平成 18 年度修士論文

Synthesis of 5-Membered Azaheterocycles by Nucleophilic *5-endo-trig* Cyclizations of *N*-Homoallylic Sulfonamides and Reactions of Vinyl Azides with 1,3-Dicarbonyls

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Abbreviations

Ac	acetyl
acac	acetylacetonate
AIBN	2,2'-azobisisobutyronitrile
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
CAN	ceric ammonium nitate
c.m	complex mixture
DAST	diethylaminosulfur trifluoride
DCC	1,3-dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
eq	equivalent
Et	ethyl
EWG	electron-withdrawing group
Fc	ferrocenyl
het	heterocycle
hfac	hexafluoroacetylacetonate
HFIP	Hexafluoro isopropanol
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
Me	methyl
Ms	methanesulfonyl
MS	molecular sieve
NOE	Nuclear Overhauser effect
Ns	2-nitrobenzenesulfonyl
Nu	nucleophile
o.n	overnight
PCC	pyridinium chlorochromate
Ph	phenyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
rt	room temperature
S_N	nucleophilic substitution
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
tet	tetragonal
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
trig	trigonal
Ts	4-toluenesulfonyl

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Preface

N-Heterocycles are present in every aspect of our daily life. They are part of our alimentation, of our body functions, part of every living being on this planet. These *N*-heterocycles have been named alkaloids[1], and they are an important family of natural products. The biosynthesis of such compounds mostly starts from amino acid units and can lead to a huge variety of complex structures.

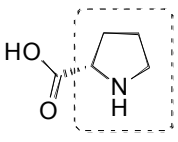
The goal of this work is to address the synthesis of 5-membered azaheterocycles, namely pyrrolidines and pyrroles. Since the construction of these *N*-heterocycles is generally the main challenge in the synthesis of this important class of natural products, my research focus is directed toward developing practical and original synthetic strategies toward this specific goal.

pyrrolidine pyrrole

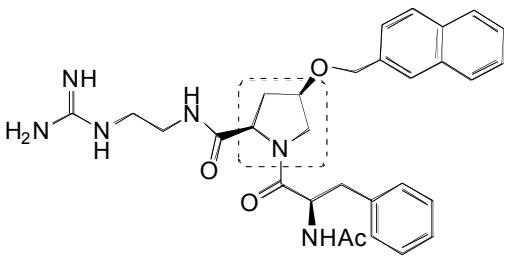
Figure 1. *N*-containing 5-membered heterocycles

The overall usefulness of these heterocycles brought tremendous synthetic efforts in the past century, and a brief overview on their preparation will be summarized here.

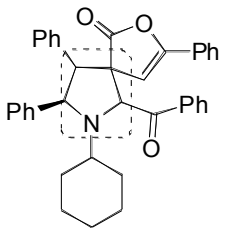
Pyrrolidine derivatives have been used as synthetic building blocks, chiral auxiliairies[2], catalysts[3] and ligands for asymmetric synthesis[4]. They are found in many bio-active natural products and drugs. One of the most famous core-unit is *l*-proline, one of the 20 main amino acids. Two other active pyrrolidine-containing compounds are shown below, a melanocortin receptor agonist developed by Procter Gamble Pharmaceutical and active against various pathogens except Bacillus subtilis.



l-proline



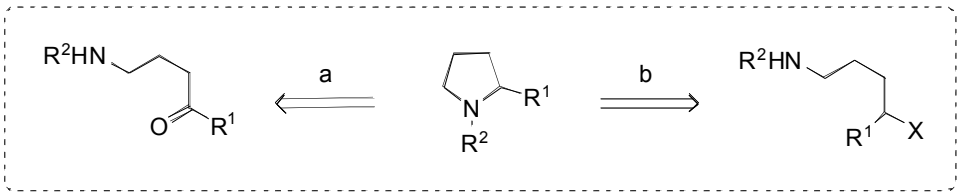
Melanocortin receptor agonist [5]



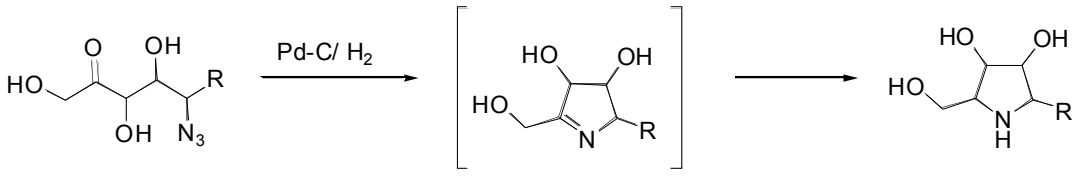
Antifungal/
antimicrobial activity [6]

Figure 2. Some bioactive pyrrolidine analogs

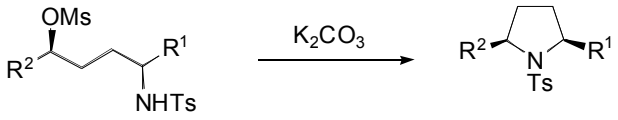
While a huge array of synthetic methodologies[7] has been developed for the pyrrolidine ring, the most general approaches are (a) a simple condensation/reduction sequence and (b) an intramolecular substitution (scheme 1). In case (a), an amine is generated *in situ* (via reduction of a nitro or azide group) and condenses with a ketone or aldehyde moiety, eliminating water. Subsequent reduction of the Schiff base affords the pyrrolidine ring. In case (b), a leaving group is substituted by an intramolecular amine equivalent. Since one equivalent of acid (HX) is generated, this type of reaction is generally done in the presence of a base.



(a) Via condensation/reduction sequence: [8]

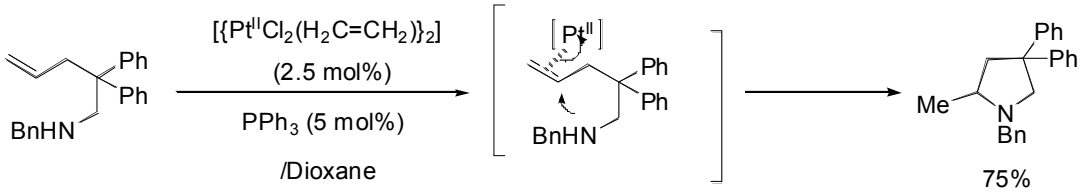


(b) Via intramolecular substitution: [9]



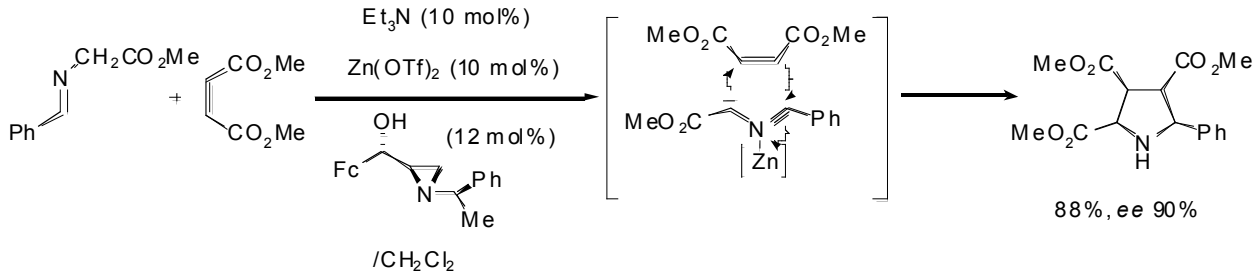
Scheme 1. Pyrrolidine synthesis: condensation/reduction or substitution

Another way, known as hydroamination,[10] involves a metal catalyst which acts as an activator for an unsaturated bond or for an intramolecular amine. Several metal complexes have been used as catalysts for the hydroamination, in which palladium,[11] lanthanides,[12] gold,[13] platinium[14] and ruthenium[15] complexes are the most common ones. In general, the metal complex activates the double bond which is subsequently attacked by the amino group. Finally, protonation of the metal-carbon bound proceeds, affording a pyrrolidine ring.



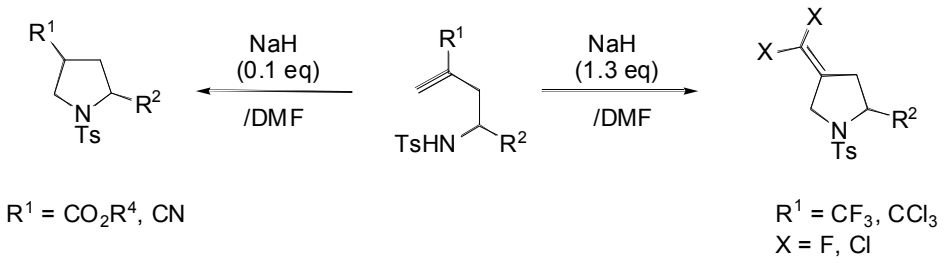
Scheme 2. Pyrrolidine synthesis: Platinium-catalyzed hydroamination[14]

Also, pyrrolidine ring can easily be constructed via a [3+2] azomethine ylide cycloaddition. The dipolarophile can be an alkene[16] or a cyclopropane[17] and the dipolar cycloaddition can be catalyzed by a variety of Lewis acid, such as $Zn(OTf)_2$.



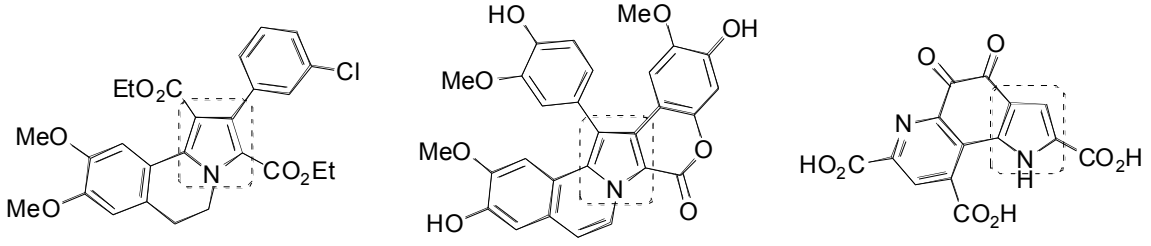
Scheme 3. Pyrrolidine synthesis: Azomethine ylide [3+2] dipolar cycloaddition[18]

Even if many synthetic methods for the pyrrolidine ring exist, certain substitution patterns remains difficult to be obtained, and new synthetic routes are still needed. One difficult approach to the synthesis of pyrrolidine ring involves an intramolecular *N*-nucleophile that adds to an alkene in a *5-endo-trig* fashion. This type of cyclization is geometrically disfavored[19] and examples in the literature are scarce. We thought that by choosing the appropriate nucleophile, electrophile and reaction conditions, this type of cyclization could be achieved efficiently. Thus, the first chapter will deal with my work on the 5-*endo-trig* nucleophilic cyclization of *N*-homoallylsulfonamides, which leads to substituted pyrrolidines.



Scheme 4. Pyrrolidine synthesis: 5-*endo-trig* nucleophilic cyclization

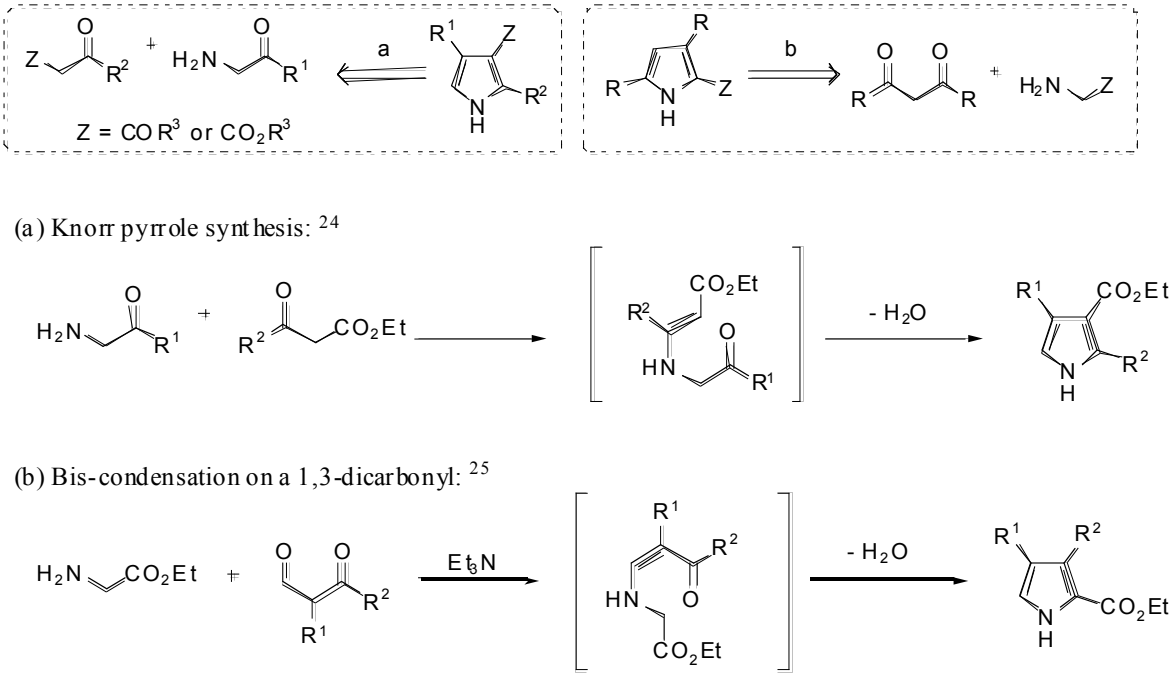
As for pyrroles,[20] they are found in many drugs and bio-active natural products, and have also been applied in material science. As examples of bio-active product, both the phosphodiesterase inhibitor and lamellarins show cytotoxic activity and can be used as lead in oncology program. PPQ (pyrroloquinoline quinone) is a natural product isolated from pseudomonas TPI and shows some activity as a redox cofactor.



phosphodiesterase inhibitor [21] Lamellarins [22] pyrroloquinoline quinone [23]

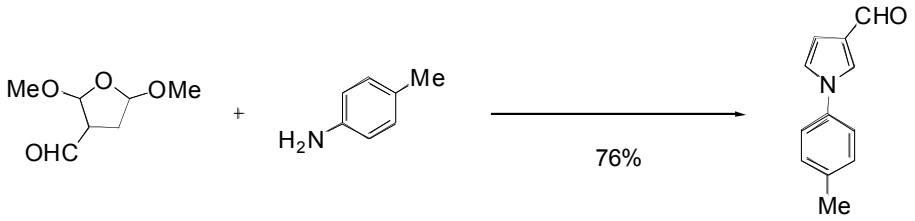
Figure 3. Some bioactive pyrrole analogs

Many methods have been developed to construct pyrrole rings, and some are widely known and general. All reactions have their own limitations, which take into account the starting materials, the substrate compatibility, the reaction conditions, and the scope. One approach involves a α-amino carbonyl compound (scheme 5), in which the amino part condenses (a) a carbonyl or (b) a dicarbonyl compounds. An enamide is generated and further cyclization with loss of water affords the pyrrole ring. This category includes the well-known Knorr pyrrole synthesis. In general, the α-amino carbonyl moiety is obtained via a nitration/reduction sequence.



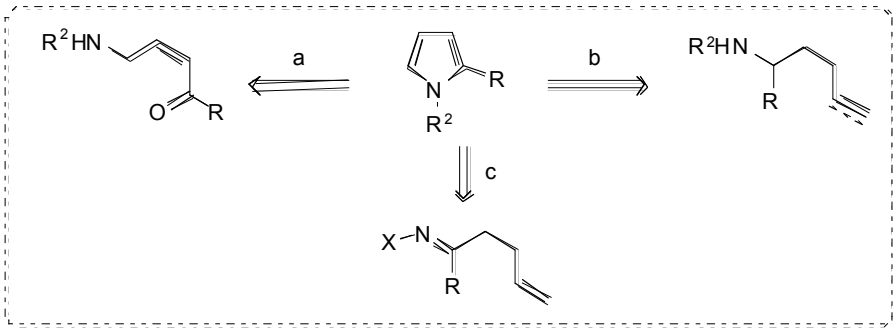
Scheme 5. Pyrrole synthesis: α-aminocarbonyl approach

The condensation of a 1,4-dicarbonyl compound with an amine is known as the Paal-Knorr pyrrole synthesis. The amine condenses with two carbonyl groups of a 1,4-dicarbonyl derivatives, eliminating water. Synthetic equivalents of 1,4-dicarbonyls such as 2,5-dimethoxytetrahydrofuran are often used.

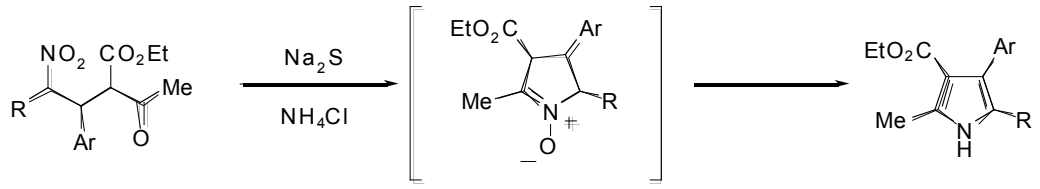


Scheme 6. Paal-Knorr pyrrole synthesis[26]

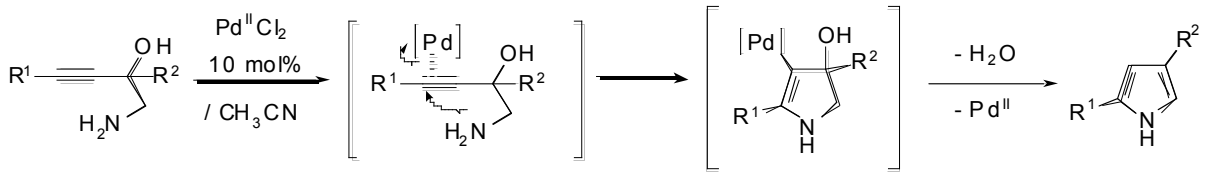
Another major approach involves the intramolecular addition of an amino group, often generated *in situ* from the reduction of a nitro, cyano or other nitrogen-containing functional group (scheme 7). The addition partner can be (a) a carbonyl or (b) an unsaturation (alkene, alkyne) of some sorts activated by a transition metal. The activation can first be done (c) at the nitrogen moiety via an oxidative addition of a transition metal to a N-X bond.



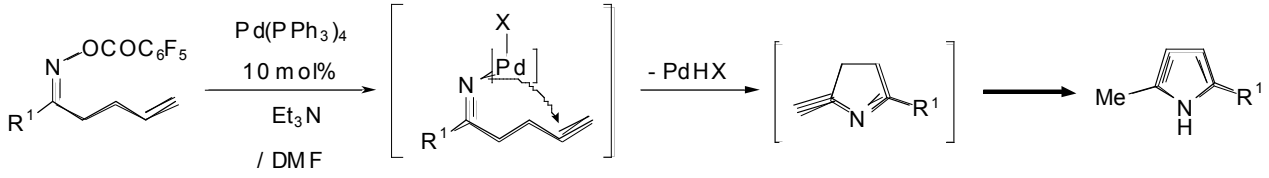
(a) Via reduction/carbonyl condensation: [27]



(b) Via metal-catalyzed addition to unsaturated bound: [28]

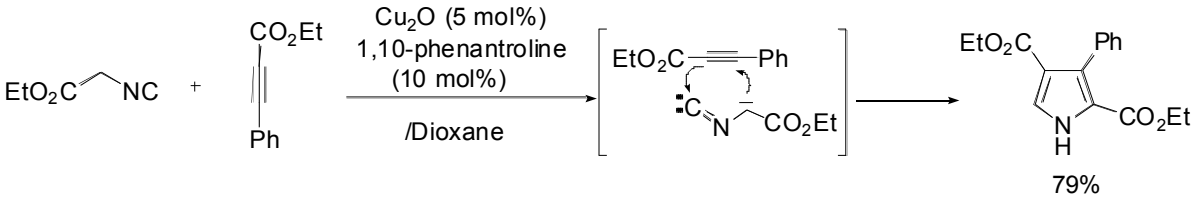


(c) Via metal-catalyzed addition to a N-X bond: [29]



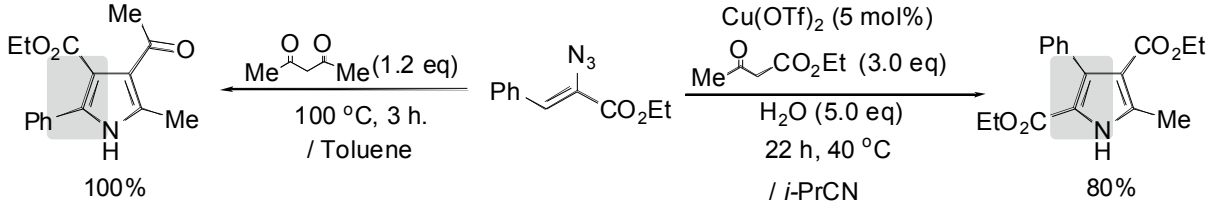
Scheme 7. Pyrrole synthesis: intramolecular nitrogen approach

Finally, dipolar cycloadditions can also yield pyrrole rings. Three major dipoles exist, mainly oxazolium oxides, azomethine ylides, and isonitriles. In the example below, a copper catalyzed [3+2] dipolar cycloaddition is performed between an isocyanoester and an alkyne.



Scheme 8. Pyrrole synthesis: Cu-catalyzed [3+2] dipolar cycloaddition [30]

Just like the pyrrolidine rings, many synthetic methods for the pyrrole ring are already presented in the literature. Still, limitations exist, like some subtitution patterns remains difficult to obtain and in many case, starting materials are not trivial to prepare. If pyrroles with different substitution pattern could be obtained from a common simple substrate, this can potentially lead to a new general methodology. The author found that depending of the reaction conditions, a nucleophile (1,3-dicarbonyl) can add to different carbon center, affording pyrrole rings with different substitution pattern. Thus, the second chapter will deal with my work on the synthesis of pyrroles starting from vinylazide and 1,3-dicarbonyls. Both the catalytic and the catalyst-free reactions will be presented.



Scheme 9. Pyrrole synthesis: Vinyl azides as building block

Chapter 1. Synthesis of pyrrolidines by the nucleophilic 5-*endo-trig* cyclizations of *N*-homoallylic sulfonamides

1.1 Introduction

J. E. Baldwin presented,[19] in 1976, a set of rules that address the geometrical issues encountered in cyclization reactions. These reactions have been classified as favored or disfavored, according to both the ring size and the nature/geometry of the reaction sites. Among the disfavored processes, the 5-*endo-trig* cyclization using *N*-nucleophiles is rarely observed, despite the fact that the process constructs the pyrrolidine ring, a common core structure in biologically active alkaloids.

For a intramolecular nucleophile to attack an unsaturated bond, the nucleophile have to reach the LUMO of the double bond, which can be difficult depending of the ring size. The angle of attack for a sp^2 carbon (Burgi-Dunitz angle) is 109°, which represents the alignement of the alkene LUMO. As shown below, the approach of the nucleophile is geometrically favored when the double bond is *out* of the forming cycle (*5-exo-trig).* When the alkene is *in* the forming cycle (*5-endo-trig)*, geometrical strain is developed. On the other hand, attack on a sp^3 carbon is geometrically favored (*5-exo-tet)* , since only a angle of 71° is needed for the nucleophile to reach the C-X bond LUMO.

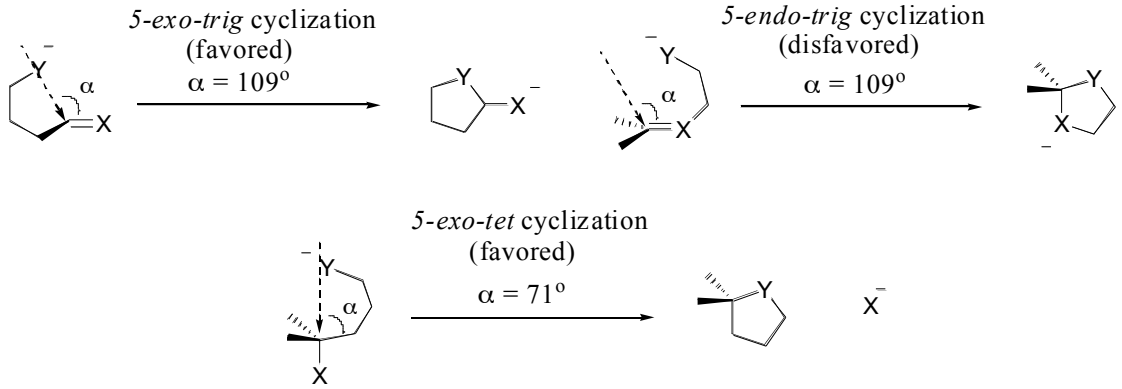
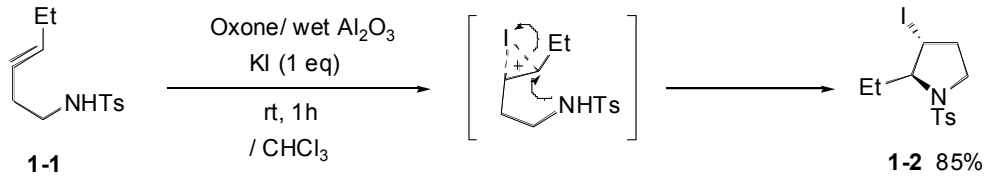


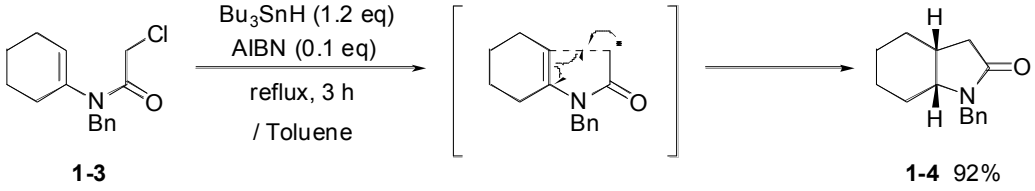
Figure 1-1. 5-exo/ 5-*endo* cyclizations

In fact, examples of *5-endo-trig* cyclization exist but generally involve a double bond activated by a metal or a complexing species (electrophile-driven reaction),[31] or involve radical (radical-initiated reaction).[32] As shown in scheme 1-1, an electrophile-driven *5-endo-trig* cyclization proceeds in the presence of iodide, which activates the double bond. The iodide breaks the sp^2 geometry, creating a pseudo sp^3 environment, which is similar to a *5-exo-tet* cyclization, a favored process, and ultimately allows the cyclization to proceed.



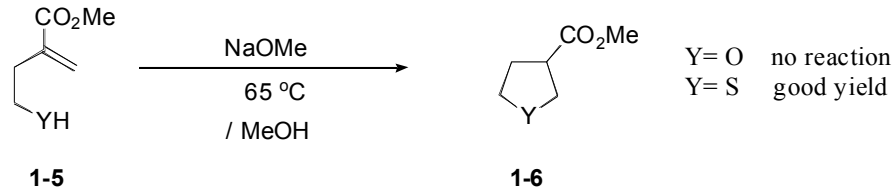
Scheme 1-1. Electrophile-driven *5-endo-trig* cyclization [33]

A radical-initiated *5-endo-trig* cyclization is depicted below. The reactive nature of the radical help to ovecome the energy needed to adopt the strained conformation. This reaction is restricted in term of substrates, and most examples involve *N*-alkyl enamides which undergo the *5-endo-trig* cyclization.



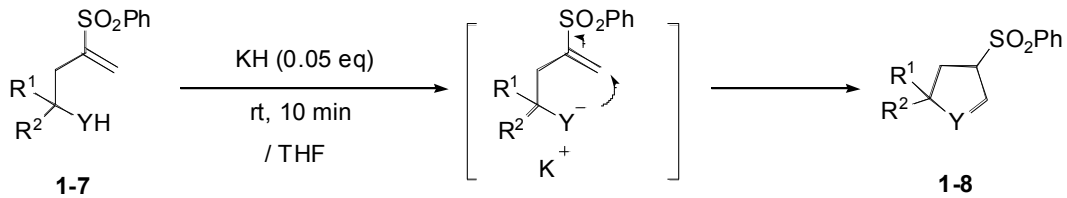
Scheme 1-2. Radical-driven 5-endo-trig cyclization [34]

The nucleophile-driven 5-*endo-trig* cyclization[35] has rarely been observed in synthetic chemistry and is still a challenge in organic synthesis. One exception exists when the nucleophile is not a first-row element; then, the *5-endo-trig* process is not disfavored anymore due to the *d* orbitals, which help to attain the desired geometry.



Scheme 1-3. Nucleophile-driven *5-endo-trig* cyclization with *S*-nucleophile [19]

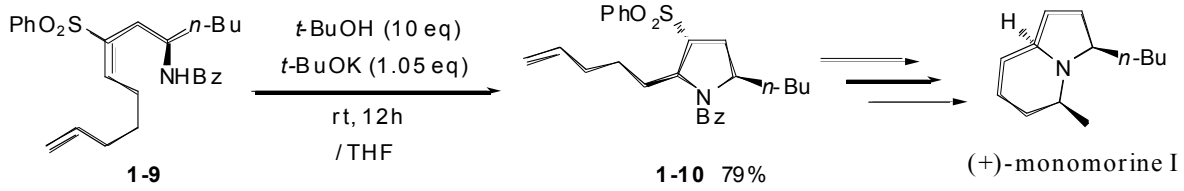
Using an alkene with a first-row nucleophile, only a limited number of publication exists, which accounts for the geometrical difficulty encountered in these cyclization. One of these rare examples is shown below, where an anionic nucleophile adds to an α,β-unsaturated sulfone. The cyclization proceeds in the presence of a catalytic amount of base.



Y= O, NPh, $C(CO_2Et)_2$ 6 examples, 65-88%

Scheme 1-4. Nucleophile-driven *5-endo-trig* cyclization [36]

Another example using α,β-unsaturated sulfone is shown here, where the amide nitrogen adds to the vinylic moiety in the presence of a base. This approach have been used in the total synthesis of the ant pheromone (+)-monomorine I.



Scheme 1-5. Nucleophile-driven *5-endo-trig* cyclization [37]

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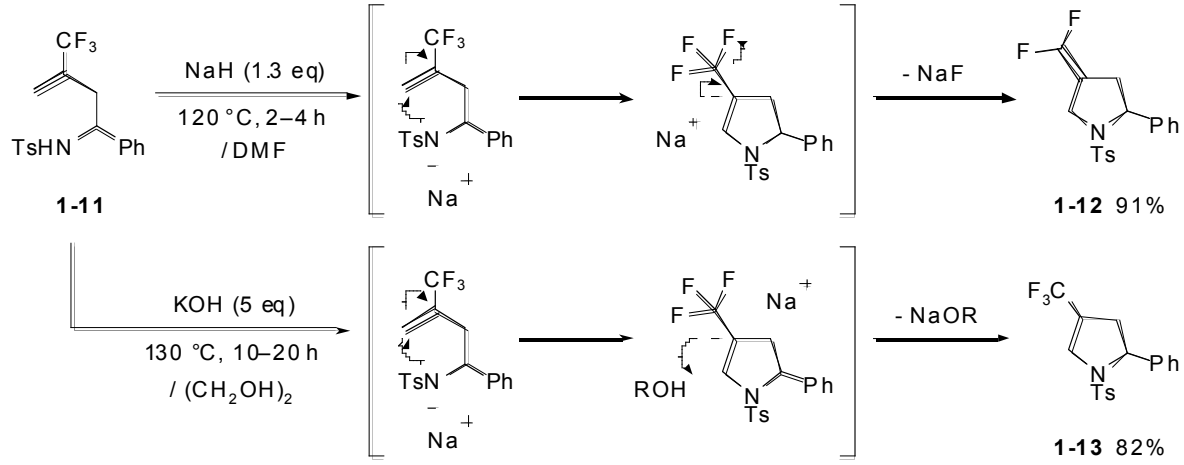
Most, if not all, of the existing nucleophile driven *5-endo-trig* cyclization reports use vinyl sulfones as electrophiles, and the reaction with other electrophiles is yet a matter of investigation.

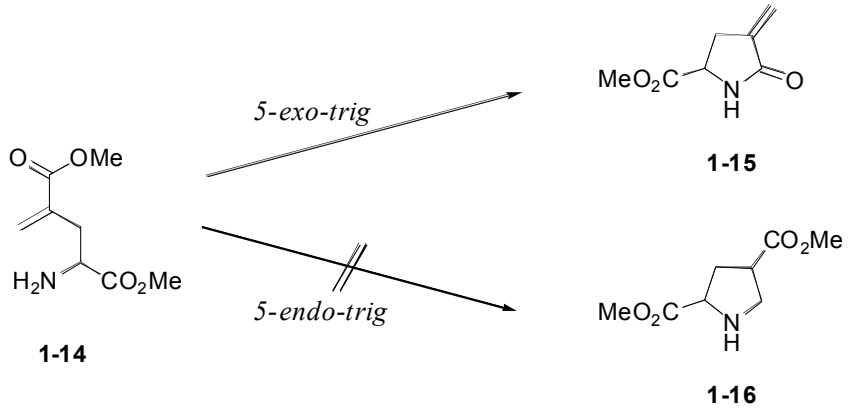
Along with our work on organofluorine chemistry, our laboratory has accomplished the disfavored 5-*endo-trig* cyclization in 2-trifluoromethyl-1-alkenes **1-11** bearing a tosylamide moiety as an intramolecular nucleophile (Scheme 1-6).[38] The amido anion attacked the alkene in an S_N2' fashion with elimination of a fluoride ion to afford difluoromethylene-substituted pyrrolidines **1-12**. In this cyclization, the 5-*endo-trig* products were obtained without any products of the favored *5-exo-tet* ring closure. It is believed that fluorines stabilize anions at the *β*-position, which favors a S_N2' type/addition-elimination mechanism. This has been proved by changing the reaction conditions, in which the protonated product, pyrrolidine **1-13**, was obtained using an alcohol as a solvent. These results show that (a) the trifluoromethyl group activates the C–C double bond in **1-11** to allow the normally disfavored 5-*endo-trig* cyclization and (b) this reaction has a high potential in the synthesis of substituted pyrrolidines.



Scheme 1-6. Nucleophilic *5-endo-trig* cyclization of *N*-(3-trifluoromethylhomoallyl) sulfonamides **1-11**

To expand the scope and determine the limits of this synthetic method for functionalized pyrrolidines, the reactions of other types of substituted alkene moieties with intramolecular

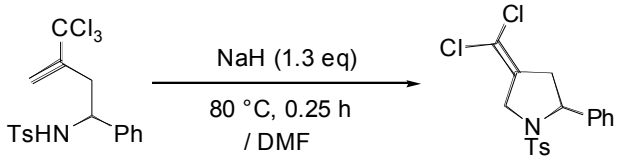
N-nucleophiles have been investigated. Two different types of electron-withdrawing groups were selected, namely (a) 3-trichloromethyl analogs for their similarity with the 3-trifluoromethyl group and (b) alkoxycarbonyl parts on the alkene, since their reaction with *N*-sulfonamide is still unknown. For this second type of substrate, Baldwin previously reported that the 5-*exo-trig* cyclization proceeded more favorably than the 5-*endo-trig* pathway in an α,β-unsaturated ester bearing an amino group.[19]



1-14 **1-15** **1-16**

Figure 1-2. Baldwin's experiment using α,β-unsaturated ester

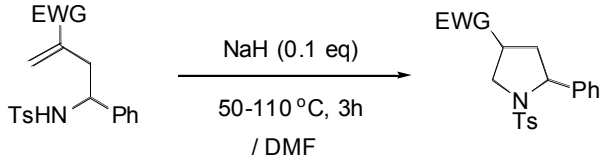
Preliminary results made by Yu Iwai[39] are shown below. At first, when trichloromethyl-substituted alkene **1-17a** was treated with NaH in DMF, the cyclization readily proceeded in a 5-*endo-trig* fashion, affording dichloromethylene-substituted pyrrolidine **1-18a**. Much to our surprise, the cyclization with the trichloromethyl moiety proceeded at a lower temperature than with the trifluoromethyl analog **1-11**.



1-17a **1-18a** 89%

Scheme 1-7. Nucleophilic *5-endo-trig* cyclization of *N*-(3-trichloromethylhomoallyl)tosylamides **1-17a**

For the α,β-unsaturated carbonyl compounds **1-19a** and **1-19b**, the *5-endo-trig* cyclization also proceeded in the presence of a catalytic amount of base.



1-19a EWG= CO_2Et **1-20a** 79%
1-19b EWG= CN **1-20b** 88%

Scheme 1-8. Nucleophilic *5-endo-trig* cyclization of *N*-(3-carbonylhomoallyl)sulfonamides **1-19a-b**

Since both trichloromethylvinyl- and α,β-unsaturated carbonyl compounds underwent the 5-*endo-trig* cyclization, the author decided to investigate other combination of electron-withdrawing groups and *N*-nucleophiles as well.

The first type of substrates studied are 3-halomethylhomoallyl derivatives. It was expected that changing the nature and number of the α-halogen may alter the reactivity and the *5-endo*/*5-exo* selectivity, favoring mixture or inversing the regioselectivity. Also, I wanted to see if the *5-endo-trig* cyclization proceeded with other type of *N*-nucleophiles in trichloromethyl-substituted alkenes.

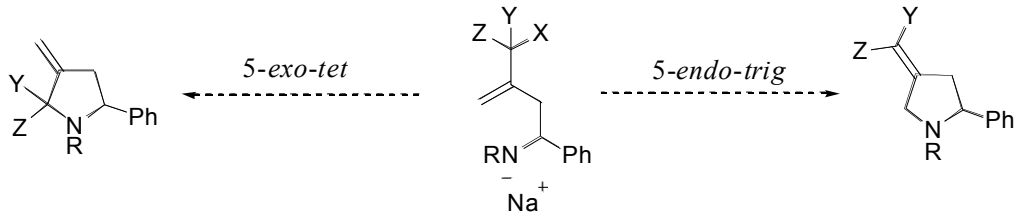


Figure 1-3. 3-halomethylhomoallyl derivatives

The second type of substrate studied are *α,β*-unsaturated carbonyl compounds. In this case, I wanted to study the reactivity of the *N*-sulfonamide nucleophile toward other substituted alkene groups, such as *α,β*-unsaturated phenyl ester and amide. Again, both the reactivity and regioselectivity might vary depending on the electron-withdrawing group attached to the alkene moiety.

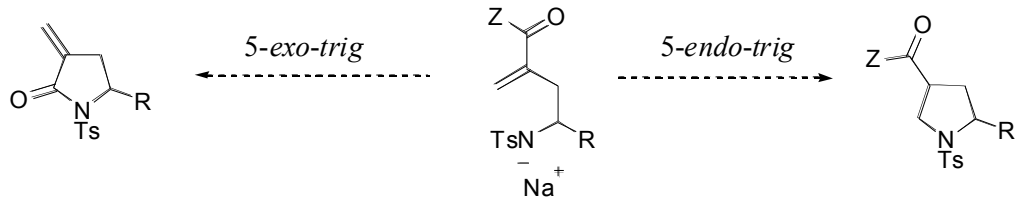


Figure 1-4. *N*-(3-carbonylhomoallyl)tosylamide derivatives

Herein I wish to report my investigation on the nucleophilic 5-*endo-trig* cyclization of *N*-homoallylic sulfonamides containing an electron-withdrawing group at the C-3 position. Part 1.2 of this chapter will deal with the preparation of 3-(halomethyl)homoallyl substrates and their cyclization using sulfonamide and other *N*-nucleophilic moieties. Part 1.3 will focus on the cyclization of *N*-(3-carbonylhomoallyl)tosylamides.

