyl- or 5-alkynyl-*N*-benzoyloxysulfonamides **5** which has one more tether than the above substrate **1**. However, instead of 6-membered piperidines, 5-membered pyrrolidines **6** were obtained as the major products. Abstraction of allylic or propargylic hydrogens by sulfonamidyl radicals was more favorable than the addition to the double or triple bonds (equation 3).

Moreover, functionalization of unreactive C-H bonds of *N*-alkylsulfonamides **7** was achieved via 1,5-hydrogen abstraction to provide pyrrolidine derivatives. For example, spiro compound **8** was prepared in a good yield (equation 4).

Thus, $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ -catalyzed cyclization of *N*-alkenyl, alkynyl and alkyl *N*-benzoyloxysulfonamides afforded efficient methods to prepare pyrrolidine derivatives via the sulfonamidyl radical formation. Remote functionalizations of unreactive C-H were also achieved in a catalytic manner.

Chapter 1 General Introduction

1.1 Chemistry of nitrogen radical

Nitrogen-containing heterocycles (azaheterocycles) are an important class of natural products, pharmacologically active compounds and pesticides.¹ For example, morphine,² the most abundant alkaloid found in opium, has been used to treat both acute and chronic severe pain (Fig 1-1). Camptothecin³ is a cytotoxic quinoline alkaloid which is unique in their ability to inhibit the DNA enzyme topoisomerase I to cause the tumor cell death. Vinblastine⁴ is an antimicrotubule drug which has been used to treat certain kinds of cancer, including Hodgkin's lymphoma, non-small cell lung cancer, breast cancer, head and neck cancer, and testicular cancer. Fipronil⁵ is a broad spectrum insecticide that disrupts the insect central nervous system by blocking the passage of chloride ions through the GABA (gamma-aminobutyric acid receptor) and glutamate-gated chloride (GluCl) channels which are the components of the central nervous system.

Fig 1-1

Accordingly, many synthetic methods have been explored for azaheterocycle formation. Because amino compounds are generally good nucleophiles, most of the synthetic methods utilize the nucleophilicity of amino groups, such as condensation with carbonyl compounds,⁶ substitution of organic halides,⁷ addition to multiple bonds,⁸ etc. In addition, electrophilic amino compounds such as oxime derivatives, hydroxylamine derivatives and *N*-haloamines are employed for amination reactions of *C*-nucleophiles.⁹

Furthermore, *N*-centered radicals have attracted much attention as the synthetic intermediates to construct azaheterocycles but have not been applied so widely as the above two methodologies.^{10,11} The precursors of *N*-centered radicals are classified in the following categories, and the author will discuss the generation of nitrogen-centered radicals by the cleavages of N-X (X=halo, O, N, C, S, etc) bonds of precursors.

Thus, the author will introduce the generation of *N*-centered radicals by cleavage of N-X bonds in Section 1.1.1-1.1.5. And their properties will be discussed in Section 1.2, including the types of nitrogen-centered radicals and typical reactions of *N*-centered radicals. Moreover, the author's work is summarized briefly in Section 1.3 in which hydroxylamine derivatives are converted to pyrrolidine derivatives via nitrogen-centered radical formations.

1.1.1 Generation of nitrogen-centered radicals by cleavage of N-halogen bond

For the homolytic cleavages of various chemical bonds, the average bond dissociation energies play key factors. Some representative average bond dissociation energies are shown in table 1-1. Average bond dissociation energies of N-N, C-N, N-O, N-Br bonds are lower than C-C and C-O bonds, and N-O bond is expected to cleave homolytically more easily as compared with C-O bond.

Table 1-1

Average bond dissociation energies(kcal/mol)

Bond	Energy	Bond	Energy	Bond	Energy
C-H	98	C-N	73	N-O	55
C-C	83	N-H	93	N-Br	58
C-O	85	N-N	38	N-Cl	75

Nitrogen-centered radicals are generated from *N*-halo substituted amino compounds,¹² such as *N*-alkyl-*N*-haloamines, *N*-haloamides. Due to the small average bond dissociation energies of N-Cl and N-Br (75 kcal/mol and 58 kcal/mol, respectively),¹³ aminyl radicals and amidyl radicals are generated through the cleavage of N-halogen bonds by heating or photo irradiation.

Hofmann-Löffler reaction is a well-known reaction involving aminyl radicals. When *N*-alkyl-*N*-haloamines were heated or photolyzed in strongly acidic solutions, pyrrolidines were obtained upon the successive basic workup (Scheme 1-1).¹⁴

Scheme 1-1

Because neutral aminyl radicals readily suffer from the dimerization and the disproportionation,¹⁵ the above reactions have to be carried out in acidic media to generate protonated aminyl radicals (aminium radicals) instead of neutral radicals. The first step is the formation of chloroammonium salt **A** and then photo irradiation converts **A** to nitrogen radical cation **B**. Intramolecular hydrogen abstraction of this aminium radical affords carbon radical **C**, which is captured by **A** to give alkyl chloride **D** and **B**. Finally, pyrrolidine is obtained by nucleophilic substitution reaction by a base treatment.

The reaction has been employed to prepare substituted pyrrolidines from acyclic amines. However, the reaction conditions such as strongly acidic conditions limited its extensive application. Some modifications made the reaction to be carried out under milder conditions.¹⁶ For example, conformationally rigid cyclic *N*-chloroamines, such as **A** could be transformed to tricyclic diamine **B** under photo irradiation in the presence of triethylamine (Scheme 1-2).

Scheme 1-2

In the presence of metal salts, such as copper, iron, or titanium or alternatively protic acids, *N*-alkyl-*N*-chloroamines cyclized to heterocyclic systems via nitrogen radicals generated from N-halogen bond cleavage. For instance, Götlich reported the CuCl-catalyzed intramolecular addition of *N*-chloroamines to carbon-carbon double bonds under neutral conditions,¹⁷ in which copper complexed aminyl radicals were proposed as the cyclization precursors (Scheme 1-3). The formation of piperidines instead of pyrrolidines

was most likely due to the rearrangement of the primary reaction product, 2-chloromethylpyrrolidine, via an aziridinium cation to the thermodynamically more stable 3-chloropiperidine.

Scheme 1-3

As the aminyl radicals were supposed to coordinate to the metal catalyst in the addition step, they investigated the influence of the catalyst structures on the stereochemical outcome of the reaction. In fact, the stereoselectivity was improved by the use of CuPF_6 -TMEDA, although the product yield was decreased (Scheme 1-4).¹⁸

catalyst	yield	dr a : b
CuCl	73%	3:1
CuPF ₆ + TMEDA	43%	10:1

Scheme 1-4

Lessard and coworkers prepared the tricyclic compounds **B1** and **B2** by *N*-radical addition to intramolecular olefinic moieties starting from *N*-haloamides by using benzoyl peroxide as an initiator (Scheme 1-5).¹⁹ The product yields were affected by the position of amide carbonyl groups. In **A2**, the radical intermediate allowed more flexibility than that **A1** to reduce the yield of the intramolecular nitrogen radical cyclization.

Scheme 1-5

1.1.2 Generation of nitrogen-centered radicals by cleavage of N-O bond

The average dissociation energy of N-O bond is very small, 55 kcal/mol.⁹ Accordingly, by the cleavage of weak N-O bonds of hydroxylamine and oxime derivatives, aminyl, amidyl, and iminyl radicals are generated.

Many research groups disclosed the generation of iminyl radicals starting from oxime derivatives. Hudson found that *N*-sulfonylimines generated from ketoximes and sulfinyl chlorides were transformed to *N*-sulfonylimines under mild conditions via a homolytic fragmentation-recombination mechanism as shown in Scheme 1-6.^{20a} Homolytic cleavage of the N–O bond of sulfinate esters **A** generates iminyl and sulfinyloxyl radicals **B**, which isomerizes to sulfonyl radicals **C**, and the recombination affords *N*-sulfonylimines.

Scheme 1-6

Hudson reaction was employed to synthesize dihydropyrroles by Weinreb, in which the resulting iminyl radicals undergo intramolecular addition to olefinic moieties, followed by trapping the resulted alkyl radicals to afford dihydropyrroles (Scheme 1-7).^{20b, c}

DIPEA = *N,N*-diisopropylethylamine

TEMPO = 2,2,6,6-Tetramethylpiperidine 1-oxyl

Scheme 1-7

When *O*-benzoyloximes were treated with tributyltin hydride and AIBN in cyclohexane, bicyclic imines were obtained via iminyl radical intermediates generated by the stannyl radical induced homolytic cleavage of N-O bonds (Scheme 1-8).²¹

Scheme 1-8

Zard discovered that the treatment of γ,δ -unsaturated *O*-acetyloximes with nickel powder and acetic acid afforded dihydropyrrroles (Scheme 1-9).²² However, large excess amounts of reagents were required in this iminyl radical formation.

Scheme 1-9

Some other reagents, such as $K_2S_2O_8$, or sesamol-NaH, also promoted the iminyl radical formation from γ,δ -unsaturated *O*-acetyloximes.²³ For example, quinolines were synthesized by the cyclization of iminyl radicals generated by the oxidation of *O*-hydroxycarbonylmethyloxime as shown in Scheme 1-10.

Scheme 1-10

A catalytic method was reported by Narasaka for the generation of iminyl radicals from *O*-acetyloximes using redox catalysts.²⁴ For example, low valent metal salts were used as redox catalysts for generation of iminyl radicals from oximes. The treatment of γ,β -unsaturated oxime derivatives with a catalytic amount of CuBr SMe_2 led to the cyclization to pyrrolidines (Scheme 1-11).²⁵ As shown in Scheme 1-11, a copper(I) salt transfers an electron to γ,β -unsaturated ketone *O*-methoxycarbonyloxime **1**, resulting anion radical **A**. The elimination of carbonate anion results iminyl radical **B**, which cyclizes to give *C*-radical intermediate **C** which is in equilibrium with tertiary and primary alkyl radicals **C1** and **C2**.

These radical species are oxidized by copper(II) to iminium intermediate **D**, which suffers from a nucleophilic attack with bromide anion to give pyrrolidine **2**.

Scheme 1-11

Göttlich demonstrated the generation of aminyl radicals from hydroxylamine derivatives by a catalytic use of CuPF₆ as shown in Scheme 1-12. When γ,β -unsaturated hydroxylamine derivatives, such as *N*-4-alkenyl-*N*-benzoyloxyamine, were treated with the copper(I) salt in the presence of an equimolar amount of BF₃ OEt₂, 2-benzoyloxymethylpyrrolidines were obtained.²⁶

Scheme 1-12

As depicted in Scheme 1-13, an interesting cyano group transfer was observed in the cyclization of *N*-benzoyloxy γ,δ -unsaturated amide initiated by amidyl radical formation with tributylstannane.²⁷

Scheme 1-13

1.1.3 Generation of nitrogen-centered radicals by cleavage of N-S bond

Beckwith's group has used sulfenamides as precursors of aminyl and amidyl radicals.²⁸ For example, the tandem cyclization of sulfonamides afforded various azaheterocycles via aminyl and amidyl radical formation by treatment with tributylstannane and AIBN (Scheme 1-14).

Scheme 1-14

The similar N-S bond cleavages of *N*-arythio or *N*-2-benzothiazolythio imines with stannanes were applied to the generation of iminyl radicals. For instance, Zard reported the formation of pyrrolidines by the cyclization of phenylsulfenimides through an intramolecular iminyl radical intermediate (Scheme 1-15 and 1-16).^{27, 29}

Scheme 1-15

1.1.4 Generation of nitrogen-centered radicals by cleavage of N-N bond

Aminyl, iminyl and amidyl radicals are also generated from azene, azide, hydrazones, benzotriazole and hydrazine via cleavage of the N-N bonds, which have the average bond dissociation energy of 38 kcal/mol.⁹

Early investigations of aminyl radical formations by N-N bond cleavage were the thermal extrusion of nitrogen gas from azenes, and the generated aminyl radicals cyclized with the internal olefinic moieties predominantly in a 5-*exo* manner, affording pyrrolidines along with the 6-*endo* cyclization products piperidines (Scheme 1-17).

Kim and coworkers have developed an intramolecular addition of *N*-stannyl aminyl radicals to carbonyl groups to form amides by the homolytic N-N bond cleavage of azido carbonyl compounds.³⁰ Treatment of azides with tributylstannane afforded stannylaminyl radicals, which added to carbonyl groups to give oxyl radical intermediates. Then,

disproportionation of the oxyl radicals generated tertiary alkyl radicals, which were trapped by tributylstannane, providing amides in high yields (Scheme 1-18).

Scheme 1-18

Narasaka and Chiba reported $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ -catalyzed pyrrole formation from vinyl azides **1a** and ethyl acetoacetate via the formation of iminyl radical **I**.³¹ Iminyl radical **I** is generated by the addition of an α -radical of the keto ester to vinyl azide **1a** with release of N_2 and adds to the carbonyl group to furnish oxyl radical intermediate **II** and then dehydration occurs to produce pyrrole. In this reaction, $\text{Mn}(\text{OAc})_3$ acts as a redox catalyst for the generation of α -radicals of keto esters and the reduction of oxyl radicals **II** (Scheme 1-19).

Zard and coworkers developed efficient routes for iminyl radical formation from xanthyl hydrazones by the N-N bond cleavage (Scheme 1-20). For example, dihydropyrrole was obtained by treatment of a xanthyl hydrazone with tributylstannane and AIBN in 79% yield.³² Modification of this xanthyl hydrazone concept made the development of the generation of amidyl radicals. That is, *N*-alkenoyl-*N'*-xanthylhydrazones were converted to acyclic lactams in high yields upon treatment with tributylstannane.

Kaim and Meyer investigated a route for iminyl radical generation from *N*-1-benzotriazolylimine, which was initiated by tin radical addition to the triazolyl group, followed by the N-N bond fission (Scheme 1-21).³³

Scheme 1-21

1.1.5 Generation of nitrogen-centered radicals by cleavage of N-C bond

Barton had developed a methodology for the generation of carbon-centered radicals from 2-thioxopyridinyloxycarbonyl (PTOC) esters^{34a} and then this approach was extended to nitrogen-centered radical formation (Scheme 1-22). Furthermore, thioxothiazolyloxy-carbonyl (TTOC) carbamates were utilized as aminyl and amidyl radical precursors.³⁴

Scheme 1-22

1.1.6 Generation of aminyl radicals from other sources

Alternatively, there have been reported some other precursors to generate nitrogen radicals. For example, Tokuda reported the generation of neutral aminyl radicals by anodic oxidation of lithium alkenylamide (Scheme 1-23).³⁵ That is, pyrrolidines were prepared in a stereoselective manner from alkenylamines by the treatment with butyllithium at -78 °C, followed by anodic oxidation in a mixture of THF and HMPA containing lithium perchlorate.

Scheme 1-23

Nikishin demonstrated that *N*-alkylmethanesulfonamides cyclized to pyrrolidines by the oxidation with Na₂S₂O₈-CuCl₂.³⁶ In this reaction, oxidation of sulfonamides affords nitrogen cation radicals **A**, in turn which generate sulfonamidyl radicals **B** with deprotonation. 1,5-Hydrogen shift undergoes to generate carbon radical intermediate **C**. Then sulfonylpyrrolidines are formed as a result of oxidation of carbon radical **C** to the corresponding carbo cation intermediate **D** and the subsequent cyclization (Scheme 1-24).

1.2 Property of nitrogen radical

Thus, *N*-centered radicals are utilized in the synthesis of azaheterocycles, where various types of *N*-radicals are involved,¹ such as aminyl radicals **1**, aminium radical cations **2**, metal-complexed aminyl radicals **3**, amidyl radicals **4**, sulfonamidyl radicals **5**, cyanamidyl radicals **6** and iminyl radicals **7** (Scheme 1-25).

Among them, neutral aminyl radicals **1** display a nucleophilic character and aminium radical cations **2**, metal-complexed aminyl radicals **3**, amidyl radicals **4**, sulfonamidyl radicals **5**, cyanamidyl radicals **6** and iminyl radicals **7** are electrophilic as compared with aminyl radicals **1**.^{1a} As shown in Table 1-2, Zard and Newcomb found³⁷ that iminyl radicals **7** cyclize with intramolecular alkenyl moieties 1 order of magnitude more slowly than the

related carbon radicals and also react less rapidly than carbon radicals with hydrogen atom transfer trapping agents such as tributylstannane and thiophenol.^{33a} Iminyl radicals **7** are 1 order of magnitude faster than similar aminyl radicals **1** in the cyclization reaction with intramolecular olefinic moieties. Iminyl radicals **7** and aminyl radicals **1** cyclize with olefinic moieties less rapidly than similar aminium radical cations **2**.

Table 1-2 Radical rate constants at 25 °C

Radical	k_c (s ⁻¹)	k_T PhSH (M ⁻¹ s ⁻¹)	k_T <i>n</i> -Bu ₃ SnH (M ⁻¹ s ⁻¹)
2.0×10^7	1.0×10^8	1.4×10^6
3.0×10^5	1.2×10^8	5.0×10^5
ca. 1.0×10^{10}	4.0×10^7	ca. 1.0×10^8
2.0×10^6	6×10^6	ca. 3.0×10^3

k_c : rate constants for cyclization; k_T : rate constants for hydrogen atom transfer agents.

Thus, the consequent reactivity of *N*-radical intermediates is roughly expected due to the substituent on the nitrogen atom and the additives, which play key roles in the synthetic utilities of nitrogen radicals. For example, the reactivities of aminyl radicals are greatly influenced by the association of a lone pair electron by a protonation or by the coordination

with a Lewis acid and also by the introduction of an electron-withdrawing group to the nitrogen atom.

Hydrogen abstraction and addition to unsaturated bonds are the most typical reactions of *N*-centered radicals (Scheme 1-26). As well as *C*-centered radicals, intramolecular reactions of *N*-centered radicals have been applied in organic synthesis, and are also the main topics of this thesis. Because the intermolecular processes are still difficult to control, these 2-types of the processes are applied as intramolecular fashions: hydrogen abstraction involving the cleavage of an intramolecular C-H σ bond (equation 1), the addition of *N*-centered radicals to the intramolecular unsaturated bonds (equation 2). Primarily, these two kinds of reactions essentially produce other radical species, *C*-centered radicals in most cases, which may undergo further radical reactions such as atom or group transfer, oxidation or reduction, and successive addition reactions, etc. So we have to control the reactions; how to generate the nitrogen radicals and how to trap the *C*-centered radicals. In addition, it would be desired to carry out the reactions in a catalytic manner.

Scheme 1-26

1.3 Perspective for the Thesis

In this thesis, the author presents catalytic synthetic methods of azaheterocycles via *N*-centered radicals which are generated from hydroxylamine derivatives by the use of a redox catalyst.^{23, 24, 35h}

By one electron reduction, a neutral amino compound is converted to the corresponding anion radical as shown in Scheme 1-27. These species are rather unstable as compared with the original neutral molecules, and the cleavage of N-X bond is induced if the bond is sufficiently weak to generate a nitrogen-centered radical and X⁻.

Scheme 1-27

For such an example, γ -alkenyl ketone *O*-2,4-dinitrophenyloximes were converted to dihydropyrroles by the treatment with sesamol and NaH in the presence of radical trapping reagents such as 1,4-cyclohexadiene (Scheme 1-28).³⁸ In this reaction, a sesamol-NaH complex acts as an electron donor to *O*-2,4-dinitrophenyloximes. The weak N-O bond of the anion radicals of the oximes cleaves to give iminyl radicals and 2,4-dinitrophenoxy anion. The iminyl radicals then add to the intramolecular alkene moiety to form *C*-radical intermediates, which are trapped with radical trapping reagents.

Scheme 1-28

Thus, in the above reaction, at least a stoichiometric amount of the reducing reagent was required to generate the anion radical intermediates and radical quenchers were used to trap the resulted C-radical intermediates to terminate the reactions. Therefore, it was desired to improve this reaction in a catalytic manner.

In fact, the above reaction was improved to a catalytic procedure. That is, γ -alkenyl ketone *O*-acyloximes were converted to dihydropyrroles by the use of CuBr SMe₂ as a redox catalyst as shown in Scheme 1-11(discussed in page 10). Oxime derivatives are reduced by copper(I), leading to the corresponding anion radicals **A** with generation of copper(II) species. The following N-O bond cleavage affords iminyl radicals **B** and acyloxy anion. The intramolecular addition of the iminyl radical gives cyclization intermediates C-radicals **C1** and **C2**, which are oxidized to carbocations **D** with copper(II) species, regenerating copper(I) species.

Scheme 1-11

Recently, some related catalytic procedures have been disclosed for *N*-radical generation and reactions by applying redox catalysts. Göttlich's group demonstrated CuPF₆-catalyzed transformation of *N*-4-alkenyl hydroxylamine derivatives to 2-(benzoyloxymethyl)pyrrolidines with the combined use of an equimolar amount of BF₃·OEt₂.³⁹ The reaction was initiated similarly by the anion radical formation and they explained the coordination of BF₃ to acyloxy group facilitated the N-O bond cleavage as shown in Scheme 1-29. However, the author would like to propose the other roles for BF₃, which coordinated the nitrogen atom of the starting materials to accelerate the reduction with copper(I) and also tuned up the reactivity of aminyl radicals more electrophilic.

Scheme 1-29

Based on these recent results, the author planned to develop a catalytic method for the synthesis of pyrrolidine derivatives starting from *N*-acyloxy *N*-alkenyl sulfonamide or carboxamide derivatives (in Figure 1-2). The acyloxy group may work as a leaving group and the introduction of a strong electron withdrawing group such as a sulfonyl or acyl group is crucial to facilitate the one electron reduction with copper(I) and increase the electrophilicity of *N*-centered radical species, which enables the reaction to proceed without the use of Lewis acids such as $\text{BF}_3 \cdot \text{OEt}_2$.

Figure 1-2

The proposed reaction is depicted in Scheme 1-30. Sulfonamide **I** accepts one electron from a metallic catalyst M^{n+} to give an anion radical intermediate **IA** along with M^{n+1} , which

is followed by the radical cyclization to give a C-radical **IB** with eliminating acyloxy anion. The resulting C-radical **IB** is then oxidized by M^{n+1} to afford a carbo cation **IC** with the regeneration of M^{n+} , giving the product **II** by the successive deprotonation.

Scheme 1-30

According to this assumption, the author had started the study on the cyclization of hydroxylamine derivatives, *N*-alkenyl-*N*-benzoyloxysulfonamides, by using metal complexes as redox catalysts.

After screening of lower valent metal catalysts, it was found that *N*-4-alkenyl- or 4-alkynyl-*N*-benzoyloxysulfonamides could be converted to 2,5-disubstituted pyrrolidines in the presence of a catalytic amount of bis[copper(I) methanesulfonate]-benzene complex, $(CuOTf)_2 \cdot C_6H_6$ (equation 1), the detail of which is discussed in chapter 2. During this study, we happened to find the intramolecular allylic or propargylic 1,5-hydrogen shift when 5-alkenyl or 5-alkynyl sulfonamides were employed instead of 4-alkenyl derivatives (equation 2). These results are explained in chapter 2.

Being inspired by the above allylic hydrogen abstraction, the author examined a catalytic abstraction of unreactive C-H bond. In fact, intramolecular 1,5-hydrogen shift occurred smoothly under the same catalytic conditions to furnish pyrrolidines (equation 3), which is discussed in chapter 3.

1.4 References and Notes

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Chapter 2 (CuOTf)₂ C₆H₆-Catalyzed Synthesis of Pyrrolidines from *N*-Alkenyl- and Alkynyl-*N*-Benzoyloxysulfonamides

As described in chapter 1, section 1.3, the author proposed a catalytic method for the synthesis of pyrrolidines starting from *N*-alkenyl- or alkynyl-*N*-benzoyloxysulfonamide or carboxamide derivatives **1**, **5** and **8**. Thus, in this chapter, the preparation of these starting materials which were used for the *N*-radical generation and the successive cyclizations are discussed in the following section 2.1. Then, the results on the catalytic cyclization of these *N*-substituted sulfonamides **1**, **5** and **8** would be described in detail in section 2.2.

2.1 Preparation of starting materials

The synthetic route of the starting materials **1**, **5** and **8** is depicted in Scheme 2-1, taking sulfonamide **1a** as a typical example.

Scheme 2-1

Ketone **1aa** was treated with hydroxylamine hydrochloride to give oxime **1ab**,¹ which was reduced to hydroxylamine **1ac** by sodium cyanoborohydride (NaBH₃CN) in methanol with the addition of a methanol solution of HCl dropwise.² Then, hydroxylamine **1ac** reacted with methanesulfonyl chloride (CH₃SO₂Cl) and triethylamine to afford sulfonamide **1ad**. In this step, if the reaction temperature and the ratio of three reagents (1:1:1) were not controlled carefully, *N,O*-disulfonylated product was formed as a byproduct. Sulfonamide **1ad** was then benzoylated to afford sulfonamide **1a**.³ Sulfonamides such as **1a-1k**, **5a-5e** and **8a-8d** were prepared based on this synthetic route as shown in the following Table 2-1.

Table 2-1

1a 18%	1b 15%	1c 16%
1d 6%	1e 26%	1f 13%
1g 8%	1h 14%
1i 12%	1j 18%	1k 23%

continued

continued

Yield: total yield of 4 steps

2.2 Results and discussion

2.2.1 Screening of the redox catalysts

N-4-Alkenyl-*N*-benzoyloxysulfonamide **1a** was chosen as a model substrate for the screening to find suitable redox catalysts (Table 2-1).

Table 2-1

entry	catalyst/mol %	additive/mol %	solvent	temp/ °C	time/h	yield/%
1	1,5-naphthalenediol (10)	CH ₃ COOH (200) 1,4-cyclohexadiene (1000)	1,4-dioxane	100	7	NR
2	1,5-naphthalenediol (20)	CF ₃ COOH (200) 1,4-cyclohexadiene (500)	1,4-dioxane	100	24	NR
3	1,5-naphthalenediol (10)	1,4-cyclohexadiene (1000)	1,4-dioxane	100	24	NR
4	Mn(acac) ₂ (100)	1,4-cyclohexadiene (1000)	1,4-dioxane	100	24	NR
5	Mn(OAc) ₂ (100)	1,4-cyclohexadiene (1000)	1,4-dioxane	100	26	NR
6	MnCl ₂ (100)	1,4-cyclohexadiene (1000)	1,4-dioxane	100	24	NR
7	CuBr.SMe ₂ (100)	—	1,4-dioxane	100	36	20
8	CuPF ₆ (10)	—	toluene	110	24	trace
9	(CuOTf) ₂ .C ₆ H ₆ (40)	1,4-cyclohexadiene (1000)	1,4-dioxane	100	5	37 %

CuOTf: CuOSO₂CF₃.

1,5-Naphthalenediol was reported to act as an organo redox catalyst for the iminyl radical formation from *O*-acetyloximes in the presence of 1,4-cyclohexadiene as a radical trapping reagent.⁴ However, the expected radical cyclization did not take place at all, when **1a** was treated with a catalytic amount of naphthalenediol and 1,4-cyclohexadiene (table 2-1, entries 1-3). Manganese(II) complexes also did not promote the reaction at all (entries 4-6).

Although the radical cyclization occurred when **1a** was treated with an equimolar amount of CuBr SMe₂ in dioxane at 100 °C,⁵ the reaction proceeded very slowly and pyrrolidine **2a** was isolated only in 20% yield together with a 65% recovery of the starting material even after 36 h (entry 7). Copper(I) hexafluorophosphate was not effective and only

a trace amount of pyrrolidine **2a** was formed after 24 h (entry 8).⁶ After screening various metal complexes, such as TiF_3 , $\text{Ni}(\text{COD})_2$, $\text{Cp}_2\text{Fe}_2\text{O}_4$, $\text{In}(\text{OTf})_3$ etc., bis(copper(I) trifluoromethanesulfonate)-benzene complex, $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$, was found to be effective, and the starting material **1a** disappeared within 5 h in 1,4-dioxane at 100 °C, yielding **2a** in 37% yield (entry 9).

