MANGANESE(III)-MEDIATED REACTIONS OF VINYL AZIDES AND 1,3-DICARBONYL COMPOUNDS OR CYCLOPROPANOLS: SYNTHESIS OF AZAHETEROCYCLES

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WANG YIFENG

School of Physical and Mathematical Sciences

A thesis submitted to the Nanyang Technological University
in partial fulfillment of the requirement for the degree of
Doctor of Philosophy

2011

Acknowledgements

First, the author owes his deepest gratitude to his supervisor, Nanyang Professor Koichi Narasaka, whose continuous support, patient guidance, and strict training enabled the author to complete his PhD course studies. The author is deeply grateful to his co-supervisor, Assistant Professor Shunsuke Chiba for the practical guidance, insightful discussion, and valuable suggestions.

Dr. Motoki Yamane is also acknowledged for the helpful suggestions in the early stage of the author's research work. The author is appreciative to Professor Loh Teck-Peng for allowing the author to work in his research laboratory for four months.

The author is indebted to Miss Toh Kah Kah and Miss Ng Pei Jian Eileen, who have made great contribution to the work described in Chapters 3 and 5.

The author wishes to thank the members in Professor Narasaka's group for the helpful discussion and kind assistance: Dr. Liu Wei-Min, Mr. Xiao Yong-Jun, Mr. Lei Mao-Yi, Mr. Hui Wei Qiang Benjamin, Mr. Ren Wei, Mr. Xu Yan-Jun, Mr. Zhang Line, Ms. Liu Zheng-Hong, Ms. Shen Shu-Su, Ms. Yue Yan-Ni, Mr. Zhu Chua, Mr. He Xin-Yao, Mr. Stephen Sanjaya, Mr. Tong Meng Kiat Benny, Miss Too Pei Chui, Miss Ang Gim Yean, and Miss Chua Sze Hui.

The author would like to thank Dr. Li Yongxin for assistance in X-ray crystallographic analysis, Mdm. Zhu Wen-Wei and Ms. Yeo Siew-Ping (Low- and High-resolution Mass Spectrometry) for training on the use of the equipment, Ms. Goh Ee-Ling for training on the use of the NMR spectrometers.

The author is grateful to Nanyang Technological University for providing a research scholarship.

Finally, the author wishes to express his sincere appreciation to his parents, Mr. Wang Wen-Ding and Mdm. Tang Han-Lan, and his wife, Ms. Wang Zhi-Juan, as well as his sister, Ms. Wang Yan for their continuous encouragement and assistance.

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List of Abbreviations

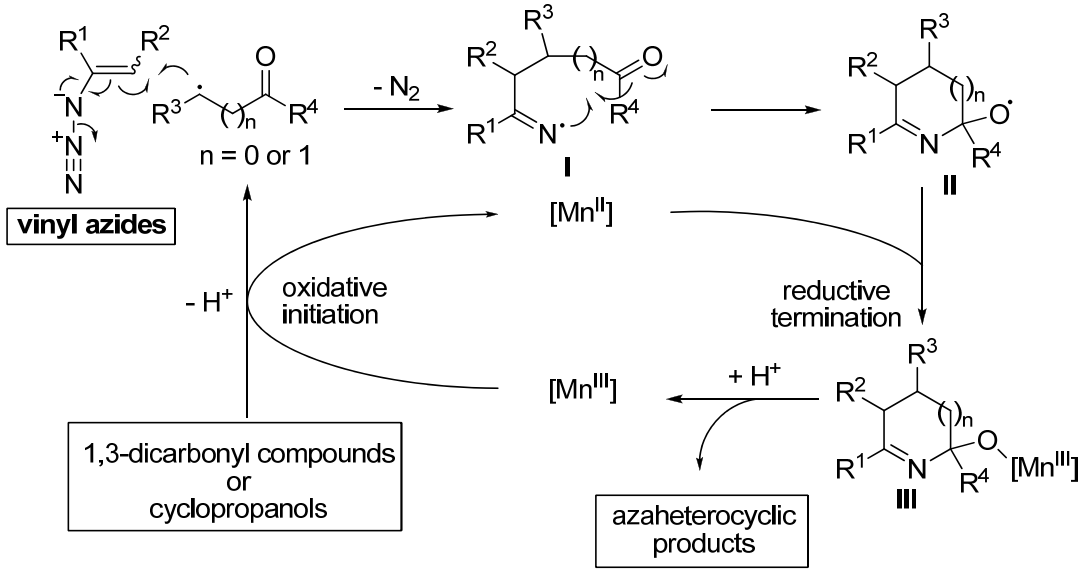
δ	chemical shift (ppm)
°C	degree centigrade
Ac	acetyl
acac	acetylacetonyl
AIBN	2,2'-azo *bis*isobutyronitrile
Ar	aryl (substituted aromatic ring)
Bn	benzyl
Boc	*t*-butoxycarbonyl
Bu	butyl
br	broad singlet
calcd	calculated
cat.	catalytic
cm^{-1}	wave number
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
dppm	*bis*(diphenylphosphino)methane
dq	doublet of quartets
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
EDG	electron donating group

ee	enantiomeric excess
EIHRMS	Electron Ionization High Resolution Mass Spectrometry
eq/equiv	equivalent
ESIHRMS	Electrospray Ionization High Resolution Mass Spectrometry
Et	ethyl
EWG	electron withdrawing group
Hz	hertz
i-Pr	*iso*-propyl
IR	infrared spectroscopy
J	coupling constants
LA	Lewis acid
M	concentration (mol/L)
M^+	parent ion peak (mass spectrum)
m	multiplet
Me	methyl
mg	milligram
MHz	megahertz
mmol	millimole
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl
NMR	nuclear magnetic resonance
pic	2-pyridinecarboxylate
q	quartet

rt	room temperature
s	singlet
t	triplet
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

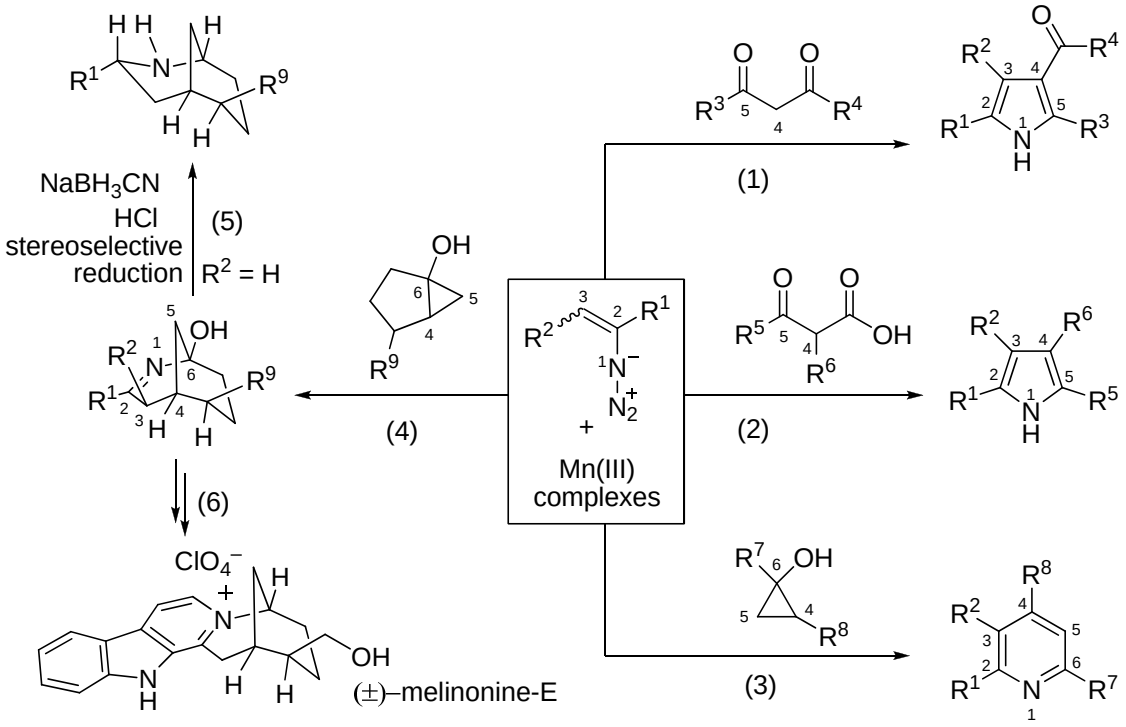
Abstract

In this thesis, the author describes efficient methods to synthesize azaheterocycles by using readily accessible vinyl azides as fundamental substrates. These methods involve iminyl radicals **I** as key intermediates, which are generated by the addition of α- or β-carbonyl radicals to the C=C bond of vinyl azides with the elimination of dinitrogen (Scheme 1). The α- and β-carbonyl radicals are generated by the oxidation of 1,3-dicarbonyl compounds and cyclopropanols with Mn(III) complexes, respectively. The construction of azaheterocyclic frameworks is achieved by the cyclization of iminyl radicals **I** onto an intramolecular carbonyl group. Importantly, the radical chain reactions are then terminated by the reduction of alkoxy radicals **II** by the resulting Mn(II) species to afford Mn(III) alkoxides **III**, from which azaheterocyclic products are formed with regeneration of active Mn(III) species. Therefore, this characteristic oxidative initiation and reductive termination process promotes these reactions in a catalytic manner.



Scheme 1. Synthetic pathway for azaheterocycles from vinyl azides and 1,3-dicarbonyl compounds or cyclopropanols by using Mn(III) complexes as catalysts

As a result, a wide range of polysubstituted *N*–H pyrroles are synthesized by the Mn(III)-catalyzed reactions of vinyl azides and 1,3-dicarbonyl compounds (including *β*-keto esters, 1,3-diketones, and *β*-keto acids), in which 1,3-dicarbonyl compounds are utilized as the precursors of *α*-carbonyl radicals (Scheme 2, Eqs. 1 and 2). Moreover, Mn(III)-mediated/catalyzed reactions of vinyl azides and cyclopropanols (precursors of acyclic *β*-carbonyl radicals) afford various pyridines (Eq. 3). Furthermore, the employment of bicyclo[3.1.0]hexan-1-ols as the progenitors of cyclic *β*-carbonyl radicals gives 2-azabicyclo[3.3.1]non-2-en-1-ols (azabicyclic compounds). Notably, stereoselective reduction of the C═N and bridgehead C−OH bonds of these azabicyclic compounds leads to *endo*-selective (refer to R^1) formation of 2-azabicyclo[3.3.1]nonane (morphan) derivatives (Eq. 5). Ultimately, an efficient synthesis of (±)-melinonine-E is accomplished by applying the methods developed in this thesis (Eq. 6).

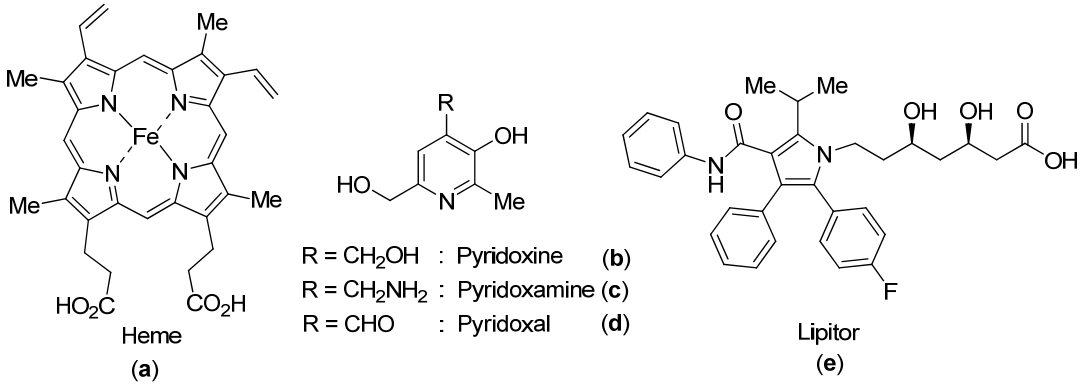


Scheme 2. Synthesis of azaheterocycles by Mn(III)-catalyzed/mediated reactions of vinyl azides and 1,3-dicarbonyl compounds or cyclopropanols

Chapter 1 General Introduction

Nitrogen-containing heterocycles (azaheterocycles) are one of the essential components in naturally occurring substances, pharmaceuticals and functional materials. In fact, the molecular structures of a wide variety of natural products are based on azaheterocyclic cores. For example, pyrrole unit occurs as a building block in many physiologically interesting natural products such as heme[1] (Figure 1-1, **a**) and related porphinoid cofactors. In addition, all three natural forms of vitamin B6[2] (Figure 1-1, **b**-**d**), such as pyridoxine, pyridoxamine and pyridoxal, are built upon a pyridine ring. Moreover, there is a great deal of pharmaceutical active molecules that contain azaheterocycles.[3] For instance, the blockbuster drug atorvastatin, commonly known as Lipitor[4] (Figure 1-1, **e**), a polysubstituted pyrrole compound, is the top-selling branded pharmaceutical in the world.

Figure 1-1. Examples of natural products and pharmaceutical agents containing azaheterocycles



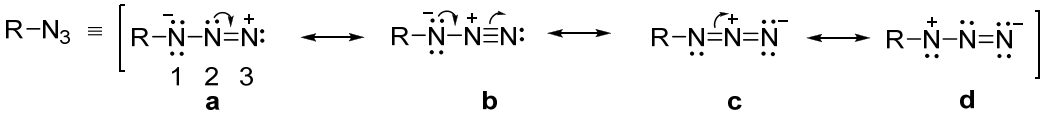
Because of high potential utility of azaheterocycles in various areas, diverse synthetic approaches toward azaheterocycles have been developed so far.[5] Among them, the processes involving the applications of organic azides as nitrogen sources to construct azaheterocycles have drawn considerable attention.[6]

In Section 1.1, the author introduces the outline of applications of organic azides for the synthesis of azahetrocycles as well as other important nitrogen-containing compounds. Moreover, Sections 1.2 and 1.3 highlight the chemistry of iminyl radicals[7] and iminyl-metals[8] for C–N bond formation, which are key concepts of the author's work.

1.1 Reactions of Organic Azides in the Synthesis of Azaheterocycles

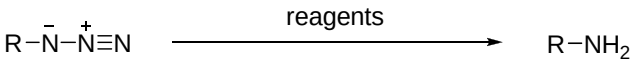
Organic azides have been employed as versatile and valuable substrates for synthesis of azaheterocycles, arising from their distinct chemical diversity. In general, organic azides are expressed as polar mesomeric structures as shown in Figure 1-2. This unique feature allows organic azides to serve as versatile synthetic intermediates such as 1,3-dipoles, precursors of amines and nitrenes, nitrogen electrophiles, nitrogen nucleophiles, radical acceptors, and so on.[6a,6c]

Figure 1-2. Polar mesomeric structures of organic azides



1.1.1 Reduction of Organic Azides to Amines

Reduction of organic azides to corresponding amines[9] is of great synthetic utility in the controlled introduction of an amine function to organic molecules (Scheme 1-1), since many azides can be readily prepared with regio- and stereo-control.[6] This reaction has been accomplished by applying a variety of reagents including $LiAlH_4$,[10] catalytic hydrogenation,[11] phosphanes[12] (Staudinger reaction, see Section 1.1.4), and so on.[6]

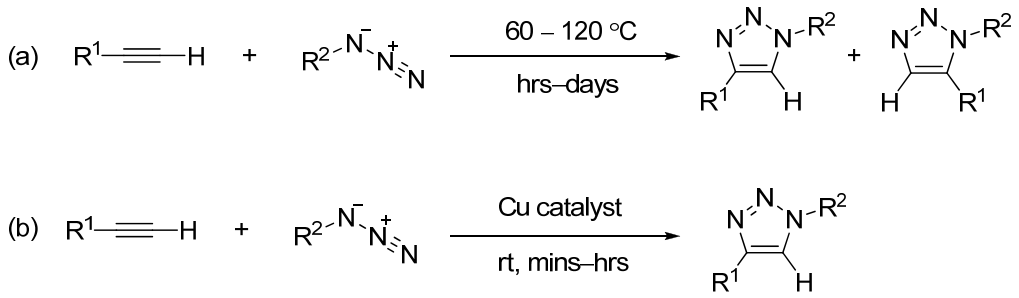


Reagents: $LiAlH_4$, H_2/catalyst, phosphanes/H_2O ...

Scheme 1-1. Reduction of organic azides to amines

1.1.2 Cycloaddition of Organic Azides onto Diploarophiles

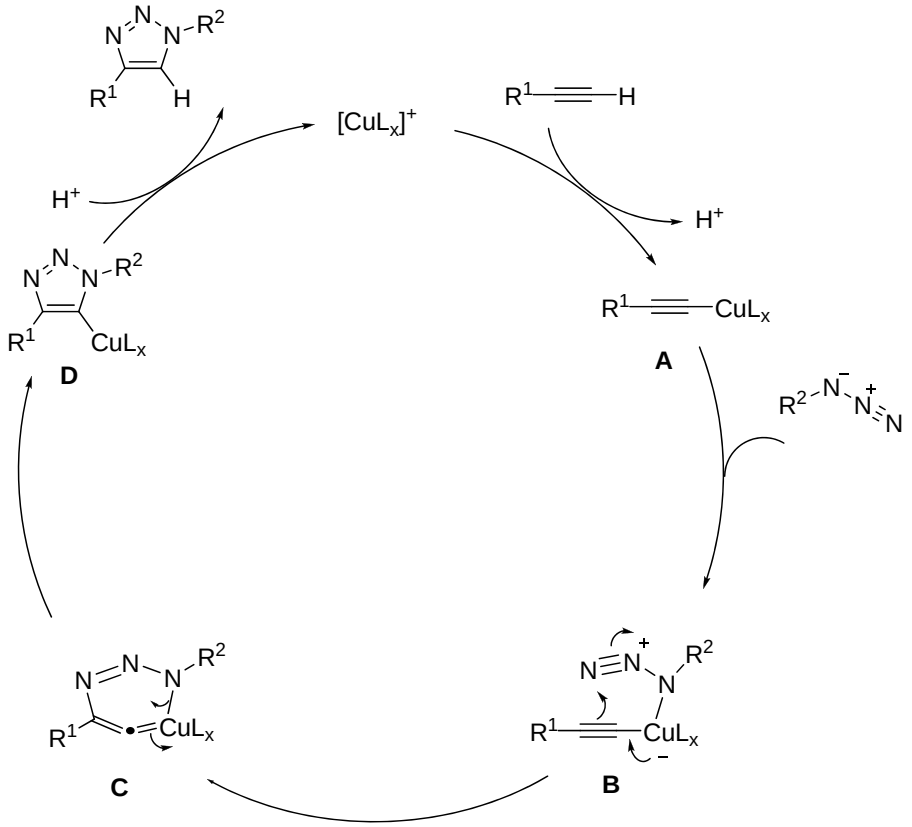
The 1,3-dipolar cycloaddition of organic azides onto dipolarophiles,[13] first reported by Huisgen,[14] is an versatile method to synthesize 1,2,3-triazole derivatives. The uncatalyzed thermal cycloaddition (Scheme 1-2, Eq. a) of organic azides to alkynes has been utilized for triazole formation, but frequently with low regioselectivity.[14] Recently, this reaction has been improved in terms of reaction rate and regioselectivity by using copper catalysts, which were independently reported by Sharpless[15 a] and Meldal[15b] (Scheme 1-2, Eq. b).



Scheme 1-2. 1,3-Dipolar cycloaddition of organic azides with alkynes

A number of copper (I) salts (CuI, CuBr, $[Cu(CH_3CN)_4]PF_6$, $(EtO)_3P{\cdot}CuI$, $[Cu(PPh_3)_3]Br$) can be used in the reaction, but the exclusion of oxygen from reaction system is required to prevent the formation of inactive Cu(II) species. Alternatively, the combination of a reducing agent, such as ascorbate, with copper(II) salts simplifies the experiment procedure without diminishing the product yield.[16]

The proposed catalytic cycle[17] of this copper-catalyzed reaction involves the formation of copper acetylide **A**, which coordinates the internal nitrogen atom of an azide to form intermediate **B**. The key bond-forming step takes place when **B** is converted to the unusual 6-membered copper metalacycle **C** and further into copper-metallated triazole **D**. The high regioselectivity is determined by the binding of both azide and alkyne to copper prior to the C–N bond formation. Eventually, protonation of **D** releases triazole and thereby regenerates $L_nCu(I)$ (Scheme 1-3).

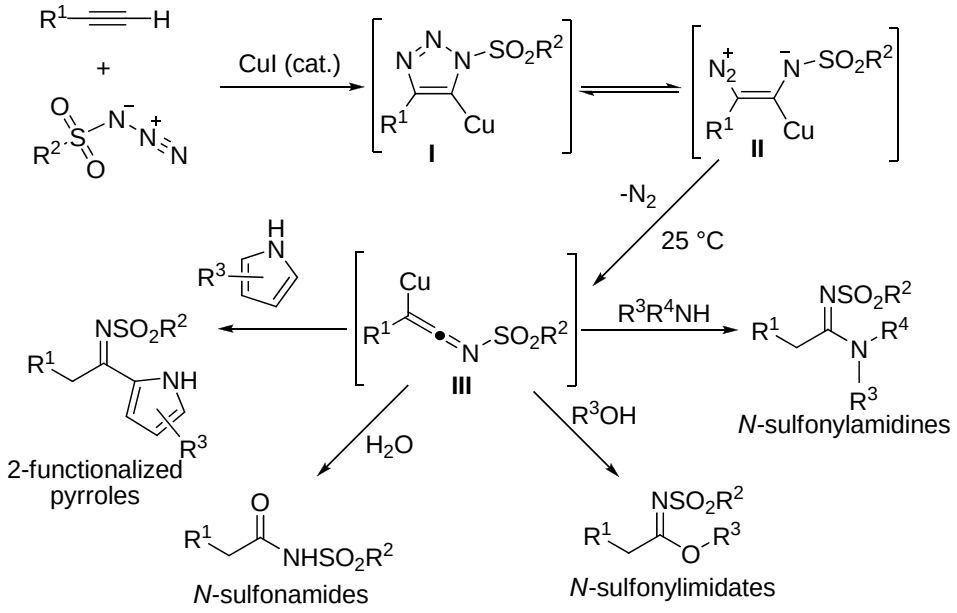


Scheme 1-3. Proposed catalytic cycle for the Cu-catalyzed triazole synthesis

Since the approach provides selective, efficient and modular synthesis of 1,2,3-triazole derivatives in high yields under milder conditions, this reaction is considered as a great contribution to "click chemistry".[18] Furthermore, this reaction proceeds well in

aqueous media and it is biocompatible, which are ideal for biochemical studies and drug discovery.[19]

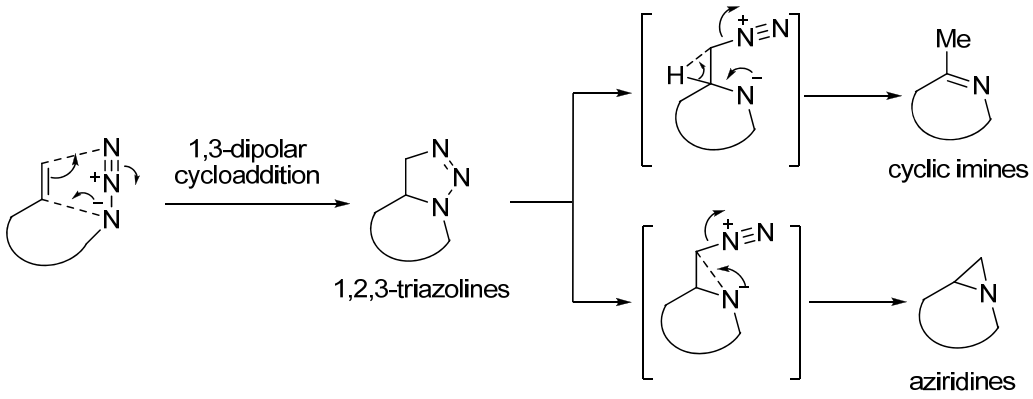
A wide range of aryl and alkyl azides have been utilized in this copper-catalyzed triazole formation. However, the employment of sulfonyl azides resulted in apparently different outcomes.[20] Chang demonstrated that the ring-opening process of *N*-sulfonyl copper triazole species **I** readily took place even at room temperature, generating *N*-sulfonylketenimine intermediates **III**.[20b] Addition of nucleophiles onto these species afforded various three-component coupling adducts in high yields under mild conditions. Amines, alcohols, water, and even pyrroles have been employed as nucleophiles, producing *N*-sulfonylamidines,[20c] *N*-sulfonylimidates,[20d] *N*-sulfonamides,[20e] and 2-functionalized pyrroles,[20f] respectively (Scheme 1-4).



Scheme 1-4. Copper-catalyzed multicomponent reactions

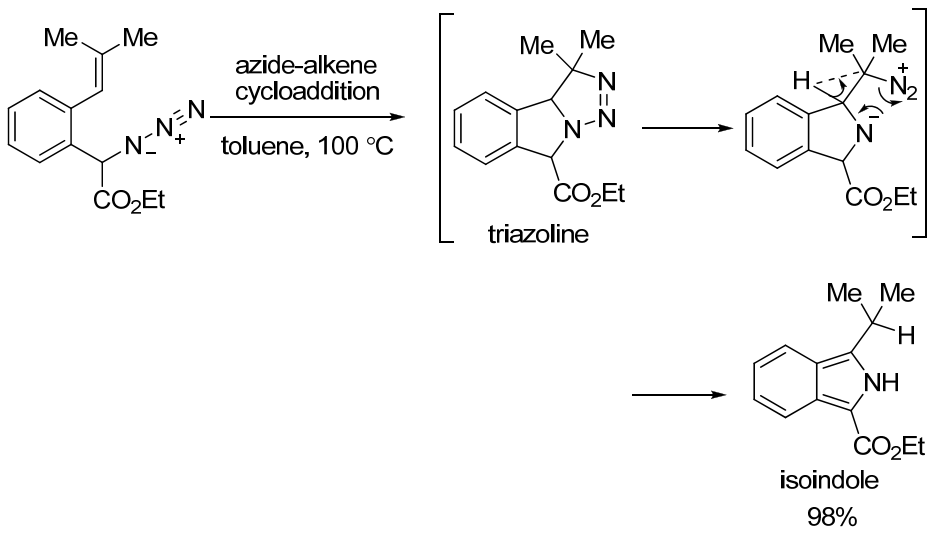
In addition to alkynes, alkenes are another important class of dipolarophiles to participate in the 1,3-dipolar cycloaddition with azides.[21] In this case, however, unstable 1,2,3-triazoline adducts are formed.[22] Subsequent decomposition occurs spontaneously to

afford either imines or 3-membered aziridines, which can undergo further transformations (Scheme 1-5).[23,24]



Scheme 1-5. 1,3-Dipolar cycloaddition of organic azides with alkenes and the subsequent decomposition to imines or aziridines

For example, our group recently reported a promising approach based on 1,3-dipolar cycloaddition of azides onto alkenes for the construction of isoindole derivatives. In this reaction, simple heating of α-azido carbonyl compounds bearing a 2-alkenylaryl unit induced an intramolecular azide-alkene 1,3-dipolar cycloaddition generating a triazoline intermediate, followed by elimination of dinitrogen and rearrangement producing the desired isoindoles (Scheme 1-6).[25]

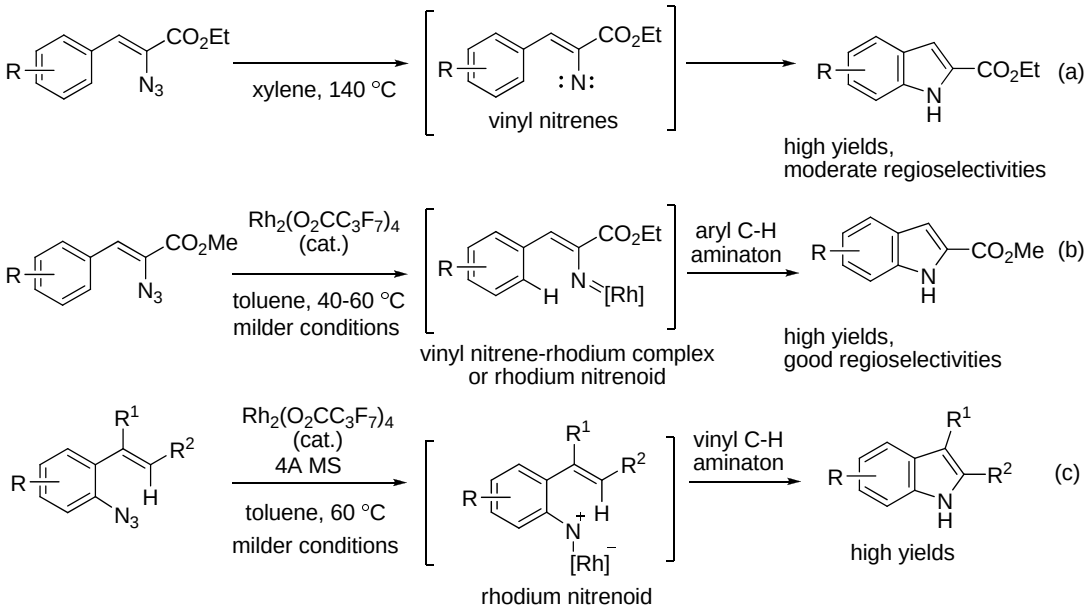


Scheme 1-6. Isoindole formation from organic azides through 1,3-dipolar cycloaddition

1.1.3 Reactions of Nitrenes Derived from Organic Azides

Nitrenes are a class of transient intermediates and they are involved in many useful transformations in the synthesis of amino compounds.[6a,6c] Hemetsbe and co-workers[26] found that thermal reaction of azidocinnamates occurred to provide indoles in quite high yields as shown in Scheme 1-7 (Eq. a). Vinyl nitrene intermediates were considered to be formed by thermolysis of vinyl azides. This procedure has been successfully employed as key steps in the syntheses of several indole alkaloids.[27]

More recently, this reaction has been improved in terms of milder reaction conditions and higher regioselectivities by the use of rhodium catalysts (Scheme 1-7, Eq. b).[28] Rhodium nitrenoids are supposed to be first generated from vinyl azides and rhodium catalyst, followed by rhodium-catalyzed aryl C–H bond amination reaction leading to indoles. The synthetic utility of this transformation is further enhanced by the employment of aryl azides to afford diverse substituted indoles through a rhodium catalyzed vinyl C–H bond amination reaction (Scheme 1-7, Eq. c).[29]

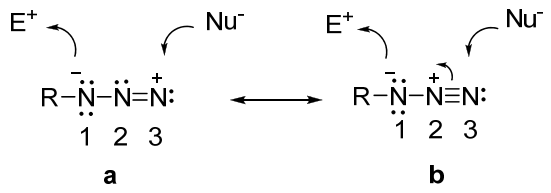


Scheme 1-7. Synthesis of indoles from vinyl azides or aryl azides

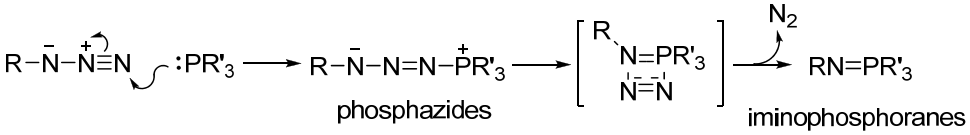
1.1.4 Reactions of Organic Azides with Nucleophiles and Electroplies

According to the mesomeric structure of organic aizdes (Section 1.1; Figure 1-2), they are able to react with nucleophiles at terminal N(3), whereas electrophiles are attacked by internal N(1) (Figure 1-3).[6b, 6c]

Figure 1-3. Reactivity of organic azides

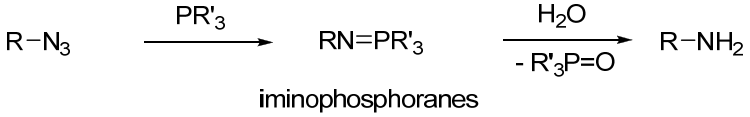


The most popular reaction involving organic azides as electrophiles is Staudinger reaction.[30,31] In this reaction, trialkylphosphines or triarylphosphines undergo nucleophilic attack to the terminal nitrogen of organic azides to form phosphazides, and the successive extrusion of dinitrogen affords iminophosphoranes (Scheme 1-8).[32]



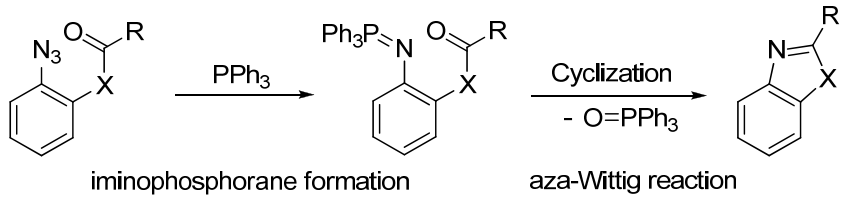
Scheme 1-8. The Staudinger reaction

These iminophosphoranes are important reagents and intermediates in organic synthesis.[33] For example, in the presence of water, the iminophosphoranes are hydrolyzed to primary amines (Scheme 1-9).



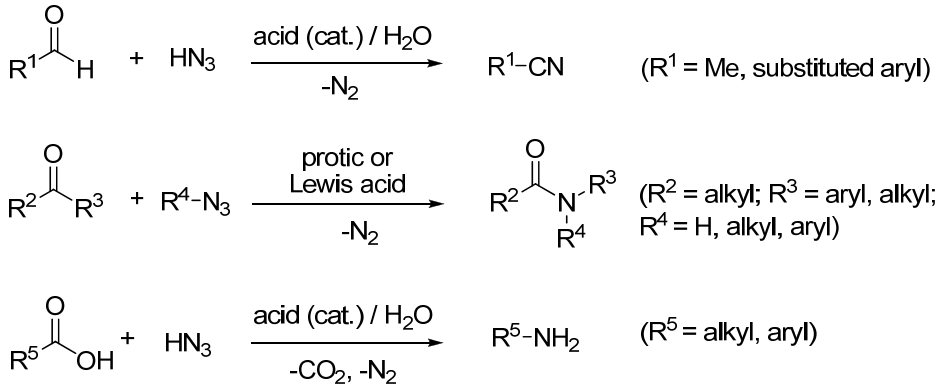
Scheme 1-9. Reduction of organic azides to amines by Staudinger reaction

Moreover, the aza-Wittig reaction of iminophosphoranes with an intramolecular carbonyl group has been used for the synthesis of azaheterocycles (Scheme 1-10).[34]



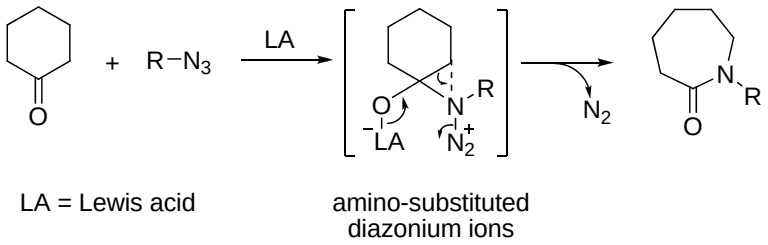
Scheme 1-10. Intramolecular aza-Wittig reaction

On the other hand, suitable (pre)electrophiles (aldehydes, ketones, epoxides, or carbenium ions) can also react with organic azides to furnish nitrogen-containing compounds. For instance, Schmidt reaction[35] involves the reactions of organic azides with aldehydes, ketones and carboxylic acids in the presence of acid catalysts (either protic or Lewis acid) to give nitriles, amides, and amines, respectively (Scheme 1-11).



Scheme 1-11. The Schmidt reaction

In the reaction of cyclic ketones (Scheme 1-12), the internal nitrogen atom of an organic azide undergoes nucleophilic addition to the activated ketone moiety to give an amino-substituted diazonium ion. The subsequent rearrangement with simultaneous elimination of dinitrogen produces a lactam.[36]



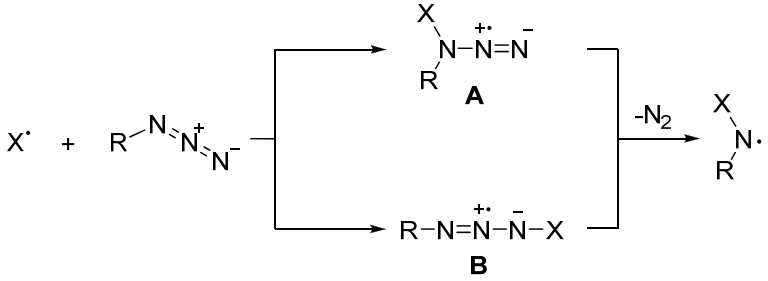
Scheme 1-12. Lewis acid mediated reaction of azides and cyclic ketones

1.1.5 Radical Reactions of Organic Azides

It has been demonstrated that organic azides can act as efficient radical traps for carbon- and heteroatom-centered radicals, resulting in reactive nitrogen-centered radicals such as aminyls or iminyls,[6,7] which are valuable intermediates for the construction of azaheterocycles.

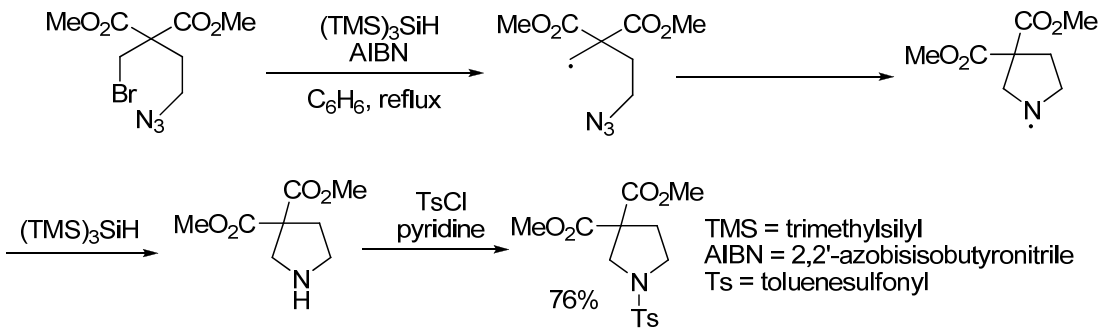
1.1.5.1 Formation of Aminyl Radicals

Organic azides can be attacked by radical species at both/either the internal and/or the terminal nitrogen, leading to 3,3-triazenyl (**A**) or 1,3-triazenyl radical (**B**), respectively. Then an aminyl radical is afforded by rapid extrusion of dinitrogen from both of triazenyl radicals (Scheme 1-13).[37] Further reactions of this kind of aminyl radical to furnish azaheterocycles have been widely exploited.



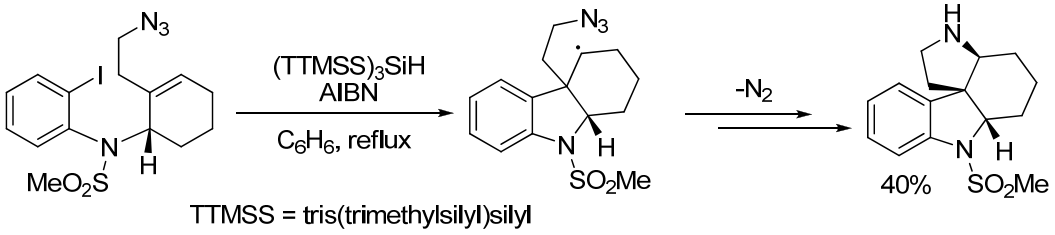
Scheme 1-13. Formation of aminyl radicals from organic azides

Kim reported that intramolecular addition of alkyl radicals to azides provided pyrrolidines through cyclic aminyl radicals (Scheme 1-14).[38] In this reaction, it was crucial to keep the azido group intact during the generation of an alkyl radical. Aliphatic bromides, iodides, and thionocarbonates were able to serve as the precursors of alkyl radicals. Both tributyltin hydride (*n*-Bu_3SnH)/AIBN and tris(trimethylsilyl)silane [$(TMS)_3SiH$]/AIBN could be used as initiators. The latter has more generality, since azides were relatively inert toward tri(trimethylsilyl)silyl radical, but susceptible to tributyltin radical.



Scheme 1-14. Cyclizations of alkyl radicals onto azido group

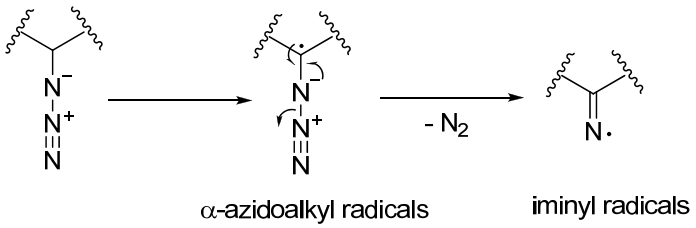
The dual ability of azides to serve as radical acceptors as well as radical precursors was successfully applied in the synthesis of aspidospermidine (Scheme 1-15).[39]



Scheme 1-15. Application to the synthesis of natural product

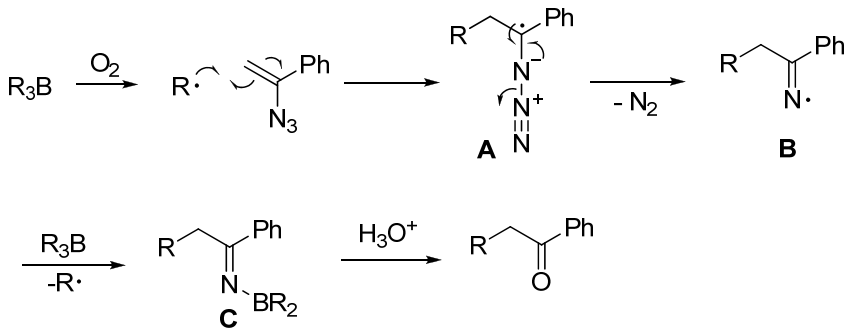
1.1.5.2 Formation of Iminyl Radicals

In contrast to the wide application of aminyl radicals in the synthesis of azaheterocycles, the utilization of iminyl radicals derived from organic azides has not been extensively explored. In general, organic azides acting as progenitors of iminyl radicals involves the generation of transient α-azidoalkyl radicals (a carbon radical adjacent to the azido function) and their fragmentation (Scheme 1-16).



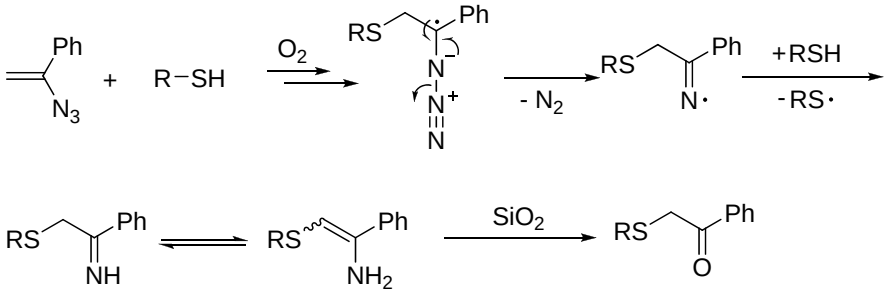
Scheme 1-16. Generation of iminyl radicals from organic azides

The first discussion of this type of iminyl radical formation was demonstrated by Roberts in 1983.[40] They studied the detailed mechanism of the reaction of α-azidostyrene with a trialkylborane to give imioborane **C**, which was hydrolyzed to ketone (Scheme 1-17). The radical chain process was initiated by the autoxidation of R_3B by molecular oxygen, affording a free alkyl radical. Addition of this alkyl radical to the C=C bond of α-azidostyrene gave α-azidoalkyl radical **A**, followed by instant fragmentation to give iminyl radical **B** with elimination of dinitrogen. The ESR spectroscopic studies have provided the evidence for the occurrence of this iminyl radical. The subsequent reaction of the iminyl radical with R_3B provided the iminoborane and alkyl radical for the next chain reaction.



Scheme 1-17. Reaction of R_3B and *α*-azidostyrene

Alternatively, the radical chain reaction of benzenethiols with *α*-azidostyrene took place in a similar pathway, yielding *β*-sulfanylated imines and enamines. Hydrolysis occurred in silica gel column chromatography, leading to ketones (Scheme 1-18).[41]



Scheme 1-18. Reaction of benzenethiols with *α*-azidostyrene

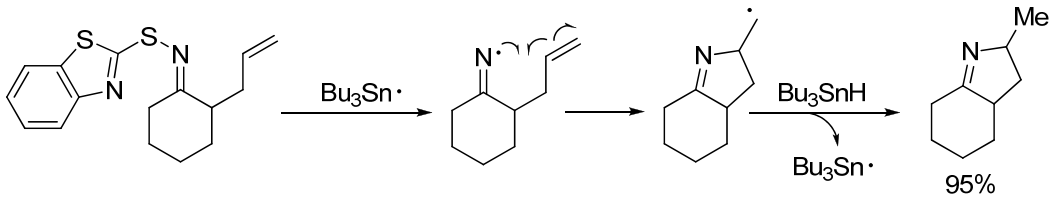
1.2 Chemistry of Iminyl Radicals

Iminyl radicals are promising species in the synthesis of azaheterocycles.[7] Although a range of routes for generating iminyl radicals have been documented, the current methods mainly focused on the homolytic cleavage of weak N–X bonds in *N*-substituted imine derivatives, such as N–S bond in sulfenimides,[42] N–N bond in hydrazones,[43] and N–O bond in *O*-substituted oximes.[7a] In addition, the intramolecular addition of carbon radicals to nitriles leading to iminyl radicals has been recently

reported.[44] Moreover, iminyl radicals are able to perform cyclization onto aromatic rings and unsaturated C–C bonds to afford azaheterocycles.[7]

1.2.1 Generation by Cleavage of N–S Bond of Sulfenimides

Zard reported a convenient method to give iminyl radicals based on the break of N–S bond in sulfenimides by stannyl radicals, making dihydropyrrole derivatives through the cyclization with intramolecular C=C bond (Scheme 1-19).[42]

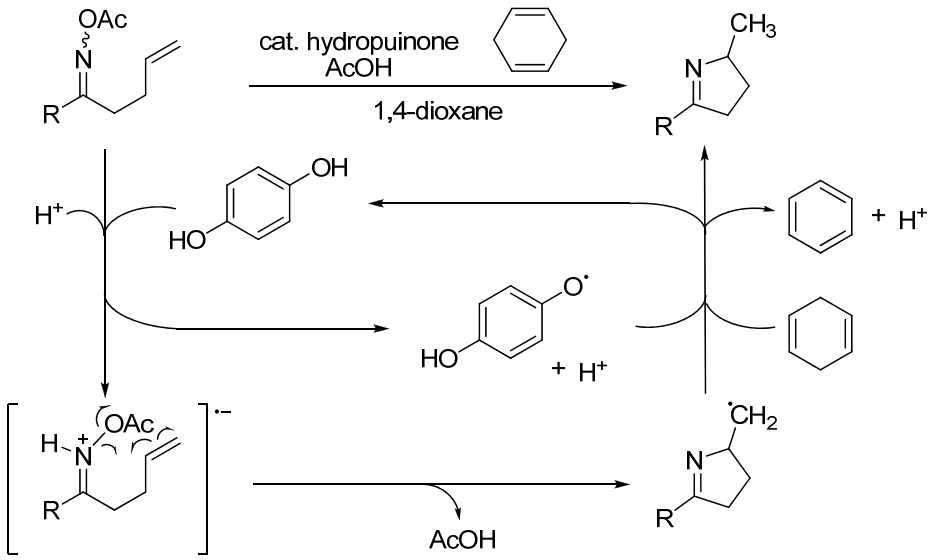


Scheme 1-19. Reaction of sulfenimides with stannyl radical

1.2.2 Generation by Cleavage of N–O Bond of Oxime Derivatives

As reported, oxime derivatives were found to be excellent sources of iminyl radicals. The homolytic cleavage of the weak N–O bond of *O*-substituted oximes has been mainly accomplished by means of stannyl radicals,[7a] electron transfer reductions,[8] and even thermolysis.[45]

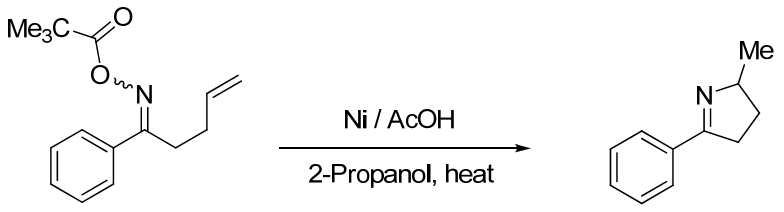
Narasaka has disclosed a catalytic method for the generation of iminyl radicals and/or their equivalents by one electron reduction of oximes. As shown in Scheme 1-20, treatment of γ,δ-unsaturated *O*-acetyloximes with acetic acid and a catalytic amount of hydroquinone led to the cyclization to dihydropyrroles.[46]



Scheme 1-20. One electron reduction of *O*-acetyloximes to give dihydropyrroles

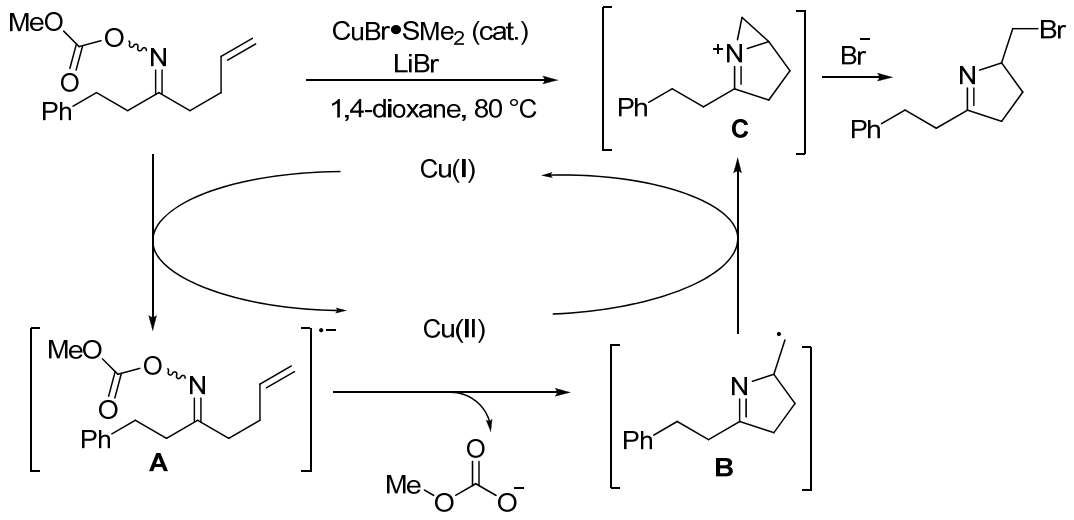
The reaction might be initated by one electron transfer from hydroquinone to the protonated *O*-acetyloximes. The resulting protonated anion radical cyclized to intramolecular C═C bond, affording a alkyl radical, followed by hydrogen abstraction from 1,4-cyclohexadiene to provide dihydropyrroles. The catalyst was regenerated by hydrogen abstraction of the resulting phenoxy radical from 1,4-cyclohexadiene.

Alternatively, low valent transition metal compounds can serve as efficient electron donors in this reaction system as well. For instance, Zard reported that treatment of *γ,δ*-unsaturated *O*-acetyloximes with nickel powder and acetic acid afforded dihyropyrroles (Scheme 1-21).[7a,47] In this reaction, however, large excess amounts of nickel powder were needed.



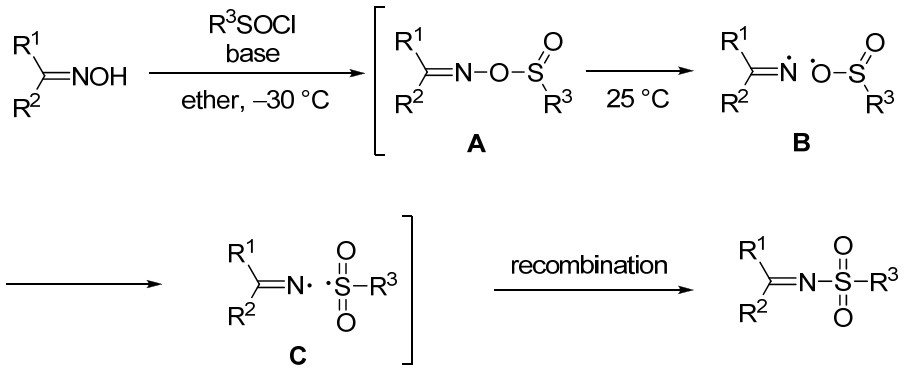
Scheme 1-21. Nickel metal as electron donor to O-substituted oximes

Narasaka investigated such transformation in a catalytic manner employing copper(I) complexes as redox catalysts.[48] When *γ*,*δ*-unsaturated *O*-(methoxy-carbonyl) oxime was treated with a catalytic amount of $CuBr{\cdot}SMe_2$ (5 mol %) with LiBr, a dihydropyrrole was obtained in high yield. An anion radcial (**A**) was supposed to be generated by electron transfer from copper(I) salt to oxime, releasing Cu(II) species. Cyclization of this anion radical with an intramolecular C=C bond proceeded to give alkyl radical **B**, which was immediately oxidized by the resulted Cu(II) species to **C** with the regeneration of Cu(I) catalyst. Iminium ion **C** was subsequently captured by lithium bromide to give the product (Scheme 1-22).



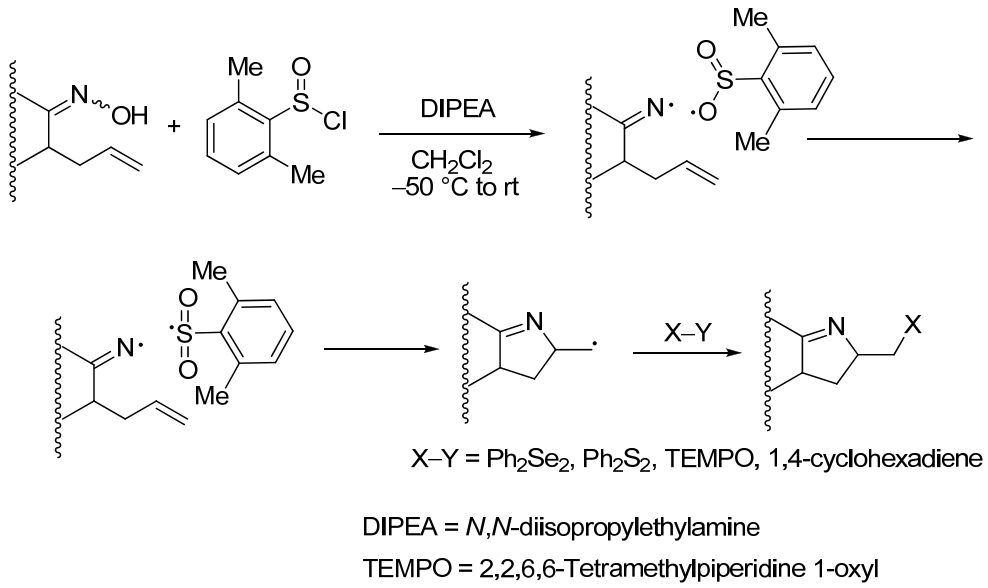
Scheme 1-22. $CuBr{\cdot}SMe_2$ as electron donor to *O*-substituted oximes

Hudson has described a method for the preparation of *N*-sulfonylimines from ketoximes and sulfinyl chlorides.[45a] This transformation proceeded via a homolytic fragmentation-recombination mechanism as shown in Scheme 1-23. Homolytic cleavage of the N–O bond of sulfinate esters **A** took place even at room temperature, leading to iminyl and sulfonyl radicals **C**. Recombination of these two species provided *N*-sulfonylimines.



Scheme 1-23. Hudson reaction

Weinreb then applied Hudson reaction to synthesize dihydropyrroles. In this case, the resulting iminyl radicals underwent intramolecular addition onto olefins, followed by capturing the resulted alkyl radicals affording dihydropyrroles (Scheme 1-24).[45b,c]

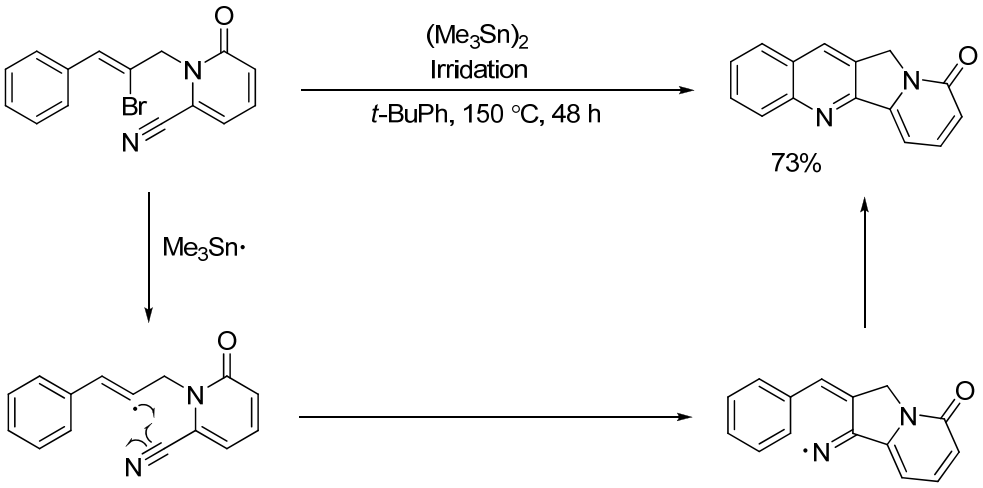


Scheme 1-24. Synthesis of dihydropyrroles by applying Hudson reaction

1.2.3 Generation of by Intramolecular Addition of Carbon Radicals to Nitriles

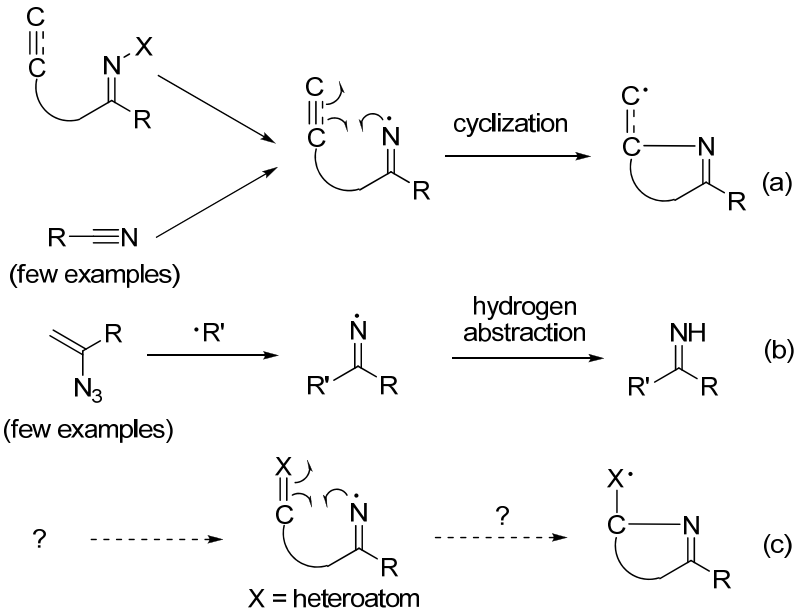
Recently, Bowman reported a new protocol for the generation of iminyl radicals arising by intramolecular cyclization of vinyl radicals onto cyano group[44] (Scheme 1-25).

The newly formed iminyl radical underwent cyclization onto arene rings, providing tetracyclic azaarenes.[49]



Scheme 1-25. Generation of iminyl radicals from nitriles

As described in Section 1.1.5.2 and this Section, although a number of methods are available for the generation of iminyl radicals, the sources of which particularly rely on the *N*-substituted imine derivatives (Scheme 1-26, Eq. a), and rarely come from nitriles (Eq. a) or vinyl azides (Eq. b). Moreover, the reactions of iminyl radicals merely concentrated on the cyclization to unsaturated C–C bonds (Eq. a) or hydrogen abstraction (Eq. b). However, the generation and reaction of iminyl radicals bearing other functional groups such as unsaturated carbon-heteroatom bonds have not been explored yet (Eq. c).

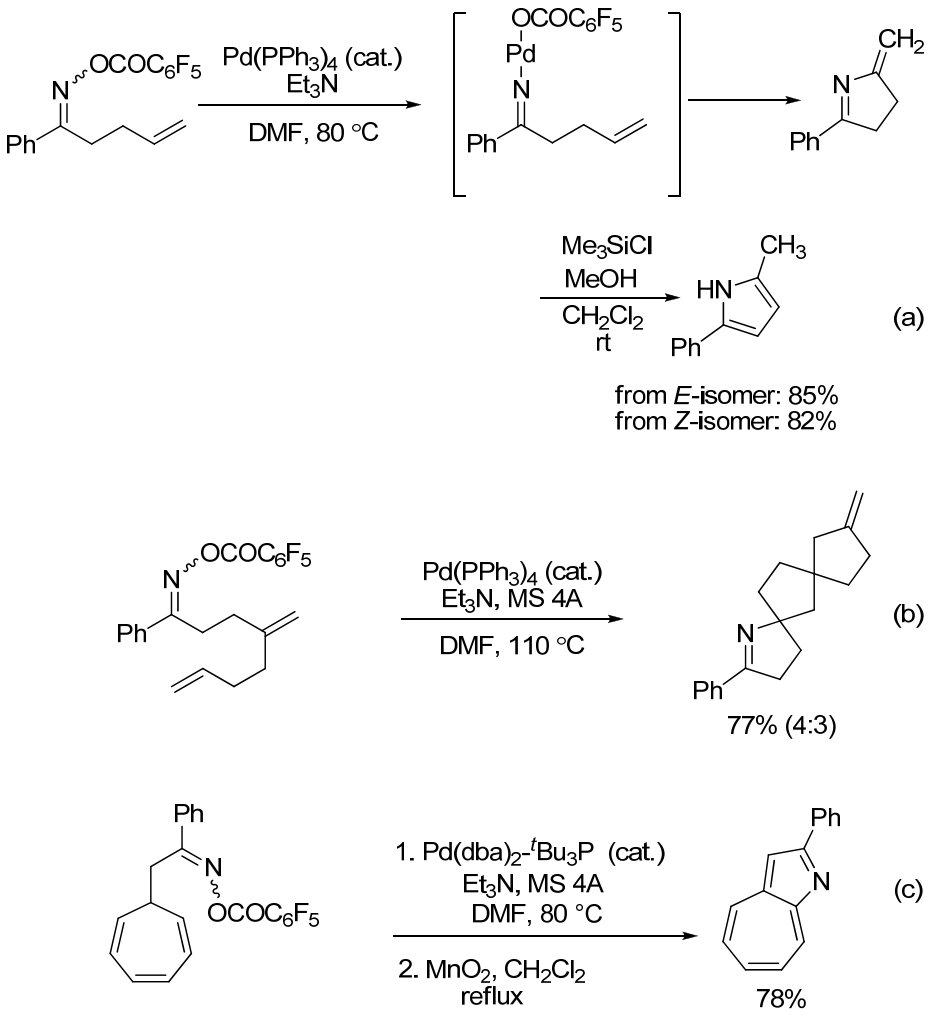


Scheme 1-26. Summary of generation and reactions of iminyl radicals

1.3 Chemistry of Iminyl-Metal Species

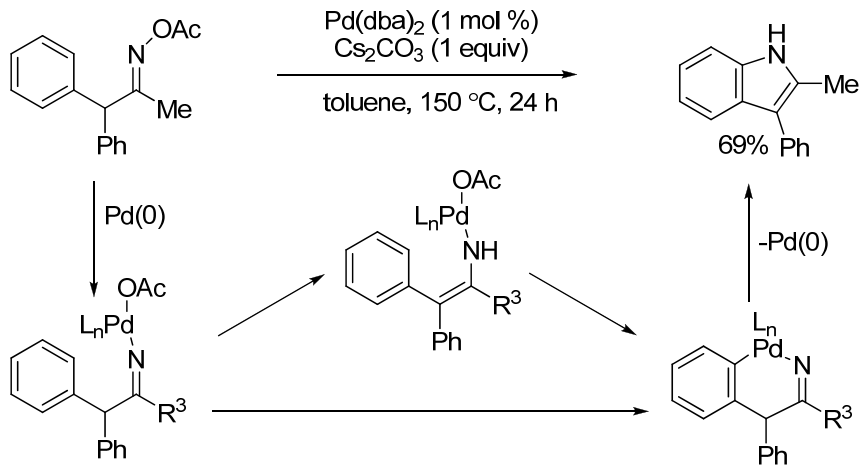
Although iminyl metal complexes represent a class of potential intermediates for the construction of azaheterocycles, examples are quite rare. An important reaction involving iminyl metal complex to deliver azaheterocycles is the amino-Heck reaction.

Narasaka demonstrated that oxidative addition of oxime derivatives to Pd(0) gave alkylideneaminopalladium species (iminyl-palladium species),[50] which successively performed cyclization onto intramolecular unsaturated C−C bonds to form a variety of azaheterocycles as shown in Scheme 1-27 (Eq. a-c).[51,52]



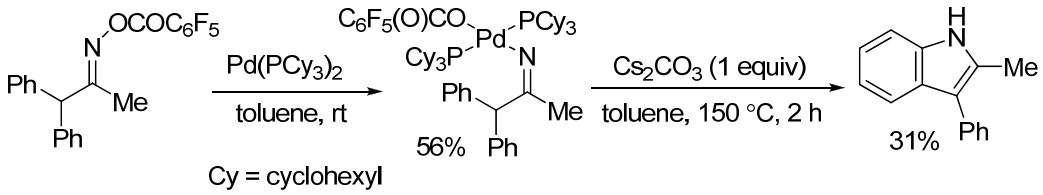
Scheme 1-27. Generation of iminyl-palladium species from oximes and their applications

Recently, Hartwig reported that such kind of iminyl-palladium complexes or their tautomers could be capable of performing intramolecular aromatic C–H amination to afford indoles as shown in Scheme 1-28.[53]



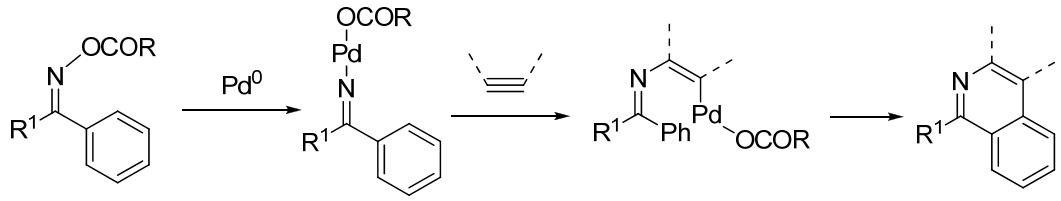
Scheme 1-28. Pd-catalyzed cyclization of oxime acetates

Notably, the iminyl-palladium complex (Scheme 1-29) has been isolated and characterized for the first time. This was the evidence for its intermediacy in these catalytic reactions.



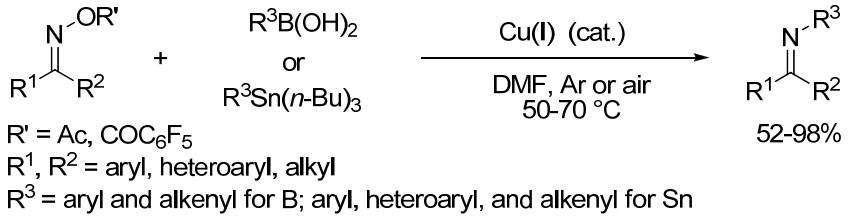
Scheme 1-29. The isolation and reaction of an iminyl-palladium complex

Intermolecular trapping of iminyl-palladium species was also achieved by the use of highly reactive electron-deficient benzyne intermediates as described in Scheme 1-30. The subsequent C–H functionalization could lead to azaheterocycles.[54]



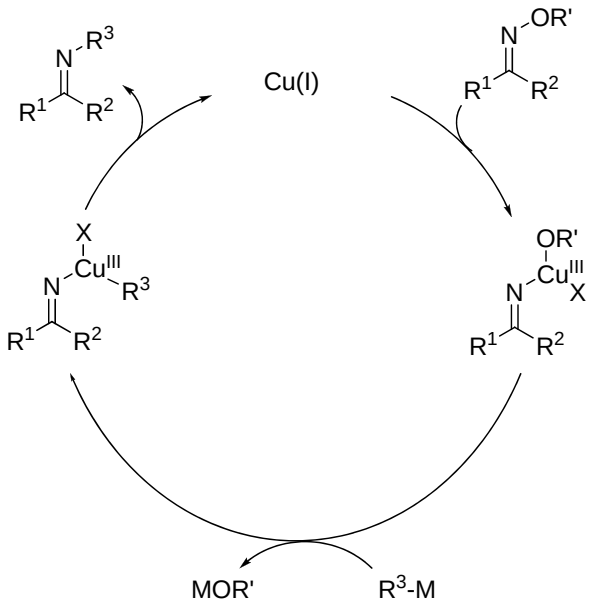
Scheme 1-30. Palladium-catalyzed reaction of acyloximes with arynes

Liebeskind recently reported a Cu(I)-catalyzed C–N cross coupling of boronic acids or organostannanes with oxime *O*-carboxylates, giving rise to *N*-substituted imines (Scheme 1-31).[55]



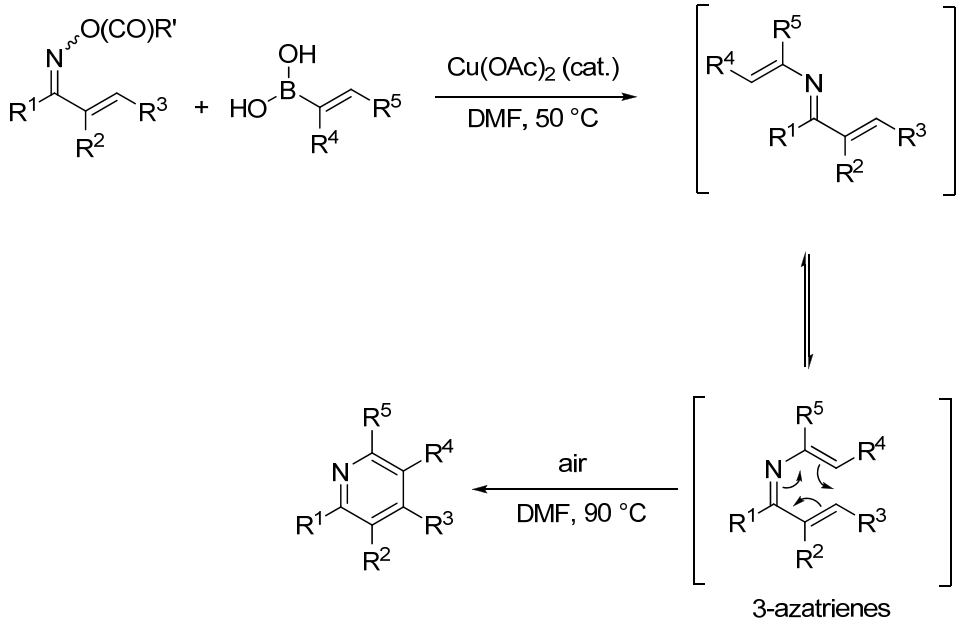
Scheme 1-31. Cu(I)-catalyzed cross coupling of boronic acids or organostannanes with oxime *O*-carboxylates

The possible reaction mechanism involved an oxidative addition of oxime *O*-carboxylates to Cu(I), leading to an iminyl-Cu(III) intermediate. This putative intermediate then underwent transmetallation with either boronic acids or organostannanes, followed by reductive elimination, producing the desired C–N bond and regenerating the active Cu(I) catalyst (Scheme 1-32).



Scheme 1-32. Possible mechanism for Cu(I)-catalyzed cross coupling

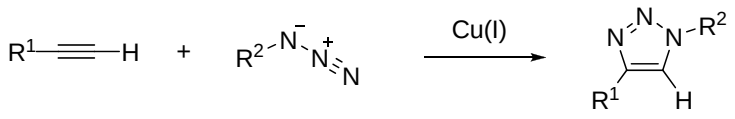
When *O*-acyloximes of α,β-unsaturated ketones were employed under these reaction conditions, 3-azatrienes were obtained. These useful intermediates then underwent eletrocyclization and suffered aerobic oxidation to provide substituted pyridines as depicted in Scheme 1-33.[56]



Scheme 1-33. Pyridine formation from oxime *O*-carboxylates and boronic acid

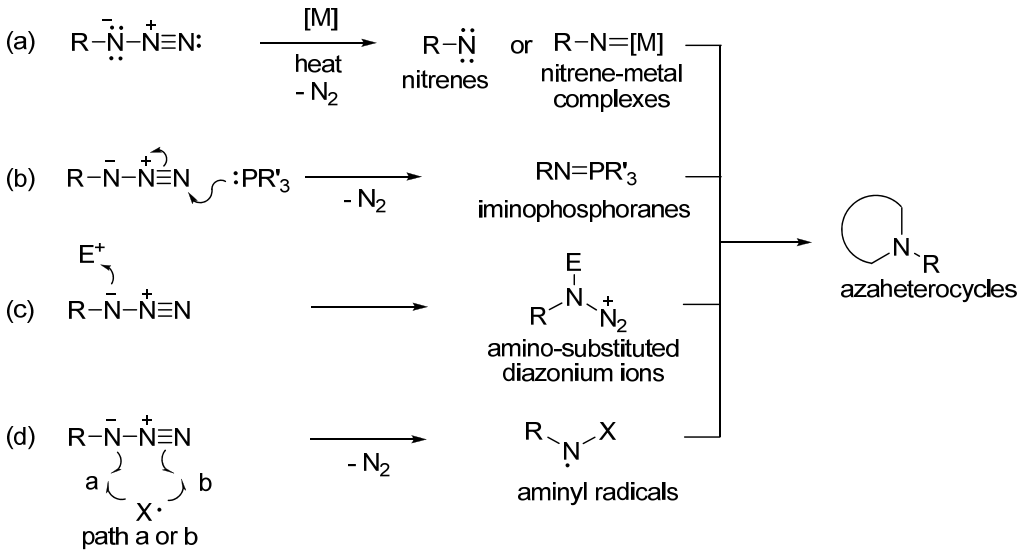
1.4 Perspective for the Thesis

The enormous utilization of organic azides for the synthesis of azaheterocycles has been discussed with many examples in Section 1.1. Evidently, organic azides have played a particularly important role in the 1,2,3-triazole formation (Scheme 1-34)



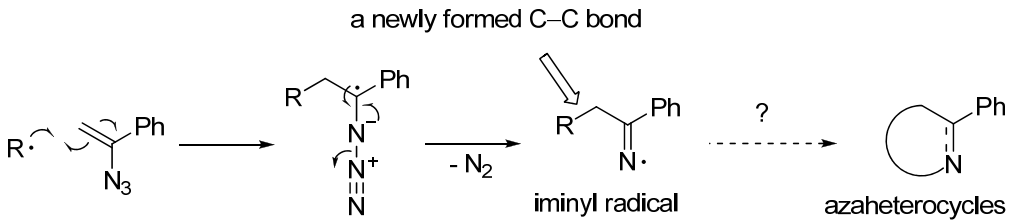
Scheme 1-34. Cu(I)-catalyzed triazole formation

Besides that, organic azides can react with a variety of reagents or reactive species (Scheme 1-35), such as nucleophiles (Eq. b), electrophiles (Eq. c) and radical species (Eq. d). In most cases, the reactions take place at the azido moiety (the terminal and/or internal nitrogen atoms), giving many useful nitrogen-containing chemical species such as nitrenes (Eq. a), iminophosphoranes (Eq. b), amino-substituted diazonium ions (Eq. c), aminyl radicals (Eq. d) and so on. These species subsequently undergo further transformations to construct azaheterocycles.



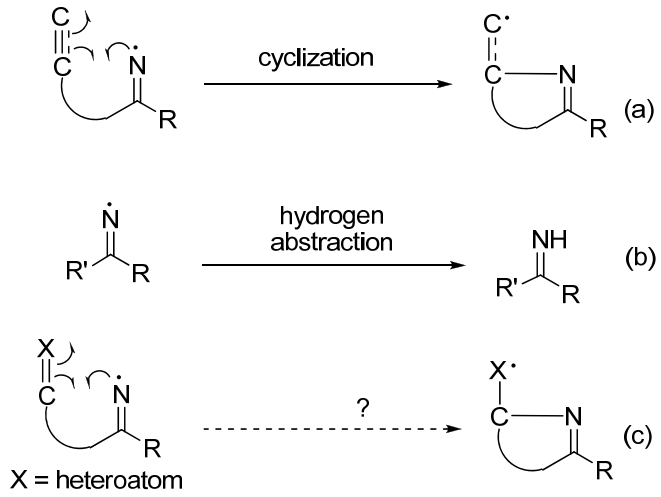
Scheme 1-35. Summary of reactions of organic azides

However, only a few examples refer to the generation of iminyl radicals from vinyl azides as mentioned in Section 1.1.5.2. It is noteworthy that the generation of iminyl radicals from vinyl azides involves the addition of alkyl radicals to the C=C bond of vinyl azides, rather than the azido motif, followed by the fragmentation of the resulting *α*-azidoalkyl radicals (Scheme 1-36). As a result, both a new C–C bond and iminyl radicals are simultaneously formed in this reaction process. Such a process may afford a potential synthetic route to form azaheterocycles if the transient iminyl radicals can be trapped by an intramolecular functional group.



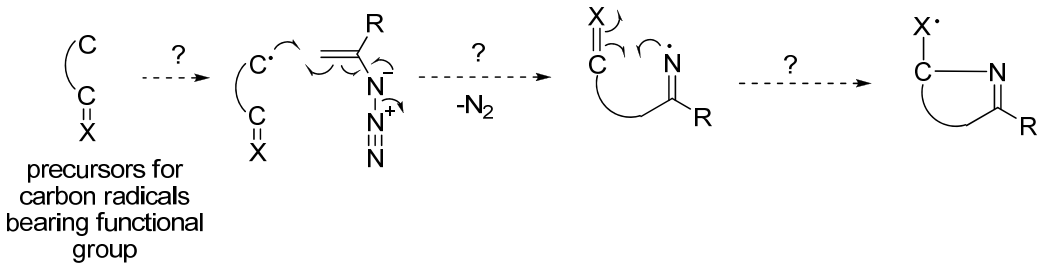
Scheme 1-36. Generation of iminyl radicals from vinyl azides

In fact, as described in Section 1.2, some reactions of iminyl radicals have been developed, but merely focusing on the cyclization onto unsaturated C–C bonds (Scheme 1-37, Eq. a) and hydrogen abstraction (Eq. b). The reactivity of iminyl radicals toward other functional groups such as unsaturated carbon-heteroatom bonds has not been explored (Eq.c).



Scheme 1-37. Reactions of iminyl radicals

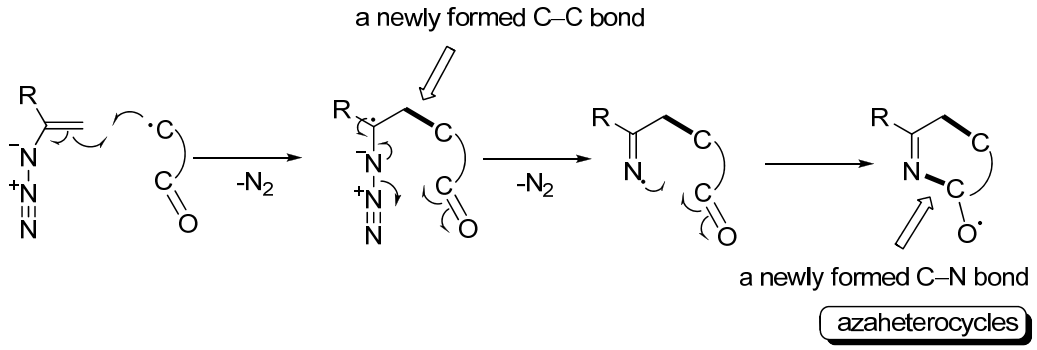
The reaction pathway to generate iminyl radicals from vinyl azides mentioned above may also provide an opportunity to find the unexplored reactivity of iminyl radicals by introducing particular functional groups at the proper position in the starting components (Scheme 1-38).



Scheme 1-38. Probe unexplored reactivity of iminyl radicals derived from vinyl azides

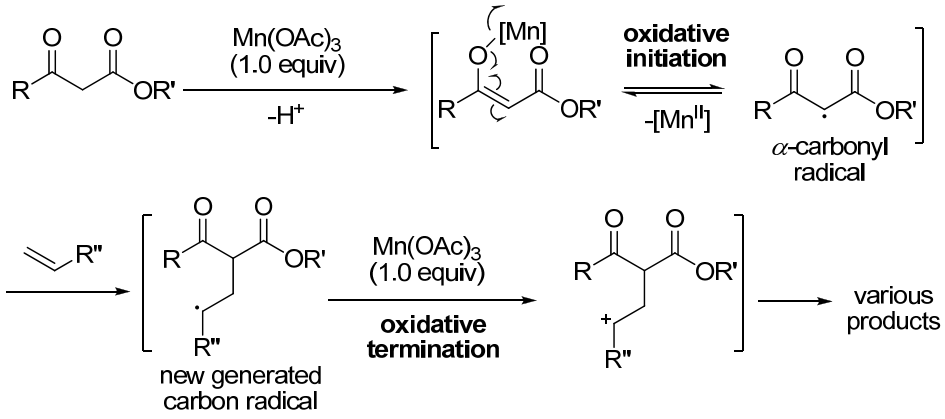
Furthermore, a variety of vinyl azides could be readily prepared by several known methods, and thus they have significant advantages in the synthesis of azaheterocycles. On the basis of these backgrounds, the author decided to develop versatile and efficient methods to synthesize azaheterocycles by utilizing vinyl azides as nitrogen sources, where iminyl radicals are involved as key intermediates.

The outline of the designed reactions is depicted in Scheme 1-39. Addition of a carbon radical which possesses an intramolecular carbonyl group to the C═C bond of a vinyl azide provides a new C–C bond with the generation of an iminyl radical. This resulting iminyl radical then intramolecularly forms a C–N bond by the cyclization with a carbonyl group, furnishing an azaheterocycle.

