Development of synthetic methods of Azaheterocycles via Vinylic substitutions and an aerobic oxidation of allylic alcohols catalysed by N-Hydroxyindoles

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2012

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List of Abbreviations

δ	chemical shift (ppm)
Δ	heating
$^{\circ}\text{C}$	degree centigrade
Ac	acetyl
AcOH	acetic acid
acac	acetylacetonyl
aq	aqueous
Ar	aryl (substituted aromatic ring)
atm	standard atmosphere
B3LYP	Becke, three-parameter, Lee-Yang-Parr
Bn	benzyl
br s	broad singlet
calcd/calc	calculated
cat.	catalytic
cm^{-1}	wave number
conc.	concentrated
conv.	conversion
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
DFT	density functional theory

DIBAL-H	diisobutylaluminum hydride
DMF	<i>N,N</i> -dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMSO	dimethyl sulfoxide
dq	doublet of quartets
dt	doublet of triplets
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
ee	enantiomeric excess
E _{pa}	Anodic peak potential
eq /equiv.	equivalent
ESIHRMS	Electrospray Ionization High Resolution Mass Spectrometry
ESR	Electron spin resonance
Et	ethyl
Fc	ferrocene
Hz	hertz
i.d.	inside diameter
<i>i</i> -Pr	<i>iso</i> -propyl
IR	infrared spectroscopy
<i>J</i>	coupling constants
kcal	kilocalorie
LDA	lithium diisopropylamide
M	concentration (mol/L)
M ⁺	parent ion peak (mass spectrum)
m	multiplet
Me	methyl
mg	milligram

MHz	megahertz
mmol	millimole
m.p.	melting point
Ms	methanesulfonyl
NMR	nuclear magnetic resonance
NBS	<i>N</i> -Bromosuccinimide
Ph	phenyl
Phen	Phenanthroline
q	quartet
R_f	retention factor
rt/r.t.	room temperature
s	singlet
SHE	standard hydrogen electrode
SM/S.M.	starting material
t	triplet
TBAC	<i>tert</i> -butyl acetate
TBS	<i>tert</i> -butyldimethylsilyl
temp.	temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	<i>p</i> -toluenesulfonyl
<i>t</i> -Bu/ ^{<i>t</i>} Bu	<i>tert</i> -butyl

Abstract

More and more new synthetic methodologies have been developed and widely applied in organic synthesis. Two major synthetic methods were developed during my PhD course: part I is synthesis of azaheterocycles based on nucleophilic vinylic substitution reaction and part II is the selective aerobic oxidation of allylic and benzylic alcohols catalyzed by *N*-hydroxyindoles and copper(I) chloride.

Unlike the well known nucleophilic substitution at an sp^3 carbon, the nucleophilic substitution at an sp^2 carbon was considered as an unfavorable process. However, some successful examples have been established in our group recently. As a synthetic application of the intramolecular concerted nucleophilic substitution at an sp^2 carbon of vinylic halides, the intramolecular cyclization of vinyl bromides with intramolecular thioamide or thiourea moieties were studied for the synthesis of five-membered heterocycles. In Chapter 2.1 and 2.2 was described the preparation of various five-membered heterocycles, including 2,5-disubstituted thiazoles **36** and 1,3,4-trisubstituted imidazole-2-thiones **56** (Scheme 1).

Scheme 1.

The formation of six-membered ring **78** is discussed in Chapter 2.4 (Scheme 2), but it was found that the intramolecular vinylic nucleophilic substitution mechanism was not the only mechanism, two other pathways were also proposed for this transformation.

Scheme 2.

Envisioning that *N*-hydroxyindole may act as a precursor of nitroxyl radicals and/or oxoammonium species, we synthesized a series of substituted *N*-hydroxyindoles. It was found that *tert*-butyl 1-hydroxy-2-methyl-6-(trifluoromethyl)-1*H*-indole-3-carboxylate (NHI-1), which can be easily prepared in high yield, acts as an efficient catalyst for highly chemoselective aerobic oxidation of alcohols with the combined use of copper(I) chloride. A variety of primary and secondary allylic and benzylic alcohols were oxidized into the corresponding α,β -unsaturated carbonyl compounds in good yields without affecting non-allylic alcohols (Scheme 3).

Scheme 3.

Furthermore, such a catalyst system exhibits a considerable stereoselectivity in the oxidation of stereoisomers of cyclic allylic alcohols, where the equatorial alcohols are oxidized in preference to the corresponding axial ones. After some mechanistic studies, this aerobic oxidation was found to be catalyzed by the nitroxyl radical of NHI-1 as the real active species.

**Part I. Development of Synthetic Methods of Azaheterocycles
via Vinylic Nucleophilic Substitutions**

Chapter 1. General Introduction of Nucleophilic Substitutions at A Vinylic Carbon

The nucleophilic substitution reaction,¹ in which one group Y in a molecule R-Y is replaced by a nucleophile (Scheme 1-1), is one of the very fundamental reactions in organic chemistry and has been widely applied in organic synthesis. Generally, in the substitution reaction, a nucleophile bringing a pair of unshared electrons (Nu⁻) attacks the substrate R-Y to form a new R-Nu bond along with the elimination of a leaving group Y⁻.

Scheme 1-1.

1.1. Nucleophilic substitution reactions at an sp³ carbon

Several mechanisms have been proposed in the past decades on the nucleophilic substitution reactions. When the nucleophilic substitution occurs at a saturated atom, such as an sp³ carbon, S_N1 (unimolecular nucleophilic substitution)² and S_N2 (bimolecular nucleophilic substitution)³ mechanisms are the most common ones.

S_N1 reaction is the first order process in the concentration of R-Y,⁴ and the concentration of nucleophile Nu⁻ is irrelevant to the reaction rate. Two steps are involved in S_N1 mechanism (Scheme 1-2): The first step is the rate-determining step that the substrate R-Y is ionized slowly with the elimination of Y⁻, followed by the rapid attack of the nucleophile Nu⁻. Thus, S_N1 reaction will give product with either complete racemization or partial inversion of the configuration of R-Y.⁵

Scheme 1-2.

For $\text{S}_{\text{N}}2$ reaction at an sp^3 carbon, the reaction rate is the first order in the concentrations of Nu^- and substrate R-Y . It proceeds via a concerted pathway: Y^- leaves simultaneously with the attack of Nu^- (Scheme 1-3).⁶ In the $\text{S}_{\text{N}}2$ reaction, the nucleophile attacks from the backside⁷ of the leaving group to give the product with inversion of the configuration, which is named as *Walden inversion*.^{8,9}

Scheme 1-3.

There are still other possible mechanisms for the nucleophilic substitution at a saturated carbon, for an example, SET (single electron transfer) mechanism,¹⁰ and so on. However, nucleophilic substitution reaction at an unsaturated atom, sp^2 carbon ($\text{S}_{\text{N}}\text{V}$), has been long neglected and was considered as an unfavorable pathway, at least in elementary organic textbooks. One suggested reason for this is that sp^2 carbons have a higher electronegativity than sp^3 carbons, leading to a greater attraction of the electrons between the C-X bond. For example, the bond length of $\text{sp}^2\text{C-Cl}$ (1.73 Å) is shorter than $\text{sp}^3\text{C-Cl}$ (1.78 Å), which may indicate decrease in the leaving ability of the Cl atom of the $\text{sp}^2\text{C-Cl}$ bond (Figure 1-1).¹¹

Figure 1-1.

1.2. Nucleophilic substitution reactions at an sp^2 carbon

Although the nucleophilic substitution reaction at a vinylic carbon was thought difficult to take place, such examples have been reported and the following possible mechanisms were suggested.¹²

1.2.1. Mechanism studies

While the nucleophilic substitution reactions at sp^3 carbon atoms are essentially classified into S_N1 and S_N2 mechanisms, a wider variety of mechanisms are possible for the vinylic substitution reactions due to the two vacant orbitals on sp^2 carbons, i.e., σ^* and π^* orbitals. The following four major types of mechanisms have been proposed.¹²

The first one is not a real direct nucleophilic substitution in the strict definition but an addition-elimination reaction (Scheme 1-4a). However, this mechanism is the most commonly employed to replace a leaving group on a vinylic substrate that is activated with an electron withdrawing group. A nucleophile initially attacks the π^* orbital of the sp^2 carbon (perpendicular or out-of-plane attack) to form a carbanion intermediate which is stabilized by the electron withdrawing group. The following β -elimination of the leaving group as Y^- gives the substitution product. This two-step pathway is called addition-elimination mechanism (Ad_N-E). To stabilize the carbanion intermediate, this type of the reaction is usually applicable for activated alkenes with strong electron withdrawing groups.

Scheme 1-4a.

On the other hand, nucleophilic substitutions of unactivated alkenes proceed via other mechanisms. In $\text{Ad}_\text{N}-\text{E}$ mechanism, as the electron withdrawing effect of R^1 and R^2 decreases more and more or the leaving ability of Y increases, the lifetime of the anionic intermediate becomes so short that the reaction proceeds in a concerted manner. This is called $\text{S}_\text{N}\text{V}_\pi$ mechanism, affording the product with retention of the configuration (Scheme 1-4b).

Another pathway is $\text{S}_\text{N}\text{V}_\sigma$ mechanism where a nucleophile attacks σ^* orbital of the C-Y bond, that is, from the backside of the leaving group in the alkene plane. This route, so-called $\text{S}_\text{N}\text{V}_\sigma$ or in-plane attack, leads to the substitution product with inversion of the configuration (Scheme 1-4c). When the ability of a leaving group Y becomes very strong, such as triflate (TfO^-), similar as $\text{S}_\text{N}1$ mechanism at an sp^3 carbon, the reaction proceeds via firstly dissociation of the C-Y bond to generate a vinylic cation intermediate, which is then attacked with a nucleophile, so-called $\text{S}_\text{N}\text{V}1$ mechanism (Scheme 1-4d).

Scheme 1-4.

Based on the above mechanistic discussion, S_NV_π and S_NV_σ mechanisms are involved in concerted nucleophilic vinylic substitution. According to the molecular orbital (MO) theory, σ^* orbital is generally higher in energy than π^* orbital, which predicts that nucleophilic attack to π^* orbital at the sp^2 carbon is more favorable than to σ^* orbital. Thus, S_NV reaction was considered to proceed more easily via S_NV_π mechanism than via S_NV_σ mechanism; however, theoretical studies revealed that this hypothesis is not always the case.

1.2.2. Theoretical studies on concerted nucleophilic vinylic substitutions

Theoretical studies have been conducted for the substitution reactions of unactivated vinyl halides.¹³ In 1994, Glukhovtsev¹⁴ reported that the activation energy for the in-plane nucleophilic attack (S_NV_σ) of a chloride ion to chloroethene is $32.6 \text{ kcal mol}^{-1}$, while that of the out-of-plane attack (S_NV_π) is $42.7 \text{ kcal mol}^{-1}$, which is about 10 kcal mol^{-1} higher (Scheme 1-5).

Scheme 1-5.

In 2000, Lee¹⁵ reported that S_NV_π mechanism is favored in the gas-phase vinylic substitution of chloroethene by hydroxide ($2.15 \text{ kcal mol}^{-1}$) or hydrosulfide ion (24.36

kcal mol⁻¹), but S_NV_σ pathway is preferred for the nucleophilic attack by chloride (29.76 kcal mol⁻¹) or bromide ion (32.11 kcal mol⁻¹) (Scheme 1-6).

Scheme 1-6.

These theoretical studies suggested that any of the concerted nucleophilic vinylic substitution hardly proceeds under mild conditions, because the required activation energies are very high.

1.2.3. Nucleophilic substitution reactions of vinyl halides

In 1968, Marchese published an intermolecular vinylic substitution reaction of β-halostyrenes with thiolate anion, affording the products with mainly retention of the configuration, although the stereoselectivity was not always perfect (Scheme 1-7).¹⁶ The similar phenomenon (retention of the configuration) was observed in the reaction with selenide anion (Scheme 1-8).¹⁷

Scheme 1-7.

Scheme 1-8.

Although the stereospecificity indicated that the reaction proceeded via S_NV_π process, it is difficult to judge whether the reactions proceed via the Ad_N-E or S_NV_π pathway. Because aryl groups can stabilize the generating negative charge to some extent, it is possible that Ad_N-E reaction occurs but the lifetime of the anionic intermediate is short enough to lead to the retention product in most cases. In fact, these substitution reactions were only observed for β -halostyrenes and not in the reactions of non-aromatic alkenes.

In addition, Apeloig and Rappoport demonstrated that hyperconjugation between the β -substituents (Nu) and an electron pair in the anionic intermediate played a key role in the stereospecificity (retention of the configuration) of these nucleophilic vinylic substitutions (Scheme 1-9).¹⁸ According to their calculation, such a hyperconjugation caused higher energy barrier (V_x) for the bond rotation and gave rise to the product with retention of the configuration.

Scheme 1-9.

Now, the substitutions of β -halostyrenes are believed to proceed through $\text{Ad}_{\text{N}}\text{-E}$ mechanism with an addition of thiolates followed by very rapid elimination of halide anions.

In 1991, Ochiai¹⁹ published the first nucleophilic substitution reaction at an unactivated sp^2 carbon. The reaction of alkenyliodonium salt **1** with bromide anion proceeded with inversion of the stereochemistry (Scheme 1-10), which indicated the $\text{S}_{\text{N}}\text{V}_{\sigma}$ mechanism as the reaction pathway, and it was supported later by a kinetic study.²⁰

Scheme 1-10.

In 2004, Shipman²¹ discovered another example. 2-Bromoallylamines **2** were cyclized to aziridines **3** via vinylic substitution by treatment with sodium amide in ammonium at a very low temperature ($-78\text{ }^{\circ}\text{C}$). The configuration of the products suggested that the amino group approached from the backside of the bromo group (Scheme 1-11), that is, in a $\text{S}_{\text{N}}\text{V}_{\sigma}$ manner.

Scheme 1-11.

In 2003 and 2004, Narasaka and Ando reported the theoretical and experimental studies on the nucleophilic substitution of vinyl halides with various intramolecular nucleophilic moieties.²² *E*-Vinyl halides having an intramolecular hydroxyl, amido, and

active methine groups, *E*-**4**, **5**, **6**, gave the nucleophilic substitution products by the base treatment, whereas the cyclization of the corresponding *Z*-isomers did not proceed at all (Scheme 1-12).

According to their theoretical studies, the S_NV_σ transition structures were obtained as a possible reaction pathway for the reaction of the *E*-isomers with low activation energies (14.4 - 23.4 kcal mol⁻¹). In contrast, for the cyclization of the corresponding *Z*-isomers, S_NV_π pathways were found suitable but with higher activation energies (> 28.9 kcal mol⁻¹), which meant that the cyclization might hardly proceed. In fact, the experimental results accorded with these theoretical calculations. Thus, the cyclization of *E*-vinyl halides having intramolecular oxygen, nitrogen and carbon nucleophiles proceeded via S_NV_σ pathway, whereas the cyclization of the corresponding *Z*-isomers did not occur.

Scheme 1-12.

In contrast to the above experiments, vinyl bromides **7** having a thiol moiety exhibited a unique reactivity. Thus, thiols **7** gave a cyclized product, dihydrothiophene, irrespective of their *E*, *Z*-stereochemistry, although the yields were low. As shown in Scheme 1-13, the experimental results and the computational analysis revealed that the cyclization of *E*- and *Z*-isomers **7** proceeded via S_NV_σ and S_NV_π pathways, respectively.

Scheme 1-13.

The yields of dihydrothiophenes were improved by using thioacetates **8** as the starting materials instead of thiols **7** to avoid their air oxidation to the disulfides. By treatment with potassium carbonate and methanol in degassed DMI, dihydrothiophenes were obtained in good yields from both *E*- and *Z*-isomers of **8** (Scheme 1-14).²³

Scheme 1-14.

Not only the terminal-bromoalkenyl thioacetates **8**, but also internal-bromoalkenes were subjected to the cyclization reaction. Under the above reaction conditions, the

nucleophilic substitution of internal-bromoalkenyl thioacetate **9** took place to give two five-membered ring products in an 85% total yield (Scheme 1-15).

Scheme 1-15.

Generally, the order of the ring-closing rate by nucleophilic substitution reactions at sp^3 carbons follows the trend of five- >> six- > four-membered ring formation, as reported by Casadei on the kinetic studies of the cyclization of diethyl(ω -bromoalkyl)malonates **10** (Scheme 1-16).²⁴ However, there is no precedent relating to ring-closing rate of the intramolecular vinylic substitutions.

Scheme 1-16.

Therefore, the formation of a six-membered ring was also examined with thioacetate **11**, having one more methylene group between thioacetate and vinyl bromide moieties of **9**. The reaction afforded an inseparable mixture of six-membered ring products in a 31% total yield, together with 19% yield of a dehydrobrominated acetylenic product (Scheme 1-17). The results demonstrated that the five-membered ring formation was much more preferable than the six-membered ring formation in this vinylic substitution reaction.

Scheme 1-17.

Furthermore, a competitive reaction between the four- and five-membered ring formations was performed. When thioacetate **12** that has two possible cyclization patterns (four- or five-membered ring) was employed, only four-membered ring thietane **13** was obtained without any formation of the five-membered product (Scheme 1-18). Thus, in the intramolecular vinylic substitution with thiolate anion, the four-membered ring formation is more preferred to the five-membered ring formation. From these results, a rough conclusion could be drawn for the order of ring-closing rates of the cyclization of vinyl bromides with intramolecular thiolate: four- > five- > six-membered ring.

Scheme 1-18.

As series of four-membered ring compounds, 2-alkylidenethietanes, were synthesized by Narasaka's group via vinylic nucleophilic substitution reactions (Scheme 1-19). Theoretical studies of the cyclization of thiolate anion **15** generated from

thioacetate **14** indicated 22.4 kcal mol⁻¹ of the activation energy for the S_NV_σ transition state and 18.2 kcal mol⁻¹ for S_NV_π in DMF. Both of the activation energies were reasonable for the cyclization of **14**, and hence it was hard to determine the reaction pathway only by the computational results.

Scheme 1-19.

The reaction pathway of the above substitution was revealed by the following experimental study on the stereospecificity of this cyclization. The treatment of both *Z*- and *E*-isomers **16** with K₂CO₃-MeOH, gave the cyclized products **17** with retention of the configurations (Scheme 1-20), which confirmed S_NV_π pathway for the 2-alkylidene thietane formation.

Scheme 1-20.

1.2.4. Nucleophilic substitution reactions at an sp^2 nitrogen

The nucleophilic substitution reaction can take place at not only an sp^2 carbon but also an sp^2 nitrogen. In fact, the work on the vinylic nucleophilic substitution reaction in Narasaka's group was developed from findings on the substitution at the sp^2 nitrogen.²⁵

During the study on the catalytic Beckmann rearrangement of oximes **18**, besides the Beckmann rearrangement product **19**, an unexpected product, quinoline **20**, was also obtained (Scheme 1-21).

Scheme 1-21.

Further experimental and theoretical studies revealed that the S_N2 type (S_NV_σ -type) reaction took place at the sp^2 nitrogen to generate **20**. That is, oxime **21** was initially converted to the perhenic acid ester and subsequently an in-plane nucleophilic attack of the phenyl group occurred at the sp^2 nitrogen to form a spirocycle intermediate **22**. This intermediate **22** successively rearranged to quinoline derivative **23** (Scheme 1-22).²⁶ This reaction pathway was rationalized by theoretical calculation, which suggested that the activation energies toward the nucleophilic substitution ($8.8 \text{ kcal mol}^{-1}$) and the Beckmann rearrangement ($8.0 \text{ kcal mol}^{-1}$) were almost same.²⁷

Scheme 1-22.

Inspired by this finding, Narasaka's group have successfully prepared a series of nitrogen containing compounds, including pyrroles, tetrahydropyridine derivatives and amines, by applying the nucleophilic substitution reaction at an sp^2 nitrogen with intramolecular or intermolecular carbon nucleophiles (Scheme 1-23).²⁸

Scheme 1-23.

1.3. Perspective

Although concerted nucleophilic substitution reaction at sp^2 atoms had been believed to hardly proceed, such reactions were recently found to proceed smoothly for appropriately designed systems, particularly in intramolecular manners. Various kinds of hetero nucleophiles such as oxygen, nitrogen and sulfur nucleophiles could be employed

as nucleophilic moieties. Accordingly, nucleophilic vinylic substitution reactions were expected to provide useful tools for the synthesis of heterocyclic compounds.

As mentioned in 1.2.3 (Schemes 1-14 to 1-20), thiolates exhibited a unique character for the nucleophilic vinylic substitution. Both S_NV_σ and S_NV_π reactions take place with relatively low activation energies. Thus, four-, five- and six-membered cyclic sulfides were prepared from vinyl bromides having intramolecular thiol (or the precursor) moieties. As a continual study of the intramolecular nucleophilic substitution of unactivated vinyl halide, the author would like to focus on applying such a protocol to the synthesis of thiazoles and related compounds.

In Chapter 2 is described the studies mainly on the preparation of 1,3-disubstituted thiazoles and 1,3,4-trisubstituted imidazole-2-thiones by using the intramolecular nucleophilic vinylic substitution as depicted in Scheme 1-24.

Scheme 1-24.

1.4. References

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Chapter 2. Application of Intramolecular Nucleophilic Substitutions at An sp^2 Carbon to The Synthesis of Five-membered Heterocycles

2.1. Synthesis of 2,5-disubstituted thiazoles

Thiazole (1,3-thiazole) moiety is an important unit in many natural, medicinal and agricultural substances. They exhibit important pharmacological and biological properties,¹ representative examples being vitamin B₁, that is essential to the human health,² an anti-inflammatory agent 2-(4-chlorophenyl)-thiazole-4-acetic acid³ and niridazole that is applied in the treatment of bilharzia and periodontitis⁴ (Figure 2-1). Therefore, thiazole formations are frequently encountered during the drug discovery.

Figure 2-1.

2.1.1. Conventional synthetic methods for thiazoles

Many synthetic approaches have been reported for thiazole derivatives,^{5, 6} and most of them are condensations between thioamides or thioureas with carbonyl compounds and intramolecular cyclizations of dicarbonyl compounds by the use of thionation reagents. Herein, these conventional methods are briefly surveyed.

2.1.1.1. Hantzsch synthesis and modified methods

The most classical way is the *Hantzsch* synthesis,⁷ which proceeds via cyclocondensation of thioamides with α -halocarbonyl compounds including α -halo-ketones, -carboxylic acids and -esters. As shown in Scheme 2-1, thioamides **24** underwent condensation with α -bromoketones at room temperature and yielded 2,4-disubstituted thiazoles **25**.⁸

Scheme 2-1.

In-situ generated α -halocarbonyl compounds were also employed for the condensation.^{9, 10} For example, α -halocarbonyl compounds were preformed from β -ketoesters and NBS in the presence of β -cyclodextrin catalyst and the successive condensation with thiourea gave 2-aminothiazoles (Scheme 2-2).¹¹

Scheme 2-2.

A series of 2,4-disubstituted thiazoles **27** were obtained by the reaction of thioamides with alkynyl(aryl)iodoniums **26** which were prepared in advance or beforehand from 2-iodo-5-methylbenzenesulfonic acid and 1-alkynes (Scheme 2-3).¹²

2.1.1.2. Cook-Heilbron synthesis

Cook-Heilbron synthesis¹³ is another traditional way to prepare thiazoles, in which α -aminonitriles react with CS₂ (or COS, dithiocarboxylic acid esters or salts) or with isothiocyanates to afford 2,4-disubstituted 5-aminothiazoles under mild reaction conditions (Scheme 2-4).

2.1.1.3. Gabriel synthesis

Gabriel synthesis¹⁴ is also a common method for the preparation of thiazoles, in which *N*-(2-oxoalkyl)amides **28** react with P₄S₁₀ or Lawesson's reagent (LR). In addition, some modified Lawesson's reagents such as *f*-LR were applied to the synthesis. As shown in Scheme 2-5, by using fluororous Lawesson's reagent *f*-LR for thionation, several 2,5-disubstituted thiazoles were prepared in moderate to good yields.¹⁵

Scheme 2-5.

2.1.1.4. Other methods

Banert et al. reported the synthesis of 2,5-disubstituted thiazoles from allenyl isothiocyanates **29**.¹⁶ The addition of nucleophiles, such as thiols, alcohols, and amines results in the ring closure to generate thiazoles (Scheme 2-6). It provides a good protocol for preparing various 2-hetero substituted 5-methylthiazoles, while the drawbacks are the use of excess amounts of allenyl isothiocyanates **29** and the requirement for very long reaction times (12 days or longer).

Scheme 2-6.

The condensation of propargylamine **30** with dithiobenzoic acids or dithioisobutyric acids afforded 5-alkylidenethiazolines **32** in good yields.¹⁷ A spontaneous cyclization onto the triple bond was supposed to occur rapidly due to the high nucleophilicity of the thioamide moiety, because none of *N*-propargyl thioamide intermediates **31** was observed during the reaction. 5-Alkylidenethiazolines **32** were isomerized to thiazoles **33** by the treatment with DBU (Scheme 2-7).

Scheme 2-7.

Such an isomerization also took place in the synthesis of 2,4-disubstituted aminothiazoles from propargyl bromide and thioureas under microwave irradiation (Scheme 2-8).¹⁸

Scheme 2-8.

As described above, various methods have been developed for the synthesis of thiazole derivatives. However, some required excess amounts of starting materials or long reaction time, and some were carried out under specific reaction conditions such as microwave irradiations.

Among the reported thiazole formations, 2,5-disubstituted thiazoles **36**, especially 2-substituted 5-alkylthiazoles formations are not very common. *Hantzsch* synthesis has been employed for such a thiazole synthesis, and the reactions listed in Schemes 2-5 to 7 are also applicable to the preparation of 2-substituted 5-alkylthiazoles, but the low yields or excessive use of the starting materials make it necessary to explore a more convenient and efficient method for the synthesis of 2-substituted 5-alkylthiazoles.

2.1.2. Project proposal

As summarized in chapter 1, the nucleophilic substitution of vinyl halides with intramolecular nucleophilic moieties, such as oxygen, nitrogen, sulfur anions were successfully applied to the synthesis of some heterocycles. Especially, a thiolate anion was found to be a unique nucleophile, which underwent the intramolecular cyclization via both of S_NV_σ and S_NV_π pathways to give four-, five- and six-membered cyclic sulfides from the vinyl bromides having thiol moieties. As a continual study of the intramolecular nucleophilic substitution of unactivated vinyl halides, the author applied this protocol to synthesize 2,5-disubstituted thiazoles **36** by designing vinyl bromides **34** bearing intramolecular thioamide or thiourea moieties.

Scheme 2-9.

It was expected that this intramolecular nucleophilic substitution reaction would provide a conceptually new method to prepare 2,5-disubstituted thiazoles **36** from *N*-2-bromoalk-2-enylthioamides **34** (Scheme 2-9). Although thioamides **34** are a kind of ambident nucleophiles (*N*-attack vs. *S*-attack), it was supposed that the *S*-anion is more nucleophilic to result in a sulfide five-membered ring formation preferably.

2.1.3. Results and discussion

2.1.3.1. Preparation of *N*-2-bromoalk-2-enyl-thioamides **34**, carbamodithioate **40**, and thioureas **42**

The starting materials *N*-2-bromoalk-2-enylthioamides **34** and thioamide analogues **40**, **42** were prepared through two routes, that is, an acylation followed by thionation or a direct thioacylation (route A) and the nucleophilic addition of carboanion or amines to isothiocyanates (route B), as described below.

Route A: As shown in Scheme 2-10, the precursors of *N*-2-bromoalk-2-enylthioamides **34**, *N*-2-bromoalk-2-enylamides **39** were firstly prepared via the acylation of 2-bromo-2-propenylamine **38** with acyl chloride in the presence of Et₃N. These amides

39 were next thionated to the corresponding thioamides **34a-g** by using Lawesson's reagent (LR) (Table 2-1).

Scheme 2-10.

Table 2-1. Preparation of *N*-2-bromoalk-2-enylamides **34a-g**

thioamides 34 (yield) ^a :			
34a (41%)	34b (64%)	34c (92%)	
34d (37%)	34e (65%)	34f (61%)	34g (87%)

^a Isolated yield, prepared from corresponding amides **39**.

In addition, phenyl (2-bromo-2-propenyl)carbamodithioate **40** was prepared directly through the thioacylation of 2-bromo-2-propenylamine **38a** with phenyl carbonchloridodithioate in the presence of Et₃N (Scheme 2-11).

Scheme 2-11.

Route B: The synthesis of an acetylenic thioamide **34h** was carried out by an alternative route via the nucleophilic addition of phenylacetylene to the readily prepared 2-bromo-3-isothiocyantoprop-1-ene **41** in a moderate yield (Scheme 2-12). The thioamide **34h** was not very stable to be stored for a long time.

Scheme 2-12.

Thioureas **42** such as 3-(2-bromo-2-propenyl)-1,1-diethylthiourea **42a** and 1-(2-bromo-2-propenyl)-3-phenylthiourea **42b** could be prepared in high yields from isothiocyanate **41** and secondary amines (Scheme 2-13).

Scheme 2-13.

N,N'-disubstituted thiourea, 1-(2-bromo-2-propenyl)-3-phenylthiourea **42c**, was prepared via the simple nucleophilic addition of 2-bromo-2-propenylamine **38a** to phenyl isothiocyanate (Scheme 2-14).

Scheme 2-14.

2.1.3.2. Preparation of *N*-[2-Bromo-4-(4-bromophenoxy)but-2-en-1-yl]-2-chlorobenzothioamide **50**

N-[2-Bromo-4-(4-bromophenoxy)but-2-en-1-yl]-2-chlorobenzothioamide **50** was synthesized through 7 steps, starting from ethyl (*E*)-4-bromobut-2-enoate **43** (Scheme 2-15). Alkylation of phenol with **43** gave **44**, followed by an addition reaction of bromine to the double bond to afford **45**. After dehydrobromination and reduction to **47**, the bromination of the hydroxyl group with PBr₃ gave 1-bromo-4-[(3,4-dibromobut-2-en-1-yl)oxy]benzene **48**, which was isolated as a mixture of the *Z*- and *E*-isomers. Allylic amide **49** was obtained as a single stereoisomer from the reaction of **48** and 2-chlorobenzamide but in 20% yield. The desired thioamide **50** was finally obtained after thionation of **49** with Lawesson's reagent. Although **50** was obtained as a single isomer (*E* or *Z*), the configuration was not determined.

Scheme 2-15.