Table 2-2

entry	catalyst/mol %	additive/mol %	solvent	temp/ °C	time/h	yield/%
1	$(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ (40)	1,4-cyclohexadiene (1000)	1,4-dioxane	100	5	37 %
2	$(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ (40)	1,4-cyclohexadiene (1000)	toluene	110	0.5	47 %
3	$(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ (10)	1,4-cyclohexadiene (1000)	toluene	110	0.5	74%
4	$(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ (10)	1,4-cyclohexadiene (1000)	toluene	80	19	50%
5	$(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ (10)	1,4-cyclohexadiene (1000)	benzene	80	1	91%
6	$(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ (10)	—	benzene	80	1	90 %
7	$(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ (10)	—	$\text{ClCH}_2\text{CH}_2\text{Cl}$	83	0.3	91 %
8	$(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ (10)	—	toluene	110	0.5	74 %
9	$(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ (5)	—	$\text{ClCH}_2\text{CH}_2\text{Cl}$	83	1	95 %
10	$\text{Cu}(\text{OTf})_2$ (5)	—	$\text{ClCH}_2\text{CH}_2\text{Cl}$	83	4	77 %

CuOTf : $\text{CuOSO}_2\text{CF}_3$.

Then the reaction conditions were screened with a catalytic use of $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ in the presence of 1,4-cyclohexadiene as a radical trapping reagent to trap the radical cyclization intermediate **A**. However, none of the hydrogen abstract product **I** was obtained and deprotonation product **2a** was obtained in 37% yield in dioxane at 100 °C.^{4,5a,7} As the solvent, comparing with 1,4-dioxane, the use of toluene and benzene gave **2a** in markedly higher yields of 74% to 91%, respectively (entries 1, 3, 5). Because 1,4-cyclohexadiene did not concern the product formation, the reactions were examined in the absence of 1,4-cyclohexadiene. In fact, the cyclization reaction proceeded smoothly as shown in entries 6 and 8. Particularly, the cyclization of **1a** proceeded smoothly when the reactions were carried out with a 10 or 5 mol% amount of $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ in refluxing 1,2-dichloroethane, affording pyrrolidine **2a** in 91% and 95% yields, respectively (entries 7, 9). Divalent copper trifluoromethanesulfonate, $\text{Cu}(\text{OTf})_2$, also catalyzed the cyclization but not as good as $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ (entry 10). In these reactions, **2a** was obtained as a mixture of two stereoisomers in a 1 : 1 *cis* : *trans* ratio (determination of the *cis* and *trans* stereochemistry of **2a** shown in the experimental section).

It was afraid that a trace amount of TfOH generated by the hydrolysis of $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ acted as an acid catalyst to activate benzoyloxy group and cause the nucleophilic substitution with the olefinic moiety. Hence, **1a** was treated with a trace amount of TfOH in refluxing 1,2-dichloroethane, however, the reaction did not proceed at all (table 2-3, entry 3), and the use of an equimolar amount of TfOH made the reaction messy without the formation of **2a** (entries 1, 2).

Table 2-3

entry	catalyst/mol %	time	yield/%
1	(CuOTf) ₂ ·C ₆ H ₆ (5) TfOH (100)	2 min	messy
2	TfOH (100)	2 min	messy
3	TfOH (0.5)	48 h	NR

The reaction was carried out in refluxing 1,2-dichloroethane in the presence of catalyst under nitrogen atmosphere.

2.2. 2 Proposed mechanism of the cyclization of *N*-benzoylsulfonamide 1a

Bis[copper(I) trifluoromethanesulfonate]-benzene complex,⁸ (CuOTf)₂ C₆H₆, is a crystalline and air-sensitive complex which can be prepared by the reaction of trifluoromethanesulfonic anhydride with copper(I) oxide in benzene. In 1972, the characterization of cationic benzene and olefin complexes of CuOTf was investigated by Kochi and Salomon with IR and NMR spectra.⁹ They reported that (CuOTf)₂ C₆H₆ complex is stable to about 100 °C when heated in a sealed evacuated tube. Benzene is released quantitatively from the copper(I)-benzene complex only when heated above 120 °C. This benzene complex was proposed to have a structure with C_{2h} symmetry as depicted in Figure 2-1 A.^{9a,b}

It is well known that copper(I) halides such as CuCl form complexes with olefins, however, the strongly coordinating halides compete with the olefins as the ligand on copper(I)

and the binding affinity of olefins to copper(I) is smaller than chloride anion.^{9a,b} Due to the weak coordinating ability of TfO^- , CuOTf allows to absorb olefins more efficiently.^{9a,b}

The weakly coordinated benzene of $(\text{CuOTf})_2 \text{C}_6\text{H}_6$ is readily displaced with various olefins to form cationic olefin complexes in organic solvents. Thus, various cationic olefin complexes of copper(I) have been prepared from $(\text{CuOTf})_2 \text{C}_6\text{H}_6$ as listed in Figure 2-1.^{9a,b} Cationic olefin complexes of CuOTf are readily soluble in polar organic solvents, whereas the olefin complexes of copper(I) halides are mostly insoluble.^{9a,b}

Figure 2-1

By using the strong affinity to olefins, a series of photocycloaddition in the presence of $(\text{CuOTf})_2 \text{C}_6\text{H}_6$ have been discovered (Scheme 2-2).¹⁰ For instance, UV irradiation of norbornene in the presence of a catalytic amount of CuOTf afforded a dimer in 88% isolated yield,^{9a} which was a substantial improvement on the 38% yield reported for the same reaction with CuBr .¹¹

Scheme 2-2

Although the strong affinity of CuOTf with olefins has been applied in organic synthesis, there has been no incident in which CuOTf was used as a redox catalyst. So the author had a lot of interests to use CuOTf for the cyclization of sulfonamides.

A proposed mechanism of the formation of pyrrolidine **2a** by $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ -catalyzed reaction is depicted in Scheme 2-3. One-electron reduction of sulfonamide **1a** with $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ generates intermediates **A** or the oxidative addition of **1a** to the copper(I) complex affords intermediate **B**. Then, the nitrogen radical **C** is formed with the elimination of benzyloxy anion from **A** or the N-Cu(III) bond cleavages of **B**, which cyclize to generate alkyl radicals **D**. Subsequently, the resulting copper(II) species oxidize the radicals **D** to afford cation intermediates **E** with the regeneration of copper(I) complex. Finally, the elimination of a proton from intermediates **E** affords pyrrolidine **2a**. The reason why $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ acted efficiently is not clear so far, but it is supposed that such a strong Lewis acid facilitates the initial electron transfer and the coordination ability to the olefinic part promotes the *N*-centered radicals **C** addition to the olefinic moiety.

Scheme 2-3

2.2.3 Cyclization of *N*-4-alkenyl *N*-benzoyloxy sulfonamides

With the optimized conditions in hand, the preparations of pyrrolidines **2** from various *N*-benzoyloxysulfonamides **1** were examined as shown in Table 2-4. For a leaving group, significant difference was not observed by replacement of benzoyloxy group to acetoxy group and both of them were better in the product yield than pentafluorobenzoate (Table 2-4, entries 1, 2 and 3).

Table 2-4

entry	substrate	Cu ^I / mol%	time/ h	products (<i>cis:trans</i>) ^[b]
1	1a	10	1	2a 95% (1:1)
2	1b	10	4	2a 91% (6:7)
3	1c	5	1	2a 61% (9:11)

CuOTf: CuOSO₂CF₃

The cyclization of *N*-benzoyloxymethanesulfonamides having α -benzyl and methyl groups was also examined (Table 2-5). Sulfonamide **1d** was transformed into 2-benzylpyrrolidine **2d** in a lower yield of 64% as compared with **1a** having α -phenethyl group

(entries 1 and 2). The cyclization of α -methyl analogue **1e** proceeded smoothly to afford 2-methylpyrrolidine **2e** in a good yield of 84%.

Table 2-5

entry	substrate	Cu ^I / mol%	time/ h	products (<i>cis:trans</i>) ^[b]
1	1a	10	1	2a 95% (1:1))
2	1d	10	1.5	2d 64% (2:7)
3	1e	4	1	2e 84% (1:1)

CuOTf: CuOSO₂CF₃.

Concerning sulfonyl groups RSO₂, methanesulfonamide **1e** was found to be suitable as compared with arenesulfonamides **1f**, **1g** and **1h**, affording the product in a higher yield (Table 2-6, entries 1-4). A lower catalyst loading, a 0.02 molar amount of (CuOTf)₂ C₆H₆, was sufficient for the cyclization of methanesulfonamide **1e** (entry 1). It was expected that arylsulfonamides could be converted to pyrrolidines in higher yields as compared with methanesulfonamide because stronger electron withdrawing groups arylsulfonamides accelerated the one electron reduction. However, the results showed cyclization products were obtained in lower yields. Arylsulfonyl groups made the cleavage of the N-Cu(III) bond

of intermediate **B** not easy as compared with methylsulfonyl group, because arenesulfonamide anion is more stable than that of methanesulfonamide.

Table 2-6

entry	substrate	Cu ^I / mol%	time/ h	products (<i>cis:trans</i>) ^[b]
1	 1e	4	1	2e 84% (1:1)
2	 1f	10	4	2f 60% (4:5)
3	 1g	10	48	2g 30% (5:4)
4	 1h	15	3	2h 55% (4:5)

CuOTf: CuOCF₃SO₂.

When benzamide **1i** was submitted to the (CuOTf)₂ C₆H₆-catalyzed reaction instead of sulfonamides, the benzoyl group participated in the product formation. That is, pyrrolidine **2i** was obtained in 36% yield along with 39% yield of an unexpected tricyclic compound **3** (Scheme 2-4). The formation of **3** suggested the presence of the carbocation intermediate, in which Friedel-Crafts alkylation occurred intramolecularly. To prevent this successive Friedel-Crafts reaction, sulfonamides are more suitable as the cyclization precursors as compared to benzamides.

Scheme 2-4

Furthermore, in Scheme 2-5, the reactions of sulfonamides having tri, di and mono-substituted alkene moieties were summarized. Sulfonamides with a trisubstituted alkene moiety such as **1a** (equation 1) gave a higher yield of the product **2a** as compared with the substrate bearing a disubstituted alkene moiety **1j** (equation 2). That is, under the same reaction conditions, **2a** was obtained in 95% yield from **1a**, whereas the yield of **2j** was 56%. The stereoisomers of **2j** were separated by column chromatography. The *trans*-isomer, *trans*-**2j**, was less polar than the *cis*-isomer whose structure was confirmed by X-ray crystal determination as shown in Figure 2-1. The significant difference of the *trans* and *cis*-isomers appeared in their ^1H NMR spectra. The protons at 3 and 4-positions of the *trans*-isomer were observed in different chemical shifts as a double-set of multiple peaks and those of the *cis*-isomer are overlapped as a single-set of multiple peaks (shown in experimental data section).

Thus, the reactions of tri and di-substituted olefinic sulfonamides gave pyrrolidines (Scheme 2-5, equations 1-2, Figure 2-2), whereas the reaction of mono-substituted one **1k** gave 6-membered cyclization product. When sulfonamide **1k** was treated with

(CuOTf)₂ · C₆H₆ under same conditions, piperidine **4** was obtained instead of pyrrolidine in 44% yield (Scheme 2-5, equation 3).

Scheme 2-5

Figure 2-2. The structure of *trans*-**2j**

The formation of piperidine **4** can be explained as depicted in Scheme 2-6. At first, the 5-exo addition of amidyl radical **B** to the vinyl group gives a carbon radical intermediate **C**. Because this primary radical is not so stable as the secondary and tertiary radicals that it may have an interaction with the nitrogen atom. This cyclized radical intermediate is then oxidized by copper(II) species to ammonium ion intermediate **D**, and finally the deprotonation occurs to give piperidine **4**. This mechanism is consistent with the conventional radical cyclizations in which five-membered rings are formed preferentially over 6-membered ring formation.^{3b}

Scheme 2-6

A similar piperidine formation was also observed by Götlich in the CuPF₆-catalyzed intramolecular cyclization of olefinic *N*-chloroamines, where the similar rearrangement pathway was proposed for the formation of piperidine derivatives (Scheme 2-7).^{3b}

Scheme 2-7

2.2.4 Cyclization of *N*-5-alkenyl *N*-benzoyloxy sulfonamides

As discussed above, *N*-4-alkenyl-*N*-benzoylsulfonamides were found to cyclize to give 5-membered ring pyrrolidines fundamentally by the (CuOTf)₂ C₆H₆-catalyzed reactions. To explore the scope of this reaction, the cyclization of *N*-5-alkenyl-*N*-benzoylsulfonamides **5** (Scheme 2-8) possessing one more methylene tether between amino and alkenyl groups was examined, expecting the formation of 6-membered compounds, 2,6-disubstituted piperidines **7**.

Scheme 2-8

Interestingly, when *N*-benzoyloxysulfonamides **5a** and **5b** which had a trisubstituted alkene moiety were subjected to the cyclization, 5-membered ring compounds, pyrrolidines **6a** and **6b**, were obtained as major products in 66% and 47% yields, respectively, whereas the expected piperidines **7a** and **7b** were isolated as minor products in 12% and 7% yields, respectively (Scheme 2-8). The *cis*-isomers of pyrrolidine derivatives *cis*-**6a** and **b** were obtained preferentially.

From the terminal vinylic substrates **5c** and **5d**, only five-membered ring products **6c** and **6d** were obtained in 61% and 82% yields, respectively (Scheme 2-9). As 1,5-hydrogen abstraction at the allylic position was supposed to proceed, *N*-benzoyloxysulfonamids **5e** which has benzylic hydrogens at δ -position was treated with $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ with the expectation of 1,5-benzylic hydrogen abstraction by the *N*-radical intermediate. In fact, pyrrolidine **5d** was obtained in 55% yield.

Scheme 2-9

The formation of pyrrolidine derivatives from sulfonamides **1** and **5** was a strong evidence to prove that copper(I)-catalyzed cyclization proceeds via amidyl radical intermediates or the equivalents.¹³ The plausible mechanism was considered as shown in Scheme 2-10.

Sulfonamide **5** accepts one electron from $(\text{CuOTf})_2 \text{C}_6\text{H}_6$ to form radical anion **A**, followed by the elimination of benzoate anion to generate nitrogen radical **B**. If nitrogen radical **B** adds to the intramolecular double bond, the six-membered ring product, piperidine **7**, is formed. Alternatively, in nitrogen radical intermediate **B**, the 1,5-hydrogen shift takes place to afford allylic radical **E**, which is oxidized with copper(II) specie to give allylic cation intermediate **F** with the regeneration of copper(I). In cationic intermediate **F**, nucleophilic attack of the amino group leads to the formation of C-N bond to yield pyrrolidine **6** by a deprotonation.

Scheme 2-10

2.2.5 Cyclization of *N*-4- and *N*-5-alkynyl-*N*-benzoyloxy sulfonamides

The copper(I)-catalyzed formation of pyrrolidines prompted us to study the similar cyclization of *N*-benzoyloxysulfonamides having alkynyl moieties. Under the standard conditions using (CuOTf)₂·C₆H₆ as a catalyst, the radical cyclization reaction of 4-alkynyl **8a** proceeded. From the crude ¹H NMR spectrum, the desired product **9a** was observed in 15% yield along with some unexpected products, **9'a**, **9'b** and **9'c** in 40, 10 and 20% yields, respectively (Scheme 2-11). 2H-Pyrroles **9'a** might be derived by the isomerization of **9a** and the 6-membered products **9'b** were derived from the addition to triple bond. Amide **9'c** might be generated by the oxidation of **9'a**, **9'b** and **9a** by oxygen. When the reaction was heated overnight, the major product became **9'c** in 51% crude yield, whereas the reaction in a sealed tube gave the original ratio of the products.

Scheme 2-11

Some metal salts such as Mn(acac)₂, Mn(OAc)₂, MnCl₂ and CuCl were also screened as redox catalysts to obtain a single product, but no good result was obtained. In the cases of manganese salts, the reactions did not proceed and the starting material **8a** was recovered. Although CuCl catalyzed the reaction, several kinds of the products were formed. When the

reaction was performed in the presence of 10 molar amounts of 1,4-cyclohexadiene, side products **9'a**, **9'b** and **9'c** were not obtained and pyrrolidine **9a** was isolated as a sole product in 56% yield (Scheme 2-12, equation 1). Until now, it was not clear that how the additive, 1,4-cyclohexadiene, prevented the generation of side products **9'a**, **9'b** and **9'c**. Acetylenic substrate **8b** was also transformed into pyrrolidine **9b** in 33% yield (equation 2). The stereochemistry of **9b** was confirmed as Z forms by the X-ray crystal analysis (Figure 2-2).

Scheme 2-12

Figure 2-2. The structure of product **9b**

The cyclization of **8a** and **8b** might proceed via intermediate **A** or **B** as shown in Scheme 2-13, which were formed by the *cis*-cyclization of *N*-radical (probably the Cu adducts) intermediate. Through the reductive elimination of the intermediates, the *Z*-isomers were generated stereoselectively.

Scheme 2-13

In addition, the cyclizations of 5-alkynyl sulfonamides, **8c** and **8d** provided pyrrolidines **10c** and **10d** in 38% and 74% yields, respectively (Scheme 2-14, equation 1, 2). The cyclization presumably proceeds via propargylic hydrogen abstraction in the amidyl radical intermediates as discussed in Scheme 2-10.

Scheme 2-14

2.3 Conclusion

In this chapter, $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ was found to act effectively as a redox catalyst for the cyclization of various *N*-alkenyl- or alkynyl-*N*-benzoyloxysulfonamides to 2,5-disubstituted pyrrolidines. The cyclization proceeds in two fashions via sulfonamidyl radical intermediates: addition reaction to unsaturated bonds or allylic (or propargylic) hydrogen abstraction.

2.4 Experimental data

2.4.1 General

All chemicals were purchased from Alfa Aesar, Merck, Sigma-Aldrich, Sinopharm Chemical and used without purification, unless otherwise stated. Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 pre-coated silica gel plates (0.2 mm thickness). Subsequent to elution, the plates were visualized using ultraviolet radiation (254 nm). Flash column chromatography was performed using Merck silica gel 60 with distilled solvents. Preparative thin-layer chromatography (PTLC) were prepared using Wakogel B-5F (Wako Pure Chemical Industries) and gradually heated to 100 °C over 2 hours and at 100 °C for an additional 2 hours.

^1H nuclear magnetic resonance (NMR) (500, 400 and 300 MHz) spectra were recorded on Bruker AVANCE 500, 400 and 300 in CDCl_3 [using CDCl_3 (for ^1H , $\delta = 7.26$) as internal standard] unless otherwise mentioned. ^{13}C NMR (125, 100 and 75 MHz) spectra were recorded on Bruker AVANCE 500, 400 and 300 in CDCl_3 [using CDCl_3 (for ^{13}C , $\delta =$

77.00) as internal standard] unless other mentioned. Chemical shifts were reported in parts per million (ppm) from tetramethylsilane for ^1H and ^{13}C experiments. Abbreviations used to explain the multiplicities were as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet or unresolved, br = broad. Coupling constants (J) are given in Hz.

Infra-red spectra were recorded on Shimazu IR Prestige-21 FT-IR Spectrometer. Samples were analyzed as a neat liquid or as a solution in chloroform using NaCl cells. High-resolution mass spectra were obtained with Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). Elemental analyses were carried out at the Elemental Analysis Laboratory. Melting points were recorded on Buchi B-54 melting point apparatus and are uncorrected.

Dry tetrahydrofuran (THF), diethyl ether (Et_2O), toluene and dichloromethane (CH_2Cl_2) were taken from a solvent purification system (PS-400-5, innovative technology Inc.). Triethylamine (Et_3N) and pyridine were distilled from CaH_2 and stored over potassium hydroxide (KOH). Ethanol (EtOH) and Methanol (MeOH) were distilled from sodium under N_2 and stored over MS 4A.

2.4.2. Synthesis of *N*-alkenyl and alkynyl-*N*-benzoyloxysulfonamides

The substrates involved in chapter 2 were prepared by the following procedures.

Scheme 2-14

There were some methods to synthesize ketone described in detail as followed.

2.4.2.1 Synthesis of ketones

Method A-1

Synthesis of 1,8-diphenyloct-7-yn-3-one (8da):

To a solution of *N,O*-dimethylhydroxylamine (0.7 g, 7.2 mmol) in CH₂Cl₂ (15 mL) was added Et₃N (1.45 g, 14.3 mmol) and a solution of 3-phenylpropanoyl chloride (1.21 g, 7.18 mmol) in CH₂Cl₂ (1 mL) dropwise at 0 °C. The resulting mixture was warmed to room temperature and stirred for 6 h. The reaction was quenched with water and organic materials were extracted with EtOAc. The combined extracts were washed with water and brine, dried over MgSO₄ and evaporated. The crude product was purified by flash column chromatography (hexane/EtOAc = 2 : 1) on silica gel to give *N*-methoxy-*N*-methyl-3-phenylpropanamide (1.16 g, 6.0 mmol) in 83% yield.

To a solution of (5-phenylpent-4-ynyl)magnesium bromide prepared from magnesium turnings (0.48 g, 20.0 mmol) and (5-bromopent-1-ynyl)benzene (2.22 g, 10.0 mmol) in THF (20 mL) was added a solution of *N*-methoxy-*N*-methyl-3-phenylpropanamide (1.16 g, 6 mmol) in THF (15 mL) dropwise. The resulting yellow-brown suspension was stirred at room temperature overnight, then quenched very carefully with 2 N aqueous HCl (70 mL) and stirred at room temperature for further 30 min. The mixture was poured into water and extracted with Et₂O. The combined extracts were dried over MgSO₄, and then the solvents were evaporated under reduced pressure. The resulting residue was purified by flash column

chromatography (hexane/EtOAc = 10 : 1) on silica gel to give the 1,8-diphenyloct-7-yn-3-one **8da** (0.84 g, 3.1 mmol) in 51% yield.

Total yield: 41%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.40-7.38 (m, 2H), 7.29-7.26 (m, 5H), 7.21-7.17 (m, 3H), 2.92 (t, 2H, $J = 7.6$ Hz), 2.77 (t, 2H, $J = 7.6$ Hz), 2.60 (t, 2H, $J = 7.2$ Hz), 2.44 (t, 2H, $J = 6.8$ Hz), 1.91-1.84 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 209.4, 141.0, 131.5, 128.4, 128.3, 128.2, 127.6, 126.0, 123.7, 89.1, 81.4, 44.4, 41.5, 29.7, 22.5, 18.7; FT-IR (neat): 3408, 2936, 2230, 1712, 1489, 1371, 1097 cm^{-1} ; HRMS (ESI): Found: m/z , 277.1593, Calcd for $\text{C}_{20}\text{H}_{21}\text{O}$ $[\text{M}+\text{H}]^+$: 277.1592.

5ca was prepared by method A-1.

1-phenyloct-7-en-3-one (**5ca**):¹²

Total yield: 68%; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.29-7.25 (m, 2H), 7.20-7.16 (m, 3H), 5.79-5.69 (m, 1H), 5.01-4.95 (m, 2H), 2.89 (t, 2H, $J = 7.6$ Hz), 2.72 (t, 2H, $J = 7.6$ Hz), 2.38 (t, 2H, $J = 7.4$ Hz), 2.05-2.00 (m, 2H), 1.70-1.63 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 209.9, 141.1, 137.9, 128.4, 128.3, 126.0, 115.2, 44.3, 42.1, 33.0, 29.7, 22.7; FT-IR(neat): 3018, 2399, 1710, 1496, 1215 cm^{-1} ; HRMS (ESI): Found: m/z , 203.1443, Calcd for $\text{C}_{14}\text{H}_{19}\text{O}$ $[\text{M}+\text{H}]^+$: 203.1436.

Method A-2

Synthesis of 6-methyl-1-phenylhept-5-en-2-one (**1da**):¹³

To a stirred solution of isopropylidene malonate (14.41 g, 0.10 mol) in CH_2Cl_2 (150 mL) was added dropwise pyridine (19.22 g, 0.24 mol) at 0 °C. Then a solution of phenylacetyl chloride (15.46 g, 0.10 mol) in CH_2Cl_2 (100 mL) was added dropwise, and stirred for 1 h at the same temperature and overnight at room temperature. The reaction was diluted with CH_2Cl_2 and washed with water, dried over MgSO_4 and evaporated to give organic materials. The resulting materials were dissolved in ethanol (100 mL) and stirred at reflux temperature overnight. The reaction mixture was concentrated in vacuum to give an orange oil. The crude product was purified by flash column chromatography (hexane/EtOAc = 6 : 1) to give ethyl 3-oxo-4-phenylbutanoate (17.30 g, 42.0 mmol) as an orange oil in 42% yield.

To a stirred solution of ethyl 3-oxo-4-phenylbutanoate (10.30 g, 50.0 mmol) in THF (80 mL) was added NaH (2.00 g, 60%, 50.0 mmol) over 15 min at 0 °C. The reaction mixture was stirred until all solid material disappeared. 1-Bromo-3-methylbut-2-ene (14.90 g, 100.0 mmol) was added dropwise, and stirred for 1 h at 0 °C and overnight at room temperature. The reaction was quenched with water and hydrochloric acid to pH 7 and extracted with EtOAc. The combined extracts were washed with water and brine, and dried over MgSO_4 and evaporated. The crude product was purified by flash column chromatography (hexane/EtOAc = 20 : 1) to give a colorless oil, ethyl 5-methyl-2-(2-phenylacetyl) hex-4-enoate (8.78 g, 32.0 mmol) in 64% yield.

To a solution of ethyl 5-methyl-2-(2-phenylacetyl)hex-4-enoate (8.23 g, 30.0 mmol) in methanol (85 mL) was stirred for 10 min at 0 °C. Sodium hydroxide pellets (11.97 g, 288.0 mmol) were added over 20 minutes after water (85 mL) was added to the reaction. The mixture was stirred overnight at room temperature. Concentrated sulphuric acid was added to acidify the solution to pH 3. The resulting solution was stirred for another 20 min at room temperature and then heated to reflux for 3 h and then cooled to room temperature. The

reaction was quenched with water, and extracted with EtOAc. The extracts were washed with water and brine, and dried over MgSO_4 and evaporated. The crude product was purified by flash column chromatography (hexane/EtOAc = 20 : 1) to give a yellow oil, 6-methyl-1-phenylhept-5-en-2-one **1da**¹⁴ (5.13 g, 25.0 mmol) in 85% yield.

Total yield: 23%; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.34-7.18 (m, 5H), 5.01 (t, 1H, $J = 6.8$ Hz), 3.67 (s, 2H), 2.46 (t, 2H, $J = 7.6$ Hz), 2.23 (t, 2H, $J = 7.2$ Hz), 1.65 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 208.0, 134.2, 132.6, 129.3, 128.6, 126.8, 122.6, 50.1, 41.8, 25.6, 22.4, 17.5; FT-IR (neat): 2923, 1714, 1454, 1074 cm^{-1} ; HRMS (ESI): Found: m/z , 203.1439, Calcd for $\text{C}_{14}\text{H}_{19}\text{O}$ $[\text{M}+\text{H}]^+$: 203.1436.

8ba were prepared by method A-2.

1-phenylhept-5-yn-2-one (**8ba**):

Total yield: 21%; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.35-7.20 (m, 5H), 3.71 (s, 2H), 2.64 (t, 2H, $J = 7.2$ Hz), 2.38-2.31 (m, 2H), 1.73 (t, 3H, $J = 2.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 206.6, 133.9, 129.4, 128.7, 127.0, 77.6, 76.1, 50.2, 41.1, 13.3, 3.4; FT-IR (neat): 3063, 3055, 1721, 1713, 1450, 1265, 1080 cm^{-1} ; HRMS (ESI): Found: m/z , 187.1121, Calcd for $\text{C}_{13}\text{H}_{15}\text{O}$ $[\text{M}+\text{H}]^+$: 187.1123.

Method A-3

Synthesis of 7-methyl-1-phenyl-6-octen-3-one (**1aa**):^{14,15}

To a stirred suspension of NaH (3.08 g, 77.0 mmol) in THF (30 mL) was added dropwise ethyl-3-oxobutanoate (9.1 g, 70.0 mmol) at 0 °C. The resulting mixture was stirred for 1 h, and *t*-BuLi (46 mL, 1.6 M in hexane) was added dropwise at the same temperature. After 1 h, a solution of benzyl bromide (11.97 g, 70.0 mmol) in THF (25 mL) was added dropwise over 1 h. The reaction mixture was stirred overnight at room temperature and quenched by aqueous HCl, and extracted with EtOAc. The combined extracts were washed with water and brine, and dried over MgSO₄ and evaporated. The crude product was purified by flash column chromatography (hexane/EtOAc = 10 : 1) to give ethyl 3-oxo-5-phenylpentanoate (9.2 g, 42.0 mmol) in 54% yield.