1.2 Nucleophilic *5-endo-trig* cyclization of *N*-(3-halomethylhomoallyl) sulfonamides

1.2.1 Preparation and cyclization of *N*-(3-bromomethylhomoallyl)tosylamide

To evaluate the advantage of trihalomethyl (CX_3) groups in the 5-*endo-trig* process, I first employed an alkene with a 3-monohalomethyl (CH_2X) group as a substrate. It was expected that the reactivity might be decreased, since only one halogen contribute to the overall electronegativity of the alkene moiety. Also, by decreasing the number of halogens, the *5-exo-tet* process may be favored over the *5-endo-trig* cyclization.

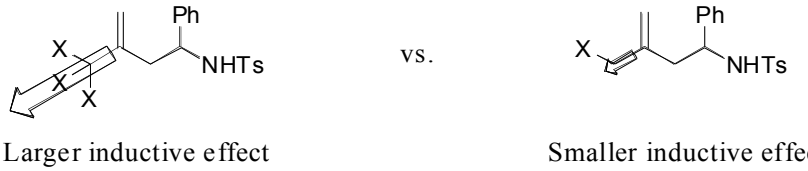
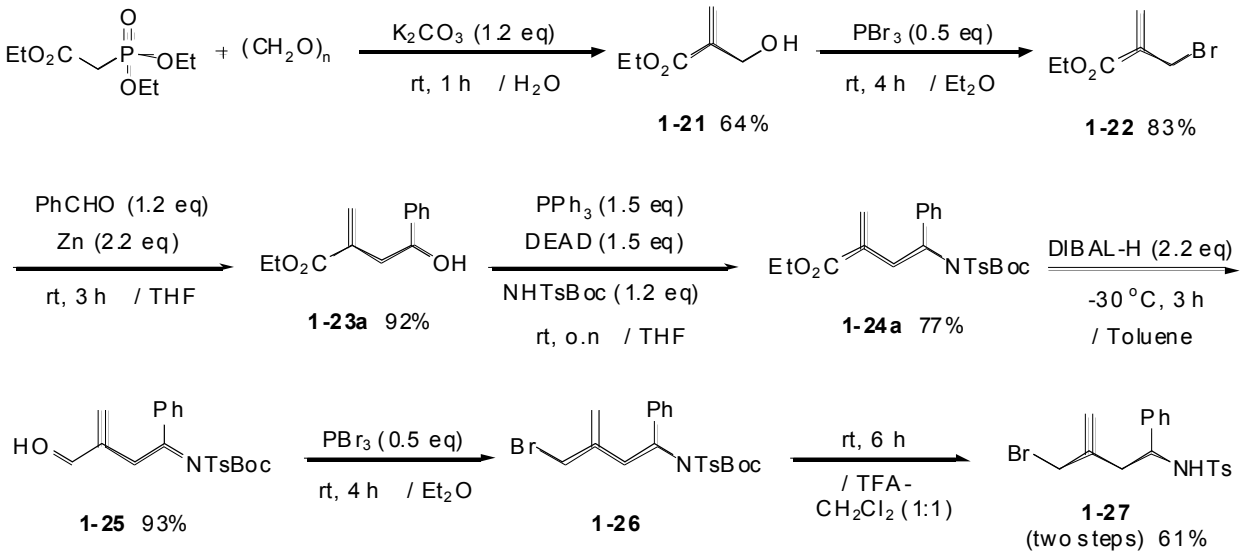


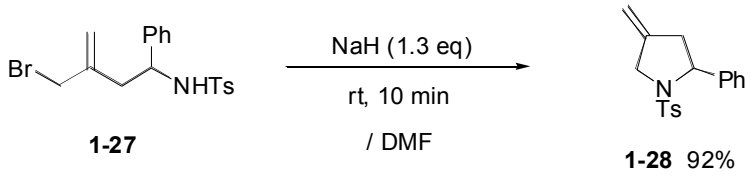
Figure 1-5. Trihalomethyl group vs monohalomethyl group as alkene activator

Despite that the *5-exo-tet*/*5-endo-trig* regioselectivity could not be determined with this example, since both cyclization process give the same pyrrolidine, I first wanted to check if the cyclization proceed with monobromo derivative **1-27** before synthetizing deuterated monohalo derivatives. At first, addition and Wittig reaction of the phosphonoacetate on formaldehyde[40] afforded alcohol **1-21**. Then, bromination followed by formation of the allylzinc and addition to benzaldehyde[41] gave alcohol **1-23a**. Mitsunobu reaction[42] on the alcohol with NHTsBoc provided ester **1-24a**. Reduction of the ester moiety using diisobutylaluminium hydride (DIBAL-H) and bromination gave the Boc protected substrate **1-26**. Deprotection of **1-26** using trifluoroacetic acid (TFA) afforded the cyclization substrate **1-27**.



Scheme 1-9. Preparation of *N*-(3-bromomethylhomoallyl)tosylamide **1-27**

Cyclization of tosylamide **1-27** proceeded smoothly at room temperature in the presence of NaH, affording pyrrolidine **1-28** in 92% yield. Since the cyclization proceeded well, we then decided to synthetize the deuterated derivative in order to determine the reaction regioselectivity.

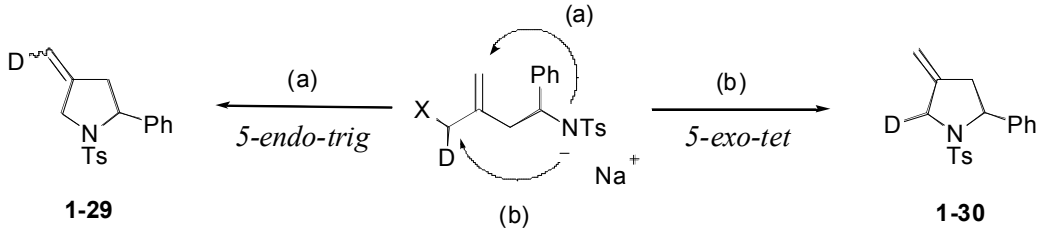


1-27 **1-28** 92%

Scheme 1-10. Cyclization of *N*-(2-bromomethylallyl)tosylamide **1-27**

1.2.2 Preparation and cyclization of deuterated *N*-(3-halomethylhomoallyl)tosylamide

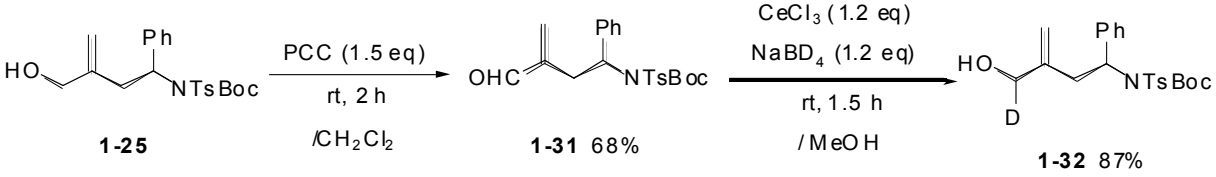
In the cyclization of *N*-(3-bromohalomethylhomoallyl)tosylamide **1-27**, the *5-exo-tet* and the *5-endo-trig* pathway can be plausible since both process afford the same pyrrolidine **1-28**. It was expected that these two pathways could be differentiated by introducing a deuterium atom in susbtrate **1-27**, since the resulting pyrrolidines are different. The deuterium atom should be easily introduced and be close to one of the two potential reaction centers, namely the vinylic and allylic positions. Inserting the deuterium at the position α to the halogen seemed the most judicious choice.



1-29 **1-30**

Scheme 1-11. Cyclization of deuterated *N*-(3-monohalomethylhomoallyl)tosylamide

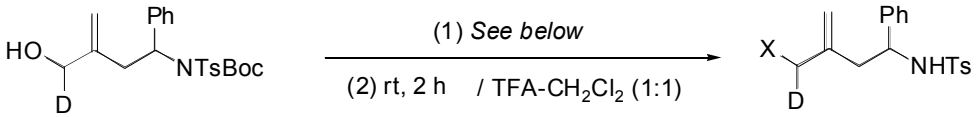
The preparation of deutered *N*-(3-halomethylhomoallyl)tosylamide derivatives is shown below. Oxidation of alcohol **1-25** with pyridinium chlorochromate (PCC) afforded aldehyde **1-31**, which was subsequently reduced with $NaBD_4$ in the presence of cerium chloride (Luche condition)[43] to give deuterated alcohol **1-32**. The halogen was then introduced using the following halogenating reagents, namely diethylamino sulfur trifluoride (DAST)[44] for fluoride, $POCl_3$ for chloride, and PBr_3 for bromide. Removal of the Boc group afforded the cyclization substrates **1-33a-c**.



1-25 **1-31** 68% **1-32** 87%

Scheme 1-12. Introduction of deuterium

Table 1-1 Preparation of *N*-(3-monohalomethylhomoallyl)tosylamides



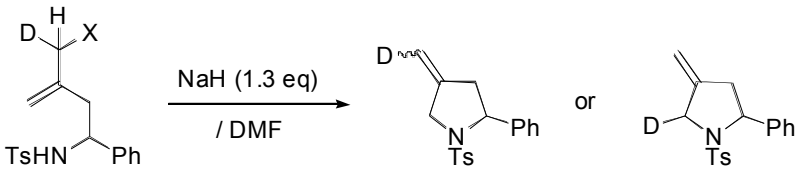
1-32 **1-33 a-c**

entry	product	X	reagent /eq	conditions	**1-33** /%*
1	**a**	F	DAST (2.0)	-78 °C, 1 h /C_2HCl_3	34
2	**b**	Cl	$POCl_3$ (1.1)	rt, o.n. /DMF	84
3	**c**	Br	PBr_3 (0.5)	rt, 3.5 h /Et_2O	82

* Two-step yield.

The monohalogenated derivatives were subjected to the cyclization by treatment with NaH in DMF. In contrast to the trihalomethylated substrates, fluoromethyl- **1-33a**, chloromethyl- **1-33b**, and bromomethyl-1-alkenes **1-33c** underwent the direct substitution without the addition to the double bond, leading to the *5-exo-tet* product **1-30** exclusively (Table 1-2).

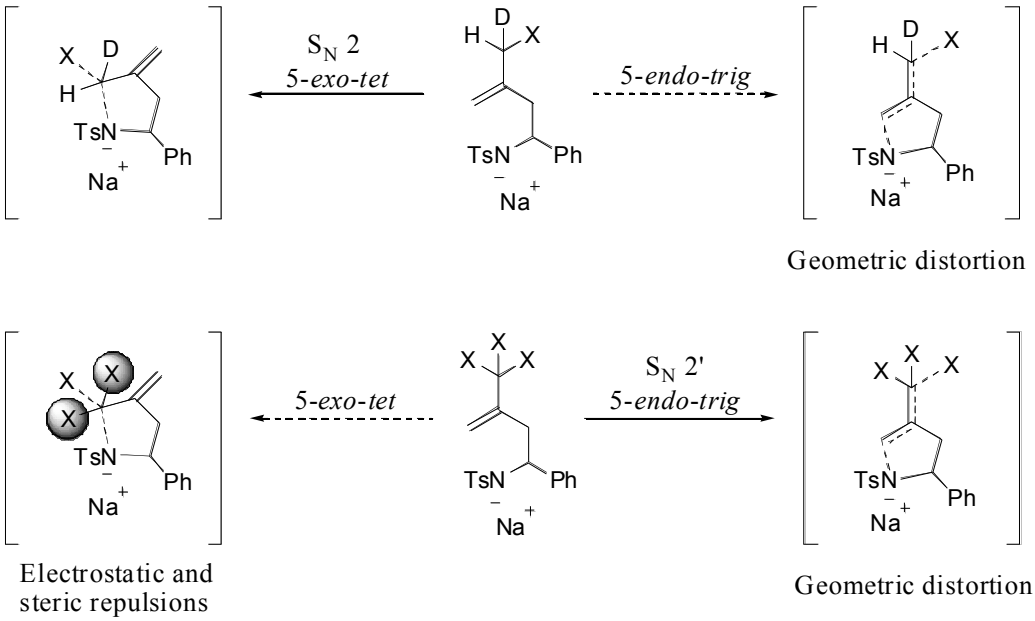
Table 1-2 Nucleophilic cyclization of *N*-(3-halomethylhomoallyl)sulfonamides **1-33a-c**



1-33a-c **1-29** **1-30**

entry	**1-33**	X	conditions	**1-29** /%	**1-30** /%
1	**a**	F	110 °C, 2 h	-	91
2	**b**	Cl	50 °C, 1 h	-	86
3	**c**	Br	rt, 0.25 h	-	89

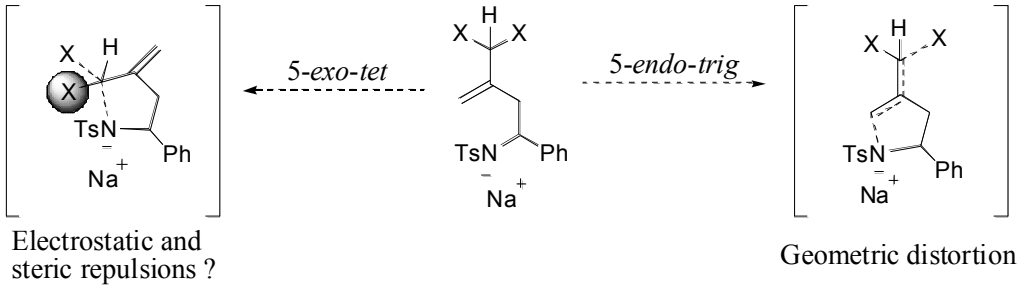
The preference in trihalomethyl (CX_3) derivatives for the 5-*endo-trig* cyclization over the normally favored 5-*exo-tet* cyclization can be explained as follows (scheme 1-13). The sulfonamidate, in the 5-*exo-tet* approach, meets severe electrostatic and steric repulsions from the halogens present on the trihalomethyl group, which consequently retards the normally favored *5-exo-trig* process. On the other hand, the 5-*endo-trig* approach, while geometrically disfavored, has no such repulsions. Because the steric and electrostatic repulsions dominate over the geometric distortion, only the 5-*endo-trig* cyclization proceeds in the trihalomethyl substrates. On the other hand, the monohalogenated derivatives have none of these extra repulsions in the S_N2 approach, and hence the favored *5-exo-tet* cyclization proceeds.



Scheme 1-13. Regiochemistry outcome of the sulfonamidate addition

1.2.3 Attempts in the preparation of *N*-(3-dihalomethylhomoallyl)tosylamide derivatives

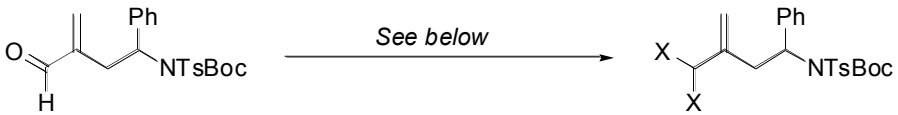
Since changing from a trihalo- to a monohalo- derivative brings a change in regioselectivity from *5-endo-trig* to *5-exo-tet*, I thought that dihalo derivatives might be a interesing limit case to study. In this substrate, can the electrostatic and steric repulsions predominate over the geometric distortion with only two halogens on the allylic carbon?



Scheme 1-14. Regiochemistry in dihalomethyl substrate

Attempts in the preparation of dihalomethylated substrates are shown below. From **1-31**, the formation of the diacetate didn't proceed and the starting material was recovered. The use of a Lewis acid like BCl_3 accelerated the decomposition of the sensitive aldehyde. Using hydrazine in the presence of $CuBr_2$ and base didn't afford substrate **1-34c** but instead gave heterocycle **1-35**, in which the hydrazine added to both the aldehyde and alkene. Further attempts toward the synthesis of dihalomethyl substrates were not tried.

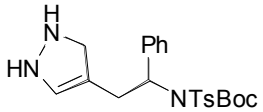
Table 1-3 Preparation of *N*-(3-dihalomethylhomoallyl)sulfonamides **1-34a-c**



1-31 **1-34a-c**

entry	product	X	reagents / eq.	conditions	**1-34** /%	**1-31** /%
1	**a**	OAc	CAN (0.1)	rt, 8 h /Ac_2O	-	82
2	**b**	Cl	BCl_3 (1.0)	reflux, 2 h /Hexane	-	-
3*	**c**	Br	(1) NH_2NH_2 (20.0), MS 4A (2) $CuBr_2$ (6.0), Et_3N (3.0)	rt, 4 h rt, 2 h /MeOH	-	-

* Obtained **1-35** in 92% yield.

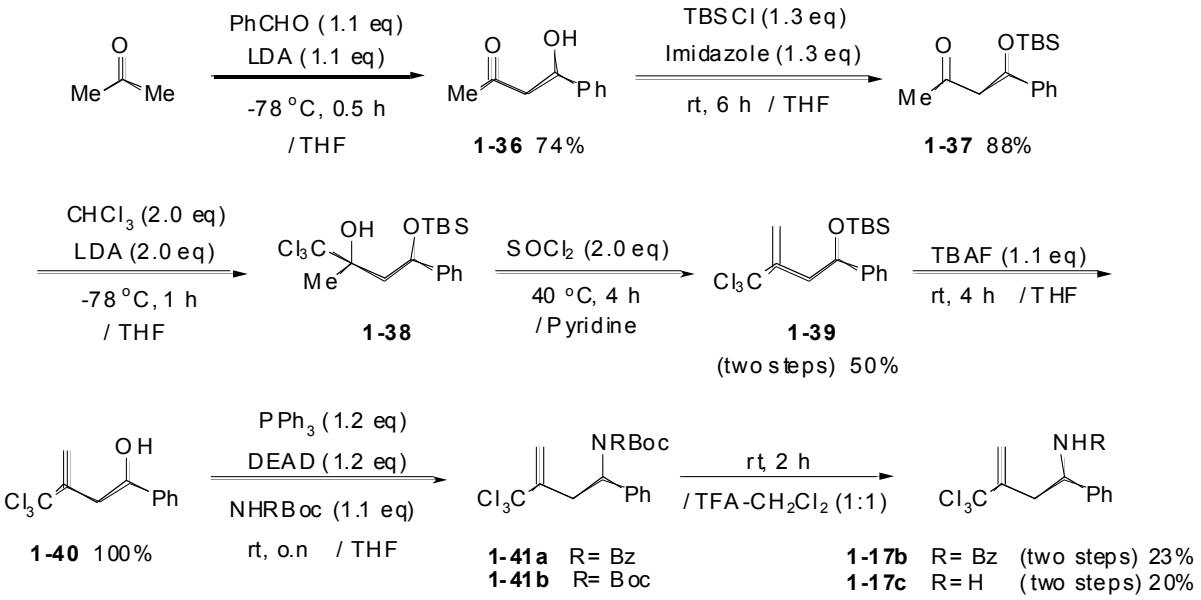


1-35

1.2.4 Preparation and cyclization of *N*-3-(trichloromethylhomoallyl)amine derivatives

Next, we decided to extend the scope of the *5-endo-trig* cyclization with 3-(trichloromethylhomoallyl)amine derivatives by using different intramolecular *N*-nucleophiles. It is expected that harder nucleophiles, such as amide, carbamate, or amine may exhibit a reactivity different from that of the corresponding tosylamide.

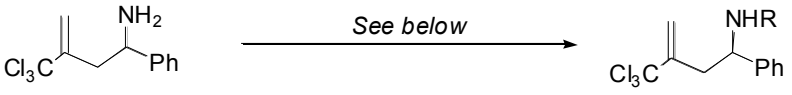
The starting materials have been prepared as follow (scheme 1-15). At first, aldol condensation of acetone with benzaldehyde afforded alcohol **1-36**, which was subsequently protected with a *t*-butyldimethylsilyl group (TBS). Addition of the trichloromethyl anion to the ketone,[45] followed by dehydratation gave alkene **1-39**. Then, deprotection of **1-37** using tetrabutyl ammonium fluoride (TBAF) gave alcohol **1-40**. Finally, the benzamide **1-17b** and the amine derivatives **1-17c** have been obtained via the Mitsunobu reaction between alcohol **1-40** and NHRBoc compounds, followed by the deprotection of the Boc-protected amino compounds **1-41a-b**.



Scheme 1-15. Preparation of substrate **1-17b-c**

The other *N*-nucleophiles were synthetized from amine **1-17c**. The 2-nitrobenzenesulfonyl (Ns, nosyl)[46] and Boc substrate were obtained by a simple treatment of the amine with nosyl chloride and Boc anhydride, while the benzylamine was acquired by a reductive amination with benzaldehyde (table 1-4).

Table 1-4 Preparation of trichloromethylhomoallyl derivatives **1-17d-f**



1-17c **1-17d-f**

entry	**1-17**	R	reagents /eq	conditions	yield /%
1	**d**	Ns	NsCl (1.1), Et_3N (1.1)	rt, 12 h /CH_2Cl_2	70
2	**e**	Boc	Boc_2O (1.1), Et_3N (1.1)	rt, 13 h /CH_2Cl_2	89
3	**f**	Bn	PhCHO (1.1), $NaBH_3CN$ (1.0)	rt, 18 h /MeOH	51

The cyclization of the *N*-nucleophiles thus obtained is summarized in table 1-5. (Trichloromethyl)alkene **1-17d** bearing a nosyl group on the nitrogen instead of a tosyl group also underwent the 5-*endo-trig* cyclization to afford pyrrolidine **1-18d**. The yield for **1-18d** was somewhat lower (69%) as compared to the *N*-tosyl analog **1-17a**. This is probably due to the decreased nucleophilicity of the nitrogen moiety. The cyclization of **1-17d** also proceeded at 50°C for 4.5 hours, but the yield was lower (52%). However, the (trichloromethyl)alkene compounds **1-17b-c** and **1-17e-f** failed to cyclize. The substrates with a free amine or a benzylamine (Bn) moiety resulted in partial or complete decomposition upon heating. The cyclization of the substrates with a benzamide (Bz) or a *t*-butoxycarbonyl (Boc) moiety gave no product, and the starting material was recovered partially. Trace amount of the desired pyrrolidine **1-18b** was observed for benzamide **1-17a**.

Table 1-5 Cyclization of 3-trichloromethyl derivatives

1-17a-f **1-18a-f**

entry	**1-17**	R	conditions	**1-18** /%	**1-17** /%
0	**a**	Ts	80 °C, 0.25 h	89	-
1	**b**	Bz	90 °C, 14 h	trace	40
2	**c**	H	50 °C, 14 h	-	-
3	**d**	Ns	90 °C, 1.5 h	69	9
4	**e**	Boc	50 °C, 4.5 h	-	30
5	**f**	Bn	50 °C, 5 h	-	18

Up to now, the best explanation to the fact that sulfonamides are better *N*-nucleophile lies in two aspects: (1) sulfonamidates partially pyramidalize in the transition state[47] and (2) the nitrogen anions are relatively stable. The pyramidalization could help the geometrically unfavorable cyclization, when compared with the planar amide and carbamate nitrogen anions. In comparison to primary and secondary amine, the stability of the *N*-sulfonamide nitrogen anions may prevent decomposition prior to the cyclization. To this point, a clearer conclusion could not be drawn on why the sulfonamidate is a good nucleophile for such cyclization.

1.3 Nucleophilic *5-endo-trig* cyclization of *N*-(3-carbonylhomoallyl) tosylamides

Then I decided to investigate another type of substrate, namely *N*-(3-carbonylhomoallyl) tosylamide derivatives. It was expected that, by changing the carbonyl moiety, both the reactivity and the *5-endo-trig/5-exo-trig* selectivity might be affected. I wanted to determine to which point the *5-endo-trig* cyclization will predominate over the favored *5-exo-trig* cyclization in a substrate which allows both process.

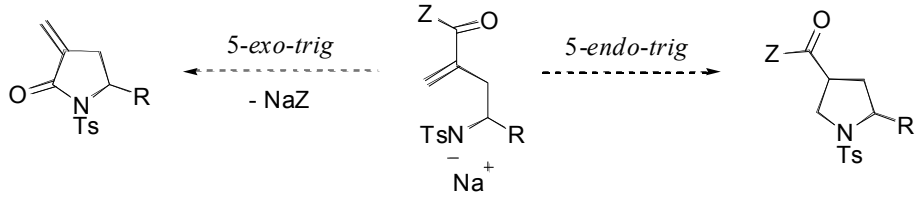
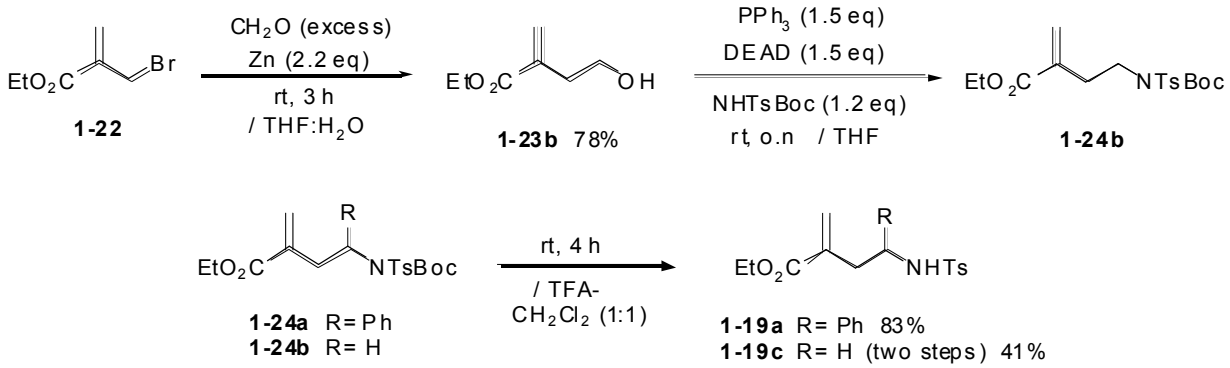


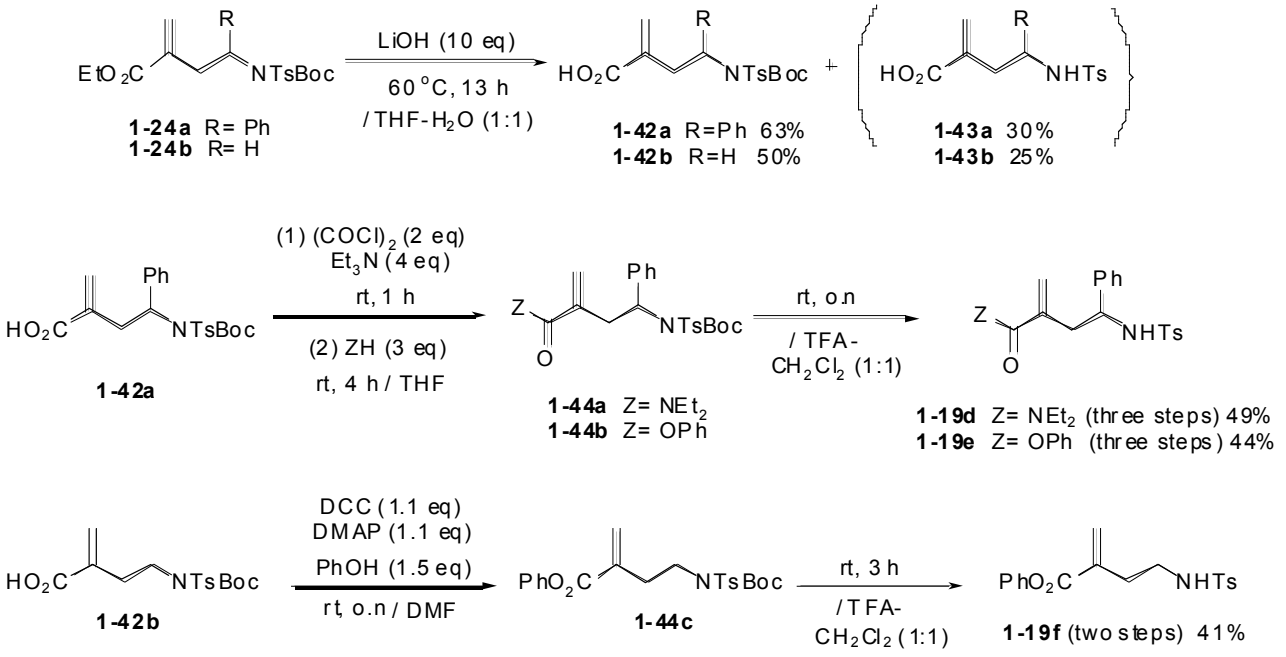
Figure 1-6. Regiochemistry in α,β-carbonyl substrate

The synthesis of the different carbonyl compounds is shown below (scheme 1-16). Starting from allylic bromide **1-22**, generation of the allylzinc followed by addition to formaldehyde afforded alcohol **1-23b**. Then, Mitsunobu reaction on alcohol **1-23b** followed by the amine deprotection on both substrates **1-24a-b** gave tosylamide **1-19a-c**.



Scheme 1-16. Preparation of substrates **1-19a** and **1-19c**

The *N,N*-diethyl amide **1-19d** and phenyl ester **1-19e-f** have been synthetized via the hydrolysis of ester **1-24** to acid **1-42**, which afforded a mixture of both Boc-protected and unprotected sulfonamides. Generation of the corresponding acyl chlorides and the successive treatment with nucleophiles (ZH) gave intermediates **1-44a-b**. Phenyl ester **1-44c** was obtained by the dicyclohexylcarbodiimide (DCC) condensation of acid **1-42b** with phenol. Finally, removal of the Boc group afforded the cyclization substrates **1-19d-f** in good yield.



Scheme 1-17. Preparation of substrates **1-19d-f**

Table 1-6 shows the cyclization results for all the synthetized *N*-(3-carbonylhomoallyl) tosylamide derivatives. For ethyl ester **1-19a**, the cyclization proceeded smoothly to give exclusively the *5-endo-trig* pyrrolidine **1-20a** in 87% yield, with a *anti:syn* ratio of 59:41. NOESY experiment on the **1-20a** mixture showed that the major isomer is the *anti* one (figure 1-7), in which no NOE signal was observed between the C-1 proton and the C-3 proton, when compared to the *syn* isomer. This has also been confirmed by using the C-2 proton, in which three protons (C-1, C-2, C-3) have a NOE signal in the *syn* isomer. It is different in the *anti* isomer where the two C-2 proton have different NOE signal partners (C-1, C-2/ C-2', C-3). Also, it was confirmed that the substituent R at the homoallylic position did not affect the course of the reaction, because substrate **1-19c** gave the *5-endo-trig* product, pyrrolidine **1-20c**, albeit in diminished yield. With phenyl ester **1-20d-e**, only the *5-exo-trig* lactam **1-45a-b** was obtained. Using amide **1-19c**, no cyclization was observed even at higher temperature (140°C) and the starting material was recovered.

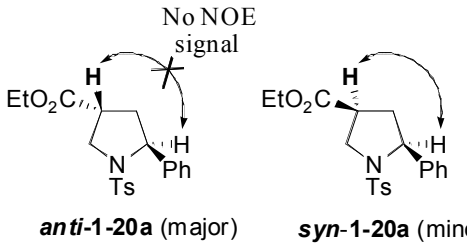
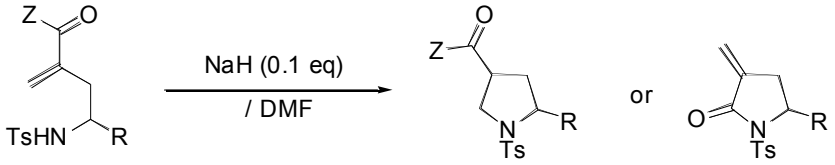


Figure 1-7. NOESY experiement: relative stereochemistry of **1-20a**

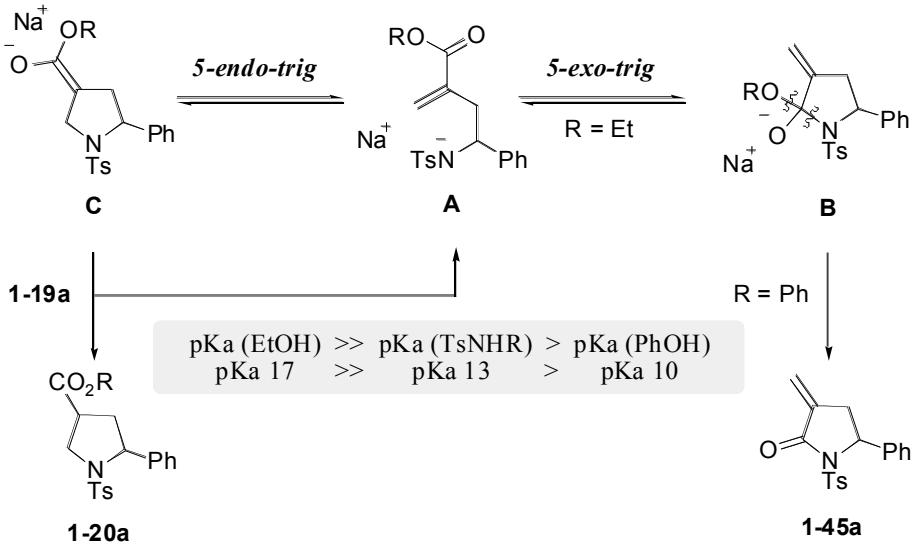
Table 1-6 Cyclization of *N*-(3-carbonylhomoallyl) tosylamide derivatives



1-19a,c-f **1-20a,c-f** **1-45a-b**

entry	**1-19**	Z	R	conditions	**1-20** /% (*anti:syn*)	**1-45** /%	**1-19** /%
1	**a**	OEt	Ph	110 °C, 3 h	87 (59:41)	-	-
2	**c**	OEt	H	110 °C, 4 h	72	-	5
3	**d**	NEt_2	Ph	140 °C, 8 h	-	-	91
4	**e**	OPh	Ph	100 °C, 1 h	-	90	-
5	**f**	OPh	H	140 °C, 8 h	-	76	-

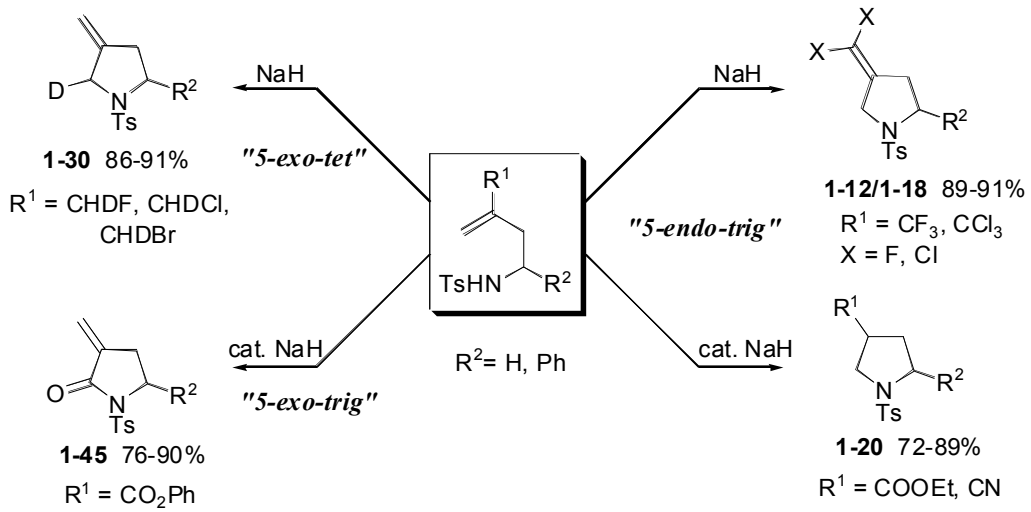
In the α,β-unsaturated ester system, both preferences can be interpreted as follows (Scheme 1-18). The *5-exo-trig* cyclization of **A** preferentially proceeds up to intermediate **B**, which has two leaving groups, a sulfonamidate and an alkoxide. Because *p*-toluenesulfonamidate is a better leaving group than ethoxide, the reaction of ethyl ester **1-19a** (R' = Et) goes back to intermediate **A**. Once the disfavored 5-*endo-trig* cyclization proceeds, further protonation of intermediate **C** with the starting sulfonamide **1-19a** occurs to give pyrrolidine **1-20a**. On the other hand, phenyl ester **1-19c** (R' = Ph) undergoes elimination of phenoxide, a better leaving group than sulfonamidate, via intermediate **B** to give lactams **1-45a**, the *5-exo-trig* product.



Scheme 1-18. Nucleophilic *5-endo-trig* and *5-exo-trig* cyclizations of α,β-unsaturated esters

1.4 Conclusion

In conclusion, we have shown that sulfonamides are good intramolecular nucleophiles for the nucleophilic 5-*endo-trig* cyclization of electron-deficient alkenes. The normally disfavored 5-*endo-trig* cyclization is effected in *N*-homoallylsulfonamides bearing a CF_3, CCl_3, CO_2Et, or CN group at the C-3 position, which provides an easy access to functionalized pyrrolidines. On the other hand, the *5-exo-tet* cyclization predominated in *N*-homoallylsulfonamides having a CHDF, CHDCl, CHDBr groups. In the case where a phenyl ester group was employed at the C-3 position, only the *5-exo-trig* cyclization was observed. Both *N*-tosyl and *N*-nosyl sulfonamides proved to be good nucleophile for the *5-endo-trig* cyclization. The nucleophilic 5-*endo-trig* cyclization can be achieved by choosing the suitable combination of nucleophile, electrophile, and reaction conditions.



Scheme 1-19. Summary

Chapter 2. Synthesis of pyrroles by the reaction of vinyl azides with 1,3-dicarbonyls

2.1 Introduction

Since their discovery by Peter Griess in 1864, organic azides have been applied to numerous organic reactions and their usefullness is well-established.[48] These compounds are valuable intermediates in organic synthesis, mostly in reactions which involve the introduction of one or more nitrogen atoms.

1,3-Dipolar cycloaddition is one of the biggest application of organic azides. Industrially, this process is well known since it produces triazole and tetrazole derivatives with alkynes[49] and nitriles,[50] respectively. On the other hand, cleavage of the nitrogen-nitrogen bond can happen, affording nitrene species. Depending on the organic azides, the N-N bond cleavage may be initiated by heating or photolysis, and by the use of a transition-metal catalyst.