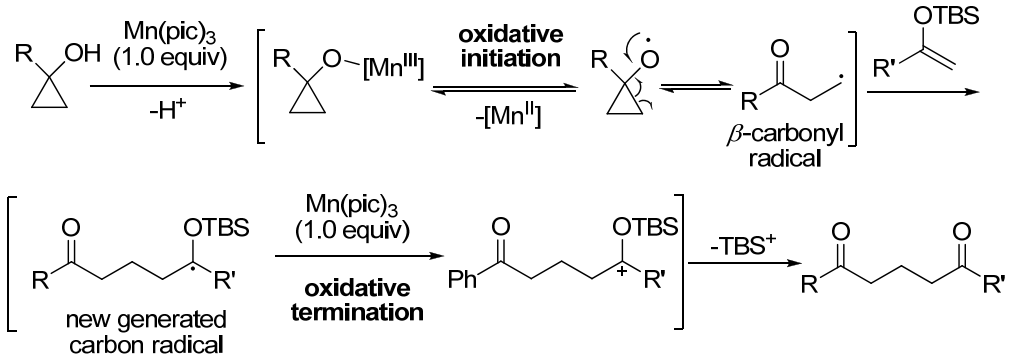


Scheme 1-39. Designed synthetic route for azaheterocycles from vinyl azides

The choice of precursors of carbon radical species is also crucial in this concept. It has been reported that oxidation of 1,3-dicarbonyl compounds (Scheme 1-40)[57] or cyclopropanols (Scheme 1-41)[58] by Mn(III) complexes can generate α- or β-carbonyl radicals, respectively. Furthermore, these two kinds of radical species can undergo addition to alkenes to form new C–C bonds with the simultaneous generation of new carbon radicals.[57,58] The subsequent oxidation of these resulted carbon radicals by Mn(III) complexes followed by further transformations leads to various kinds of products such as 1,5-diketones (Scheme 1-41). It should be noted that both initiation and termination steps of these two radical chain reactions are oxidative processes, which inevitably results in the consumption of stoichiometic amount of Mn(III) complexes.

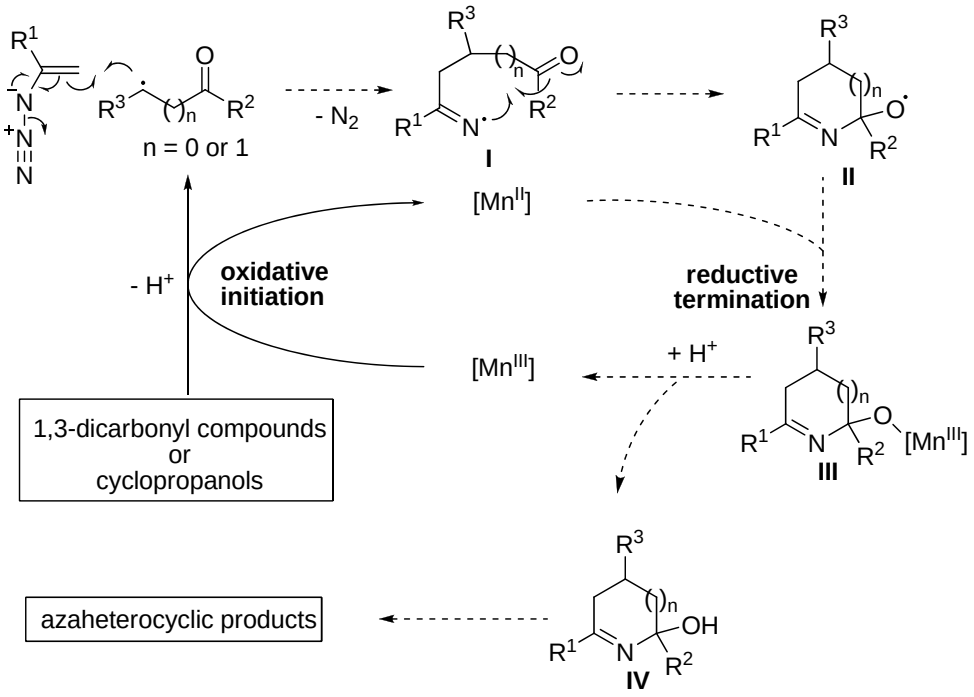


Scheme 1-40. The generation and reaction of α-carbonyl radicals from 1,3-dicarbonyl compounds



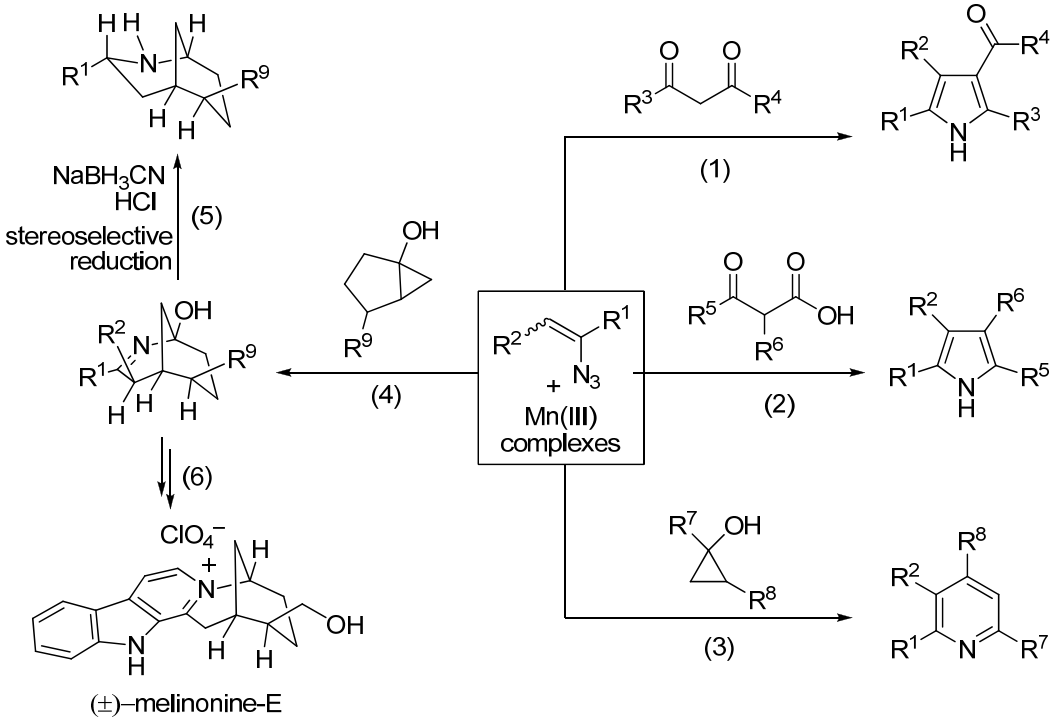
Scheme 1-41. The generation and reaction of β-carbonyl radicals from cyclopropanols

Inspired by these results, it is envisioned that 1,3-dicarbonyl compounds and cyclopropanols can be utilized as the sources of carbon radicals for the synthesis of azaheterocycles following the pathway as shown in Scheme 1-42. The reactions may be initiated by the oxidation of 1,3-dicarbonyl compounds or cyclopropanols by Mn(III) complexes to generate α- or β-carbonyl radicals and Mn(II) species. Addition of the resulting carbon radical species to the C═C bond of vinyl azides affords iminyl radicals **I**, cyclization of which with intramolecular carbonyl group may provide alkoxy radicals **II** with the construction of azaheterocyclic frameworks. At this moment, the termination of the radical chain process may be the reduction of the alkoxy radicals **II** by the previously formed Mn(II) species to Mn(III) alkoxides **III**, from which the active Mn(III) species is possible to be regenerated after protonation. Thus, this oxidative initiation and reductive termination fashion may promote this synthetic method to be conducted in a catalytic manner. Finally, a variety of azaheterocyclic compounds are expected be formed from intermediates **IV**.



Scheme 1-42. Synthetic plan for azaheterocycles from Mn(III)-catalyzed reactions of vinyl azides and 1,3-dicarbonyl compounds or cyclopropanols

According to the aforementioned plan, the author has studied the Mn(III)-mediated reactions of vinyl azides and 1,3-dicarbonyl compounds or cyclopropanols (Scheme 1-43). As a result, a series of azaheterocycles including pyrroles (Scheme 1-43, Eqs. 1 and 2), pyridines (Eq. 3), and azabicyclic compounds (Eq 4) have been successfully prepared. Furthermore, an efficient synthesis of (±)-melinonine-E (Eq. 6) has also been achieved by using an azabicyclic compound as the key intermediate. These results are explained in details in the following chapters.



Scheme 1-43. Synthesis of azaheterocycles from vinyl azides

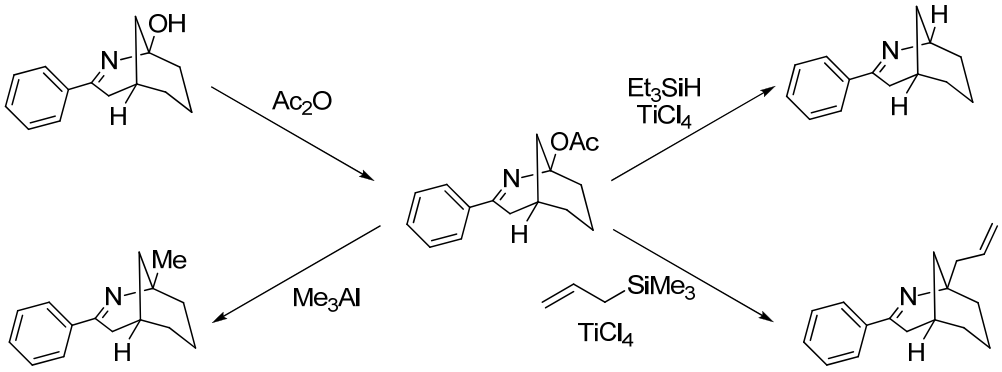
In chapter 2, the author introduces preparation methods of vinyl azides in terms of reaction conditions and generalities.

Chapter 3 focuses on the synthesis of a wide range of polysubstituted *N*–H pyrroles from various vinyl azides and 1,3-dicarbonyl compounds by using Mn(III)

complexes as catalysts. *β*-Keto esters and 1,3-diketones (Scheme 1-43, Eq. 1) as well as *β*-keto acids (Eq. 2) are employed for this pyrrole synthesis.

Chapter 4 describes the use of monocyclic cyclopropanols as precursors of *β*-carbonyl radicals and the investigation of their additions toward vinyl azides. The reaction provides an efficient synthesis of polysubstituted pyridines (Scheme 1-43, Eq. 3).

In chapter 5, the author broadens a scope of the reaction described in chapter 4 by utilizing bicyclo[3.1.0]hexan-1-ols as the sources of *β*-carbonyl radicals. In this case, 2-azabicyclo[3.3.1]non-2-en-1-ol derivatives are obtained (Scheme 1-43, Eq. 4). Notably, stereoselective reduction of the C═N and bridgehead C−OH bonds of these azabicyclic compounds leads to *endo*-selective (refer to R^1) 2-azabicyclo[3.3.1]nonane (morphan) derivatives. Moreover, versatile transformations of 2-azabicyclo[3.3.1]non-2-en-1-yl acetate to 2-azabicyclo[3.3.1]non-2-enes have been developed as well (Scheme 1-44).



Scheme 1-44. Transformations of 2-azabicyclo[3.3.1]non-2-en-1-yl acetates

Eventually, a concise synthesis of (±)-melinonine-E (Scheme 1-43, Eq. 6), a quaternary indole alkaloid, is accomplished by applying the methods developed in this chapter.

1.5 References and Notes

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(2) Mooney, S.; Leuendorf, J. E.; Hendrickson, C.; Hellmann, H. *Molecules* **2009**, *14*, 329.

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Chapter 2 Synthesis of Vinyl Azides

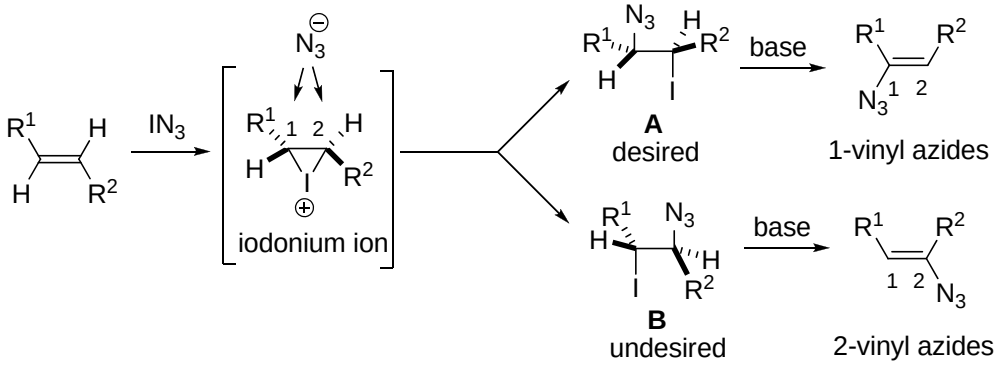
As described in Chapter 1, Section 1.4, the author has proposed a synthetic route to access azaheterocycles by utilizing vinyl azides as a nitrogen source, in which iminyl radicals are involved as key intermediates. Because vinyl azides are the most essential components for the synthesis of azaheterocycles in this thesis, it is necessary to introduce their preparation prior to the discussion of their applications.

In fact, a variety of vinyl azides can be readily prepared from simple starting materials by many known methods. However, the author found that the scope and limitation of some methods have not been clarified, especially for regioselective synthesis of vinyl azides. Therefore, some problems such as difficult separation of regioisomers and low yields of products would arise if improper methods were used. In this chapter, the author summarizes the synthetic methods of vinyl azides in terms of reaction conditions and generalities,[1] in order to provide a guide for the choice of the proper method to prepare the desired vinyl azides.

In general, vinyl azides have been prepared by three methods: 1) iodoazidation of electron-rich aryl substituted alkenes as well as alkyl substituted ones by using IN_3, followed by base treatment to induce elimination of HI (method A); 2) dibromination of electron-deficient alkenes followed by treatment with NaN_3 (method B); 3) condensation of aromatic aldehydes with azidoacetates (method C). Besides these, some other approaches to synthesize vinyl azides with installation of special substituents have also been utilized.

2.1 Iodoazidation of Electron-Rich Aryl or Alkyl Substituted Alkenes with Iodine Azide Followed by Base Treatment (Method A)

This synthetic method was based upon the iodoazidation of alkenes using IN_3, followed by treatment with base to induce elimination of HI, giving vinyl azides as shown in Scheme 2-1.[2] Normally, IN_3 was prepared *in situ* from the reaction of ICl and NaN_3. The base used in the elimination step included potassium *tert*-butoxide or DBU (1,8-diazabicyclo[5.4.0]undec-7-ene). The iodoazidation reaction involved the intermediacy of a three-membered ring iodonium ion, which would led to a regioisomeric mixture of iodoazides **A** (the desired one for this thesis) and **B** (the undesired one for this thesis) by *trans*-addition of the azido ion at C1 and C2, respectively.[3] The subsequent treatment with a base induced *anti*-elimination of HI, affording the corresponding 1- and 2-vinyl azides, respectively.



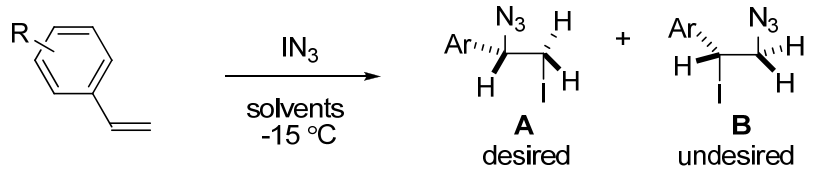
(R^1, R^2 = aryl, alkyl, or H and R^1 is more electron rich than R^2)

Scheme 2-1. Synthetic pathway of method A for the synthesis of vinyl azides

In most cases, it was difficult to separate the regioisomeric iodoazide adducts as well as 1- and 2-vinyl azides. Taking into account for the synthetic efficiency and the operational

simplification, the regiospecific synthesis of the desired regioisomer was highly needed. However, by using the original procedure (CH_3CN as a solvent),[2] an excellent regioselectivity was obtained only in the case of electron-rich styrenes such as 4-methoxystyrene (**A**:**B** > 99:1, Table 2-1, entry 1), while the employment of styrene and electron-deficient styrene derivatives always afforded a regioisomeric mixture (entries 2-3). Especially, the undesired adducts **B** were predominately formed from 4-bromostyrene (entry 3).

Table 2-1. Regioselectivities of reactions of styrenes and IN_3



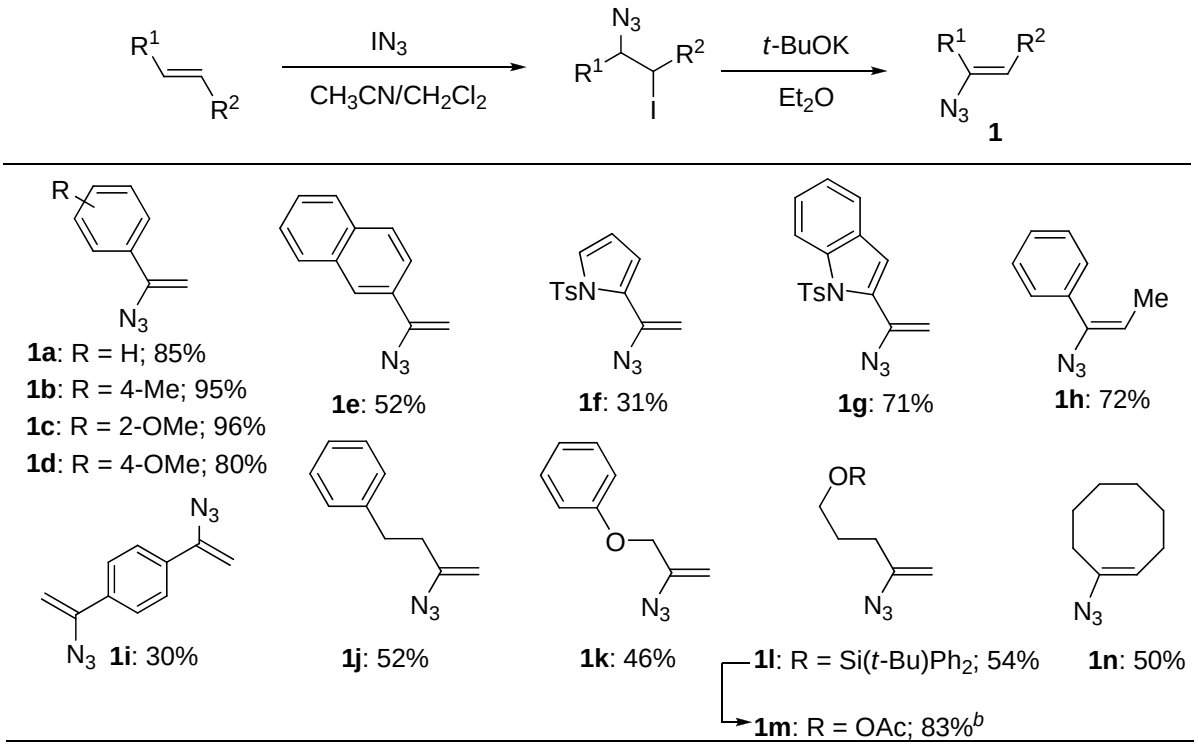
entry	R	solvents	**A**:**B**[a]
1	4-OMe	CH_3CN	> 99:1
2	H	CH_3CN	6:1
3	4-Br	CH_3CN	1:3
4	H	CH_3CN–CH_2Cl_2 (1:3)	> 99:1
5	4-Br	CH_3CN–CH_2Cl_2 (1:3)	97:3

[a] The ratio was determined by ^1H NMR.

Fortunately, it was found that the regioselectivity of the iodoazidation of styrenes was dramatically improved by using CH_2Cl_2 as a co-solvent[4] (entries 4 and 5). For instance, the reaction of styrene by using CH_3CN–CH_2Cl_2 system produced the iodoazide **A** exclusively (**A**:**B** > 99:1, entry 4). Furthermore, the desired adduct **A** was also afforded from 4-bromostyrene in high regioselectivity (**A**:**B** = 97:3) by applying such system (entry 5), but the resulted iodoazide **A** and even the subsequently formed 1-vinyl azide were still difficult to

separate from their regioisomers by silica gel column chromatography. Gratifyingly, the regioselective synthesis of the desired 1-vinyl azides from styrenes bearing electron-withdrawing groups could be readily achieved by applying Method B discussed in the next section.

Table 2-2. Synthesis of vinyl azides by method A[a]



[a] Isolated yields were noted above. [b] Vinyl azide **1m** was prepared in 83% yield from vinyl azide **1l** through the following two steps: 1) *n*-Bu_4NF, THF; 2) Ac_2O, DMAP(cat.), pyridine.

As depicted in Table 2-2, a range of electron-rich 1-aryl alkenes were converted to the corresponding vinyl azides (**1a-e**) in moderate to good yields. Especially, α-heteroaryl vinyl azides (**1f**, **1g**) were successfully prepared as well. Notably, iodoazidation of *trans*-β-methylstyrene proceeded to provide the desired iodoazide adduct in excellent regioselectivity (**A**:**B** = 94:6) in the CH_3CN–CH_2Cl_2 system. After separation of the two regioisomers by

silica gel column chromatography (in this case, it was not difficult), *anti*-elimination of HI by the treatment of potassium *tert*-butoxide gave vinyl azide **1h** as a single regioisomer. Moreover, bis(*α*-azidovinyl)benzene (**1i**) was also prepared in 30% yield.

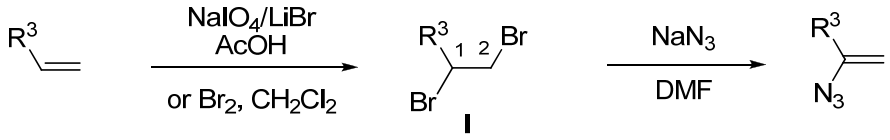
Besides *α*-aryl vinyl azides, a variety of *α*-alkyl vinyl azides (**1j-l**) were also produced in good yields from alkyl substituted alkenes. It was noteworthy that only a single regioisomer (the desired one) was also obtained in the iodoazidation reaction by applying the CH_3CN–CH_2Cl_2 system. Some functional groups such as alkoxy (**1k**) and silyloxy (**1l**) were tolerated in the reaction conditions. In addition, cyclic vinyl azide **1n** was also synthesized.

Additionally, vinyl azide **1l** was further transformed to vinyl azide **1m** in 83% yield through desilylation-acetylation sequence.

As described above, this method was suitable for the synthesis of vinyl azides from electron-rich aryl substituted and alkyl substituted alkenes.

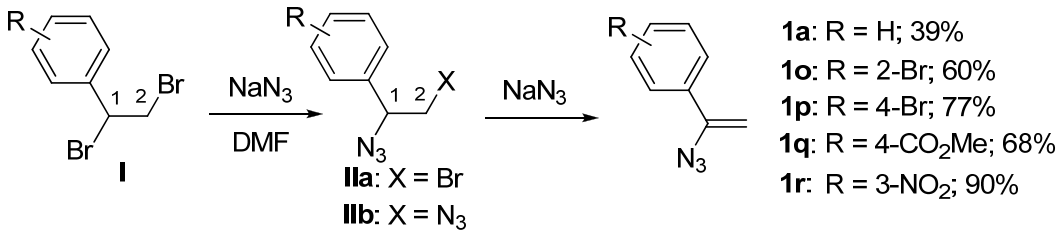
2.2 Dibromination of Electron-Deficient Alkenes and Subsequent Treatment with Sodium Azide (Method B)

This synthetic route started by a dibromination of electron-deficient alkenes to give dibromides **I** followed by treatment with NaN_3, affording vinyl azides (Scheme 2-2).



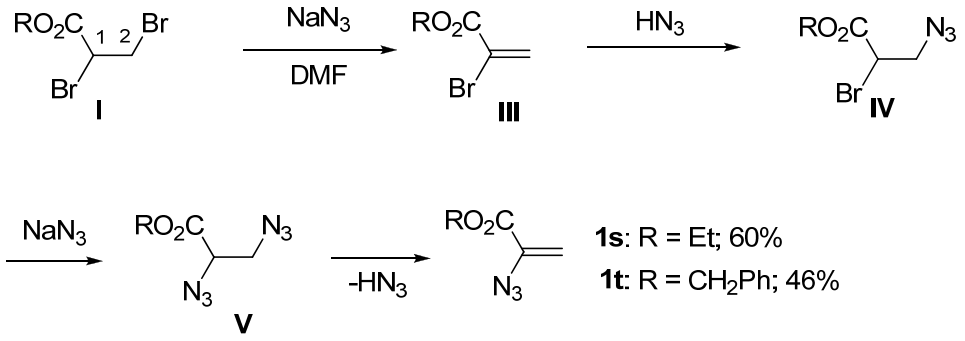
Scheme 2-2. Synthetic pathway of method B for the synthesis of vinyl azides

The reaction process for the formation of vinyl azides from dibromides **I** was varied by changing the substituent R^3. When R^3 were aryl groups (Scheme 2-3), either bromoazides **IIa** or diazides **IIb** were presumably formed in the presence of NaN_3, followed by *anti*-elimination of HBr or HN_3 affording *α*-aryl vinyl azides.[5] It was found that the presence of an electron-withdrawing group on the phenyl ring, which could make the protons on C1 more acidic than those on C2, was beneficial for this transformation. For example, *α*-aryl vinyl azides (**1o-r**) with the phenyl group bearing an electron-withdrawing group were prepared in good yields, whereas vinyl azide **1a** was only isolated in 39% yield.



Scheme 2-3. Synthesis of vinyl azides from styrenes by method B

When R^3 were alkoxycarbonyl groups (CO_2R), the formation of vinyl azides involved a different pathway (Scheme 2-4). Kondo[6] proposed that *anti*-elimination of HBr from dibromides **I** was promoted by NaN_3 to give 2-bromoacrylate **III**, to which conjugative addition of azide ion took place to afford bromoazides **IV**. The subsequent substitution of the remaining bromine atom by azide occurred to provide diazides **V**, from which HN_3 eliminated through *anti*-manner to produce vinyl azides. By applying this method, some *α*-alkoxycarbonyl vinyl azides (**1s** and **1t**) were synthesized.

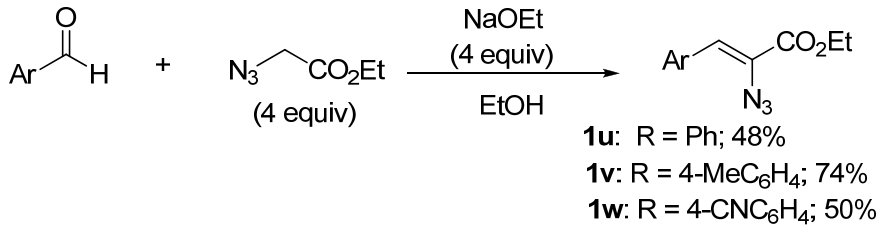


Scheme 2-4. Synthesis of vinyl azides from acrylates by method B

Obviously, this method was a preference for the employment of electron-deficient alkenes including styrenes bearing electron-withdrawing groups as well as acrylates.

2.3 Condensation of Aromatic Aldehydes and Ethyl Azidoacetate in the Presence of Sodium Ethoxide (Method C)

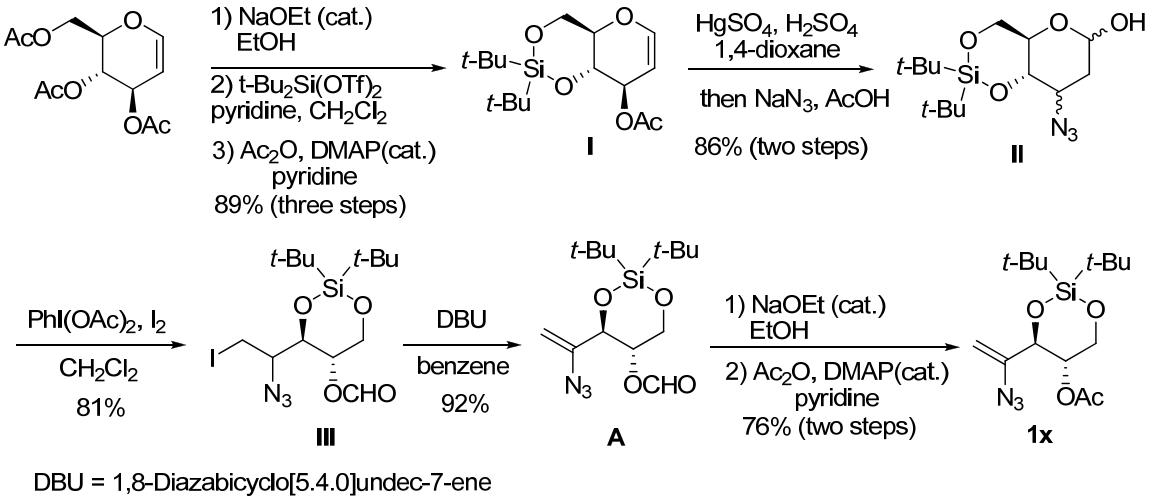
This method consisted of a dehydrative condensation of aromatic aldehydes and ethyl azidoacetate in the presence of sodium ethoxide (Scheme 2-5).[7] Such method worked well for the synthesis of *α*-ethoxycarbonyl-*β*-aryl vinyl azides from aromatic aldehydes, while alkyl aldehydes could not be employed. Vinyl azides **1u-w** were prepared by this method in moderate to good yields.



Scheme 2-5. Synthesis of vinyl azides from aromatic aldehydes with ethyl azidoacetate

2.4 Other Methods

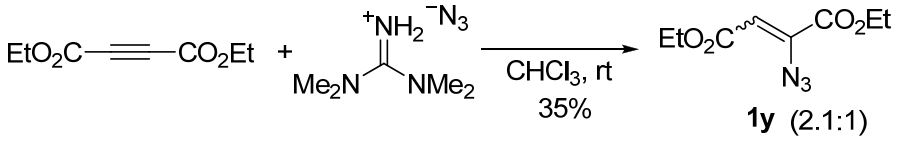
Other methods to prepare vinyl azides with the incorporation of special substituents have been reported. For example, the synthesis of vinyl azide **A** bearing a polyol unit was based on the iodobenzene diacetate mediated radical fragmentation reaction of 3-azido-2,3-dideoxy-hexopyranose **II**, which could be prepared by the acid-catalyzed reaction of glucal derivative **I** with NaN_3[8] (Scheme 2-6). In the presence of iodine, the radical fragmentation of **II** led to β-iodo azide **III**, which then underwent elimination of HI by the treatment with DBU to afford vinyl azide **A**.[9] This vinyl azide was then converted to vinyl azide **1x** through two steps reactions including base-catalyzed hydrolysis of the formyl ester moiety and then acetylation of the resulted free hydroxyl group.



Scheme 2-6. Synthesis of vinyl azide **1x**

Another synthetic route for the preparation of α-alkoxycarbonyl vinyl azides referred to the conjugative addition of tetramethylguanidinium azide to electron-deficient alkynes.[10]

Vinyl azide **1y** was synthesized by this method from diethyl acetylenedicarboxylate as shown in Scheme 2-7.



Scheme 2-7. Synthesis of vinyl azide **1y**

2.5 References and Notes

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(4) For a previous report on the iodoazidation of alkenes by using CH_3CN–CH_2Cl_2 system, see: Salunkhe, A. M.; Ramachandran, P. V.; Brown, H. C. *Tetrahedron Lett.* **1999**, *40*, 1433.

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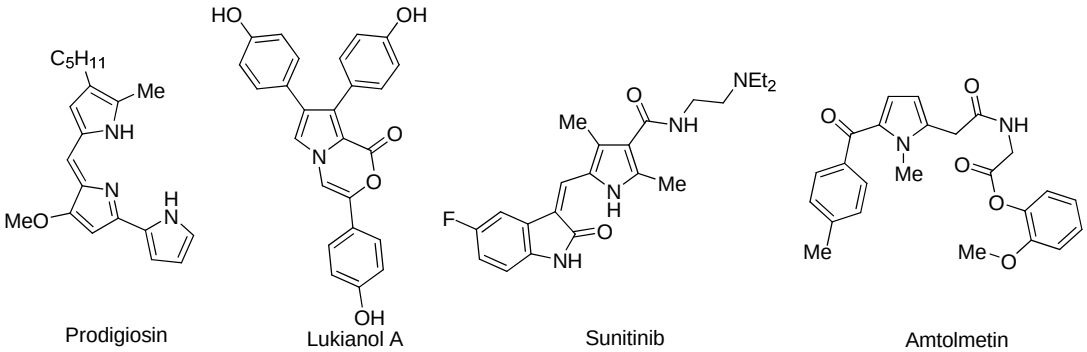
Chapter 3 Mn(III)-Catalyzed Synthesis of Pyrroles from Vinyl Azides and 1,3-Dicarbonyl Compounds

3.1 Introduction

Pyrroles are one of the most prevalent heterocyclic compounds, being present as basic cores in a tremendous range of natural products, [1] potent pharmaceutical compounds,[2] and various kinds of functional materials.[3] For instance, the natural products of the prodigiosin family consist of three pyrrole rings, in which two of them are coupled in a tandem array (Figure 3-1, **a**).[1b,4] These compounds exhibit a broad range of activity against bacteria, protozoa, and pathogenic fungi. In addition, many highly substituted pyrrole isolated from natural sources have important biological activities. For example, lukianol A (Figure 3-1, **b**) displays some activities against a cell line derived from human epiderrnatoid carcinoma.[5] Moreover, many pharmaceutical agents such as anti-cancer drug sunitinib (Figure 3-1, **c**)[6] and anti-inflammatory agent amtolmetin (Figure 3-1, **d**)[7] also contain the pyrrole motif.

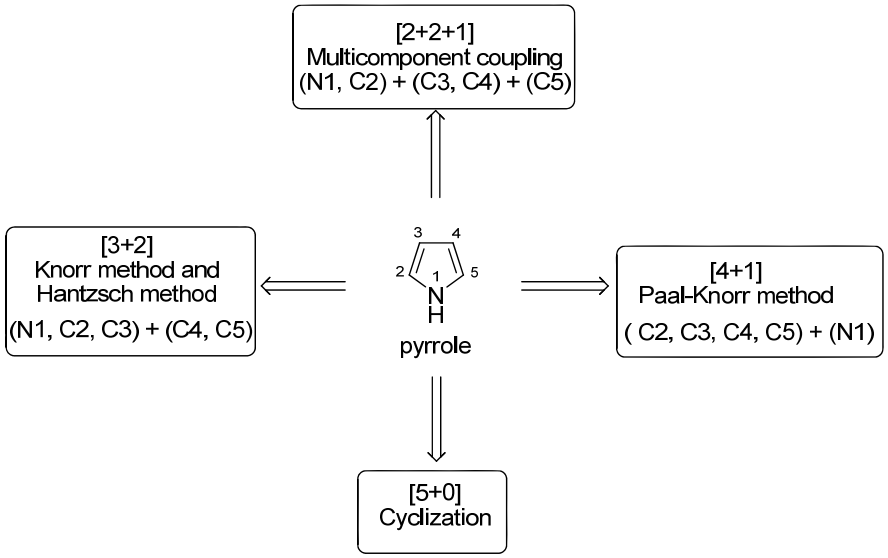
Figure 3-1. Examples of pyrrole-containing natural products and pharmaceuticals



Prodigiosin (**a**) Lukianol A (**b**) Sunitinib (**c**) Amtolmetin (**d**)

Due to the broad utility of pyrroles, a wide variety of synthetic approaches to construct pyrrole ring system have been explored (Figure 3-2).[8] Based on the retrosythetic cleavage of the pyrrole ring, these processes can be classified as [3+2] (Knorr and Hantzsch methods), [4+1] (Paal-Knorr method), [5+0] (cyclization methods), and [2+2+1] (multicomponent coupling reactions).

Figure 3-2. Various methods for the retrosynthetic cleavage of a pyrrole ring

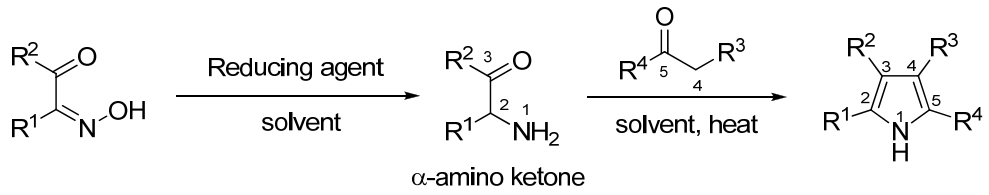


3.1.1 Classical Methods for Synthesis of Pyrroles

Generally, classical methods of constructing the pyrrole ring system include Knorr, Paal-Knorr, and Hantzsch pyrrole syntheses.[8a]

The Knorr method[9,10,11] has found a multitude of applications in the synthesis of pyrrole derivatives. As shown in Scheme 3-1, this method consists of the condensation of an α-amino ketone with an active methylene compound (R^3 = electron withdrawing

group). Since the starting α-amino ketone is quite labile and tends to undergo self-condensation, it is frequently prepared *in situ* by the reduction of α-oximino ketone.

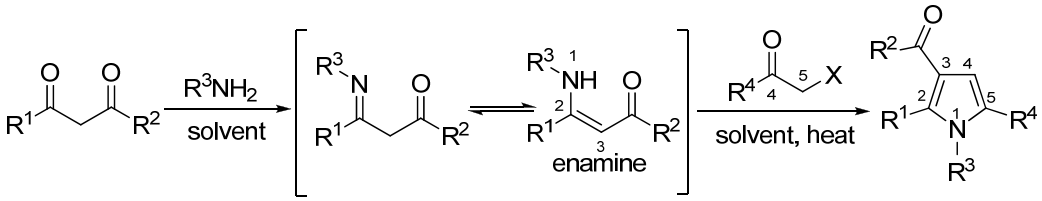


R^1 = H, aryl, CO_2R; R^2 = alkyl, aryl; R^3 = electron withdrawing group (EWG) = COR, CO_2R, CN, SO_2R; R^4 = H, alkyl, aryl, CO_2R

Scheme 3-1. Knorr pyrrole synthesis

From the viewpoint of ring disconnection, three atoms (N1, C2, and C3) in a pyrrole ring come from α-amino ketone components, whereas the other two carbon units (C4 and C5) originate from active methylene compounds. So this reaction is also considered a formal [3+2] annulation.

A similar type of annulation is the Hantzsch pyrrole synthesis.[12,13,14] As illustrated in Scheme 3-2, treatment of a 1,3-dicarbonyl compound with ammonia or a primary amine leads to an enamine, which provides three successive atoms (N1, C2, and C3) in the pyrrole skeleton. Condensation of this enamine with an α-halo ketone (contributes C4 and C5) then forms a substituted pyrrole.

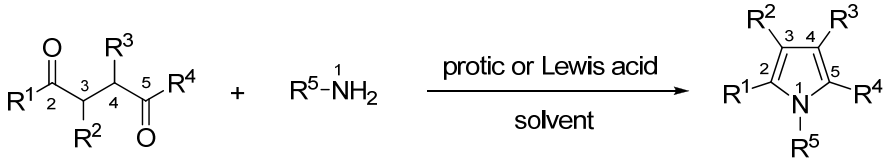


R^1, R^3, R^4 = H, aryl, alkyl; R^2 = alkoxyl; X = halogen

Scheme 3-2. Hantzsch pyrrole synthesis

Another widespread protocol for pyrrole synthesis is the Paal-Knorr method,[15,16,17] which realizes a [4+1] annulation reaction (Scheme 3-3). In this reaction, acid-catalyzed

condensation of a 1,4-dicarbonyl compound with ammonia or a primary amine affords a polysubstituted pyrrole. In this case, all four carbon atoms (C2 to C5) in pyrrole ring come from the 1,4-dicarbonyl compound.



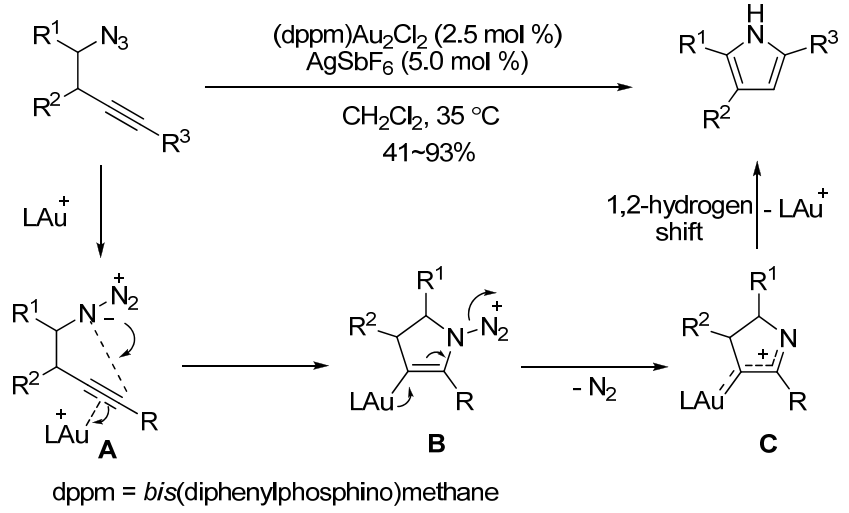
R^1, R^4 = H, alkyl, aryl; R^2, R^3 = H, aryl, alkyl, CO_2-alkyl, CO_2-aryl;
R^5 = H, alkyl, aryl, heteroaryl, NR_2, NHR, NH_2, OH

Scheme 3-3. Paal-Knorr pyrrole synthesis

3.1.2 Modern Methods for Synthesis of Pyrroles

Besides the classic methods, many new synthetic approaches such as metal-catalyzed cyclization reactions[8d,18] and multicomponent coupling reactions[8b] have been developed in recent years.

Toste reported a gold(I)-catalyzed acetylenic Schmidt reaction of homopropargyl azides for the synthesis of substituted pyrroles (Scheme 3-4).[19]

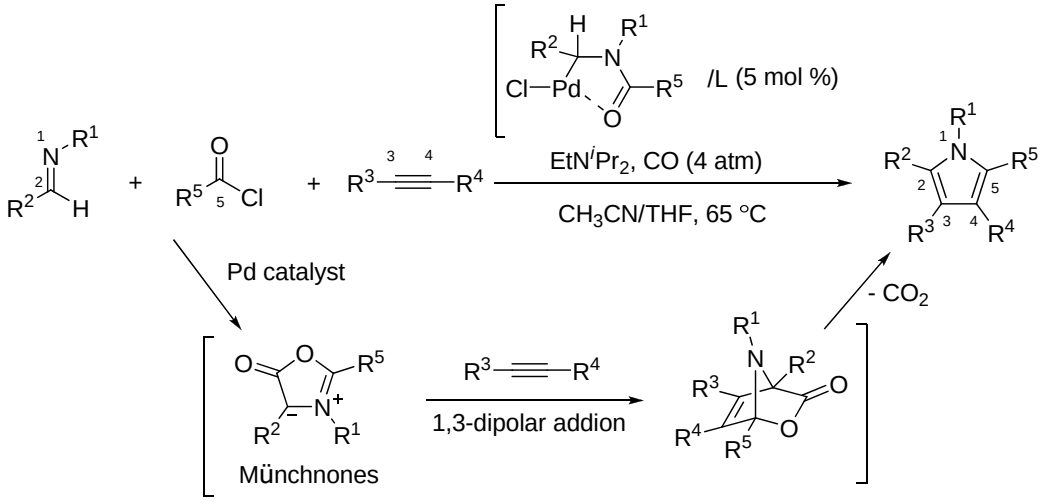


dppm = *bis*(diphenylphosphino)methane

Scheme 3-4. Au(I)-catalyzed acetylenic Schmidt reaction

This reaction might involve gold(I)-induced activation of the C≡C bond of an alkyne toward the addition by the internal nitrogen of azido group. Elimination of dinitrogen led to cationic intermediate **C**, followed by a formal 1,2-hydrogen shift producing pyrrole with the regeneration of gold(I) species. Other metal complexes including $PtCl_4$[20] and $ZnCl_2$[21] were found to catalyze this reaction efficiently as well.

Recently, Arndtsen has described a palladium catalyzed muticomponent coupling of alkynes, imines, and acid chlorides under a carbon monoxide atmosphere to construct pyrroles (Scheme 3-5).[22]

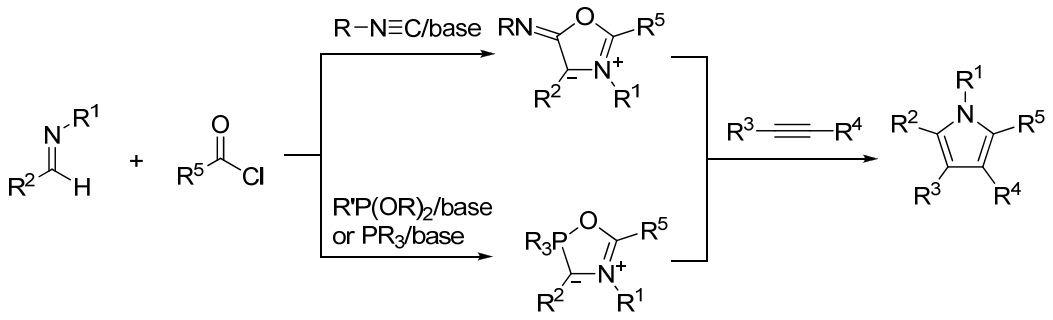


Scheme 3-5. Palladium catalyzed pyrrole synthesis

The new feature of this reaction was the generation of münchnones (mesoionic 1,3-oxazolium-5-oxides) from the palladium catalyzed coupling of a range of imines and acid chlorides in an atmosphere of carbon monoxide. These münchnones then underwent 1,3-dipolar addition with various alkynes to give polysubstituted pyrroles.

It was worth mentioning that the role of the palladium catalyst was only to mediate the formation of münchnones. Since the catalyst was not involved in the 1,3-dipolar addition, the efficiency of this synthesis might potentially be enhanced by utilizing münchnone analogues generated by other methods. Indeed, this group found that

the reaction of isocyanides[23] or phosphonites[24] or even phosphine[25] with imines and acid chlorides led to the alternative 1,3-dipoles (Scheme 3-6), which displayed the analogous reactivity of Münchnones. As expected, the subsequent 1,3-dipolar addition with alkynes produced polysubstituted pyrroles.



Scheme 3-6. Isocyanides, phosphonites, or phosphine mediated synthesis of pyrroles

Although a variety of diverse approaches for the synthesis of pyrroles have been developed so far, it is still challenging to prepare polysubstituted pyrroles with various substituents from readily available building blocks. In this chapter, the author will discuss about the development of synthetic methods to produce pyrroles from easily accessible vinyl azides and 1,3-dicarbonyl compounds.

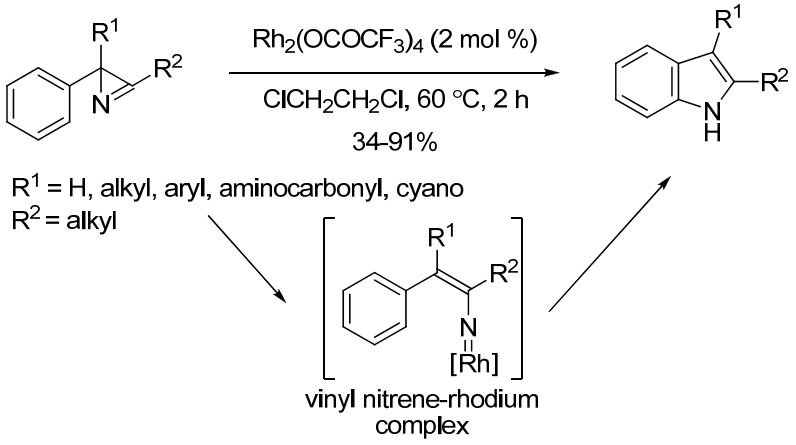
3.2 Results and Discussion

In this section, at first, is introduced the prior work that has been done in Narasaka's group on the thermal and copper-catalyzed synthesis of polysubstituted *N*-H pyrroles from vinyl azides and 1,3-dicarbonyl compounds (Sections 3.2.1 and 3.2.2). The author studied the scope of copper-catalyzed pyrrole formation from vinyl azides and ethyl acetoacetate (Section 3.2.2). On the basis of the limitation of this copper-catalyzed

reaction, he then explored more efficient catalytic methods to prepare pyrroles with broader scopes and generalities. These results will be discussed in Sections 3.2.3 to 3.2.5.

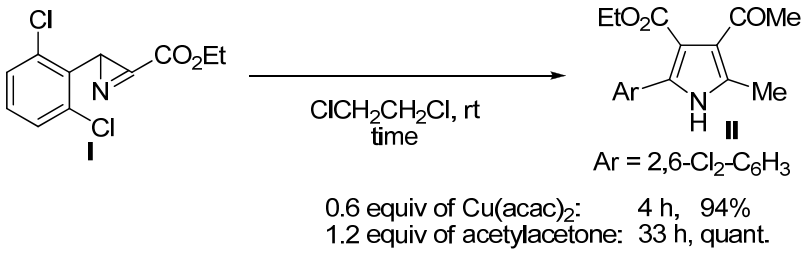
3.2.1 Thermal Reaction of Vinyl Azides and 1,3-Diketones for the Synthesis of Pyrroles

Recently, Narasaka has disclosed a Rh(II)-catalyzed isomerization of 2-aryl-2*H*-azirines to 2,3-disubstituted indoles (Scheme 3-7).[26] This transformation might proceed via aromatic C–H amination of a vinyl nitrene–rhodium complex intermediate.[27]



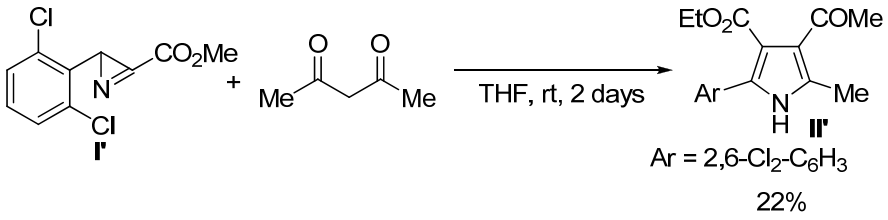
Scheme 3-7. Rh(II)-catalyzed isomerization of 2-aryl-2*H*-azirines to indoles

In order to further explore the synthetic utility of 2*H*-azirine derivatives, a number of reactions had been investigated by using various transition metals. During this course, it was found that the reaction of 2*H*-azirine **I** with 0.6 equiv of $Cu(acac)_2$ in 1,2-dichloroethane gave tetrasubstituted pyrrole **II** in 94% yield (Scheme 3-8). Furthermore, the reaction of 2*H*-azirine **I** with acetylacetone in the absence of $Cu(acac)_2$ also provided pyrrole **II** in quantitative yield.



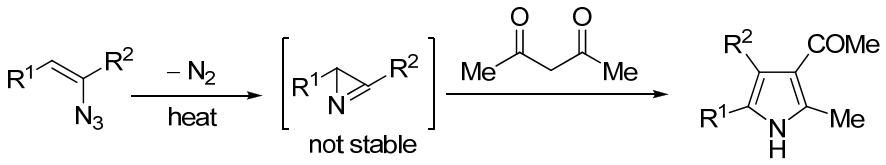
Scheme 3-8. Pyrrole formation from 2*H*-azirine **I**

In fact, an analogous reaction by using THF as solvent has been reported previously as shown in Scheme 3-9. However, pyrrole **II'** was isolated in low yield (22%).[28]



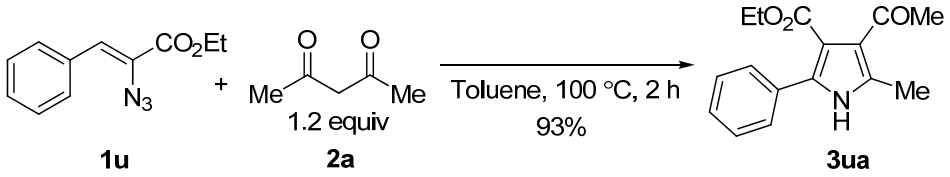
Scheme 3-9. Pyrrole formation from 2*H*-azirine **I'**

Therefore, the aforementioned reaction of 2*H*-azirine **I** with acetylacetone by employing 1,2-dichloroethane as a solvent (see Scheme 3-8) seemed to be useful for the synthesis of pyrroles. However, many 2*H*-azirines were difficult to prepare and handle due to their instability.[29] Thus, the utilization of vinyl azides as precursors of 2*H*-azirines was planned, since vinyl azides could be easily synthesized (*see* Chapter 2, synthesis of vinyl azides)[30] and were known to be transformed to the corresponding 2*H*-azirines *in situ* by thermal elimination of dinitrogen (Scheme 3-10).[30]



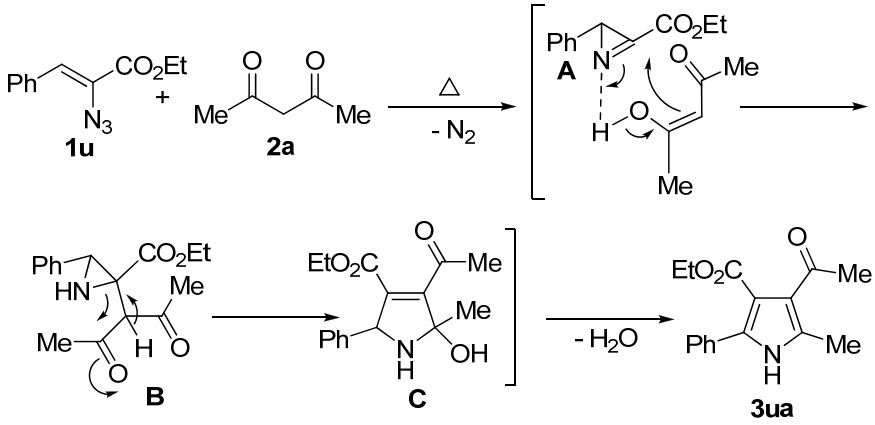
Scheme 3-10. Synthetic plan of pyrroles from thermal reaction of vinyl azides and acetylacetone

As expected, heating of a mixture of vinyl azide **1u** and acetylacetone (**2a**) in toluene at 100 °C afforded pyrrole **3ua** in 93% yield (Scheme 3-11).[31]



Scheme 3-11. Thermal pyrrole formation from vinyl azide **1u** and acetylacetone

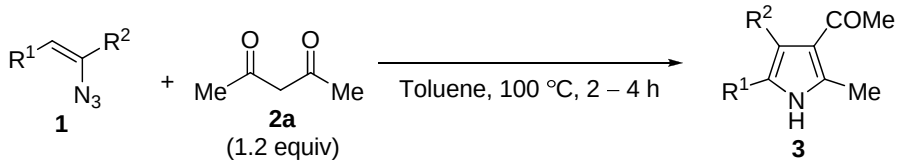
The reaction might proceed through the addition of acetylacetone to the imino carbon of **A**[32] which was derived by the thermolysis of vinyl azide **1u**, followed by the intramolecular nucleophilic attack of the nitrogen of the resulting aziridine to a carbonyl group with ring opening of the strained three-membered ring.[33] Subsequent dehydration led to the pyrrole **3ua** (Scheme 3-12).



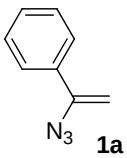
Scheme 3-12. Proposed mechanism for thermal pyrrole formation

Some tri- and tetrasubstituted *N*-H pyrroles were prepared from this thermal reaction of acetylacetone and vinyl azides **1** as shown in Table 3-1. In addition to *α*-ethoxycarbonyl vinyl azides (**1u**–**1w**), *α*-phenyl vinyl azide **1a** could also be employed in this kind of thermal reaction, affording pyrrole **3aa** in 85% yield.

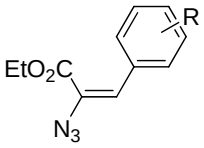
Table 3-1. Reaction of vinyl azides **1** with acetylacetone[a,b]



Vinyl azides 1:

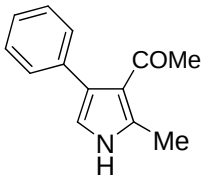


1a

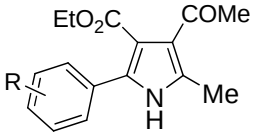


1u: R = H
1v: R = 4-Me
1w: R = 4-CN

Pyrroles 3:



3aa: 85% (**1a**+**2a**)[c]

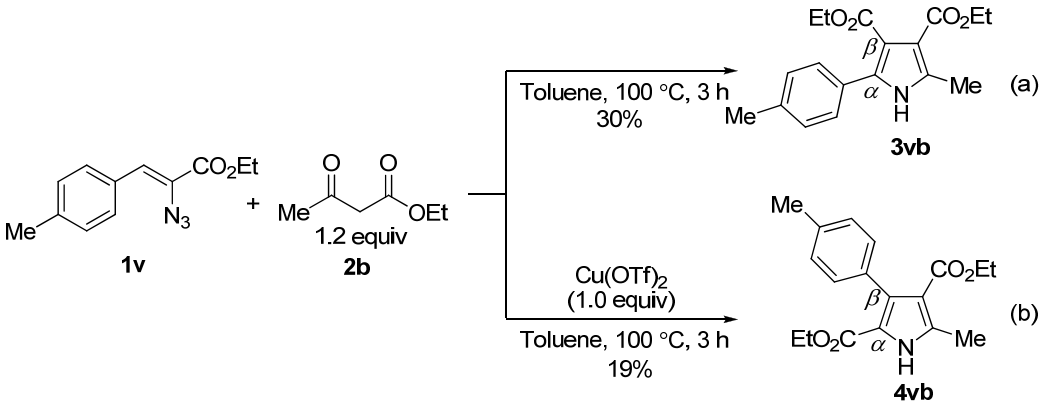


3ua: R = H; 93% (**1u**+**2a**)
3va: R = 4-Me; 90% (**1v**+**2a**)
3wa: R = 4-CN; 87% (**1w**+**2a**)

[a] Reactions were performed in toluene at 100 °C with 1.2 equiv of acetylacetone under N_2 atmosphere unless otherwise noted. [b] Isolated yields were recorded above. [c] The reaction was performed at 100 °C for 24 h.

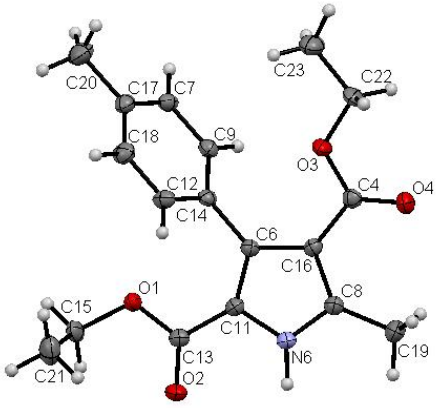
3.2.2 Cu(II)-Catalyzed Synthesis of Pyrroles from Vinyl Azides and *β*-Keto Esters

As described in the previous Section, the thermal reaction of vinyl azides with acetylacetone proceeded nicely to give polysubstituted *N*-H pyrroles in good yields. However, the reaction of vinyl azide **1v** with *β*-keto ester, ethyl acetoacetate (**2b**), gave the desired pyrrole **3vb** in very low yield (30%) (Scheme 3-13, Eq. a). The use of any additives such as acids, bases, etc. could not improve the yield. However, the reaction in the presence of a stoichiometric amount of $Cu(OTf)_2$ gave an unexpected pyrrole **4vb** in 19% yield (Eq. b), which has a reverse substitution pattern (*α*-ethoxycarbonyl, *β*-*p*-tolyl) (Figure 3-3) compared with that of the expected **3vb** (*α*-*p*-tolyl, *β*-ethoxycarbonyl).



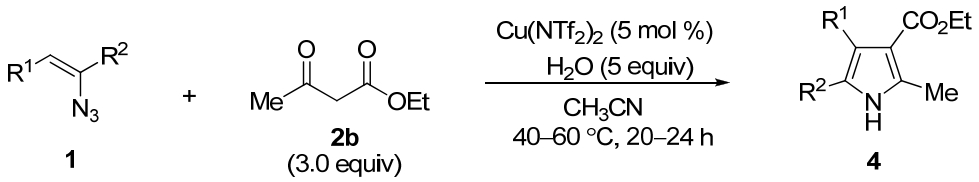
Scheme 3-13. Thermal and $Cu(OTf)_2$-mediated reaction of vinyl azide **1v** with ethyl acetoacetate

Figure 3-3. X-ray structure of pyrrole **4vb**

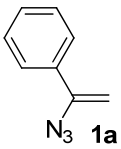


Further optimization revealed that the yield of pyrrole **4vb** was improved to 80% by using a catalytic amount of $Cu(NTf_2)_2$ in the presence of 5 equiv of water as an additive (Table 3-2). Vinyl azides bearing an ethoxycarbonyl group at the α-position were transformed to pyrroles in good to moderate yields (Table 3-2). The reaction of vinyl azide **1a** possessing an α-phenyl group, however, gave the corresponding pyrrole **4ab** in only 9% yield with 43% recovery of vinyl azide **1a**. Furthermore, when 1,3-diketones such as acetylacetone (**2a**) was employed in this reaction, no desired pyrrole (**4ua**) was observed at all.

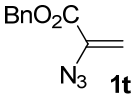
Table 3-2. $Cu(NTf_2)_2$-catalyzed synthesis of pyrroles **4** from vinyl azides **1** and ethyl acetoacetate[a,b]



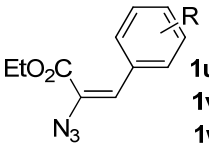
Vinyl azides 1:



1a

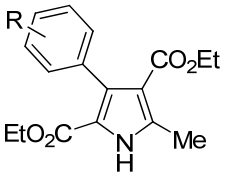


1t

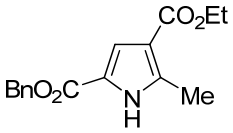


1u: R = H
1v: R = 4-Me
1w: R = 4-CN

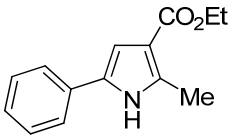
Pyrroles 4:



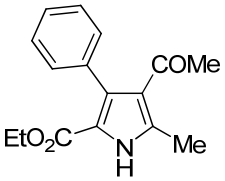
4ub: R = H; 80% (**1u+2b**)
4vb: R = 4-Me; 80% (**1v+2b**)
4wb: R = 4-CN; 86% (**1w+2b**)



4tb: 52% (**1t+2b**)



4ab: 9% (**1a+2b**)[c,d]

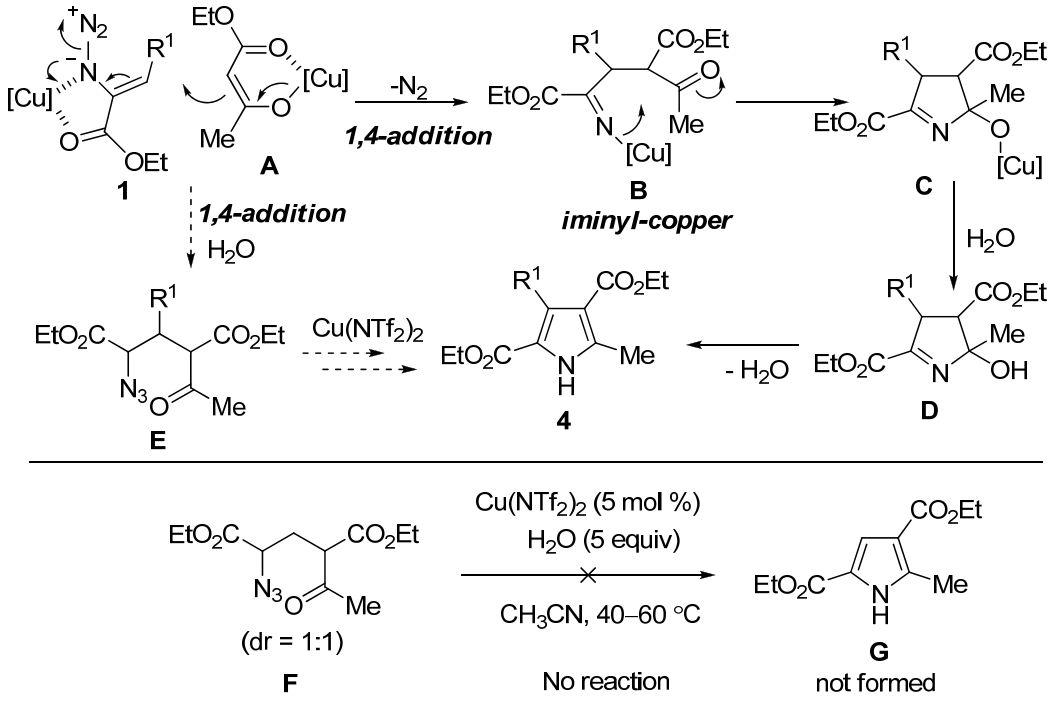


4ua: 0% (**1u+2a**)

[a] Reactions were performed in CH_3CN at 40-60 °C with 3.0 equiv of ethyl acetoacetate under N_2 atmosphere (see Experimental Section). [b] Isolated yields were recorded above. [c] The reaction was performed by the use of 5 mol % of $Cu(OTf)_2$. [d] Vinyl azide **1a** was recovered in 43% yield.

Since the $Cu(NTf_2)_2$-catalyzed reaction is performed at 40-60 °C, a 2*H*-azirine intermediate is unlikely to be generated in the reaction course. The reaction may be initiated by the 1,4-addition of copper enolate **A** to vinyl azide **1**, the internal nitrogen of which coordinates to copper (Scheme 3-14).[34] Simultaneus elimination of dinitrogen affords iminylcopper **B**, which undergoes intramolecular nucleophilic attack to the carbonyl group, affording pyrrole with the elimination of water.

It is also considered that hydrolysis of 1,4-addition intermediate would generate α-azido *δ*-keto ester **E**, which might undergo intramolecular cyclization in the presence of $Cu(NTf_2)_2$ to afford pyrrole **4**. However, treatment of the analogous *α*-azido *δ*-keto ester **F** with $Cu(NTf_2)_2$ did not gave the corresponding pyrrole **G** at all with the recovery of **F**. Therefore, the stepwise mechanism involving 1,4-addition adducts **E** as the intermediate can be excluded.



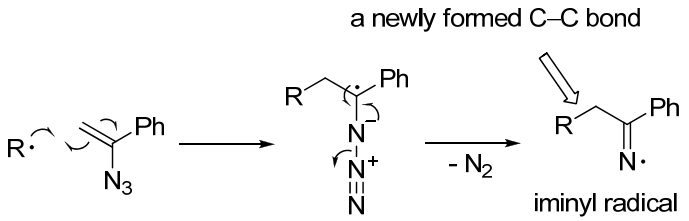
Scheme 3-14. Proposed reaction mechanism for $Cu(NTf_2)_2$-catalyzed pyrrole formation

3.2.3 $Mn(OAc)_3 \cdot 2H_2O$-Catalyzed Synthesis of Pyrroles from Vinyl Azides and *β*-Keto Esters

As discussed in the $Cu(NTf_2)_2$-catalyzed reaction, the introduction of an alkoxycarbonyl group at the *α*-position of vinyl azides is indispensable to realize high yields. It is probable because this transformation proceeded by a 1,4-anionic addition of a copper enolate to vinyl azides as shown in Scheme 3-14. Therefore, the reaction of vinyl

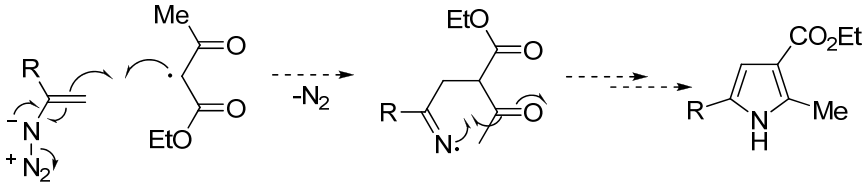
azide **1a** which is not a good Michael acceptor for the anionic addition led to pyrrole **4ab** in very low yield.

However, as mentioned in Section 1.1.4.2, vinyl azide **1a** is known as a good radical acceptor toward alkyl radicals, from which iminyl radicals are generated with the simultaneous formation of a new C–C bond (Scheme 3-15).



Scheme 3-15. Generation of iminyl radicals from vinyl azide **1a**

Accordingly, the author intended to develop a more general method for pyrrole synthesis by applying a radical addition reaction to vinyl azides. That is, as shown in Scheme 3-16, an *α*-carbonyl radical generated from a 1,3-dicarbonyl compound adds to the C═C bond of a vinyl azide to form a new C–C bond with the generation of an iminyl radical. The resulting iminyl radical then forms a new C–N bond with an intramoelcular carbonyl moiety to give a pyrrole.



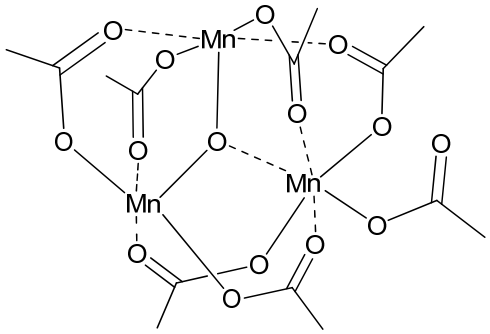
Scheme 3-16. Synthetic plan of pyrroles through radical pathway

3.2.3.1 Optimization of $Mn(OAc)_3 \cdot 2H_2O$-Catalyzed Reaction of *α*-Azidostyrene and Ethyl Acetoacetate

Manganese(III) acetate has been widely used for the oxidative generation of α-carbonyl radicals from *β*-keto esters.[35] The structure of anhydrous manganese(III) acetate

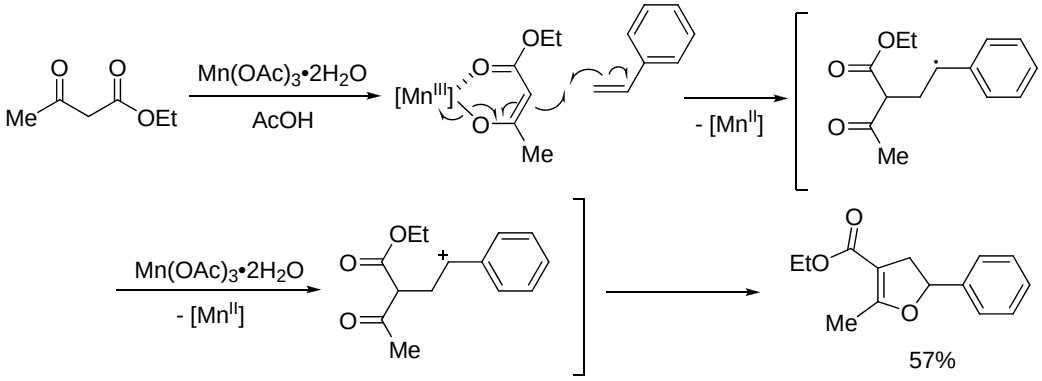
is actually an oxo-centered triangle of Mn(III) bridged by acetoxy ions[36] (Figure 3-4), thereby its chemical formula is $Mn_3O(OCOCH_3)_7$.

Figure 3-4. Structure of anhydrous manganese(III) acetate



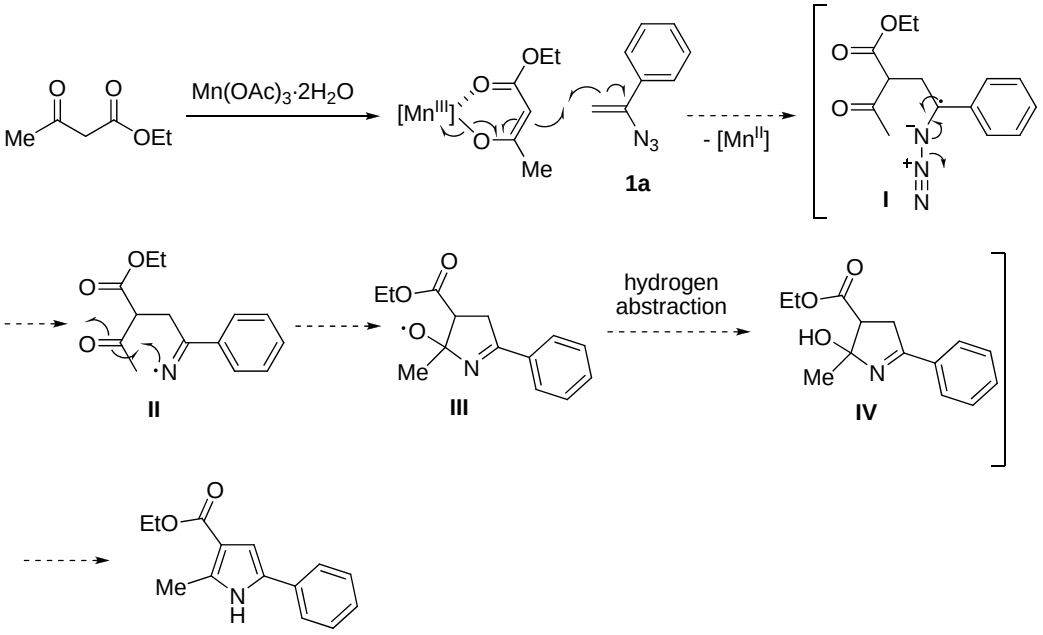
In fact, commercially available manganese(III) acetate dihydrate which exhibits comparable reactivity as its anhydrous form has been usually utilized without any further purification. Even though the real structure of manganese(III) acetate dihydrate has not been clarified yet, it is normally formulated as $Mn(OAc)_3 \cdot 2H_2O$. In this thesis, such a chemical formula is used to represent manganese(III) acetate dihydrate.

As reported, treatment of a mixture of ethyl acetoacetate and styrene with $Mn(OAc)_3 \cdot 2H_2O$ in AcOH led to the formation of dihydrofuran[37] as shown in Scheme 3-17. In this reaction, $Mn(OAc)_3 \cdot 2H_2O$ was involved not only the oxidation of ethyl acetoacetate to α-carbonyl radical, but also the oxidation of the resulted carbon radical to carbocation. Thus, at least, two equivalents of $Mn(OAc)_3 \cdot 2H_2O$ were required.



Scheme 3-17. $Mn(OAc)_3 \cdot 2H_2O$-mediated reaction of ethyl acetate and styrene

In the proposed reaction of vinyl azides **1a** and ethyl acetoacetate (Scheme 3-18), the oxidative generation of α-carbonyl radical from ethyl acetoacetate requires a stoichiometric amount of $Mn(OAc)_3 \cdot 2H_2O$. However, the generated α-azidobenzyl radical **I** would not be further oxidized by $Mn(OAc)_3 \cdot 2H_2O$ but rearranges to iminyl radical **II**, which is presumed to undergo cyclization with the intramolecular acetyl group to give alkoxy radical **III**. The radical chain reaction is assumed to be terminated by hydrogen abstraction[38] of alkoxy radical **III** from the solvent to provide **IV**. Consequently, one equivalent of $Mn(OAc)_3 \cdot 2H_2O$ is supposed to be needed in this proposed reaction process.



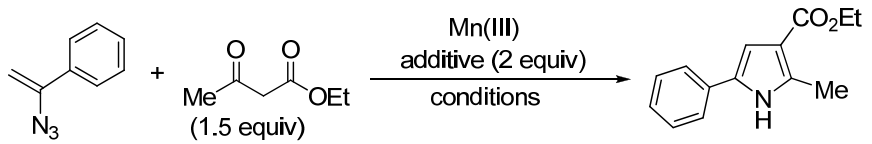
Scheme 3-18. Proposed reaction of vinyl azide **1a** and ethyl acetoacetate by using $Mn(OAc)_3 \cdot 2H_2O$

Based on this consideration, the reaction of *α*-azidostyrene (**1a**) and ethyl acetoacetate (**2b**) was initially examined by employing a stoichiometric amount of $Mn(OAc)_3 \cdot 2H_2O$ (1.5 equiv). After screening some solvents (Table 3-3, entries 1-4), the reaction was found to proceed smoothly in MeOH at 40 °C to give pyrrole **4ab** in 84% yield (entry 5). Interestingly, even by the use of a catalytic amount (20 mol %) of $Mn(OAc)_3 \cdot 2H_2O$, pyrrole **4ab** was obtained in 90% yield (entry 6). Addition of acetic

acid (2 equiv) accelerated the reaction (entry 7) and reduced the catalyst loading to 10 mol % (entry 8).

Other Mn(III) species such as Mn(III) tris(2-pyridinecarboxylate) [$Mn(pic)_3$][39,40] and Mn(III) acetylacetonate [$Mn(acac)_3$] exhibited poor catalytic activity toward this reaction. In the case of $Mn(pic)_3$, the desired pyrrole was only obtained in 28% yield with the recovery of vinyl azide **1a** (55%) after 22 h (entry 9). The employment of $Mn(acac)_3$ as a catalyst instead of $Mn(OAc)_3 \cdot 2H_2O$ only delivered the pyrrole **4ab** in 23% yield together with the recovery of vinyl azide **1a** (40%) after 30 h (entry 10).

Table 3-3. Reaction of vinyl azide **1a** with ethyl acetoacetate using Mn(III) complexes[a]



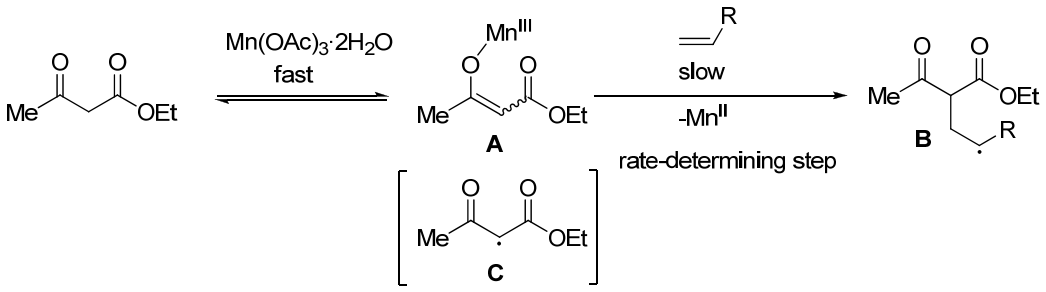
1a **2b** **4ab**

entry	[Mn(III)]/equiv	additive	solvent	temp/°C	time/h	yield/%[b]
1	$Mn(OAc)_3 \cdot 2H_2O$ (1.5)	—	DMF	rt	5	20
2	$Mn(OAc)_3 \cdot 2H_2O$ (1.5)	—	CH_3CN	rt	19	44
3	$Mn(OAc)_3 \cdot 2H_2O$ (1.5)	—	EtOH	rt	9	65
4	$Mn(OAc)_3 \cdot 2H_2O$ (1.5)	—	MeOH	rt	5	84
5	$Mn(OAc)_3 \cdot 2H_2O$ (1.5)	—	MeOH	40	2	84
6	$Mn(OAc)_3 \cdot 2H_2O$ (0.2)	—	MeOH	40	8	90
7	$Mn(OAc)_3 \cdot 2H_2O$ (0.2)	AcOH	MeOH	40	2	88
8	**$Mn(OAc)_3 \cdot 2H_2O$ (0.1)**	**AcOH**	**MeOH**	**40**	**2**	**94 (90)[c]**
9	$Mn(pic)_3$ (0.1)	AcOH	MeOH	40	22	28[d]
10	$Mn(acac)_3$ (0.1)	AcOH	MeOH	40	30	23[e]

[a] Reactions were performed under N_2 atmosphere using 0.3 mmol of **1a**. [b] Isolated yields. [c] Isolated yield using 1.0 mmol of **1a**. [d] Vinyl azide **1a** was recovered in 55% yield. [e] Vinyl azide **1a** was recovered in 40% yield.

3.2.3.2 Proposed Mechanism of $Mn(OAc)_3 \cdot 2H_2O$-Catalyzed Pyrrole Formation from *α*-Azidostyrene and Ethyl Acetoacetate

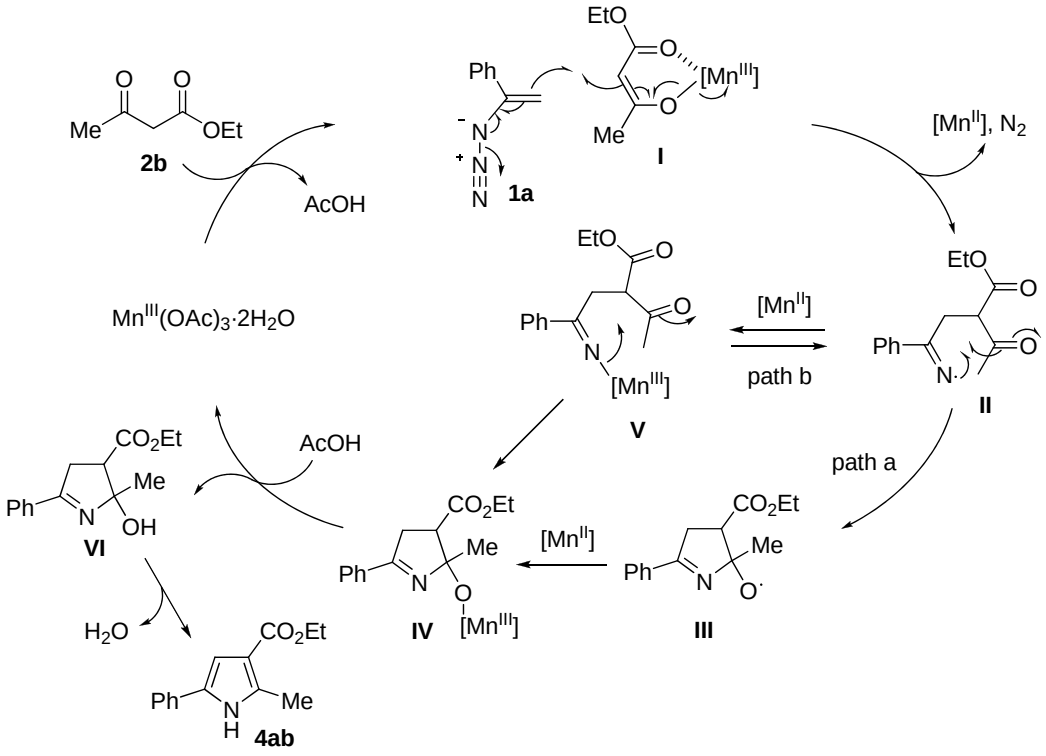
Snider has intensively investigated the mechanism of $Mn(OAc)_3 \cdot 2H_2O$-mediated reactions of ethyl acetoacetate and alkenes.[35a] It was found that enolization of ethyl acetoacetate with $Mn(OAc)_3 \cdot 2H_2O$ is fast and reversible. The formed Mn(III) enolate (**A**) reacts with alkenes slowly through a radical pathway to give alkyl radical **B** with the loss of Mn(II), and this step is thought to be the rate-determining step. In this reaction sequence, the free radical **C** does not appear to be the intermediate (Scheme 3-19).[41]



Scheme 3-19. Mechanism of $Mn(OAc)_3 \cdot 2H_2O$ mediated reactions of ethyl acetoacetate with alkenes

Based on these postulations, a possible mechanism for this $Mn(OAc)_3 \cdot 2H_2O$-catalyzed pyrrole formation from vinyl azide **1a** and ethyl acetoacetate is proposed in Scheme 3-20. This catalytic reaction may be initiated by the addition of Mn(III) enolate **I** to vinyl azide **1a** via a radical pathway, giving iminyl radical **II** with release of Mn(II) species and dinitrogen. The resulting iminyl radical **II** undergoes intramolecular additon to a carbonyl group to give alkoxy radical **III**. Reduction of this alkoxyl radical **III** by Mn(II) species gives Mn(III) alkoxide **IV** (path a). Alternatively, the reduction of iminyl radical **II** by Mn(II) species affords iminylmanganese(III) **V**, nucleophilic attack of which to a carbonyl group yields addition intermediate **IV** (path b).[42] Finally, protonation of **IV** with acetic acid followed by dehydration produces pyrrole **4ab** along with the

regeneration of Mn(III) species. The addition of AcOH is supposed to accelerate the protonation of intermediate **IV** to **VI**, facilitating the release of active Mn(III) species. In addition, the presence of AcOH is also beneficial for the dehydration step (**VI→4ab**).



