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The Development of an aza-Piancatelli Rearrangement

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Chemistry

by

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Abstract

The Development of an aza-Piancatelli Rearrangement

by

Donald Raymond Wenz

Nitrogen containing compounds are ubiquitous in nature, and this element plays a critical role in the biological activity of many useful compounds. The essential role of nitrogen has dictated the need for new methods for constructing organic compounds containing carbon–nitrogen bonds. The present work describes our efforts to develop new reactions that form new carbon–nitrogen bonds through the development of an aza-Piancatelli rearrangement, which is a new method for the construction of a variety of *trans*-4-amino cyclopentenones from readily available 2-furylcarbinols. Activation of furylcarbinols under acidic conditions initiates a cascade sequence that results in nucleophilic attack by nitrogen onto furan and ultimately terminates by way of a 4π conrotatory electrocyclization. The electrocyclization step is stereospecific giving products with defined *trans* stereochemistry on the newly produced cyclopentenone ring. The Piancatelli rearrangement can be considered complimentary to the Nazarov reaction for the formation of substituted cyclopentenones, however with the former being largely underdeveloped with respect to the nucleophilic partner that is incorporated into the final compound. We have utilized lanthanide triflate Lewis acids, which are part of a class of

Lewis acidic salts of rare earth metals, to enable the usage of amine nucleophiles with the Piancatelli rearrangement. Challenges were encountered during further developments using the aza-Piancatelli rearrangement due to inherent limitations of the original furylcarbinol system. These limitations were overcome by the utilization donor-acceptor cyclopropanes which act as an entirely new activation platform for the rearrangement. This new activation platform acts as a masked carbocation and does not suffer common side reactions such as elimination or Friedel–Crafts alkylation reactions that can be problematic using traditional furylcarbinol starting materials.

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List of Abbreviations

3Å MS - 3 angstrom molecular sieve

Å - angstrom

Bn - benzyl

Boc - tert-butyloxycarbonyl

$Ce(OTf)_3$ - cerium(III) trifluoromethanesulfonate

CH_2Cl_2 - dichloromethane

Cl_3CCN - trichloroacetonitrile

DBU - 1,8-diazabicycloundec-7-ene

DIAD - diisopropyl azodicarboxylate

DFT - density functional theory

DME - 1,2-dimethoxyethane

DMSO - dimethyl sulfoxide

$Dy(OTf)_3$ - dysprosium(III) trifluoromethanesulfonate

EDG - electron donating group

EtOAc - ethyl acetate

EWG - electron withdrawing group

H_2O - water

HOAc - acetic acid

HOMO - highest occupied molecular orbital

HOTf - trifluoromethanesulfonic acid (triflic acid)

LUMO - lowest occupied molecular orbital

MeCN - acetonitrile

$MeNO_2$ - nitromethane

MO - molecular orbital

M.S. - molecular sieve

$NaBAr^F$ - sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

$NaCNBH_3$ - sodium cyanoborohydride

NOESY - Nuclear Overhauser Effect Spectroscopy

Nu - nucleophile

OTf - trifluoromethanesulfonate

PPA - polyphosphoric acid

PPh_3 - triphenylphosphine

rt - room temperature

SEM - trimethylsilylethoxy methy

$Sc(OTf)_3$ - scandium(III) trifluoromethanesulfonate

TBDPSCl - *tert*-Butyl(chloro)diphenylsilane

TFA - trifluoroacetic acid

THF - tetrahydrofuran

TLC - thin layer chromatography

TMHD - Tris(2,2,6,6-tetramethyl-3,5-heptanedionato)

triflate - trifluoromethanesulfonate

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1. Development of an aza-Piancatelli Rearrangement

1.1 Introduction

As the 7th most abundant element in the Milky Way Galaxy and the 4th most abundant element in the human body, nitrogen is ubiquitous in nature.[1] Element number seven on the periodic table, nitrogen has five valence electrons and will typically form three bonds to fill its valence octet. Two non-bonding electrons make up nitrogen's lone pair, which are important for the unique properties of the nitrogen atom.[2] When incorporated into organic molecules, nitrogen possesses the ability to act as either an acid or a base depending on the substituents that nitrogen is bonded to. This is in part due to nitrogen's lone pair of electrons being susceptible to inductive effects and its ability to participate in conjugation. Both of these characteristics can reduce electron density on the nitrogen atom, which, in turn weakens its bond with labile atoms such as protons, making nitrogen behave as an acid. Other 2nd and 3rd row elements with lone pairs (O, P, S, etc.) are also capable of this type of reactivity. Conversely, electron rich nitrogen compounds can act as strong bases. The abundance of nitrogen in the universe as well as its broad spectrum of reactivity is some of the reasons that nature has incorporated nitrogen atoms into a huge variety of biological systems.

Unfortunately, for synthetic chemists, incorporation of nitrogen into organic molecules through the formation of new carbon nitrogen bonds is not always straightforward due to its ambident reactivity. Lewis basic nitrogen compounds have rightfully earned the reputation of being difficult to work with in the laboratory due to their high polarity, reactivity towards electrophiles and propensity to exist as an ionic acid salt. There is a never ending need to

expand the tool kit of organic chemistry to enable the rapid and straightforward incorporation of nitrogen into complex organic molecules. The overarching goals of our laboratory are towards this endeavor, and the development of new methodology for constructing carbon–nitrogen bonds is the driving philosophy behind the work presented herein. The work described in this dissertation falls under two general categories: (1) the use of cascade reactions and 4π electrocyclizations to control and construct densely functionalized cyclopentenones, and (2) the design of new modes of activation to trigger the cascade reactions that enable the formation of fully substituted all-carbon quaternary stereocenters.

1.1.1 Pericyclic Reactions

Pericyclic reactions are a subset of concerted organic reactions that proceed through a transition state comprised of a cyclic array of atoms with a corresponding cyclic array of interacting orbitals.[3] They are concerted processes, but not all concerted reactions operate through a pericyclic mechanism. The term pericyclic refers instead to the geometry of the transition state, a cyclic array of interacting molecular orbitals. The classes of pericyclic reactions are: electrocyclic, cycloaddition, sigmatropic reaction, group transfer reaction, cheletropic reaction, and dyotropic reactions, but for brevity, only electrocyclic reactions will be discussed.

Until the mid 1960's the mechanism of pericyclic processes was largely unknown, and were even sometimes called "no-mechanism" reactions because of their distinct lack of intermediates.[3] Theoretical molecular orbital models emerged that would help explain the mechanism under which these remarkably stereospecific reactions took place. Seminal papers by R.B. Woodward and R. Hoffmann in 1965 describe the "conservation of orbital

symmetry" as the controlling factor for the high stereospecificity observed for electrocyclic reactions.[4] Applying molecular orbital theory (MO) to these reactions, Woodward and Hoffman proposed that the symmetry elements of the highest occupied molecular orbital (HOMO) controls the stereochemical outcome of the reaction. The rules for the conservation of orbital symmetry are known better as the Woodward-Hoffman rules and they are able to predict the stereochemical outcome of any number of pericyclic reactions.

The underlying basis behind the Woodward-Hoffman rules is that in any given pericyclic system, in order for a new bond to form, the orbital coefficients of the HOMO at the bond forming location must have the same sign to allow for constructive orbital overlap. Woodward and Hoffman recognized that the requirement for matching HOMO coefficients was the critical factor for understanding the stereochemical outcome of pericyclic reactions. Three simple rules can be devised from this observation to predict the stereochemical outcome of any pericyclic reaction. Firstly, for thermally promoted processes, the conservation of orbital symmetry dictates that open-chain systems containing 4n electrons will cyclize in a conrotatory fashion. Secondly, systems containing 4n+2 electrons will cyclize in a disrotatory fashion under thermal conditions. Lastly, under photochemical control, these roles are reversed (4n = disrotatory, 4n+2 = conrotatory) due to an electron being promoted to an excited state leading to reversal of the orbital symmetry relationships.

Molecular orbital diagrams are helpful to better understand the foundation of these rules, with methyl substituted butadiene **1** often being used as a model system (Figure 1). This system contains four reactive π electrons, which according to the Woodward-Hoffman rules, will cyclize in a conrotatory fashion. To understand why this happens, we must consult the molecular orbital diagram shown in Figure 1. We will arbitrarily assign the coefficients of

the molecular orbitals such that the shaded region is (+) and the un-shaded region is (-). Populating the molecular orbitals with 4π electrons, we see that at the termini of the HOMO (Ψ2), the coefficients at the terminal lobes are oriented in opposite directions with (+) pointed up on the left and (-) on the right (antarafacial). Conservation of orbital symmetry dictates that bond formation only occurs between two orbitals of the same sign. In order for this criterion to be met and bond formation to occur, the π orbitals at the termini of the HOMO must rotate in the same direction (**4**), either to the left or to the right, thereby mixing orbitals with the same coefficient, conserving the orbital symmetry. This leads to conrotatory cyclization and produces products **2** (or **5**) bearing a *trans* relationship between the substituents at the bond forming carbons.

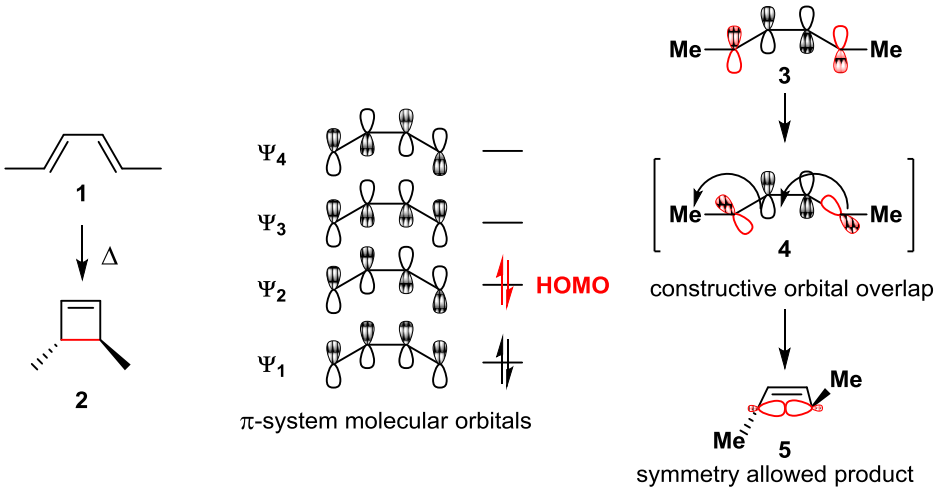


Figure 1. Molecular orbital diagram for a thermally promoted 4π electron conrotatory electrocyclization.

Substituted cyclohexatriene **6** in Figure 2 contains 6π electrons and conforms to the second rule, which states that compounds containing 4n+2 electrons will cyclize in a disrotatory fashion. Looking at the HOMO (Ψ3), we see now that the orbital coefficients at the termini are both on the same face (suprafacial). Thus, for cyclization to occur, the

orbitals must turn towards each other in a disrotatory fashion to conserve orbital symmetry, forming cyclohexadiene **7** (or **10**) bearing substituents with a *cis* relationship on the ring.

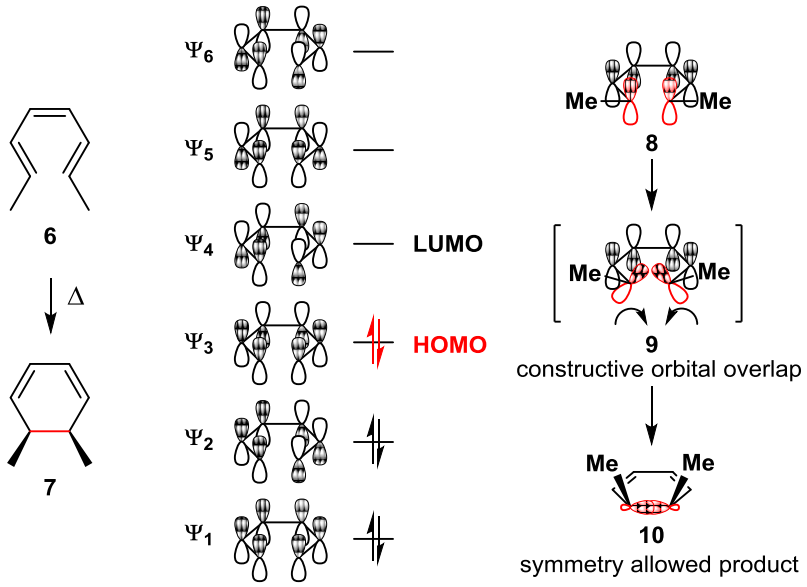


Figure 2. Molecular orbital diagram for a thermally promoted 6π electron disrotatory electrocyclization.

Promotion using light leads to the reversal of these rules since excitation by light promotes an electron into the next highest molecular orbital, which becomes the new HOMO. This has the effect of inverting the coefficients at the HOMO termini of the π system (Figure 3). Looking again at butadiene, we see that after excitation by light, the coefficients of the orbitals at the termini of the HOMO both face the same direction (suprafacial). In order for constructive orbital overlap to occur, the orbitals must now rotate inwards or outwards in a disrotatory fashion. The opposite occurs for systems containing 4n+2 electrons, where photochemical promotion gives products **12** (or **15**) resulting from conrotatory cyclization.

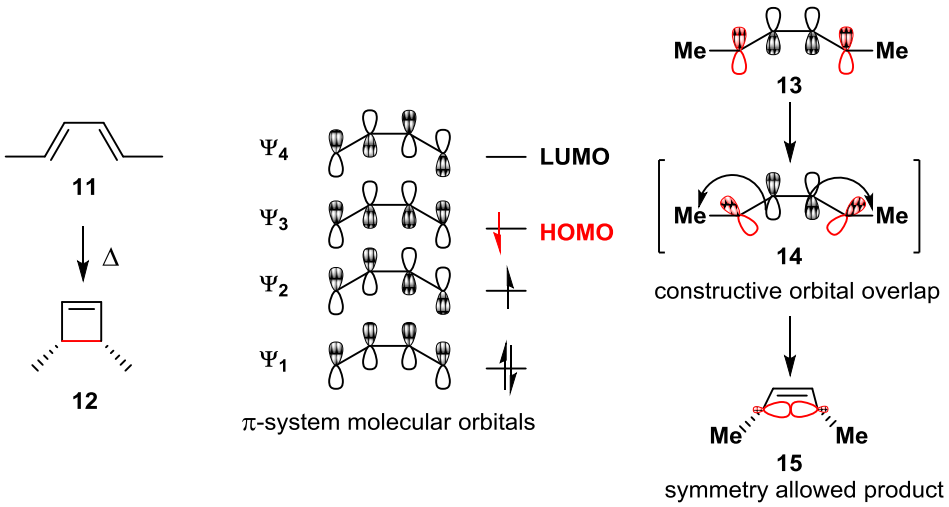


Figure 3. Molecular orbital diagram for a photochemically promoted 4π electron disrotatory electrocyclization.

Electrocyclic reactions are a class of pericyclic processes that involve the conversion of a π system with *n* π electrons to a cyclic system containing *n*-2 π electrons and a new σ bond, or vise versa. These reactions can be promoted either thermally or photochemically and are highly stereospecific. A prototypical example of an electrocyclic reaction is the cyclization of 1,3,5-hexatriene **16** to 1,3-cyclohexadiene **17**. The S-*cis*, S-*cis* intermediate **16** is required for the reaction to occur, since conformations such as **18** cannot form the required cyclic array of electrons (Figure 4).

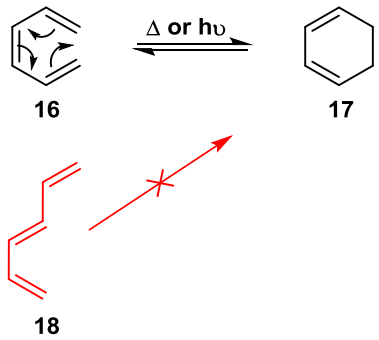


Figure 4. Electrocyclization of 1,3,5-hexatriene.

1.1.2 Pentadienyl Cations

Charged conjugated olefins can participate in electrocyclization reactions and still obey the Woodward-Hoffman rules. Pentadienyl cations are one such system. Loss of an electron from pentadiene **19** generates the resonance stabilized carbocation **20** or **21** (Figure 5). This system possesses 4 conjugated π electrons and thus, will cyclize in a conrotatory sense under thermal conditions.

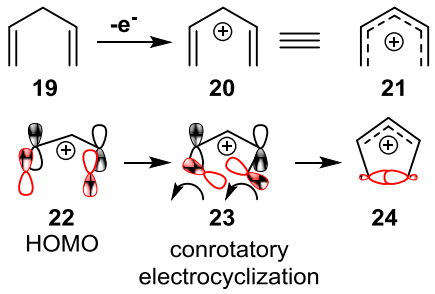
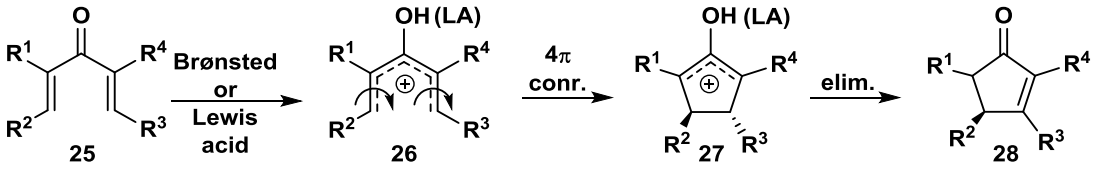


Figure 5. 4π Electrocyclization of pentadienyl cations

The most common way to form a pentadienyl cation **26** is the Brønsted or Lewis acid activation of divinyl ketones **25** (Scheme 1). This process is famously known as the Nazarov cyclization reaction, and has become so ubiquitous that the electrocyclization of any pentadienyl cation is usually referred to as a Nazarov cyclization.[5]

Scheme 1. A prototypical Nazarov cyclization.



The mechanism of the Nazarov cyclization has been studied and the rate determining step has been identified as the 4π electrocyclization.[6] The reaction is exothermic and the driving force is the formation of a more stable oxyallyl cation. The barriers for cyclization of

substituted hydroxy pentadienyl cations have been calculated by de Lera and co-workers at the B3LYP/6-311G* level of theory (Figure 6).[6e] They found that the barrier for cyclization of the classical Nazarov 3-hydroxy pentadienyl cation **29** is 19.49 kcal mol^{-1} with the resulting oxyallyl cation **31** being only 2.12 kcal mol^{-1} more stable than the parent cation (Figure 6a). Calculations revealed that 2-hydroxy pentadienyl cation **32** has almost no barrier for electrocyclization (0.6 kcal/mol) and that the product cation **34** is 40.6 kcal mol^{-1} more stable than the parent cation due to good charge stabilization in the product cation (Figure 6b). Lastly, a 1-hydroxy pentadienyl cation **35** must pass through a 13.93 kcal mol^{-1} barrier but the reaction is endothermic, with the product cation **37** remaining 6.91 kcal mol^{-1} higher in energy than the parent cation (Figure 6c). The endothermic nature of this reaction is, again, due to the location of the hydroxyl group relative to the allylic cation. In this case, the allylic cation is not stabilized by the hydroxyl group.

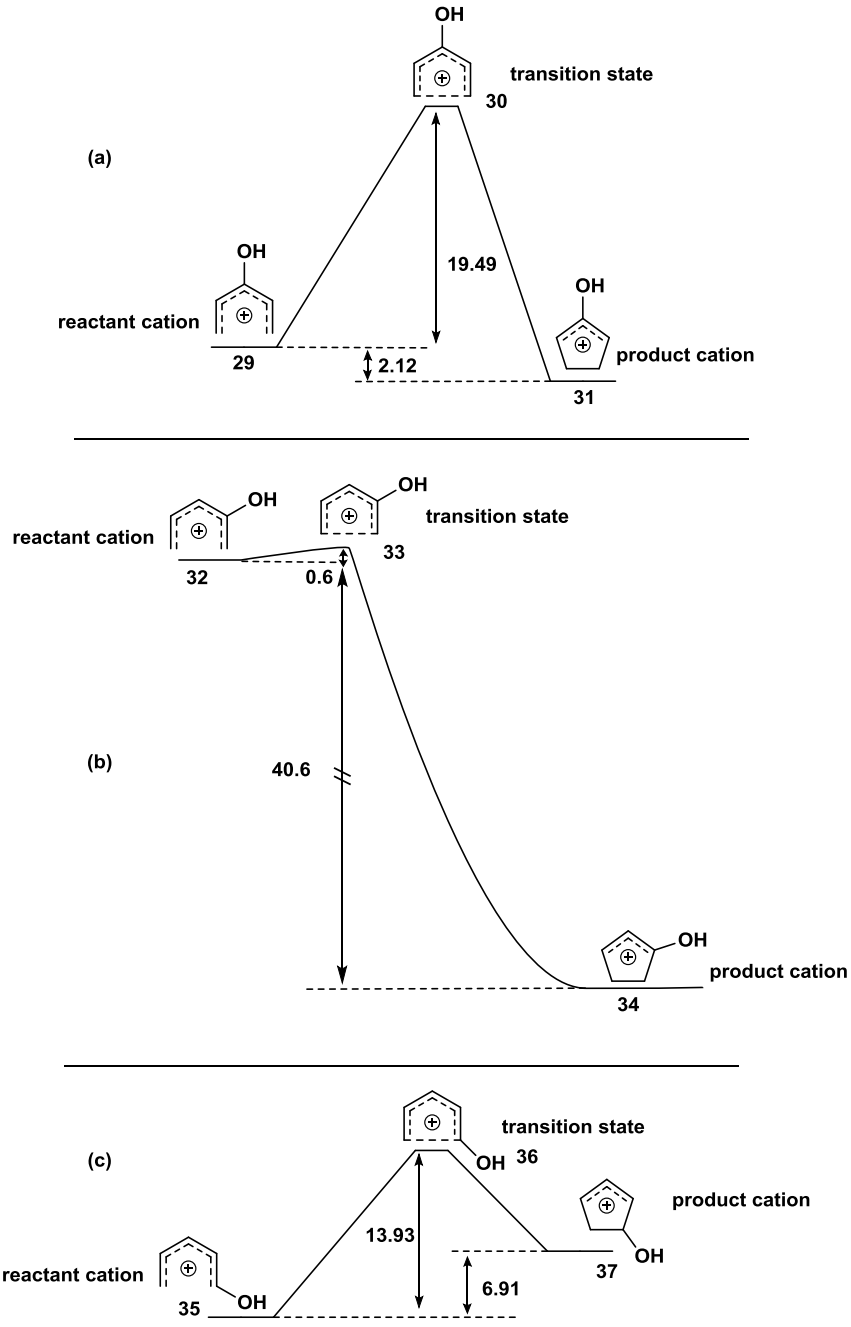


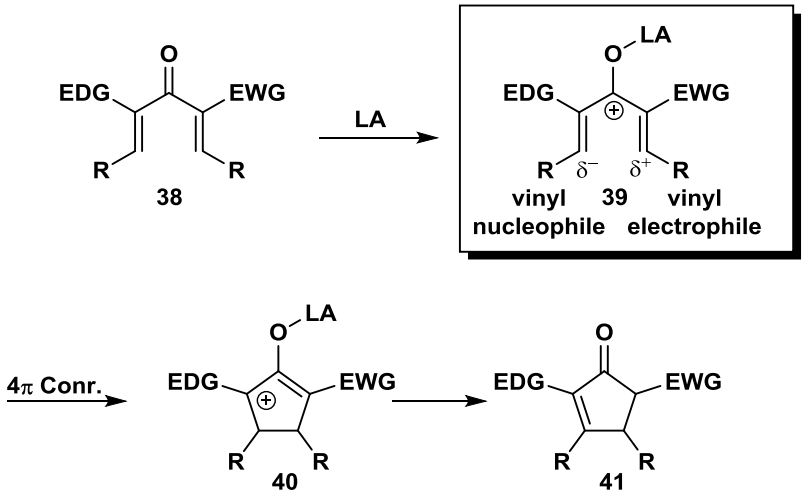
Figure 6. Reaction barriers for cyclization of hydroxy substituted pentadienyl cations. Calculated at the B3LYP/6-311G* level.

From this study, it is clear that the pentadienyl cation generated under typical Nazarov cyclization must pass through the highest energy activation barrier of the 3 possible hydroxy

pentadienyl cations which explains why this is the rate determining step for the classic Nazarov cyclization. The high barrier for cyclization of divinyl ketones can be appreciated by looking at the conditions for early Nazarov reactions that require high temperatures as well as stoichiometric amounts of strong Brønsted or Lewis acids.[5]

It is possible to lower the reaction barrier by strategically placing electron donating (EDG) or withdrawing (EWG) groups around the divinyl ketone **38** (Scheme 2).[7] Polarization of the π system can lead to the buildup of complimentary partial positive and negative charges at the terminal carbons of the divinyl ketone **39** which enhances the reactivity of the system and lowers the activation barrier for the electrocyclization. This results in an increase in reaction rate and allows for the use of milder reaction conditions.

Scheme 2. Polarized Nazarov cyclization.



The de Lera group has calculated the reaction energy profiles for various conformations of 1,4-dihydroxy pentadienyl cations **42** that behave as polarized Nazarov substrates (Figure 7).[6e] Resonance structure **47** illustrates the complimentary positive and negative charges at the termini of the dienone. The barrier for electrocyclization is only 5.95 kcal mol^{-1} and the reaction is exothermic forming products **44** 8.84 kcal mol^{-1} lower in energy than the reactant

cation. This is due to additional carbocation stabilization provided by the conjugated hydroxyl group at the 4 position.

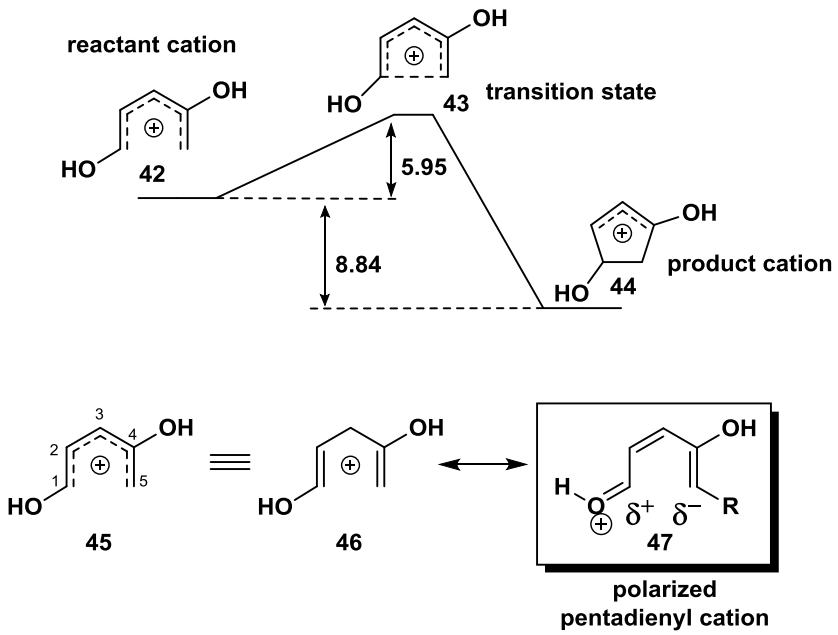


Figure 7. 1,4-Dihydroxy pentadienyl cation energy barrier profile.

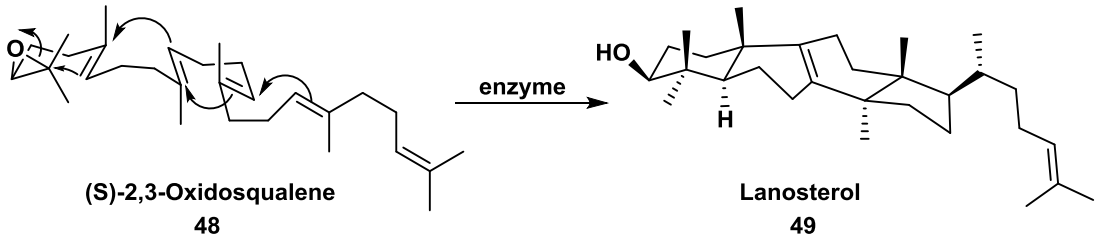
These calculations reveal how polarization of pentadienyl cations can have a favorable effect on the energy barriers for electrocyclization of pentadienyl cations.