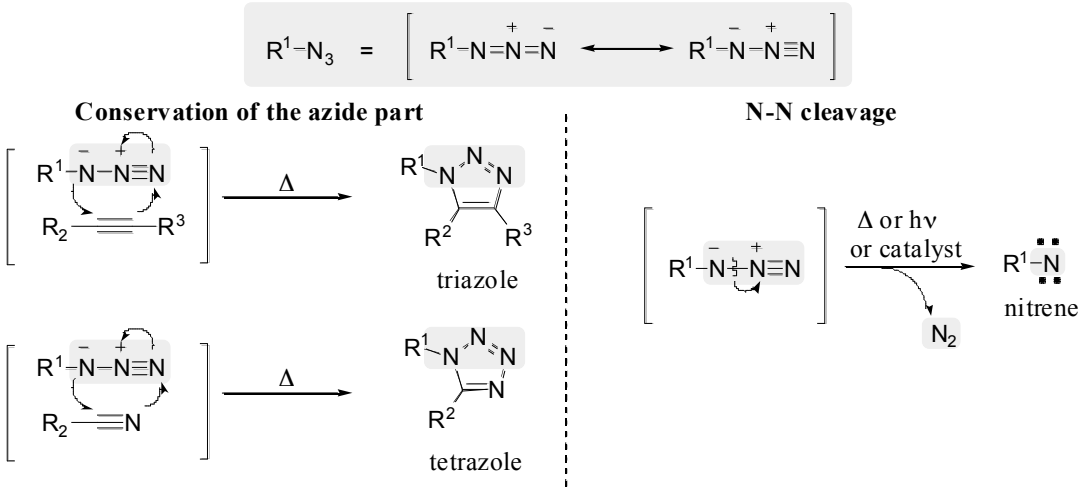
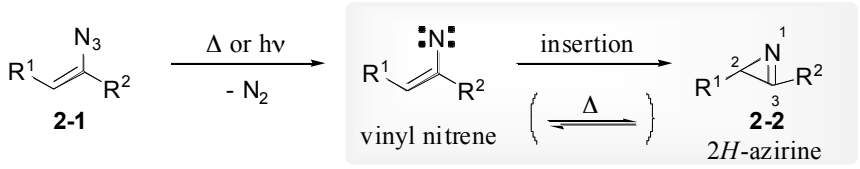


Figure 2-1. Reactivity of organic azides

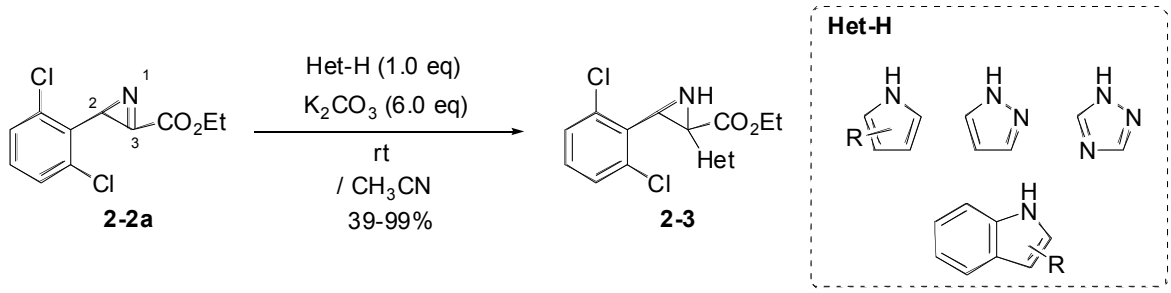
The chemistry of vinyl azides essentially involve thermal or photolytic N-N bond cleavage to generate vinyl nitrenes,[51] which are useful and versatile intermediates (scheme 2-1). Generally, vinyl nitrenes rearrange readily to the more stable 2*H*-azirines[52] via insertion to the C-C double bond, and it is possible to isolate these 2*H*-azirines. Both vinyl nitrenes and 2*H*-azirines are in equilibrum at higher temperature.[53]



Scheme 2-1. Decomposition of vinyl azides

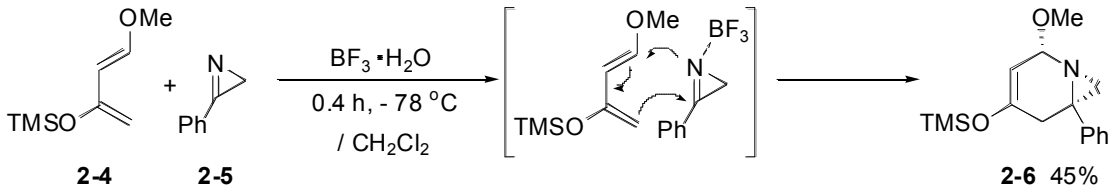
In order to understand the nature of both 2*H*-azirines and vinyl nitrenes, some of the reactions centered on these intermediates will be briefly introduced here.

2*H*-azirines are easily attacked by nucleophiles at the C-3 carbon to afford substituted aziridines. The nucleophile can be an hydride,[54] a Grignard reagent,[55] an alcohol,[56] or an amine.[57] In the presence of acid, water may be used as nucleophile, and the 2*H*-azirines are hydrolyzed to the corresponding α-amino ketones. In the example below, azaheterocycles act as nucleophile in the presence of potassium carbonate, affording trisubstituted aziridines.[58]



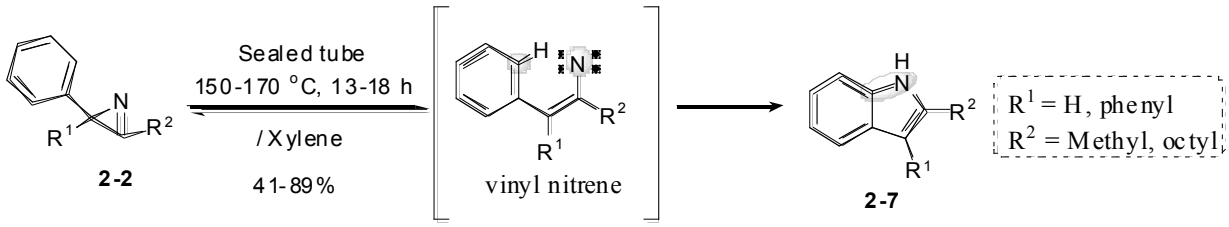
Scheme 2-2. Addition of azahetorocycles to 2*H*-azirine

Also, cycloadditions is known to proceed between 2*H*-azirines and 1,3-dienes. The example below shows a Lewis acid-catalyzed [4+2] cycloaddition between an electron-rich diene (Danishefsky's diene) with 2*H*-azirine **2-5**.[59] Here, the reaction is diastereoselective and only the *endo* adduct is obtained.



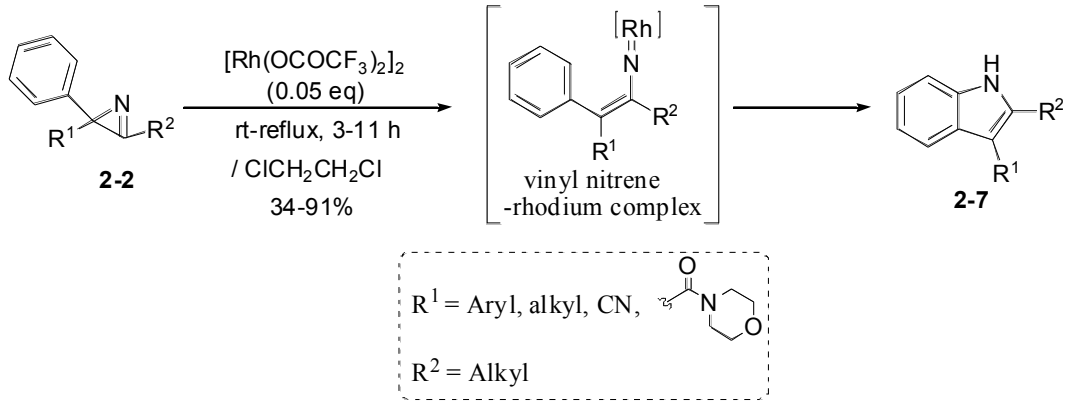
Scheme 2-3. Lewis acid-catalyzed [4+2] cycloaddition

The thermal isomerization of 2-aryl-2*H*-azirines **2-2** to indoles **2-7** is a well known process. One of the recent examples have been reported by Taber et al.[60] In this reaction, the vinyl nitrene-2*H*-azirine equilibrum is initated thermally, and the susbequent insertion of the vinyl nitrene into the Ar-H σ bond afford indole **2-7**. High temperature is needed and the range of 2-aryl-2*H*-azirines which can undergo the isomerization is quite limited.



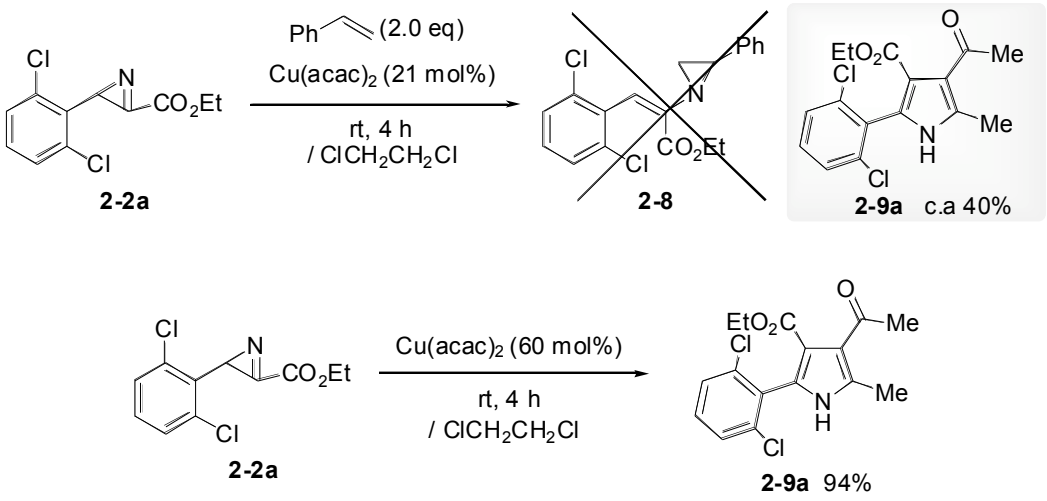
Scheme 2-4. Thermal isomerization of 2-aryl-2*H*-azirines

Recently, in our laboratory was disclosed the Rh(II)-catalyzed isomerization of 2-aryl-2*H*-azirines to 2,3-disubstituted indoles.[61] It was postulated that the treatment of 2*H*-azirines with a transition-metal catalyst may generate a vinyl nitrene-metal complexes at lower temperature than the thermal vinyl nitrene-2*H*-azirine equilibrum, and the subsequent aromatic substitution proceeds to give indoles **2-7**. $[Rh(OCOCF_3)_2]_2$ proved to be a suitable catalyst for this isomerization. The range of 2*H*-azirines which can undergo the isomerization in this rhodium(II)-catalyzed alternative is broader than the thermal method.



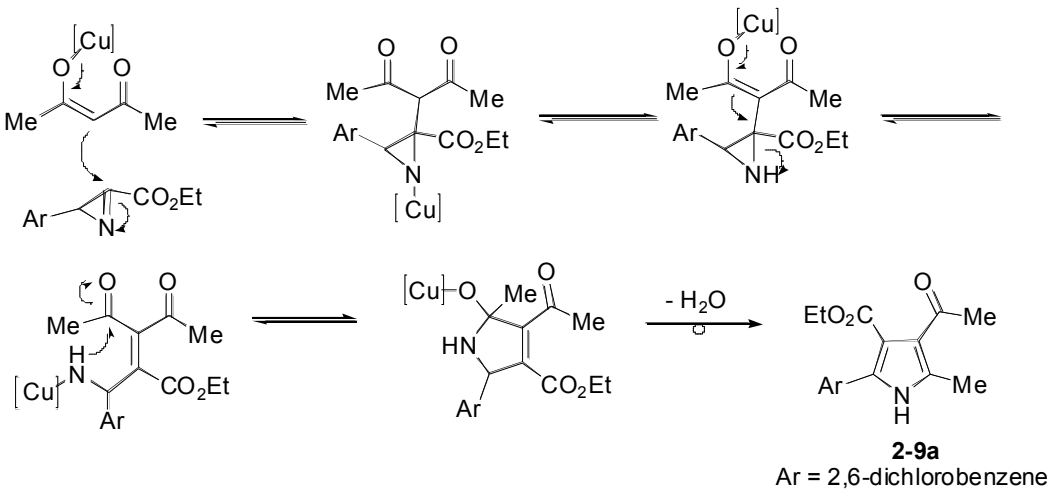
Scheme 2-5. Rhodium(II)-catalyzed isomerization of 2-aryl-2*H*-azirines

During our investigation on the reactivity of vinyl nitrene-metal complexes in a intermolecular manner, we investigated the aziridination of alkenes using 2*H*-aziridine **2-2a** as a substrate and copper(II) acetylacetonate $[Cu(acac)_2]$ as a catalyst. We hypothetized that a vinyl nitrene-copper complex would be generated and serve as a adequate aziridination intermediate. 2*H*-Azirine **2-2a** possessing a 2,6-dichlorophenyl residue was used in order to prevent the potentially interferring isomerization reaction to indole **2-7**. While no reaction was observed between the 2*H*-azirine moiety and styrene, we discovered that the reaction of azirine **2-2a** with copper(II) acetylacetonate afforded pyrrole **2-9a** in c.a 40% yield. Adding more the equivalent of $Cu(acac)_2$ increased the yield of **2-9a** significantly.



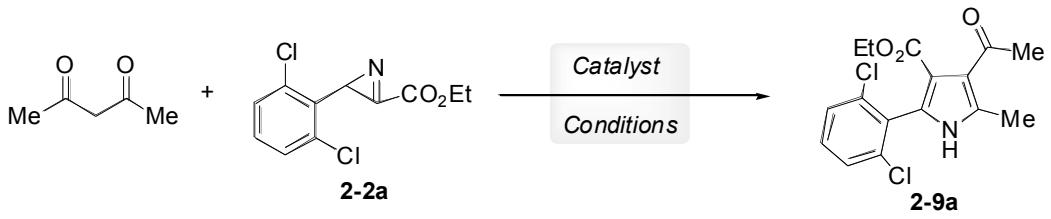
Scheme 2-6. Pyrrole formation via addition on the C-3 carbon

This reaction is believed to pass through the addition of the 1,3-diketone to the imino carbon of the 2*H*-azirine. Then, further cyclization and dehydration afford pyrrole **2-9a** (scheme 2-7). The copper ion may favor the cyclization by complexing the nitrogen atom of the 2*H*-azirine, hence increasing the electrophilicity of the C-3 carbon.



Scheme 2-7. Pyrrole formation: mechanism

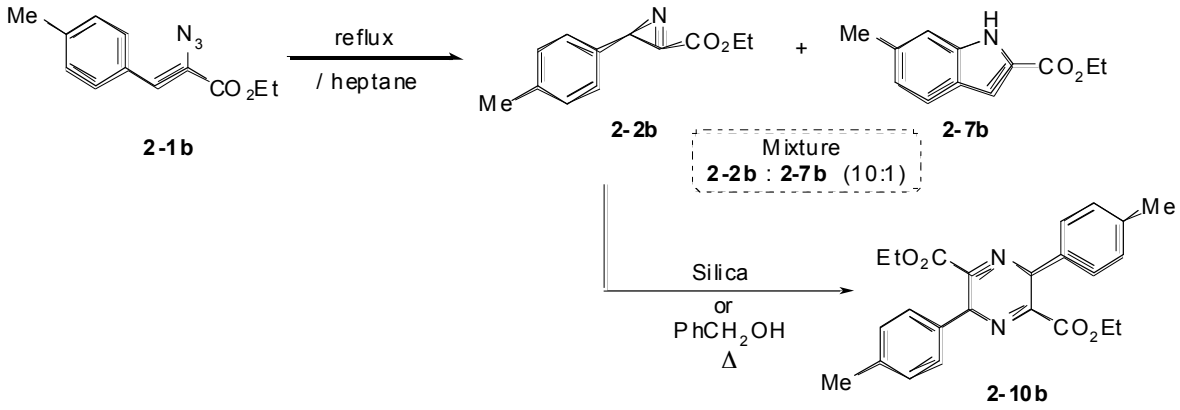
Following these results, the author decided to investigate this potential reaction for the construction of pyrrole rings. At first, I set up to decrease the amount of copper(II) acetylacetonate, so that this reaction could be done catalytically. Acetylacetone and the copper catalyst could be add separately in the reaction vessel, and their complex would be formed during the course of the reaction. Other metal salts could be used, so that different 1,3-dicarbonyl residues would be employed as nucleophile instead of acetylacetonate.



Scheme 2-8. Catalytic approach

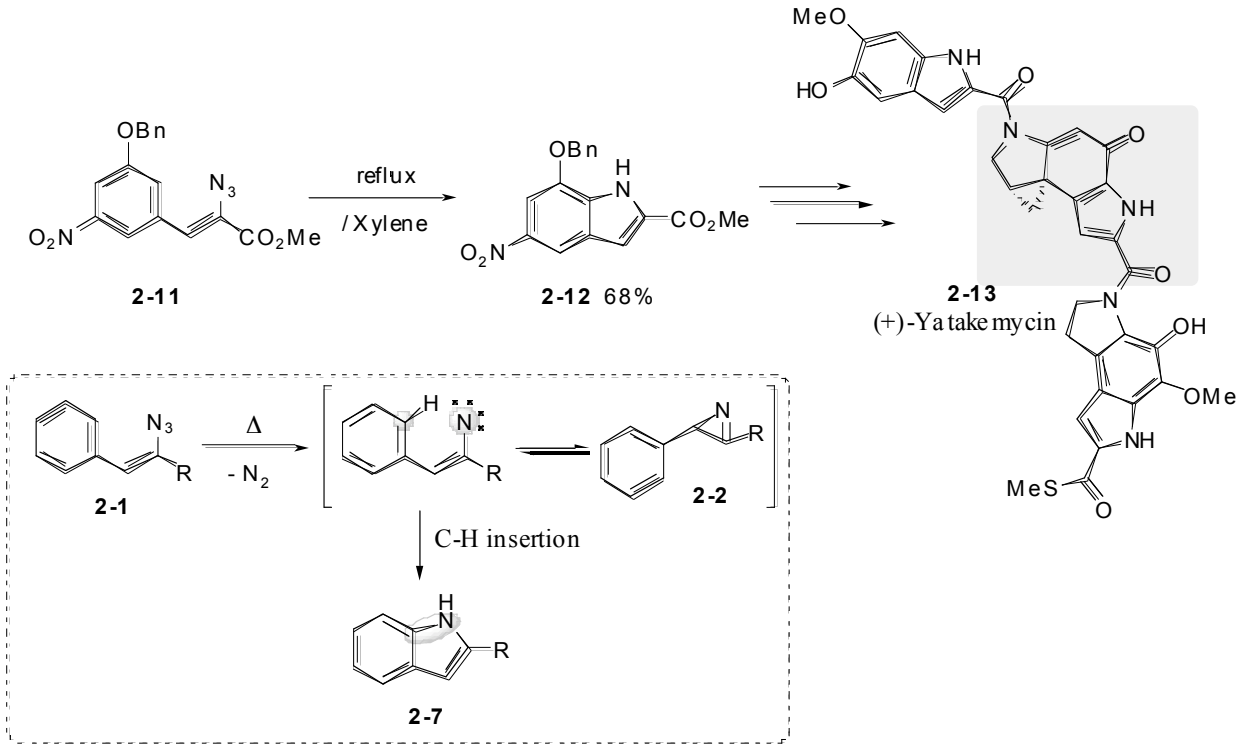
In order to understand what the author planned next, some explanations on the thermolysis of vinyl azides to 2*H*-azirines are needed and will be introduced below (scheme 2-9).

In the thermolysis of vinyl azides to 2*H*-azirines, the isolation is sometime troublesome, since dimerization to pyrazine **2-10** proceeds in the presence of a source of proton, like a protic solvent or silica.[62] Also, the thermolysis of *β*-aryl vinyl azide may be contamined by the corresponding indoles **2-7**, complicating even more the purification of azirine **2-2**. As shown below, the purification of 2-aryl-2*H*-azirine **2-2b** is hindered by the presence of both indole **2-7b** and pyrazine **2-10b**.



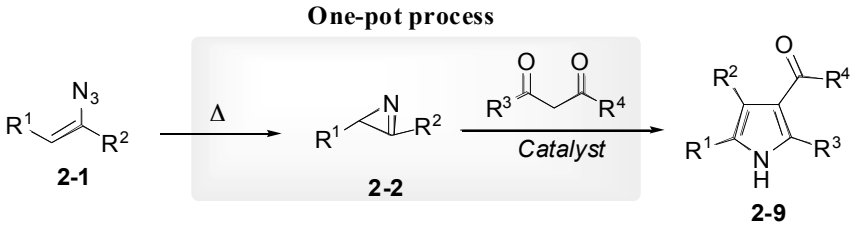
Scheme 2-9. Side reactions in the thermal generation of 2*H*-azirines

As for the indoles formation starting from *β*-aryl vinyl azides **2-1**, just like the thermal isomerization of 2-aryl-2*H*-azirines **2-2** previously presented in scheme 2-5, high temperature and prolonged reaction time are needed. The reaction is supposed to pass through a vinyl nitrene species, which subsequently undergoes C-H insertion on the aryl ring (scheme 2-10). The reaction of *β*-aryl vinyl azides to indoles have been used in the total synthesis of natural products, such as the antitumor (+)-Yatakemycin.[63]



Scheme 2-10. Thermal indole synthesis: total synthesis of (+)-Yatakemycin

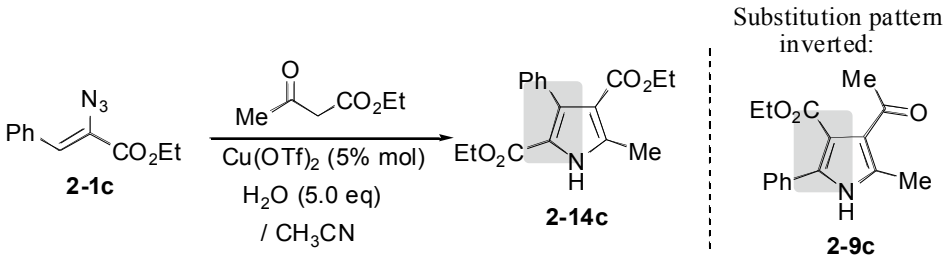
Following the 2*H*-azirine isolation problems, and for the sake of employing other, more sensitive 2*H*-azirines than the stable *β*-(2,6-dichlorophenyl)-2*H*-azirine **2-2a**, the author planned to apply this reaction directly on vinyl azides. The side reactions, namely dimerization of 2*H*-azirines and isomerization of 2-aryl-2*H*-azirines to indoles, might be circumved by making the generation of **2-2** and the copper-catalyzed 1,3-dicarbonyl addition a one-pot process. Finally, the author wished to determine the scope and limitation of this reaction, by changing both vinyl azides and the 1,3-dicarbonyl compounds.



Scheme 2-11. Vinyl azides to pyrroles

Herein, the author wish to report his investigation on the thermal and the copper-catalyzed reactions of vinyl azides with 1,3-dicarbonyl compounds. Part 2.2 of this chapter will deal with the reaction of 2*H*-azirines with acetylacetone, and the one-pot process starting from vinyl azides **2-1**. The reaction of vinyl azides with other nucleophiles than acetylacetone, like 1,3-diketones and *β*-keto esters, will also be discussed. While studying the effect of additives in the reaction of *β*-keto esters with vinyl azides, an unexpected copper(II)-catalyzed reaction was discovered. Hence, part 2.3 will

deal with the copper(II)-catalyzed reaction of vinyl azides with β-keto esters, to generate pyrroles possessing a substitution pattern like **2-14c**, which is a regioisomer of **2-9c**.

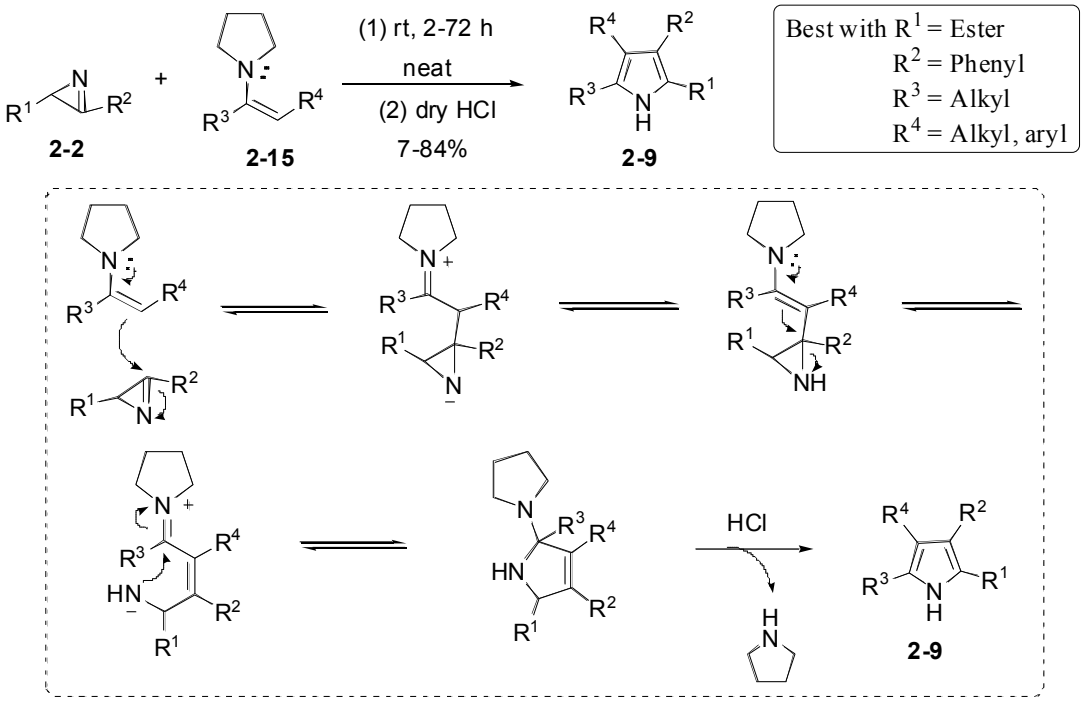


Scheme 2-12. Copper(II)-catalyzed reaction of vinyl azides with β-keto esters

2.2 Thermal reaction of vinyl azides with 1,3-dicarbonyl compounds

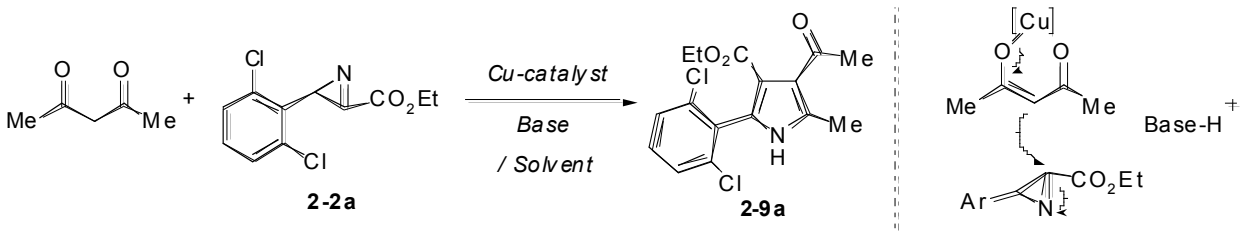
2.2.1 Thermal reaction of 2*H*-azirines with acetylacetone

Here is the closest precedent to our strategy toward the synthesis of pyrroles starting from 2*H*-azirines (scheme 2-13).[64] In this reaction, the nucleophiles, enamides, add at the iminium carbon of 2*H*-azirine and further cyclization affords pyrroles **2-9**. In comparison to our strategy, two differences are clearly noticed: (1) enamides **2-15** have to be prepared separately prior to use; (2) and acidic work-up is needed in the amine elimination step, which can decompose acid-sensitive pyrroles. Also, it was expected that the 2*H*-azirines and the nucleophiles applied to this reaction might differ with the one used in our reaction. Besides that, the yields are low for most of the cases, except for substitutions like presented in the box below.



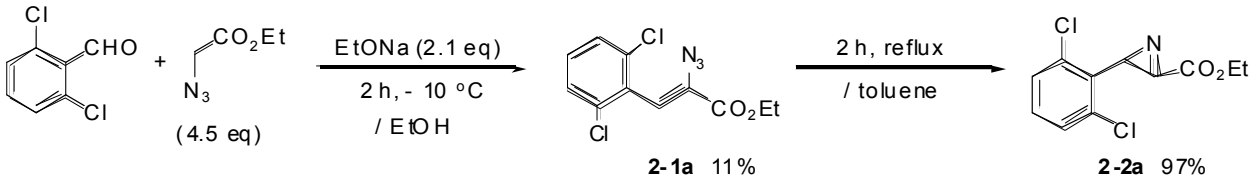
Scheme 2-13. Nucleophilic addition of enamides to 2*H*-azirines

To begin with, I set up to find a proper copper-catalyzed system for the conversion of *2H*-azirines to pyrroles, along with suitable reaction conditions. Base might be needed, since the deprotonation of the acetylacetone moiety may assist the complexation to the copper ion. For the sake of finding the proper conditions for the pyrroles synthesis without interference from the side reactions, namely isomerization to indole **2-7** and dimerization to pyrazine **2-10**, *β*-(2,6-dichlorophenyl)-2*H*-azirine **2-2a** was choosen as an 2*H*-azirine moiety.



Scheme 2-14. Strategy for pyrrole synthesis from 2*H*-azirines

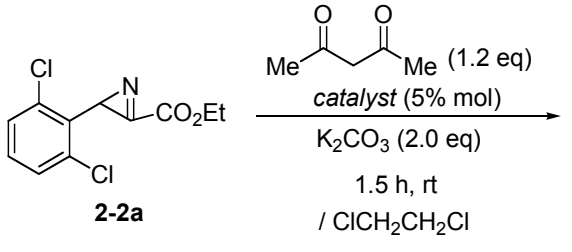
The preparation of 2*H*-azirine **2-2a** is shown below.[62] At first, deprotonation of ethyl azidoacetic acid using sodium ethanolate followed by condensation with 2,6-dichlorobenzaldehyde afforded vinyl azide **2-1a**. Thermolysis of this azide in toluene gave **2-2a** in good yield.



Scheme 2-15. Preparation of 2*H*-azirine **2-2a**

Then, the reaction of 2*H*-azirine **2-2a** with acetylacetone in the presence of different copper catalysts was investigated (table 2-1). In this reaction, potassium carbonate was used as a starting base and dichloroethane as a solvent. To our surprise, the desired pyrrole **2-9a** was obtained in good yield at room temperature in the absence of copper salt. The copper ions did not seem to affect the reaction in any way.

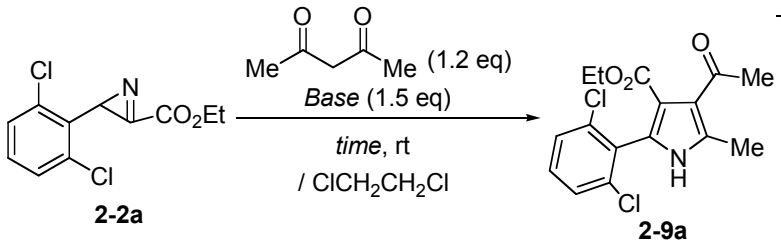
Table 2-1. Effect of copper catalyst



entry	catalyst	**2-9a** /%
1	$CuCl_2$	78
2	$Cu(OTf)_2$	82
3	none	75

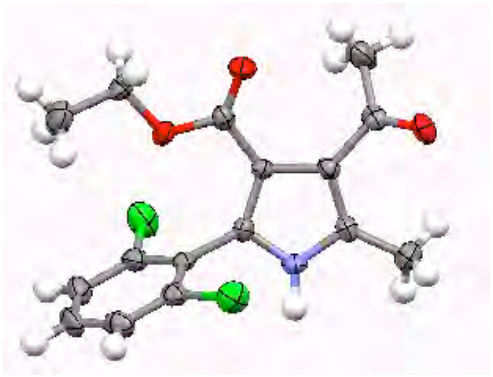
Since the reaction was not influenced by the addition of copper salts, the effect of the base on the reaction course was studied (table 2-2). With carbonate as anion, the countercation had a strong influence on both the yield and the reaction time. In the alkaline family, from sodium to cesium carbonate, the reaction time was shorten; in term of yield, potassium carbonate gave the best result. In the case of cesium carbonate (entry 3), azirine **2-2a** seems to have substantially dimerized. Using calcium carbonate as base slowed down the reaction, while copper carbonate gave pyrrole **2-9a** in a short reaction time and in good yield. Interesingly, in the absence of base, the reaction proceeded well but very slowly. In term of yield and reaction time, copper carbonate proved to be the best base for the formation of pyrrole **2-9a** starting from 2*H*-azirine **2-2a**.

Table 2-2. Effect of base



entry	base	time /h	**2-9a** /%
1	Na_2CO_3	10.5	(83)
2	K_2CO_3	1.5	75 (93)
3	Cs_2CO_3	0.7	(34)
4	$CaCO_3$	22.0	(100)
5	$CuCO_3$	1.5	98 (99)
6	none	32.5	(100)

* Yield in paranthese are ^{1}H NMR yield based on anthracene as standard.



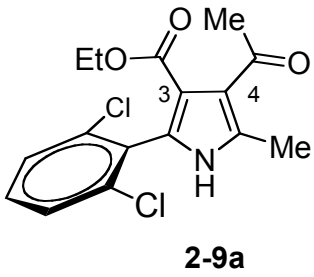
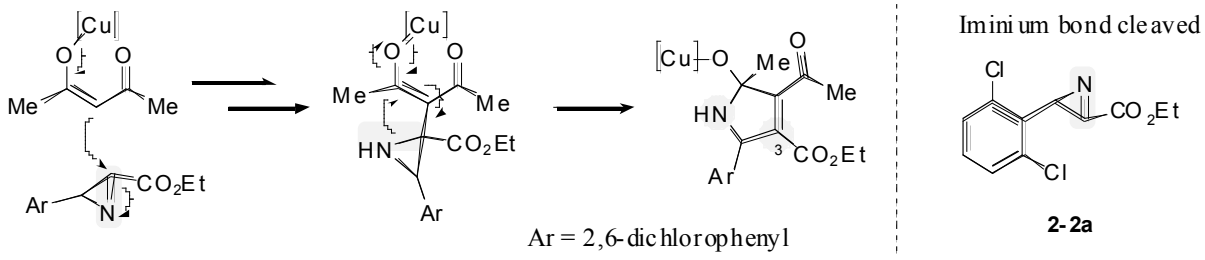


Figure 2-2. ORTEP drawing of **2-9a**

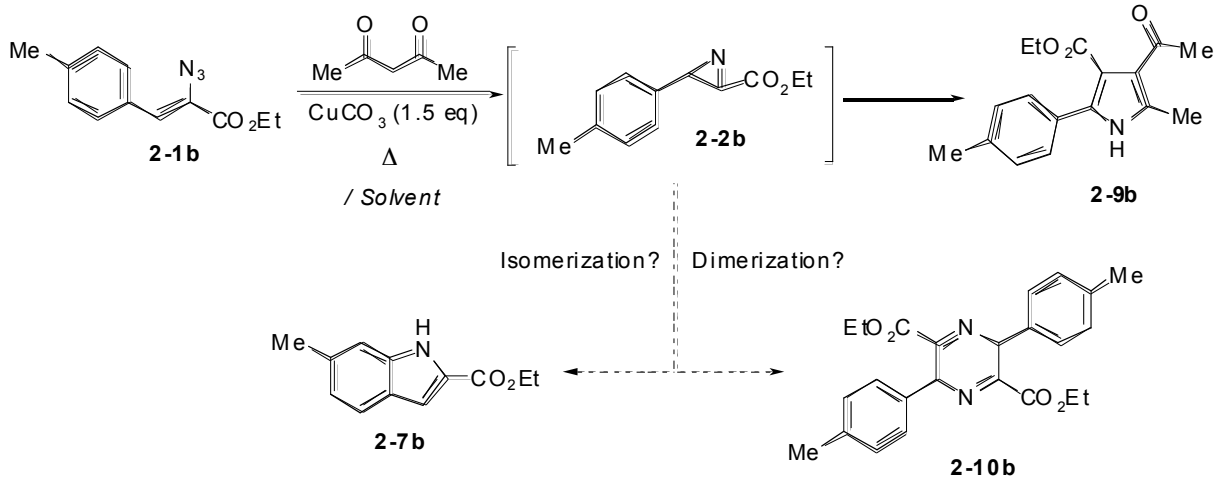
Pyrrole **2-9a** was recrystallized and its structure was confirmed by X-ray crystallographic analysis (figure 2-2). The carbonyl residues appared on the C-3 and C-4 carbons, while the aryl and methyl groups are located on the carbons adjacent to the nitrogen atom. This result confirmed that the iminium bond in azirine **2-2a** is cleaved during the reaction course (scheme 2-16), because the ester moiety is located at the C-3 position in pyrrole **2-9a**. The fully detailled mechanism was introduced earlier (scheme 2-7, section 2.1, p.27).



Scheme 2-16. Partial confirmation of the reaction mechanism

2.2.2 Thermal reaction of vinylazides with acetylacetone

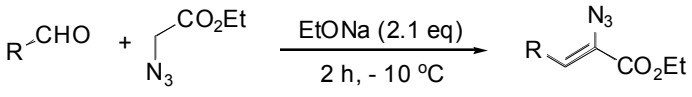
Following the good yield obtained for the reaction of azirine **2-2a** with acetylacetone in the presence of copper carbonate, the next step was to apply this reaction directly to vinyl azides **2-1**. For the purpose of finding a suitable set of conditions for this reaction and testing the addition reaction with more sensitive substrates, vinyl azide **2-1b** was used as the starting material. The corresponding 2*H*-azirine **2-2b**, at high temperature, may possibly undergo both isomerization to indole **2-7b** and dimerization to pyrazine **2-10b**, together with the desired reaction to pyrrole **2-9b**.



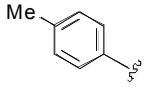
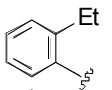
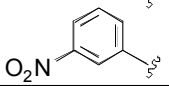
Scheme 2-17. Strategy for pyrrole synthesis from vinyl azides

Also, I wanted to apply this reaction to other vinyl azides, and their preparation is shown below. For vinyl azides **2-1b-e**, I employed the same method as the one used for vinyl **2-1a**, namely the base-initiated condensation of aldehyde with ethyl azidoacetate.