To a stirred suspension of NaH (0.16 g, 60%, 4.0 mmol) in THF (15 mL) was added with a solution of ethyl 3-oxo-5-phenylpentanoate (0.80 g, 3.6 mmol) in THF (1 mL) at 0 °C. After 20 min, 1-bromo-3-methylbut-2-ene (0.54 g, 3.6 mmol) was added at the same temperature. The reaction mixture was stirred overnight at room temperature. The reaction was quenched by aqueous HCl and extracted with EtOAc. The combined extracts were washed with water and brine, and dried over MgSO₄ and evaporated. The crude product was purified by flash column chromatography (hexane/EtOAc = 8 : 1) to give ethyl 5-methyl-2-(3-phenylpropanoyl)hex-4-enoate (0.75 g, 2.6 mmol) in 72% yield.

To a solution of ethyl 5-methyl-2-(3-phenylpropanoyl)hex-4-enoate (0.35 g, 1.2 mmol) and LiBr (0.22 g, 2.5 mmol) in DMF (2 mL) and water (50 mL) was stirred at reflux temperature overnight. The reaction was quenched by water and extracted with EtOAc. The combined extracts were washed with water and brine, and dried over MgSO₄ and evaporated. The crude product was purified by flash column chromatography (hexane/EtOAc = 10 : 1) to give 7-methyl-1-phenyloct-6-en-3-one **1aa**^{14, 15} (0.19 g, 0.88 mmol) in 73% yield.

Total yield: 28%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.29-7.25 (m, 2H), 7.20-7.16 (m, 3H), 5.03 (t, 1H, $J = 6.8$ Hz), 2.89 (t, 2H, $J = 8.0$ Hz), 2.72 (t, 2H, $J = 8.0$ Hz), 2.41 (t, 2H, $J = 7.6$ Hz), 2.24 (q, 2H, $J = 7.2$ Hz), 1.66 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 210.0, 141.2, 132.8, 128.5, 128.3, 126.1, 122.7, 44.4, 43.0, 29.8, 25.7, 22.5, 17.7; FT-IR (neat): 2922, 1713, 1452, 1088 cm^{-1} ; HRMS (ESI): Found: m/z , 217.1593, Calcd for $\text{C}_{15}\text{H}_{21}\text{O}$ $[\text{M}+\text{H}]^+$: 217.1592.

1ja, 8aa were prepared by method A-3.

(E) 1-phenyl-6-octen-3-one (1ja):¹⁶

Total yield: 71%; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.30-7.26 (m, 2H), 7.21-7.17 (m, 3H), 5.46-5.34 (m, 2H), 2.90 (t, 2H, $J = 7.6$ Hz), 2.73 (t, 2H, $J = 7.6$ Hz), 2.44 (t, 2H, $J = 7.6$ Hz), 2.24 (q, 2H, $J = 6.8$ Hz), 1.62 (d, 3H, $J = 6.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 209.6, 141.1, 129.4, 128.4, 128.3, 126.0, 125.9, 44.3, 42.7, 29.7, 26.7, 17.8; FT-IR (neat) 3018, 1713, 1215 cm^{-1} ; HRMS (ESI): Found: m/z , 203.1435, Calcd for $\text{C}_{14}\text{H}_{19}\text{O}$ $[\text{M}+\text{H}]^+$: 203.1436

1-phenyloct-6-yn-3-one (8aa):¹⁷

Total yield: 69%; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.30-7.17 (m, 5H), 2.91 (t, 2H, $J = 7.6$ Hz), 2.75 (t, 2H, $J = 7.6$ Hz), 2.58 (t, 2H, $J = 7.2$ Hz), 2.41-2.36 (m, 2H), 1.74 (t, 3H, $J = 2.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 208.2, 140.9, 128.5, 128.3, 126.1, 77.6, 76.1,

44.3, 42.1, 29.6, 13.3, 3.4; FT-IR (neat): 2918, 1714, 1454, 1091, 1029 cm^{-1} ; HRMS (ESI): Found: m/z , 201.1282, Calcd for $\text{C}_{14}\text{H}_{17}\text{O}$ $[\text{M}+\text{H}]^+$: 201.1279.

Method A-4

Synthesis of 8-methyl-1-phenylnon-7-en-3-one (5aa):¹⁸

To a solution of 6-methylhept-5-en-1-ol (2.3 g, 18.0 mmol) in CH_2Cl_2 (150 mL) was added Pyridinium chlorochromate (PCC) (5.9 g, 27.4 mmol), and the mixture was stirred at room temperature overnight. The solution was diluted with Et_2O (100 mL) and filtered through a pad of silica gel. The filtrate was concentrated and the resulting crude product was purified by flash chromatography on silica gel with Et_2O to give 6-methylhept-5-enal.

To a solution of the above 6-methylhept-5-enal in Et_2O was added a solution of phenethylmagnesium bromide (27.8 mL, 1.0 M in THF) dropwise at 0 $^\circ\text{C}$. The resulting mixture was stirred at the same temperature overnight, then quenched very carefully with 1 N aqueous HCl (30 mL) and stirred at room temperature for further 30 min. The mixture was poured into water and extracted with Et_2O . The combined extracts were dried over MgSO_4 and evaporated. The resulting residue was purified by flash column chromatography (hexane/ EtOAc = 10 : 1) on silica gel to give 8-methyl-1-phenylnon-7-en-3-ol (2.6 g, 11.3 mmol) in 60% yield (2 steps).

To a solution of 8-methyl-1-phenylnon-7-en-3-ol (2.6 g, 11.3 mmol) in CH_2Cl_2 (100 mL) was added PCC (3.65 g, 16.0 mmol), and the mixture was stirred at room temperature overnight. The solution was diluted with ether (100 mL) and filtered through a pad of silica

gel. The filtrate was concentrated and the resulting crude product was purified by flash column chromatography (hexane/EtOAc = 20 : 1) to give 8-methyl-1-phenylnon-7-en-3-one **5aa** (1.73 g, 7.6 mmol) in 67% yield.

Total yield: 40%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.29-7.25 (m, 2H), 7.20-7.17 (m, 3H), 5.07-5.04 (m, 1H), 2.89 (t, 2H, $J = 7.6$ Hz), 2.72 (t, 2H, $J = 7.6$ Hz), 2.37 (t, 2H, $J = 7.4$ Hz), 1.99-1.93 (m, 2H), 1.68 (s, 3H), 1.64-1.57 (m, 2H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 210.3, 141.2, 132.3, 128.4, 128.3, 126.0, 123.7, 44.3, 42.4, 29.7, 27.3, 25.7, 23.9, 17.7; FT-IR(neat): 2927, 1712, 1452, 1375, 1091 cm^{-1} ; HRMS (ESI): Found: m/z , 231.1735, Calcd for $\text{C}_{16}\text{H}_{23}\text{O}$ $[\text{M}+\text{H}]^+$: 231.1749.

1,6-diphenylhexan-3-one (**5ea**)

Yield: 75%; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.30-7.27 (m, 4H), 7.20-7.15 (m, 6H), 2.90 (t, 2H, $J = 8$ Hz), 2.71 (t, 2H, $J = 8$ Hz), 2.61 (t, 2H, $J = 8$ Hz), 2.40 (t, 2H, $J = 8$ Hz), 1.95-1.88 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 209.8, 141.5, 141.1, 128.44, 128.43, 128.3, 128.2, 126.0, 125.9, 44.3, 42.1, 35.0, 29.7, 25.1; FT-IR (neat): 3026, 1712, 1602, 1494, 1454 cm^{-1} ; HRMS (ESI): Found: m/z , 253.1590, Calcd for $\text{C}_{18}\text{H}_{21}\text{O}$ $[\text{M}+\text{H}]^+$: 253.1592.

Method A-5

Synthesis of 1-phenylnon-7-yn-3-one (**8ca**):¹⁹

To a solution of 2-methyl-1,3-cyclohexanedione (1.26 g, 10.0 mmol) and pyridine (1.6 mL, 20.0 mmol) in CH₂Cl₂ (50 mL) was added dropwise Tf₂O (2.0 mL, 12.0 mmol) at -78 °C. The reaction mixture was stirred for another 10 min at the same temperature and warmed to 0 °C. The reaction was quenched with 1 N aqueous HCl, and extracted with Et₂O. The combined extracts were washed with aqueous Na₂CO₃ solution and water, dried over MgSO₄ and evaporated. The crude product was purified by flash column chromatography (hexane/EtOAc = 5 : 1) on silica gel to give 2-methyl -3-(trifluoromethanesulfonyloxy)-2-cyclohexen-1-one (2.10 g, 8.0 mmol) in 80% yield.

To a solution of phenethylmagnesium chloride (7.0 mL, 1 mol/L THF solution) in toluene (40 mL) was added a solution of 2-methyl-3-(trifluoromethanesulfonyloxy)-2-cyclohexen-1-one (1.8 g, 6.9 mmol) in toluene (5 mL) at -78 °C under N₂ atmosphere. The mixture was stirred at -78 °C for 10 min, at 0 °C for 10 min, at room temperature for 30 min, and then at 60 °C for 30 min. The reaction was quenched with saturated aqueous NH₄Cl solution and extracted with Et₂O. The combined extracts were washed with water, dried over MgSO₄ and evaporated. The crude product was purified by flash column chromatography (hexane/EtOAc = 10 : 1) to give 1-phenylnon-7-yn-3-one **8ca** (0.85 g, 4.0 mmol) in 57% yield.

Total yield 46%; colorless oil; ¹H NMR (400 MHz, CDCl₃) δ: 7.30-7.17 (m, 5H), 2.90 (t, 2H, *J* = 7.6 Hz), 2.75 (t, 2H, *J* = 7.6 Hz), 2.51 (t, 2H, *J* = 7.2 Hz), 2.17-2.12 (m, 2H), 1.77-1.70 (m, 2H, overlapped), 1.76 (t, 3H, *J* = 2.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ: 209.7, 141.1, 128.5, 128.3, 126.1, 78.2, 76.3, 44.4, 41.6, 29.8, 22.8, 18.1, 3.4; FT-IR (neat): 2933, 1712, 1417, 1217, 1139, 1041 cm⁻¹; HRMS (ESI): Found: *m/z*, 215.1433, Calcd for C₁₅H₁₉O [M+H]⁺: 215.1436.

2.4.2.2 Synthesis of hydroxylamines

Synthesis of *N*-(7-methyl-1-phenyloct-6-en-3-yl)hydroxylamine (**1ab**):

To a solution of 7-methyl-1-phenyloct-6-en-3-one **1aa** (0.86 g, 4.0 mmol) in methanol (20 mL) was added pyridine (1.90 g, 24.0 mmol) and $\text{NH}_2\text{OH}\cdot\text{HCl}$ (1.67 g, 24.0 mmol) at room temperature. After the reaction mixture was stirred for 5 h, the mixture was concentrated under reduced pressure to remove the solvent. The resulting mixture was diluted with water, and extracted with Et_2O . The combined extracts were washed with water, brine and dried over MgSO_4 , and then evaporated to give crude oxime which can be used directly in the next step.

To a stirred solution of the above crude oxime in methanol (20 mL) was added NaBH_3CN (0.38 g, 6.0 mmol) at 0 °C. A solution of HCl in methanol was dropwise added to the reaction mixture to pH 3 – 4 at 0 °C. The reaction mixture was stirred for 30 min at the same temperature. Then aqueous NaOH was added dropwise to pH 10 – 11 at the same temperature and stirred for 1 h. The reaction was quenched with water, and extracted with Et_2O . The combined extracts were washed with water, brine and dried over MgSO_4 , and then evaporated. The crude product was purified by flash column chromatography (hexane/ EtOAc = 2 : 1) on silica gel to give *N*-(7-methyl-1-phenyloct-6-en-3-yl)hydroxylamine **1ab** (0.56 g, 2.4 mmol) in 60% yield (2 steps).

Total yield: 60%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.30-7.26 (m, 2H), 7.20-7.16 (m, 3H), 5.10 (t, 1H, $J = 6.8$ Hz), 2.87-2.84 (m, 1H), 2.69-2.64 (m, 2H), 2.06-2.00 (m, 2H), 1.91-1.84 (m, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 1.77-1.44 (m, 3H, overlapped); ^{13}C NMR (100 MHz, CDCl_3) δ : 142.2, 132.0, 128.4, 128.3, 125.8, 124.0, 60.8, 33.4, 32.2, 31.5, 25.7, 24.5, 17.7; FT-IR (neat): 3581, 3019, 2399, 1518, 1423, 1215 cm^{-1} ; HRMS (ESI): Found: m/z , 234.1853, Calcd for $\text{C}_{15}\text{H}_{24}\text{NO}$ $[\text{M}+\text{H}]^+$: 234.1858.

1db, 1jb, 1kb, 5ab, 5bb, 5cb, 5db, 8ab, 8bb, 8cb and 8db were prepared by same procedure.

***N*-(6-methyl-1-phenylhept-5-en-2-yl)hydroxylamine (1db):**

Total yield: 41%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.32-7.20 (m, 5H), 5.10 (t, 1H, $J = 6.4$ Hz), 3.06-3.02 (m, 1H), 2.86-2.74 (m, 2H), 2.17-2.03 (m, 2H), 1.69 (s, 3H), 1.69-1.54 (m, 1H, overlapped), 1.61 (s, 3H), 1.49-1.41 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 138.7, 131.8, 129.3, 128.4, 126.2, 124.0, 62.5, 37.7, 31.4, 25.7, 24.7, 17.7; FT-IR (neat): 3592, 3266, 1456, 1377 cm^{-1} ; HRMS (ESI): Found: m/z , 220.1705, Calcd for $\text{C}_{14}\text{H}_{22}\text{NO}$ $[\text{M}+\text{H}]^+$: 220.1701.

***(E)*-N-(1-phenyloct-6-en-3-yl)hydroxylamine (1jb):**

Total yield: 68%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.31-7.26 (m, 2H), 7.21-7.19 (m, 3H), 5.48-5.39 (m, 2H), 2.89-2.86 (m, 1H), 2.70-2.65 (m, 2H), 2.06-2.04 (m, 2H), 1.92-1.85 (m, 1H), 1.77-1.51 (m, 3H, overlapped), 1.65 (d, 3H, $J = 4.4$ Hz); ^{13}C NMR (100 MHz,

CDCl₃) δ : 142.2, 130.8, 128.42, 128.37, 125.9, 125.4, 60.7, 33.3, 32.2, 31.2, 29.0, 18.0; FT-IR (neat): 3581, 3018, 2856, 2399, 1454, 1215 cm⁻¹; HRMS (ESI): Found: m/z , 220.1700, Calcd for C₁₄H₂₂NO [M+H]⁺: 220.1701.

***N*-(hex-5-en-2-yl)hydroxylamine (1kb):**

Compound **1kb** is unstable and not purified which can be used directly in the next step.

***N*-(8-methyl-1-phenylnon-7-en-3-yl)hydroxylamine (5ab):**

Total yield: 69%; white solid; mp 31-33 °C; ¹H NMR (400 MHz, CDCl₃) δ : 7.29-7.25 (m, 2H), 7.20-7.16 (m, 3H), 5.12-5.08 (m, 1H), 2.87-2.84 (m, 1H), 2.66-2.63 (m, 2H), 2.00-1.95 (m, 2H), 1.89-1.82 (m, 1H), 1.75-1.73 (m, 1H), 1.68 (s, 3H), 1.59 (s, 3H), 1.58-1.52 (m, 1H), 1.45-1.33 (m, 3H, overlapped); ¹³C NMR (100 MHz, CDCl₃) δ : 142.3, 131.7, 128.4, 128.3, 125.8, 124.3, 61.2, 33.3, 32.2, 31.1, 28.1, 26.1, 25.7, 17.7; FT-IR(neat): 3684, 3613, 3018, 2399, 1519, 1215, 1031 cm⁻¹; HRMS (ESI): Found: m/z , 248.2014, Calcd for C₁₆H₂₆NO [M+H]⁺: 248.2014.

***N*-(7-methyloct-6-en-2-yl)hydroxylamine (5bb):¹⁸**

Total yield: 32%; white solid; mp 46-47 °C; ^1H NMR (400 MHz, CDCl_3) δ : 5.10-5.07 (m, 1H), 2.98-2.91 (m, 1H), 1.99-1.94 (m, 2H), 1.67 (s, 3H), 1.58 (s, 3H), 1.56-1.49 (m, 1H), 1.38-1.19 (m, 3H, overlapped), 1.06 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 131.6, 124.3, 57.2, 33.3, 28.1, 26.2, 25.7, 17.7, 17.6; FT-IR(neat): 3582, 3018, 2399, 1435, 1342, 1215, 1165 cm^{-1} ; HRMS (ESI): Found: m/z , 158.1544, Calcd for $\text{C}_9\text{H}_{20}\text{NO}$ $[\text{M}+\text{H}]^+$: 158.1545.

***N*-(1-phenyloct-7-en-3-yl)hydroxylamine (5cb):**²⁰

Total yield: 58%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.31-7.26 (m, 2H), 7.22-7.18 (m, 3H), 5.86-5.76 (m, 1H), 5.05-4.97 (m, 2H), 2.91-2.85 (m, 1H), 2.70-2.65 (m, 2H), 2.10-2.05 (m, 2H), 1.93-1.87 (m, 1H), 1.79-1.71 (m, 1H), 1.62-1.52 (m, 1H), 1.51-1.41 (m, 3H, overlapped); ^{13}C NMR (100 MHz, CDCl_3) δ : 142.1, 138.5, 128.4, 128.3, 125.8, 114.7, 61.0, 33.8, 33.2, 32.2, 30.9, 25.1; FT-IR(neat): 3581, 3018, 2399, 1519, 1215, 1047 cm^{-1} ; HRMS (ESI): Found: m/z , 220.1698, Calcd for $\text{C}_{14}\text{H}_{22}\text{NO}$ $[\text{M}+\text{H}]^+$: 220.1701.

***N*-(hept-6-en-2-yl)hydroxylamine (5db):**¹²

Total yield: 50%; white solid; mp 41-43 °C; ^1H NMR (400 MHz, CDCl_3) δ : 5.85-5.75 (m, 1H), 5.03-4.94 (m, 2H), 3.01-2.95 (m, 1H), 2.09-2.04 (m, 2H), 1.59-1.52 (m, 1H), 1.46-1.38 (m, 2H), 1.32-1.23 (m, 1H), 1.08 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 138.6,

114.7, 57.2, 33.9, 33.2, 25.3, 17.7; FT-IR(neat): 3444, 3018, 2399, 1519, 1423, 1215, 1047 cm^{-1} ; HRMS (ESI): Found: m/z , 130.1229, Calcd for $\text{C}_7\text{H}_{16}\text{NO}$ $[\text{M}+\text{H}]^+$: 130.1232.

***N*-(1-phenyloct-6-yn-3-yl)hydroxylamine (8ab):**

Total yield: 72%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.35-7.17 (m, 5H), 3.01-2.95 (m, 1H), 2.73-2.63 (m, 2H), 2.30-2.22 (m, 2H), 1.96-1.87 (m, 1H), 1.80-1.64 (m, 3H, overlapped), 1.77 (t, 3H, $J = 2.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 142.1, 128.43, 128.37, 125.9, 78.7, 76.2, 60.2, 33.2, 32.3, 30.5, 15.6, 3.5; FT-IR (neat): 3264, 3021, 2920, 2247, 1454, 1029 cm^{-1} ; HRMS (ESI): Found: m/z , 218.1544, Calcd for $\text{C}_{14}\text{H}_{20}\text{NO}$ $[\text{M}+\text{H}]^+$: 218.1545.

***N*-(1-phenylhept-5-yn-2-yl) hydroxylamine (8bb):**

Total yield: 58%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.33-7.29 (m, 2H), 7.24-7.20 (m, 3H), 3.16-3.13 (m, 1H), 2.87-2.73 (m, 2H), 2.26-2.24 (m, 2H), 1.80-1.58 (m, 2H, overlapped), 1.77 (t, 3H, $J = 2.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 138.6, 129.4, 128.5, 126.3, 78.7, 76.1, 62.0, 37.7, 30.5, 15.7, 3.5; FT-IR (neat): 3680, 3503, 3433, 3294, 3063, 2361, 1636, 1451, 1265 cm^{-1} ; HRMS (ESI): Found: m/z , 204.1391, Calcd for $\text{C}_{13}\text{H}_{18}\text{NO}$ $[\text{M}+\text{H}]^+$: 204.1388.

***N*-(1-phenylnon-7-yn-3-yl) hydroxylamine (8cb):**

Total yield: 56%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.29-7.15 (m, 5H), 2.88-2.85 (m, 1H), 2.68-2.64 (m, 2H), 2.13 (br, 2H), 1.93-1.84 (m, 1H), 1.77 (s, 3H), 1.77-1.69 (m, 1H, overlapped), 1.64-1.47 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ : 142.0, 128.3, 128.2, 125.8, 78.8, 75.8, 60.7, 33.2, 32.1, 30.6, 25.3, 18.9, 3.4; FT-IR (neat): 3255, 2939, 2245, 1494, 1454, 1030 cm^{-1} ; HRMS (ESI): Found: m/z , 232.1692, Calcd for $\text{C}_{15}\text{H}_{22}\text{NO}$ $[\text{M}+\text{H}]^+$: 232.1701.

***N*-(1,8-diphenyloct-7-yn-3-yl) hydroxylamine (8db):**

Compound **8db** is unstable and not purified which can be used directly in the next step.

2.4.2.3 Synthesis of *N*-hydroxy sulfonamides

Synthesis of *N*-hydroxy-*N*-(7-methyl-1-phenyloct-6-en-3-yl) methanesulfonamide (1ac):

To a solution of *N*-(7-methyl-1-phenyloct-6-en-3-yl)hydroxylamine **1ab** (1.15 g, 5.0 mmol) in CH_2Cl_2 (40 mL) in a flame-dried flask was added dropwise Et_3N (0.51 g, 5.0 mmol) and a solution of $\text{CH}_3\text{SO}_2\text{Cl}$ (0.57 g, 5.0 mmol) in CH_2Cl_2 (5 mL) at -20°C . The mixture was stirred at the same temperature for 1 h. After the reaction was quenched by saturated aqueous NaHCO_3 , the mixture was extracted with EtOAc. The combined extracts were washed with water, brine and dried over MgSO_4 , and then evaporated. The crude product was purified by flash chromatography (hexane/EtOAc = 4 : 1) on silica gel to give *N*-

hydroxy-*N*-(7-methyl-1-phenyloct-6-en-3-yl) methanesulfonamide **1ac** (1.21 g, 3.9 mmol) in 78% yield.

Yield: 78%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.29-7.26 (m, 2H), 7.20-7.17 (m, 3H), 6.48 (s, 1H), 5.06 (t, 1H, $J = 6.8$ Hz), 3.77-3.73 (m, 1H), 2.96 (s, 3H), 2.75-2.66 (m, 2H), 2.05-2.02 (m, 2H), 1.94-1.88 (m, 2H), 1.69-1.57 (m, 2H, overlapped), 1.67 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 141.7, 132.8, 128.49, 128.47, 126.0, 123.3, 59.9, 36.3, 32.9, 32.7, 30.9, 25.7, 24.8, 17.8; FT-IR (neat): 3581, 3018, 2399, 1519, 1320, 1215, 1045 cm^{-1} ; HRMS (ESI): Found: m/z , 334.1465, Calcd for $\text{C}_{16}\text{H}_{25}\text{NO}_3\text{SNa}$ $[\text{M}+\text{Na}]^+$: 334.1453.

1dc, **1ec**, **1fc**, **1gc**, **1hc**, **1jc**, **1kc**, **5ac**, **5bc**, **5cc**, **5dc**, **8ac**, **8bc** and **8dc** were prepared by same procedure.

***N*-hydroxy-*N*-(6-methyl-1-phenylhept-5-en-2-yl) methanesulfonamide (1dc):**

Yield: 78%; colorless oil; ^1H NMR (300 MHz, CDCl_3) δ : 7.30-7.22 (m, 5H), 6.09 (s, 1H), 5.04 (t, 1H, $J = 7.2$ Hz), 4.15-4.06 (m, 1H), 3.06-2.99 (m, 1H), 2.87-2.80 (m, 1H), 2.76 (s, 3H), 2.17-1.98 (m, 2H), 1.67 (s, 3H), 1.63 (s, 3H), 1.75-1.50 (m, 2H, overlapped); ^{13}C NMR (100 MHz, CDCl_3) δ : 138.4, 132.4, 129.4, 128.5, 126.5, 123.4, 61.7, 37.3, 36.1, 31.5, 25.6, 24.8, 17.7; FT-IR (neat): 3332, 2921, 1461, 1377, 1154 cm^{-1} ; HRMS (ESI): Found: m/z , 298.1473, Calcd for $\text{C}_{15}\text{H}_{24}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$: 298.1477.

***N*-hydroxy-*N*-(6-methylhept-5-en-2-yl) methanesulfonamide (1ec):**

Yield: 52%; colorless oil; ^1H NMR (400 MHz, CDCl_3): δ : 6.30 (br, 1H), 5.11-5.08 (m, 1H), 3.92-3.86 (m, 1H), 3.00 (s, 3H), 2.09-2.04 (m, 2H), 1.76-1.69 (m, 1H), 1.67 (s, 3H), 1.61 (s, 3H), 1.52-1.43 (m, 1H), 1.19 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3): δ : 132.3, 123.4, 55.7, 36.0, 34.1, 25.6, 24.6, 17.7, 15.4; FT-IR(neat): 3390, 2976, 1454, 1323, 1159, 1047 cm^{-1} ; HRMS (ESI): Found: m/z , 222.1167, Calcd for $\text{C}_9\text{H}_{20}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$: 222.1164.

***N*-hydroxy-*N*-(6-methylhept-5-en-2-yl) benzenesulfonamide (1fc):**

Yield: 23%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.95 (d, 2H, $J = 8.0$ Hz), 7.66-7.62 (m, 1H), 7.56-7.52 (m, 2H), 6.17 (s, 1H), 5.08-5.04 (m, 1H), 3.95-3.86 (m, 1H), 2.07-2.02 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.57-1.50 (m, 1H), 1.41-1.33 (m, 1H), 0.79 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ : 136.9, 133.4, 132.3, 129.0, 128.9, 123.5, 56.2, 34.4, 25.7, 24.7, 17.8, 15.0; FT-IR(neat): 3406, 3018, 2399, 1446, 1215, 1166 cm^{-1} ; HRMS (ESI): Found: m/z , 306.1133, Calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_3\text{SNa}$ $[\text{M}+\text{Na}]^+$: 306.1140.

***N*-hydroxy-*N*-(6-methylhept-5-en-2-yl) 4-nitrobenzenesulfonamide (1gc):**

Yield: 20%; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.37 (d, 2H, $J = 8.8$ Hz), 8.15 (d, 2H, $J = 8.8$ Hz), 6.86 (br, 1H), 5.06-5.03 (m, 1H), 3.98-3.90 (m, 1H), 2.07-2.01 (m, 2H), 1.69 (s, 3H), 1.57 (s, 3H), 1.56-1.50 (m, 1H), 1.43-1.34 (m, 1H), 0.78 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR

(100 MHz, CDCl₃) δ :150.5, 142.8, 132.7, 130.1, 124.0, 123.1, 56.5, 34.3, 25.7, 24.6, 17.8, 15.2; FT-IR (neat): 3392, 3018, 1533, 1533, 1350, 1309, 1215, 1170 cm⁻¹; HRMS (ESI): Found: m/z , 351.0985, Calcd for C₁₄H₂₀N₂O₅SNa [M+H]⁺: 351.0991.

***N*-hydroxy-4-methyl-*N*-(6-methylhept-5-en-2-yl) benzenesulfonamide (1hc):**

Yield: 26%; yellow oil; ¹H NMR (400 MHz, CDCl₃) δ :7.82 (d, 2H, J = 8.2 Hz), 7.32 (d, 2H, J = 8.2 Hz), 6.76 (br, 1H), 5.07-5.04 (m, 1H), 3.90-3.85 (m, 1H), 2.44 (s, 3H), 2.07-2.01 (m, 2H), 1.68 (s, 3H), 1.63 (s, 3H), 1.60-1.50 (m, 1H), 1.39-1.32 (m, 1H), 0.78 (d, 3H, J = 6.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ :144.4, 133.8, 132.1, 129.5, 128.9, 123.6, 56.1, 34.4, 25.7, 24.7, 21.6, 17.7, 14.9; FT-IR (neat): 3392, 2935, 1338, 1165 cm⁻¹; HRMS (ESI): Found: m/z , 320.1284, Calcd for C₁₅H₂₃NO₃SNa [M+Na]⁺: 320.1296.

