



**NANYANG
TECHNOLOGICAL
UNIVERSITY**

**STUDIES ON CARBO- AND AMINO-
FUNCTIONALIZATION OF ALKENES BY CONJUGATE
ADDITION AND HYDROAMINATION**

**TONG MENG KIAT BENNY
SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES
2014**

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

2014

Acknowledgements

The author would like to take this opportunity to express his sincere gratitude to his Ph.D advisor, Associate Professor Shunsuke Chiba. Without his invaluable foresight and advice, the author would not have accomplished what he has and as a result become a better individual today.

The author would also like to thank all members of the group, both past and present, for their fruitful discussion and kind assistance, namely Dr. Wang Yi-Feng, Dr. Mark Zhang Line, Dr. Peng Xingao, Dr. Stephen Sanjaya, Drs. Too Pei Chui, Miss Chua Sze Hui, Miss Toh Kah Kah, Mr Chen Hui, Mr Zhu Xu, Miss Zhang Fenglian and Miss Tnay Yalin.

The author would like to accredit the following personnel for their technical support and expertise; Dr. Li Yongxin and Dr. Rakesh Ganguly for their assistance in X-ray crystallographic analysis, Mdm. Zhu Wen-Wei for her training on the use of High Resolution Mass Spectrometry, Miss Goh Ee-Ling for her training on the use of NMR Spectrometers and Mr Hendra Widjaya for his logistical support.

The author is grateful to be awarded the Nanyang President Graduate Scholarship (NPGS) by Nanyang Technological University to undertake the Ph.D program.

The author would also like to express his gratitude to his co-supervisor and collaborators, Assistant Professor Andrew Tan Nguan Soon (NTU-SBS), Dr. Zhu Pengcheng (NTU-SBS) and Mr Chen Jiapeng Kelvin (NTU-LKC) for providing the author the opportunity to work in their laboratory.

The author would like to wish Miss Cai Yuting, Miss Chong Sin Yee and Miss Heng Yi Li all the best for their future endeavors. The author appreciates their help and providing a rare opportunity for the author to have the privilege to mentor them.

The author is also indebted to his examination committee for their time for evaluating and providing valuable and insightful comments.

Finally, the author owes his success to his mother, Mdm. Tan Swee Hup, his brothers, Mr Tong Meng Wei Benjamin and Mr Tong Meng Yong Benson, his sister, Miss Tong Meng Hui Rebecca, his uncles, Mr Tan Khawi Pian, Mr Tan Lee Piang and aunts, and Mdm. Tan Eng Yan and Mdm. Tay Lai Hoon Michelle for their unwavering support though the years.

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List of Abbreviations

δ	chemical shift (ppm)
$^{\circ}\text{C}$	degree centigrade
AIBN	Azobisisobutyronitrile
ATR	Attenuated total reflectance (FTIR)
br	broad singlet
cat.	catalytic
cm^{-1}	wave number (FTIR)
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
dddd	doublet of doublet of doublet of doublets
ddt	doublet of doublet of triplets
dt	doublet of triplets
dq	doublet of quartets
DEAD	diethyl azodicarboxylate
DMF	<i>N,N</i> -dimethylformamide
DMSO	Dimethyl sulfoxide
EIHRMS	Electron Ionization High Resolution Mass Spectrometry
ESIHRMS	Electrospray Ionization High Resolution Mass Spectrometry
Et	ethyl
HOMO	Highest Occupied Molecular Orbital
Hz	hertz
FTIR	Fourier Transform Infrared Spectroscopy
<i>J</i>	coupling constant
LUMO	Lowest Unoccupied Molecular Orbital
NHC	<i>N</i> -heterocyclic carbene
NOE	Nuclear Overhauser Effect (NMR)
M	concentration (mol/L)
M^+	parent ion peak (mass spectrum)
m	multiplet
Me	methyl

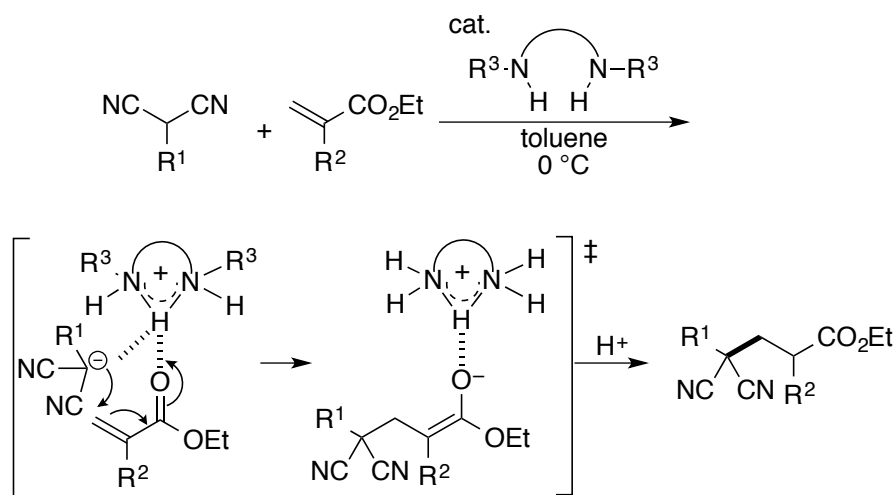
mg	milligram
MHz	megahertz
mmol	millimole
mp	melting point
NMR	nuclear magnetic resonance
q	quartet
rt	room temperature
s	singlet
T	triplet
TEMPO	2,2,6,6-tetramethylpiperidinyloxy
THF	tetrahydrofuran

Abstract

This dissertation describes studies on carbo- and amino-functionalization of alkenes using conjugate addition and hydroamination strategy.

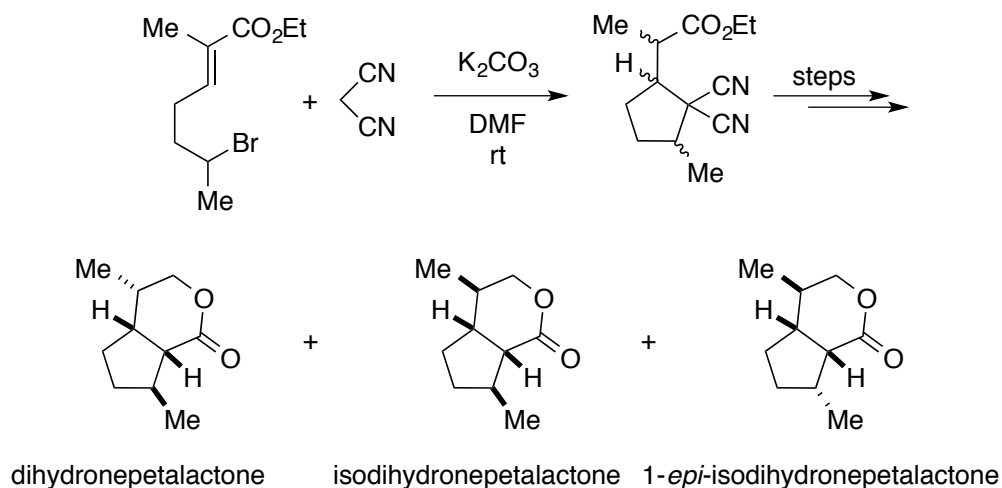
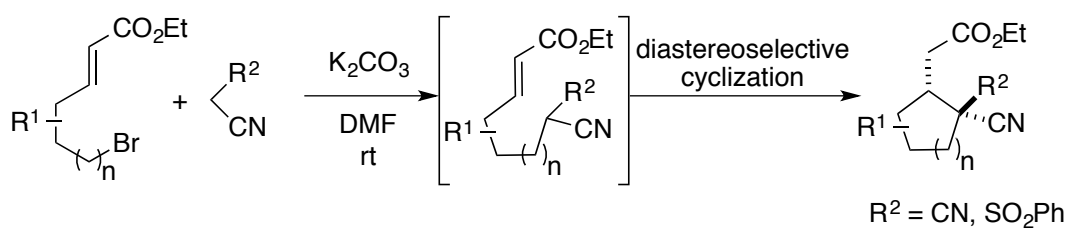
In Chapter 1, the importance and chemical functionalization of alkenes are highlighted in Chapter 1.

Chapter 2 describes development of a methodology that employs organic diamine as catalyst for conjugate addition reactions of active methine nucleophiles to acrylate derivatives. It could be speculated that hydrogen bonding plays a vital role to activate the less reactive acrylate derivatives towards conjugate addition.



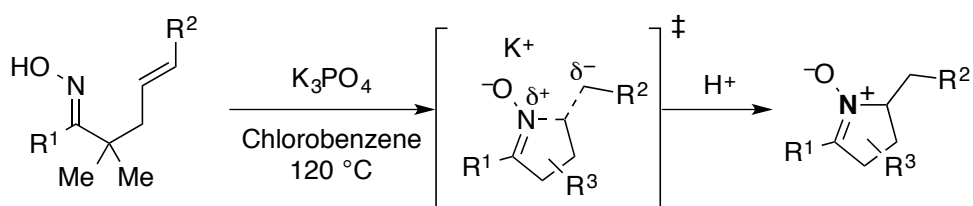
Scheme 1. Conjugate addition mediated by organic diamines

Chapter 3 entails a domino $\text{S}_{\text{N}}2$ -conjugate addition sequence for the diastereoselective synthesis of various carbocyclic compounds. The strategy is applied for synthesis of bicyclic lactone derivatives including biologically active natural products, dihydronepatalactone, isodihyronepetalactone and 1-*epi*-isodihyronepetalactone.



Scheme 2. Domino S_N2 -conjugate addition sequence

Chapter 4 describes a method for synthesis of cyclic nitrones using alkenyl oximes based on inorganic base-mediated hydroamination. DFT calculations of the reaction pathway suggested that the present hydroamination could proceed via unprecedented nucleophilic amination of unactivated alkene by the oxime nitrogen, the transition state of which is stabilized by ionic interaction of the metal cation such as K^+ on the oxime oxygen and negatively charged alkene moiety.



Scheme 3. Inorganic base mediated hydroamination of alkenyl oximes

Chapter 1. Introduction

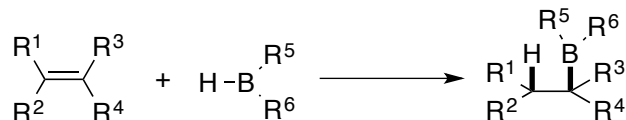
1.1. Alkene—an indispensable class of hydrocarbons

Alkenes are used to describe a class of hydrocarbons characterized by the presence of carbon-carbon double bond or unsaturation. Simple alkenes are readily available in abundance from nature and can be isolated from cracking and reforming of crude oil. They are used as building blocks for production of other chemicals on industrial scale. For bench top laboratory scale, alkenes are often handles for further functional group conversion. The vast potential of chemistry related to this important class of hydrocarbons is probably best underline by the prestigious Nobel Prize. A significant number of Nobel prizes awarded for Chemistry involved the functionalization of alkenes in the Nobel laureates' works. The prominent examples being the 1950 Nobel prize awarded to Otto Paul Hermann Diels and Kurt Alder for "*their discovery and development of the diene synthesis*", 1979 Nobel prize shared by Herbert C. Brown "*for the development of the use of boron containing compounds into important reagents in organic synthesis*" from which the important hydroboration of alkenes was developed, 2001 Nobel prize awarded to William S. Knowles, Ryoji Noyori for "*their work on chirally catalyzed hydrogenation reactions*" and K. Barry Sharpless for "*his work on chirally catalyzed oxidation reactions*", 2005 Nobel prize conferred to Yves Chauvin, Robert H. Grubbs and Richard R. Schrock for "*for the development of the metathesis method in organic synthesis*" and the recent 2010 Nobel prize bestowed to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for "*for palladium-catalyzed cross couplings in organic synthesis*" (Scheme 1-1).¹

[4+2]-cycloaddition by Diels and Alder



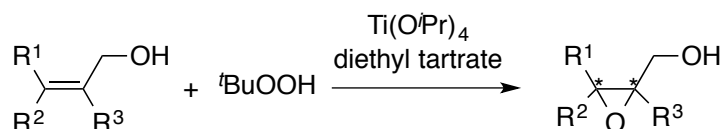
Hydroboration by Brown



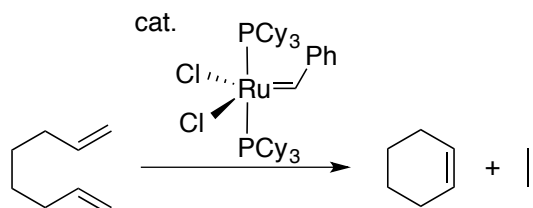
Asymmetric hydrogenation by Knowles and Noyori



Asymmetric epoxidation by Sharpless



Alkene metathesis, ring closing/ring opening metathesis by Chauvin, Grubbs and Schrock



Cross coupling by Heck, Negishi and Suzuki

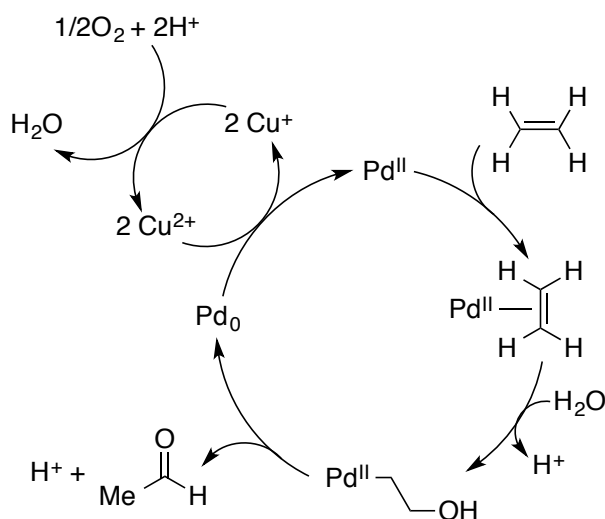


Scheme 1-1. Simplified scheme of Nobel laureates' work involving alkenes

Functionalization of alkenes remains one of the most important goals for synthetic chemists. From the viewpoint of atom economy, direct additions (both electrophilic and nucleophilic) across the alkenes represents the most efficient process, as all atoms of starting materials are transferred to the product.² However, simple alkenes are relatively inert and examples of direct additions are limited. Their electron-rich π orbitals disfavor the direct approach of electron-rich nucleophiles. This is circumvented by the use of transition metals or by lowering the electron density of the π orbitals by installing electron-withdrawing groups.³

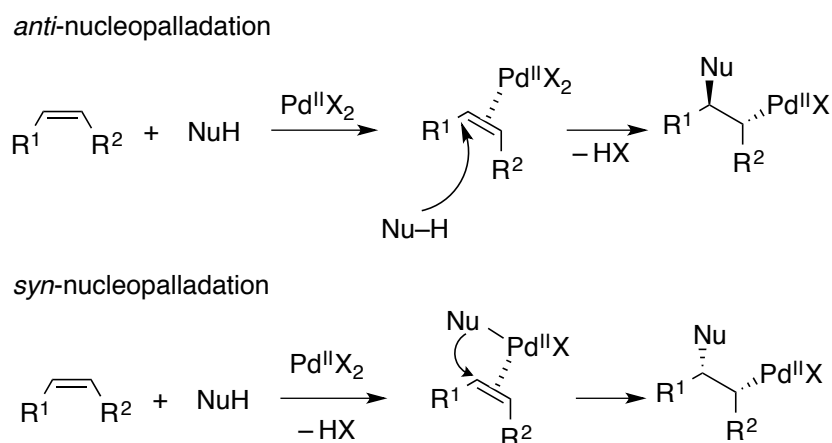
1.2.1. Wacker Oxidation-the birth of transition-metal-catalyzed reactions involving alkenes

Inarguably, the mid-20th century chemical industrial was powered by development of catalytic reactions utilizing alkenes as substrates, transforming them from feedstock chemicals to bulk chemicals, fine chemicals, pharmaceuticals, agrochemicals and polymers. Such applications continue to be an important part of today's chemical industry.⁴ The Wacker oxidation developed in 1959 was a palladium-catalyzed aerobic oxidative coupling of ethene and water to produce acetaldehyde.⁵ This reaction represents the advent of the paradigm for the development of subsequent palladium-catalyzed and other transition-metal catalyzed reactions. The direct addition of water to ethene (hydration) was seemingly of fundamental simplicity, yet it was surprisingly difficult.⁶ Instead indirect methodologies such as hydroboration and oxymercuration were developed, however which were not practical on industrial scale.⁷ Though the use of stoichiometric palladium(II) salts to effect the oxidation of ethene was known much earlier, the catalytic process was made possible by the discovery that the reduced palladium catalyst could be regenerated by copper(II) salt in the presence of molecular oxygen. The reaction is initiated with the co-ordination of the alkene with the palladium(II) also known as alkene nucleopalladation, in which by doing so activates the alkene towards nucleophilic attack of water molecule. This represents a net addition of hydroxide and palladium metal across the carbon-carbon double bond. Subsequent β -hydride elimination and tautomerization liberates palladium(0) and acetaldehyde. The palladium(0) is re-oxidized to palladium(II) by copper(II) in the presence of molecular oxygen (Scheme 1-2).⁸



Scheme 1-2. General catalytic cycle of Wacker process

An important fundamental mechanistic consideration arising from the alkene nucleopalladation is the nucleophile approach to the face of the alkene. There exist two models of such process; the *anti*-nucleopalladation and the *syn*-nucleopalladation with each intermediate giving rise to different stereoisomers (Scheme 1-3). Regioselectivity issues leading to different constitutional isomers are also of importance consideration when unsymmetrical alkenes are employed.⁴



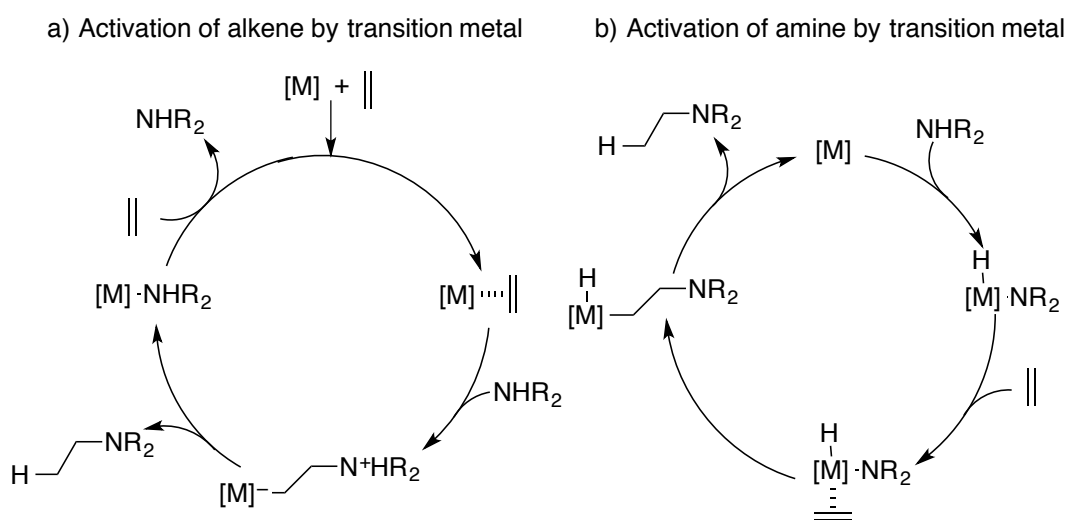
Scheme 1-3. Different modes of carbometalation leading to different stereoisomers

1.2.2. Hydroamination of non-activated alkenes

The carbometalation of the carbon-carbon double bond to a metal salt to activate alkenes is deemed so efficient that various methodologies with other nucleophiles have been developed.⁹ Among the nucleophiles, the addition of amines across the alkene is referred as hydroamination.¹⁰ This reaction results in the formation of a

new carbon-nitrogen bond and a carbon-hydrogen bond and offers promising routes to functionalized amines. Taking into account thermodynamics and kinetic aspects of hydroamination, direct nucleophilic addition of amines to the simple alkene is considered disfavored due to the electrostatic repulsion between the nitrogen with the electron rich alkene π orbitals. Due to the high negative reaction entropy, hydroamination products are not favored at high temperatures while the reaction itself is only slightly exothermic or thermoneutral.¹¹ Alternatively a [2+2]-cycloaddition between the nitrogen-hydrogen σ bond with the carbon-carbon π bond is symmetry-forbidden with huge energy difference between the π orbitals of the alkene and the σ orbitals of the N-H orbitals.²

In principal, transition-metal-catalyzed hydroamination can occur *via* two mechanisms involving either the activation of the alkene or activation of the amine. Alkene activation strategy is analogous to the Wacker oxidation with carbometalation of a suitable transition metal with the alkene, enabling the direct approach of an exogenous amine nucleophile (Scheme 1-4 a). Alternatively, hydroamination can occur *via* an initial oxidative addition of the amine N-H bond to a suitable transition metal, followed by the carbometalation between the metal and alkene. Insertion of alkene into the metal-nitrogen bond followed by reductive elimination delivers the hydroamination product (Scheme 1-4 b).¹² In general, hard bases prefer to add as external nucleophile as described by pathway a, while nonstabilized carbanions and soft bases prefer to add according to pathway b.¹⁰

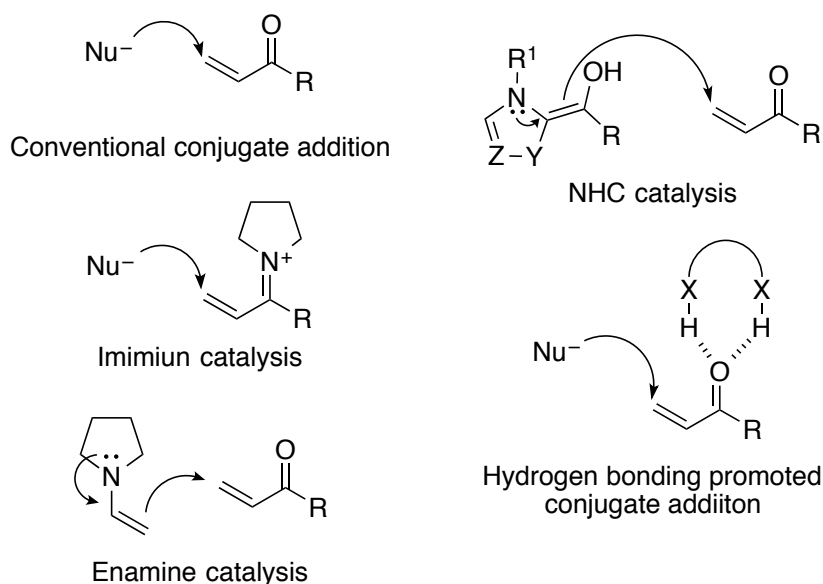


Scheme 1-4. Distinct hydroamination mechanisms

1.3.1. Nucleophilic functionalization of electron deficient alkenes

Apart from activation of simple alkenes by transition-metals, another attractive approach is *via* the installation of an electron-withdrawing moiety on the alkene, effectively rendering simple alkenes as an electron poor alkene. Such species are prone to nucleophilic attacks by other nucleophiles. The conjugate addition (the Michael reaction) constitutes an important class of reactions under such a strategy. First reported in 1887 by Arthur Michael, the conjugate addition of stabilized carbanions to α,β -unsaturated carbonyl compounds remain widely used by synthetic chemists for the construction of carbon-carbon bonds and functionalization of β -carbonyls till this date.¹³ Owing to its wide utility scope, nucleophiles having moieties capable of stabilizing carbanions such as 1,3-dicarbonyl compounds, nitroalkanes and malononitriles could be employed along with electrophiles capable of accepting electrons such as α,β -unsaturated carbonyl compounds, vinyl sulfones, acrylonitriles and nitroalkenes. Besides carbon-derived nucleophiles, heteroatoms such as nitrogen, oxygen and sulfur could also be used to construct new carbon-nitrogen, carbon-oxygen and carbon-sulfur bonds, respectively. Such combination offers synthetic chemists a plethora of possibilities.

In sharp contrast to the above well-established transition metal-catalyzed strategy, the field of organocatalysis had just witnessed tremendous advancement in the last decade. Numerous metal-free and asymmetric versions of conjugate addition reactions that proceed *via* distinct mechanisms had emerged.^{14,15,16,17,18} These fundamentally distinct mechanistic pathways offer synthetic chemists new perspectives in activating the electron-deficient alkenes and nucleophiles towards reactions and the potential to design new reactions. By employing environmentally benign and relatively inexpensive organocatalysts, synthetic chemists can avoid the use of transition metals. Furthermore, organocatalyst are relatively air/moisture stable and easy to handle.

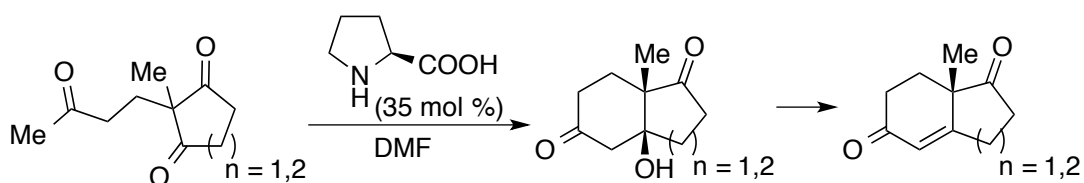


Scheme 1-6. Distinct mechanism of various organocatalyzed conjugate additions reactions

In the following sections, the author shall discuss the various modes of catalysis in details.

1.3.2. Employing primary or secondary amines for enamine catalysis

Reported in early 1970s independently by Hajos and Parrish, Wiechert, Eder and Sauer was a *L*-proline catalyzed intermolecular Aldol reaction for the synthesis of the Wieland-Miescher ketone, a useful building block for numerous biologically active compounds (Scheme 1-7). The mechanism was poorly understood at that time and its synthetic utility remained largely unexplored.¹⁹

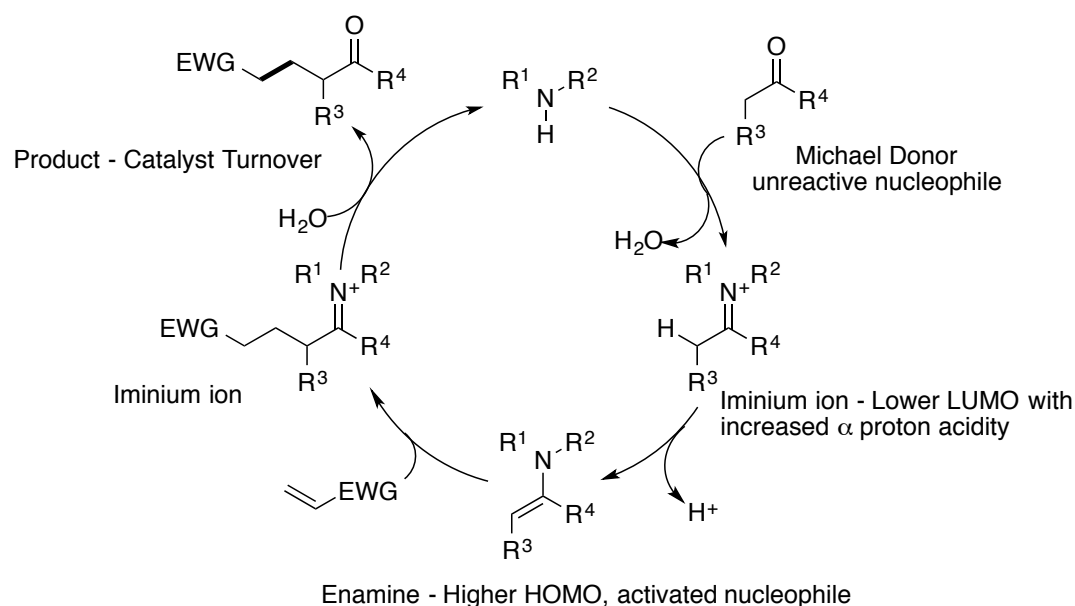


Scheme 1-7. Proline-catalysed Aldol reaction.

It was not until 2000 when List and co-workers re-exploited the same mechanism in their proline-catalyzed direct asymmetric Aldol²⁰ and Mannich reactions.²¹ Inspired by Class 1 aldolase enzymes and aldolase catalytic antibodies where the complex machinery depended on prolines for enzymatic activities,^{22,23} List and co-

workers demonstrated that simple molecules such as proline could efficiently catalyzed aldol reactions of acetone with aldehydes in excellent chemical yields and excellent enantiomeric excess. The authors termed this catalytic principle enamine catalysis.²⁴ This mode of catalysis avoids the use of preformed enolate or silyl enol ether species as the catalyst itself activates the donor. Though developed for aldol reactions, the enolate equivalent (enamine intermediate) could also be in conjugate addition reactions.

The underlying success to the above-mentioned reactions is the formation of an enamine intermediate. General scheme begins with the condensation of a secondary amine with an unreactive nucleophile followed by dehydration, affording an iminium ion bearing a lower LUMO energy with increased α proton acidity. Deprotonation to its enamine form delivers an activated nucleophile with a higher HOMO energy, thus enabling smooth conjugate additions to conjugate acceptors. Hydrolysis of the resultant iminium ion liberates the conjugate adduct and the amine catalyst (Scheme 1-8).²⁵

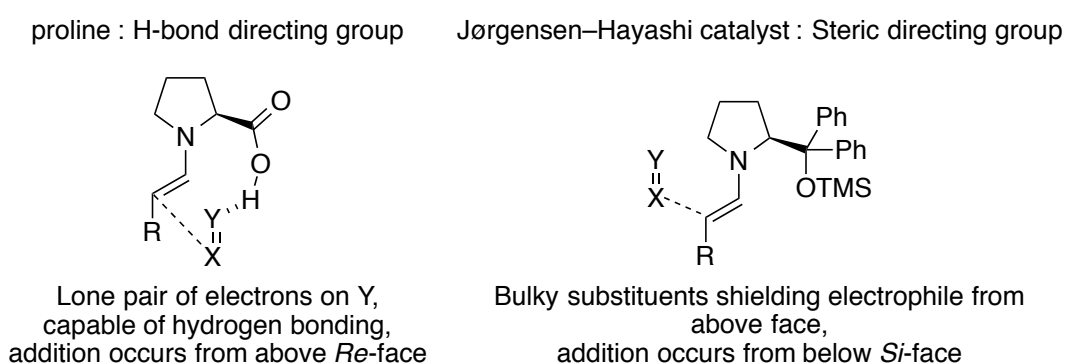


Scheme 1-8. General catalytic cycle of enamine catalysis

In the context of asymmetric conjugate addition, chiral amines are employed as catalyst.²⁶ In such instance, the chirality information resides on the amine and the key intermediate enamine geometry is important for stereochemical induction. It was found that in most cases, the enamine favors the *S-trans*-form. Depending on

the substituents on the chiral amine, electrophiles can approach from different enantiotopic face. For example, when proline was employed as the catalyst, hydrogen bonding was proposed to be responsible for the observed stereochemistry outcome especially for the cases where the electrophile possesses a lone pair of electrons. In the case where Jørgensen–Hayashi catalyst (Diarylprolinol silyl ethers) was employed, steric interaction between the catalyst and electrophile prevents the approach of the electrophile from the same enantiotopic face (Figure 1).^{27,28}

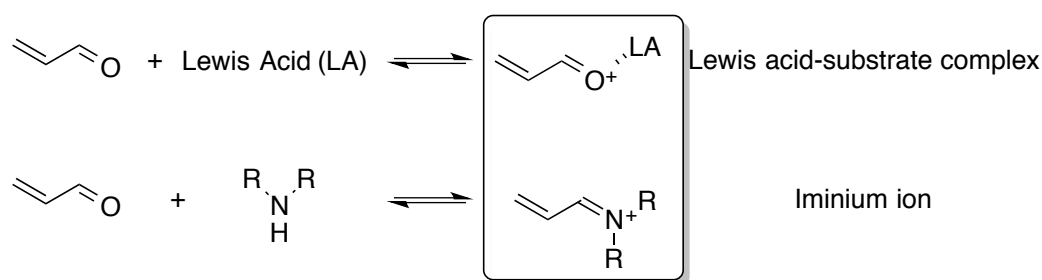
Figure 1. Stereoselectivity strategy



The enamine catalysis is by no means without limitations; enamine formation has to occur, thus limiting the substrate scope to α -unsubstituted aldehydes and ketones.

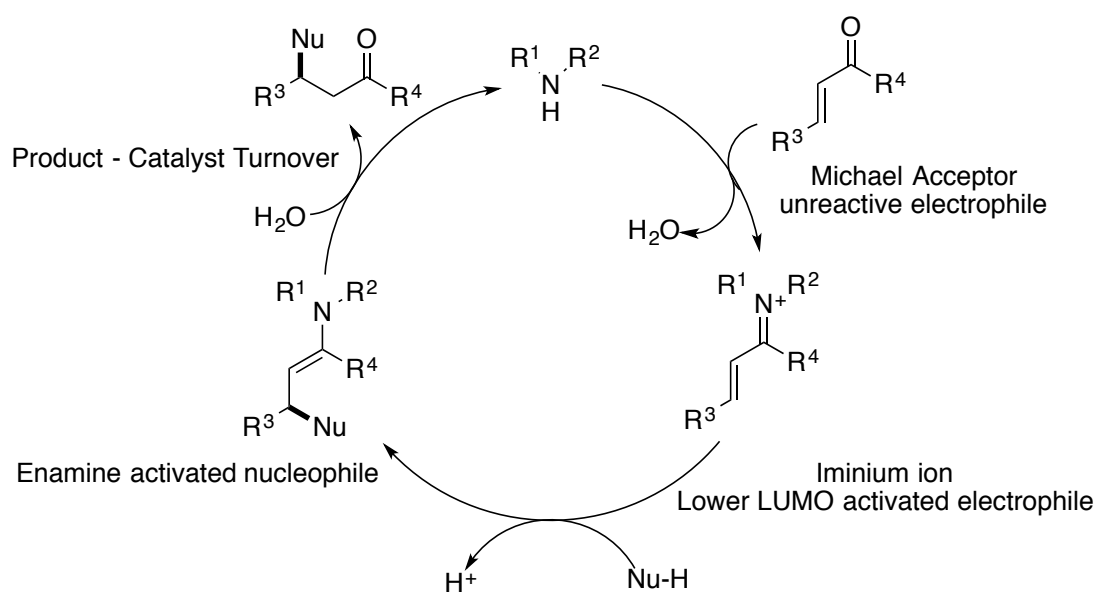
1.3.3. Employing primary or secondary amines for iminium catalyst

Almost simultaneously in 2000, MacMillan and co-workers reported the first organocatalytic activation mode involving an iminium intermediate for Diels-Alder reaction.²⁹ Drawing analogy to Lewis acid activated dienophile in [4+2]-cycloaddition, the authors reasoned that with the formation of an iminium intermediate arising from the condensation and dehydration of secondary amine catalysis with α,β -unsaturated enals, similar LUMO lowering of the α,β -unsaturated iminium ion could be achieved (Scheme 1-9).



Scheme 1-9. Analogy between Lewis acid activation and iminium activation

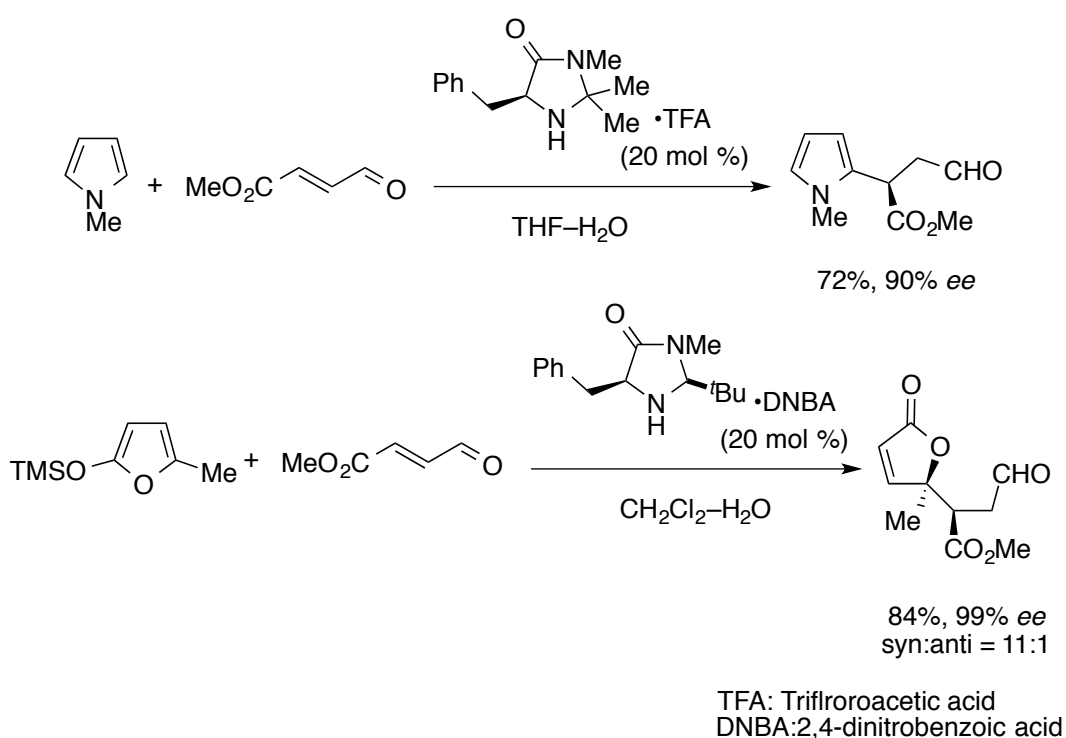
As in the case of enamine catalysis, the concept of LUMO lowering by formation of iminium ion could also be applied on conjugate acceptors in conjugate addition reactions. A general pathway begins with the condensation of a secondary amine with an unreactive α,β -unsaturated enal. Dehydration of the resultant hemiaminal affords an iminium ion that has a lower LUMO energy and thus is activated towards nucleophiles. Conjugate addition by nucleophiles delivers an enamine intermediate that is hydrolyzed to liberate the conjugate adduct and amine catalyst (Scheme 1-10).³⁰



Scheme 1-10. Catalytic Cycle of Iminium Catalysis

Likewise in the context of asymmetric conjugate addition, the iminium intermediate geometry is important for stereinduction. The covalent nature of this catalysis allowed Gilmour and co-workers to isolate and characterize the iminium intermediates with X-ray analysis, confirming the (*E*)-configuration of the iminium

salt.^{31,32} The benzyl group (Scheme 1-11) then efficiently shields the top face from further reactions as proposed by MacMillan. In a series of publications, MacMillan and co-workers demonstrated the first enantioselective organocatalyzed Friedel-Crafts alkylation of pyrroles³³ and indoles³⁴ to α,β -unsaturated enals. It is noteworthy that alkylation of electron-rich pyrrole occurs *via* 1,4-addition pathway on the electrophilic α,β -unsaturated aldehydes as compared to the usual acid-catalyzed 1,2-addition. Switching from heterocyclic compounds to silyl enol ethers, organocatalyzed Mukaiyama-Michael reaction on α,β -unsaturated aldehydes could be achieved (Scheme 1-11).³⁵



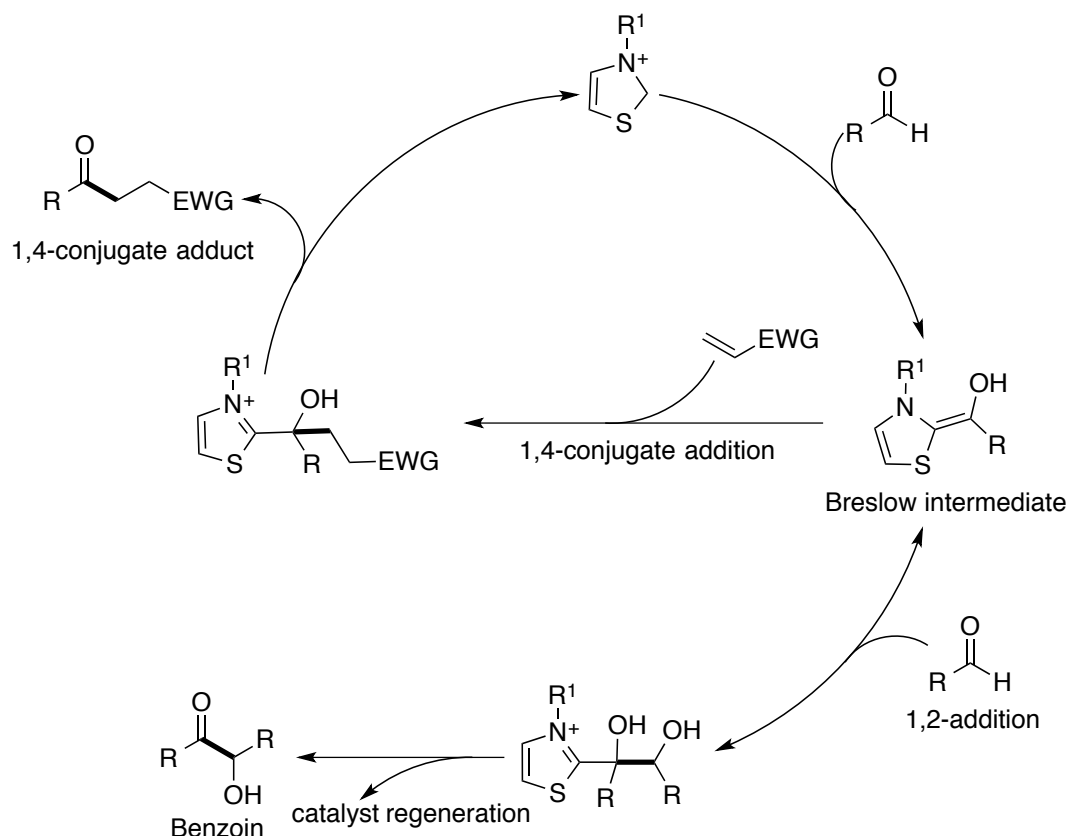
Scheme 1-11. Alkylation of pyrrole and Mukaiyama-Michael with methyl (*E*)-4-oxobut-2-enoate

As with the case of enamine catalysis, the scope of iminium catalysis is only applicable to α,β -unsaturated aldehydes and ketones whereby iminium formation is possible *via* condensation of amine catalyst with the α,β -unsaturated carbonyl compounds.

1.3.4. Employing *N*-Heterocyclic carbenes (NHCs) as organocatalyst - – Stetter Reaction

Numerous efforts had also been invested in the area on *N*-heterocyclic carbenes (NHCs) as organocatalysts in recent years.³⁶ The NHC catalysts are often economical, environmentally benign and remarkably stable under bench top conditions. They are capable of catalyzing an array of reactions including benzoin condensation, Stetter reaction, hydroacylation of alkenes and others. With reference to conjugate donors, NHCs play an important role in the Stetter Reaction. Formally, the Stetter reaction is the conjugate addition between an aldehyde derived nucleophile and a α,β -unsaturated carbonyl compound or nitriles.

Ukai and co-workers first reported that a catalytic amount of thiazolium salts resulted in the dimerization of aldehydes leading to the formation of α -hydroxyketones (Benzoin). Breslow later proposed the mechanism that is generally accepted and provided today's foundations for NHC catalysis.³⁷ The thiazolium catalyst after deprotonation undergoes 1,2-addition to the aldehyde. After proton transfer, a pivotal Breslow intermediate (enamine intermediate) is formed which adds to another molecule of aldehyde and subsequent elimination of the catalyst to furnish the benzoin product. It was known that the benzoin formation (1,2-addition) was reversible, and therefore in the presence of a conjugate acceptor, conjugate adduct (1,4-addition) could be obtained (Scheme 1-12). Such reaction was first reported by Stetter in the mid 1970s and is known as the Stetter Reaction.³⁸



Scheme 1-12. Catalytic cycle for Benzoin formation and Stetter Reaction

In the enantioselective variant of the Stetter reaction where chiral NHC catalysts are employed, synthetic chemists can fine-tune the chiral NHC catalysts for better performance in terms of chemical reactivity and enantio-selectivity by modifying the NHC structure. It was later reported that triazolium-derived NHCs are often superior compared to the thiazolium-derived NHCs for stereoinduction.

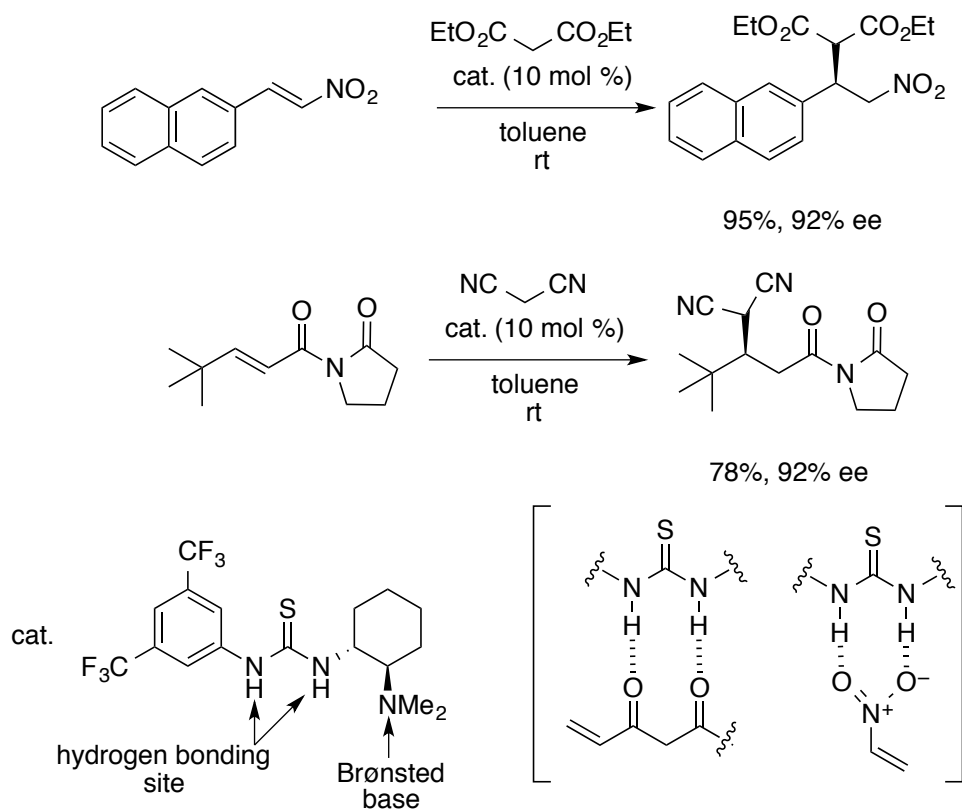
1.3.5. Activation *via* Hydrogen-bonding

In all above described mode of catalysis, hydrogen bonding is present in addition to the main mode of catalysis action.^{39,40,41} The definition of hydrogen bonding is generally accepted as “An $X-H\cdots A$ interaction is called a “hydrogen bond”, if 1. It constitutes a local bond, and 2. $X-H$ acts as a proton donor to A .”⁴² Considered to be significantly weaker in terms of energy due to their non-covalent nature, hydrogen bonding is responsible for many important biological reactions, including the complementary pairing of DNA base pairs and folding of proteins.

In principle, carbonyl's oxygen is considered hard Lewis base site due to the lone pair of electrons. Being the smallest possible hard Lewis acid, the “proton” is an

ideal choice to activate carbonyl moiety at the oxygen site in terms of atom efficiency.⁴³ Moreover, taking into account the presence of multiple, appropriately oriented hydrogen bonding network, a highly ordered transition state can be achieved *via* molecular recognition. The substrates are therefore orientated in such a way allowing smooth reaction, which leads to the lowering of activation energy. The regio- and stereoselectivity of the reaction is ascribed to the highly ordered transition state.

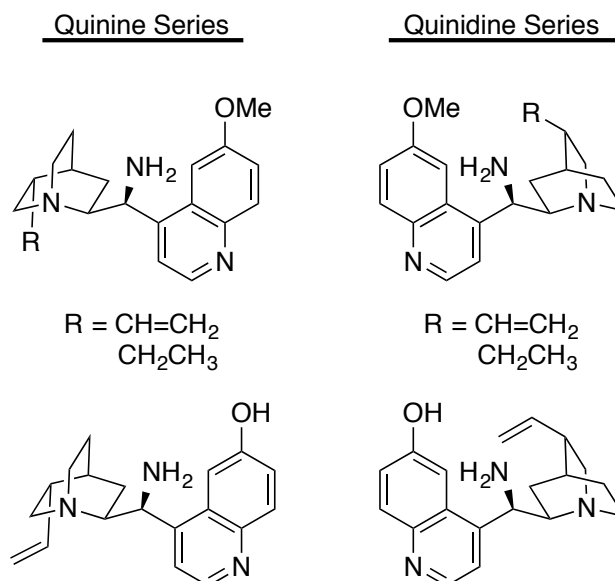
Takemoto and co-workers designed a thiourea-derived catalyst capable of activating both conjugate donor and acceptor for conjugate addition.^{44,45} By incorporating an amine moiety as basic functionality and capitalizing on thiourea's ability to activate imides and nitro functionalities *via* hydrogen bondings, such bifunctional catalyst facilitates a synergistic interaction between the reactants. It is assumed that the weakly basic amine moiety can co-exist with the weakly acidic thiourea moiety in a single molecule without deactivating each other. By installing the amine moiety on the chiral scaffold of the thiourea, the authors envisioned that nucleophilic addition of conjugate donor would occur with excellent enantioselectivity. Indeed, the thiourea catalyst proved to be general for conjugate addition reactions, malonates and malononitriles could be added to nitroalkenes^{46,47} and imides (Scheme 1-13).⁴⁸



Scheme 1-13. Bifunctional thiourea catalyzed conjugate addition

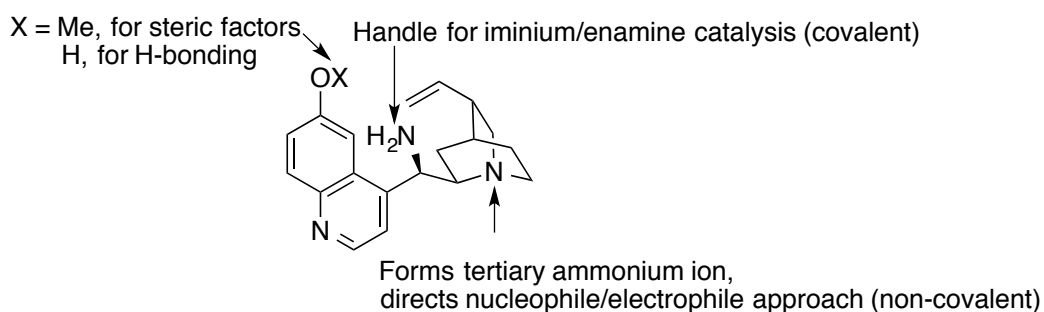
As another privileged scaffold catalyst, the Cinchona alkaloids have emerged successfully in recent years.⁴⁹ These alkaloids which are isolated from the barks of *Cinchona officinalis* can be classified into two classes; the Quinine series and the Quinidine series (Figure 2). They constitute a *pseudo*-enantiomeric pair, allowing synthetic chemist access to both antipodes of the chiral products.⁵⁰

Figure 2. Classifications of Cinchona alkaloids



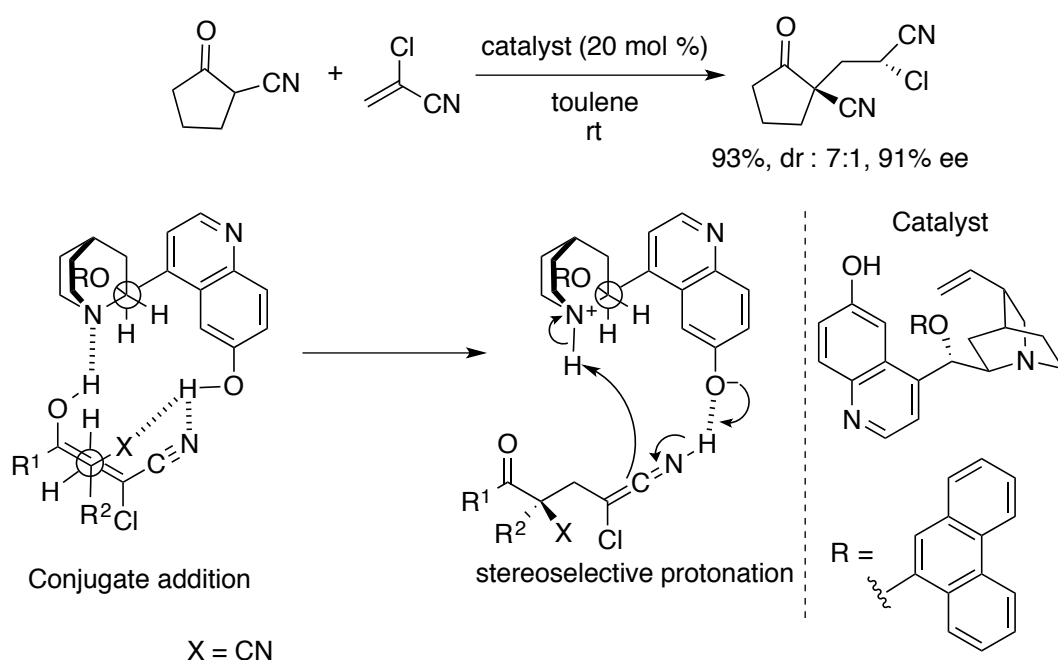
These alkaloids though small are complex molecules. In solution, they are flexible and can adopt several conformations. The conformation changes can be control *via* solvent change or protonation of the tertiary amine.⁵¹ In addition, it comprises of a quinuclidine that can function as a general Brønsted base. The resultant protonated tertiary ammonium in turn can serve to direct the approach of either nucleophiles or electrophiles, or serve as a hydrogen donor to substrates. The primary amino moiety on C9 can serve as a handle for nucleophilic aminocatalysis. The aryl alcohol serves as a hydrogen donor to substrates for hydrogen bonding. In the case of aryl methyl ether, steric interaction is desired between the catalyst and the substrates (Figure 3).⁵²

Figure 3. Possible sites for catalysis



Conformational Changes by solvent change, protonation of tertiary amine

Deng and co-workers disclosed that a quinidine-derived catalyst could effect the conjugate addition of α -cyanoketones and β -ketoesters to 2-chloroacrylonitrile *via* an asymmetric tandem conjugate addition-protonation sequence. The authors proposed that *via* a network of hydrogen bondings, a stereoselective conjugate addition is achieved followed by a stereoselective protonation of the transient enolate. The conjugate adducts are obtained in excellent chemical along with good diastereoselectivity and excellent enantiomeric excess. It is noteworthy that the enantiomer product could also be accessed by using the quinine-derived catalyst with comparable chemical yields, diastereoselectivity and enantiomeric excess (Scheme 1-14).^{53,54}



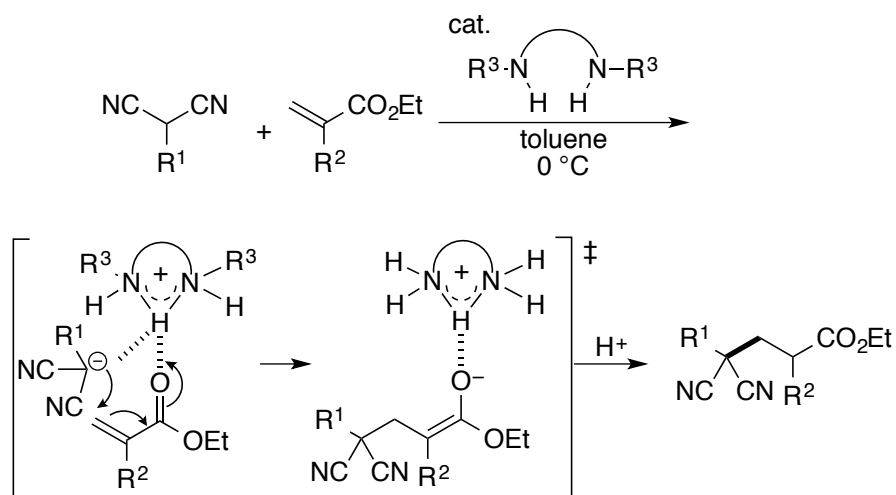
Scheme 1-14. Conjugate addition catalyzed by a quinidine-derived derivative

1.4. Summary and outlook

Taken above mentioned concepts altogether, it is in no doubt that functionalization of alkenes *via* addition reactions are of great importance and simplicity. Apart from the well-established transition metal catalyzed reactions, activation strategies based on purely organic molecules are offering synthetic chemists new perspectives on alkene functionalization.

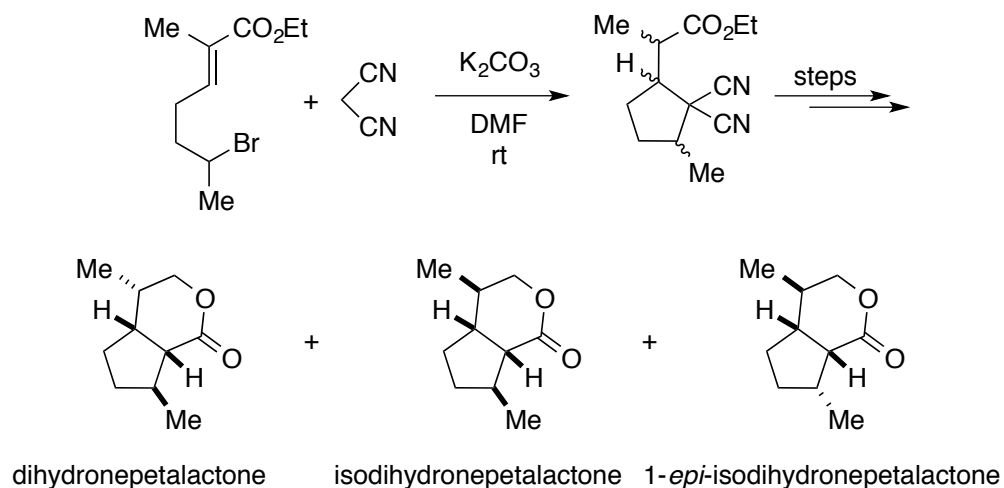
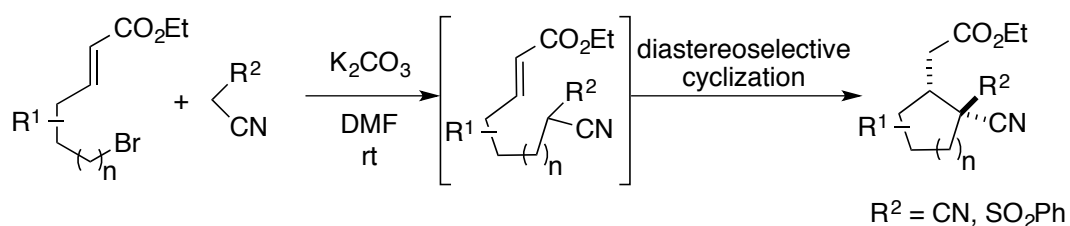
Bearing in mind the importance of nucleophilic functionalization of alkenes, the author shall in this dissertation describes his work on carbo- and amino-functionalization of alkenes *via*

- the conjugate addition of carbon nucleophiles to acrylic derivatives catalyzed by organic diamines (Chapter 2).



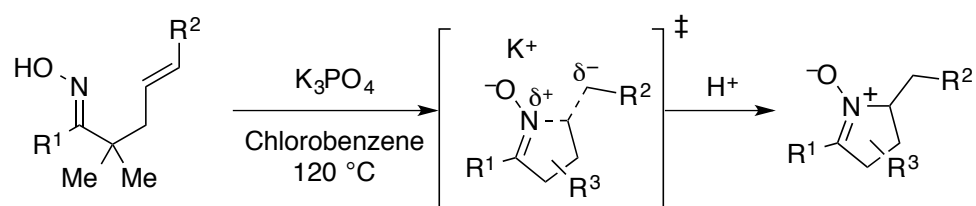
Scheme 1-15. Conjugate addition mediated by organic diamines

- domino S_N2 -conjugate addition sequence for the diastereoselective synthesis of carbocyclic compounds. Further facile molecular transformation was also presented that could deliver bi/tricyclic lactones including biologically active natural products, dihydronepetalactone, isodihyronepetalactone and 1-*epi*-isodihyronepetalactone (Chapter 3)



Scheme 1-16. Domino $\text{S}_{\text{N}}2$ -conjugate addition sequence

- inorganic base-mediated hydroamination of alkenyl oximes for synthesis of cyclic nitrones. DFT calculations of the reaction pathway suggested that the present hydroamination could proceed *via* unprecedented nucleophilic amination of unactivated alkene by the oxime nitrogen, the transition state of which is stabilized by ionic interaction of the metal cation such as K^+ on the oxime oxygen and negatively charged alkene moiety (Chapter 4).



Scheme 1-17. Inorganic base mediated hydroamination of alkenyl oximes

1.5. References and notes

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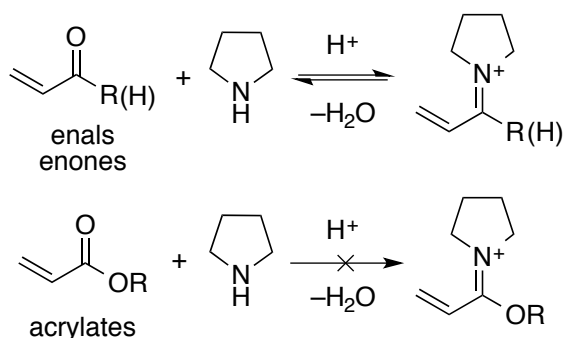
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Chapter 2. Organic diamine-catalyzed conjugate addition of active-methine compounds towards acrylic derivatives

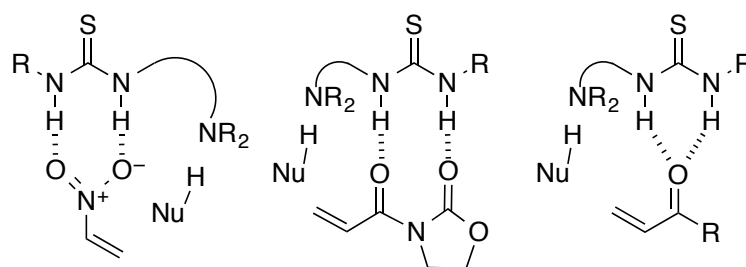
2.1. Introduction

The conjugate addition of carbon nucleophiles to electron-deficient alkenes represents one of the most straightforward and important carbon-carbon bond formation reactions in organic synthesis. Having described in the preceding chapter, aminocatalysis i.e. enamine/iminium catalysis, α,β -unsaturated enals and enones are excellent partners due to their ability to condense with the amine catalyst.^{1,2,3} Despite the successful development and understanding of the operating mechanism, such modes of catalysis are not applicable to acrylic derivatives as the corresponding iminium intermediates cannot be formed (Scheme 2-1).



Scheme 2-1. Formation of reactive iminium ion intermediate from enals and enones

Similarly with the development of bifunctional thiourea catalysts, nitroalkenes and imides have emerged as efficient conjugate acceptors *via* hydrogen bonding activation. It is accepted that activation of nitroalkenes and imides operates *via* a double hydrogen bonding orientation to both the thiourea's N-H bonds. In principle, hydrogen bonding activation is comparable to metal-centered Lewis acid activation. By virtue of hydrogen bonding, electronic density from the electrophile is further lowered, resulting in the decrease of its LUMO energy and therefore becoming activated towards conjugate donors (Scheme 2-2).^{4,5,6}

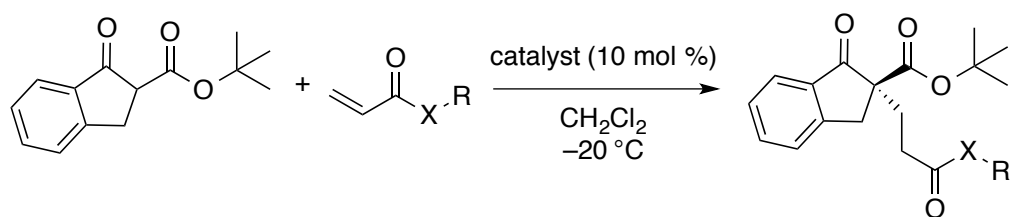


Scheme 2-2. Hydrogen bonding coupled with Brønsted base functionality by bifunctional thioureas

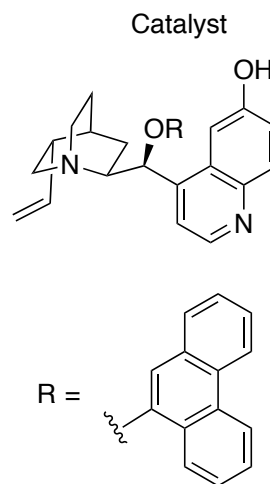
The discovery and understanding of the underlying operating principles of each catalysis led to the significant increase of reports on conjugate addition reactions, although the utilization of readily available acrylic derivatives for conjugate acceptors remain relatively scarce. There remains a wide potential for one to develop an activation mode for the acrylic derivatives.

2.2. Examples of conjugate addition where acrylic derivatives are employed as conjugate acceptors

As the first example of organo-catalyzed conjugate addition involving acrylate derivatives as an acceptor, Dixon and Rigby disclosed that various functionalized acrylates such as 1-naphthylthioacrylate, thioesters, *N*-acryloyl pyrrole and aryl acrylates were suitable partners in conjugate additions by β -keto esters mediated by cinchona-derived catalyst (Scheme 2-3). However in sharp contrast, no conjugate adduct was observed when simple acrylates such as ethyl acrylate was employed.⁷

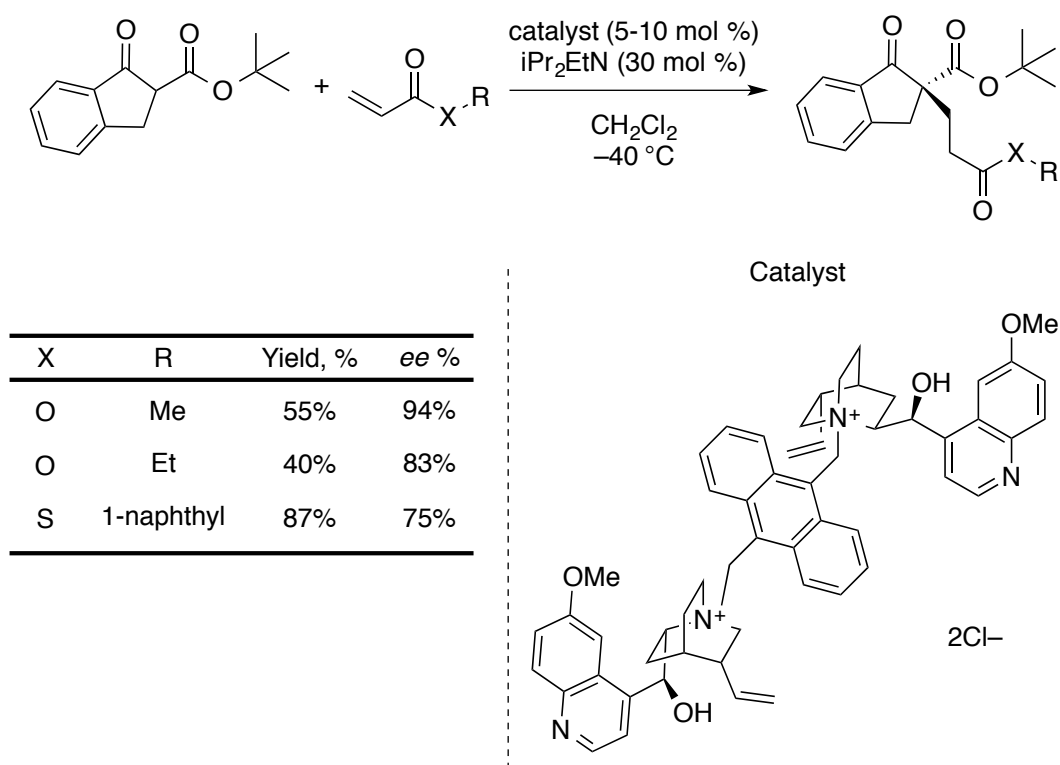


X	R	Yield, %	ee %
S	1-naphthyl	83%	96%
S	2-naphthyl	75%	95%
S	phenyl	83%	95%
O	1-naphthyl	83%	94%
O	2-naphthyl	76%	94%
O	phenyl	78%	94%
	N-pyrrole	96%	95%
O	Et	0	—
S	Et	0	—



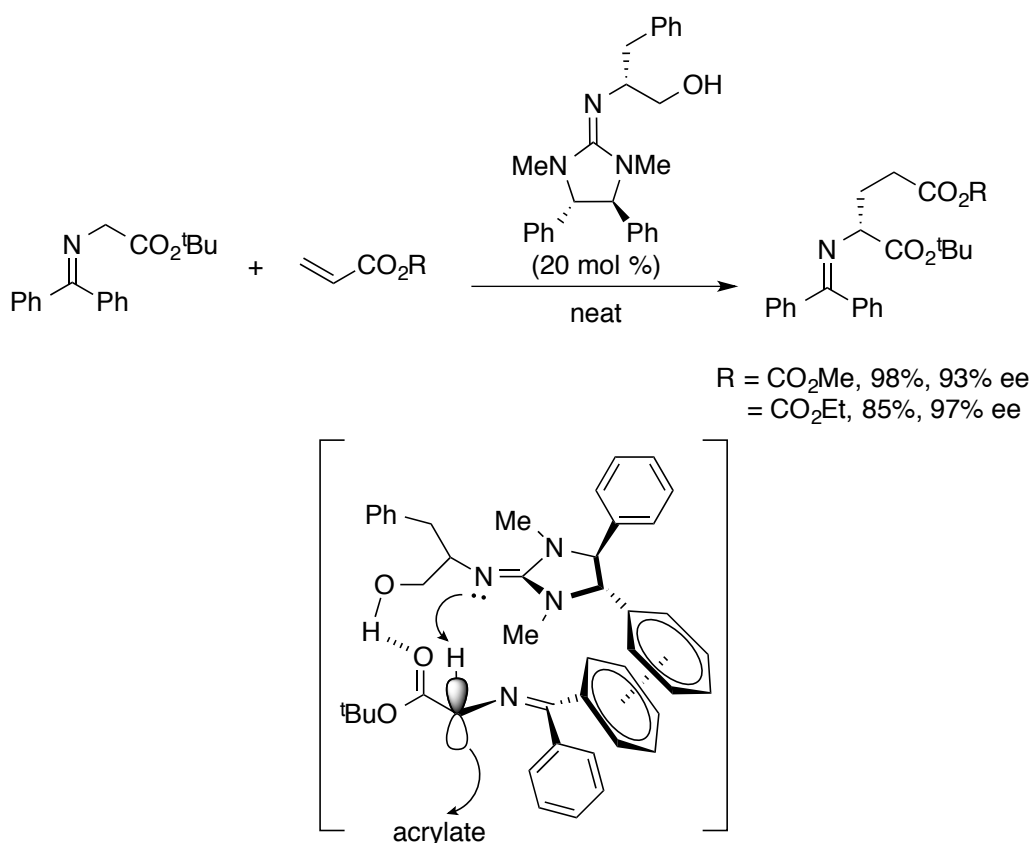
Scheme 2-3. Conjugate addition of β -keto esters to functionalized acrylates

Nájera and co-workers subsequently realized the conjugate addition of β -keto esters to simple acrylates, such as methyl and ethyl acrylates, albeit in lower yields in the presence of their dimeric Cinchona-derived ammonium salts (Scheme 2-4).⁸



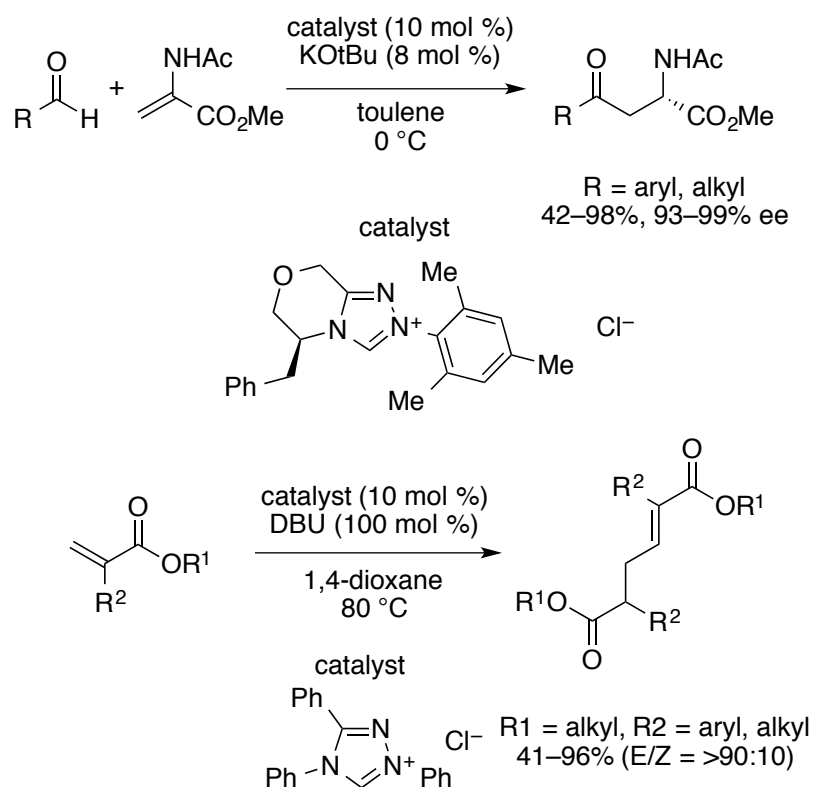
Scheme 2-4. Conjugate addition of β -keto esters to simple acrylates

Separately in a brief communication, Ishikawa and co-workers revealed that in the presence of a catalytic amount of cyclic guanidine, glycine derivative could be added in a conjugate fashion to simple acrylates (Scheme 2-5).⁹ The authors proposed that the cyclic guanidine functions as a superbases for the deprotonation of the pronucleophile, while the stereoinduction depended on 1) the π - π stacking of the aryl rings between the conjugate donor and catalyst, 2) the hydrogen bonding between the oxygen of the carbonyl group of the conjugate donor and the hydroxyl group of the catalyst.



Scheme 2-5. Conjugate addition of glycine derivative to simple acrylates

Much success on the conjugate addition to acrylates has been reported in the field of the *N*-heterocyclic carbene (NHC) catalysis in the Stetter reaction. The research group led by Glorius disclosed the synthesis of α -amino acid derivatives *via* Stetter reaction of aldehydes with *N*-acylamido acrylate involving a diastereoselective protonation step.¹⁰ The group also reported the Rauhut-Currier reaction catalyzed by the NHC, in which the dimerization of various acrylates could be realized (Scheme 2-6).¹¹



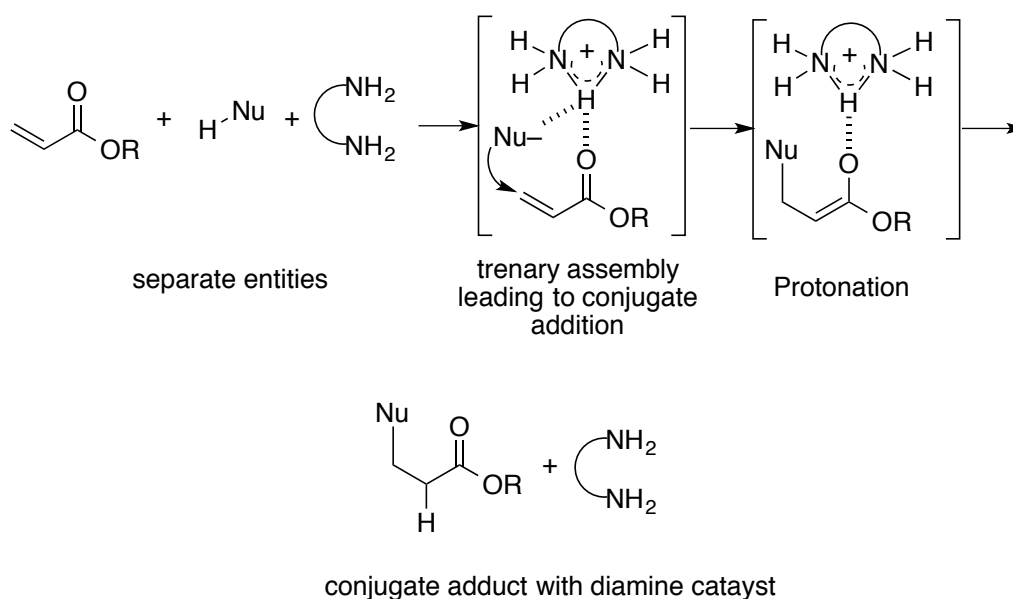
Scheme 2-6. Glorius's work on Stetter Reaction and Rauhut-Currier Reaction involving acrylates

2.3. Working hypothesis

The author envisaged that a dual activation is required in order to achieve smooth conjugate addition of carbon nucleophiles to the less reactive acrylate derivatives under milder reaction conditions, where generation of the carbon nucleophile by deprotonation should be coupled with simultaneous electrophilic activation of the acrylate acceptor within proximity. Such concept is best described by bifunctional thiourea catalysts whereby the thiourea moiety activates the acceptor *via* hydrogen bondings and an amine moiety within the catalyst serves as a Brønsted base for deprotonation of carbon nucleophiles. In such mode of action, the carbon nucleophiles are brought within proximity towards the acceptor.

The author hypothesized that organic diamines could be employed as base-catalyst to achieve this concept (Scheme 2-7). The Brønsted diamine base, which is catalytically inactive, would undergo an acid-base reaction with the pronucleophile such as active methine compounds, resulting in the formation of a cooperatively bonded single proton cationic complex. This acid-base complex would comprise of a positive charge delocalized within the ammonium salt and a

negative charge residing on the carbon nucleophile. The positively charged ammonium could then serve as the active catalyst *via* hydrogen bonding to activate the unreactive acrylate. Due to electrostatic interaction, the negatively charged nucleophile would be within proximity and therefore smooth conjugate addition could be realized. Protonation of the resulting enolate would liberate the diamine as pre-catalyst along with the conjugate adduct.