2.1.3.3. Intramolecular nucleophilic substitution of *N*-2-bromoalk-2-enylthioamides **34** and **50**

Using a variety of thioamide derivatives thus prepared, the thiazole formation via the intramolecular vinylic substitution was examined. As expected, when *N*-(2-bromoprop-2-enyl)benzothioamide **34a** was treated with potassium carbonate in *N,N*-dimethylformamide (DMF) at 80 °C, 5-methyl-2-phenyl-1,3-thiazole **36a** was obtained in 79% yield (Scheme 2-16), which suggested that an intramolecular sulfur-nucleophilic substitution occurred at a vinylic carbon.

Scheme 2-16.

As the above substitution reaction proceeded smoothly, the generality of the cyclization of various *N*-(2-bromoprop-2-enyl)thioamides **34** was investigated under the same reaction conditions. Irrespective of R^1 (aromatic, aliphatic or heterocyclic groups), the thioamides cyclized similarly to afford 2-substituted 5-methylthiazoles **36** in good yields (Table 2-2, **36a-e**), except for acetylenic thioamide **34h**. From **34h** ($R^1 = -CC-Ph$), 2-phenylethynylthiazole **36h** was obtained only in 23% yield, because the starting material **34h** was not so stable and partly decomposed under the reaction conditions.

Table 2-2. Intramolecular substitution of *N*-(2-bromoprop-2-enyl)-thioamides **34**

thiazoles **36** (reaction time, isolated yield)

Notably, the cyclization reaction of *N*-(2-bromo-3-methylbut-2-en-1-yl)benzothioamide **34f**, in which two methyl groups were introduced at the terminal position of the olefinic bond, cyclized to 5-isopropyl-2-phenylthiazole **36f** and vinylthiazoline **35f** in 15% and 59% yields, respectively (Scheme 2-17). The predominant formation of *exo*-olefin **35f** is consistent with the hypothesis shown in Scheme 2-9 that the substitution reaction firstly forms 5-alkylidene thiazolines **35**, followed by a prototropic rearrangement to afford thermodynamically more stable thiazoles. 5-Alkylidenethiazoline **35f** was isolated only in this case and the reactions of all other substrates only afford thiazoles as sole cyclization products. It was supposed that the *gem*-dimethyl groups of **34f** might stabilize the *exo*-cyclic double bond in **35f**.

Scheme 2-17.

When the reaction of cyclic vinyl bromide **34g** was examined with 1.5 equivalents of K_2CO_3 , a mixture of thiazole **36g** and thiazolidine **35g** was obtained, which could not be separated by TLC. However, under the modified reaction conditions using 3.0

equivalents K_2CO_3 at higher temperature (100 °C), thizaole **36g** was isolated as the sole product in 75% yield (Scheme 2-18).

Scheme 2-18.

The cyclization reaction of *N*-4-aryloxy-2-bromobutenylthioamide **50** proceeded smoothly, and 5-vinylthiazole **51** was obtained in 70% yield with the elimination of 4-bromophenol (Scheme 2-19). Two possible pathways are proposed to take place during the reaction. Path **A** suggests the vinylic nucleophilic substitution firstly affords the thiazoline intermediate, followed by the elimination of 4-bromophenol. Another suggestion (path **B**) is the initial allylic substitution of allyl ether moiety with the sulfur nucleophile, the resulting phenoxide anion may promote dehydrobromination to afford the final product **51**. However, the path **B** is considered hard to take place.

Scheme 2-19.

2.1.3.4. Mechanism discussion

As mentioned above, thioamides **34** and **50** were successfully transformed to 2,5-disubstituted thiazoles **36** and **51**, in which only the thiocarbonyl group attacked the vinyl bromide moiety and none of the azirine **37** formation (Scheme 2-20, path B) was observed. The reaction is supposed to proceed via the *S*-nucleophilic substitution at vinylic bromide, firstly formed 5-alkylidenethiazoles **35**, which then isomerized to thiazoles **36** (Scheme 2-20, path A).

Scheme 2-20.

In addition to the above intramolecular vinylic substitution mechanism, the other two possible reaction routes might be suspected: elimination of hydrogen bromide from thioamides **34** generates allenes **I** or acetylenes **II**, which suffer the nucleophilic attack of thioamide moiety, and followed by the isomerization to give the final product thiazoles **36** (Scheme 2-21).

Scheme 2-21.

However, as shown in Scheme 2-22, there is no chance for the dimethyl substituted thioamide **34f** to form acetylene intermediate **II** while the allene formation is possible. Furthermore, the intramolecular cyclization of the cyclic vinyl bromide **34g** proceeded smoothly (Scheme 2-18). In which the elimination of hydrogen bromide to generate neither allene nor acetylene is possible, because a large ring strain will be created during the elimination process of **34g**.

Scheme 2-22.

Furthermore, the elimination product **I** or **II** was not detected in all cyclization reactions. Therefore, the nucleophilic substitution at the sp^2 carbon (Scheme 2-20) was proven to be the most plausible pathway for this intramolecular cyclization.

2.1.3.5. Intramolecular nucleophilic substitution of carbamodithioate **40**

Phenyl (2-bromoallyl)carbamodithioate **40** was also submitted to the substitution reaction. Optimization was carried out for the reaction of carbamodithioate **40** because the reaction always gave a messy product mixture. A by-product diphenyldisulfide was isolated, which presumably proceeded via the elimination of benzenethiolate. Accordingly, the reaction was conducted in the presence of several bases. However, only CsF gave 5-methyl-2-(phenylthio)thiazole **52** with a slightly better yield of 35% (Table 2-3, entry 1) as compared with the other bases.

Table 2-3. Screening of bases for the cyclization of **40**

entry	base	temp. (°C)	time (h)	yield (%) ^a
1	CsF	80	3	35
2	CsF	60	2	33
3	K ₂ CO ₃	60	3	15
4	Et ₃ N	80	5	8
5	K ₂ CO ₃	60	3	15
6	Cs ₂ CO ₃	60	7	19
7	Cs ₂ CO ₃	80	4	28
8	Na ₂ CO ₃	80	4	19
9	K ₃ PO ₄	80	4	30
10	KOH	80	4	30

^a Isolated yield.

2.1.3.6. Intramolecular nucleophilic substitution of thioureas **42**

Reactions of thioureas **42a**, **42b** and **42c** exhibited different reactivity due to the structural difference. The cyclization of the terminal *N,N*-diethyl-3-(2-bromoallyl)thiourea **42a** hardly proceed and only a trace amount formation of thiazole **53a** with 76% starting material recovery even after 48 h (Scheme 2-23).

Scheme 2-23.

To improve the yield of the thiazole formation, the reaction of *N*-benzyl-*N*-methyl-3-(2-bromoallyl)thiourea **42b** was examined at a higher temperature (100-140 °C). An unexpected three numbered ring product, azirine **37b**, was isolated in 28% yield after 12 h, together with a trace amount of thiazole **53b** (Scheme 2-24). Azirine **37b** was thought to be formed by *N*-nucleophilic attack at high temperature (proposed in Scheme 2-20, path B) as reported by Shipman (see Chapter 1, Scheme 1-11).

Scheme 2-24.

In contrast, when thiourea **42c**, in which both of the N groups were secondary amino groups, was treated with K_2CO_3 , the cyclization reaction proceeded smoothly but gave two products, 2-aminothiazole **53c** and 1,5-disubstituted imidazole-2-thione **54** in

14% and 41% yield, respectively (Scheme 2-25). This result demonstrated that the competitive reactions between *S*- and *N*-nucleophilic attacks took place in this system.

Scheme 2-25.

The formation of imidazole-2-thione **54** caused the author's interest in the synthesis of 1,3,4-trisubstituted imidazole-2-thiones **56** from *N*-1-(2-bromoprop-2-enyl)-*N'*-disubstituted thioureas **55** (Scheme 2-26), which will be discussed in the next section.

Scheme 2-26.

2.2. Synthesis of 1,3,4-trisubstituted imidazole-2-thiones

Imidazole-2-thione is known to be a pair of tautomers, a thione form and a thiol form¹⁹ (Equation 2-1), and the thione form (imidazole-2-thione) is generally more stable than thiol indicated by the Hückel Molecular Orbital (HMO) calculations. Imidazole-2-thiones and its derivatives²⁰ have received attention in biochemistry and pharmaceutical chemistry due to their remarkable bioactivities and pharmaceutical properties, for instance, antithyroid, antioxidant, cardiotonic, antihypertensive and anti-HIV properties.²¹ Imidazole-2-thiones are also employed in *N*-heterocyclic carbene (NHC) chemistry.²² Thus, development of synthetic methods of imidazole-2-thione derivatives is an important topic as well as thiazole derivatives.

Equation 2-1.

2.2.1. Conventional synthetic methods of imidazole-2-thiones

Reported methods to prepare imidazole-2-thiones are mainly based on two pathways, one route starting from thiocyanates or thioureas that undergo condensation or cycloaddition reactions; another route goes through an *N*-heterocyclic carbene (NHC) formation from imidazolium salts.

2.2.1.1. Synthesis of imidazole-2-thiones from thiocyanates or thioureas

The Marckward's method²³ has long been known as a general synthetic tool of imidazole-2-thiones. Isothiocyanates and amino acetals were heated in refluxing ethanol to form thioureas **57**, which were isolated and next submitted to heat in aqueous hydrochloride to afford 1-substituted imidazole-2-thione **58**. As shown in Scheme 2-27, this method can be modified into a one-pot fashion; the product 1-substituted imidazole-2-thione **58** could be obtained directly without isolating the intermediate thiourea **57**.²⁴

Scheme 2-27.

Utilizing potassium thiocyanate, 1-substituted imidazole-2-thiones **60** were synthesized from *N*-substituted amino acetals **59** in the presence of acid, followed by neutralization (Scheme 2-28).²⁵

Scheme 2-28.

Starting from easily available compounds such as hydrazines **61**, α -haloketones and potassium thiocyanate, 1,4,5-trisubstituted imidazole-2-thiones **62** was formed in good yields in a one-pot reaction (Scheme 2-29).²⁶ This multistep reaction is considered

to proceed via thiocyanato hydrazone intermediates **63**. Subsequent 1,4-elimination of hydrogen thiocyanate leads to the corresponding azo-alkenes **64**, which in turn, undergo a [3+2] cycloaddition reaction; the resultant azomethine imine cycloadducts **65** are isomerized to the final products **62**.

Scheme 2-29.

The condensation between thioureas **66** and 3-hydroxy-2-butanone in refluxing 1-hexanol afforded 4,5-dimethyl 1,3-disubstituted imidazole-2-thiones **67** in moderate yields (Scheme 2-30).²⁷ Such condensation reactions provide another good way to prepare imidazole-2-thiones.

Scheme 2-30.

2.2.1.2. Synthesis of imidazole-2-thiones from imidazolium salts

Yadan reported a preparation of imidazole-2-thiones **70** from the corresponding imidazoles **68**.²⁸ This transformation was proposed to proceed through a multistep process, so-called ANRORC (addition of nucleophile, ring opening, ring close) process²⁹ via an intermediate **69** (Scheme 2-31).

Scheme 2-31.

In imidazole carbene chemistry, formations of imidazole-2-thiones are often encountered.³⁰ Unstable *N*-heterocyclic carbenes (NHC) **72** generated by the treatment of imidazolium salts **71** with bases, could be trapped by sulfur to form imidazole-2-thiones **73** (Scheme 2-32).^{31, 32}

Scheme 2-32.

Although many synthetic methods have been reported on the imidazole-2-thiones formation, the author would like to describe the first synthetic method for 1,3,4-trisubstituted imidazole-2-thiones by the intramolecular vinylic nucleophilic substitution.

2.2.2. Project proposal

During the study of the thiazole formation, when *N*-2-bromoalk-2-enyl-*N'*-alkyl thiourea **42c** was treated with K_2CO_3 , 1,5-disubstituted imidazole-2-thione **54** was formed along with the desired 2-aminothiazole **53c** as shown in Scheme 2-25. These products are supposed to be derived from the following pathways involving the two possible intermediates **I** and **II**, respectively (Scheme 2-33). 2-Aminothiazole **53c** is formed by the *S*-cyclization of **I**, while imidazole-2-thione **54** is formed by the *N*-cyclization of **II**. As shown in Scheme 2-33, there should be other two pathways; aziridine from the *N*-cyclization of intermediate **I** and thiazolidin-2-imine from the *S*-cyclization of intermediate **II**. It was proposed that formation of **I** would be suppressed by introducing a substituent at the inner nitrogen atom of thiourea **42c**.

Scheme 2-33.

Thus, as shown in Scheme 2-34, 1-(2-bromoprop-2-enyl)thioureas **55** whose *inner* nitrogen was fully substituted were designed for the synthesis of 1,3,4-trisubstituted imidazole-2-thiones **56** through the nucleophilic attack of the *outer* nitrogen, although the formation of 5-vinyl thiazolidin-2-imines **74** via *S*-attack should not be excluded.

Scheme 2-34.

2.2.3. Results and discussion

2.2.3.1. Preparation of *N,N'*-disubstituted *N*-(2-bromoprop-2-enyl)thioureas **55**

N,N'-disubstituted *N*-(2-bromoprop-2-enyl)thioureas **55** were prepared in a similar way to the route B for the synthesis of thioureas **42** (Scheme 2-14). The readily prepared *N*-substituted 2-bromoallyl amines **75**³³ reacted with isothiocyanates, yielding **55** in moderate to good yields, as summarized in Table 2-4.

Table 2-4. Preparation of 1-(2-bromoprop-2-enyl)thioureas **55**

thioureas **55** (isolated yield)

2.2.3.2. Intramolecular cyclization of *N*-(2-bromoprop-2-enyl)thioureas **55**

The cyclization of *N*-isopropyl derivative **55a** was firstly examined. By the treatment of **55a** with 1.5 mole equivalents K_2CO_3 in DMF at 80 °C, 1-isopropyl-4-methyl-3-phenylimidazole-2-thione **56a** was obtained as a major product in 78% yield, with 8% of *N*-(3-isopropyl-5-methylenethiazolidin-2-ylidene)aniline **74a** (Scheme 2-35). This result indicated that the *N*-attack proceeded very preferably, although the *S*-attack pathway (as shown in Scheme 2-34) was not completely suppressed.

Scheme 2-35.

Next, the reactions of the rest of *N*-(2-bromoprop-2-enyl)thioureas **55b-h** were examined under the same reaction conditions. Various 1,3,4-trisubstituted imidazole-2-thiones **56** were obtained in moderate to good yields, together with a trace amount to low yield of 5-vinyl thiazolidin-2-imines **74** (Table 2-5).

Table 2-5. Intramolecular cyclizations of *N*-(2-bromoprop-2-enyl)thioureas **55**

entry	thioureas	R ¹	R ²	imidazole-2-thiones 56 (yield/%) ^a	thiazolidin-2-imines 74 (yield/%) ^a
1	55a	<i>i</i> -C ₃ H ₇	H	56a (78)	74a (8)
2	55b	<i>i</i> -C ₃ H ₇	MeO	56b (81)	74b (7)
3	55d	C ₆ H ₅	H	56d (87)	74d (-)
4	55e	C ₆ H ₅	MeO	56e (91)	74e (-)
5	55c	<i>i</i> -C ₃ H ₇	NO ₂	56c (77)	74c (19)
6	55f	C ₆ H ₅	NO ₂	56f (50)	74f (33)
7	55g	C ₆ H ₅ CH ₂	H	56g (65)	74g (30)
8	55h^b	C ₆ H ₅ CH ₂	NO ₂	56h (68)	74h (25)

^a Isolated yield. ^b reaction was run at room temperature.

The products ratio of imidazole-2-thione and thiazolidin-2-imine was affected by the electronic properties of the substituents R¹ and R². When R² was an electron-donating or neutral group OMe or H, the corresponding imidazole-2-thiones **56** were obtained in high selectivity and yields (Table 2-5, entries 1-4). For example, *N*-(2-bromo-2-

propenyl)-3-(4-methoxyphenyl)-*N*-phenylthiourea **55e** was cyclized to imidazole-2-thione **56e** in 91% yield, without formation of a detectable amount of thiazolidin-2-imine.

When R^2 was an electron-withdrawing group such as NO_2 , the yields of 5-methylenethiazolidin-2-imines **74** increased to 19-33% (Table 2-5, entries 5-8). For example, the substitution reaction of *N*-(2-bromo-2-propenyl)-3-(4-nitrophenyl)-*N*-phenylthiourea **55f** gave imidazole-2-thione **56f** in 50% yield, together with 33% of thiazolidin-2-imine **74f**. In addition, when R^1 was a benzyl group as in **55g**, thiazolidin-2-imine **74g** was isolated in 30% yield. These results suggest that the electron-withdrawing R^2 group decreases the nucleophilicity of the anilino group, making the *S*-cyclization pathway competitive, although the *N*-cyclization was still the major pathway.

When *N*-(2-bromo-2-propenyl)-3-cyclohexyl-*N*-isopropylthiourea **55i** in which aryl group of **55a** at the terminal nitrogen was replaced by an *sec*-alkyl group was submitted to the cyclization reaction (Scheme 2-36), an inseparable mixture of **56i** and **76i** (suggested from NMR spectrum) was obtained.

Scheme 2-36.

2.2.3.3. Mechanism discussion

An isomerization of imidazolin-2-imine **74f** was suspected as one of the routes to imidazole-2-thione **56f**. However, when *N*-(5-methylene-3-phenylthiazolidin-2-ylidene)-

4-nitroaniline **74f** was submitted under the reaction conditions (1.5 mole equivalents K_2CO_3 in DMF at 80 °C), **74f** isomerized to dihydrothiazole **76f** without any formation of **56f** even at a high temperature (120 °C), and no further transformation took place even by adding more bases (Scheme 2-37).

Scheme 2-37.

Therefore, similar as the cyclization of thioamides **34** to thiazoles (Scheme 2-19), the transformation from thioureas **55** to imidazole-2-thiones **56** with the minor products imidazolin-2-imine **74** should also proceed via the intramolecular vinylic substitution that have been proposed in Scheme 2-33. According to the results, the nitrogen anion of the intermediate **I** should be more nucleophilic than sulfur anion. Thus, the *N*-nucleophilic substitution proceeds much faster to give imidazole-2-thiones **56** as a major product, while the *S*-nucleophilic substitution proceeds slow to afford imidazolin-2-imine **74** (Scheme 2-38).

2.3. Conclusions on the five-membered heterocycles formation

Although the nucleophilic substitution at an sp^2 carbon has been considered difficult, a series of heterocycles have been prepared by using the intramolecular nucleophilic substitution reactions of vinyl bromides.³⁴ Here, some five-membered heterocycles including 2,5-disubstituted thiazoles and 1,3,4-trisubstituted imidazole-2-thiones were successfully prepared from thioamides and their analogues. Two types of nucleophilic attacks (*S*-attack and *N*-attack) have been demonstrated during the study of the nucleophilic substitution of vinyl bromides with intramolecular nucleophiles, such as thioamide and thiourea moieties.

The intramolecular nucleophilic substitutions of *N*-2-bromoalk-2-enylthioamides **34** proceeded smoothly to afford 5-alkyl 2-substituted thiazoles **36** in moderate to good yields. *N*-2-Bromoallyl thioamides were successfully cyclized to the corresponding thiazoles with a variety of 2,5-disubstituents. Although the similar cyclization of carbamodithionate **40** was screened, 2-phenylthiothiazole **52** was obtained in a low yield (Scheme 2-39).

Scheme 2-39.

The intramolecular nucleophilic substitution reactions of *N*-(2-bromoprop-2-en-1-yl)thioureas **55** were also studied, where two types of nucleophilic attacks were observed. Thioureas **55** underwent the intramolecular *N*-attack to afford imidazole-2-thiones **56** as the major products in moderate to good yields along with the formation of thiazolidin-2-imines **74** as the minor products via the *S*-attack (Scheme-2-40). The product ratio was affected considerably by the electronic effects of the *N*-substituents.

Scheme 2-40.

Thus, it was envisioned that the intramolecular vinylic substitution method would provide unique synthetic routes for a variety of heterocycles.

2.4. Extension of the five-membered ring formation to six-membered ring formation: application of the vinylic substitution to thiazine formation

As an extension of the previous five-membered ring thiazole formations that have been described in Chapter 2.1, the author applied this method to the preparation of six-membered ring compounds (Scheme 2-41). For this purpose, the author designed a vinyl bromide **77** having an intramolecular thioamide moiety by introducing one more carbon unit to thioamides **34**. By the intramolecular thiolate attack, a six-membered ring, 2,4-disubstituted 6-vinyl-5,6-dihydro-1,3-thiazine **78** was expected to be formed.³⁵

5-membered ring formation:

6-membered ring formation:

Scheme 2-41.

2.4.1. Preparation of the starting materials

Similarly as in the preparation of *N*-2-bromoalk-2-enylthioamides **34** (Scheme 2-10), *N*-2-bromo homoallylic thioamides **77** were synthesized from homoallylic amines **81**, followed by acylation and thionation.

Firstly, as shown in Scheme 2-42, readily prepared alcohols **79**^{36,37} were converted to azides **80** via mesylation and azidation,³⁸ which were next reduced by triphenylphosphine and water or lithium aluminum hydride to afford 3-bromobut-3-enamines **81** in moderate yields.

Scheme 2-42.

The subsequent acylation of these amines **81** afforded several *N*-(3-bromobut-3-en-1-yl)amides **82**, which were next transformed into the corresponding thioamides **77a-e** in good yields by the thionation with Lawesson's reagent (LR). By following the same synthetic route, an acetylenic amide, *N*-(1-phenylhex-5-yn-3-yl)benzothioamide **83** was also prepared from the corresponding amide **84**, as summarized in Table 2-6.

Table 2-6. Preparation of *N*-(3-bromobut-3-en-1-yl)thioamides **77** and **83**

thioamides **77** (yield)^a:

^a Isolated yield, prepared from corresponding amides **82**.

^b **83** was prepared from corresponding amide **84**.

2.4.2. Intramolecular cyclization of *N*-(3-bromobut-3-en-1-yl)thioamides **77**

With *N*-(3-bromobut-3-en-1-yl)thioamides **77** in hand, the six-membered ring formation was first carried out by using *N*-(5-bromo-1-phenylhex-5-en-3-yl)benzothioamide **77a** under the same reaction conditions as employed for the formation of thiazoles. Thioamide **77a** was treated with 1.5 mole equivalents of K₂CO₃ in DMF at 80 °C. Monitored by TLC, a very weak new spot was observed after 20 h. After heated to 100 °C for 7 h, the expected six-membered ring compound, 1,3-thiazine **78a** was obtained in 36% yield, together with 61% formation of an acetylenic compound, *N*-(1-phenylhex-5-yn-3-yl)benzothioamide **83** (Scheme 2-43). The formation of **83** suggested that an elimination of hydrogen bromide from the starting material **77a** took place under the reaction conditions.

Scheme 2-43.

To improve the transformation of thioamide **77a** to **78a**, screening of reaction conditions was performed, as summarized in Table 2-7. Some bases were screened because the elimination of HBr was thought to be influenced by their basicity. The cyclization reactions of **77a** proceeded even more slowly by the treatment with weaker bases such as Et₃N and NaHCO₃ (Table 2-7, entries 2 and 3), although there was no observation of the elimination product **83** at a higher temperature (120 °C). The formation of thiazine product **78a** was accelerated by adding H₂O at 80 °C when K₂CO₃ was used (Table 2-7, entry 7), without any formation of acetylene **83**.

Table 2-7. Conditions screening for cyclization of **77a**

entry	base	additive	temp./°C	time /h	78a (S.M. recov.) ^a	83 ^a
1	K ₂ CO ₃	--	80 then 100	20 7	36%	61%
2	Et ₃ N	--	120	24	11% (87%)	--
3	NaHCO ₃	--	120	24	10% (74%)	--
4 ^b	NaOH	--	80	11	64% (3%)	15%
5	NaOH	--	100	7	80%	1%
6	NaOH	--	120	5	72%	27%
7	K ₂ CO ₃	H ₂ O	80	20	85% (3%)	--
8 ^b	NaOH	H ₂ O	80	16	92%	--
9 ^b	NaOH	H ₂ O, 5 mol% TBAB	80	12	92%	--

^a Isolated yield. ^b 0.2 mmol substrate was used, other reactions were run in 0.1 mmol substrate if not noted.

The cyclization of **77a** proceeded more smoothly when the reaction was conducted with a stronger base, i.e., NaOH (entry 4), and the addition of a drop of H₂O (*ca.* 20 μ L) further improved the yield of the desired six-membered ring **78a** (Table 2-7, entry 8). After all, the reaction could be further accelerated by adding 5 mol% *tetra*-butylammonium bromide (TBAB) as the phase transfer catalyst (Table 2-7, entry 9).

Under the optimized conditions using 1.5 mole equivalents NaOH with a drop of H₂O (*ca.* 20 μ L) and a catalytic amount of TBAB at 80 °C, *N*-(3-bromobut-3-en-1-yl)thioamides **77** smoothly underwent the cyclization reaction to afford the desired six-membered ring products **78** in good yields (Table 2-8).

Table 2-8. Intramolecular cyclization of *N*-(3-bromobut-3-en-1-yl)thioamides **77**^a

1,3-thiazines **78** (reaction time, isolated yield)

78a (12 h, 92%)	78b (10 h, 89%)	78c (24 h, 81%)	78d (12 h, 70%)

^a The reaction was carried out using 0.2 mmol substrate in 7 mL DMF.

Although the expected thiazines **78a-d** were prepared in good yields, the reaction conditions were quite different from the previous thiazole synthesis. Thus, we wondered whether the 1,3-thiazines **78** formation proceeds via the initially supposed vinylic nucleophilic substitution or the addition of the thioamide moiety to the acetylenic bond. Therefore, the cyclization of acetylene **83** was tested under the same reaction conditions. As shown in Scheme 2-44, the cyclization took place and thiazine **78a** was obtained in 65%

yield. Acetylenic thioamide **83** was consumed within 7 h, which was a shorter reaction time as compared with the reaction time of the corresponding vinyl bromide **77a** (12 h). This suggested that the dehydrobromination of **77a** and the successive addition of thioamide onto the resulted intramolecular acetylenic bond may be the main cyclization pathway for the cyclization of vinyl bromide **77a** (Table 2-8).

Scheme 2-44.

In order to get more information about the reaction mechanism, *N*-(5-bromo-6-methyl-1-phenylhept-5-en-3-yl)benzothioamide **77e**, which has no chance to form an acetylenic intermediate, was submitted to the reaction. A slow transformation from **77e** to the six-membered ring product **78e** took place, and **78e** was obtained in 37% yield together with 44% of the recovered starting material (Scheme 2-45). This suggested that the intramolecular vinylic nucleophilic substitution may take place but in a slow rate, while alternative pathway involving the allene-formation-addition of thiol moiety cannot be excluded, as proposed in Scheme 2-46, path C.

Scheme 2-45.

2.4.3. Mechanism discussion

Here, three possible routes for the transformation from thioamides **77** to 1,3,-thiazines **78** are proposed: the acetylene formation-addition of thiol moiety (path A), the intramolecular vinylic nucleophilic substitution (Scheme 2-46, path B), and the allene-formation-addition of thiol moiety pathway (path C).

Scheme 2-46.

All the three pathways are supposed to operate in the cyclization of thioamides **77**, but competitively depending on the reaction conditions. The use of K_2CO_3 at 80 °C poorly affected the cyclization of **77a**, while the cyclization of the thioamide **34a** to the five-membered ring was readily achieved under such conditions (as summarized in Scheme 2-39). This indicates that the formation of the five-membered ring is intrinsically much faster than that of the six-membered ring. The similar phenomenon was observed in the cyclization of the vinyl bromides with thiolate moiety that have been discussed in Chapter 1, Scheme 1-15 and Scheme 1-17.

When heated to 100 °C, the cyclization of **77a** proceeded but albeit with very slow rate, and gave 36% yield of the cyclization product **78a** together with 61% of acetylene product **83** (Scheme 2-42). The nucleophilic substitution (Scheme 2-46, path B) and the dehydrobromination are all supposed to happen during the cyclization. Obviously, the addition of the thioamide moiety to the acetylenic intermediate (Scheme 2-46, path A) proceeds slower than the acetylene formation, therefore, acetylene product **83** still remained.

When a strong base NaOH was employed with the additives H₂O and TBAB, the cyclization to the 1,3-thiazine product **78** took place smoothly. Both the nucleophilic substitution and the dehydrobromination are proposed to occur. Due to stronger basicity, the dehydrobromination is supposed to be faster than the former process. Thus, the following cyclization process proceeds rapidly to give six-membered product **78**, while acetylene product **83** cannot be observed at the end of the reaction.

H₂O and TBAB are considered to accelerate the elimination of HBr due to the high polarity of the solvents and the soluble tetrabutylammonium hydroxide formation, and also accelerate the addition of the thioamide moiety to the acetylenic bond.

2.5. Summary

By using the intramolecular nucleophilic substitution at the sp² carbon, a series of five-membered heterocycles, thiazoles and imidazole-2-thiones have been successfully prepared. However, when extended to the six-membered ring formations, the vinylic nucleophilic substitution cannot be confirmed as the only pathway because the pathway involving the elimination of the hydrogen bromide followed by thiolate addition is also viable.

As described in chapter 1, section 2.1, the order of the ring-closing rate of vinyl bromides with intramolecular thiolate moieties is apparently in the order of four - > five - > six-membered ring formation. For the cyclization of vinyl bromides with intramolecular thioamide moieties, we can conclude that the five-membered ring formation was much more favorable than that of six-membered ring formation.

2.6. References

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Part II. Aerobic Oxidation of Allylic and Benzylic Alcohols

Catalyzed by *N*-Hydroxyindoles

Chapter 3. Introduction of Oxidation Reactions Mediated by *N*-Hydroxy Compounds

Radical reactions, particularly catalytic radical reactions have become more and more important in recent organic synthesis. One typical example is the oxidation reaction catalyzed by nitroxyl radicals which have been developed in recent two decades with a broad synthetic potential.¹ *N*-Hydroxy compounds such as 2,2,6,6-tetramethylpiperidin-1-ol (TEMPOH) **85** and *N*-hydroxyphthalimide (NHPI) **87** play key roles as precursors of nitroxyl radicals in many catalytic processes (Figure 3-1).²

Figure 3-1.

