SIMULTANEOUS SYNTHESIS OF BOTH RINGS OF CHROMENES VIA A BENZANNULATION/ORTHO-QUINONE METHIDE FORMATION/ELECTROCYCLIZATION CASCADE AND AN APPROACH TOWARDS THE ASYMMETRIC SYNTHESIS OF CHROMENES

By

Nilanjana Majumdar

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Chemistry

2012

ABSTRACT

SIMULTANEOUS SYNTHESIS OF BOTH RINGS OF CHROMENES VIA A BENZANNULATION/ORTHO-QUINONE METHIDE FORMATION/ELECTROCYCLIZATION CASCADE AND AN APPROACH TOWARDS THE ASYMMETRIC SYNTHESIS OF CHROMENES

By

Nilanjana Majumdar

A new route to the chromene ring system has been developed which is the reaction of an *α*,*β*-unsaturated Fischer carbene complex of chromium with a propargyl ether bearing an alkenyl group on the propargylic carbon. This transformation involves a cascade of reactions that begins with a benzannulation reaction and is followed by the formation of an *o*-quinone methide, and finally results in the emergence of a chromene upon an electrocyclization in yields up to 95%. This reaction was extended to provide access to naphthopyrans by employing an aryl carbene complex. This constitutes the first synthesis of chromenes in which both rings of the chromene system are generated in a single step. The success of this method is highlighted in the synthesis of lapachenole and vitamin E.

The asymmetric version of benzannulation/*o*-quinone methide formation/electrocyclization cascade was also explored for the synthesis of chiral chromenes using optically active enynes. Enantiomeric excesses up to 60% could be obtained. Interestingly, it was observed that the double bond geometry in the chiral enyne controlled the absolute stereochemistry in the final chromene product. A mechanistic investigation was carried out to have a better understanding of the reaction pathway.

ACKNOWLEDGMENT

I would like to express my sincere gratitude to Professor William D. Wulff for his guidance and assistance during the course of my studies. Professor Wulff allowed me to work on my research with complete freedom. I am very grateful to him for all the chemical knowledge and insights I gained from him. I would like to thank Professor Jackson, Professor Borhan, and Professor Odom for the care they took in evaluating this work, and also for their comments and insights.

I would like to thank Dr. Daniel Holmes and Mr. Kermit Johnson for the patience to answer my questions, assistance for NMR.

I want to thank Dr. Keith Korthals for introducing me to the chromium carbene complexes and for helping me with my reactions in the beginning. I would also like to thank Victor Prutyanov for all his valuable suggestions for my research. I am thankful to all my present group members for their support and cooperation. It was very exciting and enjoyable to work with all of my past and present group members. I also would like to thank all my friends in Michigan State University for their valuable friendship.

I thank my parents and my husband for their infinite love and support and their priceless contribution in my life. This thesis is intended to honor them, the most important people in my life.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

KEY TO ABBREVIATIONS AND SYMBOLS

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Bz	Benzoyl
BQME	Benzannulation/*o*-Quinone Methide Formation/ Electrocyclization
CAN	Ceric Ammonium Nitrate
*m*CPBA	*meta*-Chloroperoxybenzoic Acid
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIBAL	Diisobutylaluminum Hydride
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
EDDA	Ethylenediamine Diacetate
ESI	Electrospray Ionization
HMPA	Hexamethyl phosphoramide
hν	Irradiation with Light
HQ	Hydroquinone
LDA	Lithium Diisopropylamide
L-Selectride	Lithium Tri-*sec*-butylborohydride
LUMO	Lowest Unoccupied Molecular Orbital
MOM	Methoxymethyl

MS	Mass Spectra
MsCl	Methanesulfonyl Chloride
NMO	N-Methylmorpholine N-Oxide
o-QM	*ortho*-Quinone Methide
PFB	*p*-Fluorobenzene
PMB	*p*-Methoxybenzene
p-QM	*para*-Quinone Methide
Red-Al	Sodium Dihydrobis(2-methoxyethoxy)-aluminate
TBAF	*n*-Butylammonium Tetrafluoroborate
TBS	*Tert*-butyldimethylsilyl
TIPS	Triisopropyl silyl
THF	Tetrahydrofuran
THT	Tetrahydrothiophene
TMEDA	Tetramethylethylenediamine
TMG	1,1,3,3-Tetramethylguanidine
TMS	Trimethylsilyl
Tr	Triphenyl methane
Ts	*p*-Toluenesulfonyl
TTF	Tetrathiafulvalene
QM	Quinone Methide

LIST OF SCHEMES

CHAPTER ONE

Recent Developments in the Synthesis of 2H-Chromenes

1.1. Introduction

Heterocycles undoubtedly constitute a dominant class of organic compounds with the widest variety of classifications.[1] They are a very important class of compounds not only being common in biologically active important classes of natural products, for example, alkaloids, vitamins, hormones, and antibiotics but also because of their diverse applications in different fields. Most common heterocycles are oxygen, nitrogen and sulfur-containing compounds. Oxygen-containing heterocycles are ubiquitous in nature and can be classified by the number of ring atoms. In general three- to six-membered ring compounds are more common. Six-membered heterocycles including one oxygen in the ring are commonly named as pyrans. Although, simple and saturated pyran ring systems are not so stable compounds, a fusion with aromatic rings provides the system with significant stabilization. Thus, 2H-1-benzopyrans (chrom-3-enes) are widely abundant in nature and are very special because of their extensive chemistry. Chromene compounds can be found in many biologically active natural products.[2,3,4]

These compounds exhibit a broad spectrum of biological activities[5] e.g. antidepressant, antihypertensive, antitubulin, antiviral, antioxidant, activator of potassium channels and even inhibition of phosphodiesterase IV or dihydrofolate reductase. They are also very important because of their photochromatic behavior.[6] Chromenes are referred as

"privileged structures".[7] This "privileged" status is given to them because of their ability to bind to multiple, unrelated classes of protein receptors as high affinity ligands by orienting varied substituent patterns in a well-defined three-dimensional space. Privileged structures exhibit good drug like properties and that led to the formation of natural product-like combinatorial library[8] based on 2,2-dimethylbenzopyran moieties as the template. The diverse array of biological activities of 2H-chromene containing compounds and the structural importance of benzopyran moiety has inspired the organic chemistry world for the development of new and improved synthesis of this molecular scaffold.[3]

This review covers the metal-mediated, metal-free and organocatalytic approaches toward the enantioselective as well as racemic synthesis of highly functionalized 2H-chromene derivatives. The organization of this review is based on the enantioselective as well as racemic approaches that employ various synthetic transformations. Both the synthetic applications as well as the mechanistic aspects of the described 2H-chromene syntheses are discussed.

1.2. Synthesis of Chromenes

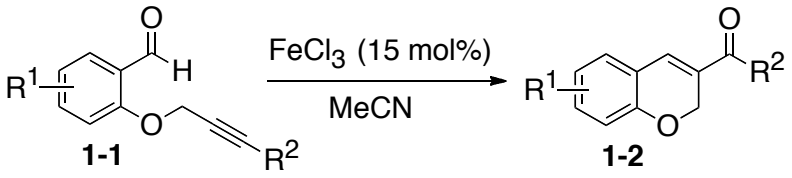
1.2.1. Racemic Approaches for the Synthesis of Chromenes

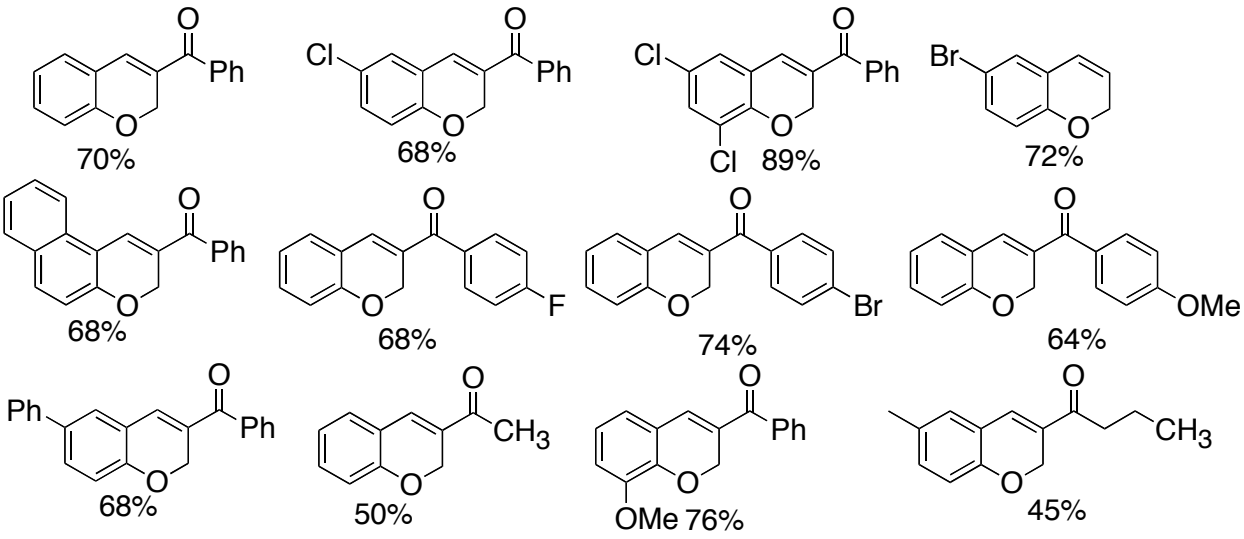
1.2.1.1. Metal-Mediated Approaches for the Synthesis of Chromenes

In 2011, Jana and coworkers reported[9] a new method for the synthesis of 3-substituted 2H-chromenes by employing intramolecular alkyne-carbonyl metathesis as the key reaction in the presence of an iron catalyst. Thus, it was shown that alkynyl ethers of

salicyaldehyde **1-1** in the presence of 10 mol% $FeCl_3$ in acetonitrile afforded the corresponding 3-substituted chromenes **1-2** in good to high yields (**Scheme 1.1**).

Scheme 1.1: Synthesis of Chromenes by Fe-Catalyzed Intramolecular Alkyne-Carbonyl Metathesis



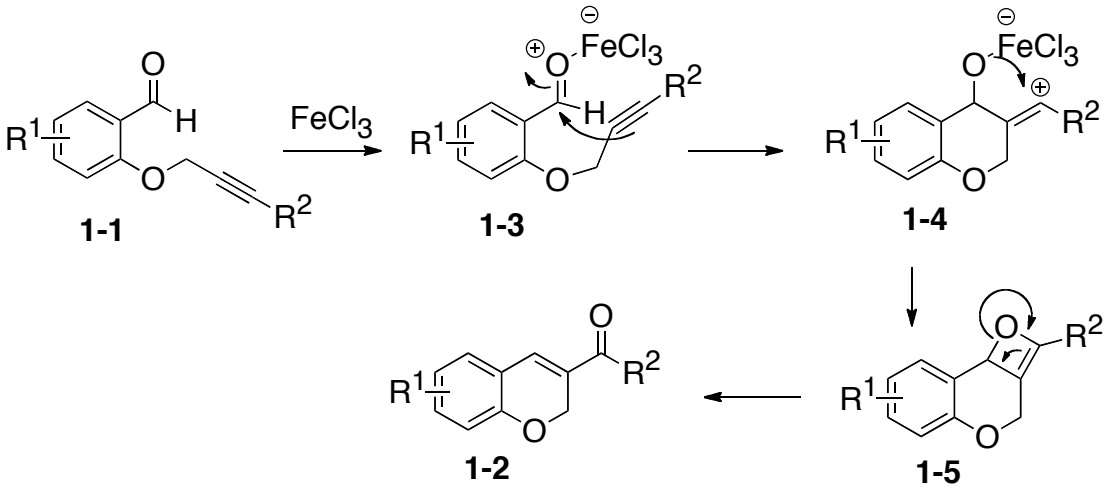


Next, they explored the possibility of the intramolecular alkyne-carbonyl metathesis reaction with a variety of substituents around the aromatic ring of the salicyaldehyde as well as on the alkyne. It was found that the reaction was quite general with respect to a variety of functional groups including Cl, Br, OMe and Ph in salicylaldehyde. The yields of the products were good irrespective of the difference in electronic nature of substituents. Moreover, the reaction proceeded smoothly in naphthalene and biphenyl

systems providing very good yields. Similarly, various substituents on the aromatic ring attached to the alkyne were well tolerated. Alkyl groups at the alkyne terminus were also tested and the yield of the corresponding products were good. However, the reaction failed for simple propargyl ether with a terminal alkyne unit. Thus, it is apparent that the reaction is more facile with an aromatic substituent on the alkyne in the starting compound.

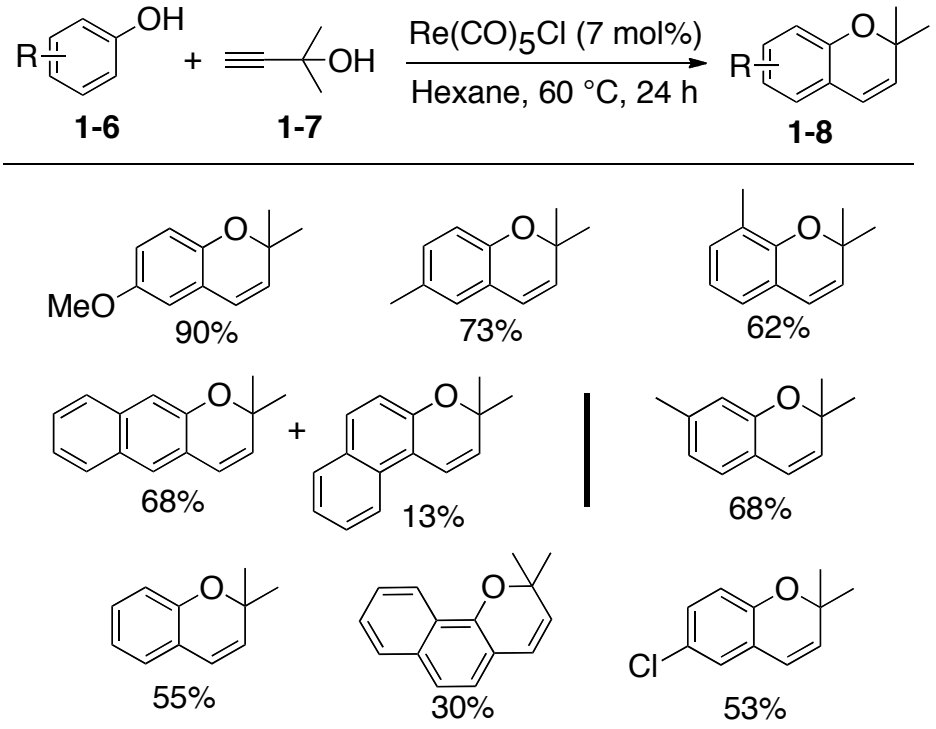
It was proposed that the reaction proceeds via a [2+2] cycloaddition. Initially, the carbonyl group was activated by the coordination with $FeCl_3$, which promoted the nucleophilic attack of the alkyne on the aldehyde forming an oxetene intermediate **1-5** via the vinylic cation intermediate **1-4**. Intermediate **1-5** subsequently proceeds via a formal [2+2] cycloreversion to the 2H-chromene **1-2** with complete regioselectivity. Notably, the exact role of $FeCl_3$ at this point is not clear (**Scheme 1.2**).

Scheme 1.2: Proposed Mechanism

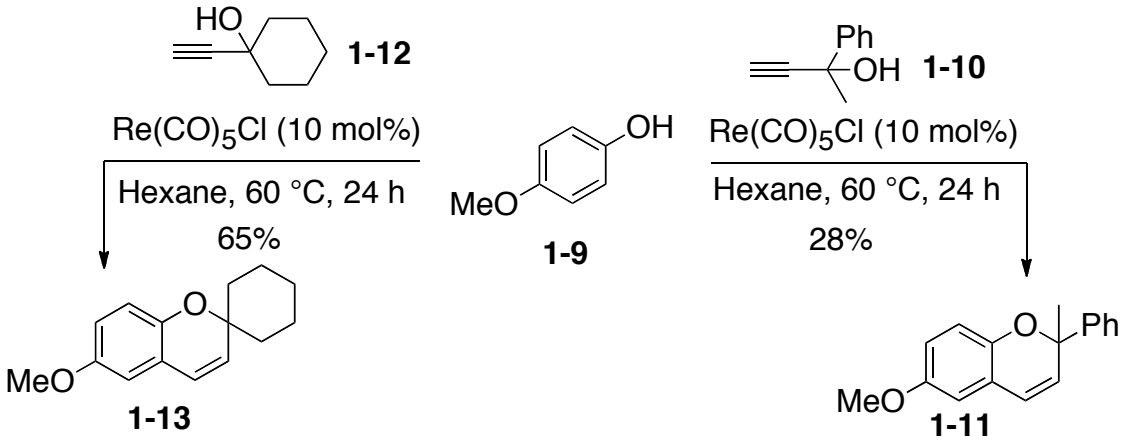


Hue et al showed[10] that the synthesis of 2,2-dimethyl-2H-chromenes could easily be achieved by a one-pot cyclocondensation of phenols and 2-methyl-3-butyn-2-ol. Thus, when phenols were treated with 2-methyl-3-butyn-2-ol in the presence of $ReCl(CO)_5$ in hexane at 60 °C, they gave the 2,2-dimethyl-2H-chromenes in high yields (**Scheme 1.3**). The substrate scope was explored and it was found that simple phenol, *p*-, *o*- and *m*-cresols gave good yields of the products. Interestingly, this developed protocol was also capable of giving the naphthopyran derivatives from β and α–naphthols, although α–naphthol showed relatively lower reactivity. Electron withdrawing groups such as 4-Cl in phenol showed good result. In addition to that, the reaction of 4-methoxyphenol with 2-phenyl-3-butyn-2-ol and 1-ethynyl cyclohexanol afforded the expected cycloadduct in 28% and 65% yields respectively (**Scheme 1.4**).

Scheme 1.3: Synthesis of Chromenes by Re-Catalyzed Cyclocondensation



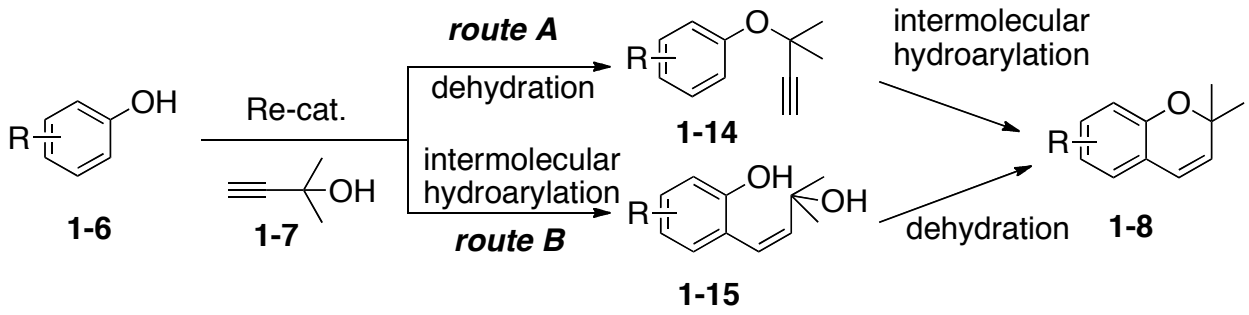
Scheme 1.4: Extended Substrate Scope



From a consideration of the high chemo- and regio-selectivity of the hydroarylation at the ortho position of the phenols, it was believed that the reaction proceeds only via

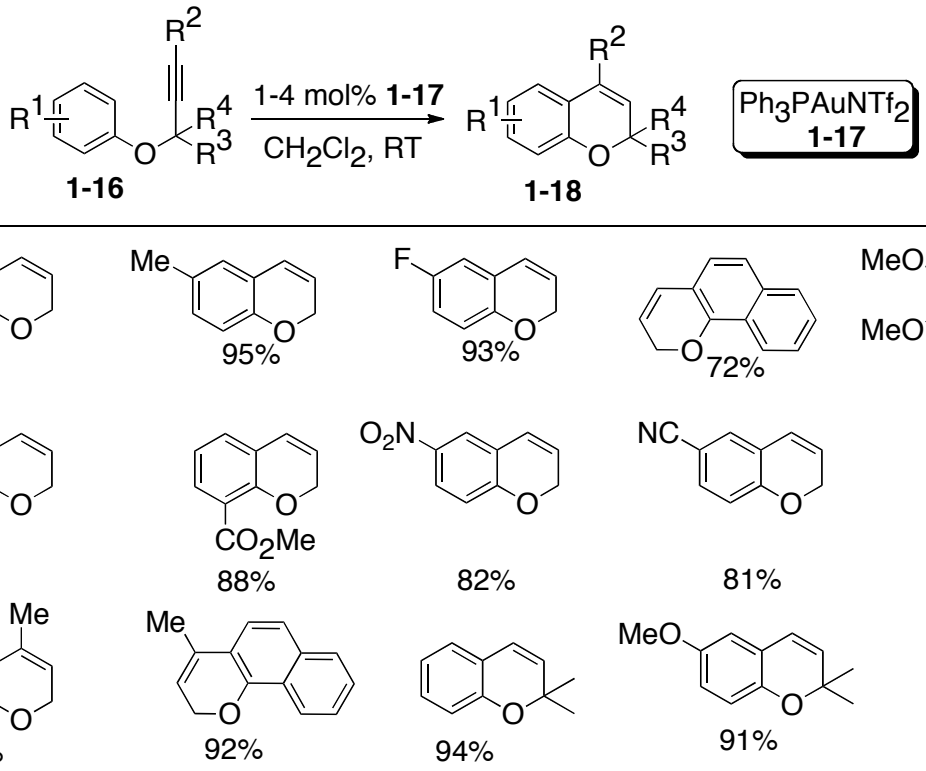
route a, which involves dehydration followed by intramolecular hydroarylation (**Scheme 1.5**).

Scheme 1.5: Proposed Mechanism



Stratakis et al showed[11] that chromenes could be obtained from propargyl aryl ethers with $Ph_3PAuNTf_2$ **1-17** as catalyst. A range of densely substituted 2H-chromenes could be produced in high yields of even unsubstituted 2H-chromenes (**Scheme 1.6**). They examined a number of electron-rich and electron-poor aryl propargyl ethers and it was observed that the reactions worked very smoothly at 25 °C to give excellent yields of chromenes in the case of electron-rich arenes. On the other hand, in case of electron-deficient arenes, the reaction rate was significantly slower. However, with increased catalytic load (4 mol%) and at elevated temperature (70 °C), the cycloisomerization preceded smoothly giving excellent yields of the final products. It is also noteworthy to mention that only in the cases of substrates bearing strong-electron withdrawing groups such as NO_2, CN and CO_2Me with the formation of chromenes, benzofuran side products were observed in up to 7% yield.

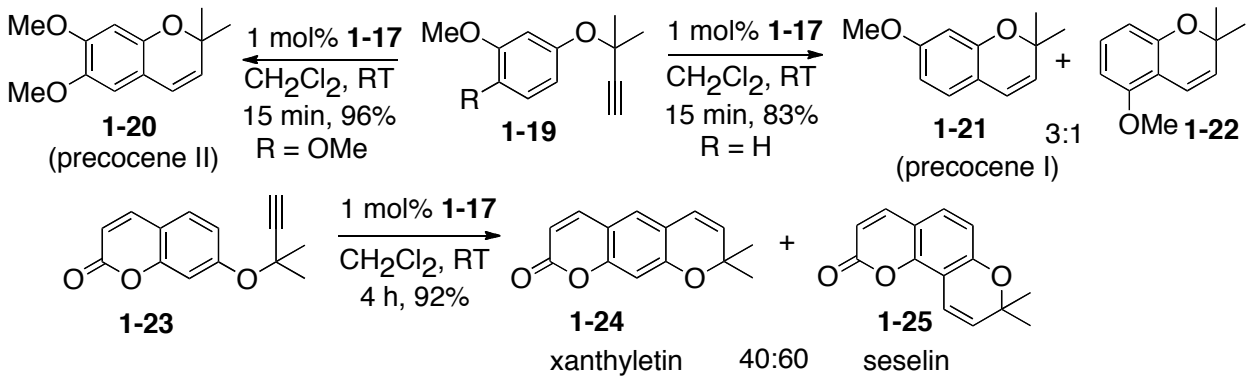
Scheme 1.6: Synthesis of Chromenes from Aryl Propargyl Ether via Au-catalysis



The catalyst proved very efficient when there was an internal alkyne in the starting ether compound. The reaction also proceeded smoothly for naphthyl ethers giving excellent yields of naphthopyran products. The yields were also excellent even when more hindered gem-dimethyl derivatives were used. In all the cases exclusively the chromene products formed with excellent yields except for electron-deficient arenes. Moreover, the optimized protocol was tested in the synthesis of some chromene containing natural products. Precocene I **1-21** was prepared from the propargyl ether **1-19** and was produced in a 3:1 ratio with its regioisomer **1-22**. The selectivity for the same reaction under thermal condition (boiling in *N,N*-diethylaniline) was 1:1 according to previous reports.[12] Precocene II could be obtained exclusively in excellent yield from **1-19** using

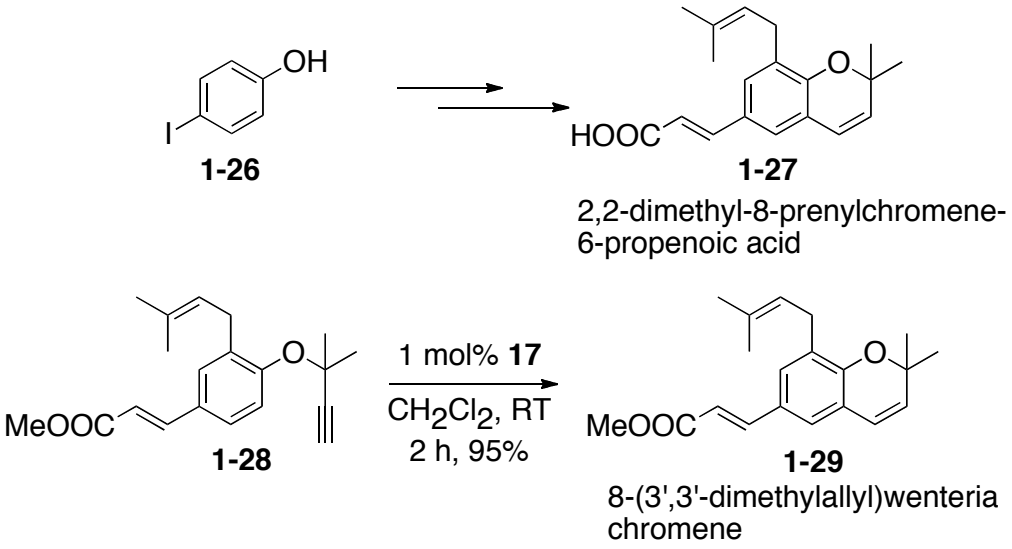
the same catalyst. Similarly, xanthyletin **1-24** and seselin **1-25** were produced in a 40:60 ratio, but could be easily separated by column chromatography (**Scheme 1.7**).

Scheme 1.7: Synthesis of Chromene-Containing Natural Products



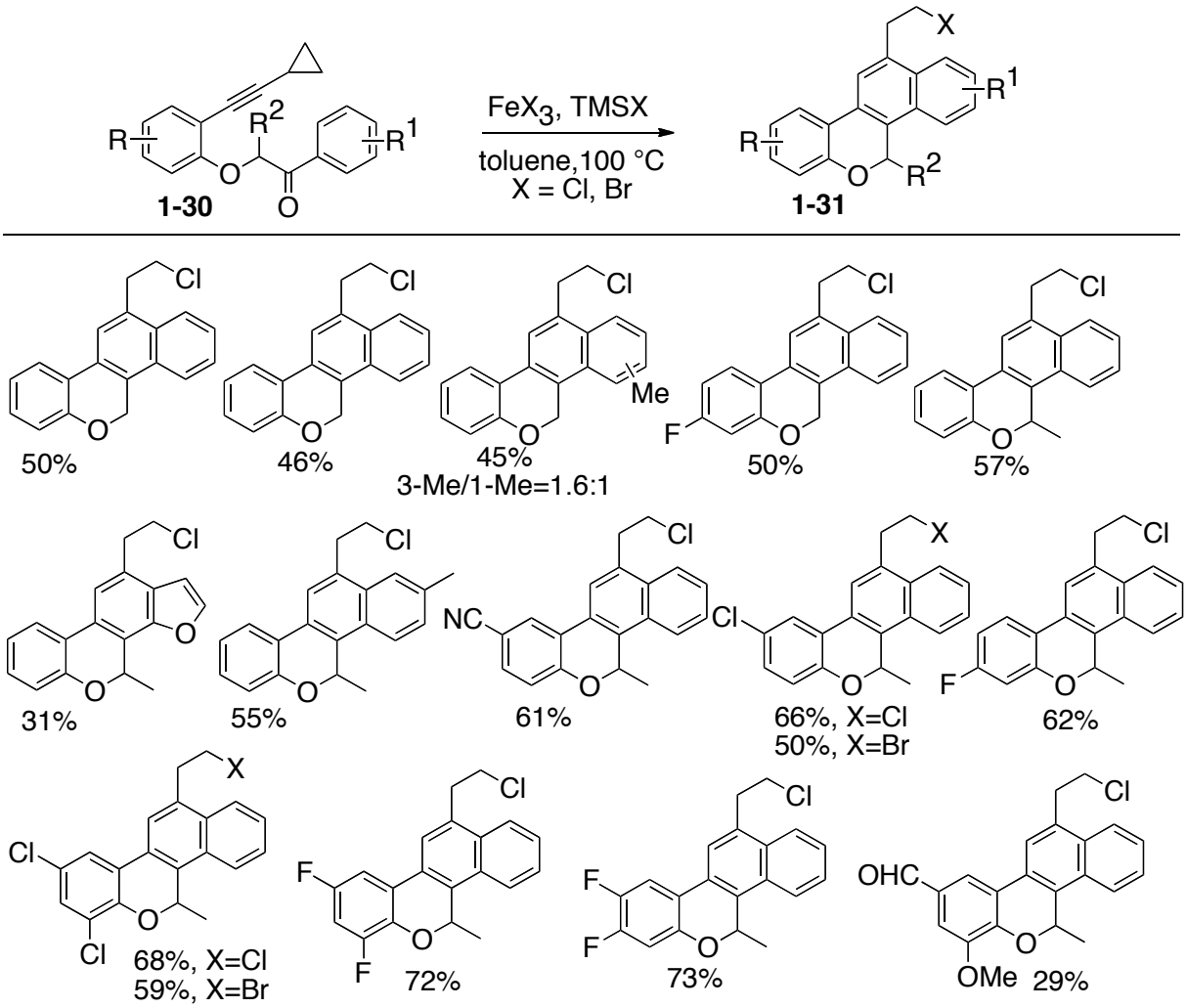
Furthermore, the catalyst was used in the concise synthesis of the naturally occurring 2,2-dimethyl-8-prenyl chromene-6-propenoic acid in 50% yield using five linear steps starting from *p*-iodophenol. The cycloisomerization step afforded the 2H-chromene **1-29** in almost quantitative yield (**Scheme 1.8**).

Scheme 1.8: Chromene-Containing Natural Products



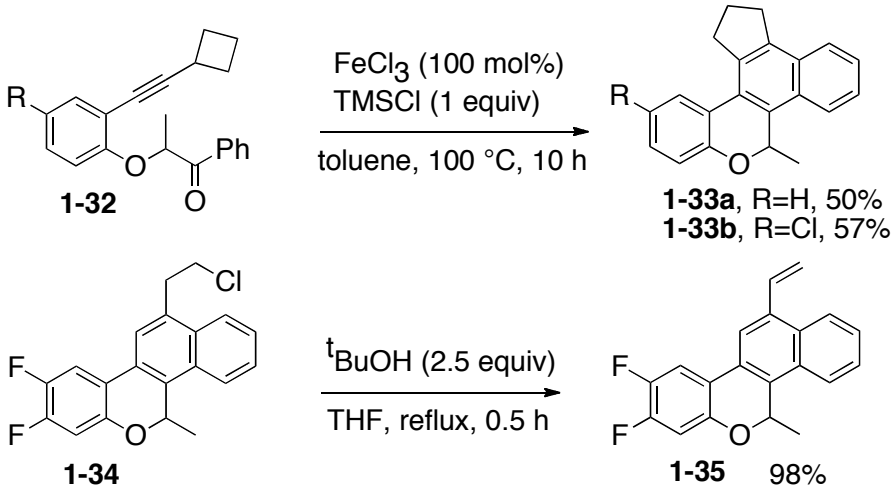
In a recent report, Li et al reported[13] that 5*H*-naphtho[1,2-*c*] chromenes could be synthesized by using an iron-mediated [3+3] annulation strategy starting from 2-(2-ethynyl) phenoxy-1-aryl ethanones. The reaction occurs at 100 °C in toluene in the presence of 100 mol% $FeCl_3$ and 1 equiv TMSCl. Substrates bearing a three-membered carbocyclic ring on the alkyne participated in this [3+3] annulation and different substituents on both aromatic rings of **1-30** were tested (**Scheme 1.9**). Starting materials bearing *p*- or *m*-methyl groups in the benzene ring attached to the carbonyl provided moderate yield. In case of the *m*-methyl substituted substrate two regioisomers were formed in 1.6:1 ratio. Usually, a methyl group at the position α to the ketone gave the best yield. Formyl, methoxy, cyano and halo groups were tolerated on the phenol bearing benzene ring.

Scheme 1.9: Fe-Mediated [3+3]-Annulation



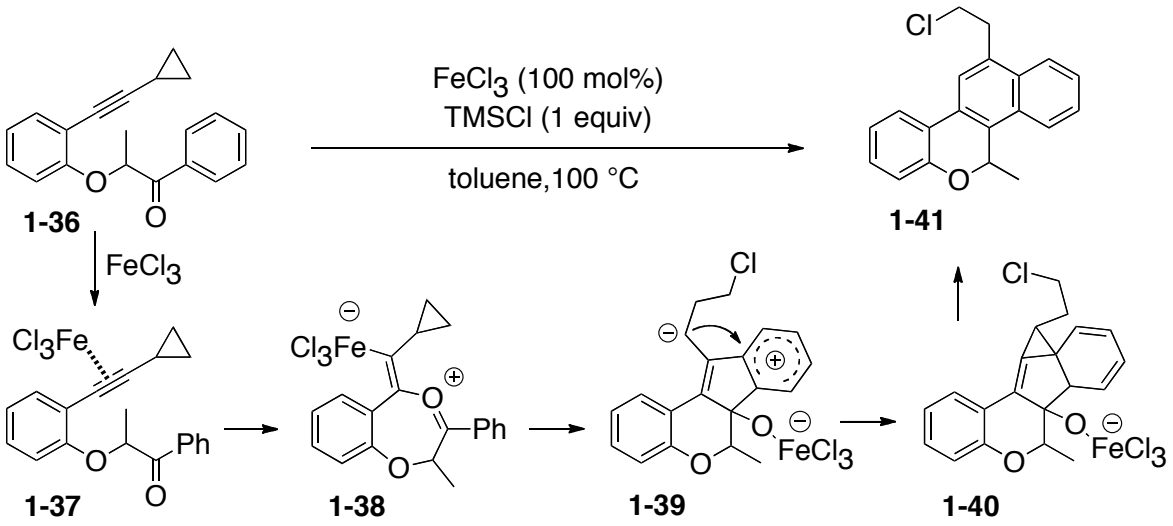
Surprisingly, substrate **1-32** containing a cyclobutane substituent on the alkyne led to a Friedel-Crafts alkylation product rather than chloro-ring opened product as observed with substrates **1-30**. The products from the cyclopropyl substituents **1-30** features interesting halo-ethyl group on the naphthalene moiety. The halo-ethyl group could be used to introduce new functionalities in these systems such as dehydrohalogenation of product, which gives an alkene in near quantitative yield for **1-35** (**Scheme 1.10**).

Scheme 1.10: Further Synthetic Transformation



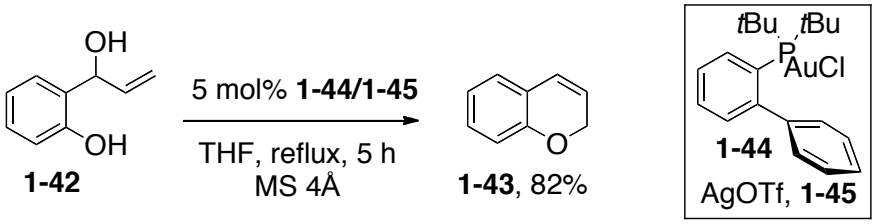
The proposed mechanism suggests that the reaction starts with the activation of alkyne by $FeCl_3$, which is then followed by the nucleophilic attack by ketone leading to intermediate **1-38** (**Scheme 1.11**). Electrophilic addition to the aromatic ring and ring opening generates intermediate **1-39**. Nucleophilic addition and then dehydroxylation and rearrangement gives product **1-41**. Intramolecular Friedel-Crafts alkylation of product **1-41** does not occur presumably due to the high strain of the resulting four-membered ring.

Scheme 1.11: Proposed Mechanism



Very recently, Aponick and coworkers demonstrated[14] that a Au(I)/AgOTf catalytic system can be very effective for the synthesis of a variety of chromenes via a dehydrative *endo*-cyclization of *o*-(1-hydroxyallyl)phenols. Thus, chromene **1-43** was prepared in high yield (82%) using the bimetallic catalytic system [Au(I)/AgOTf] by refluxing in THF for 5 h (**Scheme 1.12**). The use of other Lewis acids was not beneficial in this reaction.

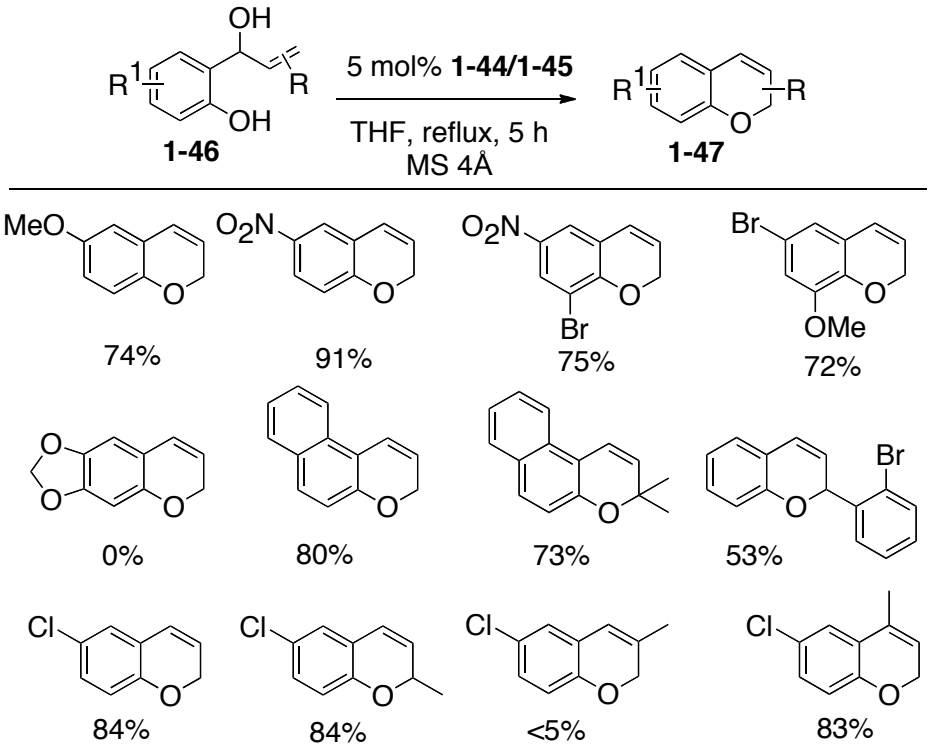
Scheme 1.12: Au-Catalyzed Dehydrative *Endo*-Cyclization



With this optimized protocol, the method was examined for generality with a variety of different substrates (**Scheme 1.13**). The reaction gave good yields for both electron-

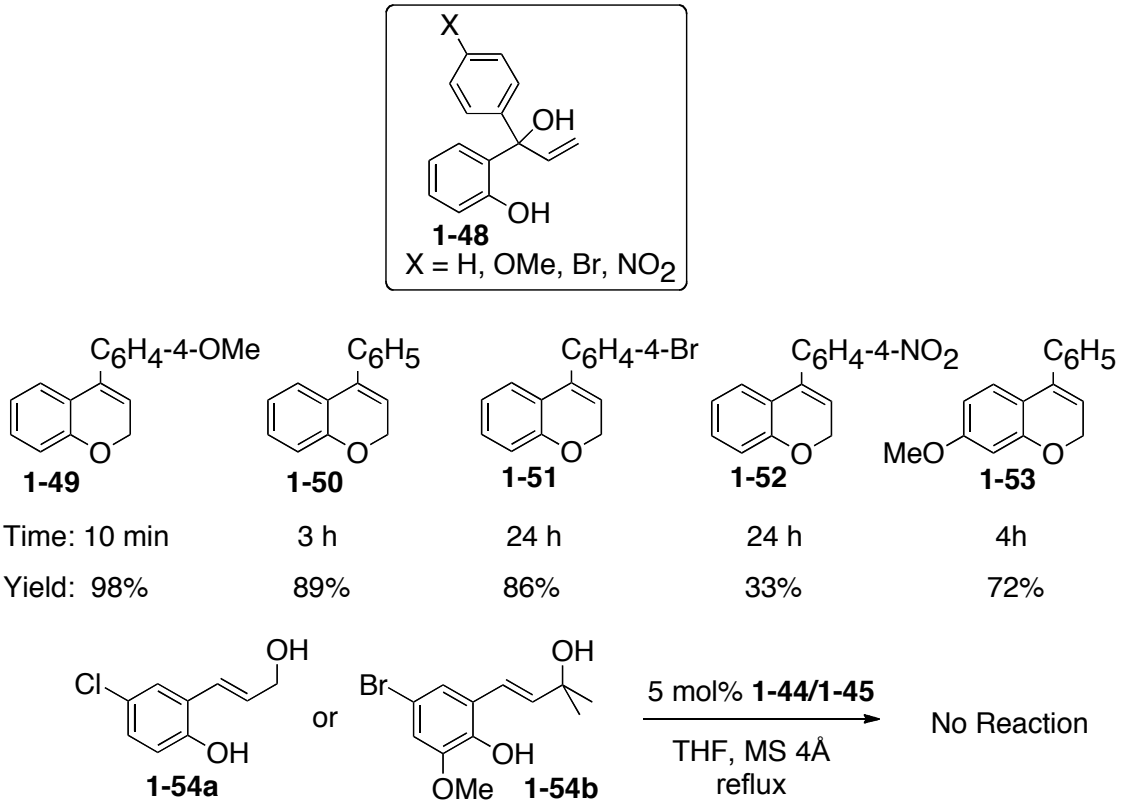
donating and electron-withdrawing groups. Moreover, it proceeded cleanly even with highly substituted phenols and naphthols. Substitution on the pyran ring was also possible by this method by introducing substituents on the alkene of the starting phenol **1-46**. Although, the method proved pretty general, it was observed that inclusion of the dioxolane moiety led to only decomposition of products. Furthermore, the viability of substituents at different positions of the pyran ring was examined and it appeared that the reaction is general regardless of the electronic nature of the substituents on either the pyran or aromatic ring except in the case of 3-methyl-6-chloro-chromene, where only a trace of this material was observed (**Scheme 1.13**).

Scheme 1.13: Substrate Scope



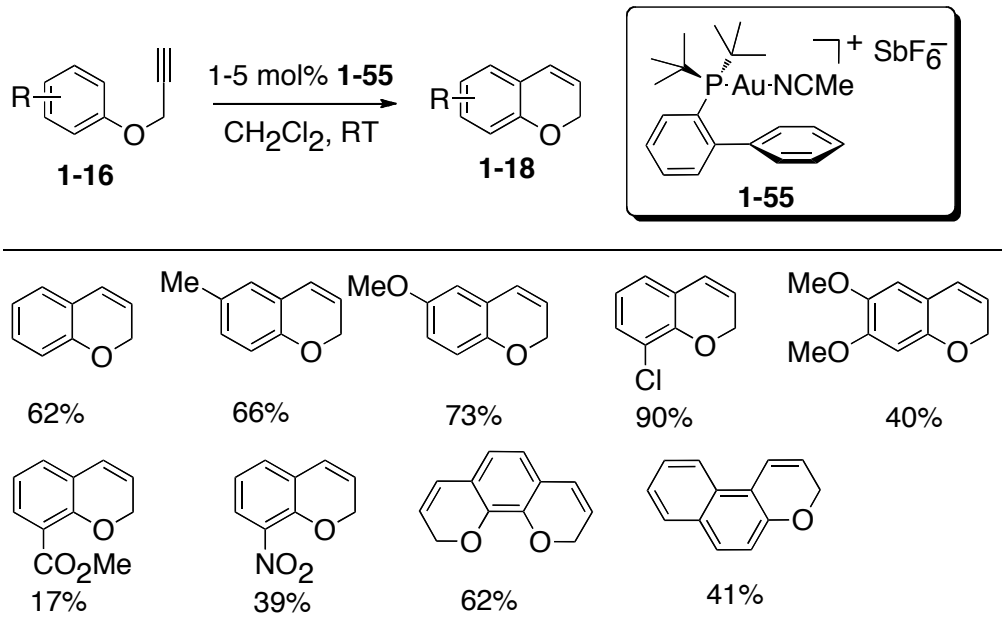
To gain insight into the mechanism, a series of *para*-substituted substrates of the type **1-48** were examined where the electronic effects of substituents were directly conjugated to what might be a cationic centre (**Scheme 1.14**). Electron-donating groups seemed to give faster reactions and better yields. It is worth mentioning that Au-complexes can serve as a π–acid to activate the alkene or as a Lewis acid to ionize the alcohol. Whatever the mechanism, the substituent studies shown in **Scheme 1.14** suggest that positive charge builds up on the allylic alcohol carbons. Surprisingly, when compounds **1-54a** or **1-54b** were subjected to the same reaction conditions there was no reaction; suggesting that the role of catalyst may change depending on the structure of the substrate.

Scheme 1.14: Mechanistic Investigation



The use of a Au(I) catalyst was reported in the cycloisomerization reaction of aryl propargyl ethers to give 2H-chromenes (**Scheme 1.15**).[15] Echavarren and co-workers[15a] used Ph_3PAuCl as the catalyst but it required stoichiometric use of silver salts to be activated. However, these silver salts are often hygroscopic, difficult to use and frequently result in an acidic reaction medium. Also, the presence of silver co-catalyst promotes unwanted side reactions. Banwell et al[16] introduced a commercially available catalyst **1-55** as a solution to these drawbacks as it is far more active than Ph_3PAuCl and does not require in situ activation by AgX.

Scheme 1.15: Au-Catalyzed Cycloisomerization

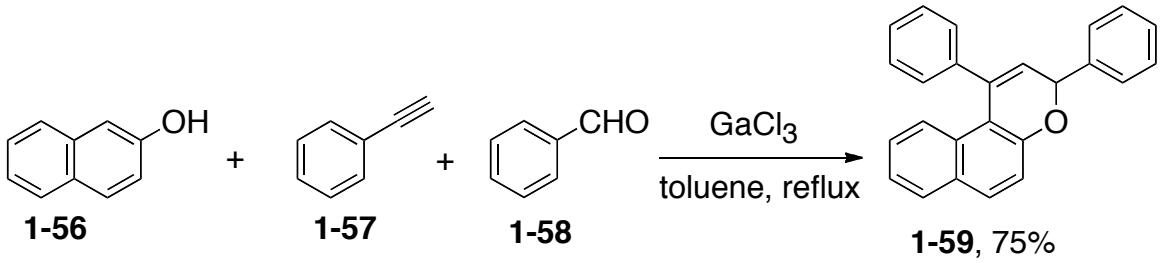


The catalyst was tested with variety of aryl propargyl ethers. Although chromenes could be synthesized exclusively in high yields, in some cases a mixture of benzopyrans and benzofurans formed causing low yields of the chromenes. Since there was no relationship found between the structure of the starting compound and selectivity of the product, the method lost some of its appeal. However, the Au catalyst **1-55** was a great improvement over the previously reported Au(I) catalysts.

Yadav and coworkers reported[17] a multicomponent one-pot approach for the synthesis of naphthopyrans by the coupling of naphthol, alkyne and aldehyde using Gallium(III) chloride (**Scheme 1.16**). Various other metal halides e.g. $FeCl_3$, $BiCl_3$, $InCl_3$, $ZnCl_2$, $CeCl_3 \cdot 7H_2O$, and metal triflates such as $In(OTf)_3$, $Bi(OTf)_3$, $Sc(OTf)_3$, $Yb(OTf)_3$ were attempted but all of them failed to give the desired product. A variety of combination of

substrates including α and β–naphthol, aromatic as well as aliphatic alkynes, aromatic aldehydes and cyclic and acyclic aliphatic aldehydes were tested in this reaction. In all cases the desired naphthopyrans were obtained in good yields. The reaction also worked nicely when simple phenol was used instead of naphthols.

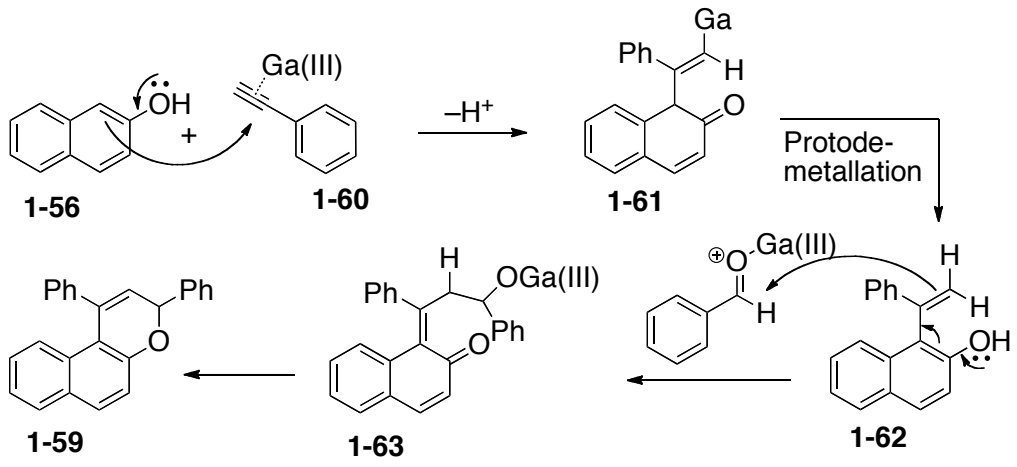
Scheme 1.16: Ga-Catalyzed Multicomponent Reaction



1-56 + **1-57** + **1-58** → **1-59**, 75%

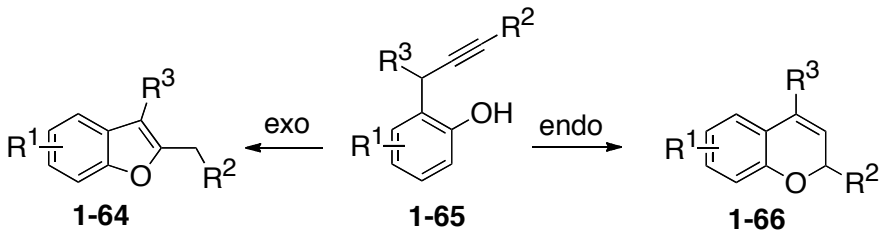
According to the proposed mechanism, Ga(III) first activates the alkyne to promote the nucleophilic attack of naphthol on the alkyne. Proto-demetallation from the resulting vinyl organometallic intermediate **1-61** gave intermediate **1-62**. A Ga(III) activated aldehyde was then attacked by intermediate **1-62**, which was followed by a cyclization to result in the chromene moiety (**Scheme 1.17**).

Scheme 1.17: Proposed Mechanism



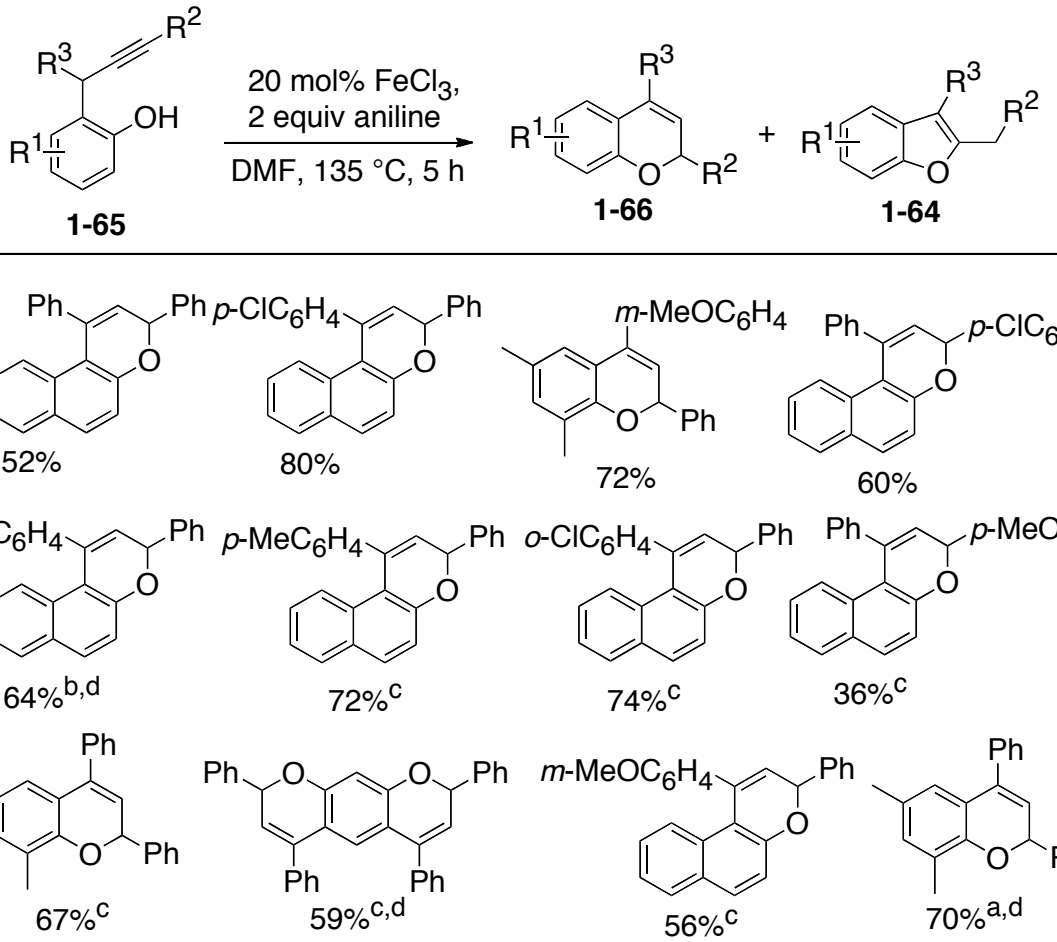
The synthesis of chromenes by metal-catalyzed intramolecular ring closure using various expensive metal catalysts e.g. Pt, Ru, Au, Ag are well known. It is also reported that for metal-mediated hydroaryloxylation of propargyl phenols, an *exo*-attack usually is more facile giving five-membered rings. However, according to Baldwin's rules, both *exo-dig* and *endo-dig* are possible pathways in these types of reaction. Thus, from the point of view of chromene synthesis it would be desirable to develop such a protocol that would produce exclusively six-membered rings. Li et al[18] reported a sustainable, environmentally friendly, regioselective intramolecular hydroaryloxylation protocol for 2-propargyl phenols and naphthols that used the less toxic and inexpensive iron (III) chloride catalyst for the synthesis of densely substituted chromenes (**Scheme 1.18**).

Scheme 1.18: Two Possible Pathways for Metal-Mediated Hydroaryloxylation



Investigating the reaction conditions they observed that aniline was necessary as an additive to give the best selectivity for the benzopyran over the benzofuran products. A variety of 2-propargylphenol and naphthol derivatives were used as the precursors to test the mode of cyclization as well as the regioselectivity of the resulting product. It was found that in presence of 20 mol% iron(II) chloride catalyst and 2 equiv of aniline the reactions proceeded smoothly providing very good yields of the corresponding six-membered heterocycles via the 6-endo-mode of cyclization. However, in few cases both five- and six-membered rings were observed although, the 6-endo-dig mode of cyclization consistently predominated over the 5-exo-dig mode of cyclization (**Scheme 1.19**).

Scheme 1.19: Fe-Catalyzed Hydroaryloxylation

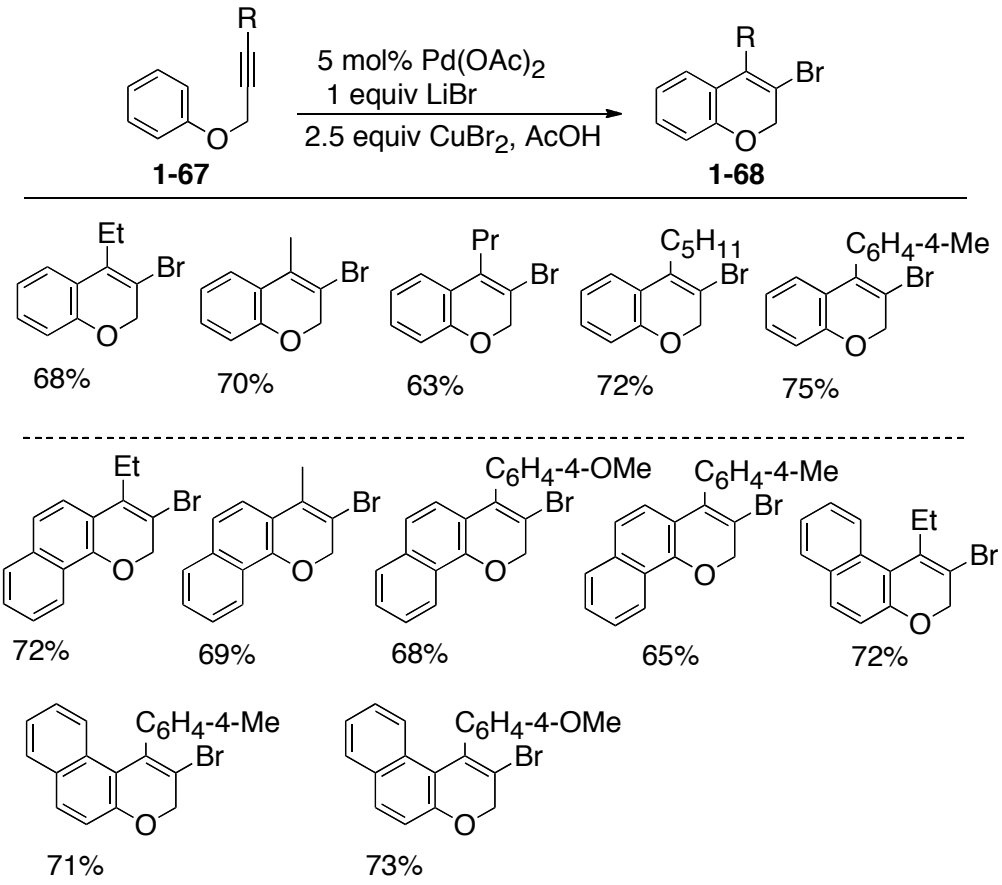


a. The regioselectivity of the crude mixture was **1-66**:**1-64** = 91:9
b. **1-66**:**1-64** = 87:13
c. **1-66**:**1-64** = 95:5
d. Products were isolated as a mixture of **1-66**+**1-64**

The cyclization of simple aryl propargyl ethers can be used as an access to 4-substituted-3-bromo-2H-chromene[19]. This process requires $Pd(OAc)_2$ as catalyst along with stoichiometric quantities of $CuBr_2$ and LiBr. Using this method, a variety of benzopyranes with a bromine at the 3-position and different alkyl and aryl groups in the 4-position could be synthesized in good yields (**Scheme 1.20**). As an extension to the

substrate scope, the method could be extended to a variety of naphthopyrans in a similar fashion starting with naphthyl propargyl ethers. In all cases the yields were moderate to good (**Scheme 1.20**).

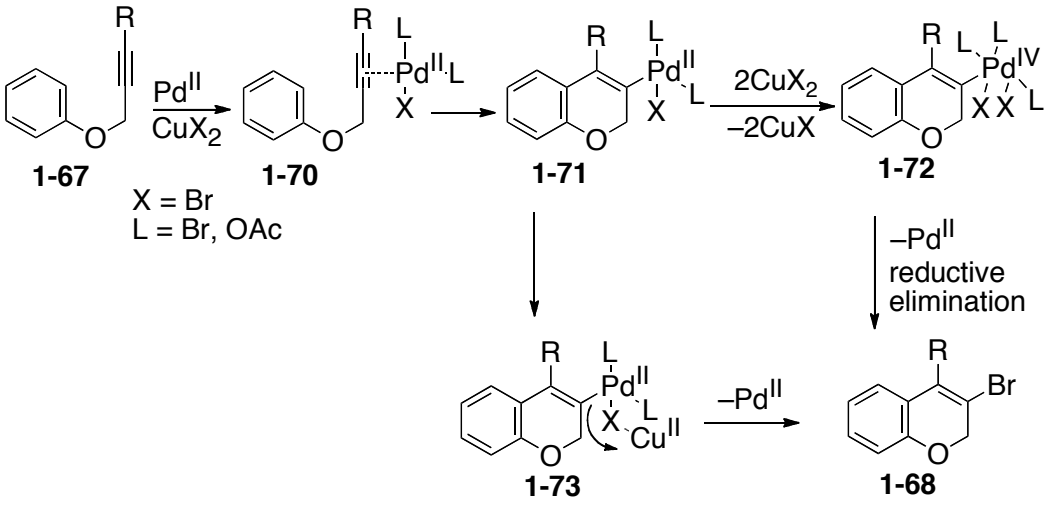
Scheme 1.20: Pd-Catalyzed Cyclization of Aryl Propargyl Ethers



It was found that $Pd(OAc)_2$ and $CuBr_2$ are both essential for the reaction to work at all while LiBr makes the reaction more efficient and selective. The proposed mechanism suggests that the cyclization is promoted by activation of the alkyne via coordination to Pd(II) resulting in the intermediate **1-70**. This species may then lead to Pd(IV)

intermediate **1-72** which by reductive elimination can form product **1-68**. It is also possible that product **1-68** can be formed from intermediate **71** via intermediate **1-73** maintaining a Pd(II) oxidation stage. In this pathway Cu(II) assists in ligand transfer to form the product (**Scheme 1.21**).

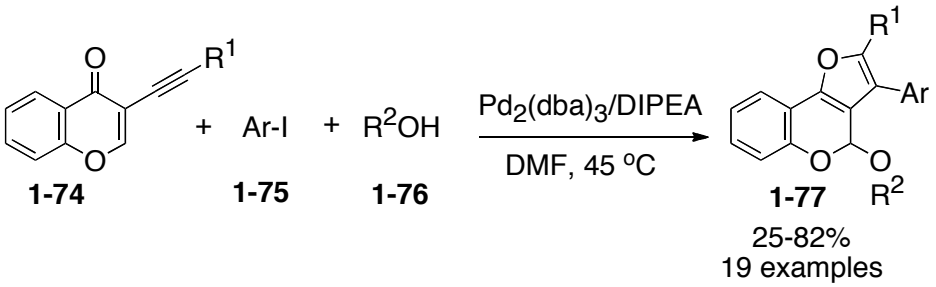
Scheme 1.21: Proposed Mechanistic Pathway



A multi-component reaction involving a palladium-catalyzed 1,4-addition and cyclization cascade was reported[20] for the synthesis of poly-substituted furo[3,2-*c*]chromenes **1-77**. The reaction requires three precursors including 3-(1-alkynyl)chromones **1-74**, aryl iodides **1-75** and alcohols **1-76**. The reaction was run at 45 °C in presence of $Pd_2(dba)_3$ catalyst (10 mol%), DIPEA as base and DMF as solvent. In this process two C-O bonds and one C-C bond were generated simultaneously with the construction of diverse array of furan-fused structures in moderate to good yields. It was found that aryl iodide bearing electron-withdrawing groups are favored the reaction because of a faster

oxidative addition step. For the arynyl moieties of chromones, the presence of electron-donating groups on the alkyne of the chromone led to an increase in yield, while electron-withdrawing groups exhibit a negative effect (**Scheme 1.22**).

Scheme 1.22: Pd-Catalyzed Multicomponent Reaction



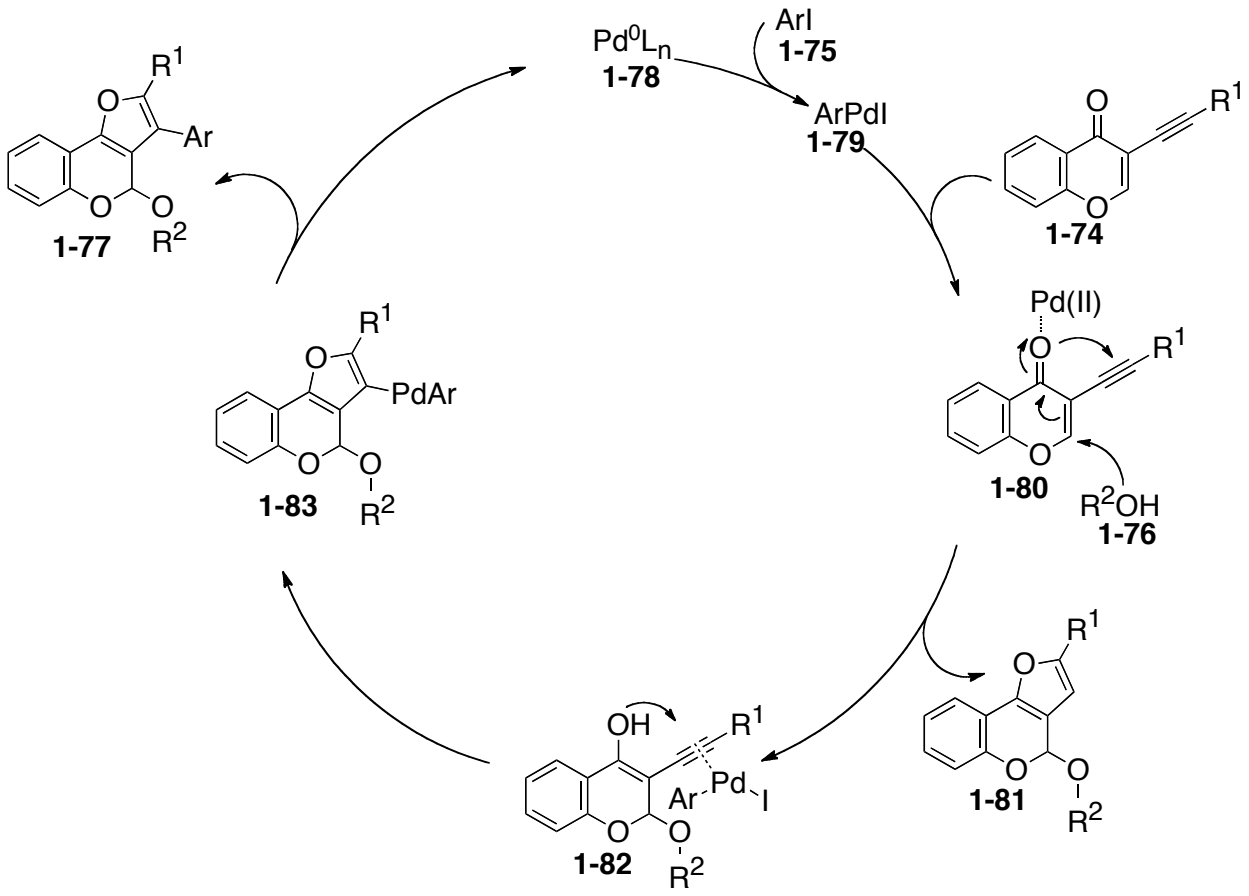
1-74 **1-75** **1-76** **1-77**

25-82%
19 examples

R^1 = C_6H_5, 4-OMe-C_6H_4, 2-F-C_6H_4, 4-CF_3-C_6H_4, $(CH_2)_3CN$, *t*Bu, $(CH_2)_4CH_3$, cyclic secondary alcohol, tertiary alcohol
Ar = aryl, het-aryl
R^2 = Me, *i*Pr, *t*-Bu, Bn, 4-NO_2-C_6H_4

The suggested mechanism is outlined in **Scheme 1.23**. The first step involves the oxidative addition of aryl iodide to palladium and a change of palladium's oxidation state from zero to (II). This Pd(II) species then activates the chromones C=O to promote the 1,4-addition of alcohol. Palladium then migrates to the alkyne to give intermediate **1-82**, which sets up the final cyclization. Finally upon reductive elimination, aryl group ends up in the furan ring of the product. This reductive elimination forms Pd(0) and the catalytic cycle is complete. From this mechanism, one can understand why an electron-donating group on the arylnyl moiety is important to stabilize intermediate **1-82** to prevent direct cyclization to **1-81.**

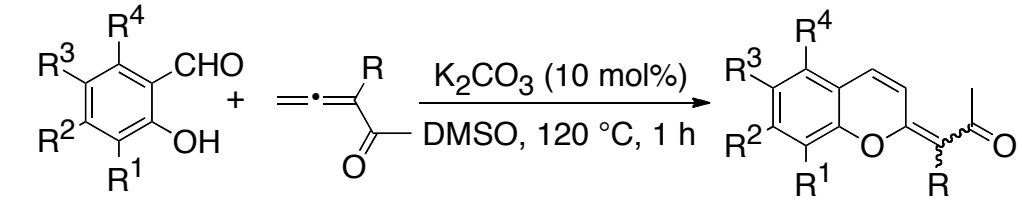
Scheme 1.23: Proposed Mechanism



Shi et al[21] developed a simple way for the synthesis of functionalized 2H-chromenes by the reaction between salicylaldehyde **1-84** and allenic ketones **1-85** or esters **1-87** in the presence of potassium carbonate as the catalyst (**Scheme 1.24** and **1.25**). The reaction appears to be general for a variety of salicylaldehydes **1-84** and allenic ketones **1-85** bearing methyl or benzyl groups at the 3-position. These reactions gave high yields of the chromenes of the type **1-86**, however, the products were obtained as a mixture of *E*- and *Z*-isomers (**Scheme 1.24**). When this method was applied to allenic esters of the type **1-87**, remarkably the chromene products were formed in high yields as exclusively

the *E*-isomer (**Scheme 1.25**). It was found that electron-donating groups on the salicylaldehyde favored higher yields in this reaction. However, with 2-hydroxyacetophenone in place of salicylaldehyde the reaction with allenic ester **1-87** provided a 79% yield of the expected chromene product **1-90** although the same reaction with an allenic ketone did not give any desired product (**Scheme 1.26**).

Scheme 1.24: Synthesis of Chromenes via K_2CO_3-Catalyzed Reaction



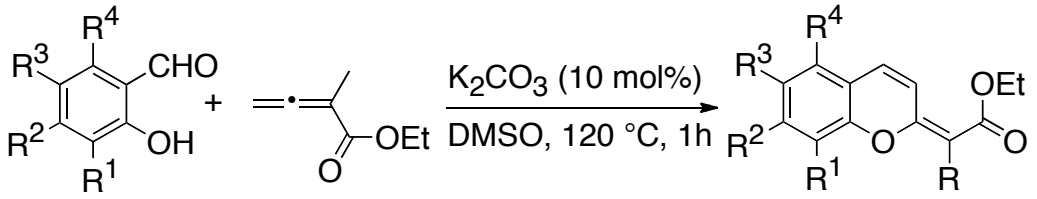
1-84a $R^1=R^2=R^3=R^4=H$

1-85a, R=Me
1-85b, R=Bn

1-86a $R^1=R^2=R^3=R^4=H$, R = Me

Series	R^1	R^2	R^3	R^4	R	Yield (%) **1-86** (*E*/*Z*)
1	H	H	H	H	Me	91 (8.3/1)
2	OMe	H	H	H	Me	>99 (2.1/1)
3	H	OMe	H	H	Me	84 (4.2/1)
4	H	H	OMe	H	Me	>99 (6/1)
5	H	H	Me	H	Me	99 (4/1)
6	H	H			Me	89 (11.5/1)
7	H	H	Br	H	Me	77 (1.7/1)
8	Cl	H	Cl	H	Me	85 (4/7)
9	H	H	H	H	Bn	93 (3.6/1)
10	OMe	H	H	H	Bn	67 (1.5/1)
11	H	H	Br	H	Bn	84 (2/1)

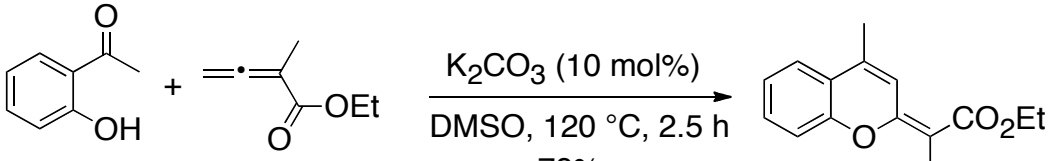
Scheme 1.25: Substrate Scope with Allenic Ester



1-84 **1-87** **1-88**

Series	R^1	R^2	R^3	R^4	Yield (%) of **1-88**
a	H	H	H	H	89
b	OMe	H	H	H	93
c	H	OMe	H	H	84
d	H	H	Me	H	79
e	H	H			88
f	H	H	Br	H	88
g	Cl	H	Cl	H	81

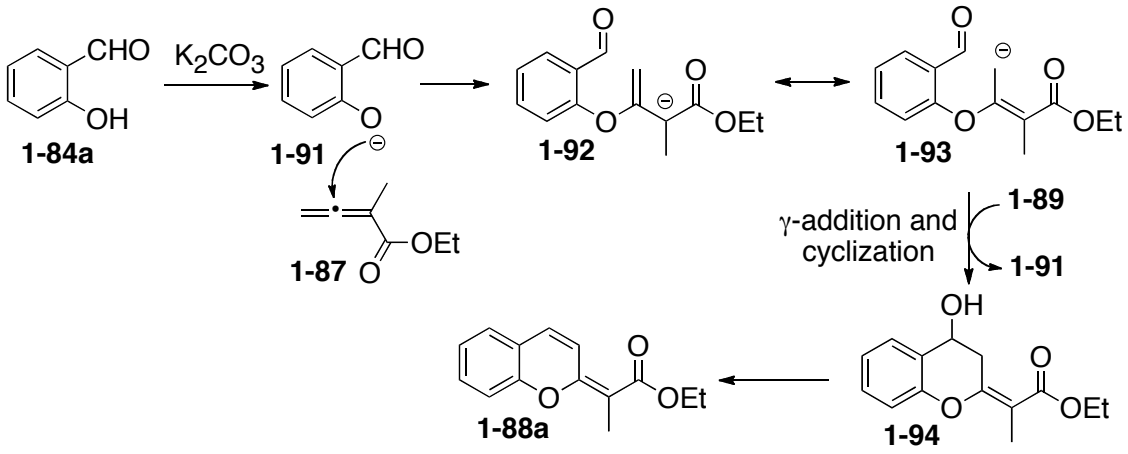
Scheme 1.26: Reaction Between 2-Hydroxyacetophenone and Allenic Ester



1-89 **1-87** **1-90**

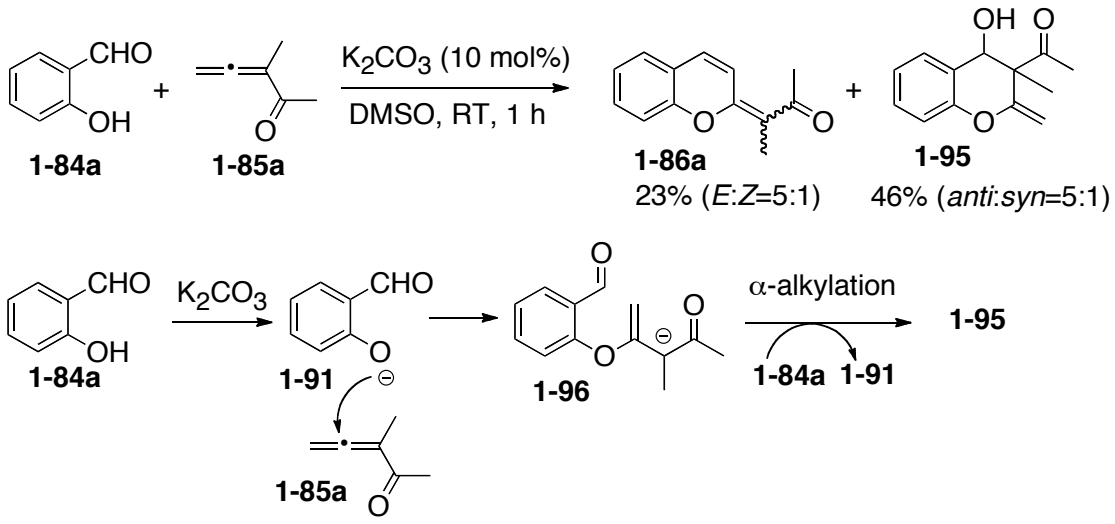
A plausible mechanism is depicted in Scheme **27**. Initially, salicylaldehyde is activated under the basic conditions and attacks the allenic ester to give intermediate **1-92**. This intermediate can participate in an aldol condensation with salicylaldehyde to furnish the chromene product **1-90** (**Scheme 1.27**).

Scheme 1.27: Plausible Mechanism

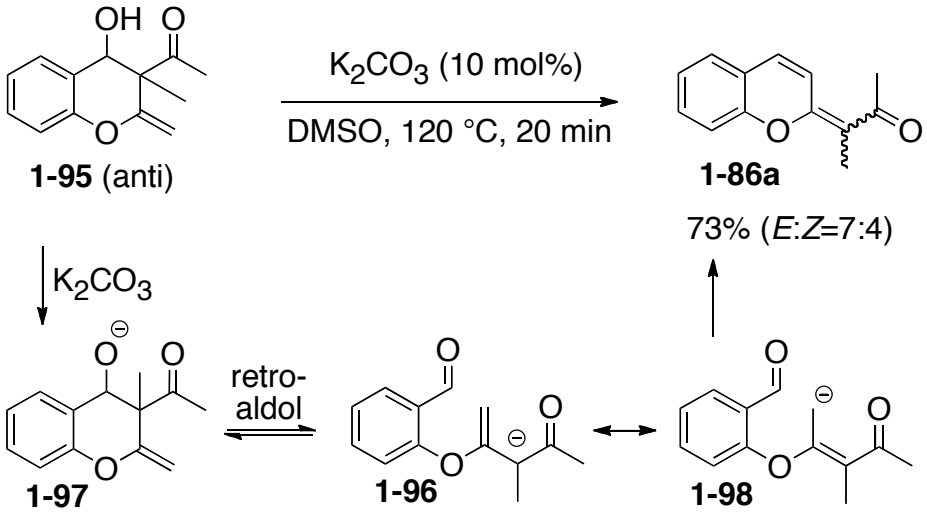


When the reaction between **1-89** and **1-95** was performed at room temperature chromene **1-96** was obtained in low yield along with **1-97**. Compound **1-97** is believed to form by α–alkylation of the aldehyde in intermediate **1-98** (**Scheme 1.28**). The aldol adduct **1-97** is the kinetic product as shown in a control experiment where **1-97** could be converted to **1-96** in high yield at a high temperature. The mechanism of this conversion was proposed to happen by a retro-aldol reaction, and then the aldol condensation of the extended enolate at the γ-carbon (**Scheme 1.29**).

Scheme 1.28: Reaction Between Salicyaldehyde and Allenic Ketone



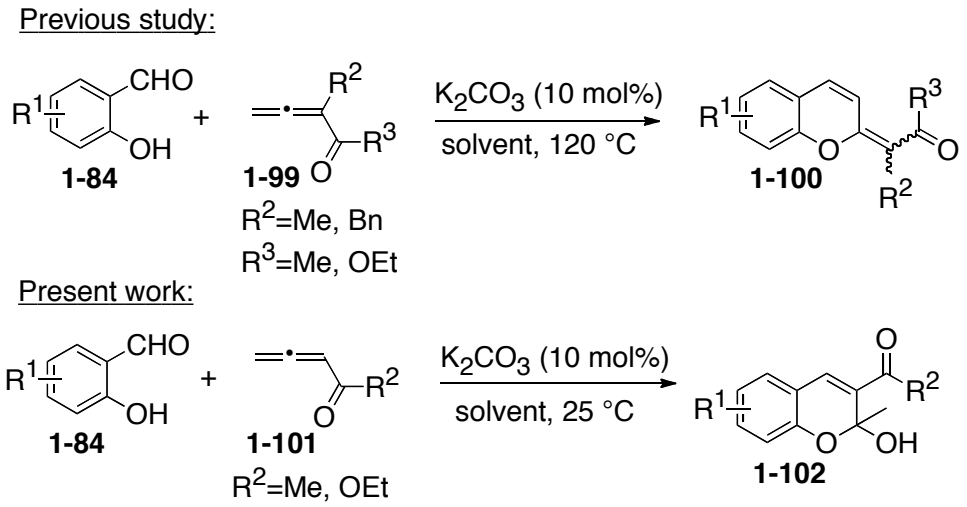
Scheme 1.29: Controlled Experiment



Shi group revisited[21] their chemistry for the synthesis of 2H-chromenes one year later and found that in the presence of K_2CO_3 as catalyst the reactions of salicylaldehydes with unsubstituted allenic esters or ketones preceded smoothly to yield 2H-

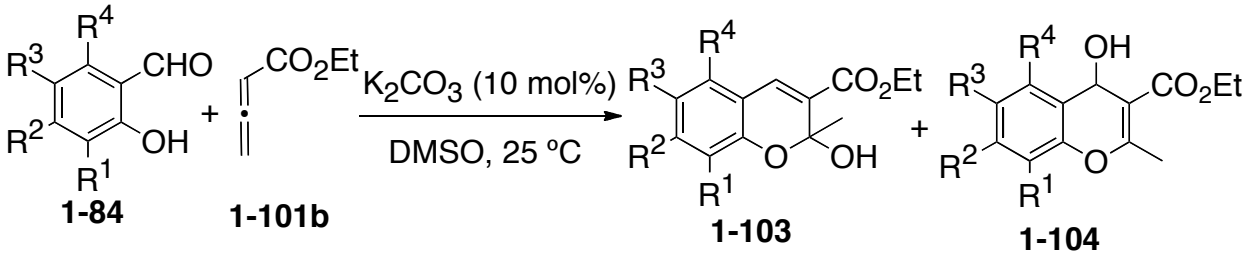
chromenes.[22] It was also demonstrated that the use of elevated temperature (120 °C) in the first report were unnecessary for unsubstituted allenic ketones and esters and instead these reactions could be run at room temperature (**Scheme 1.30**).

Scheme 1.30: Comparison Between Present and Previous Study



Interestingly, the reaction of salicylaldehydes **1-84** with unsubstituted allenic esters gave different products than the substituted allenic esters. These reactions gave either of the products **1-107** or **1-108** in moderate to good yields depending on the isolation strategy. When the reaction product was purified using neutral Al_2O_3 column chromatography only product **1-108** was obtained while purification by silica gel column chromatography exclusively provided product **1-107** (**Scheme 1.31**).

Scheme 1.31: Substrate Scope in the Reaction with Unsubstituted Allenic Esters

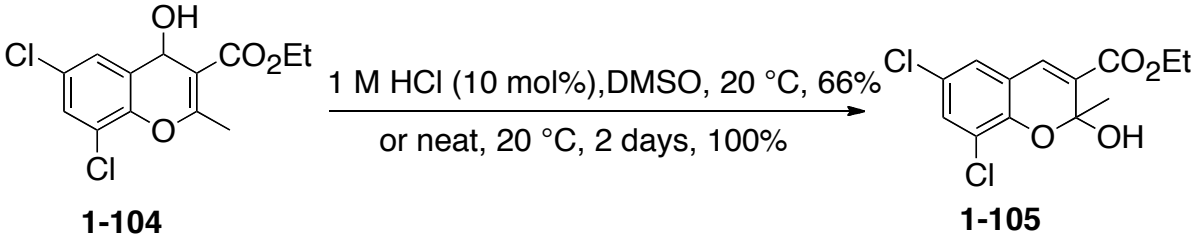


Entry	R^1	R^2	R^3	R^4	Yield (%) of **1-103**[a]	Yield (%) of **1-104**[b]
1	OMe	H	H	H	66	57
2	H	OMe	H	H	67	
3	H	H	OMe	H	71	
4	H	H	Me	H	50	
5	H			H	29	
6	H	H	Cl	H	85	
7	H	H	Br	H	60	68
8	Cl	H	Cl	H	58	63

a. Purification by column chromatography on silica gel
b. Purification by column chromatography on Al_2O_3

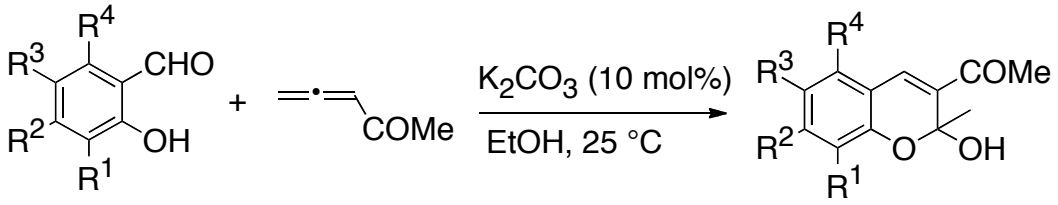
Furthermore, compound **1-109** could be converted to compound **1-110** under acidic condition or simply by allowing **1-109** to stand for 2 days at room temperature in the absence of any reagents (**Scheme 1.32**).

Scheme 1.32: Conversion of Compound **1-109** to **1-110**



Importantly, when the reaction was carried out with the unsubstituted allenic ketone **1-111** under the same conditions in DMSO, the reactions gave a number of by-products. However, these reactions gave good yields of chromene products **1-112** in ethanol as solvent (**Scheme 1.33**).

Scheme 1.33: Substrate Scope in the Reaction with Unsubstituted Allenic Ketone



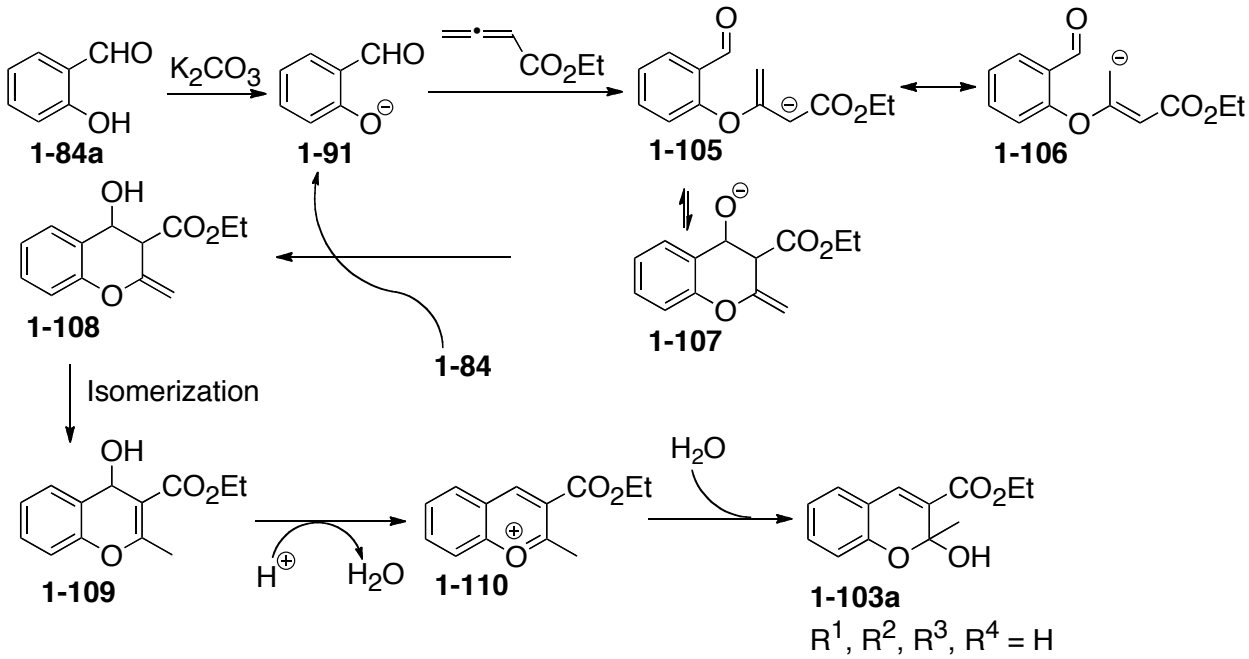
1-84 **1-101a** **1-106**

Entry	R^1	R^2	R^3	R^4	Yield (%) of 1-**106**
1	H	H	H	H	67
2	OMe	H	H	H	68
3	H	H	Me	H	68
4	H	H	Cl	H	64
5	H	H	Br	H	74
6	Cl	H	Cl	H	67

The proposed mechanism is outlined in **Scheme 1.34**. After activation by K_2CO_3, the phenolate anion of salicylaldehyde attacks the allenic ester forming the carbanion **1-113** which then attacks the aldehyde C=O to complete the cyclization. The oxyanion intermediate **1-115** abstracts a proton from salicylaldehyde **1-89** to afford compound **1-116** and regenerate **1-91**. Compound **1-116** is isomerized to **1-117** and then dehydration gives the pyrylium intermediate **1-118**, which is subsequently attacked by H_2O to form

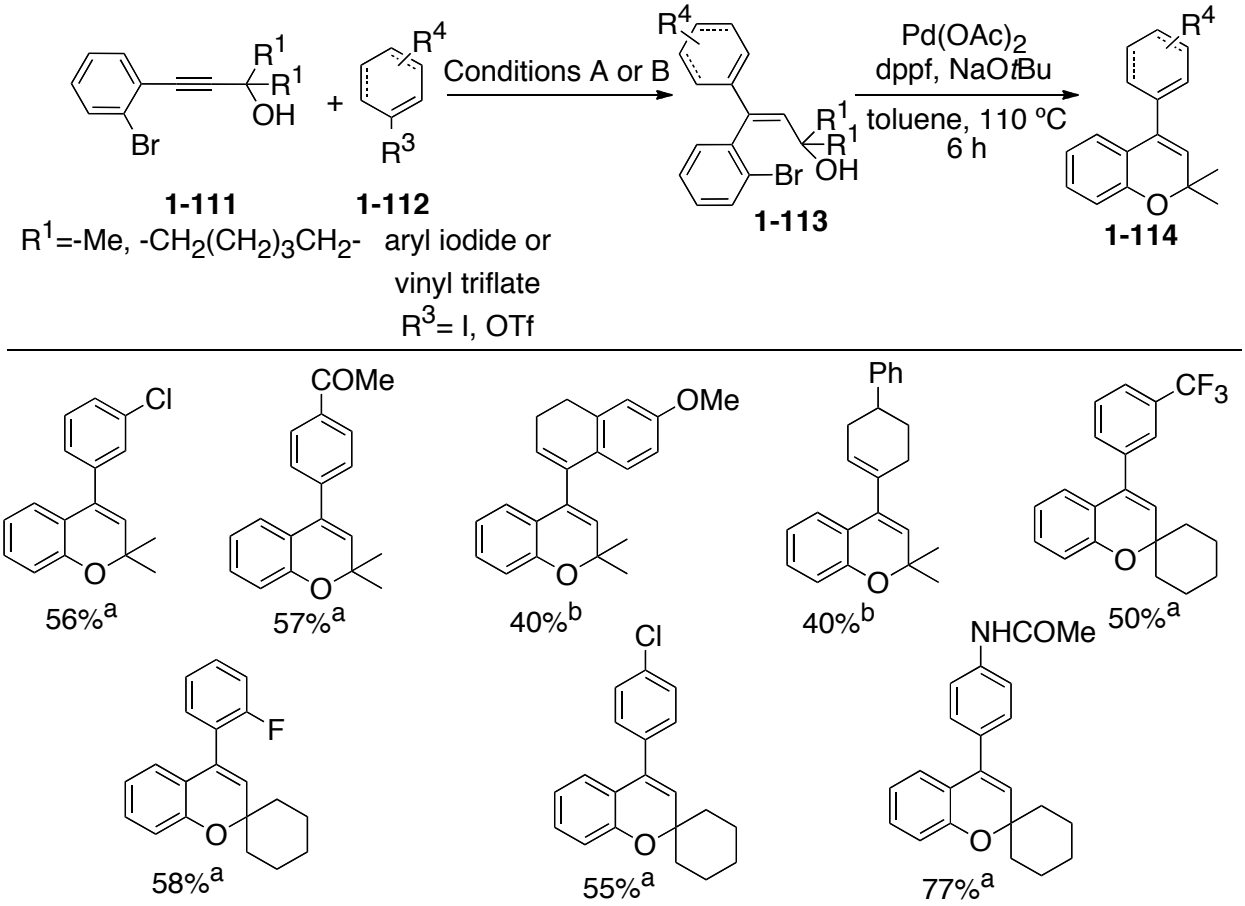
product **1-119**. Moreover, this proposed mechanism was supported by labeling experiments.

Scheme 1.34: Proposed Mechanism



2,2-Dialkyl-2H-chromenes with an aryl or a vinyl substituent at the 4–position were synthesized from the readily available tertiary 3-(*o*-bromophenyl) propynols via a palladium-catalyzed hydroarylation/hydrovinylation-cyclization sequence (**Scheme 1.35**).[23] The cyclization step involves an intramolecular Buchwald-Hartwig C–O bond forming reaction. This method was expected with different types of aryl iodides and vinyl triflates **1-121** in reactions with the propynols **1-120**. The reactions gave moderate yields of the corresponding chromene and spirochromene products.