Table 2-3. Preparation of vinyl azides **2-1b-e**

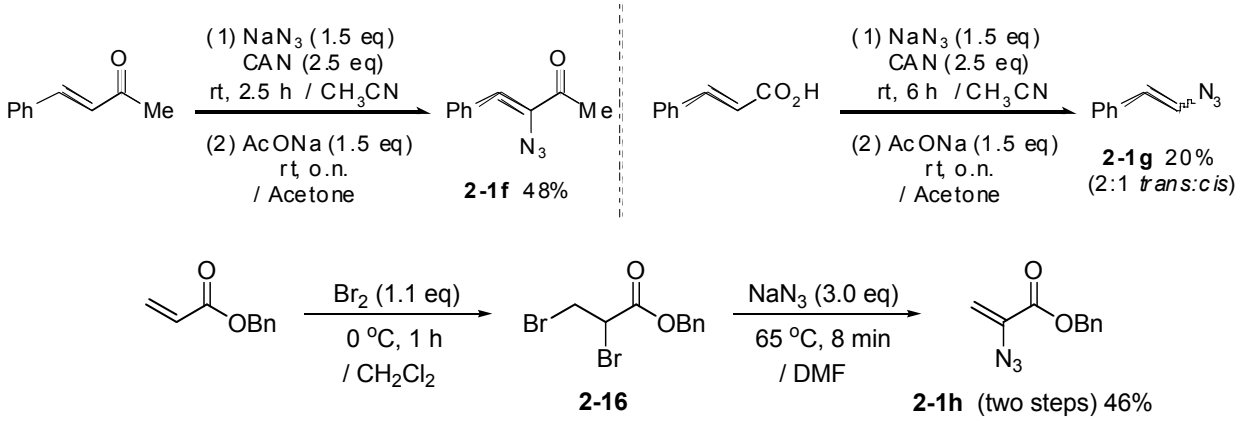


(1.0 eq) (4.5 eq) **2-1b-e**

entry		R	**2-1** /%	entry		R	**2-1** /%
1	**b**		52	3	**d**		51
2	**c**		72	4	**e**		30

Other types of vinyl azides were prepared as follow (scheme 2-18). Substrates **2-1f-g** were synthetized by the cerium(IV) ammonium nitrate (CAN)-mediated oxidative addition of azide to

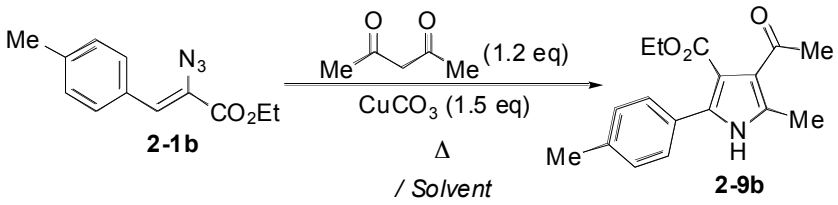
α,β-unsaturated compounds.[65] Addition of bromine to benzyl acrylate followed by substitution with sodium azide and elimination afforded vinyl azide **2-1h**.[66]



Scheme 2-18. Preparation of vinyl azide **2-1g** and **2-1h**

The reaction of vinyl azide **2-1b** with acetylacetone is shown in table 2-4. While heating at 80°C in dichloroethane afforded pyrrole **2-9b** in reasonable yield, changing the solvent to toluene and increasing the temperature gave a better result. The optimal temperature for this reaction proved to be 100°C. No indole **2-7b** was obtained, and only the intermolecular reaction of acetylacetone with vinyl azide **2-1b** proceeded.

Table 2-4. Reaction of vinyl azide **2-1b**

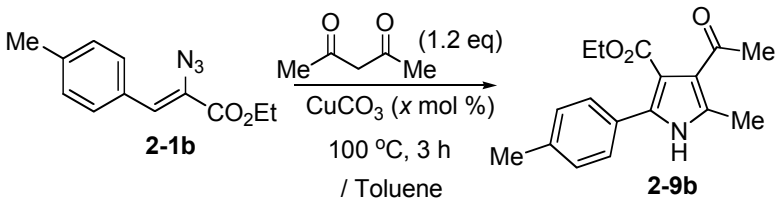


entry	solvent	time /h	T / °C	**2-9b** /%
1	$ClCH_2CH_2Cl$	12.5	80	(74)
2	Toluene	2.0	120	79 (87)
3	Toluene	3.0	100	86 (91)

* Yield in paranthese are ^1H NMR yield based on anthracene as standard.

Then, the amount of copper carbonate was studied (table 2-5). Decreasing the amount of copper carbonate has no crucial effect on the reaction time and on the yield. Furthermore, in the absence of the base, the reaction proceeded without any change in the reaction time and with higher yield of **2-9b**.

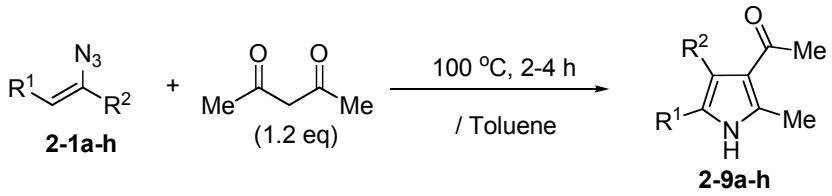
Table 2-5. Reaction of vinyl azide **2-1b**

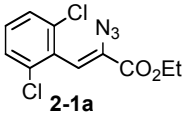
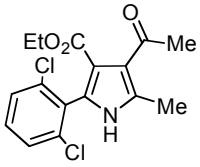
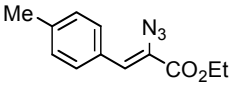
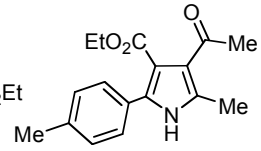
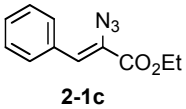
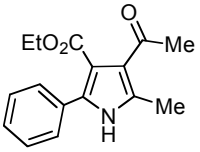
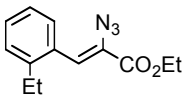
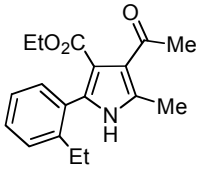


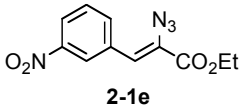
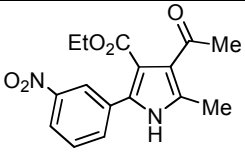
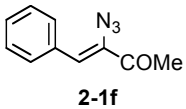
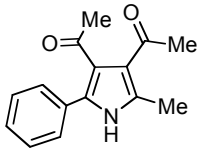
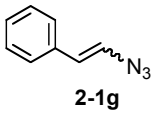
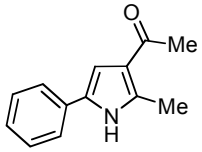
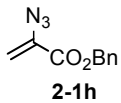
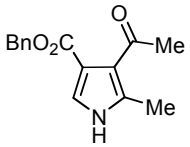
entry	$CuCO_3$ / mol %	**2-9b** /%
1	1.5	86
2	1.0	84
3	0.6	83
4	none	90

Therefore, this copper-free reaction was used for the purpose of screening the reactivity of other vinyl azides to acetylacetone. These results are summarized in table 2-6.

Table 2-6. Reaction of vinyl azide **2-1a-h**



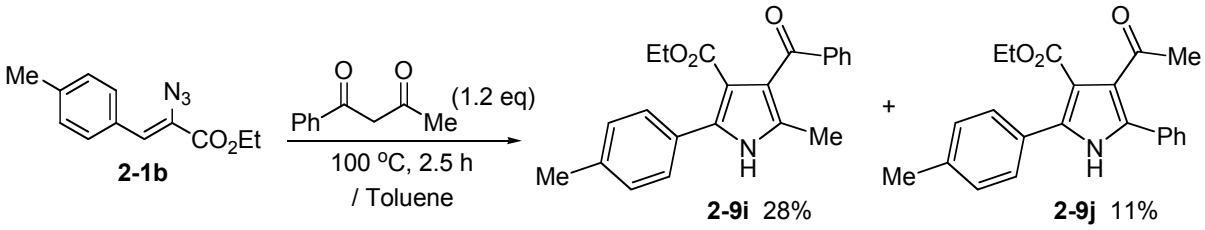
entry	Alkenyl azide	**2-9** /%
1	 **2-1a**	 **2-9a** 86%
2	 **2-1b**	 **2-9b** 90%
3	 **2-1c**	 **2-9c** quant.
4	 **2-1d**	 **2-9d** 76%

entry	Alkenyl azide	**2-9** /%
5	 **2-1e**	 **2-9e** 96%
6	 **2-1f**	 **2-9f** 54%
7	 **2-1g**	 **2-9g** 75%
8	 **2-1h**	 **2-9h** 77%

With β-aryl vinyl azides **2-1a-e** bearing an ethoxycarbonyl group, the reaction proceeded smoothly to affords pyrroles **2-9a-e** in high yield. Both electron-donating groups (entry 2 and 4) and electron-withdrawing group (entry 1 and 5) on the β-aryl group were tolerated. With the β-aryl vinyl azide **2-1f** having an acetyl instead of a ethoxycarbonyl group (entry 6), partial dimerization of the *in situ* generated vinyl nitrene proceeded together with the desired addition. With β-azidostyrene **2-1g**, where no alkoxy carbonyl group is present, the reaction also proceeded well. Finally, the 2-azidoacrylate **2-1h** posessing a terminal alkene moiety also underwent the reaction to give 2*H*-pyrrole **2-9h**. With acetylacetone as nucleophile, the reaction is quite general in term of the vinyl azides that can be used.

2.2.3 Thermal reaction of vinylazides with other 1,3-dicarbonyl compounds

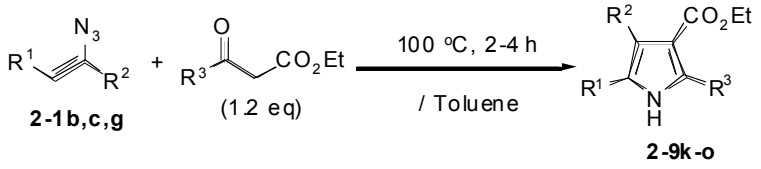
From the results above, it is clear that acetylacetone can act as a good nucleophile but what about other 1,3-diketone and β-keto ester compounds? At first, I decided to try the reaction of 1-phenylbutane-1,3-dione with vinyl azide **2-1b** (scheme 2-19). This reaction afforded a 2:1 mixture of regioisomers, pyrroles **2-9i** and **2-9j**, in moderate yield.

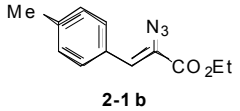
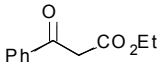
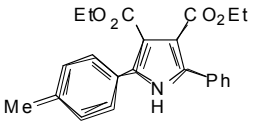
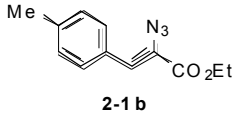
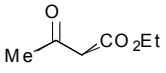
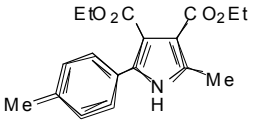
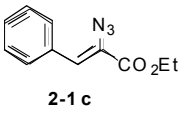
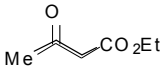
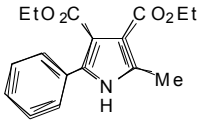
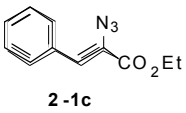
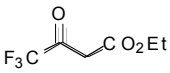
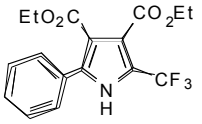
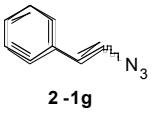
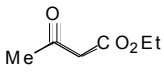
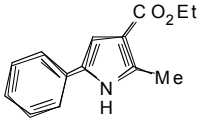


Scheme 2-19. Reaction of vinyl azide **2-1b** with 1-phenylbutane-1,3-dione

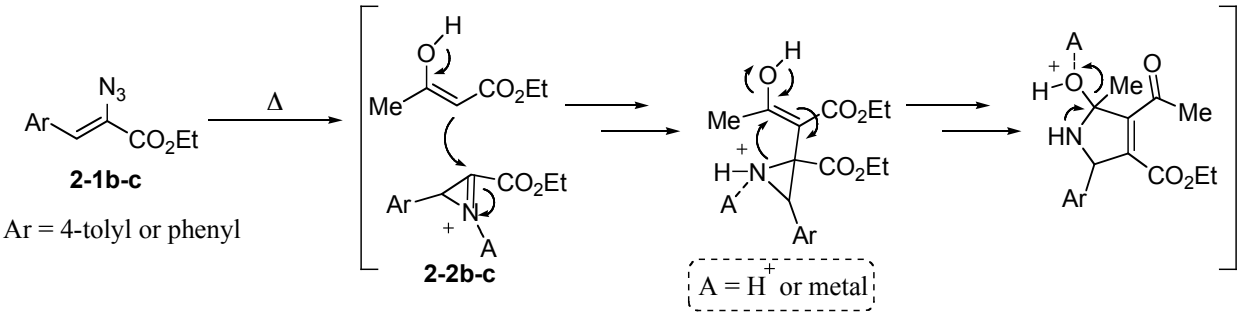
Then, I looked over the reactivity of a variety of vinyl azides with β-keto esters. These results are shown in the next page (table 2-7). With β-aryl vinyl azides **2-1b-c** possessing a ethoxycarbonyl moiety, the reaction with β-keto esters proceeded in modest yield to give pyrroles **2-9k-n**. Employing ethyl 4,4,4-trifluoro-3-oxobutanoate as nucleophile did not change much the yield, as shown in entry 4. On the other hand, the reaction of ethyl acetoacetate and β-azidostyrene **2-1g** which does not have any ethoxycarbonyl group gave trisubstituted pyrrole **2-9o** in a reasonable yield (entry 5).

Table 2-7. Reaction of vinyl azide **2-1b,c,g** with different β-keto esters



entry	alkenyl azides	β-ketoesters	**2-9** /%
1	 **2-1b**		 **2-9k** 25%
2	 **2-1b**		 **2-9l** 25%
3	 **2-1c**		 **2-9m** 30%
4	 **2-1c**		 **2-9n** 31%
5	 **2-1g**		 **2-9o** 58%

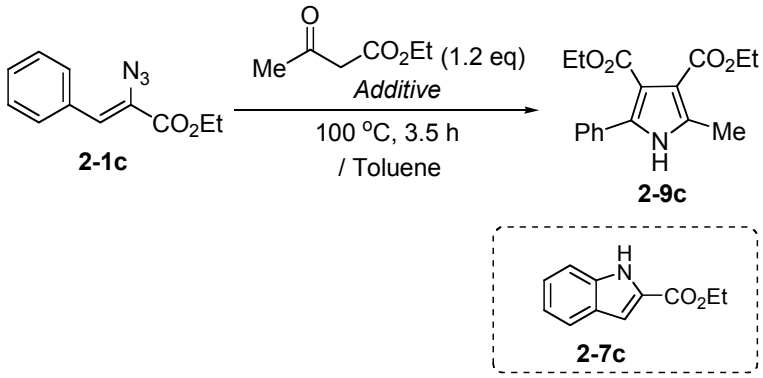
In order to improve the yield of the reaction with β-keto esters, the effect of additive was studied. It was expected that the reaction could be improved by the use of a Brønsted or Lewis acid, which may activate the *in situ* generated 2*H*-azirines **2-2b-c** toward nucleophilic attack of the β-keto esters (scheme 2-20).



Scheme 2-20. Acid additives in the addition of β-keto esters to vinyl azides

The reaction of ethyl acetoacetate with vinyl azide **2-1c** in the presence of water or a Brønsted acid is summarized in table 2-8.

Table 2-8. Effect of acid additives



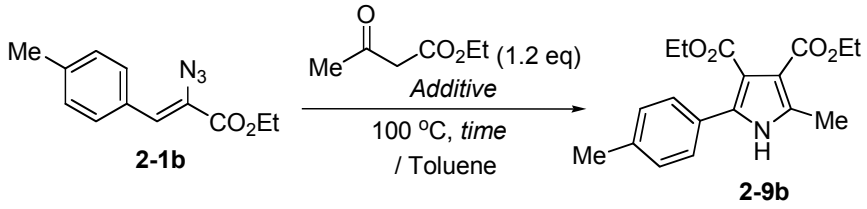
entry	additive / eq.	**2-9c** /%	**2-7c** /%
0	none	30	-
1*	none	30	-
2	H_2O (3.0)	17	16
3	AcOH (1.0)	10	-
4	Et_3NHCl (1.0)	18	-

* 3.0 equivalent of β-ketoester used.

At first, increasing the molar amounts of *β*-keto ester did not improve the yield (entry 1). The addition of water was detrimental to the reaction, and interesingly, partly initiated the isomerization of **2-1c** to indole **2-7c**. Using acetic acid or triethylammonium chloride decreased the yield significantly. In all of these experiments, it seems that dimerization/ polymerization of the vinyl nitrene generated thermally from **2-1c** happened.

Further investigations on the reaction of ethyl acetoacetate with vinyl azide **2-1b** are shown below (table 2-9). Adding molecular sieve to the reaction improved the yield marginally (entry 1), while using azeotropic conditions in benzene was slightly detrimental. In the presence of a magnesium salt (entry 3-4) and copper carbonate (entry 5), the yield decreased.

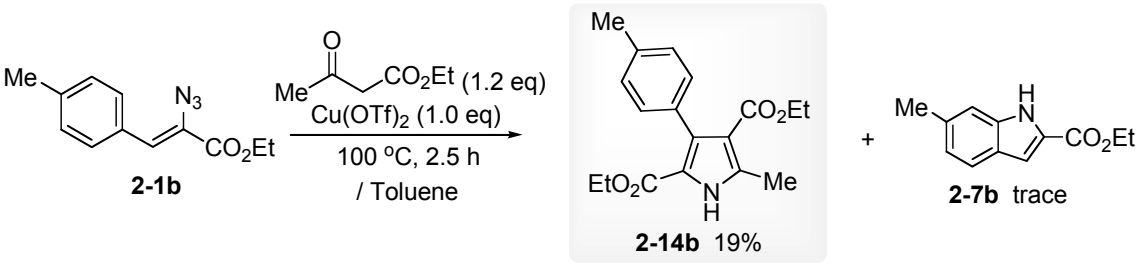
Table 2-9. Effect of additives



entry	time /h	additive / eq.	**2-9b** /%
0	2.5	none	25
1*	4.0	none	20
2	2.5	MS 4A	29
3	2.0	$MgBr_2$ (1.0)	17
4	2.0	$Mg(OTf)_2$ (1.0)	15
5	2.5	$CuCO_3$ (1.0)	17

* Reflux in benzene. Dean-Stark apparatus.

On the other hand, the addition of copper triflate [$Cu(OTf)_2$] in the reaction of ethyl acetoacetate with vinyl azide **2-1b** gave a unexpected result. While pyrrole **2-9b** was not formed, pyrrole **2-14b** along with a trace amount of indole **2-7b** could be obtained.



Scheme 2-21. Copper(II)-initiated formation of pyrrole **2-14b**

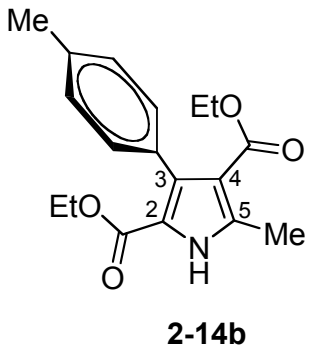
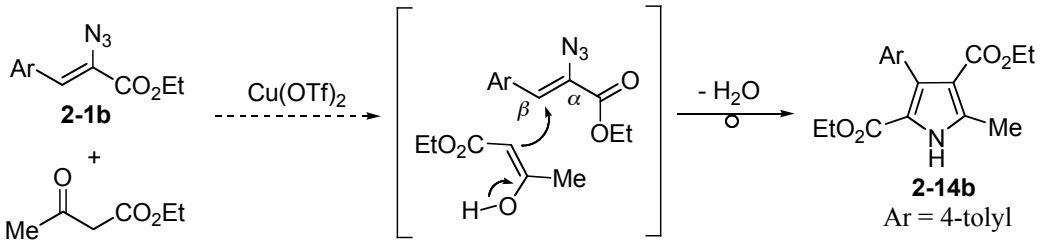


Figure 2-3. ORTEP drawing of **2-14b**

Pyrrole **2-14b** was recrystallized and its structure was confirmed by X-ray crystallographic analysis (figure 2-3). In opposite to pyrrole **2-9b**, the carbonyl residues in **2-14b** appared on the C-2 and C-4 carbons, while the tolyl and methyl groups are located on the C-3 and C-5 carbon respectivetly. The next chapter will focus on this new copper(II) triflate-initiated reaction of β-keto esters with vinyl azides, to afford pyrroles **2-14**.

2.3 Copper(II)-catalyzed reaction of vinyl azides with *β*-keto esters

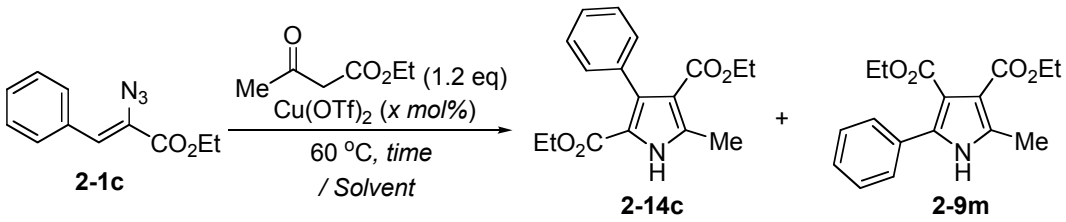
Thus, pyrrole **2-14b** was obtained when vinyl azide **2-1b** and ethyl acetacetate was treated with a stoichiometric amount of copper(II) triflate. This result catched my interest because no close precedent to this reaction exists. It is postulated that the *β*-keto ester attack at the *β*-position of the acrylate and subsequent cyclization and dehydratation afford pyrrole **2-14b** as shown in scheme 2-22. The exact role of the copper(II) triflate in the reaction is yet unclear.



Scheme 2-22. Plausible explanation for the formation of pyrrole **2-14b**

Optimization of this copper(II)-catalyzed pyrrole formation was examined. At first, several solvents were screened, and these results are summarized in table 2-10. The reaction proceeded at 60 °C in dichloroethane (entry 1). This result excludes the involvement of a thermally generated 2*H*-azirine in the reaction mechanism because higher temperature are needed in order to form 2*H*-azirine. With acetonitrile as a solvent, the yield was increased (entry 2) and, surprisingly, the reaction could be run with a catalytic amount of copper(II) triflate (entry 3). In this case, a small amount of the thermal pyrrole **2-9m** was obtained as side product. Using acetone or nitromethane as solvent afforded pyrrole **2-14c** in lower yield. With other solvents such as THF, DMF, and ethanol, the reaction did not proceed and the starting material was recovered.

Table 2-10. Solvent effect



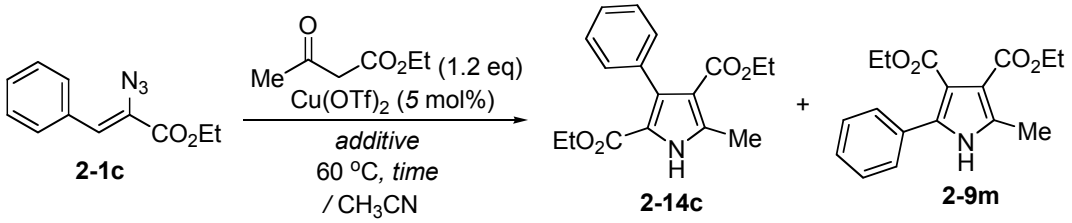
entry	solvent	$Cu(OTf)_2$ / mol%	time /h	**2-14c** /%	**2-9m** /%	**2-1c** /%
0**	toluene	100	2.0	19	-	-
1	$ClCH_2CH_2Cl$	100	10.0	15	-	-
2	CH_3CN	100	4.0	44	-	16
3	CH_3CN	5	16.0	34	14	34
4	Acetone	5	6.5	12	-	84
5	CH_3NO_2	5	9.0	9	6	13

* Other solvents screened: THF, DMF, EtOH

** With substrate **2-1b** as starting material. Done at 100 °C.

The effects of additive on the reaction are described in table 2-11. When molecular sieve 4A was used, the copper-catalyzed reaction was inhibited (entry 1). Interesingly, the addition of water had a positive effect on the reaction (entry 2 to 4). In that case, the yield was significantly increased and no side reaction to isomer **2-9m** was observed at all. The optimal amount of water was determinated to 5 molar amounts. However, the progression of the reaction stopped after few hours, and the starting material was partly recovered in all cases.

Table 2-11. Additive effect

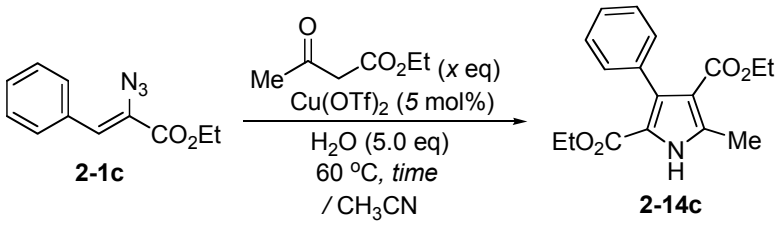


entry	additive / eq.	time /h	**2-14c** /%	**2-9m** /%	**2-1c** /%
0	none	16.0	34	14	34
1	MS 4A	9.5	4	trace	58
2	H_2O (2.0)	23.0	45	-	43
3	H_2O (5.0)	17.5	55	-	18
4	H_2O (20.0)	16.0	53	-	25
5*	H_2O (excess)	19.0	9	2	40

* Water was used as a co-solvent (H_2O:CH_3CN 1:1)

The quantity of β-keto ester had a strong influence on the yield of **2-14c** (table 2-12). Increasing the amount resulted in higher yield of the desired pyrrole **2-14c**. In term of yield versus quantity of β-keto ester employed, 3.0 equimolar amount proved to be optimal (entry 3).

Table 2-12. Amount of β-ketoester

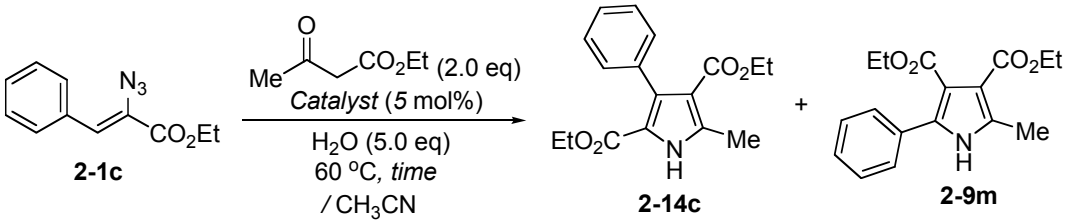


entry	β-keto ester / eq.	time /h	**2-14c** /%	**2-1c** /%
0	1.2	16.0	55	18
1	1.0	8.0	40	43
2	2.0	8.0	64	33
3	3.0	13.0	71	23

After, several copper catalysts and some other metal species were screened in the reaction of vinyl azide **2-1c** with ethyl acetoaetate (table 2-13). Among various copper catalysts, cationic copper species seemed to be effective for this pyrrole formation. The reaction did not proceed and the starting material was partially recovered with other copper salts, and with silver and iron complexes. By far, copper(II) triflate remains the catalyst of choice for the formation of pyrrole **2-14c**.

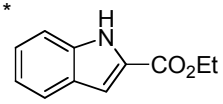
Interesingly, with $[Rh(OCOCF_3)]_2$ as catalyst, no pyrrole **2-14c** was obtained, but reaction to indole **2-7c** was achieved. In this case, a vinyl nitrene-rhodium complex might be involved as an intermediate, like the Rh(II)-catalyzed isomerization of 2-aryl-2*H*-azirines to 2,3-disubstituted indoles (scheme 2-5, section 2.1, p.26).

Table 2-13. Metal catalyst



entry	catalyst	time /h	**2-14c** /%	**2-9m** /%	**2-1c** /%
0	$Cu(OTf)_2$	8.0	64	-	33
1	CuOTf	11.0	28	6	27
2	$Cu(CH_3CN)_4PF_6$	18.5	46	-	44

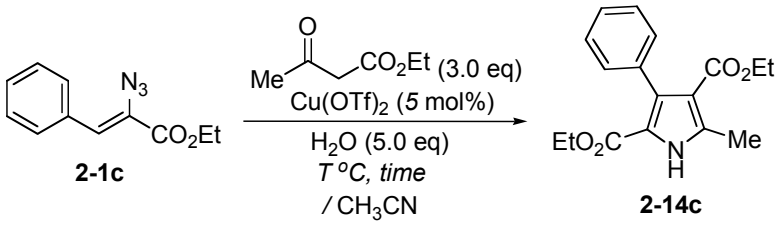
Other catalysts screened: $Cu(hfac)_2$, $CuSO_4$, $Cu(OAc)_2$, CuO, Cu_2O, $CuCl_2$, CuCl, AgOTf, $FeCl_2$, $[Rh(OCOCF_3)_2]_2$ (in $ClCH_2CH_2Cl$)*.

* 

2-7c 74%

As for the reaction temperature, the results are presented below (table 2-14). Increasing the temperature to 80°C was detrimental to the pyrrole formation (entry 1). At 40°C, the reaction was optimal and pyrrole **2-14c** was isolated in 78% yield (entry 2). Surprisingly, the reaction also proceeded at room temperature, albeit in lower yield and longer reaction time than at 40°C.

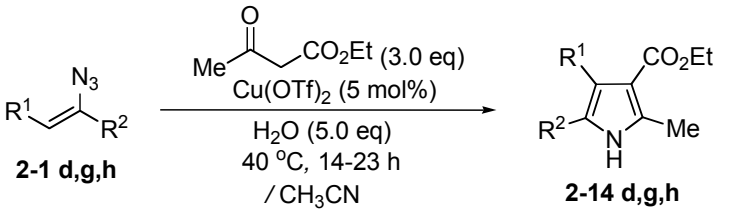
Table 2-14. Temperature effect

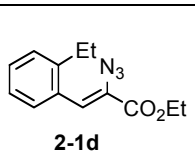
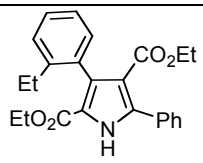
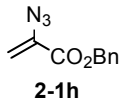
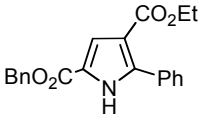
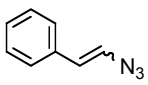


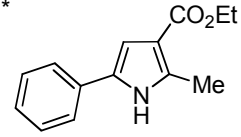
entry	T / °C	time /h	**2-14c** /%	**2-1c** /%
0	60	13.0	71	23
1	80	8.0	39	37
2	40	30.0	78	21
3	rt	50.0	55	27

The copper(II)-catalyzed reactions of ethyl acetoacetate with some other vinyl azides are shown in table 2-15. With β-aryl vinyl azide **2-1d** having a ethoxycarbonyl moiety, pyrrole **2-14d** was obtained in 44% yield (entry 1). As for 2-azidoacrylate **2-1h**, the reaction proceeded to afford trisubstituted pyrrole **2-14h** in low yield. β-Azidostyrene **2-1g** without ethoxycarbonyl moiety did not undergo the desired reaction. Instead, the thermal regioisomeric pyrrole **2-9o** was obtained in low yield (entry 3). Most of the starting material **2-1g** decomposed during the purification step.

Table 2-15. Scope of vinyl azides



entry	alkenyl azides	**2-14** /%	**2-1** /%
1	 **2-1d**  **2-14d**	44	35
2	 **2-1h**  **2-14h**	28	50
3*	 **2-1g**	-	-

* 

2-9o 10%

What makes the reaction stop, and what is the real catalyst? In the reaction vessel, other than vinyl azide **2-1**, four compounds can coordinate the copper(II) salt, namely ethyl acetoacetate, water, the product, and acetonitrile. Increasing the amount of β-keto ester was beneficial as shown in table 2-12 (p.42), and water is also good for the yield (table 2-11, p.42). While desactivation from the product cannot be ruled out, the high yield of pyrrole **2-14c** suggests otherwise. The reaction is quick at the beginning and gradually slow down, to finally stop. This fact suggests that the formation of the active species is a rapid process, and that the desactivation is slow and irreversible. It is known that water complexes quickly copper(II) cation, and acetonitrile slowly coordinate the copper(II) species.[67] One possibility is that a quick complex of the general formula $Cu(OH_2)_{4-x}(CH_3CN)_x(OTf)_2$ is formed, and this active species gradually degrade to a unactive complex of the type such as $Cu(CH_3CN)_4(OTf)_2$ (figure 2-4). If this is true, the use of a bulky nitrile as a solvent may help to keep the active catalyst over the desactivated species. Steric hinderance in the coordination sphere emerging from the complexed nitriles may favor its decomplexation.

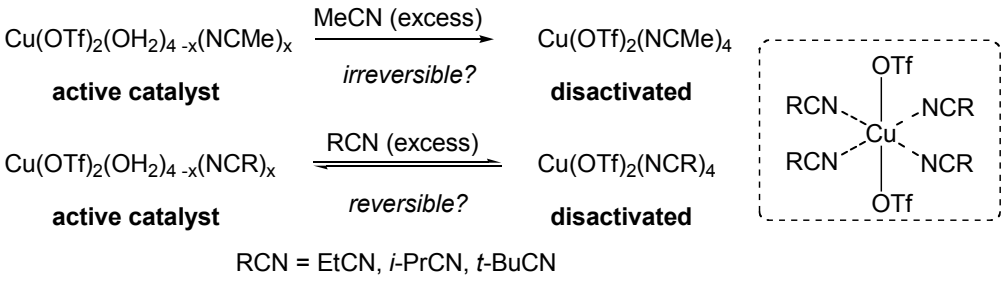
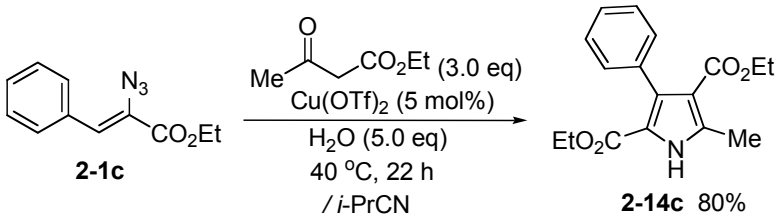


Figure 2-4. Hypothesis over the active species

The copper(II)-catalyzed reaction of vinyl azide **2-1c** with ethyl acetoacetate using isobutyronitrile as a solvent in scheme 2-23. In comparison to the reaction done in acetonitrile, the yield was slightly improved and no starting material was recovered.



Scheme 2-23. Isobutyronitrile as solvent

Still, the role of the copper(II) triflate catalyst in the reaction is unknown. One logical explanation is that a vinyl nitrene-copper complex is formed, which activate the vinyl moiety toward nucleophilic attack of the β-keto ester (figure 2-5). Although this concept is quite new and interesing in itself, we so far have no clear evidence on this mechanistic hypothesis.

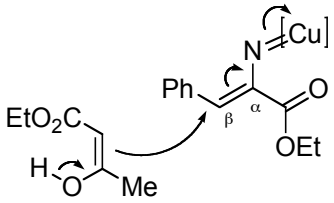
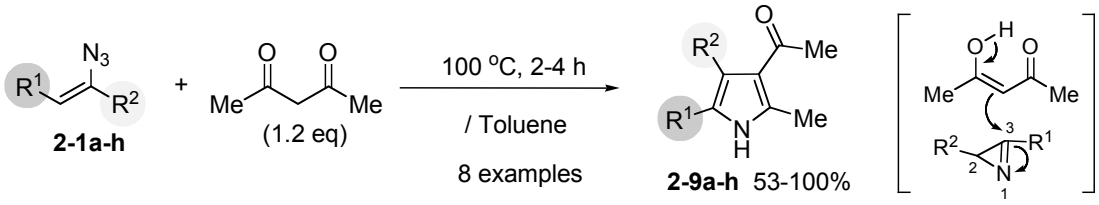


Figure 2-5. Hypothesis over the reaction mechanism

2.4 Conclusion

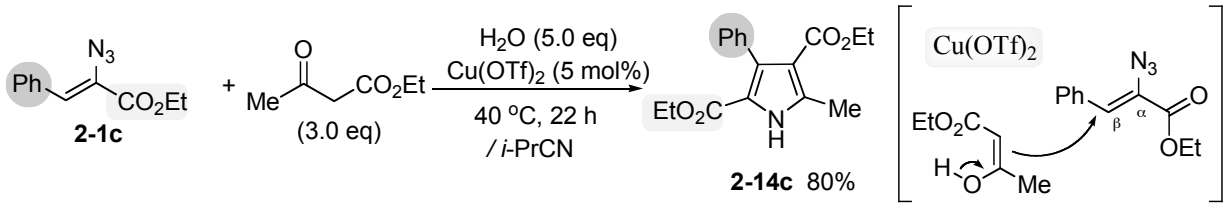
In conclusion, I have shown that vinyl azides can be a useful building block in the synthesis of substituted pyrroles. It was found that, depending on the reaction conditions, 1,3-dicarbonyl compounds can add to different carbon centers of the vinyl azides to afford a variety of pyrroles.

The first reaction was the thermal construction of polysubstituted pyrroles from vinyl azides and 1,3-diketones. In this reaction, 2*H*-azirines generated *in situ* thermally from vinyl azides were attacked by 1,3-diketones such as acetylacetone at the C-3 carbon, affording pyrroles **7**. The addition of other 1,3-diketones and *β*-keto esters was sluggish, and additives such as acids or bases did not improve the yield.



Scheme 2-24. Thermal reaction of vinyl azides with acetylacetone

The second reaction was the copper(II)-catalyzed reaction of vinyl azides with *β*-keto esters. With copper(II) triflate as a catalyst and ethyl acetoacetate as a nucleophile, pyrrole **2-14** was obtained in preference over the thermal addition pyrrole **2-9**. In this reaction, the addition of water improved the yield significantly. It has been postulated that the *β*-keto ester attacks at the *β* position of the vinyl azide to give the corresponding pyrrole **2-14**. It is noteworthy to mention that the C-2 and C-3 substituents of the product are inverted in comparison with the thermally produced pyrrole **2-9**.

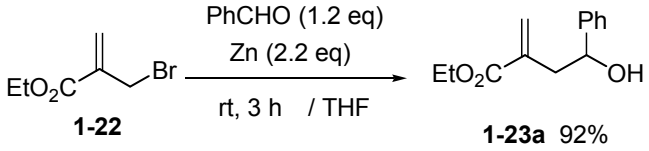


Scheme 2-25. Copper(II)-catalyzed reaction of vinyl azides with *β*-ketoesters

Experimental sections: Chapter 1

General. ^{1}H NMR (500 MHz) spectra were recorded on a Bruker DRX 500 apparatus, ^{1}H NMR (400 MHz) spectra on a JEOL-AL400 spectrometer in $CDCl_3$ [using tetramethylsilane (for ^{1}H, δ = 0) as internal standard] unless otherwise mentioned. ^{13}C NMR (125 MHz) spectra were recorded on a Bruker DRX 500 and JEOL-AL400 spectrometers in $CDCl_3$ [using $CDCl_3$ (for ^{13}C, δ = 77.00) as internal standard] unless otherwise mentioned. ^{19}F NMR (470 MHz) spectra were recorded on a JEOL-AL400 spectrometers in $CDCl_3$ [using C_6F_6 (for ^{19}F, δ = 0) as internal standard]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad. IR spectra were recorded on a Horiba FT 300-S by ATR method. High-resolution mass spectra were obtained with a JEOL MS-700P mass spectrometer. Elemental analyses were carried out at The Elemental Analysis Laboratory, Department of Chemistry, Faculty of Science, The University of Tokyo. Flash column chromatography was performed on silica gel [Merck Silica gel 60, and Kanto Chemical Co., Inc. Silica gel 60N (spherical, neutral)] and preparative thin-layer chromatography was carried out using Wakogel B-5F. Dry tetrahydrofuran (THF), diethyl ether (Et_2O), toluene, hexane, *N*,*N*-dimethylformamide (DMF), and dichloromethane (CH_2Cl_2) were dried by passing over a column of activated alumina (A-2, Purify) followed by a column of Q-5 scavenger (Engelhard). Ethanol (EtOH) was distilled from sodium and stored over Molecular Sieves 3A (MS 3A). Methanol was distilled from a trace amount of iodine and magnesium, and stored over MS 3A. Triethylamine and pyridine were distilled from CaH_2 and stored over KOH.

