Studies on Reactions of Cyclopropanated Pyrrole: Synthesis of Bis-β-homoproline, Tropane- and Pyrrolidinone-derivatives

Dissertation

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나의 가족

und für Familie Ertl

Abbreviations

Å	angstrom
p-ABSA	4-cetamidobenzenesulfonyl azide
Ac	acetyl
AcOH	acetic acid
adm	adamantyl
AIBN	2,2'-azobis(2-methylpropionitrile)
aq	aqueous
Ar	aryl
atm	atmospheric pressure
9-BBN	9-borabicyclo[3,3,1]nonane
BINAP	(1,1'-binaphthalene-2,2'-diyl)bis(diphenylphosphine)
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bp	boiling point
brine	saturated NaCl solution
Bz	benzoyl
^{o}C	degrees Celsius
Cbz	carboxybenzyl
cod	1,5-cyclooctadiene
conc.	concentrated
COSY	correlation spectroscopy
*m*CPBA	3-chloroperbenzoic acid
cm^{-1}	wavenumbers
Cy	cyclohexyl
d	day(s)
DBU	diazabicycloundecene
DABCO	1,4-diazabicyclo[2,2,2]octane
DBAD	di-*tert*-butyl azodicarboxylate
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DEAD	diethyl acetylenedicarboxylate
DEPT	distortionless enhancement by polarization transfer
DIB	(diacetyoxyiodo)benzene (=PIDA)
DIBAL-H	diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	dimethyl phthalate
DMSO	dimethyl sulfoxide
dppp	1,3-bis(diphenylphosphino) propane
dr	diastereomeric ratio
EA	ethyl acetate
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
equiv	equivalent(s)
EWG	electron-withdrawing
Et	ethyl
FT	Fourier transform
h	hour(s)

HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HIV	acquired immune deficiency syndrome
HRMS	high resolution mass spectroscopy
HPLC	high performance liquid chromatography
Hz	Hertz
i-Pr	*iso*-propyl
IPr	1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene
IR	infrared
L	ligand
LAH	lithium aluminum hydride
Me	methyl
Mes	2,4,6-trimethylphenyl
MeCN	acetonitrile
MHz	mega Hertz
min	minute
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
MS (4Å)	molecular sieves
MW	microwave
NBS	*N*-bromosuccinimide
n-BuLi	*n*-butyllithium
NMI	1-methylimidazole
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
NSAID	nonsteroidal anti-inflammatory drugs
Nu	nucleophile
p	*para*
PE	petroleum ether
PG	protecting group
Ph	phenyl
phen	phenanthroline
PIDA	phenyliodine diacetate (=DIB)
PIFA	[bis(trifluoroacetoxy)iodo] benzene
piv	2,2-dimethylpropanoyl
ppm	parts per million
pyr	pyridine
quant.	quantitative
ref.	reference
R_f	retention factor
rt	room temperature
sat.	saturated
t-Bu	*tert*-butyl
TBAB	tetrabutylammonium bromide
TEA	trimethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

v/v	volume to volume ratio	w/w	weight to weight ratio
wt%	weight percent		

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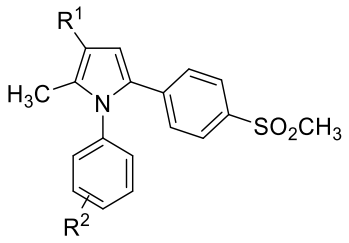
A. Introduction

1. Pyrrole Synthesis

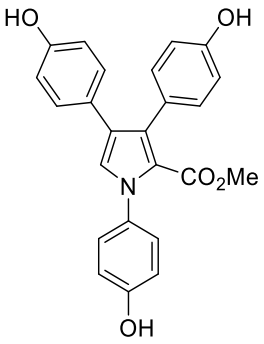
1.1. Pyrrole Natural Products

Heterocycles are abundantly found in natural products and are especially common subunits in vitamins, polyketides and alkaloids.[1] Amongst the heterocycles, the nitrogen-containing five membered aromatic ring, pyrrole, has been known to have distinctive pharmaceutical properties such as antipsychotic, anticancer, antibacterial, antifungal, antimalarial and many more (**Figure 1**).[2]

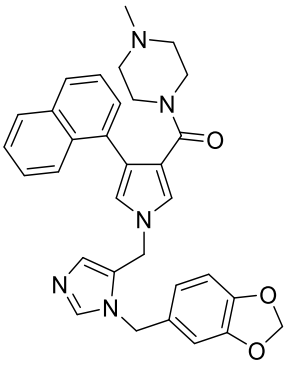
Pyrrole was first detected by F. F. Runge in 1834 as a constituent of coal tar.[3a] The reaction of spruce splint dampened with hydrochloric acid gave a red color of pyrrole. The very name, Pyrrole, comes from Greek word *pyrrhos* which means fiery or reddish.[3b] Pyrrole derivatives are found in various natural products and cofactors such as vitamin B_{12}, the porphyrins of heme, chlorophyll. Due to the broad utility, there have been developed numbers of efficient and selective synthesis of pyrrole and its derivatives.



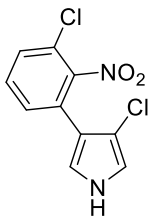
NSAIDs (**1**)[2b]
nonsteroidal anti-inflammatory drugs



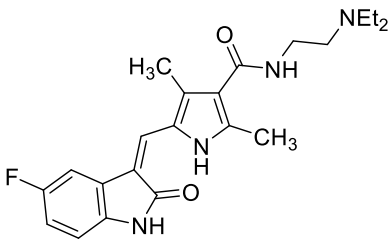
Lamellarin R (**2**)[2a, 2d]
antitumor and anti-HIV agent



LB42908 (**3**)[2e]
antitumor agent



Pyrrolinitrin (**4**)[2g, 2i]
antibiotic agent

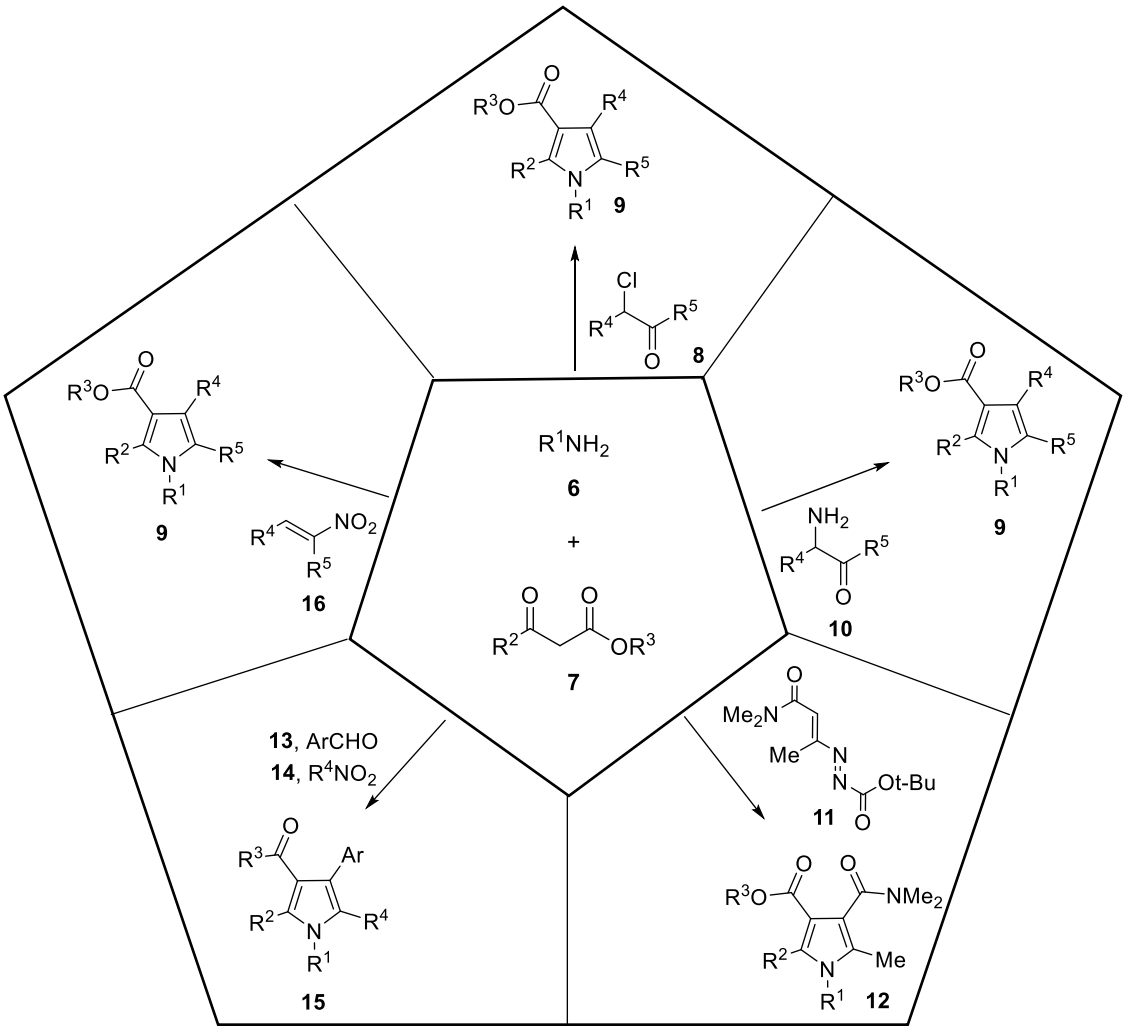


Sunitinib (**5**)[2a]
cholesterol-lowering agent

Figure 1. Various Pyrrole Natural Products

Pyrrole fragments are particularly common in marine natural products. Nonsteroidal anti-inflammatory drugs (NSAIDs) (**1**) can reduce inflammation effectively and relieve pain. However, the side effects traditional NSAIDs (tNSAIDs) have the risk of upper gastrointestinal bleeding.[2b] To circumvent this disadvantage, the synthesized NSAIDs (**1**) were examined *in vitro* and the results have shown that **1** show more anti-nociceptive activity compared to other NSAIDs. Other natural products of marine origin are Lamellarins and non-fused form of Lamellarins, Lamellarin R (**2**) and **2** exhibits antitumor and anti-HIV activities.[2a] Furthermore, LB42908 (**3**) has also proven to be effective in farnesylation inhibition and preclinical studies of **3** are currently ongoing. Next pyrrole substance is Pyrrolnitrin (**4**) which is isolated from the bacterial cells of a *Pseudomonas pyrrocinia* and known to possess antifungal, antibiotic properties. **4** is also highly active against dermatophytes.[2g, 2i] The last compound, Sunitinib (**5**) is an unnatural pyrrole-derived drug which has been used for the oral treatment of renal cancer.[2a]

1.2. Pyrrole Synthesis from β-keto carbonyl compound

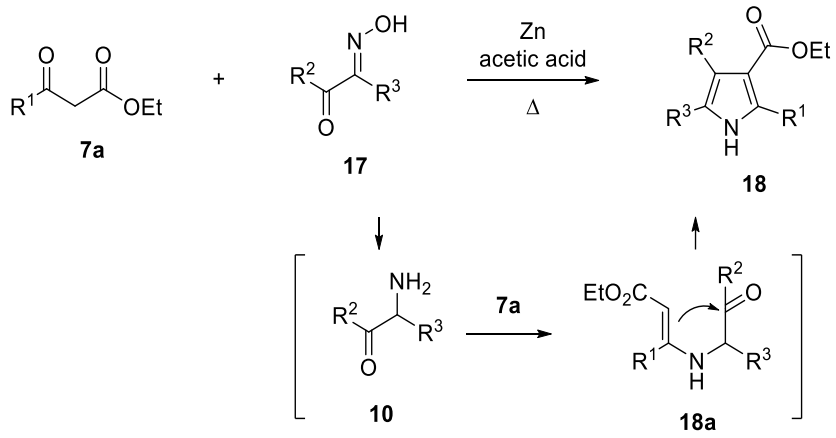


Scheme 1. Pyrrole Synthesis from β-keto carbonyl compound

The pyrrole synthesis involving β-keto carbonyl compound has a long history since late 19th century. Common synthetic pathways involve β-keto carbonyl compound **7** with amine **6** or ammonia which are readily transformed into corresponding enamine species (**Scheme 1**). This enamine attacks added electrophile followed by the cyclization and rearomatization to form various pyrrole derivatives.

1.2.1. Knorr Pyrrole Synthesis

In 1884, Ludwig Knorr had published the synthesis of pyrrole derivatives from β-ketoester **7a** and α-amino-β-ketoester **10** (Knorr pyrrole synthesis, **Scheme 2**).[4c] By the attack of the amine moiety of α-amino-β-ketoester **10** to the activated ketone of β-ketoester **7a**, two components are combined in **18a** and readily cyclizes to afford the tetrasubstituted pyrrole **18**. Since α-amino-β-ketoester **10** tends to self-condense very easily, **10** has been to be prepared *in situ* by reducing the oximoacetoacetate **17** with Zn in glacial acetic acid.

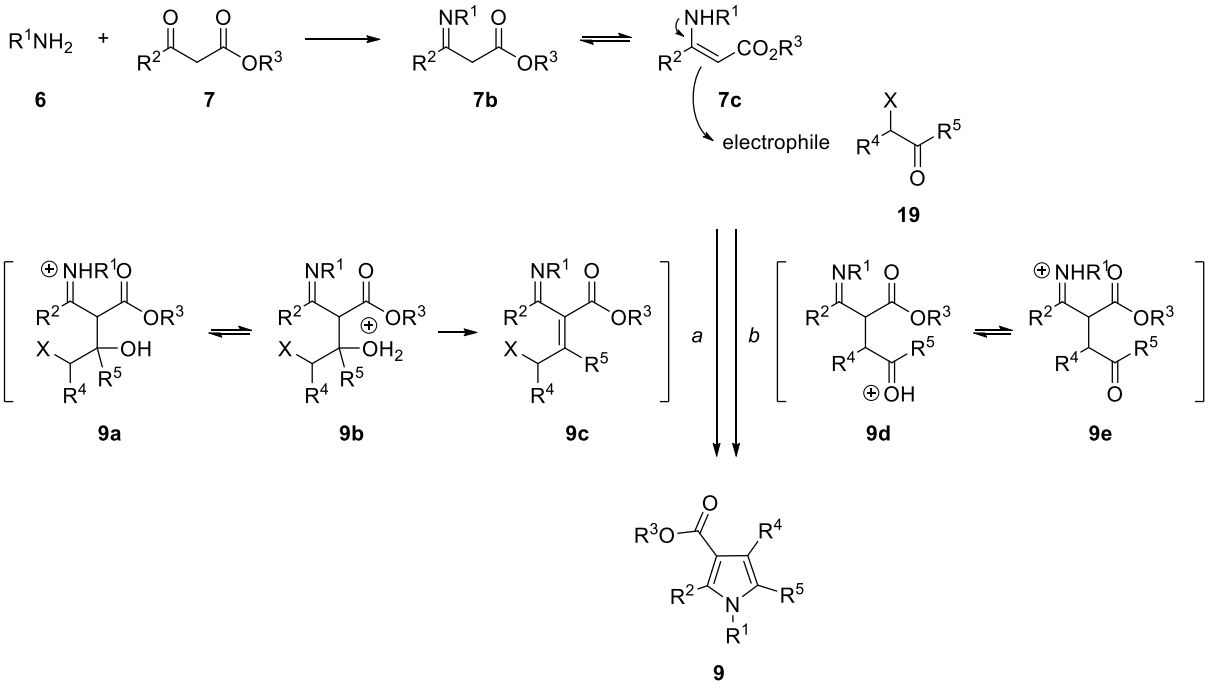


Scheme 2. Knorr Pyrrole Synthesis

1.2.2. Hantzsch Pyrrole Synthesis

One of the representative pyrrole synthesis is the Hantzsch pyrrole synthesis which was first published in 1890.[5i] In Hantzsch synthesis, the substituent X of electrophile **19** typically bears halogen group and in some cases, hydroxyl group. As shown in the **Scheme 3**, the ketone moiety of β-ketoester **7** reacts with amine first to generate the enamine species **7b** and **7b** attacks either the carbonyl group of the electrophile **19** or substitutes the leaving group X. With appropriate activation of the electrophile, the addition can be controlled. For the carbonyl group activation, there has been a reaction promoted by the Lewis acid, $Yb(OTf)_3$[5d] to afford the species **7b** (*b*, **Scheme 3**) and to promote the substitution (*a*, **Scheme 3**), there have been examples where

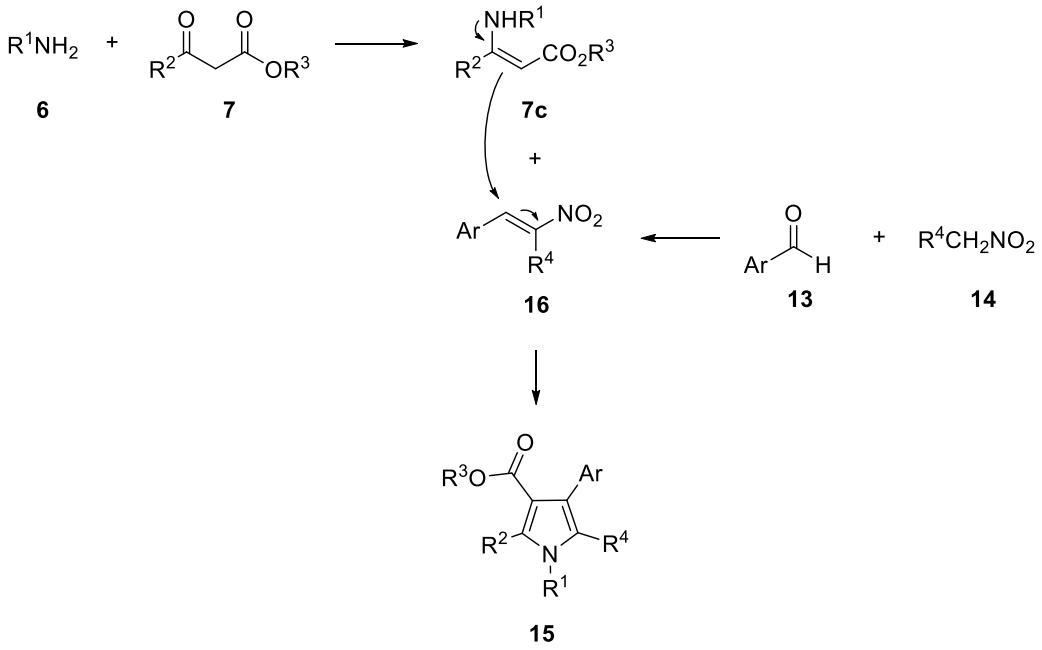
iodine or bromine were introduced to the molecule.[5a, 5h] When X is hydroxyl group, the reaction contains NH_4OAc instead of amine species **6** and without catalyst or solvent, the reaction smoothly proceeded to afford the substituted pyrrole **9**.[5b, 5c, 5f, 5g] Moreover, amine base such as DABCO[5e] reacts with **7** first in order to introduce a better leaving group and prompts the subsequent substitution to give the reaction species **9b**.



Scheme 3. Hantzsch Pyrrole Synthesis
(*a*: transformation via nucleophilic substitution, *b*: enamine pathway)

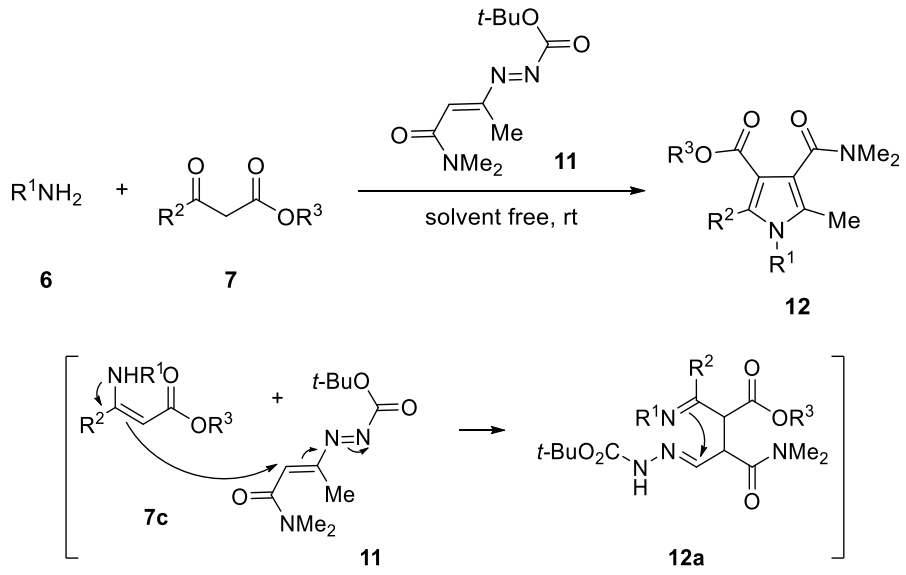
1.2.3. Pyrrole Synthesis via Michael Addition to Nitroalkenes

It was in 1953 that the reaction between the amine **6**, β-ketoester **7** and nitroalkene **16** was published by Grob and Camenisch.[6i] The first important step here is also the formation of the enamine **7b** from β-ketoester **7** and amine **6** which is followed by the Michael addition of the tautomerized enamine species **7c** to the nitroalkene **16** to afford the tetrasubstituted pyrrole **15** (**Scheme 4**). The reactions were promoted by catalyst or additive such as Zr[6a], Co[6b], Fe[6f, 6g] and Ce[6c, 6e] as metal catalyst and DIB[6d] or TFA[6h] as an additive. However, due to the unstable character of the nitroalkene, some reactions employed *in situ* generation of the nitroalkene **16** by combining nitroalkane **14** and aldehyde **13** with a catalyst such as metals,[7b 7i-7n] organocatalysts,[7a] iodine,[7k] montmorillonite clay,[7h] gluconic acid aqueous solution (GAAS)[7g] and heterogeneous ones [7c, 7d, 7f, 7h] or even catalyst free in an ionic liquid[7e].



Scheme 4. Pyrrole Synthesis via Michael Addition to Nitroalkene **16**

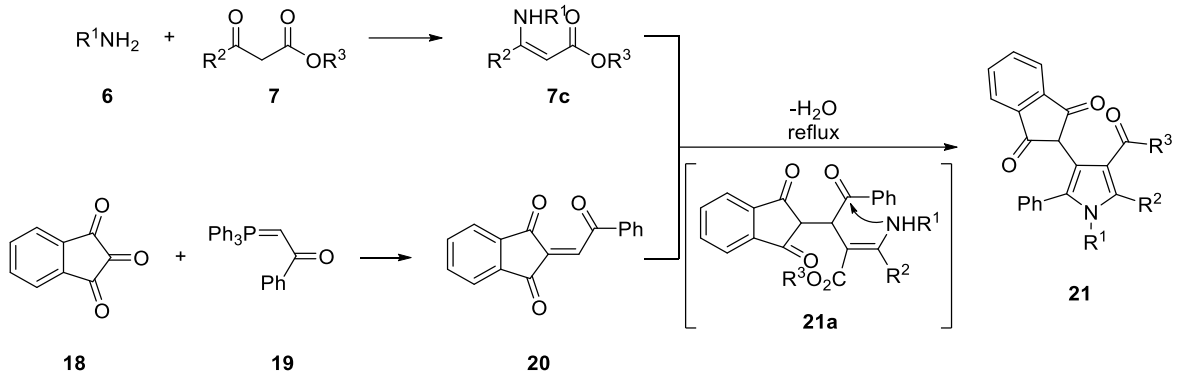
1.2.4. Pyrrole Synthesis from Other Electrophiles



Scheme 5. Pyrrole Synthesis from Diazadiene **11**

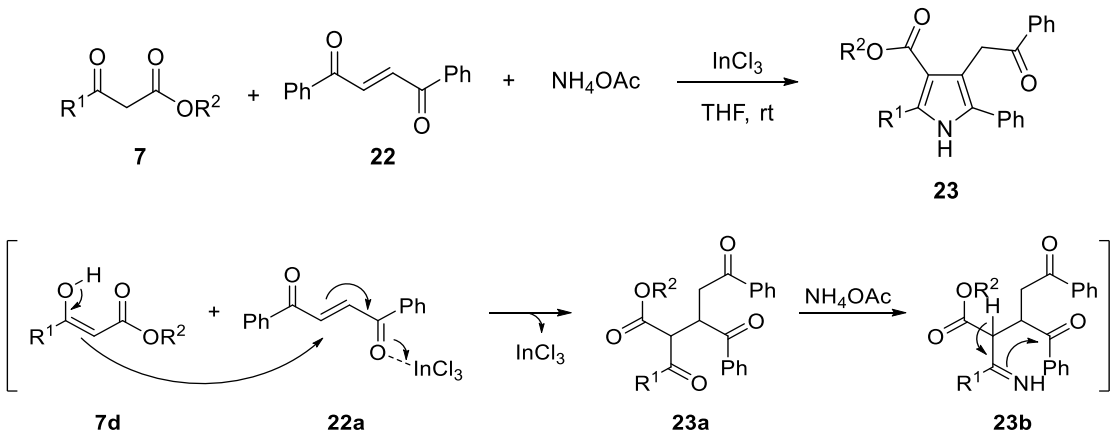
Still there have been lots of pyrrole synthesis reactions where different electrophiles were applied in presence of β-ketoester **7** and amine **6**. Similar to the reactions above, most reactions are also initiated by the formation of enamine **7c** from β-ketoester **7** and amine **6**. The electrophiles are various from Michael acceptors such as **11** in **Scheme 5**[8] to the intermediate generated from

ninhydrin **18** and phosphanylidene **19** in **Scheme 6**.[9] The enamine **7c** undergoes a Michael addition by attacking these electrophiles which initiates the cyclization to form the pyrrole **21**.



Scheme 6. Pyrrole Synthesis from Ninhydrin **18** and Phosphanylidene **19**

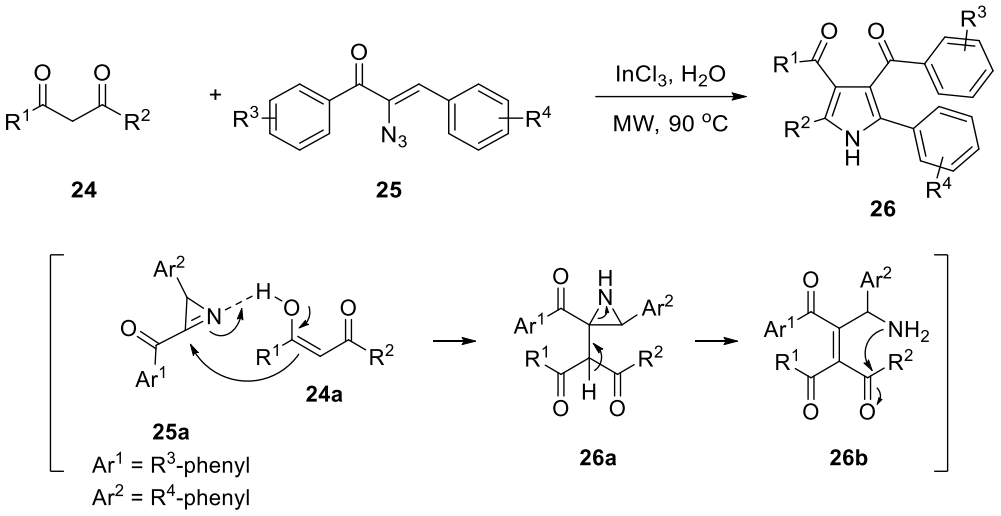
Meanwhile in 2013, Jaisankar *et al.* published their work on $InCl_3$-catalyzed synthesis of 2-pyrone and pyrrole.[10] In the process, tetrasubstituted pyrrole **23** was obtained when dibenzoylethylene **22** and NH_4OAc were used (**Scheme 7**). The reaction is initiated by the tautomerization of β-ketoester **7** to **7d** followed by the Michael addition to **22** and cyclization follows. The catalyst, $InCl_3$ is activating the carbonyl group of the Michael acceptor **22** which results in formation of the intermediate **22a**. NH_4OAc then reacts with the more reactive ketone moiety in **23a** and forms **23b** to give the final pyrrole product **23**.



Scheme 7. Pyrrole Synthesis from β-ketoester **7**, Dibenzoylethylene **24** and NH_4OAc

The last example in this chapter is not a multicomponent reaction but a reaction of 1,3-diketone **24** with α-azidochalcones **25** with $InCl_3$ or $Cu(acac)_2$ as a catalyst in water.[11] As like the reactions above, this reaction is conducted under heat and the heat disassociates the azide **25** to aziridine

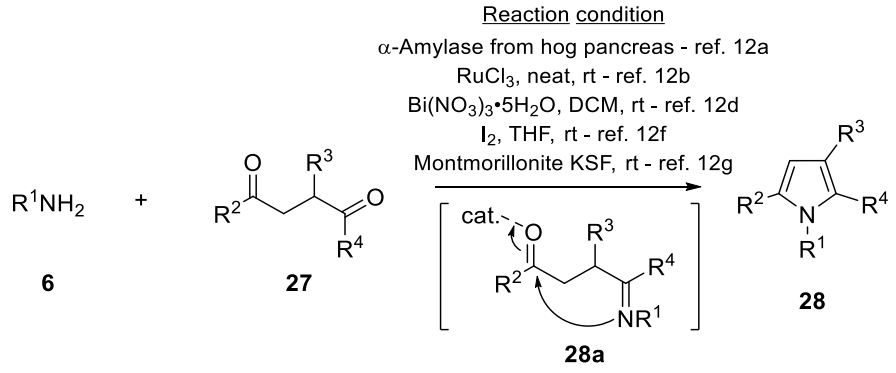
species **25a** which triggers the cyclization to pyrrole **26** via formation of intermediate **26a** and **26b** (**Scheme 8**).



Scheme 8. Pyrrole Synthesis from β-ketoester **24** and α-azidochalcone **25**

1.3. Paal-Knorr Pyrrole Synthesis

The Paal-Knorr pyrrole synthesis is one of the oldest synthetic tool to obtain various substituted pyrroles. The research was originally on the findings of furan synthesis from acetophenonoacetic acid ester by Paal and from diacetic acid ester by Knorr respectively.[12i, 12j] The reaction from the early study was mainly catalyzed by protic acid under the heat, however, the recently found reaction applies Lewis acid under milder condition such as at room temperature[12b, 12d] or in neat condition[12c, 12f] which makes the synthesis more utilizable in total synthesis.[13] The reactions are initiated by the reaction between amine **6** and 1,4-diketone **27** to generate the intermediate **28a** the imine moiety attacks the activated ketone to afford the substituted pyrrole **28** (**Scheme 9**).



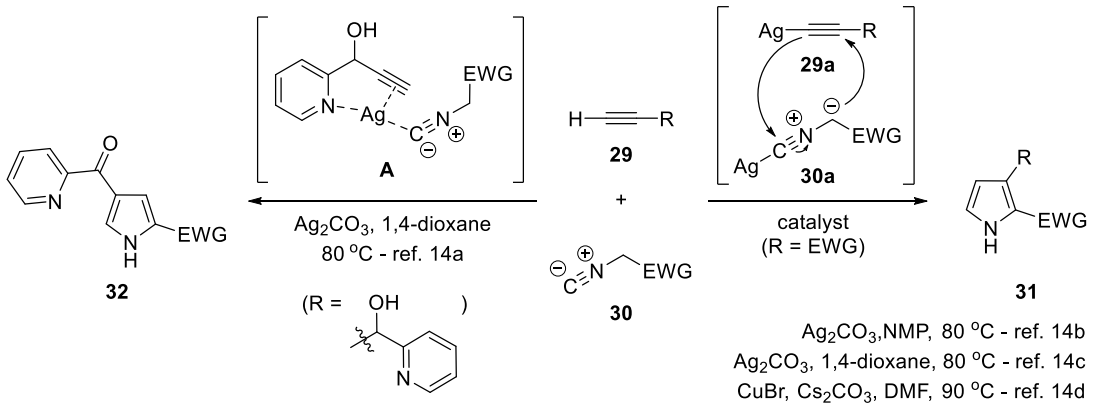
Scheme 9. Paal-Knorr Pyrrole Synthesis

1.4. Pyrrole Synthesis from Isocyanides

1.4.1. Pyrrole Synthesis via (3+2)-Cycloaddition of Isocyanides

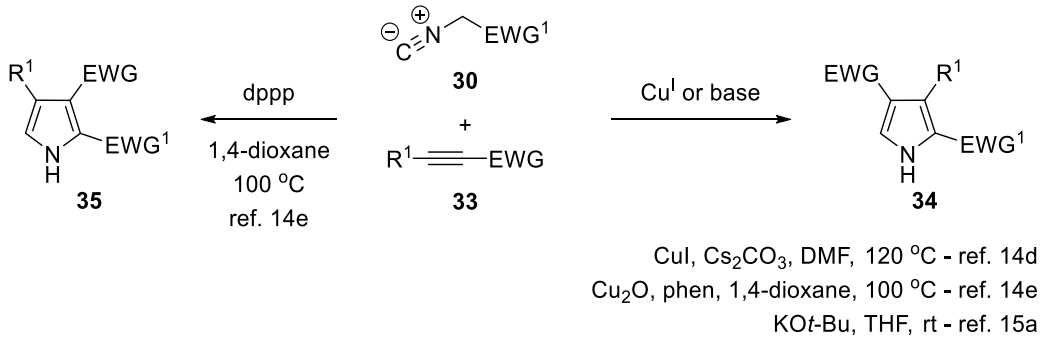
The pyrrole synthesis from isocyanides and alkyne species is one of the widely known and utilized method. It was not until 1968 that Schöllkopf and Gerhart had found that the α-proton of isocyanide **30** was abstracted and the resulting anion **30a** was generated.[14f] The α-position of isocyanide became nucleophilic and accommodated further reactions with carbon-carbon multiple bonds such as **29**.

In the reaction where inactivated terminal alkyne **29** is applied, often the terminal proton of the alkyne is substituted by the metal catalyst to generate **29a** (right, **Scheme 10**). Then the anion species **30a** reacts with **29a** in a cycloaddition manner to give **31**. The regioselectivity is controlled as **29a** and **30a** have polarized electron density by either bearing as charges or partial charges.[14b-14d] On the other hand, as the most commonly used catalyst, silver also coordinates the electron rich moiety of the reaction components such as the pyridine moiety in the intermediate **A** (left, **Scheme 10**). Then **A** undergoes cycloaddition, oxidation and gives pyrrole **32** regioselectively.[14a]



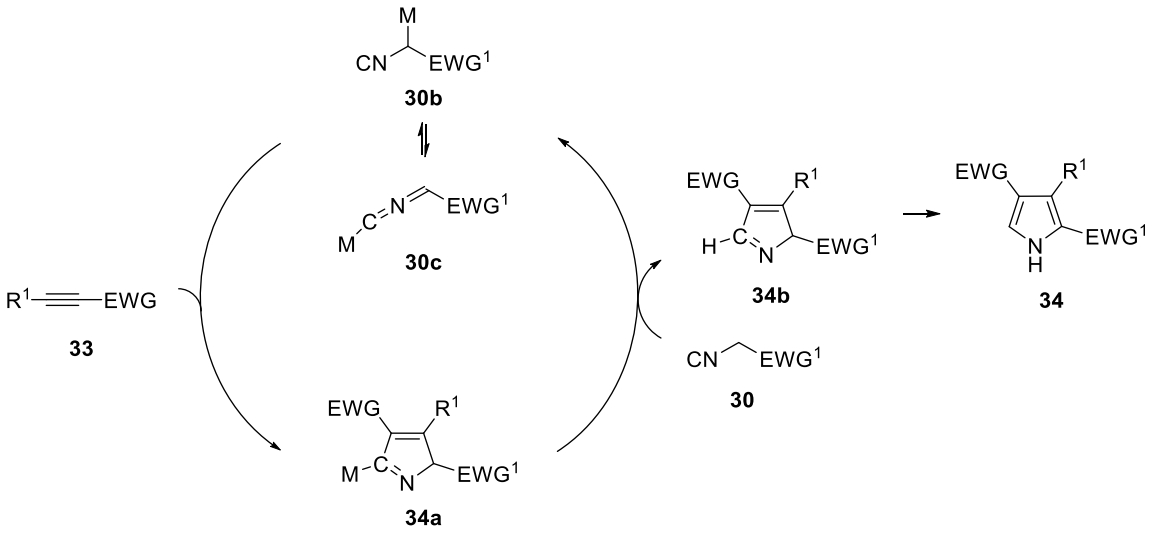
Scheme 10. Pyrrole Synthesis from Terminal Alkyne **29** and Isocyanide **30**

To explore the substrate scope for more substituted pyrrole, there have been efforts made to employ internal alkynes **33**. Since the alkynes are electronically polarized, the catalyst can be inserted easily and more conveniently. It has been known that metals efficiently promote the synthesis of **34**.[14d] Recently, few examples have been disclosed with 1,3-bis(diphenylphosphino)propane (dppp) as a catalyst[15b] or a base without any catalyst[15a] (**Scheme 11**). In most cases where metal or phosphine were used as a catalyst, the reactions were carried out at high temperature.



Scheme 11. Pyrrole Synthesis from Internal Isocyanide **30** and Alkyne **33**

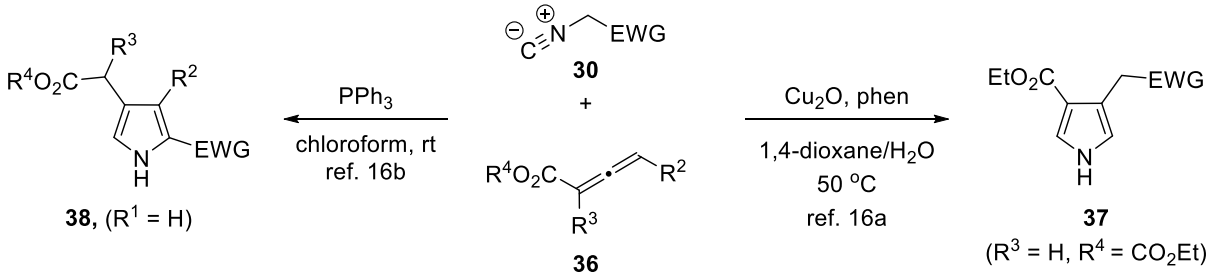
The mechanism of the reaction has been proposed as the metal catalyst first associates with the electron-rich carbon of the isocyanide **30** to form **30b** (**Scheme 12**). Based on the electron density of **30b** and **33**, the cycloaddition happens to generate the intermediate **34a**. The metal catalyst is then reacted to the other isocyanide **30** in the reaction solution and the intermediate **34a** goes through demetallation. Finally, aromatization of **34b** affords **34**.

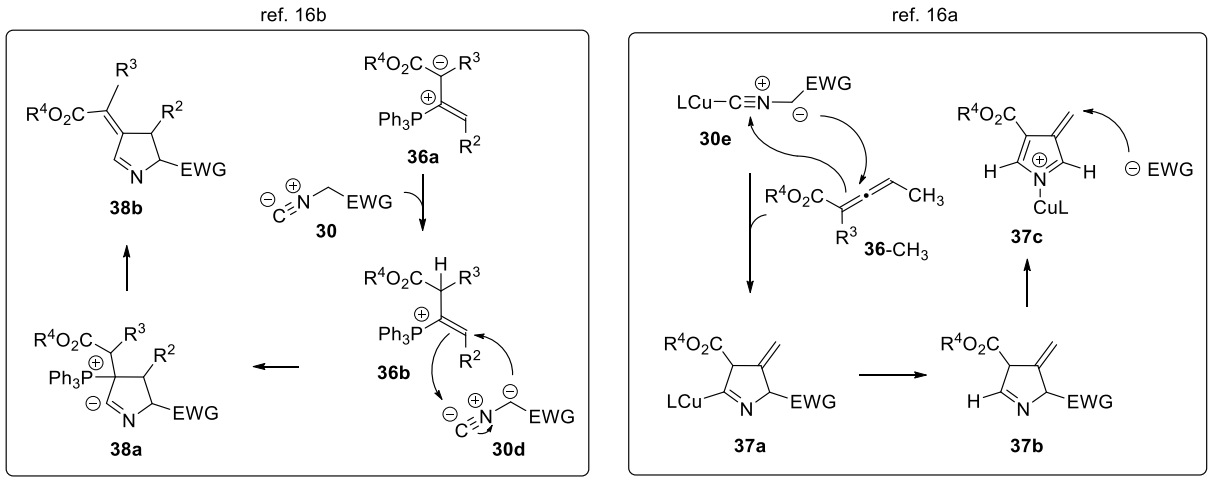


Scheme 12. Mechanism of Metal-catalyzed Pyrrole Synthesis from Isocyanide **30** and Alkyne **33**[14e]

Whereas numbers of synthetic examples of isocyanide **30** with alkynes have been published, the examples of allenoate are rare. The mostly known catalysts are Cu_2O/phen and phosphine which result in different regioselectivity on the final pyrrole products. In the phosphine-catalyzed synthesis (left, **Scheme 13**), the phosphine catalyst reacts with the middle carbon of allenoate **36** then activated isocyanide reacts with this phosphonium intermediate **36a** which readily undergoes the cyclization to give pyrrole **38**.[16b] When Cu acts as a catalyst, it reacts first with

isocyanide **30** then the intermediate **30a** undergoes the (2+3) cycloaddition with allenoate **36** (right, **Scheme 13**),. In the case where toluenesulfonyl (Ts) group is substituted as the electron withdrawing group to the isocyanide, the Ts-group migrates to afford the pyrrole product **37**. [16a]

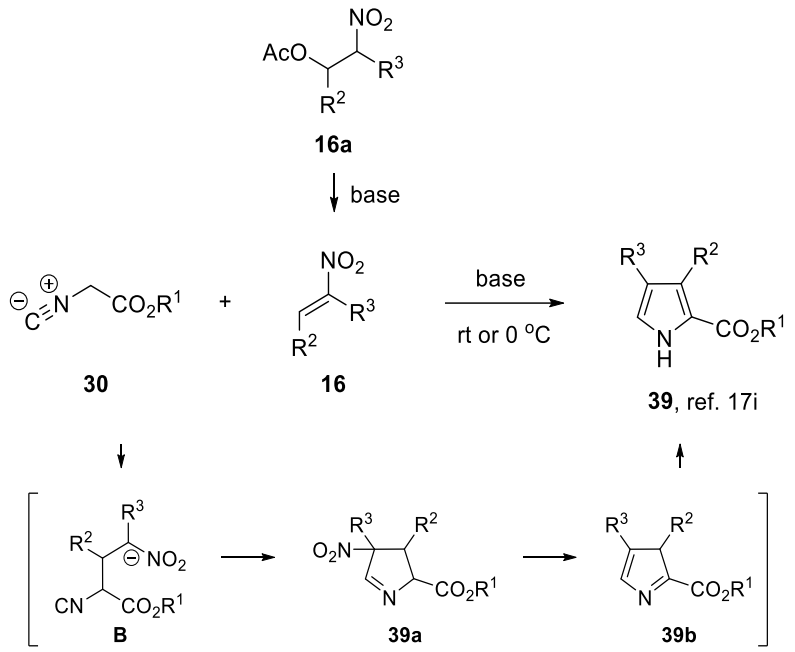




Scheme 13. Pyrrole Synthesis from Allenoate **36** and Isocyanide **30**

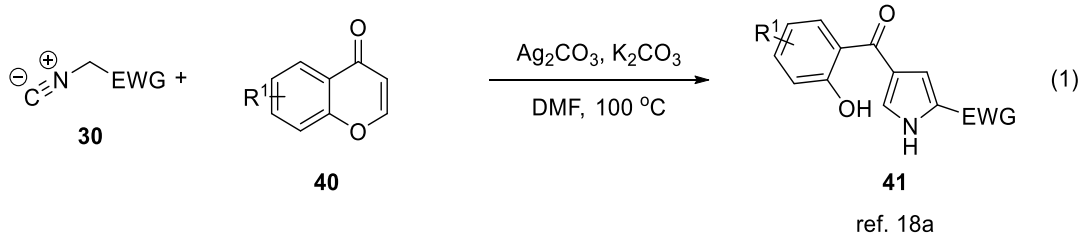
1.4.2. Other Pyrrole Synthesis from Isocyanides

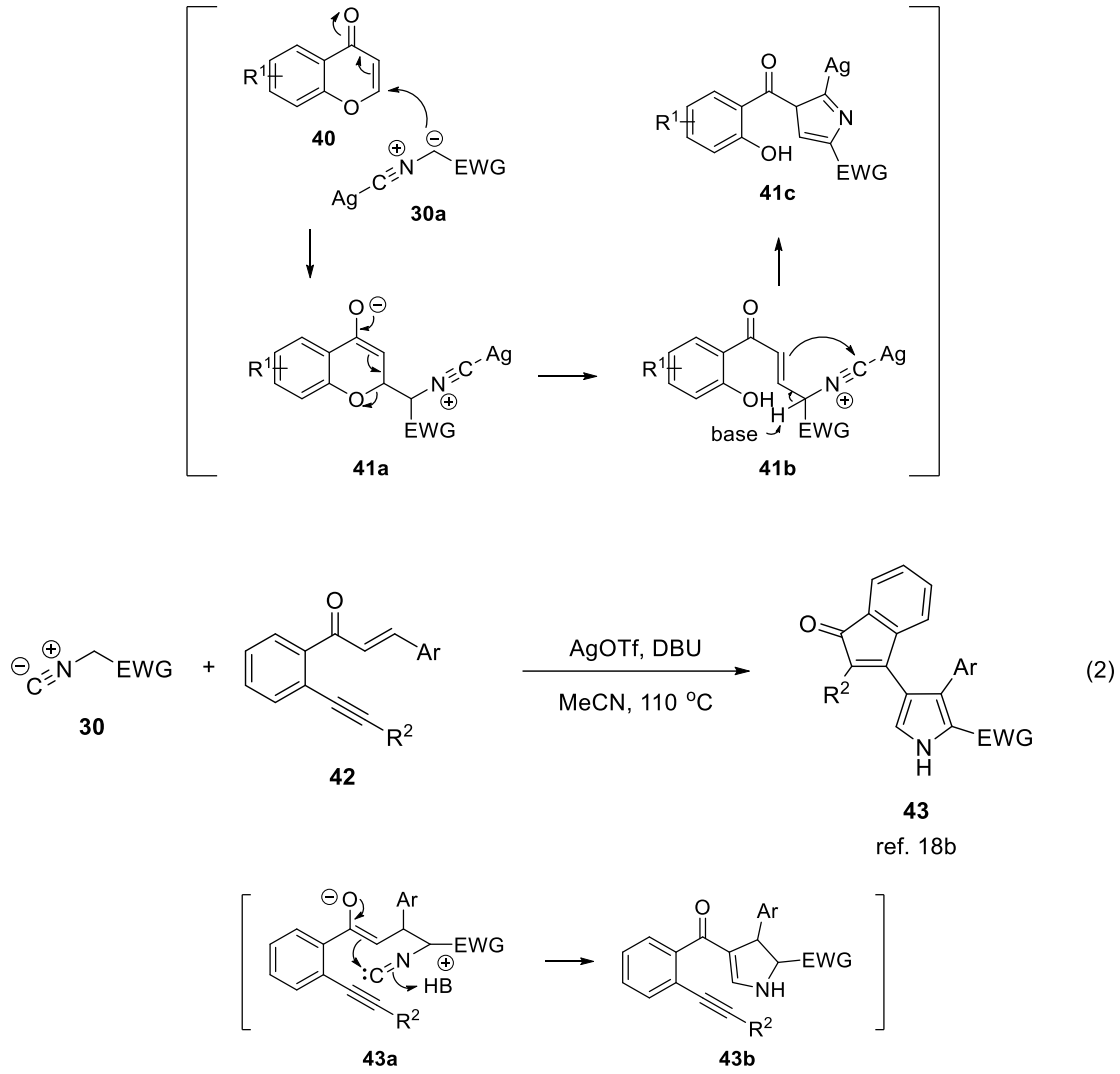
Heterocycle synthesis utilizing isocyanides has been established by Schöllkopf,[17j] Barton, Zard[17g, h] and van Leusen.[17k] Amongst the synthetic methods, one of the representative pyrrole synthesis from isocyanide **30** is the Barton-Zard pyrrole synthesis. It was published by Barton and Zard in 1985 showing the first reaction of isocyanides **30** with readily synthesized nitroalkene **16** in presence of a base (**Scheme 14**).[17i] The electron-withdrawing substituent of the isocyanides **30** has been an ester group, but in 2006, the reaction of Weinreb amide-substituted isocyanide to the corresponding pyrrole has been published.[17b, 17c] Most reaction conditions include a base such as DBU or DMAP at 0 °C or room temperature offering the mild condition available for the application to build more complex products such as **39**.[17a, d-f, i]



Scheme 14. Barton-Zard Pyrrole Synthesis[17i]

It has been well known that silver salts could promote the reaction of isocyanides with alkyne species. The silver-catalyzed reaction of isocyanides **30** has been developed to have high yields, however, what was still challenging was to suppress unwanted dimerization to uretidione of the isocyanides. In 2015, Yang *et al.* found an efficient synthesis of 2,4-disubstituted pyrrole **41** without any trace of isocyanide dimer (eq. 1 in **Scheme 15**).[18a] The pyrrole back bone formation is initiated by the deprotonation of isocyanide **30** with a base. Then the reactive anion **30a** is attached to the chromone **40** via Michael addition. Next, the α,β-unsaturated ketone moiety in **41b** is regenerated and the carbon-carbon double bond readily cyclizes the electron-deficient carbon on isocyanide moiety. The generated Ag-attached **41c** undergoes protonation and aromatization to afford pyrrole **41**. In same way, the pyrrole intermediate **43b** in Eq. 2 in **Scheme 15** could be synthesized which is followed by the oxidation of alkyne moiety by Ag to afford **43**.[18b]



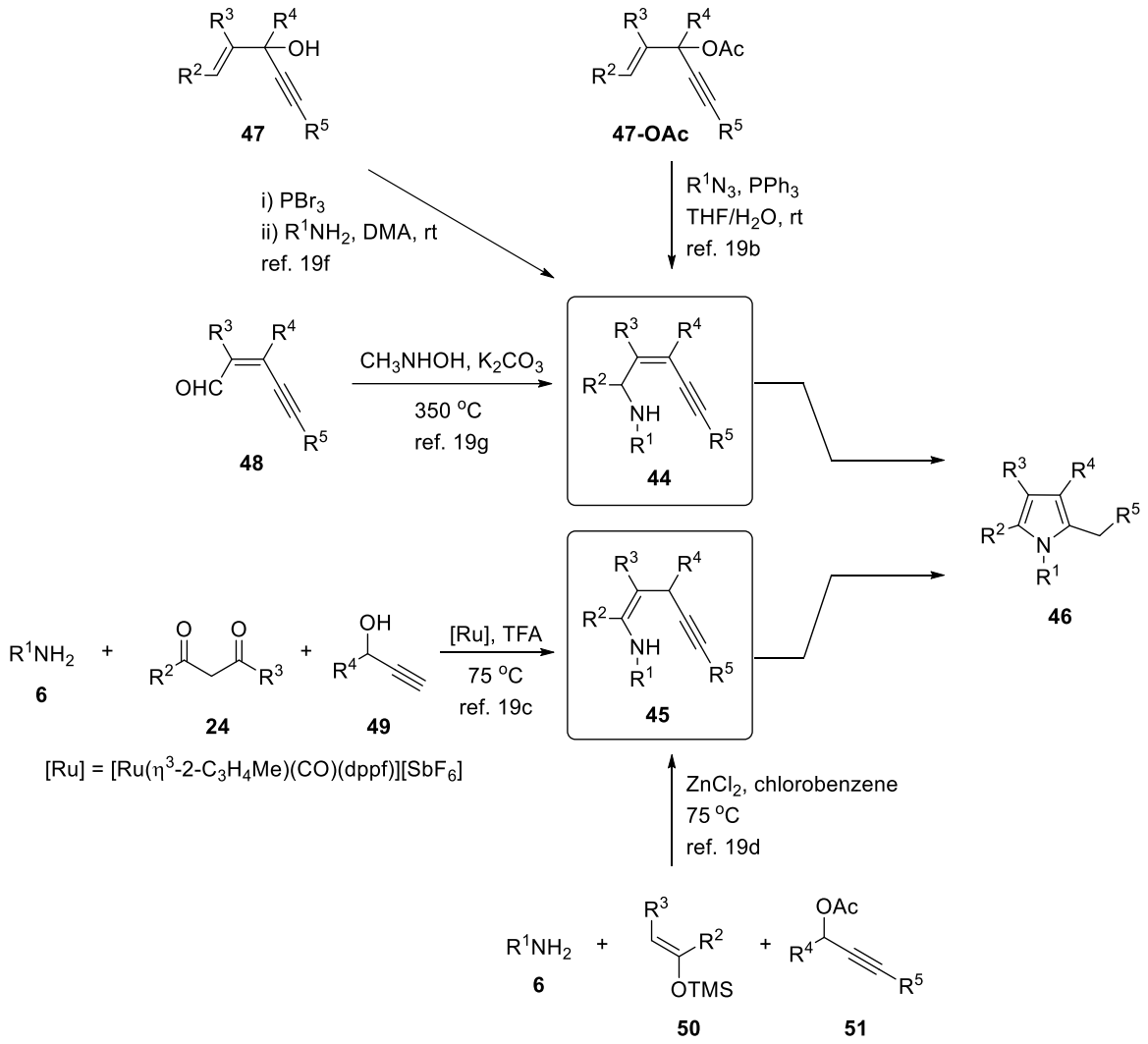


Scheme 15. Pyrrole Synthesis from α,β-unsaturated Ketones and Isocyanide **30**[18]

1.5. Pyrrole Synthesis from Various Alkyne Source

1.5.1. Intramolecular Cyclization of Enynamine to Pyrrole

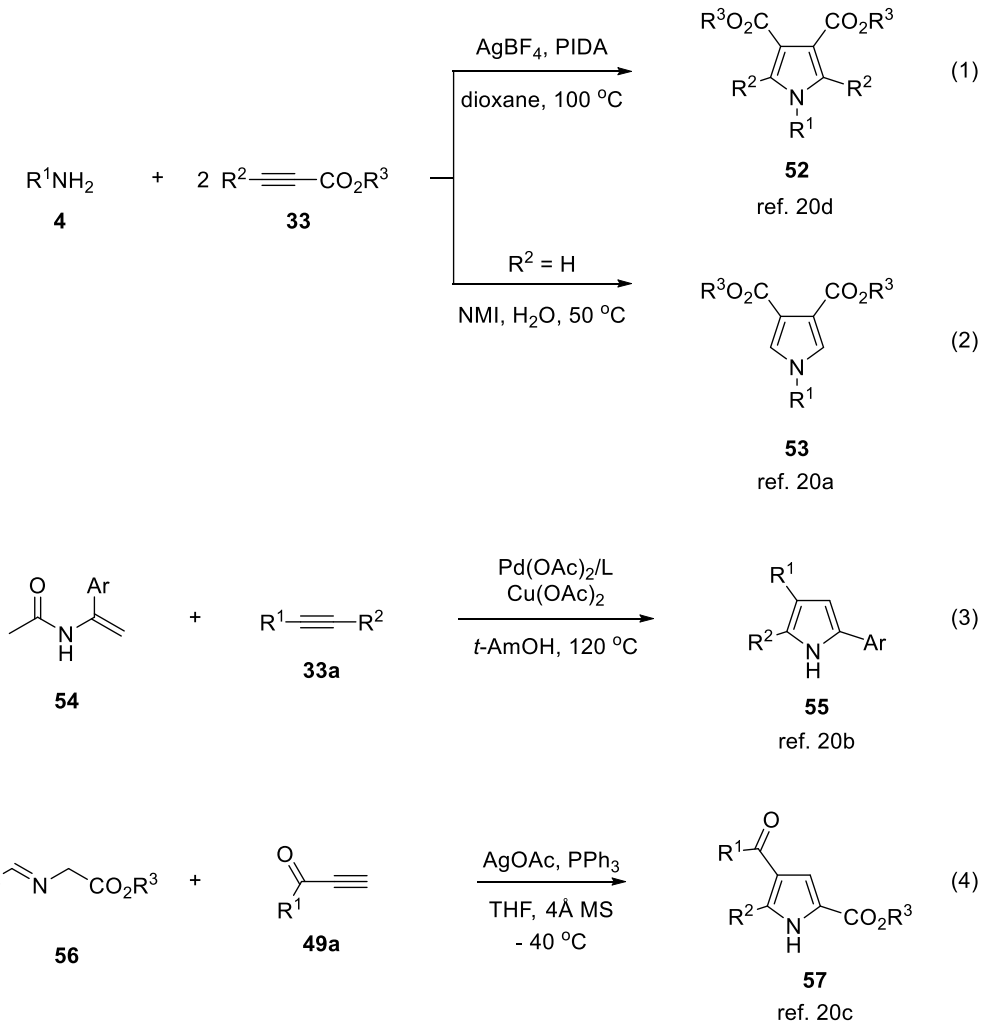
In a view point of retrosynthesis, the molecule which could generate pyrrole in most simple mechanism would be the aninoenynes. The conjugated enynamine intermediate **36** can be synthesized from the reaction of enynes **39** and **40** with amine species. Another intermediate 45 could be afforded by the metal-mediated multicomponent reaction of amine **6**, alkyne species **49** or **51** and other reaction component which could provide two carbons. In each reaction medium, the reaction affords highly substituted pyrrole **46** via *5-exo-dig* cyclization in excellent yields. Moreover, relatively recent studies applied metal catalysts such as Ru[19b], Cu[19f], Au[19e] and Zn[19d] which are known to activate the alkyne and have shown to be efficient and provide milder reaction conditions. In addition, the complexity of the starting material was overcome by introduction of *in situ* generation of enynamine[19b, c] as to synthesize **45** or use of an oxidant.[19a]



Scheme 16. Pyrrole Synthesis via Intramolecular Cyclization of Enynamine

1.5.2. Intermolecular Cyclization of Alkyne with Amine, Amide or Imine

Intermolecular reaction of alkyne species with one of the nitrogen-containing species such as amine **6**,[20a, d] amide **54**[20b] or imine **56**[20c] (**Scheme 17**) has a shorter history than the intramolecular variant. Most of the reaction are catalyzed by the catalyst such as Ag[20c, d] and Pd[20b] which could activate the alkyne species and trigger the ring formation between the nitrogen-containing species and alkyne. In the pyrrole synthesis from amine **6** and alkyne **33**, two alkyne participate in formation of the pyrrole **52** and **53**. The stereoselectivity could be controlled to avoid the steric hindrance of the substituents in pyrrole **55**, however in the synthesis of pyrrole **52**, **53** and **57**, the stereoselectivity was achieved as the amine **4** and imine **56** attacks the less hindered carbon of the alkyne species **33** and **49a**, respectively.



Scheme 17. Pyrrole Synthesis from Alkyne and Amine, Amide or Imine

2. Dearomatization of Pyrrole

As the pyrrole itself and its moiety have been occurring abundantly in complex natural products and pharmaceuticals, various functionalization of pyrrole has been investigated for decades. What has been challenging is to promote functionalization by breaking aromaticity of pyrroles. The aromaticity of pyrrole results from the six π-electrons on five pi-orbitals distributed which makes the pyrrole an electron-rich species. Therefore the functionalization via dearomatization of pyrroles has been more demanding.

Aromaticity of aromatic compound is quantified by values of aromatic stabilization energy (ASE) in homodesmotic reactions. ASE doesn't reflex the total binding energies, but it governs the reactions and chemical behavior of the molecule.[21b, 21c] As the ASE value is positively big, the system is aromatic and thus, the dearomatization of it is more difficult. The ASE values of representative aromatic compounds are shown in **Table 1**.[21]

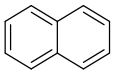
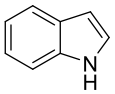
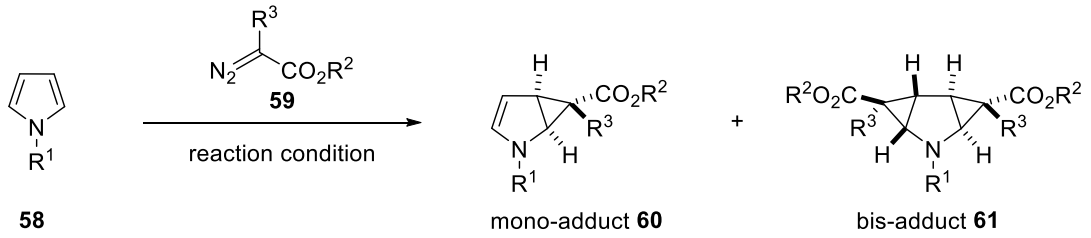
Name	Structure	Aromatic Stabilization Energy (ASE, kcal/mol)
Benzene		29.3
Naphthalene		31.6
Pyridine		29.9
Cyclopentadiene anion		22.5
Furan		14.8
Pyrrole		20.6
Thiophene		18.6
Indole		56.1

Table 1. Aromatic Stabilization Energy of Aromatic Compounds[21]

Amongst the five-membered heterocycles with 6 π-electron system, pyrrole has ASE value of ~ 21 kcal/mol to break the aromaticity which is bigger than ASE values of other heterocycles. Indeed, there have been numerous transformation methods of pyrroles, however, the reactions often have accompanied rearomatization step to compensate the instability of the intermediate so that the final product regains the stability. Those which have overcome the rearomatization were rare but the number of demonstration of the dearomative progresses has been increasing.[22]

2.1. Cyclopropanation of Pyrrole

As a famous named reaction, Simmons-Smith reaction is known as cyclopropanation reaction of alkenes which was published in 1958. It was in 1881, however, that cyclopropanation of pyrrole had been published for the first time.[23f] The study was about the cyclopropanation of pyrrole **58** in presence of base and chloroform which were readily transformed into 3-chloropyridine.

