PART I: Pd(II)-CATALYZED RING-EXPANSION OF CYCLIC 2-AZIDOALCOHOLS FOR SYNTHESIS OF AZAHETEROCYCLES
PART II: Cu(II)-CATALYZED AEROBIC OXIDATION OF BENZYL CYANIDES FOR SYNTHESIS OF CARBOXYLIC ACIDS

NANYANG TECHNOLOGICAL UNIVERSITY

PART I: Pd(II)-CATALYZED RING-EXPANSION OF CYCLIC 2-AZIDOALCOHOLS FOR SYNTHESIS OF AZAHETEROCYCLES

PART II: Cu(II)-CATALYZED AEROBIC OXIDATION OF BENZYL CYANIDES FOR SYNTHESIS OF CARBOXYLIC ACIDS

XU YANJUN

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2012

XU YANJUN

2012

PART I: Pd(II)-CATALYZED RING-EXPANSION OF CYCLIC 2-AZIDOALCOHOLS FOR SYNTHESIS OF AZAHETEROCYCLES

PART II: Cu(II)-CATALYZED AEROBIC OXIDATION OF BENZYL CYANIDES FOR SYNTHESIS OF CARBOXYLIC ACIDS

XU YANJUN

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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

2012

Acknowledgements

First, the author owes his deepest gratitude to his supervisor, Associate Professor Shunsuke Chiba, whose continuous support, patient guidance, and strict training enabled the author to complete his PhD course studies.

The author is deeply grateful to Nanyang Professor Koichi Narasaka, Professor Loh Teck-Peng, and Assistant Professor Dr. Motoki Yamane for their kindly help and useful suggestion.

The author wishes to thank the members in Assistant Professor Shunsuke Chiba's, Nanyang Professor Narasaka's, and Assistant Professor Motoki Yamane's group for the helpful discussion and kind assistance: Dr. Wang Yi-Feng, Dr. Liu Wei-Min, Dr. Ren Wei, Dr. Zhang Lin-E, Mr. Hui Wei Qiang Benjamin, Miss Yue Yan-Ni, Miss Liu Zheng-Hong, Miss Shen Shu-Su, Mr. Zhu Chuan, Mr. He Xin-Yao, Mr. Stephen Sanjaya, Miss Ang Gim Yean, Mr. Tong Meng Kiat Benny, Miss Toh Kah Kah, Miss Ng Pei Jian Eileen, Miss Too Pei Chui, Miss Chua Sze Hui, Miss Tnay Ya Lin, Mr. Chen Hui, Mr. Zhu Xu, Miss Zhang Feng Lian, Mr. Lee Jian Yuan, Miss See Jing Jing, and Mr. Wong Siong Heng Ben.

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. Xu Shuan-Fu and Mdm. Bai Wai-Ni, and his wife Ms. Dong Lin for their continuous encouragement and assistance. The author also thanks his little daughter Miss Xu Yu-Tong for bringing happiness.

Table of Contents

List of Abbreviation

δ	chemical shift (ppm)
°C	degree centigrade
Ac	acetyl
acac	acetylacetonyl
Ar	aryl (substituted aromatic ring) or argon atmosphere
BHT	2,6-Di(*tert*-butyl)-4-methylphenol
Bu	butyl
bpy	2,2'-bipyridine
brs	broad singlet
cat.	catalytic
Cbz	benzyloxycarbonyl
cm^{-1}	wave number
cod	1,5-cyclooctadiene
Cy	cyclohexane
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
dppb	1,4-Bis(diphenylphosphino)butane
dppf	1,1'-Bis(diphenylphosphino)ferroncene
dppp	1,3-Bis(diphenylphosphino)propane
dt	doublet of triplets
DMF	*N*,*N*-dimethylformamide
DMI	1,3-Dimethyl-2-imidazolidinone
DMSO	Dimethyl sulfoxide

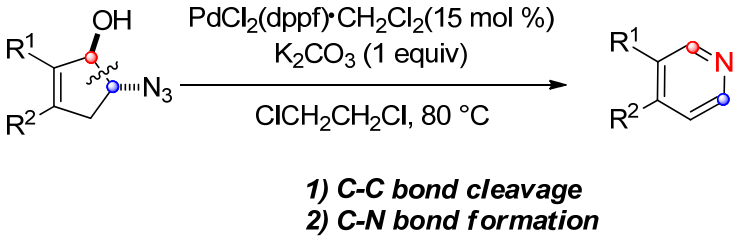
EIHRMS	Electron Ionization High Resolution Mass Spectrometry
eq/equiv	equivalent
ESIHRMS	Electrospray Ionization High Resolution Mass Spectrometry
Et	ethyl
Hz	hertz
i-Pr	*iso*-propyl
IR	infrared spectroscopy
J	coupling constants
LDA	lithium diisopropylamide
M	concentration (mol/L)
M^+	parent ion peak (mass spectrum)
m	multiplet
mcpba	3-chloroperbenzoic acid
Me	methyl
mg	milligram
MHz	megahertz
mmol	millimole
mp	melting point
nbd	2,5-norbornadiene
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl
Pr	propyl
q	quartet
rt	room temperature

s	singlet
t	triplet
t-Bu	*tert*-butyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatagraphy
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

Abstract

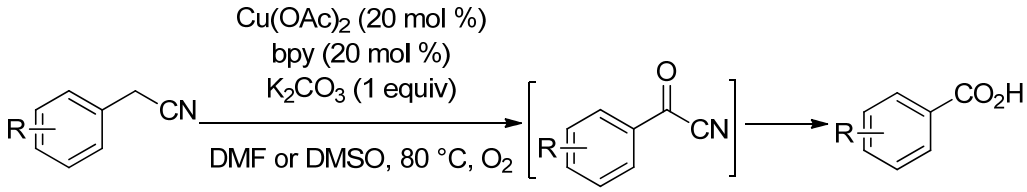
This thesis described two catalytic reactions: (1) Pd(II)-catalyzed ring-expansion of cyclic 2-azidoalcohols for synthesis of azaheterocycles; (2) Cu(II)-catalyzed aerobic oxidation of benzyl cyanides for synthesis of carboxylic acids.

In part I, a Pd(II)-catalyzed ring expansion of cyclic 2-azidoalcohols was described to synthesize azaheterocycles such as pyridine, isoquinoline, γ-carboline and pyrrole derivatives. This transformation was involved a sequence of an unprecedented C–C bond cleavage and C–N bond formation as shown in Scheme 1.



Scheme 1. Pd(II)-catalyzed ring expansion of cyclic 2-azidoalcohols for synthesis of pyridine derivatives.

In part II, a Cu(II)-catalyzed aerobic oxidation of primary benzyl cyanides for synthesis of corresponding aromatic carboxylic acids was developed. In this process, the C–H bond oxygenation of benzyl cyanides occurred to generate the benzoyl cyanide intermediates, which were hydrolyzed to provide the corresponding benzoic acids as shown in Scheme 2. Compared to classical basic hydrolysis of nitriles by nucleophilic addition of hydroxyl group to nitrile group, this oxidative hydrolysis of benzyl cyanides was initiated by deprotonation at the C–H bond adjunct to the nitrile providing one-carbon shorter benzoic acids. Moreover, this reaction has potential application to prepare ketone from the secondary benzyl cyanide.



Scheme 2. Cu(II)-catalyzed aerobic oxidation of benzyl cyanides for synthesis of aromatic carboxylic acids.

Chapter 1 General Introduction

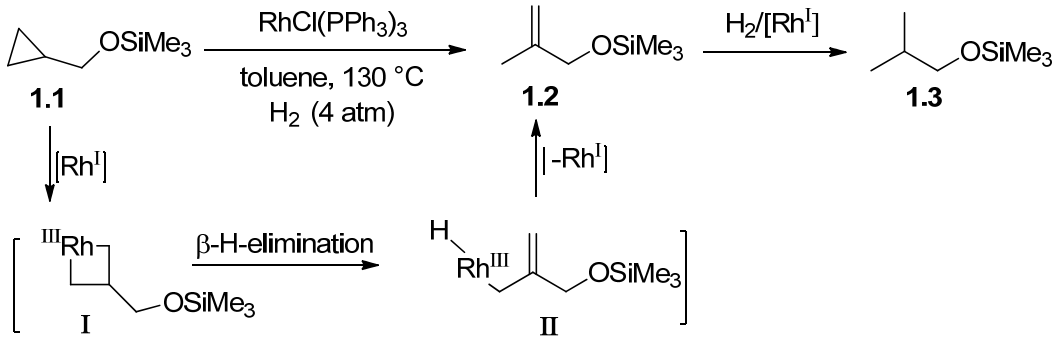
Applications of metal-mediated C–C bond cleavage in organic synthesis

Transition metal–catalyzed C–C bond cleavage has attracted attention as a versatile tool in organic synthesis.[1] Initially research on transition metal–mediated C–C bond cleavage and its applications focused on stoichiometric reactions to synthesize organometallic complexes.[1,2] As research into C–C bond cleavage has advanced, more and more catalytic reactions have been reported. The focus of this introductory chapter is to review typical catalytic C–C bond cleavages, such as the direct oxidative addition of a C–C bond to transition metals and transition metal-catalyzed β-carbon elimination. Other typical C-C bond cleavages, such as rearrangement of vinyl cyclopropanes (VCPs),[3] decarboxylation[4] and retro-allylation[5] are beyond the scope of this introduction.

1.1 Oxidative addition of a C–C bond to a transition metal

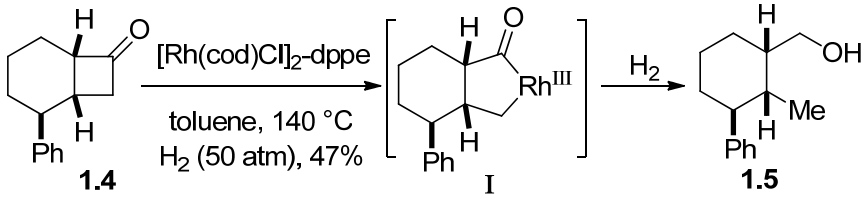
The transition metal-catalyzed direct cleavage of C–C bonds involving their oxidative addition to low-valence metals (C−C + [M] → C−[M]−C) generally occurs in strained carbocycles such as cyclopropyl and cyclobutyl skeletons.[6] Most studies of these reactions indicate that they are driven by release of ring-strain energy in the 3- or 4-membered ring, generating 4- or 5-membered metallacycles, respectively.[7] In other words, the ring-strained molecules in these catalytic reactions are converted into the ring-opened or ring-expanded compounds.

Chirik reported the selective catalytic cleavage and functionalization of a C−C bond in cyclopropane derivative **1.1** using $RhCl(PPh_3)_3$ as the catalyst (Scheme 1-1).[8] The reaction produced compound **1.2** when conducted in air and compound **1.3** when conducted in a hydrogen atmosphere. Initially, the sterically unhindered C–C bond in molecule **1.1** underwent addition by $RhCl(PPh_3)_3$ to generate the rhodacyclobutane [Rh^{III}] complex **I**. Subsequent β-hydride elimination and reductive elimination gave a branched alkene derivative **1.2** that could be reduced to alkane derivative **1.3**.



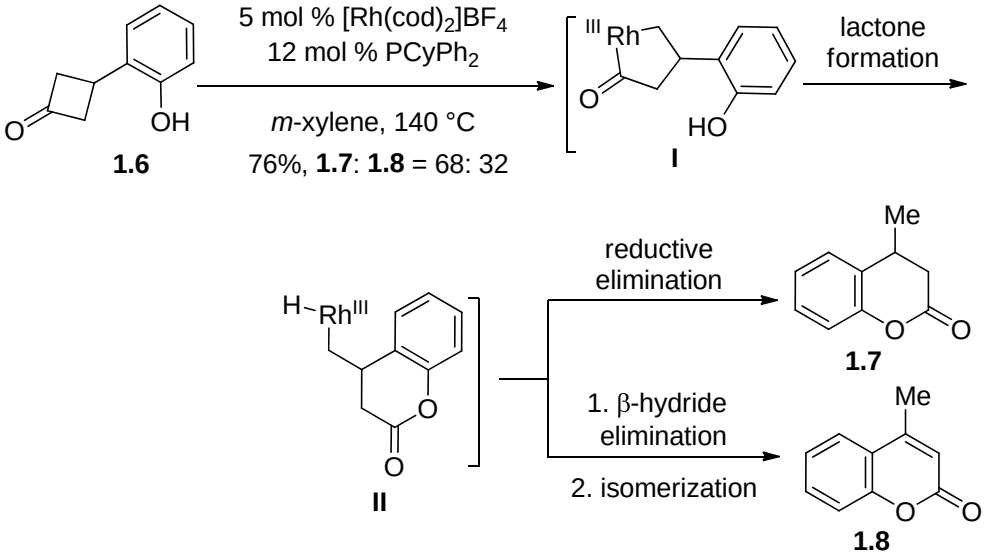
Scheme 1-1. $RhCl(PPh_3)_3$-catalyzed cleavage and functionalization of a C−C bond in a cyclopropane derivative.

Cyclobutanone derivatives can undergo a similar selective oxidative addition of a C-C bond to transition metals, as recently demonstrated by Murakami and Ito. They reported the production of ring-opened alcohol **1.5** in 47% yield from bicyclic cyclobutanones **1.4** through regioselective oxidative addition of a C–C bond to Rh^I *via* the 5-membered acylrhodium (III) intermediate **I** (Scheme 1-2).[9]



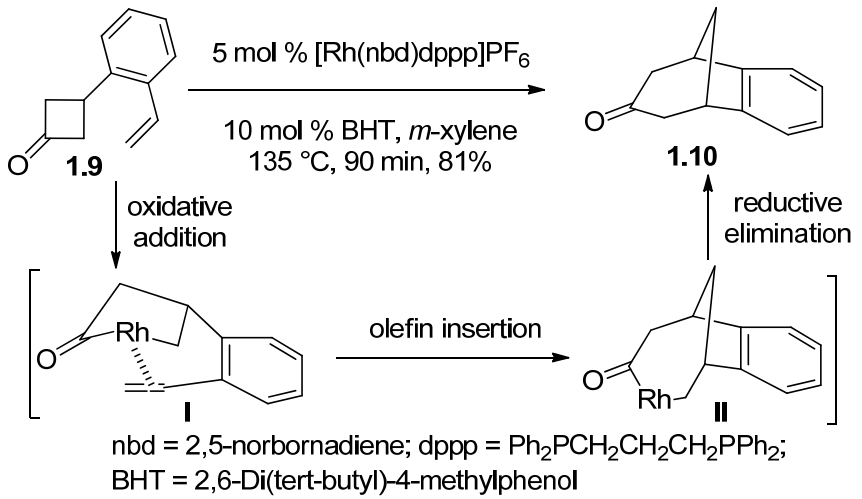
Scheme 1-2. Rh(I)-catalyzed hydrogenolysis of cyclobutanones.

When the cyclobutanone carried an *o*-phenol group such as substrate **1.6** (Scheme 1-3),[10] the six-membered lactones **1.7** and **1.8** were obtained *via* formation of the five-membered acylrhodium species **I** followed by lactone formation to generate intermediate **II.** This intermediate underwent reductive elimination to give lactone **1.7** or consecutive β-hydride elimination and isomerization to give lactone **1.8**.



Scheme 1-3. Rh-catalyzed C-C bond cleavage of cyclobutanone to synthesize lactone.

When it carried an *o*-styryl group, the five-membered acylrhodium intermediate **I** generated from compound **1.9** could undergo successive intramolecular insertion of olefin and reductive elimination to give the bicycle[3.2.1]octanone **1.10** in 81% yield (Scheme 1-4).[11]

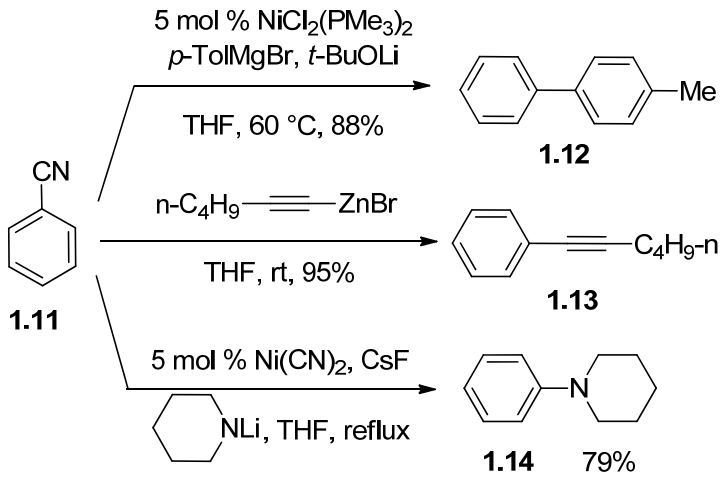


Scheme 1-4. Intramolecular insertion of olefin into a C–C bond of cyclobutanone.

1.2 Oxidative addition of C-CN bond to transition metals

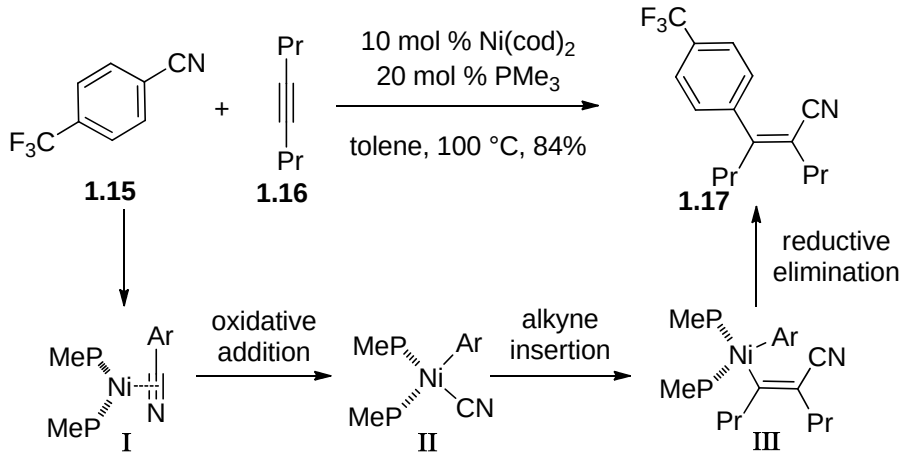
Insertion of transition metals into the C–CN bond has recently attracted much attention because of its important potential applications in synthetic chemistry.[12,13] C–CN bond cleavage could be applied to the cross-coupling of benzonitriles with various nucleophiles and to the carbocyanation of unactivated alkenes and alkynes.

While palladium complexes are among the most effective catalysts for cross-coupling aryl halides, nickel complexes are more effective catalysts for cleaving the C–CN bond of aryl cyanides. Miller and co-workers reported a series of nickel-catalyzed cross-couplings of benzonitriles using Grignard reagents, alkynylzinc reagents, and secondary amines as nucleophiles (Scheme 1-5).[14] These cross-couplings involved the oxidative addition of a C–CN bond to a low-valence nickel(0) complex, with the less hindered and electron-donating PMe_3 serving as ligand.



Scheme 1-5. Ni-catalyzed cross-coupling of aryl nitrile.

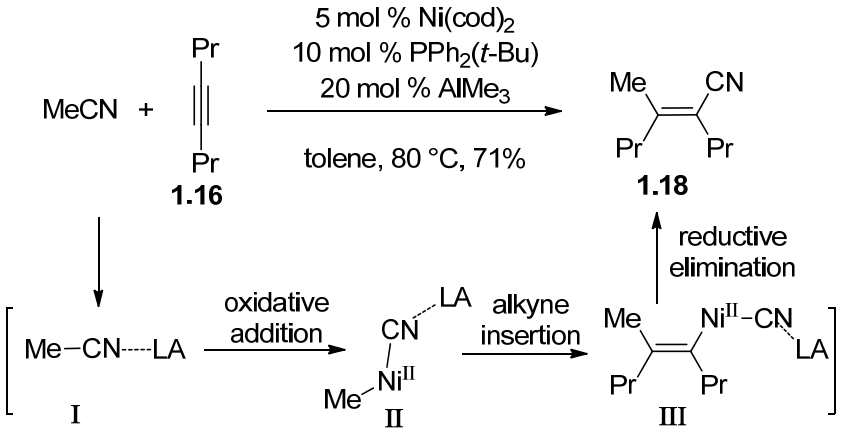
In fact, nickel-catalyzed C–CN bond activation of aryl cyanides has proven useful as a novel strategy in organic chemistry. Nakao and Hiyama have developed arylcyanation of alkynes catalyzed by low-valence nickel(0) complexes as shown in Scheme 1-6.[15] The nickel(II) complex **II** was formed through oxidative addition of benzonitrile **1.15** to nickel(0) *via* hypothetical π-coordinating intermediate **I**. Subsequent insertion of alkyne and reductive elimination afforded α,β-unsaturated nitrile **1.17** in 84% yield.



Scheme 1-6. Ni-catalyzed arylcyanation of alkyne.

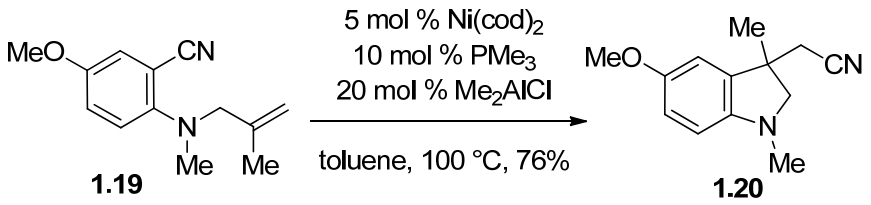
In further studies, these researchers successfully cleaved not only arylnitriles but also

similar C–CN bonds in alkenyl,[16] alkylnyl,[17] and allyl[18] carbonitriles and performed facile addition of alkynes to give the corresponding α,β-unsaturated nitriles. They found that using a Lewis acid as co-catalyst dramatically expanded the scope of the reaction to include alkyl cyanides (Scheme 1-7).[13,19] In the Lewis acid/nickel catalyst system, the Lewis acid accelerates oxidative addition of the C–CN bond to Ni(0) by coordinating with the cyano group.



Scheme 1-7. Ni-catalyzed alkylcyanation of alkyne.

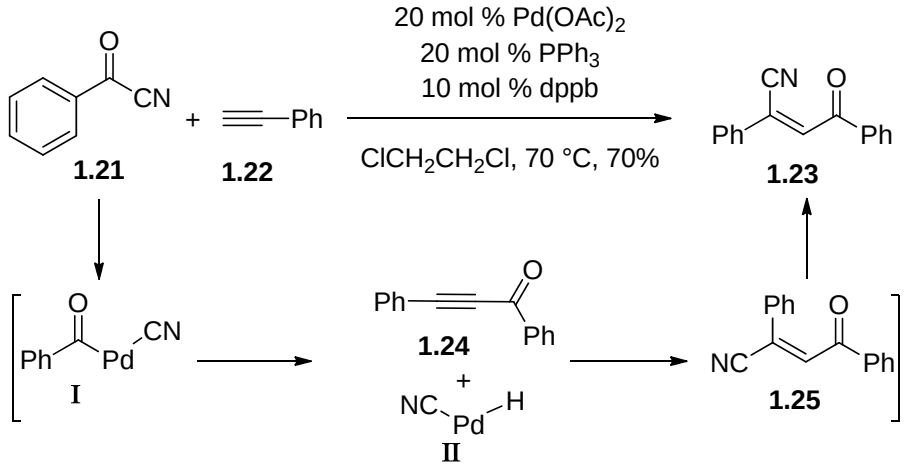
The arylcyanation of alkenes has also been reported.[20] For example, Nakao and Hiyama achieved the intramolecular arylcyanation of alkenes using the Ni-$AlMe_2Cl$ catalytic system (Scheme 1-8).[21] This reaction has proven to be a versatile protocol for synthesizing a range of synthetically interesting nitriles with a benzylic quaternary carbon.



Scheme 1-8. Intramolecular arylcyanation of alkenes.

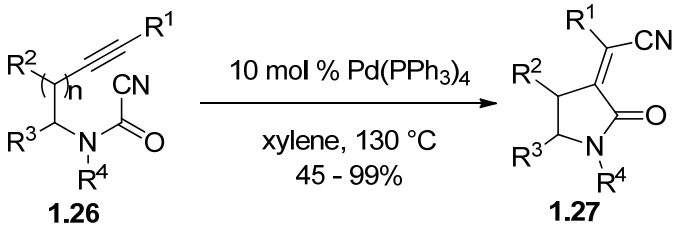
In this approach, C(O)–CN bonds are more easily cleaved than C–CN bonds owing to their polarized character. Decarbonylation of aroyl cyanides to yield benzonitriles has been described,[22] and acylcyanation of alkynes and alkenes has also recently been achieved. [23,24]

The catalytic insertion of terminal alkynes into the C(O)–CN bond of aroyl cyanides was reported by Nozaki and Takaya (Scheme 1-9).[23] The proposed mechanism is different from the related nickel-catalyzed arylcyanation of internal alkynes described above. Oxidative addition of the C(O)–CN in acyl cyanide **1.21** to the palladium(0) is proposed to generate the acylpalladium intermediate **I**, which reacts with phenylacetylene to form the alkynyl ketone **1.24** along with palladium hydride **II**. Subsequently, hydrocyanation of the alkyne **1.24** with palladium hydride **II** provides the E-alkene **1.25,** which isomerizes to the Z-product **1.23** in 70% yield.



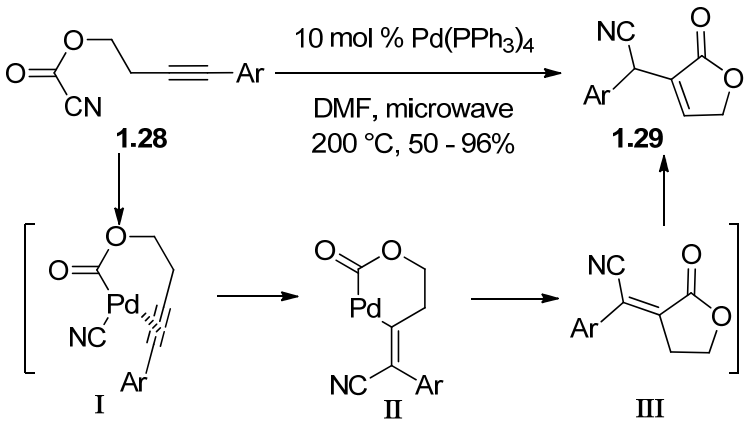
Scheme 1-9. Pd-catalyzed insertion of alkyne into the C(O)–CN bond in acyl cyanide.

Takemoto and co-workers reported the intramolecular cyanoamidation of alkynyl cyanoformamides to form tetrasubstituted alkene derivatives (Scheme 1-10).[24]



Scheme 1-10. Intramolecular cyanoamidation of alkynyl cyanoformamides.

Cyanoesterification of the C–C π-bond, a process also termed cyanocarboxylation, is rare[25] because cyanoformate esters are more reactive than aryl nitriles and cyanoformamides. Douglas reported palladium-catalyzed C–CN activation for intramolecular cyanoesterification of alkynes **1.28**, providing butenolides **1.29** in good to excellent yields (Scheme 1-11).[26]



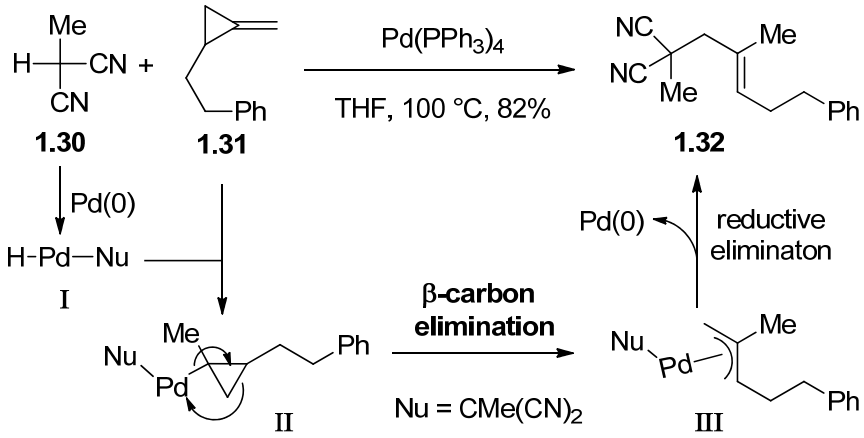
Scheme 1-11. Pd-catalyzed intramolecular cyanoesterification of alkynes.

1.3 Chemistry of β-carbon elimination

β-Carbon elimination of carbon-metal species ([M]−C−C_α−C_β) or heteroatom-metal species {[M]−X−C_α−C_β (X = O, N)} is another approach for cleaving C−C bonds.

1.3.1 β-Carbon elimination of carbon-metals ([M]−C−C_α−C_β→ C=C_α + M−C_β)

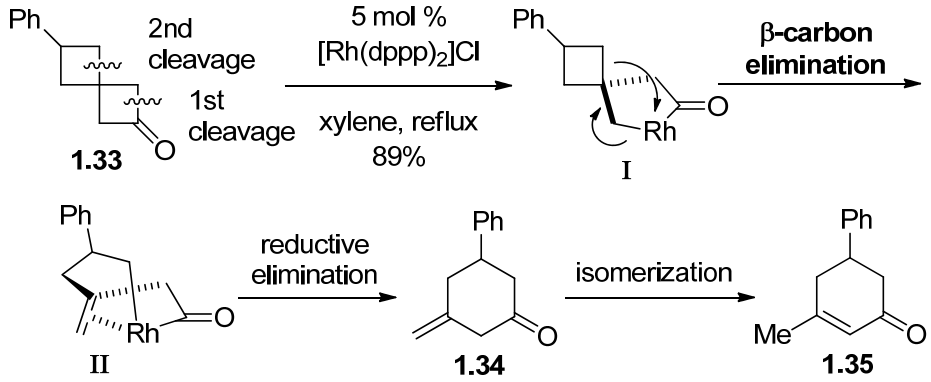
Transition metal-catalyzed β-carbon elimination of methylenecyclopropane and its derivatives has been developed.[27] Yamamoto reported that Pd-catalyzed hydrocarbonation of methylenecyclopropanes with pronucleophiles generated ring-opened compounds *via* β-carbon elimination (Scheme 1-12).[28] The reaction began with oxidative addition of the C–H bond of pronucleophile **1.30** to Pd(0) to form palladium hydride species **I**. This species hydropalladated the methylenecyclopropane derivative **1.31**, affording an alkylpalladium complex **II**, which underwent a highly regioselective β-carbon elimination to generate an allylpalladium **III**. Subsequently, reductive elimination of allylpalladium **III** yielded the olefin **1.32** in 82% yield and Pd(0). The driving force of this process was release of the ring strain in **II**.



Scheme 1-12. Pd-catalyzed ring opening in the hydrocarbonation of methylenecyclopropanes by pronucleophiles

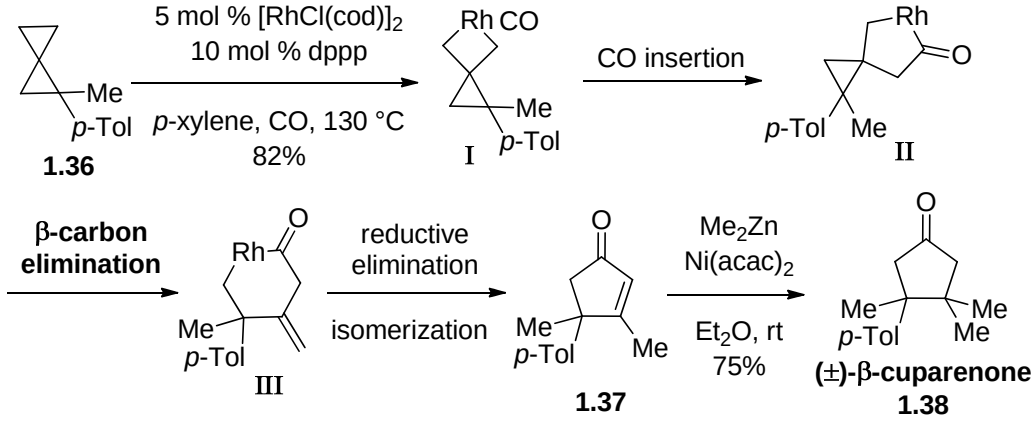
Murakami and co-workers have reported two examples of double cleavage of C–C bonds in the same compound. One example is rhodium-catalyzed successive double cleavage of

C-C bonds in strained spiro cyclobutanone **1.33** to produce the cyclohexenenone derivative **1.35** (Scheme 1-13).[29] In the first C–C bond cleavage, oxidative addition of a C–C bond in spirocyclobutanone **1.33** to Rh(I) gave the 5-membered acylrhodium (III) intermediate **I**. In the second C–C bond cleavage, β-carbon elimination of another cyclobutyl group generated the 7-membered acylrhodium(III) ring intermediate **II**. This intermediate underwent reductive elimination to provide the β,γ-unsaturated carbonyl compound **1.34,** which isomerized to the cyclohexenone derivative **1.35**.



Scheme 1-13. Rh-catalyzed double cleavage of C–C bonds in spiro cyclobutanones.

The second example of double cleavage of C–C bonds is rhodium-catalyzed carbonylation of spiropentanes. This reaction was used in the concise synthesis of (±)-β-cuparenone **1.38** (Scheme 1-14).[30] In this process, the 5-membered acylrhodium(III) ring intermediate **II** was generated *via* oxidative addition of the C–C bond to the Rh(I) followed by insertion of CO. Intermediate **II** then underwent a sequence of β-carbon elimination, reductive elimination, and isomerization to give the cyclopentenone **1.37** in 82% yield. This compound underwent 1,4-addition with Me_2Zn in the presence of $Ni(acac)_2$ as catalyst to produce the (±)-β-cuparenone **1.38**.



Scheme 1-14. Rh-catalyzed carbonylation of spiropentanes and its application.

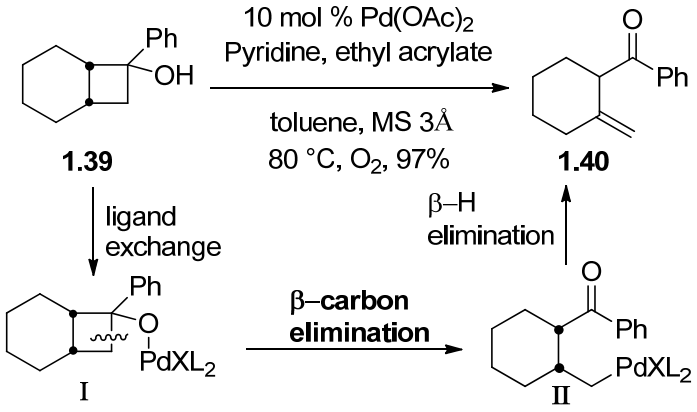
1.3.2 β-Carbon elimination of metal alcoholates ([M]−O−C_α−C_β → O=C + [M]−C_β)

Transition-metal alcoholates have been extensively explored due to their interesting reactivity and structural variety.[31] In fact, β-carbon elimination of transition-metal alcoholates ([M]−O−C_α−C_β → O=C + [M]−C_β) is an important application in organic chemistry. In most of these reactions, the release of ring strain or formation of a relatively stable bond is a primary driver of the C−C bond cleavage.

1.3.2.1 β-Carbon elimination of strained metal alcoholates

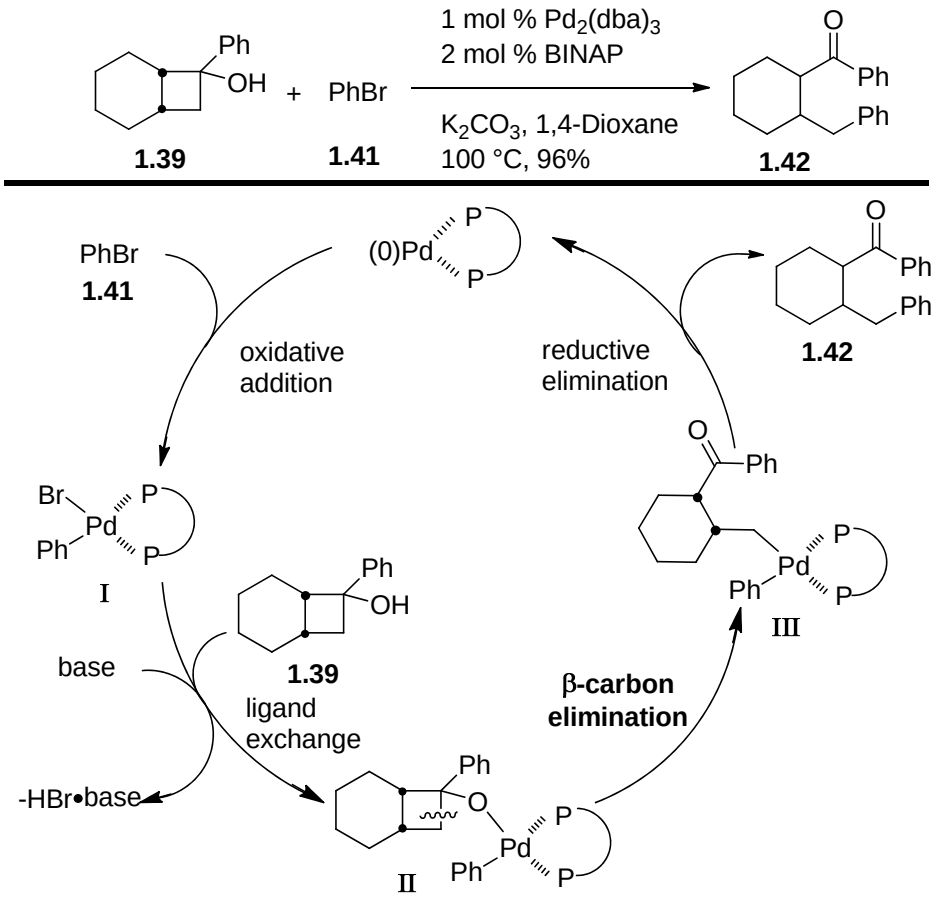
β-Carbon elimination in cyclobutanol derivatives easily occurred in the presence of transition metals as a catalyst.[32] Uemura and co-workers reported the Pd(II)-catalyzed oxidative ring cleavage of *tert*-cyclobutanols and β-carbon elimination of the palladium(II) alcoholate species to afford the corresponding *β,γ*–unsaturated ketones (Scheme 1-15).[33]

In this reaction, cyclobutanol derivative **1.39** underwent ligand exchange with palladium(II) complex to generate palladium(II) alcoholate intermediate **I**, which then underwent the key step of β-carbon elimination to afford the less hindered primary alkylpalladium(II) intermediate **II**. This intermediate underwent β-hydrogen elimination to produce the *β,γ*–unsaturated ketone **1.40** in 97% yield along with Pd(0), which was reoxidized to Pd(II) by molecular oxygen to maintain the catalytic cycle.



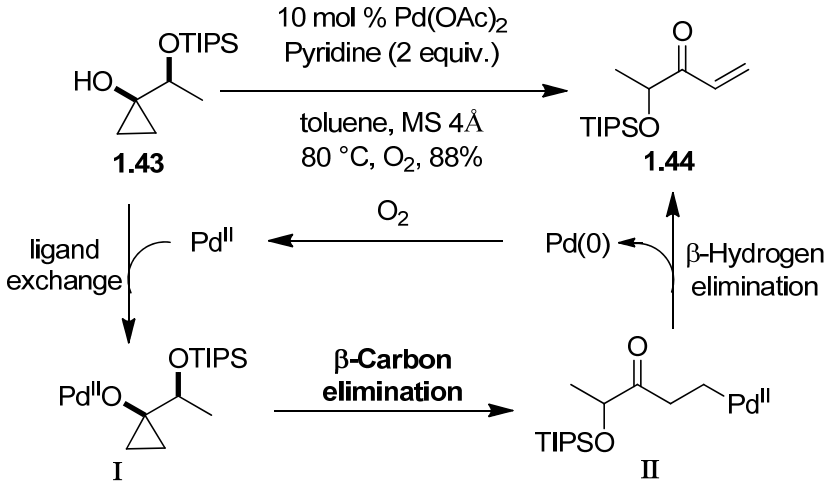
Scheme 1-15. Pd-catalyzed ring opening of cyclobutanols.

Uemura further reported the Pd-catalyzed arylation of *tert*-cyclobutanols using aryl bromide (Scheme 1-16).[34] This reaction began with oxidative addition of bromobenzene **1.41** to Pd(0)-phosphine complex to generate the active palladium(II) species **I** *in situ*. Subsequent ligand exchange and β-carbon elimination afforded the intermediate **III**, which underwent reductive elimination to produce the γ-arylated ketone **1.42** in 96% yield along with Pd(0). The ligand was shown to play two important roles in this process: (1) Pd(II) alcoholate **II** underwent β-carbon elimination to form the alkylpalladium intermediate **III** instead of undergoing reductive elimination to give ether product; (2) alkylpalladium intermediate **III** underwent reductive elimination to provide the arylation product **1.42** instead of undergoing β-hydrogen elimination.



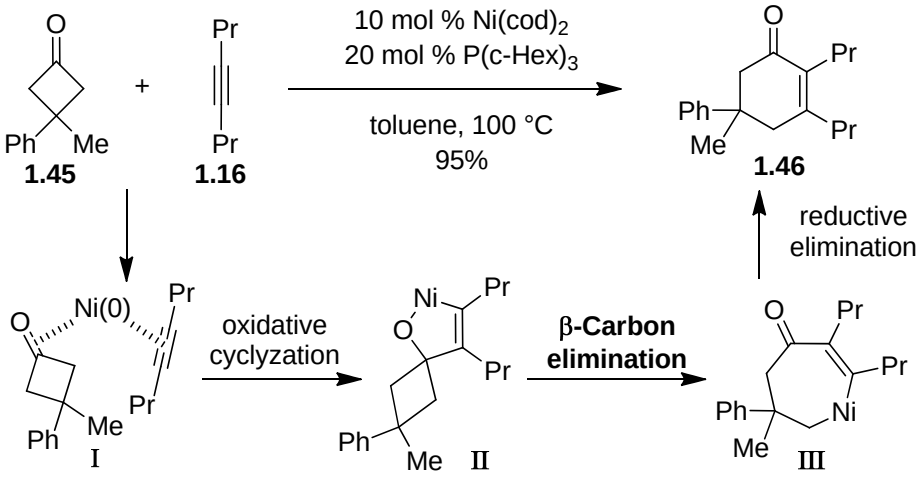
Scheme 1-16. Pd-catalyzed arylation of *tert*-cyclobutanols.

Cyclopropanol derivatives can also undergo β-carbon elimination in the presence of transition metals to release ring-strain energy.[34] For example, Cha described a Pd(II)-catalyzed conversion of cyclopropanols to α,β-unsaturated ketones (Scheme 1-17).[35a] The key step was again β-carbon elimination of the palladium-alcoholate **I** to afford the alkylpalladium intermediate **II**. This intermediate underwent β-hydrogen elimination to produce the α,β-unsaturated ketone **1.44** in 88% yield along with Pd(0), which could be oxidized by molecular oxygen to regenerate Pd(II).



Scheme 1-17. Pd-catalyzed ring opening of a cyclopropanol derivatives.

Murakami described a nickel-catalyzed intermolecular alkyne insertion into cyclobutanones to afford 2-cyclohexenones, the mechanism of which probably involved β-carbon elimination.[36] A feasible mechanism is shown in Scheme 1-18: the oxanickelacyclopentene **II** forms by oxidative cyclization of the carbonyl group of cyclobutanone **1.45** and 4-octyne with Ni(0). The 4-membered ring of the intermediate **II** then opens by β-carbon elimination and expands to give 7-membered nickelacycle **III**. Finally, reductive elimination gives the 2-cyclohexenone derivative **1.46** in 95% yield and regenerates Ni(0).

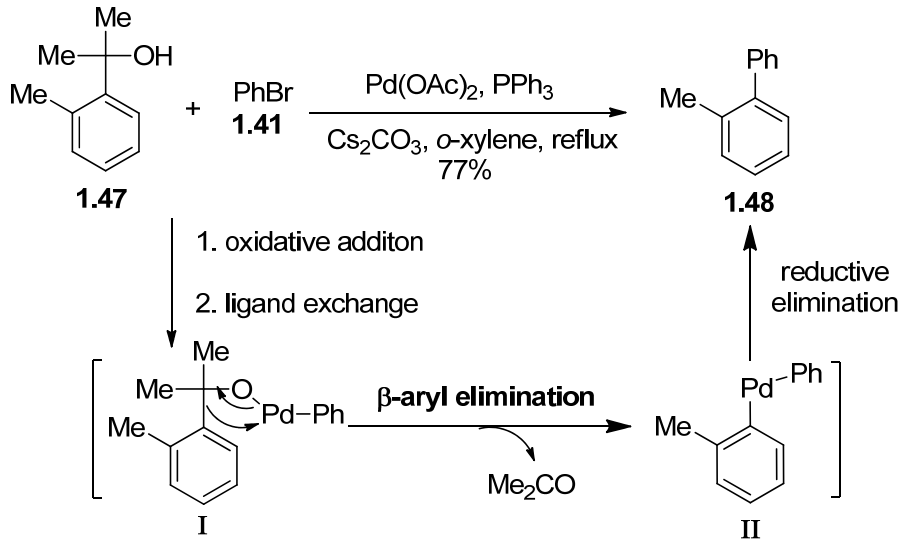


Scheme 1-18. Ni-catalyzed intermolecular alkyne insertion into cyclobutanone.

1.3.2.2 β-Carbon elimination of unstrained metal alcoholates

Unlike C–C bonds in strained cyclic molecules, the same bonds in unstrained cyclic and acyclic molecules rarely undergo *β*-carbon elimination. Nevertheless, such β-carbon cleavage can routinely be achieved in tertiary alcoholates.

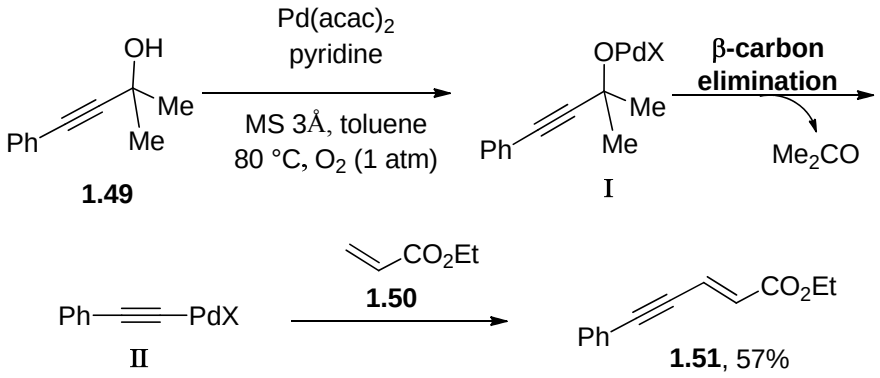
For example, α,α-disubstituted arylmethanols can undergo β-carbon (aryl) elimination in the presence of transition metals.[37] Miura and co-workers reported that the 2-methylphenyl-2-propanol **1.47** smoothly reacted with bromobenzene in the presence of $Pd(OAc)_2$ as catalyst to produce the 2-methylphenylbiphenyl **1.48** (Scheme 1-19).[38] The key step was β-carbon (aryl) elimination of the Pd(II) alcoholate **I**, forming a very stable arylpalladium(II) species **II** and releasing acetone.



Scheme 1-19. Pd-catalyzed arylation of aryl halide *via* β-carbon (aryl) elimination of α,α-disubstituted arylmethanol.

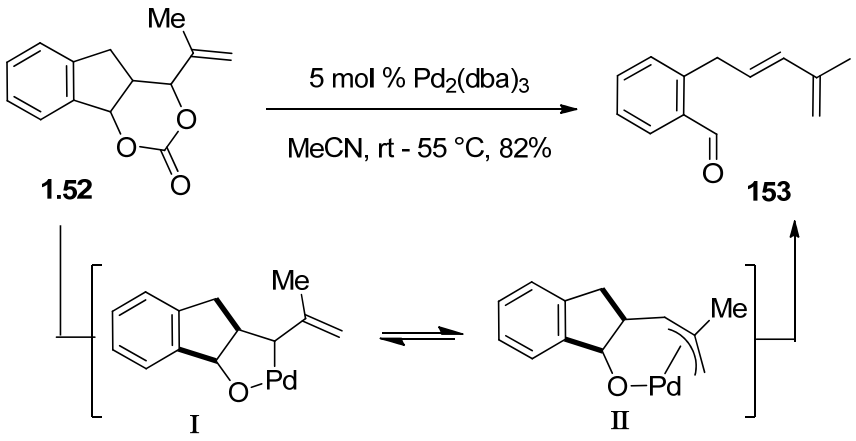
Uemura reported that using tertiary propargylic alcohols as the alkynyl source to react with ethyl acrylate in the presence of palladium catalyst gave enyne compounds as shown

in Scheme 1-20.[39] In the key step of this process, β-carbon (alkynyl) elimination of palladium alcoholate **I** gave the alkynyl-palladium intermediate **II**. This intermediate subsequently underwent a Heck-type reaction with ethyl acrylate **1.50** to produce the enyne compound **1.51** in 57% yield.



Scheme 1-20. Pd-catalyzed alkynylation of alkene *via* β-alkynyl elimination.

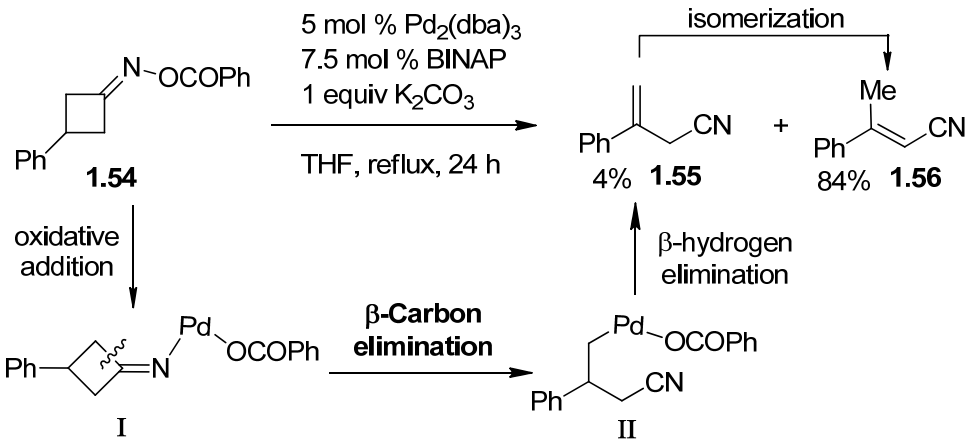
C–C bond cleavage of unstrained cyclic alcoholates is quite rare. Tamaru reported β-decarbopalladation instead of β-carbon elimination, in a process in which Pd(0) catalyzed the ring opening of 4-vinyl cyclic carbonates to furnish ω-diene aldehydes and ketones (Scheme 1-21).[40] In their study, 6-vinyl cyclic carbonate **1.52** underwent oxidative addition and decarboxylation to form 2-oxa-1-palladacyclopentane **I** or π-allylpalladium intermediate **II,** which the authors assumed could undergo β-decarbopalladation to furnish the ω-diene aldehyde **1.53**. The driving force of this process might be generation of the π-allylpalladium intermediate and conjugated diene.



Scheme 1-21. Formation of ω-diene aldehyde *via* β-decarbopalladation.

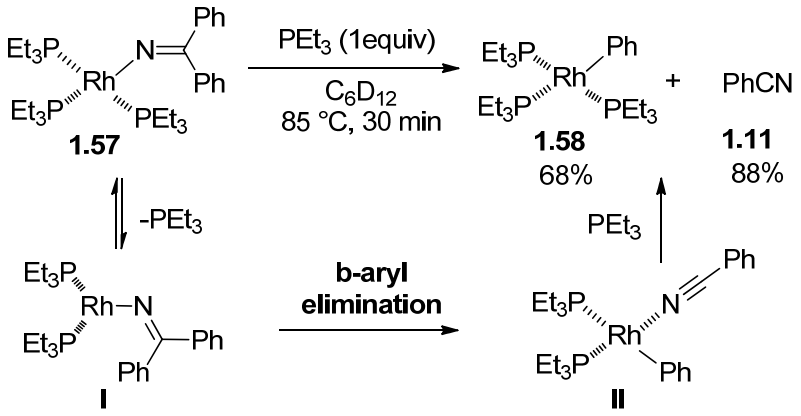
1.3.3 β-Carbon elimination of iminyl metals

β-Carbon elimination of iminyl metal species ([M]–N=C_α–C_β → N≡C_α + C_β–[M]) has also been studied throughout the years. Uemura's group described a Pd(0)-catalyzed reaction in which carbonitriles were generated from cyclobutanone *O*-acyloximes by β-carbon elimination, as shown in Scheme 1-22.[41] In their proposed mechanism, oxidative addition of the N−O bond of ketone *O*-acyloxime **1.54** to a Pd(0) complex affords the intermediate cyclobutaniminopalladium(II) species **I**, which undergoes *β*-carbon elimination to give *γ*-cyanoalkylpalladium species **II**. Subsequently, *β*-hydride elimination produces β,γ-unsaturated carbonitrile **1.55,** which isomerizes to the α,β-unsaturated carbonitrile **1.56**. The driving force for this process is the release of ring strain energy in intermediate **I** by *β*-carbon elimination.



Scheme 1-22. Pd-catalyzed ring cleavage of cyclobutanone oxime leading to nitrile formation *via* β-carbon elimination.

