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Asymmetric Dihydroxylation and Aziridination of Allenes and Related Chemistry

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ASYMMETRIC DIHYDROXYLATION AND AZIRIDINATION OF ALLENES AND RELATED CHEMISTRY

by

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GRADUATE COMMITTEE APPROVAL

of a thesis submitted by

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This thesis has been read by each member of the following graduate committee and by majority vote has been found to be satisfactory.

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BRIGHAM YOUNG UNIVERSITY

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ABSTRACT

ASYMMETRIC DIHYDROXYLATION AND AZIRIDINATION OF ALLENES AND RELATED CHEMISTRY

Renmao Liu

Department of Chemistry and Biochemistry

Doctor of Philosophy

A novel method for asymmetric synthesis of α-hydroxy ketone with excellent regio- and stereoselectivity has been established by the systematic investigation of asymmetric dihydroxylation of allenes. The efficiency of kinetic resolution of racemic allenes was also investigated by using the AD reaction on both 1,3-disubstituted and trisubstituted allenes. Steric effects, electronic effects and allene substitution are also discussed.

Aziridines were formed by copper-catalyzed intramolecular nitrene addition to alkenes. The carbamate group was used as the tether between the alkene and the nitrene. Subsequent nucleophilic attack of the aziridine was accomplished using RSH, R_2NH, N_3^-,

or ROH as the nucleophile. This addition was found to be regio- and stereoselective. This methodology has provided a new strategy for the stereoselective construction of three adjacent functional groups, in particular the 1,2 diamino-3-hydroxy unit.

The rhodium-catalyzed intramolecular aziridination of allenic *N*-sulfonyloxy carbamates has been established. Efficient ring opening of these bicyclic compounds may provide synthetic utility in organic chemistry. The intramolecular aziridination of allenic sulfamate esters was tested on a single example to afford in situ a ring opened product.

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I would like to express my special appreciation to my mentor, Professor Steven A. Fleming, for his guidance, encouragement, and great patience throughout my graduate work. I appreciate him for creating a free and comfortable environment for me so that I can enjoy chemistry and life. Thanks for our group meetings, those hiking days, those game parties and the first skiing in my life. Those beautiful times has been important part in my life.

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I would like to thank my family for their support and encouragement. I am grateful for many helpful discussions of past and present fellow graduate students. I also would like to recognize all the members of the Fleming group for their friendship. I am grateful for the financial support of this work by the Brigham Young University Department of Chemistry and Biochemistry, BYU Graduate Research Fellowship, and Jerald S. Bradshaw Organic Chemistry Fellowship.

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Chapter 1 Recent Advances on Allene Chemistry

1.1. Introduction

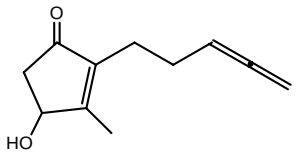
Allenes are a class of compounds characterized by a unique 1,2-diene moiety which consists of two orthogonal π-orbitals. For a long period allenes were considered to be highly unstable and mostly regarded as chemical curiosities, although in 1887 Burton and Von Pechmann prepared the first allene derivative during their initial attempt to prove the non-existence of this class of compounds. The actual structure was not confirmed until 1954.[1] Actually as early as in 1874-1875, Van't Hoff had correctly predicted the structure of allenes and pointed out that unsymmetrically substituted allenes should be chiral and exist in two enantiomeric forms.[2] However lack of methodologies for their synthesis and analytical tools to distinguish between allenes and corresponding alkynes greatly retarded the initial development of the chemistry of allenes. This situation was changed and allene chemistry was greatly promoted when IR and Raman spectroscopy were introduced as tools for structural investigations. As a result, allenes were able to be identified by their characteristic allenic C-C vibration at about 1950 cm^{-1}.

Allene chemistry has become a very fruitful and active field during the last century. The achievements in this field have been described in a number of reviews.[3] Especially during the past decade, allene chemistry has received considerable attention, has been extensively and rapidly developed, and also has been well documented.[4] Here we will give a brief description of representative examples that focus on the past several years.

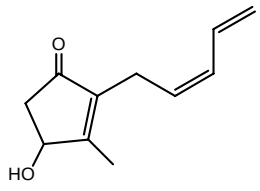
1.2. Allenic natural products and pharmacologically active allenes

The first naturally occurring allene, pyrothrolone **1** (see Fig. 1), reported by Staudinger and Ruzicka in 1924, was proved to be incorrect and its real structure was confirmed later as the conjugated diene compound **2** instead of the 1,2 diene **1**.[5] Although there were a large number of well-known natural products which were isolated in the very early stage and only identified for their allenic structures after a long period, it was not until 1952 that the first authenticated naturally occurring allene, mycomycin **3** (see Fig. 1), was isolated and characterized.[6] Subsequently, an increasing number of allenic natural products have been found.

Figure 1. Early natural allenic products.



1



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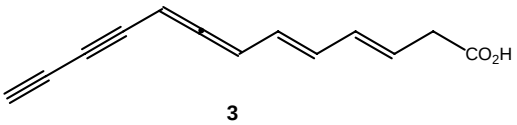
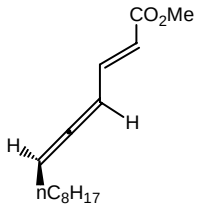


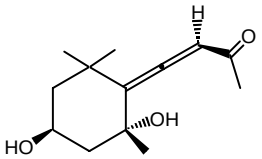
3

To date, approximately 150 natural products possessing an allenic or cumulenic structure have been reported. Most of them can be divided into four classes including: 1) linear allenes, 2) allenic carotinoids, 3) terpenoids, and 4) bromoallenes (a few examples are shown in Fig. 2). Almost all these allenic natural products are chiral and optically active though not necessarily found in enantiomerically pure forms.[7]

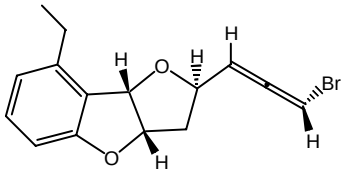
Figure 2. Examples of natural allenes.



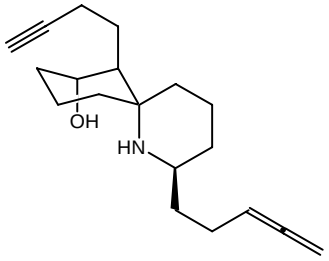
Insect pheromone **4**



Grasshopper ketone **5**



Panacene **6**

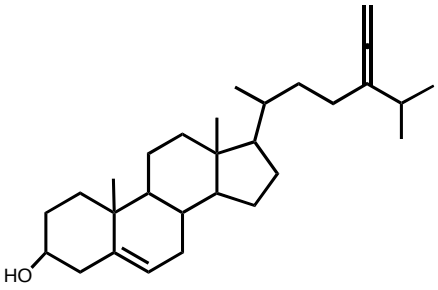


Isodihydrohistrionicotoxin **7**

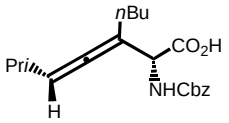
Another interest in the allenic natural products focuses on their biological activities. Insect pheromones such as allenic steroids have been recently reported. Despite the very limited understanding of the structure-activity relationships and the biogenesis of these allenic natural products, many attempts have been made to further "tune" the biological and pharmacological properties of certain active compounds simply by introducing an allenic moiety into the existing backbone of the molecule. Recent advances in this field focus on the inhibition of enzymes by allenic steroids, prostaglandins, amino acids and nucleoside analogues (Figure 3).[7]

In addition, the total synthesis of these allenic products is attracting the interest of organic chemists. Some examples will be mentioned in the following section.

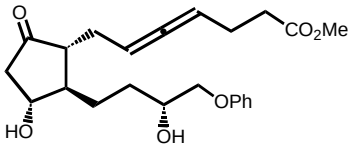
Figure 3. Examples of pharmacologically active allenes.



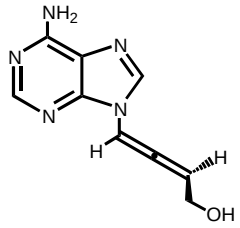
Allenic steroid **8**



Allenic aminoacid derivative **9**



Enprostil **10**



(S)-(+)-Adenallene **11**

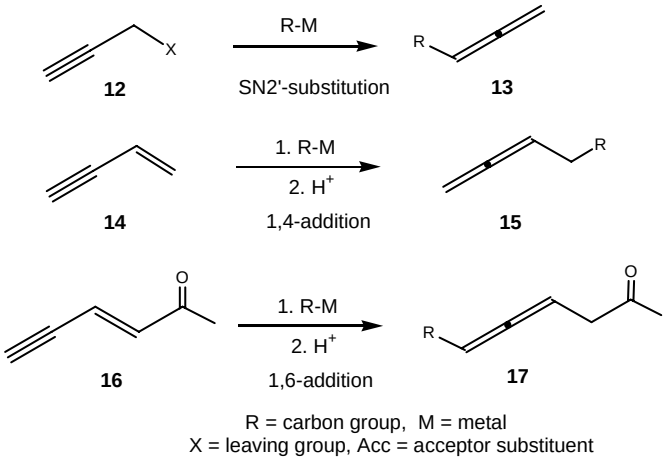
1.3. Recent advances in allene synthesis

1.3.1. Fundamental methods for the synthesis of allenes

Several types of reactions for the synthesis of allenes have been established and extensively summarized.[3,4k] These include: 1) elimination of 1,3-disubstituted alkenes; 2) isomerizations of alkynes; 3) the Doering-Moore-Skattebøl method which involves addition of a dihalocarbene to an alkene and subsequent rearrangement; 4) the direct preparation of allenes from allenyl/propargyl metal reagents; and 5) the S_N2' addition of nucleophiles to suitable propargyl derivatives. Among all these processes, three types of metal-mediated S_N2' nucleophilic substitution reactions of propargylic electrophiles present the most common methods for the formation of allenes in organic synthesis (Scheme 1).

A number of metallic compounds such as organocopper, organolithium, organomagnesium, organozinc, organoindium, organotitanium, aluminium and samarium reagents have been used in these transformations.[4k]

Scheme 1. Three types of metal-mediated nucleophilic substitution and addition reactions.



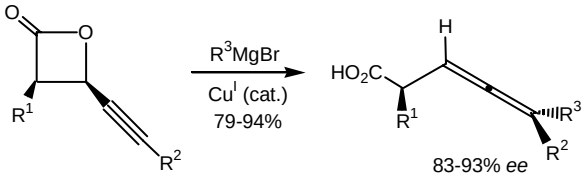
1.3.2. Asymmetric synthesis of optically active allenes

1.3.2.1. Asymmetric synthesis of allenes by substrate control

The S_N2' substitution of chiral propargylic derivatives with nucleophiles is a highly developed method which gives access to various enantiomerically enriched and pure allenes.[4e]

Recently, Nelson et al. reported the use of optically active alkynyl-substituted β-lactones as highly efficient substrates for the synthesis of allenes in copper-catalyzed S_N2' reactions (Scheme 2).[8]

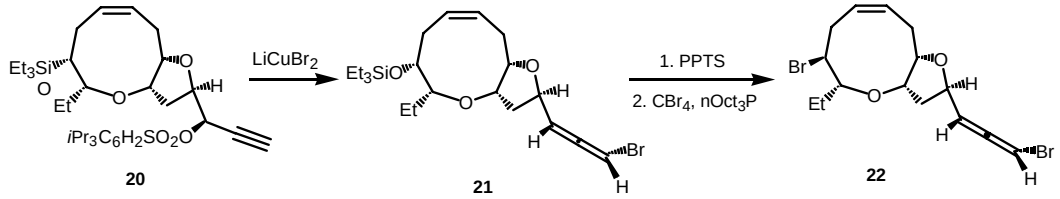
Scheme 2. Synthesis of chiral allene.



18 **19**

Another example of asymmetric copper-mediated S_N2'-substitution reaction was reported by Crimmins and coworkers for their total synthesis of (–)-isolaurallene **22** (Scheme 3).[9]

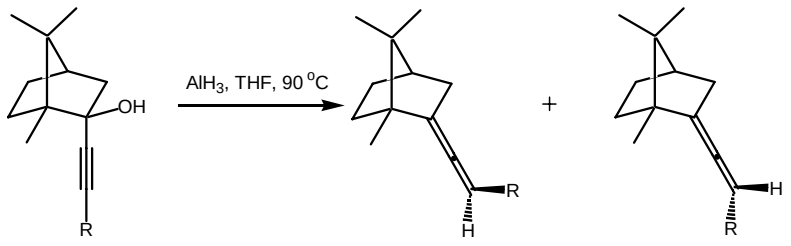
Scheme 3. Synthesis of (–)-isolaurallene.



20 **21** **22**

Aluminium hydride reagents such as AlH_3 and $LiAlH_4$ are also commonly used. Uang et al. demonstrated a highly diastereoselective synthesis of (1R)-(+)-camphor-based chiral allenes by reduction of the corresponding propargyl alcohol **23** with AlH_3 (Scheme 4).[10]

Scheme 4. Synthesis of camphor allene.

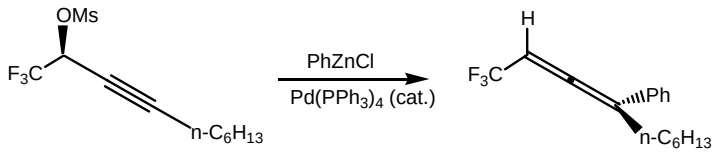


23 **24** **25**

R = CH_3, C_2H_5, C_3H_7, C_4H_9 yield (**24** + **25**): 80-92%, ratio (**24** : **25**): >95%

Palladium can also be used to generate allenes through S_N2' substitution of chiral, nonracemic propargylic derivatives. Knonno et al. prepared fluorinated allene **27** with high optical purity by reaction of the corresponding enantiomerically enriched propargylic mesylates **26** with organozinc reagents in the presence of catalytic amounts of $[Pd(PPh_3)_4]$ (Scheme 5).[11]

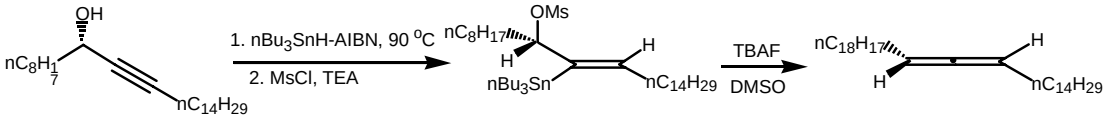
Scheme 5. Palladium catalyzed allene synthesis.



26 (96% *ee*) **27** (96% *ee*)

Recently Moore et al. described the stereoselective synthesis of novel allene **30**, isolated from Australian melolonthine scarab beetles, through regioselective addition of nBu_3SnH to propargylic alcohol **28** followed by mesylation of the hydroxyl group and elimination of nBu_3SnOMs (Scheme 6).[12]

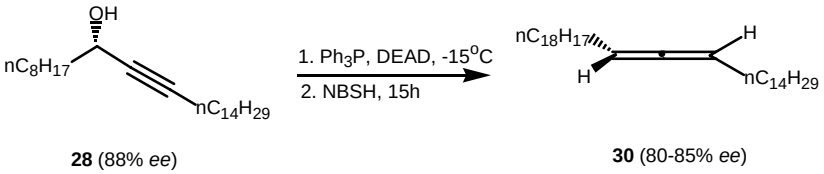
Scheme 6. Tin mediated allene synthesis.



28 (88% *ee*) **29** **30** (77% *ee*)

In the same paper, they also successfully obtained chiral nonracemic allenes by Myers' method using *o*-nitrobenzenesulfonylhydrazine (NBSH), triphenylphosphine, and diethyl azodicarboxylate (DEAD) (Scheme 7).[12]

Scheme 7. Synthesis of chiral nonracemic allene.

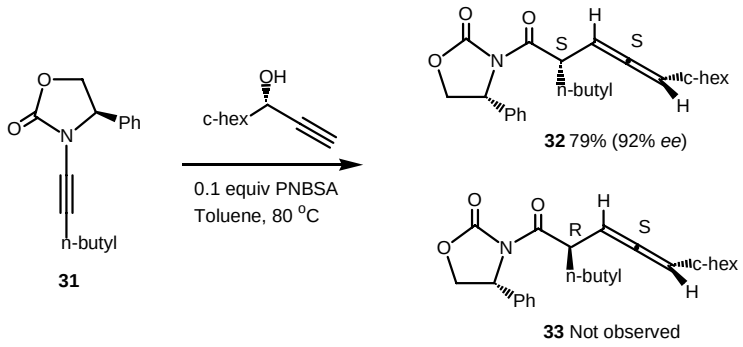


28 (88% *ee*) **30** (80-85% *ee*)

1.3.2.2. Asymmetric synthesis of allenes using chiral auxiliary

Examples of allene synthesis using a chiral auxiliary are limited. The most notable example is the synthesis of chiral nonracemic allenes from ynamides reported by Hsung's group. The stereochemistry is controlled by a chiral auxiliary which temporarily binds with the ynamide. An example is shown in Scheme 8.[13]

Scheme 8. Allene synthesis using a chiral auxiliary.

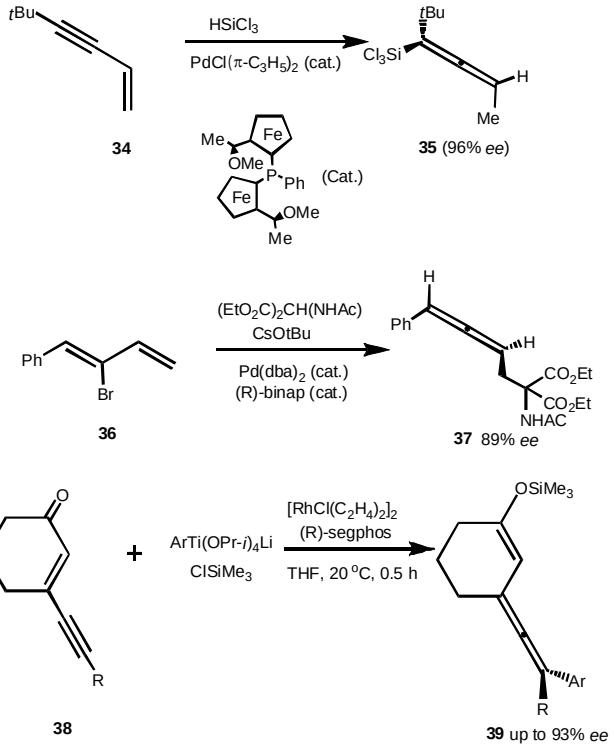


1.3.2.3. Catalytic asymmetric synthesis of allenes

Catalytic asymmetric synthesis of allenes from achiral precursors has been a challenge for a long time though it represents the most direct and atom-economical approach. A breakthrough in this field has recently been achieved by Hayashi and coworkers. They provided the first example of an efficient catalytic enantioselective

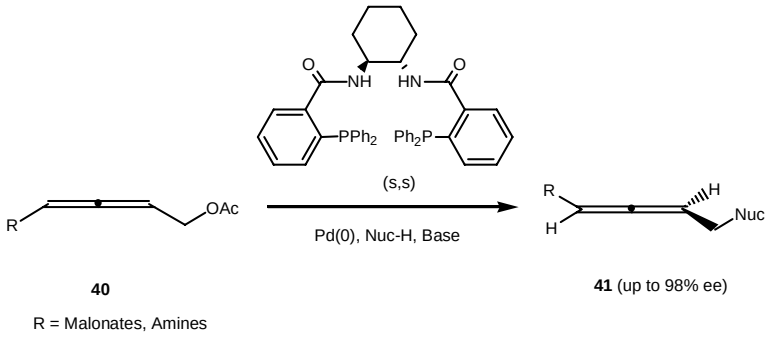
allene synthesis involving palladium-catalyzed hydrosilylation of 1-en-3-yne **34** with trichlorosilane in the presence of the chiral ferrocenyl phosphane ligand. This gave allene **35** with high ee (up to 90%) (Scheme 9).[14a] Their second approach relies on the palladium-catalyzed S_N2' substitution of prochiral 2-bromo-buta-1,3-diene **36** with soft nucleophiles (Scheme 9).[14b] They also reported rhodium-catalyzed asymmetric 1,6-addition of aryltitanates to enynones **38** to generate axially chiral allenes **39** (Scheme 9).[14c]

Scheme 9. Catalytic asymmetric synthesis of allenes.



Most recently, Trost et al. reported the synthesis of optically active allenes by dynamic kinetic asymmetric allylic alkylation of racemic allenes (Scheme 10).[15]

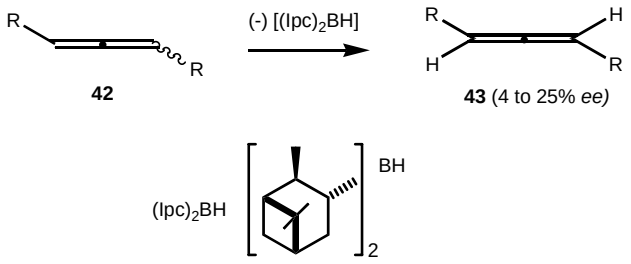
Scheme 10. Trost approach to chiral allenes.



1.3.2.4. Asymmetric synthesis of allenes by kinetic resolution of racemic allenes

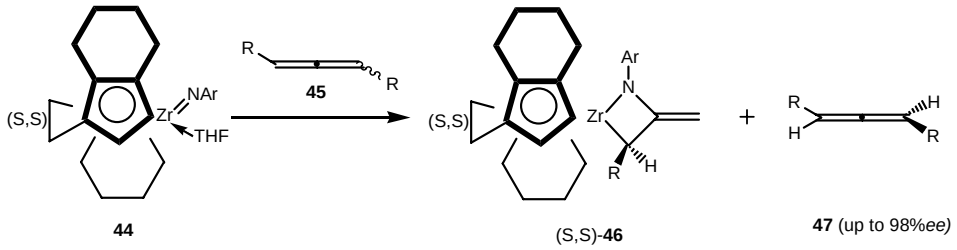
Two reactions have been used for a kinetic resolution of racemic allenes more than any others. The first one dates back to the 1960's when asymmetric hydroboration of racemic allenes was investigated. However, the efficiency was low (Scheme 11).[16]

Scheme 11. Kinetic resolution with chiral borane.



The second example was reported recently by Bergman's group. The enantiopure zirconocene imido complex **44** was employed for kinetic resolution of racemic allenes **45** to provide optically active allenes **47** in excellent *ee* (Scheme 12).[17] Their investigation only focused on a few 1,3-disubstituted allenes and the utility of this methodology on more substrates is still under further investigation.

Scheme 12. Efficient resolution of allenes.

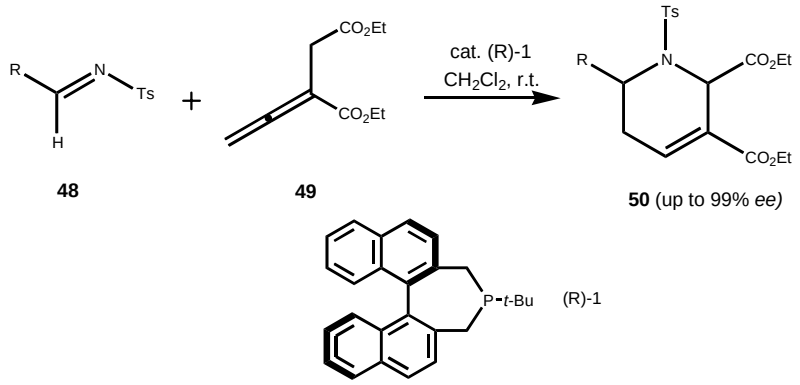


1.4. Recent synthetic applications of allenes

1.4.1. Cycloaddition

Recently Fu et al. described an asymmetric synthesis of functionalized piperidines **50** via the [4+2] annulation of imines with allenes (Scheme 13). This reaction was first reported by Kwon in 2003.[18]

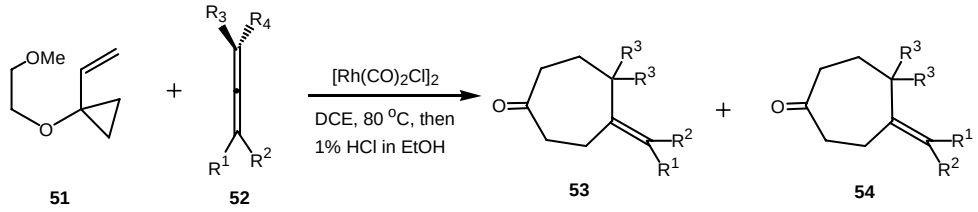
Scheme 13. Cycloaddition with allenes.

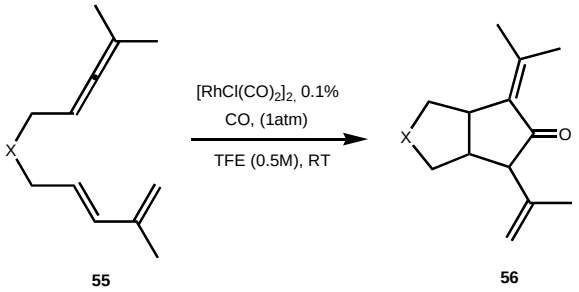


Wender and coworkers have demonstrated a series of cycloadditions involving two, three and four components using transition metal catalysts. Recently they reported two cycloaddition reactions involving allenes. The first one was a [5+2] cycloaddition of racemic allenes and vinylcyclopropanes to afford a substituted seven-member ring.[19a] The second one was a [2+2+1] cycloaddition of allenes, 1,3 dienes and CO, which is

analogous of the Pauson-Khand reaction. This produced [3.3.0] bicyclic compound **56** (Scheme 14).[19b]

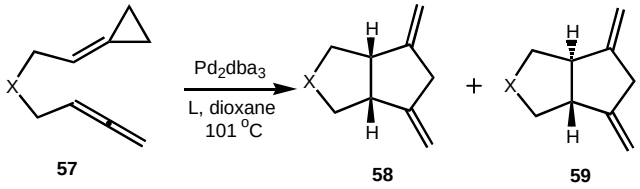
Scheme 14. Wender's cycloadditions using allenes.





Mascarenas et al. reported a palladium-catalyzed intramolecular [3+2] cycloaddition of alkylidenecyclopropanes to allenes which generates a variety of dienyl bicyclo [3.3.0] octanes **58** and **59** (Scheme15).[20]

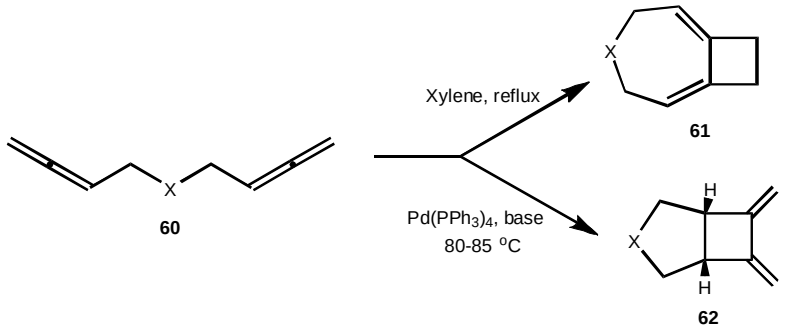
Scheme 15. Cycloaddition between allene and alkylidenecyclopropane.



More recently Ma et al. investigated a regiocontrollable [2+2] cycloaddition of 1,5-bisallenyl-substituted compounds **61**, which afforded the bicyclo [5.2.0] or [3.2.0]

compounds **(62** and **63**) (Scheme 16).[21]

Scheme 16. Intramolecular 2+2 of allenes.

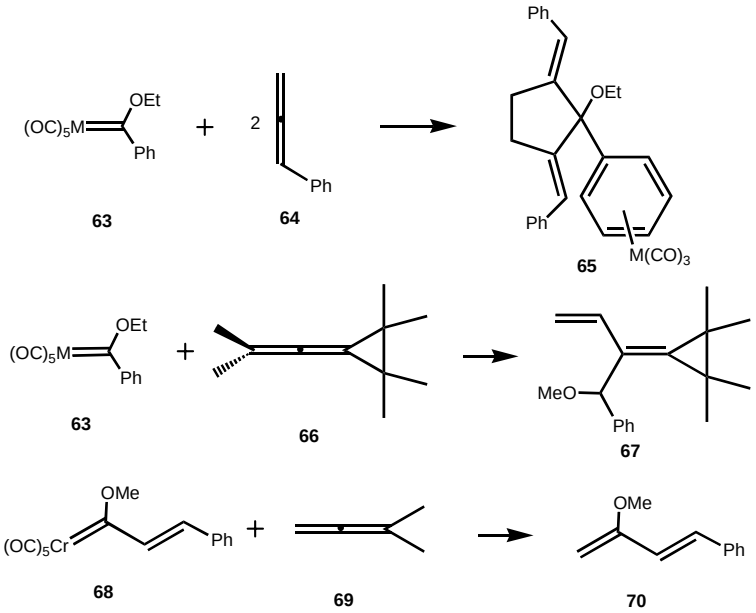


1.4.2. Cyclizations

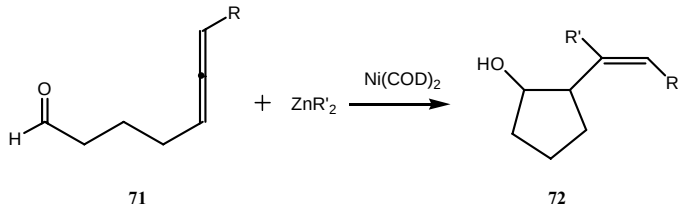
Barluenga's group has systematically investigated cyclizations of activated and deactivated allenes with alkenyl Fisher carbene complexes (Scheme 17).[22]

Montgomery and coworkers described nickel-catalyzed cyclizations between allenes and aldehydes using organozinc reagents. The cyclization occurred on the terminal carbon of the allenes and cis-disubstituted cyclopentanes were formed (Scheme 18).[23]

Scheme 17. Carbene cyclization.



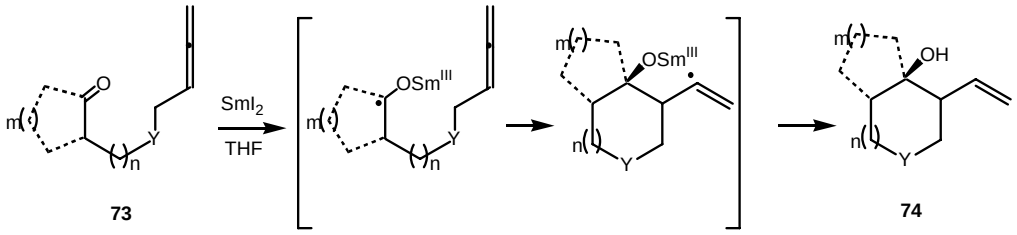
Scheme 18. Nickel catalyzed cyclization.



71 72

Ketyl-allene cyclizations promoted by samarium (II) iodide were recently reported by Molander and coworkers. The samarium initiated reaction gave the same regioselectivity but the stereoselectivity is opposite the nickel catalyzed reaction. Only trans-disubstituted cyclopentanes were obtained (Scheme 19).[24]

Scheme 19. Samarium mediated cyclization.

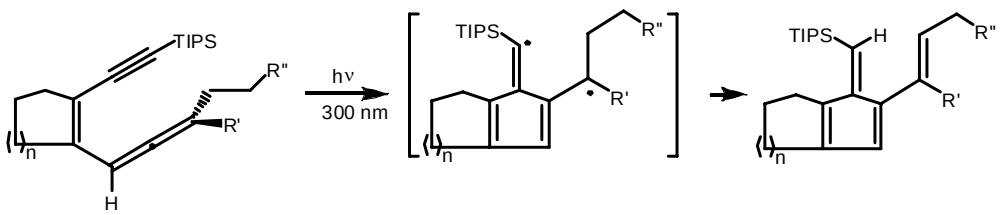


73
Y = CH_2, O, NR
m = 1,2 n = 0,1

74

Schmittel et al. demonstrated photochemical C^2-C^6 cyclizations of enyne-allenes, analogues to the Myers-Saito reaction (Scheme 20).[25]

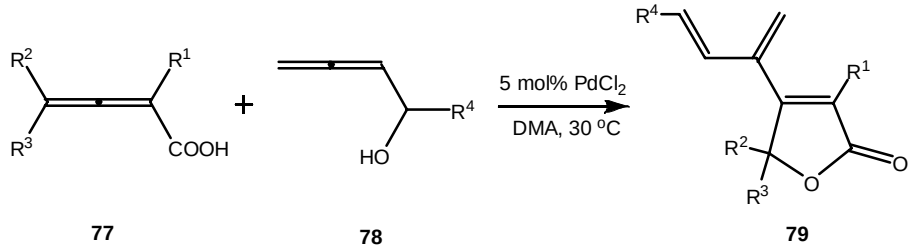
Scheme 20. Enyne allene cyclization.



75 **76**

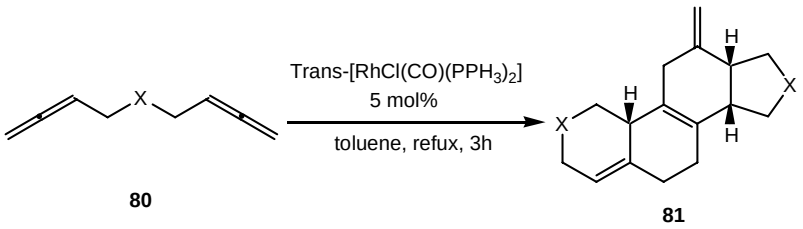
Ma and coworkers reported a PdCl-catalyzed, two-component, cross-coupling cyclization of 2,3-allenoic acids **77** with 2,3-allenols **78** to afford 4-(1', 3'-dien-2'-yl)-2(5H)-furanone derivatives **79** (Scheme 21). The sequential steps including cyclic oxypalladation, carbopalladation, and β – hydroxide elimination were proposed for the explanation of the mechanism.[26]

Scheme 21. Allene two component cyclization.



The same group described another homodimeric cyclization of 1,5-bisallenes to give steroid skeletons in one step by using a catalytic amount of rhodium compound (Scheme 22).[27]

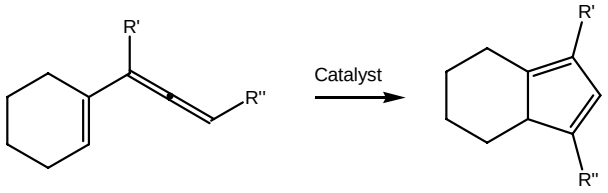
Scheme 22. Allene dimerization.



More recently, two groups independently and almost simultaneously reported metal-catalyzed cyclization of 1,2,4-trienes to make functionalized cyclopentadienes.

Toste's group used a gold (I) compound as a catalyst while Iwasuwa's group used platinum (II) catalysis (Scheme 23).[28]

Scheme 23. Allene cyclization.



82 83

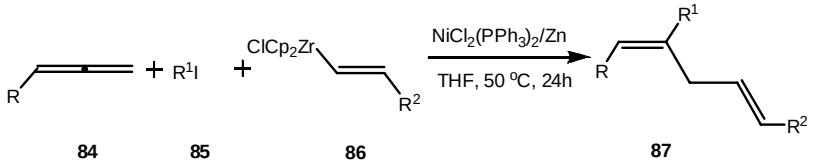
Iwasawa's conditions: $PtCl_2$ (0.05 equiv), 4 Å M.S., $ClCH_2CH_2Cl$, RT

Toste: 2% [Ph_3PAuCl], 2% $AgSbF_6$, CH_2Cl_2, -20 ^oC, 20h

1.4.3. Multicomponent coupling reactions involving allenes

Cheng et al. described a nickel-catalyzed three-component coupling reaction of allenes, aryl iodides and alkenylzirconium reagents with high regio- and stereoselectivity (Scheme 24).[29]

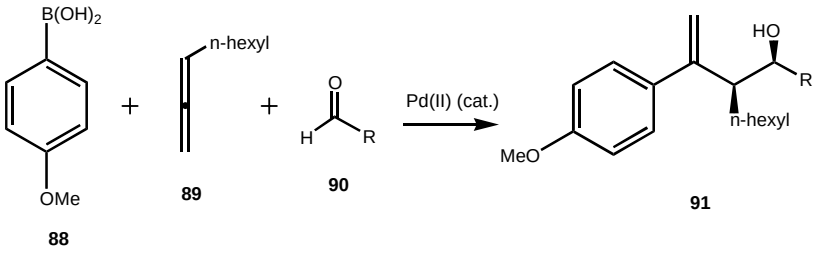
Scheme 24. Allene coupling using nickel catlysis.



84 85 86 87

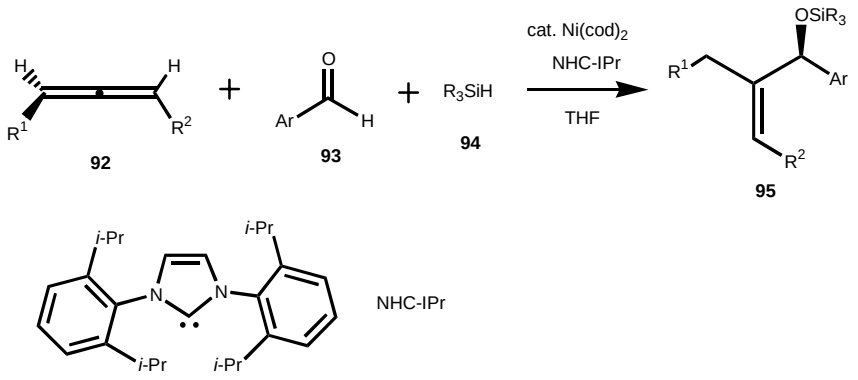
Malinakova and coworkers reported a palladium-catalyzed three-component coupling reactions of allenes with an arylboronic acid and various aldehydes (Scheme 25). [30]

Scheme 25. Allene coupling catalyzed by palladium.



Recently, Jamison et al. reported a nickel-catalyzed coupling of allenes, aldehydes, and silanes. They have investigated both achiral and chiral allenes. They also demonstrated that the axial chirality of allenes can be efficiently transferred to the newly formed stereocenter in allylic alcohols (Scheme 26).[31]

Scheme 26. Chiral allene coupling using nickel catalysis.