For example, 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) **88** is generated by the oxidation of TEMPOH **85**. Although TEMPO **88** is stable in an atmosphere, it can be further oxidized to another reactive species of oxoammonium cation **89** which is employed *in-situ* for catalytic reactions (Scheme 3-1). Phthalimido-*N*-oxyl (PINO) **90** is generated *in-situ* from NHPI **87** and is not stable under an atmosphere (Scheme 3-2).

Scheme 3-1.

Scheme 3-2.

These *N*-hydroxy compounds are used as catalysts for oxidations of organic molecules, and are divided into two types with respect to the structures: non-conjugated and conjugated *N*-hydroxy compounds. A broad range of oxidative transformations has been accomplished using these stable non-conjugated dialkylnitroxyls or reactive conjugated diacylnitroxyls with or without the combined use of co-catalysts.

3.1. Oxidation reactions mediated by non-conjugated *N*-hydroxy compounds

Non-conjugated *N*-hydroxyl radicals, di-*tert*-alkyl nitroxyls, are generally stable, and one typical radical of this class, TEMPO **88**, is the very first reported non-conjugated nitroxyl radical.³ Many other non-conjugated nitroxyls such as 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl (4-hydroxy-TEMPO) **91** and 4-acetylamino-2,2,6,6-tetramethyl-1-piperidinyloxy (4-acetamido-TEMPO) **92** (Figure 3-2), are analogous of this structure.⁴ TEMPO **88** can be stored for a long time without decomposition, because its unpaired electron is delocalized over the N-O bond. It is reduced to the corresponding TEMPOH **85** ($E^0 = -1.5$ V vs SHE) or is oxidized to oxoammonium cation **89**, which is known as a relatively strong oxidant with a high oxidation potential ($E^0 = 0.76$ V vs SHE)

(Scheme 3-1).⁵ Thus, TEMPO and its derivatives are often employed in oxidation reactions, especially in the oxidation of alcohols.

Figure 3-2.

3.1.1. Oxidations of alcohols by stoichiometric amounts of oxoammonium salts

Due to the high oxidation potential,⁶ oxoammonium salts **89** generated by the oxidation of TEMPO **85** with bromine or chlorine could be used for the oxidation of alcohols. In 1965, Golubev⁷ reported the first oxidation of alcohols by using oxoammonium chloride **93** prepared from 4-hydroxy-TEMPO **91** with chlorine (Scheme 3-3, eq. a). Methanol and 2-propanol were oxidized to formaldehyde and acetone, respectively, and the oxoammonium salt was quantitatively reduced to hydroxylamine **94** (Scheme 3-3, eq. b).

Scheme 3-3.

Endo et al. reported oxidations of various alcohols by stoichiometric amounts of oxoammonium salts.⁸ Several primary and secondary alcohols were oxidized to the corresponding carbonyl compounds with oxoammonium salts **95** (Scheme 3-4).

Scheme 3-4.

However, the requirement of stoichiometric amounts of the oxidants was not economical, and sometimes, the preparation of oxoammonium cations was so troublesome that catalytic oxidation methods⁹ were required. To generate oxoammonium cations *in-situ* from nitroxyls or *N*-hydroxyl amines, the combined use of various co-oxidants has been developed.

3.1.2. Metal-free oxidations of alcohols mediated by catalytic nitroxyls

The general catalytic cycle is described in Scheme 3-5. By using oxidants such as bromine and chlorine, a catalytic amount of TEMPO **88** is oxidized *in-situ* to form the oxoammonium cation **89**, which then acts as the real oxidant to transform alcohols into carbonyl compounds via the alcohol addition intermediate **96**. TEMPOH **85** is released after the oxidation and followed by oxidation to TEMPO **88** or directly to oxoammonium cation **89**, which enters into the next cycle.

Scheme 3-5.

Such catalytic oxidation systems have been studied by many groups, employing TEMPO or its derivatives in combination with various oxidants. Anelli reported TEMPO/NaBr/hypochlorite protocol in 1987 (Scheme 3-6).¹⁰ TEMPO **88** acts as the catalyst precursor, which is oxidized to the oxoammonium cation **89** that entered into the following catalytic cycle. As mentioned above (Scheme 3-5), oxoammonium cation **89** is the real oxidant to convert alcohols to carbonyl compounds, and is reduced to TEMPOH **85**. Sodium hypochlorite oxidizes sodium bromide to sodium hypobromite, which is more reactive to oxidize TEMPOH **85** than hypochlorite. Primary alcohols were quantitatively oxidized to aldehydes in a few minute, which were then further oxidized to the corresponding carboxylic acids under the same reaction conditions. In addition, secondary alcohols were successfully converted to ketones.

Scheme 3-6.

Besides hypochlorite and hypobromite, so-called single oxygen donors were used as the oxidants of TEMPOs, such as *m*-chloroperbenzoic acid,¹¹ sodium bromite,¹² sodium chlorite,¹³ iodine,¹⁴ oxone,¹⁵ periodic acid (H₅IO₆)¹⁶ and so on.

In addition to TEMPO derivatives, many *N,N*-dialkylnitroxyls have been prepared to achieve higher efficiency and selectivity. Iwabuchi et al. developed a class of structurally less hindered nitroxyl radicals 2-azaadamantane *N*-oxyl (AZADO) **97** and the derivatives such as 5-F-AZADO **98**.¹⁷ In addition, their oxoammonium salts like **99** were also prepared (Figure 3-3). These newly developed AZADO derivatives exhibited strong oxidizing ability and efficiently to oxidize even structurally hindered secondary alcohols which TEMPOs could not.

Figure 3-3.

For example, the combined use of NaNO₂ and 5-F-AZADO **98** in acetic acid was found to be a highly efficient aerobic oxidation system and was applicable for the oxidation of a wide range of alcohols, including carbohydrates, nucleic acids, aminoalcohols (Scheme 3-7).¹⁸ The effect of NaNO₂ is considered as a NO_x source¹⁹ which mediates the oxidation of F-AZADOH **101** with O₂.

Scheme 3-7.

Since 5-F-AZADO⁺NO₃⁻ **99** had a NO_x moiety in the same molecule, the aerobic oxidation was smoothly catalyzed by itself (Scheme 3-8). It is proposed that the nitrate anion of 5-F-AZADO⁺NO₃⁻ **99** works as an alternative electron carrier between molecular oxygen and 5-F-AZADO **98**.

Scheme 3-8.

3.1.3. Transition-metal involved oxidation of alcohols catalyzed by nitroxyls

Nitroxyls and their derivatives are not only combined with the so-called single oxygen donors, and combinations of nitroxyls with transition metal complexes (Cu,²⁰ Ru,²¹ H₅PV₂Mo₁₀O₄₀²²) were also developed for the catalytic aerobic oxidation of alcohols. In 1984, Semmelhack reported the CuCl/TEMPO catalyzed aerobic oxidation of benzylic, allylic and primary aliphatic alcohols in DMF.²³ It was proposed that oxoammonium cation **89** was the real oxidant which generated from TEMPO **88** by one-electron oxidation with Cu(II) (Scheme 3-9). The net reaction turned out to be the

oxidation of alcohols by oxygen to afford aldehydes and water as summarized in Scheme 3-9, eq. 5.

Scheme 3-9.

However, some simple aliphatic alcohols were hardly oxidized under the above reaction conditions, which were not consistent with the above proposed mechanism, since oxoammonium cations were known to be able to oxidize simple aliphatic alcohols. Therefore, based on Hammett correlation studies and primary kinetic isotope effects of the CuCl/TEMPO catalyzed aerobic oxidation, rather than the oxoammonium mechanism, a copper-mediated dehydrogenation mechanism was proposed by Sheldon (Scheme 3-10).²⁴ The mechanism is that, firstly, Cu(II)-nitroxide species **103** is formed by one-electron oxidation of Cu(I) by TEMPO **88**. Then the ligand exchange with an alcohol affords Cu(II) alkoxide **104** along with TEMPOH **85**. Cu(II) alkoxide **104** possibly coordinates with another TEMPO **88** to form a η^2 Cu(II) complex **105**,²⁵ followed by an intramolecular β -hydrogen abstraction²⁶ to afford intermediate **106**. Then reductive elimination takes place to give a carbonyl compound, Cu(I) and TEMPOH **85**, which regenerates TEMPO **88** by rapid air oxidation.

Scheme 3-10.

3.2. Oxidation reactions mediated by conjugated *N*-hydroxy compounds

As discussed above, non-conjugated nitroxyls may exist as rather stable radical forms, typically like TEMPO. On the other hand, nitroxyls bonded to π -conjugated systems are highly reactive. The reactivity difference of the nitroxyls can be rationalized by the bond dissociation energies (BDEs) of the O-H bond of their parent hydroxyl amines. For example, BDE of *N*-hydroxyphthalimide (NHPI) **87** ($89.6 \text{ kcal mol}^{-1}$)²⁷ was found 20 kcal mol^{-1} higher than TEMPOH **85** ($69.7 \text{ kcal mol}^{-1}$)²⁸ (Figure 3-4). Therefore, hydrogen abstraction by TEMPO from most organic substrates is highly endothermic so that it acts as an autoxidation inhibitor by efficiently scavenging free radicals. In contrast, the O-H bond energy in NHPI **87** is very close to that of the O-H bond in alkyl hydroperoxide ($88.2 \text{ kcal mol}^{-1}$)²⁹ and hydrogen abstraction from many organic compounds will be thermo neutral or mildly exothermic.

Figure 3-4.

Conjugated *N*-hydroxy compounds, typically NHPI **87**, are usually used as the precursors of reactive nitroxyl radicals, which are well known as effective hydrogen abstracting species. Autoxidation is one of the most important reactions mediated by NHPI.

Foricher reported the first autoxidation reaction with NHPI in 1986.³⁰ In the presence of a stoichiometric amount of NHPI **87**, various isoprenoids containing allylic hydrogen were oxidized to the corresponding hydroperoxides. For example, citronellyl acetate **107** was oxidized to the corresponding hydroperoxide **108** in the presence of 1.0 equivalent NHPI in refluxing acetone, and 97% of NHPI **87** was recovered after the reaction (Scheme 3-11). During the reaction, NHPI **87** is firstly oxidized by dioxygen to phthalimido-*N*-oxyl (PINO) **90**, which abstracts the allylic hydrogen to give an allylic radical. The allylic radical is then trapped with dioxygen to generate the peroxy radical **109**. This peroxy radical **109** abstracts hydrogen of **87** and affords hydroperoxide **108** and PINO **90**.

Scheme 3-11.

Compared to the stoichiometric use of NHPI, it is more practical to carry out the oxidation with a catalytic amount of NHPI. The combination of NHPI and variable valence metal compounds such as Co(II)/Co(III)³¹ provides effective catalytic methods for the autoxidation of a wide range substrates, which are discussed in the next sections.

3.2.1. Aerobic oxidation of alcohols

Catalytic oxidation of alcohols with NHPI was first reported by Ishii, and several alcohols were converted to carbonyl compounds or carboxylic acids by the use of NHPI **87** as the catalyst under an atmospheric dioxygen.³² α -Hydrogen abstraction of an alcohol by PINO **90** and trapping of the resulting C-radical by dioxygen were supposed to occur (Scheme 3-12). The generation of PINO **90** from NHPI **87** under oxygen was confirmed by the ESR measurements.³³

Scheme 3-12.

Although only limited alcohols such as benzylic and allylic alcohols could be oxidized by the simple use of NHPI **87**, better results were obtained by the combination of Co(OAc)₂ with NHPI **87** as shown in Scheme 3-13.^{34, 35} Furthermore, by adding *m*-chlorobenzoic acid (MCBA) or *m*-chloroperbenzoic acid (MCPBA) in this catalytic

system, primary alcohols were oxidized to the corresponding carboxylic acids and secondary alcohols were transformed to ketones in moderate to good yields (Scheme 3-13).

Scheme 3-13.

The $\text{Co(OAc)}_2/\text{NHPI}$ system is a noteworthy for many oxidation reactions, which is well known as Ishii system and have been applied to industrial processes. The role of Co species was studied by ESR measurements. The generation of PINO **90** from NHPI **87** under an oxygen atmosphere was accelerated by adding a Co(II) salt,³⁶ in which super oxocobalt(III) and peroxocobalt(III) complexes³⁷ are proposed as active oxidants (Scheme 3-14).

Scheme 3-14.

In addition to effect in the above initiation stage, another role of Co salts is to accelerate the decomposition of the intermediate hydroperoxide, ROOH, leading to the formation of an alkoxy radical as shown in Scheme 3-15.

Scheme 3-15.

Scheme 3-16.

Therefore, the oxidation process of alcohols by NHPI and Co salts system can be described as follows (Scheme 3-16). NHPI **87** is oxidized to PINO **90** by Co-oxygen complexes and abstracts the α-hydrogen of alcohol **104** to form α-hydroxy alkyl radical **111**, which is trapped by dioxygen to generate peroxy radical **112**. Two plausible pathways are proposed for the subsequent transformation of **112**. One is directly transformed into ketone **115** with the elimination of hydroperoxyl radical. In another way,

112 abstracts the hydrogen of NHPI **87** to give hydroperoxy intermediate **113**,³⁸ which then decomposes to alkoxy radical **114** in the presence of Co(II), followed by a hydrogen abstraction and dehydration to afford ketone or aldehyde **115**. A following autoxidation of aldehyde **115** to carboxylic acid occurs when R' = H. One of the roles of MCBA in Scheme 3-13 is considered be generation of a Co-MCBA complex and promotes the decomposition of hydroperoxide intermediates **112**.^{34, 35}

3.2.2. Aerobic oxidation of alkanes and aromatic hydrocarbons

Aerobic oxidation of adamantane **116** by the treatment with NHPI and Co(acac)₂ afforded 1-adamantanol **117**, 1,3-adamantanediol **119**, and 2-adamantanone **118** in 93% total yield. The product ratio demonstrated the high regioselectivity of the oxidation at the tertiary carbon (Scheme 3-17).³⁹ In stepwise reactions under the same reaction conditions, mono alcohol **117** could be oxidized to diol **119** and even to triol.

Scheme 3-17.

Toluene and 3-methylpyridine were oxidized to the corresponding carboxylic acid in good conversion and selectivity under a normal pressure of dioxygen by the use of NHPI and Co(II) acetate as catalysts (Scheme 3-18).⁴⁰ This oxidation of toluene under an oxygen atmosphere seems to be important from ecological and industrial viewpoints as a promising strategy for oxidation.

Scheme 3-18.

3.2.3. Aerobic oxidation of amines and amides

Minisci group reported the aerobic oxidation of tertiary benzylamines, such as 1-(4-methoxyphenyl)-*N,N*-dimethylmethanamine **120** to the corresponding aromatic aldehydes by the combined use of Co(OAc)₂ with either *N*-hydroxysuccinimide (NHSI) or NHPI (Scheme 3-19).⁴¹

Scheme 3-19.

A similar mechanism as the oxidation of alcohols was proposed as shown in Scheme 3-20. In this reaction, a byproduct amide **122** was obtained due to the hydrogen abstraction of aminoalcohol intermediate **121**. No such a byproduct was obtained when α -substituted benzylic amine was employed.

Scheme 3-20.

Primary and secondary benzylamines could not be submitted to the oxidation, because the amino groups reacted with NHPI to inhibit the oxidation reaction at benzylic positions. In contrast, amide derivatives **123** prepared from primary or secondary amines could be transformed to carbonyl compounds, carboxylic acids and *N*-acetylamides (Scheme 3-21).⁴²

Scheme 3-21.

Besides the aerobic oxidations of alkanes, alcohols, and amines, many other substrates such as alkenes, alkynes, ethers, sulfide, silanes could also be efficiently oxidized by the mediation of conjugated *N*-hydroxy compounds.⁴³

3.3. Perspective

In this chapter, the oxidation reactions mediated by nitroxyls⁴⁴ and related compounds are discussed. Due to the reactive species and the oxidation mechanisms, these *N*-hydroxy compounds may be roughly classified into two types, the electron-rich non-conjugated hydroxyl amines and electron-deficient conjugated hydroxyl amines. However, as summarized above, the development of the catalytic systems has been oriented to achieve high efficiency of the oxidation, whereas the improvements toward chemoselectivity are still in need. This may provide us a challenge to develop a new type of *N*-hydroxyl amine catalysts for chemoselective oxidation reactions.

Carbonyl- π conjugated *N*-hydroxy compounds such as NHPI have been successfully used in the oxidation of alkanes and alcohols. Aryl- π conjugated *N*-hydroxy compounds are also reported mainly on their generation of nitroxyl radicals,⁴⁵ such as diphenyl nitroxyl which can be used as a radical trapper,⁴⁶ however, there is no description on the catalytic abilities concerning aryl- π conjugated *N*-hydroxy compounds such as *N*-hydroxyindoles (NHIs).⁴⁷ 1-Indolyloxyl radicals **124** are supposed as electron rich radicals as compared with carbonyl- π conjugate radicals such as PINO **90**. The author was interested in *N*-hydroxyindoles as precursors of the corresponding nitroxyl radicals **124** or the oxoammonium cations **125**, which may possess unique reactivity because of their highly conjugated and electron rich structures. It is suspected that nitroxyl radicals **124** may be readily generated from *N*-hydroxyindoles (NHI) via one-electron oxidation and that the subsequent oxidation may give oxoammonium cations **125** (Scheme 3-22). They are envisioned to be able to promote some oxidation reactions.

Scheme 3-22.

Thus, the author tried to develop a selective oxidation reaction by using *N*-hydroxyindoles as the catalysts. The catalytic reactivity of those nitroxyls and oxoammonium cations discussed in the previous sections are so strong that most of alcohols are oxidized to carbonyl compounds. Since a variety of *N*-hydroxyindoles can be prepared, it may be easy to tune-up the reactivity of their nitroxyl radicals and oxoammonium cations. Finally, as depicted in Scheme 3-23, a chemoselective catalytic method was developed for the selective aerobic oxidation of allylic and benzylic alcohols. The detail of this catalytic oxidation is discussed in the following chapter.

Scheme 3-23.

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Chapter 4. Aerobic Oxidation of Allylic and Benzylic Alcohols

Catalyzed by *N*-Hydroxyindoles and Copper(I) Chloride

4.1. Aerobic oxidations of allylic and benzylic alcohols

Oxidation of alcohols to the corresponding carbonyl compounds is a very fundamental organic transformation,¹ and chemoselective oxidation of allylic or benzylic alcohols plays an important role in organic synthesis. Many methods have been developed to achieve this purpose. The traditional ones are using activated manganese (II) dioxide,² chromium (VI) reagents (Jones reagent),³ and ruthenium (IV) reagents,⁴ but always require a stoichiometric amount or excess amounts of oxidants.

Therefore, a large number of catalytic methods have emerged since 1980s.⁵ Especially, catalytic aerobic oxidations by using a green terminal oxidant, dioxygen, are prominent in the view of economical and environmental-friendly considerations. Catalytic chemoselective aerobic oxidations of allylic and benzylic alcohols have been reported mainly on the usage of transition metal complexes as catalysts, for example, Pd, Ru, or Ir. In addition, few nitroxyls were involved in such aerobic oxidations that will be mentioned below.

4.1.1. Aerobic oxidations catalyzed by transition-metal complexes

In 1996, Kaneda et al. reported the first example of a selective aerobic oxidation using metal cluster complex catalysts, where a Pd₄ cluster was utilized to catalyze the selective dehydrogenation of allylic alcohols **126** in toluene to afford α,β -unsaturated

aldehydes **127** in good yields (Scheme 4-1).⁶ However, this palladium catalyst showed low activity for the oxidation of secondary allylic alcohols and benzyl alcohols.

Scheme 4-1.

Simple palladium complexes such as Pd(PPh₃)₄ and Pd(OAc)₂ were also successfully applied to the selective aerobic oxidations.⁷ Larock reported the Pd(OAc)₂ catalyzed oxidation of primary and secondary allylic and benzylic alcohols, where the reaction rates and the product yields are improved by adding 2.0 equivalents of NaHCO₃ (Scheme 4-2).⁸

Scheme 4-2.

In 1998, an aerobic oxidation catalyzed by ruthenium hydrotalcite was reported by Kaneda.⁹ Only allylic and benzylic alcohols were oxidized by a heterogeneous catalyst Mg₆Al₂Ru_{0.5}(OH)₁₆CO₃, which is prepared from RuCl₃, MgCl₂ and AlCl₃ hydrates. The advantage of this catalyst is the reusability without an appreciable loss of the activity and selectivity (Scheme 4-3).

Scheme 4-3.

Besides allylic or benzylic alcohols, the selective oxidations of propargylic alcohols were also achieved by the treatment of an 8-quinolate-vanadium complex and triethylamine under open air conditions (Scheme 4-4).¹⁰

Scheme 4-4.

In addition, the first example of aerobic oxidative kinetic resolution of racemic secondary alcohols **128** was achieved by using a chiral bifunctional amido Ir or Rh complex under mild conditions, in which chiral alcohols *R*-**128** were recovered with up to 99% *ee* after the transformation of *S*-alcohols **128** to ketones **129** (Scheme 4-5).¹¹

Scheme 4-5.

4.1.2. Aerobic oxidations catalyzed by combination of nitroxyls and metals

As discussed in the previous chapter, electron-rich non-conjugated nitroxyls such as TEMPO have been widely applied in the oxidation of alcohols. However, such oxidation often results in oxidation of almost all kinds of alcohols without chemoselectivity. A chemoselective aerobic oxidation catalyzed by non-conjugated nitroxyls, 2,2,4,4-tetramethyloxazolidine-*N*-oxyl (TOXYL) **130** and its derivative **125**, was recently published by Lupton with the combination of copper(II) bromide.¹² A copper-centered intermediate **132** is proposed to be involved in the reaction pathway. Firstly, *tert*-butoxide induces the formation of alkoxy copper intermediate **132**, followed by α -hydrogen abstraction to form α -alkoxy radical **133**. Then reductive elimination of aldehyde proceeds giving TOXYL-H-copper(I) complex **134**, which is reoxidized to the TOXYL-copper(II) complex **132** (Scheme 4-6). With the additive of potassium *tert*-butoxide, various benzylic alcohols were converted to aldehydes or ketones. Some allylic alcohols also successfully achieved the oxidation, but 1-phenylethanol was found hard to be oxidized. The disadvantage of this process is the requirement of long reaction time.

Scheme 4-6.

Thus, chemoselective oxidation reactions of allylic and benzylic alcohols under oxygen atmosphere have been achieved by the above kinds of methods, including the transition-metal- and nitroxyl-catalyzed oxidations. However, quite limited examples of nitroxyl-mediated oxidations have been developed. There has been no report on an aerobic oxidation of alcohols in which a conjugated type of nitroxyl was involved.

4.2. Project proposal

As mentioned in the last chapter, the oxidation of alcohols can be catalyzed by some nitroxyls, for example, stable non-conjugated electron-rich 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) **88** and reactive carbonyl- π conjugated electron-deficient phthalimido-*N*-oxyl (PINO) **90** (Figure 4-1). However, the catalytic reactivity of those nitroxyls or corresponding oxoammonium cations are so strong that almost all types of alcohols are oxidized to carbonyl compounds without chemoselectivity.

Figure 4-1.

As far as we know, there is no description on the catalytic abilities of an aryl- π conjugated type of *N*-hydroxy compounds, such as *N*-hydroxyindoles.¹³ Envisioning that the N-OH group of *N*-hydroxyindoles (NHI) may act as precursors of nitroxyl radicals **124** and their reactivity is readily tuned by substituents on the indole moiety, such radical species **124** are expected to serve as mild hydrogen abstractors. In addition, the subsequent oxidation would result in oxoammonium cations **125**, which are supposed to promote oxidation of alcohols (Scheme 4-7).

Scheme 4-7.

Therefore, the author studied the catalytic abilities of *N*-hydroxyindoles (NHI) in the aerobic oxidation of allylic and benzylic alcohols in detail (Scheme 4-8).

Scheme 4-8.

4.3. Results and discussion

4.3.1. Preparation of substituted *N*-hydroxyindoles

Most of *N*-hydroxyindoles (NHIs) were synthesized via two-step reactions, that is the nucleophilic substitution of various *ortho*-fluoronitrobenzenes **135** with acetoacetates to afford 3-hydroxy-2-(2-nitrophenyl)but-2-enoates **136**,¹⁴ which were next submitted to a catalytic hydrogenation¹⁵ (Scheme 4-9). Catalyzed by a mixture of Pd/C and (Ph₃P)₄Pd, hydrogenation of enonates **136** took place to afford the cyclized product *N*-hydroxyindoles NHI-**1** to NHI-**9** in good yields (Table 4-1). However, *N*-hydroxyindoles NHI-**12** and NHI-**13** could not be obtained due to the stability, where a donating group, methyl group was introduced on the C3 position.

Scheme 4-9.

Table 4-1. Preparation of *N*-hydroxyindoles (NHI-**1** to **9**)

<i>N</i> -Hydroxyindoles (NHI) (reaction time, isolated yield prepared from 136):			
 NHI-1 (12 h, 80%)	 NHI-2 (6 h, 84%)	 NHI-3 (overnight, 63%)	 NHI-12 (unstable)
 NHI-4 (1 d, 88%)	 NHI-5 (overnight, 97%)	 NHI-6 (overnight, 82%)	 NHI-13 (unstable)
 NHI-7 (overnight, 78%)	 NHI-8 (overnight, 94%)	 NHI-9 (overnight, 50%)	

During the hydrogenation reaction, the co-catalyst, $(\text{Ph}_3\text{P})_4\text{Pd}$ acts as a poisoning agent towards the Pd/C catalyst and helps the formation of hydroxylamine intermediate, followed by the ring closure of the hydroxylamine intermediate onto the carbonyl group (Scheme 4-10).

Scheme 4-10.

Two additional *N*-hydroxyindoles NHI-**10** and NHI-**11** were prepared through a route starting from *ortho*-nitrophenylpropanoates **137** as shown in Scheme 4-11.¹⁶

Scheme 4-11.

4.3.2. Electrochemical study of NHI-1, NHI-4 and NHI-5

In order to study the redox potentials of the *N*-hydroxyindoles, cyclic voltammetry (CV) experiments were conducted for NHI-1, NHI-4 and NHI-5. By cyclic voltammetry (CV) measurements, NHI-1 demonstrates two oxidation peaks at around +0.6 V and +1.1 V, respectively (Figure 4-2).

The observation of two oxidation peaks in Figure 4-2 is consistent with our hypothesis that NHI-1 may be first oxidized to nitroxyl radical **124a** by one-electron oxidation and be further oxidized to oxoammonium cation **125a** (Scheme 4-12). No reverse peak for the second oxidation peak is found, while a weak reverse peak for the first oxidation peak is observed at round +0.05 V. These results suggest the reversibility of the transformation from NHI-1 to nitroxyl radical **124a**, while the oxidation of **124a** to oxoammonium cation **125a** is likely irreversible.

Figure 4-2. Cyclic voltammogram of NHI-1

Scheme 4-12.

The difference in the first oxidation potentials of *N*-hydroxyindoles NHI-1, NHI-4 and NHI-5 can be identified from Figure 4-3. NHI-1 exhibits a higher E_{pa} (+0.589 V) value as compared with those of NHI-4 (+0.463 V) and NHI-5 (+0.418 V), which indicates that NHI-1 possesses highest oxidation potential among these three *N*-hydroxyindoles. The difference of the three *N*-hydroxyindoles in structures is that NHI-1 having the strong electron-withdrawing group $-CF_3$ which makes it hard to be oxidized (lose one electron) to the corresponding nitroxyl radical **124a** as compared with the other two *N*-hydroxyindoles. The reverse peaks were observed in all three compounds.

Figure 4-3. Cyclic voltammogram of three *N*-hydroxyindoles

4.3.3. Preliminary study of the oxidation of alcohols catalyzed by NHIs

At the very beginning of this project, by referring Semmelhack's method using TEMPO and copper(I) chloride in DMF solution,¹⁷ a similar combination of *N*-hydroxyindoles (NHI-8 and NHI-11) and copper(I) chloride in DMF was applied to the oxidation of several alcohols.

N-Hydroxyindoles exhibited some interesting characters in the oxidation of alcohols to carbonyl compounds in the following rough screening (Scheme 4-13). In

DMF under an atmospheric oxygen at room temperature, in the presence of 10 mol% *N*-hydroxyindole (NHI) and 10 mol% CuCl, only an allylic alcohol, cinnamyl alcohol was oxidized to cinnamaldehyde, whereas oxidation of non-allylic type primary alcohols such as 3-phenylpropanol and 2-(4-methoxyphenyl)ethanol did not take place at all. In addition, NHI-**8** showed higher catalytic activity than NHI-**11** in the oxidation of cinnamyl alcohol.

Scheme 4-13.

(*E*)-2-Hexenol **138** was also partly oxidized to (*E*)-hex-2-enal **139** under the similar reaction conditions. NHI-**5** was found to give better results as compared with NHI-**8** (Scheme 4-14). Thus, a chemoselective aerobic oxidation of allylic alcohols proceeded with *N*-hydroxyindoles and copper(I) chloride as catalysts, although the yield was not satisfactory.

Scheme 4-14.

In order to study the role of copper(I) chloride as a co-catalyst and to improve the reaction efficiency, utilizing NHI-5 as the catalyst, some other transition-metals and additives were next roughly screened for the oxidation of 2-hexenol **138**. As shown in Table 4-2, some transition-metal compounds such as Cu, Fe, Ag, Co salts were tested, among which CuCl gave the best outcome although there remained 2-hexenol. Addition of *N,N,N',N'*-tetramethylethane-1,2-diamine (TMEDA) was found to inhibit the reaction, presumably by coordinate to the copper salt.

Table 4-2. Screening of different transition-metals

$ \begin{array}{ccc} \text{CH}_3\text{CH}_2\text{CH}=\text{CHCH}_2\text{OH} & \xrightarrow[\text{DMF, r.t. 48h}]{\text{O}_2} & \text{CH}_3\text{CH}_2\text{CH}=\text{CHCHO} \\ \textbf{138} & & \textbf{139} \end{array} $		
screen reaction conditions:	crude NMR ratio of S.M.:pdt.
(NHI-5)	20% / CuCl 10%	1 : 3
	20% / CuI 10%	1 : 0.17
	20% / COOCu(I) 10%	1 : 0.12
	20% / FeCl ₃ 10%	trace pdt.
	20% / FeCl ₂ 10%	trace pdt.
	20% / AgNO ₃ 10%	trace pdt.
	20% / Co(OAc) ₂ 10%	1 : 0.09
	20% / CuCl 10% / (CH ₃) ₂ NCH ₂ CH ₂ N(CH ₃) ₂ 10%	N.R.
	20% / CuCl ₂ 10% / (CH ₃) ₂ NCH ₂ CH ₂ N(CH ₃) ₂ 10%	N.R.
	10% / CuCl ₂ 10% / (CH ₃) ₂ NCH ₂ CH ₂ N(CH ₃) ₂ 10% / <i>t</i> BuOK 10%	trace pdt.
	10% / Cu(OAc) ₂ 150 %	1 : 0.16

Therefore, CuCl was chosen as the sole co-catalyst with *N*-hydroxyindoles for the chemoselective oxidations of allylic alcohols. A detailed discussion on the optimization of the reaction conditions was next described.