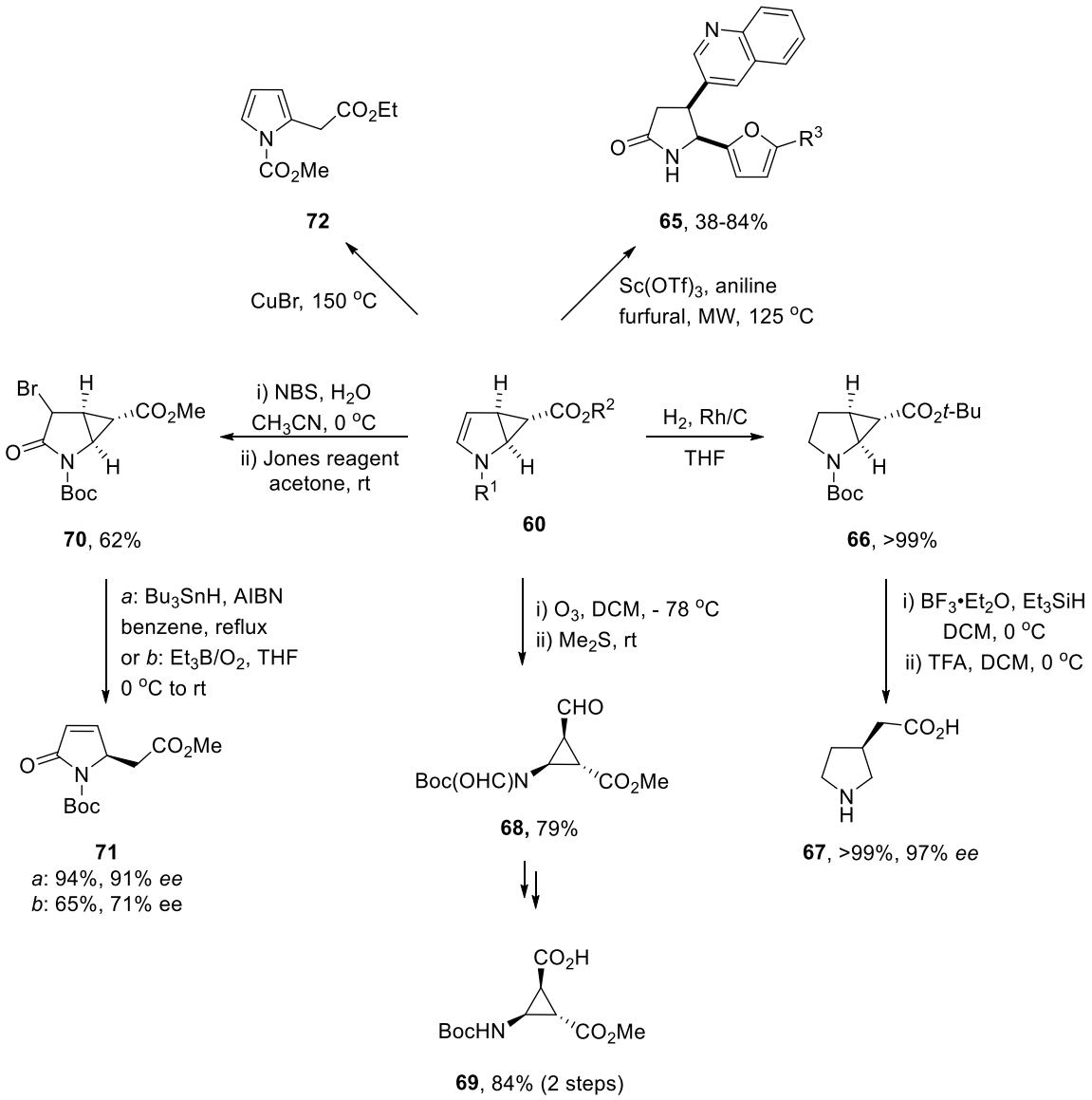


Entry	Reaction condition	R	Results
1	CuBr, 90-95 °C	R^1 = CO_2Me, R^2 = Et R^3 = H	14% **60a** + 5% **61a**[23f]
2	$Cu(OTf)_2$, $PhNHNH_2$, DCM, 0 °C	R^1 = Boc, R^2 = Me R^3 = H	39% **60-Me** 3% **61-Me**[23e]
3	$Cu(OTf)_2$, $PhNHNH_2$, DCM, 0 °C	R^1 = Boc, R^2 = Et R^3 = H	34% **60c**[23d]
4	$Cu(OTf)_2$, $PhNHNH_2$ *n*-hexane, rt	R^1 = Boc, R^2 = Et R^3 = H	63% **61c**[23c]
5	$[Rh(OAc)_2]_2$, *n*-hexane, rt	R^1 = Boc, R^2 = Et R^3 = Me	25% **61f**[23c]
6	$[Rh(OAc)_2]_2$, *n*-hexane, rt	R^1 = Boc, R^2 = Et R^3 = Ph	67% **61g**[23c]

Table 2. Cyclopropanation of Pyrrole **58**

In the publication in 1969 and 1972 by Fowler, the unique reactivity of pyrrole **58**, especially electron-withdrawing group (EWG)-protected pyrroles, to be quoted, is known to behave anomalously but not as like a diene.[23e, 23g] The electron density of protected pyrrole **58** is found to be less than that of unprotected pyrrole due to the conjugation between electron lone pair of nitrogen and carbonyl group of protecting group. This less electron-rich characteristic attributes to this unique reactivity of pyrrole. In the reaction with ethyl diazoacetate **59a** and CuBr, the CO_2Me-protected pyrrole **58a** undergoes cyclopropanation to give the mono-cyclopropanated pyrrole (mono-adduct) **60a** and bis-cyclopropanated pyrrole (bis-adduct) **61a** in 14% and 5% yield, respectively (entry 1 in **Table 2**).[23g] Next, copper-catalyzed cyclopropanation with alkyl diazoacetate was developed (entry 2, 3). The developed copper-catalyzed method gives a rise of 39% **60-Me** and 3% **61-Me** when methyl diazoacetate is applied (entry 2)[23e] and 34% **60c** when ethyl diazoacetate is applied (entry 3)[23e]. On the other hand, bis-adduct could be selectively synthesized by either copper- or rhodium-catalyzed method in *n*-hexane at room temperature

(entry 5-7). As a result, products **61c**, **61f** and **61g** could be successfully synthesized in 63%, 25% and 67%, respectively. [23c]



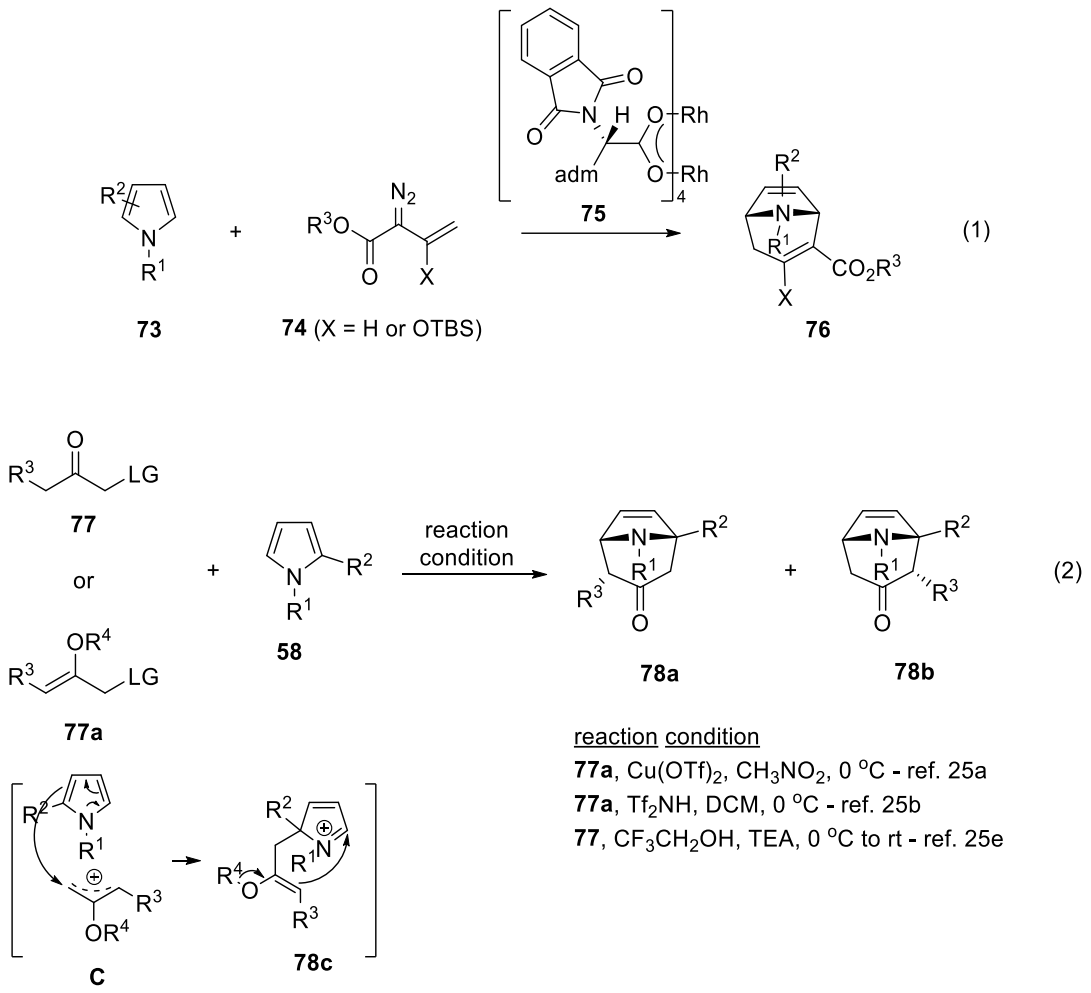
Scheme 18. Transformation of Cyclopropanated Pyrrole **60**

The synthesized mono-adduct **60** is used as versatile unit to be transformed into substituted pyrrole **72**,[24c] homo-β-proline **67**,[23a] substituted pyrrolidinone **65**[24a] and 7**1**,[24b] and β-ACC (aminocyclopropanecarboxylic acid) **69**[23e] (**Scheme 18**).

2.2. (4+3)-Cycloaddition of Pyrrole

It is believed that cycloaddition of pyrrole is one of the effective synthetic methods to build the core structure of tropane alkaloids, which comprise the large numbers of nitrogen-containing

seven-membered natural products and possibly valuable source for the drug addiction studies.[25f]

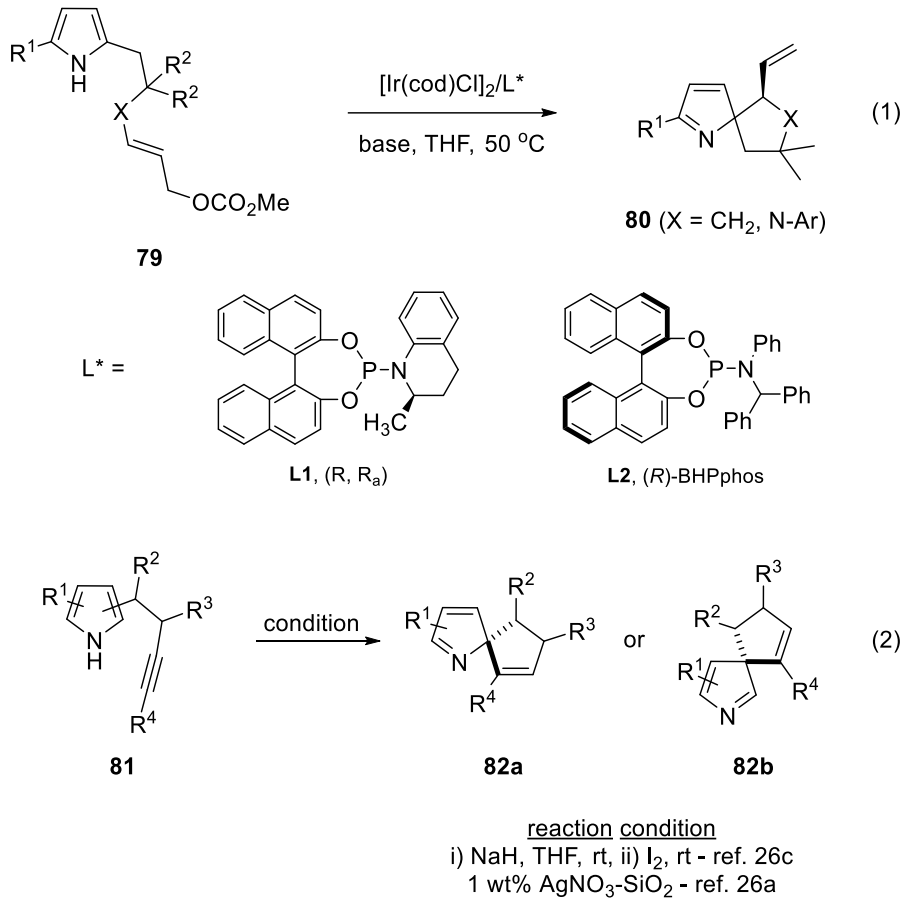


Scheme 19. Cycloaddition of Pyrrole

In 1997[25g] and 2007[25c] by Davies *et al.*, it was uncovered that the pyrrole and diazo compound could lead to formation of tropane derivatives with enantiomeric excess (eq. (1) in **Scheme 19**). The *ee* was improved by the using chiral Rh-catalyst **75** reaching the *ee* up to 98%. In the mechanism, the Rh-catalyst **75** reacts with diazoacetate **74** and release N_2 to generate Rh carbenoid. Then this rhodium carbenoid species readily reacts with pyrrole **73** to give the optically active tropane derivative product **76**. In other examples of pyrrole **58** to tropane **78** derivatives, as the leaving group (LG) of **77** or **77a** leaves the molecule, it becomes allylic cation and pyrrole attacks the cation species (**C** in eq. (2) in **Scheme 19**).[25a, 25b, 25e] Then the electron-rich moiety of the resulting intermediate **78c** reacts with the electron-deficient carbon of the pyrrole moiety. The intramolecular variant of such reaction is rare, however, the pioneering work has been under progress by Chiu *et al.*.[25i]

2.3. Spirocyclization of Substituted Pyrrole

The first successful spirocyclization of pyrrole **79** is Ir-catalyzed synthesis of spiro-2*H*-pyrroles by You *et al.* (eq. (1) in **Scheme 20**).[26d] The chirality is induced by chiral phosphoramidite ligand, **L1** which results in *ee* up to 96% when X = N-Ar and by axially chiral BHPphos ligand, **L2** with 99% *ee* when X = $C(CO_2R)_2$.[26b] The resulting spiro pyrrole **80** can be transformed into the pyrrolidine derivatives selectively through reduction, oxidation and hydrogenation.

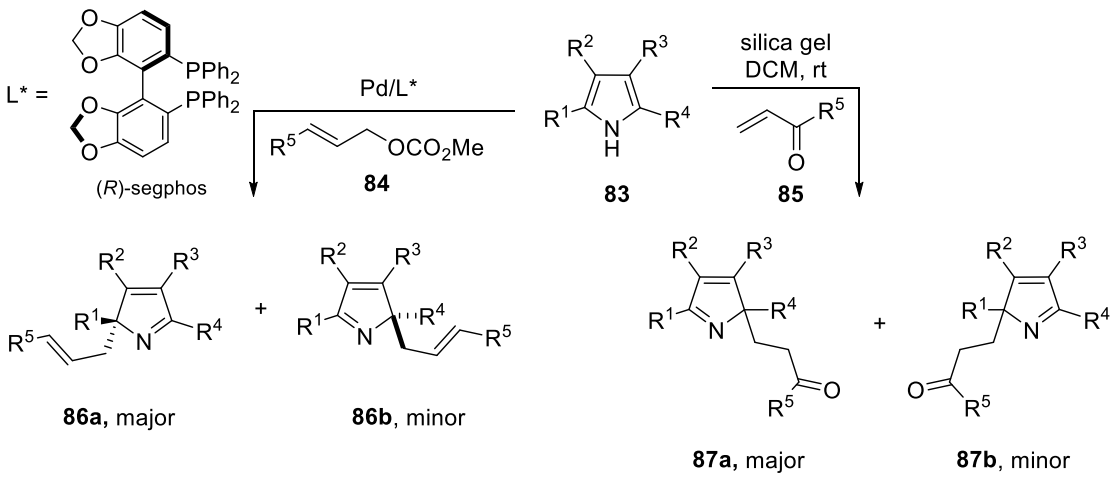


Scheme 20. Spirocyclization of Pyrrole

As shown before, the alkyne is versatile reaction component which could activated efficiently by few metals or elements. Therefore, the spirocyclization of pyrrole **81** containing alkyne moiety could be carried out also with silver and iodine (eq. (2) in **Scheme 20**). According to the location of substituent given in the substrate, 2-substituted pyrrole is transformed into **82a** and 3-substituted pyrrole into **82b**. It is worth noting that the reaction could be occurring on the utilized silver salt on silica gel which opens the possibility to perform the reaction in much larger scale with the benefit of heterogeneous catalysis.

2.4. Addition of Alkene to Pyrrole

As one of the electron-rich heterocycle, pyrrole has been introduced in various reactions with electron-deficient components. There have been numerous functionalization reactions of pyrrole which regain the aromaticity after the reaction, however, the reaction overcoming the aromaticity of pyrrole has not been extensively developed. It was not until 2014 that You *et al.* had published the Pd-catalyzed region- and enantioselective allylic addition to pyrrole.[27b] As predictable from the functional groups in the reaction components, the Pd-catalyst coordinates the olefin and the catalyst is inserted to the allylic cation as the leaving group ($^{-}OCO_2Me$) dissociates (left in **Scheme 21**). Then the nucleophile, pyrrole **83** attacks the less hindered carbon which results in the substitution of the electrophile **84**. With a help of the chiral ligand, the *ee* of the major product **86** can be reached up to 97%.[27c] In other example, the acrylate **85** was added to pyrrole **83** but it was found that silica gel could promote the reaction resulting no stereoinduction to product **87** (right in **Scheme 21**).[27a]

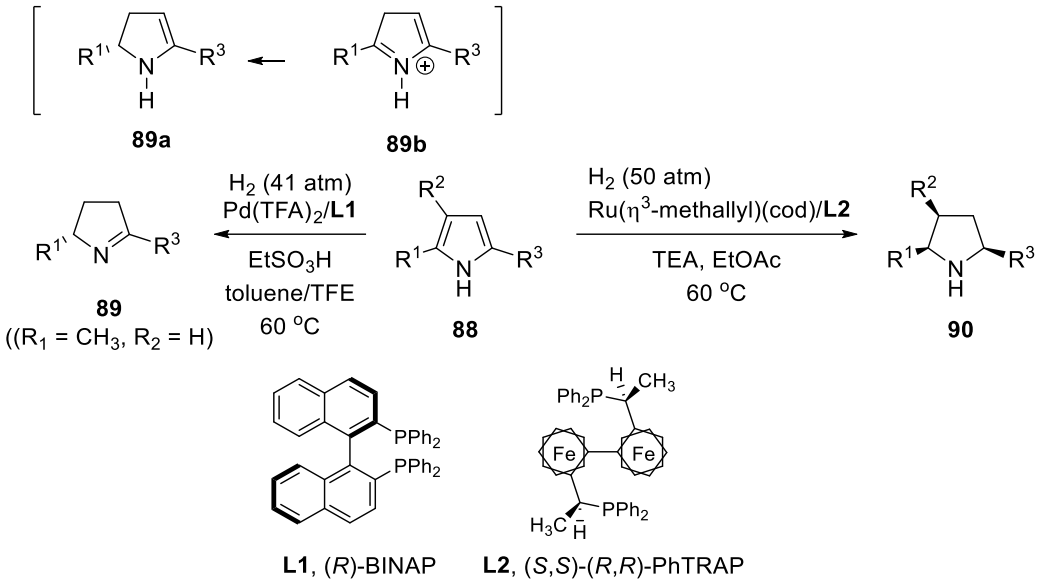


Scheme 21. Addition of Alkene to Pyrrole **83**

2.5. Reduction and Oxidation of Pyrrole

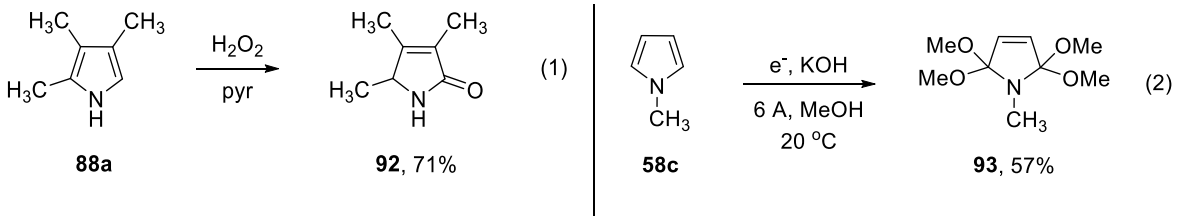
As an abundantly occurring natural resource, furans and pyrroles are generated from the process of cellulose or as a byproduct in the production of grain.[23a] Not only vastly found in natural products, but also considered as a platform to valuable optically active natural products and drugs can be furans and pyrroles. The simplest and most straightforward functionalization method can be thought as reduction to afford pyrrolidines. Indeed, the catalytic chiral hydrogenation of furans and other aromatic compounds has been developed but that of pyrrole has remained rare. The complete and partial hydrogenation of pyrrole has been reported by using chiral ligand with metal catalyst such ruthenium and palladium (**Scheme 22**).[28a, 28b] Each

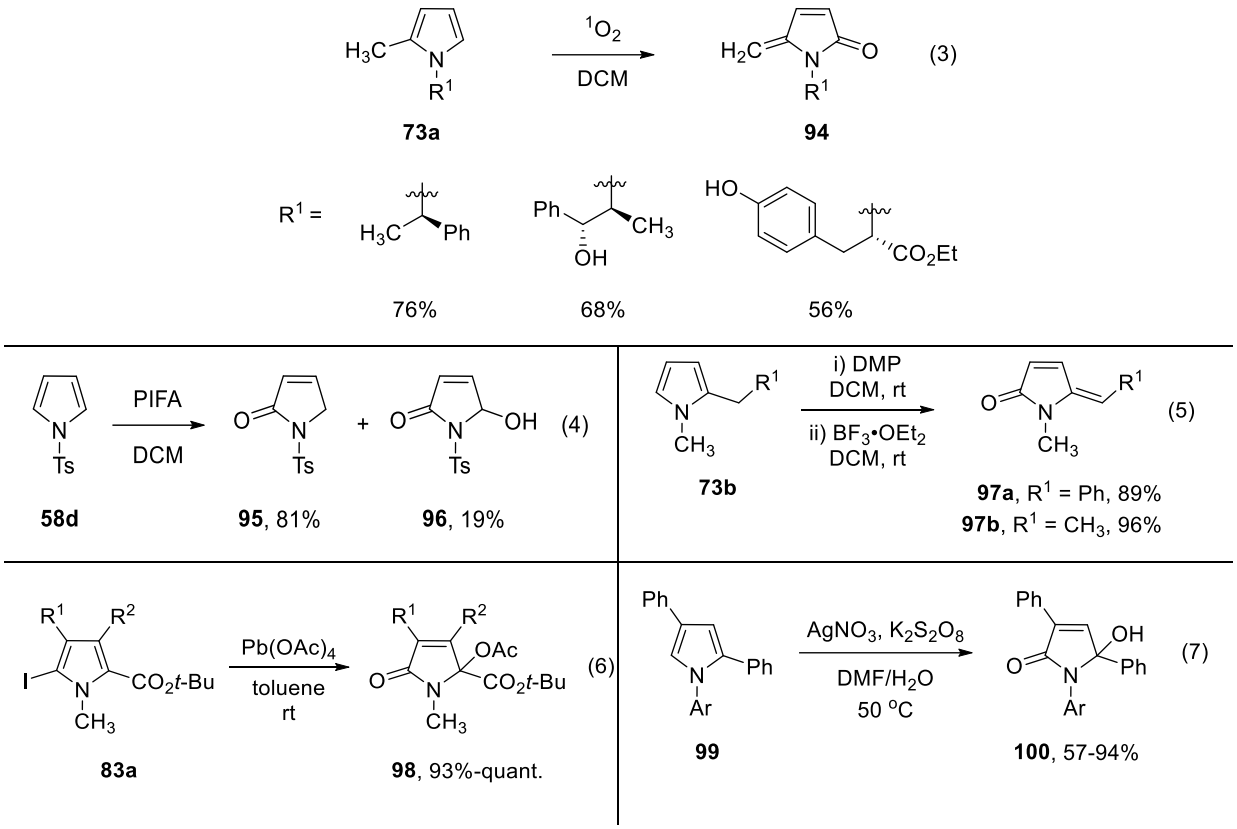
method could afford pyrrolidine derivatives with one to three stereocenters. The drawback is the use of base and strong acid at high temperature which could refrain the functional group tolerance.



Scheme 22. Hydrogenation of Pyrrole **88**

In contrast to the reduction of pyrrole, less attention has been paid to the oxidation of pyrrole. Oxidation of pyrrole lead to formation of 3-pyrrolin-2-one, however, in the process it often decomposes or polymerizes without control due to its reactive property resulting in less efficiency. In many cases, oxidants such as peroxides,[29h] singlet oxygen[29e] and hypervalent iodine[29c, 29d] have been used as well as electrochemical method.[29g] Representative reaction schemes with successful results[29b, 29f] are described in **Scheme 23**, however, many reactions remain inefficient and unpredictable.[29a]





Scheme 23. Oxidation of Pyrrole

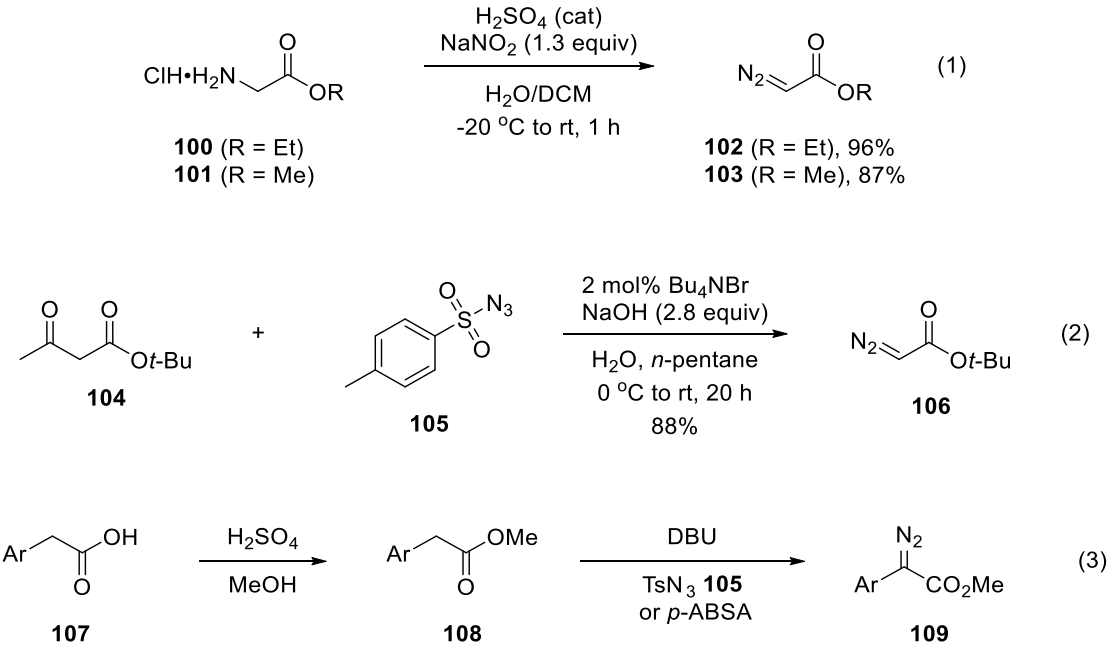
B. Main Part

1. Functionalization of Cyclopropanated Pyrrole

1.1. Cyclopropanation of Pyrrole

Cyclopropane rings are abundantly found as a substructure or a backbone of simple to complex structured molecules in nature. In addition, there have been numerous reports where cyclopropane rings were precursors to synthesize functionalized compounds.

As introduced and described in **Scheme 18** and **Scheme 19**, synthesis and application of cyclopropanated pyrroles have attracted much attention due to their versatility. In order to synthesize functionalized cyclopropanated pyrroles, preparation of various diazo compound has been known. The synthesis of the most commonly used diazo compounds are depicted in **Scheme 24**.

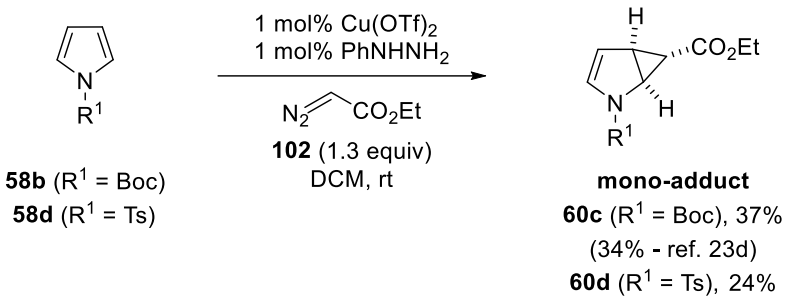


Scheme 24. Synthesis of Diazo Compounds

Ethyl and methyl diazoacetate **102** and **103** can be easily prepared in high yields from inexpensive glycine alkyl ester hydrochloride **100** and **101** with the treatment of sulfuric acid and sodium nitrite (eq. (1) in **Scheme 24**).[30c, 30d] Next, the synthesis of *t*-butyl diazoacetate **106** starts from the carbonyl compound **104** and tosyl azide **105** in presence of a phase transfer reagent Bu_4NBr and a strong base, NaOH (eq. (2)).[30b] Tosyl azide **105** is known to be a diazo transfer reagent and often used in diazo compound synthesis. In same way, **105** was also used for the synthesis of **109** (eq. (3)).[30a] Without an use of a strong base, the diazo moiety was

introduced on the carbon adjacent to the ester group.

For the cyclopropanation with ethyl diazoacetate **102**, the copper complexes have been mostly used as catalysts whereas rhodium complexes have been found more effective to react with donor-acceptor substitute diazo compound. Cyclopropanation of protected pyrrole **58** with ethyl diazoacetate **102** in presence of a copper catalyst shown in **Scheme 25**.

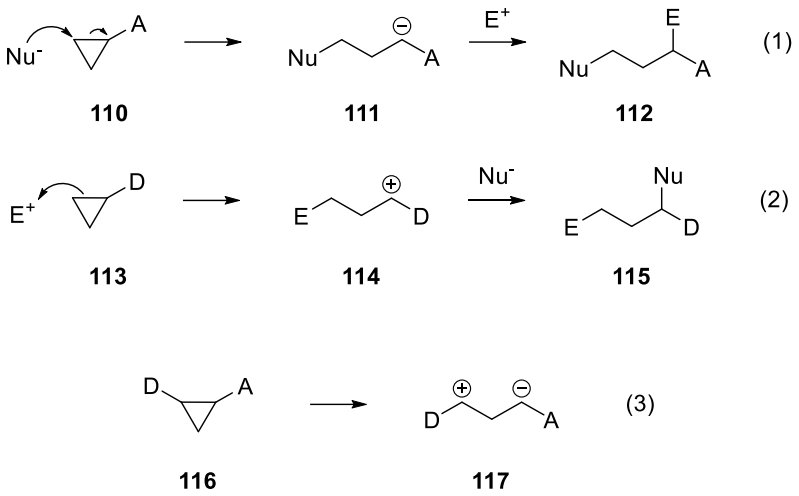


Scheme 25. Cu-catalyzed Cyclopropanation with Ethyl Diazoacetate

With the synthesized cyclopropanated pyrrole **60c** and **60d** in hand, the reactivity of **60c** was examined next.

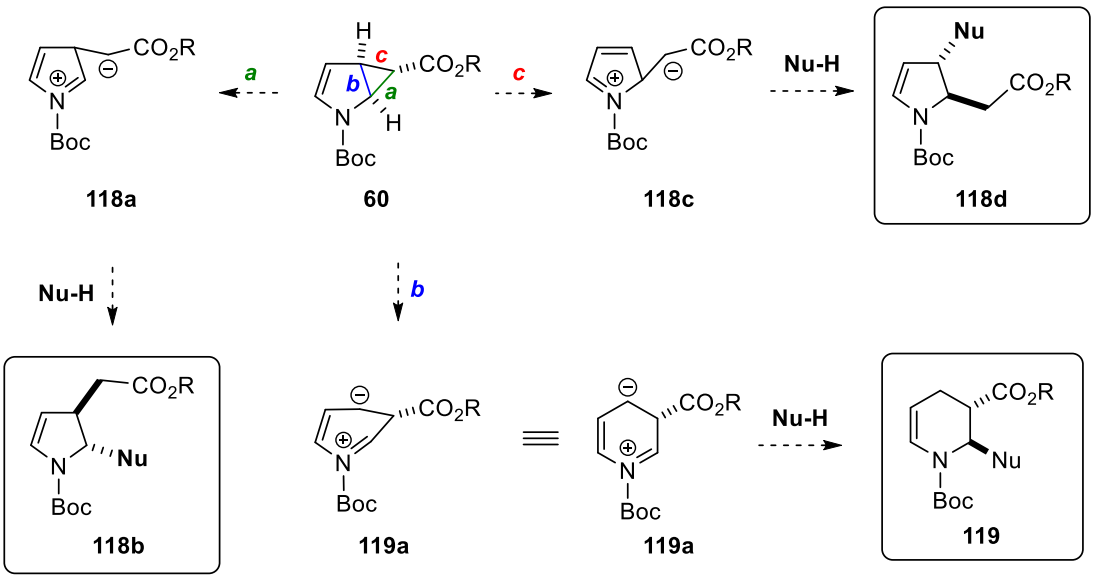
1.2. Reactions of Cyclopropanated Pyrrole

Substituted cyclopropanes have been a research target due to their reactivity for ring opening, driven by lessening of strain of three-membered ring (27.7 kcal/mol). According to the substituents on the ring, the reaction tendency differs (**Scheme 26**). When an acceptor group (A, electron-withdrawing group) is introduced onto the cyclopropane, the cyclopropanes of type **110** are amenable to react with nucleophile to generate the negatively charged intermediate **111** which is followed by the addition of an electrophile to generate **112** (eq. (1)). When a donor group (D, electron-donating group) is present on the cyclopropane ring such as in **113**, on the other hand, the ring can react with an electrophile to form the positively charged intermediate **114** (eq. (2)) which can be subsequently attacked by a nucleophile. At last, cyclopropane has a unique reactivity when it is substituted by acceptor(s) and donor(s) in vicinal positions. In the example of **116**, it is plausible that **116** dissociates to **117**. There have been numerous reports utilizing this reactivity of such cyclopropanes.[23c, 31] Representing also a donor-acceptor-substituted cyclopropane, the substrate **60** was envisioned to be able to undergo this type of reaction.



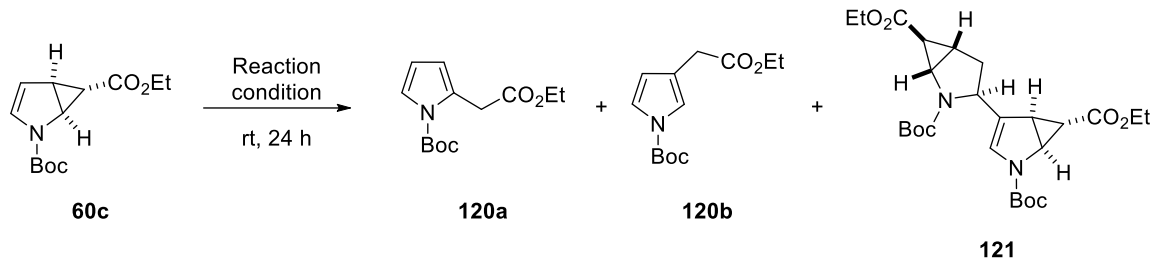
Scheme 26. Reaction Tendency of Cyclopropanes

To investigate the reactivity of the cyclopropanated pyrrole **60**, some hypotheses are proposed in **Scheme 27**. The reaction pathway *a* via the bond dissociation of bond *a*, which could be activated by two substituents, Boc-substituted amine and ester group to generate the intermediate **118a**. Then to the electron-poor adjacent carbon, the nucleophile inserts to form the pyrrolidine compound **118** forming the relative configuration in *anti*. Such method can be easily applied to the functionalization on C2 and C3 position of kainic acid analogues. On the other hand, bond dissociation of *b* would result in a piperidine intermediate **119a**, which then could react with nucleophiles followed by protonation to give a rise to the synthesis of naturally abundant piperidine derivatives.



Scheme 27. Reaction Hypothesis

To investigate which bond in cyclopropane moiety in **60c** would be activated or be vulnerable to nucleophilic attack, the substrate was subjected to different reaction conditions (**Table 3**).



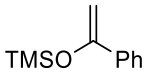
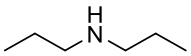
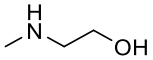
Entry	Reaction condition	Results
1	10 vol% H_2O in DCM	No reaction
2	Acetic acid (3 equiv), DCM	No reaction
3	HBr in H_2O (3 equiv), DCM	**120a** and **120b**, 52% (2:1)
4	HBr in H_2O (1 equiv), DCM	**120a** and **120b**, 43% (2:1)
5	HBr in H_2O (5 mol%), DCM	**121**, 19%
6	[MeCN]Au(JohnPhos)SbF_6 (5 mol%)[a] 10 vol% H_2O in DCM	**120a** and **120b**, 65% (8:1)

[a] JohnPhos = (2-Biphenyl)di-*t*-butylphosphine.

Table 3. Reaction of **60c** with Water and Acids

First of all, 60c was exposed to an aqueous medium to see if water alone is already a competent nucleophile or a proton source (entry 1, **Table 3**). For solubility reasons of the substrate **60c**, DCM was chosen as the solvent, however, no conversion was observed. Next, varios Brønsted acids were evaluated as additives. No conversion in pure acetic acid took place, however, using equimolar or excess HBr (entry 2, 3) triggered the substituted pyrrole **120a** and **120b** in 43-52% with a ratio of 2:1 preference for opening bond ***c*** versus bond ***a*** (*cf.* **Scheme 27**). An unexpected result with the formation of the dimer **121** was, however, obtained when only a catalytic amount of bromic acid was used (entry 5). Apparently, protonation of **60c** had occurred, the resulting iminium cation acting as an electrophile was then attacked in a diastereoselective manner from the convex face of the bicycle by a second molecule of **60c**, in which theenamine acts as a nucleophile. Ring opening to give a rise to **120** was also found when the reaction with a gold catalyst (entry 6). The gold catalyst is believed to interact through the π-system with the substrate behaving like a "large-sized proton". Another distinguishable feature of the gold catalyst is the robust character to air and oxidants which enables less complicated reaction setups and expands the scope of the reaction components such as water. Due to the size of the gold catalyst, the

selectivity of the two pyrrole product, **120a** and **120b** increased to 8:1. Water was found to have no role in entry 6. Based on the selectivity the gold catalyst can bring, further investigation of behavior or **60c** in presence of gold catalyst were conducted. As a reaction component, the nucleophiles were carefully chosen according to the studies of Mayr *et al.* to address the relation between the nucleophilicity and products generated (**Table 4**).

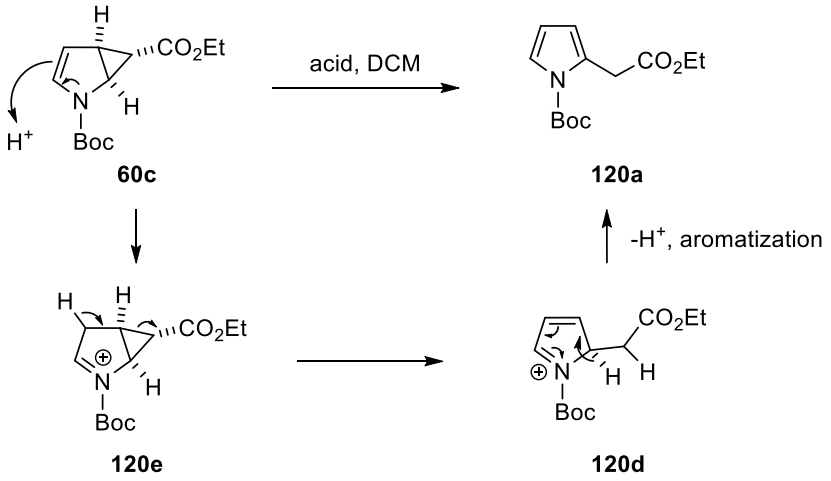
Entry	**Nucleophile**	Nucleophilicity[b]	Results
1	TES-H	3.58 in DCM	**120a** and **120b**, 70% (6:1)
2	TMS-CN	Not determined	**120a** and **120b**, 69% (7:1)
3	TMS-allyl	1.68 in DCM	No reaction
4		6.22 in DCM	**120a** and **120b**, 72% (7:1)
5		14.51 in MeCN	**120a** and **120b**, 4% (25:1) Recovered substrate: 80%
6		ca. 14 in DMSO	**120a** and **120b**, 13% (14:1) Recovered substrate: 71%

[a] JohnPhos = (2-Biphenyl)di-*t*-butylphosphine. [b] Determined by Mayr *et al.*.[32]

Table 4. Reaction of **60c** with Nucleophiles

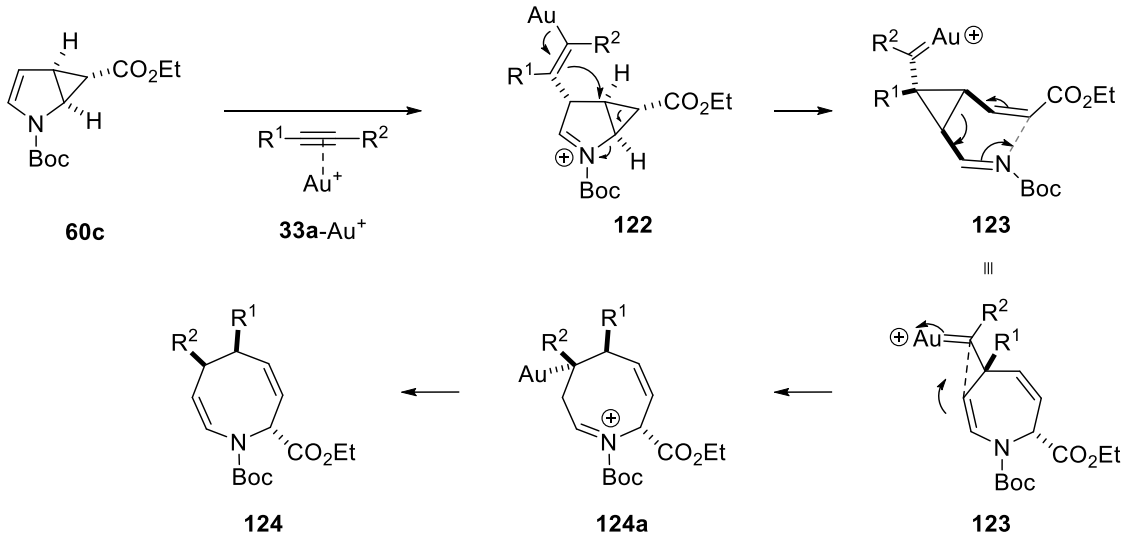
The range of nucleophiles is from hydride, carbon nucleophiles to secondary amines (**Table 4**). Except entry 3 where TMS-allyl was used, the attempts to trap the reaction intermediate with nucleophiles were not successful. Instead, the reaction with various nucleophiles was turned out to generate a mixture of pyrrole **120a** and **120b** in 4-72% yield. A decrease in yields in entry 5, 6 can be due to the inhibition of catalytic activity by amine moiety of the nucleophile. The predominant pyrrole formation is plausibly because of the short life time of the intermediate **120e** which instantly proceeds to rearomatization via **120d** (**Scheme 28**). The stability of pyrrole **120a** drives the reaction pathway towards pyrrole synthesis rather than any addition of nucleophile to **120e**. Despite strong rearomatization tendency of intermediate **120e**, its

possibility to undergo alternative pathways such as dimerization, addition or even ring expansion makes it a potentially useful and versatile intermediate.



Scheme 28. Plausible Reaction Mechanism for Pyrrole Formation

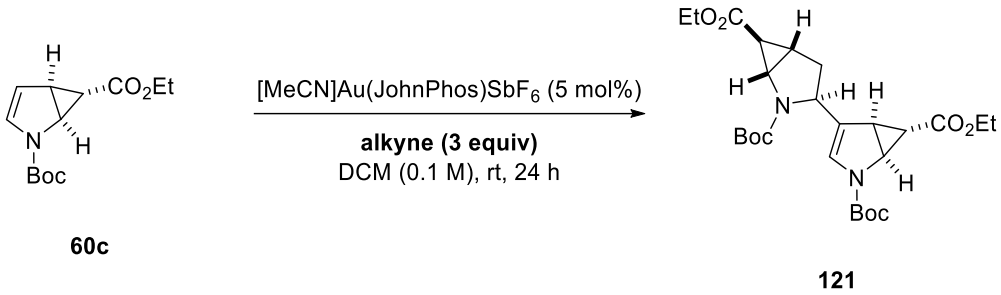
As the gold(I) catalyst has a great capability to react with the substrate **60c**, it was still reasonable to find and employ other reaction component which can be applicable in gold(I) catalysis. That was why the alkyne species was introduced in the extended investigation.



Scheme 29. Reaction Hypothesis II

In the proposed reaction sequence (**Scheme 29**), the substrate **60c** reacts with the alkyne species which is activated by gold(I) catalyst. The applied gold(I) catalyst has been known to have a great potential to promote the reactions between nucleophiles with alkynes. As the reactive

species **122** is formed, the electron rich vinyl gold moiety could proceed to the intermediate **123**. It is known that such intermediate undergoes the sigmatropic rearrangement.[33] The resulting intermediate **123** is then expanded to **124a** through the reaction between the enamine species and the positively charged vinyl gold moiety. In final reaction step, the gold catalyst leaves the molecule by gold-proton exchange to afford such nitrogen-containing eight-membered ring, **124**.



Entry	**Alkyne**	Results
1	H_3C—≡—Ph	No reaction
2	≡—CO_2Et	52% (56% brsm)
3	≡—Ph	57% (72% brsm)

[a] JohnPhos = (2-Biphenyl)di-*t*-butylphosphine.

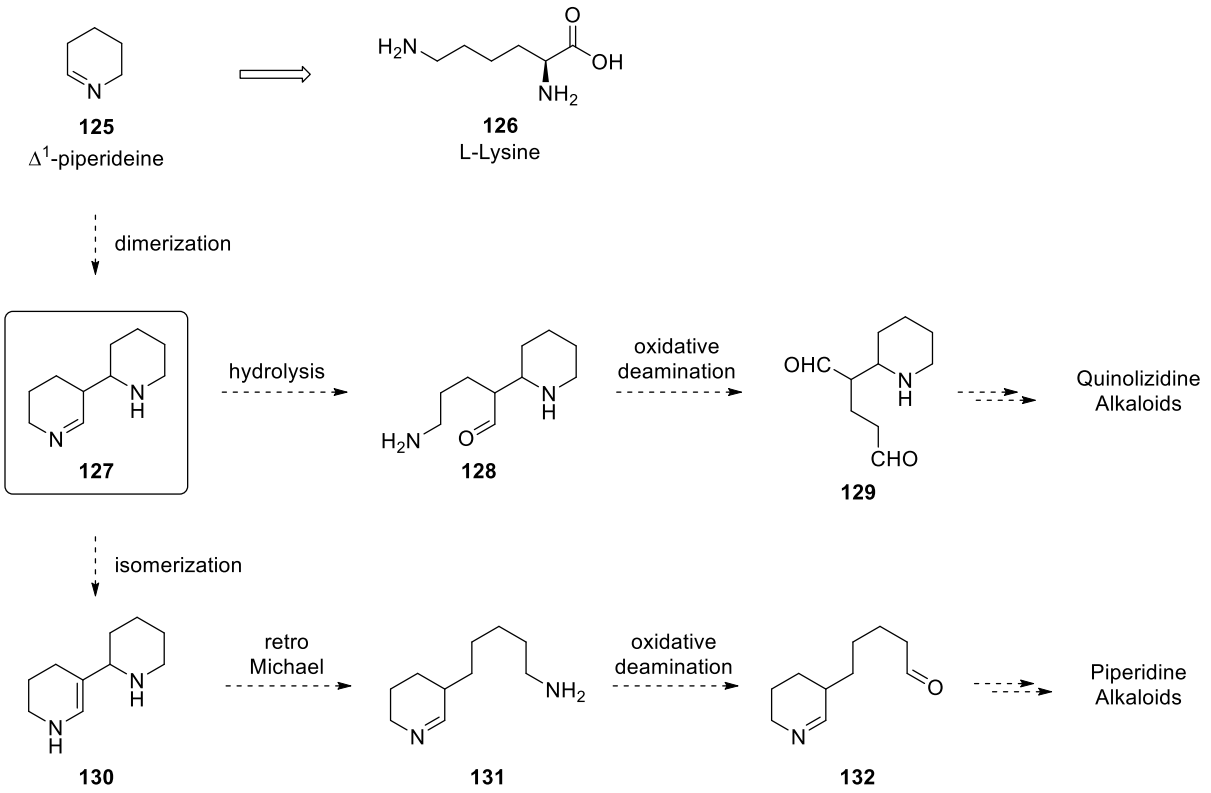
Table 5. Au(I)-catalyzed Reaction of Cyclopropanated Pyrrole and Alkyne

The reaction of substrate **60c** in cooperation with alkyne species was carried out with the commercially available gold(I) catalyst, [MeCN]Au(JohnPhos)SbF_6 (**Table 5**). In the examples where the internal alkyne and terminal alkyne were applied, the reaction showed significantly different results. **60c** only started converting to the dimer product **121** in presence of terminal alkynes but in presence of internal alkyne, no conversion was observed. Since the electronic characteristics terminal alkyne could affect the nucleophilic attack of enamine, alkynes with electron-donating or electron-withdrawing group were tested in the reaction (entry 2, 3). Regardless of the characteristics of the terminal alkyne, no emanime/alkyne coupling was observed but only dimer **121** was obtained in 50 – 57% yield as a single stereoisomer. As the substrate **60c** has shown distinctive reactivity towards dimerization, further experiments have focused on the optimization and improvement of dimerization.

1.3. Au(I)-catalyzed Dimerization of Cyclopropanated Pyrrole

1.3.1. Preliminary Studies on Dimerization

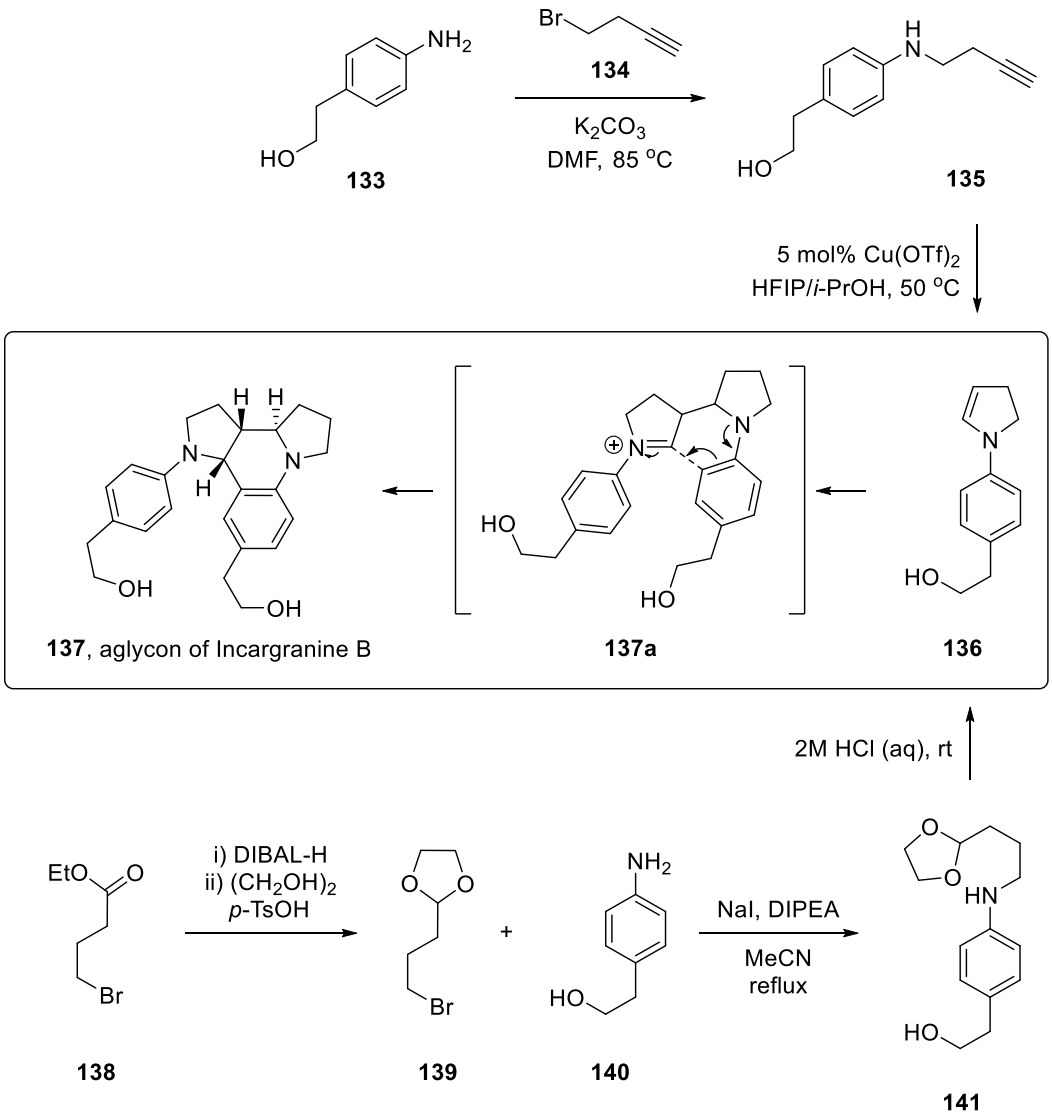
Contrary to dimerization of indole which has been found to be the most common, dimerization of nonaromatic enamine species was reported as an undesired side product or underdeveloped. As one of the few studied dimerization examples, the dimerization of piperideine has been focused due to the importance of the dimer intermediate in biosynthesis of second metabolite.[33a] The key intermediate is the dimer of Δ^1-piperideine **125** which are transformed into quinolizidine alkaloids or peperidine alkaloids (**Scheme 30**). Dimerization of pyridinium salts through a reductive process[34c, 34d] or piperidine through an oxidative process[34b, 34e] has been known since late twenty century for the same purpose.



Scheme 30. Dimerization of Piperidine Derivatives[34a]

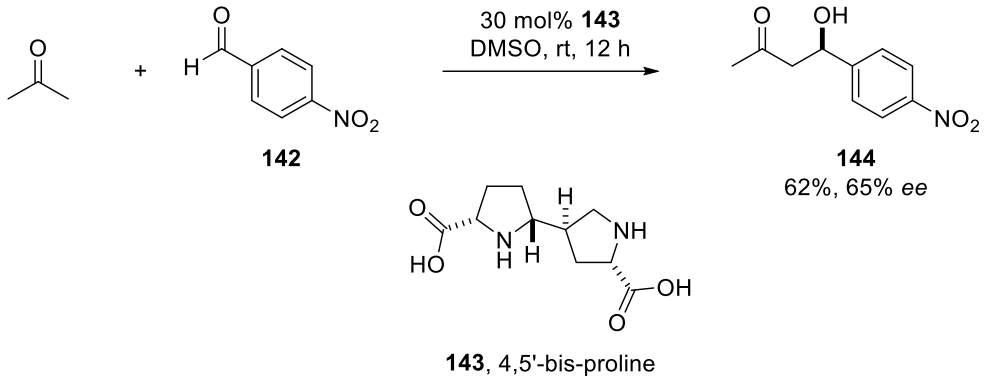
The studies on dimerization of piperidine derivatives have been also applied to 5-membered ring analogues, pyrrolidines. Due to its highly unstable nature, the substrate for the studies have been chosen to contain electron-withdrawing functional groups either on nitrogen or adjacent carbon. The resulting dimer is widely found as a substructure in incargranine alkaloids and the subunits of peptides[35a, 35b]. The representative synthesis of incargranine are described in **Scheme 31**.[35c, 35d] In retro-synthesis perspective, the most important intermediate is **136** which under the acidic

reaction condition undergoes dimerization to afford the aglycon incargranine B, **137**. There has been development of more efficient synthetic method for the intermediate **136**, however, the key step of the synthesis still remains the dimerization.



Scheme 31. Pyrroline Dimer in Natural Product Backbone

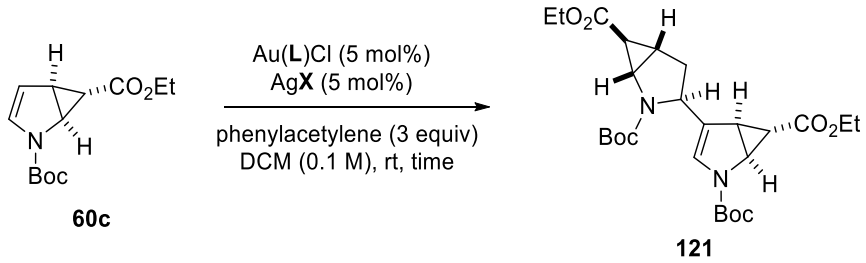
In the end, the pyrrolidine dimer backbone is also found in the catalyst **143** which is applied in the organocatalysis where *p*-nitrobenzaldehyde **142** reacts with acetone to give **144** via aldol reaction (**Scheme 32**).[36]



Scheme 32. Pyrrolidine Dimer as a Catalyst

1.3.2. Dimerization of Cyclopropanated Pyrrole

As found in results with various nucleophiles in presence of gold(I) catalyst, the reaction of substrate **60c** is predominantly to generate pyrrole **120**. The reaction pathway has, however, shifted to dimerization when terminal alkynes were applied in presence of gold(I) catalyst. To explore and improve the reaction efficiency, various gold(I) catalysts have been employed in the reaction. In gold(I)-catalyzed reaction, it is often important to have a proper ligand. According to the size and electroproperty of the ligand, the catalysis can lead various reaction pathways. What has not been highlighted enough is, however, a counterion which also has a role of coordinating the reaction components together.[37] In order to find the best combination of catalyst, ligand and counterion, the optimization has been proceeded (**Table 6**).



Entry	**L**	Ag**X**	Time	Results
1	JohnPhos[a]	$AgSbF_6$	24h	52% (78% conversion)
2	$P(C_6F_5)_3$	$AgSbF_6$	24h	- (30% conversion)
3	PPh_3	$AgSbF_6$	24h	54% (100% conversion)
4	PPh_3	$AgNTf_2$	24h	- (10% conversion)
5	PPh_3	AgOTf	24h	39 % (86% conversion)

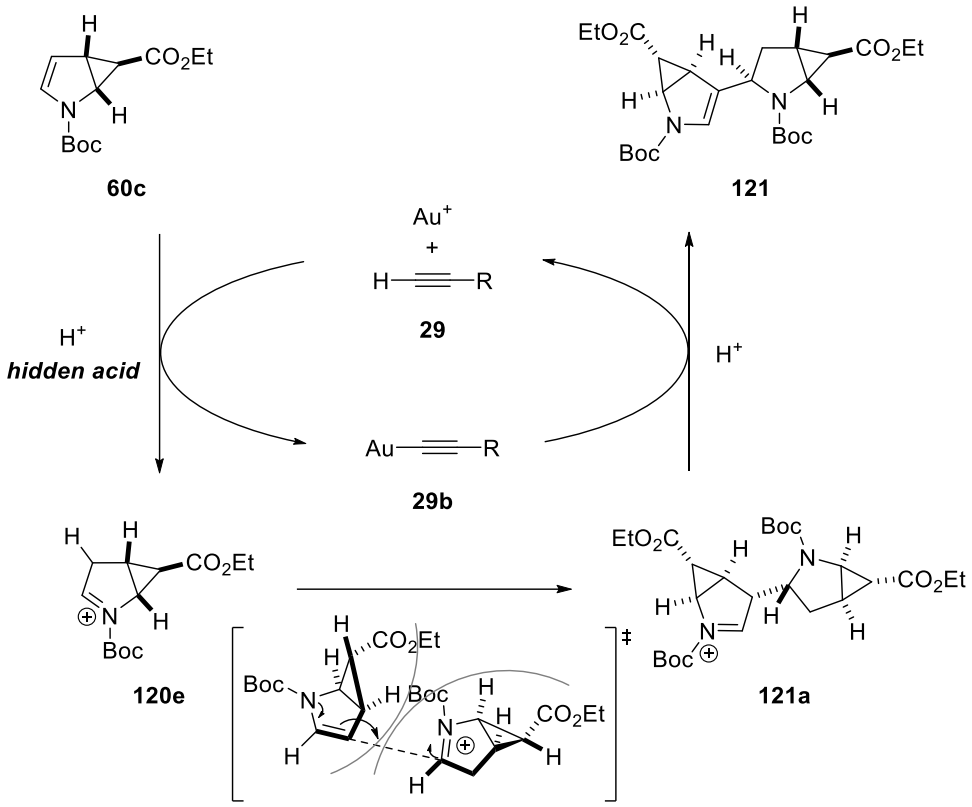
6	IPr[b]	$AgSbF_6$	24h	30% (100% conversion)
7	**IPr**[b]	**$AgNTf_2$**	**24h**	**60% (88% conversion)**
8	IPr[b]	AgOTf	24h	49% (65% conversion)

[a] JohnPhos = (2-Biphenyl)di-*t*-butylphosphine.
[b] IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

Table 6. Gold(I)-catalyzed Reaction of Cyclopropanated Pyrrole

As described in **Table 6**, the reaction condition include the use of various phosphine or imidazolidene ligand (IPr) with silver salts. As electron-rich ligand, JohnPhos ligand was utilized in the previous reactions, the most electron-withdrawing ligand was applied in next entry (entry 2). The result was dramatically changed to show no conversion of substrate **60c** which was also in contrary to the result when triphenylphosphine was used as a ligand (entry 3). The only phosphine ligand which gave complete conversion within 24 h was triphenylphosphine (entry 3), therefore, different silver salts were applied in the reaction with $Au(PPh_3)Cl$ to examine the counterion effect (entry 4 and 5). Unfortunately, the reaction didn't generate the improved or comprehensive results however soft or hard the characteristics of the silver salts varied. Surprisingly, the results from the reaction with IPr ligand (entry 6-9) which have shown the relation between the counterion and conversion rate. As the counterion is larger, the reaction has shown faster conversion which results in more engaging of positively charged gold catalyst with substrate rather than the counterion. The most effective dimer generation result was though obtained in the entry 7 where $IPrAuNTf_2$ was used as a catalyst.