Scheme 3-20. Proposed mechanism of $Mn(OAc)_3·2H_2O$-catalyzed pyrrole formation from vinyl azide **1a** and ethyl acetoacetate

Most of the reported radical reactions of 1,3-dicarbonyl compounds with alkenes using $Mn(OAc)_3·2H_2O$ as an oxidant were carried out in a stoichiometric manner, although there were a few reports on catalytic usage of $Mn(OAc)_3·2H_2O$ in the presence of reoxidants, such as Co(II)/O_2 system,[43] molecular oxygen,[44] electrooxidation,[45] and sonochemical conditions.[46] In sharp contrast, a catalytic amount of $Mn(OAc)_3·2H_2O$ was sufficient in this pyrrole formation reaction without any aid of reoxidants. The key to construct this catalytic process was the oxidation of Mn(II) to Mn(III) by the resulting alkoxy radicals or iminyl radicals (**III→IV** or **II→V**, respectively, Scheme 3-20). This

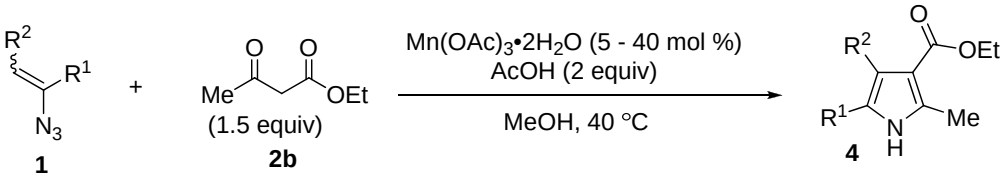
oxidative initiation/reductive termination sequence may afford an opportunity to develop a range of catalytic reactions promoted by Mn(III) complexes.

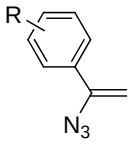
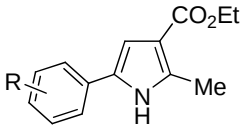
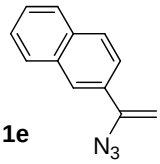
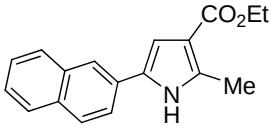
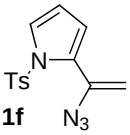
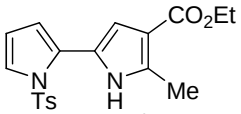
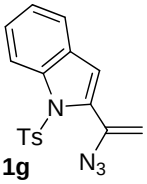
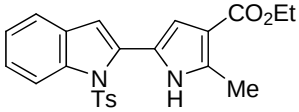
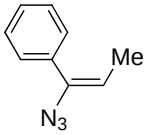
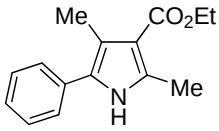
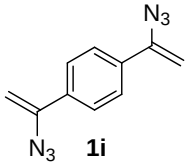
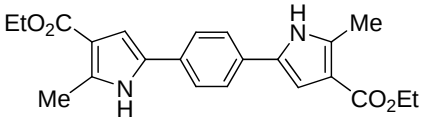
3.2.3.3 Synthesis of Pyrroles from Vinyl Azides and *β*-Keto Esters

With the optimized conditions at hands, the scope of this pyrrole formation was then studied. Firstly, the reactions of ethyl acetoacetate (**2b**) with various vinyl azides **1** were examined as shown in Table 3-4. *α*-Aryl vinyl azides reacted smoothly to afford pyrroles in good yields (entries 1-9). Relatively longer reaction time or higher catalyst loading was necessary in the cases of vinyl azides bearing electron-rich aryl groups (entries 2-4). The reactions of *α*-heteroaryl vinyl azides (entries 10 and 11) also took place smoothly, allowing the installation of heteroaryl motifs such as pyrrolyl (**4fb**) and indolyl (**4gb**) groups at the C2-position of pyrrole **4**. Trisubstituted vinyl azide **1h** also reacted with ethyl acetoacetate to give tetrasubstituted pyrrole **4hb** in good yield (entry 12). 1,4-Dipyrrolybenzene **4ib** was prepared in 48% yield by treatment of bis(*α*-azidovinyl)benzene **1i** with 40 mol % of $Mn(OAc)_3 \cdot 2H_2O$ (entry 13).

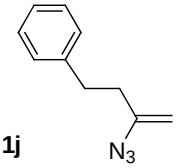
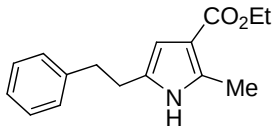
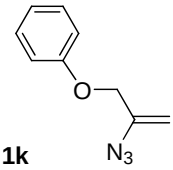
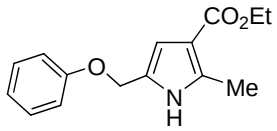
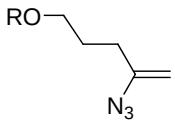
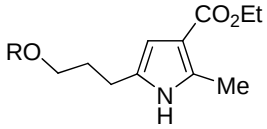
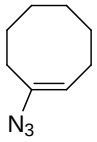
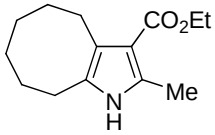
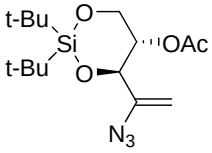
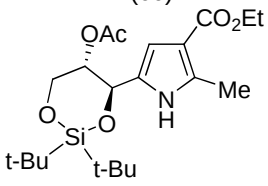
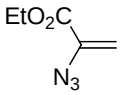
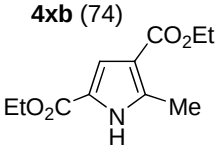
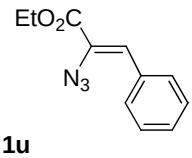
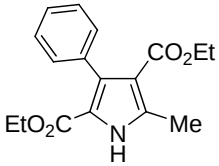
An important feature of this reaction was that *α*-alkyl vinyl azides with some functional groups were also applicable, leading to the desired pyrroles in good yields (entries 14-19). From 1-azidocyclooctene (**1n**), bicyclic pyrrole **4nb** was obtained in 60% yield (entry 18). Vinyl azide **1x** with a chiral triol moiety could be transformed to pyrrole **4xb** in 74% yield without cleavage of silyloxy and acetoxy groups by employing 40 mol % of $Mn(OAc)_3 \cdot 2H_2O$ (entry 19).

Table 3-4. $Mn(OAc)_3 \cdot 2H_2O$-catalyzed synthesis of pyrroles **4** from vinyl azides **1** and ethyl acetoacetate **2b**[a]



entry	vinyl azides	[Mn(III)]/mol %	time/h	pyrroles **4** (yield/%)[b]
				
1	**1a**: R = H	10	2	**4ab** (94)
2	**1b**: R = 4-Me	10	4	**4bb** (78)
3	**1c**: R = 2-OMe	10	4	**4cb** (75)
4	**1d**: R = 4-OMe	10	4	**4db** (53)
5	**1o**: R = 2-Br	10	2	**4ob** (94)
6	**1p**: R = 4-Br	10	2	**4pb** (86)
7	**1q**: R = 4-CO_2Me	10	2	**4qb** (88)
8	**1r**: R = 3-NO_2	10	2	**4rb** (95)
9	 **1e**	20	2	 **4eb** (83)
10	 **1f**	20	24	 **4fb** (68)[c]
11	 **1g**	20	6	 **4gb** (88)
12	 **1h**	20	2	 **4hb** (72)
13	 **1i**	40	24	 **4ib** (48)

continued...

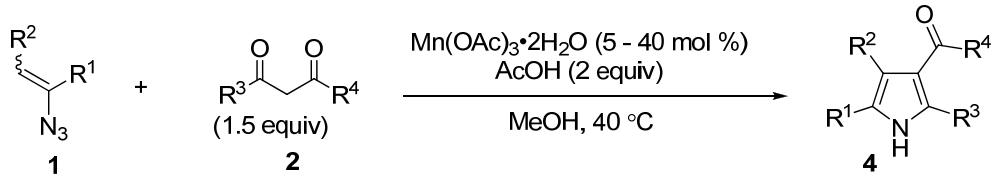
entry	vinyl azides	[Mn(III)]/mol %	time/h	pyrroles **4** (yield/%)[b]
14	 **1j**	20	3	 **4jb** (90)
15	 **1k**	20	2	 **4kb** (85)
				
17	**1l**: R = Si(*t*-Bu)Ph_2	20	2	**4lb** (85)
16	**1m**: R = Ac	20	1	**4mb** (94)
18	 **1n**	40	1	 **4nb** (60)[d]
19	 **1x**	40	5	 **4xb** (74)
20	 **1s**	5	2	 **4sb** (98)
21	 **1u**	20	24	 **4ub** (78)[e]

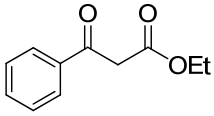
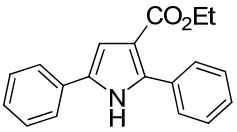
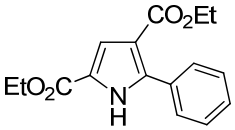
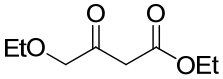
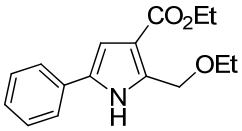
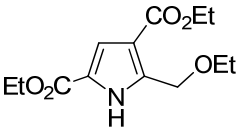
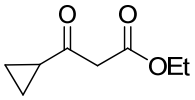
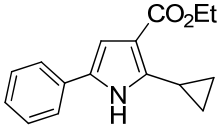
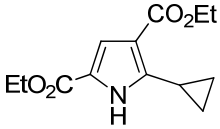
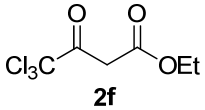
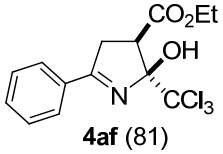
[a] Reactions were performed in MeOH at 40 °C with 1.5 equiv of ethyl acetoacetate (**2b**) under N_2 atmosphere (see Experimental Section). [b] Isolated yields. [c] Vinyl azide **1f** was recovered in 25% yield. [d] Vinyl azide **1n** was recovered in 10% yield. [e] Vinyl azide **1u** was recovered in 15% yield.

Moreover, even the electron-deficient vinyl azides such as **1s** and **1u** could be employed as well (entries 20 and 21). In the reaction of ethyl 2-azidoacrylate (**1s**), the use of only 5 mol % of $Mn(OAc)_3 \cdot 2H_2O$ was sufficient to complete the reaction within 2 h, affording pyrrole **4sb** almost quantitatively (entry 20). In the preparation of tetrasubstituted pyrrole, the higher catalyst loading (20 mol %) and longer reaction time (24 h) were required, probably due to the steric hindrance of the *β*-phenyl group of vinyl azide **1u**.

Next, the scope of *β*-keto ester components was examined using *α*-azidostyrene (**1a**) and ethyl 2-azidoacrylate (**1s**) as vinyl azides (Table 3-5). By employing *β*-keto esters **2c-2e**, phenyl, ethoxymethyl, and cyclopropyl groups were successfully installed at the C2-position of pyrroles **4** (entries 1-6). It was also found that the reaction of ethyl trichloroacetoacetate (**2f**) with vinyl azide **1a** gave 3,4-dihydro-2*H*-pyrrole **4af** as a single diastereoisomer (entry 7). The structure of **4af** was confirmed by X-ray crystallographic analysis (Figure 3-5).

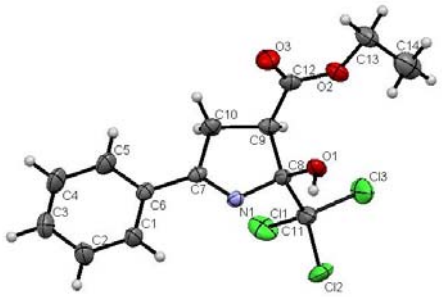
Table 3-5. $Mn(OAc)_3 \cdot 2H_2O$-catalyzed synthesis of pyrroles **4** from vinyl azides **1** and 1,3-dicarbonyl compounds **2**[a]



entry	vinyl azides **1**	1,3-dicarbonyl compounds **2**	[Mn(III)] /mol %	time /h	pyrroles **4** (yield/%)[b]
1	**1a**	 **2c**	40	4	 **4ac** (63)
2	**1s**		40	2	 **4sc** (72)
3	**1a**	 **2d**	20	3	 **4ad** (55)
4	**1s**		20	5	 **4sd** (77)
5	**1a**	 **2e**	40	8	 **4ae** (56)
6	**1s**		40	2	 **4se** (72)
7	**1a**	 **2f**	40	24	 **4af** (81)

[a] Reactions were performed in MeOH at 40 °C with 1.5 equiv of ethyl acetoacetate (**2b**) under N_2 atmosphere (see Experimental Section). [b] Isolated yields.

Figure 3-5. X-ray structure of pyrrole **4af**



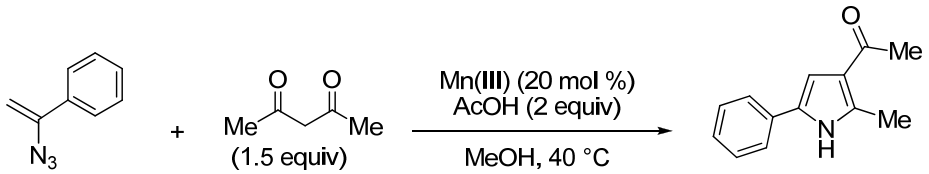
As discussed above, this $Mn(OAc)_3 \cdot 2H_2O$-catalyzed pyrrole formation has a much broader scope than that of $Cu(NTf_2)_2$-catalyzed one. Various vinyl azides including *α*-ethoxycarbonyl, *α*-aryl, and even α-alkyl substituted ones can be employed to provide the corresponding pyrroles in good yields. Besides that, trisubstituted vinyl azides are also applicable to synthesized tetrasubstituted pyrroles. Additionally, the reactions of a number of *β*-keto esters also proceed well to introduce functional groups at the C2-position of pyrroles. These results promoted the author to further explore the reaction by using other 1,3-dicarbonyl compounds such as 1,3-diketones.

3.2.4 $Mn(pic)_3$-Catalyzed Synthesis of Pyrroles from Vinyl Azides and 1,3-Diketones

As mentioned in the previous Section, *β*-keto esters were successfully applied in the $Mn(OAc)_3 \cdot 2H_2O$-catalyzed pyrrole synthesis. However, when a 1,3-diketone, acetylacetone (**2a**), was employed instead of *β*-keto esters with vinyl azide **1a** in the presence of 20 mol % of $Mn(OAc)_3 \cdot 2H_2O$, the reaction proceeded slowly, and the yield of pyrrole **4aa** was low (21%) along with the recovery of **1a** (63%) even after 24 h (Table 3-6, entry 1). The formation of **4aa**, however, encouraged the author to improve the product yield by modification of Mn(III) complexes, because the previous $Cu(NTf_2)_2$-catalyzed

reaction with acetylacetone did not give any desired pyrrole at all (See Section 3.2.2, Table 3-2). $Mn(acac)_3$ displayed almost no catalytic activity to this reaction (Table 3-6, entry 2), while the utilization of 20 mol % of $Mn(pic)_3$ afforded pyrrole **4aa** in 76% yield after 20 h (entry 3).

Table 3-6. Mn(III)-catalyzed reaction of vinyl azide **1a** and acetylacetone[a]



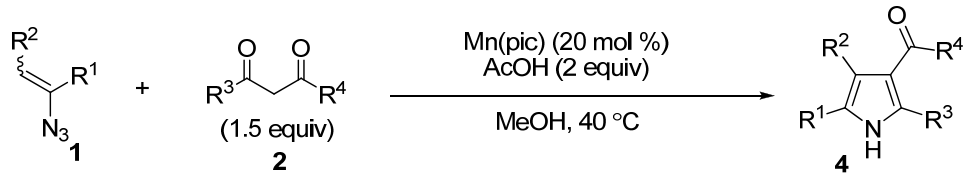
entry	Mn(III)	time/h	yield/%[b]
1	$Mn(OAc)_3 \cdot 2H_2O$	24	21 (63)[c]
2	$Mn(acac)_3$	40	0 (59)[c]
3	$Mn(pic)_3$	20	76

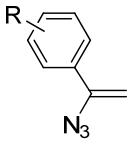
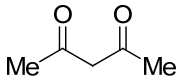
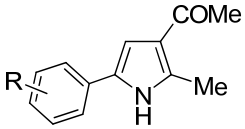
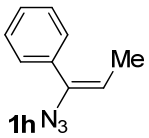
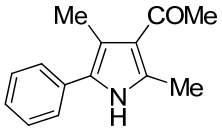
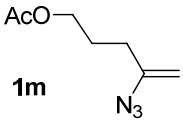
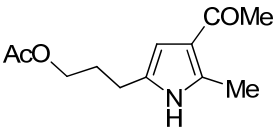
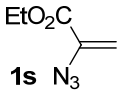
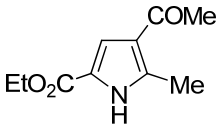
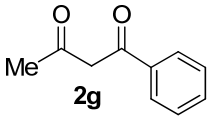
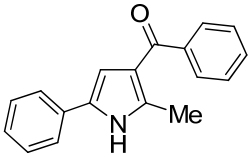
[a] Reactions were performed under N_2 atmosphere using 0.3 mmol of **1a**. [b] Isolated yields. [c] Recovery yield of **1a**.

These results indicated that ligands played an important role in the electron transfer process. In fact, Sawyer reported that the oxidation potential of Mn^{II}/Mn^{III} is ligand-dependent and the $E_{1/2}$ (V vs NHE) for $Mn(pic)_2$, $Mn(OAc)_2$ and $Mn(acac)_2$ are +0.60, +0.44, and +0.18, respectively.[47] This indicates that the oxidation ability of Mn(III) complexes obeys the following order: $Mn(pic)_3 > Mn(OAc)_3 > Mn(acac)_3$. The oxidation of enolate of acetylacetone by Mn(III) to generate the α-carbonyl radical is more difficult than that of the enolate of ethyl acetoacetate, since the former is more electron-deficient than the latter. Thus, a stronger oxidant such as $Mn(pic)_3$ is required for the oxidation of acetylacetone.

The reactions of some vinyl azides **1b**, **1r**, **1h**, and **1m** with acetylacetone (**2a**) in the presence of $Mn(pic)_3$ (20 mol %) led to the formation of pyrroles **4** in good to moderate yields (Table 3-7, entries 2-5). However, from an electron-deficient vinyl azide **1s**, the desired pyrrole **4sa** was delivered in 28% yield (entry 6). The reaction of unsymmetrical 1,3-diketone such as benzoylacetone (**2g**) and vinyl azide **1a** proceeded to afford pyrrole **4ag** in 61% yield as a sole product via C–N bond formation with a less hindered acetyl group (entry 7).

Table 3-7. $Mn(pic)_3$-catalyzed pyrrole formation from vinyl azides and 1,3-diketones[a]



entry	vinyl azides **1**	1,3-diketones **2**	time /h	pyrroles **4** (yield/%)[b]
				
1	**1a**: R = H	**2a**	20	**4aa** (76)
2	**1b**: R = 4-Me	**2a**	46	**4ba** (52)
3	**1r**: R = 3-NO_2	**2a**	36	**4ra** (80)
4	 **1h**	**2a**	24	 **4ha** (41)[c]
5	 **1m**	**2a**	48	 **4ma** (71)
6	 **1s**	**2a**	17	 **4sa** (28)
7	**1a**	 **2g**	24	 **4ag** (61)[d]

[a] Reactions were performed in MeOH at 40 °C using 20 mol % of $Mn(pic)_3$ with 1.5 equiv of 1,3-diketones under N_2 atmosphere (see Experimental Section). [b] Isolated yields. [c] Vinyl azide **1h** was recovered in 21% yield. [d] Vinyl azide **1a** was recovered in 17% yield.

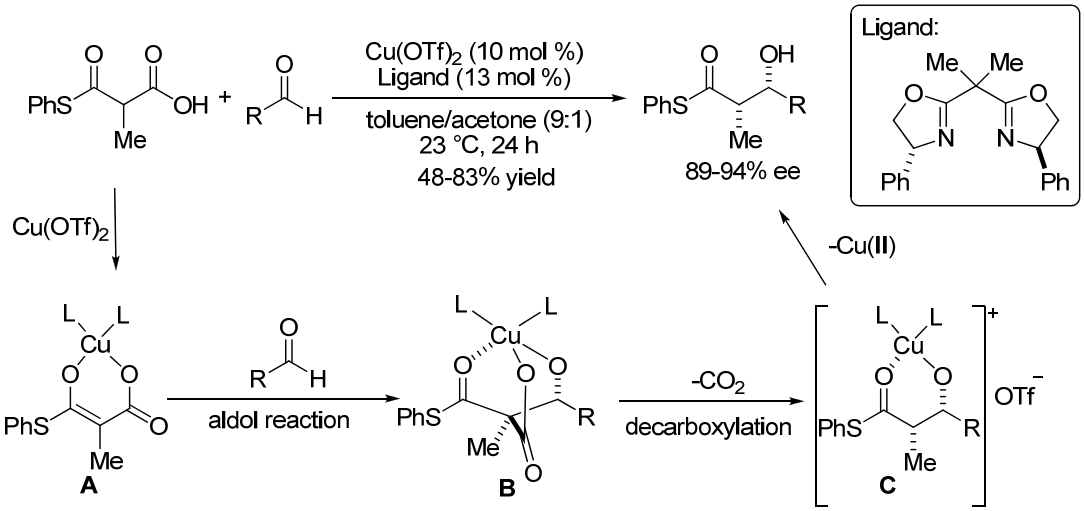
In a brief summary, in addition to *β*-keto esters, 1,3-diketones can also react with vinyl azides to form pyrroles by using a stronger oxidant, $Mn(pic)_3$, as a catalyst. Again, a

wide range of vinyl azides with various types of substituents are applicable to prepare the corresponding pyrroles efficiently.

3.2.5 $Mn(acac)_3$-Catalyzed Synthesis of Pyrroles from Vinyl Azides and *β*-Keto Acids

Besides *β*-keto esters and 1,3-diketones, *β*-keto acids were also utilized as sources of *α*-carbonyl radicals.[48] In this Section, the author will discuss the reactions of *β*-keto acids and vinyl azides to prepare pyrroles.

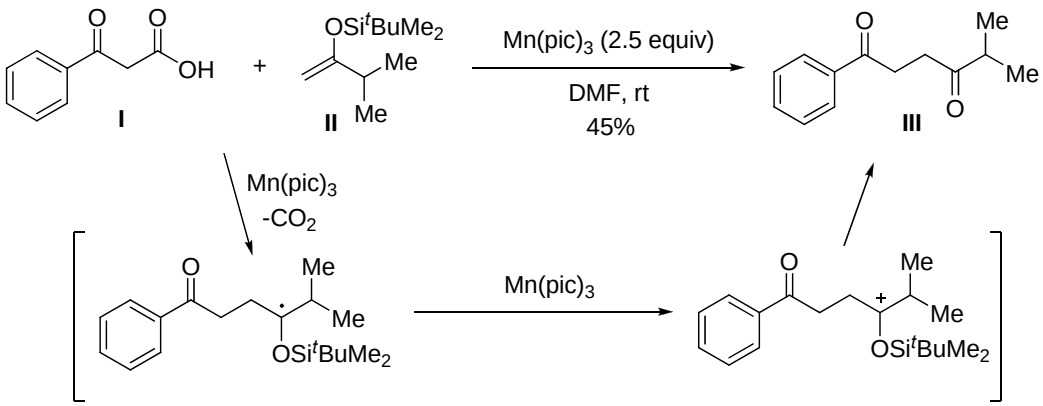
β-Keto acids are employed as precursors of *α*-carbonyl anions[49] and radicals.[48] For example, Shair has developed a Cu(II)-catalyzed enantioselective reaction between malonic acid half thioesters and aldehydes, yielding aldol products (Scheme 3-21). A thorough investigation of the reaction mechanism revealed that decarboxylation (**B** to **C**) occurred after the aldol reaction (**A** to **B**).[49]



Scheme 3-21. Cu(II)-catalyzed reaction between malonic acid half thioester and aldehydes

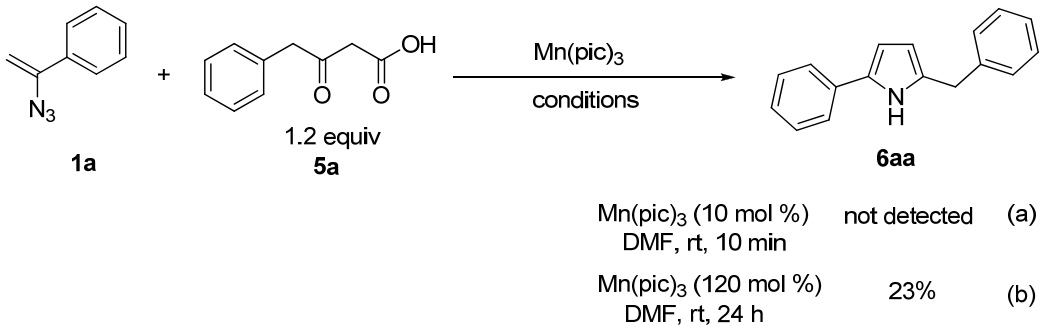
Narasaka reported that treatment of a mixture of *β*-keto acid **I** and silyl enol ether **II** with 2.5 equiv of Mn(III) tris(2-pyridinecarboxylate) [$Mn(pic)_3$] led to the formation of

1,4-diketone **III** in 45% yield (Scheme 3-22).[48] Mechanistic studies showed that α-carbonyl radical was likely to be generated by the interaction of both β-keto acid and silyl enol ether with $Mn(pic)_3$. Furthermore, the decarboxylation reaction might occur before alkenes addition.



Scheme 3-22. $Mn(pic)_3$-mediated reaction of β-keto acid and silyl enol ether

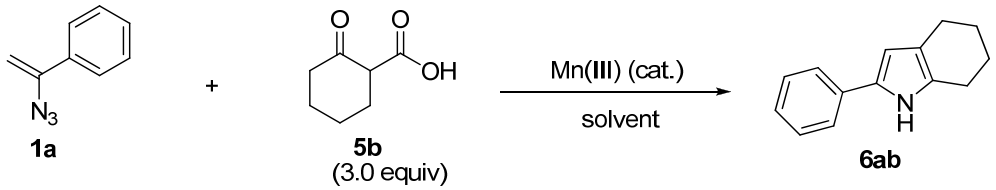
As discussed before, vinyl azides reacted smoothly with the α-carbonyl radicals derived from β-keto esters and 1,3-diketones, providing the corresponding pyrroles efficiently. Accordingly, the reaction of β-keto acid **5a** and vinyl azide **1a** by using $Mn(pic)_3$ as a catalyst (10 mol %) was examined. However, almost no pyrrole was detected with the rapid consumption of $Mn(pic)_3$ (Scheme 3-23, a). When a stoichimetric amount of $Mn(pic)_3$ was employed, the desired pyrrole **6aa** was isolated in 23% yield from a complex mixture (Scheme 3-23, b).



Scheme 3-23. $Mn(pic)_3$-mediated synthesis of pyrrole from vinyl azide and β-keto acid

Interestingly, the use of α-substituted β-keto acid **5b** instead of **5a** resulted in the formation of bicyclic pyrrole (or 4,5,6,7-tetrahydro-1*H*-indole) **6ab** in 59% yield (Table 3-8, entry 1). When the reaction was carried out by using $Mn(OAc)_3 \cdot 2H_2O$ as a catalyst, a comparable yield was obtained but a longer reaction time was necessary (entry 2). The yield of pyrrole **6ab** was further improved to 83% by the use of a catalytic amount (10 mol %) of $Mn(acac)_3$ (entry 3).

Table 3-8. Mn(III)-catalyzed pyrrole formation from vinyl azide **1a** and β-keto acid **5b**[a]



entry	[Mn(III)]	[Mn(III)]/mol %	solvent	time/h	yield/%[b]
1	$Mn(pic)_3$	20	DMF	1	59%
2	$Mn(OAc)_3 \cdot 2H_2O$	10	DMF	30	51%
3	**$Mn(acac)_3$**	**10**	**DMF**	**5**	**83%**
4	$Mn(acac)_3$	10	MeOH	17	trace
5	$Mn(acac)_3$	10	CH_3CN	36	76%

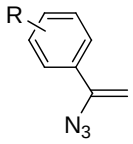
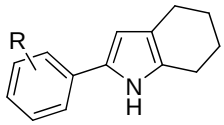
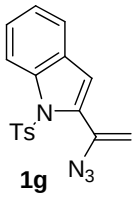
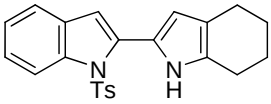
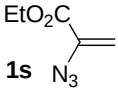
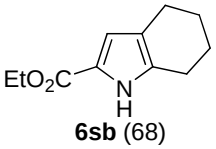
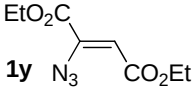
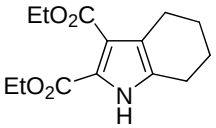
[a] Reactions were performed at room temperature under N_2 atmosphere. [b] Isolated yields.

It was noteworthy that the choice of solvent was also crucial in this reaction. When the reaction was carried out in MeOH, only a trace amount of product was obtained (Table 3-8, entry 4), whereas pyrrole **6ab** was prepared in high yield in DMF (entry 3). Although the reaction in CH_3CN also provided the desired pyrrole **6ab** in good yield, longer reaction time was needed (entry 5).

The generality of this reaction was investigated by employing a range of vinyl azides **1** and β-keto acid **5b** with $Mn(acac)_3$ as a catalyst (Table 3-9). The reaction of α-aryl vinyl azides with **5b** proceeded smoothly to give the desired bicyclic pyrroles in good yields (entries 1-5). Notably, the reaction of vinyl azide **1g** possessing an α-indolyl group

led to the formation of 2,2'-biindole **6gb** (entry 6). Moreover, α-ethoxylcarbonyl vinyl azides (**1s** and **1y**) also reacted smoothly (entries 7 and 8), giving the corresponding bicyclic pyrroles (**6sb** and **6yb**) in good yields. In the case of vinyl azide **1y**, the presence of ethoxylcarbonyl group at the β-position did not retard this reaction, providing tetrasubstituted pyrrole **6yb** in 74% yield (entry 8).

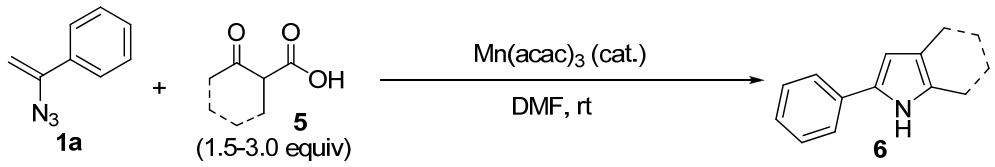
Table 3-9. Mn(III)-catalyzed pyrrole formation from vinyl azides **1** and β-keto acid **5b**[a]

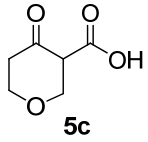
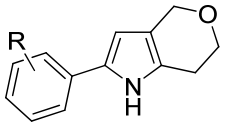
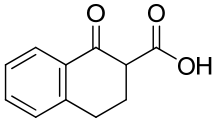
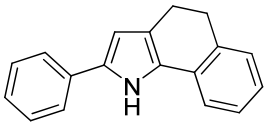
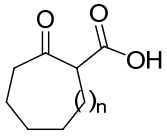
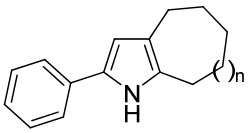
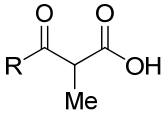
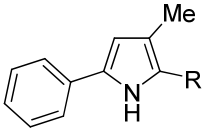
entry	vinyl azides	[Mn(III)] /mol %	time /h	pyrroles **6** (yield/%)[b]
				
1	**1a**: R = H	10	5	**6ab** (83)
2	**1c**: R = 2-OMe	20	15	**6cb** (91)
3	**1d**: R = 4-OMe	15	6	**6db** (87)
4	**1p**: R = 4-Br	15	10	**6pb** (92)
5	**1q**: R = 4-CO_2Me	20	16	**6qb** (68)
6	 **1g**	10	19	 **6gb** (76)
7	 **1s**	10	2.5	 **6sb** (68)
8	 **1y**	10	10	 **6yb** (74)

[a] Reactions were performed in DMF at rt with 1.5-3.0 equiv of β-keto acid **5b** under N_2 atmosphere (see Experimental Section). [b] Isolated yields.

The generality of various *β*-keto acids **5** was also examined using *α*-azidostyrene (**1a**) as shown in Table 3-10. Tetrahydropyrano[4,3-*b*]pyrrole **6ac** (entry 1) and 4,5-dihydro-1*H*-benzo[*g*]indole **6ad** (entry 2) were accessed in good yields from *β*-keto acids **5c** and **5d**, respectively. As the *β*-keto acid **5d** was labile in such oxidative conditions, the slow addition of **5d** through a syringe pump was required. Azabicyclic compounds with seven- and eight-membered carbocycles (**6ae** and **6af**) could be obtained from *β*-keto acids **5e** and **5f** (entries 3 and 4). In addition, the reaction of acyclic *β*-keto acids such as **5g** and **5h** also proceeded to afford trisubstituted pyrroles **6ag** and **6ah** in good yields (entries 5 and 6).

Table 3-10. Mn(III)-catalyzed pyrrole formation from vinyl azide **1a** and *β*-keto acids **5**[a]



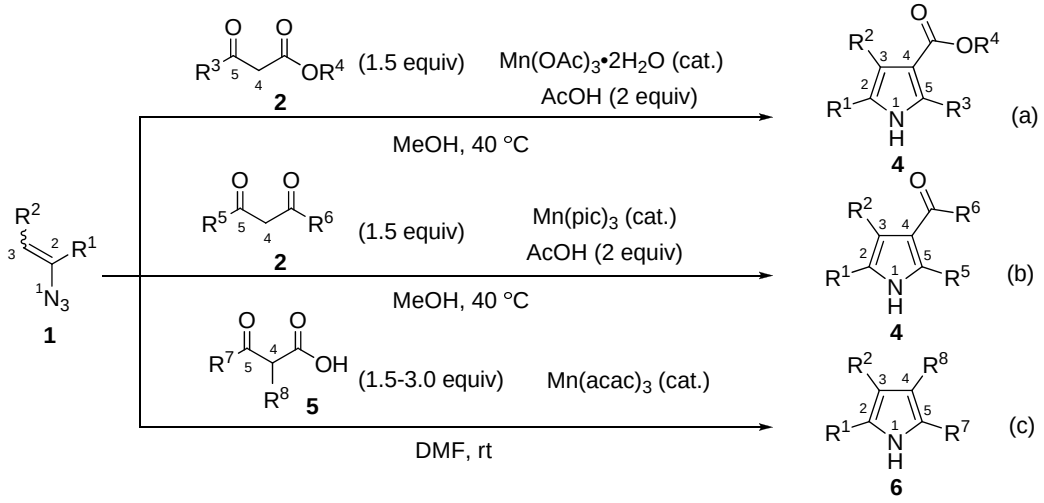
entry	β-keto acids	[Mn(III)] /mol %	time /h	pyrroles **6** (yield/%)[b]
1	 **5c**	10	5	 **6ac** (83)
2	 **5d**	40	4	 **6ad** (65)[c]
				
3	**5e** (n = 1)	15	10	**6ae** (81)
4	**5f** (n = 2)	20	15	**6af** (82)
				
5	**5g**: R = Et	10	3	**6ag** (84)
6	**5h:** R = C_6H_5	10	1	**6ah** (80)

[a] Reactions were performed in DMF at rt with 1.5-3.0 equiv of *β*-keto acid **5b** under N_2 atmosphere (see Experimental Section). [b] Isolated yields. [c] *β*-Keto acid **5d** was slowly added through a syringe pump.

3.3 Conclusion

In summary, a general Mn(III)-catalyzed method has been developed for the synthesis of tri- and tetrasubtituted *N*-H pyrroles from readily available vinyl azides and 1,3-dicarbonyl compounds (Scheme 3-24). Three types of 1,3-dicarbonyl compounds including *β*-keto esters, 1,3-diketones and *β*-keto acids are utilized in this method. For

each kind of 1,3-dicarbonyl compounds, the preferential Mn(III) catalyst is varied, depending on the nature of 1,3-dicarbonyl compounds as well as the redox potentials of Mn(III) catalysts. As a consequence, $Mn(OAc)_3 \cdot 2H_2O$ is an effective catalyst for the reactions of vinyl azides and *β*-keto esters (Eq. a), while a stronger oxidant, $Mn(pic)_3$, is required for the reactions of 1,3-diketones (Eq. b). On the other hand, $Mn(acac)_3$ is preferred for the reactions of vinyl azides and *β*-keto acids (Eq. c).



Scheme 3-24. Mn(III)-catalyzed pyrrole formation from vinyl azides and 1,3-dicarbonyl compounds

These reactions constitute a formal [3+2] annulation reaction, in which vinyl azides provide three atoms (N1, C2, C3) to pyrrole ring, whereas 1,3-dicarbonyl compounds contribute the other two carbon units (C4, C5) (Scheme 3-24).

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(43) For the catalytic radical reactions using the Mn(II)/Co(II)/O_2 redox system, see: (a) Kagayama, T.; Fuke, T.; Sakaguchi, S.; Ishii, Y. *Bull. Chem.Soc. Jpn.* **2005**, *78*, 1673. (b) Hirase, K.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2002**, *67*, 970. (c) Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2000**, 2317.

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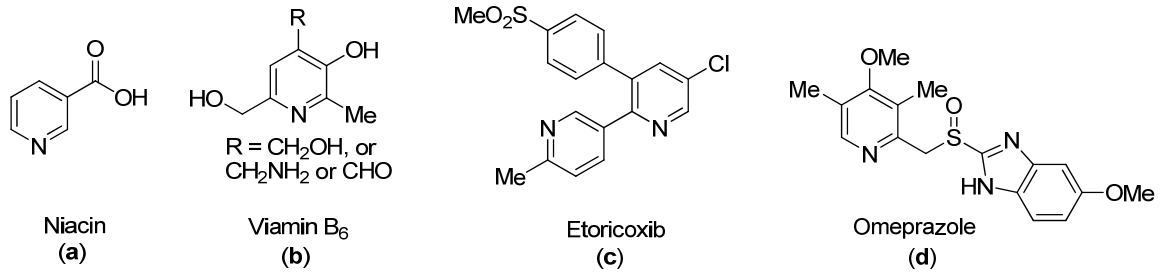
Chapter 4 Mn(III)-Mediated/Catalyzed Synthesis of Pyridines from Vinyl Azides and Cyclopropanols

4.1 Introduction

As an important series of azaheterocyclic compounds, pyridines are prevalent in a tremendous number of natural products.[1] For example, the pyridine core exists in many naturally occurring compounds such as niacin (vitamin B_3, Figure 4-1, **a**), vitamin B_6 (Figure 4-1, **b**), and a large number of isolated pyridine alkaloids.[2] Besides its abundance in nature, a large number of existing drugs are based upon a pyridine ring.[3] Two of such compounds are an *anti*-inflammatory drug etoricoxib (Figure 4-1, **c**)[4] and a well-known proton-pump inhibitor omeprazole (Figure 4-1, **d**).

Figure 4-1. Examples of pyridine-containing natural products and pharmaceutical agents

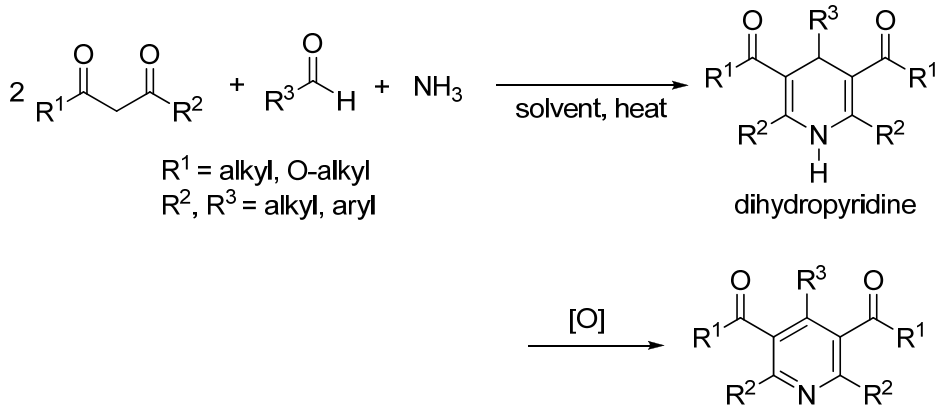


The ubiquity in nature and wide applications of pyridines in various areas have led to a large variety of synthetic methods for constructing the pyridine core.[5] In this section, the author focuses on some typical routes to access the pyridine core, rather than an exhaustive exploration of the myriad pyridine syntheses.

4.1.1 Classical Methods for Synthesis of Pyridines

The majority of traditional syntheses of pyridine ring rely on two approaches: the condensation of amines with carbonyl compounds and cycloaddition reactions.

One of the most popular condensation reactions to construct the pyridine ring is the Hantzsch synthesis.[6] This method consists of condensation of two molecules of 1,3-dicarbonyl compounds, one molecule of aldehyde and ammonia. The resulting dihydropyridines are further oxidized to corresponding pyridines (Scheme 4-1).

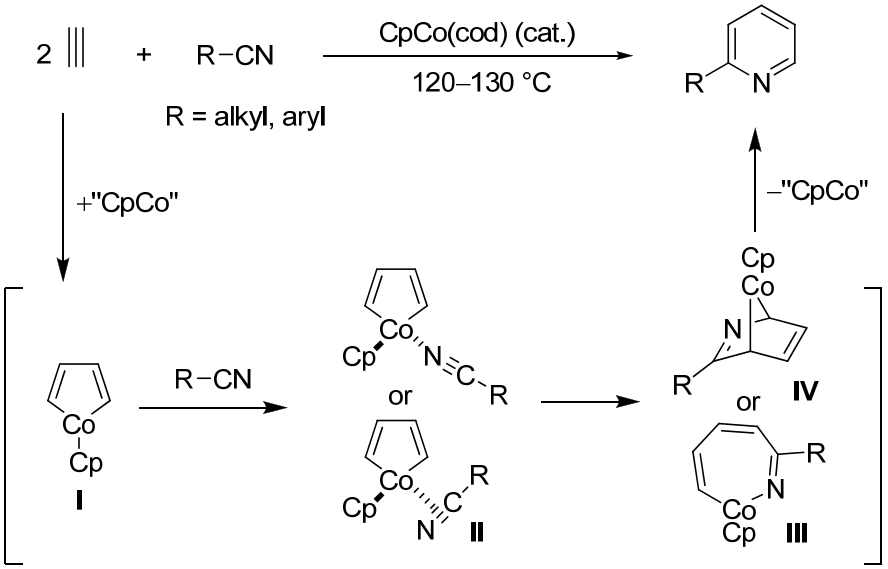


Scheme 4-1. Hantzsch pyridine synthesis

Alternative methods for the construction of pyridine ring involving condensation processes include the reaction of ammonia with 1,5-dicarbonyl compounds,[7] Bohlmann-Rahtz synthesis,[8] Kröhnke synthesis,[9] and many others.

Cycloaddition reactions provide a convergent synthesis of pyridines from simple starting materials. The transition metal mediated [2+2+2] cycloaddition of two molecules of alkynes and one molecule of nitrile provides pyridine skeleton in a particularly

straightforward fashion (Scheme 4-2). The most widely used transition metal catalysts for such cycloaddition are Co(I) complexes.[10]



Scheme 4-2. Co(I)-catalyzed pyridine formation from alkynes and nitriles

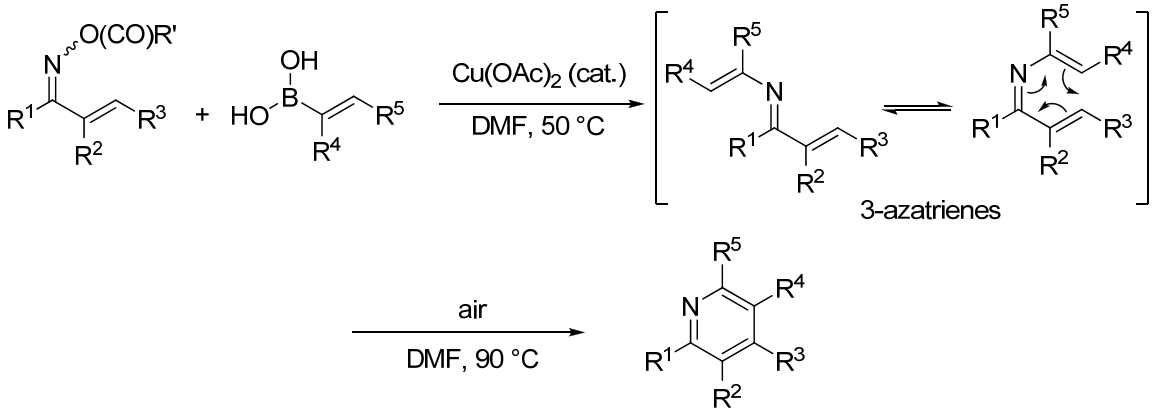
The reaction is thought to be initiated by the oxidative coupling of two alkynes to afford cobaltacycle **I**, to which then a nitrile coordinates. The resulting nitrile complex **II** is transformed to cobaltazacycloheptatriene **III** by insertion of the nitrile unit to the cobaltacycle. Alternatively, cobaltacycle intermediate **IV** is generated via Diels-Alder-type reaction. In either case, reductive elimination takes place to produce the pyridine and regenerate the cobalt(I) catalyst.

Recently, a number of the other transition metals,[7c] including Fe,[11] Rh,[12] Ru,[13] Ni,[14] Ti[15] and so on, have also been found to catalyze this process efficiently.

4.1.2 Modern Methods for Synthesis of Pyridines

Recently, much effort has been devoted to the development of mild and efficient methods for the synthesis of substituted pyridines from readily accessible starting materials. Among them, the methods based on the utilization of oximes or imines as starting materials are of great interest.

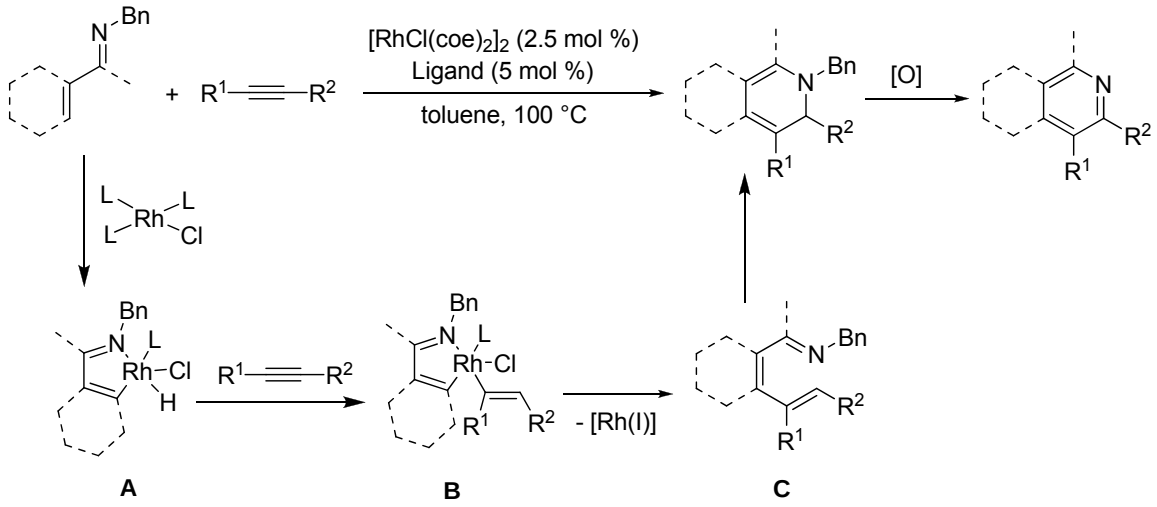
Liebeskind has reported a tandem reaction sequence to prepare highly substituted pyridines from *α,β*-unsaturated *O*-acyl oximes and alkyenylboronic acids (Scheme 4-3).[16] This formal [4+2] annulation process involves a Cu(II)-catalyzed cross coupling of boronic acids with oxime *O*-carboxylates to give 3-azatrienes (the detailed mechanism for this coupling reaction was illustrated in Chapter 1, Section 1.3, Scheme 1-31). Subsequent 6π-electron cyclization of the resulted 3-azatrienes followed by aerobic oxidation provides pyridines.



Scheme 4-3. Synthesis of pyridines from *α,β*-unsaturated *O*-acyl oximes and alkyenylboronic acids

Bergman and Ellman have developed a convenient one-pot synthesis of highly substituted pyridines from alkynes and *α,β*-unsaturated *N*-benzyl imines via a C−H alkenylation/electrocyclization/aromatization sequence.[17] A plausible mechanistic pathway

for this formal [4+2] annulation reaction is shown in Scheme 4-4. Formation of Rh(III) intermediate **A** by oxidative addition of vinylic C–H bond to Rh(I) complex is followed by migratory insertion of an alkyne to the Rh–H bond, producing intermediate **B**. Subsequent reductive elimination provides the azatriene intermediate **C**, which undergoes electrocyclization followed by oxidation to yield pyridines.



Scheme 4-4. Synthesis of Pyridines from alkynes and α,β-unsaturated N-benzyl imines

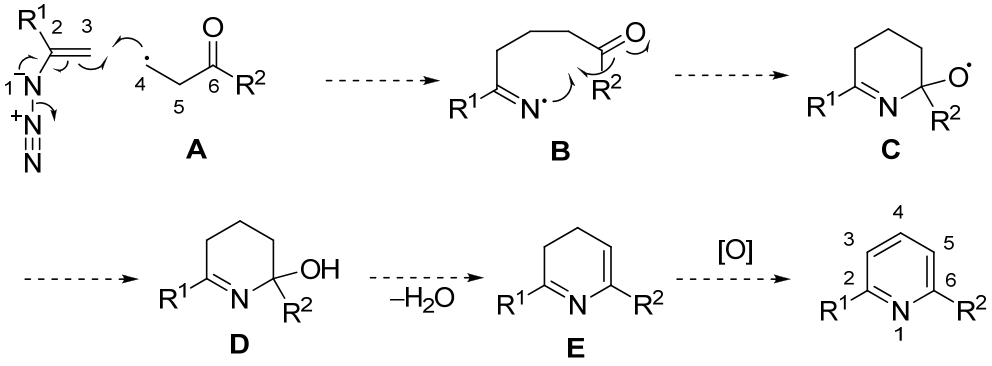
Even though a variety of methods for the synthesis of pyridines have been developed, the utilization of organic azides as nitrogen sources to prepare pyridines was rare. As describe in Chapter 1, organic azides have great advantages in the synthesis of azaheterocycles, such as easy accessibility, chemical diversity, and versatility. By taking advantage of the unique property of vinyl azides to serves as carbon radical acceptors, the author has developed a synthetic method of pyrroles by utilizing 1,3-dicarbonyl compounds as the sources of α-carbonyl radicals (Chapter 3). Encouraged by this result, the author has explored a synthetic method of pyridines from vinyl azides and cyclopropanols, where cyclopropanols work as the progenitors of β-carbonyl radicals.

4.2 Results and Discussion

4.2.1 Synthetic Plan of Pyridines from Vinyl Azides and *β*-Carbonyl Radicals

As discussed in Chapter 3, a Mn(III)-catalyzed reaction has been developed for the synthesis of tri- and tetrasubtituted *N*-H pyrroles from readily available vinyl azides and 1,3-dicarbonyl compounds. This formal [3+2] annulation reaction provides a new route to construct five-membered azaheterocycles, in which vinyl azides contribute three atoms including one nitrogen unit, and 1,3-dicarbonyl compounds donate the other two carbon atoms.

In order to further explore the synthetic utility of vinyl azides as nitrogen sources for the synthesis of other types of azaheterocycles, the author next intended to explore a formal [3+3] annulation reaction. That is, the reaction of *β*-carbonyl radicals instead of *α*-carbonyl radicals and vinyl azides is expected to afford six-membered azaheterocycles. As shown in Scheme 4-5, addition of *β*-carbonyl radical **A** to a vinyl azide generates iminyl radical **B**, which cyclizes with an intramolecular carbonyl group leading to tetrahydropyridine intermediate **C**. The subsequent dehydration and oxidation may afford a pyridine.



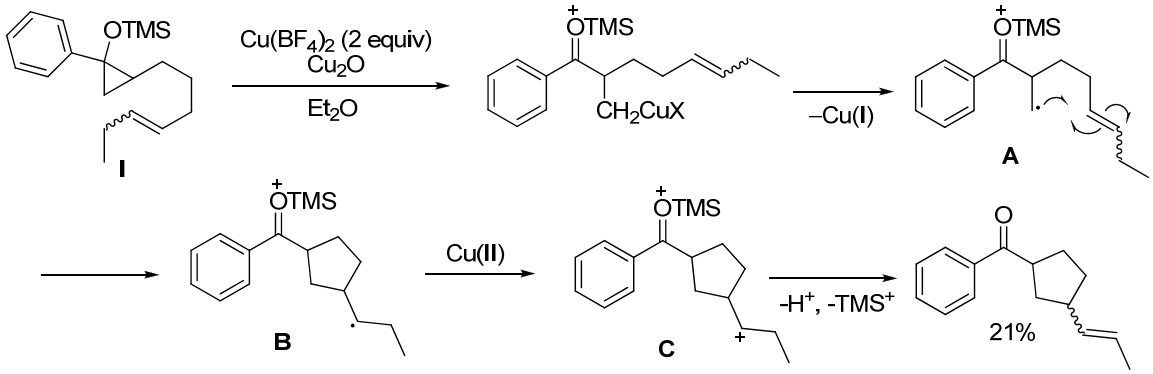
Scheme 4-5. Synthetic plan for pyridines from vinyl azides and β-carbonyl radicals

4.2.2 The Chemistry of *β*-Carbonyl Radicals Derived from Cyclopropanols

β-Carbonyl radicals are one of the basic components for the synthesis of pyridines in the synthetic plan described above,. Thus, in this section, the author begins with a brief introduction on *β*-carbonyl radicals in terms of their generation methods as well as their reactions.

It has been reported that one-electron oxidation of cyclopropanols and cyclopropyl silyl ethers can generate *β*-carbonyl radicals by opening the strained three-membered ring. The oxidants available for this process included Cu(II),[18] Fe(III),[19] Mn(III),[20] and Ag(I)[21] complexes.

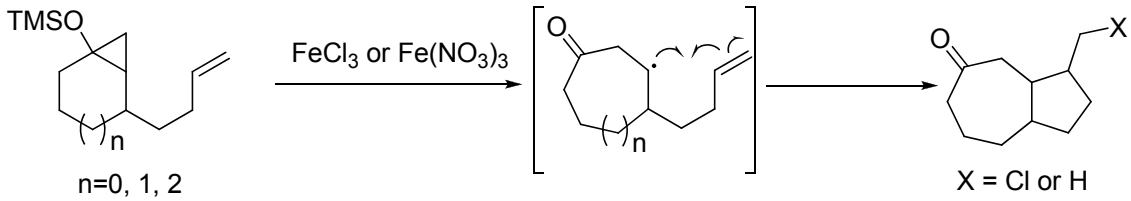
For example, Snider reported that oxidation of cyclopropyl silyl ether **I** with 2 equiv of $Cu(BF_4)_2$ generates cation radical **A**, which undergoes 5-*exo* cyclization to give alkyl radical **B**. This radical is then oxidized by Cu(II) followed by deprotonation and desilylation to give a cyclopentane compound (Scheme 4-6).[18]



Scheme 4-6. Cu(II)-mediated generation of *β*-carbonyl radical

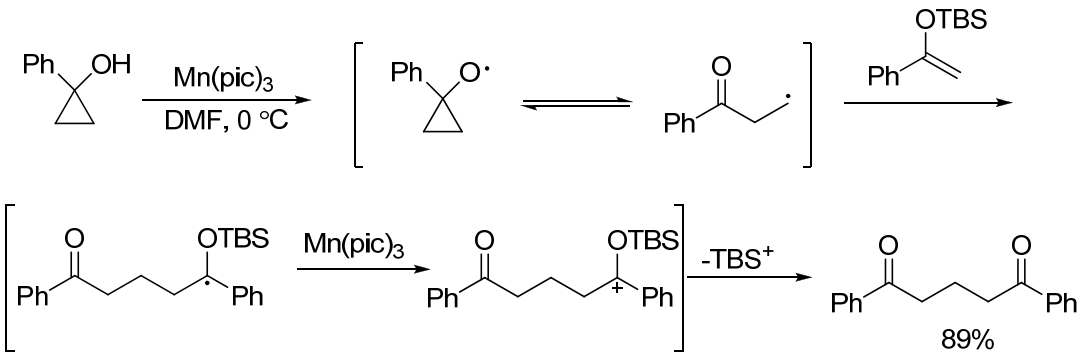
Fe(III) complexes such as $FeCl_3$ and $Fe(NO_3)_3$ were also used to generate *β*-carbonyl radicals via oxidative cleavage of cyclopropyl silyl ethers (Scheme 4-7). Similarly, the

resulted β-carbonyl radicals cyclize with the intramolecular C=C bond, followed by hydrogen or chlorine abstraction to give bicyclic ketones.[19]



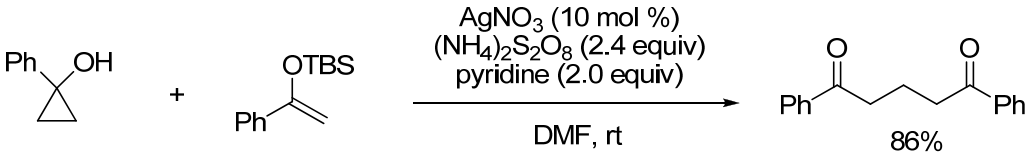
Scheme 4-7. Fe(III)-mediated generation of β-carbonyl radical

The aforementioned two methods focused on the oxidative generation of β-carbonyl radicals from cyclopropyl silyl ethers and their addition to intramolecular C=C bond. Narasaka investigated $Mn(pic)_3$-mediated generation of β-carbonyl radicals from cyclopropanols and their intermolecular addition reactions to electron rich olefins such as silyl enol ethers.[20] In this case, 1,5-diketones were formed as shown in Scheme 4-8.



Scheme 4-8. Mn(III)-mediated reaction of cyclopropanol and silyl enol ether

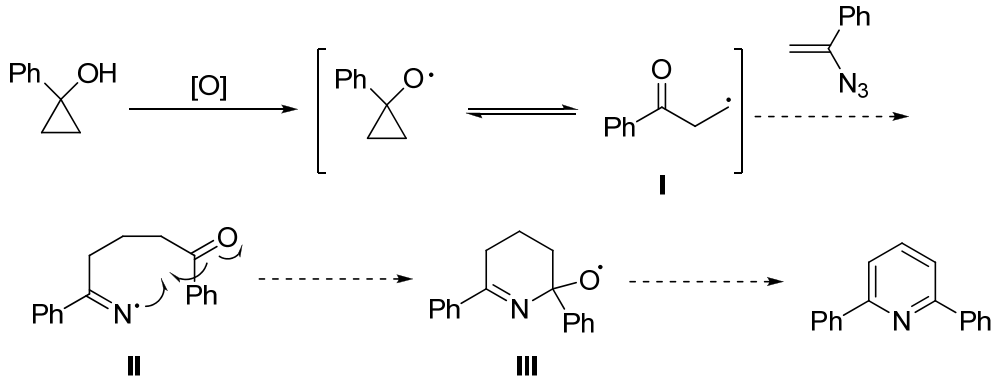
However, this reaction needed a stoichiometric amount (at least 2 equivalents) of Mn(III) complexes, which prevented its application to a large-scale synthesis. Recently, Narasaka improved this stoichiometric reaction to a catalytic process by the use of a catalytic amount of $AgNO_3$ and $(NH_4)_2S_2O_8$ as a reoxidant (Scheme 4-9).[21]



Scheme 4-9. Ag(I)-catalyzed reaction of cyclopropanol and silyl enol ether

4.2.3 Optimization of Mn(III)-Mediated/Catalyzed Reaction of *α*-Azidostyrene and 1-Phenylcyclopropanol

As described above, cyclopropanols can act as precursors of *β*-carbonyl radicals, which can further add to alkenes to provide a new C−C bond and alkyl radicals (Section 4.2.1, Schemes 4-8 and 4-9). If a vinyl azide is utilized instead of an alkene, an iminyl radical should be generated and then a pyridine will be accessed following the proposed reaction route as shown in Scheme 4-10 (see also Section 4.2.1, Scheme 4-5).



Scheme 4-10. Anticipated reaction of *α*-azidostyrene and 1-phenylcyclopropanol

Although several oxidants are available for the generation of *β*-carbonyl radicals from cyclopropanols or cyclopropyl silyl ethers, as described in the previous Section, Mn(III) complexes are preferred for the synthesis of pyridines from vinyl azides and cyclopropanols. This expectation is based upon two findings that have been concluded from the previously

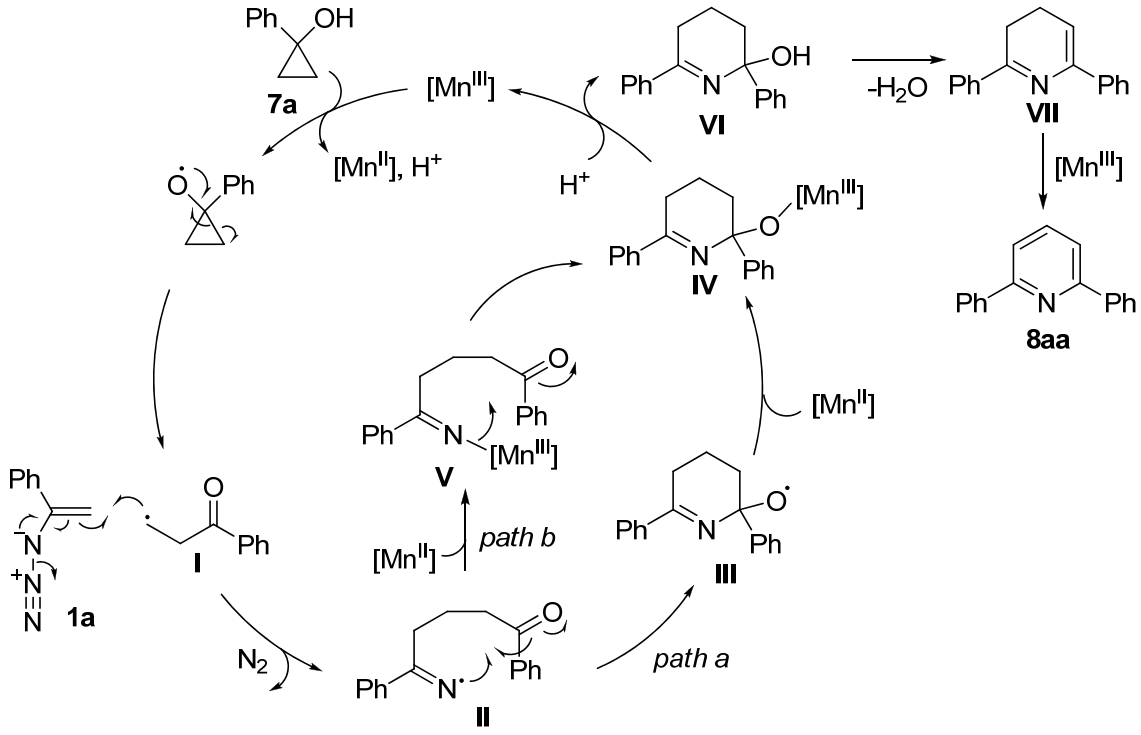
developed Mn(III)-catalyzed reactions of vinyl azides and 1,3-dicarbonyl compounds: 1) vinyl azides have been found to be stable under the Mn(III) oxidative conditions, and 2) the Mn(III)/Mn(II) catalytic cycle involving iminyl radicals as the key intermediates can promote the reaction to proceed in a catalytic manner (the detailed explanation see Chapter 3, Section 3.2.3.2).

On the basis of these speculations, the author then explored of a synthetic method towards pyridines by using vinyl azides and cyclopropanols as the starting materials and Mn(III) complexes as the oxidants.

A detailed proposed reaction pathway for the Mn(III)-mediated reaction of vinyl azide **1a** and cyclopropanol **7a** is described in Scheme 4-11. The reaction may be initiated by the addition of *β*-keto radical **I**, generated by one-electron oxidation of **7a** by Mn(III), to vinyl azide **1a**, affording iminyl radical **II** with elimination of dinitrogen. Consecutive cyclization of iminyl radical **II** to an intramolecular carbonyl group would give alkoxyl radical **III**, which is possible to be reduced by Mn(II) species to afford Mn(III) alkoxide **IV** (path a). Alternatively, the reaction of iminyl radical **II** with Mn(II) species may afford iminylmanganese(III) **V**, nucleophilic attack of which to a carbonyl group yields addition intermediate **IV** (path b). Subsequent protonation occurs to afford tetrahydropyridine **VI** with the regeneration of Mn(III) species which can be used in the next initiation step. Consequently, a catalytic amount of Mn(III) complex is supposed to be sufficient for the formation of intermediate **VI**.

Subsequent dehydration and oxidation steps are needed to complete the synthesis of pyridine **8aa**. However, Mn(III) complex is also possible to be involved in the stoichiometric oxidation of dihydropyridine **VII** to pyridine **8aa**. Therefore, a stoichiometric amount of

Mn(III) complex is expected to play dual roles for both the catalytic oxidation of **7a** and the stoichiometric oxidation of **VII** to pyridine **8aa**. Furthermore, the addition of an additive such as AcOH may accelerate the dehydration of **VI** to dihydropyridine **VII**.



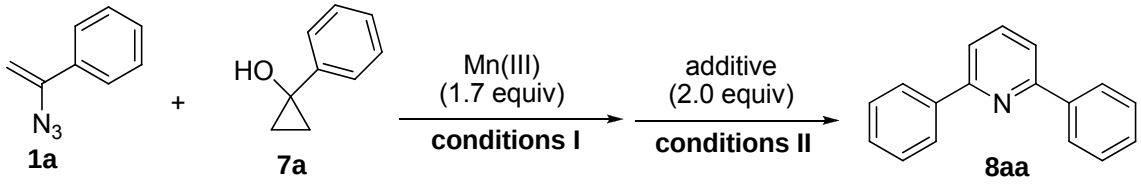
Scheme 4-11. Proposed synthetic pathway of pyridine from α-azidostyrene and 1-phenylcyclopropanol

Based on the aforementioned synthetic hypothesis, at first, the reaction of α-azidostyrene (**1a**) and 1-phenylcyclopropanol (**7a**) was examined by using a stoichiometric amount of Mn(III) complexes as the oxidant (Table 4-1). When $Mn(OAc)_3 \cdot 2H_2O$ (1.7 equiv to **1a**) was added to a mixture of vinyl azide **1a** and cyclopropanol **7a** (1.5 equiv to **1a**), a vigorous release of dinitrogen was observed. After 5 min, TLC analyses showed that vinyl azide **1a** was entirely consumed, which indicated that intermediate **VI** was generated immediately. Pyridine **8aa** was obtained in 57% yield after the addition of AcOH (entry 1).

When $Mn(pic)_3$ was used as the oxidant, the rapid conversion of vinyl azide **1a** to **VI** was detected as well, providing pyridine **8aa** in 52% yield (entry 2). However, when the reaction was carried out in acetonitrile at 40 °C, the reaction of vinyl azide **1a** and cyclopropanol **7a** was very slow, presumably because of the low solubility of $Mn(pic)_3$ in acetonitrile. Finally, pyridine **8aa** was obtained in 58% yield (entry 3).

Ultimately, utilization of $Mn(acac)_3$ was found to improve the yield of **8aa** to 84% (entry 4). It was worth mentioning that the addition of AcOH after the consumption of vinyl azide **1a** was crucial for this reaction. If AcOH was added prior to the addition of $Mn(acac)_3$, the yield of product was decreased to 66% (entry 5). Moreover, the absence of AcOH resulted in longer reaction time for the conversion of intermediate **VI** to pyridine **8aa** (entry 6).

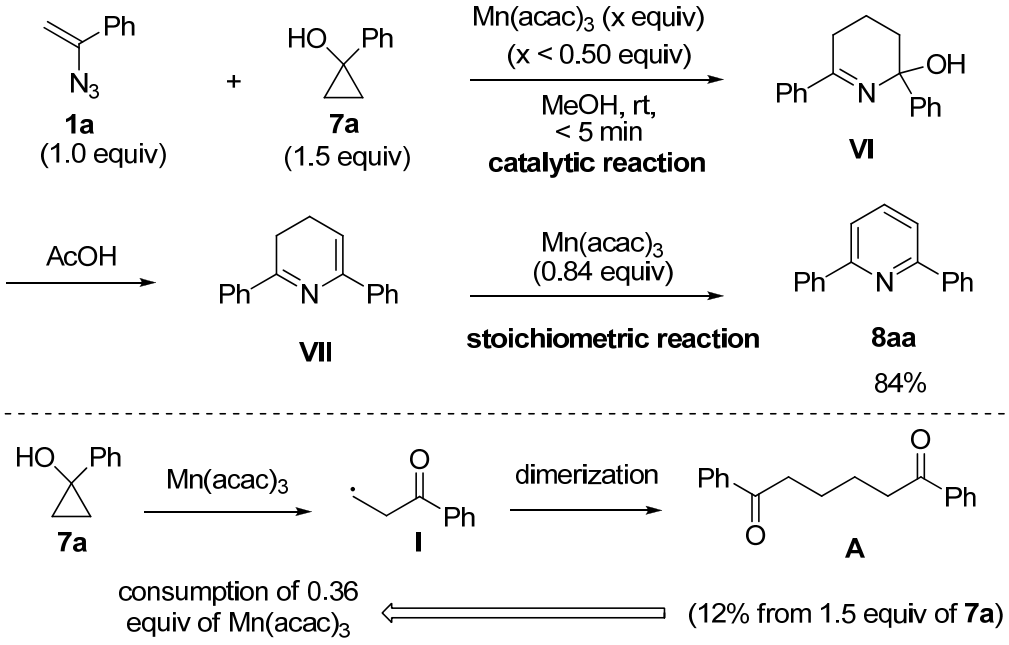
Table 4-1. Mn(III)-mediated synthesis of pyridine **8aa** from vinyl azide **1a** and cyclopropanol **7a**



entry	Mn(III)	**conditions I**	additive	**conditions II**	yield/%[a]
1	$Mn(OAc)_3{\cdot}2H_2O$	MeOH, rt, 5 min	AcOH	rt, 1 h	57
2	$Mn(pic)_3$	MeOH, rt, 5 min	AcOH	rt, 1 h	52
3	$Mn(pic)_3$[b]	MeCN, 40 °C, 5 h	—	—	58
4	**$Mn(acac)_3$**	**MeOH, rt, 5 min**	**AcOH**	**rt, 1 h**	**84**
5	$Mn(acac)_3$	MeOH, rt, 1 h	AcOH[c]	—	66
6	$Mn(acac)_3$	MeOH, rt, 5 min	—	40 °C, 3 h	74

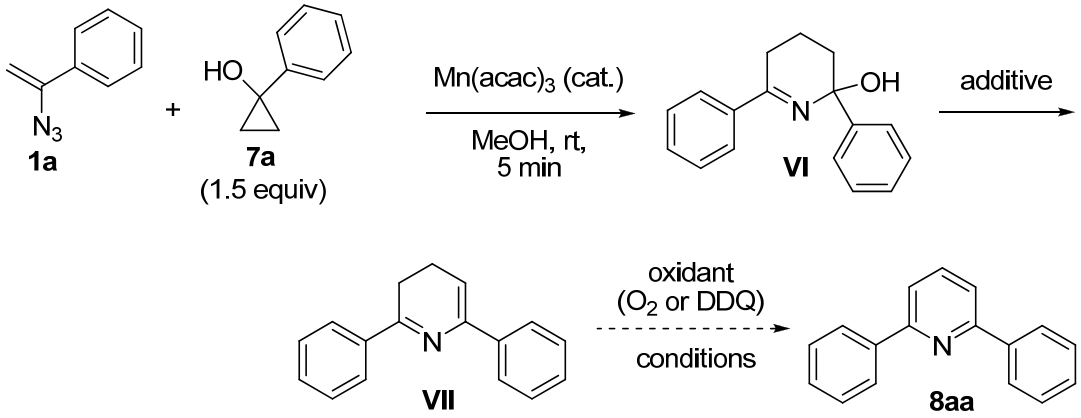
[a] Isolated yields. [b] 1.2 equiv of **7a** and 1.2 equiv of $Mn(pic)_3$ were used. [c] AcOH was added before the addition of $Mn(acac)_3$.

In the optimized reaction conditions (Table 4-1, entry 4), pyridine **8aa** was obtained in 84% yield by using1.5 equiv of cyclopropanol **7a** and 1.7 equiv of $Mn(acac)_3$. As shown in Scheme 4-12, the oxidation of dihydropyridine **VII** to pyridine **8aa** was certainly a stoichiometric process and at least 0.84 equiv of $Mn(acac)_3$ was consumed in this step (because 84% yield of pyridine **8aa** was obtained). Furthermore, some of the excess amount of cyclopropanol **7a** was also oxidized by $Mn(acac)_3$ to give β-carbonyl radical **I**, which underwent dimerization to give 1,6-diketone **A**. Indeed, compound **A** was isolated in 12% yield (calculated from 1.5 equiv **7a**, 18% calculated from **1a**), which meant that 0.36 equiv amount of $Mn(acac)_3$ (according to **1a**) was consumed in this reaction. As a consequence, there was only 0.50 equiv amount of $Mn(acac)_3$ available for the reaction of vinyl azide **1a** and cyclopropanol **7a**. If this reaction was also a stoichiometric one, the yield of pyridine **8aa** must be less than 50%. However, as mentioned before, 84% yield of pyridine **8aa** was obtained, which suggested that the formation of **VI** was probably a catalytic process as shown in the proposed reaction pathway (Scheme 4-11).



Scheme 4-12. Reaction sequence for the formation of **8aa**

The above information inspired the author to exploit an alternative catalytic synthesis of pyridine **8aa**, where the Mn(III) species is only involved as a catalyst in the reaction of vinyl azide **1a** and cyclopropanol of **7a**, but not as the oxidant for the subsequent transformation of dihydropyridine **VII** to **8aa**. The designed reaction pathway is depicted in Scheme 4-13. A catalytic amount of $Mn(acac)_3$ is first added to the reaction mixture of vinyl azide **1a** and cyclopropanol **7a** to afford intermediate **VI**, which is then treated with an acid (as the additive) and another oxidant such as molecular oxygen[22] or 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[23] for the oxidation of **VII** to **8aa**.

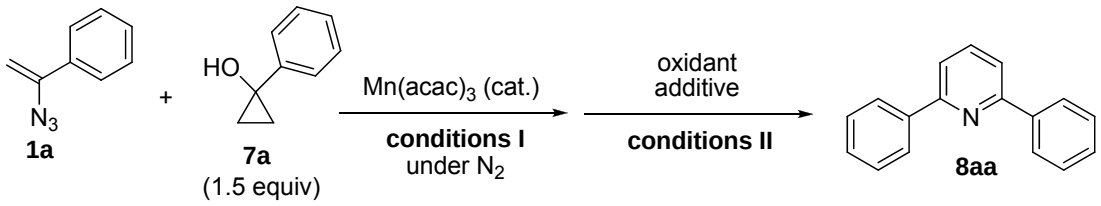


Scheme 4-13. Designed $Mn(acac)_3$-catalyzed synthesis of pyridine **8aa**

As expected, the treatment of a mixture of vinyl azide **1a** and cyclopropanol **7a** with a catalytic amount of $Mn(acac)_3$ (0.2 equiv) in MeOH also consumed vinyl azide **1a** within 5 min at room temperature, and the subsequent treatment with an oxidant and AcOH (2 equiv) provided the desired pyridine **8aa**, although the yields of **8aa** were moderate (Table 4-2, entries 1 and 2). It was noteworthy that addition of HCl (in MeOH, 2 equiv) instead of AcOH could improve the yield of **8aa** to 80% (entry 3). The use of the stronger acid (HCl) may allow the dehydration step (**VI** → **VII**) to proceed more efficiently than that of AcOH, and thus the yield of **8aa** was improved. However, such stronger acidic reaction conditions

were not compatible with some functional groups. Some examples will be given in the next Section.

Table 4-2. $Mn(acac)_3$-catalyzed synthesis of pyridine **8aa** from vinyl azide **1a** and cyclopropanol **7a**



entry	$Mn(acac)_3$ (equiv)	conditions I	oxidant (equiv)	additive (equiv)	conditions II	yield/%[a]
1	$Mn(acac)_3$ (0.2)	MeOH rt, 5 min	DDQ (1.5 equiv)	AcOH (2 equiv)	rt, 1 h	59
2	$Mn(acac)_3$ (0.2)	MeOH rt, 5 min	O_2 (1 atm)	AcOH (2 equiv)	rt, 1 h	59
3	**$Mn(acac)_3$ (0.1)**	**MeOH rt, 5 min**	**O_2 (1 atm)**	**HCl (2 equiv)**	**40 °C, 1 h**	**80**

[a] Isolated yields.

4.2.4 Mn(III)-Medicated/Catalyzed Synthesis of Pyridines from Vinyl Azides and Cyclopropanols

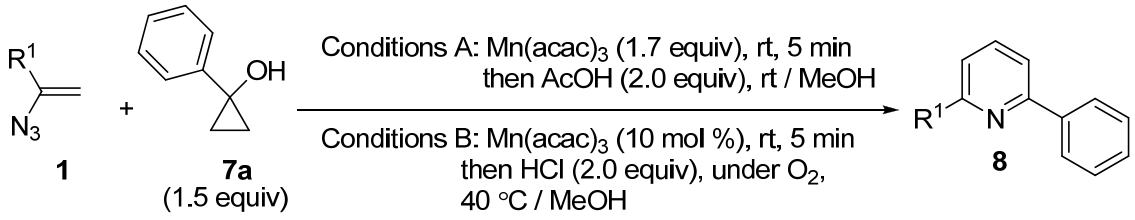
As mentioned in the previous Section, there are two optimized reaction conditions enabled by using $Mn(acac)_3$ as the oxidant. One is the stoichiometric reaction (Table 4-1, entry 3), the other one is the catalytic reaction (Table 4-2, entry 3). The scope of α-substituted vinyl azides **1** was first examined by using the stoichiometric conditions (Table 4-3, Conditions A). Then, several substrates were also tested by employing the catalytic reaction conditions (Conditions B).

By applying the $Mn(acac)_3$ as the stoichiometric oxidant (Conditions A), a range of α-aryl vinyl azides reacted smoothly with cyclopropanol **7a** to afford 2,6-diarylpyridines in

good yields (Table 4-3, entries 1-7). Especially, heteroaryl motifs such as pyrrolyl (**8fa**, entry 8) and indolyl (**8ga**, entry 9) groups were successfully installed on the pyridine ring. The reaction of electron-deficient vinyl azide **1s** also provided pyridine **8sa** in 51% yield (entry 10).

Using vinyl azides **1a**, **1c**, **1e** and **1g** as the substrates, the pyridine formation under the catalytic conditions (Conditions B) was studied (entries 1, 3, 7 and 9). Obviously, the yields of the corresponding pyridines **8** were almost comparable with those under the stoichiometric conditions.