4.3.4. Aerobic oxidation of allylic and benzylic alcohols catalyzed by *N*-hydroxyindole and copper(I) chloride

4.3.4.1. Optimization of the oxidation conditions

The detailed study on the chemoselective oxidations of alcohols was started from comparing efficiencies of various *N*-hydroxyindoles (NHIs). By using the oxidation of 3,5,5-trimethylcyclohex-2-enol **140a** into 3,5,5-trimethylcyclohex-2-enone **141a** as the model example, optimization of the reaction conditions was carried out with catalytic amounts of NHI and CuCl under an oxygen atmosphere (Scheme 4-15).

Scheme 4-15.

Under the same reaction conditions, 10 mol% of NHI and 10 mol% CuCl in DMF at 50 °C for 4 h, various NHIs were screened for the oxidation. NHIs having electron-withdrawing substituents catalyzed the oxidation more effectively than NHIs bearing electron-donating R^3 groups (Table 4-3, from entry 1 to 6, NHI-1 to NHI-6). The introduction of a bulky R^1 group at the C2 position of the indole slowed down the rate of

the oxidation (Table 4-3, NHI-7 and NHI-10). Although all these *N*-hydroxyindoles catalyzed the aerobic oxidation of **140a**, *tert*-butyl 1-hydroxy-2-methyl-6-trifluoromethyl-1*H*-indole-3-carboxylate (NHI-1) was found to be the best catalyst. These results are consistent with the electrochemical characters of NHIs (section 3.2.), where NHI-1 exhibits a higher oxidation potential as compared with others because of the strong electron-withdrawing effect of trifluoromethyl group.

Table 4-3. Screening of different *N*-hydroxyindoles^a

entry	NHI				conv. (%) ^b	yield (%) ^b	
1		R ³ =	6-CF ₃	NHI-1	97	93	
2			6-Br	NHI-2	89	75	
3			6-F	NHI-3	82	73	
4			5-F	NHI-4	84	74	
5			H	NHI-5	79	64	
6			6-Me	NHI-6	76	65	

		R ¹	R ²	R ³			
7		<i>i</i> -Pr	<i>t</i> -Bu	H	NHI-7	62	60
8		Me	Et	Me	NHI-8	82	76
9		H	Et	H	NHI-9	66	61
10		COO ^{<i>t</i>} Bu	<i>t</i> -Bu	H	NHI-10	74	64

^a All reactions were performed using alcohol (0.25 mmol) in DMF (0.5 mL) at 50 °C.

^b Determined by GC analysis using biphenyl as an internal standard.

Among various solvents including DMF, DMSO and toluene, DMF gave the best reaction efficiency (Table 4-4). The oxidation reaction was faster at 50 °C than at room temperature (Table 4-4, entry 3). As the reaction hardly proceeded with either NHI-1 (Table 4-4, entry 10) or CuCl (Table 4-4, entry 11) alone, both of NHI-1 and CuCl were necessary for this aerobic oxidation.

Table 4-4. Optimization of the reaction conditions^a

entry	x	solvent	time (h)	conv. (%) ^b	yield (%) ^b
1	10	DMF	4	97	93
2	5	DMF	4	75	64
3 ^c	10	DMF	12	89	52
4	10	DMSO	4	38	29
5	10	DCE	4	59	33
6	10	CH ₂ Cl ₂	4	32	20
7	10	CH ₃ CN	4	89	73
8	10	PhCH ₃	4	30	30
9	10	CH ₃ OH	4	62	56
10 ^d	10	DMF	24	< 1	--
11 ^e	0	DMF	24	< 1	--

^a All reactions were performed using alcohol (0.25 mmol) in DMF (0.5 mL) at 50 °C.

^b Determined by GC analysis using biphenyl as an internal standard.

^c Reaction was run at room temperature.

^d Reaction was run using 10 mol% NHI-1 without CuCl.

^e Reaction was run using 10 mol% CuCl without NHI-1.

4.3.4.2. Aerobic oxidation of allylic and benzylic secondary alcohols

The scope and limitations of this aerobic oxidation were next explored using the optimized conditions: NHI-1 (10 mol%) and CuCl (10 mol%) as catalysts in DMF at 50 °C under an atmospheric pressure of oxygen. Firstly, the aerobic oxidation of various

secondary benzylic and allylic alcohols **140** were investigated as summarized in Table 4-5. Benzylic alcohols, such as 1,2,3,4-tetrahydronaphthalenol **140b** and 2,3-dihydroindanol **140c** were oxidized smoothly to the corresponding ketones even by reducing the catalyst loading to 5 mol% (Table 4-5, entries 2 and 3). Cyclic and acyclic secondary allylic alcohols were oxidized to afford α,β -unsaturated ketones in good isolated yields (Table 4-5, entries 1, 4 and 5).

Table 4-5. NHI-1 catalyzed oxidation of allylic secondary alcohols **140**^a

entry	alcohols 140	time/h	ketones 141 (yield/%) ^b
1	140a	12	141a (83)
2 ^c	140b	10	141b (92)
3 ^c	140c	16	141c (91)
4	140d	8	141d (84)
5	140e	15	141e (76)

^a All reactions were carried out using alcohol (2.0 mmol) in DMF (4 mL).

^b Isolated yield.

^c 5 mol% catalyst loading.

When a non-allylic alcohol, 4-phenylbutan-2-ol was submitted to the oxidation under the same reaction conditions, the oxidation proceeded very sluggishly to give 4-

phenylbutan-2-one in 5% yield after 5 h, and in 17% yield after 60 h (Scheme 4-16). This result indicated that the present catalyst system was not completely chemoselective, while this selective oxidation allylic alcohols over non-allylic ones would be viable because of the very slow oxidation of the latter.

Scheme 4-16.

The competitive oxidation between allylic and non-allylic alcohol moieties was examined with diols **140f** and **140g** with a steroid skeleton. Notably, only the allylic alcohol moiety was oxidized, whereas the other one was not affected (Scheme 4-17).

Scheme 4-17.

Thus, chemoselective oxidation (allylic vs. non-allylic) was achieved by applying *N*-hydroxyindole NHI-1. In order to compare our method with the conventional *N*-hydroxy compounds, two comparative experiments were carried out for the oxidation of

diol **140g** (Scheme 4-18). One employed Semmelhack's method¹⁷ (10 mol% TEMPO and 10 mol% CuCl) for the oxidation of diol **140g** at 50 °C in DMF, where chemoselective oxidation of allylic alcohol occurred but in only 23% yield after 24 h. Even after a longer reaction time, the product yield was still very low (48 h, 37% yield). Another experiment was performed with Anelli's method¹⁸ using TEMPO (10 mol%), NaOCl (150 mol%) in CH₂Cl₂ at 0 °C, where the diol **140g** was oxidized to ketone **141g** in only 50% yield even though **140g** was completely consumed. These results demonstrate that the selective oxidation of allylic alcohols by using *N*-hydroxyindoles and CuCl provides a more efficient way.

Scheme 4-18.

As another characteristic of this method, a significant reactivity difference was observed in the oxidation of stereoisomers of cyclic allylic alcohols. For example, the reaction of diastereomeric mixture (*cis/trans* = 1/1) of 2-methyl-5-(1-methylethenyl)-2-cyclohexen-1-ol (carveol) **140h** afforded (*R*)-carvone **141h** in 42% yield after 24 h, while *trans*-**140h** was near completely recovered (Scheme 4-19, eq. a). In fact, oxidation of *cis*-**140h** (*cis/trans* >95:5) afforded ketone **141h** in 86% yield after 24 h together with 3% recovery of *trans*-**140h** (Scheme 4-19, eq. b), whereas *trans*-**140h** (*trans/cis* > 93:7) was oxidized in a slow rate (48 h, 23% yield) (Scheme 4-19, eq. c). Even by increasing the

catalyst loading and the reaction temperature to 30 mol% and 80 °C respectively, (*R*)-carvone **141h** was obtained in 27% yield after 44 h.

Scheme 4-19.

A similar phenomenon was also observed in the oxidation of secondary polycyclic allylic alcohols. Under the same reaction conditions, it took a longer time to oxidize the α -isomer of cholest-4-en-3-ol **140j** to 4-cholesten-3-one **141i** (Scheme 4-20, 24 h, 76% yield) as compared with the oxidation of the β -isomer **140i** (3 h, 81% yield). The oxidation of the less active stereoisomer **140j** could be accelerated (6 h, 72% yield) by modifying the catalytic conditions (30 mol% of NHI-1 and CuCl, 80 °C).

Scheme 4-20.

Hereby, chemoselective aerobic oxidations of a variety of *sec*-allylic and benzylic alcohols were accomplished using the catalytic NHI-1/CuCl system. The oxidation of primary alcohols was next investigated.

4.3.4.3. Aerobic oxidation of allylic and benzylic primary alcohols

Under the catalytic conditions using NHI-1 (10 mol%) and CuCl (10 mol%) in DMF at 50 °C under oxygen atmosphere, allylic and benzylic primary alcohols **142a-d** were transformed into the corresponding aldehydes **143a-d** in good yields (Table 4-6). In the oxidation of allylic primary alcohols, small amounts of the corresponding carboxylic acids **144** were detected as minor products. The formation of the carboxylic acids could not be suppressed completely, since the aldehydes were slowly autoxidized to carboxylic acids under the present reaction conditions.

Table 4-6. NHI-1 catalyzed oxidation of allylic primary alcohols **142**^a

entry	alcohols 142	time/h	aldehydes 143 (yield/%) ^b	carboxylic acid 144 (yield/%) ^b (S.M. recov. /%) ^c
1	142a	11	143a (85)	144a (13)
2	142b	12	143b (75)	144b (9)(8)
3	142c	24	143c (61)	144c (13)(3)
4	142d	18	143d (52)	144d (12)(3)

^a All reactions were carried out using alcohol (2.0 mmol) in DMF (4 mL).^b Isolated yield.

Upon the oxidation of (*E*)-tridec-2-en-1-ol **142e**, the corresponding aldehyde **143e** was obtained in 66% yield along with formation of carboxylic acid **144e**, and (*E*)-4-oxotridec-2-enal **145** in a 14% and 4% yields, respectively, which likely formed via over oxidation of **143e** (Scheme 4-21).

Scheme 4-21.

A non-allylic primary alcohol, 3-phenylpropan-1-ol was not oxidized even after two days (Scheme 4-22) again demonstrating the chemoselectivity of the *N*-hydroxyindole and copper(I) chloride catalyzed oxidation.

Scheme 4-22.

4.3.5. Mechanistic study

In order to check whether dioxygen was incorporated into the resulting carbonyl compounds, the aerobic oxidation was conducted under an $^{18}\text{O}_2$ atmosphere. When the oxidation of 1,2,3,4-tetrahydronaphthalen-1-ol **140b** was examined under $^{18}\text{O}_2$, no introduction of ^{18}O was observed in the product **141b** by HRMS study (Scheme 4-23). This indicates that the carbonyl oxygen of the ketone **141b** must originate from the hydroxyl group of the alcohol **140b**.

Scheme 4-23.

As discussed in Scheme 4-12, two active catalytic species, a nitroxyl radical **124a** and an oxoammonium salt **125a**, are considered to be generated in the reaction. Accordingly, two possible mechanisms may be proposed for this chemoselective oxidation. In one of them, the CuCl-O_2 complex¹⁹ oxidizes NHI-1 to the corresponding

oxoammonium cation **125a** (Scheme 4-24, path A), which oxidizes allylic alcohols **140** via the alcohol-addition intermediate **I**.

Another possibility is the formation of a nitroxyl radical **124a** from NHI-1 (Scheme 4-24, path B), which abstracts an allylic hydrogen via a copper centered intermediate²⁰ **II** to generate an α -hydroxy allylic radical **III**. This allylic radical **III** is then oxidized to an allylic cation, followed by deprotonation to give the carbonyl compound **141**.

Scheme 4-24.

Both of the mechanisms are possible, while path B (the hydrogen abstraction by a nitroxyl radical mechanism) is more likely, because oxoammonium cation **125a** (path A) is considered to be a strong oxidant which would oxidize a wide range of alcohols. As

only allylic or benzylic alcohols were oxidized. A weak hydrogen abstractor, nitroso radical **124a**, is able to abstract only allylic and benzylic hydrogens selectively.

At the end of the oxidation reaction, about 65% of NHI-**1** was always recovered. As discussed in the CV measurement (Scheme 4-12), the one-electron oxidation of NHI-**1** to nitroxyl radical **124a** is reversible but the oxidation to oxoammonium salt **125a** is not reversible. Therefore, the recovery of NHI-**1** indicates the transformation between NHI-**1** and the nitroxyl radical **124a** should be the more plausible pathway (path B).

Based on the path B mechanism, the reactivity difference in the oxidation of stereoisomers of cyclic allylic alcohols **140h** where the oxidation of *cis*-**140h** proceeds faster than *trans*-**140h** (Scheme 4-19), can be rationalized by looking into their conformations. Figure 4-4 shows the stable conformations of two isomers,²¹ in which the 2-propenyl group is located at the *pseudo*-equatorial position (The A value of a 2-propenyl group is about 2.1 kcal mol⁻¹ which is larger than that of a hydroxy group, i.e., 0.60-1.04 kcal mol⁻¹).²² Thus, in the stable conformations, the allylic hydrogen atoms of *cis*-**140h** and *trans*-**140h** are located at the *pseudo*-axial position and *pseudo*-equatorial positions, respectively.

Figure 4-4.

Let us look into the structure of the proposed copper centered intermediate **II** (Figure 4-5) in path B (Scheme 4-24). Firstly, the axial protons are reported more reactive than equatorial protons in radical abstraction reactions.²³ For example, bond length of the axial C-H (1.0996 Å) in cyclohexane is longer than that of equatorial C-H (1.0967 Å).^{23c} Therefore, abstraction of the *pseudo*-axial proton of **II-cis-140h** by nitroxyl radical should be more preferable than that of the *pseudo*-equatorial proton of **II-trans-140h**. In addition, there may exist a steric repulsion between the nitroxyl group and the neighboring methyl group in the conformation **II-A** (**II-trans-140h**). In the alternative conformation **II-B**, the 2-propenyl group would cause steric repulsion with the nitroxyl group. On the other hand, **II-cis-140h** does not suffer from such interactions. Due to these factors, the oxidation of *trans*-**140h** proceeds more slowly than that of the *cis*-isomer.

Figure 4-5.

A stereoselectivity was observed in the oxidations of *cis*-4-substituted cyclohexanols and *trans*-4-substituted cyclohexanols,²⁴ as shown in Scheme 4-25. By using TEMPO as the catalyst, only the *cis*-isomer, in which the α -proton is at the equatorial position, was transformed to a cyclohexanone derivative, while the *trans*-isomer remained intact. In the TEMPO oxidation, the deprotonation process was proposed

to be the rate-determine step, and the *cis*-isomer intermediate suffers the diaxial repulsion, which pushes the oxygen anion closer to the equatorial-proton and accelerates the deprotonation, while the *trans*-isomer does not. As the results, the oxidation of the *cis*-isomers was faster than that of the *trans*-isomers.

Scheme 4-25.

By following the above explanation and looking into the conformations of oxoammonium-intermediate **I** (Figure 4-6) in path A (Scheme 4-24), the allylic hydrogen of **I-*trans*-140h** is located at the *pseudo*-equatorial position and suffers from the diaxial repulsion. This predicts that the oxidation of ***trans*-140h** should be faster than that of ***cis*-140h**. However, it is inconsistent with the experimental results that ***cis*-140h** is more rapidly oxidized than ***trans*-140h**.

Figure 4-6.

Therefore, based on the above discussions, the hydrogen abstraction by the nitroxyl radical pathway (path B) should be the reasonable mechanism for this aerobic chemoselective and stereoselective oxidation of alcohols.

The reactivity difference in the oxidation of the α - and β -isomers of cholest-4-en-3-ol (**140i** and **140j**) (Figure 4-7) can also be explained according to path B. Thus, abstraction of the *pseudo*-axial proton in **140i** by the nitroxyl radical proceeds much more easily than that of the *pseudo*-equatorial proton of **140j**.

Figure 4-7.

In addition, the observation of 4% yield of (*E*)-4-oxotridec-2-enal **145** during the oxidation of (*E*)-tridec-2-en-1-ol **142d** (Scheme 4-21) also suggests the allylic hydrogen abstraction by the nitroxyl radical should take place.

4.4. Conclusions

In conclusion, various *N*-hydroxyindoles have been applied to the oxidation of alcohols with the combination of copper(I) chloride. *Tert*-butyl 1-hydroxy-2-methyl-6-(trifluoromethyl)-1*H*-indole-3-carboxylate (NHI-1) acts as a highly chemoselective catalyst in the aerobic oxidation of alcohols, where only allylic and benzylic alcohols could be oxidized to the corresponding carbonyl compounds.

By using NHI-1 and copper(I) chloride, both primary and secondary allylic and benzylic alcohols were oxidized in good yields. In addition, this catalyst system was found to exhibit a good stereoselectivity in the oxidation of stereoisomers of cyclic allylic alcohols. This catalytic method would provide a good tool for the selective aerobic oxidation of alcohols.

4.5. References and notes

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Chapter 5. Summary and Perspective

5.1. Part I

Despite the general acceptance of the concerted nucleophilic substitution at sp^3 carbons as an important fundamental reaction in organic chemistry, such nucleophilic substitution at an sp^2 carbon has been thought to hardly take place. However, a series of theoretical and experimental examples have been reported to prove the feasibility of the vinylic nucleophilic substitutions. Recently, Narasaka's group has explored the nucleophilic substitution at the sp^2 nitrogen and carbon atoms. For example, the nucleophilic substitution of vinyl bromides with intramolecular thiolate moieties was found to successfully afford four-, five- and six-membered cyclic sulfides, in a reaction rate in the order of four- > five- > six-membered ring formation (Scheme 5-1).

Scheme 5-1.

In this thesis project, the author studied the intramolecular cyclization of vinyl bromides with intramolecular thioamide or thiourea moieties to develop a synthetic method of series of five-membered heterocycles, as depicted in Scheme 5-2. In chapter 2.1 was described the successful preparation of various 2,5-disubstituted thiazoles **36** via the intramolecular *S*-attack of *N*-2-bromoalk-2-enylthioamides **34**. The cyclization of thioamide analogues such as carbamodithionate and thiourea was also carried out,

affording the corresponding thiothiazoles and aminothiazoles in low to moderate yields. In chapter 2.2, the cyclization of *N*-(2-bromoprop-2-enyl)thioureas **55** was examined, which afforded 3,4-trisubstituted imidazole-2-thiones **56** as a major product via the intramolecular *N*-attack, along with a minor product, thiazolidin-2-imines **74**.

In contrast to the five-membered ring formations, a drastic change of reaction conditions was required for the cyclization to six-membered rings. As discussed in chapter 2.4, the intramolecular cyclization of *N*-2-bromo homoallylic thioamides **77** proceeded in the presence of a strong base and water to form the six-membered ring products, 1,3-thiazines **78** (Scheme 5-3). Under these reaction conditions, the intramolecular vinylic nucleophilic substitution is not the only possible reaction pathway, and another pathway involving the formation of acetylene by dehydrobromination and the subsequent nucleophilic addition is also proposed as the main route.

Scheme 5-3.

Thus, the synthesis of five- and six-membered heterocycles has been achieved based on the intramolecular vinylic nucleophilic substitution. Although the vinylic nucleophilic substitution has been neglected as a synthetic tool, these results demonstrated significant potential utility of the vinylic substitution in organic synthesis.

Accordingly, as future plans, a wide range of heterocycles including three-, four-, five-membered rings are proposed to be prepared via vinylic nucleophilic substitutions (Scheme 5-4). During the study of the thiazole formation, a three-membered ring aziridine **37b** was obtained in 28% yield via the intramolecular *N*-attack of thioamides (Scheme 2-24). It is expected that the three-membered ring compounds may be obtained by designing suitable substrates and modifying the reaction conditions, which serve as useful building blocks in organic synthesis due to their high reactivity. Furthermore, four-membered heterocycles might be prepared by reducing one carbon unit of *N*-2-bromoalk-2-enylthioamides **34**.

Scheme 5-4.

5.2. Part II

Oxidation reactions catalyzed by *N*-hydroxy compounds have been well developed for the decades. For example, there have been developed oxidations of alkanes or alcohols catalyzed by a carbonyl- π conjugated *N*-hydroxy compound such as *N*-hydroxyphthalimide (NHPI) and the oxidation of alcohols catalyzed by a non-conjugated *N*-hydroxy compound, 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO). However, all the oxidation reactions catalyzed by *N*-hydroxyl amines focused on the achievement of high efficiency, leaving a room for the improvement of chemoselective oxidation.

Accordingly, the author planned to use a new type of *N*-hydroxy compounds as catalyst to achieve high chemoselective oxidation of alcohols. *N*-hydroxyindoles (NHI) are a kind of aryl- π conjugated *N*-hydroxy compounds with highly conjugated and electron rich structures. Their catalytic abilities have never been surveyed. Their oxidation would give nitroxyl radicals or oxoammonium cations, which would serve as reactive species for the oxidation of alcohols (Scheme 3-22).

In chapter 4 was described the aerobic oxidation of allylic and benzylic alcohols catalyzed by *N*-hydroxyindole and copper(I) chloride. Several *N*-hydroxyindoles have been prepared, among which *tert*-butyl 1-hydroxy-2-methyl-6-(trifluoromethyl)-1*H*-indole-3-carboxylate (NHI-1) worked as the most reactive and chemoselective catalyst. Primary and secondary allylic and benzylic alcohols were selectively oxidized to the corresponding carbonyl compounds in good yields without affecting ordinary alcohols (Scheme 5-5). In addition, this catalyst system was found to exhibit a considerable stereoselectivity in the oxidation of stereoisomers of cyclic allylic alcohols, where the equatorial alcohols are oxidized preferentially to the corresponding axial ones. Through

some mechanistic studies, this aerobic oxidation was found to be catalyzed by the nitroxyl radical of NHI-1 as the real active species.

Scheme 5-5.

This catalytic system is expected to provide a good method for a broad range of selective aerobic oxidations. For example, the oxidation reaction of diols with two allylic or benzylic alcohol moieties would produce diketones and dialdehydes. Furthermore, the oxidation of secondary amines to the corresponding ketones and the oxidation of benzylic or allylic hydrogen of alkanes to form alcohols or carbonyl compounds would also proceed with this catalytic system as shown in Scheme 5-6.

Scheme 5-6.

Chapter 6. Experimental

6.1. General

^1H NMR (300, 400 and 500 MHz) spectra were recorded on a Bruker Avance 300, 400 and 500 spectrometer respectively, in CDCl_3 [using CHCl_3 (for ^1H , $\delta = 7.26$) as internal standard] or in $\text{DMSO}-d_6$ [using DMSO (for ^1H , $\delta = 2.50$) as internal standard]. ^{13}C NMR (75, 100 and 125 MHz) spectra on a Bruker Avance 300, 400 and 500 spectrometers respectively, in CDCl_3 [using CHCl_3 (for ^{13}C , $\delta = 77.0$) as internal standard] or in $\text{DMSO}-d_6$ [using DMSO (for ^{13}C , $\delta = 39.5$) as internal standard]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. IR spectra were recorded on a Shimadzu IR Prestige-21 FT-IR Spectrometer. High-resolution mass spectra were obtained with either a Q-ToF Premier LC HR mass spectrometer or a Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). Melting points are uncorrected and were recorded on a Buchi B-54 melting point apparatus. 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. Gas chromatographic (GC) analysis was performed on a Shimadzu GC-2010 system equipped with an FID detector and a capillary column, DB-35 MS (0.25 mm i.d. $\times$ 30 m, 0.25 μm film thickness). The GC method is: started at 80 °C for 2 min, then heat to 250 °C at the rate of 35 °C /min, hold for 5 min.

The cyclic voltammetry (CV) experiments were conducted with a computer controlled Metrohm Autolab PGSTAT302N potentiostat. DMF solution of *N*-

hydroxyindole (1 mM) was used throughout the CV measurement. The working electrode was a 1 mm GC (glassy carbon) disk, used in conjunction with a Pt auxiliary electrode (Metrohm) and an Ag wire miniature reference electrode connected to the test solution via a salt bridge containing 0.5 M Bu₄NPF₆ in DMF. Cyclic voltammograms obtained at 22 ± (2) °C at a scan rate of 100 mV s⁻¹. Reference compound was Ferrocene.

All chemicals were purchased from Alfa Aesar, Merck, Sigma-Aldrich, Sinopharm Chemical and used without purification, unless otherwise stated. Dry tetrahydrofuran (THF), diethyl ether (Et₂O), and dichloromethane (CH₂Cl₂) were taken from a solvent purification system (PS-400-5, innovative technology Inc.). 1,3-Dimethyl-2-imidazolidinone (DMI) and *N,N*-dimethylformamide (DMF) were distilled from calcium hydride (CaH₂) and stored over Molecular Sieves 4Å (MS 4Å). Triethylamine (Et₃N) and pyridine were distilled from CaH₂ and stored over potassium hydroxide (KOH).

6.2. Experimental procedure for part I, chapter 2

6.2.1. Synthesis of 2,5-disubstituted thiazoles

Typical procedure for the synthesis of N-(2-bromoallyl)benzamide (39a):

At 0 °C, to a stirred solution of 2-bromopro-2-en-1-amine **38a** (0.53 g, 3.9 mmol) and Et₃N (0.6 mL, 4.3 mmol) in CH₂Cl₂ (15 mL) was added benzoyl chloride (0.5 mL, 3.9 mmol). The mixture was stirred at room temperature for 2 h, and was quenched with

diluted aqueous HCl solution, the organic materials were extracted with CH₂Cl₂ (10 mL×3). The combined extracts were washed with water and brine, and dried over MgSO₄, then concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel; hexane : ethyl acetate = 4 : 1 to 2 : 1) to give *N*-(2-bromoallyl)benzamide **39a** (0.65g, 2.7 mmol) in 70% yield.

White solid; m.p. 93-94 °C; *R*_f = 0.21 (silica gel; hexane : ethyl acetate = 8 : 1); ¹H NMR (400 MHz, CDCl₃) δ 7.79 (2H, dd, *J* = 1.4, 7.3 Hz), 7.51-7.55 (1H, m), 7.43-7.47 (2H, m), 6.53 (1H, br, s), 5.89 (1H, d, *J* = 1.0 Hz), 5.60 (1H, d, *J* = 1.0 Hz), 4.32 (2H, d, *J* = 6.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 167.2, 134.0, 131.9, 129.4, 128.7, 127.0, 118.3, 47.9; IR (NaCl, CHCl₃) ν 3449, 3329, 3065, 3017, 2918, 1643, 1580, 1520, 1487, 1418, 1290, 1113, 893 cm⁻¹; HRMS (ESI) calcd for C₁₀H₁₁BrNO (M⁺H⁺): 240.0024, found: 240.0023.

Compounds **39b-g** were prepared by following same procedure for **39a**.

***N*-(2-phenylallyl)cinnamamide (39b):**

82% Yield; white solid; m.p. 113-115 °C; *R*_f = 0.21 (silica gel; hexane : ethyl acetate = 2 : 1); ¹H NMR (400 MHz, CDCl₃) δ 7.68 (1H, d, *J* = 15.6 Hz), 7.50-7.53 (2H, m), 7.36-7.38 (3H, m), 6.44 (1H, d, *J* = 15.6 Hz), 5.98 (1H, br, s), 5.88 (1H, d, *J* = 2.0 Hz), 5.58 (1H, d, *J* = 2.0 Hz), 4.26 (2H, d, *J* = 6.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 165.7, 142.1, 134.6, 129.9, 129.3, 128.9, 127.9, 119.9, 118.2, 47.7; IR (NaCl, CHCl₃) ν 3250, 3217, 3061,

1655, 1612, 1545, 1449, 1420, 1341, 1270, 1221, 1119, 1042, 964, 889, 737, 683 cm^{-1} ;
HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{13}\text{BrNO}$ (M^+H^+): 266.0181, found: 266.0193.

***N*-(2-bromoallyl)undecanamide (39c):**

53% Yield; yellow solid; m.p. 58-60 $^{\circ}\text{C}$; R_f = 0.16 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 5.89 (1H, bs, s), 5.80 (1H, s), 5.53 (1H, s), 4.10 (2H, d, J = 6.0 Hz), 2.22 (2H, t, J = 7.6 Hz), 1.62-1.66 (2H, m), 1.25-1.29 (14H, m), 0.87 (3H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 173.0, 129.7, 117.9, 47.4, 36.7, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 25.7, 22.7, 14.1; IR (NaCl, CHCl_3) ν 3316, 3277, 2924, 2914, 1657, 1649, 1632, 1547, 1533, 1466, 1418, 1252, 1223, 1196, 1152, 907, 881 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{27}\text{BrNO}$ (M^+H^+): 304.1276, found: 304.1285.

***N*-(2-bromoallyl)thiophene-2-carboxamide (39d):**

68% Yield; white solid; m.p. 108-109 $^{\circ}\text{C}$; R_f = 0.17 (silica gel; hexane : ethyl acetate = 6 : 1); ^1H NMR (300 MHz, CDCl_3) δ 7.55 (1H, dd, J = 1.1, 3.7 Hz), 7.51 (1H, dd, J = 1.1, 5.0 Hz), 7.10 (1H, d, J = 3.7, 5.0 Hz), 6.31 (1H, br, s), 5.90 (1H, d, J = 2.1 Hz), 5.60 (1H, d, J = 2.1 Hz), 4.29 (2H, d, J = 6.0 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 161.7, 138.2, 130.5, 129.2, 128.5, 127.8, 118.4, 47.7; IR (NaCl, CHCl_3) ν 3323, 3073, 3017, 2976, 1638, 1531, 1504, 1420, 1288, 756 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_8\text{H}_9\text{BrNOS}$ (M^+H^+): 245.9588, found: 245.9598.