Scheme 2-7. Proposed simultaneous activation of acrylates and pronucleophiles

2.4. Results and discussion

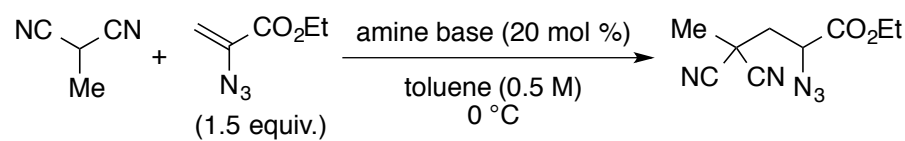
2.4.1. Optimization

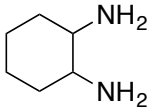
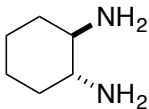
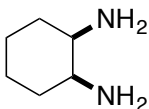
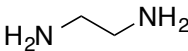
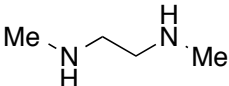
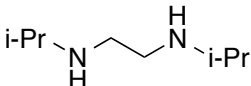
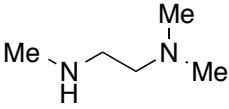
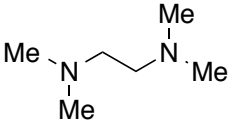
Having above described hypothesis, the author began optimization studies using 2-methylmalononitrile (**2-1a**) and ethyl 2-azidoacrylate (**2-2a**) with various organic diamines to obtain α -azido ester **2-3aa**. The α -azido ester derivatives obtained from the reaction could provide promising access to useful α -amino acids.

As expected, it was found that 1,2-diaminocyclohexanes **2-A** (*cis/trans* mixture), **2-B** (*trans*) and **2-C** (*cis*) exhibited excellent catalytic reactivity towards the conjugate addition, affording ethyl 2-azido-4,4-dicyanopentanoate (**2-3aa**) in good yields (entries 1-3). Among acyclic types of diamines examined (entries 4-8), *N,N'*-dimethylethylenediamine (DMEDA) (**2-E**) also proved efficient for the conjugate addition reaction (87% yield, entry 5), whereas the reaction was sluggish when *N,N,N',N'*-tetramethylethylenediamine (TMDEA) (**2-H**) having two tertiary

amine motifs was employed (entry 8). By increasing a methylene linker of the diamine catalyst, the reaction with propane-1,3-diamine (**2-I**) was remarkably improved with shorter reaction time resulting in the formation of **2-3aa** in 98% yield within 4 h (entry 9). Further increment of another methylene linker to butane-1,4-diamine (**2-J**) led to a reduction in the yield (entry 10). Employing polyamine such as triethylenetetramine (**2-K**) dramatically reduced the reaction time to 0.5 h, however the yield was moderate (entry 11). Utilizing a *trans*-1,2-diaminocyclohexane-derived primary thiourea **2-L** unfortunately did not promote the reaction, providing **2-3aa** only in 28% yield even after 10 days (entry 12). It was noteworthy that the utilization of a series of alkyl monoamines such as triethylamine, diisopropylethyl amine (Hunig's base) as well as aryl diamines such as aniline, 1,2-diaminobenzene, and 1,8-diaminonaphthalene also known as proton sponge did not catalyzed the reaction. Such results lend support to the hypothesized dual role of organic diamine catalysts. The ammonium cation generated by deprotonation of pronucleophiles might function as a hydrogen-bonding donor catalyst to electrophilically activate the acrylates.

Table 2-1. Diamine-Catalyzed Conjugate Addition of 2-Methyl-malononitrile (**2-1a**) and Ethyl 2-Azidoacrylate (**2-2a**)^a



entry	amine base	time	yield/% ^b
1	 2-A	13h	80%
2	 2-B	13h	78%
3	 2-C	9h	83%
4	 2-D	24h	38%(19%) ^c
5	 2-E	25h	87%
6	 2-F	36h	75%
7	 2-G	36h	77%
8	 2-H	24h	10%(15%)

continued...

9		4h	98%
	2-I		
10		4h	65%
	2-J		
11		0.5h	68%
	2-K		
12c		10 days	28%(26%) ^c
	2-L^d		
Other amine bases that resulted in no reaction after 48 h			

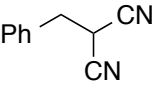
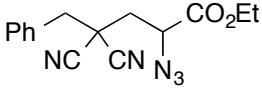
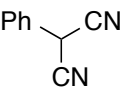
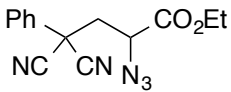
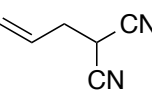
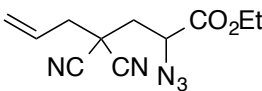
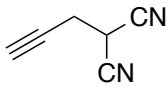
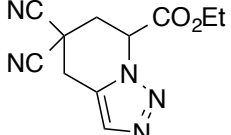
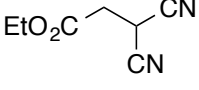
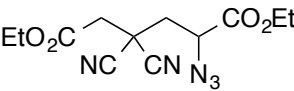
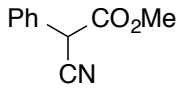
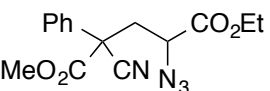
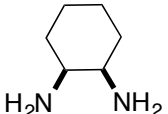
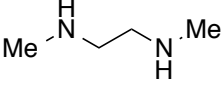
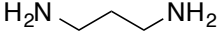
^a Reactions were performed on the scale of 0.5 mmol of **2-1a** with 1.5 equiv. of **2-2a** in toluene (1 mL) at 0 °C under a N₂ atmosphere. ^b Isolated yields. ^c Recovery yields of **2-1a**. ^d A racemic form was utilized.

2.4.2. Examination of the scope of conjugate donors

Having confirmed that organic diamines are capable of catalyzing the desired conjugate addition, the author next surveyed a variety of pronucleophiles as conjugate donors to ethyl 2-azidoacrylate (**2-2a**) (Table 2-2). As a substituent at C2 of malononitrile, benzyl, phenyl and allyl moieties could be installed without affecting the reactivity of the conjugate addition (entries 1-4). In the case of 2-propargylmalononitrile (**2-1e**), the desired conjugate addition occurred followed by a one-pot tandem intramolecular azide-alkyne cycloaddition to afford bicyclic 1,2,3-triazole **2-4ea** in moderate yield (entry 4). The reaction of malononitrile bearing an ethoxycarbonyl functionality **2-1f** occurred smoothly to give the

corresponding α -azido ester **2-3fa** in excellent yields (entry 5). Utilization of methyl 2-cyano-2-phenylacetate (**2-1g**) required a longer reaction time, affording **2-3ga** in good yields with an almost 1:1 diastereoselectivity (entry 6). It was found that different organic diamines were required for optimum results and individual reactions have been optimized by various promising diamine catalysts.

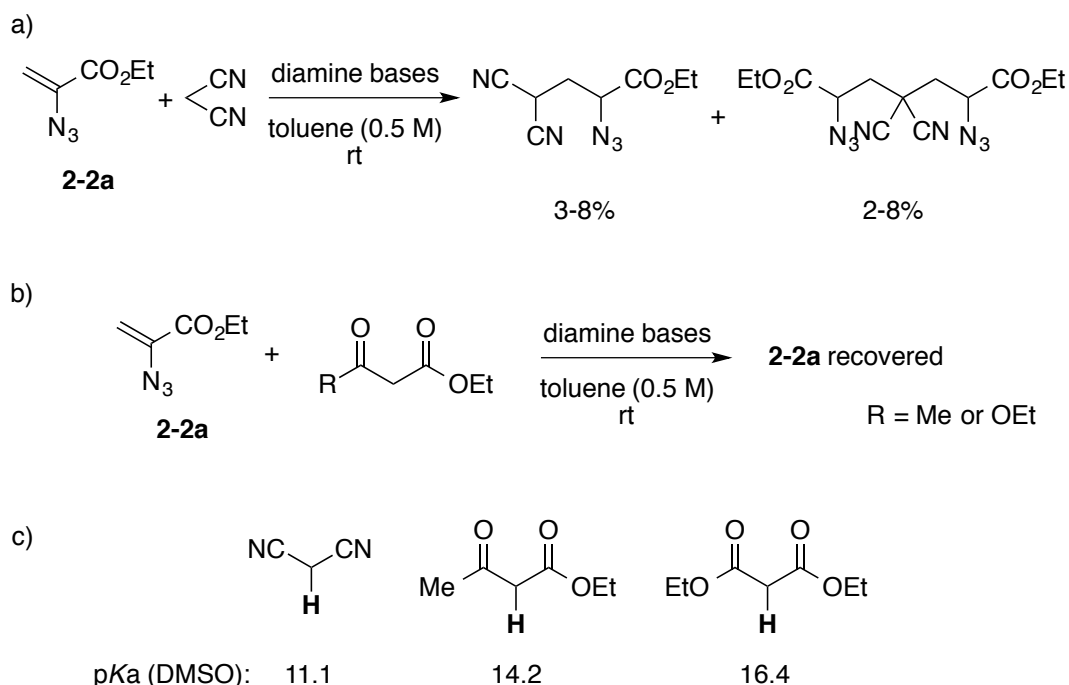
Table 2-2. Diamine-Catalyzed Conjugate Addition to Ethyl 2-Azido Acrylate (**2-2a**)^a

nucleophiles +  $\xrightarrow[\text{toluene (0.5 M), 0 }^{\circ}\text{C}]{\text{diamine base (20 mol \%)}}$ conjugate adduct			
entry	nucleophiles	conjugate adduct	diamine base, yield, ^b time
1	 2-1b	 2-3ba	2-C 72%, 12 h 2-E 75%, 32 h 2-I 86%, 3 h
2	 2-1c	 2-3ca	2-C 82%, 25 h 2-E 75%, 25 h 2-I 82%, 5 h
3	 2-1d	 2-3da	2-C 70%, 25 h 2-E 70%, 24 h 2-I 80%, 7 h
4	 2-1e	 2-4eac^c	2-C 48%, 5 h 2-E 60%, 5 h 2-I 55%, 1 h
5	 2-1f	 2-3fa	2-C 95%, 3 h 2-E 87%, 5 h 2-I 98%, 4 h
6	 2-1g	 2-3ga^d	2-C 77%, 25 h, dr: 40:60 2-E 82%, 25 h, dr: 53:47 2-I 73%, 28 h, dr: 38:62
diamine base  2-C  2-E  2-I			

^a Reactions were carried out on the scale of 0.5 mmol of **2-1** and 1.5 equiv. of vinyl azide **2-2a** in toluene (1 mL) at 0 °C under a N₂ atmosphere. ^b Isolated yields. ^c The reaction mixture was stirred at 0 °C until **2-1e** was consumed, before being heated at 40 °C for 10 h. ^d Diastereomer ratio was determined by ¹H NMR analysis. The relative stereochemistry was not determined.

The reaction of **2-2a** with malononitrile was made complicated by the formation of di- and mono-addition adducts as well as polymerization of acrylate derivatives

(Scheme 2-8-a). Pronucleophilicities derived from 1,3-diketones and malonate esters resulted in no reactions under the present conditions (Scheme 2-8-b), probably due to the lower pK_a of malononitrile derivatives (Scheme 2-8-c).¹²



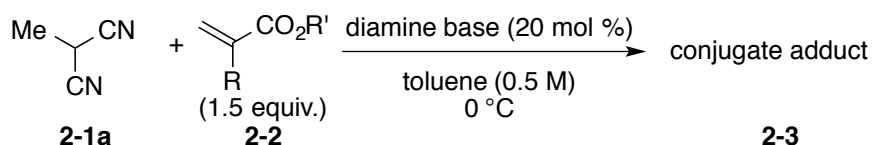
Scheme 2-8. Conjugate addition of malononitrile/malonates/ β -keto esters with **2-2a**

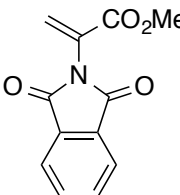
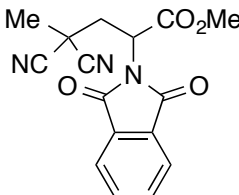
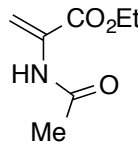
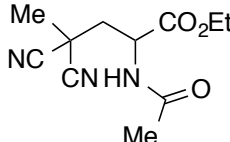
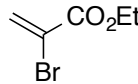
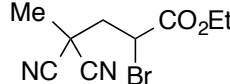
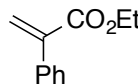
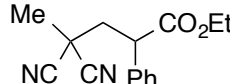
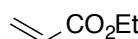
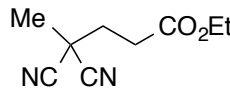
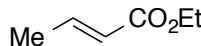
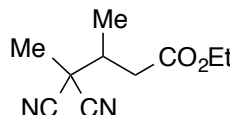
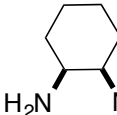
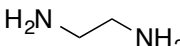
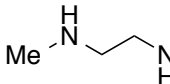
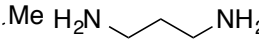
2.4.3. Examination of the scope of conjugate acceptors

Attentions were next focused on the scope of the acrylate derivatives for conjugate addition by 2-methyl-malononitrile (**2-1a**) (Table 2-3). As precursors of α -amino acid derivatives, methyl 2-phthalimidoacrylate (**2-2b**) and ethyl 2-acetamidoacrylate (**2-2c**) underwent the desired conjugate addition using ethylenediamine (**2-D**) and *N,N'*-dimethylethylenediamine (**2-E**) respectively (entries 1 and 2). In the case of ethyl 2-bromoacrylate (**2-2d**), ethyl 2-phenylacrylate (**2-2e**) and ethyl acrylate (**2-2f**), propane-1,3 diamine (**2-I**) proved to the best catalyst providing the conjugate adducts in 96%, 98% and near quantitative yields, respectively (entries 3-5). β -substituents on acrylate derivatives proved deleterious for the conjugate addition reaction, as in the case of ethyl crotonate (**2-2g**), the desired conjugate addition was sluggish providing ethyl 4,4-dicyano-3-methylpentanoate (**2-3ag**) in 26% yield even after 7 days (entry 6). Similar to the screening of conjugate donors, different organic diamines catalyzed

the conjugate addition with different efficiencies. Optimization of individual reactions has been undertaken with various promising organic diamines.

Table 2.3. Diamine-Catalyzed Conjugate Addition of 2-Methylmalononitrile (**2-1a**) to various Acrylates **2-2^a**



entry	nucleophiles	conjugate adduct	diamine base, yield, ^b time	
1	 2-2b	 2-3ab	2-C 85%, 25 h 2-D 87%, 25 h 2-E 45%, 25 h 2-I 66%, 31 h	
2	 2-2c	 2-3ac	2-C 34%, 25 h 2-D 46%, 12 h 2-E 58%, 24 h 2-I 48%, 8 h	
3	 2-2d	 2-3ad	2-C 55%, 33 h 2-D 58%, 33 h 2-E 6%, 25 h 2-I 96%, 7 h	
4	 2-2e	 2-3ae	2-C 97%, 6 h 2-D 91%, 6 h 2-E 97%, 9 h 2-I 98%, 7 h	
5	 2-2f	 2-3af	2-C 95%, 9 h 2-D 95%, 20 h 2-E 54%, 25 h 2-I 99%, 3 h	
6	 2-2g	 2-3ag	2-C 26%, 7 days 2-D 21%, 7 days 2-E 0%, 7 days 2-I 10%, 7 h	
diamine base	 2-C	 2-D	 2-E	 2-I

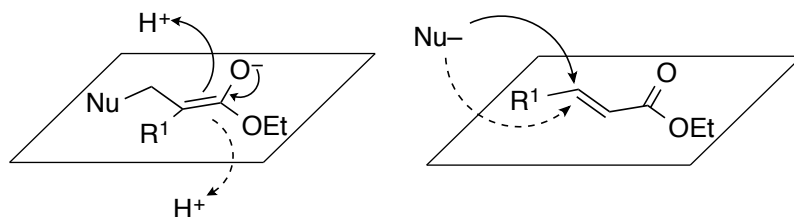
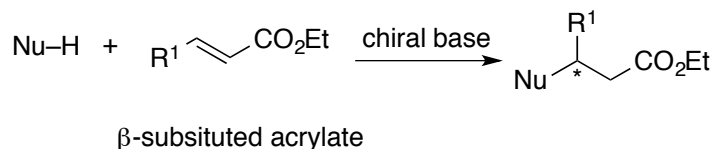
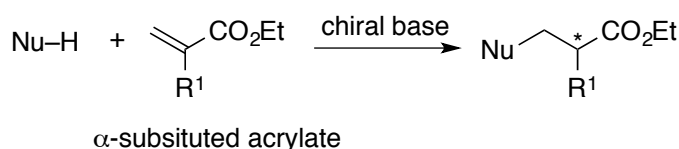
^a Reactions were carried out on the scale of 0.5 mmol of **2-1a** and 1.5 equiv. of acrylate **2-2** in toluene (1 mL) at 0 °C under a N₂ atmosphere. ^b Isolated yields

2.4.4.1. Preliminary efforts towards asymmetric induction with chiral diamine catalysts

It was found that in the process of defining the scope and limitation of the conjugate addition reaction, different organic diamines exhibited varying efficiencies with different substrates. It appears that the conjugate addition was sensitive to the structure and the amine moieties of the diamine catalyst. Such observations indicated the potential development to undertake the design and synthesis of a suitable chiral organic diamine for asymmetric version of the conjugate addition.

The conjugate addition reaction itself breaks a carbon-carbon double bond while constructing a carbon-carbon bond and a carbon-hydrogen bond. Considering α -substituted acrylates as conjugate acceptors, an α -stereogenic center will be created through the conjugate addition. From the mechanistic perspective, the construction of the α -stereogenic center arises from the protonation of the transient enolate (Scheme 2-9). While employing β -substituted acrylates as conjugate acceptors, a β -stereogenic center on the conjugate adduct will be created from the conjugate addition. The β -stereogenic center arises due to the enantiotopic facial approach of the nucleophiles (Scheme 2-9).

With reference to substrate screenings, it was found that β -substituted acrylate **2-2g** serves as a poor conjugate acceptor under the present reaction conditions. On the other hand, α -substituted acrylates **2-2a-e** worked well for the conjugate addition. Based on these backgrounds, the author considers the construction of α -stereogenic center arising from α -substituted acrylates.



Enantioselective protonation Enantioselective approach of nucleophile

Scheme 2-9. Mechanistic considerations of transition states leading to different stereoisomers

2.4.4.2. Enantioselective/Diastereoselective protonation of enolate

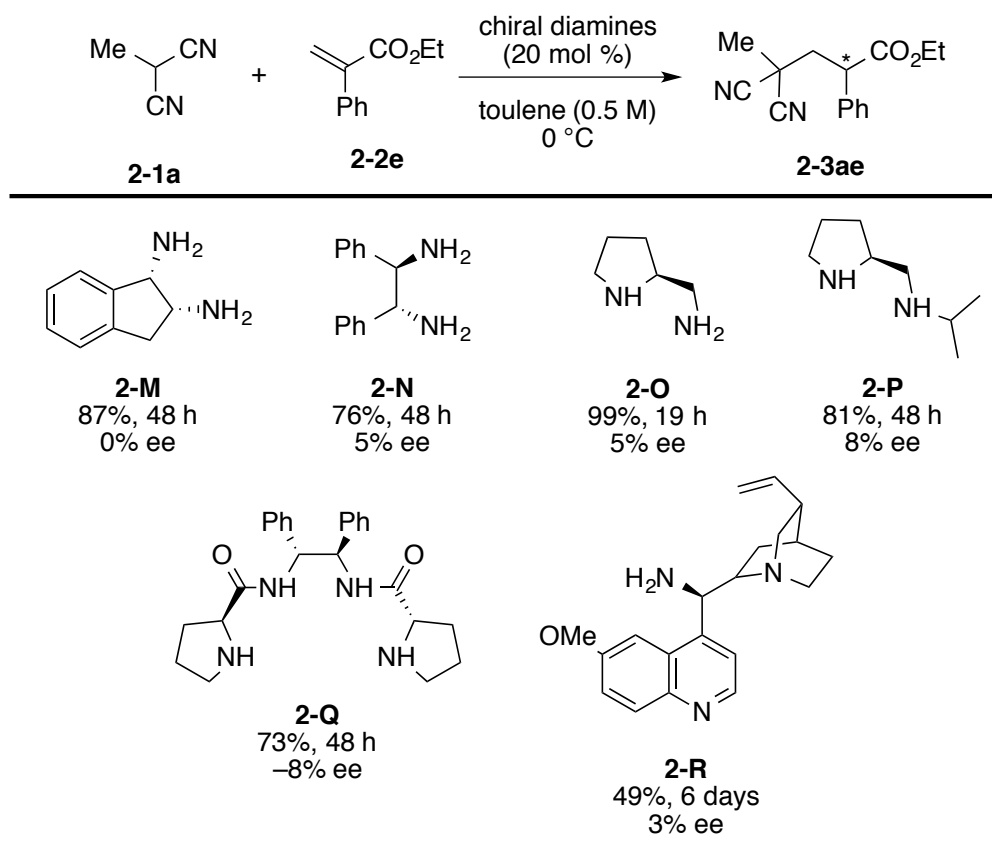
Enantioselective protonation of prochiral enolate offers the most straightforward and fundamental method for generating α -stereogenic tertiary carbonyl compounds.¹³ Taking into account the planar nature of the enolate, enantioselective protonation should occur from one of the enantiotopic faces. Seemingly of the fundamental simplicity, protonation of enolates presents unique challenges. The proton being the smallest atom is highly mobile and therefore it is difficult to ensure protonation occurs selectively from one enantiotopic face. This is complicated by the large electronegativity between the positive charged proton and the negative charged enolate that causes a very rapid protonation process, significantly increasing the background reactions.¹⁴ Moreover, it should be noted that even if protonation of the transient enolate occurs selectively, racemization could still occur before product isolation in cases when strong base are utilized. This is circumvented by carefully matching of pK_a of proton donor and product.¹¹

Taken altogether above considerations, the author next considered the feasibility of installation of an α -chiral center for the conjugate addition of 2-methyl-malononitrile (**2-1a**) to ethyl 2-phenylacrylate (**2-2e**) by employing chiral diamine catalysts (Scheme 2-9). The chiral diamine catalyst would first function as a

Brønsted base for the deprotonation of pronucleophiles. Similar proposed activation of acrylate by hydrogen bonding by the chiral ammonium diamine should facilitate conjugate addition to provide the transient enolate. Lastly the author postulate that the chiral ammonium diamine to serve as chiral Brønsted acid, protonating the enolate with an enantioselective manner.

However, when the reaction was catalyzed by (1*S*,2*R*)-2,3-dihydro-1*H*-indene-1,2-diamine (**2-M**),¹⁵ no enantiomeric excess was observed even though the desired conjugate addition occurred to provide good yields of **2-3ae**. Next, commercially available (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine (**2-N**)^{16,17} was employed, that resulted in generation of the product with 5% *ee*. Screening through proline-derived diamines, (*S*)-pyrrolidin-2-ylmethanamine (**2-O**) exhibited excellent catalytic reactivity providing **2-3ae** in near quantitative yields, while the enantioselectivity was insignificant (5% *ee*). Switching from primary amine to secondary amine, (*S*)-*N*-(pyrrolidin-2-ylmethyl)propan-2-amine (**2-P**)¹⁸ catalyzed the conjugate addition in good yields with a slight increase of enantiomeric excess (8% *ee*). Interestingly, when *C*₂-symmetric bisprolinamide **2-Q**¹⁹ was employed, the conjugate adduct showed a reverse chiral induction (-8% *ee*). Disappointingly, the reaction catalyzed by diamine **2-R** derived from quinidine²⁰ was very sluggish providing **2-3ae** in 49% with 3% *ee* after 6 days.

Although synthetically usefully enantiomeric excess could not be obtained, these results likely support the working hypothesis, in which the conjugate addition is achieved *via* the interaction of the acid-base complex derived from the pronucleophile and the diamine base with the acrylate.



^a Reactions were carried out on the scale of 0.5 mmol of **2-1a** and 1.5 equiv. of **2-2e** in toluene (1 mL) at 0 °C under a N₂ atmosphere. Isolated yields, enantiopurity was determined by chiral HPLC

Scheme 2-10. Enantioselective induction using chiral diamines^a

2.5. Conclusion

In summary, this chapter disclosed that various organic diamines are capable of catalyzing intermolecular conjugate addition of α -cyano active methine nucleophiles to various acrylate derivatives. Preliminary investigations employing chiral diamines towards the effort for the construction of α -stereogenic center on the conjugate adduct were also presented. The key to the success of the conjugate addition lies in the use of organic diamines. The organic diamine is expected to first function as the Brønsted base for deprotonation of pronucleophiles. The protonated diamine species then serves as a Lewis acid to activate the acrylate *via* hydrogen bondings. Smooth conjugate addition followed by protonation of the enolate formed the conjugate addition product along with regeneration of the diamine catalyst.

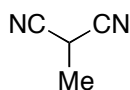
2.6. Experimental section

2.6.1. General

^1H NMR (400 MHz) spectra were recorded on a Bruker Avance 400 spectrometer in CDCl_3 [using TMS (for ^1H , for ^1H , $\delta = 0.00$) as internal standard]. ^{13}C NMR (100 MHz) spectra on a Bruker Avance 400 spectrometer in CDCl_3 [using CDCl_3 (for ^{13}C , $\delta = 77.23$) as internal standard]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad. IR spectra were recorded on a Shimadzu IR IRAffinity-1 FT-IR Spectrometer. High-resolution mass spectra were obtained with a Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). Melting points are uncorrected and were recorded on a MPA 100 OptiMelt Automated Melting Point System. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Toluene was distilled from CaH_2 . Reactions were monitored by TLC developed using KMnO_4 .

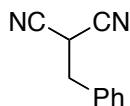
2.6.2. Synthesis of starting material 2-1

2-methylmalononitrile (**2-1a**)²¹



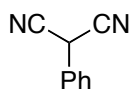
Prepared following ref. 21. ^1H NMR (400 MHz, CDCl_3) δ 1.80 (3H, d, $J = 7.3$ Hz), 3.79 (1H, q, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 16.5, 17.0, 113.8.

2-benzylmalononitrile, (**2-1b**)²¹



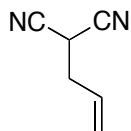
Prepared following ref. 21. ^1H NMR (400 MHz, CDCl_3) δ 3.30 (2H, d, $J = 7.0$ Hz), 3.91 (1H, t, $J = 7.0$ Hz), 7.31-7.43 (5H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 25.0, 36.5, 112.5, 128.8, 129.2(5), 129.3(0), 133.1.

2-phenylmalononitrile, (**2-1c**)²¹



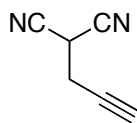
Prepared following ref. 21. ¹H NMR (400 MHz, CDCl₃) δ 5.07 (1H, s), 7.50-7.52 (5H, m); ¹³C NMR (100 MHz, CDCl₃) δ 28.1, 112.1, 126.3, 127.3, 130.1, 130.4.

2-allylmalononitrile, (**2-1d**)²¹



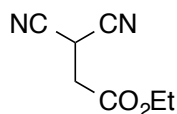
Prepared following ref. 21. ¹H NMR (400 MHz, CDCl₃) δ 2.78 (2H, t, *J* = 6.9 Hz), 3.80 (1H, t, *J* = 6.9 Hz), 5.41-5.48 (2H, m), 5.88 (1H, ddt, *J* = 7.1, 10.0, 17.1 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 23.1, 34.9, 112.3, 122.7, 129.3.

2-(prop-2-ynyl)malononitrile, (**2-1e**)²¹



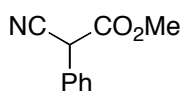
Prepared following ref. 21. ¹H NMR (400 MHz, CDCl₃) δ 2.39 (1H, t, *J* = 2.6 Hz), 2.96 (2H, dd, *J* = 2.6, 6.8 Hz), 3.93 (1H, t, *J* = 6.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 21.2, 22.9, 74.6, 75.5, 112.0.

Ethyl 3,3-dicyanopropanoate, (**2-1f**)²²



Prepared following ref. 22. ¹H NMR (400 MHz, CDCl₃) δ 1.33 (3H, t, *J* = 7.2 Hz), 3.07 (2H, d, *J* = 7.2 Hz), 4.18 (1H, t, *J* = 7.2 Hz), 4.29 (2H, q, *J* = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.2, 19.0, 35.2, 62.9, 111.9, 166.9.

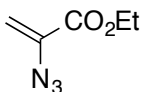
Methyl 2-cyano-2-phenylacetate, (**2-1g**)²³



Prepared following ref. 23. ¹H NMR (400 MHz, CDCl₃) δ 3.81 (3H, s), 4.74 (1H, s), 7.40-7.48 (5H, m); ¹³C NMR (100 MHz, CDCl₃) δ 43.0, 53.4, 115.7, 127.7, 128.9, 129.0, 129.9, 165.4.

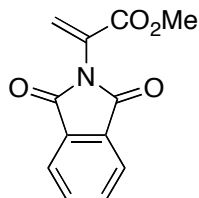
2.6.3. Synthesis of starting material 2-2

Ethyl 2-azidoacrylate (**2-2a**)²⁴



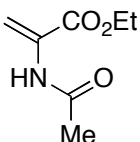
Prepared following ref. 24. ¹H NMR (400 MHz, CDCl₃) δ 1.35 (3H, t, *J* = 7.1 Hz), 4.30 (2H, q, *J* = 7.1 Hz), 5.35 (1H, d, *J* = 1.4 Hz), 5.82 (1H, d, *J* = 1.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 13.9, 62.0, 110.7, 136.1, 161.9.

Methyl 2phthalimidoacrylate (**2-2b**)²⁵



Prepared following ref. 25. ¹H NMR (400 MHz, CDCl₃) δ 3.82 (3H s), 6.00 (1H, d, *J* = 0.5 Hz), 6.70 (1H, d, *J* = 0.5 Hz), 7.79 (2H, dd, *J* = 3.1, 5.5 Hz), 7.93 (2H, dd, *J* = 3.1, 5.5 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 53.0, 124.1, 128.4, 129.2, 132.0, 134.7, 162.9, 166.6.

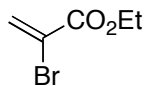
Ethyl 2-acetamidoacrylate (**2-2c**)²⁶



Prepared following ref. 26. ¹H NMR (400 MHz, CDCl₃) δ 1.35 (3H, t, *J* = 7.2 Hz), 2.13 (3H, s), 4.30 (2H, q, *J* = 7.2 Hz), 5.89 (1H, d, *J* = 0.8 Hz), 6.59 (1H, s), 7.75

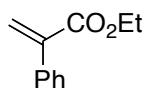
(1H, br); ¹³C NMR (100 MHz, CDCl₃) δ 14.1, 24.7, 62.2, 108.4, 131.1, 164.2, 168.8.

Ethyl 2-bromoacrylate (**2-2d**)²⁷



Prepared following ref. 27. ¹H NMR (400 MHz, CDCl₃) δ 1.34 (3H, t, *J* = 7.1 Hz), 4.29 (2H, q, *J* = 7.1 Hz), 6.27 (1H, d, *J* = 1.6 Hz), 6.96 (1H, d, *J* = 1.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 13.9, 62.5, 121.4, 130.2, 161.5.

Ethyl 2-phenylacrylate (**2-2e**)²⁸

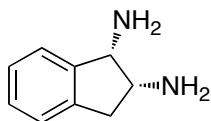


Prepared following ref. 28. ¹H NMR (400 MHz, CDCl₃) δ 1.33 (3H, t, *J* = 7.1 Hz), 4.29 (2H, q, *J* = 7.1 Hz), 5.69 (1H, d, *J* = 1.3 Hz), 6.35 (1H, d, *J* = 1.3 Hz), 7.32-7.43 (5H, m); ¹³C NMR (100 MHz, CDCl₃) δ 14.2, 61.1, 126.5, 128.0(5), 128.0(9), 128.3, 136.8, 141.6, 166.8.

Acrylate **2-2f** and **2-2g** were obtained from commercial sources and used as received.

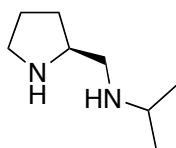
2.6.4. Synthesis of diamine catalyst

(1*S*,2*R*)-2,3-dihydro-1H-indene-1,2-diamine (**2-M**)¹⁴



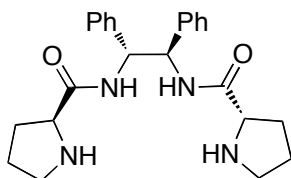
Prepared following ref. 14. ¹H NMR (400 MHz, CDCl₃) δ 2.43 (4H, br), 2.78 (1H, dd, *J* = 15.8, 4.2), 3.11 (1H, dd, *J* = 15.8, 6.3), 3.71 (1H, dd, *J* = 10.4, 5.9), 4.25 (1H, d, *J* = 5.6), 7.17 – 7.32 (3H, m), 7.32-7.34 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ 39.2, 56.0, 59.1, 124.1, 125.0, 126.6, 127.4, 140.8, 145.0.

(*S*)-*N*-(pyrrolidin-2-ylmethyl)propan-2-amine (**2-P**)²⁹



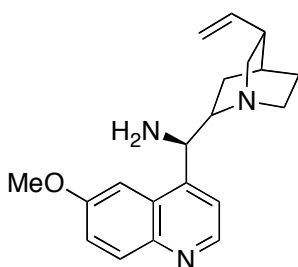
Prepared following ref. 29. ¹H NMR (400 MHz, CDCl₃) δ 1.06 (6H, dd, *J* = 6.2, 4.6 Hz), 1.26-1.37 (1H, m), 1.65-1.92 (5H, m), 2.46 (1H, dd, *J* = 8.5, 11.2 Hz), 2.62 (1H, dd, *J* = 4.7, 11.2 Hz), 2.78 (1H, septet, *J* = 6.2 Hz), 2.87-2.93 (2H, m), 3.16-3.23 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ 23.1, 23.4, 26.0, 30.1, 46.8, 49.1, 53.2, 58.8.

(2*S*,2'*S*)-*N,N'*-((1*R*,2*R*)-1,2-diphenylethane-1,2-diyl)bis(pyrrolidine-2-carboxamide) (**2-R**)¹⁸



Prepared following ref. 18. ¹H NMR (400 MHz, CDCl₃) δ 1.70- 1.81 (8H, m), 2.11 (2H, br), 2.97 (2H, br), 3.74 (2H, br), 2.97,5.22 (2H, br), 7.08-7.14 (10H, m), 8.56 (2H, br); ¹³C NMR (100 MHz, CDCl₃) δ 26.3, 30.7, 47.2, 57.9, 60.6, 127.4 (overlap), 128.2, 139.1, 175.2.

(1*R*)-(6-methoxyquinolin-4-yl)((1*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanamine (**2-S**)³⁰



Prepared following ref. 30. ¹H NMR (400 MHz, CDCl₃) δ 0.88-1.00 (1H, m), 1.12-1.21 (1H, m), 1.55-1.63 (3H, m), 2.15 (2H, br), 2.28-2.35 (1H, m), 2.90-3.12 (5H, m), 3.97 (3H, s), 4.68 (1H, d, *J* = 8.0 Hz), 5.05-5.10 (2H, m), 5.85-5.92, 7.38 (1H, dd, *J* = 4, 12 Hz), 7.53 (1H, d, *J* = 4 Hz), 7.62 (1H, br), 8.03 (1H, d, *J* = 8.0 Hz), 8.75 (1H, d, *J* = 4.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 24.4, 26.1, 27.0, 38.9, 46.8, 49.0, 51.8, 54.9, 61.8, 101.0, 113.9, 119.4, 121.1, 128.2, 131.2, 140.2, 144.1,

146.9, 147.2, 157.1.

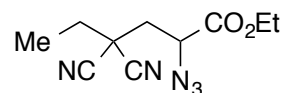
Diamines **2-A-L**, **2-N** and **2-O** were obtained from commercial sources and used as received.

2.6.5. Diamine-catalyzed conjugate addition

Typical procedure for diamine-catalyzed conjugate addition

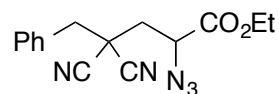
1,2-Diamine (20 mol %) was added to a mixture of acrylate (1.5 equiv) and pronucleophile (1 equiv) in toluene (0.5 M) at 0 °C. The mixture was stirred under N₂ atmosphere at 0 °C. Upon completion indicated by TLC, toluene was removed under reduced pressure and the crude mixture was subjected to column chromatography to yield conjugate addition products.

Ethyl 2-azido-4,4-dicyanopentanoate (**2-3aa**)



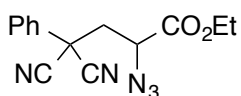
Yellow oil; IR (ATR) 2359, 2120, 1738, 1202 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.37 (3H, t, *J* = 7.2 Hz), 1.92 (3H, s), 2.29 (1H, dd, *J* = 10.0, 14.8 Hz), 2.47 (1H, dd, *J* = 4.0, 14.8 Hz), 4.27-4.37 (3H, m); ¹³C NMR (100 MHz, CDCl₃) δ 14.3, 26.0, 29.6, 39.3, 58.9, 63.2, 115.3, 115.4, 168.3; EIHRMS: Found: *m/z* 222.1000. Calcd for C₉H₁₂N₅O₂: (M+H)⁺ 222.0991.

Ethyl 2-azido-4,4-dicyano-5-phenylpentanoate (**2-3ba**)



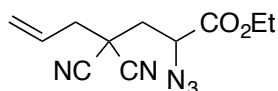
Yellow oil; IR (ATR) 2986, 2359, 2342, 2120, 1740, 1219, 1098, 770, 754, 702 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.35 (3H, t, *J* = 7.2 Hz), 2.29 (1, dd, *J* = 10, 14.8 Hz), 2.49 (1H, dd, *J* = 4.0, 14.8 Hz), 3.28 (1H, d, *J* = 13.6 Hz), 3.33 (1H, d, *J* = 13.6 Hz), 4.26-4.38 (3H, m), 7.38-7.43 (5H, m); ¹³C NMR (100 MHz, CDCl₃) δ 14.1, 36.7, 37.5, 44.1, 58.9, 63.1, 114.3, 114.5, 129.2 (overlap), 130.5, 131.4, 168.3; EIHRMS: Found: *m/z* 298.1299. Calcd for C₁₅H₁₆N₅O₂: (M+H)⁺ 298.1304.

Ethyl 2-azido-4,4-dicyano-4-phenylbutanoate, (**2-3ca**)



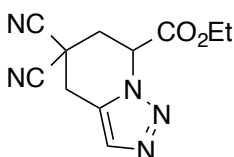
Yellow oil; IR (ATR) 2359, 2342, 2122, 1740, 1452, 1219, 1200, 772, 694 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.33 (3H, t, $J = 7.2$ Hz), 2.61 (1H, dd, $J = 9.6, 14.4$ Hz), 2.72 (1H, dd, $J = 4.0, 14.4$ Hz), 4.09 (1H, dd, $J = 4.0, 9.6$ Hz), 4.27 (2H, dq, $J = 7.2, 10.8$ Hz), 7.05-7.56 (3H, m), 7.61-7.63 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1, 39.7, 42.3, 58.6, 63.1, 114.0, 114.5, 126.0, 130.1, 130.5, 131.2, 168.1; EIHRMS: Found: m/z 284.1150. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_5\text{O}_2$: $(\text{M}+\text{H})^+$ 284.1147.

Ethyl 2-azido-4,4-dicyanohept-6-enoate (**2-3da**)



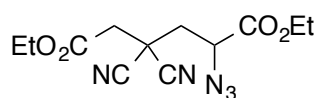
Yellow oil; IR (ATR) 2986, 2359, 2342, 2120, 1740, 1445, 1219, 1202 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.37 (3H, t, $J = 7.2$ Hz), 2.27 (1H, dd, $J = 10, 14.8$ Hz), 2.45 (1H, dd, $J = 4.0, 14.8$ Hz), 2.74-2.84 (2H, m), 4.27-4.39 (3H, m), 5.43-5.50 (2H, dd, $J = m$), 5.91 (1H, ddt, $J = 7.2, 10.0, 16.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.2, 35.0, 37.2, 42.5, 58.9, 63.1, 114.2, 114.5, 124.2, 128.0, 168.3; EIHRMS: Found: m/z 248.1149. Calcd for $\text{C}_{11}\text{H}_{14}\text{N}_5\text{O}_2$: $(\text{M}+\text{H})^+$ 248.1147.

Ethyl 5,5-dicyano-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyridine-7-carboxylate (**2-4ea**)



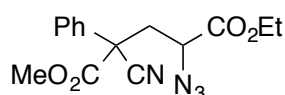
White solid; mp 128.5-130.6 $^{\circ}\text{C}$; IR (ATR) 3125, 2986, 2963, 2359, 2342, 1748, 1213 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.34 (3H, t, $J = 7.2$ Hz), 3.04-3.07 (2H, m), 3.62 (1H, d, $J = 16.8$ Hz), 3.72 (1H, d, $J = 16.8$ Hz), 4.36 (2H, q, $J = 7.2$ Hz), 5.43 (1H, dd, $J = 6.4, 7.6$ Hz), 7.69 (1H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 14.0, 28.3, 30.5, 34.2, 55.4, 63.9, 113.1, 113.2, 127.1, 131.9, 166.4; EIHRMS: Found: m/z 246.0990. Calcd for $\text{C}_{11}\text{H}_{12}\text{N}_5\text{O}_2$: $(\text{M}+\text{H})^+$ 246.0991.

Diethyl 2-azido-4,4-dicyanohexanedioate (**2-3fa**)



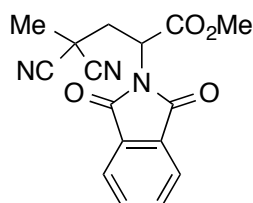
White crystals; mp 63.3-64.9 °C; IR (ATR) 2359, 2342, 2332, 2124, 1732, 1221, 1207 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.33 (3H, t, $J = 7.2$ Hz), 1.37 (3H, t, $J = 7.2$ Hz), 2.46 (1H, dd, $J = 10.4, 14.8$ Hz), 2.64 (1H, dd, $J = 4.0, 14.8$ Hz), 3.07 (1H, d, $J = 17.2$ Hz), 3.17 (1H, d, $J = 17.2$ Hz), 4.29 (2H, q $J = 7.2$ Hz), 4.31-4.37 (3H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 13.9(7), 14.0(3), 31.4, 36.9, 41.0, 58.6, 62.4, 63.1, 113.9, 114.1, 166.4, 168.1; EIHRMS: Found: m/z 294.1200. Calcd for $\text{C}_{12}\text{H}_{16}\text{N}_5\text{O}_4$: $(\text{M}+\text{H})^+$ 294.1202.

5-ethyl 1-methyl 4-azido-2-cyano-2-phenylpentanedioate (mixture of diastereomers) (**2-3ga**)



Colourless oil; IR (ATR) 3022, 2986, 2957, 2359, 2332, 2118, 1744, 1450, 1435, 1233, 1198 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.31 (3.16H, t, $J_a = 7.2$ Hz), 1.34 (4.76H, t, $J_b = 7.2$ Hz), 2.55 (1.82H, dd, $J_b = 8.0, 14.8$ Hz), 2.61 (1.21H, dd, $J_a = 4.0, 14.8$ Hz), 2.89-3.00 (3.13H, m), 3.81(4.52H, s), 3.83 (3.00H, s), 4.09-4.12 (2.94H, m), 4.23-4.29 (5.55H, m), 7.40-7.46 (7.74H, m), 7.54-7.60 (5.27H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1, 14.2, 38.6, 39.0, 51.4, 51.8, 54.4 (overlap), 59.1, 59.3, 62.6 (overlap), 117.2, 117.3, 126.0, 126.2, 129.4, 129.5 (overlap), 129.6, 133.6, 133.9, 167.4, 167.5, 169.0, 169.1; EIHRMS: Found: m/z 317.1253. Calcd for $\text{C}_{15}\text{H}_{17}\text{N}_4\text{O}_4$: $(\text{M}+\text{H})^+$ 317.1250

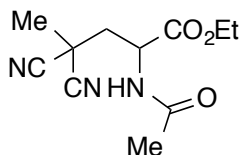
Methyl 4,4-dicyano-2-(phthalimido)pentanoate (**2-3ab**)



White crystals; mp 159.2-161.3 °C; IR (ATR) 2359, 2342, 1775, 1742, 1707, 1387, 1373 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.90 (3H, s), 2.87 (1H, dd, $J = 2.8, 15.2$ Hz), 3.11 (1H, dd, $J = 11.6, 15.2$ Hz), 3.79 (3H, s), 5.25 (1H, dd $J = 2.8,$

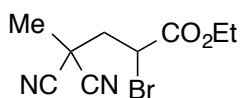
11.6 Hz), 7.78 (2H, dd, $J = 2.9, 5.4$ Hz), 7.92 (2H, dd, $J = 2.9, 5.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 25.3, 29.3, 36.7, 48.6, 53.7, 115.0, 115.5, 124.1, 131.7, 134.8, 167.6, 167.8; EIHRMS: Found: m/z 312.0988. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_3\text{O}_4$: $(\text{M}+\text{H})^+$ 312.0984.

Ethyl 2-acetamido-4,4-dicyanopentanoate (**2-3ac**)



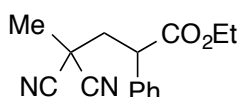
White flakes; mp 84.7-87.6 °C; IR (ATR) 3377, 3198, 2359, 2342, 1734, 1659, 1219 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.33 (3H, t, $J = 7.2$ Hz), 1.89 (3H, s), 2.09 (3H, s), 2.48 (1H, dd, $J = 7.6, 14.4$ Hz), 2.62 (1H, dd, $J = 4.8, 14.4$ Hz), 4.26 (1H, dq $J = 7.2, 10.8$ Hz), 4.31 (1H, dq $J = 7.2, 10.8$ Hz), 4.83 (1H, ddd, $J = 4.8, 6.8, 7.6$ Hz), 6.28 (1H, d, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.0, 23.0, 25.5, 28.8, 38.9, 49.8, 62.6, 115.7, 115.9, 169.9, 171.2; EIHRMS: Found: m/z 238.1196. Calcd for $\text{C}_{11}\text{H}_{16}\text{N}_3\text{O}_3$: $(\text{M}+\text{H})^+$ 238.1192.

Ethyl 2-bromo-4,4-dicyanopentanoate (**2-3ad**)



Yellow oil; IR (ATR) 2359, 2330, 1736, 1273, 1219, 1159 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.34 (3H, t, $J = 7.2$ Hz), 1.89 (3H, s), 2.60 (1H, dd, $J = 5.6, 14.8$ Hz), 2.93 (1H, dd, $J = 8.0, 14.8$ Hz), 4.30 (2H, q, $J = 7.2$ Hz), 4.47 (1H, dd, $J = 5.6, 8.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 13.8, 25.5, 30.4, 38.4, 42.3, 63.1, 114.7, 115.2, 168.0; EIHRMS: Found: m/z 259.0074. Calcd for $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_2\text{Br}$: $(\text{M}+\text{H})^+$ 259.0082.

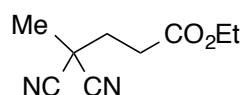
Ethyl 4,4-dicyano-2-phenylpentanoate (**2-3ae**)



Colourless oil; IR (ATR) 3022, 2984, 2359, 2322, 1730, 1456, 1219, 1175, 1159 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.23 (3H, t, $J = 7.2$ Hz), 1.80 (3H, s), 2.34 (1H, dd, $J = 6.0, 14.0$ Hz), 2.88 (1H, dd, $J = 8.0, 14.0$ Hz), 3.92 (1H, dd, $J = 6.0,$

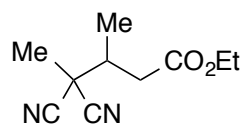
8.0 Hz), 4.12 (1H, dq, $J = 7.2, 10.8$ Hz), 4.23 (1H, dq, $J = 7.2, 10.8$ Hz), 7.32-7.39 (5H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 14.0, 25.6, 30.6, 41.7, 48.6, 61.8, 115.4, 115.5, 127.9, 128.5, 129.3, 136.8, 171.8; EIHRMS: Found: m/z 257.1295. Calcd for $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_2$: $(\text{M}+\text{H})^+$ 257.1290.

Ethyl 4,4-dicyanopentanoate (**2-3af**)



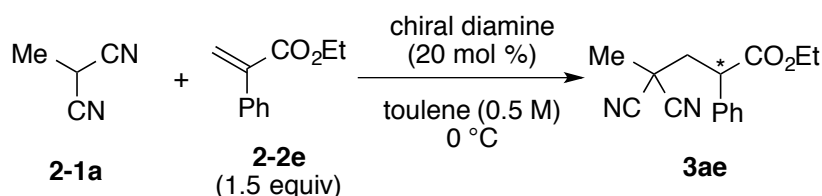
Colourless oil; IR (ATR) 2360, 2342, 2332, 1732, 1194 cm^{-1} ; ^1H MR (400 MHz, CDCl_3) δ 1.29 (3H, t, $J = 7.2$ Hz), 1.84 (3H, s), 2.30-2.34 (2H, m), 2.68-2.72 (2H, m), 4.19 (2H, q, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.3, 24.8, 30.5, 31.2, 34.3, 61.5, 115.7, 170.7; EIHRMS: Found: m/z 181.0982. Calcd for $\text{C}_9\text{H}_{13}\text{N}_2\text{O}_2$: $(\text{M}+\text{H})^+$ 181.0977.

Ethyl 4,4-dicyanopentanoate (**2-3ag**)



Pale yellow oil; IR (ATR) 2984, 2940, 1732, 1198 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.29 (3H, t, $J = 7.2$ Hz), 1.29 (3H, s), 1.80 (3H, s), 2.39 (1H, dd, $J = 10.1, 15.7$ Hz), 2.57 (1H, ddq, $J = 3.4, 6.7, 10.1$ Hz), 2.75 (1H, dd, $J = 3.4, 15.7$ Hz), 4.20 (2H, q, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.4, 15.9, 22.8, 36.8, 37.7, 38.1, 61.5, 115.3, 115.6, 170.6; EIHRMS: Found: m/z 195.1132. Calcd for $\text{C}_{10}\text{H}_{15}\text{N}_2\text{O}_2$: $(\text{M}+\text{H})^+$ 195.1132.

2.6.6. Determination of enantiomeric excess of **2-3ae**



General: Enantioselectivities were determined by Shimadzu, LC-20AD Prominence Liquid Chromatograph, column: Chiralcel, OJ-H, 046 cm ϕ x 25 cm

Mobile Phase: Hex : IPA = 90:10, 0.5 ml/min, injection volume: 0.5 μL

Detection: Diode array detector set at 210 nm.

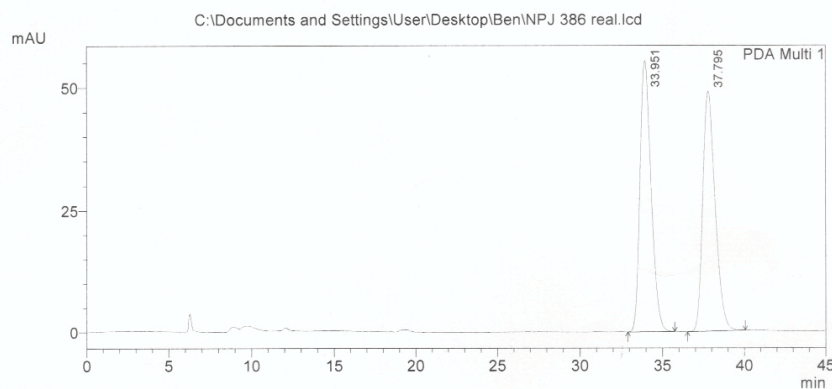
Racemic reaction:

12/3/2013 12:59:15 1 / 1

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Report File Name : Default.lcr
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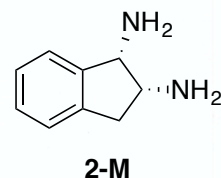
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Reaction catalyzed by diamine **2-M**, 87%, 48 h, 0% *ee*

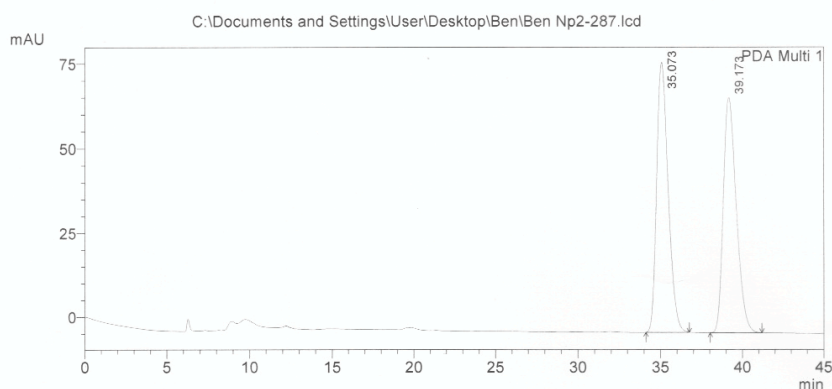
12/3/2013 13:00:56 1 / 1

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1	35.073	3900706	79988	50.168	53.390
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Total		7775296	149819	100.000	100.000

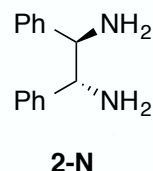
C:\Documents and Settings\User\Desktop\Ben\Ben Np2-287.lcd

Reaction catalyzed by diamine **2-N**, 76%, 48 h, 5% *ee*

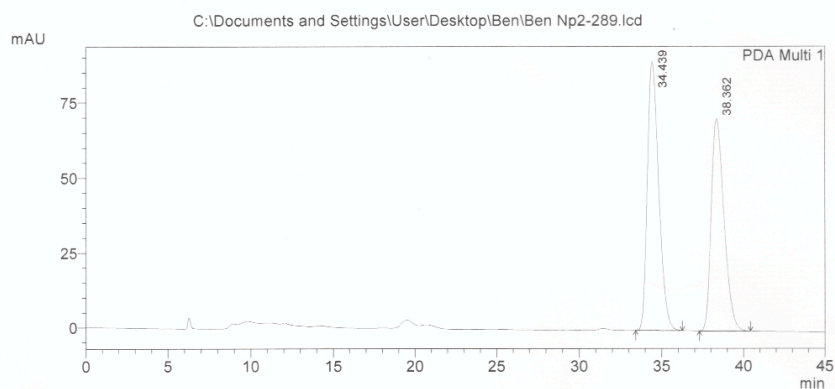
12/3/2013 13:00:34 1 / 1

==== Shimadzu LCsolution Analysis Report ====

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 Sample ID : Ben Np2-289
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 Injection Volume : 0.5 uL
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<Chromatogram>



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Total		8197857	160689	100.000	100.000

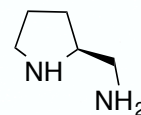
C:\Documents and Settings\User\Desktop\Ben\Ben Np2-289.lcd

Reaction catalyzed by diamine **2-O**, 99%, 19 h, 5% *ee*

12/3/2013 13:05:27 1 / 1

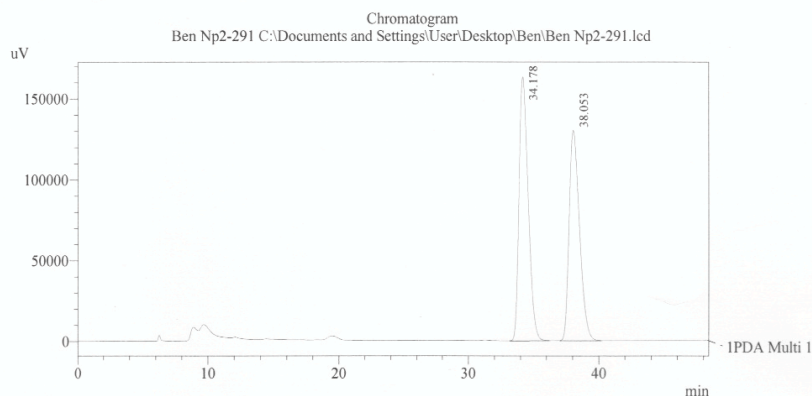
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 Sample ID : Ben Np2-291
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 Vial # : 1
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2-O

<Chromatogram>



PDA Ch1 210nm 4nm

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2	38.053	7225863	130409	47.472	44.392
Total		15221333	293769	100.000	100.000

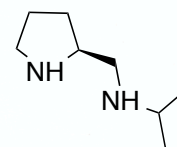
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Reaction catalyzed by diamine **2-P**, 81%, 48 h, 8% *ee*

12/3/2013 13:07:21 1 / 1

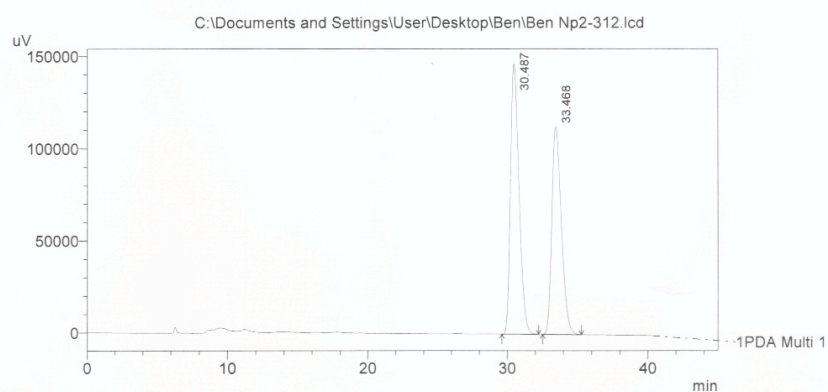
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Tray# : 1
Vial # : 1
Injection Volume : 0.5 uL
Data File Name : Ben Np2-312.lcd
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Data Processed : 6/29/2011 12:29:34 PM



2-P

<Chromatogram>



1 PDA Multi 1/210nm 4nm

PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	30.487	6226246	146625	53.948	56.480
2	33.468	5314855	112982	46.052	43.520
Total		11541101	259607	100.000	100.000

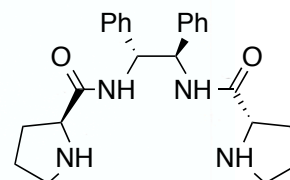
C:\Documents and Settings\User\Desktop\Ben\Ben Np2-312.lcd

Reaction catalyzed by diamine **2-Q**, 73%, 48 h, –8% *ee*

12/3/2013 13:07:59 1 / 1

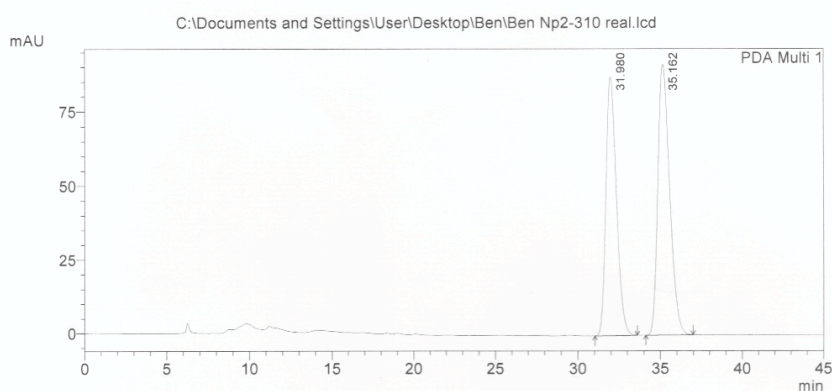
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 Sample ID : Ben Np2-310 real
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 Vial # : 1
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2-Q

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1 PDA Multi 1/210nm 4nm

PeakTable

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2	35.162	4580561	91706	54.019	51.177
Total		8479478	179193	100.000	100.000

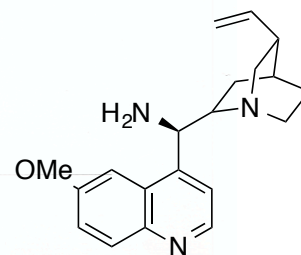
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Reaction catalyzed by diamine **2-R**, 49%, 6 days, 3% *ee*

12/3/2013 13:15:57 1 / 1

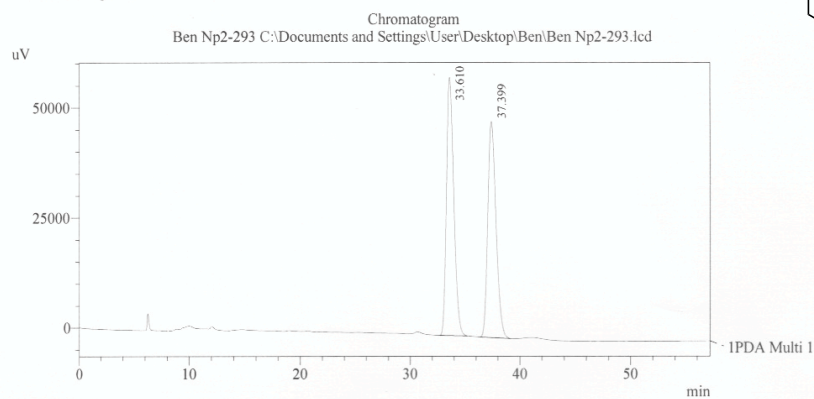
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Sample ID : Ben Np2-293
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2-R

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PDA Ch1 210nm 4nm

PeakTable

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2	37.399	2566031	49215	48.453	45.577
Total		5295871	107982	100.000	100.000

C:\Documents and Settings\User\Desktop\Ben\Ben Np2-293.lcd

2.7. References and notes

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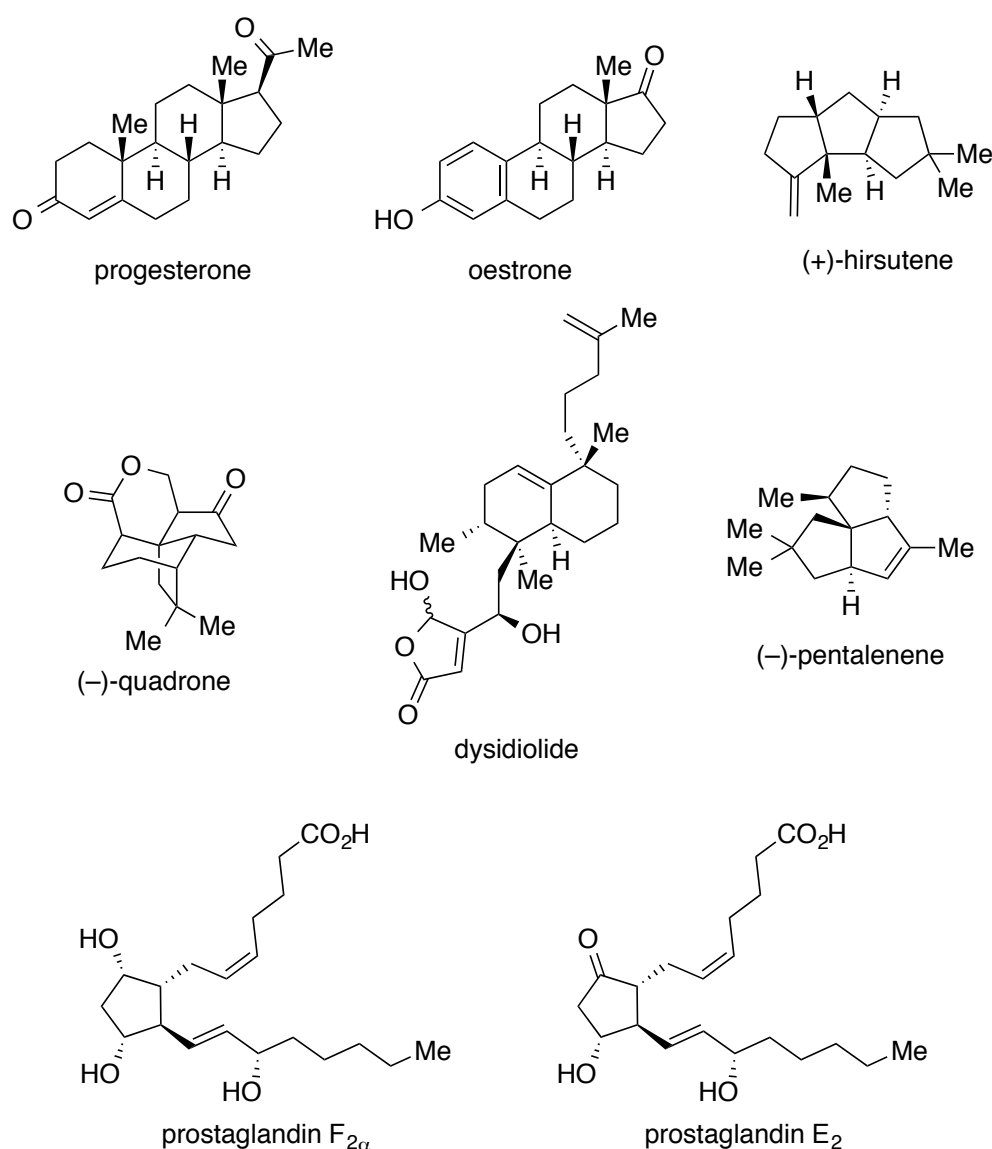
Chapter 3. Synthesis of highly substituted carbocycles by domino S_N2-conjugate addition sequence

3.1. Introduction

The construction of stereo- and regioselective carbocycles, especially cyclopentanes and cyclohexanes having rich functionality remains as one of the most fundamental challenges in synthetic organic chemistry. Their motifs are prevalent in many biological active natural products and drug molecules. In particular, the class of terpenes constitutes an amazing array of carbocyclic scaffold, commonly with unusual linkage between the rings.^{1,2} As a consequence of nature's creation, terpenes represents one of the largest and most diverse classes of metabolites. Terpenes and terpenoids play important roles in all living organism, serving as steroid hormones in mammals to secondary metabolites in plants and bacteria.³ Extensive studies have shown that these metabolites display various biological activities ranging from *anti*-cancer and *anti*-malarial activities to tumor promotion and ion-channel binding.⁴ Terpenes also defend many species of plants, animals and microorganisms against predators, pathogens and competitors.⁵ (–)-Quadrone, the first isolated natural occurring sesquiterpene possess a diquinane core fused with a bicyclo[3.2.1]octane system have been reported to be antifungal, antibacterial and has shown cytotoxicity towards several tumor cell lines.^{6,7} Another important sesquiterpene is the dysidiolide isolated from marine sponge *Dysidea etheria* de Laubenfels off Long Islands, Bahamas.⁸ It is the first natural inhibitor of dual-specificity phosphatase Cdc25A, an enzyme that plays a pivotal role in cell cycle.^{9,10, 11,12} This enzyme has been shown to be oncogenic and overexpressed in a number of tumor cell lines and therefore presents a potential new therapeutic target against these cancers. In contrast, terpenes obtained from bacteria sources are relatively fewer. Of particular interesting is the (–)-pentalenene.¹³ This triquinane isolated from the mycelia *Streptomyces griseochromogenes* serves as the common biosynthetic precursor to the pentalenolactone family of fungal metabolites exhibiting antibiotic activity.¹

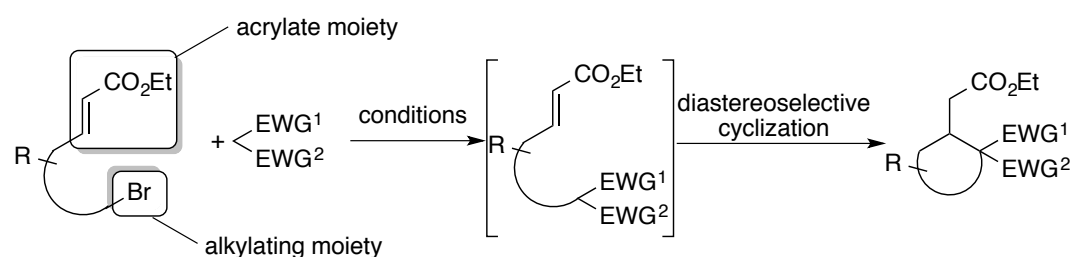
The diverse structures of terpenes render synthetic chemists highly motivated toward development of efficient strategies to construct carbocycle frameworks.¹⁴ As a result, a variety of synthetic methods have so far been developed. The prostaglandin family is found virtually in all peripheral organs as well as the

central nervous system. They play important regulatory roles in many normal cellular functions through binding to cell surface receptors such as G-protein-coupled prostanoid receptors.¹⁵ Their therapeutic properties have captured the attentions of various eminent synthetic chemists including Woodward,¹⁶ Stork,^{17,18} Corey,^{19,20,21} and Noyori.²² For synthesis of (±)-hirsutene, a triquinane metabolite of *Coriolus consors*,²³ the potential of free-radical cyclization was elegantly demonstrated by Curran.^{24,25,26} Synthetic studies of these natural products has built the foundation of modern synthetic strategies.



Scheme 3-1. Representative natural products containing cyclopentane and cyclohexane core

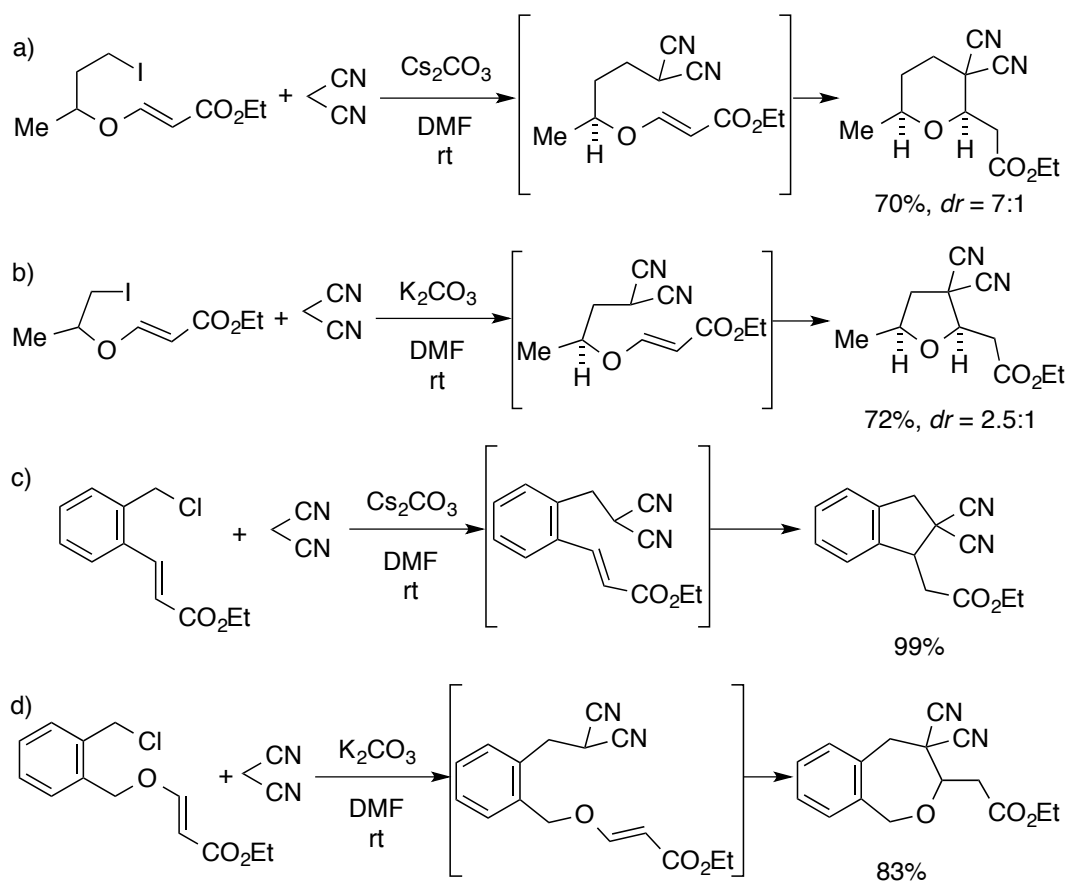
Stimulated by the importance of the carbocycles and along with the author's interest in employing carbon nucleophiles for conjugate addition towards acrylic derivatives (Chapter 2), the author proposed to construct highly functionalized cyclopentane and cyclohexane frameworks *via* a sequence of S_N2 -conjugate addition reactions. The strategy was designed by incorporation of the organohalide moiety on the acrylate for the 1st S_N2 alkylation with active methylene compounds such as malononitrile. The intermediate generated by the 1st S_N2 alkylation could undergo successive intramolecular conjugate addition, resulting in highly functionalized carbocycles. In particular, the author aims to investigate the effects of the substituents installed on the starting materials as well as active methylene nucleophiles towards the diastereoselectivity of the present annulation strategy (Scheme 3-2).



Scheme 3-2. Substrate design for tandem alkylation and conjugate addition

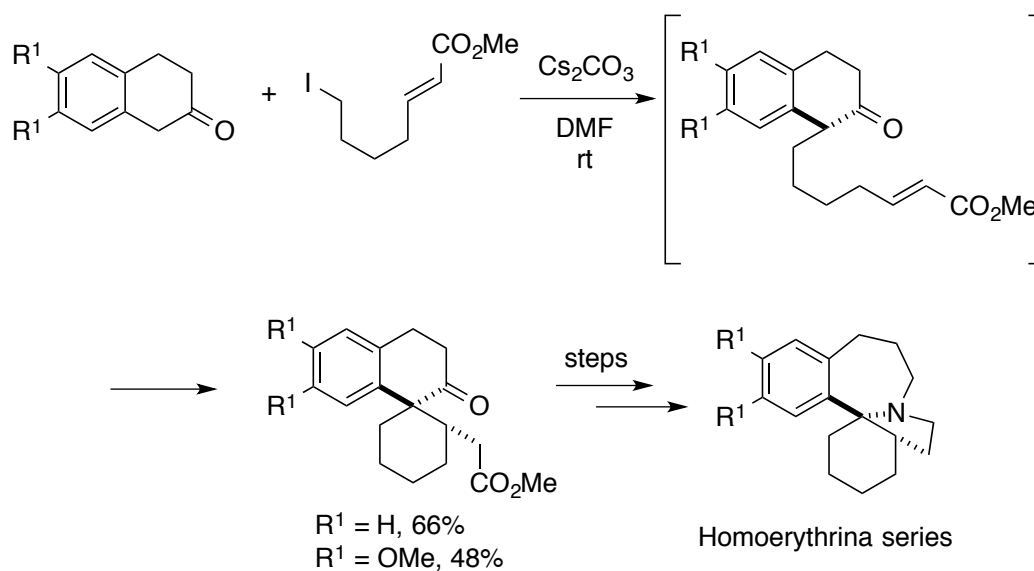
3.1.1. S_N2 -conjugate addition sequence

Synthetic studies of carbo- and heterocycles using the S_N2 -conjugate addition sequence have been investigated by the research group of Gharpure. In a series of publications, the group revealed that 2,3,3,6-tetrasubstituted tetrahydropyrans,²⁷ 2,3,3,5-tetrasubstituted tetrahydrofurans,²⁸ 1,2,2-trisubstituted indanes²⁹ and benzoxepines³⁰ could be constructed using this strategy (Scheme 3-3). However, these studies were not focused well on how the substituents affect the stereochemistry of the resulting cyclization products except for the examples of construction of tetrahydrofuran and tetrahydropyran derivatives (Scheme 3-3-a and 3-3-b).