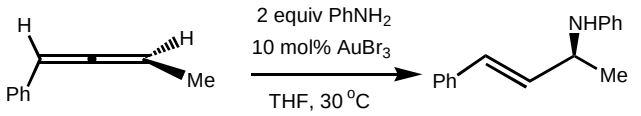


1.4.4. Nucleophilic addition to allenes

The research in this field has been well summarized in the literature.[32] The most recent significant progress on this field relies on gold-catalyzed hydroalkoxylation and hydroamination of allenes.

Yamamoto et al. described gold-catalyzed intermolecular hydroamination of allenes with arylamine and high chirality transfer from allenes to products was observed (Scheme 27).[33]

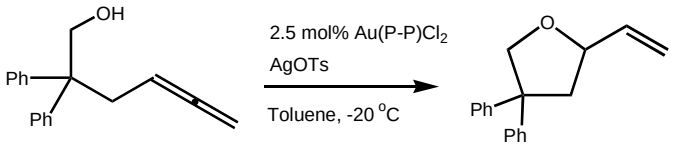
Scheme 27. Hydroamination of chiral allene.



96 (94% *ee*) **97** (88% *ee*)

Widenhoefer and coworkers described gold(I)-catalyzed enantioselective intramolecular hydroxylation of allenes (scheme 28).[34]

Scheme 28. Allene conversion to furan.

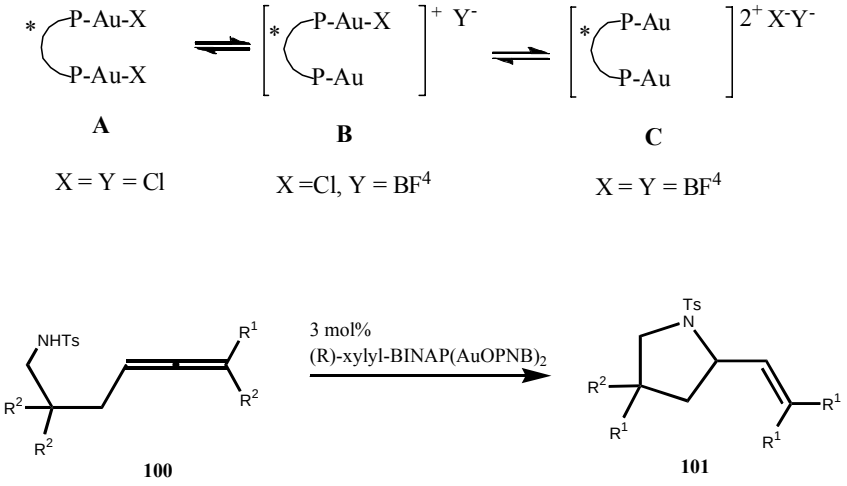


98 **99** (up to 94% *ee*)

P-P = 2,2'-bis(diarylphosphino)-biphenyl

Very recently Toste et al. reported another gold(I)-catalyzed enantioselective intramolecular hydroamination of allenes (Scheme 29). Their results revealed a remarkable counterion effect on the enantioselectivity. Monocationic species **B** afforded high enantioselectivity while dicationic species **C** catalyzed formation of product with no stereselectivity. Both species were generated in situ from precatalyst **A**.[35]

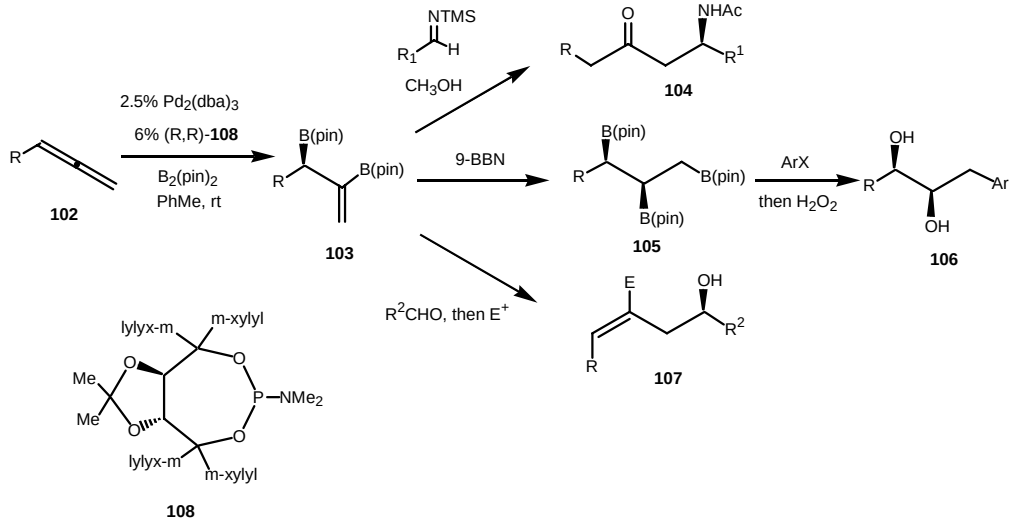
Scheme 29. Intramolecular hydroamination of allene.



1.4.5. Diboration and silaboration of allenes

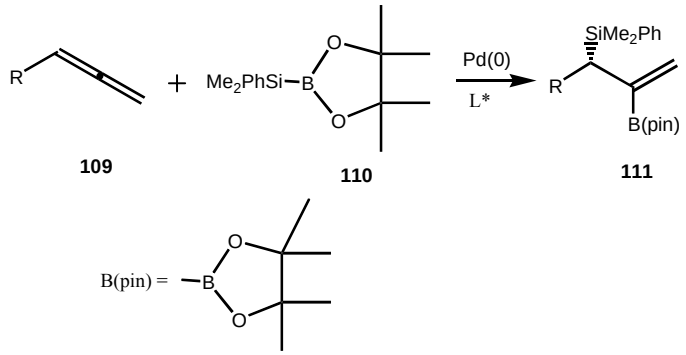
In 2004 Morken et al. reported palladium-catalyzed enantioselective diboration of prochiral allenes. Based on this reaction, they developed several sequential processes including diboration/allylation, diboration/α-aminoallylation and diboration/ hydroboration/cross-coupling (Scheme 30).[36]

Scheme 30. Palladium-catalyzed enantioselective diboration of prochiral allenes.



Recently, two groups described palladium-catalyzed silaboration of allenes (Scheme 31). Cheng et al. provide a detailed investigation of the mechanism and Suginome and coworkers developed an asymmetric version as shown in Scheme 31.[37]

Scheme 31. Silaboration of allenes.



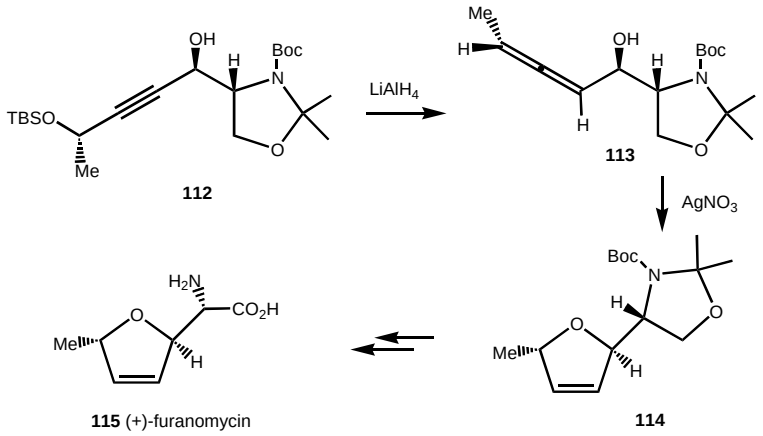
1.4.6. Application of allene transformations in total synthesis

In recent years, allenes have received increasing utility as building blocks in synthetic organic chemistry. Besides an abundance of regio- and stereoselective C-C-bond forming transformations of allenes, transfer of the axial chirality of enantiomerically enriched allenes to one or several newly formed stereogenic centers has been the key step for the total synthesis of several natural products.

VanBrunt and Standaert described the enantioselective synthesis of (+)-furanomycin in 2000.[38] In their work the formation of a α-hydroxyallene was followed by a silver-catalyzed cyclization to form dihydrofuran. During these transformations, the chirality of the stereogenic center of the propargyl alcohol was first transferred to the chirality axis of the allenic moiety of **113**, then to the newly generated stereocenter of

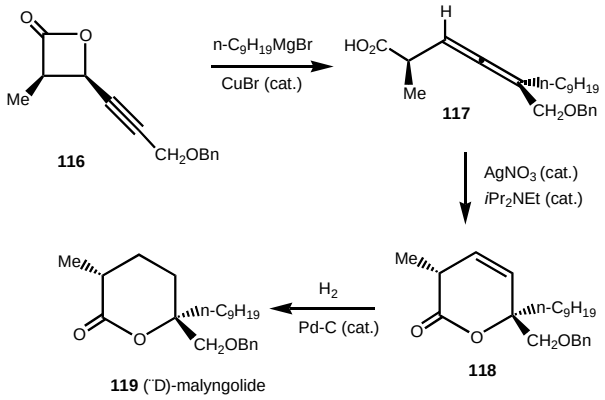
furan **114** (Scheme 32).

Scheme 32. Synthesis of (+)-furanomycin.



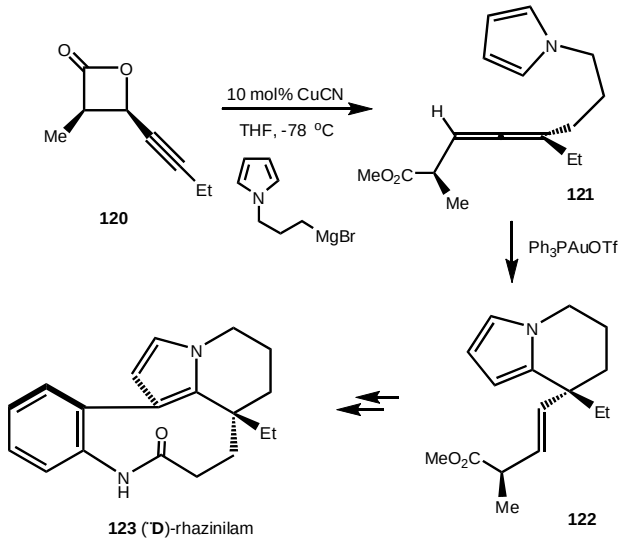
In 2000, Nelson et al. reported the enantioselective synthesis of the (—)-malyngolide, which was obtained from β-lactone in only 3 steps with 64% overall yield (Scheme 33).[8]

Scheme 33. Synthesis of (D)-malyngolide.



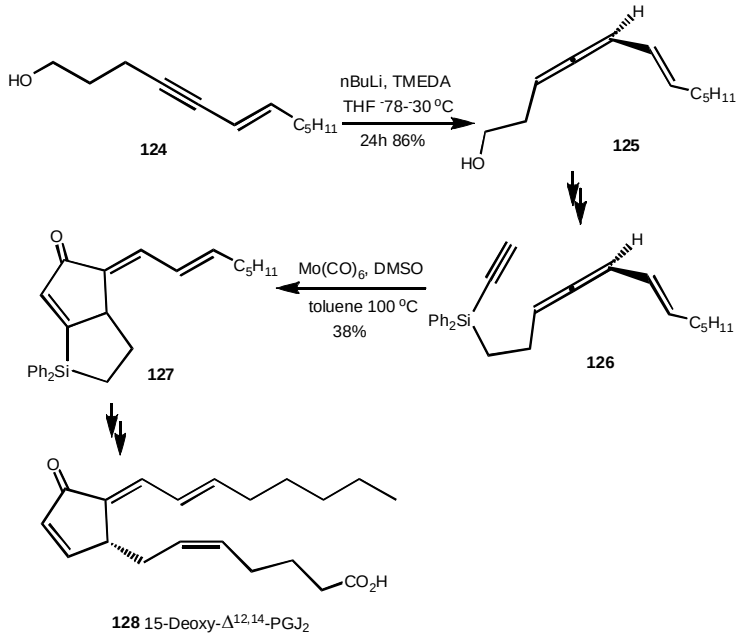
The same group recently completed the enantioselective synthesis of (—)-rhazinilam. Their key strategies involved S_N2' ring opening of β-lactone to afford enantioenriched allene, followed by intramolecular Au(I)-catalyzed pyrrole addition to enantioenriched allenes which assembled the quaternary carbon of **119** (Scheme 34).[39]

Scheme 34. Synthesis of (—)-rhazinilam.



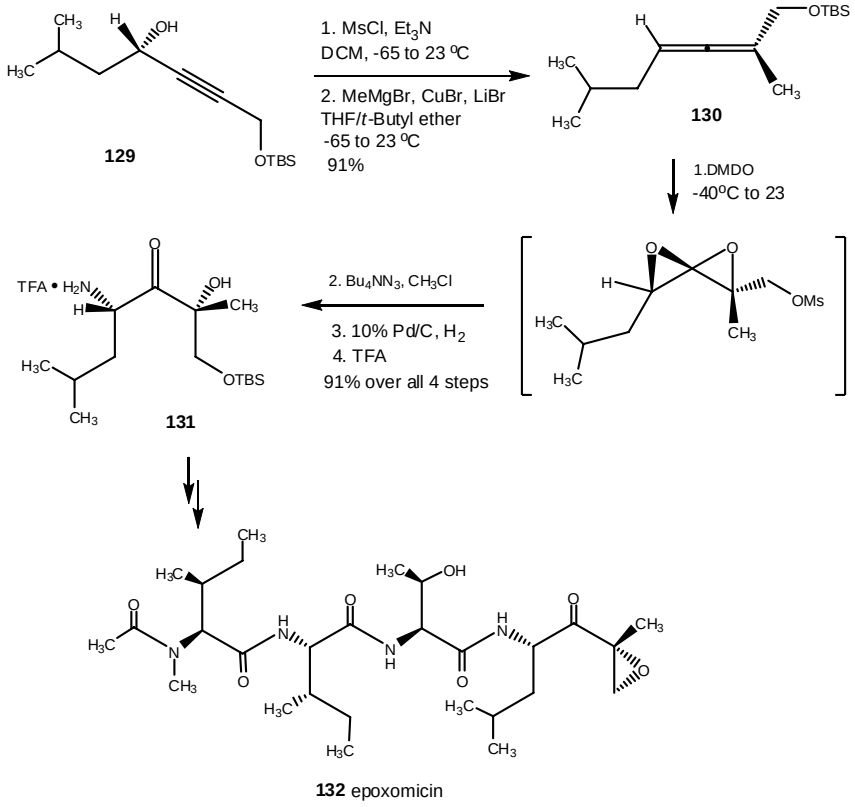
Brummond et al. reported the first total synthesis of 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 by using silicon-tethered allenic [2+2+1] cycloaddition (Pauson-Khand reaction) as the key strategy to stereoselectively assemble both double bonds of 15-deoxy-$\Delta^{12,14}$-PGJ_2 (Scheme 35).[40]

Scheme 35. Synthesis of deoxyprostaglandin J_2.



Williams et al. used a spirodiepoxide as the novel building block in their total synthesis of epoxomicin. Epoxidation of enantioenriched allene to construct chiral spirodiepoxide followed by nuclophilic opening installed three functional groups, a nucleophile, a ketone, and an alcohol, with syn selectively (Scheme 36).[41]

Scheme 36. Synthesis of epoxomicin.

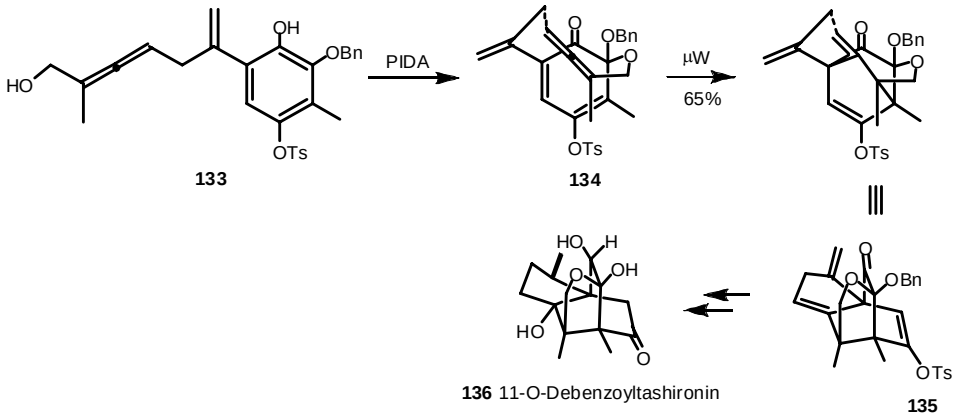


Diels－Alder reactions involving allenes also have been used in total synthesis. Danishefsky's group recently employed a remarkable oxidative dearomatization/ transannualar Diels－Alder cascade to rapidly construct a tetracylic carbon skeleton during their total synthesis of (+)-11-O-debenzoyltashironin (Scheme 37).[42]

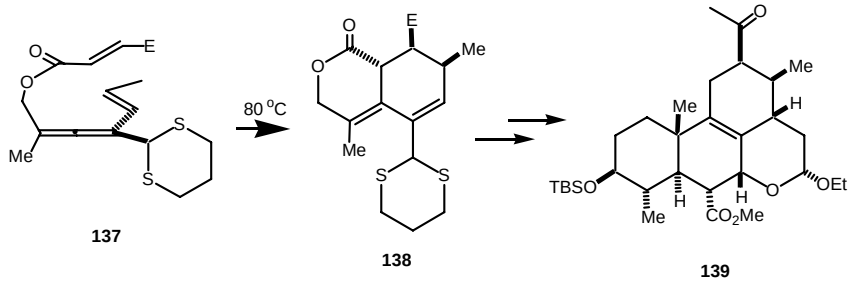
Another Diels-Alder example was demonstrated in the synthesis of the carbon skeleton

of quassinoids reported by Spino et al. (Scheme 38).[43]

Scheme 37. Synthesis of debenzoyltashironin.



Scheme 38. Synthesis of quassinoids.



1.5. Summary

Significant achievements have been made in allene chemistry during the past several years. This area is still under rapid development and it is believed that more applications of allene chemistry in synthetic organic chemistry will occur in the future.

1.6. References

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Chapter 2 Asymmetric Dihydroxylation of Allenes

2.1. Background

Organic chemists have been interested in synthetic methodology for the formation of α-hydroxy ketones for several decades. We were intrigued by the potential for asymmetric dihydroxylation of allenes as a novel approach to the synthesis of chiral α-hydroxy ketones. Efficient methods for the construction of α-hydroxy ketones has received considerable attention because this functional group is common in natural products and it can be used as a convenient building block in organic synthesis.[1]

2.1.1. Catalytic asymmetric dihydroxylation

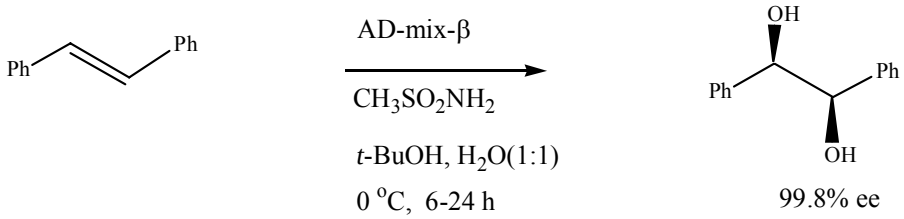
Osmium tetroxide mediated dihydroxylation has developed into a powerful tool for synthetic organic chemistry during the last century.[2a-d] In the late 1980's, as a result of several key discoveries, Sharpless et al. developed the AD-mix, which is now a commercially available premix of oxidation reagents.[2e] This osmium-mediated dihydroxylation is known as Sharpless asymmetric dihydroxylation (AD). A typical example of AD is shown as Scheme 39 and the chiral ligands involved are shown in Figure 4. It is one of the most extensively used catalytic asymmetric reactions in industry.[3] In spite of its tremendous success in organic synthesis, Sharpless asymmetric dihydroxylation is still being studied today. Some examples are shown below.

1. Mechanism.

There is a long-standing controversy about the two different mechanisms: a concerted

[3+2] pathway and a stepwise pathway which involves a [2+2] addition followed by rearrangement of the resulting osmaoxetane intermediate (Scheme 40). The [3+2] mechanism has received more support from theoretical studies than the [2+2] mechanism.[2d-e,4]

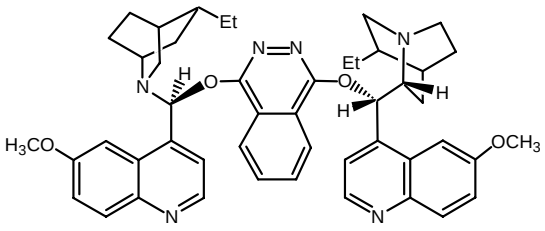
Scheme 39. Typical example for Sharpless asymmetric dihydroxylation.



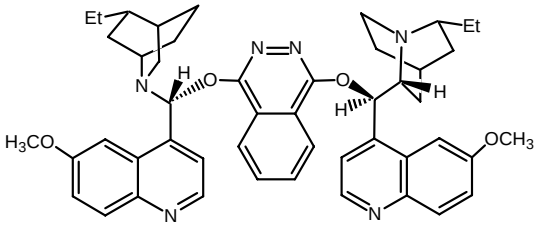
1.4 g AD-mix-β will oxidize 1 mmol olefine, contains:

0.98 g $K_3Fe(CN)_6$ (3 mmol)
0.41 g K_2CO_3 (3 mmol)
0.0078 g $(DHQD)_2$-PHAL (0.01 mmol)
0.00074 g $K_2OsO_2(OH)_4$ (0.002 mmol)

Figure 4. Chiral ligands for AD reaction.

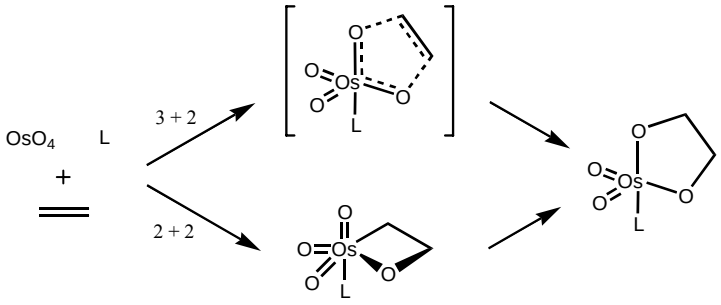


$(DHQD)_2$-PHAL
Ligand for AD-mix-β



$(DHQ)_2$-PHAL
Ligand for AD-mix-α

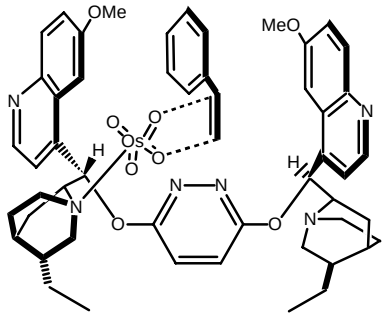
Scheme 40. Two proposed pathways for alkene dihydroxylation.



2. Transition-state model and modification of the chiral ligand.

The most known transition-state model is the U-shaped binding pocket proposed by Corey's group (Scheme 41). On the basis of this model, several new and useful catalysts have been designed.[5]

Scheme 41. Corey's U-shaped binding pocket transition-state model.



3. Immobilization of the catalysts.

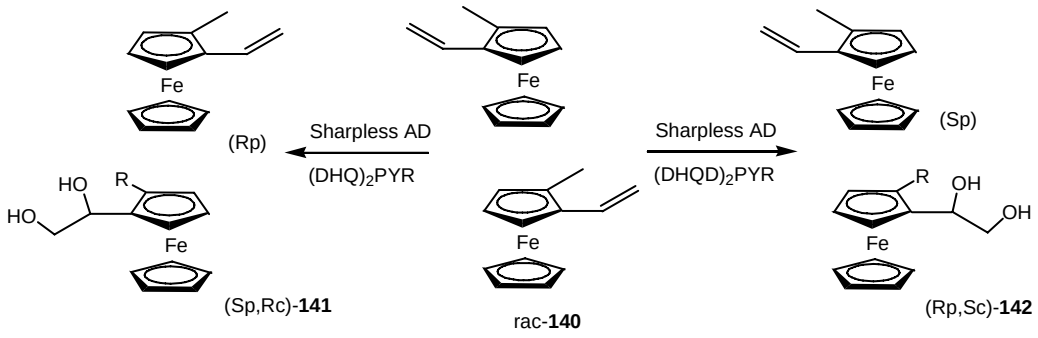
There are two major limitations of Sharpless asymmetric dihydroxylation (AD) for industrial applications: one is caused by the high toxicity and volatility of the osmium components, which is made worse by possible contamination of these toxic species in the products; the second one is the high cost of both the alkaloid-derived ligands and the metal. In order to address these issues, methods for facile catalyst separation and efficient

catalyst recovery after the AD reaction are of major interest. Much effort has been devoted to immobilization of either the alkaloid-derived ligands or the osmium component. These methods include: attaching the ligands on solid organic polymers such as polystyrene, polyacrylonitrile, polyethylene glycol or silica gel; immobilization of osmium components in microcapsules, by ionic interaction, or on supports bearing olefins.[6]

4. Kinetic resolution.

Several applications of the asymmetric dihydroxylation for the kinetic resolution of chiral racemic alkenes have been reported.[2e] Recently Walsh et al. described an interesting example of kinetic resolution of atropisomeric amides using AD reaction.[7a] More recently Moyano and coworkers reported the first non-enzymatic kinetic resolution of planar chiral ferrocene **140** by AD reaction with high efficiency (ee up to 90%) (Scheme 42).[7b]

Scheme 42. Asymmetric dihydroxylation of racemic 2-substituted-1-vinylferrocenes.



2.1.2. Asymmetric synthesis of α-hydroxy ketone

α-Hydroxy ketones are important synthons for the asymmetric synthesis of natural

products, fine chemicals and medicines. Their importance has stimulated the development of a wide variety of diastereoselective and enantioselective synthetic methods.[8] Among these effective transformations, versatile methods include the enzymatic kinetic resolution of α-hydroxy ketones[8g] and the asymmetric oxidation of enolates or enol ethers using a stoichiometric amount of chiral N-sulfonyloxaziridine,[8a] (salen)Mn catalysts,[8i] or Sharpless dihydroxylation catalysis.[8f]

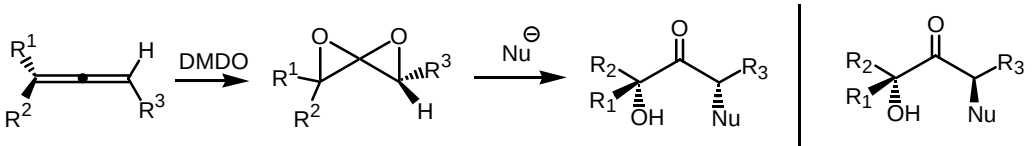
2.1.3. Oxidation of allenes

Several different methods have been developed for the oxidation of allenes in the past four decades. Early studies included ozonolysis to give the cleavage of the allenic systems,[9a] and epoxidation,[9b] mainly using peroxides and peracids as the oxidizing agent, which produces reactive intermediates such as allene oxides,[9c] cyclopropanones,[9d] and spirodiepoxides.[9e] These reactive compounds have been found in a variety of competitive pathways.[9d] Some oxidation processes were described for functionalized allenes such as allenic ketones[9f] and vinylallenes[9g] which respectively furnished 3(2H)-furanones and cyclopentenones. Among the other oxidants tested have been the Payne reagent[9h] and hypervalent iodine reagents,[9i] to respectively provide γ-lactones and enones. Almost all the procedures mentioned employed stoichiometric or excess oxidizing agents. There are also several examples of metal-catalyzed oxidations of allenes in the presence of peroxides.[9j,k]

Among these reactions are epoxidations, which have received the most attention.

Crandall's group revealed that isolable spirodiepoxides were obtained as the only products using dimethydioxirane (DMDO) as the allene oxidant. More recently Williams and coworkers have demonstrated this reaction as a useful tool in synthetic organic chemistry.[10] Their study demonstrated that chiral spirodiepoxides from chiral allenes can be opened by different types of nucleophiles with high regioselectivity and stereoselectivty to furnish densely functionalized α-hydroxy ketones (Scheme 43).

Scheme 43. Epoxidation of chiral allenes and nucleophilic opening of spirodiepoxides.

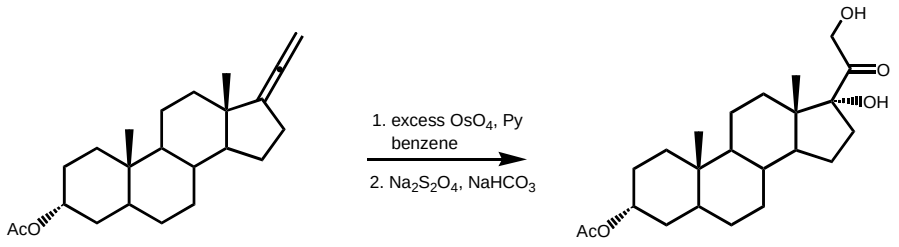


143 **144** **145** major **146** minor

Compared with systematic investigation of epoxidation of allenes, literature examples of dihydroxylation of allenes, another fundamental transformation, are sporadic and limited. To our knowledge there are only three related reports.

Crabbé et al. described the stoichiometric osmium tetroxide-mediated oxidation of an allenic compound, the steroid **147**, to give a α,α'-dihydroxyketo compound **148** (53%) as shown in Scheme 44.[11]

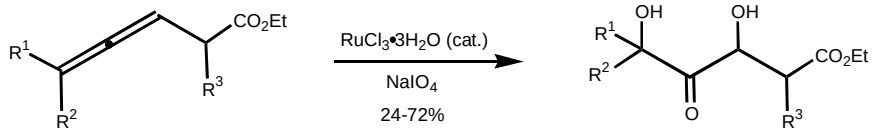
Scheme 44. Stoichiometric osmium tetraoxide-mediated oxidation.



147 **148**

Krause and coworkers reported a ruthenium-catalyzed flash oxidation of trisubstituted allenes to α,α'-dihydroxyketones. This process was limited to the allenes with aliphatic substitutents and showed low efficiency (Scheme 45).[12]

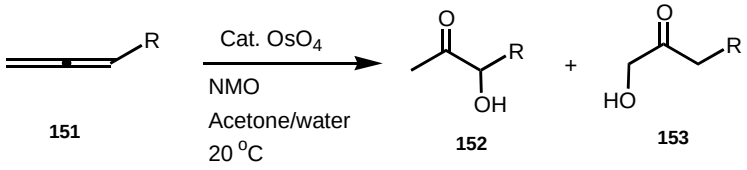
Scheme 45. Ruthenium-catalyzed oxidation.



149 **150**

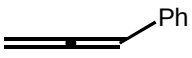
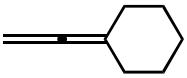
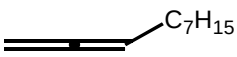
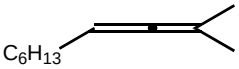
Cazes et al. described an osmium-catalyzed oxidation of several allenic compounds based on the Upjohn process which uses *N*-methylmorpholine-*N*-oxide (NMO) as the oxidizing reagent (Scheme 46). Their results showed the regioselectivity was affected by substitution of the allene (see Table 1).[13]

Scheme 46. Osmium-catalyzed oxidation of allenes.



151 **152** **153**

Table 1. Results of osmium-catalyzed oxidation of allenes.

Allene	Ratio (**152**/**153**)	%Yield
	100/0	30
	100/0	40
	77/23	43
	56/44	71

No example of catalytic asymmetric oxidation of allenes has been reported before. The following section describes our work in the area of catalytic asymmetric oxidation of allenes.

2.2. Results and disccusion

2.2.1. Asymmetric dihydroxylation of terminal allenes

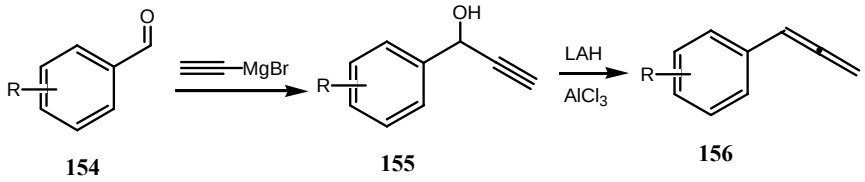
We chose to perform the allene oxidation using the Sharpless asymmetric dihydroxylation (AD) mix. The Sharpless group has rationalized their observed regio and stereoselectivity of alkene dihydroxylation using the AD mix in terms of electronic and steric factors. We felt the unique nature of the allene group would afford an opportunity to evaluate these variables further. Of course, the regioselectivity of oxidation would be a critical factor for synthetic utility, because dihydroxylation of the terminal end of a monosubstituted allene will result in an achiral α-hydroxy ketone, whereas dihydroxylation of the substituted double bond will give the useful chiral α-hydroxy ketone (see Scheme 46).

2.2.1.1 Asymmetric dihydroxylation of arylallenes

We first focused on the AD reaction of six arylallenes. Each of the allenes was synthesized by addition of ethynylmagnesium bromide to an aryl aldehyde. The resulting aryl-substituted propargyl alcohols were reduced using LAH and $AlCl_3$ in an S_N2' fashion (see Scheme 47).[14] The allenes were purified by chromatography and their spectral data

were found to be identical to literature values for each known compound and the new substances were verified spectroscopically.[15]

Scheme 47. Synthesis of arylallenes.



154 **155** **156**

Table 2. Percent yield for the two steps in synthetic scheme.

Ar	% Alkynol	% Allene
Phenyl	94	63
4-Methylphenyl	90	56
4-Methoxyphenyl	94	58
4-Chlorophenyl	95	28
2-Methylphenyl	94	44
2-Naphthyl	94	40

We have optimized the yields for the alkynol and allene steps shown in Scheme 47 and those isolated yields are listed in Table 2. Addition of ethynyl magnesium bromide gives the corresponding alkynol in excellent yield. Formation of the allene by hydride addition is a reliable reaction, but the allenes that are formed in each case are relatively volatile. This fact impacts the yield for the second step of this sequence. An additional factor is that the LAH reaction is known to give multiple products. [16] In addition to allenes by S_N2' reduction of propargyl alcohol, substantial amounts of alkynes by deoxygenation with

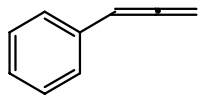
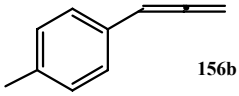
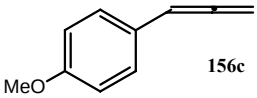
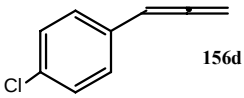
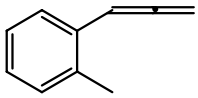
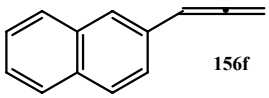
hydride and allylic alcohols by reduction of the triple bond are also formed.

Dihydroxylation of the allenes was then performed using the Sharpless AD mixes (α and β) (Scheme 48).[16] The results are shown in Table **3**.

Scheme 48. Asymmetric dihydroxylation of arylallenes.

156 **157**

Table 3. Results of asymmetric dihydroxylation of arylallenes.

Arylallene	% Yield	% Ee (configuration)	Rotation
 **156a**	45	88 (R)	-335°
 **156b**	49	89 (R)	-393°
 **156c**	79	92 (R)	-377°
 **156d**	58	82 (R)	-332°
 **156e**	52	88 (R)	-363°
 **156f**	63	92 (R)	-101°

In all cases, the major product for the dihydroxylation step resulted from addition of

the osmium tetroxide across carbons 1 and 2 of the allenes. As can be seen in Table 3, the enantioselectivity for the oxidation is excellent. The resulting hydroxy ketones were spectroscopically compared with the corresponding known substances and the new compounds were verified by spectroscopic data.[16] The optical rotations for the chiral *R*-hydroxy ketones obtained from allene oxidation using the Sharpless β-AD mix are listed in Table 3. Since optical rotations are not particularly dependable, we also checked the % ee using chiral HPLC.[17] The % ee reported in Table 3 are based on the HPLC analysis. The α-AD mix gave the *S*-enantiomers in a slightly lower % ee (78–85% ee). The undesired products (<15%) in the dihydroxylations were the result of over-oxidation of the α-hydroxy ketone, which produced the 1-aryl-1,2-diketone or other over-oxidation products by cleavage. The possible pathways for these over-oxidation products will be discussed later in the summary section.[19]

The yields shown in Table 3 and the preferred regioselectivity found in each oxidation are consistent with a reaction pathway that involves an alkene nucleophile adding to the osmium tetraoxide electrophile. This can be attributed to electronic control – the more electron rich alkene reacts with the electrophilic oxidant. An alternative explanation is that the aromatic π-system of the arylallene orients itself with respect to the osmium ligand by π-stacking. In this complex the only possible approach for the tetroxide is at the C1–C2 alkene (steric control). With the data from Table 3 we are inclined to believe that electronic influence is the major contribution to the regioselectivity, which is consistent with the observation that the 4-methoxyphenylallene results in a higher yield of

dihydroxylation. In addition, the 2-methylphenylallene does not show any result of steric impact on the dihydroxylation step. Also, the size of the naphthyl group does not adversely effect the selectivity of the dihydroxylation. One might expect steric control to be sensitive to bulk at the ortho-position of the π-system or the size of the aromatic system. The major factor controlling the enantioselectivity observed in this reaction is likely π-stacking. One would expect the ortho-methyl group to reduce the observed % ee due to the nonplanarity of the arylallene. Since no significant reduction was observed, the π-stacking region must be large enough to accommodate the twisted species.

The dihydroxylation procedure was uniformly followed to allow for comparison of the substituent effects. The percent conversion for each run was approximately 90%. Longer reaction times resulted in an increase in over-oxidation of the hydroxy ketones. The low isolated yields for the ADH reaction reported in Table 3 may be due to the inefficient recovery of the relatively volatile starting material. The yields are not based on recovered starting material, because poor recovery of the allenes does not improve the calculated yield. Another factor contributing to the low yield is the loss of material after the extensive chromatographic effort required to obtain the hydroxy ketone sufficiently pure for determination of optical activity. In either case, our HPLC analysis of the unpurified ADH reactions using the β-AD mix confirms the enhanced overall yield for the oxidation of the methoxy substituted allene.

The enantiomeric excess is excellent for these arylallenes, particularly for the β-AD mix. Comparison of the literature values for optical rotations to the values we have

obtained and then factoring in our results from chiral chromatography, we can see that the literature rotation for Ar = 4-methylphenyl (-385^{o} for the R-isomer)[16b] and for Ar = 4-methoxyphenyl (-344^{o} for the R-isomer)[16c] closely agree with our data. In the case of Ar = 4-chlorophenyl, our observed rotation (-332^{o}) is considerably higher than the literature value.[16d] The rotation we obtained for Ar = 2-methylphenyl is -363^{o} (c = 0.25, $CHCl_3$) and -101^{o} (c = 0.08, $CHCl_3$) for Ar = 2-naphthyl.

