EFFORTS TOWARDS NEW METHODS OF CATALYSIS OF THE DIELS-ALDER REACTION AND ANIONIC OXY-COPE REARRANGEMENT

Marx Ruiz-Wilson

Department of Chemistry, McGill University, Montreal

Dr. James L. Gleason

April 2014

A thesis submitted to McGill University in partial fulfillment of the requirements of Master of Science

Abstract

Despite the recent advances in catalytic organic transformations, we believe the discovery of novel and more advantageous catalytic systems would bring insights to our understanding of the reactivity and mechanistic aspects of known processes. Our particular interest in the Diels-Alder reaction and the anionic oxy-Cope rearrangements, and our efforts in the investigations towards the development of new methods of catalysis are detailed in this thesis.

Our efforts focus on the utilization of Lewis acid/base mediated method for the activation of the Diels-Alder reaction. Although the initial synthetic approach of the model substrates has proven to be challenging, we have circumvented those difficulties by designing different substrates with the similar reactivity. The results obtained with the revised substrates suggest that activation of the diene by addition of electron releasing species has a positive effect in the rate of the cycloaddition.

In our studies towards a hydride-free methodology for the catalysis of the anionic oxy-Cope rearrangement, we have shown the use of stoichiometric amounts of Bu_4NOH was able to accelerate the transformation. The observed results suggest that the rate of the reaction can also be increased with excess hydroxide in DMSO at 80°C. The use of tetraalkylammonium bases under milder conditions has proven to be ineffective to accelerate the sigmatropic rearrangement.

Résumé

Malgré les avancées récentes dans les réactions organo-catalysées, nous pensons que la découverte de nouveaux systèmes catalytiques plus performants pourrait apporter des informations pour notre compréhension de la réactivité et des aspects mécanistiques de transformations connues. Notre intérêt particulier pour la réaction de Diels-Alder et pour les réarrangements d'oxy-Cope anioniques, ainsi que nos avancées sur le développement de nouvelles méthodes de catalyse sont détaillées dans cette thèse.

Nos efforts se concentrent sur l'utilisation d'acide/base de Lewis comme méthode d'activation de la réaction de Diels-Alder. Bien que l'approche synthétique initiale des substrats modèles se soit révélée problématique, nous avons contourné ces difficultés en concevant différents substrats possédant une réactivité similaire. Les résultats obtenus avec les substrats révisés suggèrent que l'activation du diène par addition d'espèces délivrant des électrons a un effet positif sur la vitesse de la réaction de cycloaddition.

Dans nos études pour développer une méthodologie sans hydrure pour la catalyse du réarrangement d'oxy-Cope anionique, nous avons montré que l'utilisation de quantités stoechiométriques d'hydroxyde de tétrabutylammonium a été en mesure d'accélérer la transformation. Les résultats observés semblent indiquer que la vitesse de la réaction peut également être augmentée avec un excès d'hydroxyde dans le DMSO à 80 °C. En revanche, l'utilisation de bases de tétraalkylammonium dans des conditions plus douces s'est avérée inefficace pour accélérer le réarrangement sigmatropique.

Acknowledgements

I am truly grateful with my supervisor Dr. James L Gleason for the great mentoring and teaching, I can say that all my chemistry knowledge I owe to you. Thanks for being patient and always available for scientific discussions.

I would like to thank my family for all the great support through the years. Ma, you are my real-life heroine and my role model, thanks for being with me at all times. Pili, my wise little sister, I want to thank you for all the energy and passion that you transmit, you have definitely given me one of the biggest lessons, follow your dreams and you will most certainly be happy. Por todo gracias y las amo siempre. Tita y Lena, the reason why I am here and am who I am is thanks to you, I will always have you two in my thoughts and in my heart.

I want to thank my father for all the support you gave me, I know that wherever you are you must be proud of me as you always were -even when you did not agree with me grumpy old-man-

To my best friends back home, Cesar and Paco that have been promising to come visit since the day I arrived… I know the routine by now.

Flako, even when we've been friends for only 1 year, I consider you my brother from another mother. Maybe in an unaware way but you have really pushed me to be more open and perceptive towards things that I never realized I could be before – We have to watch those videos in 20 years from now, we would be just fine-

Raul Zorrita, you are seriously the closest to a male sibling that I have, I've seen you go through different faces, and I have always really enjoyed your company and discussions, I always told Alina that you are one of those people that has the power to bring out the best of me.

My little Isa, growing together, learning together and being happy together is a big part of my fuel, thanks for being with me and put up with my not so attractive sides sometimes.

To my friend Shuo for your very honest opinion on things, chemistry wise you were always a reference point and in the personal plane to me you are one of those few people that just has it all figured out. I admire you and I will always cherish your friendship.

Mario Asencio, compadre since literally day 1 at McgGill, you have been there thorough all these years when I have needed a mature and insightful opinion on things, you are one of those people who after talking to I feel that I can conquer the world, thanks for being part of this adventure and this lasts forever.

Michael Krause, Montreal would't be the same without my German friend reminding me my Mexican roots, amazing traditions we have built that I know will be long-lasting. Oh yeah thanks for your moth joke.

Tania Gutierrez, thanks my friend for making me more conscious about the incredibly complexity of a woman's mind, oh man you have the talent to translate for me the Venusian that sometimes I can't understand by myself.

Special thanks for my favorite chicken ever, Dr. Joshua Fisher, besides the great amount of chemistry-tips you also became my friend and I can say that you are definitely one of the nicer people I have ever met and that in my mind you and your lovely wife Danielle are pure inspiration for me.

Laurie Lim, thanks for being really awesome and so nice to me all the time.

To the current labmates, Florent and Damien I have only met you recently buy you guys have been really nice. Florent, thanks for your help with the resume.

The guys, Benji, Nick, Dainis, Chris, Adam, Anthony and Jon. Thanks a lot for making this experience just really cool. The lab wouldn't had been the same without those moments of pure nonsense and hilarious inappropriate comments

Thanks Former lab mates that really helped me getting started in the chemistry arts, Erica Tiong you're just awesome. Jeff St Denis, I appreciate those late nights at the lab and funny that jut today I read your thesis acknowledgements where you advise me to stick to it and don't get discouraged, well here I am, thanks big hippo. Rodrigo Mendoza and Daniel Rivalti, thanks for the great lab management lessons an your always interesting opinion on chemistry issues. Melanie Burger, although it was short our overlapping time at the lab I enjoyed being your fume hood neighbor and your always contagious laughter.

Thanks to the Infra red socks for just been awesome, but specially to Carlos for that 7th inning winner hit that I will always remember as one of biggest sports moments I have ever experienced.

Thanks to Alex Wahba for your help with HRMS and your sincere advises.

Of course, I want to thank from the bottom of my heart to the EDO team for that delicious chicken whenever I needed you (every Thursday)

Table of contents

Abbreviations

Å	Angstrom, 10-10 metres
Ac	acetyl
Aq	aqueous
Ar	aryl/ aromatic
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Bu	butyl
Bz	benzoyl
°C	degrees Celsius
cm-1	wavenumber
conv	conversion
d	deuterium
δ	parts per million
DABCO	1,8-diazobicyclo[2.2.2]octane
DCM	dichloromethane, methylene chloride
decomp.	Decomposition
dH_2O	distilled H_2O
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMPU	dimethyl pyrimidone urea
DMSO d	imethyl sulphoxide
EI	electron impact ionization
eq	equivalents
ESI	electrospray ionization
Et	ethyl
eV	electron volt
FT	Fourier transform
g	gram
h	hour
HCl	Hydrochloric acid
Hz	hertz
i	iso
IR I	nfrared
J	coupling constant in Hertz
kg	kilogram
L l	itre
LDA	lithium diisopropylamide
LICA	lithium isopropyl cyclohexyl amide
LiHMDS	lithium bis-(trimethylsilyl)amide
M	Molarity
m	meta

Me	methyl
mg	millgram
(M+H+)	protonated parent mass
MHz	megahertz
min	minutes
mL	millilitre
µL	microlitre
(M+Na+)	sodiated parent mass
mmol	millimoles
MS	mass spectroscopy
NaOH	sodium hydroxide
ND	not determined
NMR	nuclear magnetic resonance
o	ortho
PCC	
PTC	phase transfer catalysis
PTC'a	phase transfer catalysts
Ph	phenyl
PhH	benzene
PhMe	toluene
ppm	parts per million
Pr	propyl
Rf	retention factor
RT	Room temperature
s	second
t	tert
TBAB	tetrabutyl ammonium bromide
TEA	tri-ethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
Tol	toluene
Ts	para-toluenesulphonyl
UV	ultraviolet
X	electronegativity
Z	zussamen

List of figures

List of schemes

List of tables

General Introduction

The concept of catalysis was recognized early in the 19th century. Michael Faraday in 1834, was one of the first scientists to study a catalytic reaction, that between hydrogen and oxygen on platinum.[1] One year after, Berzelius also explored some catalytic reactions such as gas combustion and coined the word "catalysis", derived from the Greek word *katalusis* meaning dissolution, destruction or end. Curiously, catalysis is generally very constructive and useful in organic chemistry processes, quite the opposite to destruction. In 1911, more than half century later, Nobel Laureate P. Sabatier, defined catalysis as a mechanism whereby some compounds are intimately involved in the process of generating or accelerating chemical reactions without being products of the reaction.[1] To date, the catalysis of organic reactions it is arguable the most explored research area in organic chemistry.

The use of catalytic processes for the synthesis of complex molecules is one of the ultimate challenges that the modern organic chemist faces. Central to this area is the ability to efficiently and selectively assemble complex molecular architectures in a minimal number of synthetic steps and in an atom economic fashion. In that sense, new methods of catalysis offering different reactivity and mechanistic advantages over the classic methods represent an attractive area of study in organic chemistry.

In this investigation, we pursue the development of new methods of catalysis of two important processes in organic chemistry: the Diels-Alder reaction and the Oxy-Cope rearrangement.

The Diels-Alder reaction is one of the most powerful strategies for the formation of two new carbon-carbon bonds and up to four contiguous stereocenters in a single operation. Despite much progress in the development of catalytic asymmetric variants, the Diels-Alder reaction is still ripe with opportunities for

discovery both in its scope and in the mechanistic details of the reaction. Herein, we explore a new Lewis base catalysis of the Diels-Alder reaction.

Sigmatropic rearrangements are the perfect example of atom economic transformations. The Oxy-Cope rearrangement allows the formation of polycyclic structures in a small amount of synthetic operations. The mild conditions and the characteristic of a boat or chair conformation in the transition state, permits the prediction of stereogenic centers. Interestingly, catalysis of the Oxy-Cope rearrangement has not been explored, providing a great opportunity for the development of new and useful methodologies. In this report, we would like to communicate the first steps towards the development of a tertraalkyl ammonium hydroxide-based activation of the Oxy-Cope rearrangement.

This document will be divided into 3 chapters; chapter 1 is dedicated to the development of new strategies for the catalysis of the Diels-Alder reaction and chapter 2 discusses the investigations carried out in the area of the Oxy-Cope rearrangement activation. Experimental methodologies are detailed in chapter 3.

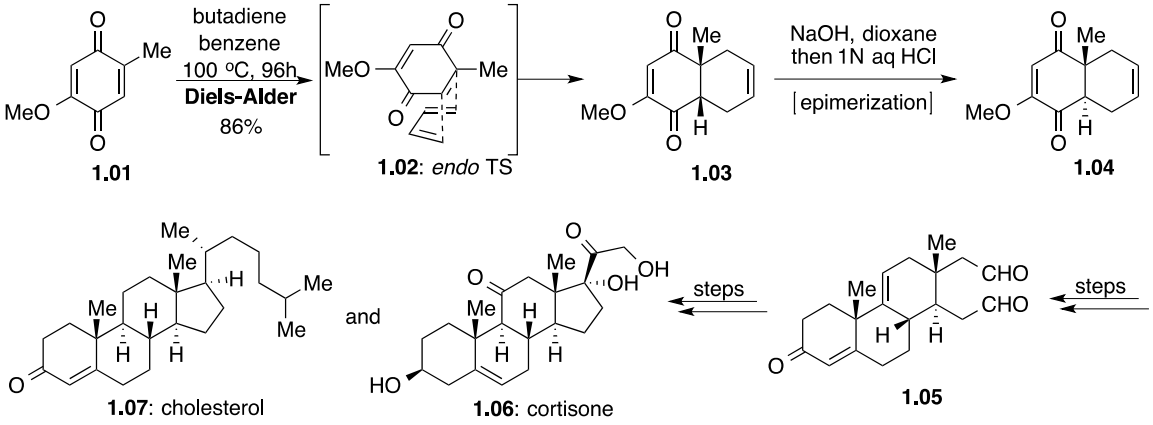
Chapter I. Novel methods for Diels-Alder catalysis

1.1 Thermal Diels-Alder reaction

Given the importance of the Diels-Alder reaction in the synthesis of useful scaffolds, the amount of resources and effort spent in research to find new and improved methodologies is not surprising. [2] After the seminal 1928 publication by Diels and Alder describing the importance of their discovery,[3] it took over two decades for the scientific community to fully start exploring the potential of the reaction. Some authors attribute this "slow start" to the effects of World War Two; nonetheless, since these investigations started, this area of research has been definitely one of the most popular and fruitful within the broad spectrum of organic reactions.

The early reports of the use of the thermally induced Diels-Alder reaction in a total synthesis came in 1952, when Woodward and collaborators disclosed their historic routes to the steroids cortisone **1.06** and cholesterol **1.07** (Scheme 1.01).[2,4]

Scheme 1.01. Pioneering quinone-based Diels-Alder reaction by Woodward *et al.*[4]

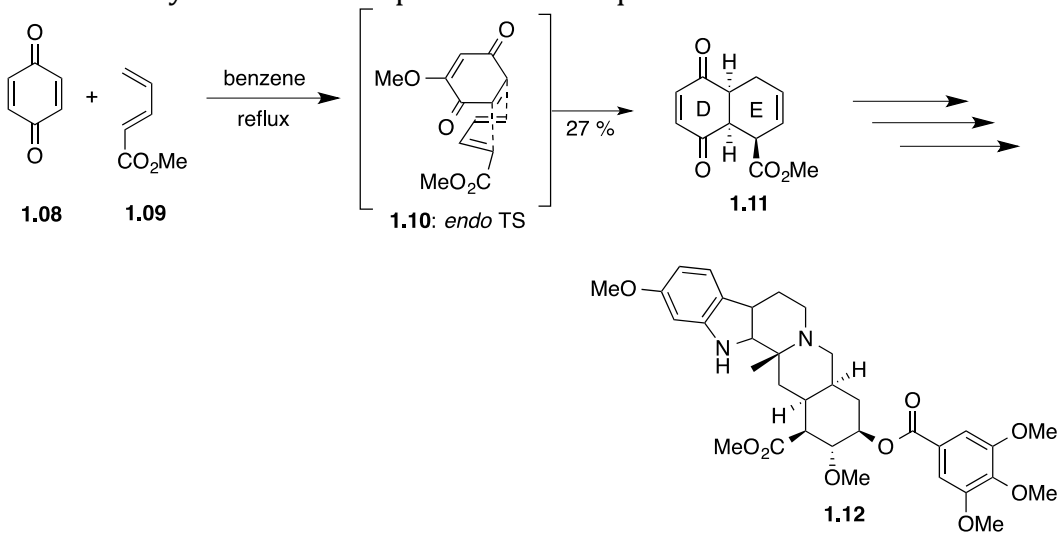


The synthesis of cortisone **1.06** and cholesterol **1.07** from quinone **1.01** and butadiene was accomplished using the Diels-Alder reaction as key step, via *endo* transition state **1.02**. Besides being one of the most elegant syntheses of its time, it also contains a couple of features that are interesting to notice: 1) Woordward

recognized that by using a differentiated quinone it would be possible to effect regioselective control of the intermolecular Diels-Alder union, as the more electron-rich methoxy-substituted olefin would be less dienophilic than its methyl-substituted counterpart. 2) It was anticipated that even though a *cis*-fused adduct would arise from the Diels-Alder reaction, conversion into the requisite thermodynamically more stable *trans*-fused system, which is present in the natural product of interest would be easy to achieve. A base-induced epimerization to obtain molecule **1.04** was realized, setting up the stage for an eventual ring contraction that would allow the access to this region of the steroid scaffold.[2,4,5]

Similar examples of synthetic strategies utilizing the inherent properties of dienes and dienophiles were shown to be useful for the synthesis of complex molecules such as reserpine **1.12** (Scheme 1.02) an indole alkaloid that has been used as antipsychotic and antihypertensive drug.[6,7]

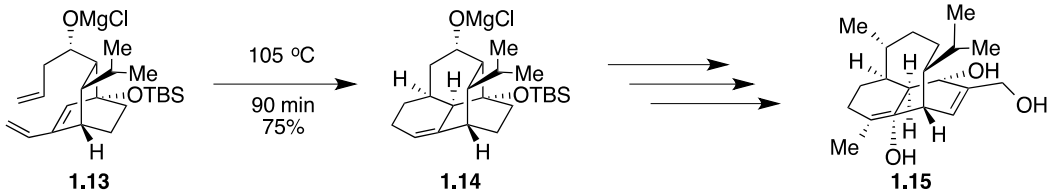
Scheme 1.02. Synthesis of reserpine **1.12** from quinone **1.08** and diene **1.09**



In recent years, the thermal Diels-Alder reaction has been used to access molecules of high structural complexity and interesting biological activities. One example is the fungus-produced diterpene Vinigrol **1.15**, which exhibit antihypertensive and platelet aggregation inhibitory activities. Baran and co-

workers accomplished the synthesis of **1.15** by accesing the complex skeleton **1.14** using a key thermal intramolecular Diels-Alder reaction followed by a Grob fragmentation. The selectivity that they observed was dictated by the intrinsic rigidity of the substrate structure. (Scheme 1.03).[8]

Scheme 1.03. Intramolecular Diels-Alder reaction in the synthesis of Vinigrol **1.15**.



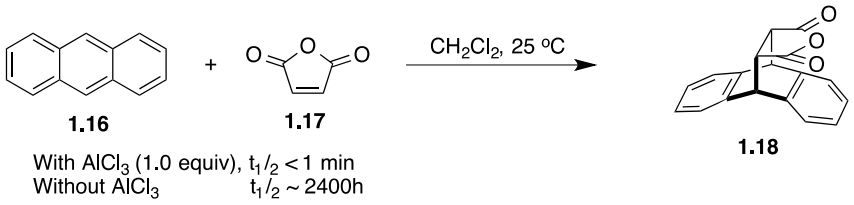
1.13 **1.14** **1.15**

As mentioned earlier, regio- and stereochemistry of thermal Diels-Alder reactions rely upon the intrinsic chemical characteristics of the diene and dienophile. Though the use of Lewis acids one can modify and tune the system electronics to obtain the desired adduct even when this would not be the preferred product under non-catalyzed conditions. Examples of this strategy are discussed in the following section.

1.2 Lewis Acid Catalysis

In 1960, Yates and Eaton reported an approximate rate of acceleration of 10^5 for the Diels-Alder reaction of anthracene **1.16** and maleic anhydride **1.17** in the presence of aluminum chloride (Scheme 1.04).[1,9]

Scheme 1.04. Acceleration of the Diels-Alder reaction with $AlCl_3$.



This example had a great impact on the practicality of the Diels-Alder reaction, since it demonstrated that the reaction could be conducted under mild reaction conditions when an electropositive metal was used to lower the energy of activation. Different analysis on the thermal cycloadditions demonstrated that Lewis acid catalysis will usually contribute approximately a 10 kcal/mol drop in the activation energy.[10,11]. Using frontier molecular theory, Houk and Strozier showed that the coordination of a Lewis acid to a typical dienophile substantially lowered its LUMO energy and as a result, enhanced the interaction with the HOMO of the diene (Figure 1.01).[12]

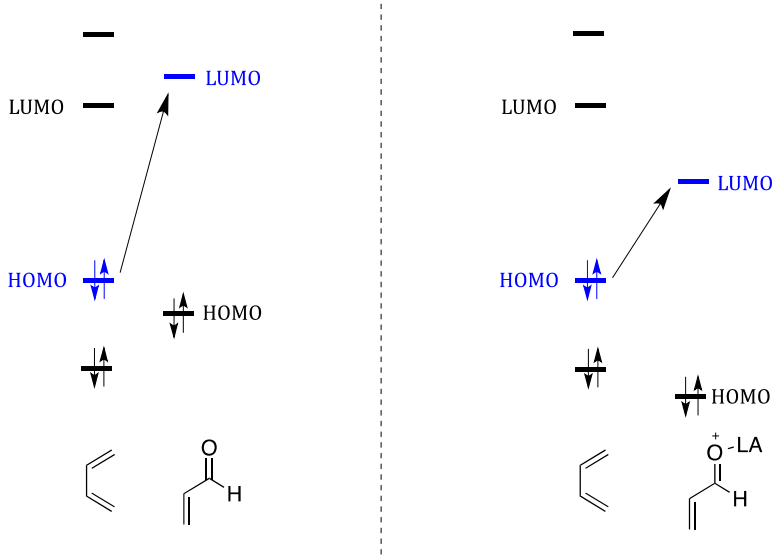


Figure 1.01. Approximate difference in activation energy gaps between a non-catalyzed Diels-Alder reaction (left) and a Lewis acid catalyzed reaction (right).

1.2.1 Regioselectivity and Stereoselectivity in Lewis acid catalysis of Diels-Alder reactions

Houk and Strozier also described the consequences of the addition of Lewis acids on the regioselectivity of Diels-Alder reactions. Based on the frontier molecular orbitals energies of acrolein and protonated acrolein, it was possible to understand that the difference in energies between the coefficients at atoms 1 and 2 of acrolein is smaller than the same difference for protonated acrolein so that reactions of the protonated molecule should be considerably more regioselective than those of the non-protonated one (Figure 1.02).[12,13]

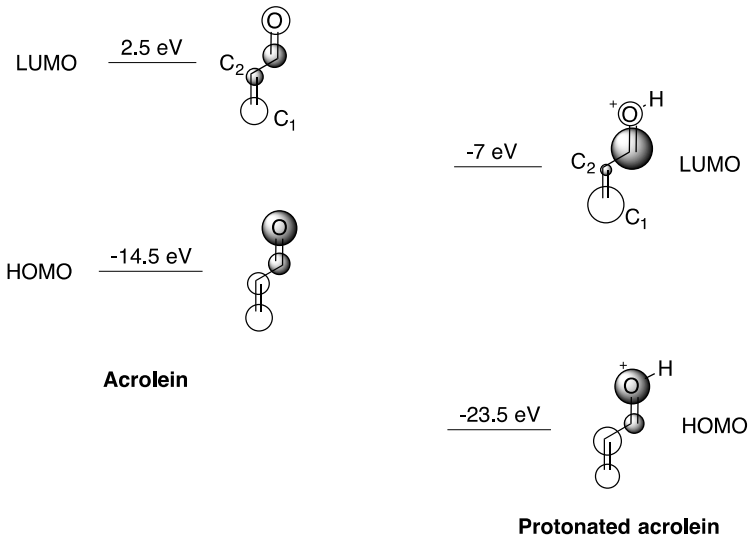
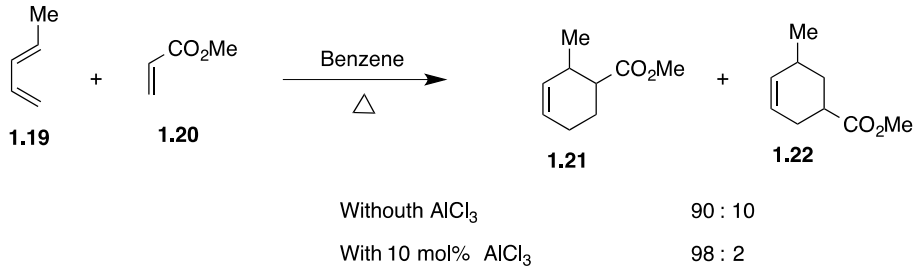


Figure 1.02. Frontier orbital energies (eV) and coefficients for acrolein and protonated acrolein

This observation was proved experimentally, the uncatalyzed reaction of (E) 1,3 pentadiene **1.19** and methyl acrylate **1.20**, showed a regioselectivity of 90:10 to favor the *ortho* adduct **1.21**, while the $AlCl_3$ catalyzed reaction showed an enhaced selectivity of 98:2 to favor the same product (Scheme 1.05).[10]

Scheme 1.05. Enhance on stereoselectivity by Lewis acid catalysis.



Stereoselectivity for *endo:exo* ratios also increases dramatically upon Lewis acid catalysis of the Diels-Alder reaction. The differences in molecular orbitals energies described for protonated acroleins, shows an increase in the coefficient size at the carbonyl carbon, this greatly increases the secondary orbital interaction as shown in **A** in contrast with the non-protonated acrolein **B** (Figure 1.03).