1.1.3 Domino Reactions

When a line of domino stones are placed on end in a line, pushing the first stone starts a chain reaction where each falling stone tips the stone next to it in the line. The initial push results in a change of state for all the stones (tipped over) that are initiated by the single event of tipping over the first stone. As the name implies, in chemistry, domino reactions (also called cascade reactions), are a class of intramolecular reactions that result in the formation of two or more bonds, whereby the formation of the first bond *generates new functionalities* that are utilized to form the subsequent bonds.[8] Thus, domino reactions are a

time-resolved process because the bonds are formed sequentially one after another only after the formation of new reactive functionalities that are generated after the previous bond has formed. This definition excludes transformations where multiple bonds are formed by reacting through independent functional groups. A number of books and reviews have been published on this subject.[8] Domino reactions aren't a human invention. One prominent example in nature is sesquiterpene cationic cascade reactions. These enzyme mediated reactions are believed to be used to form all natural steroids (Scheme 3).[9]

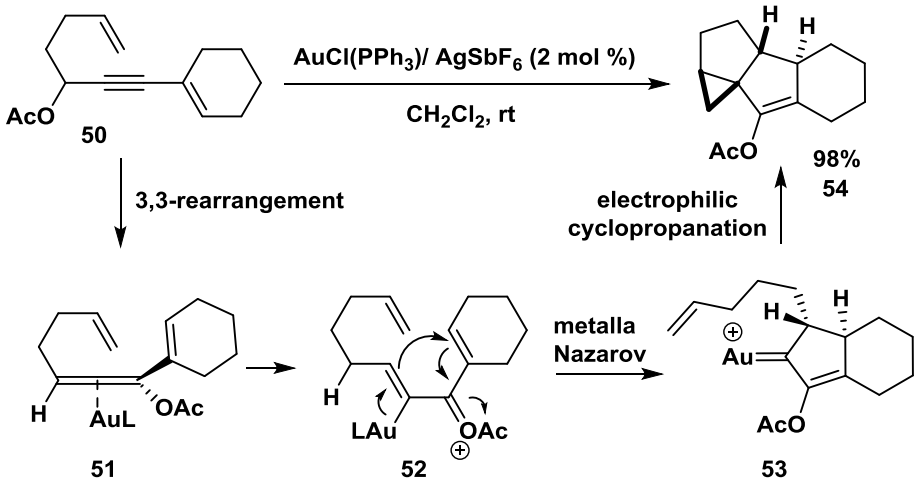
Scheme 3. Domino reaction for the biosynthesis of Lanosterol.



Domino reactions are important in organic synthesis since they offer a number of distinct advantages over a stepwise approach. Stepwise approaches typically require workup and isolation of each intermediate prior to the next bond forming reaction, while domino reactions might form all the desired bonds in one transformation sidestepping possibly lengthy isolation and purification steps. Starting from acyclic substrates, a domino reaction is capable of forming multiple ring systems in one step, often with a high degree of stereochemical control. Due to the intramolecular nature of the reactions, they exhibit high atom economy and are often fast and high yielding. One example that exemplifies these distinct advantages is a domino reaction developed by Malacria *et al* (Scheme 4).[10] The cascade is initiated with a Au(I)-catalyzed 3,3-rearrangement of the enynyl acetate **50** followed by a Nazarov cyclization, and terminates with a gold carbene mediated

cyclopropanation reaction. The product **54** contains four new stereocenters and is obtained as a single diastereomer in excellent yield.

Scheme 4. Domino rearrangement that constructs three new rings and four stereocenters.



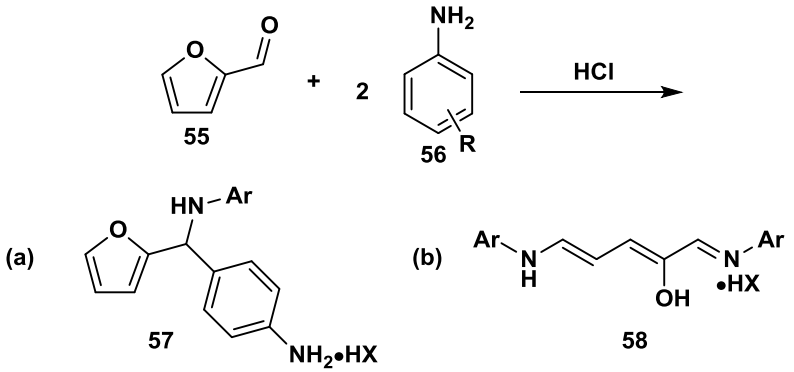
1.1.4 The Reactivity of Furan

Furan exists in the class of five membered aromatic heterocycles that also includes pyrrole and thiophene. Furan is a weakly aromatic compound that exhibits ~16 kcal mol^{-1} of aromatic resonance stabilization, which is significantly less than benzene at ~36 kcal mol^{-1}.[11] Furan is also less aromatic than the other common five membered aromatic heterocycles pyrrole (~22 kcal mol^{-1}) and thiophene (~30 kcal mol^{-1}). Because of its low resonance stabilization energy, furan has seen use as a valuable synthon in synthetic organic chemistry, especially in reactions that proceed through dearomatization of furan. Being electron rich and weakly aromatic, furan can be seen as a molecule containing a number of distinct synthons. Furan can act as a nucleophile, electrophile, participate as an electron rich diene in cycloaddition reactions, be hydrolyzed to 1,4-dicarbonyl compounds and may also participate in oxyallyl cation cycloaddition reactions.[12]

1.1.5 Stenhouse Salts

Electrophilic furan compounds have been known and studied for over 100 years. Stenhouse was the first to show that the reaction of two molecules of a primary aromatic amine **56** with one molecule of furfuraldehyde **55** in the presence of hydrochloric acid yielded purple crystalline salts (Scheme 5).[13] In the following years, a number of Stenhouse salts were prepared by Schiff,[14] Zincke and Mühlhausen,[15] and Borsche, Leditschke and Lange.[16] The structure of the highly colored salts was unknown and debated at the time. Schiff proposed that the Stenhouse salts possessed a triphenylmethane type structure **57**,[14c] while Zincke and Mühlhausen preferred the open chain representation **58**.[15]

Scheme 5. Structures of Stenhouse salts proposed by (a) Schiff and (b) Zincke and Mühlhausen.



1.1.6 Diamino Cyclopentenones from Stenhouse Salts

Foley and co-workers studied the mechanism and were the first to explicitly state that the structure must represent a system with a planar all *trans* configuration stabilized by resonance (Figure 8).[17] Their proposal was in agreement with the linear structure postulated by Zincke and Mühlhausen. [15]

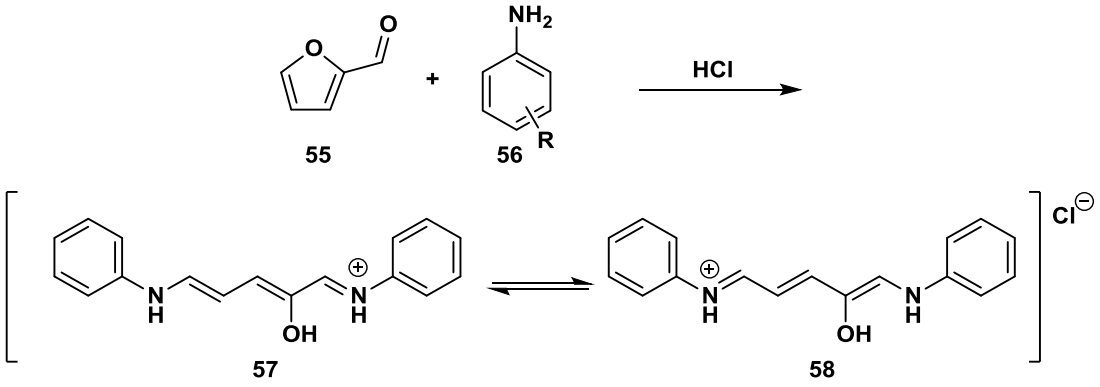


Figure 8. Structure of resonance stabilized Stenhouse salts proposed by Foley.

Stenhouse was not able to isolate the free base of the purple salts.[13b] Other groups had also tried unsuccessfully to obtain or identify the free base Stenhouse compounds until McGowan finally isolated a cream colored solid that he identified as having the atomic formula of $C_{17}H_{16}N_2O$.[18] Based primarily on UV data, McGowan proposed the following cyclic structures for this compound (Figure 9).

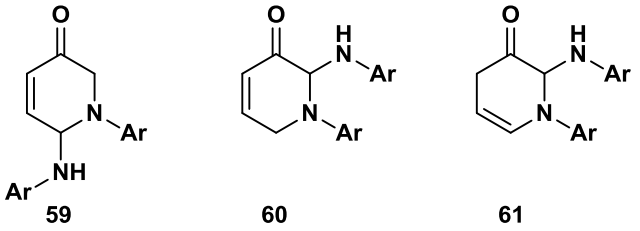
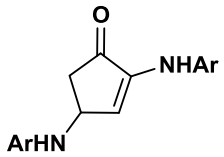


Figure 9. Structures proposed by McGowan of the free base Stenhouse compounds.

Using ^{1}H NMR, Lewis and Mulquiney definitively confirmed the structure of compounds isolated from either base treatment of a Stenhouse salt or from the nominally neutral heating of furfuraldehyde with aniline in alcohol to be the carbocyclic diamino cyclopentenone **62** (Figure 10).

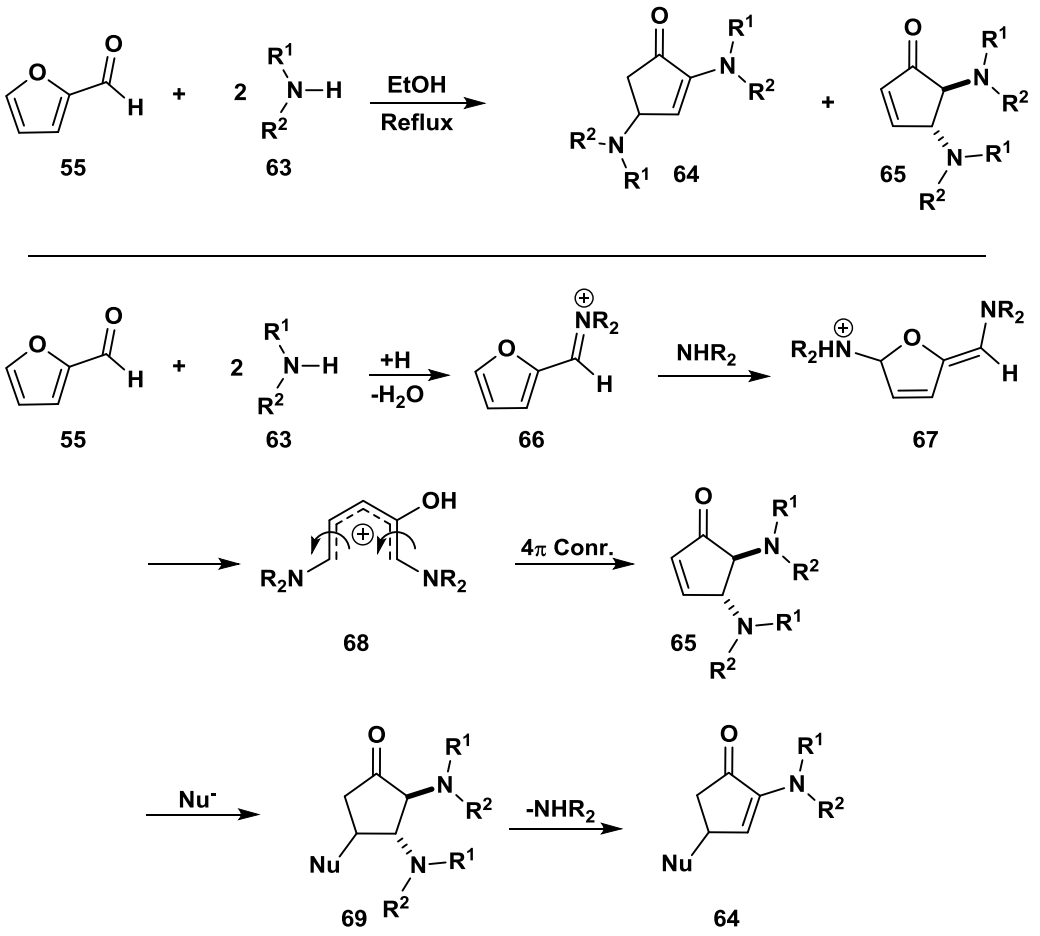


62

Figure 10. Carbocyclic cyclopentenone structure proposed by Lewis and Mulquiney.

Confirmation of the structure lead to a resurgence of interest in the reactivity of Stenhouse salts. Mulquiney conducted an extensive study on the reactivity of 2-furaldehyde with over 30 amines.[19] This survey showed that depending on the amine used, two isomeric compounds could be isolated, 2,4-diamino cyclopentenone **64** and the *trans*-4,5-diamino cyclopentenone **65** (Scheme 6).[20,19c] Secondary amines always gave *trans*-4,5-diamino cyclopentenones **65**. They found that prolonged heating in ethanol favored product **64**, which is believed to the more thermodynamically stable isomer. The mechanism is proposed to occur as follows. Condensation of the amine **63** onto the aldehyde **55** forms the charged ammonium compound **66** that activates furan to nucleophilic attack by another equivalent of amine. Ring opening of the furan and bond rotation form the cyclopentadienyl cation **68**, which, with 4π electrons undergoes a thermal conrotatory 4π electrocyclization affording **65**. Subsequent 1,4-Michael addition by an external nucleophile is followed by β-amine elimination to regenerate the enone and form the more thermodynamically stable cyclopentenone **64**. Attempts to convert 4,5-diamino cyclopentenones **65** to the 2,4-derivates **64** using acid were unsuccessful and were converted quantitatively to the Stenhouse salt.

Scheme 6. Conditions and mechanism postulated by Lewis and Mulquiney.

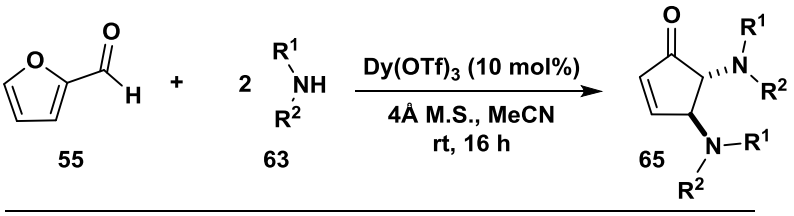


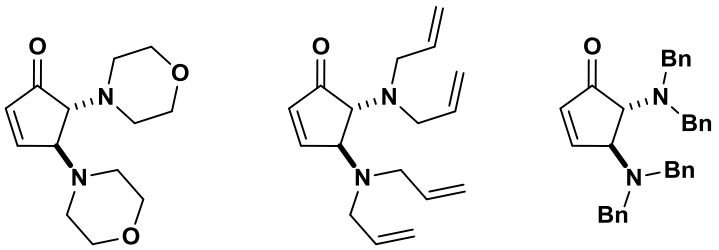
In 2007, Batey and co-workers recognized the need to improve upon the conditions that had been developed for the conversion of furfuraldehyde to diamino cyclopentenones. Conditions traditionally employed often were either too harsh or required long reaction times. In addition, reactions employing primary amines always resulted in low yields of cyclopentenone products. Batey noted that the reaction is believed to be acid catalyzed but that there were no reported examples of Lewis acids being used.

Batey and co-workers screened a variety of Lewis acids in EtOH with limited success, but discovered that when using morpholine as the amine and employing the rare earth Lewis acids dysprosium(III) trifluoromethanesulfonate ($Dy(OTf)_3$) or scandium(III)

trifluoromethanesulfonate ($Sc(OTf)_3$) in acetonitrile (MeCN) that they could prepare *trans*-4,5-diamino cyclopent-2-en-1-ones **65** in quantitative yield after 16 hrs at room temperature (Table 1).[21] Because of the lower cost, they chose to develop the reaction using $Dy(OTf)_3$. Secondary aliphatic amines and anilines gave the desired cyclopentenones in high yields (**70**-**74**). Notably, primary anilines gave the desired *trans*-diamino cyclopentenones, which had never been observed under Brønsted acid catalyzed conditions. Using primary anilines, higher yields were obtained when using $Sc(OTf)_3$. Unfortunately, primary aliphatic amines failed to react under the reaction conditions (**75**).

Table 1. Substrate scope for the Lewis acid catalyzed rearrangement of furfuraldehyde to *trans*-4,5-diamino cyclopentenones.

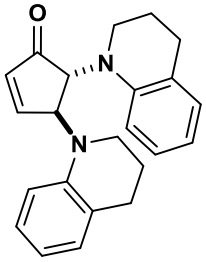




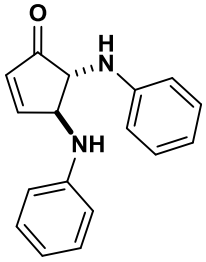
70
quantitative yield

71
82%

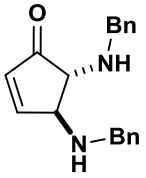
72
98%



73
quantitative yield



74
78%[a]



75
0%

[a] isolated yield using $Sc(OTf)_3$

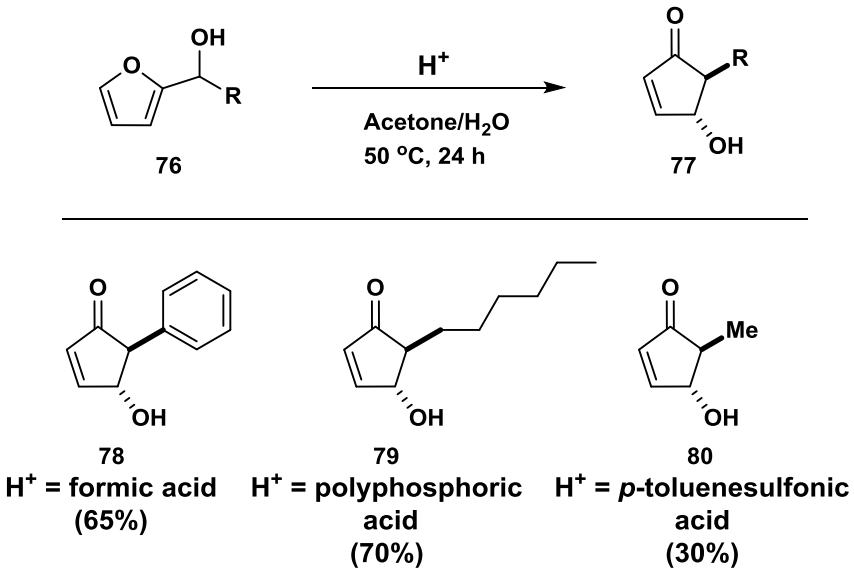
This work is important because it is the first mild and highly effective method for the formation of *trans*-4,5-diamino cyclopent-2-en-1-ones from furfural that is not prone to further rearrangement to the more thermodynamically stable 2,4-diamino cyclopentenone. Lastly, primary anilines have never been observed to produce the *trans*-4,5 diamino product under Brønsted acid catalyzed conditions. Batey and co-workers have recently applied this methodology towards the total synthesis of the alkaloid natural product (±)-agelastatin A.[22]

1.1.7 The Piancatelli Rearrangement

The utility of electrophilic furan derivatives was a hot topic in the middle of the 20th century with Schiff, Zincke, McGowen, Lewis, Mulquiney and many others studying the properties of Stenhouse salts, as well as a number of other researchers studying other reactions involving electrophilic furan compounds.[23]

In 1976 Piancatelli and co-workers published the first in a series of papers describing the acid catalyzed rearrangement of 2-furylcarbinols **76** to *trans*-4-hydroxycyclopentenones **77**.[24] This is a particularly attractive transformation because 2-furylcarbinols **76** can be obtained from furfuraldehyde in one step using a Grignard addition. Thus, in two steps from readily available starting materials, functionally useful 3-dimensional compounds can be produced from planar and renewable starting material. The reaction is highly stereospecific, giving products exclusively with a *trans* configuration. The seminal reaction conditions utilized various Brønsted acids in a water/acetone mixture at 50 ^{o}C for 24 h. The yields range from poor to moderate (30–70%) for the few substrates examined in their initial publication (Table 2). In general, alkyl substituted 2-furylcarbinols are more stable and less reactive than aryl substituted substrates.[25] An insightful review of the Piancatelli rearrangement has been published.[26]

Table 2. Conditions for the first Piancatelli rearrangement.



The reaction mechanism believed to be similar to that of the rearrangement of furfuraldehyde to diamino cyclopentenones as described by Batey.[21] Acid activation of 2-furylcarbinol **76** leads to loss of water with subsequent formation of oxocarbenium **81**, which is attacked by another molecule of water to form the hemiacetal **82**. After addition by water, proton transfer from water to the furan oxygen promotes ring opening of furan **83**. After ring opening, bond rotation allows the system to adopt the cyclic pentadienyl cation structure **84** which is poised to undergo a thermal 4π conrotatory electrocyclization. β Elimination with loss of a proton produces the final *trans*-4-hydroxycyclopentenone **77**. Mechanistic studies performed by D'Auria have revealed that stereochemical information is not transferred from the 2-furylcarbinol to the cyclopentenone product.[25] When (R)-2-furylphenylcarbinol was subjected to the reaction conditions, a racemic mixture of *trans*-4-hydroxycyclopentenone was recovered.

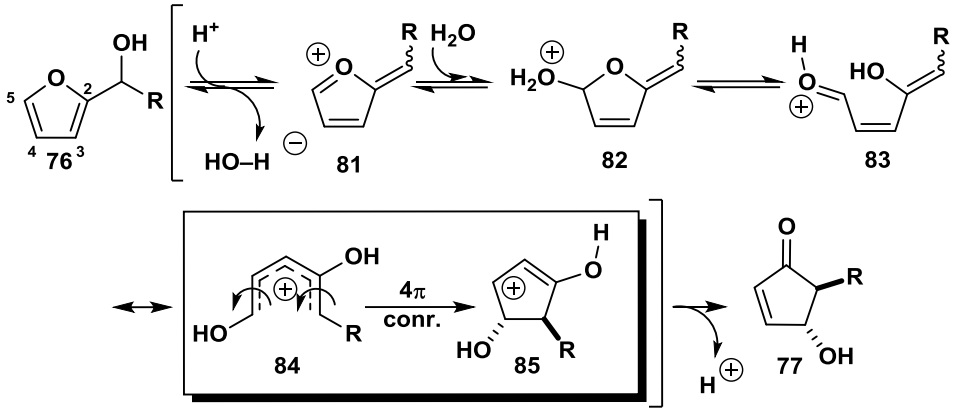
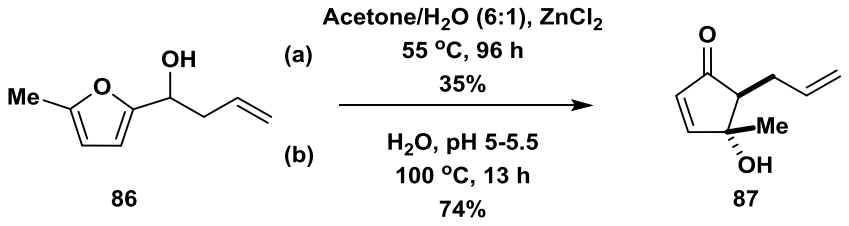


Figure 11. Proposed mechanism for the Piancatelli rearrangement.

This was an important advancement at the time because these substrates are valuable precursors to synthetic prostaglandin analogs.[27] Prior to this publication, 4-hydroxy cyclopentenones were only available by way of complex multi-step syntheses.[28]

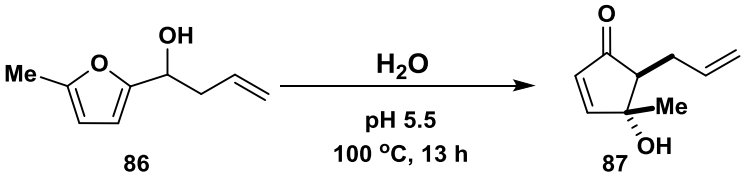
The rearrangement is most commonly performed in water in addition to another co-solvent (such as acetone, dioxane or dimethoxyethane), presumably to increase solubility of the 2-furylcarbinol substrates. Substrates bearing a methyl group in the 5 position failed to give the desired products and only produced unidentifiable side products. The usage of a mild Lewis acid, $ZnCl_2$ helped overcome this limitation.[29] However, in later publications it was discovered that using a carefully pH adjusted reaction medium, that the rearrangement of 5-methyl furylcarbinols can be more efficient using typical Brønsted acids. Furylcarbinol **86** gives only 35% yield of **87** after 96 h at 55 ^{o}C using $ZnCl_2$. In water buffered to pH 5-5.5, the reaction is complete in 13 h at 100 ^{o}C, and gives the desired product **87** in 74% yield (Scheme 7).[26] In general, the pH of the reaction mixture was found to be an important factor that influences both the rate and yield of the rearrangement.

Scheme 7. Comparison of (a) Lewis acid activation and (b) pH buffered solutions for challenging substrates.



Another important factor for obtaining good yields and rates is the concentration of the reaction mixture. In general, dilute conditions with 30:1 ratio of solvent to 2-furylcarbinol was determined a good compromise between solvent volume and high reaction rate and yield.[26] Table 3 shows the effect of concentration on the reaction rate and yield.

Table 3. Solvent concentration effects on the rearrangement.

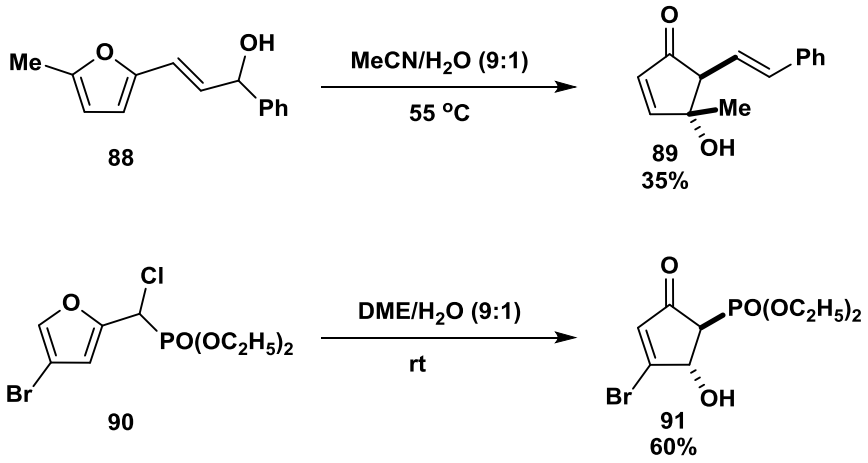


ratio H_2O/ substrate	time (h)	yield (%)
10:1	32	56
20:1	22	63
40:1	14	65
80:1	12	67

Piancatelli and co-workers have investigated alternative activating groups for the rearrangement. Conjugated furylidenecarbinol **88** is exceptionally reactive and gives cyclopentenones **89** under solvolytic conditions in the absence of acid.[30] When the hydroxyl group was replaced with the more efficient chlorine leaving group **90**, the reaction gives the

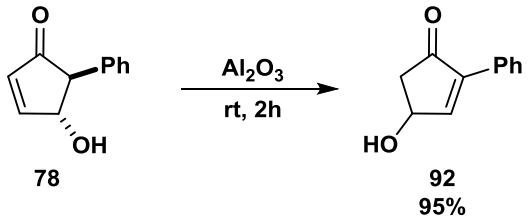
expected cyclopentenone **91** at room temperature and in good yield in the absence of acid (Scheme 8).[31]

Scheme 8. Alternative activating groups for the Piancatelli rearrangement.



Interestingly, the *trans*-4-hydroxycyclopentenone products **78** can be further rearranged into 2-substituted 4-hydroxycyclopentenones **92** under basic conditions (Scheme 9). The most effective way to facilitate this isomerization is simply by absorbing the material onto basic or neutral alumina.[32] The isomerization can also be achieved in a one pot process by first inducing the acid-catalyzed rearrangement to the *trans*-4-hydroxycyclopentenone then adjusting the pH to 7.9 and continuing to reflux for 2 hrs.[33]

Scheme 9. Isomerization of 4-hydroxycyclopentenones by absorption on basic alumina.