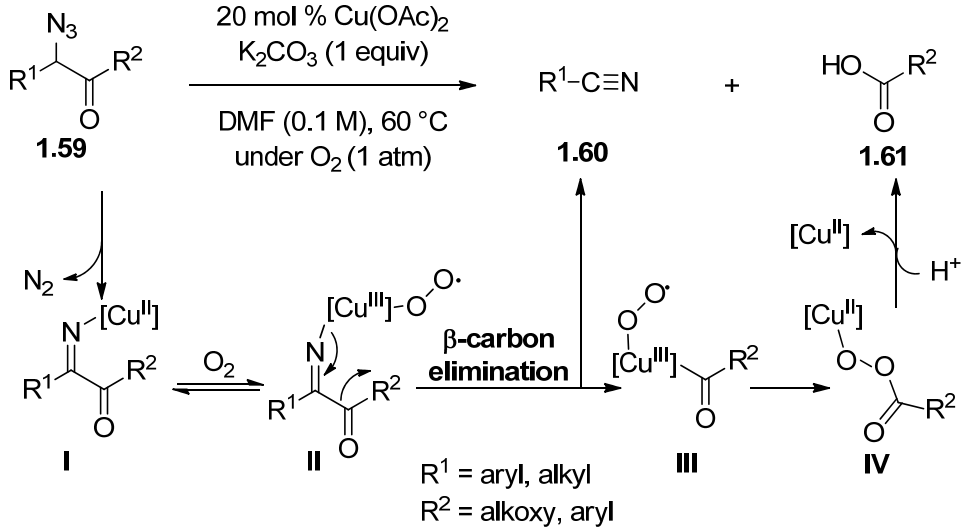
Hawtig and co-workers reported the direct observation of *β*-aryl elimination from the iminyl ligand of an isolated Rh(I) iminyl complex (Scheme 1-23).[42] This reaction generated Rh(I) aryl complexes **1.58** and free aromatic nitriles **1.11**. Formation of both the relatively stable Rh(I) complex **II** and aryl nitrile **1.11** might be the driving force of this process.



Scheme 1-23. *β*-Aryl elimination of an Rh(I) iminyl complex

Recently, our group reported a copper-catalyzed fragmentation of α-azido carbonyl compounds under an oxygen atmosphere. This process generated carbonitriles *via* C−C bond cleavage of a transient iminyl copper intermediate.[43] A plausible mechanism

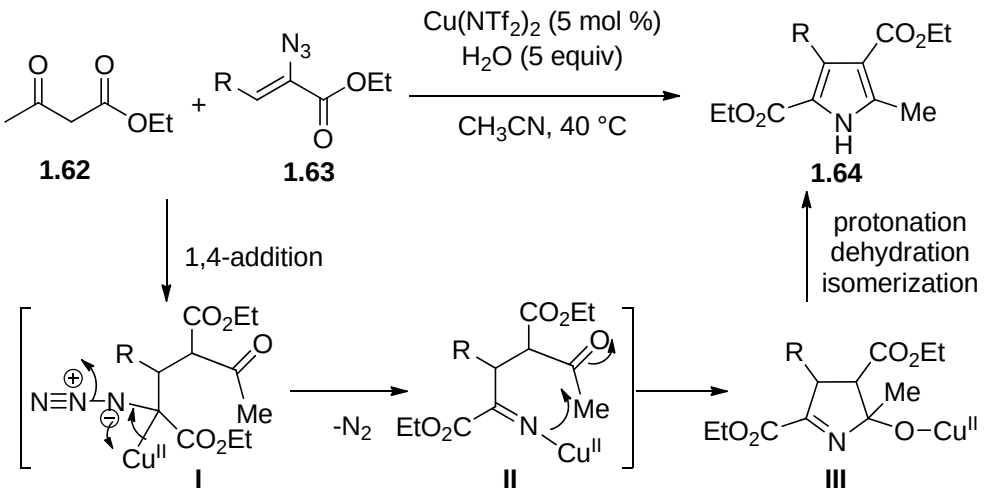
involving β-carbon elimination was proposed (Scheme 1-24). Denitrogenation of **1.59** leads to iminyl copper species **I,** which is oxidized by O_2 to afford peroxycopper(III) species **II**. This species undergoes β-carbon elimination to form nitrile **1.60** and acylcopper **III**, which isomerizes to acylperoxy copper **IV**. Protonation of acylperoxy copper **IV** yields carboxylic acid **1.61** and regenerates Cu(II) salts.



Scheme 1-24. Cu-catalyzed fragmentation of α-azido carbonyl compounds under an O_2 atmosphere, providing carbonitriles *via* C−C bond cleavage of iminyl copper.

1.4 Motivation for this thesis

Recently, our group described a Cu(II)-catalyzed synthesis of polysubstituted *N*–H pyrroles from α-ethoylcarbonyl vinyl azides and ethyl acetoacetate through 1,4-addition of the acetoacetate to the vinyl azides (Scheme 1-25).[44]



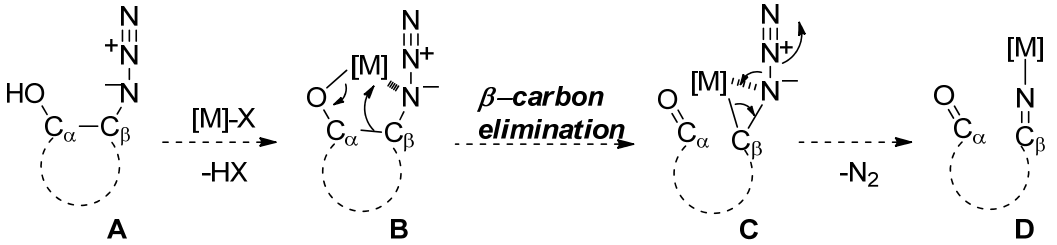
Scheme 1-25. Cu-catalyzed pyrrole formation from ethyl acetoacetate and vinyl azides through 1,4-addition.

In this process, the reaction might be initiated by 1,4-addition of ethyl acetoacetate **1.62** to vinyl azide **1.63** to generate the α-azidocarbocupper species **I**. Migration of copper from *C* to *N* via releasing N_2 afforded iminyl copper(II) intermediate **II**, which underwent intramolecular nucleophilic attack to the carbonyl group to give the *tetra*-substituted pyrrole **1.64** with elimination of water.

Inspired by the finding that copper could migrate from *C* to *N* with elimination of N_2, the author focused on exploring other methods to generate the alkylideneaminometal $\{R^1R^2C{=}N\text{-}[M]\}$ intermediate species *via* this kind of migration. Given that metal alcoholates easily undergo β-carbon elimination, the author reasoned that readily available 2-azidoalcohols would be sufficiently reactive to act as starting material in metal migration reactions.

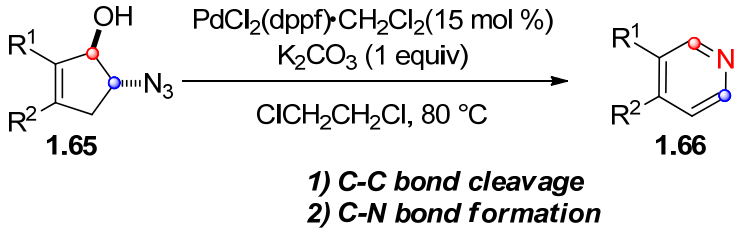
The author hypothesized the transition metal alcoholates **B** generated from

2-azidoalcohols **A** would undergo *β*-carbon elimination to give α-azidocarbometal species **C**. Subsequent metal migration from *C* to *N* with elimination of dinitrogen might afford iminyl metal species **D**, which could be used to form additional C–N bonds (Scheme 1-26). Coordination of the internal nitrogen of the azido moiety to the metal center[45] may promote these processes.



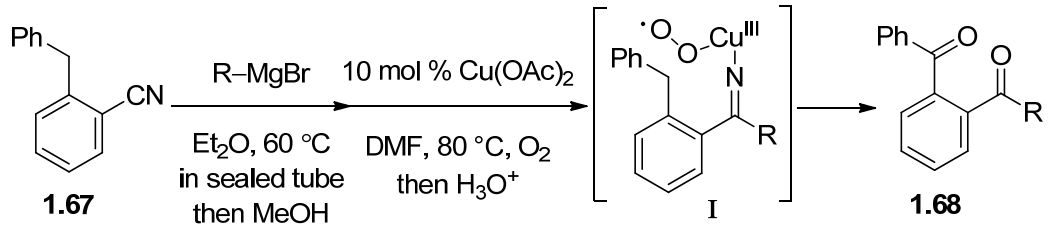
Scheme 1-26. Hypothesized mechanism to generate iminyl metal species from 2-azidoalcohols.

Based on this hypothesis, a Pd-catalyzed ring expansion of cyclic 2-azidoalcohols is described in Chapter 2 as a way to synthesize certain azaheterocycles such as pyrrole, pyridine, isoquinoline, γ-carboline and pyrazine derivatives (Scheme 1-27).[46] Among them, synthesis of 3,4-disubstituted pyridines[47] is still challenging. This ring expansion involves an unprecedented C–C bond cleavage step (β-carbon elimination of palladium(II) alcoholate) followed by C–N bond formation. The *β*-carbon elimination of palladium(II) alcoholate in this process differs from that described in section 1.3.2.



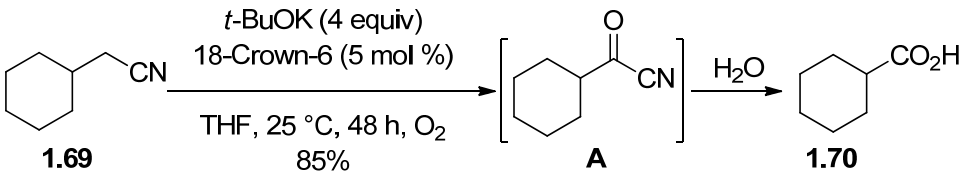
Scheme 1-27. Pyridine formation from 2-azidoalcohols *via* ring expansion.

Our group has also explored the intriguing chemical reactivity of iminyl copper species in aerobic oxidation reactions.[43,48] For example, benzylic C–H oxygenation with carbonitriles and Grignard reagents has been achieved under an oxygen atmosphere using an iminyl copper species as an intramolecular directing group (Scheme 1-28).[48c]

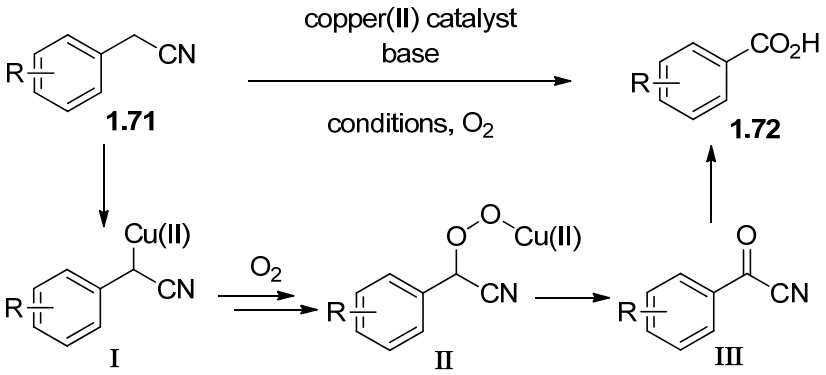


Scheme 1-28. Cu-catalyzed benzylic C-H bond oxygenation.

This C–H bond oxygenation has been combined with Gokel's oxidative hydrolysis of primary nitriles mediated by potassium *tert*-butoxide, with carboxylic acids produced as a result (Scheme 1-29).[49] The success of this approach led to the proposal that Cu-catalyzed C–H oxygenation of benzyl cyanides could be used to synthesize benzoic acids under an O_2 atmosphere as shown in Scheme 1-30. This transformation may involve C-H bond oxygenation to form the intermediate benzoyl cyanides, which subsequently hydrolyze. The details of this study are described in Chapter 3. This method appears capable of providing a much broader array of functionally substituted benzoic acids from benzyl cyanides than can be obtained through traditional methods based on classic reagents such as $KMnO_4$[50] and Jones reagent.[51]



Scheme 1-29. Oxidative hydrolysis of primary nitriles mediated by *t*-BuOK.



Scheme 1-30. Hypothesized procedure for synthesizing benzoic acids by Cu-catalyzed aerobic oxidation of benzyl cyanides.

Chapter 2

Pd(II)-Catalyzed Ring Expansion of Cyclic 2-Azidoalcohol Derivatives: Synthesis of Azaheterocycles

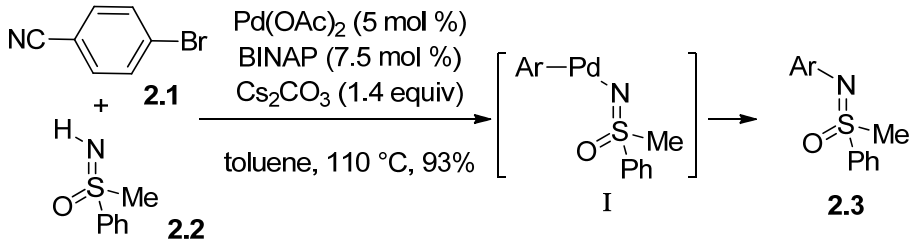
2.1 Introduction

Studies over the last 20 years have demonstrated iminyl metal species to be an important intermediate in C–N bond formation in the synthesis of nitrogen-containing compounds. This section describes methods typically used to generate iminyl metal species, as well as the application of these methods in organic chemistry.

2.1.1 Generation of iminyl transition metal species from *N*–H imines

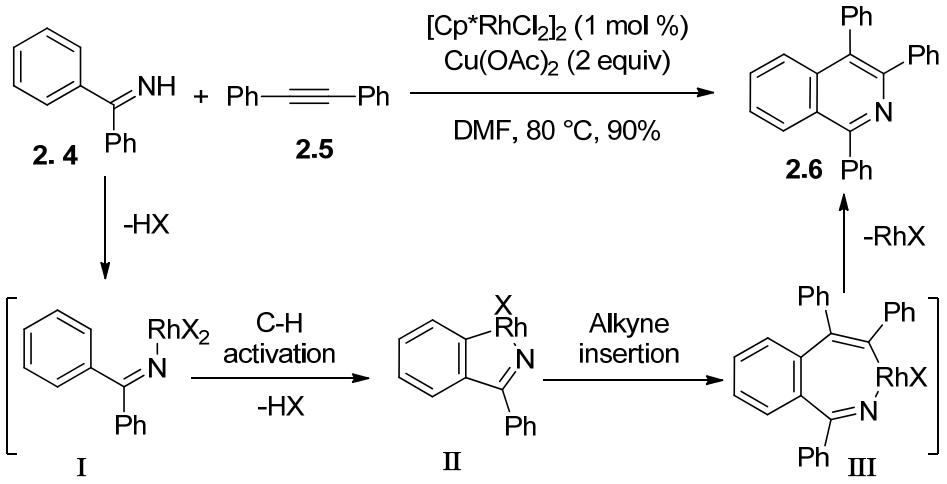
Iminyl metal species are easily generated from *N*-H imines, which have been used in a palladium-catalyzed Buchwald-Hartwig reaction to synthesize the corresponding nitrogen-containing compounds.[52]

Bolm reported a palladium-catalyzed *N*-arylation of sulfoxyimines with aryl halides *via* the iminyl palladium(II) species **I** (Scheme 2-1).[52d] In this process, oxidative addition and ligand exchange generated aryl-Pd-sulfoximide **I,** which underwent reductive elimination to provide the coupling product **2.23** in 93% yield.



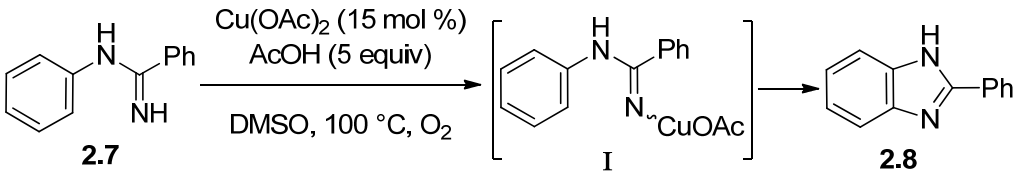
Scheme 2-1. Pd-catalyzed *N*-arylation of sulfoximines with halides.

Miura-Satoh reported Rh(III)-catalyzed coupling of aromatic imines **2.4** with internal alkynes **2.5** (Scheme 2-2).[53] Nucleophilic substitution of *N*–H imine **2.4** onto the *in situ*-generated rhodium(III) acetate complex gave the iminyl rhodium species **I**. Subsequent C−H bond activation, alkyne insertion, and reductive elimination produced isoquinoline **2.6** in 90% yield and generated Rh(I). The generated Rh(I) was reoxidized to Rh(III) complex by $Cu(OAc)_2$.



Scheme 2-2. Rh-catalyzed oxidative coupling of aromatic imines and alkynes.

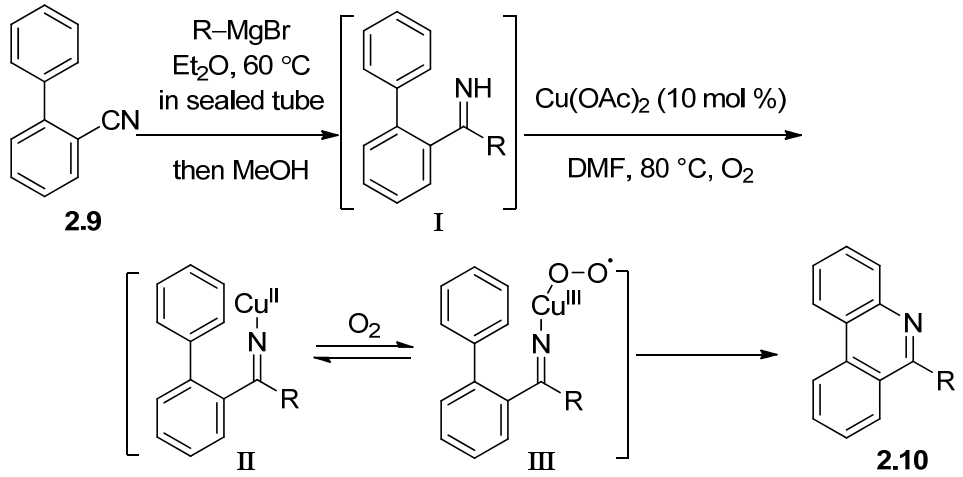
Buchwald described a new Cu-catalyzed synthesis of benzimidazole **2.8** from the readily obtained amidine **2.7** under an oxygen atmosphere. The synthesis involved C–H functionalization and C–N bond formation, during which the iminyl copper species **I** was presumably generated (Scheme 2-3).[54]



Scheme 2-3. Synthesis of benzimidazole from amidine *via* iminyl copper.

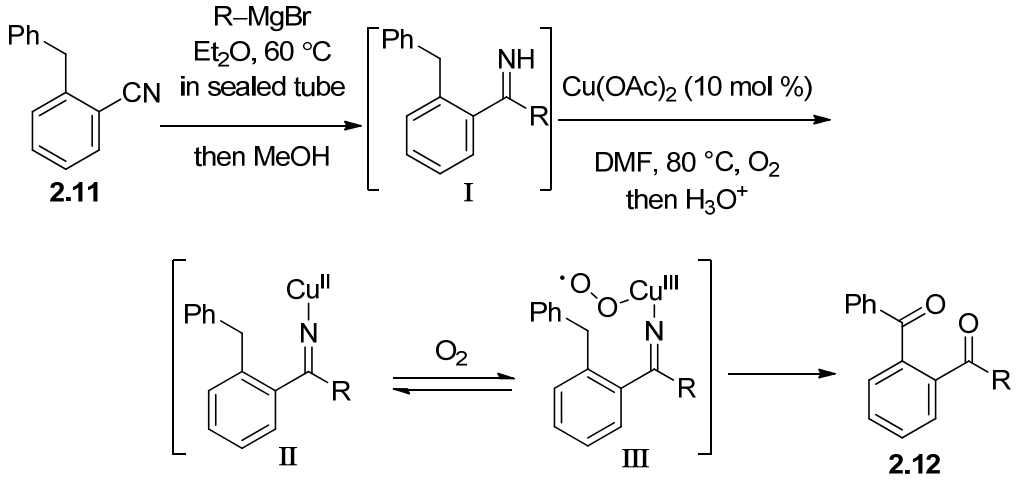
Our group recently reported a series of studies involving iminyl copper species formed by treating copper salts with *N*–H imines. These imines were obtained through nucleophilic addition of Grignard reagents to carbonitriles, followed by protonation with MeOH.

For example, phenanthridine derivatives **2.10** were synthesized starting from biaryl-2-carbonitriles **2.9** and Grignard reagents in a Cu-catalyzed one-pot reaction under an oxygen atmosphere.[48b] The process involved two steps: (1) formation of *N*–H imines **I** from biaryl-2-carbonitriles **2.9** and Grignard reagents; (2) copper-catalyzed aromatic C–H bond functionalization/C–N bond formation *via* iminyl copper species **II** and **III** (Scheme 2-4).



Scheme 2-4. Cu-catalyzed one-pot synthesis of phenanthridine derivatives starting from biaryl-2-carbonitriles and Grignard reagents under an O_2 atmosphere.

Iminyl copper species generated from *N*-H imines have also been applied as intramolecular directing groups in Cu-catalyzed one-pot benzylic C–H oxygenation reactions under an oxygen atmosphere (Scheme 2-5).[48c]



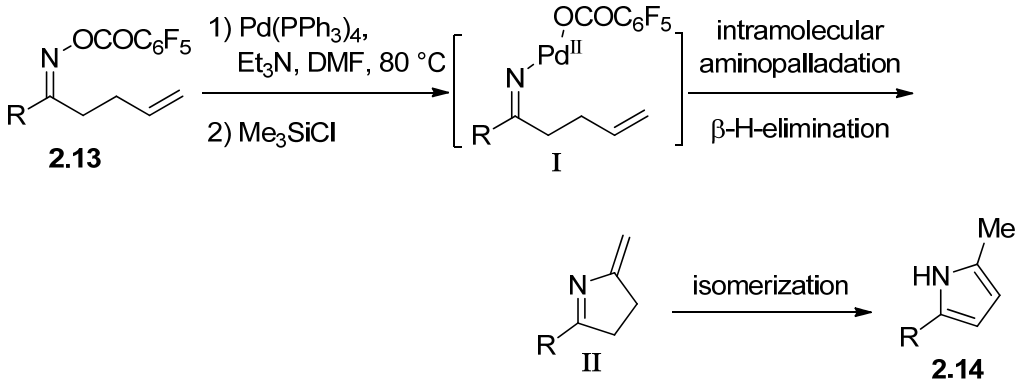
Scheme 2-5. Cu-catalyzed one-pot benzylic C–H oxygenation reactions involving *N*–H imines as intramolecular directing group.

2.1.2 Generation of iminyl metal species from *O*-acyl oximes

Iminyl metal species can be generated conveniently through oxidative addition of the N–O bond of oximes to low-valence transition metals.[55]

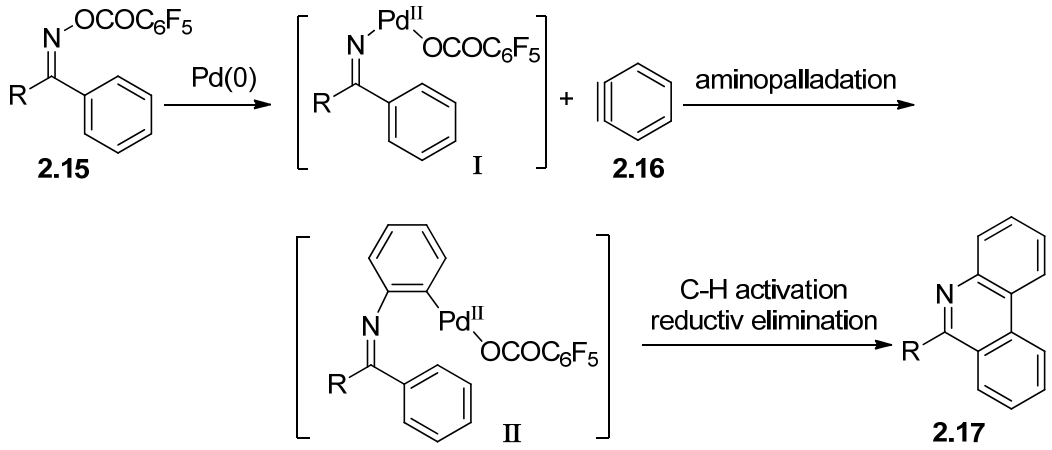
This approach generates an iminyl palladium (R^1R^2C=N–Pd) intermediate, which Narasaka and co-workers have used in intramolecular Mizoroki-Heck reactions with alkenes to synthesize a wide range of azaheterocycles.[56] For example, γ,δ-unsaturated ketone *O*-(pentafluorobenzoyl)oxime **2.13** was converted into substituted pyrroles **2.14** following treatment with a catalytic amount of $Pd(PPh_3)_4$ (Scheme 2-6).[57] The reaction began with oxidative addition of the N–O bond of acyloxime **2.13** to Pd(0), forming the

iminyl palladium species **I**. Subsequent consecutive steps of intramolecular aminopalladation, β-*H*-elimination and isomerization led to pyrrole **2.14**.



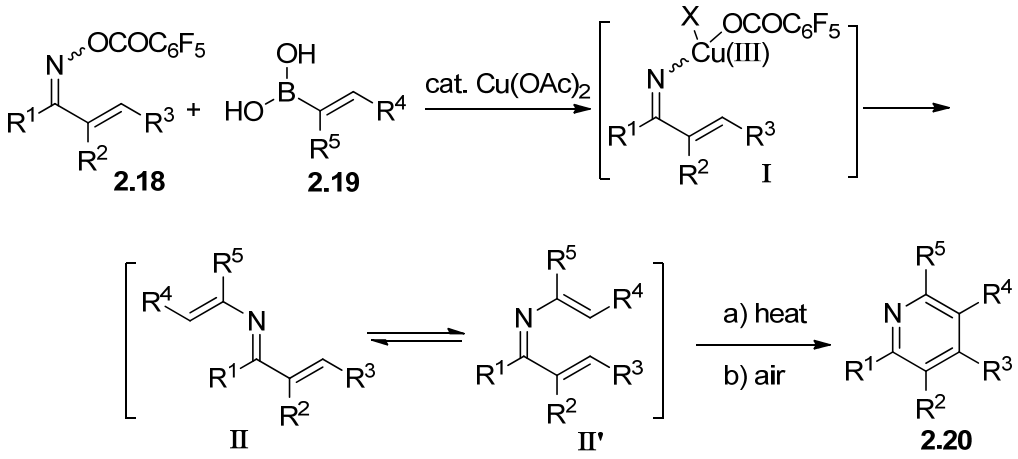
Scheme 2-6. Pd(0)-catalyzed amino-Heck reaction of *O*-pentafluorobenzoyloximes.

Zhu's group trapped an iminyl palladium(II) species in an intermolecular C≡C bond.[58] In this process, oxidative addition of the N–O bond of *O*-pentafluorobenzoyloxime **2.15** to Pd(0) led to iminyl palladium(II) species **I**, which reacted with alkyne or benzyne to afford isoquinolines and phenanthridine derivatives **2.17** *via* (i) intermolecular aminopalladation, (ii) intramolecular C–H activation of intermediate **II**, and (iii) reductive elimination (Scheme 2-7).



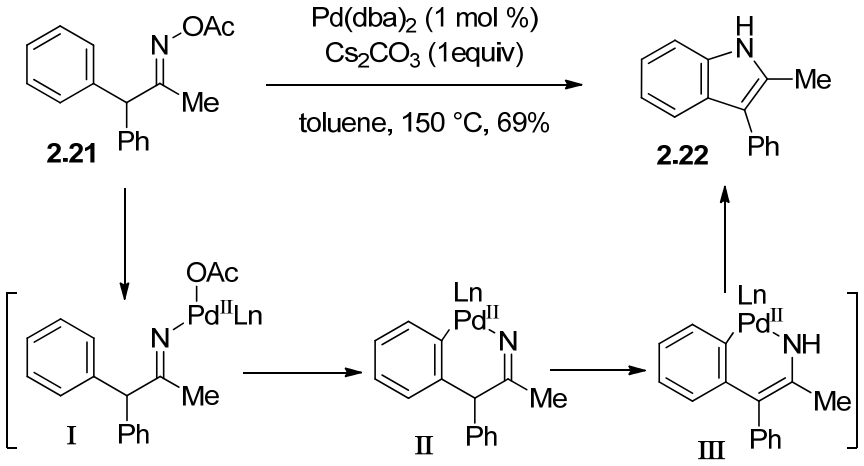
Scheme 2-7. Synthesis of phenanthridine by "catching" iminyl palladium with benzyne.

Liebeskind and co-workers achieved Cu-catalyzed C–N bond formation by cross-coupling arylboronic acids and *O*-pentafluorobenzoyloximes using iminyl copper species (R^1R^2C=N–Cu).[59] They used this cross-coupling procedure to synthesize highly substituted pyridines **2.20** (Scheme 2-8).[60] This transformation involved a reaction cascade including (i) C–N cross-coupling of alkenyl boronic acids at the N–O bond of the α,β-unsaturated ketoxime *O*-carboxylate **2.18**, (ii) a 6π-electrocyclization generating 3-azatrienes **II'**, and (iii) aerobic oxidation.



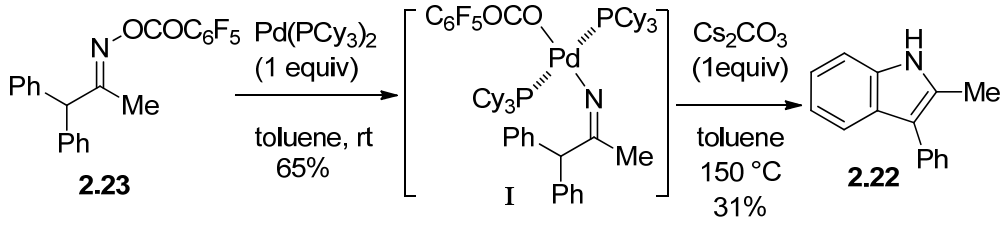
Scheme 2-8. Synthesis of substituted pyridines through cross-coupling of iminyl copper and alkenyl boronic acid.

Recently, Hartwig reported Pd-catalyzed amination of aromatic C–H bonds by oxime esters, leading to synthesis of the corresponding indoles (Scheme 2-9).[61] In this process, cyclization occurred by oxidative addition of the N–O bond to Pd(0) to generate iminyl palladium species **I**, followed by successive C–H activation, tautomerization and reductive elimination to yield the indole product **2.22**. Alternatively, the C–H cleavage step could also occur after the tautomerization.



Scheme 2-9. Pd-catalyzed cyclization of oxime acetates *via* iminyl palladium species.

Hartwig carried out mechanistic studies of this reaction, during which they reported the first X-ray diffraction structural characterization of iminyl palladium intermediate **I**. Their studies also confirmed that oxidative addition of the N–O bond to Pd(0) does occur (Scheme 2-10) .

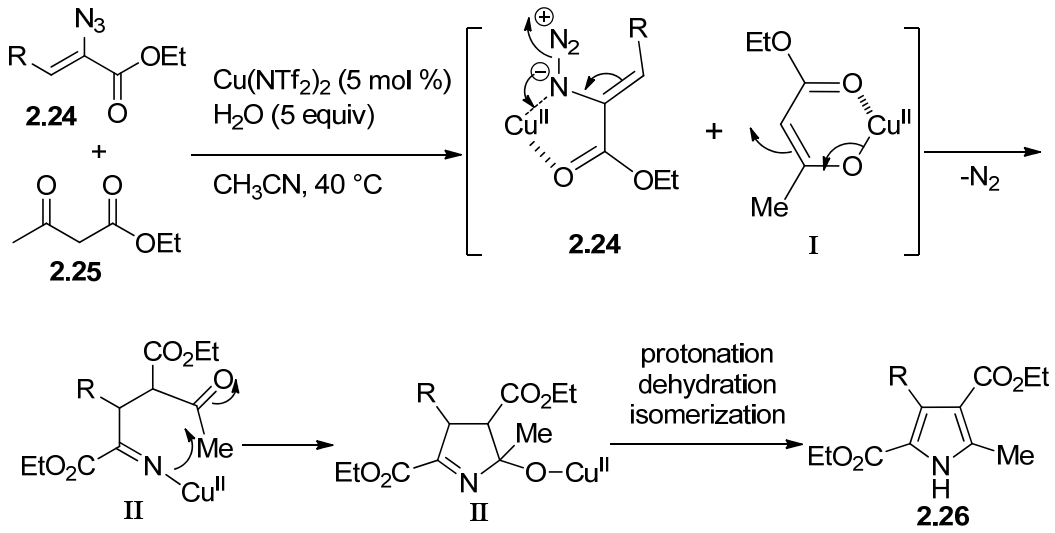


Scheme 2-10. Isolation of iminyl palladium **I** in mechanistic studies.

2.1.3 Generation of iminyl metal species from organic azides

Our group has focused on developing new methods to synthesize azaheterocycles starting from organic azides. In a series of studies, we have described the synthesis of nitrogen-containing compounds *via* iminyl metal species derived from vinyl azides and α-azido carbonyl compounds.

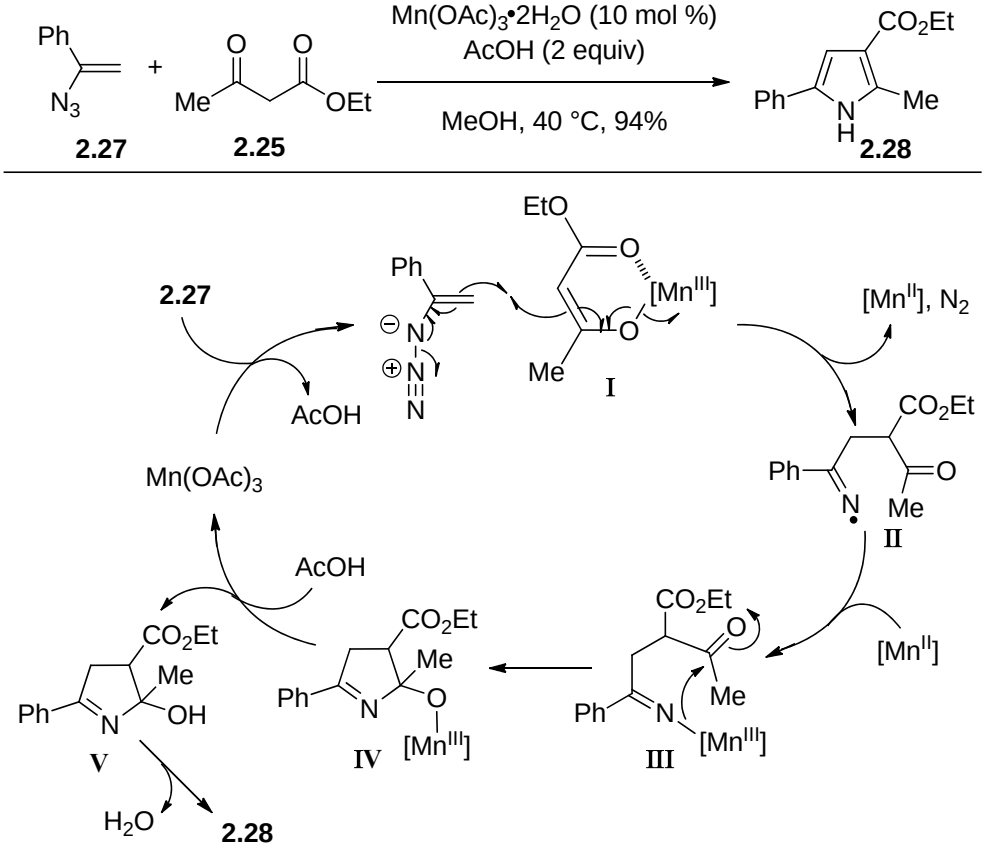
Our group has found that polysubstituted *N*–H pyrroles can be prepared by Cu(II)-catalyzed reactions of vinyl azides and 1,3-dicarbonyl compounds (Scheme 2-11).[44] The reaction was initiated by 1,4-addition of copper enolate **I** to vinyl azide **2.24**, the internal nitrogen of which probably coordinated with the copper center. Simultaneous elimination of N_2 gave iminyl copper(II) intermediate **II**, which underwent intramolecular nucleophilic attack at the carbonyl group to give the *tetra*-substituted pyrrole **2.26** with elimination of water.



Scheme 2-11. Cu-catalyzed synthesis of polysubstituted pyrrole from vinyl azide.

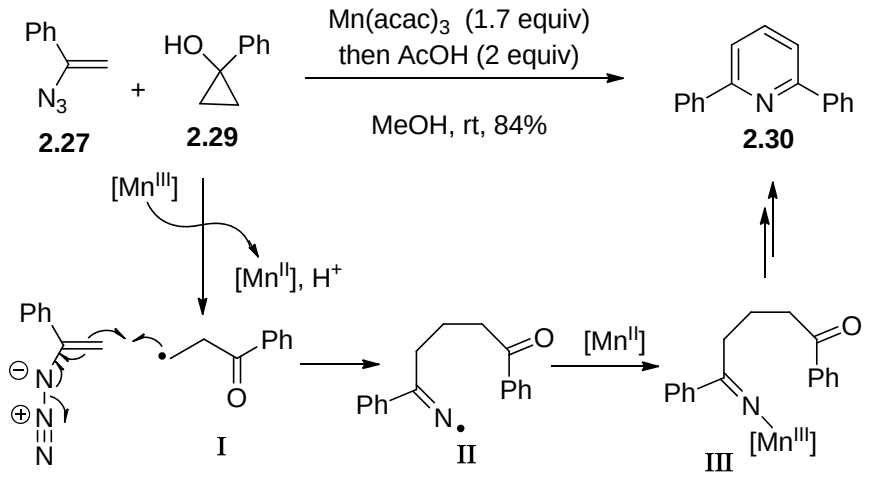
A more general method was developed to generate pyrrole from vinyl azides and 1,3-dicarbonyl compounds. In this approach, catalyzed by Mn(III) salts, a variety of 1,3-dicarbonyl compounds can be used, including β-keto esters and 1,3-diketones (Scheme 2-12).[62] It has been proposed that the catalytic reaction begins with addition of Mn(III) enolate **I** to vinyl azide **2.27**, generating iminyl radical **II** and releasing Mn(II) species and dinitrogen. The iminyl radical **II** is then reduced by the released Mn(II) species to form iminyl-Mn(III) **III**. Intramolecular nucleophilic attack at the carbonyl

group yields addition intermediate **IV**. Subsequent protonation, dehydration and isomerization produce pyrrole and regenerate the Mn(III) species.



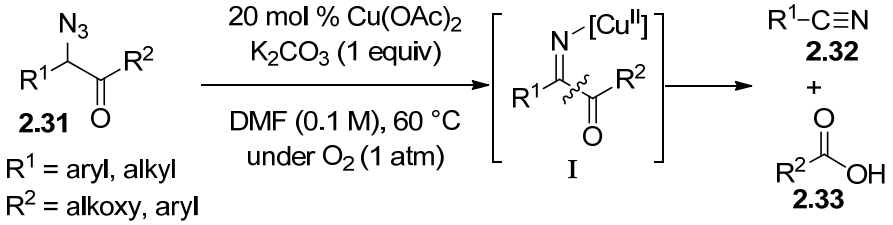
Scheme 2-12. Mn(III)-catalyzed pyrrole formation from vinyl azides.

This method was extended to synthesize pyridine derivatives from vinyl azides and monocyclic cyclopropanols as a precursor of β-carbonyl radicals (Scheme 2-13).[63] In this process, one-electron oxidation of 1-phenylcyclopropanol generated the β-carbonyl radical **I**, and subsequent addition of radical **I** to vinyl azide afforded the iminyl radical **II** species, which was reduced by Mn(II) to form the iminyl Mn(III) intermediate **III**. The carbonyl group of **III** underwent intramolecular nucleophilic addition, ultimately giving the pyridine **2.30** in 84% yield.



Scheme 2-13. Mn(III)-catalyzed pyridine formation.

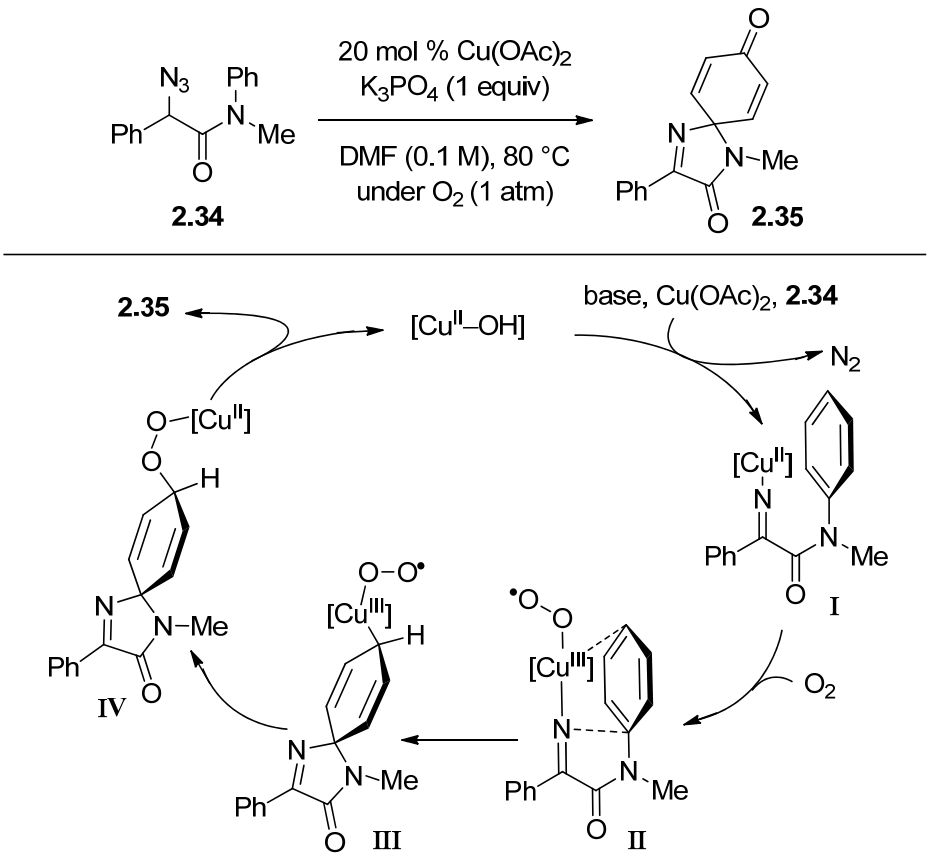
The iminyl copper species generated from α-azido carbonyl compounds has also been used to produce nitrogen-containing structures. As described in Chapter 1, our group reported the generation of iminyl copper species from α-azido compounds and their catalytic C–C bond cleavage under an O_2 atmosphere, giving the corresponding carbonitriles and carboxylic acids (Scheme 2-14).[43]



Scheme 2-14. Generation of iminyl copper species from α-azido compounds and their catalytic C–C bond cleavage.

More interestingly, exposing *α*-azido-*N*-arylamide **2.34** to similar reaction conditions provided the azaspirocyclohexadienone **2.35** without C–C bond cleavage (Scheme 2-15).[47a] This reaction began with denitrogenative formation of iminyl copper species **I**, followed by oxidation of the iminyl copper **I** with O_2-generated peroxycopper(III)

intermediate **II**. This intermediate underwent intramolecular imino-cupration to form C–N and C–Cu bonds concurrently at the *ipso* and *para* position of the benzene ring respectively, affording intermediate **III**. Subsequent isomerization of **III** to peroxydiene **IV** followed by elimination of the [Cu(II)-OH] species yielded azaspirodienones **2.35**.



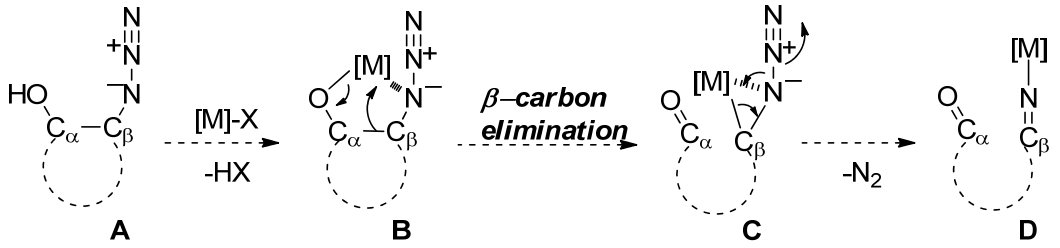
Scheme 2-15. Cu-catalyzed synthesis of azaspirocyclohexadienone **2.35** from *α*-azido-*N*-arylamide **2.34**.

2.2 Project hypothesis

The potential chemical reactivity of readily available 2-azidoalcohols has drawn our attention. We hypothesized that it may be possible to generate iminyl metal species from 2-azidoalcohols by combining β-carbon elimination of transition metal alcoholates with

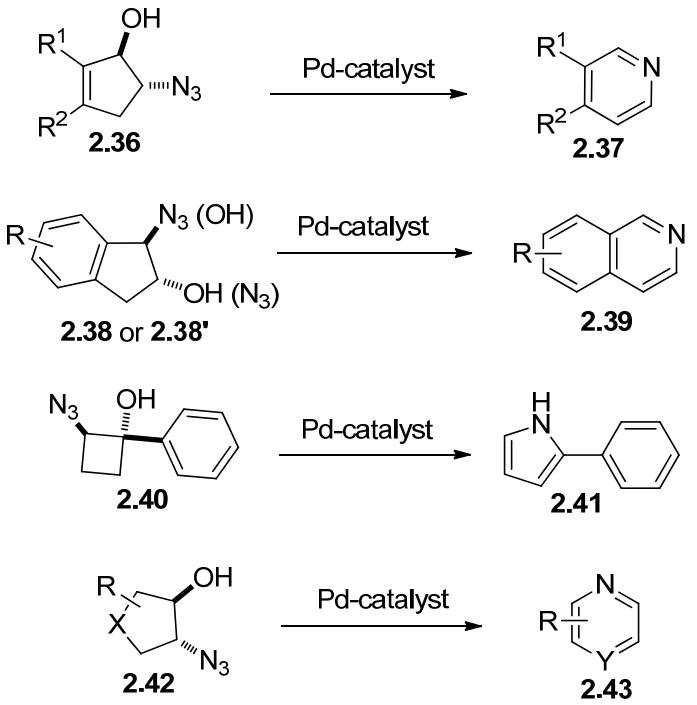
the generation of iminyl metal species from organic azides.

We hypothesized that 2-azidoalcohols **A** could be used to generate metal alcoholates **B,** which would then undergo *β*-carbon elimination to give α-azidocarbometal species **C** (Scheme 2-16). Subsequent metal migration from *C* to *N* with elimination of dinitrogen would afford iminyl metal species **D**, which could be used for further C–N bond forming reactions. We speculated that these processes would be promoted by coordination of the internal nitrogen of the azido moiety to the metal center.[64]



Scheme 2-16. Hypothesized generation of iminyl metal species from 2-azidoalcohols.

To test this hypothesis, we studied whether a palladium-catalyzed ring expansion of cyclic 2-azidoalcohols could be used to synthesize a series of azaheterocycles such as pyridine, isoquinoline, γ-carboline, pyrrole and pyrazine derivatives (Scheme 2-17).

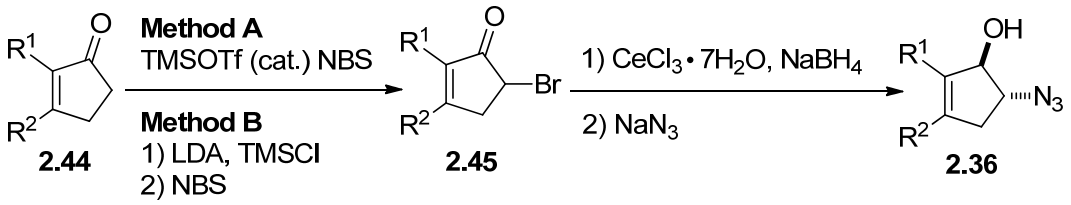


Scheme 2-17. Hypothesized reactions for synthesizing azaheterocycles from 2-azidoalcohols.

2.3 Synthesis of cyclic 2-azidoalcohols

2.3.1 Synthesis of cyclic azidoalcohols 2.36

The *trans*-2-azidocyclopenten-1-ol derivatives **2.36** were synthesized from cyclopenten-1-ones **2.44** *via* α-bromination, selective reduction of a carbonyl group and nucleophilic substitution (Scheme 2-18).



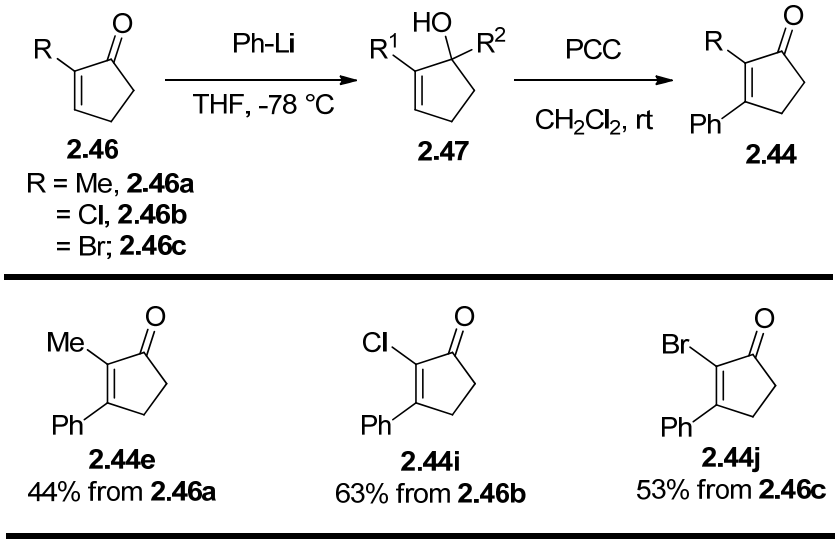
Scheme 2-18. Synthesis of azidoalcohols **2.36**.

2.3.1.1 Synthesis of substituted cyclopenten-1-ones 2.44

Cyclopenten-1-ones **2.44** were prepared by **Methods I-III** as described below.

Method I:

The 2-substituted cyclopenten-1-ones **2.46b**[65] and **2.46c**[66] were prepared according to the literature. Nucleophilic addition of phenyl lithium to **2.46** provided the corresponding allylic alcohols **2.47**. Treatment of the allylic alcohols with pyridinium chlorochromate (PCC) yielded the cyclopenten-1-ones **2.44e**, **2.44i** and **2.44j** (Scheme 2-19).

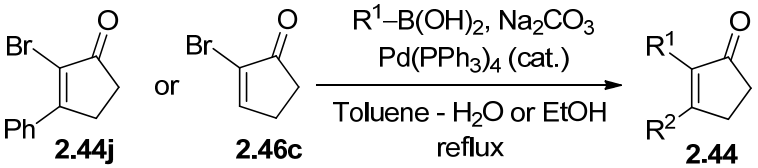


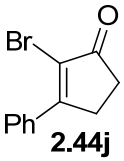
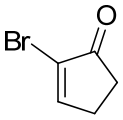
Scheme 2-19. Synthesis of **2.44e, 2.44i** and **2.44j.**

Method II:

Most cyclopent-2-enones **2.44,** specifically **2.44a-2.44d** and **2.44k-2.44p,** were synthesized by Suzuki coupling reactions of 2-bromo-cyclopent-2-enones and aryl boronic acids (Table 2-1).

Table 2-1. Preparation of **2.44** by Suzuki coupling reactions.



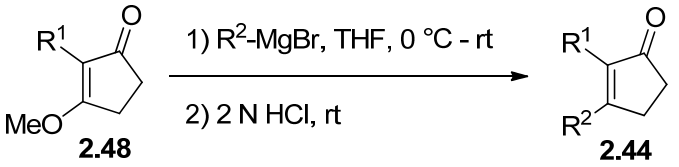
Entry	**2.44j** or **2.46j**	R^1	**2.44**	Yield (%)[a]
1	 **2.44j** R^2 = Ph	Ph	**a**	93
2		4-Me-C_6H_4	**b**	88
3		4-Cl-C_6H_4	**c**	77
4		4-F-C_6H_4	**d**	88
5	 **2.46c** R^2 = H	Ph	**k**	76
6		4-Me-C_6H_4	**l**	50
7		2-Me-C_6H_4	**m**	34
8		4-Cl-C_6H_4	**n**	47
9		4-F-C_6H_4	**o**	58
10		4-CF_3-C_6H_4	**p**	54

[a] Isolated yield.

Method III:

The compounds 2-methyl-3-methoxy-cyclopent-2-enone[67] and 2-allyl-3-methoxy-cyclopent-2-enone[68] were prepared according to the literature. Then they were treated consecutively with Grignard reagents and 2 N aqueous HCl in one pot (Table 2-2). Cyclopentenones **2.44f, 2.44g** and **2.44h** were synthesized by this method.

Table 2-2. Synthesis of cyclopentenones **2.44f, 2.44g** and **2.44h**.



2.48 **2.44**

Entry	R^1	R^2	**2.44**	Yield (%)[a]
1	Me	3,5-Me_2-C_6H_4	**f**	69
2	Ally	Ph	**g**	42
3	Me	$PhCH_2CH_2$	**h**	57

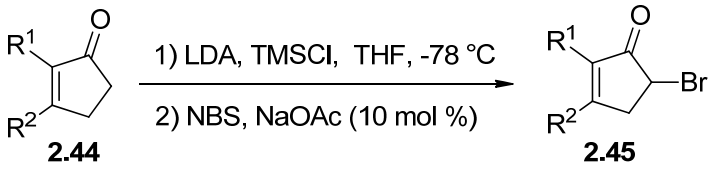
[a] Isolated yield.

2.3.1.2 α-Bromination of cyclopentenones 2.44

5-Bromocyclopenten-1-ones **2.45** were prepared from cyclopentenones **2.44** by **Method A** or **B** as described below.

Method A:

5-Bromocyclopenten-1-ones **2.45g** and **2.45h** were synthesized in two steps.[69] First the corresponding cyclopentenones **2.44** were treated with LDA and TMSCl to afford crude trimethylsilyl enol ethers, which were then treated with *N*-bromosuccinimide (NBS) in the presence of a catalytic amount of NaOAc at 0 ºC (Scheme 2-20).



2.44 **2.45**

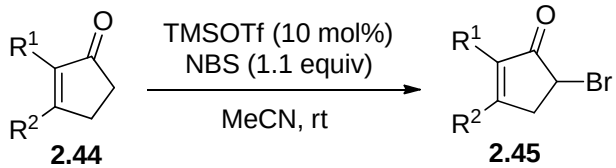
R^1 = Ally, R^2 = Ph: **2.45g** 59%
R^1 = Me, R^2 = $PhCH_2CH_2$: **2.45h** 47%

Scheme 2-20. Synthesis of **2.45g** and **2.45h** in two steps.