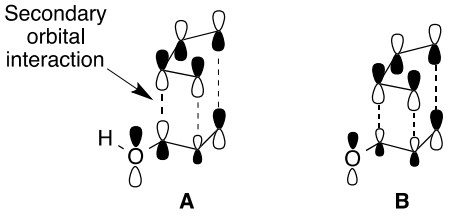
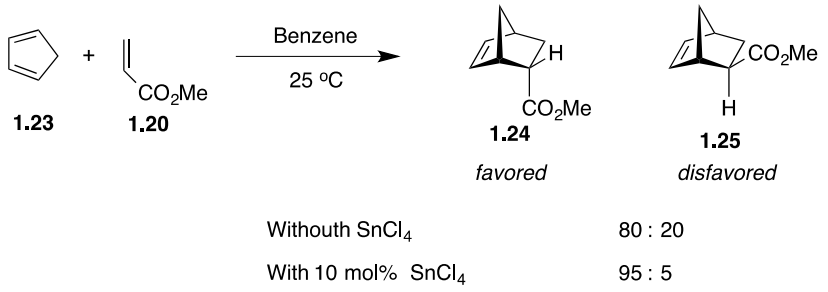


Figure 1.03. Diene-HOMO and dienophile-LUMO interactions in endo transition states

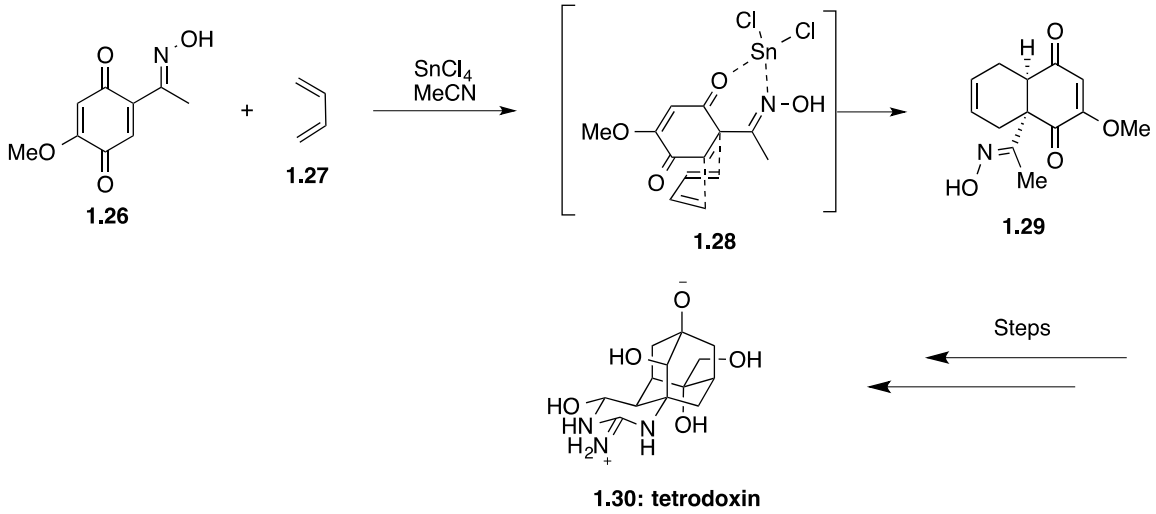
Sauer and co-workers experimentally proved this observation. While the uncatalyzed reaction between cyclopentadiene **1.23** and methyl acrylate **1.20** gave diastereoselectivities of 80:20 favoring the *endo* adduct **1.24**, the Sn_4Cl catalyzed reaction gave diastereoselectivity of 95:5 for the *endo* product under the same reaction conditions (Scheme 1.06).[14]

Scheme 1.06. Lewis acid effect on diastereoselectivity *endo:exo* ratio



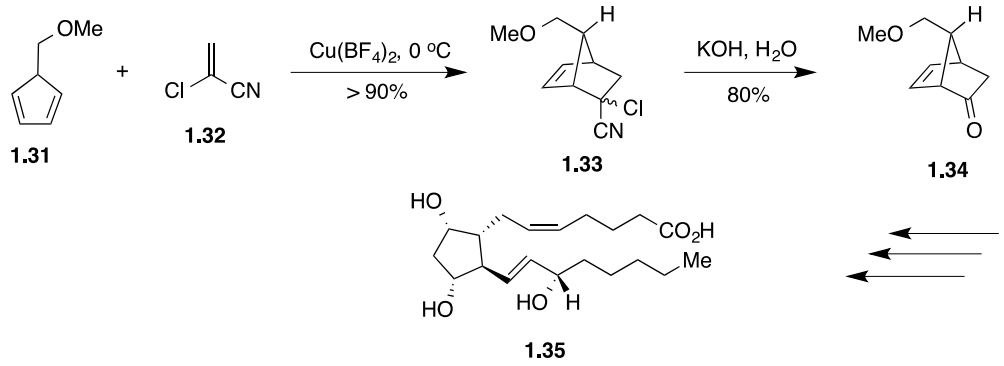
A very informative example of these concepts is illustrated in the elegant synthesis of tetrodoxin **1.30** by Kishi et al (Scheme 1.07).[15] In this synthesis, an initial Diels-Alder reaction between quinone **1.26** and butadiene **1.27** was envisioned to generate an advanced intermediate. However, the intriguing feature of this example is that the use of tin tetrachloride in the reaction proved to be critical for the chemoselective engagement of butadiene with the oxime-bound dienophile to form **1.29**. In the absence of this Lewis acid, the other olefinic bond of the quinone **1.26** reacted exclusively. Oximes are normally electron-donating species, thus deactivating the neighboring olefin for the Diels-Alder reaction. However, coordination of the Lewis acid reverses this behavior by removing electron density from this group, leading to the formation of a highly activated electron-deficient dienophile.[16]. This Lewis acid activation nicely effected regiochemical control in the cycloaddition, which have not been possible to achieve otherwise.

Scheme 1.07. Lewis acid catalysis in the synthesis of tetrodoxin **1.30**.



Although the remarkable early breakthroughs in the development of methods to achieve relative stereochemistry, the issue of controlling the absolute stereochemistry of the produced adducts was still a big challenge.[2] Corey's early work on the synthesis of prostaglandin $F_{2\alpha}$ **1.35** in enantiopure fashion demonstrated an imaginative and elegant solution to the highly stereochemical decoration around the five membered ring.[17] The solution came by the Lewis acid catalyzed Diels-Alder union between diene **1.31** and 2-chloroacrylonitrile **1.32** to obtain **1.33**, which could be hydrolyzed to a ketone **1.34,** which served as a useful precursor for the synthesis of prostaglandin $F_{2\alpha}$ **1.35** in a stereocontrolled manner (Scheme 1.08).

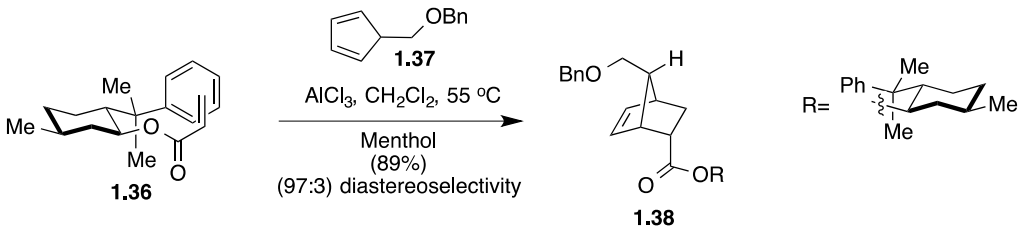
Scheme 1.08. Diels-Alder as fist step toward the synthesis of prostaglandin $F_{2\alpha}$ **1.35**



1.2.2 Lewis acid mediated Enantioselective Diels-Alder catalysis

Corey's group continued to investigate the enantioselective catalysis of the Diels-Alder reaction and in 1975, the first successfully identified solution was reported. It involved tethering the dienophile to a homochiral ring, in this case menthol, to effect the near-exclusive enantioselective formation of *endo* adduct **1.38** in 98% *ee* (Scheme 1.07).[18] Likely, this product was the result of the controlled approach of the dienophile, achieved through a minimization of steric repulsion between the $AlCl_3$-chelated carbonyl group and the menthol-derived phenyl ring and was aided by π stacking, with approach of the diene occurring from the most exposed side of the dienophile **1.36** (Scheme 1.09). This example represents one of the earliest examples of the induction of asymmetry by a chiral auxiliary.[1]

Scheme 1.09. Early example of induced asymmetry by a chiral auxiliary.[2,18]



After Corey's examples, several research groups gave a lot of attention to the development of methods that allow the formation of enantioselective adducts. Among the most noteworthy, Evans and co-workers envisioned the use of chiral α,β-unsaturated *N*-acyloxazolidinones in coordination with Lewis acids such as Et_2AlCl as potent dienophiles **1.39**.[19] This strategy gave the first guideline for the development of chiral Lewis acids that would work either with or without the need of a chiral auxiliary. One example includes the bis(oxazoline) copper(II) centered catalyst **1.40**, which was described by Evans *et al* in 2000.[20] The usefulness of this catalyst was demonstrated by its use in the synthesis of ent-shikimic acid and isopulo'upone.[21] Another important example is the proline derived chiral oxazaborolidine developed by Corey and co-workers **1.41,** which after being

activated with triflic acid, generates a potent cationic and highly reactive Lewis acid for dienophile activation (Figure 1.04).[22]

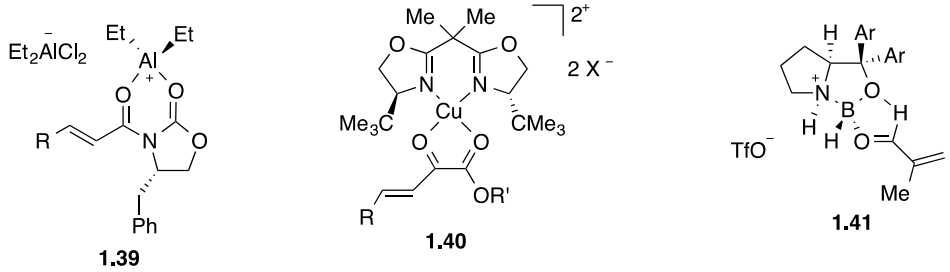


Figure 1.04. Asymmetric Lewis acid catalysts interacting with dienophiles.

In the area of enantioselective hetero-Diels-Alder catalysis, Yamamoto and collaborators described the stable chiral (acyloxy)borane (CAB) to produce dihydropyrone derivatives with high optical purities.[23] This, and the fore mentioned examples, represent very important tools that can be used to obtain molecules with high levels of enantiopurity.[2] More recently, MacMillan's group reported a different strategy for enantioselective catalysis. This and another non-classic catalytic methods will be discussed in the upcoming section.

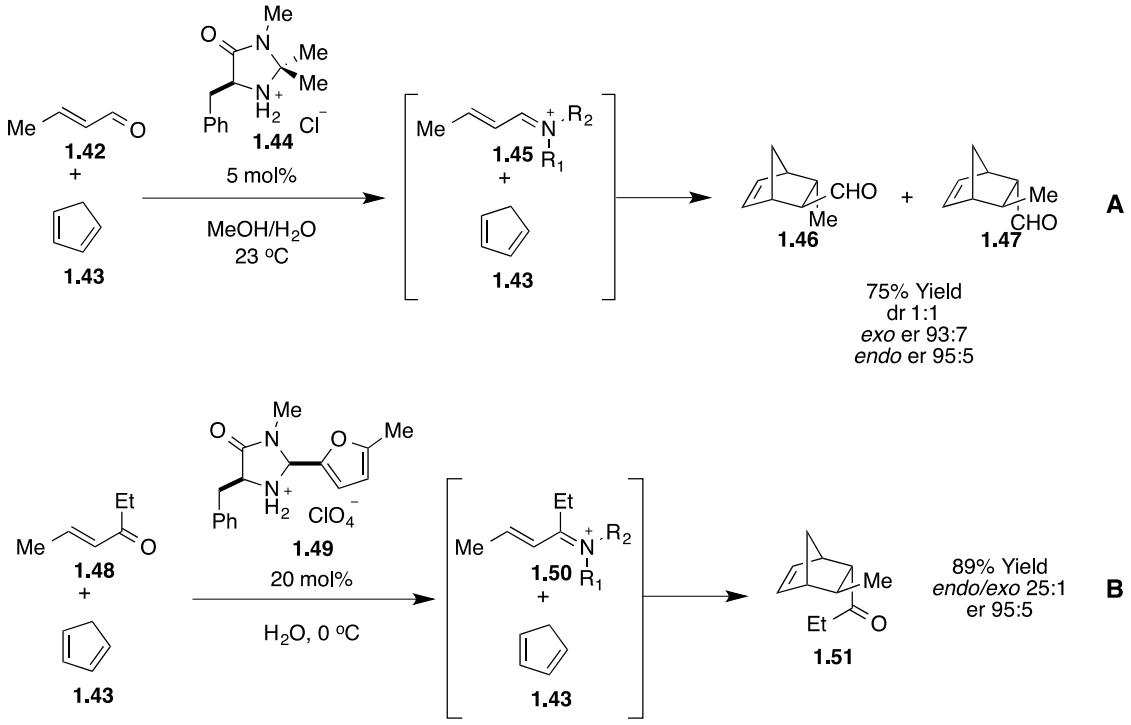
1.3 Unconventional methods for the catalysis of the Diels-Alder reaction

In recent years, alternative methods to using Lewis acids for Diels-Alder catalysis have allowed, not only good acceleration of the cycloaddition but also good enantiocontrol. These strategies, which fall under the classification of organocatalytic methods include: iminium chemistry, enamine formation, hydrogen bond catalysis and bifuctional acid-base catalysis.

1.3.1 Iminium ion catalysis

In 2000, MacMillan and co-workers disclosed the first report of iminium ion catalysis, being applied to a great number of well-known synthetic transformations including the Diels-Alder reaction.[24] Contrary to traditional Lewis acid activation, these Lewis base catalyzed Diels-Alder reactions are driven by the formation of an iminium ion intermediate such as **1.45,** which activates the dienophile by lowering its LUMO energy. Using the chiral imidazolidinone salt **1.44**, it was shown that the reaction could be performed at room temperature to give products in good yields and enantioselectivities, although variable levels of diastereoslectivity were achieved (Equation **A** in Scheme 1.10).[24,25]In subsequent studies, MacMillan demonstrated that unsaturated ketones such as **1.48,** could be used as dienophiles through the use of the chiral Lewis base catalyst **1.49**, producing adduct **1.51** in high yields and high selectivities. This solved a long standing challenge of using simple α,β-unsaturated ketones as dienophiles in the Diels-Alder reaction (Equation **B** in Scheme 1.10).[26]

Scheme 1.10. Lewis base catalyzed Diels-Alder reactions.[24,26]

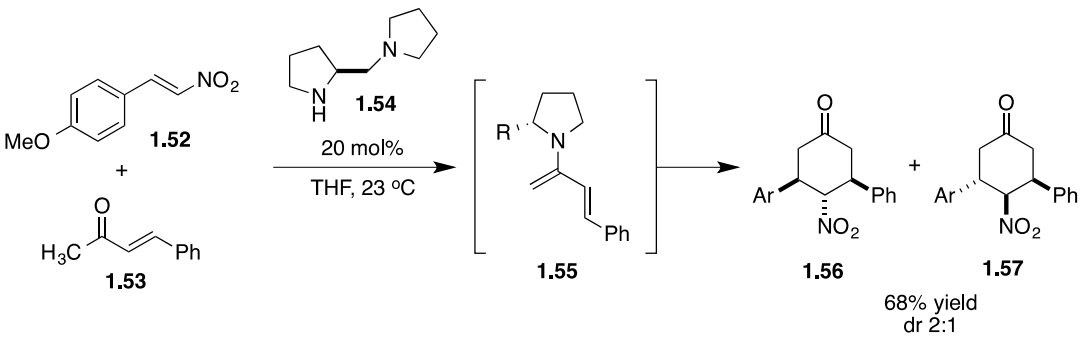


The explanation for the dramatic rate acceleration observed in these Lewis base catalyzed Diels-Alder reactions, is the formation of a highly electrophilic α,β-unsaturated iminium ions **1.45** and **1.50** (Scheme 1.10). The effect of the formation of the iminium ion is the lowering of the LUMO of the dienophile. In concept, this process is similar to that obtained by the use of Lewis acids.

1.3.2 Enamine catalysis

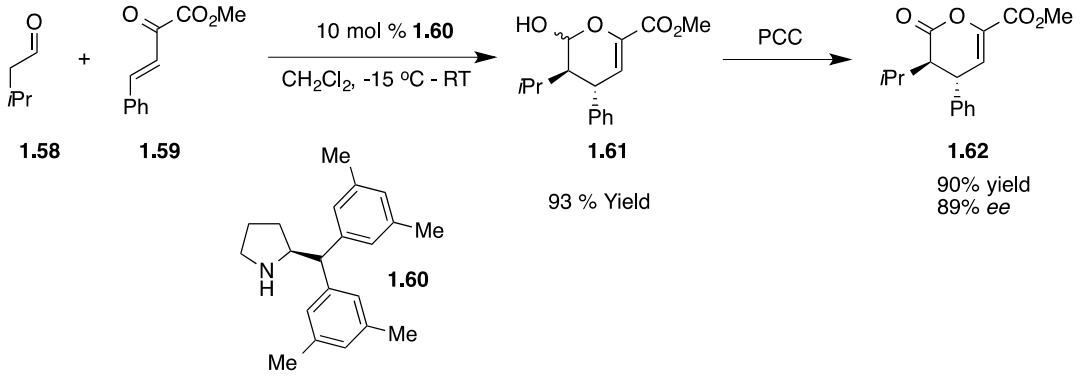
In principle, the enhanced electrophilicity achieved in Lewis base activation of the dianophile could be complimented by enhancing the nucleophilicity of the diene. As a demonstration of this idea, Barbas III and co-workers found that if an α,β-unsaturated ketone such as **1.53**, was exposed to a secondary amine, the iminium ion formed could tautomerize into a conjugated enamine **1.55** by proton transfer, which can participate in the Diels-Alder reaction as an electron enriched diene, producing adducts such as **1.56** and **1.57** (Scheme 1.11).[27]

Scheme 1.11. Enamine activation in the Diels-Alder reaction.[27]



This strategy has been expanded to the enantioselective hetero inverse-electron demand Diels-Alder reaction. Jorgensen and co-workers demonstrated that through the formation of electron rich enamines from the condensation of aldehydes such as **1.58** and proline derivatives such as **1.60** that serve as dienophiles in reactions with β,γ-unsaturated α-keto esters **1.59** good yields and enantioselectivities can be observed in the final product **1.62** after PCC oxidation of **1.61** (Scheme 1.12).[28]

Scheme 1.12. Enantioselective hetero inverse-electron demand Diels-Alder



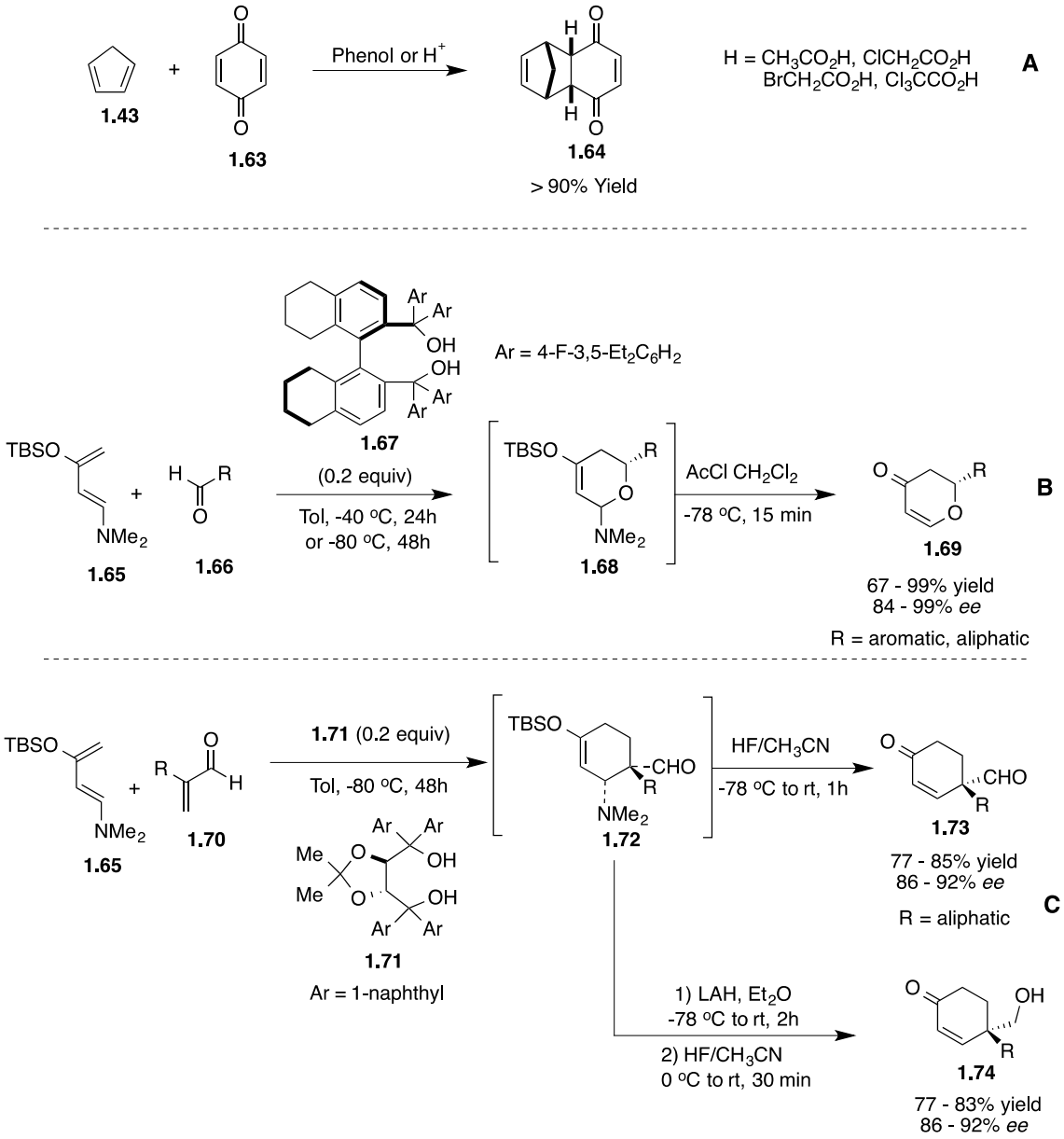
The rationale behind this strategy is to raise the HOMO of the diene or dienophile in the case of the inverse-electron demand Diels-Alder reaction, reducing the gap between the two interacting orbitals.[25]

1.3.3 Hydrogen bond catalysis

Using a different approach, hydrogen bond catalysis has also been used as a strategy to accelerate of the Diels-Alder reaction. The first report of this kind of catalysis was the one described by Wasserman and co-workers in 1942, in which they describe the catalysis of the Diels-Alder reaction by small-molecule hydrogen-bond donors, such as phenols and carboxylic acids. An example of this method was demonstrated in the reaction between benzoquinone **1.63** and cyclopentadiene **1.43** to afford adducts such as **1.64** (Equation **A** in Scheme 1.13).[29]

Hydrogen-bond catalysis has also been explored in the context of enantioselective hetero Diels-Alder reactions. Two of the pioneers of this research field are Rawal and Yamamoto. In a joint report, they describe a highly enantioselective catalytic hetero Diels-Alder reaction between amilisiloxidienes **1.65** and a wide variety of unactivated aldehydes **1.66** to obtain dihydropyranones **1.69** after workup. These reactions are promoted by the axially chiral diols of the BAMOL family **1.67** (Equation **B** Scheme 1.13).[30]

Scheme 1.13. Hydrogen bond catalysis of Diels-Alder reaction.



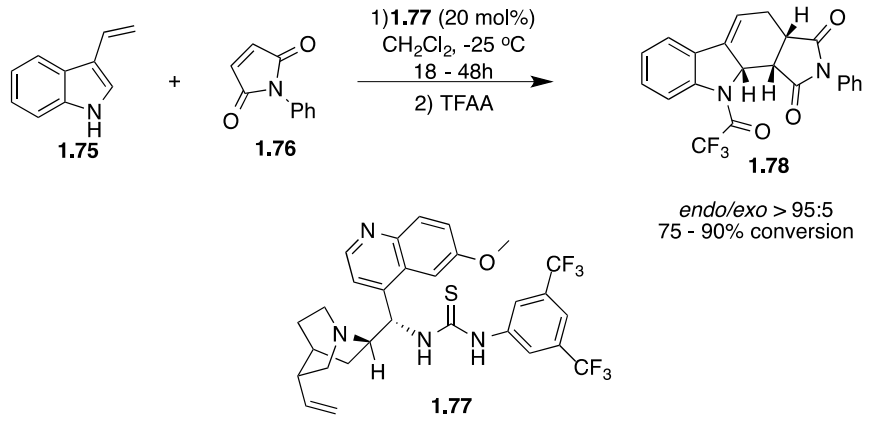
Enantioselective *all carbon* Diels-Alder reactions have also been achieved utilizing the Hydrogen-bonding catalysis strategy. Through the use of the chiral commercially available alcohol α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) **1.71** as a catalyst, Rawal and collaborators showed that the Diels-Alder products **1.73** and **1.74** could be obtained in good yields and excellent enantioselectivities after two different workups (Equation **C** in Scheme 1.13).[31]The

explanation for these observations is the Lewis acid-like character of the hydrogen-bonding of the alcohol catalyst. When the hydrogen-bonding occurs between the alcohol and the dienophile, its LUMO is lowered making it more reactivating towards Diels-Alder cycloaddition. The disadvantage of this type of catalysis is mainly the high catalyst loading requirements, while its virtues include: 1) their ground state form is the active form of the catalyst so, there is no need for further activation, 2) they are moisture tolerant and 3) they can be potentially recovered and reused.

1.3.4 Bifunctional catalysis

The last unconventional strategy to be discussed is the bifunctional acid-base catalysis. Deng and co-workers have demonstrated that cinchona alkaloid-based bifunctional catalysis for the Diels-Alder reactions of pyrones to obtain complex bicyclics adducts is possible in good yields and selectivities.[32,33] Inspired by this reports, Ricci and collaborators designed a cinchona alkaloid-based catalyst **1.77** containing a thiourea moiety that allows the enantioselective Diels-Alder reaction of 3-vinylindoles **1.75** and activated dianophiles such as **1.76** offering a direct approach to optically active tetrahydrocarbazole derivatives **1.78** (Scheme 1.14).[34]

Scheme 1.14. Cinchona alkaloid-based enantioselective Diels-Alder catalysis.



The proposed working model for this approach suggests the interaction between the basic moiety of the catalyst and the N-H group of the diene, altogether with the activation of the dienophile by the thiourea moiety (Figure 1.05).[34]

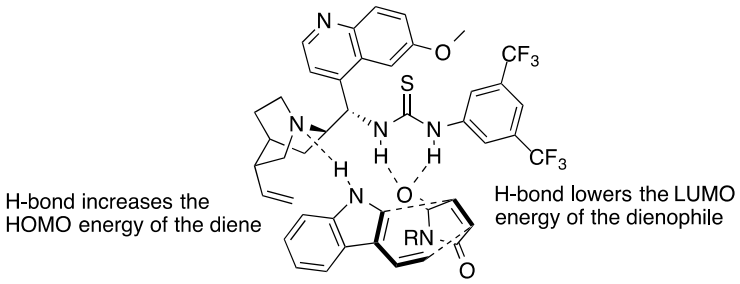


Figure 1.05. Proposed model of the bifunctional Diels-Alder catalysis.

This brief review on unconventional methods for the catalysis of the Diels-Alder reactions, shows that even though there is an impressive amount of elegant methodologies that have been developed, there are still opportunities for the discovery of new and efficient ways to trigger the Diels-Alder reaction.

1.4 Chemistry of Lewis acids and Lewis bases

1.4.1 Lewis acids and Lewis bases overview

The modern theory based on the pioneering work of Gilbert Newton Lewis (1875–1946), which describes the concept of electron donor- electron acceptor interaction, has been extensively utilized as the basis on which a grand number of organic reactions have been developed.[25] In a simplistic yet all encompassing definition, a Lewis acid is described as an electron pair acceptor species and a Lewis base as an electron pair donor species.

Intrinsic to the concept of the acid-base interaction proposed by Lewis, there is the need to satisfy the octet rule and with this, it is assumed that this interaction is stabilizing since in its most stable state an atom should have eight valence electrons. In general, the formation of an adduct leads to a thermodynamically more stable compound and as a result, it is coherent to think that the reactivity of the adduct formed would decrease relative to the starting materials from which it was

formed.[35] Examples such as the air stable trimethylphosphane-borane complex where both starting materials are pyrophoric, support this idea.[36] Nonetheless, there are several examples where stable acid-base adducts show enhanced reactivity. The previous chapter is an obvious example of this statement, as described before, the interaction between a Lewis Acid and its counterpart usually a dienophile in the Diels-Alder reaction renders an important increase in the reactivity of the molecules involved. [25]

Lewis acids have been extensively used as promoters of classic reactions. However, although Lewis bases have been widely used as co-catalysts as ligands in transition metal catalysis, the use of nonmetallic Lewis bases catalysts has not been exhaustively explored and therefore it represents a great area of opportunity.

There are two main reasons for this uneven balance in the use of Lewis bases when compared to Lewis acids as catalysts. First, the lack of Lewis acidic sites in common organic molecules and second, the limited number of opportunities for valence expansion at carbon centers. The use of a specific group of Lewis acid acceptors, such as boranes and other Group 13 elements, allows one to meet the criteria described above, since these elements can coordinate to a Lewis base and on the other hand are able to expand their coordination sphere and reach a hypervalent state.

1.4.2 Interaction Mode between Lewis bases and Lewis acids

Lewis bases catalysis is defined as the acceleration of the reaction by the action of an electron-pair donor on an electron-pair acceptor. It is intuitive to conclude that the net effect of the binding of the Lewis base to a Lewis acid will result in the transfer of electron density to the acceptor species. This increase in electron density normally renders higher nucleophilic character of the acceptor subunit. However, this is not the only possible effect of the binding of a Lewis base to a Lewis acid counterpart and a less recognized and rather counterintuitive effect can take place. This effect is the enhancement of the electrophilic character of the

acceptor unit. This observation is better rationalized by looking at the distribution of the electron density between the two atoms that constitute the new bond formed. To do so, Jensen classified all Lewis acid-base interaction in terms of the nature of the interacting orbitals[37] (Table 1.01).