Table 4-3. $Mn(acac)_3$-mediated and $Mn(acac)_3$-catalyzed pyridine formation from vinyl azides **1** and cyclopropanol **7a**[a]

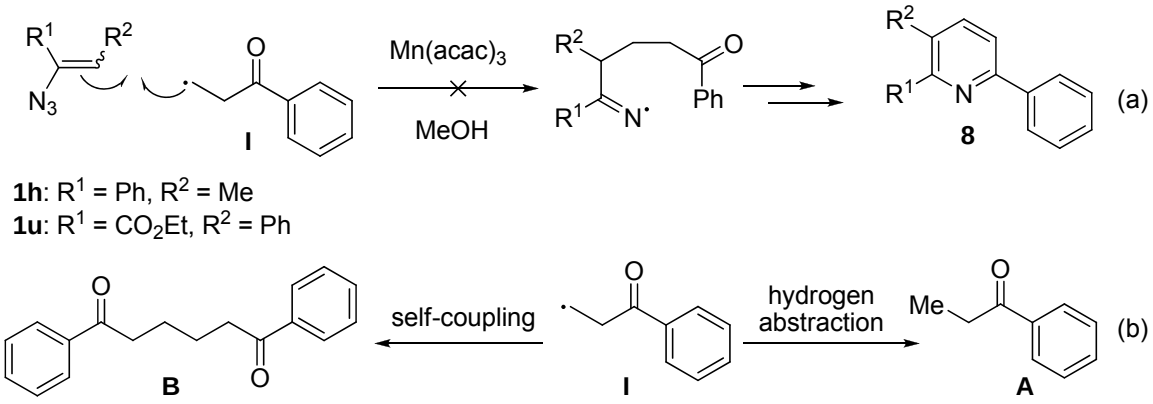


entry	vinyl azides **1**	pyridines **8**		yield[b] Conditions A	yield[b] Conditions B
1	**1a**: R = H		**8aa**	84%	80%
2	**1b**: R = 4-Me		**8ba**	84%	
3	**1c**: R = 2-OMe		**8ca**	71%	70%
4	**1d**: R = 4-OMe		**8da**	70%	
5	**1p**: R = 4-Br		**8pa**	70%	
6	**1q**: R = 4-CO_2Me		**8qa**	70%	
7	**1e**		**8ea**	75%	72%
8	**1f**		**8fa**	70%[c]	
9	**1g**		**8ga**	66%[c]	50%
10	**1s**		**8sa**	51%	

[a] Unless otherwise noted, the reactions were carried out under either Conditions A or B; **Conditions A**: treatment of a mixture of vinyl azides **1** (0.3 mmol) and cyclopropanol **7a** (1.5 equiv) with $Mn(acac)_3$ (1.7 equiv) in MeOH at room temperature under N_2 atmosphere for 5 min followed by addition of AcOH (2 equiv). **Conditions B**: treatment of a mixture of vinyl azides **1** (0.3 mmol) and cyclopropanols (1.5 equiv) with $Mn(acac)_3$ (0.1 equiv) in MeOH at room temperature under N_2 atmosphere for 5 min followed by addition of

HCl (in MeOH, 2 equiv). [b] Isolated yields. [c] A solution of cyclopropanols **7** and AcOH in MeOH was added to vinyl azide **1a** and $Mn(acac)_3$ by a syringe pump over 1 h.

When trisubstituted vinyl azide **1h** and **1u** (Table 4-4, entries 1 and 3) were subjected to the stoichiometric reaction conditions (Conditions A), no desired pyridines were obtained at all and the vinyl azides were recovered. At the same time, the formation of propiophenone (**A**) and 1,6-diketone **B** were observed (Scheme 4-14, Eq. b). This indicated that the addition of *β*-carbonyl radical **I** derived from **7a** to trisubstituted vinyl azides **1h** and **1u** was extremely slow, due to the steric hindrance of the *β*-substituents on vinyl azides (Scheme 4-14, Eq. a). As a result, the generated *β*-carbonyl radical **I** might undergo hydrogen abstraction and self-coupling to give propiophenone (**A**) and 1,6-diketone **B**, respectively (Scheme 4-14, Eq. b). Moreover, even though $Mn(acac)_3$ was slowly added to the reaction mixture by a syringe pump, which could keep a low concentration of generated *β*-carbonyl radical **I** so as to prevent its side reactions, the desired pyridine was still not formed (entry 3).

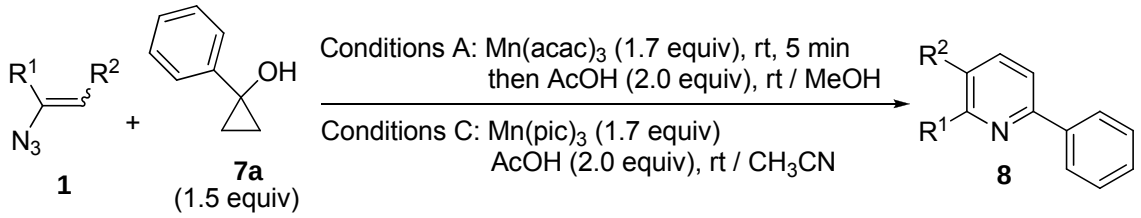


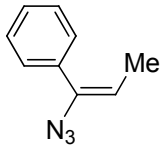
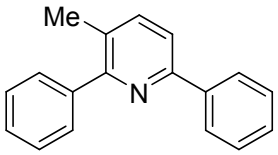
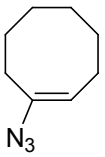
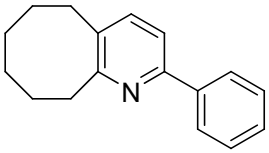
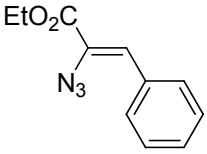
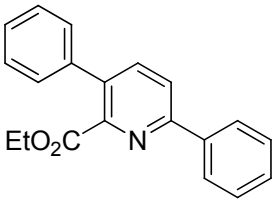
Scheme 4-14. Reaction of *β*-carbonyl radical **I** and trisubstituted vinyl azide **1h**

Fortunately, when the reaction was carried out in CH_3CN by using $Mn(pic)_3$ as the oxidant (Conditions C), the corresponding 2,3,6-trisubstituted pyridines (**8ha**, **8na**, **8ua**) were

isolated in acceptable yields (entries 1, 2 and 3). Under such reaction conditions, the side reactions of β-carbonyl radical **I** such as hydrogen abstraction and self-coupling were minimized, and the addition reaction to trisubstituted vinyl azides was enhanced in some extent, even though the reason was still unclear.

Table 4-4. Mn(III)-mediated pyridine formation from 1,2-disubstituted vinyl azides **1** and cyclopropanol **7a**[a]



entry	vinyl azides **1**		pyridines **8**		yield[b] Conditions A	yield[b] Conditions C
1		**1h**		**8ha**	0%[c]	45%
2		**1n**		**8na**		52%
3		**1u**		**8ua**	0%[c,d]	30%[e]

[a] Unless otherwise noted, the reactions were carried out under either Conditions A or C; **Conditions A**: treatment of a mixture of vinyl azides **1** (0.3 mmol) and cyclopropanol **7a** (1.5 equiv) with $Mn(acac)_3$ (1.7 equiv) in MeOH at room temperature under N_2 atmosphere for 5 min followed by addition of AcOH (2 equiv). **Conditions C**: the reactions were run using $Mn(pic)_3$ (1.7 equiv) and AcOH (2 equiv) in CH_3CN at room temperature. [b] Isolated yields. [c] Vinyl azides were remained according to ^1H NMR of the crude materials. [d] A

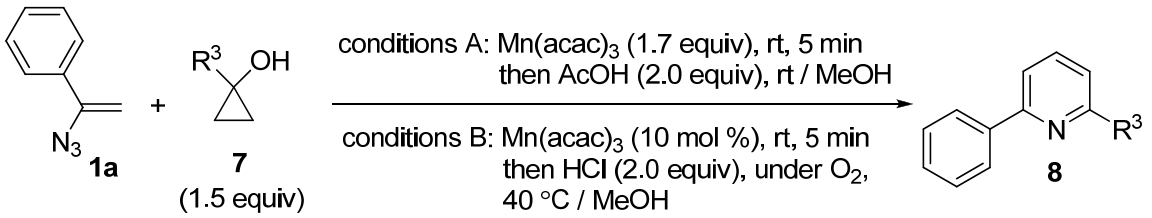
solution of cyclopropanol **7a** and AcOH in MeOH was added to vinyl azide **1u** and $Mn(acac)_3$ by a syringe pump over 1 h. [e] Vinyl azide **1u** was recovered in 20% yield.

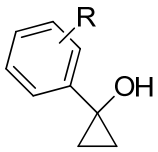
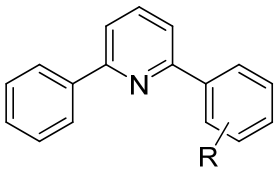
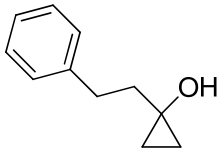
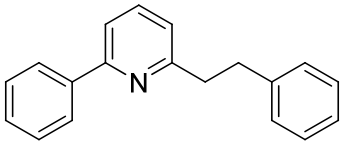
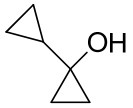
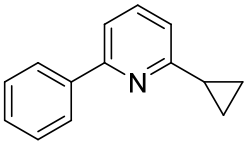
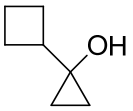
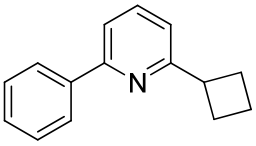
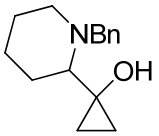
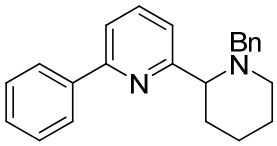
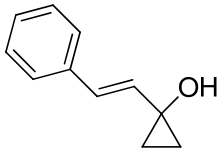
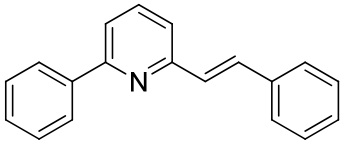
The generality of cyclopropanols was then examined using α-azidostyrene (**1a**) as shown in Table 4-5. Again, both of the stoichiometric reaction condtions (Conditions A) and the catalytic reaction conditions (Conditions C) were conducted. 1-Arylcyclopropanols were converted to the corresponding 2,6-diaryl pyridines in good yields (entries 1-3). Moreover, some alkyl groups (entries 4-7) including strained cycloalkyl groups (**8af**, **8ag**) as well as a piperidine moiety (**8ah**) could be compatible with the reaction conditions. Introduction of alkenyl (entry 8) and alkynyl (entry 9) groups (**8ai** and **8aj**) on the pyridine ring was also a particular feature of this method. 1-Methoxycarbonyl cyclopropanol (**7k**) could also react with **1a** to give pyridine **8ak** in moderate yield (entry 10).

When 1-phenyldimethylsilylcyclopropanol (**7l**) was subjected to the stoichiometric reaction conditions (Conditions A), vinyl azide **1a** was consumed, whereas no desired pyridine was detected with some unidentified products. However, when the reaction was carried out in CH_3CN by using $Mn(pic)_3$ as an oxidant, pyridine **8al** was produced in 45% yield (entry 11).

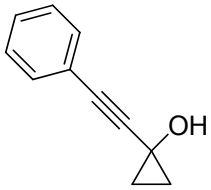
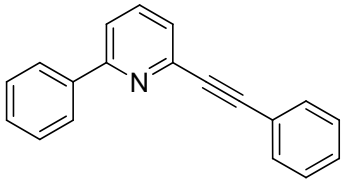
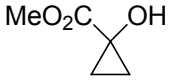
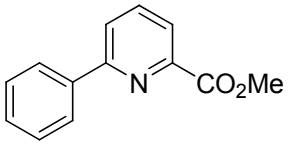
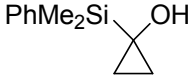
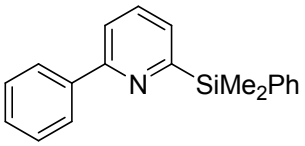
The catalytic reaction (Conditions B) provided almost comparable results for most of the substrates, except for pyridines **8ah** (entry 7) and **8aj** (entry 9). The ^1H NMR spectra of these crude reaction mixtures were messy as compared to those obtained from the stoichiometric reaction, which indicated that some unknown side reactions occurred under such acidic conditions (HCl as additive).

Table 4-5. Mn(III)-mediated pyridine formation from vinyl azide **1a** and cyclopropanols **7**[a]



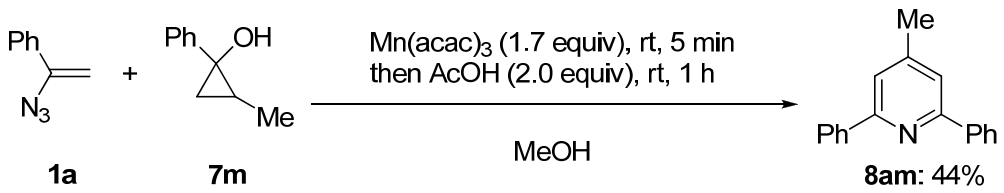
entry	cyclopropanols **7**	pyridines **8**		yield[b] Conditions A	yield[b] Conditions B
1	 **7b**: R = 4-Br		**8ab**	81%	82%
2	**7c**: R = 2-Br		**8ac**	70%	
3	**7d**: R = 4-C_6H_5		**8ad**	66%	
4	 **7e**		**8ae**	80%	70%
5	 **7f**		**8af**	73%	70%
6	 **7g**		**8ag**	78%	70%
7	 **7h**		**8ah**	82%	45%
8	 **7i**		**8ai**	54%	51%

continued...

entry	vinyl azides **1**		pyridines **8**		yield[b]	
					Conditions A	Conditions B
9		**7j**		**8aj**	55%	21%
10		**7k**		**8ak**	33%	
11		**7l**[c]		**8al**	45%	

[a] Unless otherwise noted, the reactions were carried out under either Conditions A or B; **Conditions A**: treatment of a mixture of vinyl azide **1a** (0.3 mmol) and cyclopropanols **7** (1.5 equiv) with $Mn(acac)_3$ (1.7 equiv) in MeOH at room temperature under N_2 atmosphere for 5 min followed by addition of AcOH (2 equiv). **Conditions B**: treatment of a mixture of vinyl azide **1a** (0.3 mmol) and cyclopropanols **7** (1.5 equiv) with $Mn(acac)_3$ (0.1 equiv) in MeOH at room temperature under N_2 atmosphere for 5 min followed by addition of HCl (in MeOH, 2 equiv). [b] Isolated yields. [c] The reaction was run using $Mn(pic)_3$ (1.7 equiv) in CH_3CN at room temperature.

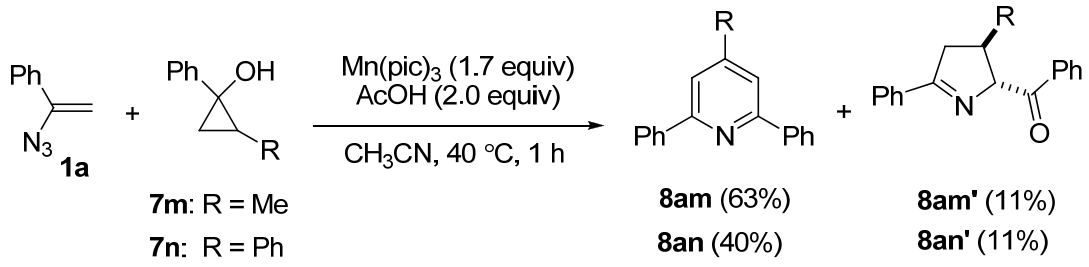
When 1,2-disubstituted cyclopropanol **7m** was subjected to the stoichiometric reaction (Conditions A), the desired 2,4,6-trisubstituted pyridine **8am** was afforded in 44% yield (Scheme 4-15).



1a **7m** **8am:** 44%

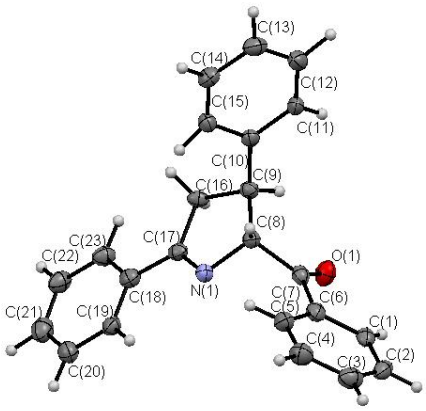
Scheme 4-15. $Mn(acac)_3$-mediated reaction of **1a** and **7m**

Surprisingly, when the reactions of vinyl azide **1a** with 1,2-disubstituted cyclopropanols (**7m**, **7n**) were conducted by using $Mn(pic)_3$ as the oxidant, not only the desired 2,4,6-trisubsituted pyridines (**8am** and **8an**) but also dihydropyrroles (**8am'** and **8an'**) were obtained (Scheme 4-16). The structure of **8an'** was confirmed by the X-ray crystallographic analysis (Figure 4-2).



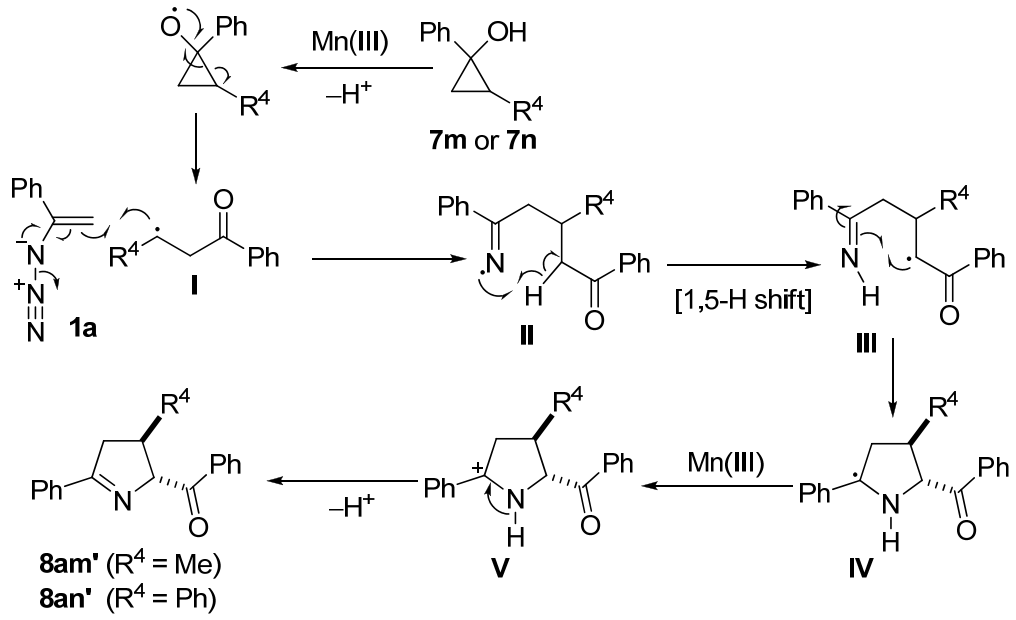
Scheme 4-16. $Mn(pic)_3$-mediated reactions of **1a** and 1,2-disubstituted cyclopropanols

Figure 4-2. X-ray structure of dihydropyrrole **8an'**



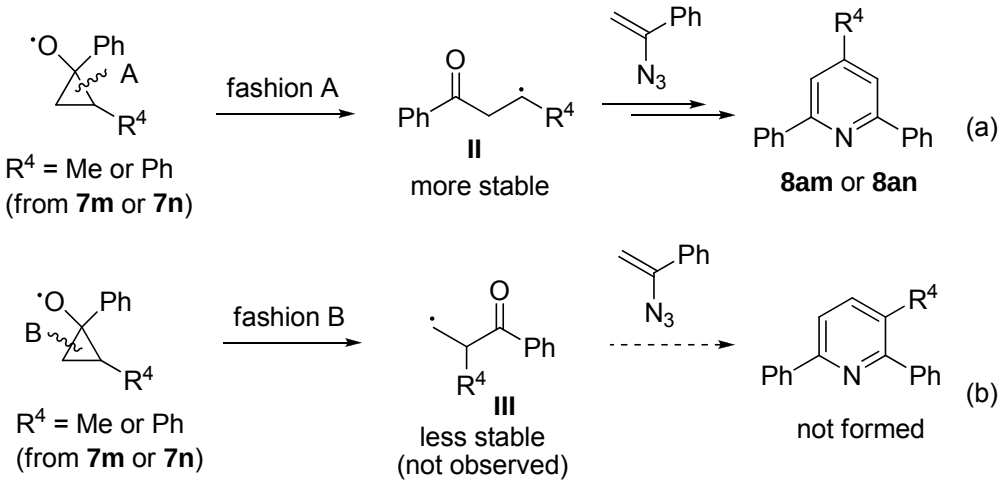
A plausible reaction pathway for such dihydropyrroles is depicted in Scheme 4-17. Generation of iminyl radical **II** by addition of *β*-carbonyl radical **I** to vinyl azide **1a** is followed by 1,5-hydrogen shift[24] to give intermediate **III**, which possesses both *N*–H imine and *α*-carbonyl radical moieties. Subsequently, the resulted carbon radical undergoes 5-*endo* cyclization to the nitrogen atom of the *N*–H imine, affording a new C–N bond with a tertiary

radical (**IV**). Oxidation of this tertiary radical by Mn(III) complex followed by deprotonation leads to dihydropyrroles **8am'** and **8an'**.



Scheme 4-17. A plausible mechanism for the formation of dihydropyrroles **8am'** and **8an'**

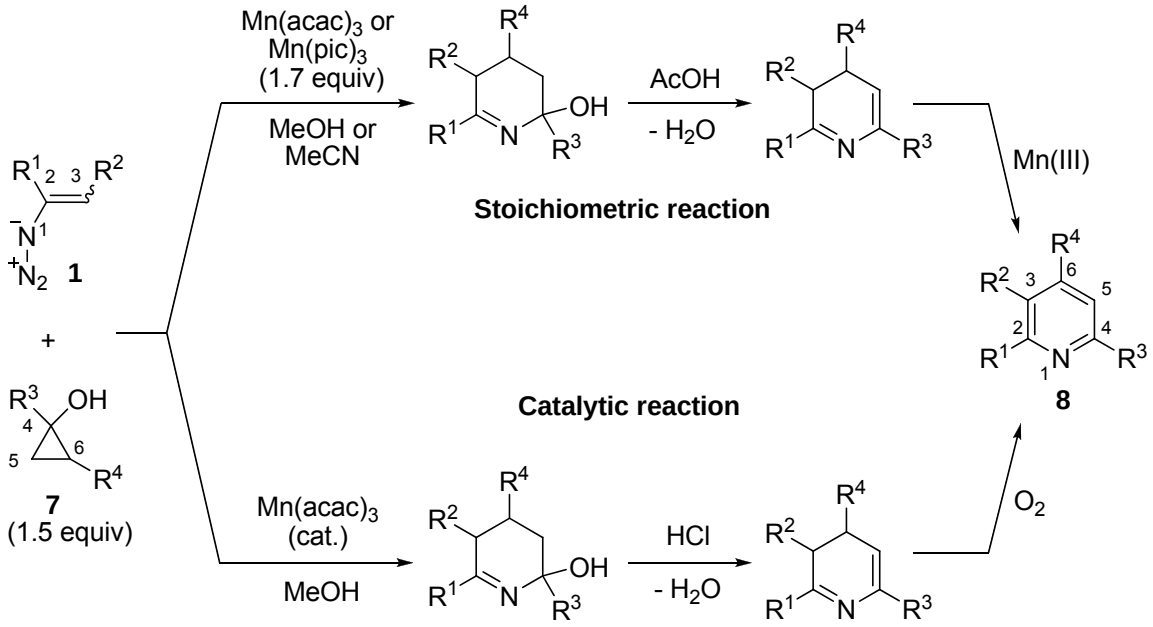
As reported, there are two manners of the C–C bond cleavage in the ring-opening of cyclopropoxy radical **I** derived from **7m** or **7n** (Scheme 4-18, fashion A and fashion B).[25] Fashion A provides a thermodynamically more stable secondary *β*-carbonyl radical **II**, while the fashion B gives a disfavored primary *β*-carbonyl radical **III**. In this Mn(III)-mediated reaction, secondary *β*-carbonyl radicals **II** are found to be formed predominantly via oxidative ring-opening of **7m** and **7n**, whereas no product derived from *β*–carbonyl radical **III** is observed.



Scheme 4-18. Two pathways for ring-opening of cyclopropoxy radicals

4.3 Conclusion

In summary, the author has developed Mn(III)-mediated/catalyzed syntheses of substituted pyridines from readily available vinyl azides and cyclopropanols (Scheme 4-19). In the stoichiometric reaction, the Mn(III) species was involved not only in the catalytic oxidative generation of β-carbonyl radicals from cyclopropanols, but also in the oxidation of the intermediate dihydropyridines to pyridines. In the catalytic reaction, the Mn(III)-catalyzed reaction of vinyl azides and cyclopropanols first afforded the annulated intermediates. Finally, the treatment with an acid and molecular oxygen yielded the desired pyridines.



Scheme 4-19. Mn(III)-mediated and Mn(III)-catalyzed pyridine formation from vinyl azides and cyclopropanols

In this formal [3+3] annulation reaction, both vinyl azides and cyclopropanols were acting as the donors for three atoms. The former provided two carbon atoms (C2, C3) and a nitrogen atom (N1), while the later contributed the other three carbon units (C4, C5, C6).

4.4 References and Notes

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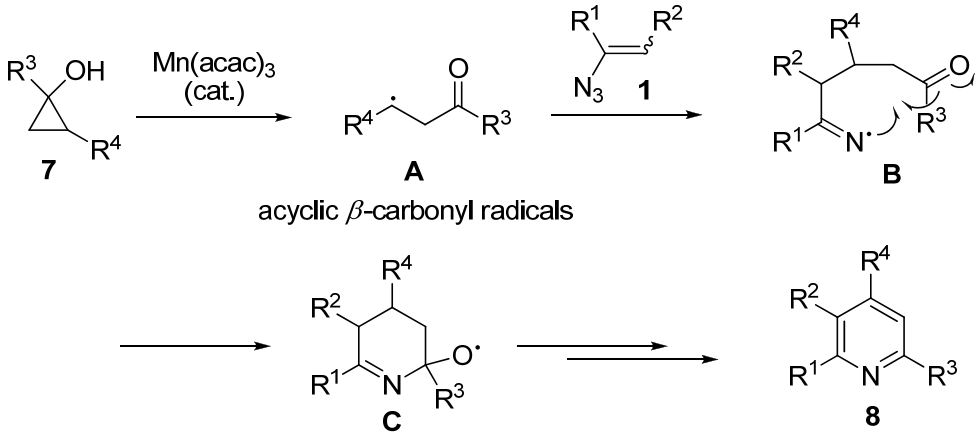
Chapter 5 $Mn(acac)_3$-Catalyzed Synthesis of Azabicyclic Compounds from Vinyl Azides and Bicyclo[3.1.0]hexan-1-ols

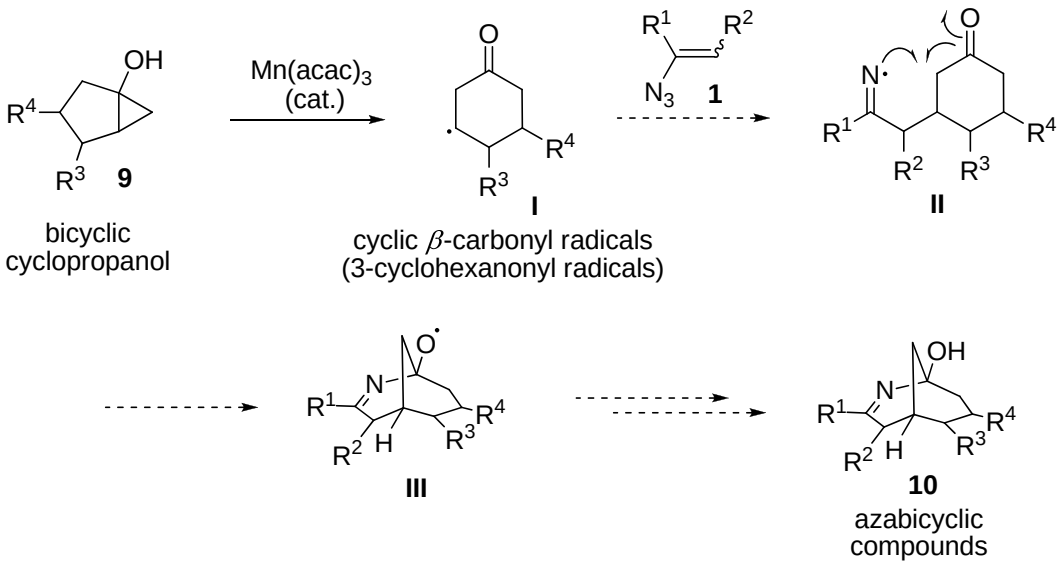
5.1 Introduction

In chapter 4, the author described a Mn(III)-catalyzed formal [3+3] annulation reaction of vinyl azides and cyclopropanols for the synthesis of substituted pyridines, where cyclopropanols **7** serve as the precursors of acyclic β-carbonyl radicals (Scheme 5-1).



Scheme 5-1. Synthesis of pyridines **8** from vinyl azides **1** and cyclopropanols **7**

Inspired by this result, the author next intended to expand this reaction by employing bicyclo[3.1.0]hexan-1-ols **9** (abbreviated as bicyclic cyclopropanols in this thesis) as sources of cyclic β-carbonyl radicals **I** (3-cyclohexanonyl radicals) (Scheme 5-2). It was envisioned that cyclization of the resulted iminyl radicals **II** with the intramolecular carbonyl group would construct azabicyclic intermediates **III**, from which azabicyclic compounds **10** should to be formed.

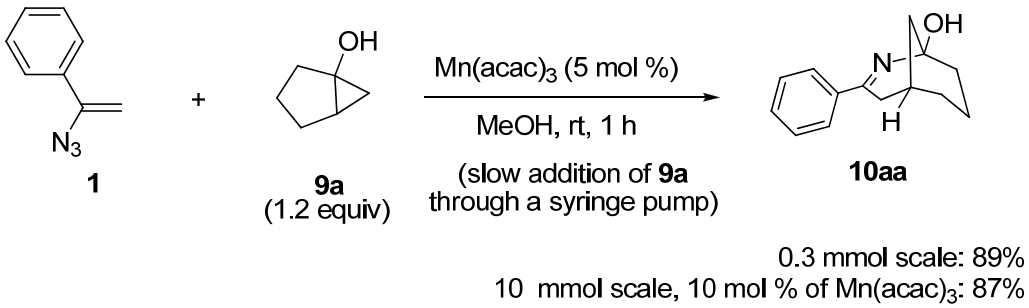


Scheme 5-2. Synthetic plan for azabicyclic compounds **10** from vinyl azides **1** and bicyclic cyclopropanols **9**

5.2 Results and Discussion

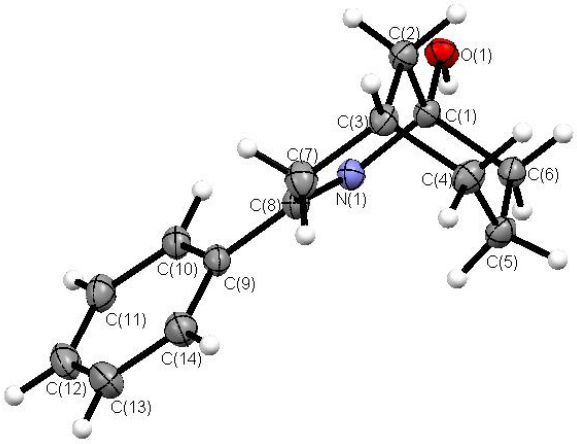
5.2.1 $Mn(acac)_3$-Catalyzed Synthesis of 2-Azabicyclo[3.3.1]non-2-en-1-ol Derivatives from Vinyl Azides and Bicyclo[3.1.0]hexan-1-ols

According to the above synthetic hypothesis for azabicyclic compounds **10**, the reaction of vinyl azide **1a** and bicyclic cyclopropanol **9a** by using $Mn(acac)_3$ as a catalyst was first examined. As expected, 2-azabicyclo[3.3.1]non-2-en-1-ol (**10aa**) was isolated in 89% yield by slow addition of **9a** through a syringe pump to a mixture of vinyl azide **1a** and $Mn(acac)_3$ (5 mol %) over 1 h (Scheme 5-3). The structure of **10aa** was confirmed by X-ray crystallographic analysis (Figure 5-1). A gram scale preparation of **10aa** was achieved in 87% yield by employing 10 mol % of $Mn(acac)_3$.



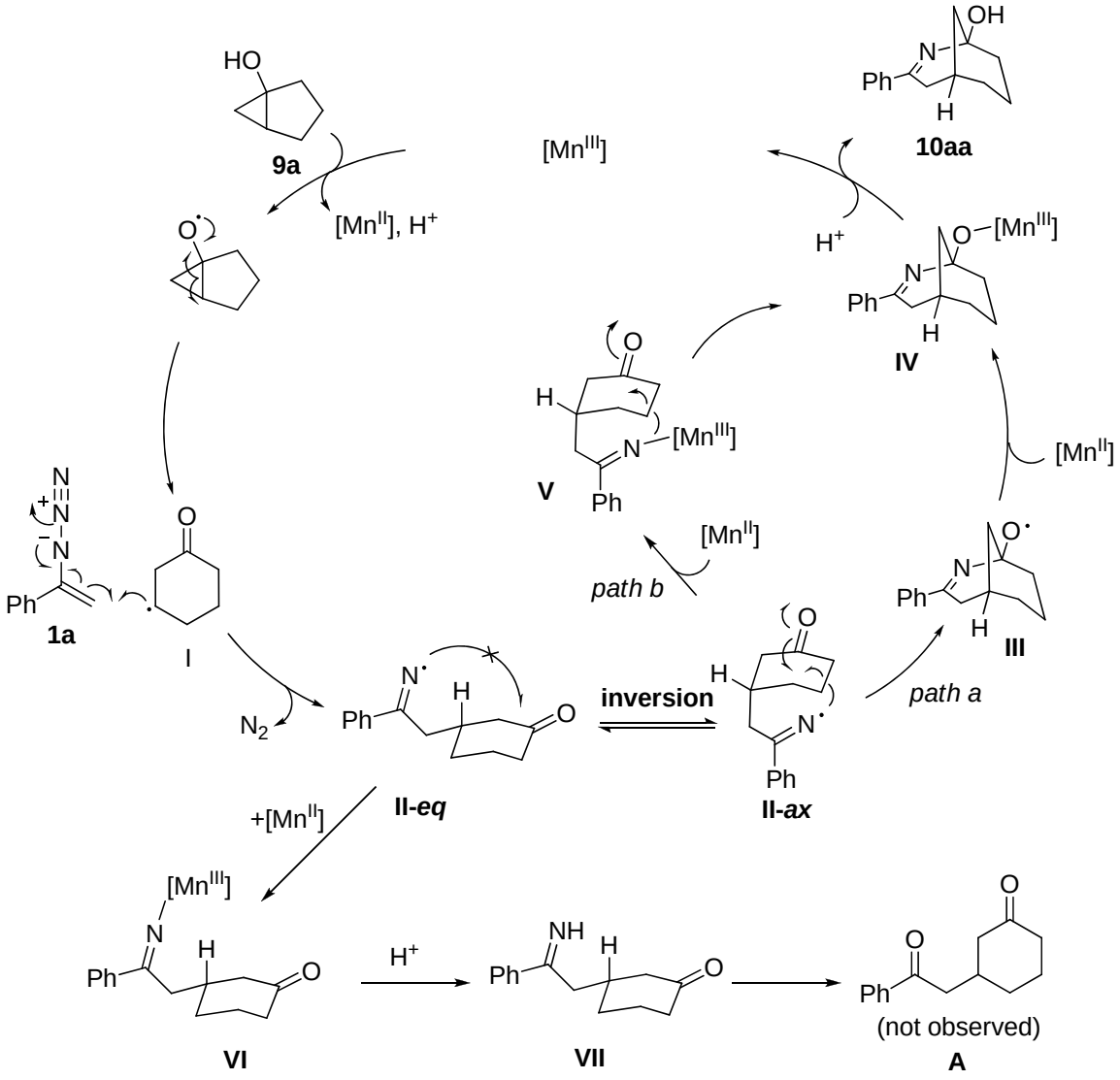
Scheme 5-3. $Mn(acac)_3$-catalyzed synthesis of azabicyclic compound **10aa**

Figure 5-1. X-ray crystal structure of **10aa**



The reaction pathway for this $Mn(acac)_3$-catalyzed synthesis of azabicyclic compound **10aa** is similar to the pyridine formation as discussed in Chapter 4. It is worth mentioning that the addition of *β*-carbonyl radical **I** derived from **9a** to the C═C of vinyl azide **1a** may afford iminyl radical **II** as two assumed major conformers[1] **II-*eq*** and **II-*ax*** (Scheme 5-4). The former one (**II-*eq***) with the iminyl radical tether in the equatorial-like position is unable to make the C–N bond formation, due to the far distance between the two reacting sites (the iminyl radical and carbonyl group). Therefore, reduction of this iminyl radial by Mn(II) followed by protonation will provide *N*-H imine **VII**, which is hydrolyzed to

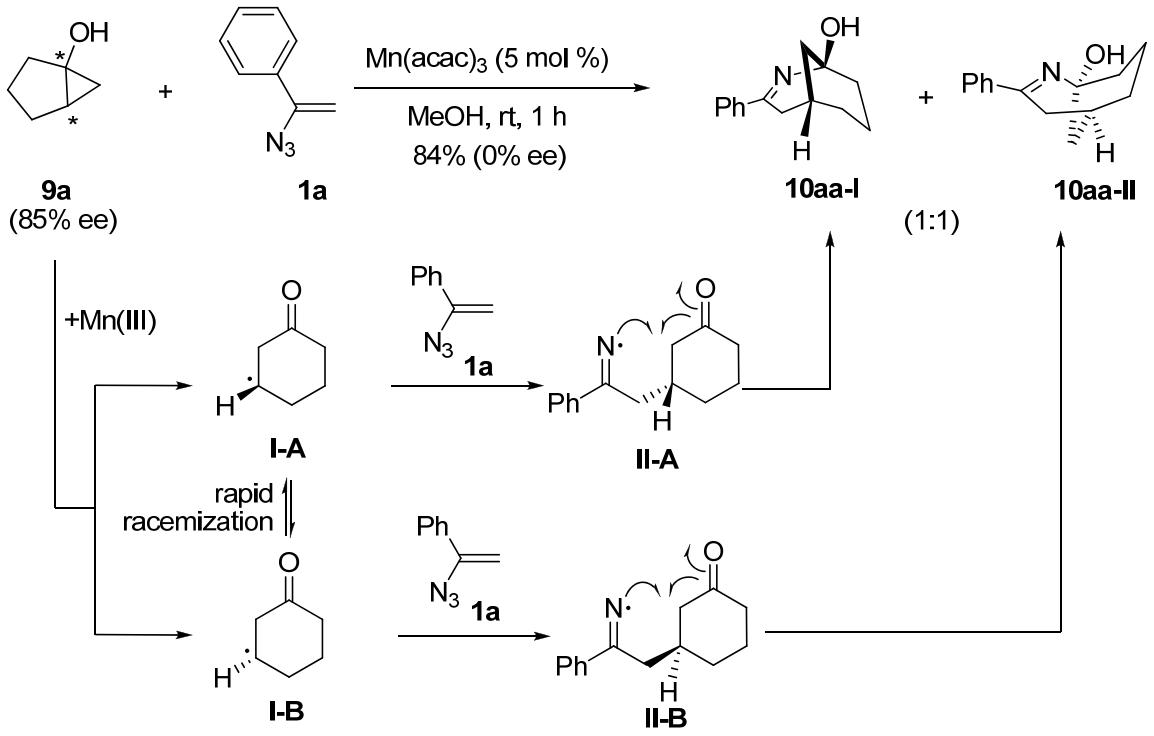
diketone **A** in the work-up process. However, such diketone was not observed at all. This may suggest that the conformational change from **II-*eq*** to **II-*ax*** should be indispensable to achieve the cyclization of the iminyl radical (for **II-*ax***) or iminylmanganese(III) (for **V**) with the carbonyl group to give alkoxy manganese(III) species **IV**.



Scheme 5-4. Proposed mechanism for the formation of **10aa**

Interestingly, the reaction of chiral bicyclo[3.1.0]hexan-1-ol (**9a**) (85% ee, the absolute configuration was not determined)[2] and **1a** afforded racemic **10aa** (Scheme 5-5).

The lack of transmission of the chirality of bicyclo[3.1.0]hexan-1-ol (**9a**) to **10aa** might indicate that the generation of ring-expanded *β*-carbonyl radical **I** from **9a** was most likely involved in the reaction mechanism,[3] since racemization of radical **I-A** and **I-B** should be quite rapid before their addition to vinyl azide **1a**.[4] As a result, addition of racemic radical species (**I-A**:**I-B** = 1:1) to vinyl azide **1a** provided a racemic mixture of **10aa-I** and **10aa-II**.



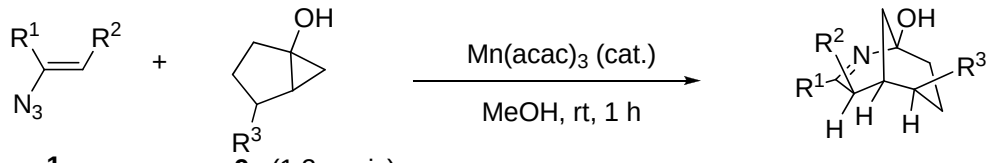
Scheme 5-5. $Mn(acac)_3$-catalyzed reaction of chiral **9a** with vinyl azide **1a**

The scope of this $Mn(acac)_3$-catalyzed synthesis of azabicyclic compounds was then investigated (Table 5-1). A range of 3-aryl-2-azabicyclo[3.3.1]non-2-en-1-ols were prepared in good to excellent yields (entries 1-7). Especially, heteroaryl moieties such as pyrrolyl (entry 8) and indolyl (entry 9) groups were successfully incorporated, even though higher catalyst loading (20 mol %) was needed to complete the reaction. The reaction of trisubstituted vinyl azide **1h** and **9a** furnished the desired **10ha** only in 28% yield along with

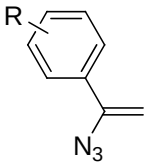
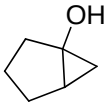
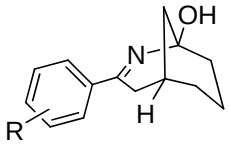
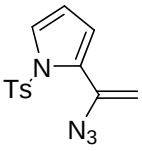
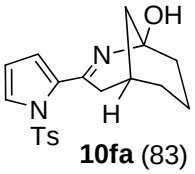
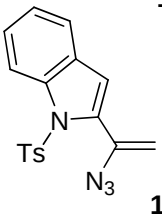
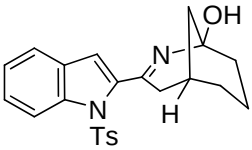
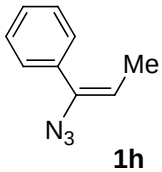
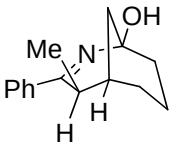
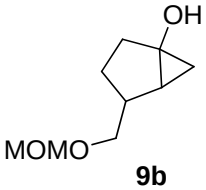
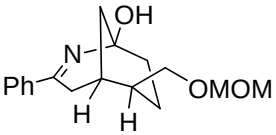
recovery of vinyl azide **1h** (68%) in the presence of 40 mol % of the catalyst (entry 10), even though cyclopropanol **9a** was completely consumed. The low yield of **10ha** might be attributed to the steric hindrance of the *β*-methyl group of vinyl azide **1h** in the addition of *β*-carbonyl radical to **1h**.

Notably, introduction of some substituents (R^3) including alkyl (**9b**, **9c**, **9d**), vinyl (**9e**) and phenyl (**9f**) groups at C-4 of bicyclo[3.1.0]hexan-1-ols did not retard the reactions, providing the corresponding 2-azabicyclo[3.3.1]non-2-en-1-ols **10** in good yields (73%-91%) and diastereoselectivities (83:17 to 94:6) (entries 11-15). The major diastereoisomers of **10ae** and **10af** were *exo*-adducts (refer to R^3, vinyl group or phenyl group for **10ae** or **10af**, respectively), which were determined by X-ray crystallographic analyses (Figure 5-2). In the case of other R^3-substituted azabicyclic compounds (**10ab**, **10ac** and **10ad**), the X-ray structures of the major isomers could not be obtained. In addition, the resulted diastereoisomers were inseparable and ^1H and ^{13}C NMR analyses of the diastereoisomeric mixtures could not afford particular information to assign the stereochemistry of these major isomers. Finally, the major isomers of these R^3-substituted azabicyclic compounds **10** were predicted as also *exo*-form based on the mechanism for the formation of *exo*-adducts of **10ae** and **10af**, which would be explained in the following course.

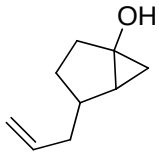
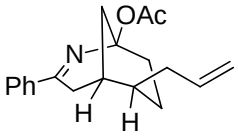
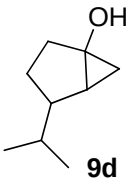
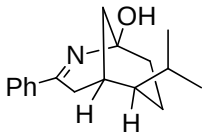
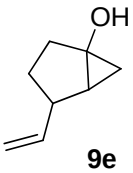
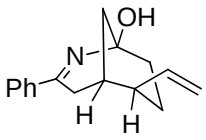
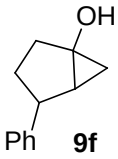
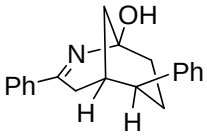
Table 5-1. Mn(III)-catalyzed synthesis of 2-azabicyclo[3.3.1]non-2-en-1-ols



1 **9** (1.2 equiv) **10**

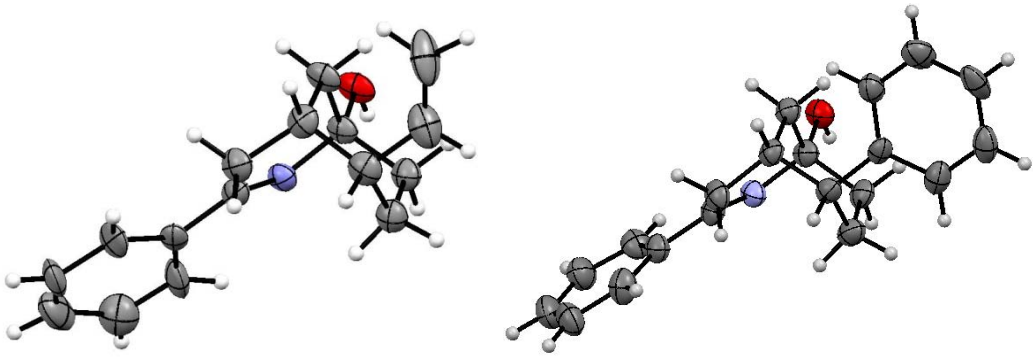
entry	vinyl azides **1**	cyclopropanols **9**	[MnIII]/mol %	products **10** (yield/%)[b]
				
1	**1a**: R = H	**9a**	5	**10aa** (89)
2	**1b**: R = 4-Me	**9a**	10	**10ba** (95)
3	**1c**: R = 2-OMe	**9a**	10	**10ca** (88)
4	**1d**: R = 4-OMe	**9a**	10	**10da** (93)
5	**1o**: R = 2-Br	**9a**	10	**10oa** (70)
6	**1p**: R = 4-Br	**9a**	10	**10pa** (83)
7	**1q**: R = 4-CO_2Me	**9a**	10	**10qa** (75)
8	 **1f**	**9a**	20	 **10fa** (83)
9	 **1g**	**9a**	20	 **10ga** (77)
10	 **1h**	**9a**	40	 **10ha** (28)[d] (*exo:endo* = 85:15)[c]
11	**1a**	 **9b**	10	 **10ab** (74) (*exo:endo* = 85:15)[c]

continued...

entry	vinyl azides **1**	cyclopropanols **9**	[MnIII]/mol %	products **10** (yield/%)[b]
12	**1a**	 **9c**	10	 **10ac'** (67)[e] (*exo:endo* = 86:14)[c]
13	**1a**	 **9d**	10	 **10ad** (90) (*exo:endo* = 85:15)[c]
14	**1a**	 **9e**	10	 **10ae** (82) (*exo:endo* = 83:17)[c]
15	**1a**	 **9f**	10	 **10af** (91) (*exo:endo* = 94:6)[c]

[a] Unless otherwise noted, the reactions were carried out by addition of a solution of cyclopropanols **9** (1.2 equiv) in MeOH via a syringe pump over 1 h to a solution of vinyl azides **1** (0.3 mmol) and $Mn(acac)_3$ under N_2 atmosphere at room temperature (*see* Experimental Setion). [b] Isolated yields. [c] Vinyl azide **1h** was recovered in 68% yield. [d] The ratio was determined by ^1H NMR, and the major *exo* isomer was shown above. [e] **10ac** was too unstable to be isolated, and it was converted to acetate **10ac'** by the treatment with Ac_2O and Et_3N in the presence of DMAP in CH_2Cl_2, the yield (67%) was calculated from vinyl azide **1a**.

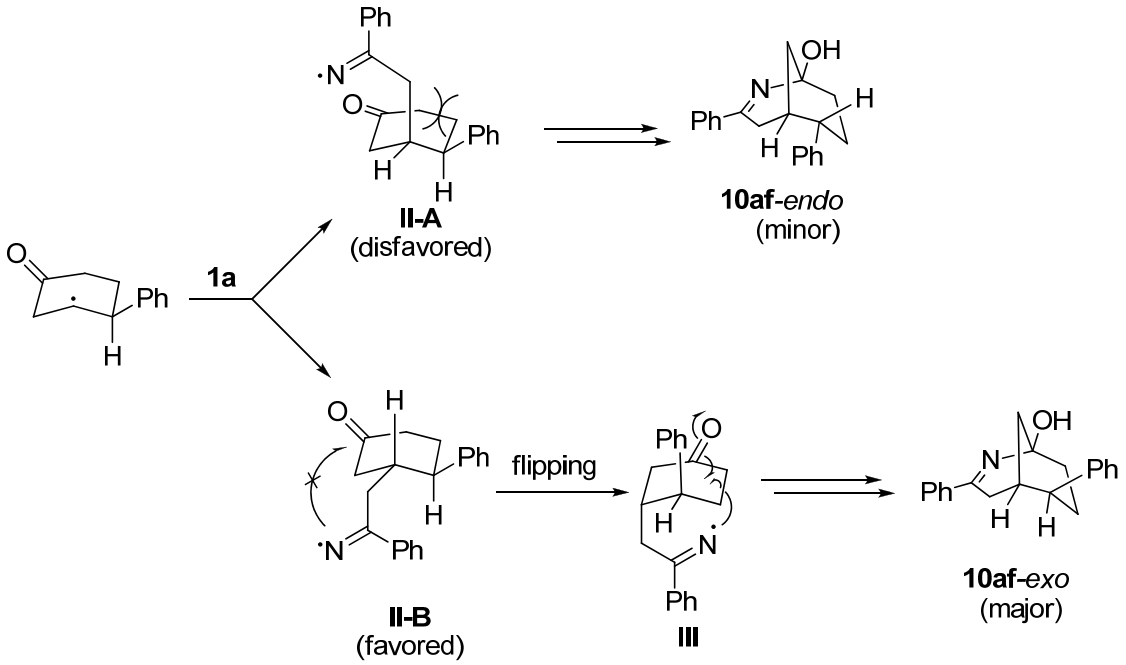
Figure 5-2. X-ray crystal structure of **10ae** (left) and **10af** (right)



As discussed above, the reaction of vinyl azide **1a** and 4-substituted bicyclo[3.1.0]hexan-1-ols gave the corresponding 2-azabicyclo[3.3.1]non-2-en-1-ols **10** in good diastereoselectivities (Table 5-1, entries 11-15). Moreover, the structure of major diastereoisomers of **10ae** and **10af** were determined as *exo*-form (refer to R^3: vinyl group or phenyl group for **10ae** or **10af**, respectively). This stereochemical outcome deserved some further discussion, which may provide valuable information to predict the stereochemistry of R^3 on azabicyclic compounds **10** (such as **10ab**, **10ac** and **10ad**) from corresponding C-4 substituted bicyclic cyclopropanols **9**.

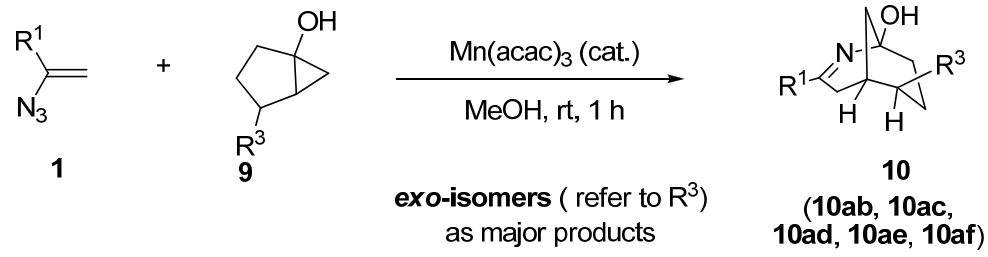
Taking 4-phenyl-bicyclo[3.1.0]hexan-1-ol (**9f**) as an example, addition of the generated *β*-carbonyl radical **I** to vinyl azide **1a** gave the iminyl radical with two diastereoisomers **II-A** and **II-B** (Scheme 5-6). However, the addition occurred preferentially in *anti* manner to the adjacent phenyl substituent based on the minimization of steric repulsion in the C–C bond formation. Therefore, *trans* stereoisomer **II-B** was formed predominantly. However, both substituents (phenyl group and iminyl radical tether) in this isomer were located at equatorial-like position, the cyclization was unable to occur because of the far distance between the two reacting sites (iminyl radical and carbonyl group). Then,

rapid ring flipping of **II-B** took place to give **III** with both substituents locating at axial-like position. Cyclization of **III** afforded the product **10af-*exo*** as a major product. On the other hand, cyclization of **II-A** led to the formation of **10af-*endo*** as a minor one.



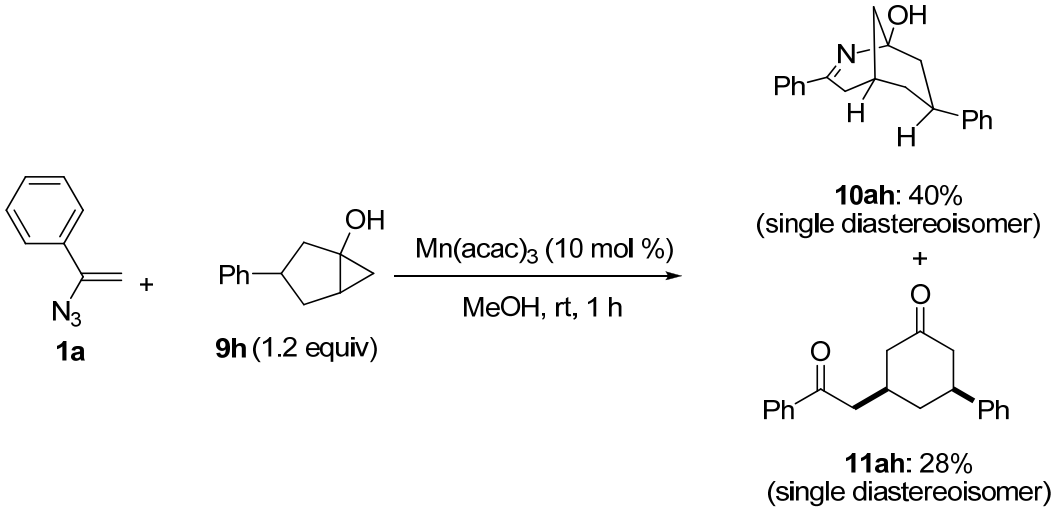
Scheme 5-6. Mechanism for the formation of *exo*-isomers as major products

Base on the above discussion, it can be deduced that the reactions of C-4 substituted (R^3) bicyclo[3.1.0]hexan-1-ols **9** presumably provides the corresponding 2-azabicyclo[3.3.1]non-2-en-1-ols **10** with the *exo*-isomer (refer to R^3) as the major product (Scheme 5-7).



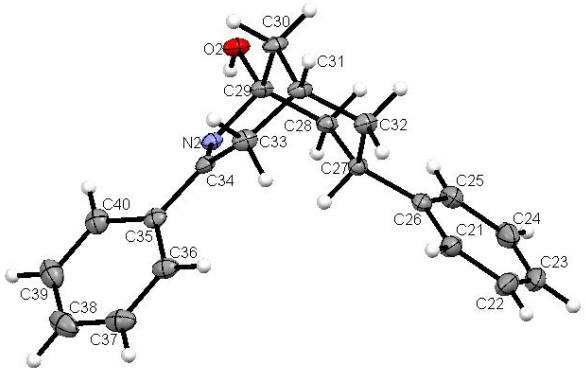
Scheme 5-7. Reactions of C-4 substituted (R^3) bicyclic cyclopropanols **9**

In the case of the reaction of 5-phenylbicyclo[3.1.0]hexan-1-ol (**9h**), both of the desired annulated product **10ah** (Figure 5-3) and an unexpected diketone **11ah** were obtained as single diastereoisomers (Scheme 5-8).



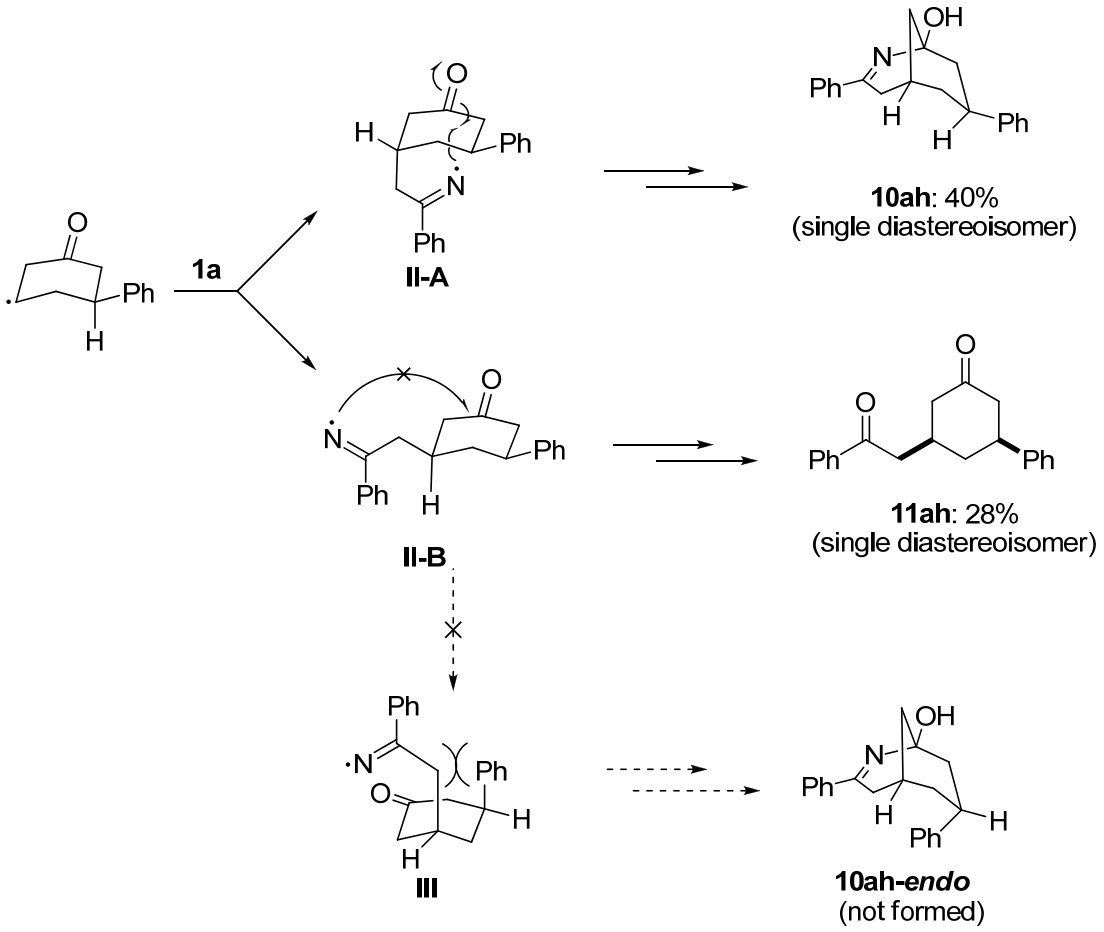
Scheme 5-8. Formation of **10ah** and diketone **11ah**

Figure 5-3. X-ray crystal structure of **10ah**



The above results were obtained because the addition of *β*-carbonyl radical **I** derived from **9h** to vinyl azide **1a** generated two diastereoisomers **II-A** and **II-B** (Scheme 5-9). In this case, the shielding effect of the *β*–phenyl group was reduced compared to the *α*–phenyl group (from **9f**), resulting in poor diastereoselectivity between **II-A** and **II-B**. The cyclization of isomer **II-A** gave the desired product **10ah** (*exo*-isomer). On the other hand, ring flipping

of **II-B** to **III** was restrained by the 1,3-diaxial interaction between the phenyl group and the iminyl radical tether, resulting in no formation of **10ah-*endo***. Finally, **II-B** was converted to diketone **11ah** as single diastereoisomer.

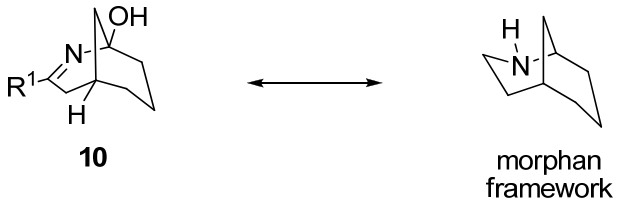


Scheme 5-9. Mechanism for the formation of **10ah** and **11ah** as single diastereoisomers

5.2.2 General Introduction on the Synthesis of 2-Azabicyclo[3.3.1]nonanes

As described in the previous section, a $Mn(acac)_3$-catalyzed synthesis of 2-azabicyclo[3.3.1]non-2-en-1-ols has been developed, which has a broad substrate scope in terms of both vinyl azides and bicyclo[3.1.0]hexan-1-ols components. Notably, good

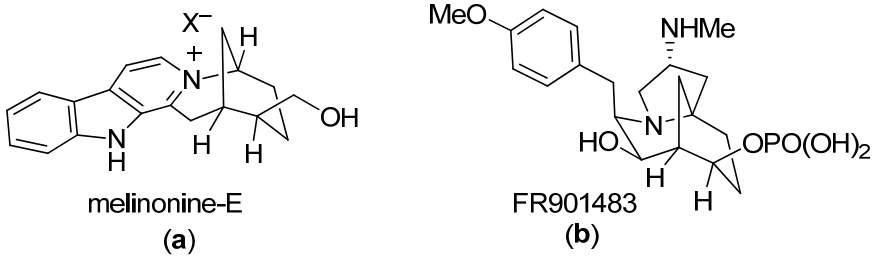
diastereoselectivities were observed by using 4-substituted bicyclo[3.1.0]hexan-1-ols as the sources of *β*–carbonyl radicals. More interestingly, as depicted in Scheme 5-10, the skeleton of azabicyclic compounds **10** is analogous to 2-azabicyclo[3.3.1]nonane (morphan) framework, which is prevalent in various natural products as well as many valuable pharmacological molecules.[5]



Scheme 5-10. Structures of compounds **10** and morphans

For instance, the morphan framework is present in a great number of indole alkaloids, such as melinonine-E (Figure 5-4, **a**).[6] Moreover, FR901483 (Figure 5-4, **b**), a powerful immunosuppressant, also contains such a morphan subunit.[7] This substance significantly increases the survival time of grafts in the rat allograft model, and thus much effort has been devoted to its total synthesis.

Figure 5-4. Examples of morphan framework containing natural products

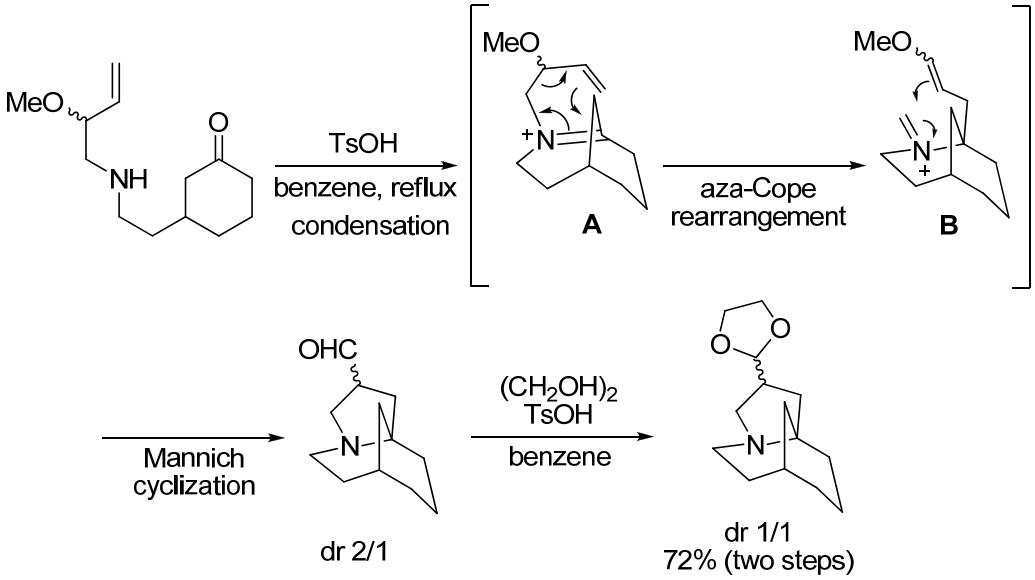


In this Section, the author will give a brief introduction on the synthesis of morphan framework. As reported, a variety of synthetic methods have been developed to access morphans,[5] the majority of which are based upon the construction of the piperidine ring motif,

rather than the cyclohexane ring. In principle, there are some modes to build such piperidine subunit (Figure 5-5) according to the retrosynthetic analysis. However, the reported strategies are exclusively based on the disconnection patterns of type A (C1–N2 bond formation) and type B (C4–C5 bond formation).

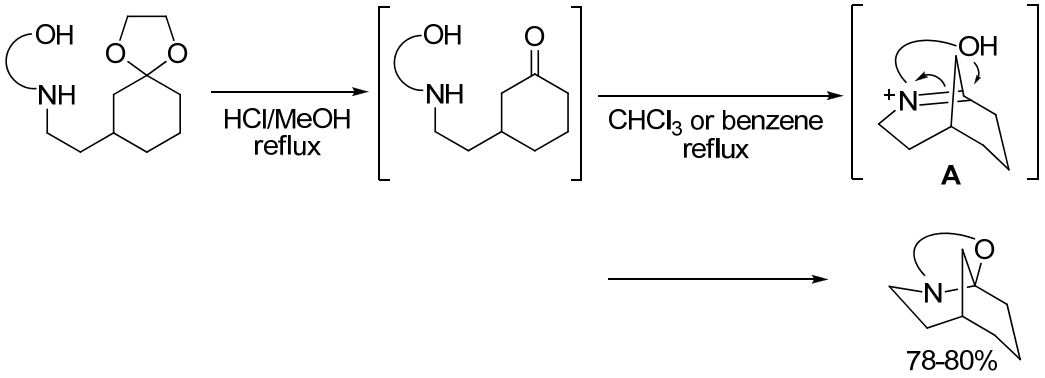
Figure 5-5. Retrosynthetic cleavage of 2-azabicyclo[3.3.1]nonane framework

The disconnection pattern of type A involves a C1–N2 bond formation in the ring closure step. For example, Brummond reported the synthesis of azatricyclic core of FR901483 by a tandem cationic aza-Cope rearrangement–Mannich cyclization from bridgehead iminium ion **A**, which was in turn resulted by the intramolecular condensation of the secondary amine with the carbonyl group (Scheme 5-11).[8]



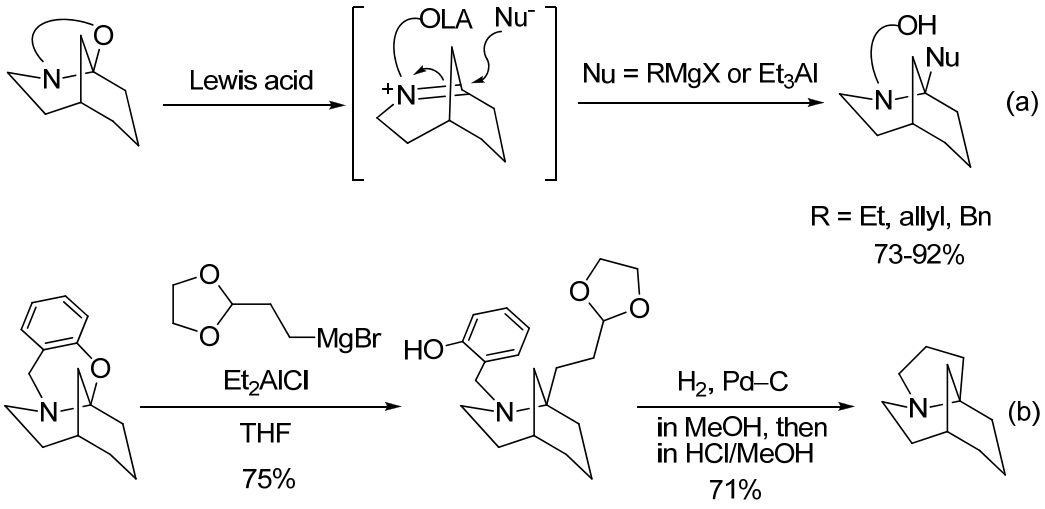
Scheme 5-11. Tandem lactamization–cationic aza-Cope rearrangement–Mannich cyclization to azatricyclic core of FR901483

When bridgehead iminium ions **A** were attacked by an intramolecular hydroxy group, a range of useful tricyclic *N*,*O*-acetals containing a morphan skeleton were formed (Scheme 5-12).[9]



Scheme 5-12. Synthesis of tricyclic *N,O*-acetals

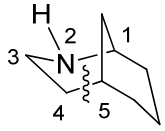
Kibayashi then investigated the reactivity of these unique tricyclic *N*,*O*-acetals and found a facile protocol to install an alkyl group onto the bridgehead position of the morphan core (Scheme 5-13). They proposed that bridgehead iminium ions might be generated in the presence of Lewis acids, and the subsequent alkylation afforded 1-alkylated morphans (Eq. a). By using this method, they successfully constructed the fundamental azatricyclic core of FR901483 in good yield (Eq. b).



Scheme 5-13. Lewis acid-mediated transformations of tricyclic *N,O*-acetals

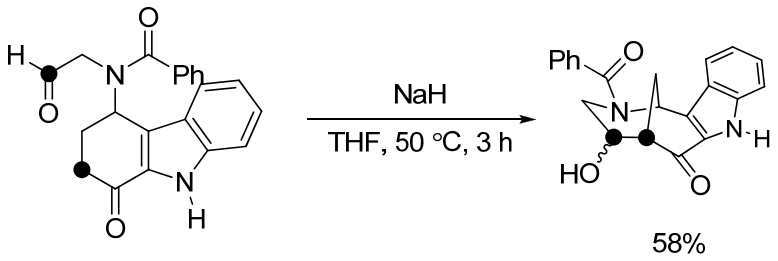
The retrosynthetic cleavage pattern of type B refers to a C4–C5 bond formation for the construction of the piperidine moiety in the morphan framework (Figure 5-6). This strategy is normally achieved by intramolecular aldol reactions, palladium-catalyzed coupling reactions, and radical cyclizations.

Figure 5-6. Retrosynthetic cleavage of type B



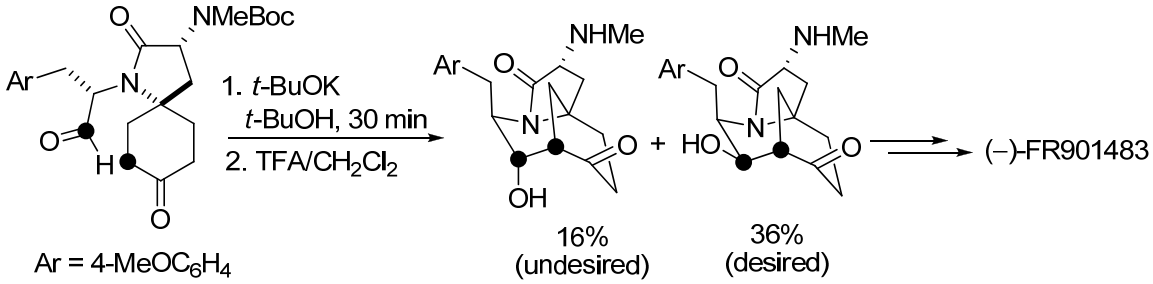
type B

Patir reported an intramolecular aldol reaction to construct the morphan framework as shown in Scheme 5-14.[10]



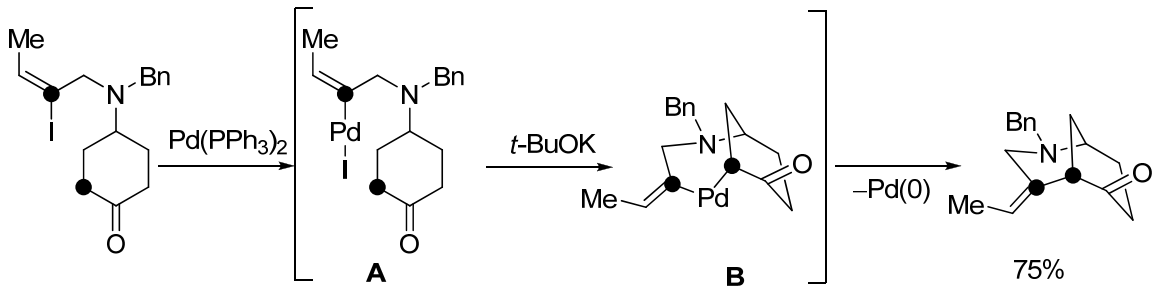
Scheme 5-14. Intramolecular aldol reaction for morphan nucleus

The first synthesis of (–)-FR901483 was accomplished by Snider in 1999.[11] The analogous aldol strategy was also employed to access the morphan ring, although low stereoselectivity and moderate yield were obtained (Scheme 5-15).[12]



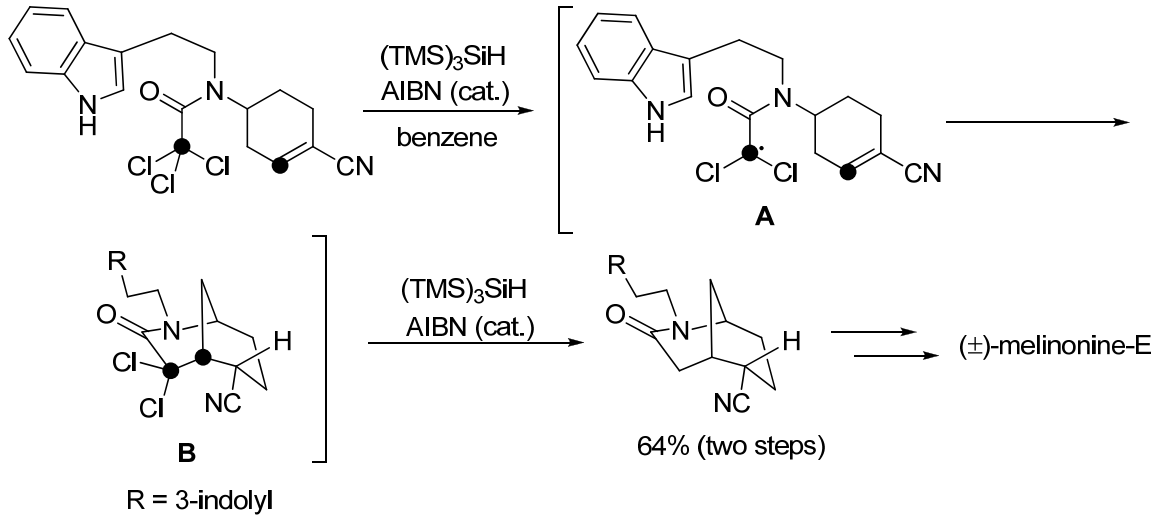
Scheme 5-15. The construction of morphan core in the synthesis of (–)-FR901483

Palladium-catalyzed processes were of great synthetic utility in the C–C bond-forming reactions, while there are only few reports on their application to build the piperidine subunit in the morphan system. Recently, Bonjoch has described a palladium-catalyzed intramolecular coupling of vinyl halides and ketone enolates to form morphan framework (Scheme 5-16).[13]



Scheme 5-16. Pd-catalyzed coupling of vinyl iodide and ketone enolate

The construction of morphan nucleus by means of radical reactions for the ring closure step has been also explored. Bonjoch reported an intramolecular cyclization of α-carbamoyl radicals with an unsaturated C–C bond to form the morphan framework,[14] from which the first synthesis of (±)-melinonine-E was accomplished (Scheme 5-17).[15]



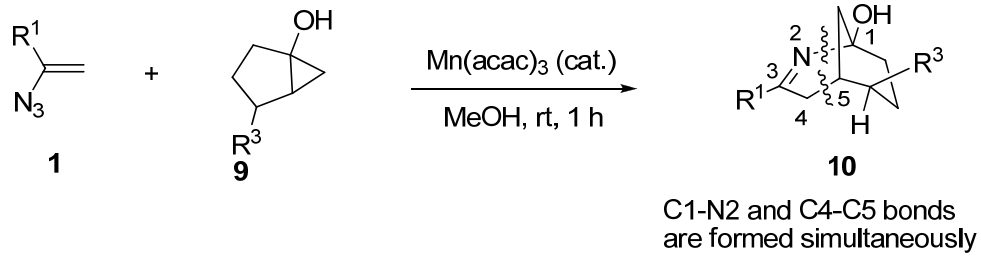
Scheme 5-17. The construction of morphan core in the synthesis of (±)-melinonine-E

5.2.3 One-pot Synthesis of 2-Azabicyclo[3.3.1]nonanes from Vinyl Azides and Bicyclo[3.1.0]hexan-1-ols

Even though a number of methods have been developed for the construction of morphan framework as described in the previous Section, most of these only involved either C1–N2 (type A) or C4–C5 bond (type B) formation in the intramolecular ring closure reactions (Figure 5-7).

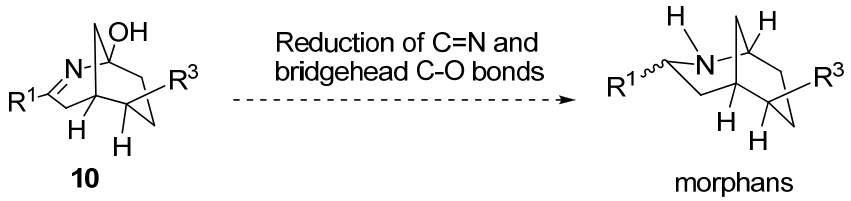
Figure 5-7. Two types of strategies to construct 2-azabicyclo[3.3.1]nonane framework

As discussed in Section 5.1, the $Mn(acac)_3$-catalyzed reactions of vinyl azides **1** and cyclopropanols **9** permit the simultaneous formation of two bonds (C1–N2 and C4–C5) towards the construction of azabicyclic compounds **10** (Scheme 5-18). This intermolecular reaction manner will provide an alternative straightforward pathway for the synthesis of useful azabicyclic compounds from readily available starting materials.



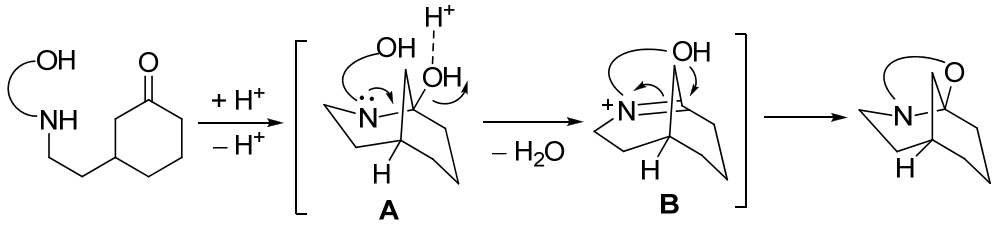
Scheme 5-18. Synthesis of azabicyclic compounds **10** through the simultaneous formation of C1–N2 and C4–C5 bonds

However, 2-azabicyclo[3.3.1]non-2-en-1-ols **10** themselves are rare in nature as compared to morphans. In order to make the Mn(III)-catalyzed synthesis of azabicyclic compounds **10** more synthetically useful, it was desired to explore facile methods to convert compounds **10** to morphans. Comparing the structures of these two types of molecules, it can be found that the transformation compounds **10** to morphans relies on the reduction of cyclic C═N bond and bridgehead C–OH bond (Scheme 5-19).



Scheme 5-19. Proposed conversion of **10** to morphans

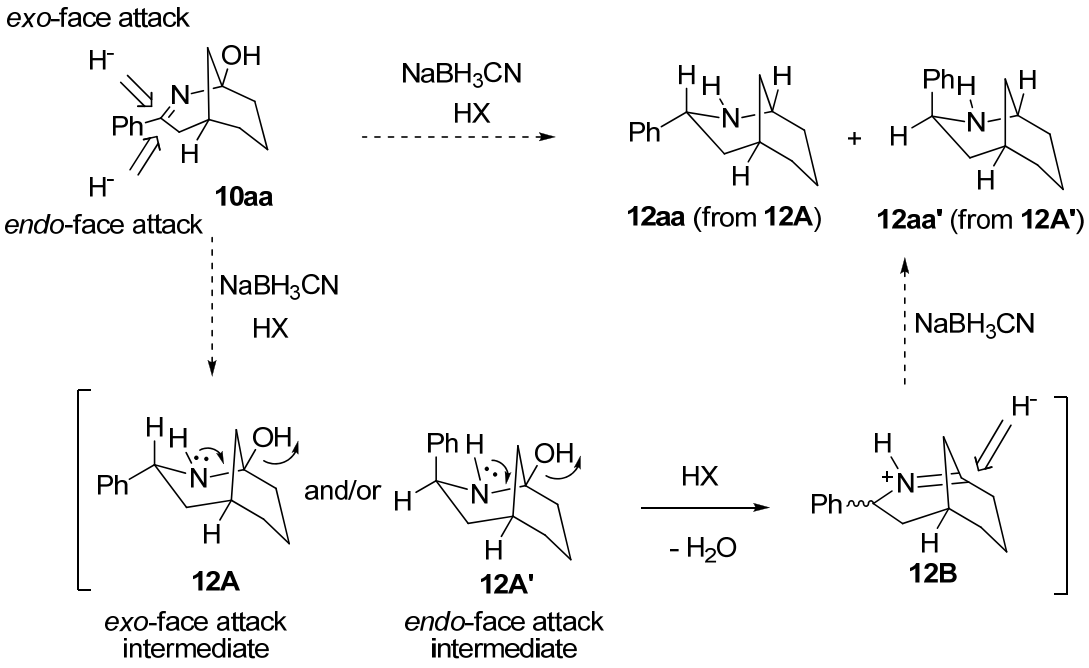
As mentioned in Section 5.2, the construction of azatricyclic framework including a morphan subunit involved a bridgehead iminium ion **B** as the key intermediate, which was derived from the acid-mediated dehydration of intermediate **A** (Scheme 5-20).