Method B:

Treating cylcopentenones **2.44** with *N*-bromosuccinimide (NBS) in the presence of a catalytic amount of TMSOTf[70] generated most 5-bromocyclopenten-1-ones **2.45,** namely **2.45a-2.45f** and **2.45i-2.45p** (Table 2-3).

Table 2-3. α-Bromination of cyclopentenones **2.44** catalyzed by TMSOTf.



2.44 **2.45**

Entry	R^1	R^2	**2.44**	Yield (%)[a]
1	Ph	Ph	**a**	65
2	4-Me-C_6H_4	Ph	**b**	67
3	4-Cl-C_6H_4	Ph	**c**	60
4	4-F-C_6H_4	Ph	**d**	63
5	Me	Ph	**e**	79
6	Ph	3,5-Me_2-C_6H_4	**f**	76
7	Cl	Ph	**i**	84
8	Br	Ph	**j**	83[b]
9	Ph	H	**k**	70
10	4-Me-C_6H_4	H	**l**	36
11	2-Me-C_6H_4	H	**m**	30
12	4-Cl-C_6H_4	H	**n**	61
13	4-F-C_6H_4	H	**o**	49
14	4-CF_3-C_6H_4	H	**p**	50

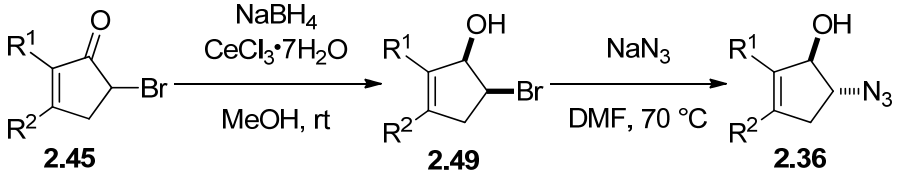
[a] Isolated yield; [b] Ratio of 5- to 4-brominated product was 13:1.

2.3.1.3 Synthesis of *trans*-azidoalcohols 2.36

Luche reduction[71] of 5-bromocyclopenten-1-ones **2.45** generated *cis*-bromohydrins **2.49,** which underwent nucleophilic substitution with NaN_3 to yield the *trans*-azidoalcohols

2.36 (Table 2-4).

Table 2-4. Synthesis of *trans*-azidoalcohols **2.36** from **2.45**.

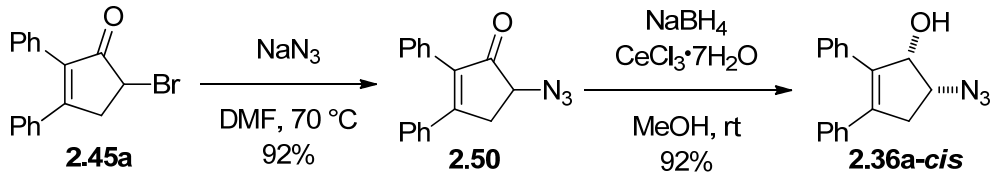


Entry	R^1	R^2	**2.36**	Yield (%)[a]
1	Ph	Ph	**a**	74
2	4-Me-C_6H_4	Ph	**b**	69
3	4-Cl-C_6H_4	Ph	**c**	53
4	4-F-C_6H_4	Ph	**d**	50
5	Me	Ph	**e**	80
6	Ph	3,5-Me_2-C_6H_4	**f**	78
7	Ally	Ph	**g**	73
8	Me	$PhCH_2CH_2$	**h**	83
9	Cl	Ph	**i**	78
10	Br	Ph	**j**	32[b]
11	Ph	H	**k**	56
12	4-Me-C_6H_4	H	**l**	75
13	2-Me-C_6H_4	H	**m**	50
14	4-Cl-C_6H_4	H	**n**	69
15	4-F-C_6H_4	H	**o**	64
16	4-CF_3-C_6H_4	H	**p**	70

[a] Isolated yield for 2 steps from **2.45** ; [b] Yield for 3 steps from **2.44j**

2.3.1.4 Synthesis of *cis*-azidoalcohols 2.36a-*cis*

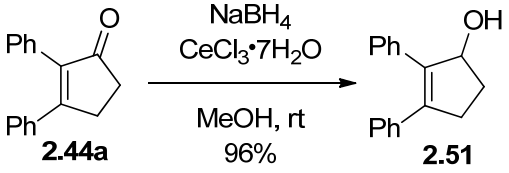
cis-Azidoalcohol (**2.36a-*cis***) was prepared from 5-bromocyclopenten-1-one **2.45a** *via* nucleophilic substitution with NaN_3 followed by Luche reduction (Scheme 2-21).



Scheme 2-21. Synthesis of *cis*-azidoalcohol (**2.36a-*cis***) from **2.45a**.

2.3.1.5 Synthesis of 2,3-diphenylcyclopenten-1-ol 2.51

For control experiments to test the role of azido group, 2,3-diphenylcyclopenten-1-ol **2.51** was prepared from 2,3-diphenylcyclopentenone **2.44a** in 96% yield by Luche reduction (Scheme 2-22).



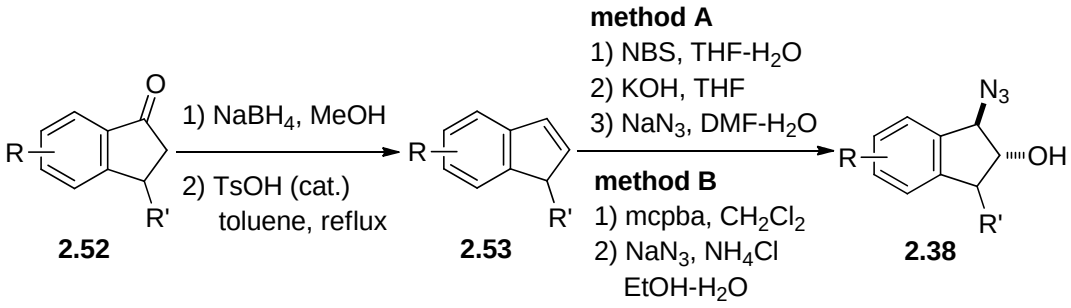
Scheme 2-22. Synthesis of 2,3-diphenylcyclopenten-1-ol **2.51**.

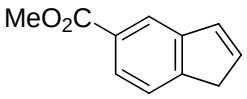
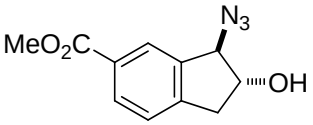
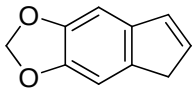
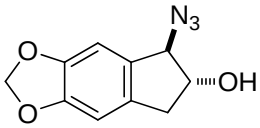
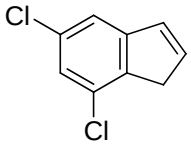
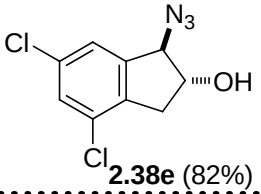
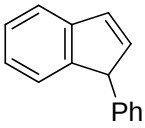
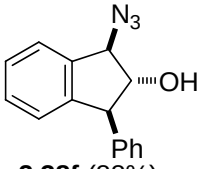
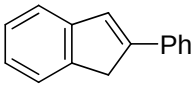
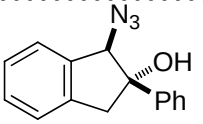
2.3.2 Synthesis of α-azidoalcohol 2.38 and 2.38'

2.3.2.1 Synthesis of 1-azido-2-indanols 2.38

1-Azido-2-indanols **2.38** were prepared from the corresponding indenes using **Method A** or **B** as shown in Table 2-5. The indenes were generally obtained from the corresponding indanones by consecutive reduction with $NaBH_4$ and dehydration in the presence of a catalytic amount of TsOH.

Table 2-5. Synthesis of 1-azido-2-indanols **2.38**.



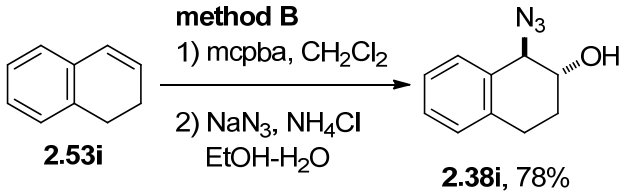
Entry	**2.53** (yield) [a]	Method	**2.38** (yield) [b]
1	 **2.53a** (97%)	**method B**	 **2.38a** (79%)
2	 **2.53b** (95%) [c]	**method A**	 **2.38b** (44%)
3	 **2.53e** (95%)	**method B**	 **2.38e** (82%)
4	 **2.53f** (94%)	**method B**	 **2.38f** (88%)
5	 **2.53g** (57%)[d]	**method B**	 **2.38g** (83%)

[a] yield from **2.52**; [b] yield from **2.53**; [c] THF as solvent in dehydration;
[d] prepared by Heck reaction from indene and bromobenzene.

Substrate **2.38b** was prepared by **Method A** as follows. The indene **2.53b** was treated with NBS in THF-H_2O to give *trans*-bromohydrin, which was treated with KOH to give

the peroxide. The peroxide then reacted with NaN_3 to produce substrate **2.38b**. Substrates **2.38a** and **2.38e-g** were prepared by **Method B** as follows. The indenes **2.53** were treated with 3-chloroperbenzoic acid (mcpba) to yield the corresponding peroxides, which reacted with NaN_3 to produce the corresponding substrates **2.38b.**

(1*R**,2*R**)-1-azido-1,2,3,4-tetrahydronaphthalen-2-ol (**2.38i**) was prepared from commercially available 1,2-dihydronaphthalene (**2.53i**) in 78% yield by epoxidation with mcpba followed by azidation with NaN_3, as described in **Method B** above (Scheme 2-23).

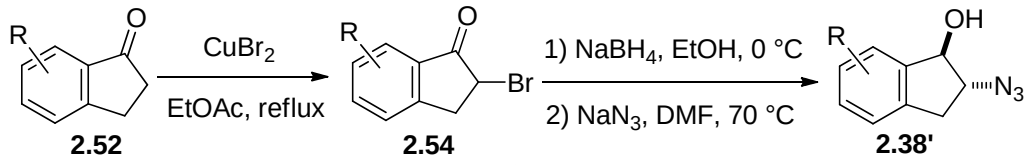


Scheme 2-23. Synthesis of **2.38i**.

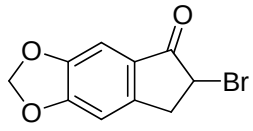
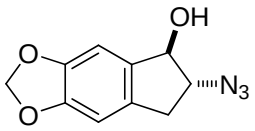
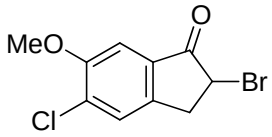
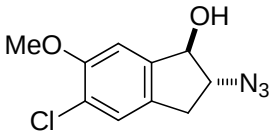
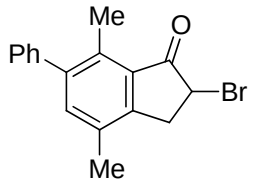
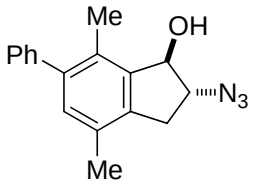
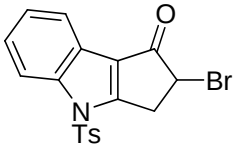
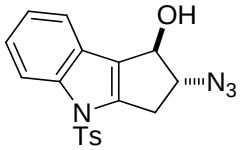
2.3.2.2 Synthesis of 2-azido-1-indanols 2.38'

Most of the 2-azide-1-indanols **2.38'** were prepared from the corresponding indanones **2.52** in 3 steps: α-bromination of indanones **2.52** with $CuBr_2$,[72] reduction of the α-bromoketone with $NaBH_4$ to give *cis*-bromohydrins, and finally substitution of *cis*-bromohydrins with NaN_3 to yield the 2-azide-1-indanols **2.38'** as shown in Table 2-6.

Table 2-6. Synthesis of 2-azide-1-indanols **2.38'**.

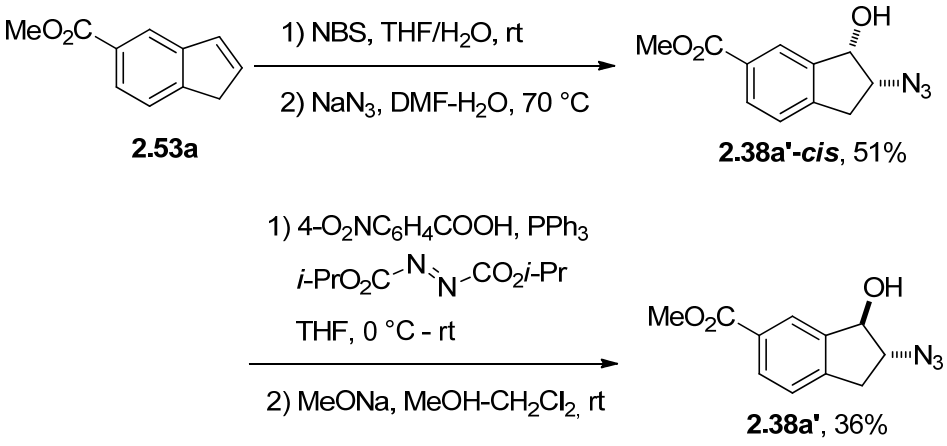


2.52 **2.54** **2.38'**

2.54 (yield) [a]	**2.38** (yield) [b]	2.54 (yield) [a]	2.38 (yield) [b]
 **2.54b** (83%)	 **2.38b'** (52%)	 **2.54c** (88%)	 **2.38c'** (65%)
 **2.54d** (83%)	 **2.38d'** (63%)	 **2.54h** (81%)	 **2.38h'** (81%)

[a] yield from **2.52**; [b] yield from **2.54**.

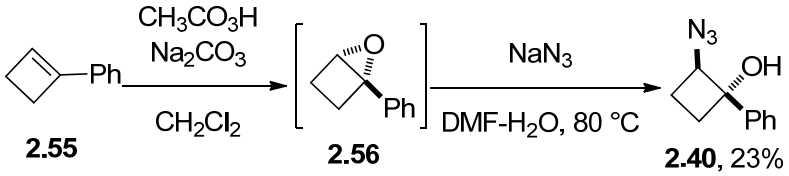
Hydroxylbromination of indene **2.53a** by NBS followed by substitution with NaN_3 gave **2.38a'-*cis***, which then underwent a Mitsunobu reaction[73] to produce **2.38a'** (Scheme 2-24).



Scheme 2-24. Synthesis of the 2-azido-1-indanol **2.38a'**.

2.3.3 Synthesis of 2-azido-1-phenylcyclobutanol 2.43

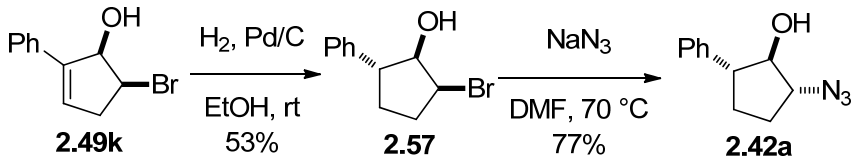
2-Azido-1-phenylcyclobutanol **2.40** as a known compound was prepared from 1-phenyl-cyclobutene **2.55** [74a] in 23% yield as published procedure [74b] (Scheme 2-25).



Scheme 2-25. Synthesis of 2-azido-1-phenylcyclobutanol **2.40**.

2.3.4 Synthesis of α-azidocyclopentanol derivatives 2.42

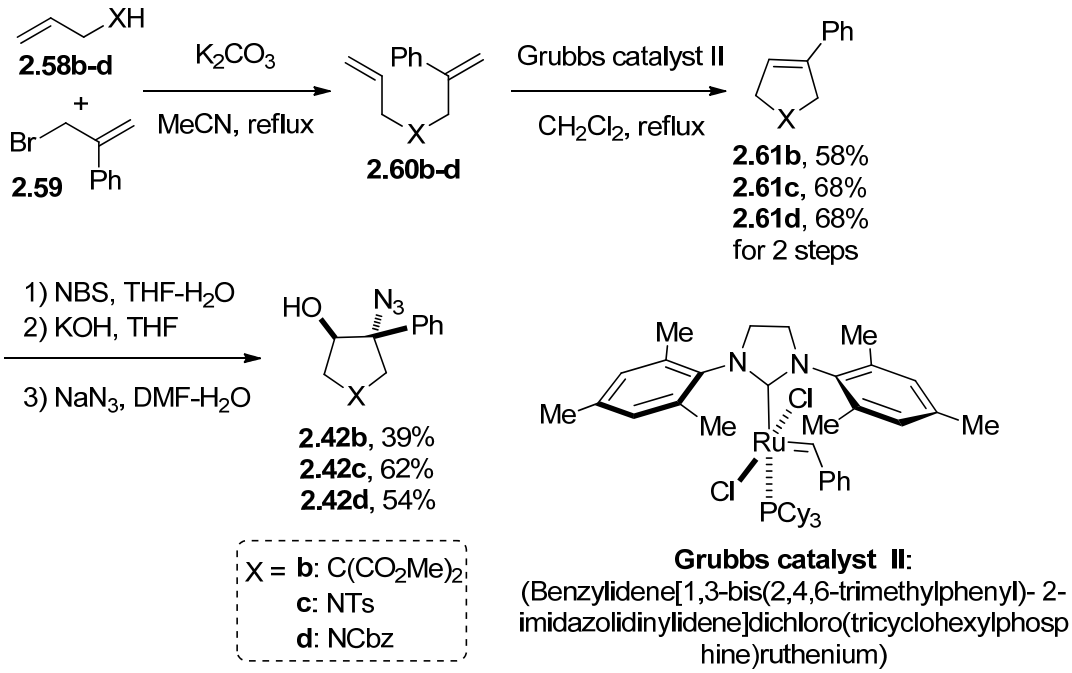
α-Azidocyclopentanol **2.42a** was synthesized from *cis*-bromohydrins **2.49k**. Due to coordination of the hydroxyl group to the palladium atom, **2.49k** underwent stereoselective hydrogenation to yield **2.57**, which underwent substitution with NaN_3 to produce the α-azidocyclopentanol **2.42a** (Scheme 2-26).



Scheme 2-26. Synthesis of α-azidocyclopentanol **2.42a**.

Cyclic α-azidoalcohols **2.42b-d** were synthesized from α-(bromomethyl)styrene **2.59** and the corresponding **2.58** (Scheme 2-27). Treatment of **2.59** and **2.58** with K_2CO_3 provided diene derivatives **2.60**, which were transformed into cyclic compounds **2.61** in the presence of Grubbs catalyst II. Compounds **2.61** were subjected to **Method A** (described

in section 2.3.2.1**)** to yield the corresponding cyclic α-azidoalcohols **2.42b-d**.



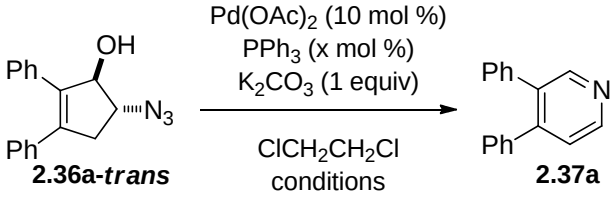
Scheme 2-27. Synthesis of cyclic α-azidoalcohols **2.42b-d**.

2.4 Results and discussion

2.4.1 Optimization of reaction conditions for metal-catalyzed pyridine formation from azidoalcohols 2.36a-*trans* and 2.36a-*cis*

In order to test whether we could use transition metal-catalyzed ring expansion of cyclic 2-azidoalcohols to synthesize azaheterocycles, (1*R**,5*R**)-5-azido-2,3-diphenylcyclopent-2-enol (**2.36a-*trans***) was chosen to carry out initial tests using 10 mol % $Pd(OAc)_2$ as the catalyst with 1 equiv of K_2CO_3 in 1,2-dichloroethane (Scheme 2-28). While this amount of $Pd(OAc)_2$ by itself did not exhibit any reactivity to **2.36a**, it showed some catalytic effect in the presence of 20 mol % PPh_3 at 60 ºC, giving the ring expansion

product 3,4-diphenylpyridine (**2.37a**) in 44% yield with 51% recovery of **2.36a**. These results indicate that the ligand plays an important role in promoting the reaction.

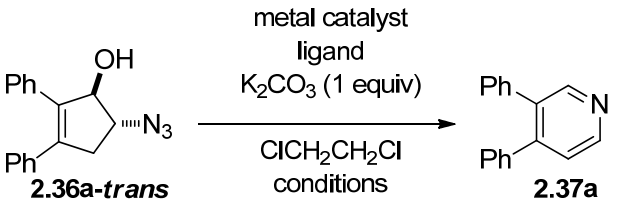


0 mol % PPh_3: 60 °C, 3 h, 0% **2.37a** + 91% **2.36a-*trans***

20 mol % PPh_3: 60 °C, 6.5 h, 44% **2.37a** + 51% **2.36a-*trans***

Scheme 2-28. Preliminary tests of Pd(II)-catalyzed ring expansion of **2.36a-*trans***.

Table 2-7. Optimization of Reaction Conditions



entry	metal catalyst (mol %)	ligand (mol %)	conditions	yield (%)[a,b]
1	$Pd(OAc)_2$ (20)	PPh_3 (40)	60 °C, 6 h	55 (5)
2	$Pd(OAc)_2$ (10)	P(*t*-Bu)$_3$ (20)	60 °C, 6 h	0 (79)
3	$Pd(OAc)_2$ (10)	dppp (10)	60 °C, 5 h	38 (51)
4	$Pd(OAc)_2$ (10)	dppb (10)	60 °C, 6 h	62 (12)
5	$Pd(OAc)_2$ (15)	dppb (15)	60 °C, 5 h	72
6	$Pd(OAc)_2$ (15)	dppf (15)	80 °C, 2.5 h	70
7	$PdCl_2$(dppb) (15)	—		64 (11)
8	$PdCl_2$(dppf) (15)	—	60 °C, 6 h	71 (13)
9[c]	**$PdCl_2$(dppf) (15)**	—	**80 °C, 8 h**	**88**
10	**$Pd(OAc)_2$ (15)**	**2,2'-bipyridine (15)**	**80 °C, 0.5 h**	**80**
11	$Pd(OAc)_2$ (15)	TMEDA (15)	80 °C, 8 h	69 (19)
12	$Pd(PPh_3)_4$ (15)	—	80 °C, 6 h	20 (18)
13	$NiCl_2$ $6H_2O$ (15)	dppf (15)	80 °C, 6 h	7 (68)
14	$[RhCl(coe)_2]_2$ (7.5)	dppf (15)	80 °C, 6 h	30 (44)
15	AuCl (15)	dppf (15)	80 °C, 6 h	7 (82)
16	CuI (15)	dppf (15)	80 °C, 6 h	0 (87)

[a] isolated yield; [b] Recovery yield of **2.36a** is in parentheses; [c] TONs = 6.7, TOFs = 0.83 h^{-1}.

Encouraged by these preliminary results, we attempted to optimize pyridine formation by

reacting (1*R**,5*R**)-5-azido-2,3-diphenylcyclopent-2-enol (**2.36a-*trans***) in the presence of some transition metal catalysts and 1 equiv of K_2CO_3 in 1,2-dichloroethane (Table 2-7). Higher catalytic loading (20 mol % of $Pd(OAc)_2(PPh_3)_2$, however, did not improve the chemical yield of **2.37a** (entry 1). The reaction with the bulky P(*t*-Bu)$_3$ ligand did not proceed at all (entry 2). β-Carbon elimination needs interaction between metal and its β-carbon, that is usually called as agostic interaction.[75] Such interaction could be achieved in the palladium-alcoholates bearing *cis*-coordination of phosphine ligands such as **A'** in the Figure 2-1, while the agostic interaction might be impossible in the reaction with the P(*t*-Bu)$_3$ ligand because of the steric hindrance. The bidentate phosphine ligands dppb and dppf proved to be optimal ligands for pyridine formation (entries 3-9) since the generated *cis*-coordination intermediates make the agostic interaction smooth (**B** in **Figure 2-1**). Using 15 mol % $PdCl_2$(dppf) at 80 ºC gave **2.37a** in the best yield (88%) (entry 9), while the reaction did not go to completion at lower temperature (entry 8). Interestingly, bidentate nitrogen ligands such as 2,2'-bipyridine and TMEDA with $Pd(OAc)_2$ also exhibited good catalytic activity (entries 10 and 11). The palladium(0) complex $Pd(PPh_3)_4$ gave inferior results (entry 12). Other metal complexes like Ni(II), Cu(I), Rh(I), and Au(I) were not viable catalysts for this transformation (entries 13-16).

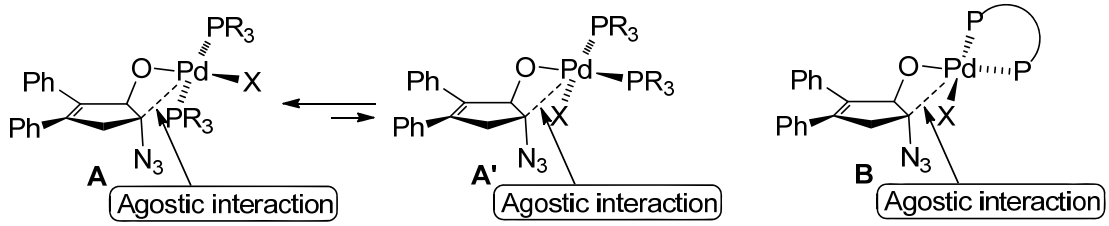
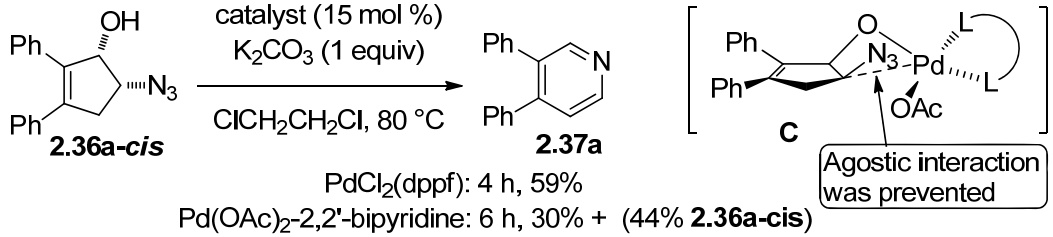


Figure 2-1: Possible intermediate **A** (or **A'**) and **B** with mono- and bidentate-phospine ligands respectively.

The reactivity of *cis*-azidoalcohols **2.36a-*cis*** was investigated under the optimal reaction conditions. Although the reactions of *cis*-azidoalcohols **2.36a-*cis*** can proceed (Scheme 2-29), it was found the yield of pyridine **2.37a** was lower (59%) than that from *trans*-azidoalcohol **2.36a-trans.** Even when *cis*-azidoalcohols **2.36a-*cis*** were allowed to react in the presence of the $Pd(OAc)_2$-2,2'-bipyridine catalyst system, pyridine 2.37a was obtained in only 30% yield and with 44% recovery of 2.36a-*cis*. The reason may be that the *cis*-azido group prevents agostic interaction (see intermediate **C**) between the azido-substituted carbon and Pd center in the palladium alcoholate intermediate generated during the reaction.

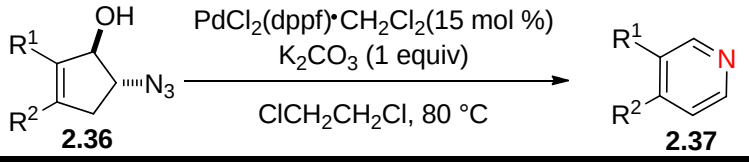


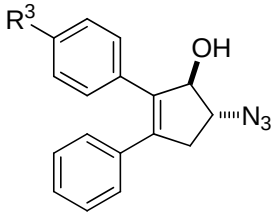
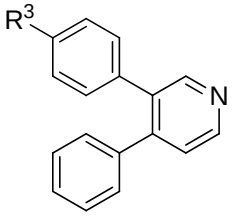
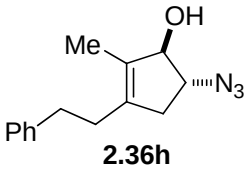
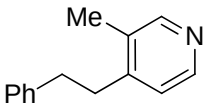
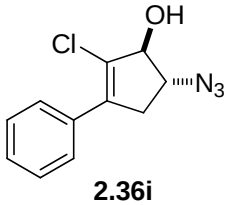
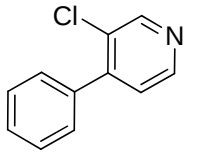
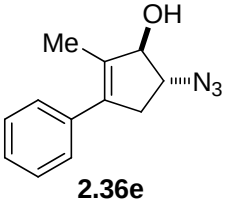
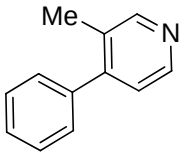
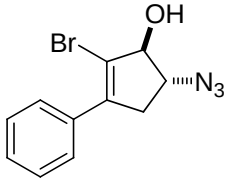
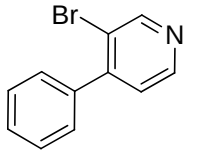
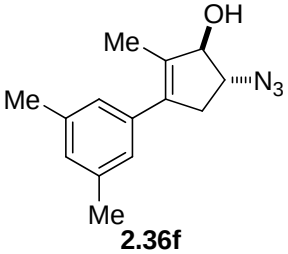
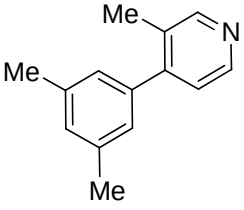
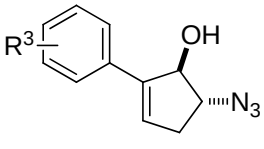
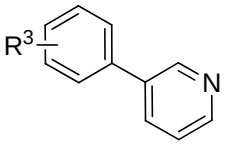
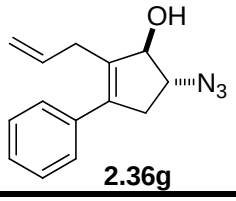
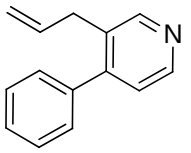
Scheme 2-29. Formation of pyridine from *cis*-azidoalcohols **2.36a-*cis***.

2.4.2 Synthesis of pyridines

Once reaction conditions had been optimized, the generality of this catalytic method for the synthesis of substituted pyridines was examined, using *trans*-azidoalcohols **2.36** (Table 2-8).

Table 2-8. Synthesis of pyridines.



Substrate	Product	Substrate	Product
			
2.36a: R^3 = H **2.36b:** R^3 = 4-Me **2.36c:** R^3 = 4-Cl **2.36d:** R^3 = 4-F	**2.37a**, 6 h, 88% **2.37b**, 2 h, 78% **2.37c,** 3 h, 88% **2.37d**,1.5 h, 89%	**2.36h**	**2.37h**, 6 h, 65%
			
2.36i	**2.37i**, 0.3 h, 90%		
			
2.36e	**2.37e**, 6 h, 83%	**2.36j**	**2.37j**, 24 h, 72% [a]
			
2.36f	**2.37f:** 5.5 h, 74%	**2.36k :** R^3 = H **2.36l :** R^3 = 4-Me **2.36m**: R^3 = 2-Me **2.36n :** R^3 = 4-Cl **2.36o :** R^3 = 4-F **2.36p :** R^3 = 4-CF_3	**2.37k**, 3 h, 83%[b] **2.37l**, 4 h, 64% **2.37m**, 5 h, 66% **2.37n**, 2 h, 84% **2.37o**, 2 h, 86% **2.37p**, 1 h, 93%
			
2.36g	**2.37g**, 6 h, 80%		

[a] $Pd(OAc)_2$-2,2-bipyridine (10 mol %) was used; [b] $PdCl_2(dppf)$ (20 mol %).

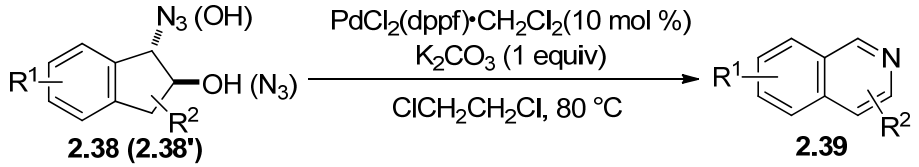
Diaryl substituted pyridines were smoothly synthesized in good to excellent yield from the corresponding 2-azidoalcohols (**2.36a-2.36d**); these pyridines carried not only alkyl groups but also halides such as fluoride and chloride on the benzene ring. The reaction also allowed the installation of methyl and allyl moieties at C-3 on the pyridine ring

(**2.37e**-**2.37g**) in good yield. 3,4-Dialkylsubstituted pyridine **2.37h** was synthesized in 65% yield. Importantly, 3-chloro-pyridine **2.37i** was prepared under the optimized reaction conditions in 90% yield and with the C–Cl bond intact, and 3-bromopyridine **2.37j** was also generated in 72% yield and with the C–Br bond intact using the $Pd(OAc)_2$-2,2'-bipyridine catalyst system. In addition to disubstituted pyridines, 3-arylpyridines with some substituents (**2.37k**-**2.37p**) were prepared in good to excellent yield using this method. The yield of pyridine **2.37** from substrates bearing an electron-donating group was lower than that from substrates bearing an electron-withdrawing group such as F, Cl and CF_3. This is consistent with the mechanism proposed in Scheme 2-31, in which the formyl group of the iminyl palladium(II) species **II** is expected to be more reactive when it contains an electron-withdrawing group.

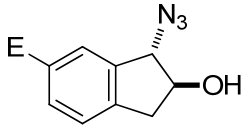
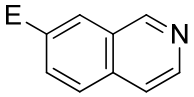
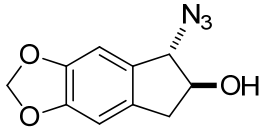
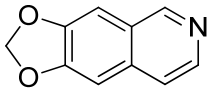
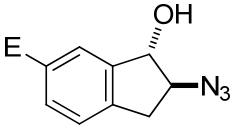
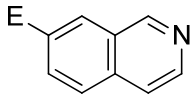
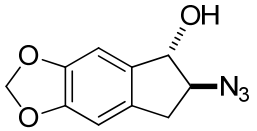
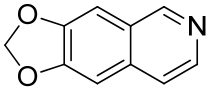
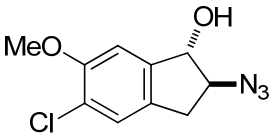
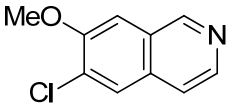
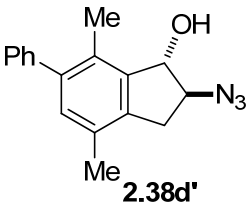
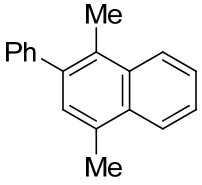
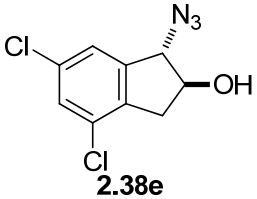
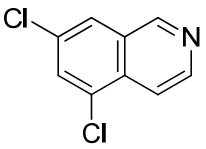
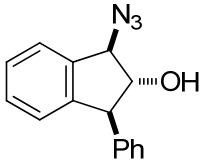
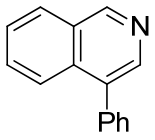
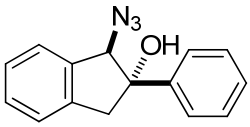
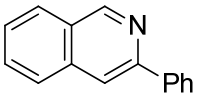
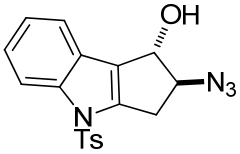
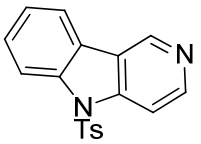
2.4.3 Synthesis of Isoquinolines and γ-Carboline

In addition to synthesis of pyridines, this catalytic ring expansion was extended to provide substituted isoquinolines and γ-carboline derivatives (Table 2-9).

Table 2-9. Synthesis of isoquinolines and γ-carboline



2.38 (2.38') **2.39**

Azidoalcohols	Product (yields %)	Azidoalcohols	Product (yields %)
 **2.38a**	 **2.39a**, 0.6 h, 81 E = CO_2Me	 **2.38b**	 **2.39b**, 1 h, 76
 **2.38a'**	 **2.39a**, 0.6 h, 96[a] E = CO_2Me	 **2.38b'**	 **2.39b**, 0.6 h, 92[a]
 **2.38c'**	 **2.39c**, 0.6 h, 96[a]	 **2.38d'**	 **2.39d**, 2 h, 90
 **2.38e**	 **2.39e**, 2 h, 90	 **2.38f**	 **2.39f**, 2 h, 73
 **2.38g**	 **2.39g**, 24 h, 64[b]	 **2.38h'**	 **2.39h**, 2 h, 93

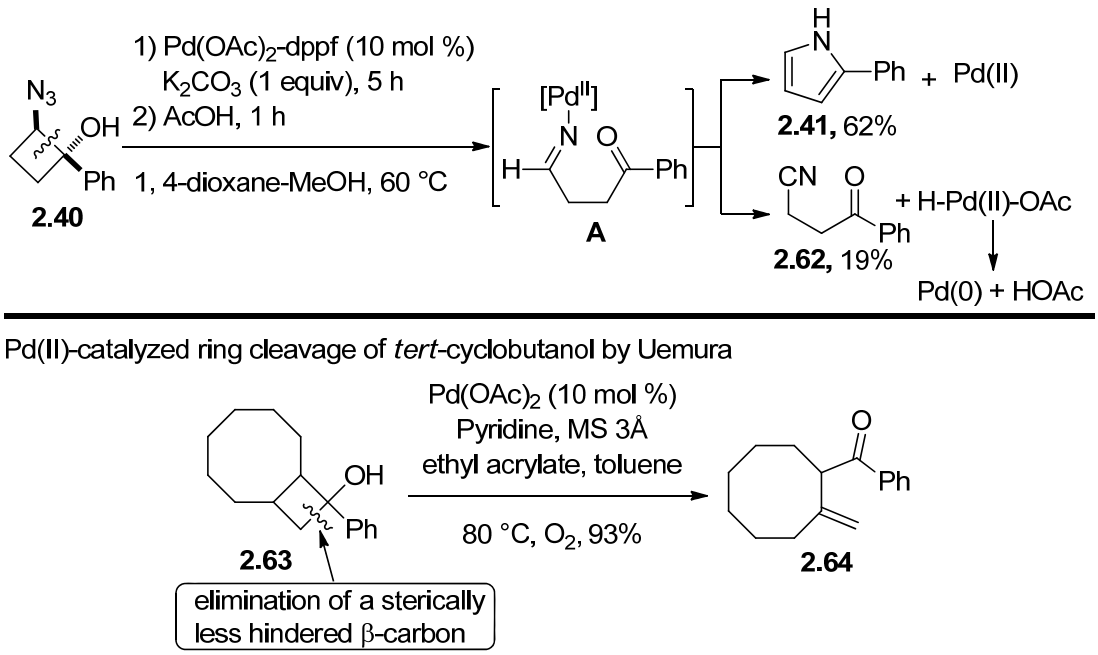
[a] 10 mol % $Pd(OAc)_2$-dppf as catalyst at rt. [b] 20 mol % $PdCl_2$-dppf was used.

It is noted that the reactions of both *trans*-1-azido-2-indanol **2.38** and 2-azido-1-indanol **2.38'** proceeded to obtain the same isoquinolines in good yields using 10 mol % catalyst (for **2.39a** and **2.39b**). The reactions of 2-azido-1-indanols **2.38a'-c'** proceeded at room temperature using a $Pd(OAc)_2$–dppf catalytic system in excellent yields, perhaps because

the benzaldehyde system generated from 2-azido-1-indanols is a more stable intermediate than the aliphatic aldehyde system generated from 1-azido-2-indanols *via* C–C bond cleavage. (See section 2.4.4 below for details of the proposed mechanism.) Both electron-donating and -withdrawing groups were incorporated into the isoquinoline ring in the products **2.39a-d**. Chloride substituents on the benzene ring were tolerated, allowing production of **2.39c** and **2.39e**; it was also possible to synthesize some alkyl- and aryl-substituted isoquinolines such as **2.439d** and **2.39f**. In terms of substrate scope, azidoalcohol **2.38f** bearing a phenyl group at C-3 and tertiary alcohol **2.38g** bearing a phenyl group at C-2 were converted into the corresponding isoquinolines in good yields using 20 mol % $PdCl_2$(dppf) as catalyst. Moreover, azidoalcohol **2.38g'** was converted into *γ*-carboline **2.39g** in 93% yield using this method.

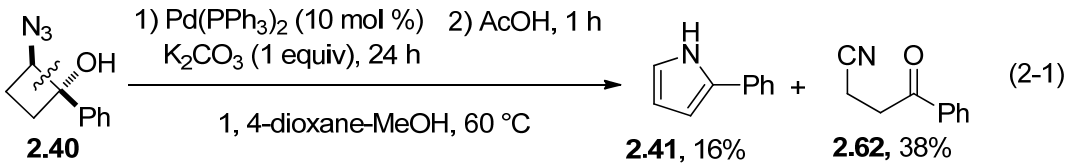
2.4.4 Proposed mechanism for ring expansion of cyclic 2-azidoalcohols

During the course of this study, reactions were conducted with certain substrates that provided significant mechanistic information about this expansion reaction. For example, 2-azidocyclobutanol **2.40** gave the desired 2-phenylpyrrole **2.41** in 62% yield along with the side product γ-keto nitrile **2.62** (19% yield). In this process, β-carbon elimination generated an iminyl palladium species, which underwent β-hydride elimination to produce **2.62**. In contrast to substituted *tert*-cyclobutanol rings, which normally undergo cleavage *via* β-elimination of a sterically less hindered carbon,[33, 34] compound **2.40** underwent selective C–C bond fission involving the azido-substituted carbon (Scheme 2-30).



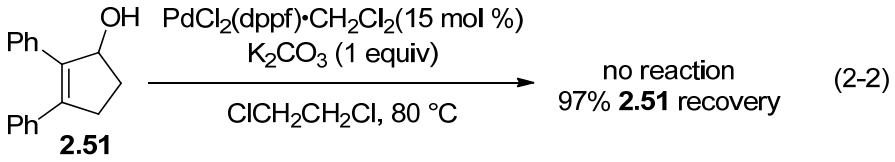
Scheme 2-30. Two contrasting types of C–C bond cleavage.

Based on Scheme 2-30, a 19% yield of nitrile **2.62** is more than the amount of 10 mol % $Pd(OAc)_2$–dppf used. This scheme proposes that nitrile **2.62** is formed by β-hydride elimination from the iminyl Pd(II) intermediate with generation of [H–Pd(II)–OAc], which then affords Pd(0) *via* reductive elimination. However, formation of the pyrrole 2.41 is more likely to be catalyzed by the Pd(II) complex. To obtain more detailed information about which Pd species catalyzes formation of nitrile **2.62**, the catalyst $Pd(OAc)_2$–dppf was replaced with 10 mol % $Pd(PPh_3)_4$ in the reaction of 2-azido-1-phenylcyclobutanol **2.40.** The major product of this reaction was nitrile **2.62** in 38% yield and the pyrrole **2.41** in 16% yield (eq 2-1). This result tentatively suggests that the Pd(0) species catalyzes the formation of nitrile **2.62** from 2-azido-1-phenylcyclobutanol **2.40**.



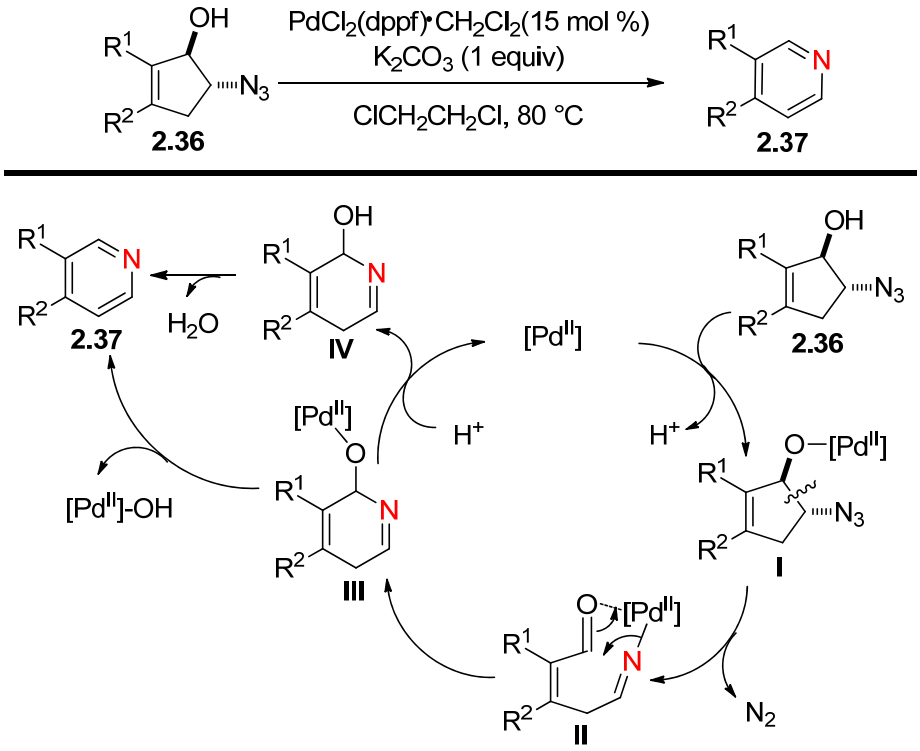
(2-1)

This conclusion was supported by a control experiment in which 2,3-diphenylcyclopent-1-enol **2.51** was allowed to react under the optimal conditions for pyridine formation (eq 2-2). No C–C bond cleavage was observed, indicating that an azido moiety plays a significant role in the present process.



(2-2)

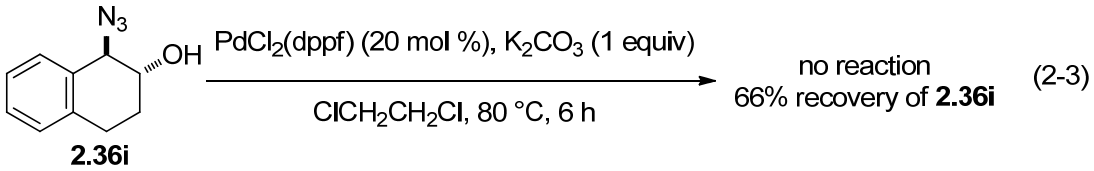
Based on these mechanistic findings, Pd(II)-catalyzed ring expansion of cyclic 2-azidoalcohols to synthesize azaheterocycles was proposed as shown in Scheme 2-31. In this process, reaction of azidoalcohol **2.36** with a Pd(II) complex in the presence of a base generate palladium(II) alcoholate **I.** Then, in the key step, alcoholate **I** undergoes β-carbon elimination, followed by elimination of dinitrogen to give alkylideneaminopalladium(II) species **II**. The iminyl palladium part of **II** acts as an intramolecular nucleophile to attack the resulting formyl group, generating the cyclized intermediate **III**. Protonation of **III** by **2.36** or H_2O followed by dehydration affords 6-membered azaheterocycles **2.37** along with the Pd(II) complex. Alternatively, elimination of the hydroxyl palladium(II) species from **III** yields azaheterocycles **2.37** directly.



Scheme 2-31. Proposed mechanism of Pd(II)-catalyzed ring expansion of cyclic 2-azidoalcohols to synthesize azaheterocycles.

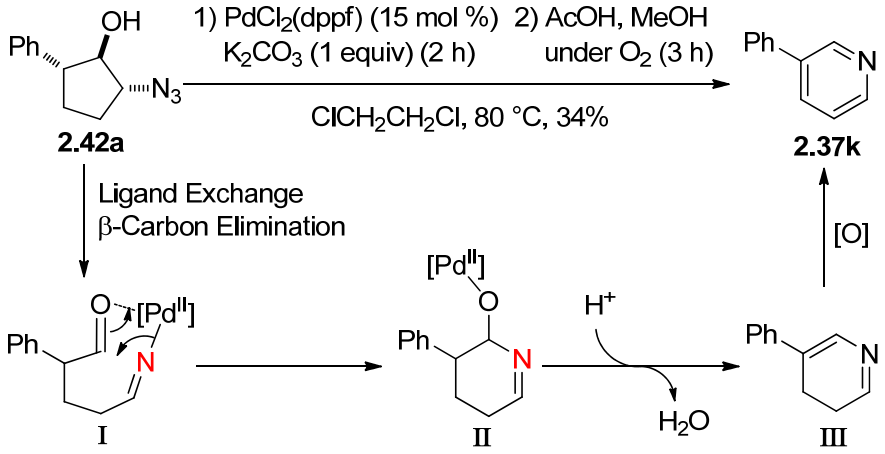
2.4.5 Reactions of other ring systems

To examine the substrate scope of the reaction, we tried to apply this method to other ring systems. However, no C–C bond fission was observed when the reaction was performed with 6-membered ring azidoalcohols **2.36i** (eq 2-3). In addition, **2.36i** was recovered in 66% yield.



(2-3)

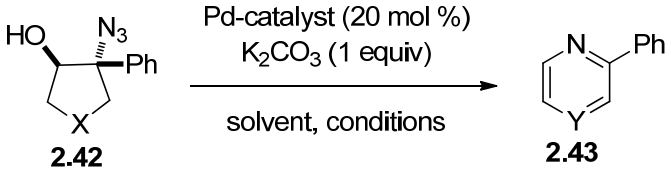
The saturated 5-membered ring azidoalcohols **2.42** were tested in this catalytic ring expansion. Reaction of 2-azidocyclopentanol **2.42a** produced pyridine **2.37k** in 34% yield. In this transformation, intermediate **II** was generated by β-carbon elimination, which upon treatment with excess AcOH under an oxygen atmosphere underwent protonation followed by dehydration to give dihydropyridine intermediate **III.** This compound was further oxidized to pyridine **2.37k** (Scheme 2-32).

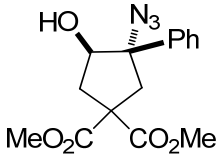
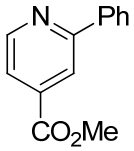
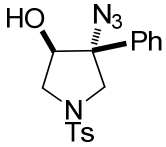
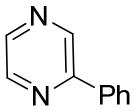
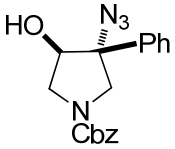


Scheme 2-32. Formation of 3-phenylpyridine **2.37k** from **2.42a**.

This reaction was also used to synthesize pyridine **2.43b** and pyrazine **2.43c** from the saturated 5-membered ring azidoalcohols **2.42b-c** (Table 2-10). $PdCl_2$(dppf) did not show any reactivity towards **2.43b** in 1,2-dichloroethane (entry 1), but $Pd(OAc)_2$-bpy catalyzed the reaction to give pyridine **2.43b** in 38% yield (entry 2). Neither $PdCl_2$(dppf) nor $Pd(OAc)_2$-bpy exhibited any reactivity to **2.43c** in 1,2-dichloroethane (entries 4-5). Interestingly, N,N-dimethylimidazolidinone (DMI) served as a general solvent to synthesize pyridine **2.43b** and pyrazine **2.43c** in moderate yields from the corresponding 2-azidoalcohols **2.42b-d** (entries 3, 6-7).

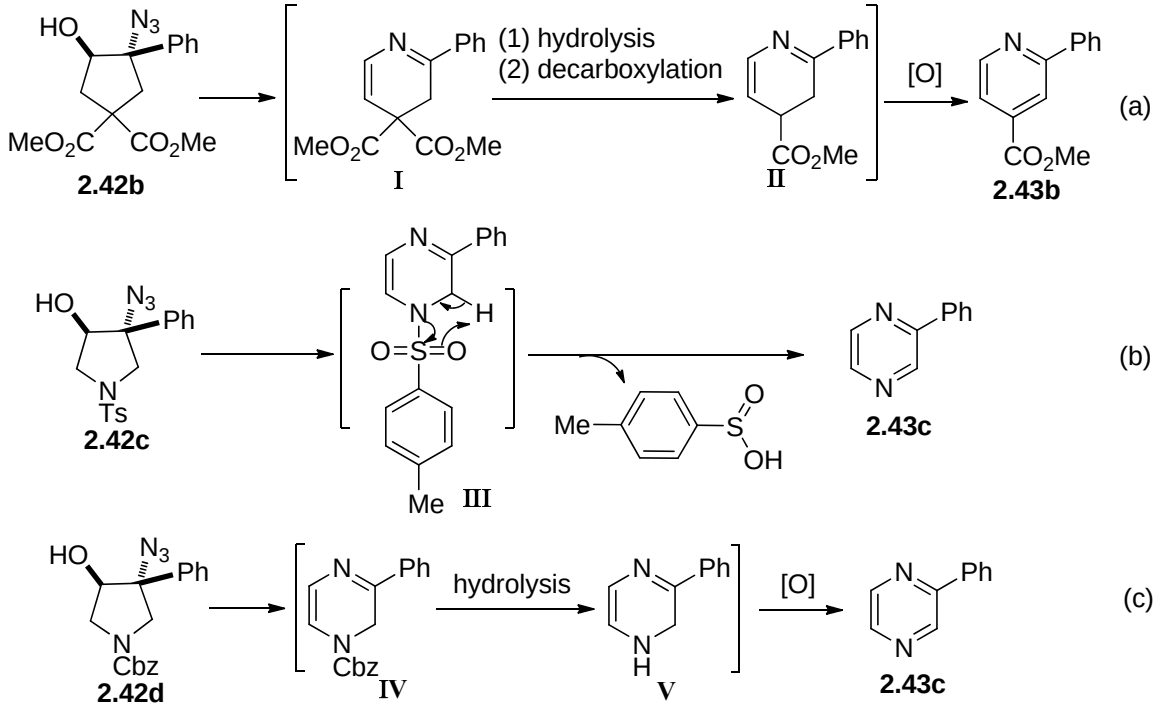
Table 2-10. Synthesis of **2.43**.