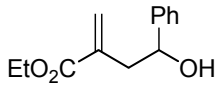
1.2 Nucleophilic *5-endo-trig* cyclization of *N*-(3-halomethylhomoallyl) sulfonamides



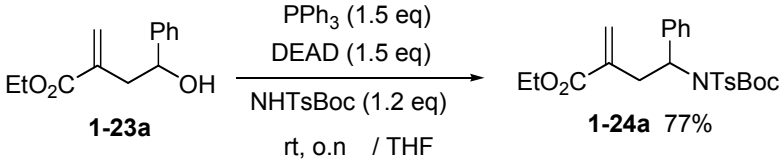
Typical procedure for the zinc-mediated allylation of aldehyde:

To a stirring solution of benzaldehyde (6.6 g, 6.3 mL, 62.2 mmol) and allylic bromide **1-22** (10.0 g, 51.8 mmol) in THF (35 mL) was added saturated aqueous ammonium chloride solution (175 mL). The reaction was cooled to 0°C and zinc dust (10.0 g, 155.4 mmol) was slowly added to the reaction mixture and stirring was continued at room temperature for 3.5 h. The reaction mixture was diluted with ethyl acetate, and then extracted twice with EtOAc. The combined organic extracts were washed with water, brine and dried over Na_2SO_4. Purification of the crude product by flash column chromatography (Silica gel, 15% ethyl acetate/hexanes) gave **1-23a** in 92% yield. (10.53 g, 47.8 mmol).

Ethyl 4-hydroxy-2-methylene-4-phenylbutanoate (1-23a)



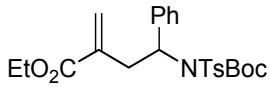
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (3H, t, *J*= 7.2 Hz), 2.64 (1H, dd, *J*= 13.9, 8.3 Hz), 2.74 (1H, dd, *J*= 13.9, 4.2 Hz), 3.01 (1H, s br), 4.17 (2H, d, *J*= 7.1 Hz), 4.84 (1H, dd, *J*= 8.3, 4.3 Hz), 5.55 (1H, s), 6.20 (1H, s), 7.21-7.32 (5H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.1, 42.3, 60.9, 72.9, 125.5, 127.2, 128.0, 128.1, 136.9, 143.8, 167.4. IR (ZnSe) ν 3560, 2983, 1707, 1306, 1190, 1140, 1026 cm^{-1}. FABHRMS: Found: *m/z* 221.1183. Calcd for $C_{13}H_{17}O_3$ $(M+H)^+$ 221.1178.



Typical procedure for the Mitsunobu reaction:

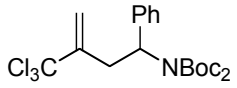
To a stirring solution of ethyl 4-hydroxy-2-methylene-4-phenylbutanoate **1-23a** (2.2 g, 10.0 mmol), PPh_3 (3.9 g, 15.0 mmol) and *N*-*t*-butoxycarbonyl-*p*-toluenesulfonamide (3.25 g, 12.0 mmol) in THF (70 mL) was added DEAD (40% in toluene, 6.8 mL, 15 mmol) at 0°C. After, the reaction mixture was stirred at room temperature for 10 h. The reaction mixture was diluted with ethyl acetate, water was added and the mixture extracted twice with EtOAc. The combined organic extracts were washed with water, brine and dried over Na_2SO_4. Purification of the crude product by flash column chromatography (Silica gel, 10% ethyl acetate/hexanes) gave **1-24a** in 77% yield. (3.63 g, 7.66 mmol).

Ethyl 4-phenyl-4-(*N*-*t*-butoxycarbonyl-*p*-tosylamino)butenoate (1-24a)



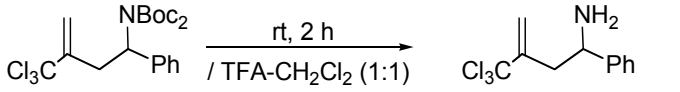
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (9H, s), 1.34 (3H, t, *J*= 7.1 Hz), 2.40 (3H, s), 3.36 (2H, d, *J*= 7.8 Hz), 4.28 (2H, q, *J*= 7.1 Hz), 5.68 (1H, s), 5.97 (1H, t, *J*= 7.7 Hz), 6.32 (1H, s), 7.21 (2H, d, *J*= 8.3 Hz), 7.24-7.34 (3H, m), 7.41 (2H, d, *J*= 7.6 Hz), 7.63 (2H, d, *J*= 8.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2, 21.6, 27.8, 34.7, 59.4, 60.9, 84.1, 127.2, 127.6, 128.1, 128.6, 128.7, 128.8, 136.9, 137.0, 139.6, 143.8, 150.7, 166.4. IR (ZnSe) ν 2981, 1718 (br), 1360, 1146, 1086, 910 cm^{-1}. FABHRMS: Found: *m/z* 474.1943. Calcd for $C_{25}H_{32}O_6NS$ $(M+H)^+$ 474.1951.

Di-*t*-butoxy(3-(trichloromethyl)-1-phenylbut-3-enyl)dicarbamate (1-41b)



Used alcohol **1-40** and $NHBoc_2$ as substrate. Purified by silica gel flash column chromatography (Silica gel, 5% Ethyl acetate/ 95% hexanes). 40% yield. (2.7 g, 5.8 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (18H, s), 3.34 (IH, dd, *J*= 15.9, 5.9 Hz), 3.46 (1H, dd, *J*= 15.9, 9.2 Hz), 5.27 (1H, s), 5.82 (1H, dd, *J*= 9.3, 5.6 Hz), 6.00 (1H, s), 7.25 (1H, t,

J= 7.4 Hz), 7.33 (2H, t, *J*= 7.4 Hz), 7.41 (2H, d, *J*= 7.8 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.9, 28.1. 32.7, 57.4, 82.5, 99.0, 117.2, 127.2, 127.3, 128.1, 139.6, 145.9, 152.8. IR (ZnSe) 2979, 2931, 1739, 1703, 1340, 1238, 1140, 1111, 912 cm^{-1}. FABHRMS: Found: *m/z* 464.1143. Calcd for $C_{21}H_{29}NO_4Cl_3$ $(M+H)^+$ 464.1165.

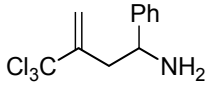


1-41b **1-17c** (two steps) 20%

Typical procedure for the deprotection of a Boc-protected amine

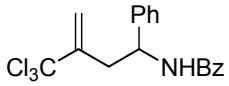
The di-Boc protected derivative **1-41b** (2.6 g, crude) was diluted in CH_2Cl_2 (30 mL) and TFA (10 mL) was added at 0°C. After 1 h at room temperature, water was added, and the mixture extracted twice with CH_2Cl_2. The combined organic phases were washed with water, brine and dried over Na_2SO_4. Obtained pure in 20% yield (two steps). (1.56 g, 5.9 mmol).

(3-(trichloromethyl)-1-phenylbut-3-en-1-amine (1-17c)

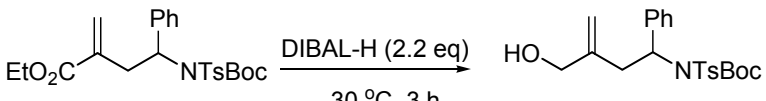


White solid. ^{1}H NMR (400 MHz, D_6-DMSO) δ 3.08 (1H, dd, *J*= 15.1, 10.7 Hz), 3.22 (1H, dd, *J*= 15.1, 3.2 Hz), 4.70 (1H, dd, *J*= 10.5, 4.4 Hz), 5.34 (1H, s), 5.87 (1H, s), 7.36-7.41 (3H, m), 7.60 (2H, d, *J*= 7.6 Hz), 8.81 (2H, s). ^{13}C NMR (126 MHz, D_6-DMSO) δ 34.8, 53.1, 98.3, 118.4, 128.1, 128.4, 128.8, 136.2, 142.8. IR (ZnSe) 3035 (br), 2900 (br), 1599, 1516, 1456, 800 cm^{-1}. FABHRMS: Found: *m/z* 264.0121. Calcd for $C_{11}H_{13}NCl_3$ $(M+H)^+$ 264.0116.

(3-(trichloromethyl)-1-phenylbut-3-enyl)benzamide (1-17b)



Used alcohol **1-40** and NHBocBz as substrate in the Mitsunobu reaction. Purified by flash column chromatography (Silica gel, 20% Ethyl acetate/ 80% hexanes). 23% yield (two steps). (220 mg, 0.60 mmol). White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08 (1H, d, *J*= 2.7 Hz), 3.10 (1H, d, *J*= 5.1 Hz), 5.40 (1H, s), 5.60 (1H, dd, *J*= 8.3, 5.1 Hz), 6.02 (1H, s), 6.43 (1H, d br, 7.9 Hz), 7.25-7.52 (8H, m), 7.73 (2H, d, *J*= 7.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 37.1, 52.5, 99.0, 116.6, 126.5, 126.9, 127.8, 128.6, 128.8, 131.7, 133.8, 140.9, 145.0, 167.1. IR (ZnSe) 3286, 2924, 2854, 1635, 1535, 1311, 910 cm^{-1}. FABHRMS: Found: *m/z* 368.0369. Calcd for $C_{18}H_{17}ONCl_3$ $(M+H)^+$ 368.0378.



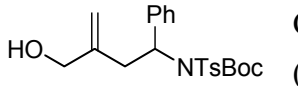
1-24a **1-25** 93%

DIBAL-H reduction of ester 1-24a:

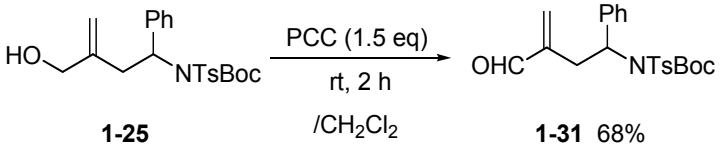
To a stirring solution of ethyl 4-phenyl-4-(*N*-*t*-butoxycarbonyl-*p*-tosylamino)butenoate **1-24a** (1.6 g,

3.4 mmol) in toluene (15 mL) was added DIBAL-H (1M in toluene, 8.0 mmol) at -30°C. After, the reaction mixture was stirred at -30°C for 3 h. The reaction mixture was then quenched with methanol and water, diluted with ethyl acetate, and the mixture extracted twice with EtOAc. The combined organic extracts were washed with water, brine and dried over Na_2SO_4. Purification of the crude product by flash column chromatography (Silica gel, 30% ethyl acetate/hexanes) gave **1-25** in 93% yield (1.42 g, 3.3 mmol).

2-methylene-4-phenyl-4-(*N*-*t*-butoxycarbonyl-*p*-tosylamino)butan-1-ol (1-25)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (9H, s), 1.92 (1H, s br), 2.34 (3H, s), 2.95 (1H, dd, *J*= 14.5, 5.7 Hz), 3.20 (1H, dd, *J*= 14.3, 9.8 Hz), 4.16 (2H, s br), 5.00 (1H, s), 5.19 (1H, s), 5.80 (1H, dd, *J*= 9.6, 6.0 Hz), 7.15 (2H, d, *J*= 8.1 Hz), 7.19-7.26 (3H, m), 7.32 (2H, d, *J*= 7.1 Hz), 7.57 (2H, d, *J*= 8.2 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.6, 27.8, 35.6, 59.3, 66.0, 84.3, 114.6, 127.3, 127.7, 128.1, 128.4, 128.9, 137.0, 139.5, 144.0, 145.0, 150.6. IR (ZnSe) ν 3535 (br), 2979, 1724, 1342, 1250, 1146, 1084 cm^{-1}. FABHRMS: Found: *m/z* 432.1857. Calcd for $C_{23}H_{30}O_5NS$ $(M+H)^+$ 432.1846.

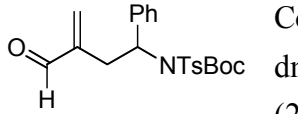


1-25 **1-31** 68%

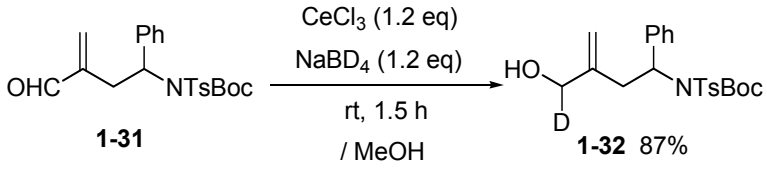
PCC oxidation of alcohol 1-25:

To a stirring solution of the 2-methylene-4-phenyl-4-(*N*-*t*-butoxycarbonyl-*p*-tosylamino)butan-1-ol **1-25** (1.7 g, 3.95 mmol) in CH_2Cl_2 (25 mL) was added celite and PCC (1.27 g, 5.90 mmol) at room temperature. After, the reaction mixture was stirred for 2 h. The reaction mixture was then filtered on a celite pad. Purification of the crude product by flash column chromatography (Silica gel, 15% ethyl acetate/hexanes) gave **1-31** in 68% yield. (1.14g, 2.66 mmol).

2-methylene-4-phenyl-4-(*N*-*t*-butoxycarbonyl-*p*-tosylamino)butanal (1-31)



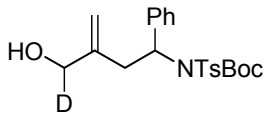
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (9H, s), 2.33 (3H, s), 3.23 (2H, dm, *J*= 6.5 Hz), 5.72 (1H, dd, *J*= 8.6, 6.6 Hz), 6.10 (1H, s), 6.35 (1H, s), 7.14 (2H, d, *J*= 8.0 Hz), 7.27-7.18 (5H, m), 7.52 (2H, *J*= 8.2 Hz), 9.50 (1H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.6, 27.8, 30.6, 59.2, 84.3, 127.3, 127.5, 128.1, 128.4, 128.9, 136.8, 137.2, 139.1, 144.0, 146.2, 150.6, 193.9. IR (ZnSe) 2981, 1724, 1689, 1354, 1277, 1250, 1146, 1086 cm^{-1}. Anal. Found: C, 64.07; H, 6.43; N, 3.10%. Cacld for $C_{23}H_{27}NO_5S$; C, 64.31; H, 6.34; N, 3.26%.



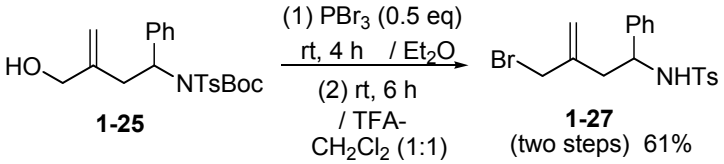
$NaBD_4$ reduction of aldehyde 1-31:

To a solution of $CeCl_3 \cdot 7\ H_2O$ (1.1 g, 2.95 mmol) and aldehyde **1-31** (1.05 g, 2.45 mmol) in MeOH (7 mL) was added successively $NaBD_4$ (125 mg, 2.95 mmol) at 0°C. After being stirred for 2 h at room temperature, the reaction was quenched by addition of saturated $NaHCO_3$ and ethyl acetate was added. The mixture was extracted twice with EtOAc, and the combined organic extracts were washed with water, brine and dried over Na_2SO_4. Purification of the crude product by flash column chromatography (30% ethyl acetate/hexanes) gave **1-32** in 87% yield. (Silica gel, 930 mg, 2.15 mmol).

1-deutero-2-methylene-4-phenyl-4-(*N*-*t*-butoxycarbonyl-*p*-tosylamino)butan-1-ol (1-32)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (9H, s), 2.18 (1H, s br), 2.32 (3H, s), 2.94 (1H, dd, *J*= 14.2, 5.8 Hz), 3.18 (1H, dd, *J*= 14.1, 9.6 Hz), 4.12 (0.5H, s br), 4.14 (0.5H, s br), 4.98 (1H, s), 5.18 (1H, s), 5.79 (1H, dd, *J*= 9.6, 5.9 Hz), 7.14 (2H, d, *J*= 8.0 Hz), 7.17-7.25 (3H, m), 7.32 (2H, d, *J*= 7.5 Hz), 7.56 (2H, d, *J*= 8.2 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5, 27.7, 35.5, 59.1, 66.0 (t, J_{CD}= 26.5 Hz), 84.2, 114.4, 127.3, 127.6, 128.0, 128.3, 128.8, 136.9, 139.5, 143.9, 144.9, 150.6. IR (ZnSe) ν 3535 (br), 2979, 1726, 1346, 1250, 1147, 1086 cm^{-1}. FABHRMS: Found: *m/z* 433.1902. Calcd for $C_{23}H_{29}DO_5NS$ $(M+H)^+$ 433.1924.

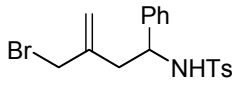


Typical procedure for the bromination of primary alcohol:

To a stirring solution of 2-methylene-4-phenyl-4-(*N*-*t*-butoxycarbonyl-*p*-tosylamino)butan-1-ol **1-25** (1.08 g, 2.5 mmol) in Et_2O (15 mL) was added PBr_3 (350 mg, 0.24 mL, 1.3 mmol) at 0°C. After, the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched with ethanol and water, diluted with ethyl acetate, and the mixture extracted twice with EtOAc. The combined organic extracts were washed with water, brine and dried over Na_2SO_4. The crude product was used directly in the next step.

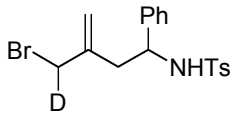
The bromine derivative of **1-25** (1.3 g, 2.5 mmol) was diluted in CH_2Cl_2 (10 mL) and TFA (5 mL) was added at 0°C. After 1 h at room temperature, water was added, and the mixture extracted twice with CH_2Cl_2. The combined organic phases were washed with water, brine and dried over Na_2SO_4. Purification of the crude product by flash column chromatography (Silica gel, 15% ethyl acetate/hexanes) gave **1-27** in 62% yield (two steps). (600 mg, 1.52 mmol).

***N*-(3-bromomethyl-1-phenyl-3-butenyl)-*p*-toluenesulfonamide (1-27)**

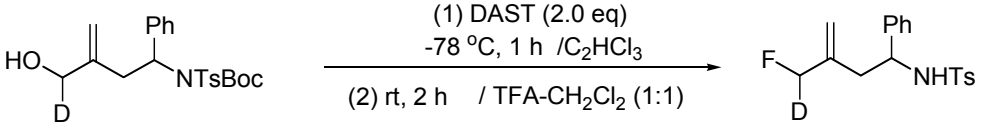


Beige solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (3H, s), 2.54 (1H, dd, *J* = 14.9, 9.0 Hz), 2.68 (1H, dd, *J*= 14.7, 6.0 Hz), 3.75 (1H, d, *J*= 10.5 Hz), 3.78 (1H, d, *J*= 10.5 Hz), 4.48 (1H, td, *J*= 9.0, 6.4 Hz), 4.96 (1H, s), 5.00-5.18 (1H, m br), 5.22 (1H, s), 7.05-7.16 (5H, m), 7.10 (2H, d, *J*= 8.3 Hz), 7.51 (2H, d, *J*= 8.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5, 35.8, 41.7, 56.1, 119.1, 126.3, 127.1, 127.5, 128.4, 129.2, 137.1, 140.1, 140.7, 143.1. IR (ZnSe) ν 3273 (br), 3032, 1452, 1427, 1321, 1153 cm^{-1}. Anal. Found: C, 54.94; H, 5.28; N, 3.42%. Cacld for $C_{18}H_{20}NO_2SBr$; C, 54.83; H, 5.11; N, 3.55%.

3-(deuterobromomethyl)-1-phenyl-*N*-tosylbut-3-en-1-amine (1-33c)



Alcohol **1-32** was employed as starting material. Purification of the crude product by flash column chromatography (Silica gel, 20% ethyl acetate/hexanes) gave **1-33c** in 82% yield (two steps). (58 mg, 0.147 mmol). Beige solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (3H, s), 2.54 (1H, dd, *J* = 14.9, 8.9 Hz), 2.66 (1H, dd, *J*= 14.7, 6.0 Hz), 3.76 (1H, s), 4.46 (1H, dd, *J*= 9.1, 6.4 Hz), 4.95 (1H, s), 5.19 (1H, s), 5.45 (1H, s br), 7.06-7.66 (7H, m), 7.52 (2H, d, *J*= 8.2 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.4, 35.6 (t, J_{CD}= 22.5 Hz), 41.6, 56.1, 119.1, 126.4, 127.0, 127.4, 128.4, 129.2, 137.2, 140.2, 140.6, 143.1. IR (ZnSe) ν 3273 (br), 2920, 1599, 1495, 1456, 1319, 1153, 1093, 1061, 908 cm^{-1}. FABHRMS: Found: *m/z* 395.0536. Calcd for $C_{18}H_{21}DO_2NSBr$ $(M+H)^+$ 395.0556.



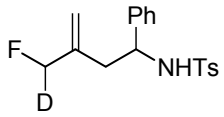
1-32 **1-33a** 34%

Fluorination of alcohol 1-32:

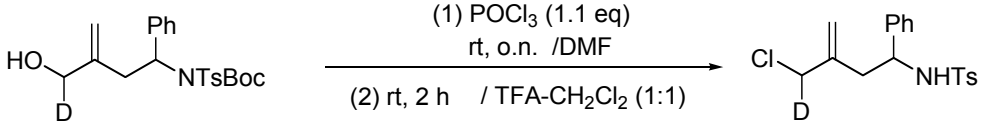
To a stirring solution of diethylamine trifluorosulfur (DAST) (390 mg, 0.32 mL, 2.45 mmol) in trichloroethylene (3 mL) was slowly added a solution of alcohol **1-32** (530 mg, 1.25 mmol) in trichloroethylene (2 mL) at -78°C. After, the reaction mixture was stirred at -78°C for 1 h. The mixture was then quenched with methanol at -50°C and $NaHCO_3$, diluted with ethyl acetate, and the mixture extracted twice with EtOAc. The combined organic extracts were washed with water, brine and dried over Na_2SO_4. The crude product was used directly in the next step.

The fluorine derivative of **1-32** was diluted in CH_2Cl_2 (4 mL) and TFA (3 mL) was added at 0°C. After 2 h at room temperature, water was added, and the mixture extracted twice with CH_2Cl_2. The combined organic phases were washed with water, brine and dried over Na_2SO_4. Purification of the crude product by preparative thin-layer chromatography (Silica gel, 100% $CHCl_3$) gave **1-33a** in 34% yield (two steps). (140 mg, 0.42 mmol).

3-(deuterofluoromethyl)-1-phenyl-*N*-tosylbut-3-en-1-amine (1-33a)



White crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (3H, s), 2.50 (2H, d, *J*= 7.3 Hz), 4.45 (1H, q, *J*= 7.2 Hz), 4.54 (0.5H, d, J_{HF} = 47.6 Hz), 4.58 (0.5H, d, J_{HF}= 47.2 Hz), 4.96 (1H, s), 5.11 (1H, d, *J*= 2.7 Hz), 5.34 (1H, d, *J*= 6.9 Hz), 7.05-7.26 (5H, m), 7.10 (2H, d, *J*= 7.8 Hz), 7.52 (2H, d, *J*= 8.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.4, 40.8, 56.4, 84.5 (dt, J_{CF} = 165.8 Hz, J_{CD} = 23.5 Hz), 117.5 (d, J_{CF} = 10.5 Hz), 126.5, 127.1, 127.5, 128.4, 129.3, 137.2, 139.9 (d, J_{CF} = 15.3 Hz), 140.3, 143.1. ^{19}F NMR (471 MHz, $CDCl_3$) δ_F 66.1 (1F, dm, J_{HF} = 47.6 Hz). IR (ZnSe) ν 3275 (br), 2922, 1599, 1495, 1319, 1153, 1093, 1059, 1020, 916 cm^{-1}. FABHRMS: Calcd for $C_{18}H_{21}DO_2NSF$ Found: *m/z* 335.1347. $(M+H)^+$ 335.1357.



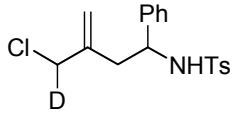
1-32 **1-33b** 84%

Chlorination of alcohol 1-32:

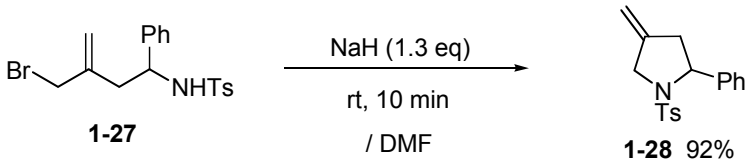
To a stirring solution of the alcohol **1-32** (230 mg, 0.55 mmol) in DMF (1 mL) was slowly added a solution of $POCl_3$ (92 mg, 55 μL, 0.60 mmol) in DMF (1 mL) at room temperature. After, the reaction mixture was stirred for 10 h. The reaction mixture was then quenched with water, diluted with ethyl acetate, and the mixture extracted twice with EtOAc. The combined organic extracts were washed with water, brine and dried over Na_2SO_4. The crude product was used directly in the next step.

The chlorine derivative of **1-32** was diluted in CH_2Cl_2 (2 mL) and TFA (1 mL) was added at 0°C. After 4 h at room temperature, water was added, and the mixture extracted twice with CH_2Cl_2. The combined organic phases were washed with water, brine and dried over Na_2SO_4. Purification of the crude product by flash column chromatography (Silica gel, 15% ethyl acetate/hexanes) gave **1-33b** in 84% yield (two steps). (160 mg, 0.456 mmol).

3-(deuterochloromethyl)-1-phenyl-*N*-tosylbut-3-en-1-amine (1-33b)



White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (3H, s), 2.52 (1H, dd, *J*= 14.8, 8.9 Hz), 2.63 (1H, dd, *J*= 14.7, 5.9 Hz), 3.83 (1H, s), 4.47 (1H, dt, 9.0, 6.1 Hz), 4.96 (1H, s), 5.08 (1H, d, *J*= 6.6 Hz), 5.17 (1H, s), 7.05-7.16 (5H, m), 7.10 (2H, d, *J*= 8.5 Hz), 7.51 (2H, d, *J*= 8.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5, 41.4, 47.2 (t, J_{CD} = 23.8 Hz), 56.1, 118.7, 126.3, 127.0, 127.4, 128.4, 129.2, 137.1, 140.2, 140.4, 143.0. IR (ZnSe) ν 3275, 3032, 1456, 1321, 1157, 1093 cm^{-1}. Anal. Found: C, 61.41; H, 5.79; N, 3.75%. Cacld for $C_{18}H_{19}ClDNO_2S$; C, 61.61; H, 6.03; N, 3.99%.

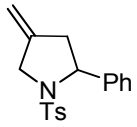


Typical procedure for the cyclization of *N*-(3-bromomethylhomoallyl)tosylamide:

To a solution of *N*-(3-bromomethyl-1-phenyl-3-butenyl)-*p*-toluenesulfonamide **1-27** (160 mg, 0.41 mmol) in DMF (10 mL) at room temperature was added NaH (14 mg, 0.53 mmol). After, the reaction mixture was stirred at room temperature for 10 minutes and then, water was added to quench the reaction. The mixture was diluted with ethyl acetate, and extracted twice with EtOAc. The combined organic extracts were washed with water, brine and dried over Na_2SO_4. Purification of the crude product by flash column chromatography (Silica gel, 20% ethyl acetate/hexanes) gave **1-28** in 92% yield. (118 mg, 0.376 mmol).

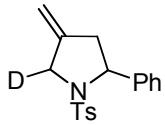
For the fluorine derivative **1-33a**, the reaction was done at 110°C for 2 h. The chlorine derivative **1-33b** was cyclized at 50°C for 1 h. For the bromine derivative **1-33c**, the cyclization proceeded at room temperature in 15 minutes. Purification of the crude product by flash column chromatography (Silica gel, 20% ethyl acetate/hexanes) gave **1-30** in 91% (from **1-33a** 97 mg, 0.31 mmol), 86% (from **1-33b** 82 mg, 0.261 mmol) and 89% (from **1-33c** 70 mg, 0.223 mmol).

4-methylene-2-phenyl-1-tosylpyrrolidine (1-28)



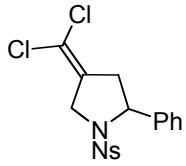
White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (3H, s), 2.40 (1H, dm, *J*= 15.3 Hz), 2.68 (1H, dd, *J*= 14.4, 1.7 Hz), 3.99 (1H, dd, *J*= 14.5, 1.7 Hz), 4.05 (1H, d, *J*= 14.2 Hz), 4.84 (1H, d, *J*= 1.7 Hz), 4.87-484 (1H, m), 4.90 (1H, s), 7.13-7.20 (7H, m), 7.49 (2H, d, *J*= 8.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5, 41.4, 52.5, 63.1, 108.1, 126.3, 127.2, 127.3, 128.3, 129.4, 135.1, 141.9, 143.1, 143.2 . IR (ZnSe) 3066, 2862, 1344, 1161, 1095 cm^{-1}. FABHRMS: Found: *m/z* 314.1193. Calcd for $C_{18}H_{20}O_2NS$ $(M+H)^+$ 314.1216.

5-deutero-4-methylene-2-phenyl-1-tosylpyrrolidine (1-30)

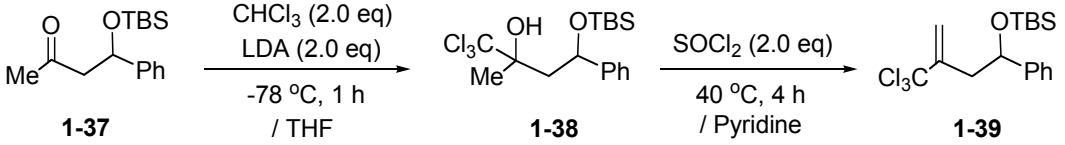


White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (3H, s), 2.40 (1H, dm, *J*= 15.4 Hz), 2.68 (1H, ddm, *J*= 15.4, 8.8 Hz), 3.99 (0.5H, s), 4.03 (0.5H, s), 4.84 (1H, s), 4.87-484 (1H, m), 4.90 (1H, s), 7.13-7.20 (7H, m), 7.50 (2H, d, *J*= 8.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5, 41.4, 52.2 (t, J_{CD}= 22.8 Hz), 63.1, 108.1, 126.3, 127.2, 127.3, 128.3, 129.4, 135.1, 141.8, 141.9, 143.2. IR (ZnSe) 3066, 2962, 2929, 1674, 1597, 1491, 1452, 1346, 1157, 1092 cm^{-1}. Anal. Found: C, 68.61; H, 6.24; N, 4.27%. Calcd for $C_{18}H_{18}NDO_2S$; C, 68.76; H, 6.41; N, 4.45%.

4-(Dichloromethylene)-2-phenyl-1-nosylpyrrolidine (1-18d)



Used **1-17d** as starting material. Purification of the crude product by flash column chromatography (Silica gel, 30% ethyl acetate/hexanes) gave **1-18d** in 69% yield. (22.7 mg, 0.055 mmol). White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (1H, dd, *J*= 17.1, 4.9 Hz), 3.22 (1H, dd, *J*= 17.0, 8.3 Hz), 4.46 (2H, s), 5.21 (1H, dd, *J*= 8.4, 4.9 Hz), 7.14-7.26 (5H, m), 7.32 (1H, td, *J*= 7.1, 2.0 Hz), 7.44 (1H, d, *J*= 8.6), 7.53-7.59 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 41.3, 52.6, 64.0, 113.4, 123.9, 126.7, 128.0, 128.6, 130.9, 131.2, 132.7, 133.3, 134.0, 139.5, 175.2. IR (ZnSe) 2921,1658, 1539, 1350, 1161, 1124, 1076, 906 cm^{-1}. FABHRMS: Found: *m/z* 413.0134. Calcd for $C_{17}H_{15}N_2O_4Cl_2S$ $(M+H)^+$ 413.0132.

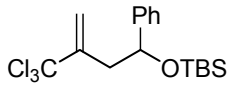


Preparation of the trichloromethylhomoallyl compound 1-39:

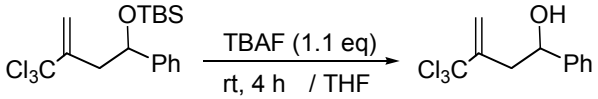
To a stirring solution of the ketone **1-37** (12.0 g, 43.1 mmol) in THF (150 mL), chloroform (10.35 mL, 19.3 mmol) was added at -78°C and the reaction mixture was slowly treated (30-45 minutes) with LDA (106.5 mL, solution in THF, 129.3 mmol). After 1.5 h, the reaction mixture was quenched with saturated aqueous ammonium chloride solution, diluted in EtOAc, and the mixture extracted twice with EtOAc. The combined organic extracts were washed with water, brine and dried over Na_2SO_4. The crude product was used directly in the next step.

The addition product of **1-37** (13.8 g, 34.7 mmol) was diluted in pyridine (35 mL) and $SOCl_2$ (9.9 g, 6.1 mL, 83.2 mmol) was added at 0°C. The reaction was then heated at 40°C for 4 h. When the reaction was completed, the mixture was cooled down to 0°C and water was slowly added. Then the mixture was diluted with ethyl acetate, and extracted twice with EtOAc. The combined organic phases were washed with water, brine and dried over Na_2SO_4. Purification of the crude product by flash column chromatography (Silica gel, 100% hexanes) gave **1-39** in 50% yield (two steps). (6.85 g, 18.1 mmol).

(3-(trichloromethyl)-1-phenylbut-3-enyloxy)(*t*-butyl)dimethylsilane (1-39)



Trace of other isomers. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.29 (3H, s), -0.08 (3H, s), 0.86 (9H, s), 2.62 (1H, dd, *J*= 15.1, 4.1 Hz), 2.70 (1H, dd, *J*= 15.0, 8.4 Hz), 4.91 (1H, dd, *J*= 8.3, 4.1 Hz), 5.16 (1H, s), 5.83 (1H, s), 7.15-7.27 (5H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ -4.7, -4.5, 18.2, 25.9, 42.7, 74.5, 99.3, 118.0, 126.0, 126.6, 127.3, 128.1, 144.7. IR (ZnSe) 2954, 2929, 2856, 1254, 1088, 1068, 937 cm^{-1}. FABHRMS: Found: *m/z* 379.0809. Calcd for $C_{17}H_{26}OCl_3Si$ $(M+H)^+$ 379.0818.

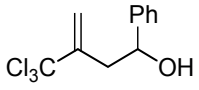


1-39 **1-40** quant.

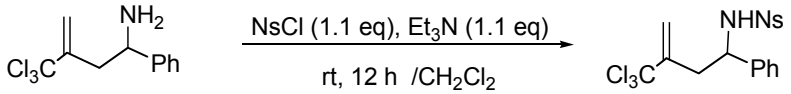
Deprotection of the silyl-protected alcohol 1-39:

To a stirring solution of the (3-(trichloromethyl)-1-phenylbut-3-enyloxy)(*t*-butyl)dimethylsilane **1-39** (6.0 g, 15.8 mmol) in THF (140 mL) was added TBAF (1M in THF, 17.4 mL, 17.4 mmol) at room temperature. After, the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was then quenched with a pH 7 buffer, diluted with ethyl acetate, and the mixture extracted twice with EtOAc. The combined organic extracts were washed with water, brine and dried over Na_2SO_4. Purification of the crude product by flash column chromatography (Silica gel, 20% ethyl acetate/hexanes) gave **1-40** in a quantitative yield. (4.2g, 15.8 mmol).

3-(trichloromethyl)-1-phenylbut-3-en-1-ol (1-40)



Trace of other isomers. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (1H, s br), 2.84-2.86 (2H, m), 5.03 (1H, dd, *J*= 7.3, 5.6 Hz), 5.37 (1H, s), 5.99 (1H, s), 7.28-7.40 (5H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 40.8, 73.0, 98.9, 117.2, 125.8, 127.9, 128.5, 131.5, 143.5. IR (ZnSe) 3365 (br), 3032, 1493, 1456, 1051, 1014, 793 cm^{-1}. FABHRMS: Found: *m/z* 264.9963. Calcd for $C_{11}H_{12}OCl_3$ $(M+H)^+$ 264.9956.

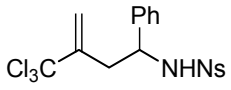


1-17c **1-17d**

Preparation of the *N*-nitrobenzenesulfonamide 1-17d:

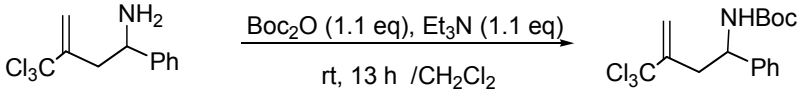
To a solution of (3-(trichloromethyl)-1-phenylbut-3-en-1-amine **1-17c** (265 mg (crude), 1.0 mmol) and 2-nitrosulfonyl chloride (245 mg, 1.1 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (110 mg, 0.15 mL, 1.1 mmol) at room temperature. After being stirred for 12 h at room temperature, the reaction was quenched by the addition of water and ethyl acetate was added. The mixture was extracted twice with EtOAc, and the combined organic extracts were washed with water, brine and dried over Na_2SO_4. Purification of the crude product by flash column chromatography (Silica gel, 20% ethyl acetate/hexanes) gave **1-17d** in 50% yield (two step). (225 mg, 0.5 mmol).

3-(trichloromethyl)-1-phenyl-*N*-(2-nitrobenzenesulfonyl)but-3-en-1-amine (1-17d)



Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.88 (1H, dd, *J*= 16.1, 5.6 Hz), 3.00 (1H, dd, *J*= 16.1, 9.0 Hz), 4.94 (1H, dt, *J*= 8.8, 6.1 Hz), 5.29 (1H, s), 5.96 (1H, d, *J*= 6.1 Hz), 5.97 (1H, s), 7.07-7.14 (5H, m), 7.37 (1H, td, *J*= 7.7, 1.3 Hz), 7.52 (1H, td, *J*= 7.6, 1.5 Hz), 7.64 (1H, dd, *J*= 7.8, 1.5 Hz), 7.69 (1H, dd, *J*= 7.8, 1.2 Hz). ^{13}C NMR (126

MHz, $CDCl_3$) δ 38.5, 58.4, 98.5, 117.9, 124.8, 126.5, 128.0, 128.2, 128.5, 130.6, 132.4, 132.9, 134.2, 139.0, 143.9. IR (ZnSe) 3344 (br), 2925, 1537, 1356, 1165, 908 cm^{-1}. FABHRMS: Found: *m/z* 448.9912. Calcd for $C_{17}H_{16}N_2O_4Cl_3S$ $(M+H)^+$ 448.9899.