From the results that the internal alkyne was inactive in the reaction, it is safe to assume that the terminal alkyne **29** acts a role in the reaction. The gold(I) species tends to exchange the place of proton in the terminal alkyne **29** to generate **29b** in **Scheme 33** releasing a proton into the reaction medium (hidden acid).[38] The hidden acid is reacted with the substrate **60c** to form the iminium species **120e** which is followed by the nucleophilic attack of another **60c**. Then dimer intermediate **121a** leaves back the proton and gold(I) catalyst into the catalytic cycle and the enamine moiety is regenerated in **121**. In conclusion, the gold(I) catalyst and alkyne species **29** act only as a catalytic component to generate the hidden acid in the reaction and the substrate is consumed to afford its dimer **121**. As the cyclopropanated pyrroles **60** have a convex surface, it is plausible that two of substrate **60c** reacts also on the less hindered and exposed convex surface. The resulting relative stereochemistry of the dimer **121** is determined by X-ray crystallography and shown in **Figure 2**.



Scheme 33. Detailed Mechanism of Dimerization (Stereochemistry Based on X-ray Analysis)

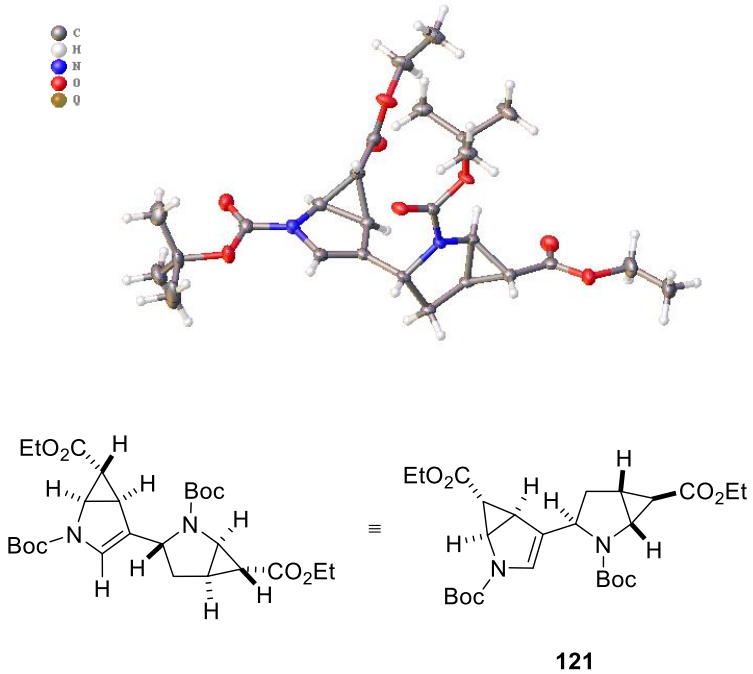
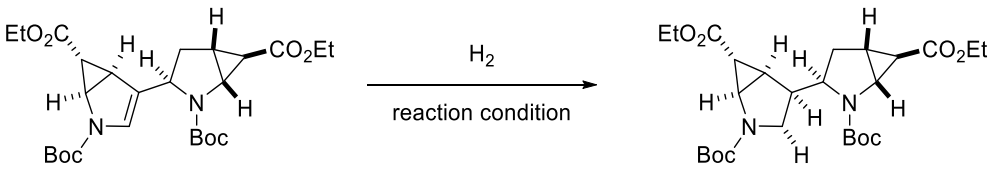


Figure 2. Relative Stereochemistry of Dimer **121** by X-ray Crystallography

As the substrate **60c** which was subjected to the reaction was racemate, it is only plausible to explain the stereochemistry of the dimer **121** in a relative term. The stereochemistry of dimer is attributed to the structure of the **60c**. In general, the nitrogen-containing cyclopentane ring and fused cyclopropane ring of cyclopropanated pyrroles possess semicircular surface and convex surface is exposed to attack or to be attacked. The interesting fact is that the nucleophile is bound to the electrophile in a way the resulting dimer have less hindrance between hydrogens and ester group when two cyclopropanated units rotate along the newly generated C-C bond.

1.3.3. Further Functionalization towards Bis-β-homoproline Derived Catalyst

As an application of the dimer **121**, some transformations to synthesize bis-β-homoproline **146** was carried out. First reaction is the hydrogenation of dimer **121**. In general hydrogenation condition, the dimer **121** didn't show any conversion. The reason of no conversion would be because of the number of the substituents on olefin or enamine of **121**. The more substituents the olefin has, the more demanding the hydrogenation is. Therefore, many attempts for hydrogenation have been performed and described in **Table 7**.



121 **145**

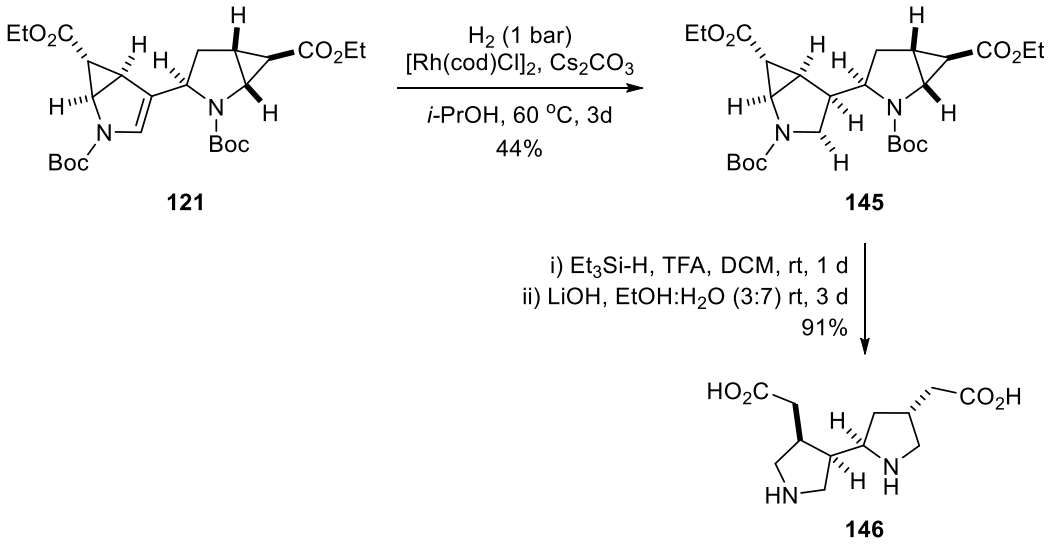
Entry	Reaction condition	Results
1	H_2 (1 bar), 10 wt% Pd/C, MeOH	No conversion
2	H_2 (1 bar), 10 wt% Pd/C, THF	No conversion
3	H_2 (10 bar), 10 wt% Pd/C, THF	No conversion
4	H_2 (1 bar), 10 wt% $Pd(OH)_2$/C, MeOH	No conversion
5	H_2 (1 bar), 10 wt% Rh/C, THF	No conversion
6	H_2 (10 bar), 10 wt% Rh/C, THF	No conversion
7	H_2 (1 bar), 5 mol% $[Ir(cod)Cl]_2$, I_2, THF, rt	No conversion
8	H_2 (10 bar), 5 mol% $[Ir(cod)Cl]_2$, I_2, THF, rt	No conversion
9	H_2 (1 bar), 4 mol% Crabtree's cat.,[a] DCM, rt	No conversion
10	H_2 (1 bar), 1 mol% $[Rh(cod)Cl]_2$, Cs_2CO_3, *i*-PrOH, 40 °C	29 % (75 % conversion)

11	H_2 (1 bar), 1 mol% $[Rh(cod)Cl]_2$, Cs_2CO_3, *i*-PrOH, 60 °C	44 %
12	H_2 (10 bar), 1 mol% $[Rh(cod)Cl]_2$, Cs_2CO_3, *i*-PrOH, rt	No conversion

[a] Crabtree's cat. = (1,5-Cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium(I) hexafluorophosphate

Table 7. Hydrogenation of Dimer **121**

Most of hydrogenation of enamines have been performed with metal/charcoal and H_2 gas. The most common catalyst, Pd/C was not reactive to hydrogenate the dimer **121** (entry 1 to 3). Next, other Pd/charcoal sources were applied but **121** was found inactive to hydrogenation (entry 4). As more active metal surface, rhodium on charcoal was also used for the hydrogenation, however, the hydrogenation didn't occur (entry 5 and 6). Then homogeneous hydrogenation methods have been adapted. The most known catalyst, Crabtree's catalyst and its similar catalysts have been also applied, however, found to be inactive for the hydrogenation of **121** (entry 7 to 9).[39] It was when the example of hydrogenation of substituted indole was found and the hydrogenation of **121** has finally shown successful results. In the literature, the reaction has been carried out at different temperature according to where the substituent was located on indole; 40 °C for 3-substituted indole and 60 °C for 2-substituted indole. Therefore the reaction of **121** was first performed at 40 °C which showed the partial conversion and low yield. It was found that the reaction condition at 60 °C enables hydrogenation of **121** forming hydrogenated dimer **145** in 44% yield.



Scheme 34. Functionalization of Dimer **121**

With the success of hydrogenation of dimer **121**, the further transformation to produce bis-β-homoproline **146** was carried out (**Scheme 34**). The first reaction of hydrogenated dimer **121** was selective ring opening and deprotection of Boc-group in presence of triethylsilane and TFA in DCM.[23a] The reaction has been used in the shortest asymmetric synthesis of proline from substrate **60**. Then by use of LiOH, the ester moiety of dimer was transformed into acid moiety of bis-β-homoproline **146**. After a treatment with DOWEX, purified **146** can be obtained in 91% yield. The relative stereochemistry of products is predicted according to the reactive convex surface of each cyclopropanated pyrrole moiety. As shown in **Scheme 32**, such bis-homoproline derivatives have shown the catalytic reactivity in aldol reaction and Mannich reaction.[36] The evaluation of the bis-β-homoproline **146** as an organocatalyst has to be further examined.

2. 1,3-Dipolar Cycloaddition of Cyclopropanated Pyrrole Towards Tropane Derivatives

2.1. History of Cocaine Synthesis

(-)-Cocaine is the most widely known and notorious tropane alkaloid which is naturally occurring and extracted from the leaves of *Erythroxylum coca*. Its enantiomer, (+)-cocaine is, however, not addictive because of its low potency which is 155-fold less compared to that of (-)-cocaine and it has faster rate of metabolism.[40b] Since the late 1800s, (-)-cocaine has been a subject of scientific investigation and found to act as a stimulant of the central nervous system. Due to its various physiological effects, it has been used as a medicine, but for several decades its abuse has become a worldwide problem and this has attributed to its ability to produce euphoria and its reinforcing properties.[40a]

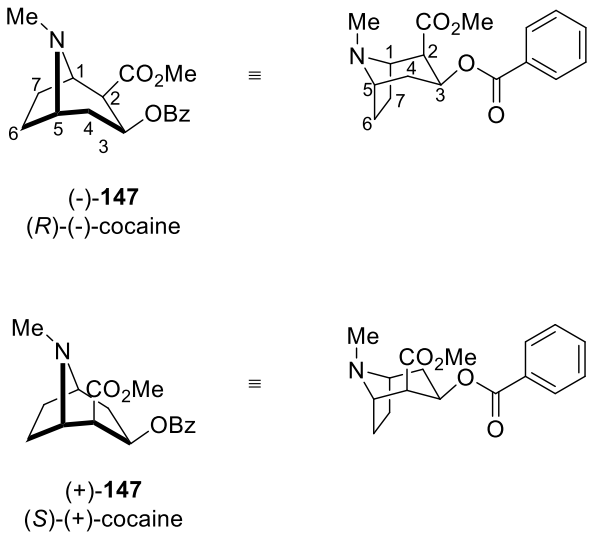
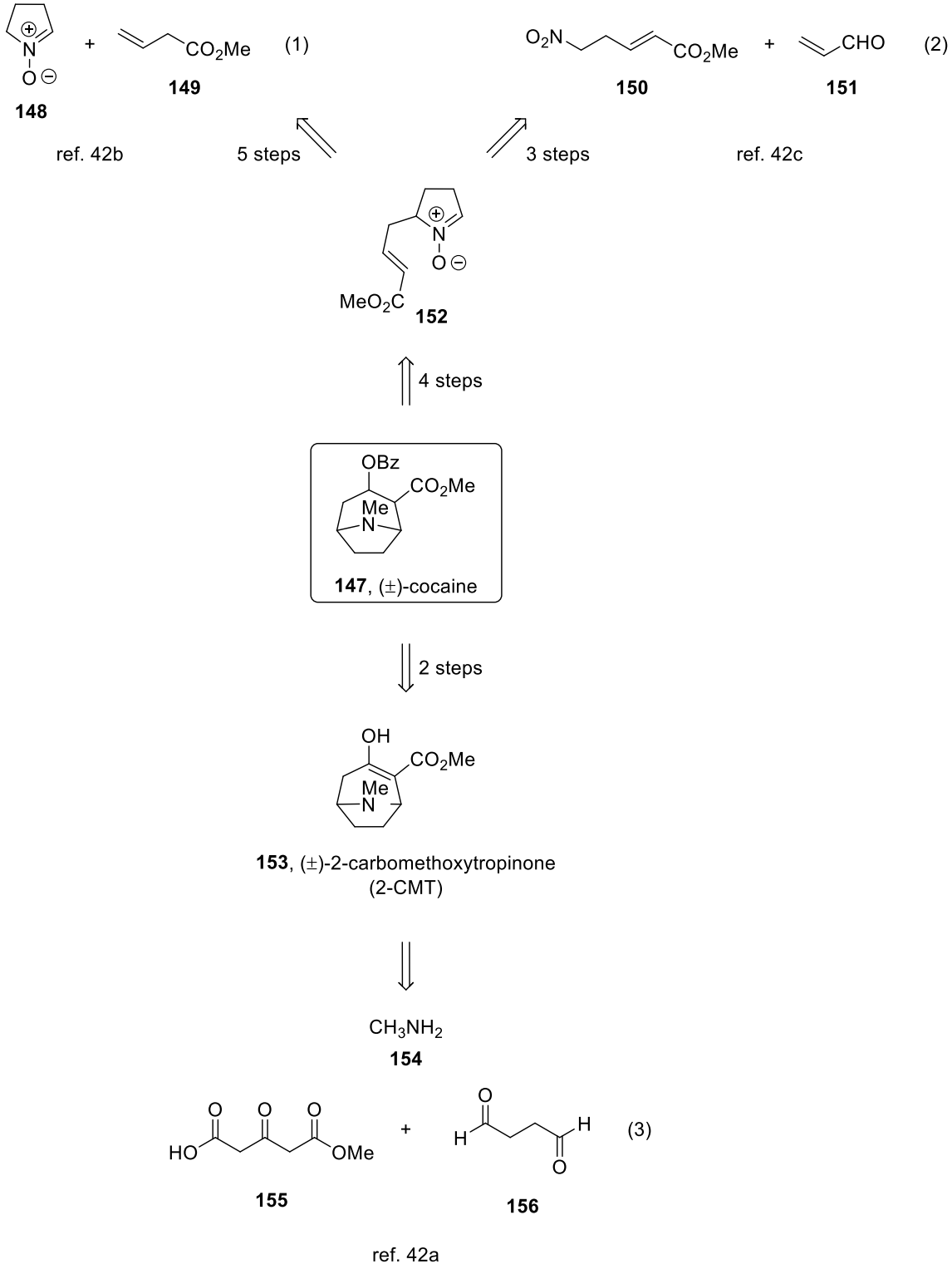


Figure 3. (*R*)-(-)-Cocaine and (*S*)-(+)-Cocaine

To take a closer look into how cocaine functions, it has been proved that cocaine blocks the reuptake of norepinephrine (NE), serotonin (5-HT), and dopamine (DA) as well as to exert effects on the cholinergic muscarine, and α receptors. In fact, it is mainly the dopaminergic pathway that has been implicated in the reinforcing properties of cocaine and it is called "dopamine hypothesis". This hypothesis assumes that cocaine binds to the dopamine transporter site which results in inhibition of dopamine reuptake. Therefore, the dopamine concentration in the synaptic cleft and it leads to potentiation of dopaminergic transmission.[41a, 41b]

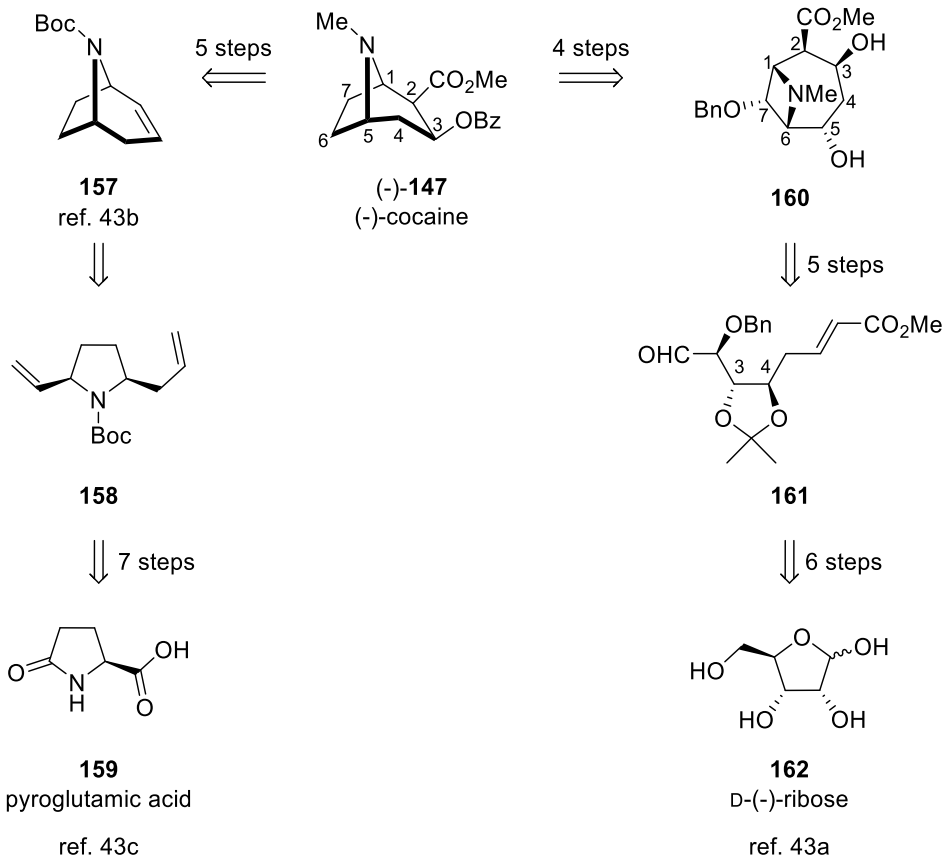
As the cocaine abuse has become a serious issue, the search for therapeutically useful antagonists and partial agonists for the addiction treatment has come to be an important agenda. Therefore, numerous synthetic methods have been developed to get access to cocaine and its new derivatives.



Scheme 35. Synthesis of (±)-Cocaine

The oldest synthesis towards cocaine is naturally the one of racemic cocaine. The first two syntheses have the intermediate **152** in common which was resulted from pyrroline oxide **148**

and methyl butenoate **149**[41b] in eq. (1) and acrylate **150** and acrolein **151** in eq. (2) (**Scheme 35**).[42c] The intermediate **152** was then converted to racemic cocaine by methylation, hydrogenolysis and benzoylation to afford the racemic cocaine **147**. The cocaine synthesis via different intermediate has been also reported by Casale in 1987 in eq. (3).[42a] The synthesis starts with the preparation of the acetonedicarboxylic acid monomethylester **155** and succinialdehyde **156** which are combined with the methylamine **154** to form 2-CMT **153**. Moreover, individual enantiomer of 2-CMT **153** has been separated by chiral resolution with a help of (-)-tartaric acid. Both 2-CMT bitartrate were then hydrated, reduced and benzoylated to afford chirally pure cocaine. In conclusion, the racemic cocaine and both enantiomers of cocaine have been obtained in good yields.

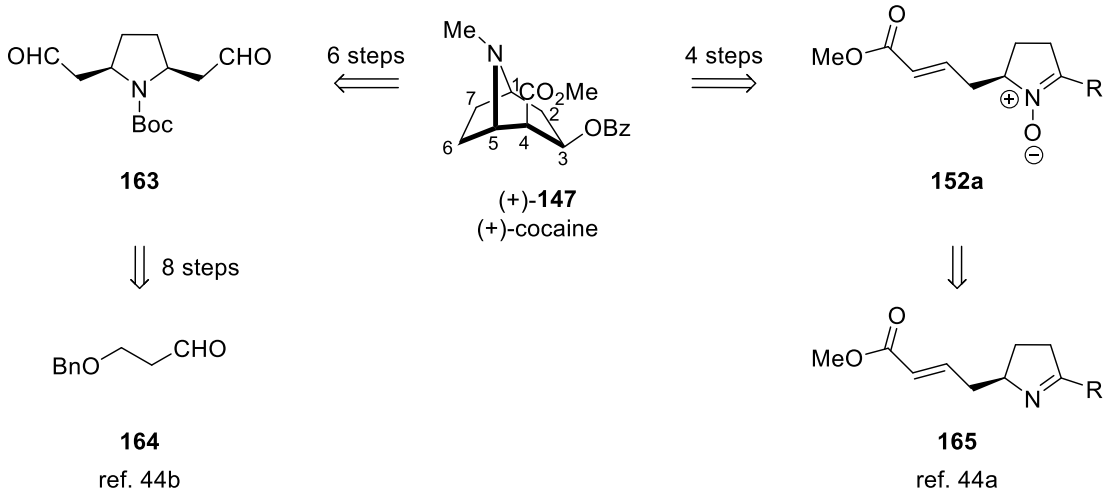


Scheme 36. Synthesis of (-)-Cocaine

To continue medical evaluation and seeking for the medication to treat substance abuse, the interest in the synthesis of notorious (-)-cocaine and new derivatives has been maintained. The ring closing metathesis of **158** as a key step, Hu *et al.* have developed an effective synthetic method which results in formation of (-)-cocaine in 46% overall yield after 9 steps from the pyroglutamic acid **159** (**Scheme 36**).[43b, 43c] On the other hand, Shing *et al.* have focused on the

synthesis of tropane backbone from inexpensive D-ribose **162** and installation of various functional groups on C7 in **160**.[43a] As a result, not only (-)-cocaine but also functionalized cocaine derivatives could be obtained after 15 steps from **162** in 13% overall yield, after 12-15 steps in 14-26% yields.

The synthesis of (+)-cocaine has attracted less interest since this enantiomer of cocaine is rapidly metabolized as mentioned before. One example is the 14-step total synthesis with **164** as the starting material which resulted in 6.5% overall yield by Pearson *et al.* in 2004 (**Scheme 37**).[44b]



Scheme 37. Synthesis of (+)-Cocaine

The synthesis has a L-proline catalyzed aldol reaction of dialdehyde **163** as a key feature which forms the backbone of (+)-cocaine, however, only with poor diastereoselectivity. On the other hand, a report by Davis *et al.* has suggested an improved synthesis of (+)-cocaine and its C1-functionalized derivatives in 9 steps.[44a] The synthesis by Tufariello *et al.* has begun with preparing **165** which is then oxidized to **152a**.[42b, 42c] The final product (+)-**147** has been successfully synthesized after the introduction of OBz group on C3-position after the *N*-oxide **152a** is cyclized. The original cyclization method was with white acid and has been improved under less harsh reaction condition using $Al(O\text{-}t\text{-}Bu)_3$ to afford desired (+)-cocaine enantioselectively.

2.2. Synthesis of Cocaine Derivatives

Based on Structure-Activity Relationship (SAR), the tropane derivatives such as cocaine analogues could have similar behavior or action in the central nervous system. The SAR data and preliminary molecular modeling studies have proposed a pharmacophore model for the

cocaine receptor[45] to illustrate the function and characteristics of each part (**Figure 4**). The amine moiety is believed to have certain interaction with the dopamine transporter (DAT) by an electrostatic or hydrogen bond although the presence of amine moiety is not necessarily essential for potent activity. More importantly, the two vicinal oxygen in ester moiety contributes to the interaction with DAT by one or two hydrogen bond. The benzoyl/phenyl group on C3 position is supposed to have the hydrophobic pocket. It has been discovered that the absolute configuration of substituents in cocaine and presence of methyl ester group play an important role in the affinity to the DAT.

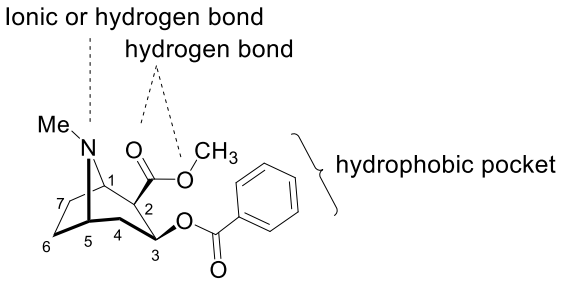


Figure 4. Schematic Representation of Putative Interaction of (-)-Cocaine with Dopamine Transporter Binding Sites[45]

Therefore, the derivatization of cocaine analogues has been conducted by varying those parts in the molecule. A representative cocaine derivative is ferruginine **166** (**Figure 5**). (+)-Ferruginine, (+)-**166** has been isolated from the species *Darlingiana ferruginea*[46b] and *D. darlingiana*.[46a] It has been found that the enantiomer of (+)-ferruginine, (-)-ferruginine, (-)-**166** is a good agonist for the nicotinic acetylcholine receptor (nAChR) as well as analogues with different substituents on nitrogen, H for norferruginine (**167**) and Me_2 for *N*-methylferruginine (**168**). It was late 1990s that the synthesis of ferruginine **166** has begun to be reported.

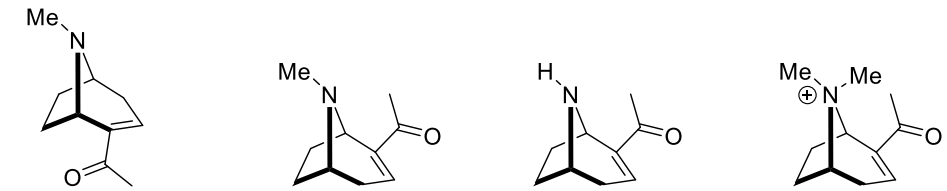
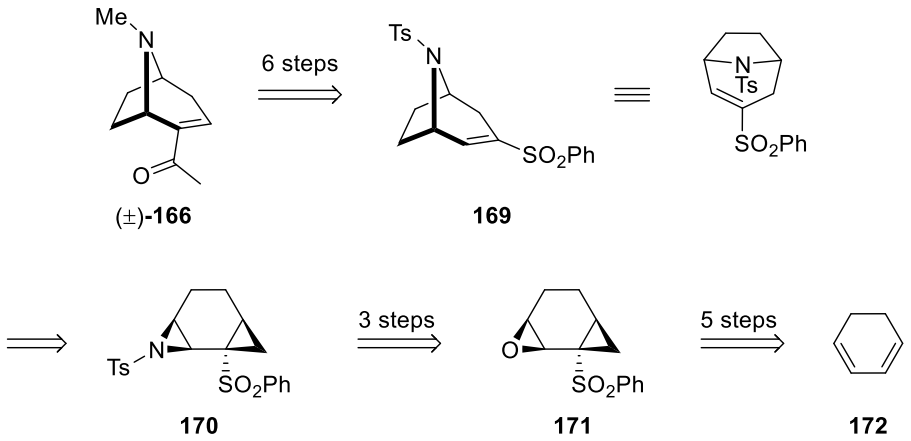


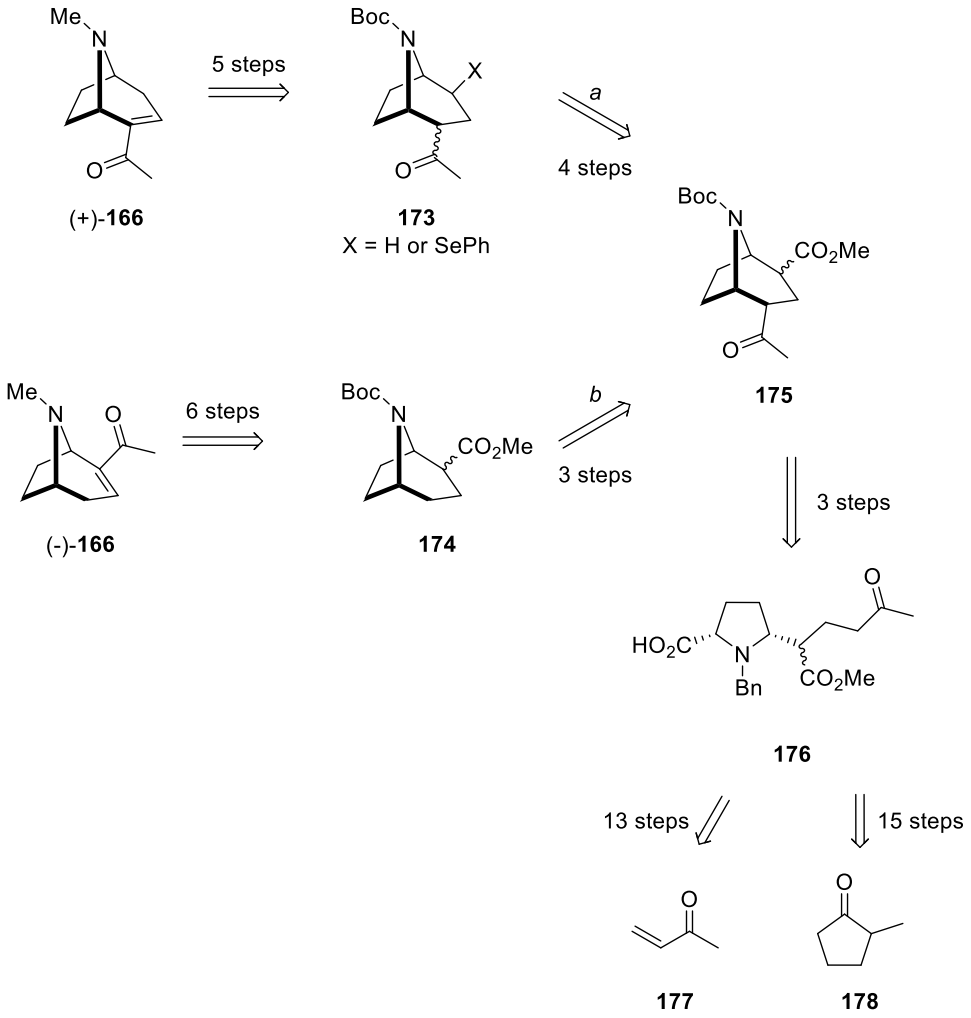
Figure 5. Ferruginine, Norferruginine and *N*-Methylferruginine

The first few studies on ferruginine synthesis have been carried out by Davies *et al.* and described in **Scheme 20**.[25] The next example starting from the very simple starting material, 1,3-cyclohexadiene **172** has been published by Bäckvall *et al.* in 2000 (**Scheme 38**).[47] The synthesis has a BF_3-catalyzed rearrangement of the intermediate **170** as a key reaction. As the intermediate **169** is generated, the further transformations to get access to the vinyl ketone moiety of the ferruginine **166** have followed. The total synthesis contains 15 steps and yields the desired ferruginine in 17% overall yield.



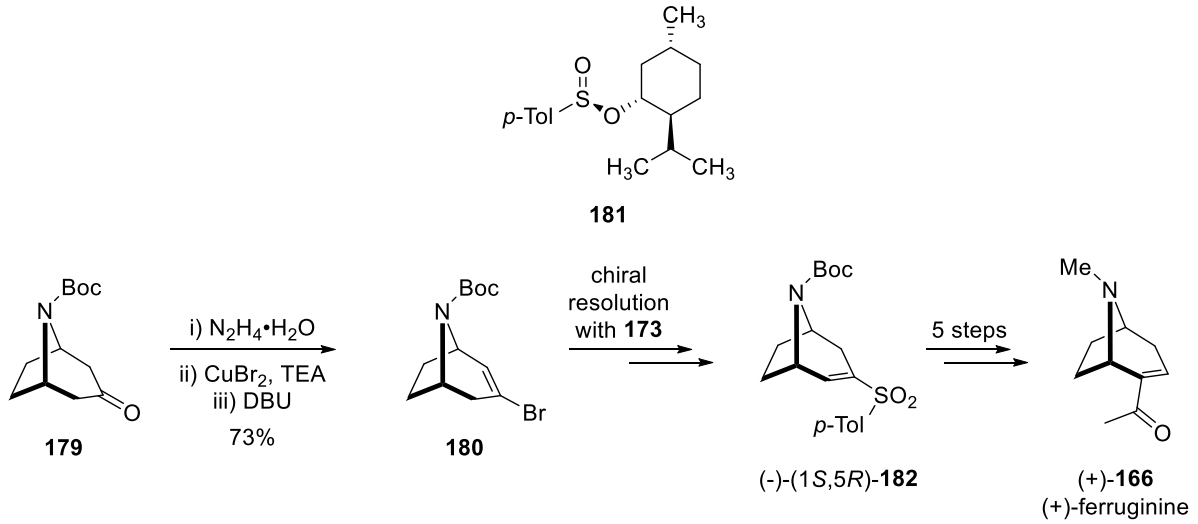
Scheme 38. Ferruginine Synthesis by Bäckvall *et al.*

In 1996, the synthesis of each (-)- and (+)-ferruginine has been published by Rapoport *et al.* (**Scheme 39**).[48] The synthesis contains the linear steps from the very simple molecules such as methyl vinyl ketone **177** or 2-methylcyclopentanone **178** to reach the formation of the intermediate **176** which is then followed by cyclization to **175**. The key intermediate **175** has been transformed via pathway *a* to afford (+)-ferruginine whereas treatment via pathway *b* affords (-)-ferruginine. Although the synthesis of enantiopure ferruginines (+)- and (-)-**166** and (+)-norferruginine, (+)-**167** is established, the synthesis is considered less efficient and not economical due to its numerous reaction steps.



Scheme 39. Ferruginine Synthesis by Rapoport *et al.*

Along with the synthesis of racemic ferrginine, there has been a development on enantioselective synthesis of (+)-ferruginine. The synthesis is the most recent and shortest is with the use of commercially available *N*-Boc-nortropinone **179** (**Scheme 40**).[49] With few treatments, the vinyl bromide **181** was obtained from the starting material, **180**. Then **180** was reacted with (-)-(1*R*,2*S*,5*R*)-menthyl-(*S*)-*p*-toluenesulfinate **181** to generate a pair of diastereomers which underwent separation by flash chromatography. Afterwards the sulfonyl group in the single diastereomer (-)-**182** was cleaved and followed by the introduction of ketone moiety to obtain the desired (+)-ferruginine, (+)-**166**. In conclusion, the formal synthesis has been achieved in 8 steps to get access to the enantiopure (+)-ferruginine from **179**.

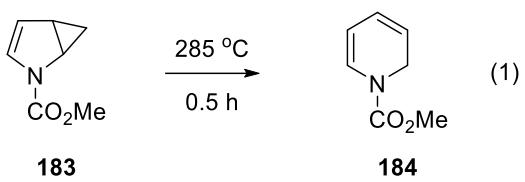


Scheme 40. Synthesis of (+)-Ferruginine by Renaud *et al.*

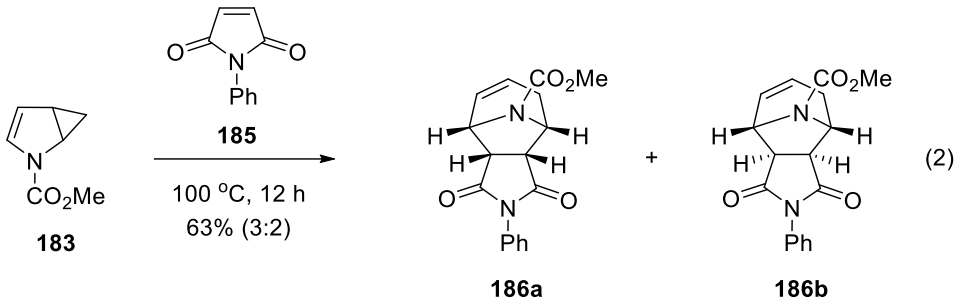
With the studies on the synthesis and functions of cocaine derivatives, the catalyst free synthesis of cocaine derivatives has been investigated. As the ground work by Fowler *et al.* has been shown, cyclopropanated pyrroles with different protecting groups were utilized as a valuable substrate.

2.3. Catalyst Free Synthesis of Tropane Derivatives

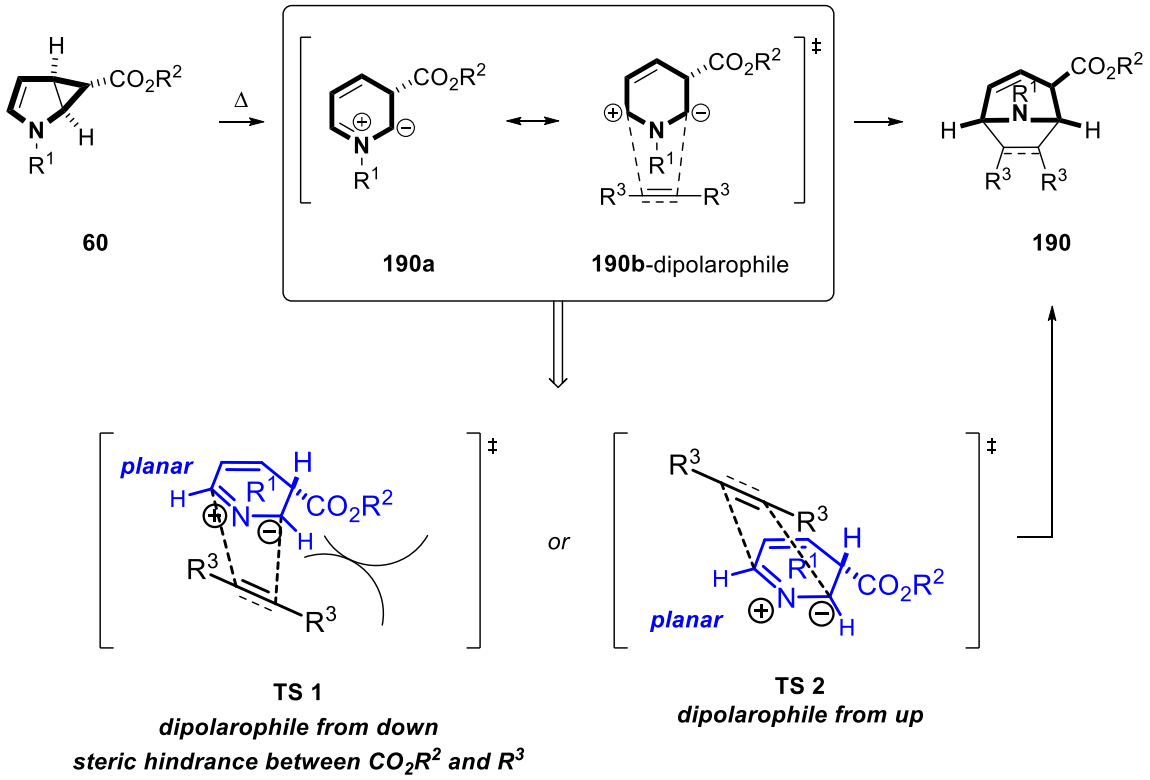
As a useful resource, cyclopropanated pyrroles have been utilized in many reactions. One of the chemists who focused on the development of synthetic methods with cyclopropanated pyrroles in early time was Fowler, F. W.. The first finding which enabled his cycloaddition studies was the pyrolysis of cyclopropanated pyrrole **183** in gas phase to dihydropyridine **184** at 285 °C (eq. (1) in **Scheme 41**).[50c] The dihydropyridine **184** was not isolated due to its highly unstable property, however, the presence of the dipole intermediate had later been demonstrated by the reactions with dipolarophile such as *N*-phenylmaleimide **185** which resulted in *endo*-cycloadduct **186a** and *exo*-cycloadduct **186b** in a ratio of 3:2 (eq. (2)). Since then, he had expanded his research area to the synthesis of cocaine-related tropane derivatives and evaluation of their reactivity.[50a]



183 **184**



Scheme 41. Findings of Fowler, F. W. *et al.*

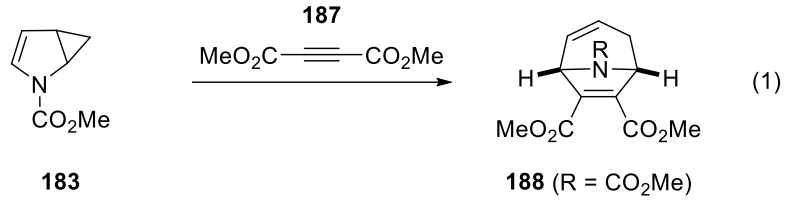


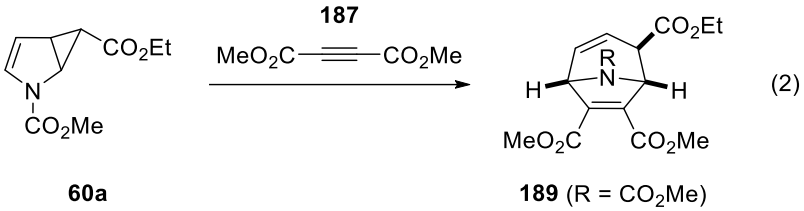
Scheme 42. Plausible Mechanism

From the results in **Scheme 41**, it can be assumed that the substrate **60** converts to dipole species **190a** under heat (**Scheme 42**). When the reaction does not contain any trapping reagent, the resulting dipole intermediate **190a** simply turns into the hydropyridine species **184**. However, when a dipolarophile is applied for trapping, its resonance **190b** could be trapped and product **190** could be obtained.

In the extended research, a substituent effect study on cyclopropanated pyrroles such as **183** and **60a** in cycloaddition has revealed that presence of the substituent, CO_2Et resulted in a slower reaction rate.[50b, 50c] It is assumedly resulted from lowering the highest occupied molecular orbital (HOMO) of substrate and higher activation energy value for the reaction of **60a** in **Table 8**.

Moreover, the study by Hoffmann suggests on Walsh orbital that the electron-withdrawing substituent of cyclopropane ring holds the electron density from the ring which results in weakening the antibonding of C4-C5 bond of cyclopropane, thus strengthening the inner bond, C4-C5 bond (**Figure 6**).[51] As a result, the C4-C5 bond of substrate **60a** becomes more difficult to dissociate which is consistent with the Δ*H** values in **Table 8**. This correspondence implicates that the equilibrium of **60a** to its dipole intermediate is less favorable, thus the reaction condition could require high reaction temperature.





Substrate	*E*a, kcal/mol	A, I./mol·sec	Δ*H**, kcal/mol
183	17.6	1.00 x 10^6	16.8
60a	20.7	6.5 x 10^6	19.9

Table 8. Substituent Effect on Cycloaddition Reaction[50b, 50c]

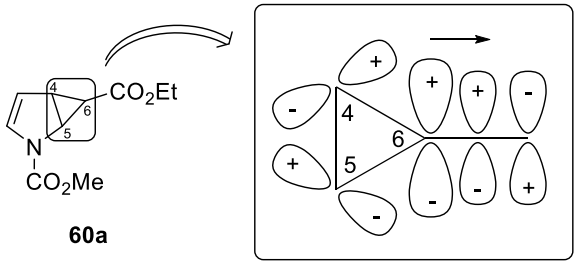
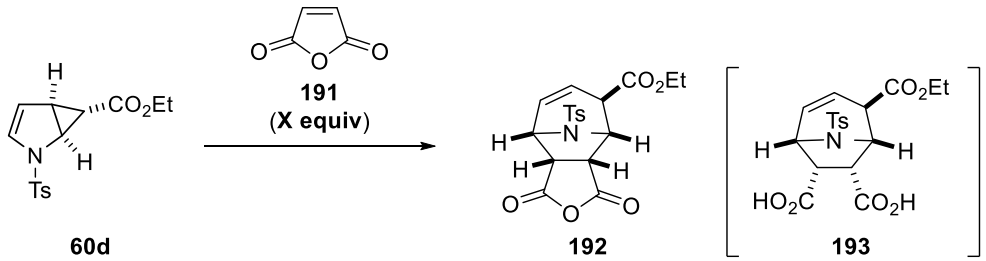


Figure 6. Walsh Orbital Pair in Cyclopropane **60a**[51]

As the test reaction at atmospheric pressure with maleic anhydride **191** was successful, the reaction mixture of substrate **60d** and **191** in solvent was heated to the indicated temperature (**Table 9**). Under atmospheric pressure, the reference reaction condition was applied with 2.8

equiv of **191** (entry 1). After 24 h, the reaction was completed to full conversion and the desired product **192** was found in 70% yield. Due to the tendency of anhydride moiety in **192** to open to diacid **193** on silica gel, the results were given based on crude yields. With elongated reaction time, the yield could be improved (entry 2) but similar results were achievable with less amount of dipolarophile under microwave radiation within 30 min (entry 3-5). For comparison, toluene as a nonpolar solvent with high boiling point and acetonitrile as a polar solvent with moderate to high boiling point were applied. Under the same reaction condition, the results from the two solvent did not show significant difference. The pure product was recrystallized in the solution of crude mixture from a mixture of DCM and hexanes. The NMR analysis has shown that only one diastereomer was formed and through the two-dimensional analysis and X-ray crystallography the absolute configuration of the cycloaddition product **192** was determined and illustrated in **Figure 7**.



Entry	**X**	Condition	Results[b]
1	2.8	Toluene, 100 °C, 24 h	70% (Full conversion)
2	1.0	Toluene, 100 °C, 2 d	84% (Full conversion)
3	1.0	Toluene, MW[a] 100 °C, 1 h	60% (Full conversion)
4	1.0	Toluene, MW[a] 150 °C, 1 h	69% (Full conversion)
5	1.1	Toluene, MW[a] 150 °C, 1 h	79% (Full conversion)
6	1.3	Toluene, MW[a] 150 °C, 30 min	74% (Full conversion)
7	1.3	CH_3CN, MW[a] 150 °C, 30 min	78% (Full conversion)

[a] MW: under microwave radiation. [b] analyzed by crude ^1H NMR data.

Table 9. Reaction Condition Optimization with **191**

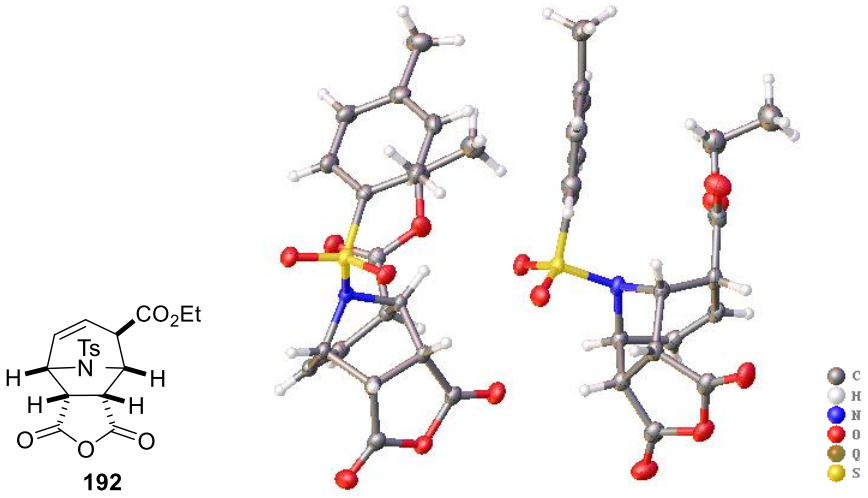
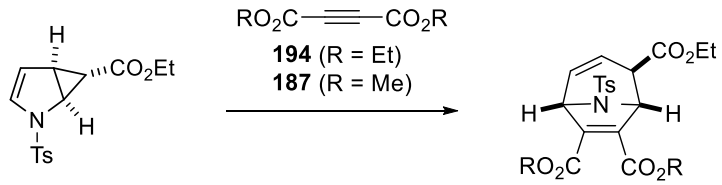


Figure 7. Structure of Product **192**

After observing the successful results with maleic anhydride **191**, the same reaction condition has been applied to the reaction of the substrate **60d** and dialkyl acetylenedicarboxylates. It turned out that the reaction did not lead to any conversion in presence of a solvent even under microwave radiation (entry 1 and 2 in **Table 10**). Therefore, the reaction of the substrate **60d** and dipolarophile **194** or **187** was performed without a solvent. At the trial with diethyl acetylenedicarboxylate (DEAD) **194** in microwave, the reaction led to full conversion and the desired product **195** was obtained by flash chromatography in 61% isolated yield (entry 3). The reaction with dimethyl acetylenedicarboxylate (DMAD) **187** under same reaction condition turned out to afford the product **196** in 60% isolated yield (entry 4). Further trials at lower reaction temperature under microwave radiation did not improve the yields (entry 5 and 6).



60d

195 (R = Et)
196 (R = Me)

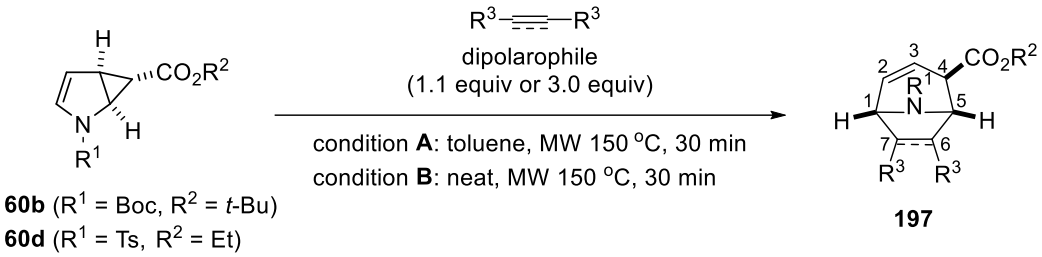
Entry	R[a]	Condition	Results[c]
1	Et	Toluene, 100 °C, 24 h	No conversion
2	Et	Toluene, MW[b] 100 °C, 1 h	No conversion
3	Et	Neat, MW[b] 150 °C, 30 min	**195**, 61% (Full conversion)
4	Me	Neat, MW[b] 150 °C, 30 min	**196**, 60% (Full conversion)

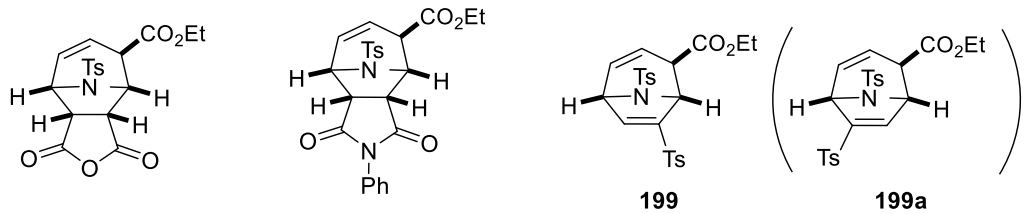
5	Me	Neat, MW[b] 120 °C, 3 h	**196**, 47% (Full conversion)
6	Me	Neat, MW[b] 100 °C, 3 h	**196**, 25% (Partial conversion)

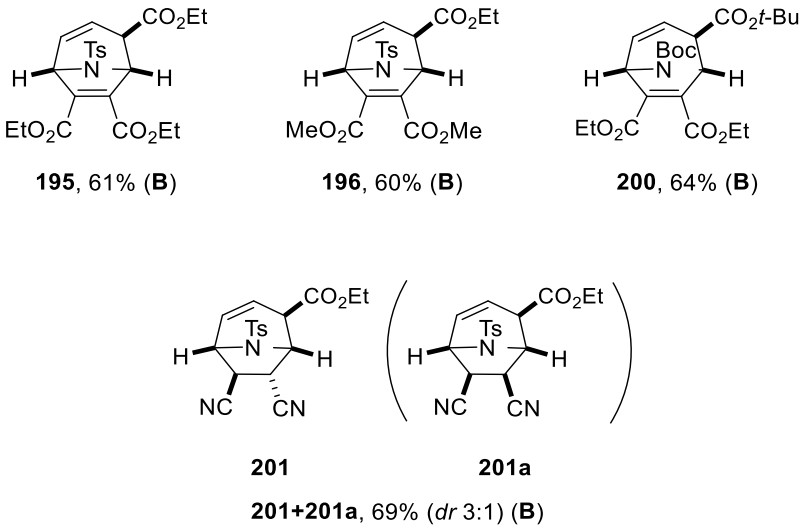
[a] 3 equiv of dialkyl acetylenedicarboxylate was applied.
[b] MW: under microwave radiation. [c] based on isolated yield.

Table 10. Reaction Condition Optimization with Alkyne Dipolarophiles

With the optimized reaction condition for the dipolarophiles either in solid phase or liquid phase, the scope of the dipolarophile has been explored (**Scheme 43**). With every solid dipolarophile applied, the reaction was performed in toluene as a solvent and corresponding cycloaddition products (**192**, **198** and **199**) were successfully obtained. Despite the lower yield of the reaction with tosylacetylene **203**, the reaction has opened the possibility to get access to cocaine after the shortest reaction steps such as deprotection of tosyl group on amine and C6 or C7-position. It is worth noting that the reaction mainly proceeds with dipolarophiles bearing electron-withdrawing group and as for the scope of mono-substituted alkyne, trimethylsilylacetylene and alkyl propiolate did not lead to any conversion. 1D and 2D NMR data of every products were analyzed and compared to that of the product **192** to determine the structure of the products depicted in **Scheme 43**.



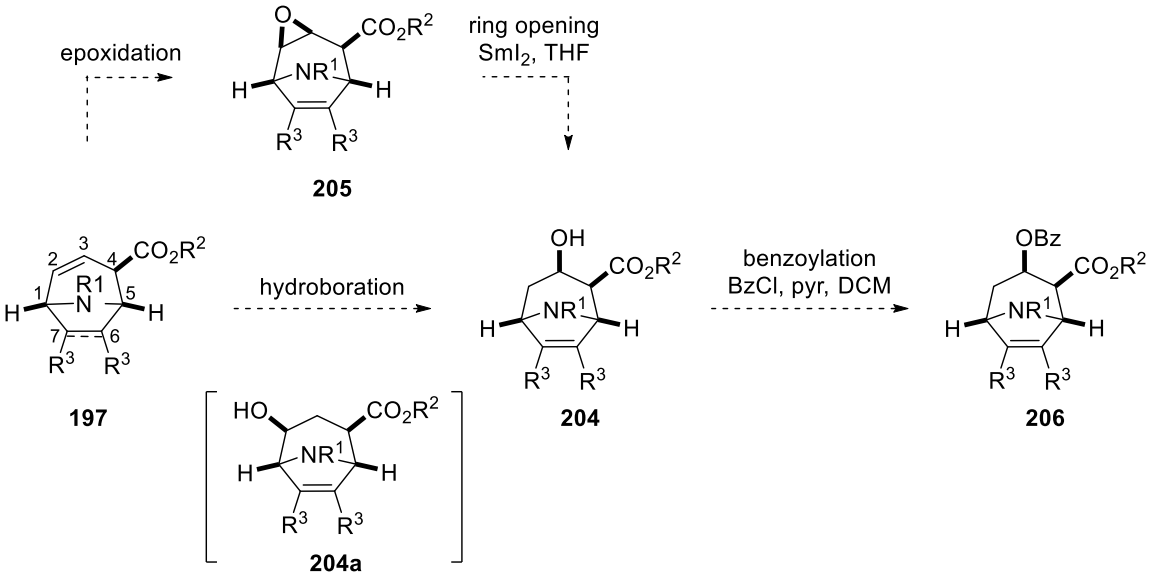




Scheme 43. Substrate Scope

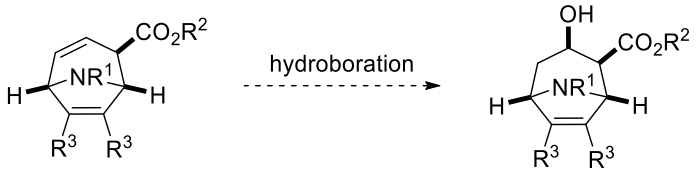
2.4. Further Transformations for Derivatization

With the cycloaddition products in hand, further transformations were performed to introduce functional groups which were essential for the biological activity of cocaine. The functionalization contained an introduction of hydroxyl group by hydroboration to generate **204**, followed by benzoylation of the alcohol towards **206**. Alternatively, the hydroxyl group ccould be prepared via epoxidation to form **205** and selective ring opening by SmI_2/THF to obtain alcohol **204**.[52] In either case, the products **204** and **205** resulting from the reactions of **197** should possess the indicated stereochemistry in **Scheme 44** since the reactions would happen on the less hindered but exposed convex side of **197**.

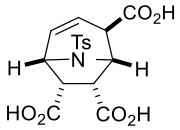
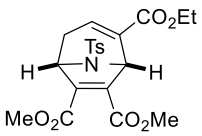


Scheme 44. Functionalization on C2-C4 Bond

In order to introduce the hydroxyl group on this olefin C2-C3 bond of **197**, hydroboration methods have been applied first (**Table 11**).[53] Unfortunately, hydroboration of the cycloaddition product **192** resulted in diacid **193** or triacid **207** depending on the workup (entry 1 to 4) and the desired alcohol **204** was not obtained. The cycloaddition product **192** has turned out to be inadequate substrate for hydroboration due to the unstable characteristics of anhydride moiety. Therefore, cycloaddition product **196** has been chosen for the next entry, however, the reaction only performed isomerization of the olefin to give **208**.



197 **204**

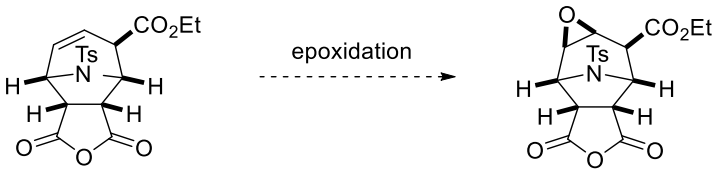
Entry	Substrate	Reaction Condition	Results
1	**192**	$NaBH_4$ (1.6 equiv), $BF_3{\cdot}Et_2O$ (1.7 equiv) diglyme, 0 °C to rt[52d]	 Triacid **207**[a]
2	**192**	9-BBN (2 equiv), THF, rt to reflux[52a]	Triacid **207** [a]
3	**192**	$BH_3{\cdot}THF$ (1M soln. 4.5 equiv), THF, 0 °C to rt with basic workup[52b]	Triacid **207** [a] with cleavage of Ts-group
4	**192**	$BH_3{\cdot}THF$ (1M soln. 4.5 equiv), THF, 0 °C to rt with neutral workup[52b, 52d]	Diacid **193**, 43%
5	**196**	$BH_3{\cdot}THF$ (1M soln. 4.5 equiv), THF, 0 °C to rt with neutral workup[52b, 52d]	 **208**, quant.

[a] The amount of triacid **207** was not determined due to the loss in aqueous workup.

Table 11. Attempts at Hydroboration

As the general hydroboration methods have not been successful, the strategy to obtain the alcohol **204** has been altered to the epoxidation to form **205** which is followed by selective ring opening to **204** (**Table 12**).[54] The initial attempts at epoxidation with peracids (entry 1 to 4) have shown that *m*CPBA was not reactive and peracetic acid in presence of base only led to decomposition.

With the peroxides (entry 5 and 6), however, the results have shown that the anhydride moiety of the substrate **192** easily opened into diacid **193** in presence of base. The similar result has been observed in the reaction with Oxone as an oxidant where the isomerization of the olefin on C2-C3 position also has given the product **210** (entry 7).



192 **209**

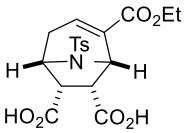
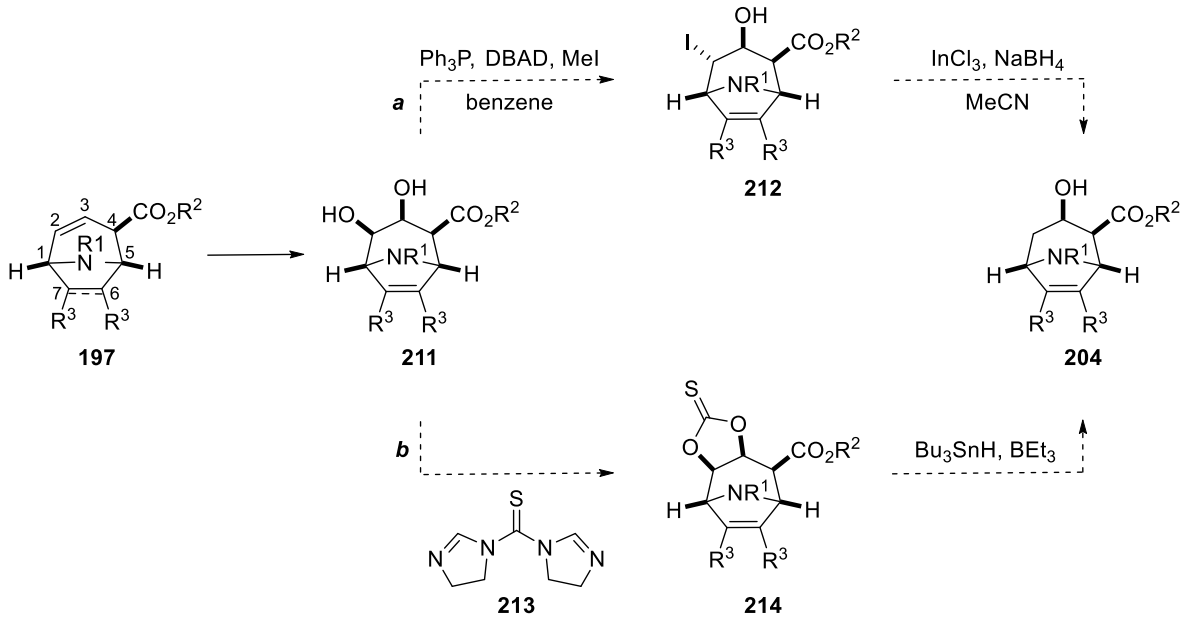
Entry	Substrate	Reaction condition	Results
1	**192**	*m*CPBA (1.1 equiv), DCM, 0 °C to rt[54d]	No conversion
2	**192**	*m*CPBA (1.35 equiv), DCM, 0 °C to 35 °C[54a]	No conversion
3	**192**	*m*CPBA (2 equiv), chloroform, 0 °C to 40 °C[54a]	No conversion
4	**192**	CH_3CO_3H (1.5 equiv), NaOAc (0.05 equiv), Na_2CO_3 (2.9 equiv) DCM, 0 °C to rt[54c]	Decomposition
5	**192**	H_2O_2 (12.5 equiv), K_2CO_3 (sat. aq. soln), MeOH, 0 °C to rt[54f]	Diacid **193**, 54%
6	**192**	t-BuOOH (5.5M soln, 3 equiv), *t*-BuOK (0.03 equiv), THF, 0 °C to rt[54b]	Partial conversion to diacid **193**
7	**192**	Oxone (15 equiv), Na_2EDTA (0.05 equiv), $NaHCO_3$ (20 equiv), Bu_4NHSO_4 (0.2 equiv) Acetone, DCM, water, rt[54c, 54e]	 Isomerized diacid **210**, quant.