Entry	Substrate	Catalyst	Solvent	Conditions	product	Yield (%)[a]
1	 **2.42b**	$PdCl_2(dppf)$	$ClCH_2CH_2Cl$	80 °C, 24 h	 **2.43b**	0 (82)
2		$Pd(OAc)_2$-bpy	$ClCH_2CH_2Cl$	80 °C, 50 h		38
3		$PdCl_2(dppf)$	DMI	120 °C, 6 h		21
4	 **2.42c**	$PdCl_2(dppf)$	$ClCH_2CH_2Cl$	80 °C, 24 h		0 (95)
5		$Pd(OAc)_2$-bpy	$ClCH_2CH_2Cl$	80 °C, 24 h		0 (99)
6		$PdCl_2(dppf)$	DMI	120 °C, 6 h	 **2.43c**	28 (41)
7	 **2.42d**	$PdCl_2(dppf)$	DMI	120 °C, 6 h		37

[a] Recovery yield of **2.42** is in parentheses. DMI: 1,3-Dimethyl-2-imidazolidinone

On the basis of the mechanism proposed in 2-31, possible synthetic routes to **2.43b** and **2.43c** were developed (Scheme 2-33). In the proposed transformation of **2.42b** into pyridine **2.43b**, the generated azadiene **I** undergoes consecutive hydrolysis and decarboxylation to afford azadiene **II**, which is then oxidized to pyridine **2.43b** (Scheme 2-33a). The substrate **2.42c** is converted into pyrazine **2.43c** *via* elimination of 4-methylbenzenesulfinic acid from azadiene **III** (Scheme 2-33b). In the conversion of **2.42d** into pyrazine **2.43c**, the generated azadiene **IV** undergoes hydrolysis to form another azadiene intermediate **V**, which is oxidized to pyrazine **2.43c** (Scheme 2-33c).



Scheme 2-33. Transformations to generate **2.43b** and **2.43c**.

2.5 Summary

In summary, we have described a Pd(II)-catalyzed ring expansion of cyclic 2-azidoalcohol derivatives for the synthesis of azaheterocycles. This process involves a series of reactions including an unprecedented C–C bond cleavage and C–N bond formation *via* an iminyl palladium(II) species. Although this method requires multi-step preparation of substrates, it can provide various substituted azaheterocycles such as pyridines, isoquinolines, pyrrole and pyrazine.

Chapter 3

A Copper-Catalyzed Aerobic Oxidation of Benzyl Cyanides for Synthesis of Carboxylic Acids

3.1 Introduction

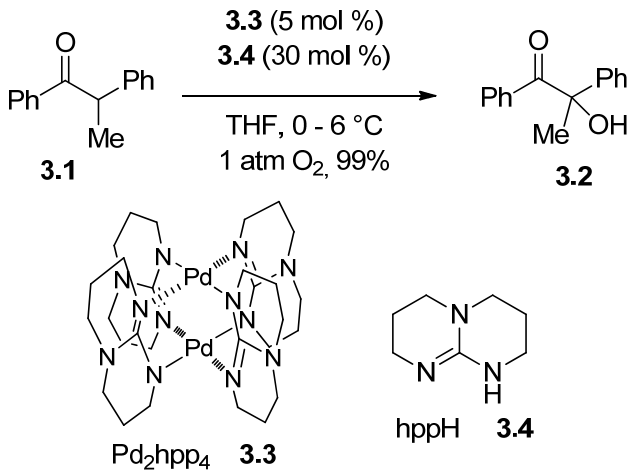
Aromatic carboxylic acids and their derivatives exist widely in nature, and their usefulness has been extended to a broad range of various fields such as food components, pharmacophores and synthetic precursors.[76] As a consequence, the synthesis of aromatic carboxylic acids occupies a significant place in organic chemistry and diverse approaches have been explored to synthesize aromatic carboxylic acids. Traditional synthetic routes include the following: oxidation of substituted arenes,[77] aryl alcohols,[78] and aldehydes,[79] as well as oxidative cleavage of aromatic alkenes,[80] alkynes,[81] diols[82] and diketones;[83] hydrolysis of aryl nitriles[84] and acyl derivatives, such as anhydrides,[85] benzoyl halides,[86] esters[87] and amides;[88] and addition of arylmetallic reagents (such as Grignard reagent,[89] organolithium,[90] arylzinc[91] and arylboron[92] reagents) or transition metal complexes[93] to carbon dioxide.

Each of these conventional methods has its drawbacks, such as many incompatible functional groups, limited scope, or the need for expensive catalysts and ligands. Thus, although diverse conventional approaches to the synthesis of carboxylic acids have been developed, efficient synthesis under aerobic conditions remains a challenge. A patentail method involves oxygenation of the C–H bond. The following sections give a brief

introduction to C–H bond oxygenation in which O_2 serves as both oxidant and oxygen source.

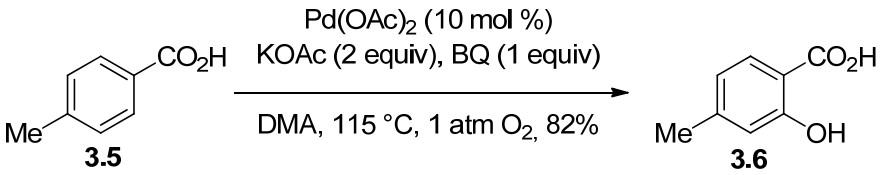
3.1.1 Palladium-catalyzed oxygenation of the C–H bond

Recently, Ritter reported the dinuclear Pd(II)-catalyzed chemo- and regioselective α-hydroxylation of carbonyl compounds using molecular oxygen or air as the only oxidant (Scheme 3-1).[94] In this oxygenation of C–H bonds, the dinuclear Pd(II) catalyst **3.3** behaved as a dioxygenase: oxygen transferred from O_2 to the product **3.2** *via* hydroxylation of the substrate **3.1** under an O_2 atmosphere.



Scheme 3-1. Dinuclear palladium-catalyzed α-hydroxylation of carbonyls with O_2.

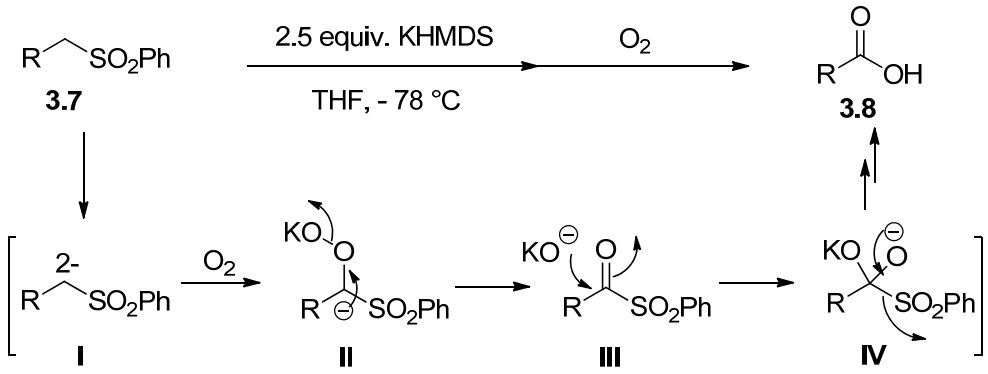
Yu's group developed a Pd(II)-catalyzed *ortho*-hydroxylation of benzoic acids using molecular O_2 (Scheme 3-2).[95] Although the details of the process remain unclear, mechanistic investigations by the Yu group point to direct oxygenation of the aryl-Pd species by molecular O_2.



Scheme 3-2. Pd(II)-catalyzed hydroxylation of arene with 1 atm O_2.

3.1.2 Non-metal-catalyzed oxygenation of the C–H bond

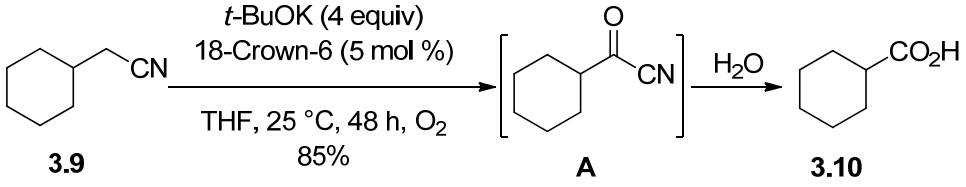
Murphree and co-workers described an aerobic oxidation of primary sulfones to lead carboxylic acids without any transition metal as catalyst (Scheme 3-3).[96] They postulated that, in the first step, treatment of the primary sulfones **3.7** with strong base provided the sulfonyl dianions **I,** which have been described in the literature and form easily under conventional conditions.[97] Subsequently, the sulfonyl dianions **I** reacted with O_2 to form the peroxide intermediates **II,** which lost a potassium-stabilized oxide moiety to afford the α-sulfone intermediates **III**. Hydrolysis of α-sulfone intermediates **III** followed by protonation produced the carboxylic acids **3.8**.



Scheme 3-3. Aerobic oxidation of primary sulfones to generate carboxylic acids

Another example of the non-metal-catalyzed oxygenation of C–H bonds is potassium *tert*-butoxide-mediated penultimate oxidative hydrolysis of primary nitriles to yield

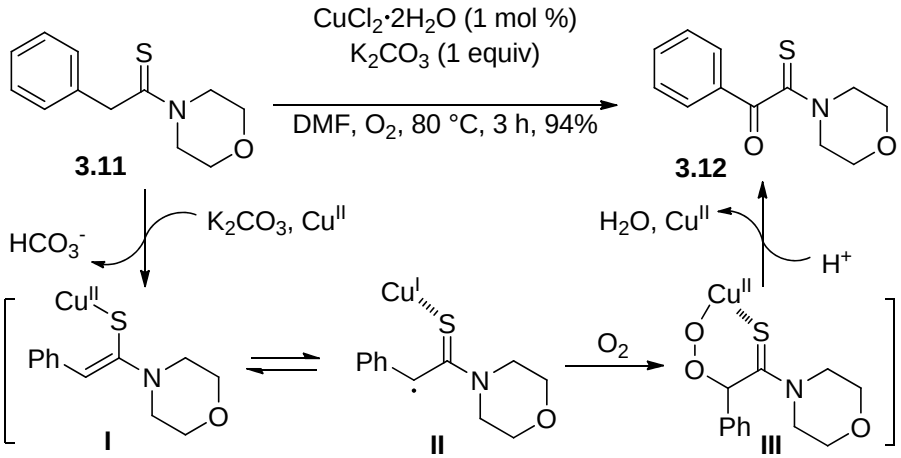
carboxylic acids, as reported by Gokel's group (Scheme 3-4).[48] This transformation involved the intermediate acyl cyanide **A**.



Scheme 3-4. Potassium *tert*-butoxide-mediated oxidative hydrolysis of nitriles.

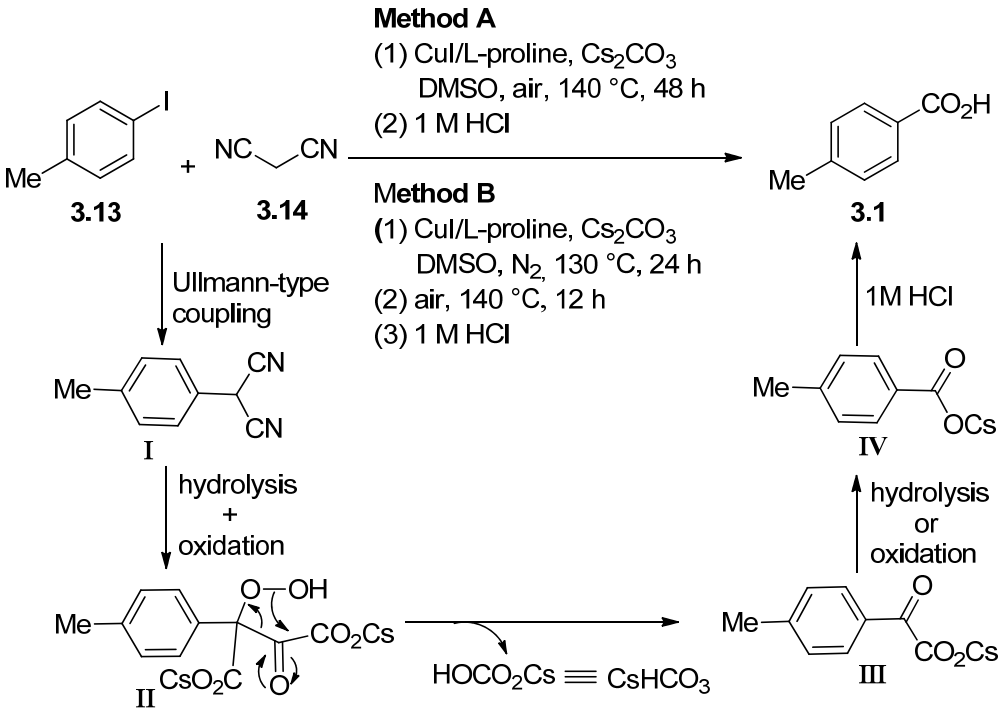
3.1.3 Copper-catalyzed oxygenation of the C–H bond

A facile aerobic Cu-catalyzed α-oxygenation of aryl thioacetamides to synthesize α-keto aryl thioamides was described by Mirjafary and co-workers (Scheme 3-5).[98] Their proposed mechanism involves a free radical pathway: base-promoted thioenolation of substrate **3.11** generates copper thioenolate **I,** which tautomerizes to give free radical **II** species that coordinate with the resulting Cu(I). In the presence of molecular O_2, oxygen incorporation by **II** occurs to provide the α-hydroperoxide equivalent **III** and regenerate Cu(II). Intermediate **III** undergoes dehydration to yield the α-keto aryl thioamide **3.12**.



Scheme 3-5. Aerobic Cu-catalyzed α-oxygenation of aryl thioacetamide.

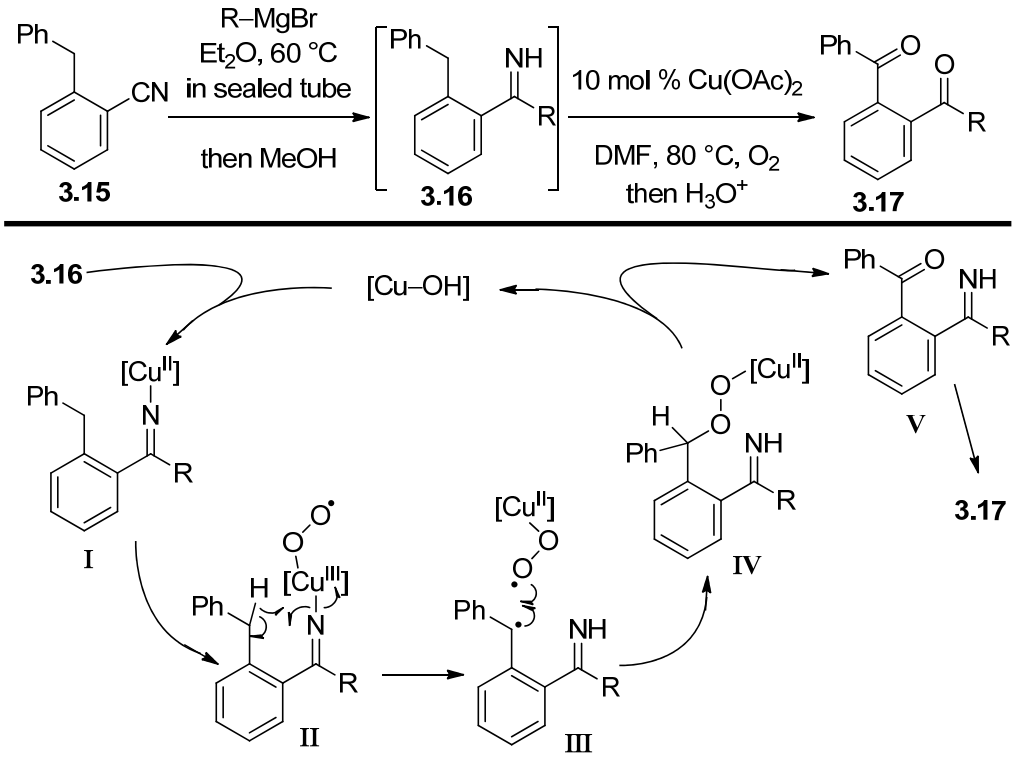
Fu's group developed a copper-catalyzed aerobic oxidative synthesis of aromatic carboxylic acids (Scheme 3-6).[99] In this efficient one-pot cascade reaction, aryl halides and malononitrile were transformed into the corresponding aromatic carboxylic acids using inexpensive CuI/L-proline as the catalyst. The process involved a sequence of Ullmann-type coupling, aerobic oxidation and hydrolysis reactions.



Scheme 3-6. Cu-catalyzed aerobic oxidative synthesis of aromatic carboxylic acids.

Recently, our group explored the intriguing chemical reactivity of the iminyl copper species in aerobic oxidation reactions.[43,47] For example, copper-catalyzed benzylic C–H oxygenation under an O_2 atmosphere was described in which the iminyl copper species acted as an internal directing group.[47c] One mechanism proposed for this C–H oxygenation is described in Scheme 3-7. In this proposal, addition of Grignard reagent to carbonitrile **3.15** followed by protonation with MeOH affords *N*–H imine **3.16,** which

reacts with the Cu(II) catalyst to give the transient iminyl copper(II) species **I,** which can be oxidized with O_2 to form peroxycoper(III) **II**. The peroxycoper(III) **II** undergoes an intramolecular 1,5-H shift to generate benzylic radical **III,** which is converted into peroxycopper(II) species **IV**. Elimination of [Cu(II)-OH] species gives keto imine **V,** which is hydrolyzed to yield the diketones **3.17**.

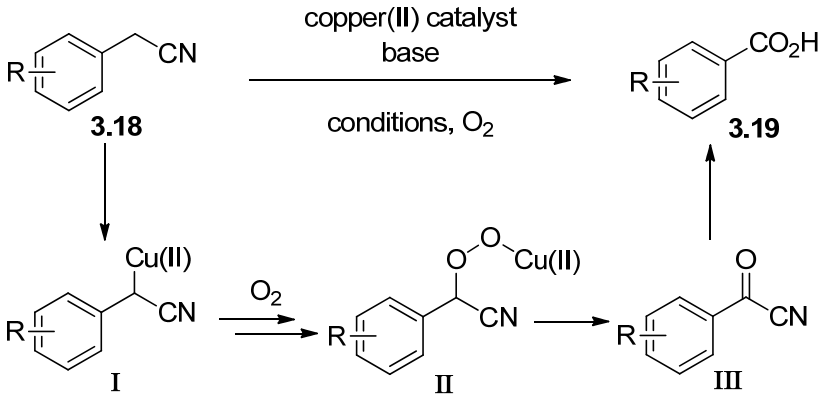


Scheme 3-7. Cu-catalyzed benzylic C–H oxygenation.

3.2 Project hypothesis

Inspired by the C–H bond oxygenation described above, we wondered about the implications of combining our group's benzylic C–H bond oxygenation (Scheme 3-7) with Gokel's potassium *tert*-butoxide-mediated penultimate oxidative hydrolysis of primary nitriles to yield carboxylic acids (Scheme 3-4) and Fu's copper-catalyzed aerobic

oxidative synthesis of aromatic carboxylic acids (Scheme 3-6). We designed a process to synthesize benzoic acids *via* Cu-catalyzed C-H oxygenation of benzyl cyanides under an O_2 atmosphere (Scheme 3-8).



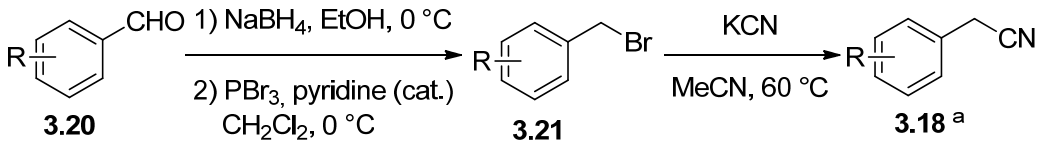
Scheme 3-8. Hypothesized Cu-catalyzed aerobic oxidation of benzyl cyanides to synthesize benzoic acids.

3.3 Synthesis of benzyl cyanides

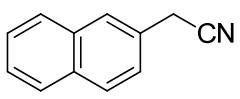
3.3.1 Substitution of benzyl bromides

A conventional method to synthesize benzyl cyanides is to convert benzaldehydes into benzyl bromide through successive reduction and bromination, then to substitute the benzyl bromide with KCN or other CN source (Table 3-1). Most of the benzyl cyanides (**3.18a-l** and **3.18r**) were prepared by this method.

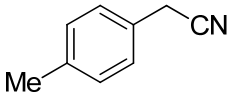
Table 3-1. Synthesis of benzyl cyanides from benzaldehydes.



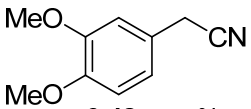
3.20 **3.21** **3.18** [a]



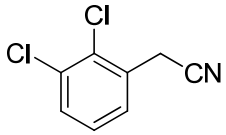
3.18a, 96%



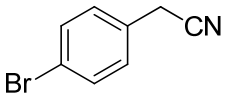
3.18b, 70%



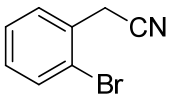
3.18c, 42%



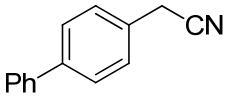
3.18d, 49%



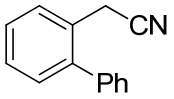
3.18e, 59%



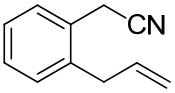
3.18f, 97% [b]



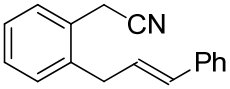
3.18g, 78%



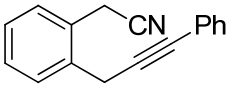
3.18h, 64%



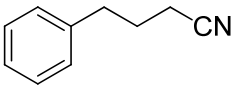
3.18i, 52%



3.18j, 30%



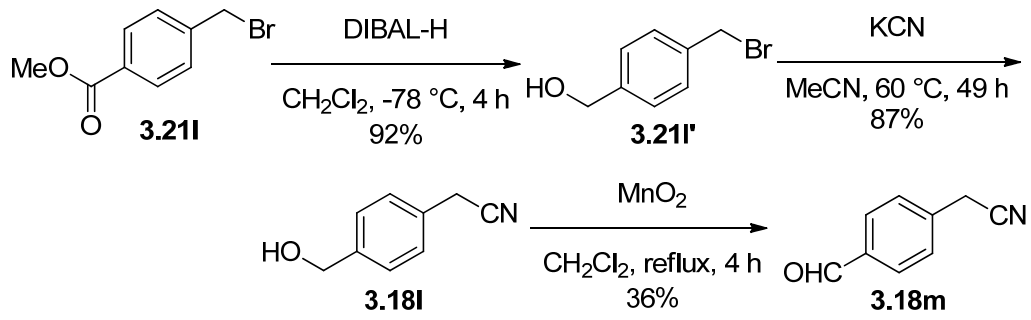
3.18k, 53%



3.18r, 93% [b]

[a] yield from **3.20** for 3 steps; [b] yield from **3.21f**; [c] yield from **3.21r** and *n*-Bu_4NCN in DMF

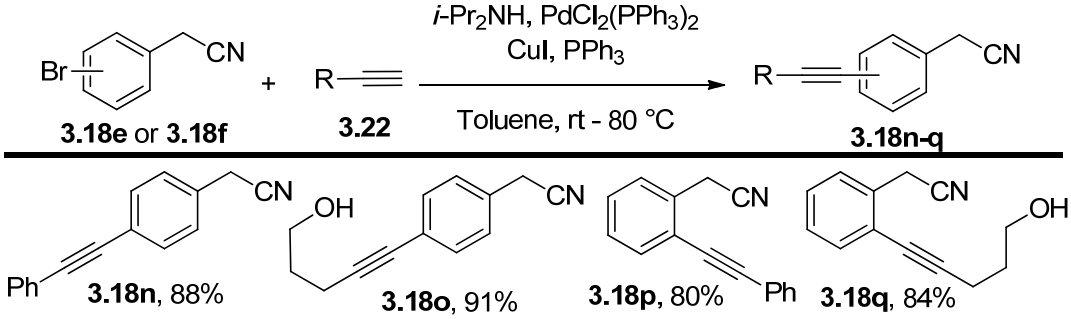
The 4-hydroxymethylbenzyl cyanide **3.18l** and 4-formylbenzyl cyanide **3.18m** were prepared from 4-methoxycarbonylbenzyl bromide **3.22l** (Scheme 3-9). Selective reduction of the 4-methoxycarbonylbenzyl bromide **3.22l** by DIBAL-H gave 4-hydroxymethylbenzyl bromide **3.22l'**, which reacted with KCN to produce 4-hydroxymethylbenzyl cyanide **3.18l**. Treatment of the 4-hydroxymethylbenzyl cyanide **3.18l** with MnO_2 gave the 4-formylbenzyl cyanide **3.18m**.



Scheme 3-9. Synthesis of **3.18l** and **3.18m**.

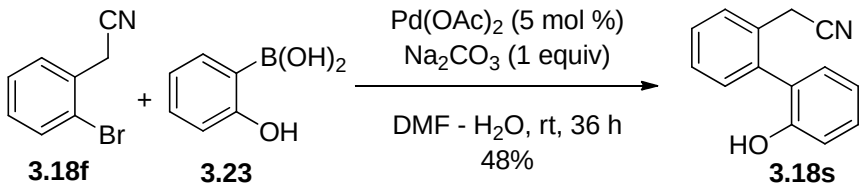
3.3.2 Coupling of bromobenzyl cyanides

The substrates **3.18n-q** with an alkynyl group on the aromatic ring were prepared by the Sonogashira coupling reaction from the corresponding terminal alkyne **3.22** and 4-bromobenzyl cyanide **3.18e** or 2-bromobenzyl cyanide **3.18f** (Scheme 3-10).



Scheme 3-10. Synthesis of **3.18n-q** by the Sonogashira coupling reaction.

The substrate **3.18s** was synthesized by the Suzuki coupling reaction from 2-bromobenzyl cyanide **3.18f** and 2-hydroxyphenyl boronic acid **3.23** (Scheme 3-11).

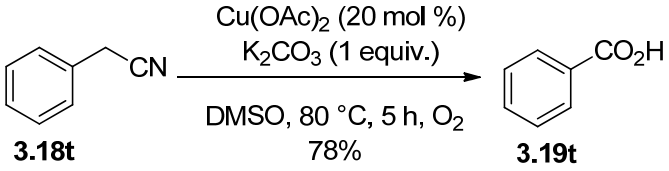


Scheme 3-11. Synthesis of **3.18s** by the Suzuki coupling reaction.

3.4 Results and discussion

3.4.1 Optimization of reaction conditions

To test the hypothesis of Cu(II)-catalyzed C–H bond oxygenation of benzyl cyanides for synthesis of carboxylic acids (Scheme 3-8), a test reaction was conducted using benzyl cyanide **3.18t** with 20 mol % of $Cu(OAc)_2$ and 1 equiv K_2CO_3 at 80 ºC under an O_2 atmosphere (Scheme 3-12). The desired benzoic acid **3.19t** was obtained in 78% yield.

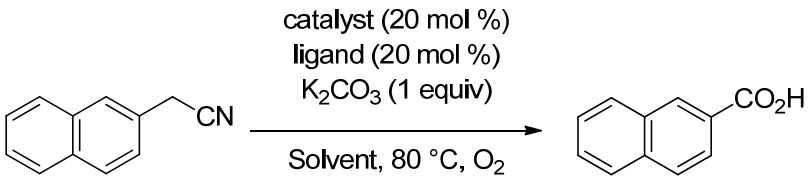


Scheme 3-12. Test reaction to achieve Cu(II)-catalyzed aerobic C–H bond oxygenation.

Inspired by these preliminary results, the 2-naphthyl acetonitrile **3.18a** was chosen as the model substrate for further optimization of the reaction conditions as shown in Table 3-2. In the presence of only 20 mol % $Cu(OAc)_2$ with 1 equiv K_2CO_3 in DMF at 80 ^oC under an O_2 atmosphere, the 2-naphthoic acid **3.19a** was obtained in 67% yield, along with a recovery yield of 27% of the substrate 2-naphthyl acetonitrile **3.18a** (entry 1). Other copper catalysts were tested (entries 5-10), with $Cu(OTf)_2$ giving good yield (86%) (entry 8), but none gave better yield than $Cu(OAc)_2$. Using 2,2'-bipyridine as ligand gave the best yield (93%) of 2-naphthoic acid **3.19a** (entry 4). The reaction was not effective at all when 10 equiv H_2O were used as additive (entry 2), nor did other bases improve the yield (entry 3).

The model reaction was also used to investigate the effect of solvent. The transformation of substrate **3.18a** was notably accelerated in DMSO, which gave the 2-naphthoic acid **3.19a** in 81% yield after only 1 hour (entry 11). The reaction proceeded in MeCN, giving 2-naphthoic acid **3.19a** in 68% yield along with a recovery yield of 8% for **3.18a** and of 12% for 2-naphthaldehyde (entry 12). However, the reaction did not proceed at all in the nonpolar solvent $ClCH_2CH_2Cl$ due to solubility issues (entry 13).

Table 3-2. Optimization of reaction conditions.



3.18a **3.19a**

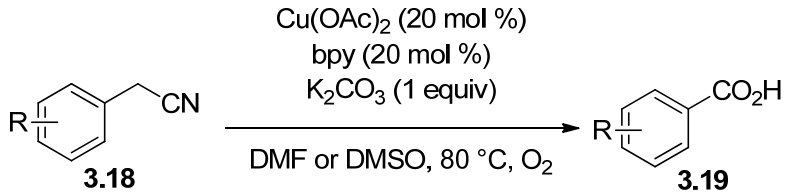
Entry	Catalyst	Ligand	Solvent	Time (h)	Yield (%)[a]
1	$Cu(OAc)_2$	—	DMF	24	67 (27)
2[b]	$Cu(OAc)_2$	—	DMF	24	67 (32)
3[c]	$Cu(OAc)_2$	—	DMF	6	64
4	**$Cu(OAc)_2$**	**bpy**	**DMF**	**12**	**93**
5	CuCN	bpy	DMF	10	76
6	$CuCl_2$	bpy	DMF	12	62 (9)
7	$CuBr_2$	bpy	DMF	12	69
8	**$Cu(OTf)_2$**	**bpy**	**DMF**	**12**	**86**
9	$Cu(OCOCF_3)_2$	bpy	DMF	12	68
10	$CuSO_4$	bpy	DMF	12	62
11	**$Cu(OAc)_2$**	**bpy**	**DMSO**	**1**	**81**
12	$Cu(OAc)_2$	bpy	MeCN	24	60 (8), (12)[d]
13	$Cu(OAc)_2$	bpy	$ClCH_2CH_2Cl$	24	0 (97)

[a] Recovery yield of **3.18a** in parentheses; [b] 10 equiv H_2O as additive were added; [c] Ag_2CO_3 used as base instead of K_2CO_3; [d] 2-Naphthaldehyde was obtained; [e] TONs = 5, TOFs = 0.42 h^{-1}. bpy: 2,2'-bipyridine.

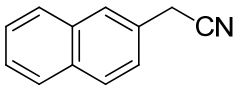
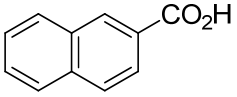
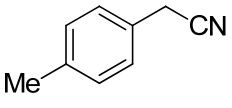
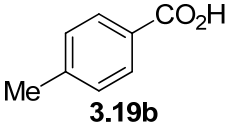
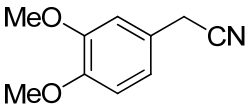
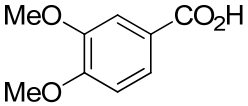
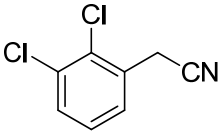
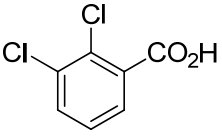
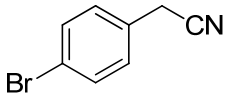
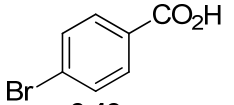
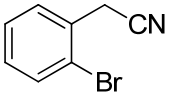
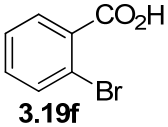
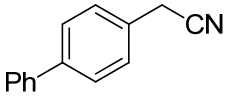
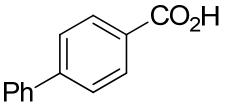
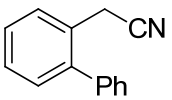
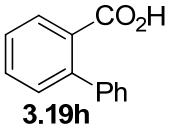
3.4.2 Copper-catalyzed synthesis of aromatic carboxylic acids

Once the optimal reaction conditions had been defined, the scope of copper-catalyzed synthesis of benzoic acids from benzyl cyanides was investigated (Table 3-3).

Table 3-3a. Copper-catalyzed synthesis of aromatic carboxylic acids.



3.18 **3.19**

Substrate	Product	Substrate	Product
 **3.18a**	 **3.19a** 12 h, 93% [a] 1 h, 81% [b]	 **3.18b**	 **3.19b** 48 h, 65% [a] (32%) [c] 16 h, 99% [b]
 **3.18c**	 **3.19c** 24 h, 62% [a] (35%)[c] 12 h, 96% [b]	 **3.18d**	 **3.19d** 16 h, 88% [a]
 **3.18e**	 **3.19e** 12 h, 87% [a]	 **3.18f**	 **3.19f** 10 h, 79% [a]
 **3.18g**	 **3.19g** 12 h, 95% [a]	 **3.18h**	 **3.19h** 30 h, 73% [a] (10%) [c] 12 h, 81% [b]

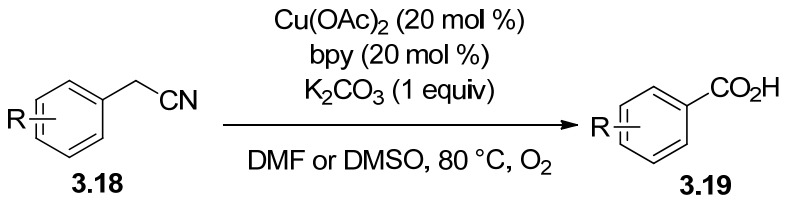
[a] In DMF; [b] In DMSO; [c] Recovery yield of **3.18** in parentheses.

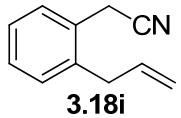
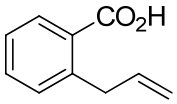
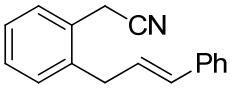
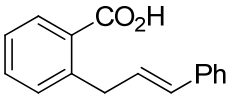
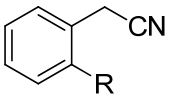
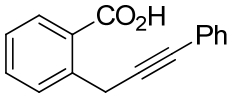
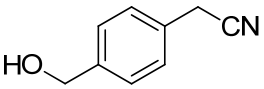
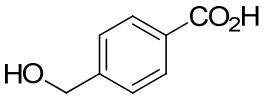
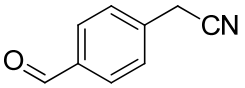
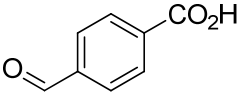
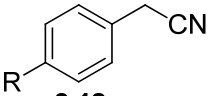
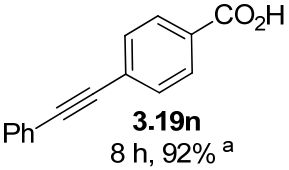
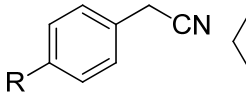
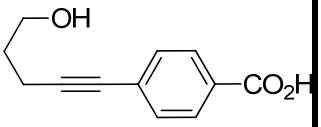
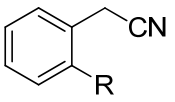
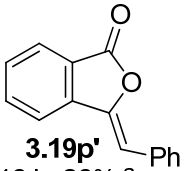
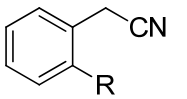
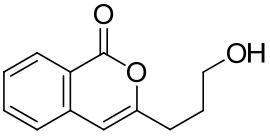
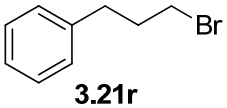
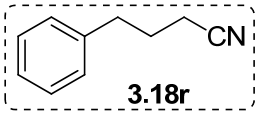
Various substituted groups were installed on the benzene ring of aromatic carboxylic acids as shown in Table 3-3a. Both electron-donating and -withdrawing groups were

incorporated onto the benzene ring (**3.19b-f**). Whereas substrates containing an electron-donating group did not react in DMF, the corresponding benzoic acid was obtained in excellent yield in DMSO (**3.19b-c**). Importantly, the reaction allowed halide groups such as Cl and Br to be installed on the benzene ring (**3.19d-f**). The benzoic acids bearing a phenyl group (**3.19g-h**), whether in the *ortho*- or *para*-positions, were obtained in excellent yield, as was benzoic acid bearing an alkyl moiety (**3.19b**).

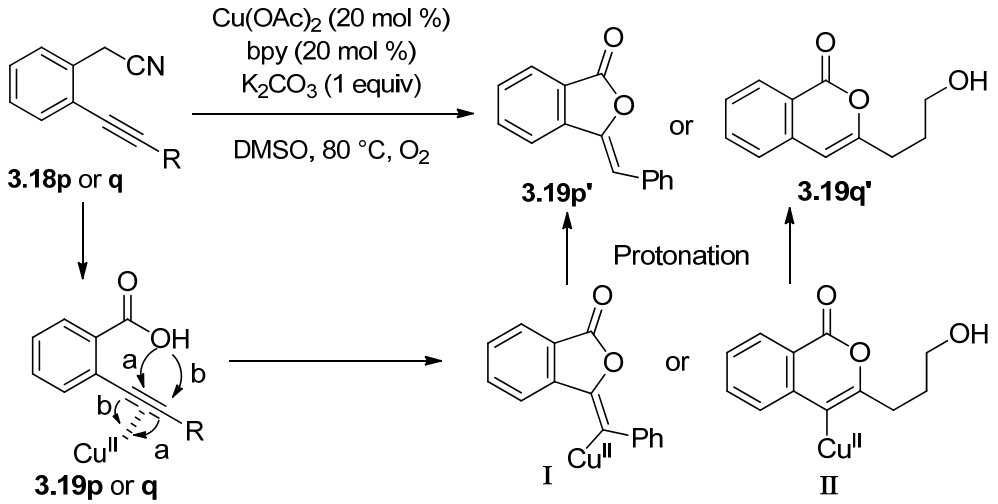
We also examined the ability of the reaction to handle certain substrates bearing special functional groups (Table 3-3b). It was possible to install an allyl group on the aromatic ring (**3.19i** and **3.19j**), while keeping the double bond intact. When the substrate contained a triple bond, the reaction gave different results depending on the type and position of the substituents: (1) the substrate with a propargyl group (**3.19k**) gave only approximately 30% yield of the corresponding benzoic acid; (2) substrates with an alkynyl group at the *para*-position of the benzene ring provided the corresponding benzoic acids in good yields (**3.19n-o**); (3) benzyl cyanides bearing a 2-alkynyl substitution gave low yields of the lactones **3.19p'-q'**, the carboxyl moieties of which reacted with an intramolecular alkyne to afford intermediate **I** (from **3.18p**) or **II** (from **3.18q**), which in turn gave the corresponding lactones after protonation (Scheme 3-13). More importantly, the hydroxyl group (**3.19l** and **3.19o**) and formyl group (**3.19m**) were tolerated in this oxidative process, even though 4-formyl benzoic acid **3.19m** was produced in only 37% yield. To extend the scope of this catalytic reaction for the synthesis of alkyl carboxylic acids, 4-phenylbutylnitrile **3.18r** was examined, but the reaction did not work: no **3.19r** was obtained and only **3.18r** was recovered.

Table 3-3b. Copper-catalyzed synthesis of aromatic carboxylic acids.



Substrate	Product	Substrate	Product
 **3.18i**	 **3.19i** 20 h, 72% [a] (15%) [c] 10 h, 78% [b]	 **3.18j**	 **3.19j** 24 h, 70% [a, d] 5 h, 72% [b, d]
 **3.18k** R = Ph—≡—CH_2	 **3.19k** 12 h, 31% [a] 2 h, 30% [b,d]	 **3.18l**	 **3.19l** 6 h, 65% [b]
 **3.18m**	 **3.19m** 4 h, 37% [a]	 **3.18n** R = Ph—≡	 **3.19n** 8 h, 92% [a]
 **3.18o** R = $HO(CH_2)_3$—≡	 **3.19o** 48 h, 67% [a] 8 h, 80% [b]	 **3.18p** R = Ph—≡	 **3.19p'** 16 h, 26% [a] 5 h, 35% [b]
 **3.18q** R = $HO(CH_2)_3$—≡	 **3.19q'** 8 h, 35% [a]	 **3.21r** + *n*-Bu_4NCN	 **3.18r** **3.19r** 24 h, 0% (93%) [e]

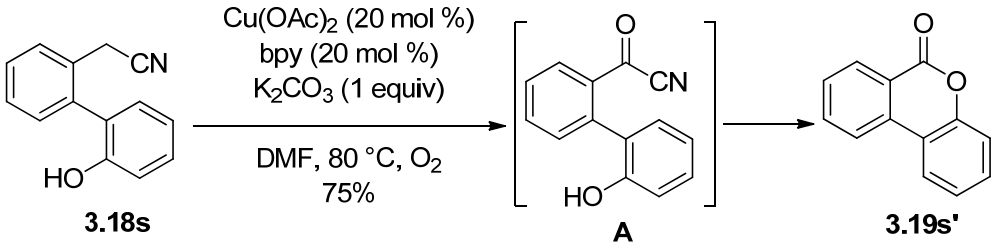
[a] In DMF; [b] In DMSO; [c] Recovery yield of **3.18** in parentheses; [d] Without bpy; [e] One-pot reaction from 3-phenylpropyl bromide (1 equiv) and *n*-Bu_4NCN (1 equiv) in DMF at 80 °C for 2 h, then added $Cu(OAc)_2$ (20 mol %) and K_2CO_3 (1 equiv) for 24 h.



Scheme 3-13. Process of lactone transformation starting from **3.18p** and **3.18q**.

3.4.3 Proposed mechanism

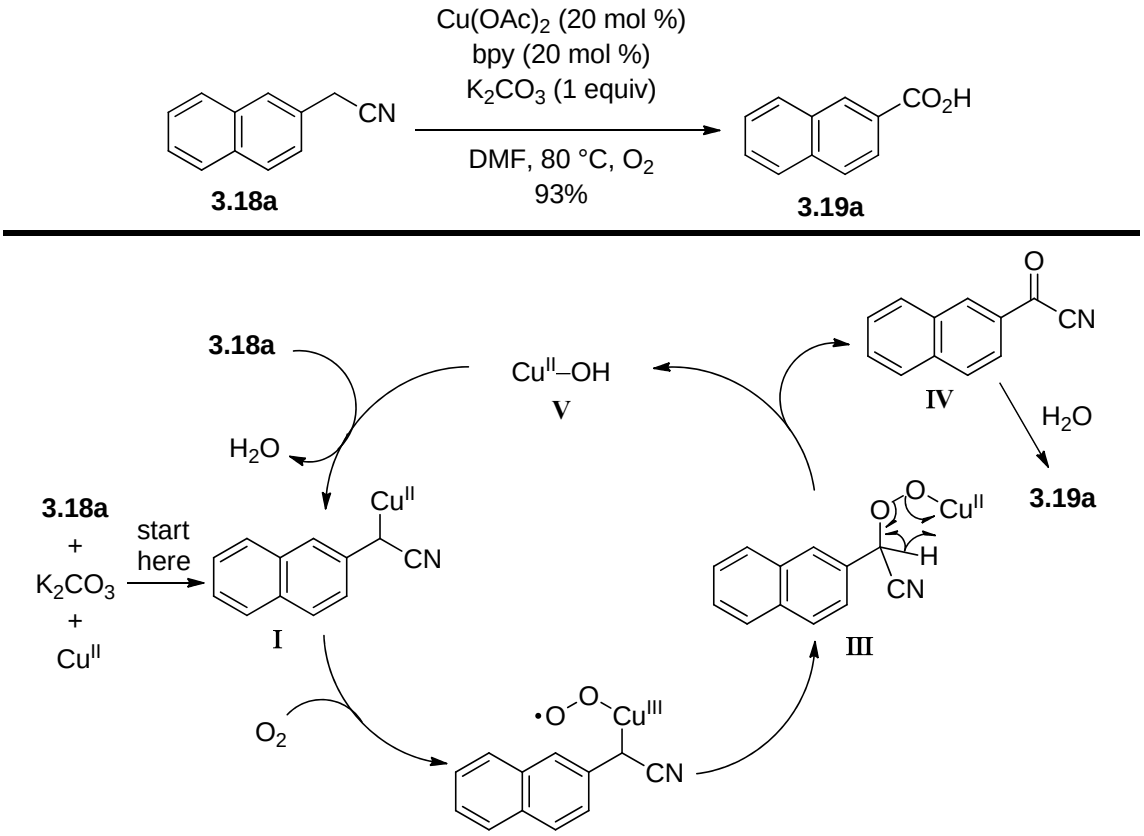
In order to propose a mechanism for this oxidative hydrolysis of benzyl cyanides, a control experiment was performed under the standard reaction conditions as shown in Scheme 3-14. The 2-(2-hydroxyphenyl)benzyl cyanide **3.18s** converted into the lactone **3.19s'** in 75% yield, suggesting that the intermediate acyl cyanide **A** was generated.



Scheme 3-14. Formation of lactone **3.19s'** from benzyl cyanide **3.18s**.

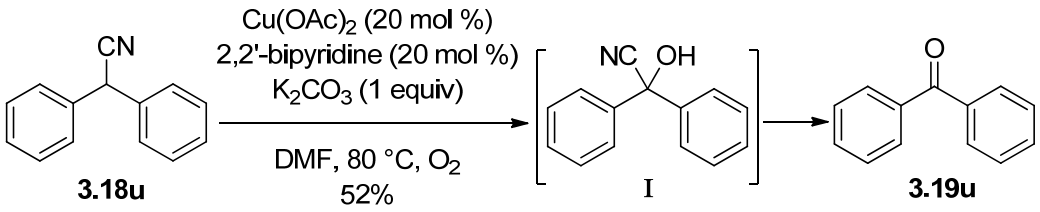
On the basis of these results, a mechanism for the Cu-catalyzed synthesis of benzoic acids from benzyl cyanides *via* C–H bond oxygenation was proposed in Scheme 3-15. In this process, treating 2-naphthyl acetonitrile **3.18a** with K_2CO_3 in the presence of catalytic

$Cu(OAc)_2$ leads to intermediate **I,** which is oxidized by O_2 to generate the peroxycopper(III) species **II**. Isomerization of **II** forms the peroxycopper(II) species **III**. Subsequently, the acyl cyanide **IV** is delivered by elimination of [Cu(II)-OH] species **V,** which can be used to participate in the next cycle. The acyl cyanide **IV** is finally converted into 2-naphthalic acid **3.19a** by hydrolysis.



Scheme 3-15. Proposed mechanism for copper-catalyzed synthesis of benzoic acids from benzyl cyanides

To examine the generality of this Cu-catalyzed oxygenation of C–H bonds in benzyl cyanides, a secondary nitrile diphenylacetonitrile **3.18u** was tested under the standard reaction conditions and the expected benzophenone **3.19u** was obtained in 52% yield *via* intermediate cyanohydrins **I** (Scheme 3-16).[100]



Scheme 3-16. Transformation of diphenylacetonitrile **3.18u** into benzophenone **3.19u**.

3.5 Summary

In summary, we have described a Cu-catalyzed synthesis of the "one carbon shorter" benzoic acids from the corresponding benzyl cyanides under an O_2 atmosphere. The oxidative hydrolysis of benzyl cyanides tolerated diverse functional groups, including alkyl, aryl, double bond, triple bond, C–Cl, C–Br, hydroxyl and formyl groups. Moreover, although the method proved unsuitable for preparing alkyl carboxylic acids, we were able to extend it to the synthesis of ketones.

Chapter 4

Experimental section

4.1 General

^{1}H NMR (500 MHz) spectra were recorded on a Bruker Avance 500 apparatus. ^{1}H NMR (400 MHz) spectra on a Bruker Avance 400 and a JEOL-AL400 spectrometers in $CDCl_3$ [using $CDCl_3$ (for ^{1}H, δ = 7.26) as internal standard] unless otherwise mentioned. ^{13}C NMR (125 MHz) spectra were recorded on a Bruker Avance 500. ^{13}C NMR (100 MHz) spectra on a Bruker Avance 400 and a JEOL-AL400 spectrometers in $CDCl_3$ [using $CDCl_3$ (for ^{13}C, δ = 77.00) as internal standard] unless otherwise mentioned. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad. IR spectra were recorded on a Shimadzu IR Prestige-21 FT-IR Spectrometer. High-resolution mass spectra were obtained with a Q-Tof Premier LC HR mass spectrometer. 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 and distilled eluting solvents. Methanol (MeOH) was distilled from sodium under N_2 and stored over MS 4Å. Tetrahydrofuran (THF), 1,4-dioxane and diethyl ether (Et_2O), when used as solvents for the reactions, were distilled from sodium and benzophenone under N_2. *N,N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were distilled from CaH_2 under N_2 and stored over MS 4Å. Toluene and dichloromethane (CH_2Cl_2) were dried by passing over a column of activated alumina (A-2, Purify) followed by a column of Q-5 scavenger (Engelhard). 1,2-Dichloroethane were distilled from CaH_2 and stored over MS 4Å. Acetonitrile (MeCN) was distilled from P_4O_{10} and

stored over MS 4Å.

4.2 The safety issues for handling of azide compounds [101, 102]

4.2.1 Sodium azide (NaN_3)

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

4.2.2 Organic azides

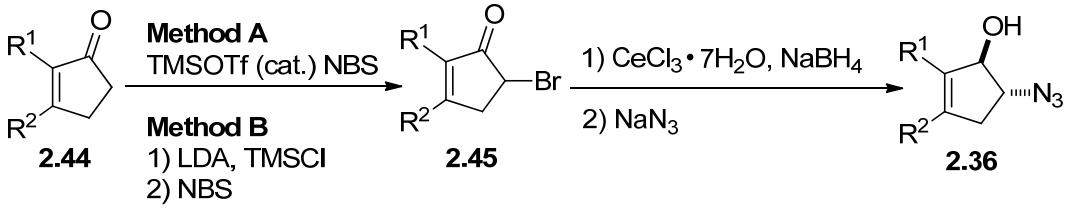
Organic azides are potentially explosive substances that can decompose with the slight input of energy from external sources (heat, light, pressure, etc). When designing the organic azides used for the project, we keep in mind the following equation. It is noted that this equation takes into account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

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

All organic azides prepared in this work are satisfied with the equation above, and 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.

4.3 Synthesis of azidoalcohols 2.36

trans-2-Azidocyclopenten-1-ols **2.36** were synthesized by the following scheme.

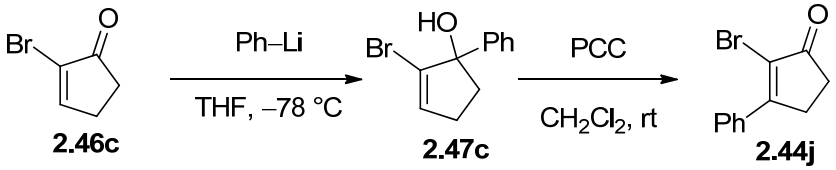


4.3.1 Synthesis of substituted cyclopenten-1-ones 2.44

Cyclopenten-1-ones **2.44** were prepared by following **Method I-III** as shown below.

Method I:[66] (**2.44e**, **2.44i** and **2.44j** were prepared by this Method).

A typical procedure: synthesis of 2-bromo-3-phenylcyclopent-2-enone (2.44j):[66]

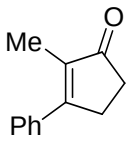


To a solution of bromobenzene (5.35 mL, 50.8 mmol) in 80 mL THF in a dry flask was added dropwise *n*-BuLi (1.6 M in hexane) (30.0 mL, 48.0 mmol) at –78 °C. After the addition was completed, the regent mixture was stirred for 2 h at –78 °C and the solution of 2-bromo-2-cyclopentenone[66] (6.45 g, 40.0 mmol) in THF (20 mL) was slowly added. The mixture was stirred at the same temperature for 4 h before quenched with water (100 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 x

100 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and then evaporated. The crude product was purified by flash chromatography (silica gel, hexanes/EtOAc = 7 : 1) to give 2-bromo-1-phenyl- 2-cyclopenten-1-ol **2.47c** (6.69 g, 28.0 mmol) in 70% yield.

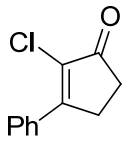
To a solution of **2.47c** (6.69 g, 28.0 mmol) in CH_2Cl_2 (50 mL) was added PCC (9.27 g, 43.0 mmol), and the mixture was stirred at room temperature for 24 h. The solution was diluted with ether (100 mL) and filtered through a pad of silica gel. The filtrate was concentrated and the resulted crude product was purified by flash chromatography (silica gel, EtOAc/hexanes = 9 : 1) to give 2-bromo-3-phenylcyclopent-2-enone (5.10 g, 21.3 mmol) in 76% yield (53% in 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67-2.70 (2H, m), 3.07-3.10 (2H, m), 7.48-7.51 (3H, m),7.87-7.90 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.7, 32.5, 121.7, 127.7, 128.6, 131.0, 134.0, 167.5, 201.6.

2-Methyl-3-phenylcyclopent-2-enone (2.44e):[103]



44% yield (2 steps) from 2-methylcyclopent-2-enone and phenyl lithium; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96 (3H, s), 2.53-2.55 (2H, m), 2.90-2.93(2H, m), 7.39-7.53 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.9, 29.2, 34.0, 127.5, 128.6, 129.4, 136.4, 136.5, 166.6, 209.8.