Scheme 3-3. Synthesis of cyclic compounds by S_N2 -conjugate addition sequence

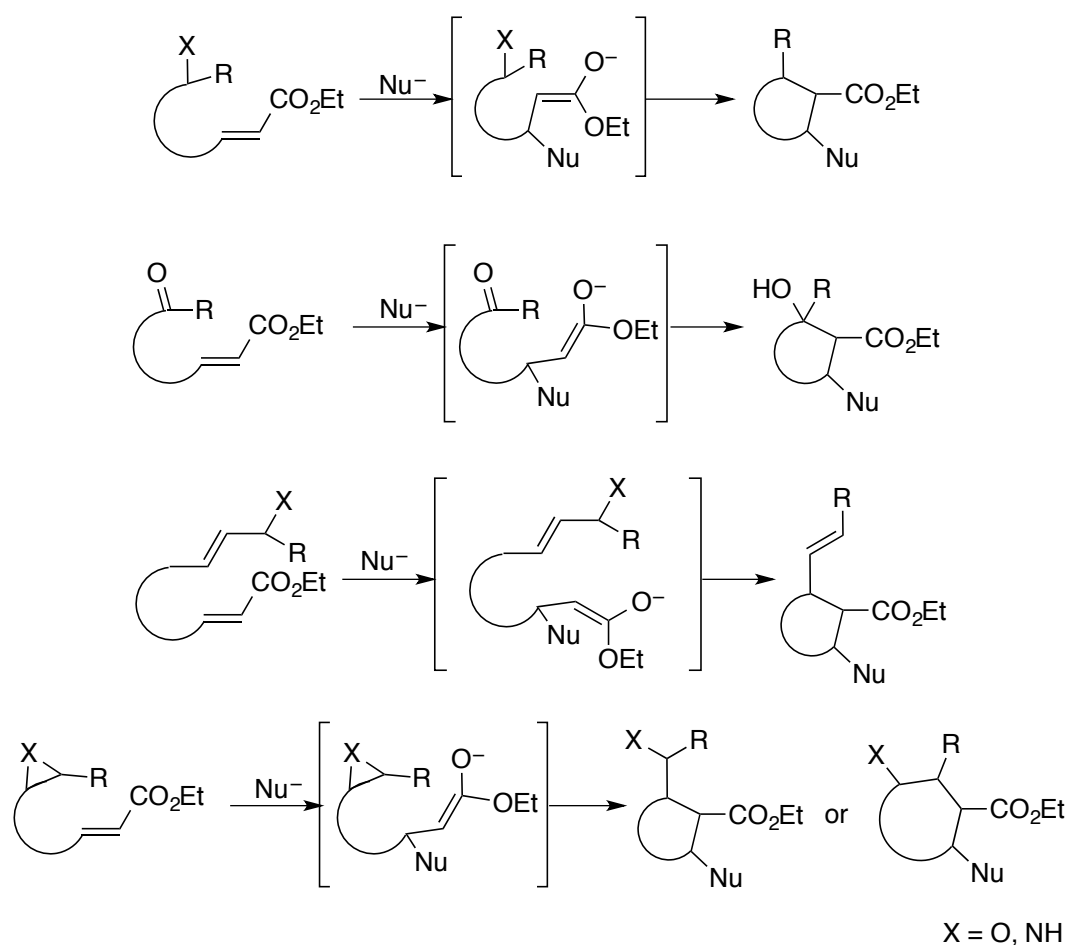
Angelo and co-workers applied the S_N2 -conjugate addition sequence for the synthesis of spiro-compounds that offered a new synthetic route for Homoerythrina alkaloids (Scheme 3-4).³¹



Scheme 3-4. Construction of spiro-compounds by S_N2 -conjugate addition sequence

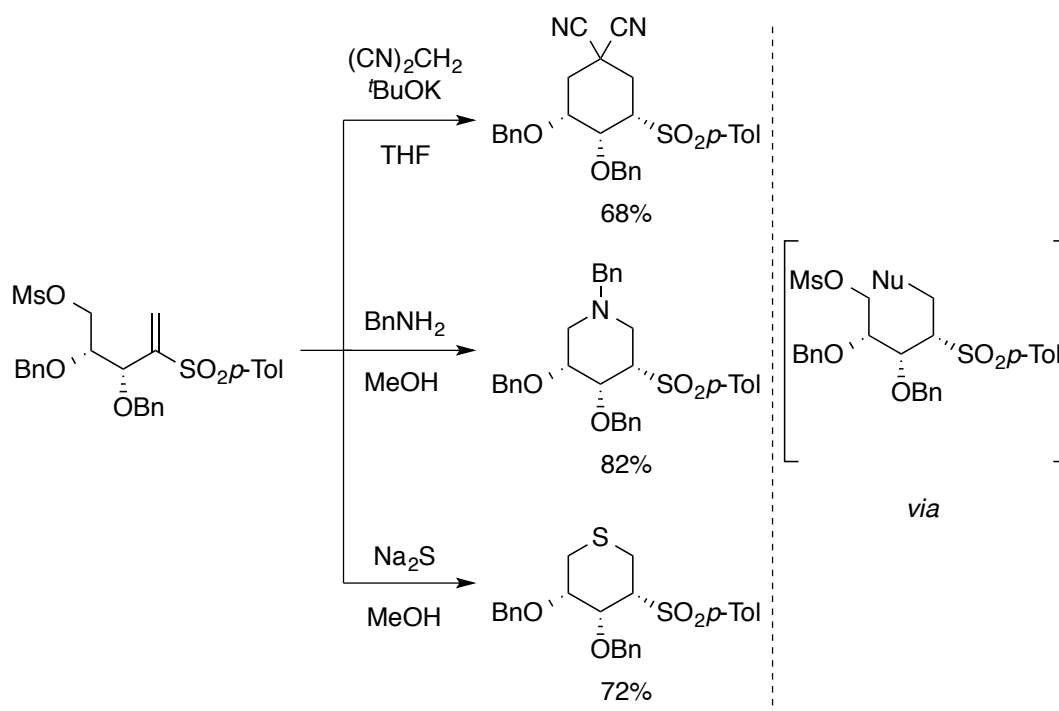
3.1.2. Michael initiated ring closure reaction (MIRC)

The competitive strategy of the S_N2 -Conjugate addition sequence is the Michael Initiated Ring Closure (MIRC) coined by Little in 1980 (Scheme 3-5).³² The MIRC is used to define a domino transformations including (1) intermolecular conjugate addition that results in the formation of an enolate; (2) successive intramolecular ring-closure of the resulting enolate with tethered electrophiles such as carbon-halogen bonds, carbonyl groups, allyl halide moieties, epoxides and aziridines



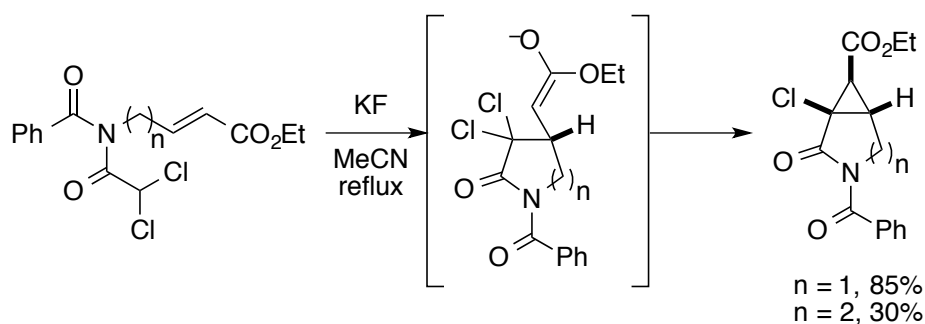
Scheme 3-5. Variants of Michael initiated ring closure reactions (MIRC)

The MIRC reactions have been applied in the construction of various cyclic compounds.³³ Pathak and colleague developed a general route to access six-membered carbo- & heterocycles using this concept (Scheme 3-6).³⁴



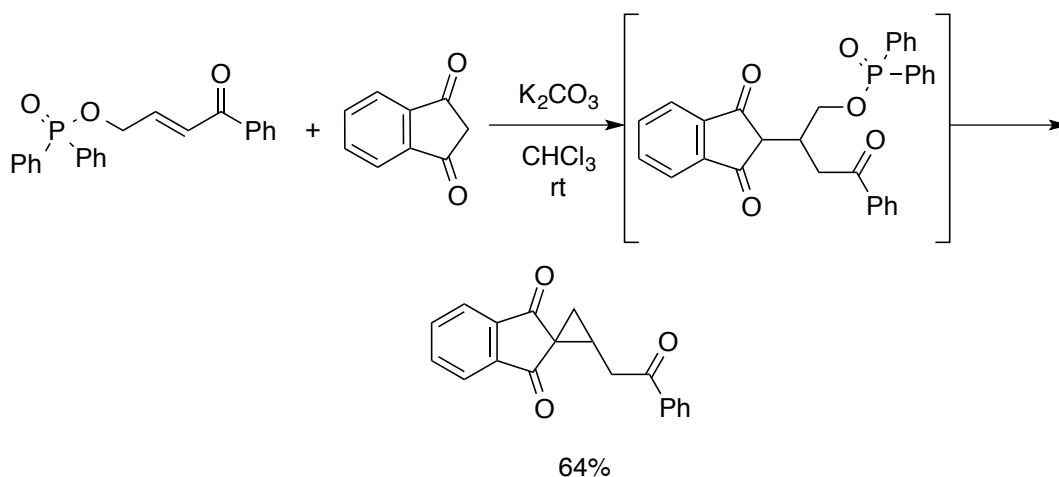
Scheme 3-6. Synthesis of six-membered carbo- and heterocycles *via* MIRC strategy.

Braish and Chan in Pfizer explored the possibility of cyclopropanation by the MIRC reactions for construction of 3-azabicyclo[3.1.0]hexane ring systems employing tethered chloroacetamides as the nucleophile to an intramolecular acrylate acceptor. They found that KF is the ideal base without degrading the starting material (Scheme 3-7).³⁵



Scheme 3-7. Construction bicyclo-scaffolds *via* MIRC strategy.

Recently, Lattanzi and Russo achieved another cyclopropanation using the MIRC reaction by employing diphenyl phosphinates as a suitable leaving group with 1,3-diketone as a nucleophile (Scheme 3-8).³⁶



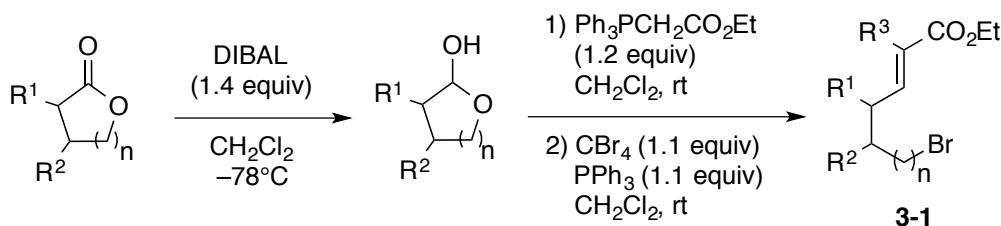
Scheme **3-8**. Cyclopropanation *via* MIRC strategy.

Based on these backgrounds, the author became interested in the base-mediated reactions of 6-halo-2-hexenoates and 7-halo-2-heptenoates with active methylene compounds that would provide cyclopentane and cyclohexane derivatives, respectively, *via* the sequence of S_N2 -conjugate addition. Especially, the author is interested in how substituents in various positions affect the diastereoselectivity in the proposed carbocycle syntheses.

3.2. Synthesis of starting materials

The required starting materials **3-1a-j**, **3-1l-m**, **3-1o^E**, **3-1q** and **3-1s-t** were prepared starting from the corresponding lactones *via* 3 step-sequence: 1) DIBAL reduction; 2) the Wittig reaction of the resulting lactols; 3) bromination of alcohols using triphenylphosphine and tetrabromomethane (Table 3-1).

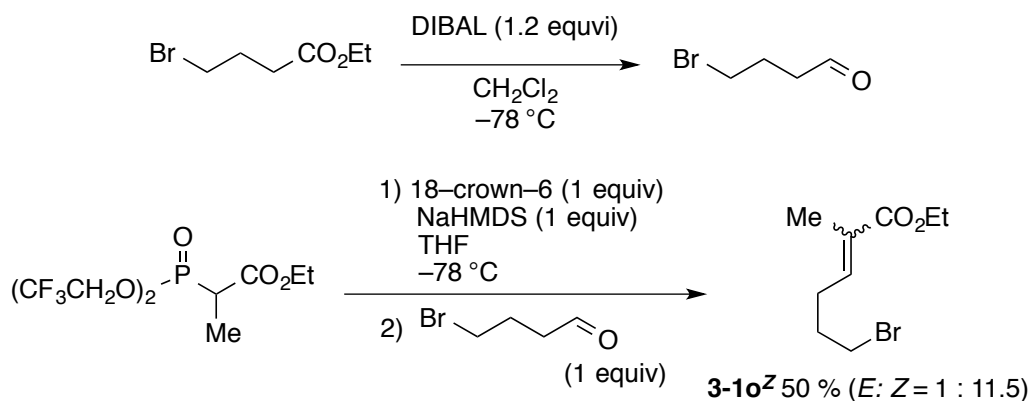
Table 3-1. Preparation of starting material **3-1** by sequential reduction-olefination-bromination



substrate	R ¹	R ²	R ³	n	yield, ^a 3-1	<i>E/Z</i> ratio ^b
a	H	H	H	1	68%	18.7:1
b	Bn	H	H	1	43%	pure <i>E</i> -isomer
c	Me	H	H	1	30%	pure <i>E</i> -isomer
d	MeO-CH ₂ -CH ₂ -	H	H	1	67%	15.7:1
e	CH ₂ =CH-CH ₂ -	H	H	1	56%	16:1
f	CH ₃ C≡C-CH ₂ -	H	H	1	58%	18.7:1
g	Me-CH(Me)-	H	H	1	24%	pure <i>E</i> -isomer
h	Ph	H	H	1	54%	pure <i>E</i> -isomer
i	OTBS	H	H	1	59%	2.17:1
j	OBn	H	H	1	86%	1.53:1
l	H	Ph	H	1	quant.	2.3:1
m	Bn	Ph	H	1	40%	pure <i>E</i> -isomer, <i>dr</i> = >99:1
o^E	H	H	Me	1	36% ^c	pure <i>E</i> -isomer
q	Bn	H	H	2	58%	pure <i>E</i> -isomer
s					51%	3.5:1
t	Bn	H	H	3	87%	75.3:1

^a Isolated yields over 3 steps. ^b *E/Z* ratio were determined by analysis of crude ¹H NMR. ^c Ethyl 2-(triphenylphosphoranylidene)propanoate was employed as Wittig reagent.

Starting material **3-1o^Z** having *Z*-alkene was prepared starting from ethyl 4-bromobutanoate *via* the DIBAL reduction followed by the Horner-Wadsworth-Emmons reaction using ethyl 2-(bis(trifluoromethyl)phosphoryl)propanoate³⁷ to obtain the target compound bearing *Z*-alkene in high selectivity (*E/Z* ratio = 1:11.5) (Scheme 3-9).



Scheme 3-9. Preparation of **3-10^Z**

3.3. Screening of reaction conditions

The S_N2-conjugate addition sequence was optimized using **3-1a** and (phenylsulfonyl)acetonitrile (**3-2a**) in order to study both the reactivity and diastereoselectivity involved in the cyclization. It was found that the reaction provided a sole diastereomer **3-3aa** (Table 3-2). The use of NaH as base in various solvents (DMF, DMSO, MeCN and THF) delivered the desired cyclopentane **3-3aa** (entries 1-4). The use of a mild base such as K₂CO₃ in DMF or DMSO could also realize the reaction (entries 5-6).

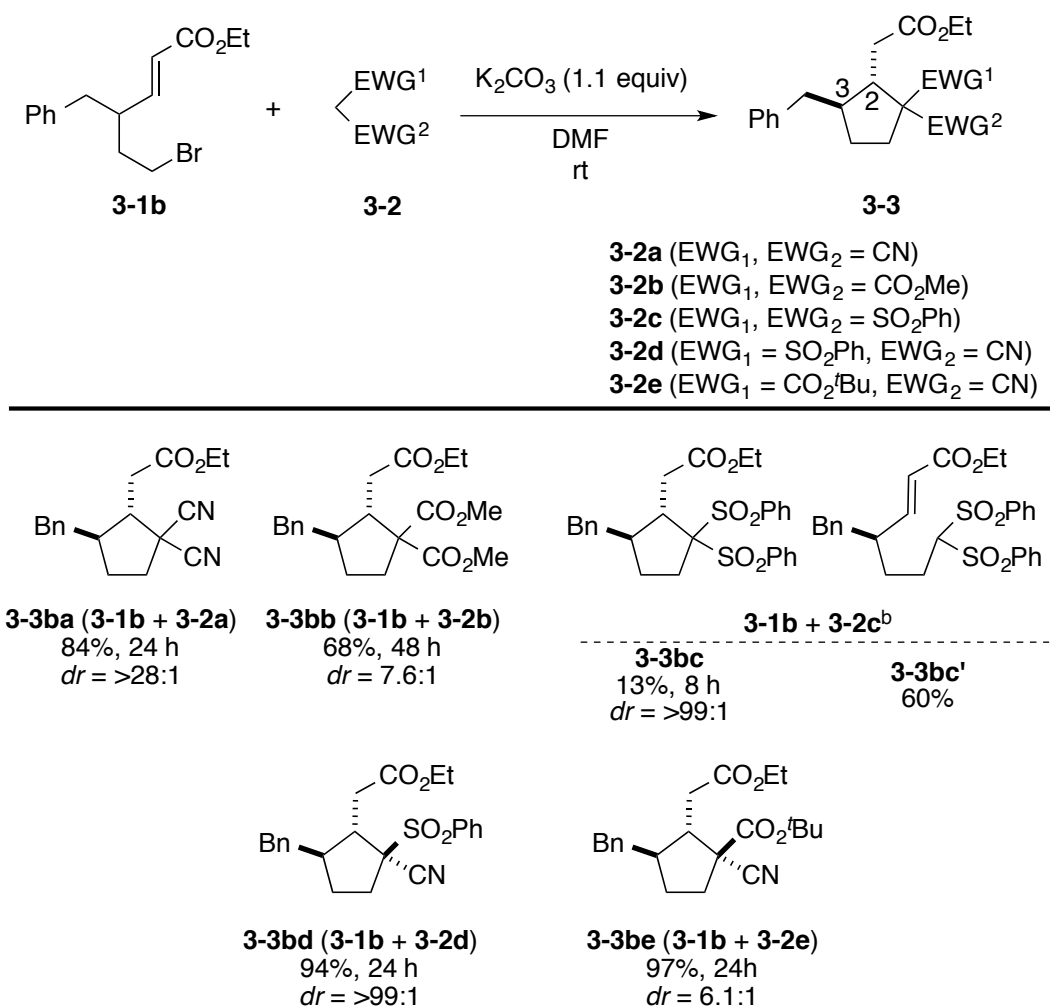
Table 3-2.

3-1a	+ 3-2a (x equiv)	bases (1.1 equiv)	conditions rt	3-3aa	
entry	bases	x	solvents	time/h	yield/%
1	NaH	2	DMF	5	75
2	NaH	2	DMSO	5	82
3	NaH	2	MeCN	10	61
4	NaH	2	THF	10	75
5	K ₂ CO ₃	1.5	DMF	17	84
6	K ₂ CO ₃	1.5	DMSO	27	74

3.3.1. Screening of nucleophiles

The author next performed studies on the base-mediated alkylation-conjugate addition reaction by subjecting (*E*)-ethyl 4-benzyl-6-bromo-2-hexenoate (**3-1b**) to a

series of active methylene compounds **3-2** in the presence of K_2CO_3 in DMF as a solvent (Scheme 3-10). It was found that malononitrile (**3-2b**) and dimethylmalonate (**3-2c**) underwent smooth reactions at room temperature to afford trisubstituted-cyclopentanes **3-3bb** and **3-3bc** in good yields with high 2,3-*trans*-diastereoselectivity. Employing bis(phenylsulfonyl)methane (**3-2d**) as a nucleophile needed higher reaction temperature (60°C), giving only 13% yield of the corresponding cyclopentane **3-3bd** as a single isomer along with isolation of the S_N2 -alkylated product **3-3bd'** in 60% yield. By utilizing (phenylsulfonyl)acetonitrile (**3-2a**) and *tert*-butyl cyanoacetate (**3-2e**), cyclopentanes **3-3ba** and **3-3be** bearing three successive stereogenic centers could be constructed. The reaction with (phenylsulfonyl)acetonitrile (**3-2a**) provided **3-3ba** as a single isomer in excellent yield, while that of *tert*-butyl cyanoacetate (**3-2e**) suffered a lower diastereoselectivity (6.1:1).



^a Reactions were performed on the scale of 0.2 mmol of **3-1b** with 1.5 equiv. of **3-2** in DMF (2 mL) at rt under a N₂ atmosphere. Isolated yields, diastereoselectivity ratios were determined by analysis of crude ¹H NMR. ^b Reaction conducted at 60 °C

Scheme **3-10**. Screening of pronucleophiles for synthesis of cyclopentanes

3.3.2. Synthesis of cyclopentanes bearing two successive stereogenic centers

Encouraged by the highly diastereoselective synthesis of cyclopentanes using malononitrile (**3-2b**), efforts were next directed at studying how the substituent R¹ affects the diastereoselectivity. Thus, the reactions of various 4-substituted 6-bromo-2-hexenoates were examined (Table 3-3). Methyl (**3-1c**), methoxy-methyl (**3-1d**), allylic (**3-1e**), propargylic (**3-1f**), isopropyl (**3-1g**) and phenyl (**3-1h**) moieties could be installed to afford the corresponding cyclopentanes in good to excellent chemical yields with high *trans*-diastereoselectivity (entries 1-6). On the other hand, poor diastereoselectivity was observed for the reactions of **3-1i** with a siloxy ether (*dr* = 1.2:1) and **3-1j** with a benzyl ether (*dr* = 1.9:1), respectively

(entries 7 and 8). Indane derivative **3-3kb** could also be accessed from benzene-tethered substrate **3-1k** in quantitative yield (entry 9).

Table 3-3. Synthesis of dicyano-cyclopentanes^a

3-1 3-2b $\xrightarrow[\text{DMF, rt}]{\text{K}_2\text{CO}_3 \text{ (1.1 equiv)}}$ 3-3						
entry	R ¹		time/h	yield/% ^b	dr ^c	
1	Me	3-1c	9	84	10:1	3-3cb
2		3-1d	18	94	12.1:1	3-3db
3		3-1e	8	86	32:1	3-3eb
4		3-1f	21	86	35:1	3-3fb
5		3-1g	14	75	35:1	3-3gb
6	Ph	3-1h	10	83	>99:1	3-3hb
7	OTBS	3-1i	24	81	1.2:1 ^d	3-3ib
8	OBn	3-1j	24	89	1.9:1 ^d	3-3jb
9		3-1k	24	quant.	—	3-3kb

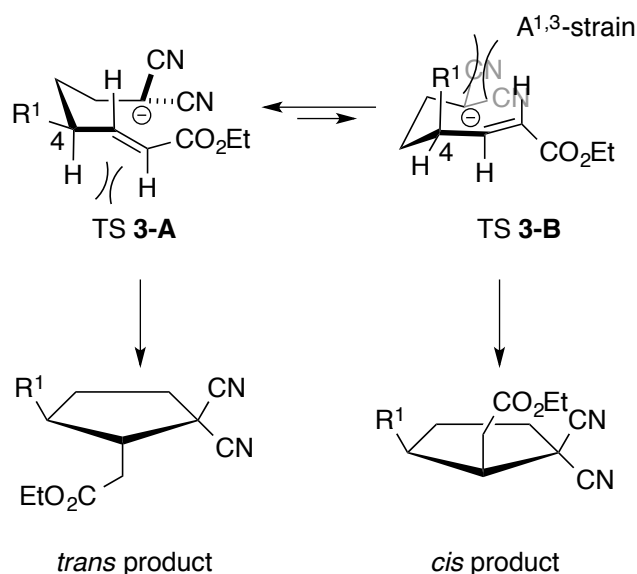
^a Reactions were performed on the scale of 0.2 mmol of **3-1** with 1.5 equiv. of **3-2b** in DMF (2 mL) at rt under a N₂ atmosphere. ^b Isolated yields.

^c Diastereoselectivity ratios were determined by analysis of crude ¹H NMR.

^d Major diastereomer was not determined.

The high *trans*-diastereoselectivity could be rationalized by the transition state during the cyclization (the intramolecular conjugate addition) (Scheme 3-11). In TS-3-B for the *cis*-product formation, the C(4) substituent R¹ presents obvious allylic 1,3-strain (A^{1,3}-strain)³⁸, while in TS-3-A for the *trans*-product formation, the C(4) substituent R¹ does not experience any significant A^{1,3}-strain.

Additionally the C(4) substituent R¹ occupies the favorable *pseudo*-equatorial position in TS-3-A.



Scheme 3-11. Allylic^{1,3}-strain in transition state leading to observed stereochemistry

3.3.3. Synthesis of cyclopentane bearing three successive stereogenic centers

Scope and limitation on synthesis of cyclopentanes bearing three successive stereogenic centers were next examined by employing (phenylsulfonyl)acetonitrile (**3-2a**) as nucleophile (Table 3-4). By varying substituent R¹, moderate diastereoselectivity (8.8:1-15.7:1) was observed for **3-3ca** and **3-3da** having methyl and methoxy methyl groups (entries 1 and 2), respectively, while single stereoisomers were isolated in good to excellent chemical yields for **3-3ea** (for allyl), **3-3fa** (for propargyl), **3-3ga** (for isopropyl), and **3-3ha** (for phenyl) (entries 3-6). It is also noted that benzene tethered substrate **3-1k** could be transformed to indane **3-3ka** having two-successive stereogenic centers (entry 7). The stereochemistry of the major isomer was confirmed by single X-ray crystallographic analyses for cyclopentanes **3-3ca** and **3-3fa**, showing 1,2-*trans*-2,3-*trans*-configuration (Figures 3-1a and 3-1b).

Table 3-4. Synthesis of cyano-sulfonyl-cyclopentanes^a

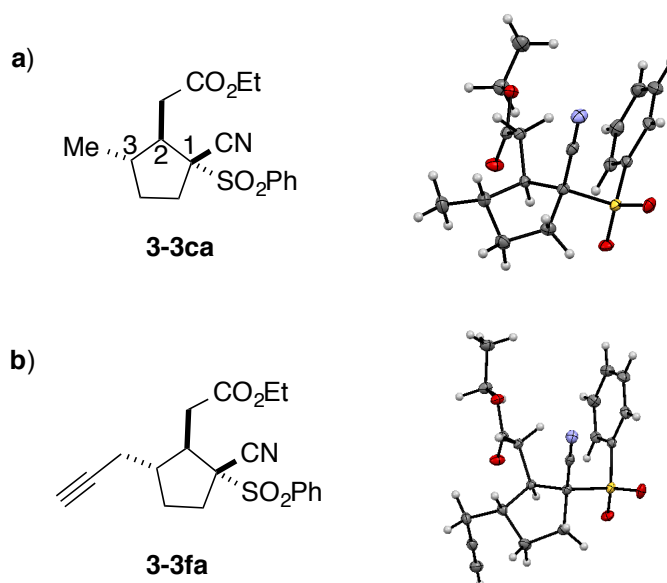
$\text{3-1} + \text{3-2a} \xrightarrow[\text{DMF, rt}]{\text{K}_2\text{CO}_3 (1.1 \text{ equiv})} \text{3-3}$

entry	R ¹		time/h	yield/% ^b	dr ^c	
1	Me	3-1c	23	73	8.8:1	3-3ca
2	MeO	3-1d	18	89	15.7:1	3-3da
3		3-1e	19	87	>99:1	3-3ea
4		3-1f	23	81	>99:1	3-3fa
5		3-1g	14	78	>99:1	3-3ga
6	Ph	3-1h	24	92	>99:1	3-3ha
7		3-1k	5	76	>99:1	3-3ka

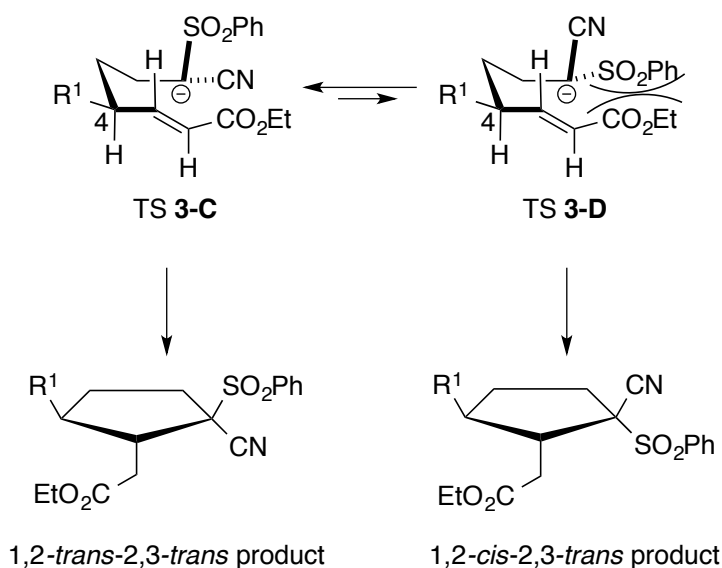
^a Reactions were performed on the scale of 0.2 mmol of **3-1** with 1.5 equiv. of **3-2a** in DMF (2 mL) at rt under a N₂ atmosphere. ^b Isolated yields.

^c Diastereoselectivity ratios were determined by analysis of crude ¹H NMR.

Figure 3-1 Ortep drawing of **3-3ca** and **3-3fa**



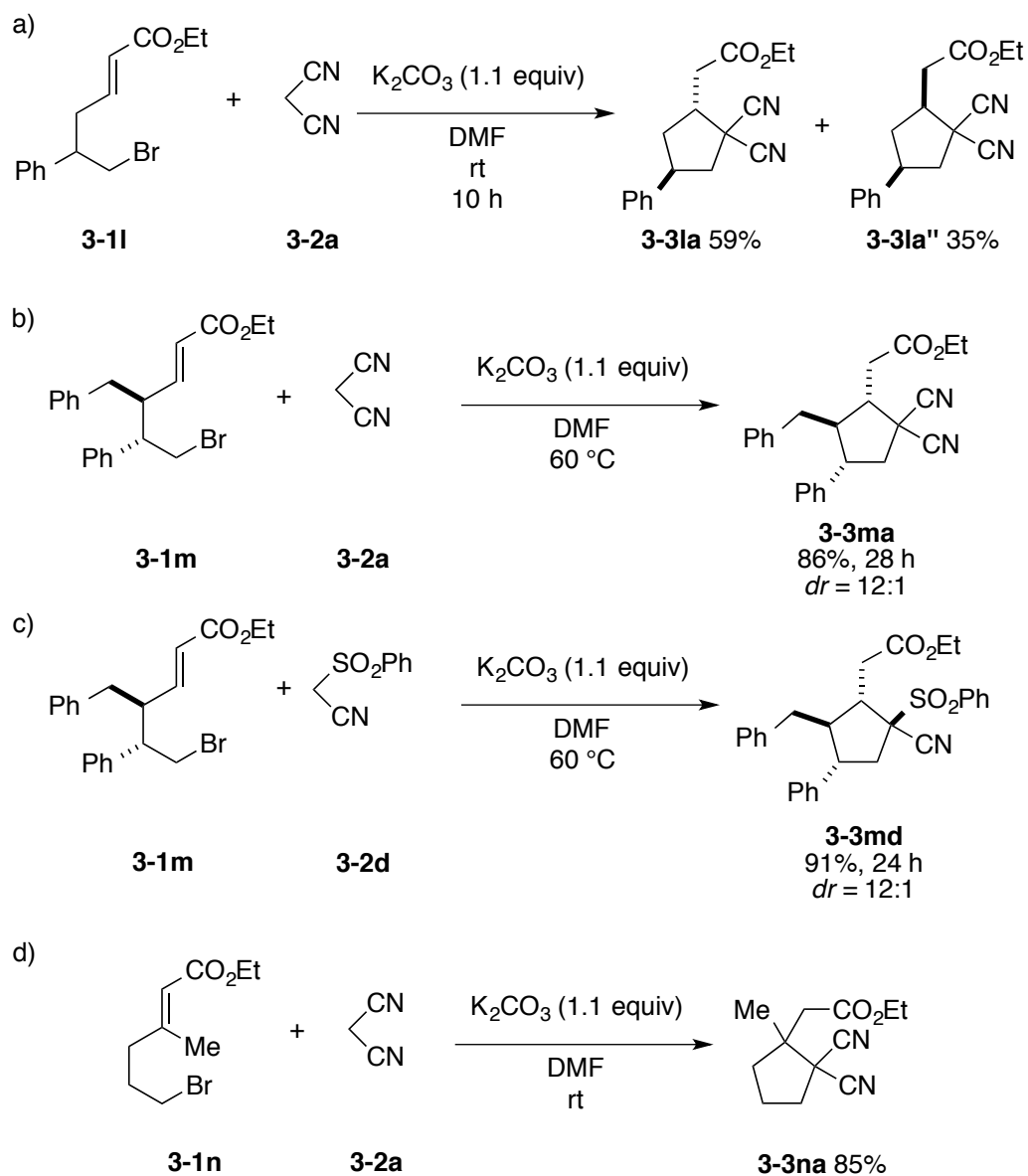
The formation of 2,3-*trans*-configuration could be explained by the A^{1,3}-strain between the C(4) substituent and the acrylate part, in which the favorable *pseudo*-equatorial position is occupied by the C(4) substituent (Scheme 3-12). In addition, 1,2-*trans*-selectivity could be originated from the steric repulsion of the bulky sulfonyl moiety with the acrylate moiety in TS, thus favoring the cyano group having “*syn*” relationship with the acrylate moiety (TS-3-C vs TS-3-D).



Scheme 3-12. Steric interaction between sulfonyl moiety and ethoxy carbonyl moiety

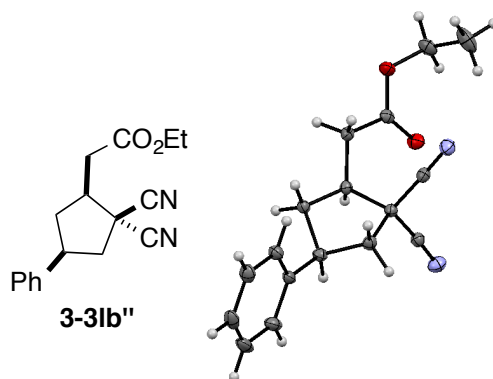
3.3.4. Effect of the substituents on the other positions for diastereoselectivity

The author next investigated the effect of the substituents of 6-bromo-2-hexenoates on the other positions (Scheme 3-13). Installation of a phenyl group on C(5) position of **3-1l** rendered the diastereoselectivity lowered in the reaction with malononitrile (**3-2b**), giving trisubstituted cyclopentane 2,4-*trans*-**3-3lb** and 2,4-*cis*-**3-3lb**'' in 1.69:1 ratio (Scheme 3-13-a). The stereochemistry of the minor diastereomer 2,4-*cis*-**3-3lb**'' was secured by single X-ray crystallographic analysis (Figure 3-2). The reactions of 4,5-*trans*-disubstituted 6-bromo-2-hexenoate **3-1m** with malononitrile (**3-2b**) and (phenylsulfonyl)acetonitrile (**3-2a**) provided tetrasubstituted cyclopentane **3-3mb** and **3-3ma**, respectively in good diastereoselectivity (Scheme 3-13-b and 3-13-c). These results indicated that the diastereoselectivity of the present strategy relies mostly on C(4) substituent. Construction of a quaternary carbon center of cyclopentane **3-3nb** was achieved in good yields by employing (*E*)-ethyl 6-bromo-3-methylhex-2-enoate (**3-1n**) with **3-2b** (Scheme 3-13-d).



Scheme **3-13**. Reactions were performed on the scale of 0.2 mmol of **3-1** with 1.5 equiv. **3-2** in DMF (2 mL) at rt or 60 °C under a N₂ atmosphere, isolated yields, diastereoselectivity ratios were determined by analysis of crude ¹H NMR.

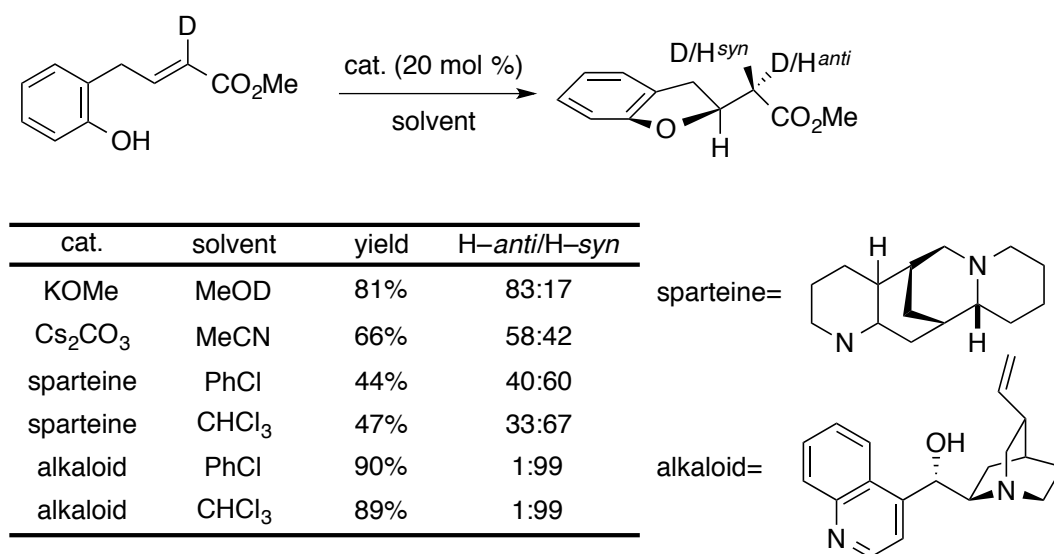
Figure 3-2. Ortep drawing of **3-3lb''**



3.3.5. Protonation of transient enolate arising from conjugate addition

The conjugate addition was commonly considered as a stepwise reaction, whereby the nucleophile attacks the β -carbon of the α,β -unsaturated compound, resulting in the formation of an enolate intermediate. Subsequent protonation of the enolate delivers the product. This stepwise 1,4-addition mechanism usually results in formation of a mixture of diastereomers.

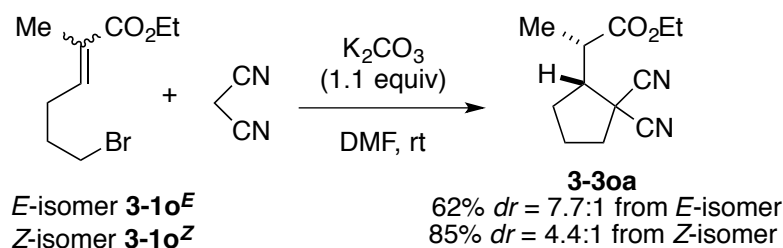
In light of recent works by Hintermann, a mechanistically different pathway has been proposed for the cinchona alkaloid-catalyzed oxa-conjugate addition (Scheme 3-14).³⁹ The authors found that oxa-conjugate addition mediated by cinchona alkaloid proceeded exclusively with the *syn*-addition across the alkene (the newly formed C–O bond and C–H bond are *syn* to each other). The authors proposed that the nucleophile attacks the β -carbon of α,β -unsaturated acceptor along with protonation on the α -carbon occurring simultaneously. Due to the 1,2-concerted addition-protonation, a stereospecific *syn*-facial 1,2-addition of the oxygen and the hydrogen atom is observed.



Scheme 3-14. Investigation of protonation in oxa-Michael reaction

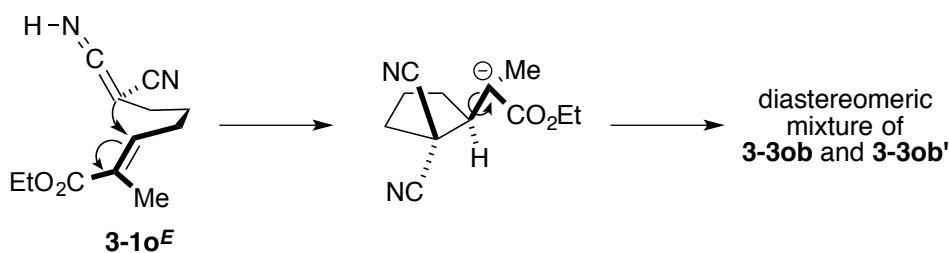
Subjecting (*E*)-ethyl 6-bromo-2-methylhex-2-enoate (**3-10^E**) to the standard reaction conditions with malononitrile (**3-2b**), cyclopentane **3-3ob** with good diastereoselectivity (7.7:1), where the (*S**,*R**)-isomer was formed as a major product (the determination of the relative stereochemistry of **3-3ob** is discussed in Section 3.3.7.1., Scheme 3-19). By utilizing (*Z*)-ethyl 6-bromo-2-methylhex-2-

enoate (**3-1o^Z**), the same (*S*^{*}, *R*^{*})-isomer was obtained as the major product albeit lower diastereoselectivity (4.4:1) (Scheme 3-15).



Scheme 3-15. Substrate design to probe protonation process

These results indicate that in the present system, the intramolecular conjugate addition and protonation occurs in a stepwise manner. Mechanistically, the free-rotating C-C bond of the resulting enolate would result in a mixture of diastereomers after the subsequent protonation (Scheme 3-16).

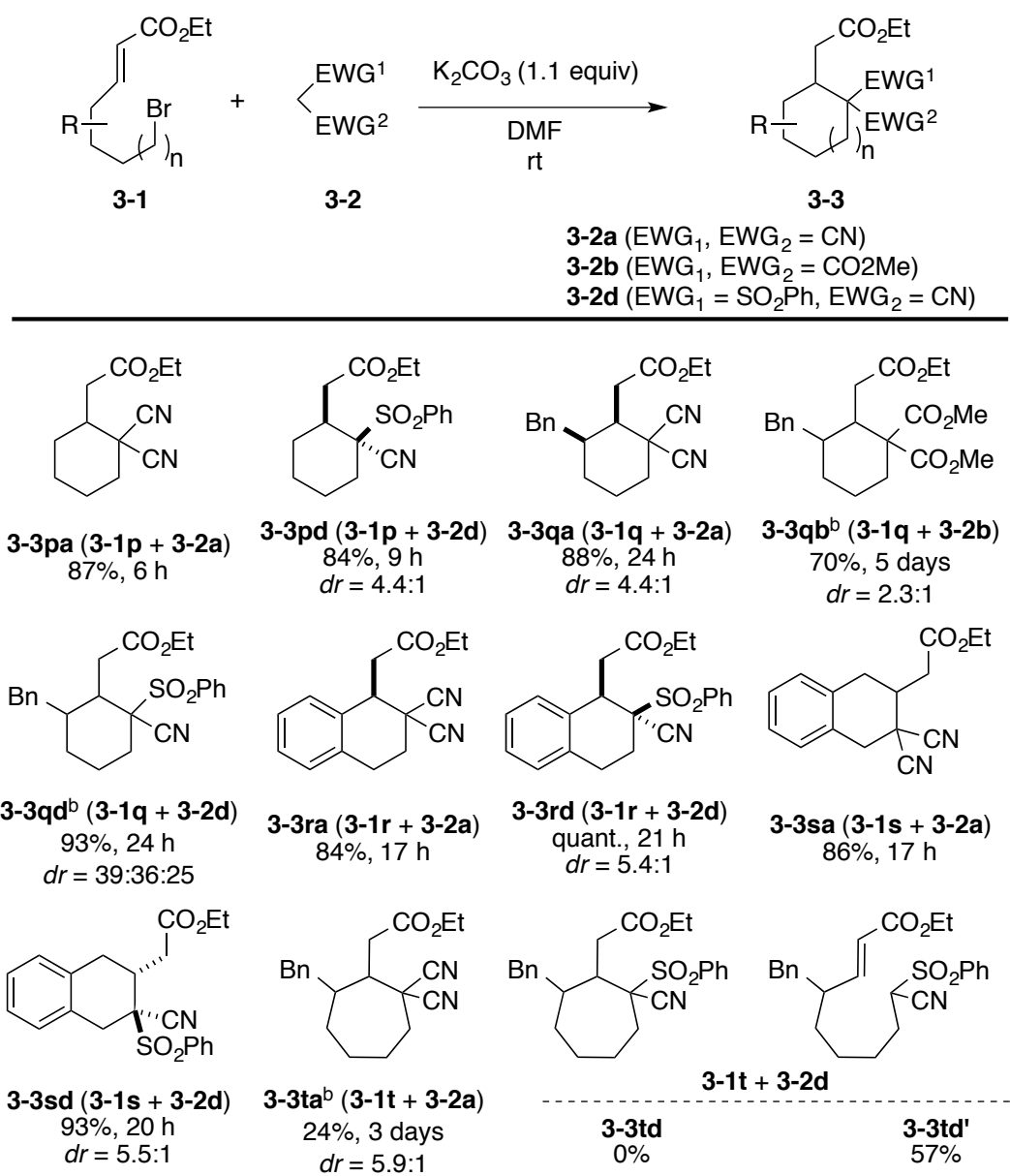


Scheme 3-16. Stepwise conjugate addition-protonation process

3.3.6. Construction of cyclohexane and cycloheptane frameworks

Attention was next directed at the construction of functionalized cyclohexane and cycloheptane frameworks. The reactions of **3-1p** with malononitrile (**3-2b**) and (phenylsulfonyl)acetonitrile (**3-2a**) proceeded smoothly to provide cyclohexanes **3-3pb** and **3-3pa** in 87% and 89% yields respectively, however the diastereoselectivity was moderate (4.4:1) when **3-2a** was employed. Starting from (*E*)-ethyl 5-benzyl-7-bromo-hep-2-enoate (**3-1q**) with malononitrile (**3-2b**), the corresponding cyclohexane **3-3qb** was obtained in 88% as a diastereomeric mixture of 4.4:1. Interestingly, the major isomer was found to bear 2,3-*cis* stereochemistry, that was secured by single X-ray crystallographic analysis (Figure 3-3). Switching to dimethylmalonate (**3-2c**) as nucleophile rendered the reaction sluggish providing cyclohexane **3-3qc** in 70% as a diastereomeric mixture of 2.3:1

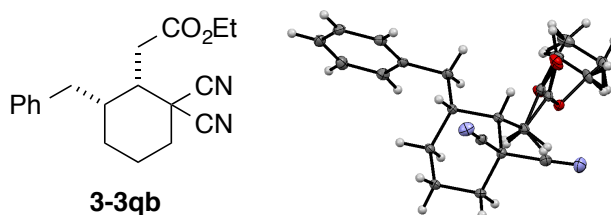
after 5 days. (Phenylsulfonyl)acetonitrile (**3-2a**) was next employed as nucleophile, however the reaction provided three inseparable diastereomers with low selectivity despite excellent isolated yield. Next, tetrahydronaphthalene derivatives could also be access in good to excellent yields starting from **3-1r** and **3-1s** with both malononitrile (**3-2b**) and (phenylsulfonyl)acetonitrile (**3-2a**) as nucleophile. In the case when (phenylsulfonyl)acetonitrile (**3-2a**) was utilized, moderate diastereoselectivity was observed. Finally, to target cycloheptane frameworks, ethyl (*E*)-4-benzyl-8-bromooct-2-enoate (**3-1t**) was utilized. By employing malanonitrile (**3-2b**) as nucleophile, cycloheptane **3-3tb** was isolated in only 24% as separable diastereomers in 5.9:1 ratio after 3 days, although stereochemistry of the major isomer was not determined. No cycloheptane **3-3ta** was observed when (phenylsulfonyl)acetonitrile (**2a**) was utilized as nucleophile even at 60 °C, just providing the alkylated product **3-3ta'** in 57% yield.



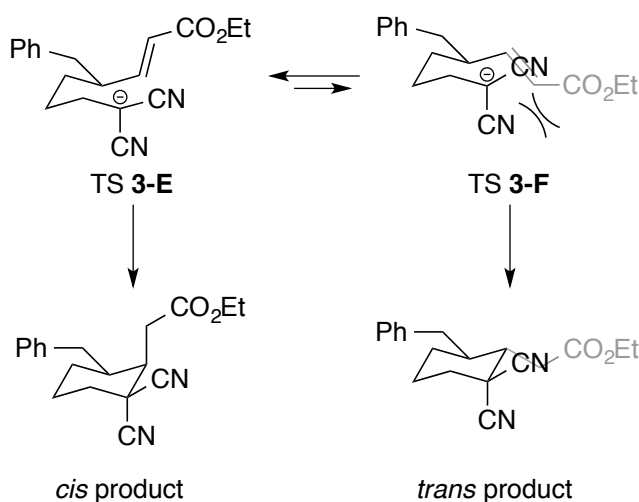
^a Reactions were performed on the scale of 0.2 mmol of **3-1** with 1.5 equiv. of **3-2** in DMF (0.2 mL) at rt under a N₂ atmosphere, isolated yields, diastereoselectivity ratios were determined by analysis of crude ¹H NMR. ^b The major diastereomer was not determined.

Scheme 3-17. Screening of pronucleophiles for synthesis of cyclohexanes and cycloheptanes

Figure 3-3. Ortep drawing of **3-3qb**



The observed *cis*-configuration for cyclohexane **3-3qb** could be rationalized by the steric repulsion between the acrylate moiety and the cyano group in the 6-membered chair-like transition state (TS-3-F). The moderate diastereoselectivity (4.4:1) could suggest that the energy gap between TS-3-E and TS-3-F may be small (Scheme 3-18).



Scheme 3-18. Steric interaction between sulfonyl moiety and ethoxy carbonyl moiety

3.3.7. Facile transformations of cyclopentane and cyclohexane derivatives

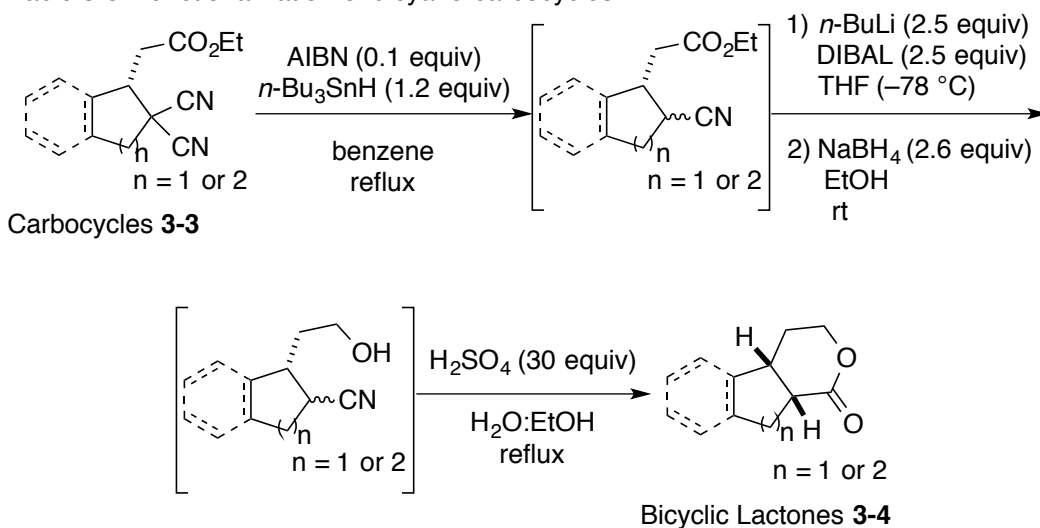
Having synthesized various carbocycles, the author next strived to develop facile chemical transformations of them into further functionalized carbocycles.

3.3.7.1. Synthesis of bicyclic lactones by sequential decyanation-chemoselective reduction-lactonization

Treatment of cyclopentane **3-3bb** having the 1,1-dicyano moiety with *n*-Bu₃SnH in the presence of a catalytic amount of AIBN induced mono-decyanation.⁴⁰ Subsequently, the resulting mono-cyanocyclopentane product was reduced by the “ate” aluminium hydride complex prepared by mixing *n*-BuLi and DIBAL,⁴¹ that realized chemoselective reduction of the ethoxycarbonyl group to a mixture of aldehyde and alcohol. This mixture was further treated with NaBH₄ to fully convert aldehyde to alcohol. Finally, the resulting alcohol was treated with aqueous acid to afford *cis*-bicyclic lactone **3-4bb** in 33% yield in 3 steps (Table 3-5, entry 1). The stereochemistry of **3-4bb** was determined by the positive NOE

correlation between the bridging hydrogens (Figure 3-4-a). By following this procedure, **3-3ob** could be converted into *cis*-bicyclic lactone **3-4ob** in 40% yield (entry 2). *Tri*-cyclic carbocycles **3-4rb** and **3-4sb** were also obtained from the corresponding tetrahydronaphthalenes **3-3rb** and **3-3sb** (entries 3 and 4). The stereochemistry for **3-4rb**, having a *cis*-bridged lactone was determined by the positive correlation of NOE between the bridging hydrogens (Figure 3-4-b). The stereochemistry of **3-3sb**, having a *trans*-bridged lactone was determined by the presence of a large coupling constant (11.9 Hz) on the α -hydrogen of the carbonyl with another bridging hydrogen. Such observation indicates a large dihedral angle coupling in which only *trans*-annulated bicyclic lactone is possible (Figure 3-4 c).⁴²

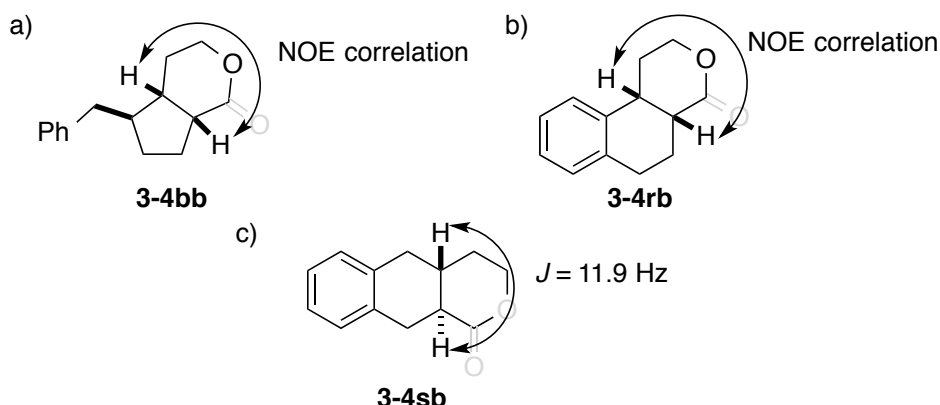
Table 3-5. Functionalization of dicyano-carbocycles



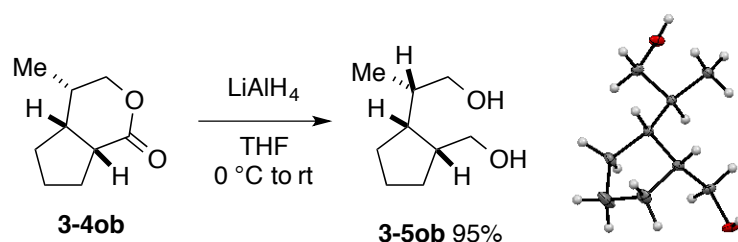
entry	Carbocycle 3-3	Bicyclic Lactones 4-4^a
1	3-3ba	3-4ba 33%
2	3-3oa	3-4oa 40%
3	3-3ra	3-4ra 43% <i>dr</i> = 3.9:1^b
4	3-3sa	3-4sa 43% <i>dr</i> = 3.1:1^b

^a Isolated yields over 3 steps. ^b Diastereoselectivity determined from analysis of crude ¹H NMR.

Figure 3-4. Determination of stereochemistries



In addition, lactone **3-4ob** was further subjected to lithium aluminium hydride reduction to afford the corresponding diol **3-5ob** (Scheme 3-19). Single X-ray crystallographic analysis of the diol revealed the relative stereochemistry of **3-4ob**, that is also used to deduce the stereochemistry in **3-3ob** (Section 3.3.5., Scheme 3-15).

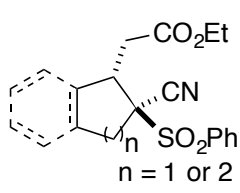
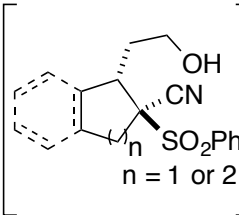
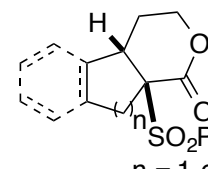
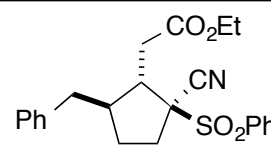
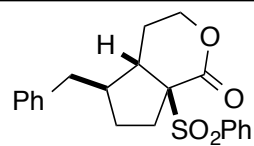
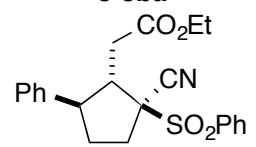
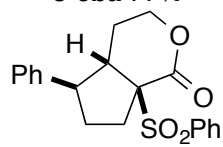
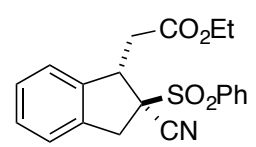
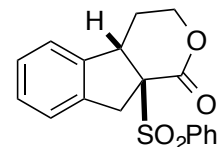
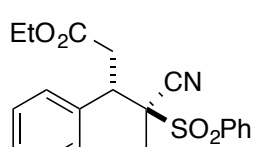
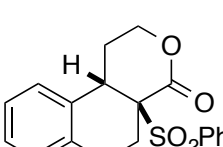
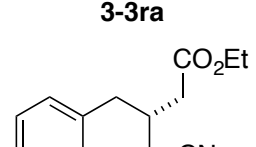
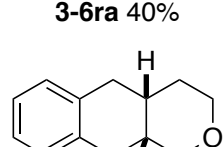


Scheme 3-19. Reduction of bicyclic lactone **3-4na** leading to the determination of protonation pathway

3.3.7.2. Synthesis of bicyclic-lactones using sequential chemoselective reduction-lactonization strategy

The chemoselective reduction using the aluminium hydride “ate” complex could be applied on cyclopentanes **3-3ba** and **3-3ha** having cyano and phenylsulfonyl groups to afford the corresponding alcohols. Acid-mediated lactonization successfully delivered *cis*-bicyclic lactones **3-6ba** and **3-6ha**, respectively in good yields (Table 3-6, entries 1 and 2). *Tri*-cyclic lactones **3-6ka**, **3-6ra** and **3-6sa** could also be accessed using this strategy (entries 3-5).

Table 3-6. Functionalization of cyano-sulfonyl-carbocycles

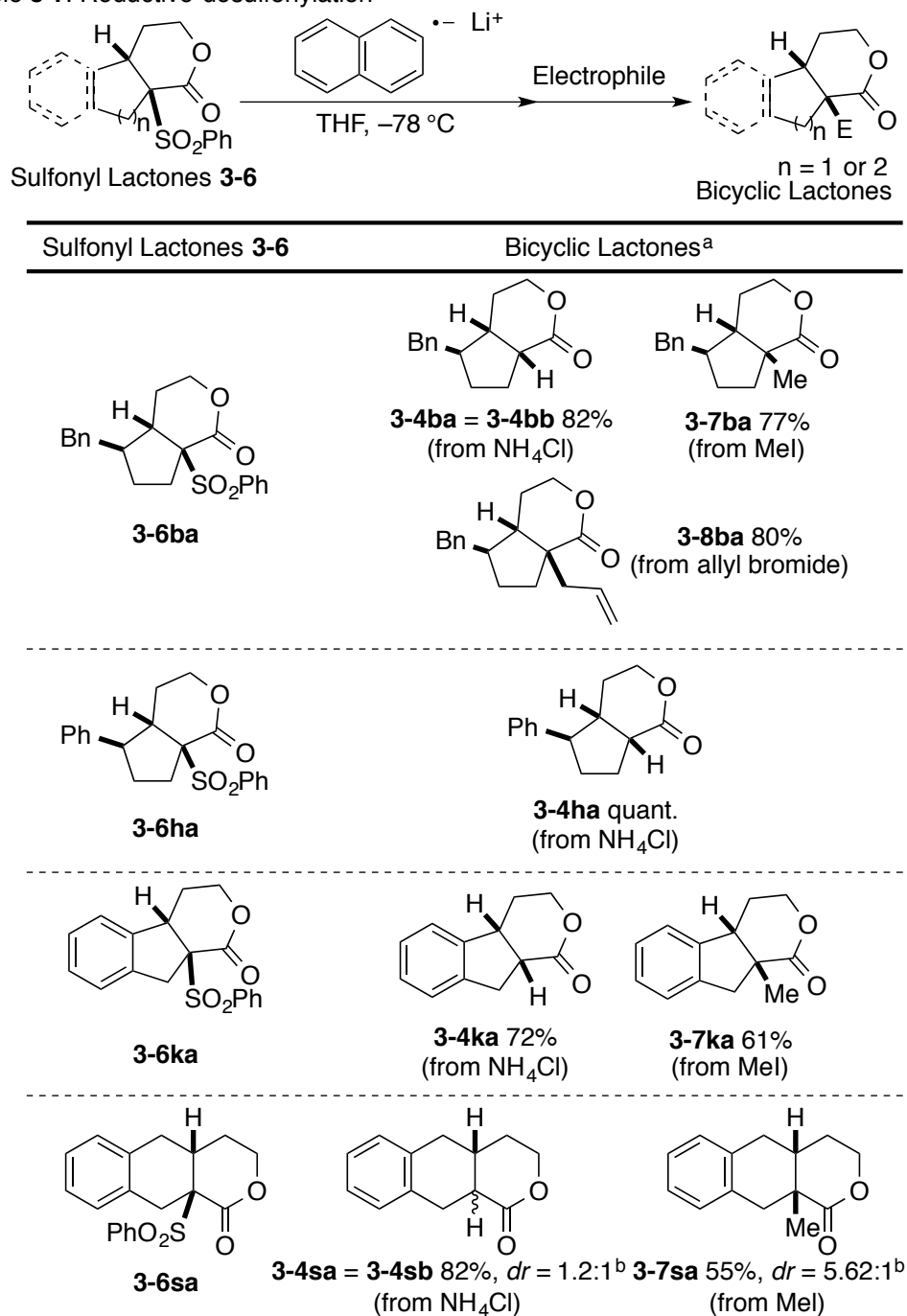
 Carbocycles 3-3 1) <i>n</i>-BuLi (2.5 equiv) DIBAL (2.5 equiv) THF (−78 °C) 2) NaBH₄ (2.6 equiv) EtOH rt []		
 Sulfonyl Lactones 3-6		
entry	Carbocycles 3-3	Sulfonyl Lactones 3-6 ^a
1	 3-3ba	 3-6ba 77%
2	 3-3ha	 3-6ha 79%
3	 3-3ka	 3-6ka 82%
4	 3-3ra	 3-6ra 40%
5	 3-3sa	 3-6sa 81%

^a Isolated yields over 2 steps.

3.3.7.3. Sequence of reductive desulfonation- protonation or -alkylation

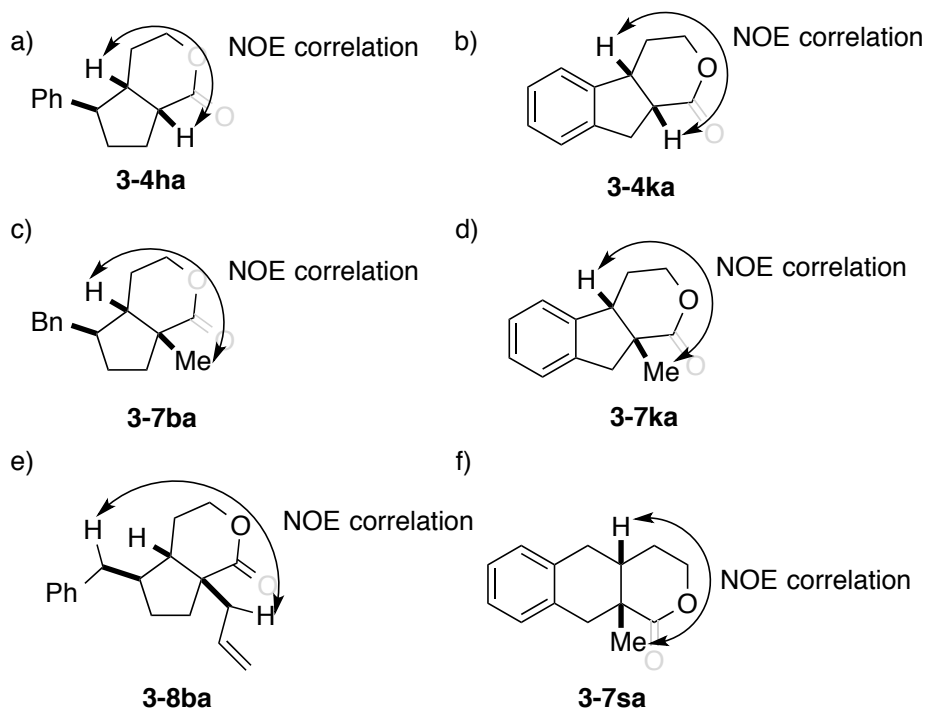
Synthetic utility of phenylsulfonyl lactones **3-6** were further demonstrated by reductive desulfonation using lithium naphthalenide (Table 3-7). Treatment of phenylsulfonyl lactones **3-6ba**, **3-6ha**, **3-6ka**, and **3-6sa** with lithium naphthalenide resulted in reductive desulfonation to form the corresponding lithium enolates. Protonation of the resulting lithium enolates generated from **3-6ba**, **3-6ha**, and **3-6ka** with aqueous NH₄Cl provided *cis*-bicyclic lactone **3-4ba**, **3-4ha** and **3-4ka**, respectively with the retention of the stereo-configuration of the starting sulfonyl lactones **3-6**. While the ¹H NMR spectrum of **3-4ba** matches those of **3-4bb**, the stereochemistries of **3-4ha** and **3-4ka** were confirmed by the positive NOE correlations between the bridging hydrogens (Figures 3-5-a and 3-5-b). Instead of protonation, the lithium enolates could be trapped with carbon electrophiles such as methyl iodide and allyl bromide, giving **3-7ba** and **3-8ba** from **3-6ba** as well as **3-7ka** from **3-6ka** with the retention of the configuration. The stereochemistries of **3-7ba** and **3-7ka** were confirmed by the positive NOE correlation between the newly installed methyl group and the bridging hydrogen (Figures 3-5-c and 3-5-d). The stereochemistry of **3-8ba** was determined with the positive NOE correlation between the benzylic hydrogens and allylic hydrogens (Figure 3-5-e). On the other hand, in the case of functionalization of the lithium enolate formed from **3-6sa**, protonation with NH₄Cl afforded **3-4sa** as a mixture of diastereomers in 1.2:1 ratio, in which the major diastereomer's ¹H NMR spectrum matches that of **3-4sb**. Methylation with methyl iodide provided **3-7sa** in 55% yield with diastereoselectivity of 5.62:1, in which the major isomer had a *cis*-bridged lactone. The stereochemistry was confirmed by the positive NOE correlation between the newly installed methyl group and the bridging hydrogen (Figure 3-5-f).

Table 3-7. Reductive desulfonylation



^a Isolated yields. ^b Diastereoselectivity ratio were determined from analysis of crude ¹H NMR.

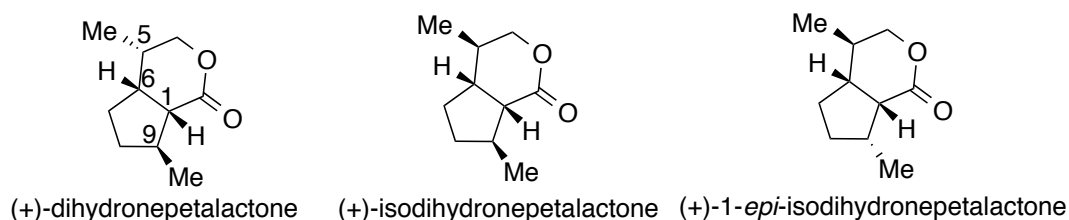
Figure 3-5. Determination of stereochemistries



3.4. Synthesis of dihydronepetalactone, isodihyronepetalactone, and 1-*epi*-isodihyronepetalactone

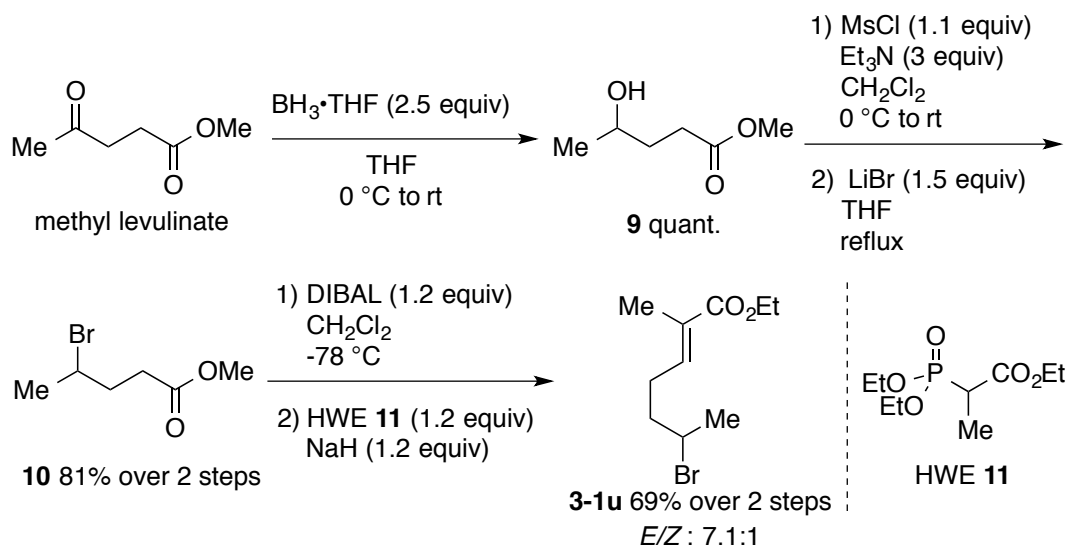
(+)-Dihyronepetalactone was isolated in 1965 from the leaves and galls of *Actinidia polygama*, having *cis*-fused bicyclic lactone with a cyclopentane framework.⁴³ In nature, it is often found as diastereomeric mixture along with (+)-isodihyronepetalactone and (+)-1-*epi*-isodihyronepetalactone and known to have physiological effects on *Felidae* animals (Figure 3-6).^{44,45,46} Recently, it was tested and approved for application in mosquito and tick repellents by United States's Environment Protection Agency (EPA),⁴⁷ leading to several patents describing its synthesis.^{48,49,50} It has been identified as one of the compound responsible for the defensive mechanism of the *Iridomyrmex Nitidiceps* (Australian cocktail ant)^{51,52} and *Creophilus maillosus* (rove beetle).⁵³ Parallel studies have also shown (+)-dihyronepetalactone repels *Harmonia axyridis* adults (Asian lady beetle).⁵⁴

Figure 3-6. Structures of nepetalactones



3.4.1. Synthetic studies

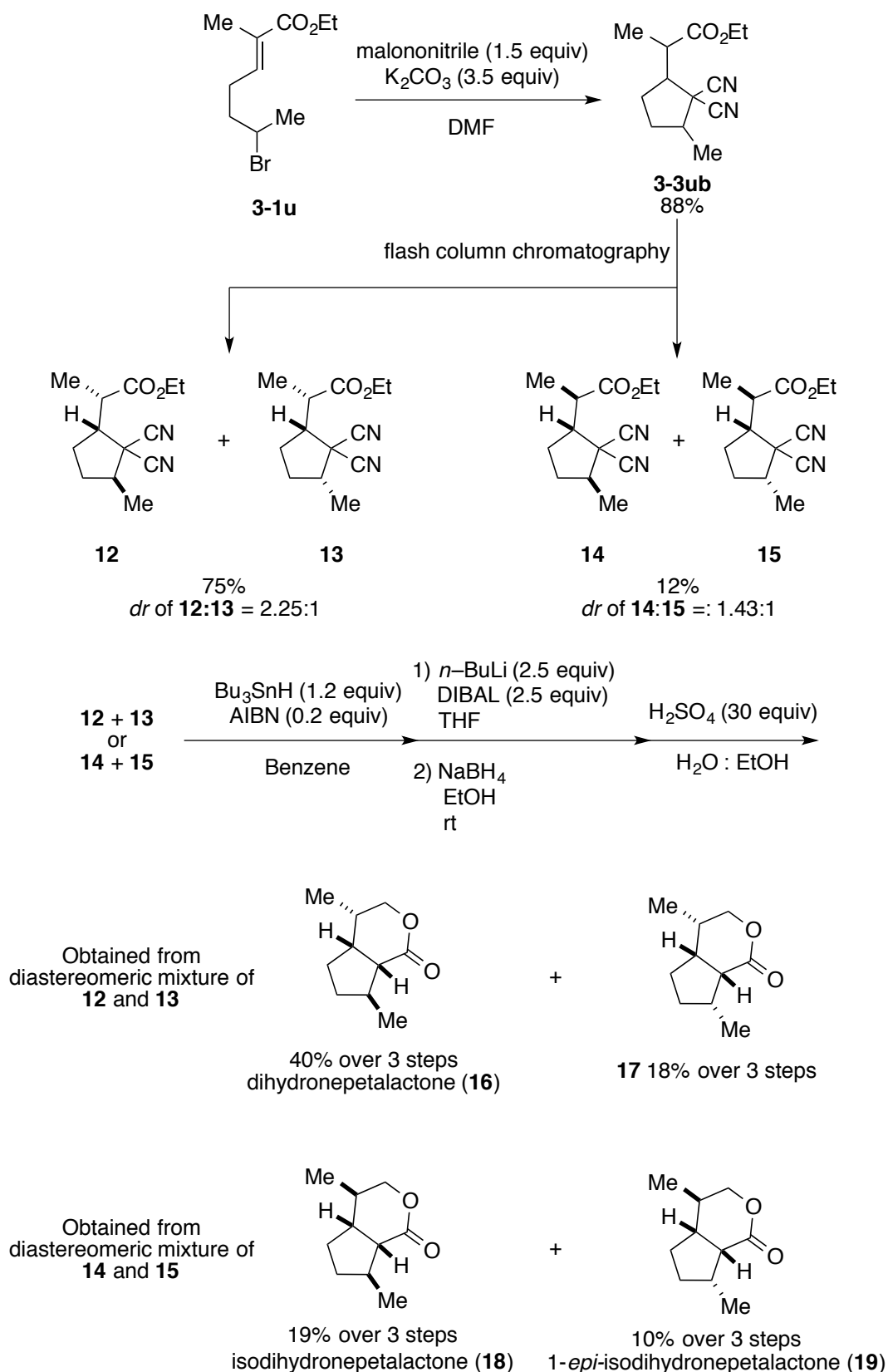
These bicyclic lactones bearing four stereogenic centers might be constructed using the strategies developed in this chapter. Starting from commercially available methyl levulinate, chemoselective reduction of its ketone moiety was achieved using $\text{BH}_3 \cdot \text{THF}$ (Scheme 3-20). The resulting alcohol **9** was converted to bromide **10** by the mesylation-bromination protocol. Finally, the installation of the acrylic functionality was achieved *via* DIBAL reduction of the ethoxy carbonyl group followed by Horner-Wadsworth-Emmons reaction of the resulting aldehyde with triethyl 2-phosphonopropionate (**11**) to furnish ethyl 6-bromo-2-methylhept-2-enoate (**3-1u**) as a 7.1:1 *E/Z* mixture.



Scheme 3-20. Preparation of precursor **3-1u**

Treatment of bromide **3-1u** with malononitrile (**3-2b**) in the presence of K_2CO_3 afforded a mixture of cyclopentane **3-3ub** including 4 diastereomeric

isomers in 87% combined yield (Scheme 3-21). At this stage, it was only possible to separate these 4 diastereomers into 2 pair of inseparable diastereomers by column chromatography. The major pair of diastereomers **12** and **13** were isolated in 75% yield. The diastereomeric ratio was determined by gas chromatography analysis to be 2.25:1. The minor pair of diastereomers **14** and **15** were isolated in 12% yield with the diastereomeric ratio being 1.43:1. Subsequent decyanation-reduction-lactonization strategy on the major pair of the diastereomers **12** and **13** delivered dihydronepetalactone (**16**) in 40% yield with another unidentified isomer **17** in 18% yield. The same transformation was also applied on the minor pair of the diastereoisomers **14** and **15**, from which isodihydronepetalactone (**18**) was obtained in 19% yield along with 1-*epi*-isodihydronepetalactone (**19**) in 10% yield. The ^1H and ^{13}C NMR spectra of dihydronepetalactone (**16**),^{46,52} isodihydronepetalactone (**18**)^{46,52} and 1-*epi*-isodihydronepetalactone (**19**)^{46,55} were all identical with those reported in the literature data. By considering the *cis*-bridged lactone might be the possible structure constructed by the present lactone formation, a total of 4 diastereomers could be generated in the final products. Since the structures of three products could be confirmed by the comparison with the literature data, the remaining unidentified isomer **17** could be speculated as (4*S**,4*aR**,7*R**,7*aR**)-4,7-dimethylhexahydrocyclopenta[*c*]pyran-1(3*H*)-one.⁵⁶ Based on these observations, the chemical structures of intermediates **12-15** could also be estimated as indicated in Scheme 3-21.



Scheme 3-21. Synthesis of dihydronepetalactone, isodihyronepetalactone and 1-*epi*-isodihyronepetalactone

3.5. Conclusion

In conclusion, the author developed a sequence of S_N2 -conjugate addition for the construction of highly functionalized cyclopentane and cyclohexane derivatives. Effects of the substituents on diastereoselectivity of the present cyclization were studied. Moreover, facile chemical transformations on the resulting carbocycles could provide access to bicyclic/tricyclic lactones.

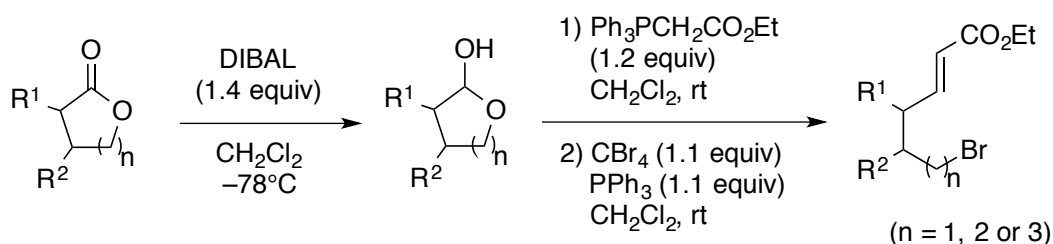
3.6. Experimental section

3.6.1. General

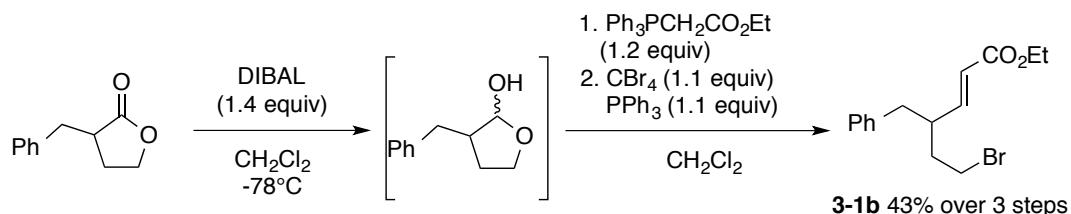
^1H NMR (400 MHz) spectra were recorded either on a Bruker Avance 400 spectrometer or ECA JEOL 400 MHz in CDCl_3 [using TMS (for ^1H , $\delta = 0.00$) as internal standard]. ^{13}C NMR (100 MHz) spectra on a Bruker Avance 400 spectrometer in CDCl_3 [using CDCl_3 (for ^{13}C , $\delta = 77.23$) as internal standard]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad. IR spectra were recorded on a Shimadzu IRAffinity-1 FT-IR Spectrometer. High-resolution mass spectra were obtained with a Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). Melting points are uncorrected and were recorded on a MPA 100 OptiMelt Automated Melting Point System. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Anhydrous DMF was purchased from Sigma-Aldrich and used as received. In the case where diastereomers could not be separated, the diastereoselectivity was determined by the analysis of crude ^1H NMR.

3.6.2. Synthesis of 6-halo-2-hexenoates, 7-halo-2-heptenoates and 8-halo-2-octenoates

6-Halo-2-hexenoates, 7-halo-2-heptenoates and 8-halo-2-octenoates **1** were synthesized from the corresponding lactones via 1) DIBAL reduction to lactols; 2) the Wittig olefination of the crude lactols; 3) bromination of the resulting alcohols by CBr_4 and PPh_3 as shown below.

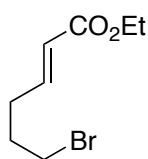


Typical Procedure for Synthesis of (*E*)-ethyl 4-benzyl-6-bromo-2-hexenoate (3-1b**):**



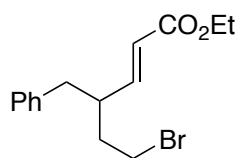
To a 2-neck round bottom flask containing 3-benzyl-2(3*H*)-tetrahydrofuran-2-one⁵⁹ (3.52 g, 20.1 mmol) in CH_2Cl_2 (50 mL) was added dropwise DIBAL (5.0 mL, 28.1 mmol 1.4 equiv), and the solution was stirred at -78°C for 6 h. Upon completion of the reaction, MeOH (10 mL) was added dropwise and the mixture was stirred at room temperature for 1 h. Filtration of the mixture through the Celite pad and removal of the solvents in vacuo afforded 3-benzyl-2-hydroxytetrahydrofuran, which is used for the next step without further purification. To a 2-neck round bottom flask including the crude mixture of 3-benzyl-2-hydroxytetrahydrofuran in CH_2Cl_2 (50 mL) was added ethyl 2-(triphenylphosphoranylidene)acetate (8.36 g, 24.0 mmol, 1.2 equiv). The mixture was stirred at room temperature under a N_2 atmosphere for 22 h. Upon completion of the reaction, the mixture was cooled to 0°C , and CBr_4 (7.29 g, 22.0 mmol, 1.1 equiv) and PPh_3 (5.77 g, 22.0 mmol, 1.1 equiv) were added. The mixture was then stirred at room temperature for 0.5 h. Hexane (30 mL) was added to the reaction mixture, and the resulting solids (including $\text{O}=\text{PPh}_3$) were filtered through the Celite pad. After removal of the solvents under reduced pressure, the resulting crude mixture was subjected to flash column chromatography (hexane : ethyl acetate = 9 : 1) to yield (*E*)-ethyl 4-benzyl-6-bromohex-2-enoate (**1b**) (2.69 g, 8.65 mmol, 43% yield).