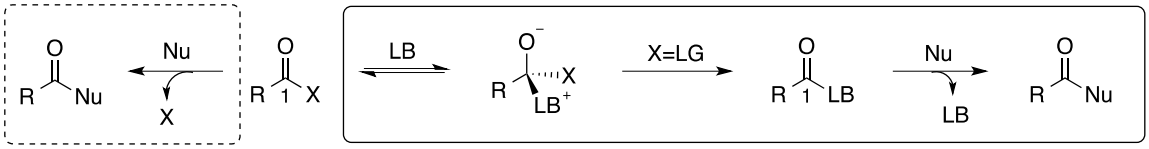
Table 1.01. Jensen's orbital analysis of molecular interactions.

Donnor (LB)	Acceptor (LA)		
	n*	σ*	π*
n	n - n*	n - σ*	n - π*
σ	σ - n*	σ - σ*	σ - π*
π	π - n*	π - σ*	π - π*

In practice, only three of these combinations are significant in terms of Lewis base catalysis. The three combinations are: 1) interaction between nonbonding electron pairs (n) and antibonding orbitals with π character (n - π*), 2) interaction between nonbonding electron pairs and antibonding orbitals with σ character (n - σ*), 3) interactions between nonbonding electron pairs and vacant nonbonding orbitals (n - n*).

The differences in the three type of interactions described above is important to understand the effect of the binding of the Lewis base donor to the Lewis acidic acceptor. The n - π* interaction is the most common form of Lewis base catalysis and generally (although incorrectly) named nucleophilic catalaysis. In this case, the nonbonding electron pair of a Lewis base interacts with a π* orbital, this type of orbital is found in alkynes, alkenes, carbonyls, azomethines and other common unsaturated functional groups. In the case of simple carbonyl compounds acting as Lewis acid acceptors, the attack of a Lewis base leads to the formation of a zwitterionic tetrahedral intermediate with enhanced nucleophilic character at the oxygen atom. In contrast, if the carbonyl compound in question possesses a good leaving group, this intermediate can collapse to a new ionic species that now possesses enhanced electrophilic character at C1 (Scheme 1.15).[25,38,39]

Scheme 1.15. Comparison between uncatalyzed nucleophilic attack to a carbonyl (left) and a Lewis base catalyzed reaction (right).[25]



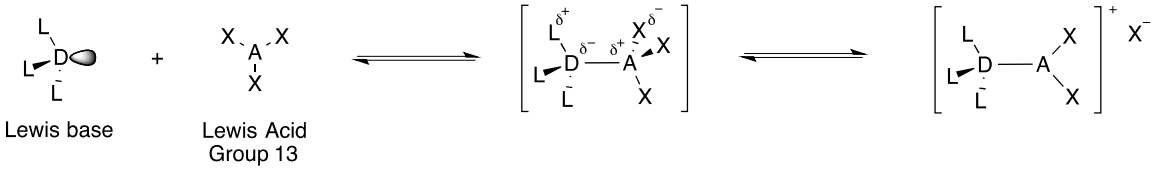
The fact that Lewis base activation can promote both nucleophilic and electrophilic character in similar substrates as observed in the MacMillan examples given in the sections iminium ion and enamine catalysis sections 1.3.1 and 1.3.2 respectively, is an exclusive aspect of Lewis base catalysis.

The other two types of interaction are less understood, nonetheless they are very versatile pathways for catalysis. The "n*" term used in the n – n* type of interaction is used to describe a specific group of Lewis acid acceptors such as boranes and other Group 13 elements. A very important requirement for this type of interaction to occur is that the Lewis acid acceptor is able to expand its coordination state to achieve a "hypervalent state".[40] To better understand the behavior of hypervalent species it is helpful to consider Gutmann's empirical analysis of acid base interactions, which is discussed in the next section.[41]

1.4.3 Gutmann analysis, distribution of electron density in acid-base adducts

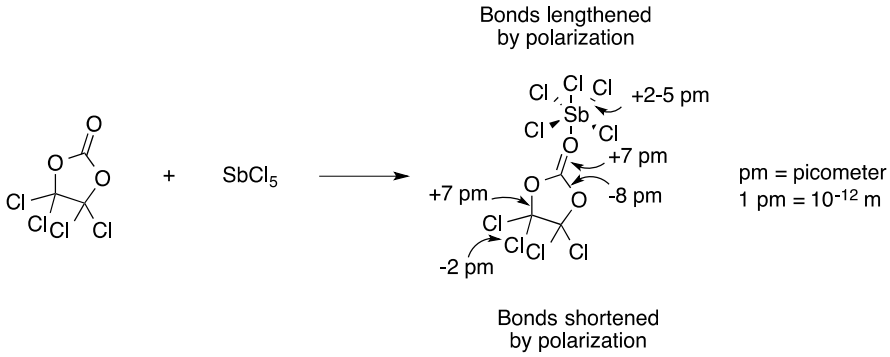
It was recognized by Gutmann that the formation of a Lewis acid-base adduct, results in an overall increase in the electron density in the acceptor fragment of the adduct. However, the distribution of this electron density is not equal in all of the atoms that constitute the acceptor half of the adduct (Scheme 1.16). This redistribution of electron density has a direct effect on the bond lengths of the ligands bound to both, donor and acceptors of an adduct.

Scheme 1.16. Electronic redistribution resulting from Lewis acid-base adduct formation.



The more interesting and catalytically important effect occurs on the Lewis acid species. As a consequence of the Lewis base bonding, the coordination number of the acceptor atom increases by one and the bonds around it are lengthened, while some of the bonds of the Lewis base counterpart are shortened to compensate for this. An example of this effect is depicted by the coordination of $SbCl_5$ and tetrachloroethylene carbonate (Scheme 1.17).[42]

Scheme 1.17. Differences in the bond lengths in $SbCl_5$ and it's complex.[42]



The coordination of tetrachloroethylene carbonate to $SbCl_5$ results in a noticeable change in bond lengths throughout the resulting adduct that is formed and, while some bonds are lengthened, others contract. This observation, corresponds to the "spill-over" effect where in this case, the augmented electron density around the antimony atom is distributed to the more electronegative, peripheral atoms.

The most important and crucial consequence of this "spill-over" effect for the purposes of our investigation, is that the Lewis acidic center is often rendered more electrophilic (δ^+) than the parent Lewis acid while its ligands are rendered more nucleophilic (δ^-).

1.4.4 Lewis base identification

As mentioned in section 2.2, Jensen classified the interactions between Lewis acids and Lewis bases according to the orbitals involved in the coordination (Table 1.01). Nonetheless, this analysis classifies all Lewis bases as n-type donors. Even when this could be seen as an over-simplification, the commonly used Lewis bases in catalytic processes are in fact n-type donors. Examples of this type of Lewis bases are atoms from Group 15 and 16 such as nitrogen, oxygen, phosphorous and sulfur. Notable exceptions are nucleophilic transition-metal species involving cobalt and iron[43] as well as N-heterocycles carbenes.[44]

The study of Lewis base energetics is a topic that is more difficult to resolve. Several Lewis base scales have been developed, each having inherent assumptions regarding the acceptor used and the secondary interactions that could limit the applicability of the scale. Parameters such as dielectric constant (ε)[45], pK_a value[46], donicity number (DN) proposed by Gutmann[42] and by Maria and Gal[47], have been used as an attempt to standardize the measurement of Lewis base strength. However, the elaboration of a "Lewis base strength" chart becomes rather hard to accomplish due to several factors: 1) the strength of an interaction must be referenced to one specific acceptor, 2) steric effects must be normalized, 3) the involvement of secondary solvent interactions, and 4) the occurrence of chemical reactions between the donor and acceptor.

The strength of a Lewis base is directly related to the ability by which an active adduct can be formed, by either an n - n*, n - σ* or n - π* interaction. Given that the formation of an adduct is an equilibrium process, the greater the enthalpic advantage for the formation of the adduct, the greater its equilibrium concentration

will be and, as a result, the greater the effect on the observed rate of the reaction catalyzed by the Lewis base.[25]

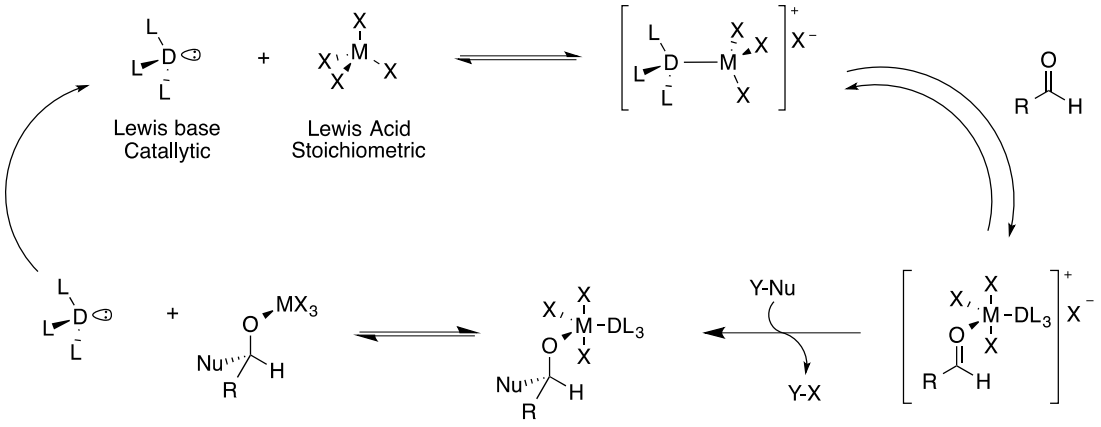
1.4.5 Lewis base activation of Lewis acids

The fundamental Lewis acid activation mechanism is based in the enhancement of the electrophilicity of the substrate. The binding of an electron-deficient Lewis acid complex to the nonbonding lone pair of some functional group has a polarization effect on the adjacent bonds, activating the substrate towards nucleophilic attack.[37]

In a concept mainly investigated and developed by Scott Denmark and collaborators, a poorly Lewis acidic species (which is not a strong activator for a given reaction by itself), could be ionized upon binding of a Lewis base, thus generating an ionic metal species with enhanced reactivity.[48] This method allows two of the main challenges in classic Lewis acid catalysis to be addressed. This includes 1) the issue of catalyst preformation, which is solved by installing the Lewis acidic moiety into the reaction substrate and 2) the problem of catalyst turnover, which is solved by the use of a noncovalently bound Lewis basic species to the Lewis acidic center.[49]

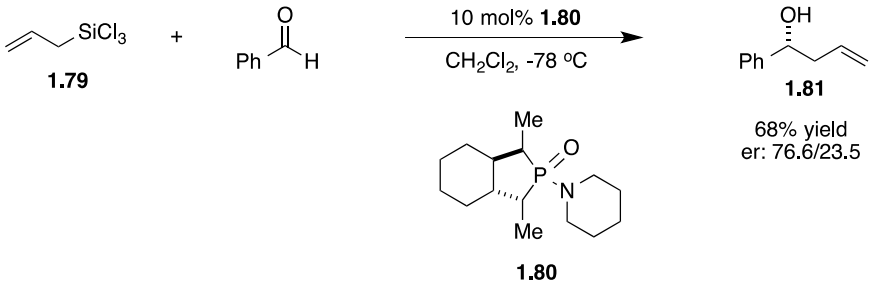
In addition to these differences with the classic Lewis acid catalysis, the stoichiometry of the reaction suffers a great change, going from being catalytic in Lewis acid to stoichiometric in Lewis acid (Scheme 1.18). This is because in each catalytic cycle the Lewis acidic moiety would become part of the product. It is clear that these types of reactions are both Lewis base-catalyzed and Lewis acid-mediated.[50]

Scheme 1.18. General representation of the Lewis base-catalyzed and Lewis acid mediated cycle.



The potential for development of this Lewis base-catalyzed and Lewis acid-mediated methodology was first reported by Denmark and collaborators with the phospohoramine-catalyzed/$SiCl_4$-mediated asymmetric ring opening of *meso*-epoxides.[51] In a similar way, Denmark and co-workers reported the addition of allylic trichlorosilanes such as **1.79** to aldehydes promoted by phosporamide **1.80** to provide the homoallylic alcohol **1.81** in good yields and good enantiomeric ratios. The origin of the activation of the use of chiral Lewis bases such as **1.80** in this reaction is suggested to be the enhanced Lewis acidity of the silicon complex together with the increased nucleophilicity of the allyl group (Scheme 1.19).[52] This methodology has been explored in different important reactions, such as the aldol reaction,[48,49,53,54] the vinylogous aldol reaction[55,56] and selenolactonization[50], obtaining great results in terms of rate acceleration and enantioselectivity.

Scheme 1.19. Lewis base promoted addition of allylic trichlorosilanes to aldehydes.

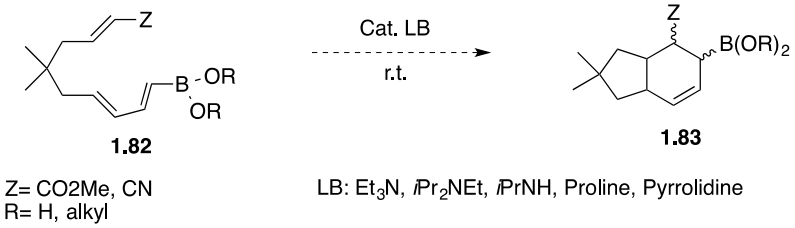


To date, only Group 14 Lewis acids such as silicon species, and one example with Group 16 selenium have been explored for this strategy. Meanwhile, only phosphoramides, thiophosphoramides, selenophosphoramides have been employed as Lewis bases and, as previously discussed, this research area is relatively new and presents great opportunities for the exploration of different organic reactions.

1.5 Purpose of the investigation

Inspired by the Denmark's strategy, we envisioned the possibility of using the Lewis base-catalysis/Lewis acid-mediated strategy in the Diels-Alder reaction. Lewis base activation of a boronic acid or boronic ester substituted substrate such as **1.82** was proposed (Scheme 1.20).

Scheme 1.20. Model system for the catalysis of the Diels-Alder reaction by Lewis bases.



Despite the fact that our concept was similar to the one described in the previous section, our proposal comprises important differences:

1) We anticipated that the use of Group 13 elements such as boron as the Lewis acidic species would easily allow the interaction with Lewis bases since the boron atom has six valence electrons and a consequent deficiency of two electrons, leaving a vacant p orbital that is prone to accept electrons.

2) While the fundamental mechanism of activation proposed by Denmark and co-workers includes increasing of the electrophilic character of the substrate, our proposal is exactly the opposite. We predicted that after the interaction of a Lewis base with the boron-containing diene, would activate our substrate via the formation of an anionic boronate complex that would increase the nucleophilic character of the diene. The overall effect on the system would be to increase the energy of the HOMO of the diene and therefore lower the energy gap between the HOMO of the diene and LUMO of the dienophile, which would ultimately promote acceleration of the Diels-Alder reaction (Figure 1.06). This proposal is an example of an n – n* type of interaction.

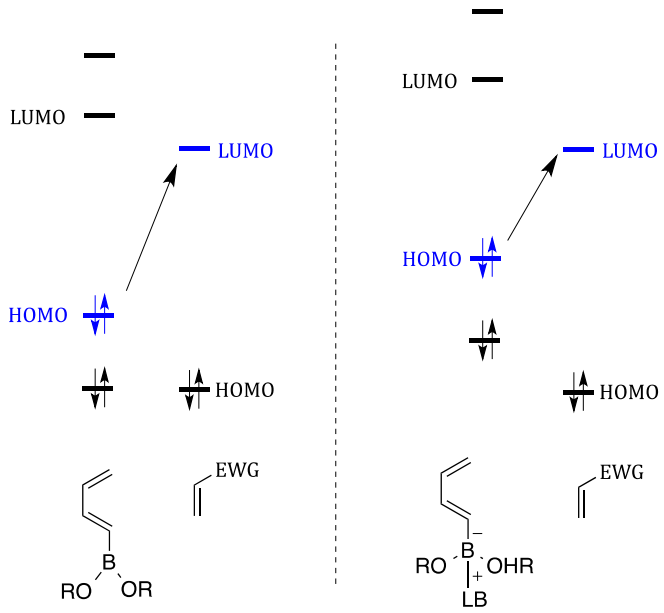
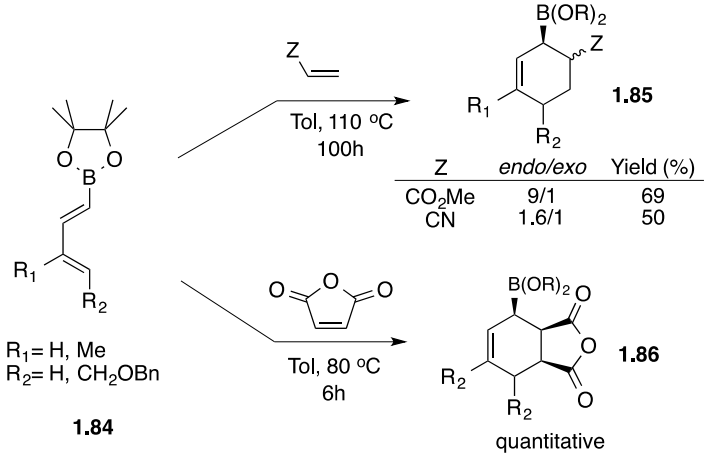


Figure 1.06. Approximate difference in orbitals energies.

3) In some cases presented by Denmark and collaborators, the Lewis acid-substrate moiety had to be formed within the same reaction mixture before interaction with the Lewis base. [49] In our proposal, the Lewis acidic moiety was thought to be part of the diene system (Scheme 1.20).

An exhaustive literature review showed that the use of 1,3 dienyl-1-boronates as dienes had been explored by Vaultier in 1987.[57] In that report, the 1,3 dienyl-1-boronates **1.84** react with activated dienophiles such as maleic anhydride in Toluene at 80 °C to give exclusively the *endo*-cycloadduct **1.86**. When a less activated dienophile was used, such as methyl acrylate or acrylonitrile a mixture of stereoisomers **1.85** was observed (Scheme 1.21).

Scheme 1.21. Diels-Alder reactions of 1,3 dienyl-1-boronates



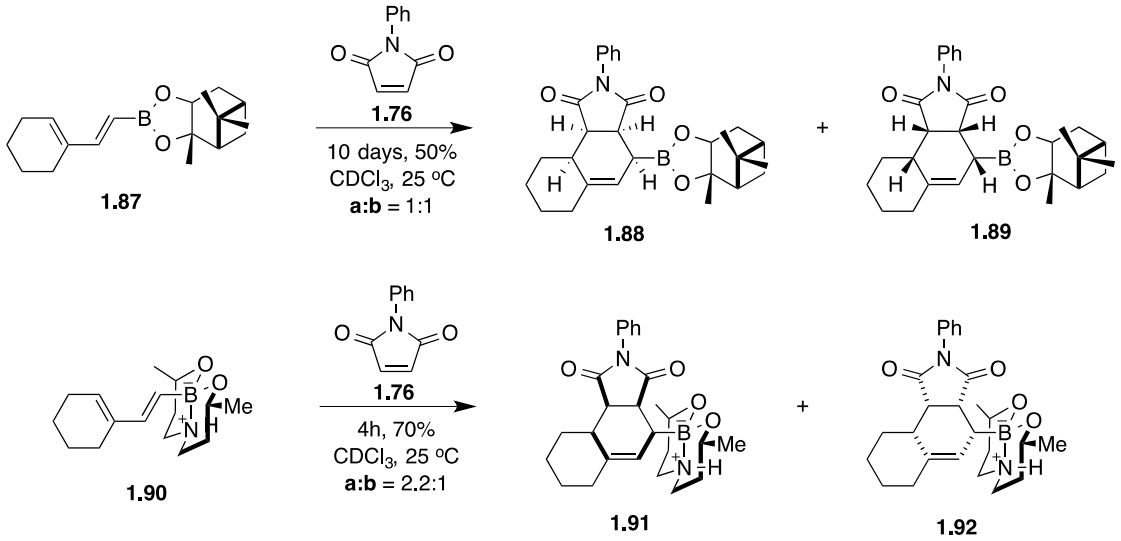
The synthetic application of this type of Diels-Alder reaction is greatly amplified by the presence of an allylboronate fragment in the product, which can undergo allylboration with aldehydes as reported by Lallemand.[58,59] However, this type of Diels-Alder reaction has two important limitations. First, the 1,3 dienyl-1-boronates show low reactivity as dienes in the Diels-Alder reaction and, second the use of highly activated dienophiles is necessary.

In order to overcome these problems, a couple of approaches have been investigated. One strategy used Lewis acids such as $EtAlCl_2$, in order to activate the

dienophile to obtain the adduct at lower temperatures and shorter reaction times as reported by Lallemand and co-workers.[60]. In 1999, Batey reported a boron- tethered intramolecular Diels-Alder reaction obtaining yields from 60 to 85% of the adduct at 60 °C and in 24 h of reaction.[61]

A related approach to our proposal attempted to make the diene more electron-rich, and as result more activated towards Diels-Alder reactions was described in 2003 by Gao and Hall. They tested the influence of an electron-donating ether in the boron-containing diene **1.87** in the reaction with N-phenylmaleimide **76**, and obtained moderate to good yields of adducts **1.88** and **1.89** in 1:1 diastereomeric ratio.[62] Earlier than that, in 1991 Wang reported the use of a chiral aminodiol, which upon coordination with the nitrogen, generated an anionic boronate **1.90** that activated the diene system towards the Diels-Alder reaction to produce adducts **1.91** and **1.92.** These reactions could be carried out in shorter time frames than the compared boronic ester **1.87**, demonstrating the rate acceleration of the reaction. A small effect on the selectivity was also observed, where they obtained a 2:1 diastereomeric ratio for **1.91 : 1.92** respectively (Scheme 1.22).[63]

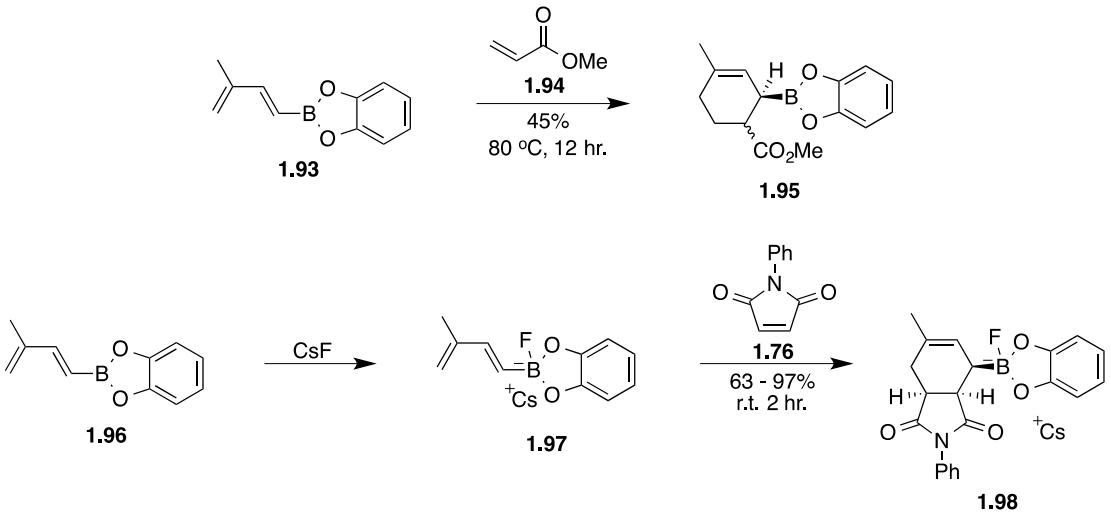
Scheme 1.22. Electron-enriched boron containing diene.



A similar approach to Gao's activation of the diene was introduced by Vaultier. This strategy also relies on the induction of the boronate anion **1.97** by

quaternarization of a catecholborane derivative **1.96** with stoichiometric amounts of CsF salt. The results suggested that the formation of the Diels-Alder adduct **1.98** is greatly accelerated when the boronate anion is formed compared to the production of adduct **1.95** from the boronic ester analogue **1.93** (Scheme 1.23).[64]

Scheme 1.23. Comparison between boronate anion and boronic ester.



As observed, there is a positive outcome in the Diels-Alder reaction when Lewis base activation of a boron containing diene is performed. However, the examples presented suggest that the desired adducts are obtained only when a highly activated dienophile is present and stoichiometric amounts of the activating Lewis base are used. A catalytic process would open new possibilities not only for activation but also for stereoinduction on the produced adducts.

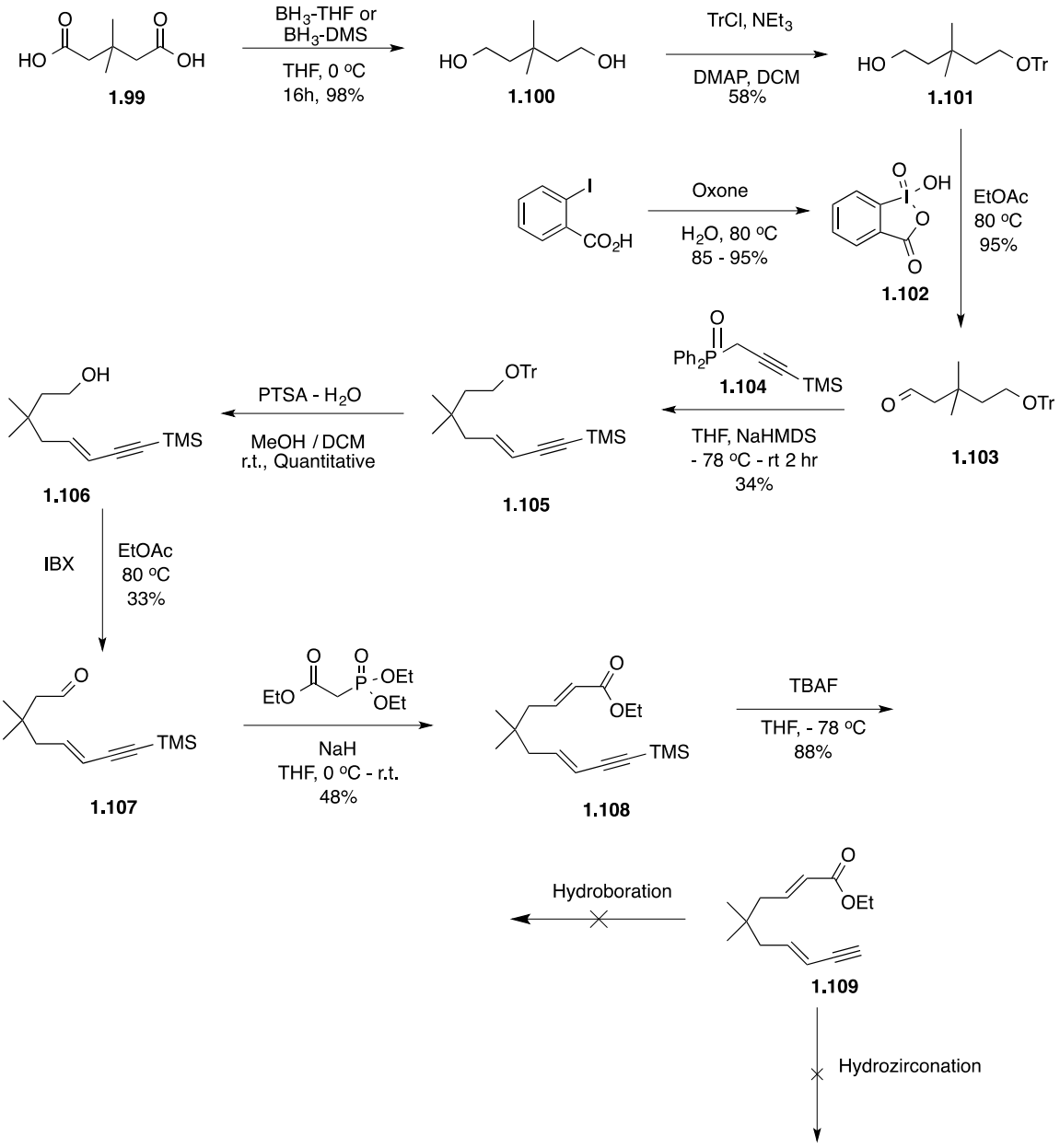
1.5.1 Results discussion

The synthetic approach to model system **1.82** is depicted in Scheme 1.24. The synthesis began with the reduction of 3,3-dimethyl glutaric acid **1.99** with borane to obtain the diol **1.100** in 98% yield. Diol **1.100** was treated with 1 equivalent of TrCl to give monoprotected alcohol **1.101** in 58% yield. IBX oxidation of alcohol **1.101** in EtOAc afforded aldehyde **1.103** in 95% yield, which was then submitted to a Horner

reaction to obtain the TMS protected enyne system **1.105** in 34% yield. Deprotection of the trityl-protected alcohol **1.105** followed by IBX oxidation of **1.106** produced aldehyde **1.107** in 33% yield. A Horner-Wadsworth-Emmons reaction was performed to yield 48% of the α, β-unsaturated ethyl ester **1.108**, which after deprotection with TBAF afforded deprotected enyne system **1.109** in 88% yield.