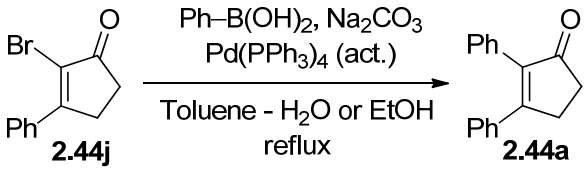
2-Chloro-3-phenylcyclopent-2-enone (2.44i): [65]



63% yield (2 steps) from 2-chlorocyclopent-2-enone and phenyl lithium; White solid; mp 93-95 °C; IR (KBr) 3019, 2934, 2402, 1710 (C=O), 1275, 962, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.64-2.66 (2H, m), 3.06-3.08 (2H, m), 7.48-7.50 (3H, m), 7.90-7.92 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 32.4, 127.8, 128.7, 130.1, 131.3, 133.3, 163.3 (**C**-Cl), 201.1 (**C**=O); HRMS (ESI): Found: *m/z*, 193.0429, Calcd for $C_{11}H_{10}ClO$ $[M+H]^+$: 193.0420.

Method II (Suzuki coupling): (**2.47a-d**, **2.47k-p** were prepared by this method)**.**

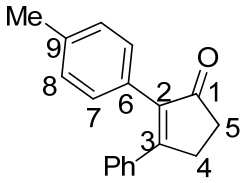
A typical procedure: synthesis of 2,3-diphenylcyclopent-2-enone (2.44a):[104]



2-Bromo-3-phenylcyclopent-2-enone **2.44j** (5.55 g, 23.2 mmol), phenylboronic acid (4.28 g, 34.9 mmol), $Pd(PPh_3)_4$ (511 mg, 0.40 mmol), and Na_2CO_3 (4.94 g, 46.6 mmol) were dissolved in toluene (75 mL) and water (75 mL), and the mixture was stirred at the reflux temperature for 24 h. The aqueous layer was extracted with EtOAc (3 x 75 mL), and the combined extracts were washed with brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the resulting crude product was purified by column chromatography on silica gel with EtOAc/Hexane (1 : 5) to give 2,3-diphenylcyclopent-

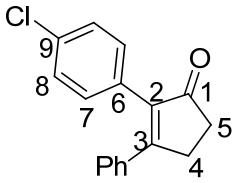
2-enone **(2.44a)** (5.09 g, 21.7 mmol) in 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70-2.73 (2H, m), 3.05-3.07 (2H, m), 7.20-7.22 (2H, m), 7.27-7.33 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.5, 34.8, 127.8, 128.0, 128.4, 128.5, 129.4, 129.8, 132.3, 135.7, 139.6, 168.0, 207.6.

3-Phenyl-2-*p*-tolylcyclopent-2-enone (2.44b):



88% yield from 2-bromo-3-phenylcyclopent-2-enone and *p*-tolylboronic acid; White solid; mp 99-101 °C; IR (KBr) 3012, 2922, 2395, 1689 (C=O), 1606, 1510, 1352, 1159, 1096 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (3H, s, C**H**$_3$), 2.68-2.71(2H, m, C**H**$_2$), 3.03-3.05 (2H, m, C**H**$_2$), 7.10 (2H, d, *J* = 8.0 Hz, 8-**H**), 7.14 (2H, d, *J* = 8.0 Hz, 7-**H**), 7.27-7.36 (5H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3 (**C**H$_3$), 29.5 (4-**C**), 34.8 (5-**C**), 128.0, 128.4, 129.2, 129.3, 129.7 (overlap), 135.9, 137.6, 139.8, 167.4, 207.8 (**C**=O); HRMS (ESI): Found: *m/z*, 249.1249, Calcd for $C_{18}H_{17}O$ $[M+H]^+$: 249.1279.

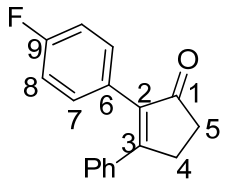
2-(4-Chlorophenyl)-3-phenylcyclopent-2-enone (2.44c):



77% yield from 2-bromo-3-phenylcyclopent-2-enone and *p*-chlorophenylboronic acid; Pale yellow oil; IR (KBr) 3016, 2917, 2396, 1691 (C=O), 1489, 1340, 1157, 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70-2.72 (2H, m, C**H**$_2$), 3.04-3.07 (2H, m, C**H**$_2$), 7.14 (2H,

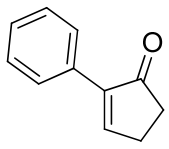
d, J = 8.4 Hz, Ar-**H**), 7.28-7.37 (7H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.6 (4-**C**), 34.8 (5-**C**), 128.0, 128.6, 128.7, 130.0, 130.6, 130.9, 133.8, 135.4, 138.6, 168.7, 207.2 (**C**=O); HRMS (ESI): Found: *m/z*, 269.0730, Calcd for $C_{17}H_{14}OCl$ $[M+H]^+$: 269.0733.

2-(4-Fluorophenyl)-3-phenylcyclopent-2-enone (2.44d):



88% yield from 2-bromo-3-phenylcyclopent-2-enone and *p*-fluorophenylboronic acid; White solid; mp 89-91 °C; IR (KBr) 3016, 2917, 2409, 1680 (C=O), 1592, 1350, 1158, 1043 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69-2.72 (2H, m, C**H**$_2$), 3.04-3.06 (2H, m, C**H**$_2$), 6.99-7.03 (2H, m, Ar-**H**), 7.17-7.21 (2H, m, Ar-**H**), 7.26-7.36 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.6 (4-**C**), 34.7 (5-**C**), 115.4 (d, J = 21.4 Hz, 8-**C**), 128.0, 128.1 (d, J = 3.5 Hz, 6-**C**), 128.5, 129.9, 131.2 (d, J = 8.0 Hz, 7-**C**), 135.6, 138.8, 161.2 (d, J = 245.7 Hz, 9-**C**), 168.3, 207.4 (**C**=O); HRMS (ESI): Found: *m/z*, 253.1023, Calcd for $C_{17}H_{14}OF$ $[M+H]^+$: 253.1029.

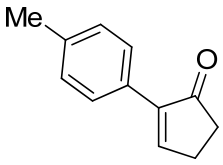
2-Phenylcyclopent-2-enone (2.44k):[103]



76% yield from 2-Bromocyclopetenone[3] and phenylboronic acid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58-2.61 (2H, m), 2.69-2.72 (2H, m), 7.30-7.40 (3H,m), 7.67 (2H, d, J = 7.6

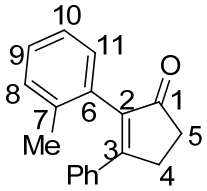
Hz), 7.81-7.83 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 35.8, 127.0, 128.3, 128.4, 131.6, 143.5, 158.9, 207.6.

2-*p*-Tolylcyclopent-2-enone (2.44l):[103]



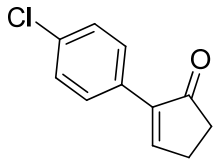
50% yield from 2-bromocyclopetenone and *p*-tolylboronic acid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (3H, s), 2.57-2.59 (2H, m), 2.69-2.71 (2H, m), 7.18 (2H, d, *J* = 7.9 Hz), 7.58 (2H, d, *J* = 7.9 Hz), 7.77 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 26.1, 35.8, 126.9, 128.8, 129.1, 138.2, 143.3, 158.1, 207.8.

2-*o*-Tolylcyclopent-2-enone (2.44m):



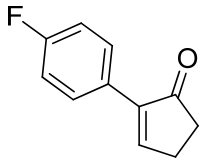
34% yield from 2-bromocyclopetenone and *o*-tolylboronic acid; Pale yellow oil; IR (KBr) 3010, 2934, 2401, 1696 (C=O), 1380, 1250, 937, 666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (3H, s, C**H**$_3$), 2.57-2.59 (2H, m, C**H**$_2$), 2.76-2.78 (2H, m, C**H**$_2$), 7.12-7.25 (4H, m, Ar-**H**), 7.60 (1H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2 (**C**H$_3$), 26.8 (4-**C**), 34.8 (5-**C**), 125.6, 128.2, 129.3, 130.2, 131.9, 136.2, 146.3, 161.1, 207.8 (**C**=O). HRMS (ESI): Found: *m/z*, 173.0969, Calcd for $C_{12}H_{13}O$ $[M+H]^+$: 173.0966.

2-(4-Chlorophenyl)cyclopent-2-enone (2.44n):[105]



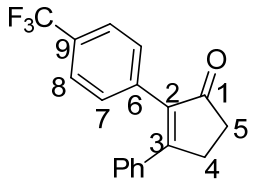
47% yield from 2-bromocyclopetenone and *p*-chlorophenylboronic acid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59-2.61 (2H, m), 2.71-2.73 (2H, m), 7.3 (2H, d, *J* = 8.1 Hz), 7.64 (2H, d, *J* = 8.1 Hz), 7.82 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 35.7, 128.3, 128.6, 130.0, 134.2, 142.3, 159.2, 207.4.

2-(4-Fluorophenyl)cyclopent-2-enone (2.44o):[106]



58% yield from 2-Bromocyclopetenone and *p*-fluorophenylboronic acid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58-2.61 (2H, m), 2.68-2.72 (2H, m), 7.04-7.08 (2H, m), 7.67-7.70 (2H, m), 7.78-7.79 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 35.7, 115.4 (d, *J* = 21.4 Hz), 127.7 (d, *J* = 3.9 Hz), 128.7 (d, *J* = 8.0 Hz), 142.4, 158.5, 162.8 (d, *J* = 246.8 Hz), 207.5.

2-(4-Trifluoromethylphenyl)cyclopent-2-enone (2.44p):

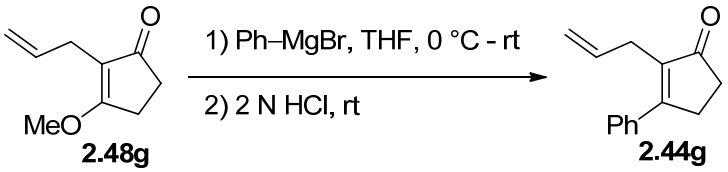


54% yield from 2-bromocyclopetenone and *p*-trifluoromethylphenylboronic acid; Pale yellow solid; mp 97-99 °C; IR (KBr) 3018, 2934, 2398, 1696 (C=O), 1326, 1173, 1068,

840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.61-2.64 (2H, m, C**H**$_2$), 2.74-2.77 (2H, m, C**H**$_2$), 7.62 (2H, d, *J* = 8.2 Hz, 7-**H**), 7.80 (2H, d, *J* = 8.2 Hz, 8-**H**), 7.91-7.93 (1H, m, 3-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3 (4-**C**), 35.7 (5-**C**), 124.1 (q, *J* = 270.4 Hz, **C**F_3), 125.3 (q, *J* = 3.8 Hz, 8-**C**), 127.3, 130.2 (q, *J* = 32.3 Hz, 9-**C**), 135.0, 142.3, 160.5, 207.0 (**C**=O). HRMS (ESI): Found: *m/z*, 227.0686, Calcd for $C_{12}H_{10}F_3O$ $[M+H]^+$: 227.0684.

Method III: (**2.44f-h** were prepared by this method).

A typical procedure: synthesis of 2-allyl-3phenyl-2cyclopenten-1-one (2.44g):



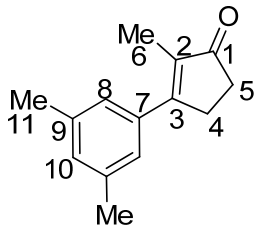
2.48g **2.44g**

To a solution of phenylmagnesium bromide prepared from magnesium turnings (0.63 g, 26.1 mmol) and bromobenzene (2.6 mL, 24.8 mmol) in THF (30 mL) was added dropwise a solution of 2-ally-3-methoxy-2cyclopenten-1-one[68] (1.88 g, 12.4 mmol) in THF (20 mL). The resulting yellow-brown suspension was stirred at room temperature overnight, then quenched carefully with 2 N aqueous HCl (70 mL) and stirred at room temperature for further 30 min. The mixture was poured into water and extracted with Et_2O (4 x 50 mL). The combined extract was dried over $MgSO_4$, filtrated and then the filtration was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel with EtOAc/Hexane (1 : 4) to afford the 2-allyl-3phenyl-2cyclopenten-1-one **2.44g** (1.03 g, 5.20 mmol) in 42% yield.

Pale yellow oil; IR (KBr) 3022, 2068, 1684 (C=O), 1613, 1361, 915, 755 cm^{-1}; ^1H NMR

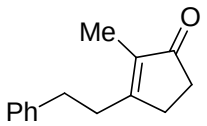
(400 MHz, $CDCl_3$) δ 2.55-2.57 (2H, m), 2.96-2.97 (2H, m), 3.15 (2H, brs), 5.00-5.07 (2H, m), 5.88-5.98 (1H, m), 7.40-7.52 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 29.7, 34.1, 115.7, 127.4, 128.6, 129.7, 134.8, 136.1, 138.1, 168.4, 209.0 (**C**=O); HRMS (ESI): Found: *m/z*, 199.1115, Calcd for $C_{14}H_{15}O$ $[M+H]^+$: 199.1123.

2-Methyl-3-(3, 5-dimethylphenyl)cyclopent-2-enone (2.44f):



69% yield from 2-methyl-3-methoxy-2cyclopenten-1-one[67] and 3,5-dimethylphenyl magnesium bromide; Pale yellow needle; mp 118-120 °C; IR (KBr) 3010, 2934, 2409, 1683 (C=O), 1446, 1348, 1102, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.95 (3H, t, *J* = 2.0 Hz, 6-**H**), 2.37 (6H, s, 11-**H**), 2.51-2.53 (2H, m, C$\mathbf{H}_2$), 2.87-2.90 (2H, m, C$\mathbf{H}_2$), 7.06 (1H, s, 10-**H**), 7.12 (2H, s, 8-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.9 (6-**C**), 21.3 (11-**C**), 29.4 (4-**C**), 33.9 (5-**C**), 125.2, 131.1, 136.2, 136.4, 138.1, 167.1 (3-**C**), 209.9 (**C**=O); HRMS (ESI): Found: *m/z*, 201.1273, Calcd for $C_{14}H_{17}O$ $[M+H]^+$: 201.1279.

2-Methyl-3-phenethylcyclopent-2-enone (2.44h):[107]



57% yield from 2-methyl-3-methoxy-2-cyclopenten-1-one and 2-phenylethylmagnesium bromide; ^1H NMR (400 MHz, $CDCl_3$) δ 1.58 (3H, s), 2.34-2.37 (2H, m), 2.45-2.47 (2H,

m), 2.71-2.75 (2H, m), 2.82-2.87 (2H, m), 7.16-7.30 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8, 29.4, 33.0, 33.3, 34.1, 126.3, 128.2, 128.5, 136.8, 140.7, 172.2, 210.0;

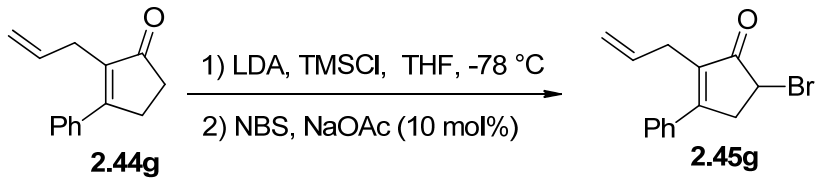
4.3.2 Synthesis of 5-bromocyclopeten-1-ones 2.45

5-Bromocyclopenten-1-ones **2.45** were prepared from **2.44** by **Method A** or **B.**

Method A: (**2.45g** and **2.45h** was prepared by this method).

A typical procedure:[69]

Synthesis of 5-bromo-2-allyl-3-phenylcyclopent-2-enone **(2.45g):**

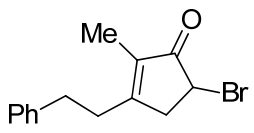


To a stirred solution of diisopropylamine (309 mg, 3.05 mmol) in THF (8 mL) was added dropwise *n*-BuLi (1.6 M in hexane) (1.8 mL, 2.88 mmol) at 0 °C. The mixture was stirred at 0 °C for 0.5 h, and then cooled to -78 °C. A solution of enone **2.47g** (400 mg, 2.02 mmol) in THF (4 mL) was added dropwise and the mixture was stirred at the same temperature for 2 h. Then a solution of TMSCl (325 mg, 2.99 mmol) in THF (3 mL) was slowly added, and the reaction mixture was stirred 6 h at -78 °C. The reaction was quenched by saturated aqueous $NaHCO_3$, and organic materials were extracted with Et_2O (3 x 30 mL). Combined extracts were washed with water, brine and dried over $MgSO_4$. The solvents were evaporated off to yield a crude material including trimethylsilly enol ether, which was used in the next step without further purification.

To a stirred solution of the trimethylsillyenol ether prepared above and NBS (534 mg, 3.00 mmol) in THF-H_2O (20 mL, 1 : 1) was added NaOAc (17 mg, 0.20 mmol) at 0 °C, and the reaction was stirred 2 h at the same temperature. After the reaction was quenched with water (50 mL), the mixture was extraced with Et_2O (3 x 30 mL). The combined extracst were washed with water, brine, and dried over $MgSO_4$. After evaporation of the solvents, the residue was purified by flash column chromatography with EtOAc/Hexane (1 : 8) to give 5-bromo-2-allyl-3-phenylcyclopent-2-enone (**2.45g**) (327 mg, 1.18 mmol) in 59% yield for 2 steps.

Yellow oil; IR (KBr) 3018, 2400, 1702 (C=O), 1429, 1361, 923 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.20 (2H, d, *J* = 5.5 Hz), 3.25 (1H, dd, *J* = 2.2, 18.6 Hz), 3.59 (1H, dd, *J* = 6.9, 18.6 Hz), 4.51 (1H, dd, *J* = 2.2, 6.9 Hz, C**H**Br), 5.04-5.12 (2H, m), 5.89-5.99 (1H, m), 7.46-7.53 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 41.1, 41.3, 116.2, 127.5, 128.8, 130.5, 133.9, 134.8, 135.8, 165.7, 201.9 (**C**=O); HRMS (ESI): Found: *m/z* 277.0228, Calcd for $C_{14}H_{14}BrO$ $[M+H]^+$: 277.0228.

5-Bromo-2-methyl-3-phenethylcyclopent-2-enone (2.45h):



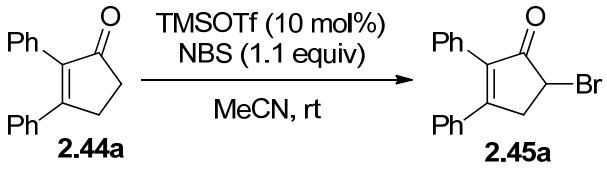
47% yield from 2.47h; Pale yellow oil; IR (KBr) 3018, 2934, 2251, 1693, 1389, 1089, 917, 652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.62 (3H, s), 2.69-2.88 (5H, m), 3.11 (1H, dd, *J* = 6.6, 18.9 Hz), 4.30 (1H, dd, *J* = 1.8 Hz, 6.6 Hz, C**H**Br), 7.15 (2H, d, *J* = 7.6 Hz), 7.20-7.31 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.2, 32.9, 33.0, 41.1, 41.3, 126.5,

128.2, 128.6, 134.9, 140.0, 169.7, 202.5 (C=O); HRMS (ESI): Found: *m/z* 279.0392, Calcd for $C_{14}H_{16}BrO$ $[M+H]^+$: 279.0385.

Method B: (2.48a-f, 2.48i-p were prepared by this method).

A typical procedure:

Syntehsis of 5-bromo-2,3-diphenylcyclopent-2-enone (**2.48a**):[70]

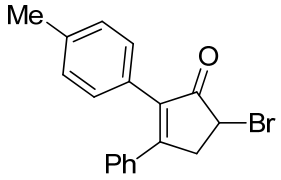


To a stirred solution of 2,3-diphenylcyclopent-2-enone **(2.44a)** (3.52 g, 15.0 mmol) and *N*-bromosuccinimide (NBS) (2.94 g, 16.5 mmol) in MeCN (80 mL) was added TMSOTf (332 mg, 1.5 mmol), and the mixture was stirred for 12 h at room tempetature. The reaction mixture was diluted with ether (200 mL), washed with H_2O. The separated organic phases was dried over Na_2SO_4 and the solvents were concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography with EtOAc/Hexane (1 : 7) to give 5-bromo-2,3-diphenylcyclopent-2-enone **(2.45a)** (3.05 g, 7.00 mmol) in 65% yield.

Yellow solid, mp 122-123 °C; IR (KBr) 3018, 2399, 1708 (C=O), 1620, 1352, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.37 (1H, dd, *J* = 2.4, 18.9 Hz, C**H**$_2$), 3.72 (1H, dd, *J* = 6.9, 18.9 Hz, C**H**$_2$), 4.65 (1H, dd, *J* = 2.4, 6.9 Hz, C**H**Br), 7.23-7.38 (10H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.0 (**C**H_2), 41.8 (**C**HBr), 128.2, 128.4, 128.61, 128.64, 129.4,

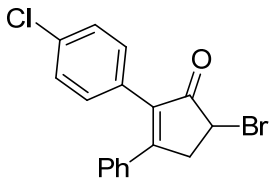
130.6, 131.4, 134.5, 137.2, 164.8, 200.5 (**C**=O); HRMS (ESI): Found: *m/z* 313.0227, Calcd for $C_{17}H_{14}BrO$ $[M+H]^+$: 313.0228.

5-Bromo-3-phenyl-2-*p*-tolylcyclopent-2-enone (2.45b):



67% yield from **2.44b**; White solid; mp 116-118 °C; IR (KBr) 3028, 2351, 1703 (C=O), 1604, 1352, 1155, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (3H, s, C**H**$_3$), 3.32 (1H, dd, *J* = 2.3, 18.8 Hz, C**H**$_2$), 3.68 (1H, dd, *J* = 6.9, 18.8 Hz, C**H**$_2$), 4.63 (1H, dd, *J* = 2.3, 6.9 Hz, C**H**Br), 7.12-7.17 (4H, m, Ar-**H**), 7.28-7.39 (5H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4 (**C**H_3), 40.9 (**C**H_2), 41.9 (**C**HBr), 128.2, 128.3, 128.6, 129.30, 129.35, 130.5, 134.7, 137.2, 138.2, 164.2, 200.7 (**C**=O); HRMS (ESI): Found: *m/z* 327.0382, Calcd for $C_{18}H_{16}BrO$ $[M+H]^+$: 327.0385.

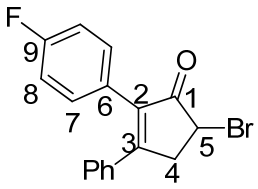
5-Bromo-2-(4-chlorophenyl)-3-phenylcyclopent-2-enone (2.45c):



60% yield from **2.44c**; Pale yellow solid; mp 145-146 °C; IR (KBr) 3016, 2399, 1707 (C=O), 1620, 1290, 1157, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.34 (1H, dd, *J* = 2.2, 18.8 Hz, C**H**$_2$), 3.69 (1H, dd, *J* = 6.9, 18.8 Hz, C**H**$_2$), 4.63 (1H, dd, *J* = 2.2, 6.9 Hz, C**H**Br), 7.18 (2H, d, *J* = 8.4 Hz, Ar-**H**), 7.31-7.42 (7H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.1 (**C**H_2), 41.6 (**C**HBr), 128.1, 128.8, 128.9, 129.7, 130.8, 130.8, 134.2, 134.4, 135.9,

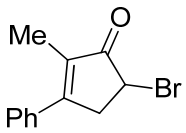
165.5, 200.2 (**C**=O); HRMS (ESI): Found: *m/z* 346.9828, Calcd for $C_{17}H_{13}BrClO$ $[M+H]^+$: 346.9838.

5-Bromo-2-(4-fluorophenyl)-3-phenylcyclopent-2-enone (2.45d):



63% yield from **2.44d**; White solid; mp 131-133 °C; IR (KBr) 3016, 2403, 1702 (C=O), 1509, 1351, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.33 (1H, dd, *J* = 2.2, 19.0 Hz, C**H**$_2$), 3.69 (1H, dd, *J* = 6.9, 19.0 Hz, C**H**$_2$), 4.63 (1H, dd, *J* = 2.2, 6.9 Hz, C**H**Br), 7.01-7.06 (2H, m, Ar-**H**), 7.22-7.24 (2H, m, Ar-**H**), 7.31-7.41 (5H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.0 (**C**H_2), 41.6 (**C**HBr), 115.7 (d, *J* = 21.5 Hz, 8-**C**), 127.2 (d, *J* = 3.5 Hz, 7-**C**), 128.1, 128.7 130.7, 131.3 (d, *J* = 8.1 Hz, 6-**C**), 134.4, 136.1, 162.7 (d, *J* = 246.8 Hz) (**C**–F), 165.1, 200.4 (**C**=O); HRMS (ESI): Found: *m/z* 331,0135, Calcd for $C_{17}H_{13}BrFO$ $[M+H]^+$: 331.0134.

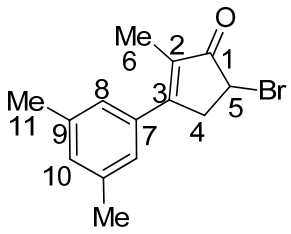
5-Bromo-2-methyl-3-phenylcyclopent-2-enone (2.45e):



79% yield from **2.44e**; Pale yellow solid, mp 100-102 °C; IR (KBr) 3019, 2400, 1696 (C=O), 1351, 1047, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.05 (3H, d, *J* = 1.8 Hz, C**H**$_3$), 3.22-3.28 (1H, m, C**H**$_2$), 3.55-3.61 (1H, m, C**H**$_2$), 4.51 (1H, dd, *J* = 2.0, 6.8 Hz, C**H**Br), 7.47 – 7.53 (5H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.4 (**C**H_3), 40.8

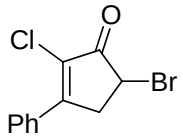
(**C**H_2), 41.3 (**C**HBr), 127.7, 128.8, 130.3, 134.2, 135.1, 163.7, 202.6 (**C**=O); HRMS (ESI): Found: *m/z* 251.0078, Calcd for $C_{12}H_{12}BrO$ $[M+H]^+$: 251.0072.

5-Bromo-2-methyl-3-(3,5-dimethylphenyl)cyclopent-2-enone (2.45f):



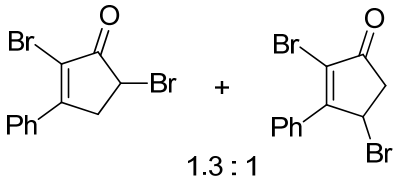
76% yield from **2.44f**; yellow solid, mp 96-98 °C; IR (KBr) 3018, 2399, 1699 (C=O), 1347, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.03 (3H, d, *J* = 1.4 Hz, 6-**H**), 2.37 (6H, s, 11-**H**), 3.20-3.25 (1H, m, 4-**H**), 3.51-3.58 (1H, m, 4-**H**), 4.48 (1H, dd, *J* = 2.1, 6.8 Hz, C**H**Br), 7.10 (1H, s, 10-**H**), 7.12 (2H, s, 8-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5 (6-**C**), 21.3 (11-**C**), 41.0 (**C**H_2), 41.4 (**C**HBr), 125.5, 132.0, 134.0, 135.1, 138.4, 164.3, 202.6 (**C**=O); HRMS (ESI): Found: *m/z* 279.0388, Calcd for $C_{14}H_{16}BrO$ $[M+H]^+$: 279.0385.

5-Bromo-2-chloro-3-phenylcyclopent-2-enone (2.45i):



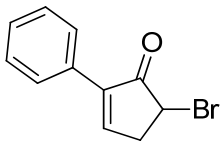
84% yield from **2.44i**; Pale yellow solid; mp 91-93°C; IR (KBr) 3018, 2932, 2401, 1723 (C=O), 1446, 964 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.36 (1H, dd, *J* = 2.1, 18.4 Hz, C**H**$_2$), 3.71 (1H, dd, *J* = 6.9, 18.4 Hz, C**H**$_2$), 4.59 (1H, dd, *J* = 2.1, 6.9 Hz, C**H**Br), 7.49-7.53 (3H, m, Ar-**H**), 7.91-7.93 (2H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.7 (**C**H_2), 40.1 (**C**HBr), 127.8, 128.1, 128.9, 132.0, 132.2, 160.7, 194.9 (**C**=O); HRMS (ESI): Found: *m/z* 270.9529, Calcd for $C_{11}H_9BrClO$ $[M+H]^+$: 270.9525.

2,5-Dibromo-3-phenylcyclopent-2-enone (2.45j):



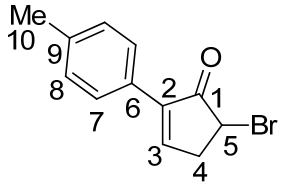
An inseparable mixture of the desired **2.45j** and 2,4-dibromo-3- phenylcyclopent-2-enone were obtained in 83% yield from **2.44j** (1.3 : 1 from ^{1}H NMR). The mixture was used for next procedure of synthesis of 2-azidoalcohol **(2.36j)** withour further purification.

5-Bromo-2-phenylcyclopent-2-enone (2.45k):[108]



70% yield from **2.44k**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.99 (1H, ddd, *J* = 2.1, 2.7, 20.2 Hz), 3.38 (1H, ddd, *J* = 2.7, 6.6, 20.2 Hz), 4.51 (1H, dd, *J* = 2.1, 6.6 Hz), 7.35-7.42 (3H, m), 7.70 (2H, d, *J* = 7.7 Hz), 7.76 (1H, dd, *J* = 2.7, 2.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.9, 42.4, 127.0, 128.6, 129.0, 130.6, 140.9, 155.1, 200.4.

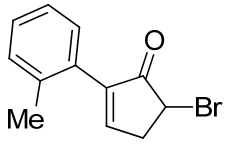
5-Bromo-2-*p*-tolylcyclopent-2-enone (2.45l):



36% yield from **2.44l**; Pale yellow solid, mp 75-77 °C; IR (KBr) 3018, 2919, 2399, 1712 (C=O), 1427, 1118, 1022, 927 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (3H, s, C**H**$_3$),

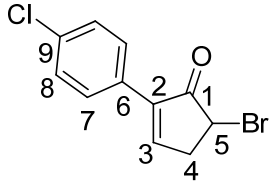
2.97 (1H, ddd, *J* = 2.4, 2.8, 20.2 Hz, C**H**$_2$), 3.36 (1H, ddd, *J* = 3.0, 6.6, 20.2 Hz, C**H**$_2$), 4.50 (1H, dd, *J* = 2.4, 6.6 Hz, C**H**Br), 7.20 (2H, d, *J* = 8.0 Hz, 8-**H**), 7.61 (2H, d, *J* = 8.0 Hz, 7-**H**), 7.72 (2H, dd, *J* = 2.8, 3.0 Hz, 3-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3 (**C**H$_3$), 37.8 (**C**H$_2$), 42.5 (**C**HBr), 126.8, 127.8, 129.2, 139.0, 140.8, 154.2, 200.5 (C=O); HRMS (ESI): Found: *m/z* 251.0063, Calcd for $C_{12}H_{12}BrO$ $[M+H]^+$: 251.0072.

5-Bromo-2-*o*-tolylcyclopent-2-enone (2.45m):



Pale yellow oil (30% yield from **2.44m**); IR (KBr) 3017, 2919, 2409, 1715 (C=O), 1047, 722 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (3H, s, C**H**$_3$), 3.04 (1H, ddd, *J* = 2.1, 2.8, 20.0 Hz, C**H**$_2$), 3.43 (1H, ddd, *J* = 2.7, 6.5, 20.0 Hz, C**H**$_2$), 4.50 (1H, dd, *J* = 2.1, 6.5 Hz, C**H**Br), 7.15-7.29 (4H, m, Ar-**H**), 7.54 (1H, dd, *J* = 2.7 Hz, 2.8 Hz, C**H**-CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1 (**C**H$_3$), 38.5 (**C**H$_2$), 41.4 (**C**HBr), 125.7, 128.7, 129.2, 130.4, 130.7, 136.5, 143.8, 157.4, 200.3 (**C**=O); HRMS (ESI): Found: *m/z* 251.0067, Calcd for $C_{12}H_{12}BrO$ $[M+H]^+$: 251.0072.

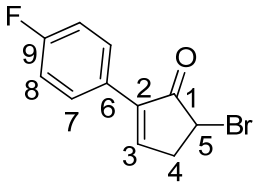
5-Bromo-2-(4-chlorophenyl)cyclopent-2-enone (2.45n):



61% yield from **2.44n**; White solid, mp 84-86 °C; IR (KBr) 3018, 2943, 2398, 1714 (C=O), 1490, 1323, 1298, 1093, 1014 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.99 (1H, ddd,

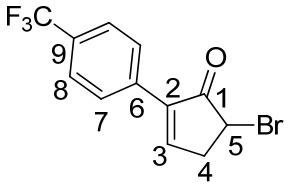
J = 2.2, 2.6, 20.3 Hz, C**H**$_2$), 3.38 (1H, ddd, *J* = 3.0, 6.6, 20.3 Hz, C**H**$_2$), 4.50 (1H, dd, *J* = 2.2, 6.6 Hz, C**H**Br), 7.36 (2H, d, *J* = 8.4 Hz, 7-**H**), 7.66 (2H, d, *J* = 8.4 Hz, 8-**H**), 7.77 (1H, dd, *J* = 2.6, 3.0 Hz, 3-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.9 (**C**H$_2$), 42.1 (**C**HBr), 128.3, 128.8, 129.0, 135.0, 139.8, 155.3, 200.2 (C=O); HRMS (ESI): Found: *m/z* 270.9521, Calcd for $C_{11}H_9BrClO$ $[M+H]^+$: 270.9525.

5-Bromo-2-(4-fluorophenyl)cyclopent-2-enone (2.45o):



49% yield from **2.44o**; Pale yellow solid, mp 65-67 °C; IR (KBr) 3019, 2943, 2401, 1713 (C=O), 1509, 1299, 1160, 925 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.99 (1H, ddd, *J* = 2.1, 2.3, 20.2 Hz, C**H**$_2$), 3.38 (1H, ddd, *J* = 2.9, 6.6, 20.2 Hz, C**H**$_2$), 4.50 (1H, dd, *J* = 2.1, 6.6 Hz, C**H**Br), 7.07-7.11 (2H, m, Ar-**H**), 7.70-7.74 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.8 (**C**H$_2$), 42.1 (**C**HBr), 115.6 (d, *J* = 21.6 Hz, 8-**C**), 126.7 (d, *J* = 3.4 Hz, 6-**C**), 128.9 (d, *J* = 8.3 Hz, 7-**C**), 139.8, 154.7, 163.1 (d, *J* = 247.8 Hz, **C**-F), 200.3 (**C**=O). HRMS (ESI): Found: *m/z* 254.9808, Calcd for $C_{11}H_9BrFO$ $[M+H]^+$: 254.9821.

5-Bromo-2-(4-trifluoromethylphenyl)cyclopent-2-enone (2.45p):



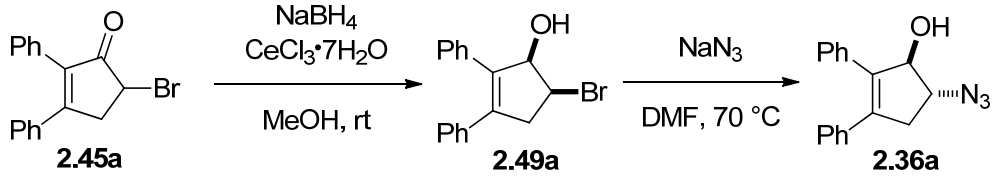
50% yield from **2.44p**; Yellow solid; mp 45-47 °C; IR (KBr) 3018, 2403, 1649 (C=O), 1606, 1326, 1130, 1068 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.03 (1H, ddd, *J* = 2.4, 2.8,

20.4 Hz, C**H**$_2$), 2.43 (1H, ddd, *J* = 3.0, 6.6, 20.4 Hz, C**H**$_2$), 4.53 (1H, dd, *J* = 2.4, 6.6 Hz, C**H**Br), 7.65 (2H, d, *J* = 8.2 Hz, 7-**H**), 7.83 (2H, d, *J* = 8.2 Hz, 8-**H**), 7.87 (1H, dd, *J* = 2.8, 3.0 Hz, 3-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.3 (**C**H$_2$), 41.9 (**C**HBr), 124.0 (q, *J* = 270.6 Hz, **C**F$_3$), 125.5 (q, *J* = 3.9 Hz, 8-**C**), 127.3, 130.9 (q, *J* = 32.5 Hz, 9-**C**), 134.0, 139.8, 156.8, 200.0 (**C**=O). HRMS (ESI): Found: *m/z* 326.9593, Calcd for $C_{12}H_8BrF_3ONa$ $[M+Na]^+$: 326.9608.

4.3.3 Synthesis of *trans*-azidoalcohols 2.36

A typical procedure:

synthesis of (1*R,5*R**)-5-Azido-2,3-diphenylcyclopent-2-enol (2.36a):**

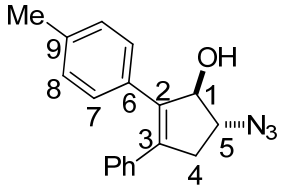


To a solution of 5-bromo-2,3-diphenylcyclopenten-1-one **(2.45a)** (3.02 g, 9.6 mmol) and $CeCl_3$•$7H_2O$ (4.32 g, 11.6 mmol) in methanol (50 mL) was added $NaBH_4$ (442 mg, 11.7 mmol) in portions over 2 min, and the mixture was stirred for 30 min at room temperature. The reaction was quenched with water (100 mL), and the organic materials were extracted with EtOAc (3 x 20 mL). The combined extracts were dried over $NaSO_4$, filtrated and the solvents were removed in vacuo to give **2.49a** (*cis*-bromohydrin) (3.00 g, 9.4 mmol) in 98% yield which can be used in next reaction without further purification.[71]

To a stirred solution of **2.49a** (2.78 g, 8.8 mmol) in anhydrous DMF (30 mL) was added NaN_3 (2.88 g, 44.3 mmol) at room temperature, and the reaction mixture was stirred at 70 °C for 2 h. The reaction was quenched with water (100 mL), and the organic materials were extraced with EtOAc (3 x 50 mL). The combined extracts were washed with brine, dried over $MgSO_4$. The solvents were removed in vacuo and the resulting crude mixture was purified by flash column chromatography with EOAc/Hexane (1 : 6) to give (1*R**,5*R**)-5-azido-2,3-diphenylcyclopent-2-enol **(2.36a)** (1.86 g, 6.7 mmol) in 74% yield (2 steps from **2.45a**).

White powder, mp 64-66 °C; IR (KBr) 3442 (OH), 3032, 2250, 1633, 1489, 1114, 1053, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.07 (1H, d, *J* = 5.4 Hz, O**H**), 2.76 (1H, dd, *J* = 5.2, 16.7 Hz, C**H**$_2$), 3.32 (1H, dd, *J* = 7.6, 16.7 Hz, C**H**$_2$), 4.09-4.13 (1H, m, C**H**N_3), 5.07-5.09 (1H, m, C**H**OH), 7.14-7.30 (10H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.0, 66.5 (**C**HN_3), 84.8 (**C**HOH), 127.6, 127.8, 128.0, 128.2, 128.6, 128.8, 135.0, 135.8, 137.4, 137.8; HRMS (ESI): Found: *m/z* 278.1300, Calcd for $C_{17}H_{16}N_3O$ $[M+H]^+$: 278.1293.

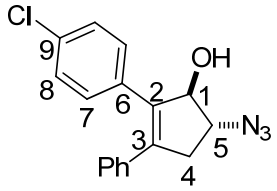
(1*R,5*R**)-5-Azido-3-phenyl-2-p-tolylcyclopent-2-enol (2.36b):**



69% yield from **2.45b**; White solid; mp 53-55 °C; IR (KBr) 3443 (OH), 2920, 2243, 2100 (N_3), 1633, 1492, 1118, 1035, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.07 (1H, d, *J* = 5.4 Hz, O**H**), 2.33 (3H, s, C**H**$_3$), 2.74 (1H, dd, *J* = 5.3, 16.7 Hz, 4-**H**), 3.31 (1H, dd, *J* =

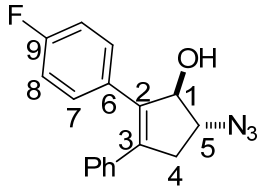
7.6, 16.7 Hz, 4-**H**), 4.08-4.12 (1H, m, C**H**N_3), 5.05-5.07 (1H, m, C**H**OH), 7.08 (2H, d, *J* = 8.2 Hz, 6-**H**), 7.11 (2H, d, *J* = 8.2 Hz, 8-**H**), 7.16-7.24 (5H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2 (**C**H_3), 40.0 (**C**H_2), 66.5 (**C**HN_3), 84.7 (**C**HOH), 127.7, 128.0, 128.2, 128.6, 129.3, 131.8, 136.0, 136.7, 137.5, 137.7; HRMS (ESI): Found: *m/z* 292.1451, Calcd for $C_{18}H_{18}N_3O$ $[M+H]^+$: 292.1450.

(1*R,5*R**)-5-Azido-2-(4-chlorophenyl)-3-phenylcyclopent-2-enol (2.36c):**



53% yield from **2.45c**; White solid; mp 81-83 °C; IR (KBr) 3447 (OH), 2937, 2252, 2102 (N_3), 1642, 1346, 1091, 1014 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (1H, brs, O**H**), 2.75 (1H, dd, *J* = 5.1, 16.8 Hz, 4-**H**), 3.29 (1H, dd, *J* = 7.5, 16.8 Hz, 4-**H**), 4.07-4.12 (1H, m) (C**H**N_3), 5.03 (1H, brs, C**H**OH), 7.15-7.25 (9H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.1 (**C**H_2), 66.6 (**C**HN_3), 84.7 (**C**HOH), 128.07, 128.09, 128.4, 128.8, 130.2, 133.4, 133.5, 135.5, 136.4, 138.4; HRMS (ESI): Found: *m/z* 312.0905, Calcd for $C_{17}H_{15}ClN_3O$ $[M+H]^+$: 312.0904.

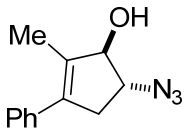
(1*R,5*R**)-5-Azido-2-(4-fluorophenyl)-3-phenylcyclopent-2-enol (2.36d):**



50% yield from **2.45d**; White solid; mp 77.5-79 °C; IR (KBr) 3018, 2102 (N_3), 1603, 1509, 1158, 840 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.11 (1H, d, *J* = 5.5 Hz, O**H**), 2.75

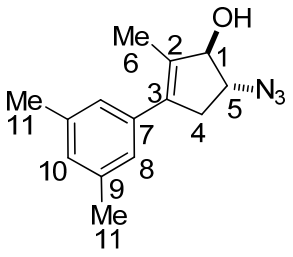
(1H, dd, *J* = 5.2, 16.7 Hz, 4-**H**), 3.29 (1H, dd, *J* = 7.6, 16.7 Hz, 4-**H**), 4.07-4.11 (1H, m, C**H**N_3), 5.02-5.04 (1H, m, C**H**OH), 6.93-6.99 (2H, m, Ar-**H**), 7.15-7.25 (7H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.0 (**C**H_2), 66.6 (**C**HN_3), 84.7 (**C**HOH), 115.6 (d, *J* = 21.9 Hz, 8-**C**), 127.9, 128.0, 128.3, 130.5 (d, *J* = 7.9 Hz, 7-**C**), 130.9 (d, *J* = 3.6 Hz, 6-**C**), 135.7, 136.6, 137.8, 162.2 (d, *J* = 245.8 Hz, 9-**C**); HRMS (ESI): Found: *m/z* 296.1200, Calcd for $C_{17}H_{15}FN_3O$ $[M+H]^+$: 296.1199.

(1*R,5*R**)-5-Azido-2-methyl-3-phenylcyclopent-2-enol (2.36e):**



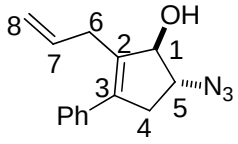
80% yield from **2.45e**; White solid; mp 65.5-67.5 °C; IR (KBr) 3018, 2101 (N_3), 1637, 1382, 1067, 1044, 699, 667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (3H, s, C**H**$_3$), 2.14 (1H, brs, O**H**), 2.67-2.73 (1H, m, C**H**$_2$), 3.01 (1H, dd, *J* = 7.8, 15.6 Hz, C**H**$_2$), 3.92-3.97 (1H, m, C**H**N_3), 4.64-4.66 (1H, m, C**H**OH), 7.26-7.29 (3H, m, Ar-**H**), 7.35-7.39 (2H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5 (**C**H_3), 67.4 (**C**HN_3), 85.3 (**C**HOH), 127.4, 127.6, 128.3, 134.3, 135.0, 136.4; HRMS (ESI): Found: *m/z* 216.1144, Calcd for $C_{12}H_{14}N_3O$ $[M+H]^+$: 216.1137.

(1*R,5*R**)-5-Azido-2-methyl-3-(3,5-dimmethylphenyl)cyclopent-2-enol (2.36f):**



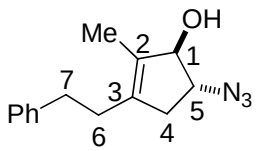
78% yield from **2.45f**; White solid; mp 98-99 °C; IR (KBr) 3464 (OH), 3016, 2100 (N_3), 1600, 1341, 1044, 851, 730, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.89 (3H, s, 6-**H**), 2.13 (1H, brd, *J* = 6.4 Hz, O**H**), 2.33 (6H, s, 11-**H**), 2.65-2.71 (1H, m, C**H**$_2$), 2.99 (1H, dd, *J* = 7.8, 15.7 Hz, C**H**$_2$), 3.90-3.95 (1H, m, C**H**N_3), 4.61-4.64 (1H, m, C**H**OH), 6.90 (2H, s, 8-**H**), 6.93 (1H, s, 10-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5 (6-**C**), 21.3 (11-C), 38.9 (**C**H_2), 67.4 (**C**HN_3), 85.4 (**C**HOH), 125.4, 129.1, 133.9, 135.3, 136.4, 137.8; HRMS (ESI): Found: *m/z* 244.1442, Calcd for $C_{14}H_{18}N_3O$ $[M+H]^+$: 244.1450.

(1*R,5*R**)-5-Azido-2-allyl-3-phenylcyclopent-2-enol (2.36g):**



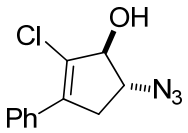
73% yield from **2.45g**; White solid; mp 53-55 °C; IR (KBr) 3439 (OH), 3030, 2253, 2100 (N_3), 1636, 1383, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.02 (1H, d, *J* = 6.3 Hz, O**H**), 2.68 (1H, dd, *J* = 5.7, 15.9 Hz, 4-**H**), 3.02-3.13 (3H, m, overlap), 3.95-4.00 (1H, m, C**H**N_3), 4.75-4.77 (1H, m, C**H**OH), 5.12-5.19 (2H, m, 8-**H**), 5.86-5.96 (1H, m, 7-**H**), 7.27-7.38 (5H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.8 (6-**C**), 39.1 (4-**C**), 67.1 (**C**HN_3), 83.8 (**C**HOH), 116.7, 127.5, 127.7, 128.3, 135.4, 135.8, 136.1, 137.1; HRMS (ESI): Found: *m/z* 242.1290, Calcd for $C_{14}H_{16}N_3O$ $[M+H]^+$: 242.1293.

(1*R,5*R**)-5-Azido-2-methyl-3-phenethylcyclopent-2-enol (2.36h):**



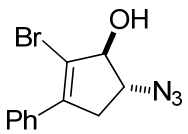
83% yield from **2.45h**; White solid; mp 56-58 °C; IR (KBr) 3418 (OH), 3019, 2400, 2100 (N_3), 1646, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (3H, s, C**H**$_3$), 1.78 (1H, d, *J* = 6.0 Hz, O**H**), 2.23-2.27 (1H, m), 2.34-2.44 (2H, m), 2.66-2.70 (3H, m), 3.75-3.79 (1H, m, C**H**N_3), 4.44-4.46 (1H, m, C**H**OH), 7.15-7.21 (3H, m, Ar-**H**), 7.26-7.30 (2H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5 (**C**H_3), 30.4 (6-**C**), 33.8 (70-**C**), 38.1 (4-**C**), 67.4 (**C**HN_3), 84.8 (**C**HOH), 126.0, 128.3, 128.4, 132.8, 135.8, 141.4; HRMS (ESI): Found: *m/z* 244.1444, Calcd for $C_{14}H_{18}N_3O$ $[M+H]^+$: 244.1450.

(1*R,5*R**)-5-Azido-2-chloro-3-phenylcyclopent-2-enol (2.36i):**



78% yield from **2.45i**; White solid; mp 72-74 °C; IR (KBr) 3408(OH), 3019, 2408, 2103 (N_3), 1642, 670, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.51 (1H, d, *J* = 4.9 Hz, O**H**), 2.77 (1H, dd, *J* = 6.2, 15.6 Hz, C**H**$_2$), 3.16 (1H, dd, *J* = 8.1, 15.6 Hz, C**H**$_2$), 4.06-4.10 (1H, m, C**H**N_3), 4.74-4.76 (1H, m, C**H**OH), 7.33-7.42 (3H, m, Ar-**H**), 7.61 (2H, d, *J* = 7.5 Hz, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.6 (**C**H_2), 65.1 (**C**HN_3), 83.2 (**C**HN_3), 126.6, 127.5, 128.4, 128.8, 133.2, 134.4; HRMS (ESI): Found: *m/z* 236.0586, Calcd for $C_{11}H_{11}ClN_3O$ $[M+H]^+$: 236.0591.

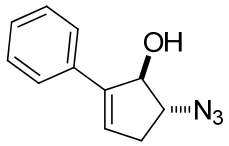
(1*R,5*R**)-5-Azido-2-bromo-3-phenylcyclopent-2-enol (2.36j):**



32% yield on 3 steps from 2-bromo-3-phenylcyclopent-2-enone (**2.44j**); White solid; mp

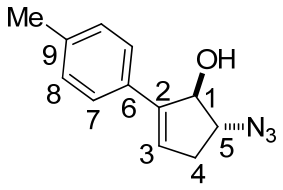
91-93 °C; IR (KBr) 3468 (OH), 2253, 2102 (N_3), 1645, 900, 745, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.58 (1H, brs, O**H**), 2.72 (1H, dd, *J* = 6.0, 15.5 Hz, C**H**$_2$), 3.11 (1H, dd, *J* = 8.0, 15.5 Hz, C**H**$_2$), 4.08-4.13 (1H, m, C**H**N_3), 4.76-4.78 (1H, m, C**H**OH), 7.36-7.42 (3H, m, Ar-**H**), 7.61 (2H, d, *J* = 7.1 Hz, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.2 (**C**H_2), 65.4 (**C**HN_3), 84.5 (**C**HOH), 117.9, 127.54, 128.43, 128.8, 133.9, 138.3; HRMS (ESI): Found: *m/z* 280.0072, Calcd for $C_{11}H_{11}BrN_3O$ $[M+H]^+$: 280.0085.

(1*R,5*R**)-5-Azido-2-phenylcyclopent-2-enol (2.36k):**



56% yield from **2.45k**; Pale yellow solid; mp 56-58 °C; IR (KBr) 3442, 2399, 2100 (N_3), 1633, 1417, 1074, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.89 (1H, brs, O**H**), 2.48 (1H, ddd, *J* = 2.5, 3.2, 17.9 Hz, C**H**$_2$), 2.98 (1H, ddd, *J* = 2.5, 7.2, 17.9 Hz, C**H**$_2$), 4.07 (1H, ddd, *J* = 3.2, 3.8, 7.2 Hz, C**H**N_3), 5.09-5.11 (1H, m, C**H**OH), 6.20 (1H, dd, *J* = 2.5, 2.5 Hz, 3-**H**), 7.25-7.51 (5H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.9 (**C**H_2), 68.3 (**C**HN_3), 81.6 (**C**HOH), 126.1, 126.7, 128.0, 128.7, 133.7, 143.0; HRMS (ESI): Found: *m/z* 202.0977, Calcd for $C_{11}H_{12}N_3O$ $[M+H]^+$: 202.0980.

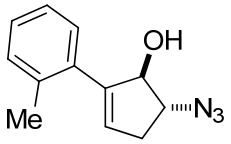
(1*R,5*R**)-5-Azido-2-*p*-tolylcyclopent-2-enol (2.36l):**



75% yield from **2.45l**; White solid; mp 162-164 °C; IR (KBr) 3439 (OH), 3030, 2252,

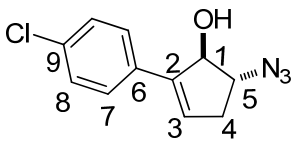
2100 (N_3), 1633, 1382, 1095, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.93 (1H, brs, O**H**), 2.35 (3H, s, C**H**$_3$), 2.46 (1H, ddd, *J* = 3.0, 3.4, 17.9 Hz, C**H**$_2$), 2.96 (1H, ddd, *J* = 2.4, 7.2, 17.9 Hz, C**H**$_2$), 4.05 (1H, ddd, *J* = 3.4, 3.8, 7.2 Hz, C**H**N_3), 5.06-5.08 (1H, m, C**H**OH), 6.13 (1H, dd, *J* = 2.4, 3.0 Hz, 3-**H**), 7.16 (2H, d, *J* = 8.0 Hz, 8-**H**), 7.39 (2H, d, *J* = 8.0 Hz, 7-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2 (**C**H_3), 35.9 (**C**H_2), 68.3 (**C**HN_3), 81.7 (**C**HOH), 125.6, 126.0, 129.4, 130.8, 137.9, 142.9; HRMS (ESI): Found: *m/z* 216.1135, Calcd for $C_{12}H_{14}N_3O$ $[M+H]^+$: 216.1137.

(1*R,5*R**)-5-Azido-2-*o*-tolylcyclopent-2-enol (2.36m):**



50% yield from **2.45m**; Colorless oil; IR (KBr) 3436 (OH), 2252, 2100, 1642, 1253, 916, 715, 652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.88 (1H, d, *J* = 5.2 Hz, OH)), 2.35 (3H, s, C**H**$_3$), 2.45-2.51 (1H, m, C**H**$_2$), 2.90-2.97 (1H, m, C**H**$_2$), 4.03-4.08 (1H, m, C**H**N3), 5.00-5.03 (1H, m, C**H**OH), 5.81-5.82 (1H, m, 3-**H**), 7.18-7.21 (4H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6 (**C**H_3), 35.7 (**C**H_2), 68.3 (**C**HN_3), 83.2 (**C**HOH), 125.8, 127.8, 128.7, 128.8, 130.6, 134.3, 136.2, 144.2; HRMS (ESI): Found: *m/z* 216.1130, Calcd for $C_{12}H_{14}N_3O$ $[M+H]^+$: 216.1137.