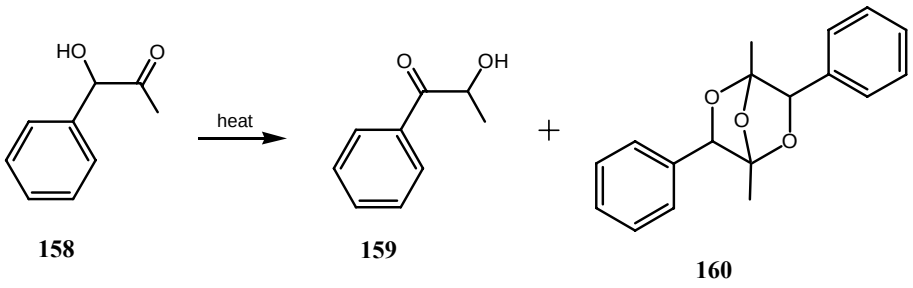
In Table 4 we compare our results with the known procedures for synthesis of 1-hydroxy-1-phenyl-2-propanone. Although the allene dihydroxylation does not yield the highest % ee, it does represent a direct route to the α-hydroxy ketone functional group comparable to the other stereoselective methods. The yields for the α- and the β-mixes are similar but the % ee was higher for the β-mix reactions in each case. It is interesting to note that this is consistent with the observation Sharpless has made concerning the use of his AD mixes.[2e] For example, asymmetric dihydroxylation of trans-5-decene gives 5,6-dihydroxydecane with 97% ee when using β-AD mix, and 94% ee when using the α-AD mix.

Table 4. Asymmetric synthesis of 1-hydroxy-1-phenyl-2-propanone.

Method (reference)	(%) Yield	% Ee
Oxaziridine addition (8b)	61	95
Enzymatic reduction (8d)	83	86
Allene ADH (this work)	45	88

Finally, we did not observe enolization nor dimerization of the hydroxy ketones under the conditions of the dihydroxylation. The enolization process to form **159** shown in Scheme 49 is reported to occur,[19] but only after prolonged time at elevated temperatures. For example, the 1-(4-chlorophenyl)-1-hydroxy-2-propanone reaches equilibrium with the isomer 1-(4-chlorophenyl)-2-hydroxy-1-propanone and its dimer (see Scheme 49) after 168 h at 55 °C. Warren et al. also described the air oxidation of the 1-aryl-1-hydroxy-2-propanone, which produces the same 1,2-diketone that we observed as mentioned above. We have observed a slow degradation of the hydroxy ketones and it appears that this process is an oxidation pathway rather than enolization or dimerization. It does result in loss of optical activity. For example, the ee of 1-phenyl-1-hydroxy-2-propanone will decrease from 88% to about 80% or lower during 6 months (the sample was stored in a refrigerator).

Scheme 49. Enolization and dimerization of α-hydroxy ketone.



158 **159** **160**

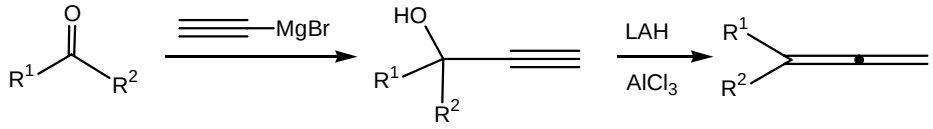
2.2.1.2 Asymmetric dihydroxylation of other terminal allenes

In order to determine the utility of this reaction we explored the AD reaction with aliphatic monosubstituted allenes and with 1,1-disubstituted allenes. We expected that the

1,1-disubstituted allene would be as regioselective as the mono-substituted examples. The fact that the resulting tertiary alcohol would be stereogenic and non-epimerizable was an attractive feature. We were also interested in the regioselectivity and the efficiency of AD of aliphatic allenes.

The synthesis of the desired allenes (see Scheme 50) was performed using the same procedure as the mono-substituted allenes reported in the previous section. That is, ethynyl Grignard was added to the corresponding ketone or aldehyde and the resulting propargyl alcohol was reduced with LAH in an S_N2' fashion.

Scheme 50. Synthesis of aliphatic and 1,1-disubstituted allenes.



161 **162** **163**

Table 5. Percent yield for the two steps in synthetic scheme.

R^1	R^2	% Alkynol	% Allene
n-Pentyl	H	94	25
Benzyl	H	76	27
n-Hex	Me	86	29
n-Bu	Et	90	21
Ph	Me	—	71

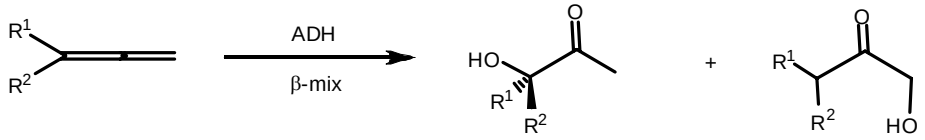
Our results for the asymmetric dihydroxylation are shown in Table 6. The major

product for the dihydroxylation of allenes **163c-d** was the corresponding hydroxy methyl ketone of each. That is, the oxidation occurs regioselectively across the more substituted alkene as expected. The enantioselectivity, however, was not very impressive. We have found that the best % ee for these non-aryl substituted allenes was on the order of 20%, but typically it was much less. The AD was more successful in the reaction with 3-phenyl-1,2-butadiene (**163e**). In this case the Sharpless β-AD mix gave the tertiary α-hydroxy ketone (**164e**) in good yield and excellent enantioselectivity (see Table 6). The identity of these resulting hydroxy ketones was verified by spectroscopic data.[21] The enantiomeric excess for each of the chiral *R* hydroxy ketones obtained from these alkyl and disubstituted allenes was determined by chiral HPLC. The optical rotations were not as useful because the known compounds did not have reported values to compare. As we found with the arylallenes, the α-AD mix is less selective but does form the enantiomeric α-hydroxy ketone in each case. It might be that the α mix is less optically pure, but both AD mixes are reported to be >95% optically pure by Aldrich.

It is interesting to compare the reactivity of 4-phenyl-1,2-butadiene (**163a**) and 1,2-octadiene (**163b**).[22] The results of the octadiene were consistent with the other alkyl disubstituted allenes. Poor enantioselectivity was observed in the formation of 3-hydroxy-2-octanone (28% yield, 58% ee). But much to our surprise, the benzyl substituted allene gave very good enantioselectivity of 3-hydroxy-4-phenyl-2-butanone (see Table 6).[23] This single result does more to clarify the selectivity of the Sharpless reagent than any of the other allenes we have studied. It is apparent that there is a

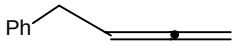
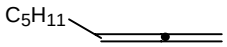
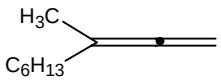
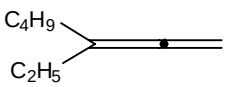
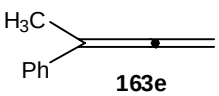
π-stacking component to the phthalizine and/or quinoline substrates of the AD mix that facilitates the oxidation process. In the previous section we concluded that π-stacking was important. We also found that the styryl nature of the phenyl substituted allenes was a major factor. But the benzyl substituted allene result indicates that although an aryl stabilized carbocation helps in the yield of dihydroxylation, it is not essential for an enantioselective reaction.

Scheme 51. Asymmetric dihydroxylation of terminal allenes.



163 **164** **165**

Table 6. Results of asymmetric dihydroxylation of terminal allenes.

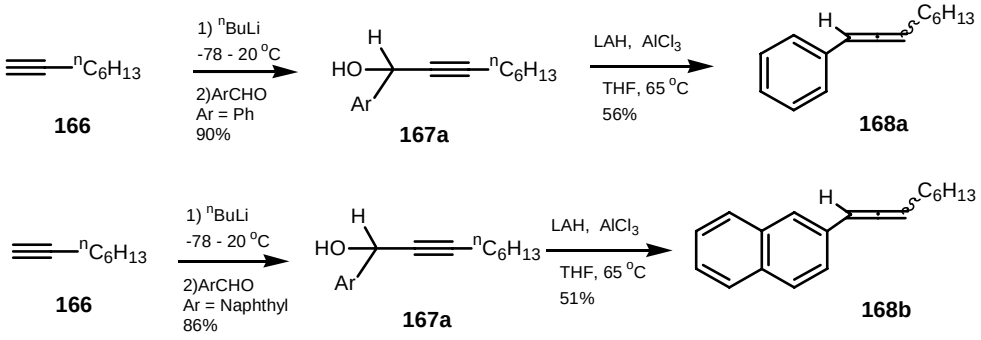
Allene	% Yield	Ratio	% Ee	Rotation
 **163a**	30	100/0	77	-40°
 **163b**	28	100/0	58	-10°
 **163c**	29	100/0	50	-9.1°
 **163d**	30	100/0	<5	-5.7°
 **163e**	72	100/0	86	-229°

2.2.2. Asymmetric dihydroxylation of 1,3-disubstituted allenes

The mono and 1,1-disubstituted allenes have shown complete regioselectivity and high stereoselectivity in the synthesis of chiral aryl substituted α-hydroxy ketones using asymmetric dihydroxylation. We also were drawn to the 1,3-disubstituted case because that class of allenes is chiral and there was potential for kinetic resolution using the AD reaction at low conversion. This was intriguing for mechanistic purposes, but it also has significant potential as a method for obtaining optically active allenes.

We first prepared the allenes on which we wanted to test the AD reaction. We found that the S_N2' reaction was successful for formation of allenes **168a** and **168b**. The first step required synthesis of their corresponding alkynols, which were formed by addition of the anion of 1-octyne to the appropriate aldehyde (Scheme 52).

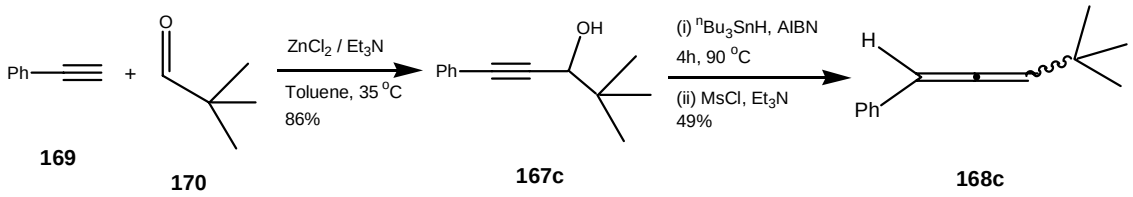
Scheme 52. Synthesis of 1-phenyl-1,2-nonadiene and 1-naphthyl-1,2-nonadiene.



The alkyne needed for the synthesis of the *tert*-butyl substituted allene **168c** (see Scheme 53) was not readily available, so the procedure of Jiang and Si[24] was used and it gave the necessary propargyl alcohol in good yield. Use of the LAH reaction on the

alkynol for the formation of **168c**, however, was not successful. Fortunately, reaction with tin hydride under radical conditions as described by McGrath and co-workers gave allene **168c**.[25]

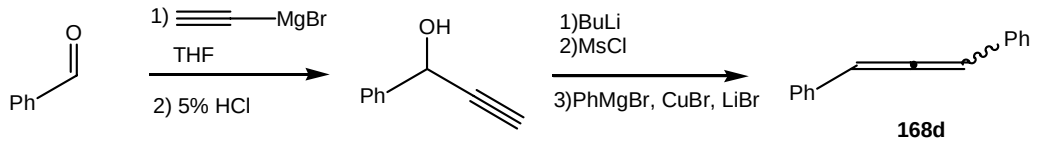
Scheme 53. Synthesis of 1-phenyl-4,4-dimethyl-1,2-pentadiene.



169 **170** **167c** **168c**

Synthesis of 1,3-diphenylallene **168d** using this tin hydride procedure was complicated by undesired by-products. Instead its synthesis was performed as described by Bergman and co-workers.[26] This method involves an S_N2' addition of a phenyl anion onto the mesylated propargyl alcohol (Scheme 54). Although this gives a good yield of the allene, we have found that this particular allene (**168d)** is not very stable.

Scheme 54. Synthesis of 1,3-diphenyl-1,2-propadiene.



168d

With these allenes in hand, we then performed AD reactions of each one. Dihydroxylation of the 1,3-disubstituted allenes presented an interesting challenge. Our previous experience with aryl substituted allenes led us to believe that we would be able to control the regioselectivity of the oxidation. We expected that the more nucleophilic

double bond of the allene would react first. Although our results were consistent with this prediction, we also found numerous over-oxidation products in these examples as shown below. The possible pathways for these over-oxidation products will be discussed later in the summary section.[19]

Allene **168a** gave a good yield of 1-hydroxy-1-phenyl-2-nonanone (**171a)**.[27] Unless considerable care was taken, the over-oxidized 1-phenyl-1,2-nonadione (**173c**) was also obtained. We were familiar with the diketone because it is a minor product in the asymmetric dihydroxylation of the mono-substituted allenes. In addition to compound **173c**, however, we also obtained the dihydroxyketone **173b** (see Scheme 55, Table 7). The stereochemical relationship between the hydroxyl groups in diol **173b** was not determined. The two over-oxidized products are not formed in high yield and several attempts to selectively form the diol in preference to dione **173c** have failed. The possibility of controlling the formation of two stereocenters with the single step oxidation by intentionally over-oxidizing 1,3-disubstituted allenes with the Sharpless β-mix has not been successful.

Scheme 55. Asymmetric dihydroxylation of 1-phenyl-1,2-nonadiene.

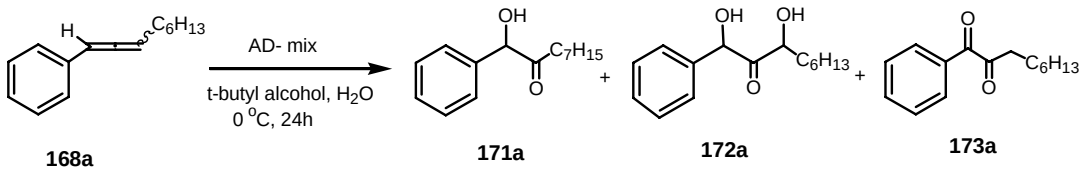
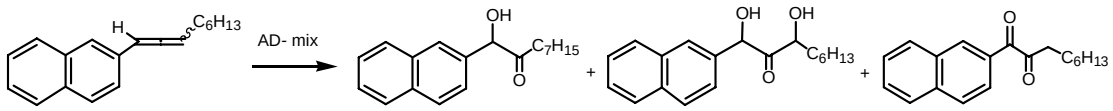


Table 7. Asymmetric dihydroxylation of 1-phenyl-1,2-nonadiene.

Amount of oxidant	AD	% **168a** (% ee)	% **171a** (% ee)	% **172a** (% ee)	% **173a**
0.004	β	25 (37)	29 (79)	25 (not determined)	<5
0.006	β	20 (45)	31 (83)	32 (82)	<5
0.004	α	25 (20)	27 (71)	25 (69)	<5

The naphthyl substituted allene (**168b**) behaved similarly to compound **168a** (see Scheme 56 and Table 8). The major product was the desired α-hydroxy ketone and the over-oxidized products were also observed. Presumably the yields of α-hydroxy ketone formation for the naphthyl compound are better because of the increased π-stacking that exists in the chiral ligand.

Scheme 56. Asymmetric dihydroxylation of 1-naphthyl-1,2-nonadiene.



168b **171b** **172b** **173b**

Table 8. Asymmetric dihydroxylation of 1-naphthyl-1,2-nonadiene.

Amount of oxidant	AD mix	% **168b** % ee	% **171b** (% ee)	% **172b** (% ee, de)	% **173b**
0.004 equiv	β	30 (2)	20 (85)	<5	<5
0.002 equiv	β	35 (6)	15 (>99)	<5	<5
0.008 equiv	β	10	35 (93)	20 (>90, 90)	<5
0.008 equiv	α	24 (15)	40 (89)	20 (>90, 81)	<5
0.008 equiv	α+ β	10	30 (19)	23 (>99, 18)	<5

We synthesized allene **168c** in order to maximize the steric preference for one enantiomer of the allene over the other. It follows that this would allow for kinetic resolution of the allene. Indeed we found that the bulkiness of the *tert*-butyl group was sufficient to stop the oxidation of one of the enantiomers. Even with prolonged reaction times the less reactive enantiomer was only slightly consumed. Instead the additional oxidant reacted to give the further oxidized product of the reactive enantiomer (see Table 9). The major oxidized product was 1-hydroxy-4,4-dimethyl-1-phenyl-2-pentanone. This α-hydroxy ketone was isolated at best in yields around 40%. This is consistent with the selective reaction with only one enantiomer of the allene (see Scheme 57). The maximum yield should be 50%. As expected the electron rich aryl-substituted alkene was the more reactive site. We also obtained trace amounts of the 1,2-pentanedione (**173c**) and the 1,3-dihydroxy-2-pentanone (**172c**) as in the AD reaction of allenes **168a** and **168b**. A fourth product isolated in this reaction was 3-hydroxy-4,4-dimethyl-1-phenyl-1,2-pentanedione (**174**).

Scheme 57. Asymmetric dihydroxylation of 1-phenyl-4,4-dimethyl-1,2-pentadiene.

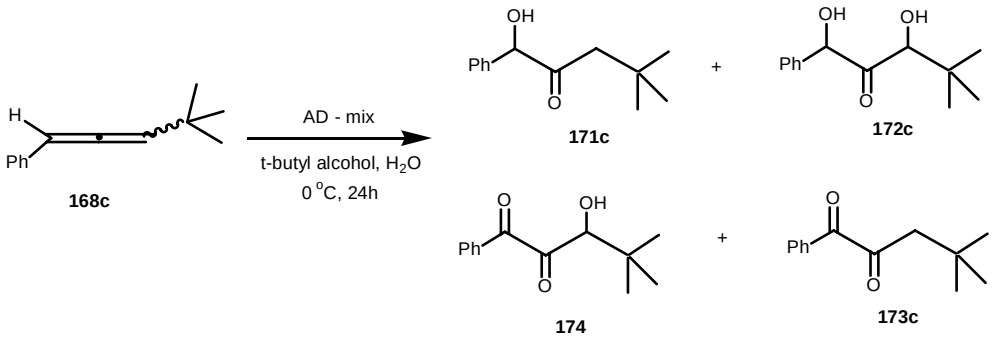


Table 9. Asymmetric dihydroxylation of 4,4-dimethyl-1-phenyl-1,2-pentadiene.

Amount of oxidant	AD	% **168c** (% ee)	% **171c** (% ee)	% **172c** (% de)	% **174c** (% ee)
0.004 equiv	β	29 (59)	15 (<5)	12 (34)	6 (54)
0.008 equiv	β	18 (>99)	40 (64)	28 (53)	20 (34)
0.008 equiv	α	11 (>94)	20 (45)	10 (21)	9 (10)

We were pleased to find that the Sharpless AD mixes were able to distinguish between the enantiomers of the sterically hindered allene **168c**. When the reaction was performed with a limiting amount of oxidant, the recovered allene was found to be nearly pure enantiomer (see Table 9). The ee value is determined by ^{1}H NMR in the presence of a mixture of the achiral salt Ag(fod) and the optically active complex (+)-Yb(hfbc)$_3$.[29] Using the AD β-mix results in recovery of the *R* enantiomer of **168c** and the α-mix allows isolation of the *S* enantiomer.[25b] The kinetic resolution of allenes has been reported previously.[28] However, the utility of our procedure is limited. But, few examples exist that compare to the procedure we report here. For example, we were unable to perform complete kinetic resolution on allenes **168a** or **168b** using this methodology. The enantiomeric enrichment of unreacted allene, when the oxidant was the limiting reagent, was typically <40% for these allenes.

We were curious about the possibility of resolving 1,3-diphenyl-1,2-propadiene (**168d**). We expected that the chiral environment would be very selective for this compound (see

Scheme 58). The limited solubility and the inherent instability of this compound made it more challenging to find the best conditions for asymmetric dihydroxylation, but we were finally successful in obtaining an excellent kinetic resolution of the chiral diphenyl allene. The best results were obtained when the reaction was run at 0 °C and to 70% conversion. The recovered allene was obtained in 98% ee as shown by HPLC analysis as shown in Table 10.

Scheme 58. Asymmetric dihydroxylation of 1,3-diphenyl-1,2-propadiene.

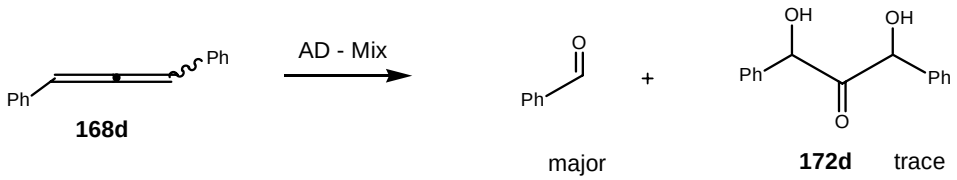


Table 10. Asymmetric dihydroxylation of 1,3-diphenyl-1,2-propadiene.

Amount of oxidant	AD mix	Temp (^{o}C)	% Allene (ee %)
0.004 equiv Os	β	25	25 (67)
0.004 equiv Os	β	0	29 (98)

2.2.3. Asymmetric dihydroxyklation of trisubstituted allenes

We have discussed the scope of this methodology with respect to terminal and 1,3-disubstituted allenes. We also have found that AD can be used for kinetic resolution of sterically hindered allenes. Though α-hydroxy ketones were observed as major products with generally high enantioselectivity from the AD reaction, other

over-oxidation products were also obtained for the 1,3-disubstituted allenes. We were interested in exploring the chemoselectivity, regioselectivity and stereoselectivity of asymmetric dihydroxylation of trisubstituted allenes. We also predicted it would be possibile to have kinetic resolution of racemic trisubstituted allenes during the reaction.

We chose five trisubstituted allenes for the AD reaction. Two of them are achiral and the other three are racemic. The allenes were synthesized efficiently by tin hydride-mediated radical process mentioned before as shown in Scheme 59.[25]

Scheme 59. Synthesis of trisubstituted allenes.

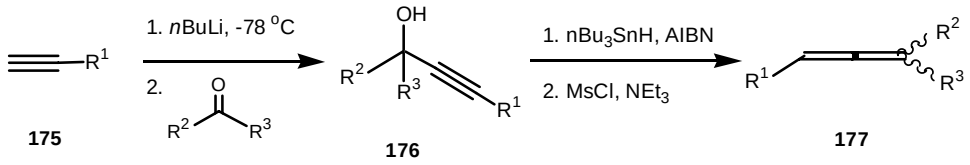


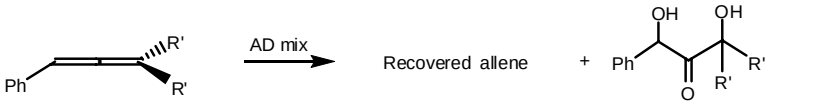
Table 11. Percent yield for the two steps in synthetic scheme.

R			% Alkynol	% Allene
R^1	R^2	R^3	**176**	**177**
Ph	Me	Me	79	39
Ph	$-CH_2(CH_2)_3CH_2-$		87	69
Ph	Me	t-Bu	96	72
Ph	Me	Ph	69	59
Hex	Me	Naph	50	31

We first tested the achiral allene **177a** and **177b**. In addition to the recovered allenes, α,α'-hydroxyketone **178** is the only isolated product (see Scheme 60). The significant

amount of allene recovered (40-70%) demonstrates that the trisubstituted allenes are less active than mono- or di-substituted allenes (Table 12). The enantioselectivity for both allenes were low.

Scheme 60. Asymmetric dihydroxylation of achiral trisubstituted allenes.



177a or 177b

a R' = CH_3

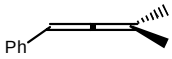
b R' = $-CH_2(CH_2)_3CH_2-$

178a or 178b

a R' = CH_3

b R' = $-CH_2(CH_2)_3CH_2-$

Table 12. Asymmetric dihydroxylation of achiral trisubstituted allenes.

Allene	% Recovered allene	%α,α'-Dihydroxyketone (% ee)
 **177a**	39	38 (51)
 **177b**	69	16 (31)

We then tested the three racemic allenes (**177c-177e**) (see Scheme 61). Our results are shown in Table 13. The over oxidized product, α,α'-dihydroxyketone **178c**, was obtained from allene **177c**. Only one diastereomer was observed as shown by HPLC with moderate ee (66%). When 36% of the allene was recovered from the asymmetric dihydroxylation it had a 77% ee which is a reasonably efficient kinetic resolution of this compound. In addition to the recovered allene and α,α'-hydroxyketone, we also observed α-hydroxydiketone **179c**. Moderate to good ee were obtained for both

α,α'-dihydroxyketone and α-hydroxydiketone. This allene also showed high diastereoselectivity for formation of the α,α'-dihydroxyketone. The *syn* product is presumed to be the major product based on a previous report.[12]

The more bulky allene, **177d**, showed good efficiency for kinetic resolution (70% ee) at low conversion. The bulkiness of the *t*-butyl group is presumably the reason for formation of both syn and anti dihydroxy ketones (**178d**). The naphthyl compound (**177e**) does not show any improvement in selectivity and it gave a poor kinetic resolution of only 45% ee.

Scheme 61. Asymmetric dihydroxylation of racemic trisubstituted allenes.

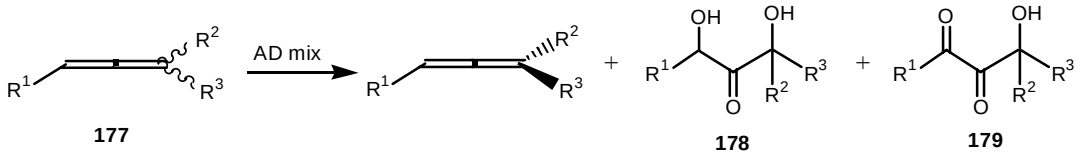
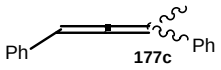
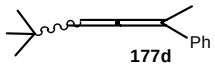
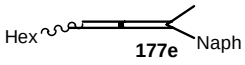


Table 13. Asymmetric dihydroxylation of racemic trisubstituted allenes.

Allene	% Recovered	%α,α'-Hydroxyketone		%α,-Hydroxydiketo
	(%ee)	Syn	Anti	(%ee)
 **177c**	36 (77)	39 (66)	—	—
 **177d**	38 (70)	10 (79)	5 (70)	33 (31)
 **177e**	26 (45)	41 (59)	—	22 (56)

2.2.4. Summary

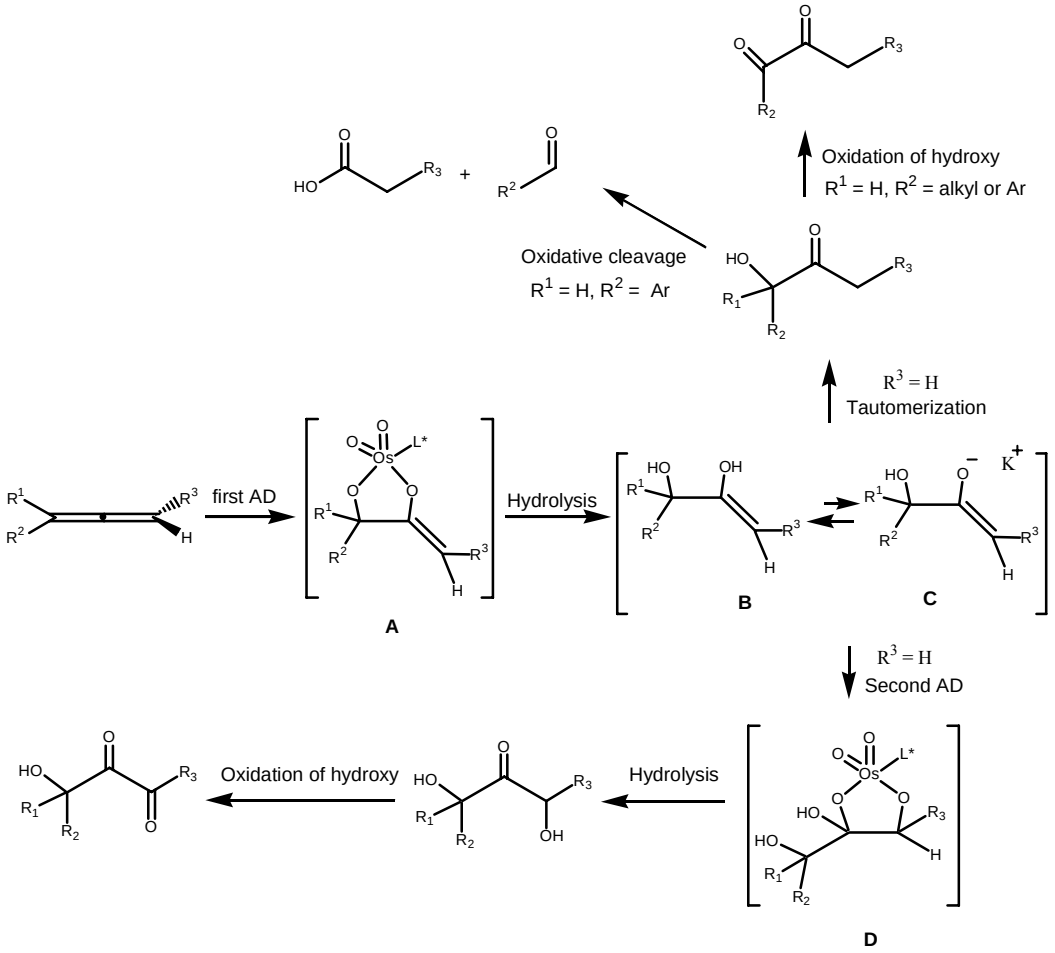
The performance of the 20 allenes discussed above in the asymmetric dihydroxylation

reaction is related to the allene substitution. The proposed pathway is shown in Scheme 62. The mechanism may help explain the observed results.

1. Regioselectivity

AD reactions prefer to occur on the more electronic rich double bond of an allene. So the double bond with more substituents or donating groups will be oxidized first. This was clearly demonstrated by oxidation of terminal allenes. The fact that only one α-hydroxyketone **171** was formed during oxidation of each allene **168a-c** also supports this conclusion.

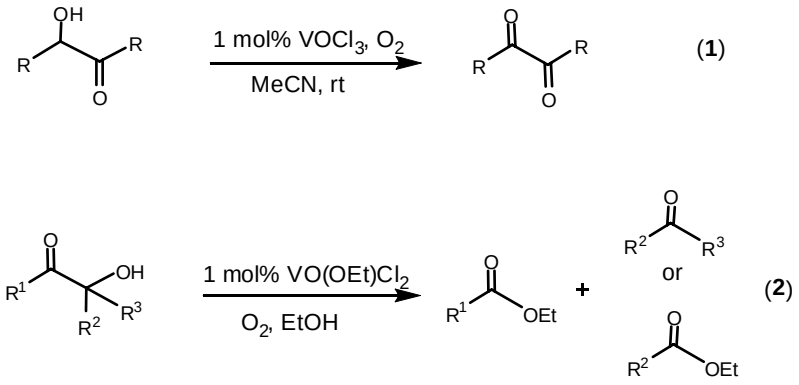
Scheme 62. Proposed pathway for AD reaction of allenes.



2. Chemoselectivity.

For the terminal allenes (R^3 = H), hydrolysis of the first oxidation intermediate **A** affords the intermediate **B** or **C**, and this less stable alkene tautomerizes rapidly to give the α-hydroxyketone. The second oxidation does not have a chance to occur. The α-hydroxyketone can be overoxidized to diketone or cleaved to aldehyde under the reaction conditions. This may be a result of aerobic oxidation of the α-hydroxyketone, an oxidation pathway which has been previously reported (Scheme 63) [19] or perhaps the oxidizing reaction conditions are the cause.

Scheme 63. Oxidation of α-hydroxy ketones.



For the 1,3-disubstituted and 1,1,3-trisubstituted allenes, the second dihydroxylation of **B** competes with tautomerization because the more stable alkene has a longer life time. This generates intermediate **C** which gives the α,α'-dihydroxyketone. Then the α,α'-dihydroxyketone can be over-oxidized to give the other observed products as shown in Scheme 60.

3. Enantioselectivity.

Aromatic substituted allenes generally showed higher enantioselectivity than alkyl substituted allenes. This can be explained by the π-π stack interaction between the aromatic rings of the ligand and allene. The π-π stack interaction has been used by Corey et al. for rationalization of their u-shaped binding pocket transition-state model for AD reaction. The benzyl substituted allene demonstrates this effect nicely.

4. Efficiency of kinetic resolution.

Aromatic substituents and bulky substituents can improve the efficiency of kinetic resolution. This was clearly demonstrated by the fact that allene **168c-d** showed higher efficiency than **168a-b**, and **177c-d** showed higher efficiency than **177d**.

2.2.5. References

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(c) Literature reference for 3-hydroxy-3-phenyl-2-butanone (**164e**) see: Harder, T.; Loehl, T.; Bohe, M.; Wagner, K.; Hoppe, D. *Tetrahedron Lett.* **1994**, *35*, 7365–7368.

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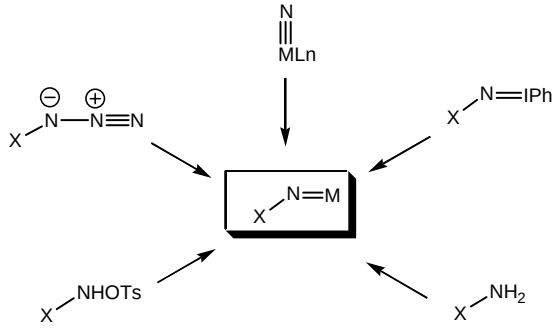
Chapter 3 Copper-Catalyzed Tethered Aziridination of Unsaturated *N*-Tosyloxy carbamates

3.1. Background

3.1.1. Transition metal-catalyzed nitrene transfer to olefin

Aziridines are useful building blocks for their synthetic versatility. In addition, they often occur as substructures in natural products and frequently exhibit diverse biological activities.[1] Although there are a number of methods to prepare aziridines,[2-6] transition metal-catalyzed nitrene addition to olefins provides an extremely important transformation to this class of compounds and remarkable advances have been made in this area during the past decade.[1b,i,j,m,o] Several pathways for generation of metal nitrene intermediates have been described in the literature (Scheme 64).

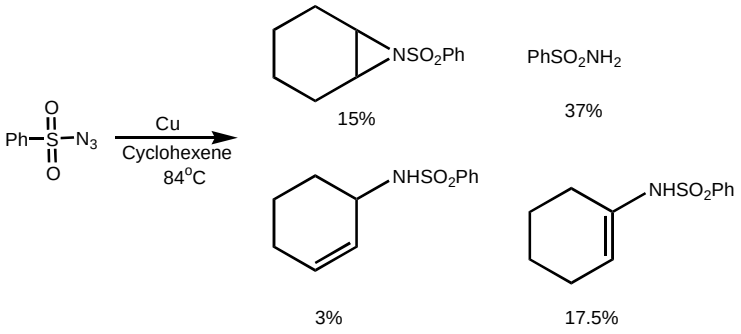
Scheme 64. Pathways for generation of metal nitrene intermediates.



The first metal-catalyzed nitrogen atom-transfer process reported by Kwart and Kahn in 1967 demonstrated the decomposition of bezenesulfonyl azide when heated in cyclohexene in the presence of copper powder.[6] The resulting products arising from C-H

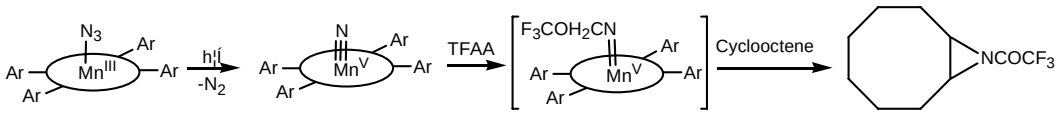
insertion and alkene aziridination were considered to be formed via a nitrene (or metal nitrenoid) intermediate (Scheme 65).

Scheme 65. The first example of metal-catalyzed nitrogen atom-transfer process.



In 1983, Groves et al. reported an example of the stoichiometric activation and transfer of nitrogen from a nitridomanganese (V) porphyrin complex to an olefin (Scheme 66).[7]

Scheme 66. Transfer of nitrogen atom from a nitridomanganese(V) porphyrin complex.

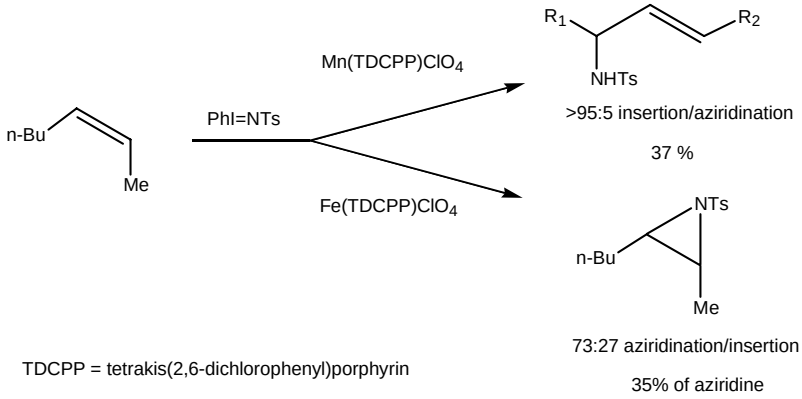


Ar = 2,4,6-trimethylphenyl

The real breakthrough came in the early 80's when Breslow and Mansuy reported their seminal findings which revealed the utility of the *N*-arenesulfonyl iminoiodinanes ($ArSO_2N{=}IPh$) as nitrene precursors either in the amination of alkanes and alkenes via a C-H insertion process, or in the aziridination of alkenes.[8] Both reactions were catalyzed by Mn(III)- or Fe(III)-porphyrin complexes (Scheme 67). However, these reactions were

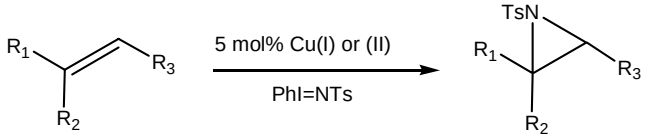
of limited application in organic synthesis due to their low efficiency and selectivity.