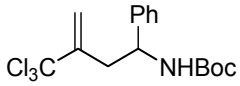


1-17c **1-17e**

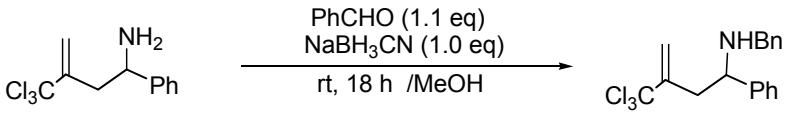
Preparation of the *t*-Butyl carbamate 1-17e:

To a solution of (3-(trichloromethyl)-1-phenylbut-3-en-1-amine **1-17c** (265 mg, 1.0 mmol) and Boc anhydride (240 mg, 1.1 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (110 mg, 1.1 mmol) at room temperature. After being stirred for 12 h at room temperature, the reaction was quenched by the addition of water and ethyl acetate was added. The mixture was extracted twice with EtOAc, and the combined organic extracts were washed with water, brine and dried over Na_2SO_4. Purification of the crude product by flash column chromatography (Silica gel, 20% ethyl acetate/hexanes) gave **1-17e** in 72% yield (two steps). (265 mg, 0.73 mmol).

***t*-Butyl 3-(trichloromethyl)-1-phenylbut-3-enylcarbamate (1-17e)**



White solid. ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (9H, s), 2.90 (2H, d, *J*= 6.6 Hz), 4.89 (1H, s br), 5.05 (1H, s br), 5.29 (1H, s), 5.98 (1H, s), 7.25-7.37 (5H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.4, 37.9, 53.5, 79.7, 98.9, 117.2, 126.2, 127.5, 128.6, 142.6, 145.2, 155.0. IR (ZnSe) 3338 (br), 2978, 1697, 1496, 1365, 1163, 1045, 1022, 970 cm^{-1}. Anal. Found: C, 52.42; H, 5.51; N, 3.68%. Calcd for $C_{16}H_{20}NO_2Cl_3$; C, 52.69; H, 5.53; N, 3.84%.

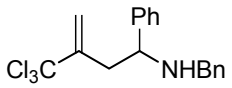


1-17c **1-17f** 51%

Reductive amination of benzaldehyde to *N*-benzylamine 1-17f:

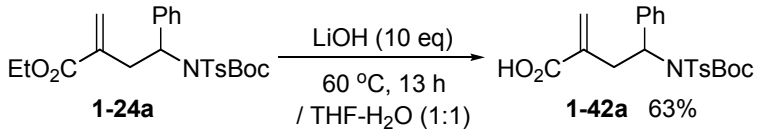
To a solution of (3-(trichloromethyl)-1-phenylbut-3-en-1-amine **1-17c** (225 mg, 0.85 mmol) and benzaldehyde (90 mg, 95 μL, 1.1 mmol) in MeOH (2.5 mL) was added $NaBH_3CN$ (110 mg, 1.1 mmol) at room temperature. After being stirred for 18 h at room temperature, the reaction was quenched by the addition of water and ethyl acetate was added. The mixture was extracted twice with EtOAc, and the combined organic extracts were washed with water, brine and dried over Na_2SO_4. Purification of the crude product by flash column chromatography (Silica gel, 15% ethyl acetate/hexanes) gave **1-17f** in 36% yield (two step). (108 mg, 0.3 mmol).

***N*-benzyl-3-(trichloromethyl)-1-phenylbut-3-en-1-amine (1-17f)**



White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76 (1H, s br), 2.81 (1H, d, *J*= 6.0 Hz), 2.83 (1H, d, *J*= 8.3 Hz), 3.52 (1H, d, *J*= 13.3 Hz), 3.70 (1H, d, *J*= 13.3 Hz), 4.00 (1H, dd, *J*= 8.2, 6.0 Hz), 5.07 (1H, s), 5.89 (1H, s), 7.24-7.43 (10H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 40.2, 51.4, 60.7, 98.9, 116.6, 126.9, 127.4, 127.4, 127.5, 128.1, 128.3, 128.6, 128.8, 146.1. IR (ZnSe) 3327, 3028, 2924, 2850, 1495, 1454, 1111, 970, 924, 793 cm^{-1}. FABHRMS: Found: *m/z* 354.0593. Calcd for $C_{18}H_{19}NCl_3$ $(M+H)^+$ 354.0586.

1.3 Nucleophilic 5-*endo-trig* cyclization of *N*-(3-carbonylhomoallyl)tosylamides

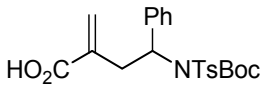


1-24a **1-42a** 63%

Typical procedure for the hydrolysis of ethyl esters:

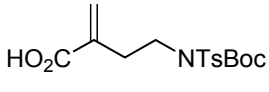
To a solution of ethyl 4-phenyl-4-(*N*-*t*-butoxycarbonyl-*p*-tosylamino)butenoate **1-24a** (2.40 g, 5.0 mmol) in THF (12 mL) was added LiOH (5M aquous solution, 10 mL, 50.0 mmol) at room temperature. After being stirred for 15 h at 60°C, the reaction was neutralized by the addition of HCl 1N and ethyl acetate was added. The mixture was extracted twice with EtOAc, and the combined organic extracts were washed with water, brine and dried over Na_2SO_4. The purification was made by flash column chromatography (Silica gel, 30% ethyl acetate/hexanes). 63% yield. (1.4 g, 3.14 mmol).

2-methylene-4-phenyl-*N*-(*t*-butoxycarbonyl)-*N*-(*p*-toluenesulfonyl)butanoic acid (1-42a)



White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (9H, s), 2.39 (3H, s), 3.32 (1H, dd, *J*= 13.6, 5.1 Hz), 3.40 (1H, dd, *J*= 13.7, 10.2 Hz), 5.84 (1H, s), 5.94 (1H, dd, *J*= 10.0, 5.1 Hz), 6.46 (1H, s), 7.20 (2H, d, *J*= 8.3 Hz), 7.25-7.34 (3H, m), 7.40 (2H, d, *J*= 7.5 Hz), 7.61 (2H, d, *J*= 8.0 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.6, 27.8, 34.2, 59.7, 84.3, 127.3, 127.6, 128.1, 128.6, 128.8, 131.6, 136.2, 136.8, 139.4, 143.9, 150.8, 171.8. IR (ZnSe) 2981 (br), 1724, 1693, 1350, 1144, 1086, 953 cm^{-1}. Anal. Found: C, 61.91; H, 6.26; N, 2.98%. Calcd for $C_{23}H_{27}NO_6S$; C, 62.00; H, 6.11; N, 3.14%.

2-methylene-*N*-(*t*-butoxycarbonyl)-*N*-(*p*-toluenesulfonyl)butanoic acid (1-42b)

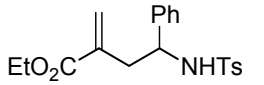


Purification by flash column chromatography (Silica gel, 20% ethyl acetate/hexanes). 50% yield. (145 mg, 0.39 mmol). Colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (9H, s), 2.43 (3H, s), 2.75 (2H, t, *J*= 6.9 Hz), 4.03 (2H, t, *J*= 6.7 Hz), 5.79 (1H, s), 6.37 (1H, s), 7.29 (2H, d, *J*= 8.1 Hz), 7.79 (2H, d, *J*= 8.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.7, 27.8, 32.9, 46.1, 84.3, 128.0, 129.2, 130.2, 136.1, 137.3, 144.2, 150.9, 170.6. IR

(ZnSe) 2979, 2925, 1726, 1695, 1350, 1300, 1157, 1088, 968 cm^{-1}. FABHRMS: Found: *m/z* 370.1328. Calcd for $C_{17}H_{24}NO_6S$ $(M+H)^+$ 370.1325.

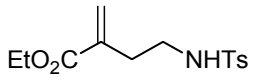
Deprotection of the Boc-protected sulfonamides 1-24a, 1-24b 1-19d, 1-19e and 1-19f:
The procedure introduced for the Boc-deprotection of substrate **1-41b** has been employed.

Ethyl 2-methylene-4-phenyl-4-(tosylamino)butanoate (1-19a)



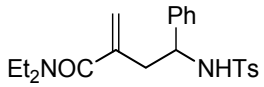
Purification by flash column chromatography (Silica gel, 30% ethyl acetate/hexanes). 83% yield (two steps). (898 mg, 2.4 mmol). White solid. ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (3H, t, *J*= 7.2 Hz), 2.36 (3H, s), 2.64 (1H, dd, *J*= 13.5, 6.0 Hz), 2.65 (1H, dd, *J*= 13.5, 8.5 Hz), 4.15 (2H, q, *J*= 7.2 Hz), 4.50 (1H, ddd, *J*= 8.5, 6.0, 6.0 Hz), 5.37 (1H, d, *J*= 6.0 Hz), 5.49 (1H, s), 6.11 (1H, s), 7.10-7.13 (4H, m), 7.17-7.22 (3H, m), 7.52 (2H, d, *J*= 8.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.1, 21.4, 40.3, 57.7, 61.1, 126.4, 127.1, 127.3, 128.3, 128.9, 129.2, 136.1, 137.5, 140.7, 142.8, 167.1. IR (ZnSe) 3280, 3061, 3030, 2981, 2927, 1707, 1457, 1321, 1153, 1093, 951 cm^{-1}. Anal. Found: C, 64.21; H, 6.27; N, 3.66%. Calcd for $C_{20}H_{23}NO_4S$; C, 64.32; H, 6.21; N, 3.75%.

Ethyl 2-methylene-4-(tosylamino)butanoate (1-19c)



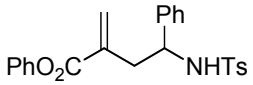
Purification by flash column chromatography (Silica gel, 25% ethyl acetate/hexanes). 41% yield (two steps). (830 mg, 2.8 mmol). White solid. ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, t, *J*= 7.2 Hz), 2.42 (3H, s), 2.46 (2H, t, *J*= 6.6 Hz), 3.12 (2H, q, *J*= 6.5 Hz), 4.16 (2H, q, *J*= 7.2 Hz), 4.72 (1H, t br, *J*= 5.9 Hz), 5.57 (1H, d, *J*= 1.2 Hz), 6.20 (1H, d, *J*= 1.0 Hz), 7.29 (2H, d, *J*= 8.3 Hz), 7.72 (2H, d, *J*= 8.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2, 21.6, 32.4, 61.0, 127.0, 127.7, 129.6, 136.8, 136.9, 143.3, 166.6. IR (ZnSe) ν 3275 (br), 2924, 2852, 1709, 1417, 1321, 1207, 1151, 1093, 1020 cm^{-1}. FABHRMS: Found: *m/z* 298.1130. Calcd for $C_{14}H_{20}O_4NS$ $(M+H)^+$ 298.1114.

***N,N*-diethyl-2-methylene-4-phenyl-4-(tosylamino)butanamide (1-19d)**



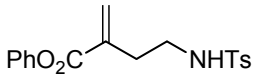
Purification by silica gel flash column chromatography (30% ethyl acetate/hexanes). 49% yield (three steps). (230 mg, 0.575 mmol). Colorless crystals. ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (3H, t br, *J*= 6.5 Hz), 1.17 (3H, t br, *J*= 6.7 Hz), 2.33 (3H, s), 2.45 (1H, dd, *J*= 14.0, 8.6 Hz), 2.52 (1H, dd, *J*= 14.0, 5.0 Hz), 3.33 (2H, m br), 3.42 (2H, m br), 4.44 (1H, dt, *J*= 8.7, 5.1 Hz), 4.94 (1H, s), 5.01 (1H, s), 7.06 (2H, d, *J*= 8.3 Hz), 7.11-7.16 (5H, m), 7.52 (2H, d, *J*= 8.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.7, 14.4, 21.4, 39.6, 41.6, 43.3, 58.6, 118.5, 126.7, 127.0, 127.1, 128.0, 128.8, 137.8, 138.8, 140.7, 142.2, 171.9. IR (ZnSe) 3269, 2974, 1593, 1435, 1329, 1155, 1093, 1065 cm^{-1}. Anal. Found: C, 65.83; H, 7.20; N, 6.90%. Calcd for $C_{22}H_{28}N_2O_3S$; C, 65.97; H, 7.05; N, 6.99%.

Phenyl 2-methylene-4-phenyl-4-(tosylamino)butanoate (1-19e)

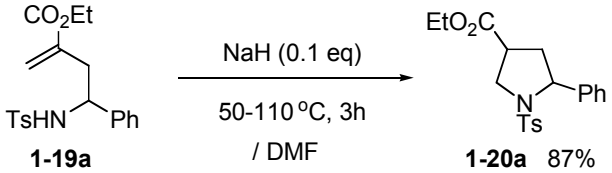


Purification by silica gel flash column chromatography (20% ethyl acetate/hexanes). 44% yield (three steps). (175 mg, 0.415 mmol). Colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (3H, s), 2.77 (2H, d, *J*= 7.4 Hz), 4.62 (1H, q, *J*= 7.3 Hz), 5.35 (1H, d, *J*= 7.1 Hz), 5.73 (1H, s), 6.40 (1H, s), 7.06-7.18 (8H, m), 7.25 (2H, t, *J*= 7.3 Hz), 7.40 (2H, t, *J*= 7.9 Hz), 7.53 (2H, d, *J*= 8.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5, 40.5, 57.6, 121.5, 126.0, 126.4, 127.1, 127.5, 128.5, 129.3, 129.5, 130.7, 135.7, 137.4, 140.5, 143.0, 150.7, 165.6. IR (ZnSe) 3276 (br), 1728, 1493, 1456, 1321, 1194, 1153, 1119, 1093, 1063, 953 cm^{-1}. FABHRMS: Found: *m/z* 422.1429. Calcd for $C_{24}H_{24}NO_4S$ $(M+H)^+$ 422.1427.

Phenyl 2-methylene-4-(tosylamino)butanoate (1-19f)

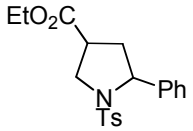


Purification by flash column chromatography (Silica gel, 20% ethyl acetate/hexanes). 41% yield (two steps). (21 mg, 0.06 mmol). White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (3H, s), 2.58 (2H, t, *J*= 6.6 Hz), 3.20 (2H, q, *J*= 6.6 Hz), 4.51 (1H, t, *J*= 6.4 Hz), 5.80 (1H, s), 6.48 (1H, s), 7.06 (2H, d, *J*= 7.3 Hz), 7.23-7.26 (1H, m), 7.29 (2H, d, *J*= 7.8 Hz), 7.39 (2H, t, *J*= 7.6 Hz), 7.73 (2H, d, *J*= 8.0 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5, 32.6, 42.0, 121.5, 126.0, 127.1, 129.5, 129.7, 129.8, 136.3, 143.5, 150.6, 165.2. IR (ZnSe) ν 3286 (br), 2924, 2854, 1730, 1462, 1327, 1198, 1159, 1128, 1092, 914 cm^{-1}. FABHRMS: Found: *m/z* 346.1115. Calcd for $C_{18}H_{20}O_4NS$ $(M+H)^+$ 346.1114.



Typical procedure for the cyclization of *N*-(3-carbonylhomoallyl) sulfonamides: To a solution of N-(1-phenyl-3-ethoxycarbonyl-3-butenyl)-4-methylbenzene sulfonamide (**1-19a**, 234 mg, 0.62 mmol) in DMF (6 mL) was added NaH (1.5 mg, 0.06 mmol) under argon. After the reaction mixture was stirred at 110 °C for 3 h, phosphate buffer (pH 7) was added to quench the reaction. The mixture was then extracted twice with EtOAc and the combined organic extracts were washed with water twice, brine and dried over Na_2SO_4. The solution was filtrated and concentrated under reduced pressure. Purified by column chromatography (Silica gel, 20:79:1 EtOAc/hexane/Et_3N). 87% yield (*anti:syn* = 59:41). (204 mg, 0.546 mmol).

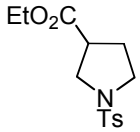
Ethyl 5-phenyl -1-tosylpyrrolidine-3-carboxylate (1-20a)



White solid. ^{1}H NMR (500 MHz, $CDCl_3$) ***anti* isomer** δ 1.18 (3H, t, *J* = 7.1 Hz), 2.06 (1H, ddd, *J* = 12.5, 6.7, 3.0 Hz), 2.13-2.20 (1H, m), 2.41 (3H, s), 3.08 (1H, dddd, *J* = 6.3, 6.3, 6.3, 6.3 Hz), 3.57 (1H, dd, *J* = 10.1, 8.7 Hz), 3.89 (1H, dd, *J* = 10.1, 7.9 Hz), 4.00-4.05 (2H, m), 4.90 (1H, dd, *J* = 8.1, 3.0 Hz), 7.20–7.31 (7H, m), 7.69 (2H, d, *J* =

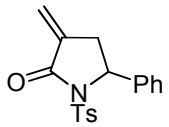
8.4 Hz). ***syn* isomer** δ 1.15 (3H, t, *J* = 7.1 Hz), 2.13-2.20 (1H, m), 2.43 (3H, s), 2.49 (1H, ddd, *J* = 13.0, 7.7, 7.7 Hz), 2.71 (1H, dddd, *J* = 6.0, 6.0, 6.0, 6.0 Hz), 3.77 (1H, dd, *J* = 11.3, 8.9 Hz), 3.91 (1H, dd, *J* = 11.3, 8.0 Hz), 4.00-4.05 (2H, m), 4.74 (1H, dd, *J* = 7.7, 7.7 Hz), 7.22–7.31 (7H, m), 7.60 (2H, d, *J* = 8.4 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) ***anti* isomer** δ14.0, 21.5, 38.3, 41.3, 50.8, 61.0, 62.8, 125.9, 126.4, 127.4, 127.5, 128.4, 134.5, 142.0, 143.5, 171.8. ***syn* isomer** δ14.0, 21.5, 39.4, 42.6, 51.1, 61.0, 63.6, 125.9, 126.3, 127.3, 127.5, 128.3, 135.1, 141.5, 143.5, 171.4. IR (ZnSe) ν 3032, 2920, 2850, 1732, 1348, 1219, 1161, 914 cm^{-1}. Anal. Found: C, 64.07; H, 6.17; N, 3.55%. Cacld for $C_{20}H_{23}NO_4S$; C, 64.32; H, 6.21; N, 3.75%.

Ethyl tosylpyrrolidine-3-carboxylate (1-20c)



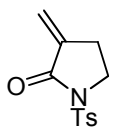
Purified by column chromatography on (Silica gel, 2% Et_2O/hexanes). 72% yield. (137 mg, 0.46 mmol). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (3H, t, *J* = 7.4 Hz), 2.01-2.07 (2H, m), 2.43 (3H, s), 2.94 (1H, quintet, *J* = 7.5 Hz), 3.30 (2H, t, *J* = 7.3 Hz), 3.38 (1H, dd, *J* = 10.2, 7.1 Hz), 3.55 (1H, dd, *J* = 10.2, 8.0 Hz), 4.05 (2H, q, *J* = 7.1 Hz), 7.33 (2H, d, *J*= 8.4 Hz), 7.71 (2H, d, *J* = 8.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.0, 21.5, 28.3, 42.7, 47.3, 49.8, 61.0, 127.4, 129.5, 133.2, 143.4, 172.0. IR (ZnSe) ν 2981, 1728, 1342, 1182, 1155, 1092, 1036, 816 cm-1. FABHRMS: Found: *m/z* 298.1108. Cacld for $C_{14}H_{20}NO_4S$ $(M+H)^+$ 298.1113.

3-methylene-5-phenyl-1-tosylpyrrolidin-2-one (1-45a)



Purified by column chromatography (Silica gel, 20% AcOEt/hexanes). 90% yield. (86 mg, 0.26 mmol). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (3H, s), 2.73 (1H, dq, *J*= 16.9, 1.7 Hz), 3.30 (1H, ddt, *J*= 16.9, 9.1, 3.2 Hz), 5.41 (1H, dd, *J*= 9.2, 1.5 Hz), 5.52 (1H, dd, *J*= 3.3, 1.8 Hz), 6.23 (1H, dd, *J*= 3.4, 2.1 Hz), 7.08-7.11 (4H, m), 7.22-7.31 (3H, m), 7.41 (2H, d, *J*= 8.2 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.6, 34.8, 59.6, 121.2, 126.5, 128.3, 128.5, 128.8, 129.0, 135.2, 137.2, 140.6, 144.8, 165.7. IR (ZnSe) 2924, 2854, 1722, 1362, 1265, 1165, 1086 cm^{-1}. FABHRMS: Found: *m/z* 328.1013. Calcd for $C_{18}H_{18}NO_3S$ $(M+H)^+$ 328.1008.

3-methylene-1-tosylpyrrolidin-2-one (1-45b)



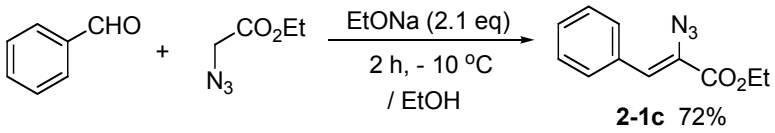
Purified by column chromatography (Silica gel, 25% ethyl acetate/hexanes). 76% yield. (11 mg, 0.044 mmol). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 (3H, s), 2.81 (2H, tt, *J*= 7.2, 2.6 Hz), 3.89 (2H, t, *J*= 7.1 Hz), 5.46 (1H, t, *J*= 2.5 Hz), 6.10 (1H, t, *J*= 2.7 Hz), 7.33 (2H, d, *J*= 8.1 Hz), 7.96 (2H, d, *J*= 8.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.8, 24.1, 43.8, 120.7, 128.2, 129.6, 134.8, 137.5, 145.2, 165.6. IR (ZnSe) 2924, 2852, 1724, 1354, 1271, 1165, 1111 cm^{-1}. FABHRMS: Found: *m/z* 252.0706. Calcd for $C_{12}H_{14}NO_3S$ $(M+H)^+$ 252.0695.

Experimental sections: Chapter 2

General. ^{1}H NMR (500 MHz) spectra were recorded on a Bruker DRX 500 and a Avance 500 apparatus, ^{1}H NMR (400 MHz) spectra on a JEOL-AL400 spectrometers in $CDCl_3$ [using tetramethylsilane (for ^{1}H, $\delta = 0$) as internal standard] unless otherwise mentioned. ^{13}C NMR (125 MHz) spectra were recorded on a Bruker DRX 500, a Avance 500 and JEOL-AL400 spectrometers in $CDCl_3$ [using $CDCl_3$ (for ^{13}C, $\delta = 77.00$) as internal standard] unless otherwise mentioned. ^{19}F NMR (470 MHz) spectra were recorded on a JEOL-AL400 spectrometers in $CDCl_3$ [using C_6F_6 (for ^{19}F, $\delta = 0$) as internal standard]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad. IR spectra were recorded on a Horiba FT 300-S by ATR method. High-resolution mass spectra were obtained with a JEOL MS-700P mass spectrometer. Elemental analyses were carried out at The Elemental Analysis Laboratory, Department of Chemistry, Faculty of Science, The University of Tokyo. Flash column chromatography was performed on silica gel [Merck Silica gel 60, and Kanto Chemical Co., Inc. Silica gel 60N (spherical, neutral)] and preparative thin-layer chromatography was carried out using Wakogel B-5F. Dry tetrahydrofuran (THF), diethyl ether (Et_2O), toluene, *N*,*N*-dimethylformamide (DMF), and dichloromethane (CH_2Cl_2) were dried by passing over a column of activated alumina (A-2, Purify) followed by a column of Q-5 scavenger (Engelhard). 1,2-Dichloroethane and acetone were distilled and stored over molecular sieve 3A (MS 3A). Ethanol (EtOH) was distilled from sodium and stored over MS 3A. Methanol was distilled from a trace amount of iodine and magnesium, and stored over MS 3A. Acetonitrile was distilled from CaH_2 and stored over MS 4A.

2.2 Thermal reaction of vinyl azides with 1,3-dicarbonyl compounds

Typical procedure for the preparation of β-aryl vinyl azides



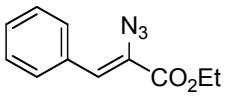
2-1c 72%

Procedure A:[62]

To stirring EtOH (30 mL) was added slowly chunks of sodium (1.08 g, 47.0 mmol). After complete dissolution of the sodium, the mixture was cooled to -20°C and a solution of benzaldehyde (1.22 g, 1.17 mL, 11.5 mmol) and ethyl azidoacetate (6.45 g, 50.0 mmol) in THF (5 mL) was slowly added. The stirring was continued at -10°C for 2 h. The reaction mixture was quenched with water, diluted with ethyl acetate, and then extracted twice with EtOAc. The combined organic extracts were washed with water, brine and dried over Na_2SO_4. The crude product was purified by flash column chromatography (Silica gel, 5% ethyl acetate/hexanes) to give **2-1c** in 72% yield (1.811 g, 8.34

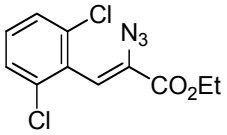
mmol).

(Z)-Ethyl 2-azido-3-phenylacrylate (2-1c)



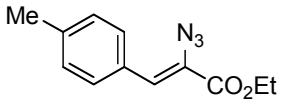
White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (3H, t, *J*= 7.0 Hz), 4.37 (2H, q, *J*= 7.0 Hz), 6.91 (1H, s), 7.31-7.40 (3H, m), 7.80 (2H, d, *J*= 7.6 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.3, 62.3, 125.2, 125.5, 128.4, 129.3, 130.5, 133.1, 163.4. Anal. Found: C, 60.84; H, 5.01; N, 19.32%. Cacld for $C_{11}H_{11}N_3O_2$; C, 60.82; H, 5.10; N, 19.34%.

(Z)-Ethyl 2-azido-3-(2,6-dichlorophenyl)acrylate (2-1a)



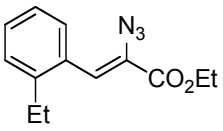
Purification by flash column chromatography (Silica gel, 5% ethyl acetate/hexanes), 11% yield (670 mg, 2.34 mmol). Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (3H, t, *J*= 7.2 Hz), 4.40 (2H, q, *J*= 7.2 Hz), 6.89 (1H, s), 7.21 (1H, t, *J*= 8.0 Hz), 7.34 (2H, d, *J*= 8.0 Hz).

(Z)-Ethyl 2-azido-3-*p*-tolylacrylate (2-1b)



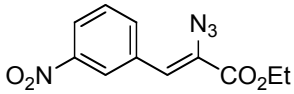
Purification by flash column chromatography (Silica gel, 5% ethyl acetate/hexanes), 52% yield. (1.40 g, 6.0 mmol). White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (3H, t, *J*= 7.1 Hz), 2.37 (3H, s), 4.37 (2H, q, *J*= 7.1 Hz), 6.90 (1H, s), 7.19 (2H, d, *J*= 7.8 Hz), 7.71 (2H, d, *J*= 7.8 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.3, 21.6, 62.2, 124.6, 125.5, 129.1, 130.4, 130.5, 139.7, 163.5. Anal. Found: C, 62.38; H, 5.79; N, 18.13%. Cacld for $C_{12}H_{13}N_3O_2$; C, 62.33; H, 5.67; N, 18.17%.

(Z)-Ethyl 2-azido-3-(2-ethylphenyl)acrylate (2-1d)

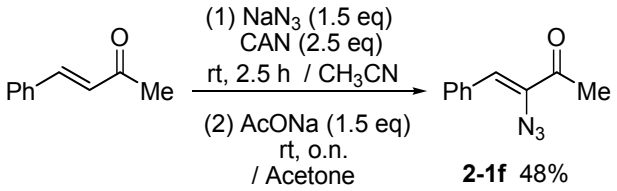


Purification by flash column chromatography (Silica gel, 5% ethyl acetate/hexanes), 51% yield. (3.02 g, 14.85 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, t, *J*= 7.4 Hz), 1.40 (3H, t, *J*= 7.1 Hz), 2.70 (2H, q, *J*= 7.5 Hz), 4.38 (2H, q, *J*= 7.1 Hz), 7.19-7.28 (3H, m), 7.91 (1H, dd, *J*= 6.8, 1.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2, 15.4, 26.8, 62.3, 123.2, 125.7, 126.3, 128.5, 129.2, 129.7, 131.1, 143.5, 163.4. IR (ZnSe) ν 2968, 2114, 1709, 1616, 1373, 1300, 1234, 1076 cm^{-1}. FABHRMS Found: *m/z* 246.1238. Calcd for $C_{13}H_{16}O_2N_3$ $(M+H)^+$ 246.1244.

(Z)-Ethyl 2-azido-3-(3-nitrophenyl)acrylate (2-1e)



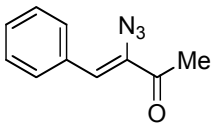
Purification by flash column chromatography (Silica gel, 10% ethyl acetate/hexanes), 30% yield. (990 mg, 3.77 mmol). Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (3H, t, *J*= 7.1 Hz), 4.40 (2H, q, *J*= 7.1 Hz), 6.90 (1H, s), 7.56 (1H, t, *J*= 8.1 Hz), 8.10 (1H, dd, *J*= 8.3, 0.5 Hz), 8.16 (1H, ddd, *J*= 8.2, 1.8, 0.9 Hz), 8.68 (1H, dd br, *J*= 1.9 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2, 62.8, 121.5, 123.4, 124.8, 128.2, 129.3, 134.7, 135.8, 148.2, 162.7. Anal. Found: C, 50.65; H, 4.02; N, 21.14%. Cacld for $C_{11}H_{10}N_4O_4$; C, 50.38; H, 3.84; N, 21.37%.



Procedure B:[65]

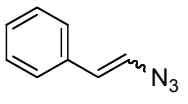
To a stirring solution of (*E*)-4-phenylbut-3-en-2-one (1.46 g, 10.0 mmol) and NaN_3 (980 mg, 15.0 mmol) in acetonitrile (50 mL), a solution of CAN (13.7 g, 25.0 mmol) in the same solvent (120 mL) was added dropwise at 0°C. On completion of the reaction, it was worked up using CH_2Cl_2-water, dried over Na_2SO_4 and concentrated. After, the crude residue was treated with anhydrous sodium acetate (1.23 g, 15.0 mmol) in acetone (50 mL) and stirred for 20 h at room temperature. The reaction mixture was quenched with water, diluted with ethyl acetate, and then extracted twice with EtOAc. The combined organic extracts were washed with water, brine and dried over Na_2SO_4. The purification was accomplished by flash column chromatography (Silica gel, 8% ethyl acetate/hexanes), affording **2-1f** in 48% yield (900 mg, 4.8 mmol).

(Z)-3-azido-4-phenylbut-3-en-2-one (2-1f)

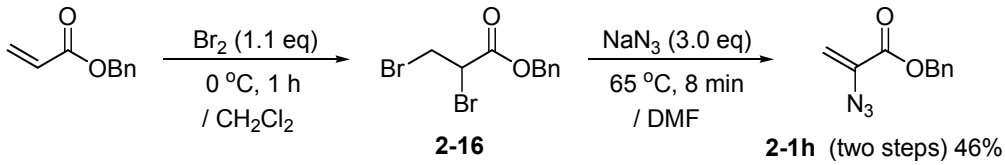


Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (3H, s), 6.70 (1H, s), 7.35-7.42 (3H, m), 7.84 (2H, d, *J*= 7.0 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.9, 126.6, 128.5, 129.7, 130.6, 133.0, 133.8, 194.2. Anal. Found: C, 64.35; H, 5.00; N, 22.64%. Cacld for $C_{10}H_9N_3O$; C, 64.16; H, 4.85; N, 22.45%.

1-(2-azidovinyl)benzene (2-1g)



Purification by flash column chromatography (Silica gel, 5% ethyl acetate/hexanes), 20% yield. (285 mg, 1.97 mmol). Mixture of isomers (*trans:cis* = 2:1). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) ***trans*** **isomer** δ 6.26 (1H, d, *J*= 13.6 Hz), 6.59 (1H, d, *J*= 13.9 Hz), 7.18-7.33 (5H, m). ***cis*** **isomer** δ 5.67 (1H, d, *J*= 8.3 Hz), 6.32 (1H, d, *J*= 8.4 Hz), 7.18-7.33 (3H, m), 7.57 (2H, d, *J*= 8.0 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 117.8, 119.7, 125.1, 125.7, 126.5, 127.2, 127.3, 128.2, 128.6, 128.8, 134.4, 134.9.

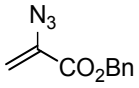


Procedure C:[66]

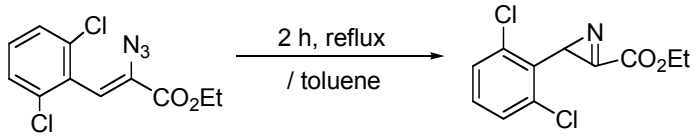
To a stirring solution of benzyl acrylate (1.76 g, 10. 85 mmol) in CH_2Cl_2 (10 mL) was added slowly Br_2 (1.87 g, 0.6 mL, 11.7 mmol) at 0°C. After the addition, an aquous solution of $Na_2S_2O_3$ (5 mL) was added and the stirring was continued at room temperature for 1 h. The reaction mixture was quenched with water, diluted with diethyl ether, and then extracted twice with Et_2O. The combined organic extracts were washed with water, brine, dried over Na_2SO_4 and concentrated. The crude

dibromo ester **2-16** in DMF (10 mL) was added to a solution of NaN_3 (2.1 g, 32.3 mmol) in DMF (70 mL) in a bath that had been heated to 65°C and the solution was maintained at this temperature for 8 minutes. (The success of the preparation is very dependent on control of the reaction time and temperature). It was then poured into cold water, and extracted with Et_2O. The combined organic extracts were washed with water, brine and dried over $MgSO_4$. The purification was accomplished by flash column chromatography (Silica gel, 5% ethyl acetate/hexanes), affording **2-1h** in 46% yield (two steps). (1.01 g, 4.97 mmol).

Benzyl 2-azidoacrylate (2-1h)



Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.26 (2H, s), 5.36 (1H, d, *J*= 1.5 Hz), 5.88 (1H, d, *J*= 1.5 Hz), 7.35-7.38 (5H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 67.7, 111.2, 128.4, 128.6, 128.7, 134.9, 136.1, 161.8.

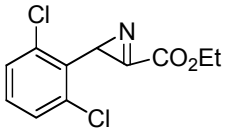


2-1a **2-2a** 97%

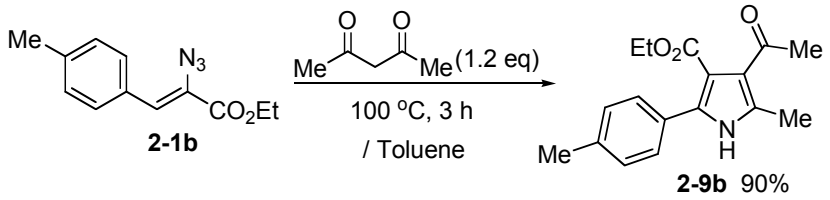
Thermal generation of ethyl 3-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate (2-2a):[62]

A stirring solution of (Z)-ethyl 2-azido-3-(2,6-dichlorophenyl)acrylate **2-1a** (495 mg, 1.7 mmol) in toluene (20 mL) was heated at reflux for 2 h. Toluene was removed *in vacuo* to afford the pure 2*H*-azirine **2-2a** in 97% yield. (430 mg, 1.67 mmol).

Ethyl 3-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate (2-2a)



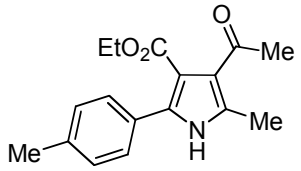
White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (3H, t, *J*= 7.1 Hz), 3.64 (1H, s), 4.52 (2H, q, *J*= 7.1 Hz), 7.17 (1H, t, *J*= 8.0 Hz), 7.28 (2H, d, *J*= 8.0 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.1, 35.7, 63.3, 128.7, 129.6, 132.4, 136.4, 158.1, 165.6. Anal. Found: C, 51.02; H, 3.76; N, 5.22%. Cacld for $C_{11}H_9NCl_2O_2$; C, 51.19; H, 3.51; N, 5.43%.



Typical procedure for the thermal reaction of vinyl azides with 1,3-dicarbonyls:

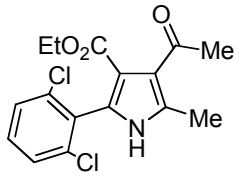
To a stirring solution of ethyl 2-azido-3-(4-methylbenzene)acrylate **2-1b** (46.3 mg, 0.20 mmol) in toluene (2 mL) was added acetylacetone (24.0 mg, 25 μL, 0.24 mmol). The reaction mixture was heated at 100 °C for 3 h. The mixture was dried up, and the crude residue was purified by flash column chromatography (Silica gel, 40% ethyl acetate/ 58% hexanes/ 2% Et_3N), affording **2-9b** in 90% yield (51.5 mg, 0.181 mmol).

Ethyl 4-acetyl-5-methyl-2-*p*-tolyl-1*H*-pyrrole-3-carboxylate (2-9b)



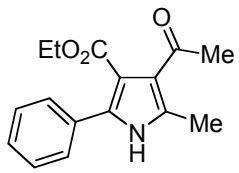
Colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (3H, t, *J*= 7.1 Hz), 2.35 (3H, s), 2.40 (6H, s), 4.21 (2H, q, *J*= 7.1 Hz), 7.15 (2H, d, *J*= 7.8 Hz), 7.34 (2H, d, *J*= 7.8 Hz), 8.79 (1H, s br). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.3, 14.0, 21.3, 30.4, 60.8, 112.8, 122.8, 127.8, 128.1, 129.0, 133.0, 133.3, 138.1, 166.2, 196.4. IR (ZnSe) ν 3273 (br), 2981, 1695, 1635, 1498, 1417, 1284, 1198, 1113, 1036 cm^{-1}. Anal. Found: C, 71.29; H, 6.71; N, 4.82%. Cacld for $C_{17}H_{19}NO_3$; C, 71.56; H, 6.71; N, 4.91%.

Ethyl 4-acetyl-2-(2,6-dichlorophenyl)-5-methyl-1*H*-pyrrole-3-carboxylate (2-9a)



Used vinyl azide **2-1a** and acetylacetone as starting material. Purified by flash column chromatography (Silica gel, 40% ethyl acetate/ 59% hexanes/ 1% Et_3N), 86% yield. (26 mg, 0.077 mmol). Colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, *J*= 7.1 Hz), 2.42 (3H, s), 2.51 (3H, s), 4.06 (2H, q, *J*= 7.1 Hz), 7.28 (1H, t, *J*= 7.7 Hz), 7.37 (2H, d, *J*= 7.8 Hz), 8.55 (1H, s br). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.1, 13.7, 31.2, 60.1, 114.8, 122.7, 127.6, 129.0, 130.4, 130.9, 134.0, 136.5, 163.8, 198.1. IR (ZnSe) ν 3263 (br), 2981, 1705, 1682, 1639, 1417, 1381, 1290, 1192, 1151, 1076, 1020 cm^{-1}. Anal. Found: C, 56.31; H, 4.44; N, 4.10%. Cacld for $C_{16}H_{15}NCl_2O_3$; C, 56.49; H, 4.44; N, 4.12%.