Scheme 1.35: Pd-Catalyzed Hydroarylation/Hydrovinylation Cyclization



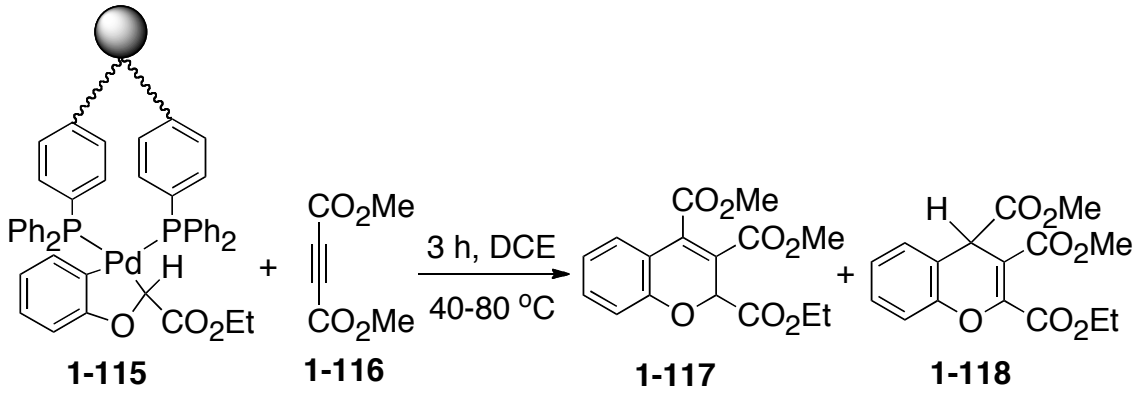
a.Conditions A (aryl idodides): Bu_3N, HCOOH, Bu_4NCl, $Pd(OAc)_2$, THF, 60 ºC
b.Conditions B (vinyl triflates): HCOOK, $Pd(OAc)_2$, DMF, 40 ºC

Since both steps involve a palladium catalyst, attempts were made to develop the chromene synthesis in **Scheme 1.35** as a pseudo-domino process[24], which would have the advantage of simplifying the procedure. This was attempted with the optimized hydroarylation conditions but no cyclization was observed even after prolonged reaction time or even at elevated temperature. Combination of cyclization and hydroarylation also failed to give the desired product. However, it was found that simply omitting the work up between two steps led to the expected chromene product in good yield. It was

obvious from this observation that addition of fresh $Pd(OAc)_2$ was necessary for the second step to give good yield of chromene. This is probably because of the irreversible precipitation of the majority of the catalyst in the first step. Since chloride ions stabilize low-ligated Pd(0) species, one equivalent of Bu_4NCl was added at the beginning instead of the addition of fresh $Pd(OAc)_2$ after the first step and the reaction seemed to work nicely. However, as a generalized procedure the reaction required the presence of Bu_4NCl and the addition of fresh $Pd(OAc)_2$, NaO*t*Bu and dppf in the second step. Attention should be called to another palladium catalyzed synthesis of 4-ethoxy-2,2-disunstituted chromenes reported by Venturello et al,[25] involving a Suzuki coupling but the scope was not examined.

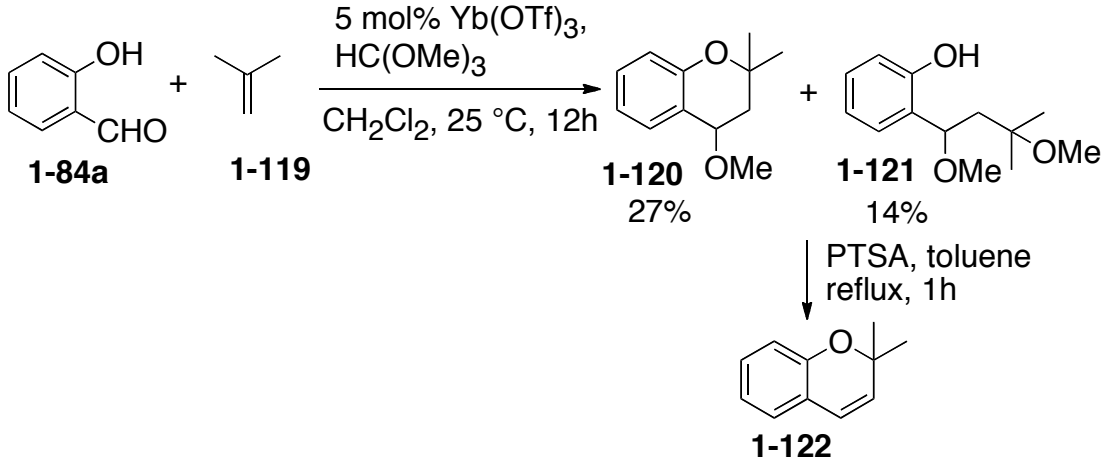
In 2006, Malinakova et al reported[26] the synthesis of polymer-supported palladacycles, which were used for the further development of a method for the synthesis of 2H-chromenes (**Scheme 1.36**). They showed that the palladacycles **1-124**, installed on a variety of resins, would react with dimethyl acetylene dicarboxylate (DMAD) **125** in DCE, to afford the 2H-chromene **1-126** in yields superior to those of analogous solution phase reactions. Small amounts of the chromatographically inseparable 4H-chromene **1-127** was also observed which was probably generated from the in-situ isomerization of the original 2H-chromene caused by the high local concentrations of the phosphine and the palladacycle at elevated temperature under the employed reaction conditions.

Scheme 1.36: Polymer Supported Synthesis of Chromenes



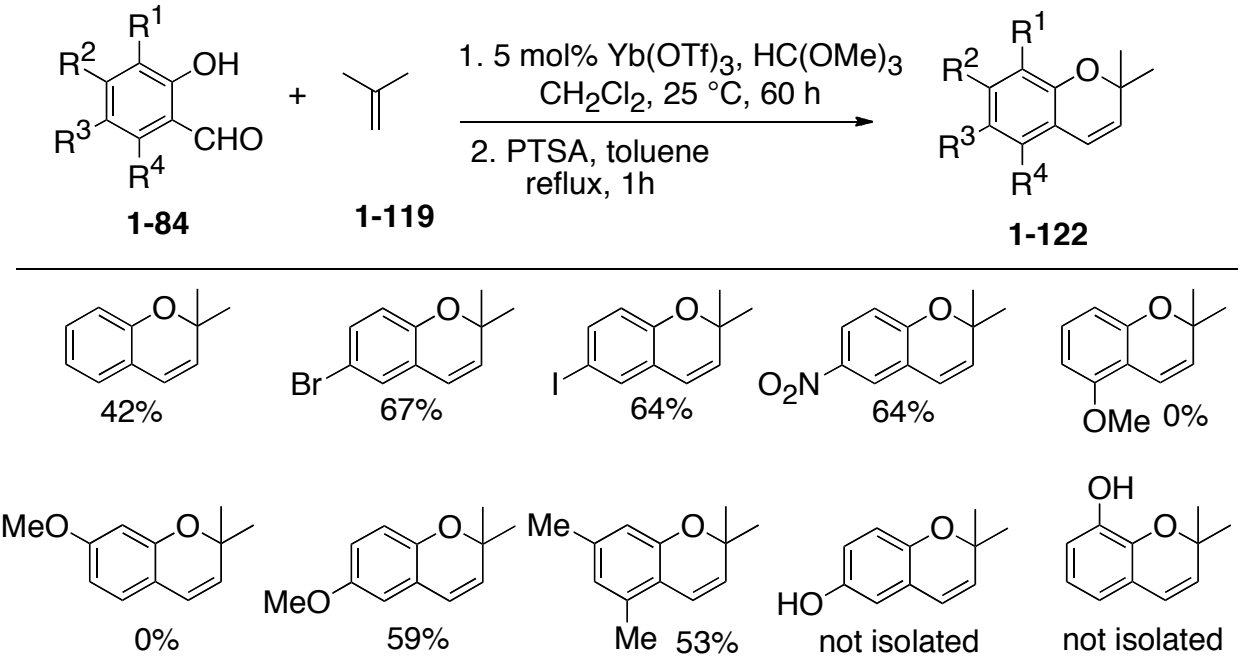
Janin et al developed[27] a two-step protocol for the synthesis of 2,2-dimethyl-2H-chromenes from salicylaldehydes and olefins (**Scheme 1.37**). For example, salicylaldehyde **1-89** and 2-methyl propene **1-128** will react in presence of ytterbium triflate to ultimately give the 2,2-dimethylchromene **131** in two steps. In the first step, compounds **1-129** and **1-130** were isolated in 27% and 14% yield. The intermediates **1-129** and **1-130** can both be converted to the chromene **131** by refluxing with *p*-toluenesulfonic acid in toluene. The overall yield of **131** is 42% (from **1-89**) when the crude reaction mixture from the first step is taken on.

Scheme 1.37: Yb-Catalyzed Synthesis of Chromenes

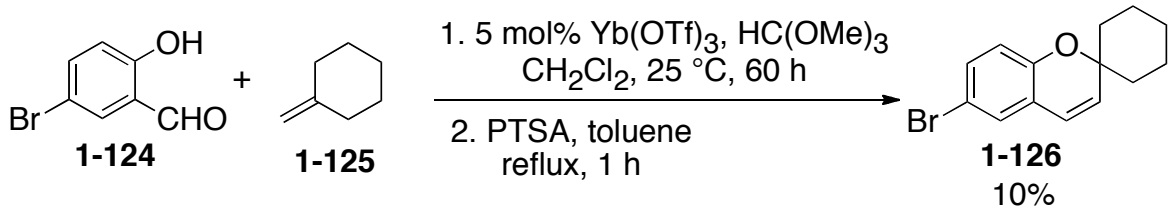


To test the generality of this protocol Janin et al carried out a number of reactions with a variety of substituents on the salicyaldehyde and it was found that the reaction worked well with both electron-withdrawing and electron-donating substituents (**Scheme 1.38**). One limitation is that the reactions fails when a OMe group is at the *ortho*- or *para*-position to the aldehyde function. In the case of the salicylaldehydes bearing an additional hydroxyl group, the products were detected in ^{1}H NMR spectra of the crude reaction mixture in 10-20% yield but they could not be isolated because of the presence of some unidentified compounds of similar polarity. This method could be extended to the preparation of the spirochromene II **1-135** although the yield was poor (10%) (**Scheme 1.39**).

Scheme 1.38: Substrate Scope

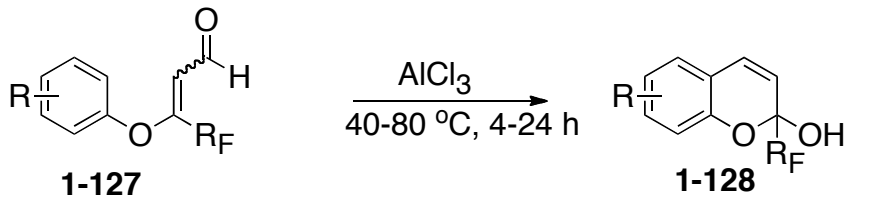


Scheme 1.39: Synthesis of Spirochromene by Yb-Catalysis



Laurent and co-workers reported[28] that the synthesis of 2-(fluoromethyl)- and 2-(perfluoroalkyl)-2-hydroxy-2H-chromenes of the type **1-137** could be achieved in good overall yield and conversion by intramolecular cyclization of 3-(perfluoroalkyl)-3-phenoxypropenals **1-136** in the presence of aluminum chloride (**Scheme 1.40**). They showed that the method is general for a large number of substituted 2-(perfluoroalkyl)-2-hydroxy-2H-chromenes **1-137**.

Scheme 1.40: $AlCl_3$-Catalyzed Intramolecular Cyclization



1-127 **1-128**

R = H, OMe, Me, Cl, CN, NO_2
R_F = CF_3, C_3F_7, C_5H_{11}

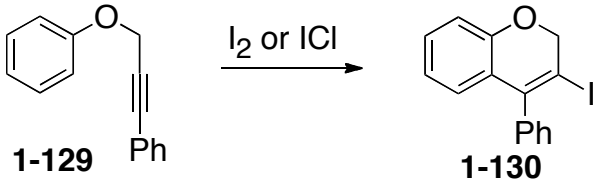
15 examples
55-92% conversion

1.2.1.2. Metal-free Approach for the Synthesis of Chromenes

Larock et al described[29] the electrophilic cyclization of substituted propargylic aryl ethers by I_2, ICl, and PhSeBr which eventually produces the 3,4-disubstituted 2*H*-benzopyrans in excellent yields. This methodology results in vinylic halides or selenides under mild reaction conditions and tolerates a range of functional groups, including methoxy, alcohol, aldehyde, and nitro groups (**Scheme 1.41** and **Scheme 1.42**). They observed that when I_2 is used as electrophile in this reaction $NaHCO_3$ is essential, however the use of ICl as an electrophile did not require $NaHCO_3$. In both cases, nitromethane proved to be the best choice of solvent. A range of substituted aryl propargyl ethers were examined under these conditions and it was found that use of I_2 or ICl as electrophile gave smooth cyclization for substrates contained either an aryl or olefinic group at the alkyne terminus. The reaction also worked well with PhSeBr as the electrophile in dichloromethane solvent. The cyclization was unsuccessful for substrates with an alkyl group on the alkyne terminus for I_2 or ICl as electrophile, but was

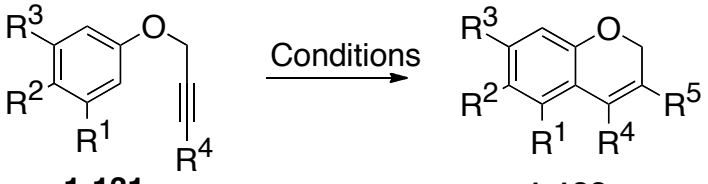
successful with PhSeBr. Surprisingly, the hydroxy-methyl substituted propargylic aryl ether successfully reacted with both I_2 and ICl. The introduction of electron-donating groups on the aromatic ring was observed to render a positive effect on the yield while electron-withdrawing groups had the opposite influence (**Scheme 1.42**).

Scheme 1.41: Electrophilic Cyclization of Propargylic Aryl Ethers



1-129 **1-130**

Scheme 1.42: Substrate Scope



1-131 **1-132**

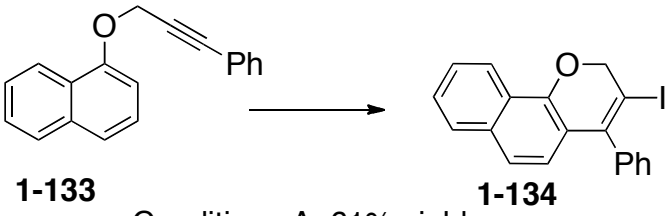
38 examples
Yield: 39-96%

R^1 = tBu, Cl, OMe
R^2 = Me, tBu, OMe, Cl, CHO
R^3 = tBu, Cl, OMe
R^4 = Ph, C_6H_4Me-p, C_6H_4OMe-p, $C_6H_4NO_2$-p, C_6H_4Me-o, cyclohexenyl, CH_2OH, Me
R^5 = I, SePh

Conditions A: $NaHCO_3$ (0.50 mmol), I_2 (0.75 mmol), CH_3NO_2 (5 mL), 25 °C, 24 h.
Conditions B: ICl (0.375 mmol), CH_3NO_2 (5 mL), -25 °C, 30 min.
Conditions C: PhSeBr (1.2 equiv), CH_2Cl_2 (5 mL), 25 °C.
Conditions D: CH_2Cl_2 was used as the solvent for condition B at -78 °C.

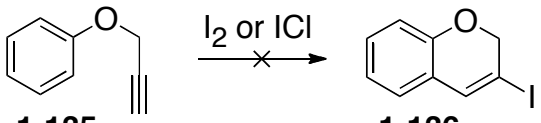
Furthermore, they also showed that the α-naphthyl propargyl ether **1-142** responded quite well in this reaction giving a modest yield of the corresponding naphthochromene **1-143**. Unfortunately, the simple phenyl propargyl ether **1-144** failed to give the desired product in this reaction (**Scheme 1.43**).

Scheme 1.43: Electrophilic Cyclization of α-Naphthayl Propargyl Ethers



1-133 **1-134**

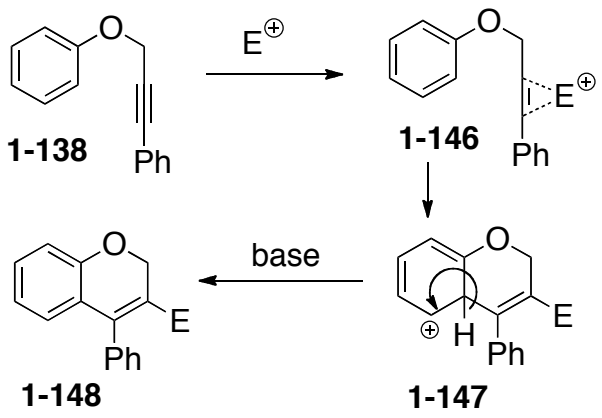
Conditions A: 61% yield
Conditions B: 50% yield



1-135 **1-136**

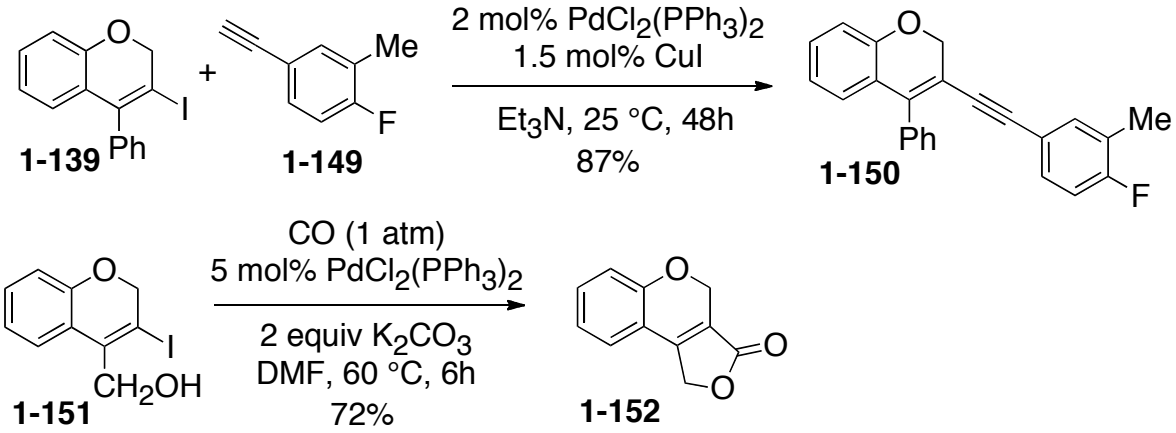
The proposed mechanism suggests that the reaction is promoted by the formation of an iodonium or selenonium intermediate from addition to the triple bond, which is then attacked by aromatic ring in the cyclization step (**Scheme 1.44**). Finally, loss of proton results in the formation of 2H-chromene.

Scheme 1.44: Proposed Mechanism



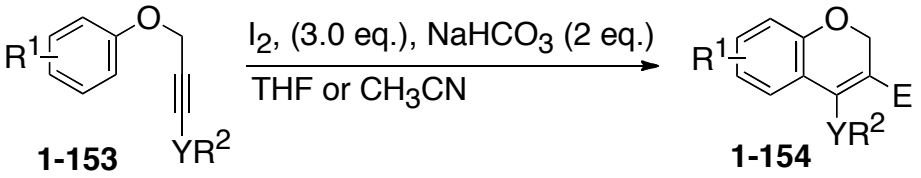
Interestingly, the iodine moiety in the final product can be used to introduce further functionalization. The two examples shown in **Scheme 1.45** involve a Sonogashira reaction to give the alkynyl chromene **1-150** in 87% yield and the formation of lactone **1-152** in 72% yield via a Pd-catalyzed CO insertion reaction on the chromene **1-151** (**Scheme 1.45**).

Scheme 1.45: Further Functionalization



Subsequently, Zeni and co-workers studied[30] the same type of electrophilic cyclization on organochalcogen substituted propargyl aryl ethers as precursors and showed that with the use of three equivalents of I_2 and Na_2CO_3 in THF or CH_3CN, the reactions proceeded smoothly to give a wide range of 3- and 4-substituted chromenes in moderate to high yields (**Scheme 1.46**). Notably, they also studied these same reactions employing Larock's[29] conditions in nitromethane to find that no reaction occurred.

Scheme 1.46: Electrophilic Cyclization of Organochalcogen Propargyl Aryl Ethers



1-153 **1-154**

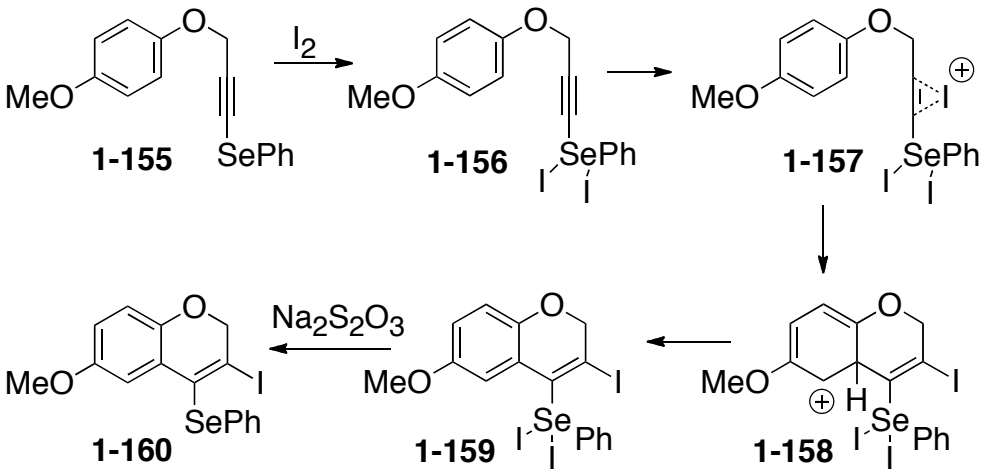
R^1 = Me, ^{t}Bu, OMe, Cl, Ph
YR^2 = Se-aryl, Se-alkyl, Te-aryl, Te-alkyl

30 examples
up to 83% yields

According to the proposed mechanism, the first step of this reaction involves the usual reaction of organochalcogen propargyl aryl ethers with I_2 to give the selenium (IV) intermediates. Subsequently, the cyclization proceeded through the following sequences: (i) coordination of the carbon-carbon triple bond to the electrophilic reagent to generate the iodonium intermediate **1-157**, (ii) attack of electrons from the aromatic ring on the activated triple bond to give the intermediate **1-158**, (iii) and the removal of a proton to restore the aromaticity providing the the cyclized organochalcogen (IV)

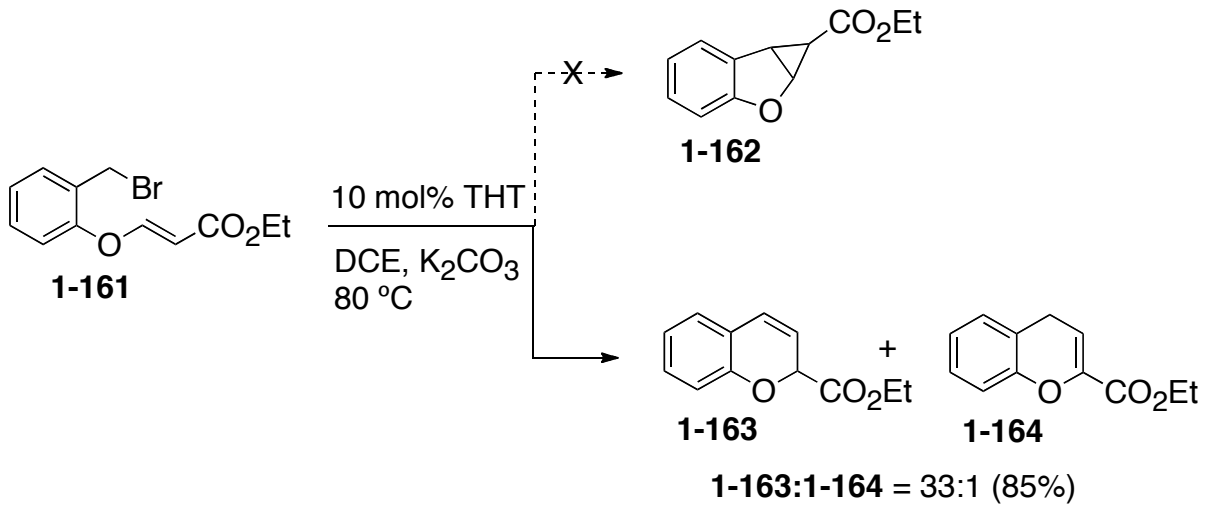
species **1-159**, which was reduced to an organochalcogen (II) species by sodium thiosulfate which was used in the workup to remove the excess iodine (**Scheme 1.47**).

Scheme 1.47: Proposed Mechanism



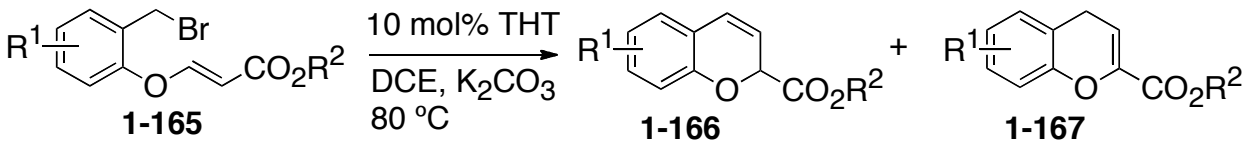
Tang and coworkers described[31] an unprecedented annulation reaction from an ylide generated from halide **161** and tetrahydrothiophene (THT) that involves tandem Michael addition/reverse Michael/allylic substitution that leads to the synthesis of 2-substituted 2H-chromenes (**Scheme 1.48**). This synthesis was rather unexpected because under the reaction conditions the cyclopropane **162** was the expected product. However, there was no trace of **162** and instead chromene **163** was obtained in 85% yield.

Scheme 1.48: Synthesis of 2-Substituted 2H-Chromenes via Michael Addition/Reverse Michael/Allylic substitution Cascade



The scope was examined with a variety of unsaturated esters and with a variety of substituents on the phenyl ether ring. The desired chromenes were obtained in high yields despite the fact that 4H-chromenes were obtained in some cases as minor products. The ratio of 2H-chromenes to 4H-chromenes seemed to be substrate dependent and in the worst case 8:1 in favor of the 2H-chromenes (**Scheme 1.49**).

Scheme 1.49: Substrate Scope

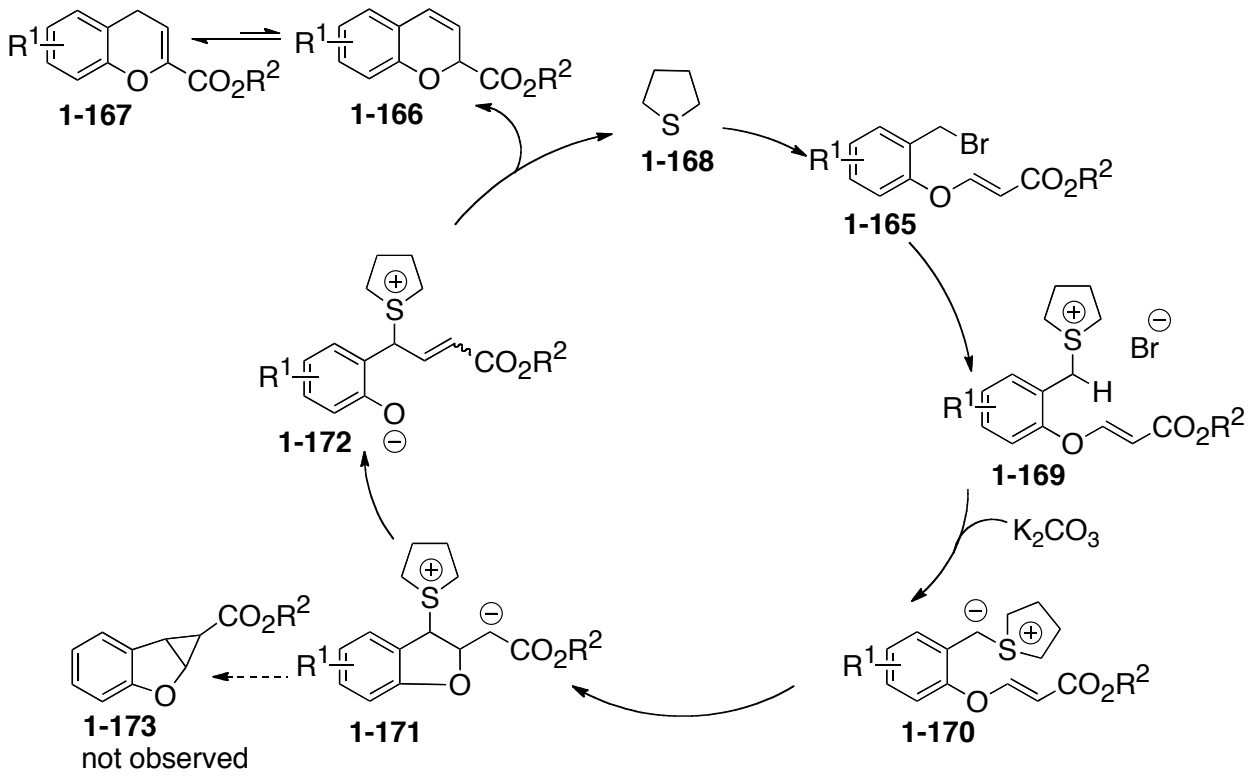


entries	R^1	R^2	yield (%)	**1-166**:**1-167**
1	H	Et	85	33:1
2	H	Et	92	35:1
3	H	Me	99	8:1
4	H	iPr	83	34:1
5	H	Bn	87	57:1
6	1-naphthyl	Et	88	37:1
7	6-tBu	Et	99	>99:1
8	6-tBu	Et	97	>99:1
9	4-Me	Et	85	20:1
10	4-Cl	Et	75	14:1
11	5-Cl	Et	76	45:1
12	4-Br	Et	81	20:1

A plausible mechanism was proposed for this reaction, which begins with the reaction of tetrahydrothiophene **1-168** with bromide **1-165** to form sulfonium salt **1-169**, which after deprotonation by K_2CO_3 forms the sulfonium ylide **1-170**. An intramolecular Michael addition, followed by a retro-Michael reaction produces intermediate **1-172**. An intramolecular S_N2' reaction of intermediate **1-172** affords the 2H-chromene **1-166** and regenerated tetrahydrothiophene **1-168** to close the catalytic cycle. 2H-chromene **1-166** could be slowly transformed to 4H-chromene **1-167** in presence of K_2CO_3 and that is the reason why the 4H-chromene **1-167** is observed as a minor product in some cases

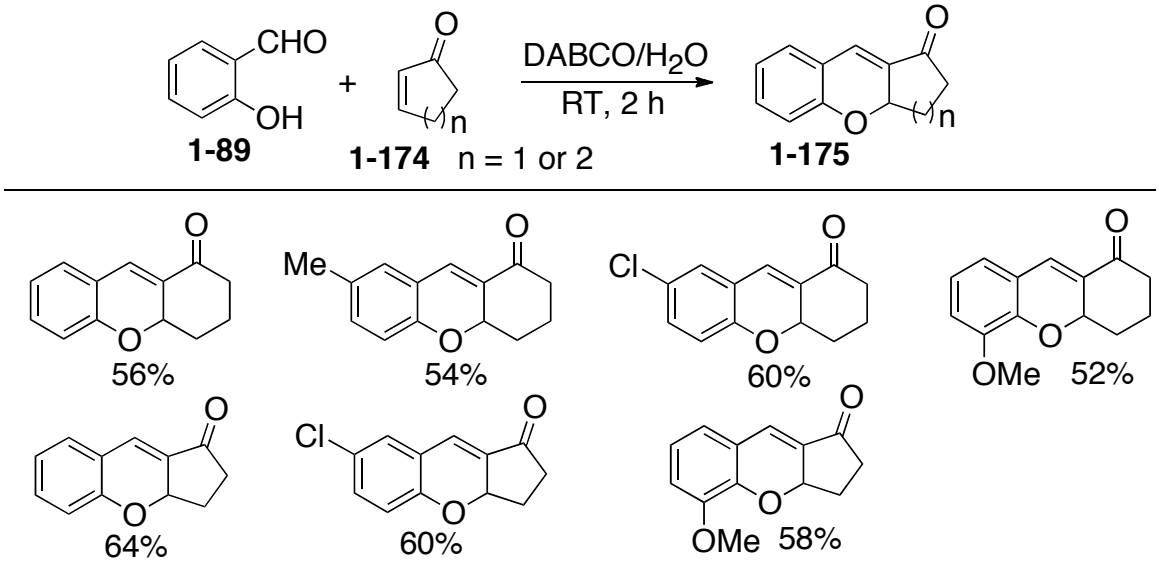
(**Scheme 1.50**). The 4H chromene **1-167** is the thermodynamic product and is the exclusive product of the reaction if the stronger base Cs_2CO_3 is employed (**Scheme 1.51**).

Scheme 1.50: Proposed Catalytic Cycle



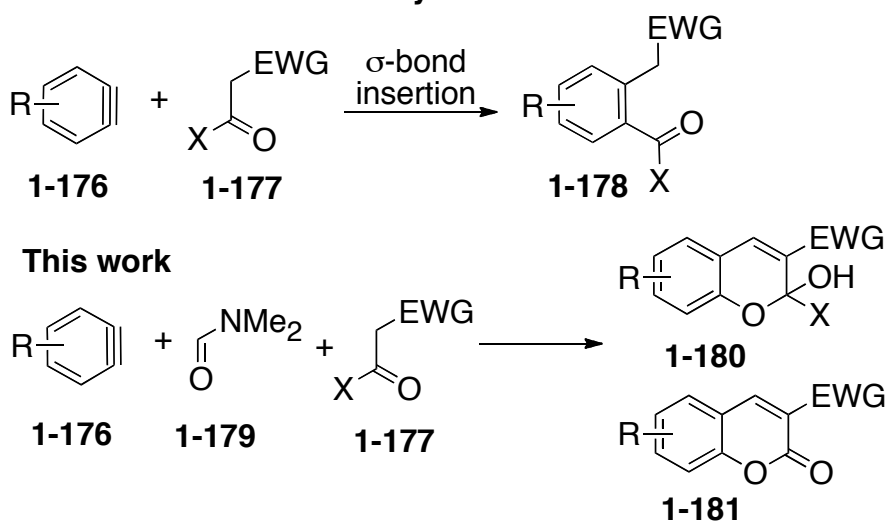
2H-chromenes can be directly synthesized from cyclic enones and salicyaldehydes.[32] This reaction is catalyzed by DABCO and can be extended to salicylaldehydes with different substituents were reacted with both cyclohexenone and cyclopentenone. The reactions resulted in the corresponding chromenes in moderate yields (**Scheme 1.51**).

Scheme 1.51: Reaction Between Salicyaldehyde and Cyclic Enones



Miyabe et al.[33] utilized the high reactivity of aryne intermediates in a multicomponent coupling reaction which involves insertion of arynes **1-176** into C=O bond of dimethylformamide **1-179** followed by the nucleophilic attack by active methylenes **1-177** to synthesize 2H-chromenes **1-180** (**Scheme 1.52**).

Scheme 1.52: Multicomponent Coupling Reaction for the Synthesis of Chromenes



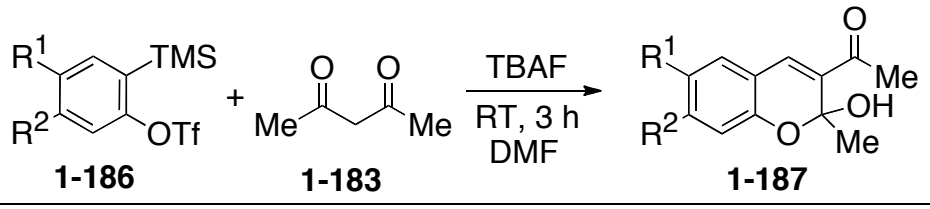
Since active methylene compounds **1-177** show high reactivity toward arynes **1-176** giving *ortho*-disubstituted arene **1-178** it posed a challenge for the present methodology, as there might be a competition of insertions between DMF and active methylenes into arynes (**Scheme 1.52**).

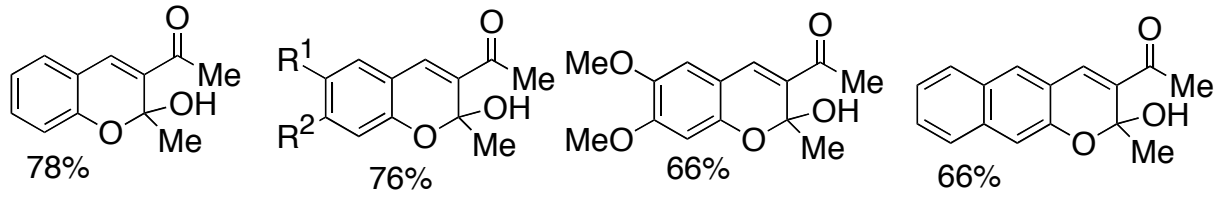
Scheme 1.53: Competition of Insertions Between DMF and Active Methylenes into Arynes

1-182 **1-179** **1-183** **1-184**, 84% **1-185**, trace

Satisfactorily, the model reaction starting with the aryne precursor **1-182**, DMF and acetylacetone **1-183** produced 84% of 2H-chromene **1-184** without any undesired product **1-185** in presence of TBAF when DMF was used as solvent (**Scheme 1.53**). To examine the generality of the reaction some other aryne precursors were reacted under same conditions and the yields were good. Substituent on aryne showed regioselectivity. Thus, 4-methoxytriflate **1-186** gave two regioisomers **1-187a** and **1-187b** in 6:5 ratio (**Scheme 1.54**).

Scheme 1.54: Substrate Scope Varying Arynes

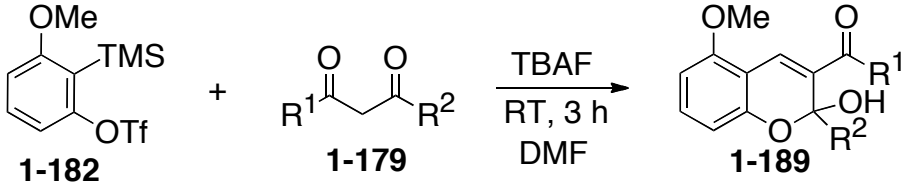




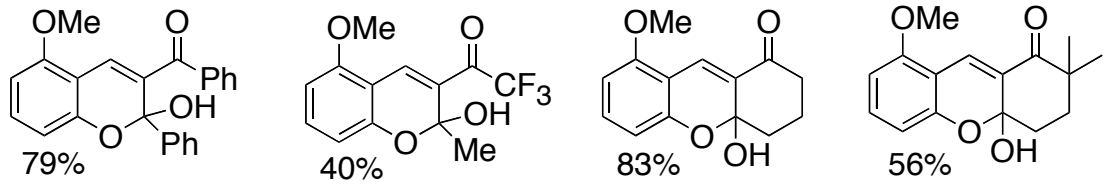
1-187a: R^1=MeO, R^2=H
1-187b: R^1=H, R^2=MeO
1-187a/**1-187b** = 6:5

The ketones were also varied and reacted with compound **1-182** under the optimized conditions. The yields were moderate to high (**Scheme 1.55**).

Scheme 1.55: Substrate Scope Varying 1,3-Diketones

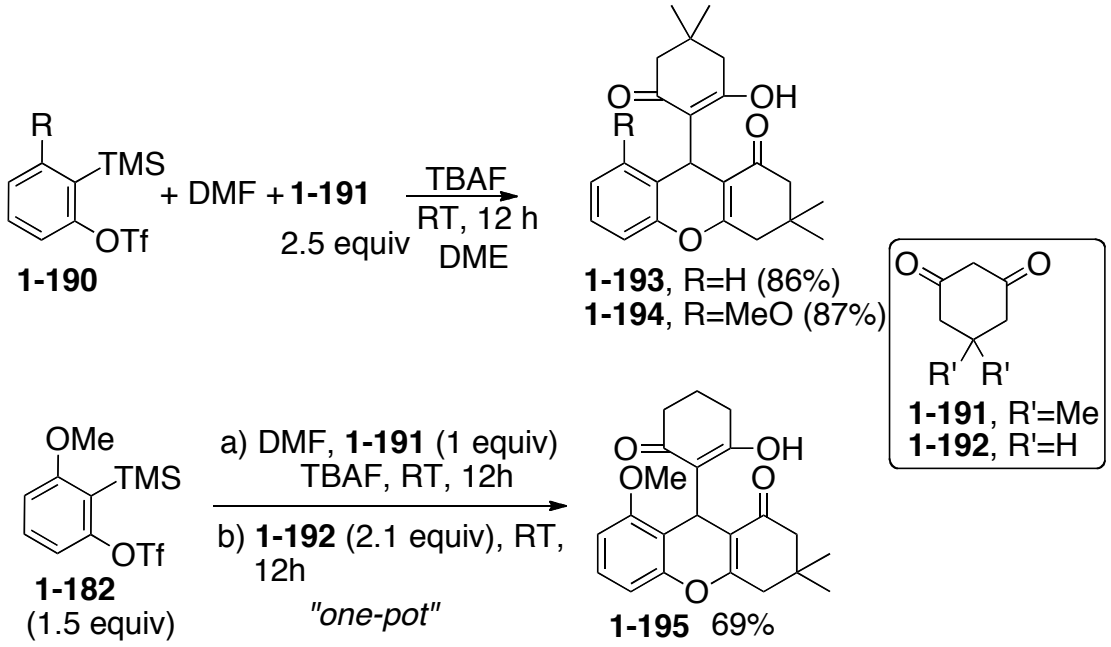


R^1, R^2 = Ph, Me, CF_3, $–CH_2CH_2CH_2–$, $–CMe_2CH_2CH_2CH_2–$



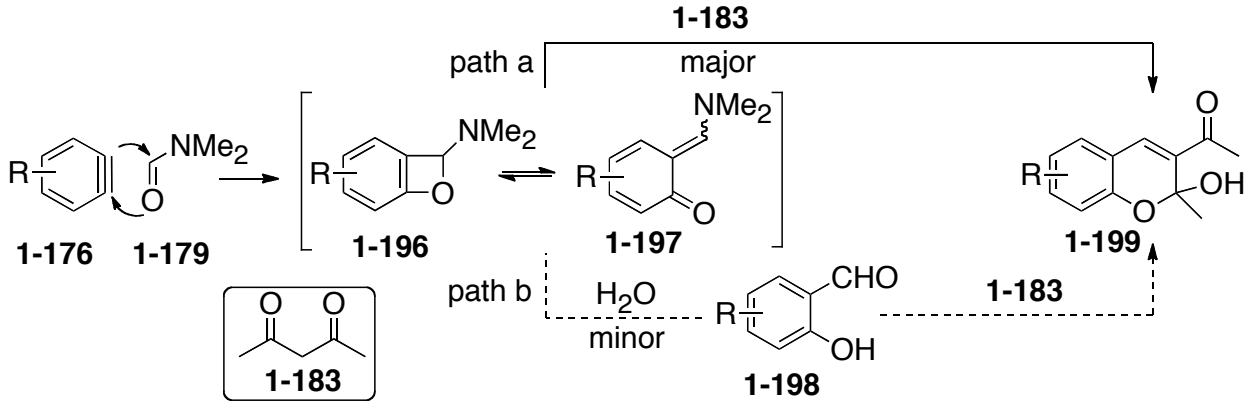
This method was applied in a convenient synthesis of a neuropeptide YY5 acceptor antagonist **1-193** and was obtained in 86% yield. Similarly products **194** and **1-195** were synthesized in 87% and 69% yields. These transformations involved formation of three C–C bonds and two C–O bonds in one-pot (**Scheme 1.56**).

Scheme 1.56: Synthetic Application



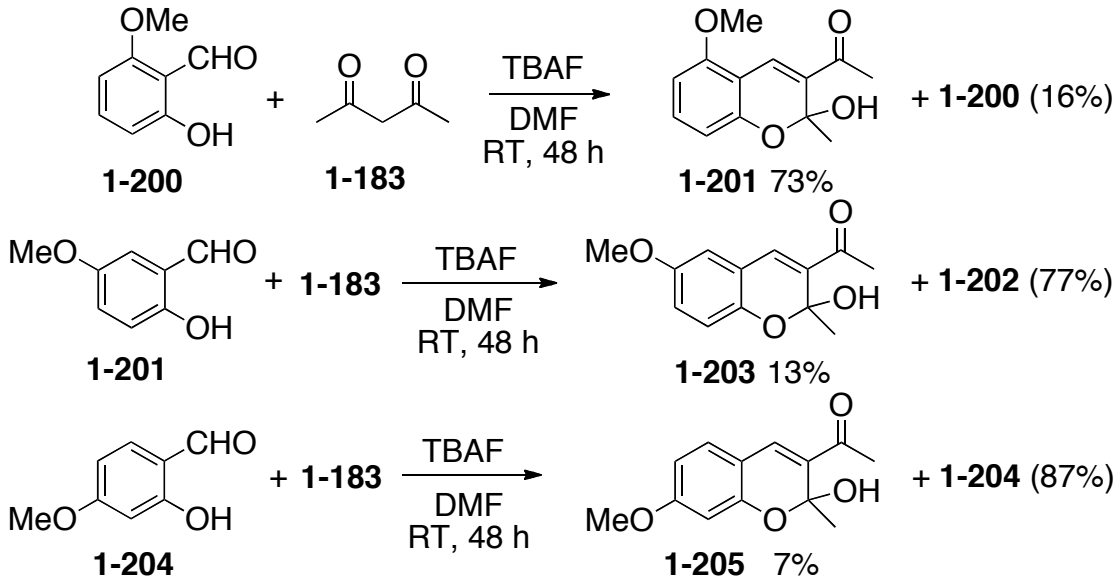
The proposed mechanism indicated two possible pathways and according to *path a*, the addition of an enolate anion to unstable intermediates **1-196** or **1-197** and elimination of dimethylamine. On the other hand, *path b*, involves the formation of salicylaldehyde by hydrolysis of **1-196** or **1-197,** which then resulted the product (**Scheme 1.57**).

Scheme 1.57: Proposed Mechanism



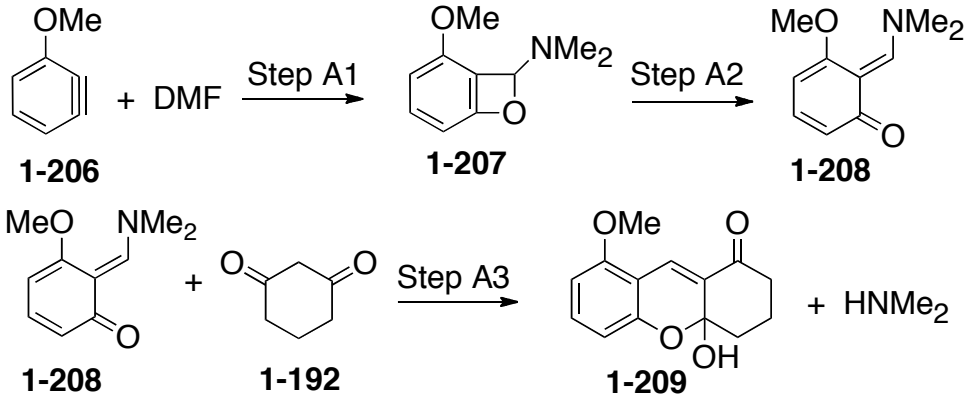
Even under careful anhydrous conditions, *path b* could not be excluded. So, three test reactions were designed which involved three different salicylaldehydes **1-200**, **1-201** and **1-204** which were reacted with acetylacetone **1-183** under same optimized conditions. Even after much elongated reaction time there was no full conversion and in each case significant amount of salicylaldehyde starting materials were recovered (**Scheme 1.58**).

Scheme 1.58: Mechanistic Investigation



These results were also supported by thermodynamic considerations. The thermodynamic data from an *ab initio* molecular orbital calculation indicates that step A1 is highly exothermic ($\Delta H = -177$ kJ mol^{-1}) because of the release of the strain energy of aryne **1-206**, which overcomes the entropy loss of the bimolecular coupling ($T\Delta S = -71$ kJ mol^{-1}). The changes in Gibbs energy indicate that all these sequential reactions are thermodynamically favorable ($\Delta G < 0$ kJ mol^{-1}) probably due to the high reactivity of all the strained reactants (**Scheme 1.59**).

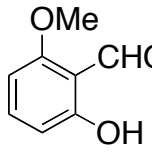
Scheme 1.59: Thermodynamic Considerations



Step	ΔG(kJ mol^{-1})	ΔH (kJ mol^{-1})	ΔS (J mol^{-1}K^{-1})
A1	–106	–177	–219
A2	–67	–63	13
A3	–17	–31	–43

At the same time reaction from salicylaldehyde (*path b*) is not favorable as indicated by ΔG (+77 kJ mol^{-1}), which in turn supports the experimental result (**Scheme 1.60**).

Scheme 1.60: Theoretical Support for Experimental Results

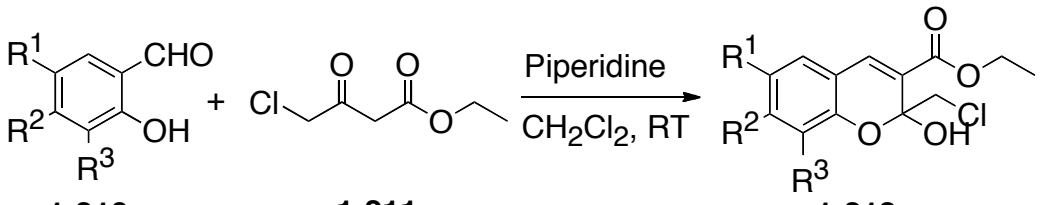


1-200 + **1-192** $\xrightarrow{\text{Step B1}}$ **1-209** + H_2O

Step	ΔG(kJ mol^{-1})	ΔH (kJ mol^{-1})	ΔS (J $mol^{-1}K^{-1}$)
B1	77	56	–62

Sridhar and Raju[34] reported the synthesis of 2H-chromenes by the reaction of substituted salicylaldehydes **1-210** and ethyl-4-chloro-3-oxobutanoate **1-211** as the starting compounds. The key step is believed to be the Knoevenagel condensation. The reaction occurs under mild conditions giving good yields in presence of piperidine as base and dichloromethane as the solvent (**Scheme 1.61**). The generality of this method was examined by using electron-donating and electron-withdrawing groups in various positions of the benzene ring. The yields were good in all cases. Notably, electron-deficient aromatic rings showed higher yields compared to electron-rich arenes (**Scheme 1.61**).

Scheme 1.61: Synthesis of Chromenes by Knoevenagel Condensation

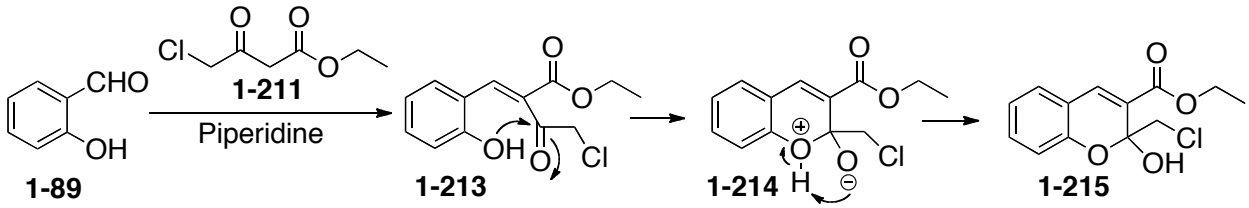


1-210 **1-211** **1-212**

R^1	R^2	R^3	Yield (%)
H	H	H	60
Br	H	H	62
Cl	H	H	64
MeO	H	H	42
H	CH_2=$CHCH_2O$	H	42
H	H	CH_2=$CHCH_2$	48
H	Me_2C=$CHCH_2O$	H	40
H	BnO	H	38
Ph	H	H	50
pyrimidin-2-yl	H	H	52

A plausible mechanism suggested that the formation of a Knoevenagel product initiate the reaction. Then cyclization takes place by the nucleophilic attack of phenolic OH to the nearest C=O to Cl to give the chromene product. Probably powerful –I effect of Cl controls this step (**Scheme 1.62**).

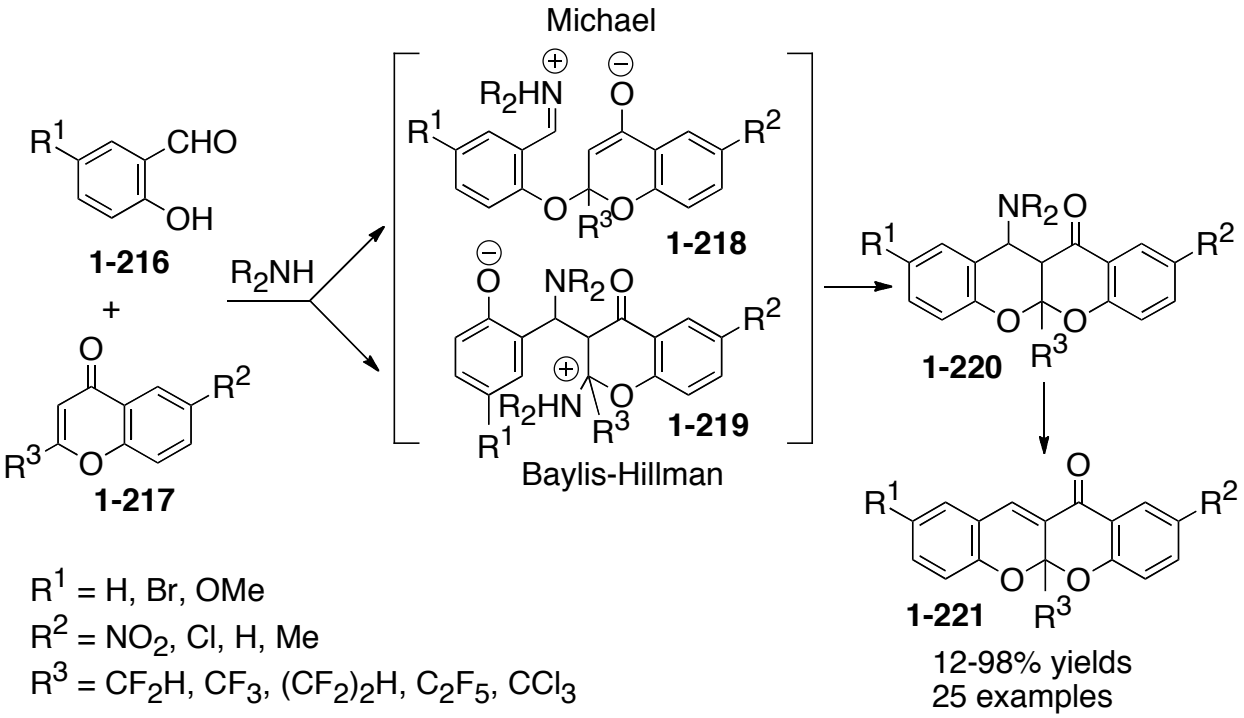
Scheme 1.62: Plausible Mechanism



1-89 **1-213** **1-214** **1-215**

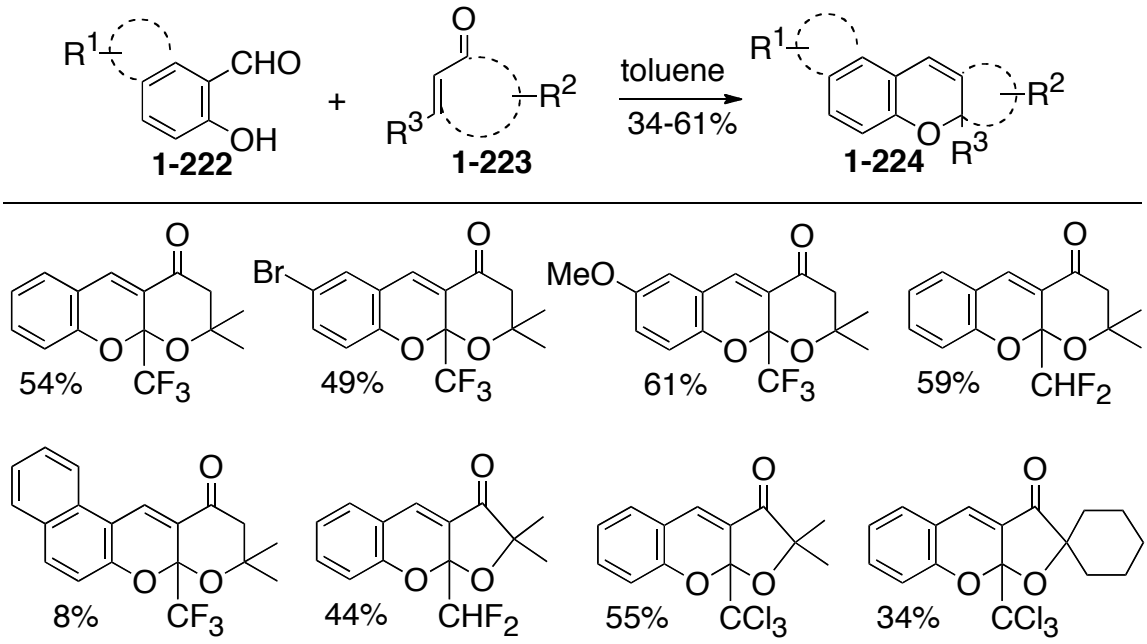
Sosnovskikh and co-workers developed[35] a convergent method for the first time for the synthesis of a variety of fused 2H-chromenes by the reaction of salicyaldehydes with chromones, γ-pyrones and β-furanones, which are activated by the polyhaloalkyl groups. The reaction underwent most likely via an oxa-Michael addition/Mannich condensation pathways. They found that 2-R_F (R_F = polyfluoro alkyl group) and 2-CCl_3-chromone smoothly reacted with a number of salicyaldehydes in the presence of piperidine in refluxing benzene to afford the corresponding chromenes in high to moderate yields without the generation of any competitive side products arising from the Baylis-Hillman reaction or any ring-opening of the pyrone ring (**Scheme 1.63**). Notably, when the same reaction was conducted with 2-hydroxyacetophenone instead of the salicyaldehyde, the reaction did not proceed at all. The reaction worked well with a wide range of substituents on both the salicyaldehydes and chromones giving reasonable to excellent yields of the products. Usually, the electron-withdrawing nitro group at the C6 position of the chromones greatly facilitates the initial nucleophilic addition of the C2 atom and the electron-donating methyl group complicates this process, which is most likely is the rate-determining step. Importantly, it is known that the Baylis-Hillman reaction is faster with electron-poor aldehydes.[36] Unlike, the 2-substituted chromones, which reacted with aromatic aldehydes to provide Baylis-Hillman products,[37,38] they did not obtain analogous compounds having 2-CF_3-chromones and *m*-nitrobenzaldehyde in the presence of Et_3N or DABCO, which was probably owing to the steric repulsion between the CF_3 group and the tertiary amine at the very beginning stage.

Scheme 1.63: Convergent method for the Synthesis of Fused Chromenes



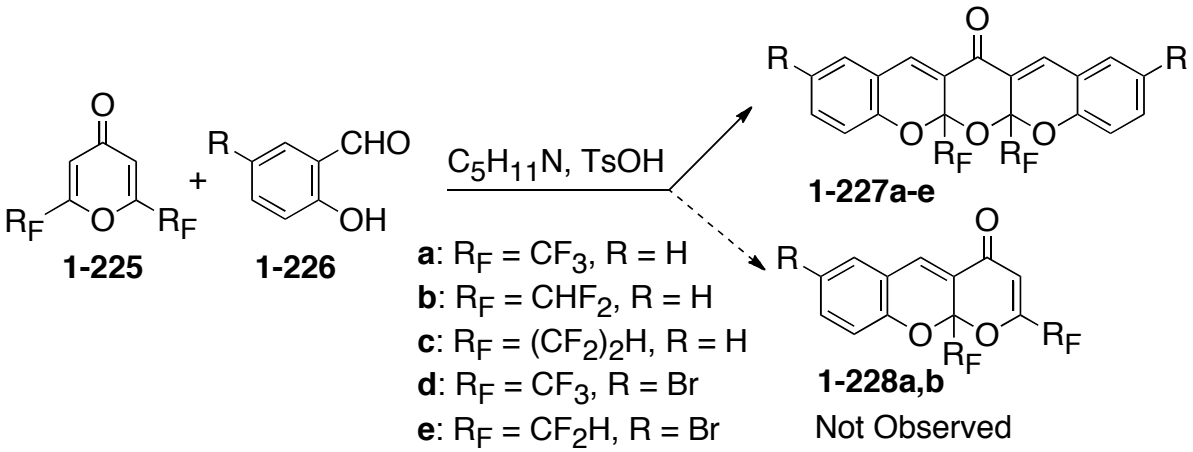
The same group also investigated the same reaction by the employment of various cyclic enones with different types of salicyaldehydes (**Scheme 1.64**). They found that the 2,3-dihydro-4H-pyran-4-ones[39] and 2,2-dimethylfuran-3(2H)-ones[40] which are activated by the polyhaloalkyl groups also smoothly reacted under the developed conditions affording good yields of the chromenes. Interestingly, employment of the sterically hindered 2-hydroxy-1-naphthaldehyde, resulted in poor yield (8%) of the desired product.

Scheme 1.64: Reaction Between Salicyaldehyde and Cyclic Enones



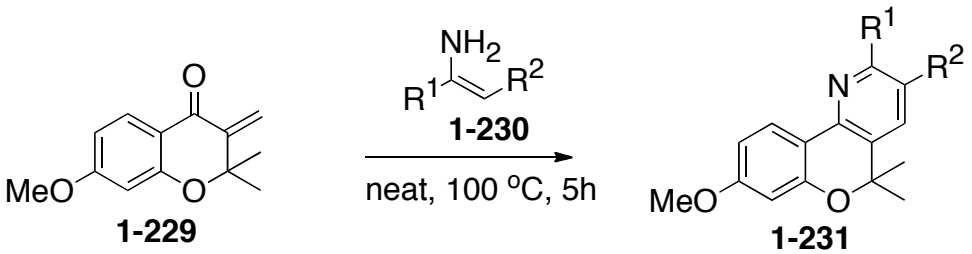
Next, they studied the reactivity of γ-pyrones **1-225** possessing two R_F groups on the 2- and 6-positions.[41] The double annulation of **1-225** with two molecules of salicyaldehyde furnished directly the linear polycyclic compounds **1-227** containing three oxygen atoms in the adjacent rings. Employment of this reaction with an excess of salicyaldehydes (3.0 equiv) in the presence of piperidine and *p*-TsOH in refluxing benzene, they obtained the chromenes in 52-82% yields. Notably, the reaction also occurred without the *p*-TsOH, though the yields were poor (42-48%) (**Scheme 1.65**). On the other hand, attempted synthesis of the corresponding mono-adduct **1-228a** and **1-228b** by the direct reaction of salicyaldehyde with a two equivalents of **1-225** in the presence of piperidine and *p*-TsOH failed.

Scheme 1.65: Double Annulation of γ-Pyrones with Salicyaldehyde



Park et al reported a diversity-oriented synthesis of privileged chromene-containing various heterocycles simply starting from *s-cis*-enones. They discovered[42] that a combination of 3-methylenechromene-4-ones **1-229** and various enamines without any solvent at 100 °C temperature gave the pyridine-fused chromenes in high yields (**Scheme 1.66**). It was found that a variety of electronically poor as well as rich substrates reacted cleanly to provide the corresponding pyridine-fused chromene derivatives in high yields.

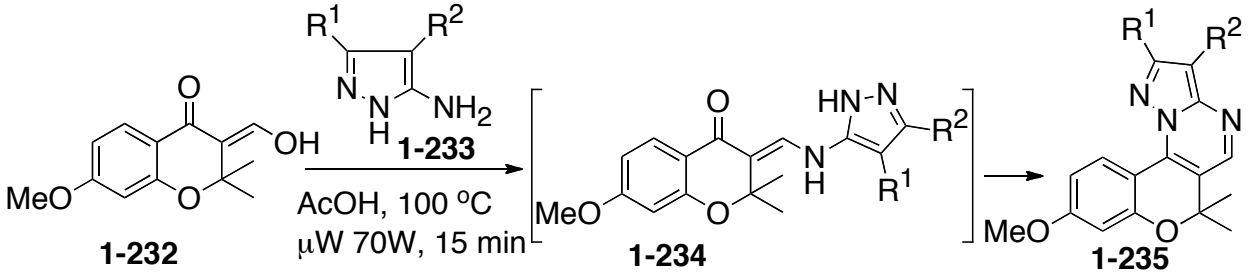
Scheme 1.66: Synthesis of Chromenes from *s-cis*-Enones



1-231a, R^1 = Me; R^2 = CO_2Me; 84%
1-231b, R^1 = 4-F-C_6H_4; R^2 = CO_2Me; 64%
1-231c, R^1 = C_6H_5; R^2 = CO_2Et; 65%
1-231d, R^1 = 4-Br-C_6H_4; R^2 = CO_2Et; 66%
1-231e, R^1 = n-Bu; R^2 = CO_2Et; 58%

They also attempted the synthesis of pyrazolopyrimidine-fused chromenes. For this purpose, the reaction was conducted with *s-cis*-enone **1-232** by the treatment of 3-aminopyrazole **1-233** derivatives under microwave-irradiation to deliver the chromene products **1-235** in excellent yields (**Scheme 1.67**). Particularly, the successful synthesis of these chromenes obviously opens up the possibility for the application of this system to other [5+6]-membered polycyclic skeletons using dinucleophiles.

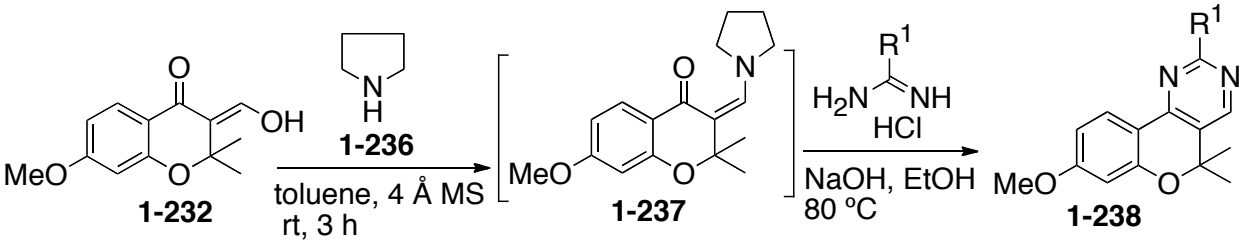
Scheme 1.67: Synthesis of Pyrazolopyrimidine-Fused Chromenes



1-235a, $R^1 = R^2 = H$; 95%
1-235b, $R^1 = H$; $R^2 = CO_2Et$; 89%
1-235c, $R^1 = Me$; $R^2 = H$; 90%
1-235d, $R^1 = C_6H_5$; $R^2 = H$; 96%
1-235e, R^1 = 4-OMe-C_6H_4; $R^2 = H$; 95%

Moreover, they also synthesized the pyrimidine-fused chromenes **1-238**. When the hydroxyl-substituted *s-cis*-enone **1-232** was subjected to the reaction with stoichiometric amount of pyrrolidine **1-236**, it furnished the corresponding pyrimidine-fused chromenes **1-238** via an enaminone intermediate **1-237** in moderate yields (**Scheme 1.68**).

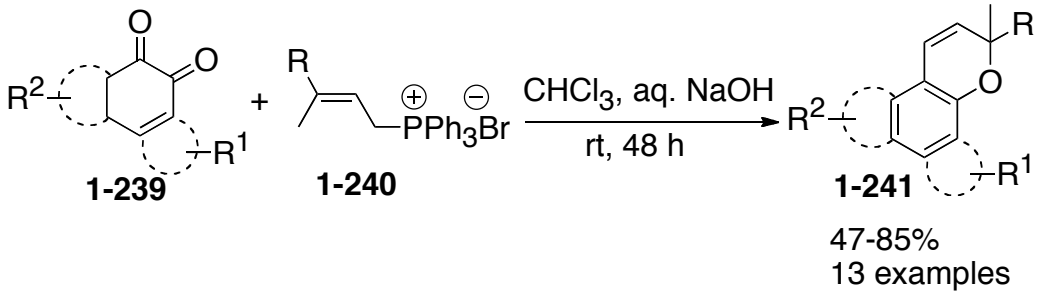
Scheme 1.68: Synthesis of Pyrimidine-Fused Chromenes



1-238a, $R^1 = C_6H_5$; 51%
1-238b, R^1 = 4-Me-C_6H_4; 42%
1-238c, R^1 = 4-Cl-C_6H_4; 59%
1-238d, R^1 = 4-OMe-C_6H_5; 56%
1-238e, R^1 = Me; 47%
1-238f, $R^1 = NH_2$; 47%
1-238g, R^1 = t-Bu; 49%

Ferreira et al reported[43] a facile and general one-pot synthesis of 2H-chromenes from *ortho*-quinones **1-239** and allyltriphenylphosphonium salts **1-240**, in the presence of aqueous NaOH and chloroform at room temperature (**Scheme 1.69**). The reaction undergoes via in-situ generated ylide, which subsequently reacted with an *ortho*-quinones to produce a *ortho*-quinonemethide intermediate that eventually cyclizes to give the 2H-chromenes in 47- 85% yields.

Scheme 1.69: Reaction Between *o*-Quinones and Allyltriphenylphosphonium Salts

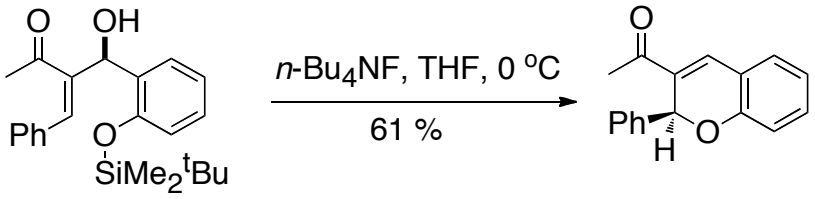


1-239 **1-240** **1-241**

47-85%
13 examples

Recently, Scheidt group has reported[44] an enantioselective synthesis of 2H-chromene from a β-hydroxy-unsaturated ketone (**Scheme 1.70**), which was in turn prepared by an α-acylvinyl anion of silyolxyallene. Although, the resulting chromene was synthesized in good yield; however, there was only one example for this chromene from β-hydroxy-unsaturated ketone.

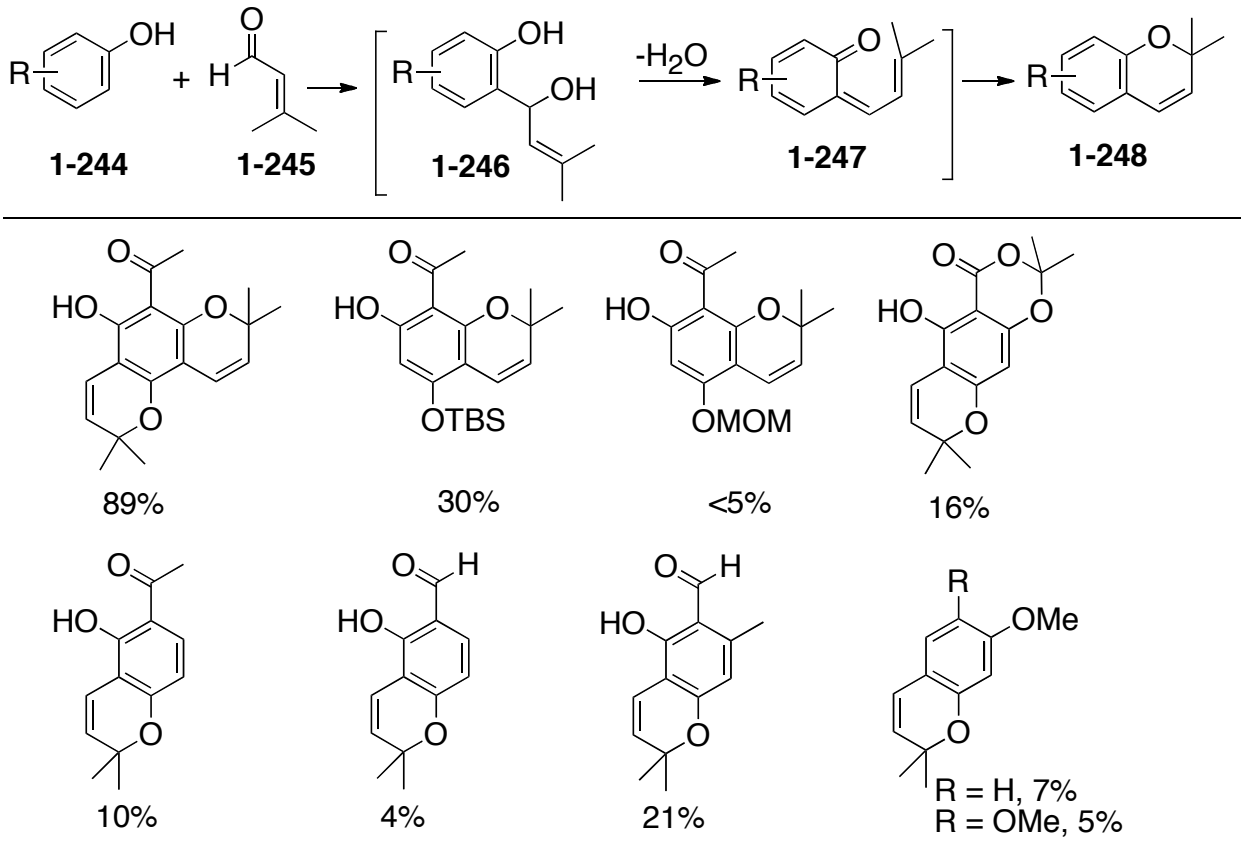
Scheme 1.70: Synthesis of 2H-Chromene from a β-Hydroxy-Unsaturated Ketone



1-242 86% ee **1-243** 68% ee

In 2009, Adler and Baldwin have reported[45] an efficient method for the synthesis of 2,2-dimethyl-2H-chromenes in a single step from the corresponding phenols with 3-methyl-butenal under microwave conditions in $CDCl_3$ (**Scheme 1.71**). In general, increasing the number of electron-donating groups on the phenol increased the effectiveness of this method, though the yields of this reaction are very poor except only in one case. Changing the aldehyde to a methyl ketone slightly improved the yield of the product.

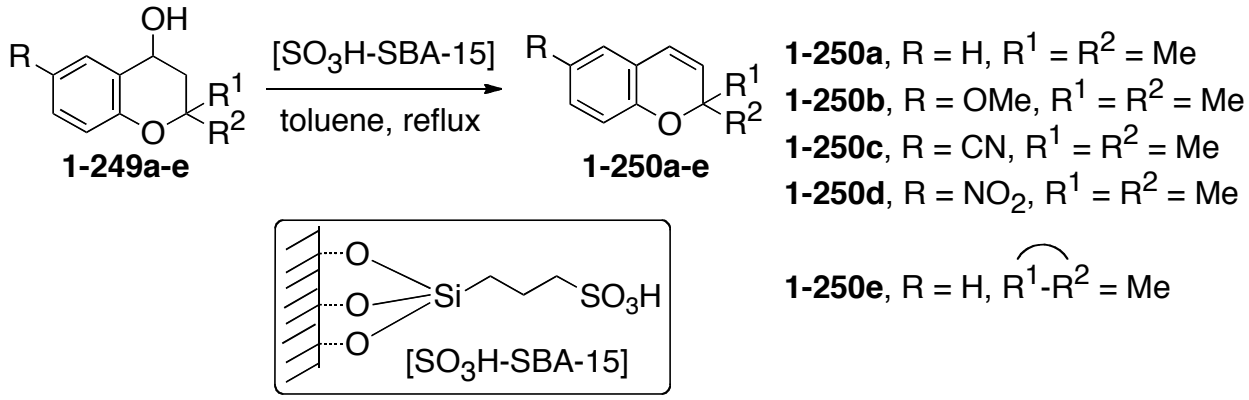
Scheme 1.71: Microwave-Assisted Synthesis of Chromenes



Kureshy et al demonstrated[46] that the sulfonic acid functionalized mesoporous SBA-15 silica can efficiently be utilized for the synthesis of chromenes **1-250** from chromanols **1-**

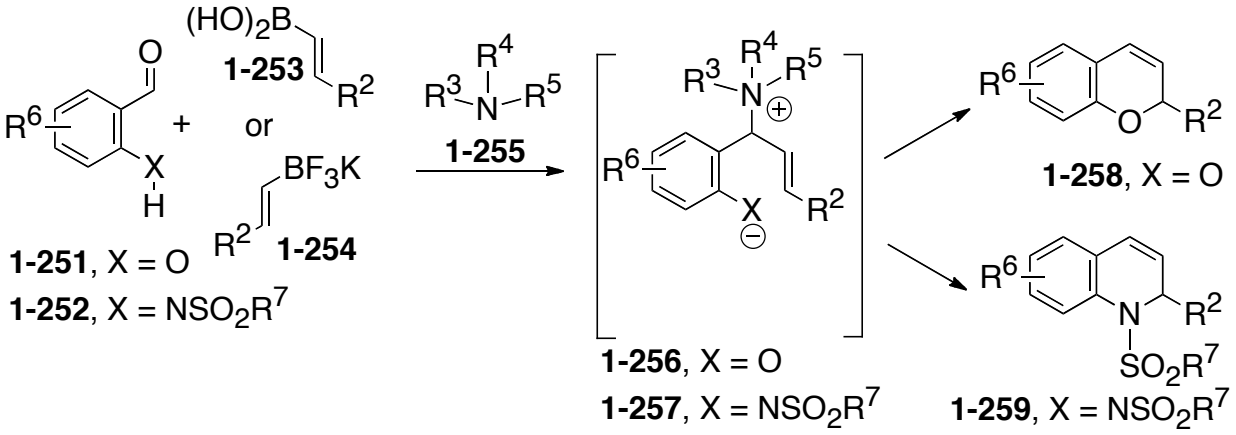
249 under the heterogeneous reaction conditions in excellent yields (**Scheme 1.72**) in a very short reaction time with added advantage of the more than ten times catalyst recyclability.

Scheme 1.72: Solid Supported Synthesis of Chromenes



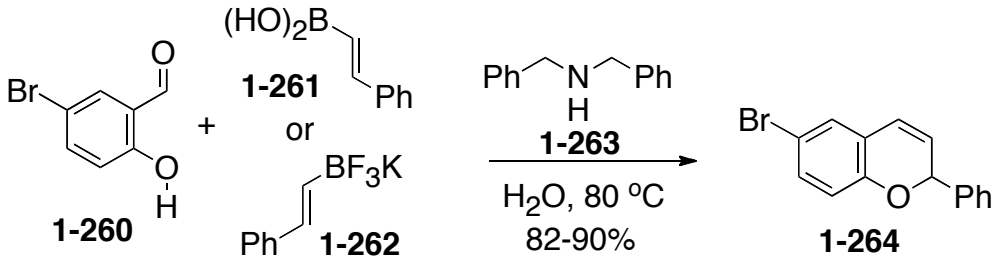
Petasis and Butkevich have recently reported[47] a unified approach for the synthesis of 2H-chromens by utilizing the one-step-three-component strategy. Thus, the reaction of salicyaldehydes **1-251** with alkenyl boronic acids **1-253** or alkenyl trifluoroborates **1-254** in the presence of an amine underwent to the initial formation of an aminophenol intermediate **1-256**, which upon cyclization afforded the 2H-chromenes **1-258**. Interestingly, a similar sequence starting with the mesyl derivatives of 2-aminobenzaldehydes **1-252** and alkenyl trifluoroborates **1-254** undergo the same type of reaction through the intermediate **1-257** to deliver the 1,2-dihydroquinolines **1-259** (**Scheme 1.73**).

Scheme 1.73: Synthesis of Chromenes Using Petasis Reaction



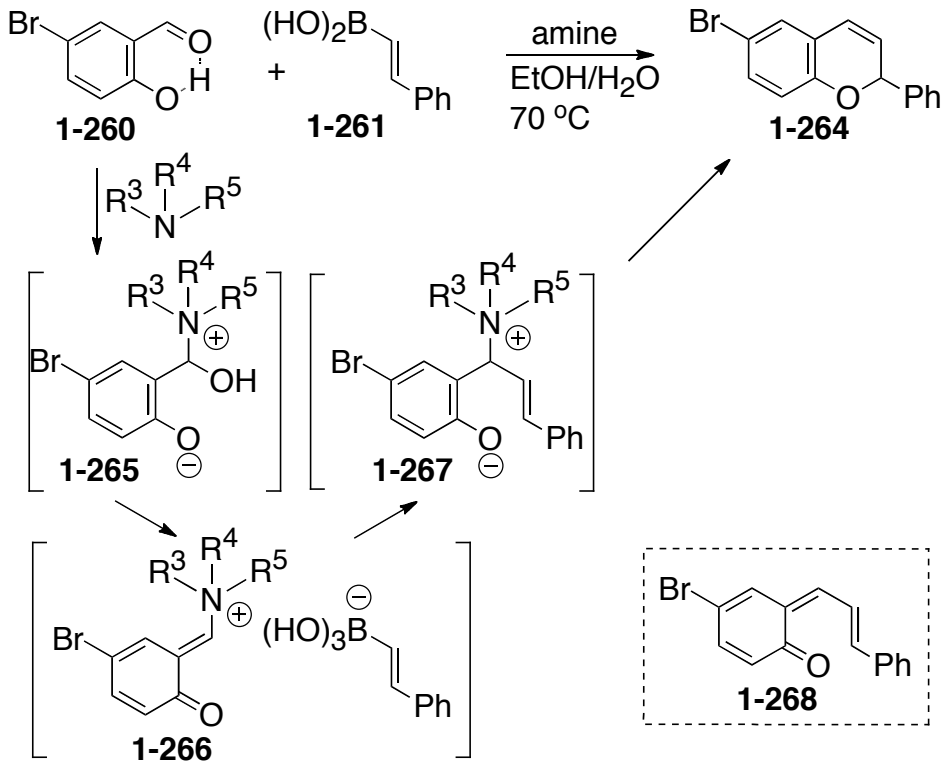
Inspired by these findings, next, they performed a more detailed investigation, which suggested that the outcome of the process depends highly on the employed reaction conditions. The secondary amines are generally the most reactive in this chemistry and a variety of conditions have been reported for this process.[48,49,50,51] This transformation worked particularly well in protic solvents even with ethanol and water. They have showed that the use of dibenzylamine in water, salicyaldehyde **1-260** was fully converted to furnish 2H-chromenes **1-264** efficiently, with both alkenyl boronic acids (e.g. **1-261**) as well as alkenyl trifluoroborates such as **1-262** (**Scheme 1.74**).

Scheme 1.74: Effect of Secondary Amines



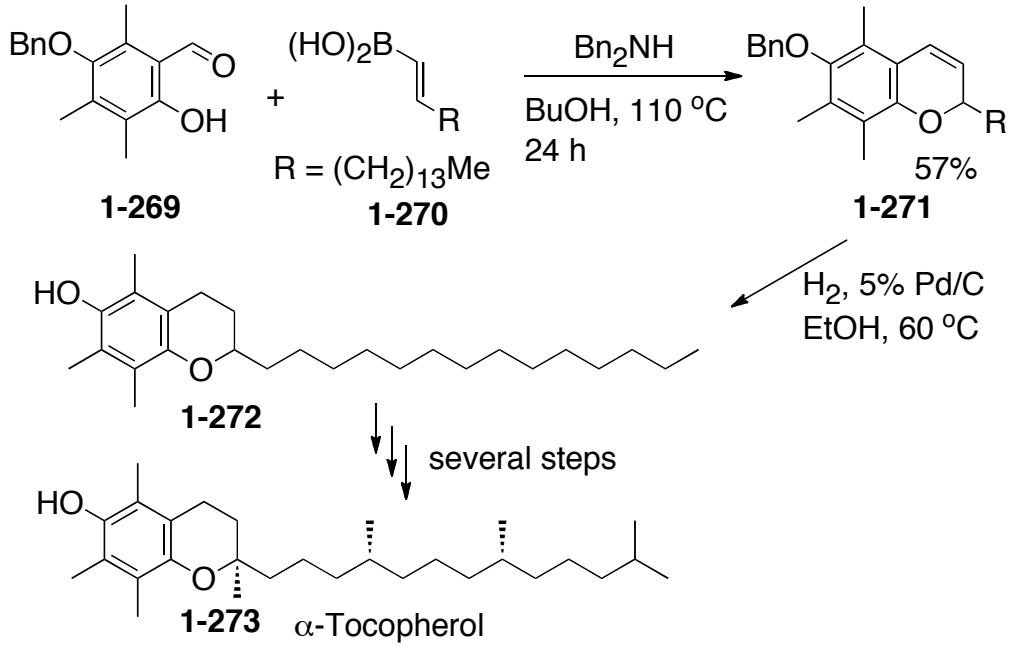
Moreover, the same research group also have studied the effect of tertiary amines as base and found that these can also mediate the transformation for the preparation of chromenes. However, tertiary amines are relatively less effective than the secondary amine, which is shown in **Scheme 1.75**. Notably, sterically congested seconday amine such as 2,2,6,6-tetramethylpiperidine proved to be less reactive than the congested Hunig's base, which resulted the desired product even through is considered to be non-nucleohilic. Besides, tetrabutylammonium hydroxide, comparatively a strong base, was observed to be entirely ineffective. The proposed mechanism includes a direct nucleophilic attack of the amine **1-255** to the aldehyde, which facilitated by the by the intramolecular H-bonding with phenolic hydroxyl group **1-260**. Intermediate **1-265** was then reacted with the boronic acid **1-261** to form an ion-pair **1-266** consisting of an electrophilic ammonium species and a nucleophilic borate species. A subsequent conjugate addition of the alkenyl group leads to an ammonium phenolate intermediate **1-267**, which underwent fragmentation to give the 2H-chromenes **1-264** via intermediate **1-268**.

Scheme 1.75: Proposed Mechanism



Furthermore, they accomplished a short synthesis of the vitamin-E by the employment of their developed methodology, as an efficient application. Thus, the reaction of **1-269** with boronic acid **1-270** and dibenzylamine afforded the chromene in 57% yield, which then transformed to the tocopherol analog **1-273**, by the catalytic hydrogenation. Here, it should be mentioned that the key transformation of this process is sluggish probably due to the bulky amine used in this reaction. After few steps, they achieved the total synthesis of vitamin E (**Scheme 1.76**).

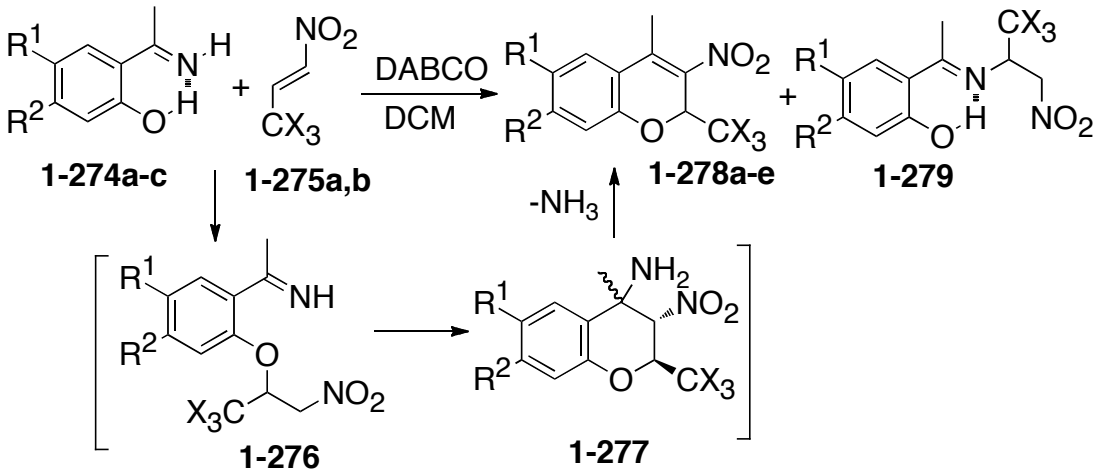
Scheme 1.76: Synthesis of Vitamin E



Sosnovskikh and co-workers have showed[52] that the reaction of N-unsubstituted imines of 2-hydroxyacetophenones with activated trihalomethyl substituted nitro alkenes in the presence of DABCO proceeds via a tandem oxa-Michael/aza-Henry addition reaction in dichloromethane or aza-Michael addition in benzene to give the highly substituted 2H-chromenes in excellent yields. Under the reaction conditions with the formation of the desired chromenes, a small amount of imines were also observed. The reaction worked efficiently by the employment of DABCO as the base, while, employment of other bases such as triethylamine resulted in lower yield. The reaction is highly dependent on the substituent present on the aryl ring. When the reaction was performed using imines possessing only electron-withdrawing halogen substituents, it did not proceed and this is perhaps due to the lower nucleophilicity of the phenolate anions. Indeed, the reaction

provided an unidentified mixture instead of the desired product, suggesting that the CX_3 group favors the initial oxa-Michael addition reaction due to its electron-withdrawing character, which lowered substantially the LUMO of the molecule[53] (**Scheme 1.77**).

Scheme 1.77: Synthesis of Chromenes via Tandem Oxa-Michael/aza-Henry Reaction

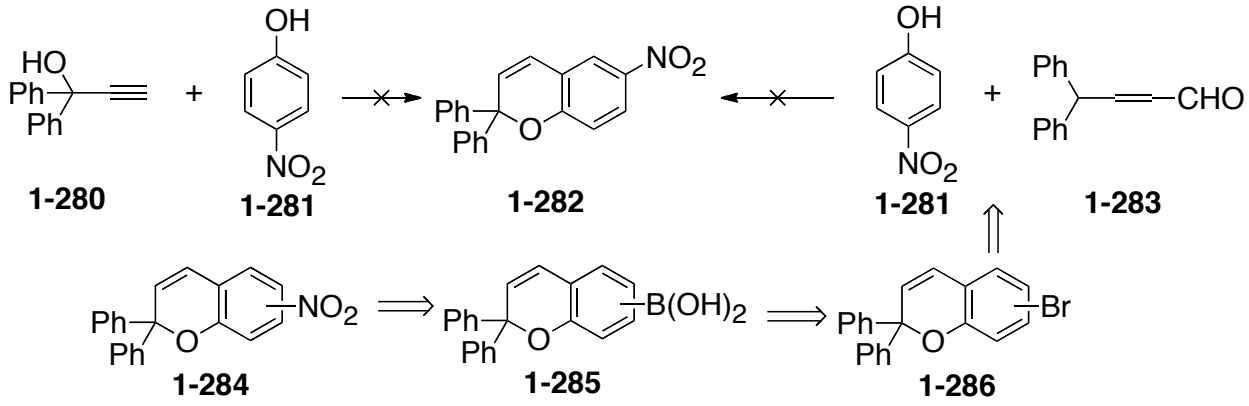


R^1	R^2	X	**1-278**	yield (%)	time (h)
H	H	Cl	**1-278a**	66	5
Me	H	Cl	**1-278b**	62	0.5
H	OMe	Cl	**1-278c**	55	8
H	H	F	**1-278d**	71	3
Me	H	F	**1-278e**	68	2
Me	H	Cl	**1-278b**	60	3

Two classic synthetic methods were available for the construction of 2,2-diphenyl-2H-1-benzopyrans such as "*one-pot-reaction*" between an appropriate phenol and the 1,1-diphenyl-2-yn-ol.[54] The second method involved the reaction of the α,β-unsaturated aldehyde with titanium (IV) salts of phenols.[55] However, to install the nitro-group

regioselectively at the chromenes by the employment of these strategies failed. Thus, Moustrou et al. developed[56] the first efficient and highly selective synthesis of a number of nitro-substituted 2,2-diphenyl-2H-1-benzopyrans in two steps starting from their brominated homologues. These were in turn obtained by a classical chromenization between the commercially available 1,1-diphenyl-2-yn-ol and various brominated phenols. Subsequently, the group showed that the nitro-chromenes could be synthesized from their boronic acids followed by the regioselective electrophilic nitration (**Scheme 1.78**).

Scheme 1.78: Uguen's Retro Synthetic Approach for Chromene Synthesis



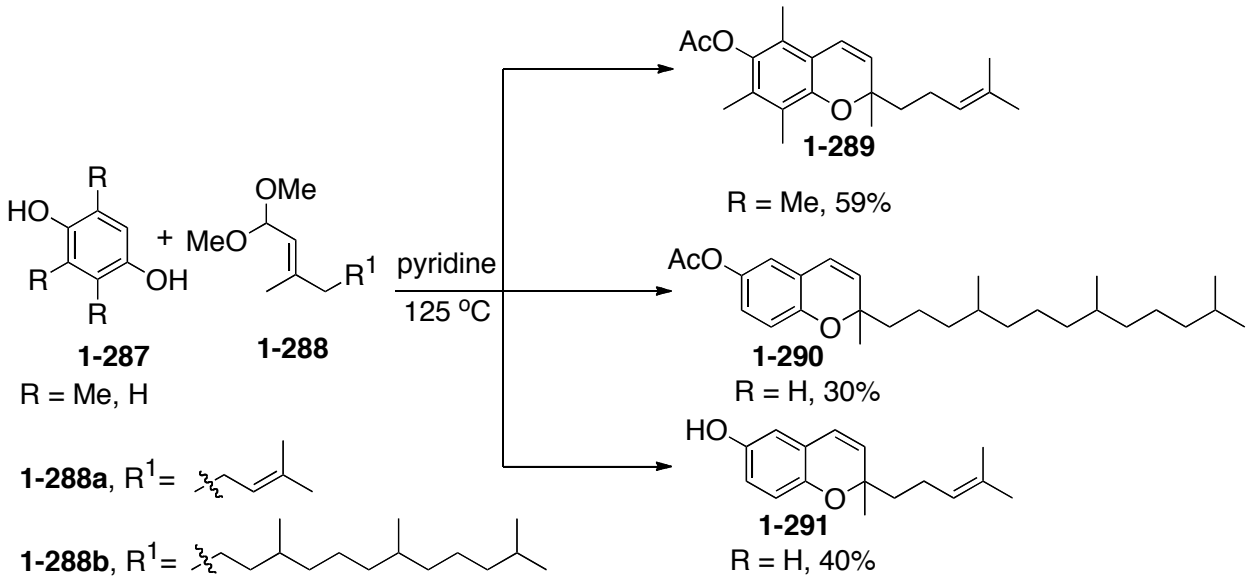
1-280 **1-281** **1-282** **1-281** **1-283**

1-284 **1-285** **1-286**

Employment of the pyridine-catalyzed condensation of phenolic compounds and α,β-unsaturated aldehyde dimethyl acetal compounds, Uguen et al[57] prepared a variety of chromenes. Densely substituted phenol **1-287** (R=Me) reacted with **1-288a** giving the 2H-chromene **1-289** in 59% yield. On the other hand, 1,4-hydroquinone **1-287** (R = H) also reacted smoothly with **1-288b** to produce **1-290**, which was then protected by

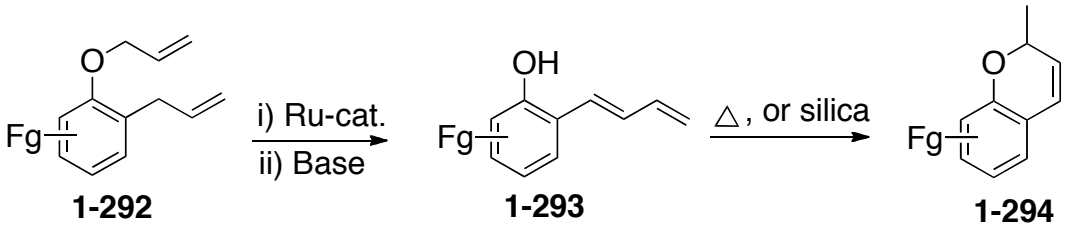
routine acetyoxylation as in case of **1-289**. Likewise, 1,4-hydroquinone **1-287** (R = H) resulted in the unprotected 2H-chromene **1-291** (*Rac*)-cordiachromene A in 40% yield (**Scheme 1.79**). The synthetic usefulness of this protocol was further showcased by an extension, which involves the efficient access to α-tocopherol acetate in high yield.