(*E*)-ethyl 6-bromohex-2-enoate (**3-1a**)⁵⁷



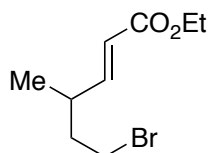
Yield: 68% (*E* : *Z* = 18.7 : 1) from γ -butyrolactone.⁵⁸ ¹H NMR (400 MHz, CDCl₃) δ 1.29 (3H, *J* = 7.1 Hz), 2.06-1.99 (2H, m), 2.41-2.36 (2H, m), 3.42 (2H, t, *J* = 6.6 Hz), 4.19 (2H, q, *J* = 7.1 Hz), 5.90 (1H, dt, *J* = 15.6, 1.6 Hz), 6.92 (1H, dt, *J* = 15.6, 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.5, 30.7, 31.0, 32.8, 60.5, 122.8, 146.9, 166.6.

(*E*)-ethyl 4-benzyl-6-bromohex-2-enoate (**3-1b**)



Yield: 43% (as a pure *E*-isomer) from 3-benzyl-2,3-dihydrofuran-2-one;⁵⁹ Colorless oil; IR (ATR) 1747 1717 1267 1252 1215 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.22 (3H, t, *J* = 7.1 Hz), 1.86-1.77 (1H, m), 2.00-1.92 (1H, m), 2.74-2.66 (3H, m), 3.18 (1H, ddd, *J* = 10.0, 8.7, 6.8 Hz), 3.33 (1H, ddd, *J* = 10.0, 7.2, 5.1 Hz), 4.12 (2H, q, *J* = 7.1 Hz), 5.77 (1H, d, *J* = 15.6 Hz), 6.72 (1H, dd, *J* = 15.6, 8.8 Hz), 7.09 (2H, d, *J* = 7.3 Hz), 7.15 (1H, t, *J* = 7.3 Hz), 7.23 (2H, t, *J* = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.1, 31.0, 36.0, 40.5, 42.4, 60.1, 122.6, 126.2, 128.3, 129.0, 138.4, 149.7, 165.8; EIHRMS: Found: *m/z* 311.0651. Calcd for C₁₅H₂₀O₂Br: (M+H)⁺ 311.0647.

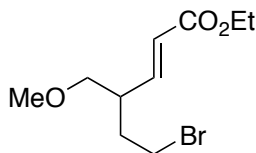
(*E*)-ethyl 6-bromo-4-methylhex-2-enoate (**3-1c**)⁶⁰



Yield: 30% (as a pure *E* form) 3-methyldihydrofuran-2-one;⁶¹ ¹H NMR (400 MHz, CDCl₃) δ 1.09 (3H, d, *J* = 6.8 Hz), 1.30 (3H, t, *J* = 7.1 Hz), 1.97-1.87 (2H, m), 2.66-2.52 (1H, m), 3.34 (1H, dt, *J* = 10.1, 7.2 Hz), 3.42 (1H, dt, *J* = 10.1, 6.5 Hz), 4.20 (2H, q, *J* = 7.1 Hz), 5.86 (1H, dd, *J* = 16.0, 1.0 Hz), 6.80 (1H, dd, *J* =

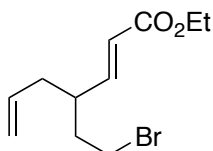
16.0, 8.0 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.5, 19.3, 31.4, 35.2, 38.7, 60.6, 121.3, 152.2, 166.8

(*E*)-ethyl 6-bromo-4-(methoxymethyl)hex-2-enoate (**3-1d**)



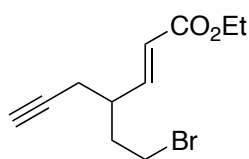
Yield: 67% (*E* : *Z* = 15.7 : 1) from 3-(methoxymethyl)dihydrofuran-2(3*H*)-one,⁶² *E* isomer was used: Colorless oil; IR (ATR) 2982, 2930, 2876, 2828, 1717, 1653, 1254, 1238, 1182, 1152, 1167, 1101 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.30 (3H, t, J = 7.1 Hz), 1.97-1.90 (1H, m), 2.14-2.06 (1H, m), 2.78-2.73 (1H, m), 3.32 (3H, s), 3.36-3.29 (3H, m), 3.48-3.38 (3H, m), 4.19 (2H, q, J = 7.1 Hz), 5.94 (1H, d, J = 15.8 Hz), 6.78 (1H, dd, J = 15.8, 8.9 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.3, 31.2, 33.8, 41.2, 59.2, 60.6, 74.8, 123.6, 148.0, 166.4; EIHRMS: Found: m/z 265.0434. Calcd for $\text{C}_{10}\text{H}_{18}\text{O}_3\text{Br}$: ($\text{M}+\text{H}$)⁺ 265.0439.

(*E*)-ethyl 4-(2-bromoethyl)hepta-2,6-dienoate (**3-1e**)



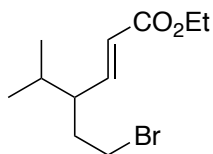
Yield: 56% (*E* : *Z* = 16 : 1) from 3-allyldihydrofuran-2(3*H*)-one,⁶³ *E* isomer was used: Colorless oil; IR (ATR) 2960, 1717, 1653, 1267, 1252, 1221, 1180, 1150, 1036, 986 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.30 (3H, t, J = 7.1 Hz), 1.94-1.80 (1H, m), 2.11-1.97 (1H, m), 2.25-2.15 (2H, t, J = 6.8 Hz), 2.62-2.50 (1H, m), 3.33-3.22 (1H, td, J = 9.3, 6.7 Hz), 3.48-3.38 (1H, m), 4.20 (2H, q, J = 7.1 Hz), 5.13-5.00 (2H, m), 5.71 (1H, ddt, J = 19.1, 9.6, 7.1 Hz), 5.88 (1H, d, J = 15.7 Hz), 6.71 (1H, dd, J = 15.7, 9.2 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.4, 31.3, 36.4, 38.5, 40.7, 60.6, 117.6, 122.8, 135.1, 150.3, 166.5; EIHRMS: Found: m/z 261.0487. Calcd for $\text{C}_{11}\text{H}_{18}\text{O}_2\text{Br}$: ($\text{M}+\text{H}$)⁺ 261.0490.

(*E*)-ethyl 4-(2-bromoethyl)hept-2-en-6-ynoate (**3-1f**)



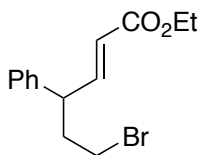
Yield: 58% (*E* : *Z* = 18.7 : 1) from 3-(but-3-yn-1-yl)dihydrofuran-2(3*H*)-one;⁶⁴ *E* isomer was used: Yellow oil; IR (ATR) 3300, 2960, 1715, 1653, 1369, 1254, 1221, 1173, 1152, 1036, 984 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.30 (3H, t, *J* = 7.1 Hz), 2.09-1.94 (2H, m), 2.22-2.09 (1H, m), 2.41-.32 (2H, m), 2.80-2.63 (1H, m), 3.32 (1H, ddd, *J* = 10.2, 8.5, 6.2 Hz), 3.45 (1H, dt, *J* = 10.2, 6.1 Hz), 4.21 (2H, q, *J* = 7.1 Hz), 5.96 (1H, d, *J* = 15.7 Hz), 6.79 (1H, dd, *J* = 15.7, 9.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.0, 22.8, 30.7, 35.2, 38.9, 60.1, 70.9, 80.3, 122.8, 148.0, 165.5; EIHRMS: Found: *m/z* 259.0333. Calcd for C₁₁H₁₆O₂Br: (M+H)⁺ 259.0334.

(*E*)-ethyl 6-bromo-4-isopropylhex-2-enoate (**3-1g**)



Yield: 24% (as a pure *E*-isomer) from 3-isopropyldihydrofuran-2(3*H*)-one;⁶⁵ Yellow oil; IR (ATR) 2961, 2936, 2901, 2874, 1717, 1653, 1250, 1202, 1181, 1152 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.89 (3H, d, *J* = 6.8 Hz), 0.92 (3H, d, *J* = 6.8 Hz), 1.30 (3H, t, *J* = 7.1 Hz), 1.71 (1H, ddd, *J* = 13.2, 13.2, 6.8 Hz), 1.92-1.83 (1H, m), 2.09-2.00 (1H, m), 2.24 (1H, tdd, *J* = 10.0, 5.9, 4.0 Hz), 3.22 (1H, td, *J* = 10.0, 6.8 Hz), 3.43 (1H, ddd, *J* = 10.0, 7.3, 4.7 Hz), 4.19 (2H, q, *J* = 7.1 Hz), 5.87 (1H, dd, *J* = 16.1, 0.8 Hz), 6.71 (1H, dd, *J* = 16.1, 10.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.4, 19.3, 20.6, 31.6, 31.9, 34.5, 47.5, 60.4, 123.5, 149.3, 166.3; EIHRMS: Found: *m/z* 263.0657. Calcd for C₁₁H₂₀O₂Br: (M+H)⁺ 263.0647.

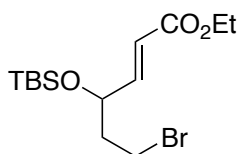
(*E*)-ethyl 6-bromo-4-phenylhex-2-enoate (**3-1h**)



Yield: 54% (as a pure *E*-isomer) from 3-phenyldihydrofuran-2(3*H*)-one;⁶⁶ Colorless oil; IR (ATR) 2961, 1715, 1651, 1267, 1242, 1206, 1173, 1040, 984 cm⁻¹

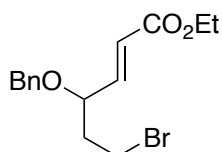
¹; ¹H NMR (400 MHz, CDCl₃) δ 1.26 (3H, t, *J* = 7.1 Hz), 2.37-2.22 (2H, m), 3.24 (1H, dt, *J* = 10.0, 6.9 Hz), 3.36 (1H, dt, *J* = 10.0, 6.3 Hz), 3.73 (1H, dt, *J* = 7.5, 7.5 Hz), 4.18 (2H, q, *J* = 7.1 Hz), 5.86 (1H, dd, *J* = 15.7, 1.3 Hz), 7.05 (1H, dd, *J* = 15.7, 7.5 Hz), 7.21 (2H, d, *J* = 7.2 Hz), 7.26 (1H, t, *J* = 7.2 Hz), 7.34 (2H, t, *J* = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.4, 37.6, 44.8, 60.4, 60.6, 121.2, 127.2, 128.0, 129.0, 141.6, 151.4, 166.9; EIHRMS: Found: *m/z* 297.0483. Calcd for C₁₄H₁₈O₂Br: (M+H)⁺ 297.0490.

(*E*)-ethyl 6-bromo-4-((*tert*-butyldimethylsilyl)oxy)hex-2-enoate (**3-1i**)



Yield: 59% (*E* : *Z* = 2.17 : 1) from 3-((*tert*-butyldimethylsilyl)oxy)dihydrofuran-2(3*H*)-one,⁶⁷ *E* isomer was used, data for *E* isomer: Colorless oil; IR (NaCl) 2955 2930 1721 1165 1098 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.06 (3H, s), 0.11 (3H, s), 0.92 (9H, s), 1.30 (3H, t, *J* = 7.1 Hz), 2.03-2.08 (2H, m), 4.21 (2H, q, *J* = 7.1 Hz), 4.48-4.52 (1H, m), 6.01 (1H, d, *J* = 15.6 Hz), 6.89 (1H, dd, *J* = 5.2, 15.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ -4.7, -4.2, 14.4, 18.3, 26.0, 29.4, 40.4, 60.7, 69.9, 121.1, 149.6, 166.6; EIHRMS: Found: *m/z* 351.0988. Calcd for C₁₄H₂₈O₃BrSi: (M+H)⁺ 351.0991.

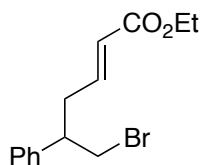
(*E*)-ethyl 4-(benzyloxy)-6-bromohex-2-enoate (**3-1j**)



Yield: 86% (*E* : *Z* = 1 : 1.53) from 3-(benzyloxy)dihydrofuran-2(3*H*)-one,⁶⁸ *E* isomer was used, data for *E* isomer: Colorless oil; IR (NaCl) 3030 2978 1717 1497 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.31 (3H, t, *J* = 7.1 Hz) 2.01-2.09 (1H, m), 2.13-2.21 (1H, m), 3.42-3.49 (1H, m), 3.50-3.57 (1H, m), 4.22 (2H, q, *J* = 7.1 Hz), 4.20-4.25 (1H, m), 4.40 (1H, d, *J* = 11.5 Hz), 4.62 (1H, d, *J* = 11.5 Hz), 6.09 (1H, d, *J* = 15.8 Hz), 6.89 (1H, dd, *J* = 6.5, 15.8 Hz), 7.28-7.38 (5H, m); ¹³C NMR (100 MHz, CDCl₃) δ 14.4, 29.5, 38.1, 60.9, 71.8, 76.2, 123.2, 128.0(9), 128.1(2), 128.7,

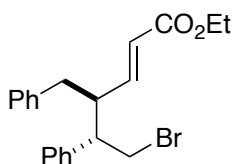
137.9, 147.0, 166.2; EIHRMS: Found: m/z 327.0594. Calcd for $C_{15}H_{20}O_3Br$: $(M+H)^+$ 327.0596.

(*E*)-ethyl 6-bromo-5-phenylhex-2-enoate (**3-1l**)



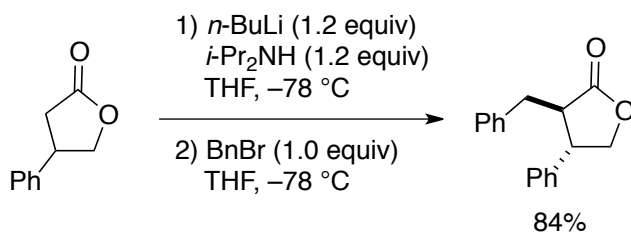
Yield: quantitative ($E : Z = 2.3 : 1$) from 4-phenyltetrahydrofuran-2(3*H*)-ol;⁶⁹ Colorless oil; IR (ATR) 3030, 2980, 2936, 2901, 1748, 1715, 1684, 1367, 1317, 1269, 1204, 1167, 1140 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, t, $J = 7.1$ Hz), 2.61 (1H, dt, $J = 14.9, 7.6$ Hz), 2.84 (1H, dt, $J = 14.0, 6.7$ Hz), 3.14 (1H, ddd, $J = 14.9, 6.8, 6.0$ Hz), 3.64-3.51 (2H, m), 4.14 (2H, q, $J = 7.1$ Hz), 5.83 (1H, d, $J = 15.6$ Hz), 6.79 (1H, dt, $J = 15.6, 7.4$ Hz), 7.18 (2H, d, $J = 7.2$ Hz), 7.27 (1H, t, $J = 7.2$ Hz), 7.34 (2H, t, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 36.7, 37.9, 47.0, 60.5, 123.8, 127.7, 127.7, 129.0, 141.1, 145.5, 166.4; EIHRMS: Found: m/z 297.0505. Calcd for $C_{14}H_{18}O_2Br$: $(M+H)^+$ 297.0490.

(4*S**,5*S**,*E*)-ethyl 4-benzyl-6-bromo-5-phenylhex-2-enoate (**3-1m**)



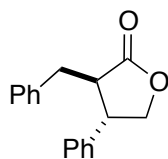
Yield: 40% (as a pure *E*-isomer) from (3*R**,4*S**)-3-benzyl-4-phenyldihydrofuran-2(3*H*)-one, which is obtained by α -alkylation of 4-phenyltetrahydrofuran-2(3*H*)-one⁶⁷ with benzyl bromide using LDA in 73% yield (see below); Colorless oil; IR (ATR) 3024 1748 1717 1669 1314 1271 1246 1217 1177 1161 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, t, $J = 7.2$ Hz), 2.38 (1H, dd, $J = 13.7, 9.9$ Hz), 2.70 (1H, dd, $J = 13.7, 3.4$ Hz), 2.87 (1H, qd, $J = 9.6, 3.4$ Hz), 3.01 (1H, td, $J = 9.0, 3.9$ Hz), 3.50 (1H, t, $J = 9.5$ Hz), 3.66 (1H, dd, $J = 10.3, 4.0$ Hz), 4.17-4.13 (2H, m), 5.65 (1H, d, $J = 15.6$ Hz), 6.76 (1H, dd, $J = 15.6, 9.9$ Hz), 6.93 (2H, $J = 7.2$ Hz), 7.13 (1H, d, $J = 7.3$ Hz), 7.26-7.17 (4H, m), 7.30 (1H, t, $J = 7.3$ Hz), 7.38 (2H, t, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 37.5, 38.9, 49.0, 51.2, 60.5, 124.1, 126.4, 127.6, 128.4, 128.5, 128.8, 129.2, 138.9, 140.2, 148.8, 166.0; EIHRMS: Found: m/z 387.0965. Calcd for $C_{21}H_{24}O_2Br$: $(M+H)^+$ 387.0960.

Procedure for α -alkylation of 4-phenyltetrahydrofuran-2(3*H*)-one



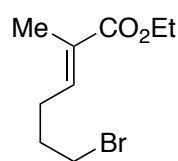
n-BuLi (3.94 ml, 1.6 M, 6.42 mmol, 1.2 equiv) was added dropwise into a solution of diisopropylamine (0.9 ml, 6.43 mmol, 1.2 equiv) in THF (10 ml) at -78 °C under a N₂ atmosphere, and the mixture was stirred at -78 °C for 0.5 h. To the mixture was added a THF solution (5 mL) of 4-phenyldihydrofuran-2(3*H*)-one⁶⁹ (0.869 g, 5.36 mmol). After stirring at -78 °C for 0.5 h, benzyl bromide (0.64 ml, 5.39 mmol, 1.0 equiv) was then added dropwise, and the solution was stirred at -78 °C for 4 h. The reaction was quenched with saturated aqueous NH₄Cl, and the organic materials were extracted three times with ethyl acetate. The combined organic extracts were washed with brine. After drying with MgSO₄ and removal of the solvents in vacuo, the resulting crude residue was purified by flash column chromatography (hexane : ethyl acetate = 9 : 1) to yield (3*R**,4*S**)-3-benzyl-4-phenyldihydrofuran-2(3*H*)-one (1.13 g, 4.50 mmol, 84% yield).

(3*R**,4*S**)-3-benzyl-4-phenyldihydrofuran-2(3*H*)-one



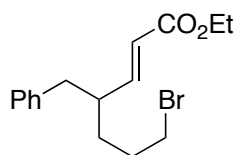
Colorless oil; IR (ATR) 3028 1773 1497 1454 1179 1144 1018 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.97 (1H, dd, *J* = 13.1, 4.9 Hz), 3.15-3.05 (2H, m), 3.34 (1H, ddd, *J* = 9.2, 9.2, 9.2 Hz), 4.05 (1H, dd, *J* = 9.2, 9.2 Hz), 4.36 (1H, dd, *J* = 9.2, 9.2 Hz), 7.32-7.12 (10H, m); ¹³C NMR (100 MHz, CDCl₃) δ 33.9, 45.7, 48.0, 72.4, 126.9, 127.5, 127.8, 128.9, 129.2, 129.8, 137.3, 138.0, 177.7; EIHRMS: Found: *m/z* 253.1227. Calcd for C₁₇H₁₇O₂: (M+H)⁺ 253.1229.

(*E*)-ethyl 6-bromo-2-methylhex-2-enoate (**3-1o**^E)⁷⁰



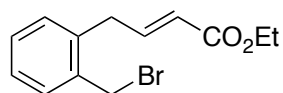
Yield: 36% (as a pure *E* form) from dihydrofuran-2(3*H*)-one; ¹H NMR (400 MHz, CDCl₃) δ 1.30 (3H, t, *J* = 8.0 Hz), 1.87 (3H, s), 2.11-1.95 (3H, m), 2.36 (2H, q, *J* = 7.1 Hz), 3.62-3.38 (2H, m), 4.20 (2H, q, *J* = 8.0 Hz), 6.70 (1H, tq, *J* = 7.5, 1.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 12.7, 14.9, 27.2, 31.7, 33.2, 60.8, 129.5, 139.9, 168.2.

(*E*)-ethyl 4-benzyl-7-bromohept-2-enoate (**3-1q**)



Yield: 58% (as a pure *E*-isomer) from 3-benzyltetrahydro-2*H*-pyran-2-one;⁶¹ Colorless oil; IR (ATR) 1717 1653 1263 1240 1209 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.27 (3H, t, *J* = 7.1 Hz), 1.55-1.36 (1H, m), 1.69-1.61 (1H, m), 1.79-1.70 (1H, m), 1.91-1.79 (1H, m), 2.53-2.44 (1H, m), 2.70 (2H, d, *J* = 7.1 Hz), 3.42-3.25 (2H, m), 4.17 (2H, q, *J* = 7.1 Hz), 5.70 (1H, dd, *J* = 15.7, 0.6 Hz), 6.78 (1H, dd, *J* = 15.7, 9.1 Hz), 7.11 (2H, d, *J* = 7.2 Hz), 7.19 (1H, t, *J* = 7.2 Hz), 7.27 (2H, t, *J* = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.4, 30.6, 32.3, 33.5, 41.2, 43.9, 60.4, 122.1, 126.4, 128.5, 129.2, 139.2, 151.5, 166.4; EIHRMS: Found: *m/z* 325.0806. Calcd for C₁₆H₂₂O₂Br: (M+H)⁺ 325.0803.

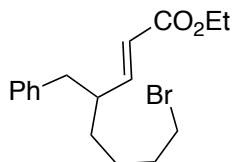
(*E*)-ethyl 4-(2-(bromomethyl)phenyl)but-2-enoate (**3-1s**)



Yield: 51% (*E* : *Z* = 3.50 : 1) from 3-isochromanone;⁷¹ *E* isomer was used; Yellow oil; IR (NaCl) 3065 3022 1715 1493 1454 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.27 (3H, t, *J* = 7.1 Hz), 3.68 (2H, dd, *J* = 1.7, 6.3 Hz), 4.18 (2H, q, *J* = 7.1 Hz), 4.47 (2H, s), 5.74 (1H, dt, *J* = 1.7, 15.6 Hz), 7.15 (1H, dt, *J* = 6.3, 15.6 Hz), 7.15-7.18 (1H, m), 7.22-7.31 (2H, m), 7.35 (1H, dd, *J* = 1.6, 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.4, 31.5, 35.2, 60.6, 122.9, 127.7, 129.6, 130.8, 130.9, 136.0,

136.9, 146.6, 166.5; EIHRMS: Found: m/z 283.0341. Calcd for $C_{13}H_{16}O_2Br$: $(M+H)^+$ 283.0334.

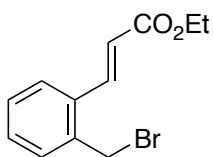
(*E*)-ethyl 4-benzyl-8-bromooct-2-enoate (**3-1t**)



Yield: 87% (*E* : *Z* = 75.3 : 1) from 3-benzylloxepan-2-one;⁷² *E* isomer was used, data for *E* isomer; Colorless oil; IR (NaCl) 3026 2980 1715 1494 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (3H, t, J = 7.1 Hz), 1.33-1.40 (2H, m), 1.43-1.51 (2H, m), 1.76-1.84 (2H, m), 2.42-2.49 (1H, m), 2.70 (2H, d, J = 7.1 Hz), 3.32-3.39 (2H, m), 4.17 (2H, q, J = 7.1 Hz), 5.70 (1H, d, J = 15.7 Hz), 6.79 (1H, dd, J = 9.0, 15.7 Hz), 7.11 (2H, d, J = 7.2 Hz), 7.19 (1H, t, J = 7.3 Hz), 7.27 (2H, t, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 26.0, 32.9, 33.7, 41.2, 44.4, 60.5, 121.9, 126.4, 128.6, 129.3, 139.5, 152.1, 166.7; EIHRMS: Found: m/z 339.0964. Calcd for $C_{17}H_{24}O_2Si$: $(M+H)^+$ 339.0960.

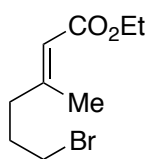
The following starting materials **3-1k**, **3-1n**, **3-1p** and **3-1r** were prepared according to literature procedures.

(*E*)-ethyl 3-(2-(bromomethyl)phenyl)acrylate (**3-1k**)⁷³



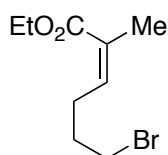
Prepared by following the procedure in ref. 73. ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (3H, t, J = 7.2 Hz), 4.29 (2H, q, J = 7.2 Hz), 4.60 (2H, s), 6.44 (1H, d, J = 15.8 Hz), 7.34-7.40 (3H, m), 7.58-7.60 (1H, m), 8.06 (1H, d, J = 15.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 30.8, 60.9, 121.3, 127.5, 129.5, 130.5, 131.0, 134.0, 136.8, 140.7, 166.8.

(*E*)-ethyl 6-bromo-3-methylhex-2-enoate (**3-1n**)⁷⁴

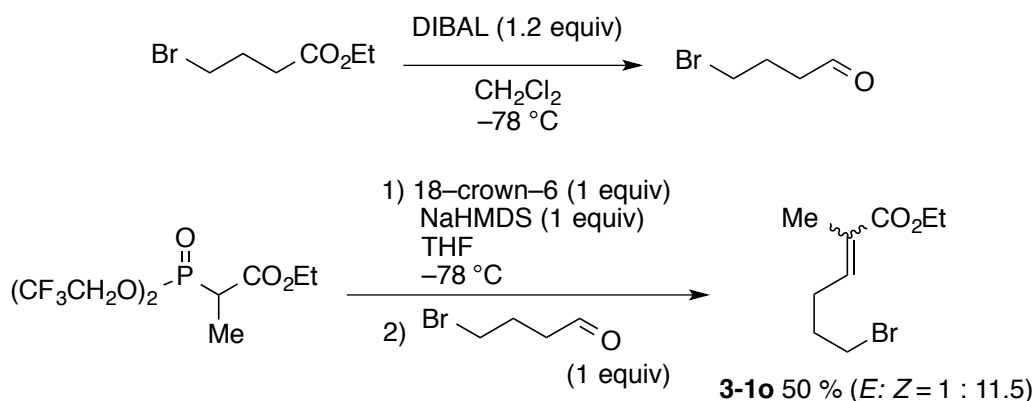


Prepared by following the procedure in ref. 74. ¹H NMR (400 MHz, CDCl₃) δ 1.28 (3H, t, *J* = 7.1 Hz), 2.10-1.98 (2H, m), 2.17 (3H, s), 2.35-2.26 (2H, m), 3.40 (2H, t, *J* = 6.6 Hz), 4.15 (2H, q, *J* = 7.1 Hz), 5.71 (1H, s); ¹³C NMR (100 MHz, CDCl₃) δ 14.5, 18.9, 30.4, 32.9, 39.2, 59.8, 116.8, 157.8, 166.8.

(*Z*)-ethyl 6-bromo-2-methylhex-2-enoate (**3-1o**)⁷⁵



Yield: 50% (*E* : *Z* = 1 : 11.5) from Horner-Wadsworth-Emmons reaction using 4-bromobutanal with ethyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)propanoate³⁷ (see below): ¹H NMR (400 MHz, CDCl₃): δ 1.23 (3H, t, *J* = 7.1 Hz), 1.83 (3H, s), 1.83-1.94 (2H, m), 2.50-2.56 (2H, m), 3.34 (2H, t, *J* = 7.1 Hz), 5.83 (1H, t, *J* = 7.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.2, 20.6, 28.2, 32.4, 33.0, 60.1, 128.6, 140.2, 167.7.

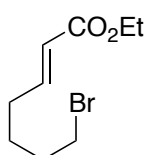


DIBAL (2.25 ml, neat, 12.6 mmol, 1.2 equiv) was added dropwise into a solution of ethyl 4-bromobutanoate (1.5 ml, 10.5 mmol, 1 equiv) in dichloromethane (20 ml) at $-78\text{ }^{\circ}\text{C}$ under a N₂ atmosphere, and the mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 0.5 h. The reaction was quenched with 1 M HCl (20 ml) carefully. The organic materials were extracted three times with

diethyl ether. The combined organic extracts were washed with brine. After drying with MgSO₄ and removal of the solvents in vacuo (note: 4-bromobutanal is volatile), the resulting crude 4-bromobutanal was used without further purification.

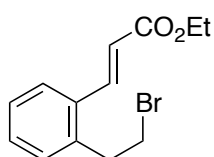
NaHMDS (3.42 ml, 1 M in THF, 3.42 mmol, 1 equiv) was added dropwise into a solution of ethyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)propanoate (1.07 g, 3.42 mmol, 1 equiv) and 18-crown-6 (90.4 mg, 3.42 mmol, 1 equiv) in THF (20 ml) at -78 °C under a N₂ atmosphere. The mixture was stirred at -78 °C for 10 mins. Crude 4-bromobutanal (0.517 g, 3.42 mmol, 1 equiv) was then added, and the solution was stirred at -78 °C for 2 h. The reaction was quenched with saturated aqueous NH₄Cl, and the organic materials were extracted three times with diethyl ether. The combined organic extracts were washed with brine. After drying with MgSO₄ and removal of the solvents in vacuo, the resulting crude residue was purified by flash column chromatography (hexane : ethyl acetate = 9 : 1) to yield (*Z*)-ethyl 6-bromo-2-methylhex-2-enoate (**3-1o^Z**) (0.367 g, 1.56 mmol, 46% yield) along with (*E*)-ethyl 6-bromo-2-methylhex-2-enoate (**3-1o^E**) (31.8 mg, 0.135 mmol, 4% yield).

(*E*)-ethyl 7-bromohept-2-enoate (**3-1p**)⁷⁶



Prepared by following the procedure in ref. 76. ¹H NMR (400 MHz, CDCl₃) δ 1.31 (3H, t, *J* = 7.1 Hz), 1.63-1.69 (2H, m), 1.87-1.94 (2H, m), 2.23-2.29 (2H, m), 3.43 (2H, t, *J* = 6.7 Hz), 4.20 (2H, q, *J* = 7.1 Hz), 5.85 (1H, d, *J* = 15.6 Hz), 6.96 (1H, dt, *J* = 7.0, 15.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.5, 26.7, 31.4, 32.2, 33.4, 60.4, 122.1, 148.3, 166.7.

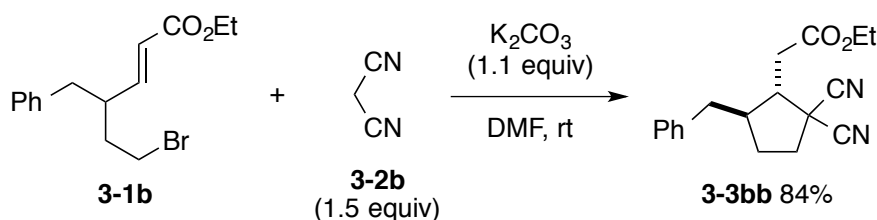
(*E*)-ethyl 3-(2-(2-bromoethyl)phenyl)acrylate (**3-1r**)⁷⁷



Prepared by following the procedure in ref. 77. ^1H NMR (400 MHz, CDCl_3) δ 1.35 (3H, t, $J = 7.1$ Hz), 3.32 (2H, t, $J = 7.6$ Hz), 3.52 (2H, t, $J = 7.6$ Hz), 4.28 (2H, q, $J = 7.1$ Hz), 6.39 (1H, d, $J = 15.7$ Hz), 7.24-7.35 (3H, m), 7.58 (1H, dd, $J = 1.2, 7.6$ Hz), 7.95 (1H, d, $J = 15.7$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.3, 32.0, 36.3, 60.4, 120.4, 126.8, 127.5, 130.0, 130.4, 133.1, 138.0, 140.9, 166.4.

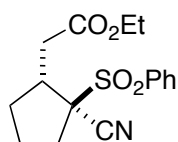
3.6.3. Synthesis of carbocycles by $\text{S}_{\text{N}}2$ -conjugate addition sequence

Typical procedure for synthesis of **3-3bb**



A mixture of malononitrile (**3-2b**) (58.0 mg, 0.878 mmol, 1.5 equiv) and K_2CO_3 (89.0 mg, 0.644 mmol, 1.1 equiv) in DMF (5 mL) was stirred at room temperature under a N_2 atmosphere for 0.5 h, and a solution of (*E*)-ethyl 4-benzyl-6-bromohex-2-enoate (**3-1b**) (182 mg, 0.585 mmol) in DMF (1 mL) was added to the mixture. After being stirred for 24 h, the reaction was quenched by adding water (10 mL), and the mixture was extracted three times with Et_2O . The combined organic extracts were washed with water and brine. After drying with MgSO_4 and removal of the solvents under reduced pressure, the resulting crude material was purified by flash column chromatography (hexane : ethyl acetate = 8 : 2) to yield ethyl 2-((1*S**,5*S**)-5-benzyl-2,2-dicyanocyclopentyl)acetate (**3-3bb**) (145 mg, 0.492 mmol, 84% yield, *dr* = >28 : 1).

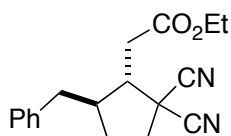
ethyl 2-((1*R**,2*S**)-2-cyano-2-(phenylsulfonyl)cyclopentyl)acetate **3-3aa**



Colorless oil; IR (ATR) 2236 1732 1327 1312 1204 1152 1084 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.26 (3H, t, $J = 7.1$ Hz), 1.53 (1H, dddd, $J = 13.2, 8.8, 8.8, 8.8$ Hz), 1.91-1.83 (2H, m), 2.10 (1H, ddd, $J = 14.0, 7.2, 7.2$ Hz), 2.35 (1H, ddd, $J = 12.8, 12.8, 6.0$ Hz), 2.46 (1H, dd, $J = 16.2, 11.4$ Hz), 2.61 (1H, ddd, $J = 12.8,$

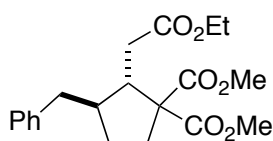
6.0, 6.0 Hz), 2.69 (1H, dd, $J = 16.2, 3.2$ Hz), 3.25-3.17 (1H, m), 4.14 (2H, q, $J = 7.1$ Hz), 7.64 (2H, t, $J = 7.7$ Hz), 7.77 (1H, t, $J = 7.7$ Hz), 8.04 (2H, t, $J = 7.7$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.4, 23.5, 32.7, 36.2, 37.7, 41.5, 61.0, 69.6, 116.8, 129.7, 130.5, 135.4, 135.5, 171.0; EIHRMS: Found: m/z 322.1113. Calcd for $\text{C}_{19}\text{H}_{20}\text{NO}_4\text{S}$: $(\text{M}+\text{H})^+$ 322.1113.

ethyl 2-((1*S**,5*S**)-5-benzyl-2,2-dicyanocyclopentyl)acetate (**3-3bb**)



84% yield, $dr = >28 : 1$ (as an inseparable mixture) from **3-1b** and **3-2b**: Yellow oil; IR (ATR) 3030 2982 2938 2247 1732 1717 1558 1522 1506 1456 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.31 (3H, t, $J = 7.2$ Hz), 1.67 (1H, dddd, $J = 13.6, 8.4, 8.4, 8.4$ Hz), 1.98 (1H, ddd, $J = 13.6, 7.2, 7.2, 7.2$ Hz), 2.19-2.09 (1H, m), 2.46-2.41 (2H, m), 2.55 (1H, dd, $J = 13.6, 9.3$ Hz), 2.67-2.61 (1H, m), 2.72-2.66 (2H, m), 2.89 (1H, dd, $J = 13.6, 5.1$ Hz), 4.22 (2H, q, $J = 7.2$ Hz), 7.14 (2H, d, $J = 7.2$ Hz), 7.23 (1H, t, $J = 7.2$ Hz), 7.30 (2H, t, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1, 29.5, 35.9, 37.8, 39.1, 39.8, 45.8, 51.3, 61.5, 114.7, 116.3, 126.8, 128.7, 128.7, 128.8, 138.9, 170.4; EIHRMS: Found: m/z 297.1597. Calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_2$: $(\text{M}+\text{H})^+$ 297.1603.

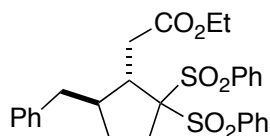
(2*S**,3*S**)-dimethyl 3-benzyl-2-(2-ethoxy-2-oxoethyl)cyclopentane-1,1-dicarboxylate (**3-3bc**)



68% yield, $dr = 7.6 : 1$ (as an inseparable mixture) from **3-1b** and **3-2c**: Colorless oil; IR (ATR) 3021 2955 2926 2855 2309 1748 1732 1717 1558 1522 1506 1456 1215 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.27 (3H, q, $J = 7.1$ Hz), 1.34-1.30 (1H, m), 1.75 (1H, dddd, $J = 12.8, 7.6, 7.6, 4.8$ Hz), 2.29-2.11 (3H, m), 2.36 (1H, dd, $J = 16.0, 8.0$ Hz), 2.40 (1H, dd, $J = 13.2, 10.4$ Hz), 2.66 (1H, dd, $J = 16.0, 5.5$ Hz), 2.90-2.81 (2H, m), 3.70 (3H, s), 3.74 (3H, s), 4.13 (2H, q, $J = 7.1$ Hz), 7.18-7.13 (3H, m), 7.27-7.24 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 14.4, 29.9, 33.4, 35.9,

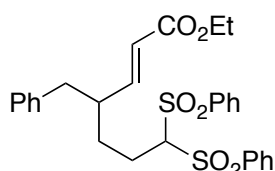
40.8, 46.8, 47.3, 52.5, 52.8, 60.7, 63.5, 126.1, 128.4, 128.9, 141.0, 171.7, 172.5, 172.6; EIHRMS: Found: m/z 363.1805. Calcd for $C_{20}H_{27}O_6$: $(M+H)^+$ 363.1808.

ethyl 2-((1*S**,5*S**)-5-benzyl-2,2-bis(phenylsulfonyl)cyclopentyl)acetate (**3-3bd**)



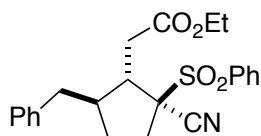
13% yield, $dr = >99 : 1$ from **3-1b** and **3-2d**: White solid; mp. 188-189 °C; IR (ATR) 3019 1748 1732 1717 1684 1558 1522 1506 1489 1215 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, t, $J = 7.1$ Hz), 1.31-1.30 (1H, m), 1.70 (1H, ddd, $J = 12.4, 6.0, 6.0$ Hz), 2.29-2.20 (2H, m), 2.50-2.43 (2H, m), 2.77 (1H, dd, $J = 13.2, 3.8$ Hz), 2.93-2.83 (2H, m), 3.28 (1H, ddd, $J = 11.1, 7.5, 3.8$ Hz), 4.09 (2H, q, $J = 7.1$ Hz), 7.13 (2H, d, $J = 7.2$ Hz), 7.19 (1H, t, $J = 7.2$ Hz), 7.27 (2H, t, $J = 7.2$ Hz), 7.61-7.55 (4H, m), 7.73-7.67 (2H, m), 8.11 (2H, d, $J = 7.5$ Hz), 8.23 (2H, d, $J = 7.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 31.1, 31.7, 33.5, 39.6, 49.0, 49.4, 61.0, 94.3, 126.3, 128.6, 128.6, 128.8, 128.9, 132.2, 132.3, 134.7, 134.8, 136.2, 137.7, 140.5, 172.5; EIHRMS: Found: m/z 527.1565. Calcd for $C_{28}H_{31}O_6S_2$: $(M+H)^+$ 527.1562.

(*E*)-ethyl 4-benzyl-7,7-bis(phenylsulfonyl)hept-2-enoate (**3-3bd'**)



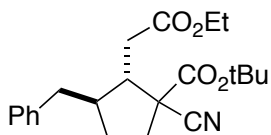
60% yield; Colorless oil; IR (ATR) 3024 1717 1705 1684 1217 1154 10078 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (3H, t, $J = 7.1$ Hz), 1.61-1.53 (1H, m), 1.84-1.76 (1H, m), 2.11-2.03 (2H, m), 2.39-2.34 (1H, m), 2.68-2.58 (2H, m), 4.19 (2H, q, $J = 7.1$ Hz), 4.30 (1H, t, $J = 5.6$ Hz), 5.65 (1H, d, $J = 15.7$ Hz), 6.64 (1H, dd, $J = 15.7, 9.2$ Hz), 7.07 (2H, d, $J = 7.0$ Hz), 7.30-7.20 (3H, m), 7.56-7.51 (4H, m), 7.67 (2H, t, $J = 7.5$ Hz), 7.89-7.84 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 23.8, 31.7, 40.9, 44.3, 60.5, 83.6, 122.7, 126.5, 128.6, 129.3, 129.3, 129.7, 134.8, 137.7, 137.7, 138.8, 150.4, 166.1; EIHRMS: Found: m/z 527.1561. Calcd for $C_{28}H_{31}O_6S_2$: $(M+H)^+$ 527.1562.

ethyl 2-((1*S**,2*S**,5*S**)-5-benzyl-2-cyano-2-(phenylsulfonyl)cyclopentyl)acetate
(**3-3ba**)



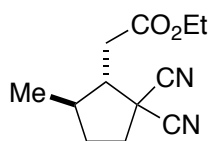
94% yield, *dr* = >99 : 1 from **3-1b** and **3-2a**; Yellow oil; IR (ATR) 2980 2359 2320 1732 1717 1327 1314 1219 1204 1152 1028 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.27 (3H, t, *J* = 7.1 Hz), 1.63 (1H, dddd, *J* = 13.6, 8.0, 8.0, 8.0 Hz), 1.77 (1H, ddd, *J* = 13.6, 7.2, 7.2 Hz), 2.05 (1H, ddd, *J* = 14.4, 7.2, 7.2 Hz), 2.28-2.20 (1H, m), 2.61-2.47 (4H, m), 2.91 (1H, dd, *J* = 13.6, 4.6 Hz), 3.06 (1H, ddd, *J* = 8.7, 8.7, 3.7 Hz), 4.16-4.10 (2H, m), 7.15 (2H, d, *J* = 8.1 Hz), 7.20 (1H, t, *J* = 8.1 Hz), 7.28 (2H, d, *J* = 8.1 Hz), 7.63 (2H, t, *J* = 7.5 Hz), 7.75 (1H, t, *J* = 7.5 Hz), 8.05 (2H, d, *J* = 7.5 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.3, 29.6, 34.1, 37.4, 39.8, 45.8, 48.3, 61.4, 70.6, 116.9, 126.5, 128.7, 128.9, 129.6, 130.6, 135.2, 135.4, 139.9, 171.0; EIHRMS: Found: *m/z* 412.1583. Calcd for C₂₃H₂₆NO₄S: (M+H)⁺ 412.1583.

(1*S**,2*S**,3*S**)-tert-butyl 3-benzyl-1-cyano-2-(2-ethoxy-2-oxoethyl)cyclopentanecarboxylate (**3-3be**)



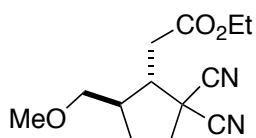
97% yield, *dr* = 6.1 : 1 (as an inseparable mixture) from **3-1b** and **3-2e**; Colorless oil; IR (ATR) 2980 2934 2913 2879 2311 1732 1371 1256 1219 1204 1152 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.29 (3H, t, *J* = 7.2 Hz), 1.54 (9H, s), 1.61-1.53 (1H, m), 1.90-1.84 (1H, m), 2.12-2.05 (1H, m), 2.19 (1H, ddd, *J* = 14.8, 7.6, 7.6 Hz), 2.31-2.26 (1H, m), 2.53-2.47 (1H, m), 2.73-2.60 (3H, m), 2.90 (1H, dd, *J* = 13.6, 4.7 Hz), 4.14 (2H, q, *J* = 7.2 Hz), 7.15 (2H, t, *J* = 7.3 Hz), 7.21 (1H, t, *J* = 7.3 Hz), 7.28 (2H, t, *J* = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.3, 27.9, 30.1, 36.1, 36.8, 40.0, 47.0, 48.9, 54.1, 61.0, 83.9, 119.3, 126.5, 128.7, 128.9, 140.1, 168.2, 171.7; EIHRMS: Found: *m/z* 372.2172. Calcd for C₂₂H₃₀NO₄: (M+H)⁺ 372.2175.

ethyl 2-((1*S**,5*R**)-2,2-dicyano-5-methylcyclopentyl)acetate (**3-3cb**)



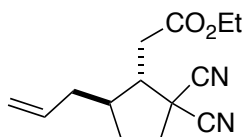
84% yield, *dr* = 10 : 1 (as an inseparable mixture) from **3-1c** and **3-2b**: Yellow oil; IR (ATR) 2376 2349 2311 2247 1771 1732 1684 1506 1456 1260 1219 1207 1165 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.11 (3H, d, J = 6.6 Hz), 1.31 (3H, J = 7.2 Hz), 1.58 (1H, dddd, J = 13.6, 8.8, 8.8, 8.8 Hz), 1.96-1.89 (1H, m), 2.16 (1H, dddd, J = 13.6, 7.2, 7.2, 7.2 Hz), 2.53-2.45 (3H, m), 2.74-2.67 (2H, m), 4.23 (2H, q, J = 7.2 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.2, 18.2, 31.8, 35.5, 38.1, 39.0, 39.4, 53.1, 61.5, 114.9, 116.5, 170.6; EIHRMS: Found: m/z 211.1293. Calcd for $\text{C}_{12}\text{H}_{17}\text{N}_2\text{O}_2$: ($\text{M}+\text{H}$) $^+$ 211.1290.

ethyl 2-((1*S**,5*R**)-2,2-dicyano-5-(methoxymethyl)cyclopentyl)acetate (**3-3db**)



94% yield, *dr* = 12.1 : 1 (as an inseparable mixture) from **3-1d** and **3-2b**: Yellow oil; IR (ATR) 2982 2934 2901 2880 2830 2812 2376 2311 2247 1732 1717 1522 1506 1456 1244 1219 1206 1169 1126 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.31 (3H, t, J = 7.2 Hz), 1.83-1.75 (1H, m), 2.16-2.06 (2H, m), 2.52-2.39 (2H, m), 2.77-2.69 (2H, m), 2.83 (1H, ddd, J = 14.0, 8.0, 8.0 Hz), 3.32 (3H, s), 3.14-3.34 (2H, m), 4.22 (2H, q, J = 7.2 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.2, 27.0, 36.4, 38.1, 39.8, 44.0, 48.9, 59.2, 61.4, 73.8, 114.7, 116.1, 170.6; EIHRMS: Found: m/z 251.1404. Calcd for $\text{C}_{13}\text{H}_{19}\text{N}_2\text{O}_3$: ($\text{M}+\text{H}$) $^+$ 251.1396.

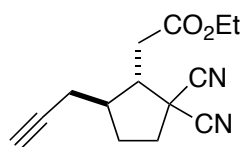
ethyl 2-((1*S**,5*S**)-5-allyl-2,2-dicyanocyclopentyl)acetate (**3-3eb**)



86% yield, *dr* = 32 : 1 (as an inseparable mixture) from **3-1e** and **3-2b**; Yellow oil; IR (ATR) 2369 2230 2249 1732 1647 1306 1219 1163 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.31 (3H, t, J = 7.2 Hz), 1.72-1.62 (1H, m), 2.00-1.93 (1H, m), 2.17-2.03 (2H, m), 2.35-2.29 (1H, m), 2.36-2.29 (2H, m), 2.61 (1H, dd, J = 15.1, 8.4 Hz),

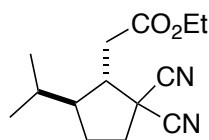
2.74-2.70 (2H, m), 4.22 (2H, q, $J = 7.2$ Hz), 5.12-5.08 (2H, m), 5.73 (1H, dddd, $J = 17.1, 9.9, 7.1, 7.1$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1, 29.0, 35.9, 37.4, 37.9, 39.2, 43.5, 50.8, 61.4, 114.6, 116.2, 117.9, 134.7, 170.4; EIHRMS: Found: m/z 247.1445. Calcd for $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_2$: $(\text{M}+\text{H})^+$ 247.1447.

ethyl 2-((1*S**,5*S**)-2,2-dicyano-5-(prop-2-yn-1-yl)cyclopentyl)acetate (**3-3fb**)



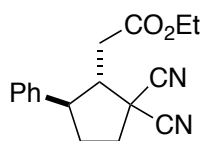
86% yield, $dr = 35 : 1$ (as an inseparable mixture) from **3-1f** and **3-2b**; Yellow oil; IR (ATR) 3460 2391 3275 2376 2111 2249 1771 1732 1717 1306 1260 1219 1165 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.32 (3H, t, $J = 7.1$ Hz), 1.90 (1H, ddd, 14.8, 7.0, 7.0 Hz), 2.07 (1H, t, $J = 2.4$ Hz), 2.11-2.09 (1H, m), 2.25-2.13 (1H, m), 2.35 (1H, ddd, $J = 17.2, 4.8, 2.6$ Hz), 2.45 (1H, ddd, $J = 17.2, 5.6, 2.6$ Hz), 2.52 (2H, t, $J = 7.3$ Hz), 2.75-2.73 (2H, m), 2.82 (1H, ddd, $J = 14.0, 9.2, 6.8$ Hz), 4.23 (2H, q, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1, 21.9, 28.9, 35.7, 37.9, 39.5, 42.1, 49.8, 61.5, 71.2, 80.2, 114.5, 115.9, 170.2; EIHRMS: Found: m/z 245.1293. Calcd for $\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}_2$: $(\text{M}+\text{H})^+$ 245.1290.

ethyl 2-((1*S**,5*S**)-2,2-dicyano-5-isopropylcyclopentyl)acetate (**3-3gb**)



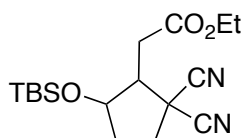
75% yield, $dr = 35 : 1$ (as an inseparable mixture) from **3-1g** and **3-2b**; Yellow oil; IR (ATR) 2378 2311 2247 1732 1246 1219 1206 1173 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.89 (3H, d, $J = 6.7$ Hz), 0.97 (3H, d, $J = 6.7$ Hz), 1.31 (3H, t, $J = 7.2$ Hz), 1.84-1.70 (3H, m), 2.03-1.94 (1H, m), 2.37 (1H, ddd, $J = 13.6, 8.0, 6.8$ Hz), 2.47 (1H, ddd, $J = 13.6, 13.6, 6.8$ Hz), 2.73-2.62 (3H, m), 4.22 (2H, q, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.2, 17.2, 22.0, 24.8, 29.0, 36.7, 38.3, 39.5, 48.9, 50.0, 61.5, 114.8, 116.4, 170.6; EIHRMS: Found: m/z 249.1599. Calcd for $\text{C}_{14}\text{H}_{21}\text{N}_2\text{O}_2$: $(\text{M}+\text{H})^+$ 249.1603.

ethyl 2-((1*S**,5*R**)-2,2-dicyano-5-phenylcyclopentyl)acetate (**3-3hb**)



83% yield, *dr* = >99 : 1 from **3-1h** and **2b**; Yellow oil; IR (ATR) 2378 2309 2249 1732 1717 1258 1219 1196 1161 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.19 (3H, t, $J = 7.2$ Hz), 2.09 (1H, dddd, $J = 13.6, 9.6, 9.6, 9.6$ Hz), 2.39 (1H, dddd, $J = 13.6, 8.0, 8.0, 5.6$ Hz), 2.55 (1H, dd, $J = 16.3, 4.8$ Hz), 2.78-2.62 (3H, m), 3.05-2.91 (2H, m), 4.01 (2H, q, $J = 7.2$ Hz), 7.22 (2H, d, $J = 7.8$ Hz), 7.29 (1H, t, $J = 7.8$ Hz), 7.36 (2H, t, $J = 7.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1, 32.4, 35.3, 38.6, 38.7, 50.8, 53.3, 61.4, 114.8, 116.3, 127.7, 128.0, 129.3, 139.3, 170.1; EIHRMS: Found: m/z 283.1443. Calcd for $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}_2$: ($\text{M}+\text{H}$) $^+$ 283.1447.

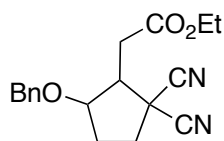
ethyl 2-(5-((*tert*-butyldimethylsilyl)oxy)-2,2-dicyanocyclopentyl)acetate (**3-3ib**)



44% yield from **3-1i** and **3-2b**, isolated as a pure diastereomer; Colorless oil; IR (NaCl) 2249 1732 1161 1142 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.06 (3H, s), 0.07 (3H, s), 0.88 (9H, s), 1.30 (3H, t, $J = 7.1$ Hz), 1.81-1.88 (1H, m), 2.06-2.13 (1H, m), 2.46-2.53 (1H, m), 2.64-2.71 (3H, m), 2.82-2.87 (1H, m), 3.96-4.00 (1H, m), 4.22 (2H, q, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ -4.8, -4.5, 14.2, 17.9, 25.8, 32.5, 34.9, 36.2, 36.5, 53.4, 61.6, 76.4, 114.9, 116.5, 170.2; EIHRMS: Found: m/z 337.1943. Calcd for $\text{C}_{17}\text{H}_{29}\text{N}_2\text{O}_3\text{Si}$: ($\text{M}+\text{H}$) $^+$ 337.1947.

37% yield from **3-1i** and **3-2b**, isolated as a pure diastereomer; White solid; mp. 66-67 $^{\circ}\text{C}$; IR (NaCl) 2249 1732 1192 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.02 (3H, s), 0.05 (3H, s), 0.89 (9H, s), 1.29 (3H, t, $J = 7.2$ Hz), 1.90-1.97 (1H, m), 2.04-2.13 (1H, m), 2.50-2.57 (1H, m), 2.72-2.79 (3H, m), 2.91 (1H, dddd, $J = 10.6, 10.6, 18.0, 18.0$ Hz), 4.18 (2H, q, $J = 7.2$ Hz), 4.44-4.46 (1H, m); ^{13}C NMR (100 MHz, CDCl_3) δ -5.3, -4.6, 14.3, 18.0, 25.7, 31.1, 34.4, 36.4, 37.3, 52.4, 61.3, 73.4, 115.3, 117.3, 171.0; EIHRMS: Found: m/z 337.1950. Calcd for $\text{C}_{17}\text{H}_{29}\text{N}_2\text{O}_3\text{Si}$: ($\text{M}+\text{H}$) $^+$ 337.1947.

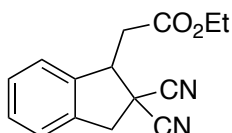
ethyl 2-(5-(benzyloxy)-2,2-dicyanocyclopentyl)acetate (**3-3jb**)



58% yield from **3-1j** and **3-2b**, isolated as a pure diastereomer; Colorless oil; IR (NaCl) 2982 2940 2249 1732 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.28 (3H, t, $J = 7.2$ Hz), 1.97-2.03 (1H, m), 2.09-2.17 (1H, m), 2.49-2.55 (1H, m), 2.61-2.67 (1H, m), 2.70 (2H, d, $J = 6.7$ Hz), 2.71-3.06 (1H, m), 3.79-3.84 (1H, m), 4.19 (2H, q, $J = 7.2$ Hz), 4.49 (1H, d, $J = 11.6$ Hz), 4.54 (1H, d, $J = 11.6$ Hz), 7.30-7.38 (5H, m); 14.3, 29.5, 35.4, 36.9, 37.2, 51.6, 61.6, 72.2, 82.3, 114.6, 116.0, 128.0, 128.3, 128.8, 137.4, 170.1; ^{13}C NMR (100 MHz, CDCl_3) δ 14.3, 29.5, 35.3, 36.9, 37.2, 61.6, 72.2, 76.9, 82.3, 114.6, 116.0, 128.0, 128.8, 137.4, 170.1; EIHRMS: Found: m/z 313.1563. Calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_3$: $(\text{M}+\text{H})^+$ 313.1552.

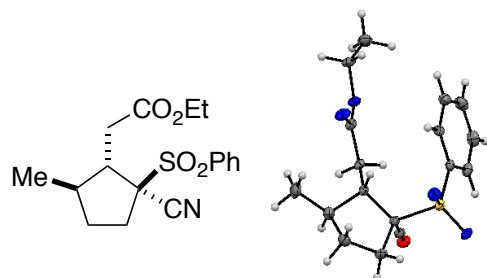
31% yield from **3-1j** and **3-2b**, isolated as a pure diastereomer; Yellow oil; IR (NaCl) 3065 3032 2249 1732 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.26 (3H, t, $J = 7.1$ Hz), 2.02-2.10 (1H, m), 2.15-2.21 (1H, m), 2.48-2.55 (1H, m), 2.69-2.77 (1H, m), 2.82 (1H, dd, $J = 5.4, 16.3$ Hz), 2.87-2.92 (1H, m), 3.02 (1H, dd, $J = 8.8, 16.3$ Hz), 4.10-4.22 (3H, m), 4.36 (1H, d, $J = 12.0$ Hz), 4.59 (1H, d, $J = 12.0$ Hz), 7.26-7.36 (5H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 14.3, 30.1, 31.1, 36.9, 37.3, 51.3, 61.3, 71.2, 76.9, 78.7, 114.9, 117.0, 127.5, 128.0, 128.6, 137.6, 171.0; EIHRMS: Found: m/z 313.1554. Calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_3$: $(\text{M}+\text{H})^+$ 313.1552.

ethyl 2-(2,2-dicyano-2,3-dihydro-1*H*-inden-1-yl)acetate (**3-3kb**)



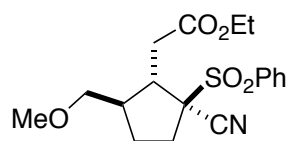
78% yield from **3-1k** and **3-2b**; Yellow oil; IR (NaCl) 3046 3032 2251 1732 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.33 (3H, t, $J = 7.2$ Hz), 2.98 (2H, d, $J = 7.2$ Hz), 3.70 (1H, d, $J = 15.8$ Hz), 3.77 (1H, d, $J = 15.8$ Hz), 4.28 (2H, q, $J = 7.2$ Hz), 7.19-7.21 (1H, m), 7.26-7.35 (3H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 14.3, 36.4, 39.7, 43.8, 50.5, 61.8, 114.6, 115.9, 124.3, 125.1, 129.0, 129.3, 136.0, 139.2, 170.2; EIHRMS: Found: m/z 255.1134. Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_2$: $(\text{M}+\text{H})^+$ 255.1134.

ethyl 2-((1*S**,2*S**,5*R**)-2-cyano-5-methyl-2-(phenylsulfonyl)cyclopentyl)acetate
(**3-3ca**)



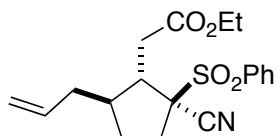
73% yield, *dr* = 8.8 : 1 (as an inseparable mixture) from **3-1c** and **3-2a** (the major diastereomer could be recrystallized from hexane/ethyl acetate); Colorless crystals (CCDC 875097); mp. 52-55 °C; IR (ATR) 2970 2237 1728 1150 1026 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.7 (3H, d, *J* = 6.2 Hz), 1.27 (3H, t, *J* = 7.2 Hz), 1.58-1.52 (1H, m), 2.04-1.93 (2H, m), 2.11 (1H, ddd, *J* = 15.2, 7.6, 7.6 Hz), 2.41 (1H, dd, *J* = 16.2, 9.5 Hz), 2.53 (1H, dd, *J* = 16.2, 3.3 Hz), 2.64 (1H, ddd, *J* = 13.7, 8.9, 4.6 Hz), 2.86 (1H, ddd, *J* = 9.2, 9.2, 3.3 Hz), 4.14 (2H, q, *J* = 7.2 Hz), 7.63 (2H, t, *J* = 7.6 Hz), 7.76 (1H, t, *J* = 7.6 Hz), 8.04 (2H, d, *J* = 7.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.3, 18.3, 32.4, 34.2, 36.9, 41.9, 47.3, 61.0, 70.4, 117.0, 129.6, 130.5, 135.2, 135.3, 170.9; EIHRMS: Found: *m/z* 336.1270. Calcd for C₁₇H₂₂NO₄S: (M+H)⁺ 336.1270.

ethyl 2-((1*S**,2*S**,5*R**)-2-cyano-5-(methoxymethyl)-2-(phenylsulfonyl)cyclopentyl)acetate (**3-3da**)



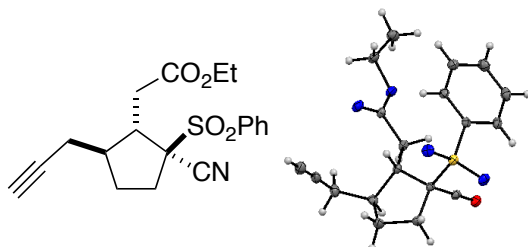
89% yield, *dr* = 15.7 : 1 (as an inseparable mixture) from **3-1d** and **3-2a**; Yellow oil; IR (ATR) 2311 2236 2160 1732 1204 1152 1126 1084 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.27 (3H, *J* = 7.2 Hz); 1.77 (1H, ddd, *J* = 13.2, 7.6, 7.6 Hz), 2.00-1.91 (1H, m), 2.11 (1H, ddd, *J* = 13.2, 6.0, 6.0 Hz), 2.23-2.18 (1H, m), 2.63-2.49 (3H, m), 3.06 (1H, ddd, *J* = 9.2, 9.2, 3.6 Hz), 3.28 (3H, s), 3.37 (2H, dd, *J* = 6.2, 3.2 Hz), 4.14 (2H, q, *J* = 7.2 Hz), 7.63 (2H, t, *J* = 7.6 Hz), 7.76 (1H, t, *J* = 7.6 Hz), 8.03 (2H, d, *J* = 7.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.3, 27.3, 34.3, 37.6, 43.5, 46.3, 58.9, 60.9, 70.6, 74.4, 116.7, 129.6, 130.5, 135.2, 135.4, 170.9; EIHRMS: Found: *m/z* 366.1378. Calcd for C₁₈H₂₄NO₅S: (M+H)⁺ 366.1375.

ethyl 2-((1*S**,2*S**,5*S**)-5-allyl-2-cyano-2-(phenylsulfonyl)cyclopentyl)acetate (**3-3ea**)



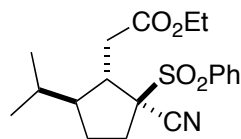
87% yield, *dr* = >99 : 1 from **3-1e** and **3-2a**; Colorless crystals; mp. 58-61 °C; IR (ATR) 1728, 1688, 1449, 1420, 1152 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.27 (3H, t, *J* = 7.1 Hz), 1.69-1.60 (1H, m), 2.13-1.91 (4H, m), 2.33-2.27 (1H, m), 2.47 (1H, dd, *J* = 16.3, 9.2 Hz), 2.64-2.51 (2H, m), 2.97 (1H, ddd, *J* = 8.8, 8.8, 3.2 Hz), 4.14 (2H, q, *J* = 7.1 Hz), 5.08-5.03 (2H, m), 5.77-5.67 (1H, m), 7.63 (2H, t, *J* = 7.7 Hz), 7.76 (1H, t, *J* = 7.7 Hz), 8.04 (2H, d, *J* = 7.7 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.2, 29.2, 34.1, 37.2, 37.5, 45.2, 45.9, 61.0, 70.5, 116.8, 117.2, 129.5, 129.6, 130.5, 130.5, 135.2, 135.3, 135.6, 170.9; EIHRMS: Found: *m/z* 362.1415. Calcd for C₁₉H₂₄NO₄S: (M+H)⁺ 362.1426.

ethyl 2-((1*S**,2*S**,5*S**)-2-cyano-2-(phenylsulfonyl)-5-(prop-2-yn-1-yl)cyclopentyl)acetate (**3-3fa**)



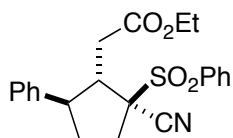
81% yield, *dr* = >99 : 1 from **3-1f** and **3-2a**; Colorless crystals (CCDC 875098); mp. 102-105 °C; IR (ATR) 3286 1736, 1152, 1028 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.28 (3H, t, *J* = 7.2 Hz), 1.96-1.80 (1H, m), 2.01 (1H, t, *J* = 2.6 Hz), 2.20-2.04 (3H, m), 2.30 (1H, ddd, *J* = 16.9, 7.5, 2.6 Hz), 2.46 (1H, ddd, *J* = 16.9, 4.8, 2.6 Hz), 2.51 (1H, dd, *J* = 16.5, 9.5 Hz), 2.63-2.58 (1H, m), 2.68 (1H, dd, *J* = 16.5, 3.3 Hz), 3.06 (1H, ddd, 9.6, 9.6, 3.3 Hz), 4.15 (2H, q, *J* = 7.2 Hz), 7.64 (2H, t, *J* = 7.5 Hz), 7.77 (1H, t, *J* = 7.5 Hz), 8.04 (2H, d, *J* = 7.5 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.2, 22.4, 29.4, 34.1, 37.2, 44.6, 44.9, 61.1, 70.3, 70.6, 81.3, 116.6, 129.6, 130.5, 135.1, 135.4, 170.8; EIHRMS: Found: *m/z* 360.1270. Calcd for C₁₉H₂₂NO₄S: (M+H)⁺ 360.1270.

ethyl 2-((1*S**,2*S**,5*S**)-2-cyano-5-isopropyl-2-(phenylsulfonyl)cyclopentyl)acetate
(**3-3ga**)



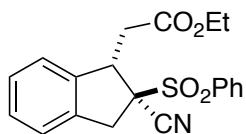
78% yield, *dr* = >99 : 1 from **3-1g** and **3-2a**; Colorless oil; IR (ATR) 2311 1732 1204 1153 1084 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.89 (3H, d, J = 6.8 Hz), 0.93 (3H, d, J = 6.8 Hz), 1.27 (3H, t, J = 7.2 Hz), 1.94-1.68 (4H, m), 2.09 (1H, ddd, J = 13.5, 13.5, 6.5 Hz), 2.45 (1H, dd, J = 16.2, 8.3 Hz), 2.51 (1H, ddd, J = 14.2, 8.3, 6.0 Hz), 2.64 (1H, dd, J = 16.2, 3.8 Hz), 3.09 (1H, ddd, J = 8.4, 8.4, 3.6 Hz), 4.18-4.10 (2H, m), 7.63 (2H, t, J = 7.9 Hz), 7.75 (1H, t, J = 7.9 Hz), 8.04 (2H, d, J = 7.9 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.2, 16.4, 22.3, 24.1, 28.3, 34.5, 37.6, 43.1, 52.3, 61.0, 70.7, 116.9, 129.5, 130.5, 135.3, 135.3, 171.0; EIHRMS: Found: m/z 364.1581. Calcd for $\text{C}_{19}\text{H}_{26}\text{NO}_4\text{S}$: ($\text{M}+\text{H}$) $^+$ 364.1583.

ethyl 2-((1*S**,2*S**,5*R**)-2-cyano-5-phenyl-2-(phenylsulfonyl)cyclopentyl)acetate
(**3-3ha**)



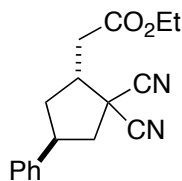
92% yield, *dr* = >99 : 1 from **3-1h** and **3-2a**; Colorless oil; IR (ATR) 2236 1734 1327 1314 1219 1150 1084 1028 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.02 (3H, t, J = 7.2 Hz), 2.31-2.10 (3H, m), 2.45-2.33 (2H, m), 2.89 (1H, ddd, J = 14.2, 8.5, 3.1 Hz), 3.08 (1H, ddd, J = 10.8, 10.8, 7.2 Hz), 3.43 (1H, ddd, J = 11.2, 6.0, 6.0 Hz), 3.55 (1H, qd, J = 10.7, 7.2 Hz), 3.66 (1H, qd, J = 10.7, 7.2 Hz), 7.34-7.24 (5H, m), 7.67 (2H, t, J = 7.5 Hz), 7.79 (1H, t, J = 7.5 Hz), 8.13 (2H, d, J = 7.5 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 13.9, 33.4, 34.6, 36.9, 47.9, 53.1, 60.7, 69.6, 116.9, 127.7, 127.9, 128.8, 129.7, 130.7, 135.0, 135.5, 139.8, 169.9; EIHRMS: Found: m/z 398.1427. Calcd for $\text{C}_{22}\text{H}_{24}\text{NO}_4\text{S}$: ($\text{M}+\text{H}$) $^+$ 398.1426.

ethyl 2-((1*S**,2*S**)-2-cyano-2-(phenylsulfonyl)-2,3-dihydro-1*H*-inden-1-yl)acetate (**3-3ka**)



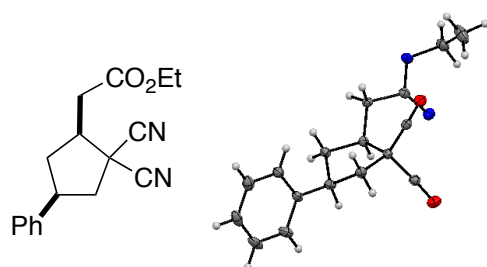
78% yield, *dr* = >99 : 1 from **3-1k** and **3-2a**; White solid; mp. 117-118 °C; IR (NaCl) 3053 2986 1732 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.28 (3H, t, J = 7.1 Hz), 2.79 (1H, dd, J = 9.3, 16.9 Hz), 2.95 (1H, dd, J = 3.4, 16.9 Hz), 3.38 (1H, d, J = 16.3 Hz), 3.87 (1H, d, J = 16.3 Hz), 4.22 (2H, q, J = 7.1 Hz), 4.63 (1H, dd, J = 3.2, 9.3 Hz), 7.10-7.24 (4H, m), 7.62 (2H, t, J = 7.8 Hz), 7.77 (1H, t, J = 7.5 Hz), 8.08 (2H, d, J = 8.1 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.2, 37.9, 40.3, 45.2, 61.3, 70.8, 116.5, 123.9, 124.4, 128.4(5), 128.5(2), 129.7, 130.5, 134.9, 135.5, 136.0, 140.7, 170.7; EIHRMS: Found: m/z 370.1111. Calcd for $\text{C}_{20}\text{H}_{20}\text{NO}_4\text{S}$: $(\text{M}+\text{H})^+$ 370.1113.

ethyl 2-((1*S**,4*R**)-2,2-dicyano-4-phenylcyclopentyl)acetate (**3-3lb**)



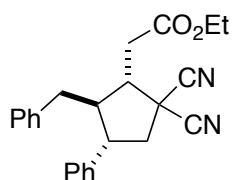
59% from **3-1l** and **3-2b**, isolated as a pure diastereomer; Colorless oil; IR (ATR) 2251 1732 1209 1196 1157 1028 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.30 (3H, t, J = 7.1 Hz), 2.12 (1H, ddd, J = 14.0, 10.0, 10.0 Hz), 2.39 (1H, ddd, J = 14.0, 9.1, 6.7 Hz), 2.45 (1H, dd, J = 9.1, 13.6 Hz), 2.67 (1H, dd, J = 16.2, 9.4 Hz), 2.93 (1H, dd, J = 16.2, 5.2 Hz), 2.96 (1H, dd, J = 12.4, 7.2 Hz), 3.19 (1H, dddd, J = 9.2, 9.2, 9.2, 5.2 Hz), 3.59 (1H, dddd, J = 10.8, 10.8, 7.1, 7.1 Hz), 4.21 (2H, q, J = 7.1 Hz), 7.22 (2H, d, J = 8.0 Hz), 7.27 (1H, t, J = 8.0 Hz), 7.35 (2H, t, J = 8.0 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.4, 36.7, 37.7, 39.9, 42.0, 46.5, 46.6, 61.6, 114.2, 115.4, 127.0, 127.6, 129.3, 142.0, 170.4; EIHRMS: Found: m/z 283.1443. Calcd for $\text{C}_{17}\text{H}_{19}\text{O}_2\text{N}_2$: $(\text{M}+\text{H})^+$ 283.1447.

ethyl 2-((1*S**,4*S**)-2,2-dicyano-4-phenylcyclopentyl)acetate (**3-3lb''**)



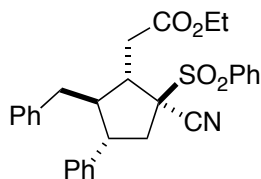
35% from **3-1l** and **3-2b**, isolated as pure diastereomer; Colorless crystals (CCDC 875099); mp. 89-92°C; IR (ATR) 2247 1730 1234 11976 1163 1153 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.31 (3H, t, $J = 7.1$ Hz), 1.75 (1H, ddd, $J = 12.0, 12.0, 12.0$ Hz), 2.66 – 2.50 (2H, m), 2.72 (1H, dd, $J = 16.6, 8.3$ Hz), 2.90 (1H, dd, $J = 16.6, 6.4$ Hz), 3.00 (1H, dd, $J = 14.0, 9.2$ Hz), 3.08 (1H, dddd, $J = 14.4, 12.4, 8.0, 6.4$ Hz), 3.48 (1H, dddd, $J = 11.6, 9.1, 9.1, 6.8$ Hz), 4.22 (2H, q, $J = 7.1$ Hz), 7.23 (2H, d, $J = 6.7$ Hz), 7.27 (1H, t, $J = 6.7$ Hz), 7.35 (2H, t, $J = 6.7$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.3, 36.2, 38.0, 40.1, 43.6, 46.3, 47.0, 61.6, 115.1, 116.5, 127.1, 127.8, 129.2, 140.7, 170.4; EIHRMS: Found: m/z 283.1449. Calcd for $\text{C}_{17}\text{H}_{19}\text{O}_2\text{N}_2$: $(\text{M}+\text{H})^+$ 283.1447.

ethyl 2-((1*S**,4*S**,5*R**)-5-benzyl-2,2-dicyano-4-phenylcyclopentyl)acetate (**3-3mb**)



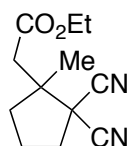
86% yield, $dr = 12 : 1$ (as an inseparable mixture) from **3-1m** and **3-2b**; Colorless crystals; mp. 89-92 °C; IR (ATR) 2343 2249 1732 1254 1028 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.27 (3H, $J = 7.2$ Hz), 2.36-2.27 (1H, m), 2.60-2.40 (4H, m), 2.94-2.76 (3H, m), 3.05 (1H, ddd, $J = 11.2, 11.2, 7.6$ Hz), 4.24-4.15 (2H, m), 6.99 (2H, d, $J = 7.2$ Hz), 7.31-7.17 (6H, m), 7.37 (2H, t, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.2, 36.3, 37.4, 37.5, 46.3, 49.8, 50.4, 52.4, 61.6, 115.1, 117.1, 127.0, 127.7, 127.9, 128.9, 129.2, 129.3, 137.7, 139.3, 170.5; EIHRMS: Found: m/z 373.1902. Calcd for $\text{C}_{24}\text{H}_{25}\text{N}_2\text{O}_2$: $(\text{M}+\text{H})^+$ 373.1916.

ethyl 2-((1*S**,2*S**,4*S**,5*R**)-5-benzyl-2-cyano-4-phenyl-2-(phenylsulfonyl)cyclopentyl)acetate (**3-3ma**)



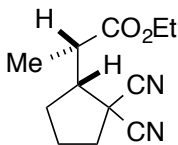
91% yield, *dr* = 12 : 1 (as an inseparable mixture) from **3-1m** and **3-2a**; Yellow oil; IR (ATR) 2980 2934 2311 1732 1217 1180 1150 1084 1030 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.19 (3H, t, J = 7.2 Hz), 2.28 (1H, dd, J = 17.9, 4.6 Hz), 2.40 (1H, dd, J = 17.9, 5.2 Hz), 2.44 (1H, dd, J = 11.6, 3.2 Hz), 2.62 (1H, dd, J = 13.6, 8.0 Hz), 2.77-2.70 (1H, m), 2.83-2.78 (1H, m), 2.86 (1H, dd, J = 14.8, 8.0 Hz), 3.22-4.14 (2H, m), 4.10-4.02 (2H, m), 7.00 (2H, d, J = 6.7 Hz), 7.32-7.13 (8H, m), 7.61 (2H, t, J = 7.6 Hz), 7.74 (1H, t, J = 7.6 Hz), 8.03 (2H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.2, 36.0, 37.7, 42.9, 45.2, 49.9, 52.8, 60.9, 69.7, 117.3, 126.5, 127.4, 127.9, 128.5, 129.0, 129.0, 129.6, 130.8, 134.5, 135.4, 138.7, 140.5, 171.0; EIHRMS: Found: m/z 488.1895. Calcd for $\text{C}_{29}\text{H}_{30}\text{NO}_4\text{S}$: ($\text{M}+\text{H}$) $^+$ 488.1896.

ethyl 2-(2,2-dicyano-1-methylcyclopentyl)acetate (**3-3nb**)



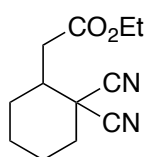
85% yield from **3-1n** and **3-2b**; Colorless oil; IR (ATR) 2311 1732 1219 1188 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.30 (3H, t, J = 7.2 Hz), 1.35 (3H, s), 2.04-1.95 (4H, m), 2.64-2.58 (1H, m), 2.56-2.48 (1H, m), 2.63 (1H, d, J = 14.7 Hz), 2.72 (1H, d, J = 14.7 Hz), 4.26-4.14 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1, 20.6, 21.3, 36.3, 37.1, 42.4, 44.5, 49.9, 61.0, 114.9, 115.3, 169.8; EIHRMS: Found: m/z 221.1283. Calcd for $\text{C}_{12}\text{H}_{17}\text{N}_2\text{O}_2$: ($\text{M}+\text{H}$) $^+$ 221.1290.

(*S**)-ethyl 2-((*R**)-2,2-dicyanocyclopentyl)propanoate (**3-3ob**)



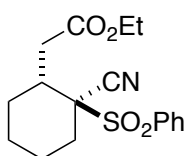
62% yield, *dr* = 7.7 : 1 from **3-1o** and **3-2b** (the major isomer could be isolated partially); Colorless oil; IR (ATR) 2311 1732 1177 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.29 (3H, t, J = 7.1 Hz), 1.49 (3H, d, J = 6.8 Hz), 1.59 (1H, dddd, J = 13.4, 10.0, 10.0, 7.6 Hz), 2.01-1.92 (2H, m), 2.15 (1H, dddd, J = 13.2, 8.0, 8.0, 5.2 Hz), 2.41 (1H, ddd, J = 13.2, 8.8, 8.8 Hz), 2.70-2.61 (2H, m), 3.75 (1H, dq, J = 10.7, 6.8 Hz), 4.17 (2H, q, J = 7.1 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1, 17.0, 22.5, 29.6, 36.9, 40.1, 43.4, 53.0, 61.0, 114.2, 116.7, 173.9; EIHRMS: Found: m/z 221.1292. Calcd for $\text{C}_{12}\text{H}_{17}\text{N}_2\text{O}_2$: ($\text{M}+\text{H}$) $^+$ 221.1290.

ethyl 2-(2,2-dicyanocyclohexyl)acetate (**3-3pb**)



87% yield, from **3-1p** and **3-2b**, Colorless oil; IR (NaCl) 2247 1736 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.29 (3H, t, J = 7.2 Hz), 1.32-1.45 (2H, m), 1.57-1.67 (1H, m), 1.81-1.88 (2H, m), 1.94-2.02 (2H, m), 2.36-2.48 (3H, m), 2.82 (1H, d, J = 12.8 Hz), 4.18 (2H, q, J = 7.2 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.2, 21.5, 24.0, 27.9, 35.4, 38.0, 38.2, 40.8, 61.2, 113.8, 115.9, 170.4; EIHRMS: Found: m/z 221.1285. Calcd for $\text{C}_{12}\text{H}_{17}\text{N}_2\text{O}_2$: ($\text{M}+\text{H}$) $^+$ 221.1290.