***(E)*-N-hydroxy-*N*-(1-phenyloct-6-en-3-yl) methanesulfonamide (1jc):**

Yield: 62%; colorless oil; ¹H NMR (400 MHz, CDCl₃) δ : 7.29-7.26 (m, 2H), 7.21-7.19 (m, 3H), 6.81 (br, 1H), 5.41-5.38 (m, 2H), 3.78-3.74 (m, 1H), 2.96 (s, 3H), 2.71-2.69 (m, 2H), 2.06-2.03 (m, 2H), 2.02-1.89 (m, 2H), 1.63 (d, 3H, J = 5.2 Hz), 1.64-1.62 (m, 2H, overlapped); ¹³C NMR (100 MHz, CDCl₃) δ : 141.7, 130.0, 128.51, 128.47, 126.2, 126.0, 59.7, 36.3, 32.8, 32.6, 30.7, 29.3, 18.0; FT-IR (neat): 3369, 2933, 1454, 1319, 1157 cm⁻¹; HRMS (ESI): Found: m/z , 298.1473, Calcd for C₁₅H₂₄NO₃S [M+H]⁺: 298.1477.

***N*-(hex-5-en-2-yl)-*N*-hydroxymethanesulfonamide (1kc):**

Yield: 50%; colorless oil; ^1H NMR (300 MHz, CDCl_3) δ : 5.85-5.74 (m, 1H), 5.08-4.96 (m, 2H), 3.93-3.86 (m, 1H), 2.99 (s, 3H), 2.20-2.11 (m, 2H), 1.83-1.71 (m, 1H), 1.59-1.49 (m, 1H), 1.20 (d, 3H, $J = 8.8$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ : 137.8, 115.2, 55.6, 36.1, 33.3, 30.3, 15.4; FT-IR (neat): 3390, 2975, 1454, 1328, 1165 cm^{-1} ; HRMS (ESI): Found: m/z , 194.0851, Calcd for $\text{C}_{15}\text{H}_{23}\text{NO}_3\text{SNa}$ $[\text{M}+\text{Na}]^+$: 194.0852.

***N*-hydroxy-*N*-(8-methyl-1-phenylnon-7-en-3-yl) methanesulfonamide (5ac):**

Yield: 80%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.30-7.26 (m, 2H), 7.25-7.18 (m, 3H), 6.43 (br, 1H), 5.09-5.05 (m, 1H), 3.78-3.71 (m, 1H), 2.96 (s, 3H), 2.79-2.63 (m, 2H), 1.99-1.86 (m, 4H, overlapped), 1.68 (s, 3H), 1.65-1.58 (m, 2H, overlapped), 1.58 (s, 3H), 1.43-1.35 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 141.7, 132.0, 128.44, 128.42, 126.0, 124.0, 60.2, 36.3, 32.9, 32.7, 30.2, 27.6, 26.5, 25.7, 17.7; FT-IR (neat): 3472, 3018, 2399, 1330, 1215, 1159, 1047 cm^{-1} ; HRMS (ESI): Found: m/z , 348.1612, Calcd for $\text{C}_{17}\text{H}_{27}\text{NO}_3\text{SNa}$ $[\text{M}+\text{Na}]^+$: 348.1609.

***N*-hydroxy-*N*-(7-methyloct-6-en-2-yl) methanesulfonamide (5bc):**

Yield: 75%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 6.67 (br, 1H), 5.11-5.08 (m, 1H), 3.89-3.84 (m, 1H), 2.99 (s, 3H), 1.99-1.97 (m, 2H), 1.68 (s, 3H), 1.68-1.61 (m, 1H, overlapped), 1.59 (s, 3H), 1.48-1.35 (m, 3H, overlapped), 1.19 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 131.8, 124.2, 56.2, 36.0, 33.6, 27.5, 26.4, 25.7, 17.7, 15.5; FT-IR (neat): 3373, 2933, 1454, 1377, 1321, 1159, 1085 cm^{-1} ; HRMS (ESI): Found: m/z , 258.1142, Calcd for $\text{C}_{10}\text{H}_{21}\text{NO}_3\text{SNa}$ $[\text{M}+\text{Na}]^+$: 258.1140.

***N*-hydroxy-*N*-(1-phenyloct-7-en-3-yl) methanesulfonamide (5cc):**

Yield: 64%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.30-7.25 (m, 2H), 7.21-7.16 (m, 3H), 6.50 (s, 1H), 5.83-5.70 (m, 1H), 5.03-4.94 (m, 2H), 3.78-3.71 (m, 1H), 2.96 (s, 3H), 2.75-2.66 (m, 2H), 2.08-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.67-1.60 (m, 2H), 1.50-1.40 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 141.6, 138.2, 128.43, 128.40, 126.0, 115.0, 60.1, 36.3, 33.3, 32.8, 32.6, 30.0, 25.5; FT-IR (neat): 3367, 3018, 2320, 1330, 1215, 1159, 1049 cm^{-1} ; HRMS (ESI): Found: m/z , 298.1469, Calcd for $\text{C}_{15}\text{H}_{24}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$: 298.1477.

***N*-(hept-6-en-2-yl)-*N*-hydroxy methanesulfonamide (5dc):**

Yield: 72%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 6.89 (s, 1H), 5.84-5.74 (m, 1H), 5.03-4.93 (m, 2H), 3.90-3.82 (m, 1H), 2.99 (s, 3H), 2.08-2.04 (m, 2H), 1.70-1.63 (m, 1H), 1.55-1.40 (m, 3H, overlapped), 1.08 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 138.5, 114.7, 56.1, 35.9, 33.4, 33.3, 25.4, 15.4; FT-IR (neat): 3371, 3018, 2399, 1639, 1379,

1327, 1215, 1163 cm^{-1} ; HRMS (ESI): Found: m/z , 208.1015, Calcd for $\text{C}_8\text{H}_{18}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$: 208.1007.

***N*-hydroxy-*N*-(1-phenyloct-6-yn-3-yl) methanesulfonamide (8ac):**

Yield: 23%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.30-7.27 (m, 2H), 7.21-7.19 (m, 3H), 6.76 (br, 1H), 3.93-3.89 (m, 1H), 2.99 (s, 3H), 2.76-2.69 (m, 2H), 2.24-2.21 (m, 2H), 1.94-1.81 (m, 4H, overlapped), 1.76 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 141.5, 128.4(overlapped), 126.0, 78.2, 76.6, 59.2, 36.2, 32.8, 32.5, 30.2, 15.9, 3.4; FT-IR (neat): 3365, 3024, 2859, 2252, 1454, 1331, 1159, 1029 cm^{-1} ; HRMS (ESI): Found: m/z , 296.1323, Calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$: 296.1320.

***N*-hydroxy-*N*-(1-phenylhept-5-yn-2-yl) methanesulfonamide (8bc):**

Yield: 72%; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.30-7.23 (m, 5H), 6.26 (s, 1H), 4.23-4.16 (m, 1H), 3.09-3.04 (m, 1H), 2.88-2.81 (m, 1H, overlapped), 2.81 (s, 3H), 2.23-2.19 (m, 2H), 1.77 (t, 3H, $J = 2.4$ Hz), 1.86-1.67 (m, 2H, overlapped); ^{13}C NMR (100 MHz, CDCl_3) δ : 137.9, 129.4, 128.6, 126.7, 78.7, 76.2, 60.9, 37.4, 36.7, 30.5, 16.0, 3.4; FT-IR (neat): 3680, 3503, 3433, 3294, 3063, 3032, 2685, 2361, 1597, 1450, 1265 cm^{-1} ; HRMS (ESI): Found: m/z , 304.0987, Calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_3\text{SNa}$ $[\text{M}+\text{Na}]^+$: 304.0983.

***N*-hydroxy-*N*-(1-phenylnon-7-yn-3-yl) methanesulfonamide (8cc):**

Yield: 80%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.30-7.19 (m, 5H), 6.77 (br, 1H), 3.80-3.73 (m, 1H), 2.97 (s, 3H), 2.80-2.64 (m, 2H), 2.16-2.12 (m, 2H), 1.97-1.85 (m, 2H), 1.76 (t, 3H, $J = 2.4$ Hz), 1.77-1.71 (m, 2H, overlapped), 1.58-1.47 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 141.6, 128.43, 128.38, 126.0, 78.6, 76.2, 60.0, 36.1, 32.9, 32.6, 29.7, 25.5, 18.4, 3.4; FT-IR (neat): 3369, 2933, 2254, 1602, 1454, 1327, 1159, 1095 cm^{-1} ; HRMS (ESI): Found: m/z , 310.1476, Calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$: 310.1477.

***N*-(1,8-diphenyloct-7-yn-3-yl)-*N*-hydroxy methanesulfonamide (8dc):**

Yield: 65%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.39-7.37 (m, 2H), 7.30-7.27 (m, 5H), 7.21-7.19 (m, 3H), 6.44 (br, 1H), 3.85-3.78 (m, 1H), 2.96 (s, 3H), 2.76-2.71 (m, 2H), 2.44 (t, 2H, $J = 6.8$ Hz), 2.05-1.91 (m, 2H), 1.86-1.81 (m, 2H), 1.72-1.67 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 141.5, 131.5, 128.5, 128.4, 128.2, 127.7, 126.0, 123.7, 89.5, 81.3, 59.7, 36.3, 32.9, 32.6, 29.7, 25.3, 19.0; FT-IR (neat): 3366, 3026, 2864, 2249, 1454, 1328, 1157 cm^{-1} ; HRMS (ESI): Found: m/z , 372.1635, Calcd for $\text{C}_{21}\text{H}_{26}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$: 372.1633.

2.4.2.4 Synthesis of substrates

Synthesis of *N*-(benzoyloxy)-*N*-(6-methylhept-5-en-2-yl) methanesulfonamide (1e):

To a solution of **1ec** (0.70 g, 3.2 mmol) in CH₂Cl₂ (15 mL) in a flame-dried flask was added dropwise Et₃N (0.32 g, 3.2 mmol) and a solution of benzoyl chloride (0.45 g, 3.2 mmol) in CH₂Cl₂ (1 mL) at 0 °C. The mixture was stirred at the same temperature for 2 h. After the reaction was quenched by saturated aqueous NaHCO₃, the mixture was extracted with EtOAc. The combined extracts were washed with water, brine and dried over MgSO₄, and then evaporated. The crude product was purified by flash chromatography (hexane/EtOAc = 10 : 1) on silica gel to give *N*-(benzoyloxy)-*N*-(6-methylhept-5-en-2-yl) methanesulfonamide **1e** (0.74 g, 2.3 mmol) in 71% yield.

Yield: 71%; colorless oil; ¹H NMR (400 MHz, CDCl₃) δ: 8.09 (d, 2H, *J* = 7.2 Hz), 7.68-7.64 (m, 1H), 7.53-7.49 (m, 2H), 5.09-5.06 (m, 1H), 4.30-4.21 (m, 1H), 3.06 (s, 3H), 2.19-2.14 (m, 2H), 1.68 (s, 3H), 1.68-1.63 (m, 1H, overlapped), 1.63 (s, 3H), 1.47 (br, 1H), 1.38 (d, 3H, *J* = 6.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ: 164.4, 134.3, 132.7, 130.1, 128.9, 127.1, 123.2, 56.9, 39.7, 34.7, 25.7, 24.8, 17.7, 17.1; FT-IR (neat): 2927, 1764, 1598, 1338, 1234, 1161, 1018 cm⁻¹; HRMS (ESI): Found: *m/z*, 348.1244, Calcd for C₁₆H₂₃NO₄SNa [M+Na]⁺: 348.1245.

1a, 1b, 1c, 1d, 1e, 1f, 1g, 1h, 1i, 5a, 5b, 5c, 5d, 8a, 8b, 8c and 8d were prepared by same procedure.

***N*-(benzoyloxy)-*N*-(7-methyl-1-phenyloct-6-en-3-yl) methanesulfonamide (1a):**

Yield: 75%; white solid; ¹H NMR (400 MHz, CDCl₃) δ: 8.09 (d, 2H, *J* = 7.2 Hz), 7.66 (t, 1H, *J* = 7.6 Hz), 7.51 (t, 2H, *J* = 8.0 Hz), 7.30-7.25 (m, 2H), 7.23-7.19 (m, 3H), 5.08 (t, 1H, *J* = 6.8 Hz), 4.13-4.06 (m, 1H), 3.07 (s, 3H), 2.93 (br, 1H), 2.77-2.70 (m, 1H), 2.15 (br, 2H), 1.91 (br, 2H), 1.76-1.49 (m, 2H, overlapped), 1.68 (s, 3H), 1.60 (s, 3H); ¹³C NMR (100 MHz,

CDCl₃) δ : 164.4, 141.5, 134.3, 132.7, 130.0, 128.9, 128.5, 128.4, 126.9, 125.9, 123.1, 61.0, 39.9, 34.0, 32.8, 31.9, 25.7, 24.9, 17.7; FT-IR (neat): 3581, 3018, 2399, 1765, 1340, 1215, 1159 cm⁻¹; HRMS (ESI): Found: m/z , 438.1714, Calcd for C₂₃H₂₉NO₄SNa [M+Na]⁺: 438.1715.

***N*-(7-methyl-1-phenyloct-6-en-3-yl) methanesulfonamide (1b):**

Yield: 63%; colorless oil; ¹H NMR (400 MHz, CDCl₃) δ : 7.30-7.26 (m, 2H), 7.20-7.17 (m, 3H), 5.05 (t, 1H, J = 7.2 Hz), 3.96-3.90 (m, 1H), 3.00 (s, 3H), 2.88 (br, 1H), 2.75-2.64 (m, 1H), 2.21 (s, 3H), 2.09 (br, 2H), 1.86 (br, 2H), 1.68 (s, 3H), 1.59 (s, 3H), 1.72-1.55 (m, 2H, overlapped); ¹³C NMR (100 MHz, CDCl₃) δ : 168.3, 141.6, 132.8, 128.5, 128.4, 126.0, 123.0, 60.9, 39.4, 33.9, 32.7, 31.8, 25.7, 24.9, 18.6, 17.7; FT-IR (neat): 2930, 1790, 1353, 1157 cm⁻¹; HRMS (ESI): Found: m/z , 376.1558, Calcd for C₁₈H₂₇NO₄SNa[M+Na]⁺: 376.1559.

***N*-(benzoyloxy)-*N*-(6-methyl-1-phenylhept-5-en-2-yl) methanesulfonamide (1d):**

Yield: 78%; colorless oil; ¹H NMR (400 MHz, CDCl₃) δ : 8.09 (d, 2H, J = 7.6 Hz), 7.68 (t, 1H, J = 7.6 Hz), 7.53 (t, 2H, J = 7.6 Hz), 7.33-7.21 (m, 5H), 4.95 (br, 1H), 4.36-4.30 (m, 1H), 3.32 (br, 1H), 3.02 (s, 3H), 2.90-2.84 (m, 1H), 2.31-2.22 (m, 1H), 2.14-2.04 (m, 1H), 1.70 (s, 3H), 1.64 (s, 3H), 1.70-1.68 (m, 2H, overlapped); ¹³C NMR (75 MHz, CDCl₃) δ : 164.4, 138.3, 134.3, 132.6, 130.1, 129.4, 128.9, 128.5, 127.0, 126.5, 123.2, 63.1, 40.3, 38.9, 31.3,

25.7, 24.9, 17.7; FT-IR (neat): 3373, 2929, 1765, 1452, 1340, 1159, 1039, 1018 cm^{-1} ; HRMS (ESI): Found: m/z , 402.1741, Calcd for $\text{C}_{22}\text{H}_{28}\text{NSO}_4$ $[\text{M}+\text{H}]^+$: 402.1739.

(*E*)-*N*-(benzoyloxy)-*N*-(1-phenyloct-6-en-3-yl) methanesulfonamide (1j):

Yield: 61%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.09 (d, 2H, $J = 8.0$ Hz), 7.66 (t, 1H, $J = 7.2$ Hz), 7.51 (t, 2H, $J = 7.6$ Hz), 7.30-7.17 (m, 5H), 5.48-5.34 (m, 2H), 4.13-4.07 (m, 1H), 3.07 (s, 3H), 3.07-2.90 (m, 1H, overlapped), 2.78-2.68 (m, 1H), 2.14 (br, 2H), 1.89 (m, 2H), 1.63 (d, 3H, $J = 5.2$ Hz), 1.71-1.59 (m, 2H, overlapped); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.4, 141.7, 134.3, 130.1, 129.8, 128.9, 128.5, 128.4, 127.0, 126.2, 125.9, 60.8, 39.9, 33.9, 32.7, 31.8, 29.4, 17.9; FT-IR (neat): 3026, 2935, 2254, 1767, 1601, 1452, 1340, 1234, 1161, 1039, 1018 cm^{-1} ; HRMS (ESI): Found: m/z , 424.1559, Calcd for $\text{C}_{22}\text{H}_{27}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 424.1559.

***N*-(benzoyloxy)-*N*-(6-methylhept-5-en-2-yl) benzenesulfonamide (1f):**

Yield: 83%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.96 (d, 4H, $J = 7.6$ Hz), 7.64-7.60 (m, 2H), 7.52-7.44 (m, 4H), 5.07-5.03 (m, 1H), 4.25-4.16 (m, 1H), 2.15 (br, 2H), 1.68 (s, 3H), 1.63 (s, 3H), 1.63-1.58 (m, 1H, overlapped), 1.37 (br, 1H), 1.12 (br, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.5, 136.7, 133.93, 133.91, 132.4, 129.8, 129.1, 129.0, 128.7, 127.3, 123.3, 57.5, 35.1, 25.7, 24.8, 17.7, 16.0; FT-IR (neat): 3018, 2399, 1770, 1448, 1371, 1215, 1168,

1018 cm^{-1} ; HRMS (ESI): Found: m/z , 410.1406, Calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 410.1402.

***N*-(benzyloxy)-*N*-(6-methylhept-5-en-2-yl) 4-nitrobenzenesulfonamide (1g):**

Yield: 60%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.33 (d, 2H, $J = 8.8$ Hz), 8.15 (d, 2H, $J = 8.8$ Hz), 7.94 (d, 2H, $J = 7.4$ Hz), 7.67-7.63 (m, 1H), 7.51-7.47 (m, 2H), 5.07-5.03 (m, 1H), 4.31-4.26 (m, 1H), 2.17 (br, 2H), 1.69 (s, 3H), 1.63 (s, 3H), 1.63-1.59 (m, 1H, overlapped), 1.42 (br, 1H), 1.21 (d, 3H, $J = 6.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ : 163.4, 150.8, 142.7, 134.4, 132.8, 130.4, 129.8, 129.0, 126.7, 124.2, 123.0, 57.9, 35.3, 25.8, 24.8, 17.8, 16.6; FT-IR(neat): 3018, 2399, 1768, 1350, 1215, 1037, 1016 cm^{-1} ; HRMS (ESI): Found: m/z , 455.1255, Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_6\text{SNa}$ $[\text{M}+\text{Na}]^+$: 455.1253.

***N*-(benzyloxy)-4-methyl-*N*-(6-methylhept-5-en-2-yl) benzenesulfonamide (1h):**

Yield: 80%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.97 (d, 2H, $J = 7.6$ Hz), 7.83 (d, 2H, $J = 8.0$ Hz), 7.64-7.60 (m, 1H), 7.49-7.45 (m, 2H), 7.31-7.26 (m, 2H), 5.07-5.03 (m, 1H), 4.21-4.16 (m, 1H), 2.42 (s, 3H), 2.17 (br, 2H), 1.68 (s, 3H), 1.63 (s, 3H), 1.63-1.55 (m, 1H, overlapped), 1.36 (br, 1H), 1.11 (br, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ : 163.7, 145.0, 133.9, 133.7, 132.4, 129.8, 129.7, 129.1, 128.7, 127.5, 123.4, 57.5, 35.3, 25.8, 24.8, 21.7, 17.8, 16.0; FT-IR (neat): 3018, 2399, 1768, 1215, 1167, 1018 cm^{-1} ; HRMS (ESI): Found: m/z , 402.1736, Calcd for $\text{C}_{22}\text{H}_{28}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 402.1739.

***N*-(benzoyloxy)-*N*-(hex-5-en-2-yl) methanesulfonamide (1k):**

Yield: 68%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.09 (d, 2H, $J = 7.6$ Hz), 7.68-7.65 (m, 1H), 7.53-7.50 (m, 2H), 5.83-5.76 (m, 1H), 5.07-4.98 (m, 2H), 4.30-4.24 (m, 1H), 3.06 (s, 3H), 2.27-2.22 (m, 2H), 1.74 (br, 1H), 1.54 (br, 1H), 1.38 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.3, 137.5, 134.4, 130.1, 128.9, 127.0, 115.5, 56.8, 39.7, 33.6, 30.4, 17.0; FT-IR (neat): 3018, 2399, 1762, 1452, 1338, 1234, 1165, 1018 cm^{-1} ; HRMS (ESI): Found: m/z , 320.0924, Calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 320.0932.

***N*-(benzoyloxy)-*N*-(8-methyl-1-phenylnon-7-en-3-yl) methanesulfonamide (5a):**

Yield: 64%; colorless oil; ^1H NMR (500 MHz, CDCl_3) δ : 8.09 (d, 2H, $J = 8.0$ Hz), 7.66-7.63 (m, 1H), 7.52-7.48 (m, 2H), 7.29-7.26 (m, 2H), 7.22-7.16 (m, 3H), 5.10-5.08 (m, 1H), 4.11-4.08 (m, 1H), 3.07 (s, 3H), 2.93 (br, 1H), 2.77-2.71 (m, 1H), 2.06-1.98 (m, 2H), 1.89 (br, 2H), 1.79-1.26 (m, 4H, overlapped), 1.78 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.4, 141.6, 134.3, 131.9, 130.0, 128.8, 128.5, 128.4, 126.9, 125.9, 124.0, 61.5, 39.8, 34.1, 32.8, 31.4, 27.6, 26.6, 25.6, 17.7; FT-IR (neat): 3018, 2399, 1764, 1452, 1342, 1215, 1159, 1018 cm^{-1} ; HRMS (ESI): Found: m/z , 430.2057, Calcd for $\text{C}_{24}\text{H}_{32}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 430.2052.

***N*-(benzoyloxy)-*N*-(7-methyloct-6-en-2-yl) methanesulfonamide (5b):**

Yield: 68%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.09 (d, 2H, $J = 7.8$ Hz), 7.68-7.64 (m, 1H), 7.53-7.49 (m, 2H), 5.10-5.06 (m, 1H), 4.26-4.21 (m, 1H), 3.06 (s, 3H), 2.00-1.95 (m, 2H), 1.64 (s, 3H), 1.64-1.57 (m, 2H, overlapped), 1.57 (s, 3H), 1.48-1.42 (m, 2H), 1.37 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.3, 134.3, 131.8, 130.1, 128.9, 127.1, 124.1, 57.5, 39.7, 33.9, 27.6, 26.4, 25.6, 17.6, 17.1; FT-IR (neat): 2933, 1768, 1452, 1359, 1234, 1163, 1018 cm^{-1} ; HRMS (ESI): Found: m/z , 362.1387, Calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 362.1402.

***N*-(benzoyloxy)-*N*-(1-phenyloct-7-en-3-yl) methanesulfonamide (5c):**

Yield: 76%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.08 (d, 2H, $J = 7.8$ Hz), 7.68-7.64 (m, 1H), 7.53-7.49 (m, 2H), 7.30-7.26 (m, 2H), 7.22-7.17 (m, 3H), 5.81-5.73 (m, 1H), 5.02-4.94 (m, 2H), 4.12-4.09 (m, 1H), 3.08 (s, 3H), 3.05-2.86 (m, 1H), 2.77-2.69 (m, 1H), 2.09-2.04 (m, 2H), 1.89 (br, 2H), 1.68-1.66 (m, 2H), 1.57-1.50 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.4, 141.5, 138.3, 134.4, 130.1, 128.9, 128.5, 128.4, 127.0, 126.0, 114.9, 61.4, 40.0, 34.1, 33.3, 32.8, 31.3, 25.7; FT-IR (neat): 3026, 2933, 1764, 1600, 1340, 1234, 1161, 1018 cm^{-1} ; HRMS (ESI): Found: m/z , 424.1551, Calcd for $\text{C}_{22}\text{H}_{27}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 424.1559.

***N*-(benzoyloxy)-*N*-(hept-6-en-2-yl) methanesulfonamide (5d):**

Yield: 77%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.28 (d, 2H, $J = 8.0$ Hz), 7.67-7.63 (m, 1H), 7.52-7.48 (m, 2H), 5.81-5.71 (m, 1H), 5.00-4.90 (m, 2H), 4.25-4.20 (m, 1H), 3.05 (s, 3H), 2.07-2.02 (m, 2H), 1.65 (br, 2H), 1.56-1.40 (m, 2H), 1.36 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.3, 138.4, 134.3, 130.1, 128.9, 127.0, 114.8, 57.3, 39.6, 33.8, 33.3, 25.5, 17.2; FT-IR (neat): 3018, 2399, 1762, 1338, 1215, 1163, 1018 cm^{-1} ; HRMS (ESI): Found: m/z , 334.1097, Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 334.1089.

***N*-(benzoyloxy)-*N*-(1,6-diphenylhexan-3-yl)methanesulfonamide (5e)**

Yield: 70%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.2 (d, 2H, $J = 8$ Hz), 7.66 (t, 1H, $J = 8$ Hz), 7.51 (t, 2H, $J = 8$ Hz), 7.33-7.28 (m, 4H), 7.24-7.19 (m, 6H), 4.20-4.13 (m, 1H), 3.07 (s, 3H), 3.05 (br, 1H), 2.79-2.71 (m, 1H), 2.67-2.64 (m, 2H), 2.00-1.75 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.5, 141.9, 141.6, 134.4, 130.1, 128.9, 128.6, 128.5(overlapped), 128.4, 127.0, 126.0, 125.9, 61.4, 39.9, 35.5, 34.1, 32.8, 31.4, 28.2; FT-IR (neat): 3206, 1764, 1600, 1494, 1452, 1338, 1159 cm^{-1} ; HRMS (ESI): Found: m/z , 452.1893, Calcd for $\text{C}_{26}\text{H}_{30}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 452.1896.

***N*-(benzoyloxy)-*N*-(1-phenyloct-6-yn-3-yl) methanesulfonamide (8a):**

Yield: 64%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.08 (d, 2H, $J = 7.6$ Hz), 7.65 (t, 1H, $J = 7.2$ Hz), 7.50 (t, 2H, $J = 7.6$ Hz), 7.31-7.17 (m, 5H), 4.30-4.24 (m, 1H), 3.09 (s, 3H), 2.95-2.74 (m, 2H), 2.36 (br, 2H), 1.92 (br, 2H), 1.76 (s, 3H), 1.86-1.76 (m, 2H, overlapped); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.4, 141.4, 134.3, 130.0, 128.9, 128.5, 128.4, 126.8, 126.0, 77.8, 77.2, 60.5, 39.8, 33.8, 32.7, 31.2, 16.0, 3.4; FT-IR (neat): 2920, 1764, 1452, 1344, 1234, 1161, 1018 cm^{-1} ; HRMS (ESI): Found: m/z , 422.1398, Calcd for $\text{C}_{22}\text{H}_{25}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 422.1402.

***N*-(benzoyloxy)-*N*-(1-phenylhept-5-yn-2-yl) methanesulfonamide (8b):**

Yield: 63%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.08 (d, 2H, $J = 8.0$ Hz), 7.67 (t, 1H, $J = 7.6$ Hz), 7.52 (t, 2H, $J = 7.6$ Hz), 7.33-7.21 (m, 5H), 4.51-4.44 (m, 1H), 3.36 (br, 1H), 3.04 (s, 3H), 2.91-2.85 (m, 1H), 2.43-2.25 (m, 2H), 1.71 (br, 5H, overlapped); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.4, 138.0, 134.5, 130.2, 129.4, 129.0, 128.6, 126.9, 126.7, 78.0, 76.5, 62.5, 40.3, 38.6, 30.5, 16.0, 3.5; FT-IR (neat): 3680, 3503, 3063, 3055, 2986, 2685, 2307, 1427, 1265 cm^{-1} ; HRMS (ESI): Found: m/z , 408.1244, Calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 408.1245.