Scheme 1.79: Uguen's Approach Towards the Synthesis of Chromenes



A new method is developed[58] to synthesize highly substituted (*Z*)-2-(buta-1,3-dienyl)phenols from highly substituted dienes by use of ring-closing metathesis/base-induced ring-opening reaction and then using the phenol products in an [1,7]-sigmatropic H-shift reactions to generate the corresponding 2-methyl-2H-chromenes (**Scheme 1.80**).

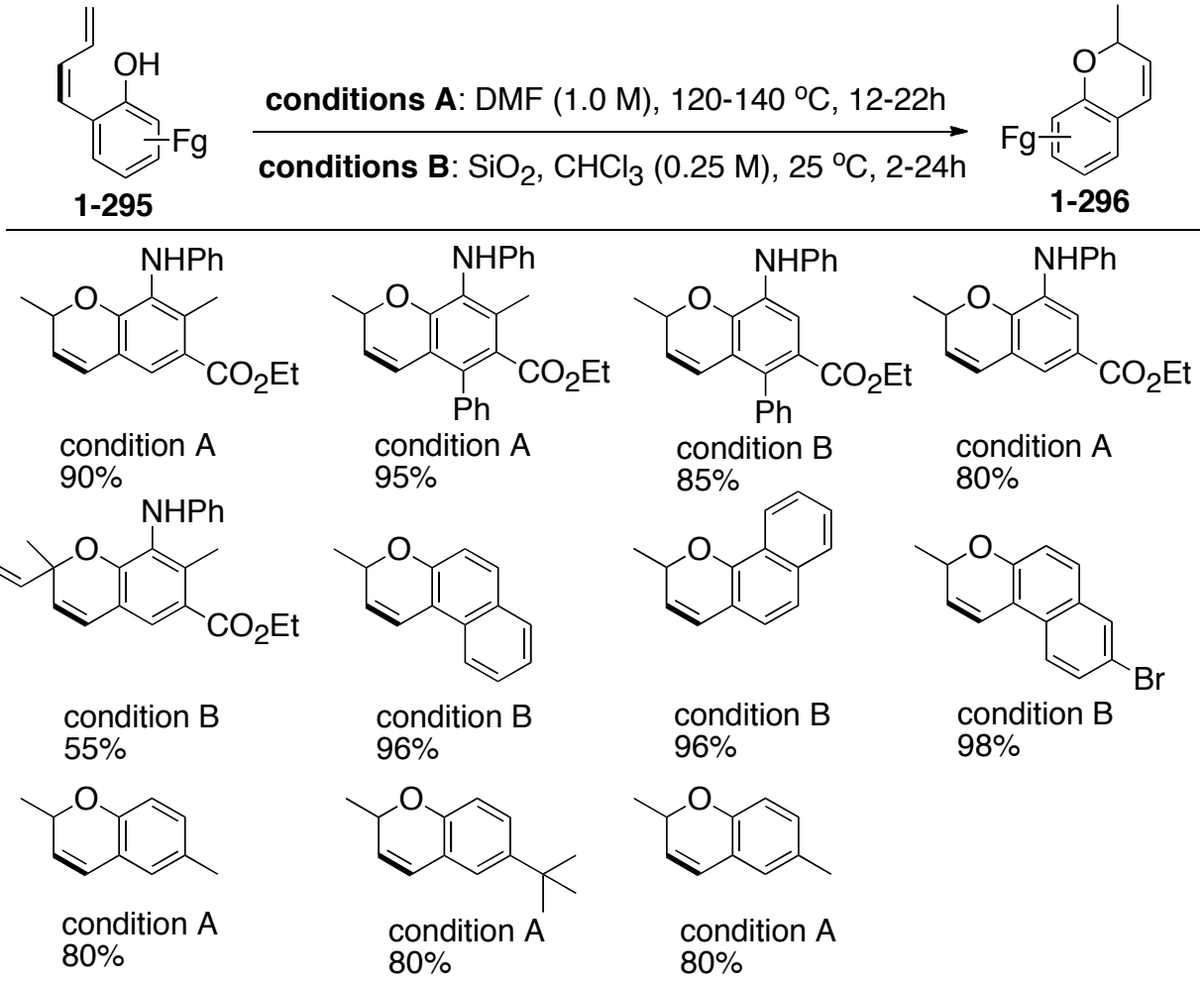
Scheme 1.80: Synthesis of Chromenes by Use of RCM/Based-Induced Ring Opening Reaction



1-292 **1-293** **1-294**

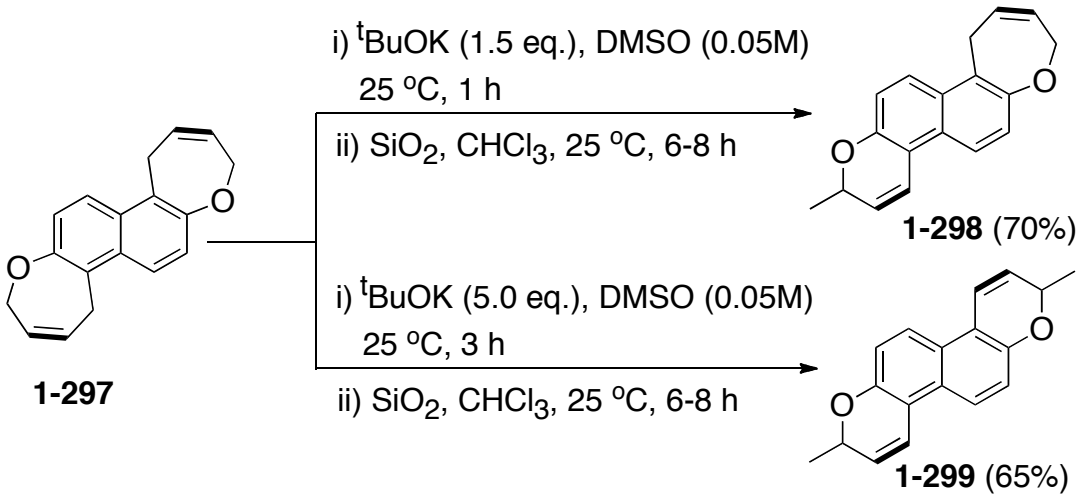
When the starting compound **1-292** was treated under ring-closing metathesis conditions it resulted in the oxepin product which under basic conditions generated the (Z)-2-(buta-1,3-dienyl)phenols **1-293**. The method was generalized by use of differently substituted substrates and for both steps the yields were over 90%. After preparation of compound **1-293** with various substitutions on the aromatic ring, they were subjected to the cyclization to the chromene products via [1,7]-sigmatropic H-shift. Two different conditions were used such as heating at 120-140 °C and treatment with silica at room temperature. Following these two conditions the chromene products were obtained in 80-98% yield range (**Scheme 1.81**).

Scheme 1.81: Substrate Scope



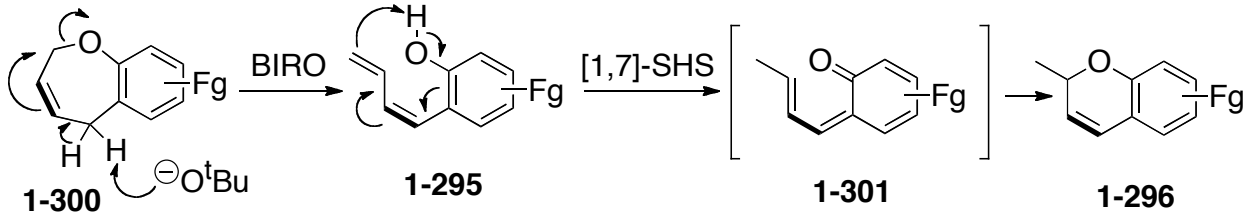
Also the C_2-symmetric benzo[*b*]oxepine **1-297** on treatment with 1.5 equiv ^{t}BuOK followed by treatment with $SiO_2/CHCl_3$ at 25 °C furnished the non-symmetric 2-methyl-2H-chromene **1-298** in 70% yield. By increasing the reaction time for the base-induced ring opening from 1 h to 3 h, the same reaction resulted in the C_2-symmetric chromene **1-299** in 65% yield (**Scheme 1.82**).

Scheme 1.82: Synthesis of Chromenes from C2-Symmetric Benzo[b]oxepine



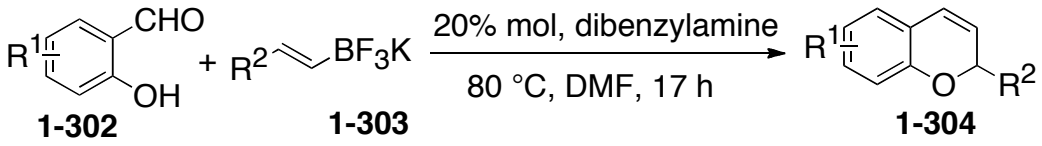
The mechanism of the reaction is outlined in **Scheme 1.83**. It involved the formation of the *o*-quinone-methide intermediate by [1,7]-sigmatropic H-shift which cyclized to give the chromene product.

Scheme 1.83: Proposed Mechanism



Das et al.[59], employing modified Petasis reaction in which potassium vinyltrifluoroborate was used instead of boronic acids along with salicyaldehyde as substrates, reported synthesis of various 2-substituted-2H-chromenes. The reaction also requires catalytic amounts of dibenzylamine as the secondary base and DMF as solvent (**Scheme 1.84**).

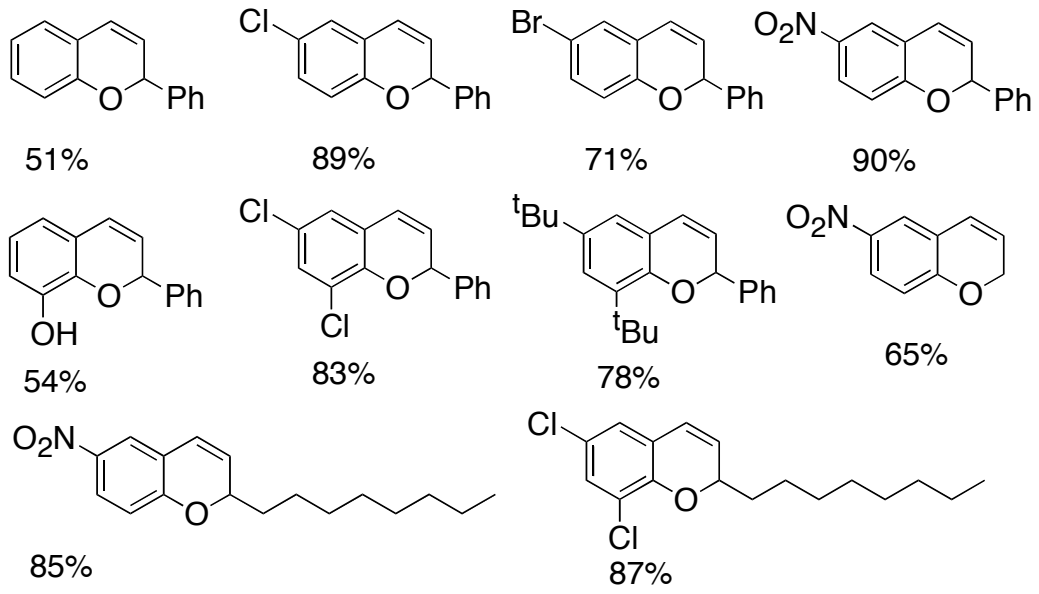
Scheme 1.84: Synthesis of Chromenes via Modified Petasis Reaction



1-302 **1-303** **1-304**

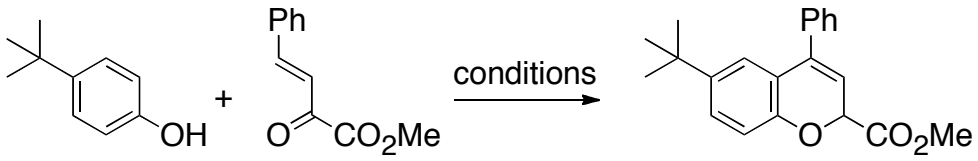
All the vinylboronate salts used for this study were commercially available. Also they can be prepared very easily. These vinylborate salts are much more stable, easier to use than the corresponding organoboronic acids. They are also more reactive because of the higher nucleophilicity of the organic group on the boron atom. The generality of this method was explored by changing the substituents both on salicyaldehyde and on the alkenyl trifluoroborate salt. Generally, the yields were moderate to high. It was noticed that electron-withdrawing groups in the para-position of salicyaldehyde OH group showed somewhat positive influence in the product yield (**Scheme 1.85**).

Scheme 1.85: Substrate Scope



Wu and Chen recently reported[60] a cascade reaction of β,γ-unsaturated-α-ketoesters with phenols in presence of tritylchloride as an oxiding agent in TFA under refluxing conditions for the construction of a variety of chromenes in excellent yields. They performed their initial investigation with 4-*tert*-butylphenol **1-305** with (3*E*)-2-oxo-4-phenylbut-3-enoate methyl ester **1-306**. After the implementation of a few conditions such as changing different oxidizing agents from metal catalysts to organo-catalysts as well as varied amount of **1-306**, they found that 1.1 equivalent of **1-306** and Ph_3CCl as an oxidant in presence of TFA, it gave the best yield of the chromene **1-307** (90%), which is actually the reverse regiochemical outcome of the previously reported[61] chromene synthesis by Jørgensen and Rutjes (**Scheme 1.86**).

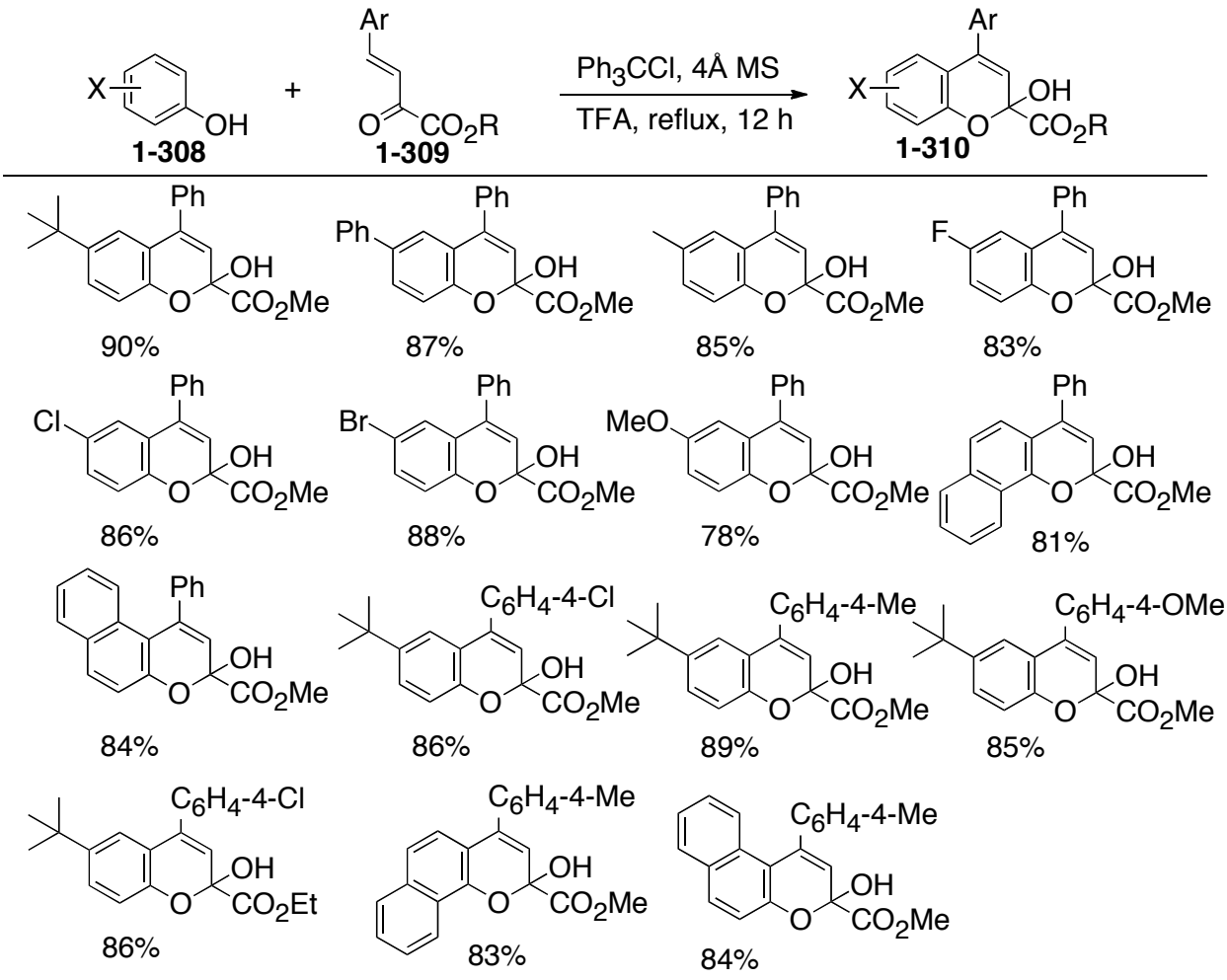
Scheme 1.86: Synthesis of Chromenes by Reaction of β,γ-Unsaturated-α-Ketoesters with Phenols



1-305 **1-306** **1-307**

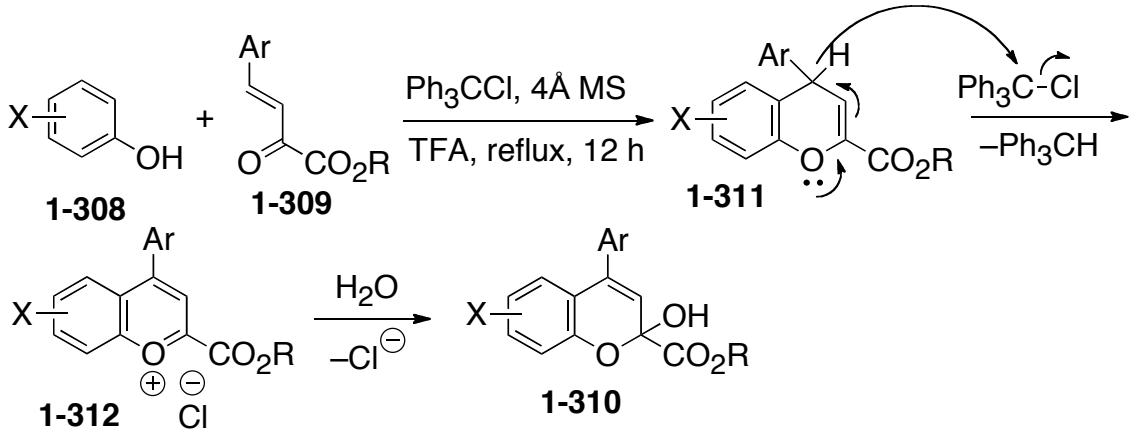
With the optimized conditions in hand, the scope of the reaction was investigated with respect to both the β,γ-unsaturated-α-ketoesters and phenol derivatives (**Scheme 1.87**). Experimentally, it has been found that with poor electron-withdrawing groups such as *tert*-butyl, phenyl and methyl at the *para*-position of phenols, the cascade reaction under the developed conditions afforded the 2H-chromenes in high yields. With the *para*-position of phenols containing electron-withdrawing substituents e.g. fluoro, chloro, bromo phenols reacted smoothly with **1-309** to give chromenes in excellent yields. On the other hand, with a strong electron-donating group such as methoxy at the *para*-position of the phenol gave slightly lower yield of the chromene product. Moreover, 1-naphthol and 2-naphthol were also reacted with **1-309** to furnish the corresponding chromene derivatives in high yields. Furthermore, the reaction appeared to be very general with respect to the β,γ-unsaturated-α-ketoesters. β,γ-Unsaturated-α-ketoesters **1-309** with either electron withdrawing or donating participated in this cascade cyclization providing the corresponding chromenes in very good yields.

Scheme 1.87: Substrate Scope



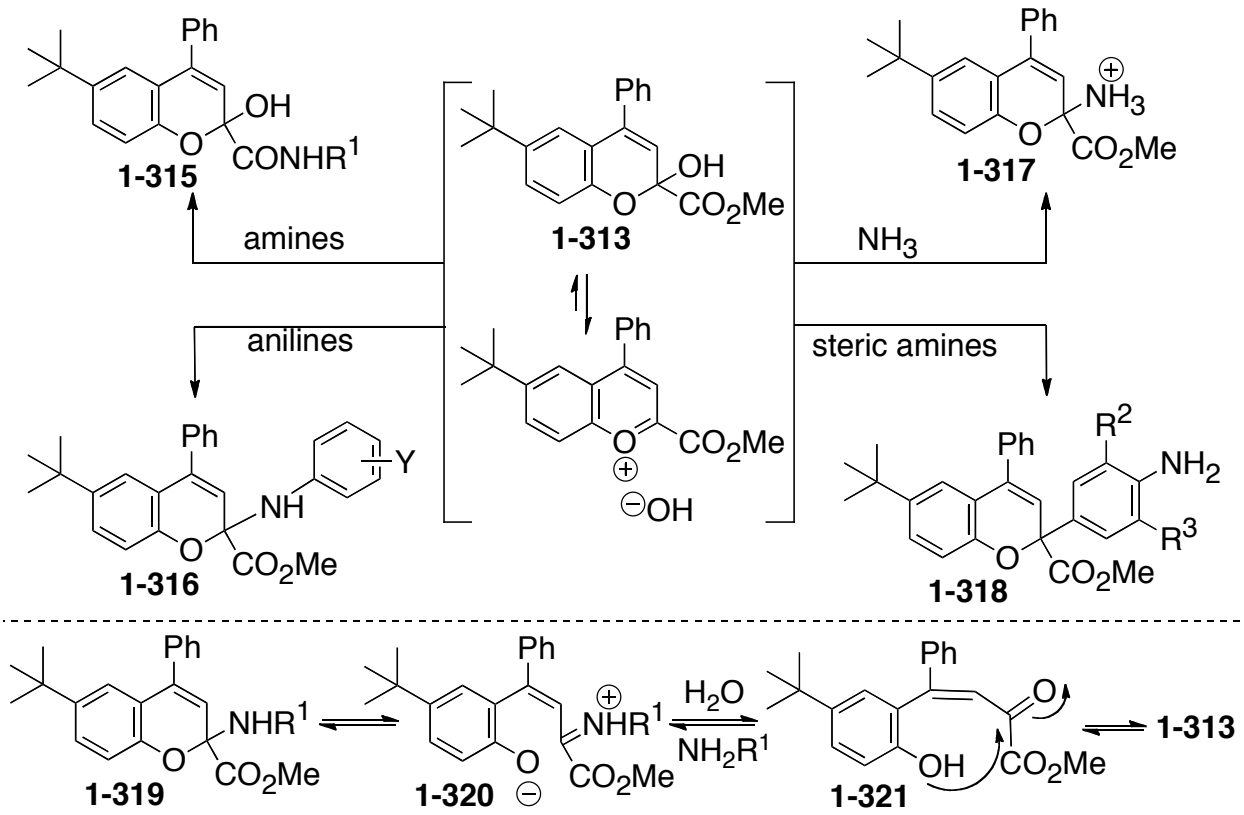
Mechanistically, the cascade cyclization is believed to proceed via Friedel-Crafts alkylation and cycloaddition of β,γ-unsaturated-α-ketoesters **1-309** with phenols **308** (**Scheme 1.88**). By intermolecular hydrogen transfer from **1-311** to trityl chloride leads to the formation of triphenylmethane and benzopyrylium ions **1-312**. Subsequent hydration of **1-312** with water afforded the 4-aryl-2H-chromenes **1-310**. Notably, the hydration process was proposed to accomplish during the basic work-up procedure.

Scheme 1.88: Proposed Mechanism



Here it should be mentioned that 2H-chromenes **1-310** are also the challenging substrates for the development of selective reaction due to their versatile functionalities of hemiacetal, hydroxyl and ester. Usually, the equilibrium between the 2-hydroxy-2H-chromenes and benzopyrylium salts has long been a subject of extensive investigation in the overlapping fields of both chemistry and biology and this is because of the relevant importance in the plant kindom and human beings.[62] Benzopyrylium salts are easily converted to the corresponding 2-hydroxy-2H-chromenes by hydration with water,[63] in neutral or basic solutions.

Scheme 1.89: Synthetic Transformation of 2H-Chromenes

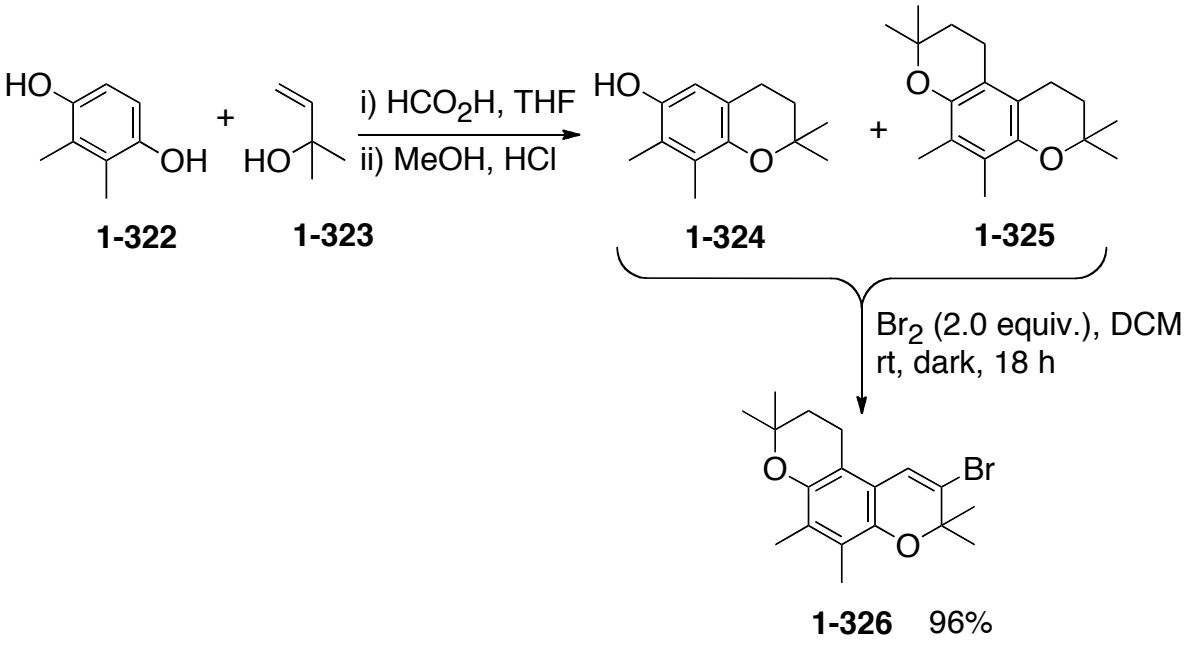


Taking advantage of this finding, the same research group investigated and developed eventually some further transformation of 2H-chromenes to their various synthetic derivatives (**Scheme 1.89**). Treating different types of amino-containing nucleophilies with hydroxyl ester **1-313** in DCM at refluxing conditions without any catalyst, various interesting chromenes could be obtained as shown in **Scheme 1.89**.

Recently, Rosenau et al attempted[64] to investigate the bromination behavior of a pyrano chromene, which was obtained as the side product in the synthesis of γ-tocopherol model compound 2,2,7,8-tetramethylchroman-6-ol **1-324**. The side product **325** was synthesized by the double alkylation of the hydroquinone **1-322** with the 2-methylbut-3-

en-1-ol, along with the model compound **1-324**. Employment of 0.66 equivalent of alcohol, 41% of the **1-324** and 12% of the **1-325** were obtained along with the recovered starting hydroquinone (47%). Surprisingly, using increased stoichiometric amounts of alcohol the amount of bis-alkylation product **1-325** was disportionately high; with 1.0 equivalent of **1-323** only 34% of **1-324** and 33% of the pyrano chromene **1-325** were formed (**Scheme 1.90**). Finally, treatment of **1-325** with two equivalents of molecular bromine furnished the product **1-326** in 96% yield.

Scheme 1.90: Bromination Behavior of PyranoChromene



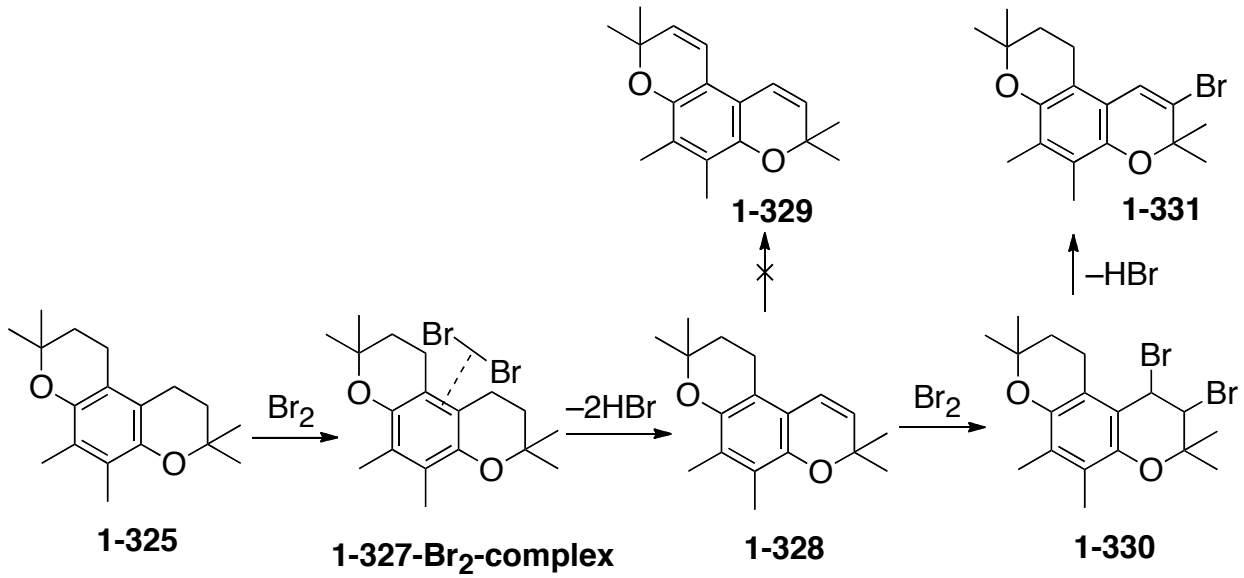
1-322 **1-323** **1-324** **1-325**

1-326 96%

The involved mechanism is outlined in **Scheme 1.91**. Treatment of **1-325** with molecular bromine gave the corresponding **1-327**-Br_2-complex. Elimination of two equivalent of HBr generates the pyranochromene **1-328**, which may be further brominated to afford

the 3-bromopyranochromene **1-331** after elimination of one equivalent HBr from **1-330**. Interestingly, the reaction of **1-328** with Br_2 does not lead to the formation of the bis-chromene **1-329**.

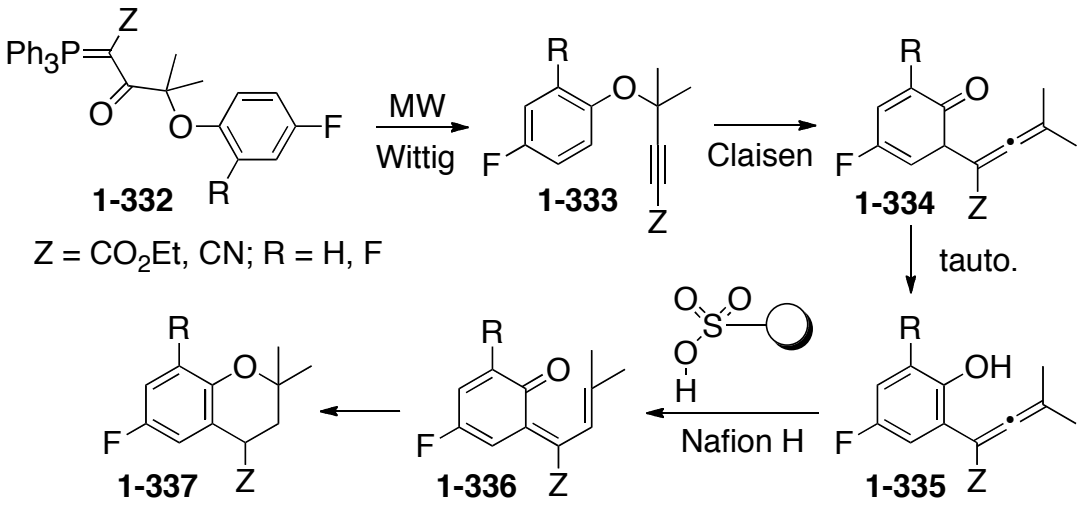
Scheme 1.91: Proposed Mechanism



Yadla and co-workers described[65] that [{2-(fluoroaryloxy)-2-methyl-propanoyl}-(cyano/ethoxycarbonyl)methylene]triphenylphosphoranes underwent microwave-assisted tandem intramolecular Wittig and Claisen rearrangement followed by internal cyclizations to give fluoro-substituted 2,2-dimethyl-2H-chromenes in good yield (**Scheme 1.92**). They showed that after the formation of aryl propargyl ethers via Wittig reaction from the precursors **1-333**, underwent Claisen rearrangement to give the corresponding rearranged product **1-334**, which by tautomerization produced the allenyl

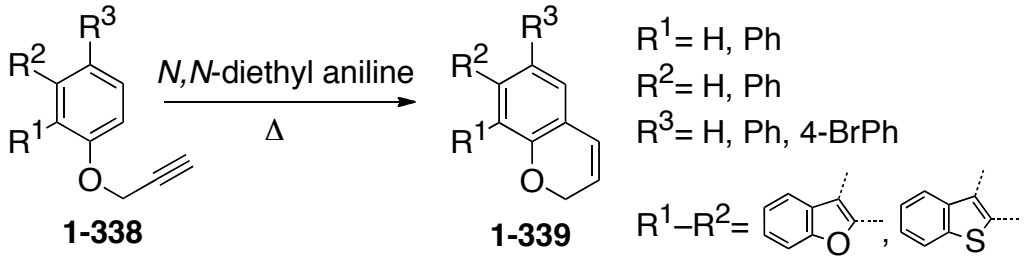
phenols **1-335**. Allenyl phenols, in the presence of Nafion H, eventually yielded the chromenes through a electrocyclization reaction.

Scheme 1.92: Microwave-Assisted Intramolecular Wittig and Claisen Rearrangement Followed by Internal Cyclizations



Mashelkar et al demonstrated[66] that aryl propargyl ethers under thermal conditions in presence of *N,N*-diethylaniline as basic solvent smoothly rearranged to provide a wide range of 2H-chromenes in high yields (**Scheme 1.93**).

Scheme 1.93: Thermal Rearrangement of Aryl Propargyl Ethers



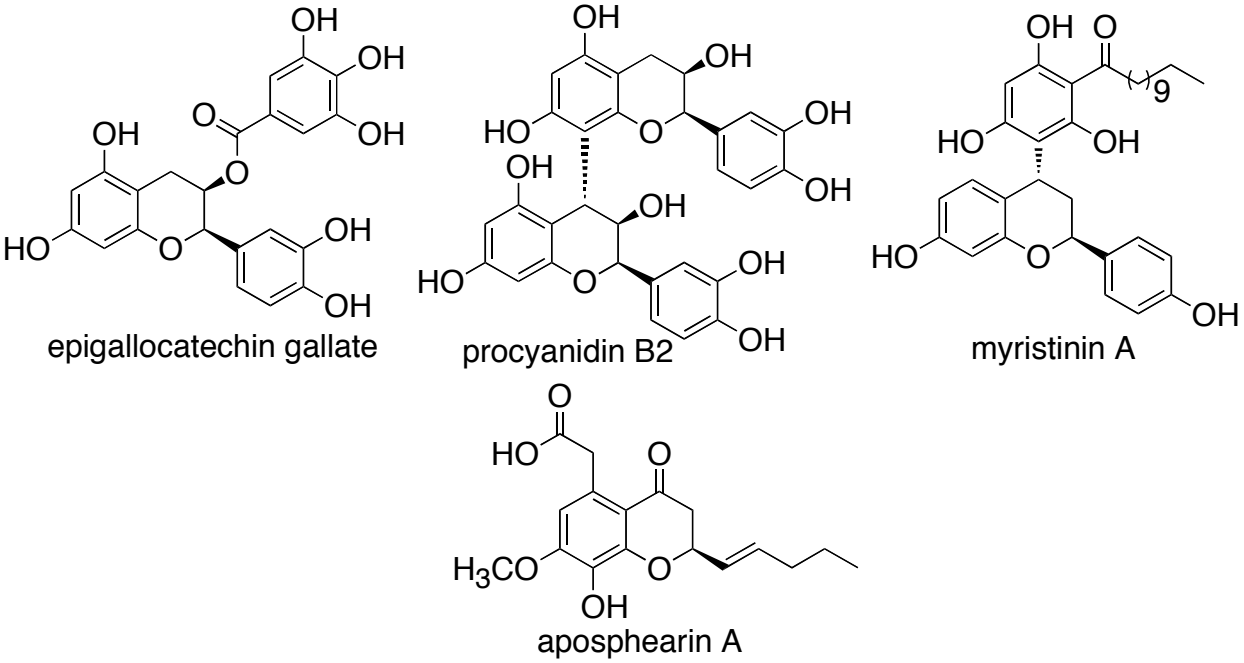
1.2.2. Asymmetric approach to the synthesis of chromene

1.2.2.1. Organocatalytic Synthesis

Organocatalysis play very significant role in the asymmetric synthesis of chromenes. The examples shown in this part of the review reveals its evolution as an efficient method for the synthesis of chiral chromenes.

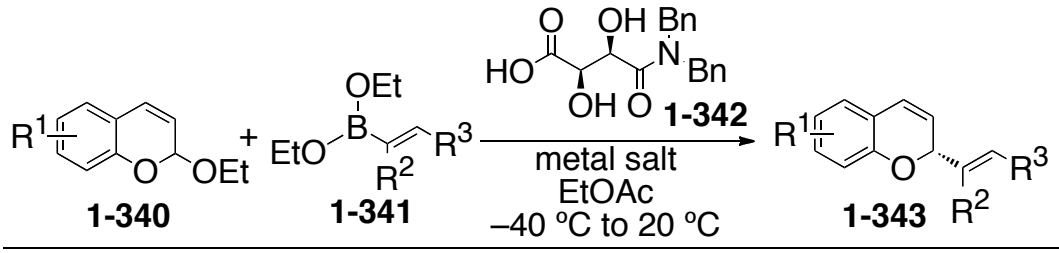
Schaus et al developed a new method[67] to synthesize chiral 2-substituted 2H–chromenes by employing a chiral Brønsted acid/Lewis acid catalytic system in an enantioselective addition of boronates to chromene acetals. Vinyl- and aryl-boronates were of particular importance, which would result in the placement of a vinyl or aryl group at the 2-position of chromene along with a chiral center. These moieties are very important because of their abundance in some natural products (**Figure 1.1**).

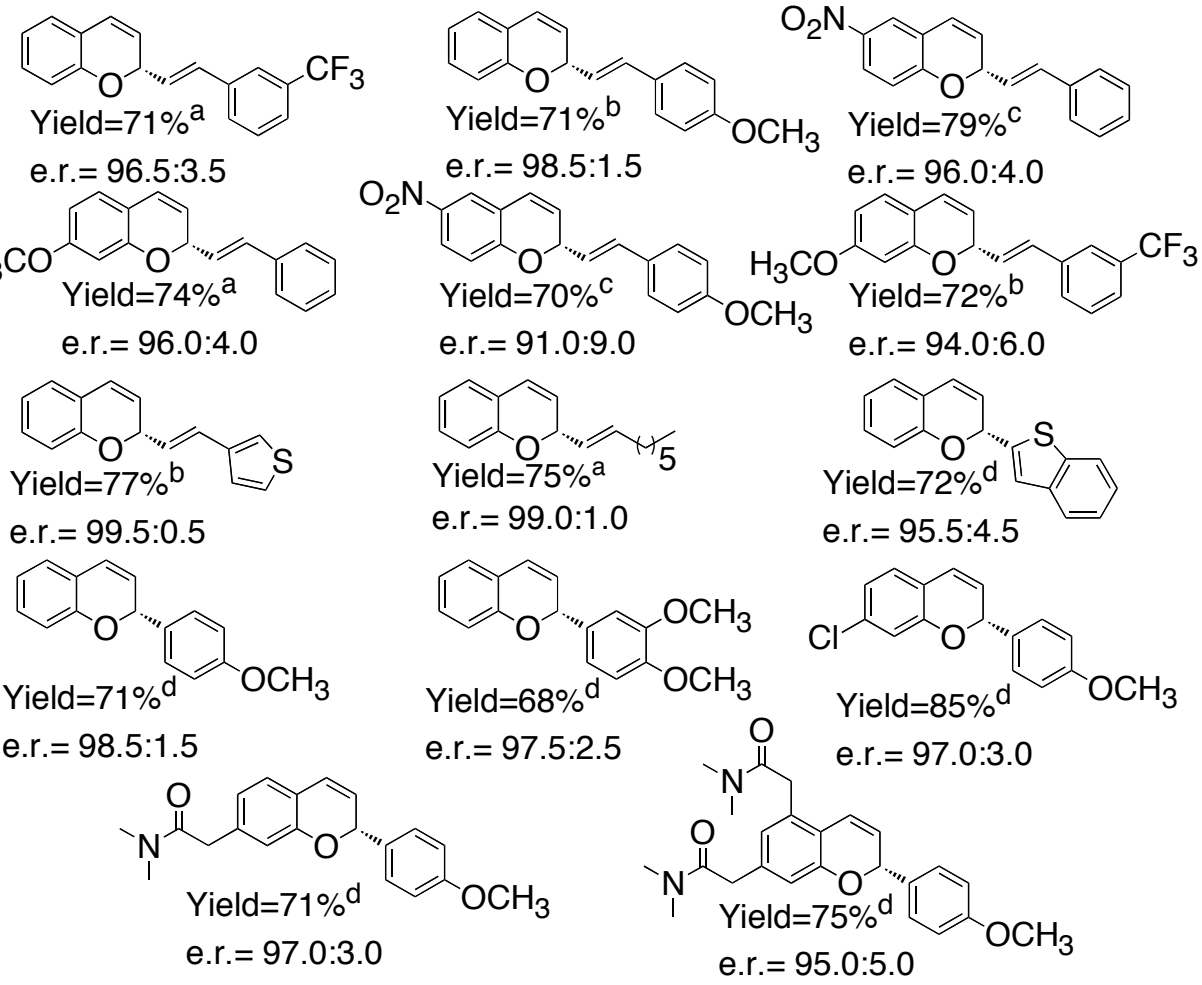
Figure 1.1: Chromene Containing Natural Products



Optimization of the reaction revealed that it required a Lewis acid catalyst to increase the efficiency of the Brønsted acid catalyst. It is noteworthy to mention that Yamamoto's group first developed this concept[68] of Lewis acid-assisted Brønsted acids. For this reaction the combination of the chiral tartaric amide with Ce^{III}, Ce^{IV} or Yb^{III} triflate salts gave the best yields and high enantioselectivity. Exploration of the substrate scope showed high enantiomeric ratio as well as high yields with some adjustments of reaction conditions. In some cases ^{t}BuOH had to be added to stabilize the starting compound. Aryl boronates were less reactive and were activated by addition of methoxy groups on the aromatic ring. Although the method proved to be very efficient, unfortunately it could not be generalized as the conditions had to be optimized for each substrate (**Scheme 1.94**).

Scheme 1.94: Asymmetric Synthesis of Chromenes Using Chiral Brønsted Acid/Lewis Acid Catalytic System



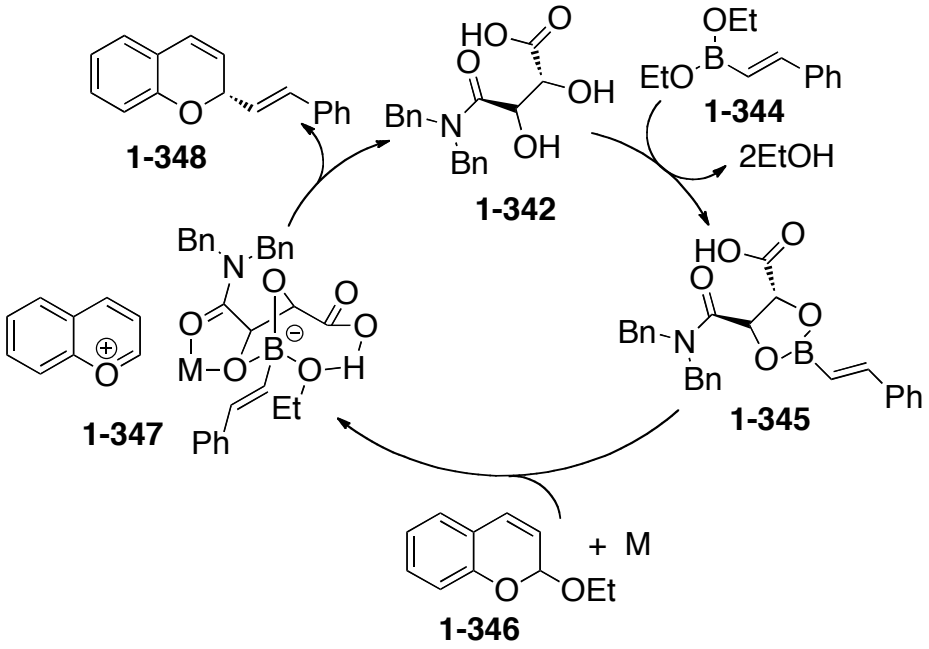


a. Condition A: 1.5 equiv boronate, 5 mol% **1-342**, 4.5 mol% $Ce(OTf)_4$
b. Condition B: 1.5 equiv boronate, 5 mol% **1-342**, 4.5 mol% $Ce(OTf)_4$, 1 eq *t*BuOH
c. Condition C: 1.5 equiv boronate, 5 mol% **1-1342**, 4.5 mol% $Yb(OTf)_3$, 1 eq *t*BuOH
d. Condition D: 3.0 equiv boronate, 10 mol% **1-342**, 9.0 mol% $Yb(OTf)_3$

A thorough spectroscopic study for the mechanistic investigation showed strong evidence for the formation of dioxaborolane **1-345**. It also indicated that the formation of

pyrylium intermediate and the complexation of $Ce(OTf)_4$ with the amide C=O of tartaric acid catalyst and with the boronate oxygen as well. Based on these valuable findings, a possible catalytic cycle was proposed which begins with the formation of dioxaborolane **1-345** from the boronate and tartaramide acid **1-342**. The complexation of Lewis acid to **1-345** increased the acidity of the boronate to promote the formation of pyrylium intermediate along with boronate complex **1-347**. The complex **1-347** was activated enough to facilitate the nucleophilic addition to the pyrylium intermediate giving the desired chromene product (**Scheme 1.95**).

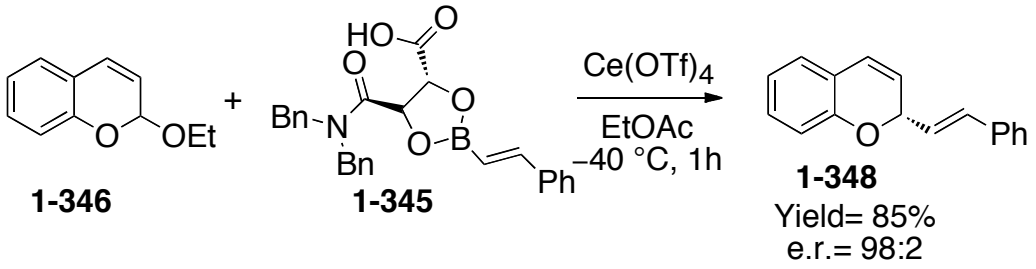
Scheme 1.95: Proposed Catalytic Cycle



Furthermore, the mechanism was supported by an experiment, which involved chromene acetal **1-346** and chiral dioxoborolane **1-345**. In presence of $Ce(OTf)_4$ as

catalyst, ethyl acetate as solvent at –40 °C in 1h the reaction resulted in the chromene product in 85% yield and 98:2 enantiomeric ratio (**Scheme 1.96**).

Scheme 1.96: Experiment in Support of Proposed Mechanism

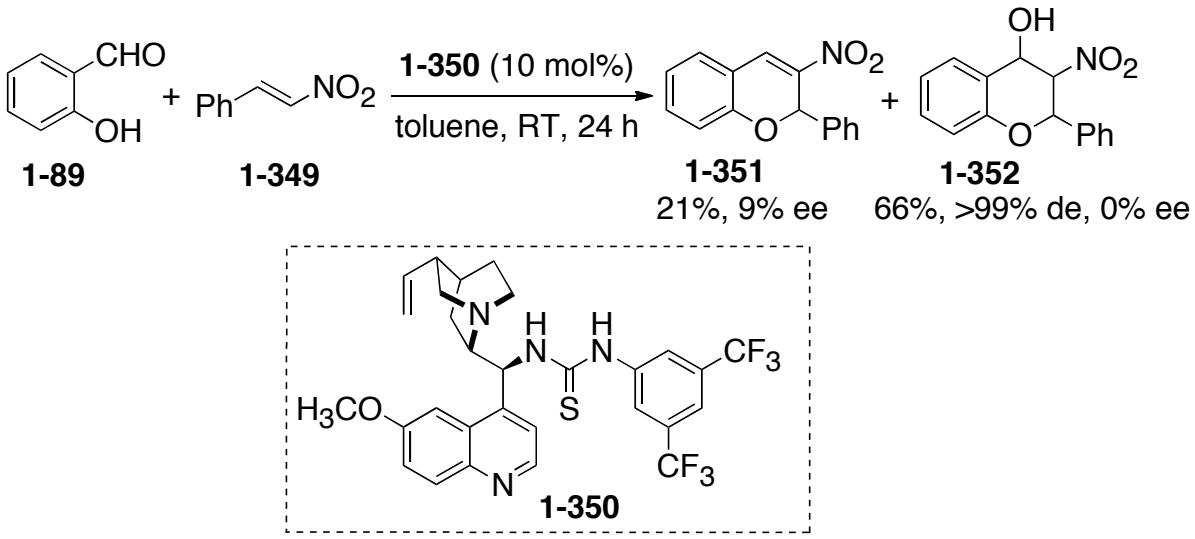


1-346 **1-345** **1-348**

Yield= 85%
e.r.= 98:2

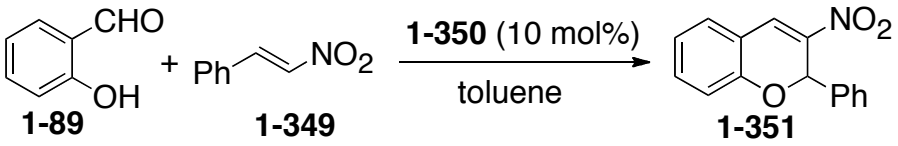
A tandem oxa-Michael-aza-Henry-desulfonamidation reaction was approached in an asymmetric way by using a bifunctional thiourea catalyst to synthesize chiral 2-aryl-3-nitro 2H-chromenes.[69] During the primary investigation of this reaction, taking salicylaldehyde **1-89** and nitrostyrene **1-349** as the model substrates, thiourea **1-350** appeared to be the most effective catalyst compared to other quinine derivatives although giving poor yield (21%) and enantioselectivity (9% ee) of the nitrochromene product. The intermediate nitrochromane **1-352** was also isolated in 66% yield as a single diastereomer (>99% de) but with no enantioselectivity (**Scheme 1.97**).

Scheme 1.97: Asymmetric oxa-Michael-aza-Henry-desulfonamidation Reaction Using a Bifunctional Thiourea Catalyst



Anticipating improvement of the reaction by increasing the binding ability with the thiourea catalyst, activated aldimines were switched as aldehyde surrogate. Salicyl N-tosylimine was chosen along with nitrostyrene. As usual, thiourea **1-350** worked best as the catalyst giving 65% yield and 46% ee of the product at room temperature. Moreover, lowering the temperature to 0 °C improved the ee to 92% though the yield was compromised (31%). Also, toluene proved to be a better solvent compared to dichloromethane for the stereoinduction (**Scheme 1.98**).

Scheme 1.98: Substrate Scope



Entry	R^1	Ar	Yield (%)[a]	ee (%)[a]
1	H	Ph	52 (31)	49 (92)
2	H	2-$MeOC_6H_4$	70 (22)	29 (66)
3	H	4-$MeOC_6H_4$	56 (23)	50 (80)
4	H	4-MeC_6H_4	69 (22)	39 (96)
5	H	4-BrC_6H_4	83	35
6	H	2,3-$(MeO)_2C_6H_3$	81 (42)	48 (97)
7	H	2,6-$Cl_2C_6H_3$	34 (23)	37 (52)
8	H	3,4-$Cl_2C_6H_3$	93 (68)	31 (46)
9	H	furyl	87 (54)	43 (51)
10	5-MeO	Ph	20	80
11	4-Br	Ph	75	41

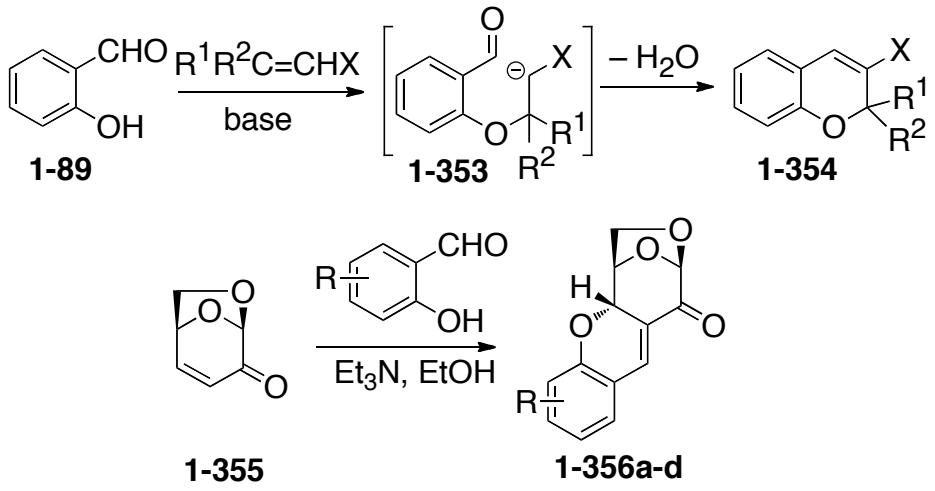
a. Values in the parenthesis were obtained at 0 °C

As for the substrate scope, both electron-donating and electron-withdrawing groups in nitrostyrene were tolerated giving good overall yields. In salicyl N-tosylimine, electron-withdrawing groups afforded better yield and moderate enantioselectivity while electron-donating groups produced lower yield and higher enantioselectivity. Comparing the reaction at room temperature and at 0 °C, it appeared that lower temperature favors ee at the price of yield. It was proposed that the low yield was due to the incomplete elimination process of tosylamide from the oxa-Michael-aza-Henry addition intermediate.

Optically active pyrano [3,4-*b*] chromenes **1-356** were synthesized by employing a stereoselective domino oxa-Michael-aldol reaction between 2-hydroxy benzaldehyde

and a chiral α,β-unsaturated ketone called levoglucosenone **1-355** using chiral-pool synthetic strategy (**Scheme 1.99**).[70] The chiral ketone **1-355** can be derived from cellulose[71] and is known for its application in asymmetric synthesis.[72,71]

Scheme 1.99: Chiral Pool Synthesis of Chromenes



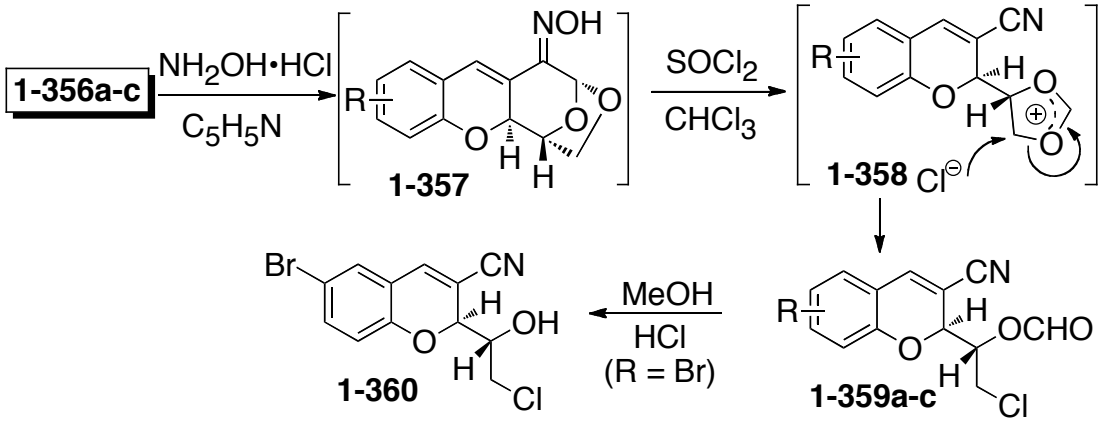
In this reaction the new chiral center arises because the attack of the phenolate anion happens from the opposite side of the anhydro bridge (**Scheme 1.100**).

Scheme 1.100: Substrate Scope

R	Yield of **1-356** (%)	Yield of **1-359** (%)
H (**a**)	84	69
5-Br (**b**)	86	67
3-MeO (**c**)	91	59
5-NO_2 (**d**)	52	

The reaction was facile with most of the substrates except for 5-nitro salicylaldehyde, which exhibited slow reactivity delivering low yield. This could be due to the poor nucleophilicity of the nitrophenolate anion. Interestingly, the oximes of pyranochromenes **1-357** could be converted into 3-cyano-2H-chromenes **1-360** in good yields via Beckmann fragmentation by treating with $SOCl_2$. The intermediate 1,3-dioxolan-2-ylium cation **1-358** was cleaved by attack of chloride anion at the least sterically hindered position. Product **1-359** could be further converted to chlorohydrin **1-360** in high yield (**Scheme 1.101**).

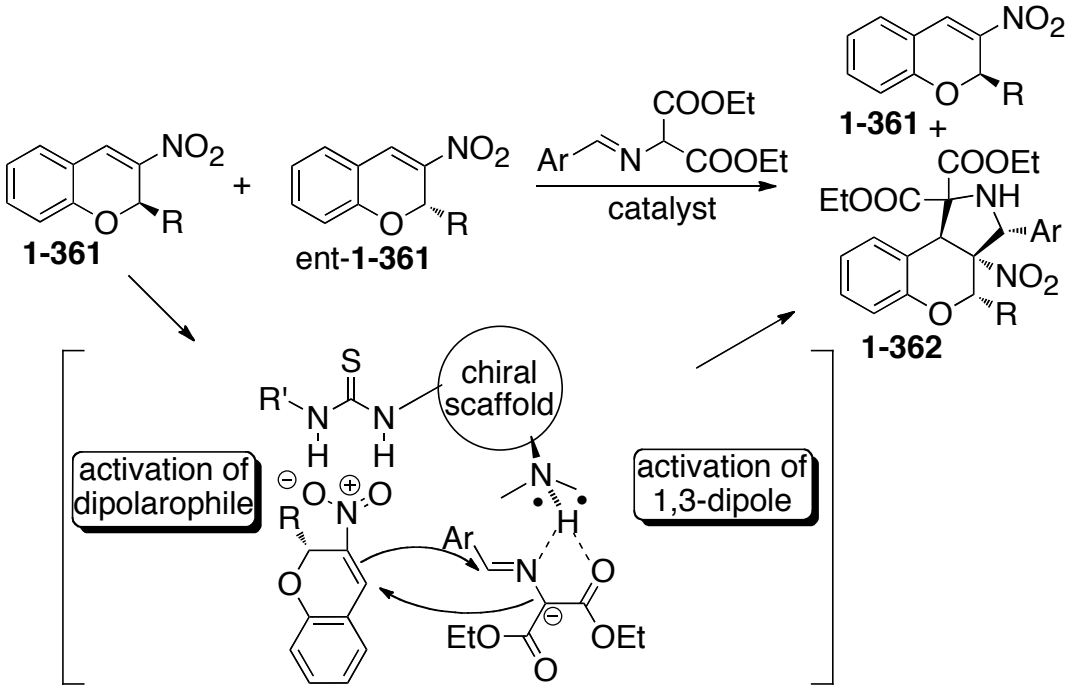
Scheme 1.101: Synthesis of 3-cyano-2H-chromenes



3-Nitro-2H-chromenes are very important structural units in perspective of their biological activities as well as nitro group being precursor to a range of useful functional groups. Although, the employment of enantioselective tandem oxa-Michael-Henry reaction using chiral amine as catalyst for the synthesis of chiral 3-nitro-2H-chromene derivatives was reported,[73] however, these methods suffered a number of drawbacks

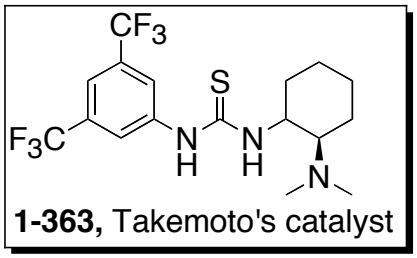
such as low ee, low yield and long reaction time (**Scheme 1.102**). Xie et al introduced an efficient kinetic resolution of racemic 3-nitro-2H-chromenes as an alternative route.[74]

Scheme 1.102: Kinetic Resolution of Racemic 3-Nitro-2H-Chromenes



They strategized this kinetic resolution by planning to use a chiral thiourea derived organocatalytic system which would render an asymmetric formal [3+2] cycloaddition of azomethine ylides with one enantiomer of nitro-chromene to form multifunctional benzopyrano-pyrrolidine derivatives while leaving behind the other enantiomer. In this way, kinetic resolution as well as formation of a new multifunctional compound with four vicinal chiral centers could easily be achieved which might be very interesting for phermaceutical chemistry.

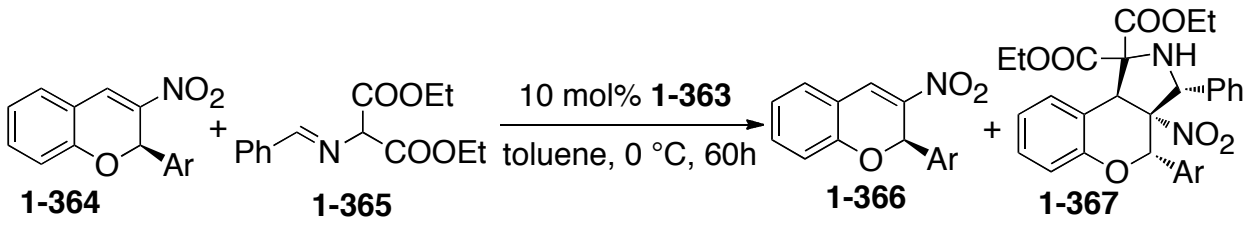
Figure 1.2: Takemoto's Catalyst



1-363, Takemoto's catalyst

In search for the best catalyst four different chiral thiourea catalysts were screened and among them Takemoto's catalyst **1-363** (**Figure 1.2**) seemed to be the potential one for this method. Toluene was the solvent of choice and the reaction was run at 0 °C. The substrate scope was examined by using differently substituted chromenes and α-amino malonate imine in presence of 10 mol% of Takemoto's catalyst. In all cases, enantiomer **1-361** could be resolved in high enantioselectivities (77-85%) and good yields. At the same time the multifunctional benzopyrano pyrrolidine product could be obtained in a range of 13-70% ee with four vicinal chiral carbon centers reported for the first time (**Scheme 1.103**).

Scheme 1.103: Substrate Scope

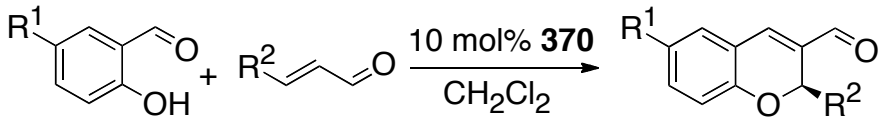


entry	Ar (**1-364**)	ee (%)/yield (%) **1-366**	ee (%)/yield (%) **1-367**
1	C_6H_5	87/41	19/25
2	4-ClC_6H_4	77/42	17/26
3	4-BrC_6H_4	79/41	35/40
4	4-$CF_3C_6H_4$	85/46	49/31
5	4-MeC_6H_4	82/47	45/27
6	4-$MeOC_6H_4$	68/49	21/23
7[a]	C_6H_5	73/37	53/47
8[b]	C_6H_5	86/43	33/29
9[b]	4-MeC_6H_4	87/45	57/35
10[b]	4-$MeOC_6H_4$	83/47	70/36
11[b]	4-ClC_6H_4	73/45	51/41
12[b]	4-BrC_6H_4	82/39	13/32

a. At –10 °C for 12h
b. At –10 °C for 36h

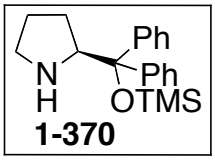
Arvidsson and coworkers developed[75] the first report of organocatalytic asymmetric synthesis of benzopyrans. They used one-pot oxa-Michael addition by an intramolecular aldol condensation between salicylaldehyde **1-368** and α,β-unsaturated aldehydes **1-369**. The reaction is activated by iminium ion formation with an organocatalyst.

Scheme 1.104: Organocatalytic Asymmetric oxa-Michael Addition for the Synthesis of Chromene



1-368 **1-369** **1-371**

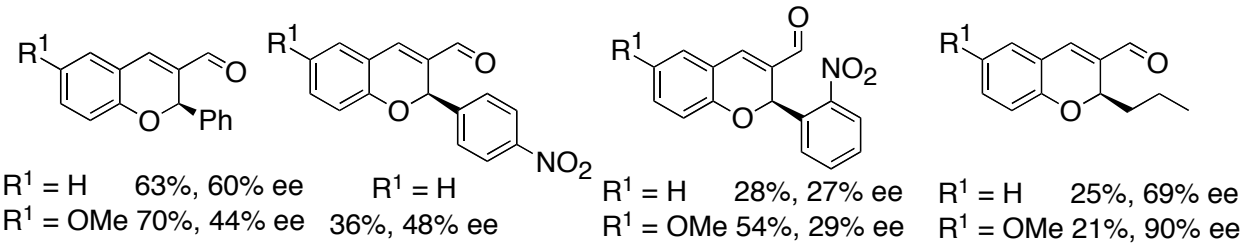
Additive	Conversion (%)	ee (%)
None	90	60
Imidazole	10	69
p-Chlorobenzoic acid	52	72



1-370

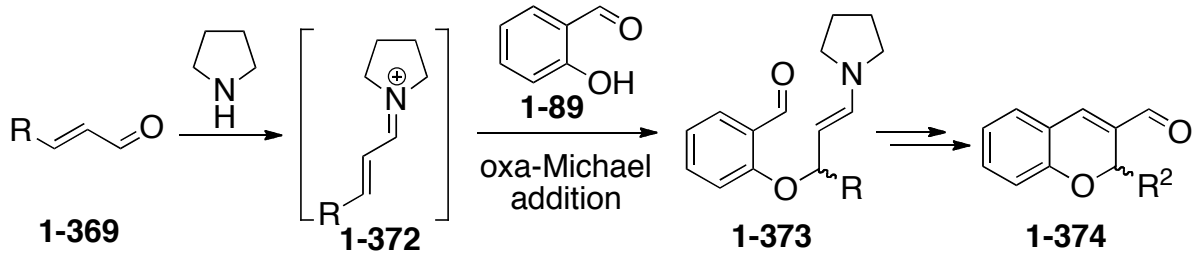
Screening of catalysts revealed that diphenylprolinol trimethylsilyl ether **1-370** was promising both for promoting the reaction as well as inducing the chirality. Influence of different organic acids and bases as additives were tested and it was observed that imidazole and *p*-chlorobenzoic acid increased the enantioselectivity of the reaction although in both cases the reaction became very sluggish with much reduced yield. Thus without any additives, the substrate scope was also investigated only with catalyst **1-370**. Different α,β-unsaturated aldehydes with varying substituents at the alkene end were reacted with both salicylaldehyde and 5-methoxy salicylaldehyde. 5-Methoxy salicylaldehyde gave much better yield but low enantioselectivity. Alkyl substituent on α,β-unsaturated aldehyde showed low yield but higher enantioselectivity (**Scheme 1.105**).

Scheme 1.105: Substrate Scope



The actual mechanism of this reaction was not clear at that time but the rapid formation of the iminium ion **1-373** was detected and it was proposed that oxa-Michael addition was the rate-determining step (**Scheme 1.106**).

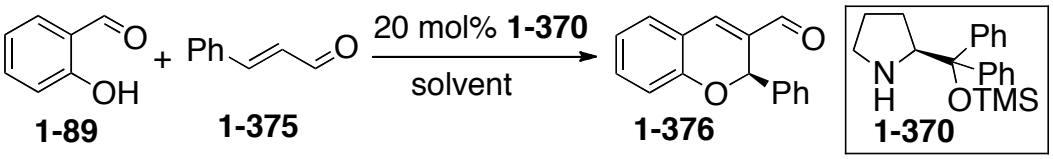
Scheme 1.106: Proposed Mechanism



Very interestingly the same methodology was also reported by Córdova group independently at about the same time.[76] They also reported the chiral synthesis of 2-substituted-2H-chromene-3-carbaldehydes by using an organocatalytic enantioselective domino oxa-Michael/aldol condensation reaction as reported by Arvidsson group.[75] Diphenyl prolinol trimethylsilyl ether **1-370** was also their choice of catalyst, which catalyzed the reaction between salicylaldehyde **1-89** and cinnamaldehyde **1-375** giving

21% ee with poor conversion (18%). After an extensive screening of reaction conditions it was found out that addition of an organic acid boosted the reaction yield and enantioselectivity and 2-nitrobenzoic acid seemed to work best in toluene at room temperature (**Scheme 1.107**).

Scheme 1.107: Enantioselective Domino oxa-Michael/Aldol Condensation

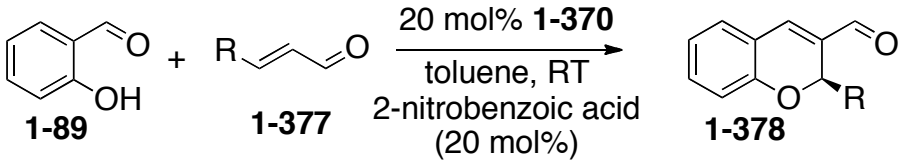


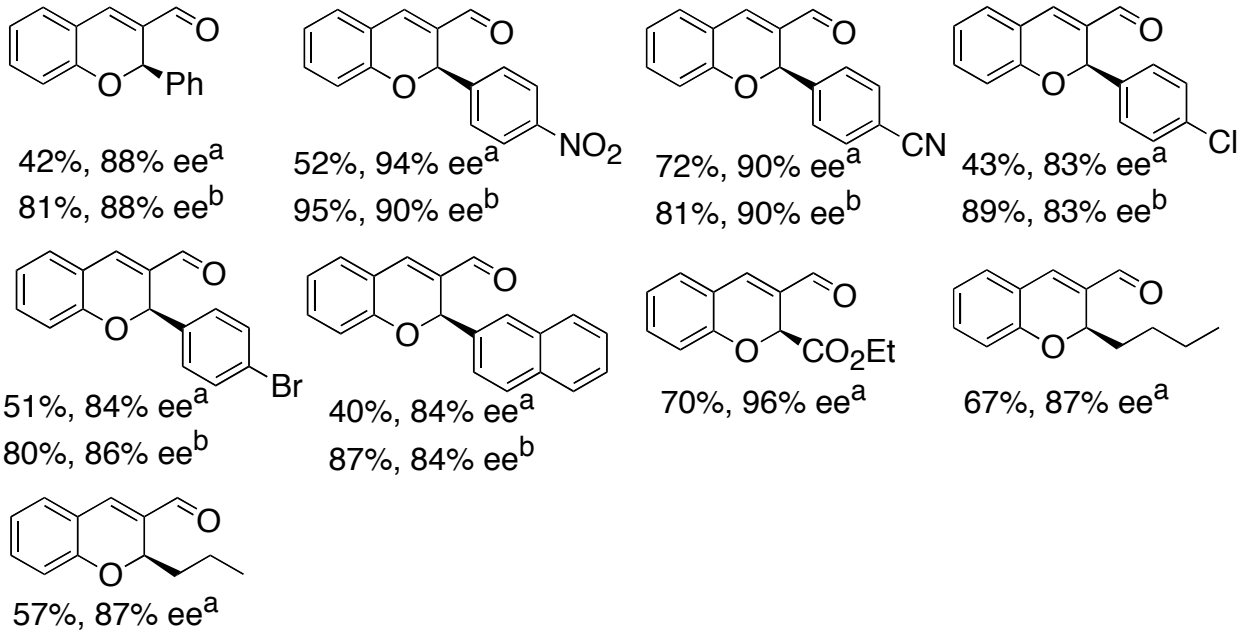
1-89 **1-375** **1-376** **1-370**

Additive	Solvent	Conversion (%)	ee (%)
None	$CHCl_3$	18	21
2-Nitrobenzoic acid	toluene	37	88

The reaction appeared to be very general with the substituents in the α,β-unsaturated aldehyde. In almost all the cases, high enantioselectivity and good overall yield were observed. However, the best enantioselectivities were observed in case of electron-deficient aldehydes though the yields were moderate. But removal of water by addition of molecular sieves solved this problem giving much higher yield for the same reactions without compromising the ee (**Scheme 1.108**).

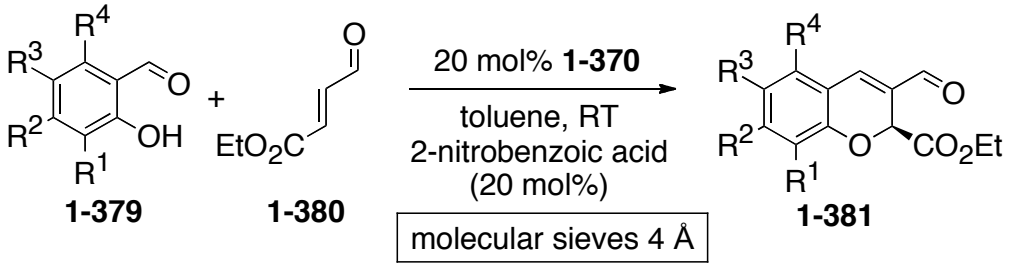
Scheme 1.108: Substituent Effect on α,β-Unsaturated Aldehyde

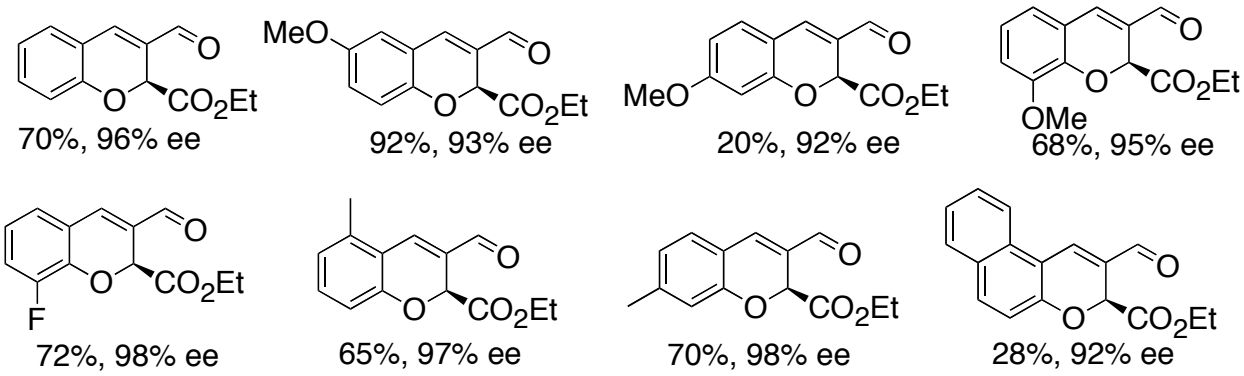




Next, they examined the substituent effect on salicylaldehyde aromatic ring and found that the reaction of **1-380** with different salicyaldehydes gave chromene derivatives in high (92-98%) ee with high yields. The yield was only low when there was 5-OMe in salicylaldehyde and also for the formation of naphthopyran (**Scheme 1.109**).

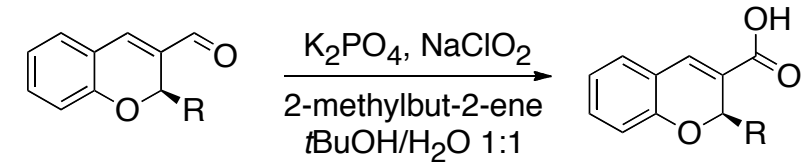
Scheme 1.109: Substituent Effect on Salicyaldehyde





To determine the stereocentre, the chromene-3-carbaldehyde products **1-382a** and **1-382b** were oxidized to the corresponding chromene carboxylic acids in high yield. X-ray analysis of the enantiopure chromene-3-carboxylic acid **1-383b** established that the absolute configuration at C_2 was *R* (**Scheme 1.110**).

Scheme 1.110: Determination of the Stereocenter

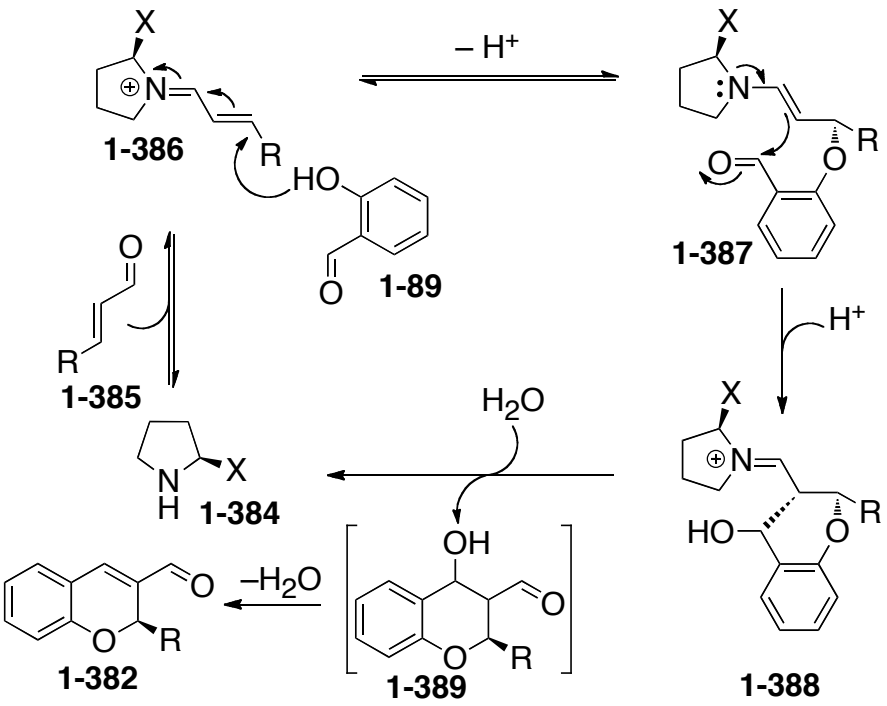


1-382a: R = 4-$NO_2C_6H_4$
1-382b: R = CO_2Et

1-383a: 76% yield
1-383b: 75% yield

The proposed mechanism suggests that the reaction leads with the iminium ion activation of α,β-unsaturated aldehyde **1-385** by the organocatalyst **1-384** followed by the nucleophilic attack by the phenolic OH of salicylaldehyde **1-89**. Since the bulky aryl groups shield the *Si-face* of the chiral iminium intermediate **1-386**, the oxa-Michael addition happens on the *Re-face* stereoselectively generating the enamine intermediate **1-387**. Subsequently, the enamine attacks the C=O of salicylaldehyde to complete the cyclization. The resulting iminium ion **1-388** gets hydrolyzed to give chromanol **1-389**. Elimination of water furnishes the final chromene product **1-382** (**Scheme 1.111**).

Scheme 1.111: Proposed catalytic cycle

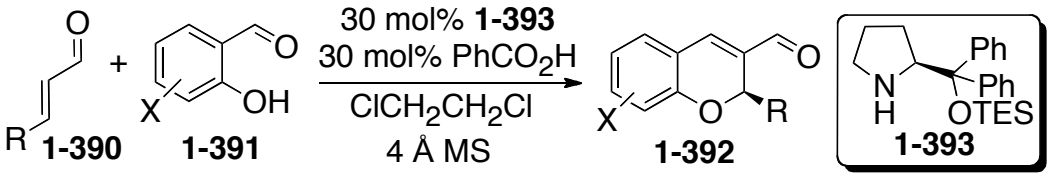


From the proposed mechanism, it can be envisioned that the addition of sub stoichiometric amount of organic acid plausibly accelerates the reaction by stabilizing

the iminium intermediate and also by activating the benzaldehyde moiety for intramolecular 6-*exo-trig* aldol condensation. Moreover, the addition of molecular sieves facilitated removing the water from the reaction medium and thus driving the condensation forward to the product formation.

In an almost identical approach, reported by Wei and Wang[77], chiral chromenes were synthesized using (*S*)-diphenylprolinol triethylsilylether **393** as the chiral organocatalyst and benzoic acid as the co-catalyst.

Scheme 1.112: Effect of Benzoic Acid as Co-Catalyst



1-390 **1-391** **1-392** **1-393**

Entry	R	X	Yield (%)	ee (%)
1	Ph	H	87	88
2	4-$NO_2C_6H_4$	H	96	95
3	4-$NO_2C_6H_4$	5-Me	98	96
4	4-$NO_2C_6H_4$	5-Cl	96	91
5	4-$NO_2C_6H_4$	4-MeO	64	86
6	4-$NO_2C_6H_4$	3-MeO	98	90
7	4-$NO_2C_6H_4$	5-MeO	95	94
8	2-$NO_2C_6H_4$	5-Cl	82	>99
9	Ph	5-MeO	97	87
10	4-$MeOC_6H_4$	5-Cl	53	75
11	Me	5-Cl	67	82
12	Me	5-MeO	84	85

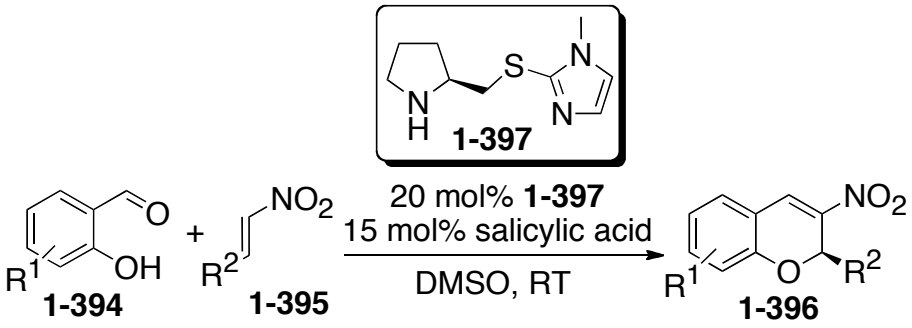
To check the efficacy of this method different salicylaldehydes and *trans*-cinnamaldehydes were examined. The experiments showed good to high yields (53-98%) with good to excellent enantioselectivity (75-99% ee) (**Scheme 1.112**). The enantioselectivity appeared to depend on the electronic nature of the cinnamaldehyde. It

was noticed that the reaction resulted in much better ee when *trans*-cinnamaldehyde was bearing an electron-withdrawing group compared to the cases where it was neutral or electron-donating substituent. On the contrary, the substituents in salicylaldehyde did not influence the reaction much.

Xu et al developed[78] a one-pot asymmetric synthesis of 3-nitro-2H-chromene by using an enantioselective tandem oxa-Michael-Henry reaction between salicylaldehydes and nitro-olefins. It is noteworthy to mention that 3-nitro-2H-chromenes are very important compounds because they can be modified to flavonols, amines and other biological targets. In this method, a chiral secondary amine organocatalyst was used along with an organic acid as co-catalyst, which facilitated the reaction via aromatic iminium activation (AIA). Although, the concept is same as for the domino oxa-Michael/aldol condensation reactions mentioned above, but this is probably the first report of activation of aromatic aldehydes through the iminium ion formation in the field of asymmetric organocatalysts.

After a thorough screening, the authors found that the combination of catalyst **1-397** and salicylic acid as co-catalyst produced the highest yield and enantioselectivity of the desired product. Importantly, a polar solvent stabilized the partially ionized intermediated and DMSO turned out to be the best choice.

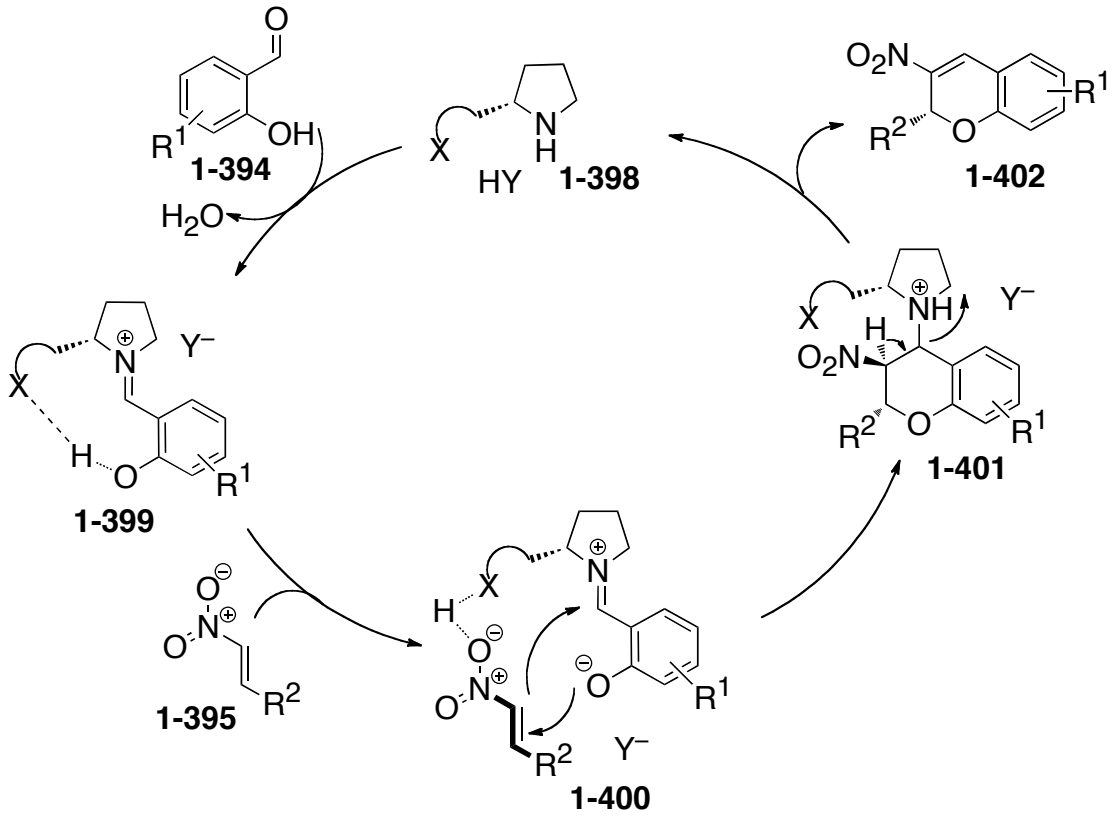
Scheme 1.113: Effect of Salicylic Acid as Co-Catalyst



Entry	R^1	R^2	Yield (%)	ee (%)
1	H	Ph	72	51
2	H	4-MeC_6H_4	81	45
3	H	4-$MeOC_6H_4$	87	52
4	H	naphthalen-2-yl	51	53
5	3-MeO	Ph	78	77
6	4-MeO	Ph	67	85
7	5-MeO	Ph	32	48
8	5-Cl	Ph	72	62
9	4-MeO	4-ClC_6H_4	57	69
10	4-MeO	4-BrC_6H_4	46	61
11	4-MeO	2-$MeOC_6H_4$	37	91
12	4-MeO	3-$MeOC_6H_4$	52	71
13	4-MeO	4-$MeOC_6H_4$	47	72
14	4-MeO	naphthalen-2-yl	35	70

Examination of the various substrates revealed that in almost all cases the enantioselectivities were moderate to high. In general, salicylaldehydes with substituents exhibited better selectivity compared to no substitution. There was no noticeable substituent effect of β-nitrostyrene (**Scheme 1.113**).

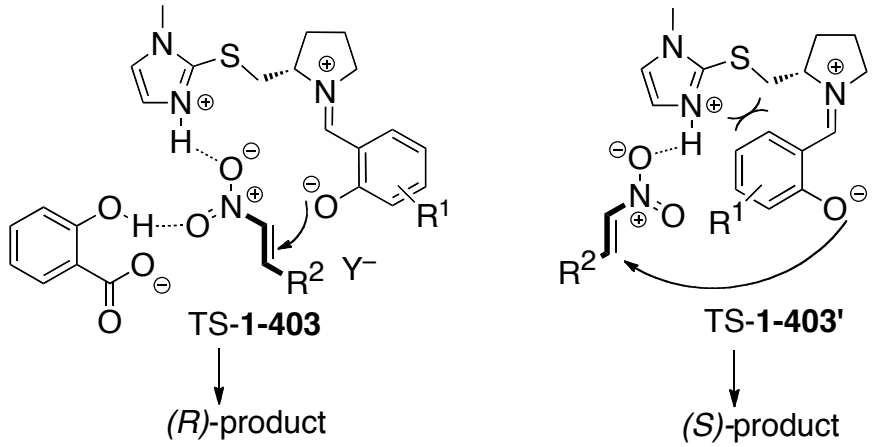
Scheme 1.114: Proposed Catalytic Cycle



According to the suggested mechanism, the iminium-activated salicylaldehyde **1-399**, also activated simultaneously by the Lewis base moiety X of the organocatalyst **1-398**, took part in a domino oxa-Michael-Henry reaction with β-nitrostyrene. Nitrostyrene was finely induced in complex **1-400**. Finally elimination from intermediate **1-401** afforded the chromene product **1-402** regenerating the catalyst. Two important transition states were proposed for this reaction: TS-**1-403** and TS-**1-403'**. TS-**1-403** seemed to be more favored compared to TS-**1-403'** because of the absence of steric congestion. As a result, in TS-**1-403** the oxa-Michael addition occurred to the *Re-face* of β-nitrostyrene

forming (*R*)-products (**Scheme 1.115**). This was also supported by the theoretical ECD spectra, simulated by TD-DFT calculations.

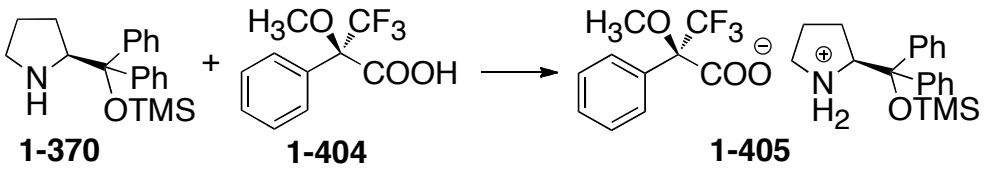
Scheme 1.115: Proposed Transition States



It was proposed that both the catalyst and co-catalyst played a dual role in this reaction. Catalyst **1-397** not only activated salicylaldehyde by iminium ion formation but also facilitated the deprotonation of its OH group to promote the Michael addition. On the other hand, salicylic acid helped the formation of iminium ion and also activated β-nitrostyrene by H-bonding to the nitro oxygen (TS-**1-403**).

A novel effort to further improve the enantioselective tandem oxa-Michael-aldol reaction by use of a combination of chiral amine and chiral acid organocatalytic system was reported by Xu and co-workers.[79] They envisioned that chiral organic acids should accelerate the catalytic tandem reaction. Also fine-tuning of the catalytic environment by modifying chiral acid/chiral base ammonium salt should improve the enantioselectivity.