Scheme 67. The earliest examples of iminoiodinane as nitrene precursor for amination and aziridination.



The situation was changed when Evans et al. reported the copper-catalyzed version of the aziridination process which greatly extended its scope (Scheme 68).[9a] Then the enantioselective variants of this reaction reported by both Evans' and Jacobsen's groups further improved its utility.[9b-f] In addition to copper compounds, other metal complexes such as rhodium,[9g,h] silver,[9i] and more recently gold complexes[9j] were also reported to be able to efficiently catalyze this reaction.

Scheme 68. Copper-catalyzed nitrene transfer.

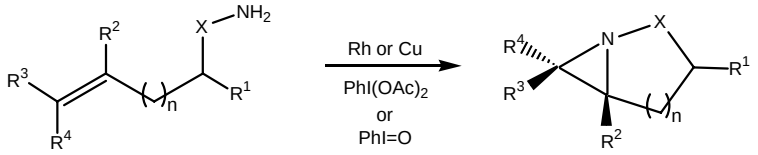


180 **181**

However, there existed one major drawback caused by the difficulty to prepare the iminoiodinanes. This consideration promoted the recent developments involving their in situ generation allowing more convenient one-pot processes. These improvements led to

more choices of nitrene sources such as carbamates esters,[10a,b] sulfamate esters[10c,d] and sulfonamides[10e,f] and more choices of hypervalent iodine reagents (Scheme 69). Both rhodium and copper complexes are efficient for these reactions.

Scheme 69. Aziridination using in situ generated nitrene.



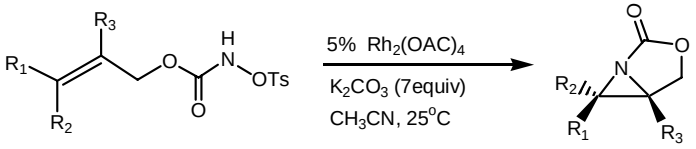
182

X = CO_2, SO_2, OSO_2

183

In spite of these advancements made for this area, another drawback is the formation of a stoichiometric amount of iodobenzene. Recently, Lebel et al. have reported a highly efficient method using rhodium-catalysis for nitrenes which undergo C-H insertion to give amines or alkene addition to give aziridines (Scheme 70).[11] They used *N*-tosyl derivatives of carbamates as nitrene sources, thus avoiding addition of hypervalent iodine reagents which generate iodobenzene. More recently, progress on the application of this new type of nitrene source has been reported.

Scheme 70. Using *N*-tosyloxy carbamates.



184

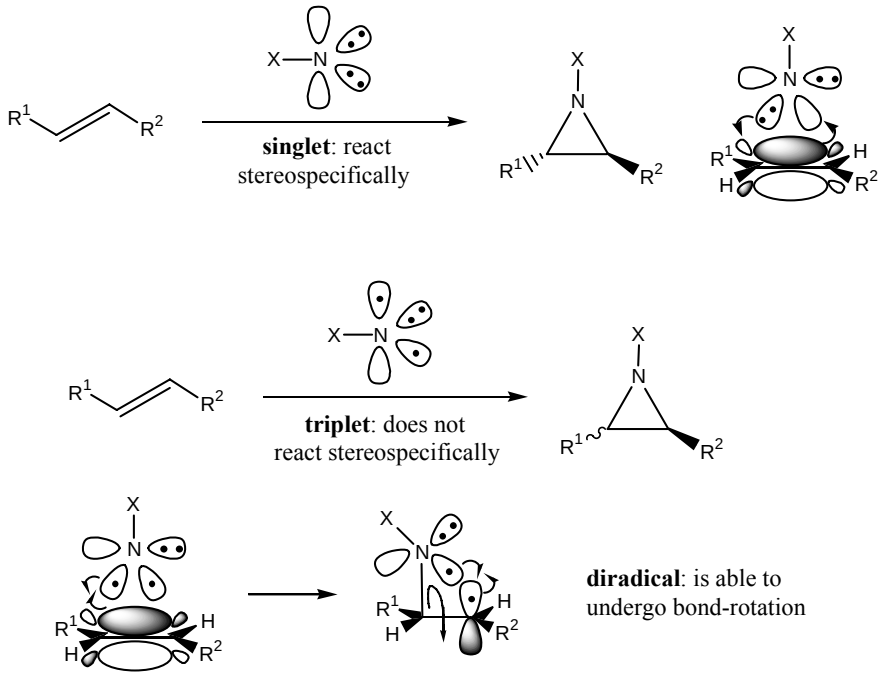
185

3.1.2. Mechanistic investigation

3.1.2.1. Nitrenes generated by thermal or photochemical decomposition

Thermal or photochemical decomposition of the corresponding azides lead to mixtures of (more reactive) singlet and (more stable) triplet nitrenes. Triplet nitrenes (bearing non-bonded electrons in three orbitals, one filled with an electron-pair and two others being half-filled with one electron each, of parallel spin) react in a two-step process with alkenes (Scheme 71), in which an N-C bond is formed in each step, whereas singlet nitrenes (bearing non-bonded electrons in two orbitals, each containing an anti-parallel electron pair) are able to form both new bonds in a concerted process and react stereospecifically with 1,2-disubstituted alkenes (Scheme 70).[12]

Scheme 71. Singlet and triplet nitrene.

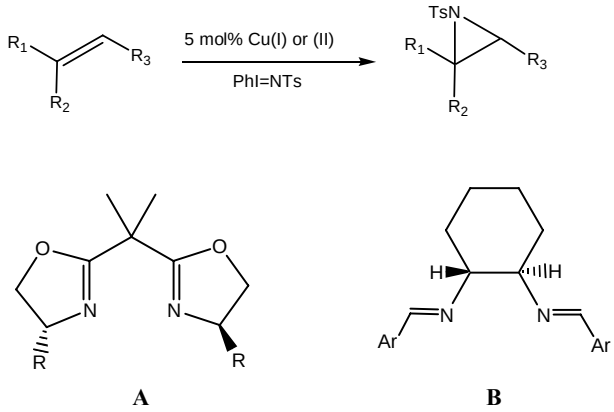


3.1.2.2. Mechanistic studies of copper-catalyzed alkene aziridination

Most of the studies in the area of copper-catalyzed alkene aziridination have been

related to the work of Evans and Jacobsen, particularly the asymmetric variants. The Evans and Jacobsen systems appear to be complementary in that the bisoxazoline ligands **A** of Evans' are most successful for *trans*-alkenes, whereas Jacobsens′ diimines **B** are most efficient for *cis* (Scheme 72).[9b,f]

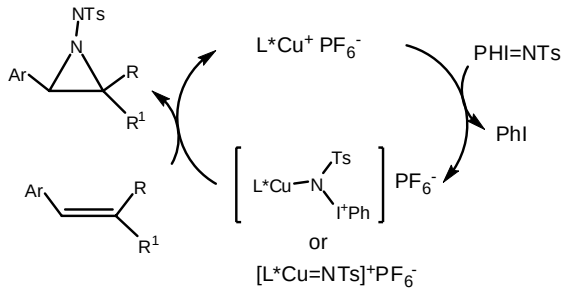
Scheme 72. Evans and Jacobsen systems.



A **B**

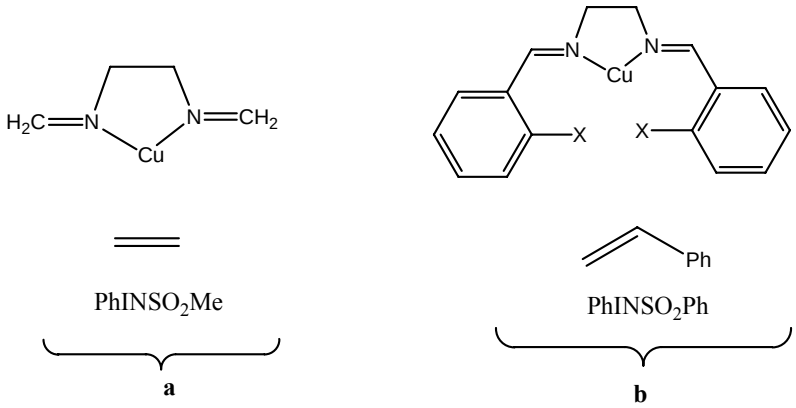
Evans has suggested that the active catalysts in their system is in the +II oxidation state (Cu^{II}) which also was confirmed to be the active species in Pérez's work.[9b,13] Jacobsen has concluded that the reaction is strictly first order in alkene as a result of kinetic studies and suggested a Cu^{III}-nitrene species to be the reactive intermediate in a Cu^{I}/Cu^{II} catalytic cycle (Scheme 73).[9f] It is becoming clear that the mechanism may be system-dependent.

Scheme 73. Jacobsen's proposed mechanism.



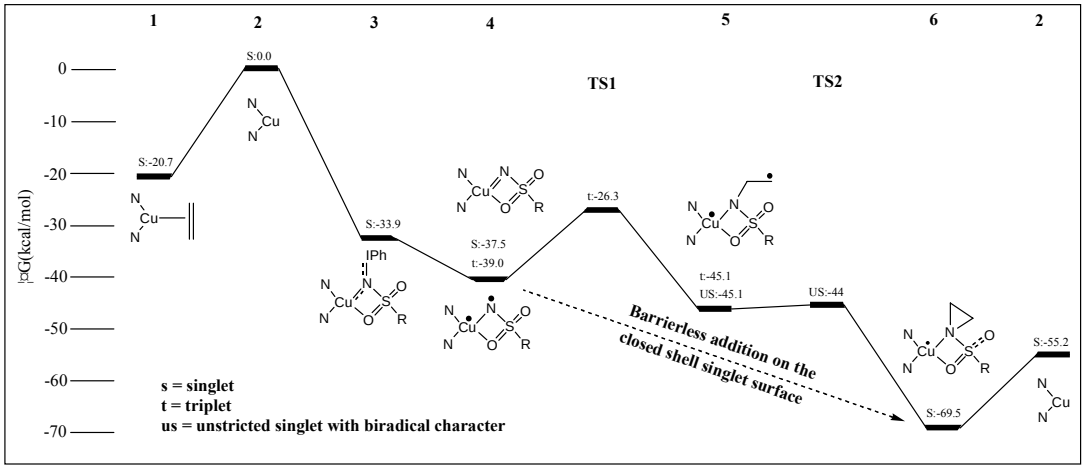
Norrby et al. has described detailed calculations in combination with kinetic experiments on the Jacobsen system using the model systems **a** and **b** (Scheme 74).[14]

Scheme 74. Norrby's systems.



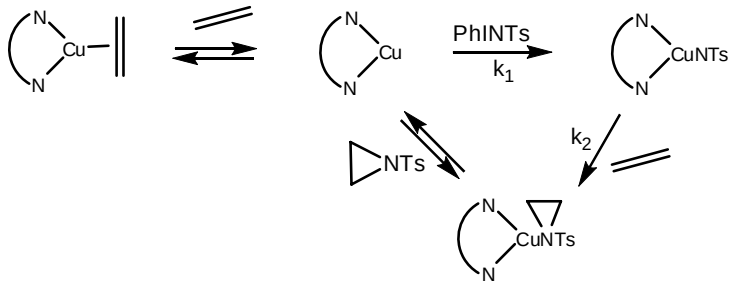
Several species and transition states have been evaluated in the quantum chemical calculations (Figure 5). The results of calculations strongly indicate that the active catalyst is a Cu(I) species, as suggested by Jacobsen. The calculated reaction profile suggests that the rate-determining step in the reaction is the formation of metallanitrene **4**.

Figure 5. Potential free energy surface of the small model system **a**.



Kinetic measurements confirmed that the reaction is indeed zero order in alkene, despite the fact that singlet experiments appear to obey a first-order kinetics. This behavior could be rationalized in terms of decomposition of the catalytically active metal complex (see Scheme 75).

Scheme 75. Catalytic cycle used in the derivation of kinetic rate laws.

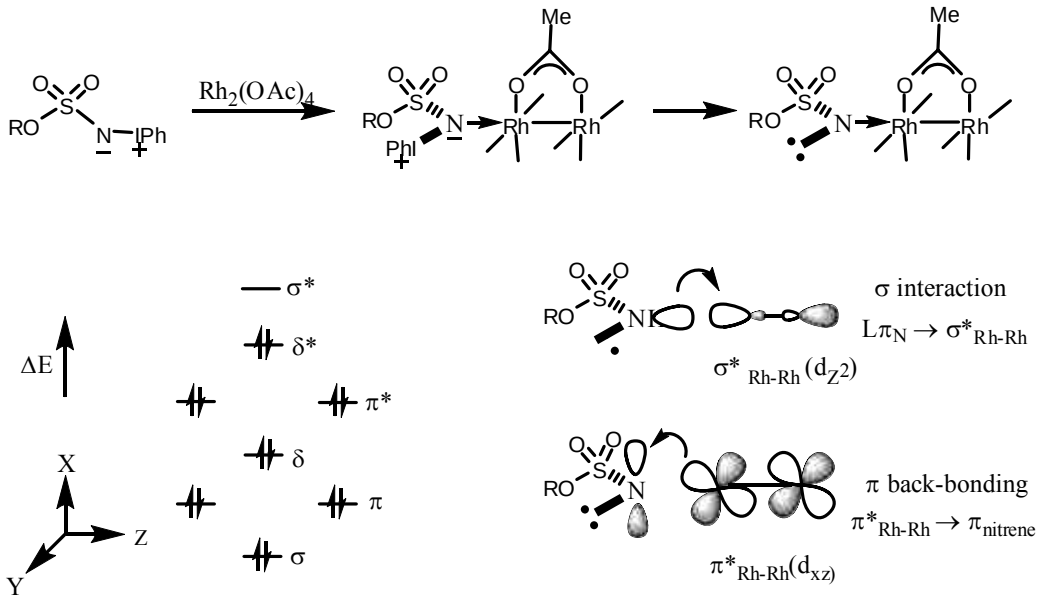


3.1.2.3. Mechanistic studies of rhodium-catalyzed alkene aziridination

Mechanism investigation on aziridination of alkenes with rhodium nitrenoid has been greatly overlooked, compared with the considerable efforts investigating the mechanistic path of C-H insertion.[1m] The C-H insertion mechanism should help us understand the mechanism of aziridination reaction because the common activated species, the rhodium nitrenoid, is presumably involved in both pathways. The electronic configuration of the dinuclear rhodium complex is uniquely disposed to bind and to stabilize a ligated nitrene. This can be explained by molecular orbital analysis (Scheme 76). Admixing the ten metal d-orbitals generates a molecular orbital representation of these D^4-symetry lantern complexes. The 14 valence electrons from the two d^7 Rh^{2+} centers occupy a $\sigma^2\pi^4\delta^2\pi^{*4}\delta^{*2}$ ground state. Such an orbital diagram is in agreement with computational and

experimental data that establish a Rh-Rh single bond for these dimeric structures.[15a] Moreover, this picture suggests that a ligand coordinated along the Rh-Rh vector may donate density to the empty Rh-Rh σ*-orbital and /or overlap through back-bonding with either of the filled π* MOs.[15b] Infrared measurements of Rh_2L_4-CO adducts demonstrate clearly a red shift in the C=O stretching frequency relative to unligated carbon monoxide. These results are consistent with electron delocalization from the Rh-Rh π* into the low-lying σ^*_{CO}. Similarly, back bonding from the rhodium π* into the $\sigma^*_{N\text{-}I}$ can occur upon coordination of an iminoiodinane to the rhodium dimer. Subsequent loss of PhI is thus facilated, and the resulting nitrene ligand is stabilized through both σ-bonding ($Lp_N \rightarrow \sigma^*_{Rh\text{-}Rh}$) and π back-bonding ($\pi^*_{Rh\text{-}Rh} \rightarrow p_N$) interaction.

Scheme 76. Molecular orbital analysis of putative metallo-nitrene.



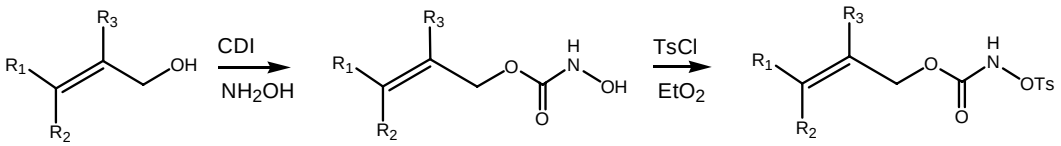
3.2. Results and Discussion

Our interest is to investigate copper complexes as catalysts in this new azridination reaction since copper complexes are readily available and have shown high efficiency in previous aziridination applications. We describe here the copper-catalyzed version of this process and, in particular, report the first example of the regio- and stereoselective nucleophilc opening of these bicyclic fused azridines.

3.2.1. Synthesis of unsaturated *N*-tosyloxy carbamate

The starting *N*-sulfonyloxy carbamates were prepared from the corresponding alcohols in a generally good yield using a known two-pot procedure as shown in Scheme 77.

Scheme 77. Synthesis of *N*-tosyloxycarbamate.



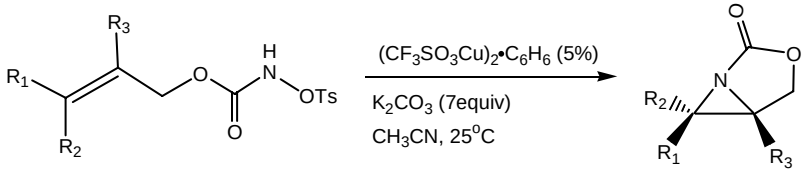
186 **187** **188**

3.2.2. Copper catalyzed aziridination of unsaturated *N*-tosyloxy carbamate

Typical experimental conditions for intramolecular aziridination employed 5-10 mol% of copper salts and excess K_2CO_3 (usually 7 equiv) in acetonitrile (0.05M) with stirring at room temperature for 16 h. Moderate to good yields were obtained (see Scheme 78 and Table 14). Different copper complexes, including $Cu(CH_3CN)_4PF_6$, $(CF_3SO_3Cu)_2 \bullet C_6H_6$, $(CF_3SO_3)_2Cu$, and CuBr, were studied using compound **188a**. Although each of these complexes led to aziridine formation, $(CF_3SO_3Cu)_2 \bullet C_6H_6$ was the most efficient for the

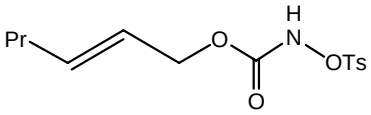
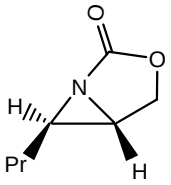
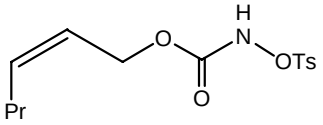
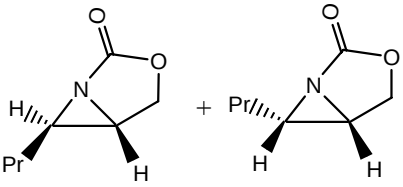
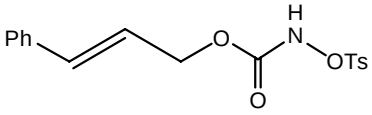
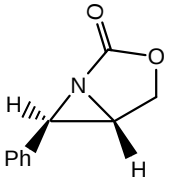
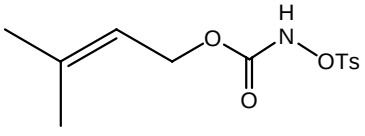
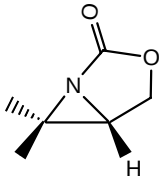
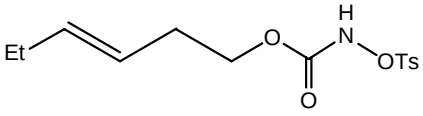
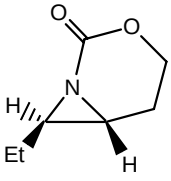
reaction. So $(CF_3SO_3Cu)_2 \bullet C_6H_6$ was chosen as our standard catalyst for this study. Use of potassium bases proved to be critical to the experiment. For example, K_2CO_3 was used as the most convenient base although other potassium bases such as KOH also were equally efficient. However other bases such as Na_2CO_3, Cs_2CO_3 and Ag_2CO_3 resulted in low conversion. Acetonitrile was used as the standard solvent. Similar yields were also obtained in acetone. Under the reaction conditions described above, the two monosubstituted allylic carbamates (**188a** and **188b**) gave modest isolated yields (53% and 42%) while the dimethyl and phenyl substituted carbamates (**188c** and **188d**) gave excellent yields (>90%). The yields of the latter two substrates were based on NMR spectral analysis of the crude products. Attempts to further purify these products by chromatography on silica gel failed because of instability of the strained bicyclic compound. The high efficiency for the latter two substrates can be attributed to their electron rich double bonds which make them a better match for the electron deficient nitrenes generated from the carbamates. This reaction also worked well for homoallylic tosyloxycarbamates (**188e**). A side reaction of detosylation produced a measurable amount of carbamates (15-30%) which decreased the efficiency of the aziridination and resulted in the relative low yield for **188a**, **188b** and **188e**. For **188e** a small amount (<8%) of insertion products also were observed. The *E* or *Z* alkene results establish that the aziridination reaction is not stereospecific, as the stereochemistry of the *Z* alkene is lost in the observed products.

Scheme 78. Intramolecular aziridination of various alkenes.



188 **189**

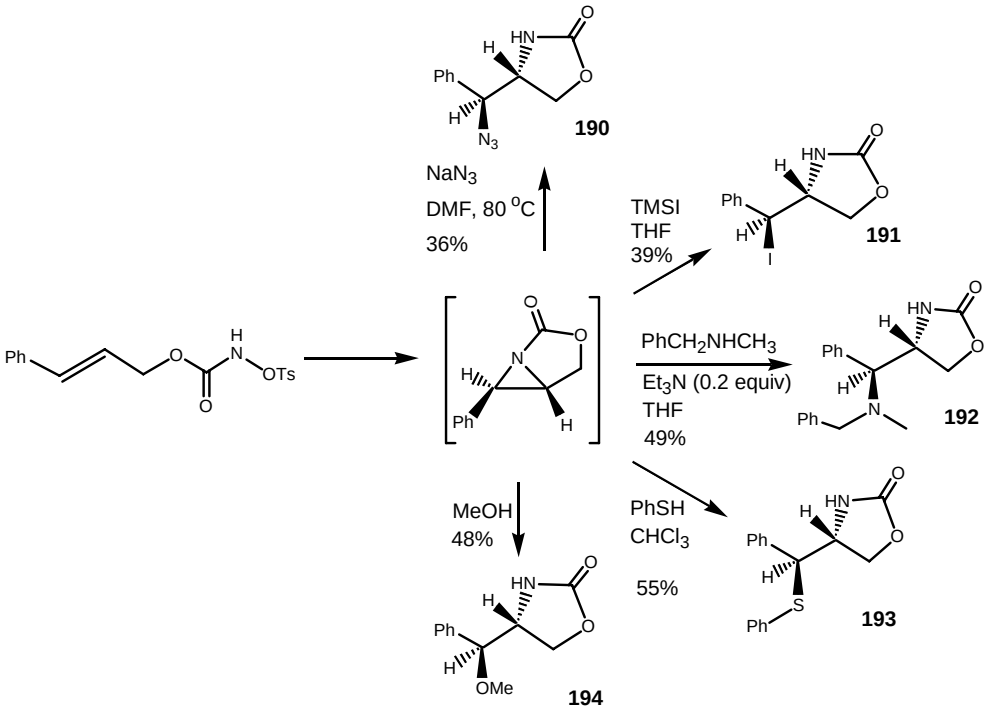
Table 14. The results of aziridination.

Substrate		% Yield	Products
	**188a**	53	 **189a**
	**188b**	42	 **189a** + **189b** minor
	**188c**	>90	 **189c**
	**188d**	>90	 **189d**
	**188e**	45	 **189e**

3.2.3. Ring opening of obtained aziridines

We also studied the electrophilic reactivity of these heterocyclic aziridines, particularly with respect to the regio- and stereoselectivity of ring opening.[10a, b, f,16] In our first analysis, crude aziridine **189c** was reacted with different nucleophiles (*N*-methyl benzylamine, thiophenol, methane, sodium azide, and TMSI). This approach afforded the oxazolidinones **190-194** in moderate overall yields for the two steps. Only one diastereomer generated by nucleopilic attack at the less substituted site of aziridine was observed for each substrate (Scheme 79). The structures were confirmed by the X-ray crystallography of **192** and analysis of 2D ^{1}H NMR.[17]

Scheme 79. Aziridination and subsequent ring opening of cinnamyl moiety.



The X-ray structure (see Figure 5) established that the ring opening occurs with high

stereoselectivity to afford **190-194** with inversion of configuration at the reaction site. We then tested the other aziridines **189a**, **189**d and **189e** and similar results were obtained (Scheme 80). The X-ray structure of **196** further confirmed that the ring opening process was regioselective (see Figure 6). We were surprised that the nucleophilic attack occurred selectively at the non-bridgehead aziridine carbon in light of the report by Duran et al.[10d] that the sulfamate fused aziridine undergoes ring opening at the bridgehead carbon. Although their work dealt with the [4.1.0] bicyclic sulfamate system rather than the bicyclo[3.1.0]carbamate structures in this thesis. In this work, even the [4.1.0] carbamate undergoes ring opening at the non-bridgehead carbon (see Scheme 80).

Figure 6. X-ray structures of **192**.

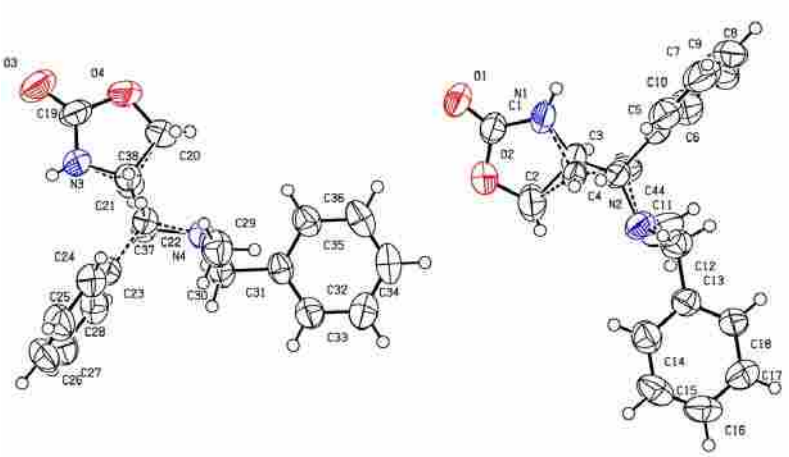
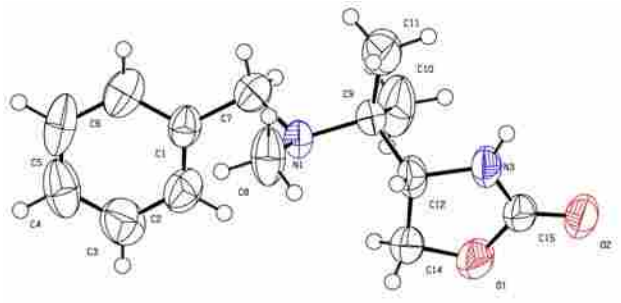
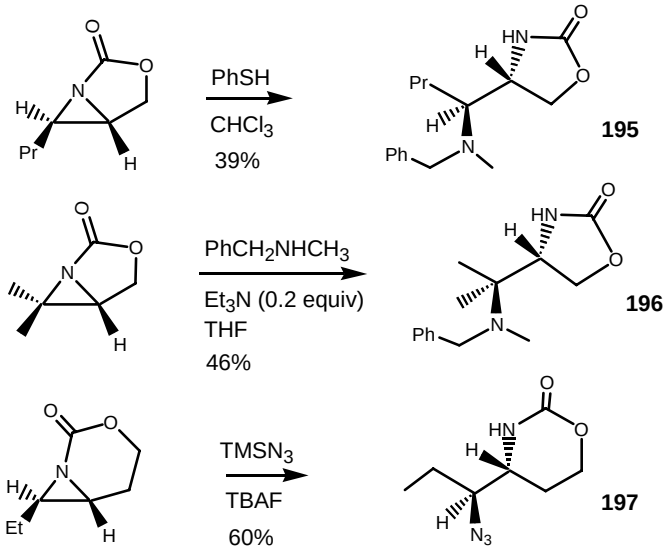


Figure 7. X-ray structures of **196**.



Scheme 80. Ring opening of bicyclic aziridines.



3.2.4. An example of aziridination of cyclic substrate

We chose to apply this methodology to cyclic substrates such as **188f** (Scheme 80). In this case an unexpected product instead of the aziridine was obtained in our first attempt. After further study, product **198** was isolated and we have surmised that it results from in situ ring-opening of the strained aziridine by the weakly nucleophili

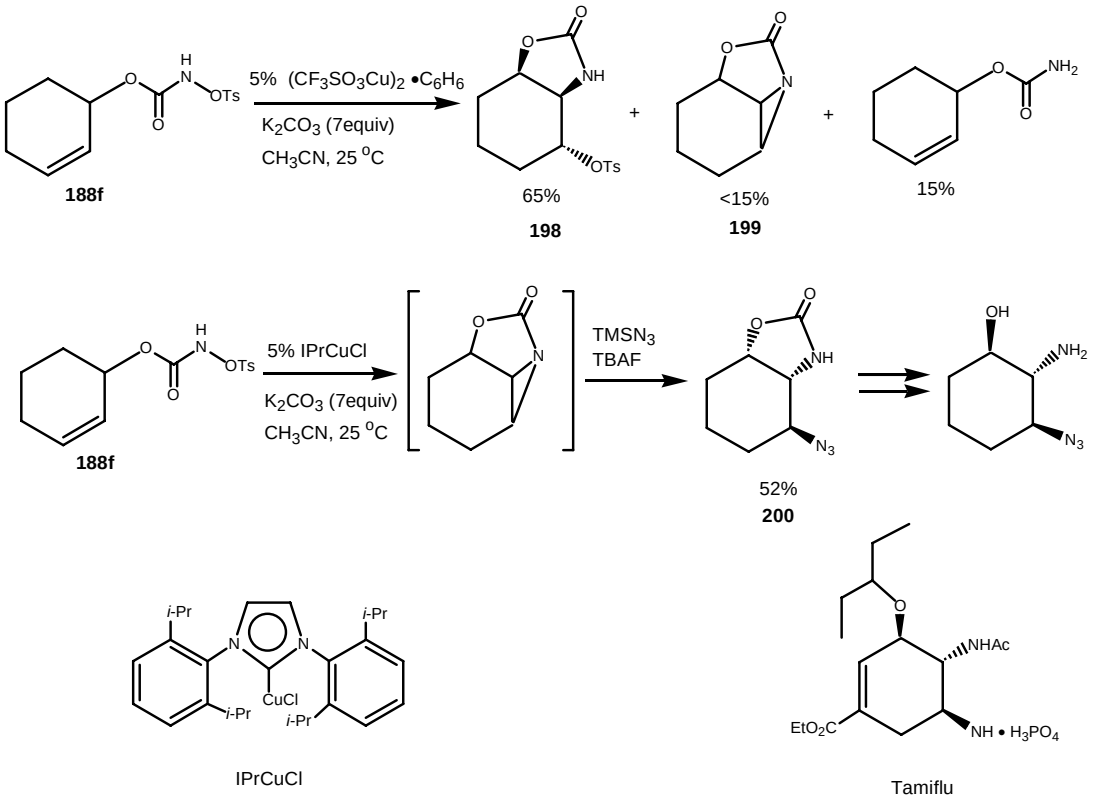
tosylate group, which is formed during the reaction. A second minor product which results from detosylation of the starting carbamate was also isolated as shown in Scheme 4. When we shortened the reaction time, we did observe a minor amount of the desired aziridine. Its presence was confirmed by ^{1}H NMR analyses of the crude reaction mixture. In an attempt to improve the aziridination process in this system, we explored the use of other copper catalysts. Recently an *N*-heterocyclic carbene copper chloride complex has been successfully used for the aziridination, a key step for the total synthesis of agelastatin A.[18,19] Considering its efficiency for the addition to the electron-deficient cyclopentene in the synthesis of agelastatin A, we chose to employ this catalyst with substrate **188f**. We were pleased to find that the desired aziridine was the major product in this run as determined by ^{1}H NMR analysis. Unfortunately, further attempt to purify the strained tricyclic compound on silica gel failed to provide the pure aziridine product because significant decomposition occurred during chromatography. So we trapped the crude aziridine by nucleophilic ring-opening using $TMSN_3$ as an in situ nucleophile (Scheme 81). This strategy provides a way to assemble three adjacent functional groups with stereochemical control, in particular the 1,2-diamine-3-hydroxy unit. It is noteworthy that this combination occurs in Tamiflu (oseltamivir phosphate) which is receiving intense scrutiny as an oral drug for avian flu.[20]

3.3. Summary

In conclusion, copper-catalyzed intramolecular aziridination of unsaturated carbamates has been described as a complement to the previous rhodium-catalyzed

version.

Scheme 81. Intramolecular aziridination of cyclohexene.



Different nucleophiles can be introduced both regioselectively and stereoselectively on these heterocycles. The unique regioselectivity for this process has been established by x-ray crystallography for two of the ring-opened products. Improvement of efficiency of the reaction and application of this strategy to the total synthesis of natural products are areas for further work.

3.4. References

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Chapter 4 Rhodium-Catalyzed Intramolecular Aziridination of Allenes

4.1. Background

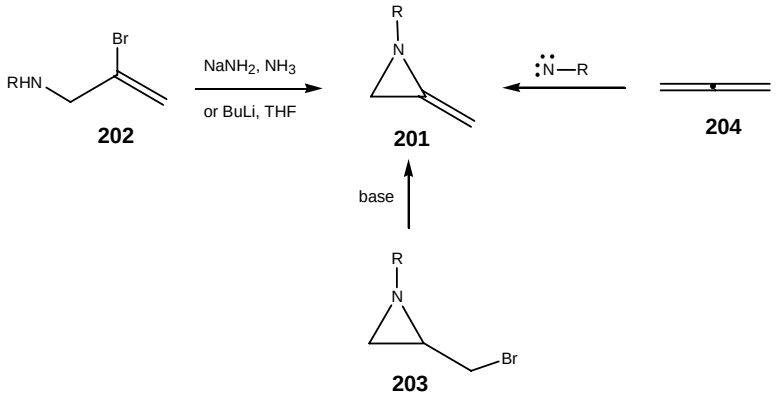
We were interested in the potential for aziridination of allenes as a novel method for the synthesis of 2-methyleneaziridines. 2-Methyleneaziridines are a rare class of highly strained and densely functionalized heterocycles. This moiety can be compared to other small ring compounds, such as oxiranes, aziridines, vinylcyclopropanes and methylenecyclopropanes, which have been widely used as synthetic intermediates. 2-Methyleneaziridines have been overlooked until recently. In the last three years, they have received increasing attention for both their synthesis and their utility in synthetic applications.[1]

4.1.1. Synthesis of 2-Methyleneaziridines

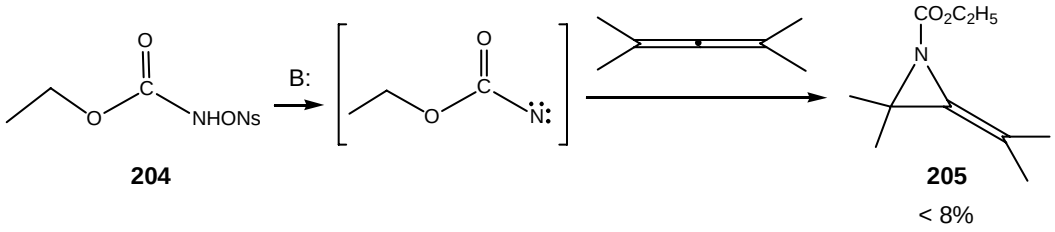
There are only a few synthetic routes making 2-methyleneaziridines (Scheme 82). The most general one is the cyclization of 2-bromo-2-propenylamine and its derivatives with sodium amide in liquid ammonia or butyllithium.[2] Another straightforward entry to 2-methyleneaziridines is the 1,2–dehydrobromination of 2-(bromomethyl)aziridines, which has been established recently.[2]

Compared with these two methods, examples of the third route, the cycloaddition of allenes with nitrenes, are very limited. To the best of our knowledge, there is only one report about this method (Scheme 83).[3]

Scheme 82. Synthetic routes for 2-methyleneaziridines.



Scheme 83. An example of nitrene addition to allenes to generate 2-methyleneaziridines.



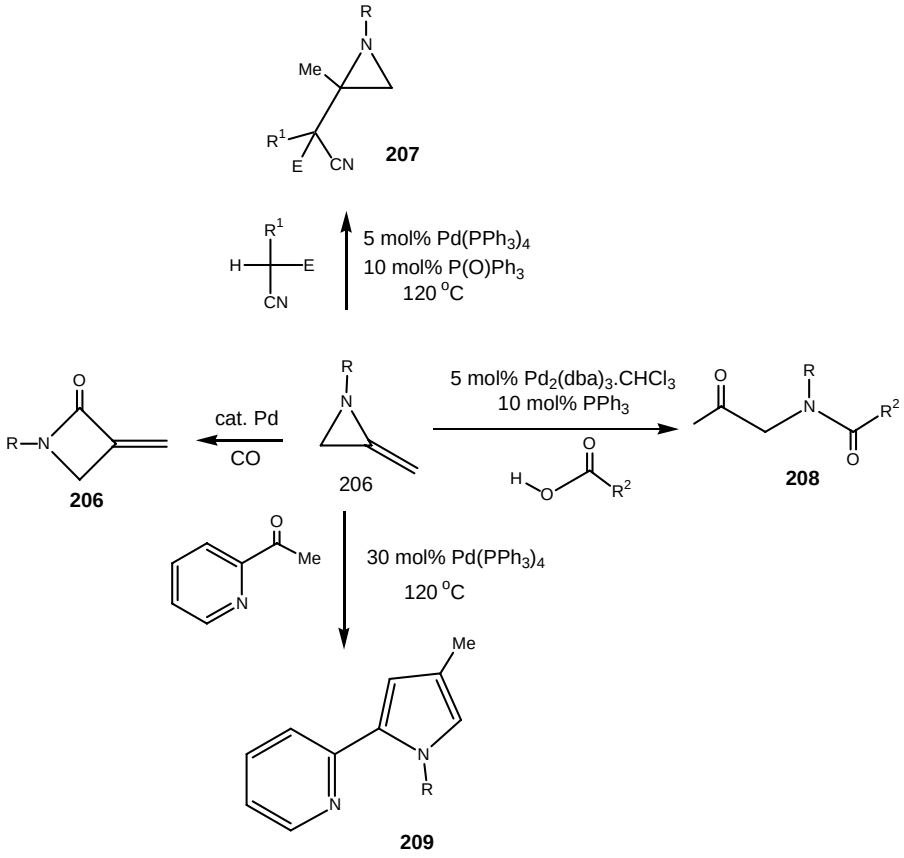
4.1.2. Synthetic applications for 2-Methyleneaziridines

Reactions involving 2-methyleneaziridines were reported sporadically in the 1970's. These reactions included: functionalization by deprotonation with n-butyllithium and subsequent reaction with electrophiles;[4a,b] transformation into heterocycles such as 1-azaspiro[2,3]hexane,[4c] pyrroles,[4c] 4-methylene-2-oxazolines,[3] 1,4-diazaspiro -[2,2]pentanes,[4d] 2-iminoazetidines;[4e] and valence isomerization to afford an isomeric methyleneaziridines and a cyclopropylideneamine.[4f]

Recent studies on 2-methyleneaziridines have mainly been done by two groups. Yamamoto's group has described several palladium-catalyzed reactions with

2-methyleneaziridines following the first example of palladium-catalyzed ring expansion reported by Alper' group (Scheme 84).[5]

Scheme 84. Palladium-catalyzed reactions of 2-methyleneaziridines.