The synthesis of the desired 1,3-dienyl-1-boronate from molecule **1.109** proved to be very challenging. Although hydroboration seemed to be the obvious approach, it was not successful for this model system. Several hydroborating agents were used (Catecholborane, dicyclohexylborane, Borane N,N-diethylaniline, 9-BBN)[65,66] without success. In the same way, hydrozirconation using Schwart's reagent[67,68] did not allow access to desired vinyl metal species that might be transformed to a vinyl borane.

Scheme 1.24. Synthesis approach of the proposed model system **1.82**



To overcome that difficulty, we decided to explore aldehyde **1.117** as a model for a vinyl borane system based on the same principle. The two model systems: **1.82** and **1.117** share the characteristics of having an electron-withdrawing group affecting the diene (Figure 1.07). And theoretically, both can be affected by a Lewis base to activate the diene towards Diels-Alder reaction.

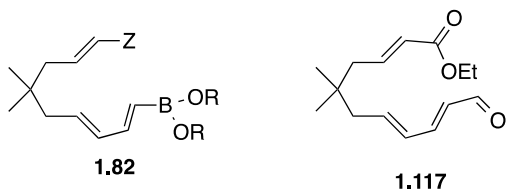
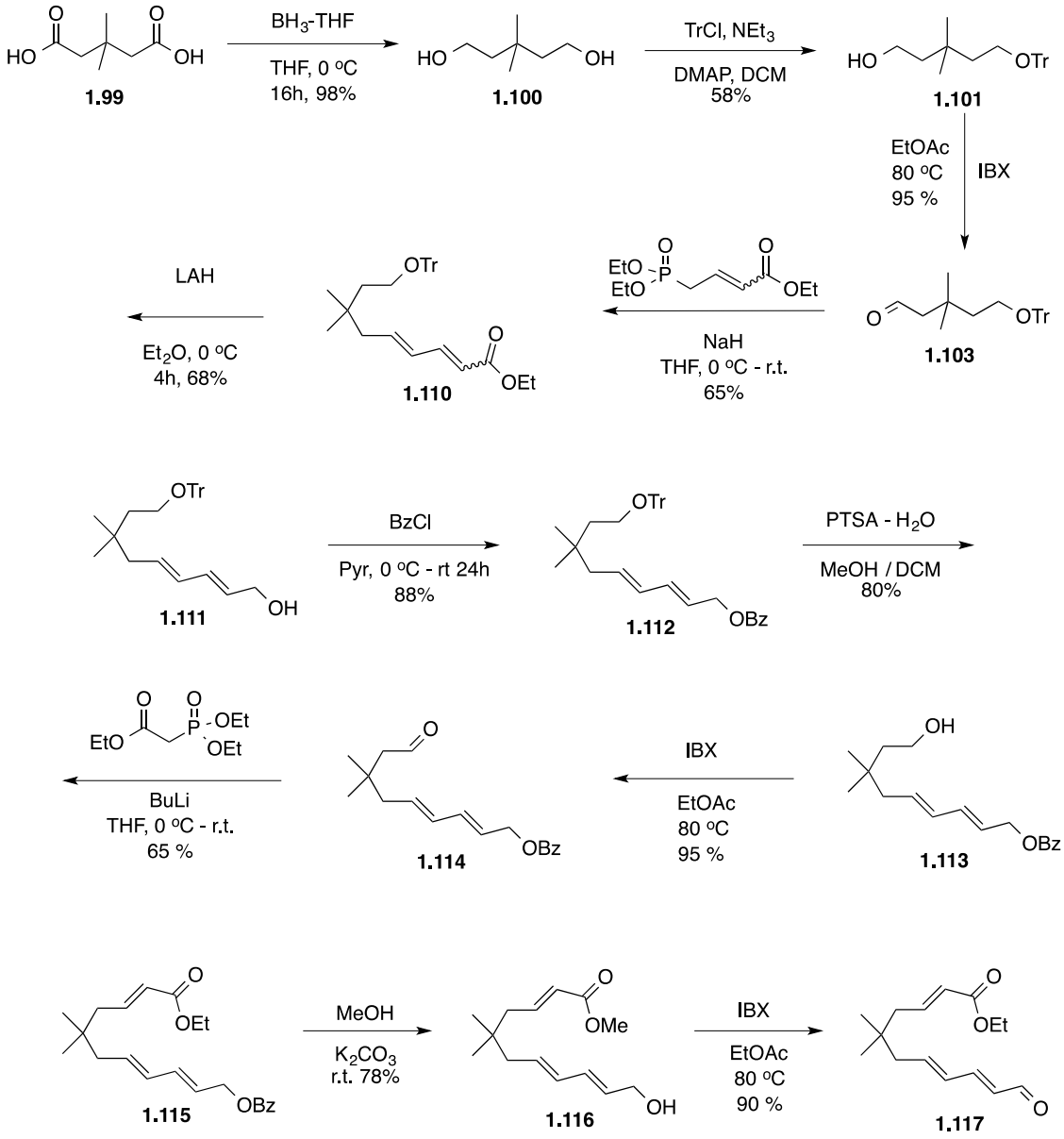


Figure 1.07. Model systems

An initial goal was to compare the rate of the intramolecular Diels-Alder reaction between the electron-withdrawing aldehyde **1.117** and its electron-donating precursor alcohol **1.116** in order to gain a better understanding of the potential reaction parameters for a catalytic reaction.

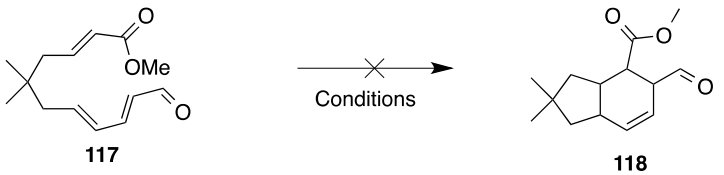
The synthesis of aldehyde **1.117** began with the reduction of dimethyl glutaric acid **1.99** with borane to obtain the diol **1.100** in 98% yield. Diol **1.100** was treated with 1 equivalent of TrCl to give monoprotected alcohol **1.101** in 58% yield. IBX oxidation of alcohol **1.101** in EtOAc afforded aldehyde **1.103** in 95% yield, which was then submitted to a Horner-Wadsworth-Emmons reaction to obtain the α, β, γ, δ –unsaturated ester **1.110** in 65% yield. LAH reduction of the ester allowed the formation of the alcohol **1.111** in 88% yield. The alcohol was then protected in the presence of BzCl affording product **1.112** in 88% yield. Deprotection of the trityl-protected alcohol **1.112** followed by IBX oxidation of **1.113**, produced aldehyde **1.114** in 95% yield. A second Horner-Wadsworth-Emmons reaction was performed to yield 65% of the α, β-unsaturated ethyl ester **1.115**. Hydrolysis of the benzyl ether moiety in **1.115** to alcohol **1.116** was achieved in the presence of MeOH and K_2CO_3. Finally, IBX oxidation afforded the final product aldehyde **1.117** in 90% yield (Scheme 1.25).

Scheme 1.25. Synthesis of aldehyde **1.117**



The cycloaddition of aldehyde **1.117** to produce adduct **1.108** was attempted with no success; the results and conditions of the reaction are shown (Table 1.02). The use of different solvents such as $CDCl_3$, DMSO-d6, Toluene-d8 and H_2O and reaction temperatures ranging from 25 to 110 °C failed to afford cycloadducts. Furthemore, the use of additives such as $Sc(OTf)_3$ to activate the dienophile, or cyclic secondary amines such as proline and pyrrolidine expecting to generate a hemiaminal on the diene moiety did not promote the reaction.

Table 1.02. Efforts towards intramolecular Diels-Alder of aldehyde **1.117**



117 **118**

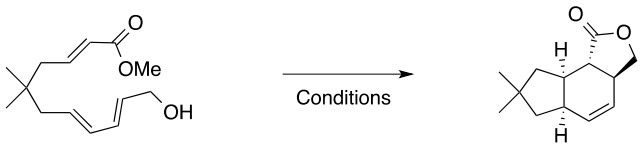
entry	catalyst	mol%	solvent	*T*[°C]	time[h]	SM Consumpt[%]	NMR yield[%]
1	--	--	$CDCl_3$	25	14	0	0
2	--	--	$CDCl_3$	25	48	5	0
3	--	--	$CDCl_3$	25	72	10	0
4	--	--	DMSO	110	14	40	0
5	--	--	DMSO	110	24	70	0
6	--	--	DMSO	110	72	100	0
7	--	--	Toluene	105	14	20	0
8	--	--	Toluene	105	24	40	0
9	--	--	Toluene	105	72	90	0
10	--	--	H_2O	100	14	90	0
11	$Sc(OTf)_3$	10	DMSO	100	12	30	0
12	Proline	50	DMSO	45	12	10	0
13	Pyrrolidine	50	DMSO	110	24	40	0

NMR tubes reactions except for 10

It was expected that the aldehyde-bearing diene would be less active towards Diels-Alder cycloaddition compared to alcohol **1.116**. As predicted, alcohol **1.116** sucesfully generated the tricycle **1.119** via subsequent lactonization. However, in almost all cases studied, the cycloaddition needed elevated temperatures (80 – 110 °C) and long reaction times to occur (Table 1.03). We were expecting that the reaction in water would increse the rate of the reaction based on the proposed hydrogen bonding and dipolar effect.[69] Using water at reflux (Entry 9 Table 1.03), it was possible to observe 65% of the adduct within 6 hours of reaction, which is consistent with this hypothesis. The addition of different Lewis acids did not

promote the cycloaddition at 25 °C in DCM (Entries 10- 12 Table 1.03).

Table 1.03. Intramolecular Diels-Alder reaction of alcohol **1.116**



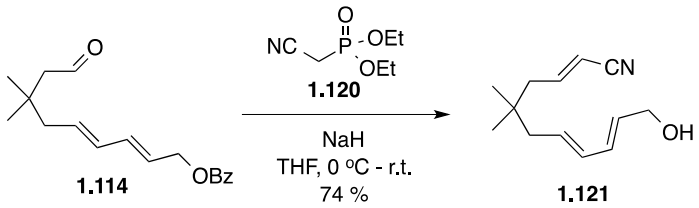
116 **119**

entry	catalyst	mol%	solvent	*T*[°C]	time[h]	SM Consumpt[%]	NMR yield [%]
1	--	--	$CDCl_3$	25	72	0	0
2	--	--	$CDCl_3$	45	48	10	0
3	--	--	DMSO	80	12	30	20
4	--	--	DMSO	110	14	100	90
5	--	--	DMSO	110	20	100	90
6	--	--	Toluene	80	12	25	20
7	--	--	Toluene	105	14	90	70
8	--	--	Toluene	105	20	100	70
9	--	--	H_2O	100	6	80	65
10	$Sc(OTf)_3$	10	DCM	25	48	20	0
11	$Y(OTf)_3$	10	DCM	25	48	10	0
12	$La(OTf)_3$	10	DCM	25	48	10	0

NMR tubes reactions except for 9 - 12

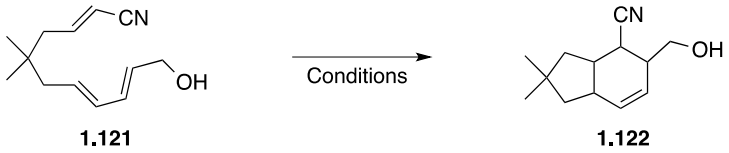
In order to avoid the secondary lactonization reaction and also to compare the reactivity of the dienophile bearing different electron-withdrawing groups, molecule **1.121** bearing a cyano group was readily accessed by a Horner-Wadsworth-Emmons reaction of aldehyde **1.114** with diethyl cyanomethylphosphonate (Scheme 1.26).

Scheme 1.26. Synthesis of substrate **1.121** for intramolecular Diels-Alder reaction



With this new substrate in hand, the intramolecular Diels-Alder reaction was attempted and the results showed similar trends as those observed with alcohol **1.116**. However, when longer reaction times were needed to observe adduct **1.122** (Table 1.04). The obtained results were expected, since the cyano group in molecule **1.104** has less electron-withdrawing character than the methyl ester in alcohol **1.116**.

Table 1.04. Intramolecular Diels-Alder reaction with substrate **1.121**

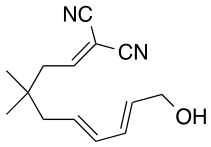


entry	solvent	*T*[°C]	time[h]	SM Consumpt[%]	NMR yield [%]
1	$CDCl_3$	25	24	0	0
2	$CDCl_3$	40	24	0	0
2	DMSO	110	3	40	25
2	DMSO	110	48	100	80
2	Toluene	105	3	30	10
2	Toluene	105	48	60	40

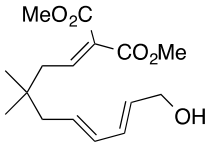
NMR tubes reactions

With the intention of obtaining a more electron-poor dienophile, the synthesis of molecules **1.123** and **1.124** bearing two electron-withdrawing groups was attempted through Knoevenagel condensation. This process proved to be

challenging for this system, the reactions usually yielded only traces of the desired products and decomposition products.



1.123



1.124

Figure 1.08. Attempted Knoevenagel condensation products

These observations set an important precedent for the development of this project. The results obtained were consistent with the predicted reactivity of the substrates. When an electron-withdrawing substituent is conjugated to the diene, lower reactivity is observed. Alternatively, when an electron-donating substituent is used in the same position, the formation of the desired adduct was obtained as shown (Tables 1.02, 1.03 and 1.04). Moreover, these results show the potential usefulness of the model system designed for future investigations in the area of the Lewis base-catalysis and Lewis-acid mediated reactions.

1.5.2 Future directions

For future directions, one proposed route to circumvent the challenges associated with the formation of the boron-containing diene is the possibility of using another Lewis acid to mediate the reaction. Hydroalumination could provide a solution to this long-standing problem in our investigation. Aluminum, being a Group 13 element just like boron, has the possibility to accept electrons in its empty p orbital. Hydroalumination of alkynes has been studied and there are known methods to access organoaluminum compounds.[70].

Chapter 2. Efforts towards the potassium-hydride-free activation of anionic Oxy-Cope rearrangements

[3,3]-Sigmatropic rearrangements, illustrated by the Claisen [71] and the Cope [72] rearrangement, have been widely utilized in the simultaneous construction of multiple stereogenic centers due to their predictable reaction path. By using these methodologies, C-C bond formation can be accomplished between relatively unreactive and sterically congested carbon centers.

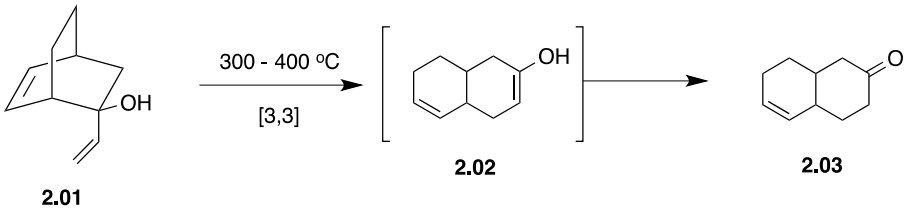
After the seminal publication in early 1940's by Cope and Hardy[72], the Cope rearrangement has evolved into a broad array of transformations that allow the access to useful scaffolds.[73,74] Among them, the anionic oxy-Cope rearrangement has become an especially powerful tool in organic synthesis, due to the mild conditions in which the rearrangements can be carried out and the predictable stereochemical outcome originating from a chair-like transition state.

Acceleration in the anionic oxy-Cope rearrangement rates has been accomplished by the use of a combination of strong bases such as KH and ionophores such as 18-crown-6. The use of organic bases to promote the acceleration of the anionic oxy-Cope rearrangement represents a great area of opportunity for new investigations.

2.1 Anionic oxy-Cope rearrangement

The first [3,3]-sigmatropic rearrangement of 1,5-diene-3-ols such as **2.01** was described by Berson *et al*.[75] In this seminal publication, they postulated that the tautomerization of enol **2.02** to δ,ε-unsaturated ketone **2.03** is the driving force for the rearrangement, making it an irreversible transformation. Nonetheless, extremely high temperature ranging between 300 and 400 ^{o}C was needed to achieve the desired rearrangement (Scheme 2.01).

Scheme 2.01. First Oxy-Cope rearrangement by Berson and co-workers.

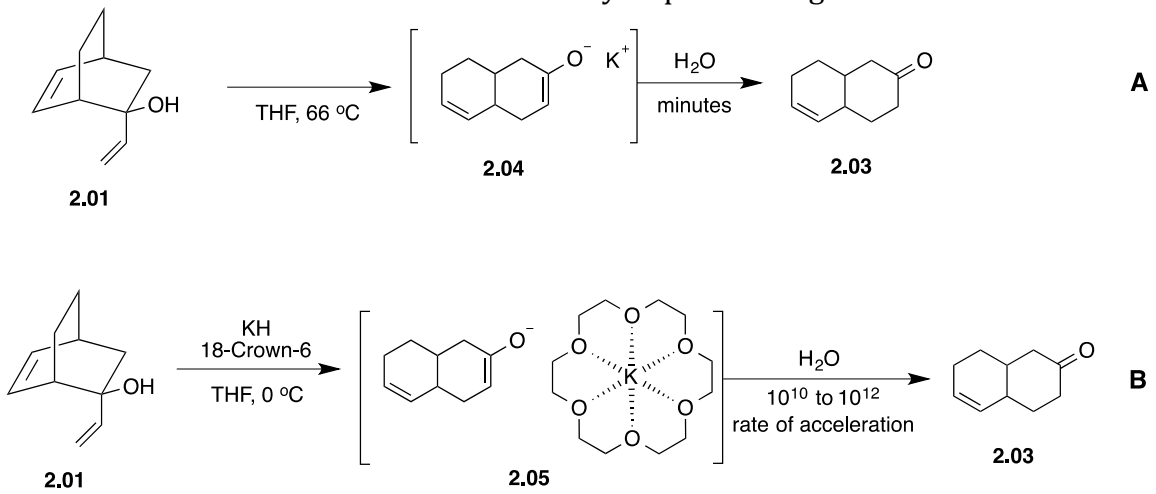


2.01 **2.02** **2.03**

A significant improvement to this methodology came in 1975, when Evans and collaborators found that the deprotonation of the alcohol in oxy-Cope substrates with different metal hydrides can accelerate the rearrangement to a great extent.[76] It was found that the rearrangement of **2.01** to **2.03** could be achieved in the presence of 1.1 eq of KH in refluxing THF (66 °C) within minutes in practically quantitative yields after aqueous quenching (Equation **A** in Scheme 2.02).

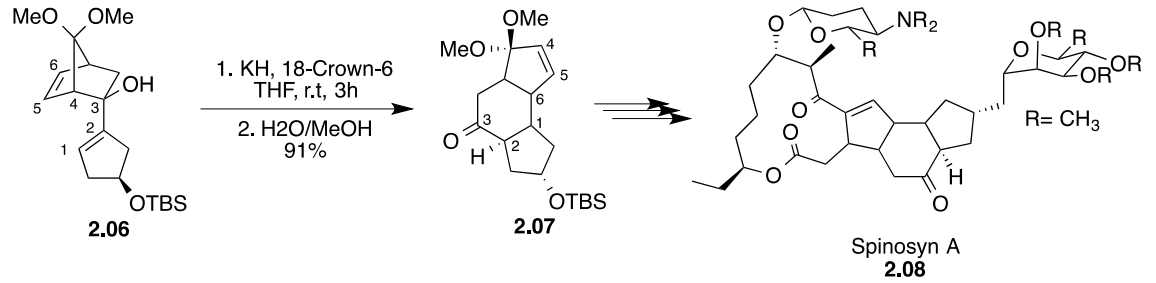
More importantly, in the same series of investigations they realized that the addition of ionophores induces localization of the negative charge on the oxy-substituent; as a result, the rearrangement proceeds at higher rates. This was proved by the additional 10^{10} to 10^{12} rate acceleration observed when the rearrangement of **2.01** to **2.03** was carried on in THF at 0 °C, in the presence of 1.1 eq of KH and 1 eq of 18-Crown-6 (Equation **B** Scheme 2.02).[76]

Scheme 2.02. Acceleration of the anionic oxy-Cope rearrangement



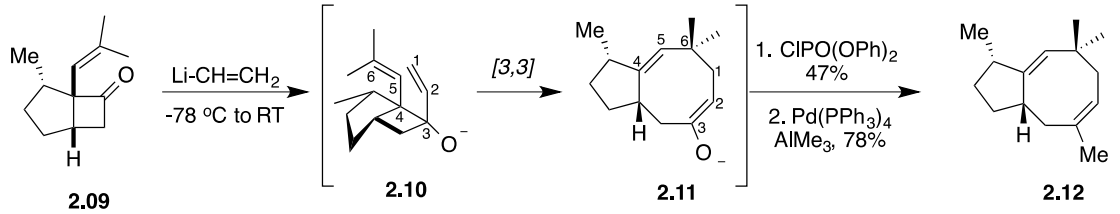
The mild reaction conditions and the relatively easy access to substrates, through 1,2-addition of vinyl organometallic reagents to the necessary β,γ-unsaturated carbonyl groups, make the anionic oxy-Cope rearrangement an attractive method in the synthesis of complex molecules. One example is the enantioselective synthesis of spinosyn A **2.08** by Paquette and collaborators[77]. A highly stereocontrolled anionic oxy-Cope rearrangement of molecule **2.06** gave access to the key tricyclic intermediate **2.07**, which eventually led to spinosyn A **2.08** (Scheme 2.03)**.**

Scheme 2.03. Anionic oxy-Cope rearrangement in the total synthesis of spinosyn A



Oxy-Cope rearrangements can also be used to constructing medium size rings. Moore and co-workers accomplished the total synthesis of (±)-precapnelladiene **2.12** by using a low temperature anion-accelerated oxy-Cope rearrangement as a key step. The 1,2-addition of vinyllithium to the carbonyl group of dialkyl squarate-derived bicycloheptenone **2.09** initiates a low temperature anion-accelerated oxy-Cope rearrangement to afford the key intermediate **2.11,** which after further transformations yields the desired natural product (±)-precapnelladiene **2.12** (Scheme 2.04).[78]

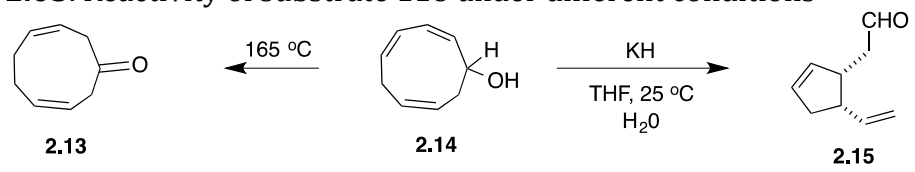
Scheme 2.04. Anionic-accelerated oxy-Cope rearrangement in the synthesis of (±)-precapnelladiene **2.12**



In the example presented above, the alkoxylate intermediate **2.10** is analogous to the classic KH-deprotonated intermediates used to accelerate the rearrangement. This represents an example of the KH-free activation of the oxy-Cope rearrangement.

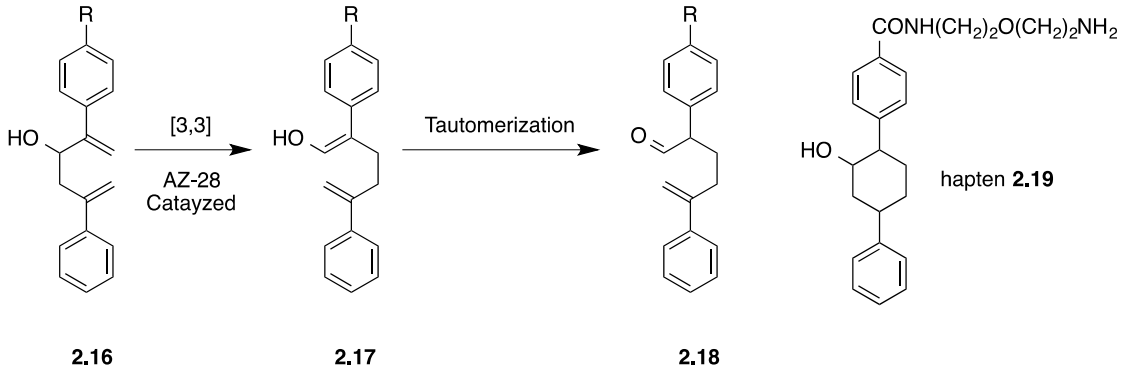
Besides the advantages that the KH-activation offers, such as lower operational temperatures and therefore fewer undesired side products, another important observation was made when substrate **2.14** was exposed to thermal or hydride conditions. Thermal activation of **2.14** resulted exclusively in an [1,5]-hydrogen migration to yield **2.13**. On the other hand, when the same substrate was treated with KH at room temperature, only the formation of aldehyde **2.15** was observed (Scheme 2.05).[79] Access to **2.15** is important as it serves as a common precursor to all the primary prostaglandins.[80] This study demonstrates that the activation obtained by generating an oxyanionic species has a great impact on the reactivity of the substrate towards the oxy-Cope rearrangement.[81].

Scheme 2.05. Reactivity of substrate 118 under different conditions



An exhaustive literature review shows that the only catalytic method known for the oxy-Cope rearrangement utilizes antibodies such as AZ-28 generated against hapten **2.19** to catalyze the rearrangement of allylic alcohol **2.16** to enol **2.17** (Scheme 2.06).[82] This increased the rate of the reaction by two orders of magnitude from 10^3 to 10^5 (K_{cat}/K_{uncat}).[83] However, this method does not represent a practical tool for the acceleration of the the oxy-Cope rearrangement in a catalytic manner.

Scheme 2.06. Antibody catalyzed oxy-Cope rearrangement.