***N*-(2-bromoallyl)furan-2-carboxamide (39e):**

74% Yield; white solid; m.p. 74-76 °C; R_f = 0.25 (silica gel; hexane : ethyl acetate = 3 : 2); ^1H NMR (400 MHz, CDCl_3) δ 7.46 (1H, d, J = 0.9 Hz), 7.15-7.16 (1H, m), 6.69 (1H, br, s), 6.51 (1H, dd, J = 1.8, 3.4 Hz), 5.88 (1H, dd, J = 0.9, 1.1 Hz), 5.58 (1H, dd, J = 0.9, 1.2 Hz), 4.28 (2H, d, J = 6.2 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 158.0, 147.5, 144.2, 129.1, 118.2, 114.9, 112.3, 46.9; IR (NaCl, CHCl_3) ν 3053, 2986, 1670, 1593, 1520, 1476, 1422, 1180, 1015, 895 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_8\text{H}_9\text{BrNO}_2$ (M^+H^+): 229.9817, found: 229.9813.

***N*-(2-bromo-3-methylbut-2-en-1-yl)benzamide (39f):**

58% Yield; pale yellow solid; m.p. 96-98 °C; R_f = 0.38 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (500 MHz, CDCl_3) δ 7.79 (2H, dd, J = 1.4, 7.7 Hz), 7.39-7.50 (3H, m), 6.57 (1H, br, s), 4.41 (2H, d, J = 5.6 Hz), 1.93 (3H, s), 1.89 (3H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 167.2, 135.2, 134.3, 131.6, 128.6, 127.0, 117.2, 44.8, 25.4, 20.8; IR (NaCl, CHCl_3) ν 3300, 3258, 3063, 2932, 1638, 1632, 1601, 1545, 1537, 1493, 1306, 1219, 1049, 716, 696 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{15}\text{BrNO}$ (M^+H^+): 268.0337, found: 268.0338.

***N*-(2-bromocyclohex-2-en-1-yl)benzamide (39g):**

62% Yield; white solid; m.p. 158-160 °C; R_f = 0.24 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (500 MHz, CDCl_3) δ 7.80 (2H, dd, J = 1.4, 8.5 Hz), 7.50-7.53 (1H, m), 7.43-7.46 (2H, m), 6.33 (1H, t, J = 3.7 Hz), 6.25 (1H, d, J = 7.2 Hz), 4.85-4.86 (1H, m), 2.12-

2.19 (2H, m), 2.03-2.10 (1H, m), 1.94-2.00 (1H, m), 1.72-1.77 (1H, m), 1.58-1.67 (1H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 167.0, 134.5, 134.3, 131.6, 128.6, 127.0, 122.2, 51.3, 31.0, 27.6, 18.1; IR (NaCl, CHCl_3) ν 3437, 3053, 2986, 2949, 2932, 1663, 1520, 1485, 706 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{15}\text{BrNO}$ (M^+H^+): 280.0337, found: 280.0334.

Preparation of *N*-(2-Bromo-4-(4-bromophenoxy)but-2-en-1-yl)-2-chlorobenzamide (49):

To the solution of phenol (3.0 g, 30 mmol) and K_2CO_3 (4.2 g, 30 mmol) in dry acetone (100 mL) was added (*E*)-4-bromobut-2-enoate **43** (6.4 g, 33 mmol), the reaction was refluxed under nitrogen for 7 h. The reaction mixture was cooled to room temperature and quenched with water, the organic materials were extracted with Et_2O (30 mL $\times$ 3), dried over MgSO_4 , and the solvents were removed in vacuo. The crude product was purified by flash column chromatography (silica gel; hexane : ethyl acetate = 50 : 1)

to afford (*E*)-ethyl 4-phenoxybut-2-enoate **44** (5.2 g, 2.5 mmol) in 84% yield. [R_f = 0.43 (silica gel; hexane : ethyl acetate = 5 : 1); ^1H NMR (500 MHz, CDCl_3) δ 7.25-7.31 (2H, m), 7.08 (1H, dd, J = 5.0 Hz, 15 Hz), 6.98 (1H, t, J = 10 Hz), 6.91 (2H, dd, J = 5.0 Hz, 10 Hz), 6.21 (1H, t, J = 15 Hz), 4.70 (2H, d, J = 5.0 Hz), 4.21 (2H, q, J = 5.0 Hz), 1.30 (3H, t, J = 5.0 Hz)].

Bromine (0.77 mL, 15 mmol) in acetic acid (20 mL) was added in a dropwise manner into the solution of **44** (3.1 g, 15 mmol) and LiBr (1.3 g, 15 mmol) in acetic acid (50 mL), the reaction mixture was allowed to stir at 50 °C for 3 h. The reaction was quenched with $\text{Na}_2\text{S}_2\text{O}_3$ solution, and extracted with CH_2Cl_2 (15 mL $\times$ 3). The combined extracts were washed with NaHCO_3 solution, dried over MgSO_4 , and concentrated in vacuo to afford ethyl 2,3-dibromo-4-(4-bromophenoxy)butanoate **45** (6.0 g, 13.5 mmol) in 90% yield. [R_f = 0.55 (silica gel; hexane : ethyl acetate = 6 : 1); ^1H NMR (300 MHz, CDCl_3) δ 7.40 (2H, d, J = 9.0 Hz), 6.83 (2H, d, J = 9.0 Hz), 4.77 (0.35H, s), 4.73 (0.65H, s), 4.66 (0.65H, dd, J = 2.4 Hz, 3.75 Hz), 4.62 (0.35H, dd, J = 2.4 Hz, 3.75 Hz), 4.43 (0.35H, d, J = 3.0 Hz), 4.40 (0.65H, d, J = 3.0 Hz), 4.31 (2H, q, J = 6.0 Hz), 1.34 (3H, t, J = 6.0 Hz)].

45 (1.33 g, 3 mmol) was dissolved in toluene (15 mL) and added Et_3N (4.4 mL, 3.0 mmol) dropwisely, the reaction mixture was stirred at room temperature for 10 min. After removal of the solvent in vacuo, the crude was purified by flash column chromatography (silica gel; hexane : ethyl acetate = 8 : 1) to give a 1/1 mixture of *E*/*Z* isomers, ethyl 2-bromo-4-(4-bromophenoxy)but-2-enoate **46** (0.9 g, 2.5 mmol) in 84% yield. [R_f = 0.50 (silica gel; hexane : ethyl acetate = 6 : 1); ^1H NMR (300 MHz, CDCl_3) δ 7.49 (0.47H, t, J = 6.0 Hz, *Z*-CH), 7.36-7.41 (1.88H, m), 6.92 (0.53H, t, J = 6.0 Hz, *E*-CH), 6.75-6.78 (2.12H, m), 4.95 (1.06H, d, J = 4.8 Hz, *E*- CH_2), 4.76 (0.94H, d, J = 4.8 Hz, *Z*- CH_2), 4.26-4.34 (2H, m), 1.25-1.39 (3H, m)].

At room temperature, to the solution of **46** (0.9 g, 2.5 mmol) in CH_2Cl_2 (15 mL), was added DIBAL-H (6.95 mL, 6.95 mmol) in toluene (1 M) in a dropwise manner, the reaction mixture was allowed to stir for 2 h. The reaction was quenched with brine, and dried over MgSO_4 , after filtration, the filtrate was concentrated under vacuo. The crude was purified by flash column chromatography (silica gel; hexane : ethyl acetate = 4 : 1) to give a 1/1 mixture of *E/Z* isomers, 2-bromo-4-(4-bromophenoxy)but-2-en-1-ol **47** (0.64 g, 2.0 mmol) in 80% yield. [R_f = 0.21 (silica gel; hexane : ethyl acetate = 3 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.37-7.39 (1.88H, m), 6.76-6.79 (2.12H, m), 6.34 (1H, m), 4.68 (0.94H, d, J = 5.4 Hz, *Z*- CH_2), 4.57 (1.06H, d, J = 6.7 Hz, *E*- CH_2), 4.39 (1.06H, s), 4.30 (0.94H, s), 2.47-2.51 (1H, m, OH)].

To the solution of **47** (0.60 g, 1.87 mmol) in CH_2Cl_2 (20 mL) was added PBr_3 (0.112 mL, 1.2 mmol) dropwisely at 0 $^\circ\text{C}$, the reaction was stirred for several minutes, the solvent was removed under reduced pressure and the crude 1-bromo-4-((3,4-dibromobut-2-en-1-yl)oxy)benzene **48** was ready for next step. At 0 $^\circ\text{C}$, to the solution of 2-chlorobenzamide (233 mg, 1.5 mmol) in DMF (10 mL) was added NaH (60 mg, 1.5 mmol), the mixture was stirred for 0.5 h. Then, was added **48** (around 290 mg, 0.75 mmol) in DMF (5 mL), continue to stir at room temperature for 3 h. After the completion of the reaction, the reaction was quenched with water and extracted with Et_2O (10 mL $\times$ 3), the combined extracts was dried over MgSO_4 , and concentrated in vacuo. The resulted crude was purified by flash column chromatography (silica gel; hexane : ethyl acetate = 4 : 1) to give *N*-(2-Bromo-4-(4-bromophenoxy)but-2-en-1-yl)-2-chlorobenzamide **49** (70 mg, 0.15 mmol) in 20% yield, it is a single stereoisomer (*E* or *Z*) although the configuration was not confirmed.

White solid; m.p. 96-98 °C; $R_f = 0.50$ (silica gel; hexane : ethyl acetate = 2 : 1); ^1H NMR (300 MHz, CDCl_3) δ 7.68 (1H, d, $J = 9.0$ Hz), 7.32-7.41 (5H, m), 6.83 (2H, d, $J = 9.0$ Hz), 6.70 (1H, br, s), 6.34 (1H, d, $J = 6.0$ Hz), 4.75 (2H, d, $J = 6.0$ Hz), 4.42 (2H, d, $J = 6.0$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 166.3, 157.1, 132.4(3), 131.7, 130.9(2), 130.4, 130.3, 127.2, 125.2, 116.7(2), 113.6, 64.7, 43.7; IR (NaCl) ν 3248, 3059, 1653, 1593, 1541, 1487, 1431, 1285, 1242, 1171, 1115, 1072, 1036, 995, 824, 750, 694 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{Br}_2\text{ClNO}_2$ (M^+H^+): 457.9158, found: 457.9169.

Typical procedure for preparation of *N*-(2-bromoallyl)benzothioamide (34a**):**

To a stirred solution of *N*-(2-bromoallyl)benzamide **39a** (0.57 g, 2.4 mmol) in THF (15 mL) was added Lawesson's reagent (1.15 g, 2.8 mmol) at room temperature, the mixture was stirred at room temperature overnight. Then the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel; hexane : ethyl acetate = 5 : 1) to give *N*-(2-bromoallyl)benzothioamide **34a** (0.25g, 0.99 mmol) in 41% yield.

Yellow oil; $R_f = 0.33$ (silica gel; hexane : ethyl acetate = 5 : 1); ^1H NMR (500 MHz, CDCl_3) δ 7.76-7.81 (3H, m), 7.47-7.50 (1H, m), 7.39-7.42 (2H, m), 5.97 (1H, dd, $J = 1.0$, 1.9 Hz), 5.70 (1H, d, $J = 1.9$ Hz), 4.73 (2H, d, $J = 5.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 199.8, 141.5, 131.5, 128.7, 126.7, 126.6, 120.6, 53.9; IR (NaCl) ν 3237, 3219, 3026, 2916,

1722, 1632, 1595, 1518, 1487, 1449, 1373, 1323, 1279, 1221, 1098, 947, 770, 692 cm^{-1} ;
HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{11}\text{BrNS}$ (M^+H^+): 255.9796, found: 255.9792.

Compounds **34b-g** and **50** were prepared by following same procedure for **34a**.

(E)-N-(2-bromoallyl)-3-phenylprop-2-enethioamide (34b):

64% Yield; yellow oil; R_f = 0.41 (silica gel; hexane : ethyl acetate = 2 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.83 (1H, d, J = 15.3 Hz), 7.53-7.55 (2H, m), 7.49 (1H, br, s), 7.34-7.38 (3H, m), 6.87 (1H, d, J = 15.3 Hz), 5.94 (1H, d, J = 1.6 Hz), 5.67 (1H, d, J = 1.6 Hz), 4.71 (2H, d, J = 5.5 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 195.4, 142.5, 134.7, 130.1, 129.0, 128.2, 127.1, 126.6, 120.4, 53.3; IR (NaCl) ν 3390, 3019, 1634, 1514, 1387, 1215, 1179, 770, 667 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{13}\text{BrNS}$ (M^+H^+): 281.9952, found: 281.9954.

N-(2-bromoallyl)undecanethioamide (34c):

92% Yield; yellow oil; R_f = 0.38 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.53 (1H, br, s), 5.88 (1H, s), 5.63 (1H, s), 4.55 (2H, d, J = 5.4 Hz), 2.68 (2H, t, J = 7.7 Hz), 1.74-1.78 (2H, m), 1.24-1.29 (14H, m), 0.86 (3H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 206.8, 126.5, 120.2, 53.2, 47.2, 31.9, 29.6 (overlapped), 29.5, 29.4, 29.3, 28.9, 22.7, 14.1; IR (NaCl, CHCl_3) ν 3244, 3190, 3036, 2955, 2920, 2853, 1632, 1522, 1456, 1398, 1314, 1263, 1142, 1101, 953, 885, 746, 718 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{27}\text{BrNS}$ (M^+H^+): 320.1048, found: 320.1053.

***N*-(2-bromoallyl)thiophene-2-carbothioamide (34d):**

37% Yield; yellow solid; m.p. 68-70 °C; R_f = 0.43 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (300 MHz, CDCl_3) δ 7.64 (1H, br, s), 7.53 (1H, dd, J = 1.1, 5.0 Hz), 7.49 (1H, dd, J = 1.1, 3.8 Hz), 7.09 (1H, dd, J = 3.8, 5.0 Hz), 5.96 (1H, d, J = 2.2 Hz), 5.68 (1H, d, J = 2.2 Hz), 4.72 (2H, d, J = 5.6 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 189.2, 146.3, 132.7, 128.0, 126.6, 124.9, 120.3, 53.3; IR (NaCl, CHCl_3) ν 3395, 3271, 3017, 2986, 1632, 1526, 1503, 1414, 1375, 1319, 1277, 1144, 1094, 901 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_8\text{H}_9\text{BrNS}_2$ (M^+H^+): 261.9360, found: 261.9355.

***N*-(2-bromoallyl)furan-2-carbothioamide (34e):**

65% Yield; yellow oil; R_f = 0.47 (silica gel; hexane : ethyl acetate = 3 : 2); ^1H NMR (400 MHz, CDCl_3) δ 8.11 (1H, br, s), 7.47 (1H, d, J = 0.6 Hz), 7.39 (1H, d, J = 3.5 Hz), 6.50 (1H, dd, J = 1.7, 3.5 Hz), 5.93 (1H, d, J = 0.9 Hz), 5.66 (1H, d, J = 2.0 Hz), 4.70 (2H, d, J = 5.8 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 182.8, 152.0, 143.9, 126.6, 119.9, 118.4, 133.0, 52.0; IR (NaCl, CHCl_3) ν 3375, 3279, 3125, 2916, 1632, 1578, 1520, 1470, 1423, 1389, 1319, 1296, 1234, 1157, 1072, 1018, 957 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_8\text{H}_9\text{BrNOS}$ (M^+H^+): 245.9588, found: 245.9590.

***N*-(2-bromo-3-methylbut-2-en-1-yl)benzothioamide (34f):**

61% Yield; yellow solid; m.p. 138-140 °C; R_f = 0.14 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.78 (2H, d, J = 7.4 Hz), 7.74 (1H, br, s), 7.38-7.49 (3H, m), 4.81 (2H, d, J = 5.0 Hz), 1.98 (3H, s), 1.95 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 192.8, 141.6, 137.2, 131.2, 128.6, 126.8, 114.5, 51.4, 25.5, 21.2; IR (NaCl, CHCl_3) ν 3337, 3275, 2627, 1595, 1582, 1516, 1487, 1450, 1377, 1325, 1252, 1022, 932, 777, 700 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{15}\text{BrNS}$ (M^+H^+): 284.0109, found: 284.0121.

***N*-(2-bromocyclohex-2-en-1-yl)benzothioamide (34g):**

87% Yield; yellow solid; m.p. 107-108 °C; R_f = 0.32 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.78 (2H, d, J = 7.6 Hz), 7.60 (1H, br, s), 7.46-7.49 (1H, m), 7.38-7.42 (2H, m), 6.42 (1H, t, J = 4.0 Hz), 5.40-5.42 (1H, m), 2.09-2.25 (4H, m), 1.75-1.83 (1H, m), 1.59-1.65 (1H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 199.0, 142.0, 135.3, 131.2, 128.5, 126.8, 120.5, 57.0, 29.2, 27.7, 18.3; IR (NaCl, CHCl_3) ν 3379, 3053, 2986, 2951, 2930, 1641, 1503, 1485, 1422, 1368, 1350, 1234, 895 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{19}\text{BrNS}_2$ (M^+H^+): 296.0142, found: 296.0133.

***N*-(2-Bromo-4-(4-bromophenoxy)but-2-en-1-yl)-2-chlorobenzothioamide (50):**

20% Yield; yellow solid; m.p. 128-130 °C; R_f = 0.55 (silica gel; hexane : ethyl acetate = 2 : 1); ^1H NMR (300 MHz, CDCl_3) δ 7.75 (1H, br, s), 7.50-7.51 (1H, m), 7.37-7.40 (3H, m), 7.27-7.35 (2H, m), 6.81 (2H, d, J = 9.0 Hz), 6.41 (1H, t, J = 6.0 Hz), 4.83 (2H, d, J = 6.0 Hz), 4.75 (2H, d, J = 6.0 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 157.0, 141.4, 132.5(3), 132.1, 130.7, 130.1(2), 128.6, 127.1, 122.6, 116.6(2), 113.7, 65.1, 49.3; IR (NaCl) ν 3163,

3036, 2972, 2922, 1541, 1489, 1423, 1387, 1337, 1288, 1242, 1177, 1105, 1061, 1003, 957, 820, 760, 737, 665 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{Br}_2\text{ClNOS}$ (M^+H^+): 473.8930, found: 473.8927.

Phenyl (2-bromoallyl)carbamdithioate (40):

Prepared from 2-bromo-2-propenyl amine and phenyl carbonchloridodithioate in 46% yield by following the similar procedure for **39a**. Yellow solid; m.p. 87-88 °C; $R_f = 0.48$ (silica gel; hexane : ethyl acetate = 6 : 1); ^1H NMR (300 MHz, CDCl_3) δ 7.44-7.60 (5H, m), 6.85 (1H, br, s), 5.78 (1H, d, $J = 2.3$ Hz), 5.55 (1H, d, $J = 2.3$ Hz), 4.49 (2H, d, $J = 5.6$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 195.7, 135.7, 131.5, 130.6, 128.2, 126.2, 120.0, 53.1; IR (NaCl, CHCl_3) ν 3345, 3088, 2982, 2916, 1661, 1638, 1570, 1491, 1373, 1331, 1256, 1113, 1098, 986, 924, 748, 687 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{11}\text{BrNS}_2$ (M^+H^+): 287.9516, found: 287.9514.

Typical procedure for preparing N-(2-bromoallyl)-3-phenylprop-2-ynethioamide (34h):

To a stirred solution of 2,3-dibromoprop-1-ene (0.62 g, 3.1 mmol) in CH_2Cl_2 (10 mL) was added KSCN (0.33 g, 3.4 mmol) at room temperature, and the reaction mixture was stirred for 3 h. The reaction was filtered, the filtrate was concentrated and the residue was directly used for next step. Toluene (10 mL) was added into the crude, and the

resulting mixture was heated to reflux overnight. The solvent was removed under reduced pressure, and the residue **41** was dissolved in anhydrous THF (6 mL), followed by adding the prepared solution of phenylethynyl lithium (3.1 mmol) in THF (6 mL) at 0 °C. The reaction mixture was then allowed to reflux overnight. The reaction was quenched by saturated NH₄Cl solution at 0 °C, and followed by extraction with Et₂O (10 mL×3). The combined organic layer was washed with water, dried over MgSO₄, and concentrated in vacuo. The crude was purified by flash column chromatography (silica gel; hexane : ethyl acetate = 8 : 1) to give *N*-(2-bromoallyl)-3-phenylprop-2-ynethioamide **34h** (283 mg, 1.0 mmol) in 32% yield.

Yellow oil; R_f = 0.27 (silica gel; hexane : ethyl acetate = 5 : 1); ¹H NMR (300 MHz, CDCl₃) δ 7.86 (1H, br, s), 7.43-7.54 (2H, m), 7.30-7.41 (3H, m), 5.95 (1H, d, J = 1.0 Hz), 5.60 (1H, d, J = 1.0 Hz), 4.62 (2H, d, J = 5.7 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 179.4, 132.5, 130.3, 128.6, 125.8, 120.4, 119.1, 90.9, 87.7, 52.5; IR (NaCl, CHCl₃) ν 3397, 3065, 3018, 2941, 2220, 1631, 1520, 1443, 1298, 1153, 1122, 1028, 896 cm⁻¹; HRMS (ESI) calcd for C₁₂H₁₁BrNS (M⁺H⁺): 281.9775, found: 281.9773.

Typical procedure for synthesis of 1-(2-Bromoallyl)-3-phenylthiourea (42c):

To a stirred solution of 2-bromoprop-2-en-1-amine **38a** (1.1 g, 8.0 mmol) in EtOH (15 mL) was added isothiocyanatobenzene (1.0 mL, 8.0 mmol). The reaction mixture was

heated to reflux for 2 h, then cooled to room temperature, the precipitate was filtered and collected to give 1-(2-Bromoallyl)-3-phenylthiourea **42c** (2.0g, 7.6 mmol) in 95% yield.

95% Yield; yellow solid; m.p. 113-114 °C; R_f = 0.58 (silica gel; hexane : ethyl acetate = 1 : 1); ^1H NMR (400 MHz, CDCl_3) δ 8.32 (1H, br, s), 7.44-7.48 (2H, m), 7.27-7.36 (3H, m), 6.30 (1H, br, s), 5.86 (1H, s), 5.59 (1H, s), 4.54 (2H, d, J = 5.6 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 180.8, 135.7, 130.4, 128.2, 127.7, 125.5, 119.2, 52.7; IR (NaCl, CHCl_3) ν 3233, 3213, 3034, 2980, 1636, 1593, 1555, 1537, 1495, 1416, 1381, 1323, 1238, 1192, 1132, 1098, 955, 880, 743, 683 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{12}\text{BrN}_2\text{S}$ (M^+H^+): 270.9905, found: 270.9911.

Compounds **42a** and **42b** were prepared by following same procedure for **42c**.

3-(2-Bromoallyl)-1,1-diethylthiourea (**42a**):

Prepared from 2-bromo-3-isothiocyano-1-propene **43** and diethyl amine in 93% yield. Yellow solid; m.p. 40-42 °C; R_f = 0.70 (silica gel; hexane : ethyl acetate = 1 : 1); ^1H NMR (500 MHz, CDCl_3) δ 5.89 (1H, d, J = 2.0 Hz), 5.63 (1H, br, s), 5.59 (1H, d, J = 2.0 Hz), 4.58 (2H, d, J = 5.3 Hz), 3.68 (4H, q, J = 7.0 Hz), 1.25 (6H, t, J = 7.1 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 180.3, 129.5, 119.1, 53.3(2), 45.4, 12.7(2); IR (NaCl, CHCl_3) ν 3261, 2976, 2930, 2851, 1647, 1528, 1410, 1323, 1287, 1244, 1138, 1082, 858, 773 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_8\text{H}_{16}\text{BrN}_2\text{S}$ (M^+H^+): 251.0218, found: 251.0213.

Benzyl-3-(2-bromoallyl)-1-methylthiourea (42b):

Prepared from 2-bromo-3-isothiocyantoprop-1-ene **43** and *N*-methyl-*N*-benzylamine in 99% yield. White solid; m.p. 80-92 °C; R_f = 0.63 (silica gel; hexane : ethyl acetate = 2 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.36 (2H, d, J = 7.2 Hz), 7.28-7.32 (3H, m), 5.84 (1H, s), 5.74 (1H, br, s), 5.57 (1H, s), 5.06 (2H, s), 4.58 (2H, d, J = 5.6 Hz), 3.23 (3H, s); HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{16}\text{BrN}_2\text{S}$ (M^+H^+): 299.0218, found: 299.0215.

Typical procedure for the intramolecular cyclization of *N*-(2-bromoprop-2-enyl)furan-2-carbothioamide (34e):

To a solution of *N*-(2-bromoprop-2-enyl)furan-2-carbothioamide **34e** (100 mg, 0.41 mmol) in DMF (20mL), was added K_2CO_3 (84 mg, 0.61 mmol), and the mixture was stirred at 80 °C. After the completion of the reaction, the mixture was quenched with a pH 9 ammonium buffer solution, and extracted with diethyl ether (10 mL $\times$ 3), the combined extracts were washed by brine and dried over MgSO_4 . The solvent was removed in vacuo, and the resulting crude was purified by PTLC (silica gel; hexane : ethyl acetate = 4 : 1) to afford the pure product 2-(furan-2-yl)-5-methylthiazole **36e** in 74% yield.

Yellow solid; m.p. 65-66 °C; R_f = 0.26 (silica gel; hexane : ethyl acetate = 6 : 1); ^1H NMR (300 MHz, CDCl_3) δ 7.46 (2H, dd, J = 4.8, 6.9 Hz), 6.90 (1H, d, J = 3.1 Hz), 6.50 (1H, dd, J = 1.7, 5.2 Hz), 2.49 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 156.7, 149.1, 143.2, 141.2, 133.2, 112.1, 108.0, 11.9; IR (NaCl) ν 3117, 2922, 1526, 1499, 1437, 1225, 1134, 1022, 883, 737 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_8\text{H}_8\text{NOS}$ (M^+H^+) 166.0327, found: 166.0326.

Compounds **36a-d**, **f-h**, **51**, **52**, **54**, **37b** and **53c** were prepared by following same procedure for **36e**. Spectral data obtained for known compounds **36d**, **36f**, **36g**, **52** and **53c** are in agreement with the data reported.

5-Methyl-2-phenylthiazole (**36a**):

79% Yield; yellow oil; R_f = 0.45 (silica gel; hexane : ethyl acetate = 5 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.89 (2H, dd, J = 1.4, 7.9 Hz), 7.50 (1H, s), 7.39-7.44 (3H, m), 2.51 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 141.4, 133.93, 133.88, 129.6, 128.9, 126.2, 12.1.

(*E*)-5-methyl-2-styrylthiazole (**36b**):

83% Yield; yellow solid; m.p. 93-96 °C; R_f = 0.24 (silica gel; hexane : ethyl acetate = 5 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.52-7.54 (2H, m), 7.46 (1H, d, J = 1.0 Hz), 7.37-7.41 (3H, m), 7.32-7.34 (1H, m), 7.28-7.29 (2H, m), 2.50 (3H, d, J = 1.0 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 165.7, 141.3, 135.9, 133.4, 133.3, 128.8, 128.7, 127.0, 121.9, 12.2; IR (NaCl) ν 3194, 3024, 2916, 1630, 1576, 1522, 1493, 1427, 1306, 1231, 1173, 1132, 1072,

964, 876, 752, 689 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{12}\text{NS}$ (M^+H^+) 202.0690, found: 202.0689.

2-Decyl-5-methylthiazole (36c):

68% Yield; brown oil; R_f = 0.45 (silica gel; hexane : ethyl acetate = 5 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.27 (1H, d, J = 1.2 Hz), 2.92 (2H, d, J = 7.7 Hz), 2.42 (3H, d, J = 1.2 Hz), 1.71-1.79 (2H, m), 1.26-1.40 (14H, m), 0.88 (3H, t, J = 6.9 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 170.1, 139.6, 132.5, 33.5, 31.9, 30.0, 29.6, 29.5, 29.3 (overlapped), 29.1, 22.7, 14.1, 11.9; IR (NaCl) ν 2922, 2853, 1537, 1466, 1456, 1377, 1188, 1165, 1138, 1082, 1045, 843, 721 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{26}\text{NS}$ (M^+H^+) 240.1786, found: 240.1784.

5-Methyl-2-(thiophen-2-yl)thiazole (36d):¹

76% Yield. R_f = 0.65 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (300 MHz, CDCl_3) δ 7.41 (2H, t, J = 3.7 Hz), 7.34 (1H, d, J = 5.1 Hz), 7.05 (1H, dd, J = 3.7 Hz, 5.0 Hz), 2.48 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 160.4, 140.9, 137.7, 133.3, 127.7, 127.0, 125.9, 12.0.

5-Isopropyl-2-phenylthiazole (36f):² 15% yield.

2-Phenyl-5-(propan-2-ylidene)-4,5-dihydrothiazole (35f):

59% Yield; white solid; m.p. 105-108 °C; R_f = 0.43 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.80 (2H, d, J = 7.4 Hz), 7.40-7.53 (3H, m), 5.06 (2H, s), 1.82 (3H, s), 1.74 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 167.0, 133.5, 131.1, 130.7, 128.5, 127.9, 121.1, 68.9, 25.4, 20.9; IR (NaCl, CHCl_3) ν 3335, 3096, 2980, 2828, 1530, 1452, 1431, 1364, 1252, 1148, 1074, 978, 858, 775, 694 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{14}\text{NS}$ (M^+H^+) 204.0847, found: 204.0850.

2-Phenyl-4,5,6,7-tetrahydrobenzo[d]thiazole (36g):³

75% Yield. R_f = 0.60 (silica gel; hexane : ethyl acetate = 3 : 1); ^1H NMR (500 MHz, CDCl_3) δ 7.88-7.89 (2H, m), 7.37-7.42 (3H, m), 2.80-2.86 (4H, m), 1.88-1.92 (4H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 164.6, 151.5, 134.1, 129.4, 129.2, 128.8(2), 126.2(2), 26.9, 23.7, 23.4, 23.0.

5-Methyl-2-(phenylethynyl)thiazole (36h):

23% Yield; white solid; m.p. 82-84 °C; R_f = 0.4 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (500 MHz, CDCl_3) δ 7.57-7.59 (2H, m), 7.48-7.50 (1H, m), 7.32-7.40 (3H, m), 2.50 (3H, d, J = 0.9 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 147.1, 141.6, 135.9, 131.9, 129.3, 128.5, 121.7, 93.2, 82.6, 12.1; IR (NaCl, CHCl_3) ν 3019, 2976, 2399, 1600, 1520, 1476, 1423, 1045, 1032, 928, 849 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{10}\text{NOS}$ (M^+H^+) 200.0534, found: 200.0533.