Shipman's group has reported a series of novel transformations of 2-methyleneaziridines including [4+3] cycloadditions, radical rearrangements, and multicomponent reactions (MCRs) (Scheme 85).[1a,6]

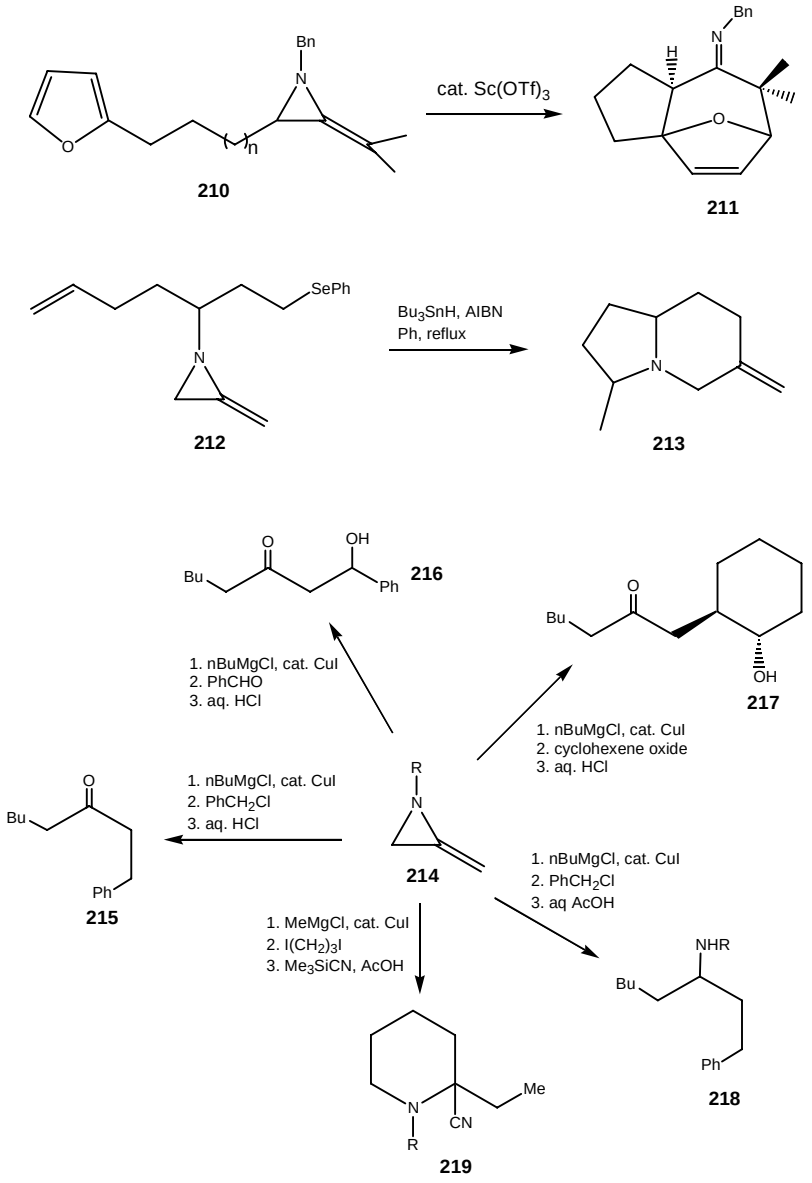
4.2. Rhodium-catalyzed intramolecular aziridination of allenes

4.2.1. Early attempt on transition-metal catalyzed aziridination of allenes

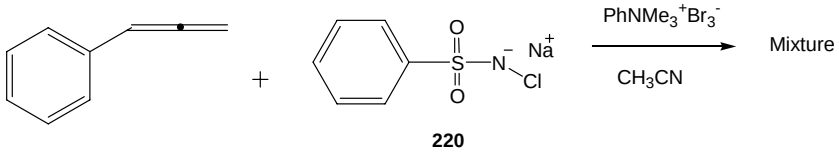
We began to examine aziridination reactions of allenes in 2003. We chose two

representative processes for our intermolecular aziridination reactions of allenes. First we employed bromine-catalyzed azridination which was reported by the Sharpless group.[7] Phenyltrimethylammonium tribromide ($PhNme_3^+Br_3^-$, also known as PTAB) was used as a bromine source. The result showed a very complicated mixture and no desired products were found (see Scheme 86).

Scheme 85. Transformations of 2-methyleneaziridines reported by Shipman's group.

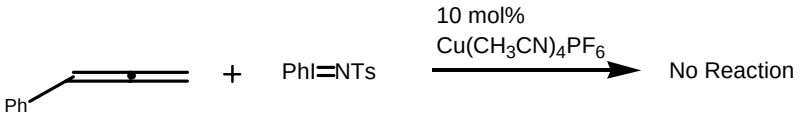


Scheme 86. The first attempt of intermolecular aziridination of allenes.



We also tried a process using iminophenyliodinanes such as TsN=IPh as the nitrene precursor (Scheme 87).[8] We were disappointed to find that although rapid decomposition of TsN=IPh occurred the allenes were stable under the reaction conditions and they were recovered unchanged.

Scheme 87. The second attempt of intermolecular aziridination of allenes.



After these first early attempts, we were hesitant to explore this reaction further. However, Lebel et al. recently reported their intramolecular aziridination using N-tosyl derivatives of carbamates as nitrene sources.[9] Their work stimulated us to retest aziridination of allenes using this intramolecular reaction.

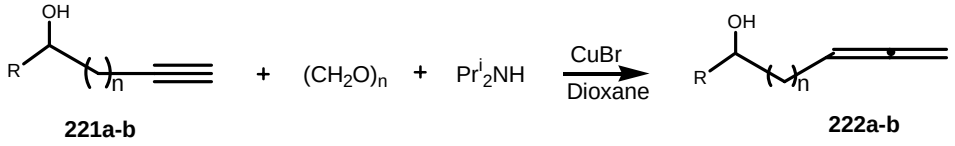
4.2.2. Synthesis of allenic alcohols

There are several methods for the synthesis of allenic alcohols (see Chapter 2). We have used four of them to prepare the starting materials needed in our study.

Allenic alcohols **222a** and **b** were conveniently synthesized via homologation of the

corresponding alcohols **221a** and **b** according to the Crabbé et al method. (see Scheme 88).[10]

Scheme 88. Synthesis of allenic alcohols **222a** and **b**.



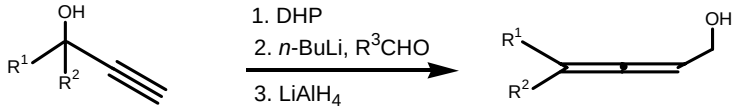
221a-b **222a-b**

222a R = C_5H_{13} n = 0

222b R = C_2H_5 n = 1

α-Allenic alcohols **222c-e** were synthesized from the corresponding propargyl alcohols according to the procedure reported by Landor et al (Scheme 89, DHP = 3,4-dihydro-2H-pyran).[11]

Scheme 89. Synthesis of allenic alcohols **222c, d** and **e**.



221c-d **222c-e**

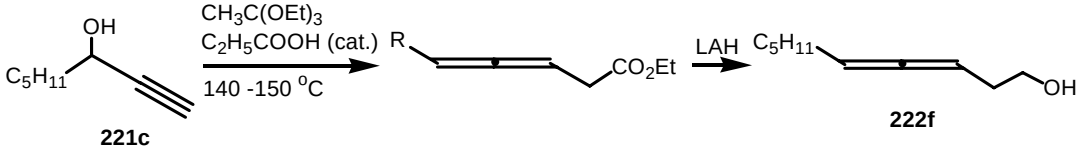
222c R^1 = H, R^2 = C_5H_{11}, R^3 = H

222d R^1 = H, R^2 = C_5H_{11}, R^3 = CH_3

222e R^1 = CH_3, R^2 = CH^3, R^3 = H

β-Allenic alcohol **222f** was synthesized in good yield by sequential reaction of an ortho ester-Claisen rearrangement and the reduction of the β-allenic ester (Scheme 90).[12]

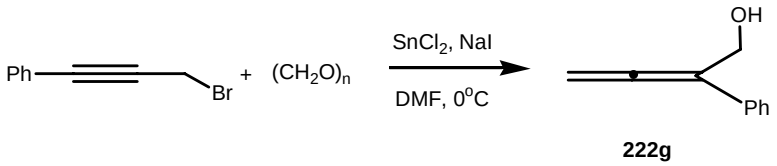
Scheme 90. Synthesis of allenic alcohols **222f**.



221c **222f**

α-Allenic alcohol **222g** was synthesized by the reaction of propargylic bromide, formaldehyde, and $SnCl_2$ (Scheme 91).[13]

Scheme 91. Synthesis of allenic alcohols **222g**.

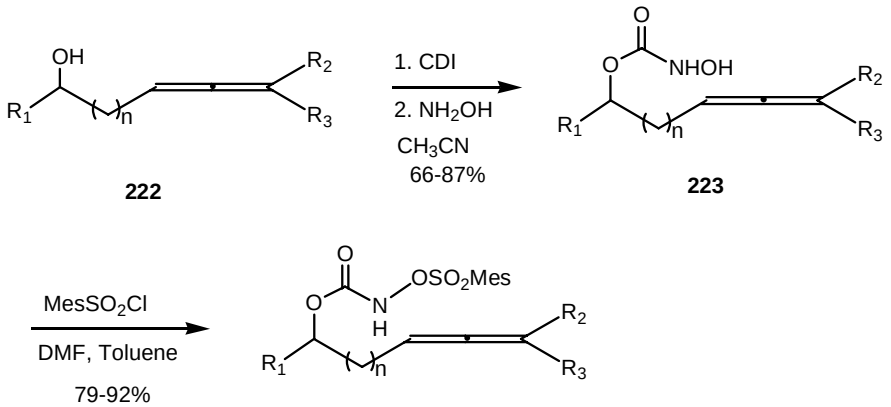


222g

4.2.3. Synthesis of allenic *N*-hydroxycarbamates and allenic *N*-sulfonyloxy carbamate

N-Sulfonyloxy carbamates were prepared from the corresponding allenic alcohols in a generally good yield using the known two-pot procedure as shown in Scheme 92 and discussed in Chapter 3.[9]

Scheme 92. Synthesis of allenic *N*-sulfonyloxy carbamates.



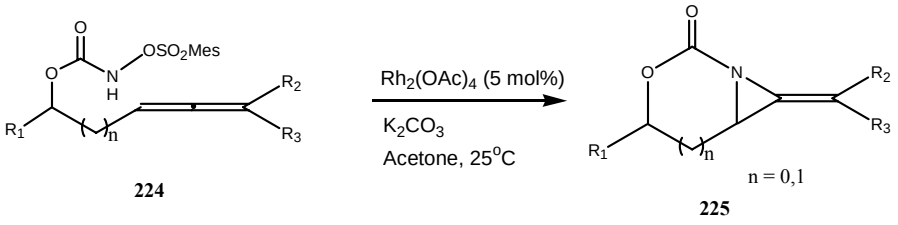
222 **223** **224**

4.2.4. Rhodium-catalyzed aziridination of allenes

Typical experimental conditions for intramolecular aziridination employed 5 mol% of

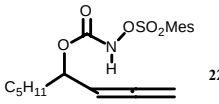
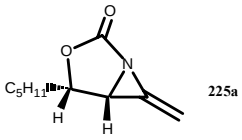
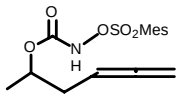
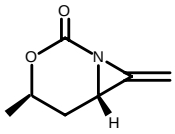
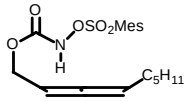
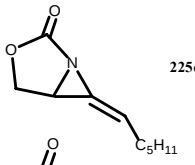
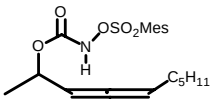
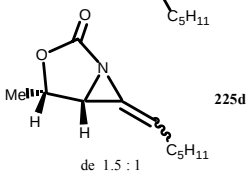
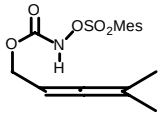
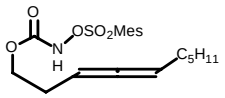
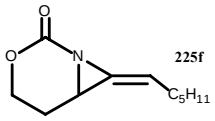
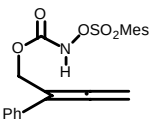
$Rh_2(OAc)_4$ and excess K_2CO_3 (usually 7 equiv) in acetone (20 ml/1 mmol) with stirring at room temperature (Scheme 93). The reaction was monitored by TLC. Generally the reaction was finished with in 7h.

Scheme 93. Intramolecular aziridination of various allenes.



224 **225**

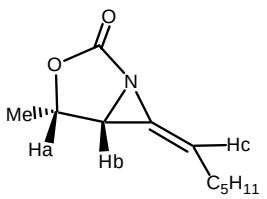
Table 15. The results of aziridination.

Substrates	%Yield	Products
 **224a**	36	 **225a**
 **224b**	43	 **225b**
 **224c**	40	 **225c**
 **224d**	76	 **225d** de 1.5 : 1
 **224e**		not isolated
 **224f**	42	 **225f**
 **224g**		not isolated

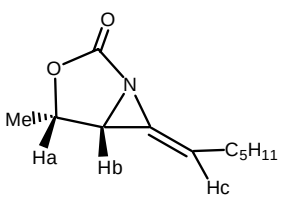
Our results for aziridination were shown as Table 15. The crude NMR spectrum for the aziridination of **224e** and **224g** showed a complicated mixture. We couldn't isolate the desired products for these two substrates. The expected methyleneaziridines **225a-d, f** were obtained in moderate yields from the sulfonyloxycarbamates **224a-d, f**. Only one diastereomer was isolated for all these substrates except for **225d**. For substrate **224f** the insertion product (see chapter 3), also was isolated (46%).

Substrate **224d** was used as the mixture of two diastereomers. We isolated two diastereomers (de 1.5:1) for the products for this substrate. In order to determine the relative stereochemistry, an nOe experiment was used on the separated diastereomers. The results show both diastereomers have strong nOe (2%) between proton Ha and Hb, no nOe was observed between proton Hb and Hc for ether diastereromer. This establishes that proton Ha and Hb are *cis* in both diastereomers. The stereochemistry is caused by the *E*/*Z* nature of alkene. This also was confirmed by the analysis of the chemical shift of the three protons. Ha and Hb have a very similar chemical shift in **225d *E*** and **225d *Z***, however there is significant difference for the chemical shift of Hc in the two diastereomers (5.56 and 5.82 respectively).

Scheme 94. nOe analysis of compound **225d**.



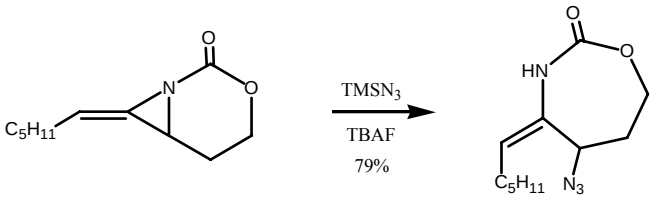
E



Z

The nuclephilic ring opening of the bicyclic methyleneaziridine was tested on **225e** (Scheme 95). The seven-member ring was obtained in good yield by using $TMSN_3$ as nucleophile reagent. The structure was confirmed by analysis of 2D NMR (COSY and HMQC).

Scheme 95. Ring opening of **225e** by azide.

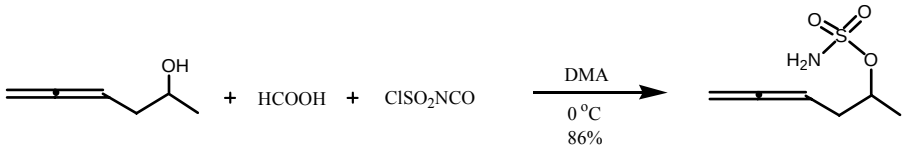


4.2.5. Intramolecular aziridination of allenic sulfamate esters

Oxidative functionalization of π-bonds using sulfamate ester starting materials has been explored for both intra- and intermolecular reaction development. Both rhodium and copper complexes proved to be efficient for this reaction in the presence of inexpensive terminal oxidants such as $PhI(OAc)_2$ and PhIO.[14] Considering the high efficiency of these transformations and the alkoxysulfonyl moiety as a readily excised amino protecting group, we decide to try this reaction with an allenic sulfamate ester.

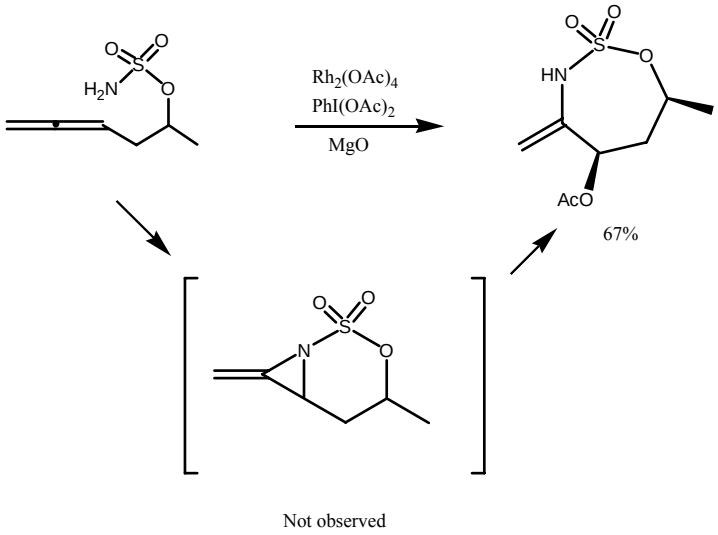
The allenic sulfamate ester was synthesized in a generally good yield using a one-pot procedure (Scheme 96, DMA = *N*, *N*-dimethylacetamide).

Scheme 96. Synthesis of allenic sulfamate.



The aziridination was conducted using 2 mol% $Rh_2(OAc)_4$, $PhI(OAc)_2$ (1.1 eq.), and MgO (2.3 eq.) (Scheme 97). We were surprised to find that the major product is the seven-member ring instead of the expected bicyclic methyleneaziridine. The structure was confirmed by analysis of 2D NMR (COSY and HMQC). One possible pathway for this product may be the in situ ring opening of methylenezairidine intermediate by an acetate.

Scheme 97. Intramolecular aziridination of allenic sulfamate ester.



4.3. Summary

The rhodium-catalyzed intramolecular aziridination of allenic N-sulfonyloxy carbamates has been established. Further, efficient ring opening of these bicyclic compounds may provide synthetic utility in organic chemistry. The intramolecular aziridination of allenic sulfamate esters was tested on a single example to afford in situ ring opening product. Improvement of the efficiency of the reaction and expansion of the

scope of nucleophilic ring opening deserve further investigation.

4.4. References

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1996, *7*, 3397. (c) Ince, J.; Shipman, M.; Ennis, D. S. *Tetrahedron Lett.* **1997**, *38*, 5887. (d) Shipman, M.; Ross, T. M.; Slawin A. M. Z. *Tetrahedron Lett.* **1999**, *40*, 6091. (e) Ennis, D. S.; Ince, J.; Rahman, S.; Shipman, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2047. (f) Prévost, N.; Shipman, M. *Org. Lett.* **2001**, *3*, 2383. (g) Hayes, J. F.; Shipman, M.; Twin, H. *J. Org. Chem.* **2002**, *67*, 935.

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Chapter 5 Experimental Details and Data

5.1. Experimental details and data for Chapter 2

5.1.1. Experimental details and data for asymmetric dihydroxylation of terminal allenes

5.1.1.1. General procedure

Melting points are uncorrected and were determined on a hot-stage apparatus. NMR spectra were recorded using a Varian 300 or 500 MHz instrument. Mass spectra (MS) were determined at 20 eV using direct probe sample introduction or on LC/MSD TOF using electrospray conditions. Chemical ionization MS utilized CH_4. Analytical HPLC was performed at a flow rate of 1 mL/min with a chiracel OD column. Isopropyl alcohol and hexane or ethanol and hexane were used as eluants. Reactions were performed under an inert atmosphere of Ar or N_2. Anhydrous $MgSO_4$ was used as drying agent for extractions. Tetrahydrofuran (THF) and diethyl ether were dried by passage through a Glass Contour solvent drying system containing cylinders of activated alumina. TLC was performed with Merck kieselgel 60-F_{254} aluminum backed sheets with visualization under 254 nm light or by anisaldehyde staining. Column chromatography was carried out using 60 Å Sorbent Technologies silica gel. The AD mixes were obtained from Aldrich Chemical and used without further purification.

5.1.1.2. General procedure for synthesis of propargyl alcohols

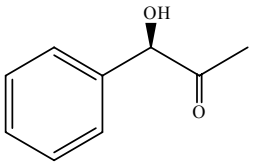
To a stirred solution of ethynylmagnesium bromide (2.0 mL, 2.0 mmol) in THF (5.0 mL) at 0 °C was slowly added the aldehyde (2.0 mmol). The reaction mixture was allowed to stir at this temperature for 2-5 h, after which it was quenched with 5 mL saturated aqueous ammonium chloride. The two phases were separated and the aqueous layer was extracted with ether. The combined organic phase was dried, filtered, and concentrated. This crude material was typically carried forward in the next reaction. Purification was performed by column chromatography using 3:1 hexane/ethyl acetate. Purified yields were between 70 and 90 percent.

5.1.1.3 General procedure for synthesis of allenes

To a stirred suspension of lithium aluminum hydride (2.0 mmol) and aluminum hydride (0.2 mmol) in THF (15 mL) at 0 °C was slowly added 1.0 mmol propargylic alcohol. The mixture was stirred at 65 °C for 5-10 h and monitored by TLC. When no alcohol could be detected, the reaction was quenched with 15 mL water. The two phases were separated and the aqueous layer was extracted with ether. The combined organic phase was dried, filtered, and concentrated. Column chromatography using pentane afforded the purified allene. Yields of recovery were 28-65% due to the volatility of the allene and formation of the by-product (allyl alcohol) reported in the literature.

5.1.1.4. General procedure for synthesis of α-hydroxy ketones (ADH)

To a stirred solution of *tert*-butyl alcohol (5 mL) and water (5 mL) at rt was added 1.4 g AD-mix (α or β) and 95 mg of methanesulfonamide. The solution was then cooled to 0 °C and the allene (1.0 mmol) was added. The slurry was stirred vigorously for fifteen hours at 0 °C or until TLC revealed an absence of allene. The reaction was quenched with sodium sulfite (1.5 g) and allowed to warm to rt and stir for an additional 30 min. Extraction was performed using CH_2Cl_2 and the organic layer was dried then concentrated. Column chromatography using dichloromethane gave the pure α-hydroxy ketone. Yields were between 45 and 80 percent with the α-mix usually giving a slightly higher yield. Optical rotations were obtained for each compound. The % ee's were determined by comparing the asymmetric dihydroxylated product to the racemic mixture obtained from a standard OsO_4/NMO dihydroxylation of the corresponding allene. Several ADH runs were performed for each allene. The conditions for the highest yield for each allene are reported below. The % ee was determined by obtaining an average ratio of the two enantiomers as a result of at least three injections. It is assumed that the response factors for the *R* and *S* enantiomers are identical. In order to avoid formation of by-products or further resolution, injections were made following minimal handling and no attempt to purify the hydroxy ketones other than a flash SiO_2 (CH_2Cl_2) plug to remove highly polar material. The synthetic procedure for the racemic dihydroxylation reaction was based on the literature.[1] We used a 4% aqueous solution of OsO_4 rather than the source they report using.



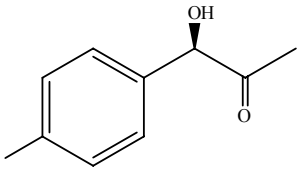
1-Hydroxy-1-phenylpropanone

See **5.1.1.4** for procedure.

The ADH reaction (β mix) was run on 0.114 g (0.98 mmol) phenylallene for 15 h then quenched and extracted. Chromatography gave: fractions 2-3, unreacted allene (6.8 mg, 6% sm recovery); fraction 5, diketone (< 5 mg); fractions 6-12, α-hydroxy ketone (66 mg, 45%).

^{1}H NMR ($CDCl_3$), δ 7.5-7.3 (m, 5 H, Ar-H), 5.12 (d, J = 7.2 Hz, 1 H, CH), 4.31 (d, J = 7.2 Hz, 1 H, OH), 2.10 (s, 3H, $COCH_3$)

$[\alpha]_D$ = -355° (*c* = 0.10 $CHCl_3$); HPLC R_T = 8.2 min, 9.2 min (major enantiomer). This is consistent with the reported spectral data.[2]



1-Hydroxy-1-(4-methylphenyl)propanone

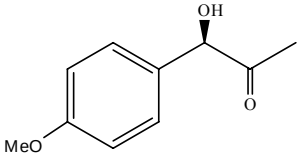
See **5.1.1.4** for procedure.

The ADH reaction (β mix) was run on 0.136 g (1.04 mmol) *p*-methylphenylallene for 13 h then quenched and extracted. Chromatography gave: fractions 4-5, unreacted allene (12 mg, 9% sm recovery); fraction 7-8, presumably diketone (trace); fractions

11-25, α-hydroxy ketone (84.2 mg, 49%).

^{1}H NMR ($CDCl_3$), δ 7.25-7.10 (m, 4 H, Ar-H), 5.08 (d, J = 6.6 Hz, 1 H, CH), 4.28 (d, J = 6.6 Hz, 1 H, OH), 2.37 (s, 3 H, $ArCH_3$), 2.09 (s, 3H, $COCH_3$)

^{13}C NMR ($CDCl_3$), δ 205, 130, 128, 127, 125, 80, 25, 21; $[\alpha]_D$ = -393° (*c* = 0.13 $CHCl_3$) HPLC R_T = 7.32 min, 7.87 min (major enantiomer). This is consistent with reported spectral data.[3]



1-Hydroxy-1-(4-methoxyphenyl)propanone

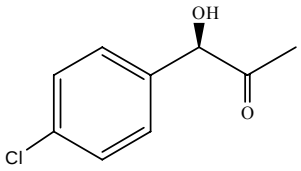
See **5.1.1.4** for procedure.

The ADH reaction (βmix) was run on 0.195 g (1.33 mmol) *p*-methoxyphenylallene for 7 h then quenched and extracted. Chromatography gave: fractions 5-7, unreacted allene (9 mg, 4% sm recovery); fraction 8-10, mixture of diketone and α-hydroxy ketone (1:1, 11 mg); fractions 11-20, α-hydroxy ketone (189 mg, 79%).

^{1}H NMR ($CDCl_3$), δ 7.22 (d, J = 14 Hz, 2 H, Ar-H), 6.92 (d, J = 14 Hz, 2 H, Ar-H), 5.15 (d, J = 7.7 Hz, 1 H, CH), 4.24 (d, J = 7.7 Hz, 1 H, OH), 3.81 (s, 3 H, $ArOCH_3$), 2.10 (s, 3H, $COCH_3$)

^{13}C NMR ($CDCl_3$), δ 206.7, 160.1, 133.1, 128.6, 114.4, 79.5, 55.3, 25.2

$[\alpha]_D$ = -377° (*c* = 0.12 $CHCl_3$); HPLC R_T = 14.4 min, 17.0 min (major enantiomer). This is consistent with literature data.[4]



1-Hydroxy-1-(4-chlorophenyl)propanone

See **5.1.1.4** for procedure.

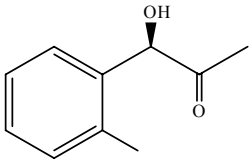
The ADH reaction (β mix) was run on 0.170 g (1.13 mmol) *p*-chlorophenylallene for 15 h then quenched and extracted. Chromatography gave: fractions 4-6, unreacted allene (14 mg, 8% sm recovery); fractions 8-17, α-hydroxy ketone (121 mg, 58%).

^{1}H NMR ($CDCl_3$), δ 7.38 (d, J = 14 Hz, 2 H, Ar-H), 7.24 (d, J = 14 Hz, 2 H, Ar-H), 5.07 (d, J = 5.4 Hz, 1 H, CH), 4.31 (d, J = 6.0 Hz, 1 H, OH), 2.08 (s, 3H, $COCH_3$;

^{13}C NMR ($CDCl_3$), δ 206.7, 136.6, 133.0, 129.4, 128.8, 79.6, 25.4

HRMS (CI) m/e calc. 183.0214, obs. 183.0201

[α] = -332° (*c* = 0.11 $CHCl_3$); HPLC R_T = 8.4 min, 11.2 min (major enantiomer). This is consistent with most of the literature data.[5]



1-Hydroxy-1-(2-methylphenyl)propanone

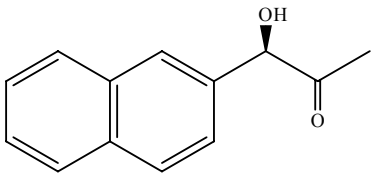
See **5.1.1.4** for procedure.

The ADH reaction (β mix) was run on 0.114 g (0.88 mmol) *o*-methylphenylallene for 10 h then quenched and extracted. Chromatography gave: fractions 3-4, unreacted allene (<5 mg); fraction 5-6, presumably diketone (trace); fractions 7-12, α-hydroxy

ketone (75.0 mg, 52%).

^{1}H NMR ($CDCl_3$), δ 7.3-7.1 (m, 4 H, Ar-H), 5.26 (d, J = 5.4 Hz, 1 H, CH), 4.17 (d, J = 6.0 Hz, 1 H, OH), 2.41 (s, 3 H, $ArCH_3$), 2.06 (s, 3H, $COCH_3$)

^{13}C NMR ($CDCl_3$), δ 207.9, 136.2, 136.0, 131.4, 128.7, 128.3, 126.7, 78.1, 25.8, 19.3;$[\alpha]_D$ = –363° (*c* = 0.25 $CHCl_3$); HPLC R_T = 6.5 min, 8.25 min (major enantiomer); HRMS m/e calc. 164.0838, obs. 164.0848



1-Hydroxy-1-(2-naphthyl)propanone

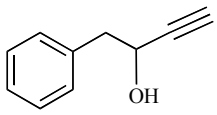
See **5.1.1.4** for procedure.

The ADH reaction (β mix) was run on 0.148 g (1.04 mmol) *p*-methylphenylallene for 13 h then quenched and extracted. Chromatography gave: fractions 5-7, unreacted allene (18 mg, 12% sm recovery); fractions 10-27, α-hydroxy ketone (115 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.05 (d, 1 H, Ar-H), 7.90-7.85 (m, 2 H, Ar-H), 7.60-7.50 (m, 4 H, Ar-H), 5.63 (d, J = 5.1 Hz, 1 H, CH), 4.36 (d, J = 5.1 Hz, 1 H, OH), 2.03 (s, 3 H, $COCH_3$)

^{13}C NMR (75 MHz, $CDCl_3$), δ 178.3, 133.6, 130.1, 129.9, 129.2, 127.9, 127.2, 127.1, 126.3, 125.6, 123.6, 79.5, 25.7

HRMS m/e calc. 200.0838, obs. 200.0854

$[\alpha]_D = -101°$ (c = 0.08g/mL $CHCl_3$); HPLC R_T = 16.6 min (major enantiomer), 21.3 min



1-Phenyl-but-3-yn-2-ol

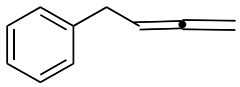
See section 5.1.1.2 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.4-7.2 (5H, m, ArH), 4.60 (1H, q, J = 4Hz, CH), 3.03 (2H, d ABq, CH_2), 2.50 (1H, d, J=2.0Hz, alkyne CH), 1.87 (1H, d, J = 6Hz, OH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.41, 129.99 (2C), 128.69 (2C), 127.25, 84.28, 74.08, 63.19, 44.06

HRMS calcd for $C_{10}H_{10}O$ 146.0732, found 146.0727

This is a known compound.[6]



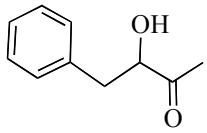
4-Phenylbuta-1,2-diene

See section 5.1.1.3 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.4-7.2 (5H, m, ArH), 5.28 (1H, pentet, J = 6.5Hz, vinyl CH), 4.72 (2H, m, $=CH_2$), 3.36 (2H, m, CH_2)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 209.19, 140.48, 128.65 (4C), 126.42, 89.75, 75.30, 35.31

This is a known compound.[7]



3-Hydroxy-4-phenyl-butan-2-one

See section 5.1.1.4 for procedure.

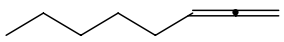
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.3-7.2 (5H, m, ArH), 4.445 (1H, m, CH), 3.39 (1H, d, J = 4.5Hz, OH), 3.17 (1H, dd, J = 14, 4Hz, diasteriotopic CH), 2.90 (1H, dd, J = 14, 7Hz, diasteriotopic CH) 2.22 (3H, s, CH_3)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 209.30, 136.64, 129.47 (2C), 128.79 (2C), 127.18, 77.87, 40.15, 26.11

HRMS calcd for $C_{10}H_{12}O_2$ 164.0837, found 164.0842

HPLC 77%ee (Chiracel OD; 10% isopropyl alcohol in hexanes; 1 ml/min) t_r(R) = 8.35 min t(S) = 10.23 min $[\alpha]_D$ =-40^o ($CHCl_3$, c = 7.2 g/l)

This is a known compound.[8]



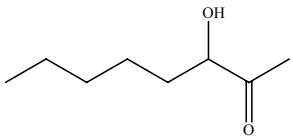
Octa-1,2-diene

See section 5.1.1.3 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J = 7Hz, CH_3), 1.30 (4H, m, 2 x CH_2), 1.41 (2H, m, CH_2), 1.99 (2H, m, CH_2), 4.65 (2H, m, =CH_2), 5.10 (1H, m, =CH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.30, 22.71, 28.47, 29.05, 31.54, 74.73, 90.34, 208.69

This is a known compound.[9]



3-Hydroxy-octan-2-one

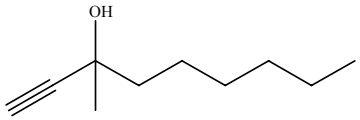
See section 5.1.1.4 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (3H, t, J = 6Hz, CH_3), 1.25-1.47 (6H, m, 3 x CH_2), 1.51-1.56 (1H, m, CH_2), 1.80-1.85 (1H, CH_2), 2.20 (3H, s, CH_3), 3.48(1H, d, J = 4, OH), 4.17-4.20(1H, m, CH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.19, 22.69, 24.61, 25.38, 31.82, 33.70, 77.05, 210.25

HPLC 58%ee (Chiracel ADH; 10% ethanol in hexanes; 0.5 ml/min) t_r(R) = 13.96 min t(S) = 12.51 min $[\alpha]_D = -10^o$($CHCl_3$, c = 2.5 g/l)

This is a known compound.[10]



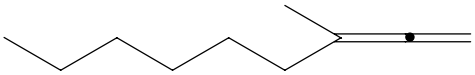
3-Methyl-non-1-yn-3-ol

See section 5.1.1.2 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J = 2Hz CH_3), 1.30-1.35 (8H, m, 4 x CH_2), 1.49 (3H, s, CH_3), 1.55-1.68 (2H, m, CH_2), 1.90 (1H, s, OH), 2.43(1H, s, CH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.29, 22.81, 24.74, 29.57, 29.94, 31.97, 43.74, 68.36, 71.40, 88.03

HRMS calcd for $C_{10}H_{17}O$ (M^+) 153.1280, found 153.1287



3-Methylnona-1,2-diene

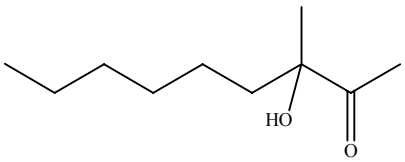
See section 5.1.1.3 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J = 6.5Hz, CH_3), 1.25-1.32 (6H, m, 3 x CH_2), 1.40-1.42 (2H, m, CH_2), 1.67 (3H, t, J = 3.5Hz, CH_3), 1.91-1.94 (2H, m, CH_2) 4.57 (2H, m, CH_2)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.33, 18.93, 22.87, 27.57, 29.17, 31.94, 33.70, 73.93, 98.73, 206.33

HRMS calcd for $C_{10}H_{18}O$ 138.1409, found 138.1404

This is a known compound.[11]



3-Hydroxy-3-methyl-nonan-2-one

See section 5.1.1.4 for procedure.