***N*-(benzoyloxy)-*N*-(1-phenylnon-7-yn-3-yl) methanesulfonamide (8c):**

Yield: 78%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.09 (d, 2H, $J = 7.6$ Hz), 7.66 (t, 1H, $J = 7.6$ Hz), 7.51 (t, 2H, $J = 7.6$ Hz), 7.31-7.17 (m, 5H), 4.15-4.09 (m, 1H), 3.08 (s, 3H),

3.08-2.94 (m, 1H, overlapped), 2.77-2.74 (m, 1H), 2.17 (br, 2H), 1.91 (br, 2H), 1.80-1.74 (m, 2H, overlapped), 1.74 (s, 3H), 1.65-1.58 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.4, 141.5, 134.3, 130.1, 128.9, 128.5, 128.4, 127.0, 126.0, 78.5, 76.1, 61.2, 40.0, 34.2, 32.8, 31.0, 25.7, 18.4, 3.4; FT-IR (neat): 2933, 2256, 1765, 1601, 1454, 1340, 1234, 1161, 1018 cm^{-1} ; HRMS (ESI): Found: m/z , 414.1737, Calcd for $\text{C}_{23}\text{H}_{28}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 414.1739.

***N*-(benzoyloxy)-*N*-(1,8-diphenyloct-7-yn-3-yl) methanesulfonamide (8d):**

Yield: 79%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.07 (d, 2H, $J = 7.6$ Hz), 7.62 (t, 1H, $J = 7.6$ Hz), 7.44 (t, 2H, $J = 7.6$ Hz), 7.35 (t, 2H, $J = 3.2$ Hz), 7.29-7.18 (m, 8H), 4.18-4.15 (m, 1H), 3.06 (s, 3H), 3.06-2.96 (m, 1H, overlapped), 2.84-2.73 (m, 1H), 2.47-2.44 (m, 2H), 1.89 (br, 4H, overlapped), 1.75 (br, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.3, 141.3, 134.3, 131.4, 130.0, 128.8, 128.43, 128.38, 128.1, 127.5, 126.8, 125.9, 123.7, 89.4, 81.2, 61.0, 39.8, 34.1, 32.7, 30.9, 25.3, 19.0; FT-IR (neat): 3392, 2933, 2252, 1765, 1599, 1452, 1340, 1234 cm^{-1} ; HRMS (ESI): Found: m/z , 476.1895, Calcd for $\text{C}_{28}\text{H}_{30}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 476.1896.

2.4.3 Cyclization of *N*-benzoyloxysulfonamides

The experimental procedure is shown below as a typical example for the synthesis of **2a**. To a solution of *N*-benzoyloxysulfonamide **1a** (0.166 g, 0.4 mmol) in 10 mL of 1,2-dichloroethane was added $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ (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; ^1H 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 cm^{-1} ; HRMS (ESI): Found: m/z , 294.1528, Calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 294.1528.

cis-2a: White solid; mp 71-73 $^\circ\text{C}$; ^1H 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 cm^{-1} ; HRMS (ESI): Found: m/z , 294.1528, Calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 294.1528.

2-benzyl-1-(methylsulfonyl)-5-(prop-1-en-2-yl)pyrrolidine (2d)

trans-2d: Colorless oil; ^1H 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 cm^{-1} ; HRMS (ESI): Found: m/z , 280.1369, Calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 280.1371.

cis-2d: Colorless oil; ^1H 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 cm^{-1} ; HRMS (ESI): Found: m/z , 280.1370, Calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 280.1371.

2-methyl-1-(methylsulfonyl)-5-(prop-1-en-2-yl) pyrrolidine (2e)

trans-2e: Colorless oil; ^1H 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 cm^{-1} ; HRMS (ESI): Found: m/z , 204.1056, Calcd for $\text{C}_9\text{H}_{18}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 204.1058.

cis-2e: Colorless oil; ^1H 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 cm^{-1} ; HRMS (ESI): Found: m/z , 204.1058, Calcd for $\text{C}_9\text{H}_{18}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 204.1058.

2-methyl-1-(phenylsulfonyl)-5-(prop-1-en-2-yl)pyrrolidine (2f)

A trans and cis mixture (0.56: 0.44), Yield: 60%; colorless oil; ^1H 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 cm^{-1} ; HRMS (ESI): Found: m/z , 266.1213, Calcd for $\text{C}_{14}\text{H}_{20}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 266.1215.

2-methyl-1-(4-nitrophenylsulfonyl)-5-(prop-1-en-2-yl) pyrrolidine (2g)

A *trans* and *cis* mixture (0.46:0.54), Yield: 30%; colorless oil; ^1H 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 cm^{-1} ; HRMS (ESI): Found: m/z , 333.0893, Calcd for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 333.0885.

2-methyl-5-(prop-1-en-2-yl)-1-tosylpyrrolidine (2h)¹⁴

A *trans* and *cis* mixture (0.56:0.44), Yield: 55%; colorless oil; ^1H 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 cm^{-1} ; HRMS (ESI): Found: m/z , 280.1374, Calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 280.1371.

(2-methyl-5-(prop-1-en-2-yl)pyrrolidin-1-yl)(phenyl)methanone

A *trans* and *cis* mixture (0.36:0.64), Yield: 36%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.53-7.51 (0.64H, m), 7.41-7.28 (4.36H, m), 4.89 (0.18H, s), 4.85 (0.18H, s), 4.68 (0.32H, s), 4.57 (0.32H, s), 4.50-4.47 (0.36H, m), 4.27-4.23 (0.64H, m), 2.23-2.09 (1H, m), 1.81 (0.54H, s), 1.76-1.34 (7.28H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 171.0, 170.0, 145.8, 144.7, 138.3, 138.1, 129.5, 128.9, 128.3, 127.7, 126.8, 126.6, 64.6, 61.7, 55.2, 53.5, 31.1, 29.1, 28.8, 27.2, 21.2, 20.2, 19.8, 19.6; FT-IR (neat): 3053, 1722, 1714, 1653, 1614, 1600, 1494, 1446, 1408, 1265 cm^{-1} ; LCMS (ESI) found: 230.12, calcd for formula $(\text{M}+\text{H}^+)$: 230.15

10,10-dimethyl-3-(prop-1-en-2-yl)-2,3,10,10a-tetrahydropyrrolo[1,2-b]isoquinolin-5(1H)-one 3

Yield: 39%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.04-8.02 (1H, m), 7.46-7.42 (1H, m), 7.33-7.29 (2H, m), 4.46-4.37 (1H, m), 3.86-3.82 (1H, m), 2.17-2.07 (2H, m), 1.99-1.87 (1H, m), 1.63-1.54 (1H, m), 1.38 (3H, s), 1.37 (3H, s), 1.02 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 162.6, 147.3, 131.7, 129.7, 127.8, 126.6, 123.0, 63.6, 53.9, 37.1, 31.4, 25.0, 23.5, 23.0, 19.6; FT-IR (neat): 3051, 1714, 1643, 1602, 1600, 1573, 1494, 1469, 1427, 1342, 1265, 1163 cm^{-1} ; LCMS (ESI) found: 230.26, calcd for formula $(\text{M}+\text{H}^+)$: 230.15.

1-(methylsulfonyl)-2-phenethyl-5-vinylpyrrolidine (2j)

trans-2j: White solid; mp 103-104 °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 $\text{C}_{15}\text{H}_{22}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 280.1371.

cis-2j: 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 cm^{-1} ; HRMS (ESI): Found: m/z , 280.1364, Calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 280.1371.

2-methyl-1-(methylsulfonyl)-1,2,3,4-tetrahydropyridine (4)

Colorless oil; ^1H 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): 2931, 1359, 1338, 1261, 1215, 1163, 1001 cm^{-1} ; HRMS (ESI): Found: m/z , 176.0747, Calcd for $\text{C}_7\text{H}_{14}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 176.0745.

2-(2-methylprop-1-enyl)-1-(methylsulfonyl)-5-phenethylpyrrolidine (6a)

trans-6a: Colorless oil; ^1H 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 cm^{-1} ; HRMS (ESI): Found: m/z , 330.1508, Calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_2\text{SNa}$ $[\text{M}+\text{Na}]^+$: 330.1504.

cis-6a: 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 cm^{-1} ; HRMS (ESI): Found: m/z , 330.1508, Calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_2\text{SNa}$ $[\text{M}+\text{Na}]^+$: 330.1504.

1-(methylsulfonyl)-2-phenethyl-6-(prop-1-en-2-yl)piperidine(7a)

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 cm^{-1} ; HRMS (ESI): Found: m/z , 330.1507, Calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_2\text{SNa}$ $[\text{M}+\text{Na}]^+$: 330.1504.

2-methyl-5-(2-methylprop-1-enyl)-1-(methylsulfonyl)pyrrolidine (6b)

trans-6b: Colorless oil; ^1H NMR (400 MHz, CDCl_3): δ : 5.11 (d, 1H, $J = 8.0$ Hz), 4.65-4.60 (m, 1H), 3.90-3.84 (m, 1H), 2.80 (s, 3H), 2.32-2.15 (m, 2H), 1.74-1.73 (m, 6H, overlapped), 1.64-1.57 (m, 2H), 1.31 (d, 3H, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3): δ : 135.8, 123.7, 57.6, 55.6, 40.0, 31.8, 30.6, 25.8, 22.8, 17.9; FT-IR (neat): 3021, 2399, 1446, 1377, 1323, 1215, 1145, 1058 cm^{-1} ; HRMS (ESI): Found: m/z , 218.1210, Calcd for $\text{C}_{10}\text{H}_{20}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 218.1215.

cis-6b: 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 cm^{-1} ;
HRMS (ESI): Found: m/z , 218.1210, Calcd for $\text{C}_{10}\text{H}_{20}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 218.1215.

2-methyl-1-(methylsulfonyl)-6-(prop-1-en-2-yl)piperidine (7b)

Colorless oil; ^1H NMR (400 MHz, CDCl_3): δ : 4.8 (s, 1H), 4.71 (s, 1H), 3.89-3.83 (m, 1H), 3.80-3.75 (m, 1H), 2.82 (s, 3H), 2.62-2.58 (m, 1H), 2.17-2.00 (m, 2H), 1.92-1.62 (m, 6H), 1.34 (d, 3H, $J = 7.0\text{Hz}$); ^{13}C NMR (100 MHz, CDCl_3): δ : 142.6, 112.9, 60.0, 57.4, 45.6, 36.2, 32.5, 29.2, 23.2, 22.4; FT-IR (neat): 3019, 2395, 1447, 1377, 1323, 1215, 1145, 1058 cm^{-1} ;
HRMS (ESI): Found: m/z , 218.1212, Calcd for $\text{C}_{10}\text{H}_{20}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 218.1215.

1-(methylsulfonyl)-2-phenethyl-5-vinylpyrrolidine (6c)

trans-6c: White solid; mp 103-104 $^{\circ}\text{C}$; ^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, $J = 16.8\text{ Hz}$), 5.20 (d, 1H, $J = 10.8\text{ Hz}$), 4.33 (t, 1H, $J = 8.0\text{ Hz}$), 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 cm^{-1} ; HRMS (ESI): Found: m/z , 280.1372, Calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 280.1371.

cis-6c: 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 cm^{-1} ; HRMS (ESI): Found: m/z , 280.1364, Calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 280.1371.

2-methyl-1-(methylsulfonyl)-5-vinylpyrrolidine (6d)

trans-6d: 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 cm^{-1} ; HRMS (ESI): Found: m/z , 190.0897, Calcd for $\text{C}_8\text{H}_{16}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 190.0902.

cis-6d: White solid; mp 55-57 $^\circ\text{C}$; ^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 cm^{-1} ; HRMS (ESI): Found: m/z , 190.0899, Calcd for $\text{C}_8\text{H}_{16}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 190.0902.

1-(methylsulfonyl)-2-phenethyl-5-phenylpyrrolidine 6e

trans-6e, Colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.35-7.20 (m, 10H), 4.89 (d, 1H, $J = 8$ Hz), 4.13-4.08 (m, 1H), 2.70-2.65 (m, 2H), 2.56-2.49 (m, 2H), 2.46 (s, 3H), 2.34-2.28 (m, 1H), 1.96-1.83 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 142.7, 141.1, 128.6, 128.4, 128.3, 127.6, 126.8, 126.0, 62.9, 61.6, 41.3, 35.7, 33.2, 32.9, 28.3; FT-IR (neat): 3028, 1604, 1494, 1454, 1319, 1143 cm^{-1} ; HRMS (ESI): Found: m/z , 330.1523, Calcd for $\text{C}_{19}\text{H}_{24}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 330.1528.

cis-6e, Colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.36-7.15 (m, 10H), 4.88-4.84 (m, 1H), 4.10-4.05 (m, 1H), 2.79-2.65 (m, 2H), 2.65 (s, 3H), 2.39-2.32 (m, 2H), 2.12-2.02 (m, 2H), 1.94-1.86 (m, 1H), 1.83-1.77 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 142.2, 141.4, 128.6, 128.5, 128.3, 127.5, 126.5, 126.0, 64.5, 61.5, 38.9, 38.4, 35.1, 33.0, 30.3; FT-IR (neat): 3026, 1602, 1494, 1454, 1336, 1151 cm^{-1} ; HRMS (ESI): Found: m/z , 330.1523, Calcd for $\text{C}_{19}\text{H}_{24}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 330.1528.

(Z)-1-(1-(methylsulfonyl)-5-phenethylpyrrolidin-2-ylidene) ethyl benzoate (9a)

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 cm^{-1} ; HRMS (ESI): Found: m/z , 422.1404, Calcd for $\text{C}_{22}\text{H}_{25}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 422.1402.

1-(1-(methylsulfonyl)-5-phenethyl-4,5-dihydro-1H-pyrrol-2-yl)ethyl benzoate

Isomer 1, Colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.09-8.07 (m, 2H), 7.59 (t, 1H, J = 7.2 Hz), 7.46 (m, 2H), 7.30-7.26 (m, 2H), 7.22-7.17 (m, 2H), 6.05-6.02 (m, 1H), 5.27-5.26 (m, 1H), 4.27-4.24 (m, 1H), 3.06 (s, 3H), 2.82-2.72 (m, 3H), 2.17-2.12 (m, 1H), 2.04-1.98 (m, 1H), 1.88-1.84 (m, 1H), 1.62 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.7, 143.9, 141.6, 133.2, 129.8, 129.6, 128.5, 128.4(overlapped), 125.8, 110.2, 68.3, 63.4, 38.5, 36.1, 33.7, 30.9, 19.6; FT-IR(neat): 3026, 1714, 1653, 1635, 1602, 1494, 1452, 1327, 1315, 1269, 1149 cm^{-1} ; LCMS (ESI) found: 422.19, calcd for formula $(\text{M}+\text{Na}^+)$: 422.15

Isomer 2, Colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.06-8.04 (m, 2H), 7.55-7.51 (m, 1H), 7.41-7.37 (m, 2H), 7.28-7.24 (m, 3H), 7.19-7.17 (m, 2H), 6.04-6.01 (m, 1H), 5.65-5.63 (m, 1H), 4.37-4.35 (m, 1H), 2.93-2.87 (m, 4H), 2.79-2.73 (m, 2H), 2.22-2.16 (m, 1H), 2.04-1.98 (m, 1H), 1.86-1.80 (m, 1H), 1.62 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.6, 143.7, 141.6, 132.9, 130.3(overlapped), 129.6, 128.38, 128.35, 125.8, 116.1, 66.4, 63.0, 38.1, 37.5, 33.9, 31.1, 18.5; FT-IR(neat): 3028, 1716, 1653, 1600, 1494, 1450, 1344, 1327, 1265 cm^{-1} ; LCMS (ESI) found: 400.06, calcd for formula $(\text{M}+\text{H}^+)$: 400.15

2-methyl-1-(methylsulfonyl)-6-phenethyl-1,4,5,6-tetrahydropyridin-3-yl benzoate

Colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.10-8.08 (m, 2H), 7.63-7.60 (m, 1H), 7.50-7.46 (m, 2H), 7.31-7.17 (m, 5H), 4.16-4.13 (m, 1H), 2.92 (s, 3H), 2.78-2.71 (m, 2H), 2.55-2.52 (m, 1H), 2.35-2.21 (m, 1H), 2.19 (s, 3H), 2.18-1.97 (m, 2H), 1.81-1.75 (m, 1H), 1.61-1.58 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.2, 142.1, 141.4, 133.5(overlapped), 129.3, 129.2(overlapped), 128.5(overlapped), 125.9, 63.3, 38.0, 36.6, 32.1, 27.7, 26.5, 18.2; FT-IR(neat): 3028, 1730, 1653, 1602, 1494, 1452, 1344, 1153 cm^{-1} ; LCMS (ESI) found: 400.01, calcd for formula ($\text{M}+\text{H}^+$): 400.15.

(E)-6-(methanesulfonyl)-4-oxo-8-phenyloct-2-en-2-yl benzoate

Colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.10-8.08 (m, 2H), 7.60-7.56 (m, 1H), 7.47-7.43 (m, 2H), 7.28-7.16 (m, 5H), 5.35-5.30 (M, 1h), 4.58-4.56 (d, 1H, $J = 9.2$ Hz), 3.46-3.41 (m, 1H), 2.91 (s, 3H), 2.72-2.67 (m, 2H), 1.98-1.95 (m, 1H), 1.85-1.79 (m, 3H), 1.53 (d, 3H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 207.8, 207.7, 166.0(overlapped), 141.0(overlapped), 133.4(overlapped), 129.8(overlapped), 129.3(overlapped), 128.59(overlapped), 128.53(overlapped), 128.32(overlapped), 128.30(overlapped), 126.1(overlapped), 75.37, 75.32, 53.54, 53.52, 41.76, 41.71, 38.08, 38.02, 34.46, 34.42, 32.0, 28.5, 16.38, 16.35; FT-IR(neat): 3286, 2933, 1729, 1712, 1600, 1583, 1494, 1452, 1315, 1269, 1147 cm^{-1} ; LCMS (ESI) found: 400.05, calcd for formula ($\text{M}+\text{H}^+$): 400.15.

(Z)-1-(5-benzyl-1-(methanesulfonyl)pyrrolidin-2-ylidene)ethyl benzoate (9b)

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 cm^{-1} HRMS (ESI): Found: m/z , 386.1424, Calcd for $\text{C}_{21}\text{H}_{24}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 386.1426.

1-(methylsulfonyl)-2-phenethyl-5-(prop-1-ynyl)pyrrolidine (10c)

***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 cm^{-1} ; HRMS (ESI): Found: m/z , 292.1375, Calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 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 cm^{-1} ; HRMS (ESI): Found: m/z , 292.1370, Calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 292.1371.

1-(methylsulfonyl)-2-phenethyl-5-(phenylethynyl)pyrrolidine (10d)

trans-10d: 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 cm^{-1} ; HRMS (ESI): Found: m/z , 354.1523, Calcd for $\text{C}_{21}\text{H}_{24}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 354.1528.

cis-10d: 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 cm^{-1} ; HRMS (ESI): Found: m/z , 354.1522, Calcd for $\text{C}_{21}\text{H}_{24}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 354.1528.

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Chapter 3 (CuOTf)₂·C₆H₆-Catalyzed Synthesis of Pyrrolidines from *N*-Alkyl-*N*-Benzoyloxysulfonamides

3.1 Introduction

As described in chapter 2, it was found that *N*-5-alkenyl- or alkynyl-*N*-benzoyloxysulfonamides were transformed to pyrrolidines instead of *N*-radical addition products piperidines by the treatment with (CuOTf)₂·C₆H₆. The reaction is supposed to proceed as shown Scheme 3-1 via 1,5-allylic or propargylic hydrogen abstraction.

Scheme 3-1

Because sulfonamidyl radicals (or the equivalents) seem to have a strong hydrogen abstracting ability, the author expected that a similar 1,5-hydrogen abstraction might occur even at nonreactive aliphatic C-H bonds. So far the author described the reactive intermediate as a neutral sulfonamidyl radical **C**. However, it is not confirmed whether the reactive intermediate is a free neutral radical **C** or the complex with copper species (**A** and/or **B**). Although it is hard to discuss the structure(s) of reactive species, so far they behave like amidyl radicals.

Scheme 3-2

Accordingly, the similar copper(I)-catalyzed cyclization was examined by employing *N*-alkyl-*N*-benzoyloxysulfonamides, expecting the intramolecular amination of aliphatic C-H bonds (Scheme 3-3).

Scheme 3-3

3.2 Preparation of the starting materials

3.2.1 Preparation of *N*-alkyl-*N*-benzoyloxysulfonamides via oximes (method A)

The starting materials, *N*-alkyl-*N*-benzoyloxysulfonamides, were prepared by the following two methods, starting from oxime derivatives (method A) or *N*-acyloxysulfonamides (method B).

N-Alkyl-*N*-benzoyloxysulfonamides depicted in Table 3-1 were prepared from oximes (method A). The synthesis started by the treatment of ketones with hydroxylamine hydrochloride in the presence of pyridine,¹ followed by the reduction with sodium cyanoborohydride (NaBH₃CN)-HCl² to furnish *N*-alkylhydroxylamines. These hydroxylamines were subjected to sulfonylation with methanesulfonyl chloride (CH₃SO₂Cl) and triethylamine,³ and then were benzoylated with benzoylchloride and triethylamine to *N*-alkyl-*N*-benzoyloxysulfonamides, **1b-e**, **1**, **m** and **4a-c**. *N*-3-Isopropylcyclohexylsulfonamide **1m** was obtained as a mixture of *cis* and *trans*-isomers which could not be separated by a column chromatography.

Method A

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nitrobenzenesulfonyl chloride in the presence of MgO in the mixture of MeOH-H₂O-THF (3:2:30) to give the corresponding *N*-sulfonyhydroxamates **I**.⁴ Then, these hydroxamates **I** were treated with benzoyl chloride and triethylamine to produce *N*-benzoyloxysulfonamides **II**.³

Table 3-2

Yield : total yield of 2 steps

Various alcohols were treated with *N*-benzoyloxysulfonamide **II** (RSO₂NHOCOPh) in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine (PPh₃) to generate the expected substrates (Table 3-3).⁵ Substrates **1i**, **1j** and **1k** were mixtures of two stereo isomers which could not be separated by a column chromatography.

Table 3-3

Among these substrates, the preparations of *N*-(benzoyloxy)-4-methyl-*N*-(methyldecahydronaphthalen-2-yl) benzenesulfonamide **α-1n** and *N*-(benzoyloxy)-*N*-(2-ethoxycyclohexyl) methanesulfonamide **4d** are explained in detail concerning the stereochemical outcomes. Ketone **1na** was reduced with sodium borohydride (NaBH₄) and alcohol **1nb** was isolated as a mixture of two stereo isomers by column chromatography. Under Mitsunobu reaction conditions, alkylated α-sulfonamide **α-1n** was obtained as a major product, and then pure **α-1n** was isolated by recrystallization from ethyl acetate and hexane (Scheme 3-4).

Scheme 3-4

For methanesulfonamide **4d**, as shown in Scheme 3-5, after the reduction of α -ethoxycyclohexanone **4da** with sodium borohydride (NaBH_4), *cis*- and *trans*-alcohols **4db**, **4dc** were formed, which could be separated by a column chromatography. Then the *cis*-isomer **4db** was submitted to Mitsunobu reaction with *N*-benzoyloxysulfonamide to yield *trans*-sulfonamide **4d**.

Scheme 3-5

3.3 Results and discussion

3.3.1 Examination of the catalytic 1,5-hydrogen shift of nonreactive C-H bonds

First, the possibility of the catalytic C-H abstraction reaction was examined by using *N*-alkyl-*N*-benzoyloxymethanesulfonamide **1a** as a model.

When sulfonamide **1a** was treated with a catalytic amount (5 mol%) of (CuOTf)₂ C₆H₆ in refluxing 1,2-dichloroethane, pyrrolidine **2a** was obtained in 82% yield with 3% yield of *N*-alkenylsulfonamide **3a** (Table 3-4, entry 1). Both of the products are supposed to be obtained via a carbocation intermediate **2a**; by a nucleophilic attack of the amino group and **3a** by a deprotonation as depicted in Scheme 3-1. Thus the expected aliphatic C-H bond abstraction occurred smoothly to form amination product **2a** and dehydrogenation product **3a** by the catalytic use of (CuOTf)₂ C₆H₆. To investigate the influence of the acyloxy and sulfonyl groups, the amination of *N*-acetoxymethanesulfonamide **1b** and *N*-benzoyloxytosylamide was examined by the use of the copper(I) catalyst.

Table 3-4

Entry	Substrates ^a	cat./Time	Products/Yield ^b	
1	 1a	5 mol% 1.5 h	 2a 82%	 3a 3%
2	 1b	5 mol% 30 h	2a 22%	SM 40%
3	 1c	10 mol% 2 h	 2c 82%	 3c trace

a: the reactions were carried out under nitrogen atmosphere b: isolated yield.

Firstly, as a leaving group $-OR^2$, benzyloxy group was found to act more efficiently than acetoxy group (Table 3-4, entries 1, 2). The reaction of *N*-acetoxyamide **1b** proceeded very slowly and gave the amination product **2a** in 22% yield with a 40% recovery of the starting sulfonamide. As compared methylsulfonyl and tosyl groups, both of **1a** and **1c** gave pyrrolidine **2a** in good yields (entries 1, 3). In the reaction of tosylamide **1c** (entry 3), a trace amount of *N*-alkenylsulfonamide product **3c** was also observed in the crude 1H NMR spectrum.

Although the reactions of benzcarboxamides having *N*-benzyloxy and *N*-acetoxy groups, **1d** and **1e**, proceeded, the total yields of **2d** and **3d** (Scheme 3-6) were low even with a high catalyst loading and a longer reaction time.

Scheme 3-6

Thus, from these comparisons, the sulfonamides are suitable as compared with carboxamides.

In the above reaction of **1a**, a *t*-alkylhydrogen was abstracted. Then the reaction of *N*-benzyloxymethanesulfonamide possessing a linear alkyl group **1f** was examined. *cis*-Disubstituted pyrrolidines **2fa** and the *trans*-isomer **2fb** were obtained in 17% and 28% yield, respectively, along with a trace amount of a dehydrogenated product **3f** with a terminal vinyl moiety, which was observed from the crude NMR spectrum but could not be purely isolated

(Scheme 3-7, equation 2). The total yield of the C-H abstraction of *t*-alkyl hydrogen sulfonamide **1a** was better than that of the secondary one **1f**, which might be depend on that a tertiary C-H bond is generally more reactive to radical abstraction than a secondary one.⁶

Scheme 3-7

These results prompted us to extend this catalytic method to the preparation of bicyclic amide derivatives by a remote C-H activation starting from sulfonamides bearing cycloalkane moieties as summarized in Table 3-5.

1-Azaspiro[4,5]nonane **2g** was prepared in a high yield of 81% (entry 1), when sulfonamide having cyclopentyl group at γ -position **1g** was treated with $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$. Similarly γ -cyclohexyl sulfonamide **1h** was functionalized smoothly to give 1-azaspiro[4,5]decane **2h** and dehydrogenation product **3h** in 36% and 34% yield, respectively (entry 2). Thus, this remote C-H activation reaction would provide a catalytic method for the synthesis of many natural products containing azaspiro substructure.⁷

Table 3-5

Entry	Substrates ^a	cat./Time	Products/Yield ^b
1	1g	15 mol% 1 h	2g 81%
2	1h	20 mol% 1 h	2h 34% 3h 36%
3	1i (<i>syn:anti</i> =1:1)	5 mol% 6 h	2i 77% 2 isomers (1:1)
4	1j (<i>syn:anti</i> =1:1)	7.5 mol% 12 h	2j 88% 2 isomers (1:1)
5	1k (<i>syn:anti</i> =1:1)	15 mol% 24 h	2k 74% 2 isomers (1:1)

a: the reactions were carried out under nitrogen atmosphere b: isolated yield.

Construction of an aza-bicyclo[4.3.0] system was accomplished starting from β -3-cyclohexenyl methanesulfonamide **1i**, tosylamide **1j**, and *p*-nitrobenzenesulfonamide **1k** (entries 3-5). From 1:1 mixtures of *syn*- and *anti*-stereoisomers of these sulfonamides **1i**, **1j** and **1k**, the pyrrolidines were formed as mixtures of two stereoisomers **2i**, **2j** and **2k** in 77%,

88% and 74% yields, respectively. Even though there were two possibilities to abstract allylic and non-allylic methylene protons, the X-ray analysis revealed that the non-allylic hydrogens were abstracted preferentially to the allylic ones. In addition, the cyclization proceeded in a stereoselective manner to give the *cis*-annulation products as depicted in entries 3-5. The X-ray structure of one of the amination products **2k** is shown in Fig 3-1.