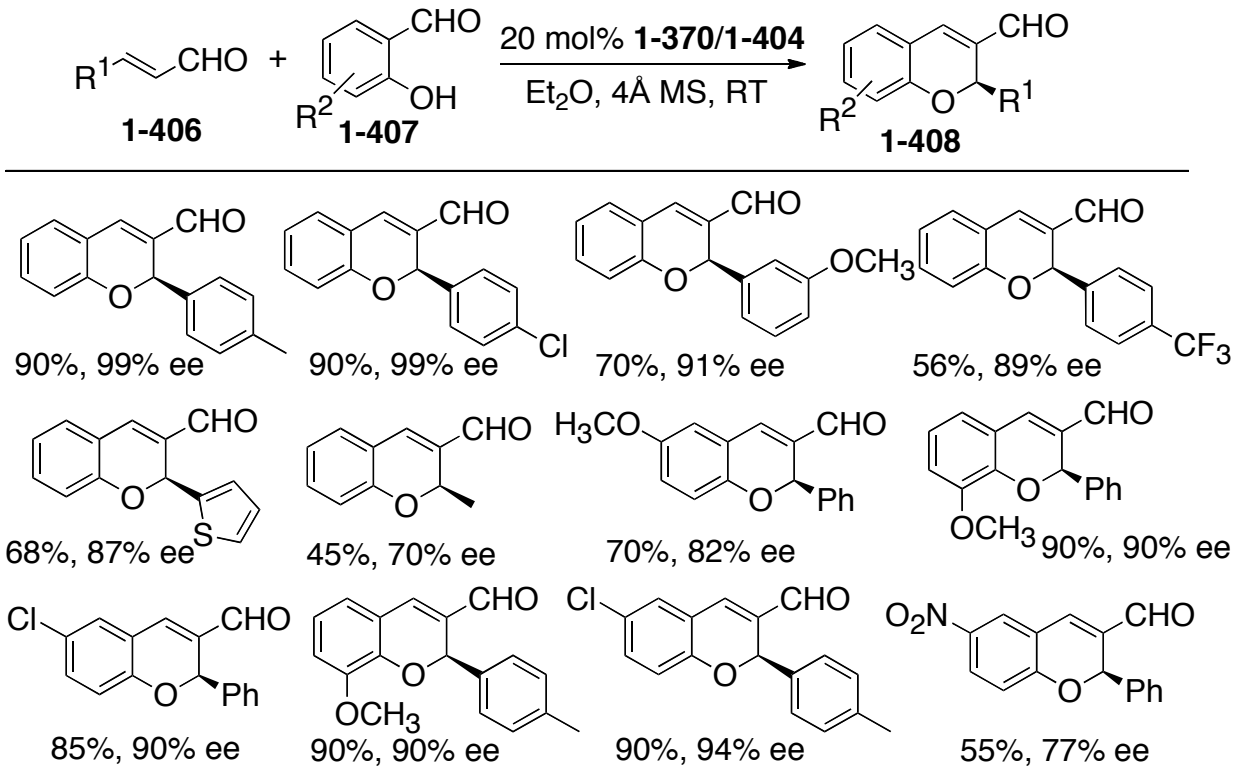
Scheme 1.116: Combination of Chiral Acid and Chiral Base



1-370 **1-404** **1-405**

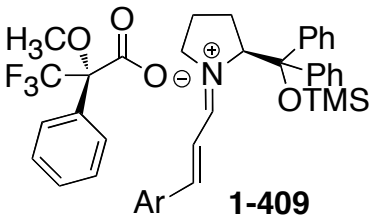
As the model chiral base, (*S*)-diphenylprolinol trimethylsilyl ether **370** was chosen because its catalytic activity was the best in the field of tandem Michael-aldol reactions as reported in the literature. To select the best chiral acid, a range of organic acids was examined in combination with chiral base **1-370**. After extensive screening, (*S*)-Mosher acid **1-404** turned out to be the definite choice as this combination of catalytic system gave the highest yield and enantioselectivity. Importantly, this new chiral acid/base system (**Scheme 1.116**) not only increased the rate of the reaction but also improved the selectivity relative to the case of just using the amine **1-370** under the same conditions.

Scheme 1.117: Application of Chiral Acid/Chiral Base Catalytic System



With this optimized condition in hand, the generality of this reaction was tested with various substrates. It was observed that the presence of electron-donating group whether in salicylaldehyde or α,β-unsaturated aldehyde helped in the increment of both yield and ee. On the contrary, electron-withdrawing groups showed a negative effect in yield and ee of the products. However, the overall yields were good (45-90%) as well as the ee (70-99%) (**Scheme 1.117**).

Figure 1.3: Chiral Intermediate



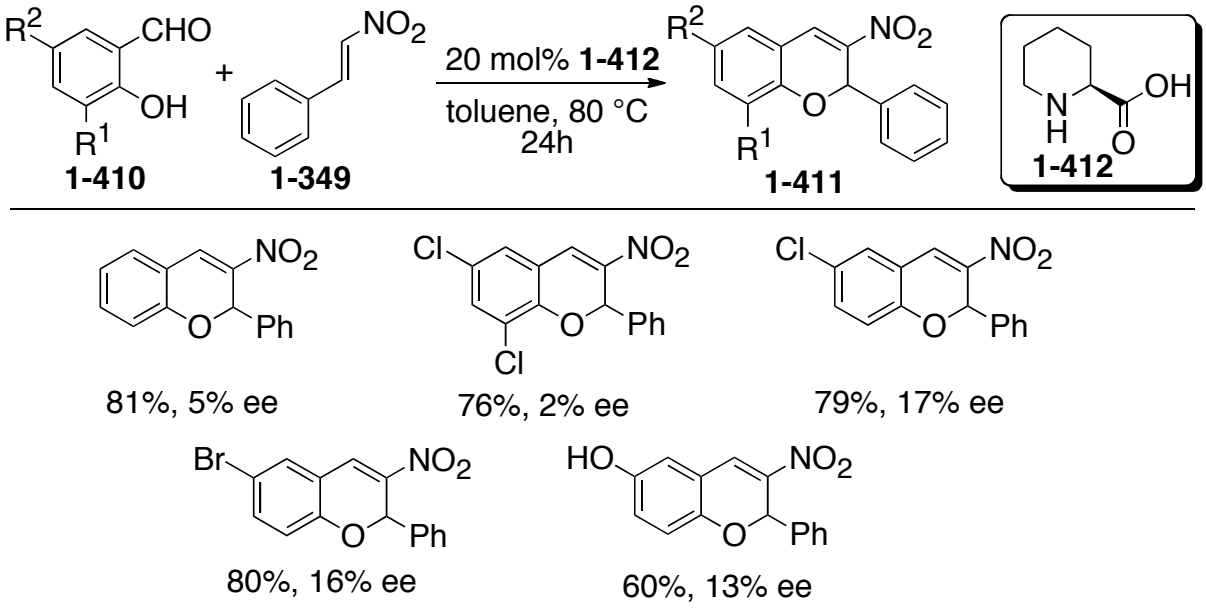
1-409

The proposed mechanism indicated that the reaction initiated with the formation of iminium ion, which was detected by both ^{1}H NMR and mass spectroscopy. (*S*)-Mosher acid has a strong ability to accelerate the formation of the iminium ion as well as creating an efficient chiral environment by interacting with the chiral amine. They form a stable ionic pair on the less sterically hindered side of the pyrrolidine ring of **1-370** (**Figure 1.3**). As a result, chirality-directing groups on its both sides flanked the secondary amine catalyst. Thus, the *Si-face* of the aldehyde shielded by the chiral framework of **1-370** and the phenyl group of (*S*)-Mosher acid by the formation of iminium ion from *trans*-cinnamaldehyde. The only choice left for the OH group of salicylaldehyde to attack the β–carbon of *trans*-cinnamaldehyde was from the *Re-face*. That was how the Michael addition step was stereocontrolled to give the chiral chromene product with high enantioselectivity.

An effort to synthesize 2-substituted-3-nitro-2H-chromenes via a domino oxa-Michael/aldol reaction in an organocatalytic way was reported by Das and Evans.[80] The authors selected simple catalysts like guanidine, 1,1,3,3-tetramethylguanidine (TMG) and pipecolinic acid for screening in this reaction. Notably, no co-catalyst was used in

the study. By optimization, picolinic acid turned out to be the best giving best yield with poor ee.

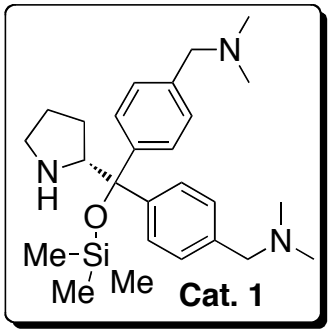
Scheme 1.118: Synthesis of 2-Substituted-3-Nitro-2H-Chromenes via a Domino Organocatalytic oxa-Michael/Aldol Reaction

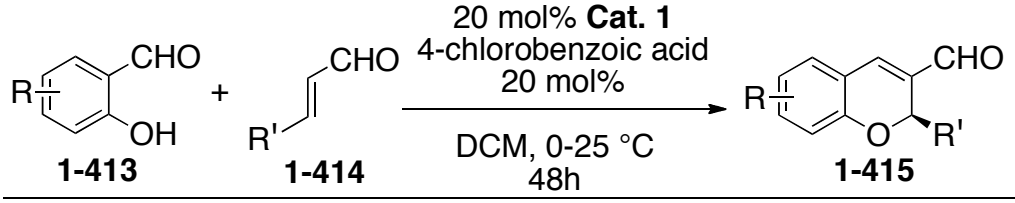


The substrate scope was studied by using variously substituted salicylaldehydes in reaction with β–nitrostyrene. Irrespective of the difference in electronic effect of the substituents, the yields were high in all cases. Although, the enantioselectivity was poor in all cases, it was comparatively better when there was only one substituent in the *para*-position to phenolic OH of salicylaldehyde (**Scheme 1.118**). An improvement in the domino oxa-Michael/aldol reaction of salicylaldehydes **1-413** with α,β-unsaturated aldehydes **1-414** was introduced by use of a recyclable tertiary amine-modified diarylprolinol silyl ether **1-415** as an effective organocatalyst.[81] The reaction worked best in presence of *p*-chlorobenzoic acid and molecular sieves. This modified catalyst

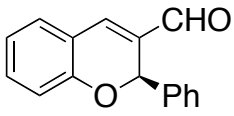
system improved previously reported[75] enantioselectivity (72-90% ee) to upto 94% ee with improved yields (**Scheme 1.119**).

Scheme 1.119: Modified Domino Organocatalytic oxa-Michael/Aldol Reaction

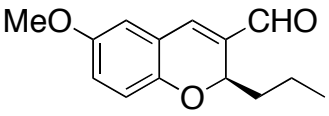




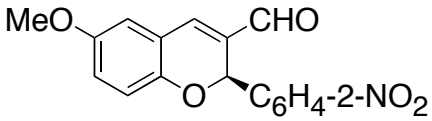
1-413 **1-414** **1-415**



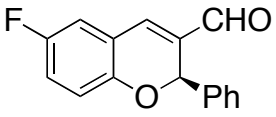
(*S*)-**1-415**, 5 °C:
83% ee, 93% yield



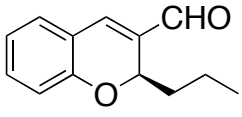
(*S*)-**1-415**, 25 °C:
93% ee, 78% yield
(*R*)-**1-415**, 5 °C:
–94% ee, 75% yield



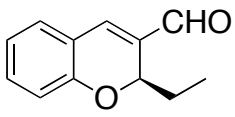
(*S*)-**1-415**, 0 °C:
53% ee, 54% yield
(*R*)-**1-415**, 5 °C:
–58% ee, 95% yield



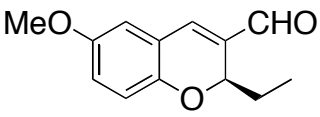
(*S*)-**1-415**, 0 °C:
80% ee, 88% yield
(*R*)-**1-415**, 5 °C:
–71% ee, 72% yield



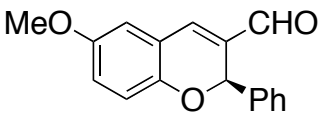
(*S*)-**1-415**, 25 °C:
85% ee, 26% yield
(*R*)-**1-415**, 5 °C:
–90% ee, 15% yield



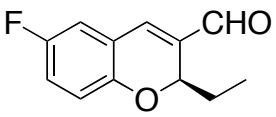
(*S*)-**1-415**, 25 °C:
83% ee, 22% yield
(*R*)-**1-415**, 5 °C:
–91% ee, 18% yield



(*S*)-**1-415**, 25 °C:
83% ee, 76% yield



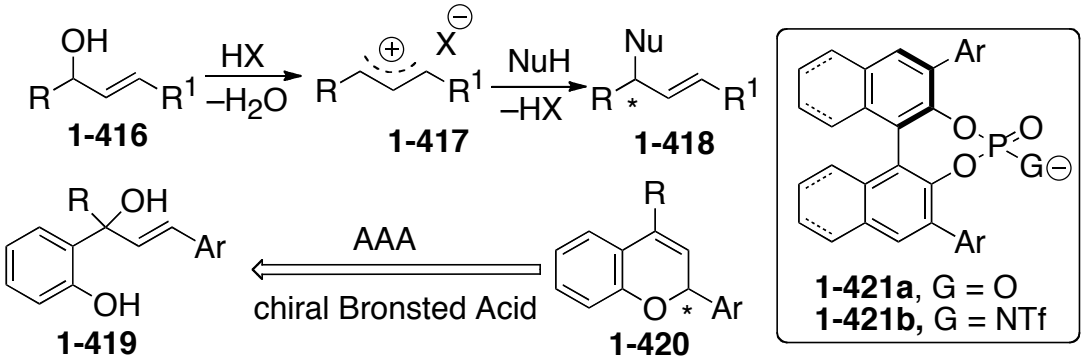
(*S*)-**1-415**, 0 °C:
75% ee, 62% yield



(*S*)-**1-415**, 25 °C:
83% ee, 45% yield

In 2011, Rueping and co-workers have presented[82] a very new concept based on the chiral organic contact ion-pairs in metal free catalytic allylic substitution for the enantioselective synthesis of chromenes. The concept involves the employment of a chiral Bronsted acid-catalyzed enantioselective allylic alkylation of alcohol that delivered the substituted optically active product with the regeneration of the chiral Brönsted acid catalyst, which could be utilized for the subsequent enantioselective synthesis of chromenes (**Scheme 1.120**).

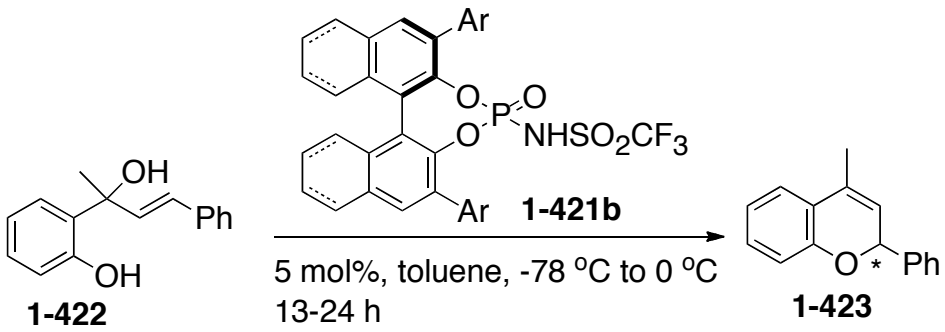
Scheme 1.120: Chiral Bronsted Acid Catalyzed Synthesis of Chromenes



For this purpose, they started their reaction with **1-422** as the model substrate. Employment of the highly acidic N-trifluorophosphoramide **1-421b** at 0 °C temperatures in toluene, promising results were obtained, i.e. the product **1-423** obtained in 77% yield with 56% ee. Subsequently, the roles of various solvents were examined and experimentally, it has been observed that in almost all solvents tested, the enantioselectivity dropped compared to that of the reaction conducted in toluene. Use of the molecular sieves played a negative influence on both the yield and selectivity.

Naturally, in order to investigate the role of substituents on the Bronsted acid catalyst they conducted a series of reaction changing different functionalities around the different positions of the binol systems. Among all the catalysts tested, comparable results were obtained with the 3,3'-position of the BINOL/HSBINOL fragments, with phenyl substituents at lower temperature (**Scheme 1.121**).

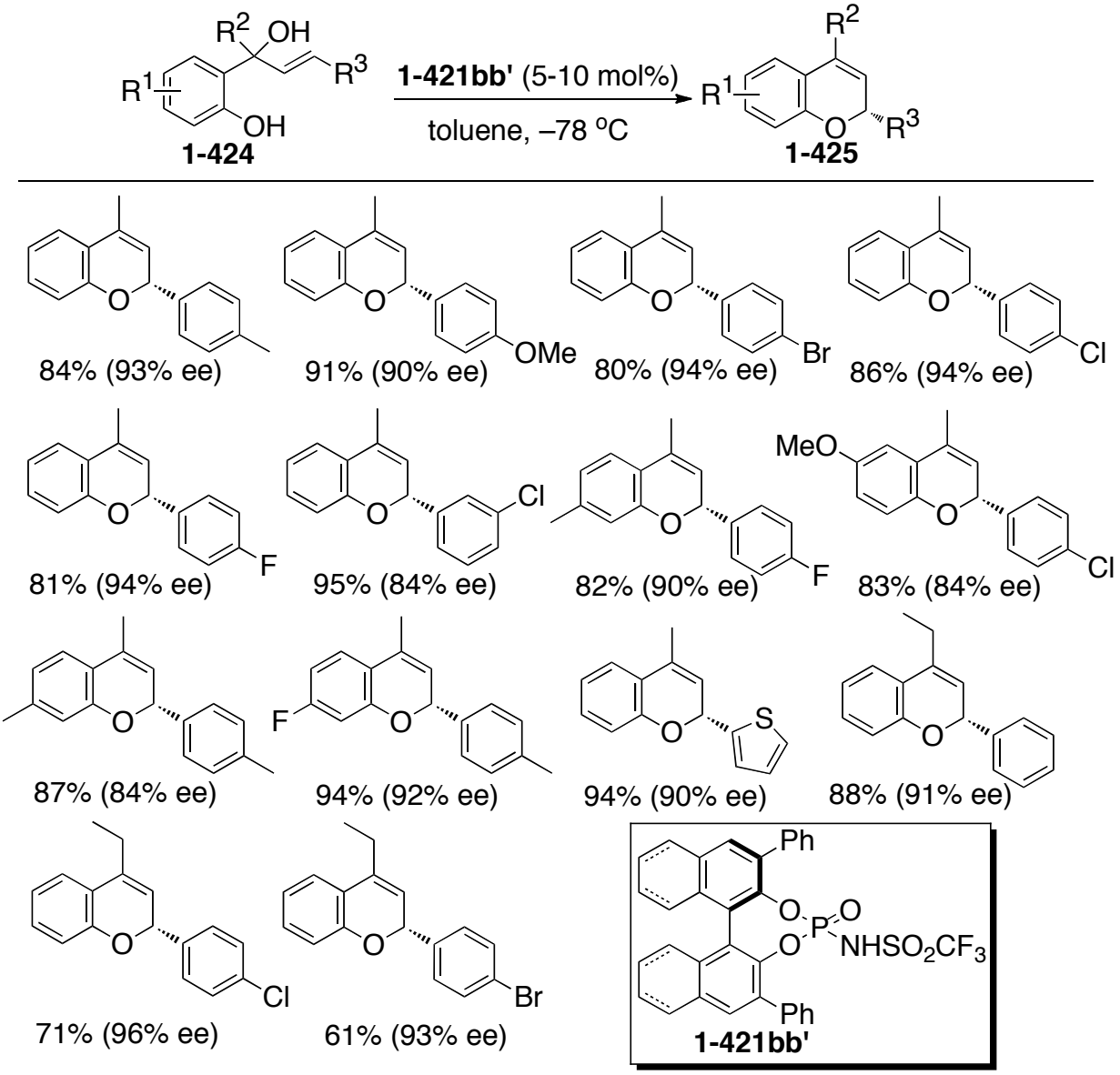
Scheme 1.121: Variation of Aryl Substituents on the Bronsted Acid Catalyst



Ar = Ph, *p*-FC_6H_4, *p*-$OMeC_6H_4$, 2,4,6-$Me_3C_6H_2$, H, Me, phenanthryl, 1-naphthyl, *p*-ClC_6H_4

To test the generality of the developed protocol, a variety of reaction altering different substituents of the substrates (**Scheme 1.122**) was performed. Both electron-donating and electron-withdrawing groups in the *para*-position of the aryl ring conjugated to the alkene moiety afforded the chromenes in good overall yields. In contrast, when the reaction was carried out with *meta*-chloro derivative, the reaction did not proceed at all. However, increasing the temperature from –78 °C to –48 °C, it gave a decent yield with good ee. The reaction was also compatible with alkyl substituents delivering excellent ee and high yield of the product.

Scheme 1.122: Substrate Scope

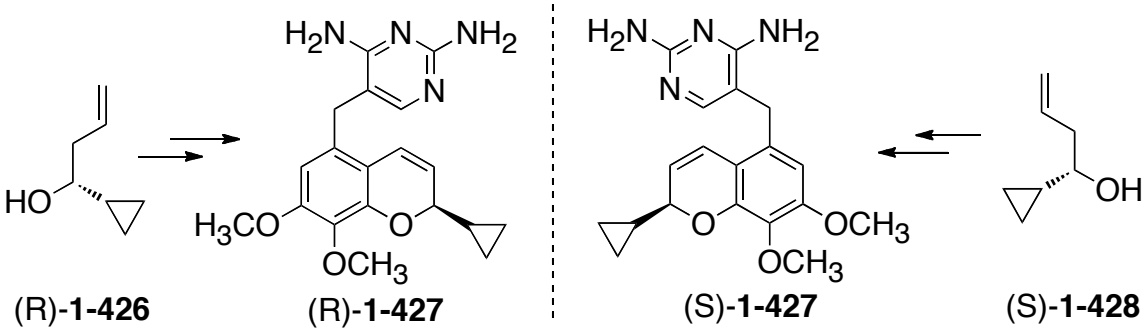


1.2.2.2. Metal-Mediated Synthesis

An enantioselective synthesis of iclaprim enantiomers **1-427** (**Scheme 1.123**), 2-substituted 2H-chromene compounds, was reported by Schneider and Tahtaoui.[83] Both

the enantiomers are dihydrofolate reductase (DHFR) inhibitors and are known to be active against a broad range of bacteria.

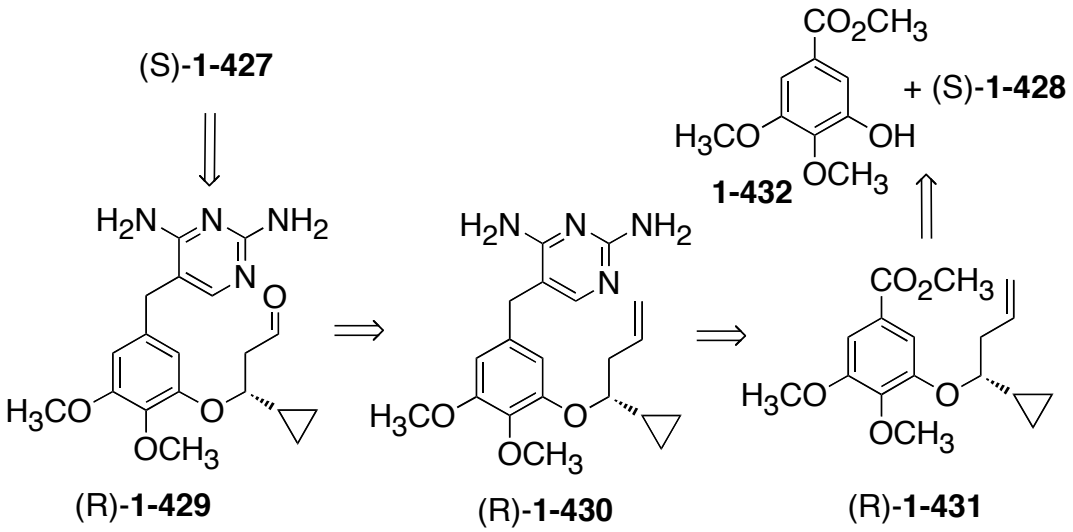
Scheme 1.123: Iclaprim Enantiomers



(R)-**1-426** (R)-**1-427** (S)-**1-427** (S)-**1-428**

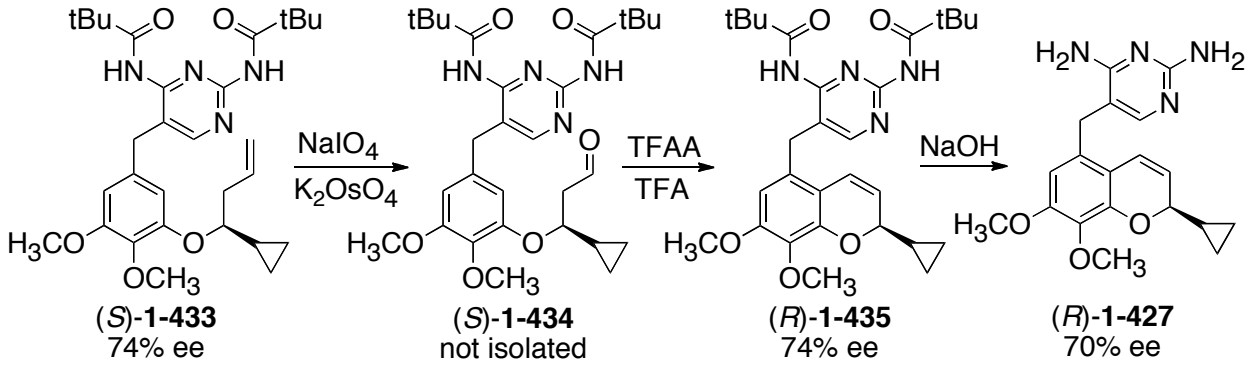
To strategize the synthesis, a retrosynthetic plan was outlined. The starting compound was designed as the chiral homoallyllic alcohol (*S*)-**1-428**, which would lead to the chiral ether (*R*)-**1-431**, precursor to chromene, by Mitsunobu reaction (**Schemes 1.123** and **1.124**). Notably, the diaminopyrimidine moiety was arranged to be installed before the cyclization to avoid any racemization.

Schemes 1.124: Retro Synthetic Pathway for the Synthesis of Iclaprim



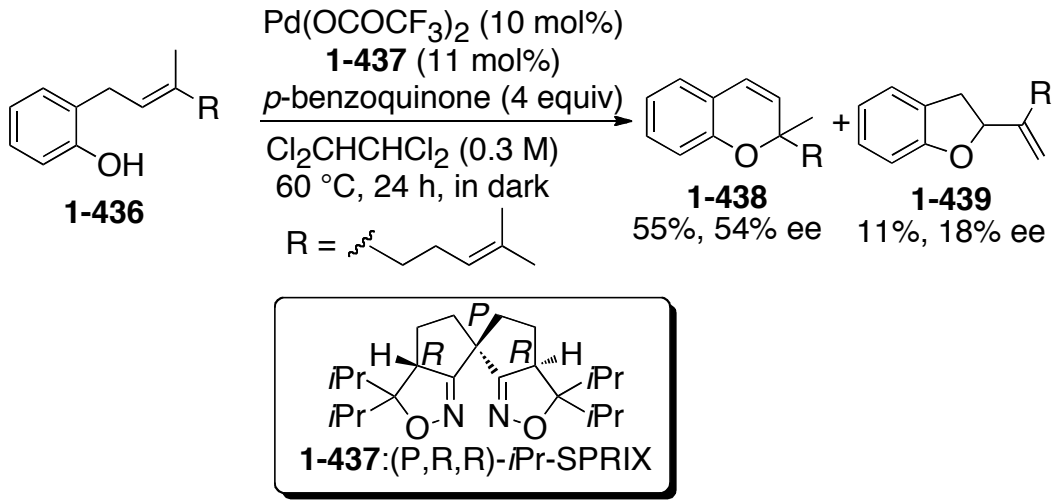
The synthesis was carried out according to the proposed plan though some steps required extensive optimization to achieve higher enantioselectivity for the chiral starting materials. Finally, for the synthesis of (*R*)-**1-427**, the precursor (*S*)- **1-433** to chromene could be obtained in 74% ee. The terminal olefin in (*S*)-**1-433** was oxidized to the corresponding aldehyde and without isolation of the product it was directly cyclized to chromene giving 65% yield over last two steps maintaining the same ee. Final step of the synthesis involved deprotection of amines, which slightly compromised the ee leading to the desired product (*R*)-**1-427** in 70% ee (**Scheme 1.125**). The overall yield of the product starting from phenol **1-432** was 27%. The other enantiomer of iclaprim (*S*)-**1-427** was achieved in similar fashion in 50% ee.

Scheme 1.125: Cyclization to Chromenes in the Synthesis of Iclaprim



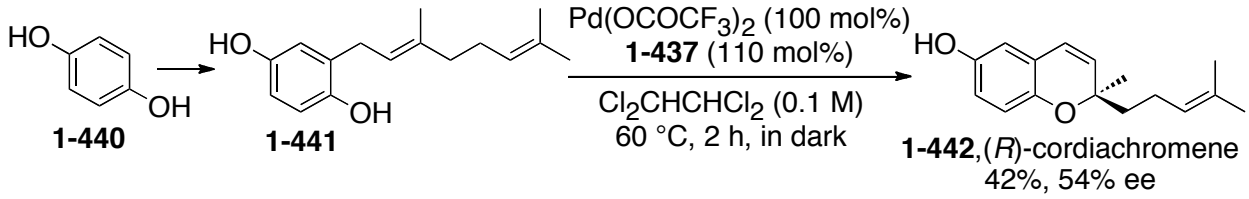
An enantioselective synthesis of (–)-cordiachromene was reported by using 6-*endo-trig* Wacker-type oxidative cyclization of 2-geranylphenols without use of any protecting-groups.[84] The reaction was optimized using 2-geranyl phenol **1-436** as the starting compound and the desired chromene **1-438** was obtained in 55% yield and 54% ee in presence of 11 mol% *i*Pr-SPRIX **1-437**, 10 mol% $Pd(OCOCF_3)_2$ and 4 equiv of *p*-benzoquinone in dichloromethane as solvent at 60 °C. Although, 5-*exo-trig* cyclization product **1-439** was also formed alongside in 11% yield and 18% ee, this was the best condition found (**Scheme 1.126**).

Scheme 1.126: Synthesis of (–)-Cordiachromene



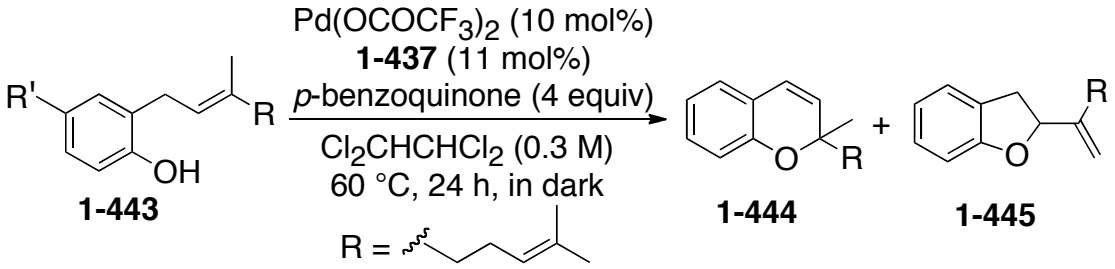
However, this optimized condition failed in the actual synthesis because of an irresistible oxidation of **1-440** into 2-geranylbenzoquinone. Stoichiometric use of the Pd catalyst turned out to be the solution to this problem giving 42% yield and 54% ee of (*R*)-cordiachromene **1-442** (**Scheme 1.127**).

Scheme 1.127: Modified Synthesis of (–)-Cordiachromene



As an application of the Pd-catalyzed oxidative 6-*endo-trig* cyclization for the facile synthesis (–)-cordiachromene, a variety of substituents on the aromatic ring were examined and the results are appended in the following **Scheme 1.128**.

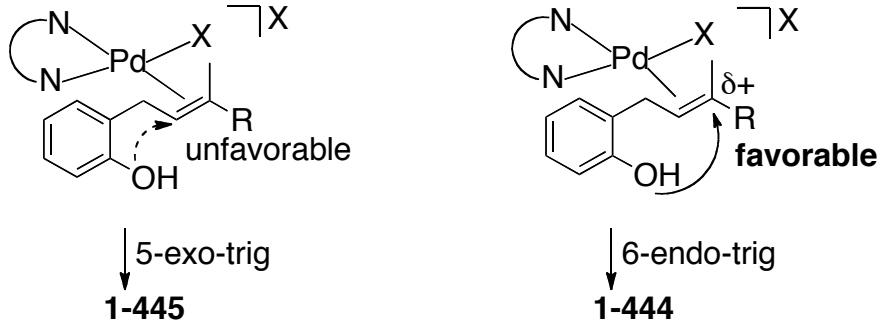
Scheme 1.128: Effect of Variation of Phenol Ethers



R'	Yield of **1-444** (%)	Ratio **1-444/1-445**	ee of **1-444** (%)
BnO	24	1/1.6	34
MeO	19	1/1.5	48
TBSO	15	1/1.4	49
MOMO	33	1/2.1	37
PivO	35	1/2.2	52
BzO	37	1/4.1	44
BocO	52	1/3.0	47
TsO	30	1/4.1	42
Br	46	1/4.7	55

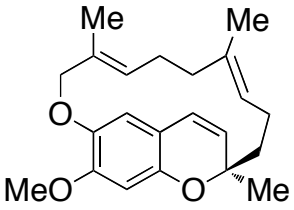
The mechanism suggested that the reaction began with the activation of the double bond by coordinating to Pd(II). This was then followed by the nucleophilic attack and subsequent β-hydride elimination. Since the positive charge formed after activation of double bond would be more stabilized at a tertiary center compared to a secondary center, 6-*endo-trig* cyclization was favored in this case compared to 5-*exo-trig* (**Figure 1.4**).

Figure 1.4: 5-*Exo-trig* vs 6-*endo-trig* Cyclization

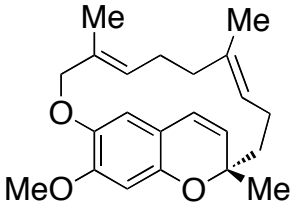


Likonide B and smenochromene D (**Figure 1.5**) are chiral chromene based natural products isolated separately from two different sponge species and they share an enantiomeric relationship. Moody et al[85] attempted to synthesize this natural product in its racemic form using Claisen rearrangement and intramolecular Mitsunobu reaction as the key steps.

Figure 1.5: Likonide B and Smenochromene D



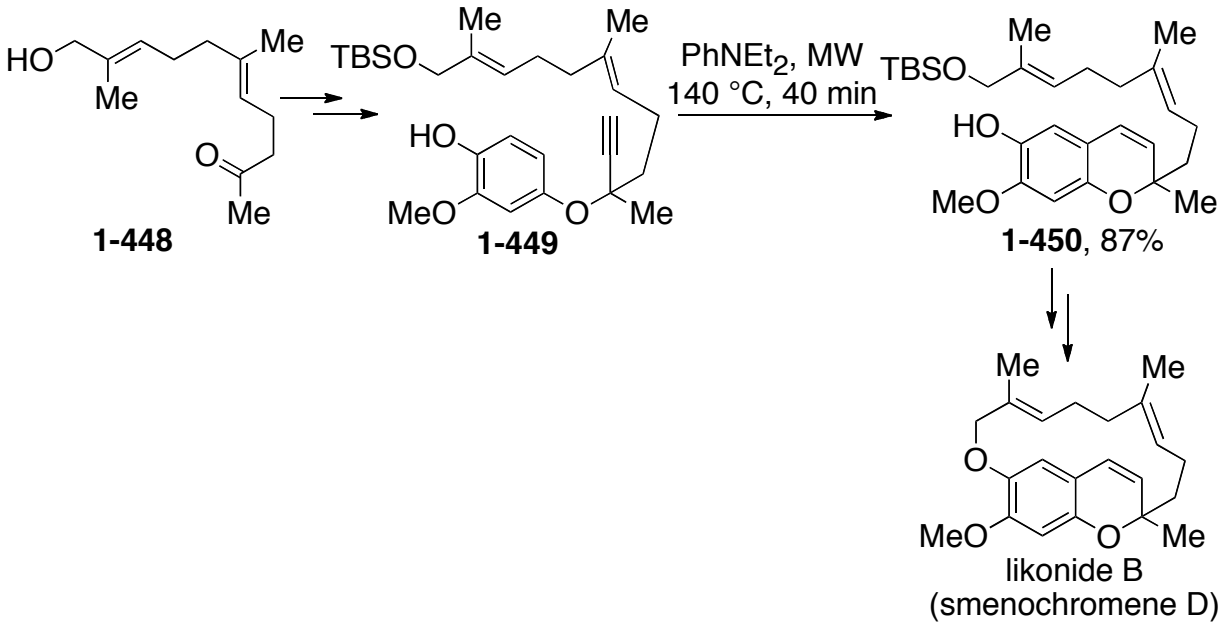
Likonide B



Smenochromene D

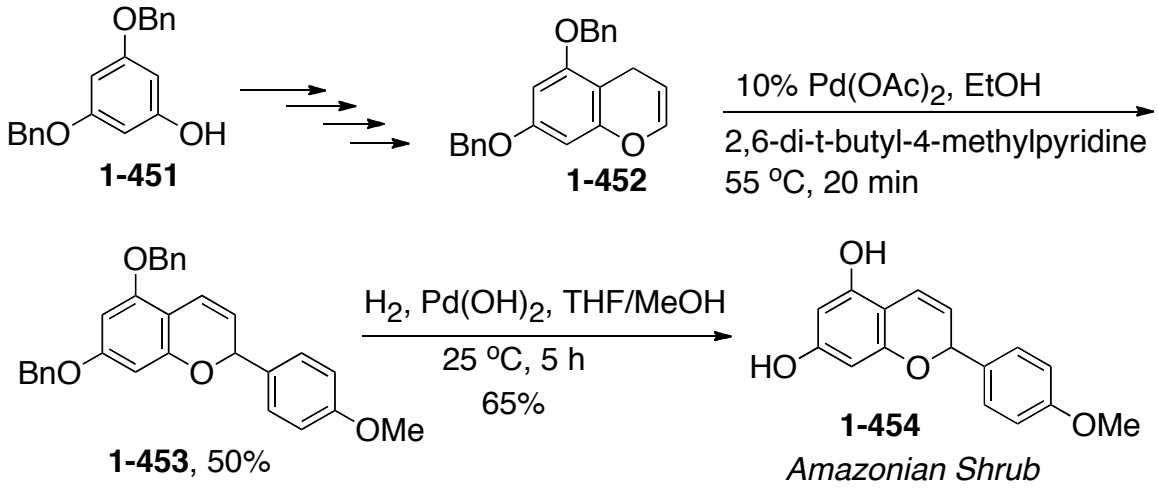
The synthesis started with a known allylic alcohol **1-448** and in a few steps the chromene precursor **1-449** was achieved in high yield. Compound **1-449** was then subjected to Claisen rearrangement for the cyclization to chromene **1-450**. It was noticed that when the hydroxyl group on the benzene ring was protected with TBS or mesylate groups, the regioselectivity of the resulting chromene was poor. Remarkably, with the unprotected phenolic hydroxyl moiety as in compound **1-449**, exclusively the desired chromene product **1-450** was obtained in 87% yield. In two more steps from **1-450**, using macrocyclization via Mitsunobu reaction the final target compound could be achieved.

Scheme 1.129: Synthesis of Likonide B



Correia and co-workers have developed[86] a nice tool for the synthesis of 2H-chromene by the sequential employment of o-allylation of phenols, Claisen rearrangement, o-vinylation, ring-closing metathesis (RCM) and finally by the Heck arylation (**Scheme 1.130**). They have reported that the Heck arylation of enol ether using arenediazonium tetrafluoroborate proved to be a viable alternative for the construction of chromen with high regioselectivity. They also have shown that the synthesis of 2H-chromene via this method opened up the way for the total synthesis of natural flavone possessing leishmanicidal activity.

Scheme 1.130: Synthesis of Natural Flavone



1.3. Conclusion

This review article emphasizes the growing interest in the development of various metal-mediated, metal-free synthetic transformations of the 2H-chromenes. Mainly, we have discussed different typical development in this area. Most importantly, we believe that further transformation of the 2H-chromenes to biologically active compounds is still in its beginning. Although further development of novel, more general, and efficient methodologies is certainly highly warranted, the progress achieved so far in this area bodes well for broad application in organic synthesis.

CHAPTER TWO

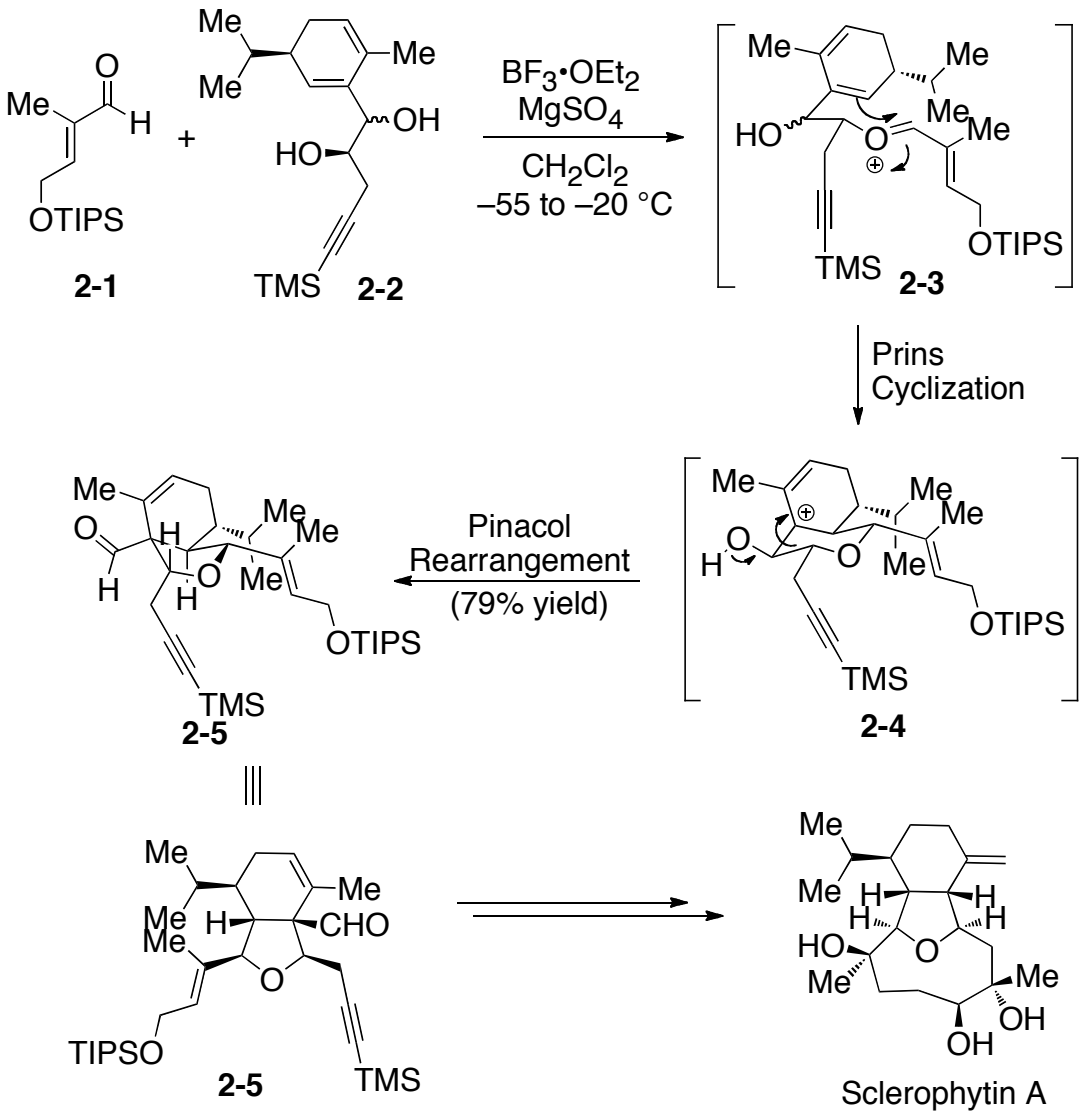
Simultaneous Synthesis of both Rings of Chromenes via a Benzannulation/*o*-Quinone Methide Formation/Electrocyclization Cascade (BQME Reaction)

2.1. Background

The development of environmentally friendly procedures for the synthesis of organic compounds is an area of growing importance.[87] In this regard cascade reactions[88] play a very important role in organic chemistry as in these reactions several bonds are formed in sequence to build a large degree of complexity in one transformation without isolating intermediates, changing reaction conditions, or adding reagents. This minimizes the waste compared to stepwise reactions, avoids isolation of intermediates, and reduces labor and time to effect the transformation.[89]

Cascade reactions have wide applications in organic synthesis. The concept has been used intellectually and artistically by organic chemists in the synthesis of many natural products. One such practical example would be the Prins-pinacol reaction used by Overman and coworkers[90] in the total synthesis of sclerophytin A (**Scheme 2.1**).

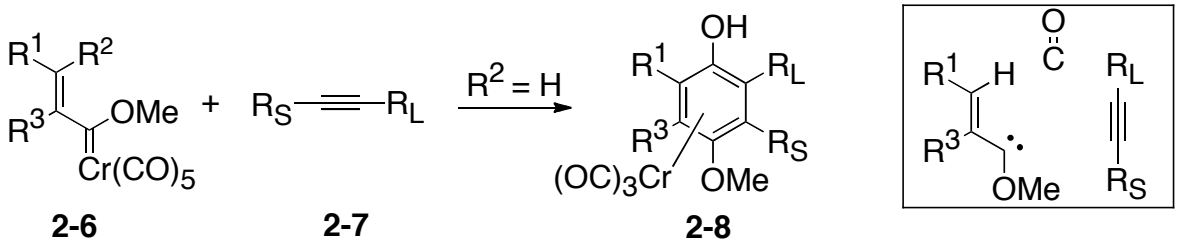
Scheme 2.1: Application of Cascade Reaction in Total Synthesis



Wulff-Dötz benzannulation reaction, first reported[91] by Dötz in 1975, is a formal [3+2+1] cycloaddition reaction between an α,β-unsaturated pentacarbonyl chromium carbene complex and an alkyne to produce a highly substituted phenol (**Scheme 2.2**). Since its discovery, this reaction has proved to be a very attractive tool in organic synthesis[92]

due to its compatibility with different functional groups, and high regio- and chemoselectivity.

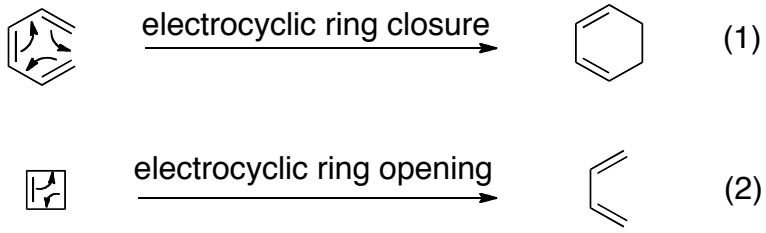
Scheme 2.2: Wulff-Dötz Benzannulation Reaction



2-6 **2-7** **2-8**

Electrocyclization reactions are a type of pericyclic reactions in which a ring can be formed by formation of a new σ bond across the ends of a conjugated polyene (electrocyclic ring closure, eqn. 1)[93] or the reverse process is also possible in which a ring can be opened to give a polyene (electrocyclic ring opening, eqn. 2).[94] This is one of the classic reactions in organic chemistry and has wide utility.

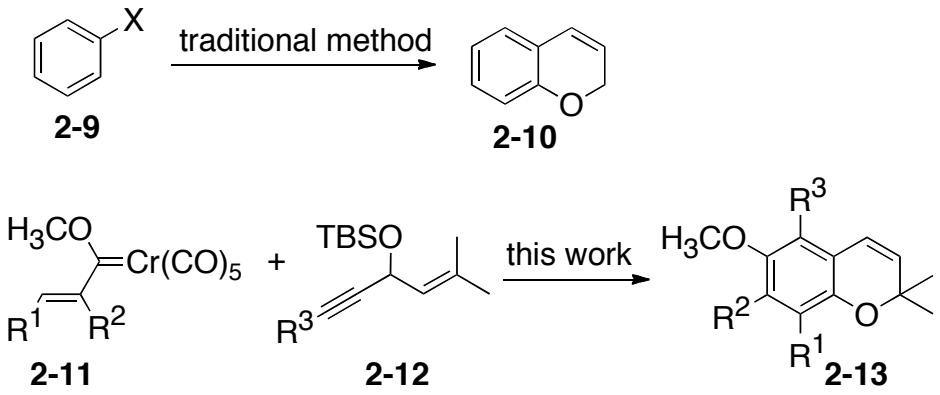
Scheme 2.3: Electrocyclic Reaction



Now it would be very interesting if an electrocyclization reaction (electrocyclic ring closure) could be combined with benzannulation reaction in a cascade process because

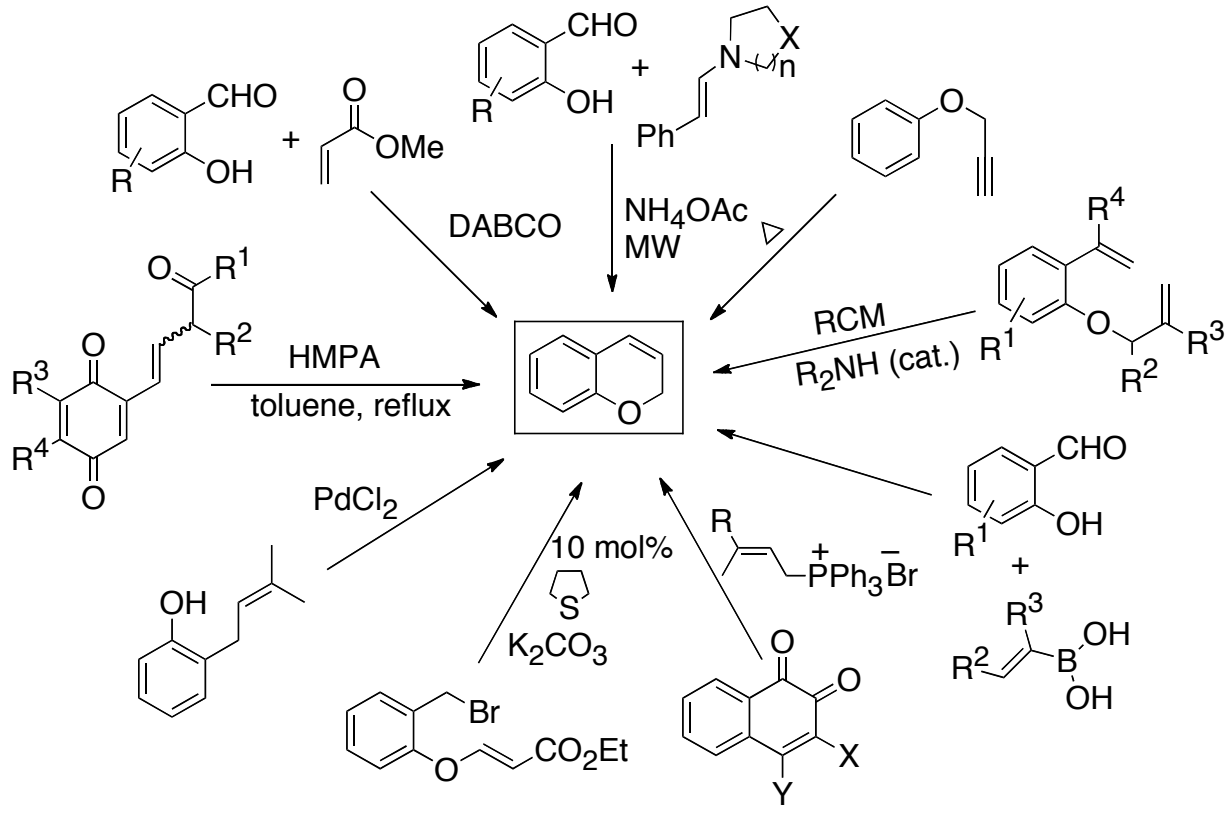
of its potential for the construction of two or more rings in one step. This idea is illustrated in **Scheme 2.4** for a proposed cascade reaction sequence leading to the formation of chromenes from a carbene complex and an alkyne.

Scheme 2.4: Traditional Method vs This Work for The Synthesis of Chromenes



The traditional approaches for the synthesis of 2*H*-chromene[95] which has been discovered till now involve starting with an intact phenol and cyclization of the pyran ring with a variety of methods which include intramolecular cyclization of Wittig intermediates,[96] microwave-assisted reaction of salicylaldehyde with enamines,[97] catalytic Petasis reaction of salicylaldehyde,[98] ring closing olefin metathesis,[99] Baylis-Hillman reaction of 2-hydroxybenzaldehydes with methyl vinyl ketone,[100] Claisen rearrangement,[101] Pd-catalyzed ring closure of 2-isoprenyl phenols,[102] electrocyclic ring closure of vinylquinone derivatives[103] and an ylide annulation reaction[104] (**Scheme 2.5**).

Scheme 2.5: Different Synthetic Approaches Towards Chromene



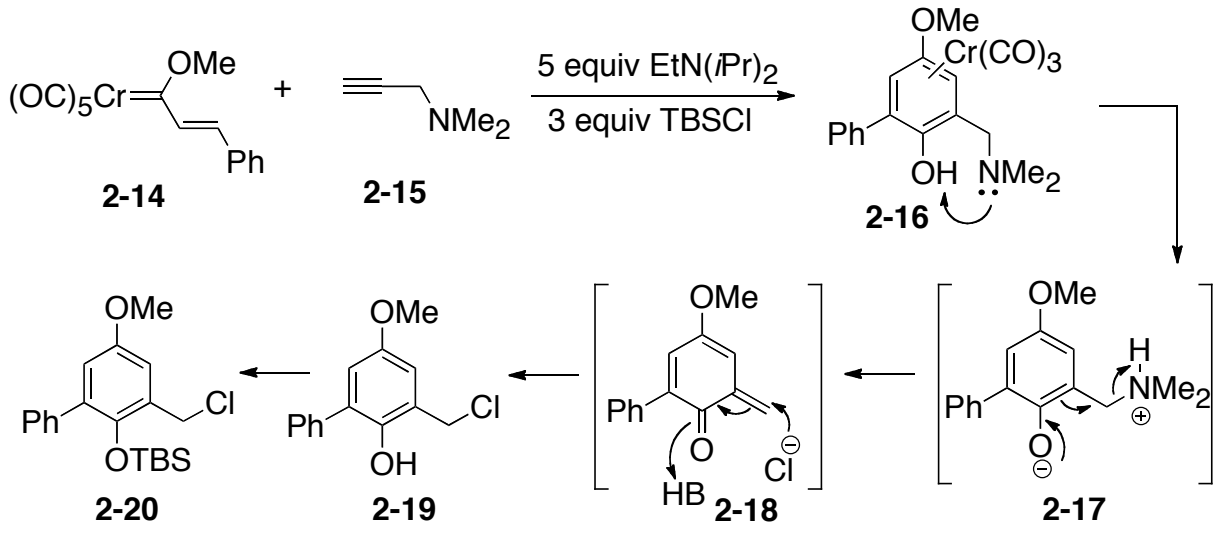
As mentioned above all the synthetic outlines shown in **Scheme 2.5** start with a preformed benzene ring and the pyran ring is constructed during the course of the synthesis. Up to now there is no report of any synthetic method in literature in which both the rings of chromene are formed in one step.

Accordingly, motivated by the high biological importance of chromene rings[105] and the lack of suitable methods to synthesize both rings of a chromene in one step, we undertook an investigation aiming at the development of an efficient method using

differently substituted alkynes in the benzannulation reaction of chromium carbene complexes.

The idea for this novel methodology came from an unexpected result observed by Dr. Korthals during the study of the benzannulation reaction of the propargyl amines. This observation was the formation of the chlorinated phenol **2-20** (**Scheme 2.6**).[106] The formation of **2-20** is proposed to proceed by the benzannulation reaction to give compound **2-16,** which in the presence of a base forms the *ortho*-quinone methide **2-18** through intermediate **2-17**. Chloride then nucleophilically attacks the vinyl carbon with subsequent rearomatization *via* phenoxide formation. The resulting phenol **2-19** is then protected by *tert*-butyl dimethylsilyl chloride to form the silyl ether **2-20**.

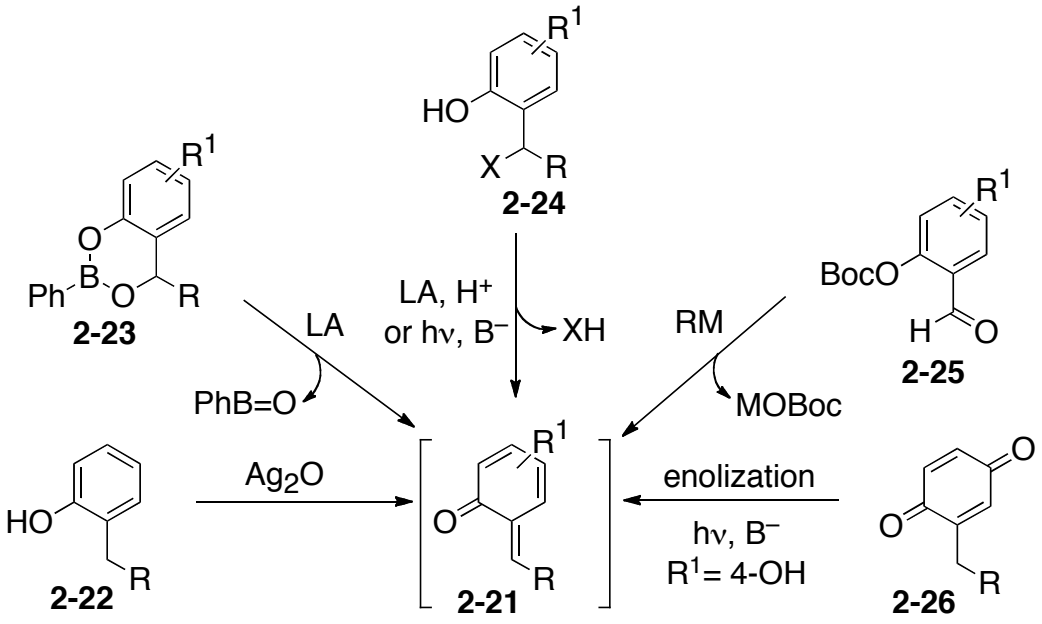
Scheme 2.6: Benzannulation between Styryl Carbene Complex and Propargyl Amine



Ortho-Quinone methides are very important intermediates, which are generally generated *in situ* and consumed in subsequent reactions. They have been employed in

many useful chemical syntheses.[107] They readily participate in inverse electron demand Diels-Alder reaction and so electron-rich dienophiles are required in this reaction.[108] The general methods for the formation of *o*-quinone methides are shown in **Scheme 2.7**. These can be prepared from benzodioxoborins **2-23** using Lewis acid,[109] from compound **2-24** either in the presence of Lewis acid or by photolysis[110] where X is leaving group. From *o*-bocsalicylaldehydes **2-25**, *o*-quinone methides can be generated using an organometallic reagent such as Grignard reagent.[111] *Ortho*-quinone methides can also be generated by the enolization of benzoquinone[112] **2-26** or by the oxidation of *o*-alkyl phenols **2-22** by using silver oxide.[113]

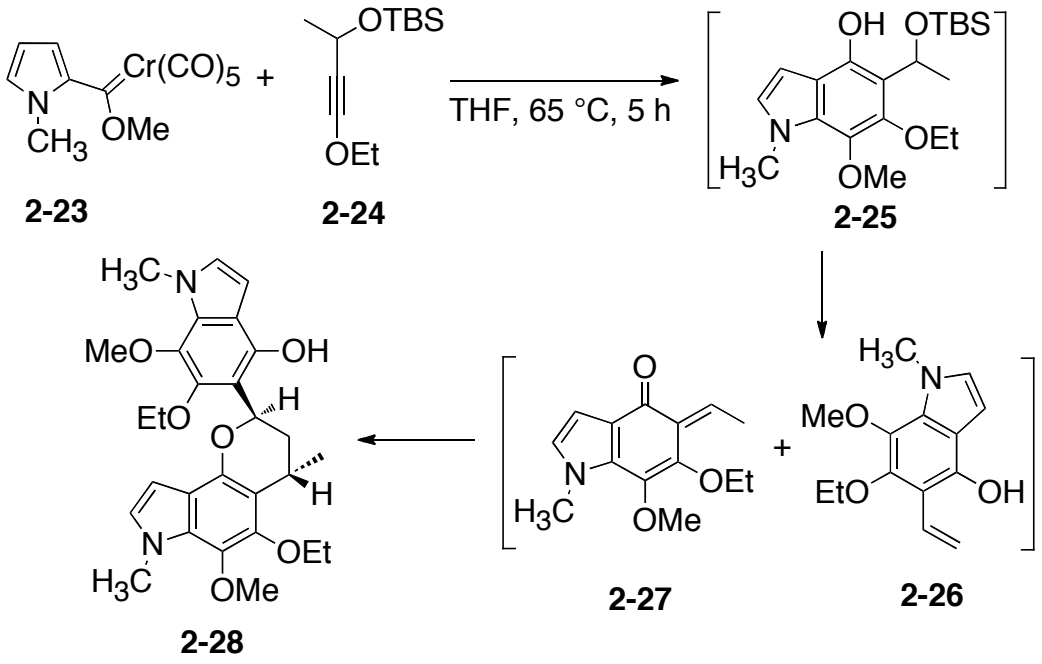
Scheme 2.7: General Methods for Generation of *o*-Quinone Methides



The generation of *o*-quinone methide as an intermediate from the reaction of a carbene complex and an alkyne has only been reported[114] once by Yamashita in 1985

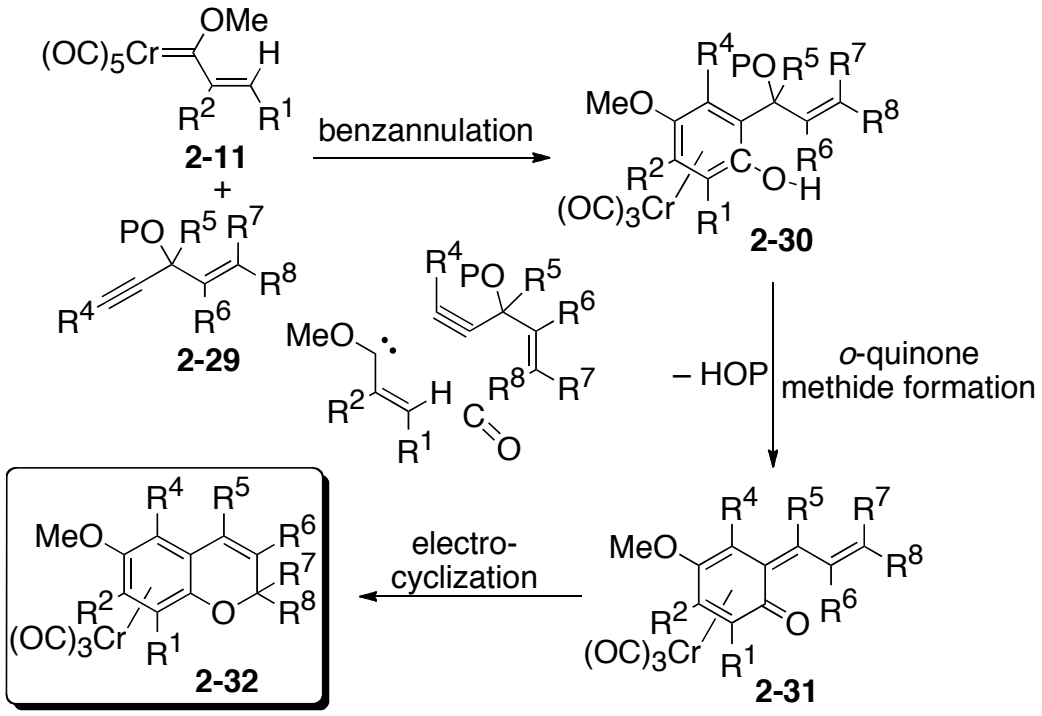
(**Scheme 2.8**). The benzannulation between carbene complex **2-23** and alkyne **2-24** forms the phenol **2-25**, which after elimination forms intermediates **2-26** and **2-27**. These intermediates then undergo a Diels-Alder reaction to form the observed product **2-28**.

Scheme 2.8: First Report of The Formation of An *o*-Quinone Methide Intermediate in a Benzannulation Reaction



The discovery of the formation of *o*-quinone methide intermediates in the benzannulation reaction gave birth to the idea of a Wulff-Dötz reaction in tandem with electrocyclization (**Scheme 2.9**).

Scheme 2.9: Synthesis of Chromenes by Benzannulation Followed by Electrocyclization

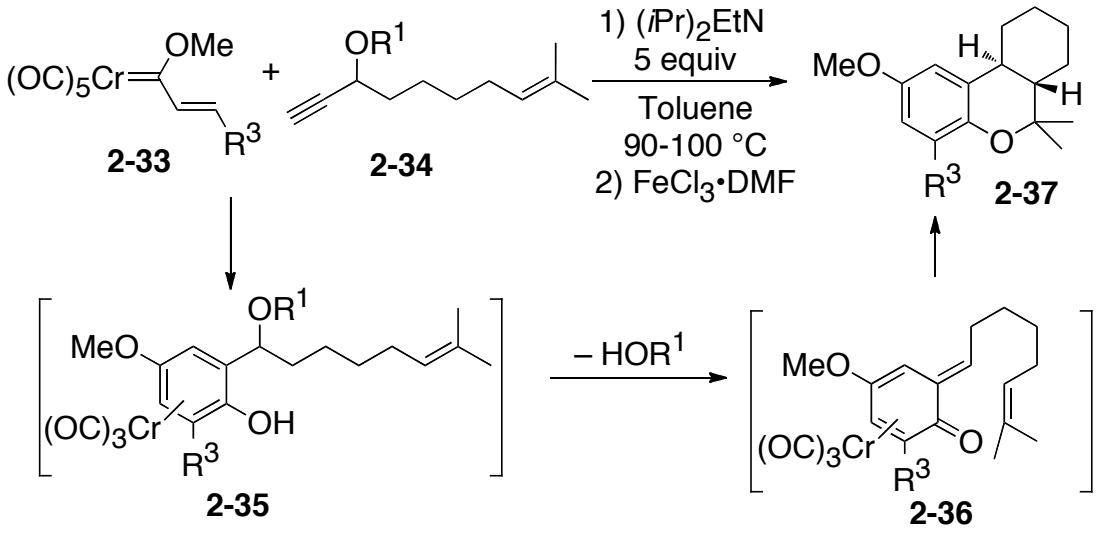


2.2. Present Work

Previous studies from our group[115] had shown that the reaction of alkenyl carbene complexes of the type **2-33** with propargyl ethers of the type **2-34** with a tethered alkene unit to generate hexahydrodibenzopyrans of the type **2-37** (**Scheme 2.10**). Significant yields of **2-37** were only observed if the reaction was performed in the presence of Hünig's base that presumably aided in the elimination of the propargyl oxygen unit from the benzannulated product **2-35** to generate the *o*-quinone methide complex **2-36**. The intramolecular Diels–Alder reaction that concludes the cascade must have occurred via the intermediate **2-36** with an *E*-alkene such that the *trans*-stereochemistry of **2-37** is established. This in turn requires that during *o*-quinone methide formation the alkyl

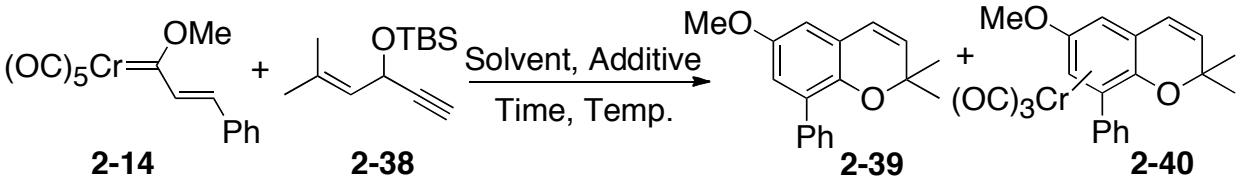
group move away from the phenol unit in **2-35** to establish the *E*-stereochemistry in the *o*-quinone methide. This was a source of concern in the original planning of the chromene synthesis in **Scheme 2.9**, since the ultimate electrocyclic ring closure would require the *Z*-configuration of the alkene in the *o*-quinone methide unit.

Scheme 2.10: Benzannulation Followed by Diels-Alder Reaction



The benzannulation/*o*-quinone methide formation/electrocyclization cascade reaction (BQME reaction) was first attempted by Dr. Korthals, which involved styryl carbene complex **2-47** with alkyne **2-48** (**Table 2.1**). [106]

Table 2.1: Initial Optimization[a]



2-14 **2-38** **2-39** **2-40**

Entry	Solvent	Additive	Temp (°C)	Time (h)	Yield of **2-39** (%)	Yield of **2-40** (%)
1	Toluene	5 equiv $NEt(iPr)_2$	100	24	Complex mixture	16
2	Toluene	5 equiv $NEt(iPr)_2$	80	24	Complex mixture	16
3	CH_2Cl_2	2 equiv $NEt(iPr)_2$	60	12	Complex mixture	10
4	CH_2Cl_2	None	60	24	46	29

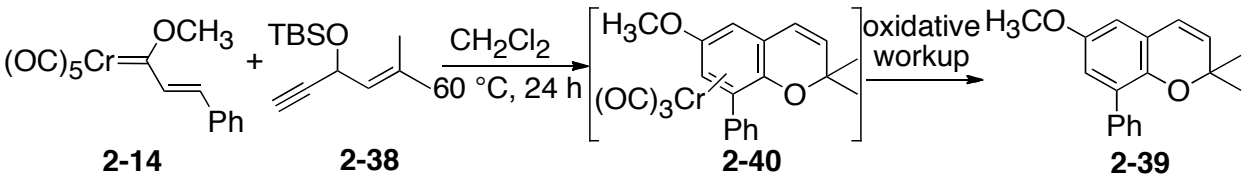
a. All reactions were carried out at 0.03 M concentration using 1.2 equiv. of enyne **2-38**.

Table 2.1 shows that entries 1 to 3 did not give respectable yields of products. But in the absence of base (entry 4) a 46% yield of chromene **2-39** and a 29% yield of chromene-chromiumtricarbonyl complex **2-40** were obtained.

Since entry 4 in **Table 2.1** previously gave the best result the reaction was repeated but it was found difficult to separate the product **2-39** and **2-40**. A non-oxidative work-up afforded an inseparable mixture of both the chromium-complexed and the chromium-free chromenes **2-39** and **2-40**. The products could not be separated by column chromatography due to the slow and continuous decomposition of compound **2-40** to **2-39**. This indicated that an oxidative work-up was necessary before isolation of

compound **2-39** which should remove the complexed chromium from **2-40** and convert it to **2-39**. When ceric ammonium nitrate (CAN) was employed as oxidizing agent neither the chromene complex **2-40** nor the chromene **2-39** could be detected in the crude reaction mixture. (entry 2). Apparently CAN is too strong an oxidant and overoxidation of **2-39** occurred. However, the corresponding chromene **2-39** could be obtained in pure form free of the metal if an oxidative workup with $FeCl_3$•DMF complex was employed. It afforded the chromene **2-39** in 76% yield (entry 3) (**Table 2.2**).

Table 2.2: Optimization for The Oxidative Work-up[a]



2-14 **2-38** **2-40** **2-39**

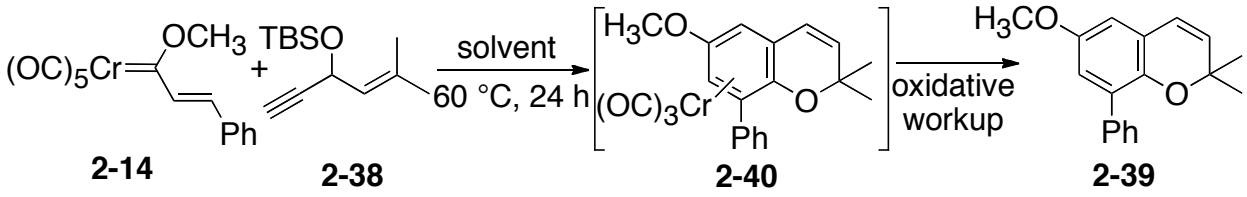
Entry	Oxidative workup	Yield of **2-39** (%)
1	None	Not determined[b]
2	CAN (7.5 equiv.)	Not determined[c]
3	$FeCl_3$•DMF (7.5 equiv.)	76

a. All reactions were carried out at 0.03 M concentration using 1.2 equiv. of enyne **2-38**. b. TLC indicated the absence of **39** and **40** and the presence of compounds more polar than either. c. A mixture of **39** and **40** from which **40** could not be separated to purity due to its slow and continuous decomposition to **39**.

The optimal conditions for the BQME cascade were investigated through a series of experiments, where sequential changes were made to the solvents used. It was found that the solvent had a profound effect in the reaction yield. As generally observed for the

benzannulation reaction alone[116], benzene, THF and hexane were equally as efficient as dichloromethane in the BQME reaction. However, when the reaction was performed in acetonitrile, the highest yield (95%) of the chromene **2-39** was realized. The reaction in toluene in presence of Hunig's base, was not beneficial, affording only a 35% yield of the product (entry 8).

Table 2.3: Optimization of Solvent[a]



2-14 **2-38** **2-40** **2-39**

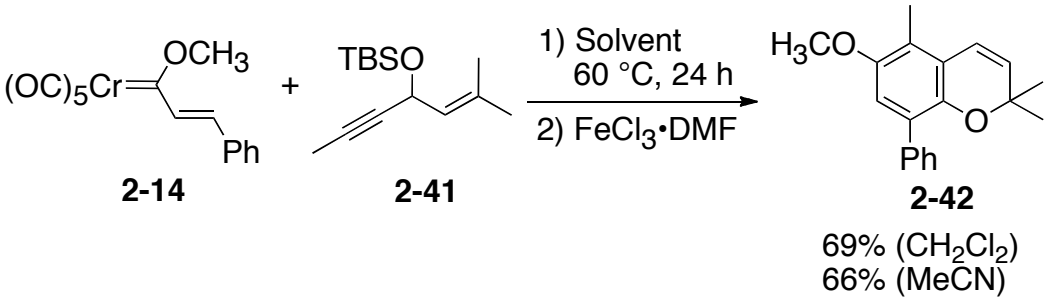
Entry	Solvent	Oxidative workup	Yield of **2-39** (%)
1	MeCN	None	95
2	Benzene	$FeCl_3$•DMF	74
3	THF	$FeCl_3$•DMF	65
4	Hexane	$FeCl_3$•DMF	70
5	Toluene	$FeCl_3$•DMF	62[a]
6	Toluene	$FeCl_3$•DMF	35[a,b]

a. All reactions were carried out at 0.03 M concentration using 1.2 equiv. of enyne **2-38**.
b. Reaction performed at 80 °C for 24 h. c. Reaction performed with 5 equiv $NEt(iPr)_2$.

With the results of the solvent screen in hand, the generality of the reaction was then explored. Attention was turned to changing the enyne from terminal to internal. With the

internal enyne **2-41** the reaction showed almost equally good results in both dichloromethane (69%) and acetonitrile (66%) solvents.

Scheme 2.11: Reaction with Internal Enyne

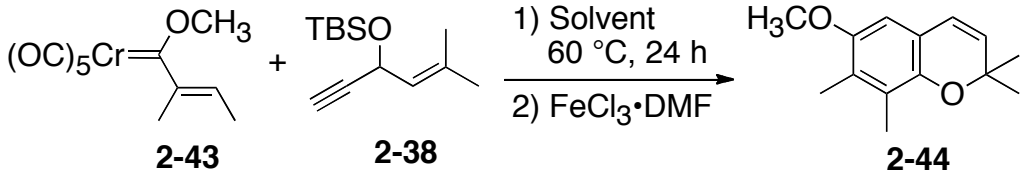


2-14 **2-41** **2-42**

69% (CH_2Cl_2)
66% (MeCN)

General utility in this chromene synthesis will certainly depend on the range of carbene complexes that can be employed. Carbene complex **2-43** was chosen as the next substrate since it is the complex that would be needed for the synthesis of Vitamin E, which is discussed in Chapter 3. The BQME cascade of carbene complex **2-43** was first performed using the terminal enyne **2-38** in dichloromethane. The yield of the expected chromene product **2-44** was 88%. This reaction was also examined in acetonitrile, benzene and THF, which afforded 65%, 73% and 74% yields of the product, respectively.

Table 2.4: Reaction between Carbene Complex **2-43** and Enyne **2-38**[a]



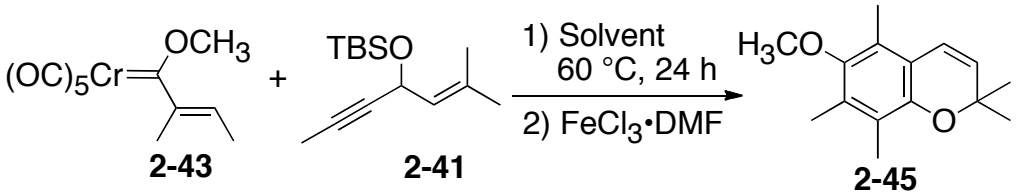
2-43 **2-38** **2-44**

Entry	Solvent	Yield of **2-44** (%)
1	CH_2Cl_2	88
2	MeCN	65
3	Benzene	73
4	THF	74

a. All reactions were carried out at 0.03 M concentration using 1.2 equiv. of enyne **2-38**.

The proposed vitamin E synthesis would require a reaction of carbene complex **2-43** with an internal enyne. Thus as a model system, the reaction of carbene complex **2-43** and enyne **2-41** was examined (**Scheme 2.12**). This BQME cascade was performed in both dichloromethane and acetonitrile solvents, which gave the chromene **2-45** in 84% and 87% yields respectively.

Scheme 2.12: Reaction between Carbene Complex **2-43** and Enyne **2-41**

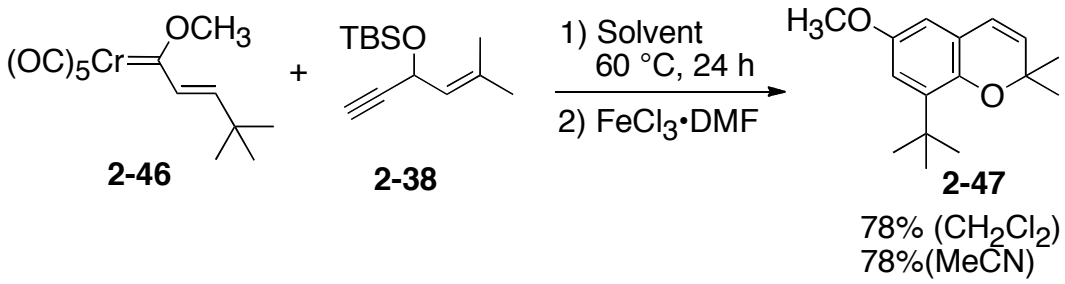


2-43 **2-41** **2-45**

84% (CH_2Cl_2)
87% (MeCN)

The sterically demanding carbene complex **2-46** also worked well in reaction with terminal enyne **2-38** affording a 78% yield of the corresponding chromene product **2-47** both in dichloromethane and acetonitrile solvents.

Scheme 2.13: Reaction between Carbene Complex **2-46** and Enyne **2-38**

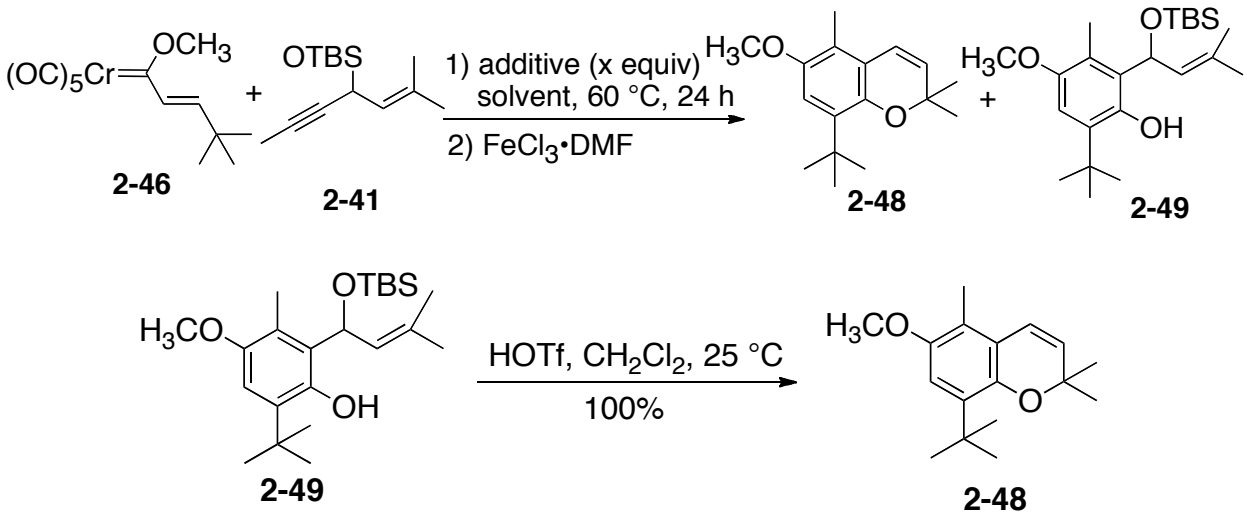


2-46 **2-38** **2-47**

78% (CH_2Cl_2)
78%(MeCN)

The reaction of the *t*-butyl carbene complex **2-46** with the internal enyne **2-41** was not as straightforward. This reaction in dichloromethane solvent gave a 76% yield of the expected chromene **2-48** as a light yellow oil. A side product **2-49** was also formed in this reaction and the ratio of **2-48** to **2-49** was 84:16. The side product was purified and identified as the uncyclized phenol compound **2-49**. When the reaction was conducted in acetonitrile the ratio of **2-48** to **2-49** was 38:62. It was found that, the phenol **2-49** could be quantitatively converted to the chromene product **2-48** by treatment of the crude reaction mixture with triflic acid.

Table 2.5: Reaction between Carbene Complex **2-46** and Enyne **2-41**



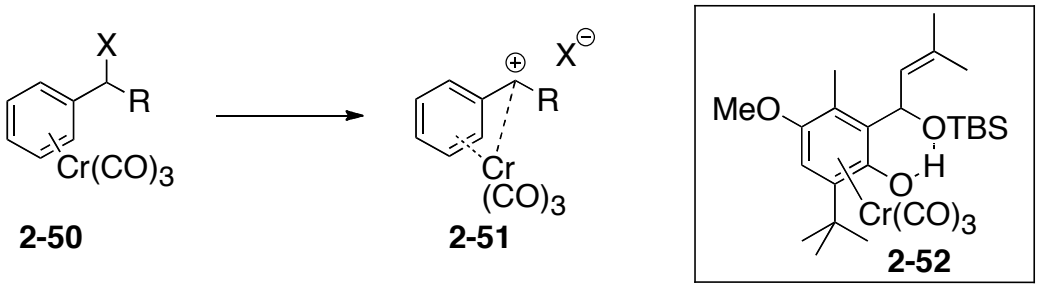
Entry	Solvent	Additive	x (equiv.)	**2-48** : **2-49**	Yield of **2-48**(%)
1	MeCN	None	0	38 : 62	65[a,b]
2	CH_2Cl_2	None	0	84 : 16	74
3	CH_2Cl_2	*iso*-propanol	10	91 : 9	–
4	CH_2Cl_2	*iso*-propanol	50	91 : 9	–
5	CH_2Cl_2	*iso*-propanol	100	≥95 : 5	–
6	CH_2Cl_2	Aniline	10	–	86

a. Oxidative workup not used. b. Isolation after treatment of crude reaction mixture with trifluoromethane sulfonic acid.

The formation of side-product **2-49** can be explained by proposing structure **2-52** in which H-bonding prevents the proper anti-orientation of the benzylic oxygen with respect to the chromium for the assisted elimination to generate the benzylic cation of

the type **2-51** which is stabilized by the chromium tricarbonyl group.[117] This benzylic cation is believed to assist the formation of the *ortho*-quinone methide intermediate. The bulky *tert*-butyl group probably influences the orientation of the leaving group X and resists the rotation to a rotamer that has X anti to the chromium.

Figure 2.1: Carbocation Stabilization by Chromium



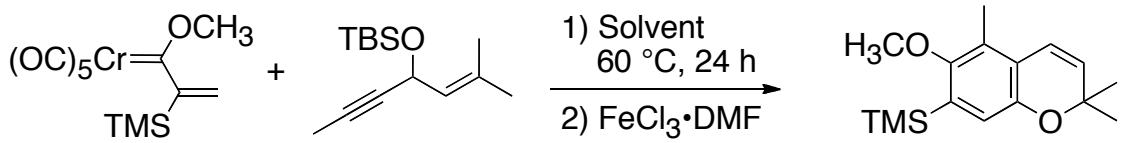
The ratio of compound **2-48** to compound **2-49** in the BQME cascade of **2-46** and **2-41** was probed as a function of added isopropanol. With 10 equivalents of isopropanol, the ratio was 91:9 compared to 84:16 without isopropanol. With 50 equivalents of isopropanol the ratio remained the same. In presence of 100 equivalents of isopropanol the ratio was ≥ 95:5. The reaction was also performed in dichloromethane in the presence of 10 equiv. of aniline as an additive and gave an 86% yield of chromene **2-48** with no trace of side product. These results are interpreted to mean that isopropanol disrupts the H-bonding in structure **2-52** allowing the formation of *ortho*-quinone methide and leading to the chromene product.

Acetonitrile would not be expected to disrupt the H-bonding since the pK_a of protonated acetonitrile was reported to be –10.[118] However, acetonitrile has the ability to displace

the chromium tricarbonyl group from the benzannulated product before it can assist the formation of the carbocation **2-51**.

The BQME cascade was not as efficient for the α-silyl vinyl carbene complex **2-53** which was reacted with the terminal enyne **2-38** to give the chromene product **2-54** in 56% yield in dichloromethane and 23% yield in acetonitrile (**Scheme 2.14**). The same carbene complex **2-53** gave a much better yield of the chromene product in its reaction with the internal enyne **2-41**. The yield of **2-55** was high (84%) in dichloromethane solvent but poor (35%) in acetonitrile (**Scheme 2.15**).

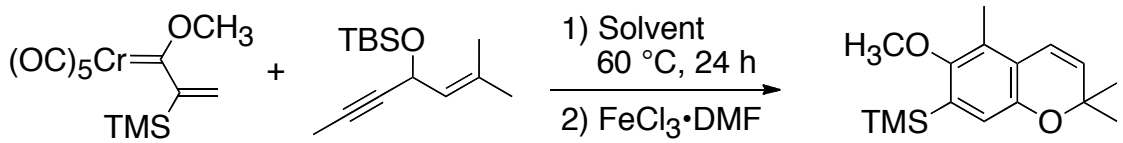
Scheme 2.14: Reaction between Carbene Complex **2-53** and Enyne **2-38**



2-53 **2-41** **2-55**

84% (CH_2Cl_2)
35% (MeCN)

Scheme 2.15: Reaction between Carbene Complex **2-53** and Enyne **2-41**



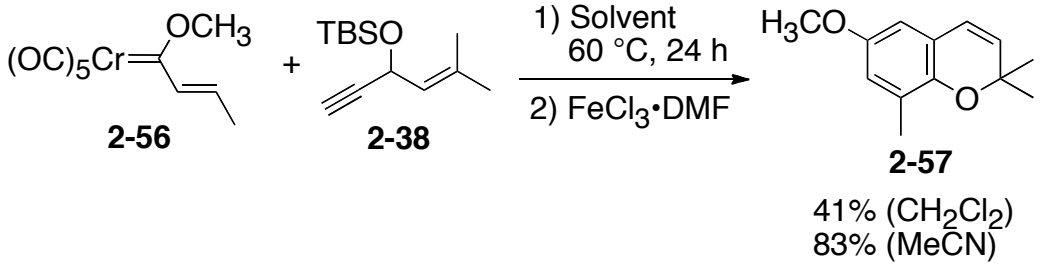
2-53 **2-41** **2-55**

84% (CH_2Cl_2)
35% (MeCN)

The BQME reaction between the *trans*-propenyl carbene complex **2-56** and terminal enyne **2-38** gave high yield (83%) of the chromene product **2-57** in acetonitrile but in

dichloromethane only a 41% yield of the chromene **2-57** was be afforded.

Scheme 2.16: Reaction between Carbene Complex **2-56** and Enyne **2-38**

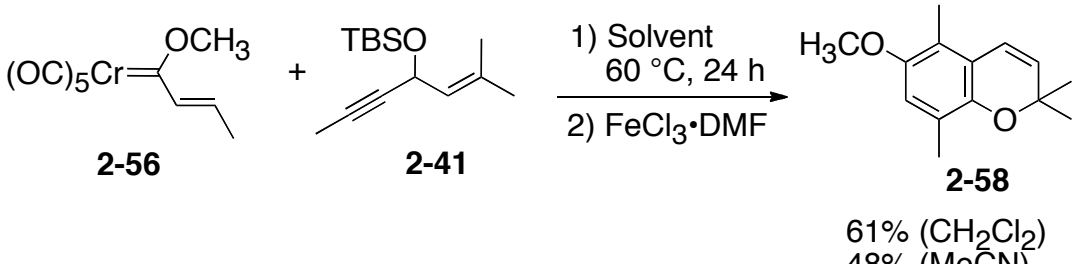


2-56 **2-38** **2-57**

41% (CH_2Cl_2)
83% (MeCN)

The effect of solvent on reactions of the *trans*-propenyl carbene complex **2-56** was reversed in its reaction with the internal alkyne **2-41**. The reaction **2-56** and **2-41** gave **2-58** in 61% yield in dichloromethane and 48% in acetonitrile.

Scheme 2.17: Reaction between Carbene Complex **2-56** and Enyne **2-41**

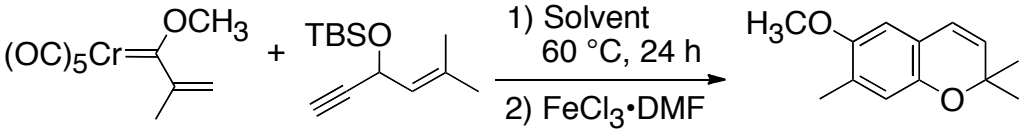


2-56 **2-41** **2-58**

61% (CH_2Cl_2)
48% (MeCN)

The BQME cascade with isopropenyl carbene complex **2-59** showed poor yields of the chromene product **2-60** both in dichloromethane and acetonitrile solvents with the terminal enyne **2-38**. However, the yield could be increased somewhat (55%) by changing the solvent to hexane.

Scheme 2.18: Reaction between Carbene Complex **2-59** and Enyne **2-38**

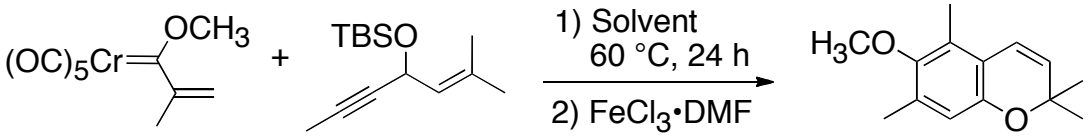


2-59 **2-38** **2-60**

45% (CH_2Cl_2)
26% (MeCN)
55% (Hexane)

The isopropenyl carbene complex **2-59** was more efficient in the chromene synthesis with the internal enyne **2-41** giving a 74% yield of **2-61** in hexane.

Scheme 2.19: Reaction between Carbene Complex **2-59** and Enyne **2-41**

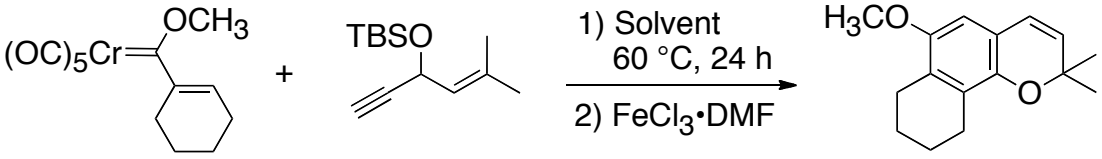


2-59 **2-41** **2-61**

68% (CH_2Cl_2)
34% (MeCN)
74% (Hexane)

The BQME reaction with the cyclohexenyl carbene complex **2-62** gave very good results for both terminal and internal enynes. The reactions with the teminal enyne **2-38** in dichloromethane and acetonitrile gave 72% and 65% yields, respectively, of chromene **2-63**.

Scheme 2.20: Reaction between Carbene Complex **2-62** and Enyne **2-38**

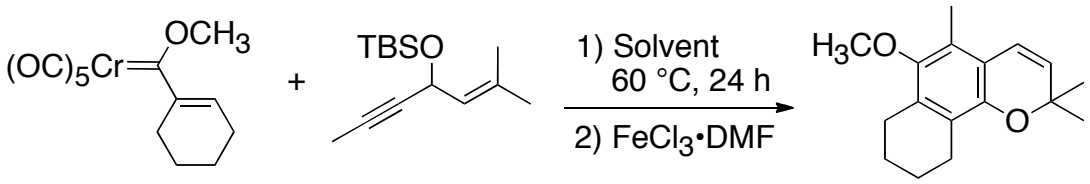


2-62 **2-38** **2-63**

72% (CH_2Cl_2)
65% (MeCN)

The reaction of cyclohexenyl complex **2-62** with internal enyne **2-41** gave an 80% yield of chromene **2-64** in dichloromethane and a 68% yield in acetonitrile.

Scheme 2.21: Reaction between Carbene Complex **2-62** and Enyne **2-41**



2-62 **2-41** **2-64**

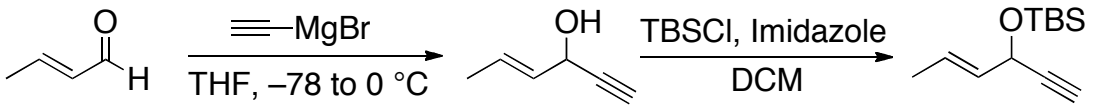
80% (CH_2Cl_2)
68% (MeCN)

To further generalize this methodology it was decided to examine different levels of substitution on the olefin of the enyne. Enyne **2-67** has only one methyl substituent on the alkene end and enyne **2-71** has no substituent at the end of double bond. Using these enynes in this reaction it would be possible to synthesize benzopyrans with either

zero or one substituents on its 2-position.

The synthesis of enyne **2-67** started with the reaction between crotonaldehyde **2-65** and ethynyl magnesium bromide resulting in the alcohol precursor **2-66**. The alcohol **2-66** was then protected with a *tert*-butyldimethylsilyl group to form enyne **2-67**.

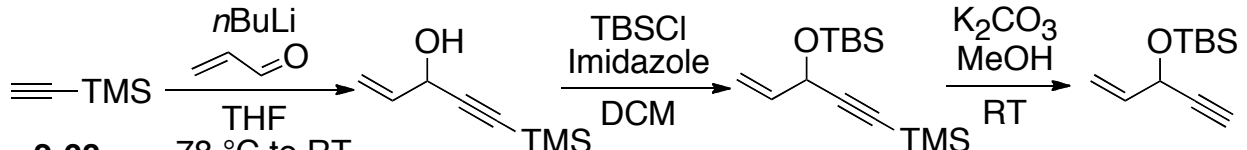
Scheme 2.22: Synthesis of Enyne **2-67**



2-65 **2-66** **2-67**
74% (from **2-65**)

The synthesis of enyne **2-71** started with acrolein, but it could not be prepared by a simple Grignard reaction pathway as mentioned above. For this synthesis, trimethylsilyl acetylene **2-68** was first deprotonated using *n*-butyllithium and then reacted with acrolein to form the corresponding alcohol **2-69,** which was then protected with *tert*-butyldimethylsilyl group to form compound **2-70**. The trimethylsilyl group in compound **2-70** was then deprotected using potassium carbonate to provide enyne **2-71**.