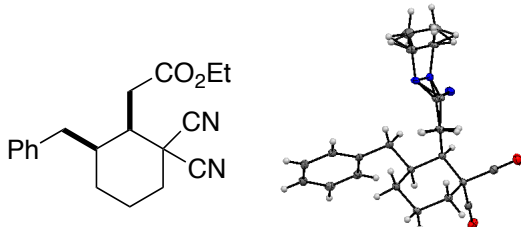
ethyl 2-((1*R**,2*S**)-2-cyano-2-(phenylsulfonyl)cyclohexyl)acetate (**3-3pa**)



84% yield, *dr* = 4.4 : 1 (as an inseparable mixture) from **3-1p** and **3-2a**: White solid; mp. 91-97 $^{\circ}\text{C}$; IR (NaCl) 3053 2986 2307 1732 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.29 (3H, t, J = 7.1 Hz), 1.32-1.48 (2H, m), 1.57-2.08 (5H, m), 2.43 (1H, 1H x 0.81, dd, J = 10.6, 16.5 Hz), 2.66 (1H, 1H x 0.19, dd, J = 11.5, 16.1 Hz), 2.77-2.84 (1H, 1H x 0.81, m), 2.91-2.95 (1H, 1H x 0.19, m), 3.27 (1H, 1H x 0.19, dd, J = 2.9, 16.1 Hz), 3.61 (1H, 1H x 0.81, dd, J = 2.9, 16.5 Hz), 4.18 (2H, q, J = 7.1 Hz), 7.64 (2H, t, J = 7.8 Hz), 7.77 (1H, t, J = 7.5 Hz), 7.99 (2H, d, J = 7.9 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.3, 22.7, 24.2, 30.5, 33.1, 36.6, 37.8, 60.9, 67.1,

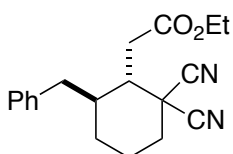
115.5, 129.6, 130.6, 134.9, 135.3, 171.3; EIHRMS: Found: m/z 336.1277. Calcd for $C_{17}H_{22}NO_4S$: $(M+H)^+$ 336.1270.

ethyl 2-((1*R**,6*S**)-6-benzyl-2,2-dicyanocyclohexyl)acetate (**3-3qb**)



72% yield, from **3-1q** and **3-2b**, isolated as a pure diastereomer; Colorless crystals (CCDC 875096); mp. 104-106 °C ;IR (ATR) 2359 1732 1522 1260 1219 1186 1152 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24-1.19 (1H, m), 1.28 (3H, t, J = 7.2 Hz), 1.53-1.48 (1H, m), 1.67-1.60 (1H, m), 1.85-1.79 (1H, m), 2.04 (1H, ddd, J = 14.4, 11.2, 3.6 Hz), 2.18 (1H, ddd, J = 14.4, 9.2, 4.4 Hz), 2.30-2.24 (1H, m), 2.44 (1H, dd, J = 13.5, 10.2 Hz), 2.60 (1H, dd, J = 17.0, 5.2 Hz), 2.69 (1H, dd, J = 16.8, 6.4 Hz), 2.73 (1H, dd, J = 14.4, 4.8 Hz), 3.02-2.98 (1H, m), 4.19 (2H, q, J = 7.2 Hz), 7.12 (2H, d, J = 7.2 Hz), 7.22 (1H, t, J = 7.2 Hz), 7.29 (2H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 20.5, 24.8, 31.6, 31.7, 37.3, 37.9, 38.2, 40.9, 61.7, 115.6, 115.7, 126.7, 128.8, 129.1, 138.9, 170.7; EIHRMS: Found: m/z 311.1759. Calcd for $C_{19}H_{23}N_2O_2$: $(M+H)^+$ 311.1760.

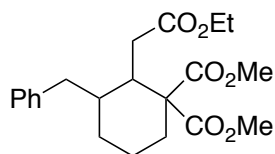
ethyl 2-((1*R**,6*R**)-6-benzyl-2,2-dicyanocyclohexyl)acetate (**3-3qb''**)



16% yield, from **3-1q** and **3-2b**, isolated as a pure diastereomer: Colorless crystals; mp. 103-105 °C; IR (ATR) 2351 2320 2311 2247 1770 1732 1684 1504 1456 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04-0.93 (1H, m), 1.29 (3H, t, J = 7.2 Hz), 1.65-1.47 (3H, m), 1.83-1.71 (2H, m), 2.00 (1H, ddd, J = 13.6, 13.6, 4.0 Hz), 2.21 (1H, dd, J = 13.6, 11.2 Hz), 2.48-2.43 (2H, m), 2.82-2.83 (2H, m), 2.89 (1H, dd, J = 13.6, 3.7 Hz), 4.26-4.17 (2H, m), 7.12 (2H, d, J = 7.2 Hz), 7.22 (1H, t, J = 7.2 Hz), 7.30 (2H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.6, 30.0, 35.9,

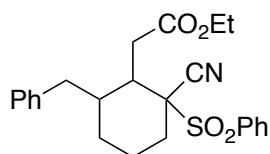
37.4, 39.9, 41.2, 45.1, 61.7, 114.3, 116.2, 126.7, 128.8, 129.3, 138.8, 171.2;
EIHRMS: Found: m/z 311.1764. Calcd for $C_{19}H_{23}N_2O_2$: $(M+H)^+$ 311.1760.

dimethyl 3-benzyl-2-(2-ethoxy-2-oxoethyl)cyclohexane-1,1-dicarboxylate (**3-3qc**)



70% yield, $dr = 2.3 : 1$ (as an inseparable mixture) from **3-1q** and **3-2c**: Colorless oil; IR (ATR) 1732 1522 1495 1252 1240 1217 1190 1180 1150 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12-0.99 (2H, m), 1.23 (3H, t, $J = 7.1$ Hz), 1.41-1.36 (1H, m), 1.66 (1H, ddd, $J = 13.6, 6.8, 3.2$ Hz), 1.80 (1H, ddd, $J = 13.6, 13.6, 3.6$ Hz), 2.26-2.13 (3H, m), 2.35 (1H, dd, $J = 13.5, 9.5$ Hz), 2.47 (1H, dd, $J = 17.2, 5.0$ Hz), 2.68 (1H, dd, $J = 13.5, 5.0$ Hz), 3.21-3.18 (1H, m), 3.65 (3H, s), 3.74 (3H, s), 4.13-4.04 (2H, m), 7.20-7.14 (3H, m), 7.29-7.25 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.2, 25.3, 26.9, 30.7, 38.1, 39.4, 39.8, 52.6, 59.2, 60.6, 125.9, 128.2, 129.1, 140.3, 171.2, 171.5, 172.7; EIHRMS: Found: m/z 377.1959. Calcd for $C_{21}H_{29}O_6$: $(M+H)^+$ 377.1964.

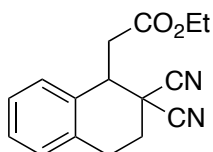
ethyl 2-(6-benzyl-2-cyano-2-(phenylsulfonyl)cyclohexyl)acetate (**3-3qa**)



93% yield, $dr = 0.39 : 0.36 : 0.25$ (as an inseparable mixture) from **3-1q** and **3-2a**: Colorless oil; IR (ATR) 1732 1497 1472 1192 1180 1150 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37-0.85 (5H, m), 1.85-1.65 (3H, m), 2.04-2.00 (1H x 0.39, 2H x 0.25, m), 2.24-2.11 (1H, 1H x 0.36, m), 2.53-2.47 (1H x 0.36, x 0.39, m), 2.75-2.64 (1H, m), 2.95-2.86 (1H, 1H x 0.25, m), 3.09-3.05 (1H x 0.39, m), 3.21-3.19 (1H x 0.36, m), 3.43-3.37 (1H x 0.39, x 0.36, m), 3.74 (1H x 0.25, dd, $J = 18.4, 2.0$ Hz), 4.25-4.11 (2H, m), 7.13-7.09 (2H, m), 7.30-7.17 (3H, m), 7.66-7.58 (2H, m), 7.79-7.73 (1H, m), 8.04-7.93 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 18.1, 22.0, 22.3, 23.5, 25.3, 26.1, 28.4, 29.8, 32.5, 33.2, 33.5, 34.6, 37.0, 37.9, 38.2, 38.6, 39.2, 39.3, 40.1, 41.6, 44.2, 61.1, 61.2, 61.3, 65.1, 67.8, 68.9, 116.1, 117.5, 117.6, 126.3, 126.5, 126.5, 128.6, 128.6, 128.6, 129.1, 129.2, 129.3, 129.4, 129.5,

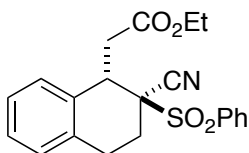
129.5, 130.7, 130.8, 131.0, 134.5, 134.7, 135.1, 135.2, 135.4, 139.2, 139.5, 140.4, 171.0, 171.8, 172.0; EIHRMS: Found: m/z 426.1739. Calcd for $C_{24}H_{28}NO_4S$: $(M+H)^+$ 426.1739.

ethyl 2-(2,2-dicyano-1,2,3,4-tetrahydronaphthalen-1-yl)acetate (**3-3rb**)



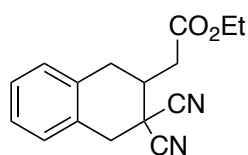
84% yield, from **3-1r** and **3-2b**, Yellow oil; IR (NaCl) 3024 2982 2249 1732 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (3H, t, $J = 7.1$ Hz), 2.45-2.53 (2H, m), 2.76 (1H, dd, $J = 8.0, 16.5$ Hz), 2.99 (1H, dd, $J = 4.4, 16.5$ Hz), 3.10 (2H, t, $J = 6.8$ Hz), 4.05 (1H, dd, $J = 4.4, 7.9$ Hz), 4.23 (2H, q, $J = 7.1$ Hz), 7.13-7.26 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 25.1, 29.2, 36.3, 39.3, 41.4, 61.7, 114.8, 115.3, 127.4, 128.3(1), 128.3(3), 129.4, 132.2, 132.8, 170.5; EIHRMS: Found: m/z 269.1281. Calcd for $C_{16}H_{17}N_2O_2$: $(M+H)^+$ 269.1290.

ethyl 2-((1*S**,2*S**)-2-cyano-2-(phenylsulfonyl)-1,2,3,4-tetrahydronaphthalen-1-yl)acetate (**3-3ra**)



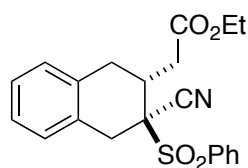
quant. yield, $dr = 5.4 : 1$ (as an inseparable mixture) from **3-1r** and **3-2a**: Yellow solid; mp 102-104 $^{\circ}C$; IR (NaCl) 3055 2986 2359 2301 1732 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, 3H x 0.17, t, $J = 7.1$ Hz), 1.27 (3H, 3H x 0.83, t, $J = 7.2$ Hz), 2.31 (2H, 2H x 0.83, dd, $J = 4.9, 7.8$ Hz), 2.43-2.49 (2H, 2H x 0.17, m), 2.55-2.63 (1H, 1H x 0.17, m), 2.77 (1H, 1H x 0.83, dd, $J = 8.0, 17.4$ Hz), 2.87-3.19 (2H, m), 3.35 (1H, 1H x 0.83, dd, $J = 3.0, 17.4$ Hz), 3.62 (1H, 1H x 0.17, dd, $J = 2.8, 15.8$ Hz), 3.97-3.99 (1H, 1H x 0.17, m), 4.12 (2H, 2H x 0.17, q, $J = 7.1$ Hz), 4.21 (2H, 2H x 0.83, q, $J = 7.2$ Hz), 7.06-7.22 (4H, m), 7.65 (2H, t, $J = 7.8$ Hz), 7.78 (1H, t, $J = 7.1$ Hz), 8.07 (2H, d, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 26.1, 29.0, 36.4, 40.8, 61.4, 66.5, 116.3, 127.3, 127.5, 127.6, 129.6, 130.9, 131.2, 134.1(6), 134.1(9), 135.5, 171.7; EIHRMS: Found: m/z 384.1271. Calcd for $C_{21}H_{22}NO_4S$: $(M+H)^+$ 384.1270.

ethyl 2-(3,3-dicyano-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (**3-3sb**)



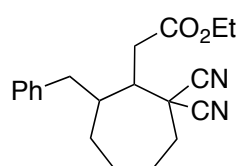
86% yield, from **3-1s** and **3-2b**, Colorless oil; IR (NaCl) 2984 2251 1732 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.32 (3H, t, $J = 7.1$ Hz), 2.57 (1H, dd, $J = 9.7, 16.0$ Hz), 2.81-2.92 (2H, m), 3.01 (1H, dd, $J = 3.2, 16.0$ Hz), 3.24-3.29 (1H, m), 3.51 (1H, d, $J = 16.6$ Hz), 3.56 (1H, d, $J = 16.6$ Hz), 4.23 (2H, q, $J = 7.1$ Hz), 7.10-7.26 (4H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 14.2, 31.3, 36.2, 37.3, 37.5, 38.4, 61.4, 113.6, 115.2, 127.2, 127.7, 128.1, 128.6, 129.2, 132.0, 170.1; EIHRMS: Found: m/z 269.1290. Calcd for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_2$: $(\text{M}+\text{H})^+$ 269.1290.

ethyl 2-((2*R**,3*S**)-3-cyano-3-(phenylsulfonyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (**3-3sa**)



93% yield, $dr = 5.5 : 1$ (as an inseparable mixture) from **3-1s** and **3-2a**: White solid; mp. 144-145 $^{\circ}\text{C}$; IR (NaCl) 3053 2305 2236 1732 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.30 (3H, t, $J = 7.1$ Hz), 2.29 (1H, 1H x 0.09, dd, $J = 11.2, 16.6$ Hz), 2.52 (1H, 1H x 0.91, dd, $J = 10.2, 15.9$ Hz), 2.86-2.93 (2H, m), 3.20-3.35 (3H, m), 3.39 (1H, 1H x 0.91, d, $J = 15.6$ Hz), 3.55 (1H, 1H x 0.09, d, $J = 16.8$ Hz), 4.11 (2H, 2H x 0.09, q, $J = 6.1$ Hz), 4.20 (2H, 2H x 0.91, q, $J = 7.1$ Hz), 6.95 (1H, d, $J = 7.4$ Hz), 7.09-7.20 (3H, m), 7.67 (2H, t, $J = 7.8$ Hz), 7.80 (1H, t, $J = 7.8$ Hz), 8.08 (2H, d, $J = 8.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.4, 33.2, 34.6, 36.3, 37.7, 61.1, 65.3, 115.8, 127.1, 127.8, 128.4(8), 128.5(2), 129.5, 129.8, 130.7, 133.5, 134.9, 135.6, 170.9; EIHRMS: Found: m/z 384.1266. Calcd for $\text{C}_{21}\text{H}_{22}\text{NO}_4\text{S}$: $(\text{M}+\text{H})^+$ 384.1270.

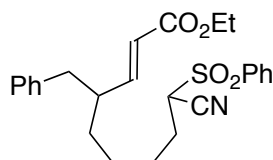
ethyl 2-(7-benzyl-2,2-dicyanocycloheptyl)acetate (**3-3tb**)



2% yield, from **3-1t** and **3-2b**, isolated as a pure diastereomer: Colorless oil; IR (NaCl) 3055 2307 1732 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.30 (3H, t, $J = 7.1$ Hz), 1.41-1.55 (2H, m), 1.65-1.78 (2H, m), 1.84-1.90 (2H, m), 1.92-1.97 (1H, m), 2.27-2.40 (2H, m), 2.47 (1H, dd, $J = 11.0, 13.4$ Hz), 2.70-2.92 (4H, m), 4.21 (2H, q, $J = 7.1$ Hz), 7.13 (2H, d, $J = 7.3$ Hz), 7.20-7.31 (3H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 14.3, 24.3, 25.1, 29.8, 36.7, 39.3, 40.8, 41.0, 43.6, 46.9, 61.7, 115.4, 116.7, 126.7, 128.8, 129.3, 139.8, 171.2; EIHRMS: Found: m/z 325.1909. Calcd for $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_2$: $(\text{M}+\text{H})^+$ 325.1916.

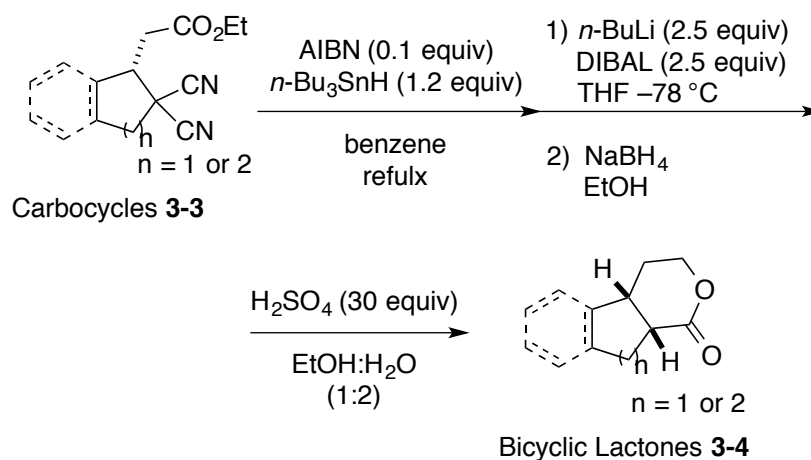
24% yield, from **3-1t** and **3-2b**, isolated as a pure diastereomer: White solid; mp. 104-106°C; IR (NaCl) 3053 2305 1734 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.30 (3H, t, $J = 7.1$ Hz), 1.43-1.53 (2H, m), 1.61-1.76 (2H, m), 1.81-1.86 (2H, m), 2.04-2.13 (1H, m), 2.41-2.49 (2H, m), 2.53-2.60 (2H, m), 2.64-2.72 (2H, m), 2.99-3.02 (1H, m), 4.22 (2H, q, $J = 7.1$ Hz), 7.18 (2H, d, $J = 7.3$ Hz), 7.21-7.33 (3H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 14.3, 22.4, 25.4, 28.9, 32.4, 36.9, 40.0(5), 40.0(9), 40.5, 43.9, 61.7, 115.9, 116.2, 126.8, 128.8, 129.2, 139.2, 171.1; EIHRMS: Found: m/z 325.1905. Calcd for $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_2$: $(\text{M}+\text{H})^+$ 325.1916.

ethyl (*E*)-4-benzyl-9-cyano-9-(phenylsulfonyl)non-2-enoate (**3-3ta'**)



57% yield, Colorless oil; IR (NaCl) 3055 2984 1713 1449 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.28 (3H, t, $J = 7.1$ Hz), 1.33-1.40 (2H, m), 1.43-1.51 (2H, m), 1.76-1.84 (2H, m), 2.42-2.49 (1H, m), 2.70 (2H, d, $J = 7.1$ Hz), 3.32-3.39 (2H, m), 4.17 (2H, q, $J = 7.1$ Hz), 5.70 (1H, d, $J = 15.7$ Hz), 6.79 (1H, dd, $J = 9.0, 15.7$ Hz), 7.11 (2H, d, $J = 7.2$ Hz), 7.19 (1H, t, $J = 7.3$ Hz), 7.27 (2H, t, $J = 7.7$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.4, 26.6, 26.7, 26.8, 33.2, 41.2, 44.3, 57.7, 60.5, 114.1, 122.0, 126.5, 128.6, 129.3, 129.8(overlapped), 135.5, 135.9, 139.4, 151.8, 166.6; EIHRMS: Found: m/z 440.1890. Calcd for $\text{C}_{25}\text{H}_{30}\text{NO}_4\text{S}$: $(\text{M}+\text{H})^+$ 440.1896.

3.6.4. Decyanation-chemoselective reduction-lactonization sequence



Typical procedure for synthesis of **3-4bb**:

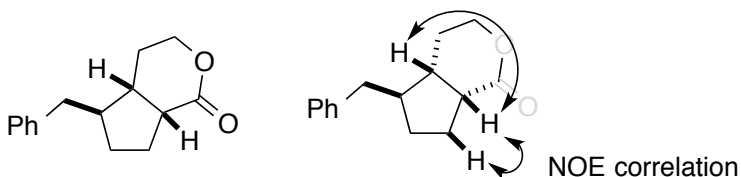
To a solution of ethyl 2-((1*S**,5*S**)-5-benzyl-2,2-dicyanocyclopentyl)acetate (**3-3bb**) (85.6 mg, 0.389 mmol) in benzene (1.3 mL, degassed), AIBN (7.3 mg, 0.044 mmol, 0.1 equiv) and *n*-Bu₃SnH (130 μ L, 0.490 mmol, 1.2 equiv) were added. The mixture was stirred at 80 $^\circ\text{C}$ for 24 h. Upon completion, the mixture was allowed to cool, DBU (1 mL) and Et₂O (20 mL) was added. The mixture was allowed to pass through a short plug of silica gel. After removal of solvents under reduced pressure, the crude mixture was subjected to column chromatography (hexane:ethyl acetate = 9 : 1) to yield the diastereomeric mixture of corresponding (2*S**)-ethyl 2-((1*R**)-2-cyanocyclopentyl)propanoate (66.1 mg, 0.339 mmol, 78% yield), which was used without further characterization.

To a dried Schlenk tube containing THF (1 mL), *n*-BuLi (0.5 mL, 1.6 M, 0.746 mmol, 2.2 equiv) and DIBAL (132 μ L, 0.746 mmol, 2.2 equiv) was added at 0 $^\circ\text{C}$, and the mixture was stirred for 5 min. The mixture was transferred to another THF solution (5 mL) containing the above crude materials (66.1 mg, 0.339 mmol) at -78°C via cannular. The resulting mixture was stirred at -78°C for 3 h, and then, NaBH₄ (33.3 mg, 0.881 mmol, 2.6 equiv) and EtOH (2 mL) were added. After the mixture was then stirred for 2 h, aqueous HCl solution (1 M, 10 mL) was carefully added. The organic materials were extracted three times with ethyl acetate. The combined organic extracts were washed with saturated aqueous NaHCO₃ and brine. After drying with MgSO₄ and removal of the solvents in vacuo, the

resulting crude residue was subjected to the next step without further characterization.

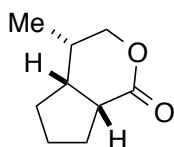
To a solution of containing the above the crude material (43.9 mg, 0.286 mmol) in EtOH (0.4 mL) and H₂O (0.7 mL), conc. H₂SO₄ (0.5 mL, 8.58 mmol, 30 equiv) was added, and the mixture was then stirred at reflux for 24 h. The reaction mixture was allowed to cool to room temperature and neutralized by adding 1 M NaOH. The mixture was then extracted three times with ethyl acetate. The combined organic extracts were washed with brine. After drying with MgSO₄, the solvents were removed under reduced pressure to afford the crude mixture, which was purified by flash column chromatography (hexane:ethyl acetate = 8 : 2) to yield the corresponding (4*aS**,7*aR**)-5-benzylhexahydrocyclopenta[*c*]pyran-1(3*H*)-one (**3-4bb**) (29.6 mg, 0.128 mmol, 33% yield over 3 steps).

(4*aS**,5*S**,7*aR**)-5-benzylhexahydrocyclopenta[*c*]pyran-1(3*H*)-one (**3-4bb**)



Colorless crystals; mp. 125-127 °C; IR (ATR): 3024 1732 1506 1456 1254 1120 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.31-1.08 (1H, m), 1.44-1.33 (1H, m), 1.99-1.58 (4H, m), 2.29-2.05 (2H, m), 2.63 (1H, dd, *J* = 13.5, 7.4 Hz), 2.73 (1H, dd, *J* = 13.5, 6.1 Hz), 2.96 (1H, ddd, *J* = 11.2, 8.8, 8.8 Hz), 4.13 (1H, ddd, *J* = 10.8, 10.8, 2.4 Hz), 4.26 (1H, ddd, *J* = 10.8, 8.0, 4.0 Hz), 7.15 (2H, t, *J* = 7.2 Hz), 7.20 (1H, t, *J* = 7.2 Hz), 7.15 (2H, t, *J* = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 28.2, 28.8, 32.5, 40.6, 42.1, 42.9, 49.5, 67.5, 126.3, 128.6, 129.0, 140.6, 175.5; EIHRMS: Found: *m/z* 231.1388. Calcd for C₁₅H₁₉O₂: (M+H)⁺ 231.1385.

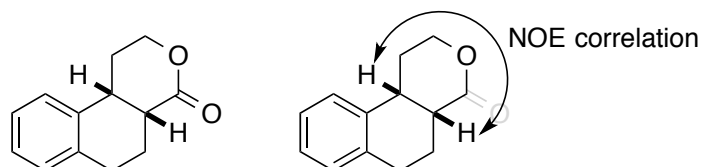
(4*S**,4*aR**,7*aR**)-4-methylhexahydrocyclopenta[*c*]pyran-1(3*H*)-one (**3-4ob**)



40% yield over 3 steps from **3-3ob**; Pale yellow oil; IR (ATR): 1719 1246 1219 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.93 (3H, d, *J* = 7.0 Hz), 1.55-1.35 (2H, m), 1.84-1.69 (3H, m), 2.27-2.16 (1H, m), 2.35-2.29 (1H, m), 2.46-2.38 (1H, m), 2.94

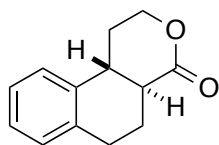
(1H, ddd, $J = 9.2, 9.2, 9.2$ Hz), 4.13-4.06 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 13.8, 26.1, 27.0, 30.5, 32.0, 40.8, 43.5, 70.7, 175.3; EIHRMS: Found: m/z 155.1078. Calcd for $\text{C}_9\text{H}_{15}\text{O}_2$: $(\text{M}+\text{H})^+$ 155.1072.

(4a*S**,10b*S**)-1,2,4a,5,6,10b-hexahydro-4*H*-benzo[*f*]isochromen-4-one (**3-4rb**)



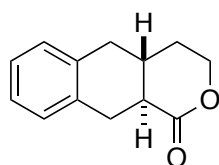
34% yield over 3 steps from **3-3rb**; Yellow solid; mp. 81-82 °C; IR (NaCl) 3171 3053 1732 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.04-2.26 (4H, m), 2.77-2.93 (2H, m), 3.01 (1H, ddd, $J = 3.4, 6.6, 9.6$ Hz), 3.36-3.42 (1H, m), 4.31-4.42 (2H, m), 7.10-7.20 (4H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 24.4, 28.1, 29.9, 35.3, 40.7, 68.3, 126.6, 126.8, 128.3, 129.4, 136.5, 136.7, 173.8; EIHRMS: Found: m/z 203.1071. Calcd for $\text{C}_{13}\text{H}_{15}\text{O}_2$: $(\text{M}+\text{H})^+$ 203.1072.

(4a*S**,10b*R**)-1,2,4a,5,6,10b-hexahydro-4*H*-benzo[*f*]isochromen-4-one (**3-4rb''**)



9% yield over 3 steps from **3-3rb**; Yellow solid; mp. 98-100 °C; IR (NaCl) 3053 3022 1721 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.75-1.86 (1H, m), 1.95-2.04 (1H, m), 2.43 (1H, ddd, $J = 3.1, 12.0, 12.0$ Hz), 2.53-2.59 (1H, m), 2.66-2.73 (1H, m), 2.94-2.97 (2H, m), 3.02-3.10 (1H, m), 4.47-4.53 (2H, m), 7.13-7.24 (4H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 23.4, 28.2, 29.0, 36.8, 42.6, 67.4, 125.8, 126.2, 126.7, 129.3, 136.0, 137.6, 173.7; EIHRMS: Found: m/z 203.1068. Calcd for $\text{C}_{13}\text{H}_{15}\text{O}_2$: $(\text{M}+\text{H})^+$ 203.1072.

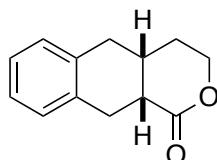
(4a*R**,10a*S**)-3,4,4a,5,10,10a-hexahydro-1*H*-benzo[*g*]isochromen-1-one (**3-4sb**)



33% yield over 3 steps from **3-3sb**; White solid; mp. 115-120 °C; IR (NaCl) 3053 2986 1732 1404 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.70-1.80 (1H, m), 2.04-2.18

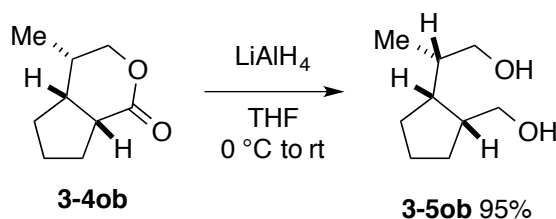
(2H, m), 2.50 (1H, ddd, $J = 5.2, 11.9, 11.9$ Hz), 2.67-2.74 (1H, m), 2.92-3.03 (2H, m), 3.32 (1H, dd, $J = 5.1, 17.1$ Hz), 4.35-4.41 (1H, m), 4.44-4.49 (1H, m), 7.08-7.15 (4H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 29.5, 30.8, 33.3, 37.4, 42.1, 68.0, 126.3, 126.4, 128.9, 129.5, 134.6, 135.0, 173.4; EIHRMS: Found: m/z 203.1071. Calcd for $\text{C}_{13}\text{H}_{15}\text{O}_2$: $(\text{M}+\text{H})^+$ 203.1072.

(4a*S**,10a*S**)-3,4,4a,5,10,10a-hexahydro-1*H*-benzo[*g*]isochromen-1-one (**3-4sb''**)



10% yield over 3 steps from **3-3sb**; Yellow oil; IR (NaCl) 2920 1728 1452 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.72-1.81 (1H, m), 2.11-2.18 (1H, m), 2.51-2.59 (2H, m), 2.84-2.92 (1H, m), 2.99-3.09 (2H, m), 3.20 (1H, dd, $J = 6.7, 15.3$ Hz), 4.33 (1H, ddd, $J = 3.4, 11.1, 11.1$ Hz), 4.42-4.47 (1H, m), 7.10-7.28 (4H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 28.9, 29.4, 31.1, 34.7, 38.8, 67.0, 126.5, 126.7, 127.1, 128.4, 135.6, 136.2, 174.3; EIHRMS: Found: m/z 203.1071. Calcd for $\text{C}_{13}\text{H}_{15}\text{O}_2$: $(\text{M}+\text{H})^+$ 203.1072.

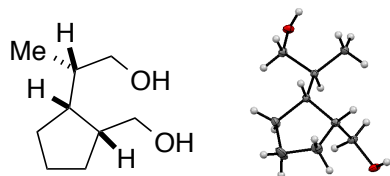
Typical procedure for the reduction of lactone **3-4ob**



To a 2-neck round bottom flask containing lithium aluminum hydride (15.0 mg, 0.395 mmol) in THF (2.0 mL) at 0 °C was added dropwise (4*S**,4a*R**,7a*R**)-4-methylhexahydrocyclopenta[*c*]pyran-1(3*H*)-one (**3-4ob**) (32.1 mg, 0.208 mmol) in THF (1.0 mL). The mixture was stirred at room temperature under a N_2 atmosphere for 3 h. Upon completion of the reaction, the mixture was cooled to 0 °C. Sat. Na_2SO_4 (0.3 mL) was added dropwise and the mixture was allowed to warm to room temperature. The resulting solids were filtered through the Celite pad. After removal of solvents under reduced pressure, the resulting crude mixture

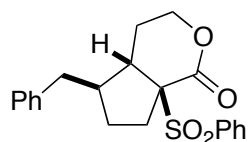
was subjected to flash column chromatography (hexane : ethyl acetate = 1:1) to yield (*S**)-2-((1*R**,2*R**)-2-(hydroxymethyl)cyclopentyl)propan-1-ol (**3-5ob**) (31.3 mg, 0.198 mmol, 95% yield).

(*S**)-2-((1*R**,2*R**)-2-(hydroxymethyl)cyclopentyl)propan-1-ol (**3-5ob**)



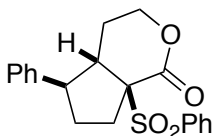
Colorless crystals (CCDC 971676); mp. 73-74 °C; IR (ATR) 3383 3321 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.10 (3H, d, J = 6.4 Hz), 1.24-1.33 (2H, m), 1.52-1.83 (8H, m), 2.18-2.23 (1H, m), 3.36 (1H, dd, J = 9.6, 9.6 Hz), 3.43 (1H, dd, J = 6.6, 10.6 Hz), 3.69-3.74 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 16.9, 22.4, 27.8, 28.4, 36.8, 42.9, 46.5, 62.0, 68.0; EIHRMS: Found: m/z 159.1387. Calcd for $\text{C}_9\text{H}_{19}\text{O}_2$: ($\text{M}+\text{H}$) $^+$ 159.1385.

(4*aS**,5*S**,7*aS**)-5-benzyl-7a-(phenylsulfonyl)hexahydrocyclopenta[*c*]pyran-1(3*H*)-one (**3-6ba**)



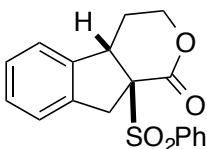
77% yield over 2 steps from **3-3ba**; Colorless crystals; mp. 127-129 °C; IR (ATR) 1721 1304 1258 1207 1136 1103 1074 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.43 (1H, ddd, J = 14.8, 11.6, 3.6 Hz), 1.79-1.65 (2H, m), 1.89 (1H, dddd, J = 14.4, 6.2, 2.4, 2.4 Hz), 2.06-1.98 (2H, m), 2.30 (1H, ddd, J = 15.2, 6.2, 3.6 Hz), 2.88-2.77 (2H, m), 3.06 (1H, ddd, J = 11.2, 7.2, 7.2 Hz), 4.24 (1H, ddd, J = 11.2, 3.2, 3.2 Hz), 4.66 (1H, ddd, J = 11.2, 11.2, 1.6 Hz), 7.24-7.18 (3H, m), 7.29 (2H, t, J = 7.3 Hz), 7.52 (2H, t, J = 7.8 Hz), 7.65 (1H, t, J = 7.8 Hz), 7.85 (2H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 29.9, 30.2, 34.9, 40.2, 43.4, 50.8, 68.5, 78.5, 126.3, 128.5, 128.7, 128.8, 130.5, 134.5, 134.5, 140.2, 168.2; EIHRMS: Found: m/z 371.1309. Calcd for $\text{C}_{21}\text{H}_{23}\text{O}_4\text{S}$: ($\text{M}+\text{H}$) $^+$ 371.1317.

(4a*S**,5*R**,7a*S**)-5-phenyl-7a-(phenylsulfonyl)hexahydrocyclopenta[*c*]pyran-1(3*H*)-one (**3-6ha**)



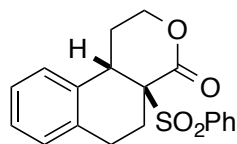
79% yield over 2 steps from **3-3ha**; Colorless crystals; mp. 170-171 °C; IR (ATR) 1717 1304 1288 1264 1207 1136 1076 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.68 (1H, ddd, *J* = 14.8, 12.0, 4.0 Hz), 1.98 (1H, ddd, *J* = 12.0, 12.0, 6.4 Hz), 2.37-2.11 (3H, m), 2.47 (1H, dd, *J* = 14.7, 6.1), 2.81 (1H ddd, *J* = 12.2, 9.7, 6.2 Hz), 3.43 (1H, ddd, *J* = 10.4, 7.6, 7.2 Hz), 4.37 (1H, ddd, *J* = 10.8, 3.6, 3.6 Hz), 4.77 (1H, ddd, *J* = 10.8, 10.8, 2.0 Hz), 7.30-7.25 (1H, t, *J* = 8.7 Hz), 7.41-7.34 (4H, m), 7.58 (2H, t, *J* = 7.6 Hz), 7.71 (1H, t, *J* = 7.6 Hz), 7.92 (2H, d, *J* = 7.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 29.3, 32.8, 35.7, 46.1, 55.8, 68.9, 127.4, 127.7, 129.0, 130.8, 134.5, 134.8, 141.5, 168.8; EIHRMS: Found: *m/z* 357.1173. Calcd for C₂₀H₂₁O₄S: (M+H)⁺ 357.1161.

(4a*S**,9a*S**)-9a-(phenylsulfonyl)-4,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-1(3*H*)-one (**3-6ka**)



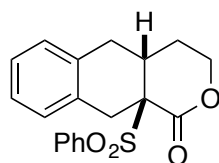
82% yield over 2 steps from **3-3ka**; White solid; mp. 125-126 °C; IR (NaCl) 3055 2986 1728 1396 1310 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.94-2.03 (1H, m), 2.63-2.70 (1H, m), 3.54 (1H, d, *J* = 17.8 Hz), 3.73 (1H, d, *J* = 17.8 Hz), 4.36 (1H, ddd, *J* = 3.6, 5.58, 11.0 Hz), 4.62-4.74 (2H, m), 7.15-7.28 (4H, m), 7.58 (2H, t, *J* = 8.1 Hz), 7.72 (1H, t, *J* = 7.5 Hz), 7.91 (2H, t, *J* = 8.1 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 22.5, 41.4, 44.6, 68.2, 76.9, 123.6, 124.6, 128.0, 128.4, 129.0, 131.1, 134.9, 135.2, 137.8, 141.7, 167.7; EIHRMS: Found: *m/z* 329.0848. Calcd for C₁₈H₁₇O₄S: (M+H)⁺ 329.0848.

(4a*S**,10b*S**)-4a-(phenylsulfonyl)-1,2,4a,5,6,10b-hexahydro-4*H*-benzo[*f*]isochromen-4-one (**3-6ra**)



40% yield over 2 steps from **3-3ra**; Yellow solid; mp. 179-180 °C; IR (NaCl) 3055 3026 1724 1307 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.97 (1H, ddd, $J = 4.1, 12.5, 12.5$ Hz), 2.03-2.11 (1H, m), 2.36 (1H, ddd, $J = 3.7, 3.7, 12.4$ Hz), 2.51-2.59 (1H, m), 2.70 (1H, ddd, $J = 3.9, 3.9, 16.6$ Hz), 2.80-2.88 (1H, m), 4.14 (1H, ddd, $J = 3.4, 8.4, 11.4$ Hz), 4.44-4.48 (1H, m), 4.65 (1H, ddd, $J = 3.4, 6.6, 11.0$ Hz), 7.10 (1H, d, $J = 7.5$ Hz), 7.19 (1H, t, $J = 7.3$ Hz), 7.24-7.32 (2H, m), 7.58 (2H, t, $J = 7.8$ Hz), 7.71 (1H, t, $J = 7.5$ Hz), 7.89 (2H, d, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 26.4, 31.0, 31.1, 35.9, 67.6, 73.3, 127.0, 127.5, 127.8, 128.7, 128.8, 131.3, 134.7, 135.0, 135.7, 136.5, 167.0; EIHRMS: Found: m/z 343.0999. Calcd for $\text{C}_{19}\text{H}_{19}\text{O}_4\text{S}$: $(\text{M}+\text{H})^+$ 343.1004.

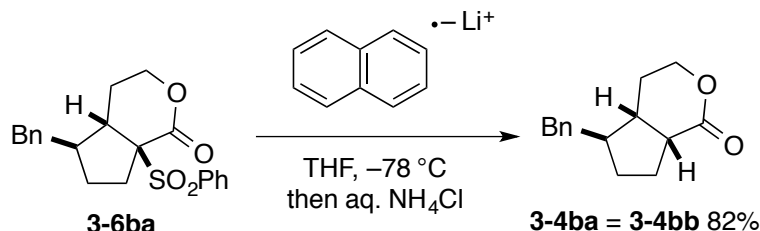
(4a*R**,10a*S**)-10a-(phenylsulfonyl)-3,4,4a,5,10,10a-hexahydro-1*H*-benzo[*g*]isochromen-1-one (**3-6sa**)



81% yield over 2 steps from **3-3sa**; White solid; mp. 197-199 °C; IR (NaCl) 3053 2986 1728 1398 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.35 (1H, dddd, $J = 3.9, 12.4, 12.4, 14.1$ Hz), 1.95-2.00 (1H, m), 2.71 (1H, dd, $J = 2.2, 14.6$ Hz), 3.04-3.09 (2H, m), 3.23 (1H, d, $J = 14.6$ Hz), 3.70-3.76 (1H, m), 4.20 (1H, ddd, $J = 2.8, 3.6, 10.8$ Hz), 4.74 (1H, ddd, $J = 1.6, 10.9, 12.6$ Hz), 7.02 (1H, d, $J = 7.2$ Hz), 7.12-7.21 (3H, m), 7.61 (2H, t, $J = 7.8$ Hz), 7.75 (1H, t, $J = 7.6$ Hz), 7.9 (2H, d, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 29.5, 34.1, 34.8, 67.6, 73.9, 127.5, 127.7, 127.9, 128.5, 129.0, 131.1, 132.8, 134.5, 135.0, 136.8, 166.4; EIHRMS: Found: m/z 343.0997. Calcd for $\text{C}_{19}\text{H}_{19}\text{O}_4\text{S}$: $(\text{M}+\text{H})^+$ 343.1004.

3.6.5. Reductive cleavage of phenylsulfonyl group of sulfonyl lactones 3-6

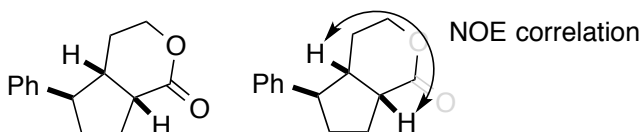
Typical procedure for reductive cleavage of phenylsulfonyl group for synthesis of 3-4ba



To a THF (3 mL) solution of (4a*S**,5*S**,7a*S**)-5-benzyl-7a-(phenylsulfonyl)hexahydrocyclopenta[*c*]pyran-1(3*H*)-one (**3-6ba**) (112 mg, 0.304 mmol) at -78°C was added dropwise a solution of lithium naphthalenide (see its preparation below) until the color of lithium naphthalenide (dark green) is not faded. After being stirred for 5 min, the reaction was quenched with saturated aqueous NH_4Cl solution. The mixture was then extracted three times with ethyl acetate, and the combined organic extracts were washed with brine. After drying with MgSO_4 and removal of the solvents under reduced pressure, the resulting crude residue was purified by flash column chromatography (hexane:ethyl acetate = 9 : 1) to afford (4a*S**,5*S**,7a*R**)-5-benzylhexahydrocyclopenta[*c*]pyran-1(3*H*)-one (**3-4ba**) (57.3 mg, 0.249 mmol, 82% yield).

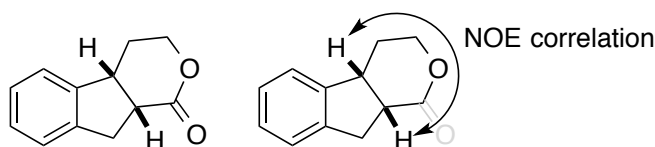
Lithium naphthalenide solution was prepared as a stock solution by mixing naphthalene (1.17 g, 9.11 mmol, 30 equiv) and lithium metal (63.3 mg, 9.11 mmol, 30 equiv) in THF (9 mL) at room temperature under a N_2 atmosphere. During stirring, the color of the mixture turned from clear to dark green. The mixture was stirred at room temperature for 30 min before usage. The remaining lithium naphthalenide was carefully quenched by addition of saturated aqueous NH_4Cl .

(4a*S**,5*R**,7a*R**)-5-phenylhexahydrocyclopenta[*c*]pyran-1(3*H*)-one (**3-4ha**)



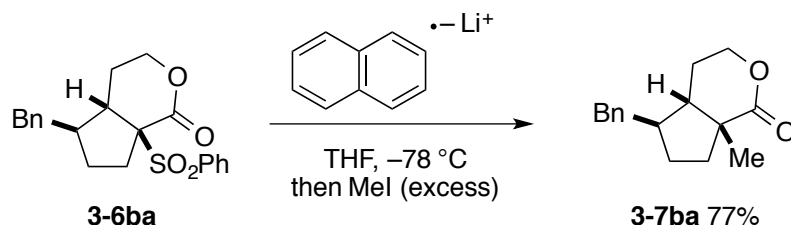
Quant. yield from **3-6ha**; Colorless crystals; mp. 70-72 °C; IR (ATR): 3080 3022 1732 1724 1717 1163 1146 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.60 (1H, dddd, *J* = 10.8, 8.8, 7.2, 5.2 Hz), 1.85-1.74 (1H, m), 2.05 (1H, dddd, *J* = 14.4, 7.3, 4.7, 2.5 Hz), 2.24-2.12 (2H, m), 2.38-2.29 (1H, m), 2.60-2.51 (1H, m), 2.67 (1H, ddd, *J* = 16.8, 10.8, 6.0 Hz), 3.15 (1H, ddd, *J* = 16.8, 10.8, 8.4 Hz), 4.23 (1H, ddd, *J* = 10.8, 10.8, 2.4 Hz), 4.39 (1H, ddd, *J* = 11.2, 8.0, 4.0 Hz), 7.29-7.24 (3H, m), 7.36 (2H, t, *J* = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 28.3, 28.4, 34.5, 42.6, 44.3, 53.7, 67.4, 127.0, 127.3, 128.9, 142.5, 175.5; EIHRMS: Found: *m/z* 217.1225. Calcd for C₁₄H₁₇O₂: (M+H)⁺ 217.1229.

(4a*R**,9a*R**)-4,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-1(3*H*)-one (**3-4ka**)



72% from **3-6ka**; Yellow solid; mp. 76-77 °C; IR (NaCl) 3053 2986 1732 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.85-1.94 (1H, m), 2.33-2.41 (1H, m), 3.38-3.47 (3H, m), 3.73-3.79 (1H, m), 4.26-4.37 (2H, m), 7.17-7.27 (4H, m); ¹³C NMR (100 MHz, CDCl₃) δ 29.0, 36.0, 42.2, 42.5, 67.2, 123.8, 124.9, 127.4, 127.7, 141.4, 144.1, 174.2; EIHRMS: Found: *m/z* 189.0915. Calcd for C₁₂H₁₃O₂: (M+H)⁺ 189.0916.

Typical procedure for reductive cleavage-alkylation sequence for synthesis of **3-7ba**

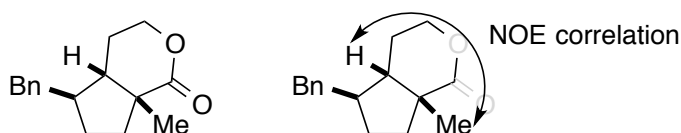


To a THF (3 mL) solution of (4a*S**,5*S**,7a*S**)-5-benzyl-7a-(phenylsulfonyl)hexahydrocyclopenta[*c*]pyran-1(3*H*)-one (**3-6ba**) (112 mg, 0.304 mmol) at -78°C was added dropwise a solution of lithium naphthalenide until the color of lithium naphthalenide (black) is not faded. After being stirred for 5 min,

MeI was added dropwise until the color of lithium naphthalenide (black) is faded to yellow. After being stirred for 5 min, the reaction was quenched with saturated aqueous NH₄Cl solution. The mixture was then extracted three times with ethyl acetate, and the combined organic extracts were washed with brine. After drying with MgSO₄ and removal of the solvents under reduced pressure, the resulting crude residue was purified by flash column chromatography (hexane:ethyl acetate = 9 : 1) to afford (4a*S**,5*S**,7a*R**)-5-benzyl-7a-methylhexahydrocyclopenta[*c*]pyran-1(3*H*)-one (**3-7ba**) (57.2 mg, 0.234 mmol, 77% yield).

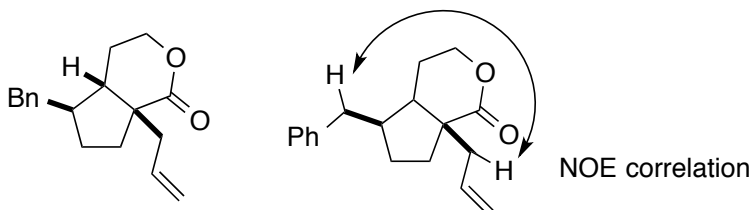
Lithium naphthalenide solution was prepared as a stock solution as described above.

(4a*S**,5*S**,7a*R**)-5-benzyl-7a-methylhexahydrocyclopenta[*c*]pyran-1(3*H*)-one (**3-7ba**)



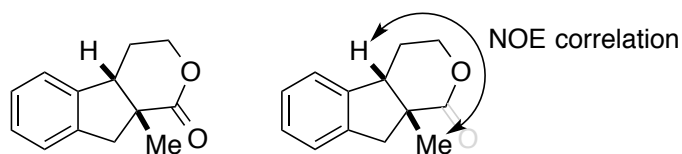
77%, from **3-6ba** and methyl iodide; Colorless crystals; mp. 67-68 °C; IR (ATR): 2965 1724 1265 1211 1179 1163 1130 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.35 (3H, s), 1.43-1.33 (2H, m), 1.68 (1H, ddd, *J* = 8.4, 8.4, 6.4 Hz), 1.94-1.72 (4H, m), 2.00 (1H, ddd, *J* = 12.8, 12.8, 6.4 Hz), 2.75-2.65 (2H, m), 4.18 (1H, ddd, *J* = 11.2, 8.8, 2.4 Hz), 4.28 (1H, ddd, *J* = 11.2, 6.2, 3.2 Hz), 7.15 (2H, d, *J* = 7.2 Hz), 7.20 (1H, t, *J* = 7.2 Hz), 7.28 (2H, t, *J* = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 28.6, 29.2, 30.8, 38.1, 41.6, 48.9, 49.9, 50.0, 61.2, 126.3, 128.6, 128.9, 140.8, 178.3; EIHRMS: Found: *m/z* 245.1545. Calcd for C₁₆H₂₁O₂: (M+H)⁺ 245.1542.

(4a*S**,5*S**,7a*S**)-7a-allyl-5-benzylhexahydrocyclopenta[*c*]pyran-1(3*H*)-one (**3-8ba**)



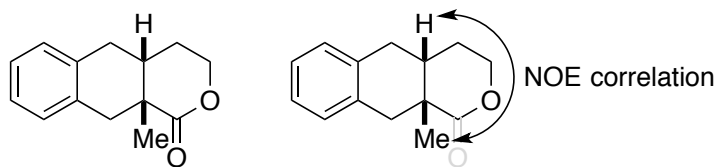
80%, from **3-6ba** and allylic bromide; Yellow oil; IR (ATR): 3024 1717 1697 1684 1437 1385 1252 1219 1150 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.46-1.30 (2H, m), 2.00-1.73 (6H, m), 2.21 (1H, dd, $J = 13.4, 8.3$ Hz), 2.58 (1H, dd, $J = 13.4, 6.5$ Hz), 2.76-2.64 (2H, m), 4.17 (1H, ddd, $J = 11.2, 8.0, 2.8$ Hz), 4.25 (1H, ddd, $J = 11.2, 6.8, 3.6$ Hz), 5.16-5.09 (2H, m), 5.74 (1H, dddd, $J = 16.8, 10.2, 8.3, 6.5$ Hz), 7.15 (2H, d, $J = 7.3$ Hz), 7.20 (1H, t, $J = 7.3$ Hz), 7.29 (2H, t, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 29.1, 30.8, 37.2, 41.4, 45.2, 46.1, 49.4, 52.9, 67.0, 119.4, 126.3, 128.6, 129.0, 133.6, 140.7, 176.9; EIHRMS: Found: m/z 271.1694. Calcd for $\text{C}_{18}\text{H}_{23}\text{O}_2$: $(\text{M}+\text{H})^+$ 271.1698.

(4a*S**,9a*R**)-9a-methyl-4,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-1(3*H*)-one (**3-7ka**)



61%, from **3-6ka** and methyl iodide; Yellow oil; IR (NaCl) 2963 2928 1732 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.48 (3H, s), 1.87-1.95 (1H, m), 2.24-2.32 (1H, m), 3.01 (1H, d, $J = 16.8$ Hz), 3.26 (1H, dd, $J = 6.3, 6.3$ Hz), 3.50 (1H, d, $J = 16.8$ Hz), 4.19-4.25 (1H, m), 4.28-4.34 (1H, m), 7.19-7.25 (4H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 26.5, 29.3, 45.4, 48.4, 50.1, 67.0, 124.1, 125.0, 127.3, 127.7, 140.3, 143.5, 177.0; EIHRMS: Found: m/z 203.1071. Calcd for $\text{C}_{13}\text{H}_{15}\text{O}_2$: $(\text{M}+\text{H})^+$ 203.1072.

(4a*R**,10a*S**)-10a-methyl-3,4,4a,5,10,10a-hexahydro-1*H*-benzo[*g*]isochromen-1-one (**3-7sa**)

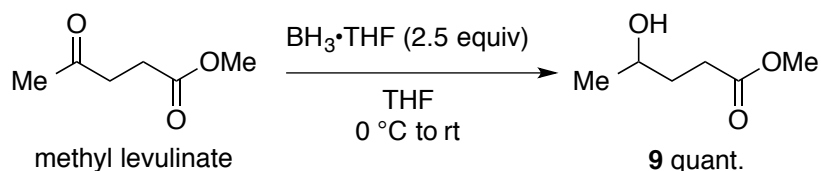


55%, $dr = 5.62:1$ (as an inseparable mixture, the major isomer could be isolated partially) from **3-6sa** and methyl iodide; Yellow oil; IR (NaCl) 3053 2970 1726 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.33 (3H, s), 1.74-1.81 (1H, m), 1.92-1.96 (1H, m), 1.13-2.17 (1H, m), 2.56 (1H, dd, $J = 5.7, 15.7$ Hz), 2.72 (1H, d, $J = 15.7$ Hz), 2.95 (1H, dd, $J = 6.0, 15.7$ Hz), 3.16 (1H, d, $J = 15.5$ Hz), 4.30-4.41 (2H, m), 7.11-7.19 (4H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 26.6, 28.8, 33.7, 38.1, 38.6,

43.2, 67.7, 126.7, 126.8, 127.9, 129.0, 135.0, 135.5, 176.8; EIHRMS: Found: m/z 217.1228. Calcd for $C_{14}H_{17}O_2$: $(M+H)^+$ 217.1229.

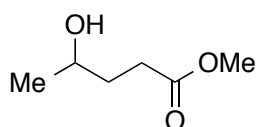
3.6.6. Synthesis of dihydronepetalactone, isodihyronepetalactone and 1-*epi*-isodihyronepetalactone

Reduction of methyl levulinate



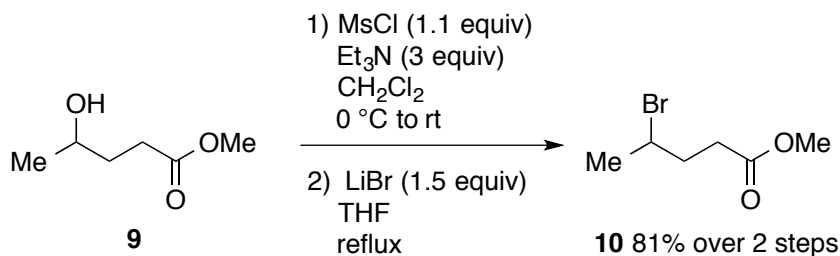
To a solution of methyl levulinate (1.3 mL, 10.5 mmol) in THF (30 mL) at 0 °C was added dropwise $\text{BH}_3\cdot\text{THF}$ (26.2 mL, 26.2 mmol, 1 M in THF, 2.5 equiv). The reaction was allowed to stirred at rt under a nitrogen atmosphere for 2 h. Upon completion, the mixture was cooled to 0 °C and water (40 mL) was added dropwise. The mixture was extracted three times with Et_2O . The combined organic extracts were washed with water and brine. After drying with MgSO_4 and removal of the solvents under reduced pressure, the resulting crude material was purified by flash column chromatography ($\text{Et}_2\text{O} : \text{CH}_2\text{Cl}_2 = 2 : 8$) to yield methyl 4-hydroxypentanoate (**9**) (1.39 g, 10.5 mmol, quant. yield)

methyl 4-hydroxypentanoate (**9**)⁷⁸



^1H NMR (400 MHz, CDCl_3) δ 1.21 (3H, d, $J = 6.2$ Hz), 1.70-1.84 (2H, m), 1.94 (1H, br), 2.46 (2H, t, $J = 7.4$ Hz), 3.68 (3H, s), 3.84 (1H, br); ^{13}C NMR (100 MHz, CDCl_3) δ 23.7, 30.7, 34.0, 51.9, 67.5, 174.8.

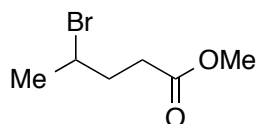
Bromination of methyl 4-hydroxypentanoate (**9**)



To a solution of alcohol **9** (1.39 g, 10.5 mmol) in CH₂Cl₂ (30 mL) at 0 °C was added NEt₃ (4.4 mL, 31.6 mmol, 3.0 equiv) and MsCl (0.90 mL, 11.6 mmol, 1.1 equiv). The reaction was allowed to stir at 0 °C under a nitrogen atmosphere for 3 h. Upon completion, the reaction was quenched by addition of water (40 mL). The mixture was extracted three times with Et₂O. The combined organic extracts were washed with water and brine. After drying with MgSO₄ and removal of the solvents under reduced pressure, the resulting crude material was used for next step without purification.

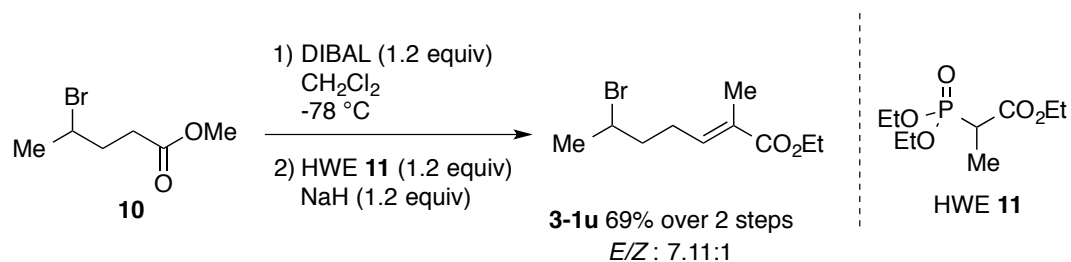
To a solution of the above crude materials in THF (30 mL) was added LiBr (1.37 g, 15.8 mmol, 1.5 equiv). The reaction was allowed to stir at reflux under nitrogen atmosphere for 13 h. Upon completion, the mixture was allowed to cooled to rt. The reaction was quenched by addition of water (40 mL). The mixture was extracted three times with Et₂O. The combined organic extracts were washed with water and brine. After drying with MgSO₄ and removal of the solvents under reduced pressure, the resulting crude material was purified by flash column chromatography (hexane : ethyl acetate = 8 : 2) to yield methyl 4-bromopentanoate (**10**) (1.65 g, 8.51 mmol, 81% yield over 2 steps)

methyl 4-bromopentanoate (**10**)⁷⁹



¹H NMR (400 MHz, CDCl₃) δ 1.74 (3H, d, *J* = 6.6 Hz), 2.00-2.19 (2H, m), 2.47-2.62 (2H, m), 3.69 (3H, s), 4.13-4.21 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ 26.6, 32.4, 36.0, 50.5, 51.8, 173.3.

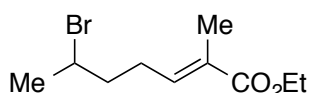
Reduction and olefination of methyl 4-bromopentanoate (**10**)



To a 2-neck round bottom flask containing bromide **10** (1.65 g, 8.51 mmol) in CH_2Cl_2 (20 mL) was added dropwise DIBAL (1.8 mL, 10.1 mmol 1.2 equiv), and the solution was stirred at -78°C for 2 h. Upon completion of the reaction, aqueous HCl (1N, 10 mL) was added dropwise, and the mixture was extracted three times with Et_2O . The combined organic extracts were washed with brine. After drying with MgSO_4 and removal of the solvents under reduced pressure, the resulting crude material was used without further purification.

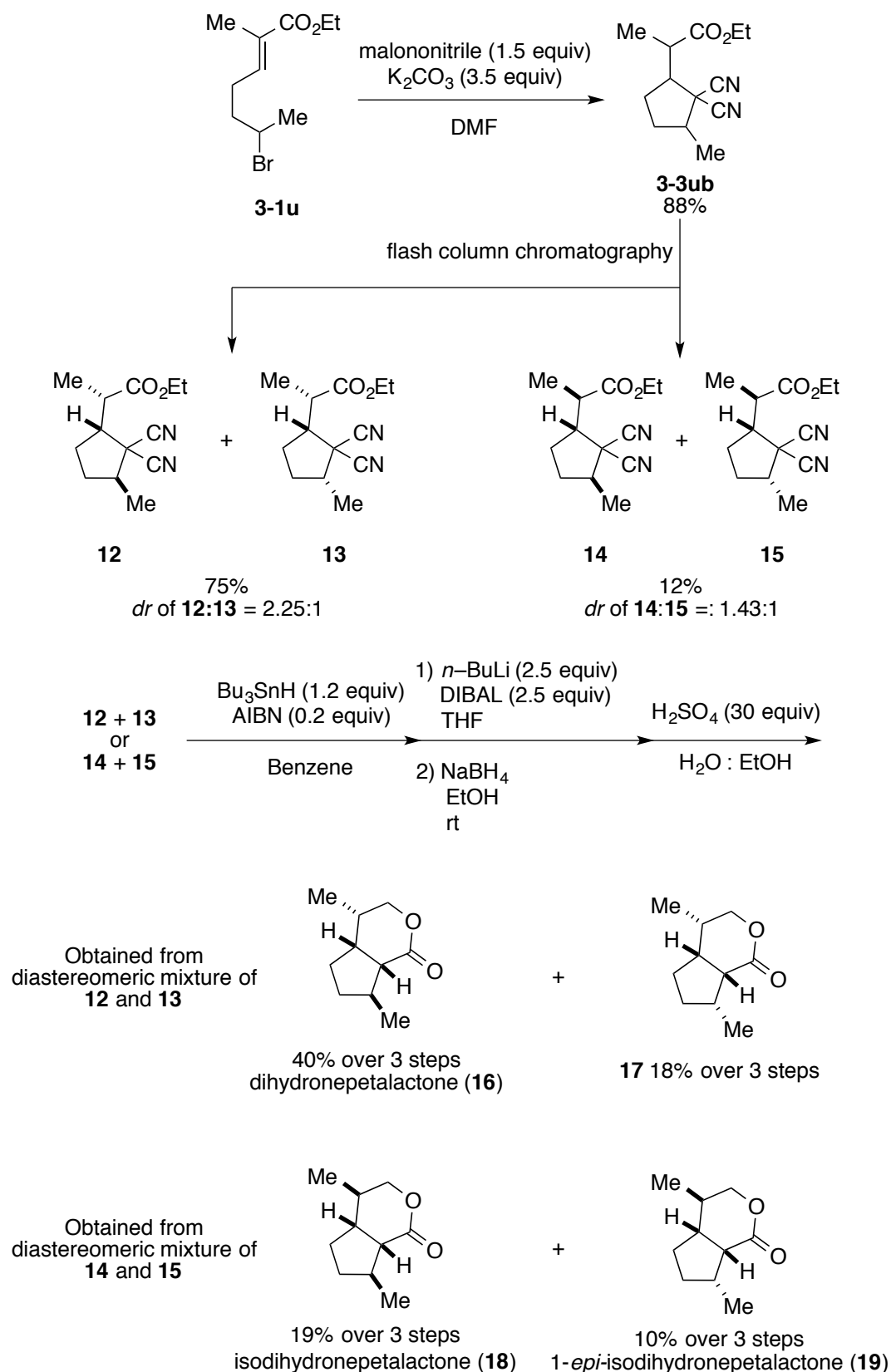
To a solution of triethyl 2-phosphonopropionate (2.2 mL, 10.3 mmol, 1.2 equiv) in THF (20 mL) at rt was added NaH (408 mg, 10.2 mmol, 1.2 equiv). The solution was stirred at rt for 15 min before cooling to -50°C . The mixture was added the above crude aldehyde and stirred at -50°C for 1 h. H_2O (10 mL) was added and the mixture was extracted three times with Et_2O . The combined organic extracts were washed with brine. After drying with MgSO_4 and removal of the solvents under reduced pressure, the resulting crude material was purified by flash column chromatography (hexane : ethyl acetate = 9 : 1) to yield ethyl (*E*)-6-bromo-2-methylhept-2-enoate (**3-1u**) (1.54 g, 5.85 mmol, 69% yield over 2 steps, *E* : *Z* = 7.11:1).

ethyl (*E*)-6-bromo-2-methylhept-2-enoate (**3-1u**)



Data for *E*-isomer; Colorless oil; IR (NaCl) 2982 2926 1709 1445 1368 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.30 (3H, t, J = 7.1 Hz) 1.73 (3H, d, J = 6.7 Hz), 1.87 (3H, s), 1.89-2.01 (2H, m), 2.32-2.41 (2H, m), 4.09-4.13 (1H, m), 4.19 (2H, q, J =

7.1 Hz), 6.71 (1H, t, $J=7.5$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 12.7, 14.5, 26.7, 27.2, 39.9, 50.9, 60.7, 129.3, 140.2, 168.2; EIHRMS: Found: m/z 249.0490. Calcd for $\text{C}_{10}\text{H}_{18}\text{O}_2\text{Br}$: (M+H) $^+$ 249.0490.



A mixture of malononitrile (**3-2u**) (842 mg, 1.27 mmol, 1.5 equiv) and K_2CO_3 (4.11 g, 29.7 mmol, 3.5 equiv) in DMF (10 mL) was stirred at room temperature

under a nitrogen atmosphere for 0.5 h, and a solution of (*E*)-ethyl 6-bromo-2-methylhept-2-enoate (**3-1u**) (2.11 g, 8.47 mmol) in DMF (5 mL) was added to the mixture. After being stirred for 72 h, the reaction was quenched by adding water (20 mL), and the mixture was extracted three times with Et₂O. The combined organic extracts were washed with water and brine. After drying with MgSO₄ and removal of the solvents under reduced pressure, the resulting crude material was purified by flash column chromatography (hexane : ethyl acetate = 8 : 2) to yield 2 pair of inseparable diastereomers of ethyl 2-(2,2-dicyano-3-methylcyclopentyl)propanoate (**3-3ub**) (1.75 g, 7.45 mmol, 88% yield)

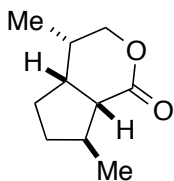
To a solution of the major pair of diastereomer of ethyl 2-(2,2-dicyano-3-methylcyclopentyl)propanoate (**3-3ub**) (1.33 g, 5.68 mmol, *dr*: 1:2.25) in benzene (19 mL, degassed), AIBN (188 mg, 1.14 mmol, 0.2 equiv) and *n*-Bu₃SnH (2.7 mL, 10.2 mmol, 1.8 equiv) were added. The mixture was stirred at 80 °C for 24 h. Upon completion, the mixture was allowed to cool and the solvents were evaporated. The crude materials were allowed to pass through a short plug of silica gel with hexanes to remove excess *n*-Bu₃SnH, after which it was flushed with Et₂O to collect the product, which was used without further purification.

To a dried Schlenk tube containing THF (2 mL), *n*-BuLi (4.9 mL, 1.6 M, 7.84 mmol, 2.5 equiv) and DIBAL (1.4 mL, 7.86 mmol, 2.5 equiv) was added at 0 °C, and the mixture was stirred for 5 min. The mixture was transferred to another THF solution (5 mL) of the above obtained crude materials at -78 °C via cannular. The resulting mixture was stirred at -78 °C for 3 h, and then, NaBH₄ (299 mg, 8.00 mmol, 2.6 equiv) and EtOH (10 mL) were added. After the mixture was then stirred for 2 h, aqueous HCl solution (1N, 10 mL) was carefully added. The organic materials were extracted three times with ethyl acetate. The combined organic extracts were washed with saturated aqueous NaHCO₃ and brine. After drying with MgSO₄ and removal of the solvents in vacuo, the resulting crude residue was used without purification.

To a solution of the above obtained crude materials in EtOH (3.8 mL) and H₂O (7.6 mL), conc. H₂SO₄ (4.9 mL, 91.9 mmol, 30 equiv) was added, and the mixture was then stirred at reflux for 24 h. The reaction mixture was allowed to cool to room temperature and neutralized by adding aqueous NaOH solution (1N). The mixture was then extracted three times with ethyl acetate. The combined organic

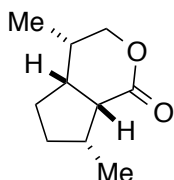
extracts were washed with brine. After drying with MgSO_4 , the solvents were removed under reduced pressure to afford the crude mixture, which was purified by flash column chromatography (hexane:ethyl acetate = 8 : 2) to yield the corresponding dihydronepetalactone (**16**) (382 mg, 2.27 mmol, 40 % yield over 3 steps), along with ethyl (*S**)-2-((1*R**,3*R**)-2,2-dicyano-3-methylcyclopentyl)propanoate (**17**) (172 mg, 1.02 mmol, 18 % yield over 3 steps).

(4*S**,4*aR**,7*S**,7*aR**)-4,7-dimethylhexahydrocyclopenta[*c*]pyran-1(3*H*)-one, dihydronepetalactone (**16**)^{46,52}



40% yield over 3 steps; ^1H NMR (400 MHz, CDCl_3) δ 0.90 (3H, d, $J = 7.0$ Hz), 1.14-1.24 (1H, m), 1.2 (3H, d, $J = 6.4$ Hz), 1.38-1.48 (1H, m), 1.72-1.78 (1H, m), 1.89-2.04 (2H, m), 2.21-2.28 (1H, m), 2.41-2.46 (1H, m), 2.48-2.55 (1H, m), 4.01-4.12 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 13.3, 19.5, 26.6, 31.2, 35.3, 40.7, 41.7, 50.7, 70.1, 174.6.

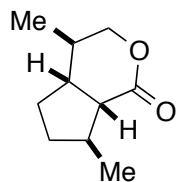
(4*S**,4*aR**,7*R**,7*aR**)-4,7-dimethylhexahydrocyclopenta[*c*]pyran-1(3*H*)-one (**17**)



18% yield over 3 steps; ^1H NMR (400 MHz, CDCl_3) δ 0.93 (3H, d, $J = 7.0$ Hz), 0.99 (3H, d, $J = 7.3$ Hz), 1.45-1.50 (1H, m), 1.57-1.77 (3H, m), 2.23-2.27 (1H, m), 2.42-2.46 (1H, m), 2.56-2.59 (1H, m), 3.13 (1H, dd, $J = 9.1, 9.1$ Hz), 3.40-4.06 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 13.9, 17.2, 24.6, 30.6, 34.1, 38.0, 41.1, 48.1, 70.4, 173.2.

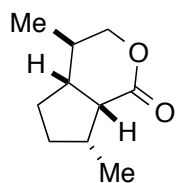
Treatment of minor pair of diastereomers ($dr = 1:1.43$) following the above procedures delivered isodihyronepetalactone (**18**) (24.0 mg, 0.142 mmol, 19 % yield over 3 steps) along with 1-*epi*-isodihyronepetalactone (**19**) (12.6 mg, 0.0750 mmol, 10 % over 3 steps)

(4*R*,4*aR*,7*S*,7*aR*)-4,7-dimethylhexahydrocyclopenta[*c*]pyran-1(3*H*)-one, isodihydronepetalactone (**18**)^{46,52}



19% yield over 3 steps; ¹H NMR (400 MHz, CDCl₃) δ 1.00 (3H, d, *J* = 6.7 Hz), 1.15-1.31 (2H, m), 1.21 (3H, d *J* = 6.4 Hz), 1.58-1.65 (1H, m), 1.85-1.90 (1H, m), 2.00-2.214 (2H, m), 2.26-2.38 (2H, m), 3.88 (1H, dd, *J* = 10.9, 10.9 Hz), 4.16 (1H, dd, *J* = 3.4, 10.9 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 16.0, 20.5, 32.1, 34.6, 35.4, 39.0, 44.9, 39.3, 73.1, 175.2.

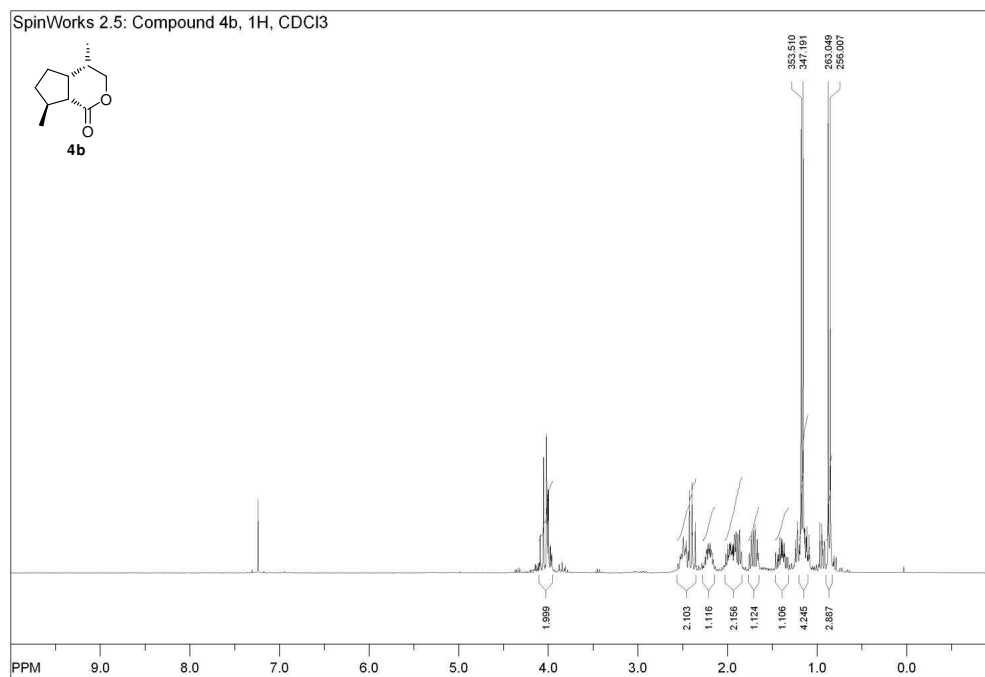
(4*S*,4*aS*,7*S*,7*aS*)-4,7-dimethylhexahydrocyclopenta[*c*]pyran-1(3*H*)-one, 1-epi-isodihydronepetalactone (**19**)^{46,55}



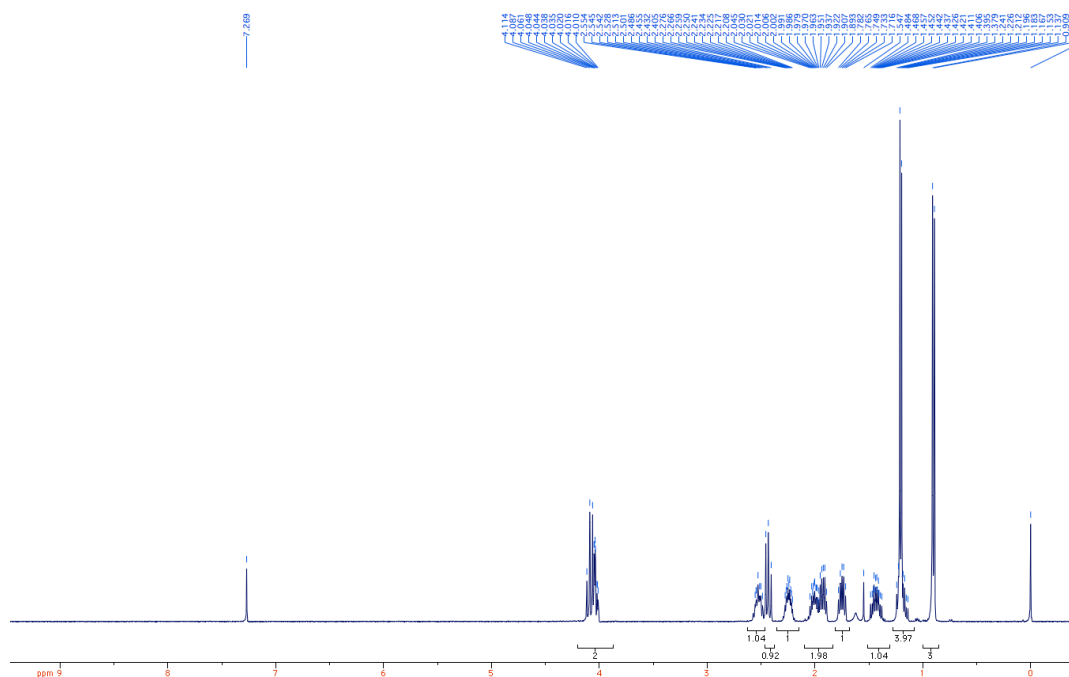
10% yield over 3 steps; ¹H NMR (400 MHz, CDCl₃) δ 0.96 (3H, d, *J* = 6.6 Hz), 0.97 (3H, d, *J* = 7.2 Hz), 1.49-1.72 (4H, m), 1.93-2.03 (2H, m), 2.60-2.66 (1H, m), 3.00 (1H, dd, *J* = 7.9, 10.1 Hz), 3.86 (1H, dd, *J* = 10.7, 10.7 Hz), 4.2 (1H, dd, *J* = 3.7, 10.7 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 15.6, 17.3, 29.9, 32.8, 35.5, 37.5, 42.9, 47.2, 74.0, 173.5.