Fig 3-1

The selective abstraction of non-allylic hydrogens may be understood as follows: By considering the conformation of *N*-radical intermediate (Scheme 3-8), the *N*-radical moiety can be approach more closely to the axial hydrogen of the non-allylic methylene group as compared with the approach to the allylic hydrogens which are situated as pseudo axial and equatorial directions.

Scheme 3-8

The stereoselective formation of the *cis*-annulation products might be caused by the larger strain in the transition state to generate the *trans*-annulation products from the cation intermediates, which is generally observed in the [4.2.0] bicyclic compound formation.⁸

In addition, when *N*-3-isopropylcyclohexylsulfonamide **11** was submitted to the copper(I)-catalyzed reaction, pyrrolidine **21** and two alkenyl sulfonamides **31a** and **31b** were obtained in the yields of 5%, 25%, and 24%, respectively (Scheme 3-9). Thus the remote functionalization was occurred in a 54% total yield even in this conformationally flexible *N*-cyclohexylsulfonamide.

Scheme 3-9

As shown in Scheme 3-10, a diastereoisomer mixture ($\alpha:\beta = 1:1$) of *N*-decahydronaphthylsulfonamide **1m** was transformed to amination product **2m** in 30% yield and a mixture of alkenyl amide **3ma** and debenzoyloxy product **3mb** in a 38% total yield in a 6:4 ratio.

Scheme 3-10

The reaction of the α -isomer of toluenesulfonamide **1n** gave no amination product like **2m** but **3na** and **3nb** in a 7:3 ratio as shown in Scheme 3-11. Accordingly, it was clearly understood that amination product **2m** in Scheme 3-10 was derived from the β -isomer of **1m** in 60% yield.

Scheme 3-11

From the above experiments, the functionalization of unreactive aliphatic C-H bonds in *N*-alkyl substituted sulfonamides was achieved by the catalytic use of $(\text{CuOTf})_2$ benzene complex. At this stage, the mechanism is reconsidered in detail by taking sulfonamide **1a** as a typical example (Scheme 3-12). One electron reduction of **1a** with the copper(I) complex generates an anion radical **A** or the oxidative addition of **1a** to the copper(I) complex affords aintermediate **B**. Then, the nitrogen radical **C** is formed with the elimination of benzoyloxy anion from **A** or the N-Cu(III) bond cleavages of **B**, although it is not confirmed whether the

nitrogen radical is free or coordinates to copper(II) species. Then 1,5-hydrogen abstraction of an aliphatic C-H bond occurs to afford carbon centered radical **D**, which is oxidized by copper(II) species to carbo cation intermediate **E** with the regeneration of copper(I) salt. Intramolecular nucleophilic attack of the amino group to the carbo cation center of intermediate **E** gives the amination product **2a**, whereas the deprotonation of the carbo cation intermediate **E** affords *N*-alkenylsulfonamides.

Scheme 3-12

In intramolecular hydrogen abstraction with radicals, 1,5-hydrogen abstractions have been observed more frequently than other processes like 1,3- 1,4- and 1,6-hydrogen transfers.^{9,10,11,12} Intramolecular hydrogen abstractions by alkoxy radicals have been the subject of many mechanistic and synthetic investigation. In these systems, hydrogen transfer invariably takes place via a 6-membered transition state. The preference for δ -hydrogen abstraction is

usually rationalized by analogy: the carbocyclic 6-membered cyclohexane ring is strain-free, while other carbocyclic ring, 4- or 5-membered ring, have some strain.^{10a} For 1,6-hydrogen transfer via 7-membered transition structure, the activation energy is higher than 1,5-hydrogen transfer.^{10a} For hydrogen abstraction by alkyl radicals, the general accepted value for activation energy is 12-25.5 kcal mol⁻¹ for 1,4-hydrogen, and about 12 kcal mol⁻¹ for 1,5-hydrogen transfer reactions, depending on the type of the carbon atoms involved.^{9a}

3.3.2 Amination of *N*-benzoyloxysulfonamides for the preparation of oxazolidines

Then this catalytic C-H abstraction was applied to the preparation of oxazoline derivatives¹³ which are well-known for their bioactivities, for an example, anti-Gram-positive bacteria.¹⁴ The expected reaction route is depicted in Scheme 3-13. After the formation of nitrogen radical **B** as explained before, the 1,5-hydrogen abstraction gives carbon radical **C**, which is supposed to be readily oxidized by copper(II) species to generate stable oxonium cation **D2**. A successive nucleophilic attack of the amino group gives oxazoline **5a**.

Scheme 3-13

In fact, when *cis*-methanesulfonamide **4a** was treated with a catalytic amount of $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$, oxazolidine **5a** was obtained in 50% yield by the crude ^1H NMR spectrum with a lower isolated yield of 25% (Scheme 3-14). The structure of **5a** was determined as the β -methyl isomer by X-ray analysis (Fig. 3-2).

Scheme 3-14

Figure 3-2. Structure of **5a**

The absolute formation of the β -methyl isomer **5a** is explained by considering the cyclization transition states of the nucleophilic attack of the amido group in the oxonium cation intermediate **D2** (scheme 3-15). By comparing transition states leading to β -methyl and α -methyl oxazolines, the nucleophilic attack of the amino group proceeds through a more less-hindered conformation **A**.

Scheme 3-15

Instead of the above *cis*-sulfonamide, the reaction was also examined by employing similar *cis*-benzamides having *N*-benzoyloxy and acetoxy groups **4b**, **4c** (Scheme 3-16). The catalytic cyclization of benzamide with acetoxy group **4c** took place much slowly as compared to the corresponding benzoyloxy benzamide **4b**. Oxazolidine **5b** was produced in 40% and 25% yields from **4b** and **4c**, respectively.

Scheme 3-16

Although *N*-benzoyloxazoline **5b** was isolated as a single product, the NMR spectrum of **5b** shows two sets of peaks due to the slow amide bond rotation as depicted in Scheme 3-17.¹⁵ For example, the peak of the methine proton, neighbor of methyl group, showed at 5.73 p.p.m. and 5.51 p.p.m. with a 0.27:0.73 ratio. The chemical shift and ratio did not change at different temperature, such as 25, 40 and 50°C.

Scheme 3-17

As compared to the above reactions of *cis*-sulfonamide **4a**, the *trans*-isomer **4d** underwent the catalytic reaction more faster and afforded the cyclization product **5d** in 35% yield with *N*-(2-hydroxycyclohexyl)methane-sulfonamide **6d** in 18% yield, which was supposed to be resulted by the hydrolysis of the oxonium intermediate (Scheme 3-18). The stereochemistry of these products was determined by X-ray analysis.

Scheme 3-18

Fig 3-3. Structure of 5d

Fig 3-4. Structure of **6d**

The stereoselective formation of **5d** is controlled by the conformation in the cyclization of the oxonium cation intermediate (Scheme 3-19). Transition state **A** has a less steric repulsion as compared with conformation **B** because the interaction between the mesyl and the axial H is smaller than that of the mesyl and methyl groups. Accordingly, the cyclization yields β -methyl product **5d** selectively.

Scheme 3-19

3.4 Conclusion

In this chapter, the unreactive C-H abstraction of *N*-alkyl-*N*-benzoyloxysulfonamides **1** and *N*-benzoyloxysulfonamides **4** has been investigated by using (CuOTf)₂ C₆H₆ as a redox

catalyst. The intramolecular amination products were formed from three types of substrates, *N*-acycloalkyl-sulfonamides (equation 1), *N*-cycloalkyl sulfonamides (equations 2 and 3) and *N*-2-alkoxycyclohexyl-sulfonamides (equation 4).

From *N*-acycloalkyl-*N*-benzoyloxysulfonamides, pyrrolidines were obtained via 1,5-hydrogen abstraction by the treatment with $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ (equation 1).

Spiro compounds could be obtained from *N*-cycloalkyl-*N*-benzoyloxysulfonamides (equation 2), and bicyclic and tricyclic compounds were formed from *N*-cyclohexyl-*N*-benzoyloxysulfonamides (equation 3).

When *N*-2-ethoxycyclohexyl-*N*-benzoyloxysulfonamides were subjected to $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$, oxazolidine derivatives were provided with good stereoselectivity via oxonium cation intermediates (equation 4).

3.5. Experimental data

3.5.1 General

All chemicals were purchased from Alfa Aesar, Merck, Sigma-Aldrich, Sinopharm Chemical and used without purification, unless otherwise stated. Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 pre-coated silica gel plates (0.2 mm thickness). Subsequent to elution, the plates were visualized using ultraviolet radiation (254 nm). Flash column chromatography was performed using Merck silica gel 60 with distilled solvents. Preparative thin-layer chromatography (PTLC) were prepared using Wakogel B-5F (Wako Pure Chemical Industries) and gradually heated to 100 °C over 2 hours and at 100 °C for an additional 2 hours.

^1H nuclear magnetic resonance (NMR) (500, 400 and 300 MHz) spectra were recorded on Bruker AVANCE 500, 400 and 300 in CDCl_3 [using CDCl_3 (for ^1H , $\delta = 7.26$) as internal standard] unless otherwise mentioned. ^{13}C NMR (125, 100 and 75 MHz) spectra

were recorded on Bruker AVANCE 500, 400 and 300 in CDCl_3 [using CDCl_3 (for ^{13}C , $\delta = 77.00$) as internal standard] unless other mentioned. Chemical shifts were reported in parts per million (ppm) from tetramethylsilane for ^1H and ^{13}C experiments. Abbreviations used to explain the multiplicities were as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet or unresolved, br = broad. Coupling constants (J) are given in Hz.

Infra-red spectra were recorded on Shimadzu IR Prestige-21 FT-IR Spectrometer. Samples were analyzed as a neat liquid or as a solution in chloroform using NaCl cells. High-resolution mass spectra were obtained with Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). Elemental analyses were carried out at the Elemental Analysis Laboratory. Melting points were recorded on Buchi B-54 melting point apparatus and are uncorrected.

Dry tetrahydrofuran (THF), diethyl ether (Et_2O), toluene and dichloromethane (CH_2Cl_2) were taken from a solvent purification system (PS-400-5, innovative technology Inc.). Triethylamine (Et_3N) and pyridine were distilled from CaH_2 and stored over potassium hydroxide (KOH). Ethanol (EtOH) and Methanol (MeOH) were distilled from sodium under N_2 and stored over MS 4A.

3.5.2. Synthesis of *N*-alkyl-*N*-benzoyloxysulfonamides

N-Alkyl-*N*-benzoyloxysulfonamides were prepared by method A and method B.

Scheme 3-20. Synthetic routes of substrates

In this chapter, substrates **1b**, **1d**, **1e**, **1m**, **1l**, **4a**, **4b** and **4c** were prepared by method A. The typical procedures of method A have been described in chapter 2, section 2.4.

3.5.2.1 Synthesis of substrates by method A

3.5.2.1.1 Synthesis of ketones

6-Methyl-1-phenylheptan-3-one (**1bc**)

6-Methyl-1-phenylheptan-3-one was prepared by the method mentioned in Chapter 2, Section 2.4.2.1 method A-1. Yield: 82%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.29-7.25 (m, 2H), 7.20-7.16 (m, 3H), 2.89 (t, 2H, $J = 8.0$ Hz), 2.73 (t, 2H, $J = 8.0$ Hz), 2.37 (t, 2H,

$J = 8.0$ Hz), 1.53-1.42 (m, 3H), 0.86 (d, 6H, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 210.5, 141.1, 128.4, 128.3, 126.0, 44.2, 41.0, 32.5, 29.8, 27.6, 22.3; FT-IR (neat): 3028, 1712, 1602, 1496, 1454 cm^{-1} ; HRMS (ESI): Found: m/z , 227.1411, Calcd for $\text{C}_{14}\text{H}_{20}\text{ONa}$ $[\text{M}+\text{Na}]^+$: 227.1412.

3-Isopropylcyclohexanone (11c)¹⁶

3-Isopropylcyclohexanone was synthesized according to the literature (*Tetrahedron* 1989, 45, 349). Yield: 82%; yellow oil; ^1H NMR (300 MHz, CDCl_3) δ : 2.41-2.32 (m, 2H), 2.31-2.11 (m, 1H), 2.10-2.03 (m, 2H), 1.89-1.84 (m, 1H), 1.64-1.05 (m, 3H), 1.45-1.31 (m, 1H), 0.86 (d, 3H, $J = 6.4$ Hz), 0.85 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 212.7, 45.4, 45.3, 41.4, 32.4, 28.3, 25.5, 19.5, 19.3; FT-IR (neat): 2956, 2933, 1714 cm^{-1} ; HRMS (ESI): Found: m/z , 141.1277, Calcd for $\text{C}_9\text{H}_{17}\text{O}$ $[\text{M}+\text{H}]^+$: 141.1279.

8a-Methyloctahydronaphthalen-2(1H)-one (1na)^{16,17}

8a-Methyloctahydronaphthalen-2(1H)-one was synthesized according to the literature (*Chem. Lett.* 1993, 993). Yield: 55%; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ : 2.58 (d, 1H, $J = 13.6$ Hz), 2.33-2.29 (m, 1H), 2.23-2.18 (m, 1H), 2.07-2.01 (m, 1H), 1.82 (d, 1H, $J = 13.6$ Hz), 1.76-1.68 (m, 2H), 1.65-1.48 (m, 4H), 1.43-1.23 (m, 4H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 213.3, 49.1, 40.3, 38.6, 38.0, 37.7, 28.3, 28.1, 27.0, 25.0, 22.1; FT-IR (neat): 2926,

2860, 1639, 1446, 1041 cm^{-1} ; HRMS (ESI): Found: m/z , 167.1438, Calcd for $\text{C}_{11}\text{H}_{19}\text{O}$ $[\text{M}+\text{H}]^+$: 167.1436.

3.5.2.1.2 Synthesis of hydroxylamine

The typical procedure of synthesis of hydroxylamines has been described in chapter 2, section 2.4.2.2.

N-(6-Methyl-1-phenylheptan-3-yl)hydroxylamine (1bb)

Yield: 85%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.30-7.26 (m, 2H), 7.21-7.18 (m, 3H), 2.85-2.82 (m, 1H), 2.70-2.65 (m, 2H), 1.90-1.84 (m, 1H), 1.76-1.72 (m, 1H), 1.56-1.44 (m, 3H), 1.43-1.17 (m, 2H), 0.89 (d, 6H, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 142.3, 128.4, 128.3, 125.8, 61.5, 34.9, 33.3, 32.2, 29.3, 28.2, 22.6, 22.5; FT-IR (neat): 3253, 3026, 1602, 1494, 1454 cm^{-1} ; HRMS (ESI): Found: m/z , 244.1682, Calcd for $\text{C}_{14}\text{H}_{23}\text{NONa}$ $[\text{M}+\text{Na}]^+$: 244.1677.

N-(2-Ethoxycyclohexyl)hydroxylamine (1lb)

Yield: 62%; pale yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 6.24 (br, 2H), 3.74-3.73 (m, 1H), 3.60-3.55 (m, 1H), 3.43-3.39 (m, 1H), 2.96-2.91 (m, 1H), 1.91-1.86 (m, 1H), 1.69-1.65 (m, 1H), 1.53-1.43 (m, 3H), 1.37-1.24 (m, 3H), 1.80 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 73.4, 63.9, 62.0, 27.1, 24.7, 23.5, 20.1, 15.6; FT-IR(Neat): ν 3262, 2972, 2934, 2897, 2860, 1101, 1063, 920 cm^{-1} ; LCMS (ESI) found: 160.03, calcd for formula ($\text{M}+\text{H}^+$): 169.23

***N*-((4a*S*,8a*R*)-8a-Methyldecahydronaphthalen-2-yl)hydroxylamine (1mb)**

Mixture of two isomers (0.6:0.4), Yield: 60%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 3.15-3.12 (m, 0.6H), 3.11-2.99 (m, 0.4H), 2.01-1.90 (m, 0.4H), 1.87-1.61 (m, 3H), 1.56-1.14 (m, 11.6H), 1.00-0.98 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 57.6, 56.8, 45.0, 41.3, 40.9, 40.6, 34.2, 33.7, 33.5, 31.2, 30.9, 28.9, 27.9, 27.3, 27.1, 26.8, 26.4, 26.1, 24.9, 22.2, 22.0, 20.5; FT-IR (neat): 3242, 2926, 1446 cm^{-1} ; HRMS (ESI): Found: m/z , 206.1567, Calcd for $\text{C}_{11}\text{H}_{21}\text{NONa}$ [$\text{M}+\text{Na}$] $^+$: 206.1521.

3.5.2.1.3 Synthesis of *N*-hydroxysulfonamides

The typical procedure of synthesis of *N*-hydroxysulfonamides has been described in chapter 2, section 2.4.2.3.

***N*-Hydroxy-*N*-(6-methyl-1-phenylheptan-3-yl)methanesulfonamide (1ba)**

Yield: 71%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.29-7.24 (m, 2H), 7.20-7.16 (m, 3H), 6.88 (m, 1H), 3.74-3.67 (m, 1H), 2.95 (s, 3H), 2.78-2.72 (m, 1H), 2.68-2.63 (m, 1H), 1.96-1.85 (m, 2H), 1.64-1.58 (m, 2H), 1.51-1.47 (m, 1H), 1.26-1.17 (m, 2H), 0.87 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ : 141.7, 128.4(overlapped), 125.9, 60.7, 36.3, 35.5, 32.9, 32.7, 28.6, 27.9, 22.6, 22.4; FT-IR (neat): 3608, 1602, 1496, 1444, 1375, 1161 cm^{-1} ; HRMS (ESI): Found: m/z , 300.1639, Calcd for $\text{C}_{15}\text{H}_{26}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$: 300.1633.

***N*-Hydroxy-*N*-(6-methyl-1-phenylheptan-3-yl)benzamide (1da)**

Yield: 82%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.70 (br, 1H), 7.45-7.34 (m, 5H), 7.26-7.24 (m, 2H), 7.22-7.15 (m, 1H), 7.11-7.09 (m, 2H), 3.85-3.80 (m, 1H), 2.71-2.63 (m, 1H), 2.54-2.48 (m, 1H), 2.19-2.14 (m, 1H), 1.87-1.78 (m, 2H), 1.55-1.38 (m, 2H), 1.25-1.15 (m, 1H), 1.04-1.00 (m, 1H), 0.85 (d, 3H, $J = 6.8$ Hz), 0.83 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 176.3, 141.1, 132.7, 130.5, 128.5, 128.4, 128.2, 127.8, 126.0, 60.8, 35.2, 34.4, 32.4, 30.3, 27.8, 22.5, 22.4; FT-IR (neat): 3441, 1647, 1602, 1456, 1377, 1147 cm^{-1} ; HRMS (ESI): Found: m/z , 348.1946, Calcd for $\text{C}_{21}\text{H}_{27}\text{NO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 348.1939.

***N*-Hydroxy-*N*-(8a-methyldecahydronaphthalen-2-yl)methanesulfonamide (1ma)**

Mixture of two isomers 0.5:0.5, Yield: 62%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.14 (s, 1H), 4.01-3.84 (m, 1H), 3.02 (s, 3H), 1.87-1.74 (m, 4H), 1.70-1.24 (m, 11H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 57.0, 56.2, 43.0, 41.0, 39.8, 39.6, 36.4, 33.8, 32.1, 30.7, 28.8, 28.4, 27.7, 27.0, 26.8, 26.6, 26.5, 26.2, 22.6, 21.9, 21.8, 20.1; FT-IR (neat): 3419, 2985, 1332, 1155 cm^{-1} ; HRMS (ESI): Found: m/z , 284.1298, Calcd for $\text{C}_{12}\text{H}_{23}\text{NO}_3\text{SNa}$ $[\text{M}+\text{Na}]^+$: 284.1296.

***N*-(2-Ethoxycyclohexyl)-*N*-hydroxymethanesulfonamide (4aa)**

Yield: 45%; colorless oil; ^1H NMR (300 MHz, CDCl_3) δ 8.26 (br, 1H), 4.22 (s, 1H), 3.75-3.70 (m, 1H), 3.63-3.53 (m, 1H), 3.44-3.35 (m, 1H), 2.98 (s, 3H), 2.19-2.06 (m, 1H), 1.96-1.93 (m, 1H), 1.84-1.80 (m, 1H), 1.64-1.60 (m, 1H), 1.44-1.24 (m, 3H), 1.21-1.16 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 79.7, 63.6, 58.0, 38.1, 27.0, 25.1, 24.2, 18.6, 15.5; FT-IR (Neat): ν 3285, 3022, 2976, 2939, 2860, 1450, 1323, 1215, 1153 cm^{-1} ; LCMS (ESI) found: 238.91, calcd for formula $(\text{M}+\text{H}^+)$: 238.32

***N*-(2-Ethoxycyclohexyl)-*N*-hydroxybenzamide (4ba)**

Yield: 76%; white solid; mp: 100 – 102 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.70-7.68 (m, 2H), 7.44-7.35 (m, 3H), 4.59 (br, 1H), 4.02 (br, 1H), 3.73-3.63 (m, 1H), 3.42-3.33 (m, 1H), 2.26 (qd, 1H, J = 4.3, 12.6 Hz), 2.09-2.04 (m, 1H), 1.89-1.86 (m, 1H), 1.76-1.71 (m, 1H), 1.48-1.36 (m, 3H), 1.20 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 168.0, 134.3, 130.2, 128.5, 127.6, 78.5, 63.5, 56.1, 27.3, 24.6, 23.6, 19.0, 15.5; FT-IR (Neat): ν 3208, 2968, 2934, 2872, 2853, 1717, 1605, 1597, 1448, 1165, 711 cm^{-1} ; LCMS (ESI) found: 264.28, calcd for formula ($\text{M}+\text{H}^+$): 264.33

3.5.2.1.4 Synthesis of substrates

N-Acetoxy-*N*-(6-methyl-1-phenylheptan-3-yl)methanesulfonamide (1b)

Yield: 82%; colorless oil; ^1H NMR (300 MHz, CDCl_3) δ : 7.29-7.24 (m, 2H), 7.19-7.15 (m, 3H), 3.91-3.85 (m, 1H), 2.99 (s, 1H), 2.90 (br, 1H), 2.70-2.62 (m, 1H), 2.20 (s, 3H), 1.87-1.80 (m, 1H), 1.61-1.46 (m, 4H), 1.38-1.17 (m, 2H), 0.87 (d, 3H, J = 6.4 Hz); 0.86 (d, 3H, J = 6.4Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 168.3, 141.6, 128.49, 128.46, 126.0, 61.8, 39.5, 35.5, 34.0, 32.8, 29.6, 27.9, 22.5, 22.4, 18.6; FT-IR (neat): 3026, 1789, 1602, 1494, 1454, 1354, 1157 cm^{-1} ; HRMS (ESI): Found: m/z , 364.1553, Calcd for $\text{C}_{17}\text{H}_{27}\text{NO}_4\text{SNa}$ [$\text{M}+\text{Na}$] $^+$: 364.1559.

N-(Benzoyloxy)-*N*-(6-methyl-1-phenylheptan-3-yl)benzamide (1d)

Yield: 82%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.58-7.56 (m, 2H), 7.45-7.42 (m, 3H), 7.36-7.33 (m, 2H), 7.31-7.30 (m, 3H), 7.27-7.25 (m, 2H), 7.23-7.14 (m, 3H), 4.40 (br, 1H), 2.98 (br, 1H), 2.71 (br, 1H), 2.01 (br, 1H), 1.89-1.79 (m, 2H), 1.58-1.50 (m, 1H), 1.34-1.25 (m, 1H), 0.89 (d, 3H, $J = 7.0$ Hz), 0.88 (d, 3H, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 170.4, 164.1, 141.5, 134.4, 134.0, 130.6, 129.8, 128.7, 128.5, 128.4, 128.3, 127.7, 127.2, 126.0, 61.1, 35.3, 34.9, 32.8, 30.6, 27.9, 22.7, 22.4; FT-IR (neat): 3028, 1766, 1662, 1600, 1494, 1450, 1319, 1143 cm^{-1} ; HRMS (ESI): Found: m/z , 430.2378, Calcd for $\text{C}_{28}\text{H}_{32}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 430.2382.

***N*-Acetoxy-*N*-(6-methyl-1-phenylheptan-3-yl)benzamide (1e)**

Yield: 90%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.52 (d, 2H, $J = 8.0$ Hz), 7.40 (t, 1H, $J = 8.0$ Hz), 7.34 (t, 2H, $J = 8.0$ Hz), 7.27-7.24 (m, 2H), 7.19-7.16 (m, 3H), 4.2 (br, 1H), 2.90 (br, 1H), 2.63 (br, 1H), 2.09 (br, 3H), 1.89 (br, 1H), 1.78 (br, 1H), 1.65 (br, 1H), 1.50-1.45 (m, 2H), 1.37 (br, 1H), 1.20 (br, 1H), 0.87 (d, 3H, $J = 6.4$ Hz), 0.86 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 169.9, 167.8, 141.4, 134.3, 130.4, 128.3, 128.2, 127.5, 125.8, 60.5, 35.1, 34.6, 32.6, 30.4, 27.7, 22.4, 22.3, 18.2; FT-IR (neat): 3026, 1789, 1651, 1600, 1494, 1446, 1367, 1186 cm^{-1} ; HRMS (ESI): Found: m/z , 368.2230, Calcd for $\text{C}_{23}\text{H}_{30}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 368.2226.

***N*-(Benzoyloxy)-*N*-(3-isopropylcyclohexyl)methanesulfonamide (1l)**

Yield: 69%; colorless oil; ^1H NMR (300 MHz, CDCl_3) δ : 8.10 (d, 2H, $J = 8.0$ Hz), 7.69-7.65 (m, 1H), 7.54-7.50 (m, 2H), 4.11-4.05 (m, 1H), 3.05 (s, 3H), 2.09 (br, 2H), 1.87-1.83 (m, 1H), 1.66-1.63 (m, 1H), 1.56-1.25 (m, 6H), 0.86-0.84 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ : 164.4, 134.3, 130.1, 128.9, 127.0, 61.3, 39.5, 32.7(overlapped), 28.3, 24.8(overlapped), 19.8(overlapped), 19.5; FT-IR (neat): 2926, 1635, 1465, 1340, 1166, 906, 732 cm^{-1} ; HRMS (ESI): Found: m/z , 340.1578, Calcd for $\text{C}_{17}\text{H}_{26}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 340.1583.

***N*-(Benzoyloxy)-*N*-(8a-methyldecahydronaphthalen-2-yl)methanesulfonamide (1m)**

Mixture of two isomers (0.5:0.5), Yield: 63%; white solid; mp: 115-117 $^{\circ}\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ : 8.11-8.09 (m, 2H), 7.70-7.65 (m, 1H), 7.55-7.50 (m, 2H), 4.41-4.26 (m, 1H), 3.05-3.04 (m, 3H), 2.1 (br, 1H), 2.00-1.50 (m, 5H), 1.43-1.39 (m, 9H), 1.20-1.00 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ : 164.5, 164.4, 134.4, 134.3, 130.1, 130.0, 128.99, 128.92, 127.0, 58.4, 57.5, 40.9, 39.7, 39.6, 39.5, 34.4, 34.2, 30.6, 28.4, 27.8, 27.2, 26.8, 26.7, 26.5, 22.08, 22.02, 20.2; FT-IR (neat): 2927, 1761, 1639, 1600, 1450, 1340, 1234, 1159 cm^{-1} ; HRMS (ESI): Found: m/z , 366.1756, Calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 366.1739.