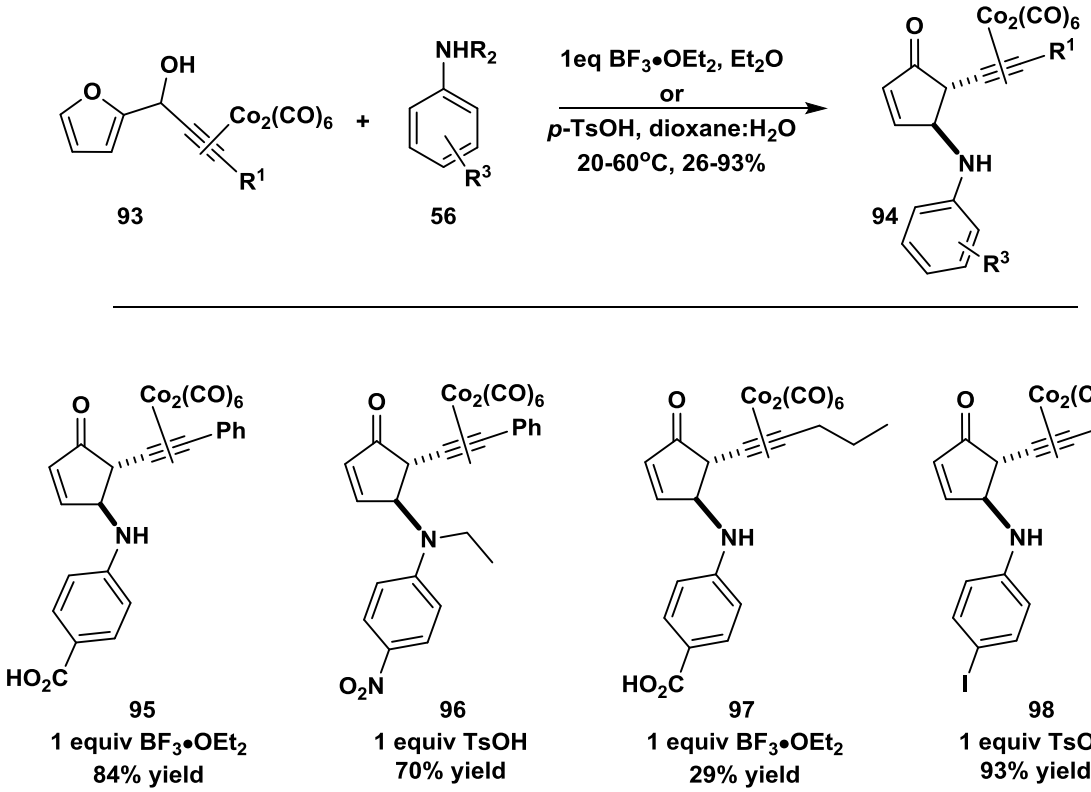


1.2 An aza-Piancatelli Rearrangement

1.2.1 Background

The Piancatelli rearrangement is an exceptionally concise method for the construction of complex and synthetically useful *trans*-4-hydroxy cyclopentenones.[26] Starting from furfuraldehyde, which is produced from biological feedstocks, in two steps an abundant 2-dimensional molecule can be converted to a stereochemically defined 3-dimensional compound containing a large number of reactive functionalities. Since the initial report on this transformation in 1976, Piancatelli and others have studied the reaction in depth using water as the external nucleophile for trapping the *in situ* generated oxocarbenium intermediate.[24,26] However, nucleophiles other than water have largely been unexplored. There has only been one previous example demonstrating the rearrangement of 2-furylcarbinols using a nucleophile other than water prior to our work. In 1993, Denisov reported the first aza-Piancatelli rearrangement.[34] This report showed that aniline nucleophiles react with activated 2-furylalkynylcarbinols **93**, to form *trans*-4-aminocyclopentenones **94** in good yield (Table 4). This report, while significant, had a very limited scope. Only alkynyl furylcarbinols that were activated with the hexacarbonyl dicobalt complex $Co_2(CO)_6$ were generally reactive, and the reaction also required stoichiometric amounts of Brønsted or Lewis acid. In addition, only three different alkynyl furylcarbinols and 3 *para*-substituted electron deficient anilines were examined.

Table 4. Substrate scope of the first reported aza-Piancatelli rearrangement.



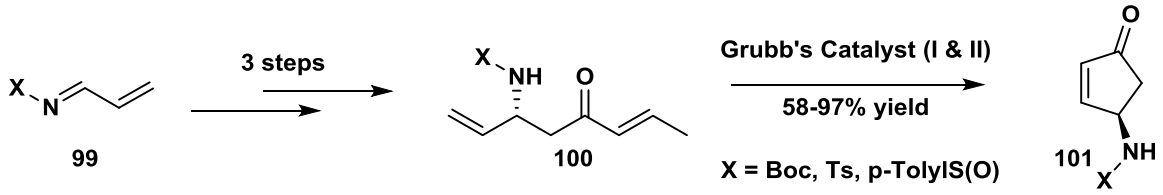
1.2.2 Significance

It is well known that 4-hydroxy-cyclopentenones are valuable biologically active scaffolds due to their ubiquity in prostaglandin natural product scaffolds.[35] However, there have been only a few investigations into the biological activity of the 4-aminocyclopent-2-en-1-one scaffold. Some authors have noted that this might be due to the lack of ways to prepare these substrates.[36] Nevertheless, amino prostaglandin analogs have been synthesized that are highly cytotoxic against L1210 leukemia cells,[37] and have promising antiviral properties due to their ability to induce the cytoprotective heat shock response.[38]

A scan through the literature revealed that that there are very few reported ways to directly access the 4-aminocyclopent-2-en-1-one scaffold. Ring closing metathesis allows

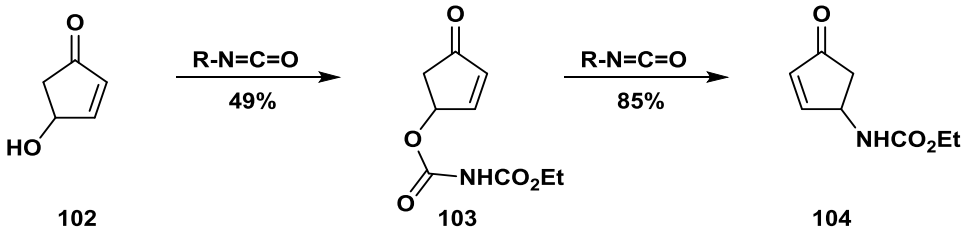
for direct access the cyclopentenone without additional oxidation steps and has been a successful strategy for forming 4-aminocyclopentenones from acyclic starting materials.[37,39] Davis used this strategy to construct 4-aminocyclopentenone **101**, however the process is lengthy, requiring four steps from the protected imine **99** (Scheme 10).[40]

Scheme 10. Ring closing metathesis for forming 4-aminocyclopentenones.



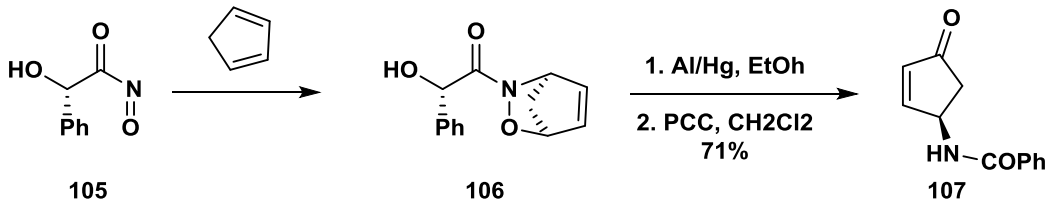
Harris reported a two step method for access to 4-aminocyclopentenones **104** starting from Piancatelli-type 4-hydroxycyclopentenones **102** in moderate yields (Scheme 11).[41]

Scheme 11. Two step rearrangement of 4-hydroxycyclopentenones.



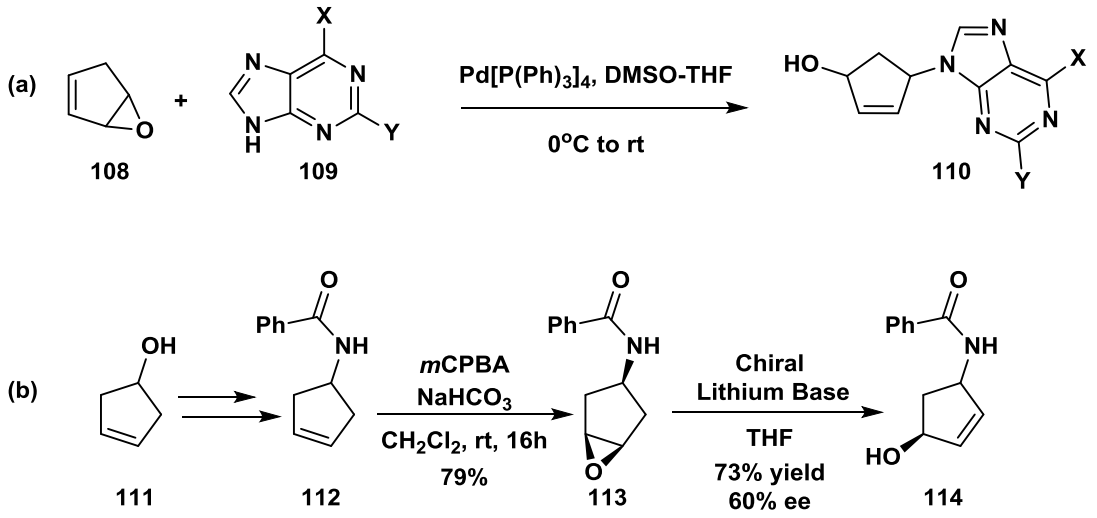
Procter utilized cyclopentadiene as the dienophile in a Diels–Alder reaction with the acyl nitroso compound **105** to form oxazine **106** (Scheme 12).[42] N–O Bond cleavage followed by oxidation of the hydroxyl group afforded the 4-amino cyclopentenone **107**.

Scheme 12. Acyl nitroso Diels–Alder approach to 4-aminocyclopentenones.



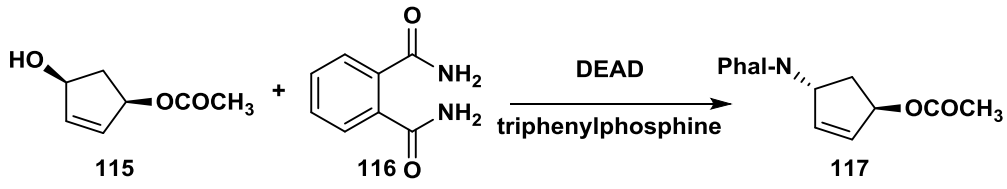
Other approaches include ring opening of epoxy cyclopentenes **108** (a),[43] or rearrangements of 4-amino substituted cyclopentene oxides **113** (b)[44] (Scheme 13). From these substrates, an additional oxidation step is necessary to form a 4-hydroxy cyclopentenone.

Scheme 13. Epoxides for synthesis of 1-hydroxy 4-aminocyclopent-2-enes.



Finally, Mitsunobu substitution reactions can be used for the displacement of either mono- or bis-protected 1,4-dihydroxycyclopent-2-enes **115** by an amino or azido function to form 1-hydroxy 4-aminocyclopent-2-enes **117** (Scheme 14).[45]

Scheme 14. Formation of 1-hydroxy 4-aminocyclopent-2-enes.



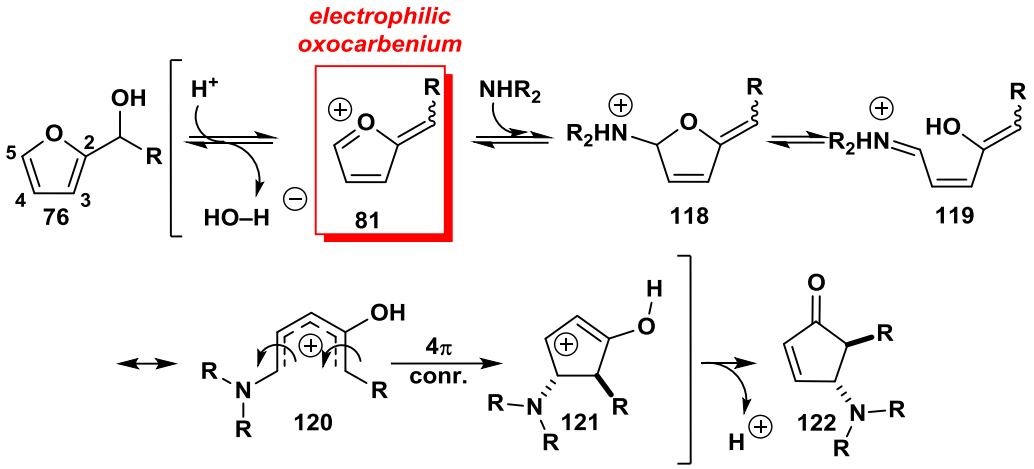
Indeed, there are a number of approaches that can be considered for the formation of 4-aminocyclopentenones. However, these strategies often require a large number of synthetic steps, and typically lack substitution around the cyclopentane ring, particularly at the 5

position α to the carbonyl. There is a need for a concise and robust synthesis of this important structural motif.

1.2.3 Objectives

After activation and loss of water from 2-furylcarbinol **76**, the Piancatelli reaction generates a reactive oxocarbenium cation intermediate **81** (Scheme 15). However, to date, very little work has been done exploring the usage of alternative nucleophiles, such as amines, for trapping the electrophilic oxocarbenium intermediate, which would result in the formation of a new class of 4-amino substituted cyclopentenones **122** as illustrated in Scheme 15.

Scheme 15. Proposed mechanism for an aza-Piancatelli rearrangement.



We envisioned that if we could develop a set of mild and general conditions for an aza-Piancatelli rearrangement that this platform would allow for the rapid construction of a large array of substituted 4-aminocyclopentenones (**124-129)** that would be valuable as synthetic building blocks (Figure 12). This objective was made more enticing due to the fact that the starting furylcarbinols can be made in as little as one step from furaldehyde, which is an extremely abundant and inexpensive starting material. Molecular complexity around the

cyclopentenone could be generated with ease since substituents around the furan ring would be directly incorporated into the 4-amino cyclopentenone. This is an important difference with regards to the other reported methods that form this motif since they all typically lack substituents around the cyclopentenone ring due to the nature of the starting materials.

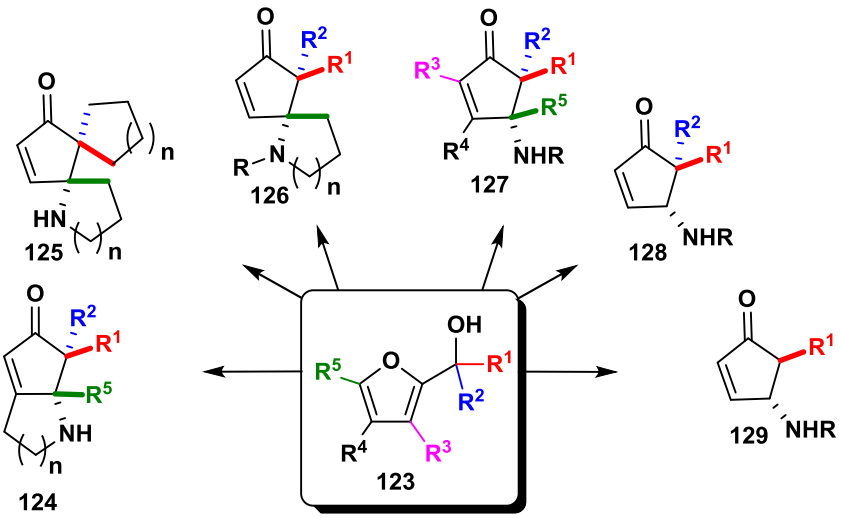


Figure 12. Possible 4-aminocyclopentenones from an aza-Piancatelli rearrangement.

1.2.4 Hypothesis

Although limited to a specially activated 2-furylalkynylcarbinols, Denisov showed that amines can indeed act as a competent nucleophile and react with an oxocarbenium cation. One limitation that Denisov encountered was that only highly activated 2-furylalkynylcarbinols reacted under his conditions employing either stoichiometric TsOH or $BF_3{\cdot}OEt_2$ acid catalysts.[34] We speculated that this could be due to catalyst inhibition by the Lewis basic amine.

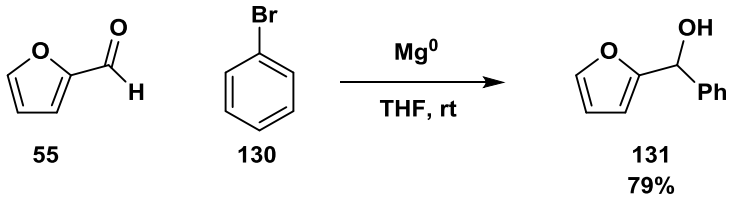
Inspired by Batey's work on the rearrangement of furfuraldehyde with $Dy(OTf)_3$,[21] we became interested in this class of Lewis acids. Rare earth lanthanide triflates having the general formula $Ln(OTf)_3$, have remarkable properties that set them apart from many

traditional Lewis acids.[46] They are inexpensive, stable to air and moisture and have low toxicity, which simplifies their usage since no special precautions need to be taken when handling them.[47] They readily form hydrates, but in our experience the hydrated species is as or more effective than the anhydrous compound (but can change some subtle characteristics of the Lewis acid). Lanthanide Lewis acids are regarded as more oxophilic than azaphilic and there are many examples that demonstrate that rare earth Lewis acid can be an effective catalyst even in the presence of Lewis basic amines.[48] Based on these promising properties, we sought to investigate their use for the aza-Piancatelli rearrangement.

1.2.5 Reaction Optimization

We began our investigation by building phenyl furylcarbinol **131** using a Grignard reaction between furfuraldehyde **55** and bromobenzene **130** (Scheme 16).[49]

Scheme 16. Grignard reaction for building furylcarbinols.



55 **130** **131** **79%**

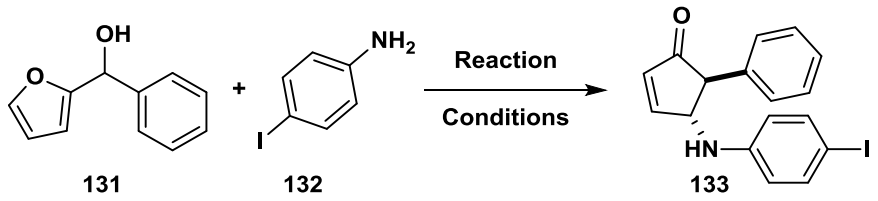
With phenyl furylcarbinol in hand, we decided that anilines would be a good class of nucleophile from which to initiate our investigations because they are known to be less Lewis basic and easier to handle than aliphatic amines. In addition, Denisov had success with electron deficient anilines in his early example of an aza-Piancatelli rearrangement.[34] Furthermore, we decided to first investigate $Sc(OTf)_3$ or $Dy(OTf)_3$ as potential Lewis acids due to Batey's success with these catalysts and for their known tolerance of Lewis basic amines.[21]

To our gratification, we discovered quickly that the reaction between 2-furylphenylcarbinol **131** and commercially available 4-iodoaniline **132** worked quite well under a variety of conditions (Table 5). We found that both $Sc(OTf)_3$ and $Dy(OTf)_3$ promoted the rearrangement at 40 ^oC in just a few hours giving high yields of the desired product (entries 1 and 2). Rare earth Lewis acids are known to be water tolerant, and no special precautions are necessary to exclude oxygen or water when setting up or running the reactions. Using $Sc(OTf)_3$ and running the reaction in 5 v/v% H_2O in MeCN at 40 ^oC produces the desired product in nearly quantitative yield, but with a much longer reaction time of 22 h (entry 3). Changing the solvent to toluene increased the reaction time, but still produced the desired product in 78% yield (entry 4).

In our experience all the rare earth triflates behave similarly as large +3 cationic Lewis acids, but also have their own nuanced differences. Using $Dy(OTf)_3$ and raising the temperature to 80 ^oC reduced the reaction time as expected, while also increasing the yield to 92% (entry 5). We investigated a variety of lanthanide triflate Lewis acids with higher catalyst loading (entries 6-8). The Lanthanum triflate is the least Lewis acidic lanthanide triflate in the series. When lanthanum triflate ($La(OTf)_3$) is employed in 20 mol % at 80 ^oC, the reaction is complete in 1.25 h in good yield (entry 6). However, both $Ce(OTf)_3$ and $Nd(OTf)_3$ (20 mol %) are complete in 5-10 minutes and also give good yields of the desired product (entries 7 and 8 respectively). From these experiments we have determined that most of the lanthanide triflate Lewis acids are capable of catalyzing the rearrangement reaction, but we decided to continue to use $Dy(OTf)_3$ as our optimal catalyst due to its low cost and high reaction performance.

It is known that Lewis acid triflates can release triflic acid (HOTf) during the course of a reaction, and that this can sometimes be the true active catalyst.[50] In order to probe this possibility, a number of control experiments were performed. When 5 mol % HOTf was, employed, the reaction was complete in 30 minutes but in only 62% yield (entry 9). When the same reaction was ran with 1 equivalent of K_2CO_3, the base was effective in neutralizing the acid and only starting materials were recovered (entry 10). When 5 mol % $Dy(OTf)_3$ and 1 equivalent of K_2CO_3 was used, the reaction was complete in 1 hr (compared to 30 min in absence of base), and still gave 93% yield (entry 11). The control experiments indicate that while it might be possible that triflic acid is being liberated, that the protic acid is not the sole source of catalytic activity and that the metal is still playing an essential role in catalyzing the reaction. In addition to this control experiment, kinetic data also indicate that the reaction is not catalyzed by adventitious triflic acid that might be released during the course of the reaction. From a collaboration with the Hein group at UC Merced, we have shown using real time *in situ* ReactIR analysis that reactions catalyzed by the Brønsted acid trifluoroacetic acid (TFA) are first order in substrate and first order in TFA, while reactions employing Lewis acidic $Dy(OTf)_3$ is zero order in substrate (the reaction rate is not dependent on substrate concentration) and first order in $Dy(OTf)_3$.[51] The rate order differences between Brønsted and Lewis acid catalysis indicates that Brønsted triflic acid that might be liberated from $Dy(OTf)_3$ is not actively catalyzing the rearrangement.

Table 5. Reaction optimization.



131 132 133

entry[a]	catalyst (mol %)	temp (°C)	time	yield (%)
1	$Dy(OTf)_3$ (5)	40	2 h	79
2	$Sc(OTf)_3$ (5)	40	3 h	83
3 [b]	$Sc(OTf)_3$ (5)	40	22 h	97
	5 v/v% H_2O			
4 [c]	$Sc(OTf)_3$ (5)	40	23 h	78
5	$Dy(OTf)_3$ (5)	80	0.5 h	92
6	$La(OTf)_3$ (20)	80	1.25 h	89
7	$Ce(OTf)_3$ (20)	80	5 min	85
8	$Nd(OTf)_3$ (20)	80	10 min	91
9	HOTf (5)	80	0.5 h	62
10 [d]	HOTf (5)	80	4 h	0
	K_2CO_3 (100)			
11	$Dy(OTf)_3$ (5)	80	1	93
	K_2CO_3 (100)			

[a] reactions preformed in reagent grade MeCN (0.1 M) open to air.
[b] Solvent was 5 v/v% H_2O in MeCN.
[c] Reaction ran in Toluene.
[d] Starting material recovered from the reaction.

Importantly, only *trans*-substituted products were obtained, which is in agreement with the proposed mechanism that terminates with a thermal 4π conrotatory electrocyclization.[52] X-Ray crystal structure analysis of **133** further confirmed the *trans* relationship in the cyclopentenone products (Figure 13).

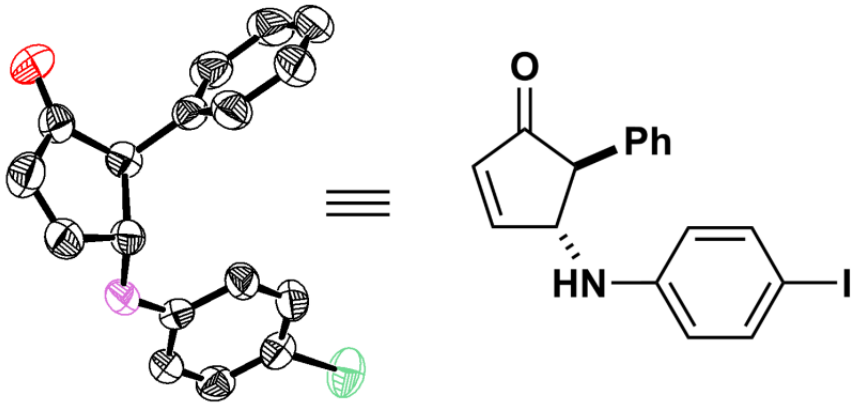


Figure 13. ORTEP drawing of *trans*-4-amino cyclopentenone 133 (left) shown with 50% thermal ellipsoids. Hydrogen atoms have been omitted for clarity. The crystal structure data can be obtained from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. CCDC # 769123

1.2.6 Substrate Scope

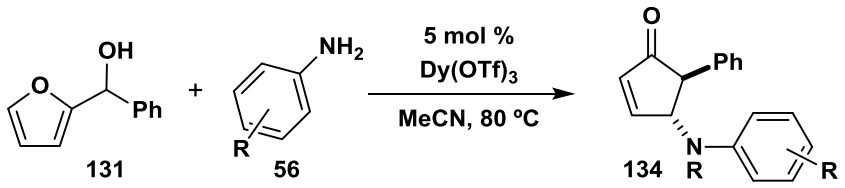
With optimized conditions in hand, (5 mol % $Dy(OTf)_3$, MeCN, 80 ^oC) we went on to probe the scope of the rearrangement with respect to the compatibility of aniline nucleophiles as well as with substituents on the furylcarbinol. We first started by examining the reaction of phenyl furylcarbinol **131** with a variety of aniline nucleophiles bearing *ortho, meta* and *para* substituents (Table 6). We found that the reaction was generally tolerant of a range of anilines from electron rich to electron poor with various substituents around the ring. Secondary acyclic anilines (**143-144**) and cyclic aniline **145** reacted to give good yields of the desired products (74%, 88%, and 67% respectively). Even sterically hindered 2,4,6-trimethylaniline **140** reacted to give the 4-aminocyclopentenone in high yield (91%).

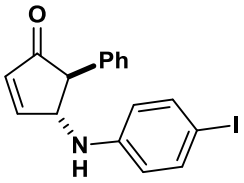
Reactions with electron deficient anilines are typically faster than those with electron rich anilines. In collaboration with the Hein group, our group has recently published a paper that sheds light on the rate differences between electron rich and electron deficient anilines.[51] Kinetics measurements using *in situ* FTIR spectrometry revealed that the rate determining step and product determining step are decoupled. These experiments revealed that coordination between the aniline and dysprosium catalyst form an inactive coordinatively saturated complex, and that the rate determining step is the dissociation aniline from this complex. Dissociation of aniline results in a free coordination site on the catalyst which allows for activation of the furylcarbinol. These findings also help to explain the rate differences observed between electron rich and electron deficient anilines. Electron rich anilines are known to be slower reacting under the reaction conditions, but in theory, should be more nucleophilic and reactive than electron deficient anilines. However, due to the stronger off-cycle binding between electron rich anilines and the Lewis acid, the equilibrium between a coordinately saturated complex and one with an open coordination site favors the coordinatively saturated complex, and results in longer reaction times when using electron rich anilines are employed. This can be clearly seen by comparing the rate of electron deficient aniline 135 (1 h) versus electron rich *p*-anisidine 136 (18 h).

In general, we found that anilines with *meta* or *para* substituents gave the highest yields. When 2,6-dimethylaniline was used, only 33% yield of the desired cyclopentenone 147 was obtained. This is due to a competitive Friedel–Crafts alkylation that occurs at the *para* position of the electron rich aniline and the furyl cation that is formed after activation and dehydration of the hydroxyl group. The remainder of the material isolated was a combination of the Friedel–Crafts adduct 149 (38%) as well as a product resulting from both

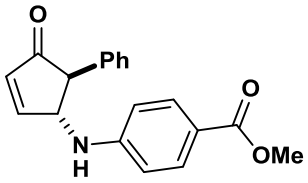
Friedel–Crafts alkylation and rearrangement 150 in 15% yield (Scheme 17).When the *para* position is blocked or more sterically hindered with *meta* substituents, this side reaction is suppressed. It is important to note that reactions that are sluggish, such as the reaction with 2,6-dimethylaniline **148**, we always observe some unidentifiable complex mixture of products in addition to Friedel–Crafts products. We believe these undesired side reactions could arise from the high reactivity of furylcarbinols, which are known to polymerize[53] and dimerize.[54]

Table 6. Scope of the rearrangement with aniline nucleophiles.