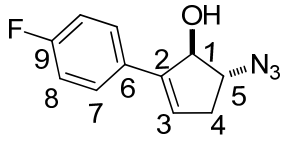
(1*R,5*R**)-5-Azido-2-(4-chlorophenyl)cyclopent-2-enol (2.36n):**



69% yield from **2.45n**; White solid; mp 74-75 °C; IR (KBr) 3442 (OH), 2926, 2250, 2098

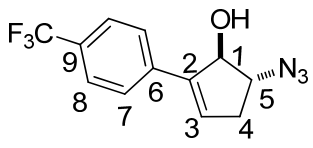
(N_3), 1633, 1348, 1093, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.94 (1H, brs, O**H**), 2.44 (1H, dd, *J* = 2.9, 18.0 Hz, C**H**$_2$), 2.94 (1H, dd, *J* = 7.2, 18.0 Hz, C**H**$_2$), 4.03-4.07 (1H, m, C**H**N_3), 5.03-5.05 (1H, m, C**H**OH), 6.18-6.20 (1H, s, 3-**H**), 7.30 (2H, d, *J* = 8.5 Hz, 7-**H**), 7.43 (2H, d, *J* = 8.5 Hz, 8-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.0 (**C**H_2), 68.4 (**C**HN_3), 81.7 (**C**HOH), 127.3, 127.4, 128.8, 132.2, 133.7, 141.9; HRMS (ESI): Found: *m/z* 236.0585, Calcd for $C_{11}H_{11}ClN_3O$ $[M+H]^+$: 236.0591.

(1*R,5*R**)-5-Azido-2-(4-fluorophenyl)cyclopent-2-enol (2.36o):**



64% yield from **2.45o**; Colorless oil; IR (KBr) 3419 (OH), 2939, 2099 (N_3), 1649, 1504, 1159, 741, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.99 (1H, d, *J* = 6.9 Hz, O**H**), 2.43 (1H, m, C**H**$_2$), 2.93-2.99 (1H, m, C**H**$_2$), 4.03-4.07 (1H, m, C**H**N_3), 5.03-5.05 (1H, m, C**H**OH), 6.12-6.13 (1H, m, 3-**H**), 7.01-7.07 (2H, m, 7-**H**), 7.46-7.51 (2H, m, 8-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.9 (**C**H_2), 68.4 (**C**HN_3), 81.8 (**C**HOH), 115.6 (d, *J* = 21.6 Hz, 8-**C**), 126.4, 127.9 (d, *J* = 8.0 Hz, 7-**C**), 129.9 (d, *J* = 3.4 Hz, 6-**C**), 142.0, 162.5 (d, *J* = 246.3 Hz, 9-**C**); HRMS (ESI): Found: *m/z* 220.0900, Calcd for $C_{11}H_{11}FN_3O$ $[M+H]^+$: 220.0886.

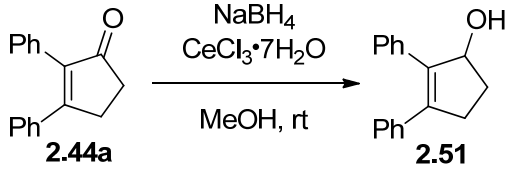
(1*R,5*R**)-5-Azido-2-(4-trifluoromethylphenyl)cyclopent-2-enol (2.36p):**



70% yield from **2.45p**; White solid; mp 79-80 °C; IR (KBr) 34421 (OH), 3018, 2402,

2099 (N_3), 1616, 1323, 1072, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.00 (1H, d, *J* = 6.8 Hz, O**H**), 2.48-2.53 (1H, m, C**H**$_2$), 2.98-3.04 (1H, m, C**H**$_2$), 4.06-4.10 (1H, m, C**H**N_3), 5.08-5.09 (1H, m, C**H**OH), 6.31-6.32 (1H, m, 3-**H**), 7.58-7.63 (4H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.0 (**C**H_2), 68.4 (**C**HN_3), 81.7 (**C**HOH), 124.1 (q, *J* = 270.3 Hz, **C**F_3), 125.6 (q, *J* = 3.7 Hz, 8-**C**), 126.4, 129.2, 129.8 (q, *J* = 32.3 Hz, 9-**C**), 137.2, 141.9; HRMS (ESI): Found: *m/z* 270.0846, Calcd for $C_{12}H_{11}F3N_3O$ $[M+H]^+$: 270.0854.

4.3.4 Synthesis of 2,3-diphenylcyclopenten-1-ol (2.51)[109]

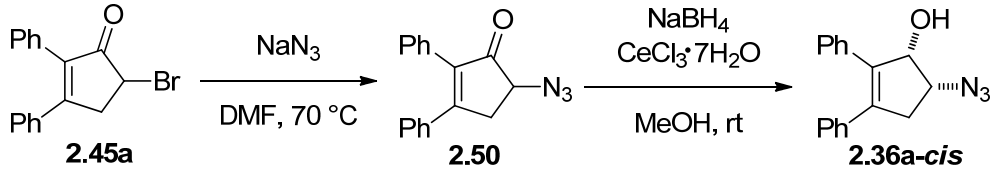


2.44a **2.51**

To a solution of **2.44a** (155 mg, 0.66 mmol) and $CeCl_3 \cdot 7H_2O$ (296 mg, 0.79 mmol) in methanol (10 mL) was added $NaBH_4$ (30 mg, 0.79 mmol), and the mixture was stirred overnight at room temperature. The reaction was quenched with water (50 mL), and the organic materials were extracted with EtOAc (3 x 20 mL). The combined extracts were dried over $NaSO_4$, and the solvents were removed in vacuum to give 2,3-diphenylcyclopenten-1-ol (**2.51**) (150 mg, 0.63 mmol) in 96% yield.

^1H NMR (400 MHz, $CDCl_3$) δ 1.74 (1H, brs), 1.94-2.01 (1H, m), 2.44-2.53 (1H, m), 2.71-2.77 (1H, m), 3,06-3.22 (1H, m), 5.21-5.23 (1H, m), 7.16-7.25 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.1, 35.2, 81.2, 127.1, 127.2, 128.11, 128.14, 128.4, 128.8, 136.3, 137.2, 139.7, 140.6.

4.3.5 Synthesis of *cis*-azidoalcohol 2.36a-*cis*



To a solution of 5-bromo-2,3-diphenylcyclopenten-1-one (**2.45a**) (315 mg, 1.00 mmol) in anhydrous DMF (3 mL) was added was added NaN_3 (71 mg, 1.1 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with water (20 mL), and the organic materials were extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine, dried over $MgSO_4$. The solvents were evaporated and the crude mixture was purified by column chromatography with EOAc/Hexane (1 : 4) to give 5-azido-2,3-diphenylcyclopenten-1-one **2.50** (253 mg, 0.92 mmol) in 92% yield.

Pale yellow solid; mp 135-137 °C; IR (KBr) 3018, 2399, 2117 (N_3), 1707, 1615, 1357, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.86 (1H, dd, *J* = 3.2, 18.0 Hz, C**H**$_2$), 3.29 (1H, dd, *J* = 7.4, 18.0 Hz, C**H**$_2$), 4.65 (1H, dd, *J* = 3.2, 7.4 Hz, C**H**N_3), 7.21-7.38 (10H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.2 (**C**H_2), 59.9 (**C**HN_3), 128.2, 128.3, 128.6 (overlaped), 129.3, 130.6, 131.2, 134.5, 137.5, 165.5, 202.6 (C=O); HRMS (ESI): Found: *m/z* 276.1151, Calcd for $C_{17}H_{14}N_3O$ $[M+H]^+$: 276.1137.

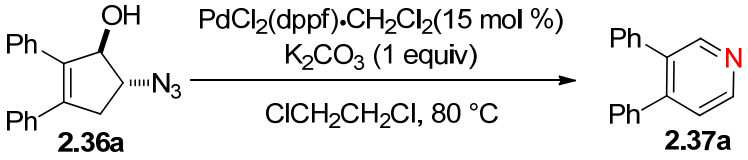
To a solution of 5-azido-2,3-diphenylcyclopenten-1-one **2.50** (207 mg, 0.75 mmol) and $CeCl_3$•$7H_2O$ (341 mg, 0.92 mmol) in methanol (10 mL) was added $NaBH_4$ (35 mg, 0.93 mmol) in portionwise over 2 min, and the mixture was stirred for 30 min at room temperature. The reaction was quenched with water (50 mL), and the organic materials

were extracted with EtOAc (3 x 20 mL). The combined extracts were dried over $NaSO_4$, and the solvents were removed in vacuo. The crude mixture was purified by column chromatography with EOAc/Hexane (1 : 5) to give (1*S**,5*R**)-5-azido-2,3-diphenylcyclopent-2-enol (**2.36a-*cis***) (192 mg, 0.69 mmol) in 92% yield.

Yellow oil; IR (KBr) 3014, 2105 (N_3), 1599, 1489, 1348, 1116, 1001 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.20 (1H, d, *J* = 6.9 Hz, O**H**), 3.03 (1H, dd, *J* = 6.8, 16.5 Hz, C**H**$_2$), 3.11 (1H, dd, *J* = 5.0, 16.5 Hz, C**H**$_2$), 4.23-4.28 (1H, m, C**H**N_3), 5.06-5.09 (1H, m, C**H**OH), 7.14-7.28 (10H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.8 (**C**H_2), 61.8 (**C**HN_3), 80.0 (**C**HOH), 127.5, 127.8, 128.1, 128.3, 128.4, 128.7, 135.2, 136.0, 137.7, 138.0; HRMS (ESI): Found: *m/z* 300.1102, Calcd for $C_{17}H_{15}N_3ONa$ $[M+Na]^+$: 300.1113.

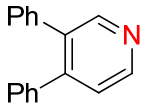
4.4 Synthesis of pyridines

A typical procedure: synthesis of 3,4-Diphenylpyridine **(2.37a):**



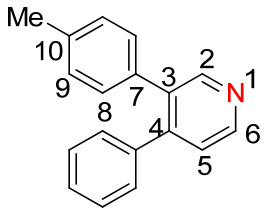
To a solution of (1*R**,5*R**)-5-azido-2,3-diphenylcyclopent-2-enol **(2.36a)** (83.9 mg, 0.303 mmol) in $ClCH_2CH_2Cl$ (2 mL) were added $PdCl_2(dppf)\cdot CH_2Cl_2$ (37.4 mg, 0.046 mmol) and K_2CO_3 (41.7 mg, 0.30 mmol), and the reaction mixture was stirred for 5 h at 80 °C. The volatile materials were removed in vacuo, and the resulting residue was purified by flash column chromatography on silica gel with EtOAc/Hexane (1 : 4) to give 3,4-diphenylpyridine **(2.37a)** (61.5 mg, 0.266 mmol) in 88% yield.

3,4-diphenylpyridine (2.37a):[110]



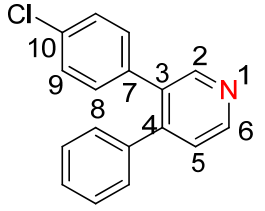
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14-7.17 (4H, m), 7.23-7.29 (6H, m), 7.33 (1H, d, *J* = 5.0 Hz), 8.61 (1H, d, *J* = 5.0 Hz), 8.64 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.6, 127.3, 127.8, 128.2 (overlap), 129.3, 129.8, 135.8, 137.7, 138.6, 147.7, 148.6, 151.0.

3-Tolyl-4-phenylpyridine (2.37b):



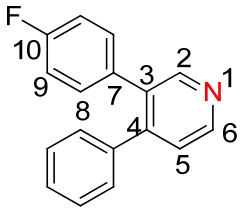
78% yield; Pale yellow solid; mp 118-120 °C; IR (KBr) 3053, 2968, 2933, 1905, 1587, 1473, 1111, 1047, 1041 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (3H, s, C**H**$_3$), 7.02 (2H, d, *J* = 8.2 Hz, 9-**H**), 7.06 (2H, d, *J* = 8.2 Hz, 8-**H**), 7.16-7.18 (2H, m, Ar-**H**), 7.24-7.27 (3H, m, Ar-**H**), 7.31 (1H, d, *J* = 5.0 Hz, 5-**H**), 8.58 (1H, d, *J* = 5.0 Hz, 6-**H**), 8.62 (1H, s, 2-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (**C**H_3), 124.6, 127.7, 128.2, 129.0, 129.3, 129.6, 134.7, 135.7, 137.0, 138.8, 147.6, 148.4 (6-**C**), 151.0 (2-**C**); HRMS (ESI): Found: *m/z* 246.1286, Calcd for $C_{18}H_{16}N$ $[M+H]^+$: 246.1283.

3-(4-Chlorophenyl)-4-phenylpyridine (2.37c):



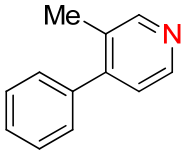
88% yield; Pale yellow solid; mp 71-73 °C; IR (KBr) 3061, 2968, 2399, 1901, 1585, 1390, 1093, 1016 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (2H, d, *J* = 8.4 Hz, 8-**H**), 7.12-7.15 (2H, m, Ar-**H**), 7.23 (2H, d, *J* = 8.4 Hz, 9-**H**), 7.27-7.29 (3H, m, Ar-**H**), 7.33 (1H, d, *J* = 5.0 Hz, 5-**H**), 8.60 (1H, s, 2-**H**), 8.63 (1H, d, *J* = 5.0 Hz, 6-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.6, 128.0, 128.4, 128.5, 129.2, 131.0, 133.5, 134.6, 136.1, 138.2, 147.7, 149.0 (6-**C**), 150.7 (2-**C**); HRMS (ESI): Found: *m/z* 266.0740, Calcd for $C_{17}H_{13}ClN$ $[M+H]^+$: 266.0737.

3-(4-Fluorophenyl)-4-phenylpyridine (2.37d):



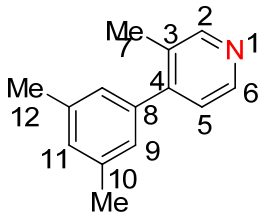
89% yield; Pale yellow solid; mp 104-106 °C; IR (KBr) 3018, 2977, 2402, 1512, 1475, 1096, 836 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (2H, dd, *J* = 8.6, 8.6 Hz, 8-**H**), 7.09-7.15 (4H, m, Ar-**H**), 7.27-7.29 (3H, m, Ar-**H**), 7.33 (1H, d, *J* = 5.0 Hz, 5-**H**), 8.61 (1H, s, 2-**H**), 8.62 (1H, d, *J* = 5.0 Hz, 6-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 115.3 (d, *J* = 21.3 Hz), 124.6, 127.9, 128.3, 129.2, 131.3 (d, *J* = 8.0 Hz), 133.6 (d, *J* = 3.5 Hz), 134.8, 138.4, 147.7, 148.8, 150.8, 162.2 (d, *J* = 245.6 Hz); HRMS (ESI): Found: *m/z* 250.1021, Calcd for $C_{17}H_{13}FN$ $[M+H]^+$: 250.1032.

3-Methyl-4-phenylpyridine (2.37e):[111]



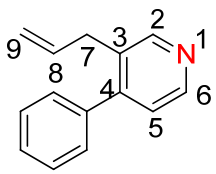
83% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (3H, s), 7.14 (1H, d, *J* = 5.0 Hz), 7.31 (2H, d, *J* = 6.8 Hz), 7.38-7.47 (3H, m), 8.46 (1H, d, *J* = 5.0 Hz, C_5**H**), 8.50 (1H, s, C_1**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 124.0, 127.9, 128.4, 128.5, 130.6, 139.1, 147.4, 149.1, 151.3.

3-Methyl-4-(3,5-dimethylphenyl)pyridine (2.37f):



74% yield; Pale yellow oil; IR (KBr) 3443, 2927, 2214, 1592, 1411, 1063, 906, 832 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (3H, s, 7-**H**), 2.36 (6H, s, 12-**H**), 6.92 (2H, s, 9-**H**), 7.03 (1H, s, 11-**H**), 7.11 (1H, d, *J* = 5.0 Hz, 5-**H**), 8.43 (1H, d, *J* = 5.0 Hz, 6-**H**), 8.47 (1H, s, 2-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2 (7-**C**), 21.3(11-**C**), 124.0, 126.3, 129.5, 130.6, 137.9, 139.0, 147.2, 149.4 (6-**C**), 151.2 (2-**C**). HRMS (ESI): Found: *m/z* 198.1274, Calcd for $C_{14}H_{16}N$ $[M+H]^+$: 198.1274.

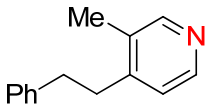
3-Allyl-4-phenylpyridine (2.37g):



80% yield; Pale yellow oil; IR (KBr) 3436, 2927, 2106, 1592, 1409, 911, 744, 665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36 (2H, d, *J* = 6.1 Hz, 7-**H**), 4.87 (1H, dd, *J* = 1.3, 17.1 Hz, 9-**H**), 5.03 (1H, dd, *J* = 1.3, 10.2 Hz, 9-**H**), 5.82 (1H, m, 8-**H**), 7.15 (1H, d, *J* = 4.9 Hz,

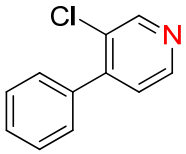
5-**H**), 7.30-7.45 (5H, m, Ar-**H**), 8.48 (1H, d, *J* = 4.9 Hz, 6-**H**), 8.51 (1H, s, 2-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.6 (7-**C**), 116.5, 124.3, 128.0, 128.3, 128.5, 132.4, 136.6, 138.7, 147.5, 149.3 (6-**C**), 151.3 (2-**C**). HRMS (ESI): Found: *m/z* 196.1126, Calcd for $C_{14}H_{14}N$ $[M+H]^+$: 196.1126.

3-Mehyl-4-phenethylpyridine (2.37h):[112]



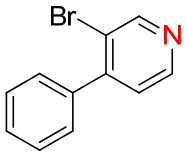
65% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (3H, s), 2.88 (4H, s, overlaped), 7.01 (1H, d, *J* = 5.0 Hz), 7.14 (2H, d, *J* = 7.0 Hz), 7.19-7.30 (3H, m), 8.32 (1H, d, *J* = 5.0 Hz), 8.34 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9, 34.4, 35.5, 123.4, 126.2, 128.3, 128.5, 131.6, 140.9, 147.5, 148.6, 150.6.

3-Chloro-4-phenylpyridine (2.37i):[111]



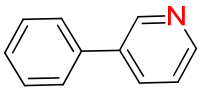
90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (1H, d, *J* = 4.9 Hz), 7.45-7.48 (5H, m), 8.51 (1H, d, *J* = 4.9 Hz), 8.67 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 125.3, 128.4, 128.9 (overlap), 130.2, 136.5, 147.6, 147.8, 150.1.

3-Bromo-4-phenylpyridine (2.37j):[113]



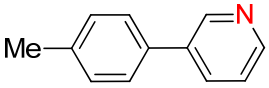
72% yield using $Pd(OAc)_2$ (10 mol %) and 2,2'-bipyridine (10 mol %); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, d, *J* = 4.9 Hz), 7.42-7.48 (5H, m), 8.54 (1H, d, *J* = 4.9 Hz), 8.82 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.9, 125.6, 128.3, 128.8 (overlap), 138.1, 148.3, 149.7, 152.1.

3-Phenylpyridine (2.37k) [114]



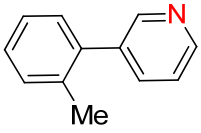
83% yield using 20 mol% of $PdCl_2$(dppf); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.42 (2H, m), 7.46-7.50 (2H, m), 7.57 (2H, d, *J* = 7.7 Hz), 7.86 (1H, d, *J* = 7.8 Hz), 8.58 (1H, d, *J* = 4.3 Hz), 8.85 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.5, 127.1, 128.1, 129.0, 134.3, 136.6, 137.8, 148.3, 138.4.

3-*p*-Tolylpyridine (2.37l):[114,115]



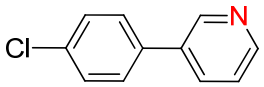
64% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 2.41 (3H, s), 7.27 (2H, d, *J* = 7.9 Hz), 7.33 (1H, dd, *J* = 4.7, 7.9 Hz), 7.47 (2H, d, *J* = 7.9 Hz), 7.84 (1H, d, *J* = 7.9 Hz), 8.55 (1H, d, *J* = 4.7 Hz), 8.83 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 123.5, 126.9, 129.8, 134.1, 134.9, 136.6, 138.0, 148.21, 148.22.

3-*o*-Tolylpyridine (2.37m):[115]



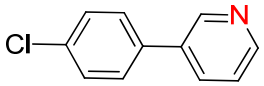
66% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (3H, s), 7.20 (1H, d, *J* = 7.9 Hz), 7.25-7.31 (3H, m), 7.33 (1H, dd, *J* = 4.8, 7.9 Hz), 7.63-7.66 (1H, m), 8.58-8.60 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 123.0, 126.0, 128.1, 129.8, 130.5, 135.6, 136.4, 137.4, 138.1, 148.1, 149.9.

3-(4-Chlorophenyl)pyridine (2.37n):[116]



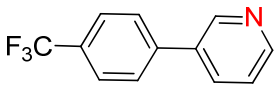
84% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (1H, dd, *J* = 4.6, 7.9 Hz), 7.44 (2H, d, *J* = 8.4 Hz), 7.50 (2H, d, *J* = 8.4 Hz), 7.82 (1H, d, *J* = 7.9 Hz), 8.59 (1H, d, *J* = 4.6 Hz), 8.81 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.6, 128.4, 129.3, 134.2, 134.4, 135.5, 136.2, 148.1, 148.8.

3-(4-Fluorophenyl)pyridine (2.37o):[117]



86% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13-7.19 (2H, m), 7.33 (1H, dd, *J* = 4.8, 7.9 Hz), 7.50-7.55 (2H, m), 7.80-7.83 (1H, m), 8.57 (1H, dd, *J* = 1.3, 4.8 Hz), 8.79 (1H, d, *J* = 2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 115.9 (d, *J* = 21.4 Hz), 123.5, 128.7 (d, *J* = 8.1 Hz), 133.9 (d, *J* = 3.4 Hz), 134.2, 135.7, 148.1, 148.5, 161.6 (d, *J* = 246.3 Hz).

3-(4-Trifluoromethylphenyl)pyridine (2.37p):[114]

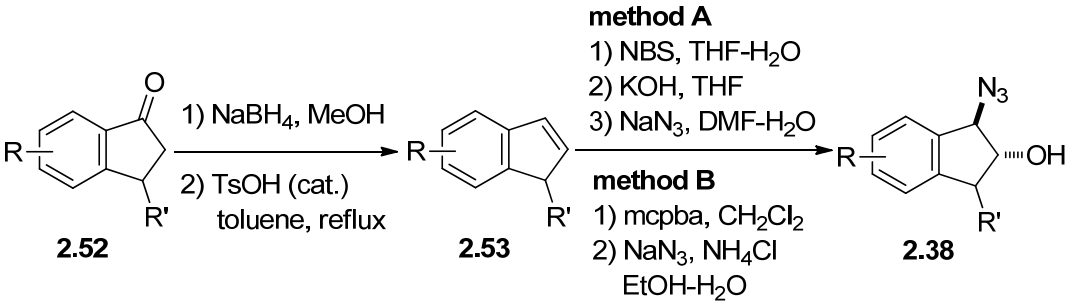


93% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (1H, dd, *J* = 4.3, 7.8 Hz), 7.67 (2H, d, *J* = 8.2 Hz), 7.72 (2H, d, *J* = 8.2 Hz), 7.87 (1H, d, *J* = 7.8 Hz), 8.64 (1H, d, *J* = 4.3 Hz), 8.86 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.7, 124.1 (q, *J* = 270.6 Hz), 126.0 (q, *J* = 3.8 Hz), 127.5, 130.2 (q, *J* = 32.4 Hz), 134.5, 135.3, 141.4, 1148.3, 149.3.

4.5 Synthesis of α-azidoalcohol 2.38 and 2.38'

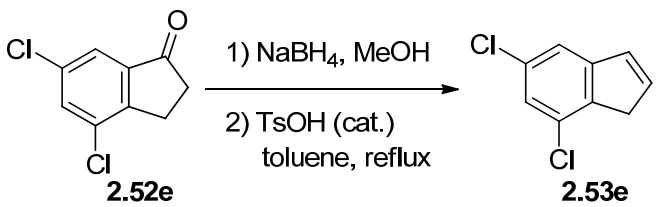
4.5.1 Synthesis of 1-azido-2-indanols 2.38

1-Azido-2-indanols **2.38** were prepared from the corresponding indenes by following **Methods A** or **B** as shown below.



4.5.1.1 Synthesis of Indenes 2.53

A typical procedure: synthesis of 4,6-Dichloroindene **(2.53e):**



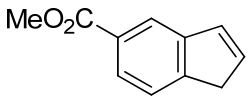
$NaBH_4$ (228 mg, 6.03 mmol) was added in small portions to a solution of 4,6-dichloro-1-

indanone **(2.52e)** (1.01 g, 5.02 mmol) in MeOH (15 ml) at 0 °C, and the reaction mixture was stirred at room temperature. After the reaction was completed, the reaction was quenched with water, and organic materials were extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were washed with water, brine, and dried over $MgSO_4$. The solvents were evaporated off to yield the 4,6-dichloroindan-1-ol, which was used for the next reaction without further pirification.

A solution of 4,6-dichloroindan-1-ol obained above and *p*-toluenesulfonic acid (43.0 mg, 0.25 mmol, 5 mol %) in toluene (20 mL) was stirred at 110 °C. After the reaction was completed, the mixture was diluted with Et_2O (50 mL) and washed with saturated aquoeus Na_2CO_3. The organic solvents wre dried over $MgSO_4$ and then removed in vacuo, providing the crude residue which was purified by flash column chromatography with EtOAc/Hexane (1 : 20) to give the pure 4,6-dichloroindene (**2.53e**) (880 mg, 4.76 mmol) in 95% yield for 2 steps.

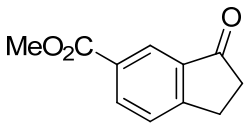
White solid, mp 36-37 °C; IR (KBr) 3072, 1600, 1575, 1544, 1433, 1386, 1154; 1H NMR (500 MHz, $CDCl_3$) δ 3.40 (2H, d, J = 1.4 Hz), 6.66-6.67 (1H, m), 6.80-6.82 (1H, m), 7.18 (1H, s), 7.28 (1H, s), ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.5, 119.8, 124.5, 130.1, 131.2, 130.1, 136.5, 139.8, 147.4; HRMS (ESI): Found: *m/z* 184.9933, Calcd for C_9H_7Cl $[M+H]^+$: 184.9925.

Methyl indene-5-carboxylate (2.53a):



97% yield from 6-methoxycarbonyl-1-indanone (**2.52a**);[118] White solid; mp 70-72 °C; IR (KBr) 3074, 2906, 1714 (C=O), 1294, 1097; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (2H, s, C**H**$_2$), 3.92 (3H, s, C**H**$_3$), 6.62 (1H, d, *J* = 1.4 Hz, 2-**H**), 6.91 (1H, s, 3-**H**), 7.50 (1H, d, *J* = 7.3 Hz, 7-**H**), 7.90 (1H, d, *J* = 7.3 Hz, 6-**H**), 8.06 (1H, s, 4-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.2 (**C**H_2), 52.0 (**C**H_3), 122.0, 123.5, 126.2, 128.5, 131.7, 135.1, 145.0, 148.8, 167.6 (**C**=O); HRMS (ESI): Found: *m/z* 175.0764, Calcd for $C_{11}H_{11}O_2$ $[M+H]^+$: 175.0759.

6-Methoxycarbonyl-1-indanone (2.52a):



White solid: mp 112-114 °C; IR (KBr) 3074, 2987, 1714 (CO_2Me), 1294, 1097; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72-2.75 (2H, m, 3-**H**), 3.17-3.20 (2H, m, 2-**H**), 3.92 (3H, s, C**H**$_3$), 7.53 (1H, d, *J* = 8.0 Hz, 4-**H**), 8.23 (1H, d, *J* = 8.0 Hz, 5-**H**), 8.39 (1H, s, 7-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0 (3-**C**), 36.4 (2-**C**), 52.3 (**C**H_3), 125.2, 126.8, 129.7, 135.3, 137.3, 159.4, 166.2 (**C**O_2Me), 205.9 (C=O); HRMS (ESI): Found: *m/z* 191.0706. Calcd for $C_{11}H_{11}O_3$ $[M+H]^+$: 191.0708.

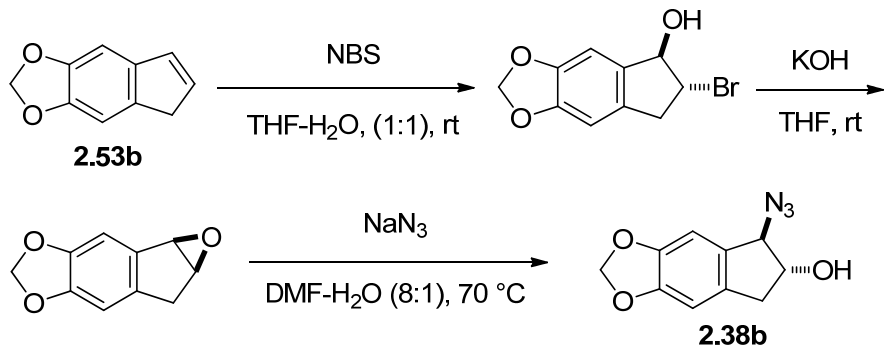
5,6-Methylenedioxy-1*H*-indene (**2.53b**)[119] and 1-Phenyl-indene (**2.53f**)[120] were kwnon compounds and prepared by this procedure from the corresponding indanones. 2-Phenyl-indene (**2.53g**) is prepared from 1*H*-indene and bromobenene by following the reporeted procedure.[121]

4.5.1.2 Synthesis of 1-azido-2-indanols 2.38

Method A[122]

A typical procedure:

synthesis of (1*R**,2*R**)-1-Azido-5,6-methylenedioxy-2-indanol (**2.38b**):



To a stirred solution of 5,6-methylenedioxy-1*H*-indene (**2.53b**) (806 mg, 5.0 mmol) in 50% aqueous THF (20 mL) was added *N*-bromosuccinimide (980 mg, 5.5 mmol) portionwise at room temperature, and the mixture was stirred at the same temperature for 12 h. The reaction was quenched by adding water and the organic materials were extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with 5% aqueous NaS_2O_3 (20 mL), brine, and dried over $MgSO_4$. The solvents were evaporated under reduced pressure, and the resulting crude product was purified by flash column chromatography with EtOAc/Hexane (1 : 3) to give (1*R**,2*R**)-2-bromo-5,6-methylenedioxy-1-indanol (838 mg, 3.3 mmol, 65% yield).

To a stirred solution of 2-bromo-1-indanol prepared above (838 g, 3.3 mmol) in THF was added powdered KOH (458 mg, 8.2 mmol) at room temperature and the mixture was stirred for 4 h. The insoluble solids were removed by filtration and the filtrate was

evaporated under reduced pressure to yield the crude epoxide, which was directly used to the next step without further purification.

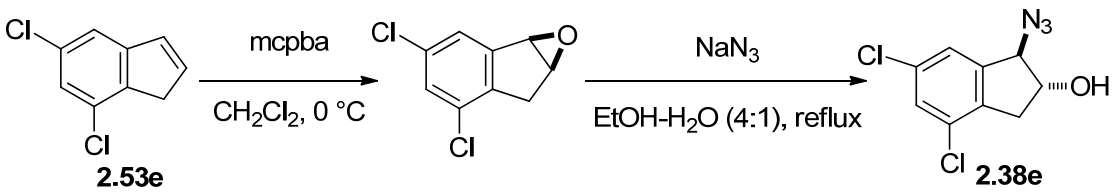
A mixture of crude epoxide obtained above, and NaN_3 (1.06 g, 16.3 mmol) in DMF-H_2O (8 : 1) (18 mL) was stirred at 70 °C for 2 h. The reaction was quenched with water (50 mL), and the organic materials were extracted with CH_2Cl_2 (3 x 30 mL). The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the crude product was purified by flash column chromatography with EtOAc/Hexane (1 : 4) to give (1*R**,2*R**)-1-Azido-5,6-methylenedioxy-indan-2-ol **(2.38b)** (476 mg, 2.2 mmol) in 67% yield on 2 steps (44% yiled on 3 steps from indene **2.52b**).

White solid; mp 77-79 °C; IR (KBr) 3423 (OH), 3018, 2895, 2098 (N_3), 1303, 1247, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.10 (1H, brs, O**H**), 2.73 (1H, dd, *J* = 5.2, 15.8 Hz, C**H**$_2$), 3.20 (1H, dd, *J* = 6.6, 15.8 Hz, C**H**$_2$), 4.47-4.50 (1H, m, C**H**N_3), 4.56 (1H, d, *J* = 4.3 Hz, C**H**OH), 5.96 (2H, s, OC**H**$_2$O), 6.69 (1H, s, 4-**H**), 6.81 (1H, s, 7-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.0 (3-**C**), 72.0 (**C**HN_3), 78.9 (**C**HOH), 101.3 (O**C**H_2O), 105.2, 105.7, 130.4, 133.2, 147.3, 148.7; HRMS (ESI): Found: *m/z* 220.0714, Calcd for $C_{10}H_{10}N_3O_3$ $[M+H]^+$: 220.0722.

Method B (**2.41a**, **2.41e-g** were pepared by this procedure)

A typical procedure:

synthesis of (1*R,2*R**)-1-azido-2,3-dihydro-4,6-dichloro-1*H*-inden-2-ol (2.38e):**



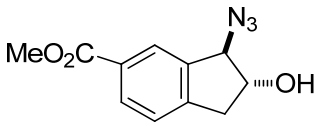
3-Chloroperoxybenzoic acid (m-CPBA) (1.27 g, 7.3 mmol) was added in small portions to a solution of 4,6-dichloro-1*H*-indene (**2.53e**) (680 mg, 3.7 mmol) in CH_2Cl_2 (20 mL) at 0 °C and the reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (30 mL), the organic materials were extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were washed with saturated aqueous Na_2CO_3 and dried over $MgSO_4$. The solvent was removed in vacuo and resulting crude epoxide was used for the next reaction without further pirification.

The crude mixture obtained above, NH_4Cl (390 mg, 7.3 mmol) and NaN_3 (585 mg, 9.0 mmol) in aqueous EtOH (20 mL, EtOH/H_2O = 4 : 1) was refluxed for 1 h. Water (40 mL) was then added to the mixture and the organic materials were extracted with CH_2Cl_2 (3 x 30 mL). The combined extracts were washed with brine and dried over $MgSO_4$. The organic solvents were evaporated under reduced pressure and the resulting crude mixtue was purified by flash column chromatography with EtOAc/Hexane (1 : 6) to give the (1*R**,2*R**)-1-azido-2,3-dihydro-4,6-dichloro- 1*H*-inden-2-ol **(2.38e)** (736 mg, 3.0 mmol) in 82% yield for 2 steps.

White solid; mp 48-50 °C; IR (KBr) 3358 (OH), 3080, 2914, 2100 (N_3), 1570, 1454, 1083, 1056; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 (1H, brs, O**H**), 2.80 (1H, dd, *J* = 6.1, 16.6 Hz, C**H**$_2$), 3.30 (1H, dd, *J* = 7.0, 16.6 Hz, C**H**$_2$), 4.50-4.55 (1H, m, C**H**N_3), 4.72 (1H, d, *J* = 5.2 Hz, C**H**OH), 7.24 (1H, s, 7-**H**), 7.32 (1H, s, 5-**H**) ; ^{13}C NMR (125 MHz, $CDCl_3$)

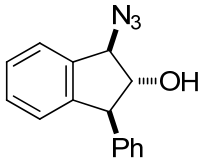
δ 37.6, 71.8 (**C**CHN_3), 78.2 (**C**HOH), 123.4, 129.1, 131.9, 134.0, 136.5, 141.2; HRMS (ESI): Found: *m/z* 244.0042, Calcd for $C_9H_8N_3OCl_2$ $[M+H]^+$: 244.0044.

(1*R,2*R**)-1-Azido-2,3-dihydro-6-methoxycarbonyl-1*H*-inden-2-ol (2.38a):**



79% yield from methyl 1*H*-indene-5-carboxylate (**2.53a**); White solid; mp 77-79 °C; IR (KBr) 3423 (OH), 3014, 2912, 2100 (N_3), 1705 (CO_2Me), 1438, 1298, 1089, 1058 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.26 (1H, brs, O**H**), 2.89 (1H, dd, *J* = 6.0, 16.6 Hz, C$\mathbf{H}_2$), 3.31 (1H, dd, *J* = 6.7, 16.6 Hz C$\mathbf{H}_2$), 3.92 (3H, s, C$\mathbf{H}_3$), 4.52-4.54 (1H, m, C**H**N_3), 4.72 (1H, d, *J* = 5.0 Hz, C**H**OH), 7.30 (1H, d, *J* = 7.8 Hz, 4-**H**), 7.99 (1H, d, *J* = 7.8 Hz, 5-**H**), 8.01 (1H, s, 7-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.0 (**C**H_2), 52.2 (**C**H_3), 71.4 (**C**CHN_3), 78.8 (**C**HOH), 124.9, 125.3, 129.6, 130.7, 138.6, 145.2, 166.7 (**C**=0); HRMS (ESI): Found: *m/z* 234.0881, Calcd for $C_{11}H_{12}N_3O_3$ $[M+H]^+$: 234.0879.

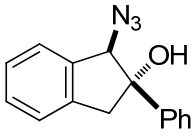
(1*R,2*R**,3*S**)-1-Azido-2,3-dihydro-3-phenyl-1*H*-inden-2-ol (2.38f):**



White solid (88% yield from 1-pheny-1*H*-indene (**2.53f**), mp 70-72 °C; IR (KBr) 3390 (OH), 3018, 2895, 2102 (N_3), 1087, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.37 (1H, brs, OH), 4.12 (1H, d, *J* = 8.5 Hz, 3-**H**), 4.31-4.36 (1H, m, C**H**N_3), 4.82 (1H, d, *J* = 7.5 Hz, C**H**OH), 6.90 (1H, d, *J* = 7.5 Hz, Ar-**H**), 7.28-7.43 (8H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.1, 69.7 (**C**CHN_3), 87.8 (**C**HOH), 123.8, 125.2, 127.5, 127.9, 128.7,

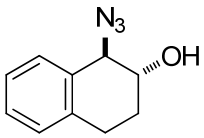
128.9, 129.0, 137.7, 140.3, 141.4; HRMS (ESI): Found: *m/z* 252.1133, Calcd for $C_{15}H_{14}N_3O$ $[M+H]^+$: 252.1137.

(1*R,2*S**)-1-Azido-2,3-dihydro-2-phenyl-1*H*-inden-2-ol (2.38g):**



83% yield from 2-Phenyl-indene (**2.53g**), White solod; mp 63-65 °C; IR (KBr) 3018, 2400, 2101 (N_3), 1604, 1478, 1320, 1156 1060, 877 cm-1; 1H NMR (400 MHz, CDCl3) δ 2.25 (1H, s, O**H**), 3.20 (1H, d, *J* = 16.2 Hz, C$\mathbf{H}_2$), 3.83 (1H, d, *J* = 16.2 Hz, C$\mathbf{H}_2$), 4.87 (1H, s, C$\mathbf{H}N_3$), 7.31-7.44 (7H, m, Ar-**H**), 7.56 (2H, d, *J* = 7.5 Hz, Ar-**H**); 13C NMR (100 MHz, CDCl3) δ 44.2 (**C**H_2), 74.0 (**C**HN_3), 85.4 (**C**HOH), 125.6, 125.7, 126.5, 127.5, 128.3, 128.4, 129.5, 138.6, 140.9, 141.1; HRMS (ESI): Found: *m/z* 252.1132, Calcd for C15H14N3O [M+H]+: 252.1137.

(1*R,2*R**)-1-azido-1,2,3,4-tetrahydronaphthalen-2-ol (2.38i)**[123]

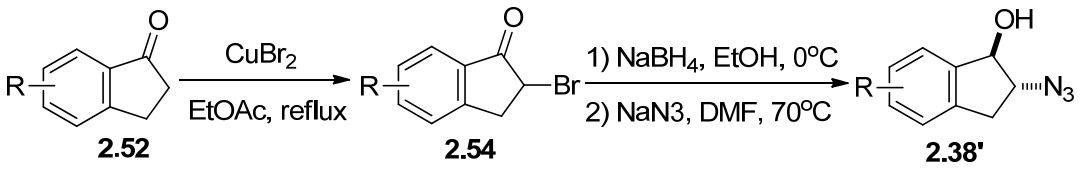


Pale yellow oil; ^{1}H NMR (400 MHz, CDCl3) δ 1.87-1.97 (1H, m), 2.13-2.21 (2H, m), 2.85-2.98 (2H, m), 3.99-4.05 (1H, m), 4.40 (1H, d, *J* = 7.2 Hz), 7.12-7.15 (1H, m), 7.22-7.27 (2H, m), 7.40-7.42 (1H, m); ^{13}C NMR (100 MHz, CDCl3) δ 26.5, 28.5, 66.6, 71.7, 126.5, 128.1, 128.6, 128.8, 132.4, 136.1.

4.5.2 Synthesis of 2-azido-1-indanols 2.38'

4.5.2.1 Synthesis of 2.38b'-d' and 2.38h'

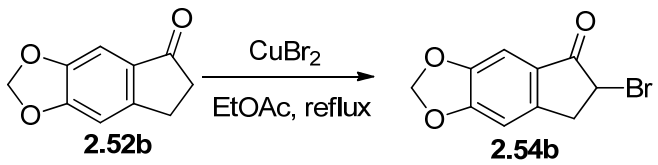
These azides were prepared from the corresponding indanone **2.52** as shown below.



2.52 **2.54** **2.38'**

4.5.2.1.1 α-Bromination:[72]

A typical procedure: preparation of 2-Bromo-5,6-methylenedioxy-1-indanone **(2.54b):**[124]

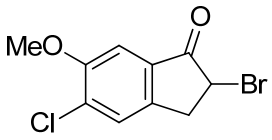


2.52b **2.54b**

To a solution of 5,6-methylenedioxy-1-indanone [CAS: 6412-87-9] (**2.52b**) (438 mg, 2.5 mmol) in EtOAc (30 mL) was added $CuBr_2$ (1.12 g, 5.01 mmol), and the mixture was stirred at reflux for 6 h. The insoluble materials were filteted off through a celite pad. The filtrate was evaporated under reduced pressure, and the resulting crude mixture was purified by flash column chromatography with EtOAc/Hexane (1 : 8) to give 2-bromo-5,6-methylenedioxy-1-indanone **(2.54b)** (524 mg, 2.1 mmol) in 83% yield.

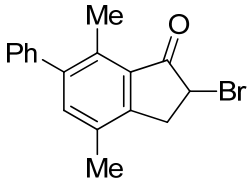
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.27 (1H, dd, *J* = 3.2, 18.0 Hz), 3.68 (1H, dd, *J* = 7.3, 18.0 Hz), 4.61 (1H, dd, *J* = 3.2, 7.3 Hz), 6.09 (2H, s), 6.79 (1H, s), 7.15 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.9, 44.4, 102.5, 103.2, 105.4, 128.1, 148.8, 148.9, 155.3, 197.4;

2-Bromo-5-chloro-2,3-dihydro-6-methoxyinden-1-one (2.54c):



88% yield from 5-chloro-6-methoxy-1-indanone (**2.52c**) (CAS: 344305-70-0); White solid; mp 141-143 °C; IR (KBr) 3018, 2941, 1714 (C=O), 1608, 1106, 1033 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.30 (1H, dd, *J* = 2.8, 17.9 Hz, C**H**$_2$), 3.73 (1H, dd, *J* = 7.4, 17.9 Hz, C**H**$_2$), 3.94 (3H, s, C**H**$_3$), 4.64 (1H, dd, *J* = 2.8, 7.4 Hz, C**H**Br), 7.29 (1H, s, 7-**H**), 7.47 (1H, s, 4-**H**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.1(**C**H_2), 44.0 (**C**HBr), 56.5 (**C**H_3), 106.0, 127.9, 132.3, 132.9, 143.8, 155.6, 198.6 (**C**=O); HRMS (ESI): Found: *m/z* 274.9467, Calcd for $C_{10}H_9BrClO_2$ $[M+H]^+$: 274.9474.

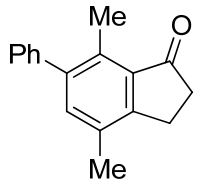
2-Bromo-2,3-dihydro-4,7-dimethyl-6-phenylinden-1-one (2.54d):



83% yield from 4,7-dimethyl-6phenyl-1-indanone **(2.52d)**, which was prepared from 4,7-dimethyl-6-bromo-1-indanone[125] and phenylbronic acid by Suzuki coupling;[126] White solid; mp 102-104 °C; IR (KBr) 3020, 2920, 1714 (C=O), 1600, 1578, 1473, 1165, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (3H, s, C**H**$_3$), 2.52 (3H, s, C**H**$_3$), 3.30 (1H, dd, *J*

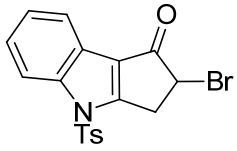
= 2.9**,** 17.9 Hz, C**H**$_2$), 3.23 (1H, dd, *J* = 7.6, 17.9 Hz, C**H**$_2$), 4.64 (1H, dd, *J* = 2.9, 7.6 Hz, C**H**Br), 7.26-7.27 (2H, m, Ar-**H**), 7.33 (1H, s, 5-**H**), 7.36 (1H, d, *J* = 7.2 Hz, Ar-**H**), 7.41-7.44 (2H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2 (**C**H$_3$), 17.3 (**C**H$_3$), 36.0 (**C**H$_2$), 45.2 (**C**HBr), 127.2, 128.2, 129.3, 131.2, 132.2, 134.7, 137.7, 140.2, 142.8, 149.8, 200.7 (**C**=O); HRMS (ESI): Found: *m/z* 315.0385, Calcd for $C_{17}H_{16}BrO$ $[M+H]^+$: 315.0385.

4,7-Dimethyl-6phenyl-1-indanone (2.52d):



Pale yellow solid; mp 75-76 °C; IR (KBr) 3020, 2918, 1703 (C=O), 1473, 1315, 1011; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (3H, s, C**H**$_3$), 2.53 (3H, s, C**H**$_3$), 2.71-2.74 (2H, m, 3-**H**), 2.97-3.00 (2H, m, 2-**H**), 7.27-7.29 (3H, m, Ar-**H**), 7.33-7.37 (1H, m, 5-**H**), 7.40-7.44 (2H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0 (**C**H$_3$), 17.4 (**C**H$_3$), 23.8 (3-**C**), 37.1 (2-**C**), 127.0, 128.1, 129.4, 132.4, 133.3, 134.5, 136.3, 140.7, 141.8, 154.2, 208.5 (**C**=O); HRMS (ESI): Found: *m/z* 237.1276, Calcd for $C_{17}H_{17}O$ $[M+H]^+$: 237.1279.

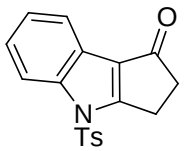
2-Bromo-2,3-dihydro-4-tosylcyclopenta[*b*]indol-1(4*H*)-one (2.54h):



81% yield from 2,3-dihydro-4-tosylcyclopenta[*b*]indol-1(4H)-one **(2.52h)** (shown below), which was prepared by tosylation of 2,3-dihydrocyclopenta[*b*]indol-1(4*H*)-one;[127] White

solid; mp 167-169 °C; IR (KBr) 3018, 2400, 1708 (C=O), 1597, 1556, 1413, 1179, 1053 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.40 (3H, s, C**H**$_3$), 3.67 (1H, dd, *J* = 2.1, 19.5 Hz,), 4.14 (1H, dd, *J* = 6.6, 19.5 Hz, C**H**$_2$), 4.84 (1H, dd, *J* = 2.1, 6.6 Hz, C**H**Br), 7.32-7.42 (4H, m, Ar-**H**), 7.83-7.87 (3H, m, Ar-**H**), 7.98 (1H, d, *J* = 8.2 Hz, Ar-**H**) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7 (**C**H_3), 36.4 (**C**H_2), 47.2 (**C**HBr), 114.1, 121.4, 122.2, 125.2, 126.2, 127.0, 130.5, 134.4, 140.4, 146.5, 162.6, 189.2 (**C**=O); HRMS (ESI): Found: *m/z* 403.9946, Calcd for $C_{18}H_{15}BrO_3NS$ $[M+H]^+$: 403.9956.

2,3-Dihydro-4-tosylcyclopenta[*b*]indol-1(4*H*)-one (2.52h):

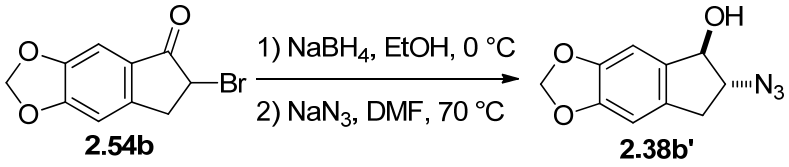


White solid; mp 179-181 °C; IR (KBr) 3018, 2403, 1702 (C=O), 1599, 1404, 1376, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (3H, s, C**H**$_3$), 2.96-2.99 (2H, m,3-**H**), 3.39-3.41 (2H, m, 2-**H**), 7.29-7.38 (4H, m, Ar-**H**), 7.81-7.83 (3H, m, Ar-**H**), 7.98 (1H, d, *J* = 8.3 Hz, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (**C**H_3), 24.0 (3-**C**), 40.4 (2-**C**), 114.0, 121.1, 122.3, 124.8, 125.61, 125.64, 126.9, 130.3, 134.9, 140.5, 146.1, 166.6, 196.1 (**C**=O); HRMS (ESI): Found: *m/z* 326.0848, Calcd for $C_{18}H_{16}O_3NS$ $[M+H]^+$: 326.0851.

4.5.2.1.2 Synthesis of 2-azido-1-indanos 2.38'

A typical procedure:

preparation of (1*R**,2*R**)-2-azido-5,6-methylenedioxy-indan-1-ol **(2.38b'):**



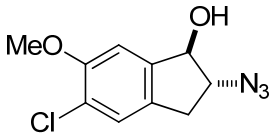
2.54b **2.38b'**

$NaBH_4$ (91 mg, 2.4 mmol) was added in small portions to a solution of 2-bromo-5,6-methylenedioxy-1-indanone (**2.54b**) (510 mg, 2.0 mmol) in MeOH (15 mL) at 0 °C, and the mixture was stirred for 2 h. The reaction was quenched with water (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined extracts were washed with water, brine and dried over $MgSO_4$. The solvents were removed in vacuo, and the resulting crude mixture including (1*R**,2*S**)-2-bromo-2,3-dihydro-5,6-methylenedioxy-1*H*-inden-1-ol which can be used in the next reaction without further purification.

To a stirred solution of (1*R**,2*S**)-2-bromo-2,3-dihydro-5,6-methylenedioxy-1*H*-inden-1-ol obtained above in anhydrous DMF (10 mL) was added NaN_3 (650 mg, 10.0 mmol) at room temperature, and the mixture was stirred at 70 °C for 2 h. The reaction was then quenched with water (30 mL), and the organic materials were extraced with CH_2Cl_2 (3 x 30 mL). The combined extracts were washed with brine, dried over $MgSO_4$. The volatile materials were removed in vacuo, and the resulting crude mixture was purified by flash column chromatography with EtOAc/Hexane (1 : 7) to give the pure (1*R**,2*R**)-2-azido-2,3-dihydro-5,6-methylenedioxy -1*H*-inden-1-ol (**2.38b'**) (227 mg, 1.0 mmol) 52% yield. White solid; mp 121-123 °C; IR (KBr) 3412 (OH), 3007, 2916, 2096 (N_3), 1608, 1504, 1309, 1093, 1053 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.22 (1H, brs, O**H**), 2.72 (1H, dd, *J* = 7.1, 15.6 Hz, 3-**H**), 3.18 (1H, dd, *J* = 7.5, 15.6 Hz, 3-**H**), 4.00-4.05 (1H, m, C**H**N_3),

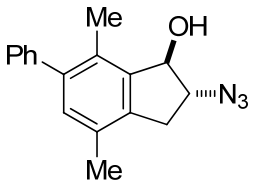
4.97-4.99 (1H, m, C**H**OH), 5.94 (2H, d, *J* = 2.9 Hz, OC**H**$_2$O), 6.65 (1H, s, 4-**H**), 6.81 (1H, s, 7-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.1 (**C**H$_2$), 70.1 (**C**HN$_3$), 80.2 (**C**HOH), 101.2 (O**C**H$_2$O), 104.6, 105.2, 131.8, 134.4, 147.5, 148.6; HRMS (ESI): Found: *m/z* 220.0715, Calcd for $C_{10}H_{10}N_3O_3$ $[M+H]^+$: 220.0722.

(1*R,2*R**)-2-Azido-2,3-dihydro-5-chloro-6-methoxy-1*H*-inden-1-ol (2.38c'):**



65% yield from **2.54c**; White solid; mp 127-128 °C; IR (KBr) 3419 (OH), 3018, 2924, 2102 (N$_3$), 1643, 1303, 1092, 1051 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (1H, d, *J* = 6.0 Hz, O**H**), 2.76 (1H, dd, *J* = 7.7, 15.4 Hz, C**H**$_2$), 3.20 (1H, dd, *J* = 7.6, 15.4 Hz, C**H**$_2$), 3.90 (3H, s, C**H**$_3$), 4.02 (1H, ddd, *J* = 6.4, 7.7, 7.6 Hz, C**H**N$_3$), 5.03 (1H, dd, *J* = 6.4 Hz, 6.0 Hz, C**H**OH), 6.94 (1H, s, 7-**H**), 7.21 (1H, s, 4-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.3 (**C**H$_2$), 56.3 (**C**H$_3$), 70.2 (**C**HN$_3$), 80.3 (**C**HOH), 107.6, 123.2, 126.5, 130.7, 141.1, 154.9; HRMS (ESI): Found: *m/z* 262.0351, Calcd for $C_{10}H_{10}N_3O_2ClNa$ $[M+Na]^+$: 262.0359.