Table 12. Attempts at Epoxidation

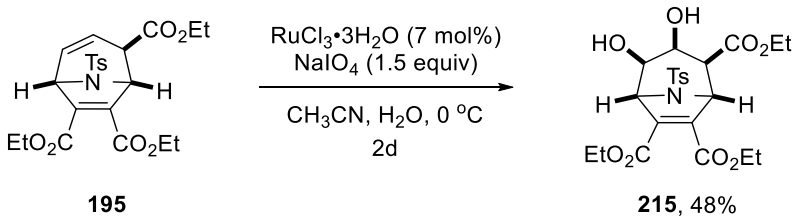
In contrary to the regioselectivity issue hydroboration of **197** may have had, the dihydroxylation on the olefin in **197** to **211** seemed to proceed without any issues. Once the diol **211** was generated, the desired alcohol **204** could be obtained via Mitsunobu reaction and dehalogenation (pathway *a*) or via Barton deoxygenation (pathway *b*) (**Scheme 45**). In pathway *a*, the regioselective Mitsunobu reaction of diol has been reported to occur to the least hindered alcohol.[55] Then the dehalogenation under Inoue reaction condition could cleave the iodine of

212 to afford the alcohol **204**.[56] On the other hand, the pathway *b* contains generation of the xanthate **214** with diimidzolyl thiocarbonyl **213** which is followed by deoxygenation of one alcohol to the desired alcohol **204**.[57]



Scheme 45. Synthetic Route to **204** via Dihydroxylation

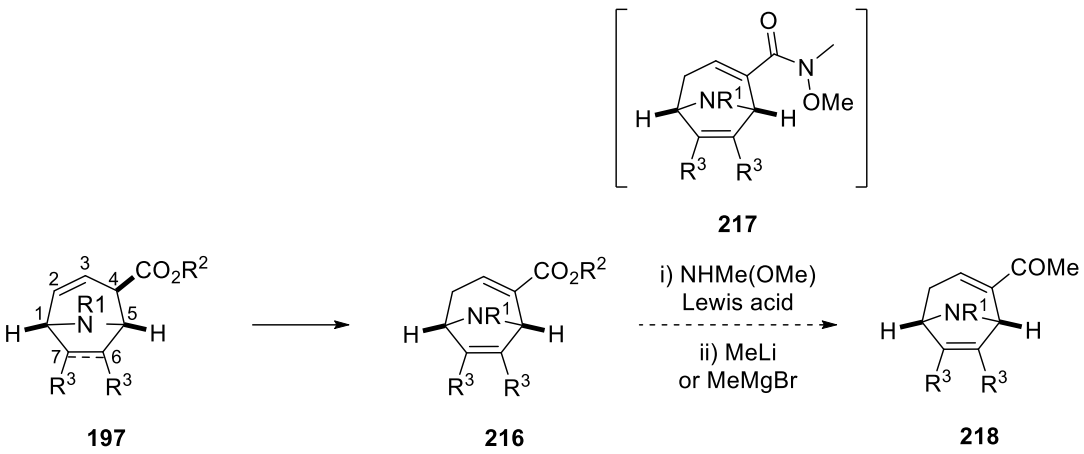
To accomplish the alternative synthetic route to **204**, dihydroxylation of **195** has been carried out with the relative benign reagents as reported (**Scheme 46**). The stereochemistry of the diol product **215** was determined by 2D NMR analysis. Unfortunately, the rest of the transformations are not yet completed.



Scheme 46. Dihydroxylation of **195**[24b]

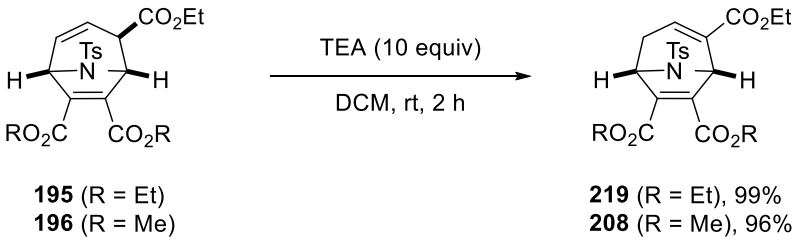
During the examination of cycloaddition with DMAD **187** or DEAD **194**, the isomerization of the olefin on C2-C3 bond has been observed. As the isomerized cycloaddition product would have more distinctive electronics or steric factor, the synthetic route to introduce the substituents which cocaine or ferruginine have has been altered (**Scheme 47**). The generated conjugated α,β-

unsaturated system can act as a Michael acceptor or more substituted olefin for the further transformations. The easiest synthetic target would be ferruginine as the isomerized product **216** only needs transformation from ester to ketone via Weinreb amide formation with NHMe(OMe). Then the conversion of the Weinreb amide **217** to the ferruginine derivative **218** can be achieved by the reaction with alkylating reagents such as methyllithium or Grignard reagent, MeMgBr.[58]



Scheme 47. Transformation via Weinreb Amide Formation

The isomerization on the double bond in **195** and **196** was first observed during the flash column chromatography for purification. Therefore, silica-gel mediated isomerization was performed. However, the conversion was not completed after 2 days. On the other hand, base-mediated isomerization proceeded in 2 h which resulted in full conversion and excellent yields (**Scheme 48**). Although the reaction proceeds excellently, the ester moiety of **218** and **207** could be also reactive under the Weinreb amide formation condition. Hence, the isomerization still needs to be explored with other cycloaddition products and the further transformations to obtain Weinreb amide **216** and ketone **217** will be carried out in the future.



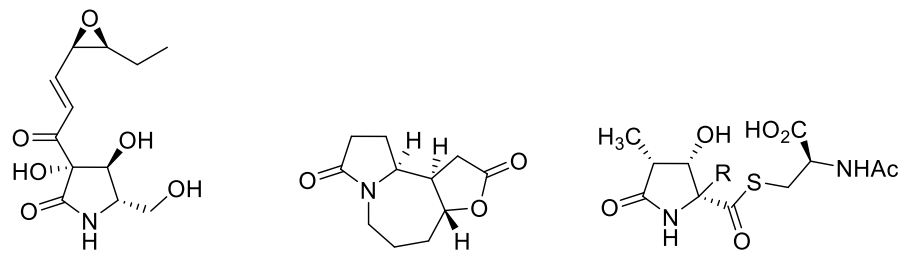
Scheme 48. Isomerization of Cycloaddition Products

3. Transformation of Cyclopropanated Pyrrole to Chiral Pyrrolidinone

As a versatile precursor and bioactive molecule itself, pyrrolidinone has been found abundantly in nature and chosen as a target molecule in the numerous syntheses. Herein the synthesis of chiral pyrrolidinone from the protected pyrrole via asymmetric cyclopropanation has been demonstrated.

3.1. Naturally Occurring Pyrrolidinone

From antifungal, antitussive to insecticidal, has been known the various effect of the pyrrolidinone analogues in nature. The representative pyrrolidinone natural products are demonstrated in **Figure 8**. (-)-Pramanicin (**220**) is isolated from a fungus belonging to the *Stagonospora* family and has shown a notable activity towards various fungal pathogens such as *Candida albicans*, *Cadida parapsilosis* and *Cryptococcus neoformans*. The *Cryptococcus neoformas* is a microorganism which is responsible for meningitis infection in AIDS patients.[59] Next, stemoamide (**221**) is one of *Stemona* alkaloids, isolated from S*temonaceae* plants and the use of the extracts of the plants is traditionally for the cure for the antitussive symptoms.[60] Last but not least, lactacystin (**222**) has been reported to be the precursor of β-lactone omuralide (*clasto*-lactacystin) which plays an active role in inhibition of the proteolytic activity of the 20*S* proteasome by acylation mainly at the *N*-terminal threonine of the chymotryptic subnit.[61]



220
(-)-Pramanicin

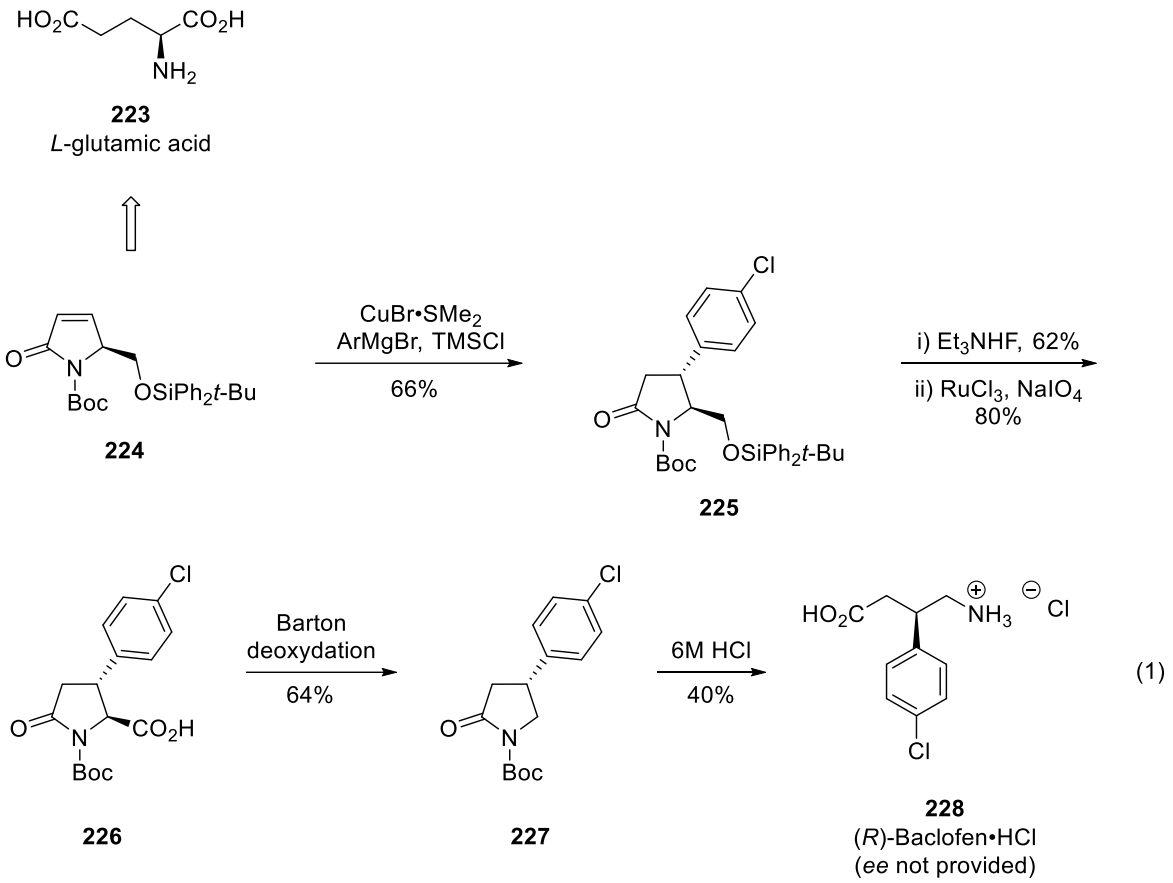
221
Stemoamide

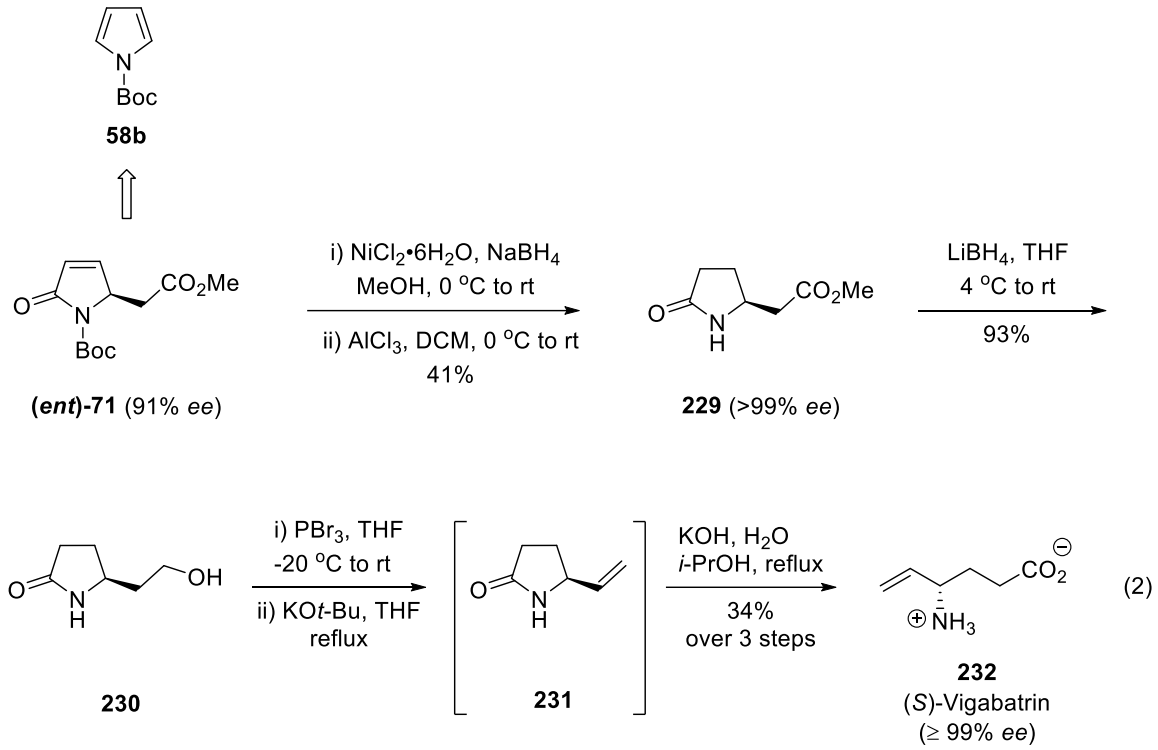
222
Lactacystin
(R = CH(OH)*i*-Pr)

Figure 8. Bioactive Pyrrolidinone Natural Product

The commonly found lactam moiety of pyrrolidinone is prone to undergo ring opening reaction and this reaction has been found often in synthesis of linear GABA (γ-aminobutyric acid).[24b, 62] Some molecules such as baclofen (**228**) and vigabatrin (**232**) are categorized as GABA which is the main inhibitory neurotransmitter in central nervous system in mammals. (*R*)-Baclofen (**228**) happens to be the most lipophilic substance with a higher affinity to $GABA_B$-receptor. The

synthesis of (*R*)-form of **228** contains **225** as the intermediate in the step (1) in **Scheme 49**. The essential ring opening step of **227** occurs with 6M HCl to afford **228** as a salt with the high optical purity. (*S*)-Vigabatrin (**232**), on the other hand, has been approved to be in treatment for antiepileptic symptoms as acting as an irreversible inhibitor for GABA-T and commercialized with the brand name of Sabril®. The enantioselective synthesis of **232** from **(*ent*)-71** contains 6 steps and the synthesis of the intermediate **71** started from the inexpensive pyrrole. Thus, the whole process to obtain (S)-vigabatrin (**232**) could be considered one of the economic but efficient enantioselective synthesis. The detailed synthesis of the intermediate **71** is described in **Scheme 54**.





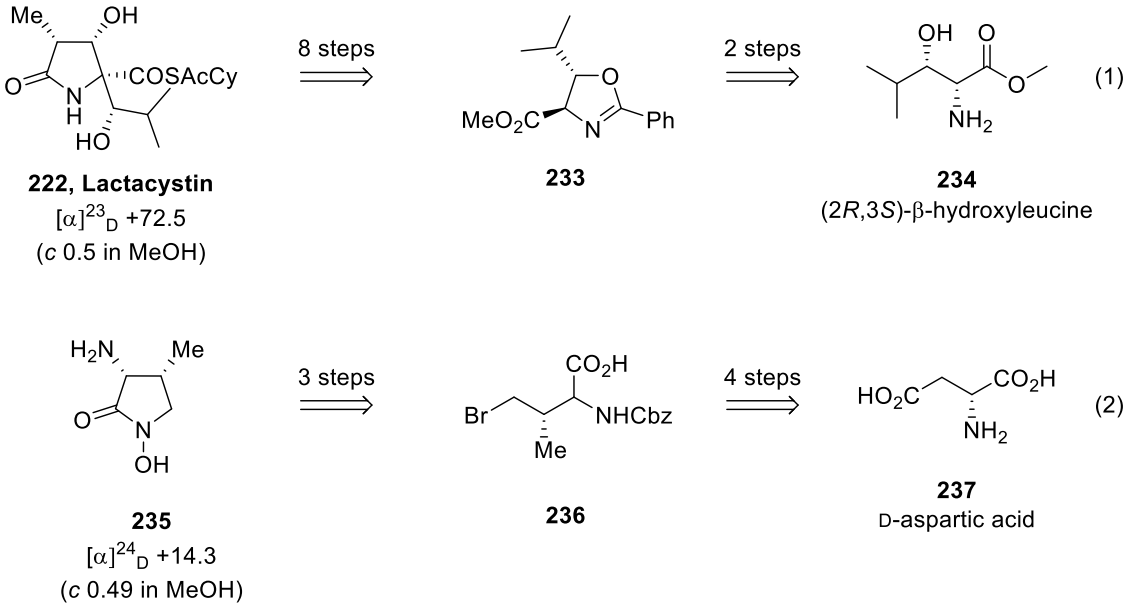
Scheme 49. Pyrrolidinone as Precursor

3.2. Synthesis of Chiral Pyrrolidinone

3.2.1. Preliminary Study on Chiral Pyrrolidinone Synthesis

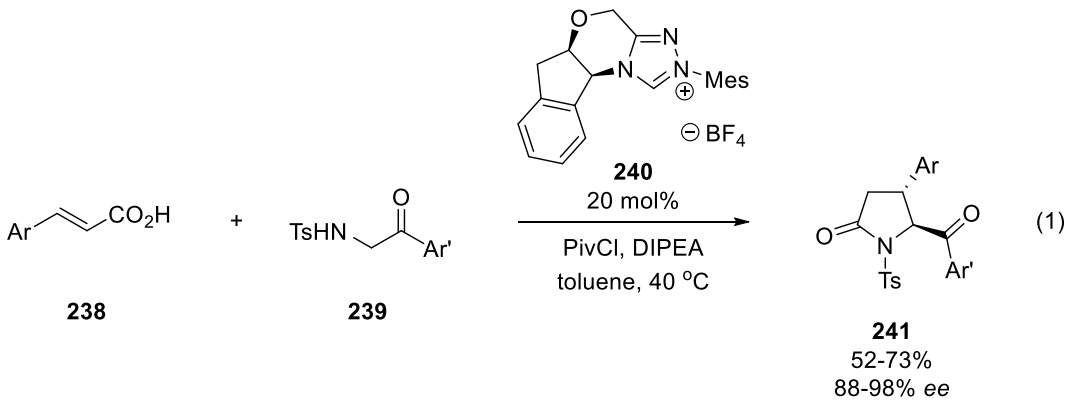
In order to generate the chiral molecules, the chirality should be introduced either by the chiral catalyst or the chiral starting substrate. For the synthesis of chiral pyrrolidinone also, there have been lots of reports employing the chiral starting material such as amino acids or the metal catalyst with chiral ligand.

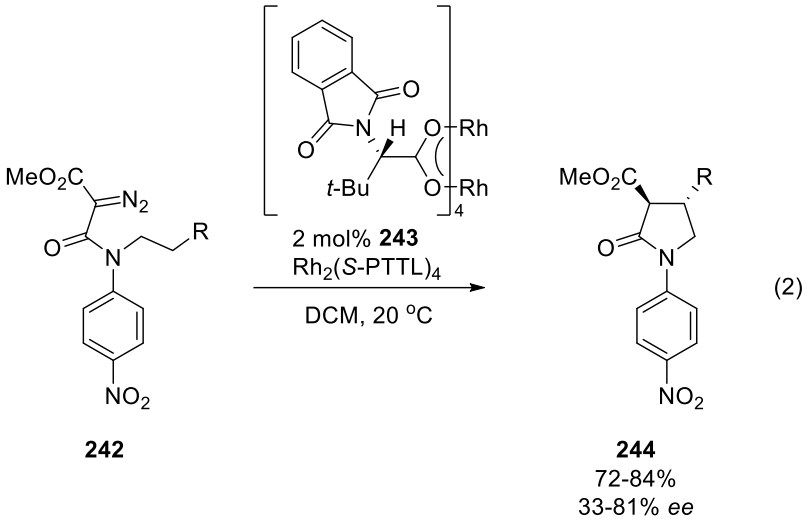
In the representative examples of enantioselective pyrrolidinone synthesis in **Scheme 50**, the highly functionalized pyrrolidinone derivatives **222** (eq. (1)) [63a, 63c] and **235** (eq. (2))[63b] have been synthesized from the rather simple amino acid. Lactacystin (**222**), which was isolated from a culture broth of *Streptomyces* sp. OM 6519 and it's been known that **222** causes transient increases in intracellular cAMP levels as well as acetylcholine esterase activity in the Neuro 2a neuroblastoma cells. The derivative **235**, on the other hand, has been claimed to be the most potent antagonists for treatment of pathological conditions showing a good penetration of the blood-brain barrier. The substituted amino acid **234** and the pure amino acid **237** can induce the chirality to the intermediate **233**and **236**, respectively in the next steps which result in the desired pyrrolidinone products **222** and **235**, respectively with high enantiomeric excess.



Scheme 50. Chiral Pyrrolidinone from Amino Acid

On the other hand, the synthesis promoted by chiral catalyst has been under examination over a long time period but only few catalysis has been known. The reported examples have shown excellent yields and stereoselectivity with the use of chiral thiourea **240** as an organocatalyst (eq. (1) in **Scheme 51**)[64a] or a chiral rhodium catalyst **243** (eq. (2) in **Scheme 51**)[64b]. The asymmetric organocatalysis with **240**, eq. (1) is applicable to the substrate from α-ketoamide **239** to cyclic imines to generate chiral pyrrolidinones **241** to piperidines with excellent enantioselectivity. On the other hand, the enantioselective C-H activation promoted by **243** is known to be the first enantioselective method to synthesize chiral pyrrolidinone and the application to a short step synthesis of (*R*)-baclofen (**228**) is also reported.

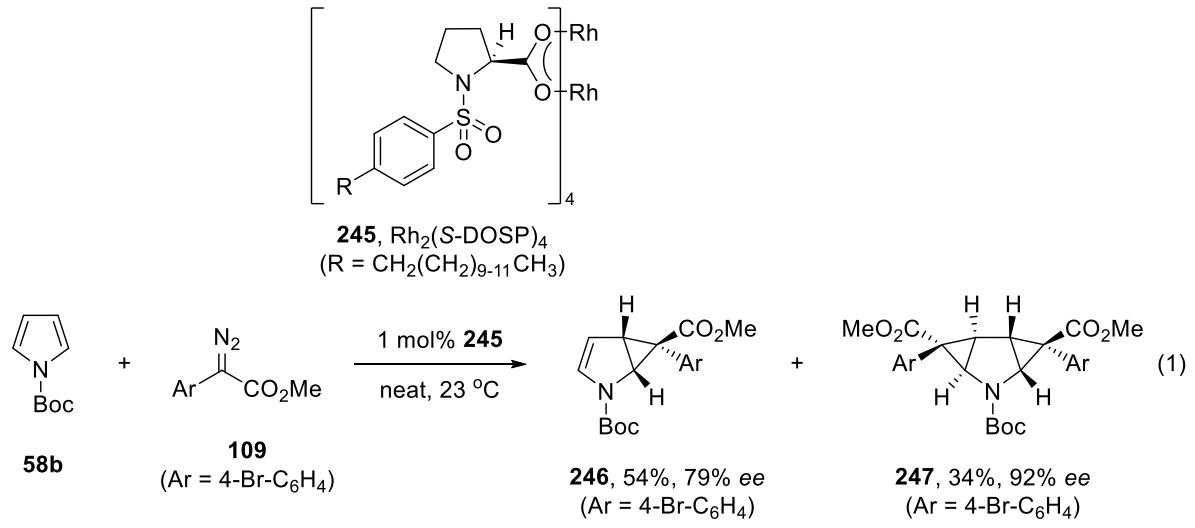


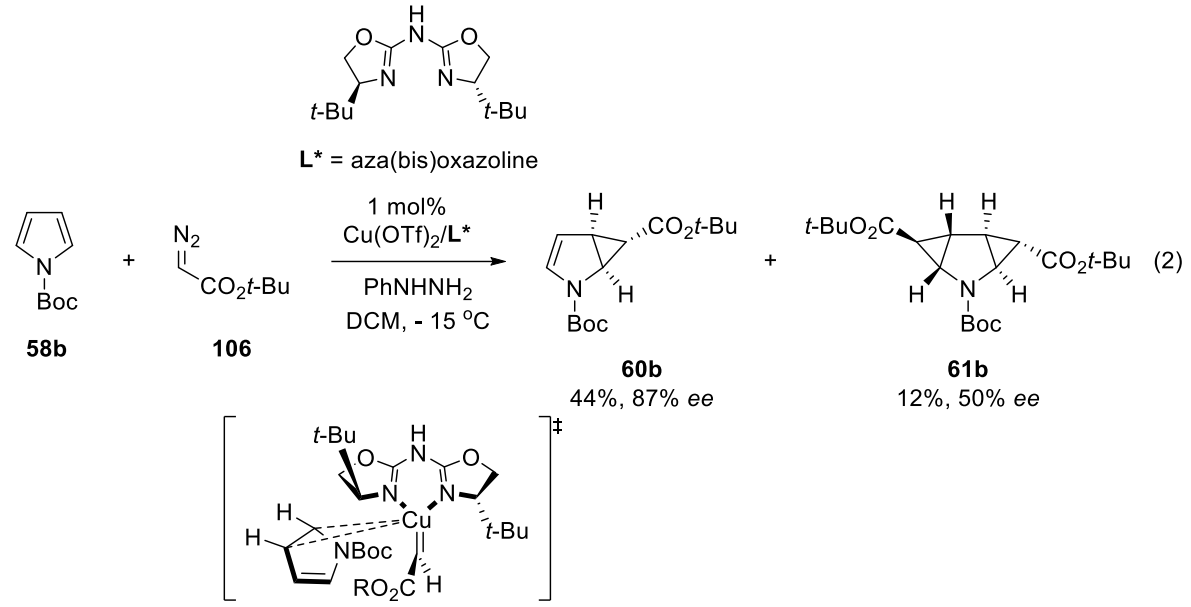


Scheme 51. Chiral Pyrrolidinone Synthesis by Asymmetric Catalysis

3.2.2. Enantioselective Cyclopropanation of Pyrrole

Pyrrole is an inexpensive but naturally abundant molecule which has potential to be utilized in the reactions as a nitrogen-containing source. Therefore the use of pyrrole in the cyclopropanation has been introduced to generate the functionalized cyclopropane ring with nitrogen source on. The asymmetric catalysis to synthesize such cyclopropane rings with enantiopurity has been the upmost task since it opens an opportunity to perform numerous reactions as in **Scheme 18** to give enantio-enriched products. Moreover, naturally occurring cyclopropane rings also have one to multiple numbers of stereocenters. The most conventional method of asymmetric cyclopropanation of pyrrole is the reaction with metal carbenoids from a chiral ligand and metal catalyst. The representative methods with rhodium- and copper-carbenoids are described in **Scheme 52**.



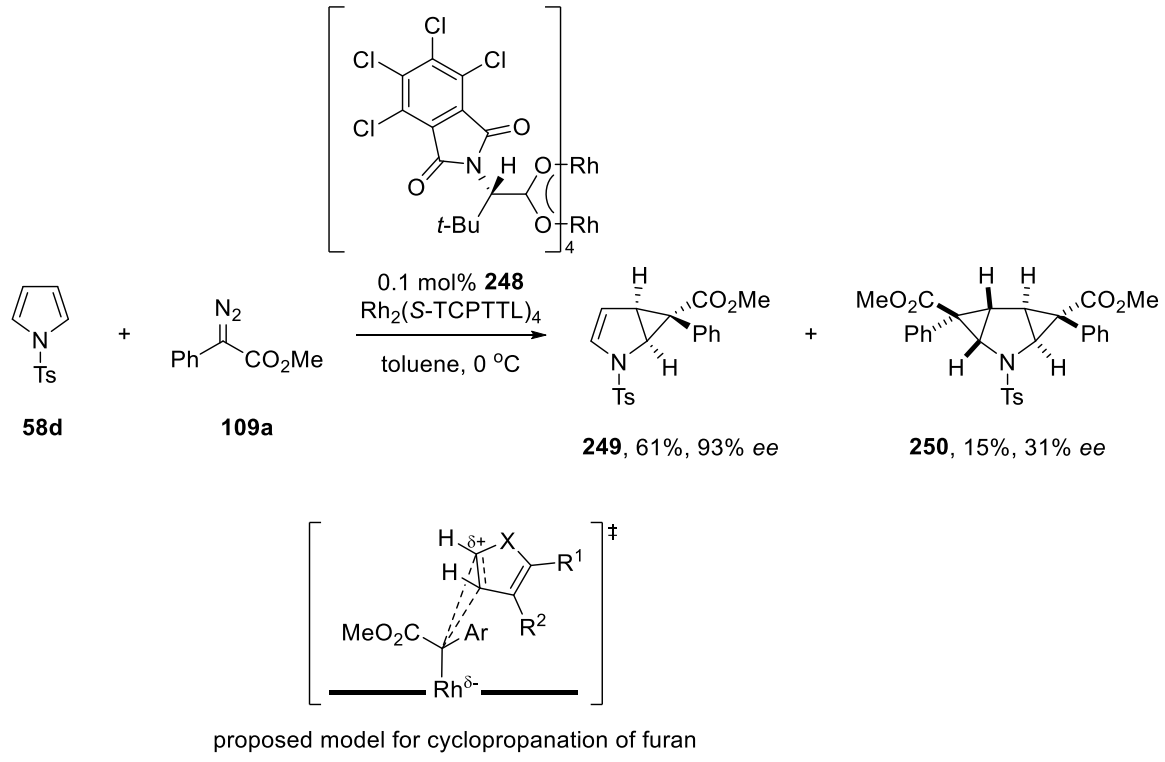


Scheme 52. Enantioselective Cyclopropanation of Pyrrole

The Rh-catalyzed cyclopropanation of pyrrole in eq. (1) in **Scheme 52** has utilized the diazo compound **109** and chiral rhodium catalyst **245** which has been developed by Davies *et al.*.[65a] The catalyst **245** and the diazo compound **109** combine to generate the chiral carbenoid species which reacts with the C-C double bond of the pyrrole **58b**. Traditionally, the metal carbenoids are categorized into three groups according to electron density the substituents can withdraw or donate by resonance: acceptor-acceptor, acceptor and acceptor-donor substituted carbenoids. Acceptor-acceptor substituted carbenoid contributes to more electrophilic and reactive carbenoid whereas acceptor-donor substituted one leads to be more stable and chemoselective.[65b, 65c] Therefore, to enhance more stereo-induction and lessen the reactivity of the generated rhodium carbenoid species, acceptor-donor substituted diazo compound **109** was chosen for the reaction. However, the carbenoid species is still reactive that it also reacts with the mono-adduct **246** to form bis-adduct **247**. This method has been the rare example of asymmetric cyclopropanation of pyrrole until the Cu-catalyzed variant, (2) in **Scheme 52** has been reported.[23a] The newly developed Cu-catalyzed asymmetric cyclopropanation and the application of the products has been the important project over a decade. The method applies $Cu(OTf)_2$ as a catalyst and chiral aza(bis)oxazoline as a ligand (L^*) at - 15 °C to afford the mono-adduct **60b** in 44% and 87% *ee* which has been then recrystallized to raise the *ee* to over 99%.

What has not been examined is the asymmetric cyclopropanation of the pyrrole which is not substituted by Boc-group. The studies of asymmetric cyclopropanation of heterocycle have been

ongoing with various chiral rhodium catalysts prepared by Davies *et al.*. In the most recent report, asymmetric cyclopropanation of substituted furan has been revealed.[65b] The synthesis has utilized Rh_2(*S*-TCPTTL)$_4$ **248** as a highly efficient and promising catalyst and the very method could be also applied to the asymmetric cyclopropanation of substituted pyrrole**s**. As a result, the scope of substituted pyrrole has widened to sulfonyl group-substituted pyrrole such as Ts- or Ms-group. Especially, it has been successful to obtain Ts-substituted cyclopropanated pyrrole **249** from **58d** and **109a** in >99% *ee* after recrystallization with only 0.1 mol% of the catalyst, Rh_2(*S*-TCPTTL)$_4$ **248** (**Scheme 53**).[66a]



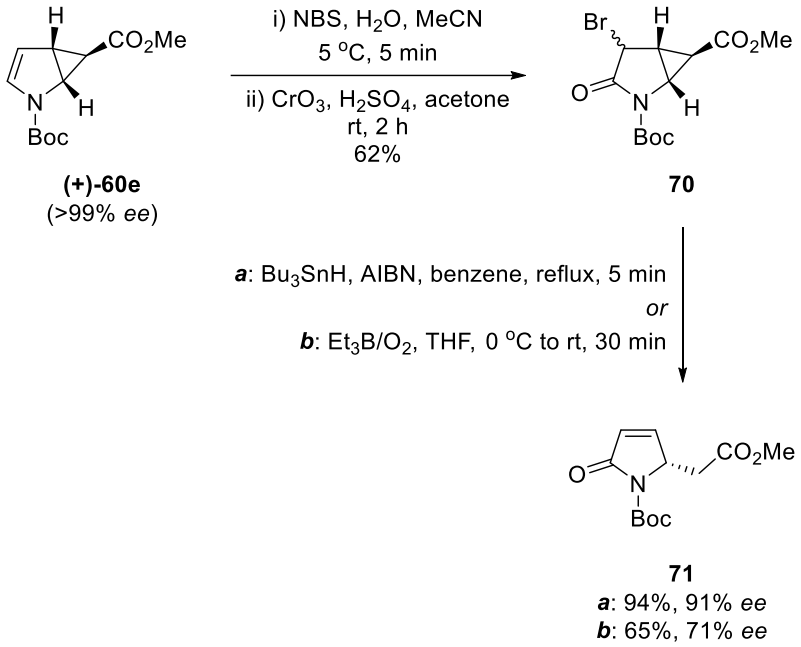
Scheme 53. Asymmetric Cyclopropanation of Ts-substituted Pyrrole[66]

3.2.3. Enantioselective Transformation towards Chiral Pyrrolidinone

The efficient enantioselective synthesis of pyrrolidinone has been investigated already by Reiser *et al.*.[24b] In the synthesis, the cyclopropanated pyrrole **60** has been used as a starting substrate. In the report published in 2006, the cyclopropanated pyrrole **60e** has been transformed into the pyrrolidinone **71** after three steps with retention of high enantiopurity. The separation of **(+)-** and **(-)-60e** has been performed by submitting the racemate **60e** into simulated moving bead (SMB) chromatography with cellulose-tris-(3,5-dimethylphenylcarbamate) Chiralcel OC as a stationary phase. In general, the SMB chromatography has shown the successful results even in 1958 g scale and for the separation of the substrate **60e** the chromatography has been carried out in 160

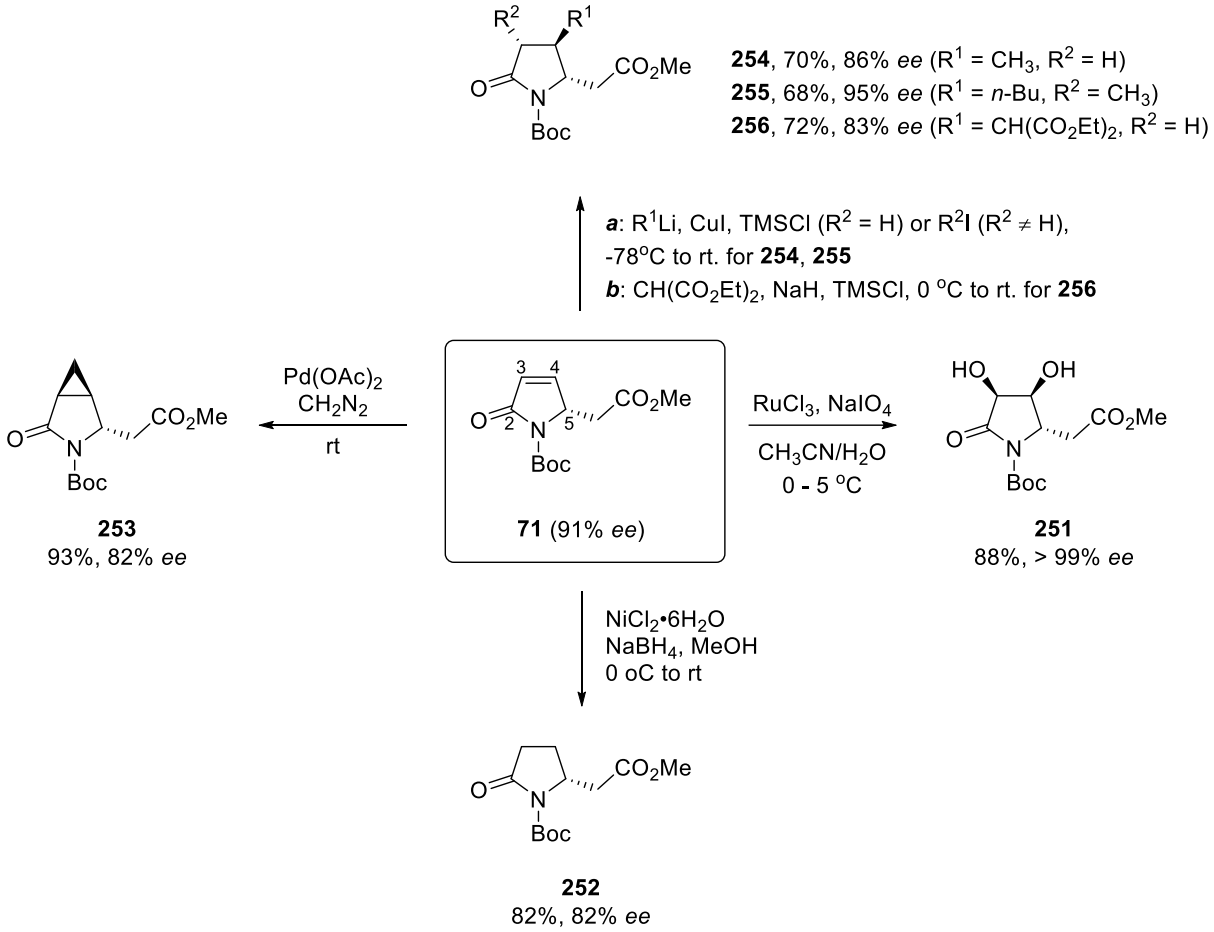
g scale to obtain the optically pure **(+)-60e** in 46% yield and 99.8% *ee*.

The obtained **(+)-60e** is then treated with NBS and water in acetonitrile to generate bromohydrin which is then oxidized by Jones reagent to give **70** (**Scheme 54**).[24b] The halogen functionality of the pyrrolidinone intermediate **70** is very reactive in radical reaction condition which could trigger the cyclopropane ring opening. For the radical cyclopropane ring opening reaction, there have been two reaction condition applied, ***a*** and ***b***. The both reaction conditions give rise to the ring opened pyrrolidinone product **71** in good yields, however, there has been decrease in *ee* of the product **71** from the reaction condition ***b*** compared to *ee* from the condition ***a***.



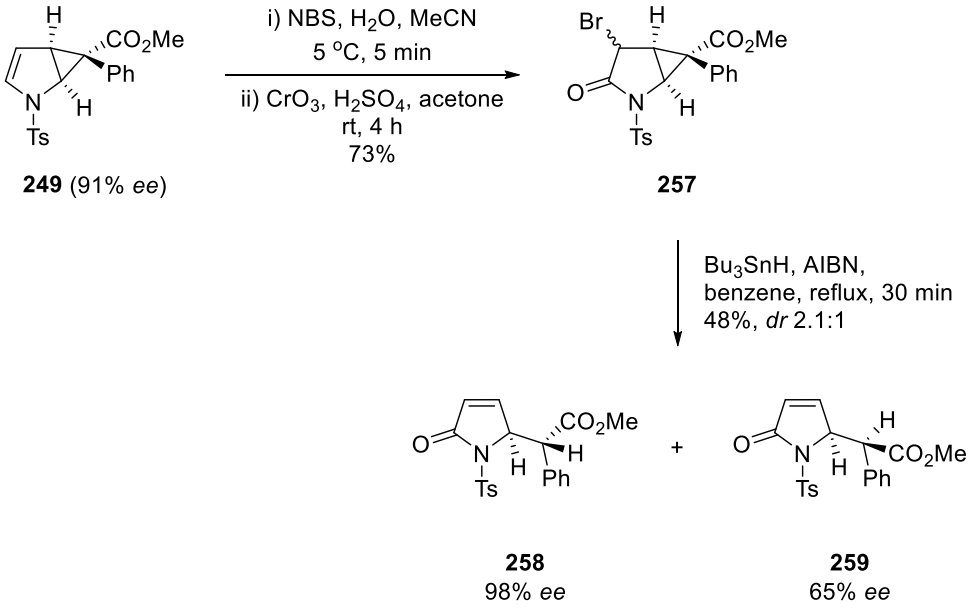
Scheme 54. Transformation in Precedent Study[24b]

The resulting pyrrolidinone **71** has been then subjected to different reaction conditions demonstrated in **Scheme 55**.[24b] As the starting substrate **71** has (*S*)-configuration on C5-position, the newly installed substituents on adjacent C4-position have (*R*)-configuration. In order to introduce the substituents, dihydroxylation (**251**), hydrogenation (**252**), cyclopropanation (**253**) and conjugate addition (**254** to **256**) have been carried out. With the use of basic reagent for each reaction, the various C3- and C4-functionalized pyrrolidinone could be generated and the products, **251** to **256** have appeared to maintain its high enantiomeric excess.



Scheme 55. Development of Pyrrolidinone

Next, for the transformation of the cyclopropanated pyrrole **249** to pyrrolidinone **258** and **259**, the same reaction route has been applied (**Scheme 56**). The bromohydrin formation from **249** and consequent oxidation by Jones reagent has been performed smoothly to generate the intermediate **257** in 73% yield. The next radical ring opening reaction of **257** has been carried out with AIBN as a radical initiator. After the elongated reaction time, the reaction has been completed to obtain a mixture of pyrrolidinone **258** and **259** in 48% yield with a diastereomeric ration of 2.1:1. The structure of **258** and **259** has been determined by 2D NMR analysis, however, the separation of the two diastereomers for X-ray analysis was not successful. It is expected to separate the two diastereomers in further reaction steps to functionalize the product **258** and **259**. As described in **Scheme 55**, the pyrrolidinone product **71** has a great potential to be developed and many reactions have shown the retention of absolute configuration. Therefore the variant for the synthesized pyrrolidinone **258** and **259** is in progress.

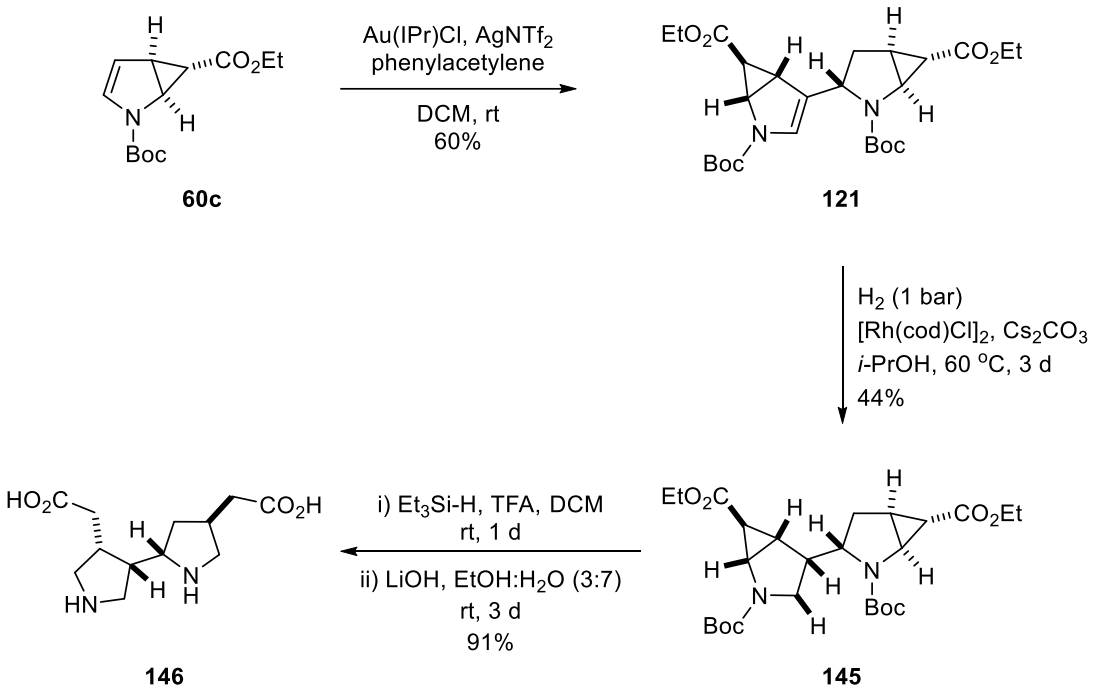


Scheme 56. Enantioselective Pyrrolidinone Transformation

C. Summary

Cyclopropanated pyrroles have been accompanied in lots of reactions due to its versatility and capability to approach to more complex molecules. The unique reactivity of cyclopropanated pyrroles results from the three-membered ring which has a tendency to release the ring strain and the substituents around it to provide the electronic characteristics.

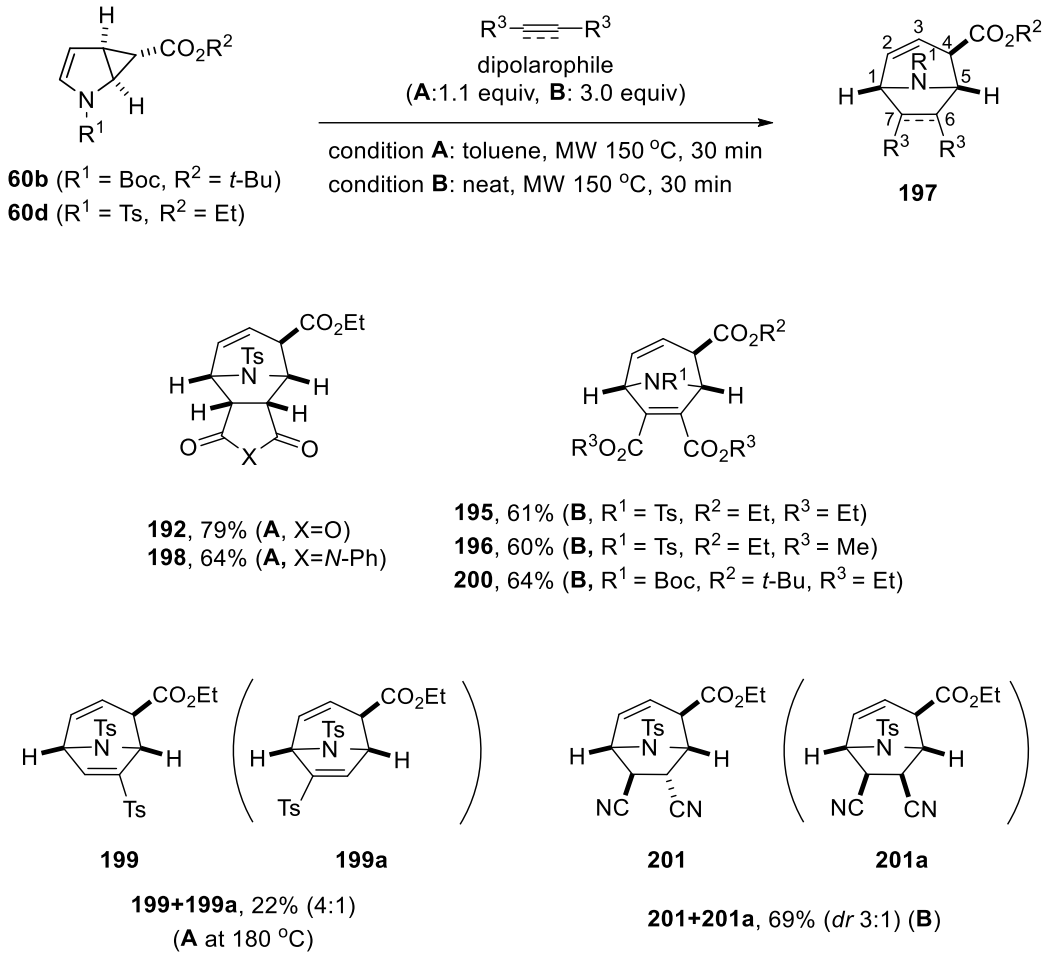
As described in first chapter in the main part, the dimerization of cyclopropanated pyrrole **60c** was catalyzed by the hidden Brønsted acid generated from the gold catalyst and phenylacetylene. Under such mild condition, dimer **121** was obtained as a single diastereomer in a good yield which could be then straightforwardly transformed into bis-β-homoproline **146** after hydrogenation, ring opening and deprotection (**Scheme 57**). The synthesis of enantiopure **146** and the evaluation of its activity as an organocatalyst are still to be explored.



Scheme 57. Dimerization of Cyclopropanated Pyrrole

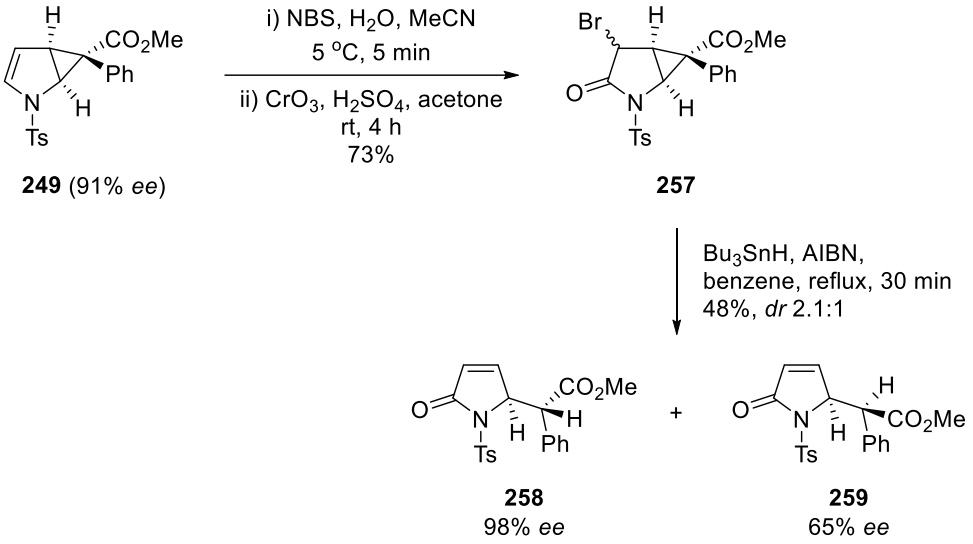
Next in second chapter, cycloaddition of substrate **60b** and **60d** has been investigated. The cycloaddition reaction utilized 1,3-dipole generated *in-situ* from substrate **60d** under heating condition which was then reacted with various dipolarophiles. The reaction could occur without a catalyst and by simple procedure, the desired tropane products could be obtained stereoselectively in high yields (**Scheme 58**). Further functionalizations to get access to cocaine

or ferruginine derivatives are currently ongoing in the working group.



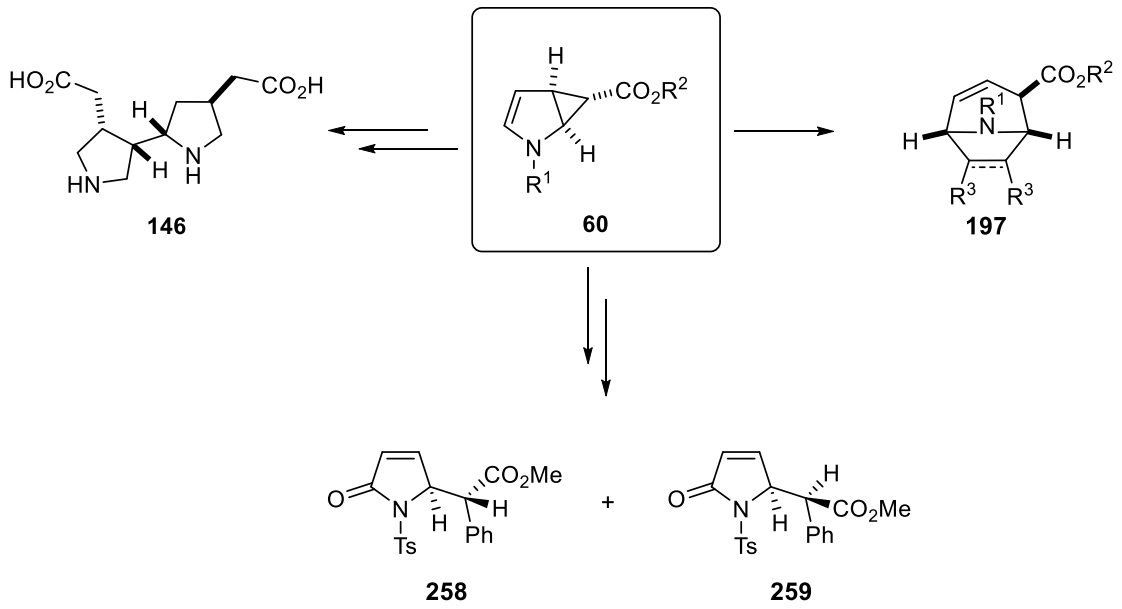
Scheme 58. Cycloaddition of Cyclopropanated Pyrrole

In the last chapter, the literature known procedure[24b] for enantioselectie pyrrolidinone synthesis has been employed to the substrate **249** (**Scheme 56**). In order to generate chiral **249**, an asymmetric rhodium-catalyzed cyclopropanation was performed which was followed by bromohydrin formation and subsequent oxidation to afford the intermediate **257**. In the end, chiral pyrrolidinone **258** and **259** were obtained by radical ring opening reaction with AIBN and *n*-Bu_3SnH. All of performed reactions has shown to retain high enantiopurity of intermediates and products.



Scheme 56. Pyrrolidinone Synthesis from Chiral Cyclopropanated Pyrrole

In summary, three different applications of cyclopropanated pyrrole **60** have been explored and demonstrated (**Scheme 58**). From bis-β-homoproline **146** to tropane- (**197**) and pyrrolidinone-derivative (**258** and **259**), such complex compounds could be successfully synthesized from substrate **60** and high stereoselectivity could be achieved in all transformations.

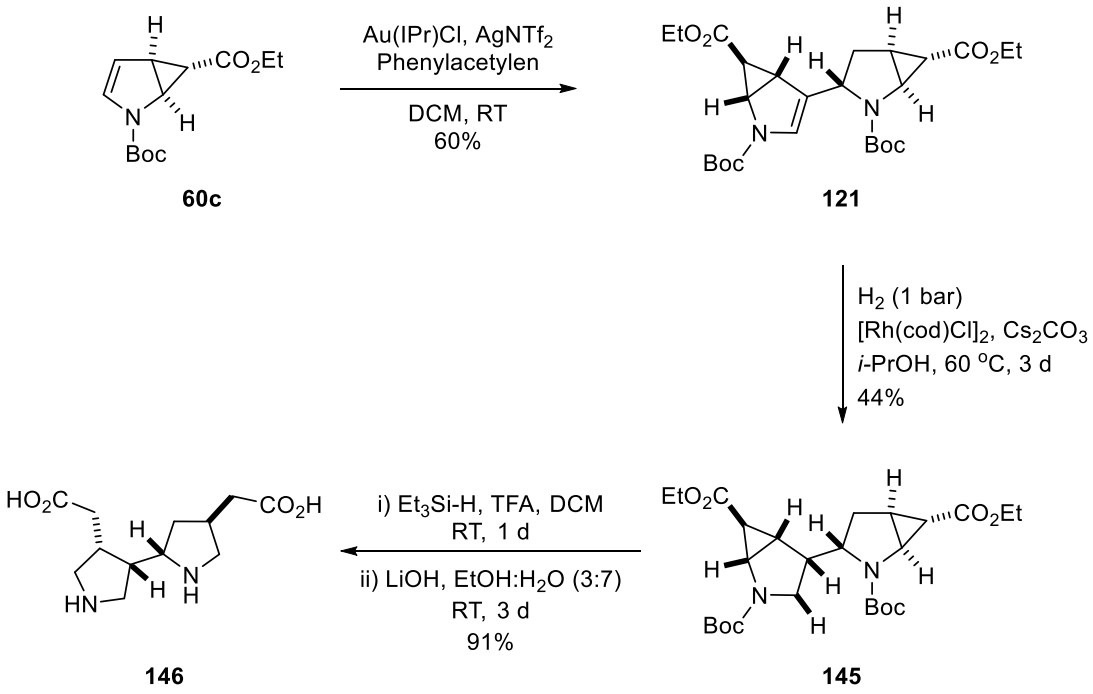


Scheme 58. Summary of Application of Cyclopropanated Pyrrole

D. Zusammenfassung

Cyclopropanierte Pyrrole finden Anwendung in zahlreichen Reaktionen bedingt durch ihre Vielseitigkeit und Eigenschaft komplexe Verbindungen zu erhalten. Die besondere Reaktivität von cyclopropaniertem Pyrrol geht aus dem Dreiring und seiner Tendenz hervor, die Ringspannung zu reduzieren sowie der daran gebundenen Substituenten und deren elektronischen Charakteristika.

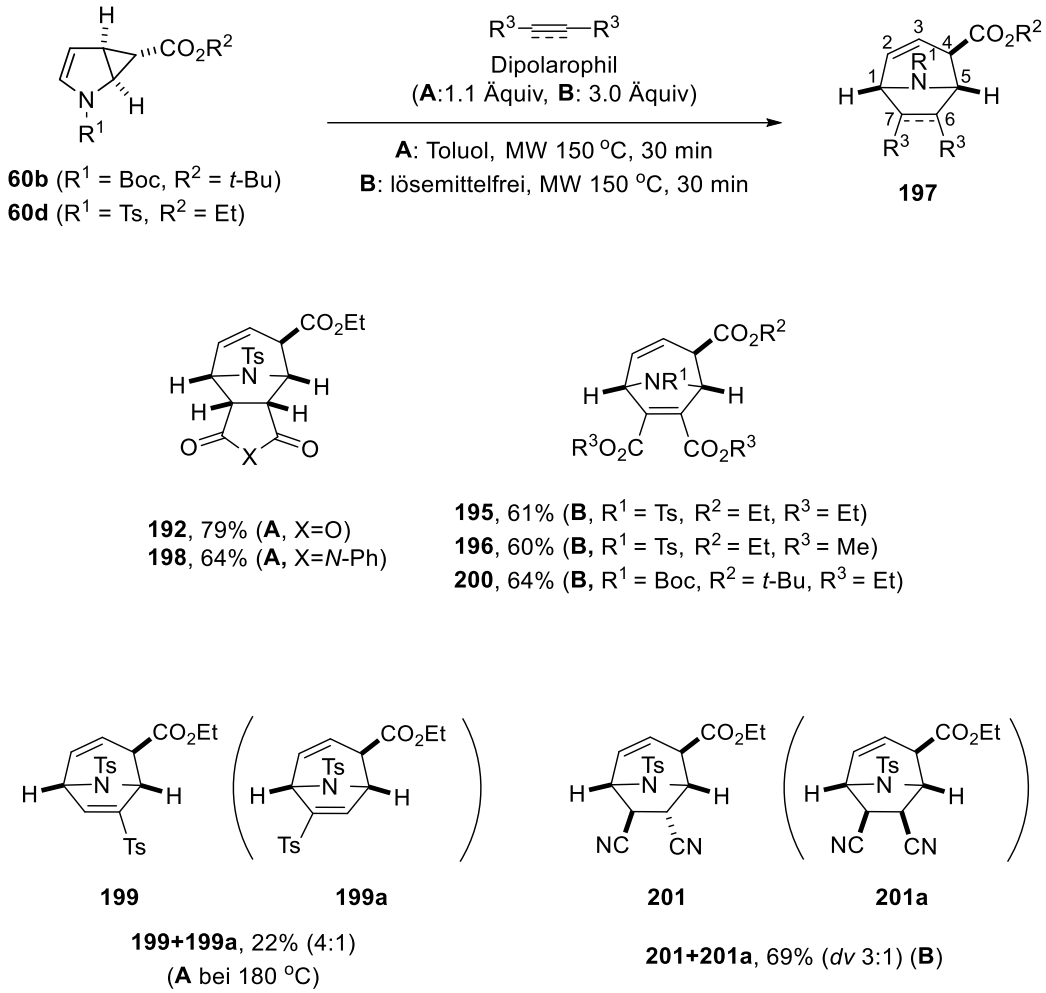
Das Erste Kapitel des Hauptteiles behandelt die Dimerisierung von cyclopropaniertem Pyrrol **60c**, katalysiert durch eine „versteckte“ Brønsted-Säure, welche aus der Reaktion des Gold-Katalysators mit Phenylacetylen hervorging. Unter diesen milden Bedingungen konnte das Dimer **121** diastereoselektiv in guten Ausbeuten erhalten werden, welches nach Hydrierung, Ringöffnung und Entfernung der Schutzgruppen zu bis-Homoprolin **146** weiter umgesetzt werden konnte (**Schema 59**). Die Darstellung des enantiomerenreinem Katalysators **146** sowie dessen Evaluierung als Organokatalysator muss allerdings noch durchgeführt werden.