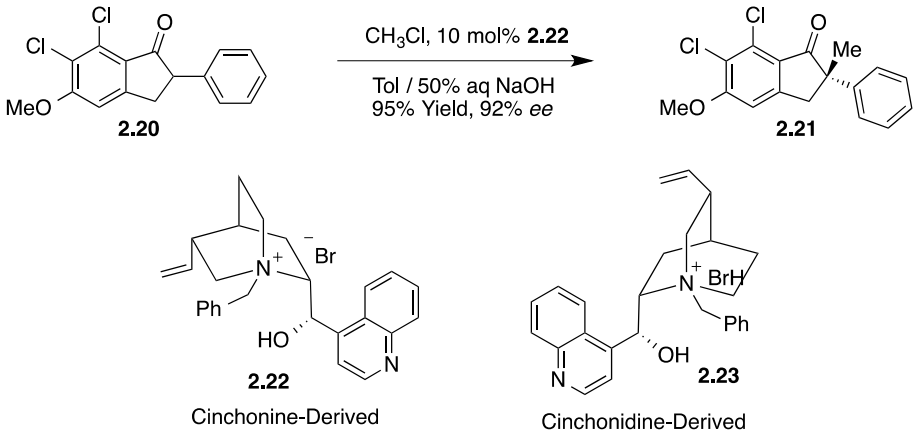
As shown in the above examples, different reaction conditions can drastically influence the rate and the outcome of the oxy-Cope rearrangement. One important trend observed by many research groups[84] states that the more ionic or "naked" the negative charge on the oxygen atom is, the greater the acceleration observed for the rearrangement.[81] This observation serves as the basis for our search for a greener, safer, and catalytic hydride-free method for the acceleration of the anionic oxy-Cope rearrangement.

2.2 Phase Transfer Catalysis

Ion-pair-mediated reactions have been increasingly useful and explored extensively in organic chemistry since their introduction.[85] Phase transfer catalysis (PTC) occupies a special place in this area of research. The use of chiral onium salts and crown ethers as effective phase transfer catalysts has been thoroughly tested for the enantioselective carbon-carbon or carbon-heteroatom bond formation under mild biphasic conditions.[84] In general terms, phase transfer catalysts (PTC's) are chemical agents that facilitate the transfer of a reactant from reaction phase A where it is soluble, to reaction phase B where in its usual state, it would not be soluble. This allows the transported molecule to be exposed to other reacting partners in phase B, thus permitting heterogeneous reactions to occur at an accelerated rate. PTC offers certain advantages over homogenous catalysis: 1) increased reactivity due to greater charge separation, 2) usually more selective than homogenous reactions due to controlled delivery of the reagent into the substrate containing phase, 3) reaction conditions usually compatible with a wide variety of water-immiscible organic solvents, 4) the biphasic nature of the process greatly simplifies the isolation of products and 5) the most commonly used catalysts such as quaternary ammonium salts are generally inexpensive and biodegradable.[86]

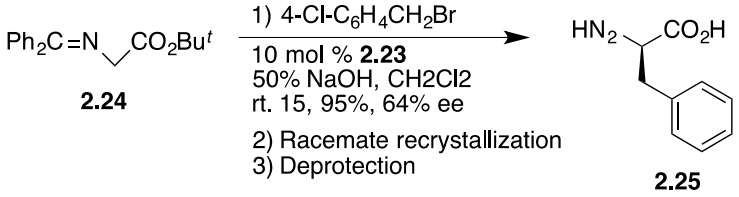
The synthesis of optically active α-amino acid derivatives represents the most successful use of PTC to date.[87] The transformation is effected using Cinchona alkaloids-derived ammonium salts first proposed by the research team at Merck & Co. Derivatives of cinchonine **2.22** and cinchonidine **2,23** were used as chiral phase transfer cataylsts for the highly enantioselective alkylation of indanone **2.20** (Scheme 2.07).[87,88]

Scheme 2.07. First report of the use of cinchona alkaloids as PTC's



In 1989, O'Donnell and collaborators reported the use of **2.23** in the enantioselective alkylation of the acylic glycine-derived substrate **2.24** obtaining moderate *ee* of 66% that could be increased up to 99% after recrystallization (Scheme 2.08). [87,89] Substrate **2.24** has since then become the staple substrate in future investigations of amino acid alkylation using PTC.

Scheme 2.08. First catalytic enantioselective alkylation of an acyclic substrate



The general PTC mechanism of the enantioselective alkylation of amino acids, specifically the glicinate Schiff base **2.24** is shown in figure 2.01. The first step is the interfacial deprotonation of the α-proton of **2.24** with base (MOH) to generate the corresponding metal enolate **2.26**, which stays at the interface of the two layers. Subsequent ion-exchange of the anion with the catalyst ($\mathbf{Q}^{*+}X^-$) generates a lipophilic chiral onium enolate **2.27**. At this point, enolate **2.27** can be transported into the organic phase, where it reacts with an alkyl halide to afford the optically active monoalkylated product **2.28**. This type of reaction is successful only if the chiral onium cation ($\mathbf{Q}^{*+}$) leads to a highly reactive chiral onium enolate **2.27** by fast ion–exchange and effective shielding of one of the two enantiotopic faces of the

enolate anion. Failure of the fast ion-exchange would lead to formation of racemic **2.28** product.[84]

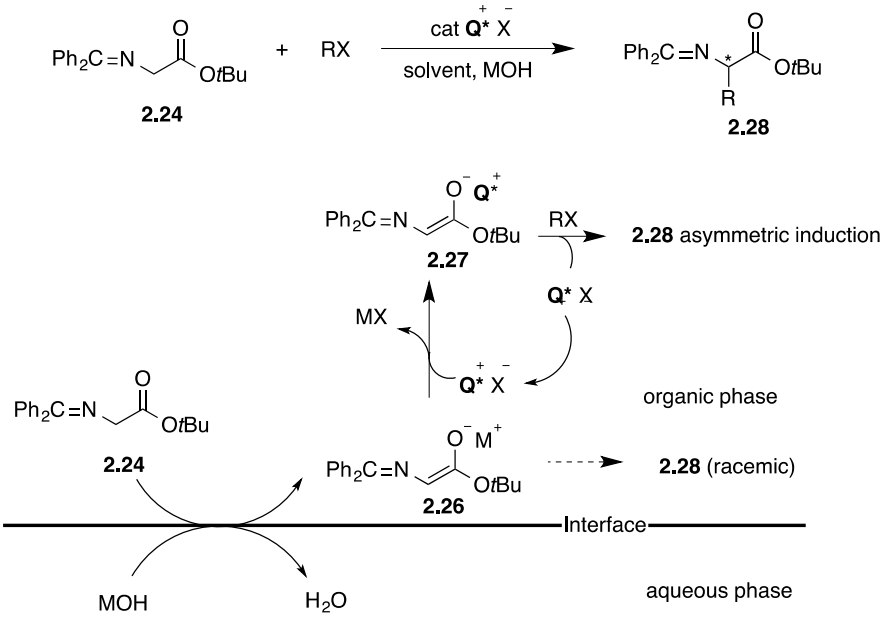


Figure 2.01 General PTC mechanism in optically active α-amino acid derivatives

An important issue to consider in this mechanism is the use of strongly basic conditions, which could lead to decomposition of the catalysts or substrates. Side reactions such as hydrolysis, racemization and dialkylation of the substrates are commonly encountered problems in this methodology. However, by tuning variables such as base, solvents, temperature, substrate concentration and stirring rates, it is possible to minimize the occurrence of the mentioned undesired reactions. Another important variable that can be tuned is the catalyst design, this has a direct effect on the ion-exchange rates and as consequence on enantioselectivities. Due to this observation, the structural design of PTC's has gained a lot of attention.

The O'Donnell group dominated the PTC area for almost a decade, in that time significant improvement in the enantioselectivity by the O-alkylaion of the cinchona quaternary ammonium salt derivatives **2.22** and **2.23** was disclosed. By the use of

these new **2.29** and **2.30** cinchona PTC's, it was possible to obtain enantiomeric excess of up to 81% (Figure 2.02). [90]

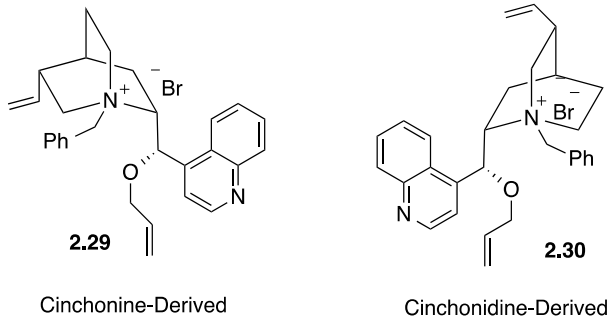


Figure 2.02. Second generation Cinchona-based PTC's

Inspired by the findings of the O'Donnell group, a third generation of cinchona-based PTC's where proposed by Lygo[91] and Corey[85] simultaneously in 1997. This third generation catalysts contain the *N*-9-anthracenylmethyl group with either a free OH as in **2.31** and **2.32**, or an *O*-allyl group as in **2.33** and **2.34**. It was found that **2.32** yielded slightly higher enantioselectivities. Corey et al rationalized that the reason of the improvement in eantioselectvities was based on the structure of the key ion pair between the enolate and the catalyst as seen in **2.27** figure 2.01.[85]

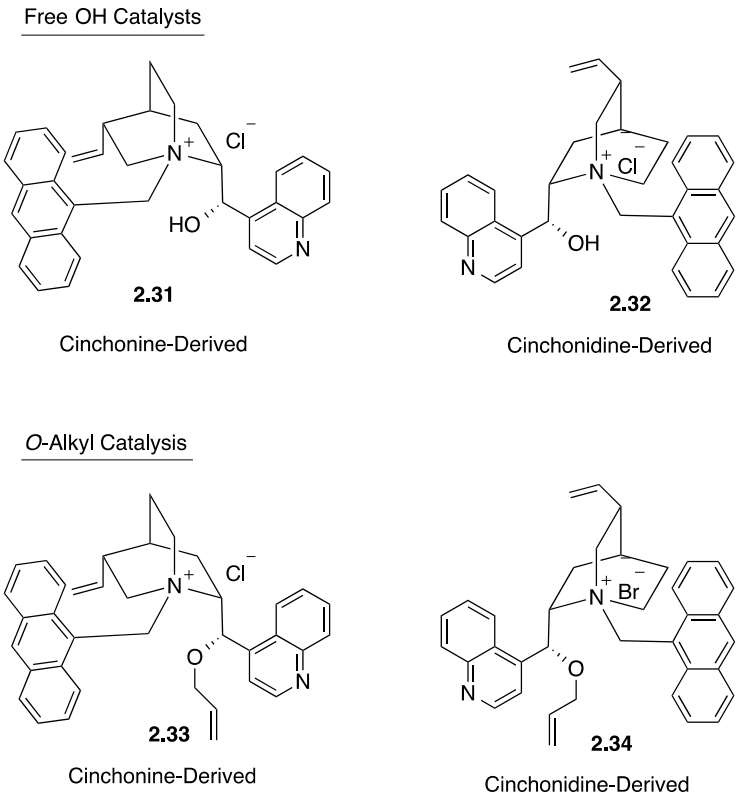


Figure 2.03. Third generation Cinchona-based phase transfer catalysts

Greater efficiency in the enantioselective alkylation of amino acids was desired. Motivated by that, Jew[92] and Park[93] groups developed dimeric Cinchona-based catalysts linked with an aromatic linker , which conferred interesting reactivity towards a wide range alkyl halides electrophiles in alkylation reactions. Catalyst **2.35** gave both excellent yields (81-94%) and enantioselectivities (97 - >99% *ee*). In a similar way, Najera reported the dimeric catalyst **2.36**, which performed comparably to **2.35** (Figure 2.04).

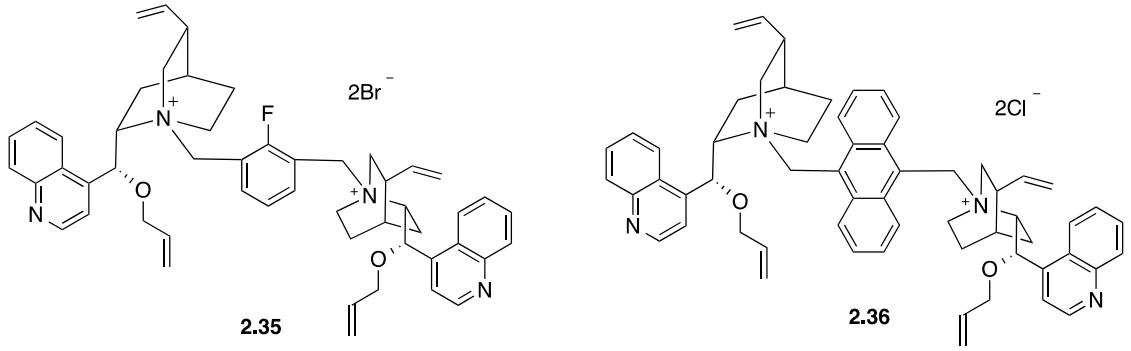


Figure 2.04. Other modifications to Cinchona-based catalysts

Non-Chincona based catalysts have been also explored with success. Maruoka developed several structurally rigid C_2-symmetric, chiral spiro ammonium salts such as **2.37** derived from optically pure naphtol derivatives.[84] On the other hand, Shibasaki reported a series of molecules analogous to **2.38**, which found use not only in alkylation chemistry but also in Michael additions.[94] Takabe and collaborators developed a series of C_3-symmetric amine-based catalysts exemplified by **2.39** (Figure 2.05). [87,95]

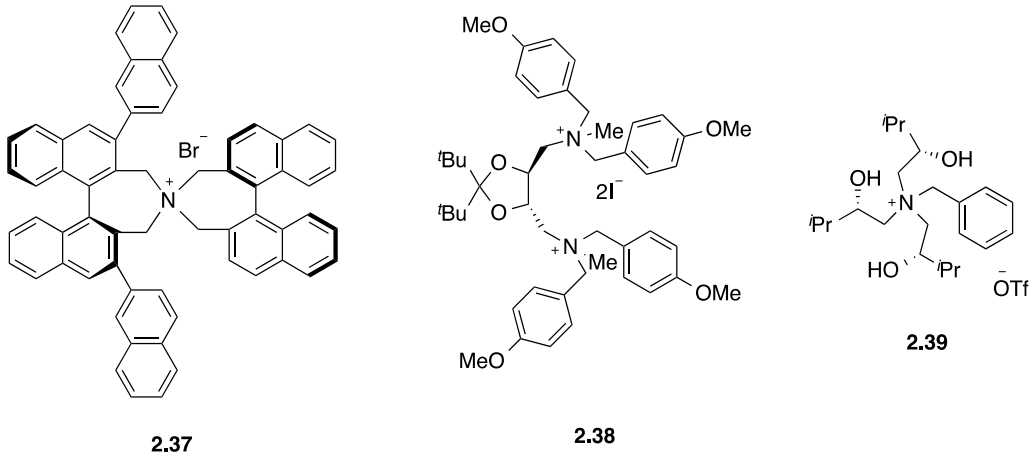


Figure 2.05. Other phase transfer catalysts

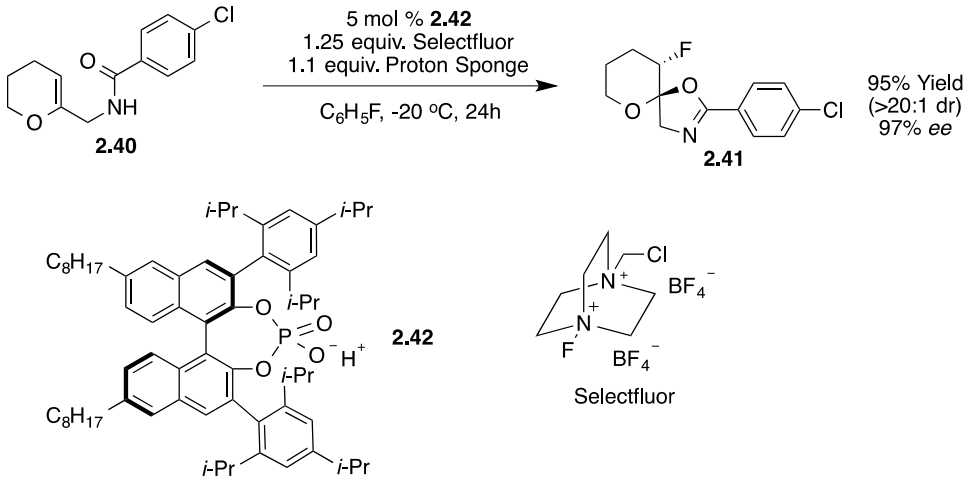
Other chemical processes such as the aldol reaction, cyclopropanation and epoxidation, have also been examined using this type of catalysis. However, despite

the efforts, no attempt has been as successful as the enantioselective functionalization of glycinate Schiff base **2.24**.

It is important to notice that the type of PTC described thus far uses chiral cations as counterion to orchestrate the activation and selectivity of a given reaction. However, the use of chiral anions to induce asymmetry in catalytic reactions has also been studied under both PTC and non-PTC conditions.

In the area of anionic PTC; Toste recently described an asymmetric electrophilic fluorination using a phosphate-based chiral anionic catalyst **2.42** in combination with Selectfluor. Substrates similar to **2.40** were successfully fluorinated in good yields (67-95%) and excellent enantio- and diastereomeric ratios (79-97% *ee*, >20:1 dr) to give **2.41** (Scheme 2.09).[96]

Scheme 2.09. Anionic Phase-transfer catalyst in asymmetric electrophilic fluorination

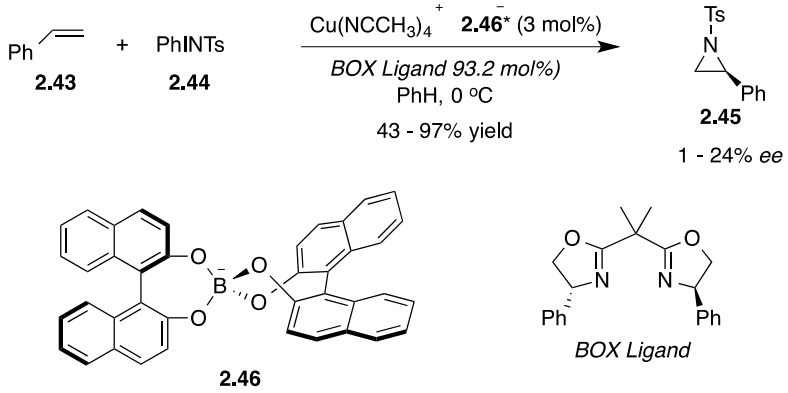


2.3 Chiral counter-anion mediated transformations

In 2000, Arndtsen introduced the use of chiral anions in the arena of cationic transition metal catalysis. In this initial report, they explained the importance of ion-pairing in copper-catalyzed olefin aziridination. The combination of cationic

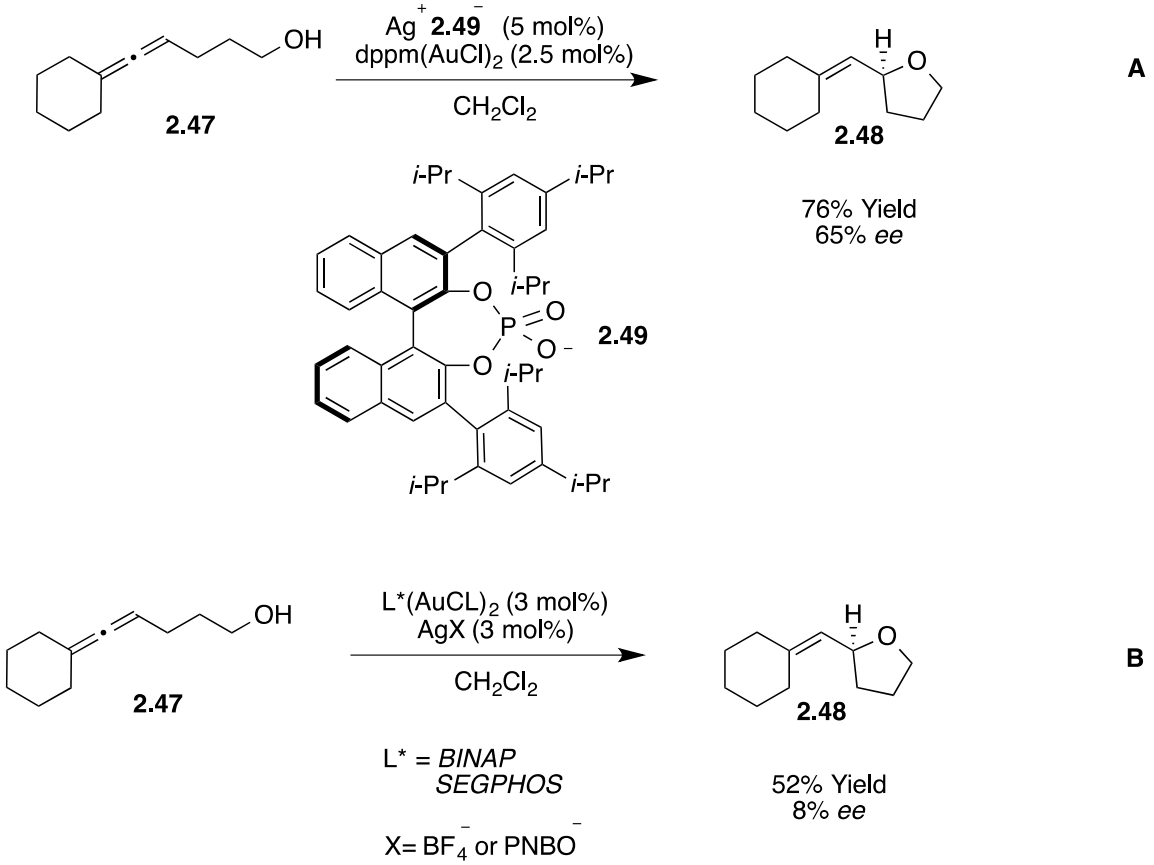
$Cu(NCCH_3)_4^+$ and the chiral borate counterion **2.46** led to the formation of aziridines such as **2.45** from styrene **2.43** and N-tosyliminobenzyliodinane (PhINT) **2.44** in moderate to good yield and low *ee*. Nonetheless, this was the first proof of concept for chiral counter anion induced enantioselectivity (Scheme 2.10).[97]

Scheme 2.10. Chiral counter anion induced enantioselectivity



In 2007, Toste *et al.* contrasted the gold-catalyzed allene heterocyclizations under simple chiral ligand or chiral counter anion conditions. The results showed that the use of a chiral counter ion granted greater enantioselectivity. Alcohol **2.47** was converted into furan derivative **2.48** in 76% yield and 65% *ee* when using the chiral phosphate-based catalyst **2.49** (Equation **A** in Scheme 2.11), in contrast to the 52% yield and low 8% *ee* obtained when a combination of chiral ligand BINAP or SEGPHOS and gold centered catalyst was used (Equation **B** in Scheme 2.11).[98]

Scheme 2.11. Chiral counter anion in the Cu-catalyzed allene heterocyclization



As demonstrated through this compilation of literature examples, counterion-based catalysis is a rapidly growing area in organic chemistry. It offers interesting advantages over homogenous catalysis and exhibits great potential applicabilities that require further exploration.

2.4 Purpose of this investigation

Given the previous success of PTC conditions using quaternary ammonium salts in the alkylation of amino acids, we propose that a similar strategy could be employed in the catalysis of oxy-Cope rearrangements. We hypothesize that an interfacial PTC mechanism could be invoked to catalyze the anionic oxy-Cope rearrangement (Figure 2.06). We postulated that an interfacial deprotonation of substrate **2.50** would lead to the formation of the metal-oxy-anion ion pair **2.51**. At

this point an ion exchange could take place forming the ion pair **2.52**. In theory, a greater radius of the cation makes ion pairing difficult, which directly results in a greater localization of the negative charge on the oxy-anion and thus activating the substrate towards the desired rearrangement product **2.53**.

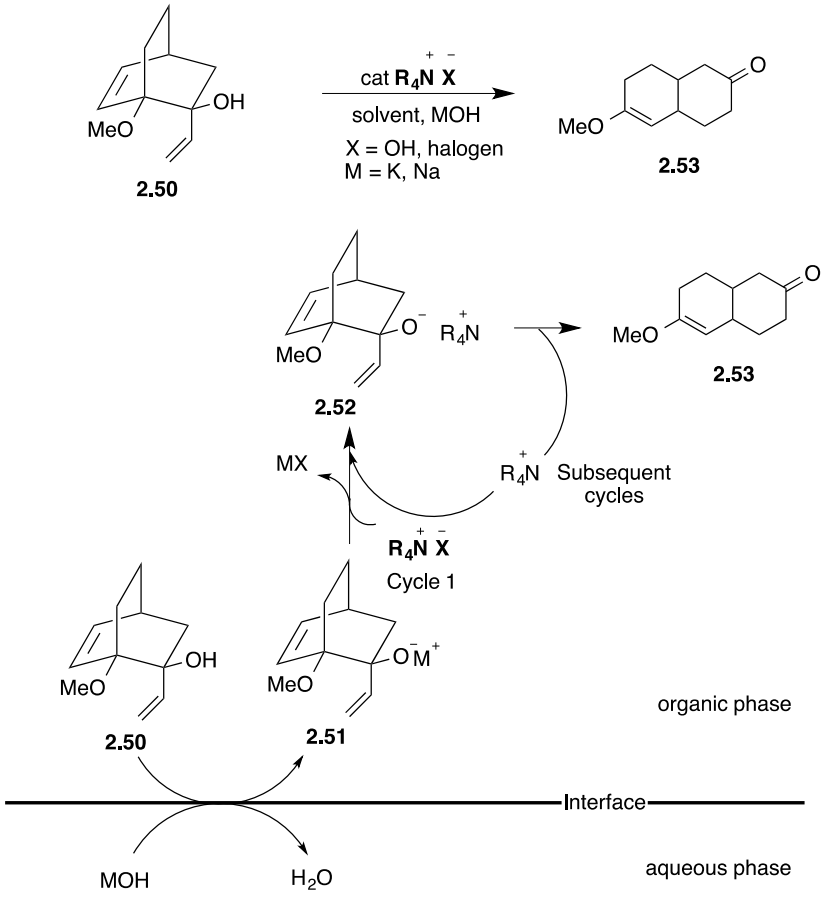


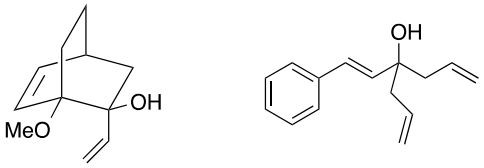
Figure 2.06. Proposed mechanism for catalysis of the oxy-Cope rearrangement

We proposed that the catalytic cycle of the tetralkylammoium species could be achieved by the regeneration of the onium species after the anionic oxy-Cope rearrangement had taken place, reentering to the catalytic cycle by cation exchange with the metal-oxy-anion ion pair **2.51.** Theoretically, this strategy would not only allow us to induce acceleration to the oxy-Cope rearrangement but also the induction of stereoselectivity by the use of chiral Cinchona alkaloid-based PTC's.

An important aspect to consider in the proposed idea is the avoidance of pyrophoric hydride bases such as KH, by using an inexpensive and biodegradable organic molecule to effect rate acceleration od the anionic oxy-cope rearrangement.

2.5 Results discussion

Substrate **2.50** and substrate **2.54** were chosen to be the starting point of this investigation. The rigid structure of substrate **2.50** provides an intrinsic activation towards the oxy-Cope rearrangement.[76] While expected to be less reactive, the use of substrate **2.54** would allow us to test the potential stereochemical induction of the chiral Chincona-based PTC's (Figure 2.07).