***N*-(Benzoyloxy)-*N*-(2-ethoxycyclohexyl)methanesulfonamide (4a)**

Yield: 81%; colorless oil; ^1H NMR (300 MHz, CDCl_3) δ 8.09 (d, 2H, $J = 7.8$ Hz), 7.64-7.60 (m, 1H), 7.48 (t, 2H, $J = 7.8$ Hz), 4.13-4.06 (m, 1H), 3.85 (br, 1H), 3.38 (br, 1H), 3.15 (br, 1H), 3.05 (s, 3H), 2.35 (br, 1H), 2.06-2.02 (m, 1H), 1.93-1.90 (m, 2H), 1.85-1.83 (m, 1H), 1.51-1.36 (m, 3H), 1.32-1.24 (m, 1H), 0.67 (br, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 164.2, 133.7, 130.0, 128.5, 128.1, 63.1, 61.4, 38.5, 28.2, 25.1, 23.4, 18.8, 14.9; FT-IR (Neat): ν 3018, 2938, 2858, 1763, 1452, 1335, 1215 cm^{-1} ; HRMS (ESI) found: 342.1366, Calcd for formula ($\text{M}+\text{H}^+$): 342.4279

***N*-(Benzoyloxy)-*N*-(2-ethoxycyclohexyl)benzamide (4b)**

Mixture of two isomers (2:3). Yield: 78%; white solid; mp: 98 – 100 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.93 (d, 2H, $J = 7.4$ Hz), 7.61-7.53 (m, 3H), 7.38 (t, 2H, $J = 7.8$ Hz), 7.29 (t, 3H, $J = 7.2$ Hz), 4.68 (br, 0.4H), 4.54 (br, 0.6H), 3.94 (s, 1H), 3.69 (br, 0.3H), 3.60 (br, 0.7H), 3.34 (br, 0.7H), 2.42-2.39 (m, 0.7H), 2.06-1.92 (m, 2H, overlapped), 1.28-1.24 (m, 1H), 1.69 (br, 1H), 1.49 (br, 1.3H), 1.39 (br, 2.3H), 1.27 (br, 1.7H), 0.60 (br, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.1, 164.3, 134.3, 133.4, 130.2, 129.7, 128.4, 127.9, 127.4, 75.6, 62.6, 59.6, 27.7, 25.4, 24.6, 18.9, 14.8; FT-IR (Neat): ν 2972, 2938, 2897, 1765, 1645, 1234, 1018, 700 cm^{-1} ; LCMS (ESI) found: 368.14, calcd for formula ($\text{M}+\text{H}^+$): 368.14

***N*-Acetoxy-*N*-(2-ethoxycyclohexyl)benzamide (4c)**

Yield: 90%; white solid; mp: 67 – 69 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.52 (d, 2H, J = 6.5 Hz), 7.39-7.31 (m, 3H), 4.54 (br, 0.3H), 4.38 (br, 0.7H), 3.84 (br, 1H), 3.62 (br, 0.3H), 3.46 (br, 1H), 3.14 (br, 0.7H), 2.23 (br, 0.7H), 2.04 (br, 0.7H), 1.89-1.78 (m, 5H, overlapped), 1.61-1.05 (m, 7.7H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.7, 167.9, 134.3, 130.2, 127.8, 127.3, 75.7, 75.1, 62.7, 59.2, 27.6, 25.2, 24.2, 18.8, 18.5, 15.2; FT-IR (Neat): ν 2974, 2934, 2862, 1803, 1651, 1369, 1149, 705 cm^{-1} ; LCMS (ESI) found: 306.11, calcd for formula ($\text{M}+\text{H}^+$): 306.37

3.5.2.2 Synthesis of substrates by method B

Substrates **1a**, **1c**, **1f**, **1g**, **1h**, **1i**, **1j**, **1k**, α -**1n** and **4d** were prepared by method B.

3.5.2.2.1 Synthesis of *N*-benzoyloxysulfonamide ($\text{RSO}_2\text{NHOCOPh}$)^{3,4}

Hydroxylamine hydrochloride (0.72 g, 10 mmol) in $\text{MeOH-H}_2\text{O}$ (3:2, 5 mL) was treated with MgO (0.34 g, 8.6 mmol), then a solution of methanesulfonyl chloride (0.49 g, 4.3 mmol) in THF (30 mL), and MgO (0.17 g, 4.3 mmol) were added. The reaction was vigorously stirred at r.t. until methanesulfonyl chloride had completely disappeared (TLC: EtOAc-hexane , 1:1; 2 h). Then, the mixture was filtered first through a pad of Celite, and then on a short plug of silica gel. The clear filtrate was dried over MgSO_4 and evaporated to dryness to

give the resulting *N*-hydroxysulfonamide (0.3 g, 62%) which was used directly in next step.

To a solution of *N*-hydroxysulfonamide (0.26 g, 2.3 mmol) in CH₂Cl₂ (15 mL) in a flame-dried flask was added dropwise Et₃N (0.24 g, 2.3 mmol) and a solution of benzoyl chloride (0.33 g, 2.3 mmol) in CH₂Cl₂ (1 mL) at 0 °C. The mixture was stirred at the same temperature for 2 h. After the reaction was quenched by saturated aqueous NaHCO₃, the mixture was extracted with EtOAc. The combined extracts were washed with water, brine and dried over MgSO₄, and then evaporated. The crude product was purified by flash chromatography on silica gel to give *N*-(benzoyloxy)methanesulfonamide **II-a** (0.28 g, 54%).

***N*-(Benzoyloxy)methanesulfonamide (II-a)**

Total yield: 33%; white solid; mp: 143-145 °C; ¹H NMR (400 MHz, CDCl₃) δ: 8.98 (s, 1H), 8.09 (d, 2H, *J* = 8.0 Hz), 7.70-7.67 (m, 1H), 7.54-7.50 (m, 2H), 3.16 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 165.5, 134.8, 130.0, 128.9, 125.7, 38.9; FT-IR (neat): 3444, 3103, 1747, 1645, 1456, 1377, 1247, 1163 cm⁻¹; HRMS (ESI): Found: *m/z*, 216.0351, Calcd for C₈H₁₀NO₄S [M+H]⁺: 216.0331.

***N*-(Benzoyloxy)-4-methylbenzenesulfonamide (II-b)**

Total yield: 65%; white solid; mp: 68-70 °C; ¹H NMR (400 MHz, CDCl₃) δ: 9.23 (s, 1H), 7.92 (d, 2H, *J* = 8.0 Hz), 7.83 (d, 2H, *J* = 8.0 Hz), 7.65-7.61 (m, 1H), 7.47-7.43 (m, 2H), 7.28-7.26 (m, 2H), 2.39 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 164.9, 145.7, 134.5, 132.2,

129.9, 129.6, 128.78, 128.75, 125.7, 21.6; FT-IR (neat): 3149, 1747, 1456, 1377 cm^{-1} ;
HRMS (ESI): Found: m/z , 276.0688, Calcd for $\text{C}_{14}\text{H}_{14}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$: 276.0694.

***N*-(Benzoyloxy)-4-nitrobenzenesulfonamide (II-c)**

Total yield: 25%; white solid; mp: 138-140 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CD_2Cl_2) δ : 9.23 (s, 1H), 8.34 (d, 2H, $J = 8.8$ Hz), 8.17 (d, 2H, $J = 8.8$ Hz), 7.92-7.90 (m, 2H), 7.70-7.66 (m, 1H), 7.51-7.47 (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ : 166.7, 153.1, 143.1, 136.9, 132.0, 131.6, 130.9, 127.1, 126.4; FT-IR (neat): 3086, 1739, 1600, 1529, 1454, 1363, 1346, 1174 cm^{-1} ;
LCMS (ESI) found: 323.16, calcd for formula $(\text{M}+\text{H}^+)$: 323.03.

3.5.2.2.2 Synthesis of alcohols

6-Methyl-1-phenylheptan-3-ol, 1-phenylheptan-3-ol, 1-cyclopentyl-5-phenylpentan-3-ol, 1-cyclohexyl-5-phenylpentan-3-ol, 1-(cyclohex-3-enyl)-4-phenylbutan-2-ol and *cis*-2-ethoxycyclohexanol were reduced by sodium borohydride from the corresponding ketones.

6-Methyl-1-phenylheptan-3-ol (1aa)

6-Methyl-1-phenylheptan-3-ol was synthesized from the reduction of ketone in Chapter 3, Section 3.5.2.1.1

Yield: 92%; colorless oil; ^1H NMR (300 MHz, CDCl_3) δ : 7.30-7.25 (m, 2H), 7.21-7.16 (m, 3H), 3.62-3.58 (m, 1H), 2.82-2.76 (m, 1H), 2.71-2.63 (m, 1H), 1.81-1.61 (m, 2H), 1.55-1.45 (m, 3H), 1.43-1.28 (m, 2H), 1.23-1.17 (m, 1H), 0.89-0.85 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ : 142.2, 128.4, 128.3, 125.7, 71.6, 39.0, 35.4, 34.7, 32.0, 28.0, 22.6, 22.5; FT-IR (neat): 3373, 3026, 1602, 1494, 1454 cm^{-1} ; HRMS (ESI): Found: m/z , 207.1752, Calcd for $\text{C}_{14}\text{H}_{23}\text{O}$ $[\text{M}+\text{H}]^+$: 207.1749.

1-Phenylheptan-3-ol (1fa)

1-Phenylheptan-3-ol was synthesized from 1-phenylheptan-3-one which was prepared by the method mentioned in chapter 2, section 2.4.2.1 method A-1. 1-Phenylheptan-3-one: yellow oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.29-7.26 (m, 2H), 7.20-7.17 (m, 3H), 2.90 (t, 2H, $J = 8.0$ Hz), 2.73 (t, 2H, $J = 8.0$ Hz), 2.38 (t, 2H, $J = 8.0$ Hz), 1.62-1.51 (m, 2H), 1.32-1.26 (m, 2H), 0.89 (t, 3H, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 210.3, 141.2, 128.4, 128.3, 126.0, 44.2, 42.7, 29.8, 25.9, 22.3, 13.8; FT-IR (neat): 3028, 1712, 1604, 1496, 1454 cm^{-1} ; HRMS (ESI): Found: m/z , 191.1431, Calcd for $\text{C}_{13}\text{H}_{19}\text{O}$ $[\text{M}+\text{H}]^+$: 191.1436.

1-Phenylheptan-3-ol (**1fa**): Yield: 93%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.30-7.25 (m, 2H), 7.21-7.16 (m, 3H), 3.62 (br, 1H), 2.83-2.76 (m, 1H), 2.70-2.63 (m, 1H), 1.81-1.71 (m, 2H), 1.49-1.28 (m, 7H), 0.90 (t, 3H, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 142.2, 128.4, 128.3, 125.8, 71.4, 39.1, 37.3, 32.1, 27.8, 22.7, 14.0; FT-IR (neat): 3373, 3026,

1602, 1494, 1454 cm^{-1} ; HRMS (ESI): Found: m/z , 193.1599, Calcd for $\text{C}_{13}\text{H}_{21}\text{O}$ $[\text{M}+\text{H}]^+$: 193.1592.

1-Cyclopentyl-5-phenylpentan-3-ol (1ga)

1-Cyclopentyl-5-phenylpentan-3-ol was prepared by the method mentioned in chapter 2, section 2.4.2.1 method A-1.

Yield: 90%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.30-7.25 (m, 2H), 7.22-7.19 (m, 3H), 3.63-3.60 (m, 1H), 2.80-2.77 (m, 1H), 2.71-2.65 (m, 1H), 1.81-1.71 (m, 5H), 1.62-1.42 (m, 8H), 1.34-1.31 (m, 1H), 1.10-1.06 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 142.2, 128.4, 128.3, 125.8, 71.6, 40.1, 39.0, 36.7, 32.8, 32.6, 32.1, 32.0, 25.2; FT-IR (neat): 3383, 3026, 1602, 1494, 1454 cm^{-1} ; HRMS (ESI): Found: m/z , 233.1917, Calcd for $\text{C}_{16}\text{H}_{25}\text{O}$ $[\text{M}+\text{H}]^+$: 233.1905.

1-Cyclohexyl-5-phenylpentan-3-ol (1ha)

1-Cyclohexyl-5-phenylpentan-3-ol was prepared by the method mentioned in chapter 2, section 2.4.2.1 method A-1.

Yield: 72%; white solid; mp: 48-50 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ : 7.30-7.25 (m, 2H), 7.21-7.16 (m, 3H), 3.60-3.58 (m, 1H), 2.79-2.75 (m, 1H), 2.70-2.64 (m, 1H), 1.80-1.63 (m, 7H), 1.52-1.42 (m, 3H), 1.40-1.11 (m, 6H), 0.91-0.86 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3)

δ : 142.2, 128.4, 128.3, 125.8, 71.7, 39.0, 37.2, 34.8, 33.4, 33.3, 33.2, 32.0, 26.6, 26.3; FT-IR (neat): 3383, 3026, 1602, 1494, 1452 cm^{-1} ; HRMS (ESI): Found: m/z , 269.1898, Calcd for $\text{C}_{17}\text{H}_{26}\text{OMNa}[\text{M}+\text{Na}]^+$: 269.1881.

1-(Cyclohex-3-enyl)-4-phenylbutan-2-ol (**1ia**)

1-(Cyclohex-3-enyl)-4-phenylbutan-2-ol was synthesized from the reaction of 2-(cyclohex-3-enyl)acetaldehyde and phenethylmagnesium bromide. The aldehyde was prepared from the oxidation of 2-(cyclohex-3-enyl)ethanol which was from the reaction 9-BBN and 4-allylcyclohex-1-ene. 2-(Cyclohex-3-enyl)ethanol¹⁸: colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 5.68-5.61 (m, 2H), 3.71 (t, 2H, $J = 6.8$ Hz), 2.12-2.03 (m, 3H), 1.76-1.67 (m, 3H), 1.57-1.51 (m, 2H), 1.40 (s, 1H), 1.30-1.22 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 127.0, 126.2, 60.8, 39.4, 31.7, 30.0, 28.8, 25.0; FT-IR (neat): 2914, 1651, 1435, 1053 cm^{-1} ; HRMS (ESI): Found: m/z , 149.0939, Calcd for $\text{C}_8\text{H}_{14}\text{ONa} [\text{M}+\text{Na}]^+$: 149.0942.

After oxidation of 4-allylcyclohex-1-ene by PCC, the aldehyde was used directly in the next step which was treated with Grignard reagent to afford the alcohol product.

1-(cyclohex-3-enyl)-4-phenylbutan-2-ol (**1ia**): Yield: 59%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.30-7.26 (m, 2H), 7.21-7.17 (m, 3H), 5.68-5.61 (m, 2H), 3.79-3.75 (m, 1H), 2.82-2.76 (m, 1H), 2.72-2.68 (m, 1H), 2.13-2.03 (m, 3H), 1.82-1.57 (m, 6H), 1.48-1.36 (m, 2H), 1.32-1.24 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 142.1(overlapped), 128.4(overlapped), 127.1, 127.0, 126.4, 126.1, 125.8(overlapped), 69.0, 68.9, 44.6, 44.4, 39.8, 39.6, 32.5, 32.0, 31.4(overlapped), 30.1, 30.0, 29.6, 28.4, 25.1, 25.0; FT-IR (neat): 3373, 3022, 1653, 1602,

1494, 1454 cm^{-1} ; HRMS (ESI): Found: m/z , 253.1583, Calcd for $\text{C}_{16}\text{H}_{22}\text{ONa}$ $[\text{M}+\text{Na}]^+$: 253.1568.

***cis*-2-Ethoxycyclohexanol (4da)**

Yield: 38%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 3.82-3.79 (m, 1H), 3.58-3.54 (m, 1H), 3.49-3.45 (m, 1H), 3.36-3.33 (m, 1H), 3.30-3.29 (m, 1H), 1.77-1.72 (m, 2H), 1.60-1.46 (m, 4H), 1.30-1.17 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ : 78.2, 68.5, 63.5, 30.4, 26.6, 22.1, 21.1, 15.6.

3.5.2.2.3 Synthesis of substrates

To a mixture of **1aa** (0.1 g, 0.5 mmol), MsNHOCOPh (0.1 g, 0.5 mmol) and PPh_3 (0.26 g, 1.0 mmol) in toluene (3.0 mL) and THF (1.0 mL), DEAD (120 μL , mmol) was added slowly at 0 $^\circ\text{C}$. After stirring 5 min at the temperature, the solvent was evaporated to half an amount. The residue was directly loaded on silica gel and purified to give *N*-(benzoyloxy)-*N*-(6-methyl-1-phenylheptan-3-yl)methanesulfonamide **1a** (0.16 g, 80%) as a colorless oil.

Yield: 80%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.09 (d, 2H, J = 8.0 Hz), 7.67-7.64 (m, 1H), 7.53-7.49 (m, 2H), 7.30-7.18 (m, 5H), 4.09-4.02 (m, 1H), 3.07 (s, 3H), 2.99 (br,

1H), 2.77-2.69 (m, 1H), 1.9 (br, 2H), 1.65-1.60 (m, 2H), 1.58-1.51 (m, 1H), 1.41 (br, 1H), 1.30-1.25 (m, 1H), 0.89-0.87 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.4, 141.6, 134.3, 130.1, 128.9, 128.5, 128.4, 127.0, 125.9, 61.9, 40.0, 35.6, 34.1, 32.9, 29.8, 29.7, 27.9, 22.5; FT-IR (neat): 3026, 1764, 1600, 1494, 1452, 1338, 1161 cm^{-1} ; HRMS (ESI): Found: m/z , 404.1890, Calcd for $\text{C}_{22}\text{H}_{30}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 404.1896.

***N*-(Benzoyloxy)-4-methyl-*N*-(6-methyl-1-phenylheptan-3-yl)benzenesulfonamide (1c)**

Yield: 63%; white solid; mp: 77-79 °C; ^1H NMR (300 MHz, CDCl_3) δ : 7.98 (d, 2H, J = 8.0 Hz), 7.82 (d, 12H, J = 8.0 Hz), 7.63-7.59 (m, 1H), 7.48-7.44 (m, 2H), 7.32-7.24 (m, 5H), 7.19-7.15 (m, 2H), 3.93-3.90 (m, 1H), 2.68 (br, 1H), 2.42 (s, 3H), 1.73-1.65 (m, 3H), 1.50-1.20 (m, 5H), 0.80 (br, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.8, 145.0, 133.9(overlapped), 129.87, 129.80, 128.9 (overlapped), 128.7, 128.6, 128.3, 127.4, 125.8, 62.6, 35.7, 34.6, 33.0, 27.8, 26.9, 22.5, 22.3, 21.6; FT-IR (neat): 3086, 1766, 1637, 1598, 1465, 1377, 1234, 1170 cm^{-1} ; HRMS (ESI): Found: m/z , 480.2210, Calcd for $\text{C}_{28}\text{H}_{34}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 480.2209.

***N*-(Benzoyloxy)-*N*-(1-phenylheptan-3-yl)methanesulfonamide (1f)**

Yield: 57%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.07 (d, 2H, J = 8.0 Hz), 7.65 (t, 1H, J = 8.0 Hz), 7.50 (t, 2H, J = 8.0 Hz), 7.29-7.22 (m, 2H), 7.21-7.16 (m, 3H), 4.12-4.05 (m, 1H), 3.06 (s, 3H), 2.99 (br, 1H), 2.77-2.70 (m, 1H), 1.90-1.48 (m, 4H), 1.47-1.28 (m, 4H), 0.9 (t, 3H, J = 8.0 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.4, 141.6, 134.3, 130.0, 128.9,

128.5, 128.4, 126.9, 125.9, 61.5, 39.8, 34.0, 32.8, 31.6, 28.6, 22.4, 13.9; FT-IR (neat): 3030, 1764, 1600, 1494, 1452, 1340, 1161 cm^{-1} ; HRMS (ESI): Found: m/z , 390.1746, Calcd for $\text{C}_{21}\text{H}_{28}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 390.1739.

***N*-(Benzoyloxy)-*N*-(1-cyclopentyl-5-phenylpentan-3-yl)methanesulfonamide (1g)**

Yield: 85%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.09 (d, 2H, $J = 8.0$ Hz), 7.66 (t, 1H, $J = 8.0$ Hz), 7.51 (t, 2H, $J = 8.0$ Hz), 7.30-7.25 (m, 2H), 7.22-7.18 (m, 3H), 4.09-4.06 (m, 1H), 3.07 (s, 3H), 2.98 (br, 1H), 2.76-2.69 (m, 1H), 1.89 (br, 1H), 1.73-1.39 (m, 11H), 1.07-1.04 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.4, 141.6, 134.3, 130.1, 128.9, 128.5, 128.4, 127.0, 125.9, 61.9, 39.9, 39.8, 34.1, 32.9, 32.6, 31.2, 25.1(overlapped); FT-IR (neat): 3026, 1762, 1600, 1494, 1452, 1340, 1161 cm^{-1} ; HRMS (ESI): Found: m/z , 430.2062, Calcd for $\text{C}_{24}\text{H}_{32}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 430.2052.

***N*-(Benzoyloxy)-*N*-(1-cyclohexyl-5-phenylpentan-3-yl)methanesulfonamide (1h)**

Yield: 79%; white solid; mp: 105-107 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ : 8.09 (d, 2H, $J = 8.0$ Hz), 7.66 (t, 1H, $J = 8.0$ Hz), 7.51 (t, 2H, $J = 8.0$ Hz), 7.30-7.25 (m, 2H), 7.22-7.18 (m, 3H), 4.08-4.01 (m, 1H), 3.07 (s, 3H), 2.98 (br, 1H), 2.77-2.69 (m, 1H), 1.89 (br, 2H), 1.68-1.62 (m, 7H), 1.42 (br, 1H), 1.40-1.11 (m, 5H), 0.91-0.83 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.4, 141.6, 134.3, 130.0, 128.9, 128.5, 128.4, 127.0, 125.9, 61.9, 39.9, 37.4, 34.1, 33.9,

33.2, 32.8, 29.2, 26.5(overlapped), 26.2(overlapped); FT-IR (neat): 3030, 1762, 1450, 1340, 1161 cm^{-1} ; HRMS (ESI): Found: m/z , 444.2204, Calcd for $\text{C}_{25}\text{H}_{34}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 444.2209.

***N*-(Benzoyloxy)-*N*-(1-(cyclohex-3-enyl)-4-phenylbutan-2-yl)methanesulfonamide (1i)**

Mixture of two isomers (0.5:0.5), Yield: 70%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.09 (d, 2H, $J = 8.0$ Hz), 7.67 (t, 1H, $J = 8.0$ Hz), 7.52 (t, 2H, $J = 8.0$ Hz), 7.30-7.26 (m, 2H), 7.23-7.18 (m, 3H), 5.68-5.61 (m, 2H), 4.25-4.20 (m, 1H), 3.07 (s, 3H), 2.97 (br, 1H), 2.79-2.71 (m, 1H), 2.12-1.69 (m, 10H), 1.28-1.20 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.46, 164.43, 141.5(overlapped), 134.4(overlapped), 130.1(overlapped), 128.9(overlapped), 128.5(overlapped), 128.4(overlapped), 127.1(overlapped), 127.04(overlapped), 127.00(overlapped), 126.1(overlapped), 126.0(overlapped), 58.9(overlapped), 39.9, 39.8, 38.7(overlapped), 34.2(overlapped), 32.8(overlapped), 31.5(overlapped), 30.3(overlapped), 28.4(overlapped), 25.0, 24.9; FT-IR (neat): cm^{-1} ; HRMS (ESI): Found: m/z , 428.1914, Calcd for $\text{C}_{24}\text{H}_{30}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 428.1896.

***N*-(Benzoyloxy)-*N*-(1-(cyclohex-3-enyl)-4-phenylbutan-2-yl)-4-methylbenzenesulfonamide (1j)**

Mixture of two isomers (0.5:0.5), Yield: 77%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.98 (d, 2H, $J = 8.0\text{Hz}$), 7.79 (d, 2H, $J = 8.0$ Hz), 7.62-7.58 (m, 1H), 7.47-7.43 (m, 2H), 7.30-

7.24 (m, 4H), 7.19-7.15 (m, 3H), 5.66-5.62 (m, 2H), 4.20-4.08 (m, 1H), 2.69 (br, 1H), 2.41 (s, 3H), 2.18-1.96 (m, 3H), 1.75-1.50 (m, 5H), 1.46-1.35 (m, 2H), 1.42-1.00 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.8(overlapped), 145.0(overlapped), 134.0(overlapped), 133.86, 133.85, 129.9(overlapped), 129.8(overlapped), 129.1(overlapped), 128.8(overlapped), 128.6(overlapped), 128.3(overlapped), 127.4 (overlapped), 127.0(overlapped), 126.9(overlapped), 126.0(overlapped), 125.9(overlapped), 59.4(overlapped), 34.7, 34.5, 33.0, 31.6(overlapped), 29.0, 26.9, 25.3, 25.06, 25.02, 22.6, 21.7(overlapped), 20.7, 14.1(overlapped) ; FT-IR (neat): 3055, 2987, 1647, 1602, 738 cm^{-1} ; HRMS (ESI): Found: m/z , 526.2018, Calcd for $\text{C}_{30}\text{H}_{33}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 526.2028.

***N*-(Benzoyloxy)-*N*-(1-(cyclohex-3-enyl)-4-phenylbutan-2-yl)-4-nitrobenzenesulfonamide (1k)**

Mixture of two isomers (0.5:0.5), Yield: 77%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 8.32-8.30 (m, 2H), 8.06 (br, 2H), 7.96-7.94 (m, 2H), 7.67-7.63 (m, 2H), 7.52-7.47 (m, 1H), 7.31-7.15 (m, 5H), 5.68-5.62 (m, 2H), 4.22-4.18 (m, 1H), 3.10 (br, 1H), 2.76-2.69 (m, 1H), 2.10-2.00 (m, 3H), 1.84-1.49 (m, 7H), 1.21-1.16 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.5(overlapped), 150.7, 142.7, 142.6, 141.1, 134.4, 130.03, 130.00, 129.8, 129.0, 128.6, 128.5, 127.1, 127.0, 126.68, 126.67, 126.2, 125.8, 124.2, 59.6 (overlapped), 38.2 (overlapped), 33.9 (overlapped), 32.79 (overlapped), 32.75 (overlapped), 30.1 (overlapped), 24.95 (overlapped), 24.90 (overlapped); FT-IR (neat): 3028, 1774, 1654, 1610, 1535, 1350, 1313, 1174 cm^{-1} ; HRMS (ESI): Found: m/z , 535.1911, Calcd for $\text{C}_{29}\text{H}_{31}\text{N}_2\text{O}_6\text{S}$ $[\text{M}+\text{H}]^+$: 535.1903.

***N*-(Benzoyloxy)-4-methyl-*N*-((2*R*,4*aS*,8*aR*)-8*a*-methyldecahydronaphthalen-2-yl)benzenesulfonamide (*α* -1n)**

Yield: 31%; colorless oil; ^1H NMR (300 MHz, CDCl_3) δ : 7.98 (d, 2H, $J = 8.0$ Hz), 7.82 (d, 2H, $J = 8.0$ Hz), 7.65-7.61 (m, 1H), 7.50-7.46 (m, 2H), 7.29-7.26 (m, 2H), 4.31-4.11 (m, 1H), 2.41 (s, 3H), 2.00-1.65 (m, 3H), 1.62-1.59 (m, 1H), 1.42-1.20 (m, 10H), 1.00 (s, 3H), 0.89-0.83 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.8, 145.0, 133.9, 133.7, 129.8, 129.6, 129.1, 128.7, 127.4, 59.1, 41.0, 39.7(overlapped), 34.3, 28.4, 27.2, 26.8, 26.6, 22.0(overlapped), 21.7; FT-IR (neat): 1766, 1367, 1458, 1377, 1342, 1170 cm^{-1} ; HRMS (ESI): Found: m/z , 442.2043, Calcd for $\text{C}_{25}\text{H}_{32}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 442.2052.

***N*-(Benzoyloxy)-*N*-((1*S*,2*S*)-2-ethoxycyclohexyl)methanesulfonamide (4d)**

Yield: 36%; white solid; mp: 89-91 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 8.06 (d, 2H, $J = 8$ Hz), 7.66 (t, 1H, $J = 8.0$ Hz), 7.51 (t, 2H, $J = 8.0$ Hz), 3.96-3.92 (m, 1H), 3.73-3.66 (m, 1H), 3.55-3.48 (m, 1H), 3.28 (br, 1H), 3.17 (s, 3H), 2.23-2.22 (m, 2H), 1.72-1.70 (m, 2H), 1.56 (br, 1H), 1.37-1.09 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.3, 134.1, 130.0, 128.8, 127.2, 65.4, 61.2, 39.1, 31.1, 24.9, 23.7(overlapped), 15.6(overlapped); FT-IR (neat): 3018, 1772, 1635, 1450, 1215 cm^{-1} ; HRMS (ESI): Found: m/z , 342.1368, Calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$: 342.1375.