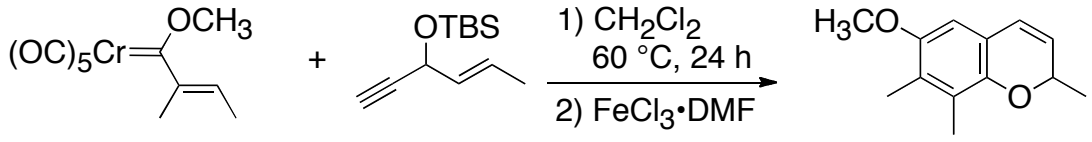
Scheme 2.23: Synthesis of Enyne **2-71**



2-68 **2-69** **2-70** 89% **2-71** 89%

The BQME cascade reaction of the enyne **2-67** with carbene complex **2-43** gave the expected chromene product **2-72** in very good yield (70%).

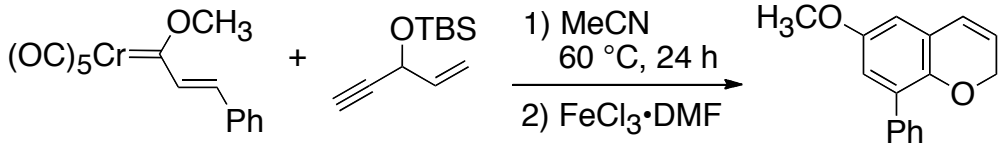
Scheme 2.24: Reaction between Carbene Complex **2-43** and Enyne **2-67**



2-43 **2-67** **2-72** 70%

In considering the BQME reaction for the enyne **2-71** the main concern was that the lower stability of the intermediate cation **51** (**Figure 2.1**) due to the absence of the substituents at the alkene terminus might be problematic. Although the reaction of carbene complex **2-14** and enyne **2-71** could have been more efficient, the chromene **2-73** could nonetheless be prepared in 47% yield.

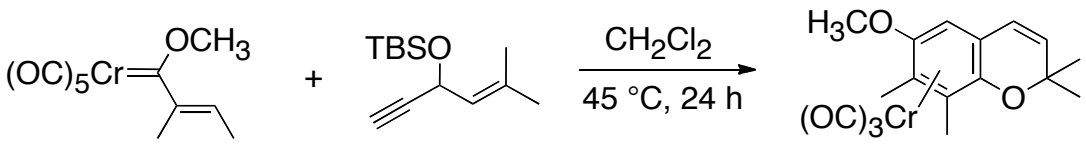
Scheme 2.25: Reaction between Carbene Complex **2-43** and Enyne **2-67**



2-14 **2-71** **2-73** 47%

The chromium tricarbonyl complex of the chromene product is generally unstable as it is slowly oxidized in air resulting in the precipitation of chromium(III) side products. An effort was made to isolate and characterize the chromium-complexed chromene product. A suitably air-stable derivative could be obtained from the reaction of carbene complex **2-43** and enyne **2-38** in dichloromethane solvent at 45 ^{o}C. The chromium tricarbonyl chromene complex **2-74** could be isolated and obtained in pure form in 61% yield.

Scheme 2.26: Synthesis of The Chromium-Complexed Compound **2-74**

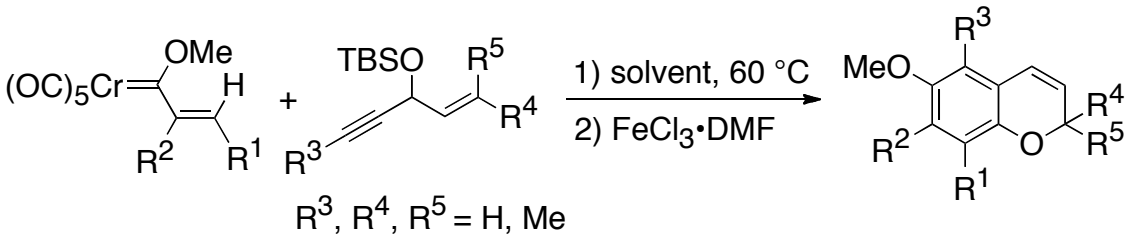


2-43 **2-38** **2-74** 61%

2.3. Conclusion

In conclusion, an efficient and novel synthetic strategy based on the benzannulation/*o*-quinone methide formation/electrocyclization cascade (BQME) has been developed. The experimental results for the substrate scope are summarized below in **Table 2.6**.

Table 2.6: Summary of The Substrate Scope



R^3, R^4, R^5 = H, Me

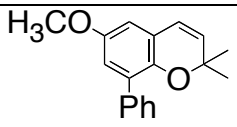
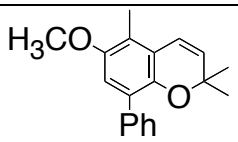
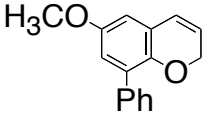
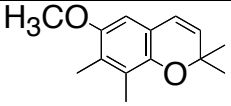
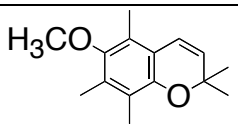
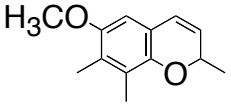
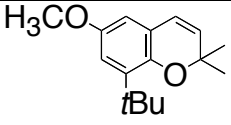
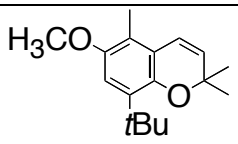
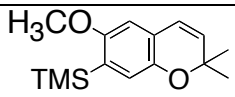
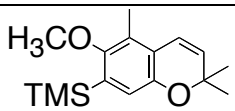
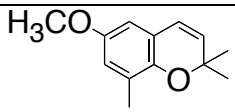
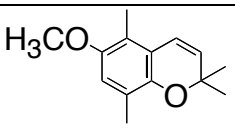
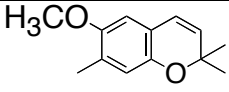
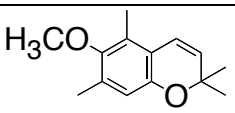
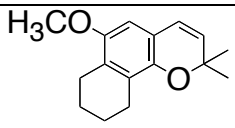
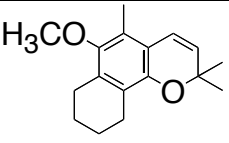
Entry	Product	Yield (%)				
		CH_2Cl_2	MeCN	Hexane	Benzene	THF
1		76	100, 91	69, 70	75, 72	68, 61
2		69	66	–	–	–
3		–	47	–	–	–
4		88, 77,75	75, 61, 60	–	73	74
5		84, 84	87	–	–	–
6		70	–	–	–	–
7		78	78	–	–	–

Table 2.6 continued….

Entry	Product	Yield (%)				
		CH_2Cl_2	MeCN	Hexane	Benzene	THF
8		76, 60,72, 86[a]	65[b]	–	–	–
9		65, 52, 52	23	–	–	–
10		87, 81	35	–	–	–
11		41	83	–	–	–
12		61	48	–	–	–
13		45, 44	28, 24	55	38	–
14		68, 68	36, 31	74	57	–
15		72	65	–	–	–
16		80	63	–	–	–

a. The reaction was performed in CH_2Cl_2 in presence of 10 equiv. of aniline. b. 65% yield is after treatment of the crude reaction mixture with triflic acid.

CHAPTER THREE

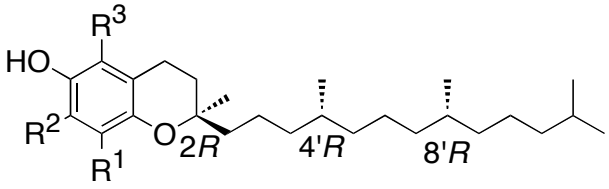
Application of Benzannulation/*o*-Quinone Methide Formation/Electrocyclization Cascade (BQME Reaction) Towards the Synthesis of Vitamin E and Lapachenole

3.1. Synthesis of Vitamin E

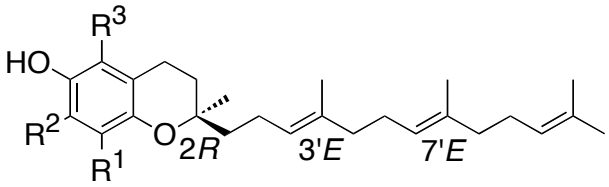
3.1.1. Background:

Vitamin E is a group of eight fat-soluble compounds that include α, β, γ, and δ forms of both tocotrienols and tocopherols (**Figure 3.1**). All naturally occurring tocopherols only exhibit the (2*R*,4'*R*,8'*R*) configuration. However, when the tocopherols are synthesized in the racemic form they contain eight different stereoisomers. On the other hand, natural tocotrienols occur with the (2*R*,3'*E*,7'*E*) stereochemistry.[119]

Figure 3.1: Vitamin E - Tocopherols and Tocotrienols



α-Tocopherol : $R^1 = R^2 = R^3 = CH_3$
β-Tocopherol : $R^1 = R^3 = CH_3$; $R^2 = H$
γ-Tocopherol : $R^1 = R^2 = CH_3$; $R^3 = H$
δ-Tocopherol : $R^1 = CH_3$; $R^2 = R^3 = H$



α-Tocotrienol : $R^1 = R^2 = R^3 = CH_3$
β-Tocotrienol : $R^1 = R^3 = CH_3$; $R^2 = H$
γ-Tocotrienol : $R^1 = R^2 = CH_3$; $R^3 = H$
δ-Tocotrienol : $R^1 = CH_3$; $R^2 = R^3 = H$

Among the four types of tocopherols, α-tocopherol is the most biologically active form of vitamin E. Vitamin E has many biological functions such as enzymatic activities,[120]

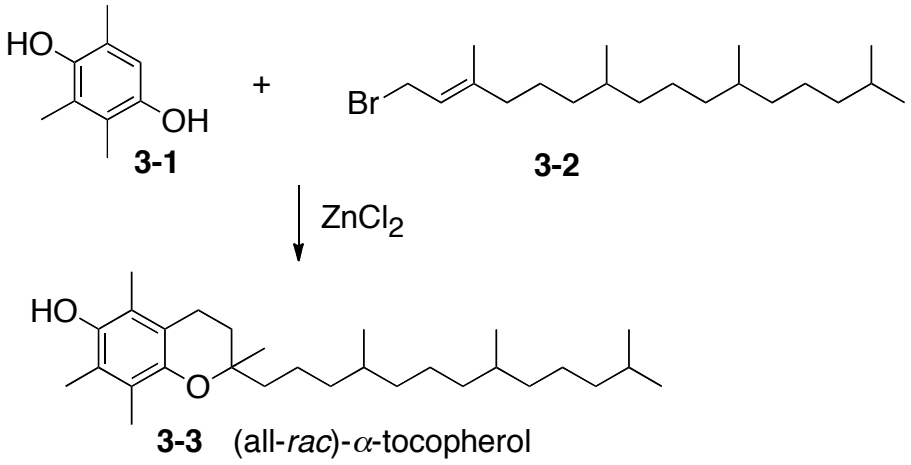
gene expressions,[121] and neurological functions[122]. However, it is primarily known for its antioxidant properties[123] that prevent the production of reactive oxygen species formed when fat undergoes oxidation. Moreover, vitamin E acts as peroxyl radical scavenger. It stops the propagation of free radicals in tissues by forming tocopheryl radical, which in turn gets reduced by a hydrogen donor. Since vitamin E is fat-soluble it can enter the cell membranes very easily and protect them from oxidative damage.[124]

Vitamin E is economically very important because of its important biological activities. The predominant commercial value of vitamin E is its use in animal feeds but it is also used in human applications for example in pharmaceuticals, in food and in cosmetics. Generally (all-*rac*)- α-tocopherol, an equimolar mixture of all eight stereoisomers, is the most important industrial product, with about 35,000 tons manufactured per year worldwide, which is mainly used as its acetate derivative.

3.1.2. Previous Synthesis of Racemic Vitamin E:

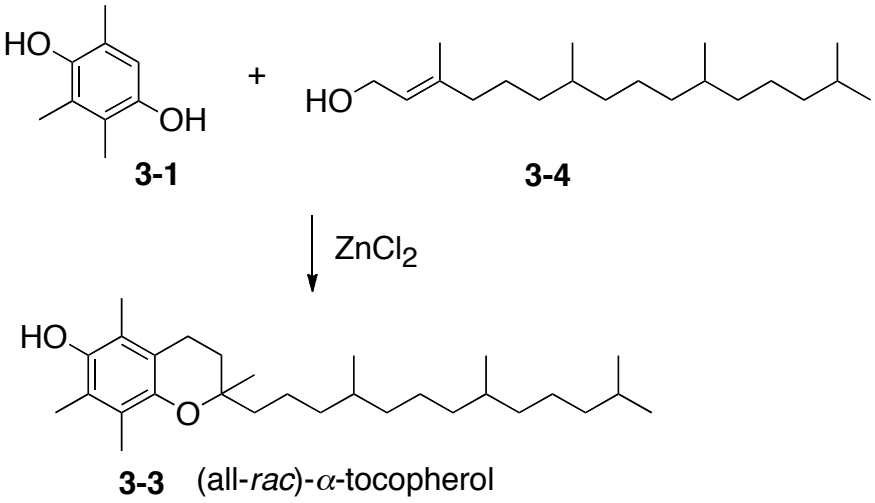
The first synthesis of (all-*rac*)- α-tocopherol was achieved by Karrer and coworkers[125] in 1938. They prepared the racemic tocopherol **3-3** in almost quantitative yield by heating trimethylhydroquinone **3-1** and racemic phytyl bromide **3-2** in presence of anhydrous zinc chloride in petroleum ether (**Scheme 3.1**).

Scheme 3.1: First Synthesis of α-Tocopherol



In the same year, Work et al reported[126] the second synthesis of vitamin E. They used phytol **3-4**, trimethylhydroquinone **3-1**, and zinc chloride and later modified the synthesis by adding decalin as the solvent (**Scheme 3.2**).

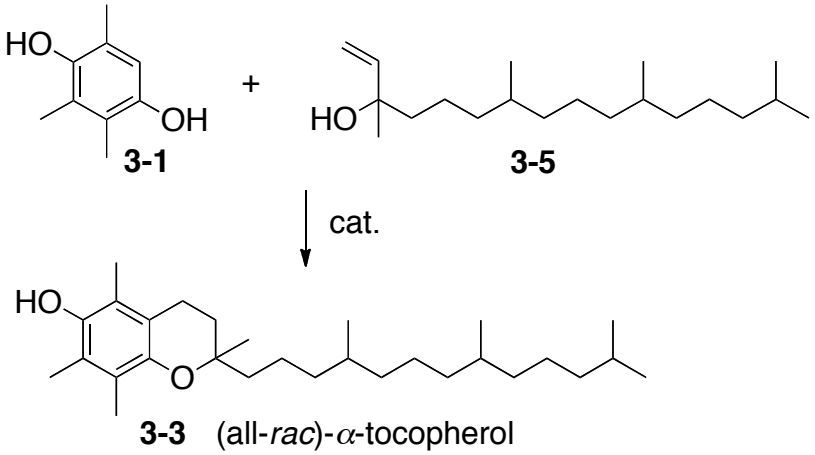
Scheme 3.2: Synthesis of Vitamin E Using Phytol



Industrially (all-*rac*)-α-tocopherol **3-3** is produced on a large scale by means of an acid-catalyzed reaction of trimethylhydroquinone **3-1** with all-*rac*-isophytol **3-5**. Several classical Lewis and Brönsted acids work well in this reaction, for example, $ZnCl_2$/HCl, BF_3 or $AlCl_3$ in various organic solvents. The mechanism of the reaction shown in **Scheme 3.3** is generally accepted as a two-step process – Friedel-Crafts C-alkylation followed by a cyclization.[119]

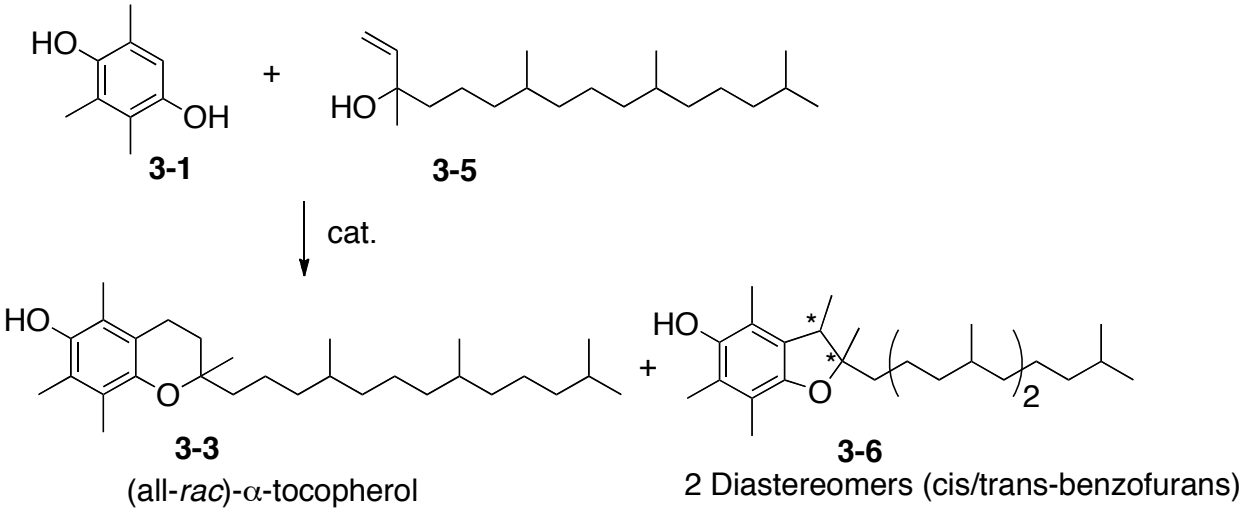
However, this industrial procedure suffers from serious limitations. The limitations include corrosion problems and contamination of wastewater, in particular with zinc and halide ions. Further drawbacks are the high, often near stoichiometric amounts of catalysts and the excess of expensive isophytol necessary for obtaining satisfying results. The isophytol **3-5** is generally prepared from petroleum bulk chemicals such as acetone, acetylene etc. but in a linear and lengthy synthesis (6-9 steps).

Scheme 3.3: Synthesis of Vitamin E Using Isophytol



There have been several efforts to improve this procedure and make it environmentally friendly aiming at high yield and selectivity and also on reusability of the catalysts.[127] The efforts were directed towards alternative reaction media such as two- or multiphase solvents systems or supercritical fluids. There has also been focus on the use of new catalytic systems including “superacidic” and supported catalysts in order to replace traditional Lewis acids and mineral acids. Some novel catalysts are clays, ion exchange resins, rare earth and indium metal halides and triflates, heteropolytungsten acids, various polyfluorinated compounds (imides, methides), and boron and phosphorous compounds.[127] These changes not only resulted in high chemical yields but also in extremely high selectivity of the condensation reaction by avoiding the formation of isomeric products specially the benzofuran compounds **3-6** (**Scheme 3.4**).[127g]

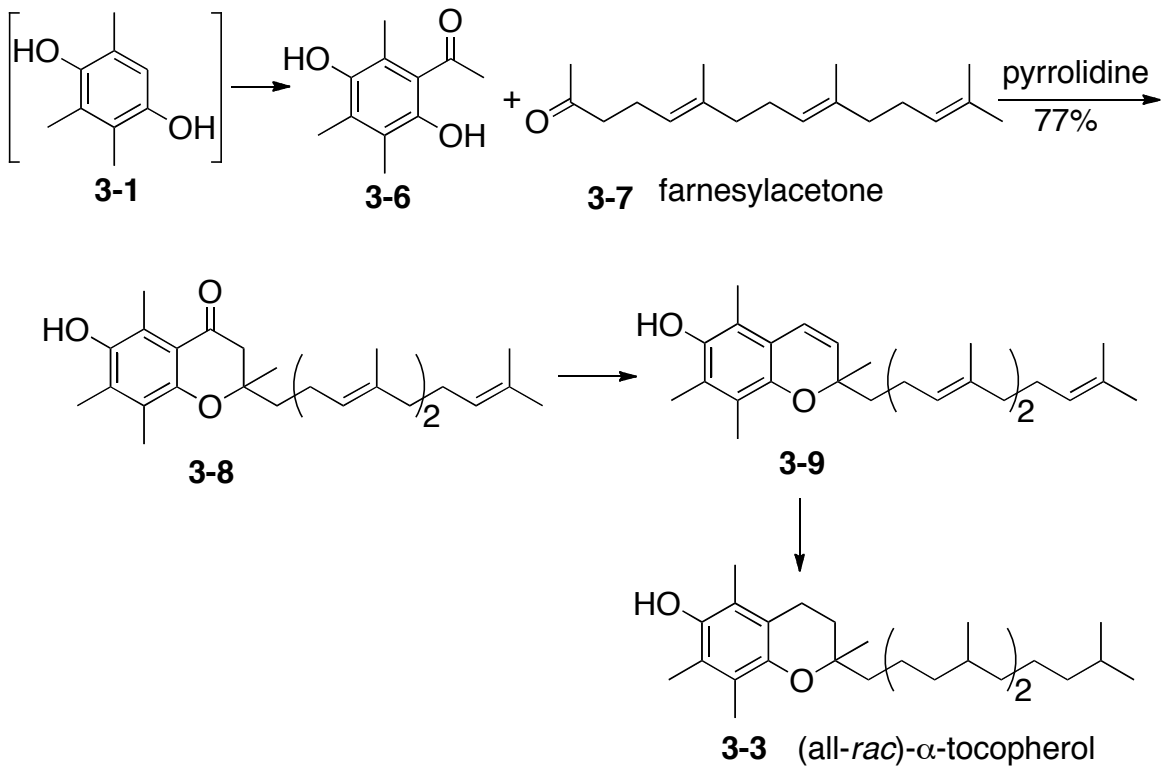
Scheme 3.4: Benzofuran Side Products in The Synthesis of Vitamin E



Isophytol **3-5** is expensive and thus there is a preference for using the primary alcohol phytol **3-4** (**Scheme 3.2**) or a corresponding ester, halide, or a similar derivative instead of the tertiary alcohol (isophytol **3-5**) in this acid-catalyzed reaction.

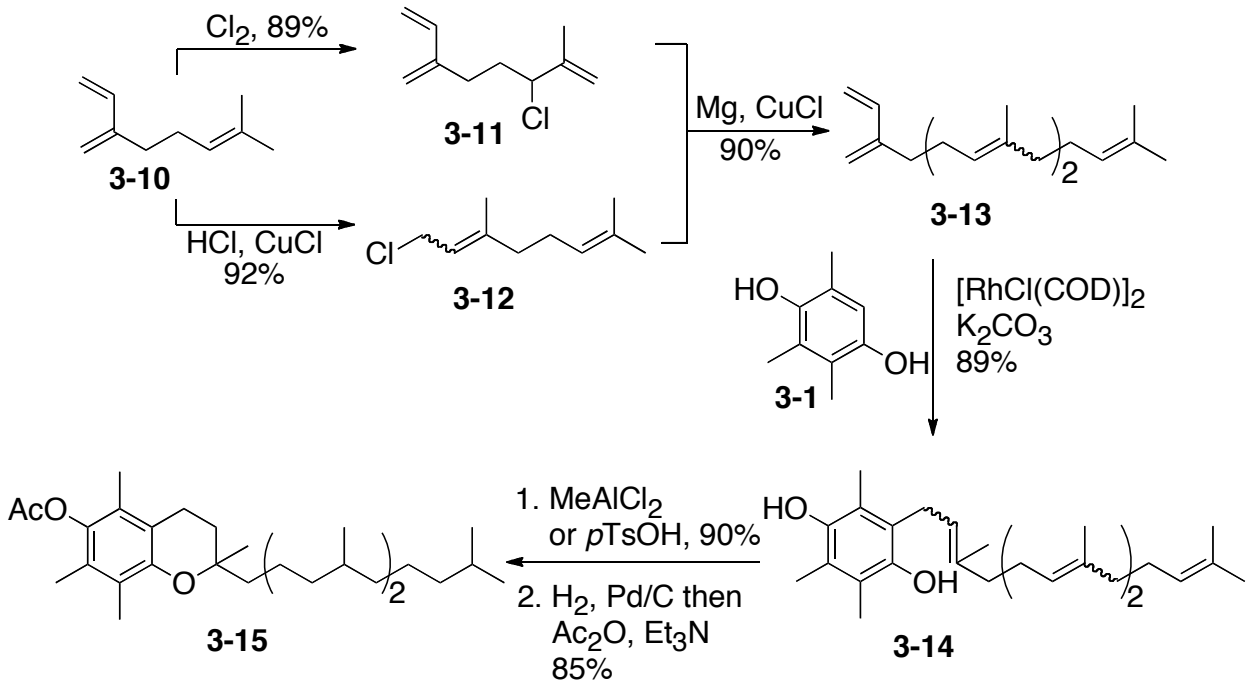
Avoiding the use of isophytol, Kabbe and Heitzer in 1978 reported[128] a synthesis of (all-*rac*)-α-tocopherol **3-3** by using aryl methyl ketone **3-6**, derived from trimethylhydroquinone **3-1** and farnesylacetone **3-7**. The condensation and cyclization occurred in the presence of pyrrolidine to give compound **3-8** in 77% yield. Subsequent reduction followed by elimination provided the dehydro-tocotrienyl derivative **3-9** in 78% yield, which could be transformed to (all-*rac*)-α-tocopherol **3-3** by catalytic hydrogenation in 96% yield (**Scheme 3.5**).

Scheme 3.5: Synthesis of Vitamin E by Kabbe and Heitzer



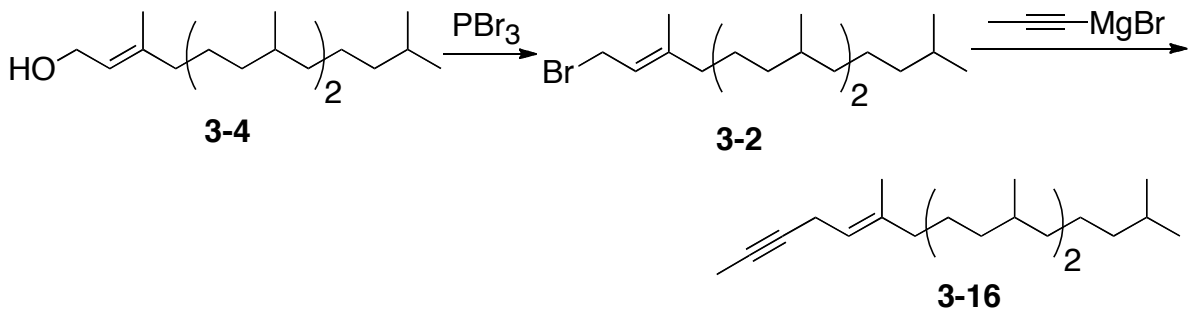
In 2000, Bienayme and coworkers reported[129] another interesting approach for the synthesis of racemic tocopherol from cheap industrially available starting materials avoiding the use of expensive isophytol **3-5**. They used the naturally available starting material myrcene **3-10**, which could be dimerized to the C20 building block **3-13** via functionalizations by chlorine and HCl/CuCl. The conjugated diene **3-13** was reacted with trimethylhydroquinone **3-1** in presence of rhodium catalyst to give compound **3-14**, which was then transformed to **3-15** by cyclization followed by catalytic hydrogenation and acetylation in an overall 50% yield (**Scheme 3.6**).

Scheme 3.6: Synthesis of Vitamin E by Bienayme and Coworkers



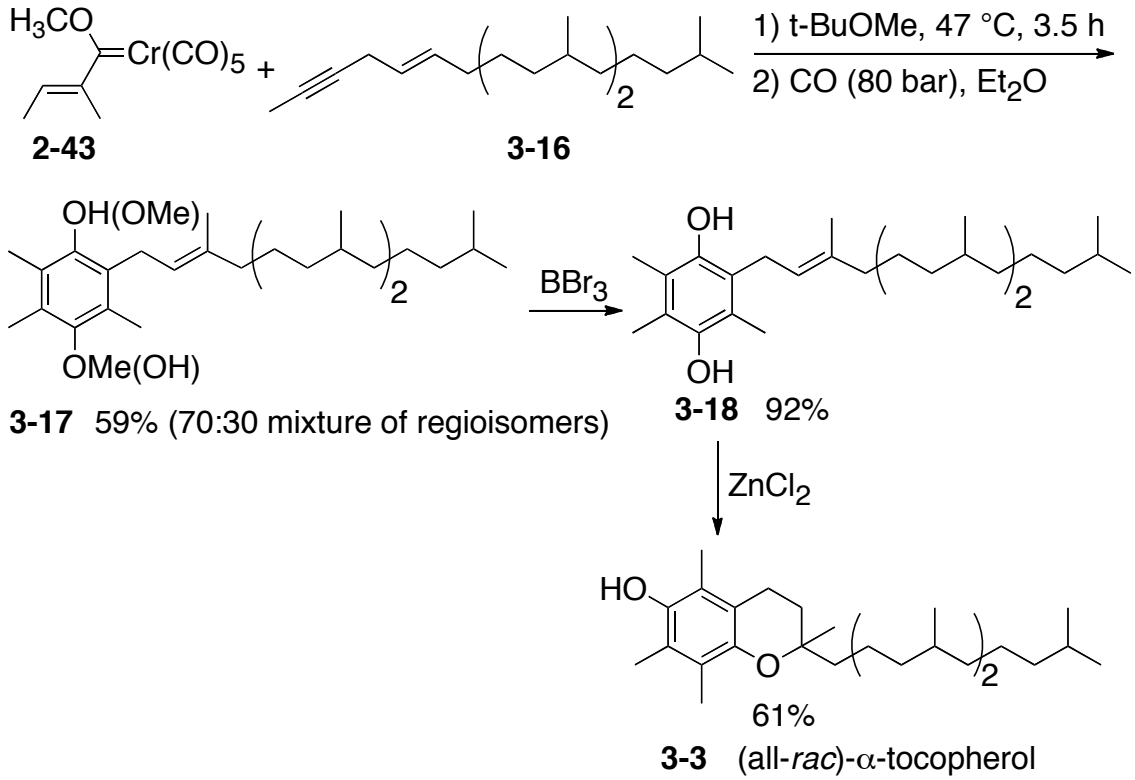
In 1983 Dötz and coworkers reported[130] a synthesis of vitamin E, which employed a benzannulation reaction between the butenyl carbene complex **2-43** and alkyne **3-16** (**Scheme 3.8**). The alkyne **3-16** was obtained from readily available phytol **3-4** via the bromide **3-2** and propynylation with a Grignard reagent (**Scheme 3.7**).

Scheme 3.7: Preparation of Enyne in Dötz Synthesis of Vitamin E



The benzannulation reaction afforded a mixture of regioisomers of the hydroquinone monoethers **3-17**. The chromium was removed from the product by ligand exchange with CO under pressure. To utilize both of the regioisomers of **3-17** the methyl ether linkage was cleaved with boron tribromide to give hydroquinone **3-18** which was the converted to vitamin E **3-3** by cyclization (**Scheme 3.8**).

Scheme 3.8: Synthesis of Vitamin E by Dötz and Coworkers



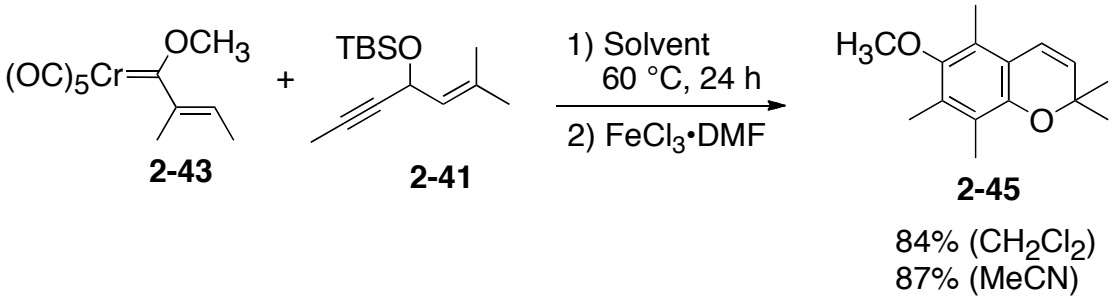
To this end, a cascade of benzannulation followed by *o*-quinone methide formation followed by electrocyclization has proved to be a very efficient method for the synthesis of chromene as described in Chapter 2. Vitamin E contains a chroman moiety which is just the reduced form of a chromene. So we anticipated that our method could be

efficiently applied to the synthesis of vitamin E. This would be the first synthesis of Vitamin E in which both rings were made in the same step.

3.1.3. Synthesis of Vitamin E via the Benzannulation/*o*-Quinone Methide Formation/Electrocyclization Cascade (BQME Reaction):

In Chapter 2 the model reaction for the synthesis of vitamin E was presented and involved the butenyl carbene complex **2-43** and enyne **2-41** which was very successful in giving very high yields of the chromene **2-45** (**Scheme 3.9**).

Scheme 3.9: Reaction between Carbene Complex **43** and Enyne **41**



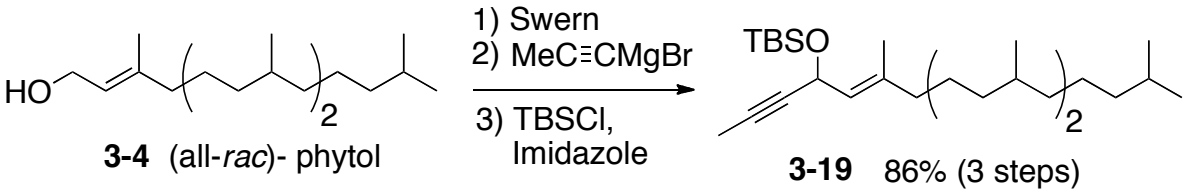
2-43 **2-41** **2-45**

84% (CH_2Cl_2)
87% (MeCN)

Building on these results, the synthesis of vitamin E was pursued with the butenyl carbene complex **2-43** and enyne **3-20** as the starting compounds. The enyne was prepared from the naturally available phytol **3-4**. First phytol **3-4** was oxidized to form the corresponding aldehyde. Then propynyl magnesium bromide was reacted with this

aldehyde to generate the corresponding alcohol. Protection of the hydroxyl group provided the enyne **3-20** in very high overall yield (86%) (**Scheme 3.10**).

Scheme 3.10: Synthesis of Enyne

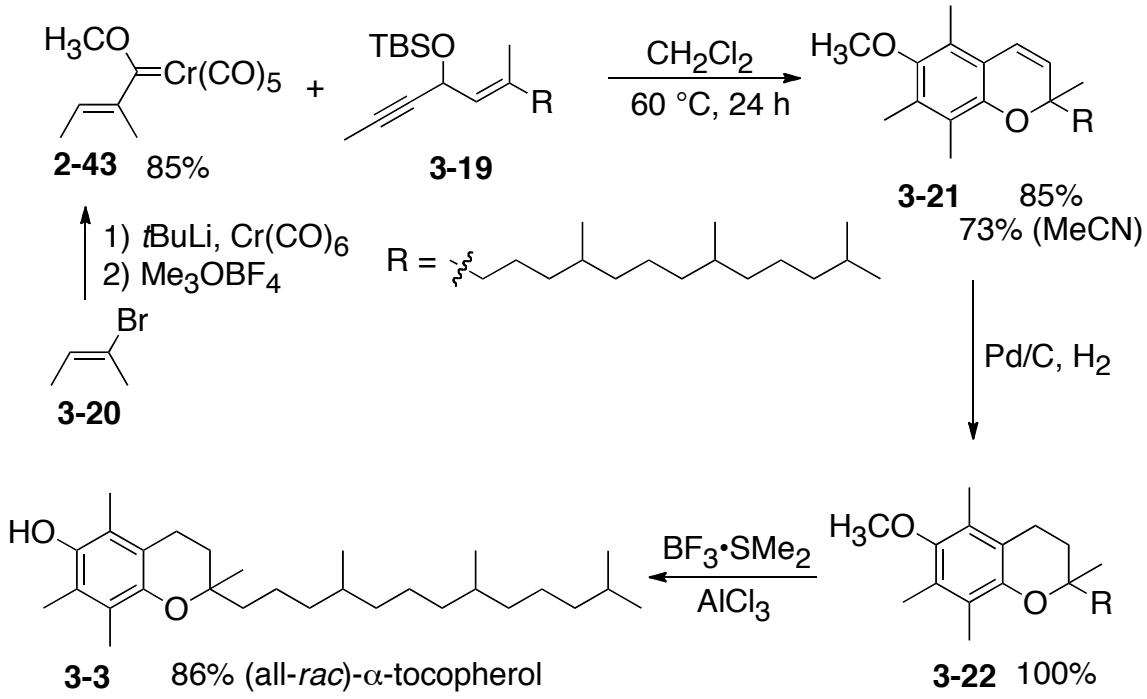


3-4 (all-*rac*)- phytol

3-19 86% (3 steps)

The reaction between carbene complex **2-43** and enyne **3-19** in dichloromethane occurred to give a very high yield (85%) of the expected chromene product **3-21**. In acetonitrile, the reaction afforded a 73% yield of the chromene product **3-21**. Catalytic hydrogenation provided quantitative conversion to the chroman product **3-22**. In one more step, the target compound (all-*rac*)-α-tocopherol **3-3** could be obtained in 86% yield by demethylation of **3-22**. The overall yield of the final product **3-3** was 73% from carbene complex **2-43** and 62% from compound **3-20** (**Scheme 3.11**).

Scheme 3.11: Synthesis of Vitamin E



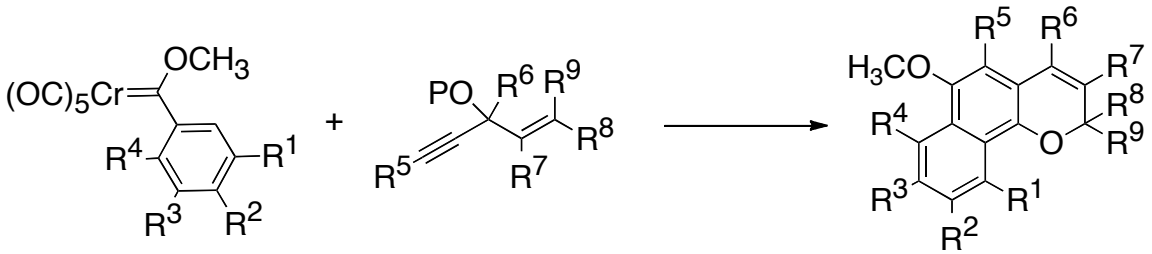
During the synthesis, the last demethylation step was also attempted with only anhydrous aluminum chloride, but the reaction gave very low yield of vitamin E along with some unidentifiable mixture of side products. However, use of trifluoroborane-dimethylsulfide complex along with anhydrous aluminum chloride proved to be the best reagents for this reaction.[131]

3.2. Synthesis of Naphthopyrans

The benzannulation/*o*-quinone methide formation/electrocyclization cascade of an aryl carbene complex of the type **3-23** with a propargyl enyne of the type **3-24** has the

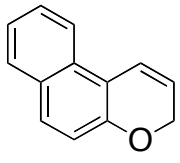
potential for providing access to 2*H*-benzo[*h*]chromenes **3-25** (naphthopyrans) in a single step (**Scheme 3.12**).

Scheme 3.12: Proposed Synthesis of Naphthopyrans

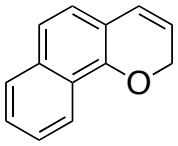


Both 2*H*-benzo[*h*]chromenes **3-27**[132] and 3*H*-benzo[*f*]chromenes **3-26**[133] are of interest because of their photochromatic behaviour which is associated with photo-induced electrocyclic ring opening to *o*-quinone methides (**Scheme 3.13**). The 2*H*-benzo[*h*]chromene core is quite common and occurs in a large number of natural and unnatural products.[134] One of the simplest members is the natural product lapachenole **3-28** (**Figure 3.2**).

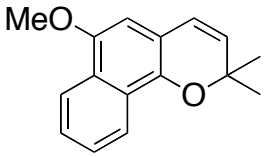
Figure 3.2: Benzochromenes and Lapachenole



3*H*-benzo[*f*]chromene
3-26

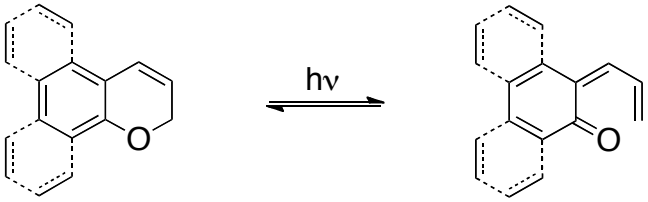


2*H*-benzo[*h*]chromene
3-27



lapachenole
3-28

Scheme 3.13: Photoinduced Electrocyclic Ring Opening

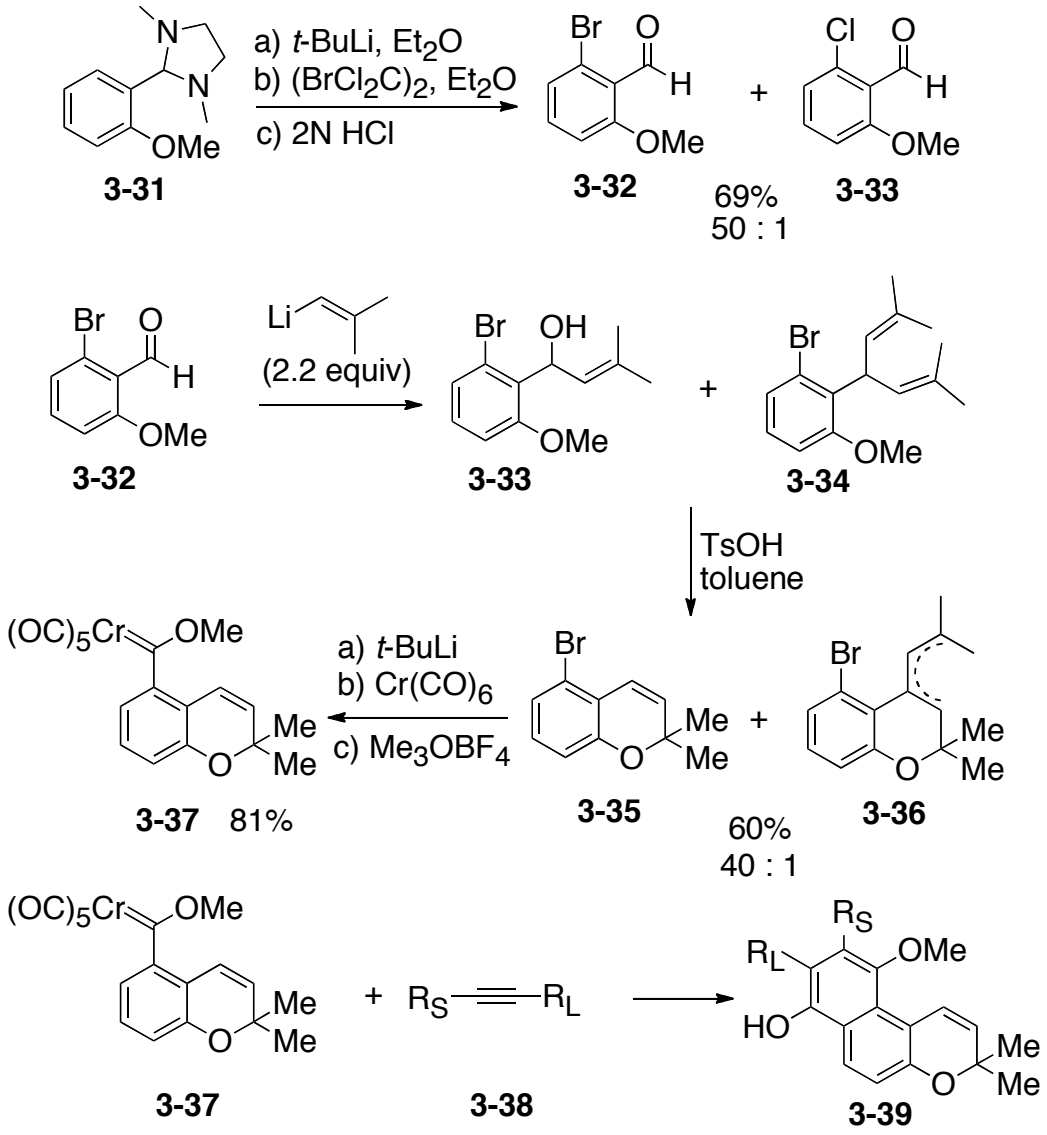


3-29 **3-30**

Lapachenole has been isolated from different sources including *Avicennia rumphiana*.[135] This compound has been used as a fluorescent photoaffinity label[132] and shown to have cancer chemopreventive activity.[135] It occurs in *Tabebuia heptaphylla* which is the source of the Paraguayan traditional medicine "tayi pytá" used in the treatment of wounds, cancer, and inflammations.[136]

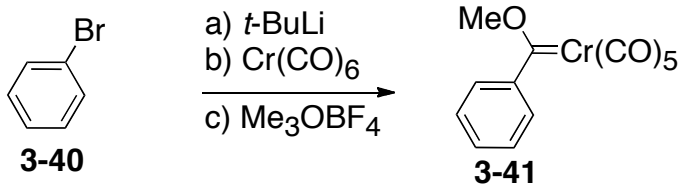
Notably, our group reported a synthetic approach to 3*H*-benzo[*f*]chromenes **3-39** via the simple benzannulation reaction of chromene carbene complex **3-37** and alkyne **3-38**. This approach required the preparation of the chromene carbene complex **3-37** which could be obtained in six steps from *o*-methoxybenzaldehyde (**Scheme 3.14**).[137]

Scheme 3.14: Previous Synthesis of 3*H*-Benzo[f]chromenes using Carbene Complexes



The proposed route to 2*H*-benzo[*h*]chromenes (**Scheme 3.12**) following our newly developed cascade method for the synthesis would be more efficient than the synthesis of 3*H*-benzo[*f*]chromenes shown in **Scheme 3.15** since the aryl carbene complexes can be directly obtained in high yield from the corresponding aryl bromide or iodide (**Scheme 3.15**).[138]

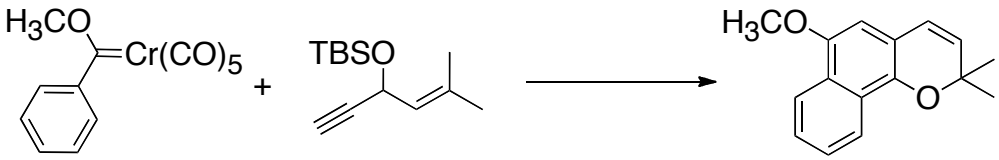
Scheme 3.15: Synthesis of Aryl Carbene Complexes



3-40 **3-41**

Thus, we first targeted the synthesis of lapachenole **3-28** as it can be obtained in one step by reacting phenyl carbene complex **3-41** with enyne **2-38** (**Scheme 3.16**).

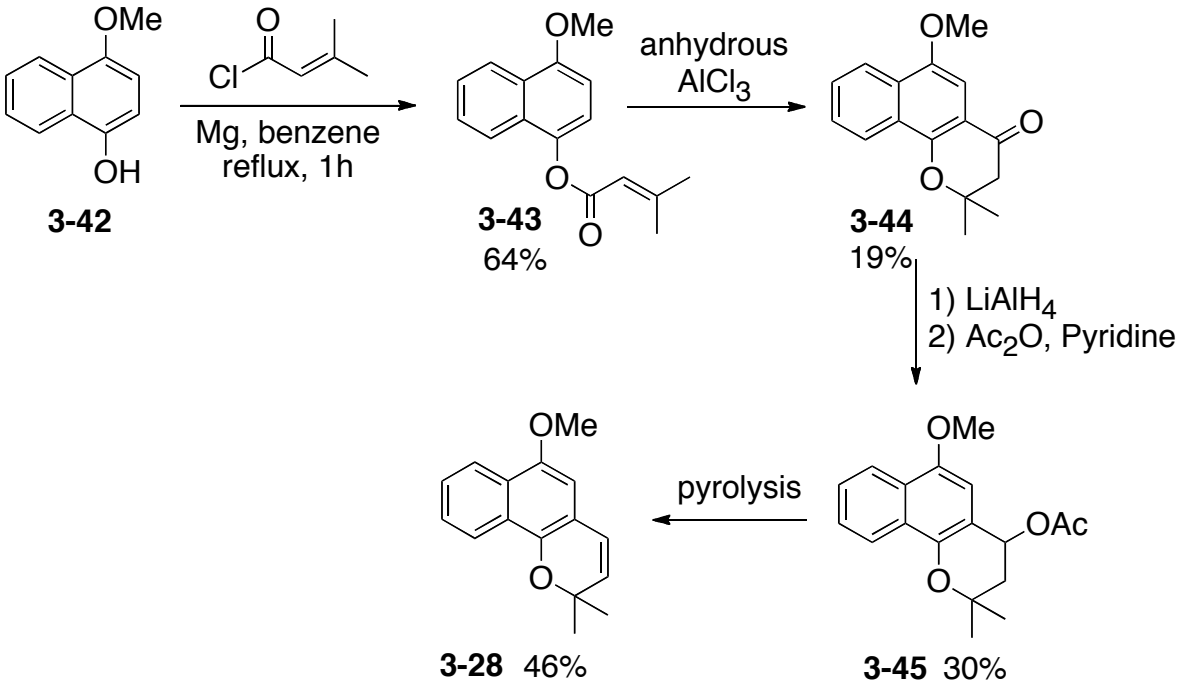
Scheme 3.16: Synthesis of Lapachenole



3-41 **2-38** **3-28**
lapachenole

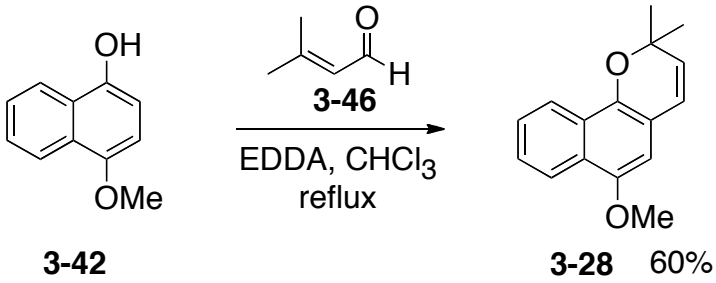
Here it should be mentioned that lapachenole has been previously synthesized by a few different approaches. In 1956, Livingstone et al reported[139] a synthesis of lapachenole starting by an esterification of 4-methoxy-1-naphthol **3-42** and β,β -dimethyl acryloyl chloride followed by Fries rearrangement and condensation. The resulting chromanone **3-44** was then reduced and acetylated. Pyrolysis of compound **3-45** provided lapachenole **3-28** as the final product (**Scheme 3.17**).

Scheme 3.17: Synthesis of Lapachenole by Livingstone and Coworkers



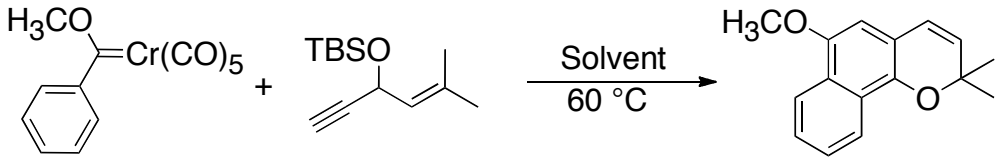
In 2007, Lee and coworkers reported[140] another synthetic approach, which is much simpler than the previously reported synthesis. A reaction between compound **3-42** and 3-methylbut-2-enal **3-46** with 20 mol% of ethylenediamine diacetate (EDDA) in refluxing $CHCl_3$ for 24 h afforded lapachenole **3-28** in 60% yield (**Scheme 3.18**).

Scheme 3.18: Synthesis of Lapachenole by Lee et al



For our synthesis, the reaction was first attempted in dichloromethane solvent using 1.2 equivalents of enyne **2-38** with carbene complex **3-41** as the limiting reagent (**Table 3.1**, entry 1). However, the reaction did not go to completion and there was a significant amount of carbene complex left unreacted. So the amount of enyne **2-38** was increased to 1.5 equivalents, which gave rise to a 28% yield of lapachenole **3-28** after air oxidation (entry 2). A change in the solvent to toluene resulted in a much cleaner reaction giving a 30% yield of the compound **3-28** after air oxidation (entry 3). The reaction in THF gave a drop in yield (entry 5). The reaction in acetonitrile solvent was also not clean and so the yield was not determined (entry 6). When the reaction was repeated in toluene but the oxidation was done using $FeCl_3$•DMF as the oxidizing agent, the yield increased to 37% (entry 4). No significant by-products were observed to form along with the desired product lapachenole in toluene. Collection of other fractions from the silica gel column yielded a complex mixture of compounds, none of which are predominant or separable. This was suggestive of the incorporation of multiple units of the enyne, and this has been observed in other reactions to produce phenols, trisubstituted benzenes or oligomers.[141] All of the reactions discussed up to this point were run at 0.035 M concentration. Previous experience suggests that improved yields could be achieved by controlling the concentration.[142] When the concentration was changed to 0.1 M in toluene, the yield of **3-28** was 26% after $FeCl_3$•DMF oxidation (entry 7). At 0.005 M concentration, the reaction afforded a 31% yield of lapachenole under the same conditions (**Table 3.1**, entry 8).

Table 3.1: Initial Optimization



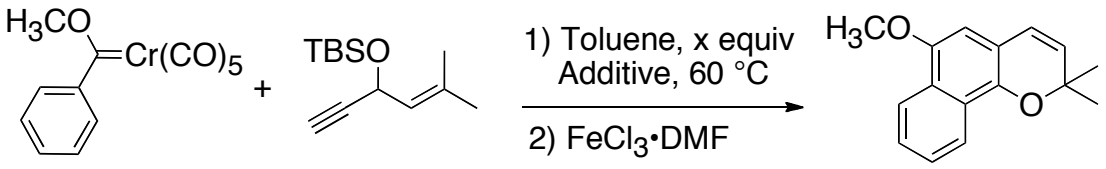
3-41 **2-38** **3-28** lapachenole

Entry	Equiv. of Enyne	Solvent	Reaction Concentration	Oxidation Type	Yield (%)
1	1.2	CH_2Cl_2	0.035 M	–	–
2	1.5	CH_2Cl_2	0.035 M	Air oxidation	28
3	1.5	Toluene	0.035 M	Air oxidation	30
4	1.5	Toluene	0.035 M	$FeCl_3$•DMF	37
5	1.5	THF	0.035 M	Air oxidation	15
6	1.5	MeCN	0.035 M	None	–
7	1.5	Toluene	0.1 M	$FeCl_3$•DMF	26
8	1.5	Toluene	0.005 M	$FeCl_3$•DMF	31

After this initial optimization it was clear that toluene was the best choice of solvent and that the use of 1.5 equivalents of enyne **2-38** was necessary. Furthermore, oxidative work up with $FeCl_3$•DMF oxidation was superior to air oxidation. However, the optimized yield of 37% was not satisfactory. Thus the effects of a variety of additives were

examined in this reaction in order to achieve improved yields. With 5 equiv Hünig's base the reaction was not clean thus the yield was not determined. With 10 equivalents of pyridine the chromene **3-28** was obtained in 39% yield. When 10 equivalents of aniline was employed, the yield was improved to 48%. With 20 equiv of aniline, the yield was 42% and with 5 equiv of aniline the yield was 26% (from NMR). To probe the effect of variations in the electronic nature of aniline, the reaction was carried out using 10 equiv of *p*-nitroaniline, 10 equiv of *p*-methoxy aniline and 5 equiv of pentafluoroaniline and the yields of **3-28** were 46%, 26% and 47% respectively. These results indicate that electron deficient anilines work better for this reaction (**Table 3.2**).

Table 3.2: Optimization with Additives



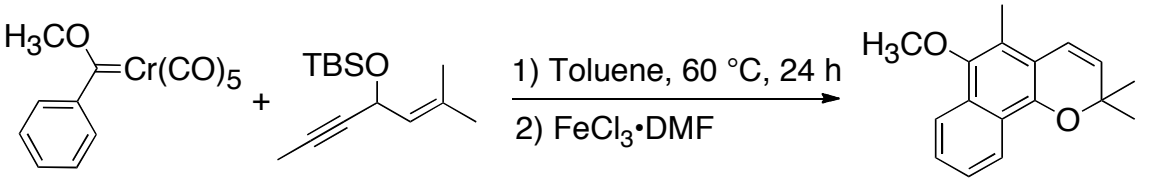
3-41 **2-38** **3-28**

Entry	Additive	X	Yield (%)[a]
1	Hunig's base	5	–
2	Pyridine	10	39
3	Aniline	10	48
4	Aniline	20	42
5	Aniline	5	26
6	*p*-Nitroaniline	10	46
7	*p*-Methoxyaniline	10	26
8	Pentafluoroaniline	5	47

a. All the reactions were carried out in 0.048 M concentration using 1.2 equivalents of enyne **2-38** for 24 h. All the yields are isolated yields.

If multiple insertions of enyne **2-38** containing a terminal alkyne function were responsible for the moderate yields of lapachenole, then increased yields would be expected for similar reactions with internal enyne **2-41**. Indeed, the synthesis of 5-methyllapachenole **3-46** was possible with a much higher yield (85%) than lapachenole **3-28** (**Scheme 3.19**).

Scheme 3.19: Synthesis of 5-Methyllapachenole

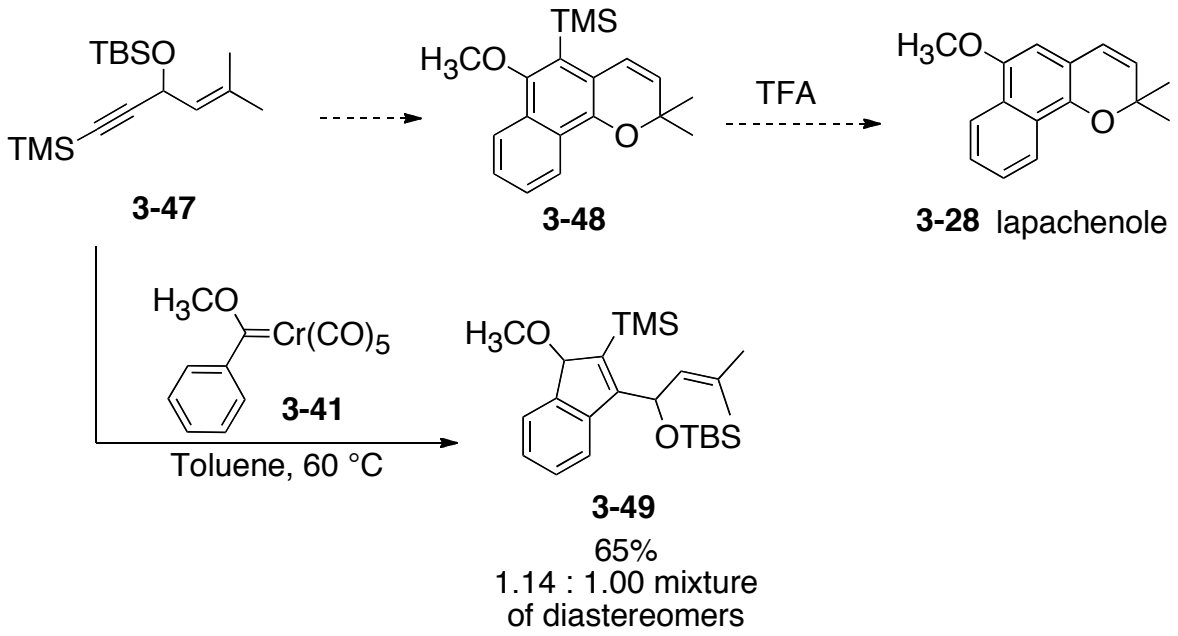


3-41 **2-41** **3-46**

5-methyllapachenole
80%
(85% with 10 equiv aniline)

An alternative approach to lapachenole that has the potential to be more efficient is the reaction of the carbene complex with the enyne **3-47** bearing an internal alkyne as the trimethylsilylated analog of enyne **2-41**. In analogy with the enyne **2-41** bearing an internal alkyne, the product from the reaction of enyne **3-47** would be expected to be naphthopyran **3-48** from which the trimethylsilyl group could be removed by protonolysis to give lapachenole **3-28**. However, it was found that the reaction of the silylated enyne **3-47** gave the indene product **3-49** rather than the expected naphthopyran **3-48**. The indene **3-49** was isolated in 65% yield as a 1.14:1.0 mixture of diastereomers and was the only product that was observed that was mobile on TLC (**Scheme 3.20**).

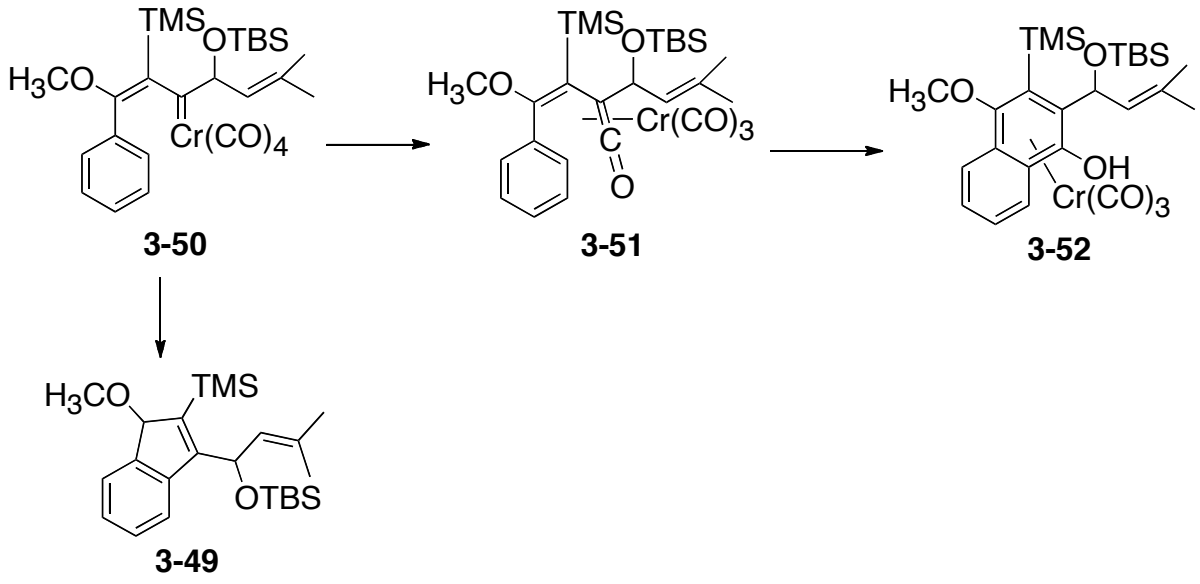
Scheme 3.20: Alternative approach to Lapachenole



This type of five-membered ring cyclized product is perhaps the most common of the many side products that have been observed in the benzannulation reaction.[143] There is a tendency to see increased amounts of five-membered ring products with increased steric bulk of the two acetylene substituents. Mechanistically, this reaction should occur by initial insertion of the alkyne function of **3-47** into the metal-carbene bond in carbene complex **3-41** to give the vinyl carbene complexed intermediate **3-50**. The subsequent events normally would be migratory insertion of a CO ligand to give the chromium complexed vinyl ketene **3-51** and then electrocyclic ring closure to give the phenol chromium tricarbonyl complex **3-52**. Apparently, in the case of the vinyl carbene complexed intermediate **3-50**, there is a preference for direct cyclization to **3-49** rather than CO insertion to give **3-51**. The reasons for this are not clear, but one might expect

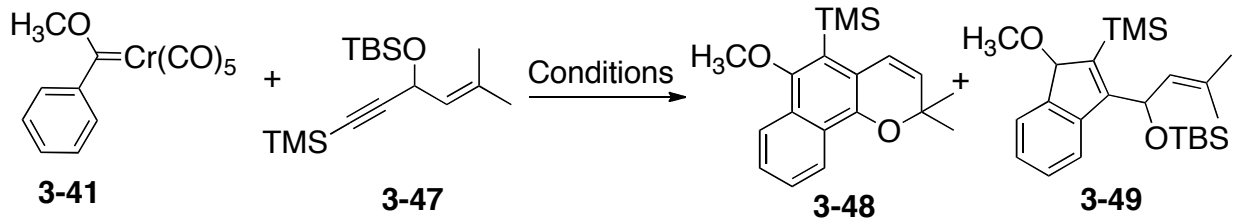
that it may be related to the increase in bond angles for the sp^2 carbons of **3-50**, as cyclization occurs to give a five-membered ring and the associated decrease in strain energy as the large substituents move further apart (**Scheme 3.21**).

Scheme 3.21: Explanation for the Formation of Indene Side-product



When the same reaction was conducted in the presence of 10 equiv of aniline, trace amount of expected chromene product **3-48** was observed in the ^{1}HNMR spectrum of the crude reaction mixture along with the side products. The chromene product **3-48** could not be isolated or characterized. Nonetheless, this inspired a repeat of the reaction in pure aniline as solvent. The reaction was also repeated in acetonitrile without addition of any additive. Unfortunately, in both cases the reaction did not occur between the carbene complex **3-41** and enyne **3-47** (**Scheme 3.22**).

Scheme 3.22: Results for the Alternative Approach



3-41 **3-47** **3-48** **3-49**

Conditions A: 1)Toluene, 10 equiv aniline, 60 °C 2) $FeCl_3$•DMF	Trace amount (from NMR)	60%
Conditions B: Aniline, 60 °C	No reaction	
Conditions C: MeCN, 60 °C	No reaction	

Although the synthesis of lapachenole was achieved in only moderate yield (48%), this approach represents a very short synthesis of lapachenole: Two steps from bromobenzene or two to three steps from the commercially available prenal. It was also shown that for the first time both rings of vitamin E were generated in a single step and the synthesis also featured very high yield (73%) in only three steps from the carbene complex **2-43**.

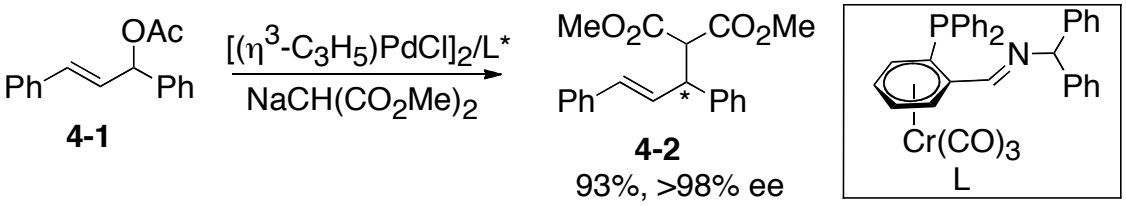
CHAPTER FOUR

Asymmetric Synthesis of Chromene by Asymmetric Benzannulation/*o*-Quinone Methide Formation/Electrocyclization Cascade (ABQME Reaction)

4.1. Background

Chiral chromium tricarbonyl complexed aromatic compounds are known to provide asymmetric induction in a number of different transformations.[144] They have been used as chiral ligands in asymmetric catalysis and also as chiral auxiliaries. Surprisingly, they are not commonly used in spite of their great potential. An example of the use of a $Cr(CO)_3$ complexed arene compound as a chiral ligand in a C–C bond forming reaction is shown in **Scheme 4.1**.[144]

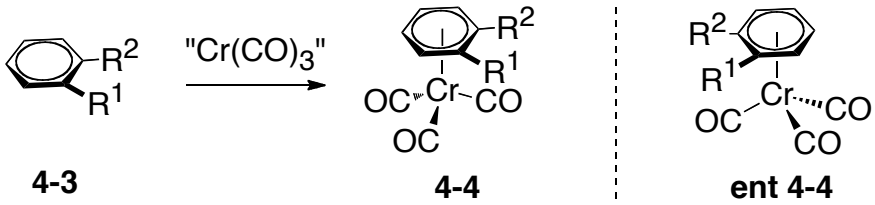
Scheme 4.1: Use of Cr-Complexed Arene as Chiral Ligand



In a multi-substituted benzene ring if the substituents are different (except for 1,4-disubstitution) the only symmetry element present is the plane of symmetry. So, if the

top and bottom half of the molecular plane can be differentiated the arene compound can be made chiral. There are several methods available to make arene rings asymmetric and one of the convenient protocols is the complexation of an easily removable $Cr(CO)_3$ fragment as is shown in **Scheme 4.2** (compound **4-4** cannot be superimposed with its mirror image ***ent*-4-4**).[144]

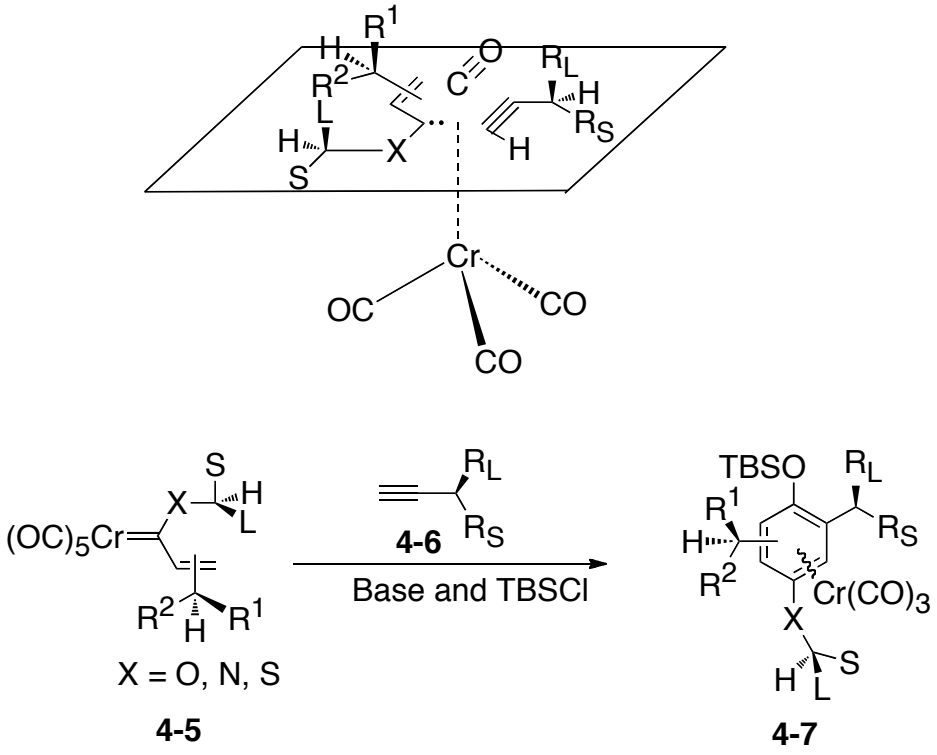
Scheme 4.2: Desymmetrization of Arenes Using Cr-Complexation



Usually, in a benzannulation reaction between a chromium carbene complex and an alkyne, the resulting product contains a $Cr(CO)_3$ unit complexed to the newly formed benzene ring. In most examples the $Cr(CO)_3$ group coordinates to the benzene ring either from top or bottom giving rise to a racemic product. There are several ways to make this reaction asymmetric. Since the arene ring is synthesized at the metal center, the asymmetric induction could occur from an existing chiral center in one of the pieces, resulting in a facial selectivity of the coordination of the chromium to the newly formed arene. As outlined in **Scheme 4.3**, three potential sources for stereoselective introduction of the $Cr(CO)_3$ group are a chiral ancillary on the heteroatom stabilizing

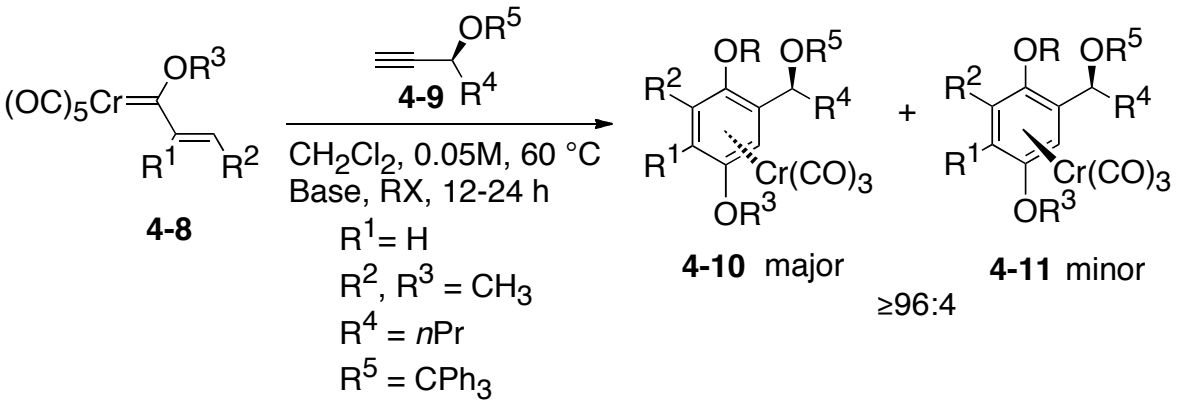
group of the carbene complex, chiral center present in the carbon substituent of the carbene complex and a chiral center present in the alkyne.[145]

Scheme 4.3: Three Potential Sources of Chiral Induction in the Benzannulation Reaction



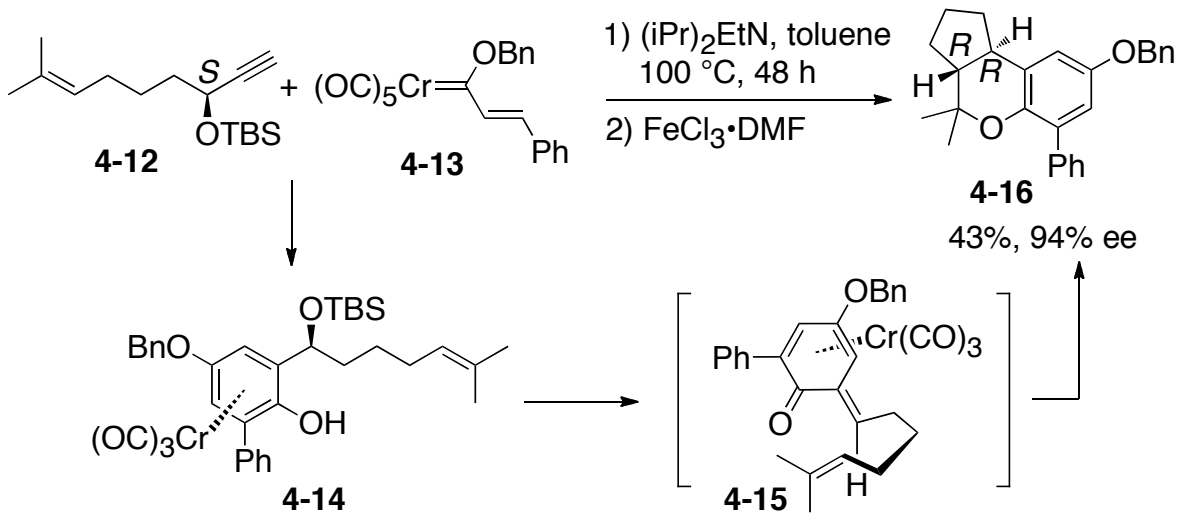
The most successful approach to date has involved the use a chiral alkyne in which the chiral center in the alkyne dictates which side of the benzene ring the chromium is delivered. Notably, our group has previously shown that very high asymmetric induction can be achieved by utilization of this approach (**Scheme 4.4**).[145a]

Scheme 4.4: Diastereoselective Benzannulation Using Chiral Alkyne



As a very efficient application of this asymmetric benzannulation, our group recently reported an excellent strategy for the asymmetric benzannulation followed by [4+2] cycloaddition.[146] The overall stereochemical outcome was termed as a traceless stereoinduction since the origin of this stereoinduction cannot be discerned by examination of the product (**Scheme 4.5**). In this method the carbene complex **4-13** underwent an asymmetric benzannulation reaction with chiral enyne **4-12** to form phenol product **4-14** which occurs with a highly diastereoselective installation of the $Cr(CO)_3$ unit. After formation of the *o*-quinone methide intermediate **4-15**, the $Cr(CO)_3$ group directs the orientation of the side chain to bring about high stereoselectivity in the subsequent Diels-Alder reaction.

Scheme 4.5: Traceless Stereoinduction

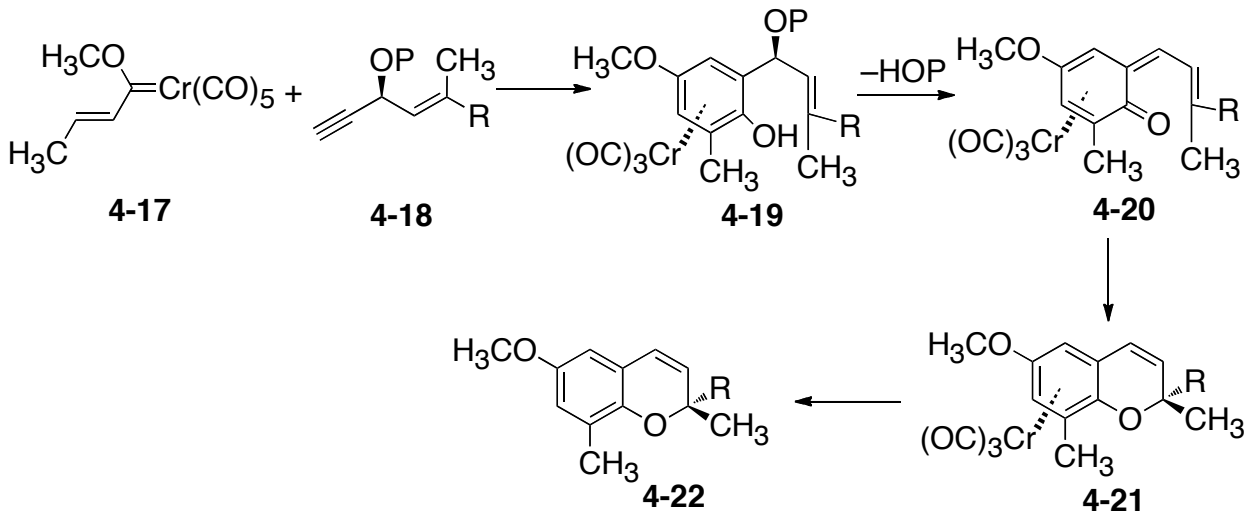


4.2. Present Work

Thus, inspired by the success of the traceless stereoinduction for the benzannulation/*o*-quinone methide formation/Diels-Alder cascade shown in **Scheme 4.5**, an investigation was undertaken aiming at the development of an asymmetric synthesis of chromene, which involving the benzannulation, *o*-quinone methide formation, and electrocyclization cascade (BQME reaction) that was the subject of Chapter 2. It was envisioned that the benzannulation reaction between chromium carbene complex **4-17** and chiral enyne **4-18** should result in the formation of the highly substituted chiral phenol complex **4-19**, with the stereoselective introduction of the $Cr(CO)_3$ group on the benzene ring. Previous observations suggest that the phenol complex **4-19** will be formed with high diastereoselection.[145a,146] Naturally, the next step would be the formation of *o*-quinone methide **4-20** followed by the electrocyclization. Importantly, this electrocyclization was expected to occur with significant asymmetric induction as a result of the presence of

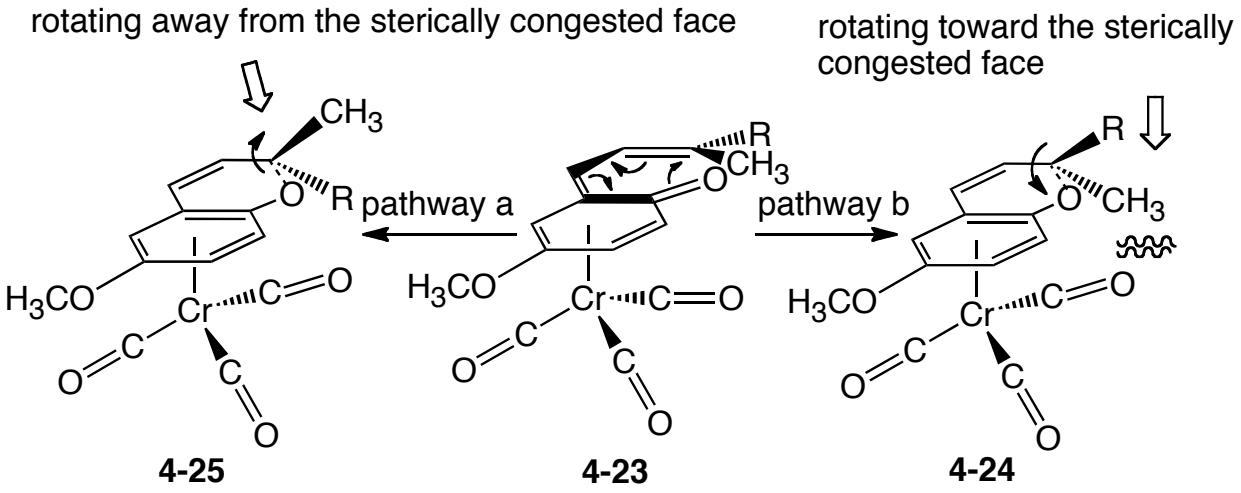
the $Cr(CO)_3$ group (**Scheme 4.6**). For convenience, this newly hypothesized protocol will be termed as ABQME (asymmetric benzannulation/ *o*-quinone methide/electrocyclization cascade) reaction.

Scheme 4.6: Asymmetric Synthesis of Chromenes via the ABQME Cascade



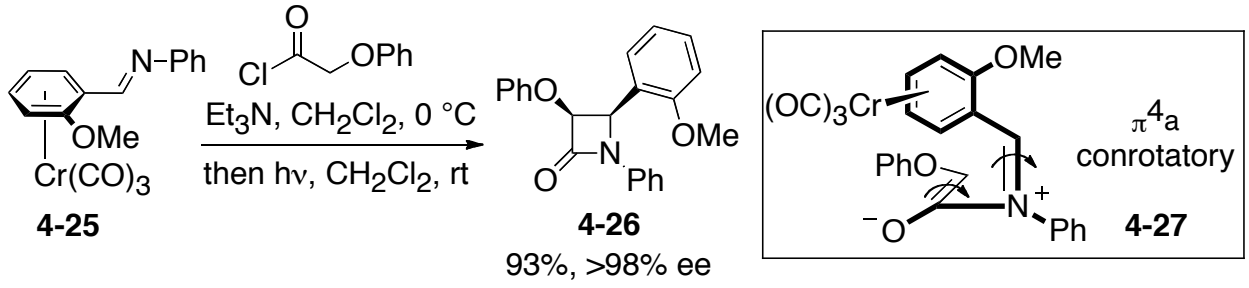
Interestingly, in the eletrocyclization step, the rotation of the alkenyl group can occur via two pathways which are indicated as “pathway a” or “pathway b” (**Scheme 4.7**). The direction if the rotation would determine the configuration of the quaternary center and this bond rotation could be influenced by the $Cr(CO)_3$ group. In case of “pathway b”, the rotation would force the angular methyl group to rotate through the congested coordination sphere of the Cr metal center and thus is expected to be less favored. On the other hand, in case of “pathway a”, the angular methyl group rotates away from the sterically congested metal center and results in the more favored configuration over that from “pathway b” (**Scheme 4.7**).

Scheme 4.7: Proposed Asymmetric Induction in Electrocyclization



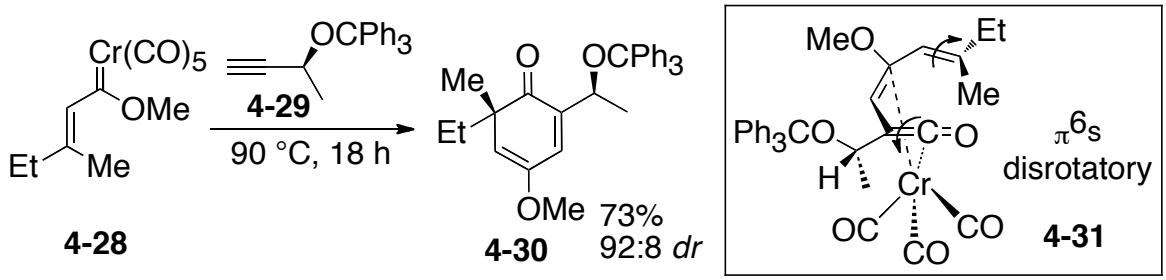
Here it should be mentioned that the asymmetric influence of a $Cr(CO)_3$ unit on an electrocyclization was previously reported in literature.[147] The Staudinger reaction of an imine derived from a chromium tricarbonyl complex of an aryl aldehyde with ketenes has been studied by Del Buttero et al[148] for a diastereoselective synthesis of β-lactams. The reaction provided the corresponding *cis*-β lactam in 98% yield as a single diastereoisomer. Subsequent photolysis of the chromium complex yielded the optically pure metal free lactam **4-26** in 95% yield (**Scheme 4.8**).

Scheme 4.8: Asymmetric Induction by a Chromium Tricarbonyl Complexed Arene in Electrocyclization



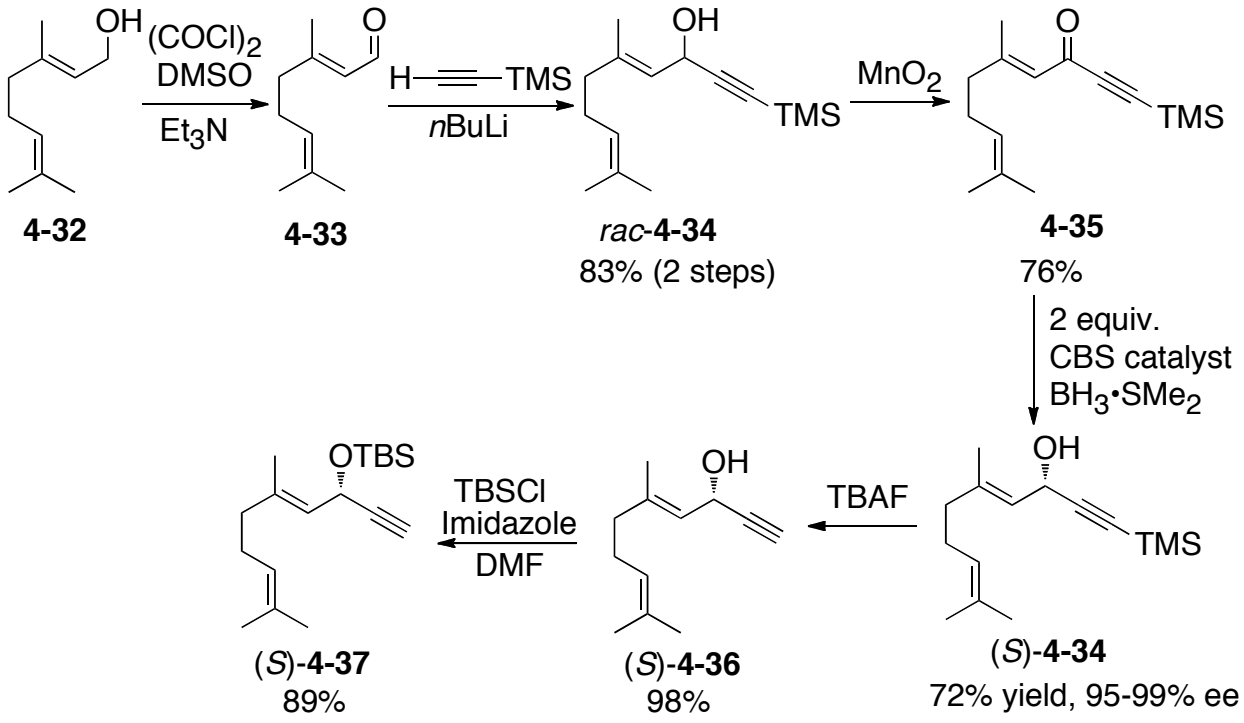
In addition, our group has also investigated the electrocyclic ring closure of metal-complexed vinyl ketenes (**Scheme 4.9**).[145b] Based on earlier work[2a] it was hypothesized that the *in-situ* generated chromium ketene complex **4-31** would be formed with high stereoselectivity, and that the observed overall diastereoselectivity for the formation of **4-30** was due to a selective 6π-electrocyclization of the ketene complex **4-31**. The major diastereomer is formed from an upward rotation of the *cis*-methyl group while the downward rotation is apparently disfavored because of the close interactions with the metal and its ligands.

Scheme 4.9: Asymmetric Induction in an Electrocyclization



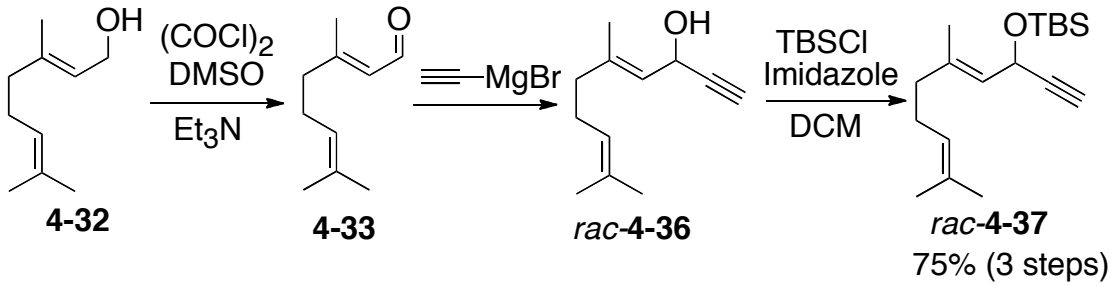
For the asymmetric synthesis of chromene, according to **Scheme 4.6** a chiral enyne would be required. The chiral enyne (*S*)-**4-37** was targeted since its synthesis could begin with geraniol **4-32** as the starting material, which would have the advantage of its low cost. Geraniol **4-32** has a double bond with an *E*-configuration. It was first converted to geranial **4-33** by a swern oxidation. There was a concern for retaining the double bond stereochemistry during this oxidation. Interestingly, it was found that the double bond geometry was unchanged under the swern oxidation conditions. Subsequently, the aldehyde **4-33** was treated with lithiated trimethylsilyl acetylene to produce the *racemic* alcohol *rac*-**4-34**. The resulting *racemic* alcohol *rac*-**4-34** was further oxidized using MnO_2 to the corresponding ketone **4-35**, which was subjected to an asymmetric CBS reduction to produce the alcohol (*S*)-**4-34** in several runs with optical purities ranging from 95-99% ee. Next, applying routine desilylation conditions, (*S*)-**4-34** could be converted to alcohol (*S*)-**4-36**, which was subsequently protected with a *tert*-butyldimethylsilyl group to give the enyne (*S*)-**4-37** (**Scheme 4.10**).

Scheme 4.10: Synthesis of Chiral Enyne from Geraniol



Before conducting the benzannulation reaction of the chiral enyne (*S*)-**4-37** with a carbene complex, the *racemic* version of the enyne *rac*-**4-37** was prepared for the purpose of optimizing the reaction conditions. The *racemic* enyne could be obtained very easily in two steps from geranial **4-33** by treatment with ethynyl magnesium bromide followed by TBS-protection of the resulting alcohol *rac*-**4-36** in 75% overall yield from geraniol **4-32** (**Scheme 4.11**).

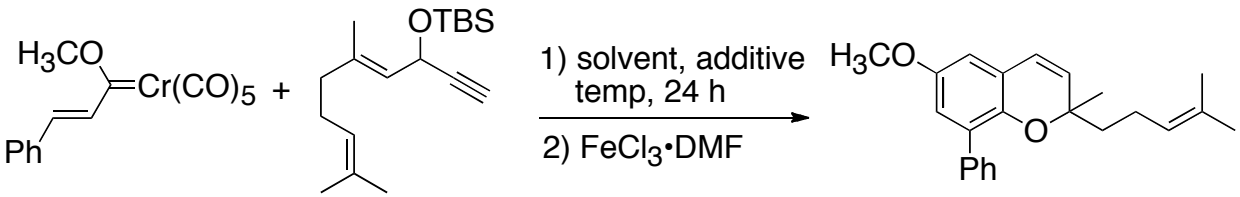
Scheme 4.11: Synthesis of Racemic Enyne *rac*-**4-37** from Geraniol



The stage was set for the optimization of ABQME reaction, and to this end a series of experiments were performed between the styryl chromium carbene complex **4-38** and *racemic* enyne *rac*-**4-37** to establish the optimal reaction conditions. The reaction was first attempted in toluene as solvent without using any additives at 80 °C for 24 h (**Table 4.1,** entry 1). But the final result was not satisfying. The product *rac*-**4-39** could be obtained in only 24% yield. In the next attempt, the reaction was conducted in dichloroethane solvent using 5 equiv of Hünig's base at 80 °C. This reaction was not clean giving a mixture of unidentified and inseparable compounds, which were not further characterized. Thus the product could not be isolated nor could the yield be determined (entry 2). Next, the reaction was carried out using the 5 equiv of Hünig's base in toluene as solvent. To our delight, the desired product *rac*-**4-39** could be obtained in 34% isolated yield (entry 3). Evidently, the reaction requires further optimization before a neat and clean result can be found. From previous experience we observed that employment of aniline as an additive exhibited a positive influence in

some cases on the racemic BQME cascade (**Table 2.5**, Chapter 2). Gratifyingly, in the present case, when the reaction was performed in toluene solvent using 10 equiv of aniline as an additive at 60 °C, the reaction showed a very clean TLC with the predominant formation of the chromene product *rac*-**4-39**. After oxidation with $FeCl_3$•DMF the chromene product *rac*-**4-39** could be isolated in 66% yield and the compound was clean both by TLC and NMR (**Table 4.1**, entry 4).