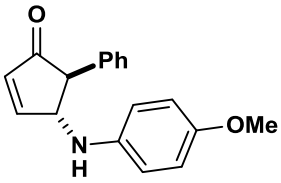




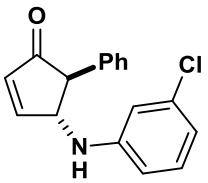
133 (0.5 h, 92%)



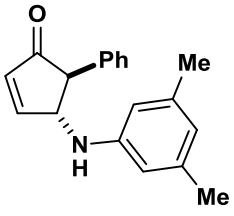
135 (1 h, 86%)



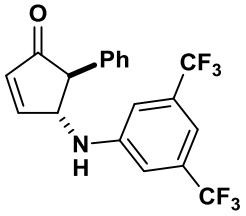
136[a] (18 h, 62%)



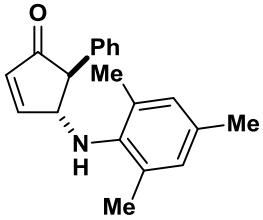
137 (20 min, 82%)



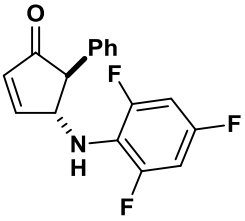
138 (3 h, 81%)



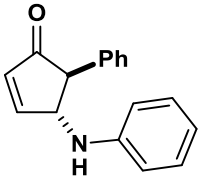
139 (24 h, 75%)



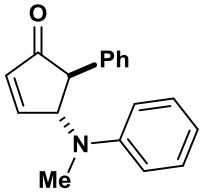
140 (4 h, 91%)



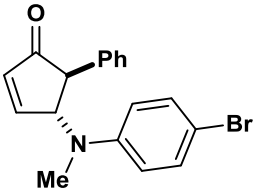
141[b] (3 h, 74%)



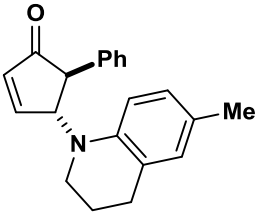
142 (1.5 h, 86%)



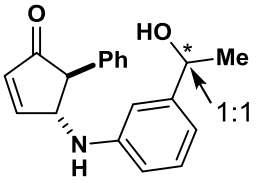
143 (2.5 h, 74%)



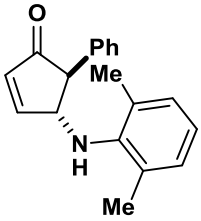
144 (45 min, 88%)



145 (18 h, 67%)



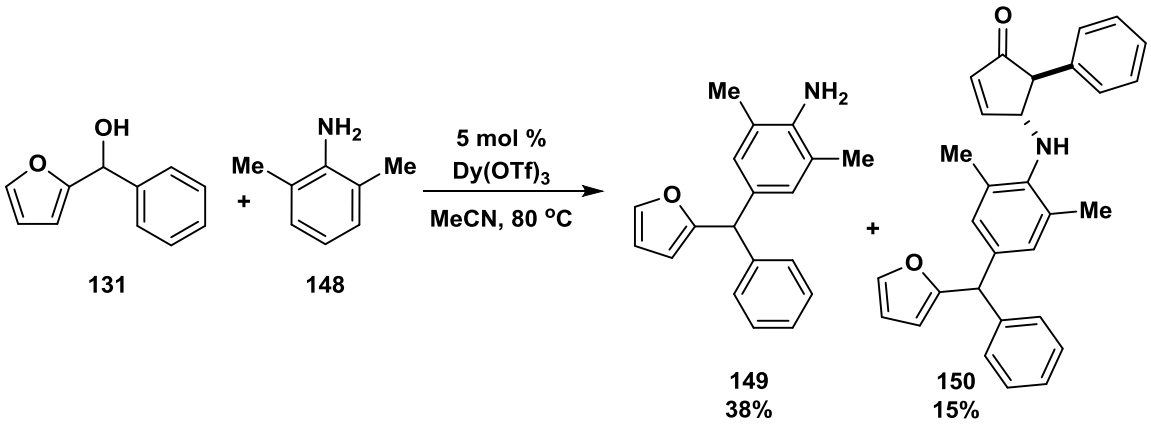
146[c] (2 h, 88%)



147 (3 h, 33%)

[a] 20 mol% $Dy(OTf)_3$
[b] 3 equiv of the corresponding aniline.
[c] Formed as a 1:1 ratio of diastereomers at the stereocenter marked with an *.
Yields reported are of the isolated products.

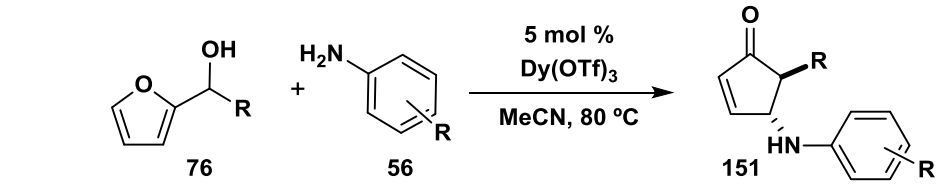
Scheme 17. Products resulting from Friedel–Crafts alkylation.

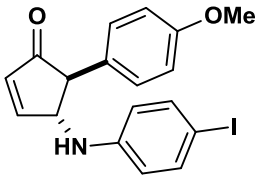
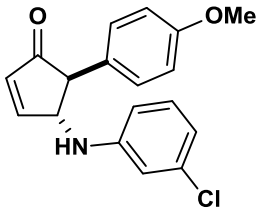
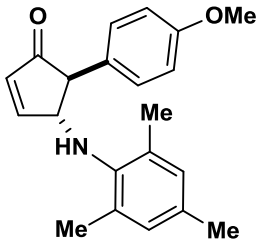
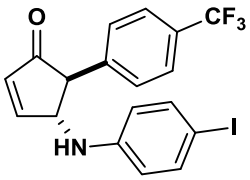
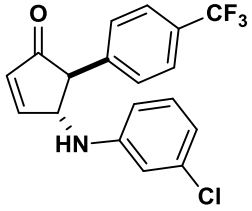
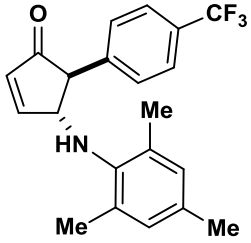
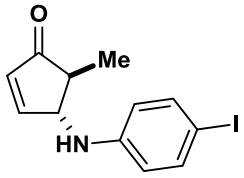
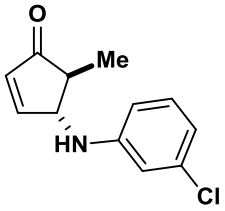
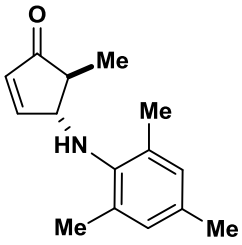
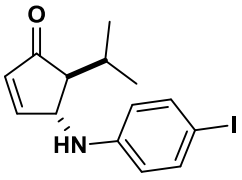
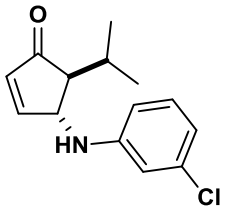
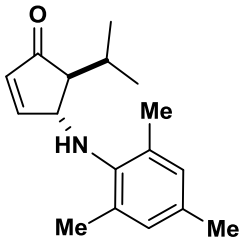


Next, we explored the effects of changing the substituents on the furylcarbinol (Table 7). Electron donating groups have an activating effect on the furylcarbinol by helping to stabilize the resultant carbocation, and allow for the reaction to be performed at room temperature in a reasonable amount of time (**152-154**). The yields are generally high when electron rich furylcarbinols are used.

Electron withdrawing groups have the opposite effect of deactivating the furylcarbinol through destabilization of the resultant carbocation, and the reactions had to once again be performed at 80 ^{o}C, but yields still remain high (**155-157**). Alkyl substituted furylcarbinols are not as easy to activate as their aryl counterparts. This phenomenon was also observed by Piancatelli and co-workers.[26] In general, high temperatures and long reaction times are required for alkyl substituted furylcarbinols, which also tend to give lower yields and leads to the formation of side products. Nevertheless, both methyl and isopropyl substituted furylcarbinols produce 4-aminocyclopentenones (**158-163**) with a variety of anilines in good yields. One notable exception was in the case of methyl furylcarbinol reacting with 3-chloroaniline. Only 10% of the desired cyclopentenone **159** was recovered with the majority of the material reacting through a Friedel–Crafts alkylation.

Table 7. Exploring the effect of substituents on the furylcarbinol.

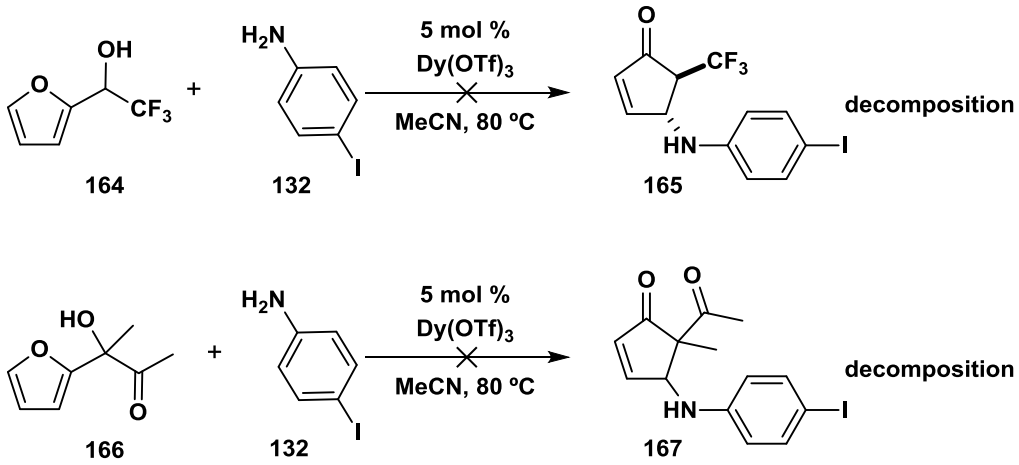


			
152[a] (1.5 h, 68%)	153[a] (6.5 h, 82%)	154[a] (5 h, 89%)	155 (4.5 h, 83%)
			
156 (2 h, 87%)	157[b] (8 h, 78%)	158 (2.5 h, 68%)	159 (3 h, 10%)
			
160 (3.5 h, 74%)	161 (5 h, 73%)	162 (6 h, 52%)	163 (24 h, 89%)

[a] Reaction conducted at rt. [b] 10 mol % $Dy(OTf)_3$ was used.

Electron deficient 2-furylcarbinols failed to rearrange and did not give the desired 4-aminocyclopentenones. Multiple attempts were made to rearrange trifluoromethyl furylcarbinol **164**, and the furyacyloin **166**, but all attempts resulted in decomposition of the starting material and recovery of the aniline (Scheme 18).

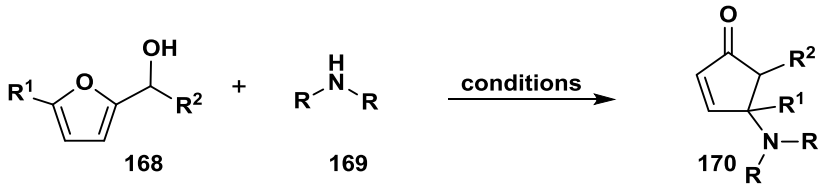
Scheme 18. Attempt to rearrange very electron deficient furylcarbinols.



1.2.7 Exploring Additional Substituents on Furan

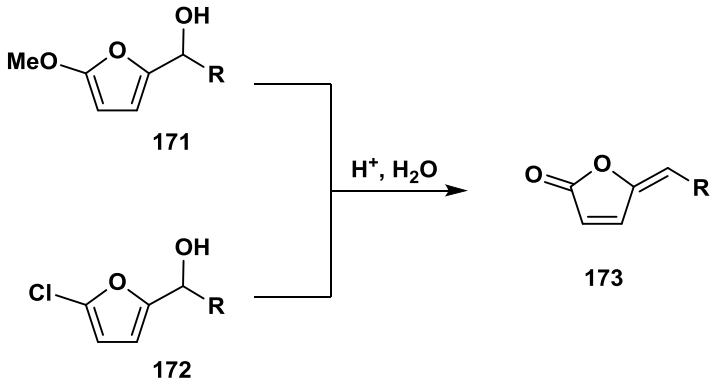
In the interest of building more complex cyclopentenones, we investigated adding substituents at the 5 position of the furan ring **168** that would be incorporated into the 4-aminocyclopentenone **170** (Scheme 19).

Scheme 19. Products arising from additional substituents on the furan ring.



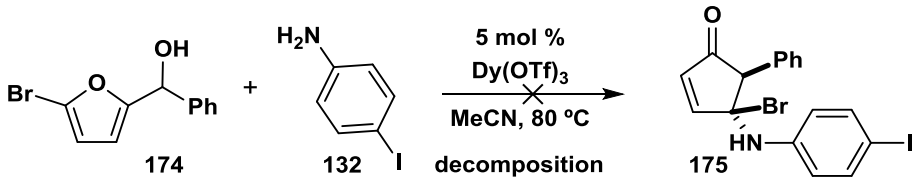
Piancatelli has shown that placing an electron withdrawing nitro group at the 5-position of furylcarbinols is deactivating, and render the furylcarbinol too stable to react even under forcing conditions.[55] In addition, labile groups such as halogens 172,[56] and activating electron donating groups such as methoxy groups 171 hydrolyze to form 4-ylidenebutenolides 173 under acid catalyzed conditions (Scheme 20).

Scheme 20. Formation of 4-ylidenebutenolides.



Using our newly optimized conditions, we attempted to rearrange 5-bromo-2-furylphenylcarbinol **174** in the presence of 4-iodoaniline **132** and 5 mol % $Dy(OTf)_3$ with the hope that the 'milder' conditions would avoid previously reported problems. Unfortunately, only decomposition of the starting material was observed (Scheme 21).

Scheme 21. Attempt to rearrange 5-bromo-2-furylphenylcarbinol.



Based on literature precedent, we expected that 5-substituted furylcarbinols **176** would prove to be more difficult due to the increased steric interaction that would be encountered at the 5 position when trying to intercept the reactive oxocarbenium cation (see Figure 14).

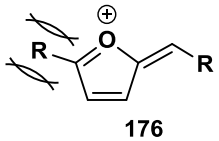
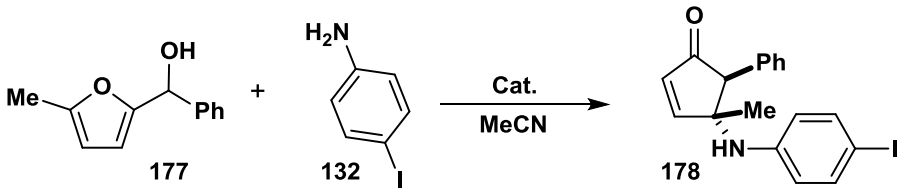


Figure 14. Steric blocking at the 5 position.

Encouraged by Piancatelli's success rearranging 5-methyl-2-furylcarbinols under both Brønsted and Lewis acid catalyzed conditions,[26] we elected to study these substrates using aniline nucleophiles. Our efforts are summarized in Table 8. Unfortunately, reactions employing either $Dy(OTf)_3$ or ytterbium triflate ($Yb(OTf)_3$) produced complex mixtures of products (entries 1-3). To evaluate if water was the potential problem, we added 3Å MS to the reaction flask, but this surprisingly shut down the reaction (entries 4 and 5). At this point we are not sure why 3Å MS are incompatible, but it is worth noting that other desiccants such as $MgSO_4$ are well tolerated. The less Lewis acidic dysprosium complex, dysprosium(III) tris(2,2,6,6-tetramethyl-3,5-heptanedionato) (TMHD) failed to react after 24 h at 80 ^oC (entry 6). Fortunately, $ZnBr_2$ produced the desired cyclopentenone **178** with a fully substituted stereocenter β to the carbonyl in 58% yield after 3 days at room temperature (entry 7). The relative stereochemistry was determined by Nuclear Overhauser effect spectroscopy (NOESY). Attempts to accelerate the reaction by heating the reaction to 80 ^oC with $ZnBr_2$ were not successful and gave a complex mixture of products (entry 8).

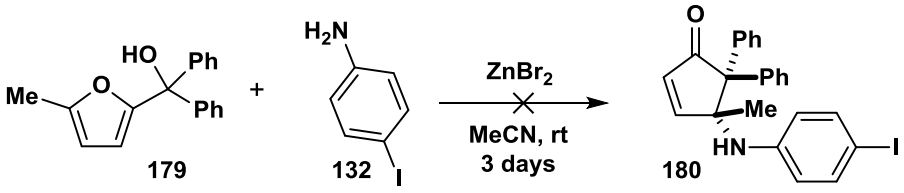
Table 8. Attempts to rearrange 5-methyl-2-phenyl furylcarbinol.



entry	catalyst (mol %)	additive	temp (^oC)	yield (%)
1	$Dy(OTf)_3$ (5)		80	decomp
2	$Dy(OTf)_3$ (100)		80	decomp
3	$Yb(OTf)_3$ (5)		80	decomp
4	$Yb(OTf)_3$ (5)	3Å MS	80	no rxn
5	$Dy(OTf)_3$ (5)	3Å MS	80	no rxn
6	$Dy(TMHD)_3$ (5)		80	no rxn
7	$ZnBr_2$ (100)		rt	58
8	$ZnBr_2$ (100)		80	decomp

Attempts were made to rearrange 5-methyl-2-furylbisphenylcarbinol **179** using $ZnBr_2$, but only substrate decomposition was observed (Scheme 22). Presumably, this is because in order to cyclize, the substrate must adopt the requisite pentadienyl cation geometry, which might be too high in energy due to the large amount of steric congestion on substrates that would form vicinal quaternary stereocenters.

Scheme 22. Attempt to rearrange 5-methyl-2-furylbisphenylcarbinol.

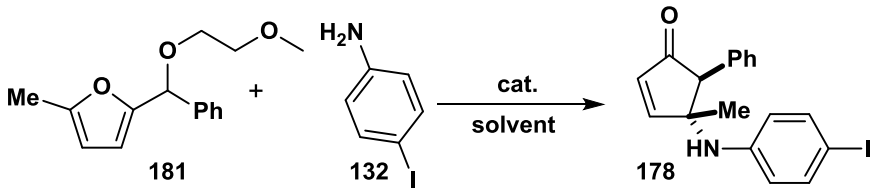


1.2.8 New Activating Groups

We hypothesized that the limited success we had while attempting to utilize 5-subsituted furylcarbinols is due to the steric congestion around the 5-substituted oxocarbenium, and that coordination between the Lewis acid and aniline might be reducing the concentration of active aniline nucleophiles from the reaction mixture, which would provide more time for the oxocarbenium to decompose. Based on this hypothesis we believed that a leaving group with more coordinating atoms would help to occupy more ligand sites on the catalyst and help to increase the amount of aniline in solution while also attenuating the acidity of the catalyst. Initially, we evaluated substituting the hydroxyl with a methoxy ethyl ether that provided more coordination sites for catalyst activation (Table 9). To our gratification, treatment of **181** with 5 mol % $Dy(OTf)_3$ at 80 ^oC resulted in the formation of 4-methyl-4-amino cyclopentenone **178** (entry 1). Although the reaction was low yielding (21%), this was the first time we were able to catalyze this more challenging rearrangement with

catalytic $Dy(OTf)_3$. Furthermore, using this new leaving group and employing $ZnBr_2$ produced the desired product **178** in good yield (69%, entry 2) at room temperature. Heating the reaction decreases the reaction time, but the yield suffers (entry 3). The rearrangement using $ZnBr_2$ gave moderate yields in THF (entry 4), but lead to decomposition products in dichloromethane (entry 5). Unfortunately, this reaction using $Dy(OTf)_3$ was not repeated at room temperature – this would be a good experiment to perform in the future based on the higher yields observed at room temperature when $ZnBr_2$ was used (entry 2 vs. 3).

Table 9. New ether leaving group.

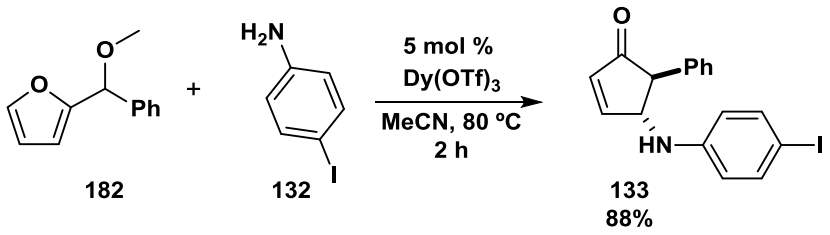


181 132 178

entry	catalyst (mol %)	solvent	time	temp (^oC)	Yield (%)
1	$Dy(OTf)_3$ (5)	MeCN	7 h	80	21
2	$ZnBr_2$ (100)	MeCN	4 days	rt	69
3	$ZnBr_2$ (100)	MeCN	2.5 h	80	41
4	$ZnBr_2$ (100)	THF	8 days	rt	53
5	$ZnBr_2$ (100)	CH_2Cl_2	7 h	rt	decomp

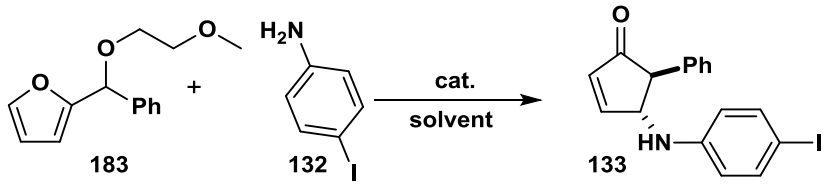
Encouraged by these results, we also probed the reactivity of our original phenyl furylcarbinol system lacking the 5-methyl substituent using ether leaving groups **182**. We found, that in general, ether leaving groups behave similarly to the hydroxyl system, producing similar yields of **133** but with slightly longer reaction times. The simple methoxy leaving group produces the expected 4-amino cyclopentenone **133** in 2 hrs and in 88% yield using 5 mol % $Dy(OTf)_3$ in MeCN at 80 ^oC (Scheme 23).

Scheme 23. Methoxy leaving group.



Similar trends were observed with the new methoxy ethyl ether leaving group **183** (Table 10). We screened a number of catalysts and solvents and $Dy(OTf)_3$ in MeCN gave the best results, forming the desired product **133** in 87% yield (entry 1). Zinc catalysts $ZnCl_2$ in MeCN (entry 2) and $ZnBr_2$ in CH_2Cl_2 (entry 3), produced **133** in moderate yield. $MgCl_2$ was not reactive (entry 4), and $TiCl_4$ lead to decomposition of the starting material (entry 5).

Table 10. Screening conditions using ether leaving groups.

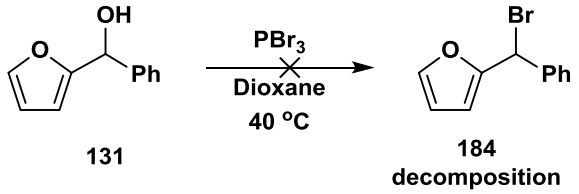


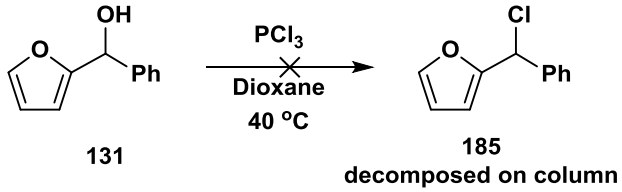
entry	catalyst (mol %)	solvent	time	temp (^oC)	yield (%)
1	$Dy(OTf)_3$ (5)	MeCN	2 h	80	87%
2	$ZnCl_2$ (25)	MeCN	28 h	80	46%
3	$ZnBr_2$ (100)	CH_2Cl_2	30 h	rt	74%
4	$MgCl_2$ (100)	CH_2Cl_2	3 days	rt	no rxn
5	TiCl4 (100)	CH_2Cl_2	3 h	0 ^oC	decomp

More labile halogen leaving groups were briefly investigated. Attempts were made to substitute the hydroxyl group on phenyl furylcarbinol **131** with either bromine or chlorine (Scheme 24). In our hands, these compounds were too unstable to handle. The bromine derivative **184** decomposed immediately, and the chlorine derivative **185** decomposed while

attempting to purify on silica gel. No further attempts were made due to the challenges associated with handling these compounds.

Scheme 24. Attempts to install halogen leaving groups.





In conclusion, we have found that ether based leaving groups are a good alternative to hydroxyl leaving groups on the original furylcarbinol substrates. With ether based leaving groups we were able rearrange challenging 5-methyl furylcarbinols to 4-methyl-4-amino cyclopentenone for the first time using catalytic amounts of $Dy(OTf)_3$. Future studies would benefit from investigating $Dy(OTf)_3$ and other lanthanide triflate Lewis acids at room temperature to compare their performance to $ZnBr_2$ at room temperature.

Overall, the effectiveness of an activating group for the Piancatelli rearrangement depends on a delicate balance between functional groups that leave too readily, or groups that are too stable to act as leaving groups. In our hands, halogen based leaving groups were too reactive and we elected not to pursue their usage any further due to their high propensity to spontaneously disassociate and lead to decomposition products.

1.2.9 Functionalization of the 4-Amino Cyclopentenone Products

One of our primary interests in developing an aza-Piancatelli rearrangement was for the potential to rapidly construct building blocks that would be useful for the synthesis of complex natural products or other biologically active compounds. Researchers at Merck were looking for new molecular scaffolds that behave as hNK1 antagonists. During a structure-activity relationship study, the team discovered that 1,2-*trans*-2,3-*trans*-cyclopentane based scaffolds **186** have comparable hNK1 binding affinities to the commercially available drug Aprepitant **187** (Figure 15).[57] Aprepitant is an FDA approved hNK1 antagonist drug that acts as antiemetic for chemotherapy-induced nausea and vomiting.

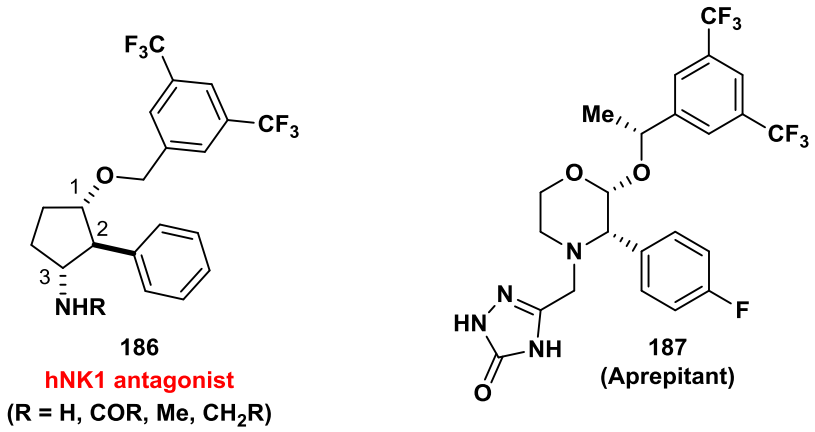
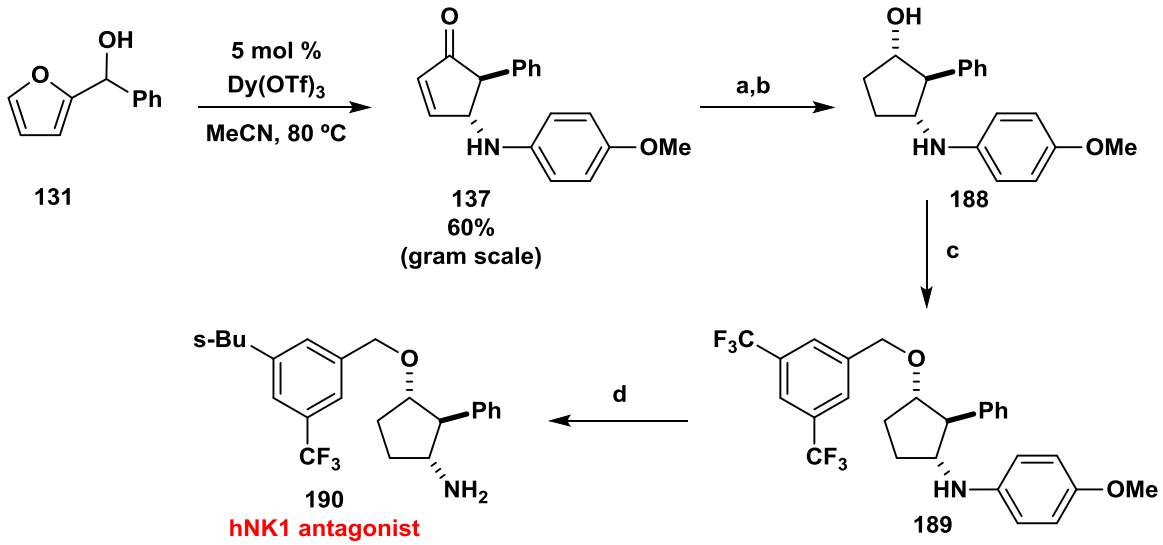


Figure 15. hNK1 Inhibitors.

We recognized that from our *trans*-4-aminocyclopentenone scaffold, that construction of the newly discovered hNK1 antagonist scaffold would be straightforward (Scheme 25). Rearrangement of phenyl furylcarbinol **131** with *para*-anisidine afforded **137** in 60% yield on gram scale. Luche reduction of the ketone followed by hydrogenation of the olefin gave access to the1,2-*trans*-2,3-*trans*-cyclopentane scaffold **188**. Alkylation of the hydroxyl

group with 3,5-bis(trifluoromethyl)benzyl bromide and sodium hydride gave the benzyl ether **189**. Lastly, removal of the *para*-methoxyphenyl group through oxidative dearylation using periodic acid (H_5IO_6) provided the primary amine **190**. We were able to build this biologically active scaffold as a racemic mixture in only five steps from simple phenyl furylcarbinol **131** in 19% overall yield. This highlights the potential application of the aza-Piancatelli rearrangement for the synthesis of biologically active molecules, as previous methods reported by Merck to access the same scaffold required greater than fifteen synthetic steps.

Scheme 25. Synthesis of an hNK1 inhibitor using the aza-Piancatelli rearrangement.



a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 98% (2:1 trans/cis); b) 10 mol% Pd/C, H_2, MeOH, 500 psi, 76% (2:1 trans/cis; 49%); c) NaH, 3,5-bis(tri-fluoromethyl)benzyl bromide, THF, 75%; d) H_5IO_6, H_2SO_4, MeCN/H_2O (1:1), rt, 58%.