Scheme 5-20. Construction of azatricyclic framework involving iminium ion intermediate

Based on the above process, analogous bridgehead iminium ions **12B** are also assumed to act as the key intermediates for the reduction of **10aa** to **12aa** and/or **12aa'** (Scheme 5-21). The transformation was anticipated to be initiated by the reduction of imine moiety of **10aa** by $NaBH_3CN$ in the presence of an acid. Because the C═N bond in the

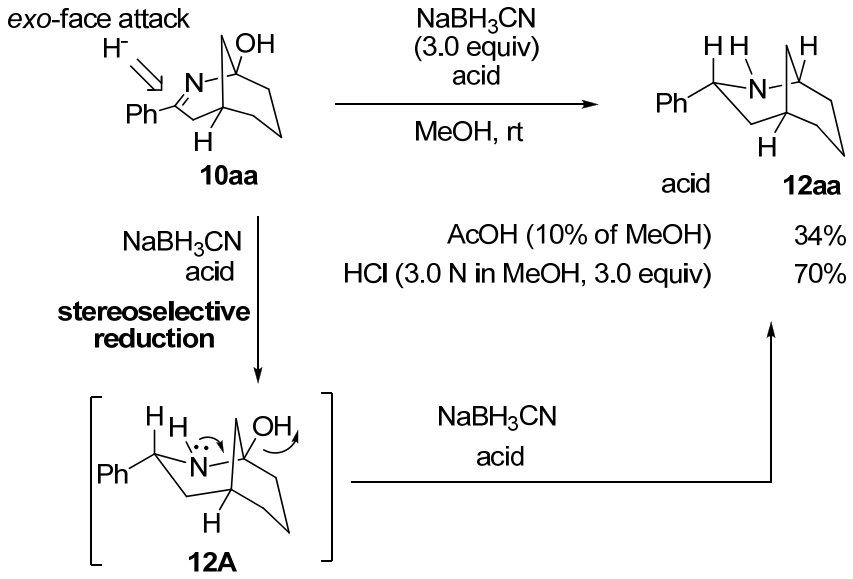
azabicyclic system of **10aa** was possible to be attacked by a hydride from either *exo*- or *endo*-face, a diastereoisomeric mixture of *α*-amino alcohols **12A** (from *exo*-face attack) and **12A'** (from *endo*-face attack) would be generated. Acid-mediated dehydration of these *α*-amino alcohols may lead to bridgehead iminium ions **12B**,[16] which would be reduced by $NaBH_3CN$ again to produce diastereoisomeric (refer to the phenyl group) cyclic amines **12aa** and **12aa'**.



Scheme 5-21. Proposed reaction pathway for the conversion of **10aa** to **12aa** and **12aa'**

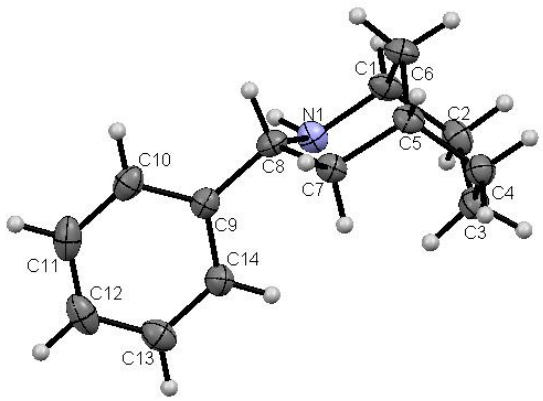
As expected, the reduction of **10aa** with $NaBH_3CN$ (3.0 equiv) in AcOH-MeOH (1:9) proceeded smoothly to produce only **12aa** (Scheme 5-22). The stereochemistry of **12aa** (with an *endo* phenyl group) was determined by X-ray crystallographic analysis (Figure 5-8). The other anticipated diastereoisomer **12aa'** was not observed at all. This result suggested that the hydride approached entirely from the less hindered *exo*-face of **10aa** to give **12A**. Further

optimization revealed that the yield of **12aa** could be dramatically improved to 70% by using HCl (3.0 in MeOH, 3.0 equiv) as an acid instead of AcOH.



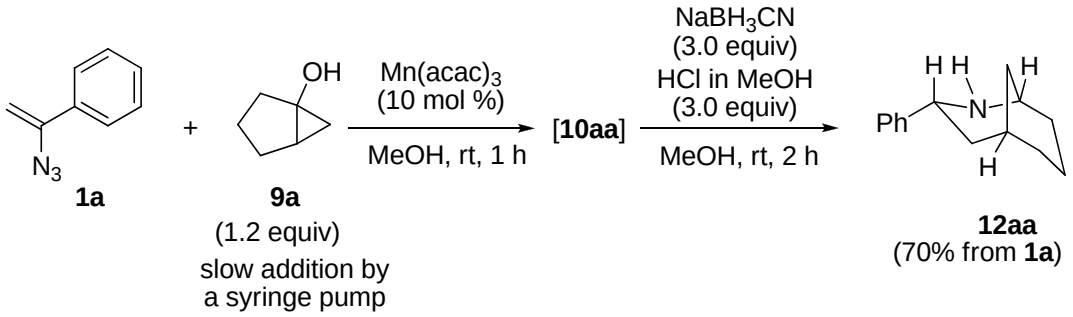
Scheme 5-22. Reduction of **10aa** by $NaBH_3CN$ in the presence of acid

Figure 5-8. X-ray crystal structure of **12aa**.



Interestingly, even a one-pot reaction starting from vinyl azide **1a** and bicyclo[3.1.0]hexan-1-ol (**9a**) could produce **12aa** in good yield (Scheme 5-23). In this case, the isolation of **10aa** was not required. After the consumption of vinyl azide **1a** (just after addition of **9a** by a syringe pump), $NaBH_3CN$ (3.0 equiv to vinyl azide **1a**) and HCl (3.0

equiv, 3.0 N in MeOH) were added to the reaction mixture, affording product **12aa** in 70% isolated yield from vinyl azide **1a**.

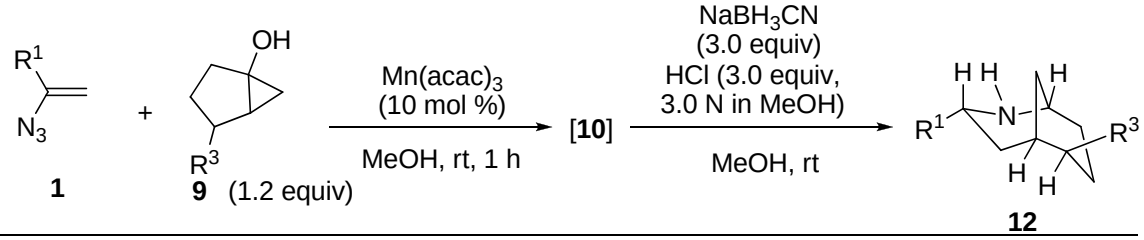


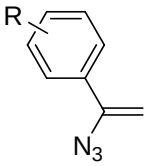
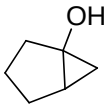
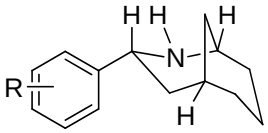
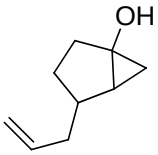
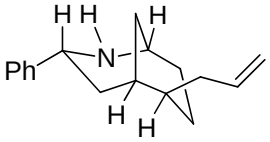
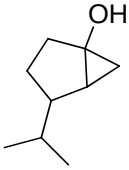
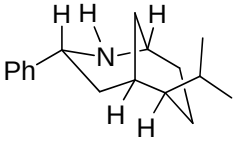
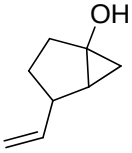
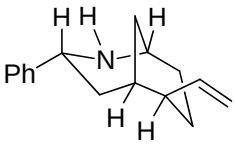
Scheme 5-23. One-pot synthesis of **12aa** from **1a** and **9a**

This one-pot synthesis of morphan derivatives exhibited a wide generality in terms of vinyl azides and cyclopropanols components (Table 5-2). A variety of 2-azabicyclo[3.3.1]nonanes (morphans) were readily prepared with *endo*-selectivity (refer to R^1) by the reduction of the corresponding 2-azabicyclo[3.3.1]non-2-en-1-ols, which were formed *in situ* by the $Mn(acac)_3$-catalyzed reaction of α-aryl vinyl azides **1** and bicyclo[3.1.0]hexan-1-ols **9**.

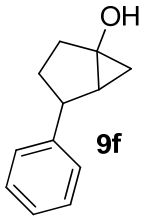
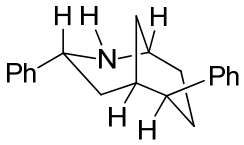
In the case of C-4 substituted (R^3) bicyclo[3.1.0]hexan-1-ols (**9c-f**), as mentioned in Table 5-1, the $Mn(acac)_3$-catalyzed annulation reaction afforded the R^3-substituted 2-azabicyclo[3.3.1]non-2-en-1-ols as a mixture of diastereoisomers with the *exo*-isomers as the major ones. When these diastereoisomeric azabicyclic compounds **10** were subjected to the $NaBH_3CN$-HCl conditions, the C═N and bridgehead C−OH bonds were reduced as expected and the stereochemistry of R^3-substitutes were not affected, giving almost the same diastereoselectivities (refer to R^3, 81:19 to 90:10) as the starting substrates **10**. Therefore, the ratios of *exo*:*endo* mentioned in parentheses (entries 5-8) refer to the substituents R^3 of **12**.

Table 5-2. One-pot preparation of 2-azabicyclo[3.3.1]nonanes **12** from vinyl azides **1** and bicyclo[3.1.0]hexan-1-ols **9**



entry	vinyl azides **1**	cyclopropanols **9**	products **12** (yield/%)[b]
			
1	**1a**: R = H	**9a**	**12aa** (70)
2	**1b**: R = 4-Me	**9a**	**12ba** (68)
3	**1d**: R = 4-OMe	**9a**	**12da** (58)
4	**1p**: R = 4-Br	**9a**	**12pa** (76)
5	**1a**	 **9c**	 **12ac** (80)[d] (*exo:endo* = 81:19)[c]
6	**1a**	 **9d**	 **12ad** (70) (*exo:endo* = 82:18)[c]
7	**1a**	 **9e**	 **12ae** (67) (*exo:endo* = 81:19)[c]

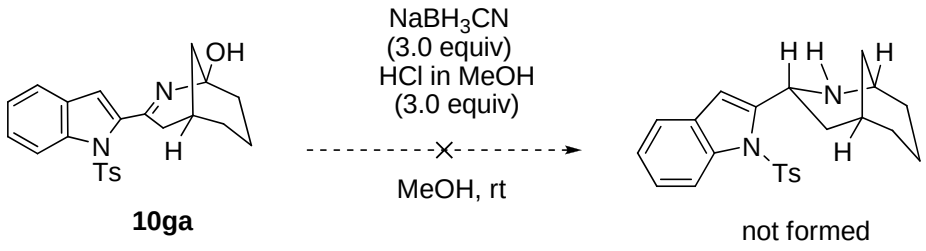
continued...

entry	vinyl azides **1**	cyclopropanols **9**	products **12** (yield/%)[b]
8	**1a**	 **9f**	 **12af** (56) (*exo:endo* = 90:10)[c]

[a] Unless otherwise noted, the reactions were carried out by addition of a solution of cyclopropanols **9** (1.2 equiv) in MeOH via a syringe pump over 1 h to a solution of vinyl azides **1** (0.3 mmol) and $Mn(acac)_3$ (10 mol %) under N_2 atmosphere at room temperature. After that, $NaBH_3CN$ (3.0 equiv) and HCl (3.0 equiv, 3.0 N in MeOH) were added, and then kept stirring for 2 h. [b] Isolated yields. [c] The ratio was determined by ^1H NMR, and the major *exo*-isomer (referred to R^3) was shown above.

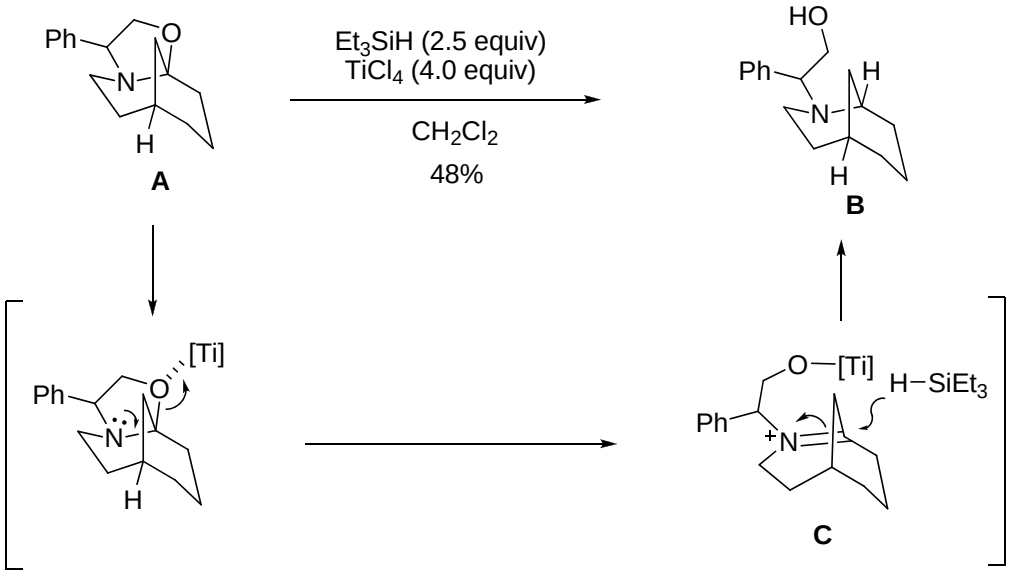
5.2.4 Lewis Acid-Mediated Reduction and Functionalizations of 2-Azabicyclo[3.3.1]non-2-en-1-yl Acetates

The one-pot process described in the previous Section represents a particularly straightforward methodology to construct morphan framework from readily available vinyl azides and bicyclo[3.1.0]hexan-1-ols. However, for compound **10ga**, the indole moiety would be reduced in the acidic reductive conditions used, since the azole ring subunit is analogous to an enamine.[17] Indeed, when **10ga** was subject to a mixture of $NaBH_3CN$ and HCl in MeOH, a complex mixture was obtained (Scheme 5-24).



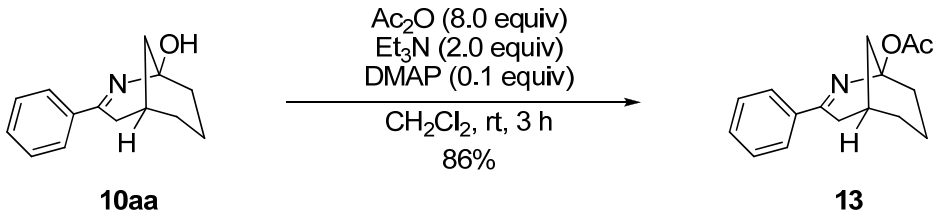
Scheme 5-24. Attempt for reduction of **10ga**

Due to this, it was desired to exploit an alternative method for selective reduction of the bridgehead C–OH bond of compounds **10**. As previously reported, the combined use of Et_3SiH and $TiCl_4$ was an efficient method to convert *N,O*-acetal **A** to amino alcohol **B**, in which the bridgehead C–O bond was reduced to C–H bond through an assumed iminium ion **C** intermediate (Scheme 5-25).[18] In this process, Lewis acid ($TiCl_4$) played an important role in the cleavage of bridgehead C–O bond.[18b] This inspired the author to examine this protocol to reduce the bridgehead C–OH bond of **10**.



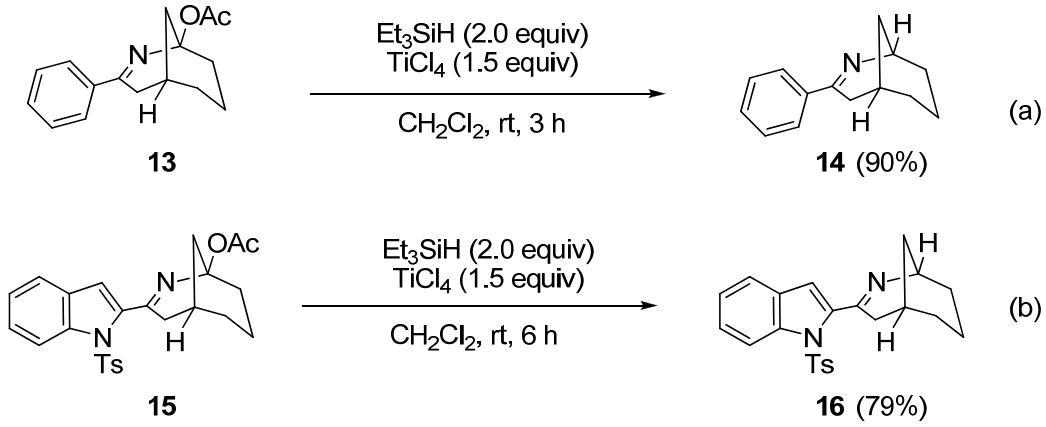
Scheme 5-25. Reduction of bridgehead C-O bond by Et_3SiH-$TiCl_4$

Because Et_3SiH is possible to be quenched by an alcohol, compound **10aa** was first converted to acetate **13** (Scheme 5-26).



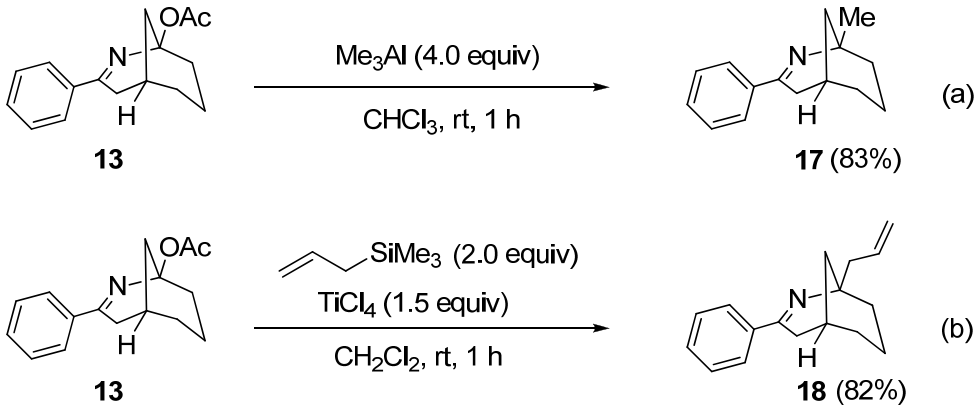
Scheme 5-26. Acetylation of **10aa**

Fortunately, when acetate **13** was treated with Et_3SiH in the presence of $TiCl_4$, C–O bond reduction occurred to afford 2-azabicyclo[3.3.1]non-2-ene **14** in excellent (90%) yield (Scheme 5-27, Eq. a). It was worth noting that the C═N bond of acetate **13** was untouched under these reaction conditions. More importantly, acetate **15** bearing an indolyl group, which was not applicable in the $NaBH_3CN$-HCl method (see Scheme 5-24), was also compatible with this reaction providing **16** in 79% yield with both the indoyl group and C═N bond intact (Eq. b).



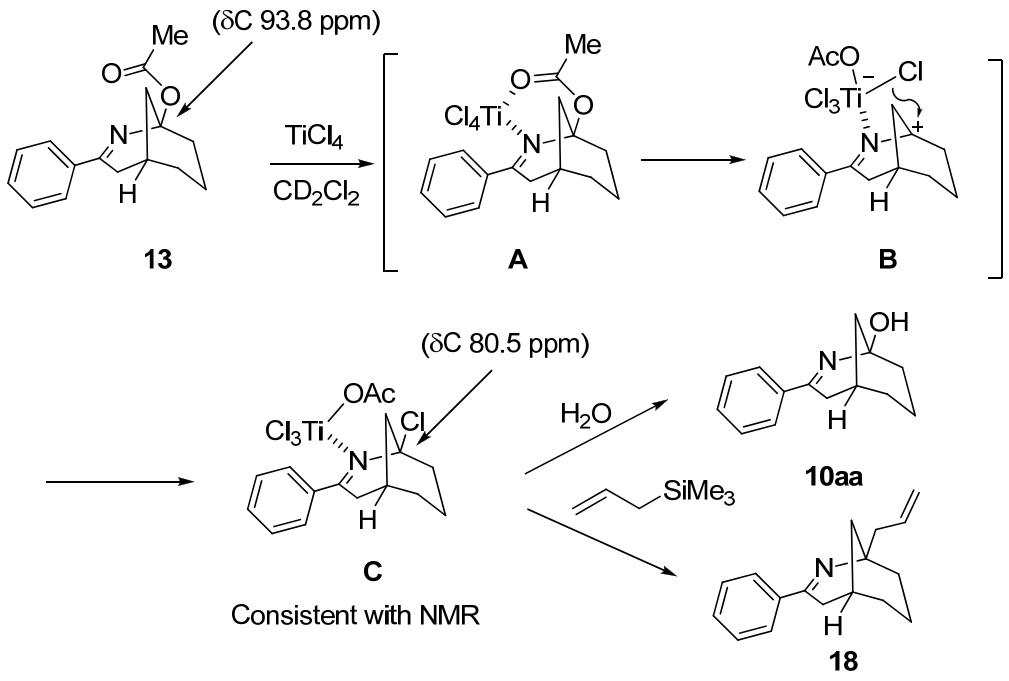
Scheme 5-27. Reduction of acetates **13** and **15** by Et_3SiH and $TiCl_4$

The above Lewis acid induced reduction of bridgehead C–O bond encouraged the author to further study the reactions of acetate **13** by varying nucleophiles and/or Lewis acid. As shown in Scheme 5-28, the treatment of acetate **13** with Me_3Al (Eq. a) or allyltrimethylsilane-$TiCl_4$ (Eq. b) provided a new quaternary carbon center at C-1 with the C═N bond intact (**17** and **18**). These transformations were of significant synthetic utility for the synthesis of bridgehead-substituted morphans.[19]



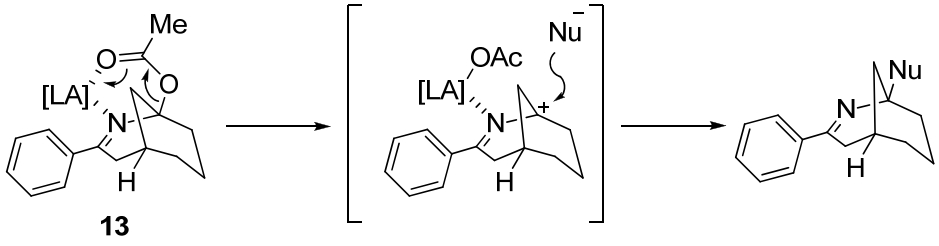
Scheme 5-28. Lewis acid-mediated transformations of acetate **13**

In order to elucidate the mechanism of these Lewis acids-mediated functionalizations, a reaction of acetate **13** with $TiCl_4$ was monitored by ^1H and ^{13}C NMR in CD_2Cl_2 (Scheme 5-29). It was found that acetate **13** immediately disappeared upon the treatment with $TiCl_4$ to give one new compound **C**. The chemical shift of the bridgehead carbon shifted to higher field from 93.8 ppm (for acetate **13**) to 80.5 ppm (for compound **C**), which might suggest that compound **C** bears a bridgehead C–Cl bond. The formation of **C** occurred presumably via coordination of $TiCl_4$ to the imino nitrogen and the acetate carbonyl oxygen followed by cleavage of the bridgehead C–O bond to generate a bridgehead carbocation, which was then immediately trapped by a chloride ion. Subsequent treatment of compound **C** with water or allyltrimethylsilane led to **10aa** or **18**, respectively.



Scheme 5-29. Elucidation of mechanism for the Lewis acids-mediated transformations

A plausible mechanism for those Lewis acids-mediated transformations is depicted in Scheme 5-30. Cleavage of the bridgehead C–O bond activated by Lewis acid generated a bridgehead carbocation that was immediately trapped by nucleophiles such as Et_3SiH, Me_3Al and allyltrimethylsilane, producing the desired bridgehead-substituted products.



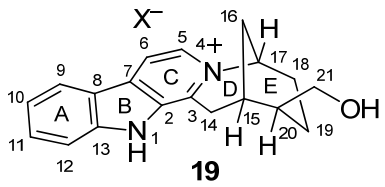
Scheme 5-30. A plausible mechanism for the Lewis acids-mediated transformations

5.2.5 Synthesis of (±)-Melinonine-E

As described previously, a facile method has been developed to synthesize 2-azabicyclo[3.3.1]non-2-en-1-ols by $Mn(acac)_3$-catalyzed reaction of vinyl azides **1** and bicyclic cyclopropanols **9** (Section 5.2.1). Furthermore, versatile transformations of these azabicyclic products to more general morphans (Section 5.2.3) and 2-azabicyclo[3.3.1]non-2-ene frameworks (Section 5.2.4) have also been explored. In order to establish the synthetic utility of these developed methods, a synthesis of (±)-melinonine-E (**19**) will be described in this Section.

The quaternary indole alkaloid melinonine-E was originally isolated from the bark of *Strychnos melinoniana*,[6a] and was characterized by a pentacyclic ring system including a core of indolo[2,3-*a*]quinolizidine and a 2-azabicyclo[3.3.1]nonane (morphan) framework[6b] as shown in Figure 5-9.

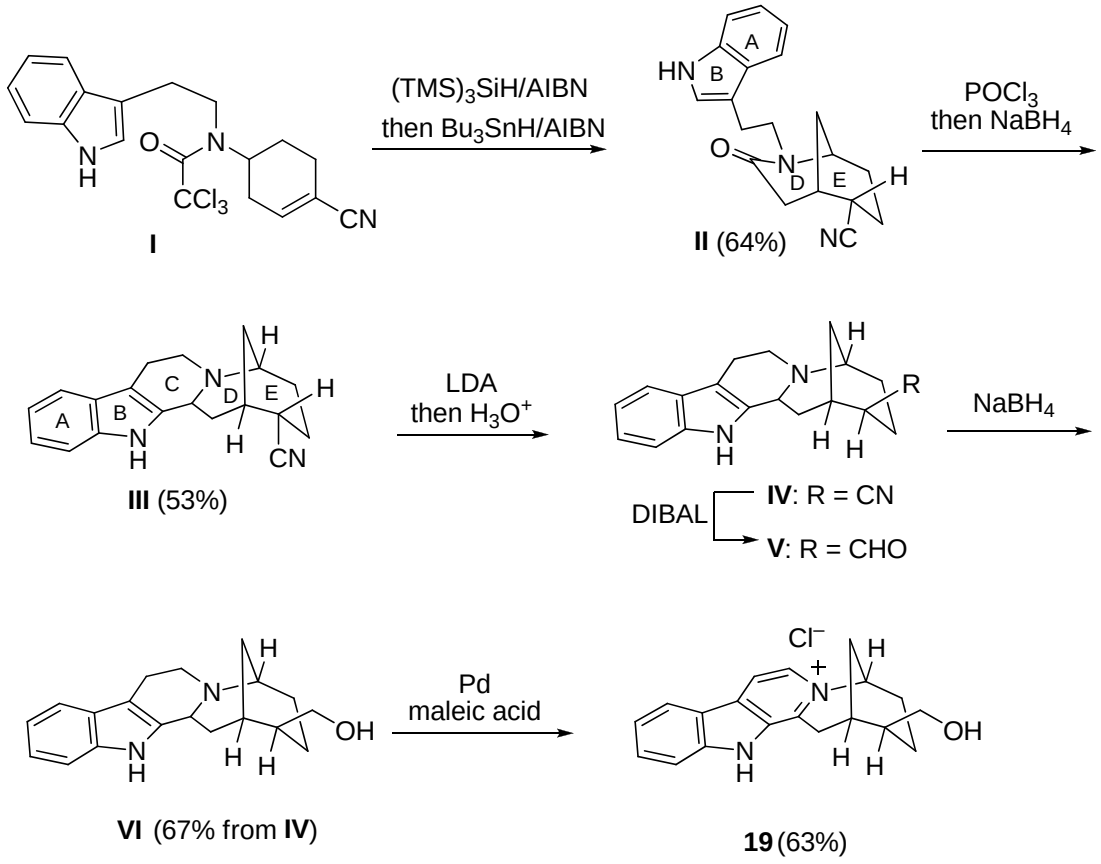
Figure 5-9. Structure of (±)-melinonine-E



19

The first total synthesis of (±)-melinonine-E was reported by Bonjoch[15] (Scheme 5-31). The key step was the elaboration of the morphan nucleus **II** (D and E rings) by a radical cyclization as shown in Scheme 5-17 (Section 5.2.2). This cyclization proceeded stereoselectively to give the product **II** as only then *endo*-cyano isomer, which differed from the naturally occurring relative stereochemistry at C-20 of melinonine-E. This undesired stereochemistry outcome required a further epimerization process (**III**→**IV**) to gain the *exo*-

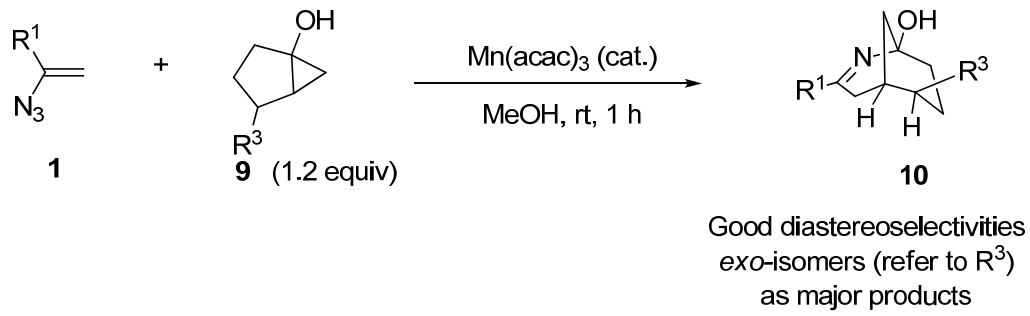
isomer after the closure of the C ring by a Bischler-Napieralski cyclization (**II→III**). The synthesis was completed by appropriate reductive transformations (**IV→VI**) followed by aromatization of the C ring (**VI→19**).



Scheme 5-31. Bonjoch's synthesis of (±)-melinonine-E

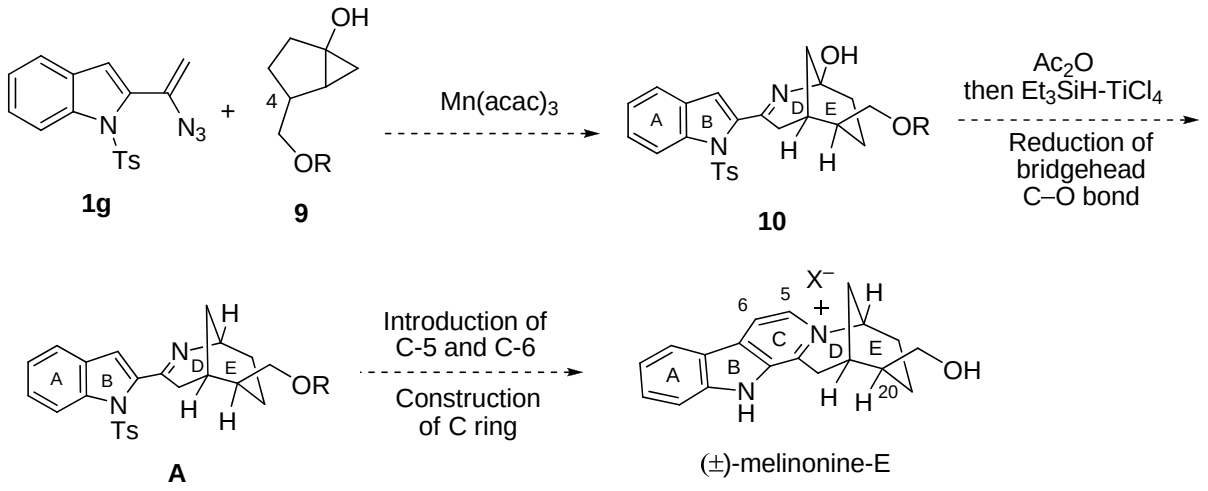
5.2.5.1 A Synthetic Plan of (±)-Melinonine-E

As mentioned in Section 5.2.1, a $Mn(acac)_3$-catalyzed synthesis of 2-azabicyclo[3.3.1]non-2-en-1-ols **10** have been developed. Particularly, the reactions of C-4 substituted cyclopropanols **9** provided the corresponding azabicyclic compounds **10** in good diastereoselectivities with the *exo*- R^3 isomers as major products (Scheme 5-32).



Scheme 5-32. Mn(III)-catalyzed synthesis of azabicyclic compounds **10**

Based on these results, a synthetic plan was proposed for the synthesis of (±)-melinonine-E (Scheme 5-33). It was envisioned that the reaction of *α*-2-indolyl vinyl azide **1g** and cyclopropanols **9** bearing a protected hydroxymethyl substitutent at C-4 would produce azabicyclic compounds **10**. More importantly, the *exo*-hydroxymethyl isomers would be the major products, consistent with the stereochemistry of the natural product (at C-20). Besides that, this compound would possess the key skeleton including both a morphan framework (D ring and E ring) and an indole motif (A ring and B ring) of (±)-melinonine-E. Because the selective reduction of bridgehead C−OH bond of compounds **10** would be conducted by applying Et_3SiH-$TiCl_4$ protocol, the success of the synthesis of (±)-melinonine-E would rely on the incorporation of two carbon units (C-5 and C-6) and then the construction of the C ring.

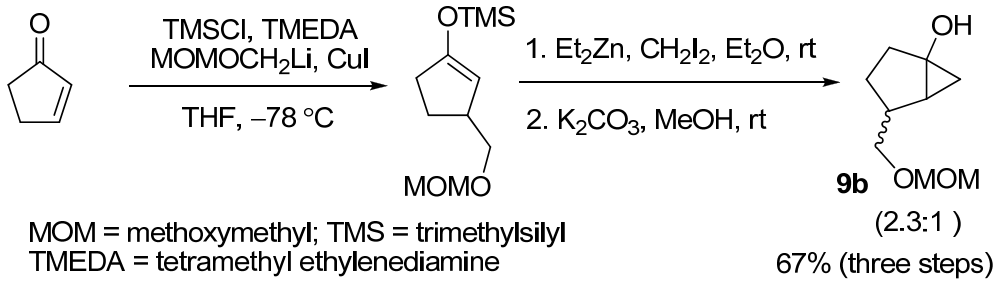


Scheme 5-33. A synthetic plan of (±)-melinonine-E

5.2.5.2 Synthesis of Protected 4-Hydroxymethyl Substituted Bicyclo[3.1.0]hexan-1-ols

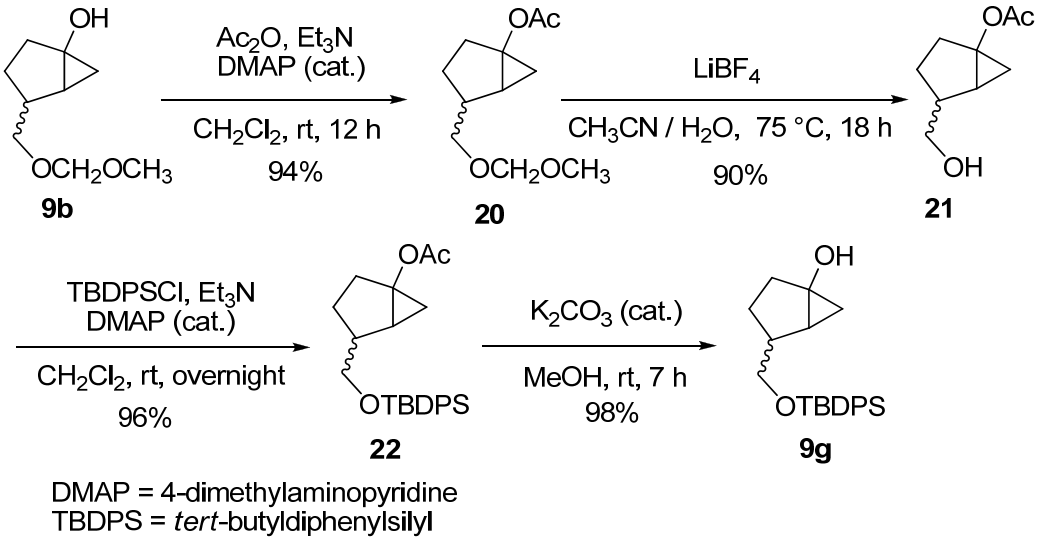
As shown in the proposed synthetic pathway for the synthesis of (±)-melinonine-E, bicyclo[3.1.0]hexan-1-ols **9** bearing a protected 4-hydroxymethyl substitutent are required for the annualtion reaction. This Section will deal with the preparation of bicyclo[3.1.0]hexan-1-ols like **9**.

In general, C-4 substituted bicyclo[3.1.0]hexan-1-ols **9** are prepared by a 1,4-addition, cyclopropanation and desilyation sequence from cyclopent-2-enone. For example, as shown in Scheme 5-34, 1,4-addition of a cuprate (from the reaction of $MOMOCH_2Li$ and CuI) to the cyclopent-2-enone in the presence of trimethylsilyl chloride gave silyl enol ether, followed by cyclopropanation and desilylation led to bicyclo[3.1.0]hexan-1-ol **9b** in 67% yield as an inseparable mixture of diastereoisomers (2.3:1).



Scheme 5-34. Preparation of **9b**

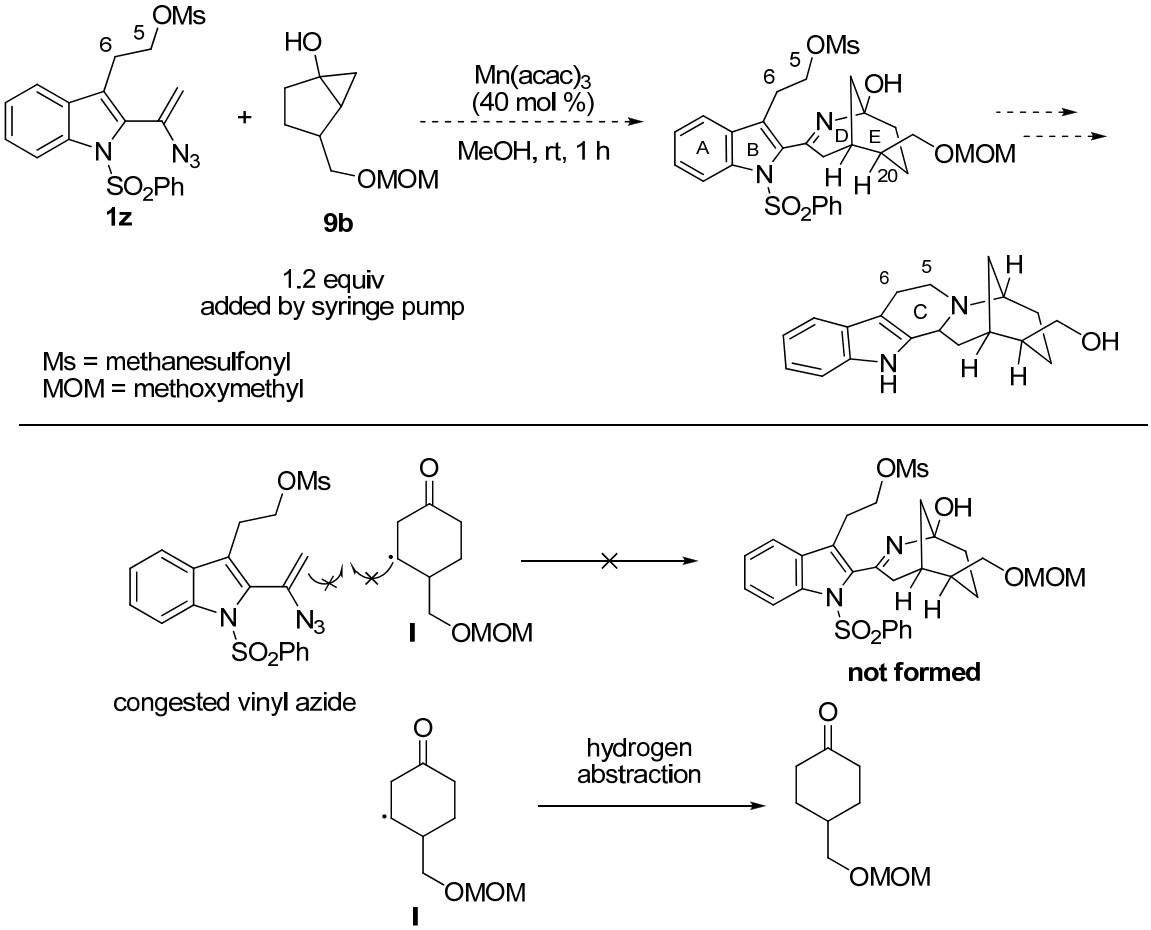
In view of that bicyclo[3.1.0]hexan-1-ols **9b** bearing an acetal moiety ($CH_3OCH_2OCH_2$) might be sensitive to Et_3SiH-$TiCl_4$ reduction conditions, the methoxymethyl group of **9b** was then converted to more inert *tert*-butyldiphenylsilyl group (Scheme 5-35). The transformations consisted of acetylation (**9b**→**20**), deprotection of methoxymethyl group (**20**→**21**), silylation (**21**→**22**), and deacetylation (**22**→**9g**).



Scheme 5-35. Preparation of **9g** from **9b**

5.2.5.3 Synthesis of (±)-Melinonine-E

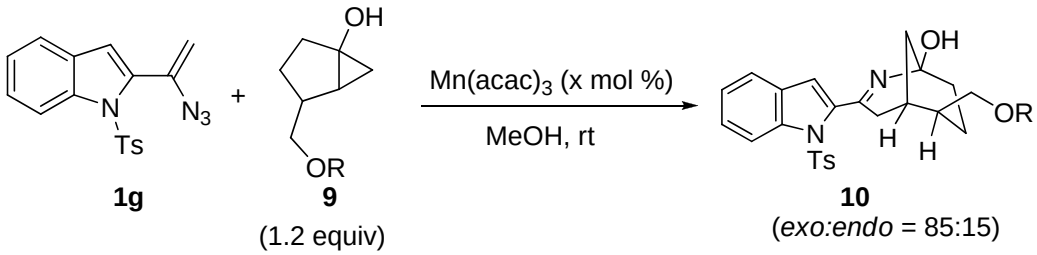
As mentioned before, the synthesis of (±)-melinonine-E required two carbon units (C-5 and C-6) for the construction of the C ring (see Scheme 5-34). Initially, these two carbon atoms were installed into the 3-position on the indole ring of starting vinyl azide **1z** prior to the Mn(III)-catalyzed annulation reaction (Scheme 5-36). However, the desired annulation reaction did not occur at all. This might be attributed to a fact that the congested vinyl azide **1z** prevented the addition of *β*-carbonyl radical to the C═C bond of vinyl azide **1z**. As a consequence, the resulted *β*-carbonyl radical underwent hydrogen abstraction to give 4-methoxymethoxymethyl cyclohexanone, and vinyl azide **1z** was recovered.



Scheme 5-36. Trial of the $Mn(acac)_3$-catalyzed reaction of **1z** and **9b**

Due to the above unsuccessful result, the introduction of two carbon units (C-5 and C-6) was considered to be conducted after the $Mn(acac)_3$-catalyzed annualtion reaction.

At first, the $Mn(acac)_3$-catalyzed reactions of vinyl azide **1g** and cyclopropanol **9b** or **9g** were examined. Fortunately, the annulated product **10gb** and **10gg** were obtained in reasonable yields with the recovery of untouched vinyl azide **1g** by using 40-50 mol % of $Mn(acac)_3$ (Scheme 5-37). Moreover, the same diastereoselectivity (*exo*:*endo* = 85:15) was observed for both reactions, and the *exo*-isomers should be major products based on the stereochemistry outcome from the reactions of C4-substituted cyclopropanols **9** (see Scheme 5-6).

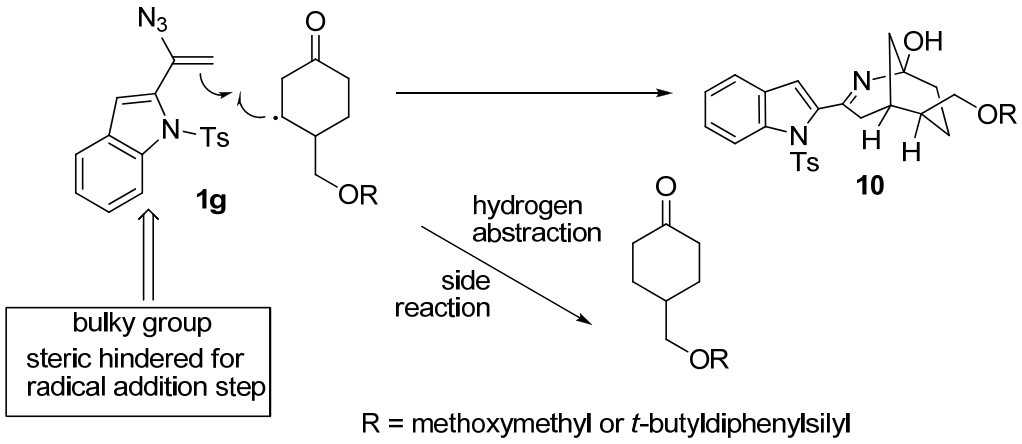


1g **9** (1.2 equiv) **10** (*exo:endo* = 85:15)

cyclopropanols **9**	Mn(III)/x mol%	results
9b: R = methoxymethyl	40	**10gb** (63%) + **1g** (18%)
9g: R = *t*-butyldiphenylsilyl	50	**10gg** (44%) + **1g** (45%)

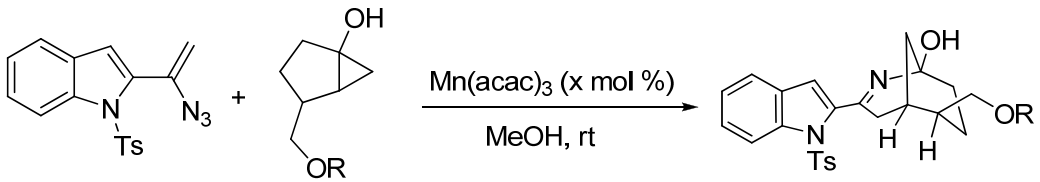
Scheme 5-37. Mn(III)-catalyzed reactions of vinyl azide **1g** and cyclopropanols **9b** or **9g**

It is worth mentioning that the moderate conversion of vinyl azide **1g** even by using high catalyst loading (40-50 mol %) might be attributed to the steric hindrance from the bulky α-indolyl group of vinyl azide **1g**, which could prevent the addition of the resulting β-carbonyl radical to vinyl azide **1g** in some extent (Scheme 5-38). Therefore, some β-carbonyl radical underwent likely hydrogen abstraction to terminate the radical chain reaction to give C-4 substituted cyclohexanones.



Scheme 5-38. The reason for moderate conversion of vinyl azide **1g** by catalytic reactions

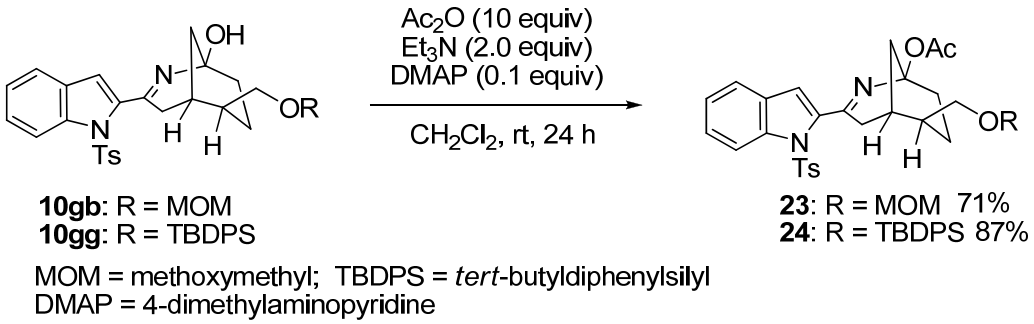
In order to improve the yields of **10gb** and **10gg**, a stoichiometric amount of $Mn(acac)_3$ (1.0-1.6 equiv) and excess amounts (2.0-3.0 equiv) of bicyclo[3.1.0]hexan-1-ol **9b** or **9g** were employed, leading to azabicyclic compounds **10gb** or **10gg** in good yield without decreasing the diastereoselectivity (Scheme 5-39). Vinyl azide **1g** could be used in a 2-gram scale. Furthermore, the resulted two diastereoisomers of **10gg** could be separated by silica gel column chromatography. The major *exo*-isomer was as required for the natural product synthesis.



cyclopropanols **9**	Mn(III)/x mol%	results
9b: R = methoxymethyl	100	**10gb** (86%)
9g: R = *t*-butyldiphenylsilyl	160	**10gg** (88%)

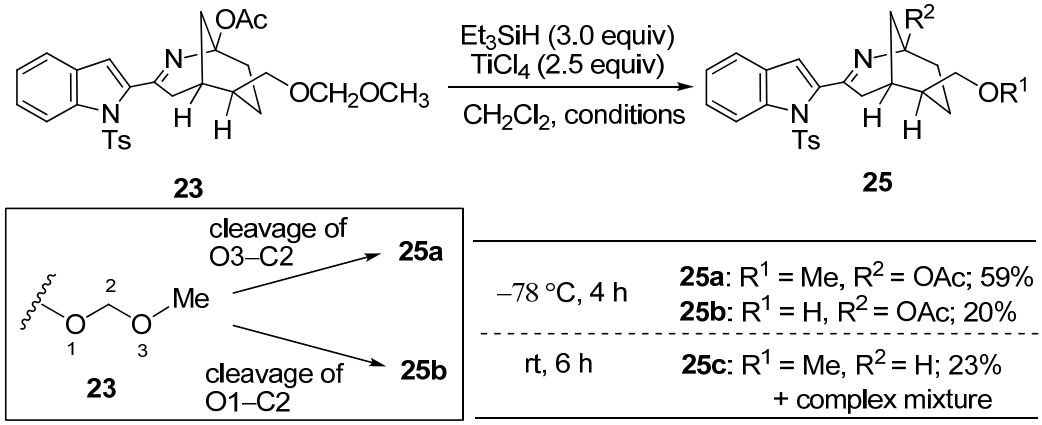
Scheme 5-39. $Mn(acac)_3$-mediated Preparation of compounds **10gb** and **10gg**

With compounds **10gb** and **10gg** in hand, the reduction of the bridgehead C−OH bond was then investigated. Compounds **10gb** and **10gg** were first converted to the corresponding acetates in good yields (Scheme 5-40).



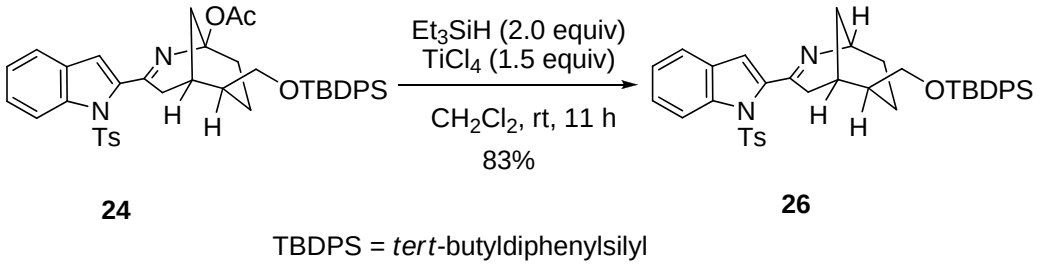
Scheme 5-40. Preparation of acetates **23** and **24**

However, the methoxymethoxymethyl group ($CH_3OCH_2OCH_2$) of acetate **23** might be labile in the conditions (Et_3SiH-$TiCl_4$) used for the reduction of bridgehead C–O bond. Indeed, when the reaction of acetate **23** was carried out at –78 ºC, cleavage of methoxymethoxy group took place to give **25a** and **25b** with the bridgehead C–O bond intact (Scheme 5-41). When the reaction was carried out at room temperature, the reductive removal of the bridgehead C–O bond of acetate **23** could proceed to give **25c**, however, many side products also resulted due to the presence of methoxymethoxymethyl group.



Scheme 5-41. Reduction of bridgehead C–O bond in the presence of MOM group

In order to prevent the aforementioned side reactions, the inert *tert*-butyldiphenylsilyl group (TBDPS) was used in place of methoxymethyl group. Fortunately, the TBDPS group was found to be stable under these reaction conditions, and the resulted reduced product **26** was isolated in 83% yield (Scheme 5-42).

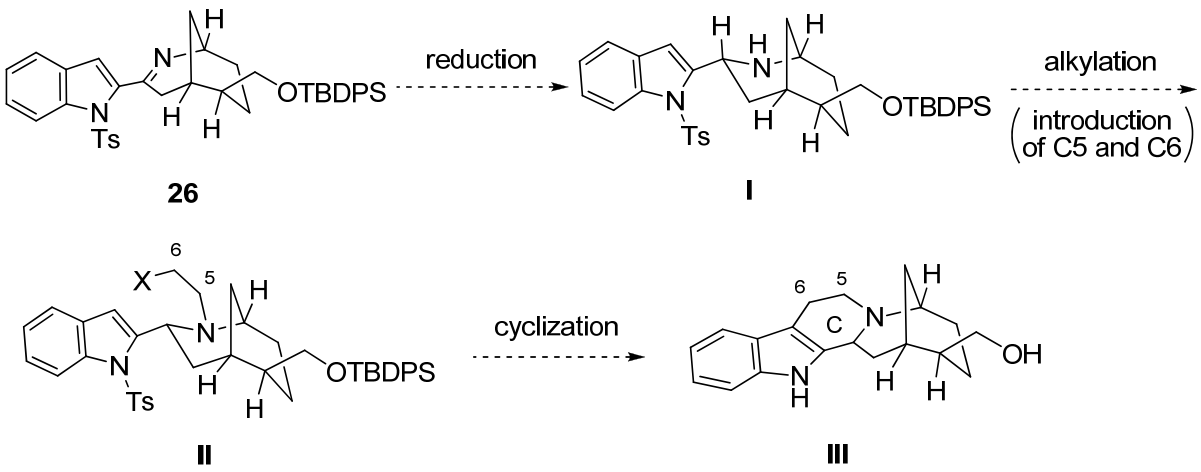


24 **26**

TBDPS = *tert*-butyldiphenylsilyl

Scheme 5-42. Reduction of bridgehead C–O bond of acetate **24**

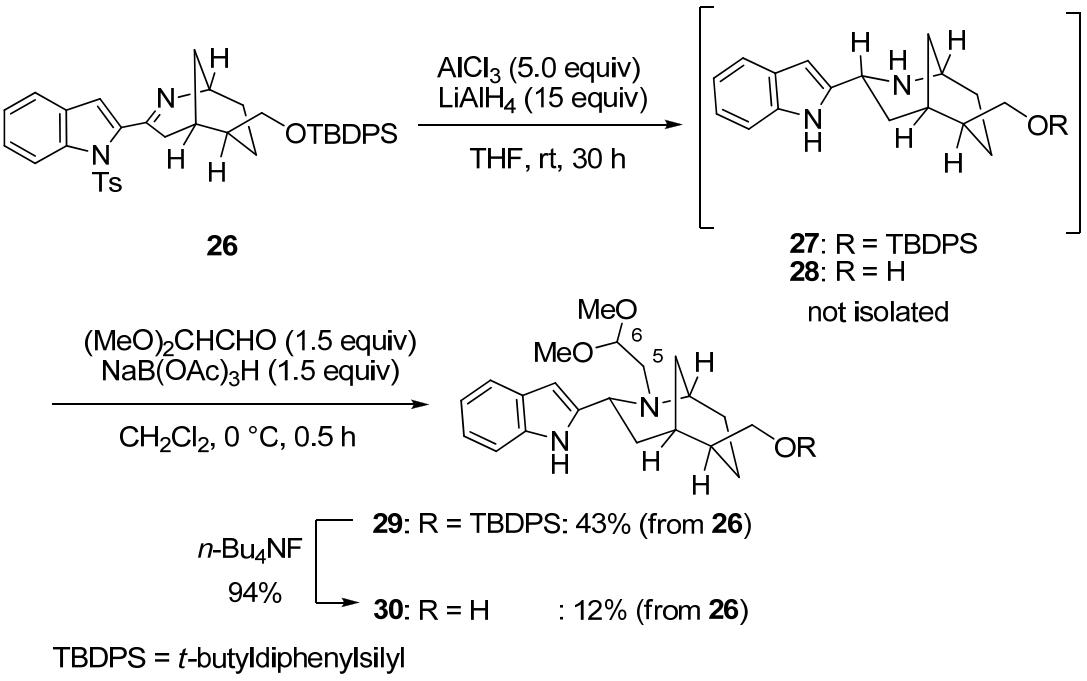
From compound **26**, a strategy for incorporation of two carbon units (C-5 and C-6) and then construction of the C ring was proposed as shown in Scheme 5-43. The reduction of the C═N bond of **26** was expected to afford cyclic *N*-H amine **I** as single diastereoisomer, since the reduction of such kind of cyclic imine in bicyclic system would be stereoselective as discussed in Section 5.2.3. After that, C-5 and C-6 were possible to be incorporated by alkylation. The subsequent cyclization reaction of **II** would construct the C ring.



Scheme 5-43. Proposed synthetic pathway for construction of C ring

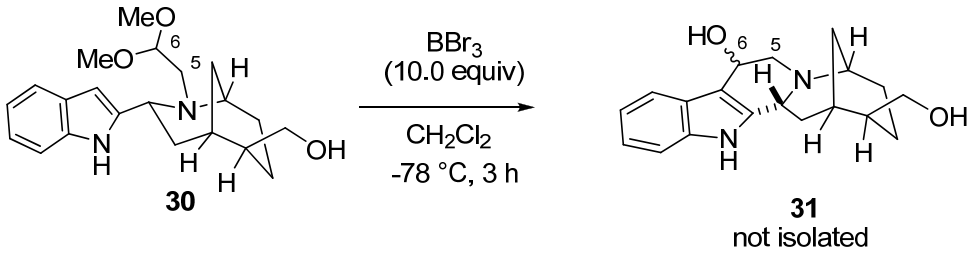
Generally, imines can be reduced by $NaBH_3CN$ in the presence of acid, however, the indole moiety of **26** is also reduced under such reaction conditions (see also Section 5.2.4, Scheme 5-24). Accordingly, alane (AlH_3, generated *in situ* from $LiAlH_4$ and $AlCl_3$[20]) was considered for the reduction of cyclic imine **26**, since indole systems have been previously found to be stable under such reaction conditions.[21] As expected, the reduction reaction proceeded well to give *N*–H amines **27** and **28** with the indole moiety intact (Scheme 5-44). Under alane reduction conditions, the tosyl group was completely removed and *tert*-butyldiphenylsilyl ether was partially deprotected giving a mixture of **27** and **28**. Moreover, the hydride exclusively approached from the less hindered *exo*-face of **26**, and only *endo*-isomers **27** and **28** (refer to 2-indoyl group) resulted.

Without purification, the crude mixture of *N*–H amines **27** and **28** was then treated with 2,2-dimethoxyacetaldehyde and $NaB(OAc)_3H$.[22] This reductive *N*-alkylation reaction afforded **29** and **30** in 43% and 12% yields (both from **26**, two steps), respectively. The remaining *tert*-butyldiphenylsiyl group of **29** was easily removed with *n*-Bu_4NF.



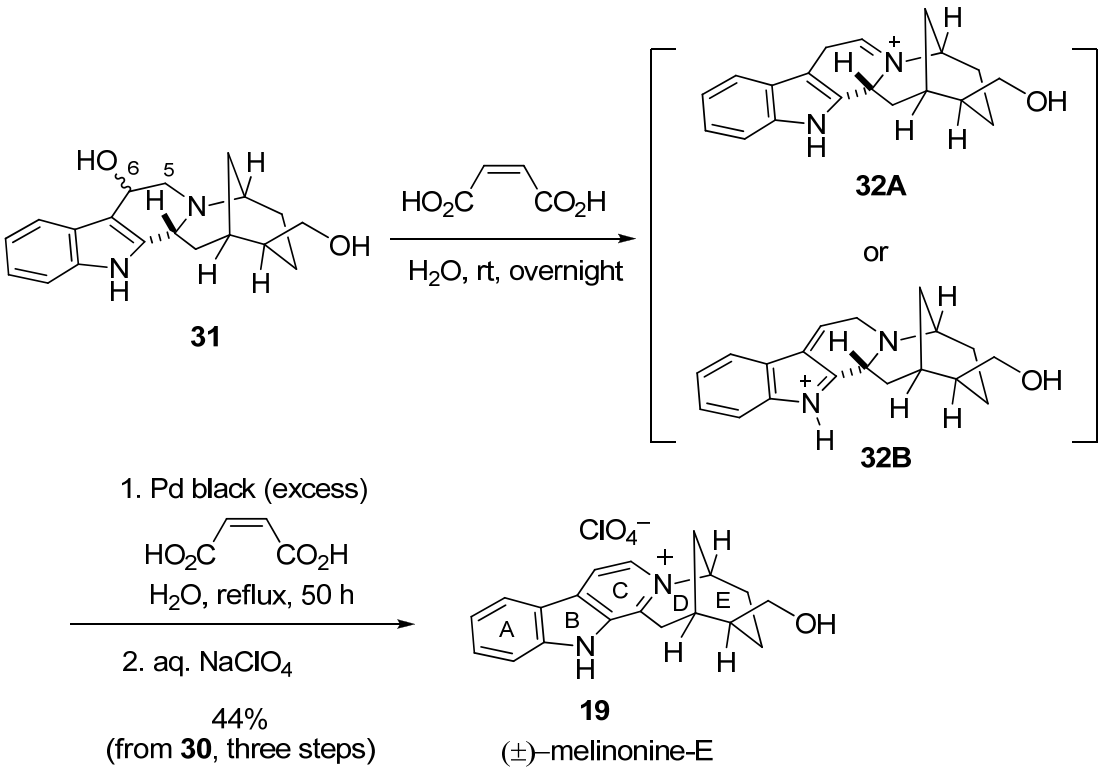
Scheme 5-44. Reduction of **26** and then introduction of C-5 and C-6 by alkylation

As a 2,2-dimethoxyethyl group possessing C5 and C6 was successfully incorporated in the molecule, the construction of C ring was next examined by means of Lewis acid-induced cyclization between the indole motif and the intramolecular acetal moiety. As expected, the BBr_3-mediated cyclization exclusively occurred at the 3-position of indole ring, affording pentacyclic compound **31** (Scheme 5-45).



Scheme 5-45. Lewis acid-mediated cyclization of **30**

The aromatization of **31** to **19** was the last step to complete the synthesis. Treatment of the crude material including **31** with maleic acid in water led to the formation of dehydration intermediate (either iminium **32A** or indolenium **32B**, not isolated, determined by LC-MS) which then underwent dehydrogenation by using palladium black, affording the natural product in good yield (44% from **30**, three steps) (Scheme 5-46). The ^{1}H and ^{13}C NMR data of the synthetic (±)-melinonine-E perchlorate were identical to reported data.[15]

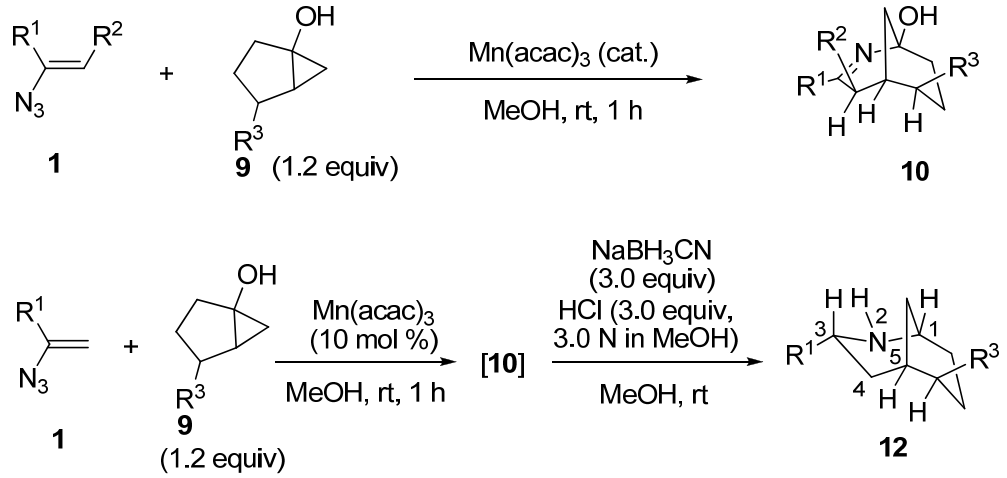


Scheme 5-46. Synthesis of (±)-melinonine-E

5.3 Conclusion

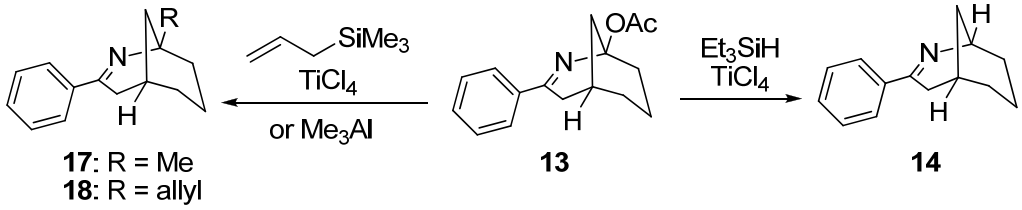
In summary, the author has developed a Mn(III)-catalyzed formal [3+3] annulation reaction of vinyl azides and bicyclo[3.1.0]hexan-1-ols to synthesize 2-azabicyclo[3.3.1]non-2-en-1-ols (Scheme 5-47, Eq. a). More importantly, a facile one-pot procedure was also

explored to access morphan nucleus by reduction of the *in situ* generated 2-azabicyclo[3.3.1]non-2-en-1-ols (Eq. b). This synthetic method involves the simultaneous formation of C1–N2 and C4–C5 bonds, which provides an alternative straightforward route to mophan derivatives from readily available starting materials.



Scheme 5-47. Synthesis of azabicyclic compounds **10** and one-pot preparation of **12**

Versatile transformations of 2-azabicyclo[3.3.1]non-2-en-1-yl acetate to 2-azabicyclo[3.3.1]non-2-enes were developed as well (Scheme 5-48). These transformations have great potential in the synthesis of morphan derivatives, especially for 1-substituted ones.



Scheme 5-48. Transformations of acetate **13**

Ultimately, the synthetic utility of the $Mn(acac)_3$-catalyzed synthesis of azabicyclic compounds was demonstrated by a concise synthesis of (±)-melinonine-E.

5.4 References and Notes

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Chapter 6 Experimental Section

6.1. General

^{1}H NMR (300MHz) spectra were recorded on a Bruker Avance 300 spectrometer and ^{1}H NMR (400MHz) spectra were recorded on a Bruker Avance 400 in $CDCl_3$ [using $CHCl_3$ (for ^{1}H, δ = 7.26) as internal standard] or in DMSO-d_6 [using DMSO (for ^{1}H, δ = 2.50) as internal standard] or in CD_2Cl_2 [using CH_2Cl_2 (for δ = 5.32) as internal standard]. ^{13}C NMR (75 MHz) spectra on a Bruker Avance 300 spectrometers and ^{13}C NMR (100 MHz) spectra on a Bruker Avance 400 spectrometers in $CDCl_3$ [using $CHCl_3$ (for ^{13}C, δ = 77.0) as internal standard] or in DMSO-d_6 [using DMSO (for ^{13}C, d = 39.5) as internal standard] or in CD_2Cl_2 [using CH_2Cl_2 (for δ = 54.0) as internal standard]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. IR spectra were recorded on a Shimadzu IR Prestige-21 FT-IR Spectrometer. High-resolution mass spectra were obtained with either a Q-Tof Premier LC HR mass spectrometer or a Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). Melting points are uncorrected and were recorded on a Buchi B-54 melting point apparatus.

Flash column chromatographs were performed using Silicycle 60 silica gel or Florisil® adsortbent (100-200 mesh) and distilled eluting solvents. Ethanol (EtOH) and Methanol (MeOH) were distilled from sodium under N_2 and stored over MS 4A. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium and benzophenone under N_2. Dichloromethane (CH_2Cl_2) was dried by passing over a column of activated alumina (A-2, Purify) followed by a column of Q-5 scavenger (Engelhard). Acetonitrile (MeCN) was distilled from P_4O_{10} and stored over MS 4A. Chloroform ($CHCl_3$), triethylamine (NEt_3), *N*,*N*-dimethylmethanamide (DMF), Acetone, and pyridine were purchased from Sigma-Aldrich

Co., Inc. $Mn(acac)_3$ was purified by reprecipitation of commercially available one (Aldrich) from benzene-hexane.

6.2. Safety issues in handling azido compounds[1,2]

6.2.1. Sodium azide (NaN_3)

Sodium azide is toxic (LD_{50} oral = 27 mg/kg for rats) and can be absorbed through skin. Appropriate gloves are necessary when using it. It decomposes explosively upon heating to above 275 °C. Sodium azide is relatively safe in aqueous solution, *unless acidified to form HN_3*, which is volatile and highly toxic.

6.2.2. Organic azides

Organic azides are potentially explosive substances that can potentially decompose with the slight input of energy from external sources (heat, light, pressure, etc). When desiging the organic azides used for the project, we keep in mind the following equation. It is noted that this equation takes into account all nitrogen atoms in the organic azide, not just those in the azido group.

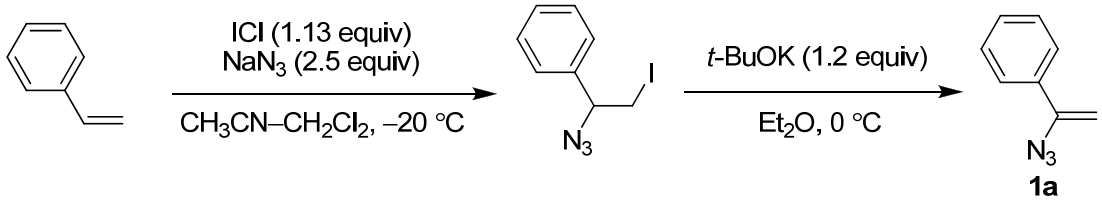
$$\frac{N_C + N_O}{N_N} \geq 3 \qquad \text{(N: atom number)}$$

All organic azides prepared in this work satisfied the above equation except for **1a**, **1i** and **1s**. They are enough stable to be stored under –20 ºC at least for 6 months. We have never experienced a safety problem with these materials.

6.3. Synthesis of vinyl azides 1

All new vinyl azides were prepared by the following procedures.

6.3.1 Synthesis of vinyl azides by method A

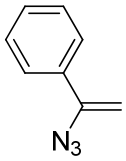


This procedure was slightly modified from Hassner's method.[3]

To a suspension of NaN_3 (7.15 g, 110 mmol) in acetonitrile (30 mL) was added dropwise a solution of iodine monochloride (8.07 g, 49.7 mmol) in CH_2Cl_2 (60 mL) at −20 °C, and the mixture was stirred at the same temperature. After 30 min, a solution of styrene (5.0 mL, 43.6 mmol) in CH_2Cl_2 (20 mL) was added slowly, and the mixture was stirred for 1 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$, and the organic materials were extracted two times with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. After evaporation of solvents, the resulting crude materials were used immediately for the next step without any furthur purification.

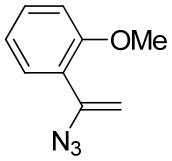
To a solution of the obtained compounds above in Et_2O (100 mL) was added *t*-BuOK (5.92 g, 52.3 mmol) at 0 °C, and the mixture was stirred for 1.5 h at the same temperature. The reaction was quenched by adding pH 9 ammonium buffer, and the organic materials were extracted with Et_2O. The Et_2O solution was washed with brine, and dried over $MgSO_4$. The solvent was removed in vacuo, and the resulting crude materials were purified by flash column chromatography (silica gel; hexane : ethyl acetate = 98 : 2) to give vinyl azide **1a** (5.38 g, 37.1 mmol, 85% yield from styrene) as a pale yellow liquid.

(1-Azidovinyl)benzene (1a):[3]



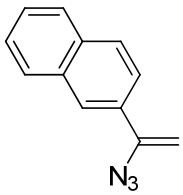
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (1H, d, *J* = 2.4 Hz), 5.45 (1H, d, *J* = 2.4 Hz), 7.37-7.40 (3H, m), 7.57-7.59 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 98.0, 125.6, 128.5, 129.1, 134.3, 145.1.

1-(1-Azidovinyl)-2-methoxybenzene (1c):



Yield: 96%; pale yellow liquid; IR (KBr) 3005, 2837, 2097, 1624, 1599, 1490, 1445, 1276, 1180, 1026 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (3H, s), 4.94 (1H, s), 5.04 (1H, s), 6.95 (1H, d, *J* = 8.4 Hz), 6.98 (1H, dd, *J* = 0.6, 7.6 Hz), 7.34-7.39 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 103.0, 110.8, 120.7, 123.5, 130.3, 130.6, 143.0, 156.7; ESIHRMS: Found: m/z 176.0823. Calcd for $C_9H_{10}N_3O$: $(M+H)^+$ 176.0824.

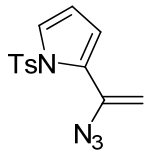
2-(1-Azidovinyl)naphthalene (1e):



Yield: 52%; white solid; mp 56-58 °C; IR (KBr) 3018, 2112, 1611, 1520, 1439, 1300, 1215 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (1H, d, *J* = 2.2 Hz), 5.60 (1H, d, *J* = 2.2 Hz), 7.51

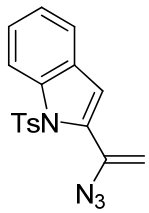
(2H, m), 7.67 (1H, d, *J* = 8.8 Hz), 7.83 (1H, d, *J* = 8.8 Hz), 7.82-7.88 (2H, m), 8.06 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 98.2, 123.0, 124.9, 126.5, 126.6, 127.6, 128.1, 128.5, 131.4, 133.0, 133.5, 144.9; ESIHRMS: Found: m/z 196.0869. Calcd for $C_{12}H_{10}N_3$: $(M+H)^+$ 196.0875.

2-(1-Azidovinyl)-1-tosyl-1*H*-pyrrole (**1f**):



Yield: 31%; pale yellow solid; mp 61-62 °C; IR (KBr) 3148, 3026, 2100, 1632, 1597, 1557, 1493, 1470, 1371, 1269, 1180, 1049 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (3H, s), 4.68 (1H, s), 5.05 (1H, s), 6.26 (1H, dd, *J* = 3.2, 3.6 Hz), 6.31-6.32 (1H, m), 7.27 (2H, d, *J* = 8.0 Hz), 6.36-6.37 (1H, m), 7.71 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 106.5, 112.0, 117.6, 124.6, 127.2, 128.4, 129.7, 135.6, 136.8, 145.2; ESIHRMS: Found: m/z 311.0577. Calcd for $C_{13}H_{12}N_4NaO_2S$: $(M+Na)^+$ 311.0579.

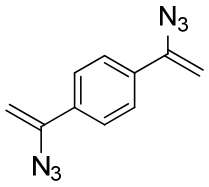
2-(1-Azidovinyl)-1-tosyl-1H-indole (1g):



Yield: 71%; pale yellow solid; mp 79-81 °C; IR (KBr) 3019, 2104, 1626, 1456, 1377, 1273, 1175, 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (3H, s), 4.94 (1H, s), 5.19 (1H, s), 6.71 (1H, s), 7.14 (2H, d, *J* = 8.0 Hz), 7.25 (1H, dd, *J* = 7.6, 8.0 Hz), 7.37 (1H, dd, *J* = 7.6, 8.0 Hz), 7.46 (1H, d, *J* = 8.0 Hz), 7.66 (2H, d, *J* = 8.0 Hz), 8.18 (1H, d, *J* = 7.6 Hz); ^{13}C NMR (100

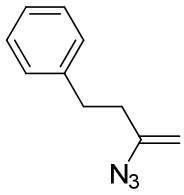
MHz, $CDCl_3$) δ 21.5, 105.7, 115.0, 115.7, 121.4, 124.3, 125.9, 126.9, 129.3, 129.5, 134.5, 134.6, 137.4, 138.7, 145.0; ESIHRMS: Found: m/z 311.0851. Calcd for $C_{17}H_{15}N_2O_2S$: $(M-N_2+H)^+$ 311.0854.

1,4-Bis(1-azidovinyl)benzene (**1i**):



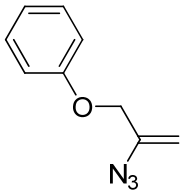
Yield: 30%; pale yellow solid; mp 107-108 °C; IR (KBr) 3019, 2104, 1607, 1508, 1404, 1303, 1215, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.99 (2H, d, *J* = 2.8 Hz), 5.48 (2H, d, *J* = 2.8 Hz), 7.55 (4H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 88.3, 125.5, 134.8, 144.4; ESIHRMS: Found: m/z 213.0883. Calcd for $C_{10}H_9N_6$: $(M+H)^+$ 213.0889.

(3-Azidobut-3-enyl)benzene (**1j**):



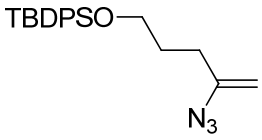
Yield: 52%; pale yellow liquid; IR (KBr) 3028, 2860, 2102, 1628, 1603, 1497, 1454, 1385, 1279, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.41 (2H, t, *J* = 7.8 Hz), 2.84 (2H, t, *J* = 7.8 Hz), 4.69 (2H, s), 7.22-7.28 (3H, m), 7.34 (2H, dd, *J* = 7.2, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.7, 35.6, 98.6, 126.1, 128.3, 128.4, 140.7, 145.9; ESIHRMS: Found: m/z 146.0962. Calcd for $C_{10}H_{12}N$: $(M-N_2+H)^+$ 146.0970.

(2-Azidoallyloxy)benzene (**1k**):



Yield: 46%; pale yellow liquid; IR (KBr) 3040, 2866, 2114, 1638, 1597, 1589, 1495, 1458, 1362, 1283, 1170, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.46 (2H, s), 4.92 (1H, s), 5.06 (1H, s), 6.95 (2H, d, *J* = 8.4 Hz), 7.00 (1H, t, *J* = 7.6 Hz), 7.31 (2H, dd, *J* = 7.6, 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.6, 101.0, 114.8, 121.5, 129.5, 142.0, 157.9; ESIHRMS: Found: m/z 148.0763. Calcd for $C_9H_{10}NO$: $(M-N_2+H)^+$ 148.0762.

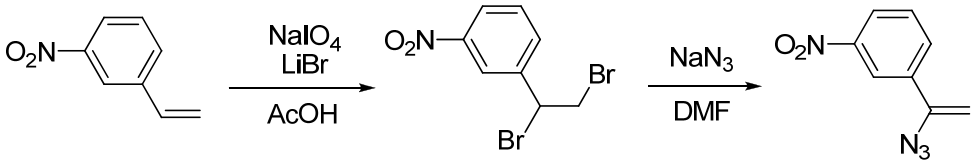
(4-Azidopent-4-enyloxy)(*tert*-butyl)diphenylsilane (**1l**):



Yield: 54%; colorless liquid; IR (KBr) 3070, 2857, 2097, 1626, 1589, 1472, 1427, 1388, 1362, 1271, 1188, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.73 (2H, tt, *J* = 6.2, 7.6 Hz), 2.20 (2H, t, *J* = 7.6 Hz), 3.68 (2H, t, *J* = 6.2 Hz), 4.62 (1H, s), 4.63 (1H, s), 7.36-7.45 (6H, m), 7.65-7.67 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 26.8, 30.1, 30.2, 62.6, 98.2, 127.6, 129.6, 133.8, 135.5, 146.3; ESIHRMS: Found: *m/z* 338.1938. Calcd for $C_{21}H_{28}NOSi$: $(M-N_2+H)^+$ 338.1940**.**

Vinyl azides **1b**,[4] **1d**,[4] **1h**[3] and **1n**[5] are known compounds and were prepared following the same procedure as **1a** from the corresponding olefins.

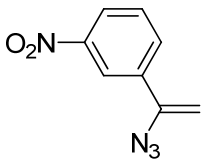
6.3.2 Synthesis of vinyl azides by method B



The procedure for dibromination of 3-nitrostyrene was slightly modified from Sudalai's method.[6] To a solution of 3-nitrostyrene (0.98g, 6.5 mmol) and LiBr (1.25g, 14.4 mmol) in acetic acid (10 mL) was added $NaIO_4$ (0.70g, 3.27 mmol) portionwise during 15 minutes. The stirring was continued at room temperature for 5 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layers were washed with saturated aq. $NaHCO_3$, $Na_2S_2O_3$, and brine. It was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give dibromide (in quantitative yield), which was used without further purification.