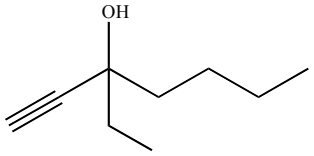
^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (3H, T, J = 6.5Hz, CH_3), 0.96-1.02 (1H, m, CH_2), 1.23-1.30 (6H, m, $CH_2CH_2CH_2$), 1.36 (3H, s, CH_3), 1.39-1.44 (1H, m, CH_2), 1.68-1.71 (2H, m, CH_2), 2.21 (3H, s, CH_3), 3.84 (H, s, OH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.26, 22.76, 23.54, 23.84, 25.70, 29.67, 31.85, 39.71, 79.03, 212.62

HRMS (CI) calcd for $C_{10}H_{21}O_2$ (MH) 173.1580, found 173.1545

HPLC50%ee (Chiracel ADH; 10% ethanol in hexanes; 1 ml/min) t_r(R) = 4.87 min t(S) = 5.81 min $[\alpha]_D$ =-9.1^o($CHCl_3$, c = 2.2 g/l)

This is a known compound.[12]

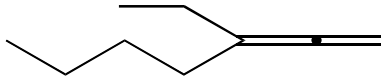


3-Ethyl-hept-1-yn-3-ol

See section 5.1.1.2 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.94 (3H, t, CH_3), 1.06 (3H, t, CH_3), 1.35 (2H, sextet, CH_2), 1.49 (2H, pentet, CH_2), 1.60-1.70 (4H, m, 2 x CH_2), 1.91 (1H, s, OH), 2.44 (1H, s, CH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.42, 14.05, 22.87, 26.28, 34.68, 41.14, 71.57, 72.23, 86.68



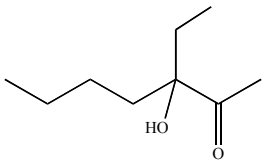
3-Ethylhepta-1,2-diene

See section 5.1.1.3 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (3H, t, J = 7.5 Hz, CH_3), 1.00 (3H, t, J = 7.5 Hz, CH_3), 1.30-1.42 (2H, m, CH_2), 1.91-1.94 (4H, m, 2 x CH_2), 4.66 (2H, pentet, J = 3.5 Hz, =CH_2)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.18, 13.97, 22.45, 25.07, 29.77, 31.86, 75.73, 105.07, 205.44

This is a known compound.[13]



3-Ethyl-3-hydroxy-heptan-2-one

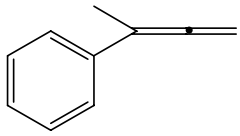
See section 5.1.1.4 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.79 (3H, t, J = 7.5 Hz, CH_3), 0.87-1.00 (3H, m, CH_2), 1.27 (2H, sextet, CH_2), 1.41 (2H, m, CH_2), 1.68-1.77 (4H, m, 2 x CH_2), 2.18 (3H, s, CH_3), 3.86 (H, bs, OH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 7.65, 14.09, 23.13, 24.03, 25.59, 31.78, 38.55, 82.17, 212.62

No optical rotation observed.

This is a known compound.[14]



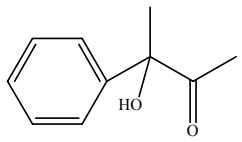
3-Phenylbuta-1,2-diene

See section 5.1.1.3 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.10 (3H, t, J = 3Hz, CH_3), 5.02 (2H, q, J = 3Hz, CH_2), 7.20-7.42 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.89, 77.09, 125.87, 126.77, 128.53, 136.92, 209.19

This is a known compound.[15]



3-Hydroxy-3-phenyl-butan-2-one

See section 5.1.1.4 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.79 (3H, s, CH_3), 2.09 (3H, s, CH_3), 4.53 (1H, s, OH), 7.31-7.45 (5H, m, Ar)

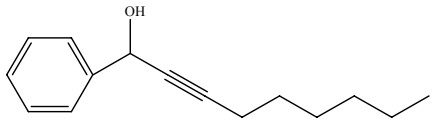
^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.67, 24.25, 80.09, 126.22, 128.29, 128.92, 141.63, 209.84

HRMS calcd for $C_{10}H_{12}O_2Na$(FAB) 187.035, found 187.0746

HPLC 86%ee (Chiracel OD; 5% isopropyl alcohol in hexanes; 0.8 ml/min) t_r(R) = 9.04 min t(S) = 9.68 min $[\alpha]_D$ = -229^o($CHCl_3$, c = 8.56 g/l)

This is a known compound.[16]

5.1.2. Experimental details and data for asymmetric dihydroxylation of 1,3-disubstituted allenes



1-Phenyl-non-2-yn-1-ol

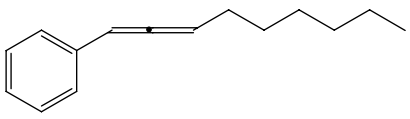
5.1.2.1 Typical procedure:[17]

1-Octyne (1.65 g, 15 mmol) was dissolved in anhydrous THF (30 mL) and to the cooled solution (-78 ^{o}C), was added *n*BuLi (6.3 mL, 1.6 M in hexane). After complete deprotonation (4 h) at -40 ^{o}C, a solution of benzaldehyde (1.59 g, 15 mmol) was added dropwise. The reaction mixture was stirred and allowed to warm to room temperature. Saturated brine was added and the mixture extracted with ether, The combined ether layers were dried ($MgSO_4$) and concentrated to afford the crude propargylic alcohol, which was purified by flash chromatography to give 2.91g (90%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, T, J = 2Hz, CH_3), 1.27-1.32 (4H, m, CH_2CH_2), 1.38-1.41 (2H, m, CH_2), 1.51-1.54 (2H, m, CH_2), 2.07 (1H, d, J = 6.5Hz, OH), 2.25-2.29 (2H, m, CH_2), 5.45 (1H, d, J = 6.5Hz, CH), 7.32-7.55 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.04, 18.84, 22.55, 28.55, 28.58, 31.32, 64.89, 79.92, 87.81, 126.64 (2C), 128.22, 128.54 (2C), 141.31

HRMS calcd for $C_{15}H_{20}O$ 216.1514, found 216.1513



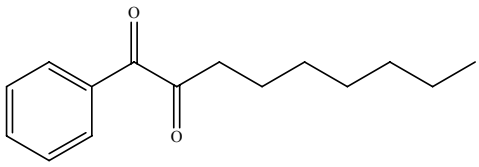
1-Phenylnona-1,2-diene

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (3H, t, J = 2Hz, CH_3), 1.13-1.38 (6H, m, 3 x CH_2), 1.45-1.49 (2H, m, CH_2), 2.10-2.14 (2H, m, CH_2), 5.56 (1H, m, CH), 6.11 (1H, m, CH), 7.16-7.29 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.28, 22.86, 28.99, 29.08, 29.36, 31.86, 94.74, 95.32, 126.78 (2C), 126.80, 128.74 (2C), 135.40, 205.37

HRMS calcd for $C_{15}H_{20}$ 200.1565, found 200.1562

This is a known compound.[18]



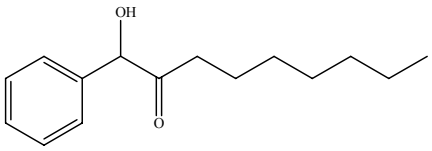
1-Phenyl-nonane-1,2-dione

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (3H, t, J = 7Hz, CH_3), 1.26-1.39 (8H, m, 4 x CH_2), 1.67-1.71 (2H, m, CH_2), 2.87 (2H, t, J = 7Hz, CH_2), 7.48-7.99 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.26, 22.79, 23.10, 29.20, 29.34, 31.83, 39.03, 129.07 (2C), 130.37 (2C), 132.25, 134.77, 192.83, 203.77

HRMS calcd for $C_{15}H_{20}O_2$ 232.1463, found 232.1471

This is a known compound.[19]



1-Hydroxy-1-phenyl-nonan-2-one

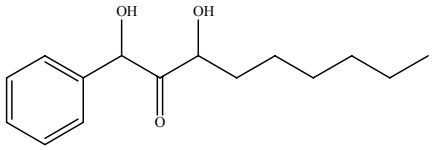
^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.85 (3H, t, J = 7Hz, CH_3), 1.16-1.26 (10H, m, 4 x CH_2), 1.46-1.55 (1H, m, CH_2), 2.27-2.40 (1H, m, CH_2), 4.374 (1H, d, J = 4Hz, OH), 5.08 (1H, d, J = 4Hz, CH), 7.31-7.39 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.23, 22.73, 23.89, 29.04, 29.11, 31.74, 38.02, 79.90, 127.65 (2C), 128.87, 129.16 (2C), 138.35, 209.89

HRMS calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1613

HPLC 83%ee (Chiracel OD; 10% isopropyl alcohol in hexanes; 1 ml/min) t_r(R) = 6.13 min t(S) = 7.07 min $[\alpha]_D$ = -212°($CHCl_3$, c = 4.7 g/l)

This is a known compound.[20]



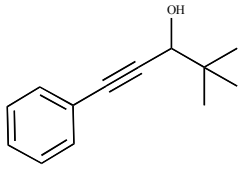
1,3-Dihydroxy-1-phenyl-nonan-2-one

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (3H, t, J = 7Hz, CH_3), 1.26-1.42 (8H, m, 4 x CH_2), 1.53-1.59 (1H, m, CH_2), 1.77-1.84 (1H, m, CH_2), 2.88 (1H, d, J = 7Hz, OH), 4.07 (1H, bs, OH), 4.20-4.22 (1H, m, CH), 5.39 (1H, s, CH), 7.19-7.40 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.24, 22.73, 24.69, 29.08, 31.75, 34.54, 73.66, 76.94, 127.60 (2C), 129.33, 129.48 (2C), 137.64, 211.77

HRMS calcd for $C_{15}H_{22}O_3Na$(FAB) 273.1467, found 273.1464

HPLC 82%ee (Chiracel OD; 10% isopropyl alcohol in hexanes; 1 ml/min) t (?) = 6.71 min t(?) = 7.39 min $[\alpha]_D$ = -171°($CHCl_3$, c = 7.8 g/l)



4,4-Dimethyl-1-phenyl-pent-1-yn-3-ol

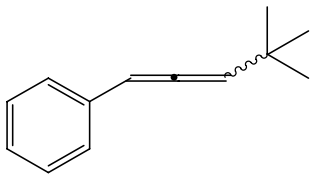
Typical procedure:[21]

To phenylacetylene (1.68 g, 16.5 mmol) in anhydrous toluene (60 mL) was added anhydrous $ZnCl_2$ (3.06 g, 22.5 mmol) and Et_3N (2.27 g, 22.5 mmol). The mixture was stirred at 35 ^oC room for 1 h, then trimethylacetaldehyde (1.29 g, 15 mmol) was added and the solution was stirred for 10 h. The reaction then was quenched using saturated brine and the mixture was extracted with ether. The combined ether layers were dried ($MgSO_4$) and concentrated to afford the crude propargylic alcohol, which was purified by flash chromatography.

^1H NMR ($CDCl_3$, 500 MHz) δ 1.07 (9H, s, $3CH_3$), 1.78 (1H, d, J = 6Hz, OH), 4.23 (1H, d, J = 6Hz, CH), 7.23-7.42 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.39, 36.15, 71.89, 85.71, 88.96, 122.82, 128.28 (2C), 128.32, 131.69 (2C)

HRMS calcd for $C_{13}H_{16}O$ 188.12018, found 188.1193



1-Phenyl-4,4-dimethylpenta-1,2-diene

5.1.2.2. Typical procedure:[17]

4,4-Dimethyl-1-phenyl-1-pentyn-3-ol (188mg, 1mmol) and AIBN (20mg) were added to a flame-dried 50 mL round-bottomed flask and heated to 92 ^{o}C using a thermostat-controlled oil bath. Tributyltin hydride was added via syringe and the reaction mixture was maintained, under N_2, at this temperature for a further 3h, after which it was cooled to 0 ^{o}C. DCM (10 mL), triethylamine (2.1 g, 2.1 mmol) and methanesulfonyl chloride (182 mg, 1.6 mmol, 1.5 equiv) were then added. The mixture was extracted with ether, and the combined ether layers were dried ($MgSO_4$) and concentrated. Repeated chromatography (in pentane) afforded pure 4,4-dimethyl-1-phenyl-1,2-pentanediene (86 mg, 50%).

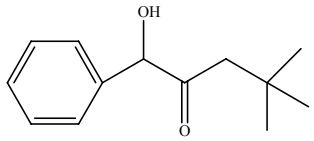
Enantiomerric excesses of allenic compounds have been determined by 1H NMR analysises with 1:1:1.5 mixtures of allenes, Ag(fod) and $Yb(hfcd)_3$ with $CDCl_3$ as solvent.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.13 (9H, s, $3CH_3$), 5.57 (1H, d, J = 6.5Hz, CH), 6.18 (1H, d, J = 6.5Hz, CH), 7.17-7.29 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.28 (3C), 32.76, 96.18, 106.91, 126.40 (2C), 126.61, 128.56 (2C), 135.30, 202.47

HRMS calcd for $C_{13}H_{16}$ 172.1253, found 172.1256

This is a known compound.[22]



1-Hydroxy-4,4-dimethyl-1-phenyl-pentan-2-one

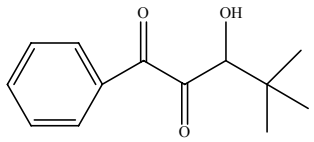
See section 5.1.1.4 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.95 (9H, s, $3CH_3$), 2.24 (2H, ABq, J = 15.5Hz, CH_2), 4.43 (1H, d, J = 4Hz, OH), 5.02 (1H, d, J = 4Hz, CH), 7.26-7.38 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 209.03, 131.64, 130.41 (2C), 129.28 (2C), 128.83, 80.85, 50.19, 31.48, 29.82 (3C)

HRMS calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1310

HPLC 64%ee (Chiracel OD; 10% isopropyl alcohol in hexanes; 1 ml/min) t(R) = 6.06 min t(S) = 7.25 min



3-Hydroxy-4,4-dimethyl-1-phenyl-pentane-1,2-dione

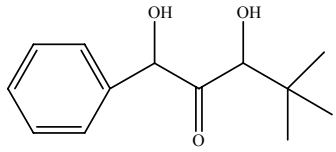
See section 5.1.1.4 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.99 (9H, s, $3CH_3$), 3.17 (1H, d, J = 6.5Hz, OH), 4.86 (1H, d, J = 6.5Hz, CH), 7.51-8.02 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.65, 191.62, 138.08, 135.15, 129.14 (2C), 127.88, 80.77, 36.48, 26.50 (3C)

HRMS calcd for $C_{13}H_{16}O_3$ 220.1099, found 220.1098

HPLC 34%ee (Chiracel OD; 10% isopropyl alcohol in hexane; 1 ml/min) t(isomer A) = 5.10 min t(isomer B) = 5.45 min



1,3-Dihydroxy-4,4-dimethyl-1-phenyl-pentan-2-one

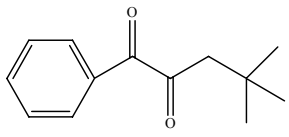
See section 5.1.1.4 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.00 (9H, s, $3CH_3$), 2.69 (1H, d, J = 9Hz, OH), 3.93 (1H, d, J = 9Hz, CH), 4.16 (1H, d, J = 6Hz, OH), 5.39 (1H, d, J = 6Hz, CH), 7.26-7.39 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.10, 36.02, 79.86, 79.90, 127.74 (2C), 129.11, 129.28 (2C), 137.01, 212.07

HRMS calcd for $C_{13}H_{18}O_3Na$(FAB) 245.1154, found 245.1173

HPLC 72%ee, 53%de (Chiracel OD; 10% isopropyl alcohol in hexane; 1 ml/min) t(1) = 5.19 min t(2) = 5.47 min t(3) = 6.55 min t(4) = 7.07min $[\alpha]_D$ = +224^{o}($CHCl_3$, c = 2.0 g/l)



4,4-Dimethyl-1-phenyl-pentane-1,2-dione

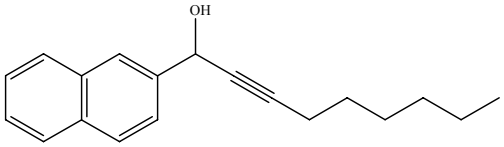
See section 5.1.1.4 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.09 (9H, s, $3CH_3$), 2.82 (2H, s, CH_2), 7.29-8.01 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 203.2, 195.6, 132.0, 129.9 (2C), 129.0 (2C), 128.3, 50.2, 31.2, 29.9

HRMS calcd for $C_{13}H_{16}O_2$ 204.1150, found 204.1158

This is a known compound.[23]



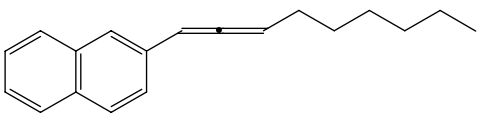
1-Naphthalen-2-yl-non-2-yn-1-ol

See section 5.1.1.2 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (3H, t, J = 7Hz, CH_3), 1.26-1.58 (8H, m, 4 x CH_2), 2.22 (H, d, J = 6Hz, OH), 2.29 (2H, m, CH_2), 6.13 (H, d, J = 6Hz, CH), 7.46-7.57 (3H, m), 7.83-7.89 (3H, m), 8.32 (H, d, J = 8.5Hz, ArH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.05, 18.90, 22.54, 28.51, 28.59, 31.31, 63.09, 79.63, 88.48, 124.05, 124.42, 125.21, 125.80, 126.30, 128.68, 129.19, 130.58, 133.99, 136.25

HRMS calcd for $C_{19}H_{22}O$ 266.1671, found 266.1683



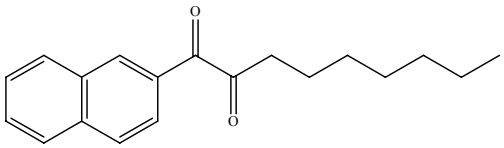
1-Naphthylnona-1,2-diene

See section 5.1.1.3 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (3H, t, J =7Hz, CH_3), 1.25-1.55 (8H, m, 4 x CH_2), 2.19 (2H, m, CH_2), 5.61 (1H, m, CH), 6.81 (1H, m, CH), 7.42-7.52 (3H, m, Ar), 7.54 (1H, d, J = 7Hz, Ar), 7.72 (1H, d, J = 7Hz, Ar), 7.84 (1H, d, J = 9Hz, Ar), 8.24 (1H, d, J = 9Hz, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.08, 22.65, 28.82, 28.91, 29.15, 31.67, 90.99, 94.07, 94.76, 123.58, 125.05, 125.61, 125.85, 127.14, 128.61, 130.79, 131.29, 133.91

HRMS calcd for $C_{19}H_{22}$ 250.1721, found 250.1722



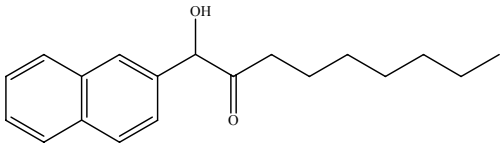
1-Naphthalen-2-yl-nonane-1,2-dione

See section 5.1.1.4 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.95 (1H, d, ArH), 8.1-7.5 (6H, m, ArH), 2.97 (2H, t, CH_2), 1.77 (2H, pentet, CH_2), 1.3 (8H, m, 4 x CH_2), 0.89 (3H, t, CH_3)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.08, 22.60, 23.07, 29.02, 29.17, 31.64, 38.93, 124.26, 125.66, 126.91, 128.02, 128.75, 129.00, 131.09, 133.64, 134.05, 135.34, 195.65, 204.10

HRMS calcd for $C_{19}H_{22}O_2$ 282.1620, found 282.1638



1-Hydroxy-1-naphthalen-2-yl-nonan-2-one

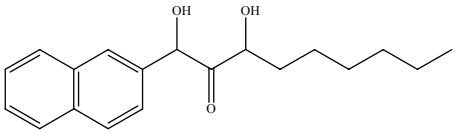
See section 5.1.1.4 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.81 (3H, t, J = 7Hz, CH_3), 1.06-1.20 (8H, m, 4 x CH_2), 1.42-1.51 (2H, m, CH_2), 2.11-2.18 (1H, m, CH_2), 2.32-2.38 (1H, m, CH_2), 4.45 (1H, s, OH), 5.60 (1H, s, CH), 7.46-7.53 (4H, m, Ar), 7.58-7.89 (2H, m, Ar), 7.99 (1H, d, J = 9Hz, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.93, 134.27, 133.48, 131.18, 129.62, 128.97, 127.87, 126.86, 126.03, 125.35, 123.55, 78.93, 53.46, 37.93, 31.48, 28.80, 28.79, 23.65, 22.49, 14.02

HRMS calcd for $C_{19}H_{24}O_2$ 284.1776, found 284.1767

HPLC 92%ee (Chiracel OD; 10% isopropyl alcohol in hexane; 1 ml/min) t_r(R) = 10.20 min t(S) = 11.48 min $[\alpha]_D$ = -177^o ($CHCl_3$, c = 3.5 g/l)



1,3-Dihydroxy-1-naphthalen-2-yl-nonan-2-one

See section 5.1.1.4 for procedure.

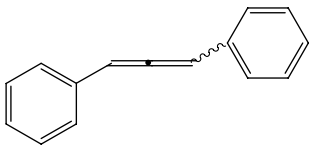
^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (3H, t, J = 7Hz, CH_3), 1.15-1.31 (8H, m, 4 x CH_2), 1.49-1.52 (1H, m, CH_2), 1.69-1.74 (1H, m, CH_2), 3.03 (1H, b, OH), 4.02 (1H, b, OH),

4.18 (1H, b, CH), 5.87 (1H, s, CH) 7.41-7.54 (4H, m, Ar), 7.87-7.95 (3H, m, Ar),

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.02, 22.49, 24.44, 28.75, 31.45, 34.58, 73.81, 75.94, 123.18, 125.32, 126.26, 127.21, 127.99, 129.11, 130.13, 130.99, 132.76, 134.31, 212.93

HRMS calcd for $C_{19}H_{24}O_3$ 300.1725, found 300.1713

HPLC 90%ee(AD-β-mix) and 81%ee(AD-α-mix) (Chiracel OD; 10% isopropyl alcohol in hexane; 1 ml/min) t(isomer A) = 12.20 min t(isomer B) = 16.12 min $[\alpha]_D = +110^o$ ($CHCl_3$, c = 4.4 g/l)



1,3-diphenylpropa-1,2-diene

Typical procedure:[24]

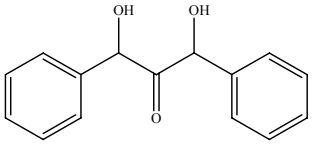
To a suspension of CuBr (747 mg, 5.1 mmol) and LiBr (446 mg, 5.1 mmol) in THF (20 mL) at -78 ^oC was added PhMgBr (902 mg, 5.1 mmol) in Et_2O (20 mL), and the resulting mixture was stirred 15 min. In a separate flask, to a solution of 1-phenyl-2-propyn-1-ol (673 mg, 5.1 mmol) in THF at -78 ^oC was added BuLi (3.4 mL, 1.6 M in hexanes, 5.1 mmol); after 5 min stirring, MsCl (0.4 mL, 5.1 mmol) was added. This solution was added to the Grignard solution via cannula and stirred 15 min at -78 ^oC. The mixture was poured into a separatory funnel containing NaCN in 2% NH_4Cl and separated. The aqueous layer was washed with Et_2O, then the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated on a rotary evaporator. This material was

chromatographed (pentane) to give the product (0.233 g, 39%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.60 (2H, s, =CH), 7.23-7.37 (10H, m, ArH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 98.65 (2C), 127.21 (4C), 127.54 (2C), 128.96 (4C), 133.81 (2C), 208.00

This is a known compound.[24]



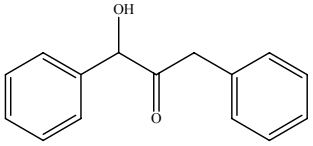
1,3-Dihydroxy-1,3-diphenyl-propan-2-one

See section 5.1.1.4 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.5-7.1 (10H, m, ArH), 5.12 (2H, s, 2 x CH), 4.05 (2H, bs, 2 x OH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 209.07, 137.30 (2C), 129.50 (4C), 129.46 (4C), 127.99 (2C), 76.47 (2C)

This compound not known, but our yield is too low for complete analysis.



1-Hydroxy-1,3-diphenyl-propan-2-one

Insufficient material for spectral data was obtained from the asymmetric dihydroxylation procedure. Racemic material has been synthesized to verify the

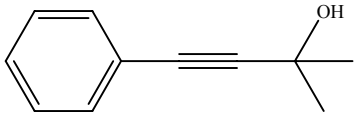
identity.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.5-6.9 (10H, m, ArH), 5.20 (1H, d, CH), 4.23 (1H, d, OH), 3.63 (2H, AB q, CH_2)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.15, 137.83, 133.12, 129.59 (2C), 129.32 (2C), 129.12, 128.91 (2C), 127.98 (2C), 127.47, 79. 45, 44.83

This is a known compound.[25]

5.1.3. Experimental details and data for asymmetric dihydroxylation of trisbustituted allenes



2-Methyl-4-phenyl-but-3-yn-2-ol

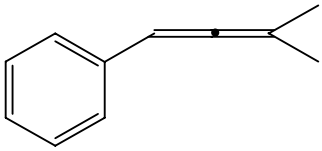
See section 5.1.2.1 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 1.62 (6H, s, $2CH_3$), 2.03 (1H, s, OH), 7.30-7.43 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 500 MHz, TMS) δ 31.71 (2C), 65.86, 82.35, 93.93, 122.90, 128.474 (2C), 131.85 (3C)

HRMS calcd for $C_{11}H_{12}O$ 160.0888, found 160.0883

This is a known compound.[26]



1-Phenyl-3-methylbuta-1,2-diene

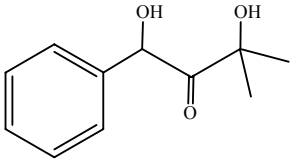
See section 5.1.2.2 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 1.82 (6H, d, J = 3Hz, $2CH_3$), 5.98 (1H, q, J = 3Hz, CH), 7.14-7.30 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 500 MHz, TMS) δ 20.50 (2C), 92.71, 99.36, 126.59, 126.82 (2C), 128.69 (2C),136.18, 203.33

HRMS calcd for $C_{11}H_{112}$ 144.0939, found 140.0941

This is a known compound.[27]



1,3-Dihydroxy-3-methyl-1-phenyl-butan-2-one

See section 5.1.1.4 for procedure.

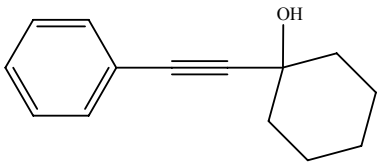
^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 1.21 (6H, d, J = 18.5Hz, $2CH_3$), 2.32 (1H, s, OH), 4.16 (1H, d, J = 6.5Hz, OH), 5.62 (1H, d, J = 6.5Hz, CH), 7.31-7.37 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 500 MHz, TMS) δ 27.75, 28.51, 76.15, 77.62, 128.18 (2C), 129.08 (1C), 129.28 (2C), 138.08, 214.57

HRMS calcd for $C_{11}H_{14}O_3NH_4$ ($[M+NH_4]^+$) 212.12812, found 212.12815

HPLC 51%ee (Chiracel OD; 5% isopropyl alcohol in hexanes; 1ml/min) t_1 = 7.89min t_2 =

9.06min $[\alpha]_D$ =-54°($CHCl_3$, c = 4.69 g/l)



1-Phenylethynyl-cyclohexanol

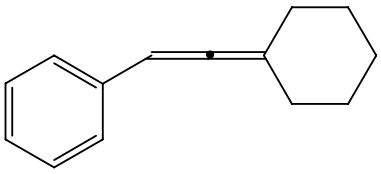
See section 5.1.2.1 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 1.30 (2H, pentet, J = 6Hz, CH_2), 1.58-1.69 (4H, m, $2CH_2$), 1.73-1.76 (2H, m, CH_2), 2.00-2.03 (2H, m, CH_2), 2.05 (1H, s, OH), 7.30-7.31 (3H, m, Ar), 7.42-7.44 (2H, m, Ar)

^{13}C NMR ($CDCl_3$, 500 MHz, TMS) δ 23.61, 25.41, 40.25 (2C), 69.35, 84.56, 92.91, 123.06, 128.41, 128.46 (2C), 131.89 (2C)

HRMS calcd for $C_{14}H_{16}ONa$(FAB) 223.10934, found 223.10965

This is a known compound.[28]



3-Phenylvinylidene cyclohexane

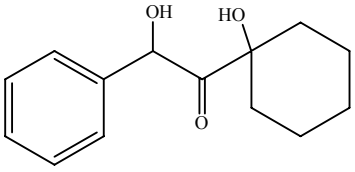
See section 5.1.2.2 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 1.54-1.73 (6H, m, $3CH_2$), 2.17-2.30 (4H, m, $2CH_2$), 5.99 (H, t, J = 2Hz, CH), 7.15-7.17 (1H, m, Ar), 7.28-7.29 (4H, m, Ar)

^{13}C NMR ($CDCl_3$, 500 MHz, TMS) δ 26.33, 27.90, 31.52, 92.54, 106.69, 126.49, 126.69 (2C), 128.70 (2C), 136.34, 199.85

HRMS calcd for $C_{14}H_{17}$ (FAB) 185.13248, found 185.13139

This is a known compound.[29]



2-Hydroxy-1-(1-hydroxy-cyclohexyl)-2-phenyl-ethanone

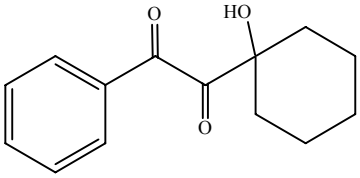
See section 5.1.1.4 for procedure.

^1H NMR ($CDCl_3$, 500 MHz, TMS) δ 1.10-1.72 (10H, m, $5CH_2$), 4.18 (1H, d, J = 6Hz, OH), 5.64 (1H, d, J = 6Hz, CH), 7.29-7.38 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 500 MHz, TMS) δ 20.65, 25.01, 34.30, 35.54, 76.12, 79.41, 128.20 (2C), 128.89, 129.18 (2C), 138.10, 214.82

HRMS calcd for $C_{14}H_{18}O_3Na$(FAB) 257.11482, found 257.11481

HPLC 31%ee (Chiracel OD; 5% ethyl alcohol in hexanes; 1ml/min) t_1 = 7.53min t_2 = 9.45min $[\alpha]_D$ =-88^o($CHCl_3$, c = 10.2 g/l)



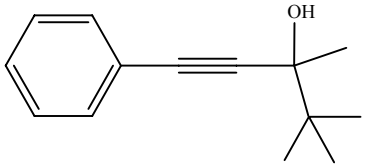
1-(1-Hydroxy-cyclohexyl)-2-phenyl-ethane-1,2-dione

See section 5.1.1.4 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 1.28-1.31 (2H, m, CH_2), 1.66-1.95 (8H, m, $4CH_2$), 2.71(1H, s, OH), 7.50-7.53 (2H, m, Ar), 7.65-7.68 (1H, m, Ar), 7.85-7.87 (2H, m, Ar)

^{13}C NMR ($CDCl_3$, 500 MHz, TMS) δ 20.82 (2C), 25.12, 34.15, 78.59, 129.2 (2C), 129.88 (2C), 132.76, 135.15, 195.91, 208.20

HRMS calcd for $C_{14}H_{17}O_3$ (FAB) 233.11722, found 233.11733



3,4,4-Trimethyl-1-phenyl-pent-1-yn-3-ol

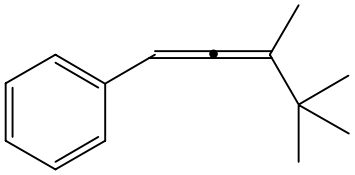
See section 5.1.2.1 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 1.11(9H, s, $3CH_3$), 1.54 (3H, s, CH_3), 1.96 (H, s, OH), 7.30-7.43(5H, m, Ar)

^{13}C NMR ($CDCl_3$, 500 MHz, TMS) δ 24.99, 25.42 (3C), 38.72, 74.58, 84.09, 93.06, 123.18, 128.36, 128.45 (2C), 131.81 (2C)

HRMS calcd for $C_{14}H_{18}O$ $[M+Na]^+$ 225.12499, found 225.12506

This is a known compound.[30]



1-Phenyl-3,4,4-trimethyl-penta-1,2-diene

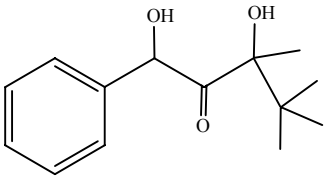
See section 5.1.2.2 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 1.13 (9H, s, $3CH_3$), 1.80 (3H, d, J = 3Hz, CH_3), 6.05 (H, q, J = 3Hz, CH), 7.15-7.28 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 500 MHz, TMS) δ 14.92, 29.38 (3C), 34.42, 94.29, 112.82, 126.46, 126.52 (2C), 128.73 (2C), 136.49, 201.99

HRMS calcd for $C_{14}H_{18}$ 186.1409, found 186.1409

This is a known compound.[31]



1,3-Dihydroxy-3,4,4-trimethyl-1-phenyl-pentan-2-one

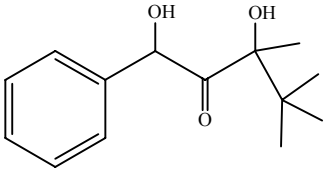
See section 5.1.1.4 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 0.87 (9H, s, $3CH_3$), 1.23 (3H, s, CH_3), 2.44 (H, s, OH), 4.12 (H, d, J = 7.5Hz, OH), 5.61(H, d, J = 7.5Hz, CH), 7.34-7.36 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 500 MHz, TMS) δ 21.79, 25.70 (3C), 38.12, 77.49, 84.38, 128.21 (2C), 128.80, 128.98 (2C), 137.81, 214.76

HRMS calcd for $C_{11}H_{14}O_3$ ($[M+NH_3]^+$) 212.12812, found 212.12815

HPLC 70%ee (Chiracel OD; 5% ethyl alcohol in hexanes; 1ml/min) t_1 = 6.97min t_2 = 7.27min $[\alpha]_D$ =-214^o($CHCl_3$, c = 3.8 g/l)



1,3-Dihydroxy-3,4,4-trimethyl-1-phenyl-pentan-2-one

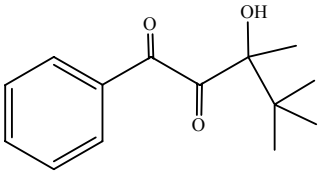
See section 5.1.1.4 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 1.01 (9H, s, $3CH_3$), 1.11 (3H, s, CH_3), 1.20 (H, s, OH), 4.14 (H, d, J=7.5Hz, OH), 5.63 (H, d, J=7.5Hz, CH), 7.30-7.36 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 500 MHz, TMS) δ 23.60, 25.20 (3C), 38.63, 77.92, 83.74, 128.22 (2C), 128.75, 129.21 (2C), 138.90, 215.89

HRMS calcd for $C_{11}H_{14}O_3$ ($[M+NH_3]^+$) 212.12812, found 212.12815

HPLC 79%ee (Chiracel OD; 5% ethyl alcohol in hexanes; 1ml/min) t_1 = 7.62min t_2 = 8.69min $[\alpha]_D$ =-116^o($CHCl_3$, c = 8.7g/l)



3-Hydroxy-3,4,4-trimethyl-1-phenyl-pentane-1,2-dione

See section 5.1.1.4 for procedure.

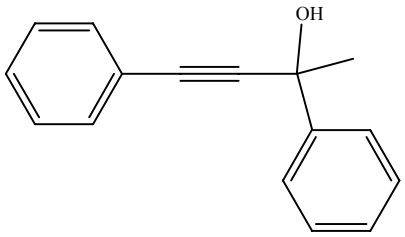
^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 1.09 (9H, s, $3CH_3$), 1.54 (3H, s, CH_3), 2.94 (H, s,

OH), 7.49-7.52 (2H, m, Ar), 7.63-7.64 (1H, m, Ar), 7.89-7.90 (2H, m, Ar)

^{13}C NMR ($CDCl_3$, 500 MHz, TMS) δ 22.07, 25.88 (3C), 38.54, 84.17, 129.13 (2C), 129.89 (2C), 132.68, 134.83, 195.02, 209.28

HRMS calcd for $C_{11}H_{14}O_3$ ($[M+NH_3]^+$) 212.12812, found 212.12815

HPLC 31%ee (Chiracel OD; 5% isopropyl alcohol in hexanes; 1ml/min) t_1 = 5.52min t_2 = 5.80min $[\alpha]_D$ =+23°($CHCl_3$, c = 6.46 g/l)



2,4-Diphenyl-but-3-yn-2-ol

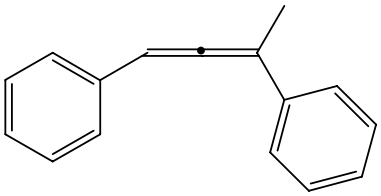
See section 5.1.2.1 for procedure.

^1H NMR ($CDCl_3$, 500 MHz, TMS) δ 1.87 (3H, s, CH_3), 2.48 (1H, s, OH), 7.31-7.33 (4H, m, Ar), 7.37-7.40 (2H, m, Ar), 7.47-7.49 (2H, m, Ar), 7.72-7.74 (2H, m, Ar)

^{13}C NMR ($CDCl_3$, 500 MHz, TMS) δ 33.52, 70.61, 85.15, 92.67, 96.41, 122.78, 125.21, 127.96, 128.52, 128.56, 128.71, 131.94, 145.88

HRMS calcd for $C_{14}H_{18}O$ $[M+Na]^+$ 225.12499, found 225.12506

This is a known compound.[32]



1,3-Diphenylbuta-1,2-diene

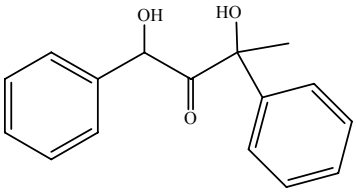
See section 5.1.2.2 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 2.23 (3H, d, J = 2.5Hz, CH_3), 6.47 (1H, q, J = 2.5Hz, CH), 7.20-7.24 (2H, m, Ar), 7.30-7.34 (6H, m, Ar), 7.45-7.47 (2H, m, Ar)

^{13}C NMR ($CDCl_3$, 500 MHz, TMS) δ 16.98, 96.78, 104.76, 126.07 (2C), 127.12 (2C), 127.23, 127.25, 128.67 (2C), 128.91 (2C), 134.76, 136.58, 207.06

HRMS calcd for $C_{14}H_{18}O$ $[M+H]^+$ 207.11683, found 207.11640

This is a known compound.[33]



1,3-Dihydroxy-1,3-diphenyl-butan-2-one

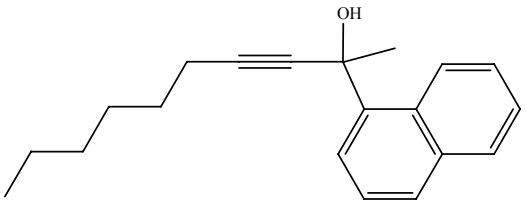
See section 5.1.1.4 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 1.55 (3H, s, CH_3), 3.47 (1H, s, OH), 3.95 (1H, d, J = 5Hz, OH), 5.47 (1H, d, J = 5Hz, CH), 7.09-7.25 (10H, m, 2Ar)

^{13}C NMR ($CDCl_3$, 500 MHz, TMS) δ 27.49, 76.35, 80.73, 125.19 (2C), 128.00, 128.23 (2C), 128.58 (2C), 128.81 (3C), 137.59, 141.71, 211.58

HRMS calcd for $C_{14}H_{18}O$ $[M+Na]^+$ 279.09917, found 279.09834

HPLC 66%ee (Chiracel OD; 5% isopropyl alcohol in hexanes; 1ml/min) t_1 = 16.30min t_2 = 17.58min $[\alpha]_D$ =-78^o($CHCl_3$, c = 12 g/l)



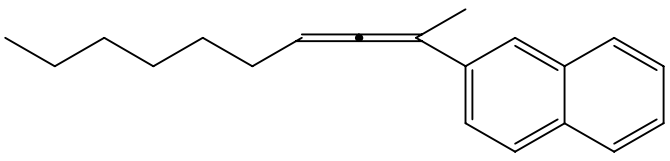
2-Naphthalen-1-yl-dec-3-yn-2-ol

See section 5.1.2.1 for procedure.