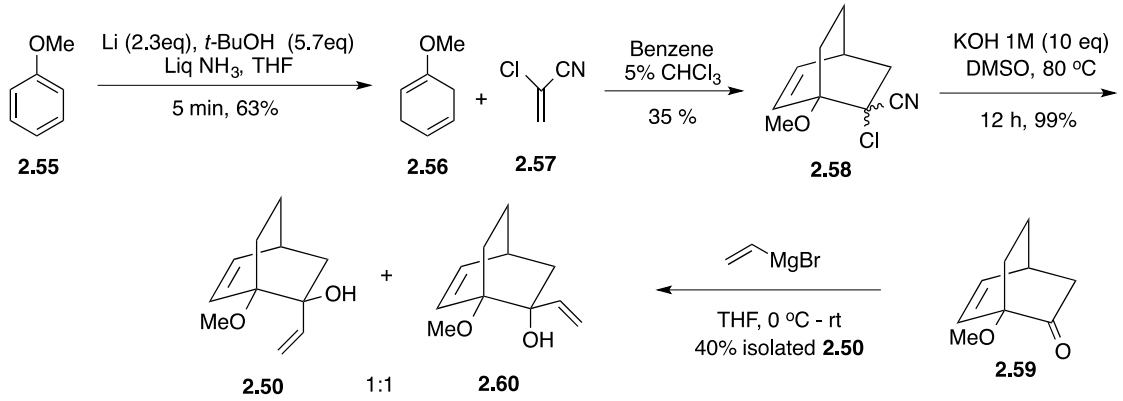


2.50 **2.54**

Figure 2.07. Substrates for anionic oxy-Cope rearrangement investigation

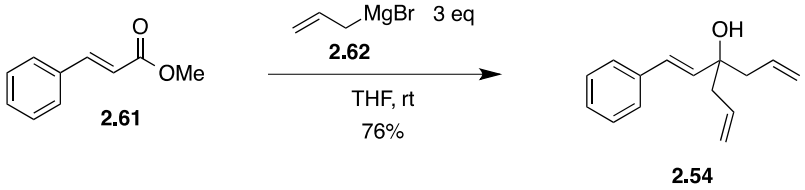
The synthesis of substrate **2.50** began with the Birch reduction of anisole **2.55** yielding 1-methoxy-1,4-cyclohexadiene **2.56.**[99] Treatment of **2.56** with 5% $CHCl_3$ generates *in situ* the corresponding 1,2-diene required for the subsequent Diels-Alder reaction with 2-chloroacrilonitrile **2.57** producing the bicyclic adduct **2.58** in 35% yield.[100] Hydrolysis of **2.58** with 10 eq of a 50% aqueous solution of KOH allowed access to ketone **2.59** in 99% yield.[101] Treatment of **2.59** with vinylmagnesium bromide afforded a separable mixture of the two stereoisomers **2.50** and **2.60** in a 1:1 ratio, giving a 40% isolated yield of **2.50** (Scheme 2.12).[76]

Scheme 2.12. Synthesis of substrate **2.50**



The synthesis of substrate **2.54** was achieved in one step by a Grignard reaction between the commercially available methyl cinnamate **2.61** and 3 eq of allylmagnesium bromide in 76% yield (Scheme 2.13).

Scheme 2.13. Synthesis of substrate **2.54**



With the two model substrates in hand, we began screening for conditions to accelerate the oxy-Cope rearrangement. It is known that the thermal induction of the oxy-Cope rearrangement for substrate **2.50** was above 200 °C as reported by Berson and collaborators.[75] This served as a benchmark temperature for our experiments.

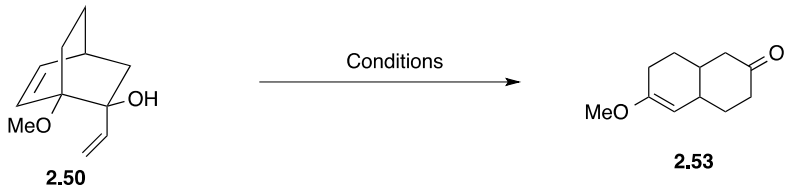
We first attempted to reproduce Evans' reported KH/18-crown-6 conditions for substrate **2.50**.[76] After several trials, no rearrangement was observed by NMR analysis at RT using stoichiometric KH and catalytic amounts of 18-crown-6 (Entries 1 and 2, Table 2.01). Longer reaction times and stoichiometric amounts of 18-crown-6 proved to be unfruitful for the promotion of the rearrangement of

substrate **2.50** as well (Entries 3 and 4, Table 2.01). To avoid moisture contamination leading to quenching of the hydride, rigorous anhydrous conditions were used to set up this series of experiments. Reactions were set up in an evacuated glove-box, utilizing a freshly opened bottle of KH and freshly distilled 18-Crown-6 and internal standard were used. However, the same results were obtained (Entry 5, Table 2.01). Higher KH/18-crown-6 loading or higher temperature was needed to observe any sign of rearrangement by NMR analysis. When a combination of 2 eq of KH and 1 eq of 18-Crown-6 was used, the rearrangement product **2.53** could be obtained in >95% NMR yield at RT after 10h (Entry 6, Table 2.01). On the other hand, the reaction can be completed with 1 eq of KH at refluxing temperature in THF after 12 h in absence of crown ether (Entry 8, Table 2.01). When NaH/15-crown-5 was employed full conversion of **2.50** was not observed after 72 h (Entry 9 and 10, Table 2.01).

After obtaining a reference point with the combination KH/18-Crown-6, we decided to try our PTC hypothesis. We began by utilizing 10 eq of a 30% aqueous solution of Bu_4NOH in a 1:1 mixture of DCM/H_2O at RT for 3 days. However, NMR of the crude did not show any traces of the desired rearrangement product **2.53** (Entry 11**,** Table 2.01). Increasing the temperature to 40 ^oC, did not offer any improvement (Entry 12, Table 2.01). We then decided to change the solvent system to one that allow us to reach higher temperatures to try promoting the rearrangement this way. Using same conditions than in entries 11 and 12 but exchanging DCM for toluene and heating to 85 ^oC showed starting material consumption by NMR but no traces of the desired product.

At that moment we rationalized the results observed, suggesting that the lack of success in the rearrangement acceleration was due to the inability of Bu_4NOH to perform deprotonation and subsequent ion-pairing. In an attempt to increase the basicity of the reaction mixture, KOH was added in addition to Bu_4NOH but the results did not vary (Entry 14, Table 2.01).

Table 2.01. Screening conditions for anionic oxy-Cope rearrangement of substrate **2.50**



2.50 **2.53**

entry	additive/cat	equiv	solvent	*T*[°C]	time[h]	SM Consumpt[%]	NMR yield [%]
1	KH 18-C-6	1 0.3	THF	rt	12	20	0
2	KH 18-C-6	1 0.5	THF	rt	12	20	0
3	KH 18-C-6	1 0.5	THF	rt	72	30	0
4	KH 18-C-6	1 1	THF	rt	12	20	0
5[a]	KH 18-C-6	1 1	THF	rt	36	15	0
6	KH 18-C-6	2 1	THF	rt	10	100	>95
7	---	---	THF	66	72	20	0
8	KH	1	THF	66	12	100	100
9	NaH 15-C-5	2 1	THF	66	72	50	20
10	NaH 15-C-5	4 1	THF	66	72	90	70
11[b]	Bu_4NOH	10	DCM/H_2O	rt	72	10	0
12[b]	Bu_4NOH	10	DCM/H_2O	40	48	10	0
13[b]	Bu_4NOH	10	Tol/H_2O	85	72	20	0
14[b]	Bu_4NOH KOH	10 10	Tol/H_2O	85	72	20	0

[a]Reaction set up in glove box, [b] 30% aqueous solution of Bu_4NOH

We hypothesized then that it was very possible that the interface deprotonation was not being performed the way we were expecting. To prove that suggestion, we moved from the PTC conditions to homogenous conditions. From reports in the literature[76,102] and by our own experience, it was known that NaH was

not the best hydride base to promote the anionic oxy-Cope rearrangement. For this reason we hypothesized that performing the rearrangement with 3 eq of NaH and 3 eq of anhydrous $BnMe_3NCl$ might initiate a cation exchange which might result in a rate acceleration compared with the results obtained with NaH/15-crown-5 combination (Entries 9 and 10, Table 2.01). Nonetheless, after 72 h at RT or after 72 h at 80 ^oC NMR analysis did not show any traces of the product **2.53** (Entries 15 and 16, Table 2.02). We decided to screen the organic anhydrous Bu_4NOH in homogeneous fashion in different solvents and temperatures (Entries 17 to 25, Table 2.02). To our delight, it was found that total consumption of starting material substrate **2.50** and >90% NMR yield of the desired rearrangement product **2.53** could be attained by the addition 4 eq of Bu_4NOH in DMSO at 80 ^oC for 12 h (Entry 25, Table 2.02). Based on these results, we decided to synthesize the cinchonium-hydroxide base **2.66** to test it in homogenous conditions.

The synthesis began by *N*-benzylation of the commercially available cinchonine **2,63** to obtain the bromide salt **2.64,** which was then treated with allyl bromide in the presence of KOH to afford the *O*-allylated salt **2.65.** Finally, cichonium-hydroxide base **2.66** was accessed by ion exchange using Ag_2O and H_2O (Scheme 2.14). Using similar conditions to the Bu4NOH promoted rearrangement, substrate **2.50** was treated with 5 eq of base **2.66** in DMSO at 80 ^oC for a period of time of 12 h. However, no rearrangement was observed (Entry 27, Table 2.02).

Scheme 2.14 Synthesis of Cinchonium-OH base

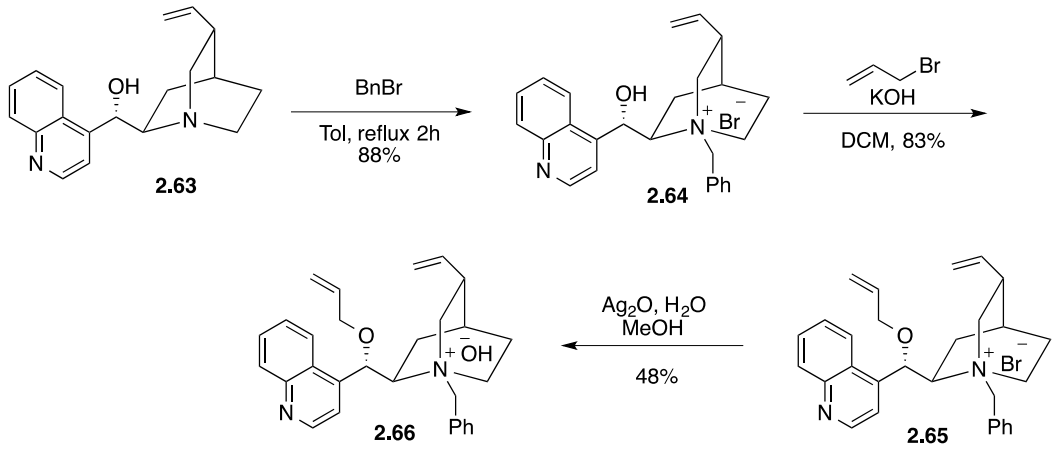
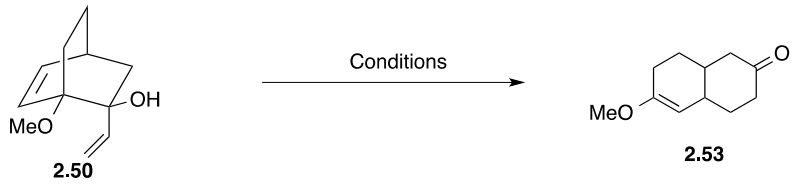


Table 2.02. Screening conditions for anionic oxy-Cope rearrangement of substrate **2.50**



2.50 **2.53**

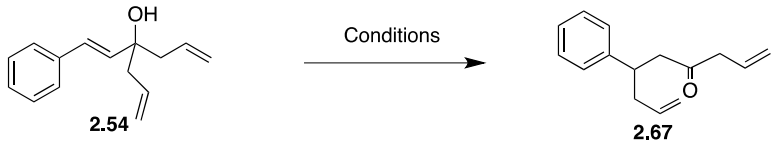
entry	additive/cat	equiv	solvent	*T*[°C]	time[h]	SM Consumpt[%]	NMR yield [%]
15[c]	$BnMe_3NCl$ NaH	3 3	THF	rt	72	>50	0
16[c]	$BnMe_3NCl$ NaH	3 3	Tol	80	72	>80	0
17[b]	Bu_4NOH	2	Benzene	30	4	10	0
18[b]	Bu_4NOH	5	Benzene	60	4	20	0
19[b]	Bu_4NOH	2	Toluene	30	4	50	30
20[b]	Bu_4NOH	5	Toluene	60	4	70	50
21[b]	Bu_4NOH	2	DMSO	rt	72	40	20
22[b]	Bu_4NOH	4	DMSO	rt	72	50	40
23[b]	Bu_4NOH	2	DMSO	60	12	80	>60
24[b]	Bu_4NOH	2	DMSO	80	12	90	>70
25[b]	Bu_4NOH	4	DMSO	80	12	100	>90
26	**2.66**	5	DMSO	rt	12	10	0
27	**2.66**	5	DMSO	80	12	30	0

[c]Anhydrous Bu_4NOHsolution used

While our attempt to use a chiral chinchona catalyst was not successful, the Bu_4NOH conditions did remove the need for pyrophoric reagents such as KH. We thus sought to examine these minder conditions on other substrates. The condition optimization process for substrate **2.54** followed a similar trend as for substrate **2.50**. We assessed the intrinsic reactivity of the substrate without any additives in a bomb flask under neat conditions and found that the rearrangement takes place at 250 °C (Entry 1, Table 2.03). With additives, the best results were obtained using

high loadings of KH and 18-crown-6 and elevated temperatures in THF (Entries 2 to 5, Table 2.03). The rate acceleration of the anionic oxy-Cope rearrangement was attempted using Bu_4NOH and Cinchonium-hydroxide **2.66** as organic bases however, we did not observe any traces of the desired rearrangement product **2.67** by NMR analysis (Entries 6 to 13, Table 2.03).

Table 2.03. Screening conditions for anionic Cope rearrangement of substrate **2.54**



entry	additive/cat	equiv	solvent	*T*[°C]	time[h]	SM Consumpt[%]	NMR yield [%]
1	---	---	---	250	16	100	80
2	KH 18-C-6	2 2	THF	rt	6	100	>90
3	KH 18-C-6	3 3	THF	rt	2	100	>90
4	---	---	THF	66	4	20	0
5	KH	4	THF	66	4	100	>90
6[a]	Bu_4NOH	2	DMSO	rt	72	60	0
7[a]	Bu_4NOH	4	DMSO	rt	72	80	0
8[a]	Bu_4NOH	2	DMSO	40	72	>80	0
9[a]	Bu_4NOH	2	DMSO	60	72	>80	0
10[a]	Bu_4NOH	4	DMSO	80	72	>80	0
11[a]	**2.66**	4	THF	66	12	50	0
12[a]	**2.66**	4	DMSO	rt	12	30	0
13[a]	**2.66**	4	DMSO	80	12	80	0

[a]Anhydrous Bu_4NOH solution used

We have showcased the first example of anionic oxy-Cope rearrangements being accelerated using tetraalkylammonium bases. Our results suggest that

tertraalkylammonium bases such as Bu_4NOH can effectively accelerate the oxy-Cope rearrangement under specific conditions and for specific substrates. However, they were not strong enough to promote the anionic oxy-Cope rearrangement at RT or with less activated substrates. The steric constrain observed in substrate **2.50** in comparison with the non-rigid structure of substrate **2,54** it is thought to be the one of the reasons of the difference in the activation of these substrates towards he oxy-Cope rearrangement.

2.6 Future directions

Given the results obtained in our investigation, it is clear that the use of organic bases such as tetraalkylammonium hydroxides specifically Bu_4NOH are able to promote acceleration in the oxy-Cope rearrangement in a substrate-dependent manner. This finding serve as an important proof of concept for future research in this area. The screening of more PTC conditions would give a better understanding of the difficulties that we have encounter.

In the arena of counterion chemistry, one interesting branch of this investigation would be the use of chiral crown ethers in combination with hydride bases such as KH. Recently, chiral crown ethers incorporating various monosaccharide units in the macrocyclic structure have found to be useful in certain asymmetric reactions, such as Michael addition, epoxidation of α,β-enones and Darzens condensation.[103,104]

References

(1) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; New York : Springer, 1999.
(2) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 1668.
(3) Berson, J. A. *Tetrahedron* **1992**, *48*, 3.
(4) Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1952**, *74*, 4223.
(5) Sarett, L. H.; Arth, G. E.; Lukes, R. M.; Beyler, R. E.; Poos, G. I.; Johns, W. F.; Constantin, J. M. *J. Am. Chem. Soc.* **1952**, *74*, 4974.
(6) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *J. Am. Chem. Soc.* **1956**, *78*, 2657.
(7) Wender, P. A.; Schaus, J. M.; White, A. W. *J. Am. Chem. Soc.* **1980**, *102*, 6157.
(8) Maimone, T. J.; Voica, A.-F.; Baran, P. S. *Angew. Chem. Int. Ed.* **2008**, *47*, 3054.
(9) Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **2001**, *82*, 4436.
(10) Inukai, T.; Kojima, T. *J. Org. Chem.* **1967**, *32*, 872.
(11) Garcia, J. I.; Martinez-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **1998**, *120*, 2415.
(12) Houk, K. N.; Strozier, R. W. *J. Am. Chem. Soc.* **1973**, *95*, 4094.
(13) Flaming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley-VCH: New York, 1977.
(14) Sauer, J. *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 211.
(15) Kishi, Y.; Aratani, M.; Fukuyama, T.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9217.
(16) Kishi, Y.; Nakatsubo, F.; Aratani, M.; Goto, T.; Inoue, S.; Kakoi, H.; Sugiura, S. *Tetrahedron Letters* **1970**, *11*, 5127.
(17) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.
(18) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.
(19) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.
(20) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.
(21) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; Matt, von, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582.
(22) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808.
(23) Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 1951.
(24) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.
(25) Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560.
(26) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.
(27) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III. *Tetrahedron Letters* **2002**, *43*, 6743.

(28) Juhl, K.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1498.
(29) Wassermann, A. *J. Chem. Soc.* **1942**, 618.
(30) Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336.
(31) Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5846.
(32) Wang, Y.; Li, H.; Wang, Y.-Q.; Liu, Y.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 6364.
(33) Singh, R. P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 2422.
(34) Gioia, C.; Hauville, A.; Bernardi, L.; Fini, F.; Ricci, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 9236.
(35) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1995**, *34*, 1059.
(36) Hewitt, F.; Holliday, A. K. *J. Chem. Soc.* **1953**, 530.
(37) Jensen, W. B. *The Lewis Acid-Base Concepts*; New York : Wiley, ©1980., 1980.
(38) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985.
(39) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412.
(40) Musher, J. I. *Angew. Chem. Int. Ed.* **1969**, *8*, 54.
(41) Gutmann, V.; Schmid, R. *Coordination Chemistry Reviews* **1974**, *12*, 263.
(42) Gutmann, V. *The Donor-Acceptor Approach to Molecular Interactions*; New York : Plenum Press, 1978.
(43) Anthony, P. J. *Iron Compounds in Organic Synthesis*; London ; San Diego : Academic Press, 1994.
(44) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534.
(45) Reichardt, C. *Solvents and Solvents Effects in Organic Chemistry*; Wiley-VCH, 2003; pp. 1–1.
(46) Stewart, R. *The Proton, Applications to Organic Chemitry*; Orlando : Academic Press, 1985.
(47) Maria, P. C.; Gal, J. F. *The Journal of Physical Chemistry* **1985**, *89*, 1296.
(48) Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774.
(49) Denmark, S. E.; Wynn, T.; Beutner, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 13405.
(50) Denmark, S. E.; Collins, W. R. *Org. Lett.* **2007**, *9*, 3801.
(51) Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428.
(52) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763.
(53) Denmark, S. E.; Heemstra, J. R. *J. Org. Chem.* **2007**, *72*, 5668.
(54) Denmark, S. E.; Chung, W.-J. *J. Org. Chem.* **2008**, *73*, 4582.
(55) Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 7800.
(56) Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 4682.
(57) Vaultier, M.; Truchet, F.; Carboni, B.; Hoffmann, R. W.; Denne, I. *Tetrahedron Letters* **1987**, *28*, 4169.
(58) Six, Y.; Lallemand, J. Y. *Tetrahedron Letters* **1999**, *40*, 1295.

(59) Lallemand, J. Y.; Six, Y.; Ricard, L. *Eur. J. Org. Chem.* **2002**, *2002*, 503.
(60) Renard, P.-Y.; Six, Y.; Lallemand, J. Y. *Tetrahedron Letters* **1997**, *38*, 6589.
(61) Batey, R. A.; Thadani, A. N.; Lough, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 450.
(62) Gao, X.; Hall, D. G. *Tetrahedron Letters* **2003**, *44*, 2231.
(63) Wang, X. *J. Chem. Soc., Chem. Commun.* **1991**, 1515.
(64) Garnier, L.; Plunian, B.; Mortier, J.; Vaultier, M. *Tetrahedron Letters* **1996**, *37*, 6699.
(65) Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127.
(66) Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, *122*, 4990.
(67) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115.
(68) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679.
(69) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2005**, *44*, 3275.
(70) UHL, W. *Coordination Chemistry Reviews* **2008**, *252*, 1540.
(71) Claisen, L. *Berichte der deutschen chemischen Gesellschaft* **1912**, *45*, 3157.
(72) Cope, A. C.; Hardy, E. M. *J. Am. Chem. Soc.* **1940**, *62*, 441.
(73) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.
(74) Ireland, R. E.; Wipf, P.; Xiang, J. N. *Journal of Organic Chemistry* **1991**, *56*, 3572.
(75) Berson, J. A.; Jones, M. *J. Am. Chem. Soc.* **1964**, *86*, 5017.
(76) Evans, D. A.; GOLOB, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765.
(77) Paquette, L. A.; Gao, Z.; Ni, Z.; Smith, G. F. *J. Am. Chem. Soc.* **1998**, *120*, 2543.
(78) MacDougall, J. M.; Santora, V. J.; Verma, S. K.; Turnbull, P.; Hernandez, C. R.; Moore, H. W. *Journal of Organic Chemistry* **1998**, *63*, 6905.
(79) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971.
(80) Paquette, L. A.; Crouse, G. D. *Tetrahedron* **1981**, *37*, 281.
(81) Paquette, L. A.; Crouse, G. D.; Sharma, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 4411.
(82) Braisted, A. C.; Schultz, P. G. *Journal of the American Chemical ...* **1994**.
(83) Black, K. A.; Leach, A. G.; Kalani, M. Y. S.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 9695.
(84) Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222.
(85) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.
(86) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518.
(87) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506.
(88) Dolling, U. H.; Davis, P.; Grabowski, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 446.
(89) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353.
(90) O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507.
(91) Lygo, B.; Wainwright, P. G. *Tetrahedron Letters* **1997**, *38*, 8595.
(92) Jew, S.-S.; Jeong, B.-S.; Yoo, M.-S.; Huh, H.; Park, H.-G. *Chem. Commun.* **2001**, 1244.
(93) Park, H.-G.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, B.-S.; Kim, M. G.; Jew, S.-S. *Tetrahedron Letters* **2003**, *44*, 3497.
(94) Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Letters* **2002**, *43*, 9539.

(95) Mase, N.; Ohno, T.; Hoshikawa, N.; Ohishi, K.; Morimoto, H.; Yoda, H.; Takabe, K. *Tetrahedron Letters* **2003**, *44*, 4073.
(96) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681.
(97) Llewellyn, D. B.; Adamson, D.; Arndtsen, B. A. *Org. Lett.* **2000**, *2*, 4165.
(98) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496.
(99) Griesbeck, A. G.; Goldfuss, B.; Leven, M.; de Kiff, A. *Tetrahedron Letters* **2013**, *54*, 2938.
(100) Madge, N. C.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1980**, 956.
(101) Hua, D. H.; Gung, W. Y.; Ostrander, R. A.; Takusagawa, F. *Journal of Organic Chemistry* **1987**, *52*, 2509.
(102) Berson, J. A.; Jones, M. *J. Am. Chem. Soc.* **1964**, *86*, 5019.
(103) BakÃ^3, ter, P. Ã.; Rapi, Z.; Keglevich, G.; Szabó, T.; Sóti, P. L.; Vígh, T.; Grűn, A.; Holczbauer, T. *Tetrahedron Letters* **2011**, *52*, 1473.
(104) Rapi, Z.; Démuth, B.; Keglevich, G.; Grűn, A.; Drahos, L.; Sóti, P. L.; Bakó, P. *Tetrahedron: Asymmetry* **2014**, *25*, 141.
(105) Wen, Y.; Liang, M.; Wang, Y.; Ren, W.; Lü, X. *Chin. J. Chem.* **2012**, *30*, 2109.

Summary and Conclusions

This thesis discussed two proposed novel methods for the catalysis of the Diels-Alder reaction and the oxy-Cope rearrangement.

Substrates for the intramolecular Diels-Alder reaction were designed. The encountered synthetic difficulties in the preparation of 1,3-dienylboronates were circumvented by the redesign and synthesis of substrates with similar reactivity such as alcohol **1.116** and aldehyde **1.117**. Results suggest that activation of the diene by electron-releasing species have a positive effect on the rate of the cycloaddition. These results serve as an important precedent for future investigation in this area, the design and synthesis of Lewis acid-containing dienes is the natural next step to this interesting investigation.

In our efforts towards the catalysis of the anionic oxy-Cope rearrangement, we have shown that even when our attempt to attain acceleration of the sigmatropic rearrangement under PTC conditions was not successful, tetraalkyammonium bases such as Bu_4NOH can effect rate acceleration of the oxy-Cope rearrangement of activated substrates; such as **2.50** under specific conditions. This example represents the first organic base mediated acceleration of the anionic oxy-Cope rearrangement. The results obtained in this investigation set an important stating point for the development of a new methodology for the catalysis of the anionic oxy-Cope rearrangement.

Chapter 3. Experimental Methods

General Procedures: Reactions were performed in flame- or oven-dried under an atmosphere of argon unless noted otherwise. Manual flash column chromatography was conducted on Silicycle 230-400 mesh silica gel using reagent grade solvents. Thin layer chromatography (TLC) was carried out on glass plates coated with 250 μm of 230-400 mesh silica gel that had been impregnated with F-254 indicator. The TLC plates were visualized with UV (254 nm) light, potassium permanganate solution or cerium ammonium molybdate solution (CAM).

Materials: Tetrahydrofuran (THF) and diethyl ether (Et_2O) were purified by distillation from sodium/benzophenone ketyl radical under an atmosphere of nitrogen. Toluene (Tol), dichloromethane (DCM), triethylamine (TEA) and diisopropylamine (DIPA) were purified by distillation from calcium hydride (CaH_2) under a dry air atmosphere. Deuterated chloroform ($CDCl_3$) was kept over 4Å molecular sieves (4Å MS). Deuterated methanol (CD_3OD), deuterated dimethylsufoxide (DMSO) and deuterated water (D_2O) were obtained in analytically pure form and stored in a dry box. All other reagents were purchased from commercial vendors and used as is.

Instrumentation. Automated flash column chromatography was conducted utilizing Combiflash® apparatus**.** Proton nuclear magnetic resonance (^{1}H-NMR) and carbon nuclear magnetic resonance (^{13}C-NMR) were obtained on Varial, 300, 400 or 500 MHz spectrometers or Bruker 400 or 500 MHz spectrometers. Chemical shifts are reported in parts per million (ppm) and are referenced to residual solvent peaks. Coupling constants are reported in Hertz (Hz). High resolution mass spectra (HR-MS) was obtained with the assistance of Dr. Alexander Wahba or Dr. Nadim Saae.