Table 4.1: Optimization for Reaction between **4-38** and *rac*-**4-37**[a]



4-38 *rac*-**4-37** *rac*-**4-39**

Entry	Solvent	Additive	Temperature (°C)	Yield (%)
1	Toluene	None	80	24
2	DCE	5 equiv (iPr)$_2$NEt	80	Not determined
3	Toluene	5 equiv (iPr)$_2$NEt	80	34
4	Toluene	10 equiv Aniline	60	66

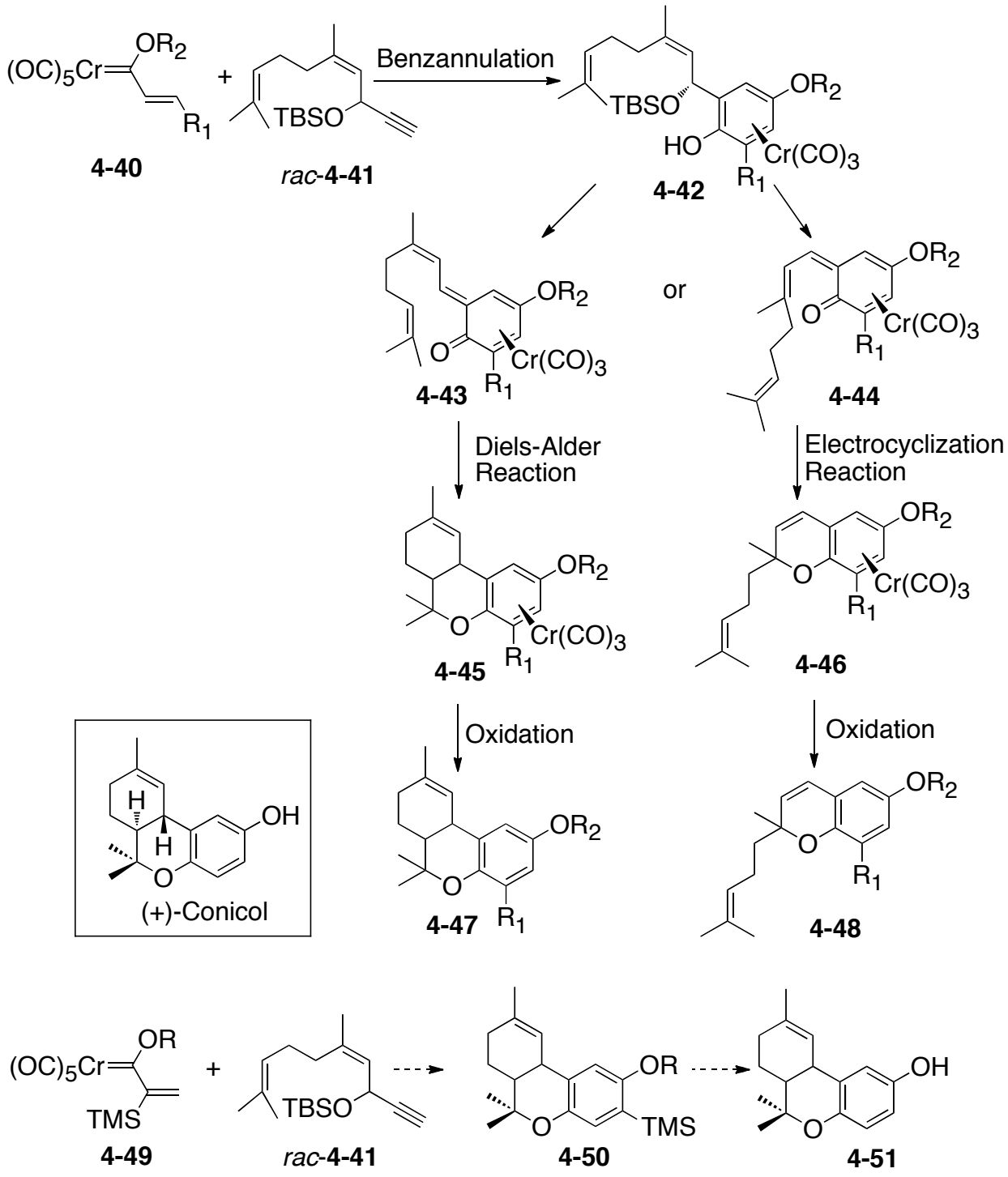
a. All the reactions were performed at 0.03 M concentration using 1.2 equiv of *rac*-**4-37**.

To this end, the method was all set to test the asymmetric synthesis of chromenes with the chiral enyne (*S*)-**4-37**.

Before performing the above-mentioned reactions on optically pure enyne (*S*)-**4-37**, we

decided to test the same reaction with the racemic enyne *rac*-**4-41**, which is the *Z*-isomer of enyne *rac*-**4-37**. This reaction was planned to set up a competition between a final electrocyclization versus a final Diels-Alder cycloaddition. As the enyne contains a double bond with *Z*-stereochemistry, the benzannulated intermediate **4-42** can open to two different *o*-quinone methide intermediates **4-43** or **4-44.** The orientation of the long side chain from the enyne can determine whether eletrocyclization or Diels-Alder addition will happen. If the side chain were oriented in such a way that the terminal double bond comes closer to *o*-quinone methide as in **4-43**, Diels-Alder addition would be the preferred reaction. To the contrary, if the orientation of the side chain brings the *Z*-double bond closer to *o*-quinone methide as in **4-44**, electrocyclization would be expected to take place. The choice between these two potential reactions can arise only in case of the enyne *rac*-**4-41** where the double bond has the *Z*-stereochemistry. Since $Cr(CO)_3$ unit should be pointing away from the propargyl ether group (OTBS) it was expected that the formation of *o*-quinone methide would prefer an E-geometry of the newly formed doule bond as in **4-43** favoring Diels-Alder reaction. Should this reaction prefer to undergo a Diels-Alder addition then it could be the basis for a different methodology, which could be applied to the synthesis of the natural product conicol (**Scheme 4.12**). Notably, conicol could be synthesized easily from the reaction of carbene complex **4-49** and enyne *rac*-**4-41** to form the benzopyran **4-50**. Desilylation of the benzopyran **4-50** eventually can afford the conicol **4-51** (**Scheme 4.12**).

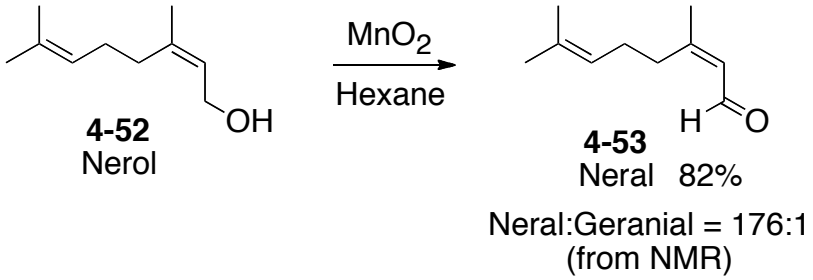
Scheme 4.12: Electrocyclization or Diels-Alder



To examine this hypothesis, first enyne *rac*-**4-41** needed to be prepared. The first step

was the oxidation of nerol **4-52** to its corresponding aldehyde neral **4-53**. The main concern for this oxidation reaction was the loss of double bond stereochemistry. As the starting compound has the *Z*-stereochemistry of double bond, there was great concern that once the oxidation would occur and the double bond would be in conjugation with the carbonyl, the double bond geometry could isomerize from *Z* to *E* as *E*-alkenes are thermodynamically more stable. However, reports in the literature[149] indicate that for the oxidation of allyl alcohols to the corresponding aldehydes the double bond stereochemistry is completely retained with MnO_2 as the oxidant. Fortunately application of the same conditions in the present case also gave retention of stereochemistry in the product enal **4-53**. In the oxidation of nerol **4-52** to neral **4-53** the ratio of neral **4-53** to geranial **4-33** was found to be 176:1 from ^{1}H NMR (based on integration of the aldehyde protons) (**Scheme 4.14**).

Scheme 4.13: Stereoselective Oxidation of Nerol



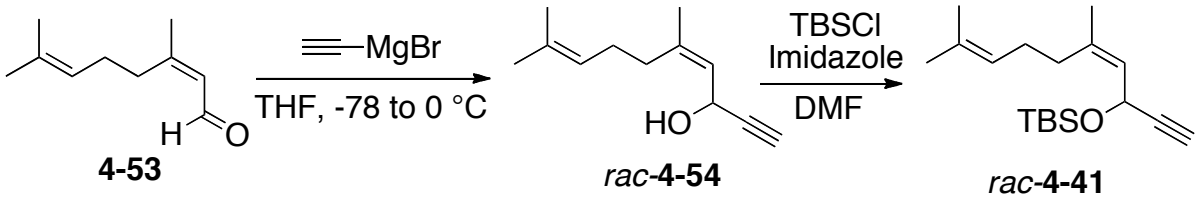
4-52
Nerol

4-53
Neral 82%

Neral:Geranial = 176:1
(from NMR)

So from neral **4-53** the *racemic* enyne *rac*-**4-41** was prepared by addition of ethynyl Grignard to produce the alcohol *rac*-**4-54** followed by TBS protection (**Scheme 4.14**).

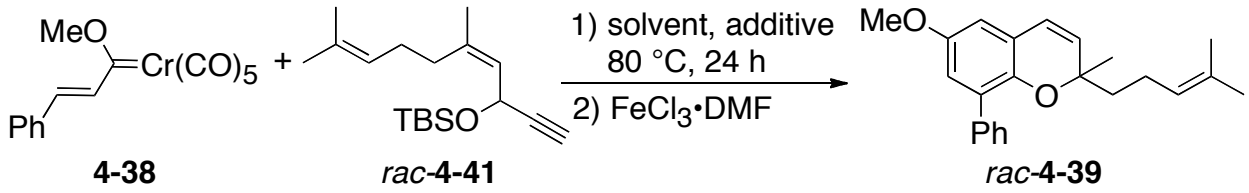
Scheme 4.14: Synthesis of Racemic Enyne *rac*-**4-41** from Nerol **4-52**



4-53 *rac*-**4-54** *rac*-**4-41**
78% over 2 steps

As the enyne *rac*-**4-41** was ready, the reaction was tested with the styryl carbene complex **4-38**. Two possibilities were expected in the product: (i) benzoyran derivative of the type **4-47** by the Diels-Alder pathway or (ii) chromene *rac*-**4-39** by the electrocyclization pathway. Experimentally it was observed that this reaction prefers electrocyclization to Diels Alder and gives the chromene product *rac*-**4-39** in very good yields in toluene, dichloromethane and also in acetonitrile solvents (**Table 4.2**). It was quite surprising as it was discussed before in **Scheme 4.12** that because of the preferred anti-orientation of OTBS group and $Cr(CO)_3$ the formation of the *o*-quinone methide **4-43** would be preferred and therefore the Diels-Alder pathway. However the experimental results showed the formation of electrocyclization products.

Table 4.2: Optimization of the Reaction between Carbene Complex **4-38** and *Z*-Enyne *rac*-**4-41**[a]



4-38 *rac*-**4-41** *rac*-**4-39**

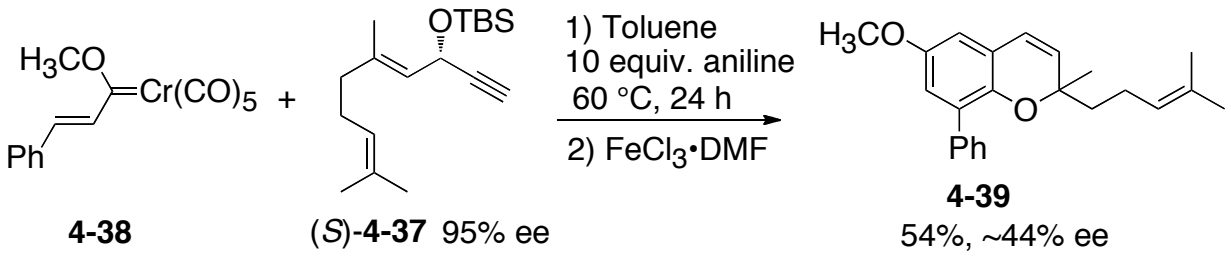
Entry	Solvent	Additive	Yield (%)
1	Toluene	None	77
2	CH_2Cl_2	None	68
3	MeCN	None	76
4	Toluene	5 equiv $(i\text{Pr})_2\text{NEt}$	57
5	Toluene	10 equiv Aniline	90

a. All the reactions were performed at 0.03 M concentration using 1.2 equiv of *rac*-**4-41.**

It was also interesting to examine the effect of additives on this reaction. Thus, the reaction was repeated in toluene in presence of 5 equiv of Hünig's base. However, this reaction was not as clean and the product *rac*-**4-39** could be isolated in 57% yield (**Table 4.2**, entry 4). Pleasingly, when the same reaction was repeated in toluene in the presence of 10 equiv of aniline, the reaction was extremely clean affording a 90% yield of the chromene product *rac*-**4-39** (entry 5). The Diels-Alder product was not detected in any of the reactions (**Table 4.2**).

After this observation, we turned our attention toward the asymmetric synthesis of chromenes. The ABQME reaction between the styryl carbene complex **4-38** and the chiral enyne (*S*)-**4-37** that was of 95% optical purity was performed at 60 °C in toluene in the presence of 10 equiv of aniline as an additive for 24 h. The chromene was obtained in 54% yield and in about 44% ee (the enantiomers could not be fully separated in HPLC). Although, the observed enantioselectivity was obviously not as high as we would have liked, nonetheless, this first attempt was encouraging enough to be indicative for further optimization (**Scheme 4.15**).

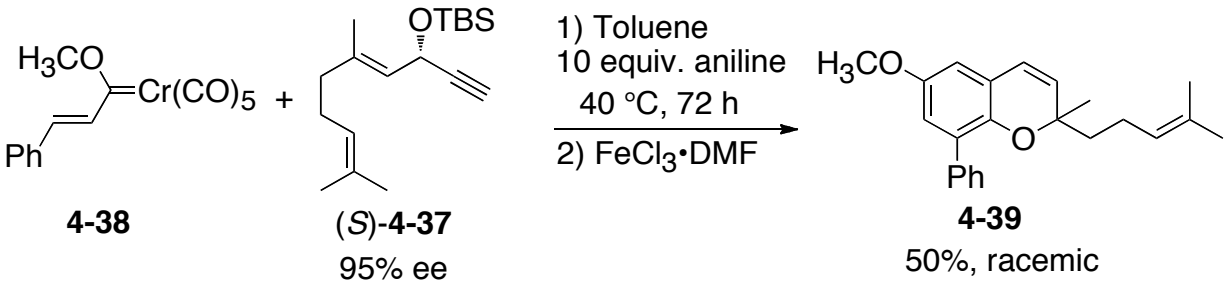
Scheme 4.15: First Attempt for the Reaction between **4-38** and (S)-**4-37**



4-38 (*S*)-**4-37** 95% ee **4-39** 54%, ~44% ee

The reaction was also conducted under the same conditions at a lower temperature (40 °C) in an attempt to improve the enantioselectivity. However, the reaction required a much longer time (72 h) to reach completion while no significant asymmetric induction was observed (**Scheme 4.16**).

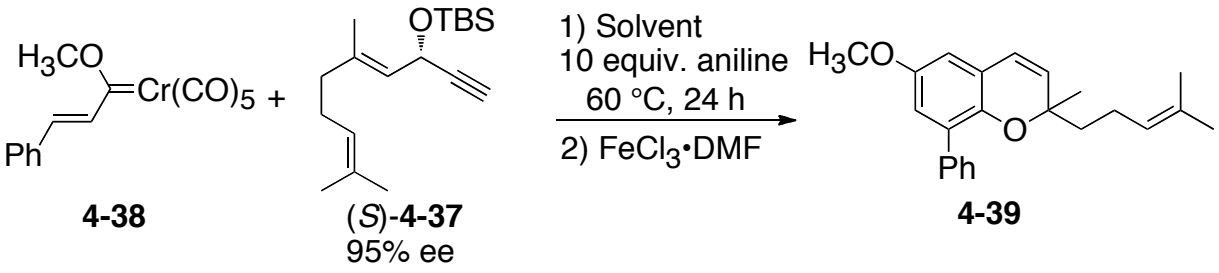
Scheme 4.16: Reaction of **4-38** and (*S*)-**4-37** at Lower Temperature



4-38 (*S*)-**4-37** 95% ee **4-39** 50%, racemic

The same reaction was also repeated in three different solvents, which were benzene, dichloromethane and hexane. All these attempts did not work successfully as the enantiomers of the chromene product could not be separated completely in HPLC even after trying several different conditions on different columns (**Table 4.3**). Although the enantiomers were not completely separated, it was easily seen that the products were almost racemic.

Table 4.3: Reaction between **4-38** and (*S*)-**4-37** in Different Solvents[a]



4-38 (*S*)-**4-37** 95% ee **4-39**

Entry	Solvent	Yield (%)	ee (%)
1	Benzene	52	Not determined
2	CH_2Cl_2	55	Not determined
3	Hexane	56	Not determined

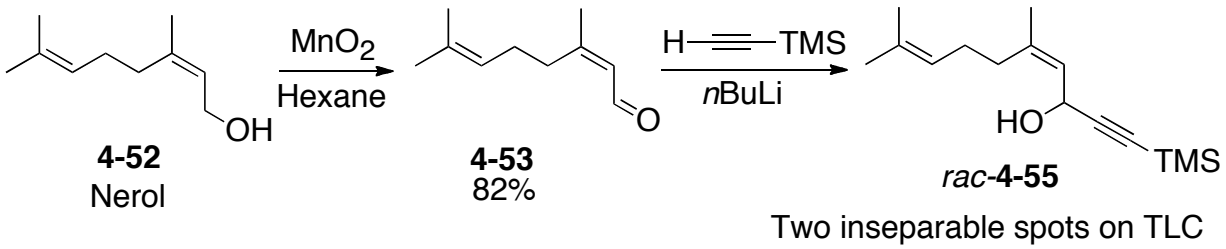
a. All the reactions were performed at 0.03 M concentration using 1.2 equiv of (*S*)-**4-37.**

From the previous results, comparing the reactions of styryl carbene complex **4-38** with *E*-enyne *rac*-**4-37** and *Z*-enyne *rac*-**4-41**, it was noticed that the reaction with *Z*-enyne *rac*-**4-44** gave much better result in terms of the yield of the product (**Table 4.2** vs **Table 4.1**). This observation was encouraging enough to lead to the investigation of the reaction between the styryl carbene complex **4-38** and the chiral version of *Z*-enyne (*S*)-**4-41** to see if increased yields and enantioselectivity would be observed for the chromene product **4-39**.

The synthesis of chiral enyne (*S*)-**4-41** was attempted in similar fashion to the method by which chiral *E*-enyne (*S*)-**4-37** was prepared (**Scheme 10**). However, in the second step, the reaction between neral **4-53** and lithiated trimethylsilyl acetylene failed to selectively give the alcohol product *rac*-**4-55**. Instead two inseparable compounds were

observed by TLC (**Scheme 4.17**).

Scheme 4.17: Attempted Synthesis of Chiral *Z*-Enyne (*S*)-**4-41** from Nerol **4-52**



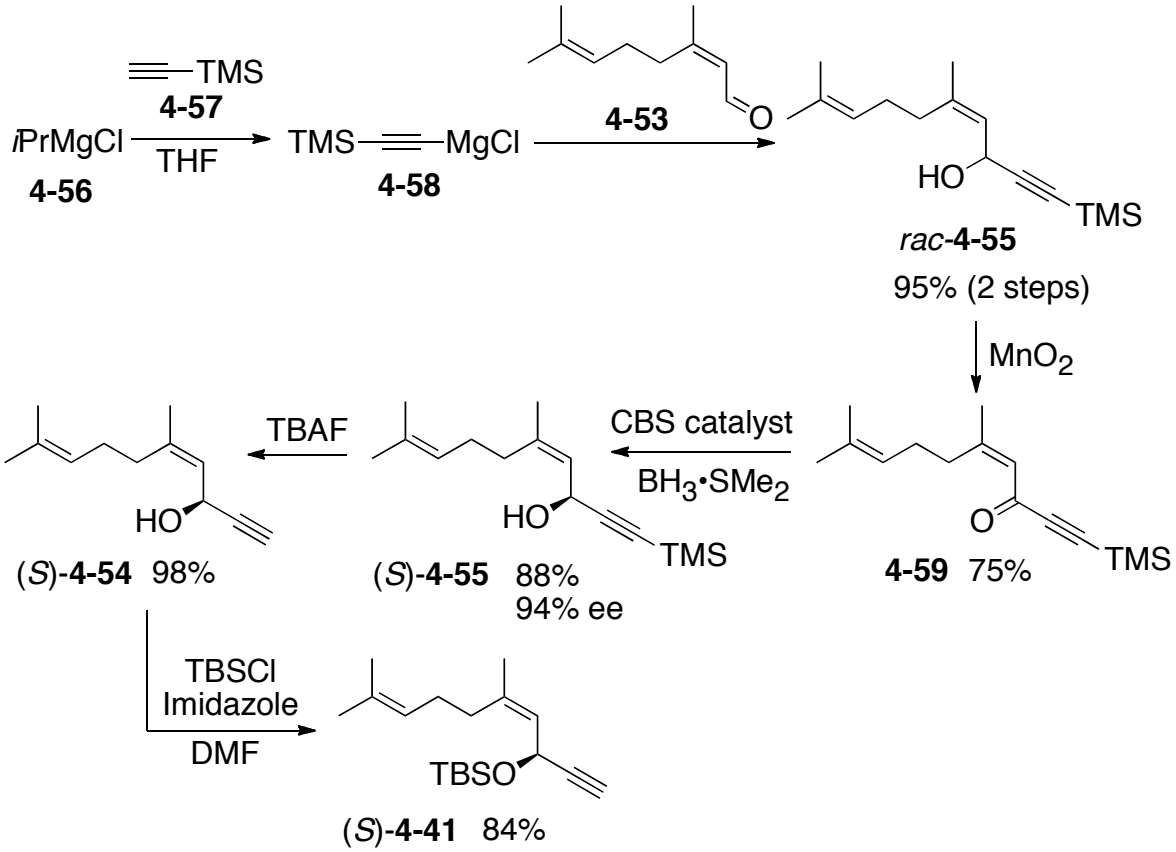
4-52
Nerol

4-53
82%

rac-**4-55**
Two inseparable spots on TLC

So the method required modification and in a new route the Grignard reagent **4-58** was prepared from trimethylsilyl acetylene and added to freshly prepared neral **4-53** (**Scheme 4.18**). Unlike the reaction with the lithium acetylide, in **Scheme 4.17**, this reaction with the corresponding Grignard selectively gave the alcohol *rac*-**4-55** in very high yield (94%). The rest of the synthesis was done following the same steps used in the synthesis of chiral enyne (*S*)-**4-41** without any complications. CBS reduction installed the chiral center in (*S*)-**4-55** successfully with 94% enantioselectivity (**Scheme 4.18**).

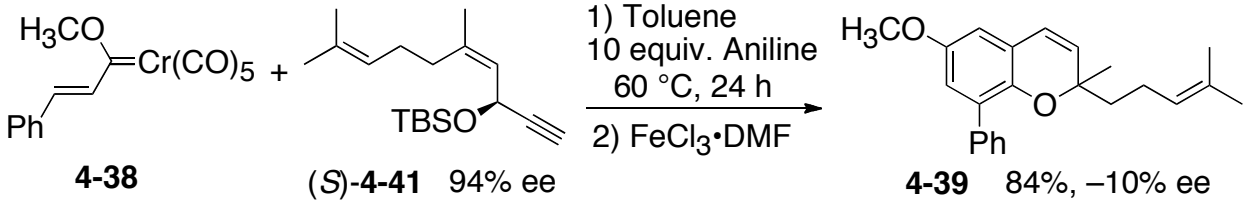
Scheme 4.18: Synthesis of Chiral Enyne (*S*)-**4-41** from Neral **4-53**



With this newly prepared chiral *Z*-enyne (*S*)-**4-41** the ABQME reaction with styryl carbene complex **4-38** was repeated under the same conditions as that developed for *E*-enyne (*S*)-**4-37** (**Scheme 4.15**). The chromene product **4-39** was obtained in 84% yield (**Scheme 4.19**). The enantioselectivity of the product **4-39** seemed to be very low (about 10% ee) and the enantiomers could not be completely separated in chiral HPLC even after trying several columns and different conditions. But a very interesting finding was observed about the enantioselectivity. It was noticed that the major enantiomer was actually the opposite enantiomer to what we observed for the reaction of *E*-enyne (*S*)-**4-**

37 (**Scheme 4.19**).

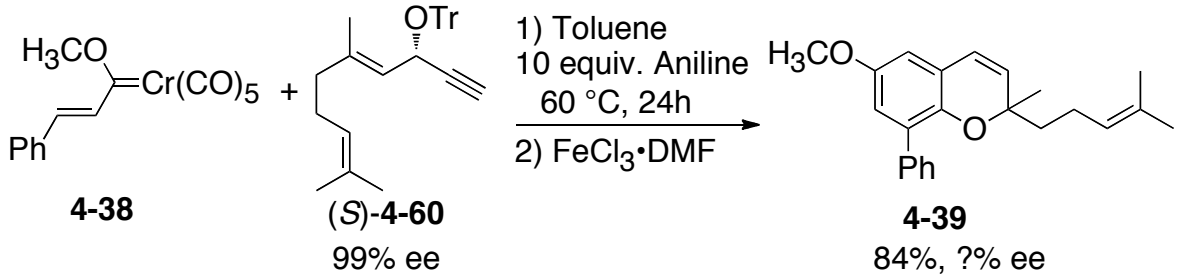
Scheme 4.19: Reaction between **4-38** and (*S*)-**4-41**



4-38 (*S*)-**4-41** 94% ee **4-39** 84%, –10% ee

For the reaction of the carbene complex **4-38** and enyne (*S*)-**4-60**, the protecting group was changed in the enyne. In a previous report[145b] it was observed that the diastereoselection in the product **4-10** in the reaction between carbene complex **4-8** and chiral alkyne **4-9** (a propargyl ether) (**Scheme 4.4**), is a function of the protecting group on the alcohol moiety. Specifically, it was found that a change of protecting group from *tert*-butyldimethylsilyl group to the much bulkier trityl group increased the selectivity significantly. In the present reaction changing the alcohol protecting group from TBS to trityl in the enyne (*S*)-**4-60** seemed to increase the enantioselectivity in the chromene product **4-39**. However, the enantiomers could not be completely separated after examining several different HPLC columns and so the exact enantioselectivity could not be determined (**Scheme 4.20**).

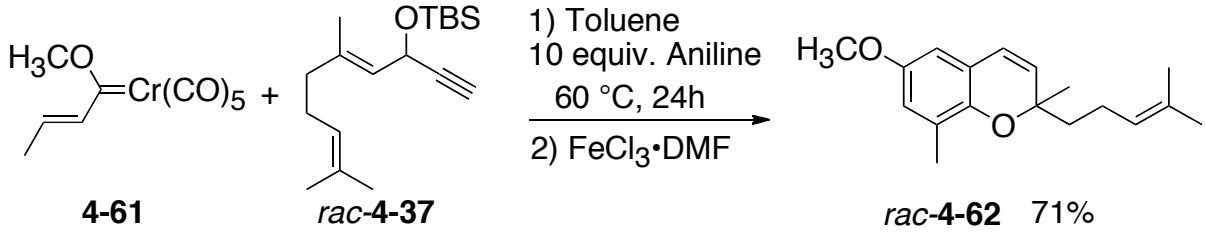
Scheme 4.20: Reaction between **4-38** and (*S*)-**4-60**



4-38 (*S*)-**4-60** 99% ee **4-39** 84%, ?% ee

At this point in an effort to avoid the problem of overlapping enantiomers in HPLC, which created problems for the determination of the enantioselectivity, the carbene complex was changed so that a different chromene product will be produced in the reaction. The first attempt was to use propenyl carbene complex **4-61** and fortunately the enantiomers of the resulting chromene *rac*-**4-62** could be separated successfully by HPLC using Chiralcel OD-H column (**Scheme 4.21**).

Scheme 4.21: Reaction between **4-61** and *rac*-**4-37**

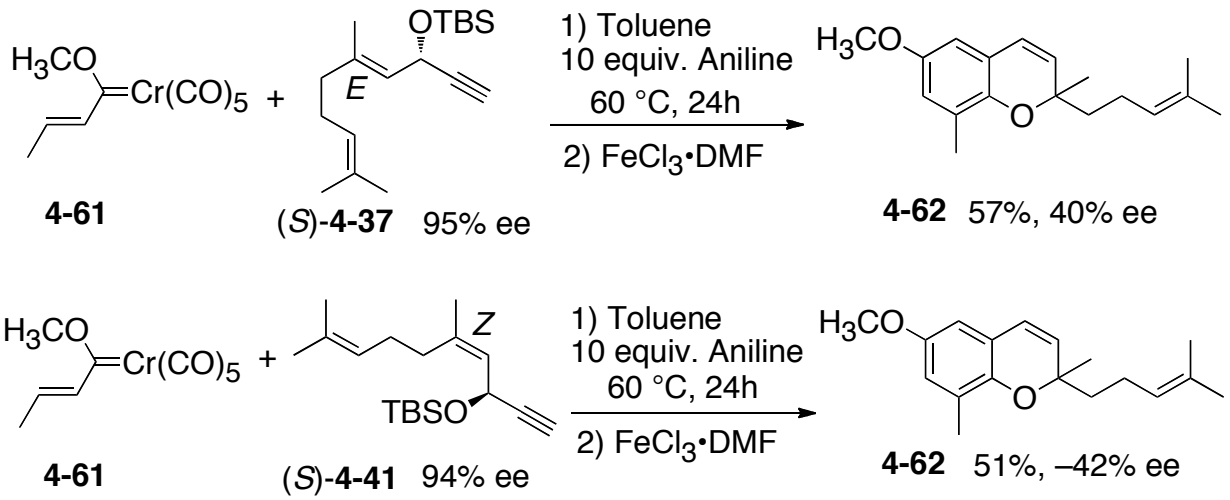


4-61 *rac*-**4-37** *rac*-**4-62** 71%

The asymmetric synthesis of chromenes was examined by reacting this new carbene complex **4-61** with *E*-enyne (*S*)-**4-37** and *Z*-enyne (*S*)-**4-41**. The enantioselectivity of the

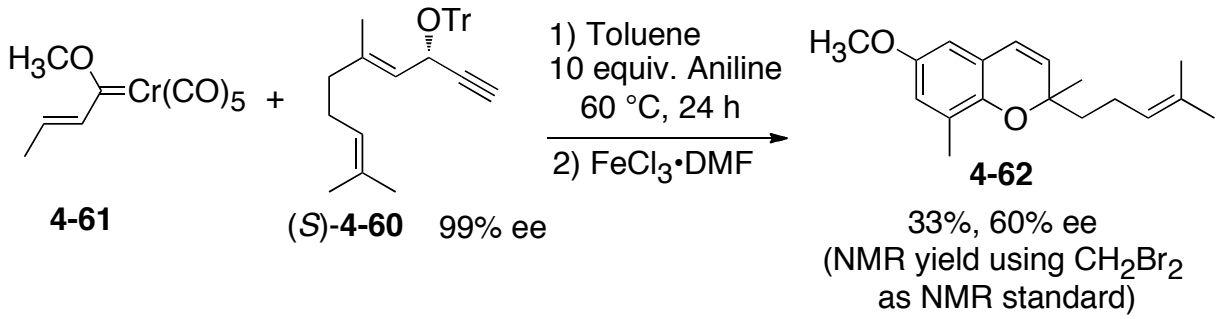
product **4-62** was 40% ee for the *E*-enyne (*S*)-**4-37** and –42% ee for the *Z*-enyne (*S*)-**4-41** (**Scheme 4.25**). This confirms the earlier observation that the enyne with *Z*-stereochemistry about the double bond produced the opposite enantiomer of the chromene product than that was observed with the *E*-enyne (*S*)-**4-37** (**Scheme 4.15** vs **Scheme 4.19**).

Scheme 4.22: Opposite Enantiomers from Enynes with Different Double Bond Geometry



When the carbene complex **4-61** was treated with enyne (*S*)-**4-60** with a trityl protecting group on its alcohol moiety the product **4-62** was produced in 60% ee, which was a significant improvement over the corresponding TBS protected enyne (*S*)-**4-37** (**Scheme 4.22** vs **Scheme 4.23**).

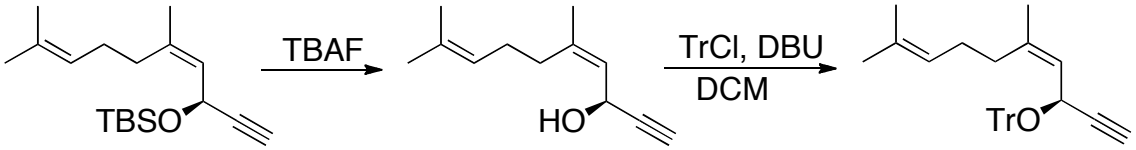
Scheme 4.23: Reaction between Carbene Complex **4-61** and Trityl *E*-Enyne (*S*)-**4-60**



4-61 (*S*)-**4-60** 99% ee **4-62** 33%, 60% ee (NMR yield using CH_2Br_2 as NMR standard)

With the improved induction observed for the trityl protected *E*-enyne (*S*)-**4-60** it became of interest to study the same reaction with trityl protected *Z*-enyne (*S*)-**4-63**. For the synthesis of this compound, enyne (*S*)-**4-41** (94% ee) was desilylated with TBAF to form alcohol (*S*)-**4-54** which was then protected with the trityl group to give (*S*)-**4-63** in a 92% yield (**Scheme 4.24**).

Scheme 4.24: Conversion of (*S*)-**4-41** to (*S*)-**4-63**

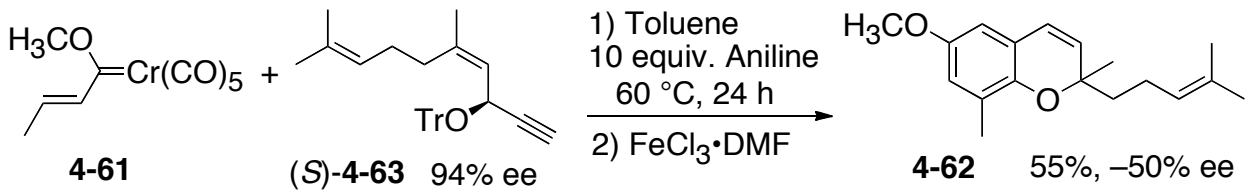


(*S*)-**4-41** 94% ee (*S*)-**4-54** 95% (*S*)-**4-63** 92%

In the reaction between the carbene complex **4-61** and *Z*-enyne (S)-**4-63** the chromene **4-62** was obtained with the major enantiomer opposite to that for the *E*-trtyl-enyne (*S*)-**4-60** but with a slightly lower absolute value for the induction (–50% ee) (**Scheme 4.25**). This fact yet again confirms that the stereochemistry of the double bond plays a vital

role in setting the configuration of the new chiral quaternary center.

Scheme 4.25: Reaction between **4-61** and (*S*)-**4-63**



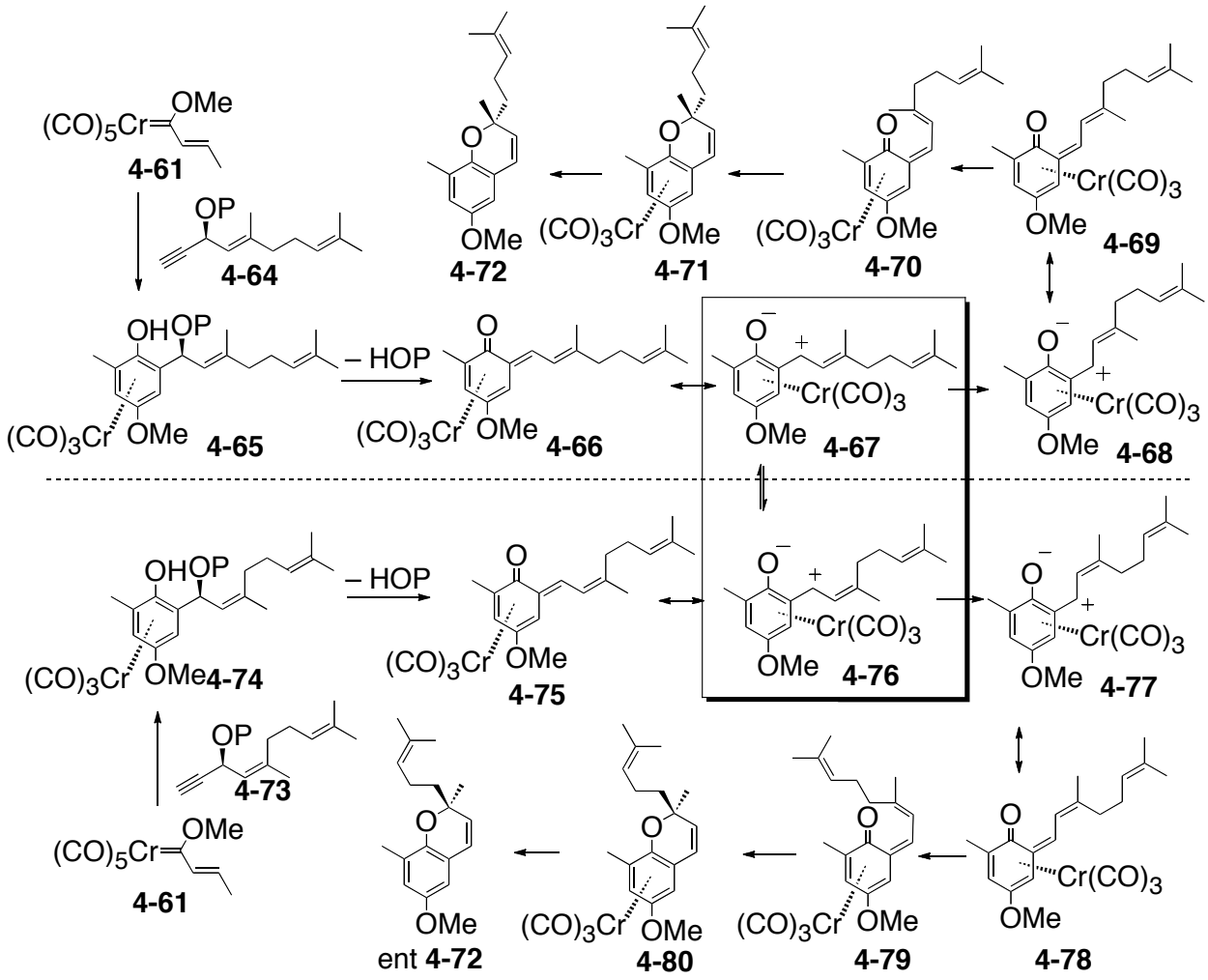
4-61 (*S*)-**4-63** 94% ee **4-62** 55%, –50% ee

4.3. Mechanistic Investigation

To explain the relationship between the double bond geometry and the absolute configuration of the chromene a mechanism was proposed as shown in **Scheme 4.26**. The mechanism shows that the reactions of the two different enynes **4-64** and **4-73** with the carbene complex **4-61** follow similar pathways. First the asymmetric benzannulation reaction with the chiral enyne stereoselectively installs the $Cr(CO)_3$ group in the resulting phenol products **4-65** and **4-74**. This is then followed by the *o*-quinone methide formation. *o*-Quinone methides **4-66** and **4-75** can be written as resonance structures **4-67** and **4-76**, which can undergo a single bond rotation to give **4-69** and **4-78**. With another bond rotation the *E*- or *Z*-double bond comes close to the *o*-quinone methide oxygen in intermediates **4-70** and **4-79** so that the electrocyclization can take place. A discussion as to how $Cr(CO)_3$ moiety might influence the asymmetric induction in this electrocyclization step has already been presented (**Scheme 4.7**) which creates the new chiral quaternary center. So obviously the position and influence of the $Cr(CO)_3$

group and also the stereochemistry of the double bond can play a very important role in determining the configuration of the new chiral center.

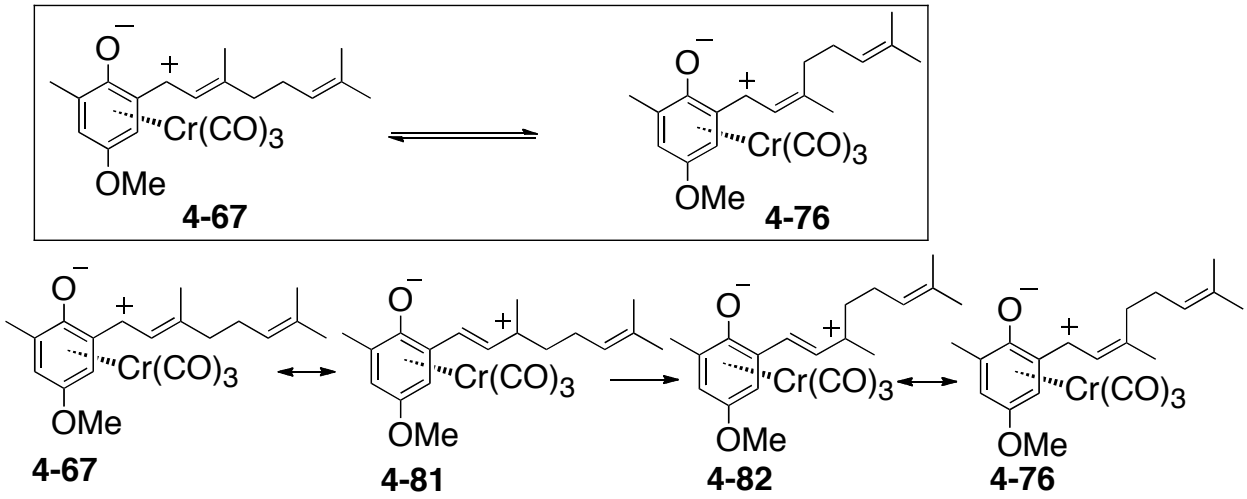
Scheme 4.26: Proposed Mechanism



The biggest limitation of this reaction that could be found from the analysis of this mechanism is the possibility of a stereochemical interconversion between structures **4-67** and **4-76** by extended resonance and bond rotation (**Scheme 4.27**). This interconversion is also believed to be responsible for the loss of enantioselectivity in the

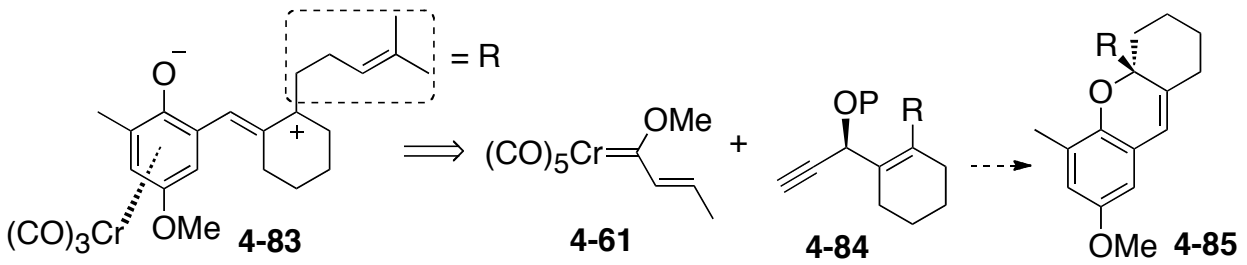
final chromene product because potentially it is the source of a leakage between the pathways to the two opposite enantiomers.

Scheme 4.27: Interconversion of **4-67** and **4-76**



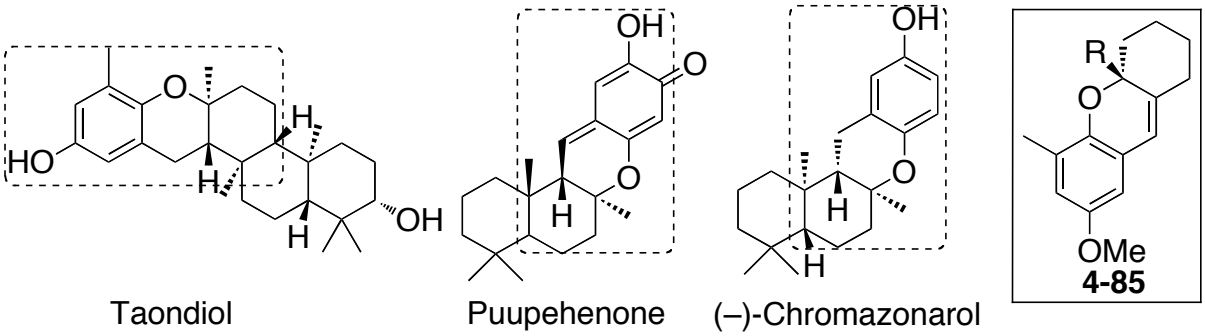
Thus, it would be a very good test reaction if the single bond rotation, which is responsible for the interconversion between **4-67** and **4-76**, could be prevented by locking it in a ring such as in cation **4-83** shown in **Scheme 4.28** below. In this way, if the mechanistic predictions are correct, a very high enantioselectivity can be expected in the chromene product **4-85**.

Scheme 4.28: Test reaction



In addition it was also found that chromene units of the type **4-85** occur in a number of biologically important natural products[150] and a few are shown in **Figure 4.1** that include the same core structure as **4-85**.

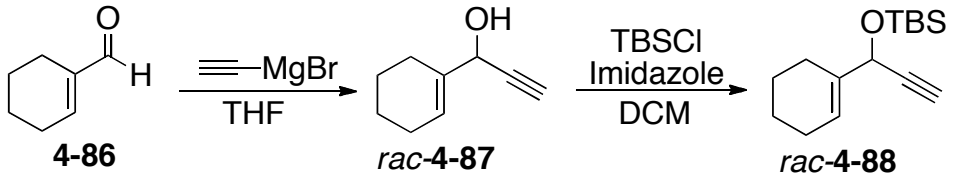
Figure 4.1: Natural Products Containing **4-85** Structure



Taondiol Puupehenone (–)-Chromazonarol

To make this test reaction successful, an enyne with a structure similar to as **4-85** was required. Initially, aldehyde **4-86** was chosen as the starting compound, which was converted to compound *rac*-**4-88** as the test enyne (**Scheme 4.29**).

Scheme 4.29: Preparation of Terminal Enyne *rac*-**4-88** from **4-86**

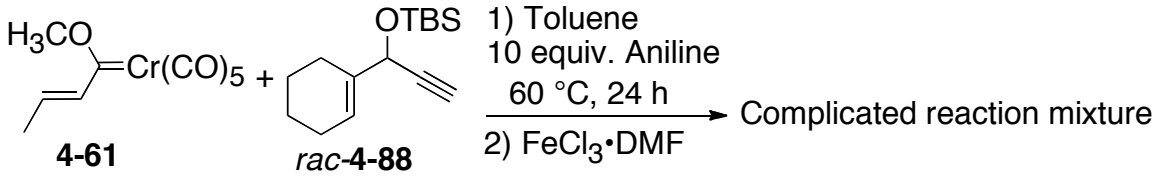


4-86 *rac*-**4-87** *rac*-**4-88**
72% (2 steps)

Unfortunately, the reaction between carbene complex **4-61** and enyne *rac*-**4-88** failed to

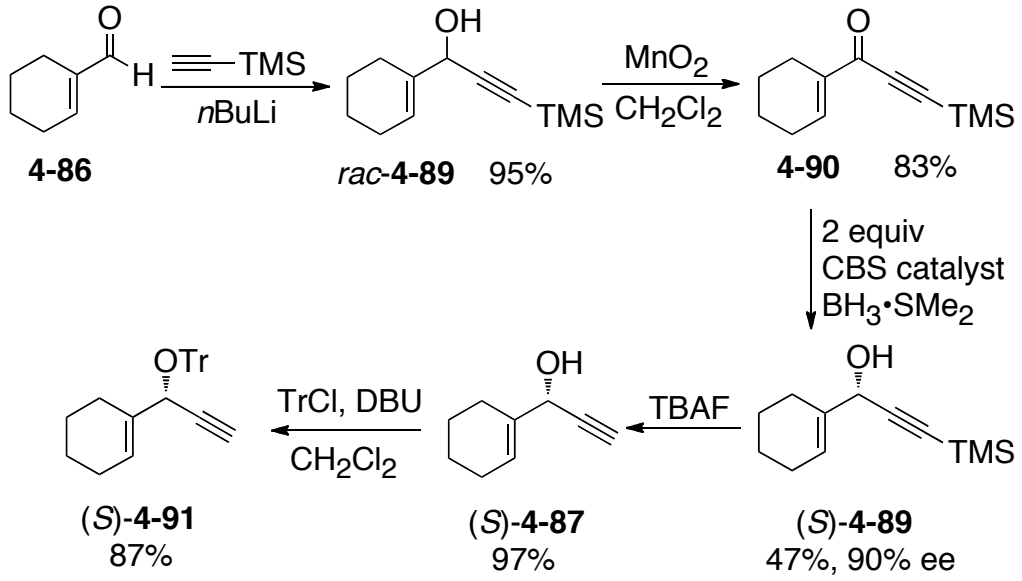
give the expected chromene product. The result was a complicated mixture of products and absorptions for the expected chromene product could not be identified in the crude ^{1}H NMR spectrum (**Scheme 4.30**).

Scheme 4.30: Reaction between Carbene Complex **4-61** and Enyne *rac*-**4-88**



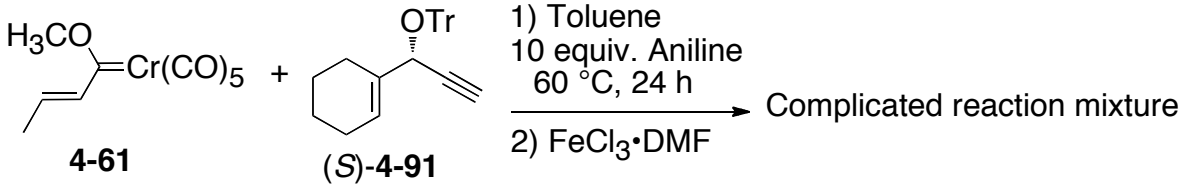
Simultaneously, the chiral enyne (*S*)-**4-91** was also prepared from 1-cyclohexene carboxaldehyde **4-86** in 90% ee. Notably, the CBS reduction of compound **4-90** was a little difficult. The reaction was warmed to 0 °C and was run for over 6 h however, the reaction still did not go to completion. This was the reason that the yield for the asymmetric reduction was low (47%). The alcohol (*S*)-**4-87** was protected with a trityl group to form the chiral enyne (*S*)-**4-91** (**Scheme 4.31**).

Scheme 4.31: Synthesis of Chiral Enyne (*S*)-**4-91**



A change in the protecting group did not change the outcome as both the reactions of compounds **4-61** and (*S*)-**4-91** (**Scheme 4.32**), and the reaction between **4-61** and *rac*-**4-88** (**Scheme 4.30**) provided a complicated mixture of products, which was not characterized.

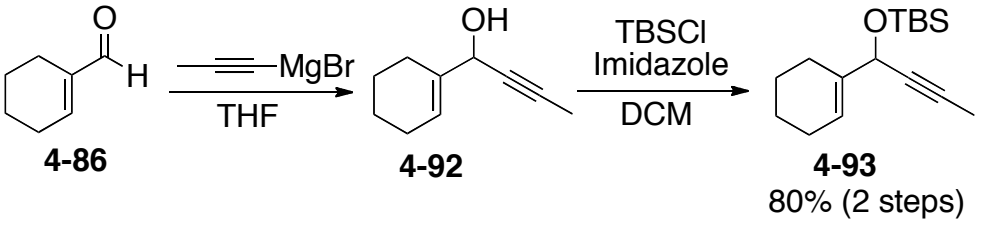
Scheme 4.32: Reaction between **4-61** and (*S*)-**4-91**



It is generally known[151] that benzannulation reaction works better with internal alkynes

than with terminal alkynes (**Table 3.2** vs **Scheme 3.19**, Chapter 3). So the next attempt at testing the mechanism in **Scheme 4.26** was to synthesize the internal enyne **4-93** which could be made very easily in two steps as shown in **Scheme 4.33** from the aldehyde **4-86** following the same procedure used in the synthesis of *rac*-**4-88** (**Scheme 4.29**).

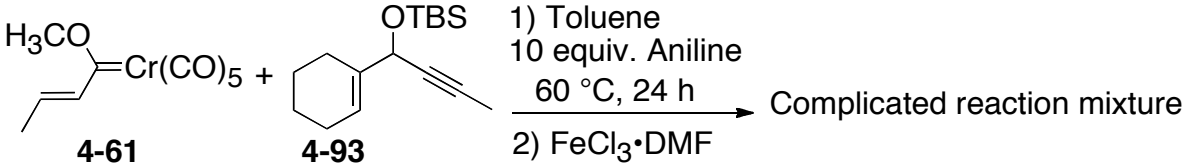
Scheme 4.33: Preparation of Internal Enyne **4-93** from **4-86**



4-86 **4-92** **4-93**
80% (2 steps)

The reaction between the carbene complex **4-61** and the internal enyne **4-93** also failed to produce the clean formation of a chromene product following the optimized conditions (**Scheme 4.34**). Instead a complicated reaction mixture was obtained which was not processed any further.

Scheme 4.34: Reaction between **4-61** and **4-93**

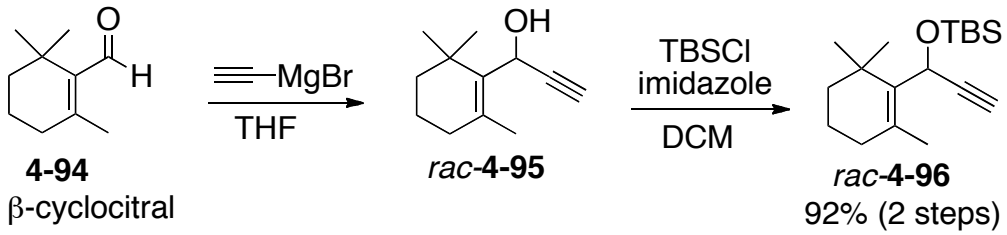


4-61 **4-93**

After the failures to obtain clean reactions with enynes *rac*-**4-88**, (*S*)-**4-88**, and *rac*-**4-93**,

the enyne *rac*-**4-96** was targeted which is a trimethyl analog of *rac*-**4-88** and should be easy to prepare from the commercially available β-cyclocitral **4-94**. The terminal enyne *rac*-**4-96** was prepared following the standard method in 92% overall yield as shown in **Scheme 4.35**.

Scheme 4.35: Preparation of Terminal Enyne *rac*-**4-96** from **4-94**



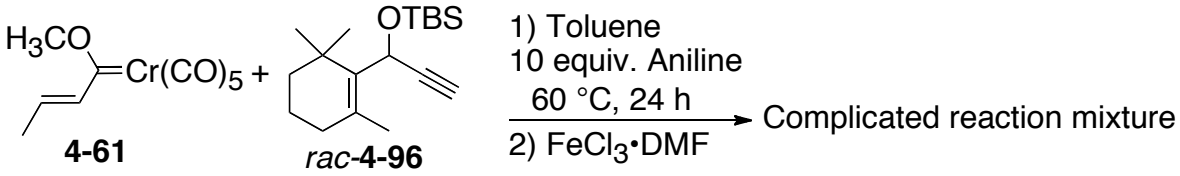
4-94
β-cyclocitral

rac-**4-95**

rac-**4-96**
92% (2 steps)

Unfortunately, under the same optimized conditions the reaction between the carbene complex **4-61** and the new enyne *rac*-**4-96** also failed to produce a clean formation of the chromene product (**Scheme 4.36**).

Scheme 4.36: Reaction between **4-61** and *rac*-**4-96**

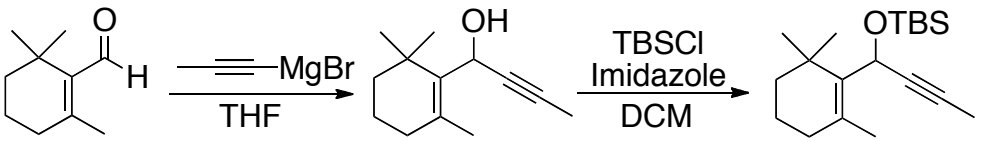


4-61

rac-**4-96**

In the continued pursuit of this enyne architecture, the internal eyne **4-98** was then prepared from the β-cyclocitral **4-94** (**Scheme 4.37**).

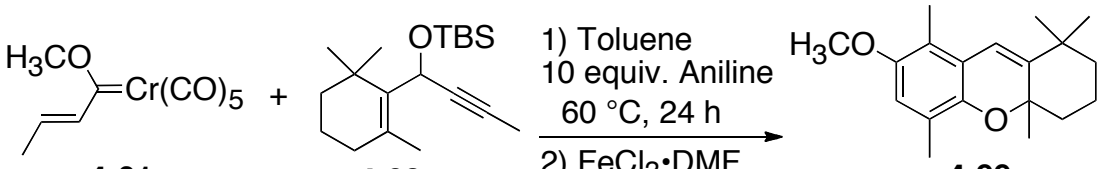
Scheme 4.37: Preparation of Internal Enyne **4-98** from **4-94**



4-94 **4-97** **4-98**
90% (2 steps)

Interestingly, the reaction between carbene complex **4-61** and enyne **4-98** gave a trace amount of the chromene product **4-99** as detected by TLC as well as by the ^{1}HNMR spectrum of the crude reaction mixture. However, the compound could not be isolated as it was part of an inseparable mixture with other unidentifiable compounds and also because the amount of chromene product produced in the reaction was very low (**Scheme 4.38**).

Scheme 4.38: Reaction between **4-61** and **4-98**

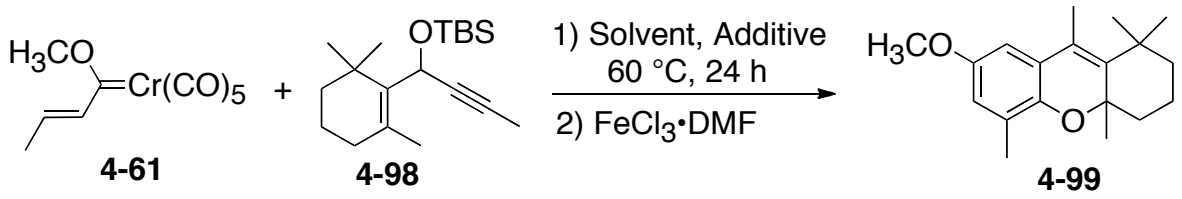


4-61 **4-98** **4-99**
trace amount

At this point, it was quite clear that the test reaction did give the chromene product with the particular reacting partners **4-61** and **4-98** albeit in very low yield. Nonetheless, the fact that some chromene was observed prompted a reconsideration of the optimization

of these reactions. Several different conditions were attempted by changing solvent and additive. The reaction was also tried without any additives in toluene and acetonitrile solvents. In three cases the chromene product was observed (**Table 4.4**). In the reaction where 5 equiv of Hünig's base was used in toluene as the solvent, the product was observed by TLC but the crude mixture was not further processed, as the reaction mixture was quite complex. However, the reactions in toluene and acetonitrile solvents exhibited promising results with predominant formation of the chromene product **4-99**. So the product was purified in each case to determine the yield. In case of the reaction in acetonitrile, the oxidation step was not necessary but for the reaction in toluene, the reaction mixture was subjected to oxidation with $FeCl_3$•DMF to get rid of the chromium. In both reactions, the final chromene products were isolated by column chromatography. In the reaction in toluene, the yield was found to be 65% while in acetonitrile the yield was 52% (**Table 4.4**).

Table 4.4: Optimization of the Reaction between **4-61** and **4-98**[a]



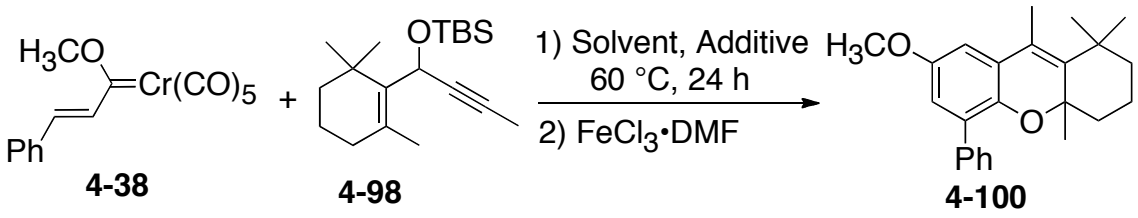
4-61 **4-98** **4-99**

Entry	Solvent	Additive	Yield (%)
1	Toluene	5 equiv (iPr)$_2$NEt	Not determined
2	Toluene	None	65%
3	MeCN	None	52%
4	CH_2Cl_2	10 equiv Aniline	<10

a. All the reactions were performed at 0.06 M concentration using 1.2 equiv of **4-98.**

As part of the optimization, carbene complex was also varied and the reaction was attempted under two different conditions between compounds **4-38** and **4-98**, both in toluene solvent but one with Hünig's base as the additive while the other one was with aniline used as the additive. But both these reactions did not show any conversion even after one week and even after increasing the temperature to 80 °C as revealed by TLC, which indicated only the presence of **4-38** and **4-98** (**Table 4.5**).

Table 4.5: Reaction between **4-38** and **4-98**[a]

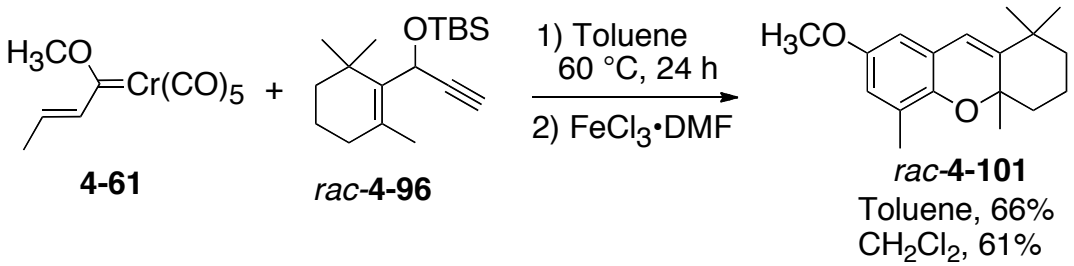


Entry	Solvent	Additive	Result
1	Toluene	5 equiv (iPr)$_2$NEt	No reaction
2	Toluene	10 equiv Aniline	No reaction

a. All the reactions were performed at 0.06 M concentration using 1.2 equiv of **4-98.**

After the success of the reaction of carbene complex **4-61** with the internal enyne **4-98** in absence of any additives (**Table 4.4**), it was considered prudent to re-examine the reaction of carbene complex **4-61** with the terminal enyne *rac*-**4-96** (**Scheme 39**) in the absence of additives. Two sets of reactions were conducted - one in toluene solvent and the other in dichloromethane. Indeed, both experiments were successful giving a 66% yield of the chromene product *rac*-**4-101** in toluene and a 61% yield in dichloromethane (**Scheme 4.44**).

Scheme 4.39: Reaction between Carbene Complex **4-61** and Enyne *rac*-**4-96**



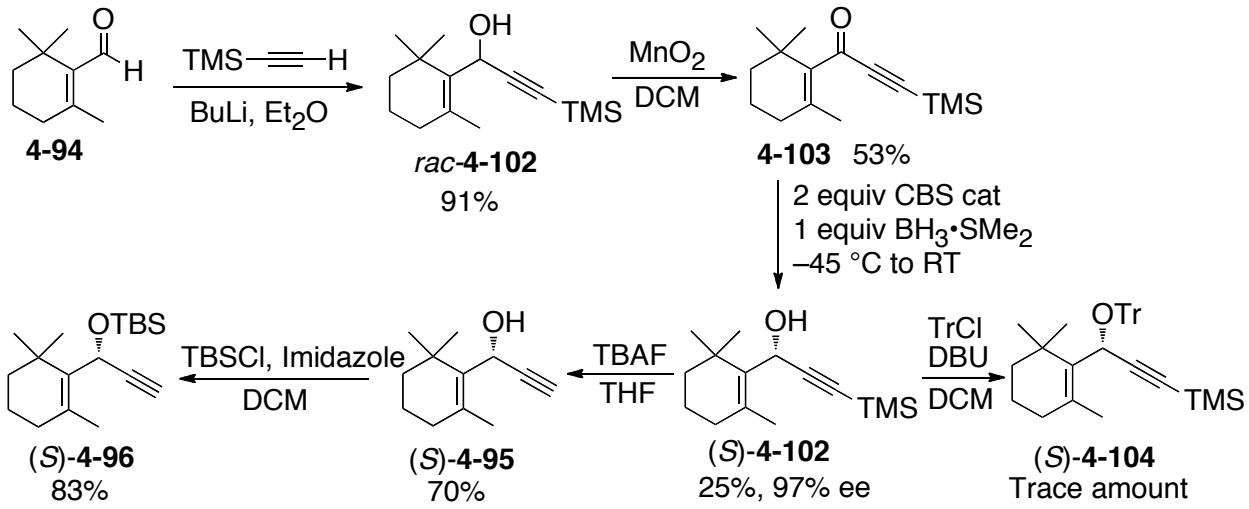
4-61 *rac*-**4-96** *rac*-**4-101**
Toluene, 66%
CH_2Cl_2, 61%

With the successful development of a clean benzannulation/*o*-quinone methide formation/electrocyclization cascade (BQME reaction) with a cyclic enyne, the next step was to develop an asymmetric synthesis of this enyne and the successful synthesis of (*S*)-**4-96** is presented in **Scheme 4.40**. It is important to mention here that CBS reduction of the ketone substrate **4-103** was unbelievably slow. The reduction time had to be lengthened to over 16 hours and the temperature had to be increased to 25 °C to see reasonable conversion. Still the reaction was not complete and that is the reason the yield was very low, only 30%. But satisfactorily the enantioselectivity was not compromised too much, and the product (*S*)-**4-102** could be isolated with 97% ee (**Scheme 4.44**).

From the previous results, it was found that a trityl protecting group on the alcohol moiety in the enyne provided higher enantioselectivity than TBS as protecting group (**Scheme 4.22** vs **4.23**). So, after the CBS reduction, the introduction of a trityl group was attempted but the substrate (*S*)-**4-102** turned out to be too bulky to react with the sterically demanding trityl chloride and there was almost no conversion. Most of the

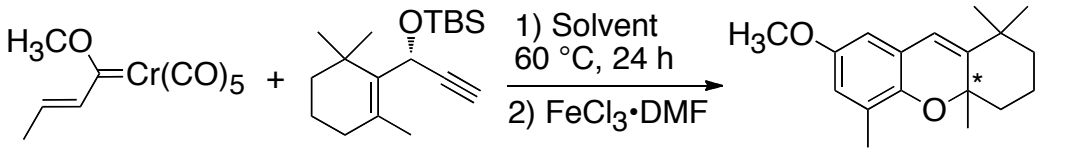
chiral alcohol (*S*)-**4-102** was recovered, desilylated and the alcohol moiety was protected with *tert*-butyldimethylsilyl group to give the enyne (*S*)-**4-96** (**Scheme 4.40**).

Scheme 4.40: Synthesis of Chiral Enyne (*S*)-**4-96** from **4-94**



After the synthesis of the chiral enyne (*S*)-**4-96**, the asymmetric test reaction was attempted in both toluene and dichloromethane (**Scheme 4.41**). Unfortunately, the result was not up to our expectation. Only a 26% ee was observed in the product obtained from the reaction in dichloromethane, while the reaction in toluene showed only a 12% ee in the chromene product **4-111**.

Scheme 4.41: Reaction between Carbene Complex **4-61** and Enyne (*S*)-**4-96**: Test Reaction



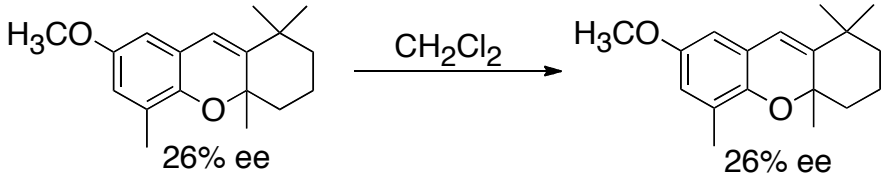
4-61

(*S*)-**4-96**
97% ee

4-101
CH_2Cl_2, 70%, 26% ee
Toluene, 63%, 12% ee

It was first thought that the reason for the low ee could be the result of racemization of the chromene product under the reaction conditions (60 °C, 24 h). The racemization can occur by a reversible eletrocyclic ring opening and closing mechanism shown in **Scheme 4.42**. So the chromene product **4-101** with 26% ee was taken up in dichloromethane and the resulting solution was stirred at 60 °C for 3 days. After that time, the enantioselectivity was checked again and no loss in ee was observed (the ee of the compound after 3 days was 26% ee).

Scheme 4.42: Change in Enantioselectivity Under The Reaction Condition



26% ee

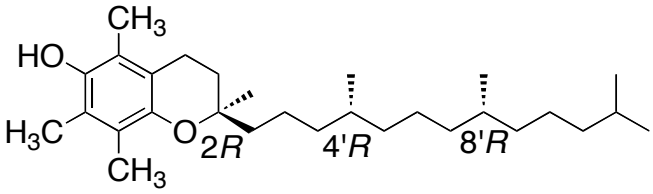
26% ee

At this Point these experimental results disproved the hypothesis of the interconversion of the intermediates **4-67** and **4-76** as the reason for the loss of enantioselectivity in the

proposed mechanistic pathway (**Scheme 4.26**). There is another possibility for the loss of enantioselectivity, which cannot be ignored. Although, the ee of the chromene **4-101** did not change under the reaction conditions, when there is a chromium attached to chromene the racemization is possible by the reversible electrocyclic ring opening and ring closing pathway.

It is also important to mention here that, an inspiration behind this project for the asymmetric synthesis of chromene was to synthesize vitamin E (2*R*,4'*R*,8'*R*)-α-tocopherol in its optically active form (**Figure 4.2**).

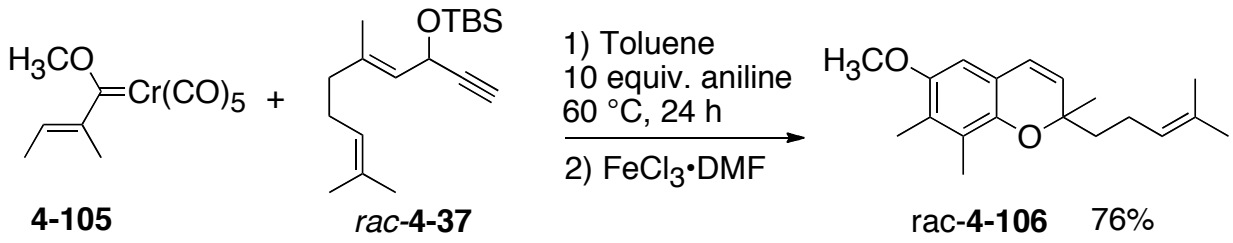
Figure 4.2: Optically Active Vitamin E



(2*R*, 4'*R*,8'*R*)-α-Tocopherol

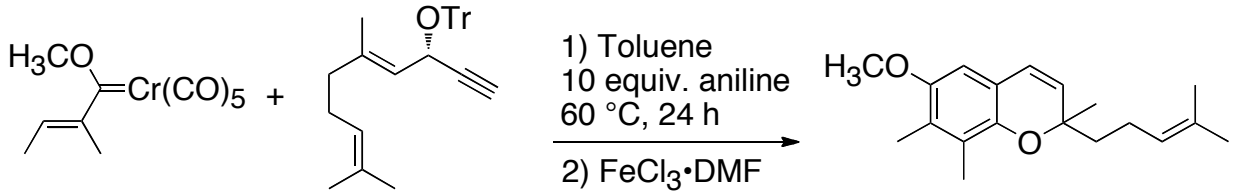
As a model reaction for α-tocopherol synthesis, the reaction between carbene complex **4-105** and racemic enyne *rac*-**4-37** was attempted and the yield of the chromene product *rac*-**4-106** was 76%. Inspired by this high yield, the reaction was performed between carbene complex **4-105** and chiral enyne (*S*)-**4-60** to determine if there would be any asymmetric induction at the newly formed quaternary center. Unfortunately, the product **4-106** turned out to be completely racemic (**Schemes 4.43** and **4.44**).

Scheme 4.43: Model Reaction for the Synthesis of Optically Active Tocopherol



4-105 *rac*-**4-37** rac-**4-106** 76%

Scheme 4.44: Model Reaction for the Synthesis of Optically Active Tocopherol



4-105 (*S*)-**4-60** 99% ee **4-106** 94%, racemic

From the previous experiences[145b] it was seen that if R^1 in carbene complex **4-8** is not hydrogen, there was a significant loss in diastereoselectivity (**Scheme 4.4**). Thus this result was not fully unexpected.

4.4. Conclusion

At this end, it can be said that the results for the asymmetric synthesis of chromene is not satisfactory since the highest selectivity that could be achieved was 60% ee. Although, the results for the test reaction did not shed much light on the prediction made for the loss of enantioselectivity, the interconversion of the intermediates **4-67** and **4-76** as the reason for the loss of enantioselectivity can be excluded as the experimental results for the test reaction disproved that hypothesis. If one looks back at the proposed

mechanism, it can be assumed that compounds **4-65** and **4-74** in **Scheme 4.26** should be formed with high enantioselectivity (~95% ee) according to the results previously reported[145a]. Therefore there must be a significant loss in the enantioselectivity somewhere in the following steps, which are leading compounds **4-65** and **4-74** to the final chromene products **4-72** and ***ent*-4-72**. Intriguingly, enantioselectivity of chromene **4-101** proved to be unaffected under the reaction conditions (dichloromethane solvent, 60 ^{o}C). However, the possibility of racemization in the chromium tricarbonyl complexed chromene **4-71** or **4-80** (**Scheme 4.26**) cannot be completely excluded, which can occur by pyran ring opening and ring closing. Also the oxidation method employing $FeCl_3$•DMF could be a possible reason for the loss of enantioselectivity as $FeCl_3$ being a very strong Lewis acid can assist in pyran ring opening and ring closing and thereby the racemization. It would also be very interesting to trap the intermediates **4-65** and **4-74** by addition of a protecting group in the reaction. The diastereoselectivity of those intermediates should give an insight about the stereoinduction in the asymmetric benzannulation reaction, which is the preliminary source for the chirality. Although very important results and some valuable insights have been gained from this study, the asymmetric BQME reaction still needs some more exploration to fully understand the mechanism which is the only key to solving the puzzle that can lead to a very high enantioselectivity in the chromenes. If successful it would open a new avenue for the asymmetric synthesis of chromenes where both the rings can be formed in one step. Also just by changing the stereochemistry of the double bond in the enyne, both the enantiomers of a chromene compound can be achieved very efficiently.

CHAPTER FIVE

EXPERIMENTAL PROCEDURES

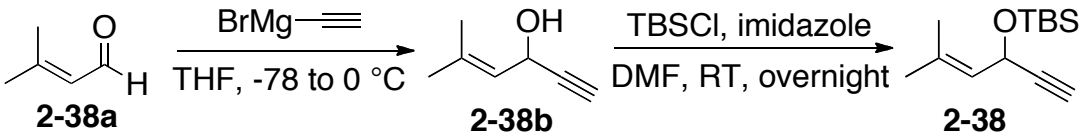
5.1. General Information

All reactions were carried out in flame-dried glassware under an atmosphere of argon unless otherwise indicated. All solvents were strictly dried prior to use: dichloromethane and acetonitrile were distilled over calcium hydride under nitrogen; tetrahydrofuran and ether were distilled from sodium and benzophenone; benzene and toluene were distilled from sodium under nitrogen. Hexanes and ethyl acetate were ACS grade and used as purchased. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded in KBr matrix (for solids) and on NaCl disc (for liquids) on a Nicolet IR/42 spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on a Varian Inova 300 MHz or Varian Unity Plus 500 MHz or Varian Inova 600 MHz spectrometer using $CDCl_3$ as solvent. Low-resolution Mass Spectrometry and High Resolution Mass Spectrometry were performed at Michigan State University Mass Facility. Analytical thin-layer chromatography (TLC) was performed on Silicycle silica gel plates with F-254 indicator. Visualization was by short wave (254 nm) and long wave (365 nm) ultraviolet light, or by staining with phosphomolybdic acid in ethanol. Column chromatography was performed with silica gel 60 (230 – 450 mesh). All reagents were purified by simple distillation or crystallization with simple solvents unless otherwise indicated.

5.2 Chapter Two and Three Experimental

Preparation of the Enynes :

Preparation of Enyne (2-38):



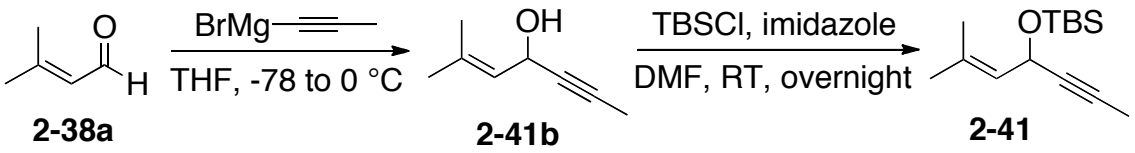
2-38a **2-38b** **2-38**

To a solution of 3-methylbut-2-enal **2-38a** (10.00 mL, 10.46 g, 124.3 mmol) in 250 mL of THF at –78 °C was added ethynylmagnesium bromide (0.5 M in THF, 250.0 mL, 150.2 mmol). The reaction mixture was stirred for 3 hours at –78 °C and warmed to room temperature. After completion (as judged by TLC) the reaction mixture was then poured into 100 mL of saturated ammonium chloride solution. The aqueous layer was separated and extracted with ethyl acetate (100 mL x 3). The organic layers were combined and dried over magnesium sulfate. The solution was filtered through fluted filter paper and the solvent was removed under reduced pressure. The resulting alcohol **2-38b** (12.80 g, 116.2 mmol) was used in the next step without further purification.

A 500 mL single neck round bottom flask was charged with all of the compound **2-38b** (12.80 g, 116.2 mmol), imidazole (11.76 g, 172.9 mmol), TBSCl (17.89 g, 118.7 mmol) and dry DMF (390 mL). The mixture was stirred at room temperature for overnight. The solution was extracted with ether (250 mL x 2), saturated ammonium chloride solution (250 mL), and water (300 mL). Each aqueous layer was then back extracted with ether

(150 mL x 3). The organic layers were combined and dried over magnesium sulfate. The crude product was purified by chromatography on silica gel with 5% ethyl acetate / hexane to give 19.84 g (87% yield, 94.90 mmol) of compound **2-38** as light yellow oil. R_f = 0.82 (30% ethyl acetate / hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.09 (s, 3H), 0.11 (s, 3H), 0.88 (s, 9H), 1.66 (d, 3H, *J* = 1.3 Hz), 1.71 (d, 3H, *J* = 1.3 Hz), 2.40 (d, 1H, *J* = 2.5 Hz), 5.03 (dd, 1H, *J* = 8.5, 2.5 Hz), 5.29-5.33 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –4.67, –4.53, 18.08, 18.22, 25.54, 25.77, 59.84, 71.62, 85.12, 125.73, 134.29; IR (neat film) 3314, 2959, 2932, 2859, 1474, 1252, 1069, 837 cm^{-1}; mass spectrum *m/z* (% rel intensity) 225 $[M+1]^+$ (0.03), 224 M^+ (0.1), 209 (2), 167 (47), 91 (23), 83 (17), 75 (100), 61 (15); Anal calcd for $C_{13}H_{24}OSi$: C, 69.58; H, 10.78. Found; C, 69.38; H, 10.92.

Preparation of Enyne (2-41):

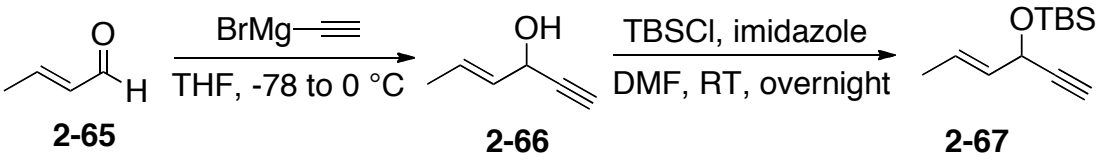


2-38a **2-41b** **2-41**

The compound **2-41** was prepared following the procedure described above for compound **2-38**. Compound **2-38a** (2.00 mL, 1.74 g, 20.7 mmol) was reacted with propynyl magnesium bromide (0.5 M in THF, 50.0 mL, 25.0 mmol) in dry THF (50 mL). The entire crude product **2-41b** was used in the next step and reacted with tert-

butyldimethylsilyl chloride (3.97 g, 26.4 mmol) and imidazole (2.60 g, 38.4 mmol) in dimethylformamide (115 mL). The final product **2-41** was obtained as a colorless oil in 98% yield (4.85 g, 20.4 mmol). R_f = 0.62 (5% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.63 (d, 3H, *J* = 1.5 Hz), 1.68 (d, 3H, *J* = 1.5 Hz), 1.79 (d, 3H, *J* = 2 Hz), 4.99 (dd, 1H, *J* = 8.5, 2.0 Hz), 5.28 (dt, 1H, *J* = 8.5, 1.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –4.62, –4.47, 3.64, 17.99, 18.27, 25.52, 25.84, 60.21, 79.80, 80.52, 126.63, 133.12; IR (neat film) 2957, 2932, 2858, 1674, 1472, 1245 cm^{-1}; HRMS (TOF MS EI$^+$) calcd for $C_{14}H_{26}OSi$ *m/z* 238.1753, meas 238.1761.

Preparation of Enyne (2-67):

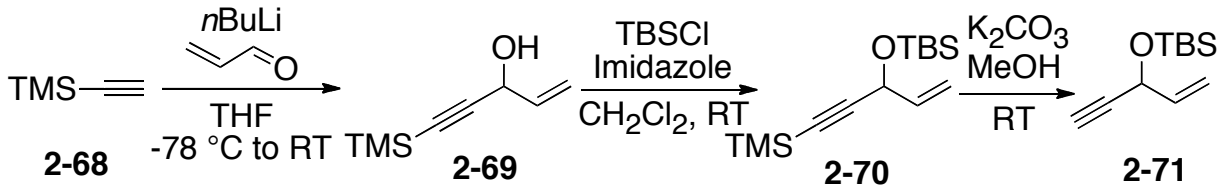


2-65 **2-66** **2-67**

The compound **2-67** was prepared following the procedure described above for compound **2-38**. Freshly distilled crotonaldehyde **2-65** (1.00 mL, 0.850 g, 12.1 mmol) was reacted with ethynyl magnesium bromide (0.5 M in THF, 30.2 mL, 15.1 mmol) in dry THF (30 mL). The entire crude product **2-66** was used in the next step and reacted with tert-butyldimethylsilyl chloride (2.18 g, 14.5 mmol) and imidazole (1.32 g, 19.3 mmol) in dimethylformamide (30 mL). The final product **2-67** was obtained as colorless

oil in 74% yield (1.89 g, 9.00 mmol). R_f = 0.67 (5% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.11 (s, 3 H), 0.12 (s, 3H), 0.89 (s, 9H), 1.68-1.71 (m, 3H), 2.45 (d, 1H, *J* = 1.5 Hz), 4.80-4.83 (m, 1H), 5.50-5.56 (m, 1H), 5.76-5.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –4.83, –4.61, 17.39, 18.31, 25.78, 63.29, 72.96, 84.10, 127.02, 130.62; IR (neat film) 3312, 2958, 2930, 2833, 1652 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{12}H_{23}OSi$ (M^++H) *m/z* 211.1518, meas 211.1512.

Preparation of Enyne (2-71):



The compound **2-71** was prepared following known literature method and spectroscopic properties were identical to those previously reported.[152a] To a solution of (trimethylsilyl) acetylene **2-68** (2.00 g, 2.90 mL, 20.4 mmol) in dry THF (130 mL) at –78 °C was added dropwise a solution of n-butyllithium (2.5 M in hexanes, 8.16 mL, 20.4 mmol) under Ar atmosphere. After 15 minutes, freshly distilled ice-cold acrolein (1.40 g, 1.67 mL, 24.5 mmol) was introduced slowly. The resulting mixture was allowed to warm gradually to 0 °C over a period of 1.5 h. After stirring for an additional 1 h at room

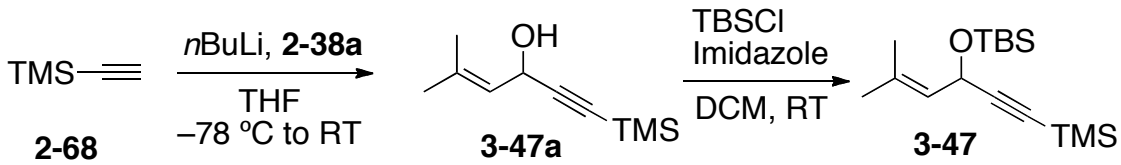
temperature, the mixture was quenched with ice-cold satd. NH_4Cl. The aqueous phase was extracted with Et_2O, dried with $MgSO_4$ and concentrated to dryness in *vacuo*. The crude compound **2-69** was pure enough (from ^1H NMR) to be used in the next step without further purification.

All the crude compound **2-69** was used in the next step along with *tert*-butyldimethylsilyl chloride (3.70 g, 24.7 mmol) and imidazole (2.20 g, 32.4 mmol) in dichloromethane (115 mL). The mixture was stirred for 16 h at room temperature. The crude product was concentrated in *vacuo* and directly chromatographed on silica gel (eluted with 100 : 1 hexane–ethyl acetate) to afford 4.85 g (18.1 mmol) of **2-70** as colorless oil, giving 89% yield over two steps. The spectroscopic properties were identical to those reported in literature.[152b]

The deprotection of trimethylsilyl group from compound **2-70** to the target enyne **2-71** was followed from known literature procedure.[152c] To a solution of **2-70** (2.31 g, 8.62 mmol) in MeOH (20 mL), K_2CO_3 (2.38 g, 17.2 mmol) was added and the mixture was stirred for 4 h at room temperature. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The concentrated mixture was directly loaded onto a silica gel column, which was eluted with 1% Ethyl acetate/Hexane to give pure compound **2-71** (1.50 g, 7.65 mmol, 89% yield) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.12 (s, 3H), 0.13 (s, 3H), 0.90 (s, 9H), 2.47 (d, 1H, J = 2.5 Hz), 4.86-4.88 (m, 1H), 5.15 (dt, 1H, J = 10, 1.5 Hz), 5.40 (dt, 1H, J = 17, 1.5 Hz), 5.89 (ddd,

1H, *J* = 17, 10, 4.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –4.94, –4.67, 18.30, 25.74, 63.44, 73.33, 83.42, 115.14, 137.40. The spectroscopic data match with the previously reported in the literature.[152b]

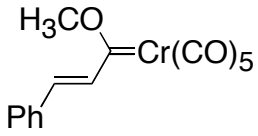
Preparation of Enyne (3-47):



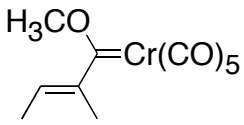
The compound **3-47** was prepared following the same procedure previously described for compound **2-71**. To a solution of (trimethylsilyl) acetylene **2-68** (1.00 g, 1.45 mL, 10.2 mmol) in dry THF (65 mL) at –78 °C was added dropwise a solution of n-butyllithium (2.5 M in hexanes, 4.08 mL, 10.2 mmol) under Ar atmosphere. After 15 minutes, ice-cold 3-methylbut-2-enal **2-38a** (1.03 g, 1.18 mL, 12.24 mmol) was introduced slowly. The resulting mixture was allowed to warm gradually to 0 °C over a period of 1.5 h. After stirring for an additional 1 h at room temperature, the mixture was quenched with ice-cold satd. NH_4Cl. The aqueous phase was extracted with Et_2O, dried with $MgSO_4$ and concentrated to dryness in *vacuo*. The crude compound **3-47a** was pure enough (from ^{1}HNMR) to be used in the next step without further purification.

All the crude compound **3-47a** was used in the next step along with tert-butyldimethylsilyl chloride (3.40 g, 22.5 mmol) and imidazole (2.50 g, 36.0 mmol) in dichloromethane (57 mL). The mixture was stirred for 16 h at room temperature. The crude product was concentrated in *vacuo* and directly chromatographed on silica gel (eluted with 100 : 1 hexane–ethyl acetate) to afford 2.95 g (9.96 mmol) of **3-47** as colorless oil, giving 97% yield over two steps. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.10 (s, 3H), 0.11 (s, 3H), 0.13 (s, 9H), 0.88 (s, 9H), 1.65 (d, 3H, J = 1.5 Hz), 1.70 (d, 3H, J = 1.5 Hz), 5.01 (d, 1H, J = 8 Hz), 5.29 (dt, 1H, J = 8, 1.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –4.51, –4.35, –0.16, 18.10, 18.30, 25.64, 25.84, 60.42, 88.19, 107.10, 125.73, 134.51; IR (neat film) 2959, 2930, 2898, 2858, 2172, 1673, 1472, 1250, 1063 cm^{-1}; HRMS (TOF MS ES^{+}) calcd for $C_{16}H_{33}OSi_2$ (M^{+}+H) *m/z* 297.2070, meas 297.2062.

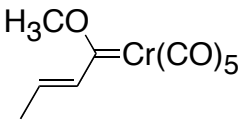
Preparation of the Carbene Complexes 2-14, 2-43, 2-56, 2-59, 2-46, 2-53, 2-62, and 3-41:



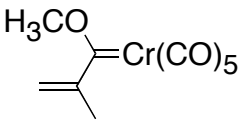
2-14



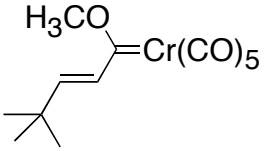
2-43



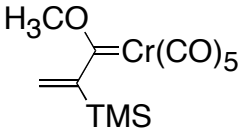
2-56



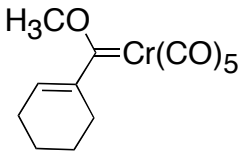
2-59



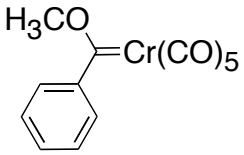
2-46



2-53



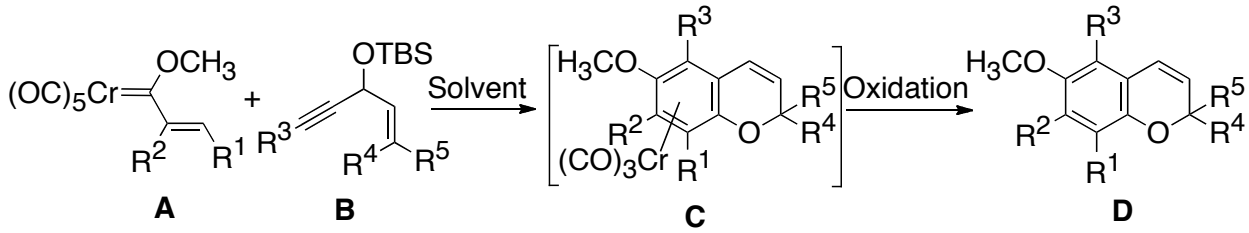
2-62



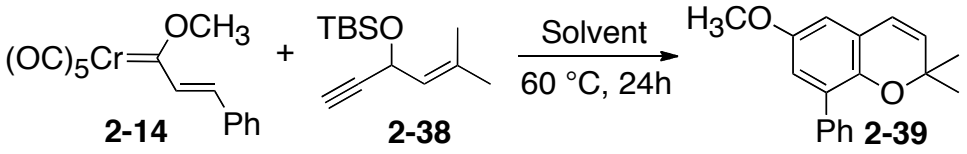
3-41

Carbene complexes **2-14,**[153] **2-43,**[154] **2-56,**[155] **2-59**,[156] **2-46**,[157] **2-53**,[158] **2-62**[159] and **3-41**[160] were prepared according to the literature methods.

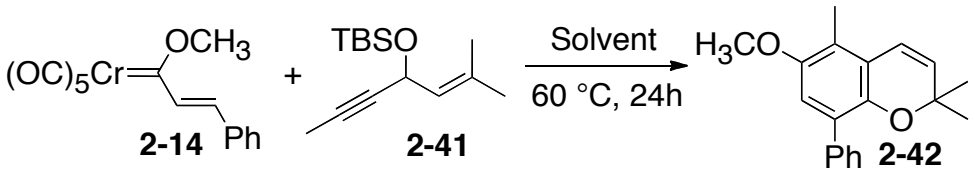
General Procedure for the Synthesis of Chromenes:



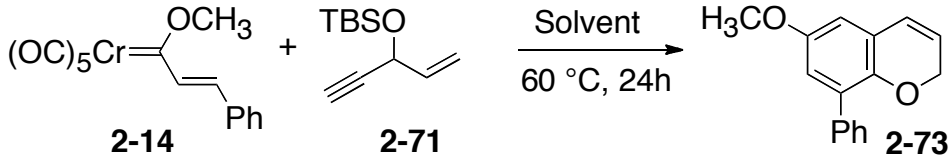
The carbene complex **A** (0.26 mmol), enyne **B** (0.32 mmol), and solvent (8.00 mL) were added to a 25 mL Schlenk flask. The reaction mixture was deoxygenated by the freeze-pump-thaw method (3 cycles) and finally the flask was back-filled with argon. The reaction mixture was stirred and heated at 60 ºC for 24 hours. The solvent was removed under reduced pressure and the crude compound was dissolved in 8 mL of diethyl ether. To this mixture, water (8 mL) and 7.5 equiv. of $FeCl_3$•DMF complex were added and stirred under air. Upon completion of the oxidation of compound **C** (judged by TLC), the organic layer was separated. The aqueous layer was washed with ether (3 x 15 mL). Organic layers were combined, washed with brine and dried over magnesium sulfate. Column chromatography with 1% ethyl acetate / hexane gave pure compound **D**.



Compound 2-39: The carbene complex **2-14** (0.30 g, 0.88 mmol) was reacted with enyne **2-38** (0.221 g, 1.06 mmol) in 27 mL of dichloromethane. The reaction gave 0.18 g (76% yield, 0.67 mmol) of compound **2-39** as light yellow oil. This reaction was conducted in five other solvents, which were acetonitrile, hexane, benzene, THF and toluene and gave 95%, 70%, 74%, 65% and 62% yields respectively. These yields in the first four solvents were the average of two runs. The reaction in toluene was done at 80 °C for 24 h. The reaction was also done in toluene in presence of 5 equiv. of Hunig's base at 80 °C for 24 h and the yield was 35%. The reaction didn't need an oxidative workup when acetonitrile was the solvent. R_f = 0.25 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.41 (s, 6H), 3.79 (s, 3H), 5.66 (d, 1H, *J* = 9.5 Hz), 6.33 (d, 1H, *J* = 9.5 Hz), 6.57 (d, 1H, *J* = 3 Hz), 6.77 (d, 1H, *J* = 3 Hz), 7.31 (t, 1H, *J* = 7 Hz), 7.40 (t, 2H, *J* = 7.5 Hz), 7.57 (dd, 2H, *J* = 8 Hz, *J* = 1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.49, 55.74, 75.88, 111.06, 115.45, 122.59, 122.73, 126.80, 127.84, 129.37, 130.17, 131.86, 138.08, 143.68, 153.41; IR (neat film) 3100, 3050, 2975, 2936, 2890, 1750, 1597, 1489, 1437, 1424, 1321, 1199 cm^{-1}; HRMS (TOF MS EI$^+$) calcd for $C_{18}H_{18}O_2$ *m/z* 266.1307, meas 266.1304.