H NMR ($CDCl_3$, 500 MHz, TMS) δ 0.89 (3H, t, J = 2Hz, CH_3), 1.27-1.32 (4H, m, $2CH_2$), 1.40-1.45 (2H, m, CH_2), 1.52-1.57 (2H, m, CH_2), 1.82 (3H, s, CH_3), 2.28 (2H, t, J = 7Hz, CH_2), 2.58(1H, s, OH), 7.43-7.45 (2H, m, Ar), 7.72-7.74 (1H, m, Ar), 7.78-7.83 (3H, m, Ar), 7.81 (1H, s, Ar)

^{13}C NMR ($CDCl_3$, 500 MHz, TMS) δ 14.22, 19.96, 22.74, 28.76, 28.80, 31.50, 33.57, 70.31, 84.06, 86.10, 123.50, 123.87, 126.11, 126.25, 127.69, 128.15, 128.46, 132.96, 133.22, 143.74

HRMS calcd for $C_{20}H_{24}O$ $[M+Na]^+$ 303.17194 found 303.17202



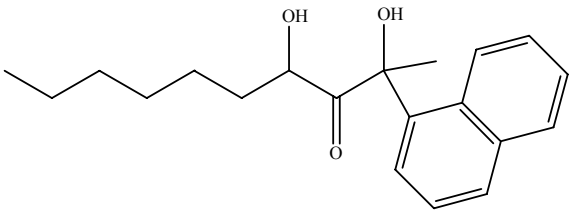
1-Naphthyl-deca-2,3-diene

See section 5.1.2.2 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 0.89 (3H, m, 1.26-1.53 (8H, m, $4CH_2$), 2.13-2.19 (2H, m, CH_2), 2.20-2.24 (3H, m, CH_3), 5.51 (1H, m, CH), 7.40-7.46 (2H, m, Ar), 7.62-7.66 (1H, m, Ar), 7.71-7.82 (4H, m, Ar)

^{13}C NMR ($CDCl_3$, 500 MHz, TMS) δ 14.30, 17.46, 22.89, 29.11, 29.23, 29.41, 31.91, 93.62, 100.78, 123.27, 125.28, 125.63, 126.20, 127.72, 127.74, 128.13, 132.44, 133.87, 135.45, 205.11

HRMS calcd for $C_{20}H_{24}$ $[M+H]^+$ 265.19508 found 265.19446



2,4-Dihydroxy-2-naphthalen-1-yl-decan-3-one

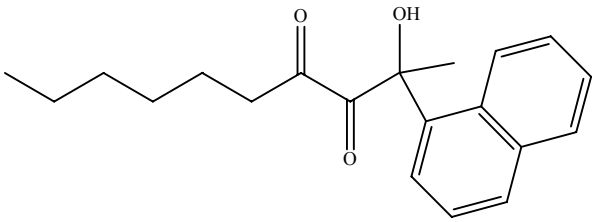
See section 5.1.1.4 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 0.75 (3H, t, J = 2Hz, CH_3), 0.85-1.30 (8H, m, $4CH_2$), 1.35-1.71 (2H, m, CH_2), 1.81 (3H, s, CH_3), 1.82 (3H, s, CH_3), 2.90 (1H, broad, OH), 3.69 (1H, broad, OH), 4.63 (1H, broad, CH), 7.48-7.55 (3H, m, Ar), 7.81-7.83 (3H, m, Ar), 7.96 (1H, s, Ar)

^{13}C NMR ($CDCl_3$, 500 MHz, TMS) δ 14.16, 22.62, 24.88, 28.09, 28.97, 31.69, 34.38, 74.69, 80.96, 123.11, 124.02, 126.61, 126.66, 127.79, 128.43, 128.71, 133.00, 133.31, 139.29, 213.35

HRMS calcd for $C_{20}H_{26}O_3$ $[M+Na]^+$ 337.17742 found 337.17786

HPLC 59%ee (Chiracel OD; 5% isopropyl alcohol in hexanes; 1ml/min) t_1 = 10.30 min t_2 = 15.99min $[\alpha]_D$ =-33^o(CHCl3, c = 9.2g/l)



2-Hydroxy-2-naphthalen-1-yl-decane-3,4-dione

See section 5.1.1.4 for procedure.

^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 0.75 (3H, t, J = 2Hz, CH_3), 0.85-1.30 (8H, m, 4CH_2), 1.35-1.71 (2H, m, CH_2), 1.81 (3H, s, CH_3), 1.82 (3H, s, CH_3), 2.90 (1H, broad, OH), 3.69 (1H, broad, OH), 4.63 (1H, broad, CH), 7.48-7.55 (3H, m, Ar), 7.81-7.83 (3H, m, Ar), 7.96 (1H, s, Ar)

^{13}C NMR ($CDCl_3$, 500 MHz, TMS) δ 14.16, 22.62, 24.88, 28.09, 28.97, 31.69, 34.38, 74.69, 80.96, 123.11, 124.02, 126.61, 126.66, 127.79, 128.43, 128.71, 133.00, 133.31, 139.29, 213.35

HRMS calcd for $C_{20}H_{24}O_3$ $[M+H]^+$ 313.17982 found 313.18110

HPLC 56%ee (Chiracel OD; 5% isopropyl alcohol in hexanes; 1ml/min) t_1 = 7.48min t_2 = 9.99 min $[\alpha]_D$ = -14^o($CHCl_3$, c = 3.5g/l)

5.2. Experimental details and data for Chapter 3

5.2.1. General Procedures

Melting points were performed on a Fisher-Johns hot stage and are uncorrected. Proton and carbon nuclear magnetic resonances were recorded on a Varian 500 MHz spectrometer. Chemical shifts and coupling constants are reported as if they are first order. Chemical shifts are reported in ppm from internal standard TMS. Mass spectra (MS) were determined on LC/MSD TOF on a electrospray conditions.

Flash column chromatography was performed using silica gel (230-400 mesh) with the necessary ratio of ethyl acetate to hexane as the solvent. Silica gel 60 strips with aluminum backing were used in analytical tlc and visualized with a hand-held UV lamp (254 nm) and then dipped into a molybdium stain followed by heating to allow permanent visualization.

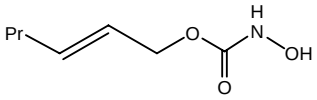
The reaction solvents acetonitrile, dimethylformamide (DMF), ether, tetrahydrofuran (THF), and triethylamine were obtained pure and dry ([H_2O] < 10 ppm) from a Seca Solvent System produced by GlassContour. Ethyl acetate and hexane used for chromatography were reagent grade and used without further purification.

All reactions were carried out under a nitrogen atmosphere, unless noted otherwise.

5.2.2. General Procedure A: synthesis of allylic N-hydroxy carbamates[34,35]

N, *N*'-Carbonyl diimidazole (1.5 eq) was added to a solution of alcohol (1.0 eq) in acetonitrile (5 mL/mmol of substrate) and stirred, under argon, at room temperature until

TLC indicated complete consumption of the alcohol (typically after 2 h). Imidazole (4.0 eq) and hydroxylamine hydrochloride (5.0 eq) were added and stirring continued until TLC showed complete consumption of the adduct. After removal of the reaction solvent, the residue was partitioned between ethyl acetate and 1M HCl followed by extraction of the aqueous phase with ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product which was purified by flash column chromatography.



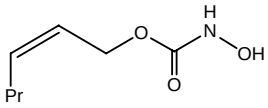
(*E*)-Hex-2-enyl N-hydroxycarbamate

This is a known compound.[35] yield: 85%, colorless oil

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (3H, t, J = 7.5Hz, CH_3), 1.40 (2H, m, CH_2), 2.03 (2H, m, CH_2), 4.60 (2H, d, J = 6Hz, CH_2), 5.56 (1H, m, CH), 5.79 (1H, m, CH), 7.52 (2H, s(br), NH and OH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.81, 22.14, 34.45, 67.18, 123.64, 137.40, 159.66

HRMS calcd for $C_7H_{13}O_3NNa$ $[M+Na]^+$ 182.07876, found 182.07912



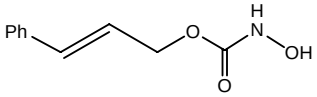
(*Z*)-Hex-2-enyl N-hydroxycarbamate

This is a known compound.[35] yield: 86%, colorless oil

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (3H, t, J = 7.5Hz, CH_3), 1.40 (2H, m, CH_2), 2.08 (2H, m, CH_2), 4.70 (2H, d, J = 7Hz, CH_2), 5.53 (1H, m, CH), 5.66 (1H, m, CH), 7.52 (2H, s(br), NH and OH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.81, 22.69, 29.67, 62.20, 123.15, 136.02, 159.76

HRMS calcd for $C_7H_{13}O_3NNa$ $[M+Na]^+$ 182.07876, found 182.07835



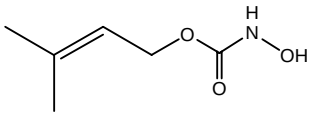
(*E*)-3-Phenylprop-2-enyl N-hydroxycarbamate

yield: 81%, light yellow oil

^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.79 (2H, d, J = 6.5Hz, CH_2), 6.25 (1H, m, CH), 6.63 (1H, d, J = 15.5Hz, CH), 7.24-7.38 (5H, m, Ar), 7.45 (2H, s(br), NH and OH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 66.96, 122.76, 126.87, 128.42, 128.83, 134.98, 136.17, 159.45

HRMS calcd for $C_{10}H_{11}O_3NNa$ $[M+Na]^+$ 216.06311, found 216.06312



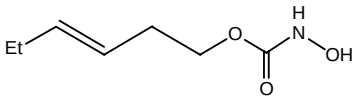
3-Methylbut-2-enyl N-hydroxycarbamate

yield: 87%, colorless oil

^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.71 (3H, s, CH_3), 1.76 (3H, s, CH_3), 4.64 (2H, d, J = 7Hz, CH_2), 5.34 (1H, t, J = 7Hz, CH), 7.60 (2H, s(br), NH and OH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.15, 25.89, 63.15, 118.28, 140.13, 159.88

HRMS calcd for $C_6H_{11}O_3NNa$ $[M+Na]^+$ 168.06311, found 168.06311



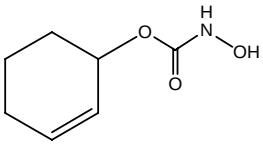
(*E*)-Hex-3-enyl N-hydroxycarbamate

yield: 95%, colorless oil

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.97 (3H, t, J = 7Hz, CH_3), 2.01 (2H, m, CH_2), 2.32 (2H, m, CH_2), 4.13 (2H, t, J = 7Hz, CH_2), 5.35 (1H, m, CH), 5.56 (1H, m, CH), 7.71 (2H, s(br), NH and OH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.76, 25.71, 32.17, 66.00, 123.70, 135.50, 159.82

HRMS calcd for $C_7H_{13}O_3NNa$ $[M+Na]^+$ 182.07876, found 182.07903



Cyclohex-2-enyl N-hydroxycarbamate

Known compound.[35] yield: 95%, colorless oil

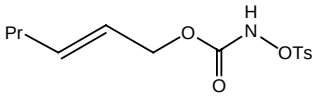
^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.61-2.10 (6H, m, $CH_2CH_2CH_2$), 5.25 (1H, br, CH), 5.73 (1H, m, CH), 5.98 (1H, m, CH), 6.63 (1H, s(br), OH), 7.17 (1H, s(br), NH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.83, 25.02, 28.57, 70.51, 125.34, 133.61, 159.37

HRMS calcd for $C_7H_{11}O_3NNa$ $[M+Na]^+$ 180.06311, found 180.06295

5.2.3. General Procedure B: synthesis of *N*-tosyloxy carbamates[34,35]

To a solution of *N*-hydroxycarbamate (6 mmol) in Et_2O at 0 °C, was added *p*-toluenesulfonyl chloride (1.26 g, 6.60 mmol). Triethylamine (0.85 mL, 6.1 mmol) was then added slowly and the resulting white suspension was stirred for 12h at room temperature. The mixture was washed with water (20 mL) and brine (20 mL), then dried over Na_2SO_4. The solvent was removed under reduced pressure and the tosyloxycarbamate was purified by flash chromatography.



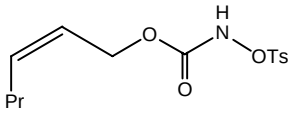
(*E*)-Hex-2-enyl *N*-tosyloxycarbamate.

This is a known compound.[34] yield: 67%, colorless oil

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J = 7Hz, CH_3), 1.38 (2H, m, CH_2), 1.99 (2H, m, CH_2), 2.46 (3H, s, CH_3), 4.42 (2H, d, J = 7.5Hz, CH_2), 5.36 (1H, m, CH), 5.69 (1H, m, CH), 7.35 (2H, d, J = 8Hz, Ar), 7.86 (2H, d, J = 8Hz, Ar), 8.21 (1H, s(br), NH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.76, 21.92, 22.03, 34.36, 67.84, 122.82, 129.72 (2C), 129.84 (2C), 130.44, 137.78, 146.19, 155.68

HRMS calcd for $C_{14}H_{19}O_5NSNa$ $[M+Na]^+$ 336.08761, found 336.08742



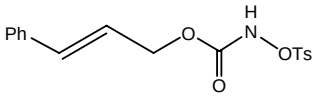
(*Z*)-Hex-2-enyl *N*-tosyloxycarbamate

yield: 63%, colorless oil

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (3H, t, J = 7.5Hz, CH_3), 1.36 (2H, m, CH_2), 2.00 (2H, m, CH_2), 2.46 (3H, s, CH_3), 4.55 (2H, d, J = 6.5Hz, CH_2), 5.33 (1H, m, CH), 5.62 (1H, m, CH), 7.35 (2H, d, J = 8Hz, Ar), 7.87 (2H, d, J = 8Hz, Ar), 7.93 (1H, s(br), NH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.81, 21.99, 22.64, 29.64, 62.93, 122.37, 129.79 (2C), 129.93 (2C), 130.50, 136.45, 146.30, 155.65

HRMS calcd for $C_{14}H_{19}O_5NSNH_4$ $[M+NH_4^+]$ 331.13222, found 331.13230



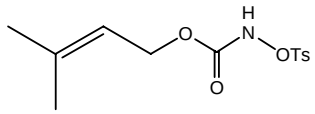
(*E*)-3-Phenylprop-2-enyl *N*-tosyloxycarbamate

yield: 82%, yellow solid

^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.34 (3H, s, CH_3), 4.65 (2H, dd, J = 6.5Hz, 1Hz, CH_2), 6.06 (1H, m, CH), 6.54 (1H, d, J = 16Hz, CH), 7.29 (2H, d, J = 8Hz, Ar), 7.32-7.34 (5H, m, Ar), 7.86 (2H, d, J = 8Hz, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.88, 67.65, 121.79, 126.87 (2C), 128.60, 128.87 (2C), 129.78 (2C), 129.92 (2C), 130.40, 135.46, 135.97, 146.38, 155.50

HRMS calcd for $C_{17}H_{17}O_5NSNa$ $[M+Na]^+$ 370.07196, found 370.07191



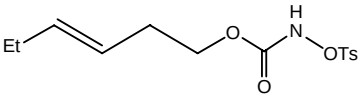
3-Methylbut-2-enyl *N*-tosyloxycarbamate

yield: 89%, colorless oil

^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.64 (3H, s, CH_3), 1.73 (3H, s, CH_3), 2.46 (3H, s, CH_3), 4.50 (2H, d, J = 7.5Hz, CH_2), 5.15 (1H, t, J = 7.5Hz, CH), 7.35 (2H, d, J = 8Hz, Ar), 7.74 (1H, s, NH), 7.87 (2H, d, J = 8Hz, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.17, 21.99, 25.93, 63.98, 117.58, 129.80 (2C), 129.86 (2C), 130.56, 140.66, 146.20, 155.78

HRMS calcd for $C_{13}H_{17}NO_5SNH_4$ $[M+NH_4]^+$ 317.11657, found 317.11625



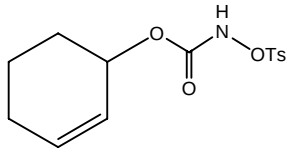
(*E*)-Hex-3-enyl *N*-tosyloxycarbamate

yield: 86%, colorless oil

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.96 (3H, t, J = 7.5Hz, CH_3), 1.99 (2H, m, CH_2), 2.18 (2H, m, CH_2), 2.46 (3H, s, CH_3), 4.00 (2H, t, J = 7Hz, CH_2), 5.26 (1H, m, CH), 5.51 (1H, m, CH), 7.36 (2H, d, J = 8Hz, Ar), 7.87 (2H, d, J = 8Hz, Ar), 8.03 (1H, s(br), NH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.81, 21.96, 25.75, 31.89, 66.88, 123.20, 129.74 (2C), 129.91 (2C), 130.54, 135.85, 146.30, 155.76

HRMS calcd for $C_{14}H_{19}NO_5SNa$ $[M+Na]^+$ 336.08761, found 336.08724



Cyclohex-2-enyl *N*-tosyloxycarbamate

yield: 84%, white solid

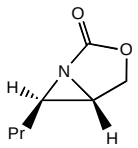
^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.54-1.63 (2H, m, CH_2), 1.69-1.76 (2H, m, CH_2), 1.95-2.05 (2H, m, CH_2), 5.07 (1H, br, CH), 5.51 (1H, m, CH), 5.91 (1H, m, CH), 7.35 (2H, d, J = 8Hz, Ar), 7.87 (2H, d, J = 8Hz, Ar), 7.95 (1H, s, NH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.57, 21.97, 24.89, 28.07, 71.55, 124.54, 129.78 (2C), 129.90 (2C), 130.59, 133.85, 146.21, 155.49

HRMS calcd for $C_{14}H_{17}O_5NSNa$ $[M+Na]^+$ 334.07196, found 334.07210

5.2.4. General Procedure C: aziridination of *N*-hydroxy carbamates[34]

The *N*-tosyloxycarbamate (1.00 mmol), K_2CO_3 (0.967 g, 7.00 mmol), and $(CF_3SO_3Cu)_2{\cdot}C_6H_6$ (25.2 mg, 0.050 mmol) were dissolved in acetonitrile (20 mL) at 25 °C. The mixture was stirred vigorously for 16 h. Dichloromethane (30 mL) was added and the solution was filtered. The filtrate was concentrated and the residue was purified by flash chromatography on silica gel using EtOAc/hexanes as eluent. The aziridine may be used directly for the next ring opening step after filtering.



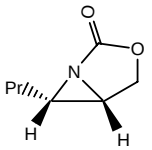
***trans*-6-Propyl-3-oxa-1-azabicyclo[3.1.0]hexan-2-one**

This is a known compound.[34] yield: 53%, colorless oil

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.98 (3H, t, J = 7Hz, CH_3), 1.50-1.61 (4H, m, CH_2CH_2), 2.40 (1H, m, CH), 3.00 (1H, m, CH), 4.41(1H, H_A of ABq, J = 5.5Hz, 9.5Hz, CH_2), 4.46 (1H, H_B of ABq, J = 1.5Hz, 9.5Hz, CH_2)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.81, 19.87, 33.27, 43.82, 48.55, 66.87, 167.46

HRMS calcd for $C_7H_{11}O_2NH$ $[M+H]^+$ 142.08626, found 142.08658



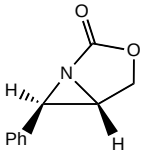
***cis*-6-Propyl-3-oxa-1-azabicyclo[3.1.0]hexan-2-one**

yield: 29%, colorless oil

^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.02 (3H, t, J = 7Hz, CH_3), 1.51-1.69 (4H, m, CH_2CH_2), 2.74 (1H, m, CH), 3.21 (1H, m, CH), 4.29(1H, H_A of ABq, J = 2Hz, 10Hz, CH_2), 4.46 (1H, H_B of ABq, J = 6Hz, 10Hz, CH_2)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.00, 20.48, 25.68, 42.90, 46.02, 64.44, 165.61

HRMS calcd for $C_7H_{11}O_2NH$ $[M+H]^+$ 142.08626, found 142.08671



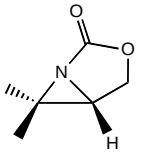
***trans*-6-Phenyl-3-oxa-1-azabicyclo[3.1.0]hexan-2-one**

yield: 90% (NMR of crude product), colorless oil

^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.23 (1H, t, CH), 3.36 (1H, d, J = 3.5Hz, CH), 4.51 (1H, H_A of ABq, dd, J = 5Hz, 9Hz, CH_2), 4.61 (1H, HB of ABq, d, J = 9Hz, CH_2), 7.26-7.38 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 46.44, 48.36, 67.40, 126.43, 128.72, 128.73, 134.50, 166.93

HRMS calcd for $C_{10}H_9O_2NH$ $[M+H]^+$ 176.07060, found 176.07075



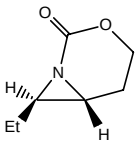
6,6-Dimethyl-3-oxa-1-azabicyclo[3.1.0]hexan-2-one

yield: 90% (NMR of crude product), colorless oil

^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.40 (3H, s, CH_3), 1.41 (3H, s, CH_3), 3.07 (1H, dd, J = 7Hz, 2Hz, CH), 4.31 (1H, dd, J = 10Hz, 2Hz, CH), 4.52 (1H, dd, J = 7Hz, 10Hz, CH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.34, 25.41, 49.90, 64.81, 165.76

HRMS calcd for $C_6H_9O_2NH$ $[M+H]^+$ 128.07060, found 128.07018



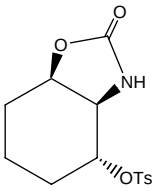
***trans*-7-Ethyl-3-oxa-1-azabicyclo[4.1.0]heptan-2-one**

yield: 45%, colorless oil

^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.07 (3H, t, J = 7Hz, CH_3), 1.40 (1H, m, CH_2), 1.63 (2H, m, CH_2), 2.24 (1H, m, CH), 2.36 (1H, m, CH_2), 2.60 (1H, m, CH), 4.29 (1H, m, CH_2), 4.40 (1H, m, CH_2)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.70, 25.15, 25.29, 40.03, 50.16, 63.58, 68.25, 161.13

HRMS calcd for $C_7H_{11}O_2NH$ $[M+H]^+$ 142.08626, found 142.08651



4-Tosyloxyhexahydrobenzo[*d*]oxazol-2-one

yield: 65%, colorless oil

^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.48 (3H, s, CH_3), 3.65 (1H, m, CH), 4.32 (1H, m, CH), 4.74 (1H, m, CH), 5.49 (1H, s(br), NH), 7.81 (2H, d, J = 7Hz, Ar), 7.39 (2H, d, J = 7Hz, Ar)

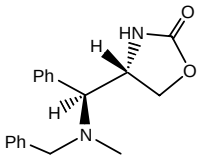
^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.71, 21.96, 26.10, 28.162, 57.30, 76.89, 83.77, 128.07(2C), 130.45 (2C), 132.97, 145.90, 158.78

HRMS calcd for $C_{14}H_{17}O_5SH$ $[M+H]^+$ 312.0906, found 312.0902

5.2.5. General Procedure for the nucleophilic ring - opening of aziridines[36]

Using *N*-methyl benzylamine.

To a solution of aziridine in THF were added N-methyl benzylamine (1.2 eq) and TEA (0.2 eq) at 25 °C under nitrogen. The reaction mixture was stirred for 5h and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel giving the desired compound. Then the compound was recrystallized in the mix of hexanes and EtOAc.



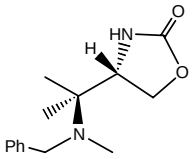
***trans*-4-[(*N*-Benzyl-*N*-methylamino)(phenyl)methyl]oxazolidin-2-one**

yield: 49%, crystal, mp = 154-155 °C

^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.10 (3H, s, CH_3), 3.36 (2H, ABq, J = 14Hz, CH_2), 3.60 (2H, d, J = 10Hz, CH), 4.44 (1H, m, CH), 4.55 (2H, m, CH_2), 4.72 (1H, s(br), NH), 7.20-7.45(10H, m, Ar)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.36, 52.37, 59.11, 69.50, 70.79, 127.57, 128.65, 128.70 (2C), 128.87 (2C), 128.95 (2C), 129.43 (2C), 133.81, 138.79, 159.04

HRMS calcd for $C_{18}H_{20}O_2N_2Na$ $[M+Na]^+$ 319.14170, found 319.14158



***trans*-4-[1-(*N*-Benzyl-N-methylamino)(1-methyl)ethyl]oxazolidin-2-one**

yield: 46%, crystal, mp = 157-158 °C

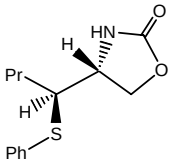
^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.07 (3H, s, CH_3), 1.11 (3H, s, CH_3), 2.08 (3H, s, CH_3), 3.52 (2H, ABq, J =13.5Hz, CH_2), 4.08 (1H, m, CH), 4.39 (1H, H_A of ABq, J = 9Hz, 9.5Hz, CH_2), 4.46 (1H, H_B of ABq, J = 5.5Hz, 9.5Hz, CH_2), 6.80 (1H, s(br), NH), 7.23-7.32 (5H, m, Ar)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.67, 17.99, 35.00, 54.67, 57.71, 58.92, 66.73, 126.97, 128.12 (2C), 128.47 (2C), 140.36, 160.76

HRMS calcd for $C_{14}H_{20}O_2N_2H$ $[M+H]^+$ 249.15975, found 249.15999

Using thiophenol on bicyclo[3.1.0] aziridines.

To a solution of aziridine in $CHCl_3$ was added thiophenol (1.5 eq) at 25 °C under nitrogen. The reaction mixture was stirred for 48h and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel giving the desired compound.



***trans*-4-[(1-Phenylthio)propyl]oxazolidin-2-one**

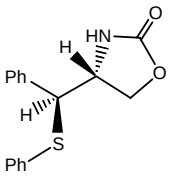
yield: 39%, light yellow oil

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.96 (3H, t, J = 7Hz), 1.44-1.56 (2H, m, CH_2), 1.59-1.63 (1H, m, CH_2), 1.72-1.76 (1H, m,CH_2), 2.98 (1H, m, CH), 3.89 (1H, m, CH), 4.25 (1H, m,

CH_2), 4.46 (1H, m, CH_2), 6.71 (1H, s(br), NH), 7.27-7.31 (3H, m, Ar), 7.41-7.42 (2H, m, Ar)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.97, 20.05, 32.32, 53.92, 56.05, 68.80, 128.05, 129.41(2C), 133.06, 133.37(2C), 160.13

HRMS calcd for $C_{13}H_{17}NO_2SH$ $[M+H]^+$ 252.1040, found 252.1048



***trans*-4-[(Phenyl)(phenylthio)methyl]oxazolidin-2-one**

yield: 55%, yellow solid

^1H NMR ($CDCl_3$, 500 MHz) δ 4.05 (1H, d, J = 9.5Hz, CH), 4.20 (1H, m, CH), 4.34 (1H, H_A of ABq, J = 5Hz, 9Hz, CH_2), 4.61 (1H, H_B of ABq, J = 8.5Hz, 9Hz, CH_2), 4.80 (1H, s(br), NH), 7.20-7.35(10H, m, Ar)

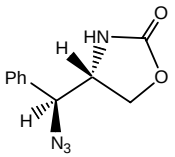
^{13}C NMR ($CDCl_3$, 75 MHz) δ 56.25, 58.18, 69.35, 128.41 (2C), 128.62, 128.68, 129.33 (2C), 129.38 (2C), 132.31, 133.69 (2C), 137.94, 158.39

HRMS calcd for $C_{16}H_{15}O_2NSH$ $[M+H]^+$ 286.08963, found 286.08921

Using sodium azide.

To a solution of aziridine in DMF was added NaN_3 (3 eq) under nitrogen. The reaction mixture was stirred for 24 h at 80 °C, cooled down to room temperature and poured into

water and brine. The mixture was extracted with Et_2O. The combined organic extracts were washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel giving the desired compound as a yellow oil.



***trans*-4-[(Azido)(phenyl)methyl]oxazolidin-2-one**

yield: 36%, light yellow oil

^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.02 (1H, m, CH), 4.38 (2H, m, CH_2), 4.57(1H, d, J = 7.5Hz, CH), 5.83(1H, s(br), NH), 7.32-7.46(5H, m, Ar)

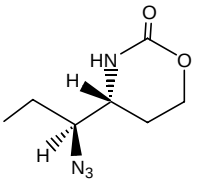
^{13}C NMR ($CDCl_3$, 75 MHz) δ 56.61, 67.41, 68.08, 127.56 (2C), 129.61 (2C), 129.67, 134.94, 159.30

HRMS calcd for $C_{10}H_{10}O_2N_4H$ $[M+H]^+$ 219.08765, found 219.08682

Using in situ azide on bicyclo[4.1.0]aziridine.

To a solution of 0.3 mmol aziridine in THF was added azidotrimethylsilane (1.1 eq) and TBAF (1.0 equiv) at 0 °C under nitrogen. The reaction mixture was warmed to room temperature, stirred for 36 h and filtered through silica gel. The filter pad was washed with EtOAc and the filtrate and washing were evaporated under reduced pressure to afford the crude product which was purified by flash chromatography on silica gel giving

the desired compound as a colorless oil (yield of 60%). Starting material was also recovered (ca. 30%).



***trans*-4-(1-(Azido)propyl)-1,3-oxazinan-2-one**

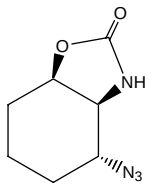
^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.06 (1H, t, J = 7Hz, CH_3), 1.50-1.56 (1H, m, Ha of CH_2), 1.62-1.68 (1H, m, Hb of CH_2), 1.91-2.02 (2H, m, CH_2), 3.40 (1H, m, CH), 3.54 (2H, m, CH), 4.22 (1H, m, Ha' of CH), 4.36 ((1H, m, Hb' of CH_2), 7.14 (1H, s(br), NH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.8, 22.39, 24.15, 53.74, 65.24, 66.88, 155.32

HRMS calcd for $C_7H_{12}N_4O_2H$ $[M+H]^+$, 185.10330, found 185.10307

Using in situ azide on tricyclic aziridine.

To a solution of 0.5 mmol crude aziridine in THF was added azidotrimethylsilane (1.1 eq) and TBAF (0.1 equiv) at 0 °C under nitrogen. The reaction mixture was warmed to room temperature, stirred for 4 h and filtered through silica gel. The filter pad was washed with EtOAc and the filtrate and washing were evaporated under reduced pressure to afford the crude product which was purified by flash chromatography on silica gel giving the desired compound as a white solid (40%).



4-Azidohexahydrobenzo[*d*]oxazol-2-one

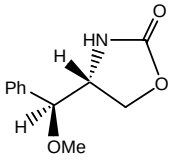
^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.38 (1H, m, CH_2), 1.59-1.79 (3H, m, CH_2CH_2), 2.05 (1H, m, CH_2), 2.20 (1H, m, CH_2), 3.38 (1H, dd, J = 6Hz, J = 8.5Hz, CH), 3.44 (1H, m, CH), 4.70 (1H, m, CH), 6.41 (1H, s, NH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.25, 26.02, 26.57, 57.03, 63.89, 76.64, 159.84

HRMS calcd for $C_7H_{10}O_2N_4H$ $[M+H]^+$, 183.08765, found 183.08779

Using methanol.

The phenyl substituted bicyclo[3.1.0]aziridine (1.0 mmol) was dissolved in methanol (5 ml) and stirred for 48 h at 25 °C under nitrogen. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel giving the desired compound.



***trans*-4-[(Methoxy)(phenyl)methyl]oxazolidin-2-one**

yield: 48%, colorless oil

^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.24(3H, s, CH_3), 3.90 (1H, m, CH), 4.07 (1H, d, J = 8Hz,

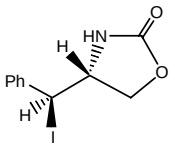
CH), 4.44 (1H, HA of ABq, J = 4Hz, J = 9Hz, CH_2), 4.51 (1H, HB of ABq, J = 8Hz, J = 9Hz, CH_2), 4.85(1H, s(br), NH), 7.30-7.43(5H, m, Ar)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 57.12, 57.19, 68.45, 85.27, 127.48 (2C), 129.28 (3C), 137.20, 159.11

HRMS calcd for $C_{11}H_{13}O_3NH$ $[M+H]^+$ 208.09682, found 208.09636

Using sodium iodide.

To a solution of phenyl substituted bicyclo[3.1.0]aziridine in THF was added iodotrimethylsilane (1.1 eq) and TBAF (0.1 eq) at 0 °C under nitrogen. The reaction mixture was warmed to room temperature, stirred for 4 h and filtered through silica gel. The filter pad was washed with EtOAc and the filtrate and washing were evaporated under reduced pressure to afford the crude product which was purified by flash chromatography on silica gel giving the desired compound.



***trans*-4-[(Iodo)(phenyl)methyl]oxazolidin-2-one**

yield: 39%, yellow oil

^1H NMR ($CDCl_3$, 500 MHz) δ 4.33(H, m, CH), 4.65 (2H, m, CH_2), 4.90 (1H, d, J = 9Hz, CH), 5.23 (1H, s(br), NH), 7.30-7.45(5H, m, Ar)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.66, 58.96, 71.36, 128.12 (2C), 129.48, 129.68 (2C),

139.13, 158.37

HRMS calcd for $C_{10}H_{10}O_2NIH$ $[M+H]^+$ 303.9829, found 303.9813; $C_{10}H_{10}O_2N$ 176.0706 ($-IM^+$), found 176.0697

5.2.6. Synthesis of N-heterocyclic carbene copper chloride complex CuIPr[37]

An oven-dried flask was charged with 1,3-bis (2,6-di-*i*-propylphenyl) imidazolium chloride (1mmol). Fresh CuCl (1mmol), NaO*t*-Bu (1mmol), and THF (5ml/mmol) were added to this flask. The resulting suspension was stirred at room temperature for 4 h, then filtered over celite and concentrated *in vacuo*. The title compound was obtained as a gray powder.

^{1}H NMR (Acetone-d_6, 500 MHz) δ 1.25-1.24 (d, J = 7Hz, 12H), 1.30-1.31 (d, J = 7Hz, 12H), 2.65-2.68 (m, 4H), 7.40-7.42 (d, J = 8.0Hz, 4H), 7.54 (dd, J = 8.0 Hz, 8.0Hz, 2H), 7.71 (2H, s)

^{13}C NMR (Acetone-d_6, 75 MHz) δ 24.02, 25.10, 124.99, 125.00, 131.31, 135.82, 146.70, 180.93

5.3. Experimental details and data for Chapter 4

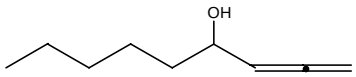
5.3.1. General Procedures

See section 5.2.1.

5.3.2. General procedure for synthesis of allenic alcohols

5.3.2.1. Procedure A:[38]

Diisopropylamine (2 eq) was added to a stirred mixture of the alkyne (1 eq), paraformaldehyde (2 eq) and copper (I) bromide (0.33 eq) in dioxane (0.1 M). The reaction was heated to reflux for 4-6 hours, then cooled to room temperature. For nonpolar compounds, the reaction mixture was poured into water and pentane, and the organic layer was washed twice with water, dried over $MgSO_4$ and evaporated under reduced pressure to directly give product. For more polar compounds, dioxane was removed under reduced pressure, and the resulting crude material was chromatographed on silica gel.

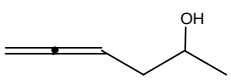


Nona-1,2-dien-4-ol

This is a known compound.[38] yield: 36%, yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J=6.5Hz, CH_3), 1.31-1.45 (6H, m, 3 x CH_2), 1.54-1.61 (2H, m, CH_2), 1.75 (1H, d, J = 7Hz, OH), 4.17 (1H, m, CH), 4.86 (2H, dd, J = 4Hz, 11.5Hz, CH_2), 5.24 (1H, m, CH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.20, 22.80, 25.25, 31.90, 37.66, 69.95, 77.56, 95.10, 207.21



4,5-Hexadiene-2-ol

yield: 26%, yellow oil.

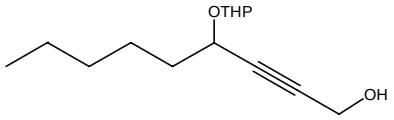
^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.22 (3H, d, J = 6Hz, CH_3), 2.14-2.19 (2H, m, CH2), 2.46 (1H, s(br), OH), 3.87 (1H, m, CH), 4.69-4.72 (2H, m, CH_2), 5.12 (1H, m, CH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.70, 38.26, 67.43, 74.79, 86.40, 209.43

5.3.2.2. Procedure B:[39]

5.3.2.2.1. Synthesis of mono-*O*-tetrahydropyranyl derivatives of butyne-1,4-diols

A solution of propargyl alcohol (30 mmol) and p-toluenesulfonic acid (13 mg) in CH_2Cl_2 (40 mL) at 25 ^{o}C was treated with 3,4-dihydro-2H-pyran (30 mmol) in a dropwise fashion, over a period of 0.5 hr. After being stirred for 10 min, the mixture was treated with Et_3N (0.02 mL), filtered through a pad of silica gel, and concentrated to give a yellow oil that was taken to the next step without further purification. The yellow oil in THF was stirred and cooled to -78 ^{o}C. Then *n*-BuLi (20 ml, 1.6 M) was added in a dropwise fashion, and the resulting solution was stirred for 1.5 h before aldehyde (1.2 eq) was slowly added. The mixture was stirred for 4 h at 0 ^{o}C, quenched with water, and extracted three times with ether. The combined organic solutions were washed with water and brine, dried over $MgSO_4$ and evaporated under reduced pressure. The resulting crude material was chromatographed on silica gel (ethyl acetate as eluent) to give yellow oil.