1.3 Hydroxyl Amines as Nucleophiles

1.3.1 The Problems Faced with non-Aniline Nucleophiles

The most challenging step of our five-step hNK1 antagonist synthesis was removal of the *para*-methoxy group, which requires harsh oxidative conditions to access the primary amine. Unfortunately, while developing the aza-Piancatelli rearrangement, a wide variety of amines were examined, but anilines remained the only broad class of nucleophiles that we initially found to be effective. In general, we found that more basic amines such as indole **191** and aliphatic amines **192,** either deactivate the catalyst by binding too strongly or by facilitating formation of inactive precipitates (Figure 16). Rare earth lanthanide Lewis acids are known to be more oxophilic than azaphilic, however, relatively few complexes of basic amines with rare earth lanthanide metals have been documented. This is in part due to the high basicity of amines which tends to result in precipitation of inactive lanthanide hydroxide compounds.[47] Although uncharacterized, in our experience, when attempting to react furylcarbinols with basic aliphatic amines, we observe the formation of white precipitates after addition of the lanthanide triflate catalyst, and typically only recover starting materials from the reaction, even after prolonged heating in a variety of solvents. Initially, to address this challenge, morpholine and morpholine•HCl were screened using 30 mol % $Dy(OTf)_3$ in the following solvents with no formation of the desired product: acetone, chloroform, dichloromethane, dimethylsulfide, ethanol, diethyl ether, ethyl acetate, nitromethane, tetrahydrofuran, and toluene. Unfortunately, even under anhydrous conditions, simple furylcarbinols fail to react in a reasonable amount of time.

When $Dy(OTf)_3$ and a furylcarbinol are allowed to react in the absence of a nucleophile, we observe decomposition of the furylcarbinol with no readily identifiable products.

Attempts to utilize more acidic amines such as amides **193**, and sulfonamides **194** lead to decomposition of the starting material. Other types of amines such as azides and nitriles also fail to react favorably. To expand the synthetic utility of the aza-Piancatelli reaction we sought to identify conditions that would allow non-aniline nucleophiles to participate.

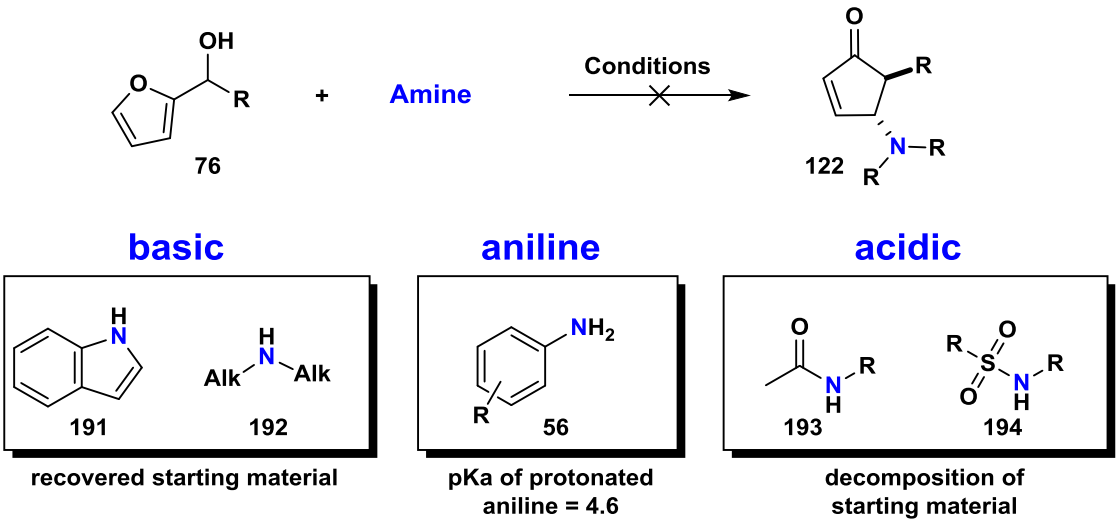


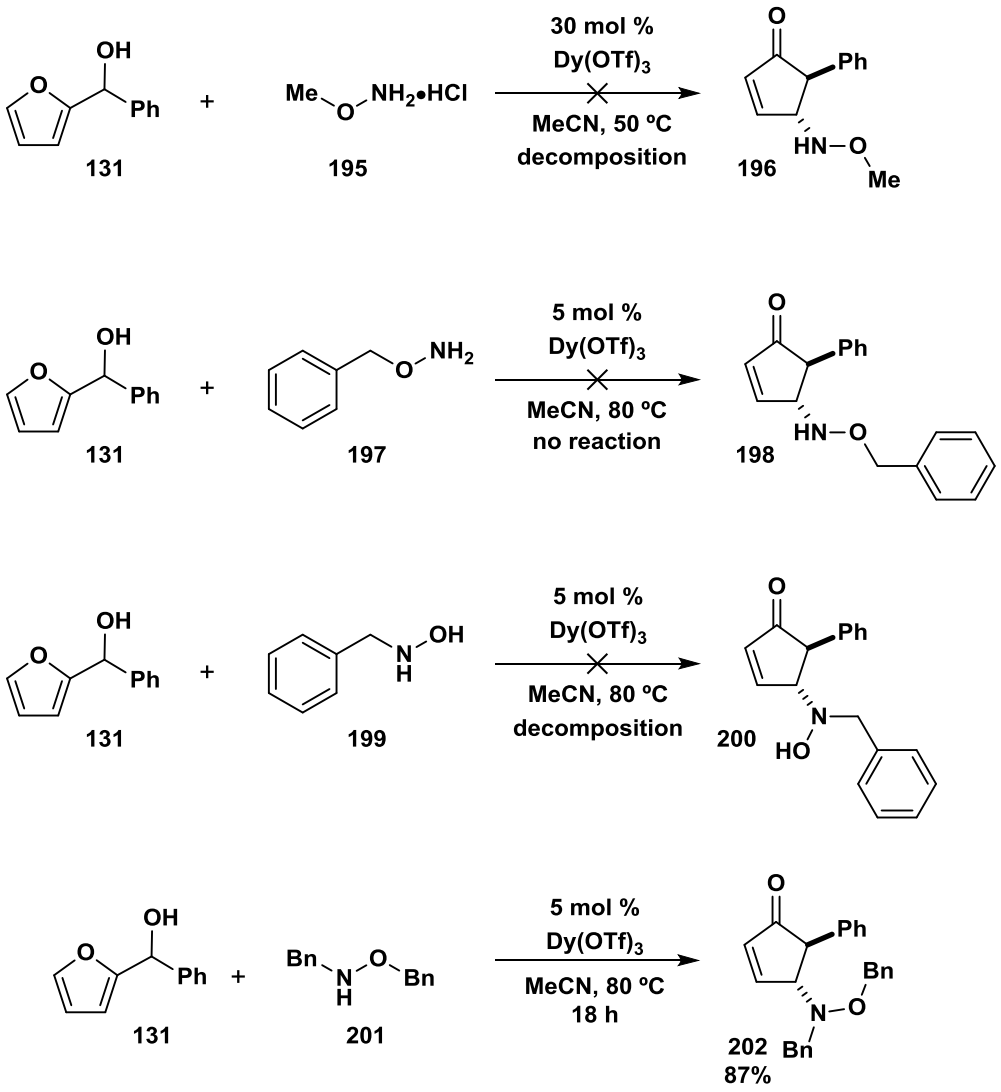
Figure 16. Attempts to utilize non-aniline amine nucleophiles.

We hypothesized that the properties of effective amine nucleophiles must lie within a narrow range of nucleophilicity/acidity (pKa). This idea also gains credibility from Piancatelli's studies where he found that the optimal pH range of his reactions was around ~5.5, suggesting that the pH of the reaction is important to its success. Based on the idea that the pKa might be a critical factor for our choice of amine, we hypothesized that hydroxylamines might be a suitable class of amine nucleophiles, since they possess similar pKa values to anilines (pKa of protonated aniline = 4.6, protonated N,O-dimethyl-hydroxylamine = 4.75).[58] Another attractive feature of hydroxylamines is the weak N–O bond, which would allow for further functionalization of the products and more synthetic versatility.

1.3.2 Reaction Optimization

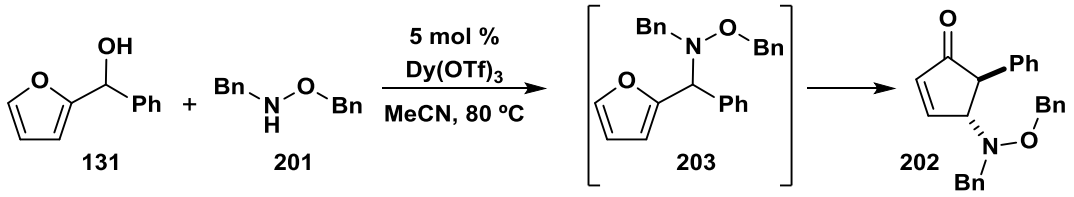
With the above analysis in mind, we began our investigation using commercially available hydroxylamines an employing our previously established reaction conditions, $Dy(OTf)_3$ in MeCN. Disappointingly, methoxyamine hydrochloride **195** lead to decomposition of the furylcarbinol. Switching to the free based primary *O*-benzylhydroxylamine **197** also failed and in this case starting material was recovered. *N*-Benzylhydroxylamine **199** also resulted in decomposition of the starting material. To our gratification, utilization of *N*-benzyl-*O*-benzylhydroxylamine **201**, where both the nitrogen and oxygen atoms were substituted, lead to formation of the desired *trans*-4-amino cyclopentenone **202** in high yield (87%), after 18 h. Importantly, only the *trans* diastereomer was formed, which is consistent with the proposed 4π electrocyclization in the aza-Piancatelli rearrangement. *N*,*O*-Protected hydroxylamines are easily synthesized by established literature procedures and they serve as valuable building blocks which inspired us to further investigate the scope of this methodology.[59]

Scheme 26. First attempts to utilize hydroxylamine nucleophiles.



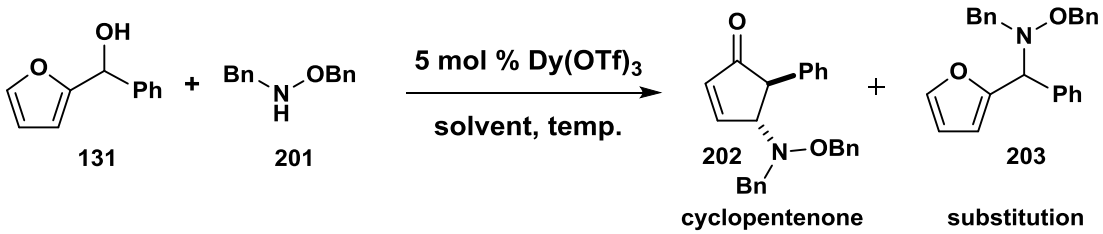
Upon investigation, we determined that reaction times in MeCN required 18 hr to go to completion. We observed over the course of the reaction was that within ~1 hour some cyclopentenone had formed, but no starting material remained. The majority of the starting material was converted to the product of substitution by the amine at the hydroxyl position to give **203** (Scheme 27). It is important to note that we have observed this type of substitution product using anilines, but only in small amounts and only with certain substrates.

Scheme 27. Substitution product intermediate.



A small solvent screen was performed to try and reduce the reaction time (Table 11). Reactions performed in toluene (entry 1) and CH_2Cl_2 (entry 2) quickly formed substitution products, but turnover to the cyclopentenone was prohibitively long, and were stopped after 4 days. Incredibly, in nitromethane ($MeNO_2$), the reaction time was significantly reduced to only 1 h, and produced the desired cyclopentenone **202** in 87% yield (entry 4).

Table 11. Solvent screen.



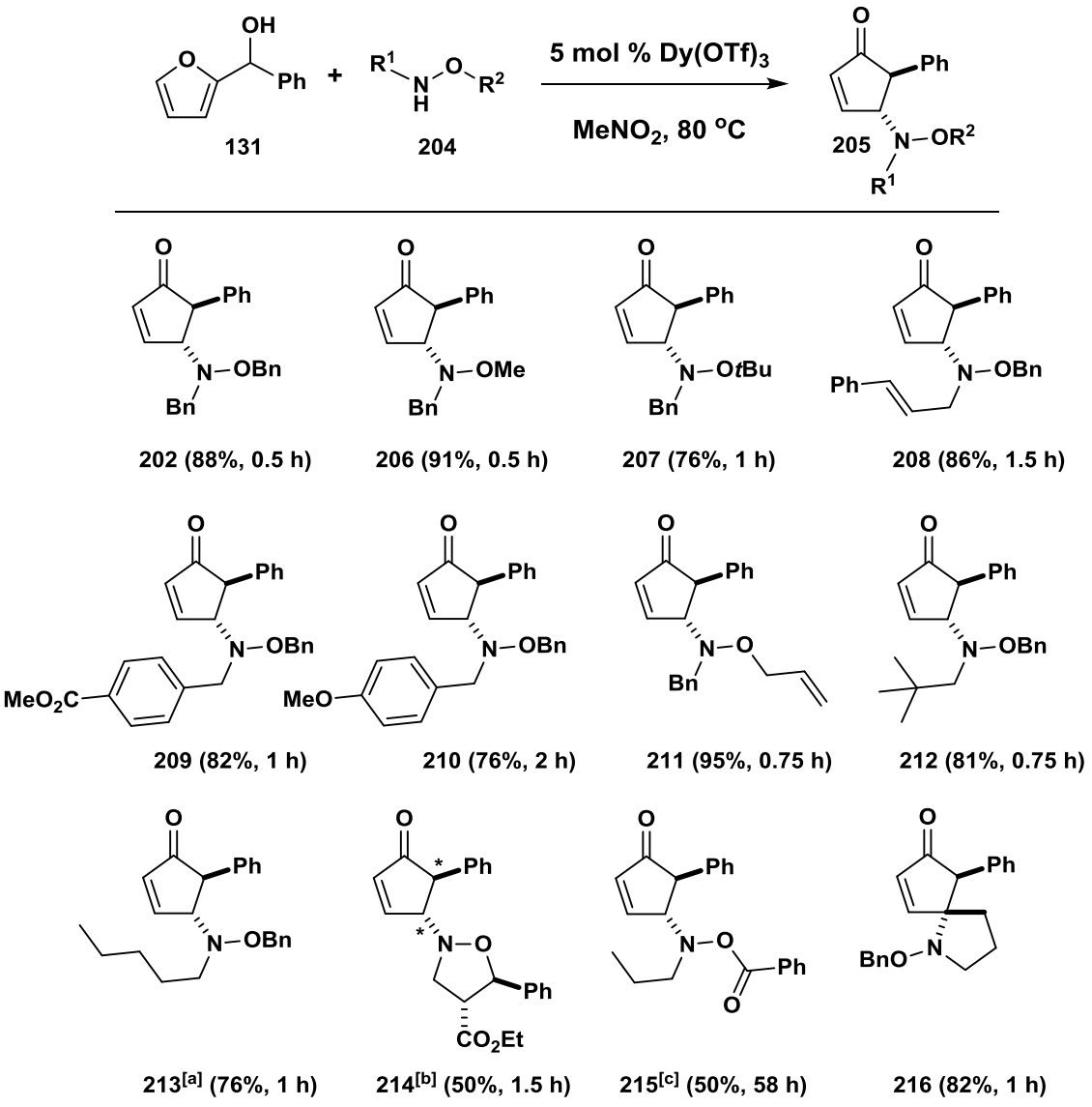
entry	solvent	time	temp.	yield of 202 (%)	yield of 203 (%)
1	toluene	4 days	80 °C	71	11
2	CH_2Cl_2	4 days	40 °C	40	41
3	MeCN	18 h	80 °C	87	0
4	$MeNO_2$	1 h	80 °C	88	0

1.3.3 Substrate Scope

With optimized reaction conditions in hand, we began by exploring the reaction between phenyl furylcarbinol **131** and a range of substituted hydroxylamines.[59] We found the reaction to be quite robust of regardless of substituents on N- or O-, with only a few exceptions. Oxygen protecting groups ranging from small methyl **206** to large *t*-Butyl **207**,

produced the desired cyclopentenones in good yield (91% and 76%, respectively). Olefins are tolerated under the reaction conditions. The cinnamaldehyde derived hydroxylamine **208** with an internal olefin reacted favorably. Terminal olefins are also well tolerated and gave cyclopentenone **211** in 95% yield. Electron donating **210** and withdrawing groups **209** were tested for electronic effects that the benzyl group might have on the rearrangement. Both substrates produced the expected cyclopentenone in good yield, and the electron donating *p*-methoxy benzyl group was only slightly slower to react, taking 2 hrs at 80 ^{o}C. Bulky *N*-*sec*-butyl **212** formed products in good yield. However, linear *N*-*n*-pentyl **213** was slow to react and required higher catalyst loading (10 mol %) for the reaction to proceed at a reasonable rate. Cyclic hydroxylamine **214** was less effective, and only 50% of the desired product was formed, with the rest of the material recovered being a mixture of unidentifiable compounds. For this case, the existing stereocenter on the cyclic hydroxylamine did not influence the conrotation of the 4π electrocyclization and isolated as a 1:1 mixture of *trans* diastereomers. Employing an electron withdrawing *O*-benzoyl substituted hydroxyl amine, required 30 mol % $Dy(OTf)_3$ and was exceptionally slow, taking 2.5 days to achieve a moderate yield of the desired product **215**. In a previous communication, our group reported the first intramolecular Piancatelli rearrangement for the formation of spirocyclic cyclopentenones.[60] Spirocyclic amine **216** demonstrates that hydroxylamines are also competent nucleophiles for the intramolecular rearrangement using hydroxylamine nucleophiles. Only one diastereomer is formed, with the amine and the phenyl group in a *trans* configuration. One notable difference between aniline and hydroxylamine nucleophiles, is that for the latter, Friedel–Crafts alkylation is not observed.

Table 12. Scope of the rearrangement with substituted hydroxylamines.

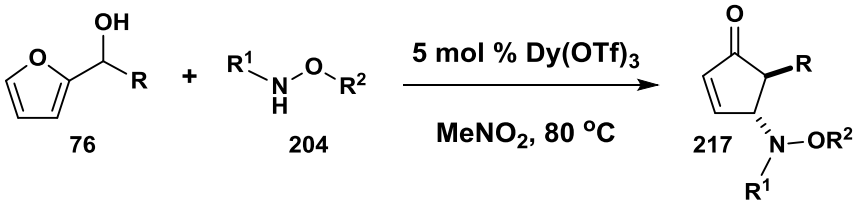


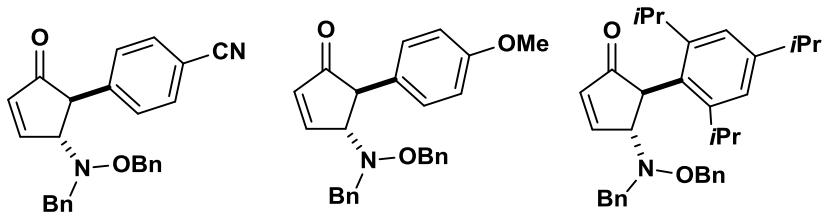
[a] Reaction performed with 10 mol % Dy(OTf)$_3$.
[b] Isolated as a 1:1 mixture of *trans* diastereomers.
[c] Reaction performed with 30 mol % Dy(OTf)$_3$ at rt
Yields reported are of the isolated products.

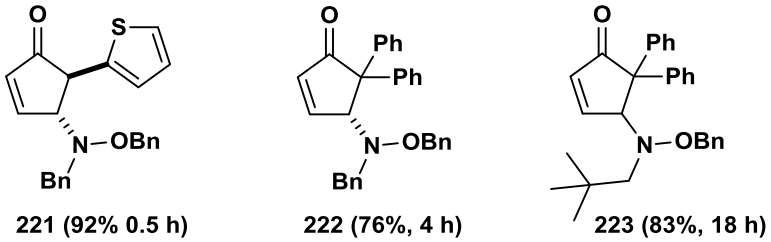
Next, we turned our attention towards investigating alternatively substituted furylcarbinols. Similar to what we have observed previously, electron deficient furylcarbinols are deactivating and slower to react. Indeed, *para*-cyano phenyl furylcarbinol required heating at 80 ^{o}C for 17 hrs, but produced the desired product **218** in good yield.

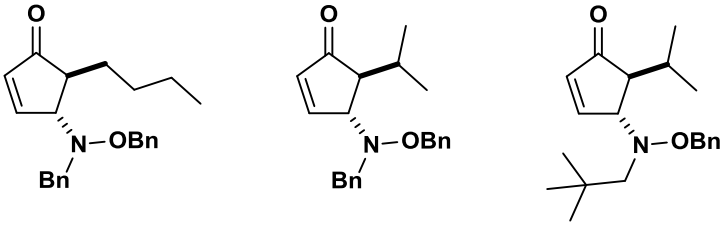
Conversely, the electron rich *para*-methoxy phenyl furylcarbinol was complete in 30 mins with 84% yield of **219**. The extremely bulky 2,4,6-triisopropyl phenyl furylcarbinol was complete in 40 mins and gave the 4-amino cyclopentenone **220** in 80% yield. Heteroaromatic thiophene substituted furylcarbinols were also successful and gave 92% of cyclopentenone **221** in only 30 mins. Bis-phenyl furylcarbinols produced cyclopentenones **222** and **223** bearing an all carbon quaternary center α to the carbonyl in good yields, but with increased reaction times. Lastly, alkyl substituted furylcarbinols were investigated. As we had observed during our investigations using aniline nucleophiles, alkyl substituted furylcarbinols are much less reactive than aryl substituted derivatives. In the case of hydroxylamines, this still holds true, and catalyst loading had to be increased to 10 mol % for the reaction to proceed in a reasonable amount of time (**224**-**226**). The yield of alkyl substituted furylcarbinols was around 50% regardless of the nucleophile used.

Table 13. Scope of the rearrangement with substituted furylcarbinols.









[a] reaction performed with 10 mol % $Dy(OTf)_3$
Yields reported are of the isolated products.

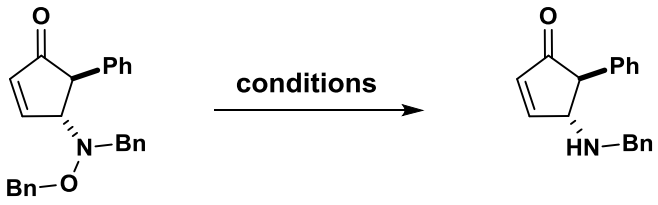
1.3.4 Breaking the N–O Bond

Our long term goal is to utilize the newly formed *trans*-4-amino cyclopentenones as a structural scaffold for the construction of more complex and valuable molecules. One extremely attractive aspect of hydroxylamines is the rich chemistry associated with them

due to the inherently weak nature of the N–O bond. There is ample precedent for breaking the N-O bond under reducing conditions to expose the free amine, and in this way, incorporating a hydroxylamine would be the equivalent of incorporating a protected nitrogen group. The some of the most common ways to facilitate N–O bond cleavage are Zn/HCl;[61] H_2, Pd/C;[62] $Mo(CO)_6$[63] and SmI_2.[59b]

Surprisingly, our initial attempts to break the N–O bond were unsuccessful (Table 14). Zinc with various acids either gave complex mixtures of products or were very slow to react (entries 1-3). We hypothesized that after breaking the N–O bond that the resultant free amine **227** might be problematic, so attempts were made to protect it *in situ*. Zinc powder in the presence of electrophilic acetic anhydride was attempted, but also failed to give the desired product (entry 4). Molybdenum hexacarbonyl lead to product decomposition (entry 5). SmI_2 in THF decomposed the starting materials (entry 6). Keck has reported that for some difficult substrates, reductive cleavage of N–O bonds can benefit from a proton source such as methanol, alas this method also leads to decomposition products (entry 7).[59b] Another attempt was made using SmI_2 to protect the amine *in situ* using acetic anhydride. SmI_2 was allowed to react for 15 minutes at rt, then 8 equivalents of acetic anhydride was added. Again, no desired product **227** was found (entry 8). Palladium on carbon (Pd/C) was also unsuccessful. In the absence of acid, only the enone was reduced (entry 9), and upon the addition of acid, only decomposition was observed (entry 10). Pearlman's catalyst ($Pd(OH)_2$) also failed to react favorably (entry 11). Sodium borohydride in the presence of a $NiCl_2$ Lewis acid only reduced the ketone to the allylic alcohol (entry 12).

Table 14. Initial attempts to break the N-O bond.

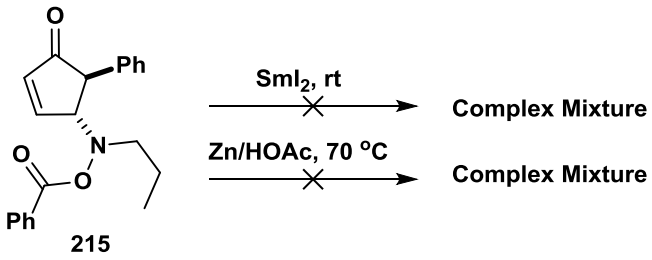


202 227

entry	reagent	solvent	temp (^{o}C)	yield (%)
1	Zn/HCl	H_2O/THF	70	0
2	Zn/HOAc	H_2O/THF	70	0
3	Zn/NH_4Cl	H_2O/THF	rt	slow rxn
4	Zn/HOAc, acetic anhydride	H_2O/THF	70	0
5	$Mo(CO)_6$	MeCN	80	0
6	SmI_2	THF	rt	0
7	SmI_2	THF/MeOH	rt	0
8	i) SmI_2 ii) acetic anhydride	THF	rt	0
9	H_2, Pd/C (1000 psi)	MeOH	rt	only ketone, quant. yield
10	H_2, Pd/C, HCl (1000 psi)		rt	0
11	H_2, $Pd(OH)_2$	EtOH	rt	0
12	$NaBH_4$, $NiCl_2$•6 H_2O	MeOH	rt	reduced enone

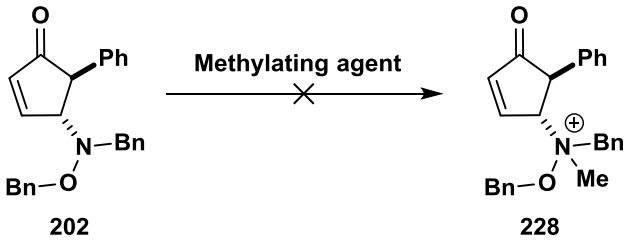
In order to understand why we are having such great difficulties clipping the N–O bond, many of the conditions mentioned in Table 14 were attempted using various hydroxylamines and α-alkyl substituted cyclopentenones with no further success. Attempts to utilize the O-benzoyl substituted hydroxylamine **215** with SmI_2 and Zn/HOAc were also unsuccessful (Scheme 28).

Scheme 28. Failed attempts to break the N–O bond.



At this point, it wasn't clear as to why breaking the N–O bond was so difficult on our substrates. We attempted to methylate the nitrogen of **202** to form the ammonium salt **228**, which should considerably weaken the N–O bond (Scheme 29). Unfortunately, the tertiary hydroxylamines are extremely unreactive. Methyl trifluoromethanesulfonate (TfOMe) failed to react at temperatures up to 80 ^{o}C (entries 1-3). Refluxing methyl iodide, and methyl iodide in the presence of silver trifluoromethanesulfonate, also proved unsuccessful (entries 4 and 5). One of the most reactive methylating agents known,[64] triethyloxonium tetrafluoroborate, or Meerwein's reagent also failed to give the quaternary amine.