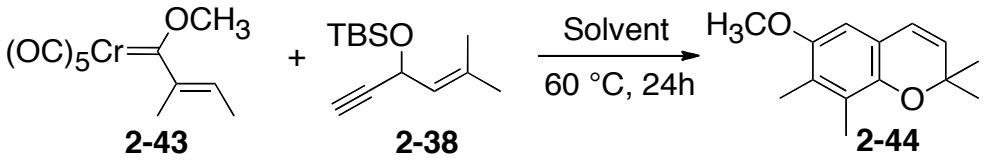


Compound 2-42: The carbene complex **2-14** (0.30 g, 0.88 mmol) was reacted with enyne **2-41** (0.251 g, 1.06 mmol) in 27 mL of dichloromethane. The reaction gave 0.171 g (69% yield, 0.611 mmol) of compound **2-42** as a light yellow oil. The reaction was also conducted in acetonitrile and gave 66% yield. R_f = 0.27 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.42 (s, 6H), 2.25 (s, 3H), 3.82 (s, 3H), 5.74 (d, 1H, *J* = 8.5 Hz), 6.62 (d, 1H, *J* = 8.5 Hz), 6.76 (s, 1H), 7.32 (t, 1H, *J* = 6 Hz), 7.42 (t, 2H, *J* = 6 Hz), 7.59 (dd, 2H, *J* = 7, 1.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.76, 27.23, 56.15, 74.70, 112.47, 119.93, 121.42, 121.87, 126.50, 126.98, 127.81, 129.38, 131.81, 138.63, 143.60, 151.57; IR (neat film) 3054, 2973, 2931, 2855, 1463, 1388, 1212, 1100 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{19}H_{21}O_2$ (M^++H) *m/z* 281.1542, meas 281.1545.



Compound 2-73: The carbene complex **2-14** (0.30 g, 0.88 mmol) was reacted with enyne **2-71** (0.207 g, 1.06 mmol) in 27 mL of acetonitrile. The reaction gave 0.10 g

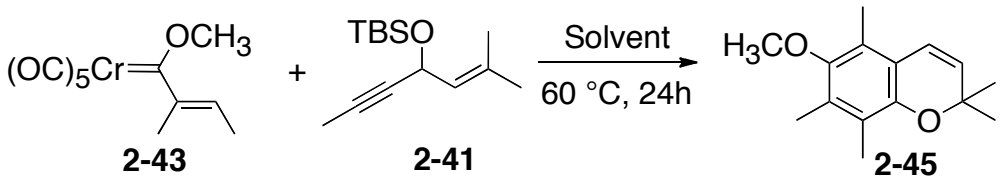
(47% yield, 0.42 mmol) of compound **2-73** as light yellow oil. R_f = 0.11 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.80 (s, 3H), 4.73-4.74 (m, 2H), 5.86-5.89 (m, 1H), 6.47 (dd, 1H, *J* = 10, 1.5 Hz), 6.59 (d, 1H, *J* = 2.5 Hz), 6.78 (d, 1H, *J* = 2.5 Hz), 7.35 (t, 1H, *J* = 7 Hz), 7.44 (t, 2H, *J* = 7.5 Hz), 7.57 (d, 2H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.64, 65.23, 111.25, 115.28, 123.17, 123.83, 125.02, 127.09, 127.98, 129.26, 129.96, 137.73, 144.72, 153.70; IR (neat film) 3062, 2965, 2952, 2836, 1598, 1471, 1435, 1429, 1319, 1199 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{16}H_{13}O_2$ (M^+–H) *m/z* 237.0916, meas 237.0910.



2-43 **2-38** **2-44**

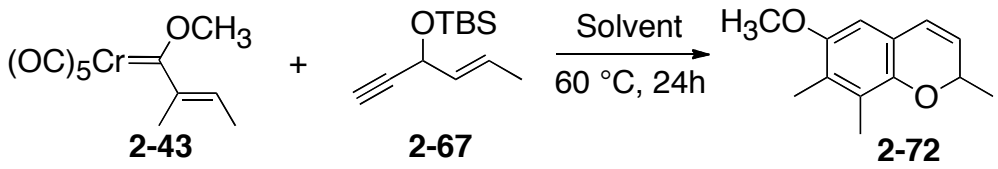
Compound 2-44: The carbene complex **2-43** (0.300 g, 1.03 mmol) was reacted with enyne **2-38** (0.278 g, 1.24 mmol) in 27 mL of dichloromethane. The reaction gave 0.199 g (88% yield, 0.913 mmol) of compound **2-44** as a light yellow oil. This reaction was conducted in three other solvents including acetonitrile, benzene and THF and gave 65%, 73% and 74% yields, respectively. The yield in acetonitrile was an average of three runs. R_f = 0.27 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.38 (s, 6H), 2.12 (s, 6H), 3.75 (s, 3H), 5.55 (d, 1H, *J* = 10 Hz), 6.25 (d, 1H, *J* = 10 Hz), 6.37 (s,

1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.58, 12.03, 27.57, 56.00, 75.37, 105.99, 118.31, 122.83, 125.51, 126.16, 130.15, 144.62, 151.40; IR (neat film) 3040, 2973, 2932, 2859, 1637, 1577, 1462, 1422, 1261 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{14}H_{19}O_2$ (M^++H) *m/z* 219.1385, meas 219.1382.



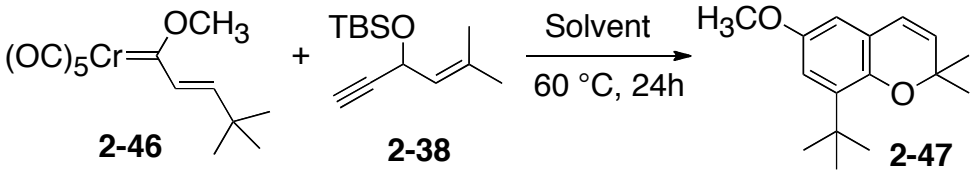
2-43 **2-41** **2-45**

Compound 2-45: The carbene complex **2-43** (0.300 g, 1.03 mmol) was reacted with enyne **2-41** (0.285 g, 1.24 mmol) in 27 mL of dichloromethane. The reaction gave 0.201 g (84% yield, 0.866 mmol) of compound **2-45** as a light yellow oil. Repeat of this reaction in the same solvent gave 84% yield again. This reaction was also conducted in acetonitrile and gave 87% yield. R_f = 0.25 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.37 (s, 6H), 2.07 (s, 3H), 2.16 (s, 3H), 2.19 (s, 3H), 3.60 (s, 3H), 5.59 (d, 1H, *J* = 10 Hz), 6.46 (d, 1H, *J* = 10 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.13, 11.53, 12.76, 27.57, 60.29, 74.65, 117.98, 119.93, 122.77, 123.11, 129.98, 146.79, 150.26 (1 sp^2 C not located); IR (neat film) 3050, 2977, 2936, 2898, 1640, 1597, 1462, 1406, 1387, 1289, 1217, 1090 cm^{-1}; HRMS (TOF MS EI$^+$) calcd for $C_{15}H_{20}O_2$ *m/z* 232.1463, meas 232.1461.



2-43 **2-67** **2-72**

Compound 2-72: The carbene complex **2-43** (0.300 g, 1.03 mmol) was reacted with enyne **2-67** (0.260 g, 1.24 mmol) in 27 mL of dichloromethane. The reaction gave 0.147 g (70% yield, 0.721 mmol) of compound **2-72** as a light yellow oil. R_f = 0.21 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.41 (d, 3H, *J* = 5.5 Hz), 2.12 (s, 6H), 3.75 (s, 3H), 4.86-4.91 (m, 1 H), 5.63 (dd, 1H, *J* = 8.5, 2.5 Hz), 6.32 (dd, 1H, *J* = 8.5, 1.5 Hz), 6.37 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.71, 12.05, 20.90, 56.11, 71.04, 106.19, 119.03, 124.36, 125.36, 126.38, 126.41, 145.27, 151.62; IR (neat film) 3050, 2974, 2931, 2845, 1608, 1579, 1463, 1425, 1386, 1321, 1228, 1109 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{13}H_{17}O_2$ (M^++H) *m/z* 205.1229, meas 205.1221.

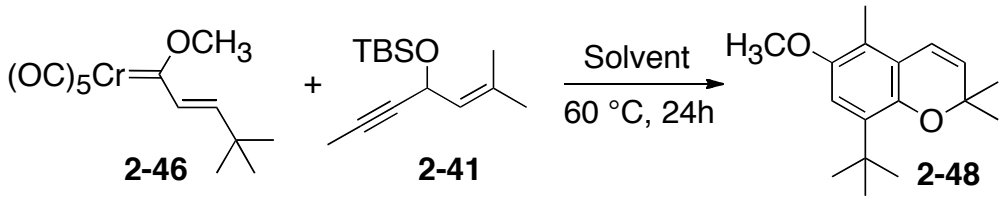


2-46 **2-38** **2-47**

Compound 2-47: The carbene complex **2-46** (0.094 g, 0.296 mmol) was reacted with enyne **2-38** (0.081 g, 0.362 mmol) in 9 mL of dichloromethane. The reaction gave 0.057

g (78% yield, 0.232 mmol) of compound **2-47** as a light yellow oil. This reaction was also conducted in acetonitrile and gave 78% yield. R_f = 0.36 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.40 (s, 9H), 1.45 (s, 6H), 3.76 (s, 3H), 5.60 (d, 1H, *J* = 10 Hz), 6.27 (d, 1H, *J* = 10 Hz), 6.42 (d, 1H, *J* = 3 Hz), 6.76 (d, 1H, *J* = 3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.34, 29.66, 34.66, 55.50, 75.54, 108.20, 113.47, 121.96, 123.16, 130.80, 138.81, 145.25, 152.88; IR (neat film) 3041, 2961, 2873, 2835, 1599, 1468, 1429, 1205 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{16}H_{23}O_2$ (M^++H) *m/z* 247.1698, meas 247.1701.

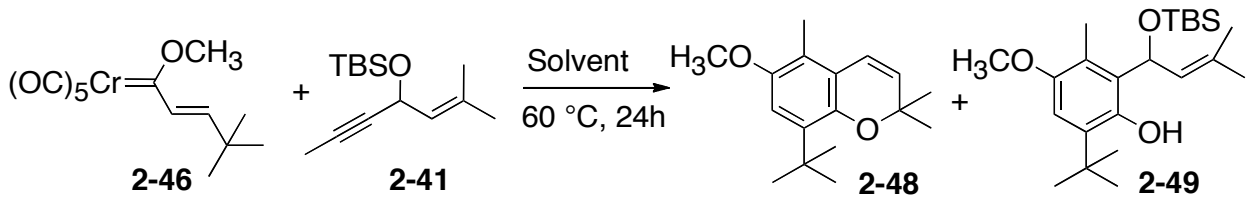
Reaction of complex 2-46 and enyne 2-41 with triflic acid workup:



Compound 2-48: The carbene complex **2-46** (0.30 g, 0.94 mmol) was reacted with enyne **2-41** (0.269 g, 1.13 mmol) in 27 mL of acetonitrile. The crude reaction mixture was then treated with few drops of trifluoromethane sulfonic acid. The reaction gave 0.159 g (65% yield, 0.649 mmol) of compound **2-48** as a light yellow oil. R_f = 0.32 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.37 (s, 9H), 1.41 (s, 6H), 2.14 (s,

3H), 3.76 (s, 3 H), 5.65 (d, 1H, *J* = 10 Hz), 6.52 (d, 1H, *J* = 10 Hz), 6.72 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.56, 27.18, 29.84, 34.66, 56.54, 74.43, 110.17, 120.16, 120.31, 121.15, 130.93, 135.13, 145.40, 150.91; IR (neat film) 2960, 2926, 1595, 1409, 1382 cm^{-1}; HRMS (TOF MS EI^+) calcd for $C_{17}H_{24}O_2$ *m/z* 260.1776, meas 260.1774.

Reaction of complex 2-46 and enyne 2-41 without triflic acid workup:



2-46 **2-41** **2-48** **2-49**

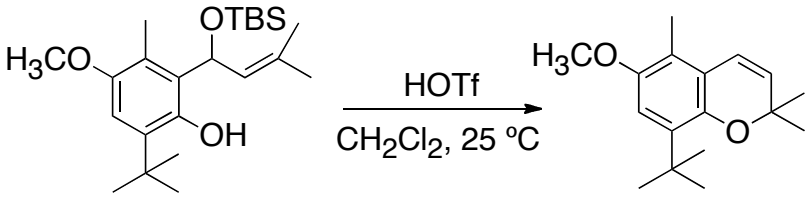
The carbene complex **2-46** (0.30 g, 0.94 mmol) was reacted with enyne **2-41** (0.269 g, 1.13 mmol) in 27 mL of dichloromethane. The reaction gave 0.187 g (76% yield, 0.719 mmol) of compound **2-48** as a light yellow oil as the major product. A side product **2-49** was also formed in the reaction and the ratio of compound **2-48** to compound **2-49** was 84:16. The ratio of compound **2-48** to compound **2-49** was tested in this reaction with isopropanol as additive. With 10 equivalents of isopropanol, the ratio was 91:9. With 50 equivalents of isopropanol the ratio remained the same. In presence of 100 equivalents of isopropanol the ratio was ≥ 95:5. The reaction was repeated again and the yield of compound **2-48** for the second run was 72%. The reaction was also performed in

dichloromethane in presence of 10 equiv. of aniline as an additive and gave 86% yield of product **2-48** with no trace of side product. When the reaction was conducted in acetonitrile the ratio of compound **2-48** to compound **2-49** was 38:62.

Isolation and Characterization of Compound 2-49: The side product **2-49** was purified from compound **2-48** by column chromatography using 40% $CHCl_3$-Hexane. In some cases column chromatography had to be repeated two or three times to get a pure fraction of compound **2-49**. R_f = 0.63 (40% Chloroform / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.02 (s, 3H), 0.11 (s, 3H), 0.86 (s, 9H), 1.40 (s, 9 H), 1.68 (s, 3H), 1.80 (s, 3H), 2.10 (s, 3H), 3.74 (s, 3H), 5.58-5.63 (m, 1H), 5.73 (d, 1H, *J* = 10 Hz), 6.75 (s, 1H), 8.74 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –5.19, –4.73, 10.91, 18.01, 18.42, 25.58, 25.86, 29.55, 34.90, 56.66, 70.64, 109.94, 120.50, 124.59, 127.53, 133.77, 134.99, 149.51, 149.77; HRMS (TOF MS ES$^-$) calcd for $C_{23}H_{39}O_3Si$ (M^+–H) *m/z* 391.2668, meas 391.2656.

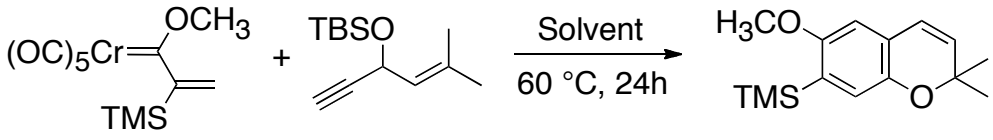
Compound **2-49** was subjected to deuterium exchange and the ^{1}H NMR spectrum of compound **2-49 OD** was taken. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.02 (s, 3H), 0.11 (s, 3H), 0.86 (s, 9H), 1.40 (s, 9 H), 1.68 (s, 3H), 1.80 (s, 3H), 2.08 (s, 3H), 3.74 (s, 3H), 5.58-5.63 (m, 1H), 5.73 (d, 1H, *J* = 10 Hz), 6.75 (s, 1H).

Acid Rearrangement of Compound 2-49 to 2-48:



2-49 **2-48**

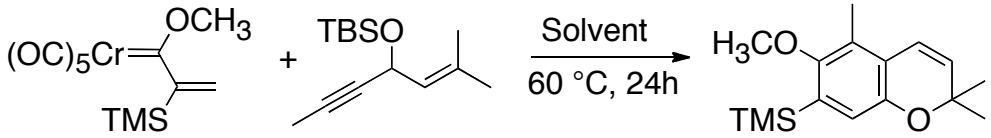
Compound 2-49 (0.043 g, 0.110 mmol) was taken up in a 25 mL round bottom flask in 5 mL of dichloromethane and few drops of trifluoromethanesulfonic acid was added. The reaction mixture was stirred for 10 minutes. The reaction was then quenched with saturated aqueous sodium carbonate solution (10 mL). The aqueous phase was extracted with dichloromethane (5 mL x 2). The organic layers were combined and dried with $MgSO_4$ and concentrated to dryness in *vacuo*. The compound **2-48** was obtained in quantitative yield (0.028 g, 0.110 mmol) and was analytically pure.



2-53 **2-38** **2-54**

Compound 2-54: The carbene complex **2-53** (0.30 g, 0.90 mmol) was reacted with enyne **2-38** (0.242 g, 1.08 mmol) in 27 mL of dichloromethane. The reaction gave 0.152 g (65% yield, 0.580 mmol) of compound **2-54** as a light yellow oil. The reaction was

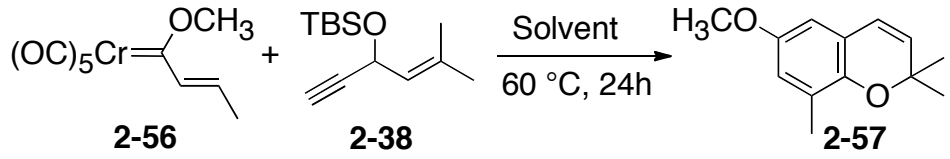
repeated two more times and both times the yield was 52%. This reaction was also conducted in acetonitrile and gave 23% yield. R_f = 0.27 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.22 (s, 9H), 1.40 (s, 6H), 3.73 (s, 3H), 5.59 (d, 1H, *J* = 10 Hz), 6.27 (d, 1H, *J* = 10 Hz), 6.45 (s, 1H), 6.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –0.94, 27.80, 55.64, 75.84, 107.60, 122.29, 122.39, 122.44, 129.03, 131.57, 146.22, 158.53; IR (neat film) 3040, 2964, 2936, 2856, 1630, 1670, 1479, 1463, 1409, 1349, 1261, 1248, 1199, 1164 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{15}H_{23}O_2Si$ (M^++H) *m/z* 263.1467, meas 263.1470.



2-53 **2-41** **2-55**

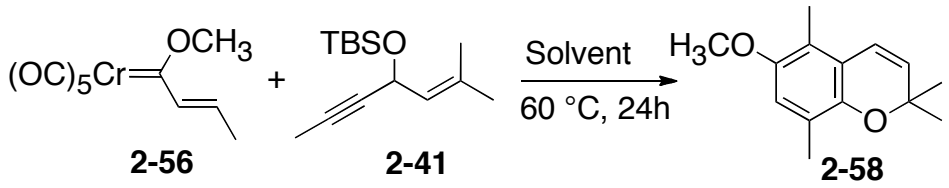
Compound 2-55: The carbene complex **2-53** (0.30 g, 0.90 mmol) was reacted with enyne **2-41** (0.256 g, 1.08 mmol) in 27 mL of dichloromethane. The reaction gave 0.215 g (87% yield, 0.779 mmol) of compound **2-55** as a light yellow oil. The reaction was repeated again and the yield was 81%. This reaction was also conducted in acetonitrile and gave 35% yield. R_f = 0.26 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.26 (s, 9H), 1.40 (s, 6 H), 2.22 (s, 3H), 3.64 (s, 3H), 5.64 (d, 1H, *J* = 10 Hz), 6.48 (d, 1H, *J* = 10 Hz), 6.67 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –0.14 11.87, 27.75, 61.44,

74.97, 119.51, 119.83, 122.06, 125.49, 131.37, 132.80, 148.46, 157.62; IR (neat film) 3050, 2977, 2955, 1620, 1590, 1456, 1391, 1368, 1289, 1248 cm^{-1}; HRMS (TOF MS EI^+) calcd for $C_{16}H_{24}O_2Si$ *m/z* 276.1546, meas 276.1553.



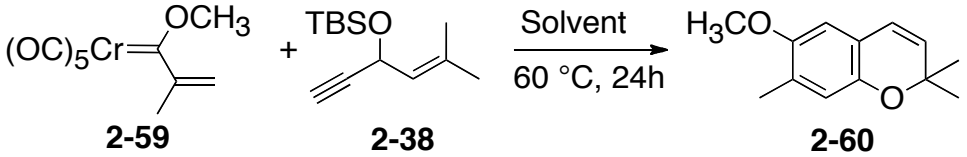
2-56 **2-38** **2-57**

Compound 2-57: The carbene complex **2-56** (0.300 g, 1.08 mmol) was reacted with enyne **2-38** (0.292 g, 1.30 mmol) in 27 mL of acetonitrile. The reaction gave 0.185 g (83% yield, 0.907 mmol) of compound **2-57** as a light yellow oil. The reaction in acetonitrile didn't need the oxidative workup. This reaction was also conducted in dichloromethane and gave 41% yield. R_f = 0.25 (1% Ethyl acetate / Hexane); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.39 (s, 6H) 2.16 (s, 3 H), 3.73 (s, 3H), 5.61 (d, 1H, *J* = 10 Hz), 6.25 (d, 1H, *J* = 10 Hz), 6.39 (d, 1 H, *J* = 3 Hz), 6.55 (d, 1H, *J* = 3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.59, 27.61, 55.57, 75.49, 108.69, 115.94, 121.30, 122.69, 126.42, 131.44, 144.80, 153.03; IR (neat film) 3040, 2974, 2935, 2838, 1592, 1465, 1207 cm^{-1}; HRMS (TOF MS EI^+) calcd for $C_{13}H_{16}O_2$ *m/z* 204.1150, meas 204.1145.



2-56 **2-41** **2-58**

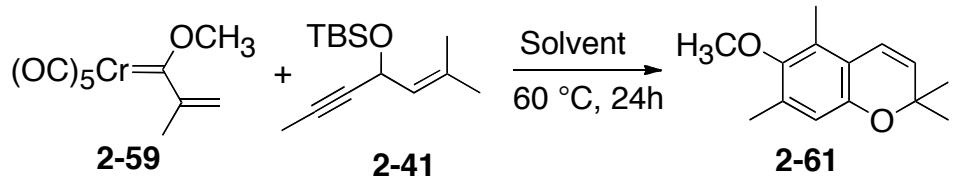
Compound 2-58: The carbene complex **2-56** (0.300 g, 1.08 mmol) was reacted with enyne **2-41** (0.310 g, 1.30 mmol) in 27 mL of dichloromethane. The reaction gave 0.145 g (61% yield, 0.665 mmol) of compound **2-58** as a light yellow oil. This reaction was also conducted in acetonitrile and gave 48% yield. The reaction in acetonitrile didn't need the oxidative workup. R_f = 0.27 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.37 (s, 6H) 2.14 (s, 3H), 2.16 (s, 3H), 3.75 (s, 3H), 5.67 (d, 1H, *J* = 10 Hz), 6.52 (d, 1H, *J* = 10 Hz), 6.53 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.49, 15.64, 27.41, 56.24, 74.38, 113.08, 119.61, 119.97, 120.47, 122.82, 131.44, 144.76, 151.08; IR (neat film) 3060, 2975, 2930, 2880, 1591, 1466, 1412, 1390, 1260, 1213, 1110 cm^{-1}; HRMS (TOF MS EI$^+$) calcd for $C_{14}H_{18}O_2$ *m/z* 218.1307, meas 218.1305.



2-59 **2-38** **2-60**

Compound 2-60: The carbene complex **2-59** (0.300 g, 1.08 mmol) was reacted with enyne **2-38** (0.292 g, 1.30 mmol) in 27 mL of dichloromethane. The reaction gave 0.10 g (45% yield, 0.490 mmol) of compound **2-60** as a light yellow oil. This reaction was also

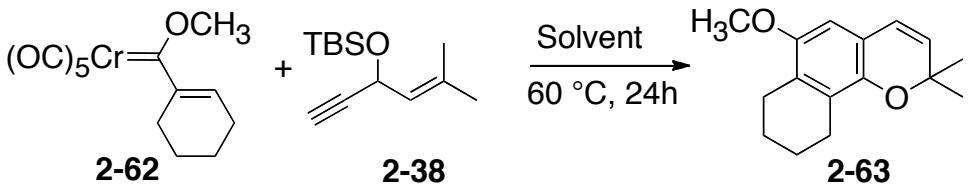
conducted in three other solvents, which were acetonitrile, hexane and benzene and gave 26%, 55% and 38% yields respectively. The yield in acetonitrile was the average of two runs. R_f = 0.25 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.38 (s, 6H), 2.14 (s, 3H), 3.75 (s, 3H), 5.53 (d, 1H, *J* = 9.5 Hz), 6.25 (d, 1H, *J* = 9.5 Hz), 6.45 (s, 1H), 6.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.20, 27.62, 55.90, 75.64, 108.19, 118.57, 119.01, 122.36, 127.51, 130.19, 146.25, 151.87; IR (neat film) 3039, 2973, 2925, 2859, 1701, 1498, 1465,1418, 1362, 1207 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{13}H_{17}O_2$ (M^++H) *m/z* 205.1229, meas 205.1236.



2-59 **2-41** **2-61**

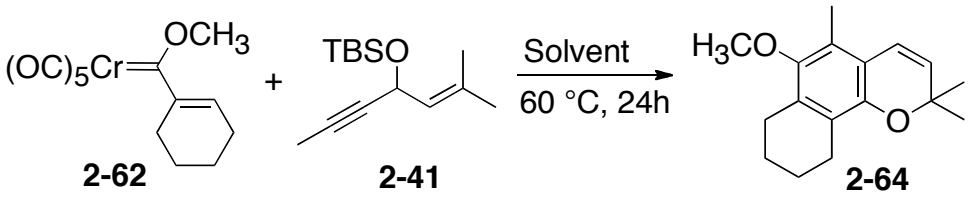
Compound 2-61: The carbene complex **2-59** (0.300 g, 1.08 mmol) was reacted with enyne **2-41** (0.31 g, 1.3 mmol) in 27 mL of dichloromethane. The reaction gave 0.16 g (68% yield, 0.73 mmol) of compound **2-61**. A repeat of the reaction gave the same yield. This reaction was also conducted in three other solvents, which were acetonitrile, hexane and benzene and gave 34%, 74% and 57% yields respectively. R_f = 0.25 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.38 (s, 6H), 2.20 (s, 6H), 3.63 (s, 3H), 5.58 (d, 1H, *J* = 10 Hz), 6.45 (d, 1H, *J* = 10 Hz), 6.46 (s, 1H); ^{13}C NMR ($CDCl_3$,

125 MHz) δ 11.27, 16.27, 27.60, 60.10, 74.90, 116.02, 118.52, 119.57, 126.30, 129.94, 131.21, 148.73, 150.66; IR (neat film) 3045, 2975, 2933, 2860, 1634, 1608, 1476, 1470, 1407, 1256 cm^{-1}; HRMS (TOF MS EI^+) calcd for $C_{14}H_{18}O_2$ *m/z* 218.1307, meas 218.1304.



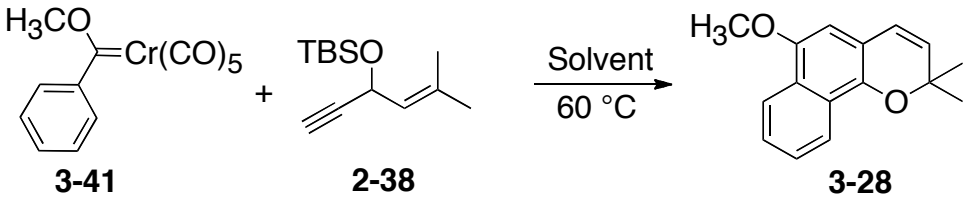
2-62 **2-38** **2-63**

Compound 2-63: The carbene complex **2-62** (0.30 g, 0.95 mmol) was reacted with enyne **2-38** (0.255 g, 1.14 mmol) in 27 mL of dichloromethane. The reaction gave 0.167 g (72% yield, 0.684 mmol) of compound **2-63** as a light yellow oil. This reaction was also conducted in acetonitrile and gave 65% yield. The reaction in acetonitrile did not need the oxidative workup. R_f = 0.36 (1% Ethyl acetate / Hexane); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.37 (s, 6H), 1.70-1.72 (m, 4H), 2.57-2.63 (m, 4H), 3.74 (s, 3H), 5.53 (d, 1H, *J* = 8 Hz), 6.24 (d, 1H, *J* = 8 Hz), 6.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.28, 22.41, 23.18, 23.60, 27.73, 55.65, 75.40, 104.80, 117.51, 122.77, 126.51, 127.04, 129.86, 144.19, 151.04; IR (neat film) 3039, 2970, 2931 2867, 1636, 1607, 1577, 1259, 1434, 1424, 1328, 1271, 1107 cm^{-1}; HRMS (TOF MS ES^+) calcd for $C_{16}H_{21}O_2$ (M^++H) *m/z* 245.1542, meas 245.1533.



2-62 **2-41** **2-64**

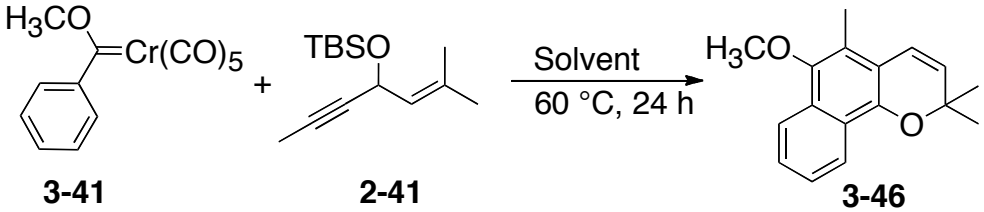
Compound 2-64: The carbene complex **2-62** (0.30 g, 0.95 mmol) was reacted with enyne **2-41** (0.271 g, 1.14 mmol) in 27 mL of dichloromethane. The reaction gave 0.196 g (80% yield, 0.759 mmol) of compound **2-64**. This reaction was also conducted in acetonitrile that gave 68% yield. The reaction in acetonitrile didn't need the oxidative workup. R_f = 0.27 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.37 (s, 6H), 1.70-1.72 (m, 4H), 2.18 (s, 3H), 2.56-2.59 (m, 2H), 2.67-2.71 (m, 2H), 3.62 (s, 3H), 5.57 (d, 1H, *J* = 8 Hz), 6.46 (d, 1H, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.26, 22.72, 22.82, 23.20, 24.23, 27.97, 60.19, 74.90, 117.53, 120.03, 122.96, 123.87, 129.83, 131.22, 146.80, 149.92; IR (neat film) 3096, 2974, 2932, 2858, 1638, 1596, 1452, 1415, 1322, 1268 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{17}H_{23}O_2$ (M^++H) *m/z* 259.1698, meas 259.1705.



3-41 **2-38** **3-28**

Lapachenole 3-28: The carbene complex **3-41** (0.30 g, 0.96 mmol) was reacted with enyne **2-38** (0.258 g, 1.15 mmol) in 20 mL of toluene in presence of 10 equiv. of aniline

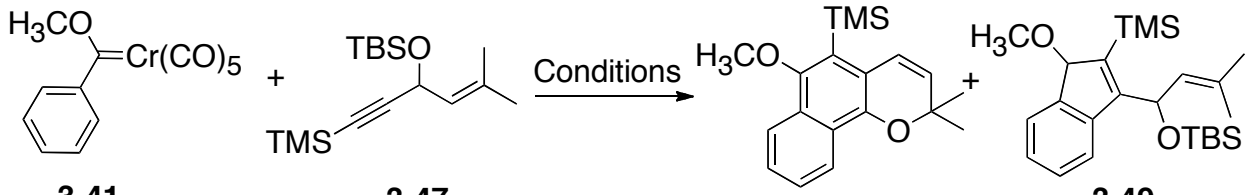
as additive. The reaction was run at 60 °C for 24 h. The reaction gave 0.11 g (48% yield, 0.46 mmol) of compound **3-28** as a light yellow oil. The compound was dissolved in a little pentane and was allowed to evaporate slowly. This process left a layer of waxy crystal. R_f = 0.23 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.48 (s, 6H), 3.94 (s, 3H), 5.64 (d, 1H, *J* = 9.5 Hz), 6.39 (d, 1H, *J* = 9.5 Hz), 6.50 (s, 1H), 7.40-7.47 (m, 2H), 8.14 (d, 2H, *J* = 8.30 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.52, 55.74, 76.16, 102.47, 114.74, 121.66, 121.78, 123.02, 125.43, 125.82, 125.88, 125.98, 129.89, 141.88, 149.22; IR (neat film) 3067, 3041, 2973, 2933, 2863, 2834, 1644, 1598, 1457, 1370 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{16}H_{17}O_2$ (M^++H) *m/z* 241.1229, meas 241.1217.



3-41 **2-41** **3-46**

5-Methyl-Lapachenole 3-46: The carbene complex **3-41** (0.30 g, 0.96 mmol) was reacted with enyne **2-41** (0.274 g, 1.15 mmol) in 20 mL of toluene in presence of 10 equiv. of aniline as additive. The reaction was run at 60 °C for 24 h. The reaction gave 0.21 g (85% yield, 0.82 mmol) of compound **3-46** as a light yellow oil. This reaction was also conducted in toluene without aniline and gave 80% yield. R_f = 0.22 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.50 (s, 6H), 2.41 (s, 3H), 3.85 (s, 3H),

5.69 (d, 1H, *J* = 10 Hz), 6.61 (d, 1H, *J* = 10 Hz), 7.38-7.46 (m, 2H), 7.98 (d, 1H, *J* = 8.30 Hz), 8.18 (d, 1H, J = 8.06 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.70, 27.47, 61.42, 75.51, 115.39, 119.97, 121.57, 122.22, 122.44, 124.66, 126.13, 128.04, 129.68, 144.57, 146.88; IR (neat film) 3069, 2975, 2934, 2843, 1643, 1455, 1378, 1360 cm^{-1}; HRMS (TOF MS ES^+) calcd for $C_{17}H_{19}O_2$ (M^++H) *m/z* 255.1385, meas 255.1377.



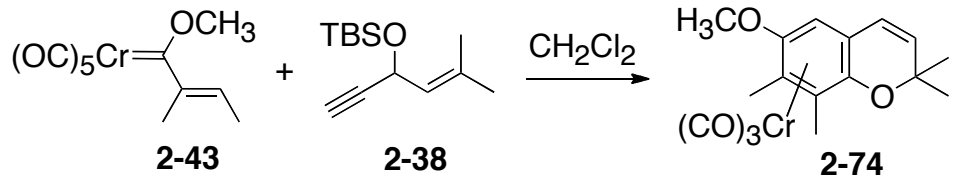
3-41 **3-47** **3-48** **3-49**

Compound 3-49: The carbene complex **3-41** (0.30 g, 0.96 mmol) was reacted with enyne **3-47** (0.341 g, 1.15 mmol) in 20 mL of toluene in presence of 10 equiv. of aniline as additive. The reaction was run at 60 °C for 24 h. The reaction gave 0.26 g (65% yield, 0.62 mmol) of compound **3-49** (1.14:1.00 mixture of diastereomers **3-49a** and **3-49b**) as light yellow oil. Compounds **3-49a** and **3-49b** were separated by preparative TLC. This reaction was also conducted in toluene in presence of 10 equiv. of aniline as additive and gave 62% yield of compound **3-49** as major product. However the crude ^1H NMR spectrum revealed a trace amount of another compound, which is tentatively identified as compound **3-48**.

Compound 3-49a: ^{1}H NMR ($CDCl_3$, 500 MHz) δ –0.05 - –0.03 (m, 6H), 0.13 (s, 9H), 0.83 (s, 9H), 1.64 (s, 3H), 1.71 (s, 3H), 3.30 (s, 3H), 5.34 (d, 1H, *J* = 1.2 Hz), 6.00 (s, 1H), 7.13-7.26 (m, 3H), 7.34 (dd, 2H, *J* = 7.9, 1.6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –0.22, 18.01, 19.29, 25.60, 25.67, 27.39, 57.07, 77.25 (overlapped with $CDCl_3$), 87.41, 119.42, 120.51, 124.39, 127.38, 127.49, 128.59, 128.86, 135.54, 138.31, 160.41; IR (neat film) 3059, 2956, 2930, 2899, 2858, 1590, 1472, 1253, 1198, 1166 cm^{-1}; HRMS (TOF MS ES^{+}) calcd for $C_{24}H_{41}O_2Si_2$ (M^{+}+H) *m/z* 417.2645, meas 417.2627.

Compound 3-49b: ^{1}H NMR ($CDCl_3$, 500 MHz) δ –0.27 (s, 9H), 0.14 (s, 6H), 0.94 (s, 9H), 1.74 (s, 3H), 1.86 (s, 3H), 3.22 (s, 3H), 5.50-5.71 (m, 1H), 6.28 (s, 1H), 7.26-7.32 (m, 2H), 7.32-7.37 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –4.86, 0.57, 18.44, 19.25, 25.96, 28.02, 56.39, 77.45, 87.17, 121.21, 123.94, 126.00, 128.05, 128.58, 129.60, 130.31, 137.15, 137.78, 158.69; IR (neat film) 3060, 2957, 2931, 2857, 1589, 1257, 1196, 1165 cm^{-1}; HRMS (TOF MS ES^{+}) calcd for $C_{24}H_{41}O_2Si_2$ (M^{+}+H) *m/z* 417.2645, meas 417.2631.

Preparation and Isolation of the Intermediate Chromium Tricarbonyl Complex (2-74):

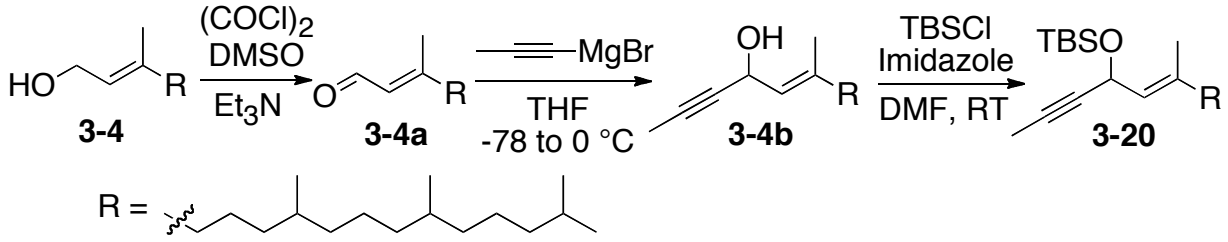


2-43 **2-38** **2-74**

To a 100 mL Schlenk flask was added carbene complex **2-43** (0.300 g, 1.03 mmol), alkyne **2-38** (0.278 g, 1.24 mmol), and dichloromethane (10 mL). The contents of the flask were heated for 24 hours at 45 °C. The solvent was quickly removed under reduced pressure at room temperature and loaded onto a silica gel column. The column was eluted with 4:1 pentane : ether. The compound **2-74** was collected and most of the solvent was removed below room temperature under a nitrogen purge through the solution. Finally rest of the solvent was removed under reduced pressure in a rotavapor without applying any heat. Yield = 61%; bright yellow crystal, mp 125 °C; R_f = 0.35 (4:1 pentane / ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.37 (s, 3H), 1.50 (s, 3H), 2.16 (s, 3H), 2.22 (s, 3H), 3.68 (s, 3H), 4.98 (s, 1H), 5.64 (d, 1 H, *J* = 10 Hz), 6.05 (d, 1H, *J* = 10 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.48, 12.76, 25.65, 29.45, 56.39, 72.47, 78.31, 85.62, 98.39, 98.62, 120.06, 128.15, 132.85, 135.31, 235.22; IR (neat film) 2975, 2928, 2855, 1945, 1874, 1458 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{17}H_{19}O_5Cr$ (M^++H) *m/z* 355.0638, meas 355.0624.

Synthesis of Vitamin E:

Preparation of Enyne (3-20):



In dichloromethane (60 mL), DMSO (1.57 g, 1.43 mL, 20.1 mmol) was treated with oxalyl chloride (0.93 g, 0.65 mL, 7.41 mmol) at -78 °C for 5 minutes. Then (all-rac)-phytol **3-4** (2.00 g, 2.35 mL, 6.74 mmol, from Sigma-Aldrich) was added and the reaction mixture was stirred for 15 minutes. Triethyl amine (4.75 g, 6.54 mL, 47.0 mmol) was added. The reaction was warmed to room temperature over an hour. The solution was poured into 100 mL of 1M HCl. The solution was extracted with ethyl acetate (3 x 100 mL). The organic layers were combined and washed with brine (50 mL). The brine layer was back extracted with 3 x 25 mL of ethyl acetate. The organic layers were combined and dried and neutralized over solid sodium bicarbonate and magnesium sulfate. The solvent was removed under reduced pressure and crude aldehyde **3-4a** was used without further purification.

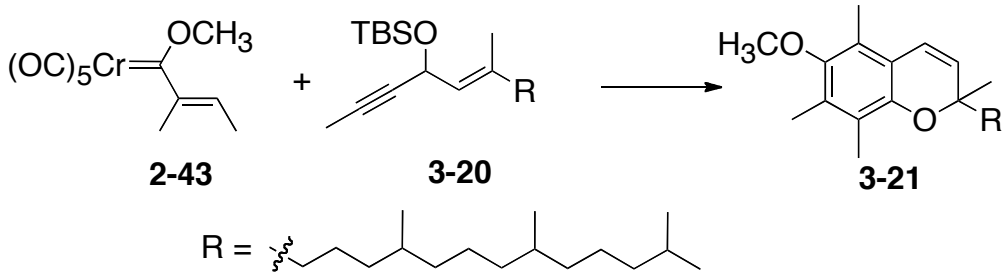
To all of the crude aldehyde from the above oxidation, was added propynyl magnesium bromide (0.5 M in THF, 19.8 mL, 9.87 mmol) over 10 minutes in THF (20 mL) at -78 °C. The solution was warmed to 0 °C and stirred for 1 h. After completion (as judged by TLC) the reaction mixture was then poured into 20 mL of saturated ammonium chloride

solution. The aqueous layer was separated and extracted with ethyl acetate (20 mL x 3). The organic layers were combined and dried over magnesium sulfate. The solution was filtered through and the solvent was removed under reduced pressure in a rotavapor. All of the crude alcohol was used in the next step.

The alcohol **3-4b** was reacted with TBSCl (1.25 g, 8.29 mmol), imidazole (0.820 g, 12.1 mmol) in dry DMF (110 mL). The mixture was stirred at room temperature for overnight. The solution was extracted with ether (100 mL x 2), saturated ammonium chloride solution (100 mL), and water (100 mL). Each aqueous layer was then back extracted with ether (25 mL x 3). The organic layers were combined and dried over magnesium sulfate. The crude product was purified by chromatography on silica gel with 5% ethyl acetate / hexane. The final enyne **3-20** was prepared in 86% yield (2.61 g, 5.82 mmol) over 3 steps following the procedure described above for compound **2-38** as a light yellow oil. R_f = 0.66 (5% Ethyl Acetate - Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.82-0.86 (m, 12H), 0.88 (s, 9H), 0.99-1.55 (m, 22H), 1.80 (d, 3H, *J* = 2 Hz), 1.94 (t, 2H, *J* = 5 Hz), 5.00-5.04 (m, 1H), 5.27-5.30 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –4.59, –4.54, –4.40, –4.33, 3.72, 16.37, 16.38, 18.31, 19.64, 19.65, 19.68, 19.70, 19.72, 19.75, 22.62, 22.71, 23.22, 24.42, 24.44, 24.46, 24.80, 24.81, 24.89, 25.88, 25.91, 26.03, 26.05, 27.97, 32.54, 32.65, 32.67, 32.68, 32.70, 32.75, 32.77, 32.79, 32.80, 36.60, 36.69, 36.70, 37.31, 37.37, 37.41, 37.46, 39.37, 39.53, 59.90, 60.25, 79.72, 80.57, 126.27, 126.84, 136.90, 136.91; IR (neat film) 1597, 1463, 1376, 1259, 1089, 1037 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{29}H_{56}OSi$ *m/z* 448.4100,

meas 448.4119.

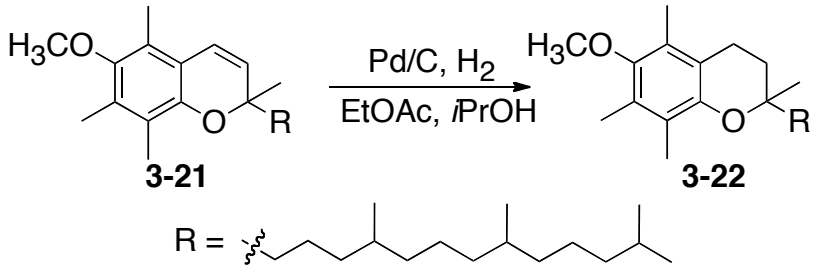
Preparation of Compound 3-21:



To a 100 mL single neck flask that had been modified by replacement of the joint with a threaded high vacuum Teflon valve was added carbene complex **2-43** (0.300 g, 1.03 mmol), alkyne **3-20** (0.556 g, 1.24 mmol), and dichloromethane (27 mL). The contents of the flask were heated for 24 hours at 60 °C. The solvent was removed under reduced pressure and dissolved in 15 mL ether and also 15 mL of water was added. In that reaction mixture $FeCl_3$•DMF complex (1.85 g, 7.75 mmol) was added. The mixture was stirred for 2 hours. The oxidation was monitored by TLC. After the oxidation was complete, the organic layer was separated and the water layer was washed with 3 x 20 mL of ether. All the organic layers were combined and dried with magnesium sulfate. The solvent was removed and the crude compound was purified by column chromatography using 1% ethyl acetate/hexane as the eluent. The yield of the product **3-21** was 85% (0.39 g, 0.88 mmol). The reaction was repeated in acetonitrile and the yield was 73%. Light yellow oil; R_f = 0.30 (1% Ethyl Acetate - Hexane); ^{1}H NMR ($CDCl_3$,

500 MHz) δ 0.8-0.86 (m, 12H), 1.00-1.62 (m, 24H), 2.67 (s, 3H), 2.16 (s, 3H), 2.19 (s, 3H), 3.60 (s, 3H), 5.56 (d, 1H, *J* = 10 Hz), 6.48 (d, 1H, *J* = 10 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.13, 11.54, 12.78, 19.57, 19.62, 19.64, 19.67, 19.74, 21.37, 21.39, 21.40, 22.62, 22.71, 24.42, 24.44, 24.46, 24.79, 24.81, 25.63, 27.97, 32.67, 32.70, 32.77, 32.79, 37.29, 37.30, 37.34, 37.36, 37.39, 37.45, 39.37, 40.92, 40.95, 60.32, 117.86, 120.14, 122.60, 123.10, 129.44, 129.46, 129.99, 146.87, 150.12; IR (neat film) 3010, 2951, 2927, 2867, 1460, 1407, 1381, 1265 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{30}H_{51}O_2$ (M^++H) *m/z* 443.3889, meas 443.3868.

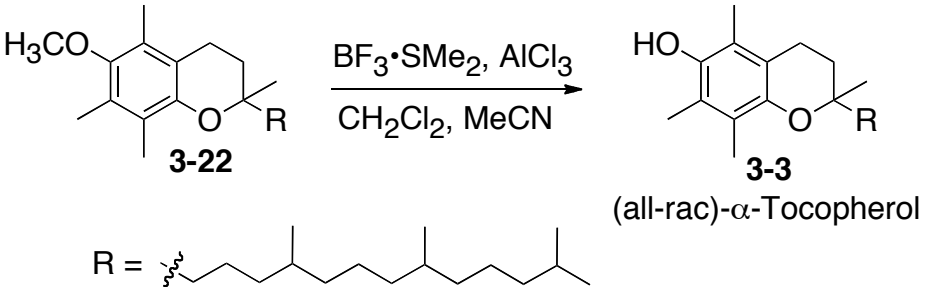
Preparation of compound 3-22:



A 10 mL single neck flask was charged with compound **3-21** (0.20 g, 0.45 mmol), ethyl acetate (6 mL), isopropanol (6 mL), and 10 % Pd on carbon (0.096 g). The flask was fitted with a septum and then high vacuum was applied very briefly through a needle and as soon as the solvent began to bubble, vacuum was replaced with hydrogen introducing hydrogen filled balloon. The reaction was stirred for overnight at room

temperature. The reaction mixture was filtered through Celite and the organic solvent was removed under reduced pressure to give compound **3-22** in 100% yield (0.20 g, 0.45 mmol) as a colorless oil. R_f = 0.28 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.81-0.86 (m, 12H), 1.00-1.58 (m, 24H), 1.70-184 (m, 2H), 2.06 (s, 3H), 2.12 (s, 3H), 2.17 (s, 3H), 2.56 (t, 2H, *J* = 5.6 Hz), 3.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.64, 11.68, 11.73, 11.77, 12.51, 12.54, 19.59, 19.62, 19.66, 19.68, 19.74, 20.64, 21.04, 22.62, 22.71, 23.88, 23.89, 24.44, 24.81, 27.97, 29.70, 31.24, 31.29, 32.68, 32.70, 32.77, 32.79, 37.29, 37.34, 37.37, 37.39, 37.42, 37.46, 37.50, 37.57, 37.59, 39.38, 40.07, 40.11, 60.27, 60.32, 60.37, 60.43, 74.75, 74.76, 117.50, 122.87, 125.67, 127.70, 147.77, 149.38; IR (neat film) 2927, 2867, 1459, 1404, 1380, 1257, 1090 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{30}H_{53}O_2$ (M^++H) *m/z* 445.4046, meas 445.4043.

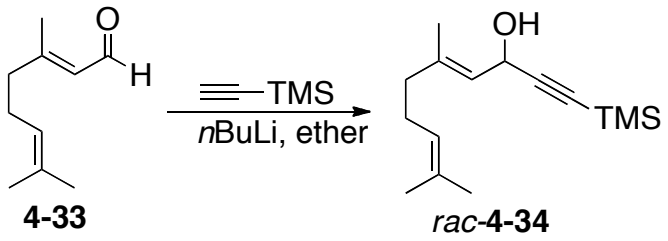
Preparation of compound (all-*rac*)-α-Tocopherol 3-3:



The final cleavage of the methoxy ether was performed with a method developed for the conversion of **3-22** to vitamin E.[161] To a solution of compound **3-22** (0.100 g, 0.225 mmol) in dichloromethane (2.5 mL) and acetonitrile (1.7 mL) were added boron trifluoride-dimethylsulfide complex (0.420 mL, 3.99 mmol) and anhydrous aluminum chloride (0.300 g, 2.25 mmol) at 0 ºC. The reaction mixture was stirred for 6 h at room temperature. The solvent was evaporated in rotavapor. The mixture was neutralized by adding ice-cold sat. aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (15 mL x 3). The organic phases were combined and washed with water and brine and dried with Na_2SO_4. After evaporation of the volatiles in rotavapor, the residue was purified by flash chromatography using Hexane/ethyl acetate (v/v, 5:1) as eluent to provide compound **3-3** (vitamin E) as light yellow oil (0.083 g, yield 86%). R_f = 0.16 (5% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.80-0.89 (m, 12H), 1.02-1.59 (m, 24H), 1.72-1.84 (m, 2H), 2.10 (s, 6H), 2.15 (s, 3H), 2.60 (t, 2H, *J* = 6.84 Hz), 4.16 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.26, 11.76, 12.19, 19.59, 19.63, 19.65, 19.68, 19.70, 19.74, 20.76, 21.04, 21.05, 21.07, 22.62, 22.71, 23.79, 24.44, 24.80, 24.81, 27.97, 31.50, 31.55, 32.68, 32.69, 32.70, 32.71, 32.78, 32.79, 37.28, 37.33, 37.39, 37.40, 37.41, 37.45, 37.46, 37.47, 37.50, 37.56, 37.59, 39.37, 39.81, 39.88, 74.51, 117.34, 118.45, 121.00, 122.61, 144.52, 145.55; IR (neat film) 3469, 2926, 2867, 1461, 1379, 1261, 1085 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{29}H_{51}O_2$ (M^++H) m/z 431.3889, meas 431.3881.

5.3 Chapter Four Experimental

Preparation of the compound *rac*-4-34:



4-33 ***rac*-4-34**

In diethyl ether (250 mL), TMS acetylene (3.06 g, 31.1 mmol) was deprotonated with *n*-butyl lithium (2.5 M in hexane, 12.5 mL, 31.1 mmol) at -78 ºC. The solution was allowed to warm to room temperature over one hour. The solution was recooled to –78 ºC and the prepared aldehyde **4-33** was added dropwise. The solution was warmed to 0 ºC and stirred for 40 minutes. The solution was then warmed to room temperature. The solution was poured into 100 mL of saturated aqueous ammonium chloride and back extracted with ether (3 x 100 mL). The organic layer was dried over magnesium sulfate, filtered through Celite, and the solvent removed under reduced pressure. Column chromatography with 10 % ethyl acetate / hexane gave 5.39 g of compound *rac*-**4-34** (83 % yield over two steps, 21.5 mmol). The spectroscopic properties match with the previously reported data.[162]

^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.15 (s, 9 H), 1.58 (s, 3 H), 1.66 (s, 3 H), 1.69 (s, 3 H), 1.76 (br s, 1 H), 2.00 - 2.14 (m, 2 H), 2.07 – 2.12 (m, 2 H), 5.03 - 5.09 (m, 2 H), 5.32 -

5.35 (m, 1 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ –0.14, 16.58, 17.69, 25.66, 26.15, 39.28, 59.49, 88.98, 106.08, 123.65, 124.30, 131.87, 140.64.

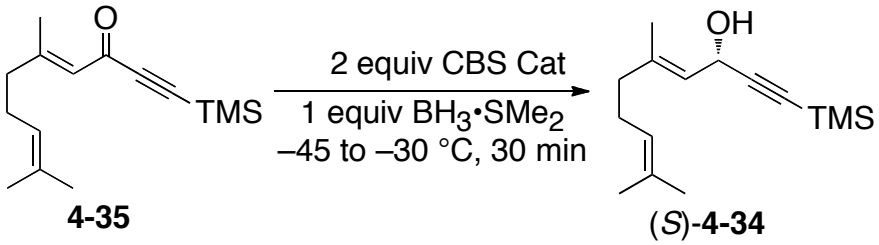
Preparation of the compound 4-35:

rac-**4-34** **4-35**

A 500 mL round bottom flask was charged with compound *rac*-**4-34** (5.16 g, 20.6 mmol), DCM (250 mL), and MnO_2 (17.43 g, 200.4 mmol). The contents of the flask were stirred overnight and filtered through Celite washing with DCM to remove the MnO_2. Column chromatography with 10 % ethyl acetate / hexane gave 3.89 g (76 % yield, 15.7 mmol) of **4-35**. The spectroscopic properties match with the previously reported data.[162]

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.22 (s, 9 H), 1.59 (s, 3 H), 1.67 (s, 3 H), 2.15 – 2.17 (m, 4 H), 2.18 (s, 3 H), 5.03 (br s, 1 H), 6.15 (s, 1 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ –0.76, 17.66, 19.86, 25.61, 26.05, 41.38, 95.81, 104.66, 122.71, 125.30, 132.71, 161.76, 176.34;

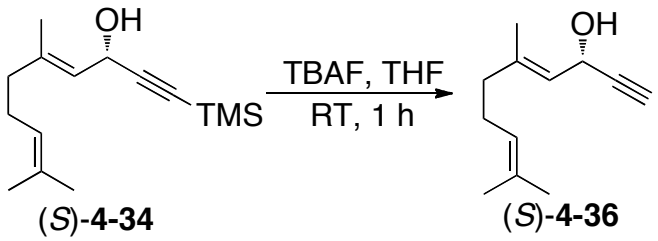
Preparation of the compound (*S*)-**4-34:**



4-35 (*S*)-**4-34**

To a solution of (*S*)-(–)-2-methyl-CBS-oxazaborolidine (2.21 g, 7.9 mmol) and compound **4-35** (0.97 g, 3.9 mmol) at –45 ºC in 40 mL of THF was added dropwise slowly BH_3•SMe_2 (2 mL of a 2 M solution in THF, 4.0 mmol). The solution was warmed to –30 ºC over 30 minutes. The TLC was checked to insure the reaction was complete. To the stirring solution was added methanol (20 mL) via syringe. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography (5 : 1 pentane : ether) to give 0.52 g (76%, 2.10 mmol) of compound (*S*)-**4-34** as light yellow oil. The spectroscopic properties were identical with those previously reported for the racemate *rac*-**4-34**. The enantioselectivity was determined to be 95% ee by chiral HPLC with Chiralcel OD-H column using 99.6 : 0.4 hexane : isoprpanol at 0.7 mL/min gave retention times of 16.05 minutes for the major and 18.38 minutes for the minor enantiomers. $[\propto]_D^{22}$ +69.3° (c 1.00, CH_2Cl_2) at 99 % ee. The reaction was also repeated and the enantioselectivity was found to be 98%, 97% and 99%. The spectroscopic properties match with the previously reported data for the racemic compound **4-34**.[162]

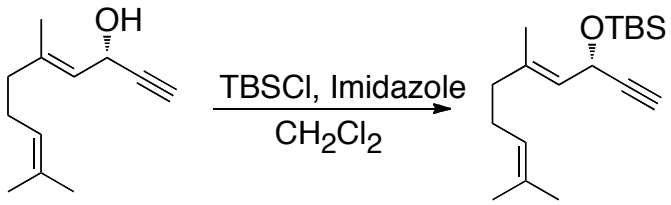
Preparation of the compound (*S*)-**4-36:**



To a stirred solution of compound (*S*)-**4-34** (0.61 g, 2.44 mmol) in 12 mL of THF, TBAF (1M in THF, 2.68 mL, 2.68 mmol) was added slowly at RT and stirred at this temperature for 1 h. The reaction mixture was then added slowly to a vigorously stirred mixture of 25 mL of brine. The aqueous layer was extracted with ether (3 x 25 mL). The organic layers were combined and dried with $MgSO_4$. Ether was distilled off under reduced pressure and the crude product was purified by column chromatography (eluent: dichloromethane) to give pure product (*S*)-**4-36** as a light yellow oil (0.43 g, 2.39 mmol, 98%). The spectroscopic properties match the previously reported data.[162]

^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.58 (s, 3 H), 1.66 (s, 3 H), 1.70 (d, 3 H, J = 1.3 Hz), 1.87 (br s, 1H), 1.95 - 2.15 (m, 2 H), 2.60 – 2.12 (m, 2 H), 2.47 (d, 1 H, J = 2.0 Hz), 5.01 - 5.08 (m, 2 H), 5.34 – 5.38 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.58, 17.66, 25.64, 26.14, 39.23, 58.88, 72.43, 84.44, 123.55, 123.97, 131.95, 140.93.

Preparation of the compound (*S*)-**4-37:**

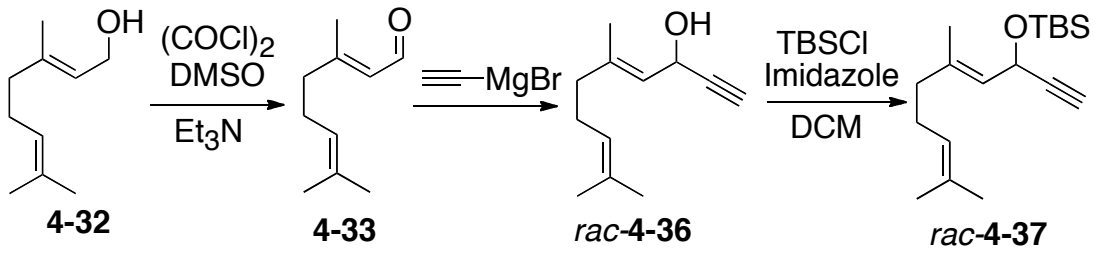


(*S*)-**4-36** (*S*)-**4-37**

To a mixture of imidazole (0.27 g, 4.0 mmol) and TBSCl (0.44 g, 2.9 mmol) in DMF (30 mL) was added compound (*S*)-**4-36** (0.47 g, 2.6 mmol, 98 % ee). The reaction mixture was stirred over night. The solution was quenched with 30 mL of saturated aqueous ammonium chloride and the aqueous layer was back extracted with ethyl acetate (2 x 30 mL). The organic layers were combined and dried over magnesium sulfate. The solution was filtered through fluted filter paper and then the solvent was removed under reduced pressure. Column chromatography with 5 % ethyl acetate / hexane gave 0.68 g (89 %, 2.31 mmol) of (*S*)-**4-37**. The spectroscopic properties match with the previously reported data.[162]

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.09 (s, 3 H), 0.1 (s, 3 H), 0.87 (s. 9H), 1.57 (s, 3 H), 1.65 (s, 6 H), 1.94 - 2.5 (m, 4 H), 2.40 (d, 1 H, J = 2.1 Hz), 5.00 - 5.12 (m, 2 H), 5.31 (dd, 1 H, J = 8.2, 1.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –4.69, –4.54, 16.45, 17.63, 18.18, 25.63, 25.75, 26.07, 39.20, 59.87, 71.56, 85.03, 123.77, 125.71, 131.60, 137.42.

Preparation of the compound *rac*-4-37:



4-32 **4-33** ***rac*-4-36** ***rac*-4-37**

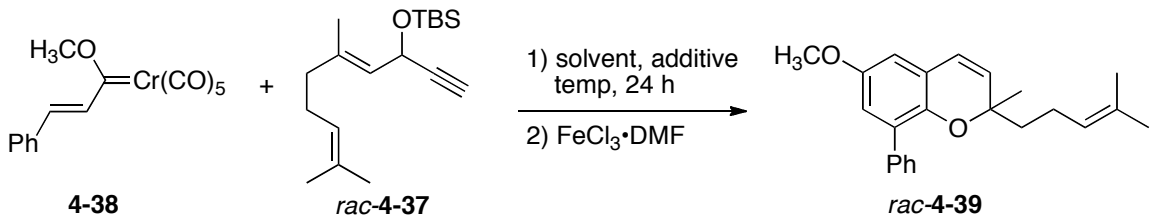
In dichloromethane (250 mL), DMSO (5.5 mL, 77.5 mmol) was treated with oxalyl chloride (2.5 mL, 28.5 mmol, 1.1 eq) at -78 °C for 5 minutes then geraniol **4-32** (4.5 mL, 25.9 mmol) was added and the reaction mixture was stirred for 15 minutes. Triethyl amine (25.3 mL, 181.0 mmol, 7 eq.) was added. The reaction was warmed to room temperature over an hour. The solution was poured into 200 mL of 1 (M) HCl. The solution was extracted with ethyl acetate (3 x 200 mL). The organic layers were combined and washed with brine (100 mL). The brine layer was back extracted with (3 x 50 mL) ethyl acetate. The organic layers were combined and dried over magnesium sulfate. The solvent was removed under reduced pressure and crude aldehyde **4-33** was used in the next step without further purification. The spectroscopic properties were identical with that previously reported in the literature.[163]

To the aldehyde **4-33** was added ethynyl magnesium bromide (0.5 M in THF, 55 mL, 27.5 mmol) over 10 minutes in 55 mL of THF at –78 ºC. The solution was warmed to 0 ºC and stirred for 1 hour. The reaction mixture was poured into 100 mL of saturated ammonium chloride and back extracted with (3 x 50 mL) ethyl acetate. The resulting organic layers were combined and dried over magnesium sulfate. The solution was

filtered through fluted filter paper and the solvent removed under reduced pressure. The crude compound *rac*-**4-36** was pure enough (from NMR) to be used in the next step without any purification.

To a mixture of imidazole (2.82 g, 41.4 mmol) and TBSCl (4.66 g, 31.1 mmol) in DMF (100 mL) all the crude compound *rac*-**4-36** was added. The reaction mixture was stirred over night. The solution was quenched with 150 mL of saturated ammonium chloride and the aqueous layer was back extracted with ether (3 x 100 mL). The organic layers were combined and dried over magnesium sulfate. The solution was filtered through fluted filter paper and then the solvent was removed under reduced pressure. Column chromatography with 5 % ethyl acetate / hexane gave 5.69 g (75 %, 19.5 mmol) of *rac*-**4-37**. Light yellow oil; R_f = 0.73 (5% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.88 (s, 9H), 1.57 (s, 3H), 1.65 (s, 6H), 1.97-2.01 (m, 2H), 2.05- 2.09 (m, 2H), 2.39 (d, 1H, *J* = 1.5 Hz), 5.03-5.06 (m, 2H), 5.28-5.32 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –4.67, –4.54, 16.49, 17.66, 18.22, 25.67, 25.76, 26.06, 39.19, 59.87, 71.56, 85.06, 123.75, 125.61, 131.70, 137.54; IR (neat film) 2958, 2934, 2858, 1606, 1388, 1262 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{18}H_{32}OSi$ (M^+–OTBS) *m/z* 161.1330, meas 161.1334.

Preparation of the compound *rac*-4-39:



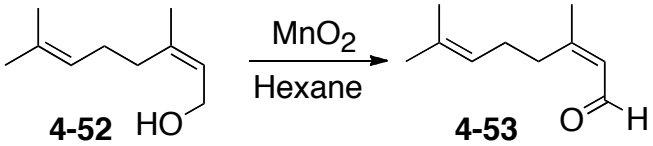
4-38 *rac*-**4-37** *rac*-**4-39**

The carbene complex **4-38** (0.09 g, 0.25 mmol), enyne *rac*-**4-37** (0.09 g, 0.29 mmol), and solvent (8.00 mL) were added to a 25 mL Schlenk flask. The reaction mixture was deoxygenated by the freeze-pump-thaw method (3 cycles) and finally the flask was back-filled with argon. The reaction mixture was stirred and heated at 80 ºC for 24 hours. The solvent was removed under reduced pressure and the crude compound was dissolved in 8 mL of diethyl ether. To this mixture, water (8 mL) and 7.5 equiv. of $FeCl_3$•DMF complex were added and stirred under air. Upon completion of the oxidation (judged by TLC), the organic layer was separated. The aqueous layer was washed with ether (3 x 15 mL). Organic layers were combined, washed with brine and dried over magnesium sulfate. Column chromatography with 1% ethyl acetate / hexane gave pure compound *rac*-**4-39** (0.02 g, 0.06 mmol, 24% yield).

The reaction was also conducted in toluene in presence of 10 equivalents of aniline as an additive at 60 ºC and the yield was 66% but in presence of 5 equivalents of Hünig's base (at 80 ºC) the yield was 34%. The reaction was also repeated in dichloroethane in presence of 5 equivalents of Hünig's base (at 80 ºC). The yield of the product was not determined as the product yield was very low and it was mixed with an inseparable

complicated side product mixture. Light yellow oil; R_f = 0.27 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.34 (s, 3H), 1.51 (s, 3H), 1.58-1.72 (s, 3H, m, 2H, overlapped), 1.95- 2.10 (m, 2H), 3.78 (s, 3H), 5.05 (t, 1H, *J* = 7 Hz), 5.63 (d, 1H, *J* = 10 Hz), 6.35 (d, 1H, *J* = 10 Hz), 6.55 (d, 1H, *J*= 2.5 Hz), 6.77 (d, 1H, *J* = 2.5 Hz), 7.30 (t, 1H, *J* = 7.5 Hz), 7.38 (t, 2H, *J* = 7.5 Hz), 7.57 (d, 2H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.49, 22.68, 25.55, 25.61, 40.89, 55.76, 78.19, 111.12, 115.43, 122.38, 123.14, 126.76, 127.76, 129.37, 129.92, 130.93, 131.60, 138.04, 143.82, 153.27, 165.56; IR (neat film) 3039, 2968, 2925, 2854, 1598, 1464, 1436, 1408, 1321, 1198 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{26}O_2$ (M^++H) *m/z* 335.2011, meas 335.1998.

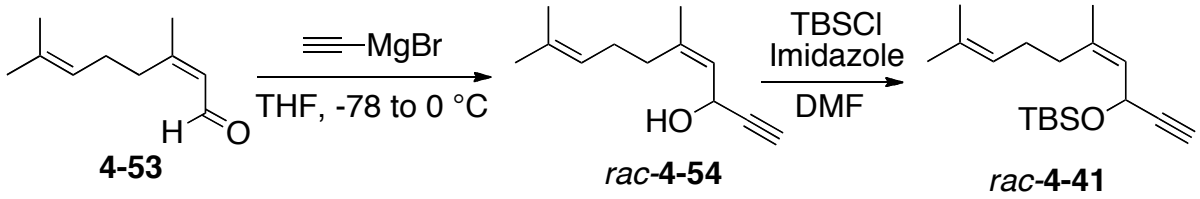
Preparation of the compound 4-53:



A mixture of 2.5 g of nerol **4-52** and 29 g of active manganese dioxide[164] in 300 ml of hexane was stirred at 0 ºC for 30 min. Filtration and removal of solvent afforded 2 g (82%) of neral **4-53** shown by NMR[165] to be >95% pure and also free of geranial (*α, β*-geometrical isomer). The procedure was followed from a similar procedure reported in the literature.[166]

Yellow Oil; R_f = 0.68 (30% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.56 (s, 3H), 1.65 (s, 3H), 1.95 (s, 3H), 2.20 (q, 2H, *J* = 7.5 Hz), 2.55 (t, 2H, *J* = 7.5 Hz), 5.04-5.10 (m, 1H), 5.84 (d, 1H, *J* = 8.5 Hz), 9.86 (d, 1H, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.68, 25.01, 25.59, 27.00, 32.53, 122.21, 128.62, 133.65, 163.75, 190.75; IR (neat film) 3025, 2969, 2918, 2859, 2756, 1676, 1632, 1443, 1395, 1378 cm^{-1}; HRMS (TOF MS ES$^-$) calcd for $C_{10}H_{16}O$ (M^+–H) *m/z* 151.1123, meas 151.1118.

Preparation of the compound *rac*-4-41:



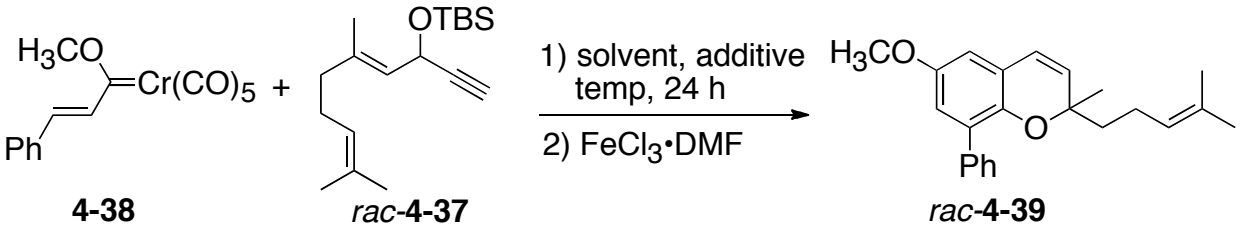
4-53 *rac*-**4-54** *rac*-**4-41**

To the aldehyde **4-53** (2.02 g, 14.62 mmol) was added ethynyl magnesium bromide (0.5 M in THF, 36 mL, 17.6 mmol) over 10 minutes in 36 mL of THF at –78 ºC. The solution was warmed to 0 ºC and stirred for 1 hour. The reaction mixture was poured into 100 mL of saturated ammonium chloride and back extracted with 3 x 50 mL of ethyl acetate. The resulting organic layers were combined and dried over magnesium sulfate. The solution was filtered through fluted filter paper and the solvent removed under reduced pressure. The crude compound *rac*-**4-54** was pure enough (from NMR) to be used in the next step without any purification.

To a mixture of imidazole (1.60 g, 23.4 mmol) and TBSCl (2.42 g, 16.0 mmol) in DMF (60 mL) compound *rac*-**4-54** (2.60 g, 14.6 mmol) was added. The reaction mixture was stirred over night. The solution was quenched with 100 mL of saturated ammonium chloride and the aqueous layer was back extracted with ether (3 x 100 mL). The organic layers were combined and dried over magnesium sulfate. The solution was filtered through fluted filter paper and then the solvent was removed under reduced pressure. Column chromatography with 5 % ethyl acetate / hexane gave 3.34 g (78 %, 11.4 mmol) of *rac*-**4-41**.

Light yellow oil; R_f = 0.72 (5% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.09 (s, 3H), 0.11 (s, 3H), 0.88 (s, 9H), 1.59 (s, 3H), 1.67 (s, 3H), 1.71 (s, 3H), 1.98-2.12 (m, 4H), 2.39 (d, 1H, J = 1.5 Hz), 5.05-5.12 (m, 2H), 5.30-5.33 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –4.62, –4.46, 17.65, 18.21, 23.18, 25.71, 25.79,26.36, 32.41, 59.53, 71.65, 85.32, 123.66, 126.25, 132.11, 137.75; IR (neat film) 2957, 2924, 2858, 1653, 1472, 1379, 1254 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{18}H_{32}OSi$ (M^+–OTBS) *m/z* 161.1330, meas 161.1336.

Synthesis of *rac*-4-39 by Reaction between 4-38 and *rac*-4-41:



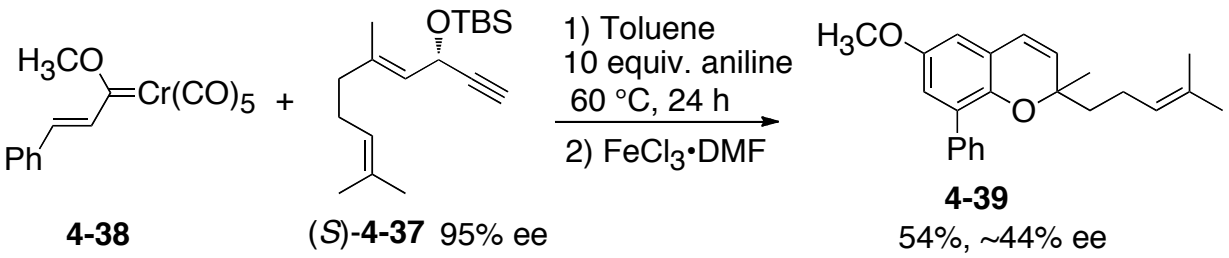
4-38 *rac*-**4-37** *rac*-**4-39**

The carbene complex **4-38** (0.10 g, 0.29 mmol), enyne *rac*-**4-41** (0.10 g, 0.35 mmol), and dichloromethane (10 mL) were added to a 25 mL Schlenk flask. The reaction mixture was deoxygenated by the freeze-pump-thaw method (3 cycles) and finally the flask was back-filled with argon. The reaction mixture was stirred and heated at 80 ºC for 24 hours. The solvent was removed under reduced pressure and the crude compound was dissolved in 10 mL of diethyl ether. To this mixture, water (10 mL) and 7.5 equiv. of $FeCl_3$•DMF complex were added and stirred under air. Upon completion of the oxidation (judged by TLC), the organic layer was separated. The aqueous layer was washed with ether (3 x 15 mL). Organic layers were combined, washed with brine and dried over magnesium sulfate. Column chromatography with 1% ethyl acetate / hexane gave pure compound *rac*-**4-39** (0.07 g, 0.20 mmol, 68%).

The reaction was performed at 80 °C in two other solvents such as toluene and acetonitrile that gave 77% and 76% yields respectively. When the reaction was conducted in toluene in presence of 10 equivalents of aniline as an additive and the

yield was 90% but in presence of 5 equivalents of Hünig's base the yield was 57%. The spectroscopic properties match the previously given data for compound *rac*-**4-39**.

Preparation of the compound 4-39:



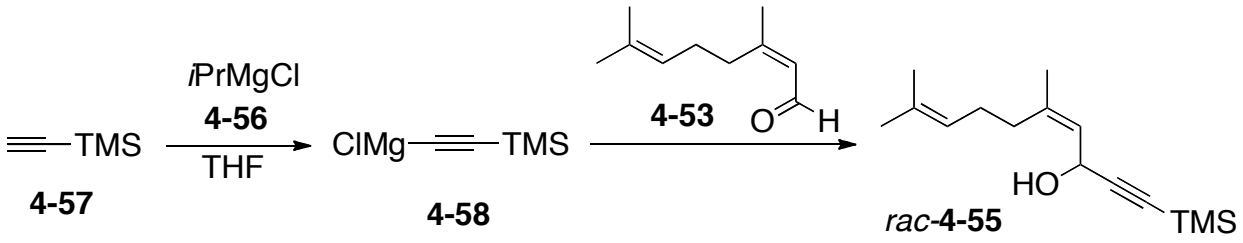
4-38 (*S*)-**4-37** 95% ee **4-39** 54%, ~44% ee

The carbene complex **4-38** (0.10 g, 0.29 mmol), enyne (*S*)-**4-37** (0.10 g, 0.36 mmol, 95% ee), aniline (0.26 mL, 0.27 g, 2.90 mmol) and solvent (10.0 mL) were added to a 25 mL Schlenk flask. The reaction mixture was deoxygenated by the freeze-pump-thaw method (3 cycles) and finally the flask was back-filled with argon. The reaction mixture was stirred and heated at 60 ºC for 24 hours. The solvent was removed under reduced pressure and the crude compound was dissolved in 10 mL of diethyl ether. To this mixture, water (10 mL) and 7.5 equiv. of $FeCl_3$•DMF complex were added and stirred under air. Upon completion of the oxidation (judged by TLC), the organic layer was separated. The aqueous layer was washed with ether (3 x 15 mL). Organic layers were combined, washed with brine and dried over magnesium sulfate. Column chromatography with 1% ethyl acetate / hexane gave pure compound **4-39** (0.05 g, 0.16 mmol, 54% yield). The spectroscopic properties are identical to that of the previously

synthesized compound *rac*-**4-39**. Chiral HPLC with Chiralcel OD-H column using 99.6 : 0.4 hexane : isopropanol at 0.5 mL/min gave retention times of 19.90 minutes for the major and 20.87 minutes for the minor enantiomers. Although the enantiomers were only partially separable but the enantioselectivity could be predicted as 44% ee for compound **4-39.**

When the reaction was repeated under the same conditions but at lower temperature (40 ºC) the yield of the product **4-39** was 50% but it was racemic. The reaction was also repeated in three other solvents such as benzene, dichloromethane and hexane at 60 ºC maintaining other conditions same and the yields of the product **4-39** was 52%, 55% and 56% respectively. Although for all these reactions, the enatiomers were not well separated, it was easily seen that the products were almost racemic.

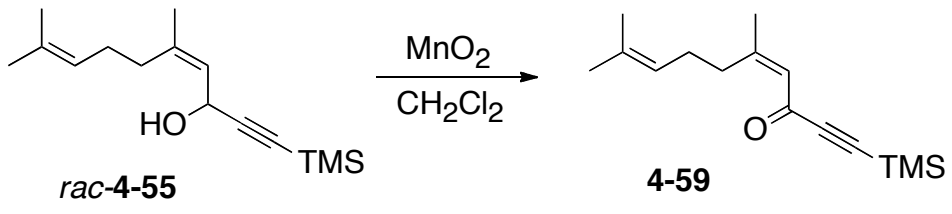
Preparation of the compound *rac*-**4-55:**



To a solution of trimethylsilyl acetylene **4-57** (1.22 mL, 0.840 g, 8.57 mmol) in 30 mL of THF at 0 °C was added isopropylmagnesium chloride **4-56** (2.0 M in THF, 4.30 mL, 8.57 mmol). The reaction mixture was then warmed to room temperature for 2 hours. Freshly prepared neral **4-53** (1.21 mL, 1.09 g, 7.14 mmol) was added to the reaction mixture at

0 °C. The reaction mixture was warmed to room temperature for 4 hours. After completion (as judged by TLC) the reaction mixture was then poured into 50 mL of saturated ammonium chloride solution. The aqueous layer was separated and extracted with ether (50 mL x 3). The organic layers were combined and dried over magnesium sulfate. The solution was filtered through celite and the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel with 10% ethyl acetate / hexane to give 1.69 g (95% yield, 6.78 mmol) of compound *rac*-**4-55** as light yellow oil. R_f = 0.42 (30% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.15 (s, 9H), 1.59 (s, 3H), 1.67 (s, 3H), 1.74 (d, 3H, *J* = 1.2 Hz), 2.08-2.14 (m, 4H), 5.03 (d, 1H, *J* = 9.0 Hz), 5.09 (br s, 1H), 5.36 (dd, 1H, *J* = 9.0 Hz, *J* = 1.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ –0.14, 17.68, 23.33, 25.66, 26.30, 32.24, 59.16, 88.94, 106.03, 123.65, 125.32, 132.71, 140.56; IR (neat film) 3334, 2965, 2927, 2859, 2172, 1665, 1447, 1378 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{15}H_{26}OSi$ (M^++H) *m/z* 251.1831, meas 251.1825.

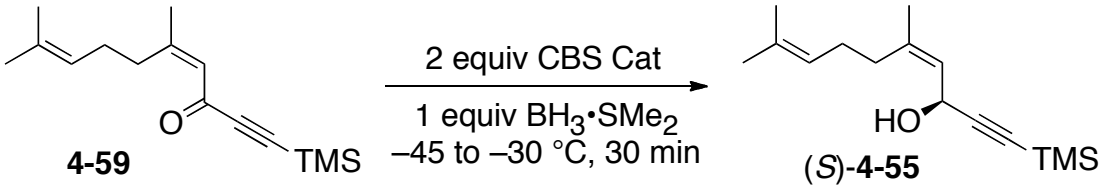
Preparation of the compound 4-59:



rac-**4-55** **4-59**

A 500 mL round bottom flask was charged with compound *rac*-**4-55** (1.04 g, 4.15 mmol), dichloromethane (50 mL), and MnO_2 (3.51 g, 40.4 mmol). The contents of the flask were stirred overnight and filtered through celite washing with dichloromethane to remove MnO_2. The crude product was purified by chromatography on silica gel with 10% ethyl acetate / hexane to give 0.78 g (75% yield, 3.14 mmol) of compound **4-59** as light yellow oil. R_f = 0.69 (30% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.21 (s, 9H), 1.60 (s, 3H), 1.66 (d, 3H, *J* = 0.6 Hz), 1.91 (d, 3H, *J* = 1.2 Hz), 2.12- 2.18 (m, 2H), 2.67 (t, 2H, *J* = 7.8 Hz), 5.10-5.13 (m, 1H), 6.12 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ –0.73, 17.64, 25.66, 25.90, 26.83, 34.19, 95.58, 104.50, 123.37, 125.97, 132.52, 162.44, 175.80; IR (neat film) 2965, 2925, 2857, 2151, 1652, 1606, 1443, 1377, 1252 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{15}H_{24}OSi$ (M^++H) *m/z* 249.1675, meas 249.1669.

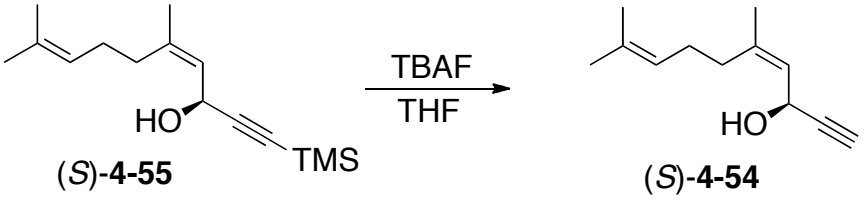
Preparation of the compound (*S*)-**4-58:**



4-59 (*S*)-**4-55**

To a solution of (*S*)-(–)-2-methyl-CBS-oxazaborolidine (1.52 g, 5.45 mmol) and compound **4-59** (0.69 g, 2.78 mmol) at –45 ºC in 25 mL of THF was added dropwise slowly BH_3•SMe_2 (2 M in THF, 1.44 mL, 2.89 mmol). The solution was warmed to –30 ºC over 30 minutes. The TLC was checked to insure the reaction was complete. To the stirring solution was added methanol (20 mL) via syringe. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography (5:1 pentane : ether) to give 0.61 g (88%, 2.44 mmol) of compound (*S*)-**4-55** as light yellow oil. Chiral HPLC with Chiralcel OD-H column using 99.6 : 0.4 hexane : isoprpanol at 0.7 mL/min gave retention times of 12.8 minutes for the major and 16.8 minutes for the minor enantiomers showing 94% ee for compound (*S*)-**4-55**. The spectroscopic properties match with the previously synthesized compound *rac*-**4-55**. When the reaction was repeated the ee was calculated to be 99%. $[\propto]_D^{22}$ +149.6° (c 1.00, CH_2Cl_2) at 99 % ee.

Preparation of the compound (*S*)-**4-54:**

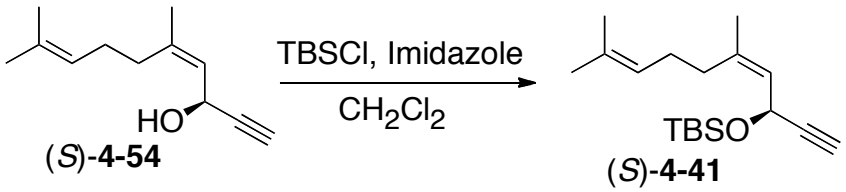


(*S*)-**4-55** (*S*)-**4-54**

To a stirred solution of compound (*S*)-**4-55** (0.61 g, 2.44 mmol) in 12 mL of THF, TBAF (1 M in THF, 2.68 mL, 2.68 mmol) was added slowly at RT and stirred at this

temperature for 1 h. The reaction mixture was then added slowly to a vigorously stirred mixture of 25 mL of brine. The aqueous layer was extracted with ether (3 x 25 mL). The organic layers were combined and dried with $MgSO_4$. Ether was distilled off under reduced pressure and the crude product was purified by column chromatography (eluent: dichloromethane) to give pure product (*S*)-**4-54** as light yellow oil (0.43 g, 2.39 mmol, 98%). R_f = 0.41 (30% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.58 (s, 3H), 1.67 (s, 3H), 1.73 (s, 3H), 1.90 (d, 1H, *J* = 4.5 Hz), 2.05-2.16 (m, 4H), 2.45 (t, 1H, *J* = 2.0 Hz), 5.02-5.11 (m, 2H), 5.37 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.63, 23.23, 25.63, 26.25, 32.22, 58.51, 72.40, 84.43, 123.49, 124.99, 132.71, 140.79; IR (neat film) 3298, 3035, 2967, 2924, 2857, 2136, 1665, 1446, 1377 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{12}H_{18}O$ (M^+–OH) *m/z* 161.1330, meas 161.1328. $[\propto]_D^{22}$ +100.8° (c 1.00, CH_2Cl_2) at 99 % ee.

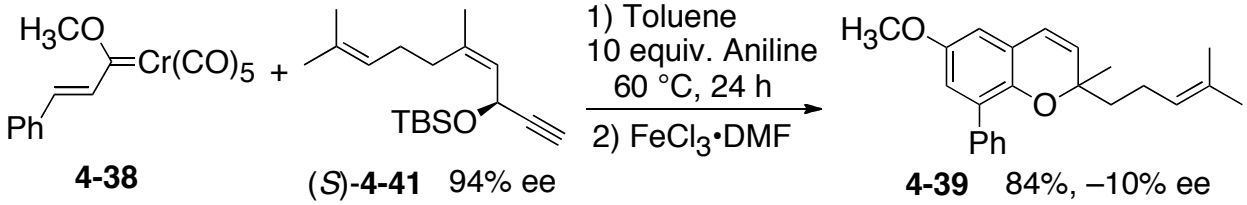
Preparation of the compound (*S*)-**4-41:**



To a mixture of imidazole (0.26 g, 3.88 mmol) and TBSCl (0.42 g, 2.81 mmol) in DCM (13 mL) compound (*S*)-**4-54** (0.43 g, 2.44 mmol) was added. The reaction mixture was

stirred over night. The solution was quenched with 50 mL of saturated ammonium chloride and the aqueous layer was back extracted with ether (3 x 25 mL). The organic layers were combined and dried over magnesium sulfate. The solution was filtered through fluted filter paper and then the solvent was removed under reduced pressure. Column chromatography with 5 % ethyl acetate / hexane gave 0.60 g (84%, 2.05 mmol) of (*S*)-**4-41**. The spectroscopic properties match with the previously given data for *rac*-**4-41**. $[\propto]_D^{22}$ +40.3° (c 1.00, CH_2Cl_2) at 99 % ee.

Synthesis of 4-39 by Reaction between Compounds 4-38 and (*S*)-4-41:

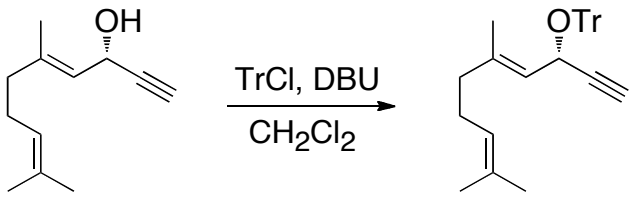


4-38 (*S*)-**4-41** 94% ee **4-39** 84%, –10% ee

The carbene complex **4-38** (0.10 g, 0.29 mmol), enyne (*S*)-**4-41** (0.10 g, 0.35 mmol, 94% ee), and solvent (10.0 mL) were added to a 25 mL Schlenk flask. The reaction mixture was deoxygenated by the freeze-pump-thaw method (3 cycles) and finally the flask was back-filled with argon. The reaction mixture was stirred and heated at 60 ºC for 24 hours. The solvent was removed under reduced pressure and the crude compound was dissolved in 10 mL of diethyl ether. To this mixture, water (10 mL) and 7.5 equiv. of $FeCl_3$•DMF complex were added and stirred under air. Upon completion of the oxidation (judged by TLC), the organic layer was separated. The aqueous layer was

washed with ether (3 x 15 mL). Organic layers were combined, washed with brine and dried over magnesium sulfate. Column chromatography with 1% ethyl acetate / hexane gave pure compound **4-39**. The spectroscopic properties match the previously reported data for compound *rac*-**4-39**. In chiral HPLC even after trying many different conditions and chiral columns the enantiomers couldn't be completely separated. So the ee was only predicted to be –10% ee. It was observed that the opposite enantiomer was the major isomer in this case compared to the reaction between **4-38** and (*S*)-**4-37** or between **4-38** and (*S*)-**4-60**.

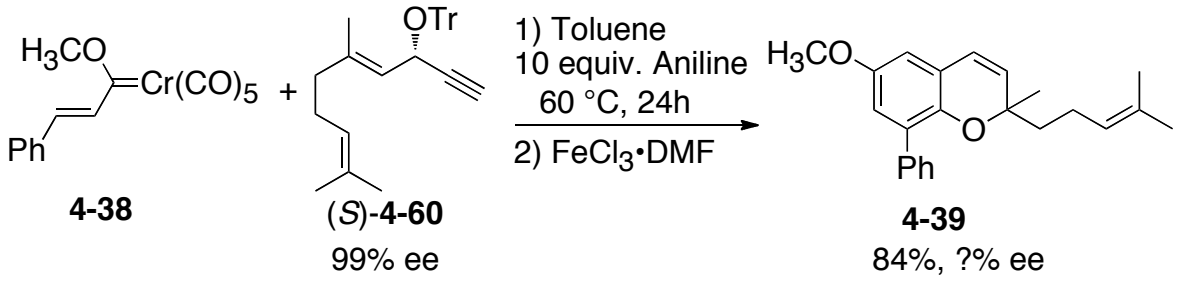
Preparation of the compound (*S*)-**4-60:**



To a solution of triphenylmethyl chloride (0.94 g, 3.37 mmol) and DBU (0.59 mL, 0.60 g, 3.93 mmol) in dichloromethane (5 mL), the alcohol substrate (*S*)-**4-36** (0.50 g, 2.81 mmol, 99% ee) was added and the mixture was stirred at room temperature for two days. The progress of the reaction was conveniently monitored by TLC analysis of crude reaction mixture. Products were isolated by washing the reaction mixture with cold water, extracting the aqueous layer with dichloromethane and drying the organic extracts with sodium sulfate. Evaporation of the solvent yielded crude triphenylmethyl

ether (*S*)-**4-60**, which was purified by short column chromatography on silica gel with 5% ethyl acetate / hexane to give 1.12 g (95% yield, 2.67 mmol) of compound (*S*)-**4-60**. Colorless condensed oil; R_f = 0.65 (5% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.37 (d, 3H, *J* = 1.5 Hz), 1.62 (s, 3H), 1.70 (d, 3H, *J* = 1.0 Hz), 1.82-1.94 (m, 2H), 1.98-2.04 (m, 2H), 2.16 (d, 1H, *J* = 2.0 Hz), 4.76 (dd, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz), 5.06-5.15 (m, 1H), 5.25 (dd, 1H, *J* = 8.0 Hz, *J* = 1.5 Hz), 7.21-7.32 (m, 10H), 7.51-7.62 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.75, 17.71, 25.69, 26.12, 39.04, 61.99, 72.04, 83.31, 88.23, 123.89, 123.98, 127.01, 127.70, 128.96, 131.64, 136.78, 144.35; IR (neat film) 3292, 3058, 3032, 2967, 2918, 2854, 1668, 1597, 1491, 1448 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{31}H_{32}O$ (M^++H) *m/z* 421.2531, meas 421.2519; $[\propto]_D^{22}$ +15.0° (c 1.00, CH_2Cl_2) at 99 % ee.

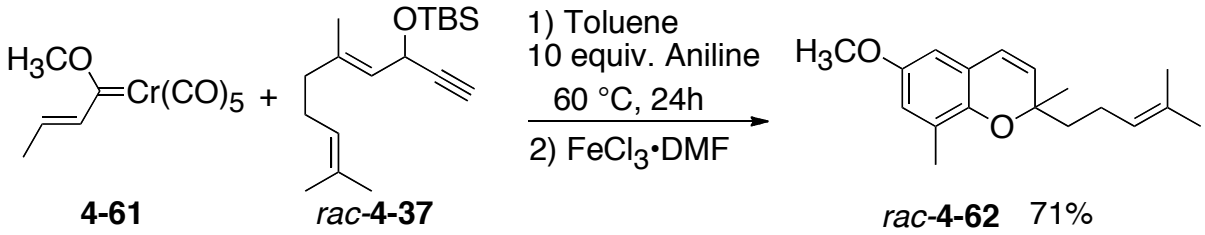
Synthesis of 4-39 by Reaction between Compounds 4-38 and (*S*)**-4-60:**



The carbene complex **4-38** (0.10 g, 0.29 mmol), enyne (*S*)-**4-60** (0.15 g, 0.36 mmol, 99% ee), aniline (0.26 mL, 0.27 g, 2.90 mmol) and solvent (10.0 mL) were added to a

25 mL Schlenk flask. The reaction mixture was deoxygenated by the freeze-pump-thaw method (3 cycles) and finally the flask was back-filled with argon. The reaction mixture was stirred and heated at 60 ºC for 24 hours. The solvent was removed under reduced pressure and the crude compound was dissolved in 8 mL of diethyl ether. To this mixture, water (8 mL) and 7.5 equiv. of $FeCl_3$•DMF complex were added and stirred under air. Upon completion of the oxidation (judged by TLC), the organic layer was separated. The aqueous layer was washed with ether (3 x 15 mL). Organic layers were combined, washed with brine and dried over magnesium sulfate. Column chromatography with 1% ethyl acetate / hexane gave pure compound **4-39** (0.08 g, 0.25 mmol, 84% yield). The spectroscopic properties match the previously given data for compound *rac*-**4-39**. In chiral HPLC even after trying many different conditions and chiral columns the enantiomers couldn't be completely separated. So the ee was not determined.