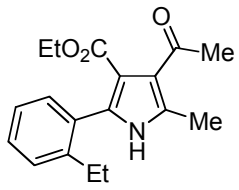
Ethyl 4-acetyl-5-methyl-2-phenyl-1*H*-pyrrole-3-carboxylate (2-9c)



Used vinyl azide **2-1c** and acetylacetone as starting materials. Purified by flash column chromatography (Silica gel, 40% ethyl acetate/ 59% hexanes/ 1% Et_3N), quantitative yield. (135.5 mg, 0.5 mmol). Colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, t, *J*= 7.1 Hz), 2.38 (3H, s), 4.20 (2H, q, *J*= 7.1 Hz), 7.29-7.35 (3H, m), 7.43 (2H, dd, *J*= 8.0, 1.5 Hz), 9.09 (1H, s br). ^{13}C NMR (126 MHz, $CDCl_3$)

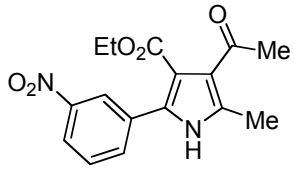
δ 13.3, 13.9, 30.3, 60.9, 113.2, 122.7, 127.8, 128.1, 128.3, 131.0, 132.7, 133.7, 166.3, 196.3. IR (ZnSe) ν 3276 (br), 2981, 1699, 1647, 1489, 1419, 1288, 1201, 1128, 1041 cm^{-1}. Anal. Found: C, 70.71; H, 6.46; N, 5.01%. Cacld for $C_{16}H_{17}NO_3$; C, 70.83; H, 6.32; N, 5.16%.

Ethyl 4-acetyl-2-(2-ethylphenyl)-5-methyl-1*H*-pyrrole-3-carboxylate (2-9d)



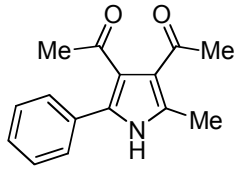
Used vinyl azide **2-1d** and acetylacetone as starting materials. Purified by flash column chromatography (Silica gel, 25% ethyl acetate/ 74% hexanes/ 1% Et_3N), 76% yield. (113.6 mg, 0.38 mmol). Colorless crystals. ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J*= 7.1 Hz), 1.06 (3H, t, *J*= 7.5 Hz), 2.35 (3H, s), 2.39 (3H, s), 2.50 (2H, q, *J*= 7.5 Hz), 3.95 (2H, q, *J*= 7.1 Hz), 7.15-7.19 (2H, m), 7.25 (1H, d, *J*= 7.5 Hz), 7.32 (1H, td, *J*= 8.7, 2.4 Hz), 9.02 (1H, s br). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.0, 13.6, 15.3, 26.3, 30.8, 60.0, 113.5, 122.2, 125.1, 127.9, 128.9, 130.5, 131.1, 133.1, 134.5, 143.7, 164.9, 198.0. IR (ZnSe) ν 3273 (br), 2974, 1701, 1635, 1419, 1381, 1288, 1188, 1143, 1109, 1045 cm^{-1}. FABHRMS: Found: *m/z* 300.1619. Calcd for $C_{18}H_{22}O_3N$ $(M+H)^+$, 300.1601.

Ethyl 4-acetyl-5-methyl-2-(3-nitrophenyl)-1*H*-pyrrole-3-carboxylate (2-9e)



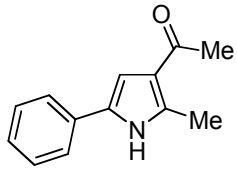
Used vinyl azide **2-1e** and acetylacetone as starting materials. Purified by flash column chromatography (Silica gel, 80% ethyl acetate/ 19% hexanes/ 1% Et_3N), 96% yield. (60.6 mg, 0.192 mmol) Yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, t, *J*= 7.1 Hz), 2.44 (3H, s), 2.48 (3H, s), 4.26 (2H, q, *J*= 7.1 Hz), 7.57 (1H, t, *J*= 8.0 Hz), 7.86 (1H, d, *J*= 7.8 Hz), 8.19 (1H, d, *J*= 8.3 Hz), 8.35 (1H, s), 8.67 (1H, s br). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.3, 14.0, 30.6, 61.2, 114.5, 122.7, 122.8, 123.5, 129.4, 130.0, 132.6, 134.0, 134.1, 148.0, 165.5, 196.4. IR (ZnSe) ν 3259 (br), 2985, 1705, 1651, 1533, 1446, 1417, 1348, 1292, 1207 cm^{-1}. Anal. Found: C, 60.61; H, 5.23; N, 8.61%. Cacld for $C_{16}H_{16}N_2O_5$; C, 60.75; H, 5.10; N, 8.86%.

3,4-diacetyl-5-methyl-2-phenyl-1*H*-pyrrole (2-9f)



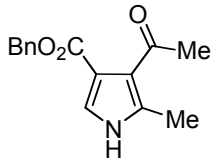
Used vinyl azide **2-1f** and acetylacetone as starting materials. Purified by flash column chromatography (Silica gel, 50% ethyl acetate/ 49% hexanes/ 1% Et_3N), 54% yield. (65 mg, 0.27 mmol). White solid. ^1H NMR (400 MHz, $CDCl_3$) δ 2.16 (3H, s), 2.25 (3H, s), 2.31 (3H, s), 7.23-7.24 (5H, m), 9.41 (1H, s br). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.5, 30.2, 31.6, 122.7, 123.9, 127.8, 128.1, 128.6, 131.0, 131.1, 133.8, 195.9, 201.0. IR (ZnSe) ν 3222 (br), 3005, 1645, 1622, 1487, 1448, 1412, 1354, 1188 cm^{-1}. FABHRMS: Found: *m/z* 242.1155. Calcd for $C_{15}H_{16}O_2N$ $(M+H)^+$, 242.1182.

1-(2-methyl-5-phenyl-1*H*-pyrrol-3-yl)ethanone (2-9g)



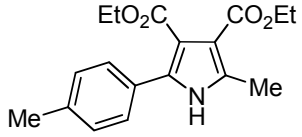
Used vinyl azide **2-1g** and acetylacetone as starting materials. Purified by flash column chromatography (Silica gel, 40% ethyl acetate/ 59% hexanes/ 1% Et_3N), 75% yield. (59.8 mg, 0.3 mmol) Pale yellow crystals. ^1H NMR (400 MHz, $CDCl_3$) δ 2.45 (3H, s), 2.61 (3H, s), 6.77 (1H, d, *J*= 2.7 Hz), 7.23 (1H, tt, *J*= 7.3, 1.5 Hz), 7.37 (2H, td, *J*= 7.8, 1.7 Hz), 7.48 (2H, dt, *J*= 7.2, 1.3 Hz), 8.90 (1H, s br). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2, 28.5, 107.4, 122.1, 123.7, 126.6, 128.9, 129.8, 131.6, 135.9, 195.1. IR (ZnSe) ν 3263 (br), 3018, 1635, 1604, 1477, 1448, 1240 cm^{-1}. Anal. Found: C, 78.24; H, 6.81; N, 6.88%. Cacld for $C_{13}H_{13}NO$; C, 78.36; H, 6.58; N, 7.03%.

Benzyl 4-acetyl-5-methyl-1*H*-pyrrole-3-carboxylate (2-9h)



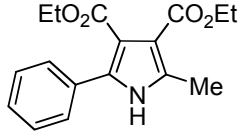
Used vinyl azide **2-1h** and acetylacetone as starting materials. Purified by flash column chromatography (Silica gel, 40% ethyl acetate/ 59% hexanes/ 1% Et_3N), 77% yield. White solid. (99.5 mg, 0.388 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 2.36 (3H, s), 2.52 (3H, s), 5.27 (2H, s), 7.22 (1H, d, *J*= 2.9 Hz), 7.30-7.41 (5H, m), 8.61 (1H, s br). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.1, 31.5, 65.6, 115.1, 122.2, 123.4, 128.0, 128.1, 128.5, 134.4, 136.1, 163.8, 198.5. IR (ZnSe) ν 3276 (br), 2960, 1705, 1637, 1520, 1435, 1410, 1288, 1151, 1026 cm^{-1}. Anal. Found: C, 69.80; H, 5.97; N, 5.31%. Cacld for $C_{15}H_{15}NO_3$; C, 70.02; H, 5.88; N, 5.44%.

Diethyl 2-methyl-5-*p*-tolyl-1*H*-pyrrole-3,4-dicarboxylate (2-9l)



Used vinyl azide **2-1b** and ethyl acetoacetate as starting materials. Purified by flash column chromatography (Silica gel, 40% ethyl acetate/ 59% hexanes/ 1% Et_3N), 25% yield. (15.6 mg, 0.05 mmol). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, t, *J*= 7.2 Hz), 1.32 (3H, t, *J*= 7.1 Hz), 2.36 (3H, s), 2.50 (3H, s), 4.26 (2H, q, *J*= 7.1 Hz), 4.27 (2H, q, *J*= 7.1 Hz), 7.17 (2H, d, *J*= 8.4 Hz), 7.35 (2H, d, *J*= 8.1 Hz), 8.30 (1H, s br). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.3, 14.1, 14.4, 21.3, 60.2, 60.9, 112.2, 114.2, 126.9, 128.0, 129.3, 130.7, 134.7, 137.8, 164.5, 166.7. IR (ZnSe) ν 3288 (br), 2981, 1676 (br), 1506, 1437, 1284, 1205, 1092, 1036 cm^{-1}. FABHRMS: Found: *m/z* 316.1554. Calcd for $C_{18}H_{22}O_4N$ $(M+H)^+$, 316.1550.

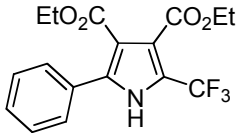
Diethyl 2-methyl-5-phenyl-1*H*-pyrrole-3,4-dicarboxylate (2-9m)



Used vinyl azide **2-1c** and ethyl acetoacetate as starting materials. Purified by flash column chromatography (Silica gel, 50% ethyl acetate/ 49% hexanes/ 1% Et_3N), 30% yield. (18 mg, 0.06 mmol). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, t, *J*= 7.2 Hz), 1.32 (3H, t, *J*= 7.2 Hz), 2.45 (3H, s), 4.25 (2H, q, *J*= 7.2 Hz), 4.26 (2H, q, *J*= 7.2 Hz), 7.26-7.36 (3H, m), 7.44 (2H, d, *J*= 7.3 Hz), 8.52 (1H, s br). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.1, 14.1, 14.4, 60.0, 61.0, 112.5, 114.6, 127.0, 127.8, 128.5, 130.2, 130.9, 135.1, 164.5,

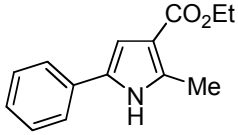
166.7. IR (ZnSe) ν 3296 (br), 2981, 1697 (br), 1429, 1286, 1209, 1093, 1024 cm^{-1}. FABHRMS: Found: *m/z* 302.1407. Calcd for $C_{17}H_{20}O_4N$ $(M+H)^+$ 302.1393.

Diethyl 2-(trifluoromethyl)-5-phenyl-1*H*-pyrrole-3,4-dicarboxylate (2-9n)



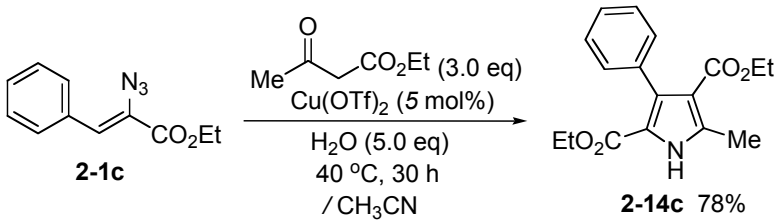
Used vinyl azide **2-1c** and ethyl 4,4,4-trifluoro-3-oxobutanoate as starting materials. Purified by flash column chromatography (Silica gel, 25% ethyl acetate/ 74% hexanes/ 1% Et_3N), 31% yield. (22.2 mg, 0.0625 mmol). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, t, *J*= 7.1 Hz), 1.35 (3H, t, *J*= 7.1 Hz), 4.20 (2H, q, *J*= 7.1 Hz), 4.33 (2H, q, *J*= 7.1 Hz), 7.37-7.39 (3H, m), 7.47 (2H, m), 9.26 (1H, s br). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 13.9, 61.1, 61.5, 114.5, 118.5, 120.0 (q, J_{CF} = 268.4 Hz), 120.2 (q, J_{CF} = 40.3 Hz), 128.5, 128.7, 129.4, 129.6, 135.9, 162.9, 163.9. ^{19}F NMR (471 MHz, $CDCl_3$) δ_F 18.0 (3F, s). IR (ZnSe) ν 3246 (br), 2985, 1701 (br), 1288, 1230, 1167, 1122 cm^{-1}. FABHRMS: Found: *m/z* 356.1138. Calcd for $C_{17}H_{17}O_4NF_3$ $(M+H)^+$, 356.1110.

Ethyl 2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate (2-9o)



Used vinyl azide **2-1g** and ethyl acetoacetate as starting materials. Purified by flash column chromatography (Silica gel, 30% ethyl acetate/ 69% hexanes/ 1% Et_3N), 58% yield. (26.6 mg, 0.116 mmol). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (3H, t, *J*= 7.1 Hz), 2.58 (3H, s), 4.30 (2H, q, *J*= 7.1 Hz), 6.83 (1H, d, *J*= 2.9 Hz), 7.21 (1H, t, *J*= 7.3 Hz), 7.35 (2H, t, *J*= 7.7 Hz), 7.45 (2H, d, *J*= 7.4 Hz), 8.61 (1H, s br). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.5, 14.6, 59.5, 107.3, 113.3, 123.6, 126.5, 128.8, 129.9, 131.7, 136.1, 165.5. IR (ZnSe) ν 3309 (br), 2979, 2925, 1668, 1608, 1481, 1448, 1277, 1234, 1097, 1061 cm^{-1}. FABHRMS: Found: *m/z* 230.1158. Calcd for $C_{14}H_{15}O_2N$ $(M+H)^+$, 230.1182.

2.3 Copper(II)-catalyzed reaction of vinyl azides with *β*-ketoesters

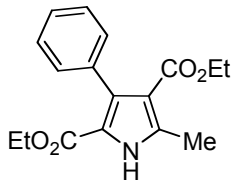


Typical procedure for the copper(II) triflate-catalyzed reaction of vinyl azides with 1,3-dicarbonyls:

To a stirring solution of $Cu(OTf)_2$ (3.6 mg, 0.01 mmol) in CH_3CN (2 mL) was added H_2O (18 mg, 18 μL, 1.00 mmol), (Z)-ethyl 2-azido-3-phenylacrylate **2-1c** (43.4 mg, 0.20 mmol) and ethyl acetoacetate (78.2 mg, 76 μL, 0.60 mmol). The reaction mixture was heated at 40°C for 30 h. The reaction mixture was quenched with a pH 9 buffer, diluted with ethyl acetate, and then extracted twice with EtOAc.

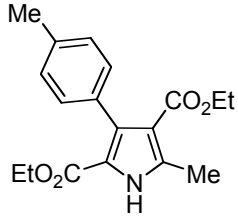
The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. Purification of the crude product by flash column chromatography (Silica gel, 30% ethyl acetate/ 69% hexanes/ 1% Et_3N), afforded **2-14c** in 78% yield. (47.2 mg, 0.157 mmol).

Diethyl 5-methyl-3-phenyl-1*H*-pyrrole-2,4-dicarboxylate (2-14c)



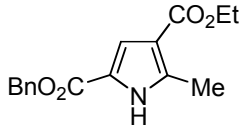
Colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J*= 7.1 Hz), 1.02 (3H, t, *J*= 7.1 Hz), 2.59 (3H, s), 4.03 (2H, q, *J*= 7.1 Hz), 4.10 (2H, q, *J*= 7.1 Hz), 7.24-7.33 (5H, m), 9.84 (1H, s br). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 13.8, 13.9, 59.9, 60.3, 113.7, 118.0, 126.6, 126.7, 129.8, 133.4, 135.0, 138.8, 161.4, 164.7. IR (ZnSe) ν 3282 (br), 2981, 1695, 1660 (br), 1487, 1427, 1269, 1196, 1088, 1020 cm^{-1}. Anal. Found: C, 67.56; H, 6.56; N, 4.49%. Cacld for $C_{17}H_{19}NO_4$; C, 67.76; H, 6.36; N, 4.65%.

Diethyl 5-methyl-3- *p*-tolyl-1*H*-pyrrole-2,4-dicarboxylate (2-14b)



Used vinyl azide **2-1b** as starting material. Purified by flash column chromatography (Silica gel, 30% ethyl acetate/ 69% hexanes/ 1% Et_3N). Colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (3H, t, *J*= 7.3 Hz), 1.09 (3H, t, *J*= 7.1 Hz), 2.37 (3H, s), 2.57 (3H, s), 4.05 (2H, q, *J*= 7.1 Hz), 4.13 (2H, q, *J*= 7.1 Hz), 7.12 (2H, d, *J*= 8.1 Hz), 7.15 (2H, d, *J*= 8.3 Hz), 9.16 (1H, s br). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 14.0, 14.1, 21.4, 59.5, 60.3, 113.9, 118.0, 127.5, 129.7, 131.5, 133.6, 136.2, 138.2, 160.9, 164.7. IR (ZnSe) ν 3284 (br), 2979, 1693, 1662, 1431, 1271, 1198, 1092, 1030 cm^{-1}. FABHRMS: Found: *m/z* 316.1566. Calcd for $C_{18}H_{22}O_4N$ $(M+H)^+$ 316.1550.

2-Benzyl 4-ethyl 5-methyl-1*H*-pyrrole-2,4-dicarboxylate (2-14h)



Used vinyl azide **2-1h** as starting material. Purified by flash column chromatography (Silica gel, 30% ethyl acetate/ 69% hexanes/ 1% Et_3N), 28% yield. (16.0 mg, 0.056 mmol). White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, t, *J*= 7.2 Hz), 2.55 (3H, s), 4.27 (2H, q, *J*= 7.1 Hz), 5.30 (2H, s), 7.29 (1H, d, *J*= 2.7 Hz), 7.32-7.42 (5H, m), 9.46 (1H, s br). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.5, 14.5, 59.8, 66.3, 114.2, 117.7, 120.2, 128.0, 128.3, 128.5, 135.7, 139.7, 160.7, 164.5. IR (ZnSe) ν 3286 (br), 2981, 1674 (br), 1500, 1273, 1234, 1188, 1117, 1082, 999 cm^{-1}. FABHRMS: Found: *m/z* 288.1242. Calcd for $C_{16}H_{18}O_4N$ $(M+H)^+$ 288.1236.

X-ray crystallographic analysis of pyrrole **2-9a**

Table 1. Crystal data and structure refinement for GL **2-9a**.

Identification code	GL **2-9a**
Empirical formula	C16 H15 Cl2 N O3

Formula weight	340.19	
Temperature	120(2) K	
Wavelength	0.71070 Å	
Crystal system	monoclinic	
Space group	P21/n	
Unit cell dimensions	a = 7.556(4) Å	α= 90°.
	b = 13.204(7) Å	β= 100.286(3)°.
	c = 16.690(10) Å	γ = 90°.
Volume	1638.2(16) $Å^3$	
Z	4	
Density (calculated)	1.379 Mg/m^3	
Absorption coefficient	0.407 mm^{-1}	
F(000)	704	
Crystal size	0.30 x 0.30 x 0.30 mm^3	
Theta range for data collection	3.09 to 25.00°.	
Index ranges	-8<=h<=7, -14<=k<=15, -19<=l<=19	
Reflections collected	10395	
Independent reflections	2855 [R(int) = 0.0332]	
Completeness to theta = 25.00°	99.3 %	
Max. and min. transmission	0.8877 and 0.8877	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2855 / 0 / 206	
Goodness-of-fit on F^2	1.010	
Final R indices [I>2sigma(I)]	R1 = 0.0350, wR2 = 0.0825	
R indices (all data)	R1 = 0.0521, wR2 = 0.0888	
Largest diff. peak and hole	0.303 and -0.254 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)for GL **2-9a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	6605(2)	2423(1)	2000(1)	18(1)
C(1)	7398(3)	3354(2)	2130(1)	18(1)
C(2)	6190(2)	4057(1)	1730(1)	16(1)
C(3)	4613(2)	3505(1)	1350(1)	14(1)
C(4)	4924(2)	2500(2)	1549(1)	15(1)
C(5)	9265(3)	3456(2)	2590(1)	27(1)

C(6)	6629(3)	5146(2)	1745(1)	18(1)
O(1)	7462(2)	5506(1)	2375(1)	31(1)
C(7)	6136(3)	5793(2)	1003(1)	33(1)
C(8)	2878(3)	3937(2)	964(1)	16(1)
O(2)	2534(2)	4830(1)	923(1)	26(1)
O(3)	1688(2)	3216(1)	674(1)	22(1)
C(9)	-107(3)	3560(2)	321(1)	24(1)
C(10)	-1255(3)	2635(2)	152(2)	34(1)
C(11)	3739(2)	1596(1)	1453(1)	16(1)
C(12)	3016(3)	1247(2)	2114(1)	20(1)
C(13)	1896(3)	406(2)	2062(1)	25(1)
C(14)	1495(3)	-106(2)	1332(2)	28(1)
C(15)	2196(3)	204(2)	660(1)	25(1)
C(16)	3302(3)	1052(2)	729(1)	20(1)
Cl(1)	3483(1)	1895(1)	3035(1)	28(1)
Cl(2)	4158(1)	1427(1)	-122(1)	31(1)

Table 3. Bond lengths [Å] and angles [°] for GL **2-9a**.

N(1)-C(4)	1.360(3)
N(1)-C(1)	1.368(3)
N(1)-H(1)	0.93(2)
C(1)-C(2)	1.387(3)
C(1)-C(5)	1.487(3)
C(2)-C(3)	1.443(3)
C(2)-C(6)	1.475(3)
C(3)-C(4)	1.379(3)
C(3)-C(8)	1.469(3)
C(4)-C(11)	1.484(3)
C(5)-H(2)	0.9800
C(5)-H(3)	0.9800
C(5)-H(4)	0.9800
C(6)-O(1)	1.222(2)
C(6)-C(7)	1.496(3)
C(7)-H(5)	0.9800
C(7)-H(6)	0.9800
C(7)-H(7)	0.9800

C(8)-O(2)	1.207(2)
C(8)-O(3)	1.339(2)
O(3)-C(9)	1.452(2)
C(9)-C(10)	1.495(3)
C(9)-H(8)	0.9900
C(9)-H(9)	0.9900
C(10)-H(10)	0.9800
C(10)-H(11)	0.9800
C(10)-H(12)	0.9800
C(11)-C(12)	1.394(3)
C(11)-C(16)	1.393(3)
C(12)-C(13)	1.389(3)
C(12)-Cl(1)	1.740(2)
C(13)-C(14)	1.379(3)
C(13)-H(13)	0.9500
C(14)-C(15)	1.386(3)
C(14)-H(14)	0.9500
C(15)-C(16)	1.390(3)
C(15)-H(15)	0.9500
C(16)-Cl(2)	1.734(2)

C(4)-N(1)-C(1)	111.12(17)
C(4)-N(1)-H(1)	124.7(13)
C(1)-N(1)-H(1)	124.0(13)
N(1)-C(1)-C(2)	107.06(18)
N(1)-C(1)-C(5)	120.82(18)
C(2)-C(1)-C(5)	132.04(19)
C(1)-C(2)-C(3)	107.11(17)
C(1)-C(2)-C(6)	121.18(18)
C(3)-C(2)-C(6)	131.71(18)
C(4)-C(3)-C(2)	106.80(17)
C(4)-C(3)-C(8)	125.41(17)
C(2)-C(3)-C(8)	126.83(17)
N(1)-C(4)-C(3)	107.87(17)
N(1)-C(4)-C(11)	119.06(17)
C(3)-C(4)-C(11)	132.50(18)
C(1)-C(5)-H(2)	109.5
C(1)-C(5)-H(3)	109.5

H(2)-C(5)-H(3)	109.5
C(1)-C(5)-H(4)	109.5
H(2)-C(5)-H(4)	109.5
H(3)-C(5)-H(4)	109.5
O(1)-C(6)-C(2)	118.30(19)
O(1)-C(6)-C(7)	120.25(19)
C(2)-C(6)-C(7)	121.41(19)
C(6)-C(7)-H(5)	109.5
C(6)-C(7)-H(6)	109.5
H(5)-C(7)-H(6)	109.5
C(6)-C(7)-H(7)	109.5
H(5)-C(7)-H(7)	109.5
H(6)-C(7)-H(7)	109.5
O(2)-C(8)-O(3)	123.39(18)
O(2)-C(8)-C(3)	124.76(18)
O(3)-C(8)-C(3)	111.83(17)
C(8)-O(3)-C(9)	116.26(15)
O(3)-C(9)-C(10)	106.82(17)
O(3)-C(9)-H(8)	110.4
C(10)-C(9)-H(8)	110.4
O(3)-C(9)-H(9)	110.4
C(10)-C(9)-H(9)	110.4
H(8)-C(9)-H(9)	108.6
C(9)-C(10)-H(10)	109.5
C(9)-C(10)-H(11)	109.5
H(10)-C(10)-H(11)	109.5
C(9)-C(10)-H(12)	109.5
H(10)-C(10)-H(12)	109.5
H(11)-C(10)-H(12)	109.5
C(12)-C(11)-C(16)	116.80(19)
C(12)-C(11)-C(4)	119.66(18)
C(16)-C(11)-C(4)	123.54(18)
C(13)-C(12)-C(11)	122.3(2)
C(13)-C(12)-Cl(1)	118.26(17)
C(11)-C(12)-Cl(1)	119.42(16)
C(14)-C(13)-C(12)	118.9(2)
C(14)-C(13)-H(13)	120.6
C(12)-C(13)-H(13)	120.6

C(13)-C(14)-C(15)	121.0(2)
C(13)-C(14)-H(14)	119.5
C(15)-C(14)-H(14)	119.5
C(14)-C(15)-C(16)	118.8(2)
C(14)-C(15)-H(15)	120.6
C(16)-C(15)-H(15)	120.6
C(15)-C(16)-C(11)	122.2(2)
C(15)-C(16)-Cl(2)	117.96(17)
C(11)-C(16)-Cl(2)	119.83(16)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for GL **2-9a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	18(1)	13(1)	22(1)	3(1)	-1(1)	2(1)
C(1)	18(1)	16(1)	20(1)	-2(1)	4(1)	-3(1)
C(2)	18(1)	13(1)	16(1)	-1(1)	3(1)	-1(1)
C(3)	15(1)	12(1)	14(1)	0(1)	3(1)	1(1)
C(4)	14(1)	17(1)	14(1)	-1(1)	2(1)	-1(1)
C(5)	22(1)	26(1)	30(1)	1(1)	-3(1)	0(1)
C(6)	16(1)	17(1)	24(1)	-2(1)	6(1)	1(1)
O(1)	38(1)	17(1)	33(1)	-7(1)	-5(1)	-6(1)
C(7)	46(2)	21(1)	29(1)	3(1)	3(1)	-8(1)
C(8)	19(1)	17(1)	14(1)	-1(1)	4(1)	-3(1)
O(2)	26(1)	14(1)	36(1)	-1(1)	-4(1)	5(1)
O(3)	14(1)	19(1)	29(1)	0(1)	-4(1)	1(1)
C(9)	16(1)	26(1)	27(1)	3(1)	-3(1)	3(1)
C(10)	23(1)	40(2)	36(2)	4(1)	-3(1)	-6(1)
C(11)	13(1)	12(1)	21(1)	3(1)	1(1)	3(1)
C(12)	18(1)	18(1)	24(1)	2(1)	4(1)	2(1)
C(13)	22(1)	23(1)	32(1)	7(1)	8(1)	-1(1)
C(14)	20(1)	19(1)	43(2)	3(1)	3(1)	-7(1)
C(15)	25(1)	19(1)	29(1)	-6(1)	0(1)	-3(1)
C(16)	20(1)	16(1)	25(1)	3(1)	3(1)	1(1)
Cl(1)	34(1)	31(1)	21(1)	-1(1)	7(1)	0(1)

Cl(2)	42(1)	29(1)	23(1)	-4(1)	11(1)	-8(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for GL **2-9a**.

	x	y	z	U(eq)
H(1)	7120(30)	1827(16)	2229(13)	24(6)
H(2)	9238	3509	3174	41
H(3)	9818	4067	2410	41
H(4)	9970	2861	2491	41
H(5)	4924	6068	983	49
H(6)	6164	5385	515	49
H(7)	6998	6352	1025	49
H(8)	-84	3937	-190	28
H(9)	-585	4011	705	28
H(10)	-786	2205	-241	51
H(11)	-2492	2836	-74	51
H(12)	-1238	2259	659	51
H(13)	1415	188	2521	30
H(14)	726	-680	1290	33
H(15)	1926	-157	160	29

Table 6. Torsion angles [°] for GL **2-9a**.

C(4)-N(1)-C(1)-C(2)	-1.3(2)
C(4)-N(1)-C(1)-C(5)	-178.28(18)
N(1)-C(1)-C(2)-C(3)	0.2(2)
C(5)-C(1)-C(2)-C(3)	176.7(2)
N(1)-C(1)-C(2)-C(6)	-179.85(17)
C(5)-C(1)-C(2)-C(6)	-3.4(3)
C(1)-C(2)-C(3)-C(4)	1.0(2)
C(6)-C(2)-C(3)-C(4)	-179.0(2)

C(1)-C(2)-C(3)-C(8)	170.16(19)
C(6)-C(2)-C(3)-C(8)	-9.8(3)
C(1)-N(1)-C(4)-C(3)	2.0(2)
C(1)-N(1)-C(4)-C(11)	-170.43(17)
C(2)-C(3)-C(4)-N(1)	-1.7(2)
C(8)-C(3)-C(4)-N(1)	-171.14(18)
C(2)-C(3)-C(4)-C(11)	169.2(2)
C(8)-C(3)-C(4)-C(11)	-0.2(3)
C(1)-C(2)-C(6)-O(1)	-38.1(3)
C(3)-C(2)-C(6)-O(1)	141.9(2)
C(1)-C(2)-C(6)-C(7)	139.7(2)
C(3)-C(2)-C(6)-C(7)	-40.4(3)
C(4)-C(3)-C(8)-O(2)	166.3(2)
C(2)-C(3)-C(8)-O(2)	-1.0(3)
C(4)-C(3)-C(8)-O(3)	-12.4(3)
C(2)-C(3)-C(8)-O(3)	-179.66(18)
O(2)-C(8)-O(3)-C(9)	-2.1(3)
C(3)-C(8)-O(3)-C(9)	176.56(16)
C(8)-O(3)-C(9)-C(10)	-171.97(17)
N(1)-C(4)-C(11)-C(12)	71.2(2)
C(3)-C(4)-C(11)-C(12)	-98.9(3)
N(1)-C(4)-C(11)-C(16)	-108.2(2)
C(3)-C(4)-C(11)-C(16)	81.7(3)
C(16)-C(11)-C(12)-C(13)	-0.7(3)
C(4)-C(11)-C(12)-C(13)	179.89(18)
C(16)-C(11)-C(12)-Cl(1)	-179.31(14)
C(4)-C(11)-C(12)-Cl(1)	1.2(3)
C(11)-C(12)-C(13)-C(14)	0.5(3)
Cl(1)-C(12)-C(13)-C(14)	179.12(16)
C(12)-C(13)-C(14)-C(15)	0.3(3)
C(13)-C(14)-C(15)-C(16)	-0.8(3)
C(14)-C(15)-C(16)-C(11)	0.5(3)
C(14)-C(15)-C(16)-Cl(2)	-179.82(16)
C(12)-C(11)-C(16)-C(15)	0.1(3)
C(4)-C(11)-C(16)-C(15)	179.57(18)
C(12)-C(11)-C(16)-Cl(2)	-179.48(14)
C(4)-C(11)-C(16)-Cl(2)	-0.1(3)

Symmetry transformations used to generate equivalent atoms:

X-ray crystallographic analysis of pyrrole **2-14b**

Table 1. Crystal data and structure refinement for GL **2-14b**.

Identification code	GL **2-14b**	
Empirical formula	C18 H21 N O4	
Formula weight	315.36	
Temperature	120(2) K	
Wavelength	0.71070 Å	
Crystal system	triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.446(5) Å	α= 69.99(2)°.
	b = 9.144(5) Å	β= 85.26(2)°.
	c = 11.754(7) Å	γ = 75.04(2)°.
Volume	824.1(9) $Å^3$	
Z	2	
Density (calculated)	1.271 Mg/m^3	
Absorption coefficient	0.090 mm^{-1}	
F(000)	336	
Crystal size	0.20 x 0.20 x 0.20 mm^3	
Theta range for data collection	3.04 to 27.48°.	
Index ranges	-10<=h<=10, -11<=k<=11, -15<=l<=13	
Reflections collected	6364	
Independent reflections	3575 [R(int) = 0.0166]	
Completeness to theta = 27.48°	94.6 %	
Max. and min. transmission	0.9823 and 0.9823	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3575 / 0 / 216	
Goodness-of-fit on F^2	0.995	
Final R indices [I>2sigma(I)]	R1 = 0.0383, wR2 = 0.0987	
R indices (all data)	R1 = 0.0511, wR2 = 0.1064	
Largest diff. peak and hole	0.252 and -0.209 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for GL **2-14b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	5976(1)	2946(1)	4932(1)	23(1)
O(2)	8504(1)	1682(1)	4532(1)	26(1)
O(3)	4370(1)	-1626(1)	9241(1)	26(1)
C(4)	5964(2)	-2297(1)	9162(1)	20(1)
O(4)	6665(1)	-3575(1)	9880(1)	27(1)
C(6)	5991(1)	132(1)	7174(1)	17(1)
C(7)	1917(1)	2708(1)	7732(1)	22(1)
C(8)	8364(2)	-1805(2)	7809(1)	21(1)
C(9)	3532(1)	1827(1)	7869(1)	20(1)
N(6)	8631(1)	-723(1)	6745(1)	21(1)
C(11)	7221(1)	465(1)	6338(1)	19(1)
C(12)	3300(1)	1213(2)	6086(1)	23(1)
C(13)	7305(1)	1733(1)	5189(1)	19(1)
C(14)	4255(1)	1069(1)	7048(1)	18(1)
C(15)	5959(2)	4188(2)	3749(1)	26(1)
C(16)	6728(1)	-1317(1)	8111(1)	19(1)
C(17)	960(2)	2848(2)	6774(1)	24(1)
C(18)	1686(2)	2081(2)	5956(1)	27(1)
C(19)	9686(2)	-3235(2)	8431(1)	30(1)
C(20)	-807(2)	3801(2)	6615(1)	37(1)
C(21)	5476(2)	3670(2)	2772(1)	39(1)
C(22)	3420(2)	-2536(2)	10165(1)	26(1)
C(23)	1782(2)	-1404(2)	10154(1)	36(1)

Table 3. Bond lengths [Å] and angles [°] for GL **2-14b**.