^1H NMR spectra of dihydronepetalactone (**16**) (ref. 52)

Compound **4b** – ^1H

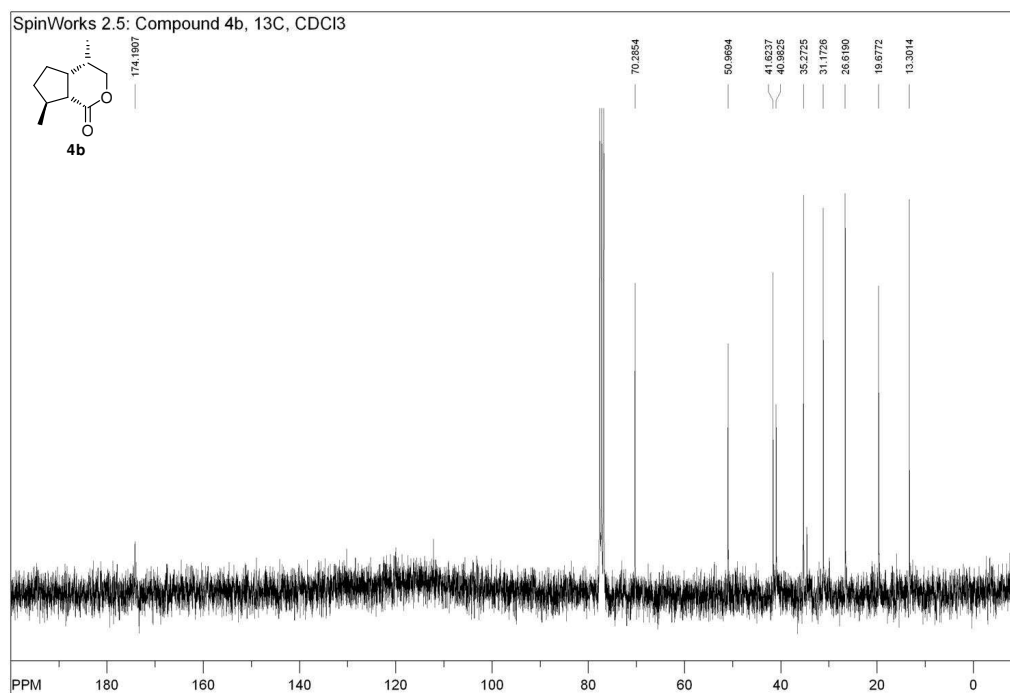


^1H NMR spectra of synthesized dihydronepetalactone (**16**)

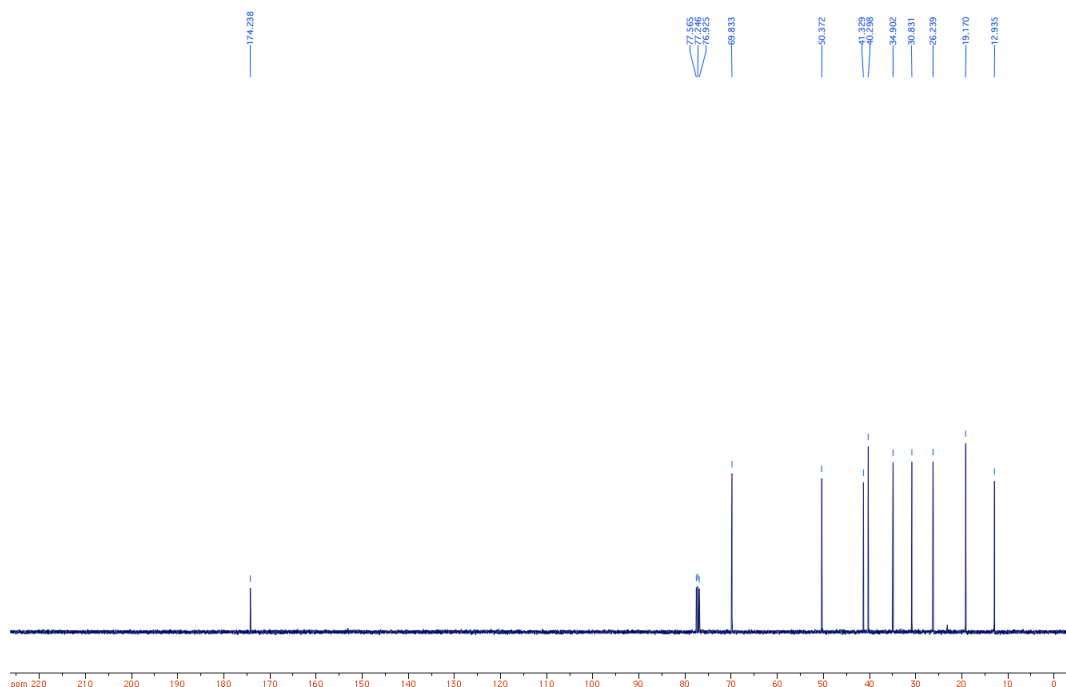


^{13}C NMR spectra of dihydronepetalactone (**16**) (ref. 52)

Compound **4b** – ^{13}C

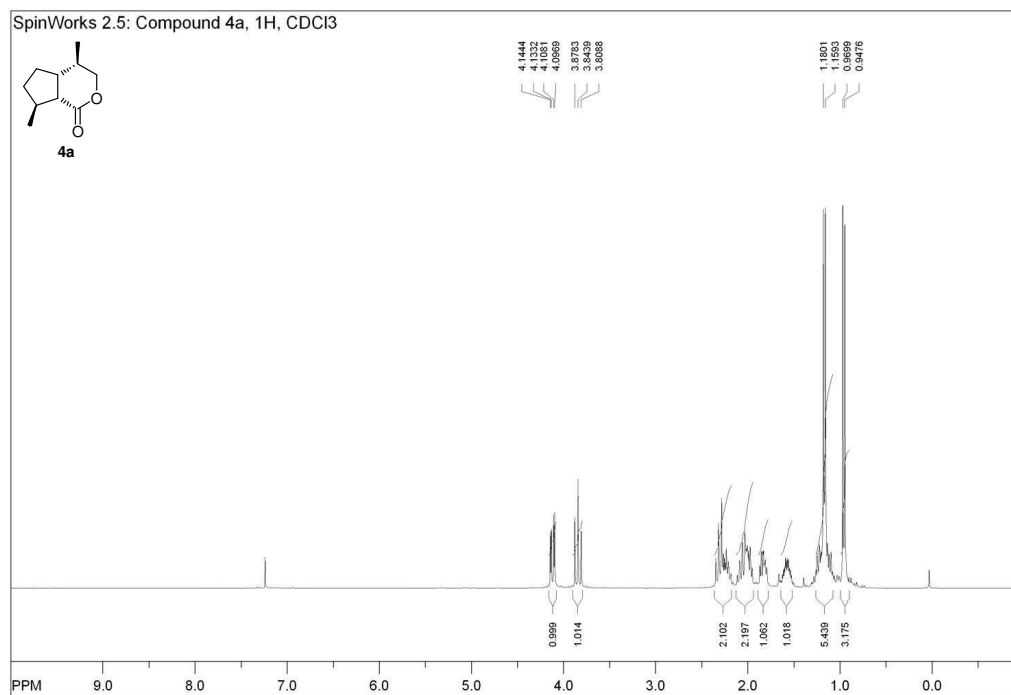


^{13}C NMR spectra of synthesized dihydronepetalactone (**16**)

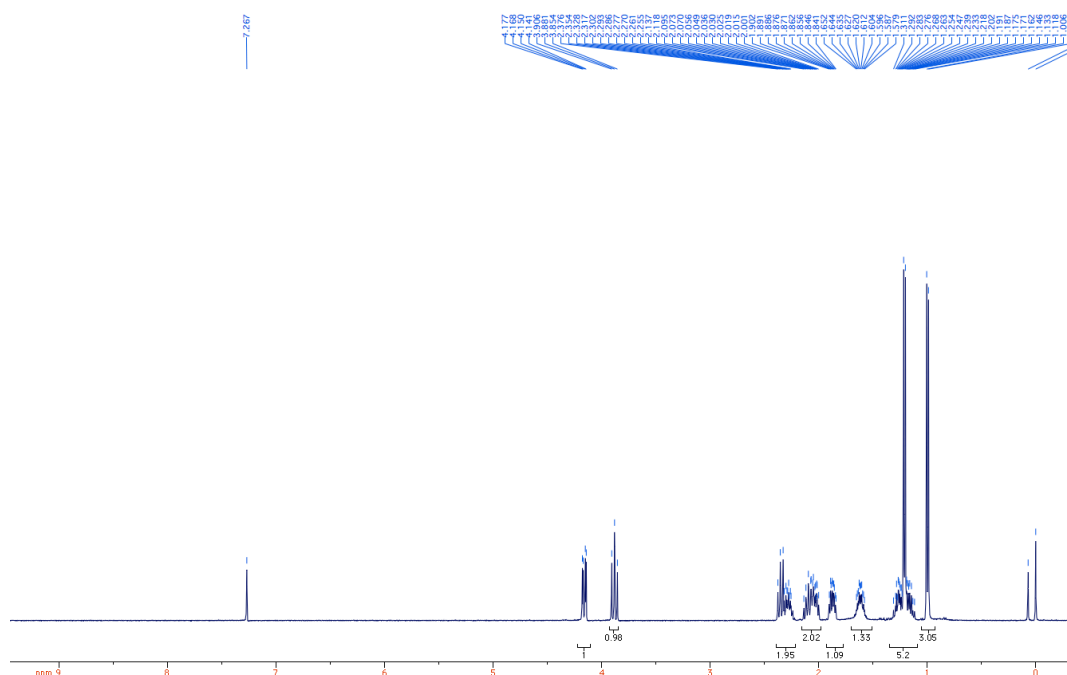


^1H NMR spectra of isodihydronepetalactone (**18**) (ref. 52)

Compound **4a** – ^1H

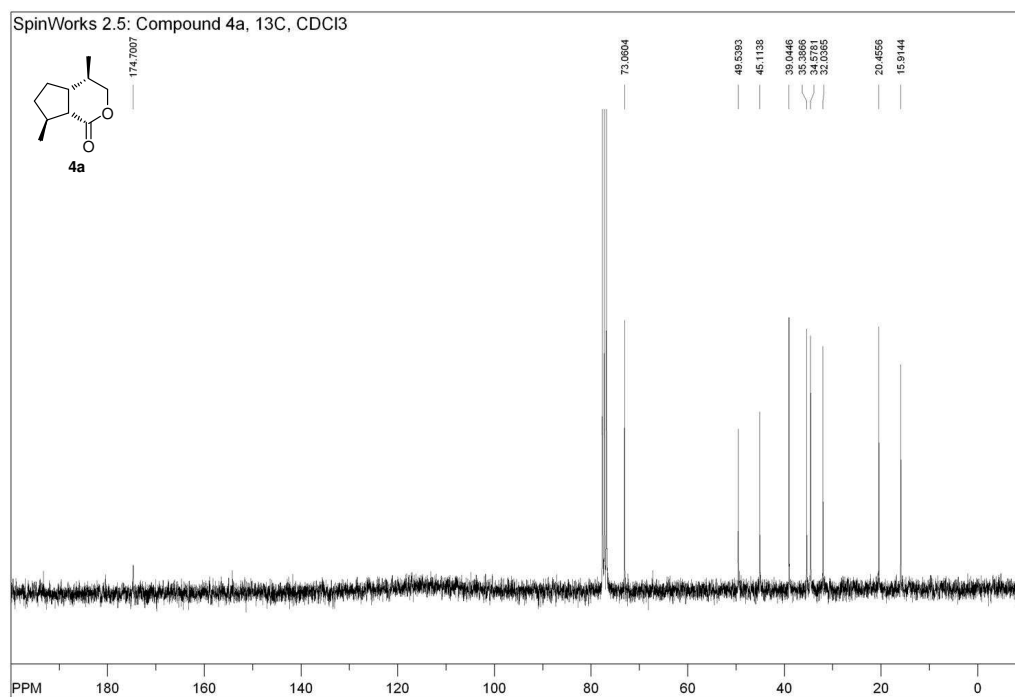


^1H NMR spectra of synthesized isodihydronepetalactone (**18**)

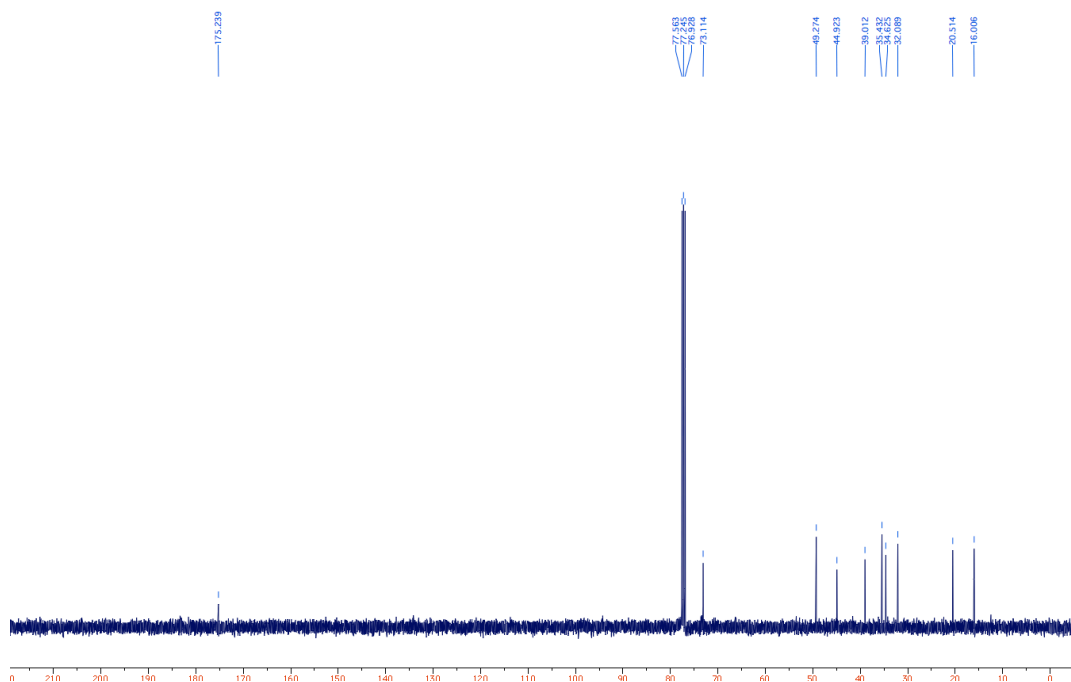


^{13}C NMR spectra of isodihydronepetalactone (**18**) (ref. 52)

Compound **4a**– ^{13}C

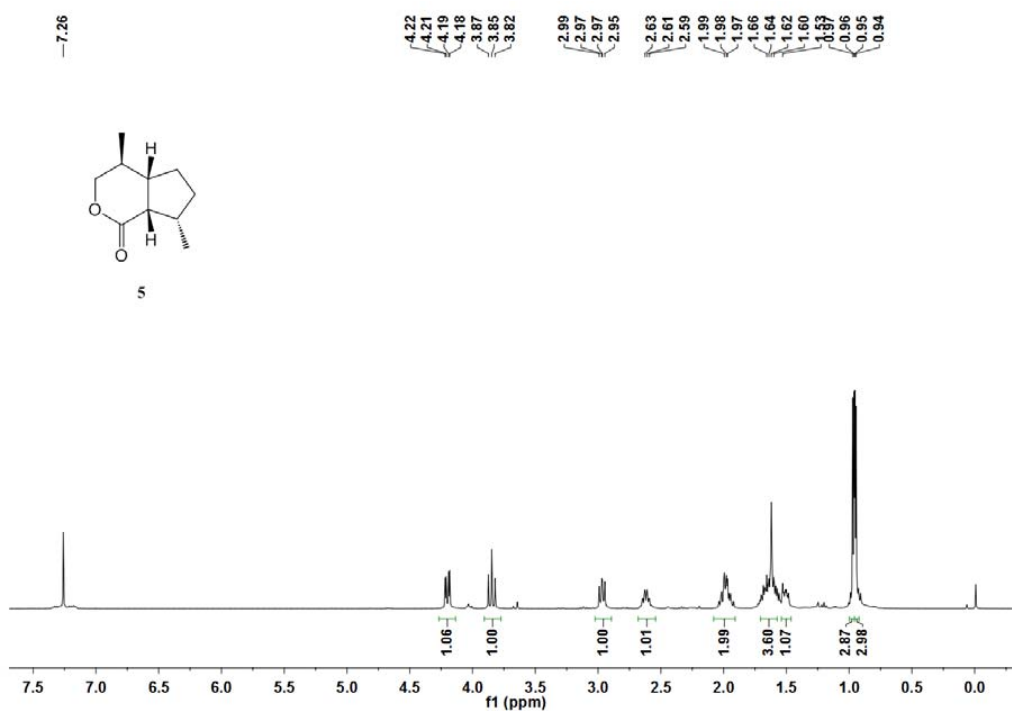


^{13}C NMR spectra of synthesized isodihydronepetalactone (**18**)

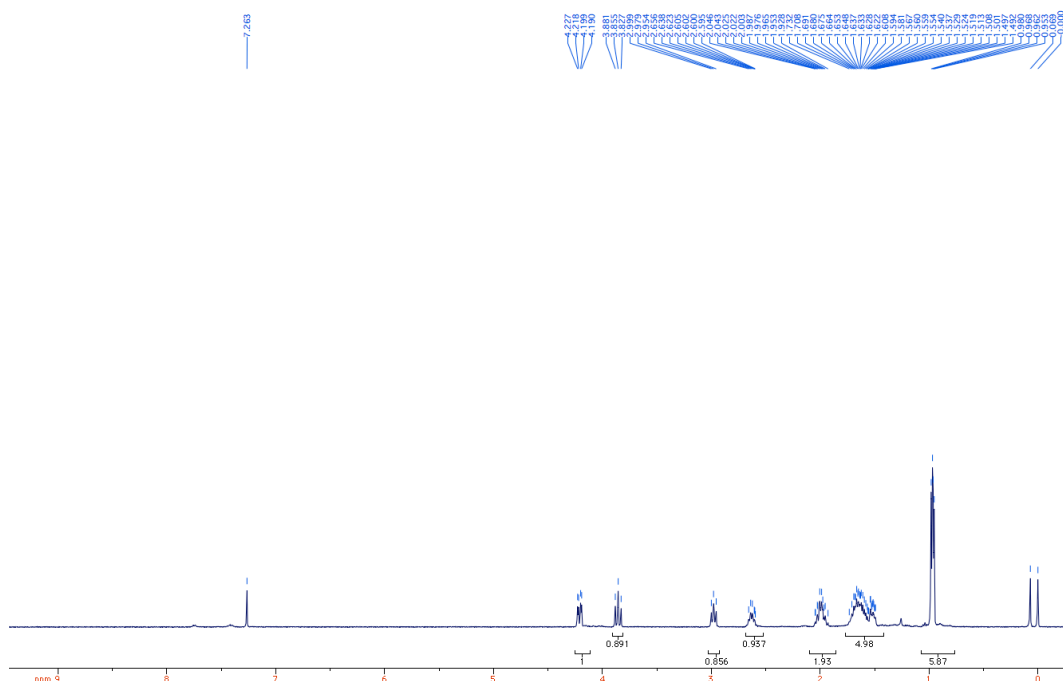


^1H NMR spectra of 1-*epi*-isodihydronepetalactone (**19**) (ref. 55)

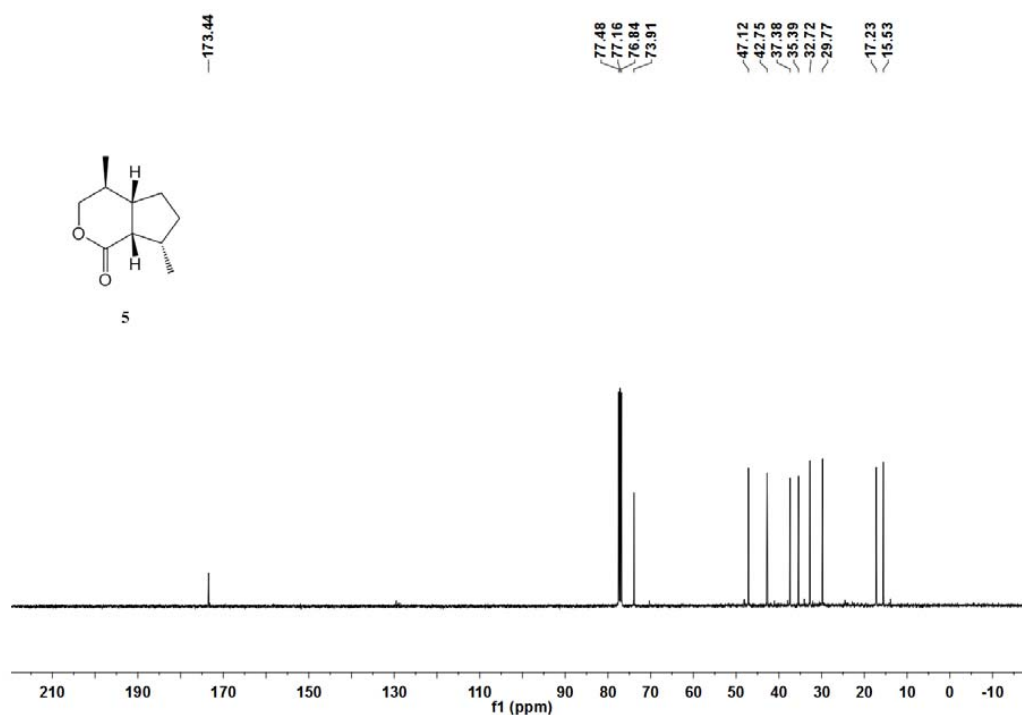
^1H and ^{13}C NMR spectra of **5**



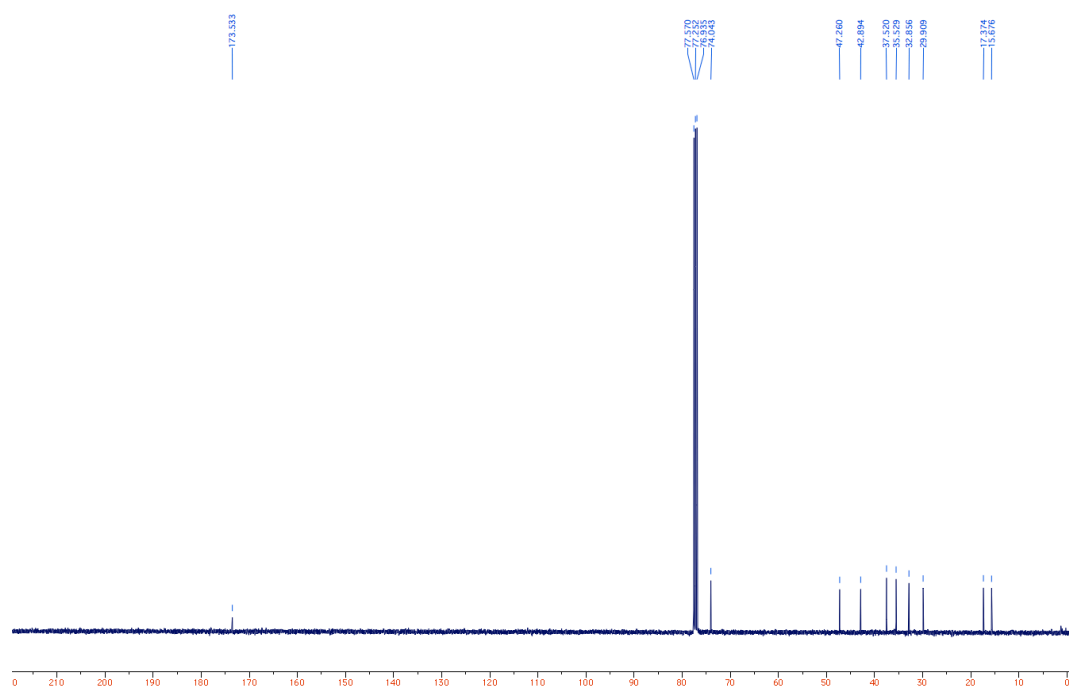
^1H NMR spectra of synthesized 1-*epi*-isodihydronepetalactone (**19**)



^{13}C NMR spectra of 1-*epi*-isodihydronepetalactone (**19**) (ref. 55)



^{13}C NMR spectra of synthesized 1-*epi*-isodihydronepetalactone (**19**)



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Chapter 4. Inorganic base-mediated hydroamination of alkenyl oximes for synthesis of cyclic nitrones

4.1. Introduction

Nitrogen-containing heterocycles (azaheterocycles) are omnipresent in biologically active alkaloids and potent pharmaceutical drugs^{1,2,3} as well as in various types of material-based applications such as organic light-emitting diodes (OLEDs).^{4, 5} Our recent statistics from Drugs.com (<http://www.drugs.com/stats/top100/2012/sales>) showed that among the top 100 prescribed medicines by U. S. national sales in 2012, about half of them are based on the azaheterocyclic cores (Figure 4-1).

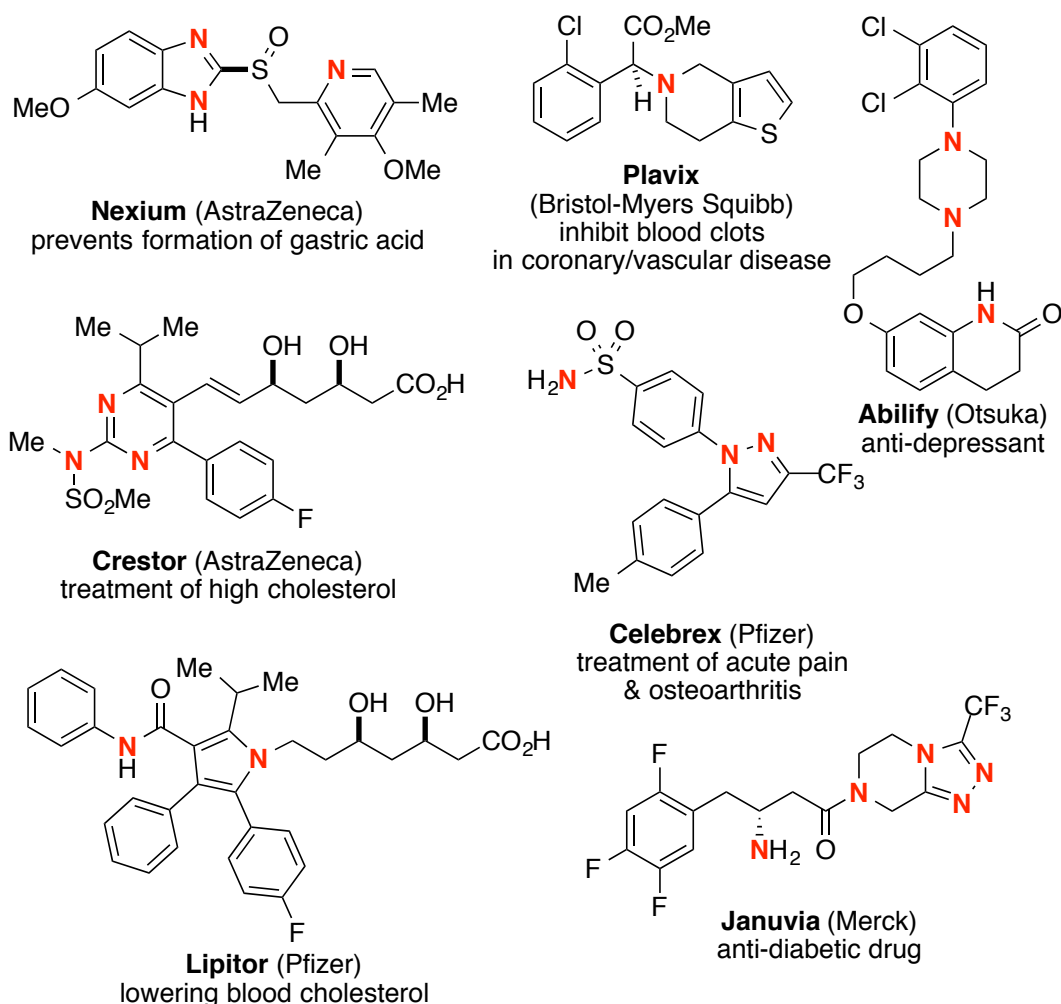
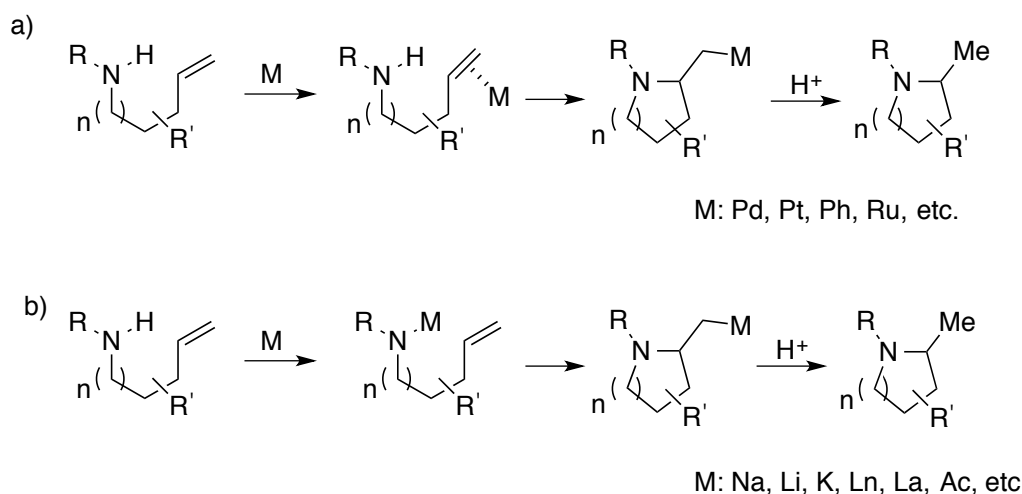


Figure 4-1. Azaheterocyclic drugs in top 100 prescribed medicines

4.1.1. Hydroamination of unactivated alkenes

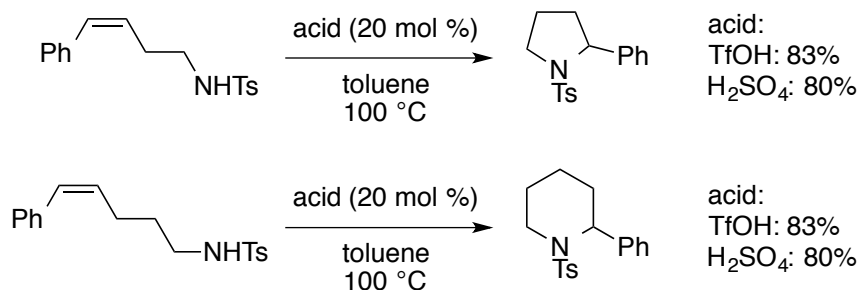
It is therefore of significant importance for synthetic chemists to develop reliable methodologies to target azaheterocycles in a step- and atom-economical manner. The addition of amines across unactivated carbon-carbon multiple bonds (alkenes or alkynes), known as hydroamination, offers a promising and straightforward route to construct a new carbon-nitrogen bond in an atom economical manner.^{6,7} Intense research efforts have realized the catalytic hydroamination of unactivated alkene *via* the use of various transition-metals, alkali metals and *f*-block elements. Typically late transition-metals catalyze hydroamination *via* the activation of the carbon-carbon multiple bonds through the coordination of the metal center to the carbon-carbon unsaturated bond (Scheme 4-1-a). This decreases the electron density of the carbon-carbon multiple bond, allowing the facile addition of nitrogen nucleophiles to the carbon-carbon unsaturated bond.^{8,9} On the contrary, alkali and *f*-block metals achieve hydroamination *via* amido-metal species, which undergo addition onto the electron-rich carbon-carbon multiple bond (Scheme 4-1-b).^{8,10}



Scheme 4-1. Metal-catalyzed hydroamination

Separately, it was found that a catalytic amount of Brønsted acids could also mediate the hydroamination of unactivated alkenes. In these processes, protonation of the alkene results in the formation of a carbocation intermediate that is trapped by the nucleophilic attack of the amine. In general, the basicity of the amines controls the reaction rate with more basic amine leading to longer reaction time.

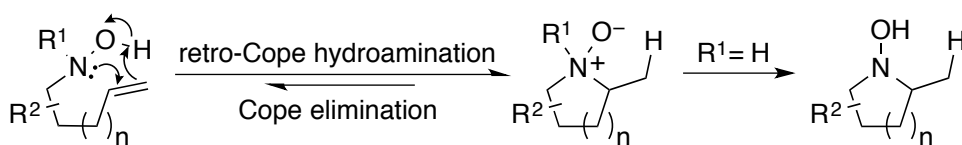
Hartwig disclosed that both triflic and sulfuric acid were capable of promoting the cyclization of alkenylamine leading to the synthesis of pyrrolidines and piperidines (Scheme 4-2).¹¹



Scheme 4-2. Brønsted acid mediated hydroamination

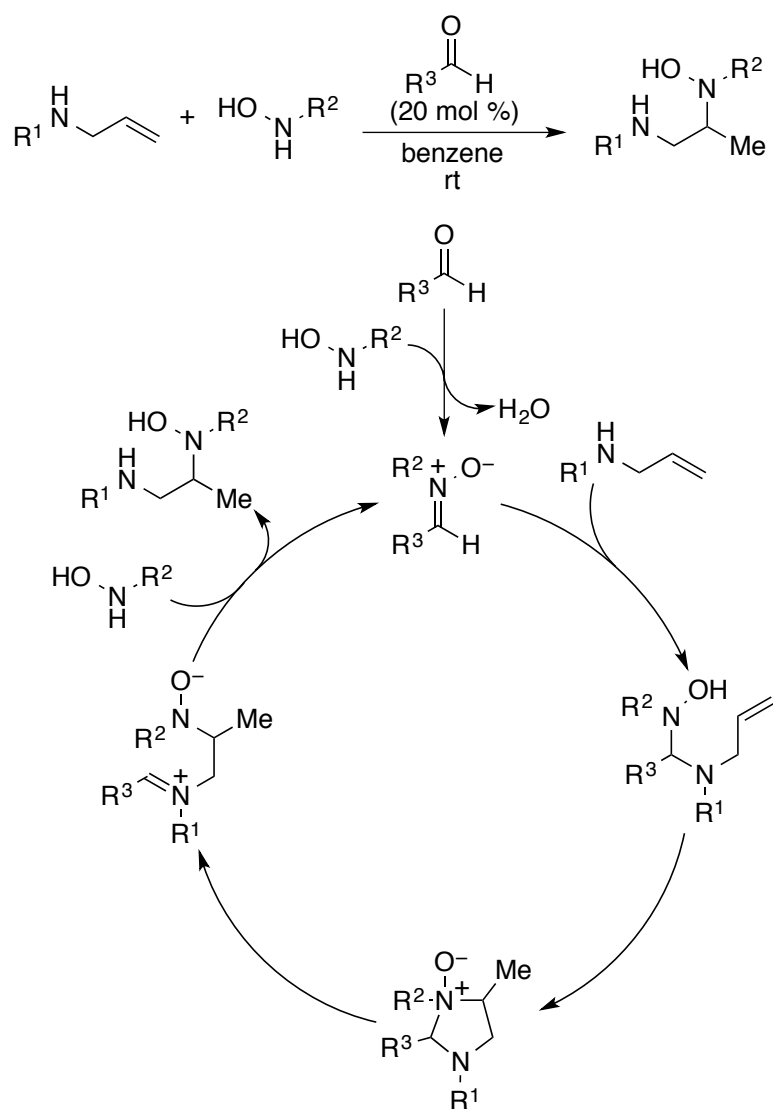
4.1.2. Retro-Cope hydroamination of hydroxylamines

There is another type of hydroamination using alkenyl hydroxylamines, that is mechanistically distinct hydroamination known as the retro-Cope hydroamination (Scheme 4-3). This process is described as a $[2\pi + 2\sigma + 2n]$ -concerted process *via* a 5-membered transition state. The reverse process is known as the Cope elimination.^{12,13}



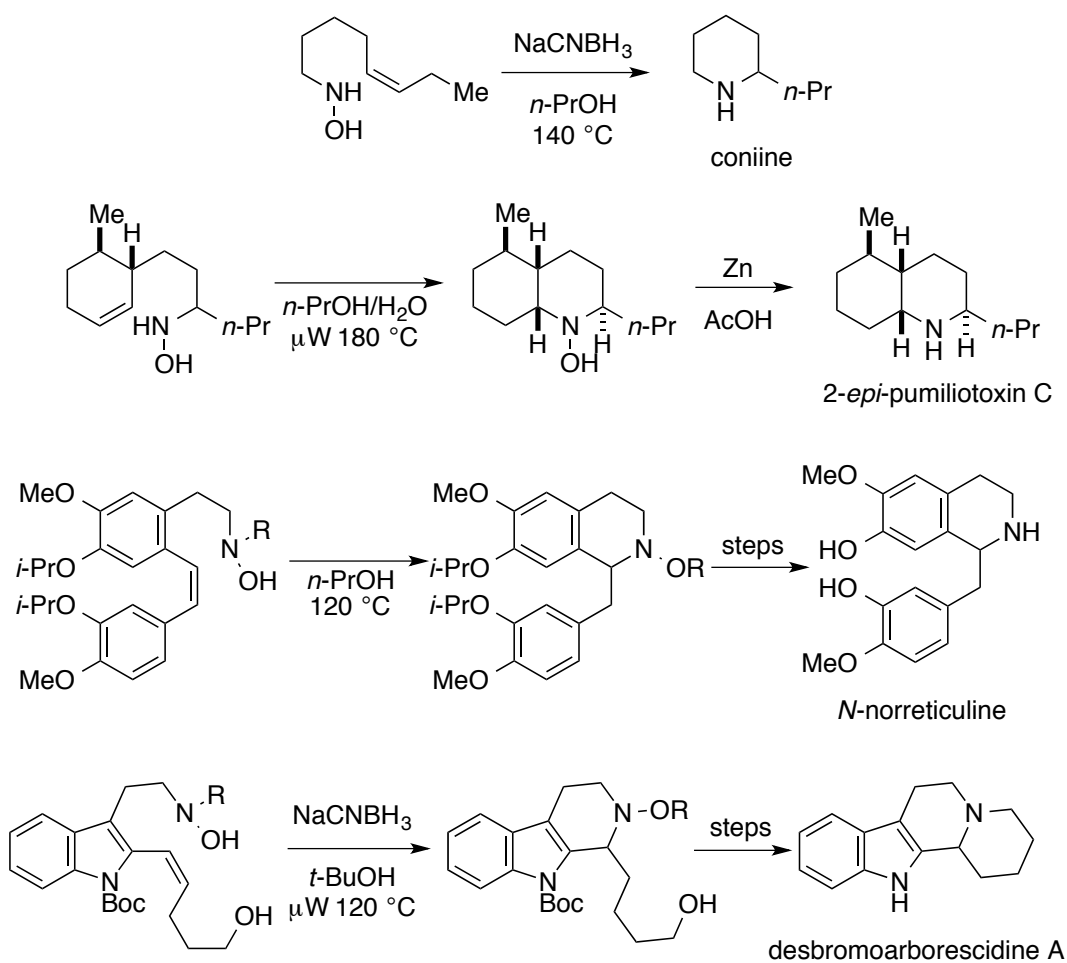
Scheme 4-3. Mechanism of retro-Cope hydroamination

The retro-Cope hydroamination has recently been applied for synthesis of various nitrogen-containing molecules by the research group of Beauchemin. The group developed a tethering strategy using simple aldehydes as catalyst for intermolecular alkene hydroamination of allyl amines with hydroxylamines (Scheme 4-4). Condensation of the aldehyde catalyst and hydroxylamines results in the formation of nitron intermediates that is further attacked by allyl amines to deliver acyclic amins. The amination intermediates undergo facile retro-Cope hydroamination, that is followed by subsequent ring-opening and iminium exchange with another hydroxylamine molecule to provide 1,2-diamine derivatives with regeneration of the nitron intermediates.^{14,15}



Scheme 4-4. Catalytic tethering strategy using aldehydes

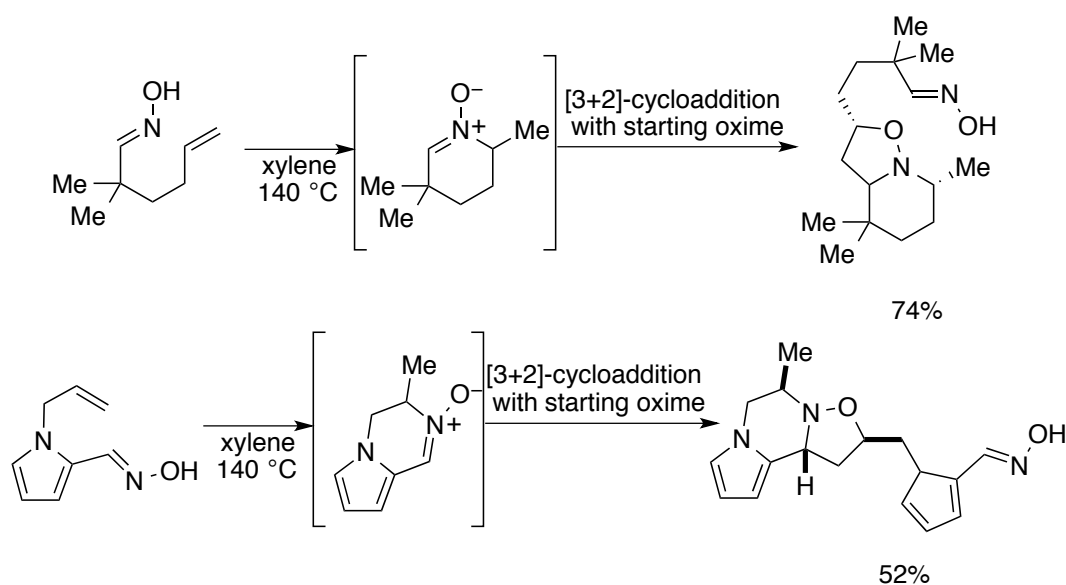
The Beauchemin's group also demonstrated the potential of the retro-Cope hydroamination strategy in the synthesis of a series of alkaloids including coniine, 2-*epi*-pumiliotoxin C, *N*-norreticuline and desbromoarborescidine A (Scheme 4-5).¹⁶



Scheme 4-5. Synthesis of alkaloids based on retro-Cope hydroamination strategy

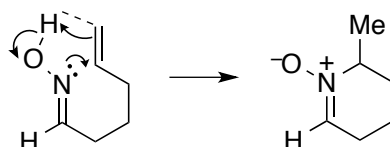
4.1.3. Retro-Cope hydroamination of alkenyl oximes

The retro-Cope hydroamination of alkenyl oximes is theoretically possible under heating conditions, providing cyclic nitrones as products. However, owing to the reactivity of these cyclic nitrones as a 1,3-dipole, further [3+2]-cycloaddition with the alkene of another molecule of alkenyl oximes is observed (Scheme 4-6).^{17,18}



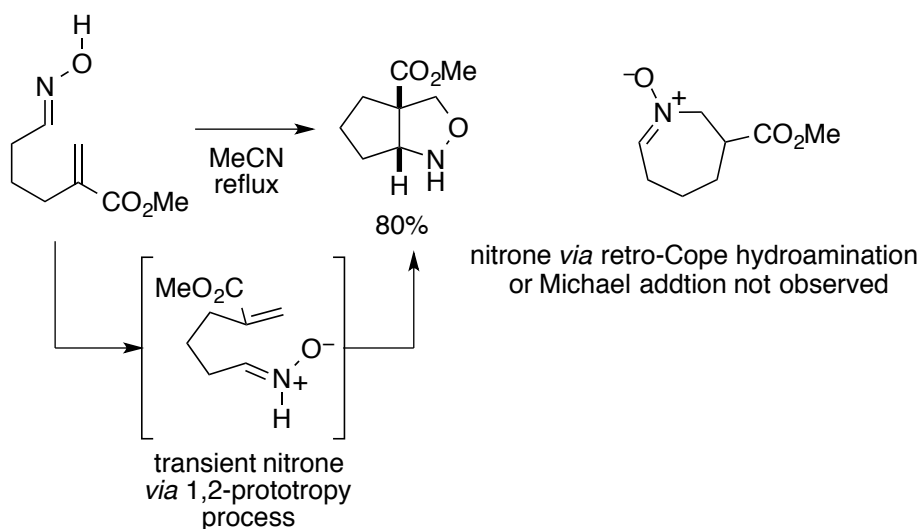
Scheme 4-6. Retro-Cope hydroamination-[3+2]-cycloaddition sequence

Moreover, due to the concerted nature of the reaction mechanism that requires the 5-membered transition state in which the lone pair of the oxime nitrogen and the alkene moiety have to interact smoothly, the retro-Cope hydroamination of alkenyl oximes are mostly limited to the construction of 6-membered cyclic nitrones from δ -alkenyl aldoximes (Scheme 4-7).



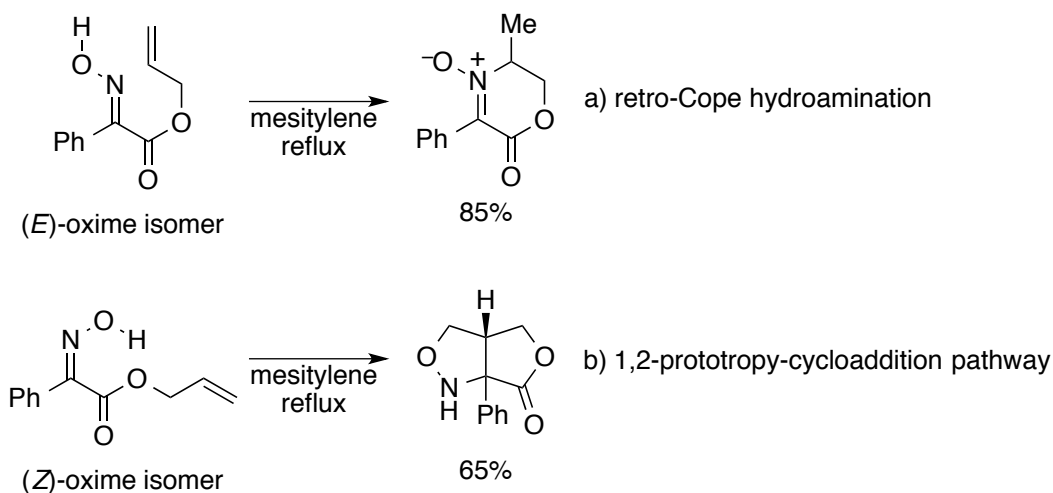
Scheme 4-7. Transition state of retro-Cope hydroamination

A competitive side-reaction along with the retro-Cope hydroamination of alkenyl oximes is formation of isoxazolidines *via* [3+2]-cycloaddition of the alkene and the nitron formed *via* 1,2-prototropy process of the oximes (Scheme 4-8).¹⁷



Scheme 4-8. 1,2-prototropy-1,3-dipolar cycloaddition sequence

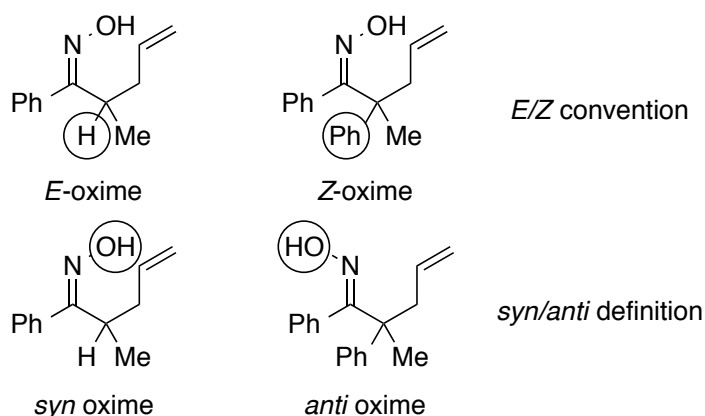
The geometry of stereochemistry of the N-O bond of oximes is crucial in determining which mechanism is operating. It was found that allyl (*E*)-2-(hydroxyimino)-2-phenylacetate react exclusively *via* retro-Cope hydroamination to provide the 6-membered cyclic nitrones (Scheme 4-9-a), while the respective allyl (*Z*)-2-(hydroxyimino)-2-phenylacetate react *via* the 1,2-prototropy-[3+2]-cycloaddition pathway to furnish fused isoxazolidines (Scheme 4-9-b).¹⁹



Scheme 4-9. Effect of the oxime's stereochemistry on reaction pathway

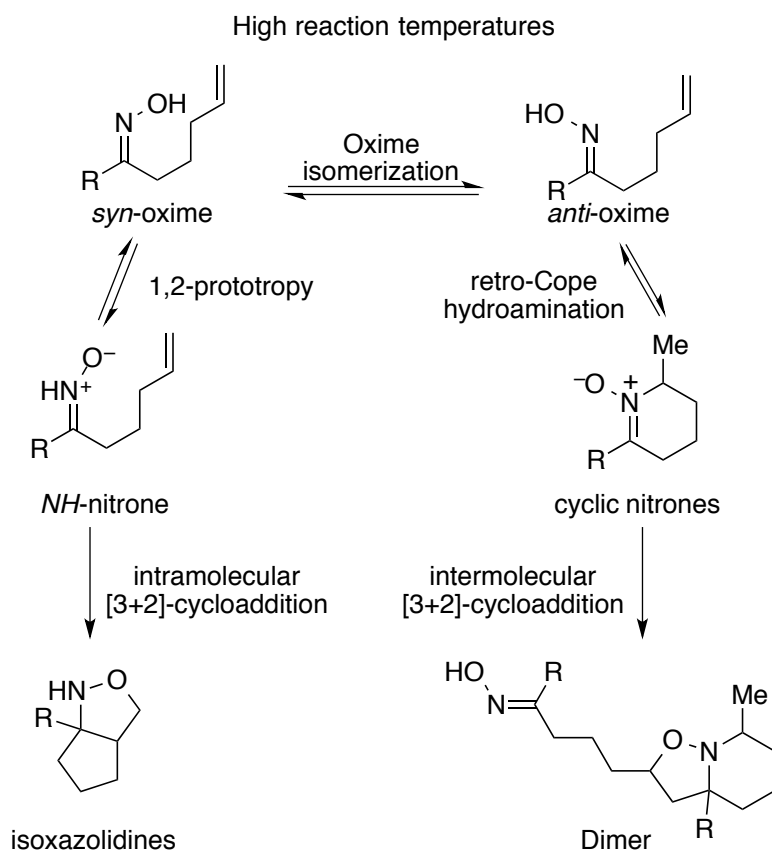
It is imperative up to this point for the author to define the terminology regarding the stereochemistry of the oximes to avoid confusion. Although the *E/Z* notation could be applied for indicating the stereochemistry of the oxime, it is substituent-

dependent based on the Cahn-Ingold-Prelog rules.^{20,21} On the other hand, the author is interested in the position of the lone pair of the oxime nitrogen to the alkene moiety. Therefore for the following sections, the author will designate “*anti*” to describe the oximes having its N–O bond opposite to the alkene moiety, likewise the term “*syn*” will be used to describe oximes having its N–O bond on the same side of the alkene moiety (Scheme 4-10).



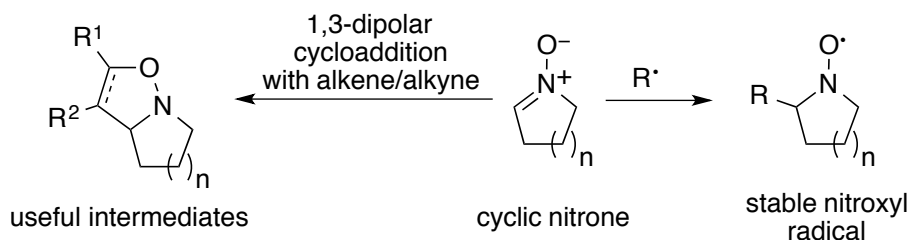
Scheme 4-10. Definition of terminology to describe stereochemistry of oximes

It is obvious that the retro-Cope hydroamination of alkenyl oximes is much more complicated with limited scope than the analogous retro-Cope hydroamination of alkenyl hydroxylamines (Scheme 4-11). The cyclization of the former reaction is in delicate balance with other competing reactions such as the 1,2-prototropy process leading to intramolecular [3+2]-cycloaddition and further intermolecular [3+2]-cycloaddition of the resultant cyclic nitrones with another molecule of starting material.^{22,23}

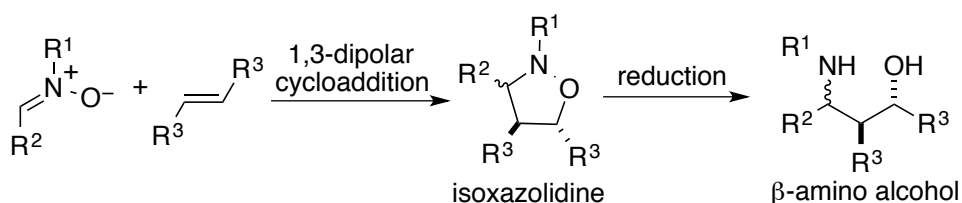


4.1.4. Cyclic nitrones and their synthetic uses

Cyclic nitrones are highly versatile molecules. They possess medicinal properties²⁴ and are employed as radical spin traps in electron spin resonance experiments in which they form stable nitroxyl radicals.^{25,26} Cyclic nitrones also serve as building blocks for the synthesis of natural and biologically active compounds²⁷ and are probably most best known as 1,3-dipole for [3+2]-cycloaddition reactions with alkenes or alkynes (Scheme 4-12).^{28,29,30,31}



The [3+2]-annulation of nitrones to alkenes (the 1,3-dipolar cycloaddition reaction) results in the formation of isoxazolidines.^{32,33} The synthetic potential of this reaction originates from its concerted nature, in which up to 3 contiguous stereogenic centers could be created. As shown in Scheme 4-13, the geometry of alkene determines 2 of the stereogenic centers in the resultant isoxazolidine.²⁸ This reaction has found wide applications due to the synthetic utility of the isoxazolidine owing to the labile nature of the N–O bond. Reductive cleavage of the N–O bond can be easily achieved with common methods such as hydrogenation with palladium or Raney nickel or reduction by zinc metal in the presence of acids to afford valuable β -amino alcohols.^{28, 29}

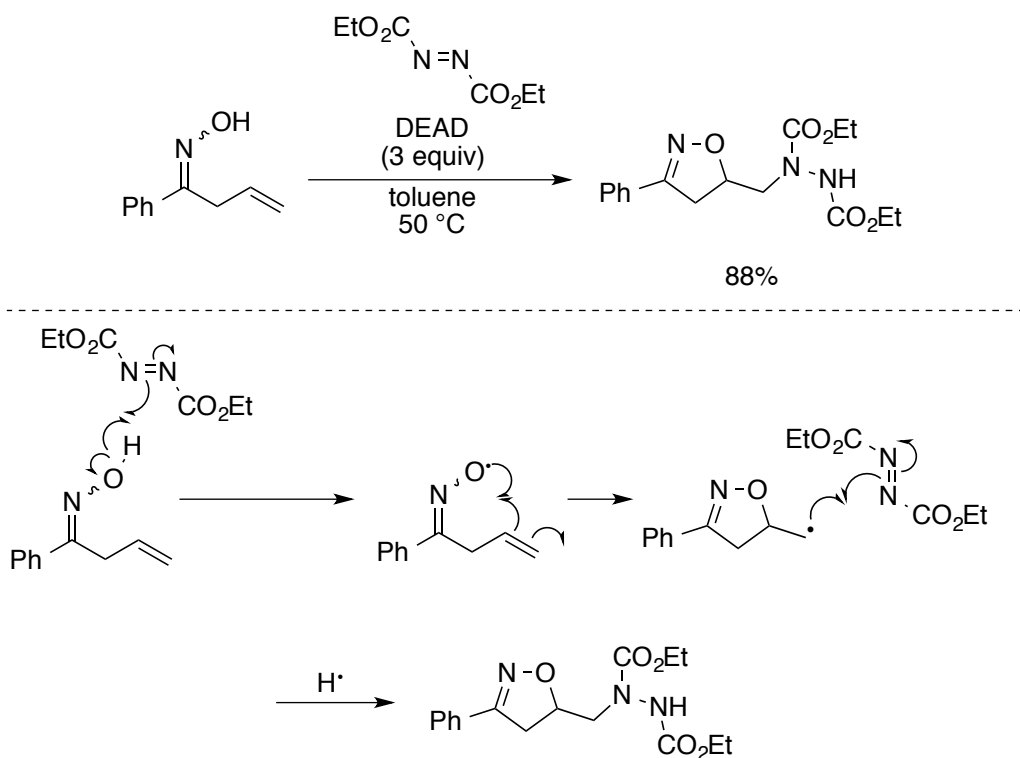


Scheme 4-13. Synthetic potential of 1,3-dipolar cycloaddition of nitrone with alkene

Having defined the potential problems of retro-Cope hydroamination of alkenyl ketoximes for synthesis of cyclic nitrones as well as the importance of cyclic nitrones, the author aimed to develop a methodology that utilizes γ -alkenyl ketoximes for synthesis of 5-membered cyclic nitrones.

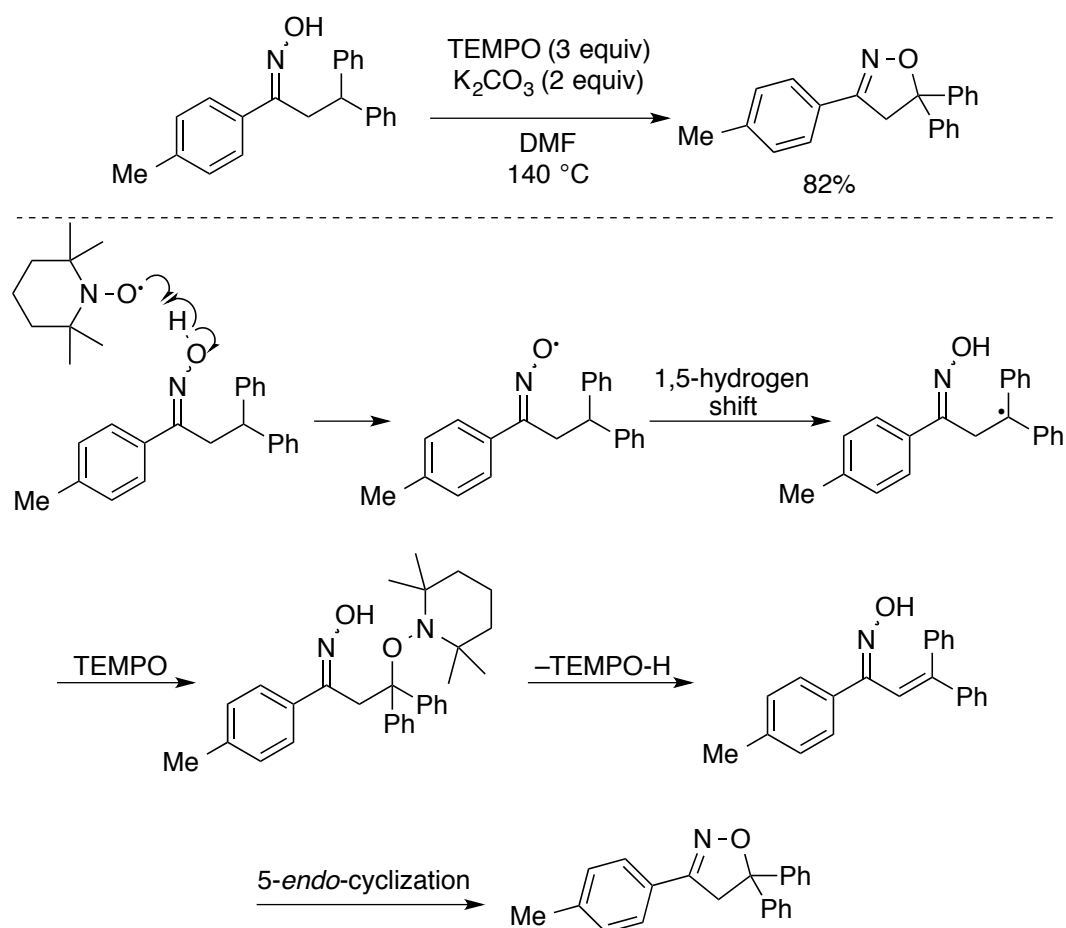
4.2. Working hypothesis based on radical chemistry of oximes

It is known that iminoxyl radical (oxime radical) can be generated by H-radical abstraction of oximes.³⁴ Trapping of the iminoxyl radical with an intramolecular alkene tether has been demonstrated by the Han's group (Scheme 4.14). Employing diethyl azodicarboxylate (DEAD) as a radical initiator, the authors achieved the cyclization of the iminoxyl radical to the alkene and subsequent termination by trapping of the resulting carbon radical with DEAD to afford isoxazoline derivatives.³⁵



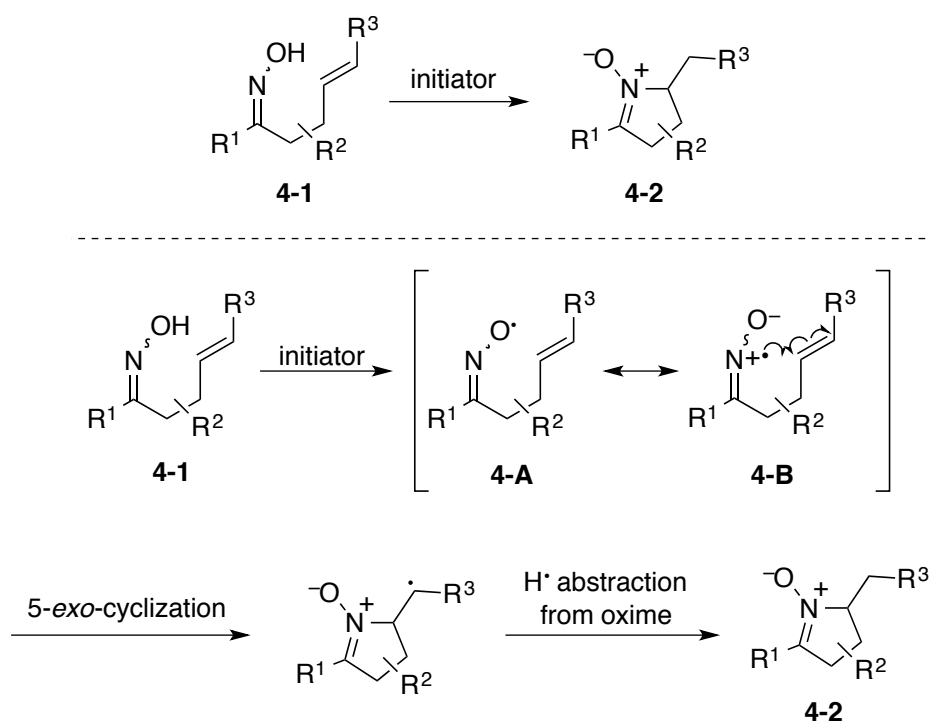
Scheme 4-14. Radical cyclization of alkenyl oxime

Independently, the author's group recently disclosed β -sp³ C–H-oxidation of oximes with 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) (Scheme 4-15). In this reaction, TEMPO removed H-radical from the starting oxime, affording the iminoxyl radical, which underwent further 1,5-H shift to give the carbon radical. The resulting carbon radical was trapped with TEMPO and subsequent elimination of TEMPO-H to give α,β -unsaturated oxime. Finally, 5-*endo*-cyclization delivered the isoxazoline derivative.³⁶



Scheme 4-15. β - sp^3 C-H-oxidation of oximes with TEMPO

On the other hand, it is known that the iminoxyl radical **4-A** is present with another resonance structure, that is the iminyl radical **4-B** with the zwitterionic structure (Scheme 4-16). The author planned to use this radical **4-B** generated from γ -alkenyl ketoximes **4-1** for construction of 5-membered ring cyclic nitrones **4-2**. The hypothesis relied on the cyclization of the nitrogen-radical **4-B** onto the alkene tether followed by termination with H-radical abstraction of the resulting C-radical from another molecule of oximes **4-1**, giving 5-membered-ring cyclic nitrones **4-2** along with regeneration of the oxime radical (**4-A** and **4-B**).



Scheme 4-16. Proposed radical cyclization of iminyl radical for synthesis of cyclic nitrones

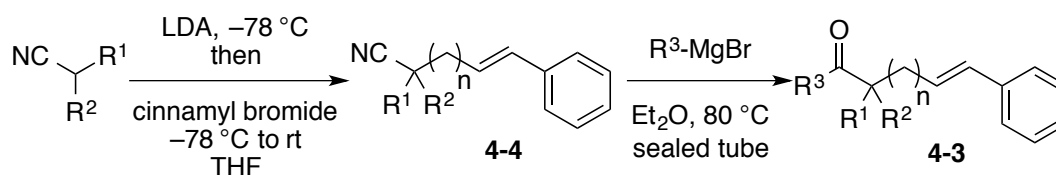
4.2.1. Synthesis of alkenyl ketoximes 4-1

First of all, the corresponding alkenyl ketones **4-3** were prepared by the following three methods (A-C):

Method A: The reactions of Grignard reagents with the corresponding alkenyl carbonitriles **4-4** (which were prepared by alkylation of their parent carbonitrile derivatives)

Ketones **4-3a-d**, **4-3f-g**, **4-3r** and **4-3v** were prepared from their corresponding carbonitriles **4-4** *via* Method A, and the results were summarized in Table 4-1.

Table 4-1. Method A



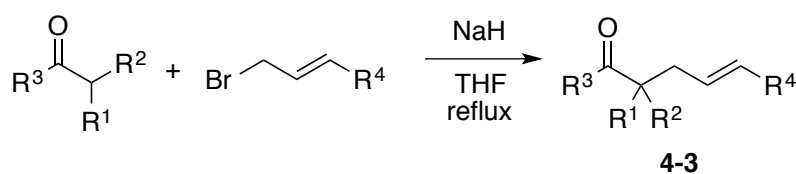
substrate	R ¹	R ²	R ³	n	Yields 4-4	Yields 4-3
a	Me	Me	Ph	1		94%
b	Me	Me	4-OMe-C ₆ H ₄	1		quant.
c	Me	Me	4-CF ₃ -C ₆ H ₄	1		91%
d	Me	Me	2-naphthyl	1	quant.	52%
f	Me	Me	2-thiophene	1		88%
g	Me	Me	Me	1		77%
r	cyclopropyl		Ph	1	78%	57%
v^a	Me	Me	Ph	2	90%	87%

^a (E)-(4-bromobut-1-en-1-yl)benzene was employed instead of cinnamyl bromide

Method B: Alkylation of the corresponding ketones

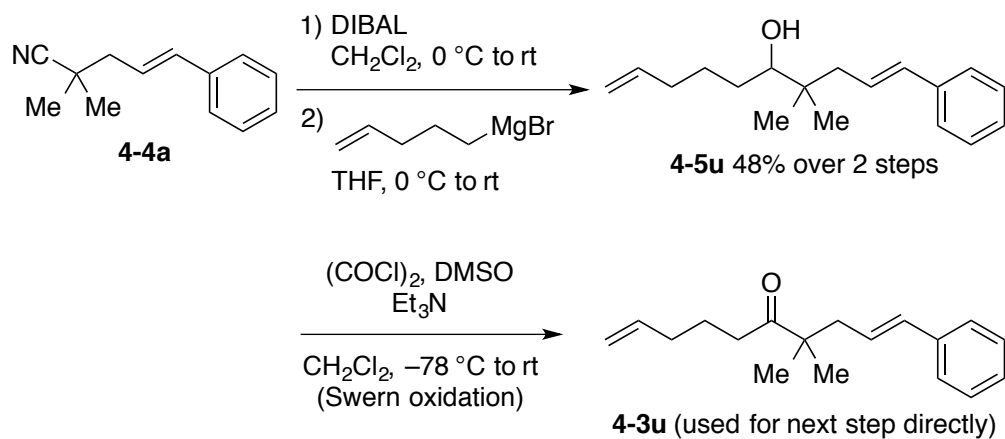
Following Method B (alkylation of ketones), ketones **4-3e**, **4-3h**, **4-3k-o** and **4-3q** were synthesized (Table 4-2).

Table 4-2. Method B



substrate	R ¹	R ²	R ³	R ⁴	yields 4-3
e	Me	Me	2-Me-C ₆ H ₄ Ph	Ph	78%
h	Me	Me	isopropyl	Ph	71%
k	Me	Me	Ph	4-OMe-C ₆ H ₄	75%
l	Me	Me	Ph	4-CF ₃ -C ₆ H ₄	55%
m	Me	Me	Ph	1-naphthyl	72%
n	Me	Me	Ph	2,6-Me ₂ -C ₆ H ₃	89%
o	Me	Me	Ph		65%
q	cyclohexyl		Ph	Ph	82%

Method C: To secure dialkenyl ketone **4-3u**, carbonitrile **4-4a** further was subjected to DIBAL reduction to generate the corresponding aldehyde, which was subsequently treated with pentenyl Grignard reagent to afford alcohol **4-5u**. Swern oxidation on alcohol **4-5u** delivered ketone **4-3u** (Scheme 4-17).



Scheme 4-17. Synthesis of ketone **4-3u**

Ketones **4-3** obtained from Methods A-C were treated with hydroxylamine hydrochloride in the presence of pyridine to give alkenyl ketoximes **4-1** (Table 4-3).

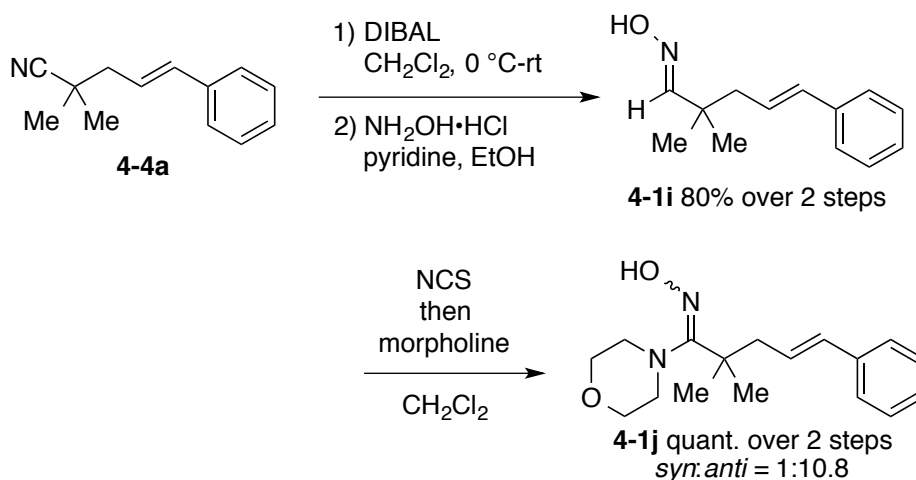
Table 4-3. Condensation of hydroxylamine hydrochloride with ketones **4-3**

substrate	R ¹	R ²	R ³	R ⁴	n	syn:anti ^a	yields 4-1
a	Me	Me	Ph	Ph	1	<i>anti</i>	81%
b	Me	Me	4-OMe-C ₆ H ₄	Ph	1	<i>anti</i>	93%
c	Me	Me	4-CF ₃ -C ₆ H ₄	Ph	1	<i>anti</i>	65%
d	Me	Me	2-naphthyl	Ph	1	<i>anti</i>	52%
e	Me	Me	2-Me-C ₆ H ₄ Ph	Ph	1	<i>anti</i>	51%
f	Me	Me	2-thiophene	Ph	1	<i>anti</i>	71%
g	Me	Me	Me	Ph	1	<i>anti</i>	93%
h	Me	Me	isopropyl	Ph	1	<i>anti</i>	72%
k	Me	Me	Ph	4-OMe-C ₆ H ₄	1	<i>anti</i>	83%
l	Me	Me	Ph	4-CF ₃ -C ₆ H ₄	1	<i>anti</i>	96%
m	Me	Me	Ph	1-naphthyl	1	<i>anti</i>	87%
n	Me	Me	Ph	2,6-Me ₂ -C ₆ H ₃	1	<i>anti</i>	92%
o	Me	Me	Ph		1	<i>anti</i>	81%
p	Me	Me	Ph	H	1	<i>anti</i>	85%
q	cyclohexyl		Ph	Ph	1	<i>anti</i>	82%
r	cyclopropyl		Ph	Ph	1	1:1.3	89%
s	H	Ph	Ph	Ph	1	1:1	84%
t	H	H	Ph	Ph	1	<i>syn</i>	83%
u	Me	Me		Ph	1	<i>anti</i>	72% ^b
v	Me	Me	Ph	Ph	2	<i>anti</i>	82%

^a *syn:anti* ratio was determined by analysis of crude ¹H NMR. ^b 2-step yield from alcohol **4-5u**.

4.2.2. Synthesis of aldoxime **4-1i** and amidoxime **4-1j**

Aldoxime **4-1i** were obtained by DIBAL reduction of carbonitrile **4-4a** followed by condensation with hydroxylamine hydrochloride. Treatment of aldoxime **4-1i** with *N*-chlorosuccinimide (NCS) followed by morpholine led to formation of amidoxime **4-1j** (Scheme 4-18).

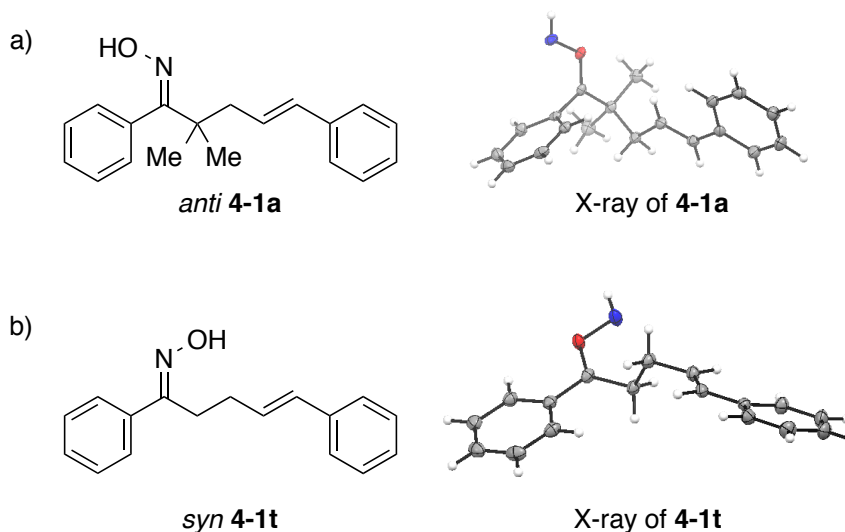


Scheme 4-18. Synthesis of amidoxime **4-1i** and aldoxime **4-1j**

4.2.3. Stereochemistry of oximes 4-1

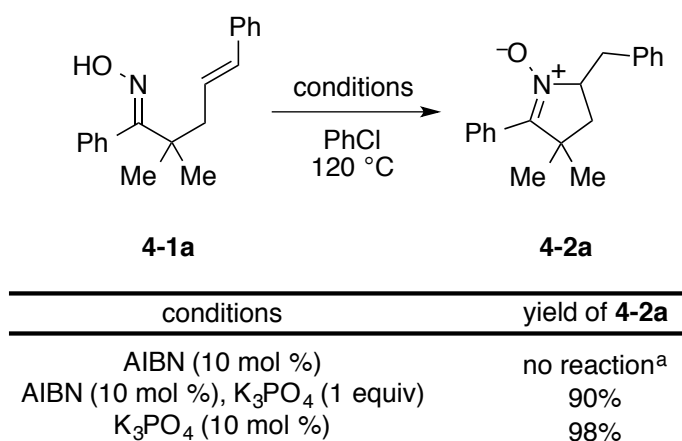
In most cases, the oxime formation produced a pure stereoisomer except for oximes **4-1j**, **4-1r** and **4-1s**. Single X-ray crystallographic analysis revealed that oxime **4-1a** adopts the *anti*-configuration (Figure 4-2-a). Analogous oximes having α -quaternary carbons isolated as a single isomer were assumed to adopt the same *anti*-configuration due to the structural similarity. In contrast, oxime **4-1t** was isolated as the *syn*-configuration (Figure 4-2-b). Oxime **4-1j** and **4-1s** were isolated as inseparable *syn/anti* mixture of oximes in 1:10.8 and 1:1 ratio, respectively (Table 4-3). Oxime **4-1r** was isolated as separable *syn/anti* oxime in 1:1.3 ratio. The stereochemistry of oximes **4-1r** could be determined by ^{13}C NMR analyses.^{37,38}

Figure 4-2. X-ray of oximes **4-1a** and **4-1t**



4.3. Investigation for synthesis of cyclic nitron **4-2a** from oxime **4-1a**

The author commenced the investigation on the proposed radical cyclization for synthesis of cyclic nitrones with the reaction of oxime **4-1a** (Scheme 4-19). The reaction of **4-1a** in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) in chlorobenzene (PhCl) at 120 °C, however, resulted in no reaction at all with 98% recovery of **4-1a**. In sharp contrast, the desired 5-membered ring cyclic nitron (**4-2a**) was formed in 95% yield when 1 equiv of K_3PO_4 was added with 10 mol% of AIBN. Surprisingly, the nitron formation could be achieved with only 10 mol% of K_3PO_4 .

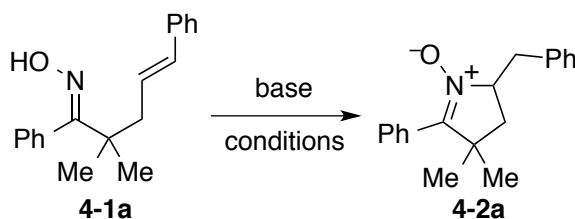


^a **4-2a** was recovered in 98% yield.

Scheme 4-19. Initial screening conditions

This unexpected finding of cyclic nitron formation from alkenyl ketoxime **4-1a** only with K_3PO_4 stimulated the author to investigate the reaction scope as well as the reaction mechanism with the strong conviction that there is something unprecedented operating in this reaction.

Further screening of suitable reaction conditions was performed using oxime **4-1a**. Heating a solution of oxime **4-1a** without additives resulted in synthetically meaningless amounts of cyclic nitron **4-2a** (entries 1-4), which clearly indicated that retro-Cope type hydroamination is ruled out as possibility for the reaction mechanism for K_3PO_4 -catalyzed formation of cyclic nitron **4-2a**. Other than chlorobenzene, toluene and *o*-xylene were also suitable as a solvent, while use of DMSO and DMF gave moderate yields of **4-2a** (entries 5-8). The reaction with a stronger base, KOt -Bu allowed lowering the reaction temperature to 60 °C, delivering 97% yield albeit longer reaction time (20 h) (entry 11). It is noted that other inorganic bases such as NaOMe and NaH (entries 12 and 13) also realized the nitron formation.