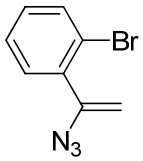
To a solution of dibromide in dry DMF (25 mL) was added NaN_3 (1.27g, 19.5 mmol). The mixture was stirred for 24 h at room temperature, then diluted with water and extracted with diethyl ether. The combined organic layers were washed three times with water and dried with $MgSO_4$. After evaporation of solvents, the crude residue was purified by flash column chromatography (silica gel; hexane : ethyl acetate = 99 : 1) to give vinyl azide **1r** (1.11 g, 5.84 mmol) in 90% yield.

1-(1-Azidovinyl)-3-nitrobenzene (**1r**):[4]



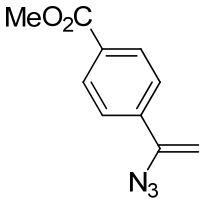
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (1H, d, *J* = 2.8 Hz), 5.61 (1H, d, *J* = 2.8 Hz), 7.54 (1H, dd, *J* = 8.0, 8.0 Hz), 7.90 (1H, d, *J* = 8.0 Hz), 8.19 (1H, d, *J* = 8.0 Hz), 8.42 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.7, 120.5, 123.7, 129.5, 131.2, 135.9, 143.0, 148.4**.**

1-(1-Azidovinyl)-2-bromobenzene (1o):



Yield: 30%; pale yellow liquid; IR (KBr) 3119, 3057, 2095, 1632, 1587, 1562, 1466, 1427, 1298, 1099, 1026 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (1H, d, *J* = 0.8 Hz), 5.11 (1H, d, *J* = 0.8 Hz), 7.23-7.26 (1H, m), 7.34-7.35 (2H, m), 7.62 (1H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.9, 122.3, 127.5, 130.5, 131.0, 133.1, 136.3, 144.5; ESIHRMS: Found: *m/z* 223.9833. Calcd for $C_8H_7BrN_3$: $(M+H)^+$ 223.9823**.**

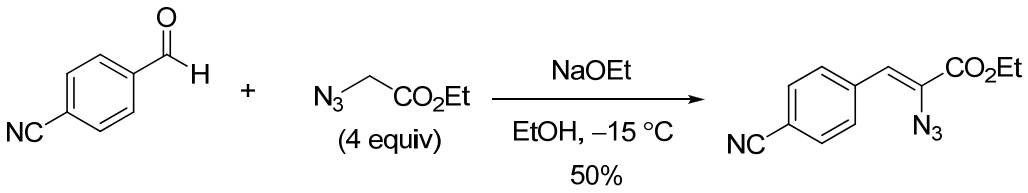
Methyl 4-(1-azidovinyl)benzoate (**1q**):



Yield: 68%; white solid; mp 84-85 °C; IR (KBr) 3020, 2953, 2106, 1714, 1611, 1568, 1437, 1406, 1282, 1117, 1018 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (3H, s), 5.06 (1H, d, *J* = 2.8 Hz), 5.56 (1H, d, *J* = 2.8 Hz), 7.63 (2H, d, *J* = 8.4 Hz), 8.02 (2H, d, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52,2, 99.6, 125.4, 129.7, 130.5, 138.3, 144.2, 166.5; ESIHRMS: Found: *m/z* 204.0777. Calcd for $C_{10}H_9N_3O_2$: $(M+H)^+$ 204.0773**.**

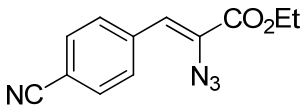
Vinyl azides **1p**,[4] **1s**[7] and **1t**[8] are known compounds and were prepared following the same procedure as **1r** from the corresponding olefins.

6.3.3 Synthesis of vinyl azides by method C[9]



To stirring EtOH (15 mL) was added slowly chunks of sodium (742 mg, 32.3 mmol). After complete dissolution of the sodium, the mixture was cooled to –15 °C and a solution of 4-cyanobenzaldehyde (1.07 g, 8.13 mmol) and ethyl azidoacetate (4.23 g, 32.8 mmol) in EtOH (20 mL) was slowly added. The stirring was continued at –15 °C for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, and then extracted twice with ethyl acetate. The combined extracts were washed with water, brine and dried over $MgSO_4$. After evaporation of solvents, the crude residue was purified by flash column chromatography (silica gel; hexane : ethyl acetate = 95 : 5) to give **1w** (991 mg, 4.09 mmol) in 50% yield.

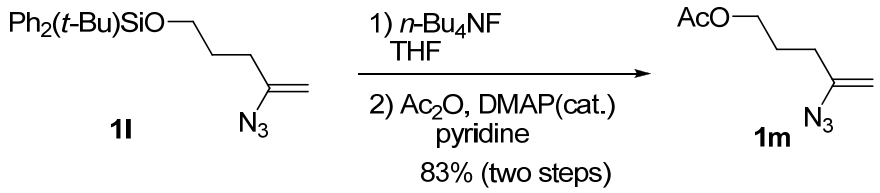
(*Z*)-Ethyl 2-azido-3-(4-cyanophenyl)acrylate (1w):



Pale yellow solid; mp 83-85 °C; IR (KBr) 3054, 2987, 2229, 2123, 1717, 1619, 1604, 1381, 1322, 1264, 1080, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (3H, t, *J* = 7.2 Hz), 4.40 (2H, q, *J* = 7.2 Hz), 6.84 (1H, s), 7.65 (2H, d, *J* = 8.3 Hz), 7.90 (2H, d, *J* = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 62.7, 112.0, 118.6, 122.0, 128.6, 130.7, 132.0, 137.5, 162.8; EIHRMS: Found: *m/z* 242.0798. Calcd for $C_{12}H_{10}N_4O_2$: M^+ 242.0804.

Vinyl azides **1u**[9] and **1v**[9] are known compounds and were prepared following the same procedure as **1w** from the corresponding benzaldehydes.

6.3.4 Synthesis of vinyl azide 1m



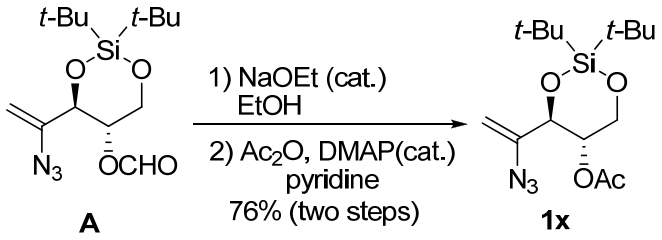
To an ice cold solution of vinyl azide **1l** (3.70 g, 10.1 mmol) in THF (10 mL) was added a 1 M solution of *n*-Bu_4NF (in THF, 15 mL, 15 mmol) and the mixture was stirred at room temperature for 2 h. The reaction was quenched with water, and organic materials were extracted three times with ethyl acetate. The combined extracts were washed with brine and dried over $MgSO_4$. The volatile materials were removed in vacuo, and resulting crude mixtures were purified by flash column chromatography (silica gel; hexane : ethyl acetate = 60 : 40) to give the corresponding alcohol (1.28 g, 10.1 mmol, quantitative yield).

To a solution of obtained alcohol (202 mg, 1.59 mmol) in pyridine (3 mL) was added aceticanhydride (0.3 mL, 3.2 mmol) and 4-dimethylaminopyridine (5 mg), and the mixture was stirred at room temperature for 1 h. The volatile materials were removed in vacuo, and resulting crude mixtures were purified by flash column chromatography (silica gel; hexane : ethyl acetate = 85 : 15) to give **1m** (224 mg, 1.32 mmol, 83% yield).

Pale yellow liquid; IR (KBr) 2961, 2857, 2099, 1741, 1628, 1446, 1430, 1389, 1366, 1271, 1238, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.82 (2H, tt, *J* = 6.4, 7.2 Hz), 2.06 (3H, s), 2.15 (2H, t, *J* = 7.2 Hz), 4.08 (2H, t, *J* = 6.4 Hz), 4.67 (1H, s), 4.71 (1H, s); ^{13}C NMR (100

MHz, $CDCl_3$) δ 20.9, 26.2, 30.3, 63.3, 98.5, 145.7, 171.0; ESIHRMS: Found: m/z 170.0940. Calcd for $C_7H_{12}N_3O$: $(M+H)^+$ 170.0930**.**

6.3.5 Synthesis of vinyl azide 1x



To an ice-cold solution of EtOH (10 mL) was added NaH (60% dispersion in mineral oil, 33 mg, 0.83 mmol), and the solution was stirred at 0 °C for 5 min. To the resulting solution of NaOEt was added vinyl azide **A**[10] (2.48 g, 7.57 mmol) with EtOH (10 mL). After stirring for 15 min, the reaction was quenched by adding pH 9 ammonium buffer and the organic materials were extracted with ethyl acetate. The combined extracts were washed with brine, and dried over $MgSO_4$. The solvent was removed in vacuo, and resulting crude materials were used for the next step without further purification.

The crude materials obtained above was dissolved in pyridine (10 mL). To this mixture was added acetic anhydride (1.2 mL, 12.7 mmol) and 4-dimethylaminopyridine (5 mg), and the solution was stirred at room temperature for 30 min. The volatile materials were removed in vacuo, and resulting crude materials were purified by flash column chromatography (silica gel; hexane : ethyl acetate = 90 : 10) to give vinyl azide **1x** (1.97 g, 5.77 mmol, 76% yield).

Pale yellow solid; mp 66-68 °C; IR (KBr) 2933, 2860, 2106, 1751, 1632, 1474, 1368, 1300, 1226, 1124, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (18H, s), 2.02 (3H, s), 3.87 (1H,

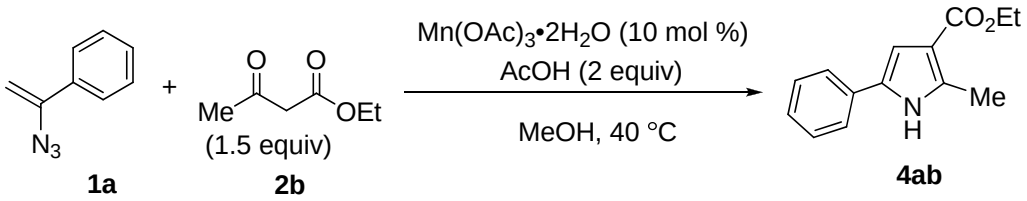
dd, J = 10.0, 10.4 Hz), 4.12 (1H, dd, J = 4.4, 10.4 Hz), 4.38 (1H, d, J = 8.8 Hz), 4.84 (1H, s), 4.98 (1H, ddd, J = 4.4, 8.8, 10.0 Hz), 5.06 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 20.8, 22.6, 27.0, 27.3, 64.9, 68.5, 76.6, 100.9, 145.6, 169.2; ESIHRMS: Found: m/z 364.1671. Calcd for $C_{15}H_{27}N_3NaO_4Si$: $(M+Na)^+$ 364.1669.

Vinyl azide **1y**[11] is a known compound and was prepared by the reported method.

6.4 Mn(III)-catalyzed synthesis of pyrroles from vinyl azides and 1,3-dicarbonyl compounds (Chapter 3)

6.4.1 $Mn(OAc)_3 \cdot 2H_2O$-catalyzed pyrrole formation from vinyl azides and β-keto esters (Section 3.2.3)

Typical procedure:

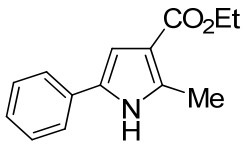


1a **2b** **4ab**

To a solution of α-azido styrene (**1a**) (145 mg, 1.00 mmol) and ethyl acetoacetate (**2b**) (191 μL, 1.50 mmol) in MeOH (10 mL) was added AcOH (114 μL, 2.00 mmol) and manganese(III) acetate dihydrate (27.6 mg, 0.10 mmol) and the reaction mixture was stirred at 40 ºC for 2 h. The reaction mixture was quenched with pH 9 ammonium buffer, and then extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by flash column

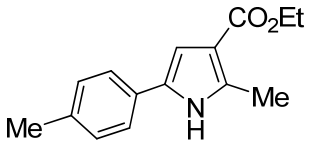
chromatography (silica gel; hexane : ethyl acetate = 85 : 15) afforded pyrrole **4ab** (207 mg, 0.90 mmol) in 90% yield.

Ethyl 2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate (4ab):[12]



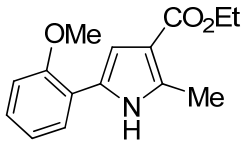
Reaction time: 2 h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (3H, t, *J* = 7.1 Hz), 2.58 (3H, s), 4.30 (2H, q, *J* = 7.1 Hz), 6.83 (1H, d, *J* = 2.8 Hz), 7.21 (1H, t, *J* = 7.3 Hz), 7.35 (2H, dd, *J* = 7.3, 7.4 Hz), 7.45 (2H, d, *J* = 7.4 Hz), 8.61 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 14.6, 59.5, 107.3, 113.3, 123.6, 126.5, 128.8, 129.9, 131.7, 136.1, 165.5.

Ethyl 2-methyl-5-*p*-tolyl-1*H*-pyrrole-3-carboxylate (4bb):



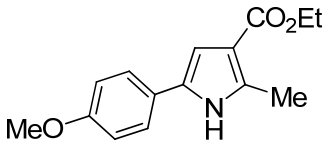
Reaction time: 4 h. White solid; mp 131-133 °C; IR (KBr) 3456 (br), 3019, 1682, 1595, 1531, 1445, 1265, 1215, 1099, 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (3H, t, *J* = 7.2 Hz), 2.34 (3H, s), 2.57 (3H, s), 4.30 (2H, q, *J* = 7.2 Hz), 6.79 (1H, d, *J* = 2.8 Hz), 7.16 (2H, d, *J* = 8.0 Hz), 7.36 (2H, d, *J* = 8.0 Hz), 8.73 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 14.5, 21.1, 59.5, 106.7, 113.1, 123.6, 129.0, 129.5, 130.1, 135.9, 136.2, 165.7; EIHRMS: Found: *m/z* 243.1254. Calcd for $C_{15}H_{17}NO_2$: M^+ 243.1254.

Ethyl 5-(2-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (4cb):



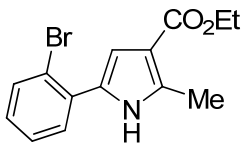
Reaction time: 4 h. White solid; mp 98-100 °C; IR (KBr) 3443 (br), 3019, 1694, 1601, 1524, 1441, 1284, 1215, 1101, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (3H, t, *J* = 7.2 Hz), 2.59 (3H, s), 3.95 (3H, s), 4.30 (2H, q, *J* = 7.2 Hz), 6.94 (1H, d, *J* = 2.8 Hz), 6.95-7.01 (2H, m), 7.18 (1H, ddd, *J* = 1.6, 7.8, 8.0 Hz), 7.64 (1H, dd, *J* = 1.6, 8.0 Hz), 9.68 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 14.5, 55.6, 59.3, 107.8, 111.5, 112.1, 120.1, 121.5, 126.5, 127.1, 127.8, 134.8, 154.7, 165.7; EIHRMS: Found: *m/z* 259.1204. Calcd for $C_{15}H_{17}NO_3$: M^+ 259.1203.

Ethyl 5-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (4db):



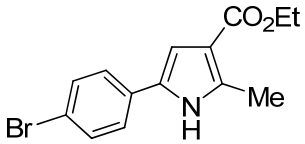
Reaction time: 4 h. White solid; mp 146-148 ºC; IR (NaCl) 3287, 3018, 1666, 1531, 1382, 1271, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (3H, t, *J* = 7.2 Hz), 2.57 (3H, s), 3.81 (3H, s), 4.29 (2H, q, *J* = 7.2 Hz), 6.71 (1H, d, *J* = 2.4 Hz), 6.90 (2H, d, *J* = 8.4 Hz), 7.38 (2H, d, *J* = 8.4 Hz), 8.50 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 14.5, 55.3, 59.5, 106.1, 113.1, 114.3, 124.8, 125.1, 130.0, 135.6, 158.5, 165.7. ESIHRMS: Found: m/z 260.1295. Calcd for $C_{15}H_{18}NO_3$: $(M+H)^+$ 260.1297.

Ethyl 5-(2-bromophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (4ob):



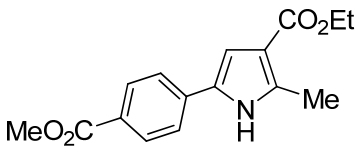
Reaction time: 2 h. White solid; mp 112-114 °C; IR (KBr) 3447 (br), 3019, 1684, 1595, 1521, 1437, 1284, 1215, 1101, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, t, *J* = 7.2 Hz), 2.56 (3H, s), 4.28 (2H, q, *J* = 7.2 Hz), 6.86 (1H, d, *J* = 2.8 Hz), 7.10 (1H, ddd, *J* = 1.6, 7.6, 7.6 Hz), 7.30 (1H, ddd, *J* = 1.2, 7.6, 7.6 Hz), 7.47 (1H, dd, *J* = 1.6, 8.0 Hz), 7.60 (1H, dd, *J* = 1.2, 8.0 Hz), 8.95 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 14.5, 59.5, 111.2, 112.7, 120.1, 127.7, 128.1, 128.2, 130.2, 132.4, 133.8, 135.8, 165.4; EIHRMS: Found: *m/z* 307.0204. Calcd for $C_{14}H_{14}BrNO_2$: M^+ 307.0202.

Ethyl 5-(4-bromophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (4pb):



Reaction time: 2 h. White solid; mp 170-171 °C; IR (KBr) 3455 (br), 3019, 1682, 1602, 1520, 1477, 1265, 1215, 1099, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (3H, t, *J* = 7.2 Hz), 2.59 (3H, s), 4.29 (2H, q, *J* = 7.2 Hz), 6.83 (1H, d, *J* = 2.8 Hz), 7.31 (2H, d, *J* = 8.8 Hz), 7.48 (2H, d, *J* = 8.4 Hz), 8.38 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 14.5, 59.7, 107.8, 113.5, 120.0, 125.1, 128.9, 130.7, 131.9, 136.6, 165.6; EIHRMS: Found: *m/z* 307.0202. Calcd for $C_{14}H_{14}BrNO_2$: M^+ 307.0202.

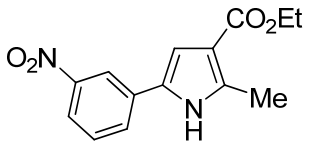
Ethyl 5-(4-(methoxycarbonyl)phenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (4qb):



Reaction time: 2 h. White solid; mp 195-196 °C; IR (KBr) 3323 (br), 3019, 1694 (br), 1611, 1526, 1437, 1281, 1215, 1101, 1070 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, *J* =

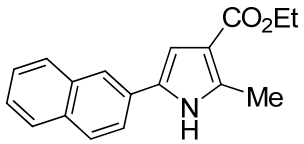
7.2 Hz), 2.51 (3H, s), 3.85 (3H, s), 4.20 (2H, q, *J* = 7.2 Hz), 6.97 (1H, d, *J* = 2.4 Hz), 7.79 (2H, d, *J* = 8.8 Hz), 7.94 (2H, d, *J* = 8.8 Hz), 11.84 (1H, s br); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.3, 14.9, 52.4, 59.3, 109.4, 113.1, 123.7, 127.0, 128.9, 130.3, 136.7, 138.4, 164.8, 166.4; EIHRMS: Found: *m/z* 287.1157. Calcd for $C_{16}H_{17}NO_4$: M^+ 287.1152.

Ethyl 2-methyl-5-(3-nitrophenyl)-1*H*-pyrrole-3-carboxylate (4rb):



Reaction time: 2 h. Pale yellow solid; mp 189-192 °C; IR (KBr) 3451 (br), 3019, 1694, 1662, 1533, 1477, 1423, 1350, 1215, 1098, 1045 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (3H, t, *J* = 7.2 Hz), 2.51 (3H, s), 4.19 (2H, q, *J* = 7.2 Hz), 7.02 (1H, d, *J* = 2.8 Hz), 7.63 (1H, dd, *J* = 8.0, 8.0 Hz), 8.01 (1H, ddd, *J* = 0.8, 2.4, 8.0 Hz), 8.12 (1H, ddd, *J* = 0.8, 2.0, 8.0 Hz), 8.51 (1H, dd, *J* = 2.0, 2.4 Hz), 11.98 (1H, s br); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.3, 14.9, 59.3, 109.3, 113.0, 117.7, 120.8, 127.9, 130.3, 130.7, 134.0, 138.2, 149.0, 164.8; EIHRMS: Found: *m/z* 274.0948. Calcd for $C_{14}H_{14}N_2O_4$: M^+ 274.0948.

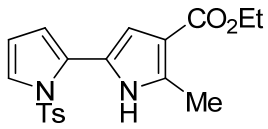
Ethyl 2-methyl-5-(naphthalen-2-yl)-1*H*-pyrrole-3-carboxylate (4eb):



Reaction time: 2 h. White solid; mp 177-179 °C; IR (KBr) 3455 (br), 3019, 1682, 1607, 1520, 1439, 1215, 1099, 1055 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, t, *J* = 7.2 Hz), 2.62 (3H, s), 4.32 (2H, q, *J* = 7.2 Hz), 6.98 (1H, d, *J* = 2.8 Hz), 7.40-7.48 (2H, m), 7.63 (1H, dd, *J* = 1.6, 8.4 Hz), 7.76-7.82 (4H, m), 8.83 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4,

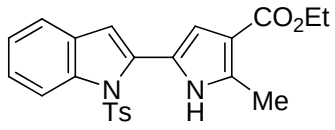
14.5, 59.6, 108.0, 113.5, 120.9, 122.9, 125.6, 126.5, 127.6, 127.7, 128.7, 129.1, 129.9, 132.1, 133.6, 136.6, 165.6; EIHRMS: Found: *m/z* 279.1253. Calcd for $C_{18}H_{17}NO_2$: M^+ 279.1254.

Ethyl 5-methyl-1'-tosyl-1*H*,1'*H*-2,2'-bipyrrole-4-carboxylate (4fb):



Reaction time: 24 h. Grey solid; mp 124-127 °C; IR (KBr) 3445 (br), 3019, 1686, 1597, 1508, 1458, 1367, 1265, 1215, 1101, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, t, *J* = 7.2 Hz), 2.35 (3H, s), 2.59 (3H, s), 4.27 (2H, q, *J* = 7.2 Hz), 6.26-6.27 (2H, m), 6.40 (1H, d, *J* = 2.8 Hz), 7.15 (2H, d, *J* = 8.0 Hz), 7.33 (2H, d, *J* = 8.0 Hz), 6.35-6.36 (1H, m), 9.00 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 14.5, 21.6, 59.4, 112.1 (overlapped), 112.7, 116.2, 119.5, 123.7, 126.5, 127.0, 129.7, 134.7, 136.0, 145.2, 165.4; ESIHRMS: Found: *m/z* 373.1211. Calcd for $C_{19}H_{21}N_2O_4S$: $(M+H)^+$ 373.1222.

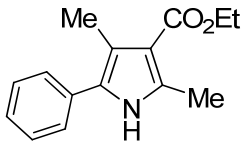
Ethyl 2-methyl-5-(1-tosyl-1*H*-indol-2-yl)-1*H*-pyrrole-3-carboxylate (4gb):



Reaction time: 6 h. Yellow solid; mp 94-96 ºC; IR (NaCl) 3368, 2980, 1681, 1558, 1446, 1371, 1174, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (3H, t, *J* = 7.2 Hz), 2.28 (3H, s), 2.63 (3H, s), 4.31 (2H, q, *J* = 7.2 Hz), 6.61 (1H, s), 6.72 (1H, d, *J* = 3.2 Hz), 7.05 (2H, d, *J* = 7.6 Hz), 7.24 (1H, dd, *J* = 7.2, 7.6 Hz), 7.30-7.34 (3H, m), 7.41 (1H, d, *J* = 7.6 Hz), 8.26 (1H, d, *J* = 8.4 Hz), 9.06 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 14.5, 21.5, 59.5, 112.3, 113.1, 113.2, 116.1, 120.58, 120.61, 124.3, 124.9, 126.7, 129.4, 130.2, 132.6, 134.0, 137.0,

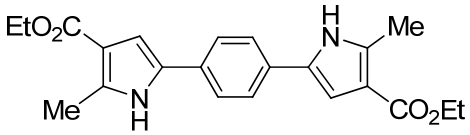
137.7, 144.9, 165.4. ESIHRMS: Found: m/z 423.1375. Calcd for $C_{23}H_{23}N_2O_4S$: $(M+H)^+$ 423. 1379.

Ethyl 2,4-dimethyl-5-phenyl-1*H*-pyrrole-3-carboxylate (4hb):



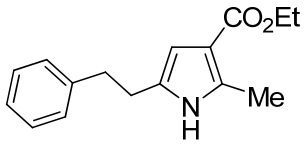
Reaction time: 2 h. White solid; mp 119-120 °C; IR (KBr) 3451 (br), 3019, 1682, 1607, 1526, 1429, 1256, 1215, 1099, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (3H, t, *J* = 7.2 Hz), 2.38 (3H, s), 2.54 (3H, s), 4.28 (2H, q, *J* = 7.2 Hz), 7.25-7.29 (1H, m), 7.37-7.42 (4H, m), 8.28 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 14.1, 14.5, 59.2, 112.3, 117.8, 126.5, 127.25, 127.3, 128.6, 132.8, 135.5, 166.3; EIHRMS: Found: *m/z* 243.1251. Calcd for $C_{15}H_{17}NO_2$: M^+ 243.1254.

Diethyl 5,5'-(1,4-phenylene)bis(2-methyl-1*H*-pyrrole-3-carboxylate) (4ib):



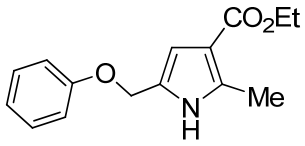
Reaction time: 24 h. Yellow solid; mp 276-279 °C; IR (KBr) 3449 (br), 3019, 1676, 1595, 1528, 1431, 1273, 1215, 1101, 1045 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.28 (6H, t, *J* = 7.2 Hz), 2.49 (6H, s), 4.18 (4H, q, *J* = 7.2 Hz), 6.78 (2H, d, *J* = 1.6 Hz), 7.64 (4H, s), 11.60 (2H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 15.0, 59.2, 106.8, 112.5, 124.2 (overlapped), 129.9, 137.0, 165.0; ESIHRMS: Found: *m/z* 381.1799. Calcd for $C_{22}H_{25}N_2O_4$: $(M+H)^+$ 381.1814.

Ethyl 2-methyl-5-phenethyl-1*H*-pyrrole-3-carboxylate (4jb):



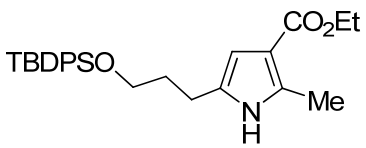
Reaction time: 3 h. White solid; mp 59-62 °C; IR (KBr) 3449 (br), 3019, 1674, 1599, 1530, 1447, 1325, 1215, 1093, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, t, *J* = 7.2 Hz), 2.43 (3H, s), 2.82 (2H, m), 2.90 (2H, m), 4.25 (2H, q, *J* = 7.2 Hz), 6.28 (1H, d, *J* = 2.8 Hz), 7.16-7.18 (2H, m), 7.22 (1H, m), 7.30 (1H, m), 7.79 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 14.5, 29.3, 35.9, 59.3, 106.9, 111.5, 126.2, 128.4, 128.5, 129.8, 134.1, 141.2, 165.7; EIHRMS: Found: *m/z* 257.1419. Calcd for $C_{16}H_{19}NO_2$: M^+ 257.1410.

Ethyl 2-methyl-5-(phenoxymethyl)-1*H*-pyrrole-3-carboxylate (4kb):



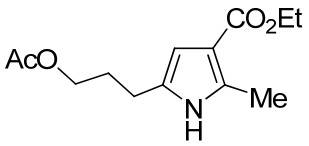
Reaction time: 2 h. White solid; mp 122-125 °C; IR (KBr) 3447 (br), 3019, 1676, 1597, 1520, 1477, 1330, 1215, 1098, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (3H, t, *J* = 7.2 Hz), 2.51 (3H, s), 4.24 (2H, q, *J* = 7.2 Hz), 4.92 (2H, s), 6.57 (1H, d, *J* = 2.8 Hz), 6.93-7.00 (3H, m), 7.29 (2H, dd, *J* = 7.2, 8.4 Hz), 8.51 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 14.5, 59.4, 62.7, 110.2, 111.9, 114.5, 121.2, 124.9, 129.5, 136.3, 158.1, 165.5; ESIHRMS: Found: *m/z* 260.1279. Calcd for $C_{15}H_{18}NO_3$: $(M+H)^+$ 260.1287.

Ethyl 5-(3-(*tert*-butyldiphenylsilyloxy)propyl)-2-methyl-1*H*-pyrrole-3-carboxylate (4lb):



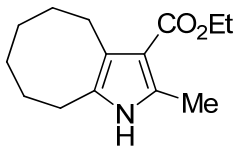
Reaction time: 2 h. Pale yellow liquid; IR (KBr) 3451 (br), 3019, 1684, 1597, 1528, 1472, 1427, 1215, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (9H, s), 1.33 (3H, t, *J* = 6.0, 7.2 Hz), 1.83 (2H, tt, *J* = 6.0, 7.2 Hz), 2.42 (3H, s), 2.68 (2H, t, *J* = 7.2 Hz), 3.73 (2H, t, *J* = 6.0 Hz), 4.25 (2H, q, *J* = 7.2 Hz), 6.22 (1H, d, *J* = 2.8 Hz), 7.37-7.47 (6H, m), 7.66-7.68 (4H, m), 8.20 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 14.6, 19.3, 23.6, 26.9, 31.8, 59.2, 63.1, 106.7, 111.4, 127.7, 129.7, 130.0, 133.6, 134.1, 135.5, 165.8; ESIHRMS: Found: *m/z* 450.2455. Calcd for $C_{27}H_{36}NO_3Si$: $(M+H)^+$ 450.2464.

Ethyl 5-(3-acetoxypropyl)-2-methyl-1*H*-pyrrole-3-carboxylate (4mb):



Reaction time: 1 h. Colorless liquid; IR (KBr) 3451 (br), 3019, 1724, 1682, 1599, 1528, 1474, 1445, 1367, 1215, 1096, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, t, *J* = 7.2 Hz), 1.91 (2H, tt, *J* = 6.4, 7.2 Hz), 2.06 (3H, s), 2.48 (3H, s), 2.57 (2H, t, *J* = 7.2 Hz), 4.12 (2H, q, *J* = 6.4 Hz), 4.24 (2H, t, *J* = 7.2 Hz), 6.23 (1H, d, *J* = 2.4 Hz), 8.42 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 14.5, 20.9, 23.5, 28.5, 59.2, 63.5, 106.9, 111.4, 129.2, 134.5, 165.8, 171.4; EIHRMS: Found: *m/z* 253.1305. Calcd for $C_{13}H_{19}NO_4$: M^+ 253.1309.

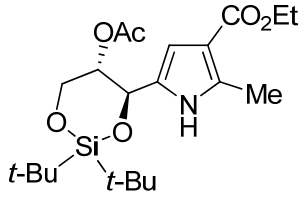
Ethyl 2-methyl-4,5,6,7,8,9-hexahydro-1*H*-cycloocta[*b*]pyrrole-3-carboxylate (4nb):



Reaction time: 1 h. Pale yellow solid; mp 146-147 °C; IR (KBr) 3453 (br), 3019, 2927, 2850, 1682, 1600, 1526, 1443, 1317, 1286, 1215, 196, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ

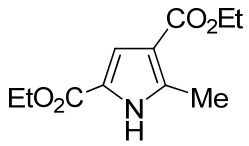
1.26-1.33 (2H, m), 1.33 (3H, t, *J* = 7.2 Hz), 1.42-1.47 (2H, m), 1.53-1.59 (2H, m), 1.61-1.67 (2H, m), 2.46 (3H, s), 2.58 (2H, t, *J* = 6.0 Hz), 2.81 (2H, t, *J* = 6.0 Hz), 4.25 (2H, q, *J* = 7.2 Hz), 7.85 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.5, 22.9, 25.6, 25.8, 26.0, 29.7, 30.8, 58.9, 110.0, 120.3, 127.6, 133.1, 166.4; EIHRMS: Found: *m/z* 235.1566. Calcd for $C_{14}H_{21}NO_2$: M^+ 235.1567.

Ethyl 5-((4*R*,5*S*)-5-acetoxy-2,2-di-*tert*-butyl-1,3,2-dioxasilinan-4-yl)-2-methyl-1*H*-pyrrole-3-carboxylate (4xb):



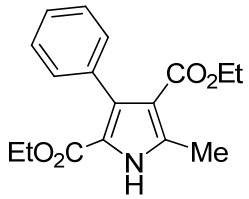
Reaction time: 5 h. Pale yellow viscous oil; IR (KBr) 3451 (br), 3019, 1732, 1684, 1601, 1522, 1474, 1429, 1215, 1096, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.09 (9H, s), 1.33 (3H, tt, *J* = 6.0, 7.2 Hz), 2.00 (3H, s), 2.52 (3H, s), 3.97 (1H, dd, *J* = 8.4, 10.8 Hz), 4.21 (dd, *J* = 4.0, 10.8 Hz), 4.25 (2H, q, *J* = 7.2 Hz), 4.94 (1H, ddd, *J* = 4.0, 8.0, 8.4 Hz), 5.01 (d, *J* = 8.0 Hz), 6.39 (1H, d, *J* = 2.4 Hz), 8.27 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 14.5, 20.6, 20.8, 22.4, 27.1, 27.4, 59.3, 64.9, 70.6, 72.3, 107.8, 111.9, 128.2, 135.1, 165.5, 169.6; ESIHRMS: Found: *m/z* 426.2303. Calcd for $C_{21}H_{36}NO_6Si$: $(M+H)^+$ 426.2312.

Diethyl 5-methyl-1*H*-pyrrole-2,4-dicarboxylate (4sb):



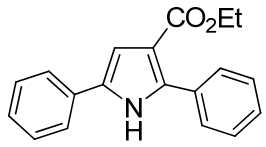
Reaction time: 2 h. White solid; mp 127-129 °C; IR (KBr) 3435 (br), 3019, 1676 (br), 1576, 1506, 1474, 1279, 1215, 1088, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, t, *J* = 7.2 Hz), 1.36 (3H, t, *J* = 7.2 Hz), 2.57 (3H, s), 4.28 (2H, q, *J* = 7.2 Hz), 4.32 (2H, q, *J* = 7.2 Hz), 7.25(1H, d, *J* = 2.8 Hz), 9.27 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 14.26, 14.34, 59.6, 60.6, 113.9, 117.5, 120.4, 140.1, 161.6, 164.7; EIHRMS: Found: *m/z* 225.0995. Calcd for $C_{11}H_{15}NO_4$: M^+ 225.0996.

Diethyl 5-methyl-3-phenyl-1*H*-pyrrole-2,4-dicarboxylate (4ub):[12]



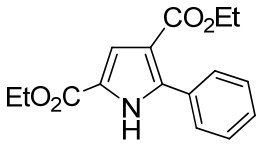
Reaction time: 24 h. ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J* = 7.2 Hz), 1.03 (3H, t, *J* = 7.2 Hz), 2.59 (3H, s), 4.02 (2H, q, *J* = 7.2 Hz), 4.10 (2H, q, *J* = 7.2 Hz), 7.25-7.33 (5H, m), 9.72 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (overlap), 13.8, 59.4, 60.3, 113.7, 118.1, 126.6, 126.8, 129.8, 133.5, 135.2, 139.0, 161.6, 164.8.

Ethyl 2,5-diphenyl-1*H*-pyrrole-3-carboxylate (4ac):[13]



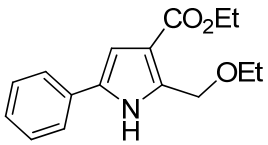
Reaction time: 4 h. ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, t, *J* = 7.2 Hz), 4.22 (2H, q, *J* = 7.2 Hz), 7.10 (1H, d, *J* = 2.8 Hz), 7.24-7.28 (1H, m), 7.34-7.43 (5H, m), 7.51 (2H, d, *J* = 8.0 Hz), 7.63 (2H, d, *J* = 8.0 Hz), 8.69 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 59.8, 109.1, 113.7, 124.0, 127.0, 128.1, 128.4, 129.0 (overlapped), 131.4, 131.7, 131.9, 137.7, 164.8.

Diethyl 5-phenyl-1*H*-pyrrole-2,4-dicarboxylate (4sc):



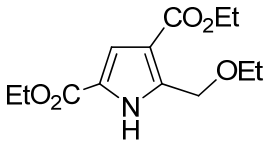
Reaction time: 2 h. White solid; mp 143-144 °C; IR (KBr) 3428 (br), 3019, 1683 (br), 1568, 1516, 1474, 1248, 1215, 1145, 1094, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, t, *J* = 7.2 Hz), 1.31 (3H, t, *J* = 7.2 Hz), 4.21 (2H, q, *J* = 7.2 Hz), 4.22 (2H, q, *J* = 7.2 Hz), 7.39 (1H, d, *J* = 2.8 Hz), 7.41-7.44 (3H, m), 7.61-7.64 (2H, m), 9.85 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 14.3, 60.0, 60.9, 114.1, 118.3, 122.2, 128.0, 129.0, 129.2, 130.8, 140.7, 161.1, 164.0; EIHRMS: Found: *m/z* 287.1151. Calcd for $C_{16}H_{17}NO_4$: M^+ 287.1152.

Ethyl 2-(ethoxymethyl)-5-phenyl-1*H*-pyrrole-3-carboxylate (4ad):



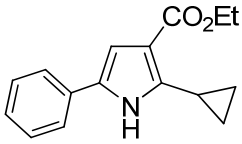
Reaction time: 3 h. Pale yellow liquid; IR (KBr) 3449 (br), 3019, 1690, 1607, 1526, 1476, 1215, 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (3H, t, *J* = 7.2 Hz), 1.36 (3H, t, *J* = 7.2 Hz), 3.66 (2H, t, *J* = 7.2 Hz), 4.29 (2H, q, *J* = 7.2 Hz), 4.91 (2H, s), 6.85 (1H, d, *J* = 3.2 Hz), 7.24 (1H, t, *J* = 8.0 Hz), 7.37 (2H, dd, *J* = 7.6, 8.0 Hz), 7.48 (2H, d, *J* = 7.6 Hz), 9.15 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 15.2, 59.7, 65.1, 66.5, 107.1, 112.6, 123.9, 126.7, 128.9, 130.9, 131.7, 136.7, 165.0; EIHRMS: Found: *m/z* 273.1354. Calcd for $C_{16}H_{19}NO_3$: M^+ 273.1359.

Diethyl 5-(ethoxymethyl)-1*H*-pyrrole-2,4-dicarboxylate (4sd):



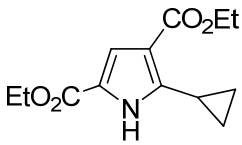
Reaction time: 5 h. Pale yellow liquid; IR (KBr) 3433 (br), 3019, 1693 (br), 1574, 1508, 1485, 1381, 1250, 1215, 1082, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (3H, t, *J* = 7.2 Hz), 1.34 (3H, t, *J* = 7.2 Hz), 1.35 (3H, t, *J* = 7.2 Hz), 3.65 (2H, q, *J* = 7.2 Hz), 4.26 (2H, q, *J* = 7.2 Hz), 4.32 (2H, q, *J* = 7.2 Hz), 4.84 (2H, s), 7.24 (1H, d, *J* = 2.8 Hz), 9.54 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.35, 14.38, 15.1, 59.9, 60.6, 65.3, 66.9, 112.5, 116.7, 121.5, 140.1, 160.7, 164.2; EIHRMS: Found: *m/z* 269.1269. Calcd for $C_{13}H_{19}NO_5$: M^+ 269.1258.

Ethyl 2-cyclopropyl-5-phenyl-1*H*-pyrrole-3-carboxylate (4ae):



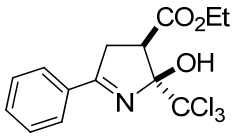
Reaction time: 8 h. Pale yellow liquid; IR (KBr) 3458 (br), 3019, 1684, 1609, 1531, 1477, 1263, 1215, 1096, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.76-0.80 (2H, m), 1.05-1.10 (2H, m), 1.37 (3H, t, *J* = 7.2 Hz), 2.61-2.68 (1H, m), 4.31 (2H, q, *J* = 7.2 Hz), 6.83 (1H, d, *J* = 2.8 Hz), 7.22 (1H, t, *J* = 7.6 Hz), 7.35 (2H, dd, *J* = 7.6, 8.0 Hz), 7.43 (2H, d, *J* = 8.0 Hz), 8.14 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8, 8.6, 14.5, 59.5, 107.8, 114.2, 123.8, 126.5, 128.8, 129.4, 131.7, 141.2, 165.5; EIHRMS: Found: *m/z* 255.1254. Calcd for $C_{16}H_{17}NO_2$: M^+ 255.1254.

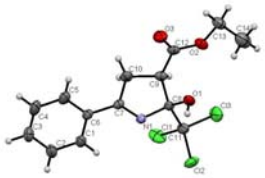
Diethyl 5-cyclopropyl-1*H*-pyrrole-2,4-dicarboxylate (4se):



Reaction time: 2 h. White solid; mp 125-126 °C; IR (KBr) 3441 (br), 3019, 1684 (br), 1576, 1508, 1472, 1379, 1252, 1215, 1094, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.79-0.83 (2H, m), 1.08-1.13 (2H, m), 1.347 (3H, t, *J* = 7.2 Hz), 1.354 (3H, t, *J* = 7.2 Hz), 2.69-2.76 (1H, m), 4.299 (2H, q, *J* = 7.2 Hz), 4.303 (2H, q, *J* = 7.2 Hz), 7.23 (1H, d, *J* = 2.8 Hz), 8.80 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.5, 8.6, 14.37, 14.40, 59.7, 60.7, 114.7, 117.7, 120.1, 145.2, 161.2, 164.7; EIHRMS: Found: *m/z* 251.1145. Calcd for $C_{13}H_{17}NO_4$: M^+ 251.1152.

(2*S,3*R**)-Ethyl 2-hydroxy-5-phenyl-2-(trichloromethyl)-3,4-dihydro-2*H*-pyrrole-3-carboxylate (4af)**:[14]



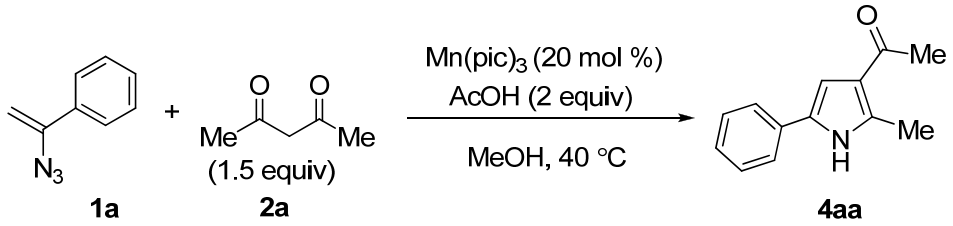


Reaction time: 24 h. White solid; mp 142-145 °C; IR (KBr) 3563 (br), 3019, 1732, 1626, 1578, 1520, 1418, 1373, 1337, 1215, 1060, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, t, *J* = 7.2 Hz), 3.40 (1H, dd, *J* = 9.6, 18.0 Hz), 3.74 (1H, dd, *J* = 4.0, 18.0 Hz), 3.89 (1H, dd, *J* = 4.0, 9.6 Hz), 4.18-4.34 (2H, m), 5.34 (1H, s), 7.45 (2H, dd, *J* = 7.2, 8.0 Hz), 7.56 (1H, t, *J* = 7.2 Hz), 7.95 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 41.0, 46.2, 61.7, 105.1, 111.0, 128.6, 128.7, 132.1, 132.4, 171.4, 178.0; ESIHRMS: Found: *m/z* 350.0108. Calcd for $C_{14}H_{15}Cl_3NO_3$: $(M+H)^+$ 350.0118.

6.4.2 $Mn(pic)_3$-catalyzed pyrrole formation from vinyl azides and 1,3-diketons

(Section 3.2.4)

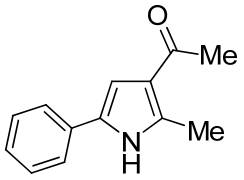
Typical procedure:



1a **2a** **4aa**

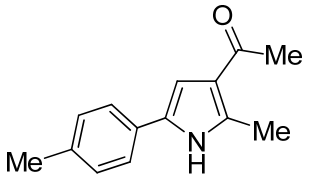
To a solution of α-azido styrene (**1a**) (52.6 mg, 0.362 mmol) and acetylacetone (**2a**) (56 μL, 0.544 mmol) in MeOH (3.6 mL) was added AcOH (43 μL, 0.743 mmol) and $Mn(pic)_3$ (31.3 mg, 0.0743 mmol) and the reaction mixture was stirred at 40 °C for 20 h. The reaction mixture was quenched with pH 9 ammonium buffer and then extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by flash column chromatography (silica gel; hexane : ethyl acetate = 85 : 15) afforded pyrrole **4aa** (55.2 mg, 0.277 mmol) in 76% yield.

1-(2-Methyl-5-phenyl-1*H*-pyrrol-3-yl)ethanone (4aa):[12]



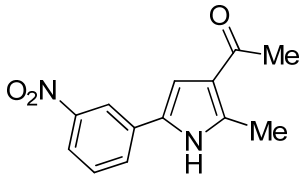
Reaction time: 20 h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (3H, s), 2.61 (3H, s), 6.77 (1H, d, *J* = 2.4 Hz), 7.23 (1H, tt, *J* = 7.3, 1.5 Hz), 7.37 (2H, dd, *J* = 7.3, 7.2 Hz), 7.48 (2H, dd, *J* = 7.2, 1.5 Hz), 8.90 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 28.5, 107.4, 122.1, 123.7, 126.6, 128.9, 129.8, 131.6, 135.9, 195.1.

1-(2-Methyl-5-*p*-tolyl-1*H*-pyrrol-3-yl)ethanone (4ba):



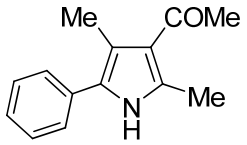
Reaction time: 46 h. White solid; mp 202-203 °C; IR (KBr) 3449 (br), 3019, 1647, 1616, 1587, 1526, 1441, 1269, 1215, 1150, 1034 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.29 (3H, s), 2.33 (3H, s), 2.48 (3H, s), 6.87 (1H, d, J = 2.8 Hz), 7.18 (1H, d, J = 8.0 Hz), 7.55 (1H, d, J = 8.0 Hz), 11.59 (1H, s br); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.9, 21.2, 28.9, 107.2, 110.0, 121.9, 123.9, 129.7, 129.8, 135.6, 135.9, 194.0; EIHRMS: Found: *m/z* 213.1146. Calcd for $C_{14}H_{15}NO$: M^+ 213.1148.

1-(2-Methyl-5-(3-nitrophenyl)-1*H*-pyrrol-3-yl)ethanone (4ra):



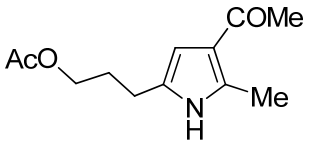
Reaction time: 36 h. Orange solid; mp 222-225 °C; IR (KBr) 3447 (br), 3019, 1647, 1616, 1587, 1528, 1474, 1340, 1276, 1215, 1105, 1034 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.37 (3H, s), 2.51 (3H, s), 7.23 (1H, s), 7.65 (1H, dd, J = 7.9, 8.0 Hz), 8.01 (1H, d, J = 8.0 Hz), 8.10 (1H, d, J = 7.9 Hz), 8.52 (1H, s), 12.00 (1H, s br); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.9, 28.8, 110.2, 117.7, 120.7, 122.4, 127.4, 130.0, 130.7, 134.1, 137.4, 149.0, 194.1; EIHRMS: Found: *m/z* 244.0844. Calcd for $C_{13}H_{12}N_2O_3$: M^+ 244.0842.

1-(2,4-Dimethyl-5-phenyl-1*H*-pyrrol-3-yl)ethanone (4ha):



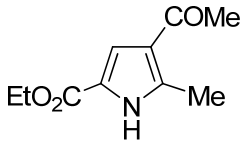
Reaction time: 24 h. White solid; mp 163-164 °C; IR (KBr) 3447 (br), 3019, 1639, 1519, 1474, 1417, 1335, 1215, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.40 (3H, s), 2.48 (3H, s), 2.58 (3H, s), 7.29-7.33 (1H, m), 7.39-7.45 (4H, m), 8.51 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 15.1, 31.0, 116.8, 122.6, 126.8, 127.6, 127.8, 128.7, 132.5, 135.0, 195.8; EIHRMS: Found: *m/z* 231.1149. Calcd for $C_{14}H_{15}NO$: M^+ 213.1148.

3-(4-acetyl-5-methyl-1*H*-pyrrol-2-yl)propyl acetate (4ma):



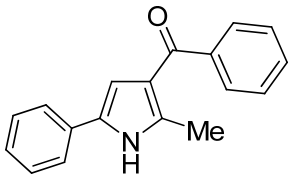
Reaction time: 48 h. White solid; mp 116-117 °C; IR (KBr) 3447 (br), 3019, 1721, 1634, 1587, 1522, 1447, 1368, 1248, 1215, 1141, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.95 (2H, tt, *J* = 6.4, 7.2 Hz), 2.07 (3H, s), 2.38 (3H, s), 2.51 (3H, s), 2.61 (2H, t, *J* = 7.2 Hz), 4.13 (2H, t, *J* = 6.4 Hz), 6.21 (1H, d, *J* = 1.6 Hz), 9.18 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 20.9, 23.5, 28.4, 28.5, 63.5, 107.3, 120.6, 129.2, 134.4, 171.4, 195.2; EIHRMS: Found: *m/z* 223.1202. Calcd for $C_{12}H_{17}NO_3$: M^+ 223.1203.

Ethyl 4-acetyl-5-methyl-1*H*-pyrrole-2-carboxylate (4sa):



Reaction time: 17 h. White solid; mp 138-140 °C; IR (KBr) 3431 (br), 3019, 1686, 1647, 1560, 1503, 1477, 1281, 1215, 1119, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, t, *J* = 7.2 Hz), 2.43 (3H, s), 2.59 (3H, s), 4.34 (2H, q, *J* = 7.2 Hz), 7.21 (1H, d, *J* = 2.4 Hz), 9.44 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.4, 28.2, 60.8, 117.3, 120.3, 122.4, 139.5, 161.2, 194.8; EIHRMS: Found: *m/z* 195.0894. Calcd for $C_{10}H_{13}NO_3$: M^+ 195.0890**.**

(2-Methyl-5-phenyl-1*H*-pyrrol-3-yl)(phenyl)methanone (4ag):



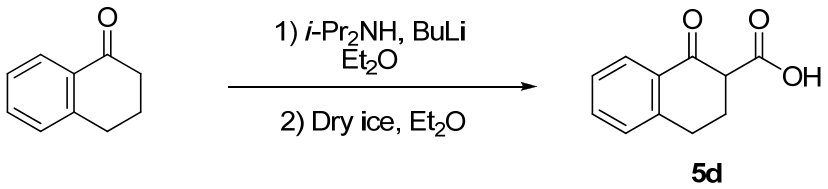
Reaction time: 24 h. Pale yellow solid; mp 205-206 °C; IR (KBr) 3431 (br), 3019, 1674, 1651, 1557, 1519, 1487, 1423, 1259, 1215, 1167, 1036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (3H, s), 6.67 (1H, d, *J* = 2.8 Hz), 7.23 (1H, t, *J* = 7.6 Hz), 7.35 (2H, dd, *J* = 7.6, 7.6 Hz), 7.45-7.48 (4H, m), 7.53 (1H, t, *J* = 7.2 Hz), 7.84 (2H, d, *J* = 7.2 Hz), 8.79 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 109.2, 121.2, 123.8, 126.7, 128.1, 128.97, 129.02, 129.7, 131.3, 131.7, 137.5, 140.4, 192.5; EIHRMS: Found: *m/z* 261.1149. Calcd for $C_{18}H_{15}NO$: M^+ 261.1148**.**

6.4.3 $Mn(acac)_3$-catalyzed pyrrole formation from vinyl azides and *β*-keto acids

(Section 3.2.5)

6.4.3 1 Synthesis of *β*-keto acids 5

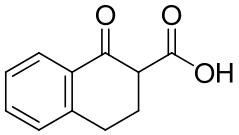
Typical procedure:



5d

To a solutiono of *i*-Pr_2NH (2.4 mL, 17.1 mmol) in Et_2O (50 mL) was added *n*-BuLi (10.7 mL, 17.1 mmol, 1.6 M in hexane) at 0 °C. After stirring for 30 min, 3,4-dihydronaphthalen-1(2*H*)-one (2.1 mL, 15.5 mmol) was added at -78 °C. The solution was stirred at the same temperature for 1 h and subsequently excess solid CO_2 was added into the reaction mixture. After gradual warming to 0 °C, the mixture was quenched with water and extracted with Et_2O. The aqueous layer was acidified with 1 N HCl at 0 °C and then extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$. Evaporation of the solvent gave **5d** (2.90 g, 15.2 mmol, 98%). The crude product was used immediately for the next step without further purification.

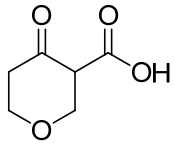
1-Oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (5d):



The product was obtained as an equilibrium mixture of enol- and keto-form (enol : keto = 71 : 29, at 25 °C); ^1H and ^{13}C NMR are given below for the enol-form.

White solid; decomposed at 90 °C; IR (NaCl) 3423, 3053, 2985, 2862, 1680, 1645, 1607, 1454, 1435, 1265 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.61 (2H, t, *J* = 7.6 Hz), 2.84 (2H, t, *J* = 7.6 Hz), 7.18 (1H, d, *J* = 7.6 Hz), 7.24-7.37 (2H, m), 7.82 (1H, d, *J* = 7.6 Hz), 11.8 (1H, s br), 12.1 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 27.6, 96.1, 124.7, 126.6, 127.5, 131.1, 140.0, 167.4, 167,5, 177.2.

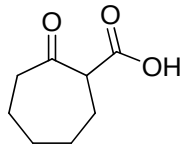
4-Oxotetrahydro-2*H*-pyran-3-carboxylic acid (5c):



β-Keto acid **5c** was prepared from dihydro-2*H*-pyran-4(3*H*)-one following the same procedure as **5d**. The product was obtained as an equilibrium mixture of enol- and keto-form (enol : keto = 85 : 15, at 25 °C); ^{1}H and ^{13}C NMR are given below for the enol-form.

Yield: 20%. White solid; decomposed at 85 °C; IR (NaCl) 3439, 2954, 2862, 1713, 1643, 1605, 1418, 1190 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (2H, t, *J* = 5.7 Hz), 3.88 (*J* = 5.7 Hz), 4.32 (2H, s) 11.5 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0, 62.9, 63.9, 96.7, 171.7, 174.1.

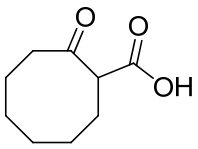
2-Oxocycloheptanecarboxylic acid (5e):



β-Keto acid **5e** was prepared from cycloheptanone following the same procedure as **5d**. The product was obtained as an equilibrium mixture of enol- and keto-form (enol : keto = 27 : 73, at 25 °C); ^{1}H and ^{13}C NMR are given below for the keto-form.

Yield: 44%; colourless liquid; IR (NaCl) 3524, 2928, 2857, 1732, 1697, 1626, 1454, 1198 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57-1.75 (5H, m), 1.83-1.97 (3H, m), 2.50-2.53 (1H, m), 2.62-2.65 (1H, m), 3.59 (1H, dd, *J* = 5.2, 13.6 Hz), 10.68 (1H, s br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2, 27.6, 29.4, 30.3, 43.8, 58.2, 175.0, 209.8.

2-Oxocyclooctanecarboxylic acid (5f):



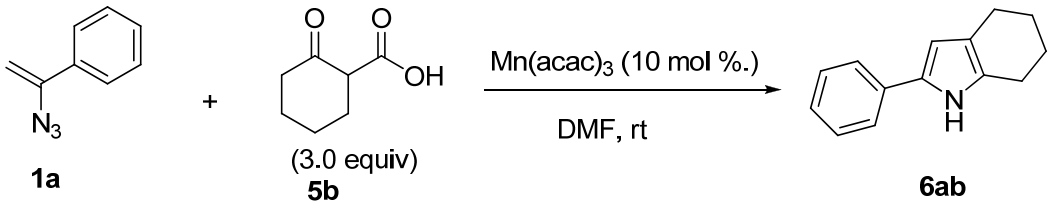
β-Keto acid **5f** was prepared from cyclooctanone following the same procedure as **5d**. The product was obtained as an equilibrium mixture of enol- and keto-form (enol : keto = 68 : 32, at 25 °C); ^{1}H and ^{13}C NMR are given below for the enol-form.

Yield: 86%. White solid; decompose at 68 °C; IR (NaCl) 3408, 3391, 2926, 1686, 1636, 1578, 1468, 1231, 1126 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47-1.59 (6H, m), 1.72-1.76 (2H, m), 2.36-2.46 (4H, m), 8.87 (1H, s br), 12.87 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2, 27.0, 29.5, 29.6, 29.7, 32.5, 98.7, 124.8, 179.1.

β-Keto acids **5a**,[15] **5b**,[16] **5g**,[16] and **5h**[16] are known compounds and were prepared by the same method as **5d** from the corresponding ketones.

6.4.3.2. Mn(acac)$_3$-catalyzed pyrrole formation from vinyl azides and β-keto acids

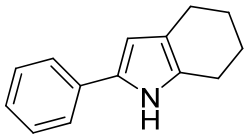
Typical procedure:



To a solution of α-azido styrene (**1a**) (52.8 mg, 0.364 mmol) and 2-oxocyclohexanecarboxylic acid (**5b**) (155.2 mg, 1.09 mmol) in DMF (3.6 mL) was added $Mn(acac)_3$ (12.8 mg, 0.0364 mmol) and stirred over 5 h. The reaction mixture quenched with

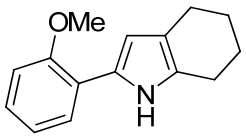
pH 9 ammonium buffer, and then extracted twice with diethyl ether. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (florisil; hexane : ethyl acetate = 97 : 3) afforded **6ab** (59.5 mg, 0.302 mmol) in 83% yield.

2-Phenyl-4,5,6,7-tetrahydro-1*H*-indole (6ab):[17]



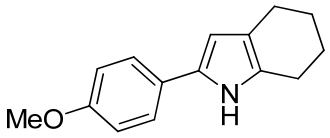
Reaction time: 5 h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76-1.89 (4H, m), 2.55 (2H, t, *J* = 6.0 Hz), 2.65 (2H, t, *J* = 6.0 Hz), 6.26 (1H, d, *J* = 2.4 Hz), 7.16 (1H, t, *J* = 7.2 Hz), 7.33 (2H, dd, *J* = 7.2, 8.4 Hz), 7.43 (2H, d, *J* = 8.4 Hz), 7.95 (1H, s br); ^{13}C NMR (100 MHz, DCl_3) δ 22.8, 22.9, 23.3, 23.7, 105.1, 118.9, 123.3, 125.5, 128.5, 128.7, 130.2, 133.2.

2-(2-Methoxyphenyl)-4,5,6,7-tetrahydro-1*H*-indole (6cb):



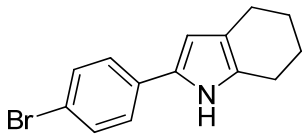
Reaction time: 15 h. Colorless oil; IR (NaCl) 3456, 2999, 2928, 1591, 1514, 1460, 1236, 1120, 1026 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82-1.91 (4H, m), 2.55 (2H, t, *J* = 6.0 Hz), 2.64 (2H, t, *J* = 6.0 Hz), 3.97 (3H, s), 6.35 (1H, d, *J* = 1.5 Hz), 6.96-7.03 (2H, m), 7.15 (1H, dd, *J* = 7.5, 7.5 Hz), 7.64 (1H, d, *J* = 7.5 Hz), 9.25 (1H, s br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 23.0, 23.5, 23.8, 55.6, 105.4, 111.5, 117.7, 121.3, 121.6, 125.9, 126.2, 127.4, 127.7, 154.5; ESIHRMS: Found: m/z 228.1388. Calcd for $C_{15}H_{18}NO$: $(M+H)^+$ 228.1388.

2-(4-Methoxyphenyl)-4,5,6,7-tetrahydro-1*H*-indole (6db):



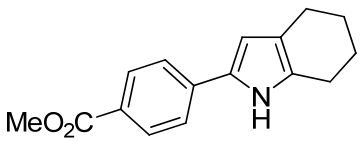
Reaction time: 6 h. White solid; decomposed at 168 °C; IR (NaCl) 3468, 3018, 2922, 1530, 1442, 1246, 1179, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.74-1.87 (4H, m), 2.53 (2H, t, *J* = 5.7 Hz), 2.63 (2H, t, *J* = 5.7 Hz), 3.81 (3H, s), 6.15 (1H, d, *J* = 2.4 Hz), 6.88 (2H, d, *J* = 9.0 Hz), 7.35 (2H, d, *J* = 9.0 Hz), 7.82 (1H, s br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 22.9, 23.4, 23.8, 55.3, 104.0, 114.2, 118.7, 124.8, 126.4, 127.7, 130.3, 157.8; ESIHRMS: Found: m/z 228.1387. Calcd for $C_{14}H_{14}NBr$: $(M+H)^+$ 228.1388.

2-(4-Bromophenyl)-4,5,6,7-tetrahydro-1*H*-indole (6pb):[18]



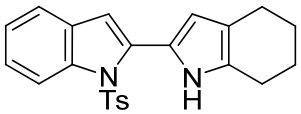
Reaction time: 10 h. ^1H NMR (300 MHz, $CDCl_3$) δ 1.74-1.85 (4H, m), 2.52 (2H, t, *J* = 6.0 Hz), 2.61 (2H, t, *J* = 6.0 Hz), 6.26 (1H, d, *J* = 2.7 Hz), 7.25 (2H, d, *J* = 8.4 Hz), 7.42 (2H, d, *J* = 8.4 Hz), 7.89 (1H, s br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.82, 22.85, 23.3, 23.7, 105.7, 118.8, 119.3, 124.8, 129.1, 131.8, 132.1.

Methyl 4-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)benzoate (6qb):



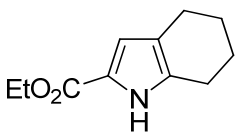
Reaction time: 16 h. White solid; mp 179–180 °C; IR (NaCl) 3442, 3377, 2926, 1681, 1608, 1429, 1290, 1184, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.74-1.89 (4H, m), 2.53 (2H, t, *J* = 6.0 Hz), 2.65 (2H, t, *J* = 6.0 Hz), 3.91 (3H, s), 6.43 (1H, d, *J* = 2.7 Hz), 7.46 (2H, d, *J* = 8.4 Hz), 7.98 (2H, d, *J* = 8.4 Hz), 8.20 (1H, s br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 22.9, 23.2, 23.6, 51.9, 107.3, 119.7, 122.4, 126.4, 129.0, 130.27, 130.30, 137.2, 167.0; ESIHRMS: Found: m/z 256.1388. Calcd for $C_{16}H_{18}NO_2$: $(M+H)^+$ 256.1388.

1'-Tosyl-4,5,6,7-tetrahydro-1*H*,1'*H*-2,2'-biindole (6gb):



Reaction time: 19 h. Yellow solid; decomposed at 160 °C; IR (NaCl) 3412, 3030, 2924, 2851, 1597, 1557, 1445, 1368, 1217, 1173, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.79-1.91 (4H, m), 2.29 (3H, s), 2.54 (2H, t, *J* = 6.0 Hz), 2.69 (2H, t, *J* = 6.0 Hz), 6.11 (1H, d, *J* = 2.4 Hz), 6.53 (1H, s), 7.04 (2H, d, *J* = 8.0 Hz), 7.22 (1H, dd, *J* = 7.6, 7.6 Hz), 7.28 (1H, dd, *J* = 7.6, 8.2 Hz), 7.33 (2H, d, *J* = 8.0 Hz), 7.38 (1H, d, *J* = 7.6 Hz), 8.25 (1H, d, *J* = 8.2 Hz), 8.56 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 22.8, 22.9, 23.3, 23.8, 110.8, 111.3, 116.2, 117.7, 120.2 (overlapped), 124.1, 124.2, 126.9, 129.2, 129.9, 130.6, 134.4, 134.7, 137.7, 144.5; ESIHRMS: Found: m/z 391.1279. Calcd for $C_{23}H_{23}N_2O_2S$: $(M+H)^+$ 391.1280.

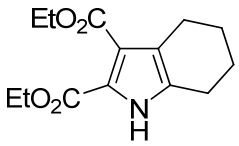
Ethyl 4,5,6,7-tetrahydro-1*H*-indole-2-carboxylate (6sb):[18]



Reaction time: 2.5 h. ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (3H, t, *J* = 7.1 Hz), 1.73-1.86 (4H, m), 2.50 (2H, t, *J* = 5.9 Hz), 2.60 (2H, t, *J* = 5.9 Hz), 4.28 (2H, q, 7.1 Hz), 6.66 (1H, d, 2.3

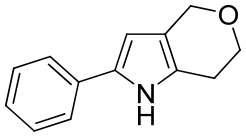
MHz), 8.70 (1H, s br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 22.9, 23.1, 23.2, 23.7, 60.1, 114.4, 119.9, 120.8, 133.4, 161.7.

Ethyl 2-phenyl-4,5,6,7-tetrahydro-1*H*-indole-3-carboxylate (6yb):



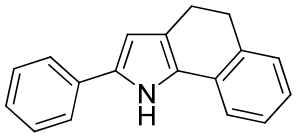
Reaction time: 10 h. White solid; mp 69-70 °C; IR (NaCl) 3298, 3015, 2982, 2936, 2855, 1715, 1674, 1504, 1429, 1321, 1273, 1233, 1152, 1065 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (3H, t, *J* = 6.9 Hz), 1.34 (3H, t, *J* = 7.2 Hz), 1.71-1.79 (4H, m), 2.57 (2H, t, *J* = 6.0 Hz), 2.60 (2H, t, *J* = 6.0 Hz), 4.30 (2H, q, *J* = 7.0 Hz), 4.31 (2H, q, *J* = 7.0 Hz), 9.42 (1H, s br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3 (overlapped), 22.1, 22.5, 22.6, 23.0, 60.4, 60.6, 119.1, 119.8, 121.1, 132.1, 160.7, 165.3; ESIHRMS: Found: m/z 266.1392. Calcd for $C_{14}H_{20}NO_4$: $(M+H)^+$ 266.1392.

2-Phenyl-1,4,6,7-tetrahydropyrano[4,3-*b*]pyrrole (6ac):



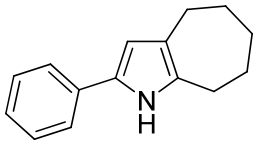
Reaction time: 5 h. White solid; decomposed at 151 °C; IR (NaCl) 3269, 3015, 2924, 1452, 1312, 1215, 1058 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.77 (2H, t, *J* = 5.4 Hz), 4.00 (2H, t, *J* = 5.4 Hz), 4.70 (2H, s), 6.24 (1H, d, *J* = 2.4 Hz), 7.19 (1H, t, *J* = 7.5 Hz), 7.35 (2H, dd, *J* = 7.5, 7.8 Hz), 7.43 (2H, d, *J* = 7.8 Hz), 8.15 (1H, s br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 65.0, 65.5, 102.0, 117.7, 123.7, 125.2, 126.2, 129.1, 131.3, 133.0; ESIHRMS: Found: m/z 200.1073. Calcd for $C_{13}H_{14}NO$: $(M+H)^+$ 200.1075.

2-Phenyl-4,5-dihydro-1*H*-benzo[*g*]indole (6ad):[19]



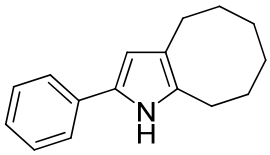
Reaction time: 4 h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (2H, m), 2.95 (2H, m), 6.42 (1H, d, *J* = 1.8 Hz), 7.06 (1H, m), 7.19–7.23 (4H, m), 7.37 (2H, dd, *J* = 7.6, 7.8 Hz), 7.51 (2H, d, *J* = 7.6 Hz), 8.42 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 29.9, 106.0, 118.2, 122.2, 123.6, 125.2, 126.2, 126.5, 128.4, 128.9 (overlapped), 129.0, 132.5, 132.6, 135.0.

2-Phenyl-1,4,5,6,7,8-hexahydrocyclohepta[*b*]pyrrole (6ae):[18]



Reaction time: 10 h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68-1.76 (4H, m), 1.81-1.83 (2H, m), 2.60 (2H, t, *J* = 5.6 Hz), 2.73 (2H, t, *J* = 5.6 Hz), 6.28 (1H, d, *J* = 2.4 Hz), 7.13 (1H, t, *J* = 7.6 Hz), 7.31 (2H, dd, *J* = 7.6, 8.0 Hz), 7.39 (2H, d, *J* = 8.0 Hz), 7.93 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9, 28.4, 29.2, 29.4, 31.9, 108.0, 123.1, 123.5, 125.3, 127.7, 128.7, 132.0, 132.9.

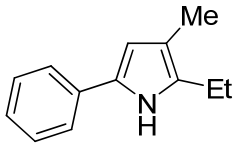
2-Phenyl-4,5,6,7,8,9-hexahydro-1*H*-cycloocta[*b*]pyrrole (6af):[18]



Reaction time: 15 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45-1.50 (4H, m), 1.63-1.72 (4H, m), 2.61 (2H, t, *J* = 6.3 Hz), 2.74 (2H, t, *J* = 6.3 Hz), 6.27 (1H, d, *J* = 2.7 Hz), 7.12 (1H, t, *J* = 7.2

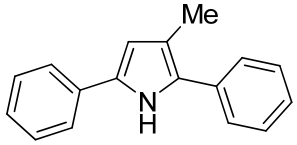
Hz), 7.32 (2H, dd, *J* =7.2, 8.1 Hz), 7.41 (2H, d, *J* = 8.1 Hz), 7.93 (1H, s br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.6, 25.7, 25.9, 29.7, 30.6, 107.1, 121.3, 122.9, 125.2, 128.6, 128.7, 130.2, 133.0.

2-Ethyl-3-methyl-5-phenyl-1*H*-pyrrole (6ag):[18]



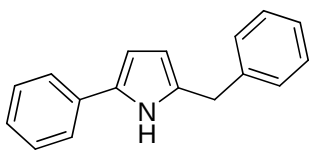
Reaction time: 3 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H, t, *J* = 7.5 Hz), 2.08 (3H, s), 2.65 (2H, q, *J* = 7.5 Hz), 6.29 (1H, d, *J* = 2.7 Hz), 7.15 (1H, t, *J* = 7.5 Hz), 7.34 (2H, dd, *J* = 7.5 Hz, 7.8 Hz), 7.42 (2H, d, *J* = 7.8 Hz), 7.96 (1H, s br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.8, 14.2, 19.1, 107.9, 115.4, 123.2, 125.4, 128.7, 129.1, 131.3, 133.0.

3-Methyl-2,5-diphenyl-1*H*-pyrrole (6ah):[18]



Reaction time: 1 h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (3H, s), 6.45 (1H, d, *J* = 2.8 Hz), 7.20 (1H, t, *J* = 7.2 Hz), 7.27 (1H, t, *J* = 7.2 Hz), 7.36 (2H, dd, *J* = 7.6 Hz, 8.0 Hz), 7.42 (2H, dd, *J* = 7.6 Hz, 8.0 Hz), 7.46–7.50 (4H, m), 8.27 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 110.0, 118.1, 123.6, 126.1, 126.2, 126.3, 128.8, 128.9, 129.4, 131.4, 132.5, 133.4.

2-Benzyl-5-phenyl-1*H*-pyrrole (6aa):

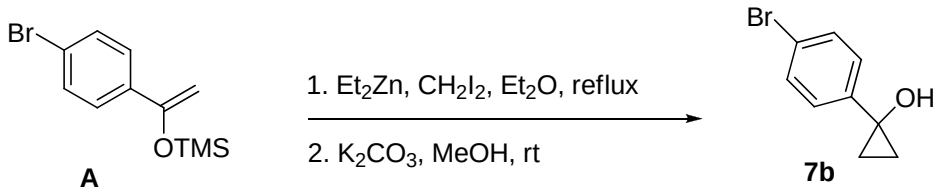


The reaction was carried out by using 1.2 equiv of $Mn(pic)_3$.

Reaction time: 24 h. Yellow solid; mp 86-88 ºC; IR (NaCl) 3460, 3019, 1605, 1512, 1494, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.03 (2H, s), 6.05 (1H, dd, *J* = 2.4, 3.2 Hz), 6.43 (1H, dd, *J* = 2.8, 3.2 Hz), 7.15 (1H, t, *J* = 7.2 Hz), 7.22-7.26 (3H, m), 7.29-7.34 (4H, m), 7.38 (2H, d, *J* = 7.2 Hz), 8.03 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.2, 106.1, 108.6, 123.4, 125.8, 126.5, 128.6, 128.7, 128.8, 131.5, 132.0, 132.8, 139.2. ESIHRMS: Found: m/z 234.1285. Calcd for $C_{17}H_{16}N$: $(M+H)^+$ 234.1283.

6.5 Mn(III)-mediated synthesis of pyridines from vinyl azides and cyclopropanols (Chapter 4)

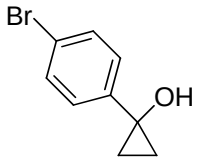
6.5.1 Synthesis of cyclopropanols



To a solution of silyl enol ether **A**[20] (3.91 g, 14.4 mmol) and diethyl zinc (32.0 mL, 31.7 mmol, 1.0 M in hexane) in Et_2O (20 mL) was added dropwise a solution of diiodomethane (2.60 mL, 31.7 mmol) in Et_2O (10 mL) over 1 h at 0 °C. The reaction was stirred at room temperature for overnight to give a cloudy solution which was allowed to cooled and then quenched by the dropwise addition of pyridine (14.0 mL). The resulting suspension was filtered through a pad of Celite and precipitate was washed thoroughly with Et_2O. After evaporation of solvents, the crude materials were dissolved in MeOH (30 mL) followed by addition of K_2CO_3 (0.12 g, 0.9 mmol). The reaction was stirred for 30 min at room temperature, quenched by adding pH 9 ammonium buffer, and the organic materials

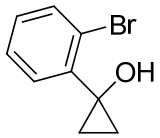
were extracted with ethyl acetate. The organic lay was washed with brine and dried over $MgSO_4$. After evaporation of solvent, resulting crude materials were purified by flash column chromatography (silica gel; hexane : ethyl acetate = 85 : 15) to give **7b** (1.96 g, 9.0 mmol, 62% yield from silyl enol ether **A**).

1-(4-Bromophenyl)cyclopropanol (7b):[21]



White solid; mp 78-79 °C; IR (KBr) 3582, 3017, 1593, 1487, 1450, 1215, 1094, 1008 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (2H, dd, *J* = 5.2, 6.8 Hz), 1.27 (2H, *J* = 5.2, 6.8 Hz), 2.44 (1H, s br), 7.16 (2H, d, *J* = 8.4 Hz), 7.44 (2H, d, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 56.2, 120.1, 126.1, 131.3, 143.4; ESIHRMS: Found: m/z 212.9912. Calcd for $C_9H_{10}BrO$: $(M+H)^+$ 212.9915.

1-(2-Bromophenyl)cyclopropanol (7c):



Cyclopropanol **7c** was prepared from the corresponding silyl enol ether following the same procedure as **7b**.

Yield: 52%. White solid; mp 51-52 °C; IR (KBr) 3584, 3017, 1591, 1474, 1440, 1342, 1215, 1113, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (2H, dd, *J* = 5.6, 6.8 Hz), 1.23 (2H, dd, *J* = 5.6, 6.8 Hz), 3.04 (1H, s br), 7.15 (1H, ddd, *J* = 0.8, 7.6, 8.0 Hz), 7.27 (1H, dd, *J* = 7.6, 8.0 Hz), 7.39 (1H, dd, *J* = 0.8, 7.6 Hz), 7.56 (1H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$)

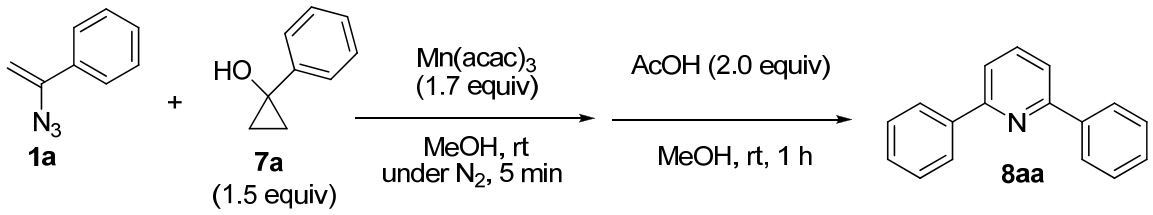
δ 14.7, 58.3, 125.6, 127.5, 129.4, 130.6, 132.9, 140.9; ESIHRMS: Found: m/z 234.9735. Calcd for C_9H_9BrNaO: $(M+Na)^+$ 234.9734.

Cyclopropanols **7a**,[22] **7e**,[22] and **7m**[22] are known compounds and were prepared by the same procedure as **7b** from the corresponding silyl enol ethers.

Cyclopropanols **7d**,[23] **7f**,[24] **7g**,[25] **7h**,[26] **7i**,[27] **7j**,[28] **7k**,[29] **7l**,[30] and **7n**[31] are known compounds and were prepared according to literatures.

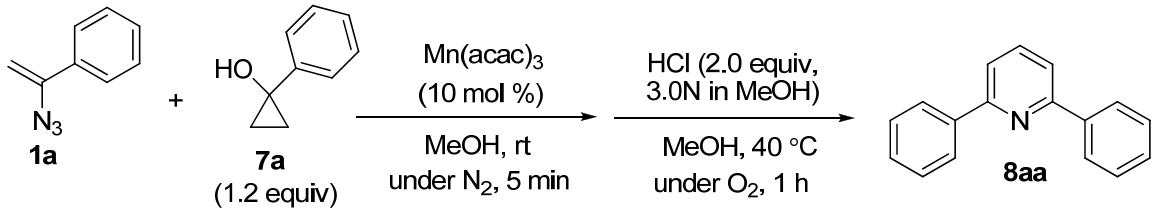
6.5.2 $Mn(acac)_3$-mediated/catalyzed pyridine formation

Typical procedure using Conditions A (stoichiometric reaction):



To a solution of α-azido styrene (**1a**) (43.5 mg, 0.30 mmol) and 1-phenylcyclopropanol (**7a**) (60.6 mg, 0.45 mmol) in MeOH (3.0 mL) was added $Mn(acac)_3$ (179.8 mg, 0.51 mmol) at room temperature under nitrogen atmosphere. After 5 min, AcOH (34 μL, 0.60 mmol) was added and the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with pH 9 ammonium buffer and then extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by flash column chromatography (silica gel; hexane : ethyl acetate = 98 : 2) afforded **8aa** (58.0 mg, 0.25 mmol) in 84% yield as a pale yellow solid.

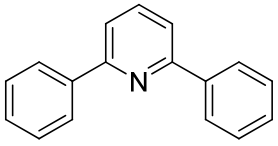
Typical procedure using Conditions B (catalytic reaction):



To a solution of α-azido styrene (**1a**) (43.6 mg, 0.30 mmol) and 1-phenylcyclopropanol (**7a**) (48.4 mg, 0.36 mmol) in MeOH (3.0 mL) was added $Mn(acac)_3$ (10.6 mg, 0.03 mmol) at room temperature under nitrogen atmosphere. After 5 min, HCl (0.20 mL, 0.60 mmol, 3.0 M in MeOH) was added and the nitrogen balloon was then replaced by oxygen balloon. The reaction mixture was heated at 40 ºC for 1 h and quenched with pH 9 ammonium buffer, and then extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by flash column chromatography (silica gel; hexane : ethyl acetate = 98 : 2) afforded **8aa** (55.6 mg, 0.24 mmol) in 80% yield as a pale yellow solid.

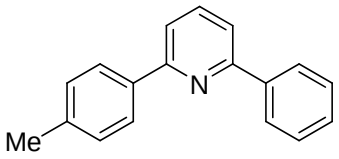
2,6-Diphenylpyridine (**8aa**):[32]

Total reaction time for Conditions A: 1 h. Total reaction time for Conditions B: 1 h.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.44 (2H, m), 7.45-7.52 (4H, m), 7.70 (2H, d, J = 7.4 Hz), 7.83 (1H, t, J = 7.6 Hz), 8.15-8.17 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.6, 127.0, 128.7, 129.0, 137.5, 139.5, 156.8.

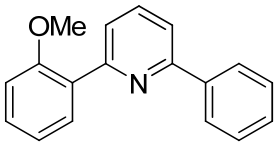
2-Phenyl-6-*p*-tolylpyridine (8ba):



Total reaction time for Conditions A: 0.5 h.

White solid; mp 79-81 °C; IR (KBr) 3015, 1566, 1445, 1267, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.43 (3H, s), 7.30 (2H, d, *J* = 8.0 Hz), 7.43 (1H, t, *J* = 7.2 Hz), 7.50 (2H, dd, *J* = 7.2, 7.6 Hz), 7.68 (2H, d, *J* = 7.6 Hz), 7.80 (1H, dd, *J* = 7.6, 8.0 Hz), 8.06 (2H, d, *J* = 8.0 Hz), 8.15-8.17 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 118.4 (overlapped), 126.9, 127.0, 128.7, 128.9, 129.4, 136. 8, 137.4, 139.0, 139.6, 156.7, 156.9; ESIHRMS: Found: m/z 246.1285. Calcd for $C_{18}H_{16}N$: $(M+H)^+$ 246.1283.

2-(2-Methoxyphenyl)-6-phenylpyridine (**8ca**):

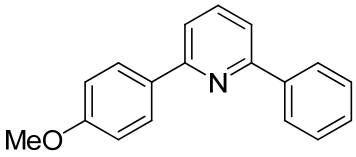


Total reaction time for Conditions A: 0.5 h. Total reaction time for Conditions B: 1 h.