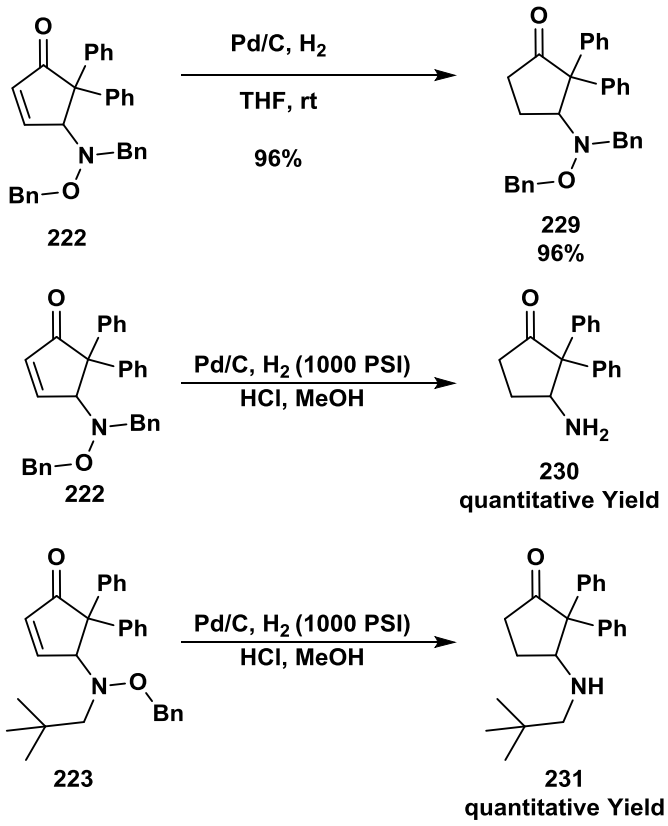
Scheme 29. Attempts to form the ammonium salt.



entry	reagent	solvent	temp (^{o}C)	yield
1	TfOMe	CH_2Cl_2	40	no rxn
2	TfOMe	toluene	80	no rxn
3	TfOMe	CCl_4	0	no rxn
4	MeI (neat)		40	no rxn
5	MeI, AgOTf	DMF	80	no rxn
6	triethyloxonium tetrafluoroborate	CH_2Cl_2	rt	no rxn

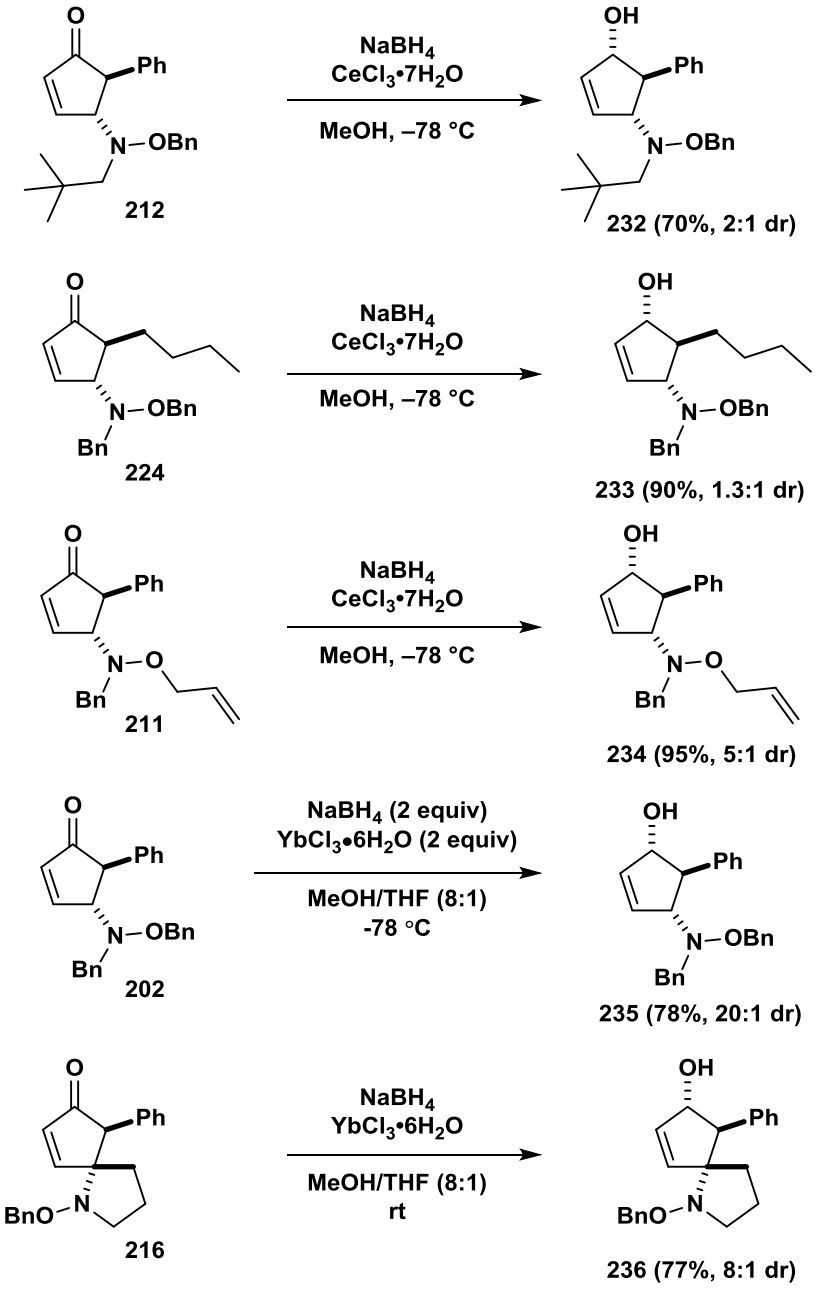
We hypothesized that the relative acidity of the proton α to the carbonyl might be responsible for the undesired behavior that we had been observing from these substrates. When we attempted to break the N–O bond on the bis-phenyl cyclopentenone **222**, which does not have an α proton, some progress was made towards our goal. Unfortunately, conditions employing Zn/H^+, SmI_2 and $Mo(CO)_6$ failed to produce the desired product. Under standard hydrogenation conditions, the enone was reduced to the ketone **229** (Scheme 30). However, at higher pressures in the presence of HCl, the enone was reduced in addition to breaking the N–O bond and removing the benzyl group to give the primary amine **230** in quantitative yield. Using *sec*-butyl hydroxylamine under these conditions gives the secondary amine **231**, also in quantitative yield.

Scheme 30. Hydrogenation conditions for breaking the N-O bond.



We were excited to finally be able to access the free amine. Knowing that the acidic α proton was problematic, we reduced the cyclopentenones to the allylic alcohol in order to tame the acidity of the α proton and also remove the electrophilic carbonyl and enone. Using standard Luche reduction conditions employing $NaBH_4$ and $CeCl_3$, afforded the desired 4-amino cyclopentenols (**232**-**236**) in good yields but with low diastereoselectivity, even at -78 ^{o}C (Scheme 31). Using modified Luche conditions and employing $YbCl_3$ as the Lewis acid, gave the desired cyclopentenols **235** and **236** in high yield and with very high diastereoselectivity, up to 20:1.[65] THF was added as a co-solvent to help solubilize the starting material.

Scheme 31. Luche reduction of cyclopentenones.



We now had a good method for the stereoselective formation of cyclopentenols bearing three contiguous stereocenters. X-ray crystallography was used to determine the relative stereochemistry of **235** (Figure 17). Interestingly, and opposite to what we were expecting, the hydride is delivered from the same face as the phenyl group and gives a 1,2-*trans*-2,3-

trans-cyclopentenol. We speculate that Lewis acid coordination with both the carbonyl and hydroxylamine blocks the back side and forces the hydride to approach from the more hindered face.

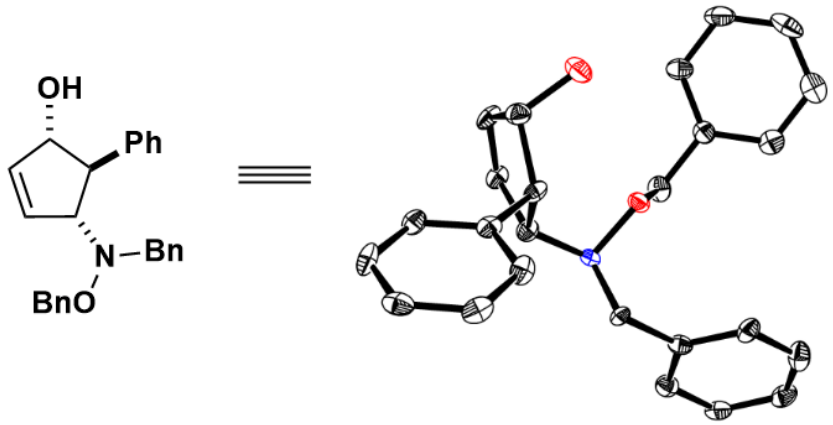
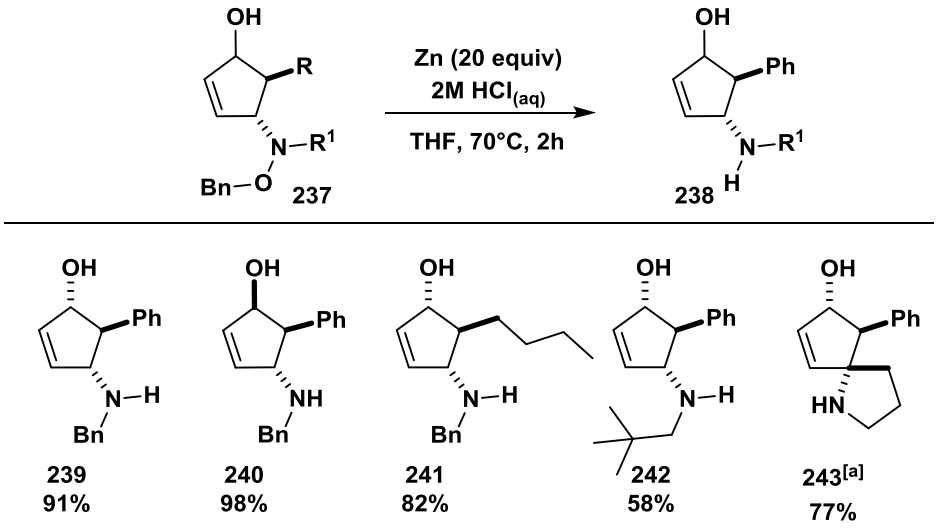


Figure 17. ORTEP drawing of 1,2-*trans*-2,3-*trans*-cyclopentenol **235** shown with 50% thermal ellipsoids. Hydrogen atoms have been omitted for clarity. The crystal structure data can be obtained from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. CCDC # 986010

With a variety of cyclopentenols in hand, we tested a variety of reducing conditions to see if we could cleanly break the N–O bond on these substrates. Reacting cyclopentenols under reducing conditions with Zinc/HOAc showed only trace amounts of what looked like the desired product by ^{1}H NMR. However, switching to a stronger acid, HCl, the N–O bond can be broken cleanly, giving cyclopentenols bearing a free alkyl amine in high yields (Table 15). Starting from either diastereomer of the *N*-benzyl-*O*-benzyl cyclopentenol, reduction with Zn/HCl cleanly afforded the secondary amines **239** and **240** in very high yield. Aliphatic substituted cyclopentenol was reduced the desired amine **241** in 82% yield. When *N*-*sec*-butyl-*O*-benzyl hydroxylamine was reduced with Zn/HCl the secondary amine

242 was produced in 58% yield. The spirocyclic hydroxylamine could also be reduced to give the spirocyclic 4-amino cyclopentenol **243** in 77% yield.

Table 15. Reductive cleavage of N-O bonds using Zn/HCl.



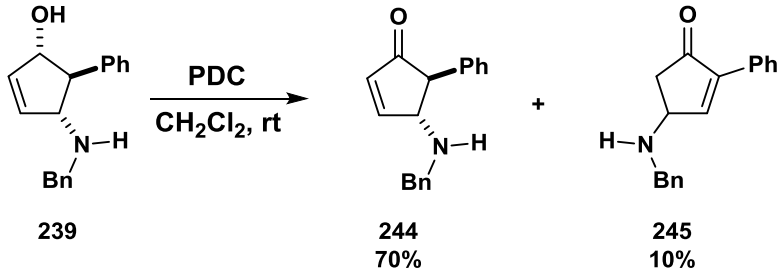
[a] From an 8:1 mixture of diastereomers
Yields reported are of the isolated products.

1.3.5 Functionalization of the Cyclopentenone Scaffold

In order to access the elusive 4-amino cyclopentenone bearing a free alkyl amine, we attempted to oxidize the allylic alcohol of the free amine products (Scheme 32). Pyridinium dichromate (PDC) was chosen after a screen of oxidants. The allylic alcohol **239** was oxidized to form the desired 4-amino cyclopentenone **244** in 60% yield in addition to the more thermodynamically stable cyclopentenone **245** in 10% yield. It is interesting to note that the more stable isomer **245** is not seen in the crude ^{1}H NMR of the reaction mixture, and is only formed after silica gel column chromatography or after extended storage in the freezer. Subsequent rearrangement in this way has been documented by Piancatelli (*vide supra*) under base catalyzed conditions. We speculate that the high basicity of the free amine

might be responsible for the instability and continued rearrangement of the cyclopentenone compounds.

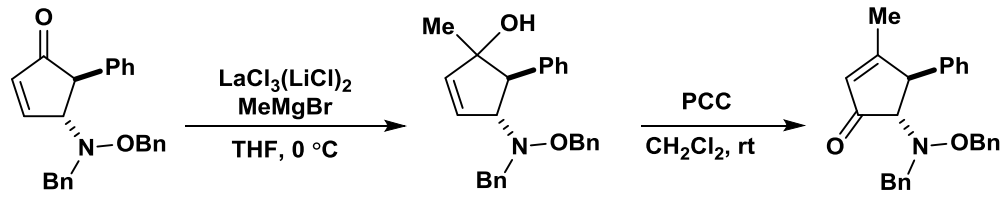
Scheme 32. Formation of amino cyclopentenones bearing an aliphatic amine.



239 **244** 70% **245** 10%

Oxidation of tertiary allylic alcohols by pyridinium chlorochromate is known to enact 1,3- transposition of the allylic oxygen.[66] We thought that this would be an interesting transformation to perform on our cyclopentenone substrates (Scheme 33). To form the tertiary alcohol, Knochel's conditions were utilized to facilitate stereoselective 1,2-addition into the carbonyl and gave **246** as a 15:1 mixture of diastereomers.[67] When methyl Grignard or methyl lithium was employed in the absence of any additives, a 1:1 mixture of diastereomers was obtained. Allylic transposition of the tertiary alcohol **246** with PCC gives the *trans*-5-amino cyclopentenone **247** in good yield as a single diastereomer.[68] This remarkable operation effectively switches the position of the amine and the R group relative to the carbonyl, forming a new class of α-amino cyclopentenones.

Scheme 33. Allylic transposition of tertiary alcohols.



202 **246** 80%, 15:1 dr **247** 76%, 1 diastereomer

1.4 Conclusion

In conclusion, we have developed effective conditions for an aza-Piancatelli rearrangement. In two steps from an inexpensive and renewable resource, furfural, the rearrangement rapidly forms compounds with defined *trans* stereochemistry. Using our optimized conditions, the reaction is operationally simple. The lanthanide Lewis acids can be weighed out at the lab bench and the reaction vessels are left open to air with no special precautions necessary to exclude oxygen or water. The ring forming step is a thermally induced 4π conrotatory electrocyclization that is responsible for the exclusive formation of *trans*-4-amino cyclopent-2-enones. The reaction is generally high yielding when utilizing anilines or hydroxylamines. We have re-optimized the reaction conditions and developed a new leaving group that allows for rearrangement of 5-substituted furylcarbinols that generate a new fully substituted stereocenter β to the carbonyl. We have also developed effective conditions for exposing the free aliphatic amine from hydroxylamine substrates. Lastly, we have applied this methodology towards our goal of building complex biologically active compounds by utilizing the aza-Piancatelli rearrangement to construct a new class of hNK1 antagonists.

1.5 References

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2. Formation of all-Carbon Quaternary Stereocenters

2.1 The Nazarov Cyclization for Forming Fully Substituted Carbon Stereocenters

Carbon–carbon σ bond forming reactions that form quaternary centers, specifically all-carbon-atom centers, remain a difficult challenge in organic synthesis.[1] Thanks to impressive contributions by a number of researchers, the Nazarov cyclization has become a useful strategy to address this difficult problem. One key feature of the Nazarov cyclization is that the bond forming 4π electrocyclization is a stereospecific process due to the requirement for the conservation of orbital symmetry. When exploited within rationally designed systems, the Nazarov cyclization is capable of directly forming multiple quaternary-carbon-atom stereocenters.[2]

The first part of chapter 2 will serve to highlight how the Nazarov cyclization has been utilized for the construction of cyclopentane compounds bearing quaternary stereocenters.[3] It is organized according to the three most common strategies used to construct quaternary stereocenters via the Nazarov cyclization, as shown visually in Figure 18. The most direct, but also most underdeveloped method is to construct the quaternary stereocenter(s) during the ring-forming step (Figure 18a). An alternative, but more general approach is to intercept the oxyallyl cation with a nucleophile prior to elimination (Figure 18b). This process is known as the interrupted Nazarov cyclization and carbon or heteroatom nucleophiles can be used. A Wagner-Meerwein rearrangement, which also takes advantage of the *in situ* generated oxyallyl cation, can also be used to construct quaternary stereocenters (Figure 18c). These three possibilities each deliver uniquely substituted cyclopentenone compounds bearing quaternary stereocenters.

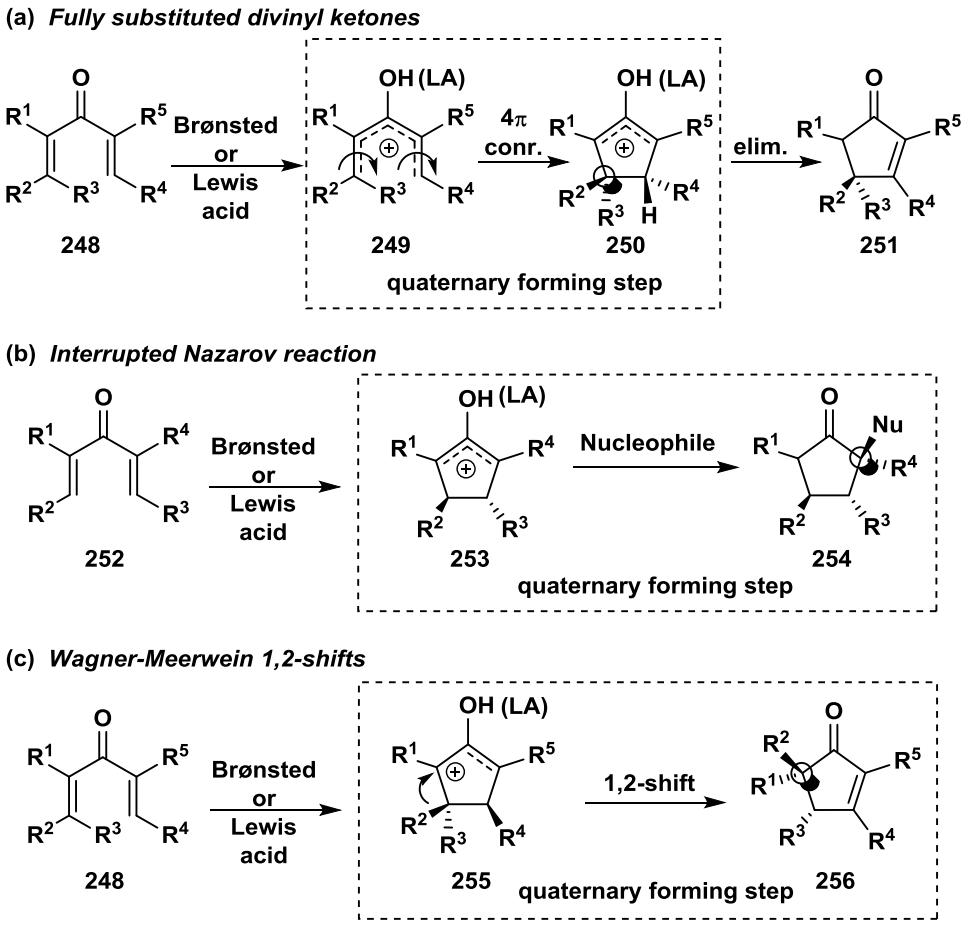


Figure 18. Three ways to form fully substituted centers using the Nazarov cyclization.

2.1.2 Terminally Substituted Dienones

Upon first glance, the most apparent route towards the construction of quaternary carbon centers using the Nazarov cyclization is by utilizing fully substituted terminal dienes. However, this approach can be challenging due to the unfavorable steric interactions encountered during the carbon–carbon bond forming event. This is further complicated by some of the traditional challenges associated with the Nazarov reaction, such as controlling the regioselectivity of the elimination step and the necessity of using forcing conditions. Often, strategies for synthesizing compounds bearing an all-carbon-atom quaternary center rely on strong Brønsted or Lewis acids and employ substrates lacking sensitive functional

groups.[4] Despite these challenges, many clever solutions have been developed to address these issues.

One powerful solution to these inherent limitations is the usage of polarized dienones **257** (Figure 19). Polarization of the π system increases the extent to which the terminal carbons may act as electron donors or acceptors **258**, which helps facilitate the reaction by lowering the barrier for the bond-forming process. This results in an increase in reaction rate and enables the use of milder reaction conditions. In addition, electron rich substituents help stabilize the positive charge **259** after cyclization which enhances control over the regioselectivity during the elimination step.

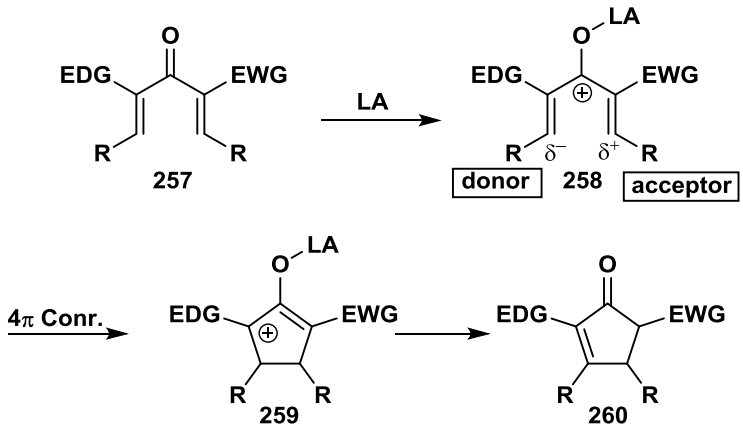
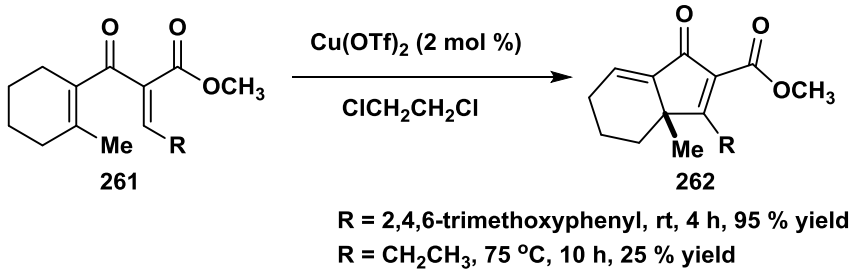


Figure 19. Polarization of the dienone.

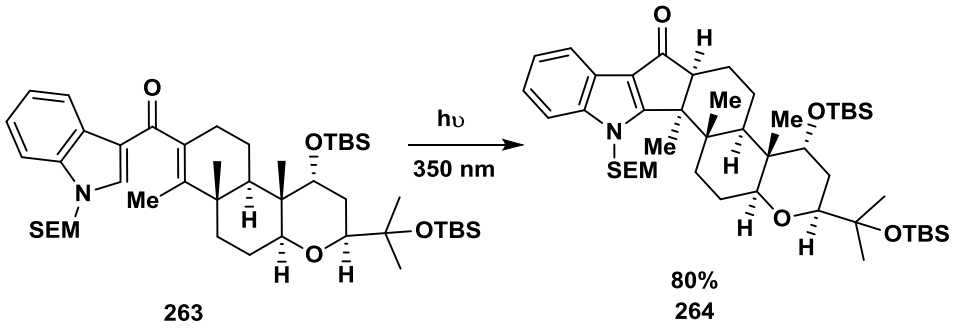
Research involving polarized dienones has proved fruitful for the development of a reliable strategy for the formation of all-carbon-atom quaternary stereocenters. Substituted dienone **261** efficiently cyclizes to form **262** when R bears an electron donating group (2,4,6-trimethoxyphenyl) (Scheme 34). However, when R = ethyl, the cyclized product is obtained in only 25% yield.[5]

Scheme 34. Polarization of the divinyl ketone for the Nazarov cyclization.



The Nazarov cyclization can also be initiated with light, and in this way, promotes disrotatory electrocyclization rather than thermally induced conrotatory cyclization.[6] When dienone **263** was irradiated with light at 350 nm, the reaction proceeded to give the desired cyclopentenone **264** in 80% yield as a single diastereomer (Scheme 35).[7] Although rare, the use of light was necessary en route to terpendole E analogs because the use of Lewis acids led to starting material decomposition and premature removal of protecting groups that were necessary for subsequent chemistry.

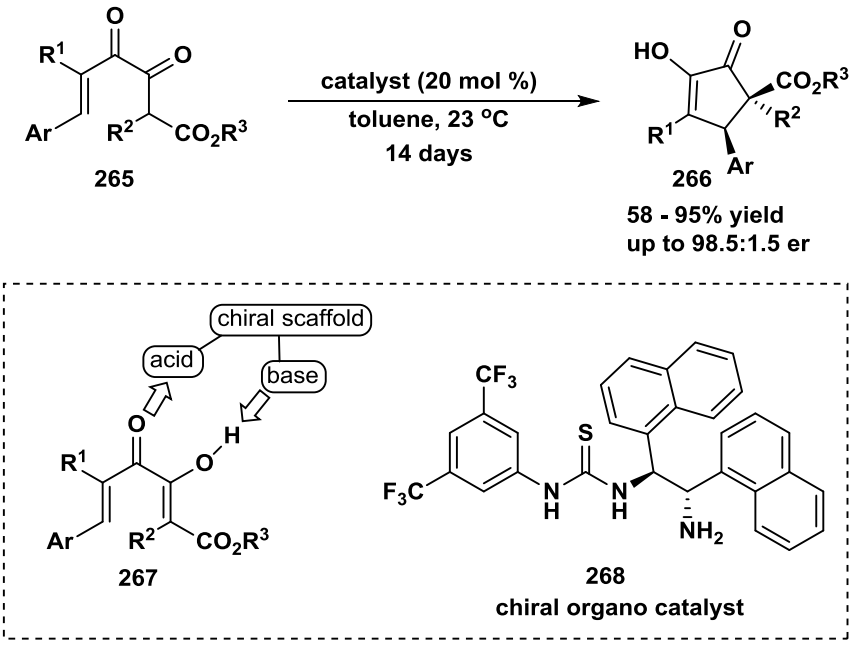
Scheme 35. Light catalyzed Nazarov for the construction of terpendole E Analogues.



Using α-ketoenones **265**, which are known to cyclize to form cyclopentenones **266** under mild Lewis acidic conditions,[8] Tius has developed an asymmetric Nazarov cyclization catalyzed by chiral thiourea organocatalysts **268** that are designed to induce complimentary two-point binding with the substrate (Scheme 36). The Brønsted acidic portion facilitates

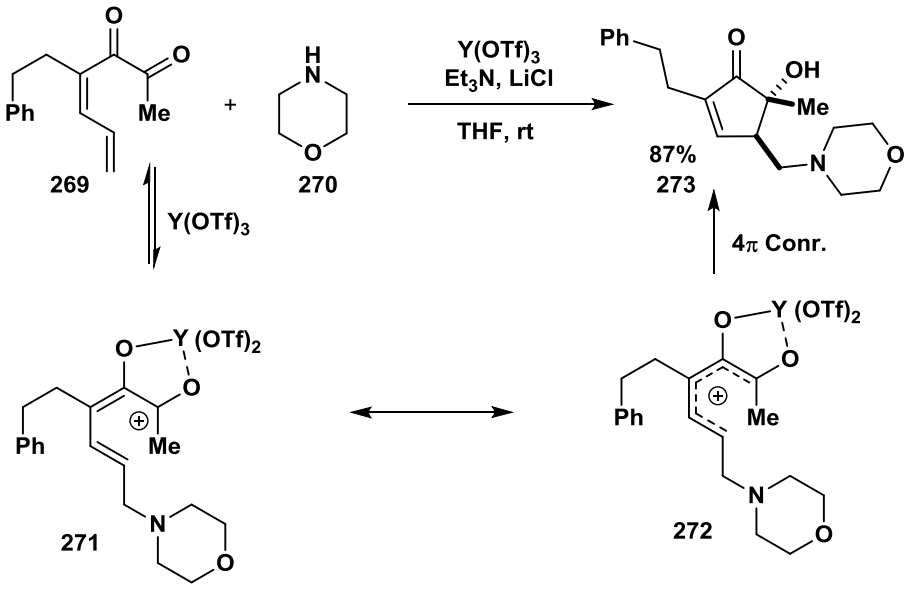
isomerization to the divinyl ketone **267**, and subsequent hydrogen bonding with the Lewis basic site of the chiral catalyst provides the rigidity necessary for the catalyst to control the torquoselectivity of the cyclization. What makes this technique particularly attractive is the mild conditions and high enantioselectivity achieved when forming cyclopentenones bearing all-carbon quaternary stereocenters.[9]

Scheme 36. Diketones for an enantioselective organocatalytic Nazarov reaction.



In a similar but distinct fashion to Tius's work (*vide infra*), Frontier has found that treatment of extended α-ketoenones **269** with a Lewis acid in the presence of a suitable carbon or nitrogen nucleophile (**270**) gives cyclization products **273** bearing tertiary alcohols in good yields (Scheme 37).[10] 1,6-Conjugate addition by the amine generates the requisite pentadienyl cation **272** which undergoes Nazarov cyclization forming the fully substituted carbon α to the carbonyl.

Scheme 37. Conjugate addition initiated Nazarov cyclization.



Examples mentioned thus far construct a fully substituted quaternary stereocenter adjacent to a tertiary stereocenter. The most challenging and still underdeveloped scenario occurs when one desires to use the Nazarov cyclization to construct two adjacent all-carbon-atom quaternary stereocenters during the ring-forming step. This is particularly challenging because steric repulsion between the R^2 and R^3 groups disfavor the formation of the s-*trans*/s–*trans* diene conformation **276** required for the 4π electrocyclization process (Figure 20).