3.5.3 Typical procedure of amination of *N*-alkyl-*N*-benzoyoxysulfoamides

To a solution of *N*-(benzoyloxy)-*N*-(1-cyclopentyl-5-phenylpentan-3-yl)methane sulfonamide **1g** (86 mg, 0.2 mmol) in 1,2-dichloroethane (4 mL) was added (CuOTf)₂ C₆H₆ (15 mg, 0.03 mmol), and the mixture was stirred for 1 h at refluxing. After the completion of the reaction, a saturated sodium bicarbonate solution was added and organic materials were extracted with ethyl acetate. The combined extracts, after dried over MgSO₄, were condensed in vacuo. The resulting crude mixture was purified by a flash column chromatography to afford **2g** in 81% yield.

Yield: 81%; white solid; mp: 65-67 °C; ¹H NMR (300 MHz, CDCl₃) δ: 7.30-7.25 (m, 2H), 7.21-7.15 (m, 3H), 3.80-3.75 (m, 1H), 2.86 (s, 3H), 2.62 (t, 2H, *J* = 9 Hz), 2.42-2.20 (m, 3H), 1.95-1.68 (m, 7H), 1.61-1.43 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ: 141.4, 128.4, 128.3, 125.9, 74.1, 61.5, 41.0, 39.3, 38.9, 37.0, 34.2, 32.8, 27.3, 22.9, 22.2; FT-IR(neat): 3053, 1602, 1496, 1454, 1336, 1147 cm⁻¹; HRMS (ESI): Found:*m/z* 308.1691, Calcd for C₁₇H₂₆NO₂S [M+H]⁺: 308.1684

2,2-Dimethyl-1-(methylsulfonyl)-5-phenethylpyrrolidine (**2a**)

Yield: 82%; colorless oil; ^1H NMR (300 MHz, CDCl_3) δ : 7.32-7.28 (m, 2H), 7.23-7.19 (m, 3H), 3.81-3.76 (m, 1H), 2.90 (s, 3H), 2.64(t, 2H, $J = 8.4$ Hz), 2.28-2.24 (m, 1H), 2.02-1.99 (m, 2H), 1.82-1.73 (m, 3H), 1.55 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 141.3, 128.4, 128.3, 126.0, 65.0, 61.9, 41.3, 40.5, 37.1, 32.9, 30.6, 26.7, 26.3; FT-IR (neat): 3018, 1602, 1494, 1454, 1215 cm^{-1} ; HRMS (ESI): Found: m/z , 282.1533, Calcd for $\text{C}_{15}\text{H}_{24}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 282.1528.

***N*-(6-Methyl-1-phenylhept-5-en-3-yl)methanesulfonamide (3a)**

Yield: 3%; colorless oil; ^1H NMR (300 MHz, CDCl_3) δ : 7.30-7.26 (m, 3H), 7.21-7.18 (m, 5H), 5.13 (t, 1H, $J = 8$ Hz); 4.22 (d, 1H, $J = 8.0$ Hz), 3.52-3.37 (m, 1H), 2.93 (s, 3H), 2.80-2.72 (m, 1H), 2.71-2.63 (m, 1H), 2.36-2.31 (m, 1H), 2.27-2.22 (m, 1H), 1.91-1.88 (m, 1H), 1.87-1.75 (m, 1H), 1.73 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 141.3, 136.0, 128.5, 128.3, 126.0, 118.7, 54.4, 41.8, 36.9, 34.0, 32.2, 25.9, 18.0; FT-IR (neat): 3446, 3053, 1654, 1379, 1149 cm^{-1} ; HRMS (ESI): Found: m/z , 282.1532, Calcd for $\text{C}_{15}\text{H}_{24}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 282.1528.

2,2-Dimethyl-5-phenethyl-1-tosylpyrrolidine (2c)

Yield: 82%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.57 (d, 2H, $J = 8.0$ Hz), 7.30-7.28 (m, 3H), 7.25-7.17 (m, 3H), 7.12 (d, 2H, $J = 8.0$ Hz), 3.72- 3.68 (m, 1H), 2.65-2.58 (m, 1H), 2.52- 2.43 (m, 1H), 2.39 (s, 3H), 2.18-2.10 (m, 1H), 1.96- 1.90 (m, 1H), 1.84- 1.76 (m, 1H),

1.74-1.64 (m, 3H), 1.57 (m, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 142.4, 141.2, 139.2, 129.2, 128.4, 128.3, 127.4, 125.8, 66.1, 61.0, 40.7, 36.7, 32.8, 31.1, 27.0, 26.4, 21.4; FT-IR (neat): 3053, 1600, 1495, 1454, 1330, 1153 cm^{-1} ; HRMS (ESI): Found: m/z , 358.1855, Calcd for $\text{C}_{21}\text{H}_{28}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 358.1841.

(2,2-Dimethyl-5-phenethylpyrrolidin-1-yl)(phenyl)methanone (2d)

Yield: 50%; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.35-7.31 (m, 6H), 7.25-7.11 (m, 4H), 6.77 (br, 2H), 3.83 (br, 1H), 2.35 (br, 1H), 2.11 (br, 1H), 2.04-1.94 (m, 2H), 1.84-1.80 (m, 1H), 1.68-1.53 (m, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 169.9, 140.6, 139.1, 128.6, 128.3, 128.2, 127.9, 126.0, 125.7, 62.4, 60.0, 39.9, 36.7, 32.6, 32.6, 28.0, 26.6, 25.3; FT-IR (neat): 3026, 1624, 1602, 1494, 1454, 1400, 1361, 1176 cm^{-1} ; HRMS (ESI): Found: m/z , 268.1671, Calcd for $\text{C}_{16}\text{H}_{23}\text{NONa}$ $[\text{M}+\text{Na}]^+$: 268.1677.

***N*-(6-Methyl-1-phenylhept-5-en-3-yl)benzamide (3d)**

Yield: 8%; colorless oil; ^1H NMR (300 MHz, CDCl_3) δ : 7.68-7.66 (m, 2H), 7.50-7.49 (m, 1H), 7.48-7.46 (m, 2H), 7.34-7.25 (m, 2H), 7.20-7.15 (m, 3H), 5.92 (d, 1H, $J = 8.8$ Hz), 5.20-5.16 (m, 1H), 4.26-4.23 (m, 1H), 2.72 (t, 2H, $J = 8.8$ Hz), 2.42-2.34 (m, 1H), 2.30-2.26 (m, 1H), 1.98-1.91 (m, 1H), 1.86-1.81 (m, 1H), 1.71 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 167.0, 141.9, 134.9, 131.2, 128.5, 128.4, 128.3 (overlapped), 126.7, 125.9, 119.4,

49.9, 36.0, 33.2, 32.6, 25.9, 18.0; FT-IR (neat): 3317, 3026, 1647, 1629, 1541, 1452, 1265 cm^{-1} ; HRMS (ESI): Found: m/z , 246.1843, Calcd for $\text{C}_{16}\text{H}_{24}\text{NO}$ $[\text{M}+\text{H}]^+$: 246.1858.

***trans*-2-Methyl-1-(methylsulfonyl)-5-phenethylpyrrolidine (2fa)**

***trans*-2fa**, Yield: 28%; colorless oil; ^1H NMR (300 MHz, CDCl_3) δ : 7.29-7.26 (m, 2H), 7.20-7.18 (m, 3H), 4.01- 3.91 (m, 1H), 3.79-3.75 (m, 1H), 2.87 (s, 3H), 2.67-2.53 (m, 2H), 2.37-2.29 (m, 1H), 2.18-2.07 (m, 2H), 1.88-1.81 (m, 1H), 1.70-1.66 (m, 1H), 1.63-1.58 (m, 1H), 1.29 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 141.1, 128.4, 128.3, 125.9, 59.9, 56.0, 40.8, 35.7, 32.7, 31.1, 27.6, 20.7; FT-IR (neat): 3026, 1604, 1496, 1454, 1321, 1149 cm^{-1} ; HRMS (ESI): Found: m/z , 268.1379, Calcd for $\text{C}_{14}\text{H}_{22}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 268.1371.

***cis*-2-Methyl-1-(methylsulfonyl)-5-phenethylpyrrolidine (2fb)**

***cis*-2fa**, Yield: 17%; colorless oil; ^1H NMR (300 MHz, CDCl_3) δ : 7.30-7.26 (m, 2H), 7.21-7.18 (m, 3H), 3.81- 3.77 (m, 1H), 3.75-3.68 (m, 1H), 2.78 (s, 3H), 2.70-2.66 (m, 2H), 2.20-2.16 (m, 1H), 2.07-1.95 (m, 2H), 1.82-1.66 (m, 3H), 1.33 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 141.5, 128.4, 128.3, 125.9, 61.5, 57.3, 38.6, 35.5, 32.5(overlapped), 30.1, 23.4; FT-IR (neat): 3024, 1602, 1494, 1452, 1330, 1149 cm^{-1} ; HRMS (ESI): Found: m/z , 268.1371, Calcd for $\text{C}_{14}\text{H}_{22}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 268.1371.

1-(Methylsulfonyl)-2-phenethyl-1-azaspiro[4.5]decane (2h)

Yield: 34%; white solid; mp: 102-104 °C; ^1H NMR (400 MHz, CDCl_3) δ : 7.28-7.25 (m, 2H), 7.19-7.15 (m, 3H), 3.77-3.72 (m, 1H), 2.86 (s, 3H), 2.60 (t, 2H, $J = 8.0$ Hz), 2.36-2.30 (m, 1H), 2.25-2.15 (m, 3H), 1.88-1.81 (m, 1H), 1.77-1.68 (m, 5H), 1.66-1.51 (m, 3H), 1.37-1.14 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 141.3, 128.4, 128.3, 125.9, 69.3, 61.6, 41.9, 40.5, 37.1, 33.9, 33.0, 32.8, 26.8, 24.83, 24.81, 24.5; FT-IR (neat): 3057, 1606, 1456, 1377, 1143 cm^{-1} ; HRMS (ESI): Found: m/z , 322.1846, Calcd for $\text{C}_{18}\text{H}_{28}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 322.1841.

***N*-(1-Cyclohexenyl-5-phenylpentan-3-yl)methanesulfonamide (3h)**

Yield: 36%, colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.31-7.26 (m, 2H), 7.21-7.18 (m, 3H), 5.43-5.40 (m, 1H), 4.22 (d, 1H, $J = 8.0$ Hz), 3.45-3.40 (m, 1H), 2.95 (s, 3H), 2.77-2.65 (m, 2H), 2.04-1.97 (m, 4H), 1.93-1.86 (m, 3H), 1.84-1.73 (m, 2H), 1.72-1.52 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ : 141.2, 136.6, 128.5, 128.3, 126.0, 121.9, 54.0, 41.9, 37.2, 33.8, 33.4, 31.9, 28.3, 25.2, 22.8, 22.4; FT-IR (neat): 3469, 3026, 1654, 1602, 1494, 1454, 1315, 1149 cm^{-1} ; HRMS (ESI): Found: m/z , 322.1849, Calcd for $\text{C}_{18}\text{H}_{28}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 322.1841.

1-(Methylsulfonyl)-2-phenethyl-2,3,3a,4,7,7a-hexahydro-1H-indole (2i)

Isomer 1; Colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.29-7.27 (m, 2H), 7.21-7.18 (m, 3H), 6.00-5.98 (m, 1H), 5.84-5.81 (m, 1H), 4.27-4.25 (m, 1H), 3.74-3.70 (m, 1H), 2.86 (s, 3H), 2.71-2.64 (m, 1H), 2.62-2.51 (m, 2H), 2.42-2.33 (m, 1H), 2.05-1.97 (m, 3H), 1.82-1.72 (m, 3H), 1.69-1.64 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 141.1, 129.5, 128.3, 128.2, 125.8, 125.4, 58.8, 58.2, 40.6, 36.6, 34.4, 32.4, 31.6, 22.4, 20.4; FT-IR (neat): 3028, 1647, 1598, 1494, 1454, 1336, 1157 cm^{-1} ; HRMS (ESI): Found: m/z , 306.1534, Calcd for $\text{C}_{17}\text{H}_{24}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 306.1528.

Isomer 2; Colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.28-7.24 (m, 2H), 7.20-7.15 (m, 3H), 5.74-5.70 (m, 1H), 5.65-5.60 (m, 1H), 4.22-4.20 (m, 1H), 3.73-3.66 (m, 1H), 2.81 (s, 3H), 2.70-2.63 (m, 1H), 2.60-2.52 (m, 1H), 2.41-2.29 (m, 2H), 2.11-1.99 (m, 3H), 1.84-1.71 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ : 141.5, 128.3(overlapped), 128.2, 128.0, 127.7, 60.2, 59.0, 38.7, 36.3, 35.6, 33.3, 31.8, 22.1, 19.5; FT-IR (neat): 3028, 1654, 1456, 1348, 1157 cm^{-1} ; HRMS (ESI): Found: m/z , 306.1529, Calcd for $\text{C}_{17}\text{H}_{24}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 306.1528.

2-Phenethyl-1-tosyl-2,3,3a,4,7,7a-hexahydro-1H-indole (2j)

Mixture of two isomer(0.5:0.5), colorless oil; ^1H NMR (300 MHz, CDCl_3) δ : 7.62-7.59 (m, 2H), 7.29-7.13 (m, 7H), 6.00-5.97 (m, 0.5H), 5.69-5.63 (m, 1.5H), 4.35-4.34 (m, 0.5H), 4.17-4.15 (m, 0.5H), 3.73-3.68 (m, 0.5H), 3.53-3.47 (m, 0.5H), 2.78-2.70 (m, 0.5H), 2.68-2.60 (m, 0.5H), 2.56-2.36 (m, 5H), 2.00-1.80 (m, 2H), 1.78-1.60 (m, 2H), 1.59-1.49 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 143.0, 142.4, 141.6, 141.2, 138.8, 135.1, 129.5, 129.2, 128.5, 128.4, 128.3, 128.29, 128.27, 127.4, 127.1, 127.0, 125.9(overlapped), 125.79, 125.72, 59.9,

59.2, 58.9, 58.3, 38.6, 36.2, 34.7, 34.5, 33.0, 32.2, 31.8, 31.6, 22.2, 22.0, 21.4, 21.3, 20.3, 19.4; FT-IR (neat): 3028, 1654, 1602, 1494, 1458, 1377, 1344, 1263, 1161 cm^{-1} ; HRMS (ESI): Found: m/z , 382.1842, Calcd for $\text{C}_{23}\text{H}_{28}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 382.1841.

1-(4-Nitrophenylsulfonyl)-2-phenethyl-2,3,3a,4,7,7a-hexahydro-1H-indole (2k)

Mixture of two isomers (0.5:0.5), white solid; mp: 105-107 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ : 8.27 (d, 1H, $J = 8.8$ Hz), 8.19 (d, 1H, $J = 8.8$ Hz), 7.84-7.78 (m, 2H), 7.31-7.15 (m, 5H), 5.92-5.89 (m, 0.5 Hz), 5.71-5.68 (m, 1H), 5.64-5.61 (m, 0.5H), 4.40-4.38 (m, 0.5H), 4.20-4.18 (m, 0.5H), 3.64-3.62 (m, 0.5H), 3.48-3.39 (m, 0.5H), 2.76-2.67 (m, 1H), 2.54-2.39 (m, 2.4H), 1.96-1.86 (m, 3H), 1.78-1.60 (m, 4H), 1.45-1.42 (m, 0.5H); ^{13}C NMR (100 MHz, CDCl_3) δ : 149.4, 147.2, 143.8, 141.1, 140.8(overlapped), 129.8, 128.55, 128.53, 128.4, 128.2, 128.0, 127.6, 126.1, 126.0, 124.9, 124.2, 123.9, 60.2, 59.7, 59.3, 58.7, 38.5, 36.4, 35.0, 34.6, 33.1, 32.3, 31.94, 31.90, 22.2, 21.9, 20.5, 19.4; FT-IR (neat): 3026, 1654, 1610, 1533, 1350, 1174 cm^{-1} ; HRMS (ESI): Found: m/z , 413.1537, Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 413.1535.

7,7-Dimethyl-6-(methylsulfonyl)-6-azabicyclo[3.2.1]octane (2l)

Colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 4.04-4.01 (m, 1H), 2.90 (s, 3H), 2.23-2.18 (m, 1H), 1.93-1.85 (m, 4H), 1.64-1.53 (m, 5H), 1.46-1.44 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3)

δ : 66.6, 59.3, 46.1, 41.3, 35.9, 31.1, 28.3, 27.1, 22.7, 18.3; FT-IR (neat): 2850, 1313, 1138 cm^{-1} ; HRMS (ESI): Found: m/z , 218.1221, Calcd for $\text{C}_{10}\text{H}_{20}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 218.1215.

***N*-(3-(Propan-2-ylidene)cyclohexyl)methanesulfonamide (3la)**

Colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 4.36 (d, 1H, $J = 8.0$ Hz), 3.52-3.46 (m, 1H), 2.97 (s, 3H), 2.57-2.53 (m, 1H), 2.18-2.13 (m, 2H), 2.10-2.07 (m, 1H), 1.90-1.86 (m, 1H), 1.68-1.67 (m, 6H), 1.66-1.53 (m, 3H), 1.51-1.40 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 127.0, 125.1, 52.5, 41.8, 37.5, 33.5, 29.3, 23.9, 20.1; FT-IR (neat): 3415, 1654, 1311, 1141 cm^{-1} ; HRMS (ESI): Found: m/z , 218.1211, Calcd for $\text{C}_{10}\text{H}_{20}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 218.1215.

***cis*-N-(3-(Prop-1-en-2-yl)cyclohexyl)methanesulfonamide (3lb)**

Colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 4.69 (d, 2H, $J = 6.0$ Hz), 4.11 (d, 1H, $J = 8.0$ Hz), 3.38-3.30 (m, 1H), 2.97 (s, 3H), 2.10-2.08 (m, 2H), 2.06-1.97 (m, 1H), 1.88-1.83 (m, 1H), 1.75-1.68 (m, 4H), 1.43-1.33 (m, 1H), 1.20-1.03 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 148.8, 109.1, 53.3, 44.2, 42.3, 39.7, 34.4, 30.4, 24.8, 20.8; FT-IR (neat): 3439, 1643, 1327, 1151 cm^{-1} ; HRMS (ESI): Found: m/z , 218.1219, Calcd for $\text{C}_{10}\text{H}_{20}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 218.1215.

10-Methanesulfonyl-10-azatricyclo[7.2.1.0^{1,6}]dodecane (2m)

Colorless oil; ^1H NMR (300 MHz, CDCl_3) δ : 4.08-4.06 (m, 1H), 3.24 (d, 1H, $J = 9.2$ Hz), 2.96 (d, 1H, $J = 9.2$ Hz), 2.81 (s, 3H), 2.08-1.98 (m, 2H), 1.76-1.71 (m, 2H), 1.64-1.53 (m, 3H), 1.46-1.26 (m, 8H); ^{13}C NMR (75 MHz, CDCl_3) δ : 59.8, 59.3, 44.9, 41.5, 36.6, 36.5, 28.8, 28.2, 26.2, 25.4, 23.2; FT-IR (neat): 2927, 1327, 1141 cm^{-1} ; HRMS (ESI): Found: m/z , 266.1200, Calcd for $\text{C}_{12}\text{H}_{21}\text{NO}_2\text{SNa}$ $[\text{M}+\text{Na}]^+$: 266.1191.

4-Methyl-*N*-(8a-methyldecahydronaphthalen-2-yl)benzenesulfonamide (3nb)

Colorless oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.76 (d, 2H, $J = 8.0$ Hz), 7.29 (d, 3H, $J = 8.0$ Hz), 4.54 (d, 1H, $J = 8.0$ Hz), 3.42-3.32 (m, 1H), 2.42 (s, 3H), 1.78-1.72 (m, 1H), 1.67-1.65 (m, 1H), 1.59-1.53 (m, 2H), 1.46-1.38 (m, 2H), 1.29-1.08 (m, 8H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 143.0, 138.5, 129.6, 126.9, 50.4, 40.8, 39.6, 38.0, 34.2, 28.7, 26.8, 26.6, 21.9, 21.5; FT-IR (neat): 3275, 3055, 1598, 1465, 1321, 1159 cm^{-1} ; HRMS (ESI): Found: m/z , 322.1848, Calcd for $\text{C}_{18}\text{H}_{28}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 404.1896.

2-Methyl-3-(methanesulfonyl)octahydrobenzo[d]oxazole (5a)

White solid; mp: 138 – 140 °C; ^1H NMR (300 MHz, CDCl_3) δ 5.06 (q, 1H, $J = 5.2$ Hz), 3.93-3.90 (m, 1H), 3.67-3.59 (m, 1H), 2.87 (s, 3H), 2.17-2.12 (m, 1H), 2.03-1.96 (m, 1H), 1.73-1.60 (m, 2H), 1.57 (d, 3H, $J = 5.2$ Hz), 1.52-1.38 (m, 3H), 1.26-1.14 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 88.1, 76.0, 57.8, 37.8, 27.4, 23.3, 23.0, 19.7; FT-IR (Neat): ν 3013, 2980, 2943, 2916, 2895, 2864, 1317, 1153, 1088 cm^{-1} ; HRMS (ESI) found: 220.1009, calcd for formula ($\text{M}+\text{H}^+$): 220.3079

2-Methylhexahydrobenzo[d]oxazol-3(2H)-yl(phenyl)methanone (5b)

Colorless oil; ^1H NMR (300 MHz, CDCl_3) δ 7.50-7.37 (m, 5H), 5.74 (br, 0.3H), 5.52 (br, 0.7H), 4.39 (br, 0.3H), 3.93 (br, 0.7H), 3.81 (br, 0.3H), 3.35 (br, 0.7H), 2.15-2.06 (m, 1H), 1.66-1.45 (m, 8H), 1.31-1.20 (m, 1H), 1.05 (br, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.0, 137.3, 128.4, 126.5, 86.4, 85.8, 75.6, 57.4, 27.4, 23.3, 21.4, 19.8; FT-IR (Neat): ν 3011, 2940, 2866, 1624, 1413, 1215 cm^{-1} ; HRMS (ESI) found: 246.1497, calcd for formula ($\text{M}+\text{H}^+$): 246.3279

2-Methyl-3-(methylsulfonyl)octahydrobenzo[d]oxazole (5d)

White solid; mp: 99-101 °C; ^1H NMR (400 MHz, CDCl_3) δ : 5.21 (q, 1H, $J = 5.6$ Hz), 3.64-3.58 (m, 1H), 2.88 (s, 3H), 2.75-2.69 (m, 1H), 2.39-2.35 (m, 1H), 2.15-2.12 (m, 1H), 1.88-1.79 (m, 2H), 1.54-1.37 (m, 5H), 1.35-1.24 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 89.0,

80.5, 65.1, 35.0, 29.9, 29.2, 23.8, 23.4, 22.7; FT-IR (neat): 2922, 1377, 1153, 1072 cm^{-1} ; HRMS (ESI): Found: m/z , 220.1008, Calcd for $\text{C}_9\text{H}_{18}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$: 220.1007.

***N*-(*Trans*-2-hydroxycyclohexyl)methanesulfonamide (6d)**

White solid; mp: 114-116 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ : 4.79 (d, 1H, $J = 8.0$ Hz), 3.34-3.28 (m, 1H), 3.10-3.04 (m, 4H), 2.57 (br, 1H), 2.11-2.07 (m, 2H), 1.74-1.71 (m, 3H), 1.33-1.23 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ : 73.6, 59.9, 41.4, 34.1, 32.9, 24.7, 24.0; FT-IR (neat): 3527, 2943, 1375, 1153 cm^{-1} ; HRMS (ESI): Found: m/z , 194.0859, Calcd for $\text{C}_7\text{H}_{16}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$: 194.0851.

3.6 References and notes

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Chapter 4 Summary

In this thesis, the author discussed on the development of $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ -catalyzed methods to synthesize azaheterocycles from hydroxylamine derivatives, which involved sulfonamidyl radicals as the key intermediates. Three types of the reactions were developed such as 1) sulfonamidyl radicals addition to unsaturated double or triple bonds, 2) allylic or propargylic hydrogen abstraction and 3) unreactive hydrogen abstraction.

In chapter 2, the transformation from *N*-4-alkenyl-*N*-benzoyloxysulfonamides to 2,5-disubstituted pyrrolidines was studied and $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ was found to act as an efficient redox catalyst (eq 1). The reaction is supposed to proceed as follows: Initially, *N*-4-alkenylsulfonamide **I** accepts one electron from the copper(I) catalyst to give an anion radical intermediate **IA** along with copper(II) species, which is followed by the radical cyclization to give *C*-radical intermediate **IB** with eliminating an acyloxy anion. The resulting *C*-radical **IB** is then oxidized by copper(II) to afford carbo cation intermediate **IC** with the regeneration of copper(I). Finally, by the successive deprotonation, the product, pyrrolidine **II**, is obtained.

Furthermore, from *N*-4-alkynylsulfonamides, 2,5-disubstituted pyrrolidines were

obtained by similar $(\text{CuOTf})_2$ C_6H_6 -catalyzed cyclization (eq 2).

When *N*-5-alkenyl- or alkynyl-*N*-benzoyloxysulfonamides which have one more methylene tether between the amino and the olefinic moieties were subjected to this catalyst reaction, instead of the expected 6-membered products, 5-membered ring pyrrolidines were isolated as the major products, which were resulted by the allylic (or propargylic) hydrogen abstraction (eq 3).

In chapter 3 was described the unreactive C-H functionalization of *N*-alkyl-*N*-benzoyloxysulfonamides. The reaction was initiated by the amidyl radical formation and the successive intramolecular 1,5-hydrogen shift (eq 4).

N-Acyclic alkyl and *N*-cyclic alkyl sulfonamides were converted to the corresponding intramolecular amination products (eq 5 and 6) and/or dehydrogenated product (eq 7).

N-acyclic alkyl sulfonamides

N-cyclic alkyl sulfonamides

Oxazolidines were also prepared from *N*-2-ethoxycyclohexyl-*N*-benzoyloxy-sulfonamides via oxonium intermediates (eq 8).

Thus, remote functionalization of unreactive C-H bonds of *N*-alkylsulfonamides was achieved in a catalytic manner to furnish pyrrolidine derivatives.

List of Publications and Conferences

1. Wei-Min Liu, Zhen-Hong Liu, Wei-Wen Cheong, Lu-Yi Teo Priscilla, Yongxin Li and Koichi Narasaka

“Synthesis of 2,5-disubstituted pyrrolidines from *N*-alkenyl and alkynyl *N*-benzoyloxysulfonamides catalyzed by $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ ”

Bull. Korean Chem. Soc. **2010**, *31*, 563.

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

2. Wei-Min Liu, Zhen-Hong Liu, Koichi Narasaka

“(CuOTf)₂ C₆H₆-Catalyzed Synthesis of Pyrrolidines from Alkenyl and Alkynyl *N*-Benzoyloxysulfonamides”

Joint symposium on organic chemistry for young chemists in Nanyang Technological University, 28th January **2010** (Oral presentation)

3. Wei-Min Liu, Zhen-Hong Liu, Koichi Narasaka

“(CuOTf)₂ C₆H₆-Catalyzed Synthesis of Pyrrolidines from Alkenyl and Alkynyl *N*-Benzoyloxysulfonamides”

6th Asian-European Synposium on metal mediated efficient reactions, 7-9 June **2010** (Poster presentation)

4. Zhen-Hong Liu, Wei-Min Liu, Koichi Narasaka

“C-H Abstraction Catalyzed by $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$: Transformation of *N*-Alkyl, Alkenyl and Alkynyl *N*-Benzoyloxysulfonamides to Pyrrolidines”

242nd ACS National Meeting & Exposition 28, August to 1 September, **2011**, Denver, USA (Poster presentation)

5. Zhen-Hong Liu, Wei-Min Liu, Koichi Narasaka

“C-H Abstraction Catalyzed by (CuOTf)₂ C₆H₆ : Transformation of *N*-Alkyl, Alkenyl and Alkynyl *N*-Benzoyloxysulfonamides to Pyrrolidines”

International Symposium on Catalysis and Fine Chemicals 2011 (C&FC2011),
December 4-8, **2011**, Nara Prefectural New Public Hall, Japan (Poster presentation)

6. Zhen-Hong Liu, Wei-Min Liu, Koichi Narasaka

“Unreactive C-H Abstraction Catalyzed by (CuOTf)₂ C₆H₆ : Transformation of *N*-Alkyl-*N*-Benzoyloxysulfonamides to Pyrrolidines”

2nd International Conference on Molecular and Functional Catalysis (ICMFC-2), July 30-31, **2012**, Biopolis, Singapore (Poster presentation)