2-(2-Chlorophenyl)-5-vinylthiazole (51):

70% Yield; white solid; m.p. 33-35 °C; R_f = 0.71 (silica gel; hexane : ethyl acetate = 3 : 1); ^1H NMR (400 MHz, CDCl_3) δ 8.21 (1H, d, J = 8.0 Hz), 7.77 (1H, s), 7.50 (1H, d, J = 4.0 Hz), 7.32-7.39 (2H, m), 6.86 (1H, dd, J = 10.8 Hz, 17.2 Hz), 5.66 (1H, d, J = 17.2 Hz), 5.33 (1H, d, J = 11.2 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 162.0, 140.9, 139.5, 132.0, 131.9, 130.8, 130.7, 130.4, 127.1, 126.7, 117.0; IR (NaCl) ν 3090, 3065, 2930, 2853, 1618, 1558, 1522, 1506, 1474, 1435, 1418, 1277, 1121, 1063, 1040, 972, 905, 862, 750, 727, 648, 631 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_9\text{ClNS}$ (M^+H^+) 222.0144, found: 222.0145.

5-Methyl-2-(phenylthio)thiazole (52):⁴

36% Yield. R_f = 0.42 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (300 MHz, CDCl_3) δ 7.55-7.58 (2H, m), 7.36-7.39 (4H, m), 2.38 (3H, s).

N-benzyl-*N*,2-dimethyl-1H-azirine-1-carbothioamide (37b):

28% Yield; yellow oil; R_f = 0.79 (silica gel; hexane : ethyl acetate = 2 : 1, twice); ^1H NMR (400 MHz, CDCl_3) δ 7.25-7.35 (5H, m), 6.82 (1H, d, J = 1.3 Hz), 4.63 (2H, s), 3.00 (3H, s), 2.29 (3H, d, J = 1.3 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 170.4, 137.1, 136.4(2), 128.6(2), 127.5, 127.4, 120.9, 56.3, 37.9, 12.0; IR (NaCl, CHCl_3) ν 2970, 1541, 1452, 1412, 1367, 1103, 1028, 931 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{15}\text{N}_2\text{S}$ (M^+H^+) 219.0956, found: 219.0951.

5-Mmethyl-*N*-phenylthiazol-2-amine (53c),⁴ 14% yield.

5-Methyl-1-phenyl-1H-imidazole-2(3*H*)-thione (54):

41% Yield; white solid; m.p. 228 °C (decomposed); $R_f = 0.19$ (silica gel; hexane : ethyl acetate = 1 : 1); ^1H NMR (400 MHz, CDCl_3) δ 8.39 (1H, br, s), 7.30-7.35 (4H, m), 7.01-7.04 (1H, m), 6.93 (1H, s), 2.35 (3H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 164.0, 140.8, 135.3, 129.4, 122.5, 122.1, 117.7, 11.9; IR (NaCl, CHCl_3) ν 3146, 3080, 3038, 2938, 2806, 2733, 1624, 1595, 1502, 1400, 1321, 1217, 1167, 1098, 1013, 779, 716, 696 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{11}\text{N}_2\text{S}$ (M^+H^+) 191.0643, found: 191.0649.

6.2.2. Synthesis of 1,3,4-trisubstituted imidazole-2-thiones

Compounds **55a-i** were prepared from *N*-substituted 2-bromoallyl amines **75**⁵ and different isothiocyanates via the similar procedures for **42c**.

1-(2-Bromoallyl)-1-isopropyl-3-phenylthiourea (55a):

72% Yield; faint yellow solid; m.p. 82-84 °C; $R_f = 0.33$ (silica gel; hexane : ethyl acetate = 3 : 1); ^1H NMR (300 MHz, CDCl_3) δ 7.23-7.30 (5H, m), 7.15 (1H, t, $J = 6.0$ Hz), 5.82 (1H, d, $J = 1.9$ Hz), 5.69 (1H, d, $J = 2.2$ Hz), 5.47 (1H, septet, $J = 6.7$ Hz), 4.19 (1H, s), 1.15 (1H, d, $J = 6.7$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 182.5, 139.6, 128.6(2), 127.6,

126.2(2), 126.0, 117.9, 52.0, 51.8, 20.0(2); IR (NaCl) ν 3221, 3117, 3046, 2970, 2934, 1593, 1533, 1497, 1449, 1339, 1321, 1223, 1123, 1109, 1061, 986, 891, 735, 694, 638 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{18}\text{BrN}_2\text{S}$ (M^+H^+): 313.0374, found: 313.0374.

1-(2-Bromoallyl)-1-isopropyl-3-(4-methoxyphenyl)thiourea (55b):

60% Yield; colorless oil; R_f = 0.17 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.16 (2H, d, J = 8.0 Hz), 7.12 (1H, br, s), 6.87 (2H, d, J = 8.0 Hz), 5.96 (1H, d, J = 2.0 Hz), 5.78 (1H, d, J = 2.0 Hz), 5.63 (1H, septet, J = 6.4 Hz), 4.24 (2H, s), 3.80 (3H, s), 1.22 (6H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 183.1, 157.8, 132.2, 128.0(2), 127.2, 117.8, 113.8(2), 55.3, 51.79, 51.75, 19.7(2); IR (NaCl) ν 2974, 2934, 2833, 1514, 1456, 1362, 1331, 1242, 1177, 1107, 1063, 1034, 910, 829, 733, 667 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{20}\text{BrN}_2\text{OS}$ (M^+H^+): 343.0480, found: 343.0479.

1-(2-Bromoallyl)-1-isopropyl-3-(4-nitrophenyl)thiourea (55c):

53% Yield; yellow solid; m.p. 123-125 $^{\circ}\text{C}$; R_f = 0.12 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 8.20 (2H, d, J = 9.2 Hz), 7.56 (2H, d, J = 9.2 Hz), 7.37 (1H, br, s), 6.00 (1H, s), 5.87 (1H, s), 5.61 (1H, septet, J = 6.0 Hz), 4.30 (2H, s), 1.27 (6H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 181.9, 145.4, 144.3, 127.4, 124.4(2), 123.9(2), 118.4, 52.5, 52.2, 19.8(2); IR (NaCl) ν 3366, 3071, 2974, 2930, 1593, 1533, 1495, 1456, 1423, 1395, 1366, 1335, 1281, 1252, 1240, 1175, 1109, 1055, 907, 847, 752, 660 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{17}\text{BrN}_3\text{O}_2\text{S}$ (M^+H^+): 358.0225, found: 358.0225.

1-(2-Bromoallyl)-1,3-diphenylthiourea (55d):

60% Yield; white solid; m.p. 105-107 °C; R_f = 0.35 (silica gel; hexane : ethyl acetate = 5 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.53 (2H, t, J = 7.6 Hz), 7.41-7.47 (3H, m), 7.29-7.33 (4H, m), 7.19 (1H, t, J = 6.4 Hz), 7.10 (1H, br, s), 5.80 (1H, s), 5.59 (1H, s), 5.26 (2H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 182.2, 140.5, 139.0, 130.7(2), 129.3, 128.7(2), 128.1, 127.9(2), 126.3, 125.8(2), 119.6, 61.6; IR (NaCl) ν 3219, 3048, 2909, 1505, 1489, 1339, 1221, 1115, 1070, 976, 698 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{16}\text{BrN}_2\text{S}$ (M^+H^+): 347.0218, found: 347.0214.

1-(2-Bromoallyl)-3-(4-methoxyphenyl)-1-phenylthiourea (55e):

40% Yield; faint yellow solid; m.p. 82-84 °C; R_f = 0.54 (silica gel; hexane : ethyl acetate = 2 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.51-7.55 (2H, m), 7.40-7.46 (3H, m), 7.19 (2H, d, J = 8.0 Hz), 6.99 (1H, br, s), 6.84 (2H, d, J = 8.0 Hz), 5.80 (1H, d, J = 2.0 Hz), 5.58 (1H, d, J = 1.6 Hz), 5.26 (2H, s), 3.78 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 182.9, 158.0, 140.5, 131.9, 130.6(2), 129.2, 128.1, 127.9(2), 127.8(2), 119.5, 113.8(2), 61.6, 55.4; IR (NaCl) ν 3356, 3048, 2907, 2835, 1508, 1489, 1350, 1339, 1238, 1221, 1117, 1034, 976, 829, 764, 700, 669 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{18}\text{BrN}_2\text{OS}$ (M^+H^+): 377.0323, found: 377.0321.

1-(2-Bromoallyl)-3-(4-nitrophenyl)-1-phenylthiourea (55f):

68% Yield; yellow solid; m.p. 116-118 °C; R_f = 0.57 (silica gel; hexane : ethyl acetate = 2 : 1); ^1H NMR (400 MHz, CDCl_3) δ 8.15 (2H, d, J = 8.0 Hz), 7.63 (2H, d, J = 8.0 Hz), 7.57 (2H, t, J = 8.0 Hz), 7.50 (1H, t, J = 8.0 Hz), 7.42 (2H, d, J = 8.0 Hz), 7.32 (1H, br, s), 5.78 (1H, d, J = 2.0 Hz), 5.60 (1H, d, J = 1.6 Hz), 5.25 (2H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 180.6, 144.7, 144.4, 139.9, 130.9(2), 129.8, 127.7(2), 127.3, 124.2(2), 123.6(2), 120.2, 61.4; IR (NaCl) ν 3362, 3065, 2913, 1593, 1553, 1506, 1489, 1427, 1373, 1339, 1300, 1271, 1217, 1115, 1074, 982, 895, 847, 731, 698 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{15}\text{BrN}_3\text{O}_2\text{S}$ (M^+H^+): 392.0068, found: 392.0042.

Benzyl-1-(2-bromoallyl)-3-phenylthiourea (55g):

94% Yield; white solid; m.p. 139-140 °C; R_f = 0.34 (silica gel; hexane : ethyl acetate = 5 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.32-7.43 (7H, m), 7.25-7.27 (3H, m), 7.20 (1H, t, J = 7.4 Hz), 5.92 (1H, s), 5.76 (1H, s), 5.07 (2H, s), 4.67 (2H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 183.8, 139.5, 135.3, 129.2(2), 128.8(2), 128.3, 127.2(2), 126.7, 126.2, 125.5(2), 118.9, 58.2, 54.1; IR (NaCl) ν 3275, 3030, 2945, 2901, 1526, 1506, 1489, 1339, 1221, 1107, 905, 731, 702 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{18}\text{BrN}_2\text{S}$ (M^+H^+): 406.0225, found: 406.0224.

Benzyl-1-(2-bromoallyl)-3-(4-nitrophenyl)thiourea (55h):

64% Yield; yellow solid; m.p. 102-104 °C; R_f = 0.14 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (300 MHz, CDCl_3) δ 8.17 (2H, d, J = 9.2 Hz), 7.35-7.53 (8H, m), 5.92 (1H, d, J = 2.0 Hz), 5.79 (1H, d, J = 2.0 Hz), 5.07 (2H, s), 4.70 (2H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 182.7, 145.4, 144.2, 134.7, 129.4(2), 128.6, 127.2(2), 126.3, 124.4(2),

123.4(2), 119.7, 58.4, 54.2; IR (NaCl) ν 3219, 3115, 3030, 1533, 1506, 1456, 1340, 1296, 1265, 1223, 1107, 1078, 1011, 893, 857, 735, 702, 625 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{17}\text{BrN}_3\text{O}_2\text{S}$ (M^+H^+): 361.0374, found: 361.0372.

1-(2-Bromoallyl)-3-cyclohexyl-1-isopropylthiourea (55i):

95% Yield; white solid; m.p. 47-49 $^{\circ}\text{C}$; R_f = 0.66 (silica gel; hexane : ethyl acetate = 3 : 1); ^1H NMR (300 MHz, CDCl_3) δ 5.82 (1H, d, J = 3.0 Hz), 5.70 (1H, d, J = 3.0 Hz), 5.61 (1H, septet, J = 6.0 Hz), 5.32 (1H, d, J = 9.0 Hz), 4.30-4.42 (1H, m), 4.04 (2H, s), 2.03 (2H, dd, J = 4.1 Hz, 12.3 Hz), 1.63-1.69 (2H, m), 1.36-1.49 (2H, m), 1.11-1.25 (4H, m), 1.17 (6H, d, J = 6.0 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 180.8, 127.5, 117.5, 65.6, 53.9, 51.4, 50.9, 32.5, 25.4, 24.6, 19.8(2), 15.2; IR (NaCl) ν 2976, 2928, 2853, 1616, 1520, 1395, 1368, 1339, 1182, 1109, 1061, 893, 734, 669 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{24}\text{BrN}_2\text{S}$ (M^+H^+): 319.0844, found: 319.0850.

Typical procedure for the intramolecular cyclization of 1-(2-bromoprop-2-enyl)-1-isopropyl-3-phenylthiourea (55a):

To a solution of 1-(2-bromoprop-2-enyl)-1-isopropyl-3-phenylthiourea **55a** (100 mg, 0.31 mmol, 1.0 equiv.) in DMF (20 mL), was added K_2CO_3 (66 mg, 0.48 mmol, 1.5

equiv.), and the mixture was stirred at 80 °C. After the completion of the reaction, the mixture was quenched with a pH 9 ammonium buffer solution, and extracted with ethyl acetate (10 mL×3), the combined extracts were washed by brine and dried over MgSO₄. The solvent was removed in vacuo, and the resulting crude was purified by PTLC (silica gel; ethyl acetate : hexane = 1 : 2) to afford the pure product 1-isopropyl-4-methyl-3-phenyl-1*H*-imidazole-2(3*H*)-thione **56a** in 78% yield and *N*-(3-isopropyl-5-methylenethiazolidin-2-ylidene)aniline **74a** in 8% yield.

Faint yellow crystals (CCDC 706193)⁶; m.p. 185-186 °C; *R*_f = 0.39 (silica gel; hexane : ethyl acetate = 3 : 1, twice); ¹H NMR (300 MHz, CDCl₃) δ 7.41-7.50 (3H, m), 7.28-7.32 (2H, m), 6.59 (1H, d, *J* = 1.0 Hz), 5.17 (1H, septet, *J* = 6.8 Hz), 1.93 (3H, d, *J* = 1.0 Hz), 1.38 (6H, d, *J* = 6.8 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 162.2, 136.5, 129.4(2), 129.0, 128.5(2), 126.5, 110.1, 48.5, 21.8(2), 11.0; IR (NaCl) ν 2976, 1518, 1499, 1408, 1344 cm⁻¹; HRMS (ESI) calcd for C₁₃H₁₇N₂S (M⁺H⁺): 233.1112, found: 233.1112.

Compounds **56b-h** and **74a-c, f-h, 76f** were prepared by following same procedure for **56a**.

Isopropyl-3-(4-methoxyphenyl)-4-methyl-1*H*-imidazole-2(3*H*)-thione (**56b**):

81% Yield; white solid; m.p. 186-188 °C; R_f = 0.34 (silica gel; hexane : ethyl acetate = 3 : 1); ^1H NMR (500 MHz, CDCl_3) δ 7.20 (2H, d, J = 8.8 Hz), 6.99 (2H, d, J = 8.8 Hz), 6.57 (1H, s), 5.16 (1H, septet, J = 6.8 Hz), 3.83 (3H, s), 1.92 (3H, s), 1.38 (6H, d, J = 6.8 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 162.3, 159.7, 129.5(2), 129.2, 126.8, 114.6(2), 109.9, 55.5, 48.6, 21.8(2), 10.9; IR (NaCl) ν 2974, 1516, 1408, 1342, 1250 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{19}\text{N}_2\text{OS}$ (M^+H^+): 263.1218, found: 263.1217.

Isopropyl-4-methyl-3-(4-nitrophenyl)-1*H*-imidazole-2(3*H*)-thione (56c):

77% Yield; yellow solid; m.p. 192-194 °C; R_f = 0.13 (silica gel; hexane : ethyl acetate = 3 : 1, twice); ^1H NMR (300 MHz, CDCl_3) δ 8.39 (2H, d, J = 6.0 Hz), 7.57 (2H, d, J = 6.0 Hz), 6.66 (1H, s), 5.16 (1H, septet, J = 6.6 Hz), 2.00 (3H, s), 1.42 (6H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 162.5, 147.6, 142.0, 130.2, 129.8, 125.8, 124.7(2), 111.3, 48.8, 21.7(2), 11.1; IR (NaCl) ν 2978, 1599, 1530, 1499, 1404, 1350, 1179 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{16}\text{N}_3\text{O}_2\text{S}$ (M^+H^+): 278.0963, found: 278.0961.

4-Methyl-1,3-diphenyl-1*H*-imidazole-2(3*H*)-thione (56d):

87% Yield; yellow solid; m.p. 172-174 °C; R_f = 0.59 (silica gel; hexane : ethyl acetate = 2 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.65-7.67 (2H, m), 7.47-7.57 (5H, m), 7.38-7.41 (3H, m), 6.75 (1H, s), 2.00 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 164.4, 138.4, 136.6, 129.6(2), 129.2, 129.1(2), 128.6(2), 128.2, 126.8, 126.1(2), 115.3, 11.0; IR (NaCl) ν 2970,

1634, 1597, 1499, 1456, 1400, 1358, 1310, 1123, 1074, 1015 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{S}$ (M^+H^+): 267.0956, found: 267.0956.

3-(4-Methoxyphenyl)-4-methyl-1-phenyl-1H-imidazole-2(3H)-thione (56e):

91% Yield; white solid; m.p. 163-165 $^{\circ}\text{C}$; R_f = 0.46 (silica gel; hexane : ethyl acetate = 2 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.65 (2H, d, J = 8.0 Hz), 7.49 (2H, t, J = 8.0 Hz), 7.40 (1H, d, J = 8.0 Hz), 7.30 (2H, d, J = 6.8 Hz), 7.05 (2H, d, J = 6.8 Hz), 6.73 (1H, d, J = 1.0 Hz), 3.87 (3H, s), 2.00 (3H, d, J = 1.0 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 164.5, 159.9, 138.4, 129.5(2), 129.2, 129.1(2), 128.1, 127.2, 126.1(2), 115.1, 114.8(2), 55.5, 10.9; IR (NaCl) ν 2965, 1599, 1514, 1501, 1464, 1404, 1360, 1300, 1252, 1167, 1038 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{17}\text{N}_2\text{OS}$ (M^+H^+): 297.1062, found: 297.1059.

4-Methyl-3-(4-nitrophenyl)-1-phenyl-1H-imidazole-2(3H)-thione (56f):

50% Yield; yellow solid; m.p. 189-191 $^{\circ}\text{C}$; R_f = 0.39 (silica gel; hexane : ethyl acetate = 2 : 1); ^1H NMR (500 MHz, CDCl_3) δ 8.42 (2H, d, J = 8.8 Hz), 7.62-7.65 (4H, m), 7.51 (2H, t, J = 7.7 Hz), 7.43 (1H, t, J = 7.4 Hz), 6.81 (1H, s), 2.05 (3H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 164.5, 147.8, 141.9, 137.9, 129.9(2), 129.2(2), 128.5, 126.0(2), 125.9, 124.9(2), 116.4, 11.0; IR (NaCl) ν 2965, 1599, 1514, 1501, 1464, 1404, 1360, 1300, 1252,

1167, 1038 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{14}\text{N}_3\text{O}_2\text{S}$ (M^+H^+): 312.0807, found: 312.0807.

Benzyl-4-methyl-3-phenyl-1*H*-imidazole-2(3*H*)-thione (56g):

65% Yield; white solid; m.p. 138-140 $^{\circ}\text{C}$; R_f = 0.39 (silica gel; hexane : ethyl acetate = 2 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.44-7.54 (3H, m), 7.33-7.39 (7H, m), 6.42 (1H, s), 5.29 (2H, s), 1.89 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 163.9, 136.7, 136.0, 129.5(2), 129.1, 128.9(2), 128.6(2), 128.4(2), 128.2, 126.4, 113.7, 51.0, 10.9; IR (NaCl) ν 2960, 1499, 1410, 1396, 928, 669 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{17}\text{N}_2\text{S}$ (M^+H^+): 281.1112, found: 281.1111.

Benzyl-4-methyl-3-(4-nitrophenyl)-1*H*-imidazole-2(3*H*)-thione (56h):

68% Yield; yellow solid; m.p. 170-172 $^{\circ}\text{C}$; R_f = 0.26 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 8.39 (2H, d, J = 8.0 Hz), 7.59 (2H, d, J = 8.0 Hz), 7.39-7.40 (5H, m), 6.48 (1H, s), 5.28 (2H, s), 1.95 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 164.1, 147.7, 142.1, 135.5, 130.0(2), 129.0(2), 128.6(2), 128.4, 125.6, 124.8(2), 114.8, 51.1, 11.0; IR (NaCl) ν 2928, 2853, 1520, 1489, 1464, 1396, 1339, 1319, 1107, 1074, 854, 702 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{16}\text{N}_3\text{O}_2\text{S}$ (M^+H^+): 326.0963, found: 326.0964.

***N*-(3-isopropyl-5-methylenethiazolidin-2-ylidene)aniline (74a):**

8% Yield; faint yellow oil; $R_f = 0.74$ (silica gel; hexane : ethyl acetate = 3 : 1, twice); ^1H NMR (400 MHz, CDCl_3) δ 7.23-7.29 (2H, m), 7.03 (1H, t, $J = 6.8$ Hz), 6.92 (2H, d, $J = 6.8$ Hz), 5.20 (1H, s), 5.05 (1H, s), 4.67 (1H, septet, $J = 6.8$ Hz), 4.26 (1H, s), 1.27 (6H, d, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 166.8, 137.9, 134.5, 128.8(2), 123.1, 122.2(2), 105.1, 50.8, 46.2, 19.3(2); IR (NaCl) ν 2986, 1614, 1587, 1220 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{17}\text{N}_2\text{S}$ (M^+H^+): 233.1112, found: 233.1119.

***N*-(3-isopropyl-5-methylenethiazolidin-2-ylidene)-4-methoxyaniline (74b):**

7% Yield; faint yellow oil; $R_f = 0.70$ (silica gel; hexane : ethyl acetate = 3 : 1, twice); ^1H NMR (400 MHz, CDCl_3) δ 6.80-6.86 (4H, m), 5.19 (1H, s), 5.05 (1H, s), 4.65 (1H, septet, $J = 6.8$ Hz), 4.25 (2H, s), 3.78 (3H, s), 1.26 (6H, d, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 155.7, 138.0, 122.9(2), 114.1(2), 105.0, 55.4, 50.8, 46.2, 19.2(2); IR (NaCl) ν 2985, 1614, 1504, 1421, 1036 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{19}\text{N}_2\text{OS}$ (M^+H^+): 263.1218, found: 263.1219.

***N*-(3-isopropyl-5-methylenethiazolidin-2-ylidene)-4-nitroaniline (74c):**

19% Yield; yellow oil; $R_f = 0.67$ (silica gel; hexane : ethyl acetate = 3 : 1); ^1H NMR (400 MHz, CDCl_3) δ 8.14 (2H, d, $J = 8.8$ Hz), 7.99 (2H, d, $J = 8.8$ Hz), 5.28 (1H, s), 5.13 (1H, s), 4.68 (1H, septet, $J = 6.8$ Hz), 4.32 (2H, s), 1.28 (6H, d, $J = 6.8$ Hz); ^{13}C NMR (100

MHz, CDCl₃) δ 157.8, 143.1, 136.6, 124.9(2), 122.5(2), 106.2, 50.8, 46.6, 19.3(2); IR (NaCl) ν 2976, 1614, 1569, 1556, 1504, 1464, 1421, 1335, 1220, 1169, 1109, 1065, 945, 860 cm⁻¹; HRMS (ESI) calcd for C₁₃H₁₆N₃O₂S (M⁺H⁺): 278.0963, found: 278.0961.

***N*-(5-methylene-3-phenylthiazolidin-2-ylidene)-4-nitroaniline (74f):**

33% Yield; yellow solid; m.p. 128-130 °C; R_f = 0.59 (silica gel; hexane : ethyl acetate = 2 : 1); ¹H NMR (400 MHz, CDCl₃) δ 8.16 (2H, d, *J* = 8.8 Hz), 7.58 (2H, d, *J* = 8.8 Hz), 7.43 (2H, t, *J* = 8.4 Hz), 7.22 (1H, t, *J* = 8.0 Hz), 7.03 (2H, d, *J* = 8.0 Hz), 5.35 (1H, d, *J* = 1.9 Hz), 5.18 (1H, d, *J* = 1.7 Hz), 6.81 (2H, d, *J* = 2.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 157.3, 143.6, 139.8, 135.2, 129.2(2), 128.6, 125.7, 125.0(2), 123.1(2), 122.4(2), 106.7, 58.1; IR (NaCl) ν 2963, 2930, 2853, 1636, 1622, 1576, 1499, 1458, 1339, 1292, 1263, 1182, 1098, 1076, 1016, 1009, 876, 862, 802, 750 cm⁻¹; HRMS (ESI) calcd for C₁₆H₁₄N₃O₂S (M⁺H⁺): 312.0807, found: 312.0806.

***N*-(3-benzyl-5-methylenethiazolidin-2-ylidene)aniline (74g):**

30% Yield; colorless oil; R_f = 0.68 (silica gel; hexane : ethyl acetate = 2 : 1); ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.39 (4H, m), 7.29-7.33 (3H, m), 7.07 (1H, t, *J* = 7.3 Hz), 6.99 (2H, d, *J* = 7.5 Hz), 5.13 (1H, s), 5.05 (1H, s), 4.77 (2H, s), 4.17 (2H, s); ¹³C NMR (125 MHz, CDCl₃) δ 156.7, 151.6, 137.4, 136.7, 128.9(2), 128.7(2), 128.3(2), 127.6, 123.3, 122.1(2), 105.4, 55.4, 49.7.

***N*-(3-Benzyl-5-methylenethiazolidin-2-ylidene)-4-nitroaniline (74h):**

25% Yield; yellow solid; m.p. 84-86 °C; R_f = 0.65 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 8.17 (2H, d, J = 8.0 Hz), 7.33-7.41 (5H, m), 7.05 (2H, d, J = 8.0 Hz), 5.20 (1H, d, J = 1.6 Hz), 5.12 (1H, d, J = 1.6 Hz), 4.77 (2H, s), 4.23 (2H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 157.6, 157.2, 143.2, 136.1, 136.0, 128.9(2), 128.2(2), 127.9, 125.0(2), 122.5(2), 106.5, 55.4, 49.7; IR (NaCl) ν 3030, 2928, 2853, 1634, 1618, 1576, 1497, 1327, 1221, 1107, 1078, 982, 870, 858, 837, 754, 696, 623 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{16}\text{N}_3\text{O}_2\text{S}$ (M^+H^+): 326.0963, found: 326.0960.

***N*-(5-methyl-3-phenylthiazol-2(3H)-ylidene)-4-nitroaniline (76f):**

Isomerized from **74f**, yellow solid; m.p. 131-133 °C; R_f = 0.56 (silica gel; hexane : ethyl acetate = 2 : 1); ^1H NMR (400 MHz, CDCl_3) δ 8.20 (2H, d, J = 8.0 Hz), 7.56 (2H, d, J = 8.0 Hz), 7.49 (2H, t, J = 8.0 Hz), 7.36 (1H, t, J = 8.0 Hz), 7.15 (2H, d, J = 8.0 Hz), 6.60 (1H, s), 2.20 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 157.6, 138.3, 129.3(2), 127.4(2), 125.5(2), 125.3(2), 123.5(2), 121.7(2), 112.4, 13.3; IR (NaCl) ν 2985, 1557, 1504, 1334, 1109 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{14}\text{N}_3\text{O}_2\text{S}$ (M^+H^+): 312.0807, found: 312.0814.

6.2.3. Synthesis of 5,6-dihydro-4H-1,3-thiazines

Typical procedure for the preparation of 5-bromo-6-methyl-1-phenylhept-5-en-3-amine (81c):

At 0 °C, to the solution of the readily prepared 5-bromo-6-methyl-1-phenylhept-5-en-3-ol **79c**^{7,8} (1.04 g, 3.7 mmol) in Et₂O (15 mL) was added methanesulfonyl chloride (0.85 mL, 11.1 mmol), followed by the dropwise addition of Et₃N (1.55 mL, 11.1 mmol). The reaction mixture was stirred at 0 °C for 1 h, and was quenched with *sat.* NaHCO₃ solution. The organics were extracted with Et₂O (15 mL×3), the combined extracts were dried over MgSO₄, and concentrated in vacuo. The obtained crude 5-bromo-6-methyl-1-phenylhept-5-en-3-yl methanesulfonate was set up for the next step.⁹ The crude was dissolved in DMF (15 mL), and was added NaN₃ (0.43 g, 6.60 mmol). The reaction mixture was allowed to stir at 60 °C overnight, after cool to room temperature, the reaction was quenched with water and extracted with Et₂O (15 mL×3), and the combined extracts were dried over MgSO₄. The solvents were removed in vacuo to afford the crude azide **80c**. To the solution of **80c** in dry THF (10 mL) was added LiAlH₄ (0.1g, 2.7 mmol) under an N₂ atmosphere. The reaction was stirred at room temperature overnight, and was quenched with water in a dropwise manner, followed by adding NaOH solution, and water. The organics were extracted with Et₂O (15 mL×3), the combined extracts were dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel; hexane : ethyl acetate = 1 : 1 to 1 : 4) to give the polar 5-bromo-6-methyl-1-phenylhept-5-en-3-amine **81c** (0.63g, 2.24 mmol) in 60% yield.

Yellow oil; $R_f = 0.10$ (silica gel; hexane : ethyl acetate = 1 : 2); ^1H NMR (400 MHz, CDCl_3) δ 7.27-7.30 (2H, m), 7.17-7.22 (3H, m), 3.18-3.24 (1H, m), 2.75-2.82 (1H, m), 2.50-2.69 (3H, m), 1.91 (3H, m), 1.83 (3H, m), 1.74-1.82 (1H, m), 1.60-1.69 (1H, m), 1.43 (2H, br, s); ^{13}C NMR (100 MHz, CDCl_3) δ 142.2, 132.9, 128.42(2), 128.38(2), 125.8, 119.1, 50.1, 45.8, 38.9, 32.8, 25.6, 21.0; IR (NaCl) ν 3366, 3024, 2916, 2855, 1651, 1600, 1495, 1454, 1369, 1221, 1042, 804, 748, 700 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{21}\text{BrN}$ (M^+H^+): 282.0857, found: 282.0855.