3.1 Diels-Alder Methodology

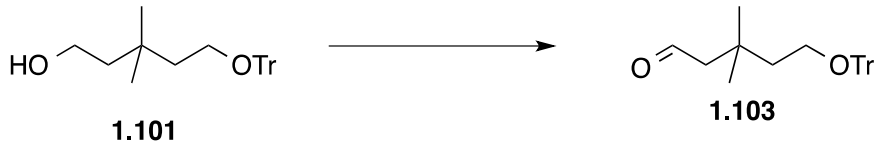
1.99 **1.100**

3,3-dimethylpentane-1,5-diol (1.100). To a solution of dimethylglutaric acid **1.99** (5.0 g, 31.2 mmol, 1 eq) in 310 mL of THF at 0 ^{o}C, a 1 M solution of borane in THF (74.9 mL, 74.9 mmol, 2.4 eq)was slowly added by syringe and the resulting mixture was stirred overnight at RT. The next morning the reaction mixture was cooled down to 0 ^{o}C and it was quenched with 100 mL of MeOH, the mixture was concentrated *in vacuo* and another 100 mL of MeOH were added and concentrated again *in vacuo*, the procedure was repeated an additional two times. The crude material was purified by automated silica gel chromatography (10 – 40% EtOAc/Hexanes over 40 min) to afford the title compound **1.100** as a transparent oil (4.1 g, 99% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.74 (t, *J* = 7.1 Hz, 4H), 2.01 (s, 2H), 1.58 (t, *J* = 7.1 Hz, 4H), 0.95 (s, 6H).

1.100 **1.101**

3,3-dimethyl-5-(trityloxy)pentan-1-ol (1.101): 3,3-dimethylpentane-1,5-diol **1.100** (3.90 g, 29.5 mmol, 1 eq), was dissolved in DCM (148 mL) at RT. To that mixture, triethylamine (6.15 mL, 44.3 mmol, 1.5 eq) was added drop wise and the reaction mixture was stirred for 10 min. After that time, Triphenylmethyl Chloride (8.23g, 29.5 mmol, 1 eq) was added in one batch followed by 4-dimethylaminopyridine (.360 g, 2.95 mmol, 0.1 eq) and the reaction mixture was stirred for 14 hours. The reaction was diluted with DCM (80 mL) and quenched with H_2O (80 mL) and $NaHCO_3$ (80 mL, sat . aqueous) and stirred for 15 min. Aqueous layers were extracted with DCM (3 X 60 mL), organic layers were combined, dried

over Na_2SO_4, filtered and concentrated *in vacuo* to yield a yellow syrup. This material was purified by silica gel chromatography (1:6 EtOAc:Hexanes) to afford the title compound **1.101** as a white solid (5.57g, 50% yield) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.49 – 7.39 (m, 6H), 7.34 – 7.27 (m, 7H), 7.25 – 7.20 (m, 2H), 3.17 (t, *J* = 6.7 Hz, 2H), 1.75 (t, *J* = 6.7 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 4H), 0.96 (d, *J* = 6.1 Hz, 6H).



1.101 **1.103**

3,3-dimethyl-5-(trityloxy)pentanal (1.103). 3,3-dimethyl-5-(trityloxy)pentan-1-ol **1.101** (4.48 g, 11.9 mmol, 1 eq) was dissolved in 120 mL of EtOAc in a 500 mL round bottomed flask. IBX (6.69 g, 23.9 mmol, 2 eq) was added in one batch and the suspension was heated up to 85 ^{o}C and stirred at that T^o for 3 h. After that time, the reaction suspension was allowed to slowly cool down and stirred overnight at RT. Next day, the white powder was filtered out trough a fritted funnel and celite. The filtrate was concentrated *in vacuo* to yield compound **1.103** as white crystals in quantitative yield. The crude was used without further purification in the next reaction. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.79 (t, *J* = 3.0 Hz, 1H), 7.46 – 7.38 (m, 7H), 7.34 – 7.24 (m, 8H), 3.16 (t, *J* = 6.8 Hz, 2H), 2.22 (d, *J* = 3.0 Hz, 2H), 1.72 (t, *J* = 6.8 Hz, 2H), 0.96 (s, 6H).

1.103 **1.105**

(*E*)-(6,6-dimethyl-8-(trityloxy)oct-3-en-1-yn-1-yl)trimethylsilane (1.105). Diphenyl(3-(trimethylsilyl)prop-2-yn-1-yl)phosphine oxide **1.104** (3.50 g, 11.2 mmol, 2 eq) and 3,3-dimethyl-5-(trityloxy)pentanal **1.103** (2.08 g, 5.60 mmol, 1 eq) were azeotroped in Tol and concentrated *in vacuo* (3 X 10 mL). After that, both reagents were exposed to HV for 2 h. After that time, the Horner reagent diphenyl(3-

(trimethylsilyl)prop-2-yn-1-yl)phosphine oxide was dissolved in 56 mL of dry THF and 3,3-dimethyl-5-(trityloxy)pentanal **1.103** was dissolved in 35 mL of dry THF as well. Both solutions were cooled down to -78 ^{o}C and stirred for 10 min. Then, a 0.63 M solution of NaHMDS in THF (17.8 mL, 11,2 mmol, 2 eq) was added dropwise to the solution of the Horner reagent diphenyl(3-(trimethylsilyl)prop-2-yn-1-yl)phosphine oxide and it was stirred at -78 ^{o}C for 30 min. To make sure that the deprotonation has taken place, the flask was taken out of the cold bath and let the reaction mixture stir at RT for 5 min and cooled down again to -78 ^{o}C and stirred for an additional 15 min. At that time, 3,3-dimethyl-5-(trityloxy)pentanal **1.103** was cannulated into the reaction mixture at -78 ^{0}C and the reaction was followed by TLC upon completion after 45 min. The reaction mixture was allowed to warm to RT, it was quenched with H_2O (50 mL) and NH_4Cl (50 mL). Aqueous layers were extracted with EtOAc (3 × 100 ml) and the combined organic extracts were washed with brine (2 × 150 ml), dried over Na_2SO_4 filtered and concentrated *in vacuo*, after purification by automated silica gel chromatography (0 – 15% EtOAc/Hexanes over 35 min) to afford the title compound **1.105** as a yellow oil (0.89 g, 34% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.39 (m, 6H), 7.34 – 7.25 (m, 5H), 7.27 – 7.14 (m, 4H), 6.16 (dt, *J* = 15.8, 7.8 Hz, 1H), 5.38 (dd, *J* = 15.8, 1.5 Hz, 1H), 3.09 (t, *J* = 7.3 Hz, 2H), 1.89 (dd, *J* = 7.8, 1.5 Hz, 2H), 1.58 (t, *J* = 7.3 Hz, 2H), 0.79 (s, 6H), 0.18 (d, *J* = 8.4 Hz, 9H).

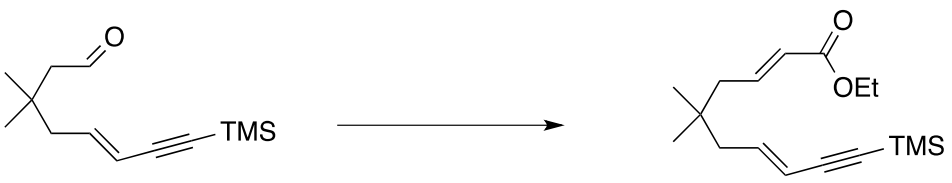
1.105 **1.106**

(*E*)-3,3-dimethyl-8-(trimethylsilyl)oct-5-en-7-yn-1-ol (1.106). (*E*)-(6,6-dimethyl-8-(trityloxy)oct-3-en-1-yn-1-yl)trimethylsilane **1.105** (0.89 g, 1.91 mmol, 1 eq) was dissolved in 38 mL of MeOH and 30 mL of DCM. The mixture was stirred for 10 min, at that time, PTSA-H_2O (0.108 g, 0.572 mmol, 0.3 eq) was directly added to the reaction mixture and it was followed by TLC upon completion for 4 h. The

reaction was quenched by the addition of 20 mL of $NaHCO_3$, diluted with EtOAc (30 mL) and the aqueous layers were extracted with EtOAc (50 mL X 3), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by automated silica gel chromatography (0 – 10% EtOAc/Hexanes over 15 min) to afford the title compound **1.106** as a transparent oil in quantitative yield. 1H NMR (400 MHz, Chloroform-d) δ 6.22 (dt, J = 15.7, 7.7 Hz, 1H), 5.50 (d, J = 15.7 Hz, 1H), 3.80 – 3.63 (m, 2H), 2.02 (dd, J = 7.7, 1.4 Hz, 2H), 1.56 – 1.47 (m, 2H), 0.92 (s, 6H), 0.19 (d, J = 5.3 Hz, 9H).

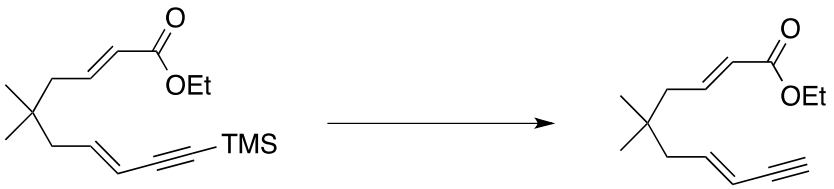
1.106 **1.107**

(*E*)-3,3-dimethyl-8-(trimethylsilyl)oct-5-en-7-ynal (1.107). (*E*)-3,3-dimethyl-8-(trimethylsilyl)oct-5-en-7-yn-1-ol **1.106** (430 mg, 1.93 mmol, 1 eq) was dissolved in 20 mL of EtOAc in a 100 mL round bottomed flask. IBX (1.07 g, 3.83 mmol, 2 eq) was added in one batch and the suspension was heated up to 85 ^oC and stirred at that T^o. The reaction was followed by TLC upon complete consumption of the starting material in around 2.5 h. After that time, the reaction suspension was allowed to slowly cool down and stirred for 3 h at RT. After that time, the white powder was filtered out trough a fritted funnel and celite. The filtrate was concentrated *in vacuo* and purified by automated silica gel chromatography (0 – 10% EtOAc/Hexanes over 20 min) to afford the title compound **1.107** as a transparent oil (33% yield). ^1H NMR (400 MHz, Chloroform-*d*) δ 9.83 (t, *J* = 2.8 Hz, 1H), 6.19 (dt, *J* = 15.9, 7.8 Hz, 1H), 5.53 (dt, *J* = 15.9, 1.5 Hz, 1H), 2.28 (d, *J* = 2.8 Hz, 2H), 2.14 (dd, *J* = 7.8, 1.4 Hz, 2H), 1.07 (s, 6H), 0.19 (d, *J* = 3.8 Hz, 9H).



1.107 **1.108**

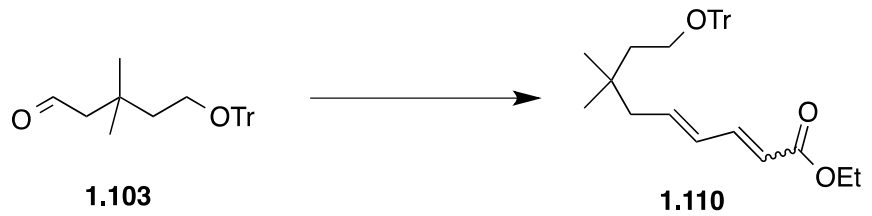
Ethyl (2*E*,7*E*)-5,5-dimethyl-10-(trimethylsilyl)deca-2,7-dien-9-ynoate (1.108). Horner-Wasdsworth-Emmons reagent trietlyl phopshopnoacetate (215 mg, 0.957 mmol, 1.5 eq) was dissolved in 9 mL of dry THF and cooled down to 0 °C and stirred at that T° for 15 min. At that point, NaH (38 mg, 0.957 mmol, 1.5 eq) was added to the solution and a change of color from yellow to red was observed. The mixture was stirred for an additional 15 min at 0 °C. At that time, a solution of (*E*)-3,3-dimethyl-8-(trimethylsilyl)oct-5-en-7-ynal **1.107** (142 mg, 0.638 mmol, 1 eq) in 7 mL of dry THF was cannulated into the reaction mixture dropwise. The reaction mixture was allowed to warm up to rt and stirred overnight. Next day, the reaction was quenched with H_2O (10 mL) and NH_4Cl (10 mL). Aqueous layers were extracted with EtOAc (3 × 20 ml) and the combined organic extracts were washed with brine (2 × 150 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by automated silica gel chromatography (0 – 10% EtOAc/Hexanes over 20 min) to afford the title compound **1.108** as a transparent oil (0.90 g, 48% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.05 – 6.87 (m, 1H), 6.20 (dt, *J* = 15.6, 7.7 Hz, 1H), 5.89 – 5.77 (m, 1H), 5.66 – 5.45 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.09 (dd, *J* = 7.9, 1.4 Hz, 2H), 2.02 (dd, *J* = 7.7, 1.4 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.92 (s, 6H), 0.19 (d, *J* = 1.5 Hz, 9H).



1.108 **1.109**

Ethyl (2*E*,7*E*)-5,5-dimethyldeca-2,7-dien-9-ynoate (1.109). A 1 M solution of TBAF in THF (769 μL, 0.769 mmol, 2.5 eq) was dissolved in 8 mL of dry THF, the

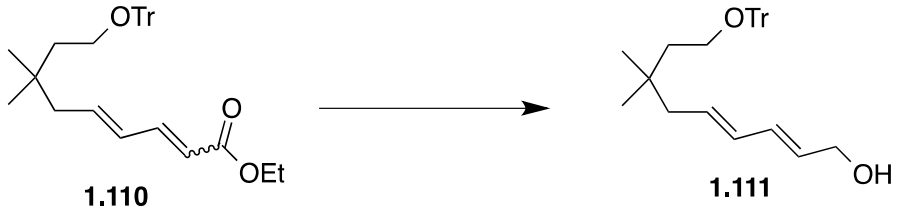
solution was cooled down to -78 °C and stirred for 20 min. At that time, a solution of ethyl (2*E*,7*E*)-5,5-dimethyl-10-(trimethylsilyl)deca-2,7-dien-9-ynoate **1.108** (90 mg, 0.308 mmol, 1 eq) in 5 mL of THF was cannulated into the reaction flask dropwise. The reaction mixture was stirred at -78 °C while being monitored by TLC upon complete consumption of the starting material. After 3 h, the reaction mixture was allowed to warm up to RT and quenched with NH_4Cl (10 mL). Aqueous layers were extracted with EtOAc (3 × 15 ml) and the combined organic extracts were washed with brine (1 × 20 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by automated silica gel chromatography (0 – 10% EtOAc/Hexanes over 15 min) to afford the title compound **92** as a transparent oil (0.60 g, 88% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.07 – 6.84 (m, 1H), 6.24 (dt, *J* = 15.8, 7.8 Hz, 1H), 5.82 (dd, *J* = 15.5, 1.4 Hz, 1H), 5.64 – 5.37 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.81 (s, 1H), 2.09 (dd, *J* = 8.0, 1.4 Hz, 2H), 2.06 – 1.99 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.94 (d, *J* = 9.0 Hz, 6H).



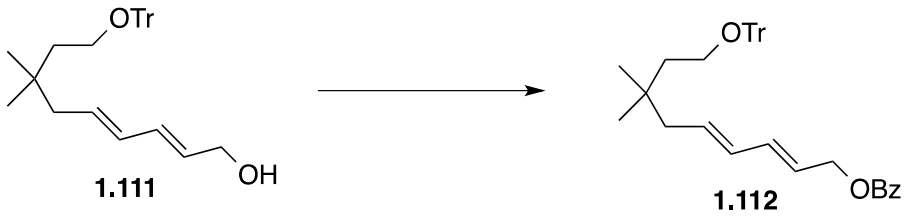
1.103 **1.110**

Ethyl (4*E*)-7,7-dimethyl-9-(trityloxy)nona-2,4-dienoate (1.110). Commercially available triethyl 4-phosphonocrotonate (3.75 mL, 16.9 mmol, 1.3 eq) was dissolved in 169 mL of THF and cooled down to 0 °C and stirred for 10 min, at that time NaH (0.677 g, 16.9 mmol, 1.3 eq) was added in one batch to the solution and it was stirred at 0 °C for 25 min, a light change in color was observed, from pale yellow to dark yellow. After that time, a solution of 3,3-dimethyl-5-(trityloxy)pentanal **1.103** (4.85 g, 13.02 mmol, 1 eq) was cannulated into the reaction flask and the reaction mixture was allowed to warm up to RT and stirred at that T overnight. Next morning, the reaction was quenched with H_2O (50 mL) and NH_4Cl (50 mL). Aqueous layers were extracted with EtOAc (3 × 40 ml) and the combined organic extracts

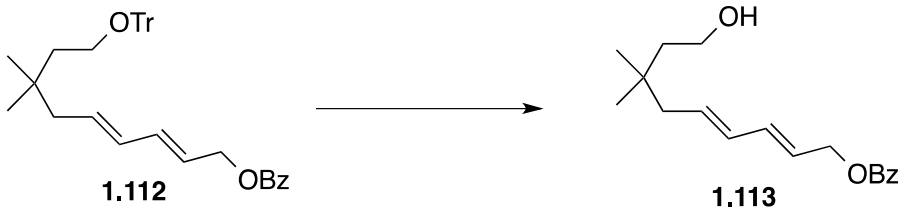
were washed with brine (1 × 80 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by automated silica gel chromatography (0 – 10% EtOAc/Hexanes over 25 min) to afford the title compound **1.110** as a yellow oil (3.5 g, 51% yield) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.25 (m, 13H), 7.24 (d, *J* = 1.4 Hz, 2H), 7.21 (q, *J* = 1.4 Hz, 1H), 6.08 – 6.02 (m, 2H), 5.75 (d, *J* = 15.4 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.11 (t, *J* = 7.3 Hz, 2H), 1.96 (d, *J* = 6.1 Hz, 2H), 1.58 (t, *J* = 7.3 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.80 (s, 6H).



(4*E*)-7,7-dimethyl-9-(trityloxy)nona-2,4-dien-1-ol (1.111). To a suspension of LAH (0.396 g, 9.923 mmol, 1.5 eq) in 100 mL of Et_2O at 0 °C was added a solution of Ethyl (4*E*)-7,7-dimethyl-9-(trityloxy)nona-2,4-dienoate **1.110** (3.1 g, 6.615 mmol, 1 eq) dissolved in 60 mL of Et_2O by cannula. The reaction mixture was stirred at 0 °C while being monitored by TLC upon completion (4 h). After that time, Fieser workup was performed. After concentration of the crude *in vacuo*. the crude mixture was purified by automated silica gel chromatography (10 – 20% EtOAc/Hexanes over 20 min) to afford the title compound **1.111** as a pale yellow oil (1.92 g, 68% yield) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 – 7.41 (m, 6H), 7.34 – 7.27 (m, 6H), 7.25 – 7.13 (m, 2H), 6.26 – 6.15 (m, 1H), 5.93 (dd, *J* = 15.1, 10.4 Hz, 1H), 5.78 – 5.60 (m, 2H), 4.17 (dd, *J* = 6.0, 1.3 Hz, 2H), 3.10 (t, *J* = 7.3 Hz, 2H), 1.88 (d, *J* = 7.6 Hz, 2H), 1.58 (t, *J* = 7.3 Hz, 2H), 0.78 (s, 6H).

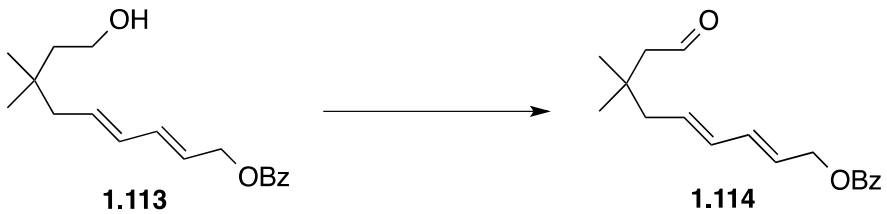


(5*E*)-9-(benzyloxy)- 3,3-dimethylnona-5,7-dien-1 yl)oxy) methanetriyl)tribenzene (1.112). To a solution of (4*E*)-7,7-dimethyl-9-(trityloxy)nona-2,4-dien-1-ol **1.111** (3.16 g, 7.41 mmol, 1 eq) in 100 mL of dry pyridine at RT was added BzCl (1.29 mL, 11.1 mmol, 1.5 eq) and the reaction was followed by TLC upon completion (24 h). At that time, the reaction was quenched with 30 mL of H_2O and 20 mL of 2M HCl. The reaction was diluted in 100 mL of EtOAc, aqueous layers were extracted with EtOAc (3 × 20 ml) and the combined organic extracts were washed with brine (1 × 50 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by automated silica gel chromatography (0 – 10% EtOAc/Hexanes over 20 min) to afford the title compound **1.112** as a transparent oil (3.0 g, 78% yield)). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10 – 8.03 (m, 2H), 7.49 – 7.41 (m, 10H), 7.35 – 7.17 (m, 10H), 6.33 (dd, *J* = 15.3, 10.4 Hz, 1H), 5.94 (dd, *J* = 15.3, 10.4 Hz, 1H), 5.72 (tt, *J* = 14.7, 7.1 Hz, 2H), 4.84 (d, *J* = 6.6 Hz, 2H), 3.10 (t, *J* = 7.2 Hz, 2H), 1.89 (d, *J* = 7.6 Hz, 2H), 1.58 (t, *J* = 7.2 Hz, 2H), 0.80 (s, 6H).

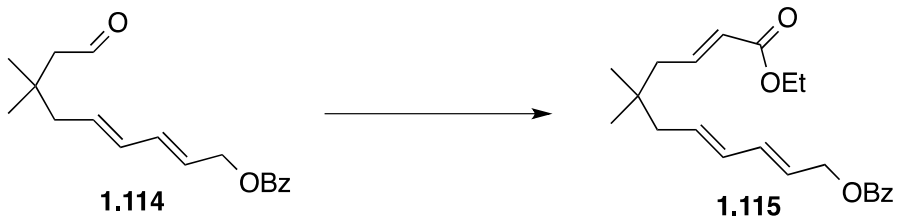


(2*E*,4*E*)-9-hydroxy-7,7-dimethylnona-2,4-dien-1-yl benzoate (1.113). (5*E*)-9-(benzyloxy)- 3,3-dimethylnona-5,7-dien-1 yl)oxy) methanetriyl)tribenzene **1.112** (3.0 g, 5.65 mmol, 1 eq) was dissolved in a solvent system of 113 mL of MeOH and 100 mL of DCM. PTSA (0.323 g, 1.70 mmol, 0.3 eq) was added to the reaction mixture and the reaction was followed by TLC upon completion (12 h). The reaction

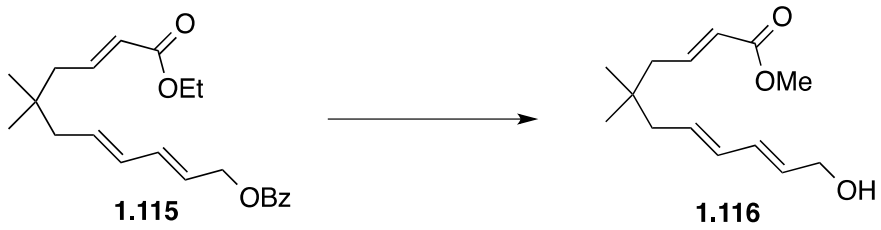
was quenched by the addition of 40 mL of $NaHCO_3$, diluted with EtOAc (50 mL) and the aqueous layers were extracted with EtOAc (30 mL X 3), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by automated silica gel chromatography (0 – 20% EtOAc/Hexanes over 15 min) to afford the title compound **1.113** as a transparent oil (1.3 g, 80 yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 (t, 2H), 7.61 – 7.51 (m, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 6.36 (dd, *J* = 15.3, 10.4 Hz, 1H), 6.07 (dd, *J* = 15.1, 10.4 Hz, 1H), 5.78 (dt, *J* = 14.6, 7.1 Hz, 2H), 4.84 (dd, *J* = 6.4, 1.2 Hz, 2H), 3.76 – 3.63 (m, 2H), 2.02 (d, *J* = 7.1 Hz, 1H), 1.57 – 1.47 (m, 2H), 0.91 (s, 6H).



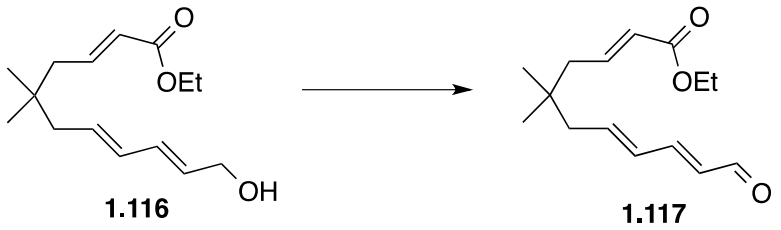
(2*E*,4*E*)-7,7-dimethyl-9-oxonona-2,4-dien-1-yl benzoate (1.114). To a solution of (2*E*,4*E*)-9-hydroxy-7,7-dimethylnona-2,4-dien-1-yl benzoate **1.113** (1.28 g, 4.44 mmol, 1 eq) in 45 mL of EtOAc was added IBX (2.49 g, 8.88 mmol, 2 eq) in one batch and the suspension was heated up to 85 ^{o}C and stirred at that T^o. The reaction was followed by TLC upon complete consumption of the starting material (4 h). After that time, the reaction suspension was allowed to slowly cool down and stirred for 3 h at RT. After that time, the white powder was filtered out trough a fritted funnel and celite. The filtrate was concentrated *in vacuo* and purified by automated silica gel chromatography (0 – 15% EtOAc/Hexanes over 20 min) to afford the title compound **1.114** as a transparent oil (0.880 g, 89% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.84 (t, *J* = 3.0 Hz, 1H), 8.13 – 7.99 (m, 2H), 7.61 – 7.52 (m, 1H), 7.44 (dd, *J* = 8.3, 7.0 Hz, 3H), 6.36 (dd, *J* = 15.2, 10.5 Hz, 1H), 6.09 (dd, *J* = 15.2, 10.5 Hz, 1H), 5.90 – 5.70 (m, 2H), 4.84 (dd, *J* = 6.5, 1.2 Hz, 2H), 2.27 (d, *J* = 3.0 Hz, 2H), 2.13 (dd, *J* = 7.9, 1.1 Hz, 2H), 1.06 (s, 6H).



(2*E*,4*E*,9*E*)-11-ethoxy-7,7-dimethyl-11-oxoundeca-2,4,9-trien-1-yl benzoate (1.115). Commercially available triethyl phosphonoacetate (1.08 mL, 5.45 mmol, 2 eq) was dissolved in 55 mL of THF and cooled down to 0 ^{o}C and stirred for 10 min, at that time *n*-BuLi (2.12 mL, 5.45 mmol, 2 eq) was slowly added by syringe to the solution. A light change in color was observed, from transparent to pale yellow. After that time, a solution of (2*E*,4*E*)-7,7-dimethyl-9-oxonona-2,4-dien-1-yl benzoate **1.114** (0.780 g, 2.72 mmol, 1 eq) was cannulated into the reaction flask and the reaction mixture was allowed to warm up to RT and the reaction was followed by TLC upon completion (5h). Next morning, the reaction was quenched with 30 mL of H_2O and 30 mL of NH_4Cl. Aqueous layers were extracted with EtOAc (3 × 20 ml) and the combined organic extracts were washed with brine (1 × 30 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by automated silica gel chromatography (0 – 10% EtOAc/Hexanes over 25 min) to afford the title compound **1.115** as a pale yellow oil (0.446 g, 46% yield)). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 (dt, *J* = 7.5, 1.0 Hz, 2H), 7.60 – 7.53 (m, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.04 – 6.90 (m, 1H), 6.36 (dd, *J* = 15.2, 10.4 Hz, 1H), 6.07 (dd, *J* = 15.2, 10.4 Hz, 1H), 5.87 – 5.67 (m, 3H), 4.84 (dd, *J* = 6.5, 1.2 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.09 (dd, *J* = 7.9, 1.4 Hz, 2H), 2.02 (d, *J* = 7.7 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.91 (s, 6H).