Schema 59. Dimerisierung von cyclopropaniertem Pyrrol

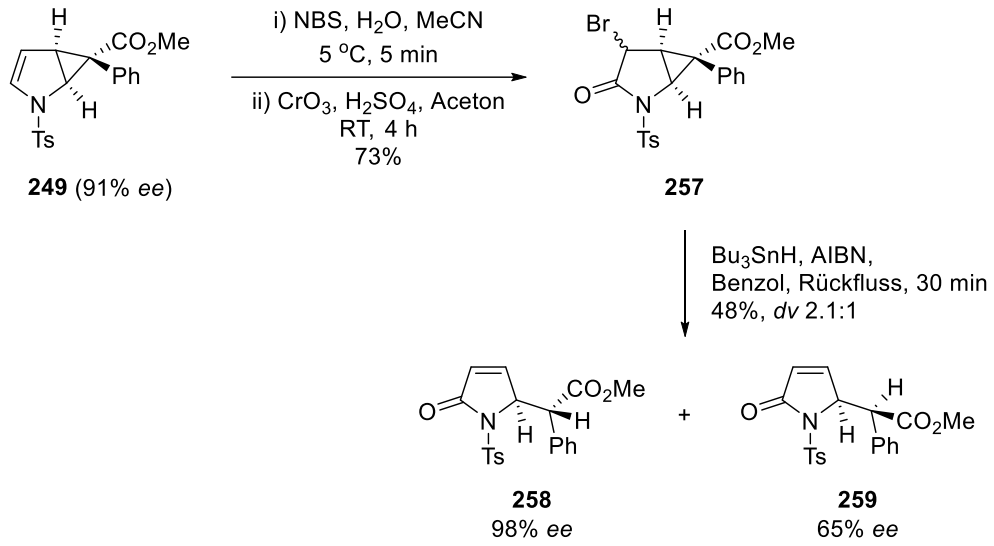
Im zweiten Kapitel wurde **60b** und **60d** in einer Cycloadditionsreaktion untersucht. Darin wurde ein durch Hitze *in-situ* erzeugter 1,3-Dipol, ausgehend von **60b** und **60d**, mit unterschiedlichen Dipolarophilen umgesetzt. Die Reaktion verlief in einer einfachen Prozedur ohne Katalysator

und die gewünschten Tropan-Derivate konnten stereoselektiv in guten Ausbeuten erhalten werden (**Schema 60**). Weitere Funktionalisierungen dieser Cycloadditionsprodukte, um Zugang zu Substanzen wie Kokain oder Feruginderivate zu erhalten, sind Gegenstand akuteller Projekte in der Reiser Gruppe.



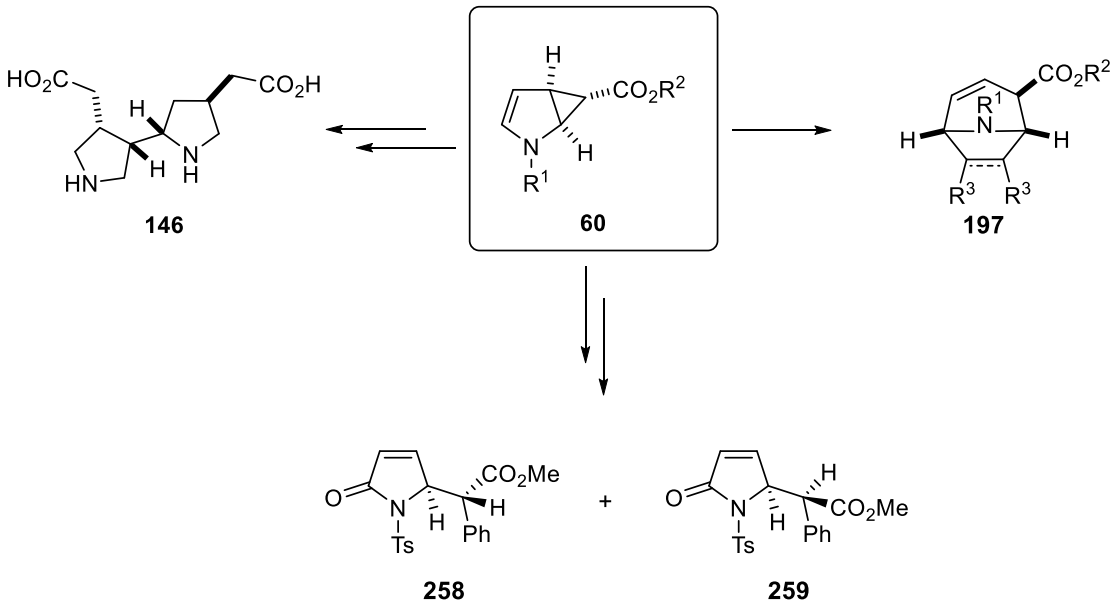
Schema 60. Cycloadditionsreaktion von cyclopropaniertem Pyrrol

Das letzte Kapitel beschreibt die Anwendung der enantiomerenreinen Literatursynthese[24b] für Pyrrolidinone auf **249** (**Schema 61**). Die asymmetrische, rhodiumkatalysierte Cyclopropanierung diente zur Darstellung von chrialem **249**, welches durch Bromohydrin Bildung und anschließender Oxidation zum Intermediat **257** weiter umgesetzt wurde. Im letzten Reaktionsschritt wurden die chiralen Pyrrolidinone **258** und **259** in einer radikalischen Ringöffnung durch AIBN und *n*-Bu_3SnH erhalten. In allen Reaktionsschritten konnte eine sehr gute Erhaltung der Enantiomerenreinheit der Intermdiate und Produkte beobachtet werden.



Schema 61. Pyrrolidinonsynthese ausgehend von chiralem cyclopropanierten Pyrrol

Zusammengefasst wurden drei unterschiedliche Anwendungen von cyclopropaniertem Pyrrol untersucht und beschrieben (**Schema 58**). Komplexe Strukturen wie bis-β-Homoprolin **146** oder Tropan- (**197**) und Pyrrolidinonderivate (**258** und **259**) konnten ausgehend von Verbindung **60** erfolgreich synthetisiert und in hohen Diastereomerenverhältnissen erhalten werden.



Schema 58. Zusammenfassung der Anwendungen von cyclopropaniertem Pyrrol

E. Experimental Part

1. General Information

All moisture sensitive reactions were performed in prior flame-dried Schlenk flasks under nitrogen atmosphere.

Solvents and chemicals

DCM, ethyl acetate and hexanes (60/40) were distilled prior to use for column chromatography. Anhydrous solvents were prepared according to standard procedures. Commercially available chemicals were used as received, without further purification otherwise mentioned.

^{1}H NMR spectra were recorded on Bruker Avance 300 (300 MHz), Bruker Avance 400 (400 MHz) and Bruker Avance III 600 TCI Cryo (600 MHz). The chemical shifts are reported in () (ppm) relative to chloroform-d ($CDCl_3$ 7.26 ppm), acetone-d_6 ($(CD_3)_2CO$ 2.05 ppm), or deuterium oxide (D_2O, 4.79 ppm). The spectra were analyzed by first order, the coupling constants (*J*) are reported in Hertz (Hz). Characterization of the signals: s, singlet; d, doublet; t, triplet, q; quartet, quin; quintet, m; multiplet, dd; doublet of doublet, dt; doublet of triplet, sept; septet. Integration is determined as a relative number of atoms.

^{13}C NMR spectra were recorded on Bruker Avance 300 (75.5 MHz) and Bruker Avance 400 (100.6 MHz). The chemical shifts are reported in () (ppm) relative to chloroform ($CDCl_3$, 77.23 ppm or acetone-d_6 ($(CD_3)_2CO$ 29.84 ppm). ^{13}C NMR resonance assignment was aided by the use of DEPT 135 techniques (DEPT = Distortionless Enhancement by Polarization Transfer) to determine the number of hydrogens attached to each carbon atom and is declared as: + = primary or tertiary (positive DEPT signal), - = secondary (negative DEPT signal), Cq = quaternary (no DEPT signal) carbon atoms.

High-performance liquid chromatography (HPLC) was performed on a Varian 920-LC with DAD. Phenomenex Lux Cellulose-1 and 2, Chiracel OD-H and AS served as chiral stationary phase and mixtures of *n*-heptane and *i*PrOH were used for elution.

Infra-red spectroscopy (IR) in form of ATR-IR spectroscopy was carried out on a Biorad Excalibur FTS 3000 Spectrometer, equipped with a Specac Gate Diamond Single Reflection ATR-System or on an Agilent Cary 630 FT-IR.

Mass spectrometry (MS) was performed in the Central Analytic Department of the University of Regensburg on a Finnigan MAT 95, an Agilent Q-TOF 6540 UHD, a Finnigan MAT SSQ 710 A and a ThermoQuest Finnigan TSQ 7000.

Melting points (mp) were measured on an OptiMelt MPA 100. Obtained values were not corrected.

Thin layer chromatography (TLC) was performed on alumina plates coated with silica gel (Merck silica gel 60 F 254, d = 0.2 mm, Machery-Nagel ALUGRAM® Xtra SIL G/UV254, d = 0.2 mm). Visualization was accomplished by UV light (λ = 254 nm or 366 nm), ninhydrin/acetic acid solution, potassium permanganate solution, vanillin/sulfuric acid solution or *Seebach´s Magic Stain*.

Column chromatography was performed on silica gel 60 (0.063-0.200 nm, Merck) or flash silica gel 60 (0.040-0.063 nm, Merck).

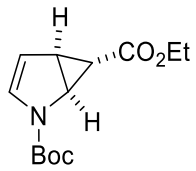
X-ray crystallography of single crystals was performed in the X-ray crystallographic department of the University of Regensburg on Agilent Technologies SuperNova, Agilent Technologies Gemini R Ultra or GV 1000.

2. Synthesis of compounds

Following compounds were already available on stock in our laboratories:
N-Boc pyrrole (**58b**), ethyl diazoacetate (**102**), *tert*-butyl diazoacetate (**106**), 2-(*tert*-butyl) 6-*tert*-butyl-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (**60b**), methyl 2-diazo-2-phenylacetate (**109a**), Rh_2(*S*-TCPTTL)$_4$ (**248**), Jones reagent.

Following compounds were synthesized according to literature procedures and spectroscopic data matched well with those reported: 1-tosyl-1H-pyrrole (**58d**), trimethyl(tosylethynyl)silane (**202a**), ethynyl *p*-tolyl sulfone (**202**)

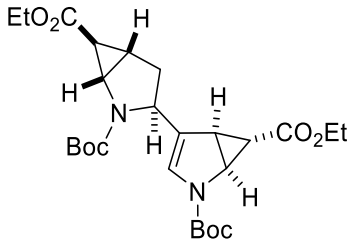
2-(*tert*-butyl) 6-ethyl-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (60c)



According to literature procedure[23a] in a flame- dried flask under N_2-atmosphere, $Cu(OTf)_2$ (324 mg, 0.89 mmol, 0.01 equiv) and anhydrous DCM (25 mL) were placed and stirred for 10 min. A solution of *N*-Boc-pyrrole **58b** (15.0 g, 89.7 mmol, 1 equiv) in DCM (45 mL anhydrous) was then poured into the solution. To this mixture, 5 vol% solution of phenylhydrazine (88.2 µL, 0.89 mmol, 0.01 equiv) in DCM was added and then ethyl diazoacetate **102** (168.1 g, 134.6 mmol, 1.5 equiv, 11.38 wt% solution in DCM anhydrous) was added via a syringe pump (addition rate: 1 drop/10 sec). The reaction mixture was stirred for additionally 6 h, filtered through basic alumina and washed with DCM (360 mL). The solvent was evaporated and the crude product was purified by column chromatography (PE/EA = 20:1) to obtain **60c** (9.32 g, 33.13 mmol, 37%) as a white solid.

R_f = 0.52 (PE/EA = 10:1); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.72 – 6.27 (m, 1H), 5.37 (d, *J* = 14.3 Hz, 1H), 4.36 (m, 1H), 4.22 – 4.06 (m, 2H), 2.80 (d, *J* = 3.9 Hz, 1H), 1.56 – 1.41 (m, 9H), 1.32 – 1.19 (m, 3H), 1.03 – 0.90 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.2, 172.9, 151.3, 150.9, 129.8, 129.6, 109.9, 81.7, 60.6, 44.2, 44.1, 32.1, 30.9, 28.2, 23.1, 14.2 (signal doubling due to rotamers); **IR** (neat) ν (cm^{-1}) 3097, 3049, 2982, 2940, 2904, 1700, 1588, 1474, 1461, 1398, 1342, 1262, 1249, 1167, 1141, 1044, 1013, 939, 937, 902, 831, 814, 764, 729, 719; **mp** = 43 °C; **LRMS** (ESI) *m/z* = 254.1389 $[M+H]^+$, 529.2517 $[2M+Na]^+$; **HRMS** (ESI) *m/z* = 254.1389 $[M+H]^+$; calc. for $[C_{13}H_{20}NO_4]^+$ = 254.1387.

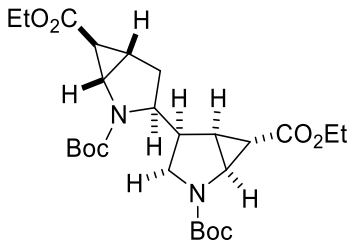
2-(*tert*-butyl) 6-ethyl 4-(2-(*tert*-butoxycarbonyl)-6-(ethoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (121)



In a flame-dried flask, [Au(IPr)Cl] (6.2 mg, 0.01 mmol, 5 mol%) and $AgNTf_2$ (4.0 mg, 0.01 mmol, 5 mol%) in DCM (1 mL) were mixed and stirred under N_2 atmosphere. After 10 min, phenylacetylene (66 μL, 0.6 mmol, 3 equiv) and substrate **60c** (50.6 mg, 0.2 mmol, 1 equiv) in DCM (1 mL) was also added in sequence. After 24 h, the reaction solution was filtered through a short pad of silica gel and the filtrate was concentrated under reduced pressure. The desired dimer product **121** (31 mg, 0.06 mmol, 60%) was isolated by flash column chromatography.

R_f = 0.35 (PE/EA = 5:1); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.35 (d, *J* = 45.2 Hz, 1H), 4.32 (dd, *J* = 36.3, 6.3 Hz, 2H), 4.11 (q, *J* = 7.1 Hz, 4H), 3.78 (d, *J* = 5.7 Hz, 1H), 2.71 (d, *J* = 6.4 Hz, 1H), 2.36 – 2.23 (m, 1H), 2.16 (d, *J* = 13.4 Hz, 2H), 1.64 (d, *J* = 1.7 Hz, 1H), 1.50 – 1.40 (m,, 18H), 1.24 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (224 MHz, $CDCl_3$) δ 172.9, 170.5, 154.9, 150.9, 124.5, 81.6, 80.4, 60.7, 60.5, 57.0, 56.7, 45.3, 44.0, 43.6, 30.6, 29.2, 28.3, 28.2, 24.7, 22.3, 14.2, 14.1; **IR** (neat) ν (cm^{-1}) 2978, 2935, 1700, 1636, 1477, 1476, 1394, 1364, 1297, 1252, 1152, 1115, 1051, 986, 850, 760; **mp** = 122 °C; **LRMS** (ESI) *m/z* = 407.2 $[M+H-C_5H_8O_2]^+$, 529.2 $[M+Na]^+$, 1035.5 $[2M+Na]^+$; **HRMS** (ESI) *m/z* = 507.2707 $[M+H]^+$; calc. for $[C_{26}H_{39}N_2O_8]^+$ = 507.2701.

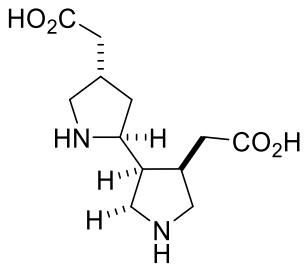
2,2'-di-*tert*-butyl-6,6'-diethyl-2,2'-diaza[3,4'-bi(bicyclo[3.1.0]hexane)]-2,2',6,6'-tetracarboxylate (145)



To a flask were added $[Rh(cod)Cl]_2$ (1 mg, 0.002 mmol, 2 mol%) and Cs_2CO_3 (3.6 mg, 0.01 mmol, 0.1 equiv) in *i*-PrOH (0.5 mL) and the solution was stirred for 10 min at room temperature. Next, a solution of dimer **121** (58 mg, 0.11 mmol, 1 equiv) in *i*-PrOH (0.5 mL) was added and the hydrogen gas was introduced by the balloon. The reaction solution was then stirred for 3 d 65 °C under hydrogen atmosphere. Upon completion, the reaction solution was filtered through a pad of Celite and the filtrate was concentrated. The crude mixture was finally purified by flash column chromatography to afford the hydrogenated dimer **145** (25 mg, 0.05 mmol) in 44% yield.

R_f = 0.49 (DCM/acetone = 95:5); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.11 (qd, *J* = 7.1, 2.4 Hz, 4H), 4.01 (td, *J* = 7.7, 2.3 Hz, 1H), 3.95 – 3.73 (m, 1H), 3.60 (dd, *J* = 14.9, 7.0 Hz, 1H), 3.51 (dd, *J* = 6.7, 1.6 Hz, 1H), 2.83 – 2.71 (m, 1H), 2.65 – 2.56 (m, 1H), 2.19 (dtd, J = 7.2, 3.6, 2.1 Hz, 1H), 2.10 (dt, J = 6.1, 3.9 Hz, 1H), 2.00 (dd, J = 4.1, 1.6 Hz, 1H), 1.98 – 1.90 (m, 1H), 1.53 – 1.44 (m, 2H), 1.45 (s, 9H), 1.43 (s, 9H), 1.24 (t, *J* = 7.0 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.0, 170.2, 155.6, 154.5, 80.4, 80.3, 77.2, 60.6, 60.5, 45.3, 45.1, 34.8, 34.7, 32.5, 32.4, 28.4, 28.3, 28.2, 26.2, 22.3, 14.2, 14.2; **IR** (neat) ν (cm^{-1}) 2963, 2933, 2878, 1700, 1477, 1457, 1364, 1256, 1159, 1115, 1047, 1025, 1010, 954, 919, 854, 772, 716; **mp** = 97 °C; **LRMS** (ESI) *m/z* = 509.2 $[M+H]^+$, 1039.5 $[2M+Na]^+$.

2,2'-([2,3'-bipyrrolidine]-4,4'-diyl)diacetic acid (146)

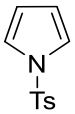


As described in literature,[23a] the hydrogenated dimer **145** (42 mg, 0.08 mmol, 1 equiv) was dissolved in DCM. Et_3SiH (53 µL, 0.33 mmol, 4 equiv) and TFA (38 µL, 0.49 mmol, 6 equiv) were added dropwise and the solution was stirred for 1.5 days. The volatiles were removed under reduced pressure. Then hydration of the ester moiety was performed according to the literature.[67] LiOH (12 mg, 0.50 mmol, 6 equiv) was added to the solution of the crude in a mixture of EtOH and H_2O (1 mL, 3:7). The solution was stirred for 2 days at ambient

temperature. Upon completion, the solvent was evaporated under reduced pressure and the residue was triturated with MeOH to precipitate remaining LiOH. The MeOH layer was evaporated under reduced pressure to give the final product **146** (21 mg, 0.08 mmol) in a quantitative yield.

R_f = 0.55 (MeCN/H_2O = 1:1); **^{1}H NMR** (300 MHz, D_2O) δ 3.88 (q, J = 7.3 Hz, 1H), 3.78 (dq, J = 11.8, 6.0 Hz, 2H), 3.61 – 3.38 (m, 10H), 3.00 (td, J = 12.3, 11.3, 8.8 Hz, 3H), 2.94 – 2.80 (m, 3H), 2.68 – 2.43 (m, 12H), 2.34 (dt, J = 13.0, 7.3 Hz, 2H), 2.24 – 2.16 (m, 6H), 1.91 (td, J = 8.1, 3.4 Hz, 2H), 1.83 (td, J = 7.9, 3.2 Hz, 4H), 1.47 (q, J = 12.0 Hz, 2H), 1.31 (q, J = 11.6, 11.1 Hz, 1H).; **^{13}C NMR** (75 MHz, D_2O) δ 180.1, 177.3, 61.2, 61.0, 58.0, 50.2, 46.8, 40.5, 40.0, 37.8, 34.4, 34.1; **mp** = >250 °C (decomposes at 250 °C); **LRMS** (ESI) *m/z* = 255.1 [M-H^+-$C_{12}H_{19}N_2O_4$]$^-$.

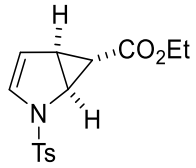
1-tosyl-1H-pyrrole (58d)



According to the literature procedure,[68] a solution of distilled pyrrole (15.5 mL, 223.6 mmol, 1 equiv) in THF (60 mL) was added to a suspension of NaH (13.4 g as a 60% dispersion in mineral oil, 335.4 mmol, 1.5 equiv) in THF (60 mL) at 0 °C and stirred for an hour. At the same temperature was then added a solution of tosyl chloride (42.6 g, 223.6 mmol, 1 equiv) in THF (60 mL) and the solution was stirred for 3 h at room temperature. Upon completion, water was slowly added to the solution and the organic layer was separated, dried over Na_2SO_4 and the solvent was evaporated. The crude mixture was purified by flash column chromatography to give the desired *N*-Ts-pyrrole **58d** in a quantitative yield.

R_f = 0.44 (PE/EA = 5:1); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80 – 7.67 (m, 2H), 7.33 – 7.26 (m, 2H), 7.16 – 7.14 (m, 2H), 6.30 – 6.27 (m, 2H), 2.39 (s, 3H).

ethyl 2-tosyl-2-azabicyclo[3.1.0]hex-3-ene-6-carboxylate (60d)



According to the literature procedure,[23a] $Cu(OTf)_2$ (279 mg, 0.77 mmol, 1 mol%) and *N*-Ts-Pyrrole **58d** (17 g, 77 mmol, 1 equiv) were dissolved in anhydrous DCM (75 mL) in a flame-dried flask and stirred for 10 min. To the very flask, 5 vol% solution of phenylhydrazine (76 μL, 0.77 mmol, 1 mol%) in anhydrous DCM was added and the reaction solution turned reddish brown. Next, 13 wt% solution of ethyl diazoacetate **102** in anhydrous DCM (88g, 100.1 mmol, 1.3 equiv) was added in a dropwise fashion (addition rate = 1 drop/10 sec). After the addition was completed, the reaction mixture was stirred for an additional hour. Then the solution was filtered through a pad of basic alumina and washed with DCM. The solvent was evaporated and the crude mixture was purified on the flash column chromatography to afford the desired product **60d** (5.7 g, 18.5 mmol, 24%) as a white crystalline.

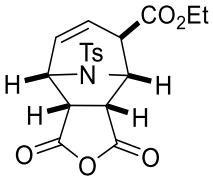
R_f = 0.36 (PE/EA = 5:1); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.33 (dd, *J* = 3.9, 0.7 Hz, 1H), 5.45 (dd, *J* = 4.0, 2.6 Hz, 1H), 4.21 – 3.99 (m, 3H), 2.70 (dt, *J* = 6.0, 2.6 Hz, 1H), 2.44 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.49 – 0.43 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.1, 144.4, 133.5, 130.4, 129.9, 127.4, 113.7, 77.4, 77.0, 76.6, 60.8, 45.3, 31.5, 21.6, 21.0, 14.2; **IR** (neat) ν (cm^{-1}) 3124, 2986, 2907, 1715, 1588, 1495, 1446, 1402, 1379, 1346, 1290, 1163; **mp** = 66 °C; **LRMS** (ESI) *m/z* = 308.0960 $[M+H]^+$ 637.1651 $[2M+Na]^+$; **HRMS** (ESI) *m/z* = 346.0508 $[M+K]^+$; calc. for $[C_{15}H_{17}NO_4S+K]^+$ = 346.0510.

General procedure for dipolar cycloaddition of substrate 60b and 60d

In a microwave vial, the substrate (1 equiv) and dipolarophile (1.1 equiv or 3 equiv as described) were placed. When the dipolarophile was at solid phase at 150 °C, toluene was applied into the vial to dissolve. With a lid on, the solution was stirred at room temperature for 5 min and then under microwave radiation at 150 °C for 30 min (except the reaction with ethynyl *p*-tolyl sulfone **202**). When the dipolarophile melted at 150 °C, the reaction components without a solvent were placed in the vial and then put under microwave radiation at 150 °C for 30 min. After the completion, the solution was concentrated under reduced pressure and the desired product was

purified by column chromatography.

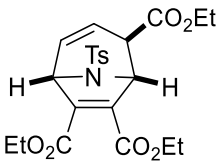
ethyl 1,3-dioxo-9-tosyl-3,3a,4,5,8,8a-hexahydro-1H-4,8-epiminocyclohepta[c]furan-5-carboxylate (192)



According to the general procedure, the substrate **60d** (307 mg, 1 mmol, 1 equiv) and maleic anhydride **191** (108 mg, 1.1 mmol, 1.1 equiv) in toluene (1 mL) were reacted at 150 ºC for 30 min in the microwave reactor. The crude mixture was filtered through a short pad of silica gel and the solvent was evaporated at low pressure to give the desired cycloaddition product **192** (320 mg, 0.789 mmol, 79 %) as a white foamy solid.

R_f = 0.10 (PE/EA 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 – 7.69 (m, 2H), 7.40 – 7.29 (m, 2H), 6.13 (ddd, *J* = 9.6, 5.8, 1.8 Hz, 1H), 5.94 (ddd, *J* = 9.6, 4.5, 1.4 Hz, 1H), 5.14 (dq, *J* = 8.4, 1.6 Hz, 1H), 4.83 (ddd, *J* = 7.2, 5.9, 1.6 Hz, 1H), 4.18 (dd, *J* = 10.0, 8.4 Hz, 1H), 4.11 – 3.93 (m, 2H), 3.83 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.49 (dt, *J* = 4.4, 1.7 Hz, 1H), 2.44 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.6, 168.8, 167.4, 144.9, 134.9, 129.8, 128.5, 128.0, 126.2, 61.7, 58.6, 56.0, 55.9, 50.3, 45.1, 21.6, 13.9; **IR** (neat) ν (cm^{-1}) 2989, 1864, 1774, 1722, 1595, 1446, 1368, 1325, 1308, 1259, 1242, 1221, 1208, 1185, 1156, 1088, 1021, 1006, 987, 917, 902, 857, 813, 763, 719, 667; **mp** = 155 ºC; **LRMS** (ESI): *m/z* = 428.0771 [M+Na-$C_{19}H_{19}NO_7S$+Na]$^+$, 833.1654 [2M+Na]$^+$.

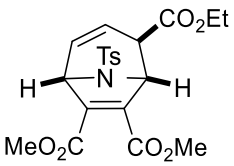
triethyl 8-tosyl-8-azabicyclo[3.2.1]octa-3,6-diene-2,6,7-tricarboxylate (195)



According to the general procedure, the substrate **60d** (123 mg, 0.4 mmol, 1 equiv) and diethyl acetylenedicarboxylate, **194** (0.2 mL, 1.2 mmol, 3 equiv) in toluene (0.4 mL) were reacted under the microwave radiation at 150 °C for 30 min. The crude mixture was concentrated under reduced pressure and the desired cycloaddition product **195** (115 mg, 0.24 mmol, 61%) was isolated by column chromatography. The product **195** was also partially isomerized to the product **219** on silica gel and they were found to be inseparable.

R_f = 0.38 (PE/EA 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 – 7.50 (m, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 6.30 (ddd, *J* = 9.5, 5.8, 2.1 Hz, 1H), 5.66 (ddd, *J* = 9.5, 3.9, 1.6 Hz, 1H), 5.36 (m, 1H), 4.79 (dd, *J* = 5.8, 1.1 Hz, 1H), 4.17 (qd, *J* = 7.1, 2.3 Hz, 2H), 4.07 (qd, *J* = 7.1, 2.4 Hz, 4H), 3.12 (ddd, *J* = 3.5, 2.2, 1.1 Hz, 1H), 2.32 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.16 (td, *J* = 7.1, 1.7 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.9, 162.2, 161.4, 147.4, 143.9, 135.2, 134.2, 130.2, 129.9, 127.9, 124.3, 64.5, 61.9, 61.5, 61.4, 61.4, 43.5, 21.5, 14.1, 14.0; **IR** (neat) ν (cm^{-1}) 2982, 2933, 2908, 1711, 1640, 1599, 1447, 1446, 1394, 1370, 1353, 1286, 1241, 1163, 1091, 1081, 1036, 965, 938, 910, 855, 816, 735, 705, 687; **LRMS** (ESI): *m/z* = 478.1533 $[M+H-C_{23}H_{28}NO_8S]^+$, 500.1350 $[M+Na]^+$, 977.2815 $[2M+Na]^+$; **HRMS** (ESI): *m/z* = 500.1350 $[M+Na]^+$; calc. for $[C_{23}H_{27}NO_8S+Na]^+$ = 500.1349.

2-ethyl 6,7-dimethyl 8-tosyl-8-azabicyclo[3.2.1]octa-3,6-diene-2,6,7-tricarboxylate (196)

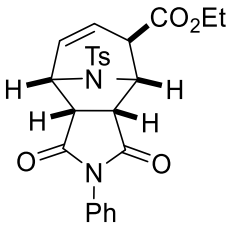


As described above, the substrate **60d** (123 mg, 0.4 mmol, 1 equiv) and dimethyl acetylenedicarboxylate, **187** (148 µL, 1.2 mmol, 3 equiv) in toluene (0.4 mL) were reacted under the microwave radiation at 150 °C for 30 min. The crude mixture was concentrated under reduced pressure and the desired cycloaddition product **196** (161 mg, 0.36 mmol, 60%) was isolated by flash chromatography. However, the product **196** was partially isomerized to **208** on silica gel and the two compounds were found to be inseparable.

R_f = 0.43 (PE/EA 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 – 7.60 (m, 2H), 7.26 (m, 2H), 6.37 (ddd, *J* = 9.5, 5.8, 2.1 Hz, 1H), 5.73 (ddd, *J* = 9.5, 4.0, 1.6 Hz, 1H), 5.44 (q, *J* = 1.3 Hz,

1H), 4.87 (dd, *J* = 5.8, 1.1 Hz, 1H), 4.28 – 4.18 (qd, *J* = 6.8, 0.9 Hz, 2H), 3.71 (s, 3H), 3.70 (s, 3H), 3.17 (ddd, *J* = 4.0, 2.1, 1.1 Hz, 1H), 2.40 (s, 3H), 1.33 – 1.28 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.9, 162.5, 161.7, 147.7, 144.2, 135.2, 134.2, 130.1, 129.8, 127.9, 124.3, 64.4, 61.8, 61.5, 52.3, 52.3, 43.4, 21.5, 14.1; **IR** (neat) ν (cm^{-1}) 2982, 2956, 2931, 2856, 1711, 1644, 1599, 1439, 1349, 1287, 1245, 1163, 1126, 1088, 1022, 1021, 965, 936, 857, 816, 782, 753, 706, 690; **LRMS** (ESI): *m/z* = 450.1211 $[M+H]^+$, 472.1027 $[M+Na]^+$, 921.2170 $[2M+Na]^+$; **HRMS** (ESI): *m/z* = 450.1211 $[M+H]^+$; calc. for $[C_{21}H_{24}NO_8S]^+$ = 450.1217.

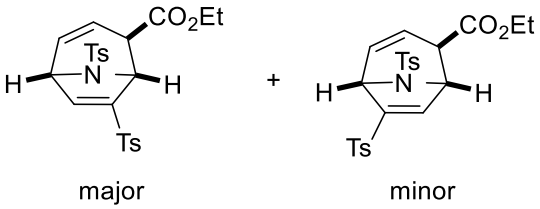
ethyl 1,3-dioxo-2-phenyl-9-tosyl-1,2,3,3a,4,5,8,8a-octahydro-4,8-epiminocyclohepta[c]pyrrole-5-carboxylate (198)



According to the general procedure described above, the substrate **60d** (154 mg, 0.5 mmol, 1 equiv) and *N*-phenylmaleimide **185** (95 mg, 0.55 mmol, 1.1 equiv) in toluene (0.5 mL) were reacted at 150 °C for 30 min under microwave radiation. The crude was purified by flash column chromatography to afford the desired product **198** as a white foamy solid (154 mg, 0.32 mmol, 64%).

R_f = 0.29 (PE/EA 2:1); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.87 – 7.78 (m, 2H), 7.55 – 7.41 (m, 3H), 7.40 – 7.34 (m, 2H), 7.22 – 7.15 (m, 2H), 6.18 (ddd, *J* = 9.6, 5.8, 1.8 Hz, 1H), 6.00 (ddd, *J* = 9.6, 4.4, 1.4 Hz, 1H), 5.23 (dq, *J* = 8.3, 1.5 Hz, 1H), 5.00 – 4.83 (m, 1H), 4.12 – 3.96 (m, 2H), 3.96 – 3.84 (m, 2H), 3.57 (dt, *J* = 4.4, 1.7 Hz, 1H), 2.48 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.6, 173.2, 169.3, 144.6, 135.5, 131.3, 129.8, 129.3, 129.0, 128.5, 128.0, 126.3, 125.6, 61.5, 58.3, 55.9, 54.4, 49.5, 45.0, 21.6, 13.9; **IR** (neat) ν (cm^{-1}) 2982, 1707, 1595, 1498, 1457, 1579, 1353, 1327, 1304, 1185, 1156, 1088, 1049, 1029, 932, 906, 862, 817, 735, 717, 691, 664; **mp** = 71 °C; **LRMS** (ESI): *m/z* = 481.1441 $[M+H]^+$, 983.2617 $[2M+Na]^+$; **HRMS** (ESI): *m/z* = 481.1432 $[M+H]^+$; calc. for $[C_{25}H_{25}N_2O_6S]^+$= 481.1428.

ethyl 7,8-ditosyl-8-azabicyclo[3.2.1]octa-3,6-diene-2-carboxylate (199, major)
ethyl 6,8-ditosyl-8-azabicyclo[3.2.1]octa-3,6-diene-2-carboxylate (199a, minor) (*dr* 4:1)

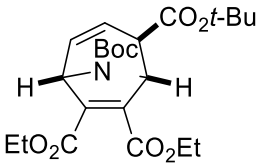


major minor

According to the general procedure, substrate **60d** (61.5 mg, 0.2 mmol, 1 equiv) and Ts-acetylene **202** (47 mg, 0.26 mmol, 1.3 equiv) in toluene (0.4 mL) were reacted at 180 °C for 15 min to afford the desired product **199** (21 mg, 0.04 mmol, 22 %) as a white solid with a diastereomeric ratio of 4:1.

R_f = 0.46 (PE/EA 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) – major: δ 7.64 (dd, *J* = 8.6, 2.4 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 2.3 Hz, 1H), 6.23 (ddd, *J* = 9.5, 5.7, 2.1 Hz, 1H), 5.71 (ddd, *J* = 9.5, 4.0, 1.7 Hz, 1H), 5.35 (dt, *J* = 1.8, 0.9 Hz, 1H), 4.73 (ddd, *J* = 5.7, 2.3, 0.8 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.27 (ddt, *J* = 3.7, 2.0, 1.1 Hz, 1H), 2.50 (s, 3H), 2.41 (s, 3H), 1.32 – 1.23 (m, 3H) - minor: δ 7.85 – 7.79 (m, 2H), 7.54 – 7.50 (m, 2H), 7.32 (d, *J* = 11.2 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.27 (d, *J* = 2.5 Hz, 1H), 6.16 (ddd, *J* = 9.5, 5.7, 2.1 Hz, 1H), 5.56 (ddd, *J* = 9.6, 3.9, 1.5 Hz, 1H), 5.24 – 5.18 (m, 1H), 4.82 (d, *J* = 5.7 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.88 (dt, *J* = 2.4, 1.4 Hz, 1H), 2.48 (s, 3H), 2.43 (s, 3H), 1.30 – 1.26 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) – major: δ 168.8, 148.0, 145.3, 143.8, 142.2, 135.7, 134.6, 130.0, 129.7, 128.9, 128.1, 127.8, 125.5, 62.1, 61.8, 60.0, 44.6, 21.8, 21.6, 14.1. – minor: δ 168.9, 155.5, 145.4, 143.9, 135.6, 134.8, 134.4, 131.7, 129.9, 129.8, 128.3, 127.8, 122.5, 62.7, 62.0, 60.4, 58.9, 42.8, 21.0, 14.2.; **IR** (neat) ν (cm^{-1}) 3064, 2986, 2930, 1710, 1595, 1446, 1353, 1305, 1223, 1148, 1096, 1036, 969; **mp** = 49 °C; **LRMS** (ESI): *m/z* = 488.1199 $[M+H]^+$, 997.2157 $[2M+Na]^+$; **HRMS** (ESI): *m/z* = 488.1196 $[M+H]^+$; calc. for $[C_{24}H_{26}NO_6S_2]^+$ = 488.1196.

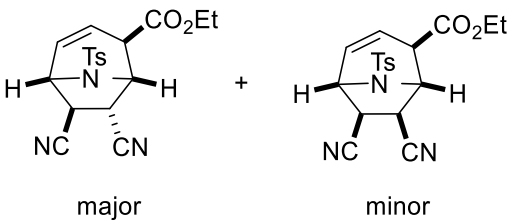
2,8-di-*tert*-butyl 6,7-diethyl 8-azabicyclo[3.2.1]octa-3,6-diene-2,6,7,8-tetracarboxylate (200)



According to the general procedure, substrate **60b** (56 mg, 0.2 mmol, 1 equiv) and diethyl acetylenedicarboxylate **194** (96 µL, 0.6 mmol, 3 equiv) were reacted at 150 °C for 30 min to give the desired product **200** (57 mg, 0.13 mmol, 64%) as a colorless oil.

R_f = 0.30 (PE/EA 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.29 (ddd, *J* = 9.6, 5.3, 2.1 Hz, 1H), 5.60 (ddd, *J* = 9.6, 3.8, 1.8 Hz, 1H), 5.45 (dt, *J* = 1.9, 0.9 Hz, 1H), 4.87 (brs, 1H), 4.20 (qd, *J* = 7.1, 1.8 Hz, 4H), 3.09 - 3.08 (m, 1H), 1.42 (s, 9H), 1.38 (s, 9H), 1.25 (td, *J* = 7.1, 1.1 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.0, 163.0, 162.4, 152.3, 130.6, 124.5, 81.7, 80.7, 61.9, 61.5, 61.5, 28.2, 27.9, 14.0; **IR** (neat) ν (cm^{-1}) 2982, 2937, 1707, 1640, 1476, 1457, 1392, 1368, 1305, 1252, 1159, 1115, 1077, 1033, 869, 844, 775. ; **LRMS** (ESI): *m/z* = 452.2303 $[M+H]^+$, 474.2111 $[M+Na]^+$, 925.4337 $[2M+Na]^+$; **HRMS** (ESI): *m/z* = 452.2281 $[M+H]^+$; calc. for $[C_{23}H_{34}NO_8]^+$ = 452.2279.

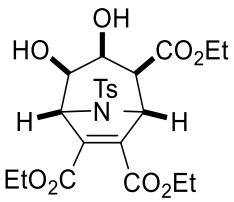
ethyl 6,7-dicyano-8-tosyl-8-azabicyclo[3.2.1]oct-3-ene-2-carboxylate (201, major and 201a, minor) (*dr* 3:1)



According to the general procedure, substrate **60d** (158 mg, 0.5 mmol, 1 equiv) and fumaronitrile **203** (117 mg, 1.5 mmol, 3 equiv) were reacted in neat condition at 150 °C for 30 min to afford the desired product **201** (133 mg, 0.34 mmol, 69%) as a white foamy solid with a diastereomeric ratio of 3:1.

R_f = 0.13 (PE/EA 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) - major: δ 7.75 (dd, *J* = 8.5, 2.3 Hz, 2H), 7.32 (dd, *J* = 8.0, 6.1 Hz, 2H), 6.29 (ddd, *J* = 9.7, 6.0, 2.1 Hz, 1H), 5.93 (ddd, *J* = 9.6, 4.2, 1.4 Hz, 1H), 5.10 (dq, *J* = 7.5, 1.5 Hz, 1H), 4.95 (ddd, *J* = 6.0, 1.5, 0.7 Hz, 1H), 3.97 – 3.83 (m, 2H), 3.75 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.49 (d, *J* = 4.5 Hz, 1H), 3.44 (dt, *J* = 4.2, 1.6 Hz, 1H), 2.43 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 3H) – minor: δ 7.75 (dd, *J* = 8.5, 2.3 Hz, 2H), 7.32 (dd, *J* = 8.0, 6.1 Hz, 2H), 6.23 (ddd, *J* = 9.6, 5.8, 1.8 Hz, 1H), 5.96 (ddd, *J* = 9.6, 4.5, 1.4 Hz, 1H), 5.17 (t, *J* = 1.6 Hz, 1H), 4.77 (td, *J* = 5.6, 1.7 Hz, 1H), 4.03 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.97 – 3.83 (m, 1H), 3.61 (dd, *J* = 7.6, 5.4 Hz, 1H), 3.24 (dd, *J* = 7.8, 1.8 Hz, 1H), 3.17 (dt, *J* = 4.1, 1.8 Hz, 1H), 2.44 (s, 3H), 1.16 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) - major: δ 168.4, 144.8, 135.4, 130.5, 129.7, 128.0, 124.3, 117.0, 116.7, 61.9, 59.0, 58.2, 45.3, 42.0, 37.5, 21.6, 13.8, minor - 167.9, 145.1, 134.8, 129.9, 128.5, 128.1, 124.9, 116.9, 115.7, 61.9, 61.4, 57.1, 50.2, 42.5, 37.6, 21.7, 13.9; **IR** (neat) ν (cm^{-1}) 2980, 2960, 2248, 1730, 1595, 1495, 1446, 1334, 1288, 1257, 1200, 1159, 1088, 1033, 995, 982, 902, 857, 916, 742, 712, 663.; **mp** = 89 °C; **LRMS** (ESI): *m/z* = 403.1440 $[M+NH_4]^+$, 793.2100 $[2M+Na]^+$; **HRMS** (ESI): *m/z* = 403.1439 $[M+NH_4]^+$; calc. for $[C_{19}H_{23}N_4O_4S]^+$ = 403.1434.

triethyl 3,4-dihydroxy-8-tosyl-8-azabicyclo[3.2.1]oct-6-ene-2,6,7-tricarboxylate (215)

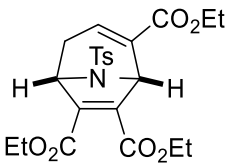


As described in the literature[24b], to a vigorously stirred solution of the cycloaddition product **195** (137 mg, 0.29 mmol, 1 equiv) in CH_3CN (1.7 mL) in ice bath was added a solution of $RuCl_3 \cdot 3H_2O$ (4 mg, 0.02 mmol, 7 mol%) and $NaIO_4$ (95 mg, 0.45 mmol, 1.5 equiv) in distilled water (0.3 mL). The mixture was allowed to warm to room temperature and stirred for 2 d and then the suspension was filtered through a thin pad of silica gel, which was washed with EA. Concentration of the filtrate and flash chromatography yielded the diol **215** (69 mg, 0.135 mmol) in 48% yield.

R_f = 0.25 (PE/EA 2:1); **^{1}H NMR** (400 MHz, CD_3COCD_3) δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.41

(d, *J* = 7.9 Hz, 2H), 5.04 (s, 1H), 4.85 (d, *J* = 3.3 Hz, 1H), 4.34 (d, *J* = 11.5 Hz, 1H), 4.25 (dd, *J* = 16.5, 7.1 Hz, 2H), 4.16 (ddd, *J* = 9.8, 6.5, 3.0 Hz, 4H), 3.94 (dt, *J* = 11.5, 3.9 Hz, 1H), 3.87 (d, *J* = 5.8 Hz, 1H), 3.83 (t, *J* = 9.9 Hz, 1H), 3.36 (dd, *J* = 6.3, 2.5 Hz, 1H), 2.43 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.24 (td, *J* = 7.1, 2.9 Hz, 6H); **^{13}C NMR** (101 MHz, CD_3COCD_3) δ 171.9, 161.4, 161.3, 144.2, 139.2, 136.5, 134.5, 130.1, 127.6, 69.2, 65.7, 65.6, 64.8, 64.5, 61.7, 61.2, 46.3, 20.5, 13.5, 13.3, 13.3; **IR** (neat) ν (cm^{-1}) 3440, 2982, 1700, 1394, 1364, 1256, 1163, 1025, 931, 880, 723; **LRMS** (ESI): *m/z* = 512.1592 $[M+H]^+$, 529.1857 $[M+NH_4]^+$, 1045.2928 $[2M+Na]^+$; **HRMS** (ESI): *m/z* = 534.1400 $[M+Na]^+$; calc. for $[C_{23}H_{29}NO_{10}S+Na]^+$ = 534.1404.

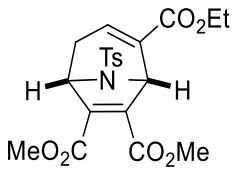
triethyl 8-tosyl-8-azabicyclo[3.2.1]octa-2,6-diene-2,6,7-tricarboxylate (219)



To a solution of the cycloaddition product **195** (115 mg, 0.24 mmol, 1 equiv) in DCM (1 mL) was added trimethylamine (33 µL, 2.4 mmol, 10 equiv) and the solution was stirred for 2 h. After evaporating the volatile elements in the solution, the isomerized product **219** (113 mg, 0.23 mmol) was obtained in 97 % yield.

R_f = 0.38 (PE/EA 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.62 (m, 2H), 7.29 – 7.21 (m, 2H), 6.66 (ddt, *J* = 4.1, 3.1, 1.1 Hz, 1H), 5.37 (q, *J* = 1.0 Hz, 1H), 4.92 (dq, *J* = 5.9, 1.1 Hz, 1H), 4.21 (qd, *J* = 7.2, 3.2 Hz, 2H), 4.17 – 3.99 (m, 4H), 2.94 (dddd, *J* = 19.9, 5.9, 3.1, 1.1 Hz, 1H), 2.39 (s, 3H), 2.38 – 2.26 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.2, 161.8, 161.5, 147.5, 144.0, 136.8, 133.8, 133.3, 133.0, 129.9, 127.9, 61.4, 61.4, 61.2, 61.2, 61.1, 28.5, 21.5, 14.2, 13.9; **IR** (neat) ν (cm^{-1}) 2982, 2933, 2908, 1711, 1640, 1599, 1447, 1446, 1394, 1370, 1353, 1286, 1241, 1163, 1091, 1081, 1036, 965, 938, 910, 855, 816, 735, 705, 687; **LRMS** (ESI): *m/z* = 478.1543 $[M+H]^+$, 977.2832 $[2M+Na]^+$; **HRMS** (ESI): *m/z* = 500.1349 $[M+Na]^+$; calc. for $[C_{23}H_{27}NO_8S+Na]^+$ = 500.1349.

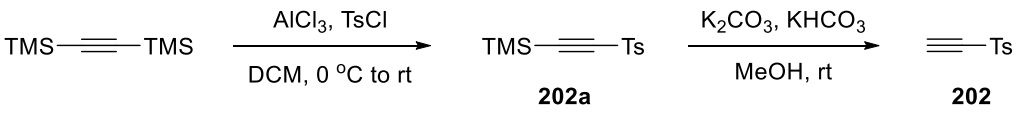
2-ethyl 6,7-dimethyl 8-tosyl-8-azabicyclo[3.2.1]octa-2,6-diene-2,6,7-tricarboxylate (208)



To a solution of the cycloaddition product **196** (161 mg, 0.36 mmol, 1 equiv) in DCM (1 mL) was added trimethylamine (50 µL, 3.6 mmol, 10 equiv) and the solution was stirred for 2 h. After evaporating the volatile elements in the solution, the isomerized product **208** (155 mg, 0.35 mmol) was obtained in 96 % yield.

R_f = 0.43 (PE/EA 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 – 7.58 (m, 2H), 7.28 – 7.23 (m, 2H), 6.65 (ddt, *J* = 4.1, 3.2, 1.0 Hz, 1H), 5.36 (q, *J* = 1.0 Hz, 1H), 4.91 (dq, *J* = 5.9, 1.1 Hz, 1H), 4.29 – 4.14 (m, 2H), 3.68 (s, 3H), 3.62 (s, 3H), 2.93 (dddd, *J* = 19.9, 5.9, 3.1, 1.1 Hz, 1H), 2.39 (s, 3H), 2.33 (ddd, *J* = 20.0, 4.0, 1.0 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.2, 162.1, 162.0, 147.5, 144.3, 136.8, 133.8, 133.4, 133.3, 129.9, 127.9, 61.3, 61.3, 61.1, 52.3, 52.2, 28.5, 21.5, 14.2; **IR** (neat) ν (cm^{-1}) 2982, 2956, 2931, 2856, 1711, 1644, 1599, 1439, 1349, 1287, 1245, 1163, 1126, 1088, 1022, 1021, 965, 936, 857, 816, 782, 753, 706, 690; **LRMS** (ESI): *m/z* = 450.1225 $[M+H]^+$, 921.2192 $[2M+Na]^+$; **HRMS** (ESI): *m/z* = 472.1037 $[M+Na]^+$; calc. for $[C_{21}H_{23}NO_8S]^+$ = 472.1036.

Synthesis of ethynyl *p*-tolyl sulfone (202)



trimethyl(tosylethynyl)silane (202a)

As described in literature,[69] bis(trimethylsilyl)acetylene (3.4 g, 20 mmol, 1 equiv) in DCM (20 mL) was reacted with $AlCl_3$ (2.94 g, 22 mmol, 1.1 equiv) and TsCl (4.19 g, 22 mmol, 1.1 equiv) in DCM (20 mL) at 0 °C to afford trimethyl(tosylethynyl)silane **202a** (4.08 g, 16.1 mmol) in 81% yield.

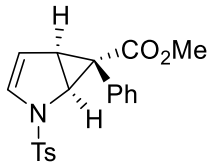
R_f = 0.47 (PE/EA = 10:1); **^{1}H NMR** (300 MHz, CDCl3) δ 7.90 – 7.84 (m, 2H), 7.41 – 7.30 (m, 2H), 2.46 (s, 3H), 0.20 (s, 9H).

ethynyl *p*-tolyl sulfone (202)

Next, ethynyl *p*-tolyl sulfone **202** (570 mg, 3.16 mmol) was synthesized in 80% yield from trimethyl(tosylethynyl)silane **202a** (1.58 g, 6.26 mmol, 1 equiv), K_2CO_3 (1.88 g, 13.6 mmol, 2.17 equiv), $KHCO_3$ (1.36 g, 13.6 mmol, 2.17 equiv) in MeOH (19 mL) and water (22 mL) at room temperature.

R_f = 0.40 (PE/EA = 10:1); **^{1}H NMR** (300 MHz, CDCl3) δ 7.93 – 7.87 (m, 2H), 7.42 – 7.37 (m, 2H), 3.45 (s, 1H), 2.48 (s, 3H).

methyl (1*S*,5*S*,6*R*)-6-phenyl-2-tosyl-2-azabicyclo[3.1.0]hex-3-ene-6-carboxylate (249)

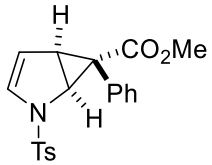


In a flame dried flask with a magnetic stirring bar in, *N*-Ts-pyrrole (3.1 g, 14 mmol, 2 equiv), Rh_2(*S*-TCPTTL)$_4$ (12.6 mg, 0.007 mmol, 0.1 mol%) and dry toluene (28 mL) were placed under N_2-atmosphere. The solution was stirred till complete dissolution and was cooled to 0 °C. To this solution, a solution of (1-diazoethyl)benzene **109a** (1.23 g, 7 mmol, 1 equiv) in dry toluene (14 mL) was added at a rate of 1 drop/10 sec at 0 °C. Upon completion of addition, the reaction mixture was concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel and the desired product **249** (1.35 g, 3.7 mmol, 52%) was obtained as a white solid.

R_f = 0.38 (PE/EA = 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 – 7.67 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.25 - 7.27 (m, 3H), 7.19 (dd, *J* = 6.9, 2.8 Hz, 2H), 5.95 (dd, *J* = 3.9, 1.5 Hz, 1H), 5.28 (dd, *J* = 3.9, 2.5 Hz, 1H), 4.53 (dd, *J* = 6.5, 1.5 Hz, 1H), 3.61 (s, 3H), 3.14 (dd, *J* = 6.6, 2.5 Hz,

1H), 2.45 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.6, 144.4, 134.9, 132.4, 130.8, 130.3, 129.9, 127.8, 127.4, 127.2, 111.3, 52.8, 52.2, 38.7, 28.0, 21.6; **IR** (neat) ν (cm^{-1}) 3127, 3049, 2960, 1700, 1584, 1491, 1439, 1357, 1316, 1267, 1223, 1163, 1081, 1003, 965, 813, 746, 701, 667; **mp** = 131 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= -673.6 (c = 1.0, $CHCl_3$); **LRMS** (ESI): *m/z* = 370.1113 $[M+H]^+$, 761.1973 $[2M+Na]^+$; **HRMS** (ESI) *m/z* = 370.1108 $[M+H]^+$; calc. for $[C_{20}H_{20}NO_4S]^+$ = 370.1112.; **HPLC analysis** (Phenomenex Lux Cellulose-1, *n*-heptane:*i*-PrOH = 95:5, 0.5 mL/min, λ = 215 nm) t_r = **29.56 min** (major), 34.82 min (minor), 91% *ee*.

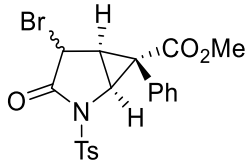
methyl 6-phenyl-2-tosyl-2-azabicyclo[3.1.0]hex-3-ene-6-carboxylate (*rac*-249)



In a flame-dried round-bottomed flask with a magnetic stirring bar in, *N*-Ts-pyrrole (6.2 g, 28 mmol, 2 equiv) and $Cu(OTf)_2$ (506 mg, 1.4 mmol, 10 mol%) were dissolved in anhydrous DCM (21 mL) under N_2-atmosphere. The solution was stirred till complete dissolution and a solution of (1-diazoethyl)benzene **109a** (2.47 g, 14 mmol, 1 equiv) in anhydrous DCM (28 mL) was added at a rate of 1 drop/10 sec. Upon completion of addition, the reaction mixture was filtered through a pad of basic alumina and filtrate was concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel to obtain the desired product *rac*-**249** (1.2 g, 3.2 mmol, 23%) as a white solid.

HPLC analysis (Phenomenex Lux Cellulose-1, *n*-heptane:*i*-PrOH = 95:5, 0.5 mL/min, λ = 215 nm) t_r = 31.97 min, 37.10 min, racemate.

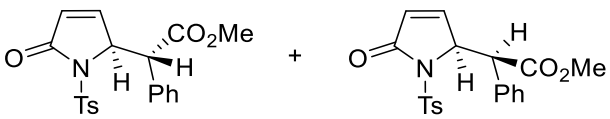
methyl (1*S*,5*S*,6*R*)-4-bromo-3-oxo-6-phenyl-2-tosyl-2-azabicyclo[3.1.0]hexane-6-carboxylate (257) [24b]



To a solution of **249** (369 mg, 1 mmol, 1 equiv) in acetonitrile (1 mL) and water (2 mL) was added NBS (179.8 mg, 1 mmol, 1 equiv) in small portions at 0 °C. After stirring for 5 min, the reaction mixture was extracted with DCM, and the combined DCM layers were dried over Na_2SO_4. After concentration *in vacuo*, the crude mixture was dissolved in acetone (4.5 mL) and Jones reagent (2 mmol) was added to the solution and the solution was stirred for 4 h at room temperature. Upon completion, the reaction was then quenched by sat. solution of $NaHCO_3$ and extracted with DCM. The combined DCM layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The desired product **257** was obtained by flash column chromatography on silica gel as a white crystalline (338 mg, 0.73 mmol, 73 %).

R_f = 0.55 (PE/EA = 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 – 7.79 (m, 2H), 7.43 – 7.26 (m, 7H), 4.67 (dd, *J* = 7.7, 0.9 Hz, 1H), 4.28 (d, *J* = 0.9 Hz, 1H), 3.67 (s, 3H), 2.94 (d, *J* = 7.7 Hz, 1H), 2.46 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.8, 167.2, 145.9, 134.5, 132.4, 129.9, 129.2, 129.2, 128.1, 127.1, 53.2, 46.7, 41.1, 40.5, 28.1, 21.8; **IR** (neat) ν (cm^{-1}) 3094, 3068, 3032, 2997, 2923, 2852, 1752, 1715, 1596, 1495, 1450, 1435, 1368, 1330, 1306, 1249, 1238, 1207, 1169, 1160, 1144, 1115, 1100, 1085, 1064, 1025, 989, 970, 931, 918, 876, 814, 789, 754, 738, 707; **mp** = 176 °C; **LRMS** (ESI) *m/z* = 483.0 $[M+NH_4]^+$, 951.0 $[2M+Na]^+$; **HRMS** (ESI) *m/z* = 481.0430 $[M+NH_4]^+$; calc. for $[C_{20}H_{22}BrN_2O_5S]^+$ = 481.0427.

methyl (*R*)-2-((*S*)-5-oxo-1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)-2-phenylacetate (258)
methyl (*S*)-2-((*S*)-5-oxo-1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)-2-phenylacetate (259)
(*dr* 2.l:1)



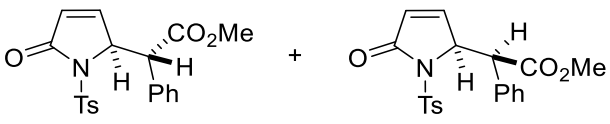
major minor

To a flame-dried three neck flask, substrate **257** (95 mg, 0.2 mmol, 1 equiv) was dissolved in benzene (1 mL). Tributyltin hydride (59.5 µL, 0.225 mmol, 1.1 equiv) and AIBN (5 mg, 0.031 mmol, 15 mol%) were added at reflux. The reaction mixture was stirred for 30 min, and then the solvent was evaporated. The crude mixture was dissolved in EtOAc (2 mL) and a sat. solution of KF (2 mL) was added. The solution was then stirred at room temperature for 24 h.

The precipitate was removed by filtration and the separated organic layer was dried over Na_2SO_4. After the concentration, the crude mixture was purified on the flash chromatography on silica gel to afford the mixture of two diastereomers **258** and **259** (38 mg, 0.1 mmol, 48%, 66% brsm) as a white solid.

R_f = 0.23 (PE/EA = 5:1); **^{1}H NMR** (300 MHz, $CDCl_3$) – major: δ 8.02 (d, *J* = 8.4 Hz, 2H), 7.44 – 7.36 (m, 5H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.20 (dd, *J* = 6.2, 2.0 Hz, 1H), 6.07 (dd, *J* = 6.2, 1.9 Hz, 1H), 5.01 (d, *J* = 4.6 Hz, 1H), 4.98 – 4.89 (m, 1H), 3.47 (s, 3H), 2.44 (s, 3H) – minor: δ 7.93 (d, *J* = 8.4 Hz, 2H), 7.53 (dd, *J* = 6.1, 2.1 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.26 – 7.23 (m, 3H), 7.13 – 7.01 (m, 2H), 5.71 (dd, *J* = 6.1, 1.7 Hz, 1H), 5.28 (dt, *J* = 3.7, 1.9 Hz, 1H), 4.96 (t, *J* = 2.0 Hz, 1H), 3.78 (s, 3H), 2.44 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.3, 169.7, 169.4, 169.0, 150.5, 149.5, 145.3, 145.1, 135.7, 135.3, 133.6, 131.5, 129.7, 129.5, 129.4, 129.2, 128.5, 128.5, 128.4, 128.2, 128.2, 128.1, 126.6, 126.0, 66.6, 64.8, 52.7, 52.5, 52.3, 51.9, 22.6, 21.7.; **IR** (neat) ν (cm^{-1}) 2952, 1730, 1595, 1495, 1454, 1435, 1357, 1327, 1275, 1163, 1137, 1088, 992, 816, 705; **mp** = 43 °C; **LRMS** (ESI) *m/z* = 386.1 $[M+H]^+$, 793.1 $[2M+Na]^+$; **HRMS** (ESI) *m/z* = 403.1324 $[M+NH_4]^+$; calc. for $[C_{20}H_{23}N_2O_5S]^+$ = 403.1322; **HPLC analysis** (Phenomenex Lux Cellulose-1, *n*-heptane:*i*-PrOH = 90:10, 1.0 mL/min, λ = 215 nm) major diastereomer: t_r = **25.80 min,** 34.13 min, 98% *ee*. minor diastereomer: t_r = **19.95 min**, 71.87 min, 65% *ee*.

methyl 2-(5-oxo-1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)-2-phenylacetate (*rac*-258 and *rac*-259, *dr* 1.9 : 1)[24b]



major minor

As described above, the *rac*-**257** (40 mg, 0.086 mmol, 1 equiv), tributyltin hydride (25 μL, 0.09 mmol, 1.1 equiv) and AIBN (1.4 mg, 0.0086 mmol, 10 mol%) were used for the reaction. The reaction mixture was stirred for 30 min, and then the solvent was evaporated. The crude mixture was dissolved in EtOAc (1 mL) and a sat. solution of KF (1 mL) was added. The solution was then stirred at room temperature for 24 h. The precipitate was removed by filtration and the separated organic layer was dried over Na_2SO_4. After the concentration, the crude mixture was

purified on the flash chromatography on silica gel to afford the mixture of diastereomers, *rac*-**258** and *rac*-**259** (12.5 mg, 0.032 mmol, 37%) as a white solid.

HPLC analysis (Phenomenex Lux Cellulose-1, *n*-heptane:*i*-PrOH = 90:10, 1.0 mL/min, λ = 215 nm) major diastereomer: t_r = 26.94 min, 34.46 min, minor diastereomer: t_r = 19.55 min, 71.74 min.