O(1)-C(13)	1.3289(16)
O(1)-C(15)	1.4623(15)
O(2)-C(13)	1.2221(15)
O(3)-C(4)	1.3379(16)
O(3)-C(22)	1.4482(15)

C(4)-O(4)	1.2154(16)
C(4)-C(16)	1.4683(18)
C(6)-C(11)	1.3883(17)
C(6)-C(16)	1.4299(17)
C(6)-C(14)	1.4856(18)
C(7)-C(9)	1.3842(18)
C(7)-C(17)	1.3920(19)
C(7)-H(18)	0.9500
C(8)-N(6)	1.3476(17)
C(8)-C(16)	1.3940(18)
C(8)-C(19)	1.4896(19)
C(9)-C(14)	1.3889(18)
C(9)-H(19)	0.9500
N(6)-C(11)	1.3778(17)
N(6)-H(1)	0.985(14)
C(11)-C(13)	1.4584(18)
C(12)-C(18)	1.3804(19)
C(12)-C(14)	1.3927(18)
C(12)-H(20)	0.9500
C(15)-C(21)	1.502(2)
C(15)-H(14)	0.9900
C(15)-H(15)	0.9900
C(17)-C(18)	1.391(2)
C(17)-C(20)	1.5108(19)
C(18)-H(21)	0.9500
C(19)-H(2)	0.9800
C(19)-H(3)	0.9800
C(19)-H(4)	0.9800
C(20)-H(5)	0.9800
C(20)-H(6)	0.9800
C(20)-H(7)	0.9800
C(21)-H(8)	0.9800
C(21)-H(9)	0.9800
C(21)-H(10)	0.9800
C(22)-C(23)	1.497(2)
C(22)-H(16)	0.9900
C(22)-H(17)	0.9900
C(23)-H(11)	0.9800

C(23)-H(12)	0.9800
C(23)-H(13)	0.9800

C(13)-O(1)-C(15)	115.82(10)
C(4)-O(3)-C(22)	117.92(10)
O(4)-C(4)-O(3)	123.01(11)
O(4)-C(4)-C(16)	125.14(12)
O(3)-C(4)-C(16)	111.85(10)
C(11)-C(6)-C(16)	105.84(11)
C(11)-C(6)-C(14)	125.54(11)
C(16)-C(6)-C(14)	128.52(10)
C(9)-C(7)-C(17)	121.09(12)
C(9)-C(7)-H(18)	119.5
C(17)-C(7)-H(18)	119.5
N(6)-C(8)-C(16)	107.41(11)
N(6)-C(8)-C(19)	121.28(11)
C(16)-C(8)-C(19)	131.29(12)
C(7)-C(9)-C(14)	121.07(11)
C(7)-C(9)-H(19)	119.5
C(14)-C(9)-H(19)	119.5
C(8)-N(6)-C(11)	110.54(11)
C(8)-N(6)-H(1)	125.6(8)
C(11)-N(6)-H(1)	123.7(8)
N(6)-C(11)-C(6)	108.20(11)
N(6)-C(11)-C(13)	117.33(11)
C(6)-C(11)-C(13)	134.48(12)
C(18)-C(12)-C(14)	120.93(12)
C(18)-C(12)-H(20)	119.5
C(14)-C(12)-H(20)	119.5
O(2)-C(13)-O(1)	123.38(12)
O(2)-C(13)-C(11)	122.61(12)
O(1)-C(13)-C(11)	114.00(11)
C(9)-C(14)-C(12)	117.92(12)
C(9)-C(14)-C(6)	121.77(11)
C(12)-C(14)-C(6)	120.30(11)
O(1)-C(15)-C(21)	110.67(12)
O(1)-C(15)-H(14)	109.5
C(21)-C(15)-H(14)	109.5

O(1)-C(15)-H(15)	109.5
C(21)-C(15)-H(15)	109.5
H(14)-C(15)-H(15)	108.1
C(8)-C(16)-C(6)	108.01(11)
C(8)-C(16)-C(4)	122.36(11)
C(6)-C(16)-C(4)	129.32(11)
C(18)-C(17)-C(7)	117.65(12)
C(18)-C(17)-C(20)	120.63(12)
C(7)-C(17)-C(20)	121.71(12)
C(12)-C(18)-C(17)	121.34(12)
C(12)-C(18)-H(21)	119.3
C(17)-C(18)-H(21)	119.3
C(8)-C(19)-H(2)	109.5
C(8)-C(19)-H(3)	109.5
H(2)-C(19)-H(3)	109.5
C(8)-C(19)-H(4)	109.5
H(2)-C(19)-H(4)	109.5
H(3)-C(19)-H(4)	109.5
C(17)-C(20)-H(5)	109.5
C(17)-C(20)-H(6)	109.5
H(5)-C(20)-H(6)	109.5
C(17)-C(20)-H(7)	109.5
H(5)-C(20)-H(7)	109.5
H(6)-C(20)-H(7)	109.5
C(15)-C(21)-H(8)	109.5
C(15)-C(21)-H(9)	109.5
H(8)-C(21)-H(9)	109.5
C(15)-C(21)-H(10)	109.5
H(8)-C(21)-H(10)	109.5
H(9)-C(21)-H(10)	109.5
O(3)-C(22)-C(23)	105.59(11)
O(3)-C(22)-H(16)	110.6
C(23)-C(22)-H(16)	110.6
O(3)-C(22)-H(17)	110.6
C(23)-C(22)-H(17)	110.6
H(16)-C(22)-H(17)	108.8
C(22)-C(23)-H(11)	109.5
C(22)-C(23)-H(12)	109.5

H(11)-C(23)-H(12)	109.5
C(22)-C(23)-H(13)	109.5
H(11)-C(23)-H(13)	109.5
H(12)-C(23)-H(13)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for GL **2-14b**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	22(1)	19(1)	21(1)	-2(1)	4(1)	-1(1)
O(2)	19(1)	31(1)	23(1)	-5(1)	6(1)	-5(1)
O(3)	20(1)	24(1)	26(1)	0(1)	8(1)	-4(1)
C(4)	21(1)	21(1)	18(1)	-7(1)	1(1)	-5(1)
O(4)	27(1)	24(1)	23(1)	0(1)	1(1)	-2(1)
C(6)	17(1)	18(1)	17(1)	-7(1)	1(1)	-5(1)
C(7)	22(1)	19(1)	24(1)	-8(1)	6(1)	-5(1)
C(8)	20(1)	22(1)	19(1)	-6(1)	1(1)	-4(1)
C(9)	21(1)	19(1)	18(1)	-5(1)	2(1)	-7(1)
N(6)	16(1)	24(1)	20(1)	-5(1)	3(1)	-2(1)
C(11)	17(1)	19(1)	20(1)	-6(1)	1(1)	-3(1)
C(12)	20(1)	28(1)	23(1)	-12(1)	4(1)	-6(1)
C(13)	18(1)	20(1)	20(1)	-8(1)	2(1)	-5(1)
C(14)	17(1)	16(1)	19(1)	-4(1)	4(1)	-6(1)
C(15)	32(1)	17(1)	21(1)	-1(1)	3(1)	-2(1)
C(16)	19(1)	18(1)	19(1)	-7(1)	1(1)	-3(1)
C(17)	18(1)	23(1)	28(1)	-5(1)	2(1)	-4(1)
C(18)	21(1)	34(1)	27(1)	-11(1)	-2(1)	-5(1)
C(19)	24(1)	30(1)	26(1)	-3(1)	0(1)	1(1)
C(20)	23(1)	44(1)	41(1)	-15(1)	0(1)	1(1)
C(21)	48(1)	33(1)	28(1)	-6(1)	-9(1)	-2(1)
C(22)	26(1)	26(1)	24(1)	-2(1)	7(1)	-11(1)
C(23)	28(1)	34(1)	40(1)	-5(1)	11(1)	-9(1)

Table 5. Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$)

for GL **2-14b**.

	x	y	z	U(eq)
H(18)	1455	3226	8302	26
H(19)	4156	1739	8536	24
H(20)	3766	706	5511	28
H(14)	7060	4401	3576	31
H(15)	5173	5196	3759	31
H(21)	1058	2156	5295	32
H(2)	10672	-3248	7929	45
H(3)	9322	-4214	8558	45
H(4)	9934	-3185	9215	45
H(5)	-1524	3079	6987	56
H(6)	-1065	4322	5750	56
H(7)	-976	4621	7004	56
H(8)	6255	2674	2762	58
H(9)	5485	4510	1986	58
H(10)	4373	3489	2932	58
H(16)	3954	-2914	10967	32
H(17)	3303	-3479	9976	32
H(11)	1904	-546	10436	54
H(12)	1034	-1988	10691	54
H(13)	1336	-935	9328	54
H(1)	9655(17)	-802(17)	6278(13)	36(4)

Table 6. Torsion angles [°] for GL **2-14b**.

C(22)-O(3)-C(4)-O(4)	-5.36(17)
C(22)-O(3)-C(4)-C(16)	173.99(10)
C(17)-C(7)-C(9)-C(14)	0.72(18)
C(16)-C(8)-N(6)-C(11)	0.18(14)
C(19)-C(8)-N(6)-C(11)	178.61(11)
C(8)-N(6)-C(11)-C(6)	-0.26(14)
C(8)-N(6)-C(11)-C(13)	-179.87(10)
C(16)-C(6)-C(11)-N(6)	0.22(13)
C(14)-C(6)-C(11)-N(6)	-176.53(11)

C(16)-C(6)-C(11)-C(13)	179.74(13)
C(14)-C(6)-C(11)-C(13)	3.0(2)
C(15)-O(1)-C(13)-O(2)	5.08(16)
C(15)-O(1)-C(13)-C(11)	-175.73(10)
N(6)-C(11)-C(13)-O(2)	7.81(18)
C(6)-C(11)-C(13)-O(2)	-171.67(12)
N(6)-C(11)-C(13)-O(1)	-171.38(10)
C(6)-C(11)-C(13)-O(1)	9.1(2)
C(7)-C(9)-C(14)-C(12)	-0.47(17)
C(7)-C(9)-C(14)-C(6)	179.37(10)
C(18)-C(12)-C(14)-C(9)	-0.08(18)
C(18)-C(12)-C(14)-C(6)	-179.92(11)
C(11)-C(6)-C(14)-C(9)	-118.86(14)
C(16)-C(6)-C(14)-C(9)	65.14(17)
C(11)-C(6)-C(14)-C(12)	60.98(17)
C(16)-C(6)-C(14)-C(12)	-115.03(14)
C(13)-O(1)-C(15)-C(21)	80.44(14)
N(6)-C(8)-C(16)-C(6)	-0.04(13)
C(19)-C(8)-C(16)-C(6)	-178.25(13)
N(6)-C(8)-C(16)-C(4)	174.04(11)
C(19)-C(8)-C(16)-C(4)	-4.2(2)
C(11)-C(6)-C(16)-C(8)	-0.12(13)
C(14)-C(6)-C(16)-C(8)	176.50(11)
C(11)-C(6)-C(16)-C(4)	-173.65(11)
C(14)-C(6)-C(16)-C(4)	3.0(2)
O(4)-C(4)-C(16)-C(8)	2.33(19)
O(3)-C(4)-C(16)-C(8)	-177.01(11)
O(4)-C(4)-C(16)-C(6)	175.04(12)
O(3)-C(4)-C(16)-C(6)	-4.29(17)
C(9)-C(7)-C(17)-C(18)	-0.41(18)
C(9)-C(7)-C(17)-C(20)	179.78(11)
C(14)-C(12)-C(18)-C(17)	0.38(19)
C(7)-C(17)-C(18)-C(12)	-0.13(19)
C(20)-C(17)-C(18)-C(12)	179.68(12)
C(4)-O(3)-C(22)-C(23)	171.77(11)

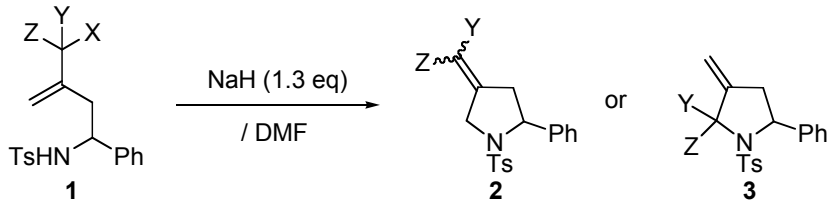
Symmetry transformations used to generate equivalent atoms:

Summary

In this thesis, two different approaches to the synthesis of 5-membered azahetoerocycles have been introduced, namely the nucleophilic 5-*endo-trig* cyclizations of *N*-homoallylic sulfonamides to pyrrolidines and the reactions of vinyl azides with 1,3-dicarbonyls to pyrroles.

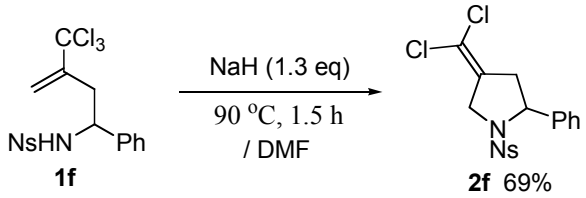
In chapter 1, the nucleophilic *5-endo-trig* cyclization of [*N*-(3-halomethyl)homoallyl] and *N*-(3-carbonylhomoallyl) sulfonamides has been studied.

When trihalomethyl group was used as electron withdrawing group attached to the alkene, the sulfonamide underwent the *5-endo-trig* cyclization in the presence of a stoechiometric amount of NaH in DMF. On the other hand, deuterated *N*-[3-(halomethyl)homoallyl]sulfonamides cyclized in a *5-exo-tet* fashion.



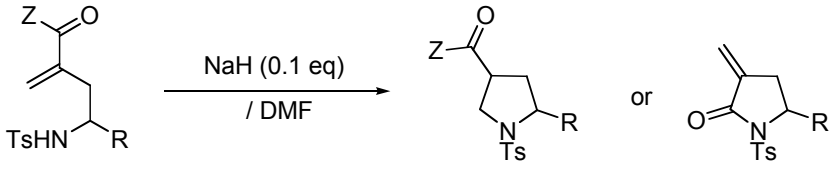
entry	**1**	CYZ	X	conditions	**2** /%	**3** /%
1	**a**	CF_2	F	130 °C, 3 h	91	-
2	**b**	CCl_2	Cl	80 °C, 0.25 h	89	-
3	**c**	CHD	F	110 °C, 2 h	-	91
4	**d**	CHD	Cl	50 °C, 1 h	-	86
5	**e**	CHD	Br	rt, 0.25 h	-	89

(Trichloromethyl)alkene **1f** bearing a nosyl (2-nitrobenzenesulfonyl) group on the nitrogen instead of a tosyl group also underwent the 5-*endo-trig* cyclization to afford pyrrolidine **2f**. However, other examined (trichloromethyl)alkenes with an intramolecular free amine (NH_2-), benzylamine ($PhCH_2NH$-), benzamide (PhCONH-) or carbamate (*t*-BuOCONH-) moieties failed to cyclize.



With an ethoxycarbonyl moiety as an electron withdrawing group attached to the alkene, the sulfonamide underwent the 5-*endo-trig* cyclization to give pyrrolidine **5a-b**, when treated with a catalytic amount of NaH in DMF. In contrast to ethyl esters **4a-b**, phenyl esters **4d-e** afforded the *5-exo-trig* cyclization products **6d** and **6e** exclusively. Thus, both 5-*endo-trig* and 5-*exo-trig*

cyclization products can be obtained by choosing an appropriate alkoxy group in the starting esters (CO_2Et or CO_2Ph).

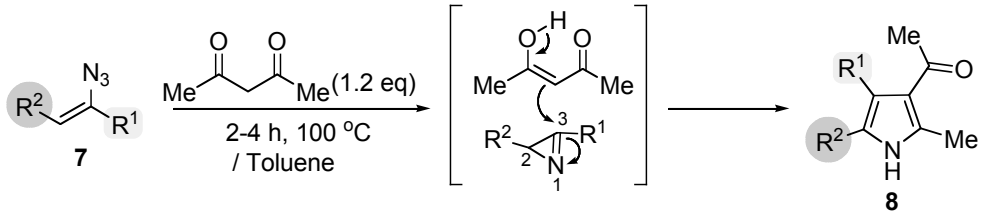


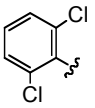
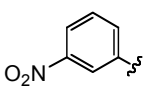
4 **5** **6**

entry	**4**	Z	R	conditions	**5** /% (*anti:syn*)	**6** /%
1	**a**	OEt	Ph	110 °C, 3 h /DMF	87 (59:41)	-
2	**b**	OEt	H	110 °C, 4 h /DMF	72	-
3	**c**	OPh	Ph	100 °C, 1 h /DMF	-	90
4	**d**	OPh	H	140 °C, 8 h /DMF	-	76

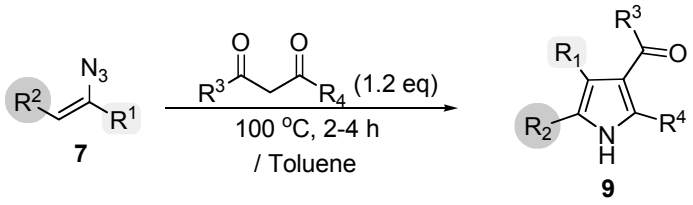
In chapter 2, the thermal and copper(II)-catalyzed reactions of vinylazides with 1,3-dicarbonyl compounds have been investigated.

The first discovered reaction was the thermal construction of polysubstituted pyrroles from vinyl azides and 1,3-dicarbonyls. In this reaction, 2*H*-azirines generated *in situ* thermally from vinyl azides were attacked at the C-3 carbon by 1,3-diketones such as acetylacetone, affording pyrroles **8**. With acetylacetone as nucleophile, the reaction is quite general in terms of the vinyl azides..



entry	**7**	R^1	R^2	**8** /%	entry	**7**	R^1	R^2	**8** /%
1	**a**	CO_2Et		quant.	4	**d**	H		75
2	**b**	CO_2Et		86	5	**e**	COMe		54
3	**c**	CO_2Et		96	6	**f**	CO_2Bn	H	77

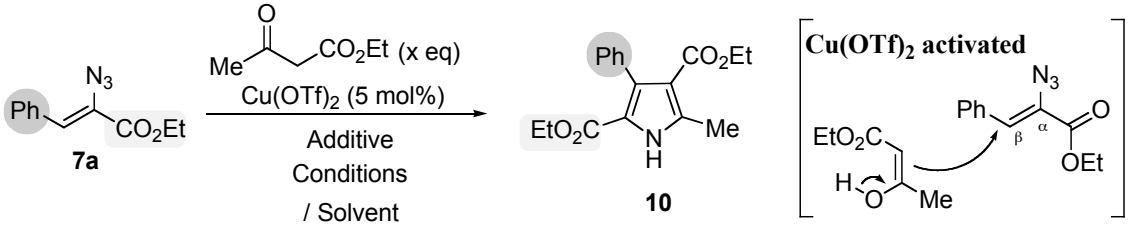
On the other hand, the addition of other 1,3-diketones and *β*-keto esters to vinyl azides was sluggish, and additives such as acids or bases did not improve the yield. The reaction worked better with *β*-azidostyrene **7d**, which does not have any ethoxy carbonyl moiety.



entry	7	R^1	R^2	1,3-dicarbonyl	9 /%
1*	g	CO_2Et	Me	Ph, Me	**9a** 39% (2:1 mixture)
2	a	CO_2Et		Me, CO_2Et	**9b** 30%
3	a	CO_2Et		F_3C, CO_2Et	**9c** 31%
4	d	H		Me, CO_2Et	**9d** 58%

* **9a** R^3= Ph R^4= Me 28%, **9a'** R^3= Me R^4= Ph 11%

The second reaction was the copper(II)-catalyzed formation of pyrroles from vinyl azides and *β*-keto esters. By the use of copper(II) triflate as catalyst and ethyl acetoacetate as a nucleophile, pyrrole **10** was obtained in preference over its thermally generated regioisomer **9**. In this reaction, the addition of water improved the yield significantly. Also, the use of isobutyronitrile as a solvent brought the reaction to completion. It is postulated that the *β*-keto ester attacks at the *β* position of the vinyl azide to give the corresponding pyrrole **10**. The role of the copper catalyst in the reaction is yet unclear. The C-2 and C-3 substituents of the product were exchanged in comparison with the thermally produced regioisomer **9b**.



entry	*β*-ketoester	additive	solvent	conditions	**10** /%	**7a** /%
1	1.2	none	CH_3CN	8 h, 60 °C	34	34
2	1.2	H_2O (5.0)	CH_3CN	16 h, 60 °C	55	18
3	3.0	H_2O (5.0)	CH_3CN	13 h, 60 °C	71	23
4	3.0	H_2O (5.0)	CH_3CN	30 h, 40 °C	78	21
5	3.0	H_2O (5.0)	*i*-PrCN	22 h, 40 °C	80	-

References

1 (a) D. O'Hagan, *Nat. Prod. Rep.*, **2000**, *17*, 435 and references therein. (b) J. W. Daly, T. F. Spende, S. W. Pelletier, *Alkaloids: Chemical and Biological Perspectives,* Wiley, New York, **1986**.

2 Few selected examples: (a) J. D. White, Q. Xu, C. -S. Lee, F. A. Valeriote, *Org. Biol. Chem.* **2005**, *2*, 2092 (b) J. K. Whitesell, *Chem. Rev.* **1989**, *89***,** 1581. (c) M. Nyerges, D. Bendell, A. Arany, D. E. Hibbs, S. J. Coles, M. B. Hursthouse, P. W. Groundwater, O. Meth-Cohn *Synlett* **2003**, 947.

3 P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138 and references herein.

4 Few selected examples: (a) L. Hoang, S. Bahmanyar, K. N. Houk, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 16. (b) C. J. Rogers, T. J. Dickerson, A. P. Brogan, K. D. Janda, *J. Org. Chem.* **2005**, *70*, 3705. (c) F. Fache, E. Schultz, M. L. Tommasino, M. Lemaire. *Chem. Rev.* **2000**, *100*, 2159. (d) L. A. Paquette, *Chiral Reagents for Asymmetric Synthesis*, Wiley, Chichester, **2003**.

5 X. Tian, T. B. Field, A. G. Switzer, A. W. Mazur, F. H. Ebetino, J. A. Wos, S. M. Berberich, L. R. Jayasinghe, C. M. Obringer, M. E. Dowty, B. B. Pinney, J. A. Framer, *J. Med. Chem.* **2006**, *49*, 4745.

6 A. A. Raj, R. Raghunathan, M. R. SrideviKumari, N. Raman, *Bio. Med. Chem.* **2003**, *11*, 407.

7 M. Pichon, B. Figadere, *Tet. Asymm.* **1996**, *7*, 927.

8 M. Paulsen, I. Sangster, K. Heyns, *Chem. Ber.* **1967**, *100*, 802. For other examples, see: (a) S. E. Denmark, L. E. Marcin, *J. Org. Chem.* **1995**, *60*, 3221. (b) J. Gebauer, P. Dewi, S. Blechert, *Tet. Lett.* **2005**, *46*, 43. (c) K. M. Brinner, J. A. Ellman, *Org. Bio. Chem.* **2005**, *3*, 2109.

9 J. E. Backvall, H. E. Schink, Z. D. Renko, *J. Org. Chem.* **1990**, *55*, 826. For other examples, see: (a) D. Craig, P. S. Jones, G. J. Rowlands, *Synlett* **1997**, 1423. (b) I. S. Young, J. L. Williams, M. A. Kerr, *Org. Lett.* **2005**, *7*, 953.

10 For a review see: T. E. Muller, M. Beller, *Chem. Rev* **1998**, *98*, 675.

11 Few selected examples: (a) G. B. Bajracharya, Z. Huo, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 4883. (b) S. R. Fix, J. L. Brice, S. S. Stahl, *Angew. Chem. Int. Ed*, **2002**, *41*, 164.

12 For a review see: S. Hong, T. J. Marks, *Acc. Chem. Res.* **2004**, 37*, 673.*

13 Few selected examples: (a) M. Shi, L. Liu, J. Tang, *Org. Lett.* **2006**, *8*, 4043. (b) X. Han, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2006**, *45*, 1747.

14 For a example, see: C. F. Bender, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2005**, *127*, 1070.

15 For an example, see: T. Kondo, T. Okada, T. Mitsudo, *J. Am. Chem. Soc.* **2002**, *124*, 186.

16 For some selected examples see: (a) P. D. Pohlhaus, R. K. Bowman, J. S. Johnson, *J. Am. Chem. Soc.* **2004**, *126*, 2294. (b) S. Peddibholta, J. J. Tepe, *J. Am. Chem. Soc.* **2004**, *126*, 12776.

17 For some selected examples see: (a) E. Nakamura, S. Yamago, *Acc. Chem. Res.* **2002**, *35*, 867. (b) M. Lautens, W. Han, *J. Am. Chem. Soc.* **2002**, *124*, 6312. (c) C. Marti, E. M. Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 11505. (d) Y. Kang, Y. Tang, X. Sun, *Org. Biomol. Chem.* **2006**, *4*, 299.

18 O. Dogan, H. Koyuncu, P. Garner, A. Bulut, W. J. Youngs, M. Panzner, *Org. Lett.* **2006**, *8*, 4687.

19 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.,* **1976**, 734; J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman and R. C. Thomas, *J. Chem. Soc., Chem. Commun.,* **1976**, 736; J. E. Baldwin, R. C. Thomas, L. Kruse and L. Silberman, *J. Org. Chem.*, **1977**, 42, 3846.

20 A. R. Katritzky, C. W. Rees, E. F. V. Scriven, *Comprehensive Heterocyclic Chemistry II: Volume 2*, Pergamon, 1.

21 U. Niewoehner, M. Bauser, J. Ergueden, D. Flubacher, P. Naab, T. Repp, J. Stoltefuss, N. Burkhardt, A. Sewing, M. Schauer, K. Schlemmer, O. Weber, S. J. Boyer, M. Miglarese, S. Ying, *PCT. Int. Appl.* **2003**, 89p.

22 N. Fujikawa, T. Ohta, T. Yamaguchi, T. Fukuda, F. Ishibashi, M. Iwao, *Tetrahedron* **2006**, *62*, 594.

23 K. Hiroya, S. Matsumoto, M. Ashikawa, H. Kida, T. Sakamoto, *Tetrahedron,* **2005**, *61*, 12330.

24 (a) A. Treibs, R. Schmidt, R. Zinsmeister, *Chem. Ber.,* **1957**, *90*, 79. (b) S. K. Khetan, M. V. George, *Tetrahedron*, **1969**, *25*, 527.

25 (a) H. Walizei, E. Breitmaier, *Synthesis*, **1989**, 337. (b) J. B. Paine III, J. R. Brough, K. K. Buller, E. E. Erikson, *J. Org. Chem.,* **1987**, *52*, 3986.

26 P. R. Bovy, D. B. Reitz, J. T. Collins, T. S. Chamberlain, G. M. Olins, V. M. Corpus, E. G. McMahon, M. A. Palomo, J. P. Koepke, G. J. Smits, D. E. McGraw, J. F. Gaw, *J. Med. Chem.,* **1993**, *36*, 101.

27 J. Boberg, K-H. Garburg, K-J. Gorlich, B. Pipereit, M. Ruhr, *Liebigs. Ann. Chem.,* **1985**, 239.

28 K. Utimoto, H. Miwa, H. Nozaki, *Tet. Lett.,* **1981**, *43*, 4277.

29 M. Kitamura, K. Narasaka, *Chemical Records* **2002**, *2*, 268.

30 S. Kamijo, C. Kanazawa, Y. Yamamoto, *J. Am. Chem. Soc.* **2005***, 127*, 9260.

31 For a recent review, see: (a) D. W. Knight, "Progress in Heterocyclic Chemistry," ed. By G. W. Gribble and T. L. Gilchrist, Pergamon, Amsterdam, 2002, Vol. 14, Chap. 2. For recent reports, see: (a) A. D. Jones, A. L. Redfern, D. W. Knight, I. R. Morgan, A. C. Williams, *Tetrahedron*, **2006**, *62*, 9247. (b) N. S. Karanjule, S. D. Markad, V. S. Shinde, D. D. Dhavale, *J. Org. Chem*. **2006**, *71*, 4667. (c) A. D. Jones, W. Knight, *Chem. Comm*, **1996**, 915. (d) Y. Landais, D. Planchenault, *Synlett*, **1995**, 1991. (e) B. H. Lipshutz, T. Gross, *J. Org. Chem.* **1995**, *69*, 3572. (f) M. Kimura, H. Harayama, S. Tanaka, Y. Tamaru, *Chem. Comm.* **1994**, 2531.

32 For recent reports, see: (a) A. J. Clark, C. P. Dell, J. M. McDonagh, J. Geden and P. Mawdsley, *Org. Lett.*, **2003**, *5*, 2063; (b) C. Chatgilialoglu, C. Ferreri, M. Guerra, V.

Timokhin, G. Froudakis and T. Gimisis, *J. Am. Chem. Soc.,* **2002**, *124*, 10765. For recent reviews, see: (a) H. Ishibashi, *Chem. Rec.*, **2006**, *6*, 23; (b) H. Ishibashi, T. Sato and M. Ikeda, *Synthesis*, **2002**, 695; (c) A. F. Parsons, *C. R. Acad. Sci.,* **2001**, *4*, 391.

33 M. C. Marcotullio, V. Campagna, S. Sternativo, F. Costantino, M. Curini, *Synthesis* **2006**, *16*, 2760.

34 H. Ishibashi, H. Matsukida, A. Toyao, O. Tamura, Y. Takeda, *Synlett* **2000**, *10*, 1497.

35 J. Ichikawa, Y. Wada, M. Fujiwara and K.Sakoda, *Synthesis*, **2002**, 1917 and references therein. See also: (a) J. Clayden, D. W. Watson, M. Helliwell, and M. Chambers, *Chem. Comm.*, **2003**, 2582. (b) R. Naitoh, Y. Nakamura, E. Katano, Y. Nakamura, E. Okada and M. Asaoka, *Heterocycles,* **2004**, *63*, 1009.

36 P. Auvray, P. Knoechel, F. J. Normant, *Tet. Lett.* **1985**, *26*, 4455.

37 M. B. Berry, D. Craig, P. S. Jones, G. J. Rowlands, *Chem. Comm.,* **1997**, 2141.

38 (a) J. Ichikawa, R. Nadano, Y. Iwai, T. Mori, *J. Org. Chem.*, **2006**, *71*, 8748. (b) J. Ichikawa, T. Mori, Y. Iwai, *Chem. Lett.*, **2004**, *33*, 1354.

39 Yu Iwai's master thesis, University of Tokyo, **2003**.

40 For an example, see: J. Robertson, J. W. P. Dallimore, P. Meo, *Org. Lett.,* **2004**, *6*, 3857.

41 S. Hanessian, H. Park, R. Yang, *Synlett.*, **1997**, 351.

42 O. Mitsunobu, *Synthesis*, **1981**, 1.

43 For an example, see: H. Mizutani, M. Watanabe, T. Honda, *Tetrahedron*, **2002**, *58*, 8929.

44 For an example, see: M. M. Kabat, L. M. Garofalo, A. R. Daniewski, S. D. Hutchings, W. Liu, M. Okabe, R. Radinov, Y. Zhou, *J. Org. Chem.,***2001**, *66*, 6141.

45 For an example, see: C. Pedregal, W. Prowse, *Bioorg. Med. Chem.,* **2002**, *10*, 433.

46 T. Fukuyama, C.-K. Jow, M. Cheung, *Tet. Lett.* **1995**, *36*, 6373.

47 T. Ohwada, I. Okamoto, K. Shudo and K. Yamaguchi, *Tet. Lett.* **1998**, *39*, 7877.

48 For a review, see: S. Brase, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem. Int. Ed.* **2005**, *44*, 5188.

49 For some recent reports, see: (a) B. E. Blass, K. R. Coburn, A. L. Faulkner, W. L. Seibela, A. Srivastava, *Tet. Lett.* **2003**, *44*, 2153. (b) S. Roper, M. H. Franz, R. Wartchow, H. M. R. Hoffmann, *Org. Lett.* **2003**, *5*, 2773.

50 R. Huisgen, *J. Org. Chem.* **1968**, *33*, 2291. For a recent report, see: Z. P. Demko, K. B. Sharpless, *Org. Lett.* **2002**, *4*, 2525.

51 For a recent report, see: A. S. Timen, E. Risberg, P. Somfai, *Tet. Lett.* **2003**, *44*, 5339.

52 A. R. Katritzky, C. W. Rees, E. F. V. Scriven, *Comprehensive Heterocyclic Chemistry II: Volume 1A*, Pergamon, 1. For a recent review, see: F. Palacios, A. M. O. Retana, E. M. Marigorta, J. M. los Santos, *Eur. J. Org. Chem.* **2001**, 2401.

53 For a review, see: B. C. G. Soderberg, *Curr. Org. Chem.* **2000**, *4*, 727.

54 A. Hassner, F. W. Fowler, *J. Am. Chem. Soc.* **1968**, *90*, 2869.

55 R. M. Carlson, S. Y. Lee, *Tet. Lett.* **1969**, *45*, 4001.

56 N. J. Leonard, B. Zwanenburg, *J. Am. Chem. Soc.* **1967**, *89*, 4456.

57 G. Smolinsky, B. I. Feuer, *J. Org. Chem.* **1966**, *31*, 1423.

58 M. J. Alves, P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro, T. L. Gilchrist, *Tet. Lett.* **2000**, *41*, 4991.

59 C. A. Ray, E. Risberg, P. Somfai, *Tetrahedron* **2002**, *58*, 5983.

60 D. F. Taber, W. Tian, *J. Am. Chem. Soc.* **2006**, *128*, 1058. For some previous reports, see: (a) K. Isomura, G. Ayabe, S. Hatano, H. Taniguchi, *J. Chem. Soc., Chem. Comm.* **1980**, 1252. (b) L. A. Wendling, R. G. Bergman, *J. Org. Chem.* **1976**, *41*, 831.

61 S. Chiba, G. Hattori, K. Narasaka, *Chem. Lett.* **2007**, *36*, 52. For a report using $PdCl_2(PhCN)_2$ as calatyst, see: K. Isomura, K. Uto, H. Taniguchi, *J. Chem. Soc., Chem. Comm.* **1977**, 664.

62 D. Knittel, *Synthesis* **1985**, 186.

63 M. S. Tichenor, J. D. Trzupek, D. B. Kastrinsky, F. Shiga, I. Hwang, D. L. Boger, *J. Am. Chem. Soc.* **2006**, *128*, 15683. For some other examples, see: (a) R. E. Bolton, C. J. Moody, C. W. Rees, G. Tojo, *J. Chem. Soc., Perkin Trans. 1* **1987**, *109*, 931. (b) D. L. Boger, R. S. Coleman, *J. Am. Chem. Soc.* **1987**, *109*, 2717. (c) J. K. MacLeod, A. Ward, A. C. Willis, *Aust. J. Chem.* **1998**, *51*, 177. (d) J. K. Macleod, L. C. Monahan, *Tet. Lett.* **1988**, *29*, 391.

64 K. W. Law, T-F. Lai, T. C. W. Mak, M. P. Sammes, A. R. Katritzky *J. Chem. Soc., Perkin Trans. I* **1984**, *106*, 111. For another example, see: G. L'abbe, P. V. Stappen, J-P. Dekerk, *J. Chem. Soc., Chem. Comm.* **1982**, 784.

65 V. Nair, T. G. George, *Tet. Lett.* **2000**, *41*, 3199.

66 T. L. Gilchrist, R. Mendonca, *Synlett* **2000**, *12*, 1843.

67 D. B. Rorabacher, *Chem. Rev.* **2004**, *104*, 651.

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Synthesis of 5-Membered Azaheterocycles by Nucleophilic 5-*endo-trig* Cyclizations of *N*-Homoallylic Sulfonamides and Reactions of Vinyl Azides with 1,3-Dicarbonyls

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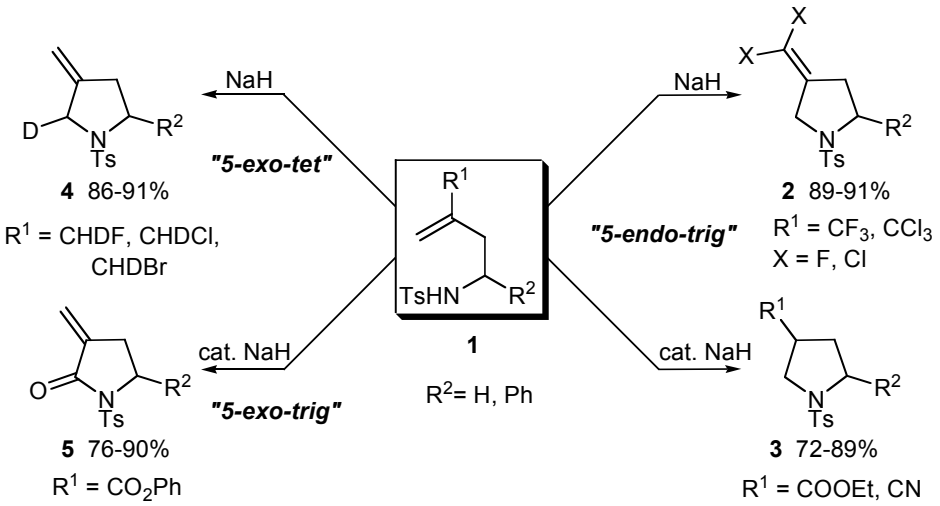
5-Membered azaheterocycles, such as pyrrolidine and pyrrole derivatives, are widely present in bioactive natural products, drugs and functional materials. The overall usefulness of these heterocycles brought tremendous synthetic efforts in the past century. Whereas many synthetic methods for these rings have been developed, polysubstituted pyrroles and pyrrolidines remains difficult to obtain, and new synthetic routes are still needed. I envisioned two strategies for the synthesis of 5-membered azaheterocycles. (1) Although nucleophilic 5-*endo-trig* cyclizations are disfavored according to Baldwin's rules, it would be achieved by using the suitable combination of nucleophile moiety and substituent on the alkene part, thus affording pyrrolidine rings efficiently. (2) Vinyl azide would serve as a versatile building block in the synthesis of polysubtituted pyrroles by the reaction with 1,3-dicarbonyl compounds. Herein is my report on the synthesis of these heterocycles.

(1) Nucleophilic 5-*endo-trig* cyclizations of *N*-homoallylic sulfonamides

One potential approach to the synthesis of pyrrolidines involves an intramolecular addition of *N*-nucleophile to an alkene moiety in a *5-endo-trig* fashion. This type of cyclization is geometrically disfavored and examples in the literatures are scarce. When trihalomethyl group was used as electron withdrawing group attached to the alkene, sulfonamide **1** undergoes the *5-endo-trig* cyclization in the presence of stoiechiometric NaH in DMF. With *α,β*-unsaturated carbonyl moiety, the *5-endo-trig* cyclization also proceeds with a catalytic amount of NaH in DMF. By changing the *α,β*-unsaturated ester moiety from ethyl to phenyl ester, the *5-endo/5-exo* regioselectivity was inverted and lactam **5** was obtained.

Scheme 1.



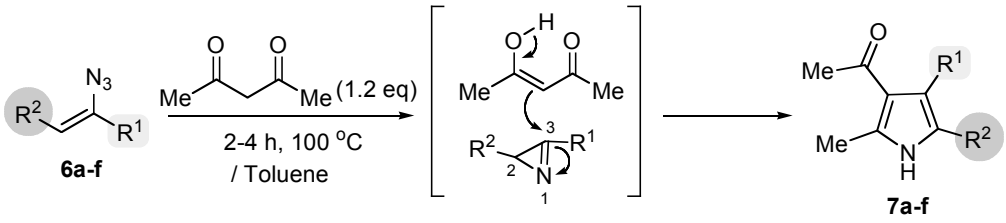
Of several *N*-nucleophiles screened, *N*-tosylamide proved to be the most efficient one for the *5-endo-trig* cyclization. By choosing the appropriate nucleophile (*N*-sulfonamide), electron-withdrawing group and reaction conditions, the 5-*endo-trig* cyclization could be achieved efficiently.

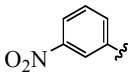
(2) Reactions of Vinyl Azides with 1,3-Dicarbonyls

The development of synthetic methods for polysubstituted pyrroles having different substitution pattern, starting from a common simple substrate, is highly valuable in organic synthesis. It was found that, depending on the reaction conditions, 1,3-dicarbonyls can add to different carbon centers of the vinyl azides to afford a variety of pyrroles.

The first approach involves the thermal construction of polysubstituted pyrroles from vinyl azides and 1,3-diketones. In this reaction, 2*H*-azirine generated *in situ* thermally from vinyl azides are attacked by 1,3-diketones such as acetylacetone at the C-3 carbon, affording pyrroles **7**.

Scheme 2.

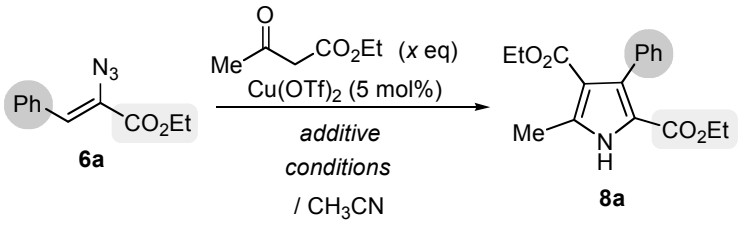


entry		R^1	R^2	**7** /%
1	**6a**	CO_2Et		**7a** quant.
2	**6b**	CO_2Et		**7b** 86%
3	**6c**	CO_2Et		**7c** 96%

entry		R^1	R^2	**7** /%
4	**6d**	H		**7d** 75%
5	**6e**	COMe		**7e** 54%
6	**6f**	CO_2Bn	H	**7f** 77%

The second approach involves the copper(II)-catalyzed reaction of vinyl azide with *β*-ketoester. While the thermal reaction proceed well with acetylacetone, the addition of other 1,3-diketones and *β*-ketoesters is sluggish, and additives such as Lewis acid and base did not improve the yield. On the other hand, using copper(II) triflate as additive and ethyl acetoacetate as a nucleophile, pyrrole **8a** was obtained in preference over the thermal addition pyrrole **7**. In this reaction, the addition of water improved the yield significantly. It is postulated that the *β*-ketoester attacks at the *β* position of the Cu-activated vinyl azide to give the corresponding pyrrole **8a**. The C-2 and C-3 substituents of the product are inverted in comparison with the thermally produced pyrrole **7**.

Scheme 3.



β-ketoester	additive	conditions	**8a** /%
1.2 eq.	none	8 h, 60 °C	34
1.2 eq.	H_2O (5.0 eq)	16 h, 60 °C	55
3.0 eq.	H_2O (5.0 eq)	13 h, 60 °C	71
3.0 eq.	H_2O (5.0 eq)	30 h, 40 °C	78