4-(Tetrahydro-pyran-2-yloxy)-non-2-yn-1-ol

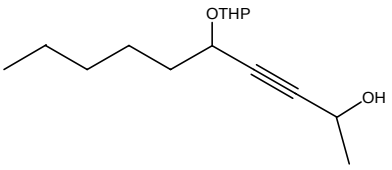
This is a known compound.[39] Diastereomers were obtained.

yield: 87%, yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.94 (3H, t, J = 6.5Hz, CH_3), 1.34-1.37 (4H, m, 2 x CH_2), 1.48-1.88 (10H, m 5 x CH_2), 3.59 (1H, m, CH), 3.66 (1H, s(br), OH), 3.84 (1H, m, CH), 4.31 (2H, s, CH_2), 4.47 (1H, t, J = 6.5Hz, CH), 5.04 (1H, t, 3.5Hz, CH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.97, 19.08, 22.50, 25.10, 25.40, 30.33, 31.50, 35.65, 50.50, 62.04, 64.90, 83.92, 83.96, 95.16

HRMS calcd for $C_{14}H_{24}O_3H$ $[M+H]^+$ 241.17982, found 241.17998

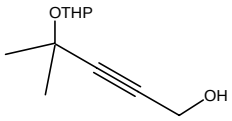


5-(Tetrahydro-pyran-2-yloxy)-dec-3-yn-2-ol

Diastereomers were obtained. yield: 52%, yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J = 6.5Hz, CH_3), 1.28-1.33 (4H, m, 2 x CH_2), 1.44 (3H, d J = 6Hz, CH_3), 1.39-1.86 (10H, m, 5 x CH_2), 2.51 (1H, s(br), OH), 3.55(1H, m, Ha of CH_2), 4.02 (1H, m, Hb of CH_2), 4.29 (1H, t, J = 6Hz, CH), 4.56 (1H, m, CH), 4.76 (1H, t, J = 3Hz, CH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.19, 19.23, 22.71, 24.43, 25.03, 25.57, 30.67, 31.65, 35.74, 58.43, 62.37, 67.68, 84.12, 86.74, 98.34



4-Methyl-4-(tetrahydro-pyran-2-yloxy)-pent-2-yn-1-ol

yield: 80%, yellow oil.

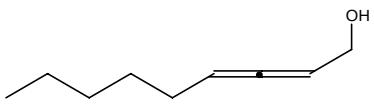
^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.48 (3H, s, CH_3), 1.53 (3H, s, CH_3), 1.55 (4H, m, 2 x CH_2), 1.71 (1H, m, Ha of CH_2), 1.84 (1H, m, Hb of CH_2), 3.51-3.55 (1H, m, Ha' of CH_2), 3.63 (1H, t, J = 6Hz, OH), 3.94-3.98 (1H, m, Hb' of CH_2), 4.27 (1H, d, J = 6Hz, CH), 5.09 (1H, t, J = 3.5Hz, CH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.11, 25.41, 29.99, 30.50, 31.89, 50.57, 62.97, 71.02, 82.80, 87.31, 95.72

HRMS calcd for $C_{11}H_{18}O_3H$ $[M+H]^+$ 199.13287, found 199.13250

5.3.2.2.2. Synthesis of α-allenic alcohols

The yellow oil obtained above was added dropwise to a suspension of $LiAlH_4$ (1.1 eq) in diethyl ether. The mixture was reflux for 4 h, quenched with the minimum amount water, and filtered through Celite. The solid residue was washed four times with ether, and then the solvent was evaporated. Purification of the crude oils on silica gel (ethyl acetate:hexane in 30:70) yields the colorless allenic alcohols.



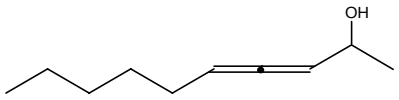
Nona-2,3-dien-1-ol

This is a known compounds.[39] yield: 57%, yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J=6.5Hz, CH_3), 1.29-1.32 (4H, m, 2 x CH_2), 1.41 (2H, m, CH_2), 1.99-2.05 (2H, m, CH_2), 2.39 (1H, s(br), OH), 4.10 (2H, s(br), CH_2), 5.26-5.31 (2H, m, 2 x CH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.13, 22.56, 28.73, 28.92, 31.38, 60.91, 91.76, 93.67, 203.26

HRMS calcd for $C_9H_{16}OH$ $[M + H]^+$ 141.12739, found 141.12740



Deca-3,4-dien-2-ol

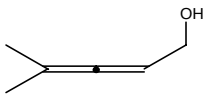
yield: 56%, yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J = 6.5Hz, CH_3), 1.29 (3H, d, J = 6.5Hz, CH_3), 1.28-1.32 (7H, m, 2 x CH_2), 1.39-1.43 (2H, m, CH_2), 1.90 (1H, s(br), OH), 1.20-2.04 (2H, m, CH_2), 4.30-4.33 (1H, m, CH), 5.24-5.30 (2H, m, 2 x CH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.19, 22.63, 23.55, 28.85, 28.95, 31.45, 66.12, 94.45, 97.11, 201.87;

14.19, 22.63, 23.62, 28.85, 28.96, 31.45, 66.35, 94.64, 97.11, 201.96

HRMS calcd for $C_{10}H_{18}OH$ $[M+H]^+$ 155.14304, found 155.14238



4-Methyl-penta-2,3-dien-1-ol

yield: 79%, yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.71 (6H, d, J = 3Hz, $2CH_3$), 2.58 (1H, s(br), OH), 4.06 (2H, d, J = 6Hz, CH_2), 5.17 (1H, m, CH)

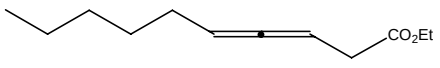
^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.54 (2C), 61.03, 89.79, 97.82, 200.89

HRMS calcd for $C_{10}H_{18}O$, found

5.3.2.3. Procedure C[40]

5.3.2.3.1. Synthesis of β-allenic ester by a Claisen-rearrangement

A mixture of the propargyl alcohol, 4-7 eq of triethyl orthoacetate and a catalytic amount of propionic acid were heated to 145 ^oC for several hrs with removal of ethanol by distillation. When the distillation ceased the reaction was mostly done and after 1-2 more hrs the reaction mixture was cooled to room temperature and ether was added. The solution was washed twice with 1N H_2SO_4 and then with sat. $NaHCO_3$-solution. Drying over $MgSO_4$ and removal of the solvent gave a crude product which was then purified on a silica gel column.



Deca-3,4-dienoic acid ethyl ester

This is a known compounds.[40] yield: 91%, yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J = 6.5Hz, CH_3), 1.24-1.31 (7H, m, CH_3, 2 x CH_2), 1.38-1.43 (2H, m, CH_2), 1.97-2.04 (2H, m, CH_2), 3.01 (2H, dd, J = 2.5Hz, 7Hz),

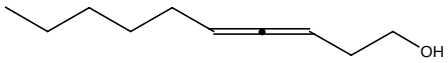
4.15 (2H, q, J = 7Hz, CH_3), 5.17-5.23 (2H, m, 2 x CH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.14, 14.29, 22.58, 28.58, 28.77, 31.38, 35.18, 60.79, 84.18, 92.28, 171.82, 205.08

HRMS calcd for $C_{12}H_{20}O_2H$ [M+H] 197.15361, found 197.15419

5.3.2.3.2 Reduction of β-allenic ester with $LiAlH_4$

To a suspension of LAH (1.5 eq) in diethyl ether was added a solution of the β-allenic ester in ether at -78 ^oC under nitrogen. The mixture was let warm up to room temperature in 6 hrs and the 3 mL of water were added at 0 ^oC. The white slurry was filtered and after addition of ether the solution was washed with brine, dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification of the crude oils on silica gel yields the colorless allenic alcohols.



Deca-3,4-dien-1-ol

This is a known compound.[40] yield : 89%, colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J = 6.5Hz, CH_3), 1.29-1.32 (4H, m, $2CH_2$), 1.35-1.43 (2H, m, CH_2), 1.96-2.01 (2H, m, CH_2), 2.22-2.26 (2H, m, CH_2), 2.35 (1H, s(br), OH), 3.68 (2H, t, J = 6Hz, CH_2), 5.07-5.15 (2H, m, 2CH)

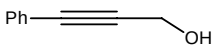
^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.15, 22.60, 28.93, 31.42, 31.41, 32.41, 62.13, 87.23, 91.68, 204.69

HRMS calcd for $C_{10}H_{18}OH$ [M+H] 155.14304, found 155.14245

5.3.2.4. Procedure D

Synthesis of 3-Phenylprop-2-yn-1-ol[41]

Phenylacetylene was dissolved in dry tetrahydrofuran (0.5 mL/mol) and cooled to -78 ^{o}C whilst stirring. Then 1.6 M butyllithium (1.1 eq) was added dropwise. After addition the reaction mixture was warmed to 0 ^{o}C and paraformaldehyde (2 eq) was added in one portion. Then the reaction mixture was stirred overnight at room temperature. Finally the mixture was treated with H_2O, extracted with diethyl ether and dried with $MgSO_4$. The solvent was removed under vacuum and the residue purified on a silica gel column.



3-Phenyl-prop-2-yn-1-ol

This is a known compounds.[41] yield: 85%, yellow oil.

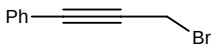
^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.26 (1H, t, J = 5.5Hz, OH), 4.48 (2H, d, J = 5.5Hz, CH_2), 7.24-7.30 (3H, m, Ar), 7.41-7.43 (2H, m, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.38, 85.57, 87.43, 122.62, 128.37 (2C), 128.50, 131.74 (2C)

Synthesis of 1-brom-3-Phenylprop-2-yne[41]

The propargyl alcohol (56 mmol) was added to a solution of Ph_3P (1 eq) and CBr_4 (1

eq) in C_6H_6 (60 mL) at 0 ^oC. After 2h, the solvent was evaporated *in vacuo*. The residue was extracted with hexane and the combined extracts were washed (saturated NaCl solution), dried, filtered and concentrated *in vacuo* to give the propargyl bromide.



1-Phenyl-3-Bromo-propyne

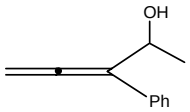
This is a known compound.[41] yield: 32%, yellow oil.

^1H NMR ($CDCl_3$, 500 MHz) δ 4.16 (2H, s, CH_2), 7.32 (3H, m, Ar), 7.45 (2H, m, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.55, 84.41, 86.91, 122.29, 128.52 (2C), 129.06, 132.06(2C)

Synthesis of 3-(Phenyl)penta-3,4-dien-2-ol[42]

A suspension of tin(II) chloride (1.1 eq), 1-brom-3-Phenylprop-2-yne (20 mmol), and sodium iodide (1.1 eq) in DMF (45 mL) was stirred at room temperature for 1h. The reaction mixture was then cooled to 0 ^oC and acetaldehyde was added. The resulting mixture was stirred at this temperature for 12 h, quenched with water, and extracted with diethyl ether. The combined organic layers were washed with water, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel to afford the product.



3-(Phenyl)penta-3,4-dien-2-ol

yield: 40%, yellow oil.

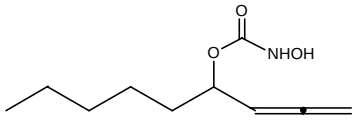
^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.42 (3H, d, J = 6Hz, CH_2), 1.98 (1H, s(br), OH), 4.83 (1H, q, J = 6Hz, CH), 5.23 (2H, s, CH_2), 7.22 (1H, m, Ar), 7.33 (2H, m, Ar), 7.44 (2H, m, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.72, 65.68, 80.96, 111.00, 126.87 (2C), 127.24, 128.74 (2C), 134.66, 206.87

HRMS calcd for $C_{11}H_{12}OH$ [M+H] 161.09609, found 161.09601

5.3.3. General procedure for synthesis of allenic *N*-hydroxy carbamates[34,35]

Same as procedure 5.2.2.



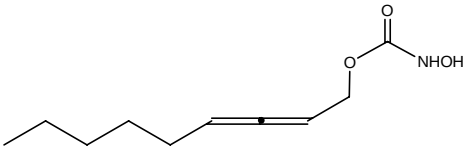
Nona-1,2-dienyl 4-hydroxycarbamate

yield: 60%, colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (3H, t, J=6.5Hz, CH_3),1.25-1.37 (6H, m, 3 x CH_2), 1.60-1.72 (2H, m, CH_2), 4.86 (2H, m, CH_2), 5.22 (2H, m, 2 x CH), 7.46 (1H, s (br), NH), 7.65 (1H, s (br), OH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.14, 22.66, 24.95, 31.61, 34.30, 74.39, 77.54, 90.75, 159.33, 208.68

HRMS (CI) calcd for $C_{10}H_{17}NO_3Na$ (M +Na) 222.11006, found 222.10987



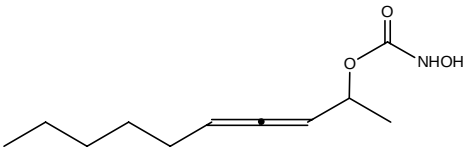
Nona-2,3-dienyl hydroxycarbamate

yield: 87%, colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J=6.5Hz, CH_3), 1.25-1.43 (6H, m, 3 x CH_2), 1.97-2.09 (2H, m, CH_2), 4.58-4.64 (2H, m, CH_2), 5.24-5.31(2H, m, 2 x CH), 7.56 (1H, s(br), NH), 7.69 (1H, s(br), OH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.21, 22.61, 28.40, 28.81, 31.39, 64.96, 86.70, 93.30, 159.54, 205.86

HRMS (CI) calcd for $C_{10}H_{17}NO_3NH_4$ $[M + NH_4]^+$ 217.15467, found 217.15472



Deca-3,4-dienyl 2-hydroxycabamate

yield: 55%, colorless oil.

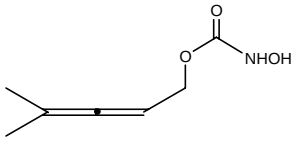
^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J=5Hz, CH_3), 1.22-1.35 (9H, m, CH_3, 3 x CH_2), 1.99-2.03 (2H, m, CH_2), 5.23-5.35(3H, m, 3 x CH), 7.42 (1H, s(br), NH), 7.58 (1H, s(br), OH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.20, 19.81, 22.62, 28.55, 28.86, 31.45, 71.19, 92.50,

94.46, 159.30, 203.97;

14.20, 20.091, 22.62, 28.57, 28.88, 31.46, 71.48, 92.57, 94.54, 159.30, 204.06

HRMS (CI) calcd for $C_{11}H_{19}NO_3NH_4$ $[M + NH_4]^+$, 231.17087, found 231.17069



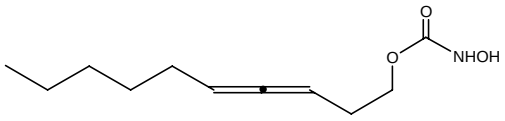
4-Methyl-penta-2,3-dienyl hydroxycarbamate

yield: 66%, yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.70 (6H, d, J = 4.5Hz, $2CH_3$), 4.58 (2H, d, J = 12Hz, CH_2), 5.10 (1H, m, CH), 7.54-7.64 (2H, s(br), OH, NH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.31 (2C), 65.27, 84.70, 97.65, 159.57, 203.80

HRMS calcd for $C_7H_{11}NO_3H$ $[M+H]^+$ 158.08117, found 158.08100



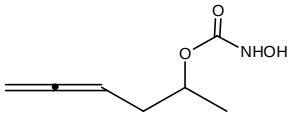
Deca-3,4-dienyl hydroxycarbamate

yield: 90%, colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J = 7Hz, CH_3), 1.26-1.42 (6H, m, $3CH_2$), 1.95-2.05 (2H, m, CH_2), 2.30-2.39 (2H, m, CH_2), 2.31 (3H, s, CH_3), 2.67 (3H, s, CH_3), 4.18 (2H, t, J = 7Hz, CH_2), 5.03-5.06 (1H, m, CH), 5.11-5.15 (1H, m, CH), 7.72 (1H, s, OH), 7.91 (1H, s (br), NH))

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.17, 22.59, 28.65, 28.77, 28.88, 31.41, 65.62, 86.26, 92.06, 159.75, 204.67

HRMS calcd for $C_{11}H_{19}NO_3H$ $[M+H]^+$ 214.14377, found 214.14381



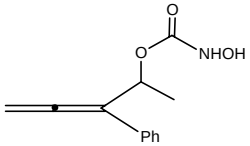
Hexa-4,5-dienyl 2-hydroxycarbamate

yield: 63%, yellow oil.

^1H NMR ($CDCl_3$, 500 MHz) δ 1.28 (3H, d, J = 6Hz, CH_3), 2.23-2.31 (2H, m, CH_2), 4.68-4.71 (2H, m, CH_2), 4.90-4.94 (1H, m, CH), 5.05 (1H, m, CH), 7.62 (2H, br, OH and NH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.70, 22.50, 35.14, 72.77, 75.06, 85.30, 159.37, 209.61

HRMS calcd for $C_7H_{11}NO_3Na$ $[M+Na]^+$ 180.06311, found 180.06294



3-(Phenyl)penta-3,4-dien-2-hydroxycarbamate

yield: 56%, yellow oil.

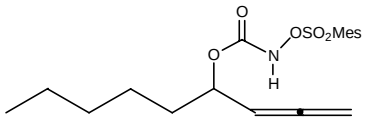
^1H NMR ($CDCl_3$, 500 MHz) δ 1.48 (3H, d, J = 6.5Hz, CH_3), 5.25 (2H, d, J = 7.5Hz, CH_2), 5.91 (1H, m, CH), 7.21 (1H, dd, J = 7Hz, 7Hz, Ar), 7.32 (2H, m, Ar), 7.36 (2H, d, J = 7Hz, Ar)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.62, 70.39, 81.01, 107.18, 126.56 (2C), 127.40, 128.82 (2C), 133.92, 159.13, 208.78

HRMS calcd for $C_{12}H_{13}NO_3H$ $[M+H]^+$ 220.09682, found 220.09559

5.3.4. General procedure for mesitylation of *N*-sulfonyloxy carbamates[34,35]

To a solution of substrate (1.0 mmol) in toluene:DMF (4:1, 5 mL/mmol), cooled to 0 ^oC, was added 2-mesitylenesulfonyl chloride (1.0 eq) followed by dropwise addition of triethylamine (1.0 eq). The reaction was maintained at 0 ^oC until TLC indicated complete consumption of starting material, then quenched by addition of 1M HCl and extracted wither. The organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product which was purified by flash column chromatography as indicated.



Nona-1,2-dienyl 4-mesitylenesulfonyloxycarbamate

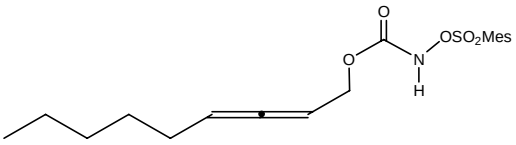
yield: 79%, colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (3H, t, J = 7Hz, CH_3), 1.19-1.27 (6H, m, 3 x CH_2), 1.50 (2H, m, CH_2), 2.32 (3H, s, CH_3), 2.68 (3H, s, CH_3), 4.79 (2H, m, CH_2), 4.98 (1H, m, CH), 5.06 (1H, m, CH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.19, 21.37, 22.65, 23.23 (2C), 24.84, 31.53, 34.09,

75.50, 77.70, 90.15, 128.54, 131.88 (2C), 142.25 (2C), 144.71, 155.22, 208.65

HRMS calcd for $C_{19}H_{27}NO_5SNa$ $[M+Na]^+$ 404.15021, found 404.15053



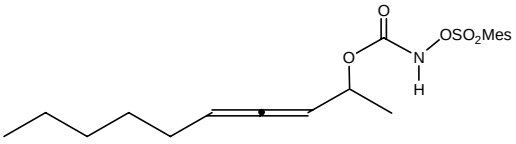
Nona-2,3-dienyl mesitylenesulfonyloxycarbamate

yield: 86%, colorless oil.

^1H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J = 6.5Hz, CH_3), 1.21-1.40 (6H, m, 3 x CH_2), 1.99 (2H, m, CH_2), 2.32 (3H, s, CH_3), 2.65 (6H, s, 2 x CH_3), 4.70 (2H, m, CH_2), 5.06 (1H, m, CH), 5.23 (1H, m, CH), 6.99 (2H, s, Ar), 7.77 (1H, s (br), NH))

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.26, 21.39, 22.63, 23.17 (2C), 28.36, 31.41, 65.70, 86.07, 93.53, 128.44, 131.91 (2C), 131.94, 142.21 (2C), 144.78, 155.43, 206.02

HRMS calcd for $C_{19}H_{27}NO_5SH$ $[M+H]^+$ 382.16827, found 382.16812



Deca-3,4-dienyl 2-mesitylenesulfonyloxycarbamate

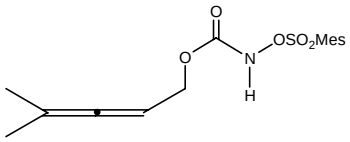
yield: 57%, colorless oil.

^1H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J = 6.5Hz, CH_3), 1.19 (3H, CH_3), 1.27-1.32 (4H, m, 2 x CH_2), 1.36-1.40 (2H, m, CH_2), 1.98 (2H, m, CH_2), 2.32 (3H, s, CH_3), 2.68 (3H, s, CH_3), 5.01-5.05 (1H, m, CH), 5.14-5.19 (1H, m, CH), 5.22-5.28 (1H, m, CH),

6.98 (2H, s, Ar), 7.84 (1H, s, NH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.22, 19.44, 19.74, 21.34, 22.62, 23.20, 28.51, 28.79, 31.46, 72.41, 91.80, 94.62, 128.63, 131.88 (2C), 142.22 (2C), 144.66, 155.20, 204.02; 14.22, 19.44, 19.74, 21.34, 22.62, 23.20, 28.51, 28.88, 31.46, 72.66, 91.94, 94.62, 128.63, 131.88 (2C), 142.22 (2C), 144.66, 155.20, 204.15

HRMS calcd for $C_{20}H_{29}NO_5SH$ $[M+H]^+$ 396.18392, found 396.18356



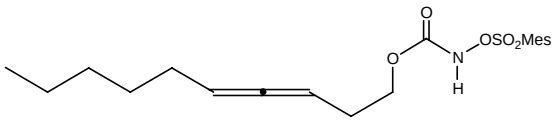
4-Methyl-penta-2,3-dienyl mesitylenesulfonyloxycarbamate

yield: 82%, yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.67 (6H, d, J = 3Hz, $2CH_3$), 2.32 (3H, s, CH_3), 2.68 (6H, s, $2CH_3$), 4.43 (2H, d, J = 6.5Hz), 4.93 (1H, m, CH), 6.99 (2H, s, Ar), 7.98 (1H, s (br), NH))

^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.26 (2C), 21.33, 23.12 (2C), 66.00, 83.98, 97.83, 128.44, 131.91 (2C), 142.14 (2C), 144.71, 155.61, 203.94

HRMS calcd for $C_{16}H_{21}NO_5SH$ $[M+H]^+$340.12132, found 340.12173



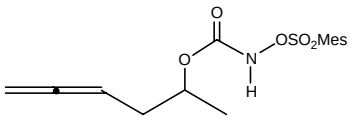
Deca-3,4-dienyl mesitylenesulfonyloxycarbamate

yield: 70%, colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (3H, t, J = 7Hz, CH_3), 1.25-1.38 (6H, m, $3CH_2$), 1.94-1.96 (2H, m, CH_2), 2.17-2.31 (2H, m, CH_2), 2.31 (3H, s, CH_3), 2.67 (3H, s, CH_3), 4.05 (2H, t, J = 7Hz, CH_2), 4.92-4.96 (1H, m, CH), 5.08-5.12 (1H, m, CH), 6.98 (2H, s, Ar), 8.21 (1H, s (br), NH))

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.20, 21.16, 21.27, 22.60, 23.08, 28.20, 28.74, 28.88, 31.41, 66.34, 85.89, 92.28, 128.43, 131.82 (2C), 142.065, 144.70 (2C), 155.85, 204.62

HRMS calcd for $C_{20}H_{29}NO_5SNa$ $[M+Na]^+$418.16586, found 418.16508



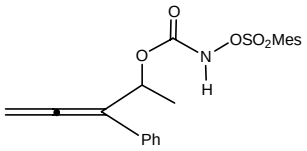
Hexa-4,5-dienyl 2-**mesitylenesulfonyloxycarbamate**

yield: 60%, yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.11 (3H, d, J = 6Hz, CH_3), 2.06-2.18 (2H, m, CH_2), 2.32 (3H, s, CH3), 2.68 (6H, s, 2 x CH_3), 4.63-4.66 (2H, m, CH_2), 4.79 (1H, m, CH), 4.87 (1H, m, CH), 6.99 (2H, s, Ar), 7.90 (1H, s, NH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.36, 21.34, 23.23 (2C), 34.81, 74.10, 75.29, 85.01, 128.50, 131.90 (2C), 142.18 (2C), 144.80, 155.33, 209.57

HRMS calcd for $C_{16}H_{21}NO_5SH$ $[M+H]^+$ 362.10326, found 326.10197



3-(Phenyl)penta-3,4-dienyl 2-mesitylenesulfonyloxycarbamate

yield: 69%, yellow solid.

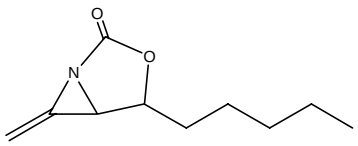
^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.31 (3H, d, J = 6Hz, CH_3), 2.28 (3H, s, CH_3), 2.63 (3H, s, 2 x CH_3), 5.23 (2H, m, CH_2), 5.74 (1H, m, CH), 6.93 (2H, s, Ar), 7.20-7.30 (5H, m, Ar), 7.84 (1H, s(br), NH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.16, 21.38, 23.16 (2C), 74.48, 81.16, 106.68, 126.37 (2C), 127.45 (2C), 128.39, 128.79 (2C), 131.83 (2C), 133.67, 142.21, 144.69, 155.15, 208.76

HRMS calcd for $C_{21}H_{23}NO_5SNa$ $[M+Na]^+$ 424.11891, found 424.11898

5.3.5. General procedure for the aziridination of allenic *N*-mesityloxy carbamates[34]

The *N*-mesityloxycarbamate (1.00 mmol), K_2CO_3 (0.967 g, 7.00 mmol), and $Rh_2(OAc)_4$ (22 mg, 0.050 mmol) were dissolved in spectrograde acetone (20 mL) at 25 ^{o}C. The mixture was stirred vigorously for 5-16 h. Dichloromethane (10 mL) was added and the solution was filtered over. The filtrate was concentrated and the residue was purified by flash chromatography on silica gel using EtOAc/hexanes as eluent.



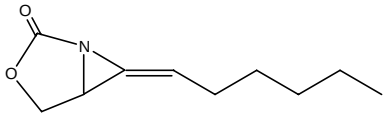
6-Methylene-4-pentyl-3-oxa-1-aza-bicyclo[3.1.0]hexan-2-one

yield: 36%, pale yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (3H, t, J = 6.9Hz, CH_3), 1.27-1.52 (6H, m, 3 x CH_2), 1.64-1.79 (2H, m, CH_2), 3.68 (1H, d, J = 5.7Hz, CH), 4.77 (1H, m, CH), 5.20 (1H, d, J = 2.7 Hz, CH), 5.40 (1H, d J = 2.7Hz)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.03, 22.53, 25.24, 31.51, 32.70, 44.49, 78.63, 91.58, 130.51, 162.98

HRMS calcd for $C_{10}H_{15}NO_2H$ $[M+H]^+$ 182.11756, found 182.11763



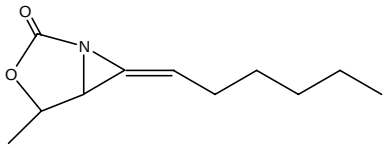
6-Hexylidene-3-oxa-1-aza-bicyclo[3.1.0]hexan-2-one

yield: 40%, pale yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (3H, t, J = 6.5Hz, CH_3), 1.26-1.35 (4H, m, 2 x CH_2), 1.44-2.23 (2H, m, CH_2), 3.68 (1H, m, CH), 4.46 (2H, m, CH_2), 5.76 (1H, t, J = 6.5 Hz, CH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.15, 22.59, 28.53, 28.85, 31.45, 41.50, 66.58, 107.67, 124.80, 164.22

HRMS calcd for $C_{10}H_{15}NO_2NH_4$ $[M+NH_4]^+$ 199.14410, found 199.14409



6-Hexylidene-4-methyl-3-oxa-1-aza-bicyclo[3.1.0]hexan-2-one

yield: 76%, pale yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J = 6.5Hz, CH_3), 1.26-1.50 (6H, m, 3 x CH_2), 1.44 (3H, d, J = 5.5Hz, CH_3), 2.17-2.22 (2H, m, CH_2), 3.67 (1H, d, J = 5Hz, CH), 4.90 (1H, m, CH), 5.82 (1H, t, J = 7Hz, CH)

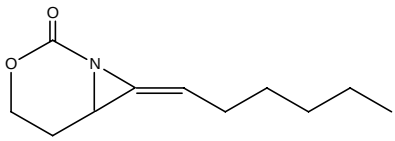
^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.15, 18.52, 22.60, 29.11, 29.16, 31.51, 45.77, 74.73, 108.61, 132.07, 163.75

HRMS calcd for $C_{11}H_{17}NO_2H$ $[M+NH]^+$ 196.13321, found 196.13242

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J = 6.5Hz, CH_3), 1.28-1.35 (4H, m, 2 x CH_2), 1.43 (3H, d, J = 6Hz, CH_3), 1.45-1.49 (2H, m CH_2), 2.32-2.37 (2H, m, CH_2), 3.65 (1H, d, J = 5.5Hz, CH), 4.87 (1H, m, CH), 5.56 (1H, t, J = 7Hz, CH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.19, 18.04, 22.61, 27.86, 29.04, 31.45, 45.94, 67.31, 74.61, 108.80, 132.07, 163.48

HRMS calcd for $C_{11}H_{17}NO_2H$ $[M+NH]^+$ 196.13321, found 196.13253



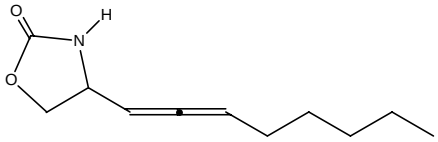
7-Hexylidene-3-oxa-1-aza-bicyclo[4.1.0]heptan-2-one

yield: 42%, pale yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J = 7Hz, CH_3), 1.26-1.47 (6H, m, $3CH_2$), 1.59-1.65 (1H, m, Ha of CH_2), 2.13-2.20 (2H, m, CH_2), 2.35-2.41 (1H, m, Hb of CH_2), 3.43 (1H, t, J = 7Hz, CH), 4.35-4.38 (1H, m, Ha' of CH_2), 4.52-4.57 (1H, m, Hb' of CH_2), 5.58 (1H, t, J = 7Hz, CH),

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.20, 22.62, 24.44, 28.37, 28.99, 31.49, 39.62, 68.96, 103.38, 125.62, 156.52

HRMS calcd for $C_{11}H_{17}NO_2Na$ $[M+Na]^+$ 218.11515, found 218.11506



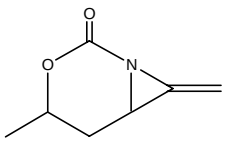
4-Octa-1,2-dienyl-oxazolidin-2-one

yield:46%, yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J = 7Hz, CH_3), 1.26-1.38 (6H, m, $3CH_2$), 1.99-2.05 (2H, m, CH_2), 4.18 (1H, m, Ha of CH_2), 4.36 (1H, m, CH), 4.53 (1H, m, H_b of CH_2), 5.16 (1H, m, CH), 5.36 (1H, m, CH), 6.14 (1H, d(br), J = 30Hz, NH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.21, 22.58, 28.48, 28.74, 31.39, 52.21, 70.48, 91.33, 95.45, 159.78, 203.88

HRMS calcd for $C_{11}H_{17}NO_2H$ $[M+H]^+$ 196.13321, found 196.13327



4-Methyl-7-methylene-3-oxa-1-aza-bicyclo[4.1.0]heptan-2-one

yield: 43%, yellow oil.

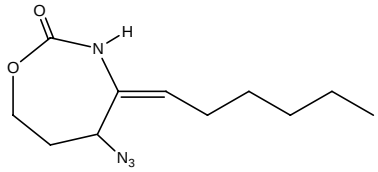
^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.38 (3H, d, J = 6.5Hz, CH_3), 2.33-2.41 (2H, m, CH_2), 3.40 (1H, dd, J = 9Hz, 6.5Hz, CH), 4.74-4.78 (2H, m, CH), 4.98 (1H, d, J = 7Hz, Ha of CH_2), 5.14 (1H, d, J = 7Hz, Hb of CH_2)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.92, 30.92, 39.06, 77.51, 85.98, 133.31, 155.87

HRMS calcd for $C_7H_9NO_2H$ $[M+H]^+$ 140.07060, found 140.07065

5.3.6. General procedure for nucleophilic ring opening of methyleneaziridine

Same procedure as previous azide reaction.



5-Azido-4-hexylidene-[1,3]oxazepan-2-one

yield: 79%, pale yellow oil.

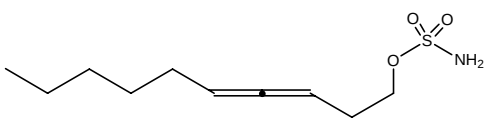
^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J = 7Hz, CH_3), 1.25-1.38 (6H, m, $3CH_2$), 1.54-1.62 (2H, m, CH_2), 2.52-2.56 (2H, m, CH_2), 3.87 (1H, t, J = 8Hz, CH), 4.38-4.41 (2H, m, CH_2), 5.05 (1H, t, J = 4Hz, CH_1), 6.22(1H, s(br), NH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.15, 22.63, 25.92, 28.90, 31.40, 33.02, 67.65, 67.75, 108.10, 132.21, 157.78

HRMS calcd for $C_{11}H_{18}N_4O_2H$ $[M+H]^+$ 239.15025, found 239.15081

5.3.7. General procedure for the preparation of allenic sulfamate esters[43]

Formic acid (1.70mL, 45mmol, 1.5 eq) was added dropwise to neat chlorosulfonyl isocyanate (3.90 mL, 45 mmol, 1.5 eq) at 0 ^oC with rapid stirring. Gas evolution was observed during the addition process. The resulting viscous suspension was stirred for 18 h at room temperature. The reaction mixture was cooled to 0 ^oC, DMA (8 mL) was added and the solution was stirred for 5 min. A solution of the allenic alcohol (1eq) in DMA (16 mL) was added dropwise, the resulting solution was allowed to room temperature and stirring was continued until the reaction was complete (3-4 h) as determined by TLC. The reaction was quenched by the successive addition of EtOAc (80 mL) and saturated aqueous NaCl (20 mL). The mixture was poured into EtOAc (80 mL) and H_2O (30 mL). The organic phase was collected and the aqueous layer was extracted with EtOAc (1 x 30 mL). The organic extractes were combined, washed with saturated aqueous NaCl (2 x 30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexane-EtOAc as eluent



Sulfamic acid deca-3,4-dienyl ester

yield: 86%, yellow oil.

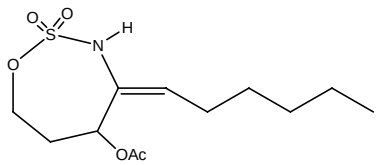
^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J = 6.5Hz, CH_3), 1.29-1.43 (6H, m, 3 x CH_2), 1.96-2.06 (2H, m, CH_2), 2.41-2.45 (2H, m, CH_2), 4.24 (2H, t, J = 7Hz, CH_2), 5.07-5.10 (1H, m, CH), 5.16-5.20 (1H, m, CH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.22, 22.61, 28.63, 28.75, 28.87, 31.44, 70.62, 85.64, 92.57, 204.82

HRMS calcd for $C_{10}H_{19}NO_3SNH_4$ $[M+NH_4]^+$ 251.14239, found 251.14262

5.3.8. General procedure for the aziridination of allenic sulfamate esters[43]

To a solution of sulfamate ester (1.25 mmol) in 8 mL of CH_2Cl_2 were added sequentially MgO (116 mg, 3.0 mmol, 2.3 eq), $PhI(OAc)_2$ (443 mg, 1.4 mmol, 1.1 eq), and 25 μmol (0.02 eq) of $Rh_2(OAc)_4$ as indicated. The suspension was stirred vigorously and heated at 40 ^{o}C until complete consumption of starting material was indicated by thin layer chromatography (1-2 h). The reaction was cooled to 25 ^{o}C, diluted with 20 mL of CH_2Cl_2, and filtered through a pad of Celite. The filter cake was rinsed with 2 x 15 mL of CH_2Cl_2 and the combined filtrates were evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford the product.



Acetic acid 4-hexylidene-2,2-dioxo-2l6-[1,2,3]oxathiazepan-5-yl ester

yield: 67%, yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, t, J = 6.5Hz, CH_3), 1.31-1.45 (6H, m, 3 x CH_2), 2.08-2.34 (4H, m, 2 x CH_2), 4.22 (1H, m, Ha of CH_2), 4.66 (1H, m, Hb of CH_2), 5.89 (1H, t(br), CH), 5.93 (1H, t, J = 8 Hz, CH), 6.53 (1H, s(br), NH)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.07, 21.18, 22.49, 27.25, 28.60, 31.39, 34.51, 65.37, 66.65, 127.50, 136.63, 169.64

HRMS calcd for $C_{12}H_{21}NO_5SH$ $[M+H]^+$ 292.12132, found 292.12181

5.4. References

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