Table 4-4. Optimization of base mediated intramolecular hydroamination^a

entry	base (equiv.)	solvents	temp. (°C)	time/h	Yield of 4-2a / % ^b
1	none	toluene	110	24	0(92) ^c
2	none	<i>o</i> -xylene	150	24	4(70) ^c
3	none	DMSO	120	24	6(58) ^c
4	none	PhCl	120	24	5(78) ^c
5	K ₃ PO ₄ (0.1)	toluene	110	12	98
6	K ₃ PO ₄ (0.1)	<i>o</i> -xylene	120	10	98
7	K ₃ PO ₄ (0.1)	DMSO	120	4	59(29) ^c
8	K ₃ PO ₄ (0.1)	DMF	120	24	12(72) ^c
9	K ₂ CO ₃ (0.1)	PhCl	120	24	21(77) ^c
10	KO ^t Bu (0.1)	PhCl	120	0.6	96
11	KO ^t Bu (0.1)	PhCl	60	20	97
12	NaOMe (0.1)	PhCl	120	7	67(30) ^c
13	NaH (0.1)	PhCl	120	7	88

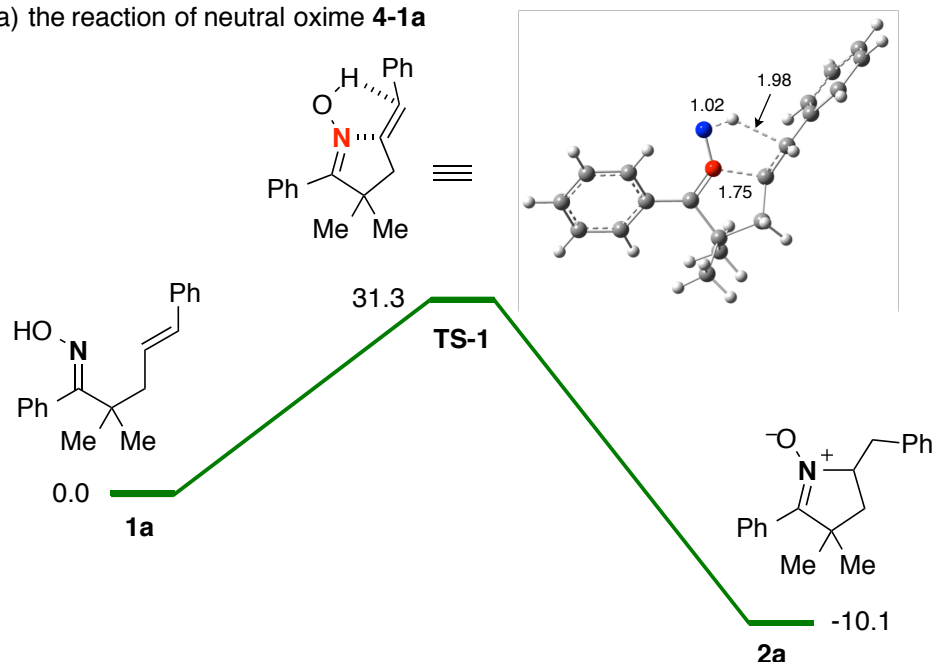
^a Reactions were performed on the scale of 0.2 mmol of **4-1a** in solvents (0.1 M).

^b Isolated yields. ^c Recovery yields of **4-1a**.

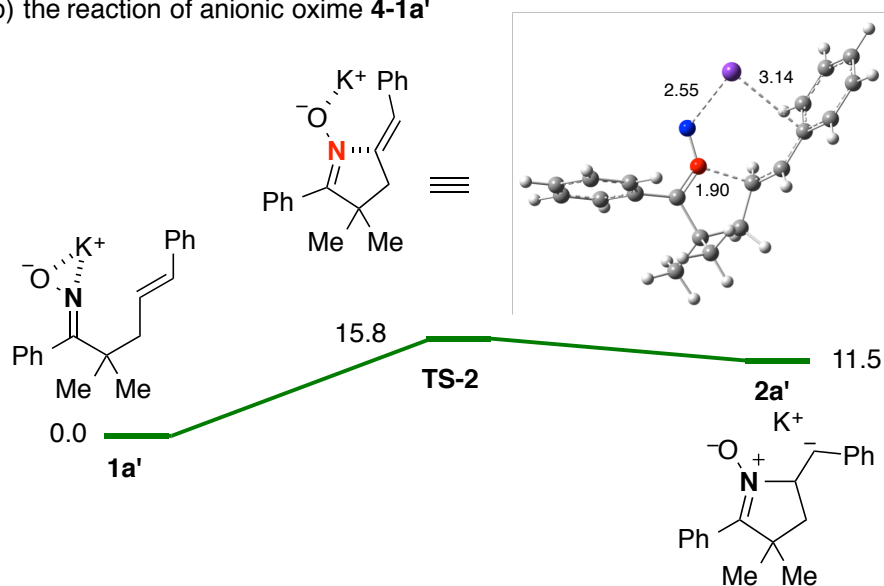
Consequently, the author investigated the reaction mechanism pertaining to the role of the inorganic bases by DFT calculations at the B3LYP(SCRFF)/6-311+G(d,p) level, taking into account the chlorobenzene solvent effect.^{39,40,41,42,43} The cyclization of neutral oxime **4-1a** was first examined (Scheme 4-20-a). A transition state for the retro-Cope hydroamination was obtained to yield **4-2a**, although the activation barrier was very high (31.3 kcal mol⁻¹). On the contrary, investigation of the anionic oxime **4-1a'** (Scheme 4-20-b) gave a distinct transition state with the K⁺ ion on the oxime oxygen atom interacting closely with the *ipso*-carbon of the phenyl moiety. Such spatial organization of K⁺ ion effectively stabilize the negative charges that accumulate as the cyclization progress and highlight the unique role of the K⁺ ion in the present cyclic nitronium formation. Moreover, the activation barrier was found to be very low, 15.8 kcal mol⁻¹. Thus, the present hydroamination could proceed *via* unprecedented nucleophilic

amination of unactivated alkene by the oxime nitrogen, the transition state of which is stabilized by ionic interaction of the K^+ ion on the oxime oxygen and negatively charged alkene moiety.

(a) the reaction of neutral oxime **4-1a**



(b) the reaction of anionic oxime **4-1a'**



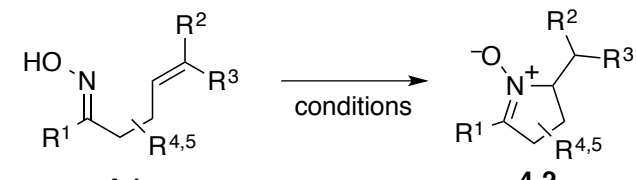
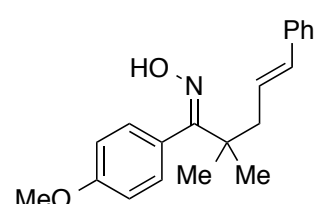
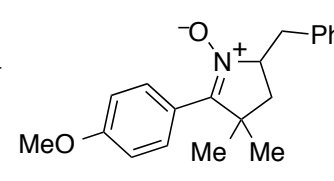
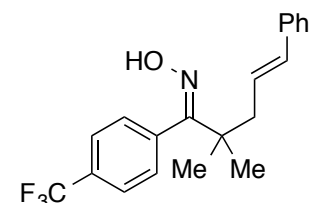
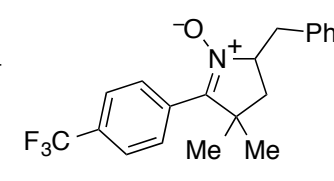
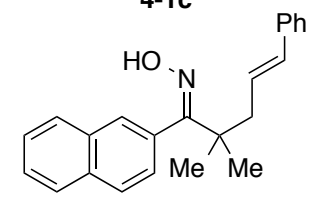
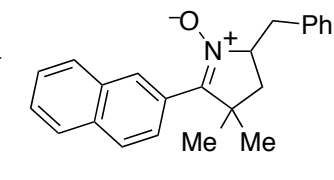
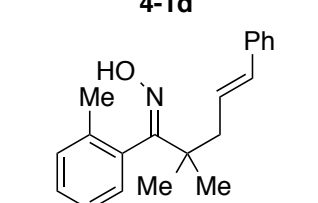
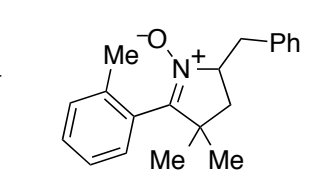
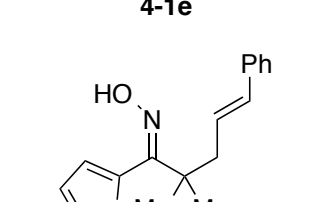
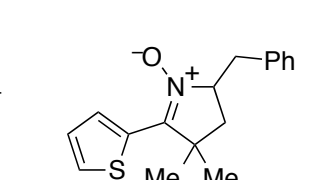
Scheme **4-20**. Energy diagram (in kcal mol⁻¹) for cyclization of neutral oxime **4-1a** (a) and anionic oxime **4-1a'** (b), as obtained at the B3LYP(SCRFF)/6-311 +G(d,p) level. Zero-point-energy (ZPE) effects are included. Key bond distances are given in Å in the three-dimensional models of the transition states

4.3.1. Substrate scope for synthesis of cyclic nitrones

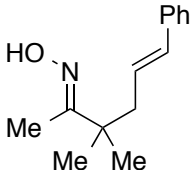
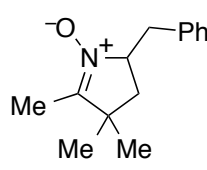
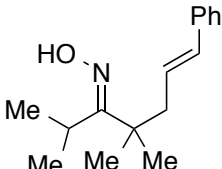
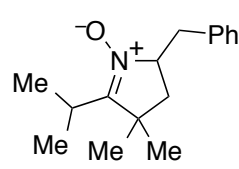
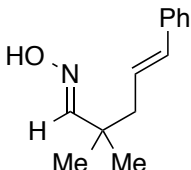
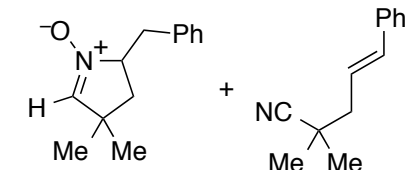
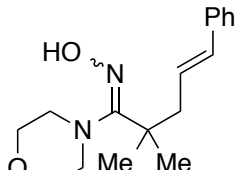
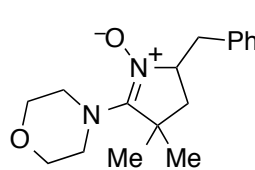
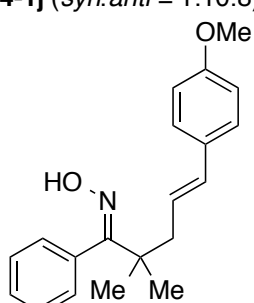
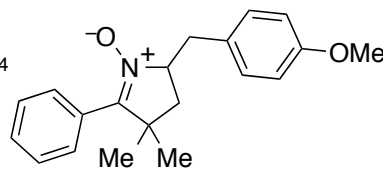
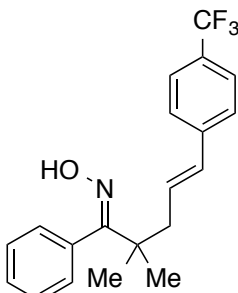
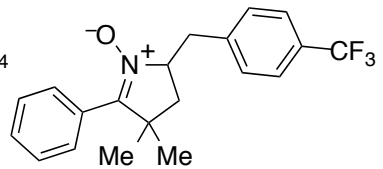
The author next explored the scope and limitations of this unprecedented K_3PO_4 -mediated hydroamination with regard to the γ,δ -unsaturated ketoximes **4-1** for the synthesis of 5-membered cyclic nitrones **4-2** (Table 4-5). As substituent R^1 , the reaction tolerated the installation of not only electron-rich and -deficient benzene rings (entries 1 and 2) but also sterically bulky aryl groups (entries 3 and 4) as well as a 2-thienyl moiety (entry 5) providing good to excellent yields. Alkyl groups such as methyl group and isopropyl group could also be introduced at R^1 (entries 6 and 7). While the reaction of aldoxime **4-1i** afforded nitrone **4-2i** in 24% yield, along with the corresponding nitrile **4-4a** in 47% yield *via* dehydration of aldoxime **4-1j** (entry 8), a morpholino moiety could also be introduced at R^1 (entry 9). Investigation of the effect of substituents attached to the alkene (R^2 and R^3) revealed that the electronic nature of the alkene influences the present hydroamination process significantly. It took a very long time (48 h) for the reaction of oxime **4-1k** bearing an electron-rich methoxyphenyl group on the alkene to be completed, even with 40 mol% of K_3PO_4 , whereas the reaction of oxime **4-1l** having an electron-deficient group (trifluorophenyl) proceeded very rapidly and was completed within 1 h (entries 10 and 11). Sterically bulky aryl groups (entries 12 and 13) could be installed as R^2 , but the reaction of oxime **4-1n** bearing a 2,6-dimethylphenyl group was very slow. Oxime **4-1o** having the trisubstituted *E*-alkene with Ph as R^2 and Me as R^3 afforded the corresponding nitrone **4-2o** as a 1.2:1 diastereomeric mixture, which supports the stepwise hydroamination mechanism involving a carbanion intermediate like **4-2a'** in Scheme 4-20-b. On the other hand, hydroamination of the terminal alkene of oxime **4-1p** (R^2 and R^3 = H) required higher temperature (150 °C) and a stoichiometric amount of K_3PO_4 , to give nitrone **2p** in 54% yield along with 38% recovery of oxime **4-1p** (entry 15). Spirocyclic nitrones were nicely constructed using the present hydroamination (entries 16 and 17). Besides α -geminal disubstituted oximes, α -monophenyl and non-substituted oximes **4-1s** and **4-1t** were examined. While oxime **4-1s** is a 1:1 *syn/anti*-mixture and oxime **4-1t** is a pure *syn*-form (i.e. the oxime N-O bond lies at the same side with the alkene), the stoichiometric use of K_3PO_4 gave the corresponding nitrones **4-2s** and **4-2t** in 50% and 76% yields, respectively (entries 18 and 19). These results suggested that the

stereochemistry of the oxime N-O bond does not influence the present hydroamination.

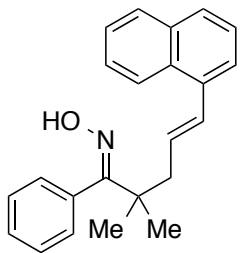
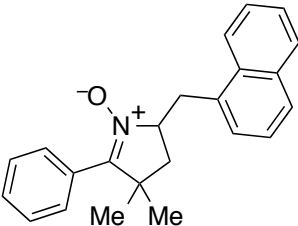
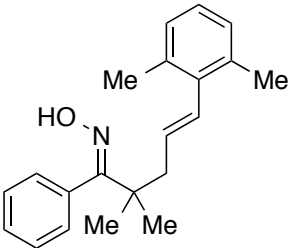
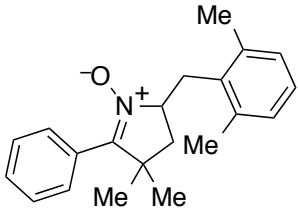
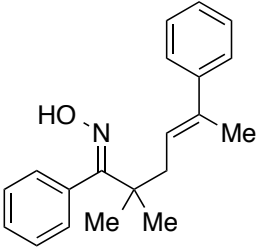
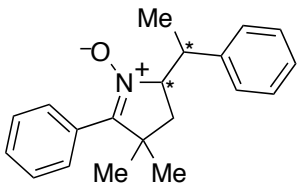
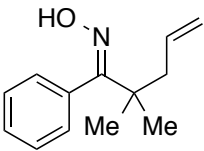
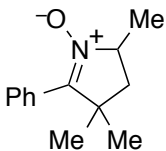
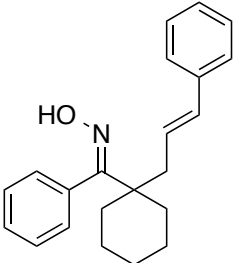
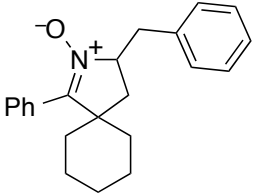
Table 4-5. Substrate scope for synthesis of cyclic nitrones **4-2**^a

				
entry	oxime 4-1	conditions	nitrone 4-2	yields ^b
1	 4-1b	10 mol% K ₃ PO ₄ PhCl, 120 °C 20 h	 4-2b	96%
2	 4-1c	10 mol% K ₃ PO ₄ PhCl, 120 °C 22 h	 4-2c	93%
3	 4-1d	10 mol% K ₃ PO ₄ PhCl, 120 °C 8 h	 4-2d	98%
4	 4-1e	10 mol% K ₃ PO ₄ PhCl, 120 °C 24 h	 4-2e	75%
5	 4-1f	10 mol% K ₃ PO ₄ PhCl, 120 °C 1.5 h	 4-2f	97%

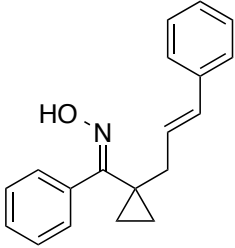
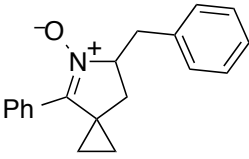
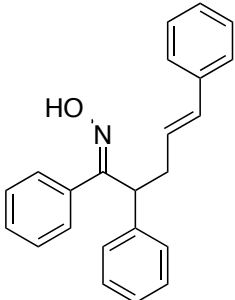
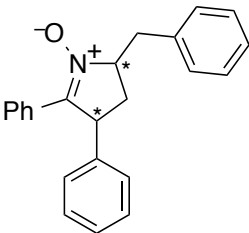
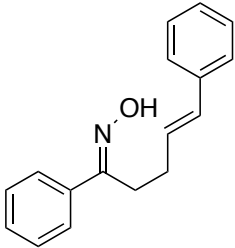
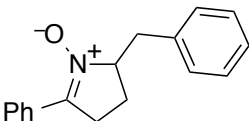
continued...

entry	oxime 4-1	conditions	nitron 4-2	yields ^b
6	 4-1g	10 mol% K ₃ PO ₄ PhCl, 120 °C 24 h	 4-2g	96%
7	 4-1h	10 mol% K ₃ PO ₄ PhCl, 120 °C 3 h	 4-2h	91%
8	 4-1i	100 mol% K ₃ PO ₄ PhCl, 120 °C 48 h	 4-1i 24% 4-4a 47%	
9	 4-1j (<i>syn:anti</i> = 1:10.8)	100 mol% K ₃ PO ₄ PhCl, 120 °C 48 h	 4-1j	89%
10	 4-1k	40 mol% K ₃ PO ₄ PhCl, 120 °C 48 h	 4-2k	87%
11	 4-1l	10 mol% K ₃ PO ₄ PhCl, 120 °C 1 h	 4-2l	96%

continued...

entry	oxime 4-1	conditions	nitron 4-2	yields ^b
12	 4-1m	10 mol% K ₃ PO ₄ PhCl, 120 °C 1 h	 4-2m	98%
13	 4-1n	40 mol% K ₃ PO ₄ PhCl, 120 °C 48 h	 4-2n	73%
14	 4-1o	100 mol% K ₃ PO ₄ PhCl, 120 °C 24 h	 4-2o	82% <i>dr</i> = 1.2:1 ^c
15	 4-1p	100 mol% K ₃ PO ₄ <i>o</i> -xylene, 150 °C 24 h	 4-2p	54% (38% 4-1p recovered)
16	 4-1q	10 mol% K ₃ PO ₄ PhCl, 120 °C 20 h	 4-2q	96%

continued...

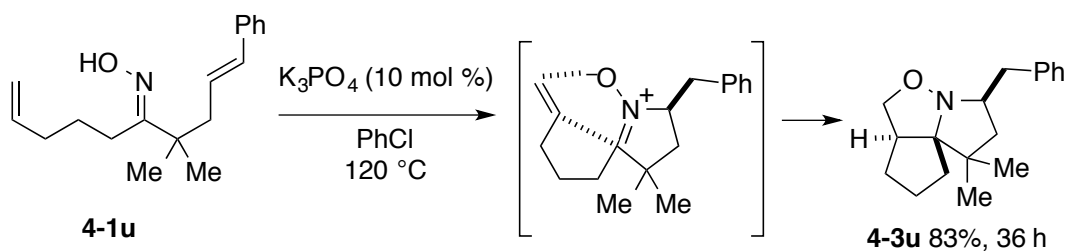
entry	oxime 4-1	conditions	nitron 4-2	yields ^b
17	 4-1r	100 mol% K ₃ PO ₄ PhCl, 120 °C 43 h	 4-2r	62%
18	 4-1s (<i>syn/anti</i> : 1:1)	100 mol% K ₃ PO ₄ PhCl, 120 °C 24 h	 4-2s	50% <i>dr</i> = 2.2:1 ^c
19 ^d	 4-1t	100 mol% K ₃ PO ₄ PhCl, 120 °C 36 h	 4-2t	76%

^a Unless otherwise noted, reactions were performed on the scale of 0.2 mmol scale.

^b Isolated yields. ^c Diastereoselectivity ratio was determined by analysis of crude ¹H NMR while the relative stereochemistry was not determined. ^d Reaction performed using 5 mmol of **4-1t**.

4.3.2. Domino oxime cyclization-1,3-dipolar cycloaddition sequence

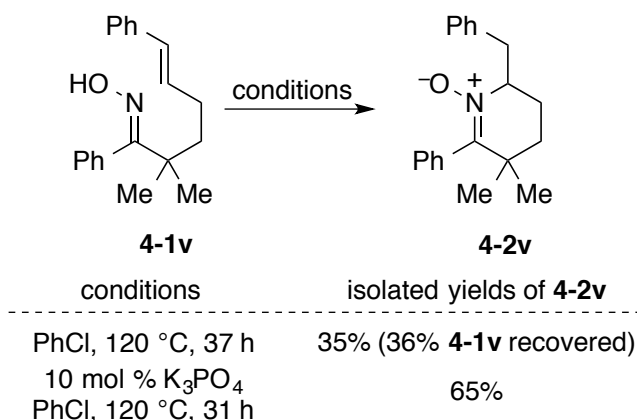
Inspired by the operational simplicity to access various cyclic nitrones from alkenyl oximes, the author next considered the possibility of a domino sequence of the present hydroamination-[3+2]-cycloaddition (Scheme 4-22). Indeed, treatment of oxime **4-1u** with 10 mol% of K₃PO₄ in chlorobenzene at 120 °C for 36 h yielded tricyclic azaheterocycle **4-3u** in good yields as a single stereoisomer.



Scheme 4-22. Nitron formation followed by 1,3-dipolar cycloaddition

4.3.3. Synthesis of 6-membered ring cyclic nitrones from δ -unsaturated oximes

The current anionic stepwise hydroamination proved beneficial for synthesis of 6-membered ring cyclic nitrones from δ -alkenyl ketoximes (Scheme 4-23). A thermal reaction of oxime **4-1v** without K_3PO_4 yielded only 35% yield of 6-membered ring cyclic nitrone **4-2v** along with 36% recovery of oxime **4-1v**. On the other hand, the addition of 10 mol% K_3PO_4 could complete the reaction within 31 h to provide nitrone **4-2v** in 65% yield.



Scheme 4-23. Thermal vs base mediated cyclization of oxime **4-1v**

4.4 Conclusion

In summary, this chapter presents an operationally simple yet mechanistically distinct methodology for the intramolecular hydroamination of alkenyl ketoximes. The unique deprotonation-cyclization-protonation sequence provides access to various 5-membered cyclic nitrones that could not be prepared by the retro-Cope hydroamination.

4.5 Experimental section

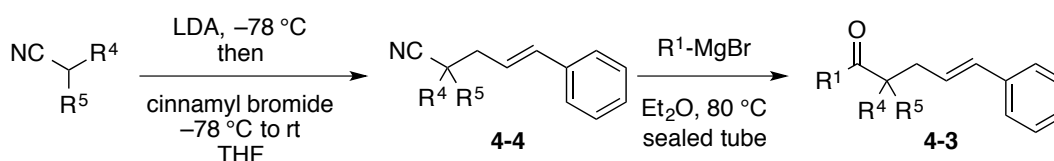
4.5.1. General

^1H NMR spectra were recorded on a Bruker Avance 400 or 500 MHz spectrometer in CDCl_3 [using TMS (for ^1H , $\delta = 0.00$) as internal standard]. ^{13}C NMR spectra on a Bruker Avance 400 or 500 MHz spectrometer in CDCl_3 [using CDCl_3 (for ^{13}C , $\delta = 77.00$) as internal standard]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad. IR spectra were recorded on a Shimadzu IR IRAffinity-1 FT-IR Spectrometer. High-resolution mass spectra were obtained with a Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). Melting points are uncorrected and were recorded on a MPA 100 OptiMelt Automated Melting Point System. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Anhydrous chlorobenzene and K_3PO_4 ($\geq 98\%$, reagent grade, CAS Number 7778-53-2) were purchased from Sigma-Aldrich and was used as received.

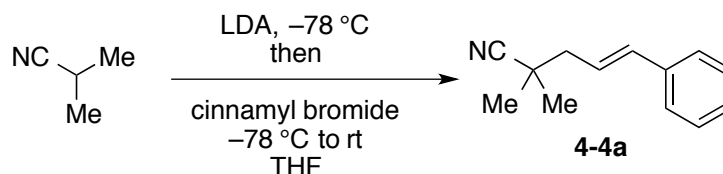
4.5.2. Synthesis of oximes 4-1

4.5.2.1. Preparation of alkenyl ketones 4-3: Method A

Alkenyl ketones **4-3a-d**, **4-3f-g**, **4-3r** and **4-3v** were prepared by addition of the Grignard reagents to the corresponding alkenyl carbonitriles **4-4**, which were obtained by α -alkylation of carbonitriles as shown below.

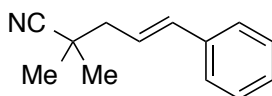


Typical procedure for preparation of alkenyl carbonitriles 4-4: (*E*)-2,2-dimethyl-5-phenylpent-4-enenitrile (4-4a**)⁴⁴**



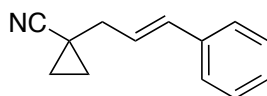
To a 2-neck round bottom flask containing diisopropylamine (3.8 mL, 27.1 mmol) in dry THF (30 mL) cooled to $-78\text{ }^{\circ}\text{C}$ was added dropwise *n*-BuLi (17.0 mL, 1.6 M, 27.2 mmol). The solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. A solution of isobutyronitrile (2.0 mL, 22.3 mmol) was added dropwise and the solution was stirred at $-78\text{ }^{\circ}\text{C}$ for further 30 min. To the reaction mixture was added dropwise a solution of cinnamyl bromide (5.27 g, 26.7 mmol) in dry THF (10 mL). Upon completion of the addition, the reaction was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched by adding saturated aqueous NH_4Cl (20 mL), and the mixture was extracted three times with Et_2O . The combined organic extracts were washed with water and brine. After drying with MgSO_4 and removal of the solvents under reduced pressure, the resulting crude material was purified by flash column chromatography (hexane:ethyl acetate = 9:1) to yield (*E*)-2,2-dimethyl-5-phenylpent-4-enenitrile (**4-4a**) (4.13 g, 22.3 mmol, quantitative yield).

(*E*)-2,2-dimethyl-5-phenylpent-4-enenitrile (**4-4a**)⁴⁴



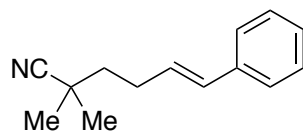
^1H NMR (400 MHz, CDCl_3): δ 1.41 (6H, s), 2.47 (2H, dd, $J = 1.1, 7.5$ Hz), 6.28 (1H, dt, $J = 7.5, 15.7$ Hz), 6.28 (1H, d, $J = 15.7$ Hz), 7.26-7.29 (1H, m), 7.35 (2H, t, $J = 7.2$ Hz), 7.42 (2H, d, $J = 7.5$ Hz); ^{13}C NMR (100 MHz, CDCl_3): δ 26.6, 32.8, 44.6, 123.8, 125.0, 126.6, 127.9, 128.8, 135.0, 137.0.

1-cinnamylcyclopropane-1-carbonitrile (**4-4r**)



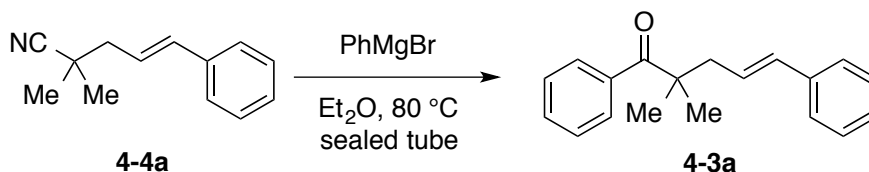
78% yield from cyclopropanecarbonitrile with cinnamyl bromide; Yellow oil; IR (NaCl) 3082, 3059, 3026, 2236 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 0.88-0.91 (2H, m), 1.25-1.28 (2H, m), 2.39 (2H, d, $J = 7.0$ Hz), 6.22 (1H, dt, $J = 7.0, 15.8$ Hz), 6.52 (1H, d, $J = 15.8$ Hz), 7.22-7.26 (1H, m), 7.32 (2H, t, $J = 7.2$ Hz), 7.38 (2H, d, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3): 10.0, 13.6, 38.3, 123.5, 124.4, 126.5, 127.9, 128.8, 133.7, 136.9; EIHRMS: Found: m/z 184.1124. Calcd for $\text{C}_{13}\text{H}_{14}\text{N}$: ($\text{M}+\text{H}$)⁺ 184.1126.

(*E*)-2,2-dimethyl-6-phenylhex-5-enenitrile (**4-4v**)



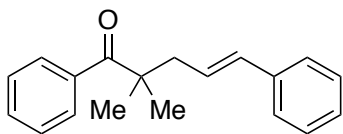
90% yield from isobutyronitrile with (*E*)-(4-bromobut-1-en-1-yl)benzene;⁴⁵ Colorless oil; IR (NaCl) 3082, 3059, 3024, 2976, 2234 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.39 (6H, s), 1.68-1.72 (2H, m), 2.38-2.44 (2H, m), 6.19 (1H, dt, $J = 6.8, 15.6$ Hz), 6.45 (1H, d, $J = 15.6$ Hz), 7.20-7.25 (1H, m), 7.28-7.35 (4H, m); ^{13}C NMR (100 MHz, CDCl_3): 26.9, 29.1, 32.5, 40.9, 125.1, 126.2, 127.4, 128.7, 128.9, 131.1, 137.6; EIHRMS: Found: m/z 200.1441. Calcd for $\text{C}_{14}\text{H}_{18}\text{N}$: ($\text{M}+\text{H}$)⁺ 200.1439.

Typical procedure for preparation of alkenyl ketones 4-3 by addition of Grignard reagents to alkenyl carbonitriles 4-4: (*E*)-2,2-dimethyl-1,5-diphenylpent-4-en-1-one (**4-3a**)



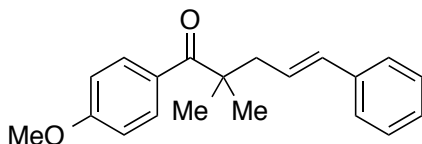
To a sealed tube containing (*E*)-2,2-dimethyl-5-phenylpent-4-enenitrile (**4-4a**) (561 mg, 3.03 mmol) in Et_2O (3.0 mL) was added phenylmagnesium bromide (3.0 M in Et_2O) (4.5 mL, 13.5 mmol). The solution was stirred at 80 °C for 24 h. Upon completion of the reaction, the solution was cooled to 0 °C and poured carefully into saturated aq. NH_4Cl . The mixture was extracted three times with Et_2O . The combined organic extracts were washed with water and brine. After drying with MgSO_4 and removal of the solvents under reduced pressure, the resulting crude material was purified by flash column chromatography (hexane:ethyl acetate = 9:1) to yield (*E*)-2,2-dimethyl-1,5-diphenylpent-4-en-1-one (**4-3a**) (753 mg, 2.85 mmol, 94% yield).

(*E*)-2,2-dimethyl-1,5-diphenylpent-4-en-1-one (**4-3a**)³⁵



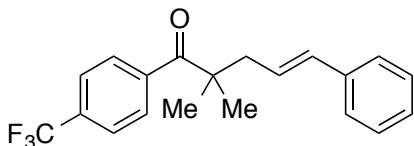
¹H NMR (400 MHz, CDCl₃) δ 1.38 (6H, s), 2.63 (2H, dd, *J* = 1.1, 7.4 Hz), 6.12 (1H, dt, *J* = 7.4, 15.7 Hz), 6.34 (1H, d, *J* = 15.7 Hz), 7.18-7.21 (1H, m), 7.25-7.30 (4H, m), 7.38-7.47 (3H, m), 7.65-7.67 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ 25.9, 44.1, 48.1, 125.8, 126.1, 127.1, 127.6, 128.1, 128.4, 130.8, 133.2, 137.3, 139.1, 208.8.

(*E*)-1-(4-methoxyphenyl)-2,2-dimethyl-5-phenylpent-4-en-1-one (**4-3b**)



Quantitative yield from (*E*)-2,2-dimethyl-5-phenylpent-4-enenitrile (**4-4a**) with 4-methoxyphenyl magnesium bromide; Yellow oil; IR (NaCl) 3026, 2968, 1667 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.39 (6H, s), 2.65 (2H, dd, *J* = 1.1, 7.5 Hz), 3.84 (3H, s), 6.11 (1H, dt, *J* = 7.5, 15.7 Hz), 6.34 (1H, d, *J* = 15.7 Hz), 6.90 (2H, d, *J* = 8.8 Hz), 7.15-7.19 (1H, m), 7.24-7.29 (4H, m), 7.83 (2H, d, *J* = 8.8 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 26.3, 44.6, 47.9, 55.4, 113.4, 126.1, 126.2, 127.14, 128.5, 130.7, 130.7, 133.1, 137.5, 162.0, 205.8; EIHRMS: Found: *m/z* 295.1693. Calcd for C₂₀H₂₃O₂: (M+H)⁺ 295.1698.

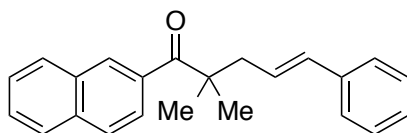
(*E*)-2,2-dimethyl-5-phenyl-1-(4-(trifluoromethyl)phenyl)pent-4-en-1-one (**4-3c**)



91% yield from (*E*)-2,2-dimethyl-5-phenylpent-4-enenitrile (**4-4a**) with 4-trifluoromethoxyphenyl magnesium bromide; Yellow oil; IR (NaCl) 3059, 3026, 2974, 1682, 1169, 1136 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.37 (6H, s), 2.61 (2H, dd, *J* = 1.2, 7.5 Hz), 6.12 (1H, dt, *J* = 7.5, 16.0 Hz), 6.35 (1H, d, *J* = 16.0 Hz), 7.19-7.23 (1H, m), 7.28-7.30 (4H, m), 7.65-7.71 (4H, m); ¹³C NMR (100 MHz, CDCl₃): 25.7, 43.9, 48.4, 123.7 (q, ¹*J*_{C-F} = 271.0 Hz), 125.1(9) (q, ³*J*_{C-F} = 3.8 Hz),

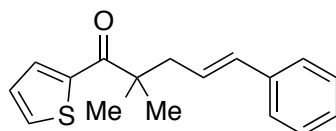
125.2(4), 126.1, 127.4, 127.6, 128.5, 132.3 (q, $^2J_{\text{C-F}} = 32.3$ Hz), 133.7, 137.2, 142.6, 208.4; EIHRMS: Found: m/z 333.1468. Calcd for $\text{C}_{20}\text{H}_{20}\text{OF}_3$: $(\text{M}+\text{H})^+$ 333.1466.

(*E*)-2,2-dimethyl-1-(naphthalen-2-yl)-5-phenylpent-4-en-1-one (**4-3d**)



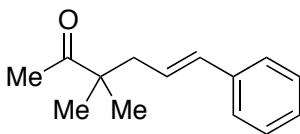
52 % yield from (*E*)-2,2-dimethyl-5-phenylpent-4-enenitrile (**4-4a**) with naphthalene-2-yl magnesium bromide; Yellow solid; mp. 101-103 °C; IR (NaCl) 3057, 3026, 1667 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 1.44 (6H, s), 2.70 (2H, d, $J = 7.6$ Hz), 6.16 (1H, dt, $J = 7.6, 15.6$ Hz), 6.36 (1H, d, $J = 15.6$ Hz), 7.17-7.19 (1H, m), 7.22-7.29 (4H, m), 7.5-7.56 (2H, m), 7.75 (1H, d, $J = 8.5$ Hz), 7.84 (2H, d, $J = 8.5$ Hz), 7.88 (1H, d, $J = 8.0$ Hz), 8.20 (1H, s); ^{13}C NMR (125 MHz, CDCl_3): δ 26.3, 44.6, 48.5, 124.9, 126.1, 126.3, 126.8, 127.4, 127.9, 128.1, 128.4, 128.6(7), 128.7(1), 129.3, 132.5, 133.5, 134.5, 136.5, 137.5, 208.8; EIHRMS: Found: m/z 315.1747. Calcd for $\text{C}_{23}\text{H}_{23}\text{O}$: $(\text{M}+\text{H})^+$ 315.1749.

(*E*)-2,2-dimethyl-5-phenyl-1-(thiophen-2-yl)pent-4-en-1-one (**4-3f**)



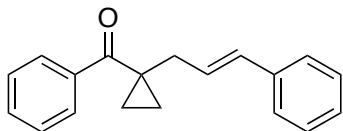
88% yield from (*E*)-2,2-dimethyl-5-phenylpent-4-enenitrile (**4-4a**) with 2-thiophene magnesium bromide; Yellow oil; IR (NaCl) 3080, 3059, 3024, 2972, 1643 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.43 (6H, s), 2.70 (1H, dd, $J = 1.2, 7.5$ Hz), 6.12 (1H, dt, $J = 7.5, 15.7$ Hz), 6.36 (1H, d, $J = 15.7$ Hz), 7.12 (1H, dd, $J = 4.0, 5.2$ Hz), 7.17-7.20 (1H, m), 7.24-7.30 (4H, m), 7.58 (1H, d, $J = 5.2$ Hz), 7.82-7.7 (1H, d, $J = 4.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3): δ 26.2, 44.8, 48.0, 126.0, 126.4, 127.4, 127.9, 128.7, 132.1, 132.7, 133.5, 137.6, 142.9, 198.3; EIHRMS: Found: m/z 271.1158. Calcd for $\text{C}_{17}\text{H}_{19}\text{OS}$: $(\text{M}+\text{H})^+$ 271.1157.

(*E*)-3,3-dimethyl-6-phenylhex-5-en-2-one (**4-3g**)⁴⁶



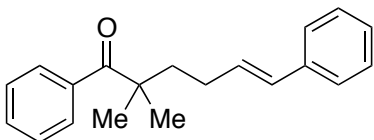
77% yield from (*E*)-2,2-dimethyl-5-phenylpent-4-enenitrile (**4-4a**) with methyl magnesium bromide; ¹H NMR (400 MHz, CDCl₃): δ 1.18 (6H, s), 2.16 (3H, s), 2.41 (2H, dd, *J* = 1.2, 7.5 Hz), 6.09 (1H, dt, *J* = 7.5, 15.7 Hz), 6.40 (1H, d, *J* = 15.7 Hz), 7.18-7.34 (5H, m); ¹³C NMR (100 MHz, CDCl₃): δ 24.5, 25.6, 43.3, 48.4, 103.1, 126.0, 126.4, 127.4, 128.7, 133.27, 213.6.

(1-cinnamylcyclopropyl)(phenyl)methanone (**4-3r**)



57% yield from 1-cinnamylcyclopropane-1-carbonitrile (**4-4r**) with phenyl magnesium bromide; Colorless oil; IR (NaCl) 3080, 3059, 3024, 1672 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.86-0.97 (2H, m), 1.26-1.56 (2H, m), 2.65 (2H, d, *J* = 6.6 Hz), 6.05 (1H, dt, *J* = 6.6, 15.9 Hz), 6.16 (1H, d, *J* = 15.9 Hz), 7.16-7.20 (1H, m), 7.22-7.27 (4H, m), 7.43 (2H, t, *J* = 7.4 Hz), 7.51 (1H, t, *J* = 7.4 Hz), 7.78 (2H, d, *J* = 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 13.0, 30.3, 39.1, 126.3, 126.6, 127.4, 128.4, 128.5, 128.6, 131.9, 132.1, 137.4, 138.0, 203.7; EIHRMS: Found: *m/z* 263.1441. Calcd for C₁₉H₁₉O: (M+H)⁺ 263.1436.

(*E*)-2,2-dimethyl-1,6-diphenylhex-5-en-1-one (**4-3v**)



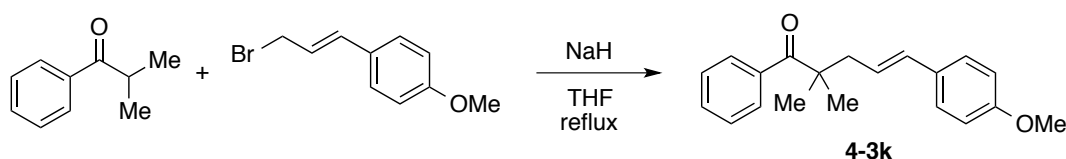
87% yield from (*E*)-2,2-dimethyl-6-phenylhex-5-enenitrile (**4-4v**) with phenyl magnesium bromide; Colorless oil; IR (NaCl) 3057, 3024, 2968, 1672 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.36 (6H, s), 1.91-1.95 (2H, m), 2.13-2.19 (2H, m), 6.13 (1H, dt, *J* = 7.2, 15.6 Hz), 6.32 (1H, d, *J* = 15.6 Hz), 7.12-7.19 (1H, m), 7.25-7.32 (4H, m), 7.33-7.41 (2H, m), 7.42-7.48 (1H, m), 7.67 (2H, d, *J* = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 26.4, 28.8, 40.8, 47.9, 126.1, 127.1, 127.8, 128.4, 128.7, 130.3, 130.5, 131.1, 137.8, 139.3, 209.1; EIHRMS: Found: *m/z* 279.1739.

Calcd for C₂₀H₂₃O: (M+H)⁺ 279.1749.

4.5.2.2. Preparation of alkenyl ketones 4-3: Method B

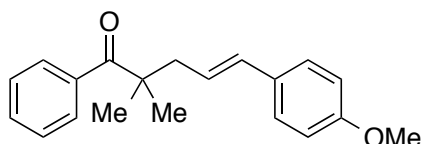
Alkenyl ketones **4-3e**, **4-3h**, **4-3k-o** and **4-3q** (as a precursor of alkenyl oximes **4-1**) were prepared by α -alkylation of the corresponding ketones with bromoalkenes.

Typical Procedure for Synthesis of Alkenyl Ketones 4-3: (*E*)-5-(4-methoxyphenyl)-2,2-dimethyl-1-phenylpent-4-en-1-one (**4-3k**)³⁵



To a 2-neck round bottom flask containing isobutyrophenone⁴⁷ (0.60 mL, 3.88 mmol) in dry THF (15 mL) was added NaH (186 mg, 4.65 mmol). The solution was stirred at rt for 30 min. A solution of (*E*)-1-(3-bromoprop-1-en-1-yl)-4-methoxybenzene⁴⁸ (1.06 g, 4.66 mmol) in THF (5.0 mL) was added dropwise and the solution was stirred at reflux for 8 h. Upon completion of the addition, the reaction was allowed to cool to rt. The reaction was quenched by adding saturated aqueous NH₄Cl (20.0 mL), and the mixture was extracted three times with Et₂O. The combined organic extracts were washed with water and brine. After drying with MgSO₄ and removal of the solvents under reduced pressure, the resulting crude material was purified by flash column chromatography (hexane:diethyl ether = 20:1) to yield (*E*)-5-(4-methoxyphenyl)-2,2-dimethyl-1-phenylpent-4-en-1-one (**4-3k**) (857 mg, 2.91 mmol, 75%).

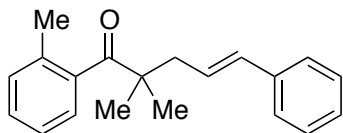
(*E*)-5-(4-methoxyphenyl)-2,2-dimethyl-1-phenylpent-4-en-1-one (**4-3k**)



Colorless oil; IR (NaCl) 1672, 1250 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.36 (6H, s), 2.60 (2H, dd, *J* = 1.1, 7.5 Hz), 3.78 (3H, s), 5.97 (1H, dt, *J* = 7.5, 15.7 Hz), 6.28 (1H, d, *J* = 15.7 Hz), 6.80-6.83 (2H, m), 7.21-7.25 (2H, m), 7.34-7.47 (3H, m),

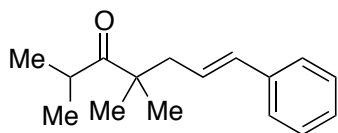
7.64-7.66 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 25.9, 44.1, 48.2, 55.3, 113.9, 123.6, 127.2, 127.6, 128.1, 130.2, 130.7, 132.6, 139.2, 158.9, 208.9; ESIHRMS: Found: m/z 295.1703. Calcd for $\text{C}_{20}\text{H}_{23}\text{O}_2$: $(\text{M}+\text{H})^+$ 295.1698.

(*E*)-2,2-dimethyl-5-phenyl-1-(*o*-tolyl)pent-4-en-1-one (**4-3e**)



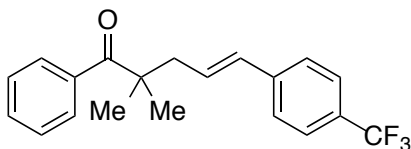
78% yield from 2-methyl-1-(*o*-tolyl)propan-1-one⁴⁹ with cinnamyl bromide; Yellow oil; IR (NaCl) 3019, 2970, 1684 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.26 (6H, s), 2.23 (3H, s), 2.56 (2H, d, $J = 8.0$ Hz), 6.21 (1H, dt, $J = 8.0, 15.8$ Hz), 6.40 (1H, d, $J = 15.8$ Hz), 7.34-7.16 (9H, m); ^{13}C NMR (100 MHz, CDCl_3): δ 20.1, 25.4, 43.4, 49.0, 124.7, 125.1, 126.1, 126.3, 127.4, 128.8, 128.9, 131.1, 133.7, 134.4, 137.6, 141.4, 214.0; ESIHRMS: Found: m/z 279.1751. Calcd for $\text{C}_{20}\text{H}_{23}\text{O}$: $(\text{M}+\text{H})^+$ 279.1749.

(*E*)-2,4,4-trimethyl-7-phenylpent-6-en-3-one (**4-3h**)



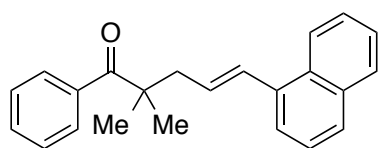
71% yield from 2,4-dimethylpentan-3-one⁵⁰ with cinnamyl bromide; colorless oil; IR (NaCl) 3026, 2970, 1697 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.05 (6H, d, $J = 6.7$ Hz), 1.19 (6H, s), 2.42 (2H, dd, $J = 1.2, 7.5$ Hz), 3.13 (1H, septet, $J = 6.7$ Hz), 6.09 (1H, dt, $J = 7.5, 15.8$ Hz), 6.39 (1H, d, $J = 15.8$ Hz), 7.19-7.21 (1H, m), 7.22-7.33 (4H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 20.1, 23.9, 34.3, 42.7, 48.5, 126.1, 126.2, 127.1, 128.5, 133.0, 137.4, 219.5; ESIHRMS: Found: m/z 231.1750. Calcd for $\text{C}_{16}\text{H}_{23}\text{O}$: $(\text{M}+\text{H})^+$ 231.1749.

(*E*)-2,2-dimethyl-1-phenyl-5-(4-(trifluoromethyl)phenyl)pent-4-en-1-one (**4-3l**)



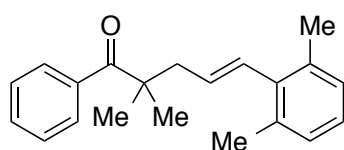
55% yield from isobutyrophenone with (*E*)-1-(3-bromoprop-1-en-1-yl)-4-(trifluoromethyl)benzene;⁵¹ yellow oil; IR (NaCl) 1668, 1327, 1215 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.39 (6H, s), 2.66 (2H, d, *J* = 7.3 Hz), 6.23 (1H, dt, *J* = 7.3, 15.8 Hz), 6.37 (1H, d, *J* = 15.8 Hz), 7.36-7.43 (4H, m), 7.46-7.48 (1H, m), 7.49-7.53 (2H, m), 7.65-7.67 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ 26.0, 29.7, 44.2, 48.1, 124.2 (q, ¹*J*_{C-F} = 270.0 Hz), 125.4 (q, ³*J*_{C-F} = 3.7 Hz), 126.2, 127.6, 128.2, 128.9, 129.0 (q, ²*J*_{C-F} = 32.2 Hz), 130.9, 132.0, 139.0, 140.8, 208.4; ESIHRMS: Found: *m/z* 333.1468. Calcd for C₂₀H₂₀OF₃: (M+H)⁺ 333.1466.

(*E*)-2,2-dimethyl-5-(naphthalene-1-yl)-1-phenylpent-4-en-1-one (**4-3m**)



72% yield from isobutyrophenone with (*E*)-1-(3-bromoprop-1-en-1-yl)naphthalene;⁵² yellow oil; IR (NaCl) 3059, 2970, 1670 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.44 (6H, s), 2.76 (2H, dd, *J* = 1.2, 7.5 Hz), 6.13 (1H, dt, *J* = 7.5, 15.5 Hz), 7.07 (1H, d, *J* = 15.5 Hz), 7.38-7.42 (3H, m), 7.43-7.49 (4H, m), 7.69-7.74 (3H, m), 7.80-7.83 (1H, m), 7.95-7.98 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ 26.0, 44.5, 48.2, 123.8, 123.9, 125.6, 125.7, 125.8, 127.6, 127.7, 128.1, 128.4, 129.2, 130.7, 130.9, 131.0, 133.5, 135.2, 139.1, 208.6; ESIHRMS: Found: *m/z* 315.1749. Calcd for C₂₃H₂₃O: (M+H)⁺ 315.1749.

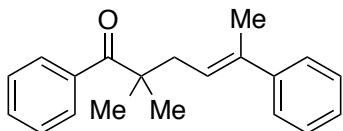
(*E*)-5-(2,6-dimethylphenyl)-2,2-dimethyl-1-phenylpent-4-en-1-one (**4-3n**)



89% yield from isobutyrophenone with (*E*)-2-(3-bromoprop-1-en-1-yl)-1,3-dimethylbenzene;⁵³ colorless oil; IR (NaCl) 3065, 3020, 2972, 1672 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.40 (6H, s), 2.22 (6H, s), 2.69 (2H, dd, *J* = 1.3, 7.4 Hz), 5.59 (1H, dt, *J* = 7.4, 16.1 Hz), 6.32 (1H, d, *J* = 16.1 Hz), 6.97-7.05 (3H, m), 7.37-7.41 (2H, m), 7.43-7.48 (1H, m), 7.68-7.71 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ 21.0, 26.0, 44.7, 48.0, 126.3, 127.6, 127.7, 128.1, 130.7, 130.9, 131.0, 135.9,

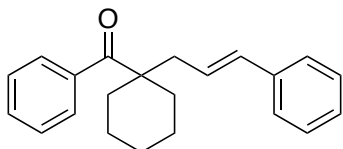
137.2, 138.9, 208.4; ESIHRMS: Found: m/z 293.1906. Calcd for $C_{21}H_{25}O$: $(M+H)^+$ 293.1905.

(*E*)-2,2-dimethyl-1,5-diphenylhex-4-en-1-one (**4-3o**)



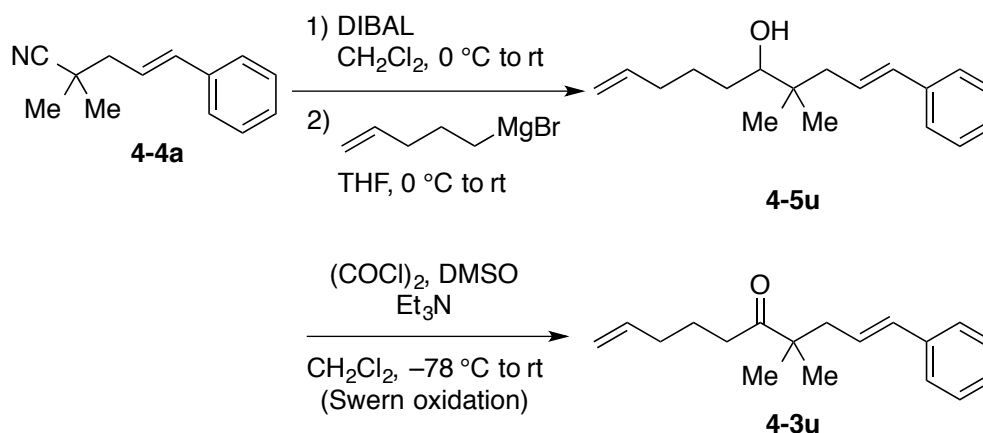
65% yield from isobutyrophenone with (*E*)-(4-bromobut-2-en-2-yl)benzene;⁵⁴ colorless oil; IR (NaCl) 3055, 3022, 1680, 1666 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (6H, s), 1.96 (3H, s), 2.64 (2H, d, $J = 7.4$ Hz), 5.68 (1H, t, $J = 7.4$ Hz), 7.19-7.23 (1H, m), 7.25-7.32 (4H, m), 7.37-7.41 (2H, m), 7.43-7.47 (1H, m), 7.64-7.66 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 25.9, 39.6, 48.5, 123.7, 125.7, 126.7, 127.5, 128.0(9), 128.1(4), 130.7, 137.4, 139.2, 143.9, 209.1; ESIHRMS: Found: m/z 279.1751. Calcd for $C_{20}H_{23}O$: $(M+H)^+$ 279.1749.

(1-cinnamylcyclohexyl)(phenyl)methanone (**4-3q**)



82% yield from cyclohexyl(phenyl)methanone with cinnamyl bromide; yellow oil; IR (NaCl) 3059, 3026, 1666 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26-1.38 (3H, m), 1.47-1.58 (5H, m), 2.23-2.27 (2H, m), 2.69 (2H, dd, $J = 1.0, 7.5$ Hz), 6.10 (1H, dt, $J = 7.5, 15.7$ Hz), 6.37 (1H, d, $J = 15.7$ Hz), 7.16-7.20 (1H, m), 7.24-7.30 (4H, m), 7.36-7.40 (2H, m), 7.42-7.46 (1H, m), 7.62-7.64 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 25.8, 34.3, 42.4, 52.8, 125.2, 126.1, 127.2, 127.3, 128.1, 128.4, 130.5, 133.1, 137.2, 140.1, 209.0; ESIHRMS: Found: m/z 305.1905. Calcd for $C_{22}H_{25}O$: $(M+H)^+$ 305.1905.

4.5.2.3. Preparation of (*E*)-4,4-dimethyl-1-phenyldeca-1,9-dien-5-one (4-3u): Method C



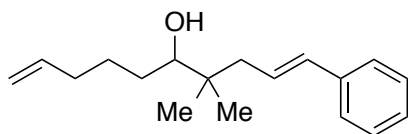
Synthesis of alcohol 4-5u: To a 2-neck round bottom flask containing (*E*)-2,2-dimethyl-5-phenylpent-4-enenitrile (**4-4a**) (572 mg, 3.09 mmol) in dry CH₂Cl₂ (30.0 mL) cooled to 0 °C was added dropwise DIBAL (0.60 mL, 3.37 mmol). The solution was stirred at rt for 1 h. Upon completion of the reaction, the solution was cooled 0 °C and aqueous 6 N HCl (20 mL) was added dropwise. The reaction was allowed to warm to rt and stirred for another 1 h. The mixture was extracted three times with CH₂Cl₂. The combined organic extracts were washed with brine. After drying with MgSO₄ and removal of the solvents under reduced pressure, the resulting crude material including the corresponding aldehyde was used for the next step without further purification.

To a 2-neck round bottom flask containing the above-obtained aldehyde in dry THF (10 mL) at 0 °C was added a THF solution of pent-4-en-1-ylmagnesium bromide [prepared from 5-bromopentene (0.6 mL, 5.07 mmol) and freshly polished magnesium (150 mg, 6.17 mmol) in dry THF (15 mL)]. The solution was stirred at rt for 4 h. Upon completion of the reaction, the solution was cooled to 0 °C. The reaction was quenched by adding aqueous 1N HCl (20 mL), and the mixture was extracted three times with ethyl acetate. The combined organic extracts were washed with NaHCO₃ and brine. After drying with MgSO₄ and removal of the solvents under reduced pressure, the resulting crude material was purified by flash column chromatography (hexane:ethyl acetate = 9:1) to yield (*E*)-4,4-dimethyl-1-phenyldeca-1,9-dien-5-ol (**4-5u**) (383 mg, 1.48 mmol, 48 % yield).

over 2 steps).

Synthesis of ketone 4-3u: To a 2-neck round bottom flask containing oxalyl chloride (0.20 mL, 2.36 mmol) in dry CH₂Cl₂ (20 mL) was added dropwise DMSO (0.40 mL, 5.63 mmol) at –78 °C. The solution was stirred at –78 °C for 30 min. To the mixture was added dropwise a solution of alcohol **4-5u** in CH₂Cl₂ (5 mL) and the solution was stirred at –78 °C for 1 h. To the solution, triethylamine (1.4 mL, 10.0 mmol) was added dropwise and the solution was further stirred at room temperature for 1 h. The solution was then cooled 0 °C. The reaction was quenched by adding saturated aqueous NH₄Cl (20 mL), and the mixture was extracted three times with CH₂Cl₂. The combined organic extracts were washed with water and brine. After drying with MgSO₄ and removal of the solvents under reduced pressure, the resulting crude material was used for the next step for the synthesis of oxime without further purification.

(*E*)-4,4-dimethyl-1-phenyldeca-1,9-dien-5-ol (**4-5u**)

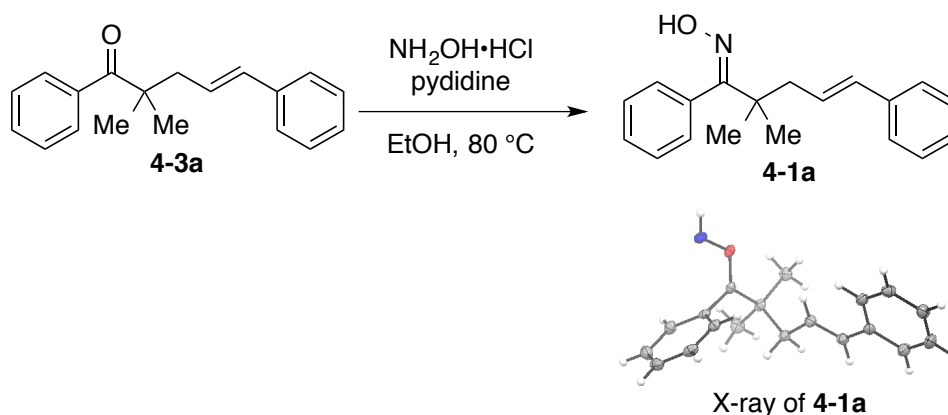


48 % yield (2 steps); Colorless oil; IR (NaCl) 3416, 2959, 2943, 1639, 1470 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.92 (3H, s), 0.97 (3H, s), 1.26-1.60 (4H, m), 1.63-1.71 (1H, m), 2.04-2.16 (3H, m), 2.28 (1H, dd, *J* = 7.6, 13.6 Hz), 3.31 (1H, d, *J* = 9.6 Hz), 4.94-5.03 (2H, m), 5.82 (1H, ddt, *J* = 6.7, 10.3, 17.2 Hz), 6.27 (1H, dt, *J* = 7.6, 15.6 Hz), 6.4 (1H, d, *J* = 15.6 Hz), 7.20 (1H, t, *J* = 7.2 Hz), 7.29 (2H, t, *J* = 7.2 Hz), 7.35 (2H, d, *J* = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 22.9, 23.6, 26.5, 30.9, 33.9, 38.3, 43.0, 78.7, 114.8, 126.2, 127.2, 127.6, 128.7, 132.5, 138.0, 139.0; EIHRMS: Found: *m/z* 259.2061. Calcd for C₁₈H₂₇O: (M+H)⁺ 259.2062.

4.5.2.4. Synthesis of ketoximes 4-1

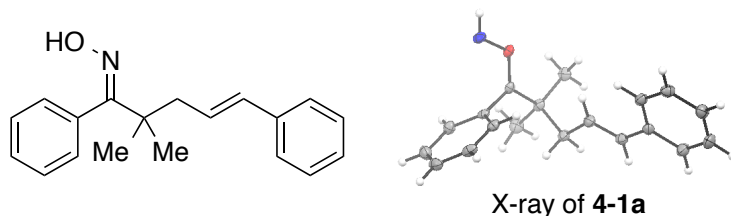
Synthesis of oximes 4-1a-h, k-v: these oximes **4-1** were synthesized *via* condensation of ketones **4-3** with hydroxylamine hydrochloride in the presence of pyridine.

Typical Procedure for Synthesis of Alkenyl ketoximes 1: (1*Z*,4*E*)-2,2-dimethyl-1,5-diphenylpent-4-en-1-one oxime (4-1a**)**



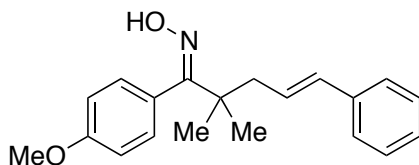
To a 2-neck round bottom flask containing ketone **4-3a** (700 mg, 2.65 mmol) in EtOH (10 mL) and pyridine (4.0 mL) was added hydroxylamine hydrochloride (368 mg, 5.30 mmol) and the solution was stirred at 80 °C. Upon completion of the reaction, the solution was cooled to room temperature. EtOH and pyridine were removed under reduced pressure and the resulting crude material was dissolved in ethyl acetate (20.0 mL) and washed with water and brine. After drying with MgSO₄ and removal of the solvents under reduced pressure, the resulting crude material was purified by flash column chromatography (hexane:ethyl acetate = 10:1) to yield (1*Z*, 4*E*)-2,2-Dimethyl-1,5-diphenylpent-4-en-1-one oxime (**4-1a**) (600 mg, 2.15 mmol, 81 % yield).

(1*Z*, 4*E*)-2,2-Dimethyl-1,5-diphenylpent-4-en-1-one oxime (**4-1a**)³⁵



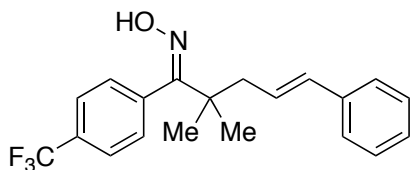
¹H NMR (400 MHz, CDCl₃) δ 1.18 (6H, s), 2.40 (2H, d, *J* = 7.2 Hz), 6.26 (1H, dt, *J* = 7.2, 15.8 Hz), 6.40 (1H, d, *J* = 15.8 Hz), 7.14 (2H, d, *J* = 7.6 Hz), 7.21 (1H, t, *J* = 7.4 Hz), 7.30 (2H, t, *J* = 7.3 Hz), 7.35-7.45 (6H, m); ¹³C NMR (100 MHz, CDCl₃) δ 26.0, 40.8, 43.6, 126.1, 126.4, 127.1, 127.7, 128.0, 128.1, 128.5, 133.0, 133.4, 137.6, 165.6.

(1Z, 4E)-1-(4-methoxyphenyl)-2,2-dimethyl-5-phenylpent-4-en-1-one oxime (**4-1b**)



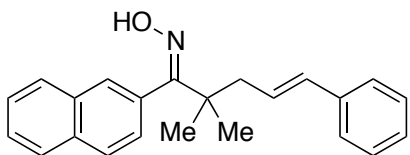
93% yield; White solid; mp. 155-156 °C; IR (NaCl) 3291, 3244, 1609, 1215, 1173, 934 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.18 (6H, s), 2.38 (2H, d, $J = 7.2$ Hz), 3.83 (3H, s), 6.24 (1H, dt, $J = 7.2, 15.6$ Hz), 6.38 (1H, d, $J = 15.6$ Hz), 6.95-9.68 (2H, m), 7.05-7.08 (2H, m), 7.21-7.23 (1H, m), 7.28-7.36 (4H, m), 7.45 (1H, s); ^{13}C NMR (100 MHz, CDCl_3): δ 26.3, 41.1, 43.9, 55.4, 113.9, 125.5, 126.4, 126.9, 127.3, 128.7, 129.3, 133.0, 137.9, 159.5, 165.9; EIHRMS: Found: m/z 310.1808. Calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_2$: $(\text{M}+\text{H})^+$ 310.1807.

(1Z, 4E)-2,2-Dimethyl-5-phenyl-1-(4-(trifluoromethyl)phenyl)pent-4-en-1-one oxime (**4-1c**)



65% yield; white solid; mp. 129-130 °C; IR (NaCl) 3393, 3368, 1616, 1325, 1215 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.18 (6H, s), 2.37 (2H, dd, $J = 0.9, 7.2$ Hz), 6.21 (1H, dt, $J = 7.2, 15.8$ Hz), 6.39 (1H, d, $J = 15.8$ Hz), 7.20-7.36 (7H, m), 7.68 (2H, d, $J = 8.0$ Hz), 8.27 (1H, br); ^{13}C NMR (100 MHz, CDCl_3) δ 26.0, 40.7, 43.6, 124.0 (q, $^1J_{\text{C-F}} = 270.5$ Hz), 125.1 (q, $^3J_{\text{C-F}} = 3.6$ Hz), 125.9, 126.1, 127.2, 128.2, 128.5, 130.3 (q, $^2J_{\text{C-F}} = 32.3$ Hz), 133.3, 137.3(8), 137.4(3), 164.7; ESIHRMS: Found: m/z 348.1576. Calcd for $\text{C}_{20}\text{H}_{21}\text{NOF}_3$: $(\text{M}+\text{H})^+$ 348.1575.

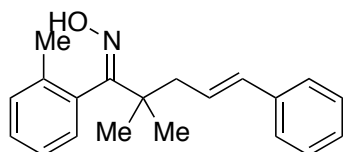
(1Z, 4E)-2,2-dimethyl-1-(naphthalen-2-yl)-5-phenylpent-4-en-1-one oxime (**4-1d**)



52 % yield; White solid; mp. 167-168 °C; IR (NaCl) 3391, 3383, 1636 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.23 (6H, s), 2.43 (2H, d, $J = 7.1$ Hz), 6.28 (1H, dt, $J =$

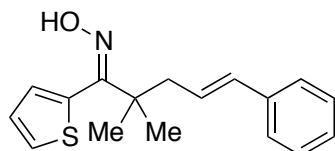
7.1, 15.8 Hz), 6.39 (1H, d, $J = 15.8$ Hz), 7.21-7.32 (5H, m), 7.36 (1H, d, $J = 7.2$ Hz), 7.49-7.51 (2H, m), 7.63 (1H, s), 7.85-7.91 (3H, m), 8.34 (1H, br); ^{13}C NMR (100 MHz, CDCl_3): δ 26.2, 41.3, 43.9, 126.2, 126.3, 126.4(7), 126.5(2), 126.6, 126.8, 127.3, 127.9, 128.0, 128.4, 128.7 (overlapped), 131.3, 133.0, 133.3, 137.8, 165.8; EIHRMS: Found: m/z 330.1850. Calcd for $\text{C}_{23}\text{H}_{24}\text{NO}$: $(\text{M}+\text{H})^+$ 330.1858.

(1Z, 4E)-2,2-dimethyl-5-phenyl-1-(*o*-tolyl)pent-4-en-1-one oxime (**4-1e**)



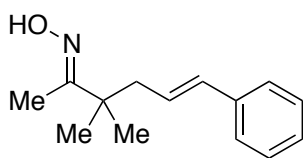
51% yield (pyridine as solvent, reflux); White solid; mp. 94-95 °C; IR (NaCl) 3308, 1647 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.14 (3H, s), 1.17 (3H, s), 2.24 (3H, s), 2.40 (1H, dd, $J = 7.6, 13.8$ Hz), 2.54 (1H, dd, $J = 7.6, 13.8$ Hz), 6.26 (1H, dt, $J = 7.6, 15.6$ Hz), 6.38 (1H, d, $J = 15.6$ Hz), 7.05 (1H, d, $J = 7.2$ Hz), 7.19-7.33 (8H, m), 8.76 (1H, br); ^{13}C NMR (100 MHz, CDCl_3): δ 20.4, 25.8, 26.7, 41.4, 44.1, 125.5, 126.3, 126.4, 126.9, 127.2, 128.4, 128.7, 130.2, 133.3, 133.7, 136.1, 137.8, 165.1; EIHRMS: Found: m/z 294.1857. Calcd for $\text{C}_{20}\text{H}_{24}\text{NO}$: $(\text{M}+\text{H})^+$ 294.1858.

(1Z, 4E)-2,2-dimethyl-5-phenyl-1-(thiophen-2-yl)pent-4-en-1-one oxime (**4-1f**)



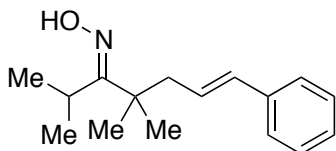
71 % yield; Yellow solid; mp. 119-120 °C; IR (NaCl) 3418, 3389, 1645 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.26 (6H, s), 2.45 (2H, d, $J = 7.3$ Hz), 6.16 (1H, dt, $J = 7.3, 15.6$ Hz), 6.36 (1H, d, $J = 15.6$ Hz), 7.11-7.12 (2H, m), 7.19-7.23 (1H, m), 7.26-7.34 (4H, m), 7.45-7.47 (1H, m), 8.91 (1H, br); ^{13}C NMR (100 MHz, CDCl_3): δ 26.5, 41.6, 44.1, 126.3(9), 126.3(8), 126.6, 127.1, 127.3, 128.3, 128.7, 130.8, 133.2, 137.8, 159.0; EIHRMS: Found: m/z 286.1266. Calcd for $\text{C}_{17}\text{H}_{20}\text{NOS}$: $(\text{M}+\text{H})^+$ 286.1266.

(2*E*, 5*E*)-3,3-dimethyl-6-phenylhex-5-en-2-one oxime (**4-1g**)



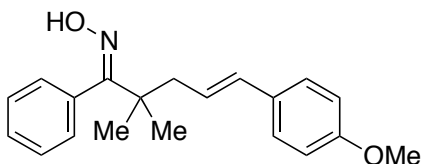
93 % yield; White solid; mp. 102-103 °C; IR (NaCl) 3362, 3325, 1659 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.16 (6H, s), 1.89 (3H, s), 2.36 (2H, dd, $J = 1.1, 7.4$ Hz), 6.10 (1H, dt, $J = 7.4, 15.6$ Hz), 6.38 (1H, d, $J = 15.6$ Hz), 7.17-7.21 (1H, m), 7.26-7.34 (4H, m), 8.49 (1H, br); ^{13}C NMR (100 MHz, CDCl_3): δ 10.4, 25.5, 41.0, 43.9, 126.3, 126.6, 127.3, 128.7, 132.8, 137.8, 163.5; EIHRMS: Found: m/z 218.1546. Calcd for $\text{C}_{14}\text{H}_{20}\text{NO}$: $(\text{M}+\text{H})^+$ 218.1545.

(3*E*, 6*E*)-2,4,4-trimethyl-7-phenylhept-6-en-3-one oxime (**4-1h**)



72% yield; white solid; mp. 124-125 °C; IR (NaCl) 3445, 3420, 1636 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.14 (6H, s), 1.34 (6H, d, $J = 7.0$ Hz), 2.38 (2H, dd, $J = 1.0, 7.3$ Hz), 2.64 (1H, septet, $J = 7.0$ Hz), 6.17 (1H, dt, $J = 7.3, 15.8$ Hz), 6.40 (1H, d, $J = 15.8$ Hz), 7.17-7.21 (1H, m), 7.25-7.30 (2H, m), 7.33-7.35 (2H, m), 8.24 (1H, br); ^{13}C NMR (100 MHz, CDCl_3) δ 18.5, 25.2, 29.5, 41.6, 43.2, 126.1, 127.0, 128.5, 132.5, 137.7, 168.1; ESIHRMS: Found: m/z 246.1858. Calcd for $\text{C}_{16}\text{H}_{24}\text{NO}$: $(\text{M}+\text{H})^+$ 246.1858.

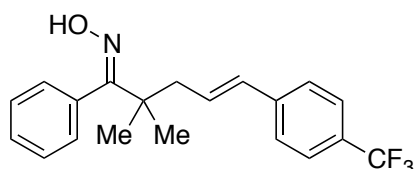
(1*Z*, 4*E*)-5-(4-Methoxyphenyl)-2,2-dimethyl-1-phenylpent-4-en-1-one oxime (**4-1k**)



83% yield; white solid; mp. 142-143 °C; IR (NaCl) 3383, 3364, 1607, 1215 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.17 (6H, s), 2.36 (2H, dd, $J = 1.1, 7.3$ Hz), 3.80 (3H, s), 6.09 (1H, dt, $J = 7.3, 15.8$ Hz), 6.32 (1H, d, $J = 15.8$ Hz), 6.82-6.86 (2H, m), 7.13-7.15 (2H, m), 7.26-7.30 (2H, m), 7.35-7.45 (3H, m), 7.97 (1H, s); ^{13}C

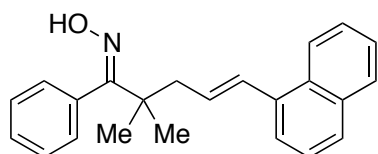
NMR (100 MHz, CDCl₃) δ 26.0, 40.8, 43.6, 55.3, 113.9, 124.2, 127.2, 127.7, 128.0, 128.1, 130.5, 132.3, 133.5, 158.8, 165.8; ESIHRMS: Found: m/z 310.1809. Calcd for C₂₀H₂₄NO₂: (M+H)⁺ 310.1807.

(1*Z*, 4*E*)-2,2-Dimethyl-1-phenyl-5-(4-(trifluoromethyl)phenyl)pent-4-en-1-one oxime (**4-1l**)



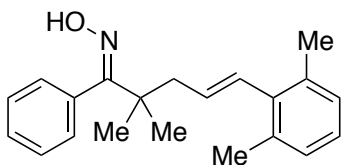
96% yield; white solid; mp. 138-139 °C; IR (NaCl) 3290, 3269, 1614, 1325, 1215 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.18 (6H, s), 2.42 (2H, d, J = 6.5 Hz), 6.31-6.44 (2H, m), 7.12-7.14 (2H, m), 7.36-7.46 (5H, m), 7.54 (2H, d, J = 8.2 Hz), 8.10 (1H, br); ¹³C NMR (100 MHz, CDCl₃) δ 26.1, 40.7, 43.6, 124.3 (q, ¹J_{C-F} = 270.0 Hz), 125.4 (q, ³J_{C-F} = 3.6 Hz), 126.2, 127.7, 128.0, 128.9 (q, ²J_{C-F} = 32.2 Hz), 129.5, 130.0, 131.7, 133.3, 140.9(8), 140.9(9), 165.5; ESIHRMS: Found: m/z 348.1576. Calcd for C₂₀H₂₁NOF₃: (M+H)⁺ 348.1575.

(1*Z*, 4*E*)-2,2-Dimethyl-5-(naphthalene-1-yl)-1-phenylpent-4-en-1-one oxime (**4-1m**)



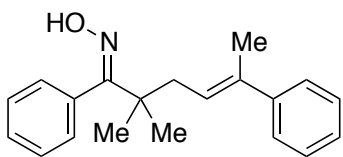
87% yield; white solid; mp. 141-142 °C; IR (NaCl) 3393, 1653, 1215 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.24 (6H, s), 2.52 (2H, dd, J = 1.3, 7.4 Hz), 6.27 (1H, dt, J = 7.4, 15.6 Hz), 7.13 (1H, d, J = 15.6 Hz), 7.16-7.18 (2H, m), 7.36-7.52 (6H, m), 7.56 (1H, d, J = 7.1 Hz), 7.68 (1H, s), 7.75 (1H, d, J = 8.2 Hz), 7.83-7.85 (1H, m), 8.08-8.11 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ 26.1, 40.8, 44.0, 123.8, 123.9, 125.6, 125.7, 125.9, 127.5, 127.7, 128.0(9), 128.1(4), 128.5, 130.0, 130.3, 131.1, 133.4, 133.6, 135.5, 165.8; ESIHRMS: Found: m/z 330.1857. Calcd for C₂₃H₂₄NO: (M+H)⁺ 330.1858.

(1Z, 4E)-5-(2,6-Dimethylphenyl)-2,2-dimethyl-1-phenylpent-4-en-1-one oxime (**4-1n**)



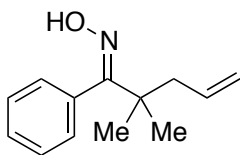
92% yield; white solid; mp. 132-133 °C; IR (NaCl) 3304, 3296, 1418, 1215 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.19 (6H, s), 2.29 (6H, s), 2.41 (2H, dd, $J = 1.3, 7.2$ Hz), 5.72 (1H, dt, $J = 7.2, 16.1$ Hz), 6.35 (1H, d, $J = 16.1$ Hz), 7.00-7.06 (3H, m), 7.13-7.16 (2H, m), 7.35-7.45 (3H, m), 8.23 (1H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 21.1, 26.0, 40.6, 44.1, 126.3, 127.6, 127.7, 128.0, 128.1, 130.6, 131.4, 133.5, 135.9, 137.5, 165.4; ESIHRMS: Found: m/z 308.2013. Calcd for $\text{C}_{21}\text{H}_{26}\text{NO}$: $(\text{M}+\text{H})^+$ 308.2014.

(1Z, 4E)- 2,2-Dimethyl-1,5-diphenylhex-4-en-1-one oxime (**4-1o**)



81% yield; white solid; mp. 105-106 °C; IR (NaCl) 3385, 1653, 941 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.21 (6H, s), 1.98 (3H, d, $J = 1.0$ Hz), 2.35 (2H, d, $J = 7.0$ Hz), 5.86 (1H, dt, $J = 1.0, 7.0$ Hz), 7.11-7.13 (2H, m), 7.21-7.25 (1H, m), 7.29-7.33 (2H, m), 7.34-7.44 (5H, m), 7.67 (1H, br); ^{13}C NMR (100 MHz, CDCl_3) δ 16.3, 26.0, 39.0, 41.1, 124.3, 125.8, 126.7, 127.7, 128.0, 128.1, 128.2, 133.4, 136.8, 144.0, 165.8; ESIHRMS: Found: m/z 294.1859. Calcd for $\text{C}_{20}\text{H}_{24}\text{NO}$: $(\text{M}+\text{H})^+$ 294.1858.

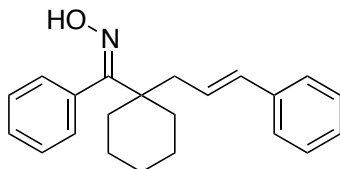
(Z)- 2,2-Dimethyl-1- phenylpent-4-en-1-one oxime (**4-1p**)³⁵



85 % yield; ^1H NMR (400 MHz, CDCl_3) δ 1.12 (6H, s), 2.21 (2H, d, $J = 7.1$ Hz), 5.05 (2H, dd, $J = 10.2, 15.2$ Hz), 5.78-5.89 (1H, m), 7.13 (2H, d, $J = 7.4$ Hz), 7.35-

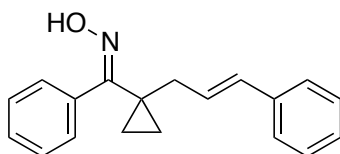
7.44 (3H, m), 8.52 (1H, br); ^{13}C NMR (100 MHz, CDCl_3) δ 25.8, 40.2, 44.3, 117.8, 127.7, 128.0(0), 128.0(5), 133.4, 134.6, 165.5.