Compounds **82a-e**, **84** were prepared by following the same procedures for **39a**.

***N*-(5-Bromo-1-phenylhex-5-en-3-yl)benzamide (82a):**

75% Yield; white solid; m.p. 130-131 $^{\circ}\text{C}$; $R_f = 0.27$ (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (300 MHz, CDCl_3) δ 7.68-7.71 (2H, m), 7.39-7.52 (3H, m), 7.16-7.30 (5H, m), 6.08 (1H, d, $J = 8.3$ Hz), 5.67 (1H, s), 5.23 (1H, d, $J = 1.6$ Hz), 4.40-4.52 (1H, m), 2.73-2.89 (4H, m), 1.19-2.05 (2H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 167.1, 141.4, 134.6, 131.5, 129.7, 128.6(4), 128.4(2), 126.8(2), 126.1, 119.8, 48.8, 45.9, 35.6, 32.5; IR (NaCl) ν 3318, 3022, 2918, 1630, 1539, 1489, 1456, 899, 700, 640 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{21}\text{BrNO}$ (M^+H^+): 358.0807, found: 358.0801.

***N*-(5-Bromo-1-phenylhex-5-en-3-yl)-3-phenylpropanamide (82b):**

93% Yield; white solid; m.p. 102-103 °C; R_f = 0.34 (silica gel; hexane : ethyl acetate = 2 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.17-7.30 (8H, m), 7.12 (2H, d, J = 6.8 Hz), 5.52 (1H, s), 5.44 (1H, s), 5.22 (1H, d, J = 8.8 Hz), 4.17-4.26 (1H, m), 2.95 (2H, d, J = 7.6 Hz), 2.54-2.71 (4H, m), 2.44 (2H, td, J = 7.2 Hz, 8.0 Hz), 1.81-1.89 (1H, m), 1.62-1.77 (1H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 171.7, 141.5, 140.8, 129.7, 128.59(2), 128.49(2), 128.43(2), 128.35(2), 126.3, 126.0, 119.5, 48.2, 46.0, 38.6, 35.6, 32.4, 31.6; IR (NaCl) ν 3254, 3080, 3028, 2928, 2909, 2862, 1636, 1558, 1541, 1506, 1456, 887, 743, 700 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{25}\text{BrNO}$ (M^+H^+): 386.1120, found: 386.1118.

***N*-(5-Bromo-1-phenylhex-5-en-3-yl)thiophene-2-carboxamide (82c):**

70% Yield; white solid; m.p. 131-132 °C; R_f = 0.30 (silica gel; hexane : ethyl acetate = 2 : 1, twice); ^1H NMR (400 MHz, CDCl_3) δ 7.46 (1H, d, J = 4.0 Hz), 7.42 (1H, d, J = 4.0 Hz), 7.25-7.29 (2H, m), 7.18 (3H, t, J = 8.0 Hz), 7.05 (1H, dd, J = 4.0 Hz, 4.8 Hz), 6.05 (1H, br, s), 5.66 (1H, s), 5.52 (1H, s), 4.37-4.46 (1H, m), 2.72-2.85 (4H, m), 1.92-2.04 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 161.5, 141.3, 138.9, 129.9, 129.5, 128.5(2), 128.3(2), 127.9, 127.6, 126.0, 119.8, 48.8, 45.9, 35.5, 32.4; IR (NaCl) ν 3292, 3080, 3030, 2945, 2907, 1616, 1541, 1506, 1456, 1418, 1361, 1306, 1246, 1126, 897, 725, 700, 665 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{19}\text{BrNOS}$ (M^+H^+): 364.0371, found: 364.0367.

***N*-(5-Bromohex-5-en-3-yl)benzamide (82d):**

80% Yield; white solid; m.p. 105-107 °C; R_f = 0.29 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.76 (2H, dd, J = 5.4 Hz, 7.2 Hz), 7.41-7.52 (3H, m), 6.04 (1H, br, s), 5.68 (1H, d, J = 1.2 Hz), 5.52 (1H, d, J = 1.6 Hz), 4.30-4.39 (1H, m), 2.71-2.81 (2H, m), 1.58-1.78 (2H, m), 1.00 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 167.2, 134.8, 131.5, 130.0(2), 128.6(2), 126.9, 120.0, 50.1, 45.7, 27.0, 10.5; IR (NaCl) ν 3264, 3030, 2968, 2930, 2897, 1624, 1558, 1545, 1506, 1489, 1456, 1360, 1125, 901, 698 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{17}\text{BrNO}$ (M^+H^+): 282.0494, found 282.0490.

***N*-(5-Bromo-6-methyl-1-phenylhept-5-en-3-yl)benzamide (82e):**

67% Yield; white solid; m.p. 120-122 °C; R_f = 0.33 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.69 (2H, d, J = 7.5 Hz), 7.48 (1H, t, J = 7.2 Hz), 7.41 (2H, t, J = 7.2 Hz), 7.25-7.29 (2H, m), 7.15-7.20 (3H, m), 6.16 (1H, d, J = 8.0 Hz), 4.41-4.46 (1H, m), 2.97 (1H, dd, J = 7.1 Hz, 14.8 Hz), 2.82 (1H, dd, J = 6.2 Hz, 14.8 Hz), 2.75 (2H, t, J = 8.0 Hz), 1.96-2.05 (2H, m), 1.86 (3H, s), 1.79 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 167.0, 141.6, 134.7, 133.6, 131.3, 128.51(2), 128.46(2), 128.3(2), 126.8(2), 125.9, 116.8, 50.0, 42.2, 35.4, 32.6, 25.5, 20.9; IR (NaCl) ν 3308, 3030, 2934, 2855, 1636, 1558, 1540, 1506, 1489, 1456, 696 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{25}\text{BrNO}$ (M^+H^+): 386.1120, found: 386.1118.

***N*-(1-Phenylhex-5-yn-3-yl)benzamide (84):**

93% Yield; white solid; m.p. 95-97 °C; R_f = 0.31 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.72 (2H, d, J = 8.0 Hz), 7.41-7.53 (3H, m), 7.17-7.30 (5H, m), 6.23 (1H, d, J = 8.0 Hz), 4.34-4.38 (1H, m), 2.63-2.77 (3H, m), 2.50 (1H, ddd, J = 2.8 Hz, 4.0 Hz, 16.8 Hz), 2.02-2.08 (3H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 167.1, 141.3, 134.5, 133.5, 131.6, 130.2, 128.63, 128.58, 128.50, 128.39, 126.9(2), 126.1, 80.1, 71.3, 47.3, 35.2, 32.5, 24.3; IR (NaCl) ν 3325, 3300, 3030, 2953, 2930, 2860, 1636, 1558, 1526, 1506, 1489, 1456, 750, 700, 667, 642 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{20}\text{NO}$ (M^+H^+): 278.1545, found: 278.1547.

Compounds **77a-e**, **83** were prepared by following the same procedures for **34a**.

***N*-(5-Bromo-1-phenylhex-5-en-3-yl)benzothioamide (77a):**

95% Yield; yellow solid; m.p. 88-89 °C; R_f = 0.33 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (300 MHz, CDCl_3) δ 7.62-7.64 (2H, m), 7.42-7.51 (2H, m), 7.20-7.38 (6H, m), 5.73 (1H, s), 5.58 (1H, s), 5.07-5.14 (1H, m), 2.87-3.00 (2H, m), 2.77-2.82 (2H, m), 2.07-2.14 (2H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 198.9, 142.1, 141.1, 131.1, 128.9, 128.7(2), 128.5(2), 128.4(2), 126.6(2), 126.2, 120.3, 54.5, 44.2, 34.5, 32.5; IR (NaCl) ν 3310, 3030, 2928, 2855, 1541, 1522, 1489, 1456, 1339, 1213, 980, 895, 752, 700, 691, 664 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{21}\text{BrNS}$ (M^+H^+): 374.0578, found: 374.0575.

***N*-(5-Bromo-1-phenylhex-5-en-3-yl)-3-phenylpropanethioamide (77b):**

85% Yield; white solid; m.p. 66-67 °C; R_f = 0.43 (silica gel; hexane : ethyl acetate = 2 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.26-7.31 (4H, m), 7.17-7.22 (4H, m), 7.12-7.14 (2H, m), 6.86 (1H, m), 5.56 (1H, s), 5.48 (1H, s), 4.81-4.90 (1H, m), 2.87-3.00 (2H, m), 3.09 (2H, t, J = 7.2 Hz), 2.86 (2H, t, J = 7.2 Hz), 2.73 (1H, dd, J = 6.0 Hz, 14.9 Hz), 2.48-2.63 (3H, m), 1.74-1.97 (3H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 203.7, 141.1, 140.1, 128.7, 128.6(2), 128.5(4), 128.3(2), 126.5, 126.2, 120.0, 53.8, 49.1, 43.9, 35.2, 34.2, 32.2; IR (NaCl) ν 3308, 3022, 2951, 2930, 2857, 1541, 1526, 1506, 1456, 1418, 1184, 1105, 893, 750, 733, 700, 640 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{25}\text{BrNS}$ (M^+H^+): 402.0891, found: 402.0890.

***N*-(5-Bromo-1-phenylhex-5-en-3-yl)thiophene-2-carbothioamide (77c):**

78% Yield; yellow solid; m.p. 109-111 °C; R_f = 0.32 (silica gel; hexane : ethyl acetate = 2 : 1, twice); ^1H NMR (400 MHz, CDCl_3) δ 7.47 (1H, d, J = 5.0 Hz), 7.40 (1H, d, J = 8.0 Hz), 7.16-7.29 (6H, m), 7.02 (1H, t, J = 4.0 Hz), 5.71 (1H, s), 5.57 (1H, s), 5.02-5.11 (1H, m), 2.85-2.96 (2H, m), 2.77 (2H, t, J = 7.8 Hz), 2.04-2.16 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 188.1, 146.8, 141.1, 132.3, 128.7, 128.6(2), 128.4(2), 127.7, 126.2, 124.2, 120.4, 54.2, 44.3, 34.5, 32.4; IR (NaCl) ν 3325, 3057, 3030, 2926, 2857, 1531, 1499, 1456, 1387, 1362, 1267, 1200, 1076, 974, 899, 750, 702, 662 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{19}\text{BrNOS}$ (M^+H^+): 380.0142, found: 380.0137.

***N*-(5-Bromohex-5-en-3-yl)benzothioamide (77d):**

98% Yield; white solid; m.p. 57-59 °C; R_f = 0.39 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (300 MHz, CDCl_3) δ 7.71 (2H, d, J = 7.9 Hz), 7.34-7.47 (4H, m), 5.73 (1H, s), 5.56 (1H, s), 4.89-5.01 (1H, m), 2.88 (2H, d, J = 6.2 Hz), 1.71-1.87 (2H, m), 1.2 (3H, J = 7.4 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 199.1, 142.3, 131.0, 129.1, 128.6(2), 126.6(2), 120.0, 55.7, 43.9, 25.9, 10.4; IR (NaCl) ν 3165, 3030, 2965, 2928, 2851, 1558, 1526, 1506, 1456, 1387, 1375, 1236, 1215, 1009, 959, 897, 768, 706, 696 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{17}\text{BrNS}$ (M^+H^+): 298.0265, found 298.0272.

***N*-(5-Bromo-6-methyl-1-phenylhept-5-en-3-yl)benzothioamide (77e):**

95% Yield; yellow solid; m.p. 91-93 °C R_f = 0.40 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.63 (2H, d, J = 7.5 Hz), 7.42-7.50 (2H, m), 7.36 (2H, t, J = 7.6 Hz), 7.16-7.29 (5H, m), 5.07-5.15 (1H, m), 2.96-3.08 (2H, m), 2.79 (2H, d, J = 7.8 Hz), 2.04-2.20 (2H, m), 1.89 (3H, s), 1.82 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 198.7, 142.2, 141.2, 134.4, 130.9, 128.6(2), 128.4(2), 128.3(2), 126.5(2), 126.1, 115.7, 55.7, 40.7, 34.7, 32.6, 25.6, 21.1; IR (NaCl) ν 3219, 3022, 2947, 2914, 2855, 1541, 1522, 1506, 1489, 1373, 980, 752, 708, 696 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{25}\text{BrNS}$ (M^+H^+): 402.0891, found: 402.0891.

***N*-(1-Phenylhex-5-yn-3-yl)benzothioamide (83):**

58% Yield; yellow oil; $R_f = 0.60$ (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.67 (2H, d, $J = 8.0$ Hz), 7.59 (1H, d, $J = 8.0$ Hz), 7.47 (1H, t, $J = 8.0$ Hz), 7.38 (2H, t, $J = 8.0$ Hz), 7.18-7.31 (5H, m), 4.89-4.97 (1H, m), 2.90 (1H, d, $J = 16.0$ Hz), 2.72-2.92 (2H, m), 2.57 (1H, d, $J = 16.0$ Hz), 2.13-2.29 (2H, m), 2.09 (1H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 198.9, 142.0, 141.0, 131.2, 128.7(2), 128.6(2), 128.4(2), 126.7(2), 126.3, 79.7, 71.6, 53.3, 34.3, 32.5, 22.5; IR (NaCl) ν 3080, 3062, 3024, 2922, 2855, 1622, 1603, 1540, 1522, 1506, 1489, 1456, 1229, 943, 920, 872, 764, 748, 691, 667 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{20}\text{NS}$ (M^+H^+): 294.1316, found: 294.1317.

Typical procedure for intramolecular cyclization of *N*-(5-bromo-1-phenylhex-5-en-3-yl)benzothioamide (77a):

To a solution of *N*-(5-bromo-1-phenylhex-5-en-3-yl)benzothioamide **77a** (75 mg, 0.2 mmol) in DMF (7 mL), was added NaOH (12 mg, 0.3 mmol), *n*-Bu₄NBr (3.2 mg, 0.01 mmol) and a drop of H₂O. The mixture was stirred at 80 °C. After the completion of the reaction (12 h), the mixture was quenched with a pH 9 ammonium buffer solution, and extracted with ethyl acetate (10 mL×3), the combined extracts were washed by brine and dried over MgSO₄. The solvent was removed in vacuo, and the resulting crude was purified by PTLC (silica gel; ethyl acetate : hexane : = 1 : 3) to afford 6-methylene-4-phenethyl-2-phenyl-5,6-dihydro-4*H*-1,3-thiazine **78a** in 92% yield.

Yellow oil; $R_f = 0.76$ (silica gel; hexane : ethyl acetate = 5 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.86 (2H, d, $J = 6.9$ Hz), 7.39-7.45 (3H, m), 7.26-7.32 (4H, m), 7.21 (1H, d, $J = 6.9$ Hz), 5.15 (2H, d, $J = 13.6$ Hz), 3.74-3.96 (1H, m), 2.90-3.00 (2H, m), 2.57 (1H, d, $J = 14.2$ Hz), 2.22 (1H, dd, $J = 8.8$ Hz, 14.2 Hz), 2.07-2.12 (1H, m), 1.93-1.98 (1H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 198.9, 142.0, 141.0, 131.2, 128.7(2), 128.6(2), 128.4(2), 126.7(2), 126.3, 79.7, 71.6, 53.3, 34.3, 32.5, 22.5; IR (NaCl) ν 3080, 3063, 3024, 2920, 2855, 1622, 1603, 1542, 1521, 1506, 1489, 1456, 1229, 943, 920, 872, 764, 746, 690, 667 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{20}\text{NS}$ (M^+H^+): 294.1316, found: 294.1320.

Compounds **78b-e** were prepared by following the same procedures for **78a**.

6-Methylene-2,4-diphenethyl-5,6-dihydro-4H-1,3-thiazine (78b):

89% Yield; colorless liquid; $R_f = 0.63$ (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (300 MHz, CDCl_3) δ 7.05-7.20 (10H, m), 4.93 (2H, d, $J = 2.4$ Hz), 3.49-3.52 (1H, m), 2.86-2.92 (2H, m), 2.57-2.70 (4H, m), 2.30 (1H, dd, $J = 3.3$ Hz, 14.1 Hz), 1.93-2.04 (1H, m), 1.61-1.88 (2H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 157.7, 142.1, 140.7, 137.3, 128.44(2), 128.38(2), 128.29(2), 128.25(2), 126.0, 125.7, 109.5, 57.0, 42.3, 36.8, 33.5, 33.4, 31.9; IR (NaCl) ν 3055, 3030, 2928, 2853, 1558, 1522, 1506, 1456, 1265, 732, 702 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{24}\text{NS}$ (M^+H^+): 322.1629, found: 322.1622.

4-Ethyl-6-methylene-2-phenyl-5,6-dihydro-4H-1,3-thiazine (78c):

81% Yield; colorless liquid; $R_f = 0.75$ (silica gel; hexane : ethyl acetate = 3 : 1); ^1H NMR (300 MHz, CDCl_3) δ 7.80-7.84 (2H, m), 7.34-7.42 (3H, m), 5.13 (2H, d, $J = 8.8$ Hz), 3.58-3.67 (1H, m), 2.54 (1H, dd, $J = 3.2$ Hz, 14.2 Hz), 2.18 (1H, dd, $J = 9.0$ Hz, 15.0 Hz), 1.60-1.85 (2H, m), 1.09 (1H, t, $J = 7.4$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 155.8, 138.3, 137.7, 130.5, 128.3(2), 126.5(2), 109.7, 60.0, 33.2, 28.4, 10.4; IR (NaCl) ν 3080, 3063, 3030, 2961, 2932, 1622, 1603, 1540, 1522, 1506, 1489, 1456, 1229, 978, 939, 926, 868, 764, 691, 667 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{16}\text{NS}$ (M^+H^+): 218.1003, found: 218.1004.

6-Methylene-4-phenethyl-2-(thiophen-2-yl)-5,6-dihydro-4H-1,3-thiazine (78d):

70% Yield; colorless liquid; $R_f = 0.48$ (silica gel; hexane : ethyl acetate = 3 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.47 (1H, d, $J = 3.6$ Hz), 7.38 (1H, d, $J = 4.8$ Hz), 7.17-7.30 (5H, m), 7.03 (1H, dd, $J = 3.6$ Hz, 4.8 Hz), 5.13 (2H, d, $J = 10.0$ Hz), 3.69-3.76 (1H, m), 2.81-2.95 (2H, m), 2.54 (1H, dd, $J = 3.2$ Hz, 14.4 Hz), 2.22 (1H, dd, $J = 8.4$ Hz, 14.0 Hz), 1.99-2.08 (1H, m), 1.85-1.92 (1H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 149.9, 143.3, 142.2, 136.9, 128.6(3), 128.4(2), 127.2, 126.5, 125.8, 110.2, 57.4, 37.1, 34.2, 32.2; IR (NaCl) ν 3080, 3060, 3024, 2922, 2853, 1616, 1593, 1558, 1521, 1506, 1456, 1420, 1236, 1051, 895, 872, 833, 810, 745, 698 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{18}\text{NS}_2$ (M^+H^+): 300.0881, found: 300.0883.

4-Phenethyl-2-phenyl-6-(propan-2-ylidene)-5,6-dihydro-4H-1,3-thiazine (78e):

37% Yield; colorless liquid; $R_f = 0.63$ (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (300 MHz, CDCl_3) δ 7.91 (2H, dd, $J = 3.0$ Hz, $J = 9.0$ Hz), 7.38-7.45 (3H, m), 7.17-7.34 (5H, m), 3.65-3.72 (1H, m), 2.86-3.00 (2H, m), 2.67 (1H, d, $J = 12.0$ Hz), 2.06-2.22 (2H, m), 1.89-1.98 (1H, m), 1.85 (3H, s), 1.82 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 162.3, 157.2, 142.4, 138.9, 130.4, 128.6(2), 128.32, 128.30(2), 126.7(2), 125.9, 125.7, 120.6, 58.3, 37.4, 32.6, 29.7, 21.0, 20.1; IR (NaCl) ν 3062, 3030, 2911, 2855, 1558, 1541, 1522, 1506, 1489, 1456, 1361, 1231, 939, 908, 764, 733, 698 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{24}\text{NS}$ (M^+H^+): 322.1629, found: 322.1628.

6.3. Experimental procedure for part II, chapter 4

Typical procedure for preparation of (E)-tert-butyl 3-hydroxy-2-(2-nitro-4-trifluoromethylphenyl)but-2-enoate (136a):

At 0 $^{\circ}\text{C}$, *tert*-butyl acetoacetate (6.62 mL, 40 mmol) was added dropwisely into the suspension of sodium hydride (60%) (1.68 g, 42 mmol) in dry 200 mL THF under an N_2 atmosphere. The mixture was then left to stir at 0 $^{\circ}\text{C}$ till clear solution. 1-Fluoro-2-nitro-4-trifluoromethylbenzene (2.8 mL, 20 mmol) was next added into the mixture dropwisely and

allowed to stir under reflux. After completion of the starting material (7 h), the reaction mixture was cooled to room temperature. Subsequently, the mixture was quenched and diluted with 300 mL water, extracted with ethyl acetate (50 mL×3). The resulting extracts were dried over anhydrous MgSO₄, filtered and removed the solvents under reduced pressure. The crude was purified by flash column chromatography (silica gel; hexane : ethyl acetate = 250 : 1) to give pure (*E*)-*tert*-butyl 3-hydroxy-2-(2-nitro-4-trifluoromethylphenyl)but-2-enoate **136a** (6.47 g, 18.6 mmol) in 93% yield.

All the product **136** obtained is a mixture of enol-form (major) and ketone-form (minor) isomers determined from NMR spectrum. The ratio was pointed out in ¹H NMR, ¹³C NMR was recorded based on the enol-form isomer.

tert-Butyl 3-hydroxy-2-(2-nitro-4-trifluoromethylphenyl)but-2-enoate (**136a**):

Yellow oil; R_f = 0.70 (silica gel; hexane : ethyl acetate = 3 : 1); ¹H NMR (400 MHz, CDCl₃) δ 13.26 (0.94H, OH, s), 8.30 (0.06H, s), 8.23 (0.94H, s), 7.88 (0.06H, dd, *J* = 1.2 Hz, 8.0 Hz), 7.82 (0.94H, dd, *J* = 1.2 Hz, 8.0 Hz), 7.66 (0.06H, d, *J* = 8.0 Hz), 7.44 (0.94H, d, *J* = 8.0 Hz), 5.30 (0.06H, s), 2.44 (0.18H, s), 1.90 (2.82H, s), 1.49 (0.54H, s), 1.34 (8.46H, s); ¹³C NMR (100 MHz, CDCl₃) δ 173.27, 169.95, 149.69, 134.72, 134.51, 130.72 (q, *J* = 34 Hz), 128.97 (q, *J* = 3 Hz), 124.21, 121.56 (q, *J* = 4 Hz), 101.35, 83.12, 27.82(3), 20.02; IR (KBr) ν 3020, 2982, 1645, 1539, 1354, 1323, 1152 cm⁻¹; HRMS (ESI) calcd for C₁₅H₁₈F₃NO₅ (M⁺H⁺): 348.1059, found: 348.1055.

Compounds **136b-h** were prepared by the following the same procedures for **136a**.

***tert*-Butyl 2-(4-bromo-2-nitrophenyl)-3-hydroxybut-2-enoate (136b):**

Prepared from 4-bromo-1-fluoro-2-nitrobenzene and *tert*-butyl acetoacetate, overnight, 74% yield. Yellow oil; $R_f = 0.52$ (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 13.20 (0.93H, OH, s), 8.18 (0.07H, d, $J = 2.0$ Hz), 8.11 (0.93H, d, $J = 2.0$ Hz), 7.76 (0.07H, dd, $J = 2.0$ Hz, 8.4 Hz), 7.69 (0.93H, dd, $J = 2.0$ Hz, 8.4 Hz), 7.37 (0.7H, d, $J = 8.4$ Hz), 7.16 (0.93H, d, $J = 8.4$ Hz), 5.20 (0.7H, s), 2.40 (0.21H, s), 1.87 (2.79H, s), 1.48 (0.63H, s), 1.34 (8.37H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 172.88, 170.20, 150.02, 135.61, 135.05, 129.66, 127.30, 121.16, 101.30, 82.78, 27.83(3), 19.95; IR (KBr) ν 3000, 2982, 2930, 1645, 1531, 1350, 1252, 1152 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{16}\text{BrNO}_5\text{Na}$ (M^+Na^+): 380.0110 (Br^{79}), found: 380.0113 and 382.0089 (Br^{81}), found: 382.0088.

***tert*-Butyl 2-(4-fluoro-2-nitrophenyl)-3-hydroxybut-2-enoate (136c):**

Prepared from 1,4-difluoro-2-nitrobenzene (1.1 equiv.) and *tert*-butyl acetoacetate (1.0 equiv.), 2 d, 25% yield. Yellow oil; $R_f = 0.74$ (silica gel; hexane : ethyl acetate = 3 : 1); ^1H NMR (400 MHz, CDCl_3) δ 13.17 (0.84H, OH, s), 7.77 (0.16H, dd, $J = 2.4$ Hz, 8.0 Hz), 7.70 (0.84H, dd, $J = 2.4$ Hz, 8.0 Hz), 7.32-7.25 (2H, m), 5.23 (0.16H, s), 2.39 (0.48H, s), 1.86 (2.62H, s), 1.48 (1.44H, s), 1.33 (7.56H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 172.85, 170.48, 161.14 (d, $J = 250$ Hz), 150.05, 135.21 (d, $J = 7$ Hz), 126.83 (d, $J = 5$ Hz), 119.85 (d, $J = 11$ Hz), 112.02 (d, $J = 26$ Hz), 101.27, 82.58, 27.85(3), 19.91; IR (KBr) ν 3204, 2980, 2930, 1724, 1647, 1535, 1352, 1269, 1155 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{16}\text{FNO}_5\text{Na}$ (M^+Na^+): 320.01910, found: 320.0909.

***tert*-Butyl 2-(5-fluoro-2-nitrophenyl)-3-hydroxybut-2-enoate (136d):**

Prepared from 2,4-difluoro-1-nitrobenzene (1.1 equiv.) and *tert*-butyl acetoacetate (1.0 equiv.), potassium *tert*-butoxide as the base, overnight, 65% yield. Yellow oil; $R_f = 0.72$ (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 13.18 (0.92H, OH, s), 8.12 (0.08H, dd, $J = 5.2$ Hz, 9.2 Hz), 8.05 (0.92H, dd, $J = 5.2$ Hz, 9.2 Hz), 7.22-7.16 (0.16H, m), 7.13 (0.92H, dt, $J = 2.8$ Hz, 9.2 Hz), 6.97 (0.92H, dd, $J = 2.8$ Hz, 8.8 Hz), 5.31 (0.08H, d, $J = 4.0$ Hz), 2.42 (0.24H, s), 1.90 (2.76 H, s), 1.49 (0.72H, s), 1.34 (8.28H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 172.63, 170.13, 163.98 (d, $J = 255$ Hz), 145.87, 134.00 (d, $J = 10$ Hz), 126.82 (d, $J = 10$ Hz), 120.50 (d, $J = 22$ Hz), 115.05 (d, $J = 23$ Hz), 101.79 (d, $J = 1$ Hz), 82.71, 27.80(3), 19.88; IR (KBr) ν 3204, 2980, 2930, 1720, 1655, 1520, 1352, 1254, 1155 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_5\text{Na}$ (M^+Na^+): 320.0910, found: 320.0912.

***tert*-Butyl 3-hydroxy-2-(2-nitrophenyl)but-2-enoate (136e):**

Prepared from 1-fluoro-2-nitrobenzene and *tert*-butyl acetoacetate, 1 d, 40% yield. Yellow oil; $R_f = 0.70$ (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 13.17 (1H, OH, s), 7.97 (1H, dd, $J = 1.2$ Hz, 8.0 Hz), 7.57 (1H, dt, $J = 1.2$ Hz, 7.6 Hz), 7.42 (1H, dt, $J = 1.2$ Hz, 8.0 Hz), 7.27 (1H, dd, $J = 1.6$ Hz, 7.6 Hz), 1.87 (3H, s), 1.33 (9H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 172.48, 170.59, 149.73, 133.77, 132.55, 130.65, 128.13, 124.21, 102.21, 82.36, 27.80(3), 19.90; IR (KBr) ν 3019, 2980, 2930,

1720, 1645, 1526, 1354, 1252, 1155 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_5\text{Na}$ (M^+Na^+): 302.1004, found: 302.1007.

***tert*-Butyl 3-hydroxy-2-(4-methyl-2-nitrophenyl)but-2-enoate (136f):**

Prepared from 1-fluoro-4-methyl-2-nitrobenzene and *tert*-butyl acetoacetate, overnight, 31% yield. Yellow oil; $R_f = 0.57$ (silica gel; hexane : ethyl acetate = 3 : 1); ^1H NMR (300 MHz, CDCl_3) δ 13.14 (0.85H, OH, s), 7.98 (0.15H, d, $J = 8.4$ Hz), 7.90 (0.85H, d, $J = 8.4$ Hz), 7.26-7.20 (1.15H, m), 7.04 (0.85H, d, $J = 1.2$ Hz), 5.27 (0.15H, s), 2.43 (3H, d, $J = 2.7$ Hz), 2.37 (0.45H, s), 1.87 (2.55H, s), 1.48 (1.35 H, s), 1.33 (7.65H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 172.08, 170.70, 147.39, 143.62, 134.24, 130.73, 128.64, 124.43, 102.55, 82.24, 27.83(3), 21.33, 19.92; IR (KBr) ν 3021, 2980, 2930, 1645, 1520, 1350, 1254, 1155 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_5\text{Na}$ (M^+Na^+): 316.1161, found: 316.1164.

***tert*-Butyl 3-hydroxy-4-methyl-2-(2-nitrophenyl)pent-2-enoate (136g):**

Prepared from 1-fluoro-2-nitrobenzene and *tert*-butyl 4-methyl-3-oxopentanoate, 3 d, 25% yield, 74% of starting material recovered. Yellow oil; $R_f = 0.75$ (silica gel; hexane : ethyl acetate = 3 : 1); ^1H NMR (400 MHz, CDCl_3) δ 13.22 (0.79H, OH, s), 8.01 (0.21H, d, $J = 8.0$ Hz), 7.96 (0.79H, d, $J = 8.0$ Hz), 7.63 (0.21H, t, $J = 7.2$ Hz), 7.56 (0.79H, dd, $J = 7.2$ Hz), 7.52-7.42 (1.21, m), 7.26 (0.79H, d, 7.6 Hz), 5.52 (0.21H, s), 2.86 (0.21H, quint, $J = 6.8$ Hz), 2.37 (0.79H, quint, $J = 6.8$ Hz), 1.47 (1.89H, s), 1.33 (7.11 H, s), 1.28 (0.51H, d, $J = 6.8$ Hz), 1.20 (0.63H, d, $J = 6.8$ Hz), 1.14 (3H, d, $J = 6.8$ Hz), 1.04 (2.37H, d, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 179.42, 171.03, 149.96, 133.61, 132.48, 130.69,

128.09, 124.19, 100.19, 82.21, 31.52, 27.82(3), 19.42, 19.37; IR (KBr) ν 3021, 2980, 2934, 1643, 1526, 1354, 1155 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_5\text{Na}$ (M^+Na^+): 330.1317, found: 330.1320.