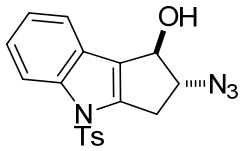
(1*R,2*R**)-2-Azido-2,3-dihydro-4,7-dimethyl-6-phenyl-1*H*-inden-1-ol (2.38d'):**



63% yield from **2.54d**; Pale yellow solid; mp 98-100 °C; IR (KBr) 3412 (OH), 3018, 2920, 2104 (N$_3$), 1473, 1504, 1079, 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (1H,

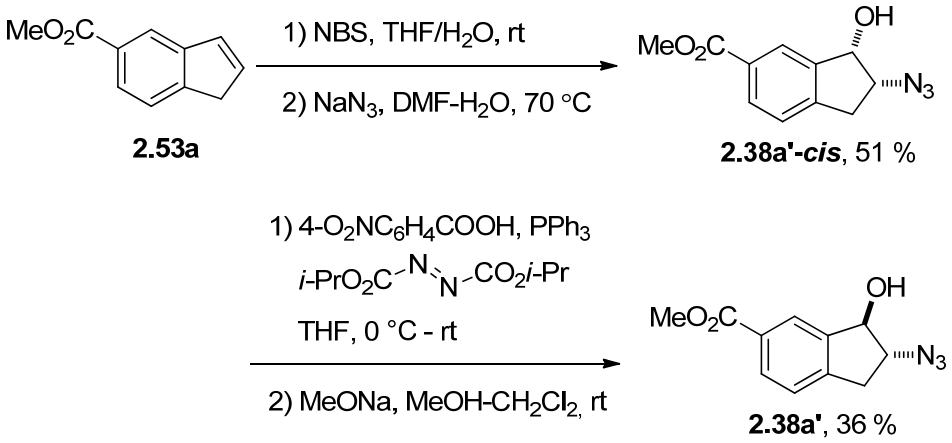
brs, O**H**), 2.27 (3H, s, C**H**$_3$), 2.29 (3H, s, C**H**$_3$), 2.82 (1H, dd, *J* = 3.4, 16.7 Hz, C**H**$_2$), 3.36 (1H, dd, *J* = 6.7, 16.7 Hz, C**H**$_2$), 4.21-4.24 (1H, m, C**H**N$_3$), 5.19-5.21 (1H, m, C**H**OH), 7.06 (1H, s, 5-**H**), 7.28-7.43 (5H, m, Ar-**H**): ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9 (**C**H$_3$), 18.4 (**C**H$_3$), 34.5 (**C**H$_2$), 68.6 (**C**HN$_3$), 80.5 (**C**HOH), 126.8, 128.1, 129.3, 130.3, 131.5, 132.3, 138.2, 140.1, 141.5, 142.1; HRMS (ESI): Found: *m/z* 280.1443, Calcd for $C_{17}H_{18}N_3O$ $[M+H]^+$: 280.1450.

(1S*,2S*)-2-Azido-1,2,3,4-tetrahydro-4-tosylcyclopenta[*b*]indol-1-ol (2.38h'):



81% yield from **2.54h**; White solid; mp 156-158 °C; IR (KBr) 3421 (OH), 2976, 2094 (N$_3$), 1751, 1368, 1102, 1035, 940 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (1H, brd, *J* = 7.0 Hz, O**H**), 2.35 (3H, s, C**H**$_3$), 3.06 (1H, dd, *J* = 4.2, 17.5 Hz, C**H**$_2$), 3.71 (1H, dd, *J* = 7.4, 17.5 Hz, C**H**$_2$), 4.38-4.42 (1H, m, C**H**N$_3$), 5.18-5.20 (1H, m, C**H**OH), 7.23-7.31 (4H, m, Ar-**H**), 7.48 (1H, d, *J* = 7.5 Hz, Ar-**H**), 7.72 (2H, d, *J* = 8.1 Hz, Ar-**H**), 7.99 (1H, d, *J* = 8.2 Hz, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (**C**H$_3$), 33.3 (**C**H$_2$), 72.9 (**C**HN$_3$), 76.2 (**C**HOH), 114.3, 119.2, 123.9, 124.4, 125.3, 126.6, 130.1, 135.2, 139.7, 141.2, 145.3; HRMS (ESI): Found: *m/z* 369.1031, Calcd for $C_{18}H_{17}N4OS$ $[M+H]^+$: 369.1021.

4.5.2.2 Synthesis of 2.38a'

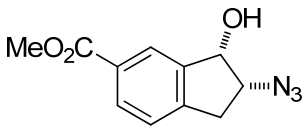


To a stirred solution of **2.38a'-*cis*** (which was prepared *via* hydroxybromination and substitution in 51% yield on 2 steps) (645 mg, 2.77 mmol) and 4-nitrobenzoic acid (926 mg, 5.54 mmol) in THF (10 mL) was added dropwise a solution of PPh_3 (1.45 g, 5.54 mmol) in THF (10 mL) and a solution of diisopropyl azodicarboxylate (1.12 g, 5.54 mmol) in THF (10 mL) at 0 °C, and the mixture was stirred for 30 min at the same temperature, and then for 1 h at room temperature. The mixture was evaporated under reduced pressure to give the crude residue, which was purified by flash column chromatography with EtOAc/Hexane (1 : 8) to give 4-nitrobenzoate (385 mg, 1.01 mmol) in 37% yield.

To a stirred solution of NaOMe (136.4 mg, 2.53 mmol) in MeOH (20 mL) was added dropwise a solution of 4-nitrobenzoate (385 mg, 1.01 mmol) in CH_2Cl_2 (15 mL) at room temperature, and the mixture was stirred for 1 h at the same temperature. The volatile materials were evaporated under reduced pressure, and to the resulting residue was added brine. The organic compounds were extracted with CH_2Cl_2 (3 x 25 mL) and the combined extracts were dried over $MgSO_4$. After evaporation of the solvent, the residue was

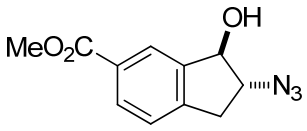
purified by flash column chromatography with EtOAc/Hexane (1 : 6) to give the pure (1*R**,2*R**)-2-azido-2,3-dihydro-6-methoxycarbonyl-1*H*-inden-1-ol (**2.38a'**) (232 mg, 0.98 mmol) in 36% yield on 2 steps.

(1*S,2*R**)-2-Azido-2,3-dihydro-6-methoxycarbonyl-1*H*-inden-1-ol (2.38a'-*cis*):**



White solid; mp 96-98 °C; IR (KBr) 3429 (OH), 3018, 2953, 2110 (N_3), 1716 (CO_2Me), 1620, 1099, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.59 (1H, d, *J* = 8.3 Hz, O**H**), 3.15-3.17 (2H, m, C**H**$_2$), 3.90 (3H, s, C**H**$_3$), 4.34-4.38 (1H, m, C**H**N_3), 5.15 (1H, dd, *J* = 5.2, 8.3 Hz, C**H**OH), 7.30 (1H, d, *J* = 7.9 Hz, 4-**H**), 7.97 (1H, d, *J* = 7.9 Hz, 5-**H**), 8.09 (1H, s, 7-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.4 (**C**H_2), 52.1 (**C**H_3), 65.7 (**C**HN_3), 76.0 (**C**HOH), 125.0, 126.0, 129.7, 130.5, 142.3, 144.4, 166.8 (**C**O_2Me); HRMS (ESI): Found: *m/z* 234.0878, Calcd for $C_{11}H_{12}N_3O_3$ $[M+H]^+$: 234.0879.

(1*R,2*R**)-2-Azido-2,3-dihydro-6-methoxycarbonyl-1*H*-inden-1-ol (2.38a'):**

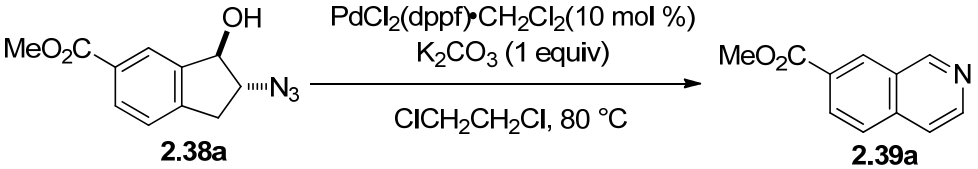


White solid; mp 84-86 °C; IR (KBr) 3423 (OH), 3018, 2953, 2104 (N_3), 1741, 1114, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.72 (1H, brs, O**H**), 2.84 (1H, dd, *J* = 7.9, 16.2 Hz, C**H**$_2$), 3.30 (1H, dd, *J* = 7.6, 16.2 Hz, C**H**$_2$), 3.90 (3H, s, C**H**$_3$), 4.08 (1H, ddd, *J* = 7.9, 6.3, 7.6 Hz, C**H**N_3), 5.10 (1H, d, *J* = 6.3 Hz, C**H**OH), 7.26 (1H, d, *J* = 7.9 Hz, 4-**H**), 7.96 (1H, d, *J* = 7.9 Hz, 5-**H**), 8.04 (1H, s, 7-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.3 (**C**H_2), 52.2

(**C**H_3), 69.8 (**C**HN_3), 79.8 (**C**HOH), 124.8, 125.4, 129.7, 130.4, 142.1, 143.8, 166.9 (**C**=O); HRMS (ESI): Found: *m/z* 234.0878, Calcd for $C_{11}H_{12}N_3O_3$ $[M+H]^+$: 234.0879.

4.6 Synthesis of isoquinolines and γ-carboline 2.39:

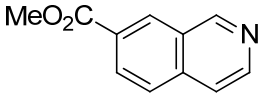
A typical procedure: synthesis of isoquinoline 2.39a from 2.38a:



2.38a **2.39a**

To a solution of azidoalcohol **2.38a** (70.1 mg, 0.301 mmol) in 2 mL $ClCH_2CH_2Cl$ were added $PdCl_2(dppf)\cdot CH_2Cl_2$ (24.6 mg, 0.030 mmol) and K_2CO_3 (41.7 mg, 0.30 mmol), and the reaction mixture was stirred for 40 min at 80 °C. The volatile materials were then removed in vacuo, and the residue was purified by flash column chromatography with EtOAc/Hexane (1 : 3) to give isoquinoline **2.39a** (45.8 mg, 0.244 mmol) in 81% yield.

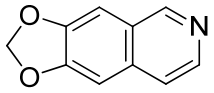
Methyl isoquinoline-7-carboxylate (2.39a):



96% yield from **2.39a'** using 10 mol % of $Pd(OAc)_2$-dppf at room temperature; Yellow solid, mp 99-101 °C; IR (KBr) 2976, 2399, 1702 (CO_2Me), 1631 (C=N), 1436, 1298, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.99 (3H, s, C**H**$_3$), 7.67 (1H, d, *J* = 5.7 Hz, 4-**H**), 7.85 (1H, d, *J* = 8.6 Hz, 5-**H**), 8.25 (1H, d, *J* = 8.6 Hz, 6-**H**), 8.60 (1H, d, *J* = 5.7 Hz,

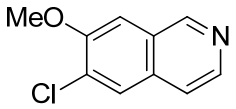
3-**H**), 8.71 (1H, s, 8-**H**), 9.34 (1H, s, 1-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.4, 120.3, 126.8, 127.8, 128.9, 129.7, 130.7, 137.8, 145.1 (3-**C**), 153.8 (1-**C**), 166.3 (**C**O_2Me); HRMS (ESI): Found: *m/z* 188.0716, Calcd for $C_{11}H_{10}NO_2$ $[M+H]^+$: 188.0716.

[1,3]Dioxolo[4,5-*g*]isoquinoline (2.39b):[128]



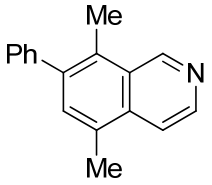
76% yield from **2.38b** and 92% yield from **2.38b'** using 10 mol % of $Pd(OAc)_2$-dppf at room temperature; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (2H, s), 7.05 (1H, s), 7.17 (1H, s), 7.45 (1H, d, *J* = 5.6 Hz), 8.34 (1H, d, *J* = 5.6 Hz), 8.97 (1H, s) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.5, 102.4. 103.1, 120.0, 126.0, 134.1, 142.3, 148.3, 150.3, 150.9.

6-Chloro-7-methoxyisoquinoline (2.39c):



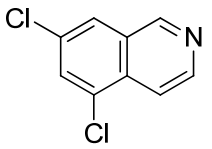
96% yield from **2.38c'** using 10 mol % of $Pd(OAc)_2$-dppf at room temperature; Pale yellow solid; mp 123-124 °C; IR (KBr) 3018, 2968, 2399, 1583 (C=N), 1490, 1456, 1440 1051, 997 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.03 (3H, s, C**H**$_3$), 7.26 (1H, s, 8-**H**), 7.49 (1H, d, *J* = 5.7 Hz, 4-**H**), 7.84 (1H, s, 5-**H**), 8.42 (1H, d, *J* = 5.7 Hz, 3-**H**), 9.13 (1H, s, 1-**H**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.3 (**C**H_3), 105.9, 119.1, 127.5, 128.2, 129.1, 131.1, 142.1 (3-**C**), 150.8 (1-**C**), 154.0 (7-**C**); HRMS (ESI): Found: *m/z* 194.0377, Calcd for $C_{10}H_9NOCl$ $[M+H]^+$: 194.0373.

5,8-Dimethyl-7-phenylisoquinoline (2.39d):



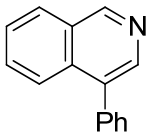
90% yield from **2.38d'**; Pale yellow solid; mp 134-136 °C; IR (KBr) 3059, 3018, 2974, 2399, 1599 (C=N), 1386, 1037 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (6H, s, overlapped), 7.35-7.48 (6H, m), 7.77 (1H, d, *J* = 5.8 Hz, 4-**H**), 8.60 (1H, d, *J* = 5.8 Hz, 3-**H**), 9.56 (1H, s, 1-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2 (**C**H_3), 18.3 (**C**H_3), 117.1, 127.1, 128.1, 128.2, 129.6 (overlaped), 130.9, 133.0, 134.8, 140.0, 141.6, 142.7 (3-**C**), 150.1 (1-**C**); HRMS (ESI): Found: *m/z* 234.1286, Calcd for $C_{17}H_{16}N$ $[M+H]^+$: 234.1283.

5,7-Dichloroisoquinoline (2.39e):



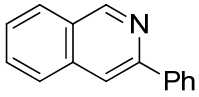
90% yield from **2.38e**; Pale yellow solid, mp 150-152 °C; IR (KBr) 3018, 2399, 2103, 1584 (C=N), 1483, 1349, 1156 1039, 867 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (1H, s, 6-**H**), 7.89 (1H, s, 8-**H**), 7.97 (1H, d, *J* = 5.9 Hz, 4-**H**), 8.64 (1H, d, *J* = 5.9 Hz, 3-**H**), 9.19 (1H, s, 1-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.7, 125.4, 129.4, 130.9, 132.1, 132.2, 132.3, 144.5 (3-**C**), 151.6 (1-**C**). HRMS (ESI): Found: *m/z* 1197.9879, Calcd for $C_9H_6NCl_2$ $[M+H]^+$: 197.9877.

4-Phenylisoquinoline (2.39f):[114]



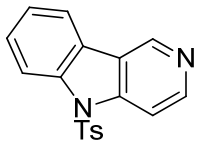
73% yield from **2.38f**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.55 (5H, m), 7.61-7.70 (2H, m), 7.91 (1H, d, *J* = 8.2 Hz), 8.04-8.06 (1H, m), 8.49 (1H, s, C_3**H**), 9.26 (1H, s, C_1**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.8, 127.1, 127.91, 127.96, 128.4, 128.6, 130.1, 130.5, 133.3, 134.2, 136.9, 142.7, 151.9.

3-Phenylisoquinoline (2.39g):[129]



62% yield from **2.38g**; 1H NMR (400 MHz, CDCl3) δ 7.42 (1H, t, *J* = 7.4 Hz), 7.51 (2H, dd, *J* = 7.4, 7.6 Hz), 7.59 (1H, dd, *J* = 7.4, 8.1 Hz), 7.70 (1H, dd, *J* = 7.4, 8.1 Hz), 7.87 (1H, d, *J* = 8.1 Hz), 7.98 (1H, d, *J* = 8.1 Hz), 8.07 (1H, s), 8.12 (1H, d, *J* = 7.6 Hz), 9.34 (1H, s, C_1**H**); 13C NMR (100 MHz, CDCl3) δ 116.5, 126.9, 127.0, 127.1, 127.5, 127.7, 128.5, 128.8, 130.5, 136.6, 139.6, 151.3, 1

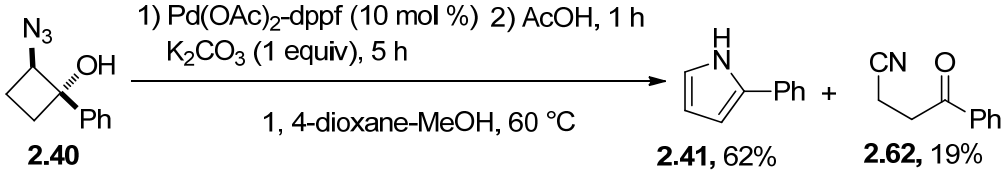
5-Tosyl-5*H*-pyrido[4,3-*b*]indole (5-*N*-Tosyl-γ-Carboline) (2.39h):



93% yield from **2.38h'**: Pale yellow solid, mp 191-193 °C; IR (KBr) 3432, 3018, 2403, 1639 (C=N), 1175, 984, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (3H, s, C$\mathbf{H}_3$), 7.15 (2H, d, *J* = 8.3 Hz), 7.41 (1H, dd, *J* = 7.6, 7.7 Hz), 7.55 (1H, dd, *J* = 7.6, 8.2 Hz), 7.75 (2H, d, *J* = 8.3 Hz), 7.99 (1H, d, *J* = 7.7 Hz), 8.19 (1H, d, *J* = 5.8 Hz, 4-**H**), 8.30 (1H, d, *J*

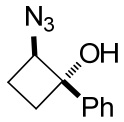
= 8.2 Hz), 8.65 (1H, d, *J* = 5.8 Hz, 3-**H**), 9.55 (1H, s, 1-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.57 (**C**H_3), 109.6, 114.8, 120.4, 122.2, 123.9, 124.5, 126.5, 128.3, 129.9, 134.6, 138.0, 142.8, 143.4, 145.6 (3-**C**), 147.2 (1-**C**); HRMS (ESI): Found: *m/z* 323.0854, Calcd for $C_{18}H_{15}N_2O_2S$ $[M+H]^+$: 323.0854.

4.7 Reaction of 2-azido-1-phenylcyclobutanol 2.40



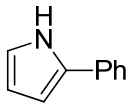
To a solution of (1*S**,2*R**)-2-azido-1-phenylcyclobutanol (**2.40**) prepared by the reported procedure[75] (56.9 mg 0.301 mmol) in 1,4-dioxane (2 mL) and MeOH (0.2 mL) were added $Pd(OAc)_2$ (6.9 mg, 0.0307 mmol), dppf (17.2 mg, 0.0310 mmol), and K_2CO_3 (41.9 mg, 0.303 mmol), and the reaction mixture was stirred at 60 °C for 5 h. MeOH (3 mL) and AcOH (0.2 mL, excess) were then added, and the reaction mixture was stirred at 60 °C for additional 1 h. The reaction was quenched with excess Na_2CO_3 (solid), filtered through a pad of celite and washed with EtOAc (20 mL). The solvent was removed in vacuo, and the resulting residue was purified by flash column chromatography to give 2-phenylpyrrole (**2.41**) (26.3 mg, 0.185 mmol) in 62% yield and nitrile **2.62** (9.3 mg, 0.058 mmol) in 19% yield.

(1*S,2*R**)-2-azido-1-phenylcyclobutanol (2.40):**[75]



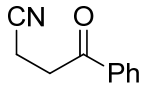
^{1}H NMR (400 MHz, CDCl3) δ 1.66-1.74 (1H, m), 2.03-2.10 (1H, m), 2.20-2.34 (1H, m), 2.74-2.79 (1H, m), 3.99 (1H, dd, *J* = 8.9, 8.9 Hz), 7.37-7.47 (3H, m), 7.57 (2H, d, *J* = 8.6 Hz); ^{13}C NMR (100 MHz, CDCl3) δ 19.5, 29.9, 64.6, 80.7, 126.5, 128.6, 128.9, 139.3.

2-Phenylpyrrole (2.41):[130]



^{1}H NMR (400 MHz, CDCl3) δ 2.32 (3H, s), 6.30 (1H, dd, *J* = 2.8, 5.7 Hz), 6.54 (1H, m), 6.87 (1H, m), 7.19 (1H, t, *J* = 7.4 Hz), 7.35 (2H, t, *J* = 7.4 Hz), 7.47 (1H, d, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, CDCl3) δ 105.9, 110.1, 118.8, 123.8, 126.2, 128.9, 132.1, 132.7.

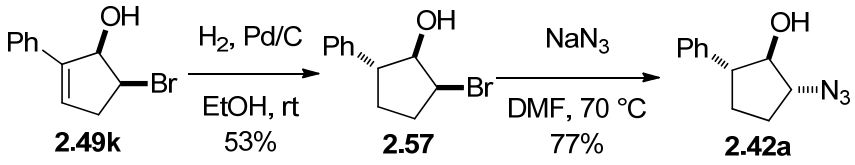
4-Oxo-4-phenylbutanenitrile (2.62):[131]



^{1}H NMR (400 MHz, CDCl3) δ 2.78 (2H, t, *J* = 7.2 Hz), 3.39 (2H, t, *J* = 7.2 Hz), 7.50 (2H, m), 7.60 (1H, m), 7.95 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, CDCl3) δ 11.8, 34.2, 119.2, 128.0, 128.9, 133.9, 135.5, 195.3.

4.8 Reaction of saturated 5-membered ring azidoalcohols

4.8.1 Synthesis of (1*R**,2*R**,5*R**)-2-azido-5-phenylcyclopentanol (2.42a)



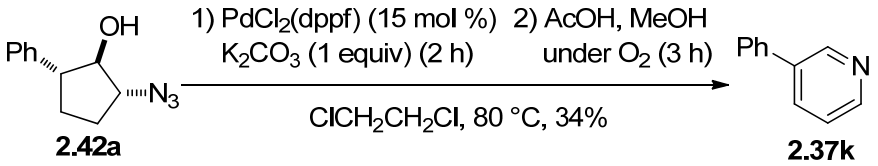
To a stirred solution of (1*R**,5*S**)-5-bromo-2-phenylcyclopent-1-ol (123.1 mg, 0.515 mmol) which was obtained by $NaBH_4$ reduction of **2.44k** in EtOH (10 mL) was added Pd/C (10 wt %, 27.1 mg, 0.0255 mmol) at room temperature, and the reaction mixture was stirred for 3 h under H_2 atmosphere. The reaction mixture was filtered through a pad of celite and washed with EtOH (20 mL). The solvent was removed in vacuo, and the resulting residue was purified by flash column chromatography to give (1*R**,2*S**,5*R**)-2-bromo-5-phenylcyclopentanol **2.57** (65.2 mg, 0.270 mmol) in 53% yield.

To a stirred solution of obtained 2-bromo-5-phenylcyclopentanol **2.57** (65.2 mg, 0.270 mmol) in anhydrous DMF (5 mL) was added NaN_3 (88.2 mg, 1.36 mmol) at room temperature, and the reaction mixture was stirred at 70 °C for 3 h. The reaction was quenched with water (30 mL), and the organic materials were extraced with EtOAc (3 x 20 mL). The combined extracts were washed with brine, dried over $MgSO_4$. The solvents were removed in vacuo and the resulting crude mixture was purified by flash column chromatography with EOAc/Hexane (1 : 6) to give (1*R**,2*R**,5*R**)-2-azido-5-phenylcyclopentanol (**2.42a**) (42.3 mg, 0.208 mmol) in 77% yield.

Colorless oil; IR (KBr) 3032, 2090 (N_3), 1641, 1492, 1383, 1165 1081, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35 (1H, d, *J* = 2.3 Hz, O**H**), 1.78-1.84 (1H, m), 2.13-2.19 (2H, m), 2.37-2.44 (1H, m), 3.35-3.39 (1H, m), 4.00-4.03 (1H, m, C**H**N_3), 4.13-4.14 (1H,

m, C**H**OH), 7.30-7.32 (3H, m, Ar-**H**), 7.37-7.40 (2H, m, Ar-**H**); ^{13}C NMR (125 MHz, CDCl3) δ 26.4, 28.9, 48.6, 67.6 (**C**HN_3), 79.2 (**C**HOH), 127.1, 128.6, 128.7, 138.3; HRMS (ESI): Found: *m/z* 204.1140, Calcd for $C_{11}H_{14}N_3O$ $[M+H]^+$: 204.1137.

4.8.2 Reaction of (1*R**,2*R**)-2-azido-5-phenylcyclopentanol (2.42a)



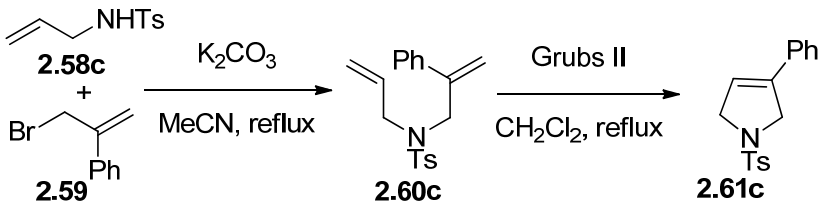
To a solution of (1*R**,2*R**,5*R**)-2-azido-5-phenylcyclopentanol (**2.42a**) (61.3 mg, 0.302 mmol) in CH_2Cl_2 (2 mL) were added Pd(dppf)·CH_2Cl_2 (36.8 mg, 0.045 mmol), and K_2CO_3 (42.2 mg, 0.30 mmol), and the reaction mixture was stirred for 2 h at 80 °C. MeOH (3 mL) and AcOH (0.2 mL, excess) were then added, and the reaction mixture was stirred at 80 °C for additional 3 h under O_2 atmosphere. After cooled to rt, the solvent was removed in vacuo, and the resulting residue was purified by flash column chromatography on silica gel with EtOAc/Hexane (1 : 3) to give 3-phenylpyridine (**2.37k**) (16.0 mg, 0.103 mmol) in 34% yield.

4.8.3 Synthesis of 2.42b-c

4.8.3.1 Syntesis of 2.61b-c

A typical procedure: [132]

Synthesis of 3-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole **2.61c:**

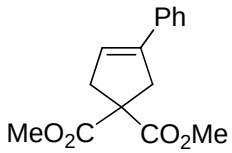


To a solution of α-(bromomethyl)styrene **2.59** (2.96 g, 15.02 mmol) and *N*-allyl-*p*-toluenesulfonamide **2.58c** (3.83 g, 18.080 mmol) in acetonitrile (30 mL) was added K_2CO_3 (2.75 g, 19.90 mmol) and the reaction mixture was refluxed for 12 h. The reaction was quenched with water (100 mL) and the organic materials were extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with brine and dries over $MgSO_4$. The solvents were removed in vacuo and the resulting crude mixture was purified by flash column chromatography with EtOAc/Hexane (1:6) to give the pure *N*-allyl-*N*-(2-phenylallyl)-*p*-toluenesulfonamide **2.60c** (3.92 g, 11.97 mmol) in 80% yield.

To a solution of *N*-allyl-*N*-(2-phenylallyl)-*p*-toluenesulfonamide **2.60c** (2.85 g, 8.71 mmol) in 40 mL CH_2Cl_2 was added Grubs(II) catalyst (221.6 mg, 0.26 mmol), and the reaction mixture was refluxed for 24 h. After removing the solvent, the residue was purified by flash column chromatograph with EtOAc/Hexane (1:4) to give the pure 3-phenyl-1-tosyl-2,5-dihydro-1*H*-pyrrole **2.61c**[41] (2.21 g, 7.38 mmol) in 85% yield.

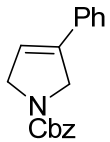
White solid, ^{1}H NMR (400 MHz, CDCl3) δ 2.41 (3H, s), 4.29-4.31 (2H, m), 4.47-4.49 (2H, m), 6.00 (1H, dd, *J* = 1.9, 2.0 Hz), 7.21-7.33 (7H, m), 7.75 (2H, d, *J* = 8.2 Hz); ^{13}C NMR (100 MHz, CDCl3) δ 21.5, 54.9, 55.6, 118.9, 125.4, 127.4, 128.4, 128.7, 129.8, 132.4, 134.0, 137.3, 143.6.

Dimethyl 3-phenylcyclopent-3-ene-1,1-dicarboxylate 2.61b:[133]



58% yield for 2 steps; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.21-3.22 (2H, m), 3.43.43 (2H, m), 3.76 (6H, s), 6.02 (1H, dd, *J* = 2.0, 2.1 Hz), 7.24 (1H, d, *J* = 7.6 Hz), 7.31 (2H, dd, *J* = 7.3, 7.6 Hz), 7.40 (2H, d, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.2, 41.3, 52.9, 58.9, 122.2, 125.6, 127.5, 128.4, 135.2, 139.5, 172.4.

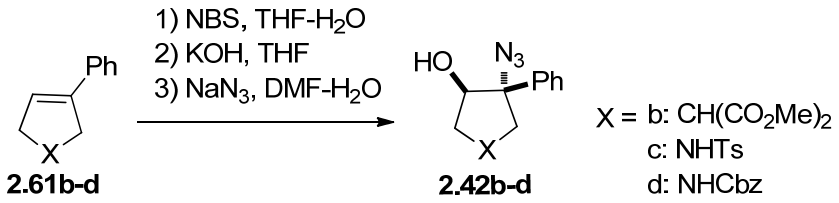
Benzyl 3-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxylate 2.61d:[132]



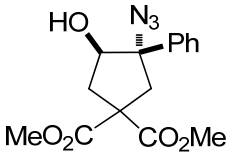
68% yield from diene **2.60d** which was prepared from benzyl allylcarbamate **2.58d** and α-(bromomethyl)styrene by treatment with NaH in THF at 0 ^{o}C-rt in 54 % yield. Pale white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38-4.41 (2H, m), 4.56-4.60 (2H, m), 5.20-5.21 (2H, m), 6.13-6.18 (1H, m), 7.29-7.43 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.1, 53.6, 53.8, 54.3, 66.9, 67.0, 119.21, 119.4, 125.41, 125.44, 127.92, 128.00, 128.05, 128.19, 128.22, 128.50, 128.53, 128.65, 128.69, 132.2, 132.3, 133.1, 136.8, 137.5, 154.6. (NMR spectra reported for a mixture of two rotamers.)

4.8.3.2 Syntesis of 2.42b-d

The preparation of **2.84b-c** were followed the **Method A** in section **5.4.1.2**.

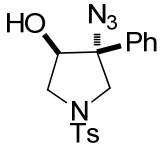


(3*S,4*R**)-dimethyl 3-azido-4-hydroxy-3-phenylcyclopentan-1,1-dicarboxylate 2.42b**



39% yield from **2.61b** in 3 steps; Pale yellow oil; IR (KBr) 3495, 3026, 2954, 2843, 2104 (N_3), 1734, 1435, 1309, 1178, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.05 (1H, brs, O**H**), 2.51 (1H, d, *J* = 15.0 Hz, C**H**$_2$), 2.92 (1H, dd, *J* = 4.2, 15.0 Hz, C**H**$_2$), 3.05-3.15 (2H, m) , C**H**$_2$, 3.77 (3H, s, C**H**$_3$), 3.81 (3H, s, C**H**$_3$), 4.27 (1H, brs, C**H**OH), 7.36-7.44 (5H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.1, 40.3, 53.2 (**C**H_3), 53.5 (**C**H_3), 58.1 , 77.6 (**C**N_3), 78.1 (**C**HOH), 127.4, 128.8, 129.1, 136.3, 171.6 (C=O), 173.3 (C=O); HRMS (ESI): Found: *m/z* 320.1257, Calcd for $C_{15}H_{18}N_3O_5$ $[M+H]^+$: 320.1246.

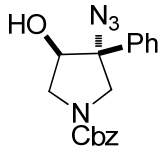
(3*R,4*R**)-4-Azido-4-phenyl-1-tosylpyrrolidin-3-ol 2.42c**



62% from **2.61c** in 3 steps; Pale yellow solid, mp 110-112 °C; IR (KBr) 3431, 3018, 2885, 2399, 2106 (N_3), 1598 (S=O), 1346, 1166, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.64 (1H, brs, O**H**), 2.41 (3H, s, C**H**$_3$), 3.53 (1H, d, *J* = 11.0 Hz, C**H**$_2$), 3.69 (1H, dd, *J* = 3.8, 11.0 Hz, C**H**$_2$), 3.89 (1H, d, *J* = 11.0 Hz, C**H**$_2$), 3.98 (1H, d, *J* = 11.0 Hz, C**H**$_2$), 4.25-4.26 (1H, m, C**H**OH), 7.27 (2H, d, *J* = 7.0 Hz, Ar-**H**), 7.32 (2H, d, *J* = 8.1 Hz, Ar-**H**),

7.37-7.46 (3H, m, Ar-**H**), 7.77 (2H, d, J = 8.1 Hz, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 (**C**H_3), 52.1 (**C**H_2), 54.0 (**C**H_2), 75.3 (**C**N_3), 75.4 (**C**HOH), 127.1, 127.4, 129.51, 129.55, 129.7, 133.6, 134.1, 143.7; HRMS (ESI): Found: *m/z* 359.1176, Calcd for $C_{17}H_{19}N_4O_3S$ $[M+H]^+$: 359.1178.

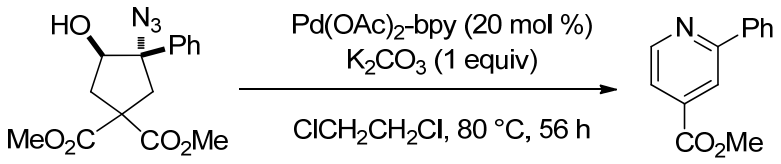
(3*R,4*R**)-Benzyl 3-azido-4-hydroxy-3-phenylpyrrolidine-1-carboxylate 2.42d**



54% from **2.61d** in 3 steps; Pale yellow solid, mp 115-116 °C; IR (KBr) 3412, 3016, 2885, 2953, 2104 (N_3), 1689 (C=O), 1448, 1429, 1147, 1097 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (1H, brs, O**H**), 3.60-3.63 (1H, m, C**H**$_2$), 3.82-3.86 (1H, m, C**H**$_2$), 4.00-4.90 (2H, m, C**H**$_2$), 4.35 (1H, brs, C**H**OH), 5.16 (2H, s, C**H**$_2$), 7.32-7.49 (10H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.5, 50.8, 52.4, 52.8, 67.1, 67.3, 74.3, 74.7, 75.3, 75.4, 127.30, 127.37, 127.9, 128.0, 128.11, 128.18, 128.53, 128.58, 129.3, 129.4, 129.5, 134.1, 134.2, 136.50, 136.54, 155.0, 155.1; HRMS (ESI): Found: *m/z* 339.1540, Calcd for $C_{18}H_{19}N_4O_3$ $[M+H]^+$: 339.1547. (NMR spectra reported for a mixture of two rotamers.)

4.8.4 Pd-catalayzed ring-expansion reaction of 2.42b-c

A typical procedure: ring-expansion reaction of **2.42b**

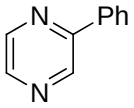


2.42b **2.43b**

To a solution of (3*S**,4*R**)-dimethyl 3-azido-4-hydroxy-3-phenylcyclopentane-1,1-dicarboxylate **2.42b** (48.0 mg, 0.150 mmol) in 2 mL $ClCH_2CH_2Cl$ were added $Pd(OAc)_2$ (6.8 mg, 0.0303 mmol), bpy (4.8 mg, .0307mmol) and K_2CO_3 (20.9 mg, 0.151 mmol), and the reaction mixture was stirred for 56 h at 80 °C. The volatile materials were then removed in vacuo, and the residue was purified by flash column chromatography with EtOAc/Hexane (1 : 4) to give pyridine **2.43b**[134] (12.1 mg, 0.058 mmol) in 38% yield.

Yellow powder, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (3H, s), 7.44-7.52 (3H, m), 7.77 (1H, dd, *J* = 1.0, 5.0 Hz), 8.04 (2H, dd, *J* = 1.0, 8.4 Hz), 8.30 (1H, s), 8.83 (1H, d, *J* = 5.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.7, 119.7, 121.1, 127.0, 128.8, 129.5, 138.1, 138.5, 150.4, 158.5, 166.4.

2-Phenylpyrazine 2.43c:[135]



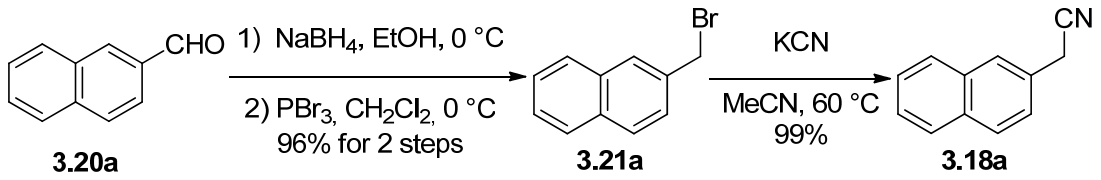
28% (recovery of **2.42c** in 41 % yield) and 37 % from **2.42c** and **2.42d** by treatment with $PdCl_2$(dppf) in DMI at 120 ^{o}C respectively. Yellow powder, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.54 (3H, m), 8.01 (2H, dd, *J* = 2.0, 8.2 Hz), 8.51 (1H, d, *J* = 2.0 Hz), 8.64 (1H, s), 9.0 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.9, 129.0, 129.9, 136.3, 142.2, 142.9, 144.2, 152.8.

4.9 Cu-catalyzed aerobic oxidative synthesis of benzoic acids from corresponding benzyl cyanides

4.9.1 Synthesis of benzylcyanides

4.9.1.1 substitution of benzyl bromides by KCN

A typical procedure: synthesis of 2-naphthalic acetonitrile **3.18a**



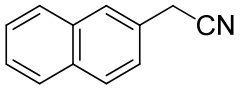
To a solution of 2-naphthaldehyde (**3.20a**) (1.57 g, 10.05 mmol) in EtOH (25 ml) at 0 °C was added $NaBH_4$ (458.6 mg, 12.12 mmol) in small portions, and the reaction mixture was stirred for 1 h. the reaction was quenched with water 50 mL, and organic materials were extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were washed with water, brine, and dried over $MgSO_4$. The solvents were evaporated off to yield the 2-naphthalic methanol in quantitative yield.

To a solution of 2-naphthalic methanol (377.4 mg, 2.39 mmol) and a drop of pyridine in CH_2Cl_2 (10 mL) was added the PBr_3 (0.15 mL, 1.6 mmol) solution in CH_2Cl_2 (10 mL) dropwise, and the reaction mixture was stirred for additional 3 h. the reaction was quenched with saturated Na_2CO_3 (50 mL), and organic materials were extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were washed with water, brine, and dried over $MgSO_4$. The solvents were evaporated off to yield the crude residue which was purified by flash column chromatography with EtOAc/Hexane (1 : 20) as elute to give

(2-bromomethyl)naphthalene **3.21a** (507.5 mg, 2.30 mmol) in 96% yield.

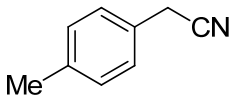
The mixture of (2-bromomethyl)naphthalene **3.21a** (630.3 mg, 3.85 mmol) and KCN (556.8 mg, 8.55 mmol) in MeCN (10 mL) was refluxed for 24 h. the reaction was cooled to room temperature and the solvent was removed under reduced pressure to give the crude residue which was purified by flash column chromatography with EtOAc/Hexane (10: 1) to provide the 2-naphthyl acetonitrile **3.18a** in quantitative yield (96% for 3 steps).

2-Naphthyl-acetonitrile 3.18a[136]



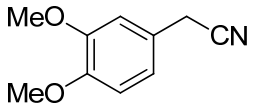
White powder, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (2H, s), 7.37 (1H, d, J = 8.4 Hz), 7.49-7.54 (2H, m), 7.82-7.87 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 117.8, 125.4, 126.5, 126.80, 126.88, 127.2, 127.73, 127.77, 129.0, 132.7, 133.3.

4-Methylbenzyl cyanide 3.18b[136]



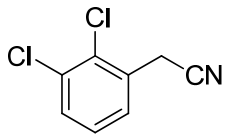
70% Yield from *p*-tolylaldehyde **3.20b** in 3 steps; colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (3H, s), 3.70 (2H, s), 7.16 (2H, d, J = 8.2 Hz), 7.20 (2H, d, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 23.2, 118.0, 126.8, 127.8, 129.7, 137.8.

3,4-Dimethoxybenzyl cyanide 3.18c[137]



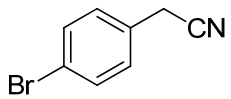
42% Yield from 3,4-dimethoxybenzaldehyde **3.20c** in 3 steps; colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (2H, s), 3.86 (3H, s), 3.88 (3H, s), 6.80 (1H, s), 6.82 (1H, d, *J* = 8.4 Hz), 6.84 (1H, d, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 55.9 (overlap), 110.9, 111.5, 118.1, 120.2, 122.1, 148.8, 149.4.

2,3-Dichlorobenzyl cyanide 3.18d



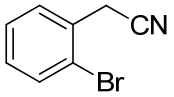
49% Yield from 2,3-dichlorobenzaldehyde **3.20d**; white powder, mp 68-70 ^{o}C; IR (KBr), 3018, 2399, 2252 (CN), 1521, 1427, 1051 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (2H, s, C**H**$_2$CN), 7.25-7.29 (1H, m, Ar-**H**), 7.44-7.49 (2H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0 (**C**H_2CN), 116.4 (**C**N), 127.7, 127.8, 130.4, 130.5, 131.9, 133.8; HRMS (ESI): Found: *m/z* 185.9879, Calcd for $C_8H_6NCl_2$ $[M+H]^+$: 185.9877.

4-Bromobenzyl cyanide 2.18e[138]



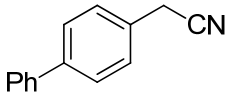
59% Yield from 4-bromobenzaldehyde **3.20e**; yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (2H, s), 7.19 (2H, d, *J* = 8.1 Hz), 7.50 (2H, d, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 117.3, 122.1, 128.9, 129.6, 132.3.

2-Bromobenzyl cyanide 2.18f [138]



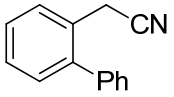
97% Yield from 2-bromobenzyl bromide **3.21e**; colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (2H, s), 7.20 (1H, dd, *J* = 7.6, 7.9 Hz), 7.35 (1H, dd, *J* = 7.5, 7.6 Hz), 7.52 (1H, d, *J* = 7.5 Hz), 7.59 (1H, d, *J* = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 116.8, 123.6, 128.1, 129.7, 129.8, 129.9, 133.1.

4-Phenylbenzyl cyanide 3.18g[136]



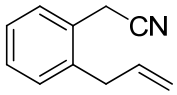
78% Yield from 4-phenylbenzaldehyde **3.20g** which was prepared by Suruki coupling from 4-bromobenzaldehyde and phenylboronic acid; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (2H, s), 7.35-7.47 (5H, m), 7.57-7.62 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 117.8, 127.0, 127.6, 127.8, 128.3, 128.83, 128.88, 140.2, 141.1.

2-Phenylbenzyl cyanide 3.18h[136]



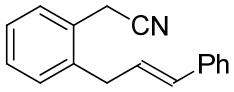
64% Yield from 2-phenylbenzaldehyde **3.20h** which was prepared by Suruki coupling from 2-bromobenzaldehyde and phenylboronic acid; colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (2H, s), 7.29-7.31 (3H, m), 7.38-7.48 (5H, m), 7.55-7.57 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 118.2, 127.75, 127.79, 128.23, 128.25, 128.7, 128.9, 130.4, 139.9, 141.8.

2-allylbenzyl cyanide 3.18i



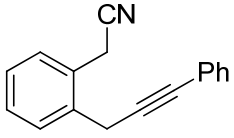
52% Yield from 2-allybenzaldehyde **3.20i** which was prepared by the modified reported procedure[139]; brown oil; IR (KBr), 3018, 2252 (CN), 1637 (C=C), 1490, 1454, 1415, 908, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.41 (2H, d, *J* = 6.1 Hz), 3.71 (2H, s, C**H**$_2$CN), 4.95-5.01 (1H, m), 5.11-5.14 (1H, m), 5.88-5.98 (1H, m), 7.21-7.32 (3H, m, Ar-**H**), 7.40 (1H, dd, *J* = 1.8, 8.5 Hz, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 37.3, 116.7, 117.8, 127.3, 128.6, 128.9, 130.3, 135.4, 137.4; HRMS (ESI): Found: *m/z* 158.0972, Calcd for $C_{11}H_{12}N$ $[M+H]^+$: 158.0970.

2-Cinnamylphenylbenzyl cyanide 3.18j



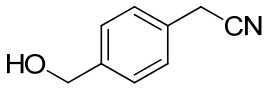
30% Yield from 2-cinnamylbenzaldehyde **3.20j** which was prepared by the modified reported procedure;[48] yellow oil; IR (KBr), 3028, 2252 (CN), 1645, 1454, 1096, 906, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.41 (2H, d, *J* = 5.6 Hz), 3.75 (2H, s, C**H**$_2$CN), 6.26-6.39 (2H, m), 7.20-7.44 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4(**C**H_2), 36.5 (**C**H_2CN), 117.7 (**C**N), 126.1, 127.0, 127.4, 127.5, 128.6, 128.7, 129.1, 130.4, 131.8, 136.9, 137.7; HRMS (ESI): Found: *m/z* 234.1285, Calcd for $C_{17}H_{16}N$ $[M+H]^+$: 234.1283.

2-(3-Phenylprop-2-yn-1-yl)benzyl cyanide 3.18k



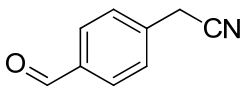
53% Yield from 2-(3-phenylprop-2-yn-1-yl)benzaldehyde **3.20k** which was prepared by the modified reported procedure;[48] yellow solid, mp 43-45 ^{o}C; IR (KBr), 2252 (CN), 2104 (C≡C), 1645, 1454, 1093, 912, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (2H, s), 3.89 (2H, s, C**H**$_2$CN), 7.29-7.37 (5H, m, Ar-**H**), 7.41-7.50 (4H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3 (**C**H$_2$), 24.0 (**C**H$_2$CN), 83.5 (C≡C), 85.5 (C≡C), 117.4 (**C**N), 123.0, 127.9, 128.1, 128.32, 128.37, 128.7, 129.1, 129.7, 131.6, 134.7; HRMS (ESI): Found: *m/z* 232.1122, Calcd for $C_{17}H_{14}N$ $[M+H]^+$: 232.1126.

4-Hydroxymethylbenzyl cyanide 3.18l



53% Yield from 4-hydroxymethylbenzyl bromide **3.21l'** which was prepared by the reported procedure[140]; light yellow solid, mp 37-39 ^{o}C; IR (KBr), 3394 (OH), 2252 (CN), 1635, 1561, 1421, 1209, 802, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (1H, brs, O**H**), 3.74 (2H, s, C**H**$_2$CN), 4.68 (2H, s, C**H**$_2$OH), 7.29-7.37 (4H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3 (**C**H$_2$CN), 64.6 (**C**H$_2$OH), 117.8 (**C**N), 127.6, 128.1, 129.0, 140.9; HRMS (ESI): Found: *m/z* 148.0759, Calcd for $C_9H_{10}NO$ $[M+H]^+$: 148.0762.

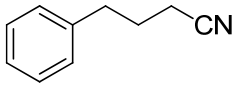
4-formalbenzyl cyanide 3.18m



36% Yield from oxidation of 4-Hydroxymethylbenzyl cyanide **3.18l** by MnO_2; light yellow crystal, mp 51-53 ^{o}C; IR (KBr), 3020, 2252 (CN), 1705 (C=O), 1608, 1581, 1413, 1172, 920, 848 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (2H, s, C**H**$_2$CN), 7.51 (2H, d, *J*

= 8.2 Hz, Ar-**H**), 7.89 (2H, d, *J* = 8.2 Hz, Ar-**H**), 10.02 (1H, s, C**H**O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8 (**C**H_2CN), 116.8 (**C**N), 128.6, 130.4, 136.1, 136.4, 191.4 (**C**HO); HRMS (ESI): Found: *m/z* 146.0606, Calcd for C_9H_8NO $[M+H]^+$: 146.0606.

4-phenylbutylnitrile 3.18r[44]

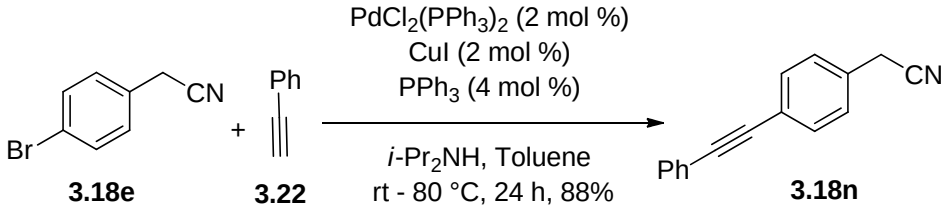


93% Yield from 3-phenyl-1-propyl bromide **3.21r**; colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95-2.02 (2H, m), 2.30 (2H, t, *J* = 7.1 Hz), 2.76 (2H, t, *J* = 7.4 Hz), 7.18-7.33 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 26.9, 34.3, 119.5, 126.5, 128.4, 128.6, 139.7.

4.9.1.2 Synthesis of benzyl cyanides by coupling reaction

A typical procedure:

Synthesis of 4-phenylethynylbenzyl cyanide **3.18n** by **Sonogashira coupling.**

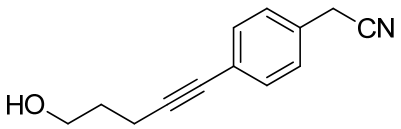


4-Bromobenzyl cyanide **3.18e** (987.1 mg, 5.04 mmol), $PdCl_2(PPh_3)_2$ (70.5 mg, 0.10 mmol), PPh_3 (53.8 mg, 0.21 mmol) and CuI (19.8 mg, 0.10 mmol) were put in a dry flask under N_2 atmosphere. After addition of *i*-Pr_2NH_2 (2 mL) and toluene (15 mL), the mixture

was stirred at room temperature for half hour and phenylacetylene (0.6 mL, 5.46 mmol) was added. The reaction carried out at 80 ^{o}C for 24 h. After cooling to room temperature, the reaction was quenched with saturated NH_4Cl (50 mL) and extracted with Et_2O (3 x 30 mL). The combined extracts were washed with water, brine, and dried over $MgSO_4$. The solvents were evaporated off to obtain the crude residue which was purified by flash column chromatography with EtOAc/Hexane (1 : 15) to give 4-phenylethynylbenzyl cyanide **3.18n**[141] (962.1 mg, 4.23 mmol) in 88% yield.

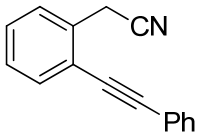
Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (2H, s), 7.30 (2H, d, *J* = 8.4 Hz), 7.34-7.37 (3H, m), 7.52-7.56 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 88.4, 90.2, 117.4, 122.9, 123.3, 127.9, 128.4, 128.5, 129.8, 131.6, 132.2.

4-(5-hydroxypent-1-yn-1-yl)benzyl cyanide 3.18o



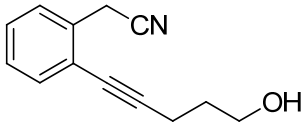
91% Yield from 4-bromobenzyl cyanide **3.18e** and 4-pentyn-1-ol; Pale yellow solid, mp 39-40 ^{o}C; IR (KBr), 3421 (O**H**), 2951, 2250 (CN), 1668, 1508, 1413, 1029, 912, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (1H, brs, O**H**), 1.81-1.88 (2H, m, $CH_2C\mathbf{H}_2CH_2$), 2.53 (2H, t, *J* = 7.0 Hz, $CH_2C\mathbf{H}_2CH$), 3.72 (2H, s, $C\mathbf{H}_2CN$), 3.78-3.81 (2H, m, $C\mathbf{H}_2OH$), 7.22 (2H, d, *J* = 7.9 Hz, Ar-**H**), 7.37 (2H, d, *J* = 7.9 Hz, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9 ($HOCH_2\mathbf{C}H_2$), 23.4 ($\mathbf{C}H_2CN$), 31.3 ($\mathbf{C}H_2C{\equiv}C$), 61.6 ($\mathbf{C}H_2OH$), 80.2 (C≡C), 90.4 (C≡C), 117.5 (**C**N), 123.7, 127.8, 129.2, 132.2; HRMS (ESI): Found: *m/z* 200.1081, Calcd for $C_{13}H_{14}NO$ $[M+H]^+$: 200.1075.

2-phenylethynylbenzyl cyanide 3.18p[142]



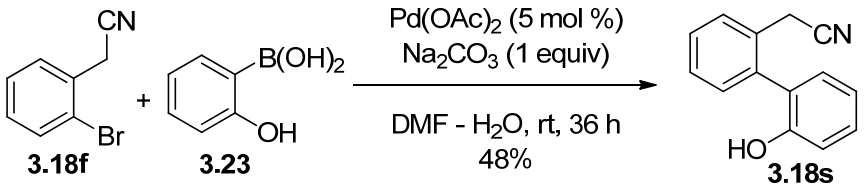
80% Yield from 2-bromobenzyl cyanide **3.18f** and phenylacetylene; Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (2H, s), 7.32-7.39 (5H, m), 7.50 (1H, d, *J* = 7.4 Hz), 7.55-7.59 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 86.0, 95.7, 117.4, 122.5, 122.8, 128.2, 128.5, 128.9, 129.0, 131.6, 131.7, 132.4.