Preparation of the compound *rac*-4-62:



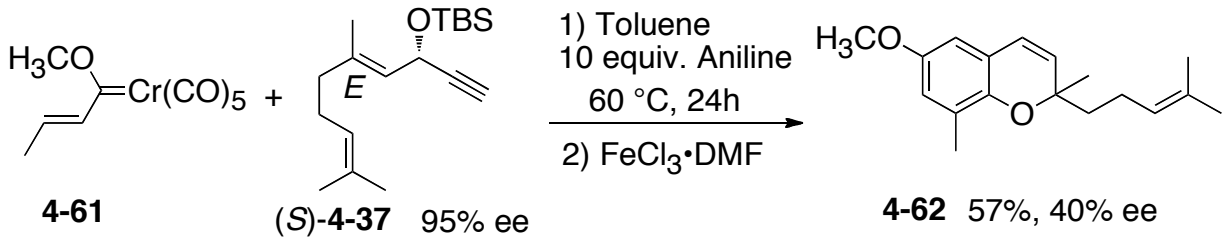
4-61 *rac*-**4-37** *rac*-**4-62** 71%

The carbene complex **4-61** (0.05 g, 0.18 mmol), enyne *rac*-**4-37** (0.06 g, 0.22 mmol), aniline (0.16 mL, 0.17 g, 1.80 mmol), and solvent (5.00 mL) were added to a 25 mL

Schlenk flask. The reaction mixture was deoxygenated by the freeze-pump-thaw method (3 cycles) and finally the flask was back-filled with argon. The reaction mixture was stirred and heated at 60 ºC for 24 hours. The solvent was removed under reduced pressure and the crude compound was dissolved in 8 mL of diethyl ether. To this mixture, water (8 mL) and 7.5 equiv. of $FeCl_3$•DMF complex were added and stirred under air. Upon completion of the oxidation (judged by TLC), the organic layer was separated. The aqueous layer was washed with ether (3 x 15 mL). Organic layers were combined, washed with brine and dried over magnesium sulfate. Column chromatography with 1% ethyl acetate / hexane gave pure compound *rac*-**4-62** (0.04 g, 0.13 mmol, 71% yield).

Yellow oil; R_f = 0.28 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.34 (s, 3H), 1.56 (s, 3H), 1.65 (s, 3H), 1.64-1.70 (m, 2H), 2.02- 2.20 (m, 2H), 2.14 (s, 3H), 3.72 (s, 3H), 5.06-5.12 (m, 1H), 5.56 (d, 1H, *J* = 10 Hz), 6.27 (d, 1H, *J* = 10 Hz), 6.36 (d, 1H, *J* = 2.5 Hz), 6.54 (d, 1H, *J* = 2.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.62, 17.55, 22.69, 25.66, 25.90, 40.83, 55.65, 77.81, 108.77, 116.01, 121.10, 123.07, 124.25, 126.20, 130.57, 131.57, 144.98, 152.90; IR (neat film) 3037, 2967, 2925, 2855, 1733, 1676, 1592, 1473, 1440 cm^{-1}; HRMS (TOF MS ES^+) calcd for $C_{18}H_{24}O_2$ (M^++H) *m/z* 273.1855, meas 273.1843.

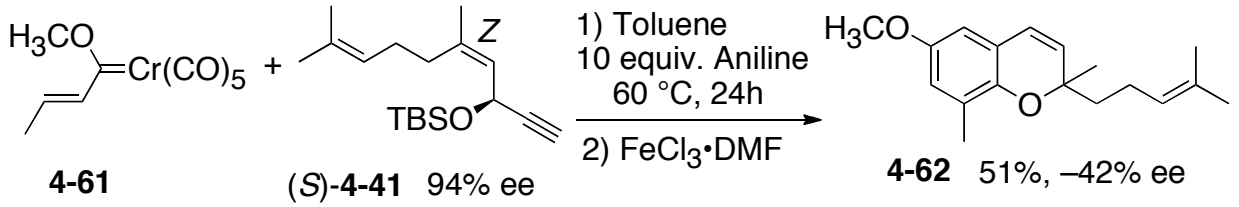
Synthesis of 4-62 by Reaction between 4-61 and (*S*)-4-37:



4-61 (*S*)-**4-37** 95% ee **4-62** 57%, 40% ee

The carbene complex **4-61** (0.05 g, 0.18 mmol), enyne (*S*)-**4-37** (0.06 g, 0.22 mmol, 95% ee), aniline (0.16 mL, 0.17 g, 1.80 mmol), and solvent (5.00 mL) were added to a 25 mL Schlenk flask. The reaction mixture was deoxygenated by the freeze-pump-thaw method (3 cycles) and finally the flask was back-filled with argon. The reaction mixture was stirred and heated at 60 ºC for 24 hours. The solvent was removed under reduced pressure and the crude compound was dissolved in 8 mL of diethyl ether. To this mixture, water (8 mL) and 7.5 equiv. of $FeCl_3$•DMF complex were added and stirred under air. Upon completion of the oxidation (judged by TLC), the organic layer was separated. The aqueous layer was washed with ether (3 x 15 mL). Organic layers were combined, washed with brine and dried over magnesium sulfate. Column chromatography with 1% ethyl acetate / hexane gave pure compound **4-62** (0.03 g, 0.10 mmol, 57% yield). The spectroscopic data is identical to that of *rac*-**4-62.** Chiral HPLC with Chiralcel OD-H column using 99.6 : 0.4 hexane : isopropanol at 0.5 mL/min gave retention times of 14.61 minutes for the minor and 17.41 minutes for the major enantiomers showing 40% ee for compound **4-62.**

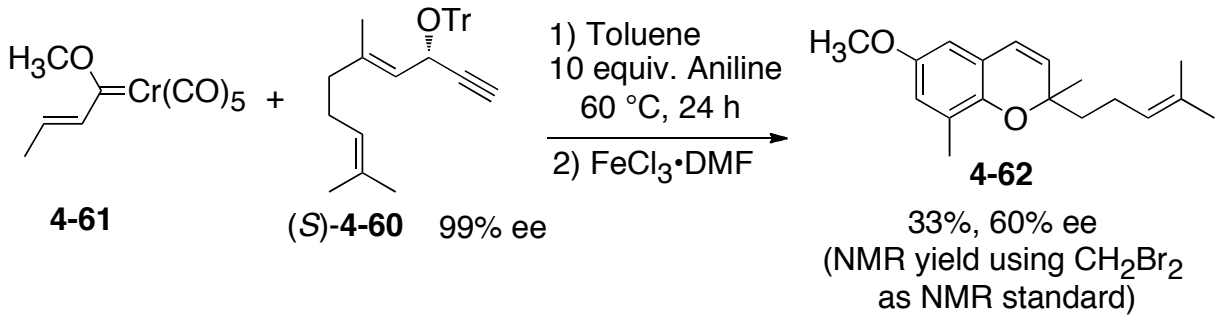
Synthesis of 4-62 by Reaction between 4-61 and (*S*)-4-41:



4-61 (*S*)-**4-41** 94% ee **4-62** 51%, –42% ee

The carbene complex **4-61** (0.05 g, 0.18 mmol), enyne (*S*)-**4-41** (0.06 g, 0.22 mmol, 94% ee), aniline (0.16 mL, 0.17 g, 1.80 mmol), and solvent (5.00 mL) were added to a 25 mL Schlenk flask. The reaction mixture was deoxygenated by the freeze-pump-thaw method (3 cycles) and finally the flask was back-filled with argon. The reaction mixture was stirred and heated at 60 ºC for 24 hours. The solvent was removed under reduced pressure and the crude compound was dissolved in 8 mL of diethyl ether. To this mixture, water (8 mL) and 7.5 equiv. of $FeCl_3$•DMF complex were added and stirred under air. Upon completion of the oxidation (judged by TLC), the organic layer was separated. The aqueous layer was washed with ether (3 x 15 mL). Organic layers were combined, washed with brine and dried over magnesium sulfate. Column chromatography with 1% ethyl acetate / hexane gave pure compound **4-62** (0.025 g, 0.09 mmol, 51% yield). The spectroscopic data is identical to that of *rac*-**4-62.** Chiral HPLC with Chiralcel OD-H column using 99.6 : 0.4 hexane : isopropanol at 0.5 mL/min gave retention times of 14.35 minutes for the major and 17.12 minutes for the minor enantiomers showing –42% ee for compound **4-62.**

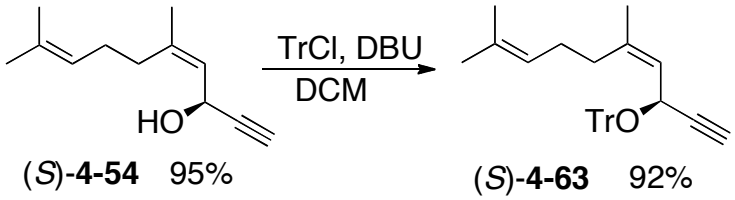
Synthesis of 4-62 by Reaction between 4-61 and (*S*)-4-61:



4-61 (*S*)-**4-60** 99% ee **4-62** 33%, 60% ee (NMR yield using CH_2Br_2 as NMR standard)

The carbene complex **4-61** (0.05 g, 0.18 mmol), enyne (*S*)-**4-61** (0.09 g, 0.22 mmol, 99% ee), aniline (0.16 mL, 0.17 g, 1.80 mmol), and solvent (5.00 mL) were added to a 25 mL Schlenk flask. The reaction mixture was deoxygenated by the freeze-pump-thaw method (3 cycles) and finally the flask was back-filled with argon. The reaction mixture was stirred and heated at 60 ºC for 24 hours. The solvent was removed under reduced pressure and the crude compound was dissolved in 8 mL of diethyl ether. To this mixture, water (8 mL) and 7.5 equiv. of $FeCl_3$•DMF complex were added and stirred under air. Upon completion of the oxidation (judged by TLC), the organic layer was separated. The aqueous layer was washed with ether (3 x 15 mL). Organic layers were combined, washed with brine and dried over magnesium sulfate. Compound **4-62** was obtained in 33% NMR yield using dibromomethane as internal standard. The spectroscopic data is identical to that of *rac*-**4-62.** Chiral HPLC with Chiralcel OD-H column using 99.6 : 0.4 hexane : isopropanol at 0.3 mL/min gave retention times of 28.98 minutes for the minor and 33.97 minutes for the major enantiomers showing 60% ee for compound **4-62.** $[\propto]_D^{22}$ –51.5° (c 1.00, CH_2Cl_2) at 60% ee.

Preparation of the compound (*S*)-**4-63:**



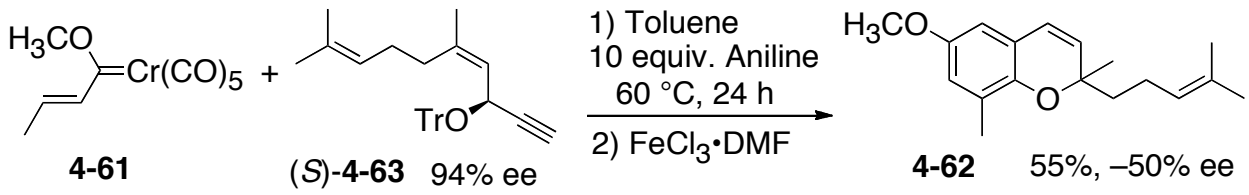
(*S*)-**4-54** 95% (*S*)-**4-63** 92%

To a solution of triphenylmethyl chloride (0.29 g, 1.03 mmol) and DBU (0.18 mL, 0.18 g, 1.20 mmol) in dichloromethane (2 mL), the alcohol substrate (*S*)-**4-54** (0.15 g, 0.85 mmol) was added and the mixture was stirred at room temperature for two days. The progress of the reaction was conveniently monitored by TLC analysis of crude reaction mixture. Products were isolated by washing the reaction mixture with cold water, extracting the aqueous layer with dichloromethane and drying the organic extracts with sodium sulfate. Evaporation of the solvent yielded crude triphenylmethyl ether (*S*)-**4-63**, which was purified by short column chromatography on silica gel with 5% ethyl acetate / hexane to give 0.33 g (92% yield, 0.78 mmol) of compound (*S*)-**4-63**.

White condense oil; R_f = 0.65 (5% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.53 (s, 3H), 1.64 (s, 3H), 1.66 (s, 3H), 1.65-1.77 (m, 1H), 1.78-1.88 (m, 1H), 1.90-2.02 (m, 2H), 2.15 (d, 1H, *J* = 2.0 Hz), 4.77 (dd, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz), 4.99 (t, 1H, *J* = 6.5 Hz), 5.33 (d, 1H, *J* = 8.0 Hz), 7.20-7.39 (m, 10H), 7.50-7.62 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.53, 23.03, 25.63, 26.11, 32.58, 61.60, 72.19, 83.62, 88.13,

123.84, 124.64, 127.00, 127.66, 128.99, 131.80, 137.16, 144.30; IR (neat film) 3295, 3086, 3058, 2967, 2925, 2857, 1665, 1597, 1491, 1448 cm^{-1}; HRMS (TOF MS ES^+) calcd for $C_{31}H_{32}O$ (M^++H) *m/z* 421.2531, meas 421.2551; $[\propto]_D^{22}$ +3.7° (c 1.00, CH_2Cl_2) at 94 % ee.

Reaction between 4-61 and (*S*)-**4-63:**

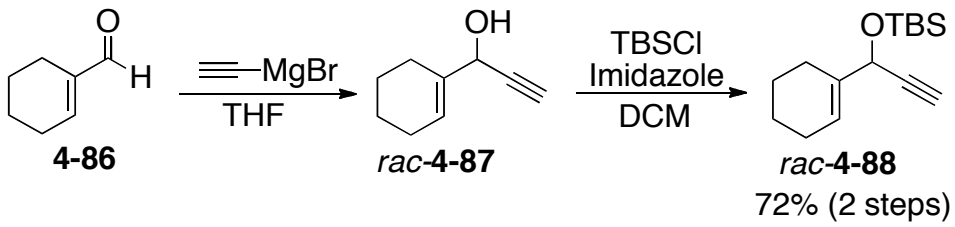


4-61 (*S*)-**4-63** 94% ee **4-62** 55%, –50% ee

The carbene complex **4-61** (0.08 g, 0.29 mmol), enyne (*S*)-**4-63** (0.15 g, 0.36 mmol), aniline (0.26 mL, 0.27 g, 2.90 mmol), and solvent (10 mL) were added to a 25 mL Schlenk flask. The reaction mixture was deoxygenated by the freeze-pump-thaw method (3 cycles) and finally the flask was back-filled with argon. The reaction mixture was stirred and heated at 60 ºC for 24 hours. The solvent was removed under reduced pressure and the crude compound was dissolved in 10 mL of diethyl ether. To this mixture, water (10 mL) and 7.5 equiv. of $FeCl_3$•DMF complex were added and stirred under air. Upon completion of the oxidation (judged by TLC), the organic layer was separated. The aqueous layer was washed with ether (3 x 15 mL). Organic layers were combined, washed with brine and dried over magnesium sulfate. Column

chromatography with 1% ethyl acetate / hexane gave pure compound **4-62** (0.04 g, 0.16 mmol, 55% yield). The spectroscopic data is identical to that of *rac*-**4-62.** Chiral HPLC with Chiralcel OD-H column using 99.6 : 0.4 hexane : isopropanol at 0.5 mL/min gave retention times of 12.17 minutes for the major and 14.34 minutes for the minor enantiomers showed –50% ee for compound **4-62.**

Preparation of the compound *rac*-**4-88:**



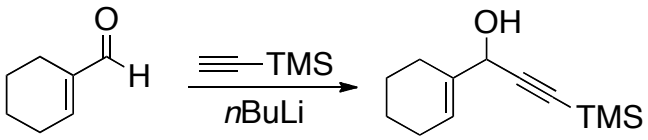
4-86 *rac*-**4-87** *rac*-**4-88**
72% (2 steps)

To a solution of 1-cyclohexene-1-carboxaldehyde **4-86** (0.52 mL, 0.50 g, 4.54 mmol) in 10 mL of THF at –78 °C was added ethynylmagnesium bromide (0.5 M in THF, 10.1 mL, 4.54 mmol). The reaction mixture was stirred for 3 hours at –78 °C and warmed to room temperature. After completion (as judged by TLC) the reaction mixture was then poured into 25 mL of saturated ammonium chloride solution. The aqueous layer was separated and extracted with ethyl acetate (25 mL x 3). The organic layers were combined and dried over magnesium sulfate. The solution was filtered through fluted filter paper and the solvent was removed under reduced pressure. The crude compound *rac*-**4-87** was pure enough (from ^{1}HNMR) to be used in the next step without further purification. All of the crude compound *rac*-**4-87** was used in the next step along with *tert*-butyldimethylsilyl

chloride (0.82 g, 5.45 mmol) and imidazole (0.49 g, 7.26 mmol) in dichloromethane (12 mL). The mixture was stirred for 16 h at room temperature. The crude product was concentrated in *vacuo* and directly chromatographed on silica gel (eluted with 100 : 1 hexane–ethyl acetate) to afford 0.82 g (3.27 mmol) of *rac*-**4-88** as colorless oil, giving 72% yield over two steps.

R_f = 0.71 (5% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ –0.25 (s, 3H), –0.22 (s, 3H), 0.55 (s, 9H), 1.18-1.35 (m, 4H), 1.65-1.80 (m, 4H), 2.08 (s, 1H), 4.36 (br s, 1H), 5.49 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –4.99, –4.68, 18.30, 22.33, 22.51, 24.01, 24.94, 25.78, 66.98, 72.67, 84.17, 123.40, 137.06; IR (neat film) 2956, 2930, 2858, 2228, 1463, 1387, 1363, 1254 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{15}H_{26}OSi$ (M^+–H) *m/z* 249.1675, meas 249.1667.

Preparation of the compound *rac*-4-89:



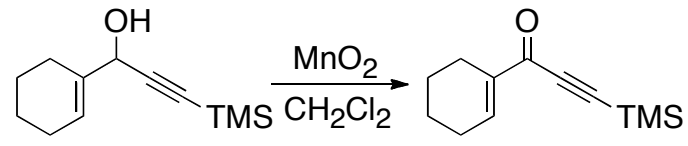
4-86 *rac*-**4-89** 95%

In diethyl ether (80 mL), TMS acetylene (1.43 mL, 0.98 g, 10.0 mmol) was deprotonated with *n*-butyl lithium (2.5 M in hexane, 4.18 mL, 10.0 mmol) at –78 ºC. The solution was

allowed to warm to room temperature over one hour. The solution was recooled to –78 ºC and 1-Cyclohexene-1-carboxaldehyde **4-86** (1.04 mL, 1.00g, 9.09 mmol) was added dropwise. The solution was warmed to 0 ºC and stirred 40 minutes. The solution was then warmed to room temperature. The reaction mixture was poured into 100 mL of saturated ammonium chloride and back extracted with ether (3 x 100 mL). The organic layer was dried over magnesium sulfate, filtered through Celite, and the solvent removed under reduced pressure. Column chromatography with 10 % ethyl acetate / hexane gave 1.79 g (95 % yield, 8.60 mmol) of compound *rac*-**4-89**.

Yellow oil; R_f = 0.43 (30% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.16 (s, 9H), 1.51-1.54 (m, 4H), 1.55-1.56 (br s, 1H), 2.00-2.02 (m, 3H), 2.03-2.05 (m, 1H), 4.69 (s, 1H), 5.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –0.14, 22.16, 22.48, 24.12, 25.03, 67.23, 90.65, 104.69, 125.14, 136.67; IR (neat film) 3372, 2932, 2859, 2838, 2171, 1437, 1397, 1250 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{12}H_{20}OSi$ (M^++H) *m/z* 209.1362, meas 209.1371.

Preparation of the compound 4-90:

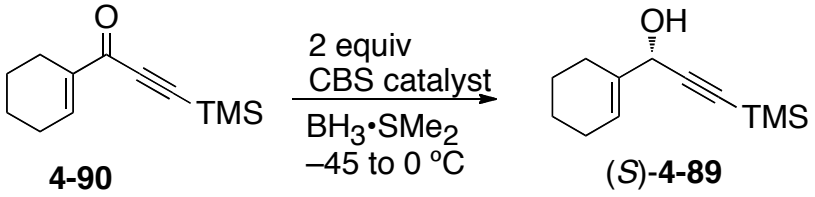


rac-**4-89** 95% **4-90** 83%

A 250 mL round bottom flask was charged with compound *rac*-**4-89** (1.79 g, 8.60 mmol), DCM (60 mL), and MnO_2 (7.57 g, 87.1 mmol). The contents of the flask were stirred overnight and filtered through Celite washing with DCM to remove the MnO_2. Column chromatography with 5 % ethyl acetate / hexane gave 1.48 g (83 % yield, 7.16 mmol) of **4-90**.

Yellow oil; R_f = 0.65 (30% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.21 (s, 9H), 1.56-1.64 (m, 4H), 2.18-2.20 (m, 2H), 2.26-2.32 (m, 2H), 7.31-7.35 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –0.70, 21.51, 21.53, 22.21, 26.49, 97.48, 100.21, 140.31, 147.97, 179.22; IR (neat film) 2938, 2863, 2152, 1632, 1449, 1421, 1382, 1271, 1251, 1221 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{12}H_{18}OSi$ (M^++H) *m/z* 207.1205, meas 207.1210.

Preparation of the compound (*S*)-**4-89:**

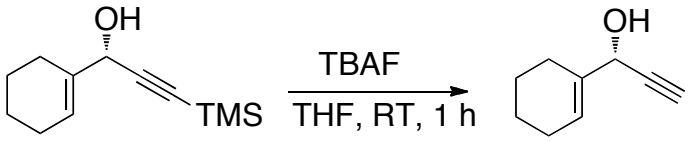


4-90 (*S*)-**4-89**

To a solution of (*S*)-(–)-2-methyl-CBS-oxazaborolidine (2.16 g, 7.77 mmol) and compound **4-90** (0.80 g, 3.88 mmol) at –45 °C in 40 mL of THF was added dropwise

slowly BH_3•SMe_2 (0.38 mL, 0.31 g, 4.04 mmol). The solution was warmed to –30 ºC and eventually to 0 ºC for over 6 h. The TLC was checked. Although the reaction was not complete the reaction was worked up. To the stirring solution was added methanol (20 mL) via syringe. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography (5 : 1 pentane : ether) to give 0.38 g (47%, 1.82 mmol) of compound (*S*)-**4-89** as light yellow oil. The spectroscopic properties were identical with those given for the racemate *rac*-**4-89**. Chiral HPLC with Chiralcel OD-H column using 99.6 : 0.4 hexane : isoprpanol at 0.7 mL/min gave retention times of 13.8 minutes for the minor and 14.9 minutes for the major enantiomers showed 90% ee for compound (*S*)-**4-89**. $[\propto]_D^{22}$ +19.4° (c 1.00, CH_2Cl_2) at 90 % ee.

Preparation of the compound (*S*)-**4-87:**



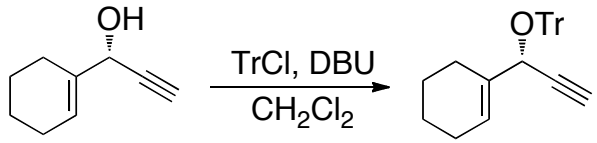
(*S*)-**4-89** (*S*)-**4-87**

To a stirred solution of compound (*S*)-**4-89** (0.20 g, 0.96 mmol) in 6 mL of THF, TBAF (1M in THF, 1.15 mL, 1.15 mmol) was added slowly at RT and stirred at this temperature for 1 h. The reaction mixture was then added slowly to a vigorously stirred mixture of 12 mL of brine. The aqueous layer was extracted with ether (3 x 20 mL). The organic layers were combined and dried with $MgSO_4$. Ether was distilled off under

reduced pressure and the crude product was purified by column chromatography (eluent: dichloromethane) to give pure product (*S*)-**4-87** (0.126 g, 0.93 mmol, 97%).

Yellow oil; R_f = 0.37 (30% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.50-1.52 (m, 4H), 1.82-2.42 (m, 4H), 2.50 (d, 1H, *J* = 2.0 Hz), 4.70 (s, 1H), 5.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.10, 22.38, 23.96, 24.93, 66.54, 73.79, 83.13, 125.23, 136.45, IR (neat film) 3298, 3035, 2967, 2924, 2857, 2136, 1665, 1446, 1377 cm^{-1}; $[\propto]_D^{22}$ +19.4° (c 1.00, CH_2Cl_2) at 90 % ee.

Preparation of the compound (*S*)-**4-91:**



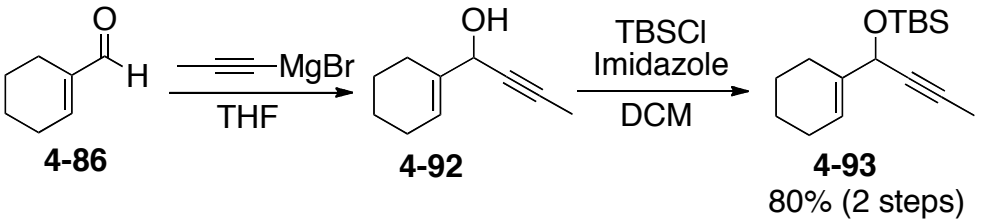
(*S*)-**4-87** (*S*)-**4-91**

To a solution of triphenylmethyl chloride (0.32 g, 1.15 mmol) and DBU (0.19 mL, 0.20 g, 1.34 mmol) in dichloromethane (2 mL), the alcohol substrate (*S*)-**4-87** (0.13 g, 0.96 mmol) was added and the mixture was stirred at room temperature for two days. The progress of the reaction was conveniently monitored by TLC analysis of crude reaction mixture. Products were isolated by washing the reaction mixture with cold water,

extracting the aqueous layer with dichloromethane and drying the organic extracts with sodium sulfate. Evaporation of the solvent yielded crude triphenylmethyl ether, which was purified by short column chromatography on silica gel with 5% ethyl acetate / hexane to give 0.33 g (87% yield, 0.83 mmol) of compound (*S*)-**4-91**.

White solid; Melting Pt. 119-120 ºC; R_f = 0.65 (5% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.42-1.62 (m, 4H), 1.68-1.88 (m, 2H), 2.02-2.22 (m, 2H), 2.27 (d, 1H, *J* = 2.0 Hz), 4.47 (br s, 1H), 5.25 (br s, 1H), 7.20-7.39 (m, 10H), 7.53-7.61 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.53, 23.03, 25.63, 26.11, 32.58, 61.60, 72.19, 83.62, 88.13, 123.84, 124.64, 127.00, 127.66, 128.99, 131.80, 137.16, 144.30; IR (neat film) 3287, 3086, 3058, 2928, 2857, 2837, 1597, 1491, 1448 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{28}H_{26}O$ (M^++H) *m/z* 379.2062, meas 379.2080; $[\propto]_D^{22}$ –24.2° (c 1.00, CH_2Cl_2) at 90 % ee.

Preparation of the compound 4-93:



4-86 **4-92** **4-93**
80% (2 steps)

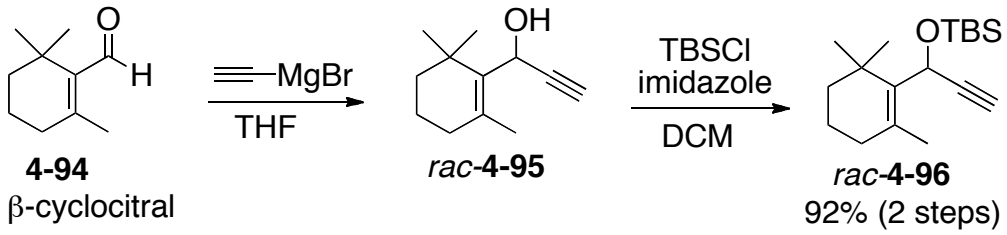
To a solution of 1-cyclohexene-1-carboxaldehyde **4-86** (0.41 mL, 0.40 g, 3.64 mmol) in 10 mL of THF at –78 °C was added proynylmagnesium bromide (0.5 M in THF, 8.73 mL, 4.36 mmol). The reaction mixture was stirred for 3 hours at –78 °C and warmed to room temperature. After completion (as judged by TLC) the reaction mixture was then poured into 25 mL of saturated ammonium chloride solution. The aqueous layer was separated and extracted with ethyl acetate (25 mL x 3). The organic layers were combined and dried over magnesium sulfate. The solution was filtered through fluted filter paper and the solvent was removed under reduced pressure. The crude compound **4-92** was pure enough (from ^{1}HNMR) to be used in the next step without further purification.

The entire crude compound **4-92** was used in the next step along with *tert*butyldimethylsilyl chloride (0.66 g, 4.40 mmol) and imidazole (0.40 g, 5.87 mmol) in dichloromethane (12 mL). The mixture was stirred for 16 h at room temperature. The crude product was concentrated in *vacuo* and directly chromatographed on silica gel (eluted with 100 : 1 hexane–ethyl acetate) to afford 0.77 g (2.92 mmol) of **4-93** giving 80% yield over two steps.

Yellow oil; R_f = 0.72 (5% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.89 (s, 9H), 1.52-1.66 (m, 4H), 1.82 (d, 3H, J = 2.0 Hz), 1.98-2.10 (m, 4H), 4.66 (br s, 1H), 5.77-5.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –4.95, –4.57, 3.65, 18.35, 22.41, 22.57, 24.14, 24.93, 25.86, 67.35, 79.50, 80.80, 122.59, 137.95; IR

(neat film) 2930, 2857, 1472, 1463, 1253 cm^{-1}; HRMS (TOF MS ES^+) calcd for $C_{16}H_{28}OSi$ (M^++H) *m/z* 265.1988, meas 265.1997.

Preparation of the compound *rac*-4-96:



4-94
β-cyclocitral

rac-**4-95**

rac-**4-96**
92% (2 steps)

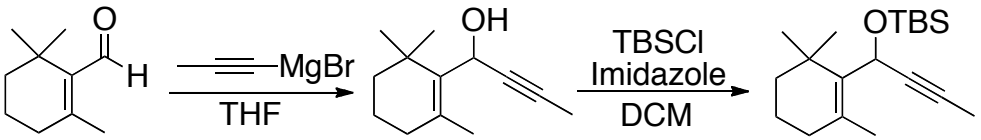
To a solution of *β*-cyclocitral **4-94** (0.53 mL, 0.50 g, 3.28 mmol) in 10 mL of THF at –78 °C was added ethynylmagnesium bromide (0.5 M in THF, 7.88 mL, 3.94 mmol). The reaction mixture was stirred for 3 hours at –78 °C and warmed to room temperature. After completion (as judged by TLC) the reaction mixture was then poured into 25 mL of saturated ammonium chloride solution. The aqueous layer was separated and extracted with ethyl acetate (25 mL x 3). The organic layers were combined and dried over magnesium sulfate. The solution was filtered through fluted filter paper and the solvent was removed under reduced pressure. The crude compound *rac*-**4-95** was pure enough (from ^{1}H NMR) to be used in the next step without further purification.

All the crude compound *rac*-**4-95** was used in the next step along with *tert*-butyldimethylsilyl chloride (0.59 g, 3.95 mmol) and imidazole (0.36 g, 5.26 mmol) in dichloromethane (15 mL). The mixture was stirred for 16 h at room temperature. The

crude product was concentrated in *vacuo* and directly chromatographed on silica gel (eluted with 100 : 1 hexane–ethyl acetate) to afford 0.88 g (3.02 mmol) of *rac*-**4-96**, giving 92% yield over two steps.

Yellow oil; R_f = 0.69 (5% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.09 (s, 3H), 0.17 (s, 3H), 0.87 (s, 9H), 1.02 (s, 3H), 1.04 (s, 3H), 1.38-1.44 (m, 2H), 1.50-1.59 (m, 2H), 1.84 (s, 3H), 1.95 (t, 2H, J = 6.5 Hz), 2.37 (d, 1H, J = 2.0 Hz), 4.95 (d, 1H, J = 2.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –4.96, –4.58, 18.04, 19.24, 20.82, 25.71, 27.76, 28.70, 33.56, 34.56, 39.83, 60.06, 71.12, 86.38, 133.12, 137.34; IR (neat film) 2956, 2930, 2907, 2859, 1464, 1388, 1364, 1252 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{18}H_{32}OSi$ (M^+–OTBS) *m/z* 161.1330, meas 161.1329.

Preparation of the compound 4-98:



4-94 **4-97** **4-98**
90% (2 steps)

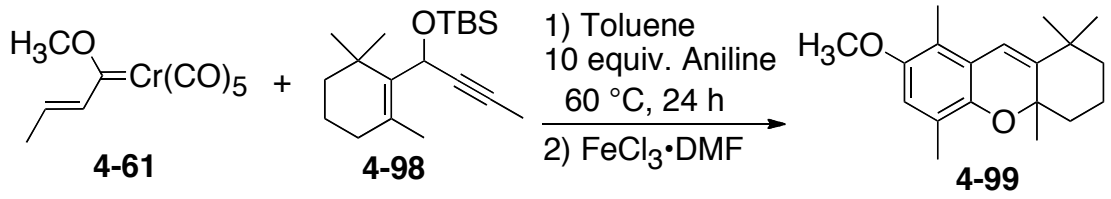
To a solution of β-cyclocitral **4-94** (1.06 mL, 1.00 g, 6.56 mmol) in 20 mL of THF at –78 °C was added propynylmagnesium bromide (0.5 M in THF, 16.0 mL, 7.88 mmol). The reaction mixture was stirred for 3 hours at –78 °C and warmed to room temperature.

After completion (as judged by TLC) the reaction mixture was then poured into 25 mL of saturated ammonium chloride solution. The aqueous layer was separated and extracted with ethyl acetate (25 mL x 3). The organic layers were combined and dried over magnesium sulfate. The solution was filtered through fluted filter paper and the solvent was removed under reduced pressure. The crude compound **4-97** was pure enough (from ^{1}HNMR) to be used in the next step without further purification.

All the crude compound **4-97** was used in the next step along with *tert*-butyldimethylsilyl chloride (1.18 g, 7.90 mmol) and imidazole (0.72 g, 10.5 mmol) in dichloromethane (30 mL). The mixture was stirred for 16 h at room temperature. The crude product was concentrated in *vacuo* and directly chromatographed on silica gel (eluted with 100 : 1 hexane–ethyl acetate) to afford 1.81 g (5.92 mmol) of **4-98**, giving 90% yield over two steps.

Yellow oil; R_f = 0.65 (5% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.08 (s, 3H), 0.15 (s, 3H), 0.88 (s, 9H), 1.01 (s, 3H), 1.04 (s, 3H), 1.39 (t, 2H, *J* = 5.5 Hz), 1.50-1.58 (m, 2H), 1.79 (d, 3H, *J* = 2.5 Hz), 1.82 (s, 3H), 1.94 (t, 2H, *J* = 6.5 Hz), 4.93 (d, 1H, *J* = 2.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –4.94, –4.49, 3.71, 18.10, 19.33, 20.69, 25.80, 27.86, 28.72, 33.54, 34.50, 39.95, 60.50, 78.88, 81.78, 133.04, 138.10; IR (neat film) 2955, 2930, 2858, 2227, 1471, 1469, 1387, 1252 cm^{-1}; HRMS (TOF MS ES^{+}) calcd for $C_{19}H_{34}OSi$ (M–OTBS) *m/z* 175.1487, meas 175.1480.

Preparation of the compound 4-99:



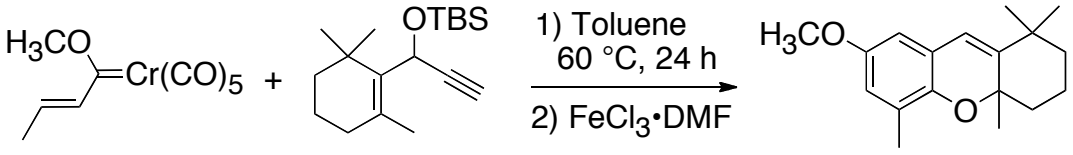
4-61 **4-98** **4-99**

The carbene complex **4-61** (0.08 g, 0.30 mmol), enyne **4-98** (0. 10 g, 0.36 mmol), and solvent (5.00 mL) were added to a 25 mL Schlenk flask. The reaction mixture was deoxygenated by the freeze-pump-thaw method (3 cycles) and finally the flask was back-filled with argon. The reaction mixture was stirred and heated at 60 ºC for 24 hours. The solvent was removed under reduced pressure and the crude compound was dissolved in 8 mL of diethyl ether. To this mixture, water (8 mL) and 7.5 equiv. of $FeCl_3$•DMF complex were added and stirred under air. Upon completion of the oxidation (judged by TLC), the organic layer was separated. The aqueous layer was washed with ether (3 x 15 mL). Organic layers were combined, washed with brine and dried over magnesium sulfate. Column chromatography with 1% ethyl acetate / hexane gave pure compound **4-99** (0.06 g, 0.21 mmol, 71% yield).

However, when the reaction was performed under the same conditions in presence of 10 equivalents of aniline, only trace amount of the product could be detected in ^1H NMR. In the reaction using 5 equiv. of Hünig's base the reaction gave a complicated mixture of products so it was not processed any further. In acetonitrile solvent without use of any additive the yield of the product **4-99** was 52%.

Yellow oil; R_f = 0.25 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.14 (s, 3H), 1.26 (s, 3H), 1.31 (s, 3H), 1.40-1.55 (m, 2H), 1.60- 1.72 (m, 2H), 1.83-1.91 (m, 1H), 2.05-2.15 (m, 1H), 2.14 (s, 6H), 3.74 (s, 3H), 6.45 (s, 1H), 6.49 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.56, 15.54, 19.05, 25.08, 30.63, 30.75, 35.72, 39.69, 40.02, 56.25, 76.47, 112.14, 113.90, 118.95, 122.39, 122.46, 143.71, 148.70, 151.27; IR (neat film) 3067, 2934, 2866, 1588, 1466, 1415, 1382, 1366, 1242 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{19}H_{26}O_2$ (M^++H) *m/z* 287.2011, meas 287.2007.

Preparation of the compound *rac*-4-101:



4-61 *rac*-**4-96** *rac*-**4-101**

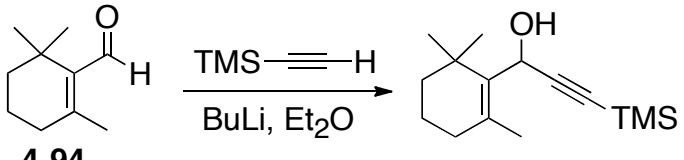
The carbene complex **4-61** (0.08 g, 0.30 mmol), enyne *rac*-**4-96** (0.11 g, 0.36 mmol), and solvent (5.00 mL) were added to a 25 mL Schlenk flask. The reaction mixture was deoxygenated by the freeze-pump-thaw method (3 cycles) and finally the flask was back-filled with argon. The reaction mixture was stirred and heated at 60 ºC for 24 hours. The solvent was removed under reduced pressure and the crude compound was dissolved in 8 mL of diethyl ether. To this mixture, water (8 mL) and 7.5 equiv. of $FeCl_3$•DMF complex were added and stirred under air. Upon completion of the oxidation

(judged by TLC), the organic layer was separated. The aqueous layer was washed with ether (3 x 15 mL). Organic layers were combined, washed with brine and dried over magnesium sulfate. Column chromatography with 1% ethyl acetate / hexane gave pure compound *rac*-**4-101** (0.05 g, 0.20 mmol, 66% yield).

When the reaction was repeated in dichloromethane solvent, under the same conditions the yield of the product *rac*-**4-101** was 61%.

Yellow solid; Melting Pt. 88-89 ºC; R_f = 0.28 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.13 (s, 3H), 1.23 (s, 3H), 1.33 (s, 3H), 1.38-1.54 (m, 2H), 1.59-1.72 (m, 2H), 1.88 (td, 1H, *J* = 13.5 Hz, *J* = 5 Hz), 2.04-2.10 (m, 1H), 2.14 (s, 3H), 3.72 (s, 3H), 6.20 (s, 1H), 6.38 (d, 1H, *J* = 3 Hz), 6.50 (d, 1H, *J* = 3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.53, 19.06, 25.22, 30.40, 30.65, 35.52, 39.60, 39.98, 55.60, 77.56, 108.11, 115.05, 116.90, 123.60, 126.11, 143.84, 148.86, 153.29; IR (neat film) 3044, 2935, 2868, 1597, 1480 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{18}H_{24}O_2$ (M^++H) *m/z* 273.1855, meas 273.1850.

Preparation of the compound *rac*-**4-102:**



4-94

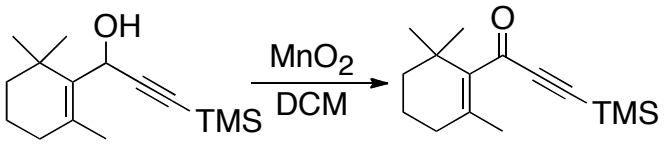
rac-**4-102**

91%

In diethyl ether (250 mL), TMS acetylene (5.15 mL, 3.54 g, 36.1 mmol) was deprotonated with *n*-butyl lithium (2.5 M in hexane, 15.1 mL, 36.1 mmol) at -78 ºC. The solution was allowed to warm to room temperature over one hour. The solution was recooled to –78 ºC and *β*-cyclocitral **4-94** (5.30 mL, 5.00g, 32.8 mmol) was added dropwise. The solution was warmed to 0ºC and stirred 40 minutes. The solution was then warmed to room temperature. The solution was poured into 300 mL of saturated ammonium chloride and back extracted with ether (3 x 150 mL). The organic layer was dried over magnesium sulfate, filtered through Celite, and the solvent removed under reduced pressure. Column chromatography with 10 % ethyl acetate / hexane gave 7.50 g (91 % yield, 30.0 mmol) of compound *rac*-**4-102**.

Yellow Oil; R_f = 0.39 (30% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.15 (s, 9H), 1.03 (s, 3H), 1.09 (s, 3H), 1.43 (t, 2H, *J* = 5.74 Hz), 1.51-1.64 (m, 2H), 1.93 (s, 3H), 1.98 (t, 2H, *J* = 5.37 Hz), 4.92-5.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –0.17, 19.09, 20.88, 27.59, 28.42, 33.56, 34.61, 39.42, 60.10, 88.78, 106.91, 134.26, 137.90; IR (neat film) 3393, 2959, 2931, 2868, 2830, 2169, 1457, 1365, 1250 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{12}H_{18}OSi$ (M^+–OH) *m/z* 233.1726, meas 233.1722.

Preparation of the compound 4-103:

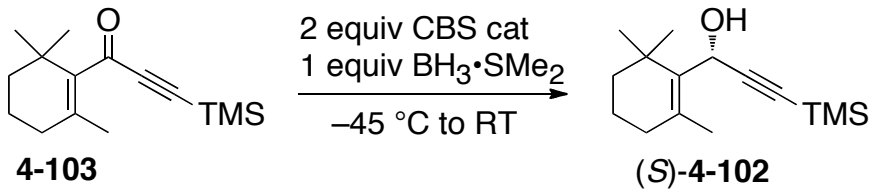


rac-**4-102** **4-103** 53%

A 250 mL round bottom flask was charged with compound *rac*-**4-102** (5.00 g, 20.0 mmol), DCM (120 mL), and MnO_2 (16.7 g, 192.1 mmol). The contents of the flask were stirred overnight and filtered through Celite washing with DCM to remove the MnO_2. Column chromatography with 5 % ethyl acetate / hexane gave 2.63 g (53 % yield, 10.6 mmol) of **4-103**.

Yellow Oil; R_f = 0.70 (30% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.18 (s, 9H), 1.11 (s, 6H), 1.38-1.42 (m, 2H), 1.58-1.65 (m, 2H), 1.69 (s, 3H), 1.98 (t, 2H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –0.88, 18.59, 20.92, 28.38, 32.08, 33.72, 39.11, 98. 82, 104.28, 135.89, 141.87, 185.87; IR (neat film) 2961, 2935, 2869, 2145, 1643, 1459, 1381, 1363, 1252 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{15}H_{25}OSi$ (M^++H) *m/z* 249.1675, meas 249.1683.

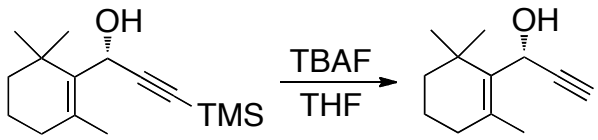
Preparation of the compound (*S*)-**4-107:**



4-103 (*S*)-**4-102**

To a solution of (*S*)-(–)-2-methyl-CBS-oxazaborolidine (4.49 g, 16.1 mmol) and compound **4-103** (2.00 g, 8.06 mmol) at –45 ºC in 80 mL of THF was added dropwise slowly BH_3•SMe_2 (0.80 mL, 0.64 g, 8.39 mmol). The solution was warmed to –30 ºC and eventually to 0 ºC for over 16 h. The TLC was checked. Although the reaction was not complete the reaction was worked up. To the stirring solution was added methanol (100 mL) via syringe. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography (5 : 1 pentane : ether) to give 0.50 g (25%, 2.00 mmol) of compound (*S*)-**4-102** as light yellow oil. The spectroscopic properties were identical with those given for the racemate *rac*-**4-102**. Chiral HPLC with Chiralcel OD-H column using 99.6 : 0.4 hexane : isopropanol at 0.7 mL/min gave retention times of 8.1 minutes for the major and 10.9 minutes for the minor enantiomers showed 97% ee for compound (*S*)-**4-102**. $[\propto]_D^{22}$ –75.0° (c 1.00, CH_2Cl_2) at 97 % ee.

Preparation of the compound (*S*)-**4-95:**

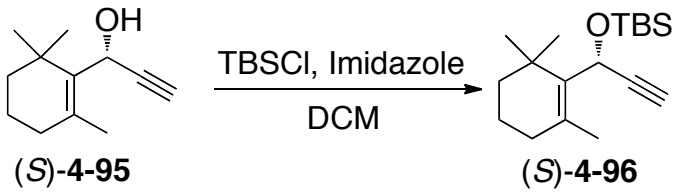


(*S*)-**4-102** (*S*)-**4-95**

To a stirred solution of compound (*S*)-**4-102** (0.50 g, 2.00 mmol) in 10 mL of THF, TBAF (1M in THF, 2.20 mL, 2.20 mmol) was added slowly at RT and stirred at this temperature for 1 h. The reaction mixture was then added slowly to a vigorously stirred mixture of 15 mL of brine. The aqueous layer was extracted with ether (3 x 20 mL). The organic layers were combined and dried with $MgSO_4$. Ether was distilled off under reduced pressure and the crude product was purified by column chromatography (eluent: dichloromethane) to give pure product (*S*)-**4-95** (0.25 g, 1.40 mmol, 70% yield).

Yellow oil; R_f = 0.42 (30% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.02 (s, 3H), 1.07 (s, 3H), 1.40-1.46 (m, 2H), 1.50-1.60 (m, 2H), 1.94 (s, 3H), 1.97 (t, 2H, *J* = 6.0 Hz), 2.48 (d, 1H, *J* = 1.8 Hz), 5.02 (d, 1H, *J* = 2.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 19.10, 20.90, 27.55, 28.38, 33.56, 34.66, 39.36, 59. 53, 72.32, 84.99, 134.55, 137.83; IR (neat film) 3298, 3035, 2967, 2924, 2857, 2136, 1665, 1446, 1377 cm^{-1}; HRMS (TOF MS ES$^+$) calcd for $C_{12}H_{18}O$ (M^++H) *m/z* 179.1436, meas 179.1431; $[\propto]_D^{22}$ –76.3° (c 1.00, CH_2Cl_2) at 97 % ee.

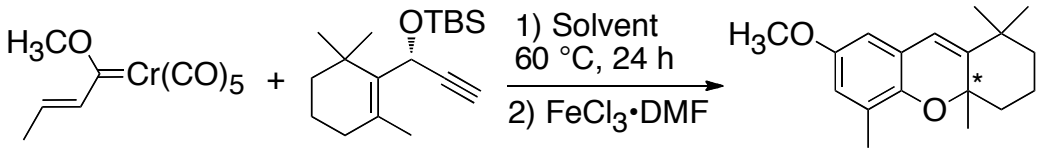
Preparation of the compound (*S*)-**4-96:**



(*S*)-**4-95** (*S*)-**4-96**

The alcohol (*S*)-**4-95** (0.20 g, 1.12 mmol) was added to a mixture of *tert*-butyldimethylsilyl chloride (0.20 g, 1.35 mmol) and imidazole (0.12 g, 1.79 mmol) in dichloromethane (7 mL). The mixture was stirred for 16 h at room temperature. The crude product was concentrated in *vacuo* and directly chromatographed on silica gel (eluted with 100 : 1 hexane–ethyl acetate) to afford 0.27 g (0.93 mmol) of (*S*)-**4-96** as colorless oil, giving 83% yield over two steps. The spectroscopic properties were identical with those given for the racemate *rac*-**4-96**. $[\propto]_D^{22}$ –50.8° (c 1.00, CH_2Cl_2) at 97 % ee.

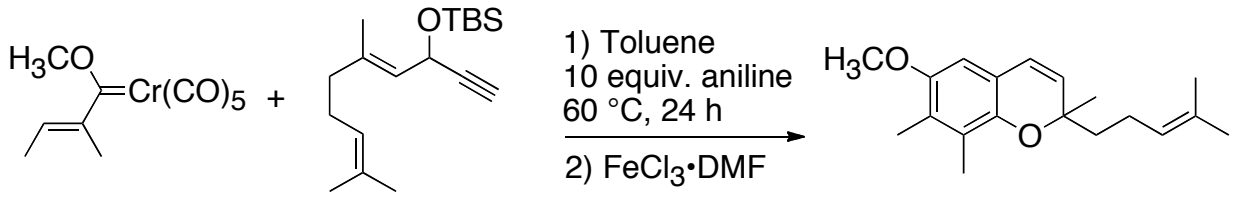
Preparation of the compound 4-101:



4-61 (*S*)-**4-96** 97% ee **4-101**

The carbene complex **4-61** (0.08 g, 0.30 mmol), enyne (*S*)-**4-96** (0.11 g, 0.36 mmol, 97% ee), and dichloromethane (5.00 mL) were added to a 25 mL Schlenk flask. The reaction mixture was deoxygenated by the freeze-pump-thaw method (3 cycles) and finally the flask was back-filled with argon. The reaction mixture was stirred and heated at 60 ºC for 24 hours. The solvent was removed under reduced pressure and the crude compound was dissolved in 8 mL of diethyl ether. To this mixture, water (8 mL) and 7.5 equiv. of $FeCl_3$•DMF complex were added and stirred under air. Upon completion of the oxidation (judged by TLC), the organic layer was separated. The aqueous layer was washed with ether (3 x 15 mL). Organic layers were combined, washed with brine and dried over magnesium sulfate. Column chromatography with 1% ethyl acetate / hexane gave pure compound **4-101** (0.06 g, 0.21 mmol, 70% yield). The reaction was repeated in toluene solvent under the same conditions and the product **4-101** was obtained in 63% yield (0.05 g, 0.19 mmol). Chiral HPLC with Chiralcel OD-H column using 99.8 : 0.2 hexane : isoprpanol at 0.5 mL/min gave retention times of 9.07 minutes for the major and 10.5 minutes for the major enantiomers showed 26% ee for compound **4-101**. $[\propto]_D^{22}$ +3.6 ° (c 1.00, CH_2Cl_2) at 26 % ee. The rection was repeated under the same conditions just by changing the solvent to toluene and the enantioselectivity for the product **4-101** was found to be 12 % ee and the yield was 63%. The spectroscopic properties were identical to that reported for compound *rac*-**4-101**.

Preparation of the compound *rac*-4-106:



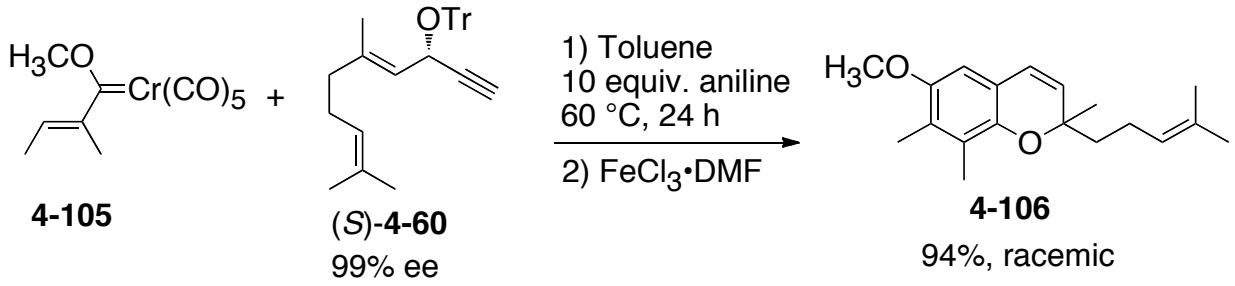
4-105 *rac*-**4-37** rac-**4-106** 76%

The carbene complex **4-105** (0.08 g, 0.28 mmol), enyne *rac*-**4-37** (0.10 g, 0.33 mmol), aniline (0.25 mL, 0.26 g, 2.70 mmol) and solvent (8.00 mL) were added to a 25 mL Schlenk flask. The reaction mixture was deoxygenated by the freeze-pump-thaw method (3 cycles) and finally the flask was back-filled with argon. The reaction mixture was stirred and heated at 60 ºC for 24 hours. The solvent was removed under reduced pressure and the crude compound was dissolved in 8 mL of diethyl ether. To this mixture, water (8 mL) and 7.5 equiv. of $FeCl_3$•DMF complex were added and stirred under air. Upon completion of the oxidation (judged by TLC), the organic layer was separated. The aqueous layer was washed with ether (3 x 15 mL). Organic layers were combined, washed with brine and dried over magnesium sulfate. Column chromatography with 1% ethyl acetate / hexane gave pure compound *rac*-**4-106** (0.06 g, 0.21 mmol, 76% yield).

Yellow oil; R_f = 0.27 (1% Ethyl acetate / Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.34 (s, 3H), 1.56 (s, 3H), 1.65 (s, 3H), 1.65-1.68 (m, 2H), 2.05- 2.20 (m, 2H), 2.11 (s, 6H), 3.74 (s, 3H), 5.06-5.15 (m, 1H), 5.52 (d, 1H, J = 10 Hz), 6.27 (d, 1H, J = 10 Hz), 6.36 (s, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.61, 12.06, 17.55, 22.73, 25.66, 25.79, 40.75, 56.13, 77.69, 106.15, 118.14, 123.20, 124.34, 125.35, 126.27, 129.34, 131.51, 144.76, 151.29; IR (neat film) 3038, 2967, 2926, 2857, 1640, 1608, 1577, 1462, 1424, 1378 cm^{-1}; HRMS (TOF MS ES^+) calcd for $C_{19}H_{26}O_2$ (M^++H) *m/z* 287.2011, meas 287.2021.

Preparation of the compound 4-106:



4-105

(*S*)-**4-60**
99% ee

4-106
94%, racemic

The carbene complex **4-105** (0.05 g, 0.17 mmol), enyne *rac*-**4-60** (0.09 g, 0.20 mmol), aniline (0.15 mL, 0.16 g, 1.70 mmol) and solvent (5.00 mL) were added to a 25 mL Schlenk flask. The reaction mixture was deoxygenated by the freeze-pump-thaw method (3 cycles) and finally the flask was back-filled with argon. The reaction mixture was stirred and heated at 60 ºC for 24 hours. The solvent was removed under reduced pressure and the crude compound was dissolved in 8 mL of diethyl ether. To this mixture, water (8 mL) and 7.5 equiv. of $FeCl_3$•DMF complex were added and stirred under air. Upon completion of the oxidation (judged by TLC), the organic layer was separated. The aqueous layer was washed with ether (3 x 15 mL). Organic layers were

combined, washed with brine and dried over magnesium sulfate. Column chromatography with 1% ethyl acetate / hexane gave pure compound **4-106** (0.05 g, 0.16 mmol, 94% yield). Chiral HPLC with Chiralcel OD column using 99.8 : 0.2 hexane : isopropanol at 0.5 mL/min gave retention times of 14.03 minutes for the major and 16.17 minutes for the minor enantiomers showed compound **4-106** to be racemic. The spectroscopic properties were identical with those given for the racemate *rac*-**4-106**.

REFERENCES

REFERENCES AND NOTES

1) Comprehensive Heterocyclic Chemistry III, ed. Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K. Elsevier Ltd, Oxford, 2008 and previous editions of this series.

2) a) Ellis, G. P. Chromenes, chromanones, and chromones, Wiley-Interscience, New York, 1977; (b) Hepworth, J. D. in Comprehensive Heterocyclic Chemistry, ed. Katritzky, A. R.; Rees, C. W.; Boulton, A. J.; McKillop, A. Pergamon Press, Oxford, 1984, vol. 3, pp. 737–883.

3) For reviews on chromene synthesis see: Brimble, M. A.; Gibson, J. S.; Sperry, J. in Comprehensive Heterocyclic Chemistry III, ed. Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K. Elsevier Ltd, Oxford, 2008, vol. 7, pp. 419–699 and previous editions of this series.

4) For reviews on applications see: Fravel, W. B.; Nedolya, N. A. in Comprehensive Heterocyclic Chemistry III, ed. Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K. Elsevier Ltd, Oxford, 2008, vol. 7, pp. 701–726 and previous editions of this series.

5) a) Engler, T. A.; La Tessa, K. O.; Iyengar, R.; Chai, W.; Agrios, K. *Bioorg. Med. Chem.* **1996**, *4*, 1755–1769; b) Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K. H. *Tetrahedron* **2001**, *57*, 1559–1563; c) Elomri, A.; Mitaku, S.; Michel, S.; Skaltsounis, A.-L.; Tillequin, F.; Koch, M.; Pierre, A.; Guilbaud, N.; Leonce, S.; Kraus-Berthier, L.; Rolland, Y.; Atassi, G. *J. Med. Chem.* **1996**, *39*, 4762–4766; d) Lago, J. H. G.; Ramos, C. S.; Casanova, D. C. C.; Morandim, A.; de, A.; Bergamo, D. C. B.; Cavalheiro, A. J.; Bolzani, V.; da, S.; Furlan, M.; Guilharaes, E. F.; Young, M. C. M.; Kato, M. J. *J. Nat. Prod.* **2004**, *67*, 1783–1788; e) Bernard, C. B.; Krishnamurty, H. G.; Chauret, D.; Durst, T.; Philogene, B. J. R.; Sanchez Vindas, P.; Hasbun, C.; Poveda, L.; San Roman, L.; Arnason, J. T. *J. Chem. Ecol.* **1995**, *21*, 801–814; f) Jankun, J.; Selman, S. H.; Swiercz, R. *Nature* **1997**, *387*, 561.

6) a) Paramonov, S.; Delbaere, S.; Fedorova, O.; Fedorov, Y.; Lokshin, V.; Samat, A.; Vermeersch, G. J. *Photochem. Photobiol. A* **2010**, *209*, 111. (b) Evans, R. A.; Such, G. K. *Aust. J. Chem.* **2005**, *58*, 825.

7) a) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347. (b) Elinson, M. N.; Ilovaisky, A. I.; Merkulova, M. M.; Belyakov, P. A.; Chizhov, A. O.; Nikishin, G. I. *Tetrahedron* **2010**, *66*, 4043. (c) Aponick, A.; Biannic, B.; Jong, M. R. *Chem. Commun.* **2010**, *46*, 6849.

8) a) Nicolaou, K. C.; Pffefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939. (b) An, H.; Eum., S. J.; Koh, M.; Lee, S. K.; Park, S. B. *J. Org. Chem.* **2008**, *73*, 1752. (c) Oh, S.; Jang, H. J.; Ko, S. K.; Ko, Y.; Park, S. B. *J. Comb. Chem.* **2010**, *12*, 548. (d) Kapeller, D. C.; Bräse, S. *Synlett* **2011**, 161.

9) Bera, K.; Sarkar, S.; Biswas, S.; Maiti, S; Jana, U. *J. Org. Chem.* **2011**, *76*, 3539-3544.

10) Zeng, H.; Ju, J.; Hua, R. *Tetrahedron Lett.* **2011**, *52*, 3926-3928.

11) Lykakis, I. N.; Efe, C.; Gryparis, C.; Stratakis, M. *Eur. J. Org. Chem.* **2011**, 2334-2338.

12) Anderson, W. K.; La Voie, E. J.; Whitkop, P. G. *J. Org. Chem.* **1974**, *39*, 881-884.

13) Wang, Z.-Q.; Lei, Y.; Zhou, M.-B.; Chen, G.-X.; Song, R.-J.; Xie, Y.-X.; Li, J.-H. *Org. Lett.* **2011**, *13*, 14-17.

14) Aponick, A.; Biannic, B.; Jong, M. R. *Chem. Commun.* **2010**, *46*, 6849-6851.

15) a) Nevado, C.; Echavarren, A. M. *Chem. Eur. J.* **2005**, *11*, 3155–3164. b) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133–4136. c) Curtis, N. R.; Prodger, J. C.; Rassias, G.; Walker, A. J. *Tetrahedron Lett.* **2008**, *49*, 6279–6281; d) Rassias, G.; Stevenson, N. G.; Curtis, N. R.; Northall, J. M.; Gray, M.; Prodger, J. C.; Walker, A. J. *Org. Process Res. Dev.* **2010**, *14*, 92–98.

16) Menon, R. S.; Findlay, A. D.; Bissember, A. C.; Banwell, M. G. *J. Org. Chem.* **2009**, *74*, 8901-8903.

17) Yadav, J. S.; Reddy, B. V. S.; Biswas, S. K.; Sengupta, S. *Tetrahedron Lett.* **2009**, *50*, 5798-5801

18) Xu, X.; Liu, J.; Liang, L.; Li, H.; Li, Y. *Adv. Synth. Catal.* **2009**, *351*, 2599-2604.

19) Savitha, G.; Felix, K.; Perumal, P. T, *Synlett* **2009**, 2079-2082.

20) Zhao, L.; Cheng, G.; Hu, Y. *Tetrahedron Lett.* **2008**, *49*, 7364-7367.

21) Shi, M.; Dai, L.-Z.; Shi, Y.-L.; Zhao, G.-L. *Adv. Synth. Catal.* **2006**, *348*, 967-972.

22) Dai, L.-Z.; Shi, Y.-L.; Zhao, G.-L.; Shi, M. *Chem. Eur. J.* **2007**, *13*, 3701-3706.

23) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Verdecchia, M. *Synlett* **2006**, 909-915.

24) Poli, G.; Giambastiani, G. *J. Org. Chem.* **2002**, *67*, 9456.

25) Deagostino, A.; Farina, V.; Prandi, C.; Zavattaro, C.; Venturello, P. *Eur. J. Org. Chem.* **2006**, 3451-3456.

26) Hershberger, J.; Zhang, L.; Lu, G.; Malinakova, H. C. *J. Org. Chem.* **2006**, *71*, 231-235.

27) Prado, S.; Janin, Y. L.; Bost, P.-E. *J. Heterocyclic Chem.* **2006**, *43*, 1605-1608.

28) Kharrat, S. E.; Laurent, P.; Blancou, H. *J. Org. Chem.* **2006**, *71*, 8637-8640.

29) Worlikar, S. A.; Kesharwani, T.; Yao, T.; Larock, R. C. *J. Org. chem.* **2007**, *72*, 1347-1353

30) Godoi, B.; Speranca, A.; Back, D. F.; Brandao, R.; Nogueira, C. W.; Zeni, G. *J. Org. Chem.* **2009**, *74*, 3469-3477.

31) Ye, L.-W.; Sun, X.-L.; Zhu, C.-Y.; Tang, Y. *Org. Lett.* **2006**, *8*, 3853-3856.

32) Ravichandran, S.; Subramanl, K.; Arunkumar, R. *Int. J. Chem. Tech. Res.* **2009**, *1*, 329-331.

33) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 6638-6642.

34) Raju, B. C.; Saidachary, G.; Kumar, J. A.; Sridhar, B. *Helv. Chim. Acta* **2011**, *94*, 248.

35) Sosnovskikh, V. Y.; Korotaev, V. Y.; Chizhov, D. L.; Kutyashev, I. B.; Yachevskii, D. S.; Kazheva, O. N.; Dyachenko, O. A.; Charushin, V. N. *J. Org. Chem.* **2006**, *71*, 4538-4543.

36) Fort, Y.; Berthe, M. C.; Caubere, P. *Tetrahedron* **1992**, *48*, 6371- 6384.

37) Basavaiah, D.; Rao, A. J. *Tetrahedron Lett.* **2003**, *44*, 4365-4368.

38) Luo, S.; Mi, X.; Xu, H.; Wang, P. G.; Cheng, J.-P. *J. Org. Chem.* **2004**, *69*, 8413-8422.

39) a) Sosnovskikh, V. Ya.; Mel'nikov M. Yu. *Zh. Org. Khim.* **1998**, *34*, 203-205 (*Russ. J. Org. Chem.* **1969**, *34*, 175-177). b) Sosnovskikh, V. Ya.; Mel'nikov M. Yu. *Zh. Org. Khim.* **1998**, *34*, 303-306 (*Russ. J. Org. Chem.* **1998**, *34*, 276-279). c) Sosnovskikh, V. Ya.; Mel'nikov M. Yu. *Khim. Geterotsikl. Soedin.* **1996**, 1003-1004 (*Chem. Heterocycl. Compd.* **1996**, *32*, 863-864).

40) a) Sosnovskikh, V. Ya. *Zh. Org. Khim.* **1992**, *28*, 1307-1308 (*Russ. J. Org. Chem.* **1992**, *28*, 1250-1251). b) Sosnovskikh, V. Ya.; Mel'nikov M. Yu.; Kutsenko, V. A. *Zh. Org. Khim.* **1996**, *32*, 1440 (*Russ. J. Org. Chem.* **1996**, *32*, 1393).

41) a) Yachevskii, D. S.; Chizhov, D. L.; Ratner, V. G.; Pashkevich, K. I. *Izv. Acad. Nauk, Ser. Khim.* **2001**, 1176-1180 (*Russ. Chem. Bull.* **2001**, *50*, 1233-1237). b) Yachevskii, D. S.; Chizhov, D. L.; Pashkevich, K. I.; Charushin, V. N. *ARKIVOC* **2004**, *xi*, 71-76.

42) An,H.; Eum, S.-J.; Koh, M.; Lee, S. K.; Park, S. B. *J. Org. Chem.* **2008**, *73*, 1752-1761.

43) de C da Silva, F.; Jorqueira, A; Gouvêa, R. M.; de Souza, M. C. B. V.; Howie, R. A.; Wardell, J. L.; Wardell, S. M. S. V.; Ferreira, V. F. *Synlett* **2007**, 3123-3126.

44) Reynolds, T. E.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 7806-7809.

45) Adler, M. J.; Baldwin, S. W. *Tetrahedron Lett.* **2009**, *50*, 5075-5079.

46) Kureshy, R.; Ahmad, I.; Pathak, K.; Khan, N. H.; Abdi, S. H. R.; Jasra, R. V. *Catalysis Communication* **2009**, *10*, 572-575.

47) Petasis, N. A.; Butkevich, A. N. *J. Organomet. Chem.* **2009**, *694*, 1747-1753.

48) Petasis, N. A.; Boral, S. *Tetrahedron Lett.* **2001**, *42*, 539–542.

49) Wang, Q.; Finn, M. G. *Org. Lett.* **2000**, *2*, 4063–4065.

50) Kabalka, G.; Venkataiah, B.; Das, B. C. *Synlett* **2004**, 2194–2196.

51) Liu, F.; Evans, T.; Das, B. C. *Tetrahedron Lett.* **2008**, *49*, 1578–1581.

52) Korotaev, V. Y.; Sosnovskikh, V. Y.; Kutyashev, I. B.; Barkov, A. Y.; Matochkina, E. G.; Kodess, M. I. *Tetrahedron* **2008**, *64*, 5055-5060.

53) Linderman, R. J.; Jamois, E. A. *J. Fluorin Chem.* **1991**, *53*, 79-91.

54) a) Pozzo, J. L.; Harie, G.; Lokshin, V.; Samat, A.; Guglielmetti, R. *Mol. Cryst. Liq. Cryst.* **1997**, *297*, 255–262; (b) Harie, G.;Samat, A.; Guglielmetti, R. *Mol. Cryst. Liq. Cryst*. **1997**, *297*, 263–268; (c) Pozzo, J. L.; Samat, A.; Guglielmetti, R.; Dubest, R.; Aubard, J. *Helv. Chim. Acta* **1997**, *80*, 725–738.

55) a) Casiraghi, G.; Casnati, G.; Salerno, G. *J. Chem. Soc. C* **1971**, 2546–2548; (b) Sartori, G.; Casiraghi, G.; Bolzoni, L.; Casnati, G. *J. Org. Chem*. **1979**, *44*, 803–805; (c) Casnati, G.; Cariraghi, G.; Pochini, A.; Sartori, G.; Ungaro, R. *Pure Appl. Chem*. **1983**, *55*, 1677–1688; (d) Pozzo, J. L.; Samat, A.; Guglielmetti, R.; Lokshin, V.; Minkin, V. *Can. J. Chem.* **1996**, *74*, 1649–1659; (e) Kumar, A. U.S. Patent 5,411,679, 1995.

56) Bougdid, L.; Heynderickx,A.; Delbaereb, S.; Moustrou, C. *Tetrahedron* **2007**, *63*, 8242-8249.

57) Gembus, V.; Sala-Jung, N.; Uguen, D. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 843-854.

58) Ramachary, D. B.; Narayana, V. V.; Ramkumar, K. *Eur. J. Org. Chem.* **2008**, 3907-3911.

59) Liu, F.; Evans, T.; Das, B. C. *Tetrahedron Lett.* **2008**, *49*, 1578-1581.

60) Wu, Y.-C.; Li, H.-J.; Liu, L.; Liu, Z.; Wang, D.; Chen, Y.-J. *Org. Bimol. Chem.* **2011**, *9*, 2868-2877.

61) van Lingen, H. L.; Zhuang, W.; Hansen, T.; Rutjes, F. P. J. T.; Jørgensen, K. A. *Org. Biomol. Chem.,* **2003**, *1*, 1953–1958.

62) a) Mazza, G.; Brouillard, R. *Food Chem.,* **1987**, *25*, 207–225; b) Goto, T.; Kondo, T. *Angew. Chem., Int. Ed. Engl.,* **1991**, *30*, 17–33; c) Brouillard, R.; Dangles, O.; *The Flavonoids, Advances in Research since 1986*, Harborne, J. B. Ed., Chapman and Hall, London, **1993**; d) Santos, H.; Turner, D. L.; Lima, J. C.; Figueiredo, P.; Pina, F.; Macu¨ anita, A. L. *Phytochemistry* **1993**, *33*, 1227–1232; e) Tamura, H.; Yamagami, A. *J. Agric. Food Chem.,* **1994**, *42*, 1612–1615; f) Costantino, L.; Rastelli, G.; Albasini, A. *Pharmazie*, **1995**, *50*, 573–574.

63) McClelland, R. A.; Gedge, S. *J. Am. Chem. Soc.,* **1980**, *102*, 5838–5848.

64) Bohmdorfer, S.; Kloser, E.; Patel, A.; Gille, L.; Mereiter, L.; Rosenau, T. *Tetrahedron* **2011**, *67*, 6181-6185.

65) Rao, V. V. V. N. S. R.; Yadla, R.; Rao, P. S. *Synth. Commun.* **2006**, *37*, 535-543.

66) Kenny, R. S.; Mashelkar, U.; Rane, D. M.; Bezawada, D. K. *Tetrahedron* **2006**, *62*, 9280-9288.

67) Moquist, P. N.; Kodama, T.; Schaus, S. E. *Angew. Chem. Int. Ed.* **2010**, *49*, 7096-7100.

68) Yamamoto, H.; Futatsugi, K. *Angew. Chem.* **2005**, *117,* 1958-1977; *Angew. Chem. Int. Ed.* **2005**, *44*, 1924-1942.

69) Zhang, Z.; Jakab, G.; Schreiner, P. R. *Synlett* **2011**, 1262-1264

70) Samet, A. V.; Lutov, D. N.; Firgang, S. I.; Lyssenko, K. A.; Semenov, V. V. *Tetrahedron Lett*. **2011**, *52*, 3026-3028.

71) a) Witczak, Z. J. Ed. Levoglucosenone and Levoglucosans: Chemistry and Applications; ATL Press: Mount Prospect, 1994.; (b) Witczak, Z. J.; Tatsuka, K. Eds. Carbohydrate Synthons in Natural Products Chemistry. Synthesis, Functionalization, and Applications. ACS Symposium Series 841; American Chemical Society: Washington, DC, 2003.

72) For reviews, see: a) Miftakhov, M. S.; Valeev, F. A.; Gaisina, I. N. Russ. *Chem. Rev*. **1994**, *63*, 869; b) Witczak, Z. J. New Stereoselective Functionalization of Cellulose-Derived Pyrolysis Derivatives: Levoglucosenone and Its Dimer. In Materials, Chemicals, and Energy from Forest Biomass; ACS Symposium Series 954; American Chemical Society: Washington, DC, 2007; pp 332–349; Some recent examples: c) Nishikawa, T.; Urabe, D.; Isobe, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4782; d) Awad, L.; Demange, R.; Zhu, Y.-H.; Vogel, P. *Carbohydr. Res.* **2006**, *341*, 1235; e) Samet, A. V.; Shestopalov, A. M.; Lutov, D. N.; Rodinovskaya, L. A.; Shestopalov, A. A.; Semenov, V. V. *Tetrahedron: Asymmetry* **2007**, *18*, 1986; f) Samet, A. V.; Lutov, D. N.; Konyushkin, L. D.; Strelenko, Y. A.; Semenov, V. V. *Tetrahedron: Asymmetry* **2008**, *19*, 691; g) Sarotti, A. M.; Spanevello, R. A.; Suarez, A. G. *Tetrahedron* **2009**, *65*, 3502.

73) *a*) Xu, D.-Q.; Wang, Y.-F.; Luo, S.-P.; Zhang, S.; Zhong, A.-G.; Chen, H.; Xu, Z.-Y. *Adv. Synth. Catal.*, **2008**, *350*, 2610; *b*) Karthikeyan, T.; Sankararaman, S. *Tetrahedron: Asymmetry*, **2008**, *19*, 2741.

74) Xie, J.-W.; Fan, L.-P.; Su, H.; Li, X.-S.; Xu, D.-C. *Org. Biomol. Chem.* **2010**, *8*, 2117-2122.

75) Govender, T.; Hojabri, L.; Moghaddam, M.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2006**, *17*, 1763-176.7

76) Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem. Eur. J.* **2007**, *13*, 574-581.

77) Li, H.; Wang, J.; E-Nunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. *Chem. Commun.* **2007**, 507-509.

78) Xu, D.-Q.; Wang, Y.-F.; Luo, S.-P.; Zhang, S.; Zhong, A.-G.; Chen, H.; Xu, Z.-Y. *Adv. Synth. Catal.* **2008**, *350*, 2610-2616.

79) Luo, S.-P.; Li, Z.-B.; Wang, L.-P.; Guo, Y.; Xia, A.-B.; Xu, D.-Q. *Org. Biomol. Chem.* **2009**, *7*, 4539-4546.

80) Das, B. C.; Mohapatra, S.; Campbell, P. D.; Nayak, S.; Mahalingam, S. M.; Evans, T. *Tetrahedron lett.* **2010**, *51*, 2567-2570.

81) Shen, H.; Yang, K.-F.; Shi, Z.-H.; Jiang, J.-X.; Lai, G.-Q.; Xu, L.-W. *Eur. J. Org. Chem.* **2011**, 5031-5038.

82) Rueping, M.; Uria, U.; Lin, M.-Y.; Atodiresei, I. *J. Am. Chem. Soc.* **2011**, *133*, 3732-3735.

83) Tahtaoui, C.; Demailly, A.; Guidemann, C.; Joyeux, C.; Schneider, P. *J. Org. Chem.* **2010**, *75*, 3781-3785.

84) Takenaka, K.; Tanigaki, Y.; Patil, M. L.; Rao, C. V. L.; Takizawa, S.; Suzuki, T.; Sasai, H. *Tetrahedron: Asymmetry* **2010**, *21*, 767-770.

85) a) Bruder, M.; Smith, S. J.; Blake, A. J.; Moody, C. J. *Org. Biomol. Chem.* **2009**, *7*, 2127-2134. b) Bruder, M.; Moody, C. J. *Synlett* **2008**, 575-577.

86) Machado, A. H. L.; de Sousa, M. A.; Patto, D. C. S.; Azevedo, L. F. S.; Bombonato, F. I.; Correia, C. R. D. *Tetrahedron Lett.* **2009**, *50*, 1222-1225.

87) For a review, see: *Green Chemistry-Theory and Practice*; Anastas, P. T., Warner, J. C., Eds.; Oxford University, Press: Oxford, **1998** and references cited therein.

88) a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**, p. 672; b) Tietze, L. F.; Beifuss, U. *Angew. Chem.* **1993**, *105*, 137–170; *Angew.Chem. Int. Ed. Engl.* **1993**, *32*, 131–163; c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136; d) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619-1665; e) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143–2173; f) Ho, T.-L. *Tandem Organic Reactions*, Wiley, New York, **1992**, p. 502; g) Bunce, R. A. *Tetrahedron*

1995, *51*, 13103–13159.

89) a) Trost, B. M. *Science* **1991**, *254*, 1471–1477; b) Trost, B. M. *Angew. Chem.* **1995**, *107*, 285–307; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281; c) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, **2000**, p. 135; d) Matlack, A. S. *Introduction to Green Chemistry*, Marcel Dekker, New York, **2001**, p. 570.

90) D. W. C. MacMillan, L. E. Overman, L. D. Pennington, *J. Am. Chem. Soc.* **2001**, *123*, 9033 – 9044.

91) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 644.

92) Waters, M. L.; Wulff, W. D. *Organic Reactions, Vol. 70*, 121 – 656.

93) Fleming, I. *Pericyclic Reactions*; Oxford University Press, **1999**; p 57

94) Hoffmann, R., Woodward, R. B. *Acc. Chem.* **1968**, *1*, 17–22.

95) Fei, L.; Evans, T.; Das, B. C. *Tetrahedron Lett.* **2008**, *49*, 1578.

96) Hanamoto, T.; Shindo, K.; Matsuoka, M.; Kiguchi, Y.; Kondo, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3082.

97) Varma, R. S.; Dahiya, R. *J. Org. Chem.* **1998**, *63*, 8038.

98) a) Wang, Q.; Finn, M. G. *Org. Lett.* **2000**, *2*, 4063. (b) Kabalka, G. W.; Venkataiah, B.; Das, Bhaskar. C. *Synlett* **2004**, 2194.

99) Chang, S.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 864.
100) Kaye, P. T.; Nocanda, X. W. *J. Chem. Soc., Perkin Trans 1* **2000**, 1331.

101) Hlubeck, J.; Ritchie, E.; Taylor, W. C. *Tetrahedron Lett.* **1969**, 1369.

102) Iyer, M.; Trivedi, G. R. *Synth. Commun.* **1990**, *20*, 1347.

103) Parker, K. A.; Mindt, T. L. *Org. Lett.* **2001**, *3*, 3875.

104) Ye, L. Wu.; Sun, Xiu-L.; Zhu, Chun-Y.; Tang, Y. *Org. Lett.* **2006**, *8*, 3853.

105) a) Engler, T. A.; La Tessa, K. O.; Iyengar, R.; Chai, W.; Agrios, K. *Bioorg. Med. Chem.* **1996**, *4*, 1755–1769; b) Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.;

Morris-Natschke, S. L.; Lee, K. H. *Tetrahedron* **2001**, *57*, 1559–1563; c) Elomri, A.; Mitaku, S.; Michel, S.; Skaltsounis, A.-L.; Tillequin, F.; Koch, M.; Pierre, A.; Guilbaud, N.; Leonce, S.; Kraus-Berthier, L.; Rolland, Y.; Atassi, G. *J. Med. Chem.* **1996**, *39*, 4762–4766; d) Lago, J. H. G.; Ramos, C. S.; Casanova, D. C. C.; Morandim, A.; de, A.; Bergamo, D. C. B.; Cavalheiro, A. J.; Bolzani, V.; da, S.; Furlan, M.; Guilharaes, E. F.; Young, M. C. M.; Kato, M. J. *J. Nat. Prod.* **2004**, *67*, 1783–1788; e) Bernard, C. B.; Krishnamurty, H. G.; Chauret, D.; Durst, T.; Philogene, B. J. R.; Sanchez Vindas, P.; Hasbun, C.; Poveda, L.; San Roman, L.; Arnason, J. T. *J. Chem. Ecol.* **1995**, *21*, 801–814; f) Jankun, J.; Selman, S. H.; Swiercz, R. *Nature* **1997**, *387*, 561.

106) Unpublished result, see Ph.D. thesis of Keith Korthal, Michigan State University **2007**.

107) For review, see: Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367.

108) Hug, R.; Hansen, H.; Schmid, H. *Helv. Chim. Acta.* **1972**, 1675 -1691.

109) For phenylboric acid derivatives see: Murphy, W.; Tuladhar, S.; Duffy, B. J. *Chem. Soc. Perkin Trans. 1* **1992**, 605 - 609.

110) a) For a review of photo induced formation of *o*-quinone methides, see: Wan, P.; Barker, B.; Diao, L.; Fischer, M.; Shi, Y.; Yang, C. *Can. J. Chem.* **1996**, *74*, 465 – 475; b) Migani, A.; Gentili, P.; Negri, F.; Olivucci, M.; Romani, A.; Favaro, G.; Becker, R. *J. Phys. Chem.* **2005**, *109*, 8684 - 8692.

111) Jones, R.; Van De Water, R.; Lindsey, C.; Hoarau, C.; Ung, T.; Pettus, T. *J. Org. Chem.* **2001**, 66, 3435 - 3441.

112) Jurd, L.; Roitman, J. *Tetrahedron* **1978**, *34*, 57 - 62.

113) a) Bolon, D. *J. Org. Chem.* **1970**, *35*, 715 - 719. (b) Bolon, D. *J. Org. Chem.* **1970**, *35*, 3666 - 3670.

114) a) Yamashita, A.; Timko, J. M.; Watt, W. *Tetrahedron Lett.* **1988**, *29*, 2513. b) Yamashita, A. *Tetrahedron Lett.* **1985**, *26*, 1159.

115) Korthals, K. A.; Wulff, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 2898.

116) a) Wulff, W. D.; Bax, B. M.; Brandvold, T. A.; Chan, K. S.; Gilbert, A. M.; Hsung, R. P.; Mitchell, J.; Clardy, J. *Organometallics* **1994**, *13*, 102-126; b) Chan, K. S.; Peterson, G. A.; Brandvold, T. A.; Faron, K. L.; Challener, C. A.; Hydahl, C.; Wulff,

W. D. *J. Organomet. Chem.* **1987**, *334*, 9-56; c) Bos, M. E.; Wulff, W. D.; Miller, R. A.; Chamberlin, S.; Brandvold, T. A. *J. Am. Chem. Soc.* **1991**, *113*, 9293-9319; d) Wulff, W. D.; Tang, P.-C. Chan, K. S.; McCallum, J. S.; Yang, D. C.; Gilbertson, S. R. *Tetrahedron* **1985**, *41*, 5813-5832.

117) Davies, S. G.; Donhoe, T. J. *Synlett* **1993**, 323-332.

118) Pearson, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 6109.

119) Netscher, T. *Vitam Horm.* **2007**, *76*, 155-202.

120) Schneider, C. *Mol. Nutr. Food Res.* **2005**, *49*, 7–30.

121) a) Devaraj, S; Hugou, I.; Jialal, I. *J. Lipid Res.* **2001**, *42*, 521–527; b) Azzi, A; Stocker, R. *Prog. Lipid Res.* **2000**, *39*, 231–255; c) Villacorta, L.; Graca-Souza, A. V.; Ricciarelli, R.; Zingg, J. M.; Azzi, A. *Circ. Res.* **2003**, *92*, 104–110.

122) Muller, D. P. *Mol. Nutr. Food Res.* **2010**, *54*, 710–718.

123) Traber, M. G.; Jan F. Stevens, J. F. *Free Radic. Biol. Med*. **2011**, *51*, 1000–1013.

124) a) Burton, K. G. W.; Ingold, K. U. *Acc. Chem. Res.* **1986,** *19,* 194-201; b) Burton, K. G. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1981,***103,* 6472-6477.

125) a) Karrer, P.; Fritzsche, H.; Ringier, B. H.; Salomon, H. *Nature* **1938**, *141*, 1057; b)Karrer, P.; Fritzsche, H.; Ringier,B. H.; Salomon, H. *Helv. Chim. Acta* **1938**, *21*, 520-525.

126) Bergel, F.; Jacob, A.; Todd, A. R.; Work, T. S. *Nature* **1938**, *142*, 36-36.

127) a) Baldenius, K. U.; von dem Bussche-Hünnefeld, L.; Hilgemann, E.; Hoppe, P.; Stürmer, R. "*Ullmann's Encyclopedia of Industrial Chemistry and 594–597"* **1996**, A27, 478–488. VCH Verlagsgesellschaft, Weinheim. b) Bonrath, W.; Netscher, T. *Appl. Catal. A: General* **2005**, *280*, 55–73. c) Bonrath, W.; Haas, A.; Hoppmann, E.; Netscher, T.; Pauling, H.; Schager, F.; Wildermann, A. *Adv. Synth. Catal.* **2002**, *344*, 37–39. d) Bonrath, W.; Dittel, C.; Giraudi, L.; Netscher, T.; Pabst, T. *Catal. Today* **2007**, *121*, 65–70. e) Hasegawa, A., Ishihara, K., and Yamamoto, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 5731–5733. f) Ishihara, K., Kubota, M., and Yamamoto, H. *Synlett* **1996**, 1045–1046. g) Kokubo, Y., Hasegawa, A., Kuwata, S., Ishihara, K., Yamamoto, H., and Ikariya, T. *Adv. Synth. Catal.* **2005**, *347*, 220–224. h) Matsui, M.; Karibe, N., Hayashi, K., and Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3569–3571. i) Odinokov, V. N.; Spivak, A. Y.; Emelyanova, G. A.; Mallyabaeva, M. I.; Nazarova, O. V.; Dzhemilev, U. M. *ARKIVOC* **2003**,*13*, 101–

118. j) Wildermann, A., Foricher, Y., Netscher, T., and Bonrath, W. *Pure Appl. Chem.* **2007**, *79*, 1839-1846.

128) Kabbe, H. J.; Heitzer, H. *Synthesis* **1978**, 888–889.

129) Bienayme, H.; Ancel, J.-E.; Meilland, P.; Simonato ,J.-P. *Tetrahedron Lett*. **2000**, *41*, 3339–3343.

130) Dötz, K. H.; Kuhn, W. *Angew. Chem., Int*. *Ed. Engl.* **1983***, 22,* 732*.*

131) Liu, K.; Chougnet, A.; Woggon, W.-D. *Angew. Chem., Int. Ed.* **2008**, *47*, 5827-5829.

132) Wen, B.; Doneanu, C. E.; Gartner, C. A.; Roberts, A. G.; Atkins, W. M.; Nelson, S. D. *Biochemistry* **2005**, 44, 1833.

133) For citations to the literature, see ref 17.

134) *Chromenes, chromanones, and chromones*; Ellis, G. P., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 1977; Vol 31.

135) Itoigawa, M.; Ito, C.; Tan, H. T.-W.; Okuda, M.; Tokuda, H.; Nishino, H.; Furukawa, H. *Cancer Lett*. **2001**, *174*, 135.

136) Schmeda-Hirschmann, G.; Papastergiou, F. Z. *Naturforsch*. **2003**, *58c*, 495–501.

137) Rawat, M.; Prutyanov, V.; Wulff, W. D. *J. Am. Chem. Soc.* **2006**, *128*, 11044–11053.

138) Complex **3-41** was prepared as described by the literature procedure with methyl triflate as the alkylating agent. (a) Fischer, E. O.; Maasböl, A. *Chem. Ber*. **1967**, *100*, 2445. (b) Fischer, E. O.; Kreiter, C. G.; Kollmeier, H. J.; Muller, J.; Fischer, R. D. *J. Organomet. Chem*. **1971**, *28*, 237.

139) Livingstone, R.; Watson, R. B. *J. Chem. Soc.*, **1956**, 3701-3704.

140) Lee, Y. R.; Kim, Y. M. *Helv. Chim*. *Acta* **2007**, *90*, 2401-2413.

141) For examples and leading references, see: Wulff, W. D.; Bax, B. M.; Brandvold, T. A.; Chan, K. S.; Gilbert, A. M.; Hsung, R. P. *Organometallics* **1994**, *13*, 102.

142) a) Wulff, W. D.; Bax, B. M.; Brandvold, T. A.; Chan, K. S.; Gilbert, A. M.; Hsung, R. P.; Mitchell, J.; Clardy, J. *Organometallics* **1994**, *13*, 102-126. b) Chan, K. S.;

Peterson, G. A.; Brandvold, T. A.; Faron, K. L.; Challener, C. A.; Hydahl, C.; Wuff, W. D. *J. Organomet. Chem.* **1987**, *334*, 9-56. c) Bos, M. E.; Wulff, W. D.; Miller, R. A.; Chamberlin, S.; Brandvold, T. A. *J. Am. Chem. Soc.* **1991**, *113*, 9293-9319. d) Gross, M. F.; Finn, M. G. *J. Am. Chem. Soc.* **1994**, *116*, 10921-10933.

143) a) Waters, M. L.; Wulff, W. D. *Org. React.* **2008**, *70*, 121–623. (b) Dötz, K. H.; Stendel, J. Jr. *Chem. Rev.* **2009**, *109*, 3227.

144) Gibson, S. E.; Ibrahim, H. *Chem. Commun.* **2002**, 2465–2473.

145) a) Hsung, R. P.; Wulff, W. D. *J. Am. Chem. Soc.* **1994,** *116***,** 6449-6450; b) Hsung, R. P.; Wulff, W. D.; Challener, C. A. *Synthesis* **1996**, 773-789.

146) Korthals, K. A.; Wulff, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 2898.

147) Thompson, S.; Coyne, A. G.; Knipe, P. C.; Smith, M. D. *Chem. Soc. Rev.* **2011**, *40*, 4217–4231.

148) Baldoli, C.; Del Buttero, P.; Licandro, E.; Maiorana, S.; Papagni, A. *Tetrahedron: Asymmetry* **1994**, *5*, 809–812.

149) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616-5617.

150) a) González, A.G.; Darias, J.; Martin, J.D.; Pascual, C. *Tetrahedron* **1973**, *29*,1605–1609; b) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R. *Tetrahedron Lett.* **1997**, *38*, 2325–2328; c) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Herrador, M. M.; Chahboun, R.; Galera P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2325-2328.

151) Waters, M. L.; Wulff, W. D. *Org. React.* **2008**, *70*, 121-623.

152) For the preparation of compound **2-69**, see: (a) Ratnayake, A. S.; Hemscheidt, T. *Org. Lett.* **2002**, *4*, 4667- 4669. For the preparation of compound **2-70**, see: (b) Young, D. G. J.; Burlison, J. A.; Peters, U. *J. Org. Chem.* **2003**, *68*, 3494-3497. For TMS deprotection, see: (c) Crouch, R. D. *Tetrahedron* **2004**, *60*, 5833-5871.

153) Aumann, R.; Heinen, H. *Chem. Ber.* **1987**, *120*, 537-540.

154) Dötz, K. H.; Kuhn, W.; Ackermann, K. *Z. Naturforsch.* **1983**, *38b*, 1351-1356.

155) Wulff, W. D.; Bauta, W. E.; Kaesler, R. W.; Lankford, P. J.; Miller, R. A.; Murray, C. K.; Yang, D. C. *J. Am. Chem. Soc.* **1990**, *112*, 3642-3659.

156) Minatti, A.; Dötz, K. H. *J. Org. Chem.* **2005**, *70*, 3745-3748.

157) Fogel, L.; Hsung, R. P.; Wulff, W. D. *J. Am. Chem. Soc.* **2001**, *123*, 5580-5581.

158) Chamberlin, S.; Wulff, W. D.; Bax, B. *Tetrahedron* **1993**, *49*, 5531-5547.

159) Chan, K. S.; Peterson, G. A.; Brandvold, T. A.; Faron, K. L.; Challener, C. A.; Hyldahl, C.; Wulff, W. D. *J. Organomet. Chem.* **1987**, *334*, 9.

160) Complex **53** was prepared as described by the literature procedure with methyl triflate as the alkylating agent. (a) Fischer, E. O.; Maasböl, A. *Chem. Ber*. 91, **1967**,*100*, 2445. (b) Fischer, E. O.; Kreiter, C. G.; Kollmeier, H. J.; Muller, J.; Fischer, R. D. *J. Organomet. Chem*. **1971**, *28*, 237.

161) Liu, K.; Chougnet, A.; Woggon, W.-D. *Angew. Chem. Int. Ed.* **2008**, *47*, 5827-5829.

162) Ph.D. Thesis by Dr. K. Korthals.

163) a) Surendra, K.; Krishnaveni, N.; Reddy, M.; Nageswar, Y.; Rao, K. *J. Org. Chem.* **2003**, *68* (5), 2058 - 2059. (b) Barlow, L.; Pattenden, G. *J. Chem. Soc., Perkin 1* **1976**, 1029 - 1034. (c) Venuto, P.; Day, A. *J. Org. Chem.* **1964**, *29* (9), 2735 - 2738. (d) Kappeler, H.; Grutter, H.; Schinz, H. *Helv. Chim. Acta* **1953**, *36*, 1862 - 1876.

164) Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952,** 1094.

165) Lodewyk, M. W.; Lui, V. G.; Tantillo, D. J. *Tetrahedron Lett.* **2010**, *51*, 170-173.

166) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616-5617.