F. Appendix

1. NMR Spectra

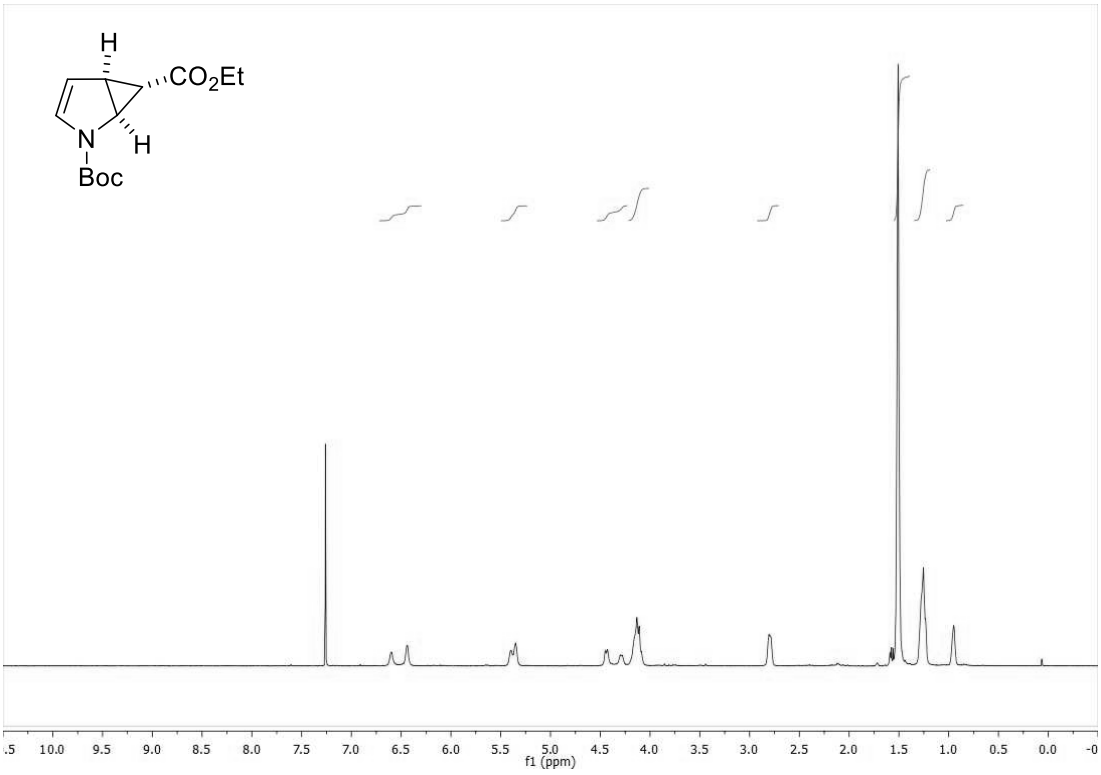
^{1}H NMR spectra: upper image

^{13}C NMR spectra (DEPT135 integrated): lower image

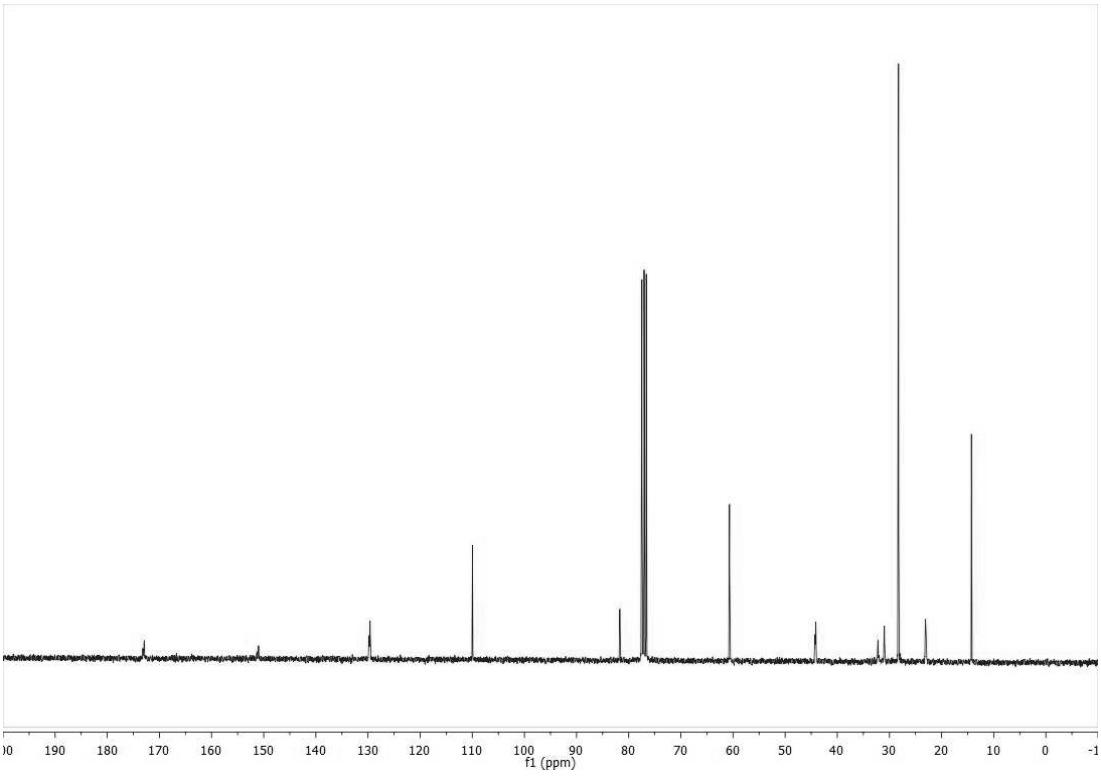
Solvent and frequency are stated in each spectrum.

2-(*tert*-butyl) 6-ethyl-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (60c)

^{1}H NMR (300 MHz, $CDCl_3$)

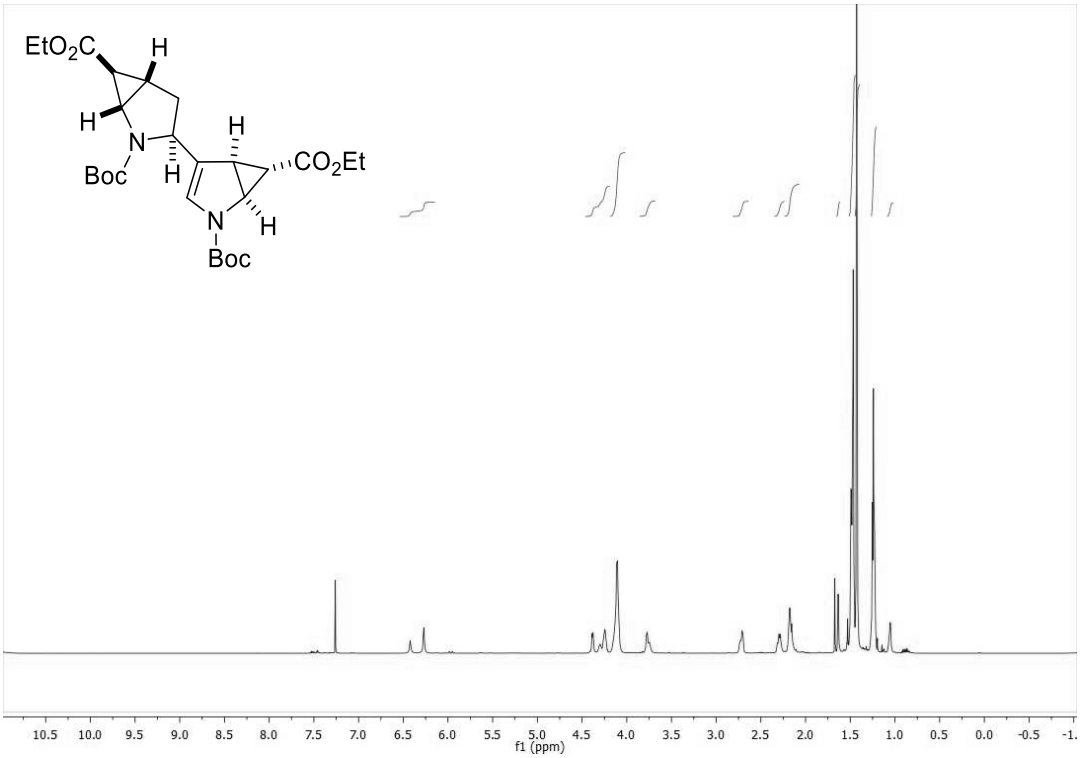


^{13}C NMR (75 MHz, $CDCl_3$)

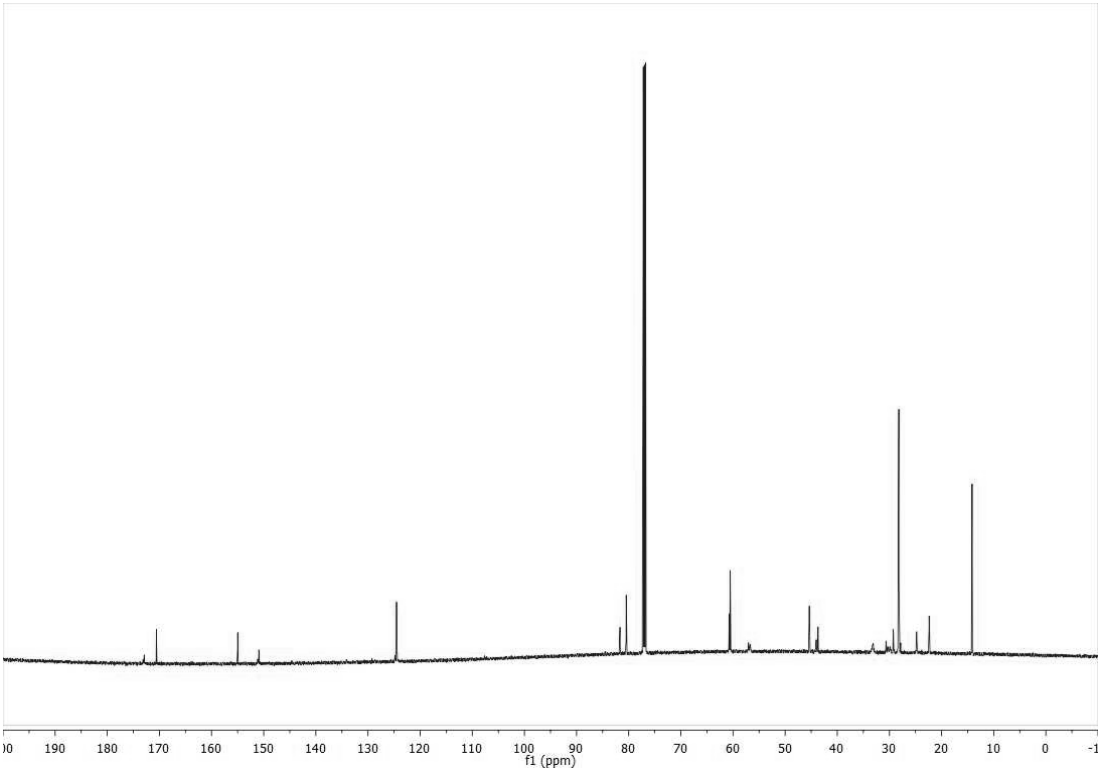


2-(*tert*-butyl) 6-ethyl 4-(2-(*tert*-butoxycarbonyl)-6-(ethoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (121)

^{1}H NMR (600 MHz, $CDCl_3$)

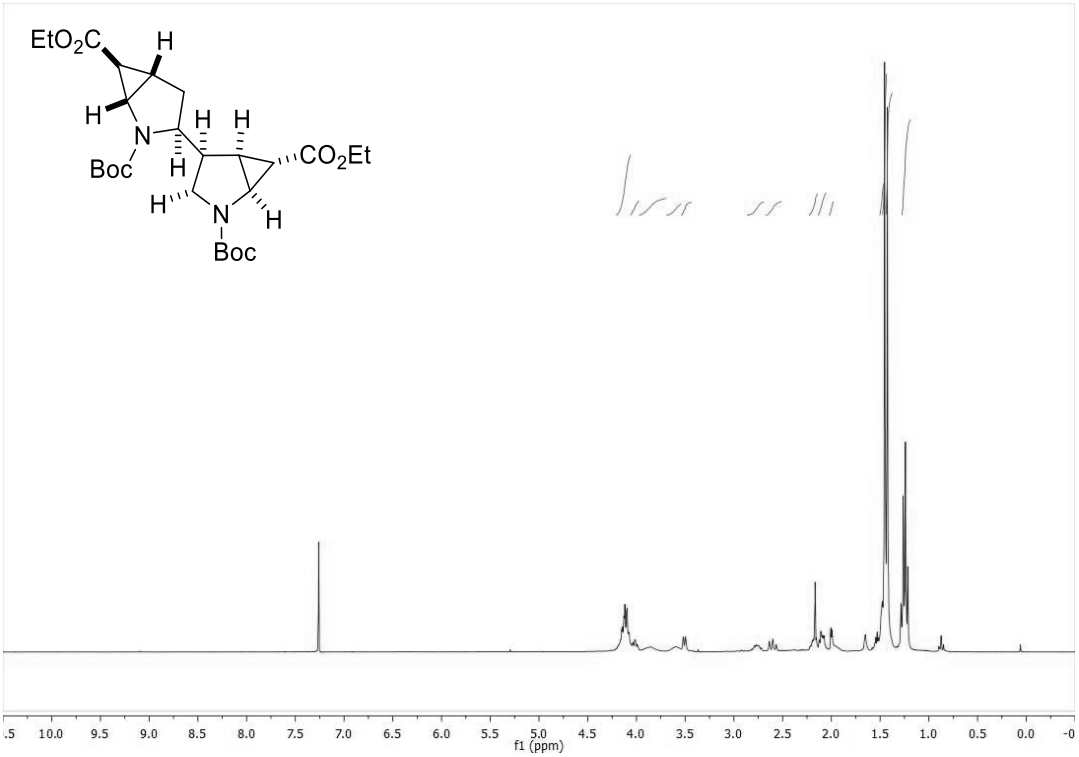


^{13}C NMR (224 MHz, $CDCl_3$)

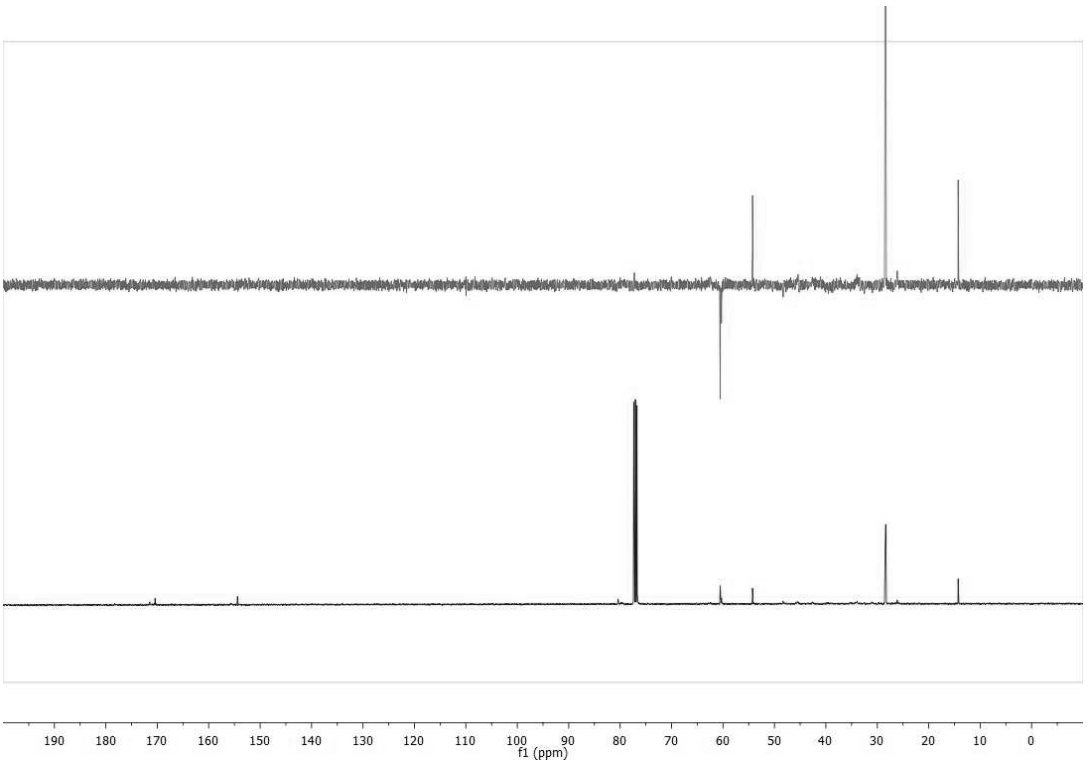


2,2'-di-*tert*-butyl-6,6'-diethyl-2,2'-diaza[3,4'-bi(bicyclo[3.1.0]hexane)]-2,2',6,6'-tetracarboxylate (145)

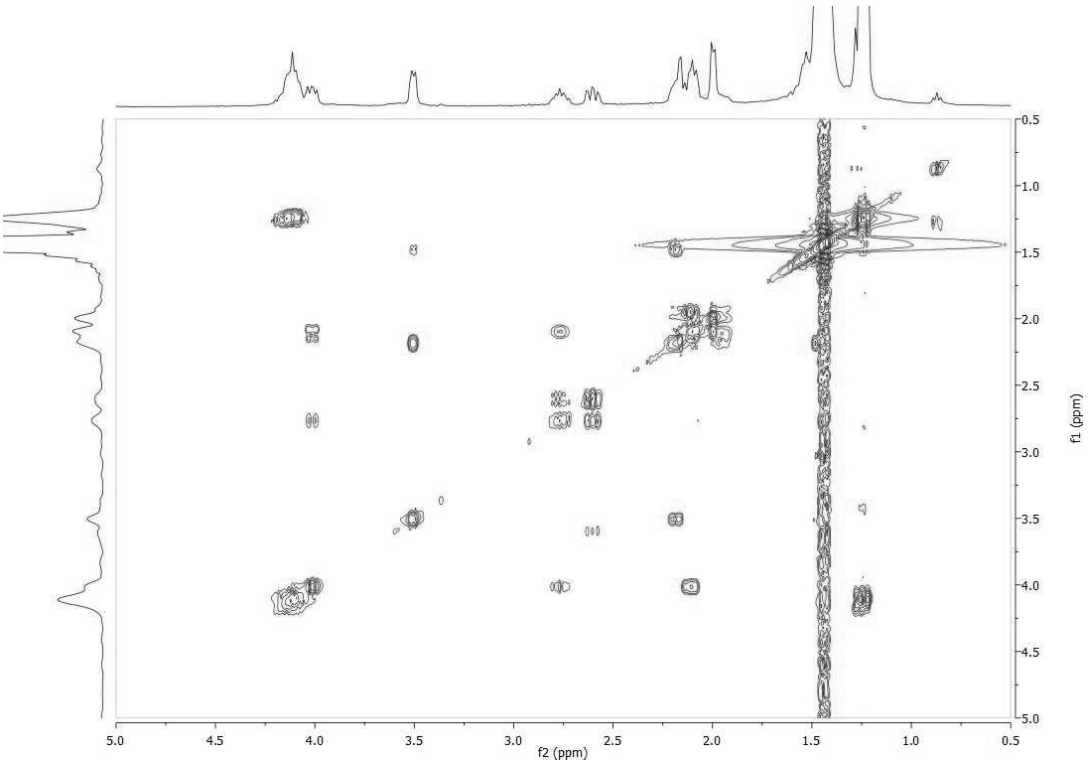
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

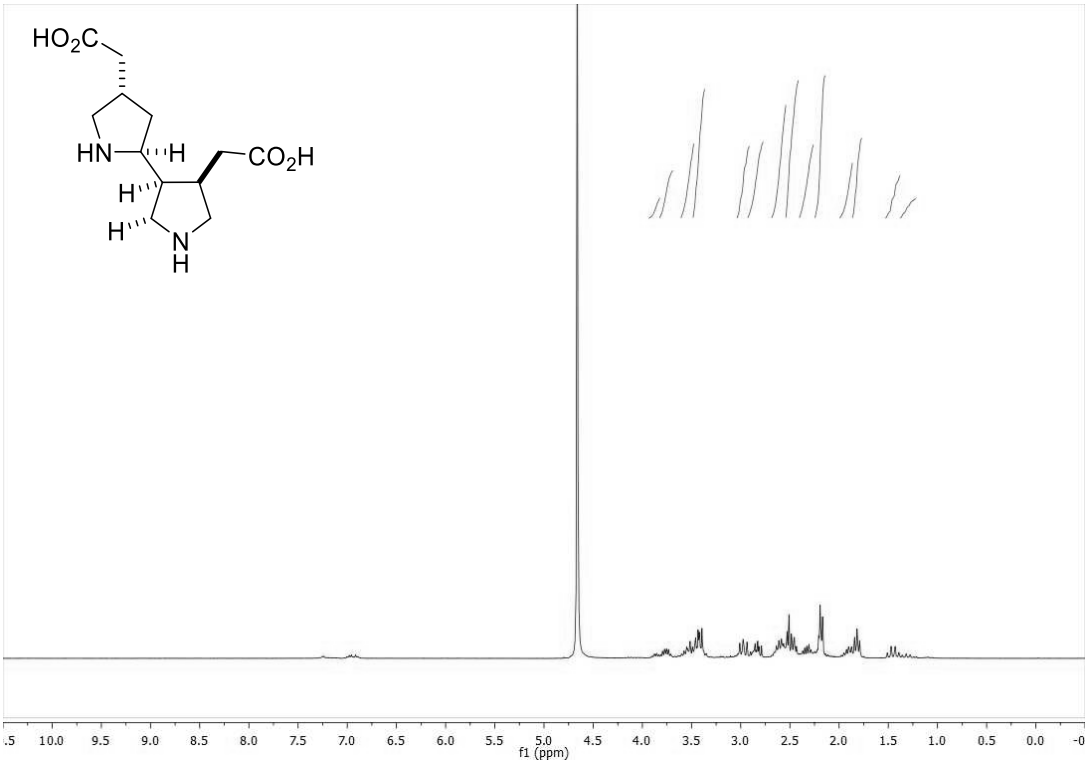


COSY (400 MHz, $CDCl_3$)

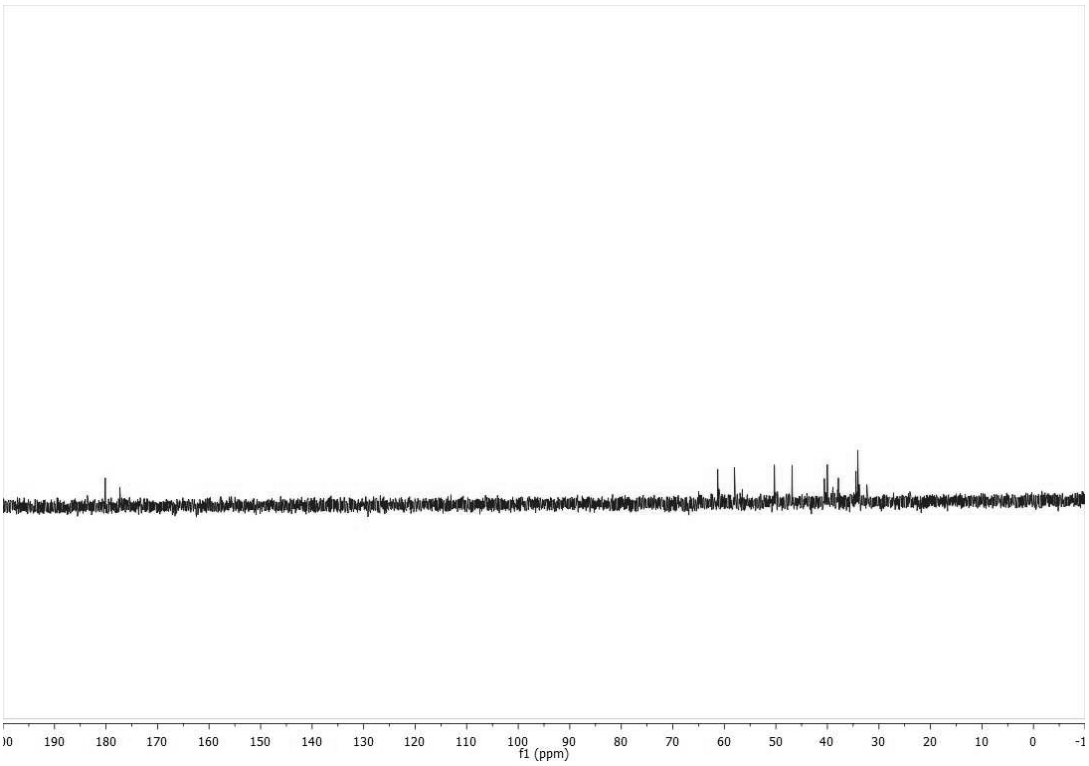


2,2'-([2,3'-bipyrrolidine]-4,4'-diyl)diacetic acid (146)

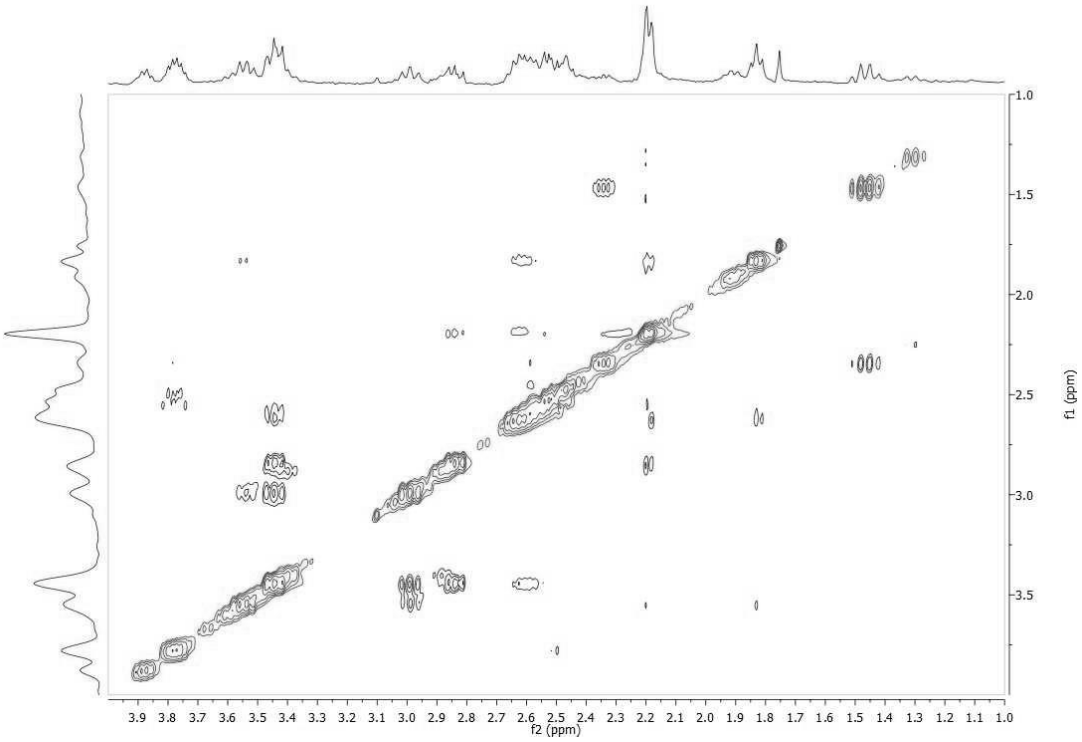
^{1}H NMR (400 MHz, D_2O)



^{13}C NMR (101 MHz, D_2O)

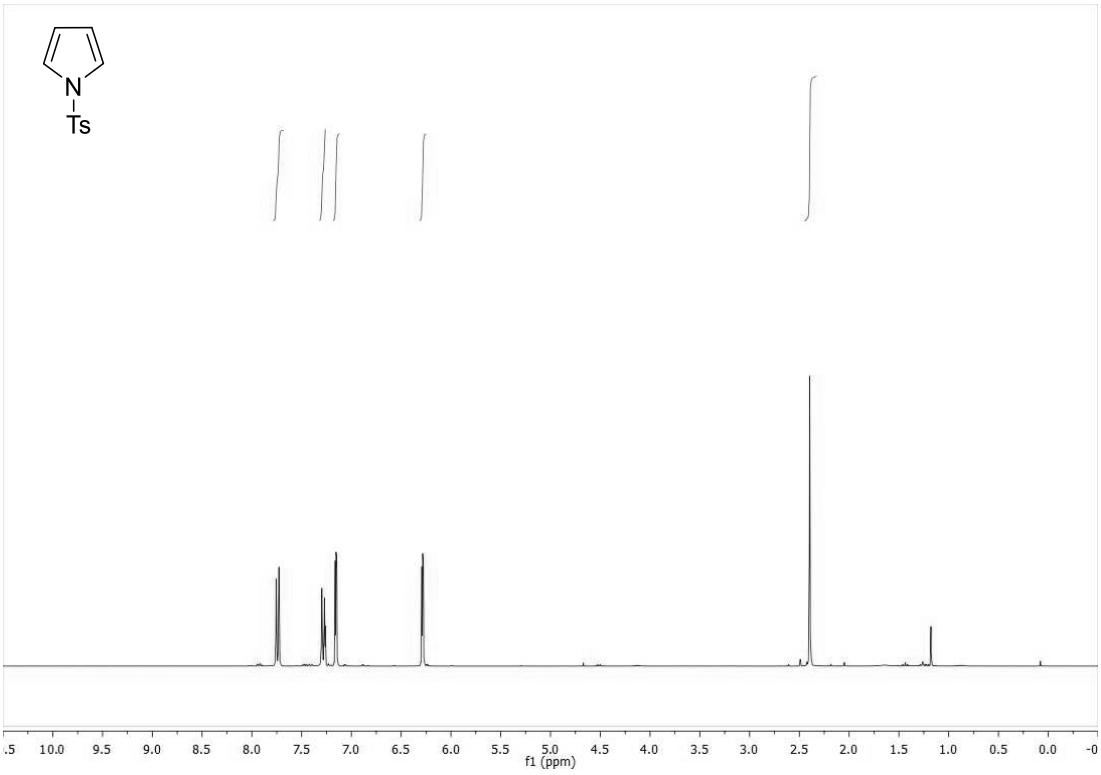


NOESY (400 MHz, D_2O)



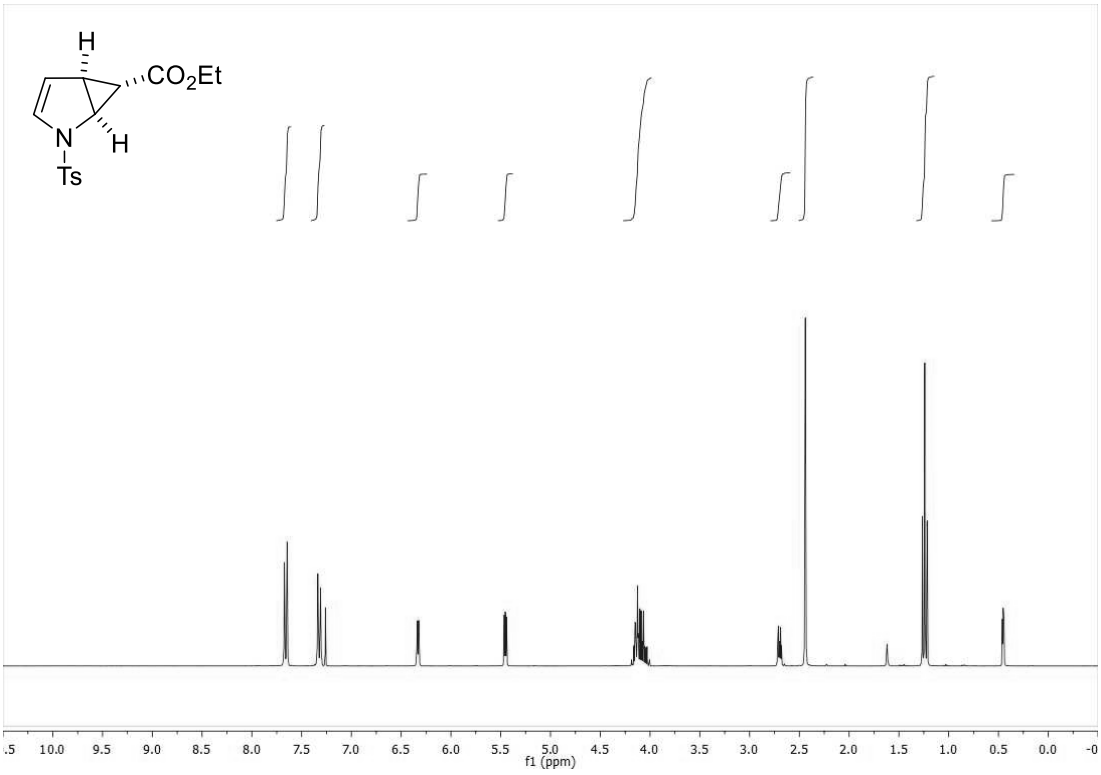
1-tosyl-1H-pyrrole (58d)

^{1}H NMR (300 MHz, $CDCl_3$)

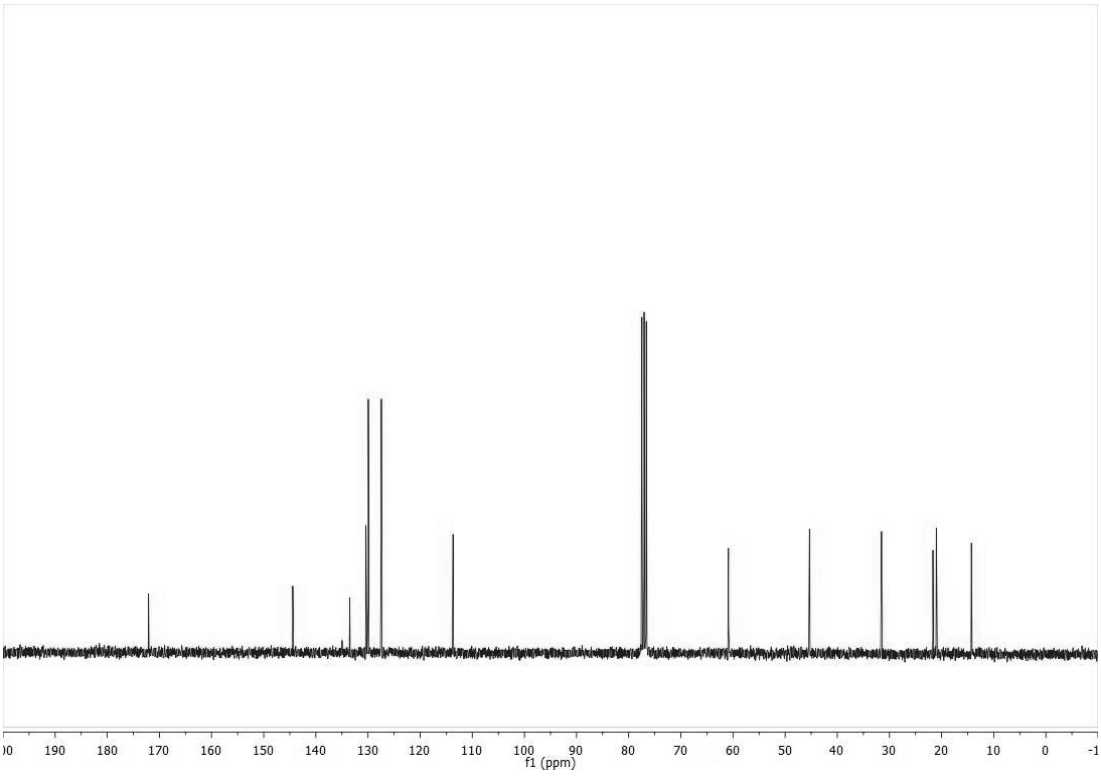


ethyl 2-tosyl-2-azabicyclo[3.1.0]hex-3-ene-6-carboxylate (60d)

^{1}H NMR (300 MHz, $CDCl_3$)

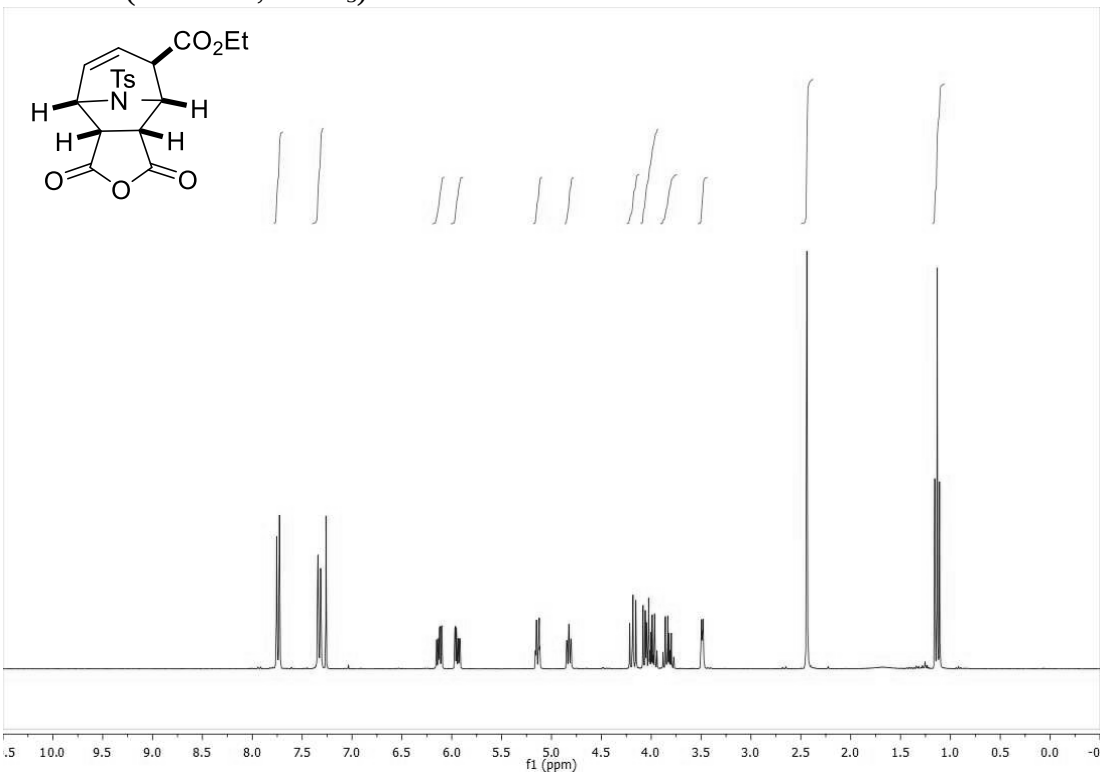


^{13}C NMR (75 MHz, $CDCl_3$)

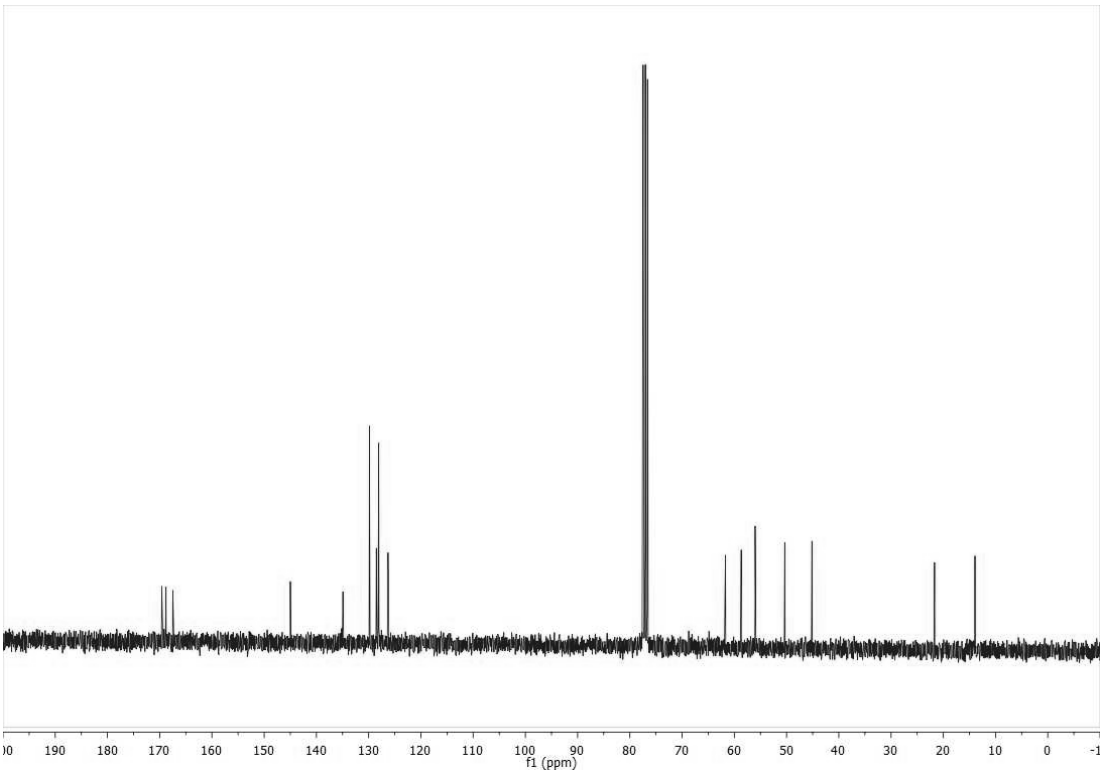


ethyl 1,3-dioxo-9-tosyl-3,3a,4,5,8,8a-hexahydro-1H-4,8-epiminocyclohepta[c]furan-5-carboxylate (192)

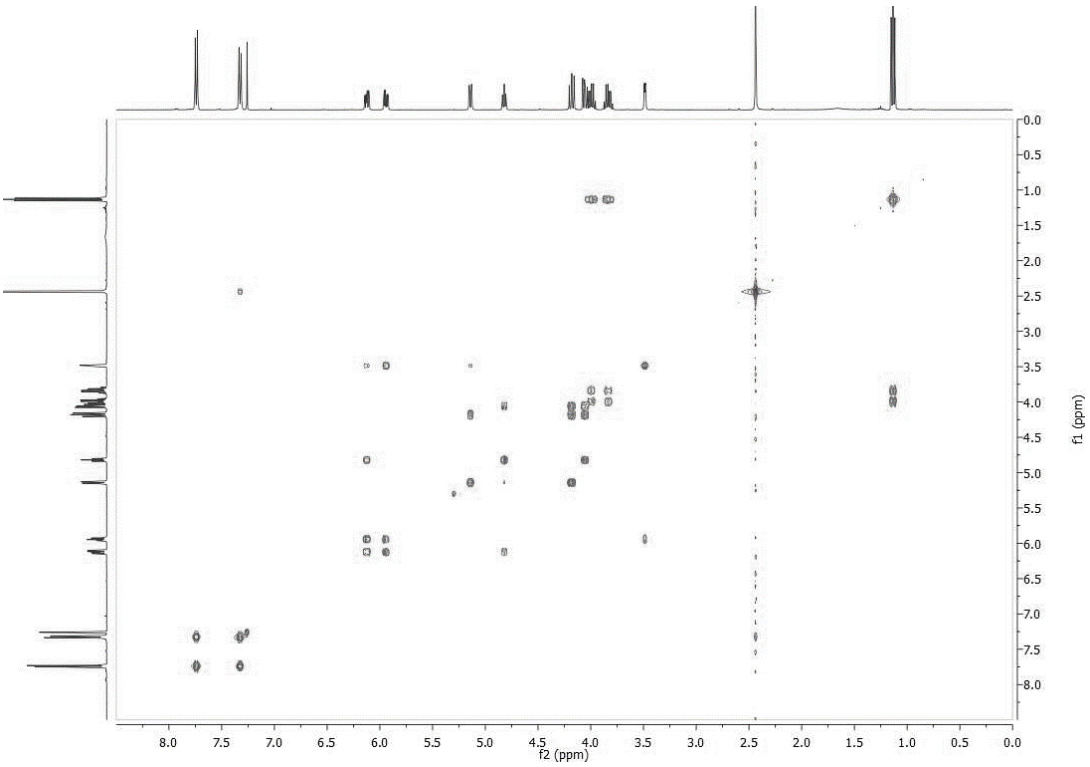
^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)

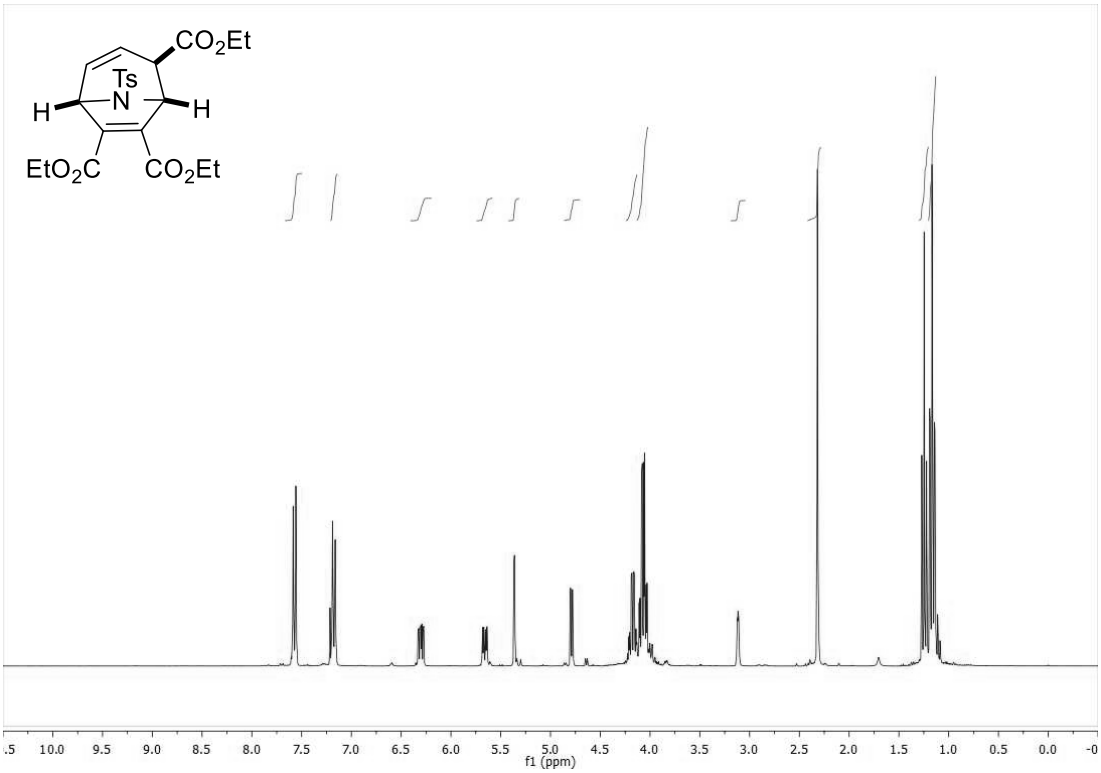


COSY (400 MHz, $CDCl_3$)

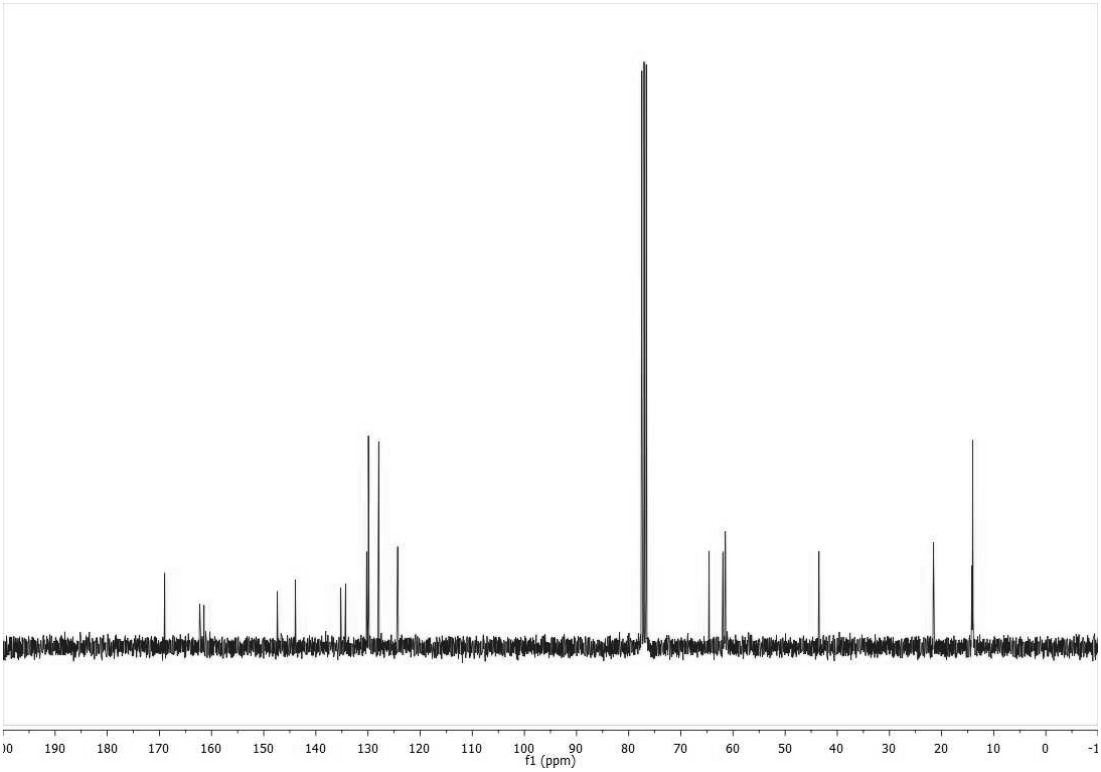


triethyl 8-tosyl-8-azabicyclo[3.2.1]octa-3,6-diene-2,6,7-tricarboxylate (195)

^{1}H NMR (300 MHz, $CDCl_3$)



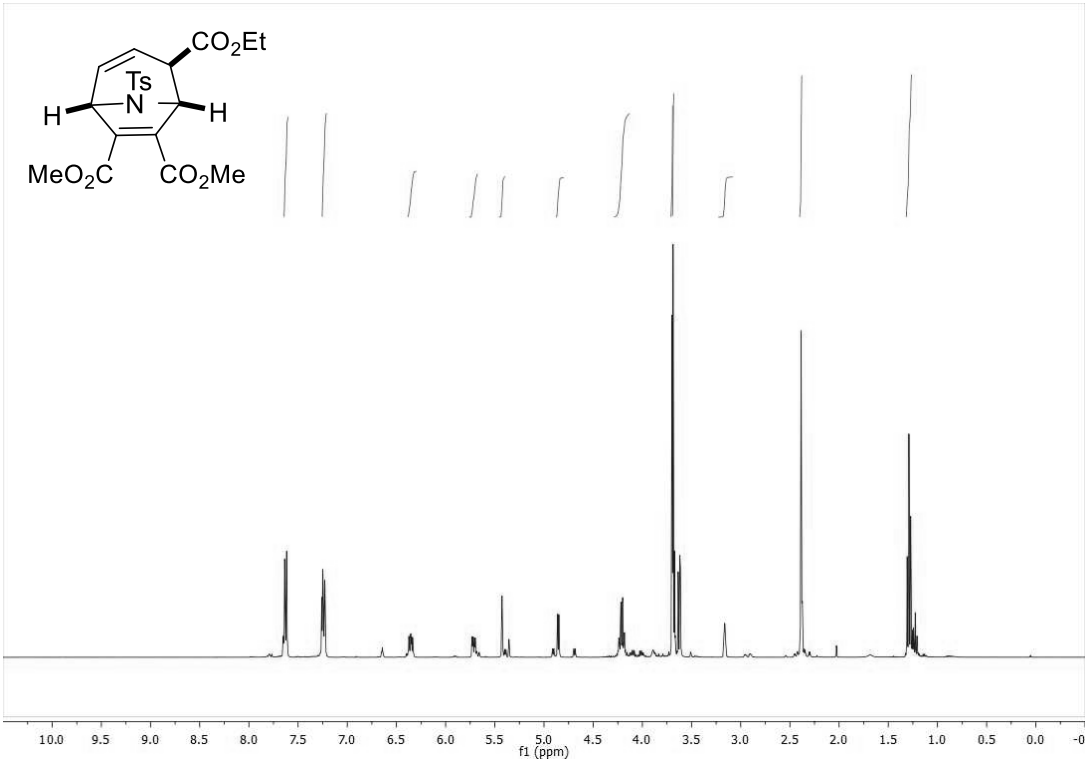
^{13}C NMR (75 MHz, $CDCl_3$)



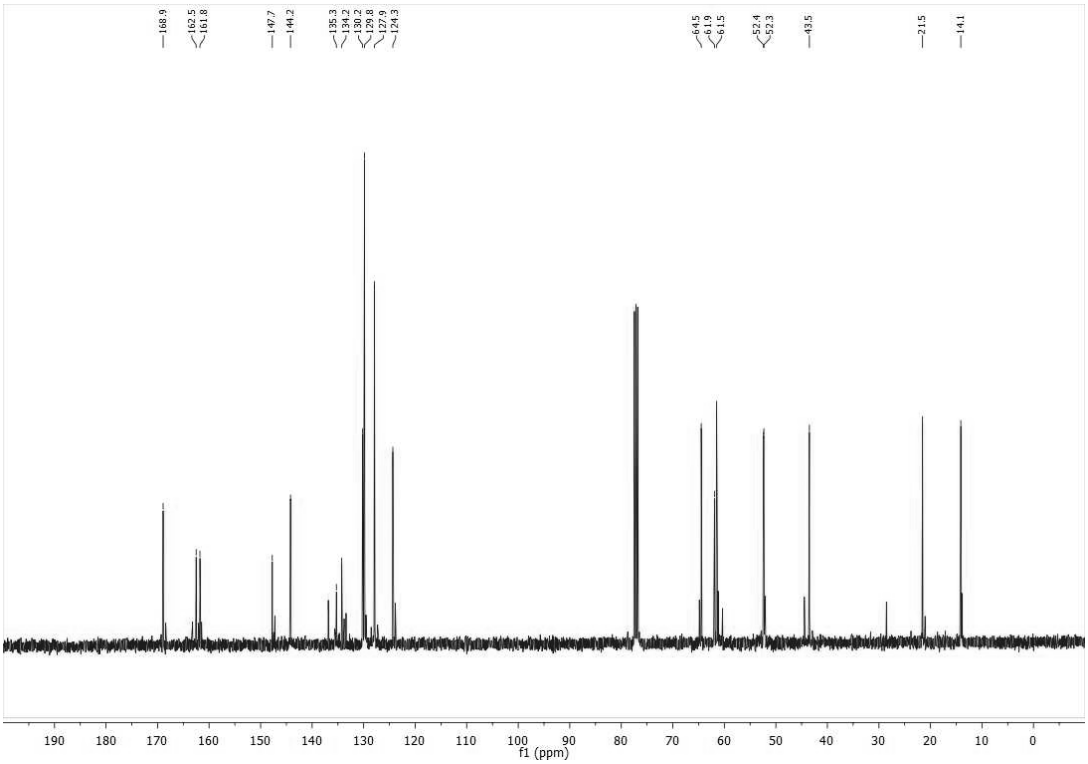
2-ethyl 6,7-dimethyl 8-tosyl-8-azabicyclo[3.2.1]octa-3,6-diene-2,6,7-tricarboxylate (196)

(as an inseparable mixture of product **196** and isomerized product **208**)

^{1}H NMR (300 MHz, $CDCl_3$)

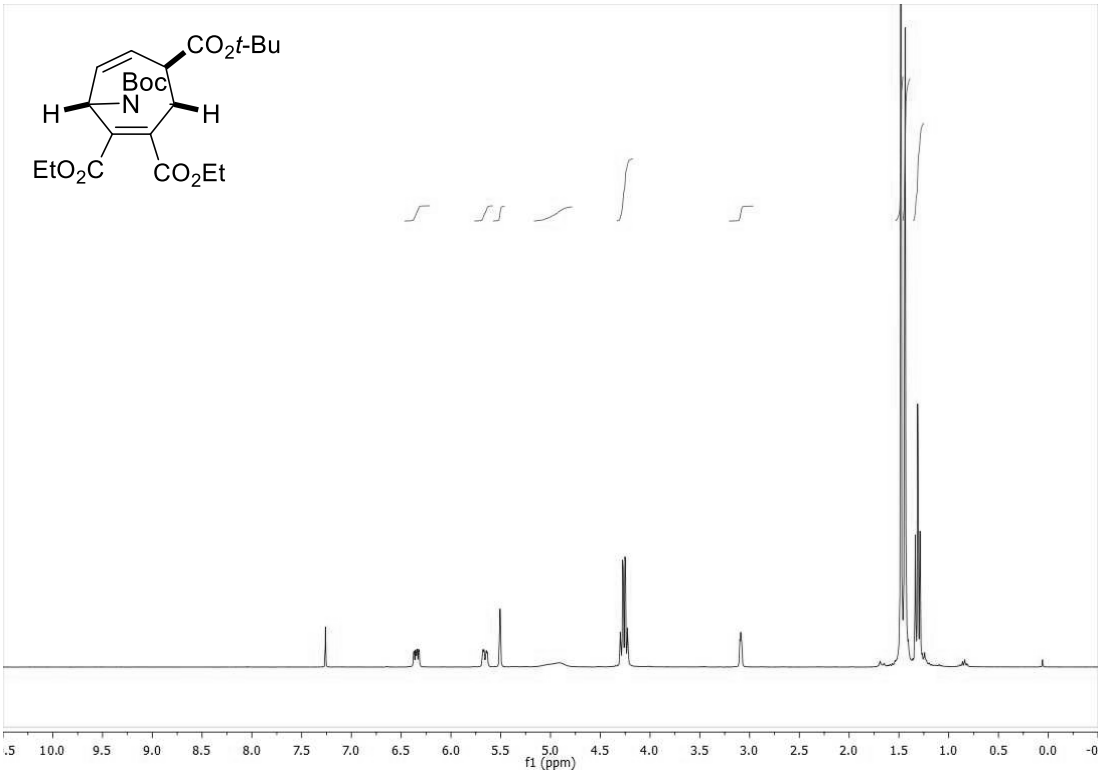


^{13}C NMR (75 MHz,$CDCl_3$) (For clarification, the peaks from the product **196** is marked.)