Ethyl 3-hydroxy-2-(2-nitrophenyl)but-2-enoate (136h):

Prepared from 1-fluoro-4-methyl-2-nitrobenzene and ethyl acetoacetate, overnight, 53% yield. Colorless oil; R_f = 0.57 (silica gel; hexane : ethyl acetate = 3 : 1); ^1H NMR (400 MHz, CDCl_3) δ 13.03 (0.93H, OH, s), 8.06 (0.07H, d, J = 1.6 Hz, 8.4 Hz), 8.00 (0.93H, d, J = 1.6 Hz, 8.4 Hz), 7.61 (0.93H, dt, J = 1.2 Hz, 7.6 Hz), 7.49 (1.07H, dt, J = 1.2 Hz, 8.4 Hz), 7.30 (1H, dd, J = 1.2 Hz, 7.6 Hz), 5.34 (0.07H, s), 4.21 (1H, dq, J = 7.2 Hz, 3.6 Hz), 4.03 (1H, dq, J = 7.2 Hz, 3.6 Hz), 2.39 (0.21H, s), 1.87 (2.79H, s), 1.28 (0.21, t, J = 7.2 Hz), 1.11 (2.79H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 173.11, 170.92, 149.61, 133.89, 132.72, 129.92, 128.49, 124.36, 100.89, 60.86, 19.73, 13.75; IR (KBr) ν 3019, 2983, 1649, 1528, 1353, 1252, 1223 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_5\text{Na}$ (M^+Na^+): 274.0691, found: 274.0697.

Typical procedure for the synthesis of (E)-Ethyl 3-hydroxy-2-(2-nitrophenyl)acrylate (136i):¹⁰

At 0 °C, TiCl₄ (5 mL, 5 mmol) and Et₃N (0.85 mL, 6 mmol) were successively added dropwise to a stirred solution of *ortho*-nitrophenylacetate (0.59 mg, 2.5 mmol) and HCO₂Me (0.605 mL, 7.5 mmol) in CH₂Cl₂ (13 mL) under an N₂ atmosphere. The mixture was stirred at the same temperature for 1 h and at room temperature for 1 h. Water was added to the mixture, which was extracted twice with ethyl acetate. The combined organic phase was washed with brine, dried over Mg₂SO₄, and concentrated. The obtained crude was purified by flash column chromatography (silica gel; hexane : ethyl acetate = 3 : 1) to give (*E*)-Ethyl 3-hydroxy-2-(2-nitrophenyl)acrylate **136i** (0.41 g, 1.75 mmol) in 70% yield.

Colorless oil; *R*_f = 0.38 (silica gel; hexane : ethyl acetate = 3 : 1); ¹H NMR (400 MHz, CDCl₃) δ 12.01 (0.85H, OH, d, *J* = 12.8 Hz), 10.14 (0.15H, CHO, s), 8.11 (0.15H, dd, *J* = 1.2 Hz, 8.4 Hz), 8.02 (0.85H, dd, *J* = 1.2 Hz, 8.4 Hz), 7.61 (1H, dt, *J* = 1.6 Hz, 7.6 Hz), 7.48 (1H, dt, *J* = 1.6 Hz, 7.8 Hz), 7.33-7.27 (2H, m), 4.18 (2H, q, *J* = 7.2 Hz), 1.26 (0.45H, t, *J* = 7.2 Hz), 1.18 (2.55H, t, *J* = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 169.92, 162.12, 149.09, 133.27, 132.17, 129.14, 128.53, 124.76, 106.57, 61.26, 13.69; IR (KBr) ν 3229, 1669, 1520, 1354, 1177 cm⁻¹; HRMS (ESI) calcd for C₁₁H₁₁NO₅Na (M⁺Na⁺): 260.0535, found: 260.0536.

Typical procedure for preparation of tert-butyl 1-hydroxy-2-methyl-6-trifluoromethyl-1H-indole-3-carboxylate (NHI-1): ¹¹

5% Palladium on carbon (1.7 g, 0.82 mmol) in flask was added ethyl acetate (20 mL) and $(\text{PPh}_3)_4\text{Pd}$ (0.19 g, 0.016 mmol), followed by *tert*-butyl 3-hydroxy-2-(2-nitro-4-trifluoromethylphenyl)but-2-enoate **136a** (5.7 g, 16.42 mmol) in ethyl acetate (40 mL) and acetic acid (15 mL). The reaction mixture was degassed and changed to a hydrogen balloon (1 atm), allowed to stir at room temperature till completion (12 h), the mixture was filtered through celite and flushed with ethyl acetate. The solvents were removed under reduced pressure, then purified by flash column chromatography (silica gel; hexane : ethyl acetate = 8 : 1) to give pure *tert*-butyl 1-hydroxy-2-methyl-6-(trifluoromethyl)-1*H*-indole-3-carboxylate **NHI-1** (4.21 g, 13.1 mmol) in 80% yield.

Colorless crystal (CCDC 818557)¹²; m.p. 163-165 °C; R_f = 0.38 (silica gel; hexane : ethyl acetate = 3 : 1); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.91 (1H, OH, s), 8.14 (1H, d, J = 8.4 Hz), 7.74 (1H, s), 7.46 (1H, d, J = 8.4 Hz), 2.69 (3H, s), 1.59 (9H, s); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 163.66, 144.19, 131.70, 124.99 (q, J = 270 Hz), 124.70, 122.25 (q, J = 31.5 Hz), 121.13, 117.60 (d, J = 3 Hz), 105.77 (d, J = 4 Hz), 99.78, 79.55, 28.19(3), 10.56; IR (KBr) ν 3090, 3071, 1643, 1537, 1448, 1333, 1163, 1120 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{17}\text{F}_3\text{NO}_3$ (M^+H^+): 316.1161, found: 316.1169.

Compounds NHI-2 to NHI-9 were prepared by the following the same procedures for NHI-1.

***tert*-Butyl 6-bromo-1-hydroxy-2-methyl-1*H*-indole-3-carboxylate (NHI-2):**

Prepared from *tert*-butyl 2-(4-bromo-2-nitrophenyl)-3-hydroxybut-2-enoate **136b**, 6 h, 84% yield. White solid; m.p. 130-132 °C; R_f = 0.13 (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, DMSO- d_6) δ 11.70 (1H, OH, s), 7.87 (1H, d, J = 8.5 Hz), 7.57 (1H, d, J = 1.6 Hz), 7.28 (1H, dd, J = 1.8 Hz, 8.5 Hz), 2.63 (3H, s), 1.57 (9H, s); ^{13}C NMR (100 MHz, DMSO- d_6) δ 163.80, 142.19, 133.50, 124.17, 122.08, 121.15, 114.39, 111.00, 99.45, 79.33, 28.21(3), 10.44; IR (KBr) ν 3181, 1653, 1462, 1368, 1267, 1142, 1128 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{27}\text{BrNO}_3$ (M^+H^+): 326.0392(Br^{79}), found: 326.0386 and 328.0371(Br^{81}), found: 328.0378.

***tert*-Butyl 6-fluoro-1-hydroxy-2-methyl-1*H*-indole-3-carboxylate (NHI-3):**

Prepared from *tert*-butyl 2-(4-fluoro-2-nitrophenyl)-3-hydroxybut-2-enoate **136c**, overnight, 63% yield. White solid; m.p. 138-140 °C; R_f = 0.46 (silica gel; hexane : ethyl acetate = 3 : 1); ^1H NMR (400 MHz, DMSO- d_6) δ 11.64 (1H, OH, s), 7.93 (1H, dd, J = 5.6 Hz, 8.8 Hz), 7.21 (1H, dd, J = 2.0 Hz, 9.2 Hz), 7.01 (1H, t, J = 9.2 Hz), 2.63 (3H, s), 1.57 (9H, s); ^{13}C NMR (100 MHz, DMSO- d_6) δ 163.96, 158.85 (d, J = 235 Hz), 142.14 (d,

$J = 3$ Hz), 132.78 (d, $J = 13$ Hz), 121.68 (d, $J = 10$ Hz), 118.75, 109.53 (d, $J = 23$ Hz), 99.35, 94.89 (d, $J = 27$ Hz), 79.19, 28.24(3), 10.47; IR (KBr) ν 3204, 1655, 1111 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{17}\text{FNO}_3$ (M^+H^+): 266.1192, found: 226.1189.

***tert*-Butyl 5-fluoro-1-hydroxy-2-methyl-1*H*-indole-3-carboxylate (NHI-4):**

Prepared from *tert*-butyl 2-(5-fluoro-2-nitrophenyl)-3-hydroxybut-2-enoate **136d**, 1 d, 88% yield. White solid; m.p. 183-185 $^{\circ}\text{C}$; $R_f = 0.26$ (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.66 (1H, OH, s), 7.61 (1H, dd, $J = 2.4$ Hz, 10.4 Hz), 7.42 (1H, q, $J = 4.4$ Hz), 7.04 (1H, dt, $J = 2.4$ Hz, 9.2 Hz), 2.63 (3H, s), 1.57 (9H, s); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 163.92, 158.33 (d, $J = 232$ Hz), 142.68, 129.52, 122.68 (d, $J = 11$ Hz), 109.97 (d, $J = 11$ Hz), 109.73, 105.32 (d, $J = 25$ Hz), 99.18 (d, $J = 4.0$ Hz), 79.25 (d, $J = 2.0$ Hz), 28.22(3), 10.56; IR (KBr) ν 3138, 1643, 1520, 1368, 1115 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{17}\text{FNO}_3$ (M^+H^+): 266.1192, found: 266.1195.

***tert*-Butyl 1-hydroxy-2-methyl-1*H*-indole-3-carboxylate (NHI-5):**

Prepared from *tert*-butyl 3-hydroxy-2-(2-nitrophenyl)but-2-enoate **136e**, overnight, 97% yield. White solid; m.p. 129-131 $^{\circ}\text{C}$; $R_f = 0.25$ (silica gel; hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.50 (1H, OH, s), 7.95 (1H, s), 7.41 (1H, s), 7.14-7.20 (2H, m), 2.64 (3H, s), 1.58 (9H, s); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 164.27, 141.24, 132.82, 122.21, 121.71, 121.26, 120.27, 108.41, 99.13, 78.88, 28.28(3), 10.45; IR (KBr) ν

3229, 1655, 1520, 1152, 1111 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_3$ (M^+H^+): 248.1287, found: 248.1290.

***tert*-Butyl 1-hydroxy-2,6-dimethyl-1*H*-indole-3-carboxylate (NHI-6):**

Prepared from *tert*-butyl 3-hydroxy-2-(4-methyl-2-nitrophenyl)but-2-enoate **136f**, overnight, 82% yield. White solid; m.p. 149-151 $^{\circ}\text{C}$; R_f = 0.31 (silica gel; hexane : ethyl acetate = 3 : 1); ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 11.43 (1H, OH, s), 7.78 (1H, s), 7.31 (1H, d, J = 8.1 Hz), 7.01 (1H, d, J = 8.1 Hz), 2.63 (3H, s), 2.40 (3H, s), 1.58 (9H, s); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 164.30, 140.92, 131.29, 129.94, 123.12, 122.53, 120.16, 108.15, 98.59, 78.78, 28.28(3), 21.40, 10.49; IR (KBr) ν 3204, 1651, 1454, 1416, 1368, 1148, 1121 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_3$ (M^+H^+): 316.1161, found: 316.1169.

***tert*-Butyl 1-hydroxy-2-isopropyl-1*H*-indole-3-carboxylate (NHI-7):**

Prepared from *tert*-butyl 3-hydroxy-4-methyl-2-(2-nitrophenyl)pent-2-enoate **136g**, overnight, 78% yield. White solid; m.p. 198-200 $^{\circ}\text{C}$; R_f = 0.47 (silica gel; hexane : ethyl acetate = 3 : 1); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.51 (1H, OH, s), 7.96 (1H, d, J = 7.6 Hz), 7.41 (1H, d, J = 8.0 Hz), 7.20 (1H, t, J = 7.0 Hz), 7.14 (1H, t, J = 7.6 Hz), 4.25 (1H, septet, J = 7.2 Hz), 1.58 (9H, s), 1.42 (6H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 164.24, 148.94, 133.14, 122.13, 121.80, 121.31, 120.82, 108.48, 98.02, 79.06, 28.30(3), 24.43, 19.94(2); IR (KBr) ν 3188, 1645, 1520, 1449, 1364, 1150, 1113 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_3$ (M^+H^+): 276.1600, found: 276.1601.

Ethyl 1-hydroxy-2-methyl-1*H*-indole-3-carboxylate (NHI-8):

Prepared from ethyl 3-hydroxy-2-(2-nitrophenyl)but-2-enoate **136h**, overnight, 94% yield.

Faint yellow solid; m.p. 105-107 °C; R_f = 0.34 (silica gel; hexane : ethyl acetate = 3 : 1);

^1H NMR (400 MHz, DMSO- d_6) δ 11.58 (1H, OH, s), 7.99 (1H, d, J = 7.6 Hz), 7.44 (1H, d, J = 8.0 Hz), 7.19 (1H, t, J = 8.8 Hz), 4.29 (2H, q, J = 7.2 Hz), 2.68 (3H, s), 1.36 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, DMSO- d_6) δ 164.77, 141.62, 132.91, 122.11, 121.92, 121.49, 120.39, 108.56, 97.84, 58.90, 14.47, 10.49; IR (KBr) ν 3204, 1659, 1541, 1451, 1155, 1113 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{14}\text{NO}_3$ (M^+H^+): 220.0974, found: 220.0978.

Ethyl 1-hydroxy-1*H*-indole-3-carboxylate (NHI-9):

Prepared from (*E*)-ethyl 3-hydroxy-2-(2-nitrophenyl)acrylate **136i**, overnight, 50% yield.

Faint yellow solid; m.p. 100-102 °C; R_f = 0.18 (silica gel; hexane : ethyl acetate = 3 : 1);

^1H NMR (400 MHz, DMSO- d_6) δ 11.96 (1H, OH, s), 8.15 (1H, s), 8.03 (1H, d, J = 7.6 Hz), 7.51 (1H, d, J = 8.0 Hz), 7.31-7.21 (2H, m), 4.28 (2H, q, J = 7.2 Hz), 1.34 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO- d_6) δ 163.87, 133.53, 130.58, 122.72, 122.31, 121.75, 120.61, 109.37, 101.03, 59.12, 14.46; IR (KBr) ν 3150, 1655, 1090 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{12}\text{NO}_3$ (M^+H^+): 206.0817, found: 206.0819.

Typical procedure for the synthesis of Di-*tert*-butyl 1-hydroxy-1*H*-indole-2,3-dicarboxylate (NHI-10):¹³

NaOH (15 mg, 0.34 mmol) was added into the solution of di-*tert*-butyl 2-(2-nitrophenyl)succinate **137a** (60 mg, 0.17 mmol) in DMSO (2 mL), the reaction mixture was stirred at room temperature for 5 min, and was quenched with water. After acidic work-up and extraction with Et₂O (5 mL×4), the combined extracts were washed with brine and dried over MgSO₄, the solvents were removed in vacuo. The residue was purified by PTLC (silica gel; hexane : ethyl acetate = 2 : 1) to give Di-*tert*-butyl 1-hydroxy-1*H*-indole-2,3-dicarboxylate **NHI-10** (18 mg, 0.054 mmol) in 32% yield.

Yellow oil; R_f = 0.70 (silica gel; hexane : ethyl acetate = 2 : 1); ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.18 (1H, OH, s), 7.99 (1H, d, J = 8.0 Hz), 7.48 (1H, d, J = 8.0 Hz), 7.33 (1H, t, J = 7.4 Hz), 7.24 (1H, t, J = 7.6 Hz), 1.58 (9H, s), 1.56 (9H, s); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 162.41, 159.59, 134.03, 132.66, 123.85, 122.43, 121.23, 120.82, 109.62, 83.24, 80.02, 28.10(3), 27.73(3); IR (KBr) ν 3167, 2982, 1732, 1697, 1531, 1368, 1256, 1152 cm⁻¹; HRMS (ESI) calcd for C₁₈H₂₅NO₅ (M⁺H⁺): 334.1654, found: 334.1656.

Ethyl 3-cyano-1-hydroxy-1*H*-indole-2-carboxylate (NHI-11)¹⁴:

Spectral data obtained for the known compounds **141a-f**, **h**, **i** and **143a-e**, **144a-d**, **145** are in agreement with the data reported.

3,5,5-Trimethylcyclohex-2-enone (141a):¹⁵

83% Yield; colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 5.89 (1H, s), 2.19 (2H, s), 2.17 (2H, s), 1.94 (3H, s), 1.04 (6H, s).

3,4-Dihydronaphthalen-1(2H)-one (141b):¹⁶

92% Yield; colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 8.05 (1H, dd, *J* = 0.8 Hz, 7.6 Hz), 7.47 (1H, dt, *J* = 1.6 Hz, 7.6 Hz), 7.31 (1H, dt, *J* = 0.4 Hz, 7.2 Hz), 7.26-7.25 (1H, m), 2.97 (2H, t, *J* = 6.0 Hz), 2.66 (2H, t, *J* = 5.2 Hz), 2.15 (2H, quint, *J* = 6.4 Hz).

2,3-Dihydro-1H-inden-1-one (141c):¹⁷

91% Yield; white solid; ¹H NMR (400 MHz, CDCl₃) δ 7.76 (1H, d, *J* = 7.6 Hz), 7.59 (1H, dt, *J* = 1.2 Hz, 7.6 Hz), 7.48 (1H, d, *J* = 6.8 Hz), 7.37 (1H, t, *J* = 7.4 Hz), 3.15 (2H, t, *J* = 6.0 Hz), 2.69 (2H, t, *J* = 6.0 Hz).

(E)-4-Phenylbut-3-en-2-one (141d):¹⁸

84% Yield; faint yellow solid; ^1H NMR (400 MHz, CDCl_3) δ 7.55-7.50 (3H, m), 7.41-7.40 (3H, m), 6.72 (1H, d, $J = 15.6$ Hz).

(*E*)-Tetradec-3-en-2-one (141e):¹⁹

76% Yield; colorless liquid; ^1H NMR (400 MHz, CDCl_3) δ 6.80 (1H, td, $J = 6.8$ Hz, 15.6 Hz), 6.07 (1H, d, $J = 16.0$ Hz), 2.25-2.19 (5H, m), 1.46 (2H, q, $J = 6.8$ Hz), 1.31-1.24 (14H, m), 0.88 (3H, t, $J = 6.8$ Hz).

2-((8*S*,9*S*,10*R*,13*S*,14*S*,17*S*)-10,13-Dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-hydroxyethyl acetate (141f)

is a mixture of two isomers:²⁰

51% yield; white solid; ^1H NMR (400 MHz, CDCl_3) δ 5.73 (1H, s), 4.17 (1H, d, $J = 11.2$ Hz), 3.89 (1H, dd, $J = 7.2$ Hz, 11.2 Hz), 3.81-3.79 (1H, m), 2.43-2.17 (6H, m), 2.10 (3H, s), 2.06-2.01 (1H, m), 1.86-1.84 (1H, m), 1.73-1.68 (3H, m), 1.59-1.40 (4H, m), 1.29-1.21 (23H, m), 1.19 (3H, s), 1.07-1.04 (3H, m), 0.82 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 199.51, 171.37, 171.17, 123.67, 72.32, 68.65, 54.97, 53.72, 52.09, 42.52, 39.23, 38.51, 35.57, 35.37, 33.83, 32.75, 31.95, 24.65, 24.46, 20.81, 20.77, 17.26, 12.14.

33% Yield; white solid; ^1H NMR (400 MHz, CDCl_3) δ 5.73 (1H, s), 4.94-4.90 (1H, m), 3.78 (1H, d, $J = 12.4$ Hz), 3.54 (1H, dd, $J = 5.2$ Hz, 12.4 Hz), 2.47-2.25 (5H, m), 2.09 (3H, s), 2.04-1.99 (1H, m), 1.84-1.24 (12H, m), 1.18 (3H, s), 1.08-1.05 (3H, m), 0.71 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 199.54, 171.28, 171.24, 123.73, 77.18, 64.49, 54.96, 53.70, 49.14, 42.11, 38.75, 38.50, 35.58, 35.40, 33.85, 32.74, 31.89, 24.82, 24.17, 21.31, 20.83, 17.27, 12.41.

(8*S*,9*S*,10*R*,13*S*,14*S*,17*S*)-17-(2-((*tert*-butyldimethylsilyl)oxy)-1-hydroxyethyl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-3(2*H*)-one (141g):

It is a mixture of two isomers according to the X-ray structure (CCDC 843877).²¹

90% Yield; colorless crystal; m.p. 118-121 °C; ^1H NMR (400 MHz, CDCl_3) δ 5.79 (1H, s), 3.70 (1H, dd, $J = 2.8$ Hz, 9.6 Hz), 3.68-3.66 (1H, m), 3.41 (1H, dd, $J = 7.6$ Hz, 9.6 Hz), 2.56-2.28 (6H, m), 2.13-2.09 (1H, m), 1.93-1.48 (9H, m), 1.31-1.25 (3H, m), 1.27 (3H, s), 1.14-0.98 (2H, m), 0.98 (9H, s), 0.90 (3H, s), 0.15 (6H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 199.62, 171.55, 123.70, 73.96, 66.66, 55.04, 53.85, 51.98, 42.58, 39.22, 38.61, 35.65, 35.45, 33.92, 32.87, 32.09, 25.83(3), 24.63, 24.29, 20.83, 18.21, 17.34, 12.26, -5.38, -5.46; IR (KBr) ν 3582, 2936, 1661, 1614, 1472, 1254, 1109, 1082, 837 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{47}\text{O}_3\text{Si}$ (M^+H^+): 447.3294, found: 447.3294.

(*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclohex-2-enone (141h):²²

Faint yellow liquid; ^1H NMR (400 MHz, CDCl_3) δ 6.77-6.75 (1H, m), 4.78 (2H, d, J = 19.6 Hz), 2.73-2.65 (1H, m), 2.61-2.56 (1H, m), 2.49-2.24 (3H, m), 1.79 (3H, t, J = 1.2 Hz), 1.76 (3H, s).

Cholest-4-en-3-one (141i):²³

White solid; ^1H NMR (400 MHz, CDCl_3) δ 5.72 (1H, s), 2.43-2.27 (4H, m), 2.06-1.99 (2H, m), 1.87-1.81 (2H, m), 1.68-1.23 (12 H, m), 1.18 (3H, s), 1.15-1.00 (8H, m), 0.91 (3H, d, J = 6.4 Hz), 0.87 (3H, d, J = 2.0 Hz), 0.85 (3H, d, J = 1.6 Hz), 0.71 (3H, s).

Aldehydes **143** and carboxylic acids **144** were obtained from the oxidation of primary allylic and benzylic alcohols **142** following the same procedure for **141**.

4-Methoxybenzaldehyde (143a):²⁴

85% Yield; colorless liquid; ^1H NMR (400 MHz, CDCl_3) δ 9.89 (1H, s), 7.85 (2H, d, J = 8.8 Hz), 7.01 (2H, d, J = 8.4 Hz), 3.90 (3H, s).

2-Naphthaldehyde (143b):²⁵

75% Yield; white solid; ^1H NMR (500 MHz, CDCl_3) δ 10.17 (1H, s), 8.35 (1H, s), 8.02 (1H, d, $J = 8.1$ Hz), 7.96 (2H, dd, $J = 1.4$ Hz, 10.0 Hz), 7.93 (1H, dd, $J = 8.6$ Hz, 14.1 Hz), 7.65 (1H, t, $J = 7.5$ Hz), 7.60 (1H, dd, $J = 7.5$ Hz).

(S)-4-(Prop-1-en-2-yl)cyclohex-1-enecarbaldehyde (143c):²⁶

61% Yield; colorless liquid; ^1H NMR (400 MHz, CDCl_3) δ 9.44 (1H, s), 6.84-6.83 (1H, m), 4.76 (2H, d, $J = 19.2$ Hz), 2.51-2.42 (2H, m), 2.31-2.08 (3H, m), 1.94-1.90 (1H, m), 1.77 (3H, s), 1.50-1.41 (1H, m).

trans-Cinnamaldehyde (143d):²⁴

52% Yield; colorless liquid; ^1H NMR (400 MHz, CDCl_3) δ 9.71 (1H, d, $J = 8.0$ Hz), 7.58-7.56 (2H, m), 7.50 (1H, s), 7.46-7.43 (2H, m), 6.72 (1H, dd, $J = 7.6$ Hz, 16.0 Hz).

(E)-Tridec-2-enal (143e):²⁷

66% Yield; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 9.51 (1H, d, $J = 7.6$ Hz), 6.83 (1H, td, $J = 6.8$ Hz, 15.6 Hz), 6.12 (1H, dd, $J = 8.0$ Hz, 7.6 Hz), 2.34 (2H, q, $J = 7.2$ Hz), 1.50 (2H, t, $J = 7.2$ Hz), 1.30-1.27 (14H, m), 0.88 (3H, t, $J = 7.2$ Hz).

4-Methoxybenzoic acid (144a):²⁸

13% Yield; white solid; ^1H NMR (400 MHz, CDCl_3) δ 8.07 (2H, d, $J = 8.8$ Hz), 6.95 (2H, d, $J = 8.8$ Hz), 3.88 (3H, s).

2-Naphthoic acid (144b):²⁸

9% Yield; white solid; ¹H NMR (400 MHz, CDCl₃) δ 8.70 (1H, s), 8.12 (1H, d, *J* = 8.8 Hz), 7.98 (1H, d, *J* = 8.4 Hz), 7.90 (2H, dd, *J* = 5.6 Hz, 8.4 Hz), 7.63-7.54 (2H, m).

(S)-4-(Prop-1-en-2-yl)cyclohex-1-enecarboxylic acid (144c):²⁹

13% Yield; white solid; ¹H NMR (300 MHz, CDCl₃) δ 7.15 (1H, d, *J* = 5.1 Hz), 4.75 (2H, d, *J* = 2.3 Hz), 2.50-2.12 (5H, m), 1.93-1.88 (1H, m), 1.75 (3H, s), 1.54-1.43 (1H, m).

trans-Cinnamic acid (144d):³⁰

12% Yield; white solid; ¹H NMR (400 MHz, CDCl₃) δ 7.80 (1H, d, *J* = 16.0 Hz), 6.56 (2H, d, *J* = 3.2 Hz), 7.50-7.42 (3H, m), 6.46 (2H, d, *J* = 8.0 Hz).

(E)-Tridec-2-enoic acid (144e):

14% Yield; colorless oily solid (lit. m.p. 35-36 °C); ¹H NMR (400 MHz, CDCl₃) δ 7.12-7.05 (1H, m), 5.82 (1H, d, *J* = 15.6 Hz), 2.23 (2H, q, *J* = 7.2 Hz), 1.46 (2H, q, *J* = 7.2 Hz), 1.30-1.26 (12H, m), 0.80-0.86 (5H, m); ¹³C NMR (100 MHz, CDCl₃) δ 172.26, 152.53, 120.58, 32.31, 31.87, 29.56, 29.50, 29.35, 29.30, 29.13, 27.85, 22.66, 14.08; IR (KBr) ν 2926, 2681, 1695, 1649, 1285, 982, 930 cm⁻¹; HRMS (ESI) calcd for C₁₃H₂₅O₂ (M⁺H⁺): 213.1855, found: 213.1855.

(E)-4-Oxotridec-2-enal (145):³¹

4% Yield; white solid; m.p. 45-47 °C (lit. m.p. 48-48.5 °C); ¹H NMR (400 MHz, CDCl₃) δ 9.79 (1H, d, *J* = 7.12 Hz), 6.88 (1H, d, *J* = 16.24 Hz), 6.78 (1H, dd, *J* = 7.12 Hz, 16.24 Hz), 2.69 (2H, t, *J* = 7.34 Hz), 1.30-1.27 (14H, m), 0.88 (3H, t, *J* = 6.84 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 200.12, 193.38, 144.91, 137.29, 41.20, 31.81, 29.35, 29.33, 20.20, 29.07, 23.65, 22.62, 14.06.

6.4. References

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List of Publications

1. Shu-Su Shen, Mao-Yi Lei, Yun-Xuan Wong, Mun-Ling Tong, Priscilla Lu-Yi Teo, Shunsuke Chiba and Koichi Narasaka

“Intramolecular nucleophilic substitution at an sp^2 carbon: synthesis of substituted thiazoles and imidazole-2-thiones”

Tetrahedron Letters **2009**, 5, 3161-3163.

2. Shu-Su Shen, Vita Kartika, Ying Shan Tan, Richard D. Webster and Koichi Narasaka

“Selective aerobic oxidation of allylic and benzylic alcohols catalyzed by *N*-hydroxyindole and copper(I) chloride”

Tetrahedron Letters **2012**, 53, 986-990.

Conferences

1. Shu-Su Shen, Mao-Yi Lei, Koichi Narasaka

“Intramolecular nucleophilic substitution at an sp^2 carbon: Synthesis of substituted thiazoles and imidazole-2-thiones”

Joint symposium on organic chemistry for young chemists in Nanyang Technological University, 28th January 2010 (Oral presentation)
2. Shu-Su Shen, Koichi Narasaka

“Intramolecular nucleophilic substitution at an sp^2 carbon: Synthesis of substituted thiazoles and imidazole-2-thiones”

6th Asian-European Symposium on metal mediated efficient reactions, 7-9 June 2010 (Poster presentation)
3. Shu-su Shen, Koichi Naraska

“Selective aerobic oxidation of allylic and benzylic alcohols catalyzed by *N*-hydroxyindole-CuCl”

The first NTU-TITech joint Student Workshop, 8-10 June 2011, Tokyo, Japan (Oral presentation)
4. Shu-su Shen, Koichi Naraska

“Selective aerobic oxidation of allylic and benzylic alcohols catalyzed by *N*-hydroxyindole-CuCl”

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