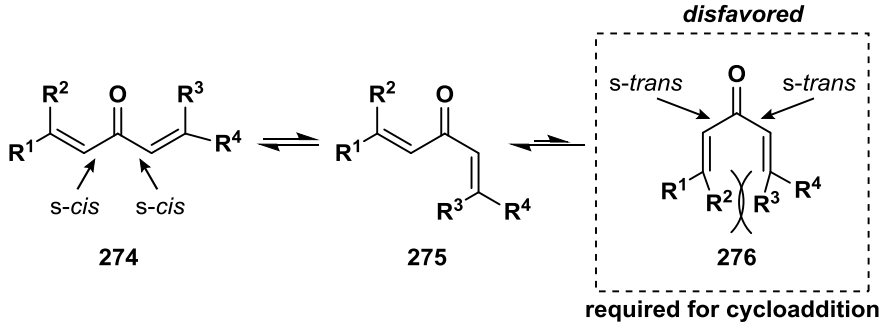
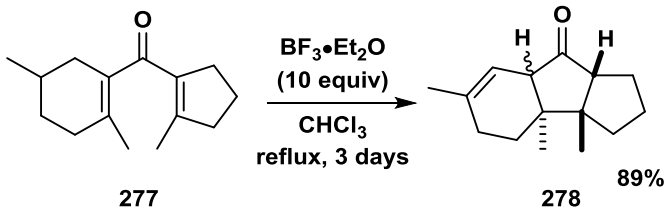


Figure 20. Rotational conformers of divinyl ketones.

Until the development of the polarized Nazarov cyclization, there were only a limited number of examples of such a sterically congested system leading to cyclopentanones. These examples required harsh reaction conditions and utilized systems lacking sensitive functional groups.[11] One example of such a system was constructed by Harding in an effort towards the synthesis of (±)-trichodiene (Scheme 38). Although harsh reaction conditions were used, the sterically congested tricyclic ketone **278** was obtained in excellent yields.[12]

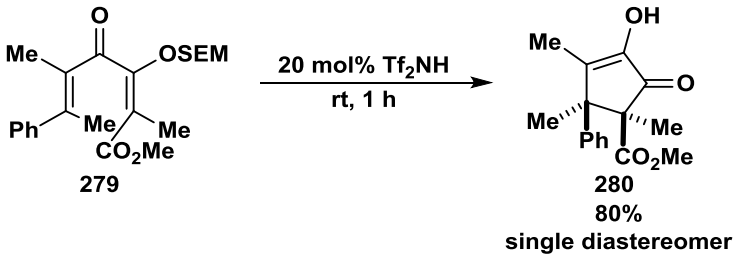
Scheme 38. Fully substituted terminal divinyl ketones.



Tius has taken full advantage of the increased reactivity of polarized Nazarov substrates for the synthesis of vicinal all-carbon-atom quaternary stereocenters. The challenging task of joining two pro-quaternary carbon atoms together to form vicinal all-carbon-atom centers was made possible by careful design of polarized dienones.[13] Nazarov cyclization of **279** gives **280** bearing two adjacent all-carbon centers as a single diastereomer (Scheme 39). It was noted that the design of the polarized dienone is crucial. If the electron withdrawing ester group is replaced with an amide, the reaction does not take place under these conditions. The [2-(trimethylsilyl)ethoxy]methyl (SEM) group is also important to maintain high diastereoselectivity. When the SEM group was replaced with a 4-methoxyphenyl (PMP) group, the diastereoselectivity was eroded from a single diastereomer to 1:3. This is likely due to slower hydrolytic loss of a PMP group versus a SEM group, which could facilitate a reversible Nazarov, *retro*-Nazarov process, which provides the opportunity for

enol ether isomerization and in turn, erosion of diastereoselectivity. During the preparation of this manuscript, Tius and co-workers reported that chiral phosphoric acids are capable of inducing enantioselectivity in these substrates in up to 99:1 er.[14] This is the first example of an asymmetric organocatalytic Nazarov reaction that forms vicinal all-carbon quaternary stereocenters.

Scheme 39. Formation of vicinal quaternary centers.



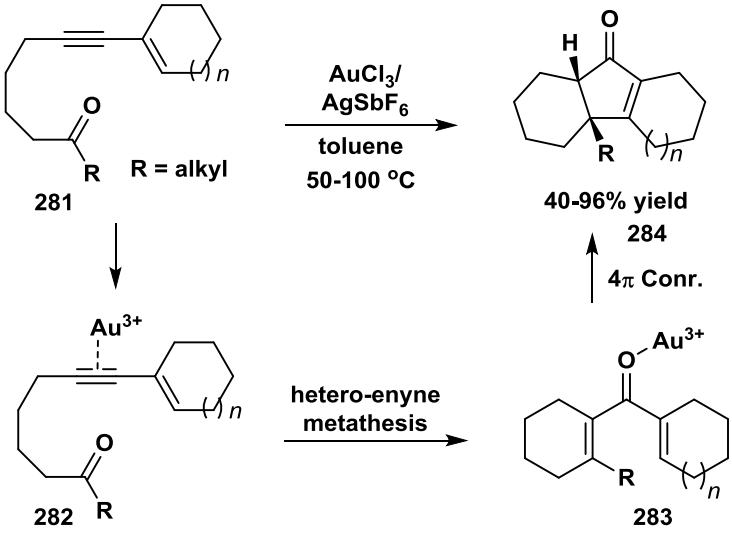
2.1.3 Masked Pentadienyl Cations

Nazarov cyclizations are not limited to typical dienone starting materials. There are a number of important cascade transformations that are capable of generating pentadienyl cations *in situ* from substrates that would otherwise be unrecognizable as pentadienyl cation precursors.

Yamamoto and co-workers have demonstrated the ability of a gold complex to activate both alkynes as well as C=O unsaturated bonds in a single transformation for the *in situ* formation of a divinyl ketone and subsequent Nazarov cyclization.[15] Gold (III) activation of the internal alkyne **281** facilitates hetero-enyne metathesis, forming dienone **283,** which then undergoes an Au(III) mediated Nazarov cyclization (Scheme 40). The reactions are typically performed at elevated temperatures (50–100 ^{o}C) and result in moderate to good yields (40–

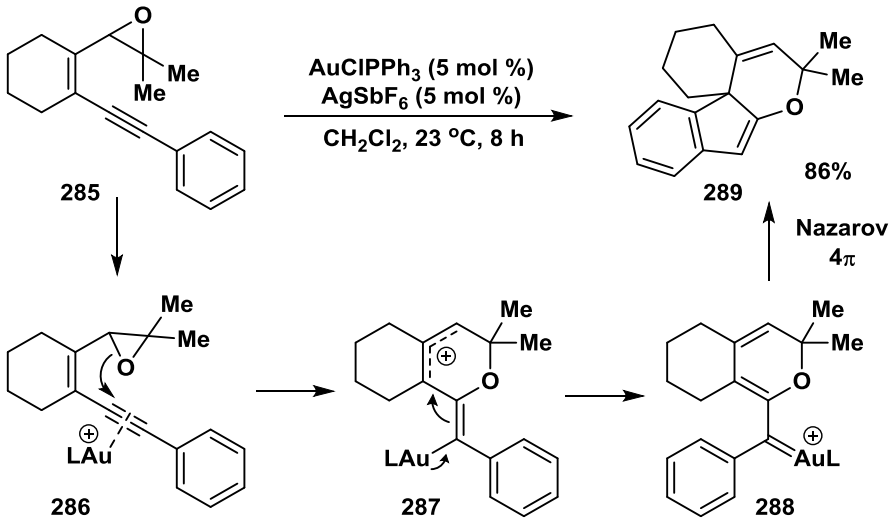
96%). A high degree of diastereoselectivity is usually observed in the desired cyclopentenone products, **284**.

Scheme 40. Gold(I) catalyzed cascade/Nazarov reaction.



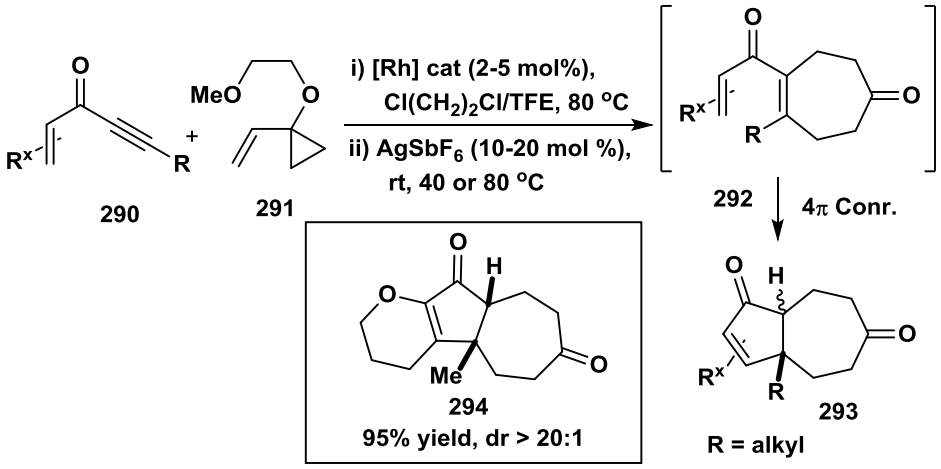
Similarly, a cascade reaction co-catalyzed by $AuClPPh_3$ and $AgSbF_6$ has been developed (Scheme 41).[16] The cascade sequence is believed to generate a pentadienyl cation after forming gold carbene **288**, which undergoes a Nazarov-type cyclization to form **289**. The reaction takes place under mild conditions to give highly substituted 2*H*-pyrans in good yields with high diastereoselectivity.

Scheme 41. Cascade sequence that generates a pentadienyl cation equivalent.



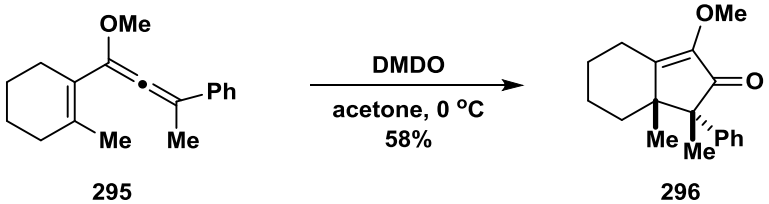
Departing from gold catalyzed rearrangements, a there are many elegant examples of the *in situ* formation of pentadienyl cations. The [5+2] cycloaddition reaction of vinyl cyclopropanes **291** is a powerful strategy for the formation of seven membered rings.[17] Recently, Wender and co-workers applied this methodology in an elegant example that rapidly builds molecular complexity. The tandem reaction sequence forms the requisite dienone **292**, which when treated with catalytic amounts of TMSOTf or $AgSbF_6$ *in situ* cyclize to give fused bicyclo[5.3.0]decanes **293** and **294** (Scheme 42).[18] Both terminal and internal alkynes participate in the reaction.

Scheme 42. [5+2] Cycloaddition of vinyl cyclopropanes.



Frontier and co-workers have shown that oxidation of vinyl alkoxyallenes generates a pentadienyl cation that cyclizes to form cyclopentenones containing quaternary carbon centers in moderate yields, and has been used in natural product synthesis.[19] Variation of the substituents on the vinyl group and on the allene terminus allows for the formation of quaternary stereocenters α or β to the carbonyl. The fully substituted vinyl alkoxyallene **295** cyclizes to form **296** as a single diastereomer bearing vicinal all-carbon quaternary stereocenters (Scheme 43). The polarized nature of the *in situ* generated pentadienyl cation allows for the mild reaction conditions employed.

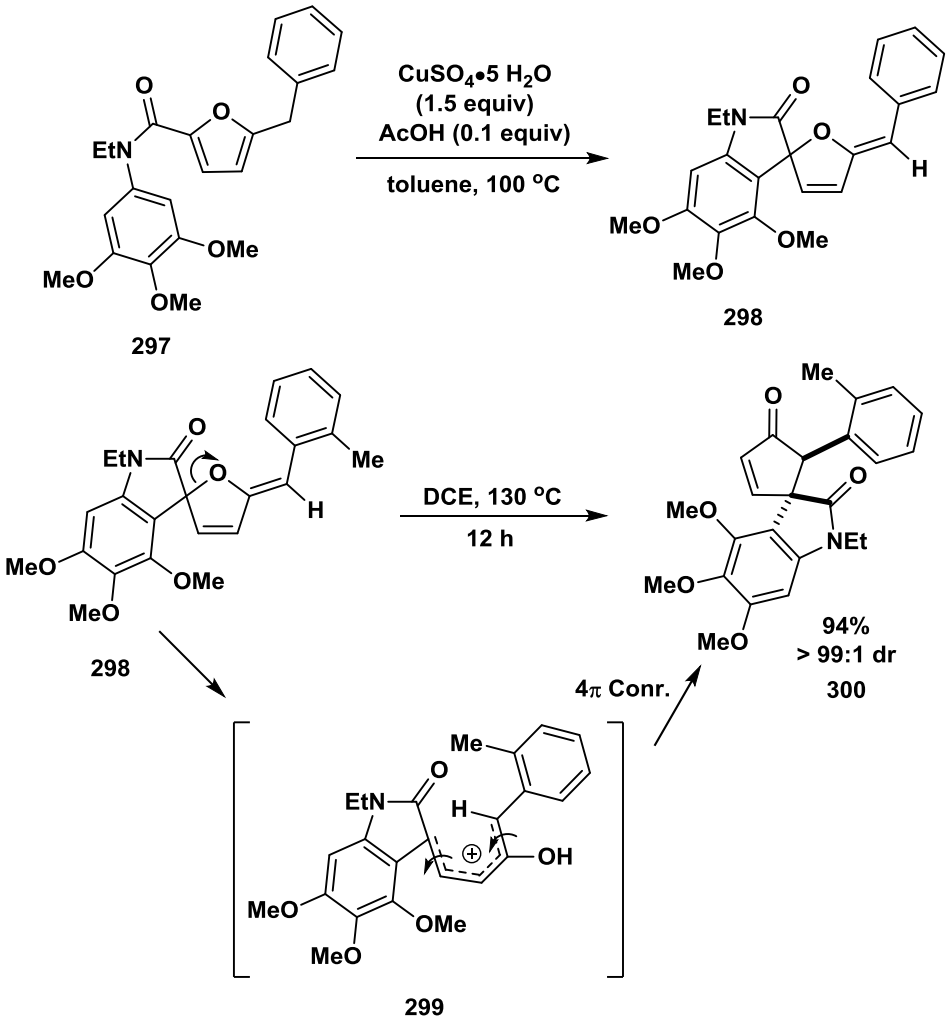
Scheme 43. Oxidative Nazarov reaction.



A carbon based Piancatelli rearrangement would also be a powerful way to rapidly form new types of substituted cyclopentenones. The Yin group has been working towards this

goal using carbon based nucleophiles to trap the oxocarbenium intermediate.[20] At high temperatures, tethered electron rich aryl groups at the 5-position of furan **297** react with furan through a Friedel-Crafts reaction to form spirooxindole **298** (Scheme 44). Subsequent heating of **298** to 130 ^{o}C in dichloroethane leads to the spirocyclic cyclopentenones **300** in very high yield as a single diastereomer.

Scheme 44. The carbon-Piancatelli rearrangement.



2.1.4 Interrupted Nazarov Processes

The interrupted Nazarov reaction describes transformations where a nucleophile intercepts oxyallyl cation **301** prior to elimination, leading to more substituted cyclopentanes (Figure 21). The most well known types of nucleophiles for this process react directly with the tertiary cation in an S_N1 like addition (**302**), or through (3+2) (**303**) and (4+3) (**304**) cycloadditions.

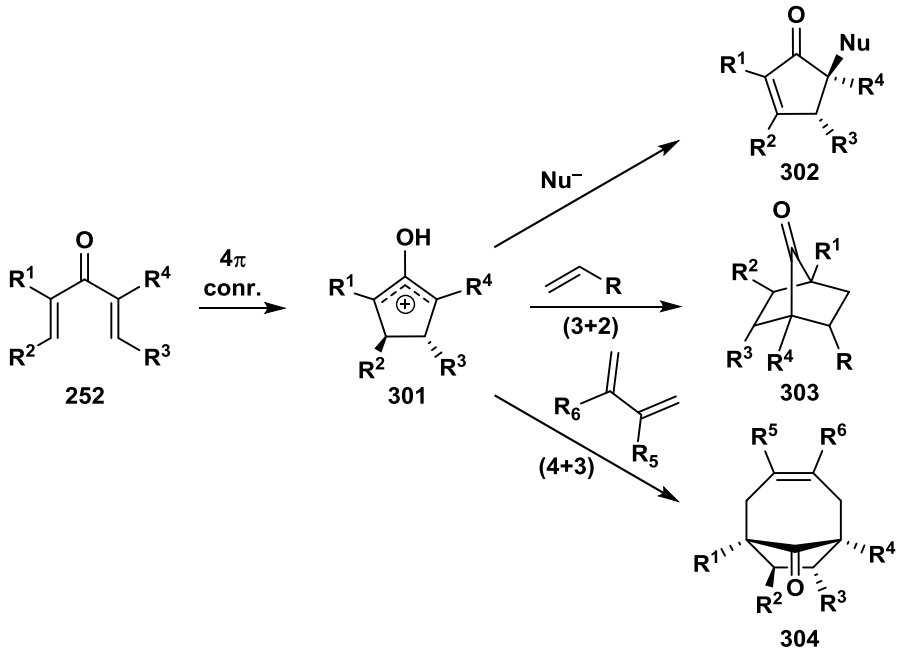


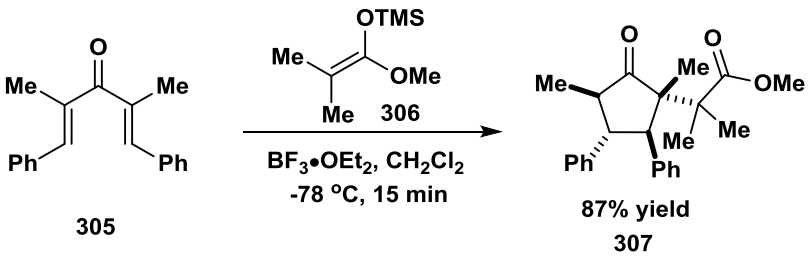
Figure 21. Methods for intercepting the Nazarov oxyallyl cation.

The interrupted Nazarov reaction is especially useful for constructing multiple contiguous stereocenters. Conservation of orbital symmetry dictates that the 4π electrocyclization rotates the terminal carbons of the divinyl ketone in a conrotatory fashion and, in turn, generates products stereospecifically. The newly formed stereocenters direct the interrupting nucleophile, leading to compounds with multiple new stereocenters. Importantly, a high degree of stereochemical control is usually observed.

A comprehensive review of the interrupted Nazarov was published by West in 2009.[2c] A great number of interrupted Nazarov reactions covered in this review form fully substituted carbon centers, and only recent papers in this area will be discussed herein.

West has recently reported that silyl enol ethers **306** can be a useful trap for the interrupted Nazarov reaction with the capability of forming cyclopentenones **307** with up to two contiguous all-carbon quaternary stereocenters (Scheme 45).[21] In order to avoid potential competitive Mukaiyama Michael addition reactions, dibenzylidenepentanone **305** was chosen for their initial investigations because it is known to cyclize rapidly even at low temperatures. A range of silyl enol ethers were examined. High diastereoselectivity was observed using acyclic divinyl ketones. However, cyclic divinyl ketones that form fused polycyclic cyclopentanones gave mixtures of diastereomers. Slower reacting divinyl ketones required higher temperatures (0 ^{o}C or rt) in order to suppress Mukaiyama Michael addition. This is the first general report of the use of enolates to interrupt the Nazarov reaction and form all carbon quaternary stereocenters. Importantly, due to the high nucleophilicity of the silyl enol ethers, no (3+2) cycloadducts were observed. Recently, West and co-workers have reported for the first time the ability to utilize aryl alkynes in the interrupted Nazarov as a homologous enolate equivalent.[22]

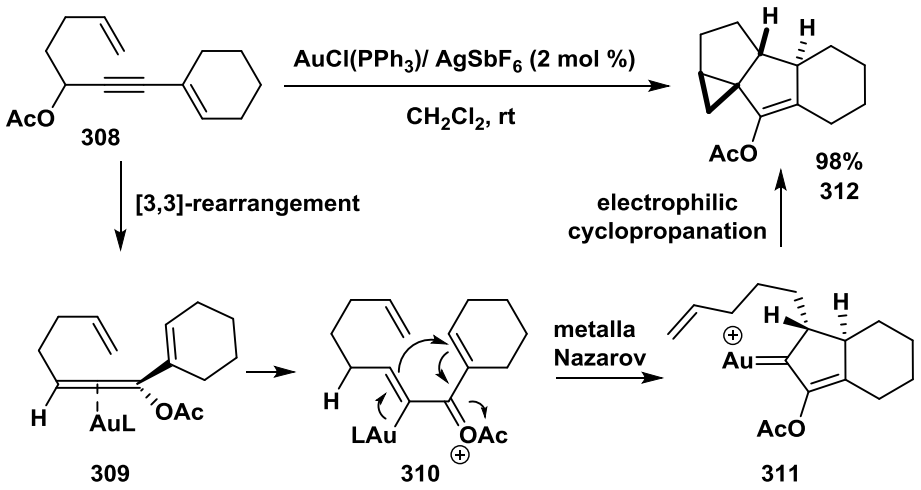
Scheme 45. Interrupting the Nazarov with silyl enol ethers.



Introduction of simple alkyl groups into the terminus of the allyl cation still remains a challenge. West has recently reported that triorganoaluminum reagents can both initiate the Nazarov cyclization and transfer an alkyl group to the resultant allylic cation to form cyclopentanones bearing an all carbon quaternary center α to the carbonyl.[23]

A unique interrupted Nazarov reaction that terminates through formation of a cyclopropane ring was developed by Malacria *et al*.[24] The gold catalyzed rearrangement generates the pentadienyl cation **310** which cyclizes through a metalla-Nazarov reaction (Scheme 46). This results in gold carbenoid **311** which reacts with a tethered olefin to form substituted cyclopropanes **312** in high yield and with high diastereoselectivity.

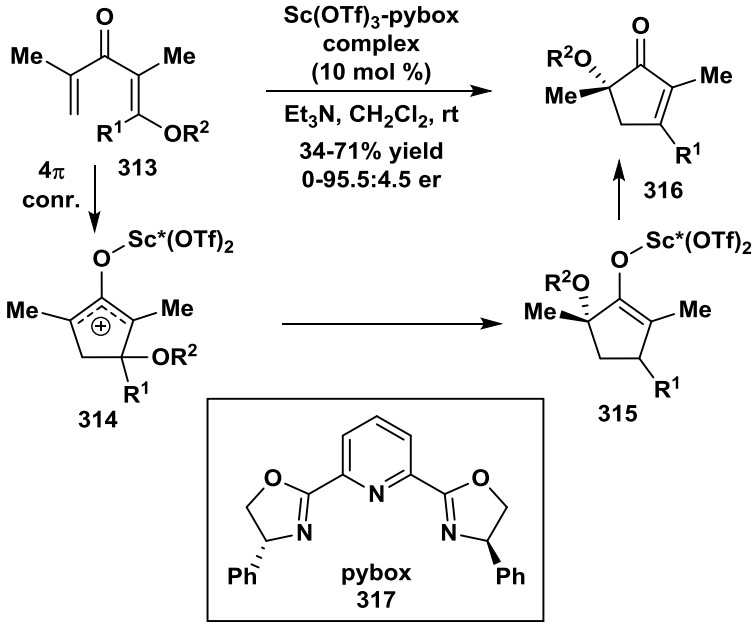
Scheme 46. Gold(I) catalyzed Nazarov reaction.



Shindo and Yanji have reported an asymmetric interrupted Nazarov reaction using chiral $Sc(OTf)_3$-pybox complexes in the presence of 0.7 equiv Et_3N (Scheme 47).[25] After 4π electrocyclization (**313** to **314**), the chiral pybox ligand **317** directs the incoming alkoxy nucleophile stereoselectively to give tertiary alkoxy ethers **316** α to the carbonyl. Optimization experiments indicated that when the amount of pybox ligand was reduced from 1.8 to 1.1 equivalents relative to $Sc(OTf)_3$, the stereoselectivity was completely eroded.

The reasoning for this is that pybox coordination with $Sc(OTf)_3$ releases triflic acid which is capable of catalyzing the reaction in the absence of the chiral complex. Addition of 0.7 equiv Et_3N was found to be optimal for quenching the triflic acid and restoring asymmetric induction. Crossover experiments indicated that the stereocenter was formed through intermolecular attack by an alkoxide. When *i*-PrOH was used as the solvent, their highest level of enantioselectivity was observed, (95.5:4.5 er) presumably due to an accelerated rate of addition into the allylic cation. In general, stereoselectivity is enhanced when the R^2 substituent is large.

Scheme 47. Enantioselective interrupted Nazarov using oxygen nucleophiles.



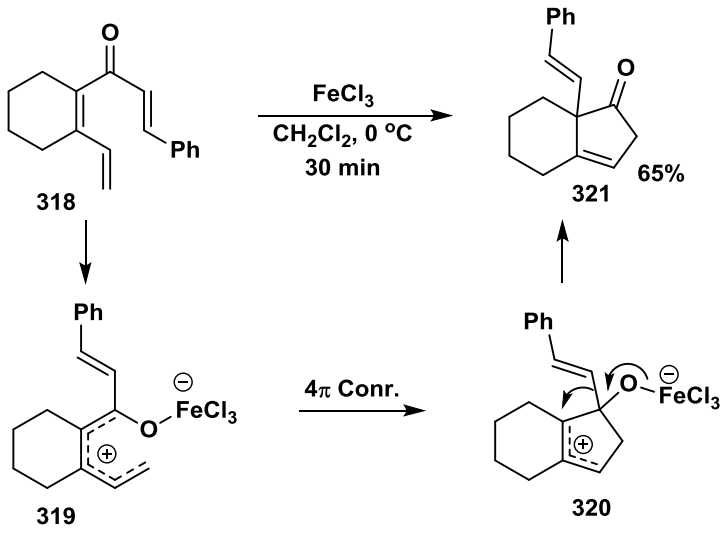
2.1.5 Nazarov/Wagner-Meerwein Shifts

Originally discovered at the turn of the 20th century, Wagner- Meerwein rearrangements are transformations encountered during the formation of carbocationic intermediates. This class of rearrangements encompasses all [1,2]-sigmatropic shifts of hydrogen, alkyl or aryl

groups into a carbocation and results in the formation of a more stable carbocation.[26] Wagner-Meerwein shifts have been observed in Nazarov processes but were often produced in low yield or considered undesirable side products.[26-27]

To our knowledge, the first person to intentionally exploit this process was Denmark.[27c] Denmark and co workers found that dienones **318** bearing a vinyl group at the β carbon of the enone did not cyclize by way of the expected dienone (Scheme 48). Instead, $FeCl_3$ promoted enolization led to enolate **319** which underwent 4π electrocyclization to form **320**, from which a [1,2] cationic shift of the vinyl group took place to form cyclopentenones **321** in moderate yield.

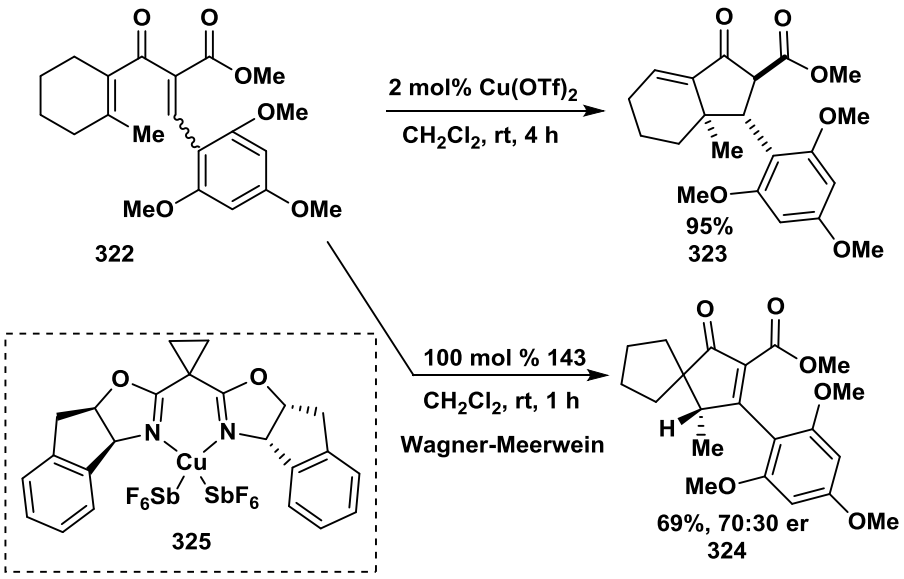
Scheme 48. Iron catalyzed isomerization and electrocyclization to form substituted cyclopentenones.