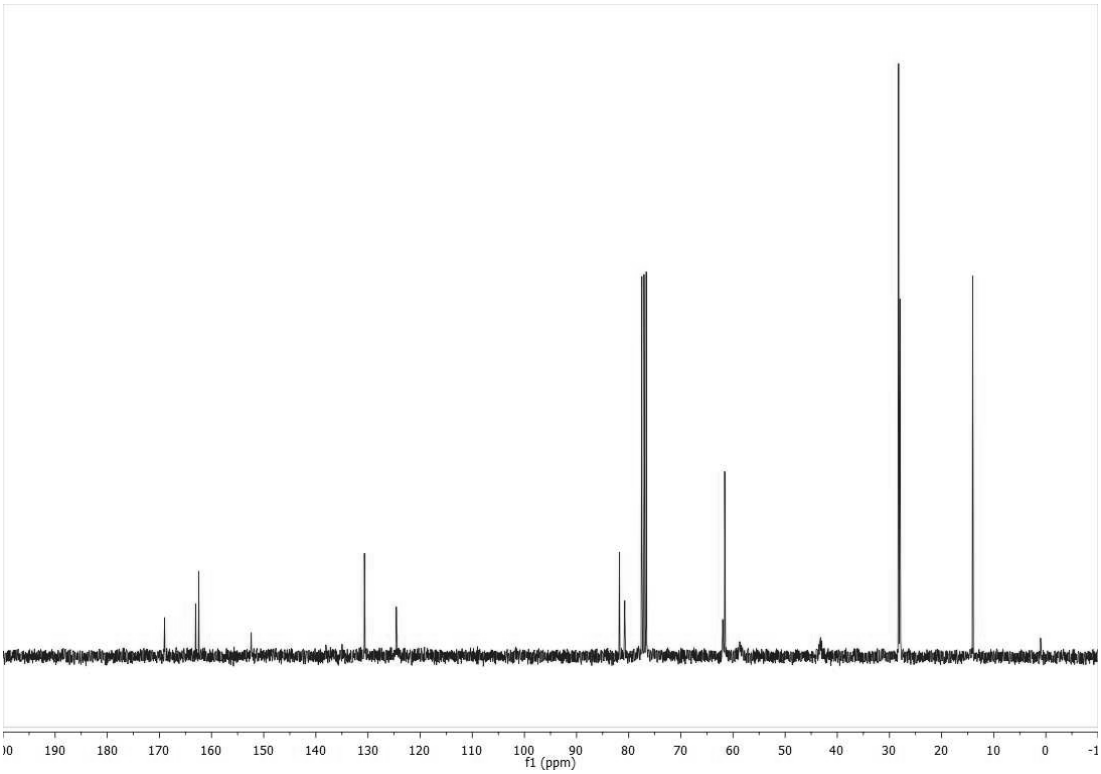


2,8-di-*tert*-butyl 6,7-diethyl 8-azabicyclo[3.2.1]octa-3,6-diene-2,6,7,8-tetracarboxylate (200)

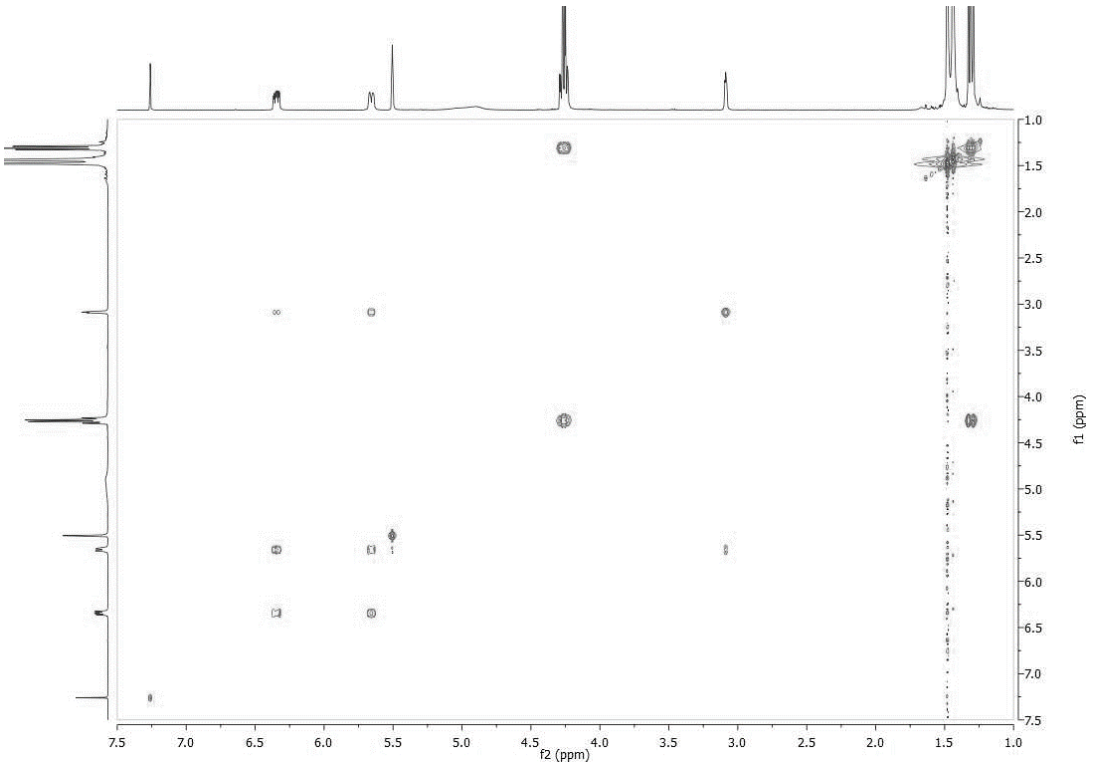
^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)

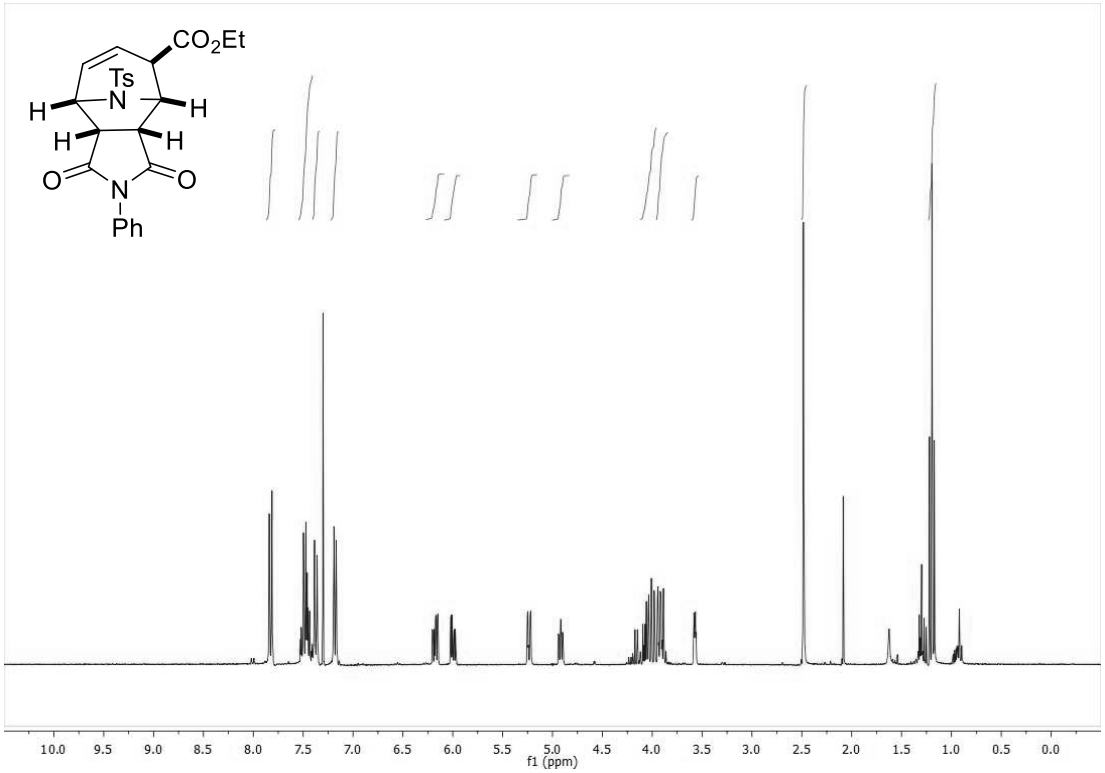


COSY (400 MHz, $CDCl_3$)

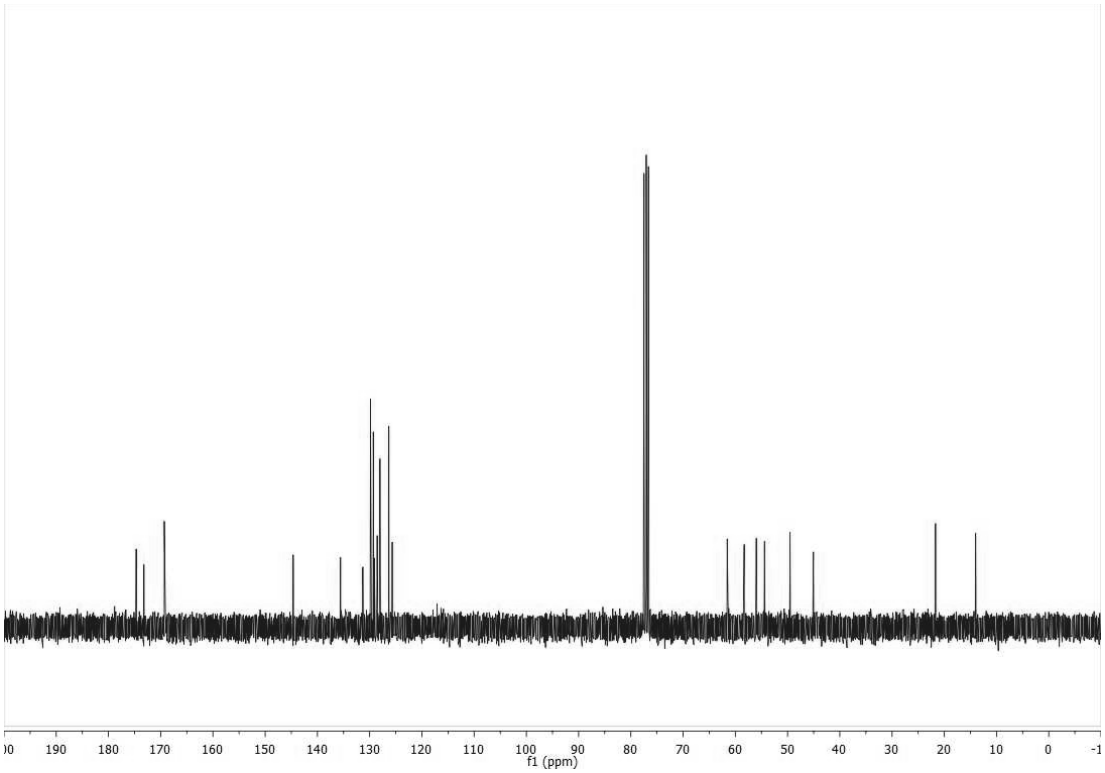


ethyl 1,3-dioxo-2-phenyl-9-tosyl-1,2,3,3a,4,5,8,8a-octahydro-4,8-epiminocyclohepta[c]pyrrole-5-carboxylate (198)

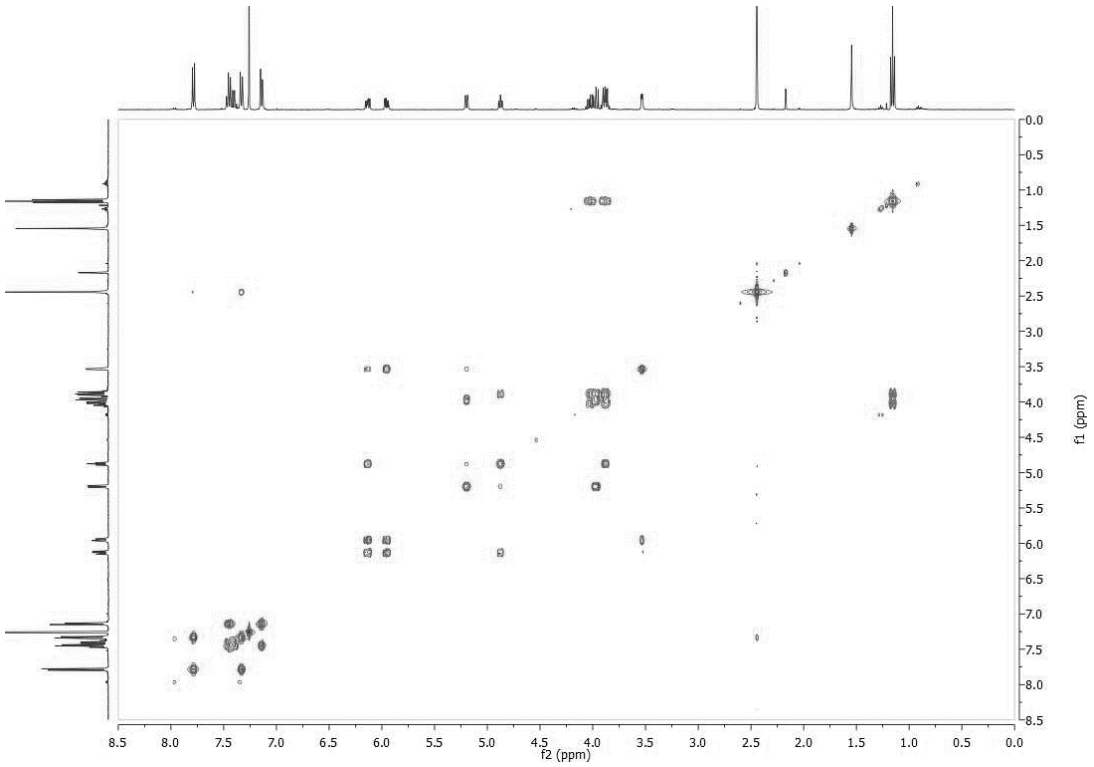
^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)

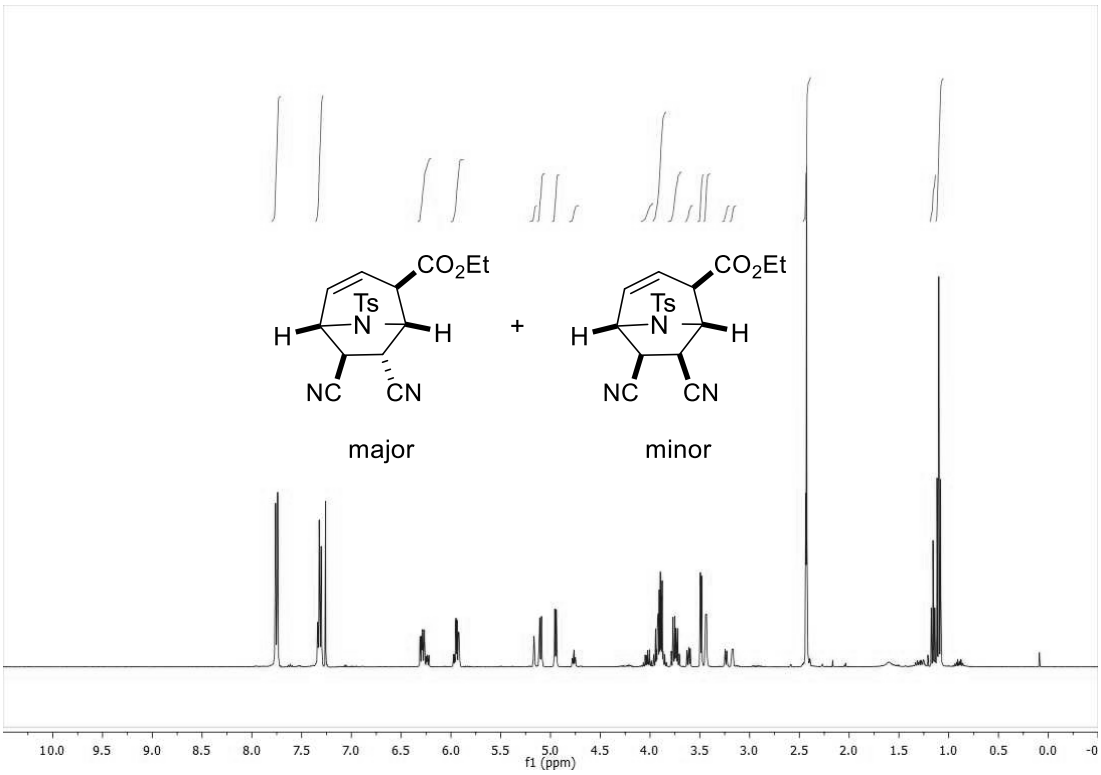


COSY (400 MHz, $CDCl_3$)

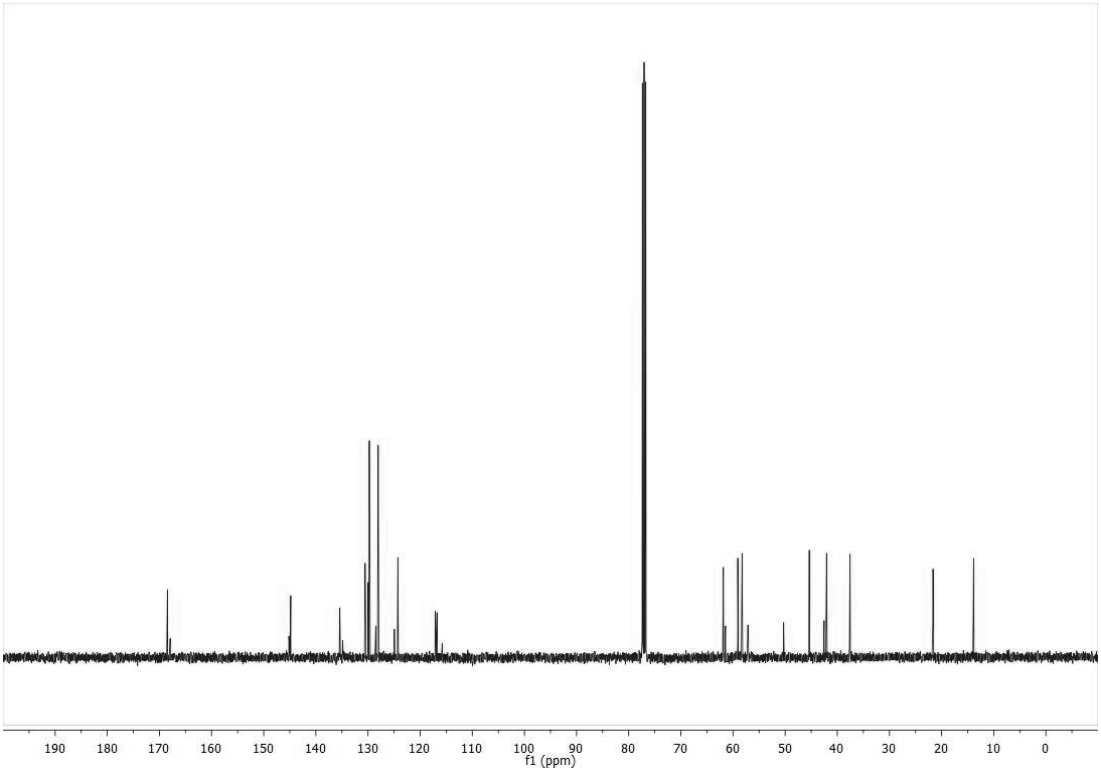


ethyl 6,7-dicyano-8-tosyl-8-azabicyclo[3.2.1]oct-3-ene-2-carboxylate (201) (*dr* 3:1)

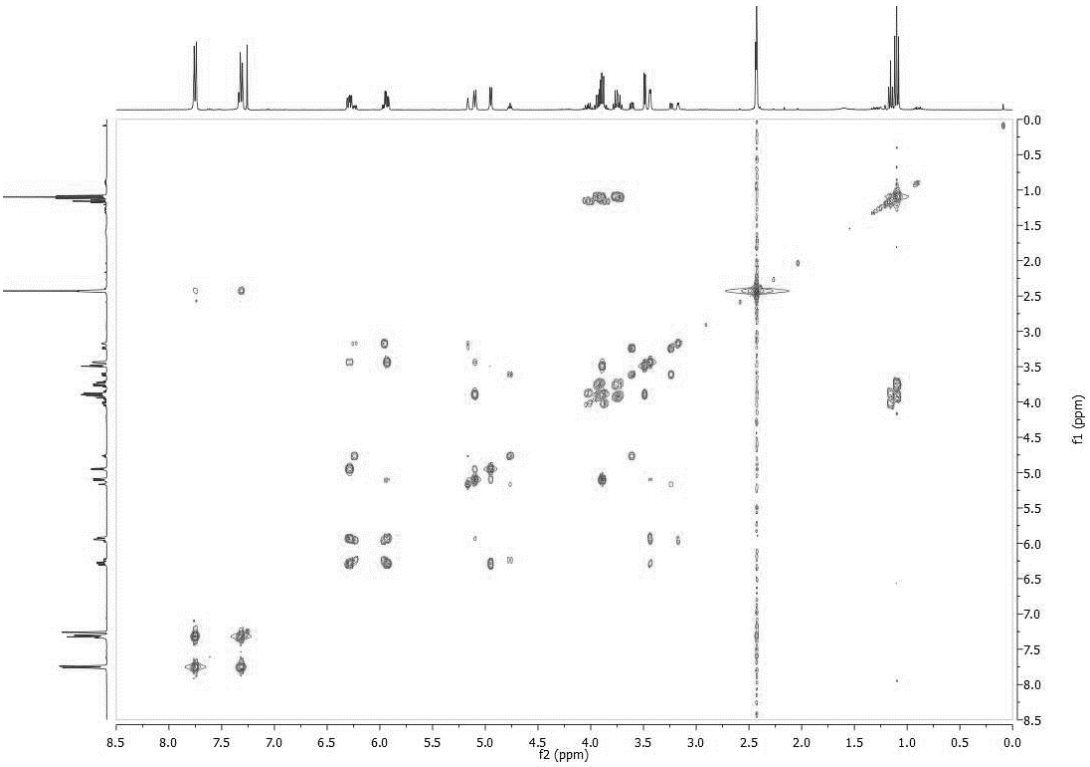
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

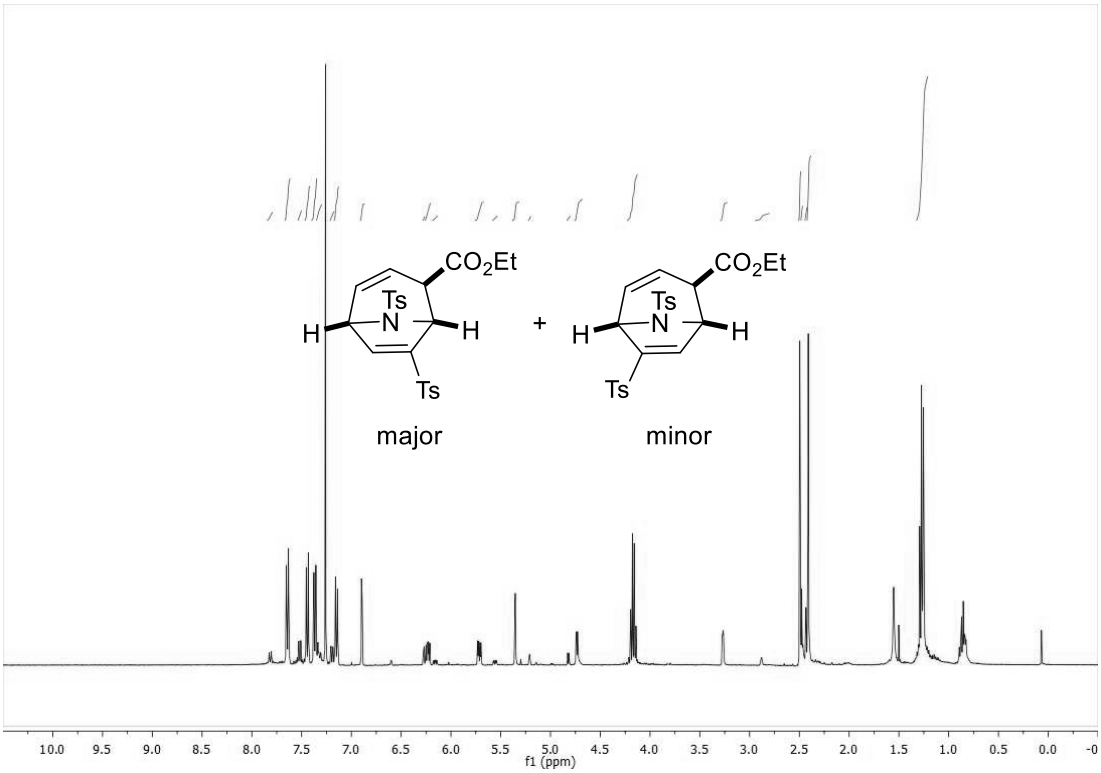


COSY (400 MHz, $CDCl_3$)

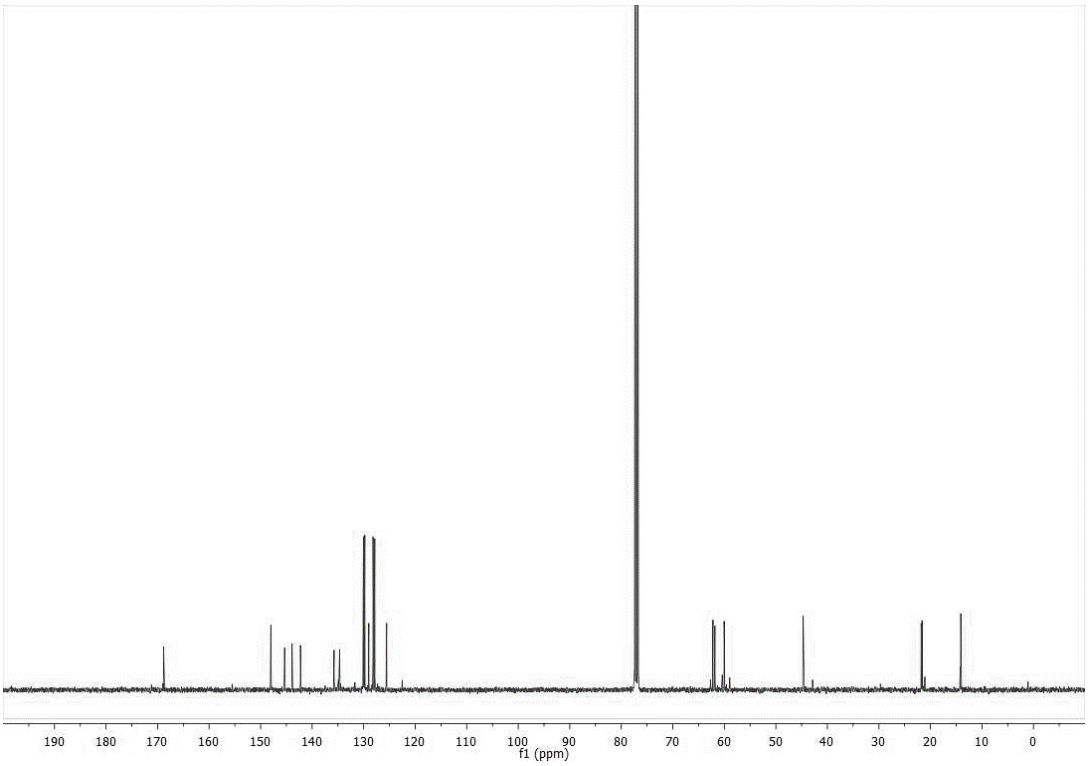


ethyl 7,8-ditosyl-8-azabicyclo[3.2.1]octa-3,6-diene-2-carboxylate (199) (*dr* 4:1)

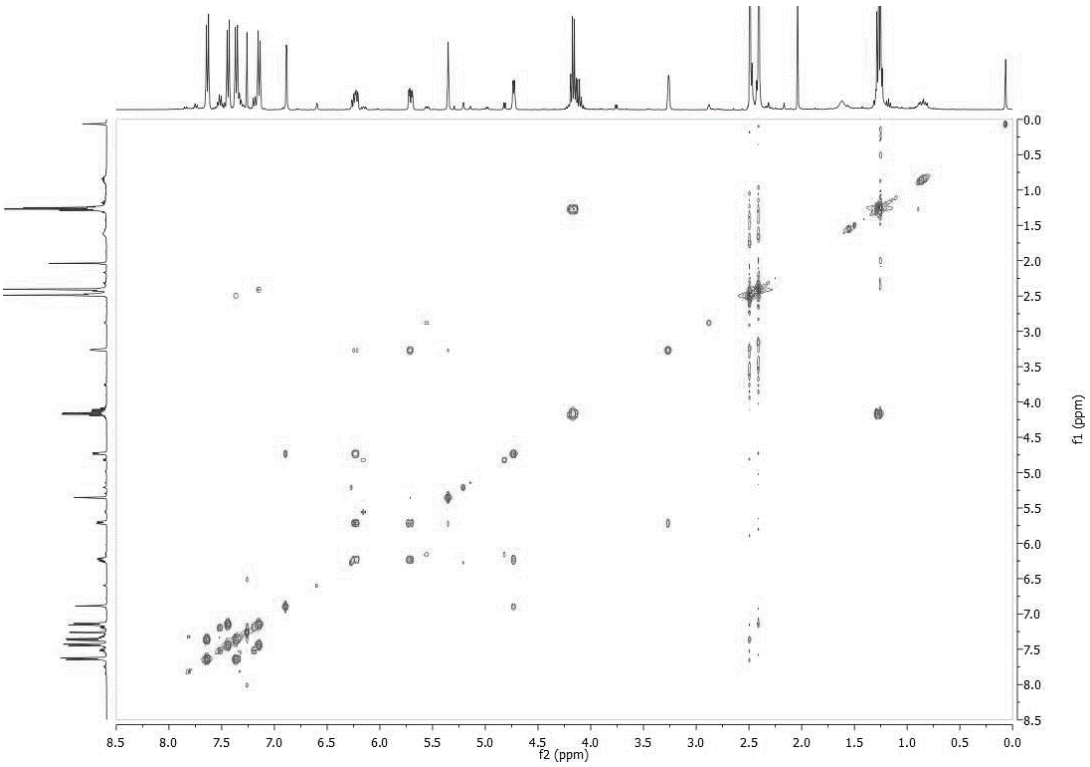
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

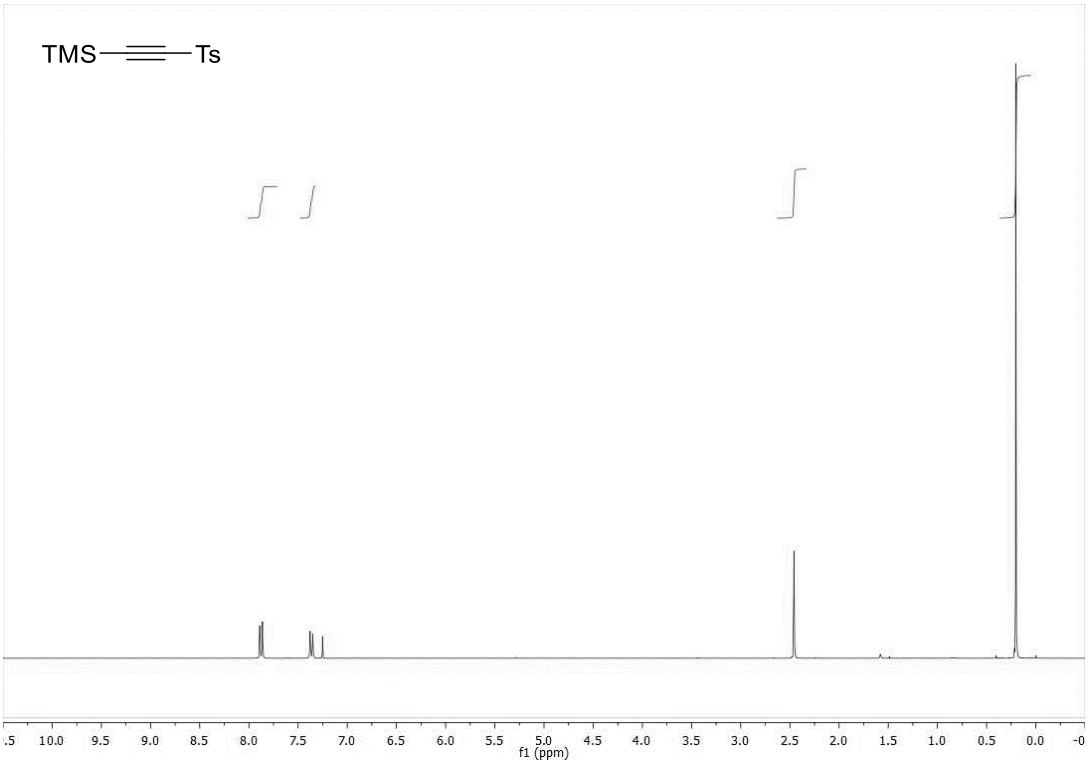


COSY (400 MHz, $CDCl_3$)



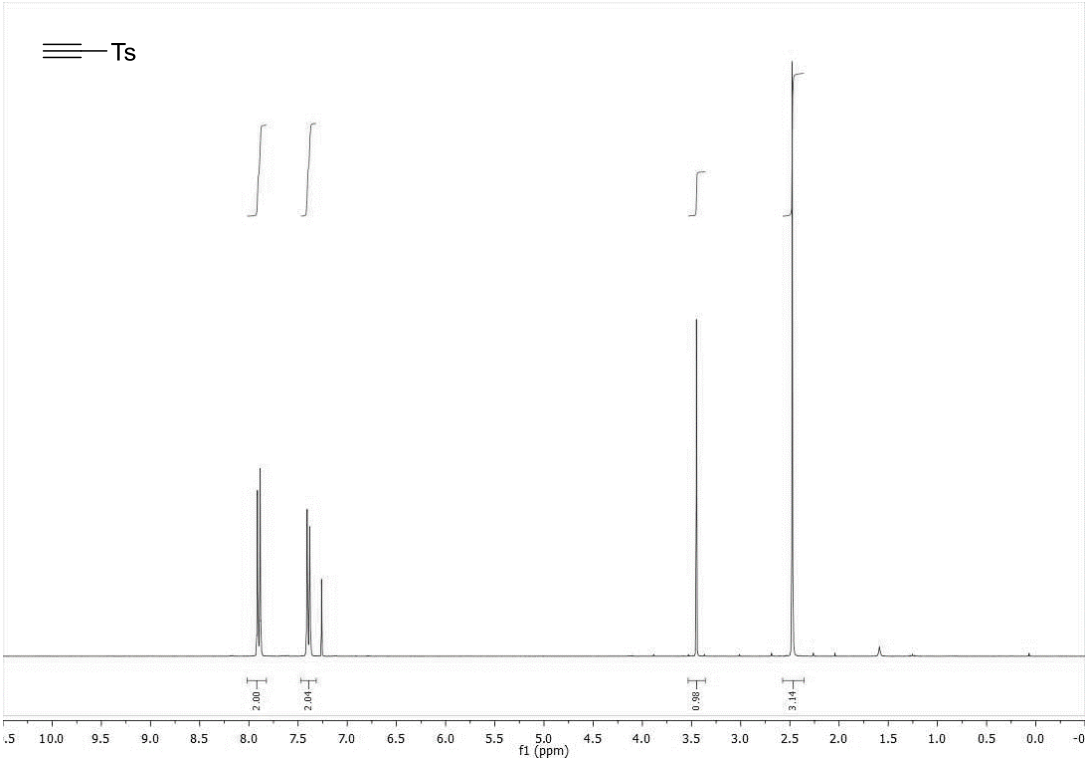
trimethyl(tosylethynyl)silane (202a)

^{1}H NMR (300 MHz, $CDCl_3$)



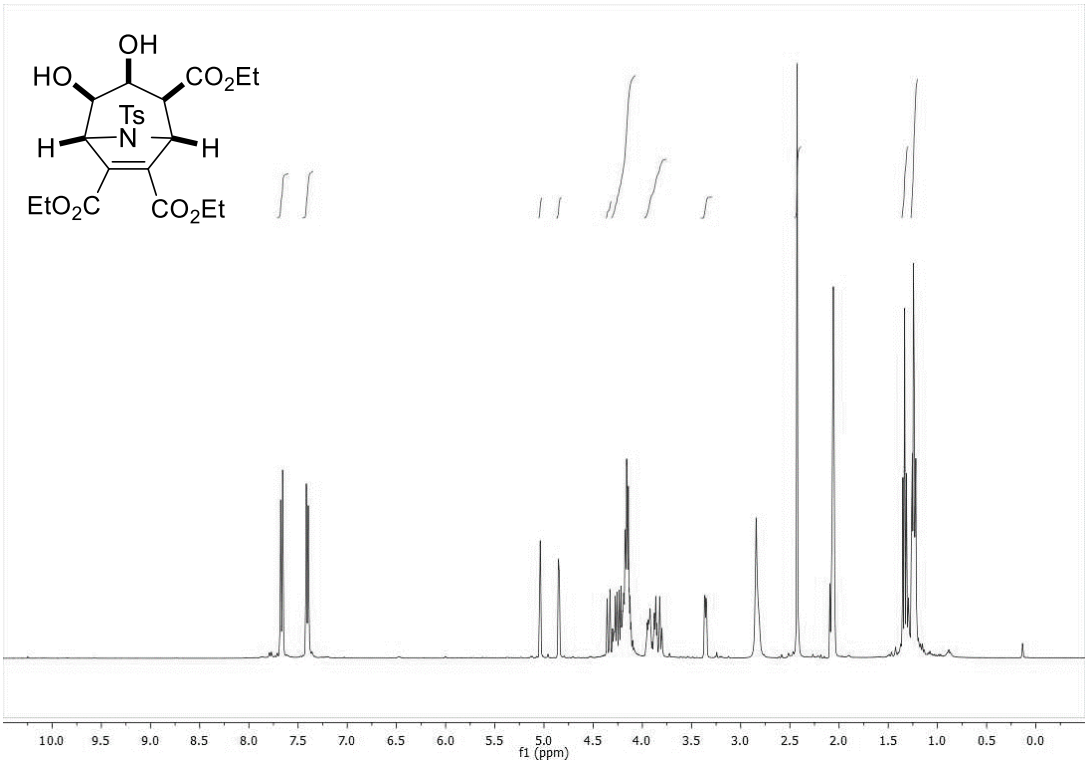
ethynyl *p*-tolyl sulfone (202)

^{1}H NMR (300 MHz, $CDCl_3$)

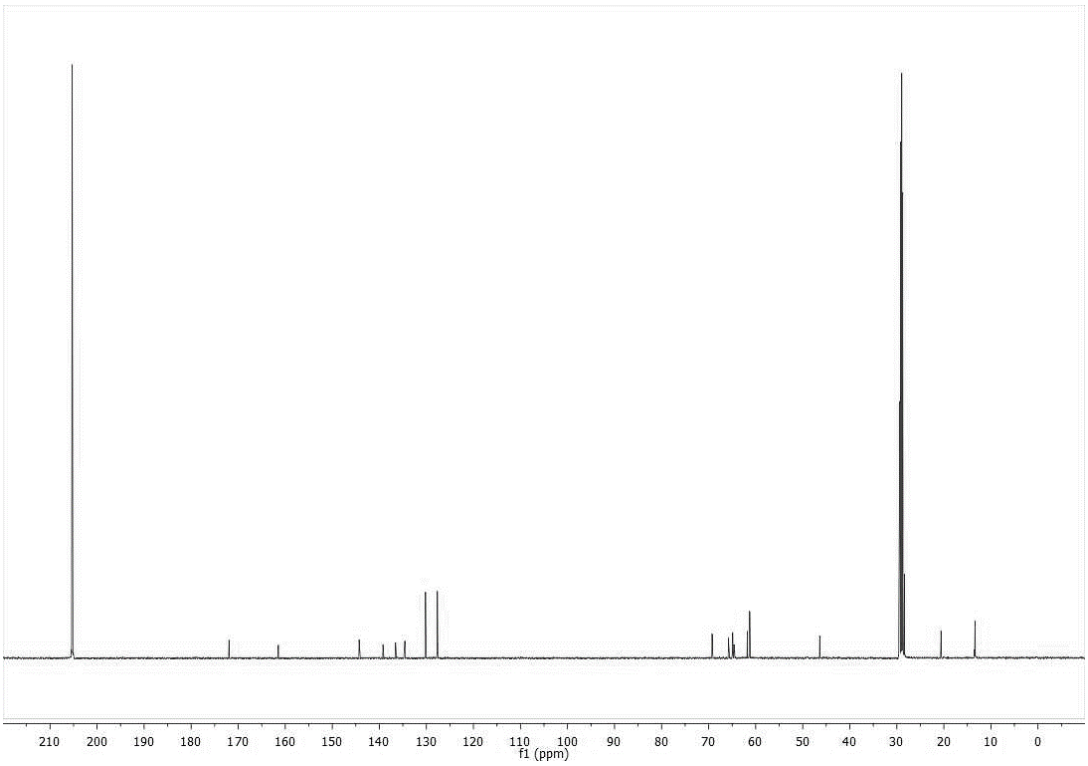


triethyl 3,4-dihydroxy-8-tosyl-8-azabicyclo[3.2.1]oct-6-ene-2,6,7-tricarboxylate (215)

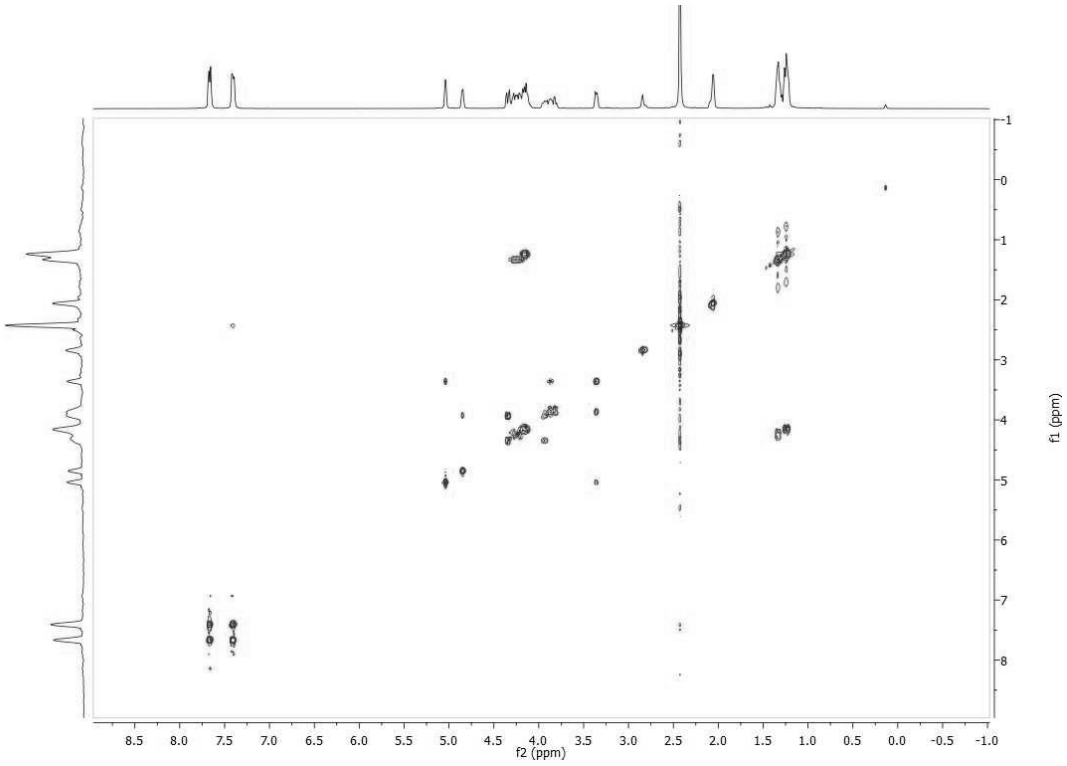
^{1}H NMR (400 MHz, CD_3COCD_3)



^{13}C NMR (101 MHz, CD_3COCD_3)

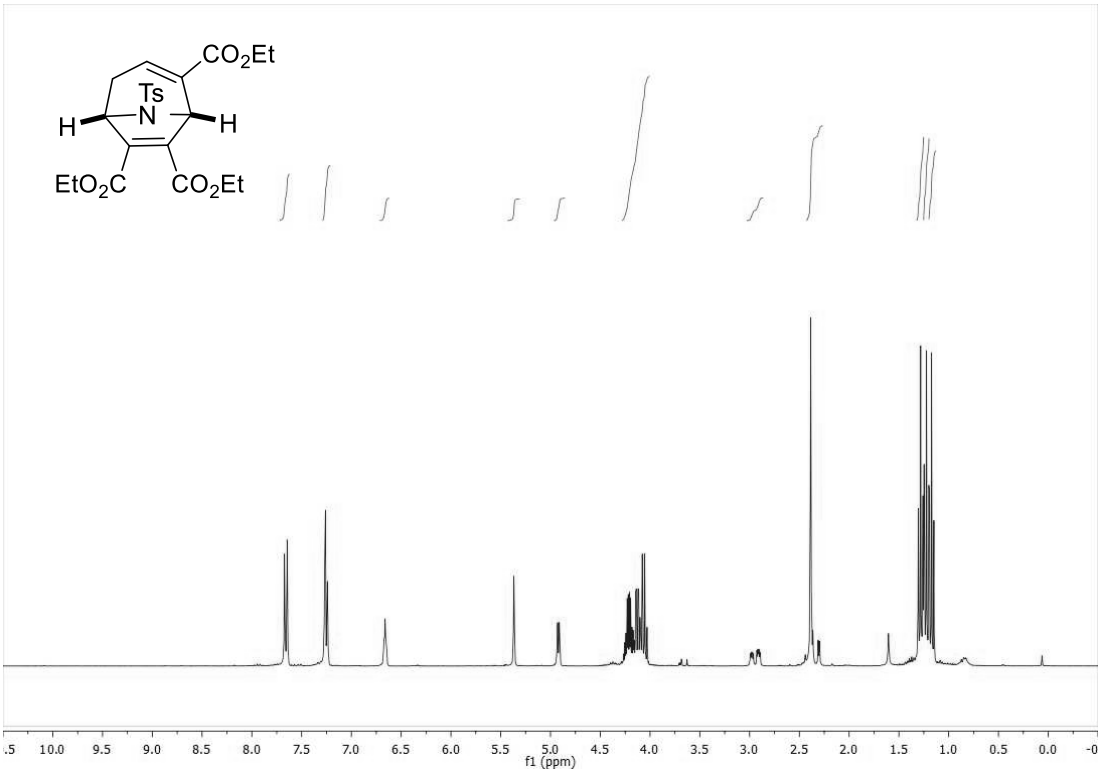


COSY (400 MHz, CD_3COCD_3)

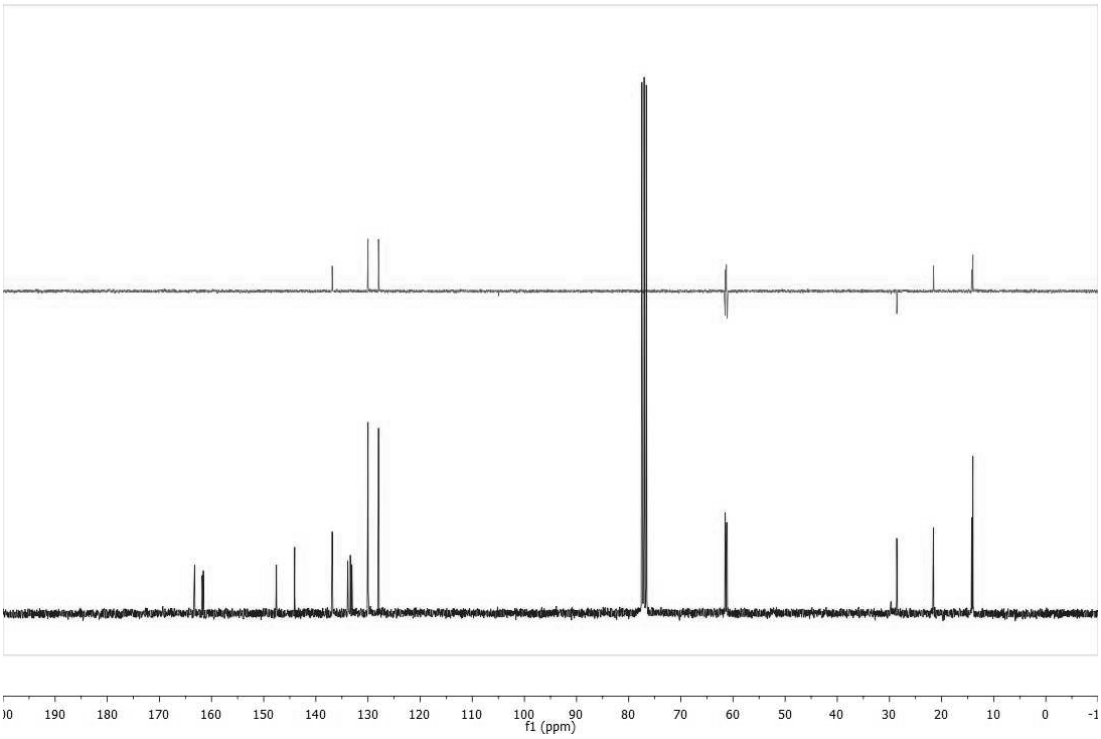


triethyl 8-tosyl-8-azabicyclo[3.2.1]octa-2,6-diene-2,6,7-tricarboxylate (219)

^{1}H NMR (300 MHz, $CDCl_3$)

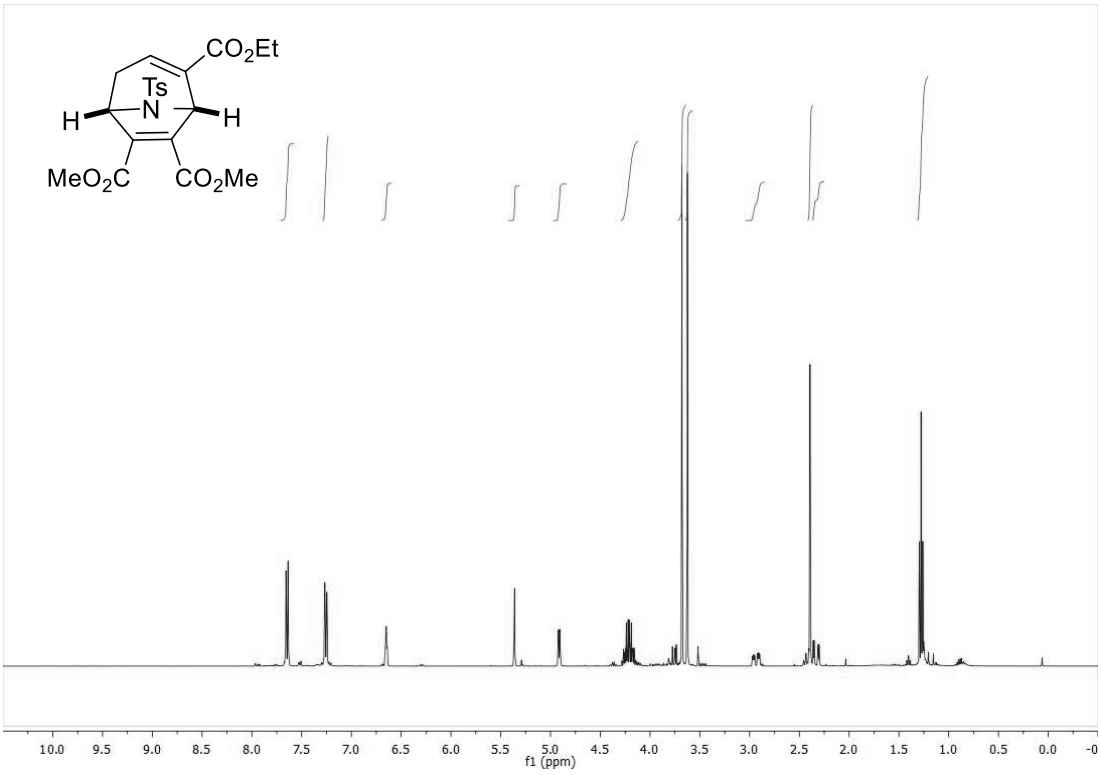


^{13}C NMR (75 MHz, $CDCl_3$)

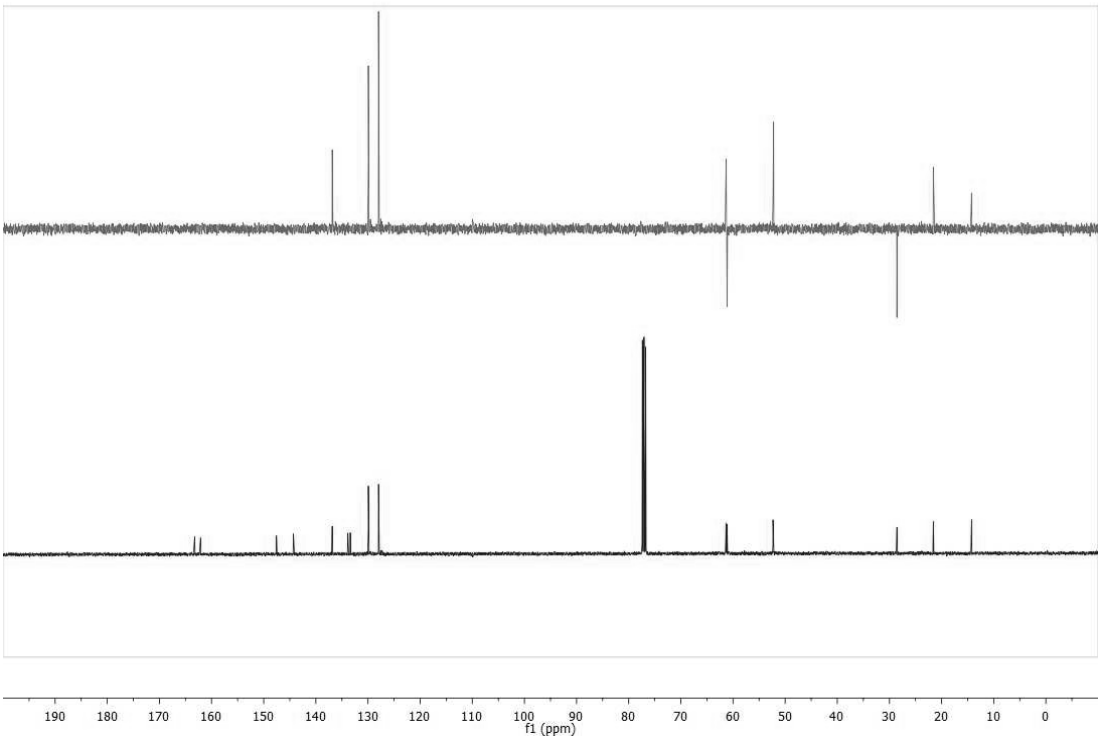


2-ethyl 6,7-dimethyl 8-tosyl-8-azabicyclo[3.2.1]octa-2,6-diene-2,6,7-tricarboxylate (208)

^{1}H NMR (400 MHz, $CDCl_3$)

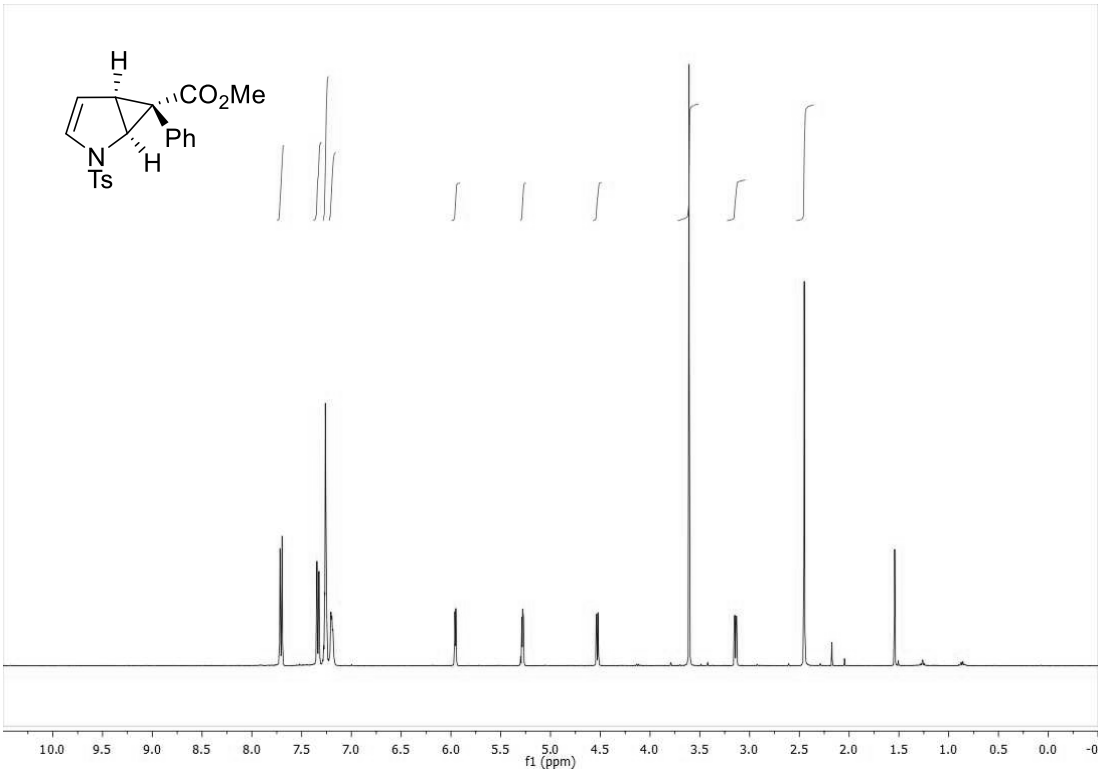


^{13}C NMR (101 MHz, $CDCl_3$)

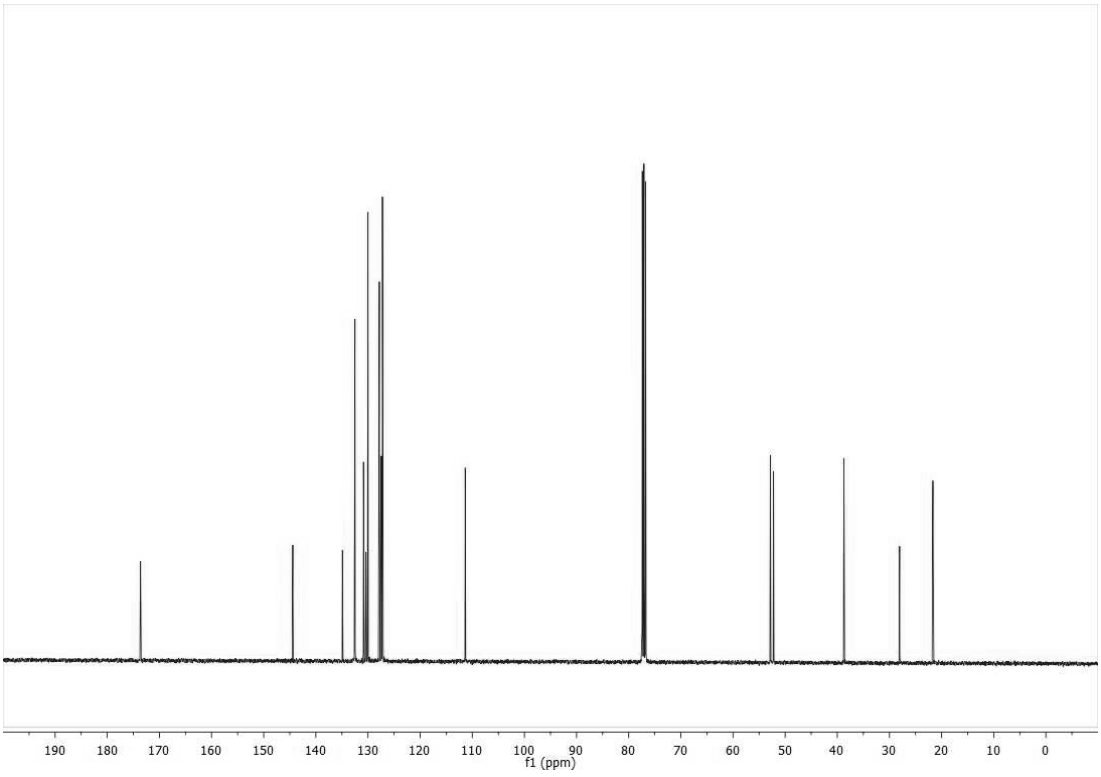


methyl (1*S*,5*S*,6*R*)-6-phenyl-2-tosyl-2-azabicyclo[3.1.0]hex-3-ene-6-carboxylate (249)

^{1}H NMR (400 MHz, $CDCl_3$)

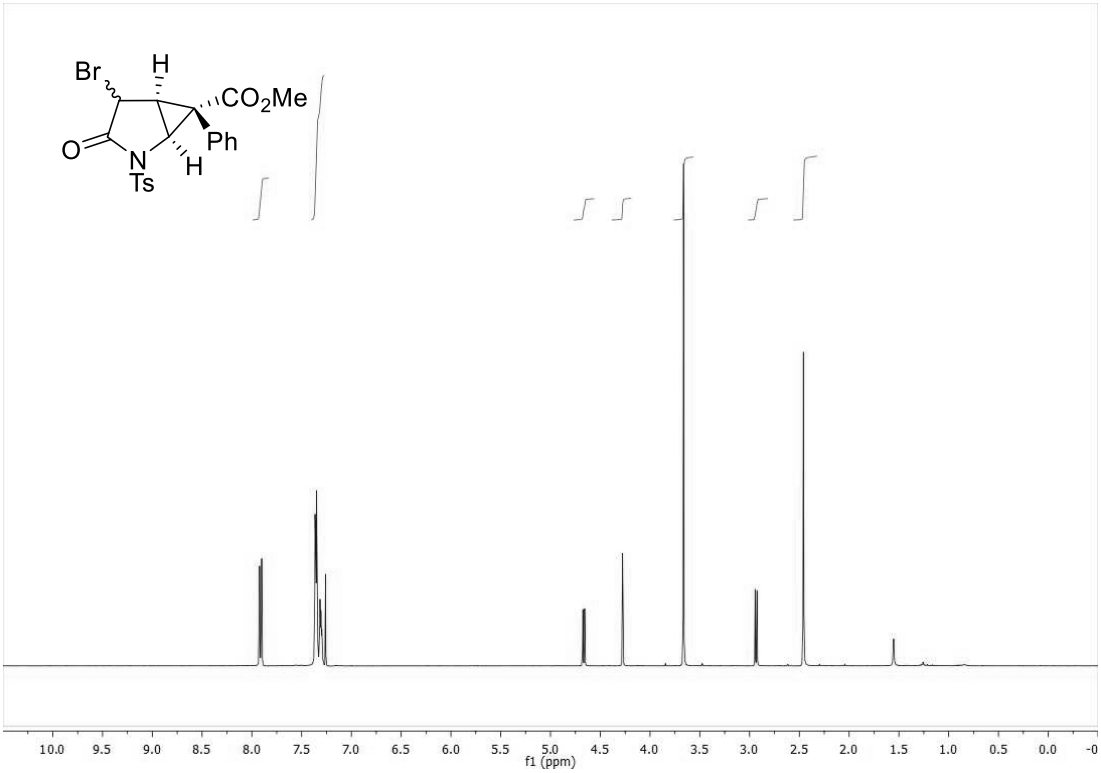


^{13}C NMR (101 MHz, $CDCl_3$)

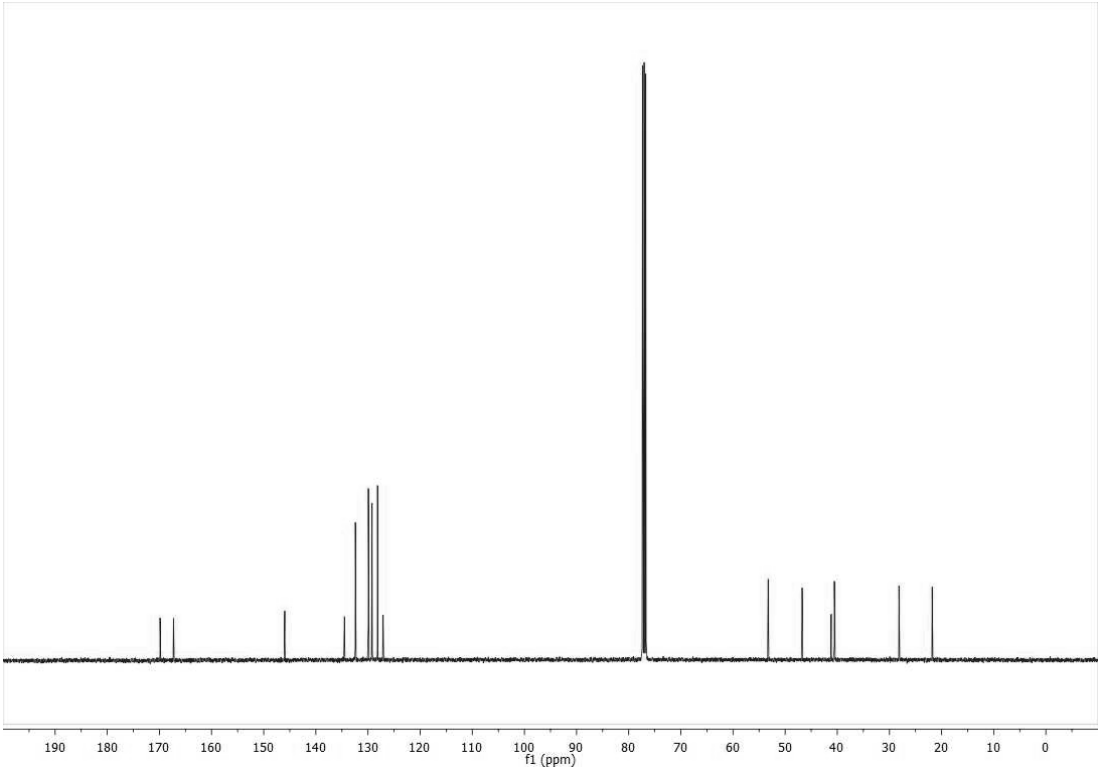


methyl (1*S*,5*S*,6*R*)-4-bromo-3-oxo-6-phenyl-2-tosyl-2-azabicyclo[3.1.0]hexane-6-carboxylate (257)