Colorless liquid; IR (KBr) 2938, 1599, 1567, 1490, 1442, 1257, 1180, 1053 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.90 (3H, s), 7.03 (1H, d, *J* = 8.0 Hz), 7.14 (1H, t, *J* = 7.6 Hz), 7.38-7.43 (2H, m), 7.49 (2H, dd, *J* = 7.6, 7.6 Hz), 7.67 (1H, d, *J* = 8.0 Hz), 7.78 (1H, dd, *J* = 7.6, 8.0 Hz), 7.85 (1H, d, *J* = 7.6 Hz), 8.03 (1H, d, *J* = 7.6 Hz), 8.12 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 111.4, 118.3, 121.0, 123.5, 126.9, 128.6, 128.7, 129.2,

129.9, 131.5, 136.3, 139.7, 155.4, 156.7, 157.2; ESIHRMS: Found: m/z 262.1231. Calcd for $C_{18}H_{16}NO$: $(M+H)^+$ 262.1232.

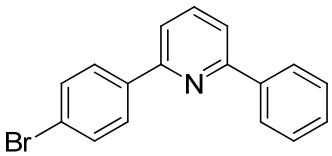
2-(4-Methoxyphenyl)-6-phenylpyridine (**8da**):[33]



Total reaction time for Conditions A: 0.5 h.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (3H, s), 7.03 (2H, d, *J* = 8.0 Hz), 7.43 (1H, t, *J* = 7.2 Hz), 7.51 (2H, dd, *J* = 7.2, 8.0 Hz), 7.64 (2H, d, *J* = 8.0 Hz), 7.82 (1H, dd, *J* = 8.0, 8.0 Hz), 8.11-8.15 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 114.0, 117.8, 117.9, 126.9, 128.2, 128.6, 128.8, 132.1, 137.3, 139.6, 156.4, 156.6, 160.4.

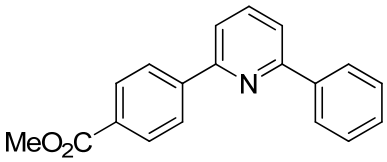
2-(4-Bromophenyl)-6-phenylpyridine (**8pa**):[34]



Total reaction time for Conditions A: 0.5 h.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (1H, t, *J* = 7.2 Hz), 7.51 (2H, dd, *J* = 7.2, 7.6 Hz), 7.62 (2H, d, *J* = 8.4 Hz), 7.67 (1H, d, *J* = 7.6 Hz), 7.71 (1H, d, *J* = 8.0 Hz), 7.82 (1H, dd, *J* = 7.6, 8.0 Hz), 8.04 (2H, d, *J* = 8.4 Hz), 8.13 (1H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.3, 118.9, 123.4, 126.9, 128.5, 128.7, 129.1, 131.8, 137.6, 138.3, 139.2, 155.6, 157.0.

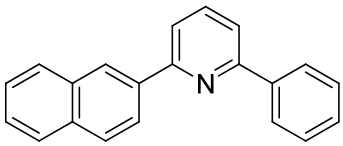
Methyl 4-(6-phenylpyridin-2-yl)benzoate (**8qa**):



Total reaction time for Conditions A: 0.5 h.

White solid; mp 140-141 °C; IR (KBr) 3019, 1713, 1589, 1565, 1446, 1281, 1115 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (3H, s), 7.45 (1H, t, *J* = 7.2 Hz), 7.52 (2H, dd, *J* = 7.2, 7.6 Hz), 7.74 (2H, d, *J* = 8.0 Hz), 7.85 (1H, dd, *J* = 7.6, 8.0 Hz), 8.14-8.18 (4H, m), 8.23 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.2, 119.1, 119.4, 126.9, 127.0, 128.7, 129.1, 130.0, 130.3, 137.6, 139.2, 143.6, 155.5, 157.1, 167.0; ESIHRMS: Found: m/z 276.0995. Calcd for $C_{16}H_{15}NO_2$: $(M+H)^+$ 276.1000.

2-(Naphthalen-2-yl)-6-phenylpyridine (8ea):

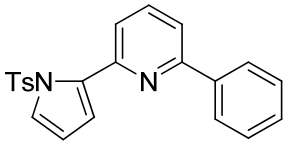


Total reaction time for Conditions A: 0.5 h. Total reaction time for Conditions B: 1 h.

White solid; mp 112-114 °C; IR (KBr) 3016, 1597, 1567, 1476, 1446, 1210, 1130, 1023 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (1H, t, *J* = 7.2 Hz), 7.52-7.56 (4H, m), 7.72-7.74 (1H, m), 7.85-7.87 (2H, m), 7.89-7.91 (1H, m), 7.99 (2H, dd, *J* = 7.6, 8.0 Hz), 8.21(2H, d, *J* = 7.6 Hz), 8.34 (1H, d, *J* = 8.8 Hz), 8.63 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.7, 118.9, 124.8, 126.2, 126.3, 126.5, 127.0, 127.7, 128.3, 128.72, 128.74, 129.0, 133.5, 133.7, 136.8,

137.5, 139.5, 156.7, 157.0; ESIHRMS: Found: m/z 282.1280. Calcd for $C_{21}H_{16}N$: $(M+H)^+$ 282.1283.

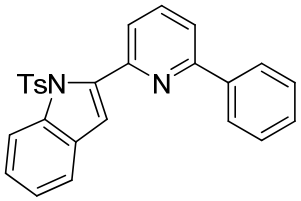
2-Phenyl-6-(1-tosyl-1*H*-pyrrol-2-yl)pyridine (8fa):



Total reaction time for Conditions A: 1 h.

Pale yellow solid; mp 130-131 °C; IR (KBr) 3019, 1597, 1572, 1483, 1442, 1368, 1214, 1172, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.32 (3H, s), 6.37 (1H, dd, *J* = 3.2, 3.2 Hz), 6.48 (1H, dd, *J* = 2.0, 3.2 Hz), 7.05 (2H, d, *J* = 8.4 Hz), 7.40-7.42 (3H, m), 7.44 (1H, d, *J* = 7.6 Hz), 7.47 (1H, dd, *J* = 2.0, 3.2 Hz), 7.52 (2H, d, *J* = 8.4 Hz), 7.66 (1H, d, *J* = 8.0 Hz), 7.75 (1H, d, *J* = 7.6 Hz), 7.79-7.81 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 111.8, 116.4, 119.5, 123.8, 124.6, 127.2 (overlapped), 128.4, 128.7, 129.5, 135.5, 136.3, 136.5, 139.1, 144.4, 150.7, 156.5; ESIHRMS: Found: m/z 375.1165. Calcd for $C_{22}H_{19}N_2O_2S$: $(M+H)^+$ 375.1167.

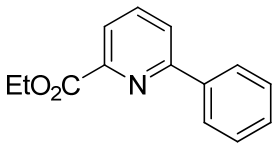
2-(6-Phenylpyridin-2-yl)-1-tosyl-1H-indole (8ga):



Total reaction time for Conditions A: 1 h.

White solid; mp 138-139 °C; IR (KBr) 3019, 1598, 1566, 1473, 1442, 1372, 1215, 1175, 1058 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 2.26 (3H, s), 6.88 (1H, s), 7.03 (2H, d, *J* = 8.4 Hz), 7.25 (1H, t, *J* = 7.6 Hz), 7.36 (1H, dd, *J* = 7.2, 8.4 Hz), 7.40-7.50 (4H, m), 7.61 (2H, d, *J* = 8.4 Hz), 7.76 (1H, d, *J* = 8.0 Hz), 7.83 (1H, dd, *J* = 7.6, 7.6 Hz), 8.00 (2H, d, *J* = 7.2 Hz), 8.21 (1H, d, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 114.3, 116.0, 119.8, 121.3, 124.1, 124.4, 125.1, 127.1, 127.2, 128.6, 128.9, 129.3, 130.2, 134.8, 136.2, 137.9, 139.2, 141.2, 144.4, 151.3, 156.4; ESIHRMS: Found: m/z 425.1322. Calcd for $C_{26}H_{21}N_2O_2S$: $(M+H)^+$ 425.1324.

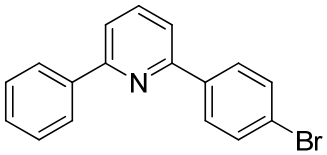
Ethyl 6-phenylpicolinate (8sa):[35]



Total reaction time for Conditions A: 8 h.

^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (3H, t, *J* = 7.6 Hz), 4.49 (2H, q, *J* = 7.6 Hz), 7.43 (1H, t, *J* = 7.2 Hz), 7.49 (2H, dd, *J* = 6.8, 7.2 Hz), 7.88-7.91 (2H, m), 8.03-8.08 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 61.8, 123.2, 123.4, 127.2, 128.8, 129.4, 137.6, 138.5, 148.3, 157.6, 165.5.

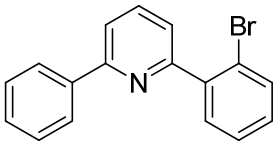
2-(4-Bromophenyl)-6-phenylpyridine (**8ab**):



Total reaction time for Conditions A: 0.5 h. Total reaction time for Conditions B: 1 h.

This compound is identical to compound **8pa**.

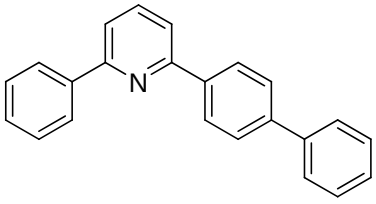
2-(2-Bromophenyl)-6-phenylpyridine (8ac):[36]



Total reaction time for Conditions A: 0.5 h.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.29 (2H, m), 7.41-7.50 (3H, m), 7.55 (1H, d, *J* = 7.6 Hz), 7.65 (1H, d, *J* = 7.6 Hz), 7.70 (1H, d, *J* = 7.6 Hz), 7.73 (1H, d, *J* = 7.6 Hz), 7.83 (1H, dd, *J* = 7.6, 7.6 Hz), 8.09 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.1, 121.9, 122.9, 127.1, 127.5, 128.7, 129.0, 129.6, 131.7, 133.4, 136.6, 139.3, 141.4, 157.0, 158.0.

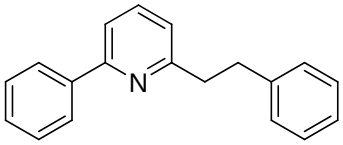
2-(Biphenyl-4-yl)-6-phenylpyridine (8ad):[33]



Total reaction time for Conditions A: 9 h.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (1H, d, *J* = 7.6 Hz), 7.44-7.55 (5H, m), 7.68-7.76 (6H, m), 7.84 (1H, dd, *J* = 7.6, 8.0 Hz), 8.19 (2H, d, *J* = 7.6 Hz), 8.26 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.5, 118.6, 127.0, 127.1, 127.35, 127.39, 127.5, 128.7, 128.8, 129.0, 137.5, 138.4, 139.5, 140.7, 141.7, 156.4, 156.9.

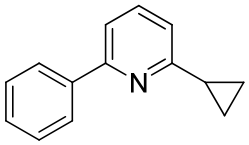
2-Phenethyl-6-phenylpyridine (8ae):



Total reaction time for Conditions A: 0.5 h. Total reaction time for Conditions B: 1 h.

Colorless liquid; IR (KBr) 2924, 2857, 1590, 1570, 1496, 1446, 1217, 1153, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.17 (4H, s, overlapped), 7.02 (1H, d, *J* = 7.6 Hz), 7.17-7.30 (5H, m), 7.40 (1H, t, *J* = 7.2 Hz), 7.48 (2H, dd, *J* = 7.2, 7.6 Hz), 7.54 (1H, d, *J* = 8.0 Hz), 7.62 (1H, dd, *J* = 7.6, 8.0 Hz), 8.01 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.7, 40.1, 117.9, 121.2, 125.8, 127.0, 128.3, 128.5, 128.6, 128.7, 136.8, 139.7, 141.8, 156.8, 161.0; ESIHRMS: Found: m/z 260.1440. Calcd for $C_{19}H_{18}N$: $(M+H)^+$ 260.1439.

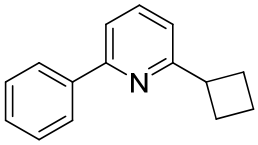
2-Cyclopropyl-6-phenylpyridine (8af):



Total reaction time for Conditions A: 0.5 h. Total reaction time for Conditions B: 30 h.

Colorless liquid; IR (KBr) 3087, 3007, 1591, 1569, 1453, 1441, 1212, 1162, 1050 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98-1.02 (2H, m), 1.13-1.17 (2H, m), 2.06-2.13 (1H, m), 7.07 (1H, d, *J* = 8.0 Hz), 7.38 (1H, t, *J* = 7.6 Hz), 7.45 (2H, dd, *J* = 7.6, 8.0 Hz), 7.49 (1H, d, *J* = 7.6 Hz), 7.59 (1H, dd, *J* = 7.6, 8.0 Hz), 8.01 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.9, 17.2, 116.9, 119.6, 126.8, 128.5, 128.7, 136.4, 139.7, 156.3, 162.4; ESIHRMS: Found: m/z 196.1128. Calcd for $C_{14}H_{14}N$: $(M+H)^+$ 196.1126.

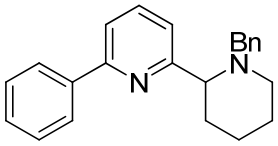
2-Cyclobutyl-6-phenylpyridine (8ag):



Total reaction time for Conditions A: 0.5 h. Total reaction time for Conditions B: 2 h.

Colorless liquid; IR (KBr) 2933, 2860, 1589, 1569, 1443, 1217, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.92-2.00 (1H, m), 2.03-2.15 (1H, m), 2.37-2.50 (4H, m), 3.71-3.79 (1H, m), 7.11 (1H, d, *J* = 7.6 Hz), 7.41 (1H, t, *J* = 7.2 Hz), 7.48 (2H, dd, *J* = 7.2, 7.6 Hz), 7.54 (1H, d, *J* = 7.6 Hz), 7.67 (1H, dd, *J* = 7.6, 7.6 Hz), 8.01 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 28.5, 42.3, 117.5, 119.3, 126.9, 128.59, 128.63, 136.7, 139.8, 156.4, 164.5; ESIHRMS: Found: m/z 210.1281. Calcd for $C_{15}H_{16}N$: $(M+H)^+$ 210.1283.

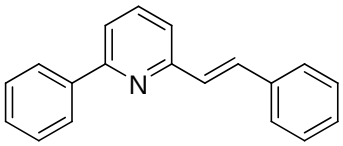
2-(1-Benzylpiperidin-2-yl)-6-phenylpyridine (8ah):



Total reaction time for Conditions A: 0.5 h. Total reaction time for Conditions B: 2 h.

Pale yellow liquid; IR (KBr) 3018, 2929, 1591, 1570, 1446, 1214, 1102, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39-1.49 (1H, m), 1.56-1.65 (3H, m), 1.82 (1H, d, *J* = 12.4 Hz), 1.96-2.06 (2H, m), 3.00-3.03 (2H, m), 3.50 (1H, dd, *J* = 2.4, 11.2 Hz), 3.76 (1H, d, *J* = 13.6 Hz), 7.21 (1H, t, *J* = 6.8 Hz), 7.25-7.32 (4H, m), 7.40 (1H, t, *J* = 7.6 Hz), 7.47 (2H, dd, *J* = 7.6, 7.6 Hz), 7.56 (1H, d, *J* = 7.6 Hz), 7.61 (1H, d, *J* = 7.6 Hz), 7.73 (1H, dd, *J* = 7.6, 7.6 Hz), 8.00 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 25.9, 35.5, 53.1, 60.1, 70.7, 118.8, 119.6, 126.6, 127.0, 128.0, 128.64 (overlapped), 128.67, 137.3, 139.5, 139.8, 156.5, 165.2; ESIHRMS: Found: m/z 329.2017. Calcd for $C_{23}H_{25}N_2$: $(M+H)^+$ 329.2018.

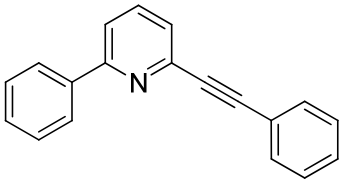
(*E*)-2-Phenyl-6-styrylpyridine (8ai):[37]



Total reaction time for Conditions A: 4 h. Total reaction time for Conditions B: 2 h.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (1H, d, *J* = 16.0 Hz), 7.32 (2H, dd, *J* = 7.2, 7.6 Hz), 7.39 (2H, dd, *J* = 7.6, 7.6 Hz), 7.44 (1H, d, *J* = 7.6 Hz), 7.48-7.52 (2H, m), 7.59-7.63 (3H, m), 7.73 (1H, dd, *J* = 7.6, 8.0 Hz), 7.78 (1H, d, *J* = 16.0 Hz), 8.09 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.9, 120.4, 127.0, 127.1, 128.2, 128.3, 128.7 (overlapped), 128.9, 132.8, 136.8, 137.2, 139.6, 155.3, 157.1.

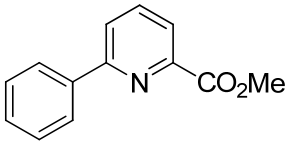
2-Phenyl-6-(phenylethynyl)pyridine (8aj):



Total reaction time for Conditions A: 5 h. Total reaction time for Conditions B: 2 h.

Pale yellow solid; mp 82-83 °C; IR (KBr) 3016, 2228, 1598, 1562, 1491, 1442, 1213, 1167, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.39 (3H, m), 7.43 (1H, t, *J* = 7.2 Hz), 7.47 - 7.50 (3H, m), 7.62-7.65 (2H, m), 7.68 (1H, d, *J* = 7.6 Hz), 7.75 (1H, dd, *J* = 7.6, 8.0 Hz), 8.00 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 88.9, 89.1, 119.8, 122.4, 125.7, 127.2, 128.3, 128.7, 128.9, 129.2, 132.1, 136.8, 138.9, 143.3, 158.0; ESIHRMS: Found: m/z 256.1128. Calcd for $C_{19}H_{14}N$: $(M+H)^+$ 256.1126.

Methyl 6-phenylpicolinate (8ak):

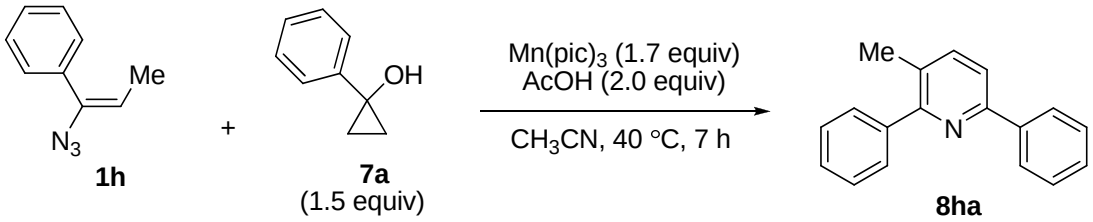


Total reaction time for Conditions A: 10 h.

White solid; mp 47-48 °C; IR (KBr) 3011, 1736, 1582, 1554, 1492, 1435, 1242, 1137, 1027; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (3H, s), 7.43-7.51 (3H, m), 7.91 (2H, d, *J* = 8.0 Hz), 8.04-7.08 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.8, 123.3, 123.7, 127.2, 128.8, 129.4, 137.7, 138.5, 148.0, 157.7, 166.0; ESIHRMS: Found: m/z 214.0871. Calcd for $C_{13}H_{12}NO_2$: $(M+H)^+$ 214.0868.

6.5.3 Mn(pic)$_3$-mediated pyrridine formation

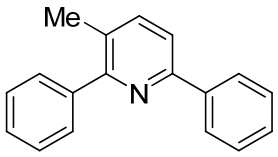
Typical procedure (Conditions C):



To a solution of (*E*)-(1-azidoprop-1-enyl)benzene (**1h**) (48.0 mg, 0.30 mmol) and 1-phenylcyclopropanol (**7a**) (60.7 mg, 0.45 mmol) in MeOH (3.0 mL) was added AcOH (35 μL, 0.60 mmol) and Mn(pic)$_3$ (215.9 mg, 0.51 mmol), and the reaction mixture was stirred at 40 ºC for 7 h. The reaction mixture was quenched with pH 9 ammonium buffer and then extracted twice with ethyl acetate. The combined organic extracts were washed with brine,

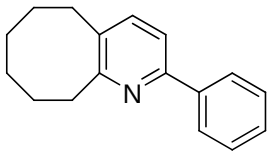
dried over $MgSO_4$, and concentrated. Purification of the crude product by flash column chromatography (silica gel; hexane : ethyl acetate = 98 : 2) afforded **8ha** (33.0 mg, 0.14 mmol) in 45% yield.

3-Methyl-2,6-diphenylpyridine (8ha):[38]



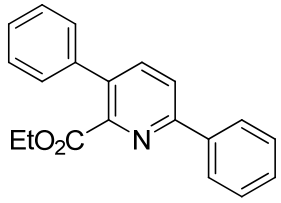
Reaction time: 7 h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (3H, s), 7.38 -7.49 (6H, m), 7.64 - 7.66 (4H, m), 8.06 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 118.7, 126.8, 127.9, 128.1, 128.56, 128.6, 129.19, 129.25, 139.3, 139.4, 140.9, 154.5, 158.1.

2-Phenyl-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine (**8na**):



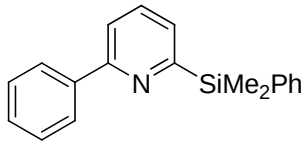
Reaction time: 8 h. Colorless liquid; IR (KBr) 3019, 2929, 1594, 1570, 1457, 1215, 1123, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (4H, m), 1.73 (2H, m), 1.84 (2H, m), 2.80 (2H, t, *J* = 6.2 Hz), 3.05 (2H, t, *J* = 6.2 Hz), 7.37 (1H, t, *J* = 7.2 Hz), 7.43-7.49 (4H, m), 7.98 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 26.1, 30.8, 31.6, 32.2, 34.9, 118.3, 126.8, 128.3, 128.6, 134.6, 137.2, 140.0, 154.9, 160.9; ESIHRMS: Found: m/z 238.1593. Calcd for $C_{17}H_{20}N$: $(M+H)^+$ 238.1596.

Ethyl 3,6-diphenylpicolinate (8ua):



Reaction time: 11 h. White solid; mp 67-69 °C; IR (KBr) 3019, 1735, 1588, 1454, 1275, 1120, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, t, *J* = 7.2 Hz), 4.22 (2H, q, *J* = 7.2 Hz), 7.40-7.51 (8H, m), 7.82 (1H, d, *J* = 8.0 Hz), 7.88 (1H, d, *J* = 8.0 Hz), 8.09 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 61.5, 121.5, 127.1, 128.0, 128.3, 128.5, 128.8, 129.4, 134.9, 138.08, 138.12, 138.80, 149.5, 155.9, 167.4; ESIHRMS: Found: m/z 304.1335. Calcd for $C_{20}H_{18}NO_2$: $(M+H)^+$ 304.1338.

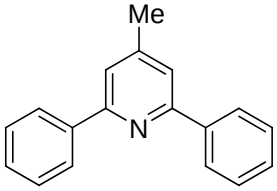
2-(Dimethyl(phenyl)silyl)-6-phenylpyridine (8al):



The reaction was performed in the absence of AcOH. Reaction time: 24 h. Flash column chromatography was using Florisil® adsorbent (100-200 mesh) by hexane/ethyl acetate (99 : 1) as eluent.

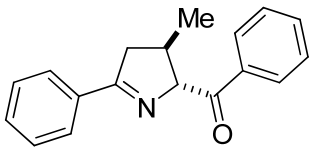
Pale yellow liquid; IR (KBr) 3068, 2958, 1570, 1557, 1448, 1246, 1110, 1026, 823 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 0.66 (6H, s), 7.37 -7.38 (4H, m), 7.42 (1H, d, *J* = 7.2 Hz), 7.48 (2H, dd, *J* = 7.2, 7.6 Hz), 7.61 (1H, dd, *J* = 7.2, 7.6 Hz), 7.65-7.67 (3H, m), 8.11 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -3.0, 119.3, 126.9, 127.8, 127.9, 128.6, 128.7, 129.1, 134.3, 134.6, 137.7, 139.8, 156.6, 166.3; ESIHRMS: Found: m/z 290.1364. Calcd for $C_{19}H_{20}NSi$: $(M+H)^+$ 290.1365.

4-Methyl-2,6-diphenylpyridine (8am):[39]



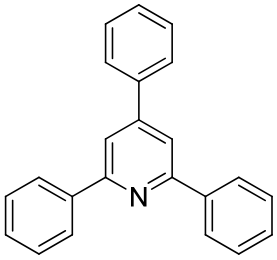
Reaction time: 2 h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (3H, s), 7.42 (2H, t, *J* = 7.4 Hz), 7.49-7.54 (6H, m), 8.11 (4H, d, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 119.7, 127.0, 128.6, 128.8, 139.6, 148.3, 156.8.

((2*R,3*R**)-3-Methyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)(phenyl)methanone (8am'):**



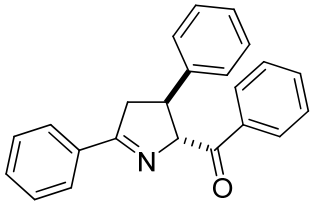
Pale yellow liquid; IR (KBr) 3018, 2968, 1685, 1598, 1576, 1448, 1346, 1215, 1117 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, d, *J* = 7.2 Hz), 2.70 (1H, dd, *J* = 5.2, 17.2 Hz), 2.89 - 2.96 (1H, m), 3.32 (1H, ddd, *J* = 1.6, 8.4, 17.2 Hz), 5.39 (1H, d, *J* = 4.0 Hz), 7.38 - 7.44 (3H, m), 7.51 (2H, dd, *J* = 7.6, 7.6 Hz), 7.60 (1H, t, *J* = 7.2 Hz), 7.87 (2H, d, *J* = 7.2 Hz), 8.21 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 34.1, 43.4, 84.3, 127.9, 128.4, 128.5, 129.2, 130.8, 133.2, 134.2, 136.2, 174.8, 197.7; ESIHRMS: Found: m/z 264.1384. Calcd for $C_{18}H_{18}NO$: $(M+H)^+$ 264.1388.

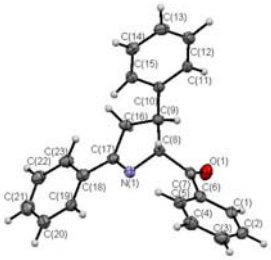
2,4,6-Triphenylpyridine (8an):[40]



Reaction time: 6 h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.56 (9H, m), 7.76 (2H, d, *J* = 7.6 Hz), 7.91 (2H, s), 8.21 (4H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 117.1, 127.1, 127.2, 128.7, 128.97, 129.04, 129.1, 139.1, 139.6, 150.2, 157.5.

((2*R,3*S**)-3,5-Diphenyl-3,4-dihydro-2H-pyrrol-2-yl)(phenyl)methanone (8an'):**



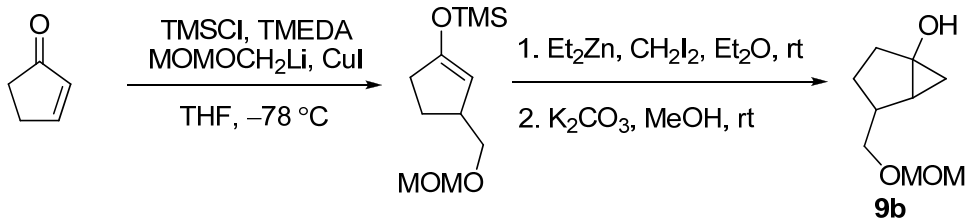


Colorless crystal (CCDC-735781);[41] mp 127-128 °C; IR (KBr) 3019, 1689, 1598, 1576, 1448, 1346, 1215, 1026 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.24 (1H, ddd, *J* = 1.2, 5.2, 17.2 Hz), 3.67 (1H, ddd, *J* = 2.4, 9.6, 17.2 Hz), 4.10 (1H, ddd, *J* = 4.8, 5.2, 9.6 Hz), 5.86 (1H, ddd, *J* = 1.2, 2.4, 4.8 Hz), 7.22 - 7.25 (3H, m), 7.30 - 7.34 (2H, m), 7.40 - 7.49 (5H, m), 7.57 (1H, tt, *J* = 1.2, 7.2 Hz), 7.91 (2H, dd, *J* = 1.2, 7.6 Hz), 8.15 (2H, dd, *J* = 1.2, 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.4, 44.7, 85.7, 126.8, 127.1, 128.1, 128.5 (overlapped), 128.9, 129.4, 131.0, 133.3, 133.8, 135.9, 144.4, 174.3, 196.8; ESIHRMS: Found: m/z 326.1547. Calcd for $C_{23}H_{20}NO$: $(M+H)^+$ 326.1545.

6.6 $Mn(acac)_3$-catalyzed synthesis of azabicyclic compounds from vinyl azides and cyclopropanols (Chapter 5)

6.6.1 Synthesis of bicyclo[3.1.0]hexan-1-ols

6.6.1.1 Synthesis of 4-((methoxymethoxy)methyl)bicyclo[3.1.0]hexan-1-ol (9b):



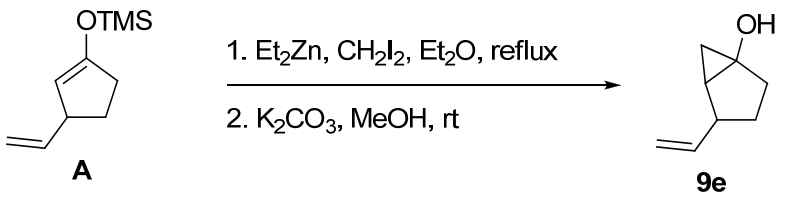
9b

To a solution of *n*-Bu_3SnCH_2MOM[42] (4.31 g, 11.8 mmol) in THF (30 mL) was added *n*-BuLi/hexanes (1.6 M, 7.4 mL, 11.8 mmol) at –78 °C under a nitrogen atmosphere. After 5 min the reaction mixture was transferred *via* cannula to a stirred solution of CuI (1.12 g, 5.9 mmol) and TMEDA (2.65 mL, 17.7 mmol) in THF (15 mL) at –78 °C under a nitrogen atmosphere and the resulting mixture stirred for 30 min. A sample of cyclopent-2-enone (0.49 ml, 5.9 mmol) was added to another flask containing 20 mL of THF. The enone solution was cooled to –78 °C and TMSCl (2.25 mL, 17.7 mmol) was then added. After stirring the enone/TMSCl mixture for 2 min at the same temperature, the solution was transferred *via* cannula to the flask containing the cuprate at -78 °C. After 1 h, the reaction was quenched with saturated aqueous ammonium chloride solution (10 mL) and allowed to warm to room temperature. Following dilution with water (100 mL) and 10% aqueous ammonia solution (5 mL), the mixture was extracted twice with diethyl ether (150 mL) and the combined organic layers washed with brine (100 mL) and dried (MgSO4). After removal of solvents under reduced pressure, the resulting crude materials were used immediately for the next step without any furthur purification.

To the solution of silyl enol ether obtained above and diethyl zinc (8.8 mL, 8.8 mmol, 1.0 M in hexane) in Et_2O (5 mL) was added dropwise a solution of diiodomethane (0.71 mL, 8.8 mmol) in Et_2O (5 mL) over 30 min at 0 °C. The reaction was stirred at room temperature for 3 h to give a cloudy solution which was allowed to cooled and then quenched by the dropwise addition of pyridine (2.80 mL). The resulting suspension was filtered through a pad of Celite and the precipitate was washed thoroughly with Et_2O. After evaporation of solvents, the crude materials were dissolved in MeOH (15 mL) followed by addition of K_2CO_3 (76.8 mg, 0.6 mmol). The reaction was stirred for 30 min at room temperature and then quenched by adding pH 9 ammonium buffer, and the organic materials were extracted with ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation of solvent, the resulting crude materials were purified by flash column chromatography (silica gel; hexane : ethyl acetate = 80 : 20) to give **9b** (0.68 g, 3.95 mmol, 67% yield from cyclopent-2-enone) as an inseparable mixture of diastereomers (ca. 2.3 : 1 for cyclopropanation), and ^1H and ^{13}C NMR were described for the major product.

Colorless liquid; IR (KBr) 3583, 2950, 1146, 915 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.59-0.64 (1H, m), 0.91 (1H, dd, *J* = 6.0, 6.0 Hz), 1.26-1.29 (1H, m), 1.51-1.56 (1H, m), 1.94-2.06 (4H, m), 2.56 (1H, s br), 3.36 (3H, s), 3.40-3.48 (2H, m), 4.62 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 24.3, 26.8, 31.4, 39.9, 55.2, 64.0, 71.1, 96.5; ESIHRMS: Found: m/z 195.0994. Calcd for $C_9H_{16}O_3Na$: $(M+Na)^+$ 195.0997.

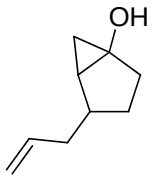
6.6.1.2 Synthesis of 4-vinylbicyclo[3.1.0]hexan-1-ol (9e):



To a solution of silyl enol ether **A**[43] (1.95 g, 10.7 mmol) and diethyl zinc (15.3 mL, 15.3 mmol, 1.0 M in hexane) in Et_2O (10 mL) was added dropwise a solution of diiodomethane (1.22 mL, 15.3 mmol) in Et_2O (10 mL) over 1 h at 0 °C. The reaction was heated at reflux for 3 h to give a cloudy solution which was allowed to cooled and then quenched by the dropwise addition of pyridine (2.0 mL). The resulting suspension was filtered through a Celite pad, the precipitate was washed thoroughly with Et_2O. After evaporation of solvents, the crude materials were dissolved in MeOH (15 mL) followed by addition of K_2CO_3 (0.14 g, 1.1 mmol). The reaction was stirred for 30 min at room temperature and then quenched by adding pH 9 ammonium buffer, and the organic materials were extracted with ethyl acetate. The organic lay was washed with brine, and dried over $MgSO_4$. After evaporation of solvent, resulting crude materials were purified by flash column chromatography (silica gel; hexane : ethyl acetate = 85 : 15) to give **9e** (1.11 g, 8.9 mmol, 84% yield from silyl enol ether **A**) as an inseparable mixture of diastereomers (ca. 4 : 1 for cyclopropanation); ^1H and ^{13}C NMR are described for the major product.

Colorless liquid; IR (KBr) 3588, 2950, 1636, 907 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.66 (1H, dd, *J* = 4.8, 4.8 Hz), 0.90-0.95 (1H, m), 1.29-1.50 (3H, m), 1.92-2.00 (3H, m), 2.43 (1H, dd, *J* = 7.2, 7.6 Hz), 4.90-5.07 (2H, m), 5.93 (1H, ddd, *J* = 7.2, 10.4, 17.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 27.5, 28.5, 31.2, 42.7, 64.5, 112.6, 142.5; ESIHRMS: Found: m/z 125.0964. Calcd for $C_8H_{13}O$: $(M+H)^+$ 125.0966.

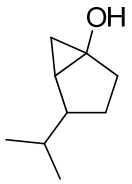
4-Allylbicyclo[3.1.0]hexan-1-ol (9c):



Cyclopropanol **9c** was prepared from the corresponding silyl enol ether following the same procedure as **9e**. An inseparable mixture of diastereomers (ca. 4 : 1 for cyclopropanation) was obtained; ^{1}H and ^{13}C NMR are described for the major product.

Yield: 21%. Colorless liquid; IR (NaCl) 3300, 2997, 1641, 1231cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.60 (1H, dd, *J* = 4.2, 5.4 Hz), 0.88 (1H, ddd, *J* = 1.5, 5.4, 5.4 Hz), 1.24-1.28 (2H, m), 1.44 (1H, dd, *J* = 7.8, 13.5 Hz), 1.83 (1H, dd, *J* = 7.2, 13.5 Hz), 1.89-2.00 (3H, m), 2.05-2.17 (2H, m), 5.01-5.06 (2H, m), 5.75-5.85 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 26.3, 29.2, 31.2, 38.1, 39.8, 64.4, 115.7, 137.4; ESIHRMS: Found: m/z 139.1121. Calcd for $C_9H_{15}O$: $(M+H)^+$ 139.1123.

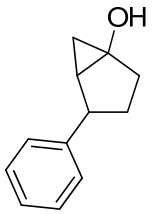
4-Isopropylbicyclo[3.1.0]hexan-1-ol (9d):



Cyclopropanol **9d** was prepared from the corresponding silyl enol ether following the same procedure as **9e**. An inseparable mixture of diastereomers (ca. 4 : 1 for cyclopropanation) was obtained; ^{1}H and ^{13}C NMR are described for the major product.

Yield: 35%. Colorless oil; IR (NaCl) 3374, 2957 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (1H, dd, *J* = 4.4, 4.8 Hz), 0.80 (1H, m), 0.90 (3H, d, *J* = 6.8 Hz), 0.92 (3H, d, *J* = 6.8 Hz), 1.23-1.28 (2H, m), 1.53-1.63 (3H, m), 1.88-1.94 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9, 20.6, 20.7, 25.1, 28.2, 32.2, 33.0, 47.0, 66.4; ESIHRMS: Found: m/z 163.1099. Calcd for $C_9H_{16}ONa$: $(M+Na)^+$ 163.1099.

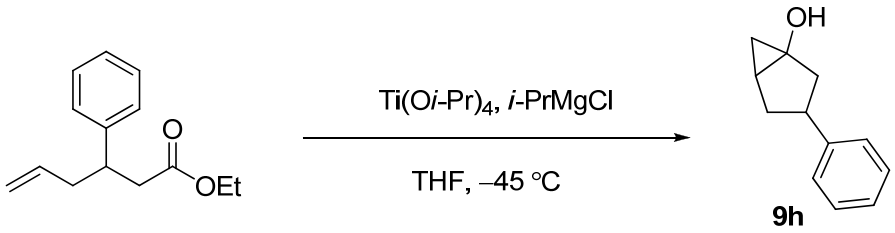
4-Phenylbicyclo[3.1.0]hexan-1-ol (**9f**):



Cyclopropanol **9f** was prepared from the corresponding silyl enol ether following the same procedure as **9e**. Only a single diastereoisomer was obtained.

Yield: 50%. White solid; mp 85-86 °C; IR (KBr) 3584, 3017, 1600, 1489, 1450, 1334, 1215, 1138, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.78 (1H, dd, *J* = 4.4, 5.6 Hz), 1.06 (1H, ddd, *J* = 2.0, 5.6, 9.2 Hz), 1.53 (1H, dd, *J* = 4.4, 9.2 Hz), 1.59-1.71 (2H, m), 2.00 (1H, dd, *J* = 7.6, 11.6 Hz), 2.09-2.18 (1H, m), 2.27 (1H, s br), 3.04 (1H, d, *J* = 7.6 Hz), 7.22 (1H, t, *J* = 7.6 Hz), 7.26 (2H, d, *J* = 7.6 Hz), 7.33 (2H, dd, *J* = 7.6, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 29.9, 30.6, 31.4, 45.1, 65.4, 125.9, 127.1, 128.4, 146.9; ESIHRMS: Found: m/z 175.1118. Calcd for $C_{12}H_{15}O$: $(M+H)^+$ 175.1123.

6.6.1.3 Synthesis of 3-phenylbicyclo[3.1.0]hexan-1-ol (9h):

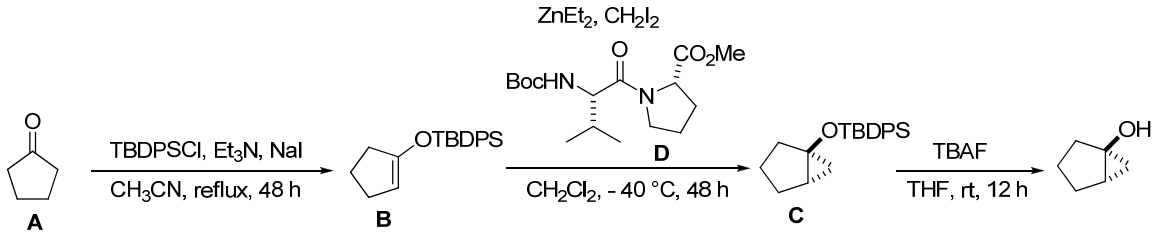


This compound was prepared according to reported procedure.[44]

To a solution of ethyl 3-phenylhex-5-enoate (438.0 mg, 2.01 mmol) and Ti(O*i*-Pr)$_4$ (1.14 mml, 4.02 mmol) in Et_2O (20 mL) was added *i*-PrMgCl (4.0 mL, 8.03 mmol, 2.0 M in THF) at -45 ºC. The mixture was kept at the same temperature for 2 h and then warmed up to 0 ºC for overnight. After addition of THF (6.0 mL) and H_2O (3.0 mL), the resulting white

suspension was filtered through a Celite pad, and the precipitate was washed thoroughly with Et_2O. The aqueous layer was extracted with Et_2O, the combained organic layers were washed with brine and dried over $MgSO_4$. After evaporation of solvent, the resulting crude materials were purified by flash column chromatography (florisil® adsorbent (100-200 mesh); hexane : ethyl acetate = 90 : 10) to give **9h** (55.7 mg, 0.32 mmol) in 16% yield as an inseparable mixture of diastereomers (*ca*. 1.1 : 1); ^1H and ^{13}C NMR are described for the major product. Colorless liquid; IR (NaCl) 3379, 3028, 1602, 1494, 1452, 1344, 1227, 1150, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.62 (1H, dd, *J* = 4.5, 5.4 Hz), 0.84-0.94 (1H, m), 1.47-1.51 (1H, m), 1.68 (1H, ddd, *J* = 1.2, 5.7, 13.2 Hz), 1.98-2.05 (1H, m), 2.16 (1H, ddd, *J* = 1.5, 11.7, 12.0 Hz), 2.32 (1H, dd, *J* = 6.0, 13.2 Hz), 2.43 (1H, dd, *J* = 7.2, 12.0 Hz), 3.61-3.72 (1H, m), 7.14-7.31 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.5, 24.1, 35.2, 40.7, 41.3, 63.5, 126.1, 127.0, 128.3, 143.8; ESIHRMS: Found: m/z 175.1122. Calcd for $C_{12}H_{15}O$: $(M+H)^+$ 175.1123.

6.6.1.4 Synthesis of chiral bicyclo[3.3.1]hexan-1-ol (9a):



Synthesis of silyl enol ether B: To a solution of cyclopentanone (2.00 g, 23.7 mmol), triethylamine (4.13 mL, 29.7 mmol) and *tert*-butylchlorodiphenylsilane (8.58 g, 29.7 mmol) in anhydrous acetonitrile (25 mL) was added NaI (4.44 g, 29.7 mmol) at 0 °C under a nitrogen atmosphere. After stirring under reflux for 48 h, the resulting mixture was diluted with hexane and fitered through a pad of Celite. The precipitate was then washed thoroughly with hexane. The organic materials were extracted with hexane, and the combined hexane solution was washed with brine, and dried over $MgSO_4$. After evaporation of solvent, the

product was purified by flash column chromatography (silica gel; hexane : ethyl acetate = 99 : 1) to give silyl enol ether **B** (6.15 g, 19.1 mmol) in 80% yield.

Colorless liquid; IR (KBr) 2930, 1645 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.73-1.80 (2H, m), 2.10-2.14 (2H, m), 2.21-2.25 (2H, m), 4.39 (1H, dd, *J* = 2.0, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 21.3, 26.6, 28.6, 33.4, 103.5, 127.6, 129.7, 133.4, 135.4, 154.9; ESIHRMS: Found: m/z 323.1822. Calcd for $C_{18}H_{16}NO$: $(M+H)^+$ 323.1831.

Asymmetric cyclopropanation of B (a modified procedure of Shi's asymmetric Simmons Smith cyclopropanation of silyl enol ether[45] was used):

Flask A: Et_2Zn (1.2 mL, 1.2 mmol, 1.0 M in hexane, 1.0 equiv) was added to a solution of dipeptide **D**[46] (394.1 mg, 1.2 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) at room temperature. After 1 h, the solution was cooled to 0 °C, and CH_2I_2 (322.5 mg, 97 μL, 1.2 mmol, 1.0 equiv) was added. The reaction mixture was stiired for additional 0.5 h at 0 °C.

Flask B: To a solution of diethyl zinc (1.2 mL, 1.2 mmol, 1.0 M in hexane, 1.0 equiv) in CH_2Cl_2 (1.0 mL) was added CH_2I_2 (643 mg, 193 μL, 2.4 mmol, 2.0 equiv) at –78 °C, a white precipitate was formed. After stirred for another 1 h at the same temperature, ethyl methoxyacetate (EMA) (142.0 mg, 145 μL, 1.2 mmol, 1.0 equiv) was added. The reaction mixture was warmed to –50 °C at which point a homogenous solution was formed and then re-cooled to –78 °C.

Flask C: A sample of I_2 (152 mg, 0.6 mmol, 0.5 equiv) was added to the third flask, vacuum was applied for 10 seconds and CH_2Cl_2 (1.0 mL) was added. The reaction mixture was cooled to 0 °C, and then Et_2Zn (0.3 mL, 0,3 mmol, 1.0 M in hexane, 0.25 equiv) was

added. After 1 h, the reaction mixture was cooled to –78 °C. The solutions in Flask A and Flask B were then transferred to Flask C via a cannula respectively, followed by the addition of the solution of silyl enol ether **B** (387.0 mg, 1.2 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL). Upon warming to –40 °C and stirring at the same temperature for 48 h, the reaction mixture was poured into hexane and filtered. The filtrate was concentrated and purified by flash column chromatography (silica gel; hexane : ethyl acetate = 98 : 2) to give silyl ether **C** (368 mg, 1.09 mmol) in 91 % yield.

Colorless liquid; $[\alpha]^{20}_D$ = +4.74 (*c* 1.94, $CHCl_3$) (lit. $[\alpha]^{20}_D$ = +3.9 (*c* 1.21, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.35 (1H, dd, *J* = 4.8, 4.8 Hz), 0.74-0.78 (1H, m), 0.84-0.92 (1H, m), 1.03 (9H, s), 1.19-1.52 (4H, m), 1.73-1.83 (2H, m), 7.35-7.44 (6H, m), 7.67-7.70 (4H, m); ^{13}C NMR (100 MHz,$CDCl_3$) δ 14.7, 18.9, 20.9, 24.0, 26.4, 26.9, 33.7, 66.4, 127.42, 127.44, 129.48, 129.52, 134.8, 134.9, 135.8, 135.9.

Synthesis of chiral cyclopropanol 9a: To a solution of silyl ether **C** (348 mg, 1.03 mmol) in THF (2.0 mL) was added a solution of TBAF (406 mg, 1.55 mmol) in THF (1.5 mL) at 0 °C. The reation mixture was stirred at room temperature for 12 h and then quenched by water, and the organic materials were extracted with Et_2O. The Et_2O solution was washed with brine, and dried over $MgSO_4$. The solvent was removed in vacuo and the resulting crude materials were purified by flash column chromatography (silica gel; hexane : diethyl ether = 70 : 30) to give (1*S**,5*S**)-bicyclo[3.1.0]hexan-1-ol (72.8 mg, 0.74 mmol) in 72% yield (85% ee).

Colorless liquid; $[\alpha]^{20}_D$ = –1.68 (*c* 2.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (1H, dd, *J* = 4.8, 5.2 Hz), 0.79-0.83 (1H, m), 1.05-1.14 (1H, m), 1.29 (1H, ddd, *J* = 4.0, 4.4, 9.2 Hz), 1.49 (1H, dd, *J* = 8.0, 12.4 Hz), 1.62 (1H, ddd, *J* = 8.0, 8.4, 13.2 Hz), 1.81-1.94 (2H, m), 2.00

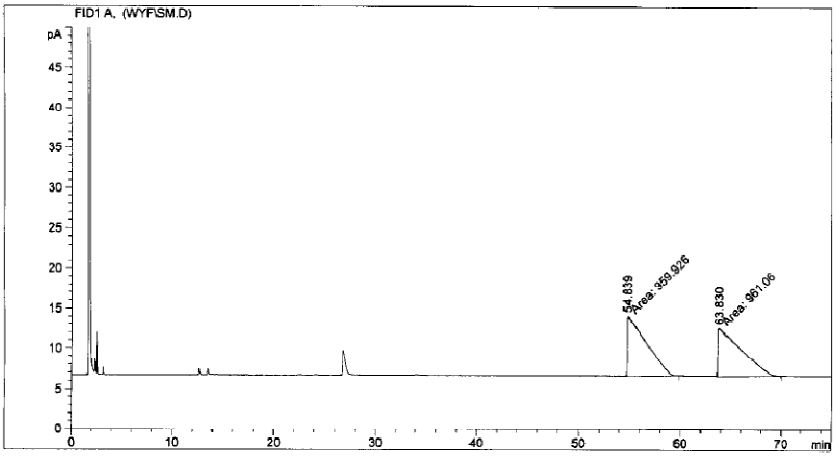
(1H, dd, J = 8.0, 11.2 Hz), 2.40 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 21.2, 24.0, 26.5, 33.5, 64.5.

Determination of enantiomeric excess of 9a

General: Enantioselectivities were determined by capillary GC analysis (Chiraldex B-DM column (30 m x 0.25 mm) using a flame ionization detector.

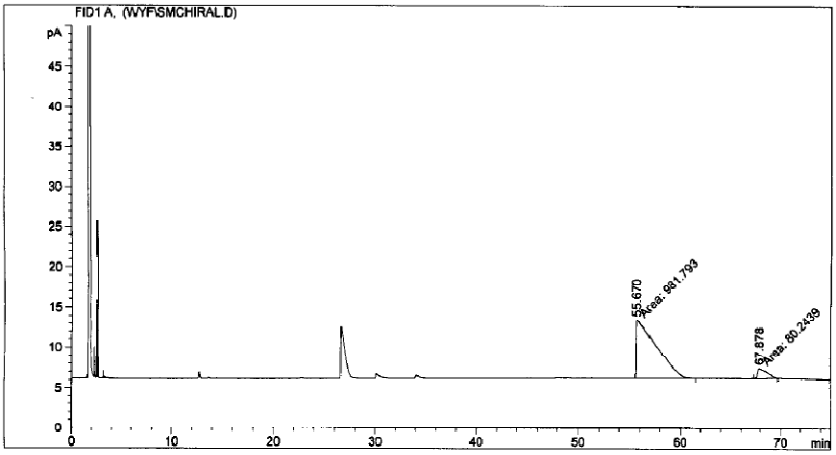
GC Conditions: Column: Chiraldex B-DM (Cat No. 77023), Advanced Separation Technologies, Inc. Oven: 50 °C; Carrier: Helium, head pressure 20 psi; Detection: FID 200 °C

Racemic 9a



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	54.839	MM	2.1148	959.92615	7.56532	49.97050
2	63.830	MM	2.6252	961.05963	6.10140	50.02950
Totals :				1920.98578	13.66673	

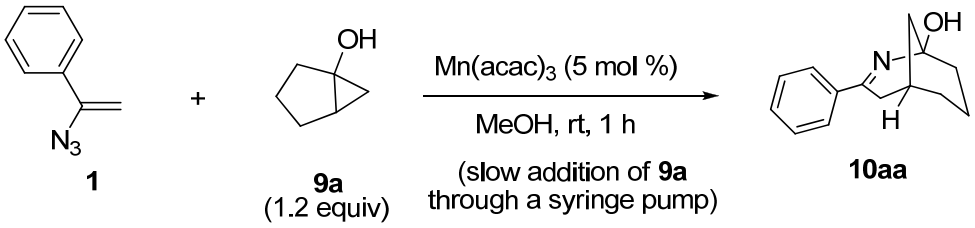
Chiral 9a



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	55.670	MM	2.2617	981.79303	7.23495	92.44434
2	67.878	MM	1.1007	80.24392	1.21505	7.55566
Totals :				1062.03695	8.45000	

6.6.2 $Mn(acac)_3$-catalyzed formation of 2-azabicyclo[3.3.1]non-2-en-1-ol derivatives 10 from vinyl azides 1 with bicyclic cyclopropanols 9 (Section 5.2.1)

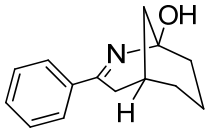
Typical procedure:

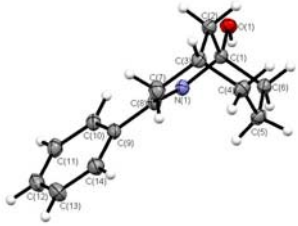


To a solution of α-azido styrene (**1a**) (1.45 g, 10.0 mmol) and $Mn(acac)_3$ (0.35 g, 1.0 mmol) in MeOH (100 mL) was added a solution of bicyclo[3.1.0]hexan-1-ol (**9a**) (1.18 g, 12.0 mmol) in MeOH (30 mL) via a syring pump over 4 h. The reaction mixture was qunched with

pH 9 ammonium buffer and then extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (silica gel; hexane : ethyl acetate = 60 : 40) afforded **10aa** (1.87 g, 8.7 mmol) in 87% yield.

(1*S,5*S**)-3-Phenyl-2-azabicyclo[3.3.1]non-2-en-1-ol (10aa):**





Colorless crystal (CCDC-735782);[47] mp 119-120 °C; IR (KBr) 3580, 2930, 1632, 1579, 1446, 1357, 1215, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18-1.30 (1H, m), 1.47–1.69 (5H, m), 1.81-1.84 (1H, m), 1.90 (1H, dd, *J* = 2.8, 12.0 Hz), 2.42 (1H, d, *J* = 18.8 Hz), 2.50-2.52 (1H, m), 2.61 (1H, s br), 2.83 (1H, dd, *J* = 6.8, 18.8 Hz), 7.38-7.41 (3H, m), 7.84 (2H, dd, *J* = 1.6, 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 27.9, 31.9, 33.4, 36.1, 37.6, 84.0, 126.4, 128.2, 130.0, 138.5, 165.7; ESIHRMS: Found: m/z 216.1390. Calcd for $C_{14}H_{18}NO$: $(M+H)^+$ 216.1388.

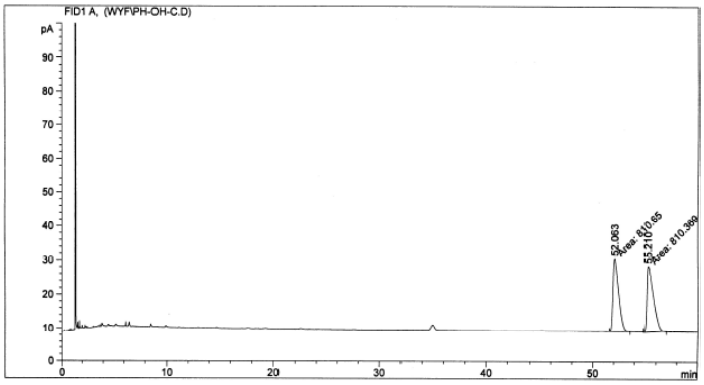
The reaction of vinyl azide **1a** (50.4 mg, 0.347 mmol) with chiral bicyclo[3.1.0]hexan-1-ol (**9a**) (85% ee, 40.9 mg, 0.417 mmol) using 5 mol % $Mn(acac)_3$ afforded *racemic* **10aa** (62.5 mg, 0.290 mmol) in 84% yield.

Determination of enantiomeric excess of 9a

General: Enantioselectivities were determined by capillary GC analysis (Chiraldex B-DM column (30 m x 0.25 mm) using a flame ionization detector.

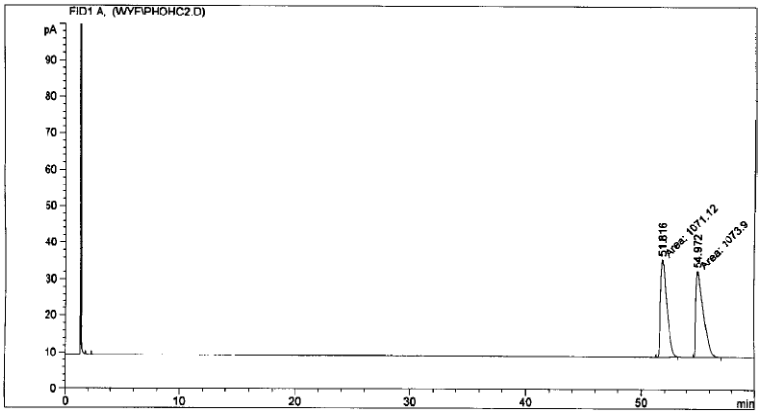
GC Conditions: Column: Chiraldex B-DM (Cat No. 77023), Advanced Separation Technologies, Inc. Oven: 150 °C; Carrier: Helium, head pressure 27 psi; Detection: FID 250 °C

Racemic 10aa:



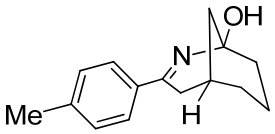
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	52.063	MM	0.6316	810.64984	21.39109	50.00368
2	55.210	MM	0.6985	810.36853	19.33482	49.99132
Totals :				1621.01837	40.72590	

10aa obtained by the reaction with chiral 9a:



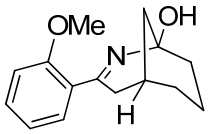
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	51.816	MM	0.6644	1071.12158	26.86929	49.93530
2	54.972	MM	0.7559	1073.89709	23.67736	50.06470
Totals :				2145.01868	50.54665	

(1*S,5*S**)-3-*p*-Tolyl-2-azabicyclo[3.3.1]non-2-en-1-ol (10ba):**



White solid; mp 122-123 °C; IR (NaCl) 3404, 2931, 1707, 1609, 1416, 1452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15-1.30 (1H, m), 1.45-1.68 (5H, m), 1.81–1.86 (1H, m), 1.88 (1H, dd, *J* = 3.2, 16.4 Hz), 2.37 (3H, s), 2.41 (1H, d, *J* = 20.0 Hz), 2.48-2.50 (1H, m), 2.80 (1H, dd, *J* = 6.9, 18.6 Hz), 2.87 (1H, s br), 7.19 (2H, d, *J* = 8.0 Hz), 7.73 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 21.3, 28.1, 32.0, 33.4, 36.3, 37.8, 84.1, 126.4, 129.0, 135.9, 140.2, 165.4; ESIHRMS: Found: m/z 230.1550. Calcd for $C_{15}H_{20}NO$: $(M+H)^+$ 230.1545.

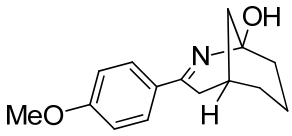
(1*S, 5*S**)-3-(2-Methoxyphenyl)-2-azabicyclo[3.3.1]non-2-en-1-ol (10ca):**



White solid; mp 124-125 °C; IR (NaCl) 3422, 2928, 1624, 1602, 1420, 1246, 1130 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50-1.77 (6H, m), 1.82–1.85 (1H, m), 1.89 (1H, dd, *J* = 2.8, 12.4 Hz), 2.42 (1H, d, *J* = 19.2 Hz), 2.43 (1H, m), 2.70 (1H, s br), 2.77 (1H, dd, *J* = 6.8, 19.2 Hz), 3.86 (3H, s), 6.93 (1H, d, *J* = 8.0 Hz), 6.99 (1H, dd, *J* = 7.2, 7.6 Hz), 7.33 (1H, d, *J* = 7.6 Hz) 7.34 (1H, dd, *J* = 7.2, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 28.3, 31.9, 35.9, 36.6,

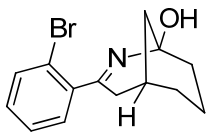
37.8, 55.5, 83.9, 111.1, 120.8, , 128.8, 130.0, 130.4, 156.7, 169.9; ESIHRMS: Found: m/z 246.1493. Calcd for $C_{15}H_{20}NO_2$: $(M+H)^+$ 246.1494.

(1*S, 5*S**)-3-(4-Methoxyphenyl)-2-azabicyclo[3.3.1]non-2-en-1-ol (10da):**



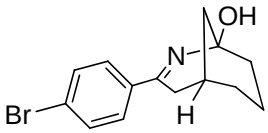
White solid; mp 120-121 °C; IR (NaCl) 3421, 2932, 1624, 1574, 1452, 1244, 1119 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20-1.27 (1H, m), 1.46–1.67 (5H, m), 1.80-1.83 (1H, m), 1.88 (1H, d, *J* = 12.4 Hz), 2.39 (1H, d, *J* = 18.8 Hz), 2.49 (1H, m), 2.73 (1H, s br), 2.79 (1H, dd, *J* = 6.8, 18.8 Hz), 3.84 (3H, s), 6.90 (2H, d, *J* = 8.4 Hz), 7.80 (2H, d, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 28.1, 32.0, 33.1, 36.3, 37.7, 55.3, 84.0, 113.5, 128.0, 131.2, 161.2, 164.6; ESIHRMS: Found: m/z 246.1495. Calcd for $C_{15}H_{20}NO_2$: $(M+H)^+$ 246.1494.

(1*S,5*S**)-3-(2-Bromophenyl)-2-azabicyclo[3.3.1]non-2-en-1-ol (10oa):**



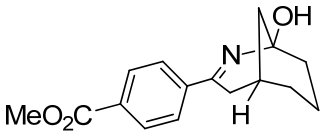
White solid; mp 145-146 °C; IR (NaCl) 3420, 2924, 1707, 1647, 1138, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.63-1.75 (5H, m), 1.86–1.91 (2H, m), 2.34 (1H, d, *J* = 19.6 Hz), 2.38-2.46 (1H, m), 2.69 (1H, dd, *J* = 6.6, 19.6 Hz), 2.77 (1H, s br), 7.21 (1H, ddd, *J* = 1.8, 7.5, 7.8 Hz), 7.27 (1H, dd, *J* = 1.8, 7.2 Hz), 7.34 (1H, dd, *J* = 7.2, 7.5 Hz), 7.57 (1H, d, *J* = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 28.0, 31.6, 35.9, 36.8, 37.4, 83.9, 119.9, 127.6, 128.9, 129.7, 133.1, 141.9, 170.1; ESIHRMS: Found: m/z 294.0492. Calcd for $C_{14}H_{17}NOBr$: $(M+H)^+$ 294.0494.

(1*S,5*S**)-3-(4-Bromophenyl)-2-azabicyclo[3.3.1]non-2-en-1-ol (10pa):**



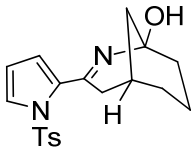
White solid; mp 149-150 °C; IR (NaCl) 3582, 2928, 1711, 1628, 1586, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13-1.25 (1H, m), 1.47–1.68 (5H, m), 1.80-1.83 (1H, m), 1.89 (1H, dd, *J* = 1.6, 11.6 Hz), 2.36 (1H, d, *J* = 18.8 Hz), 2.51-2.52 (1H, m), 2.72 (1H, s br), 2.78 (1H, dd, *J* = 7.2, 18.8 Hz), 7.52 (1H, d, *J* = 8.4 Hz), 7.72 (1H, d, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 28.0, 31.9, 33.2, 36.0, 37.6, 84.2, 124.6, 128.1, 131.4, 137.3, 164.4; ESIHRMS: Found: m/z 294.0490. Calcd for $C_{14}H_{17}NOBr$: $(M+H)^+$ 294.0494.

Methyl 4-((1*S,5*S**)-1-hydroxy-2-azabicyclo[3.3.1]non-2-en-3-yl)benzoate (10qa):**



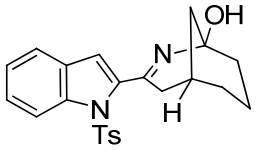
Pale yellow solid; mp 142-143 °C; IR (NaCl) 3580, 2930, 1719, 1630, 1568, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17–1.26 (1H, m), 1.47-1.70 (5H, m), 1.81–1.86 (1H, m), 1.90 (1H, d, *J* = 3.0, 12.0 Hz), 2.41 (1H, d, *J* = 18.9 Hz), 2.52-2.54 (1H, m), 2.70 (1H, s br), 2.83 (1H, dd, *J* = 6.9, 18.9 Hz), 3.93 (3H, s), 7.88 (2H, d, *J* = 8.4 Hz), 8.05 (1H, d, *J* = 8.4 Hz); ^{13}C NMR (75 MHz, CDCl3) δ 19.3, 28.0, 31.9, 33.5, 36.0, 37.6, 52.2, 84.3, 126.5, 129.6, 131.3, 142.5, 164.8, 166.7; ESIHRMS: Found: m/z 274.1445. Calcd for $C_{16}H_{20}NO_3$: $(M+H)^+$ 274.1443.

(1*S,5*S**)-3-(1-Tosyl-1*H*-pyrrol-2-yl)-2-azabicyclo[3.3.1]non-2-en-1-ol (10fa):**



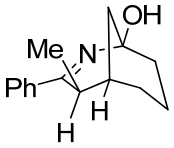
White solid; mp 168-169 °C (decomposed); IR (KBr) 3573, 3013, 2917, 1642, 1597, 1460, 1361, 1214 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30-1.44 (2H, m), 1.51–1.66 (5H, m), 1.74 (1H, dd, *J* = 3.2, 12.0 Hz), 2.61 (1H, s br), 2.18 (1H, d, *J* = 18.8 Hz), 2.37-2.39 (1H, m), 2.39 (3H, s), 2.75 (1H, dd, *J* = 6.8, 18.8 Hz), 6.29 (1H, dd, *J* = 3.2, 3.6 Hz), 6.51 (1H, dd, *J* = 1.6, 3.2 Hz), 7.28 (2H, d, *J* = 8.0 Hz), 7.51 (1H, dd, *J* = 1.6, 3.6 Hz), 7.73 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 21.6, 28.0, 31.6, 35.2, 35.9, 37.5, 84.0, 111.0, 116.4, 126.2, 126.9, 129.4, 134.2, 138.0, 144.2, 159.0; ESIHRMS: Found: m/z 359.1424. Calcd for $C_{19}H_{23}N_2O_3S$: $(M+H)^+$ 359.1429.

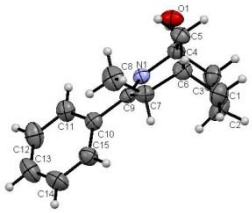
(1*S,5*S**)-3-(1-Tosyl-1*H*-indol-2-yl)-2-azabicyclo[3.3.1]non-2-en-1-ol (10ga):**



White solid; mp 158-159 °C; IR (KBr) 3589, 3018, 2943, 1635, 1598, 1452, 1370, 1215, 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50-1.71 (5H, m), 1.87–1.96 (3H, m), 2.27 (3H, s), 2.39 (1H, d, *J* = 19.2 Hz), 2.48-2.52 (1H, m), 2.90 (1H, s br), 3.11 (1H, dd, *J* = 6.8, 19.2 Hz), 6.73 (1H, s), 7.12 (2H, d, *J* = 8.0 Hz), 7.21 (1H, dd, *J* = 8.0, 8.0 Hz), 7.33 (1H, dd, *J* = 8.0, 8.4 Hz), 7.43 (1H, d, *J* = 8.0 Hz), 7.67 (2H, d, *J* = 8.0 Hz), 8.10 (1H, d, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 21.5, 28.1, 31.8, 35.6, 37.7, 37.8, 84.2, 113.0, 115.7, 121.5, 124.3, 125.5, 127.1, 129.5, 130.1, 134.1, 137.5, 140.5, 144.8, 164.5; ESIHRMS: Found: m/z 409.1578. Calcd for $C_{23}H_{25}N_2O_3S$: $(M+H)^+$ 409.1586.

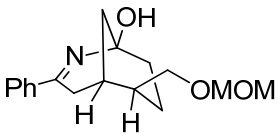
(1*S,4**R*,5*S**)-4-Methyl-3-phenyl-2-azabicyclo[3.3.1]non-2-en-1-ol (10ha):**





An inseparable mixture (*exo* : *endo* = 85 : 15). A pure *exo* isomer was obtained by recrystallization from ethyl acetate/hexane; ^{1}H and ^{13}C NMR are described for the *exo* isomer. Colorless crystal (CCDC-735783);[47] mp 153-154 °C; IR (KBr) 3594, 3019, 2942, 1623, 1598, 1457, 1215, 1110 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, d, *J* = 7.2 Hz), 1.25–1.32 (1H, m), 1.49–1.78 (7H, m), 2.11 (1H, m), 2.66 (1H, q, *J* = 7.2 Hz), 2.73 (1H, s br), 7.38-7.40 (3H, m), 7.68-7.71 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 19.9, 31.9, 32.1, 36.1, 36.6, 37.6, 84.6, 127.0, 128.4, 129.5, 138.8, 171.1; ESIHRMS: Found: m/z 230.1547. Calcd for $C_{15}H_{20}NO$: $(M+H)^+$ 230.1545.

(1*S,5*S**,6*S**)-6-((Methoxymethoxy)methyl)-3-phenyl-2-azabicyclo[3.3.1]non-2-en-1-ol (10ab):**

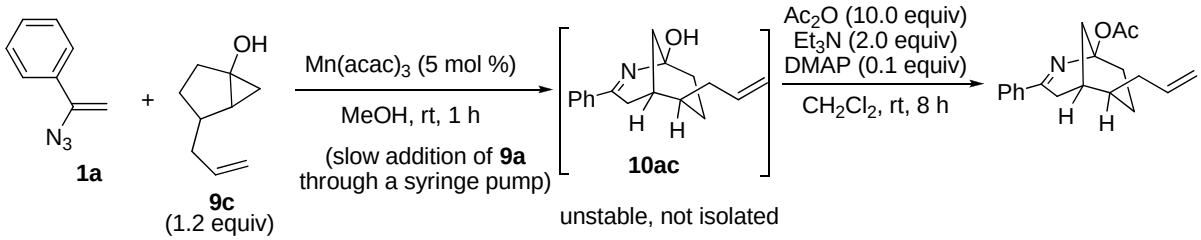


An inseparable mixture (*exo* : *endo* = 85 : 15); ^{1}H and ^{13}C NMR are described for the *exo* isomer.

Pale yellow solid; mp 48-52 °C; IR (KBr) 3594, 3019, 2948, 1631, 1581, 1450, 1215, 1112, 1039 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33-1.42 (1H, m), 1.50-1.56 (2H, m), 1.69-1.78 (2H, m), 1.82-1.91 (1H, m), 1.94-1.97 (1H, m), 2.42 (1H, d, *J* = 18.8 Hz), 2.51 (1H, m), 2.92

(1H, dd, *J* = 7.2, 18.8 Hz), 3.52 (3H, s), 3.52 (1H, dd, *J* = 7.6, 9.2 Hz), 3.62 (1H, dd, *J* = 8.4, 9.2 Hz), 4.08 (1H, s br), 4.63 (2H, s), 7.37-7.40 (3H, m), 7.79 (2H, dd, *J* = 1.6, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 29.1, 31.2, 33.1, 35.1, 39.2, 55.1, 68.3, 84.0, 96.4, 126.4, 128.2, 130.1, 138.3, 165.6; ESIHRMS: Found: m/z 290.1755. Calcd for $C_{17}H_{24}NO_3$: $(M+H)^+$ 290.1756.

(1*S,5*S**,6*S**)-6-Allyl-3-phenyl-2-azabicyclo[3.3.1]non-2-en-1-yl acetate (10ac'):**

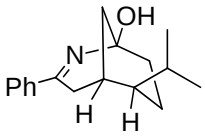


Compound **10ac** was prepared according to the same procedure as **10aa** from vinyl azide **1a** (43.8 mg, 0.30 mmol) and cyclopropanol **9c** (50.2 mg, 0.36 mmol) by using $Mn(acac)_3$ (11.6 mg, 0.03 mmol) as a catalyst. However, compound **10ac** itself was too unstable to be isolated. Therefore, the crude product **10ac** (71.1 mg, 0.28 mmol) was then treated with Ac_2O (0.30 mL, 2.79 mmol), DMAP (4.0 mg, 0.03 mmol), and Et_3N (80 μL, 0.56 mmol) in CH_2Cl_2 (1.0 mL) at room temperature for 8 h. After that, the reaction was diluted with CH_2Cl_2 and water, the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (silica gel; hexane : ethyl acetate = 90 : 10) afforded **10ac'** (60.2 mg, 0.20 mmol) in 67% yield (from **1a**).

An inseparable mixture (*exo* : *endo* = 86 : 14); ^{1}H and ^{13}C NMR are described for the *exo* isomer.

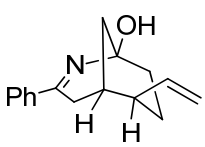
Yellow liquid; IR (NaCl) 3561, 2932, 1730, 1634, 1447, 1252 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44-1.48 (2H, m), 1.61-1.63 (1H, m), 1.75-1.78 (1H, m), 2.09 (3H, s), 2.20-2.33 (6H, m), 2.46 (1H, d, *J* = 18.8 Hz), 2.95 (1H, dd, *J* = 6.4, 18.8 Hz), 5.00-5.09 (2H, m), 5.70-5.80 (1H, m), 7.37-7.38 (3H, m), 7.80 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 22.8, 28.0, 29.1, 31.8, 35.4, 36.2, 39.0, 93.8, 116.2, 126.6, 128.2, 130.0, 137.2, 138.6, 165.6, 170.0; ESIHRMS: Found: m/z 298.1805. Calcd for $C_{19}H_{24}NO_2$: $(M+H)^+$ 298.1807.

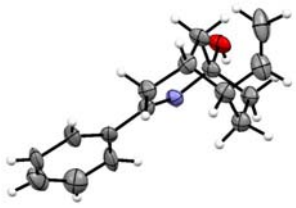
(1*S,5*S**,6*S**)-6-Isopropyl-3-phenyl-2-azabicyclo[3.3.1]non-2-en-1-ol (10ad):**



An inseparable mixture (*exo* : *endo* = 85 : 15). A pure *exo* isomer was obtained by recrystallization from ethyl acetate/hexane; ^1H and ^{13}C NMR are described for the *exo* isomer. Colorless crystal; mp 142-143 °C; IR (NaCl) 3581, 3016, 1708, 1630, 1533, 1215, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, d, *J* = 6.4 Hz), 0.98 (3H, d, *J* = 6.4 Hz), 1.02-1.05 (1H, m), 1.27 -1.31 (1H, m), 1.47-1.51 (1H, m), 1.61-1.89 (4H, m), 1.99 (1H, dd, *J* = 2.4, 12.4 Hz), 2.39 (1H, d, *J* = 19.2 Hz), 2.56 (1H, m), 2.83 (1H, s br), 2.95 (1H, dd, *J* = 7.2, 19.2 Hz), 7.28-7.43 (3H, m), 7.84 (2H, dd, *J* = 2.4, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 21.0, 21.9, 26.2, 29.3, 31.2, 33.2, 35.3, 46.8, 84.1, 126.4, 128.3, 130.0, 138.6, 165.2; ESIHRMS: Found: m/z 258.1857. Calcd for $C_{17}H_{24}NO$: $(M+H)^+$ 258.1858.

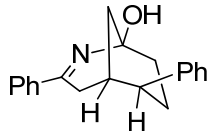
(1*S,5*S**,6*R**)-3-Phenyl-6-vinyl-2-azabicyclo[3.3.1]non-2-en-1-ol** (**10ae**)**:**

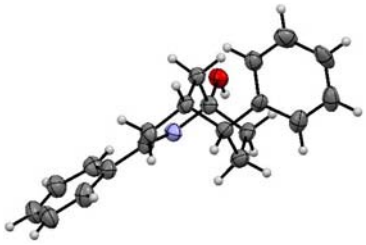




An inseparable mixture (*exo* : *endo* = 83 : 17). A pure *exo* isomer was obtained by recrystallization from ethyl acetate/hexane; ^{1}H and ^{13}C NMR are described for the *exo* isomer. Colorless crystal (CCDC-735784);[47] mp 113-114 °C; IR (KBr) 3594, 3019, 1637, 1598, 1450, 1215, 1107 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42-1.51 (1H, m), 1.62-1.68 (3H, m), 1.87 (1H, ddd, *J* = 4.4, 12.8, 13.6 Hz), 2.07 (1H, dd, *J* = 2.8, 12.4 Hz), 2.27 (1H, m), 2.44 (1H, m), 2.48 (1H, d, *J* = 18.8 Hz), 2.64 (1H, s br), 2.95 (1H, dd, *J* = 7.2, 18.8 Hz), 5.13-5.17 (2H, m), 5.99 (1H, ddd, *J* = 6.0, 10.8, 17.0 Hz), 7.39-7.43 (3H, m), 7.84 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 31.3, 33.2, 33.3, 34.7, 42.5, 84.2, 114.8, 126.4, 128.3, 130.1, 138.5, 140.4, 164.9; ESIHRMS: Found: m/z 242.1546. Calcd for $C_{16}H_{20}NO$: $(M+H)^+$ 242.1545.

(1*S,5*S**,6*R**)-3,6-Diphenyl-2-azabicyclo[3.3.1]non-2-en-1-ol (10af):**

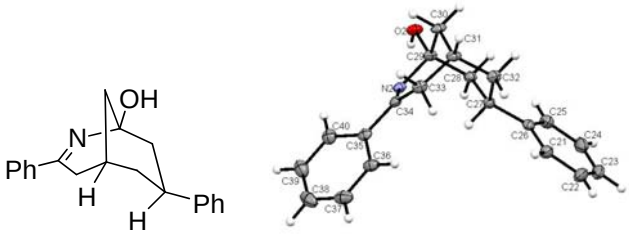




An inseparable mixture (*exo* : *endo* = 94 : 6). A pure *exo* isomer was obtained by recrystallization from ethyl acetate/hexane; ^{1}H and ^{13}C NMR are described for the *exo* isomer. Colorless crystal (CCDC-735785);[47] mp 183-184 °C; IR (KBr) 3587, 3014, 1629, 1579, 1446, 1215, 1117 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44-1.48 (1H, m), 1.64-1.73 (1H, m), 1.81-1.86 (1H, m), 1.90 (1H, dd, *J* = 7.2 Hz), 2.04 (1H, ddd, *J* = 4.4, 13.2, 13.6 Hz), 2.13-2.17 (1H, m), 2.68 (1H, d, *J* = 18.8 Hz), 2.82 (1H, s br), 2.87-2.91 (2H, m), 3.08 (1H, dd, *J* = 7.2, 18.8 Hz), 7.23 (1H, t, *J* = 7.2 Hz), 7.35 (2H, dd, *J* = 7.2, 8.0 Hz), 7.41-7.45 (5H, m), 7.89 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 30.8, 34.0, 34.4, 35.1, 43.0, 84.1, 125.9, 126.5, 127.2,

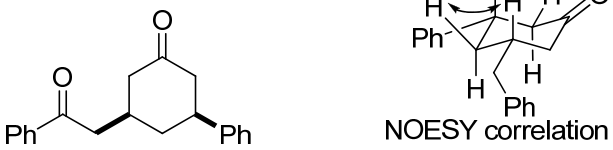
128.33, 128.35, 130.2, 138.5, 143.3, 164.7; ESIHRMS: Found: m/z 292.1699. Calcd for $C_{20}H_{22}NO$: $(M+H)^+$ 292.1701.

(1*R,5*S**,7*S**)-3,7-Diphenyl-2-azabicyclo[3.3.1]non-2-en-1-ol (10ah):**



Colorless crystal; mp 162-163 °C; IR (NaCl) 3446, 2924, 1631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.73-1.78 (2H, m), 1.84-1.91 (2H, m), 2.02 (1H, dd, *J* = 3.0, 12.2 Hz), 2.08-2.13 (1H, m), 2.54-2.66 (3H, m), 2.85 (1H, s br), 3.93 (1H, dd, *J* = 6.8, 18.8 Hz), 7.17-7.20 (3H, m), 7.28-7.30 (2H, m), 7.43-7.46 (3H, m), 7.88-7.91 (2H, dd, *J* = 2.0, 7.6 Hz); ^{13}C NMR (100 MHz, CDCl3) δ 28.1, 33.6, 35.8, 37.5, 39.9, 45.0, 84.3, 126.3, 126.5, 127.0, 128.35, 128.43, 130.3, 138.4, 144.6, 165.6; ESIHRMS: Found: m/z 292.1704. Calcd for $C_{20}H_{22}NO$: $(M+H)^+$ 292.1701.

(3*S,5*R**)-3-(2-Oxo-2-phenylethyl)-5-phenylcyclohexanone (11ah)**:



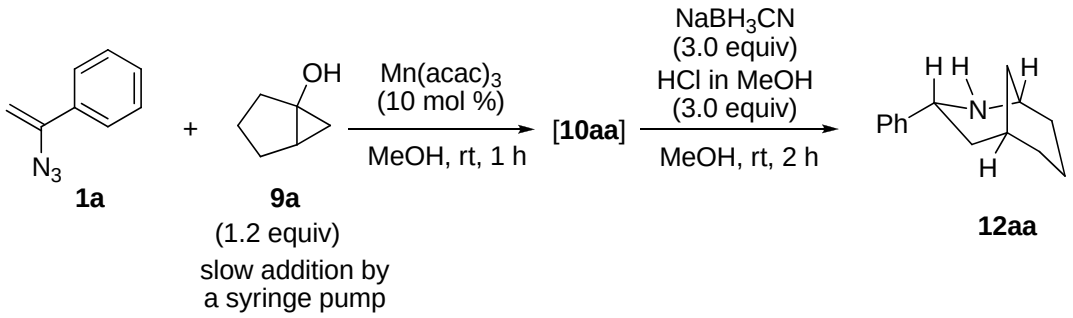
The structure of **11ah** was determined by ^1H and ^{13}C NMR, ^1H-^1H COSY, HMBC, and HMQC spectra. The stereochemistry was deduced by NOESY correlation analysis.

White solid; mp 87-88 ^oC; IR (NaCl) 3026, 2955, 1713, 1682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.70 (1H, ddd, *J* = 12.0, 12.0, 13.0 Hz), 2.23-2.29 (2H, m), 2.52 (1H, dd, 13.5, 14.0

Hz), 2.60-2.68 (3H, m), 3.02-3.14 (3H, m), 7.24-7.27 (3H, m), 7.35 (2H, dd, *J* = 7.5, 7.5 Hz), 7.50 (2H, dd, *J* = 7.5, 7.5 Hz), 7.60 (1H, t, *J* = 7.5 Hz), 7.95-7.97 (2H, d, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.1, 39.4, 43.3, 45.1, 47.2, 48.5, 126.5, 126.8, 128.0, 128.69, 128.70, 133.3, 136.8, 143.8, 198.1, 209.4; ESIHRMS: Found: m/z 293.1547. Calcd for $C_{20}H_{21}O$: $(M+H)^+$ 293.1542.