2-(5-hydroxypent-1-yn-1-yl)benzyl cyanide 3.18q



84% Yield from 2-beomobenzyl cyanide **3.18e** and 4-pentyn-1-ol; Yellow oil; IR (KBr), 3394 (OH), 3070, 2879, 2250 (CN), 1633, 1487, 1448, 1409, 1056, 912, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (1H, brs, O**H**), 1.85-1.91 (2H, m,), 2.58 (2H, t, *J* = 7.0 Hz), 3.79-3.83 (2H, m, C**H**$_2$OH), 3.85 (2H, s, C**H**$_2$CN), 7.25-7.32 (2H, m), 7.40-7.43 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0 (HOCH$_2$**C**H$_2$), 22.8 (**C**H$_2$CN), 31.2 (**C**H$_2$C≡C), 61.4 (**C**H$_2$OH), 78.0 (C≡C), 96.3 (C≡C), 117.6 (**C**N), 123.4, 128.0, 128.1, 128.4, 131.5, 132.4; HRMS (ESI): Found: *m/z* 200.1087, Calcd for $C_{13}H_{14}NO$ $[M+H]^+$: 200.1075.

Synthesis of 2-(2-hydroxyphenyl)benzyl cyanide 3.18s



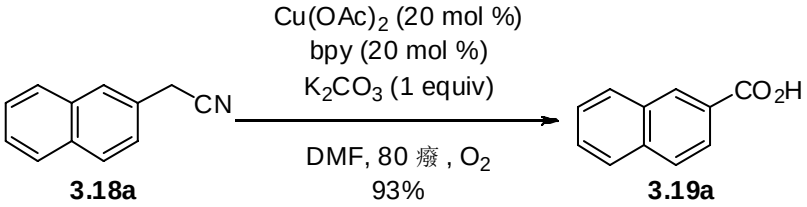
To a solution of 2-bromobenzyl cyanide **3.18f** (1.56 g, 8.00 mmol) and 2-hydroxyphenylboronic acid (1.27 g, 9.20 mmol) in DMF/H_2O (20/10 mL) were added Na_2CO_3 (860.1 mg, 8.11 mmol) and $Pa(OAc)_2$ (93.8 mg, 0.42 mmol) under N_2 atmosphere. The reaction was stirred for 40 h at room temperature. After quenched with NH_4Cl, the reaction was extracted with EtOAc (3 x 40 mL). The combined extracts were washed with water, brine, and dried over $MgSO_4$. The solvents were evaporated off to obtain the crude residue which was purified by flash column chromatography with EtOAc/Hexane (1 : 4) to give 2-(2-hydroxyphenyl)benzyl cyanide **3.18s** (801.8 mg, 3.83 mmol) in 48% yield.

White solid, mp 61-63 ^oC; IR (KBr), 3373 (OH), 3019, 2258 (CN), 1608, 1506, 1485, 1273, 835, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.51 (1H, d, *J* = 18.6 Hz, C**H**$_2$CN), 3.63 (1H, d, *J* = 18.6 Hz, C**H**$_2$CN), 5.04 (1H, brs, O**H**), 6.94 (1H, d, *J* = 8.1 Hz, Ar-**H**), 7.00-7.04 (1H, m, Ar-**H**), 7.12 (1H, d, *J* = 7.5 Hz, Ar-**H**), 7.28-7.32 (2H, m, Ar-**H**), 7.41-7.48 (2H, m, Ar-**H**), 7.60 (1H, d, *J* = 7.5 Hz, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7 (**C**H$_2$CN), 115.9, 118.0 (**C**N), 121.1, 125.9, 128.7, 128.9, 129.0, 129.6, 129.9, 130.5, 131.0, 136.3, 152.4 (**C**OH); HRMS (ESI): Found: *m/z* 232.07282, Calcd for $C_{14}H_{11}NONa$ $[M+Na]^+$: 232.0738.

4.9.2 Cu-catalyzed C–H oxygenation of benzyl cyanides

A typical procedure:

Synthesis of 2-naphthoic acid from 2-naphthyl acetonitrile **3.18a**

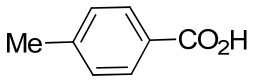


3.18a **3.19a**

To a solution of 2-naphthyl acetonitrile **2.18a** (50.3 mg, 0.30 mmol) in 2 mL was added K_2CO_3 (41.9 mg, 0.30 mmol), $Cu(OAc)_2$ (11.0 mg, 0.060 mmol) and bipyridine (9.4 mg, 0.060 mmol) under O_2 atmophere. The reaction was stirred for 12 h at 80 ^oC. After cooling to room temperature, the reaction was quenched with 1 N HCl (30 mL) and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with water, brine, and dried over $MgSO_4$. The solvents were evaporated off to obtain the crude residue (^{1}HNMR yield: 93 % with $Cl_2CHCHCl_2$ as internal standard) which was purified by flash column chromatography with EtOAc/Hexane/AcOH (25 : 75 : 1) to give 2-naphthoic acid **3.19a**[99] (47.5 mg, 0.276 mmol) in 92% yield.

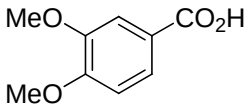
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.65 (2H, m), 7.90-7.94 (2H, m), 7.99 (1H, d, *J* = 8.0 Hz), 8.12 (1H, dd, *J* = 1.6, 8.6 Hz), 8.73 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 125.4, 126.5, 126.7, 127.8, 128.3, 128.6, 129.5, 132.1, 132.4, 135.9, 172.0.

***p*-Toluic acid 3.19b**[99]



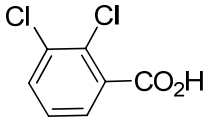
99% Yield in DMSO; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (3H, s), 7.26 (2H, d, *J* = 8.1 Hz), 8.00 (2H, d, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 126.5, 129.2, 130.2, 144.6, 172.1.

3,4-Dimethoxybenzoic acid 3.19c[143]



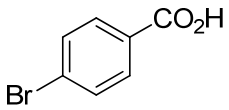
96% Yield in DMSO; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (3H, s), 3.95 (3H, s), 6.91 (1H, d, *J* = 8.5 Hz), 7.59 (1H, d, *J* = 1.7 Hz), 7.76 (1H, dd, *J* = 1.7, 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.02, 56.07, 110.3, 112.3, 121.7, 124.6, 148.6, 153.7, 171.8.

2,3- Dichlorobenzoic acid 3.19d



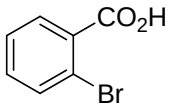
88% Yield in DMF; White solid, mp 161-163 ^{o}C; IR (KBr), 3396 (OH), 3018, 2399, 1705 (C=O), 1419, 1307, 1051, 912 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (1H, dd, *J* = 7.9, 7.9 Hz), 7.65 (1H, dd, *J* = 1.2, 7.9 Hz), 7.85 (1H, dd, *J* = 1.2, 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.1, 130.1, 131.0, 132.6, 134.1, 135.0, 169.3 (**C**=O); HRMS (ESI): Found: *m/z* 212.9492, Calcd for $C_7H_4O_2Cl_2Na$ $[M+Na]^+$: 212.9486.

4-Bromobenzoic acid 3.19e[99]



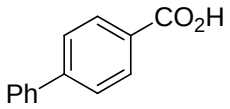
87% Yield in DMF; White solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (2H, d, *J* = 8.5 Hz), 7.89 (2H, d, *J* = 8.5 Hz), 13.2 (1H, brs); ^{13}C NMR (100 MHz, DMSO-d_6) δ 127.3, 130.4, 131.7, 132.1, 167.0.

2-Bromobenzoic acid 3.19f[143]



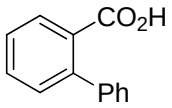
79% Yield in DMF; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.43 (2H, m), 7.70 (1H, dd, *J* = 2.1, 7.0 Hz), 8.00 (1H, dd, *J* = 2.1, 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.6, 127.3, 130.3, 132.4, 133.5, 134.9, 171.0.

4-Phenylbenzoic acid 3.19g[99]



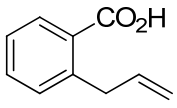
95% Yield in DMF; White solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 (1H, t, *J* = 7.3 Hz), 7.52 (2H, dd, *J* = 7.3, 7.6 Hz), 7.76 (2H, d, *J* = 7.6 Hz), 7.82 (2H, d, *J* = 8.3 Hz), 8.05 (2H, d, *J* = 8.3 Hz), 13.02 (1H, brs); ^{13}C NMR (100 MHz, DMSO-d_6) δ 127.2, 127.4, 128.7, 129.5, 130.1, 130.4, 139.5, 144.7, 167.6.

2-Phenylbenzoic acid 3.19h[144]



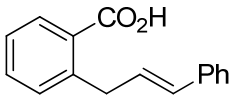
81% Yield in DMSO; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.44 (7H, m), 7.56 (1H, m), 7.93 (1H, dd, *J* = 1.2, 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.1, 127.3, 128.0, 128.4, 130.6, 131.2, 132.0, 141.0, 143.3, 173.1.

2-Allylbenzoic acid 3.19i[145]



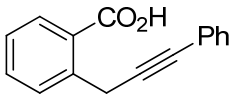
78% Yield in DMSO; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (2H, d, *J* = 6.5 Hz), 5.02-5.07 (2H, m), 6.00-6.10 (1H, m), 7.30-7.33 (2H, m), 7.48 (1H, dd, *J* = 7.2, 7.5 Hz), 8.05 (1H, d, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.5, 115.7, 126.3, 128.2, 131.1, 131.6, 133.0, 137.3, 142.7, 172.8.

2-Cinnamylbenzoic acid 3.19j



72% Yield in DMSO; Yellow solid, mp 125-127 ^{o}C; IR (KBr), 3431 (OH), 3028, 2252, 1695 (C=O), 1298, 1271, 908, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 (2H, d, *J* = 4.4 Hz, C**H**$_2$), 6.40-6.50 (2H, m, C**H**=C**H**), 7.17-7.54 (8H, m, Ar-**H**), 8.09 (1H, d, *J* = 7.4 Hz, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.7 (**C**H$_2$), 126.1, 126.4, 127.0, 128.2, 129.1, 131.1, 131.2, 131.7, 133.2, 137.5, 143.0, 173.2 (**C**=O); HRMS (ESI): Found: *m/z* 239.1065, Calcd for $C_{16}H_{15}O_2$ $[M+H]^+$: 239.1072.

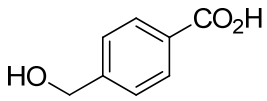
2-(3-Phenylpropargyl)benzoic acid 3.19k



30% Yield in DMSO; Yellow solid, mp 143-145 ^{o}C; IR (KBr), 3373 (OH), 2899, 2252, 1670 (C=O), 1489, 1319, 908, 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (2H, s, C**H**$_2$), 7.29-7.30 (3H, m, Ar-**H**), 7.36 (1H, t, *J* = 7.6 Hz, Ar-**H**), 7.46-7.51 (2H, m, Ar-**H**), 7.58 (1H, m), 7.86 (1H, d, *J* = 7.6 Hz, Ar-**H**), 8.12 (1H, d, *J* = 7.6 Hz, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 83.6, 87.2, 123.6, 126.8, 127.4, 127.8, 128.2, 130.0, 131.6, 131.7, 133.5, 139.4, 172.6 (**C**=O); HRMS (ESI): Found: *m/z* 237.0912, Calcd for $C_{16}H_{15}O_2$

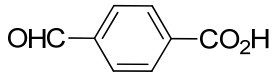
$[M+H]^+$: 237.0916.

4-(Hydroxymethyl)benzoic acid 3.19l[146]



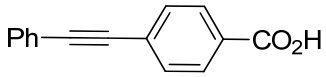
65% Yield in DMSO; white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.60 (2H, s), 5.38 (1H, brs), 7.45 (2H, d, *J* = 8.2 Hz), 7.93 (2H, d, *J* = 8.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 62.9, 126.6, 129.5, 129.6, 148.2, 167.7.

4-Formylbenzoic zcid 3.19m[147]



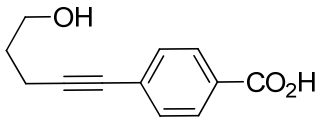
37% Yield in DMF; white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (2H, d, *J* = 8.2 Hz), 8.14 (2H, d, *J* = 8.2 Hz), 10.12 (1H, s), 13.4 (1H, brs); ^{13}C NMR (100 MHz, DMSO-d_6) δ 130.0, 130.3, 136.0, 139.3, 167.0, 193.4.

4-(Phenylethynyl)benzoic acid 3.19n[148]



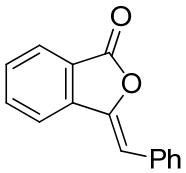
92% Yield in DMF; white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46-7.47 (3H, m), 6.60-7.61 (2H, m), 7.67 (2H, d, *J* = 8.2 Hz), 7.98 (2H, d, *J* = 8.2 Hz), 13.18 (1H, brs); ^{13}C NMR (100 MHz, DMSO-d_6) δ 89.0, 92.4, 122.2, 127.0, 129.3, 129.7, 130.0, 131.0, 131.9, 132.0, 167.1.

4-(5-Hydroxypent-1-yn-1-yl)benzoic acid 3.19o



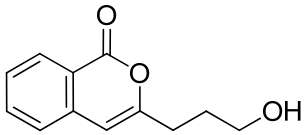
80% Yield in DMSO; White solid, mp 153-155 ^{o}C; IR (KBr), 3360 (OH), 3018, 2953, 2399, 1683 (C=O), 1429, 1321, 914, 864 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.66-1.73 (2H, m, $CH_2C\mathbf{H}_2CH_2$), 2.48 (2H, t, *J* = 7.0 Hz, C**H**$_2$C≡C), 3.51 (2H, t, *J* = 6.2 Hz, C**H**$_2$OH), 3.90 (1H, brs, O**H**), 7.48 (2H, d, *J* = 8.2 Hz, Ar-**H**), 7.88 (2H, d, *J* = 8.2 Hz, Ar-**H**), 13.1 (1H, brs, CO_2**H**); ^{13}C NMR (100 MHz, DMSO-d_6) δ 15.8 ($CH_2\mathbf{C}H_2CH_2$), 31.8 (**C**H_2C≡C), 59.8 (**C**H_2OH, 80.3 (C≡C), 94.3 (C≡C), 128.1, 129.8, 130.2, 131.8, 167.2 (**C**O_2H); HRMS (ESI): Found: *m/z* 205.0864, Calcd for $C_{12}H_{13}O_3$ $[M+H]^+$: 205.0865.

(Z)-3-benzylideneisobenzofuran-1-one 3.19p' [149]



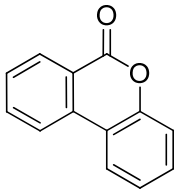
35% Yield in DMSO; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (1H, s), 7.30 (1H, dd, *J* = 7.2, 7.5 Hz), 7.39 (2H, dd, *J* = 7.5, 7.8 Hz), 7.52 (1H, t, *J* = 7.5 Hz), 7.70 (1H, dd, *J* = 7.2, 7.8 Hz), 7.76 (1H, d, *J* = 7.8 Hz), 7.84 (2H, d, *J* = 7.8 Hz), 7.93 (1H, d, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.0, 119.8, 123.4, 125.6, 128.4, 128.7, 129.7, 130.1, 133.1, 134.4, 140.6, 144.6, 167.0.

3-(3-hydroxypropyl)isochromen-1-one 3.19q' [150]



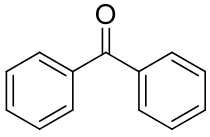
35% Yield in DMF; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (1H, brs), 1.93-2.00 (2H, m), 2.63 (2H, t, *J* = 7.4 Hz), 3.72 (2H, t, *J* = 6.1 Hz), 6.29 (1H, s), 7.33 (1H, d, *J* = 7.7 Hz), 7.42-7.46 (1H, m), 7.64-7.68 (1H, m), 8.22 (1H, d, *J* = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.8, 29.9, 61.6, 103.3, 120.1, 125.1, 127.7, 129.5, 134.7, 137.5, 157.4, 162.3.

Benzocoumarin 3.19s' [151]



75% Yield in DMF; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.38 (2H, m), 7.46 (1H, dd, *J* = 7.5, 7.9 Hz), 7.57 (1H, dd, *J* = 7.5, 7.9 Hz), 7.81 (1H, dd, *J* = 7.5, 7.9 Hz), 8.06 (1H, d, *J* = 7.9 Hz), 8.12 (1H, d, *J* = 7.9 Hz), 8.40 (1H, d, *J* = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 117.8, 118.0, 121.3, 121.6, 122.7, 124.5, 128.9, 130.4, 130.6, 134.7, 134.8, 151.3, 161.2.

Benzophenone 3.19u [152]



52% Yield in DMF; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (2H, dd, *J* = 7.2, 7.4

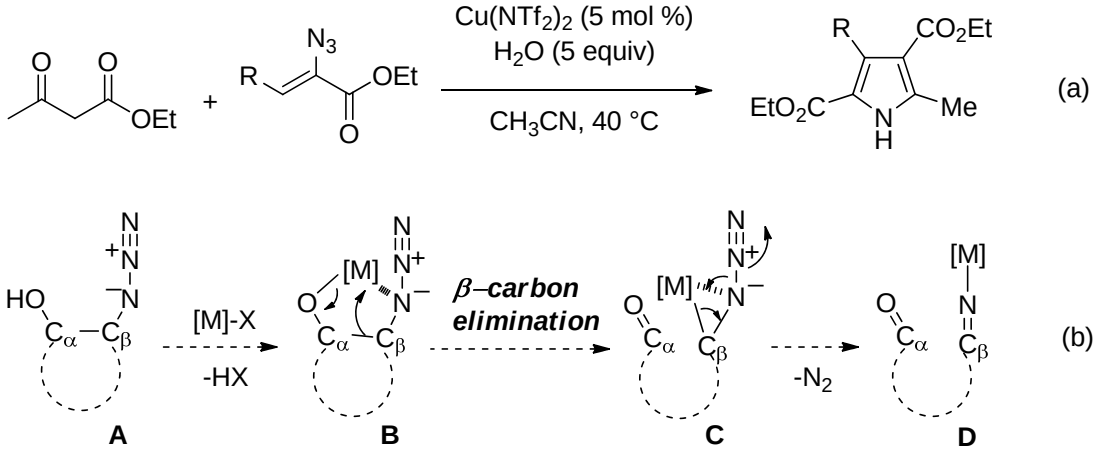
Hz), 7.57 (1H, t, J = 7.4 Hz), 7.81 (2H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.2, 130.0, 132.4, 137.6, 196.7.

Chapter 5

Conclusion

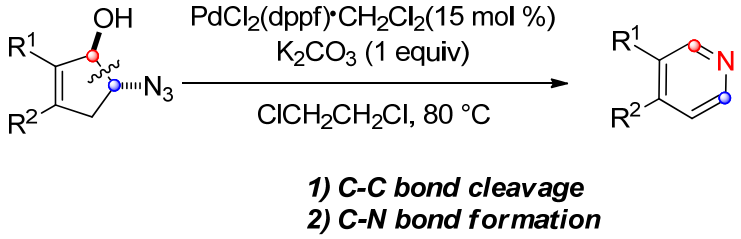
In this thesis, the author described two catalytic reaction: (1) Pd(II)-catalyzed ring-expansion of cyclic 2-azidoalcohols for synthesis of azaheterocycles (Chapter 2); (2) Cu(II)-catalyzed aerobic oxidation of benzyl cyanides for synthesis of carboxylic acids (Chapter 3).

Inspired by our group's previous finding that is Cu(II)-catalyzed synthesis of polysubstituted *N*–H pyrroles from α-ethoylcarbonyl vinyl azides and ethyl acetoacetate *via* iminyl metal species (Scheme 5-1a), a hypothesis (Scheme 5-1b) was proposed: the transition metal alcoholates **B** generated from 2-azidoalcohols **A** would undergo *β*-carbon elimination to give α-azidocarbometal species **C**. Subsequent metal migration from *C* to *N* with elimination of dinitrogen might afford iminyl metal species **D**, which could be used for further C–N bond forming reactions.



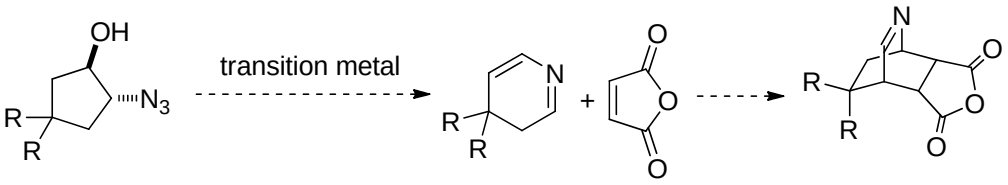
Scheme 5-1. Hypothesis of generating iminyl metal species from 2-azidoalcohols.

Based on this hypothesis, a Pd-catalyzed ring expansion reaction of cyclic 2-azidoalcohol derivatives was disclosed and described in chapter 2 (Scheme 5-2). This intriguing Pd-catalyzed ring expansion can provide some azaheterocycles such as pyridine, isoquinoline, pyrrole and pyrazine derivatives, which might has important synthetic applications in the future.



Scheme 5-2. Pd(II)-catalyzed ring expansion of cyclic 2-azidoalcohols for synthesis of some azaheterocycles.

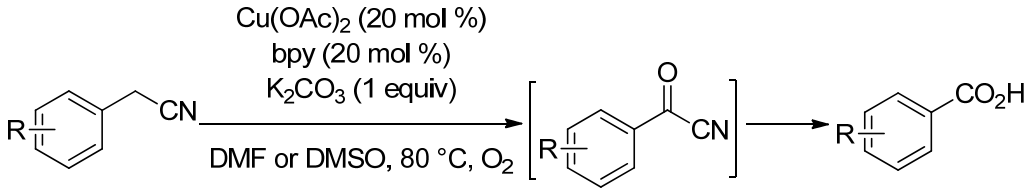
As the author mentioned in chapter 2, the azadiene might be generated from the 2-azidoalcohol bearing a saturated 5-membered ring system. In the future, it can be considered catching the generated azadiene by dienophile to synthesize some interesting azacycles through Aza-Diels-Alder reaction[153] as shown in Scheme 5-3.



Scheme 5-3. To trap azadiene by dienophile.

In chapter 3, a copper-catalyzed aerobic oxidation of benzyl cyanides was described, where the benzoic acids was obtained *via* benzoyl cyanides (Scheme 5-4). The oxidative hydrolysis of benzyl cyanides could tolerate various functional groups including alkyl,

aryl, double bond, triple bond, C–Cl, C–Br, hydroxyl and formal group. Moreover, this catalytic C–H bond oxygenation of benzyl cyanides could be extended to synthesis of ketones. It is predictable this transformation of one-carbon shorter carboxylic acid from benzyl cyanides must be useful in synthetic applications. It might be an interesting work to trap the generated benzoyl cyanides by this copper-catalyzed oxygenation to obtain other carbonyl compounds.



Scheme 5-4. Cu(II)-catalyzed aerobic oxidation of benzyl cyanides for synthesis of aromatic carboxylic acids.

Reference and Notes:

1 (a) Satoh, T.; Miura, M. *Top*. *Organomet*. *Chem*. **2005**, *14*, 1. (b) Jun, C.-H. *Chem*. *Soc*. *Rev*. **2004**, *33*, 610. (c) Rybtchinski, B.; Milstein, D. *Angew*. *Chem*. *Int*. *Ed*. **1999**, *38*, 870; (d) Bishop, K. C. *Chem. Rev.* **1976**, *76*, 461; (e) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 461.

2 (a) Periana, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1984**, *106*, 7272; (b) Crabtree, R. H.; Dion, R. P.; Gibboni, D. J.; McGrath, D. V.; Holt, E. M. *J. Am. Chem. Soc.* **1986**, *108*, 7222; (c) Halcrow, M. A.; Urbanos, F. Chaudret, B. *Organometallics* **1993**, *12*, 955.

3 Oxgaard, J.; Wiest O. *Eur. J. Org. Chem.* **2003**, 1454.

4 (a) Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846; (b) Baudoin, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 1373; (c) Goossen, L. J.; Rodriguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100.

5 (a) Kondo,T.; Kodoi, K.; Nishinaga, E.; Okada, T.; Morisaki, Y.; Watanabe, Y.; Mitsudo, T. *J. Am. Chem. Soc.* **1998**, *120*, 5587; (a) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* 2005, *7*, 3577; (c) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Organomet. Chem.* **2007**, *692,* 505; (d) Iwasaki, M.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129,* 4463; (e) Nishimura, T.; Katoh, T.; Hayashi, T. *Angew. Chem. Int. Ed.* **2007**, *46,* 4937; (f) Sumida, Y.; Takada, Y.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Chemistry – An Asian Journal* **2008**, *3*, 119.

6 (a) Noyori, R.; Odagi, T.; Takaya, H. *J. Am. Chem. Soc.* **1970**, *92*, 5780; (b) Baba, A.; Ohshiro, Y.; Agawa, T. *J. Organomet. Chem.* **1976**, *110*, 121; (c) Perthuisot, C.;

Jones, W. D. *J. Am. Chem. Soc.* **1994**, *116*, 3647; (d) Kondo, T.; Kaneko, Y.; Taguchi, Y.; Nakamura, A.; Okada, T.; Shiotsuki, M.; Ura, Y.; Wada, K.; Mitsudo, T. *J. Am. Chem. Soc.* **2002**, *124*, 6824.

7 (a) Huffman, M. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1991**, *113*, 2771; (b) Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815; (c) Masselot, D.; Charmant, J. P. H.; Gallagher, T. *J. Am. Chem. Soc.* **2006**, *128*, 694; (d) Shibata, T.; Nishizawa, G.; Endo, K. *Synlett* **2008**, 765; (e) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, *47*, 1100.

8 S. C. Bart and P. J. Chirik, *J. Am. Chem. Soc.* **2003**, *125*, 886.

9 (a) Murakami, M.; Amii, H.; Ito, Y. *Nature* **1994**, *370*, 540; (b) Murakami, M.; Amii, H.; Shigeto K.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 8285.

10 Murakami, M.; Tsuruta, T.; Ito, Y. *Angew. Chem. Int. Ed.* **2000**, *39*, 2484.

11 (a) Murakami, M.; Itahashi, T.; Ito, Y. *J. Am. Chem. Soc.* **2002**, *124*, 13976; (b) Matsuda, T.; Fujimoto, A.; Ishibashi, M.; Murakami, M. *Chem. Lett.* **2004**, *33*, 876.

12 (a) Burmeister J. L.; Edwards, L. M. *J. Chem. Soc. A* **1971**, 1663; (b) Tobisu, M.; Chatani, N. *Chem. Soc. Rev.* **2008**, *37*, 300; (c) Nájara, C.; Sansano, J.M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2452; (d) Nakazawa, H.; Kawasaki, T.; Miyoshi, K.; Suresh, C. H.; Koga, N. *Organometallics* **2004**, *23*, 117; (e) Hashimoto, H.; Matsuda, A.; Tobita, H. *Organometallics* **2006**, *25*, 472; (f) Nakazwa, H.; Kamata, K.; Itazaki, M. *Chem. Commun*. **2005**, 3004.

13 (a) Parshall, G. W. *J. Am. Chem. Soc.* **1974**, *96*, 2360. (b) Abla, M.; Yamamoto, T. *J. Organomet. Chem.* **1997**, *532*, 267. (c) Churchill, D.; Shin, J. H.; Hahn, J. M.; Bridgewater, B. M.; Parkin, G. *Organometallics* **1999**, *18*, 2403. (d) Taw, F. L.;

Mueller, A. H.; Bergman, R. G.; Brookhart, M. *J. Am. Chem. Soc.* **2003**, *125*, 9808. (e) Brunkan, N. M.; Brestensky, D. M.; Jones, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 3627; (f) Evans, M. E.; Li, T.; Jones, W. D. *J. Am. Chem. Soc.* **2010**, *132*, 16278.

14 (a) Miller, J. A. *Tetrahedron Lett.* **2001**, *42*, 6991; b) Miller, J. A.; Dankwardt, J.W. *Tetrahedron Lett.* **2003**, *44*, 1907; (c) Miller, J. A.; Dankwardt, J. W.; *Synthesis* **2003**, 1643; d) Penney, J. M.; Miller, J. A. *Tetrahedron Lett.* **2004**, *45*, 4989.

15 (a) Nakao, Y.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 13904. (b) Nakao, Y.; Oda, S.; Yada, A.; Hiyama, T. *Tetrahedron* **2006**, *62*, 7567.

16 Nakao, Y.; Yada, A.; Ebata, S.; Hiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 2428.

17 Nakao, Y.; Hirata, Y.; Tanaka, M.; Hiyama, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 385.

18 (a) Nakao, Y.; Yukawa, T.; Hirata, Y.; Oda, S.; Satoh, J.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 7116. (b) Hirata, Y.; Yukawa, T.; Karshihara, N.; Nakao, Y.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131,* 10964.

19 Nakao, Y.; Yada, A.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, *132,* 10024.

20 (a) Nakao, Y.; Yada, A.; Satoh, J.; Ebata, S.; Oda, S.; Hiyama, T. *Chem. Lett.* **2006**, *35*, 790; (b) Watson, M. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 12594.

21 Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874.

22 (a) Blum, J.; Oppenheimer, E.; Bergmann, E. D. *J. Am. Chem. Soc.* **1967**, *89*, 2338. (b) Murahashi, S.-I.; Naota, T. Nakajima, N. *J. Org. Chem.* **1986**, *51*, 898.

23 (a) Nozaki, K.; Sato, N.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 2679; (b) Nozaki, K., Sato, N.; Takaya, H. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1629.

24 (a) Kobayashi, Y.; Kamisaki, H.; Takeda, H.; Yasui, Y.; Yanada, R.; Takemoto, Y.

Tetrahedron **2007**, *63*, 2978; (b) Kobayashi, Y.; Kamisaki, H.; Yanada, R.; Takemoto, Y. *Org. Lett,* **2006**, *8*, 2711.

25 (a) Nakao, Y.; Hirata, Y.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 7420; (b) Nishihara, Y.; Inoue, Y. ; Itazaki, M.; Takagi, K. *Org. Lett.* **2005**, *7*, 2639.

26 Rondla, N. J.; Levi, S. M.; Ryss, J. M.; Vanden Berg, R. A.; Douglas, C. J. *Org. Lett.* **2011**, *13*, 1940.

27 (a) Lautens, M.; Meyer, C.; Lorenz, A. *J. Am. Chem. Soc*. **1996**, *118*, 10676. (b) Fournet, G.; Balme, G.; Goré, J. *Tetrahedron* **1988**, *44*, 5809; (c) Bräse, S.; de Meijere, A. *Angew. Chem., Int. Ed.* **1995**, *34*, 2545.

28 Tsukada, N.; Shibuya, A.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8123.

29 Murakami, M.; Takhashi, K.; Amii, H.; Ito, Y. *J. Am. Chem. Soc.* **1997**, *119*, 9307.

30 Matsuda, T.; Tsuboi, T.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12596.

31 (a) Bryndza, H. E.; Tam, W. *Chem. Rev.* **1988**, *88*, 1163; (b) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals,* 3rd Ed., Wiley: New York, **2001**, 64.

32 (a) Nishimura, T.; Uemura, S. *Synlett* **2004**, 201; (b) Matsuda, T.; Makino, M.; Murakami, M. *Org. Lett.* **2004**, *6,* 1257; (c) Seiser, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 9294; (d) Seiser, T.; Roth, O. A.; Cramer, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6320; (e) Shigeno, M.; Yamamoto, T.; Murakami, M. *Chem.–Eur. J.* **2009**, *15*, 12929.

33 Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc*. **1999**, *121*, 2645.

34 Nishimura, T.; Uemura, S. *J. Am. Chem. Soc*. **1999**, *121*, 11010.

35 (a) Park, S. H.; Cha, J. K. *Org. Lett.* **2000**, *2*, 147; b) Okumoto, H.; Jinnai, T.; Shimizu, H.; Harada, Y.; Mishima, H.; Suzuki, A. *Synlett* **2000**, 629; c) Kim, S.; Takeuchi, K.; Osakada, *J. Am. Chem. Soc.* **2002**, *124*, 762.

36 Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2005**, *127*, 6932.

37 (a) Wakui, H.; Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2004**, *126*, 8658; (b) Terao, Y.; Wakui, H.; Nomoto, M.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2003**, *58*, 5236.

38 Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407.

39 Nishimura, T.; Araki, H.; Maeda, Y.; Uemura, S. *Org. Lett.* **2003**, *5*, 2997.

40 Hayarama, H.; Kuroki, T.; Kimura, M.; Tanaka, S.; Tamaru, Y. *Angew. Chem. Int. Ed.* **1997**, *36*, 2352.

41 (a) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **2000***, 122,* 12049; (b) Nishimura, T.; Nishiguchi, Y.; Maeda, Y.; Uemura, S. *J. Org. Chem.* **2004**, *69*, 5342.

42 Zhao, P. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005***, 127,* 11618.

43 Chiba, S.; Zhang, L.-E.; Ang, J.-Y.; Hui, B. W.-Q. *Org. Lett,* **2010**, *12*, 2052.

44 Chiba, S.; Wang, Y.; Lapointe, G.; Narasaka, K. *Org. Lett.* **2008**, *10*, 313.

45 Cenini, S.; Gallo, E.; Caselli, A.; Ragaini, F.; Fantauzzi, S.; Piangiolino, C. *Coord. Chem. Rev.* **2006**, *250*, 1234.

46 Chiba, S.; Xu, Y. J.; Wang, Y. F. *J. Am. Chem. Soc.* **2009***, 131,* 12886.

47 (a) Chang, M. Y.; Lin, C. H.; Chen, Y. L. *Tetrahedron Lett.* **2010**, *51*, 1430; (b) Yamamoto, K.; Yamazaki, S.; Murata, I.; Fukazawa, Y. *J. Org. Chem.* **1987**, *52*, 5239; (c) Chang, M. Y.; Lin, C. Y.; Hung, C. Y. *Tetrahedron* **2007**, *63*, 3312; (d) Boruah, M.;

Konwar, D. *Synlett* **2001**, 795

48 (a) Chiba, S.; Zhang, L.; Lee, J.-Y. *J. Am. Chem. Soc.* **2010**, *132,* 7266; (b) Zhang, L.; Ang, G. Y.; Chiba, S. *Org. Lett.* **2010**, *12,* 3682; (c) Zhang, L.; Ang, G. Y.; Chiba, S. *Org. Lett.* **2011**, *13,* 1622.

49 DiBase, S. A.; Wolak, R. P.; Dishong, D. M.; Gokel, G. W. *J. Org. Chem.*, **1980**, *45*, 3630.

50 Lifshitz, E.; Goldfarb, D.; Vega, S.; Luz, Z.; Zimmermann, H. *J. Am. Chem. Soc.* **1987**, *109*, 7280.

51 Newman, M. S.; Arkell, A.; Fukunaga, T. *J. Am. Chem. Soc.* **1960**, *82*, 2498.

52 (a) Wolfe, J. P.; Khman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367; (b) Mann, G.; Hartwig, J. F.; Driver, M. S. Fernandez-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827; (c) Barluenga, J.; Aznar, F.; Valds, C. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 343; (d) Bolm, C.; Hildebrand, J. P. *J. Org. Chem.* 2000, 65, 169.

53 Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Comm.* **2009**, 5141.

54 Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47,* 1932.

55 (a) M. Kitamura, K. Narasaka, *Chem. Rec*. **2002**, *2*, 268; (b) K. Narasaka, M. Kitamura, *Eur. J. Org. Chem.* **2005**, 4505 and references therein.

56 (a) H. Tsutsui, K. Narasaka, M. Kitamura, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1451; (b) J. Ichikawa, K. Sakoda, J. Mihara, N. Ito, *J. Fluorine Chem*. **2006**, *127*, 489; (c) M. Kitamura, S. Zaman, K. Narasaka, *Synlett* **2001**, 974; (d) M. Kitamura, S. Chiba, O. Saku, K. Narasaka, *Chem. Lett*. **2002**, 606; (e) S. Zaman, M. Kitamura, K. Narasaka, Bull. *Chem. Soc. Jpn*. **2003**, *76*, 1055; (f) S. Chiba, M. Kitamura, O. Saku, K.

Narasaka, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 785.

57 a) Tsutsui, H.; Narasaka, K. *Chem. Lett*. **1999**, 45; b) Tsutsui, H.; Narasaka, K. *Chem. Lett.* **2001**, 526.

58 T. Gerfaund, L. Neuville, J. Zhu, *Angew. Chem. Int. Ed.* **2009**, *48*, 572.

59 Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2007**, *9*, 1947.

60 Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918.

61 Tan, Y. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676.

62 Wang, Y. F.; Toh, K. K.; Chiba, S.; Narasaka, K. *Org. Lett.* **2008**, *10,* 5019.

63 Wang, Y. F.; Chiba, S. *J. Am. Chem. Soc.* **2009**, *131*, 12570.

64 Barz, M.; Herdweck, E.; Thiel, W. R. *Angew*. *Chem*. *Int*. *Ed*. **1998**, *37*, 2262.

65 Kim, K. M.; Chung, K. H.; Kim, J. N.; Ryu, E. K. *Synthesis*, **1993**, 283. For preparation of **2.46b**: consecutive treatment of cyclopent-2-enone with mcpba in presence of excess HCl in DMF and Et_3N in CH_2Cl.

66 Harmata, M.; Barnes, C. L.; Brackley, J.; Bohnert, G.; Kirchhoefer, P.; Krti, L.; Rashatasakhon, P. *J. Org. Chem*. **2001**, *66*, 5232. For preparation of **2.46c**: consecutive treatment of cyclopent-2-enone with Br_2 and Et_3N in CH_2Cl.

67 Quesada, M. L.; Schlessinger, R. H.; Parsons, W. H. *J. Org. Chem.* **1978**, *43*, 3968.

68 Ruprah, P. K.; Cros, J.-P.; Pease, J. E.; Whittingham, W. G.; Williams, J. M. J. *Eur. J. Org. Chem*. **2002**, 3145.

69 Sunnemann, H. W.; Hofmeister, A.; Magull, J.; de Meijere, A. *Chem. Eur. J.* **2007**, *13*, 3739.

70 Guha, S. K.; Wu, B.; Kim, B. S.; Baik, W.; Koo, S. *Tetrahedron Lett*. **2006**, *47*, 291.

71 For selected reports on *cis*-selective reduction of cyclic α-bromoketones, see: (a) Ros,

A.; Magriz, A.; Dietrich, H.; Fernández, R.; Alvarez, E.; Lassaletta, J. L. *Org. Lett.* **2006**, *8*, 127. (b) Meth-Cohn, O.; Moore, C.; Van Rooyen, P. H. *J. Chem. Soc. Perkin Trans. I* **1985**, 1793.

72 King, L. C.; Ostrum, G. K. *J. Org. Chem.* **1964**, *29*, 3459.

73 Mitrochkine, A.; Gil, G.; Reglier, M. *Tetrahedron Asymmetry* **1995**, *6*, 1535.

74 (a) Shi, M.; Liu, L.-P.; Tang, J. *J. Am. Chem. Soc.* **2006**, *128*, 7430; (b) Miller, D. D.; Hsu, F.; Salman, K. N.; Patil, P. N. *J. Med. Chem.* **1976**, *19*, 180.

75 (a) Brayshaw, S. K.; Sceats, E. L.; Green, J. C.; Weller, A. S. *Proc. Nat. Acad. Sci.* **2007**, *104*, 6921; (b) Brayshaw, Green, J. C.; Kociok-Köhn, G.; S. K.; Sceats, E. L.; Weller, A. S. *Angew. Chem. Int. Ed.*, **2006**, *45*, 452.

76 Bew, S. P. In *Comprehensive Organic Functional Groups Transformation II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2005; pp 19.

77 (a) Fraga-Dubreuil, J.; Garcia-Verdugo, E.; Hamley, P. A.; Vaquero, E. M.; Dudd, L. M.; Pearson, I.; Housley, D.; Partenheimer, W.; Thomas, W. B.; Whiston, K.; Poliakoff, M. *Green Chem.* **2007**, *9*, 1238; (b) Gupta, M.; Paul, S.; Gupta, R.; Loupy, A. *Tetrahedron Lett.* **2005**, *46*, 4957.

78 (a) Wiles, C.; Watts, P.; Haswell, S. J**.** *Tetrahedron Lett.* **2006**, *47*, 5261; (b) Firouzabadi, H.; Seddighi, M.; Mottaghinejad, E.; Bolourchian, M. *Tetrahedron* **1990**, *46*, 6869.

79 (a) Dam, J. H.; Madsen, R. *Eur. J. Org. Chem.*, **2009**, 4666; (b) Ganton, M. D.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 4777.

80 (a) Hirai, Y.; Kojima, T.; Mizutani, Y.; Shiota, Y.; Yoshizawa, K.; Fukuzumi, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 5772; (b) Hirashima, S.-I.; Kudo, Y.; Nobuta, T.;

Tada, N.; Itoh, A. *Tetrahedron Lett.* **2009**, *50*, 4328; (c) Shaikh, T. M.; Hong, F.-E. *Adv. Syn. Cat*. **2011**, *353*, 1491.

81 (a) Miyamoto, K.; Sei, Y.; Yamaguchi, K.; Ochiai, M. *J. Am. Chem. Soc.* **2009**, *131*, 1382; (b) Lee, K.; Kim, Y.-H.; Han, S. B.; Kang, H.; Park, S.; Seo, W. S.; Park, J. T.; Kim, B.; Chang, S. *J. Am. Chem. Soc*. **2003**, *125*, 6844.

82 (a) Iwahama, T.; Yoshino, Y.; Keitoku, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.*, **2000**, *65*, 6502; (b) Boisselier, V. L.; Dunach, E.; Postel, M. *J. Organomet. Chem.*, **1994**, *482*, 119.

83 (a) Mecinović, J.; Hamed, R. B.; Schofield, C. J. *Angew. Chem. Int. Ed.*, **2009**, *48*, 2796; (b) Zhang, Y.; Jiao, J. and; Flowers, R. A. *J. Org. Chem.*, **2006**, *71*, 4516; (c) Kang, S.; Joo, Cheonik.; Han, H.; Kim, S. M.; Yang, J. W. *Tetrahedron Lett.* **2011**, *52*, 502.

84 (a) Cohen, M. A.; Sawden, J.; Turner, N. J. *Tetrahedron Lett.*, **1990**, 31, 7223; (b) Meth-Cohn, O.; Wang, M.-X. *Tetrahedron Lett.*, **1995**, 36, 52, 9561.

85 Soai, K.; Yokoyama, S.; Mochida, K. *Synthesis*, **1987**, 647.

86 Bender, M. L.; Chen, M. C. *J. Am. Chem. Soc*. **1963**, *85*, 30.

87 (a) Bhattacharya, A.; Patel, N. C.; Vasques, T.; Tichkule, R.; Parmar, G.; Wu, J.-J. *Tetrahedron Lett.* **2006**, *47*, 565; (b) Krief, A.; Kremer, A. *Chem. Rev.* **2010**, *110*, 4772.

88 (a) Itahara, T. *Heterocycles*, **1986**, 24, 2557; (b) Dong, C.-Z.; Julia, M.; Tang, J. *Eur. J. Org. Chem.*, **1998**, 1689.

89 Polyzos, A.; O'Brien, M.; Petersen, T. P.; Baxendale, I. R.; Ley, S. V. *Angew. Chem. Int. Ed.*, **2011**, 50, 1190。

90 (a) Jones, C.; Waugh, M. *J. Organomet. Chem.*, **2007**, *692*, 5086; (b) Kirby, A. J.; Percy, J. M. *Tetrahedron*, **1988**, *44*, 6903.

91 (a) Kobayashi, K.; Kondo, Y. *Org. Lett.*, **2009**, *11*, 2035; (b) Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.*, **2008**, *130*, 7826.

92 Ukai, K.; Aoki, M.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.*, **2006**, *128*, 8706.

93 (a) Correa, A.; Martin, R. *J. Am. Chem. Soc.*, **2009**, *131*, 15974. (b) Shimizu, K.; Takimoto, M.; Sato, Y.; Mori, M. *Org. Lett.* **2005**, *7*, 195.

94 Chuang, G. J.; Wang, W.; Lee, E.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133,* 1760.93

95 Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009,** *131*, 14654.

96 Bonaparte, A. C.; Betush, M. P.; Penseri, B. M.; Mastarone, D. J.; Murphy, R. K.; Murphree, S. S. *Org. Lett.*, **2011**, *13*, 1447.

97 (a) White, J. D.; Blakemore, P. R.; Milicevic, S. *Org. Lett.* **2002**, *4*, 1803. (b) White, J. D.; Avery, M. A.; Choudhry, S. C.; Dhingra, O. P.; Kang, M.; Whittle, A. J. *J. Am. Chem. Soc.* **1983**, *105*, 6517.

98 Moghaddam, F. M.; Mirjafary, Z.; Javan, M. J. *Synlett* **2008**, 892.

99 Yong, D. S.; Yong, H. J.; Fu, H. *Chem. Common.* **2011**, *47*, 2348.

100 (a) Watt, D. S.; *J. Org. Chem.* **1974**, *39*, 2799; (b) Parker, K. A.; Kallmerton, J. L. *Tetrahedron Lett.* **1977**, *18*, 4557.

101 See http://www.ehs.ucsb.edu/units/labsfty/labrsc/factsheets/Azides_FS26.pdf.

102 Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.

103 (a) Doris, E.; Dechoux, L.; Mioskowski, C. *J. Am. Chem. Soc.,* **1995**, *117*, 12700. (b) Iwasawa, N.; Matsuo, T.; Iwamoto, M.; Ikeno, T. *J. Am. Chem. Soc.* **1998**, *120*, 3903.

104 Itami, K.; Mitsudo, K.; Fujita, K.; Ohashi, Y.; Yoshida, J. *J. Am. Chem. Soc.* **2004**,

126, 11058.

105 Pour, M.; Spulak, M.; Balsanek, V.; Kunes, J.; Kubanova, P.; Buchta, V. *Bioorg. Med. Chem.* **2003**, *11*, 2843.

106 Meurer, L. C.; Finke, P. E. *Tetrahedron Lett.* **2002**, *43,* 4569.

107 Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2417.

108Gottschling, S. E.; Grant, T. N.; Milnes, K. K.; Jennings, M. C.; Baines, K. M. *J. Org. Chem.* **2005**, *70*, 2686.

109 Taniguchi, K.; Tsubaki, K.; Take, K.; Okumura, K.; Terai, T.; Shiokawa, Y. *Chem. Pharm. Bull.* **1994**, *42*, 896.

110 Chang, M.-Y.; Lin, C.-Y.; Hung, C.-Y. *Tetrahedron* **2007**, *63*, 3312.

111 Comins, D. L.; Killpack, M. O. *Heterocycles*, **1990**, *31*, 2025.

112 Katritzky, A. R.; Beltrami, H.; Sammes, M. P. *J. Chem. Res. Miniprint,* **1981**, *5*, 1684.

113 Karig, G.; Moon, M.-T.; Thasana, N.; Gallagher, T. *Org. Lett.* **2002**, *4*, 31.

114 Gordillo, A.; de Jesus, E.; Lopez-Mardomingo, C. *Org. Lett*. **2006**, *8*, 3517.

115 Gavryushin, A.; Kofink, C.; Manolikakes, G.; Knochel, P. *Tetrahedron* **2006**, *62*, 7521.

116 Su, S.-J.; Tanaka, D.; Li, Y.-J.; Sasabe, H.; Takeda, T.; Kido, J. *Org. Lett*. **2008**, *10,* 941.

117 Feuerstein, M.; Doucet, H.; Santelli, M. *J. Organomet. Chem.* **2003**, *687*, 327.

118 Synthetic procedure of **8a**: To a solution of 1-indanone-6-carboxylic acid (1.76 g, 10.0 mmol) in DMSO (20 mL) were added K_2CO_3 (2.07 g, 15.0 mmol) and MeI (1.70 g, 12.0 mmol), and the mixture was stirred for 30 min at room temperature

before the reaction was quenched with water. The organic materials were extracted with ether (3 x 30 mL), and the combined extracts were washed with water. The solvents were removed in vacuo, providing pure 6-methoxycarbonyl-1-indanone **(8a)** (1.89 g, 9.94 mmol) in 98% yield.

119 Eydoux, F.; Chlenov, M. A.; Reglier, M. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 941.

120 Odedra, A.; Datta, S.; Liu, R.-S. *J. Org. Chem.* **2007**, *72*, 3289.

121Nikitin, K.; Müller-Bunz, H.; Ortin, Y.; McGlinchey, M. J. *Org. Biomol. Chem.* **2007**, *5*, 1952.

122 Takahashi, M.; Ogasawara, K. *Synthesis* **1996**, 954.

123 Lakshman, M.; Nadkarni, D. V.; Lehr, R. E. *J. Org. Chem.* **1990**, *55*, 4892.

124 Peglion, J.-L.; Goument, B.; Millan, M.; Newman, A.; Dekeyne, A. *Eur. Patent Application* EP 906912, (Chem. Abstr. 130), 282085.

125 Liu, C. Y.; Knochel, P. *J. Org. Chem.* **2007**, *72*, 7106.

126 Synthetic procedure: 4,7-Dimethyl-6-bromo-1-indanone (1.20 g, 5 mmol), phenylboronic acid (1.22 g, 10mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), and Na_2CO_3 (2.12 g, 10 mmol) were mixed in toluene (25 ml) and water (25 ml) and the mixture was allowed to reflux under N_2 for 24 h. The mixture was then cooled, and the aqueous layer was extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to leave the crude product, which was purified by flash column chromatography on silica gel to give 4,7-dimethyl-6-phenyl-1-Indanone **2.56f** (1.15 g, 4.9 mmol) in 98% yield.

127 Sørensen, U. S.; Pombo-Villar, E. *Helv. Chim. Acta*. **2004**, *87*, 82.

128 Ishizaki, M.; Kurihara, K.; Tanazawa, E.; Hoshino, O. *J. Chem. Soc. Perkin Trans. I*

1993, 101.

129 Ramakrishna, T. V. V.; Sharp, P. R. *Org. Lett*. **2003**, *5*, 877.

130 Rieth, R. D.; Mankad, N. P.; Calimano, E.; Sadighi, J. P. *Org. Lett.* **2004**, *6*, 3981.

131 Miura, K.; Fujisawa, N.; Saito, H.; Wang, D.; Hosomi, A.. *Org. Lett.* **2001**, *3*, 2591.

132 Verendel, J. J.; Zhou, T.; Li, J.-Q.; Paptchikhine, A.; Lebedev, O.; Anderson, P. G. *J. Am. Chem. Soc.* **2010** , *132*, 8880.

133 Ma, S.; Jiao, N.; Zhao, S.; Hou, H. *J. Org. Chem.* **2002**, *67*, 2837.

134 Bedford, R. B.; Hall, M. A.; Huwe, M.; Hodges, G. R.; Wilkinson, M. C. *Chem. Commun.* **2009**, *45*, 6430.

135 Vallee, F.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 1514.

136 Shang, R.; Ji, D.-S.; Liu, L.; Chu, L.; Fu, Y. *Angew. Chem. Int. Ed.* **2011**, *50*, 4470.

137 Velcicky, J.; Soicke, A.; Steiner, R.; Schmalz, H.-G. *J. Am. Chem. Soc.* **2011**, *133*, 6948.

138 Mirjafari, A.; Mohammadpoor-Baltork, I.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Khosropour, A. R. *Tetrahedron Lett.* **2010**, *51*, 3274.

139 Knobloch, K.; Eberbach, W. *Org. Lett.* **2000**, *2*, 1117.

140 Bridger, G. J.; Skerlj, R. T.; Bogucki, D. E.; Wang, Z.; Zhou, Y.; Nan, S.; Boehringer, E. M.; Wilson, T.; Crawford, J.; Metz, M.; Hernandez-Abad, P. E.; Hatse, S.; Princen, K.; De Clercq, E.; Schols, D. *J. Med. Chem.* **2010** , *53*, 1250.

141 Komaromi, A.; Novak, Z. *Chem. Commun.* **2008**, *40*, 4968.

142 Shen, H.; Xie, Z. *J. Am. Chem. Soc.* **2010**, *132*, 11473.

143Nair, V.; Varghese, V.; Paul, R. R.; Jose, A.; Sinu, C. R.; Menon, R. S. *Org. Lett.* **2010**, *12*, 2653.

144 Mousseau, J. J.; Vallee, F.; Lorion, M. M.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 14412.

145 Nicolai, S.; Piemontesi, C.; Waser, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 4680.

146 Trincado, M.; Gruetzmacher, H.; Vizza, F.; Bianchini, C. *Chem. Eur. J.* **2010**, *16*, 2751.

147 Gu, L.; Zhang, Y. *J. Am. Chem. Soc.* **2010**, *132*, 914.

148 Zhao, D.; Gao, C.; Su, X.; He, Y.; You, J.; Xue, Y. *Chem. Commun.* **2010**, 46, 9049.

149 Park, J. H.; Bhilare, S. V.; Youn, S. W. *Org. Lett.* **2011**, *13*, 2228.

150 Subramanian, V.; Batchu, V. R.; Barange, D.; Pal, M. *J. Org. Chem.* **2005**, *70*, 4778.

151 Jung, M. E.; Allen, D. A. *Org. Lett.* **2009**, *11*, 757.

152 Cui, L.-Q.; Liu, K.; Zhang, C. *Org. Biomol. Chem*. **2011**, *9*, 2258.

153 (a) D. L. Boger *Chem. Rev.* **1986**, *86*, 781; (b) K. Takao, R. Munakata, K. Tadano *Chem. Rev.* **2005**, *105*, 4779; (c) S. Reymond, J. Cossy *Chem. Rev.* **2008**, *108*, 5359.

List of Publication

1. Shunsuke Chiba, Yan-Jun Xu, and Yi-Feng Wang

   "**A Pd(II)-Catalyzed Ring-Expansion Reaction of Cyclic 2-Azidoalcohol Derivatives: Synthesis of Azaheterocycles**"

   Journal of the American Chemical Society **2009**, *131*, 12186-12187.

2. **Yan-Jun Xu**, Shunsuke Chiba

   "A Pd(II)-Catalyzed Ring-Expansion Reaction of Cyclic 2-Azidoalcohol Derivatives: Synthesis of Azaheterocycles"

   6th Asian – European symposium On Metal Mediated Efficient Reactions, 7 – 9 June 2010 , Singapore