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

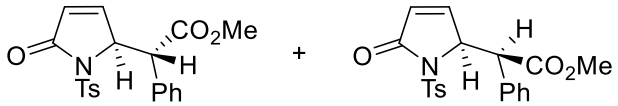


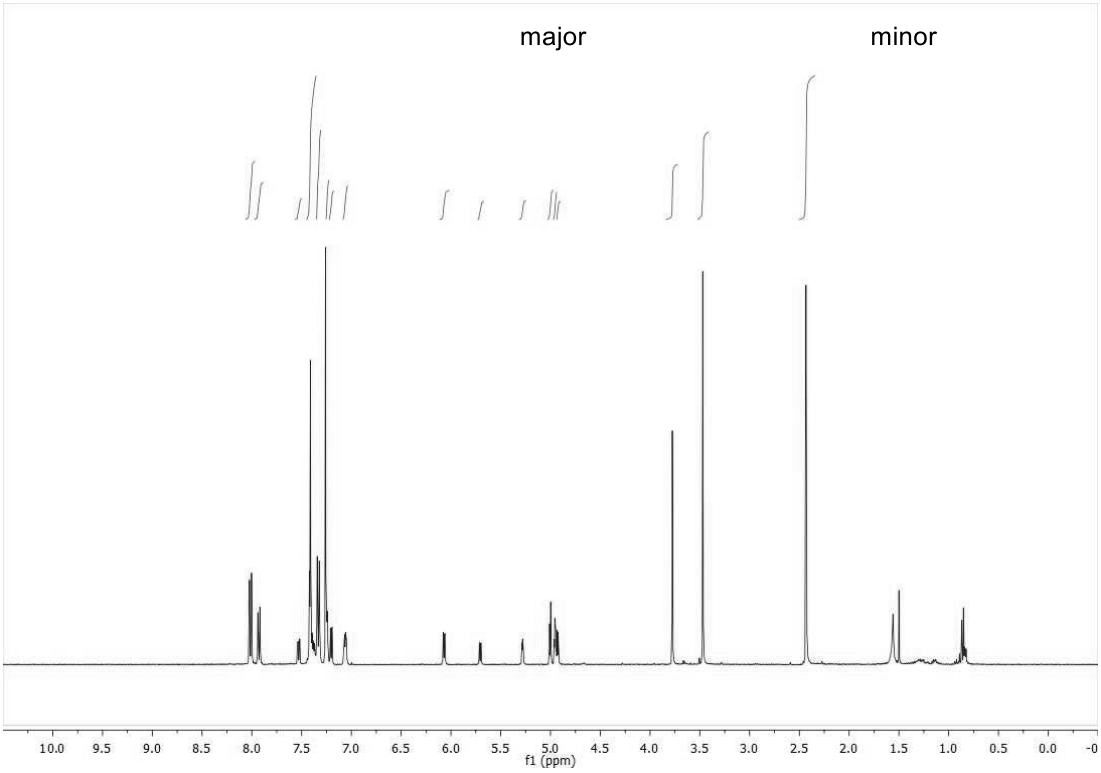
methyl (*R*)-2-((*S*)-5-oxo-1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)-2-phenylacetate (258)

methyl (*S*)-2-((*S*)-5-oxo-1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)-2-phenylacetate (259)

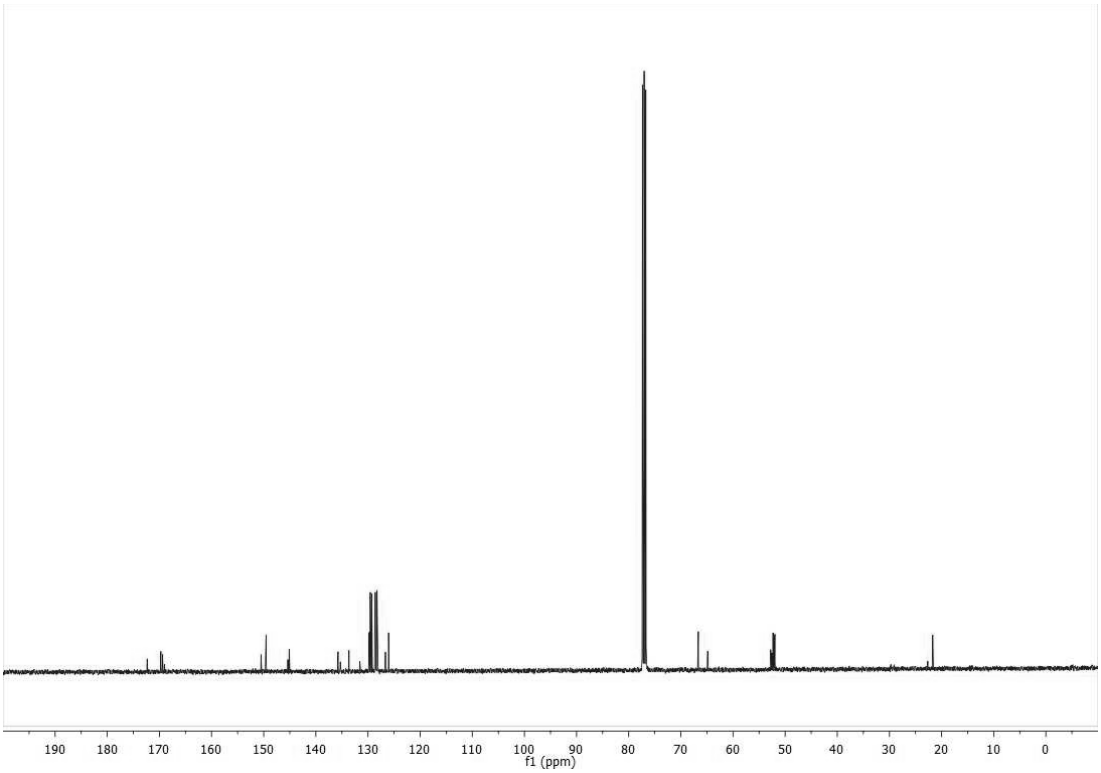
(*dr* 2.2 : 1)

^{1}H NMR (400 MHz, $CDCl_3$)

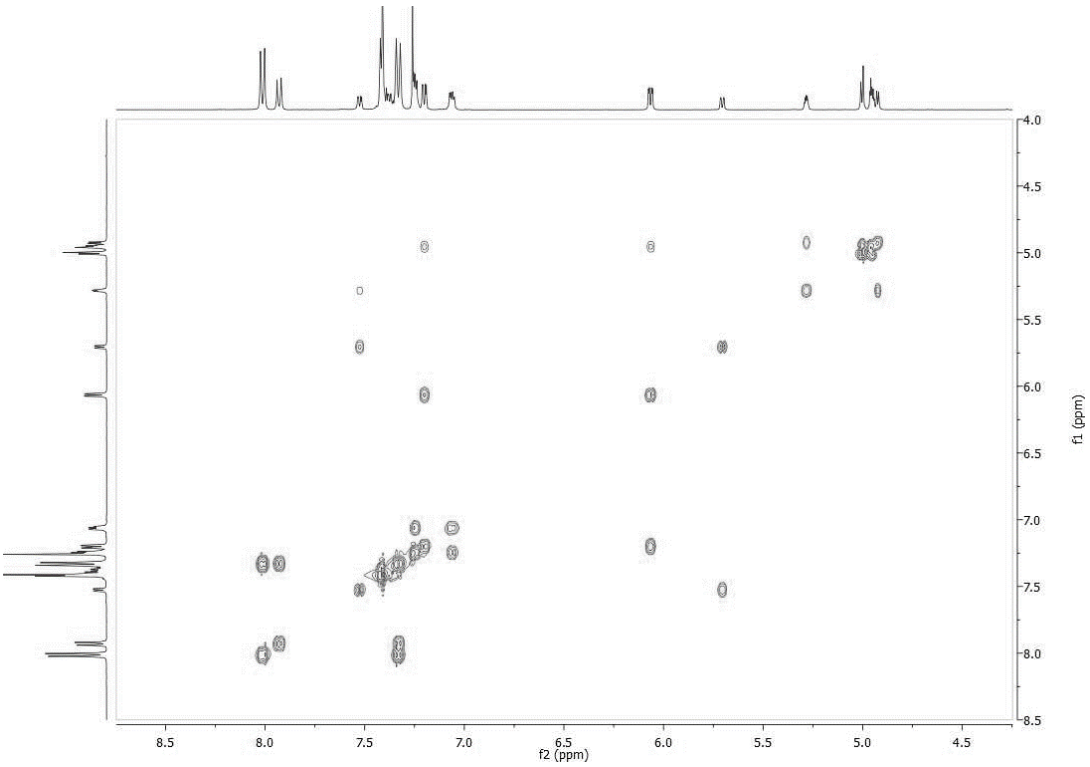




^{13}C NMR (101 MHz, $CDCl_3$)

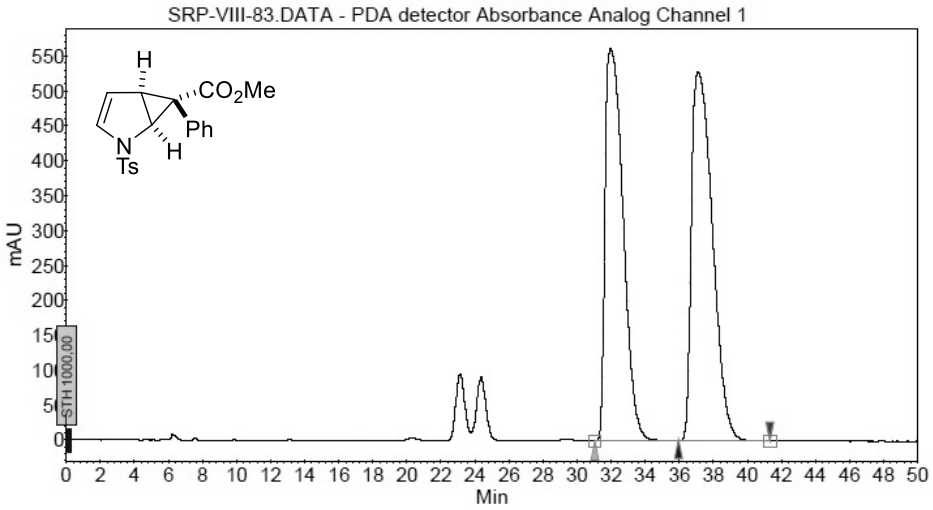


COSY (400 MHz, $CDCl_3$)



2. HPLC Chromatograms

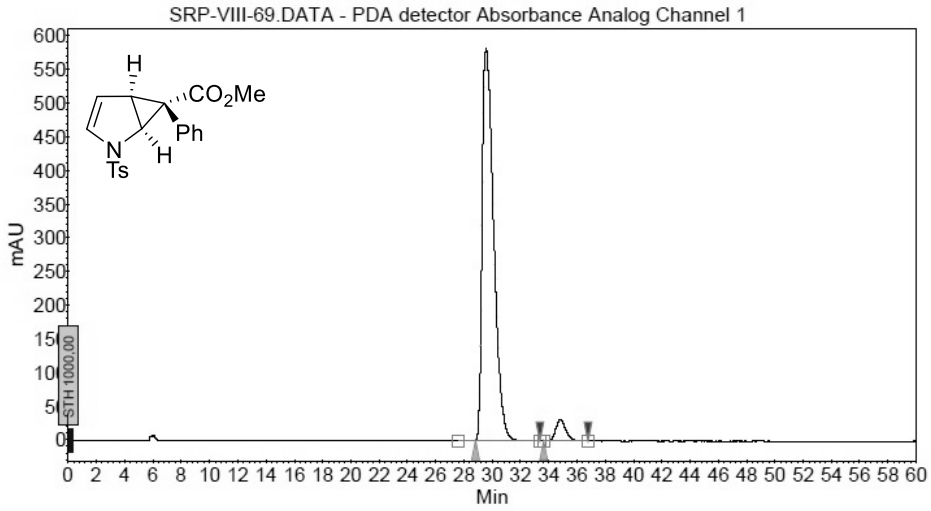
methyl 6-phenyl-2-tosyl-2-azabicyclo[3.1.0]hex-3-ene-6-carboxylate (*rac*-249)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	31,97	47,82	562,8	694,4	47,818
2	UNKNOWN	37,10	52,18	529,0	757,8	52,182
Total			100,00	1091,8	1452,2	100,000

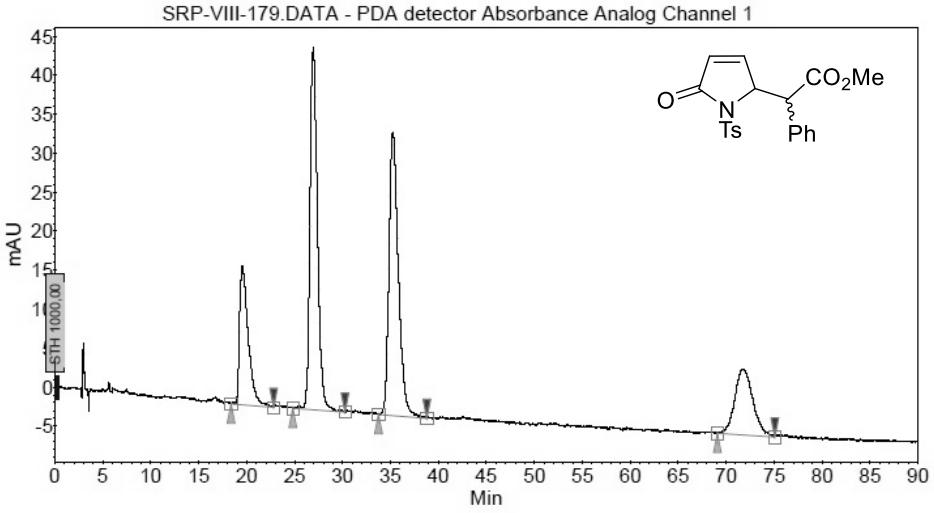
methyl (1*S*,5*S*,6*R*)-6-phenyl-2-tosyl-2-azabicyclo[3.1.0]hex-3-ene-6-carboxylate (249)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
2	UNKNOWN	29,56	95,32	582,8	549,0	95,318
1	UNKNOWN	34,82	4,68	31,6	27,0	4,682
Total			100,00	614,4	576,0	100,000

methyl-2-(5-oxo-1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)-2-phenylacetate[24b] **(*dr* 2.2 : 1)**

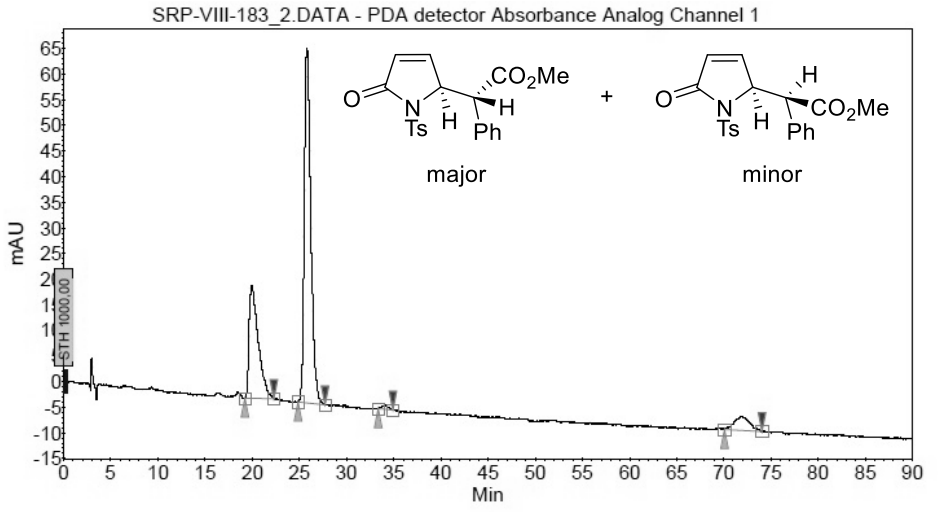


Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	19,55	15,48	17,9	18,7	15,480
2	UNKNOWN	26,94	34,75	46,5	41,9	34,747
3	UNKNOWN	35,24	34,46	36,3	41,5	34,456
4	UNKNOWN	71,74	15,32	8,5	18,5	15,316
Total			100,00	109,2	120,5	100,000

methyl (*R*)-2-((*S*)-5-oxo-1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)-2-phenylacetate (258)

methyl (*S*)-2-((*S*)-5-oxo-1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)-2-phenylacetate (259)

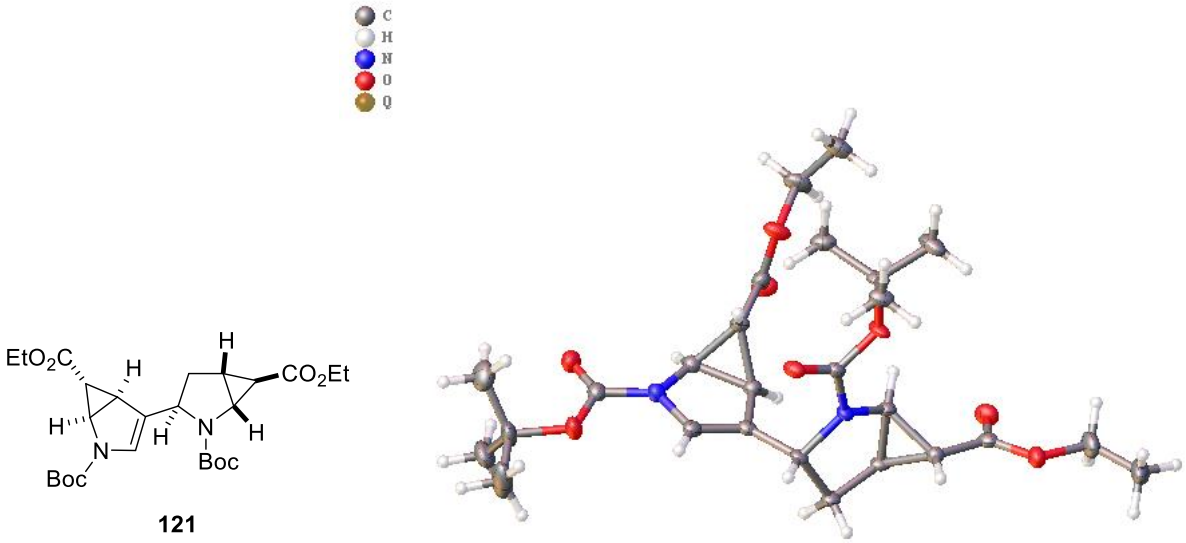


Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	19,95	28,62	22,1	24,7	28,623
2	UNKNOWN	25,80	64,54	69,1	55,6	64,543
4	UNKNOWN	34,13	0,74	0,8	0,6	0,735
3	UNKNOWN	71,87	6,10	2,7	5,3	6,099
Total			100,00	94,7	86,1	100,000

3. X-ray Crystallographic Data

2-(*tert*-butyl) 6-ethyl 4-(2-(*tert*-butoxycarbonyl)-6-(ethoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (121)



121

Table 1. Crystal data and structure refinement for **121**

Identification code	Q150
Empirical formula	$C_{26}H_{38}N_2O_8$
Formula weight	506.58
Temperature/K	123.00(18)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	9.63860(10)
b/Å	10.77080(10)
c/Å	26.1296(3)
a/°	90
b/°	90
γ/°	90
Volume/Å^3	2712.66(5)
Z	4
ρ_{calc}g/cm^3	1.240
μ/mm^{-1}	0.758
F(000)	1088.0

Crystal size/mm^3	0.22×0.13×0.03
Radiation	CuK$_\alpha$ (λ = 1.54184)
2Θ range for data collection/^{o}	3.383 to 74.160
Index ranges	-11≤h≤12, -13≤k≤13, -30≤l≤32
Reflections collected	58614
Independent reflections	5517 [R_{int} = 0.0629, R_{sigma} = 0.0258]
Data/restraints/parameters	5517/0/334
Goodness-of-fit on F^2	1.177
Final R indexes [I>=2σ (I)]	R_1 = 0.0417, wR_2 = 0.1152
Final R indexes [all data]	R_1 = 0.0422, wR_2 = 0.1155
Largest diff. peak/hole /e Å^{-3}	0.312/-0.214
Flack parameter	0.5(2)

Table 2. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **121**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
O4	6696(2)	7349.8(19)	6662.6(8)	23.1(4)
O3	8332.4(19)	6532(2)	7201.7(8)	24.8(4)
O1	7128(2)	5314(2)	9032.5(8)	29.3(5)
O5	7192(2)	1945(2)	6382.2(9)	30.2(5)
O7	3750(2)	3622(2)	5096.4(8)	30.4(5)
O2	7182(2)	3567(2)	8561.2(8)	30.6(5)
O6	8768(2)	3393(2)	6163.9(9)	29.7(5)
O8	2668(2)	5446(2)	5298.7(8)	31.4(5)
N1	6101(2)	6056(2)	7312.1(8)	18.3(4)
N2	4195(2)	4630(2)	5840.1(9)	24.3(5)
C5	5143(3)	4606(3)	7880.2(10)	19.5(5)
C9	4542(3)	5200(2)	6663.7(10)	19.4(5)
C16	7030(3)	6705(3)	7025.5(10)	19.5(5)
C11	6478(3)	4025(3)	6229.1(10)	21.3(5)
C3	6842(3)	4649(3)	8616.5(10)	22.6(6)
C13	7480(3)	3003(3)	6266.8(10)	22.4(5)

C12	5035(3)	3651(3)	6049.1(10)	22.8(6)
C10	5246(3)	3978(3)	6600.4(10)	20.8(5)
C14	3979(3)	5542(3)	6218.7(10)	22.6(5)
C15	6470(3)	5107(2)	7674.4(10)	18.0(5)
C7	3960(3)	5272(3)	7610(1)	21.3(5)
C23	3534(3)	4492(3)	5377.6(11)	25.1(6)
C4	6068(3)	5370(3)	8230.8(10)	20.3(5)
C8	4631(3)	5937(3)	7148.6(10)	18.6(5)
C17	9518(3)	7138(3)	6940.1(11)	24.0(6)
C18	9619(3)	6677(3)	6390.7(12)	29.6(6)
C20	9387(3)	8534(3)	6974.9(13)	28.6(6)
C19	10755(3)	6685(4)	7250.2(14)	37.1(8)
C21	9873(3)	2468(3)	6168.6(15)	35.0(7)
C24	1842(3)	5499(3)	4817.3(12)	34.2(7)
C2	7875(4)	4653(4)	9434.1(12)	41.1(8)
C25	932(4)	4356(4)	4774.8(15)	46.2(9)
C22	11186(3)	3123(4)	6299.2(17)	43.1(9)
C27	2817(4)	5630(4)	4366.3(13)	43.2(9)
C1	7987(4)	5483(5)	9887.4(13)	50.2(10)
C26	979(6)	6657(5)	4892.8(17)	65.0(14)
O4	6696(2)	7349.8(19)	6662.6(8)	23.1(4)
O3	8332.4(19)	6532(2)	7201.7(8)	24.8(4)
O1	7128(2)	5314(2)	9032.5(8)	29.3(5)
O5	7192(2)	1945(2)	6382.2(9)	30.2(5)
O7	3750(2)	3622(2)	5096.4(8)	30.4(5)
O2	7182(2)	3567(2)	8561.2(8)	30.6(5)
O6	8768(2)	3393(2)	6163.9(9)	29.7(5)
O8	2668(2)	5446(2)	5298.7(8)	31.4(5)
N1	6101(2)	6056(2)	7312.1(8)	18.3(4)
N2	4195(2)	4630(2)	5840.1(9)	24.3(5)
C5	5143(3)	4606(3)	7880.2(10)	19.5(5)
C9	4542(3)	5200(2)	6663.7(10)	19.4(5)
C16	7030(3)	6705(3)	7025.5(10)	19.5(5)

C11	6478(3)	4025(3)	6229.1(10)	21.3(5)
C3	6842(3)	4649(3)	8616.5(10)	22.6(6)
C13	7480(3)	3003(3)	6266.8(10)	22.4(5)
C12	5035(3)	3651(3)	6049.1(10)	22.8(6)
C10	5246(3)	3978(3)	6600.4(10)	20.8(5)
C14	3979(3)	5542(3)	6218.7(10)	22.6(5)
C15	6470(3)	5107(2)	7674.4(10)	18.0(5)
C7	3960(3)	5272(3)	7610(1)	21.3(5)
C23	3534(3)	4492(3)	5377.6(11)	25.1(6)
C4	6068(3)	5370(3)	8230.8(10)	20.3(5)
C8	4631(3)	5937(3)	7148.6(10)	18.6(5)
C17	9518(3)	7138(3)	6940.1(11)	24.0(6)
C18	9619(3)	6677(3)	6390.7(12)	29.6(6)
C20	9387(3)	8534(3)	6974.9(13)	28.6(6)
C19	10755(3)	6685(4)	7250.2(14)	37.1(8)
C21	9873(3)	2468(3)	6168.6(15)	35.0(7)
C24	1842(3)	5499(3)	4817.3(12)	34.2(7)
C2	7875(4)	4653(4)	9434.1(12)	41.1(8)
C25	932(4)	4356(4)	4774.8(15)	46.2(9)
C22	11186(3)	3123(4)	6299.2(17)	43.1(9)
C27	2817(4)	5630(4)	4366.3(13)	43.2(9)
C1	7987(4)	5483(5)	9887.4(13)	50.2(10)
C26	979(6)	6657(5)	4892.8(17)	65.0(14)

Table 3: Anisotropic Displacement Parameters ($\times 10^4$) for **121**. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2a^{*2} \times U_{11} + ... + 2hka^* \times b^* \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O4	15.9(9)	25.7(10)	27.6(10)	6.6(8)	2.0(8)	0.6(7)
O3	9.5(8)	35.1(11)	29.7(10)	10.5(8)	0.6(7)	-2.7(8)
O1	24.6(10)	41.3(12)	21.9(9)	2.1(9)	-4.2(8)	1.7(9)
O5	29.3(11)	26.3(11)	35.0(11)	2.7(8)	8.2(9)	2.2(9)
O7	27.7(11)	39.0(12)	24.7(10)	-6.9(9)	-4.1(8)	1.2(9)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O2	27.7(11)	29.9(11)	34.1(11)	4.0(9)	-0.3(9)	6.5(9)
O6	15.6(9)	27.4(10)	46.1(12)	-1.7(9)	3.2(9)	3.2(8)
O8	27.6(11)	41.5(12)	25(1)	-5.9(9)	-10.1(8)	7.5(10)
N1	11.1(10)	24.8(11)	19(1)	1.4(9)	-0.9(8)	-3.2(9)
N2	20.0(11)	29.6(12)	23.2(11)	-2.4(9)	-2.7(9)	1.6(10)
C5	13.7(12)	22.3(12)	22.6(12)	-0.9(10)	5(1)	-3.7(10)
C9	12.3(11)	21.6(12)	24.3(13)	0(1)	1.3(9)	-1.7(10)
C16	12.9(11)	24.1(13)	21.4(12)	-2.2(10)	0.6(10)	0(1)
C11	15.9(12)	26.3(13)	21.8(12)	-0.1(10)	3(1)	1.3(10)
C3	15.4(12)	30.4(15)	21.8(12)	3.6(11)	4.7(10)	0.5(11)
C13	20.3(13)	28.4(14)	18.6(12)	-2.6(10)	2.2(10)	0.7(11)
C12	18.5(12)	27.8(13)	22.1(13)	-1.0(11)	0.8(10)	-0.7(11)
C10	17.1(12)	24.9(13)	20.3(12)	-0.6(10)	2.3(10)	-0.4(10)
C14	15.6(12)	28.7(13)	23.4(13)	-3.6(11)	1.7(10)	-1.4(11)
C15	13.1(11)	21.5(12)	19.3(11)	-0.6(10)	3.4(9)	-1.6(9)
C7	14.1(12)	28.7(13)	21.1(12)	-1.1(10)	3(1)	-3.4(10)
C23	19.0(13)	33.8(15)	22.3(13)	-0.1(12)	-0.1(10)	-2.5(12)
C4	17.7(12)	23.6(12)	19.4(12)	-0.5(10)	0.5(10)	0.1(10)
C8	9.9(11)	23.4(12)	22.5(12)	-1.1(10)	0.5(9)	-2.5(10)
C17	12.4(12)	28.7(14)	30.8(14)	6.5(11)	5.6(10)	-3.7(11)
C18	22.5(13)	30.0(14)	36.4(16)	1.0(12)	10.0(12)	0.9(12)
C20	19.0(13)	27.4(14)	39.6(16)	-3.0(12)	4.4(12)	-2.0(11)
C19	15.5(13)	48.4(19)	47.5(19)	18.2(16)	-0.8(13)	-1.1(13)
C21	20.5(14)	33.5(16)	51.0(19)	-2.8(15)	4.7(14)	9.1(13)
C24	29.2(16)	48.4(19)	25.2(14)	-7.0(13)	-12.9(12)	5.7(15)
C2	32.5(18)	63(2)	27.6(15)	9.7(15)	-9.6(13)	3.4(17)
C25	27.9(17)	73(3)	38.0(18)	0.7(17)	-12.5(14)	-8.5(17)
C22	20.7(15)	42.4(19)	66(2)	-1.1(17)	-3.9(15)	5.4(14)
C27	50(2)	49(2)	30.9(16)	9.1(15)	-6.3(15)	-4.5(18)
C1	29.8(18)	94(3)	26.7(16)	-1.2(19)	-7.9(13)	-6(2)
C26	73(3)	74(3)	48(2)	-18(2)	-32(2)	39(3)

Table 4: Bond Lengths in Å for **121**

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O4	C16	1.218(3)	C5	C4	1.520(4)
O3	C16	1.351(3)	C9	C10	1.490(4)
O3	C17	1.483(3)	C9	C14	1.335(4)
O1	C3	1.330(4)	C9	C8	1.498(4)
O1	C2	1.458(4)	C11	C13	1.468(4)
O5	C13	1.211(4)	C11	C12	1.523(4)
O7	C23	1.209(4)	C11	C10	1.535(4)
O2	C3	1.219(4)	C3	C4	1.475(4)
O6	C13	1.338(3)	C12	C10	1.497(4)
O6	C21	1.458(3)	C15	C4	1.531(3)
O8	C23	1.340(4)	C7	C8	1.545(4)
O8	C24	1.489(3)	C17	C18	1.522(4)
N1	C16	1.361(3)	C17	C20	1.512(4)
N1	C15	1.438(3)	C17	C19	1.522(4)
N1	C8	1.485(3)	C21	C22	1.488(5)
N2	C12	1.437(4)	C24	C25	1.517(5)
N2	C14	1.410(4)	C24	C27	1.514(5)
N2	C23	1.374(4)	C24	C26	1.512(5)
C5	C15	1.489(3)	C2	C1	1.488(6)
C5	C7	1.521(4)			

Table 5: Bond Angles in ° for **121**

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C16	O3	C17	119.9(2)	C9	C10	C11	113.1(2)
C3	O1	C2	115.3(3)	C9	C10	C12	104.7(2)
C13	O6	C21	117.4(2)	C12	C10	C11	60.29(17)
C23	O8	C24	119.5(2)	C9	C14	N2	111.0(3)
C16	N1	C15	124.4(2)	N1	C15	C5	106.4(2)
C16	N1	C8	120.9(2)	N1	C15	C4	115.5(2)

C15	N1	C8	111.4(2)	C5	C15	C4	60.43(17)
C14	N2	C12	109.1(2)	C5	C7	C8	105.5(2)
C23	N2	C12	121.1(3)	O7	C23	O8	127.4(3)
C23	N2	C14	128.6(3)	O7	C23	N2	122.6(3)
C15	C5	C7	107.8(2)	O8	C23	N2	110.0(3)
C15	C5	C4	61.16(17)	C5	C4	C15	58.40(16)
C4	C5	C7	117.7(2)	C3	C4	C5	115.1(2)
C10	C9	C8	122.4(2)	C3	C4	C15	115.1(2)
C14	C9	C10	109.4(2)	N1	C8	C9	110.1(2)
C14	C9	C8	127.9(3)	N1	C8	C7	102.4(2)
O4	C16	O3	126.1(2)	C9	C8	C7	113.0(2)
O4	C16	N1	123.2(2)	O3	C17	C18	109.9(2)
O3	C16	N1	110.7(2)	O3	C17	C20	110.2(2)
C13	C11	C12	115.0(2)	O3	C17	C19	102.5(2)
C13	C11	C10	116.2(2)	C18	C17	C19	110.3(3)
C12	C11	C10	58.62(17)	C20	C17	C18	112.7(3)
O1	C3	C4	112.3(2)	C20	C17	C19	110.6(3)
O2	C3	O1	123.8(3)	O6	C21	C22	107.4(3)
O2	C3	C4	123.9(3)	O8	C24	C25	109.8(3)
O5	C13	O6	124.0(3)	O8	C24	C27	109.3(3)
O5	C13	C11	124.9(3)	O8	C24	C26	102.5(3)
O6	C13	C11	111.2(2)	C27	C24	C25	112.2(3)
N2	C12	C11	115.9(2)	C26	C24	C25	111.1(3)
N2	C12	C10	105.6(2)	C26	C24	C27	111.5(4)
C10	C12	C11	61.08(17)	O1	C2	C1	108.4(3)

Table 6: Hydrogen Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **121**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	**x**	**y**	**z**	U_{eq}
H5	5064.76	3710.88	7940.5	23
H11	6826.38	4843.37	6127.04	26

Atom	x	y	z	U_{eq}
H12	4850.83	2787.3	5952.29	27
H10	5192.17	3341.94	6867.85	25
H14	3507.59	6284.19	6165.43	27
H15	7239.38	4540.78	7599.08	22
H7A	3523.25	5867.05	7837.32	26
H7B	3264.46	4682.28	7495.75	26
H4	5769.27	6211.89	8320.43	24
H8	4215.74	6759.62	7100.91	22
H18A	9621.61	5785.68	6388.02	44
H18B	10460.41	6979.04	6238.89	44
H18C	8837.6	6975.44	6198.83	44
H20A	8592.48	8801.46	6782.52	43
H20B	10207.11	8914.61	6837.66	43
H20C	9277.61	8773.15	7326.52	43
H19A	10653.94	6944.39	7599.69	56
H19B	11592.73	7029.12	7111.01	56
H19C	10799.23	5795.04	7235.51	56
H21A	9950.67	2076.72	5835.43	42
H21B	9675.51	1831.16	6420.74	42
H2A	8792.73	4424.18	9314.58	49
H2B	7380.3	3900.28	9525.38	49
H25A	1504.73	3632.17	4739.1	69
H25B	339.72	4431.79	4480.97	69
H25C	373.46	4279.88	5077.52	69
H22A	11349.8	3772.79	6055.24	65
H22B	11942.73	2543.93	6290.88	65
H22C	11111.34	3473.88	6635.79	65
H27A	3492.89	6261	4438.89	65
H27B	2297.22	5859.05	4067.45	65
H27C	3279.18	4854.27	4306.62	65
H1A	8507.42	6211.15	9797.12	75
H1B	8451.62	5052.58	10159.69	75

Atom	x	y	z	U_{eq}
H1C	7075.54	5721.78	9997.83	75
H26A	430.79	6572.79	5197.67	97
H26B	377.91	6769.44	4603.53	97
H26C	1579.34	7363.67	4925.32	97

Ethyl 1,3-dioxo-9-tosyl-3,3a,4,5,8,8a-hexahydro-1H-4,8-epiminocyclohepta[c]furan-5-carboxylate (192)

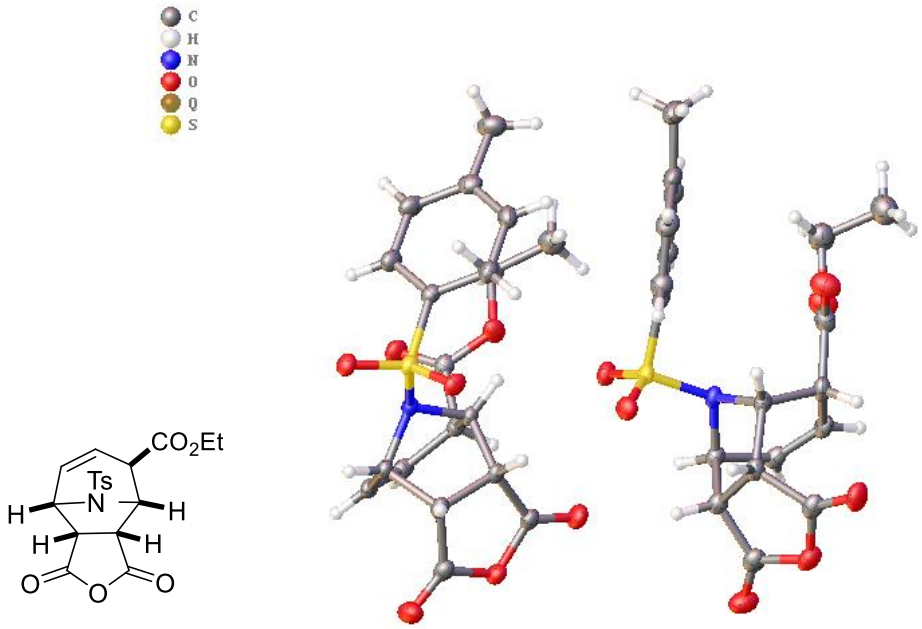


Table 1. Crystal data and structure refinement for **192**

Identification code	Q042
Empirical formula	$C_{19}H_{19}NO_7S$
Formula weight	405.41
Temperature/K	297.77(10)
Crystal system	triclinic
Space group	P-1
a/Å	10.9204(3)
b/Å	12.1622(4)
c/Å	14.6939(4)
a/°	94.115(2)
b/°	90.637(2)
γ/°	108.297(3)
Volume/Å^3	1846.97(10)
Z	4
ρ_{calc}g/cm^3	1.458
μ/mm^{-1}	1.947
F(000)	848.0

Crystal size/mm^3	0.24×0.14×0.07
Radiation	CuK$_\alpha$ (λ = 1.54184)
2Θ range for data collection/^{o}	3.840 to 73.737
Index ranges	-13≤h≤13, -15≤k≤15, -18≤l≤18
Reflections collected	48338
Independent reflections	7407 [R_{int} = 0.0885, R_{sigma} = 0.0422]
Data/restraints/parameters	7407/0/509
Goodness-of-fit on F^2	1.032
Final R indexes [I>=2σ (I)]	R_1 = 0.0400, wR_2 = 0.1064
Final R indexes [all data]	R_1 = 0.0490, wR_2 = 0.1128
Largest diff. peak/hole /e Å^{-3}	0.875/-0.414

Table 2. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **192**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
S(001)	3440.0(4)	6725.9(4)	10344.0(3)	18.31(11)
S(002)	5991.8(4)	6280.6(4)	7335.3(3)	20.77(11)
O(003)	2826.0(12)	6826.3(11)	11191.3(8)	24.0(3)
O(004)	4647.3(12)	6482.6(11)	10381.0(9)	23.7(3)
O(005)	2284.1(13)	2464.3(11)	8548.2(9)	25.6(3)
O(006)	4656.2(13)	6143.6(12)	7154.0(9)	26.4(3)
O(007)	6331.7(13)	5815.9(12)	8139.4(8)	27.1(3)
O(008)	2016.5(13)	6733.8(12)	7331.6(9)	27.4(3)
O(009)	147.5(13)	6307.6(12)	8064.7(9)	27.6(3)
O(00A)	7742.3(14)	2806.2(13)	6027.9(9)	30.8(3)
O(00B)	3395.4(14)	3436.5(12)	7430.2(9)	30.6(3)
O(00C)	1433.0(15)	1894.5(12)	9877.9(10)	34.7(3)
O(00D)	9691.3(14)	4155.2(14)	6228.7(10)	34.2(3)
O(00E)	7701.0(15)	7280.9(13)	4595.8(10)	36.1(3)
O(00F)	9295.5(15)	7937.7(13)	5665.5(10)	37.5(3)
O(00G)	5628.6(15)	1810.0(13)	6004.9(11)	38.2(4)
N(00H)	2339.1(14)	5752.0(12)	9672.4(9)	18.1(3)

N(00I)	6501.4(14)	5747.4(13)	6398.4(9)	18.9(3)
C(00J)	2734.9(16)	5455.9(15)	8746.8(11)	18.0(3)
C(00K)	1742.9(17)	4597.1(15)	10027.6(11)	19.8(3)
C(00L)	1490.3(17)	5059.7(15)	8140.2(11)	20.7(3)
C(00M)	3338.0(17)	4477.3(15)	8910.8(11)	19.1(3)
C(00N)	492.5(17)	4051.4(15)	9485.5(12)	21.5(4)
C(00O)	2717.4(17)	3931.1(15)	9768.4(11)	19.9(3)
C(00P)	5784.6(17)	4523.3(15)	6074.4(11)	20.1(3)
C(00Q)	4806.1(18)	8396.2(16)	9292.2(12)	23.8(4)
C(00R)	7794.2(17)	4588.0(16)	6816.7(11)	21.7(4)
C(00S)	1123.3(17)	6100.1(16)	7853.7(11)	21.8(4)
C(00T)	3670.9(17)	7967.2(15)	9745.5(11)	20.3(3)
C(00U)	3053.2(18)	3475.1(16)	8191.2(12)	22.1(4)
C(00V)	7867.9(16)	5765.4(16)	6424.0(11)	20.2(3)
C(00W)	2702.3(18)	8489.1(16)	9705.7(13)	26.2(4)
C(00X)	6146.9(18)	4380.1(16)	5093.6(12)	23.0(4)
C(00Y)	4961.7(19)	9336.4(17)	8773.7(13)	27.7(4)
C(00Z)	7277.9(19)	5000.3(17)	4801.4(12)	25.1(4)
C(010)	2066.1(19)	2666.7(16)	9464.8(12)	24.3(4)
C(011)	6386.3(17)	3813.9(16)	6684.1(12)	22.0(4)
C(012)	4002(2)	9850.7(16)	8700.0(13)	26.9(4)
C(013)	8554.6(19)	3892.7(18)	6338.3(12)	26.6(4)
C(014)	8274.6(18)	5881.8(17)	5426.7(12)	24.3(4)
C(015)	6560.5(19)	8469.4(17)	6778.8(12)	25.3(4)
C(016)	7201.4(19)	9652.8(17)	6872.6(13)	27.7(4)
C(017)	393.1(17)	4255.3(15)	8619.1(12)	22.2(4)
C(018)	6900.6(17)	7764.2(16)	7372.4(12)	22.6(4)
C(019)	8496(2)	9400.9(18)	8117.5(14)	30.7(4)
C(01A)	8512.0(19)	7152.6(18)	5236.0(13)	27.8(4)
C(01B)	8159.7(19)	10135.5(17)	7553.1(13)	28.5(4)
C(01C)	2881.0(19)	9423.7(17)	9187.7(14)	29.9(4)
C(01D)	6455(2)	2695.0(18)	6217.6(13)	27.7(4)
C(01E)	7869.3(19)	8212.5(18)	8034.9(13)	27.9(4)

C(01F)	1766(2)	7730.6(18)	6968.7(14)	31.0(4)
C(01G)	8777(2)	11427.1(18)	7697.3(16)	35.5(5)
C(01H)	4167(2)	10841.3(19)	8105.7(15)	37.7(5)
C(01I)	2892(2)	8287(2)	6400.3(15)	38.5(5)
C(01J)	7809(2)	8489(2)	4422.6(16)	39.1(5)
C(01K)	8901(3)	8984(2)	3810.4(17)	45.5(6)

Table 3: Anisotropic Displacement Parameters ($\times 10^4$) for **192**. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2a^{*2} \times U_{11} + ... + 2hka^* \times b^* \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S(001)	17.7(2)	20.7(2)	17.76(19)	-1.42(15)	-0.17(15)	8.39(16)
S(002)	22.5(2)	25.0(2)	15.94(19)	-0.73(15)	2.89(15)	9.55(17)
O(003)	26.3(7)	26.1(7)	19.2(6)	-2.8(5)	1.7(5)	8.9(5)
O(004)	19.9(6)	26.9(7)	27.1(6)	-0.9(5)	-3.7(5)	12.3(5)
O(005)	31.6(7)	23.3(6)	23.2(6)	-1.6(5)	3.7(5)	11.1(5)
O(006)	22.0(7)	31.7(7)	26.8(6)	-1.4(5)	4.7(5)	11.3(5)
O(007)	34.4(7)	29.1(7)	17.7(6)	1.5(5)	2.8(5)	9.8(6)
O(008)	24.5(7)	32.3(7)	30.7(7)	10.6(6)	2.9(5)	14.4(6)
O(009)	24.0(7)	31.1(7)	32.6(7)	4.0(6)	1.3(5)	15.6(6)
O(00A)	33.8(8)	32.8(7)	31.5(7)	-1.7(6)	-0.4(6)	19.7(6)
O(00B)	40.1(8)	31.5(7)	22.7(6)	-1.5(5)	7.6(6)	15.5(6)
O(00C)	48.5(9)	25.3(7)	30.0(7)	5.3(6)	7.7(6)	10.6(6)
O(00D)	28.3(8)	47.3(9)	34.3(7)	2.5(6)	3.6(6)	22.2(7)
O(00E)	38.7(8)	36.1(8)	33.6(7)	8.9(6)	-5.2(6)	10.9(6)
O(00F)	38.8(9)	34.9(8)	34.9(8)	6.0(6)	-7.8(6)	5.4(7)
O(00G)	40.0(9)	26.5(8)	47.9(9)	-1.4(6)	-2.8(7)	11.5(7)
N(00H)	17.4(7)	20.1(7)	17.5(6)	-0.3(5)	1.8(5)	7.5(6)
N(00I)	17.8(7)	24.9(8)	15.6(6)	-1.2(5)	0.5(5)	9.6(6)
C(00J)	17.7(8)	21.6(8)	16.7(7)	0.1(6)	2.2(6)	9.5(6)
C(00K)	21.3(9)	21.8(8)	18.7(8)	1.0(6)	3.5(6)	10.4(7)
C(00L)	20.9(9)	23.7(9)	19.4(8)	-1.4(7)	-1.6(6)	10.8(7)
C(00M)	18.2(8)	23.7(9)	18.5(8)	0.4(7)	1.0(6)	11.4(7)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(00N)	17.4(8)	20.9(8)	27.7(9)	0.1(7)	4.3(7)	8.4(7)
C(00O)	20.2(8)	23.9(9)	18.6(8)	0.8(7)	0.4(6)	11.7(7)
C(00P)	19.8(8)	23.1(9)	19.0(8)	-0.3(6)	-1.1(6)	9.4(7)
C(00Q)	23.2(9)	26.6(9)	23.4(8)	-1.7(7)	2.5(7)	11.3(7)
C(00R)	21.2(9)	29.1(9)	17.6(8)	1.9(7)	-0.6(6)	11.9(7)
C(00S)	21.7(9)	26.3(9)	18.3(8)	-1.4(7)	-2.9(7)	9.7(7)
C(00T)	21.8(9)	19.3(8)	20.0(8)	-2.2(6)	-1.1(6)	7.5(7)
C(00U)	23.4(9)	25.3(9)	21.5(8)	0.7(7)	1.2(7)	13.4(7)
C(00V)	17.6(8)	26.9(9)	18.1(8)	0.5(7)	-0.8(6)	10.1(7)
C(00W)	20.5(9)	25.3(9)	34.4(10)	0.6(8)	2.4(7)	9.7(7)
C(00X)	28.3(9)	26.5(9)	17.7(8)	-1.4(7)	-4.4(7)	14.7(8)
C(00Y)	28.1(10)	27.2(10)	26.0(9)	-0.5(7)	6.8(7)	6.5(8)
C(00Z)	34.1(10)	31.3(10)	15.1(7)	0.9(7)	2.5(7)	17.9(8)
C(010)	30(1)	25.1(9)	22.1(8)	2.0(7)	1.3(7)	14.6(8)
C(011)	23.5(9)	26.0(9)	18.7(8)	1.9(7)	-0.8(7)	11.1(7)
C(012)	34.6(11)	20.4(9)	24.2(9)	-2.7(7)	-2.2(8)	7.5(8)
C(013)	29.8(10)	34.4(10)	21.1(8)	2.5(7)	-1.2(7)	17.9(8)
C(014)	22.8(9)	34.3(10)	19.4(8)	4.5(7)	4.0(7)	13.6(8)
C(015)	26.4(9)	29.8(10)	21.8(8)	-2.4(7)	0.2(7)	13.1(8)
C(016)	32(1)	28.5(10)	26.8(9)	1.8(7)	5.6(8)	15.4(8)
C(017)	18.0(8)	22.1(9)	27.2(9)	-2.6(7)	-3.0(7)	8.2(7)
C(018)	23.3(9)	25.1(9)	20.8(8)	-2.4(7)	4.1(7)	10.4(7)
C(019)	27.7(10)	33.0(11)	29.3(9)	-5.4(8)	-2.6(8)	8.6(8)
C(01A)	26.8(10)	35.6(11)	21.6(8)	5.9(8)	2.6(7)	9.8(8)
C(01B)	29(1)	28(1)	30.1(9)	-2.1(8)	8.3(8)	12.1(8)
C(01C)	26(1)	26.2(10)	40.4(11)	-0.7(8)	-1.2(8)	13.3(8)
C(01D)	32.2(10)	30.4(10)	25.4(9)	4.1(8)	-0.7(8)	16.4(9)
C(01E)	30.1(10)	30.9(10)	23.9(9)	0.6(7)	-0.8(7)	11.7(8)
C(01F)	31.5(11)	30.8(10)	34.5(10)	9.9(8)	-2.6(8)	13.9(8)
C(01G)	35.4(11)	28.3(10)	42.2(11)	-4.4(9)	5.4(9)	10.5(9)
C(01H)	49.1(13)	27.7(10)	37.5(11)	5.1(9)	0.7(10)	13.4(9)
C(01I)	48.8(13)	34.8(12)	34.2(11)	9.4(9)	6.6(9)	14.7(10)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(01J)	39.5(12)	44.2(13)	37.6(11)	7.7(10)	2.9(9)	18(1)
C(01K)	50.6(15)	46.9(14)	38.1(12)	6.8(10)	6.8(10)	13.4(11)

Table 4: Bond Lengths in Å for **192**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S(001)	O(003)	1.4363(12)	O(008)	C(01F)	1.458(2)
S(001)	O(004)	1.4402(12)	O(009)	C(00S)	1.208(2)
S(001)	N(00H)	1.6535(15)	O(00A)	C(013)	1.382(3)
S(001)	C(00T)	1.7529(18)	O(00A)	C(01D)	1.403(2)
S(002)	O(006)	1.4347(14)	O(00B)	C(00U)	1.185(2)
S(002)	O(007)	1.4391(13)	O(00C)	C(010)	1.188(2)
S(002)	N(00I)	1.6557(14)	O(00D)	C(013)	1.197(2)
S(002)	C(018)	1.7618(19)	O(00E)	C(01A)	1.335(2)
O(005)	C(00U)	1.395(2)	O(00E)	C(01J)	1.477(3)
O(005)	C(010)	1.388(2)	O(00F)	C(01A)	1.196(3)
O(008)	C(00S)	1.328(2)	O(00G)	C(01D)	1.186(3)
N(00H)	C(00J)	1.486(2)	C(00R)	C(013)	1.506(2)
N(00H)	C(00K)	1.486(2)	C(00T)	C(00W)	1.397(2)
N(00I)	C(00P)	1.488(2)	C(00V)	C(014)	1.539(2)
N(00I)	C(00V)	1.485(2)	C(00W)	C(01C)	1.378(3)
C(00J)	C(00L)	1.541(2)	C(00X)	C(00Z)	1.324(3)
C(00J)	C(00M)	1.561(2)	C(00Y)	C(012)	1.385(3)
C(00K)	C(00N)	1.507(3)	C(00Z)	C(014)	1.511(3)
C(00K)	C(00O)	1.562(2)	C(011)	C(01D)	1.503(3)
C(00L)	C(00S)	1.527(2)	C(012)	C(01C)	1.399(3)
C(00L)	C(017)	1.506(2)	C(012)	C(01H)	1.505(3)
C(00M)	C(00O)	1.531(2)	C(014)	C(01A)	1.532(3)
C(00M)	C(00U)	1.507(2)	C(015)	C(016)	1.385(3)
C(00N)	C(017)	1.324(3)	C(015)	C(018)	1.391(3)
C(00O)	C(010)	1.509(3)	C(016)	C(01B)	1.395(3)
C(00P)	C(00X)	1.511(2)	C(018)	C(01E)	1.379(3)

C(00P)	C(011)	1.560(2)	C(019)	C(01B)	1.388(3)
C(00Q)	C(00T)	1.384(3)	C(019)	C(01E)	1.387(3)
C(00Q)	C(00Y)	1.387(3)	C(01B)	C(01G)	1.500(3)
C(00R)	C(00V)	1.561(2)	C(01F)	C(01I)	1.500(3)
C(00R)	C(011)	1.532(3)	C(01J)	C(01K)	1.498(3)

Table 5: Bond Angles in ° for **192**.

Atom	**Atom**	**Atom**	**Angle/°**	**Atom**	**Atom**	**Atom**	**Angle/°**
O(003)	S(001)	O(004)	117.57(8)	N(00I)	C(00P)	C(011)	102.85(13)
O(003)	S(001)	N(00H)	105.80(8)	C(00X)	C(00P)	C(011)	110.08(14)
O(003)	S(001)	C(00T)	111.16(8)	C(00T)	C(00Q)	C(00Y)	119.22(17)
O(004)	S(001)	N(00H)	112.48(7)	C(011)	C(00R)	C(00V)	106.35(14)
O(004)	S(001)	C(00T)	107.89(8)	C(013)	C(00R)	C(00V)	116.45(15)
N(00H)	S(001)	C(00T)	100.67(8)	C(013)	C(00R)	C(011)	104.45(15)
O(006)	S(002)	O(007)	118.27(8)	O(008)	C(00S)	C(00L)	110.53(15)
O(006)	S(002)	N(00I)	105.99(7)	O(009)	C(00S)	O(008)	124.89(17)
O(006)	S(002)	C(018)	109.55(8)	O(009)	C(00S)	C(00L)	124.57(17)
O(007)	S(002)	N(00I)	111.71(8)	C(00Q)	C(00T)	S(001)	119.00(14)
O(007)	S(002)	C(018)	108.05(9)	C(00Q)	C(00T)	C(00W)	120.80(17)
N(00I)	S(002)	C(018)	102.08(8)	C(00W)	C(00T)	S(001)	120.17(14)
C(010)	O(005)	C(00U)	111.20(14)	O(005)	C(00U)	C(00M)	109.69(14)
C(00S)	O(008)	C(01F)	116.73(14)	O(00B)	C(00U)	O(005)	119.74(17)
C(013)	O(00A)	C(01D)	111.03(14)	O(00B)	C(00U)	C(00M)	130.55(18)
C(01A)	O(00E)	C(01J)	116.10(17)	N(00I)	C(00V)	C(00R)	103.34(14)
C(00J)	N(00H)	S(001)	117.12(11)	N(00I)	C(00V)	C(014)	104.37(13)
C(00J)	N(00H)	C(00K)	103.21(12)	C(014)	C(00V)	C(00R)	115.68(14)
C(00K)	N(00H)	S(001)	116.69(11)	C(01C)	C(00W)	C(00T)	118.86(18)
C(00P)	N(00I)	S(002)	116.72(11)	C(00Z)	C(00X)	C(00P)	121.46(17)
C(00V)	N(00I)	S(002)	116.33(11)	C(012)	C(00Y)	C(00Q)	121.26(18)
C(00V)	N(00I)	C(00P)	103.15(13)	C(00X)	C(00Z)	C(014)	122.05(16)
N(00H)	C(00J)	C(00L)	105.81(13)	O(005)	C(010)	C(00O)	109.64(15)
N(00H)	C(00J)	C(00M)	102.96(13)	O(00C)	C(010)	O(005)	120.05(17)

C(00L)	C(00J)	C(00M)	114.62(14)	O(00C)	C(010)	C(00O)	130.31(17)
N(00H)	C(00K)	C(00N)	105.92(14)	C(00R)	C(011)	C(00P)	102.81(14)
N(00H)	C(00K)	C(00O)	103.27(13)	C(01D)	C(011)	C(00P)	114.16(14)
C(00N)	C(00K)	C(00O)	109.84(14)	C(01D)	C(011)	C(00R)	104.81(15)
C(00S)	C(00L)	C(00J)	111.07(15)	C(00Y)	C(012)	C(01C)	118.37(18)
C(017)	C(00L)	C(00J)	111.08(14)	C(00Y)	C(012)	C(01H)	120.55(19)
C(017)	C(00L)	C(00S)	110.28(14)	C(01C)	C(012)	C(01H)	121.08(18)
C(00O)	C(00M)	C(00J)	105.62(13)	O(00A)	C(013)	C(00R)	110.05(16)
C(00U)	C(00M)	C(00J)	116.95(14)	O(00D)	C(013)	O(00A)	120.77(17)
C(00U)	C(00M)	C(00O)	104.56(14)	O(00D)	C(013)	C(00R)	129.16(19)
C(017)	C(00N)	C(00K)	120.57(16)	C(00Z)	C(014)	C(00V)	109.92(15)
C(00M)	C(00O)	C(00K)	103.94(13)	C(00Z)	C(014)	C(01A)	115.24(15)
C(010)	C(00O)	C(00K)	113.12(15)	O(00F)	C(01A)	O(00E)	124.58(19)
C(010)	C(00O)	C(00M)	104.80(14)	O(00F)	C(01A)	C(014)	122.26(17)
N(00I)	C(00P)	C(00X)	105.68(14)	C(016)	C(01B)	C(01G)	120.67(19)
C(01A)	C(014)	C(00V)	106.98(15)	C(019)	C(01B)	C(016)	118.71(19)
C(016)	C(015)	C(018)	118.63(18)	C(019)	C(01B)	C(01G)	120.58(19)
C(015)	C(016)	C(01B)	121.00(18)	C(00W)	C(01C)	C(012)	121.43(17)
C(00N)	C(017)	C(00L)	122.31(16)	O(00A)	C(01D)	C(011)	109.39(16)
C(015)	C(018)	S(002)	119.17(15)	O(00G)	C(01D)	O(00A)	119.93(18)
C(01E)	C(018)	S(002)	118.99(15)	O(00G)	C(01D)	C(011)	130.68(19)
C(01E)	C(018)	C(015)	121.66(18)	C(018)	C(01E)	C(019)	118.69(18)
C(01E)	C(019)	C(01B)	121.26(19)	O(008)	C(01F)	C(01I)	106.51(16)
O(00E)	C(01A)	C(014)	113.01(17)	O(00E)	C(01J)	C(01K)	111.00(19)

Table 6: Hydrogen Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **192**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
H(00J)	3373.77	6129.1	8514.46	22
H(00K)	1615.84	4653.24	10686.42	24
H(00L)	1650.98	4632.88	7587.19	25

Atom	x	y	z	U_{eq}
H(00M)	4272.91	4816.75	9018.89	23
H(00N)	-215.54	3567.29	9761.88	26
H(00O)	3362.65	4025.55	10261.47	24
H(00P)	4850.66	4334.92	6139.34	24
H(00Q)	5457.02	8057.85	9334.86	29
H(00R)	8038.41	4719.6	7468.86	26
H(00V)	8404.25	6424.19	6823.83	24
H(00W)	1949.59	8210.41	10023.51	31
H(00X)	5562.17	3844.24	4686.21	28
H(00Y)	5724.71	9627.23	8469.66	33
H(00Z)	7464.78	4889.96	4192.2	30
H(011)	5959.73	3689	7268.38	26
H(014)	9093.6	5715.29	5371.56	29
H(015)	5916.03	8152.73	6328.2	30
H(016)	6989.79	10133.12	6475.96	33
H(017)	-381.4	3889.03	8294.7	27
H(019)	9153.95	9711.46	8559.52	37
H(01C)	2242.27	9778.42	9161.62	36
H(01J)	8097.73	7727.59	8418.57	34
H(01A)	1686.68	8275.36	7462.37	37
H(01B)	971.89	7481.71	6598.05	37
H(01K)	9009.31	11740.74	7119.35	53
H(01L)	9536.81	11598.21	8085.61	53
H(01M)	8179.37	11768.83	7979.19	53
H(01D)	4357.09	11556.62	8482.64	57
H(01E)	3384.66	10719.02	7751.62	57
H(01F)	4863.62	10880.17	7703.67	57
H(01G)	2977.43	7729.63	5928.66	58
H(01H)	3666.04	8551.86	6779.94	58
H(01I)	2754.8	8934.88	6128.43	58
H(01N)	7949.38	8961.65	4997.8	47
H(01O)	7008.01	8505.1	4140.5	47

Atom	x	y	z	U_{eq}
H(01P)	8768.13	8509.94	3244.38	68
H(01Q)	9698.28	9000.92	4101.58	68
H(01R)	8935.13	9759.65	3693.08	68

4. Curriculum Vitae

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- Thesis: Studies on Reactions of Cyclopropanated Pyrrole: Synthesis of Bis-β-homoproline, tropane- and pyrrolidinone-derivatives

M. S. in Department of Chemistry, POSTECH (GPA 3.73/4.3) *Sep. 2010 – Feb. 2013*

- Advisor: Prof. Dr. Young Ho Rhee
- Thesis: A Novel Route to Synthesis of β-alkoxyacrylates via Au(I)-catalyzed Intermolecular Reaction of Allylic Ethers and Alkynoates

B. S. in Department of Applied Chemistry, Kyung Hee University (GPA 3.57/4.3)

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- Studied Au(I)-catalyzed enantioselective hydroamination of unsymmetric allenes

Fellowship

Forschungsstipendien für Doktoranden und Nachwuchswissenschaftler
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Publication

1. Park, S. R.; Kim, C.; Kim, D.; Thrumurtulu, N.; Yeom, H.; Jun, J.; Shin, S.; Rhee, Y. H. "An Entry to β-alkoxyacrylates via Gold-catalyzed Intermolecular Coupling of Alkynoates and Allylic Ethers" *Org. Lett.* **2013**, *15*, 1166.
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I. Declaration

Herewith I declare that this present thesis is a presentation of my original work prepared single-handed. Wherever contributions from others are involved, all of them are marked clearly, with reference to the literature, license, and acknowledgment of collaborative research.

Regensburg, 7 May 2019

Saerom Park