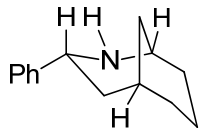
6.6.3 One-pot preparation of 2-azabicyclo[3.3.1]nonanes from vinyl azides and bicyclo[3.1.0]hexan-1-ols (Section 5.2.3)

Typical procedure:



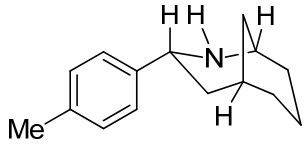
To a solution of (1-azidovinyl)benzene (**1a**) (44.2 mg, 0.305 mmol) and $Mn(acac)_3$ (10.6 mg, 0.030 mmol) in MeOH (2 mL) was added a solution of bicyclo[3.1.0]hexan-1-ol (**9a**) (35.9 mg, 0.365 mmol) in methanol (1 mL) via a syring pump over 1 h. Sodium cyanoborohydride (57.4 mg, 0.913 mmol) followed by HCl (0.30 mL, 0.913 mmol, 3.0 N in MeOH) was added to the mixture and stirred for 2 h at room temperature. The reaction was then quenched by addition of saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (aluminum oxide, pH = 10; CH_2Cl_2 : MeOH = 99: 1) afforded **12aa** (43.0 mg, 0.21 mmol) in 70% yield.

(1*R,3*R**,5*S**)-3-phenyl-2-azabicyclo[3.3.1]nonane (12aa):**



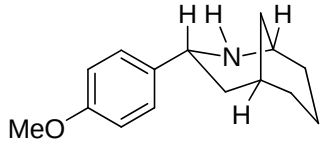
Pale yellow crystal (CCDC-735786);[47] mp 79-80 °C; IR (KBr) 3423, 3019, 2930, 1455, 1215, 1123, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26-1.63 (8H, m), 2.07-2.29 (4H, m), 3.47 (1H, m), 4.14 (1H, dd, *J* = 4.4, 12.4 Hz), 7.24 (1H, t, *J* = 7.2 Hz), 7.32 (2H, dd, *J* = 7.2, 7.6 Hz), 7.46 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 25.0, 28.8, 33.2, 34.7, 37.9, 46.5, 52.6, 126.8, 126.9, 128.2, 146.2; ESIHRMS: Found: m/z 202.1598. Calcd for $C_{14}H_{20}N$: $(M+H)^+$ 202.2596.

(1*R,3*R**,5*S**)-3-*p*-Tolyl-2-azabicyclo[3.3.1]nonane (12ba):**



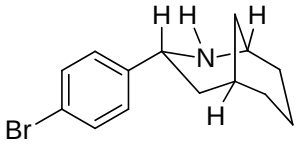
White solid; mp 102-104 °C; IR (NaCl) 3340, 3019, 2930, 1514, 1456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24-1.27 (1H, m) 1.36-1.58 (7H, m), 2.08-2.23 (4H, m), 2.33 (3H, m), 3.45 (1H, s br), 4.10 (1H, dd, *J* = 4.8, 12.8 Hz), 7.13 (2H, d, *J* = 8.0 Hz), 7.34 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 21.1, 25.0, 28.8, 33.3, 34.7, 37.9, 46.6, 52.3, 126.8, 128.9, 136.4, 143.2; ESIHRMS: Found: *m/z* 216.1751. Calcd for $C_{15}H_{22}N$: $(M+H)^+$ 216.1752.

(1*R,3*R**,5*S**)-3-(4-Methoxyphenyl)-2-azabicyclo[3.3.1]nonane (12da):**



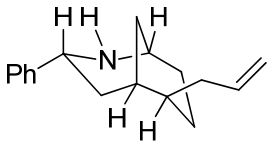
Colourless crystal; mp 51-53 °C; IR (NaCl) 3390, 3015, 2932, 1611, 1512, 1244 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23-1.60 (8H, m), 2.01-2.28 (4H, m), 3.44 (1H, s br), 3.79 (3H, s), 4.08 (1H, dd, *J* = 4.5, 12.3 Hz), 6.85 (2H, d, *J* = 8.7 Hz), 7.37 (2H, d, *J* = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7, 25.0, 28.7, 33.3, 34.7, 37.9, 46.6, 51.9, 55.2, 113.6, 127.9, 138.4, 158.5; ESIHRMS: Found: *m/z* 232.1704. Calcd for $C_{15}H_{22}NO$: $(M+H)^+$ 232.1701.

(1*R,3*R**,5*S**)-3-(4-Bromophenyl)-2-azabicyclo[3.3.1]nonane (12pa):**



White solid; mp 93-95 °C; IR (NaCl) 3333, 3017, 2928, 1487 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25-1.60 (8H, m), 2.01-2.25 (4H, m), 3.44 (1H, br), 4.09 (1H, dd, *J* = 4.8, 12.6 Hz), 7.33 (2H, d, *J* = 8.4 Hz), 7.42 (2H, d, *J* = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7, 25.0, 28.8, 33.2, 34.7, 38.1, 46.4, 52.1, 120.4, 128.7, 131.3, 145.5; ESIHRMS: Found: *m/z* 280.0696. Calcd for $C_{14}H_{19}NBr$: $(M+H)^+$ 280.0701.

(1*R, 3*R**, 5*S**, 6*S**)-6-Allyl-3-phenyl-2-azabicyclo[3.3.1]nonane (12ac):**

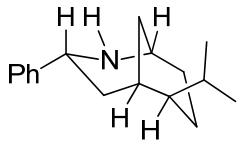


An inseparable mixture (*exo* : *endo* = 81 : 19). ^1H and ^{13}C NMR are described for the *exo* isomer.

White solid; mp 60-62 °C; IR (NaCl) 3341, 3073, 2924, 1638, 1601, 1557, 1489 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40-1.52 (5H, m), 1.78-1.88 (2H, m), 1.92-2.02 (2H, m), 2.15-2.26 (2H, m), 2.40-2.51 (1H, m), 3.43 (1H, m), 4.22 (1H, dd, *J* = 4.8, 12.3 Hz), 4.92-5.05 (2H, m), 5.69-5.86 (1H, m), 7.23 (1H, t, *J* = 7.2 Hz), 7.32 (2H, dd, *J* = 7.2, 7.5 Hz), 7.46 (2H, d, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 22.7, 29.1, 29.9, 36.1, 39.8, 40.2, 46.4,

53.0, 115.2, 126.90, 126.92, 128.2, 138.4, 145.8; ESIHRMS: Found: *m/z* 242.1913. Calcd for $C_{17}H_{24}N$: $(M+H)^+$ 242.1909.

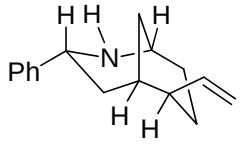
(1*R, 3*R**, 5*S**, 6*S**)-6-Isopropyl-3-phenyl-2-azabicyclo[3.3.1]nonane (12ad):**



An inseparable mixture (*exo* : *endo* = 82 : 18). ^{1}H and ^{13}C NMR are described for the *exo* isomer.

White solid; mp 69-77 °C; IR (NaCl) 3349, 3022, 2940, 1634, 1366, 1136 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, d, *J* = 6.8 Hz), 0.96 (3H, d, *J* = 6.8 Hz), 1.37-1.67 (7H, m), 1.81-1.86 (1H, m), 1.97-2.00 (1H, m), 2.16-2.22 (2H, m), 2.35-2.40 (1H, m), 3.41 (1H, br), 4.21 (1H, dd, *J* = 4.8, 12.8 Hz), 7.23 (1H, t, *J* = 7.2 Hz), 7.32 (2H, dd, *J* = 7.2, 7.6 Hz), 7.46 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 21.3, 22.4, 23.1, 26.0, 26.5, 30.7, 39.7, 46.5, 47.9, 53.1, 126.9, 127.0, 128.3, 146.1; ESIHRMS: Found: *m/z* 244.2067. Calcd for $C_{17}H_{26}N$: $(M+H)^+$ 244.2065.

(1*R, 3*R**, 5*S**, 6*R**)-6-Vinyl-3-phenyl-2-azabicyclo[3.3.1]nonane (12ae):**

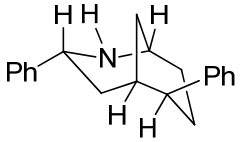


An inseparable mixture (*exo* : *endo* = 81 : 19). ^{1}H and ^{13}C NMR are described for the *exo* isomer.

Yellow liquid; IR (NaCl) 3348, 3024, 2930, 1636, 1603, 1574 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42-1.64 (6H, m), 1.99-2.27 (4H, m), 2.54-2.56 (1H, m), 3.44 (1H. br), 4.21 (1H, d, *J* = 4.6, 12.3 Hz), 5.05-5.15 (2H, m), 5.98-6.09 (1H, m), 7.21-7.34 (3H, m), 7.46 (2H, d, *J* =

7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 23.3, 30.4, 30.7, 39.6, 43.9, 46.0, 53.0, 113.8, 126.91, 126.94, 128.3, 142.0, 146.1; ESIHRMS: Found: *m/z* 228.1750. Calcd for $C_{16}H_{22}N$: $(M+H)^+$ 228.1752.

(1*R, 3*R**, 5*S**, 6*R**)-6-Phenyl-3-phenyl-2-azabicyclo[3.3.1]nonane (12af):**



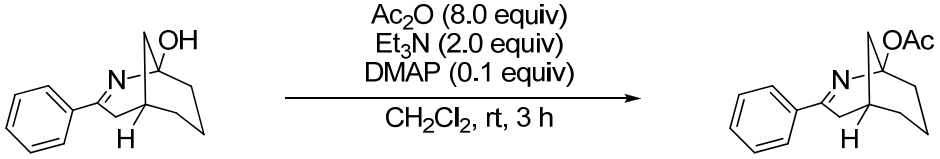
An inseparable mixture (*exo* : *endo* = 90 : 10). ^{1}H and ^{13}C NMR are described for the *exo* isomer.

Yellow liquid; IR (NaCl) 3356, 3024, 2932, 1601, 1568 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33-1.38 (1H, m), 1.62-1.78 (2H, m), 1.96-2.01 (4H, m), 2.31-2.41 (1H, m), 2.47-2.51 (1H, m), 2.70-2.83 (2H, m), 3.53 (1H, s br), 4.26 (1H, dd, *J* = 4.5, 12.3 Hz), 7.17-7.37 (6H, m), 7.44 (2H, d, *J* = 7.5 Hz), 7.51 (2H, d, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 22.8, 31.5, 32.0, 40.1, 44.7, 46.3, 53.2, 125.4, 127.0 (overlapped), 127.8, 128.0, 128.3, 145.3, 146.0; ESIHRMS: Found: *m/z* 278.1911. Calcd for $C_{20}H_{24}N$: $(M+H)^+$ 278.1909.

6.6.4 Lewis acid-mediated reduction and functionalizations of 2-azabicyclo[3.3.1]non-2-en-1-yl acetates (Section 5.2.4)

6.6.4.1 Synthesis of 2-azabicyclo[3.3.1]non-2-en-1-yl acetates 13 and 15

(1*S,5*S**)-3-Phenyl-2-azabicyclo[3.3.1]non-2-en-1-yl acetate (13)**

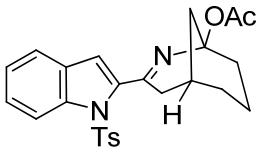


10aa **13**

To a solution of compound **10aa** (1.00 g, 4.7 mmol), Et_3N (1.31 mL, 9.4 mmol), DMAP (57.2 mg, 0.47 mmol) in CH_2Cl_2 (10 mL) was added Ac_2O (3.55 mL, 37.6 mmol). After 4 h, the reaction was diluted with CH_2Cl_2 and water, the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (silica gel; hexane : ethyl acetate = 90 : 10) afforded **13** (1.04 g, 4.04 mmol) in 86% yield.

White solid; mp 87-88 °C; IR (KBr) 3019, 2939, 1723, 1636, 1446, 1215, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30-1.38 (1H, m), 1.53-1.61 (3H, m), 1.93-2.04 (2H, m), 2.10 (3H, s), 2.14 (1H, dd, *J* = 2.8, 12.0 Hz), 2.39-2.51 (3H, m), 2.84 (1H, dd, *J* = 6.4, 18.8 Hz), 7.36-7.39 (3H, m), 7.81 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 22.8, 28.1, 32.0, 33.3, 33.5, 34.2, 93.8, 126.6, 128.2, 130.0, 138.7, 166.2, 169.9; ESIHRMS: Found: m/z 280.1311. Calcd for $C_{16}H_{19}NO_2Na$: $(M+Na)^+$ 280.1313**.**

(1*S,5*S**)-3-(1-Tosyl-1*H*-indol-2-yl)-2-azabicyclo[3.3.1]non-2-en-1-yl acetate (15):**



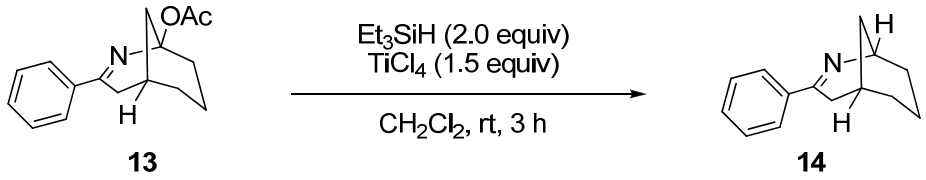
Compound **15** was prepared from **10ga** following the same procedure as compound **13.**

Yield: 82%. Pale yellow solid; mp 88-90 °C; IR (KBr) 3053, 2986, 1730, 1637, 1450, 1369, 1265, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59-1.62 (1H, m), 1.68-1.74 (3H, m), 1.97-2.11 (3H, m), 2.12 (3H, s), 2.25 (3H, s), 2.49-2.51 (1H, m), 2.58-2.62 (2H, m), 3.11 (1H, dd, *J* = 6.4, 19.2 Hz), 6.78 (1H, s), 7.08 (2H, d, *J* = 8.0 Hz), 7.20 (1H, dd, *J* = 7.6, 7.6 Hz), 7.32 (1H, dd, *J* = 7.6, 7.6 Hz), 7.40 (1H, d, *J* = 7.6 Hz), 7.66 (2H, d, *J* = 8.0 Hz), 8.09 (1H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 21.5, 22.8, 28.4, 31.8, 33.2, 34.6, 37.6, 93.3, 114.8, 115.9,

121.6, 124.4, 125.6, 127.3, 129.4, 130.3, 133.5, 137.8, 140.9, 144.6, 164.6, 169.8; ESIHRMS: Found: m/z 451.1698. Calcd for $C_{25}H_{27}N_2O_4S$: $(M+H)^+$ 451.1692**.**

6.6.4.2 Synthesis of 2-azabicyclo[3.3.1]non-2-enes 14 and 16

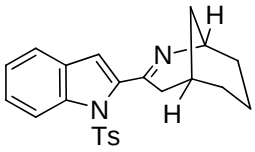
Synthesis of (1*R,5*S**)-3-phenyl-2-azabicyclo[3.3.1]non-2-ene (14)**



$TiCl_4$ (0.30 mL, 0.3 mmol, 1.0 M in CH_2Cl_2) and Et_3SiH (65 μL, 0.41 mmol) were added to a solution of acetate **13** (52.6 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL), and the resulting mixture was stirred at room temperature for 3 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The resuting residue was chromatographed (silica gel; hexane : ethyl acetate = 70 : 30) to give 3-phenyl-2-azabicyclo[3.3.1]non-2-ene (**14**) (36.5 mg, 0.183 mmol) in 90% yield.

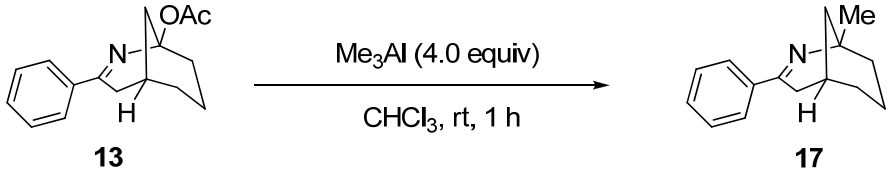
Pale yellow liquid. IR (KBr) 2920, 1630, 1577, 1445, 1237, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30-1.39 (1H, m), 1.44-1.48 (1H, m), 1.58-1.76 (5H, m), 1.93-1.96 (1H, m), 2.27 (1H, m), 2.49 (1H, d, *J* = 18.8 Hz), 2.89 (1H, dd, *J* = 7.2, 18.8 Hz), 4.27 (1H, m), 7.38-7.39 (3H, m), 7.79-7.82 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 25.4, 29.5, 30.0, 33.0, 34.3, 52.3, 126.0, 128.2, 129.5, 139.9, 167.3; ESIHRMS: Found: m/z 200.1442. Calcd for $C_{14}H_{18}N$: $(M+H)^+$ 200.1439**.**

2-((1*R,5*S**)-2-Azabicyclo[3.3.1]non-2-en-3-yl)-1-tosyl-1*H*-indole (16):**



Compound **16** was prepared from **15** following the same procedure as compound **14.** Yield: 79%. Pale yellow solid; mp 55-57 °C; IR (KBr) 3067, 2926, 1639, 1450, 1369, 1236, 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.58-1.76 (6H, m), 1.90-1.93 (1H, m), 2.04-2.06 (1H, m), 2.26 (3H, s), 2.27 (1H, m), 2.45 (1H, d, *J* = 19.6 Hz), 3.18 (1H, dd, *J* = 7.2, 19.6 Hz), 4.27 (1H, s br), 6.69 (1H, s), 7.11 (2H, d, *J* = 8.0 Hz), 7.19 (1H, dd, *J* = 7.6, 7.6 Hz), 7.30 (1H, dd, *J* = 7.6, 7.6 Hz), 7.41 (1H, d, *J* = 7.6 Hz), 7.66 (2H, d, *J* = 8.0 Hz), 8.08 (1H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 21.5, 25.5, 29.56, 29.60, 32.8, 38.7, 52.6, 112.5, 115.7, 121.3, 124.2, 125.2, 127.1, 129.4, 130.3, 134.0, 137.3, 142.0, 144.6, 166; ESIHRMS: Found: m/z 393.1633. Calcd for $C_{23}H_{25}N_2O_2S$: $(M+H)^+$ 393.1637**.**

6.6.4.3 Synthesis of (1*R**,5*S**)-1-methyl-3-phenyl-2-azabicyclo[3.3.1]non-2-ene (17)



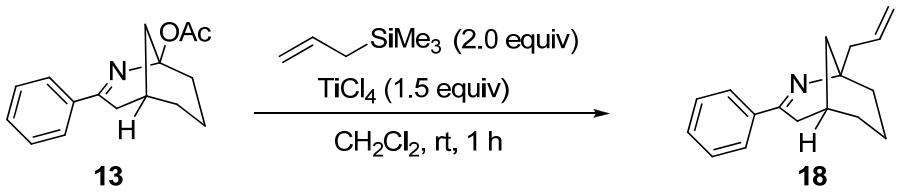
13 **17**

To a stirred, ice-cooled solution of acetate **13** (53.0 mg, 0.21 mmol) in $CHCl_3$ (1.6 mL) was added under nitrogen atmosphere Me_3Al (0.41 mL, 0.82 mmol, 2.0 M in toluene) via syringe and the mixture was stirred 0 °C. After 5 min the cold bath was removed and the reaction mixture allowed to stand for 1 h at room temperature. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The resuting residue was

chromatographed (silica gel; hexane : ethyl acetate = 90 : 10) to give 1-methyl-3-phenyl-2-azabicyclo[3.3.1]non-2-ene (**17**) (36.4 mg, 0.17 mmol) in 83% yield.

Pale yellow liquid; IR (KBr) 2939, 1628, 1577, 1446, 1228, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24-1.31 (1H, m), 1.35 (3H, s), 1.37-1.41 (1H, m), 1.46-1.54 (3H, m), 1.58-1.63 (2H, m), 1.69-1.72 (1H, m), 2.31-2.33 (1H, m), 2.41 (1H, d, *J* = 18.8 Hz), 2.77 (1H, dd, *J* = 7.2, 18.8 Hz), 7.36-7.37 (3H, m), 7.77-7.78 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 26.5, 31.6, 32.4, 33.8, 36.5, 36.7, 53.5, 126.2, 128.2, 129.3, 140.3, 166.2; ESIHRMS: Found: m/z 214.1595. Calcd for $C_{15}H_{20}N$: $(M+H)^+$ 214.1596**.**

6.6.4.4 Synthesis of (1*R**,5*S**)-1-allyl-3-phenyl-2-azabicyclo[3.3.1]non-2-ene (18)



13 **18**

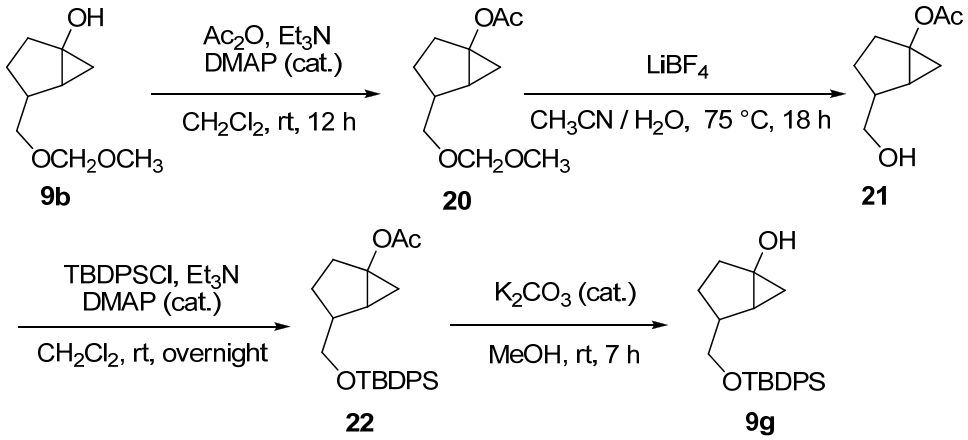
$TiCl_4$ (0.3 mL, 0.30 mmol, 1.0 M in CH_2Cl_2) was added at room temperature to a solution of allyltrimethylsilane (65 μL, 0.41 mmol) and acetate **13** (52.2 mg, 0.20 mmol) in CH_2Cl_2 (1.7 mL). After stirring the reaction mixture for 1 h, 1 N aq. HCl (1.5 mL) and THF (1.5 mL) were added. The reaction mixture was stirred vigorously for 30 min, poured into $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The resuting residue was chromatographed (silica gel; hexane : ethyl acetate = 95 : 5) to give 1-allyl-3-phenyl-2-azabicyclo[3.3.1]non-2-ene (**18**) (39.6 mg, 0.17 mmol) in 82% yield.

Pale yellow liquid; IR (KBr) 2914, 1638, 1578, 1446, 1215, 1123 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24-1.33 (1H, m), 1.37-1.44 (1H, m), 1.48-1.55 (3H, m), 1.62-1.70 (3H, m), 2.30-

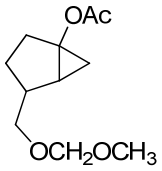
2.36 (2H, m), 2.44-2.51 (2H, m), 2.73 (1H, dd, J = 6.8, 18.8 Hz), 5.06-5.14 (2H, m), 5.93-6.03 (1H, m), 7.37-7.39 (3H, m), 7.80-7.83 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 26.3, 32.7, 33.8, 34.2, 35.0, 48.9, 56.1, 116.8, 126.2, 128.2, 129.4, 135.5, 140.1, 166.4; ESIHRMS: Found: m/z 240.1751. Calcd for $C_{17}H_{22}N$: $(M+H)^+$ 240.1752**.**

6.6.5 Synthesis of (±)-melinonine-E (Section 5.2.5)

6.6.5.1 Synthesis of cyclopropanol 9g



4-((Methoxymethoxy)methyl)bicyclo[3.1.0]hexan-1-yl acetate (20):

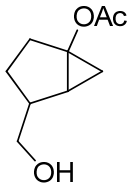


To a solution of cyclopropanol **9b** (2.28 g, 13.3 mmol, ca. 2.3:1 diastereoisomeric mixture), Et_3N (2.77 mL, 19.9 mmol), DMAP (162.0 mg, 1.33 mmol) in CH_2Cl_2 (80 mL) was added Ac_2O (1.50 mL, 15.9 mmol). After 1 h, the reaction was diluted with CH_2Cl_2 and water, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by flash column chromatography (silica gel; hexane : ethyl acetate = 90 : 10)

afforded **20** (2.67 g, 12.5 mmol) in 94% yield as an inseparable mixture of diastereomers (ca. 2.3 : 1); ^{1}H and ^{13}C NMR are described for the major product.

Colorless liquid; IR (KBr) 2985, 1740, 1150, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83-0.88 (1H, m), 0.93-0.96 (1H, m), 1.30-1.38 (1H, m), 1.48 (1H, dd, *J* = 4.8, 9.6 Hz), 1.60 (1H, dd, *J* = 9.2, 13.6 Hz), 1.99 (3H, s), 1.98-2.22 (2H, m), 2.23 (1H, m), 3.37 (3H, s), 3.50 (1H, dd, *J* = 7.6, 9.6 Hz), 3.56 (1H, dd, *J* = 7.2, 9.6 Hz), 4.65 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 21.2, 24.1, 24.8, 28.0, 39.6, 55.2, 66.2, 70.5, 96.5, 171.2; ESIHRMS: Found: m/z 215.1281. Calcd for $C_{11}H_{19}O_4$: $(M+H)^+$ 215.1283**.**

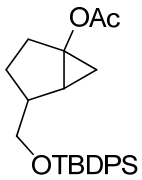
4-(Hydroxymethyl)bicyclo[3.1.0]hexan-1-yl acetate (21):



A solution of compound **20** (1.81 g, 8.44 mmol, ca. 2.3:1 diastereoisomeric mixture) and lithium tetrafluoroborate (7.1 g, 76 mmol) in 120 mL of CH_3CN and 6 mL of H_2O was heated at 75 ºC for 18 h. The reaction was then quenched with saturated aqueous NH_4Cl solution in ice bath and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The product was isolated by flash column chromatography (silica gel; hexane : ethyl acetate = 70 : 30) in 90% yield (0.971 g, 7.58 mmol). The resulted diastereoisomers could be partially separated, the yield mentioned above was the combined yield of two isomers. ^{1}H and ^{13}C NMR are described for the major product. The two isomers (ca. 2.3:1) were used together for the next reaction.

Colorless liquid; IR (KBr) 3412, 2951, 1741, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.74 (1H, dd, *J* = 4.8, 6.0 Hz), 0.96 (1H, ddd, *J* = 2.0, 6.0, 9.6 Hz), 1.33-1.43 (1H, m), 1.51 (1H, dd, *J* = 4.4, 9.6 Hz), 1.74 (1H, dd, *J* = 9.2, 13.6 Hz), 1.98-2.05 (2H, m), 2.03 (3H, s), 2.23 (1H, m), 3.20 (1H, dd, *J* = 2.8, 9.6 Hz), 3.63 (1H, ddd, *J* = 4.8, 9.6, 10.8 Hz), 3.80 (1H, ddd, *J* = 2.8, 3.6, 10.8 Hz), ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 21.3, 24.5, 26.3, 29.4, 42.2, 66.9, 67.4, 172.0; ESIHRMS: Found: m/z 171.1020. Calcd for $C_9H_{15}O_3$: $(M+H)^+$ 171.1021**.**

4-((*tert*-Butyldiphenylsilyloxy)methyl)bicyclo[3.1.0]hexan-1-yl acetate (22):

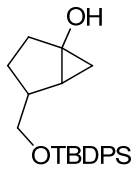


To a solution of alcohol **21** (2.36 g, 13.9 mmol, ca. 2.3:1 diastereoisomeric mixture), Et_3N (3.90 mL, 27.8 mmol), DMAP (170.0 mg, 1.39 mmol) in CH_2Cl_2 (80 mL) was added *tert*-butyldiphenylsilyl chloride (5.40 mL, 20.8 mmol). After 12 h, the reaction was diluted with CH_2Cl_2 and water, the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (silica gel; hexane : ethyl acetate = 95 : 5) afforded **22** (5.46 g, 13.4 mmol) in 96% yield as an inseparable mixture of diastereomers (ca. 2.3 : 1); ^1H and ^{13}C NMR are described for the major product.

Colorless liquid; IR (KBr) 3070, 1744, 1471, 1427, 1361, 1240, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86-0.92 (1H, m), 0.94-0.98 (1H, m), 1.07 (9H, s), 1.26-1.32 (1H, m), 1.48 (1H, dd, *J* = 4.8, 8.4 Hz), 1.64 (1H, dd, *J* = 9.2, 14.0 Hz), 1.88-1.94 (1H, m), 2.00 (3H, s), 2.02-2.07 (1H, m), 2.16-2.23 (1H, m), 3.61 (1H, dd, *J* = 7.6, 9.6 Hz), 3.68 (1H, dd, *J* = 7.2, 9.6 Hz), 7.37-7.43 (6H, m), 7.68-7.69 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 19.3,

21.2, 23.9, 24.4, 26.8, 28.4, 41.9, 66.3, 66.5, 127.6, 129.5, 133.9, 135.6, 171.3; ESIHRMS: Found: m/z 409.2194. Calcd for $C_{25}H_{33}O_3Si$: $(M+H)^+$ 409.2199.

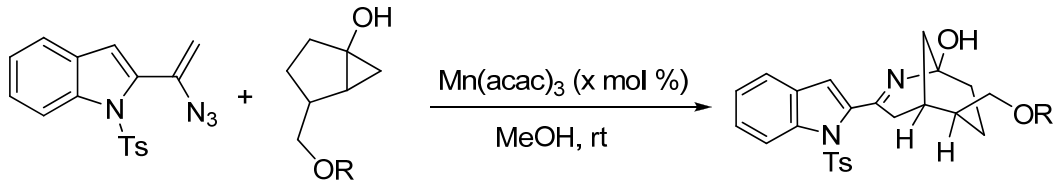
4-((*tert*-Butyldiphenylsilyloxy)methyl)bicyclo[3.1.0]hexan-1-ol (9g):



To a solution of acetate **22** (5.41 g, 13.2 mmol, ca. 2.3:1 diastereoisomeric mixture) in MeOH (60 mL) was added K_2CO_3 (180.0 mg, 1.33 mmol). The reaction was stirred for 1 h at room temperature and then quenched by adding pH 9 ammonium buffer, and the organic materials were extracted with ethyl acetate. The organic lay was washed with brine and dried over $MgSO_4$. After evaporation of solvent, resulting crude materials were purified by flash column chromatography (silica gel; hexane : ethyl acetate = 80 : 20) to give cyclopropanol **9g** (4.60 g, 12.5 mmol) in 95% yield as an inseparable mixture of diastereomers (ca. 2.3 : 1); ^1H and ^{13}C NMR are described for the major product.

Viscous liquid; IR (KBr) 3342, 3089, 1602, 1497, 1456, 1267, 1236, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.62 (1H, dd, *J* = 3.6, 4.4 Hz), 0.89-0.90 (1H, m), 1.10 (9H, s), 1.22-1.32 (2H, m), 1.57-1.61 (1H, m), 1.75 (1H, s br), 1.87-1.99 (2H, m), 2.04-2.08 (1H, m), 3.59-3.61 (2H, m), 7.40-7.46 (6H, m), 7.69-7.72 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 19.3, 23.8, 26.6, 26.9, 31.5, 42.3, 64.1, 66.9, 127.6, 129.6, 133.9, 135.6; ESIHRMS: Found: m/z 389.1919. Calcd for $C_{23}H_{30}O_2SiNa$: $(M+H)^+$ 389.1913.

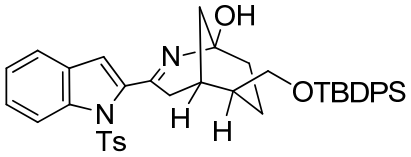
6.6.5.2 $Mn(acac)_3$-mediated synthesis of 2-azabicyclo[3.3.1]non-2-en-1-ols 10gg and 10gb



1g **9** **10**

R = methoxymethyl (**9b**) or R = *t*-butyldiphenylsilyl (**9g**)

(1*S,5*S**,6*S**)-6-((*tert*-Butyldiphenylsilyloxy)methyl)-3-(1-tosyl-1*H*-indol-2-yl)-2-azabicyclo[3.3.1]non-2-en-1-ol (10gg)**



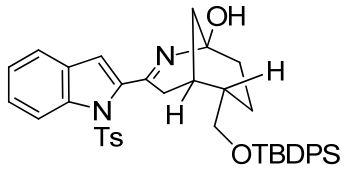
To a solution of vinyl azide **1g** (2.00 g, 5.91 mmol) and $Mn(acac)_3$ (3.35 g, 9.42 mmol) in MeOH (150 mL) was added a solution of bicyclo[3.1.0]hexan-1-ol **9g** (6.52 g, 17.8 mmol) in MeOH (100 mL) via a syring pump over 9 h. The reaction mixture was qunched with pH 9 ammonium buffer, and then extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. Purification of the crude materials by flash column chromatography (silica gel; hexane : ethyl acetate = 80 : 20) afforded **10gg** (3.01 g, 4.45 mmol) in 75% yield as pure *exo*-isomer.

Whitle solid; mp 83-85 °C; IR (KBr) 3391, 3051, 2930, 1632, 1597, 1450, 1369, 1265, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (9H, s), 1.63-1.72 (5H, m), 1.84-1.90 (2H, m), 2.26 (3H, s), 2.48 (1H, d, *J* = 19.6 Hz), 2.58 (1H, m), 3.00 (1H, s br), 3.20 (1H, dd, *J* = 7.2, 19.6 Hz), 3.68 (1H, dd, *J* = 7.2, 10.0 Hz), 3.73 (1H, dd, *J* = 8.0, 10.0 Hz), 6.74 (1H, s), 7.12 (2H, d, *J* = 8.0 Hz), 7.22 (1H, dd, *J* = 7.6, 7.6 Hz), 7.34 (1H, dd, *J* = 7.6, 8.0 Hz), 7.38-7.45 (7H, m), 7.66-7.68 (6H, m), 8.11 (1H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 20.3, 21.5, 26.9, 29.0, 30.8, 33.4, 39.4, 41.6, 64.3, 84.1, 113.3, 115.7, 121.5, 124.3, 125.6, 127.1, 127.67,

127.69, 129.5, 129.64, 129.66, 130.1, 133.65, 133.67, 134.0, 135.51, 135.52, 137.6, 140.5, 144.8, 164.2; ESIHRMS: Found: m/z 677.2859. Calcd for $C_{40}H_{45}N_2O_4SiS$: $(M+H)^+$ 677.2869.

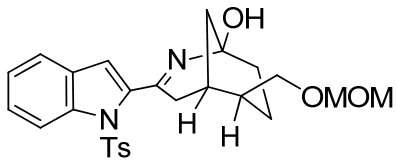
The *endo*-isomer was also isolated in 13% yield (0.52g, 0.07 mmol).

(1*S,5*S**,6*R**)-6-((*tert*-Butyldiphenylsilyloxy)methyl)-3-(1-tosyl-1*H*-indol-2-yl)-2-azabicyclo[3.3.1]non-2-en-1-ol (*endo*-isomer)**



Pale yellow solid; mp 96-98 °C; IR (KBr) 3399, 3051, 2930, 1632, 1597, 1450, 1369, 1265, 1177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.07-1.18 (1H, m), 1.53-1.57 (1H, m), 1.72-1.99 (5H, m), 2.25 (3H, s), 2.42 (1H, d, *J* = 19.6 Hz), 2.59 (1H, m), 2.73 (1H, dd, *J* = 6.8, 19.6 Hz), 3.20 (1H, s br), 3.57 (1H, dd, *J* = 9.2, 10.0 Hz), 3.65 (1H, dd, *J* = 5.6, 10.0 Hz), 6.66 (1H, s), 7.12 (2H, d, *J* = 8.4 Hz), 7.22 (1H, dd, *J* = 7.6, 7.6 Hz), 7.33-7.44 (8H, m), 7.64-7.66 (6H, m), 8.12 (1H, d, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 21.5, 21.7, 26.9, 28.8, 32.1, 36.4, 37.7, 43.0, 65.6, 84.4, 113.4, 115.7, 121.5, 124.3, 125.6, 127.0, 127.6, 127.7, 129.5, 129.6, 129.7, 130.1, 133.5, 133.7, 133.9, 135.5, 135.6, 137.6, 140.4, 144.8, 164.4; ESIHRMS: Found: m/z 677.2866. Calcd for $C_{40}H_{45}N_2O_4SiS$: $(M+H)^+$ 677.2869.

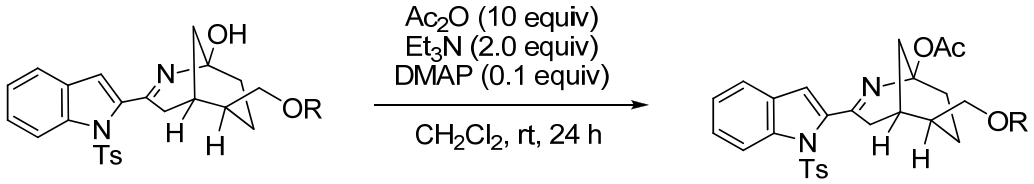
(1*S,5*S**,6*S**)-6-((methoxymethoxy)methyl)-3-(1-tosyl-1H-indol-2-yl)-2-azabicyclo[3.3.1]non-2-en-1-ol (10gb)**



This compound was prepared from vinyl azide **1a** and cyclopropanol **9b** by using 1.0 equiv of $Mn(acac)_3$ following the same procedure as compound **10gg**.

An inseparable mixture (*exo* : *endo* = 85 : 15). A pure *exo* isomer was obtained by recrystallization from ethyl acetate/hexane; ^1H and ^{13}C NMR are described for the *exo* isomer. Yield: 86%. White solid; mp 176-178 °C; IR (KBr) 3420, 3053, 2953, 1631, 1598, 1450, 1348, 1265, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.62-1.82 (5H, m), 1.90–1.92 (1H, m), 2.00 (1H, dd, *J* = 2.8, 12.8 Hz), 2.27 (3H, s), 2.47 (1H, d, *J* = 19.6 Hz), 2.53 (1H, m), 2.85 (1H, s br), 3.20 (1H, dd, J = 7.2, 19.6 Hz), 3.38 (3H, s), 3.56 (1H, dd, *J* = 7.2, 9.6 Hz), 3.65 (1H, dd, *J* = 8.6, 9.6 Hz), 4.65 (2H, s), 6.74 (1H, s), 7.12 (2H, d, *J* = 8.0 Hz), 7.22 (1H, dd, *J* = 7.6, 7.6 Hz), 7.33 (1H, dd, *J* = 7.6, 7.6 Hz), 7.43 (1H, d, *J* = 7.6 Hz), 7.66 (2H, d, *J* = 8.0 Hz), 8.10 (1H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 21.5, 29.3, 30.8, 33.4, 39.0, 39.3, 55.2, 68.3, 84.1, 96.5, 113.2, 115.7, 121.5, 124.4, 125.6, 127.1, 129.5, 130.1, 134.1, 137.6, 140.4, 144.8, 164.1; ESIHRMS: Found: m/z 483.1958. Calcd for $C_{26}H_{31}N_2O_5S$: $(M+H)^+$ 483.1954.

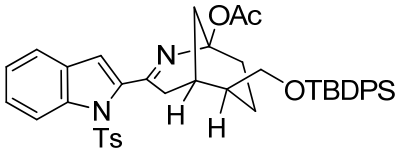
6.6.5.3 Synthesis of 2-azabicyclo[3.3.1]non-2-en-1-yl acetates 23 and 24



10gb: R = MOM
10gg: R = TBDPS

23: R = MOM
24: R = TBDPS

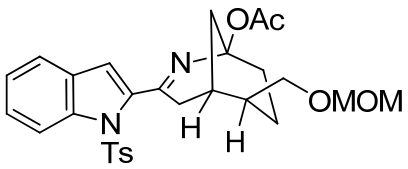
(*1S*,5S*,6S)-6-((*tert*-Butyldiphenylsilyloxy)methyl)-3-(1-tosyl-1*H*-indol-2-yl)-2-azabicyclo[3.3.1]non-2-en-1-yl acetate (24)**



To a solution of compound **10gg** (3.01 g, 4.45 mmol), Et_3N (1.24 mL, 8.90 mmol), DMAP (108.6 mg, 0.90 mmol) in CH_2Cl_2 (30 mL) was added Ac_2O (4.2 mL, 44.5 mmol). After 24 h, the reaction was diluted with CH_2Cl_2 and water, the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (silica gel; hexane : ethyl acetate = 90 : 10) afforded **24** (2.78 g, 3.87 mmol) in 87% yield.

White solid; mp 86-87 °C; IR (KBr) 3053, 2957, 1732, 1638, 1599, 1450, 1369, 1265, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (9H, s), 1.66-1.68 (1H, m), 1.87-1.93 (4H, m), 2.01 (1H, d, *J* = 12.4 Hz), 2.09 (3H, s), 2.25 (3H, s), 2.44 (1H, d, *J* = 12.4 Hz), 2.57 (1H, m), 2.69 (1H, d, *J* = 19.2 Hz), 3.20 (1H, dd, *J* = 6.4, 19.6 Hz), 3.71 (1H, dd, *J* = 7.2, 10.0 Hz), 3.75 (1H, dd, *J* = 8.4, 10.0 Hz), 6.79 (1H, s), 7.08 (2H, d, *J* = 8.0 Hz), 7.22 (1H, dd, *J* = 7.2, 7.6 Hz), 7.33 (1H, dd, *J* = 7.2, 8.4 Hz), 7.39-7.45 (7H, m), 7.66-7.69 (6H, m), 8.10 (1H, d, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 19.6, 21.5, 22.7, 26.9, 28.4, 29.3, 30.4, 39.2, 41.4, 64.5, 93.1, 114.9, 115.9, 121.6, 124.4, 125.6, 127.2, 127.7 (overlapped), 129.4, 129.7 (overlapped), 130.3, 133.6, 133.69, 133.71, 135.54, 135.56, 137.9, 141.0, 144.7, 164.1, 169.7; ESIHRMS: Found: m/z 719.2977. Calcd for $C_{42}H_{47}N_2O_5SiS$: $(M+H)^+$ 719.2975**.**

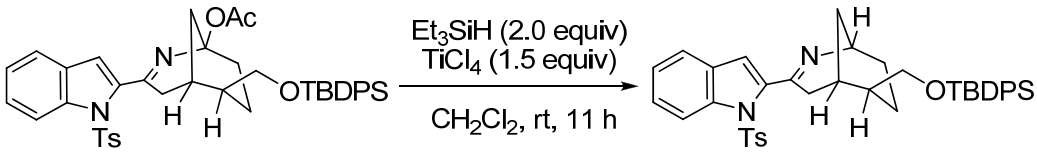
(1*S,5*S**,6*S**)-6-((methoxymethoxy)methyl)-3-(1-tosyl-1H-indol-2-yl)-2-azabicyclo[3.3.1]non-2-en-1-yl acetate (23)**



This compound was prepared from **10gb** according to the procedure of acetate **24**.

Yield: 71%. White solid; mp 90-92 °C; IR (KBr) 3053, 2936, 1732, 1638, 1597, 1450, 1369, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.65-1.67 (2H, m), 1.93–1.98 (3H, m), 2.11 (3H, s), 2.18 (1H, d, *J* = 12.8 Hz), 2.25 (3H, s), 2.48 (1H, d, *J* = 12.8 Hz), 2.53-2.55 (1H, m), 2.69 (1H, d, *J* = 19.2 Hz), 3.19 (1H, dd, *J* = 6.8, 19.2 Hz), 3.38 (3H, s), 3.59 (1H, dd, *J* = 6.4, 9.6 Hz), 3.67 (1H, dd, *J* = 8.4, 9.6 Hz), 4.66 (2H, s), 6.79 (1H, s), 7.08 (2H, d, *J* = 8.0 Hz), 7.20 (1H, dd, *J* = 7.6, 7.6 Hz), 7.32 (1H, dd, *J* = 7.6, 7.6 Hz), 7.40 (1H, d, *J* = 7.6 Hz), 7.66 (2H, d, *J* = 8.0 Hz), 8.09 (1H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 21.5, 22.7, 28.3, 29.7, 30.3, 38.9, 39.0, 55.3, 68.5, 93.1, 96.5, 115.0, 115.9, 121.6, 124.4, 125.6, 127.2, 129.4, 130.3, 133.6, 137.8, 140.9, 144.7, 164.2, 169.8; ESIHRMS: Found: m/z 525.2051. Calcd for $C_{28}H_{33}N_2O_6S$: $(M+H)^+$ 525.2059.

6.6.5.4 Synthesis of 2-((1*R**,5*S**,6*S**)-6-((*tert*-butyldiphenylsilyloxy)methyl)-2-azabicyclo[3.3.1]non-2-en-3-yl)-1-tosyl-1*H*-indole (26)

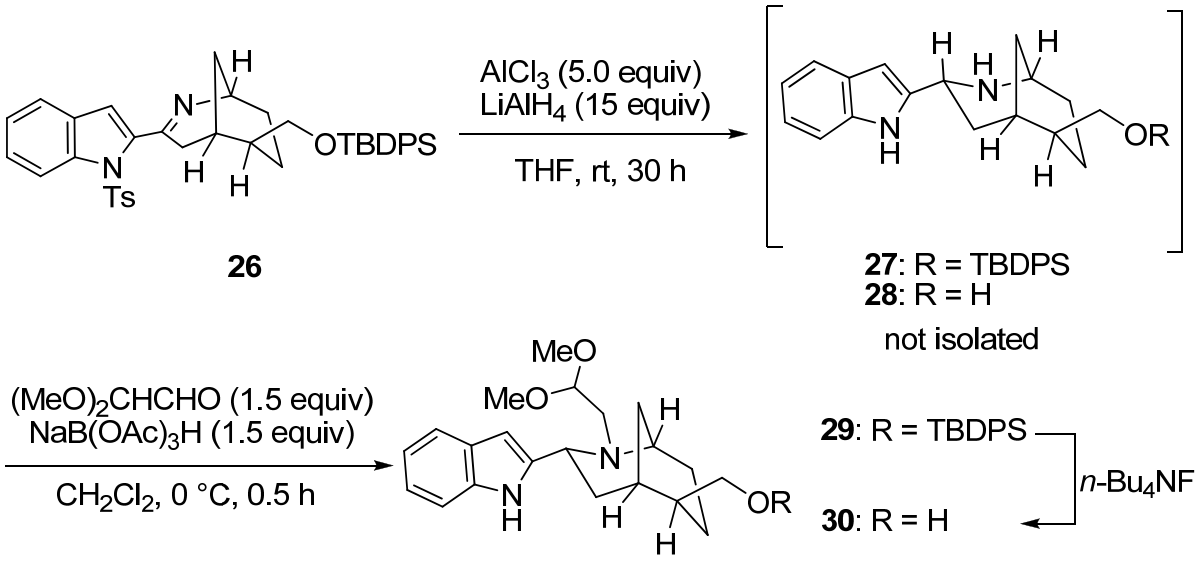


24 **26**

$TiCl_4$ (3.30 mL, 3.30 mmol, 1.0 M in CH_2Cl_2) and Et_3SiH (0.71 mL, 4.43 mmol) were added to a solution of acetate **24** (1.59, 2.22 mmol) in CH_2Cl_2 (25.0 mL), and the resulting mixture was stirred at room temperature for 11 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The resuting residue was chromatographed (silica gel; hexane : ethyl acetate = 90 : 10) to give 3-phenyl-2-azabicyclo[3.3.1]non-2-ene **26** (1.22 g, 1.85 mmol) in 83% yield.

White solid; mp 70-72 °C; IR (KBr) 3053, 2932, 1639, 1598, 1450, 1369, 1265, 1176 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (9H, s), 1.52-1.71 (4H, m), 1.78-1.84 (2H, m), 1.95-1.96 (1H, m), 2.26 (3H, s), 2.32 (1H, m), 2.52 (1H, d, *J* = 19.2 Hz), 3.28 (1H, dd, *J* = 7.2, 19.2 Hz), 3.73 (1H, dd, *J* = 7.2, 10.0 Hz), 3.76 (1H, dd, *J* = 7.6, 10.0 Hz), 4.16 (1H, s br), 6.70 (1H, s), 7.11 (2H, d, *J* = 8.0 Hz), 7.21 (1H, dd, *J* = 7.6, 7.6 Hz), 7.31 (1H, dd, *J* = 7.6, 8.0 Hz), 7.39-7.45 (7H, m), 7.65-7.71 (6H, m), 8.10 (1H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 19.2, 21.5, 24.6, 25.0, 26.2, 26.9, 40.3, 42.4, 52.4, 64.7, 112.6, 115.7, 121.3, 124.2, 125.2, 127.0, 127.6, 129.4, 129.6, 130.3, 133.8, 134.0, 135.6, 137.3, 142.0, 144.6, 166.1; ESIHRMS: Found: m/z 661.2921. Calcd for $C_{40}H_{45}N_2O_3SiS$: $(M+H)^+$ 661.2920.

6.6.5.5 Synthesis of 2-((1*R,3*R**,5*S**,6*S**)-6-((*tert*-butyldiphenylsilyloxy)methyl)-2-(2,2-dimethoxyethyl)-2-azabicyclo[3.3.1]nonan-3-yl)-1*H*-indole (29) and ((1*S**,3*R**,5*S**,6*S**)-2-(2,2-dimethoxyethyl)-3-(1*H*-indol-2-yl)-2-azabicyclo[3.3.1]nonan-6-yl)methanol (30)**



To a solution of $AlCl_3$ (182.0 mg, 1.36 mmol) in THF (8.0 mL) was added $LiAlH_4$ (155.5 mg) in several portions at 0 ºC. After 30 min, a solution of cyclic imine **26** (180.0 mg, 0.27 mmol) in THF (2.0 mL) was slowly added. The reaction mixture was then stirred for

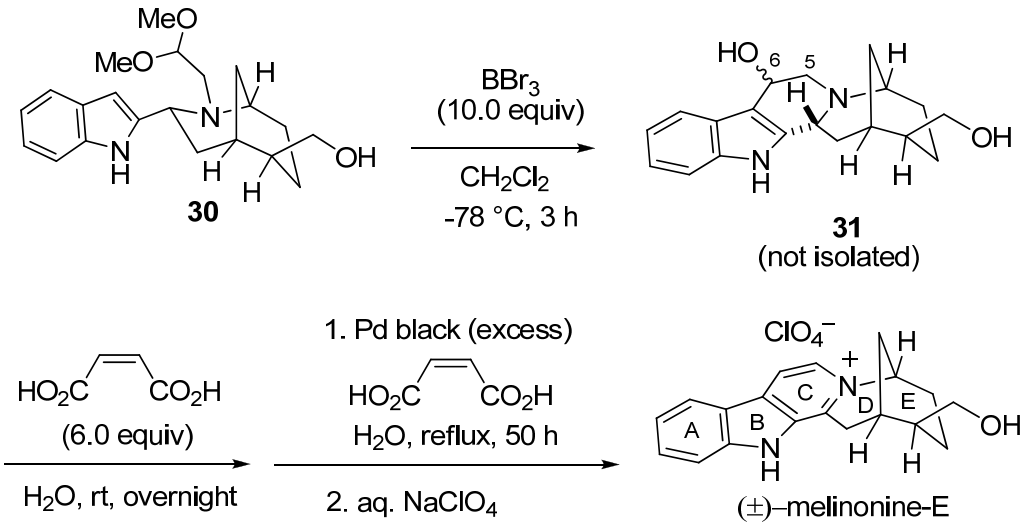
another 40 h, and quenched by slow addition of saturated aqueous NH_4Cl solution in ice bath followed by adding 1N NaOH to pH = 8. The resulting suspension was filtered through a Celite pad and the precipitate was washed thoroughly with CH_2Cl_2. The aqueous layer was further extracted with CH_2Cl_2, and the combined organic layers were washed with brine and then dried over $MgSO_4$. After evaporation of solvents, the crude materials were dissolved in CH_2Cl_2 (4.0 mL) followed by addition of $NaB(OAc)_3H$ (89.1 mg, 0.41 mmol) and 2,2-dimethoxyacetaldehyde (62 μL, 0.41 mmol, 60% in H_2O) at 0 ºC. The reaction was stirred for another 30 min at room temperature, quenched by adding saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The crude material was purified by flash column chromatography (silica gel; hexane : ethyl acetate = 90 : 10 then 70 : 30) to give compounds **29** (70.3 mg, 0.12 mmol) and **30** (12.0 mg, 0.03 mmol) in 43% and 12% yields, respectively. The reaction by using cyclic imine **26** in a larger scale (641.0 mg, 0.97 mmol) required longer reaction time (3 days) for the alane reduction reaction, the subsequent reductive *N*-alkylation afforded compound **29** (103.9 mg, 0.17 mmol) and **30** (113.1 mg, 0.32 mmol) in 18% and 33% yields, respectively. Treatment of compound **29** (103.9 mg, 0.17 mmol) with n-$Bu_4NF{\cdot}3H_2O$ (84.9 mg, 0.26 mmol) in THF for 36 h at room temperature afforded compound **30** (58.4 mg, 0.16 mmol) in 94% yield.

Compound **29**: pale yellow viscous liquid; IR (KBr) 3051, 2932, 1643, 1598, 1456, 1265, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (9H, s), 1.29-1.39 (2H, m), 1.45-1.52 (2H, m), 1.59-1.68 (2H, m), 1.87 (1H, d, J = 13.6 Hz), 2.17-2.20 (1H, m), 2.24-2.35 (2H, m), 2.43 (1H, dd, J = 3.2, 13.6 Hz), 2.76 (1H, dd, J = 7.6, 13.6 Hz), 2.93 (1H, s br), 3.21 (3H, s), 3.28 (3H, s), 3.73 (2H, d, J = 7.6 Hz), 4.07 (1H, dd, J = 5.6, 12.0 Hz), 4.43 (1H, d, J = 3.2, 7.6 Hz), 6.31 (1H, s), 7.08 (1H, dd, J = 7.2, 7.6 Hz), 7.15 (1H, dd, J = 7.2, 7.6 Hz), 7.37-7.47 (7H, m), 7.55 (1H, d, J = 7.6 Hz), 7.69-7.71 (4H, m), 9.04 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 17.8, 19.2, 22.5, 24.9, 26.9, 29.7, 39.1, 42.6, 53.1, 53.7, 53.8, 55.3, 58.4, 64.3, 99.2, 103.3, 110.8, 119.2, 119.8, 120.9, 127.6, 128.7, 129.5, 133.9, 135.6, 135.9, 143.4; ESIHRMS: Found: m/z 597.3514. Calcd for $C_{37}H_{49}N_2O_3Si$: $(M+H)^+$ 597.3512.

Compound **30**: pale yellow viscous liquid; IR (KBr) 3408, 3053, 2936, 1643, 1456, 1265, 1126 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46-1.62 (7H, m), 1.94 (1H, d, *J* = 13.6 Hz), 2.12-2.15 (1H, m), 2.28-2.35 (2H, m), 2.44 (1H, dd, *J* = 2.8, 13.6 Hz), 2.75 (1H, dd, *J* = 7.2, 13.6 Hz), 3.00 (1H, s br), 3.20 (3H, s), 3.26 (3H, s), 3.71 (2H, d, *J* = 7.6 Hz), 4.08 (1H, dd, *J* = 5.6, 12.0 Hz), 4.43 (1H, d, *J* = 2.8, 7.2 Hz), 6.30 (1H, s), 7.06 (1H, dd, *J* = 7.6, 8.0 Hz), 7.13 (1H, dd, *J* = 7.6, 8.0 Hz), 7.36 (1H, d, *J* = 8.0), 7.52 (1H, d, *J* = 8.0 Hz), 9.05 (1H, s br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 22.6, 25.1, 29.6, 39.0, 42.9, 53.3, 53.7, 53.8, 55.3, 58.3, 63.6, 99.3, 103.3, 110.9, 119.3, 119.8, 121.0, 128.7, 135.9, 143.2; ESIHRMS: Found: m/z 359.2332. Calcd for $C_{21}H_{31}N_2O_3$: $(M+H)^+$ 359.2335.

6.6.5.6 Synthesis of (±)-melinonine-E



To a solution of compound **30** (67.2 mg, 0.187 mmol) in CH_2Cl_2 (2.0 mL) was added BBr_3 (1.5 mL, 1.5 mmol, 1.0 M in CH_2Cl_2) at -78 ºC. After stirring for an additional 3 h, the

reaction mixture was quenched by adding saturated $NaHCO_3$ solution (10 mL) at the same temperature. Upon warmed to room temperature, the aqueous layer was extracted with CH_2Cl_2, dried over $MgSO_4$ and then concentrated. The resulting residue was treated with maleic acid (130.5 mg, 1.12 mmol) in H_2O (3 mL) for overnight, to which was added palladium black (199.4 mg, 1.87 mmol). The reaction mixture was reflux for 26 h, and the insoluble materials were filtered through a Celite pad and washed with hot methanol. After evaporation of solvents, the residue was dissolved in H_2O (3.0 mL), and a fresh portion of palladium black (398.3 mg, 3.74 mmol) was added. The reaction mixture was reflux for 24 h, then filtered through a Celite pad again and washed with hot MeOH. Removal of solvent provided a yellowish solid, which was suspended in H_2O (1.0 mL) and neutralized with saturated aqueous $NaHCO_3$ (2.0 mL). To this reaction mixture, a solution of $NaClO_4 \cdot H_2O$ (79.0 mg, 0.56 mmol) in H_2O (1.0 mL) was added. The precipitate was collected and washed with water to give (±)-melinonine-E perchlorate (32.1 mg, 0.082 mmol, 44% from **30**) as a yellow solid. The ^1H and ^{13}C NMR data (shown below) of this compound are identical to the reported ones.[48]

^1H NMR (400 MHz, CD_3OD) δ 1.17-1.27 (1H, m), 1.65 (1H, dm, *J* = 15.2 Hz), 1.92 (1H, dm, *J* = 14.8 Hz), 2.03 (1H, m), 2.16-2.25 (2H, m), 2.44 (1H, dm, *J* = 14.0 Hz), 2.71 (1H, s br), 3.52 (1H, d, *J* = 19.2 Hz), 3.75 (1H, d, *J* = 7.2, 10.8 Hz), 3.84 (1H, d, *J* = 8.0, 10.8 Hz), 3.98 (1H, d, *J* = 7.2, 19.2 Hz), 5.10 (1H, s br), 7.47 (1H, m), 7.76-7.79 (2H, m), 8.36 (1H, m), 8.38 (1H, m), 8.51 (1H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 18.7, 25.9, 26.1, 29.6, 33.3 (t, coupled with D),[49] 43.5, 63.0, 63.5, 114.1, 117.4, 121.7, 123.7, 124.3, 132.5, 133.0, 133.9, 135.5, 142.8, 145.5. ESIHRMS: Found: m/z 293.1656. Calcd for $C_{19}H_{21}N_2O$: $(M\text{-}ClO_4^-)^+$ 293.1654.

6.7 References and Notes

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(14) CCDC-694297 contains the supplementary crystallographic data for compound **4af**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB21 EZ, UK; fax: (+44)1223-336-033; or deposit@cdc.cam.ac.uk).

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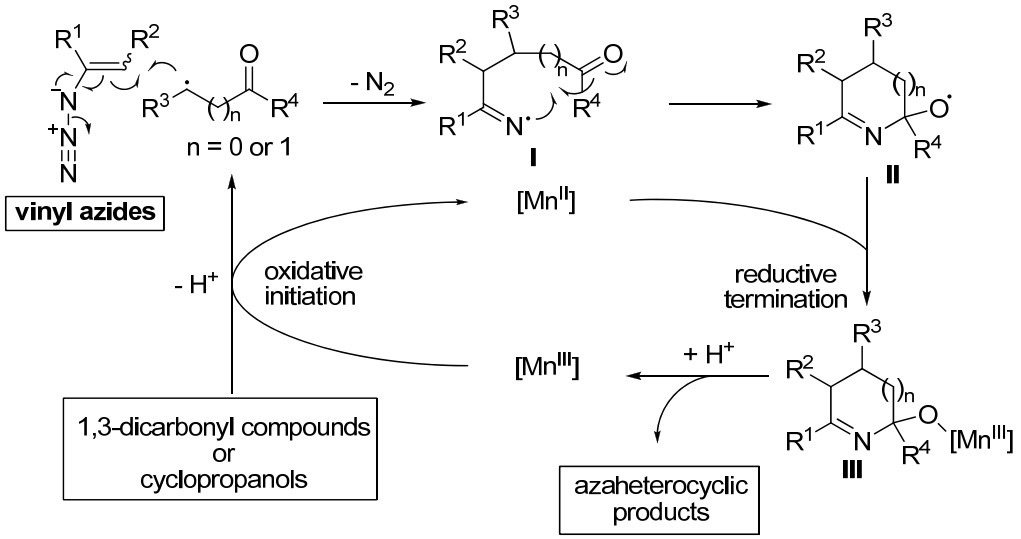
Chapter 7 Summary and Perspective

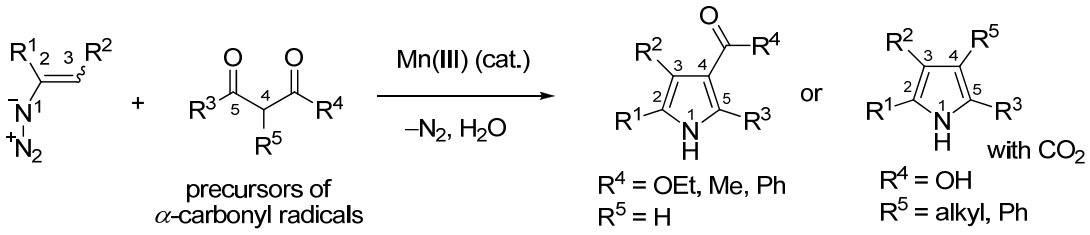
In this thesis, the author has developed efficient methods to synthesize azaheterocycles by using vinyl azides as the basic substrates. A particular feature of these methods is that addition of α- or β-carbonyl radicals to the C═C bond of vinyl azides affords the key intermediate iminyl radicals **I**, cyclization of which with intramolecular carbonyl group constructs azaheterocyclic frameworks (Scheme 7-1). The involved α- and β-carbonyl radicals are generated by the oxidation of 1,3-dicarbonyl compounds and cyclopropanols by Mn(III) complexes, respectively. The radical chain reactions are terminated by the reduction of alkoxy radicals **II** by the resulted Mn(II) species to afford Mn(III) alkoxides **III**, from which azaheterocyclic products are formed with regeneration of active Mn(III) species. Therefore, this characteristic oxidative initiation and reductive termination process promotes these reactions to be conducted in a catalytic manner.



Scheme 7-1. Synthesis of azaheterocycles by Mn(III)-mediated reactions of vinyl azides and 1,3-dicarbonyl compounds or cyclopropanols

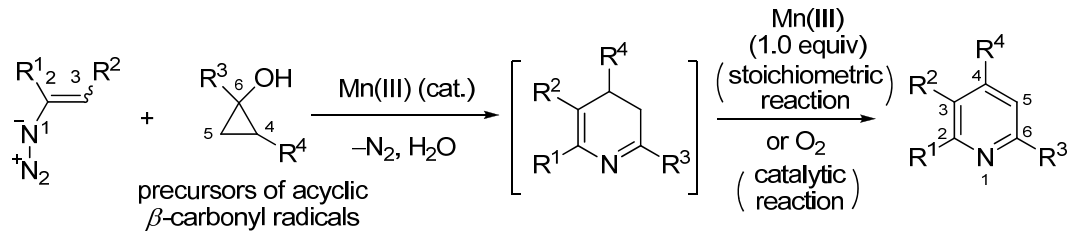
Chapter 2 introduced conventional preparation methods of vinyl azides in terms of reaction conditions. A number of vinyl azides have been readily prepared from simple starting materials.

Chapter 3 described the Mn(III)-catalyzed reactions of vinyl azides and 1,3-dicarbonyl compounds (including β-keto esters, 1,3-diketones, and β-keto acids) for the synthesis of polysubstituted *N*–H pyrroles (Scheme 7-2), in which 1,3-dicarbonyl compounds were utilized as the precursors of α-carbonyl radicals.



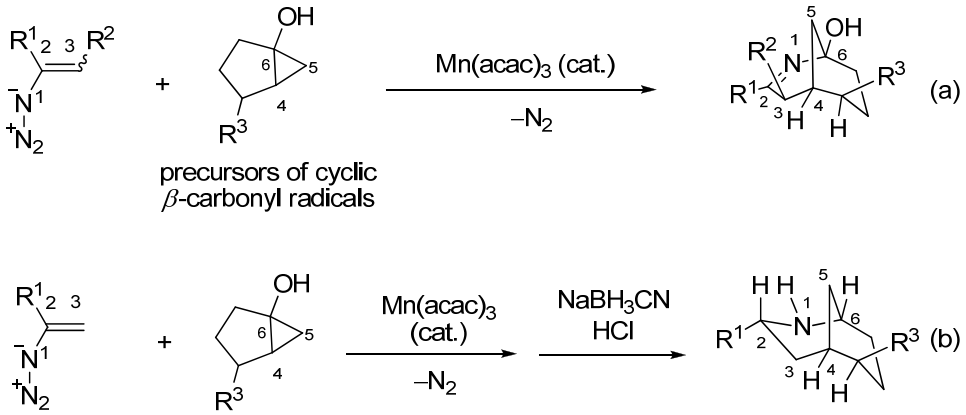
Scheme 7-2. Mn(III)-catalyzed pyrrole formation from vinyl azides and 1,3-dicarbonyl compounds

Chapter 4 focused on the Mn(III)-mediated/catalyzed synthesis of substituted pyridines from vinyl azides and cyclopropanols (Scheme 7-3). In the Mn(III)-mediated reactions (stoichiometric reactions), Mn(III) complexes played dual roles for the catalytic oxidation of cyclopropanols to β-carbonyl radicals and the oxidation of intermediate dihydropyridines to pyridines. In the catalytic reaction, Mn(III) complexes were only involved in the oxidative generation of β-carbonyl radicals, and the oxidation of dihydropyridines was achieved by molecular oxygen.



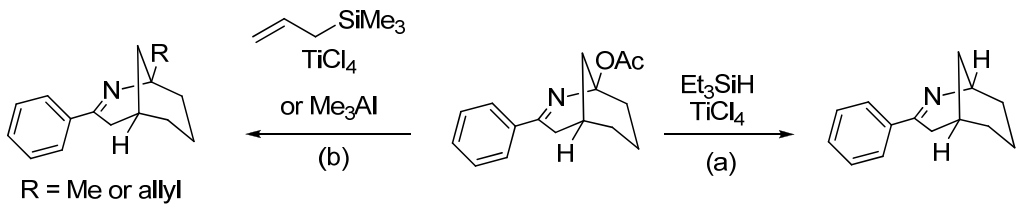
Scheme 7-3. Mn(III)-mediated and Mn(III)-catalyzed pyridine formation from vinyl azides and cyclopropanols

In chapter 5 was discussed the extension of the above reactions by using bicyclo[3.1.0]hexan-1-ols as the precursors of cyclic *β*-carbonyl radicals to synthesize 2-azabicyclo[3.3.1]non-2-en-1-ols (Scheme 7-4, Eq. a). Moreover, most of these resulted azabicyclic compounds were converted to 2-azabicyclo[3.3.1]nonane (morphan) derivatives from vinyl azides in a one-pot procedure (Eq. b). In this process, both the C═N and bridgehead C−OH bonds of these azabicyclic compounds were stereoselectively reduced by $NaBH_3CN$-HCl to provide *endo*-selective (refer to R^1) products.



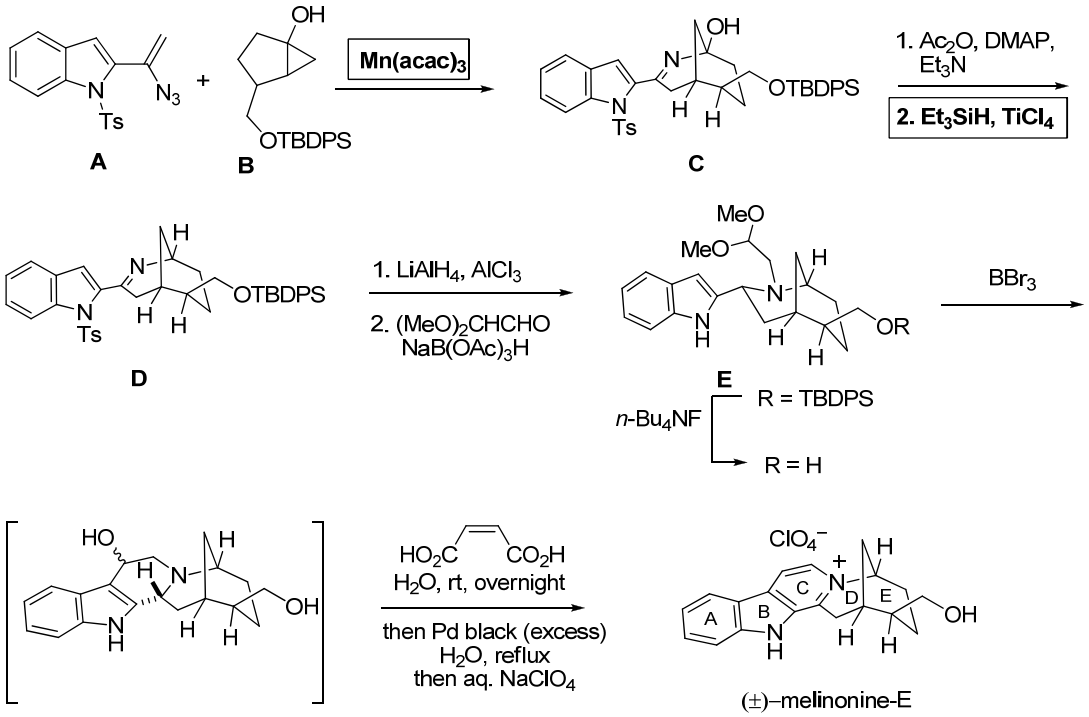
Scheme 7-4. Mn(III)-catalyzed synthesis of 2-azabicyclo[3.3.1]non-2-en-1-ols and one-pot preparation of 2-azabicyclo[3.3.1]nonanes

Notably, selective reduction of the bridgehead C−O bond of 2-azabicyclo[3.3.1]non-2-en-1-yl acetate was achieved by employing Et_3SiH-$TiCl_4$ protocol (Scheme 7-5, Eq. a). Moreover, introduction of a carbon substituent at 1-position was performed by Lewis acid-induced alkylation and allylation reactions (Eq. b).



Scheme 7-5. Transformations of 2-azabicyclo[3.3.1]non-2-en-1-yl acetate

Finally, (±)-melinonine-E was synthesized by applying the following reactions developed in this thesis as the key reactions (Scheme 7-6): 1) $Mn(acac)_3$-catalyzed synthesis of 2-azabicyclo[3.3.1]non-2-en-1-ol **C** from vinyl azide**s A** and cyclopropanol **B**; and 2) Et_3SiH-$TiCl_4$ reduction of bridgehead C−O bond of azabicyclic compound **C**. From the reduction product **D**, (±)-melinonine-E was prepared by four steps transformations including alane reduction of the cyclic imine unit, reductive *N*-alkylation of the resulted cyclic amines, BBr_3-mediated cyclization of the indole moiety with the intramolecular acetal motif, and aromatization of C ring.



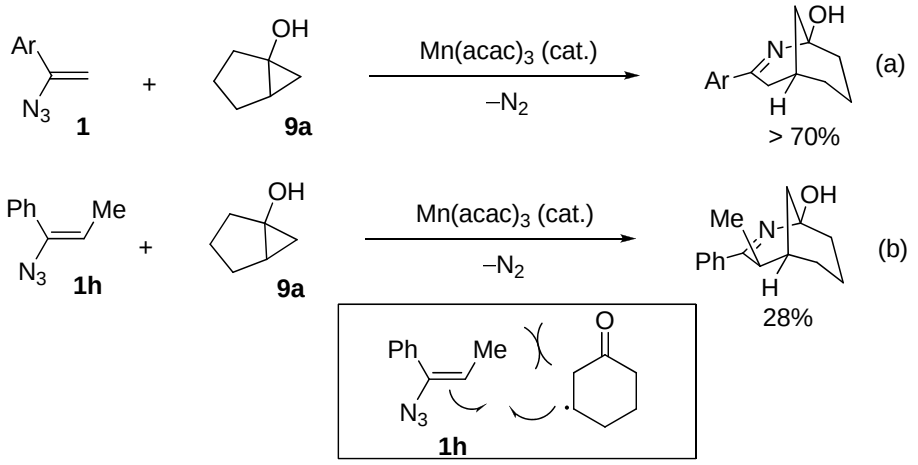
Scheme 7-6. Synthesis of (±)-melinonine-E

In conclusion, a series of azaheterocycles such as pyrroles, pyridines, and azabicyclic compounds have been successfully prepared by Mn(III)-catalyzed/mediated reactions of vinyl azides and 1,3-dicarbonyl compounds or cyclopropanols. In these formed azaheterocycles, vinyl azides donate three atoms including one nitrogen unit,

while 1,3-dicarbonyl compounds and cyclopropanols contribute the remaining carbon atoms of the ring skeletons.

These synthetic methods have significant advantages such as broad substrate scopes and generalities for pyrrole and pyridine formation, mild reaction conditions, employment of readily accessible starting materials, good diastereoselectivities in the preparation of 6-substituted 2-azabicyclo[3.3.1]non-2-en-1-ols, and so on.

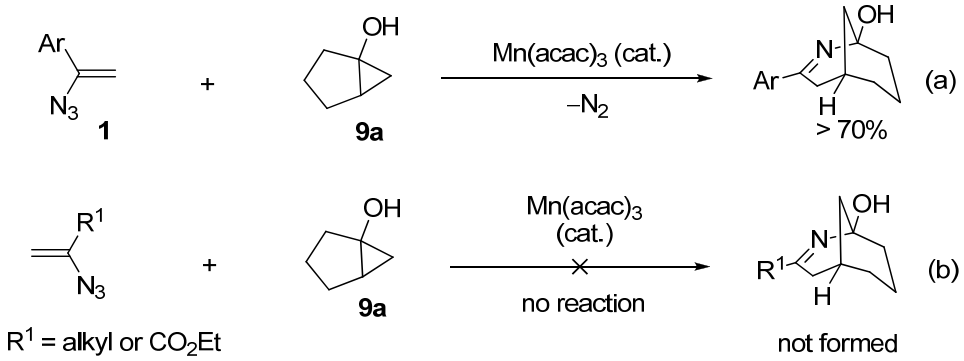
However, there are still some limitations of these methods, especially for the synthesis of azabicyclic compounds. For example, even though the $Mn(acac)_3$-catalyzed reactions of α-monosubstituted vinyl azides **1** and **9a** afforded the desired azabicyclic compounds in good yield (> 70%) (Scheme 7-7, Eq. a), the presence of a β-substituent in vinyl azides **1** (such as the β-methyl group in **1h**) prevented the radical addition reaction, resulting in low yield of the product, presumably due to the steric hindrance (Eq. b).



Scheme 7-7. Reaction of 1,2-disubstituted vinyl azide and cyclic β-carbonyl radical

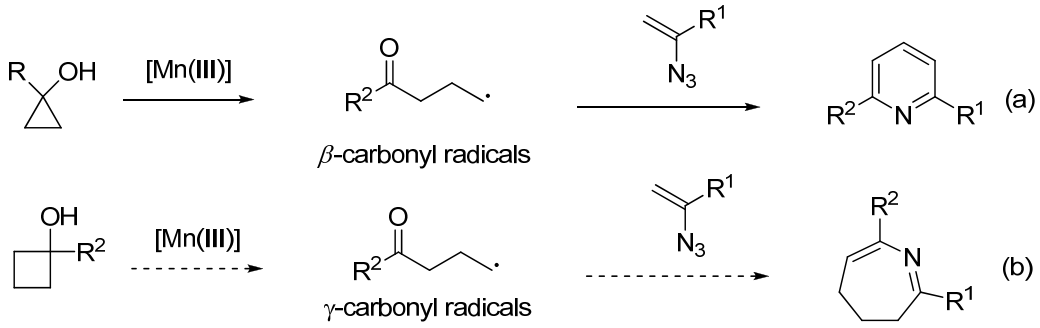
Moreover, the reactions of α-aryl vinyl azides **1** produced azabicyclic compounds in good yields (Scheme 7-8, Eq. a), whereas the employment of α-alkyl or α-ethoxycarbonyl substituted vinyl azides gave no desired product at all with the recovery of vinyl azides (Eq. b). These results suggested that the presence of α-aryl group might

play an important role in the radical addition reaction, such as stabilization of α-azido alkyl radical intermediates.



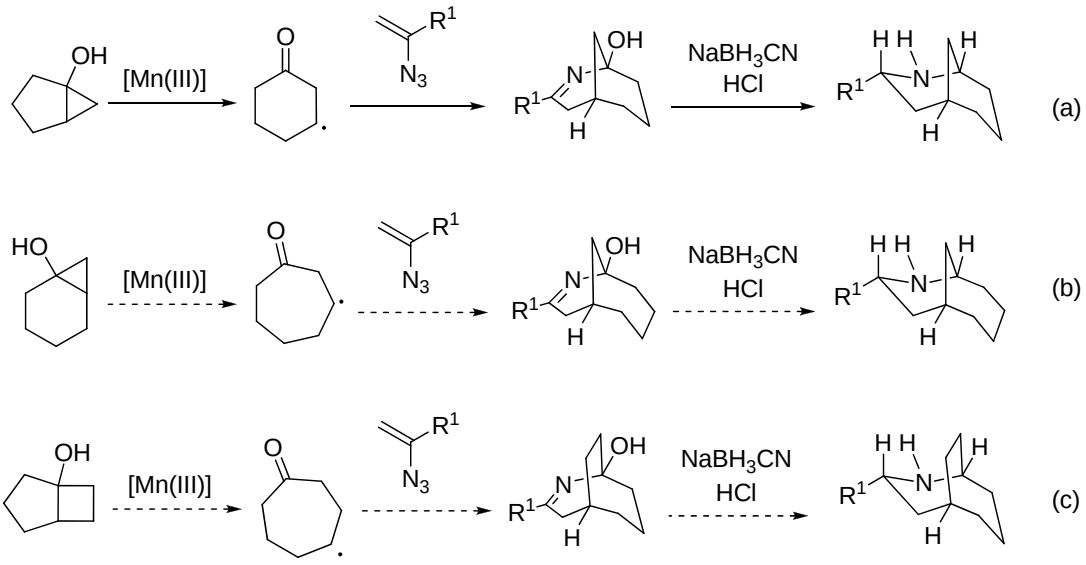
Scheme 7-8. Unsuccessful results of Mn(III)-catalyzed reactions of vinyl azides and bicyclo[3.1.0]hexan-1-ols

In spite of these limitations, the present synthetic methods by using vinyl azides to construct azaheterocycles developed in this thesis are expected to be further applicable in the preparation of various types of azaheterocycles by varying the sources of carbonyl radicals. As described in Chapter 3, β-carbonyl radicals derived from cyclopropanols were involved in the synthesis of six-membered azaheterocycles such as pyridines (Scheme 7-9, Eq. a). According to this reaction, it may be predicted that the reactions of γ-carbonyl radicals which may be generated from cyclobutanols with vinyl azides are possible to produce seven-membered azaheterocycles (Eq. b).



Scheme 7-9. Proposed Mn(III)-catalyzed reaction of vinyl azides and cyclobutanols

Moreover, it has been found that the reactions of vinyl azides and cyclic *β*-carbonyl radicals originated from bicyclo[3.1.0]hexan-1-ols provided 2-azabicyclo[3.3.1]non-2-en-1-ols (Scheme 7-10, Eq. a). Furthermore, reduction of the C═N and bridgehead C−O bonds of these formed azabicyclic compounds by $NaBH_3CN$-HCl provided *endo*-selective (refer to R^1) 2-azabicyclo[3.3.1]nonane derivatives. Presumably, utilization of an analogous cyclic *β*-carbonyl radical derived from bicyclo[4.1.0]heptan-1-ol may lead to 2-azabicyclo[4.3.1]dec-2-en-1-ols, reduction of which by $NaBH_3CN$-HCl would give 2-azabicyclo[4.3.1]decanes stereoselectively (Eq. b). In addition, 2-azabicyclo[3.3.2]decane derivatives are probable to be prepared through the similar reaction pathway from bicyclo[3.2.0]heptan-1-ol (Eq. c).



Scheme 7-10. Proposed Mn(III)-catalyzed reaction of vinyl azides and bicyclo[4.1.0]heptan-1-ol and bicyclo[3.2.0]heptan-1-ol

List of Publications

1. Shunsuke Chiba, Yi-Feng Wang, Guillaume Lapointe, and Koichi Narasaka

   "Synthesis of Polysubstituted *N*-H Pyrroles from Vinyl Azides and 1,3-Dicarbonyl Compounds"

   Organic Letters **2008**, *10*, 313-316.

2. Yi-Feng Wang, Kah Kah Toh, Shunsuke Chiba, and Koichi Narasaka

   "Mn(III)-Catalyzed Synthesis of Pyrroles from Vinyl Azides and 1,3-Dicarbonyl Compounds"

   Organic Letters **2008**, *10*, 5019-5022.

3. Yi-Feng Wang and Shunsuke Chiba

   "Mn(III)-Mediated Reactions of Cyclopropanols with Vinyl Azides: Synthesis of Pyridine and 2-Azabicyclo[3.3.1]non-2-en-1-ol Derivatives"

   Journal of the American Chemical Society **2009**, *131*, 12570-12572.

4. Yi-Feng Wang, Kah Kah Toh, Eileen Pei Jian Ng, and Shunsuke Chiba

   "Mn(III)-Mediated Formal [3+3] Annulation of Vinyl Azides and Cyclopropanols: A Divergent Synthesis of Azaheterocycles"

   Manuscript in preparation.