(Z)-(1-cinnamylcyclohexyl)(phenyl)methanone oxime (**4-1q**)



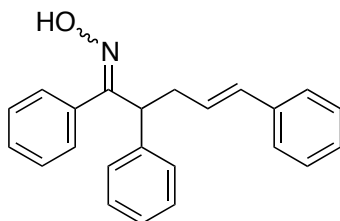
82% yield; white solid; mp. 153-153 °C; IR (NaCl) 3383, 3366, 1645 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.26-1.59 (8H, m), 1.76-1.81 (2H, m), 2.42 (2H, dd, J = 0.9, 7.1 Hz), 6.26 (1H, dt, J = 7.1, 15.8 Hz), 6.43 (1H, d, J = 15.8 Hz), 7.16-7.23 (3H, m), 7.27-7.30 (2H, m), 7.34-7.43 (5H, m), 8.22 (1H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 22.2, 26.0, 33.8, 40.6, 44.1, 126.1, 126.2, 127.0, 127.7, 128.0, 128.1, 128.5, 132.6, 133.3, 137.7, 163.8; ESIHRMS: Found: m/z 320.2017. Calcd for $\text{C}_{22}\text{H}_{26}\text{NO}$: $(\text{M}+\text{H})^+$ 320.2014.

(Z)-(1-cinnamylcyclopropyl)(phenyl)methanone oxime (**4-1r**)



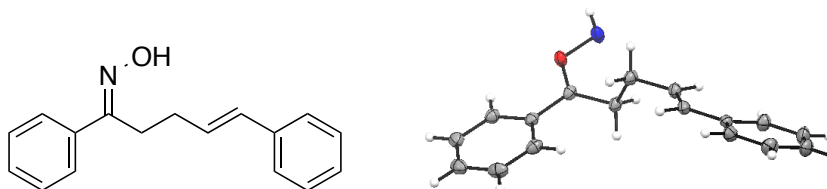
51% yield along with the formation of *E(syn)*-oxime in 38% yield; White solid; mp. 115-116 °C; IR (NaCl) 3308, 3296, 1495 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 0.71 (2H, br), 1.03 (2H, br), 2.27 (2H, d, J = 6.5 Hz), 6.10 (1H, dt, J = 6.5, 16.0 Hz), 6.21 (1H, d, J = 16.0 Hz), 7.15-7.20 (1H, m), 7.23-7.29 (4H, m), 7.36-7.40 (5H, m), 8.85 (1H, br); ^{13}C NMR (100 MHz, CDCl_3): δ 11.6, 24.8, 39.1, 126.3, 127.2, 127.3, 128.3, 128.4, 128.6, 128.9, 132.0, 133.1, 137.8, 160.7; EIHRMS: Found: m/z 278.1546. Calcd for $\text{C}_{19}\text{H}_{20}\text{NO}$: $(\text{M}+\text{H})^+$ 278.1545.

(4E)-1,2,5-triphenylpent-4-en-1-one oxime (**4-1s**)



84% yield from (*E*)-1,2,5-triphenylpent-4-en-1-one⁵⁵ (isolated as an inseparable 1:1 *syn/anti* oxime isomers); White solid; mp. 108-109 °C; IR (NaCl) 3252, 1615, 970 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.70-2.78 (1H, 1H x 1, m), 2.81-3.02 (3H, 2H x 1, 1H x 1, m), 3.93 (1H, 1H x 1, t, *J* = 7.6 Hz), 5.16 (1H, 1H x 1, t, *J* = 7.6 Hz), 6.14-6.21 (2H, 1H x 1, 1H x 1, m), 6.32 (1H, 1H x 1, d, *J* = 16.0 Hz), 6.41 (1H, 1H x 1, d, *J* = 15.6 Hz), 7.05-7.06 (2H, m), 7.16-7.34 (26H, 13H x 1, 10H x 1, m), 7.40 (2H, d, *J* = 7.6 Hz), 8.56 (1H, 1H x 1, br), 9.16 (1H, 1H x 1, br); ¹³C NMR (100 MHz, CDCl₃): δ 34.2, 36.8, 42.5, 52.5, 126.3, 126.3, 126.9, 127.2, 127.3, 127.8, 127.9, 128.1, 128.1(9), 128.2(4), 128.3, 128.6, 128.7, 128.8, 129.0, 132.1, 132.2, 133.8, 135.6, 137.8, 139.9, 140.2, 160.2, 161.4; EIHRMS: Found: *m/z* 328.1702. Calcd for C₂₃H₂₂NO: (M+H)⁺ 328.1701.

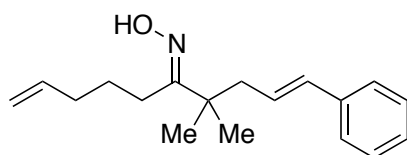
(1*E*, 4*E*)-1,5-Diphenylpent-4-en-1-one oxime (**4-1t**)



X-ray of **4-1t**

83% yield from (*E*)-1,5-diphenylpent-4-en-1-one (**4-3t**);⁵⁶ colourless crystals (CCDC 961674); mp. 96-97 °C; IR (NaCl) 3333, 3308, 1597 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.51 (2H, ddd, *J* = 7.7, 7.7, 7.7 Hz), 2.99 (2H, dd, *J* = 7.7, 7.7 Hz), 6.24 (1H, dt, *J* = 7.7, 15.8 Hz), 6.41 (1H, d, *J* = 15.8 Hz), 7.17-7.21 (1H, m), 7.25-7.32 (4H, m), 7.37-7.41 (3H, m), 7.62-7.64 (2H, m), 8.12 (1H, br); ¹³C NMR (100 MHz, CDCl₃) δ 26.1, 29.7, 126.0, 126.4, 127.0, 128.5, 128.6, 129.2, 129.3, 130.6, 135.6, 137.5, 159.1; ESIHRMS: Found: *m/z* 252.184. Calcd for C₁₇H₁₈NO: (M+H)⁺ 252.1388.

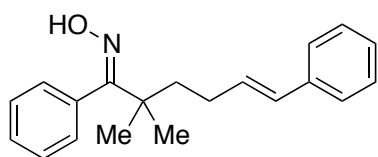
(1*E*,5*E*)-4,4-dimethyl-1-phenyldeca-1,9-dien-5-one oxime (**4-1u**)



72 % yield (2 steps); White solid; mp. 57-58 °C; IR (NaCl) 3308, 3271, 3026, 2968, 1639, 916 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.15 (6H, s), 1.65-1.73 (2H,

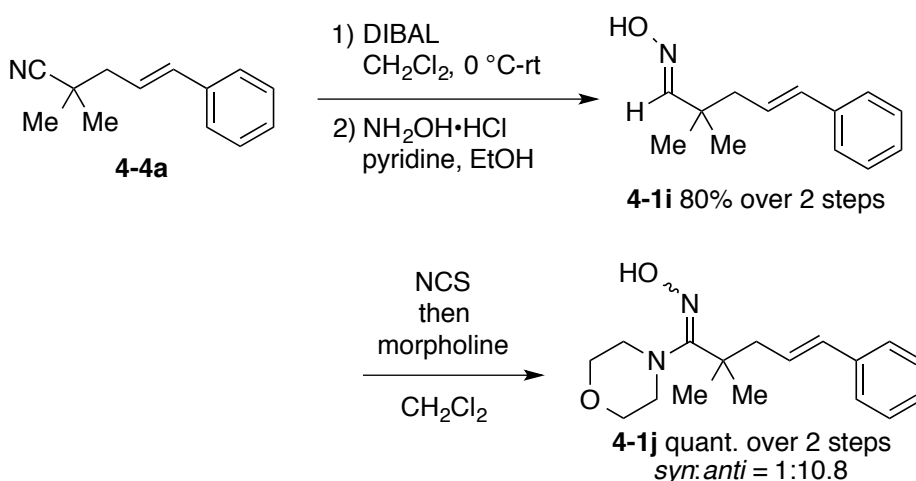
m), 2.11-2.16 (2H, m), 2.28-2.32 (2H, m), 2.36 (2H, d, $J = 7.3$ Hz), 5.01 (2H, m), 5.82 (1H, ddt, $J = 6.7, 10.3, 17.0$ Hz), 6.12 (1H, dt, $J = 7.3, 15.6$ Hz), 6.38 (1H, d, $J = 15.6$ Hz), 7.19 (1H, t, $J = 7.1$ Hz), 7.25-7.34 (4H, m), 8.36 (1H, br); ^{13}C NMR (100 MHz, CDCl_3): δ 25.6 (overlapped), 25.8, 34.7, 41.2, 44.0, 115.2, 126.3, 126.9, 127.2, 128.7, 132.8, 137.8, 138.5, 166.5; EIHRMS: Found: m/z 272.2014. Calcd for $\text{C}_{18}\text{H}_{26}\text{NO}$: $(\text{M}+\text{H})^+$ 272.2014.

(1*Z*, 5*E*)-2,2-dimethyl-1,6-diphenylhex-5-en-1-one oxime (**4-1v**)



82 % yield; White solid; mp. 109-110 °C; IR (NaCl) 3271, 3265, 1647, 941 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.77 (6H, s), 1.59-1.63 (2H, m), 2.26-2.32 (2H, m), 6.19 (1H, dt, $J = 6.8, 15.6$ Hz), 6.34 (1H, d, $J = 15.6$ Hz), 7.12 (2H, d, $J = 6.8$ Hz), 7.19 (1H, t, $J = 6.8$ Hz), 7.25-7.44 (7H, m), 7.72 (1H, br); ^{13}C NMR (100 MHz, CDCl_3): δ 26.3, 28.5, 39.7, 40.7, 126.1, 127.0, 127.7, 128.2, 128.3, 128.7, 130.0, 130.7, 130.8, 137.9, 165.3; EIHRMS: Found: m/z 294.1857. Calcd for $\text{C}_{20}\text{H}_{24}\text{NO}$: $(\text{M}+\text{H})^+$ 294.1858.

4.5.2.5. Synthesis of aldoxime 4-1i and amidoxime 4-1j



Synthesis of aldoxime 4-1i: To a 2-neck round bottom flask containing (*E*)-2,2-dimethyl-5-phenylpent-4-enenitrile (**4-4a**) (572 mg, 3.09 mmol) in dry CH_2Cl_2 (30.0 mL) cooled to 0 °C was added dropwise DIBAL (0.60 mL, 3.37 mmol). The

solution was stirred at room temperature for 1 h. Upon completion of the reaction, the solution was cooled 0 °C and aqueous 6N HCl (20 mL) was added dropwise. The reaction was allowed to warm to room temperature and stirred for another 1 h. The mixture was extracted three times with CH₂Cl₂. The combined organic extracts were washed with brine. After drying with MgSO₄ and removal of the solvents under reduced pressure, the resulting crude material including the corresponding aldehyde was used for the next step without further purification.

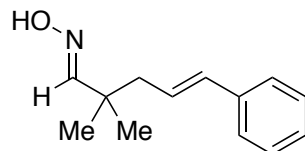
To a 2-neck round bottom flask containing the above-obtained crude materials in EtOH (20.0 mL) and pyridine (5.0 mL) was added hydroxylamine hydrochloride (322 mg, 4.63 mmol) and the solution was stirred at room temperature for 3 h. Upon completion of the reaction, EtOH and pyridine were removed under reduced pressure and the resulting crude material was dissolved in ethyl acetate (20 mL) and washed with water and brine. After drying with MgSO₄ and removal of the solvents under reduced pressure, the resulting crude material was purified by flash column chromatography (hexane:ethyl acetate = 9:1) to yield (1*E*, 4*E*)-2,2-dimethyl-5-phenylpent-4-enal oxime (**4-1i**) (502 mg, 2.47 mmol, 80 % yield over 2 steps).

Synthesis of amidoxime 4-1j: To a 2-neck round bottom flask containing (1*E*, 4*E*)-2,2-dimethyl-5-phenylpent-4-enal oxime (**4-1i**) (486 mg, 2.39 mmol) in dry CH₂Cl₂ (20 mL) was added NCS (329 mg, 2.46 mmol). The solution was stirred at 40 °C for 2 h. Upon completion of the reaction, the solution was cooled to room temperature. The organic materials were washed with water and brine. After drying with MgSO₄ and removal of the solvents under reduced pressure, the resulting crude material including the corresponding chloro-oxime was used for the next step without further purification.

To a 2-neck round bottom flask containing the above-obtained chloro-oxime in dry CH₂Cl₂ (20 mL) was added morpholine (0.50 mL, 5.72 mmol) and triethylamine (1.0 mL, 7.17 mmol). The solution was stirred at 30 °C for 17 h. Upon completion of the reaction, the solution was cooled to rt. The organic materials were washed with water and brine. After drying with MgSO₄ and removal of the solvents under reduced pressure, the resulting crude material was purified by flash column chromatography (hexane:ethyl acetate = 9:1) to yield

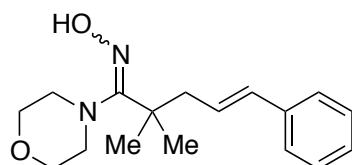
(1*Z*,4*E*)-2,2-dimethyl-1-morpholino-5-phenylpent-4-en-1-one oxime (**4-1j**) (1.00 g, 3.48 mmol, quantitative yield over 2 steps, *syn:anti* = 1:10.8).

(1*E*,4*E*)-2,2-dimethyl-5-phenylpent-4-enal oxime (**4-1i**)⁵⁷



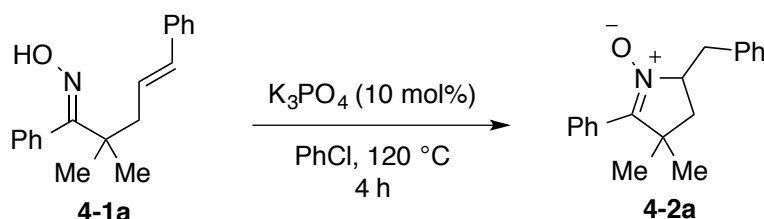
¹H NMR (400 MHz, CDCl₃): δ 1.14 (6H, s), 2.32 (2H, dd, *J* = 1.1, 7.5 Hz), 6.18 (1H, dt, *J* = 7.6, 15.6 Hz), 6.40 (1H, d, *J* = 15.6 Hz), 7.21-7.23 (1H, m), 7.26-7.36 (4H, m), 7.40 (1H, s), 7.41 (1H, br); ¹³C-NMR (100 MHz, CDCl₃): δ 25.4, 37.4, 44.6, 125.9, 126.4, 127.4, 128.7, 133.4, 137.6, 158.9.

(1*Z*,4*E*)-2,2-dimethyl-1-morpholino-5-phenylpent-4-en-1-one oxime (**4-1j**)



(isolated as an inseparable 1:11 *syn/anti*-mixture); Data for the major isomer; Yellow solid; mp. 110-111 °C; IR (NaCl) 3287, 3242, 1257, 1215 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.20 (6H, s), 2.44 (2H, dd, *J* = 0.8, 7.2 Hz), 3.18 (4H, t, *J* = 4.6 Hz), 3.72 (4H, t, *J* = 4.6 Hz), 6.18 (1H, dt, *J* = 7.2, 16.0 Hz), 6.39 (1H, d, *J* = 16.0 Hz), 7.18-7.22 (1H, m), 7.25-7.35 (4H, m), 8.38 (1H, br); ¹³C NMR (100 MHz, CDCl₃): δ 26.0, 42.4, 44.1, 49.4, 67.8, 126.3, 127.1, 127.3, 128.7, 132.8, 137.8, 162.8; EIHRMS: Found: *m/z* 289.1917. Calcd for C₁₇H₂₅N₂O₂: (M+H)⁺ 289.1916.

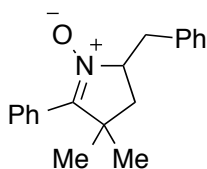
4.5.3. Typical procedure for K₃PO₄-Mediated hydroamination of alkenyl ketoximes 4-1



To a 25 mL schlenk tube containing (1*Z*,4*E*)-2,2-dimethyl-1,5-diphenylpent-4-en-1-one oxime (**4-1a**) (55.9 mg, 0.200 mmol) in PhCl (2.0 mL) was added K₃PO₄ (4.2 mg, 0.020 mmol) and the solution was stirred at 120 °C for 4 h. Upon completion of the reaction, the solution was cooled to room temperature. The solvent was removed under reduced pressure* and the resulting crude material was purified by flash column chromatography (hexane:ethyl acetate:triethylamine = 4:1:0.25) to yield 2-benzyl-4,4-dimethyl-5-phenyl-3,4-dihydro-2*H*-pyrrole 1-oxide (**4-2a**) (54.7 mg, 0.196 mmol) in 98 % yield.

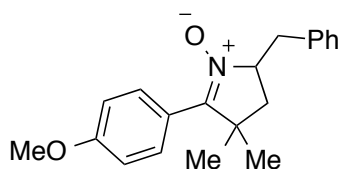
(*When the reactions were conducted using 40 mol% or 100 mol% of K₃PO₄, the inorganic salts were removed through Celite filtration prior to removal of the solvent in vacuo.)

2-benzyl-4,4-dimethyl-5-phenyl-3,4-dihydro-2*H*-pyrrole 1-oxide (**4-2a**)



White solid; mp. 116-117 °C; IR (NaCl) 1575, 1533 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.09 (3H, s), 1.31 (3H, s), 1.80 (1H, dd, *J* = 8.5, 12.9 Hz), 2.04 (1H, dd, *J* = 8.1, 12.9 Hz), 3.16 (1H, dd, *J* = 8.4, 13.6 Hz), 3.53 (1H, dd, *J* = 3.9, 13.6 Hz), 4.43 (1H, dddd, *J* = 3.9, 8.1, 8.4, 8.5 Hz), 7.25-7.35 (5H, m), 7.39-7.46 (3H, m), 7.81-7.84 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ 27.4, 27.9, 38.1, 40.1, 42.9, 71.6, 126.8, 128.2(8), 128.3, 128.5, 129.1, 129.4, 129.7, 136.8, 148.4; ESIHRMS: Found: *m/z* 280.1701. Calcd for C₁₉H₂₂NO: (M+H)⁺ 280.1701.

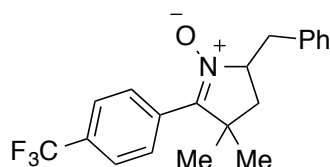
2-benzyl -5-(4-methoxyphenyl)-4,4-dimethyl-3,4-dihydro-2*H*-pyrrole 1-oxide (**4-2b**)



96% yield; white solid; mp. 131-132 °C; IR (NaCl) 1605, 1510, 1254 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.14 (3H, s), 1.33 (3H, s), 1.77 (1H, dd, *J* = 8.6, 12.8 Hz), 2.00 (1H, dd, *J* = 8.0, 12.8 Hz), 3.11 (1H, dd, *J* = 8.6, 13.6 Hz), 3.56 (1H, dd, *J* = 3.9, 13.6 Hz), 4.40 (1H, dddd, *J* = 3.9, 8.0, 8.6, 8.6 Hz), 6.94-6.98 (2H, m),

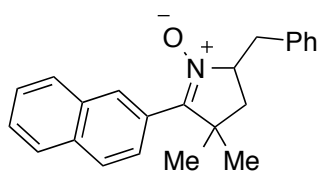
7.22-7.33 (5H, m), 7.97-8.01 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 27.4, 28.1, 38.2, 40.5, 42.8, 55.2, 71.3, 113.6, 121.4, 126.7, 128.5, 129.7, 129.9, 136.9, 147.9, 160.2; ESIHRMS: Found: m/z 310.1807. Calcd for $\text{C}_{20}\text{H}_{24}\text{NO}$: $(\text{M}+\text{H})^+$ 310.1807.

2-benzyl-4,4-dimethyl-5-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-pyrrole 1-oxide (**4-2c**)



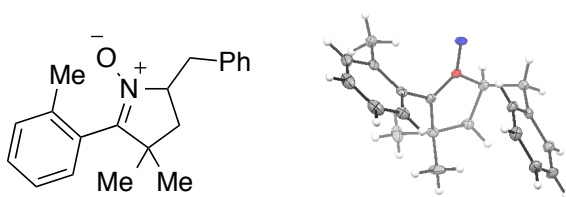
93% yield; white solid; mp. 106-107 °C; IR (NaCl) 1498, 1325, 1217 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.08 (3H, s), 1.33 (3H, s), 1.84 (1H, dd, $J = 8.5, 12.9$ Hz), 2.07 (1H, dd, $J = 8.0, 12.9$ Hz), 3.18 (1H, dd, $J = 8.3, 13.6$ Hz), 3.49 (1H, dd, $J = 3.9, 13.6$ Hz), 4.46 (1H, dddd, $J = 3.9, 8.0, 8.3, 8.5$ Hz), 7.24-7.28 (3H, m), 7.31-7.35 (2H, m), 7.70 (2H, d, $J = 8.3$ Hz), 7.98 (2H, d, $J = 8.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 27.4, 27.8, 37.9, 40.1, 42.9, 72.0, 123.8 (q, $^1J_{\text{C-F}} = 270.4$ Hz), 125.2 (q, $^3J_{\text{C-F}} = 3.8$ Hz), 126.9, 128.6, 129.7, 131.0 (q, $^2J_{\text{C-F}} = 32.3$ Hz), 132.7, 136.4, 147.0; ESIHRMS: Found: m/z 348.1571. Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}$: $(\text{M}+\text{H})^+$ 348.1575.

2-benzyl-4,4-dimethyl-5-(naphthalene-2-yl)-3,4-dihydro-2*H*-pyrrole 1-oxide (**4-2d**)



98% yield; white solid; mp. 129-130 °C; IR (NaCl) 1546, 1503 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.16 (3H, s), 1.39 (3H, s), 1.84 (1H, dd, $J = 8.6, 12.8$ Hz), 2.07 (1H, dd, $J = 8.0, 12.8$ Hz), 3.17 (1H, dd, $J = 8.5, 13.6$ Hz), 3.59 (1H, dd, $J = 3.9, 13.6$ Hz), 4.48 (1H, dddd, $J = 3.9, 8.0, 8.5, 8.6$ Hz), 7.24-7.28 (1H, m), 7.30-7.36 (4H, m), 7.47-7.53 (2H, m), 7.81-7.84 (1H, m), 7.88-7.90 (3H, m), 8.50 (1H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 27.4, 28.0, 38.1, 40.4, 43.0, 71.6, 125.1, 126.2, 126.5, 126.8, 127.0, 127.5, 127.8, 128.4, 128.6, 128.7, 129.7, 132.9, 133.5, 136.8, 148.4; ESIHRMS: Found: m/z 330.1853. Calcd for $\text{C}_{23}\text{H}_{24}\text{NO}$: $(\text{M}+\text{H})^+$ 330.1858.

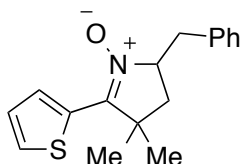
2-Benzyl-4,4-dimethyl-3,4-dihydro-2*H*-pyrrole 1-oxide (**4-2e**)



X-ray of **4-2e**

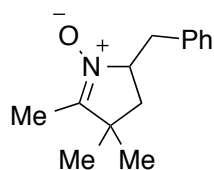
75% yield (observed as a mixture of rotatomer of 3:2 at room temperature); white crystals (CCDC 961658); mp. 123-124 °C; IR (NaCl) 1574 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 0.93 (3H, 3H x 0.6, s), 1.01 (3H, 3H x 0.4, s), 1.05 (3H, 3H x 0.6, s), 1.34 (3H, 3H x 0.4, s), 1.84-1.92 (1H, 1H x 1, m), 2.08-.215 (1H, 1H x 1, m), 2.25 (3H, 3H x 0.4, s), 2.33 (3H, 3H x 0.6, s), 2.94 (1H, 1H x 0.4, dd, *J* = 9.6, 13.6 Hz), 3.27-3.37 (2H, 2H x 0.6, m), 3.72 (1H, 1H x 0.4, dd, *J* = 4.0, 13.6 Hz), 4.42-4.50 (1H, 1H x 1, m), 6.95-7.34 (9H, 9H x 1, m); ¹³C NMR (100 MHz, CDCl₃) δ 19.6(6), 19.6(9), 26.8(7), 26.9(2), 27.0, 27.8, 37.6, 38.5, 38.6, 40.3, 43.4, 43.7, 71.3, 71.7, 125.2, 125.5, 126.7, 126.8, 127.6, 128.2, 128.3, 128.4, 128.5, 128.8, 129.2, 129.3, 129.6, 129.9, 130.4(1), 130.4(4), 136.4, 136.8, 138.0, 138.6, 150.0, 150.5; ESIHRMS: Found: *m/z* 294.1860. Calcd for C₂₀H₂₄NO: (M+H)⁺ 294.1858.

2-Benzyl-4,4-dimethyl-5-(thiophen-2-yl)-3,4-dihydro-2*H*-pyrrole 1-oxide (**4-2f**)



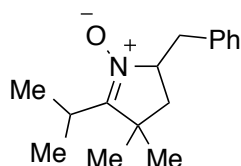
97% yield; light yellow solid; mp. 89-90 °C; IR (NaCl) 1553 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.34 (3H, s), 1.42 (3H, s), 1.83 (1H, dd, *J* = 8.2, 13.0 Hz), 2.08 (1H, dd, *J* = 8.3, 13.0 Hz), 3.07 (1H, dd, *J* = 8.7, 13.6 Hz), 3.58 (1H, dd, *J* = 3.8, 13.6 Hz), 4.42 (1H, dddd, *J* = 3.8, 8.2, 8.3, 8.7 Hz), 7.15-7.18 (1H, m), 7.20-7.23 (3H, m), 7.28 (2H, t, *J* = 7.5 Hz), 7.50 (1H, d, *J* = 5.0 Hz), 7.63 (1H, d, *J* = 3.9 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 27.3, 28.4, 38.3, 40.7, 42.5, 70.3, 126.0, 126.7(1), 126.7(4), 128.3, 128.6, 129.5, 129.8, 136.6, 144.8; ESIHRMS: Found: *m/z* 286.1267. Calcd for C₁₇H₂₀NOS: (M+H)⁺ 286.1266.

2-Benzyl-4,4,5-trimethyl-3,4-dihydro-2*H*-pyrrole 1-oxide (**4-2g**)



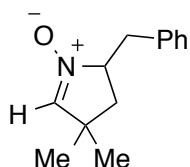
96% yield; yellow oil; IR (NaCl) 1480 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.87 (3H, s), 1.08 (3H, s), 1.65 (1H, dd, $J = 7.3, 13.1$ Hz), 1.93 (1H, dd, $J = 8.6, 13.1$ Hz), 1.94 (3H, s), 3.04 (1H, dd, $J = 8.4, 13.6$ Hz), 3.43 (1H, dd, $J = 3.8, 13.6$ Hz), 4.8 (1H, dddd, $J = 3.8, 7.3, 8.4, 8.6$ Hz), 7.21-7.24 (3H, m), 7.28-7.31 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 9.3, 26.2, 26.5, 37.9, 38.0, 42.0, 71.2, 127.7, 128.5, 129.6, 136.7, 151.2; ESIHRMS: Found: m/z 218.1541. Calcd for $\text{C}_{14}\text{H}_{20}\text{NO}$: $(\text{M}+\text{H})^+$ 218.1545.

2-Benzyl-5-isopropyl-4,4-dimethyl-3,4-dihydro-2*H*-pyrrole 1-oxide (**4-2h**)



91% yield; colorless oil; IR (NaCl) 1593 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.83 (3H, s), 1.11 (3H, s), 1.31 (3H, d, $J = 7.1$ Hz), 1.35 (3H, d, $J = 7.1$ Hz), 1.62 (1H, dd, $J = 7.6, 13.1$ Hz), 1.89 (1H, dd, $J = 8.7, 13.1$ Hz), 2.68 (1H, septet, $J = 7.1$ Hz), 3.16 (1H, dd, $J = 7.6, 13.7$ Hz), 3.26 (1H, dd, $J = 4.0, 13.7$ Hz), 4.24 (1H, dddd, $J = 4.0, 7.6, 7.6, 8.7$ Hz), 7.20-7.23 (3H, m), 7.26-7.30 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 16.8(6), 16.9, 26.1, 26.6, 26.7, 37.5, 38.2, 42.8, 70.9, 126.6, 128.3, 129.9, 136.5, 156.2; ESIHRMS: Found: m/z 246.1859. Calcd for $\text{C}_{16}\text{H}_{24}\text{NO}$: $(\text{M}+\text{H})^+$ 246.1858.

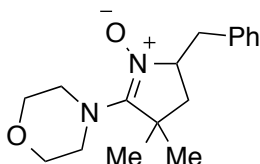
2-Benzyl-4,4-dimethyl-3,4-dihydro-2*H*-pyrrole 1-oxide (**4-2i**)



24% yield along with formation of carbonitrile **4-4a** in 47% yield; colorless oil; IR (NaCl) 1583, 1456 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.93 (3H, s), 1.15 (3H, s), 1.77 (1H, dd, $J = 7.6, 13.2$ Hz), 2.01 (1H, dd, $J = 8.6, 13.2$ Hz), 3.06 (1H, dd, $J =$

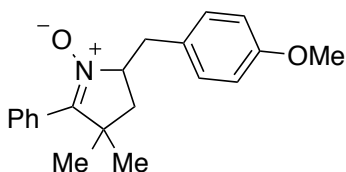
8.4, 13.7 Hz), 3.39 (1H, dd, $J = 3.8, 13.7$ Hz), 4.34 (1H, dddd, $J = 3.8, 7.6, 8.4, 8.6$ Hz), 6.70 (1H, s), 7.22-7.26 (3H, m), 7.31 (2H, t, $J = 7.44$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 27.2, 27.4, 37.8, 39.4, 39.7, 73.0, 126.9, 128.6, 129.7, 136.3, 142.7; ESIHRMS: Found: m/z 204.1384. Calcd for $\text{C}_{13}\text{H}_{18}\text{NO}$: $(\text{M}+\text{H})^+$ 204.1388.

2-Benzyl-4,4-dimethyl-5-morpholino-3,4-dihydro-2*H*-pyrrole 1-oxide (**4-2j**)



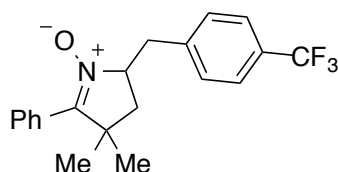
89% yield; yellow oil; IR (NaCl) 1498, 1254, 1115 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.11 (3H, s), 1.26 (3H, s), 1.62 (1H, dd, $J = 8.0, 12.7$ Hz), 1.84 (1H, dd, $J = 7.6, 12.7$ Hz), 2.91 (1H, dd, $J = 8.6, 13.4$ Hz), 3.43 (1H, dd, $J = 3.6, 13.4$ Hz), 3.57-3.62 (2H, m), 3.72-3.83 (4H, m), 3.86-3.91 (2H, m), 4.10 (1H, dddd, $J = 3.6, 7.6, 8.0, 8.6$ Hz), 7.21-7.24 (3H, m), 7.28-7.31 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 26.9, 27.3, 38.2, 40.6, 40.8, 46.6, 66.1, 67.1, 126.5, 128.4, 129.6, 136.9, 151.8; ESIHRMS: Found: m/z 289.1914. Calcd for $\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_2$: $(\text{M}+\text{H})^+$ 289.1916.

2-(4-Methoxybenzyl)-4,4-Dimethyl-5-phenyl-3,4-dihydro-2*H*-pyrrole 1-oxide (**4-2k**)



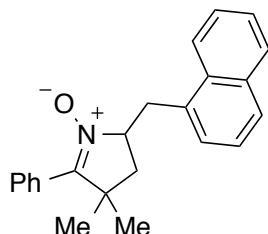
87% yield; white solid; mp. 139-140 $^{\circ}\text{C}$; IR (NaCl) 1512, 1246 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.08 (3H, s), 1.31 (3H, s), 1.79 (1H, dd, $J = 8.4, 12.8$ Hz), 2.03 (1H, dd, $J = 8.1, 12.8$ Hz), 3.15 (1H, dd, $J = 8.0, 13.8$ Hz), 3.40 (1H, dd, $J = 3.9, 13.8$ Hz), 3.79 (3H, s), 4.39 (1H, dddd, $J = 3.9, 8.0, 8.1, 8.4$ Hz), 6.84-6.88 (2H, m), 7.19-7.21 (2H, m), 7.36-7.48 (3H, m), 7.80-7.83 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 27.4, 27.9, 37.0, 39.9, 42.9, 55.2, 71.6, 113.9, 128.2(5), 128.2(8), 128.6, 129.1, 129.3, 130.7, 148.5, 158.5; ESIHRMS: Found: m/z 310.1807. Calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_2$: $(\text{M}+\text{H})^+$ 310.3807.

4,4-Dimethyl-5-phenyl-2-(4-(trifluoromethyl)benzyl)-3,4-dihydro-2*H*-pyrrole 1-oxide (**4-2l**)



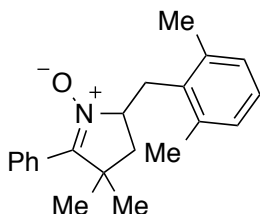
96% yield; white solid; mp. 130-131 °C; IR (NaCl) 1532, 1325, 1217 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.11 (3H, s), 1.33 (3H, s), 1.74 (1H, dd, $J = 8.8, 12.8$ Hz), 2.06 (1H, dd, $J = 7.9, 12.8$ Hz), 3.28 (1H, dd, $J = 8.0, 13.7$ Hz), 3.54 (1H, dd, $J = 3.9, 13.7$ Hz), 4.46 (1H, dddd, $J = 3.9, 7.9, 8.0, 8.8$ Hz), 7.40-7.47 (5H, m), 7.58 (2H, d, $J = 8.1$ Hz), 7.82-7.84 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 27.1, 27.9, 37.7, 40.1, 42.9, 71.1, 124.2 (q, $^1J_{\text{C-F}} = 270.1$ Hz), 125.2 (q, $^3J_{\text{C-F}} = 3.7$ Hz), 128.2, 128.4, 128.9, 129.2 (q, $^2J_{\text{C-F}} = 32.2$ Hz), 129.5, 130.1, 141.0(0), 141.0(1), 148.7; ESIHRMS: Found: m/z 348.1578. Calcd for $\text{C}_{20}\text{H}_{21}\text{NOF}_3$: $(\text{M}+\text{H})^+$ 348.1575.

4,4-Dimethyl-2-(naphthalene-1-ylmethyl)-5-phenyl-3,4-dihydro-2*H*-pyrrole 1-oxide (**4-2m**)



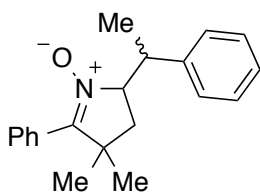
98% yield; white solid; mp. 126-127 °C; IR (NaCl) 1522 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.26 (3H, s), 1.27 (3H, s), 1.86 (1H, dd, $J = 8.6, 12.9$ Hz), 1.97 (1H, dd, $J = 7.7, 12.9$ Hz), 3.14 (1H, dd, $J = 9.5, 13.2$ Hz), 4.51-4.60 (2H, m), 7.38-7.52 (6H, m), 7.54-7.59 (1H, m), 7.76-7.80 (1H, m), 7.87 (1H, d, $J = 7.5$ Hz), 7.92-7.95 (2H, m), 8.29 (1H, d, $J = 8.5$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 26.9, 28.2, 36.0, 41.7, 43.0, 71.1, 123.9, 125.4, 125.8, 126.4, 127.4, 127.6, 128.2, 128.3, 128.7, 129.0, 129.4, 132.0, 133.4, 133.9, 148.0; ESIHRMS: Found: m/z 330.1858. Calcd for $\text{C}_{23}\text{H}_{24}\text{NO}$: $(\text{M}+\text{H})^+$ 330.1858.

2-(2,6-Dimethylbenzyl)-4,4-Dimethyl-5-phenyl-3,4-dihydro-2*H*-pyrrole 1-oxide
(**4-2n**)



73% yield; white solid; mp. 103-104 °C; IR (NaCl) 1556 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.34 (3H, s), 1.38 (3H, s), 1.89 (1H, dd, *J* = 9.4, 12.5 Hz), 2.08 (1H, dd, *J* = 7.3, 12.5 Hz), 2.44 (6H, s), 2.98 (1H, dd, *J* = 10.4, 13.8 Hz), 4.00 (1H, dd, *J* = 3.4, 13.8 Hz), 4.33 (1H, dddd, *J* = 3.4, 7.3, 9.4, 10.4 Hz), 7.03-7.09 (3H, m), 7.37-7.47 (3H, m), 7.96-7.99 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ 20.6, 26.3, 28.2, 32.2, 42.6, 42.9, 70.7, 126.5, 128.2, 128.3, 128.5, 129.0, 129.4, 134.8, 137.0, 147.5; ESIHRMS: Found: *m/z* 308.2014. Calcd for C₂₁H₂₆NO: (M+H)⁺ 308.2014.

4,4-Dimethyl-5-phenyl-2-(1-phenylethyl)-3,4-dihydro-2*H*-pyrrole 1-oxide (**4-2o**)

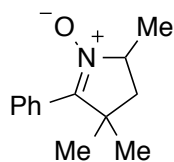


82% combined yield of the separable diastereomers (*dr* = 1.3:1; the stereochemistry was not determined)

Minor isomer: white solid; mp. 154-155 °C; IR (NaCl) 1574, 1531 cm⁻¹; isomer (a): ¹H NMR (400 MHz, CDCl₃) δ 1.29 (3H, s), 1.3 (3H, d, *J* = 7.2 Hz), 1.3 (3H, s), 1.75 (1H, dd, *J* = 7.9, 12.9 Hz), 1.95 (1H, dd, *J* = 9.9, 12.9 Hz), 4.07 (1H, dq, *J* = 3.8, 7.2 Hz), 4.46 (1H, ddd, *J* = 3.8, 7.9, 9.9 Hz), 7.23-7.28 (1H, m), 7.32-7.38 (4H, m), 7.39-7.47 (3H, m), 7.86-7.88 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ 11.8, 27.3, 27.9, 35.8, 37.9, 42.5, 74.8, 126.7, 127.9, 128.2(9), 128.3(3), 128.6, 129.1, 129.4, 142.1, 148.9; ESIHRMS: Found: *m/z* 294.1859. Calcd for C₂₀H₂₄NO: (M+H)⁺ 294.1858.

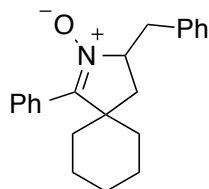
Major isomer: white solid; mp. 132-133 °C; IR (NaCl) 1580, 1495 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.22 (3H, s), 1.41 (3H, d, $J = 7.4$ Hz), 1.69 (1H, dd, $J = 7.2, 13.1$ Hz), 1.98 (1H, dd, $J = 9.3, 13.1$ Hz), 4.17 (1H, dq, $J = 3.6, 7.4$ Hz), 4.37 (1H, ddd, $J = 3.6, 7.2, 9.3$ Hz), 7.22-7.26 (1H, m), 7.30-7.43 (7H, m), 7.52-7.55 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 16.3, 27.0, 28.8, 34.7, 37.6, 43.0, 76.0, 127.0, 128.1, 128.3, 128.8, 129.2, 129.3, 139.7, 149.6; ESIHRMS: Found: m/z 294.1859. Calcd for $\text{C}_{20}\text{H}_{24}\text{NO}$: $(\text{M}+\text{H})^+$ 294.1858.

2,4,4-Trimethyl-5-phenyl-3,4-dihydro-2*H*-pyrrole 1-oxide (**4-2p**)



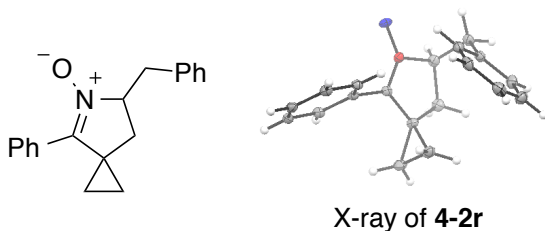
54% yield; white solid; mp. 70-71 °C; IR (NaCl) 1574, 1531 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.36 (3H, s), 1.39 (3H, s), 1.57 (3H, d, $J = 6.6$ Hz), 1.74 (1H, dd, $J = 8.8, 12.6$ Hz), 2.28 (1H, dd, $J = 7.6, 12.6$ Hz), 4.24 (1H, ddq, $J = 6.6, 7.6, 8.8$ Hz), 7.38-7.90 (3H, m), 7.91-7.92 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 18.9, 26.7, 28.3, 42.9, 44.1, 66.6, 128.2, 129.2, 129.3, 147.2; ESIHRMS: Found: m/z 204.1389. Calcd for $\text{C}_{13}\text{H}_{18}\text{NO}$: $(\text{M}+\text{H})^+$ 204.1388.

2-Benzyl-1-phenyl-2-azaspiro[4.5]dec-1-ene 2-oxide (**4-2q**)



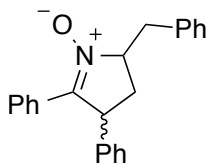
96% yield; white solid; mp. 103-104 °C; IR (NaCl) 1574 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.87 (1H, d, $J = 12.5$ Hz), 0.92-1.04 (1H, m), 1.16-1.42 (3H, m), 1.45-1.62 (5H, m), 1.76 (1H, dd, $J = 7.4, 13.2$ Hz), 2.22 (1H, dd, $J = 8.8, 13.2$ Hz), 3.25 (1H, dd, $J = 7.7, 13.6$ Hz), 3.40 (1H, dd, $J = 3.9, 13.6$ Hz), 4.44 (1H, dddd, $J = 3.9, 7.4, 7.7, 8.8$ Hz), 7.28-7.36 (5H, m), 7.39-7.49 (5H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 21.6, 22.0, 24.9, 33.2, 33.8, 35.0, 38.0, 47.4, 71.6, 126.8, 128.3, 128.4, 128.7, 129.1, 129.5, 129.8, 136.5, 150.0; ESIHRMS: Found: m/z 320.2011. Calcd for $\text{C}_{22}\text{H}_{26}\text{NO}$: $(\text{M}+\text{H})^+$ 320.2014.

6-Benzyl-4-phenyl-5-azaspiro[2.4]hept-4-ene 5-oxide (**4-2r**)



62% yield; yellow crystals (CCDC 961676); mp. 100-101 °C; IR (NaCl) 1580 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.40 (1H, ddd, *J* = 5.4, 10.4, 11.6 Hz), 0.55 (1H, ddd, *J* = 6.5, 10.4, 11.8 Hz), 0.66 (1H, ddd, *J* = 6.5, 9.5, 11.8 Hz), 0.82 (1H, ddd, *J* = 5.4, 10.4, 11.8 Hz), 1.94 (1H, dd, *J* = 4.8, 12.7 Hz), 2.32 (1H, dd, *J* = 9.3, 12.7 Hz), 3.30-3.40 (2H, m), 4.48-4.55 (1H, m), 7.26-7.40 (10H, m); ¹³C NMR (100 MHz, CDCl₃) δ 11.7, 12.5, 25.7, 33.3, 37.7, 72.5, 126.8, 127.5, 128.3, 128.4(3), 128.4(7), 129.5, 129.9, 136.5, 146.2; ESIHRMS: Found: *m/z* 278.1546. Calcd for C₁₉H₂₀NO: (M+H)⁺ 278.1545.

2-Benzyl-4,5-diphenyl-3,4-dihydro-2*H*-pyrrole 1-oxide (**4-2s**)



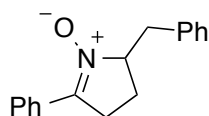
50% combined yield of the separable diastereomers (*dr* = 2.2:1; the stereochemistry was not determined)

Minor isomer: yellow solid; mp. 169-170 °C; IR (NaCl) 1541 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.84 (1H, ddd, *J* = 6.8, 6.8, 13.6 Hz), 2.73 (1H, ddd, *J* = 9.2, 9.2, 13.6 Hz), 3.25 (1H, dd, *J* = 8.6, 13.6 Hz), 3.50 (1H, dd, *J* = 3.7, 13.6 Hz), 4.48 (1H, dddd, *J* = 3.7, 6.8, 8.6, 9.2 Hz), 4.58 (1H, dd, *J* = 6.8, 9.2 Hz), 6.82-6.84 (2H, m), 7.15-7.30 (11H, m), 8.15-8.18 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ 32.7, 38.4, 47.2, 74.6, 126.8, 126.9, 127.2, 128.1, 128.2, 128.7, 128.8, 129.0, 129.8(0), 129.8(5), 136.5, 142.1, 143.1; ESIHRMS: Found: *m/z* 328.1700. Calcd for C₂₃H₂₂NO: (M+H)⁺ 328.1701.

Major isomer; yellow solid; mp. 144-145 °C; IR (NaCl) 1547 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.05 (1H, ddd, *J* = 3.2, 8.0, 13.2 Hz), 2.44 (1H, ddd, *J* = 9.2, 12.8,

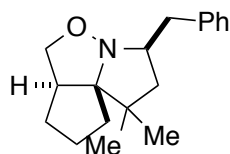
13.2 Hz), 3.17 (1H, dd, $J = 8.2, 13.6$ Hz), 3.55 (1H, dd, $J = 4.0, 13.6$ Hz), 4.24 (1H, dd, $J = 1.2, 9.2$ Hz), 4.61 (1H, dddd, $J = 3.2, 4.0, 8.2, 12.8$ Hz), 7.06-7.08 (2H, m), 7.15-7.28 (9H, m), 7.30-7.32 (3H, m), 8.20-8.23 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 33.9, 38.0, 46.7, 73.7, 126.8, 127.0, 127.1, 128.0, 128.2, 128.6, 128.8, 129.1, 129.6, 129.9, 136.5, 142.3; ESIHRMS: Found: m/z 328.1703. Calcd for $\text{C}_{23}\text{H}_{22}\text{NO}$: $(\text{M}+\text{H})^+$ 328.1701.

2-Benzyl-5-phenyl-3,4-dihydro-2*H*-pyrrole 1-oxide (**4-2t**)



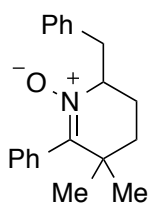
76% yield; white solid; mp. 127-128 °C; IR (NaCl) 1574, 1553 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.91-1.99 (1H, m), 2.16-2.25 (1H, m), 2.59-2.67 (1H, m), 2.91 (1H, ddd, $J = 4.8, 9.6, 16.8$ Hz), 3.19 (1H, dd, $J = 7.9, 13.6$ Hz), 3.40 (1H, dd, $J = 3.7, 13.6$ Hz), 4.41-4.53 (1H, m), 7.20-7.27 (5H, m), 7.42-7.46 (3H, m), 8.31-8.33 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 21.49, 28.72, 38.00, 75.78, 126.8, 127.2, 128.3, 128.5, 129.4, 129.5, 130.1, 136.5, 140.1; ESIHRMS: Found: m/z 252.1390. Calcd for $\text{C}_{17}\text{H}_{18}\text{NO}$: $(\text{M}+\text{H})^+$ 252.1288.

3-Benzyl-1,1-dimethylhexahydro-1*H*,6*H*-cyclopenta[*c*]pyrrolo[1,2-*b*]isoxazole (**4-3u**)



83% yield; white solid; mp. 67-68 °C; IR (NaCl) 1601 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.00 (3H, s), 1.13 (3H, s), 1.46-1.56 (2H, m), 1.59-1.86 (6H, m), 2.65-2.71 (2H, m), 3.14-3.23 (2H, m), 3.55 (1H, dd, $J = 2.9, 8.4$ Hz), 4.25 (1H, t, $J = 8.6$ Hz), 7.16-7.20 (3H, m), 7.26-7.29 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 24.5, 25.7, 28.1, 33.6, 34.3, 40.4, 43.1, 43.2, 48.2, 63.6, 74.3, 88.3, 126.0, 128.3, 129.2, 139.9; ESIHRMS: Found: m/z 272.2014. Calcd for $\text{C}_{18}\text{H}_{26}\text{NO}$: $(\text{M}+\text{H})^+$ 272.2014.

2-Benzyl-5,5-dimethyl-6-phenyl-2,3,4,5-tetrahydropyridine 1-oxide (**4-2v**)



65% yield; white solid; mp. 50-51 °C; IR (NaCl) 1556 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.91 (3H, s), 1.04 (3H, s), 1.59-1.72 (2H, m), 1.83-1.95 (1H, m), 1.97-2.07 (1H, m), 3.34 (1H, dd, *J* = 8.4, 13.4 Hz), 3.44 (1H, dd, *J* = 3.6, 13.4 Hz), 4.11-4.17 (1H, m), 7.17 (2H, d, *J* = 7.0 Hz), 7.24-7.38 (6H, m), 7.44 (2H, t, *J* = 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 22.5, 27.5, 28.2, 32.4, 37.0, 38.5, 68.5, 126.7, 128.0, 128.1, 128.4, 128.5, 129.9, 133.9, 137.4, 153.3; ESIHRMS: Found: *m/z* 294.1858. Calcd for C₂₀H₂₄NO: (M+H)⁺ 294.1858.

4.5.4. DFT calculations

4.5.4.1. Complete list of authors of Gaussian 09

Gaussian 09, revision B.01; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G.A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Comperts, R.; Startmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenbuerg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc.: Wallingford CT, 2010.

4.5.4.2. Charge Distribution in 4-TS-2

Mulliken population analysis (R. S. Mulliken *J. Chem. Phys.* **1955**, 23, 1833-1840.) was performed for **4-TS-1**, to understand how atomic charges are distributed within the molecule.

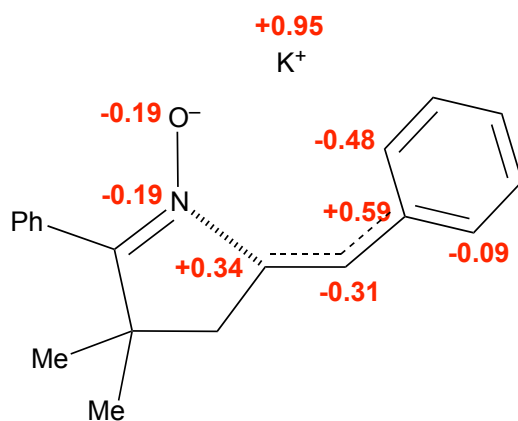
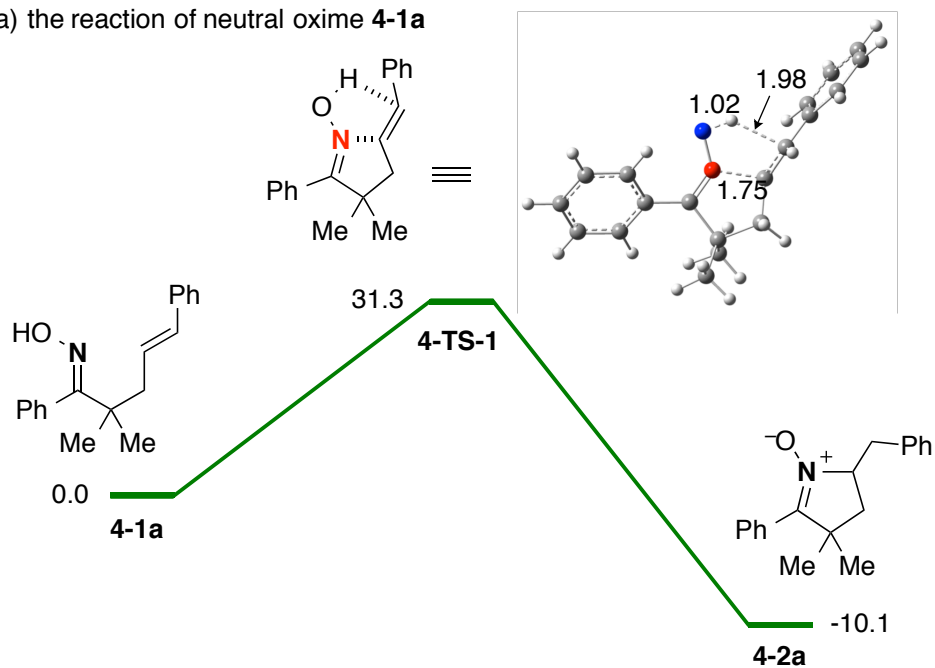


Figure S1. Key Mulliken charges for 4-TS-2

4.5.4.3. Reaction energy profile for oxime 4-1a

(a) the reaction of neutral oxime **4-1a**



(b) the reaction of anionic oxime **4-1a'**

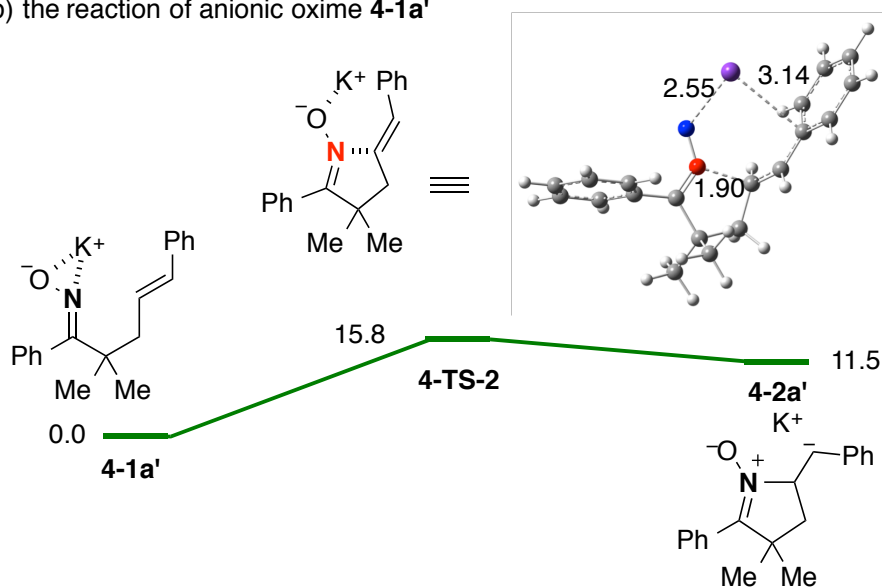


Figure S2. Energy diagrams (in kcal mol⁻¹) for the reaction of neutral oxime **4-1p** (a) and anionic oxime **4-1p'** (b), as obtained at the B3LYP(SCRF)/6-311+G(d,p) level. Zero-point-energy (ZPE) effects are included. Key bond distances are given in Å in the three-dimensional images of transition states.

4.5.4.4. Raw DFT energy data

Table S1. Raw energy data obtained from DFT calculations at the B3LYP(SCRF)/6-311+G(d,p) level.

(a) R'' = Ph

	E [au]	ZPE [au]	ΔE [kcal mol ⁻¹]	$\Delta(E+ZPE)$ [kcal mol ⁻¹]
4-1a	-866.814657	0.351632	0.0	0.0
4-TS-1	-866.763714	0.350529	32.0	31.3
4-2a	-866.834236	0.355184	-12.3	-10.1

	E [au]	ZPE [au]	ΔE [kcal mol ⁻¹]	$\Delta(E+ZPE)$ [kcal mol ⁻¹]
4-1a'	-1466.216073	0.339107	0.0	0.0
4-TS-2	-1466.190391	0.338618	16.1	15.8
4-2a'	-1466.198531	0.339863	11.0	11.5

(b) R'' = H

	E [au]	ZPE [au]	ΔE [kcal mol ⁻¹]	$\Delta(E+ZPE)$ [kcal mol ⁻¹]
4-1p	-635.698003	0.270500	0.0	0.0
4-TS-3	-635.646295	0.268395	32.4	31.1
4-2p	-635.727639	0.273903	-18.6	-16.5

	E [au]	ZPE [au]	ΔE [kcal mol ⁻¹]	$\Delta(E+ZPE)$ [kcal mol ⁻¹]
4-1p'	-1235.099132	0.258089	0.0	0.0
4-TS-4	-1235.058243	0.257878	25.7	25.5
4-2p'	-1235.059729	0.259105	24.7	25.4

4.5.4.5. XYZ coordinates of optimized geometries

=== 4-1a ===

C	-2.988455	-0.756889	0.526594
C	-4.148327	-0.036525	0.832602
C	-4.936063	-0.394438	1.926352
C	-4.573031	-1.474548	2.728819
C	-3.413660	-2.191990	2.435605
C	-2.625968	-1.834870	1.343143
H	-4.436030	0.813379	0.225036
H	-5.831622	0.174070	2.150637
H	-5.186028	-1.752654	3.578641
H	-3.119392	-3.029262	3.058485
H	-1.722448	-2.393128	1.126959
C	-2.121961	-0.371340	-0.636003
N	-1.132403	0.429847	-0.518246
O	-0.961845	0.911211	0.797797
H	-0.190084	1.483473	0.712930
C	-2.391359	-0.953056	-2.034122
C	-1.289448	-0.566190	-3.034208
H	-0.319823	-0.958986	-2.721131
H	-1.531319	-0.988684	-4.013896
H	-1.195617	0.514302	-3.143657
C	-2.454291	-2.494104	-1.937355
H	-2.627371	-2.914556	-2.931629
H	-1.513134	-2.902669	-1.559277
H	-3.261173	-2.830358	-1.283292
C	-3.777733	-0.452354	-2.555849
H	-3.997690	-0.993471	-3.481669
H	-4.543810	-0.755469	-1.831843
C	-3.881854	1.024464	-2.804295
C	-4.277099	1.565895	-3.964205
H	-3.627009	1.673251	-1.969427
H	-4.523940	0.891853	-4.783094
C	-4.433096	2.994896	-4.281625
C	-4.121922	4.028696	-3.379865
C	-4.915102	3.355952	-5.550885
C	-4.290475	5.362337	-3.735441
H	-3.742331	3.792199	-2.392716
C	-5.085084	4.692168	-5.908444
H	-5.159903	2.575279	-6.263961
C	-4.773472	5.703268	-5.001620
H	-4.042770	6.141584	-3.023006
H	-5.459808	4.941696	-6.894994
H	-4.902856	6.744222	-5.275144

=== 4-TS-1 ===

C	-2.742905	-0.813789	0.463436
C	-3.393829	-1.808218	1.210230
C	-2.908768	-2.187950	2.458297
C	-1.755891	-1.596534	2.972234
C	-1.095552	-0.613927	2.234712
C	-1.587596	-0.215636	0.996137
H	-4.289618	-2.279270	0.830108
H	-3.431195	-2.948346	3.026934
H	-1.375218	-1.897724	3.941368
H	-0.197251	-0.151150	2.626500
H	-1.074338	0.555133	0.438052
C	-3.250860	-0.404446	-0.861434
N	-3.179178	0.773616	-1.351154
O	-2.604068	1.873407	-0.857300
H	-2.528355	2.397554	-1.734186
C	-3.885449	-1.318214	-1.944831
C	-3.190829	-2.687826	-2.013223
H	-3.403156	-3.305363	-1.138961
H	-3.547540	-3.225892	-2.895830

H	-2.106488	-2.581101	-2.100092
C	-5.402804	-1.493840	-1.713725
H	-5.827046	-2.089916	-2.526133
H	-5.620665	-2.011410	-0.777871
H	-5.922133	-0.533129	-1.691358
C	-3.626026	-0.523298	-3.267238
H	-2.614198	-0.736010	-3.625860
H	-4.329729	-0.835774	-4.042304
C	-3.755965	0.966956	-2.987382
C	-2.998959	1.994116	-3.612070
H	-4.788307	1.247609	-2.775216
H	-2.065874	1.699247	-4.087984
C	-3.526532	3.294705	-3.993481
C	-4.762656	3.823971	-3.542904
C	-2.779924	4.126570	-4.866413
C	-5.214125	5.077188	-3.945822
H	-5.380205	3.251771	-2.858426
C	-3.232358	5.380150	-5.261294
H	-1.826106	3.764642	-5.239327
C	-4.458823	5.875212	-4.808608
H	-6.168897	5.437735	-3.574825
H	-2.622814	5.976683	-5.933353
H	-4.813571	6.851985	-5.116579

=== 4-2a ===

C	-2.675893	-0.968729	0.511660
C	-3.197642	-2.241241	0.817287
C	-2.706046	-2.984844	1.885304
C	-1.668206	-2.487411	2.672132
C	-1.132795	-1.233625	2.379637
C	-1.631673	-0.477671	1.323353
H	-4.003641	-2.657175	0.230965
H	-3.136645	-3.956096	2.101380
H	-1.284018	-3.068215	3.502980
H	-0.323825	-0.834977	2.981668
H	-1.222802	0.500169	1.120148
C	-3.180453	-0.203333	-0.635085
N	-3.087991	1.111132	-0.708990
O	-2.640966	1.929382	0.170100
H	-2.647662	3.531832	-1.709273
C	-3.899538	-0.758350	-1.869442
C	-3.232680	-2.005669	-2.473968
H	-3.354291	-2.892520	-1.851096
H	-3.685308	-2.219910	-3.446652
H	-2.162765	-1.842842	-2.627387
C	-5.394969	-1.031059	-1.573201
H	-5.896241	-1.349295	-2.491834
H	-5.537639	-1.815535	-0.829043
H	-5.898411	-0.132496	-1.206921
C	-3.779105	0.434424	-2.856007
H	-2.865342	0.327075	-3.447324
H	-4.622789	0.478172	-3.545487
C	-3.670740	1.674328	-1.979889
C	-2.805006	2.818011	-2.520275
H	-4.653426	2.067921	-1.700793
H	-1.824451	2.420352	-2.798497
C	-3.445415	3.503397	-3.708579
C	-4.502848	4.404587	-3.525177
C	-3.008992	3.248717	-5.013419
C	-5.111021	5.026460	-4.613954
H	-4.847623	4.627922	-2.520259
C	-3.613522	3.870911	-6.106492
H	-2.184154	2.562654	-5.176693
C	-4.668945	4.759995	-5.910547

H	-5.925549	5.723436	-4.450047
H	-3.256929	3.662809	-7.109321
H	-5.138846	5.245810	-6.758255

=== 4-1a' ===

C	-2.992398	-0.714126	0.513819
C	-4.209250	-0.079078	0.794360
C	-4.977400	-0.446430	1.900624
C	-4.540290	-1.458917	2.752711
C	-3.326322	-2.095867	2.492085
C	-2.563660	-1.724695	1.386350
H	-4.559195	0.719928	0.150465
H	-5.916042	0.061343	2.096033
H	-5.136194	-1.746811	3.611911
H	-2.972672	-2.881428	3.151613
H	-1.619047	-2.222244	1.196169
C	-2.150496	-0.326628	-0.668103
N	-1.166497	0.506197	-0.545693
O	-0.905962	1.046117	0.658132
C	-2.440247	-0.945293	-2.046429
C	-1.349518	-0.593737	-3.072251
H	-0.375876	-0.972668	-2.753135
H	-1.596371	-1.050781	-4.036633
H	-1.260295	0.482882	-3.219959
C	-2.508312	-2.485617	-1.927947
H	-2.711210	-2.932275	-2.906657
H	-1.559144	-2.888705	-1.562807
H	-3.296057	-2.804667	-1.241801
C	-3.826065	-0.463549	-2.592508
H	-4.041137	-1.004782	-3.520735
H	-4.594775	-0.768392	-1.871392
C	-3.943315	1.011426	-2.835789
C	-4.329447	1.563815	-3.994215
H	-3.695374	1.651397	-1.992186
H	-4.551052	0.900338	-4.828996
C	-4.493607	2.996653	-4.291202
C	-4.360062	4.009471	-3.323578
C	-4.806318	3.385753	-5.604776
C	-4.525778	5.348435	-3.660978
H	-4.133383	3.749841	-2.296010
C	-4.972838	4.727173	-5.944376
H	-4.919776	2.622231	-6.367797
C	-4.832588	5.717130	-4.973527
H	-4.421315	6.109863	-2.895608
H	-5.214069	4.997299	-6.966637
H	-4.964505	6.761704	-5.231759
K	0.908831	2.182114	-0.675464

=== 4-TS-2 ===

C	-3.184002	-0.743936	0.357821
C	-4.012573	-1.418613	1.263604
C	-3.564005	-1.726122	2.547720
C	-2.278066	-1.362977	2.946444
C	-1.445689	-0.686075	2.055081
C	-1.896143	-0.377681	0.772264
H	-5.015795	-1.698573	0.962831
H	-4.219660	-2.248234	3.235908
H	-1.927830	-1.603563	3.944015
H	-0.444904	-0.398064	2.358244
H	-1.244473	0.150360	0.084943
C	-3.666195	-0.404475	-1.010287
N	-4.133686	0.760064	-1.314259
O	-4.242967	1.779440	-0.518612
C	-3.555806	-1.345638	-2.203850
C	-2.066033	-1.555954	-2.563673
H	-1.517240	-2.003642	-1.730697

H	-1.978644	-2.228181	-3.422921
H	-1.582897	-0.610175	-2.821229
C	-4.194657	-2.719055	-1.924059
H	-4.145997	-3.344411	-2.821131
H	-3.673338	-3.247250	-1.121276
H	-5.245914	-2.616896	-1.640534
C	-4.310839	-0.630075	-3.366523
H	-3.836489	-0.881560	-4.318118
H	-5.331208	-1.020549	-3.404262
C	-4.382439	0.885453	-3.194150
C	-3.466324	1.748174	-3.822618
H	-5.398491	1.262848	-3.111648
H	-2.491988	1.345542	-4.090942
C	-3.657014	3.147104	-4.065449
C	-4.865612	3.862395	-3.800497
C	-2.596736	3.933898	-4.611256
C	-4.991461	5.222223	-4.066397
H	-5.719844	3.335517	-3.388898
C	-2.732031	5.291335	-4.868229
H	-1.654725	3.442542	-4.838074
C	-3.930846	5.964829	-4.597895
H	-5.937817	5.712017	-3.855006
H	-1.890731	5.835993	-5.286946
H	-4.036204	7.023889	-4.801104
K	-3.381722	4.112496	-1.093010

=== 4-2a' ===

C	-2.907326	-0.760602	0.357115
C	-3.955110	-0.605263	1.275986
C	-3.783830	-0.954884	2.612970
C	-2.558879	-1.455610	3.055842
C	-1.507665	-1.604523	2.152868
C	-1.681108	-1.263008	0.811776
H	-4.905303	-0.207847	0.938949
H	-4.605814	-0.834110	3.309766
H	-2.424977	-1.725291	4.097378
H	-0.550390	-1.986211	2.489951
H	-0.854981	-1.374788	0.120133
C	-3.111495	-0.402586	-1.066103
N	-3.330715	0.822884	-1.442124
O	-3.366305	1.869975	-0.691454
C	-3.244056	-1.383282	-2.226416
C	-2.137730	-2.449174	-2.266517
H	-2.188405	-3.120266	-1.405229
H	-2.251454	-3.057220	-3.169035
H	-1.143857	-1.994537	-2.292737
C	-4.621149	-2.082876	-2.145833
H	-4.736418	-2.779259	-2.981757
H	-4.720427	-2.651084	-1.216921
H	-5.440722	-1.360548	-2.190036
C	-3.161536	-0.435692	-3.449779
H	-2.122076	-0.360019	-3.782990
H	-3.754860	-0.804503	-4.288879
C	-3.631971	0.950909	-3.001954
C	-3.024403	2.101760	-3.672356
H	-4.725579	1.012226	-2.998698
H	-2.017698	1.958683	-4.059270
C	-3.686645	3.300968	-4.011241
C	-5.019718	3.653087	-3.598170
C	-3.020828	4.318483	-4.783568
C	-5.613586	4.858260	-3.956677
H	-5.591083	2.957885	-2.991668
C	-3.625877	5.518018	-5.120709
H	-2.009688	4.119299	-5.129853
C	-4.938382	5.819077	-4.719173
H	-6.629421	5.056023	-3.623772

H	-3.068224	6.237268	-5.715137
H	-5.408337	6.757475	-4.988246
K	-2.771010	4.285329	-1.381110

$R'' = H$

=== 4-1p ===

C	-2.993521	-0.756332	0.524673
C	-4.164009	-0.051279	0.825561
C	-4.945269	-0.412098	1.923067
C	-4.565061	-1.479612	2.734354
C	-3.395060	-2.181718	2.446121
C	-2.613853	-1.821744	1.349997
H	-4.464721	0.789338	0.211459
H	-5.849170	0.144591	2.143535
H	-5.172921	-1.759803	3.587183
H	-3.087375	-3.008968	3.075879
H	-1.701881	-2.367646	1.137746
C	-2.133103	-0.367090	-0.641202
N	-1.152751	0.446044	-0.528913
O	-0.986812	0.937084	0.784103
H	-0.223186	1.519465	0.694857
C	-2.397165	-0.960063	-2.035777
C	-1.298029	-0.569652	-3.037708
H	-0.324978	-0.950753	-2.720884
H	-1.534962	-1.001638	-4.014473
H	-1.214566	0.510774	-3.154931
C	-2.444754	-2.501150	-1.928991
H	-2.615865	-2.929652	-2.920165
H	-1.498831	-2.898021	-1.550291
H	-3.246913	-2.841006	-1.271009
C	-3.786930	-0.476255	-2.561459
H	-3.999124	-1.020425	-3.487473
H	-4.553046	-0.782974	-1.839684
C	-3.907105	1.000398	-2.814510
C	-4.297546	1.547225	-3.965144
H	-3.664158	1.659188	-1.982614
H	-4.545725	0.938470	-4.830057
H	-4.384448	2.621986	-4.082218

=== 4-TS-3 ===

C	-2.722496	-0.833938	0.485402
C	-3.337191	-1.876519	1.197129
C	-2.864617	-2.258706	2.449786
C	-1.761442	-1.617008	3.010308
C	-1.139504	-0.581741	2.312505
C	-1.618151	-0.186036	1.067324
H	-4.197545	-2.386402	0.786581
H	-3.359896	-3.059418	2.986972
H	-1.391193	-1.918742	3.983407
H	-0.280927	-0.076622	2.740096
H	-1.135118	0.625206	0.539984
C	-3.215962	-0.405515	-0.842146
N	-3.107856	0.762353	-1.339156
O	-2.484974	1.860494	-0.957677
H	-2.507022	2.341455	-1.914797
C	-3.887227	-1.297531	-1.931222
C	-3.227884	-2.684805	-2.020782
H	-3.450635	-3.310516	-1.155185
H	-3.599561	-3.203892	-2.908934
H	-2.141285	-2.603328	-2.109718
C	-5.404827	-1.440166	-1.684538
H	-5.856273	-2.035537	-2.483357
H	-5.622318	-1.939773	-0.738384
H	-5.901013	-0.467070	-1.664655

C	-3.624923	-0.526719	-3.273445
H	-2.608112	-0.744854	-3.615870
H	-4.315481	-0.890250	-4.040952
C	-3.775171	0.972838	-3.088275
C	-2.999357	2.004529	-3.627687
H	-4.791016	1.265301	-2.820770
H	-2.077758	1.771089	-4.155614
H	-3.480145	2.941643	-3.885142

=== 4-2p ===

C	-2.674682	-0.973273	0.516025
C	-3.200454	-2.244599	0.819777
C	-2.710093	-2.992442	1.885483
C	-1.669683	-2.500456	2.672348
C	-1.130078	-1.248044	2.381660
C	-1.627521	-0.488046	1.327544
H	-4.008802	-2.656354	0.233674
H	-3.143944	-3.962635	2.099939
H	-1.286552	-3.084416	3.501489
H	-0.318892	-0.853566	2.983512
H	-1.215531	0.488762	1.125738
C	-3.178262	-0.202888	-0.627921
N	-3.081369	1.111396	-0.698842
O	-2.627421	1.925811	0.179924
H	-2.724878	3.625182	-1.797880
C	-3.897053	-0.753512	-1.865149
C	-3.230241	-1.999527	-2.472338
H	-3.351842	-2.887809	-1.851432
H	-3.682437	-2.211777	-3.445737
H	-2.160305	-1.836186	-2.625102
C	-5.393096	-1.026160	-1.572142
H	-5.893395	-1.342080	-2.492214
H	-5.537624	-1.812345	-0.830086
H	-5.896337	-0.128107	-1.204236
C	-3.773936	0.443333	-2.846230
H	-2.860106	0.338887	-3.438375
H	-4.618728	0.493684	-3.535145
C	-3.663250	1.681324	-1.967103
C	-2.807021	2.810175	-2.516797
H	-4.646859	2.070273	-1.683752
H	-1.802599	2.454192	-2.761243
H	-3.267601	3.195435	-3.430077

=== 4-1p' ===

C	-2.993034	-0.711806	0.510811
C	-4.208917	-0.073552	0.788059
C	-4.979859	-0.437781	1.893454
C	-4.546472	-1.449906	2.747916
C	-3.333300	-2.089734	2.490621
C	-2.567932	-1.721872	1.385686
H	-4.555151	0.725595	0.142347
H	-5.917788	0.072234	2.086473
H	-5.144534	-1.735216	3.606490
H	-2.982361	-2.874843	3.152149
H	-1.623916	-2.221499	1.198083
C	-2.147486	-0.327641	-0.669554
N	-1.158872	0.499119	-0.543715
O	-0.898773	1.035603	0.662130
C	-2.435721	-0.948146	-2.047578
C	-1.348035	-0.590870	-3.074644
H	-0.372320	-0.965971	-2.757447
H	-1.594606	-1.047906	-4.039102
H	-1.263445	0.486181	-3.221598
C	-2.491851	-2.489117	-1.926708
H	-2.691830	-2.938808	-2.904638
H	-1.539466	-2.884334	-1.561242

H	-3.276949	-2.813027	-1.239777
C	-3.824914	-0.477828	-2.591800
H	-4.040979	-1.027084	-3.515278
H	-4.590792	-0.777641	-1.866355
C	-3.950300	0.995951	-2.851018
C	-4.352858	1.543601	-3.998152
H	-3.695109	1.652010	-2.020644
H	-4.612711	0.935015	-4.860090
H	-4.440718	2.618675	-4.115343
K	0.927474	2.164481	-0.657992

=== 4-TS-4 ===

C	0.187601	-0.957595	1.214364
C	-0.442193	-0.366480	2.330038
C	-0.068561	-0.700901	3.628590
C	0.953152	-1.621825	3.859984
C	1.590181	-2.214176	2.770872
C	1.210177	-1.891831	1.470332
H	-1.224160	0.358871	2.162698
H	-0.579387	-0.236136	4.465168
H	1.247307	-1.874763	4.872476
H	2.386681	-2.932760	2.930610
H	1.726525	-2.372059	0.652391
C	-0.245854	-0.629976	-0.159716
N	-0.810749	0.500007	-0.487946
O	-1.021886	1.526623	0.266474
C	-0.095161	-1.534407	-1.392049
C	1.352921	-1.504603	-1.942129
H	2.082779	-1.913043	-1.241172
H	1.408649	-2.100653	-2.858508
H	1.652569	-0.482568	-2.184085
C	-0.532068	-2.988078	-1.132476
H	-0.550528	-3.538995	-2.078059
H	0.141618	-3.517096	-0.455547
H	-1.537115	-3.022642	-0.702754
C	-1.047910	-0.885726	-2.435958
H	-0.690848	-1.085653	-3.448050
H	-2.034919	-1.347986	-2.338640
C	-1.173770	0.624612	-2.189946
C	-0.387091	1.590764	-2.900324
H	-2.212084	0.937124	-2.059445
H	0.446202	1.235040	-3.502872
H	-0.914192	2.448955	-3.311933
K	0.380810	3.492062	-0.742967

=== 4-2p' ===

C	0.196598	-0.946649	1.194344
C	-0.447057	-0.362647	2.305095
C	-0.083242	-0.702974	3.604869
C	0.941703	-1.619068	3.839799
C	1.592894	-2.202661	2.754194
C	1.221710	-1.877110	1.452603
H	-1.230024	0.360555	2.134705
H	-0.603177	-0.245133	4.439446
H	1.228803	-1.874667	4.853597
H	2.393120	-2.915925	2.917843

H	1.747400	-2.347867	0.635033
C	-0.215218	-0.630345	-0.184634
N	-0.766300	0.509593	-0.523889
O	-0.995708	1.524554	0.240461
C	-0.086419	-1.548925	-1.405859
C	1.352445	-1.548196	-1.978051
H	2.078291	-1.995889	-1.296763
H	1.373020	-2.127295	-2.906367
H	1.681289	-0.532200	-2.204487
C	-0.543806	-2.991958	-1.126007
H	-0.592973	-3.545912	-2.068446
H	0.136609	-3.528668	-0.461732
H	-1.539549	-3.007098	-0.674433
C	-1.051993	-0.866898	-2.412900
H	-0.716975	-1.005035	-3.441353
H	-2.042066	-1.324424	-2.317518
C	-1.123400	0.631192	-2.046376
C	-0.289066	1.648113	-2.761356
H	-2.163360	0.966826	-1.994527
H	0.517069	1.181837	-3.340094
H	-0.914246	2.230638	-3.448484
K	0.142324	3.688343	-0.719294

4.6. References and notes

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List of Publications

1. Benny Meng Kiat Tong and Shunsuke Chiba
“Diamine-Catalyzed Conjugated Addition to Acrylate Derivatives”
Organic Letters, **2011**, *13*, 2948.
2. Benny Meng Kiat Tong, Hui Chen, Sin Yee Chong, Yi Li Heng and Shunsuke Chiba
“Formal [4+1]- and [5+1]-Annulation by an S_N2-Conjugate Addition Sequence: Stereoselective Synthesis of Highly Substituted Carbocycles”
Organic Letters, **2012**, *14*, 2826. (Additions and Corrections: *Organic Letters*, **2013**, *15*, 6111.)
3. Peng Xingao, Benny Meng Kiat Tong, Hajime Hirao and Shunsuke Chiba
“Inorganic Base-Mediated Hydroamination of Alkenyl Oximes for Synthesis of Cyclic Nitrone”
Angewandte Chemie International Edition, **2014**, *53*, 1959.

The results of the following publications are not included in this thesis

4. Benny Meng Kiat Tong, Benjamin Wei-Qiang Hui, Sze Hui Chua and Shunsuke Chiba
“Synthesis of Isoindoles *via* 1,3-Dipolar Cycloaddition of α -Azido Carbonyl Compounds onto Intramolecular Alkenes and Their Conversion into Substituted Aromatic Hydrocarbons”
Synthesis, **2011**, 3552.
5. Pengcheng Zhu, Benny Meng Kiat Tong, Runze Wang, Selin Foo, Hang Chung Chong, Xiao Ling Wang, Gim Yean Ang, Shunsuke Chiba and Nguan Soon Tan
“Nox4-dependent ROS modulation by amino endoperoxides to induce apoptosis in cancer cells”
Cell Death and Disease, **2013**, *4*, e552.