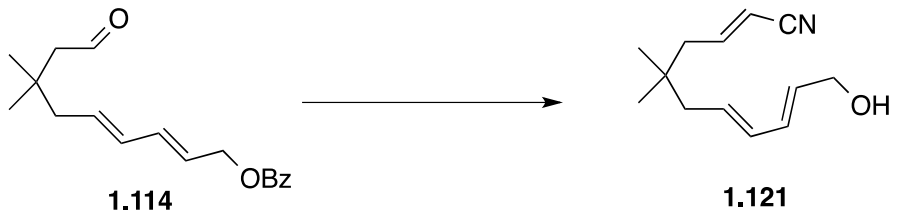


Ethyl (2*E*,7*E*,9*E*)-11-hydroxy-5,5-dimethylundeca-2,7,9-trienoate (1.116). To a solution of (2*E*,4*E*,9*E*)-11-ethoxy-7,7-dimethyl-11-oxoundeca-2,4,9-trien-1-yl benzoate **1.115** (380 mg, 1.066 mmol, 1 eq) in 16 mL of MeOH at RT was added K2CO3 (221 mg, 1.60 mmol, 1.5 eq) in one batch and the reaction was stirred at RT while being monitored by TLC, upon completion (3h). The reaction was quenched with 2.5 mL of a 2M aq solution of HCl, and diluted with 5 mL of EtOAc. Aqueous layers were extracted with EtOAc (3 × 5 ml) and the combined organic extracts were washed with brine (1 × 10 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by automated silica gel chromatography (0 – 10% EtOAc/Hexanes over 20 min) to afford the title compound **1.116** as a yellow oil (200 mg, 78% yield)). 1H NMR (400 MHz, Chloroform-*d*) δ 6.98 (dt, *J* = 15.6, 7.9 Hz, 1H), 6.30 – 6.18 (m, 1H), 6.05 (dd, *J* = 15.1, 10.4 Hz, 1H), 5.89 – 5.63 (m, 3H), 4.21 – 4.14 (m, 2H), 3.73 (s, 3H), 2.09 (dd, *J* = 7.9, 1.4 Hz, 2H), 2.03 – 1.98 (m, 2H), 0.91 (s, 6H).



Ethyl (2*E*,7*E*,9*E*)-5,5-dimethyl-11-oxoundeca-2,7,9-trienoate (1.117). To a solution of Ethyl (2*E*,7*E*,9*E*)-11-hydroxy-5,5-dimethylundeca-2,7,9-trienoate **1.116** (95 mg, 0.399 mmol, 1 eq) in 8 mL of EtOAc was added IBX (223 mg, 0.797 mmol, 2 eq) in one batch and the suspension was heated up to 85 ^{o}C and stirred at that T^{o}. The reaction was followed by TLC upon complete consumption of the starting

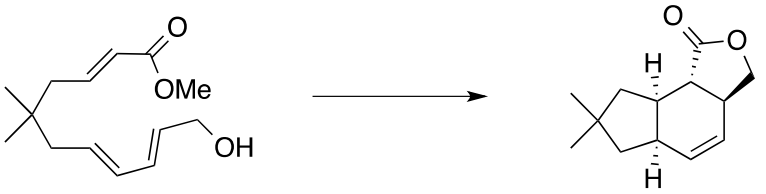
material (5 h). After that time, the reaction suspension was allowed to slowly cool down and stirred for 3 h at RT. After that time, the white powder was filtered out trough a fritted funnel and celite. The filtrate was concentrated *in vacuo* and purified by automated silica gel chromatography (0 – 30% EtOAc/Hexanes over 20 min) to afford the title compound **1.117** as a transparent oil (85 mg, 90% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.55 (d, *J* = 8.0 Hz, 1H), 7.09 (dd, *J* = 15.3, 10.3 Hz, 1H), 6.97 (dt, *J* = 15.5, 7.9 Hz, 1H), 6.39 – 6.21 (m, 2H), 6.10 (dd, *J* = 15.3, 8.0 Hz, 1H), 5.84 (d, *J* = 15.5 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.19 – 2.09 (m, 4H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 16.3 Hz, 6H).



1.114 **1.121**

(2*E*,7*E*,9*E*)-11-hydroxy-5,5-dimethylundeca-2,7,9-trienenitrile (1.121). Diethyl cyanomethylphosphonate (45 μL, 0.280 mmol, 2 eq) was dissolved in 3 mL of THF and cooled down to 0 °C and stirred for 25 min at that T. At that time NaH (22 mg, 0.559 mmol, 4 eq) was added in one batch to the solution and it was stirred at 0 °C for 30 min, a light change in color was observed, from pale yellow to dark yellow. After that time, a solution of (2*E*,4*E*)-7,7-dimethyl-9-oxonona-2,4-dien-1-yl benzoate **1.114** (40 mg, 0.139 mmol, 1 eq) was cannulated into the reaction flask and the reaction mixture was allowed to warm up to RT and the reaction was followed by TLC upon completion (2h). After that time, the reaction was quenched with 3 mL of H_2O and 3 mL of NH_4Cl. Aqueous layers were extracted with EtOAc (3 × 5 ml) and the combined organic extracts were washed with brine (1 × 10 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by automated silica gel chromatography (0 – 20% EtOAc/Hexanes over 15 min) to afford the title compound **1.121** as a yellow oil (29 mg, 35% yield) Note: it was found that under the described conditions, the benzyl alcohol protecting group gets

hydrolyzed to the alcohol. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.78 – 6.49 (m, 1H), 6.32 – 6.18 (m, 1H), 6.06 (ddd, *J* = 15.4, 10.5, 5.3 Hz, 1H), 5.85 – 5.60 (m, 2H), 5.47 – 5.27 (m, 1H), 4.18 (q, *J* = 5.9, 5.0 Hz, 2H), 2.33 (dd, *J* = 8.0, 1.3 Hz, 1H), 2.10 (dd, *J* = 7.8, 1.5 Hz, 1H), 2.07 – 1.96 (m, 2H), 1.32 (td, *J* = 5.9, 2.8 Hz, 1H), 0.95 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.31, 152.19, 132.65, 132.60, 131.50, 131.31, 130.62, 130.50, 130.44, 130.38, 128.13, 128.05, 117.41, 116.09, 101.69, 101.22, 63.42, 63.35, 45.63, 45.31, 45.21, 43.83, 35.14, 34.78, 26.85, 26.77.

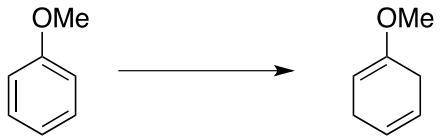


1.116 **1.119**

General procedure for Diels-Alder reactions in NMR tubes. In a 3 dram vial, substrate **1.116**, (15 mg, 0.0629 mmol), were dissolved in 1.5mL of the solvent of interest DMSO-d6. After that, the solution was transferred to a NMR tube and it was heated up to 110 ^{o}C in an oil bath for 14 h to obtain cycloadduct **119** (90% NMR yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.97 (d, *J* = 9.8 Hz, 1H), 5.54 (dt, *J* = 9.8, 3.3 Hz, 1H), 4.52 (td, *J* = 8.8, 0.9 Hz, 1H), 3.91 (ddd, *J* = 10.8, 8.9, 0.9 Hz, 1H), 3.27 – 3.11 (m, 1H), 2.53 (dd, *J* = 12.6, 8.4 Hz, 1H), 2.14 (dt, *J* = 21.9, 7.3 Hz, 1H), 1.83 (dd, *J* = 12.6, 6.5 Hz, 1H), 1.78 – 1.69 (m, 1H), 1.64 (qd, *J* = 11.8, 6.5 Hz, 1H), 1.32 (t, *J* = 12.2 Hz, 1H), 1.13 (d, *J* = 12.5 Hz, 1H), 1.08 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.40, 132.90, 123.87, 72.13, 44.94, 44.65, 44.14, 42.78, 40.97, 37.10, 36.87, 31.95, 31.79.

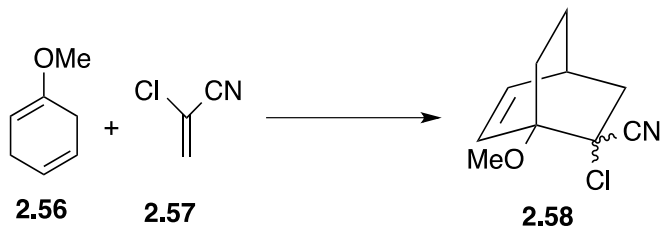
Conditions for the rest of the Diels-Alder reactions are specified in tables **1.2**, **1.3** and **1.4.**

3.2 Anionic oxy-Cope methodology



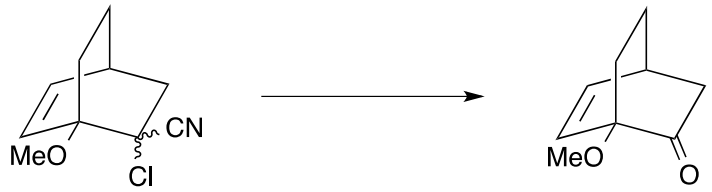
2.55 **2.56**

1-methoxycyclohexa-1,4-diene 2.56. A 1-L three-necked round-bottomed flask equipped with stir bar, argon inlet and a cold finger was flame dried. Upon cooling, the flask was charged with 10 mL of dry THF, anisole (6.3 g, 58.3 mmol) and *tert*-butanol (32 mL, 335 mmol). At this point the cold finger was cooled down to -78 ^{o}C and ammonia (200 mL) was condensed into the reaction flask. The flask was kept at RT while the addition of ammonia (45 min). Upon condensation, lithium (1.0 g, 144.1 mmol) was added in small pieces (lithium was cleaned with hexanes, MeOH and THF before added to the reaction mixture). The addition was made adding one piece and waiting until the dark blue color disappeared and adding the next lithium piece then. When the last piece of lithium was added, the blue color was permanent and it was allowed to stir for 5 min. After that time, the reaction was carefully quenched adding 15 mL of MeOH drop wise. A white suspension was observed and the quenching procedure was continued carefully adding 150 mL of water. The reaction flask was placed in an oil bath at 40 ^{o}C to accelerate the evaporation of ammonia. After 1 h of evaporation, the reaxtion mixture was extracted with petroleum ether (4 x 80 mL). Organic layers were combined, washed with water (2 x 50 mL), dried over Na_2SO_4 and concentrated *in vacuo* using an ice bath to reduce loss of the desired product. The product was a transparent oil (4.0 g, 63%). Not further purification was needed. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.73 – 5.63 (m, 2H), 4.63 (t, *J* = 3.5 Hz, 1H), 3.55 (s, 3H), 2.84 – 2.78 (m, 2H), 2.75 – 2.69 (m, 2H).



2.56 **2.57** **2.58**

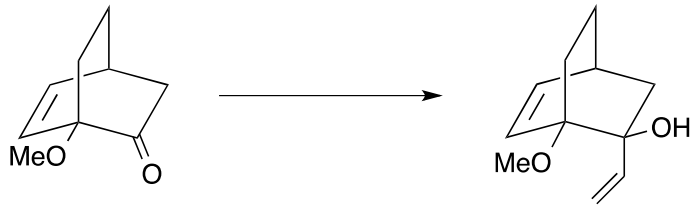
(1*R*,4*S*)-2-chloro-1-methoxybicyclo[2.2.2]oct-5-ene-2-carbonitrile 2.58. In a 100 mL round-bottomed flask, were mixed methoxy 1,4-cyclohexadiene (1.23 g, 11.2 mmol), 2-chloro acrylonitrile (0.81 g, 9.31 mmol) and chloroform (0.045 mL, 0.558 mmol) dissolved in 15 mL of Tol. The reaction mixture was heated up to 85 ^{o}C. After 18 h of reaction, the mixture was allowed to cool down to RT. The solvent was evaporated and the crude mixture was purified by automated silica gel chromatography (0 – 10% EtOAc/Hexanes over 30 min) to afford the title compound **2.58** as a yellow oil (0.77 g, 35% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.51 (dd, *J* = 8.8, 6.4 Hz, 1H), 6.46 – 6.37 (m, 2H), 6.25 (dt, *J* = 8.8, 1.1 Hz, 1H), 3.53 (d, *J* = 2.4 Hz, 6H), 2.73 – 2.61 (m, 3H), 2.54 (dt, *J* = 14.2, 3.3 Hz, 1H), 2.29 – 2.09 (m, 2H), 2.02 – 1.84 (m, 3H), 1.84 – 1.62 (m, 3H), 1.55 – 1.43 (m, 2H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 136.78, 134.01, 131.27, 130.06, 120.00, 119.48, 80.66, 80.63, 61.56, 61.42, 52.48, 52.46, 46.82, 46.58, 29.50, 29.47, 24.57, 24.55, 22.27, 21.74. HRMS (ESI): *m/z* calculated for (M+H^{+}) = 198.0607, found = 197.0680



2.58 **2.59**

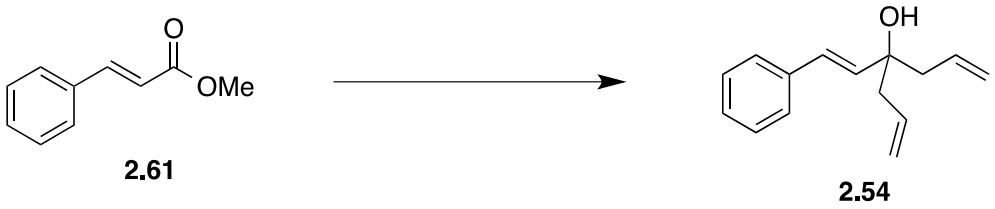
(1*R*,4*S*)-1-methoxybicyclo[2.2.2]oct-5-en-2-one 2.59. To a solution of (1*R*,4*S*)-2-chloro-1-methoxybicyclo[2.2.2]oct-5-ene-2-carbonitrile (0.601 g, 3.05 mmol) in 30 mL of DMSO, were added 30 mL of a 1 M aqueous solution of KOH (1.53g, 30.5 mmol) and the reaction mixture was heated up to 80 ^{o}C and stirred at that T^{o} for 12 h. After that time, the reaction was neutralized with Na_2CO_3 (20 mL, sat . aqueous)

and extracted with Et2O (3 x 30 mL). Organic layers were washed with H2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude of the reaction yielded the title compound **2.59** as a brown oil (0.460 g, 99% yield). No further purification was needed. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.50 – 6.44 (m, 1H), 6.27 (dt, *J* = 8.7, 1.4 Hz, 1H), 3.54 (s, 3H), 2.99 – 2.92 (m, 1H), 2.15 – 2.12 (m, 2H), 1.96 – 1.88 (m, 1H), 1.87 – 1.79 (m, 1H), 1.78 – 1.71 (m, 1H), 1.71 – 1.62 (m, 1H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 209.96, 135.88, 129.63, 84.71, 53.22, 40.34, 31.59, 26.69, 25.26



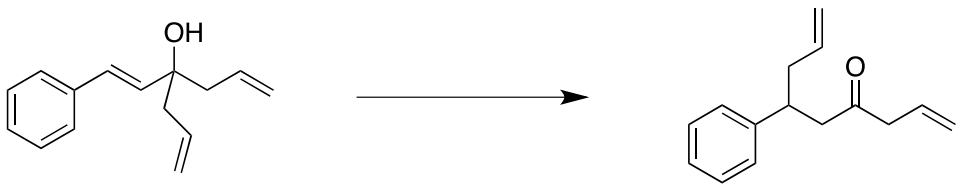
2.59 **2.50**

(1*R*,2*S*,4*S*)-1-methoxy-2-vinylbicyclo[2.2.2]oct-5-en-2-ol 2.50. To a solution of (1*R*,4*S*)-1-methoxybicyclo[2.2.2]oct-5-en-2-one (0.460 g, 3.02 mmol) in 20 mL of THF at 0 ^{o}C was added drop wise a solution of vynilmagnesium bromide in THF (6.04 mL, 6.04 mmol) and it was allowed to warm up to RT and stirred for 3 h. After that time, the mixture was diluted with EtOAc and quenched with 10 mL of H_2O followed NH_4Cl (5 mL, sat . aqueous). Aqueous layer extracted with EtOAc (3 x 20 mL), the organic layers where combined and washed with brine, dried over Na_2SO_4, concentrated *in vacuo* and purified by automated silica gel chromatography (0 – 5% EtOAc/Hexanes over 45 min) to afford the title compound **2.50** as a transparent oil (0.22 g, 40% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.34 – 6.20 (m, 2H), 5.91 (dd, *J* = 17.2, 10.7 Hz, 1H), 5.22 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.02 (dd, *J* = 10.6, 1.5 Hz, 1H), 3.35 (s, 3H), 2.59 – 2.50 (m, 1H), 2.17 (s, 1H), 2.10 – 2.01 (m, 1H), 1.86 – 1.77 (m, 1H), 1.63 (dd, *J* = 2.9, 1.6 Hz, 2H), 1.59 – 1.36 (m, 2H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 145.08, 134.07, 132.19, 110.80, 82.83, 78.71, 51.92, 41.86, 30.29, 25.10, 21.86. HRMS (ESI): *m/z* calculated for (M+Na$^+$) = 203.1150, found = 203.1043



2.61 **2.54**

(*E*)-4-styrylhepta-1,6-dien-4-ol 2.54 To a solution of methyl cinnamate (1.0 g, 6.17 mmol) in 40 mL of THF at 0 ^{o}C, was added a 1M solution of allylmagnesium bromide in THF (21.6 mL, 21.6 mmol). The reaction mixture was allowed to warm up to RT and it was stirred for 4 h. After that time, the reaction was diluted with 20 mL of EtOAc and quenched with NH_4Cl (15 mL, sat . aqueous). Aqueous layers were extracted with EtOAc (3 x 20 mL), organic phases combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by automated silica gel chromatography (0 – 15% EtOAc/Hexanes over 30 min) to afford the title compound **2.54** as a transparent oil (1.0 g, 76% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.42 – 7.36 (m, 2H), 7.35 – 7.27 (m, 2H), 7.25 – 7.19 (m, 0H), 6.61 (d, *J* = 16.0 Hz, 1H), 6.25 (d, *J* = 16.0 Hz, 1H), 5.93 – 5.72 (m, 2H), 5.26 – 5.07 (m, 4H), 2.54 – 2.26 (m, 4H). ^{13}C NMR (126 MHz, $cdcl_3$) δ 136.81, 134.65, 133.26, 128.50, 127.35, 126.37, 119.15, 73.74, 45.50. HRMS (ESI): *m/z* calculated for ($M+Na^+$) = 237.1358, found = 237.1550

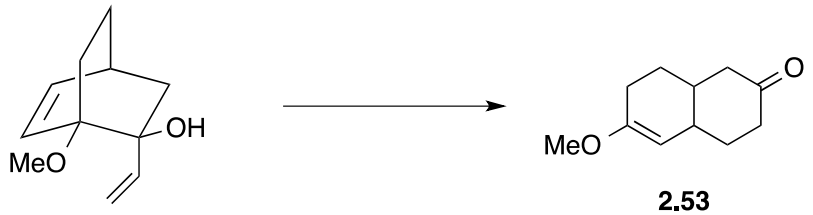


2.54 **2.67**

General Procedure for Oxy-Cope rearrangement using KH and 18-Crown-6: In a pre-weighed and flame dried 10 mL round bottomed flask, was added a 30% suspension of KH in mineral oil. 5 mL of dry THF were added to the flask and the flask was swirled for 30 seconds. At that time, the suspension was allowed to settle for 1 min and the liquid was carefully cannulated out of the flask. The same procedure was repeated three additional times. The flask was then set under HV to

evaporate all remaining THF. The flask was weighed one more time to calculate the amount of pure KH present in the flask (103 mg, 2.57 mmol, 3 eq). After that, THF (1 mL) was added and the suspension was stirred under an argon atmosphere. On a separated flame dried 10 mL round bottomed flask, substrate **2.54,** (1 eq) was weighed, dissolved in THF (1 mL) and cannulated into the flask containing KH, followed by 18-Crown-6 (678 mg, 2.57 mmol, 3 eq). The reaction was stirred at RT for 2 hr. After that time, the reaction was diluted with EtOAc (2 mL) quenched by the addition of H_2O (1 mL) and NH_4Cl (1 mL), the aqueous layers were extracted with EtOAc (3 x 5 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was dissolved in CD_3Cl and 1H NMR was performed to establish convertion ratios. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.31 – 7.26 (m, 2H), 7.22 – 7.15 (m, 3H), 5.81 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.69 – 5.59 (m, 1H), 5.15 – 5.10 (m, 1H), 5.04 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.01 – 4.94 (m, 2H), 3.27 (p, *J* = 7.3 Hz, 1H), 3.11 – 2.93 (m, 2H), 2.83 – 2.68 (m, 2H), 2.41 – 2.33 (m, 2H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 207.47, 143.98, 136.13, 130.33, 128.44, 127.45, 126.43, 118.82, 116.75, 109.98, 48.40, 48.18, 40.71, 40.56.

Conditions for the rest of the oxy-Cope rearrangements are specified in tables **2.1**, **and 2.2**

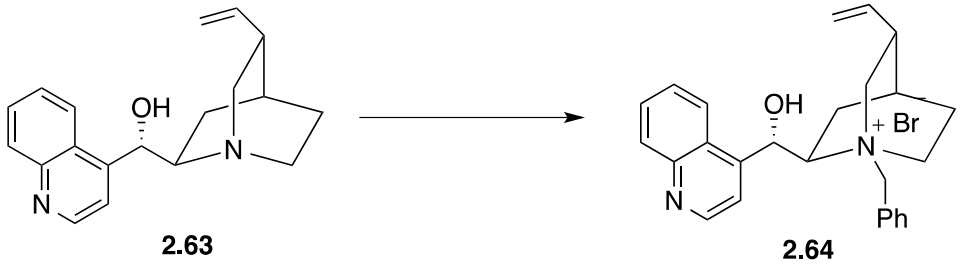


2.50 **2.53**

General Procedure for Oxy-Cope rearrangement using Bu_4NOH: To a flame dried 10 mL round bottomed flask, substrate **2.50** (25mg, 0.138 mmol, 1 eq) was added and dissolved in 1 mL of DMSO. On a separated flame dried 10 mL round bottomed flask, Bu_4NOH (144 mg, 0.555 mmol, 4 eq) was weighed and dissolved in 1 mL of DMSO and cannulated into the reaction flask. The reaction was heated up to

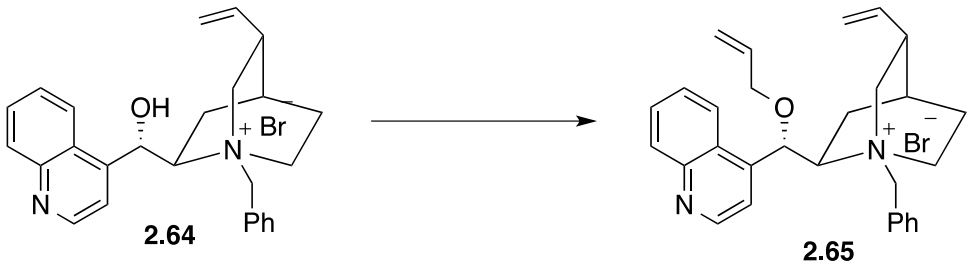
80 °C and stirred for 12 h. After that time, the reaction was cooled down to RT (if heated up) diluted with 2 mL of EtOAc and quenched by the addition of 2 mL of NH_4Cl, aqueous layers were extracted with EtOAc (3 x 5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was dissolved in CD_3Cl and 1H NMR was performed to establish convertion ratios. ^1H NMR (300 MHz, Chloroform-*d*) δ 4.52 (d, *J* = 3.6 Hz, 1H), 3.53 (s, 3H), 2.70 – 2.55 (m, 1H), 2.44 – 2.18 (m, 6H), 2.16 – 2.05 (m, 2H), 1.92 – 1.57 (m, 3H).

Conditions for the rest of the oxy-Cope rearrangements are specified in tables **2.1**, **and 2.2**



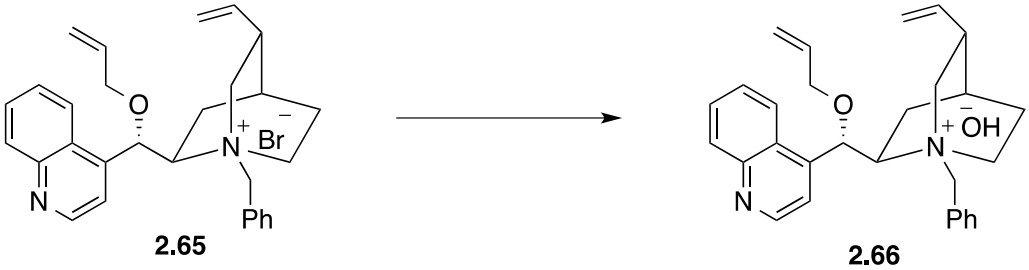
2.63 **2.64**

Compound 264 was prepared according to the literature reported procedure. To a suspension of commercially available Cinchonine (1.0 g, 3.39 mmol, 1 eq) in 12 mL of Tol was added BzBr(0.403 mL, 3.39 mmol, 1 eq) and the reaction was heated up to reflux for 4 h. After that time, the reaction mixture was allowed to slowly cool down to RT, at that moment 50 mL of Et_2O were added and a light brown precipitated was observed. Filtration through filter paper yielded salt **2.64** in 88 % yield. The spectroscopic data for salt 878787 were in agreement with the data reported in the literature.[90]



2.64 2.65

Compound 2.65 was prepared according to the literature reported procedure. To a suspension of salt **2.64 (**800 mg, 1.72 mmol, 1 eq) in 3 mL of DCM, a 50% aqueous solution of KOH (0.850 mL, 8.59 mmol, 5 eq) followed by addition of allyl Br (0.442 mL, 5.16 mmol, 3 eq) by syringe. After 20 min of reaction, the solution became homogeneous and it was allowed to stirred at RT overnight. Next day, the mixture was diluted with 10 mL of H_2O, extracted with DCM (3x 5mL) dried over Na_2SO_4, filtered and concentrated *in vacuo*. The solid was dried over HV for 2 days to afford 83% of salt **2.65** The spectroscopic data for salt 878787 were in agreement with the data reported in the literature.[90]



2.65 2.66

Cinchonium-hydroxy compound **2.66** was prepared according to the literature reported procedure. To a solution of salt **2.65** (500 mg, 0.989 mmol, 1 eq) in 50 mL of MeOH, was added Ag_2O (916 mg, 3.956 mmol, 4 eq) followed by H_2O (17.8 µL, 0.989 mmol, 1 eq) and stirred at RT for 3 days. After that time, Ag_2O was filtered off and the filtrate was concentrated *in vacuo* and purified by silica gel chromatography using a solvent system of 40% Et2O in Pet Et_2O to yield 48% of the cinchonium-base **2.66** The spectroscopic data for salt **2.66** were in agreement with the data reported in the literature.[105]