The Frontier group has been interested in studying tandem Nazarov/Wagner-Meerwein rearrangements to enable new uses for the Nazarov reaction. They discovered that when using stoichiometric amounts of Cu(II) complexes, the Nazarov cyclization of dienones **322**

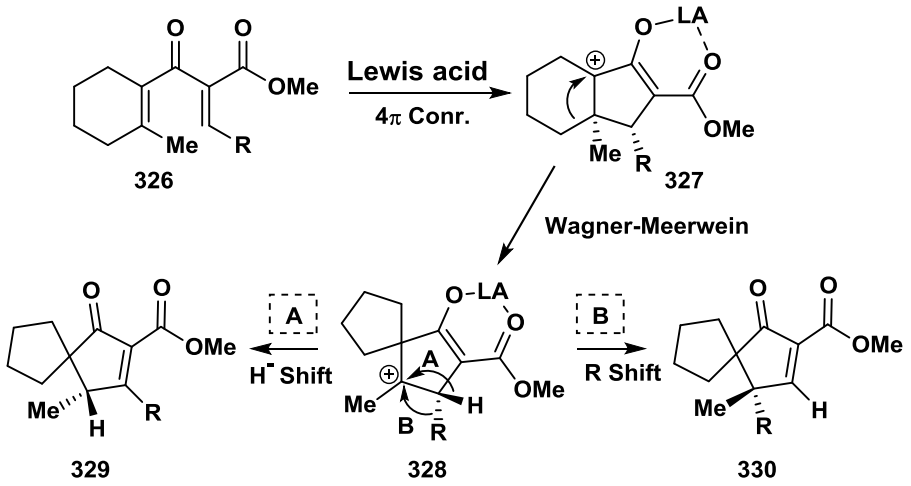
leads to the spirocyclic cyclopentenones **324**, rather than the expected fused system **323** (Scheme 49).[28] Using the chiral copper complex **325**, the spirocyclic products were formed with enantiomeric ratios from 64.5:35.5 to 82:18. The differences in reactivity observed for catalytic and stoichiometric amounts of Cu(II) is believed to be due to the Lewis basic carbonyl oxygens. The Lewis basicity of the carbonyl oxygens is thought to enhance the rate of elimination to form fused products. However, when stoichiometric amounts of Cu(II) are employed, the carbonyl oxygens are saturated by the catalyst and elimination is suppressed, permitting the Wagner-Meerwein rearrangement to occur to form spirocycle **324**.

Scheme 49. Copper catalyzed Nazarov cyclization leading to different products.



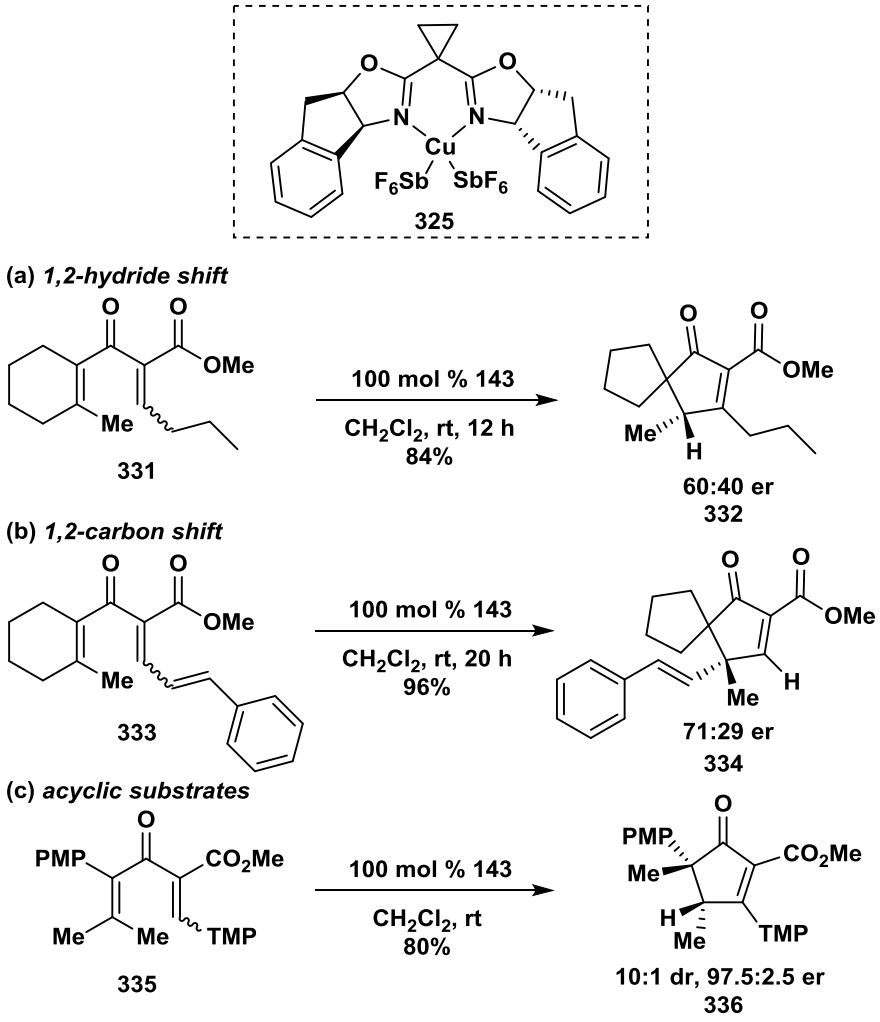
Concerning the mechanism of the Wagner-Meerwein shift, the cationic [1,2] shifts happen in a suprafacial manner with retention of stereochemistry. In the case of Frontier's rearrangements, two consecutive [1,2] shifts are observed (Figure 22). After electrocyclization to form **327** the first [1,2] cationic shift generates cation **328**, and then depending on the migratory aptitude of the group, either a hydride or an R group undergoes subsequent [1,2] migration to form structures **329** or **330** respectively.

Figure 22. Cationic Wagner-Meerwein shifts.



The chemoselectivity of the second [1,2]-shift is dependent on the migratory aptitude and steric profile of the migrating group and promoter. Alkyl substituted dienone **331** undergoes a hydride shift to give cyclopentenone **332** in 84% yield and 60:40 er (Scheme 50). With a higher migratory aptitude, cinnamyl substituted dienone **333** undergoes [1,2]-suprafacial migration to give **334** bearing vicinally substituted all carbon quaternary stereocenters in 96% yield as a single diastereomer with a 71:29 er.[29] Acyclic substrates also undergo cationic shifts. Divinyl ketone **335** reacts to form cyclopentenone **336** with 10:1 dr and in 97.5:2.5 er.[30]

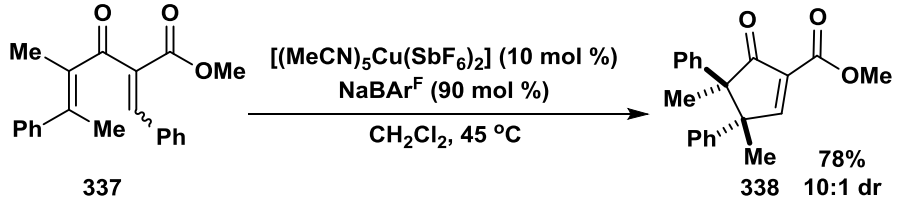
Scheme 50. Meerwein-Wagner (a) 1,2-hydride shift (b) 1,2-carbon shift (c) 1,2-shifts on acyclic substrates.



It is believed that stoichiometric copper is required to suppress elimination by coordinating with and attenuating the Lewis basicity of the carbonyl oxygens. Based on this theory, Frontier has found that addition of a non catalytic sodium salt, sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr^F$), is able suppress elimination and promote [1,2]-migration. Indeed, only 10 mol % Cu(II) is necessary to promote [1,2]-migration when 90 mol % $NaBAr^F$ is added (Scheme 51).[30,29b] Eisenberg and Frontier have developed iridium(III) catalysts that are efficient promoters of the Nazarov reaction[31] that are also

capable of catalytic promotion of tandem Nazarov/Wagner-Meerwein reactions in the presence of $NaBAr^F$ (not shown).[32]

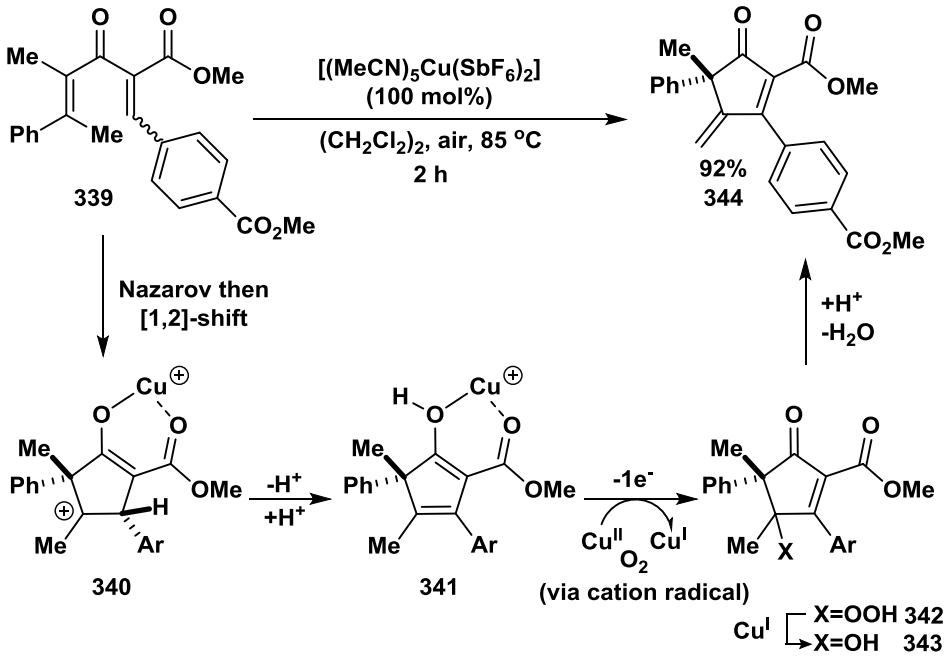
Scheme 51. Nazarov/Wagner-Meerwein [1,2]-shift enabled by addition of $NaBAr^F$.



BAr^F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

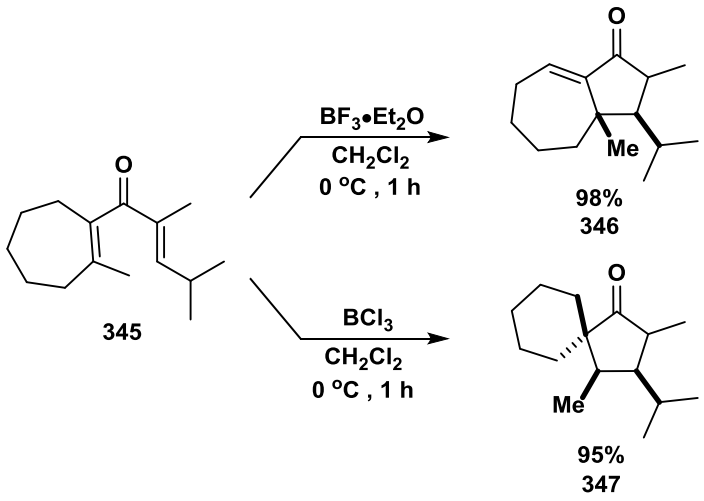
In general, Nazarov substrates bearing electron donating groups at the C5 terminus of the dienone react more efficiently and selectively than substrates bearing electron withdrawing groups. While attempting to overcome this limitation, the Frontier group discovered that by changing solvents to dichloroethane and allowing oxygen into the system, the rearrangement terminates by a Cu(II) promoted oxidation to form 4-alkylidene cyclopentenones **344** (Scheme 52).[33] Mechanistic experiments suggest that after the Nazarov cyclization of **339**, a [1,2]-carbon shift takes place to form carbocationic intermediate **340**. Next, loss of the acidic C5 proton forms the extended enol **341**. Oxidation by copper(II) gives an enol cation radical, which is intercepted by dioxygen to produce the unstable hydroperoxide **342**. The hydroperoxide is reduced to the alcohol **343** through a Fenton-type fragmentation, which subsequently eliminates to form the 4-alkylidene cyclopentenone **344**.[34] This methodology has been applied to the construction of complex natural products.[35]

Scheme 52. Formation of 4-alkylidene cyclopentenones by carbon catalyzed rearrangement and oxidation.



In their efforts towards the synthesis of the diterpenoid guanacastepene A, Chiu studied a Nazarov reaction that would lead directly to the core of the natural product (Scheme 53).[4c] Remarkably, the choice of Lewis acid leads to either classic Nazarov elimination when using BF_3•Et_2O (**346**), or a Wagner-Meerwein shift when using BCl_3 (**347**) to give fused or spirocyclic cyclopentenones in high yields and good diastereoselectivity.

Scheme 53. Reactivity differences affected by choice of Lewis acid.



2.1.6 Conclusion

Continuous development of the Nazarov reaction has led to powerful new ways to use this reaction for forming densely substituted cyclopentane scaffolds. The Nazarov reaction offers a number of unique features that make it particularly attractive for this task. The 4π conrotatory electrocyclization of the pentadienyl cation generates two new stereocenters upon cyclization and forms a reactive oxyallyl cation that can undergo subsequent stereoselective reactions. The creative forces that have advanced the Nazarov reaction have developed a number of ways to generate the pentadienyl cation and to harness the reactivity of the resultant oxyallyl cation to stereoselectively control the formation of fully substituted carbon stereocenters at nearly any position around the cyclopentane ring.

The work described here illustrates the three general methods for forming fully substituted carbon stereocenters using the Nazarov reaction. When starting with a fully substituted terminal dienone, or when forming one *in situ*, up to two contiguous quaternary stereocenters can be formed by joining these C–C bonds together during the 4π

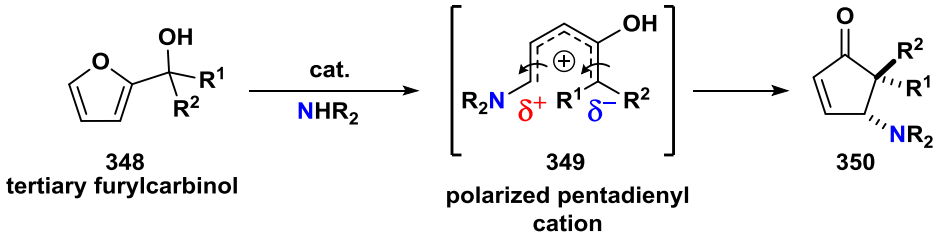
electrocyclization. Under classical Nazarov conditions, this is often challenging due to steric considerations and may result in undesirable side products. However, polarization of divinyl ketones is an effective strategy for lowering the barrier to cyclization, which helps to increase reaction efficiency when bringing sterically congested dienones together. The second method is trapping of the oxyallyl cation in what is known as the interrupted Nazarov. After cyclization, the stereocenters formed from conrotatory electrocyclization direct the addition of an incoming nucleophile. These processes are often highly stereoselective and in many cases give only a single diastereomer of products with multiple contiguous stereocenters. Lastly, once thought of as a troublesome side reaction, cationic [1,2]-Wagner-Meerwein shifts can be exploited for the formation of fully substituted carbon centers, with a high degree of stereochemical control.

2.2 Tertiary Furylcarbinols for the aza-Piancatelli Rearrangement

2.2.1 Hypothesis

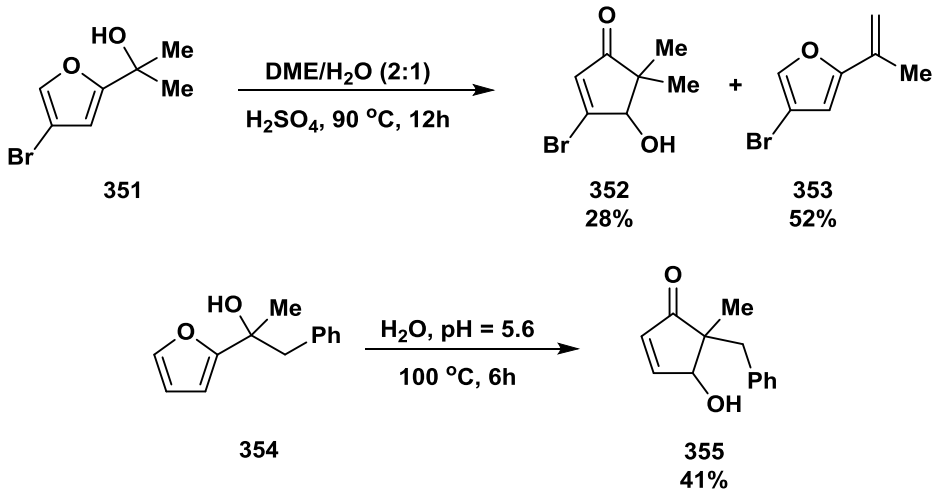
After the successful development of an aza-Piancatelli rearrangement, we wished to explore the scope of more elaborate furylcarbinols which would produce higher substituted cyclopentenone products. Formation of all-carbon quaternary stereocenters is a challenging task, but as previously shown, it has been well established that polarized Nazarov pentadienyl cations can be an effective way to form these challenging motifs. We were encouraged by the observation that the Piancatelli rearrangement also cyclizes by way of a polarized pentadienyl cation **347**, and were enticed by the possibility of using the aza-Piancatelli to form an all-carbon quaternary stereocenter α to the carbonyl **350** (Scheme 54).

Scheme 54. Hypothetical rearrangement of tertiary furylcarbinols.



The usage of tertiary furylcarbinols in the original Piancatelli rearrangement has only been briefly investigated (Scheme 55). Rearrangement of the bismethyl furylcarbinol **351** produced only 28% of the desired cyclopentenone **352**, while the majority of the starting material undergoes a competitive elimination reaction to form olefin **353** in 52% yield.[36] Even under controlled pH adjusted reaction conditions, only moderate yields of the cyclopentenone **355** were obtained.[37]

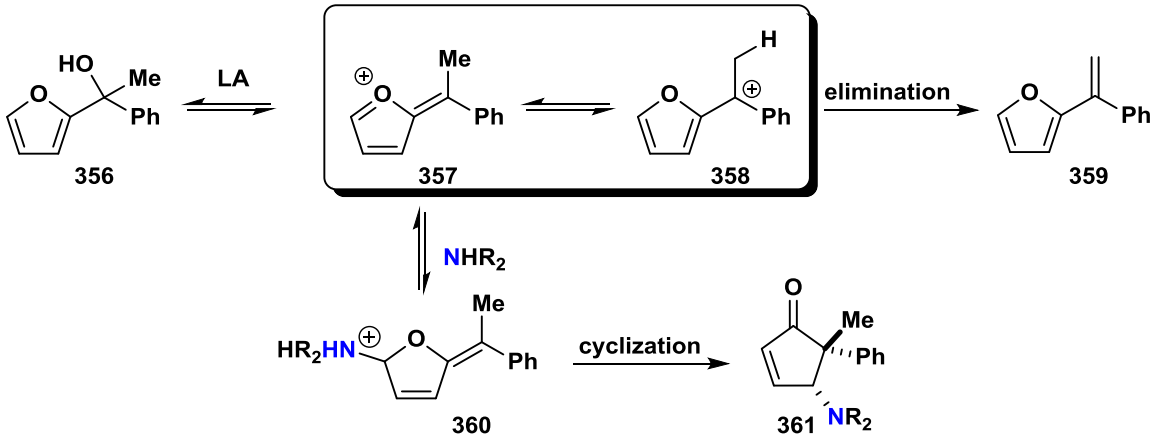
Scheme 55. Reactivity of tertiary furylcarbinols in the Piancatelli rearrangement.



The poor yields that Piancatelli obtained when attempting to utilize tertiary furylcarbinols are due to a competitive elimination reaction (Scheme 56). After activation and loss of water from the furylcarbinol, the intermediate carbocation can exist in two major resonance forms: oxocarbenium **357** and tertiary carbocation **358**. The tertiary carbocation

resonance form is very susceptible to elimination when there is a proton α to the cation, and leads to the elimination product **359**.

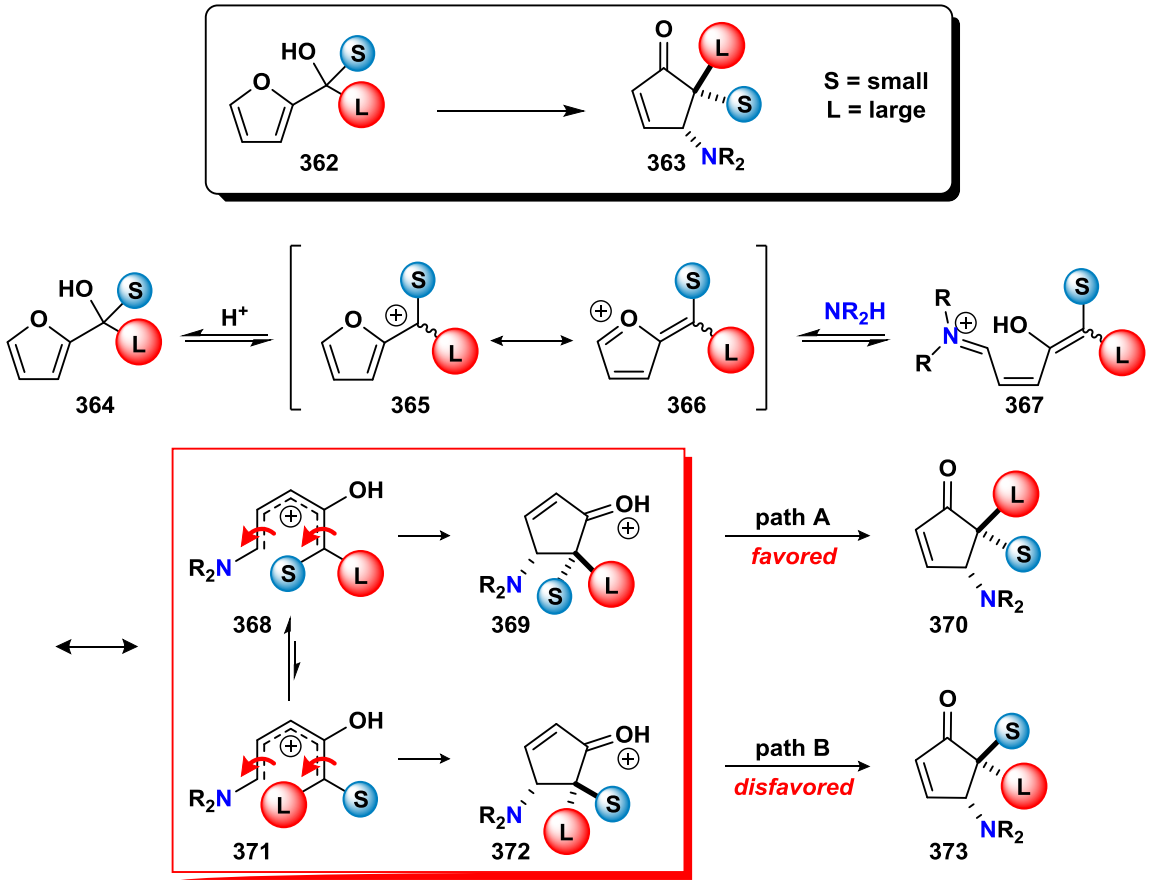
Scheme 56. Competitive elimination using tertiary furylcarbinols.



We were interested in doing a full examination into the behavior of tertiary furylcarbinols using our newly developed conditions for the aza-Piancatelli rearrangement. We proposed that our new catalytic and potentially milder conditions would favor formation of the cyclopentenone and be less susceptible to the undesired elimination pathway. Additionally, if the conrotatory electrocyclization is the stereodetermining step, then the size of the substituents at the termini of the pentadienyl cation would help to control the relative stereochemistry set during ring formation. This rational is based on the idea that, prior to electrocyclization, two olefin geometries are possible for the pentadienyl cation intermediate **368** or **371** (Scheme 57). Intermediate **368** on path A orients the smaller group on the inward side of the pentadienyl cation, and for path B, the larger group would be oriented inward for **371**. We hypothesized that path A should be preferred over path B because the larger of two groups would cause more steric repulsion while trying to adopt the requisite pentadienyl

cation geometry. Based on this model, the reaction should preferentially produce cyclopentenones **370** with a *trans* relationship between the aniline and larger substituent.

Scheme 57. Rational for controlling diastereoselectivity.



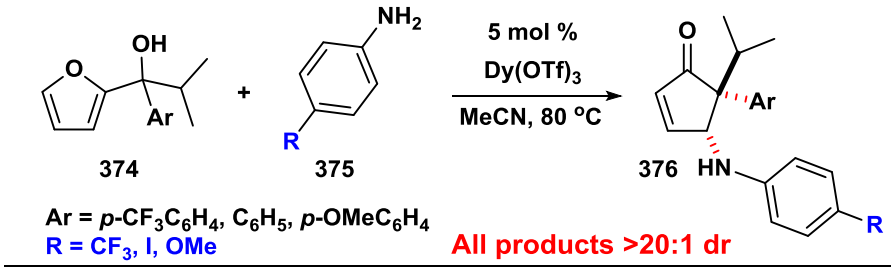
2.2.2 Results

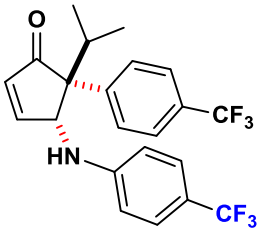
Our investigation began with the synthesis of tertiary furylcarbinols bearing an alkyl group and a neutral, electron donating (EDG) or electron withdrawing (EWG) aryl groups (Table 16). These substrates were allowed to react with electron donating or withdrawing anilines. Starting with bulky isopropyl substituted furylcarbinols **374**, we found the transformation to be highly diastereoselective (>20:1) in all cases while obtaining modest to poor yields of **377**-**385**. The relative stereochemistry also agreed with our predictions that

the bulky isopropyl group would be oriented outwards in the pentadienyl cation transition state and form a cyclopentenone with a *trans* relationship between the aniline and alkyl substituent. The relative stereochemistry was determined by Nuclear Overhauser effect spectroscopy (NOESY) (Figure 23).

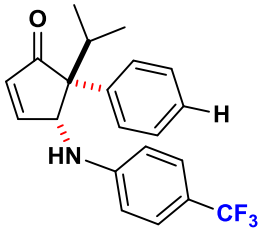
We briefly investigated the affect of changing the order of addition of the reagents. The reactions are normally setup by dissolving the furylcarbinol in MeCN, then adding the aniline followed by addition of the catalyst and then heating. An experiment was performed where 4-iodoaniline was premixed with 5 mol % $Dy(OTf)_3$ in MeCN then heated to 80 ^{o}C. Next, phenyl isopropyl furylcarbinol was added. The reaction was complete in 30 minutes and gave **381** in 43% yield, which is comparable to the standard method.

Table 16. Investigation using isopropyl substituted tertiary furylcarbinols.

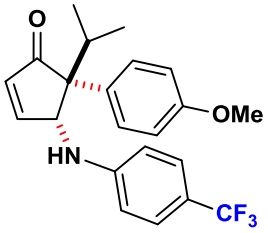




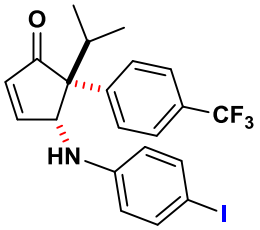
377 (73%, 2h)



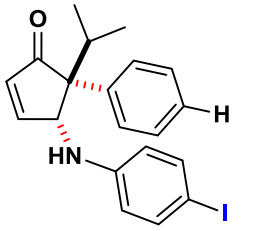
378 (69%, 30 min)



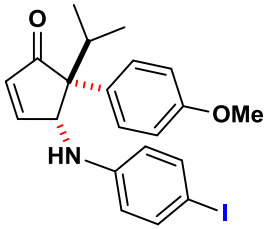
379 (69%, 10 min)



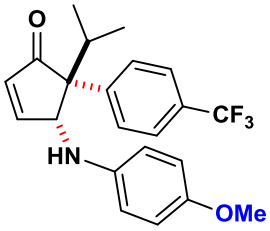
380 (52%, 3 h)



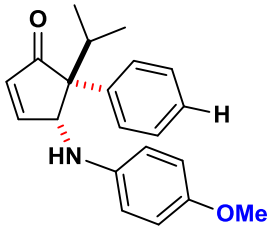
381 (43%, 1 h)



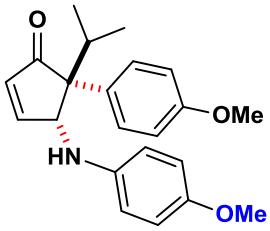
382 (42%, 15 min)



383 (16%, 72 h)



384 (69%, 46 h)



385 (79%, 5 h)

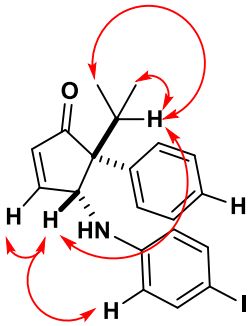
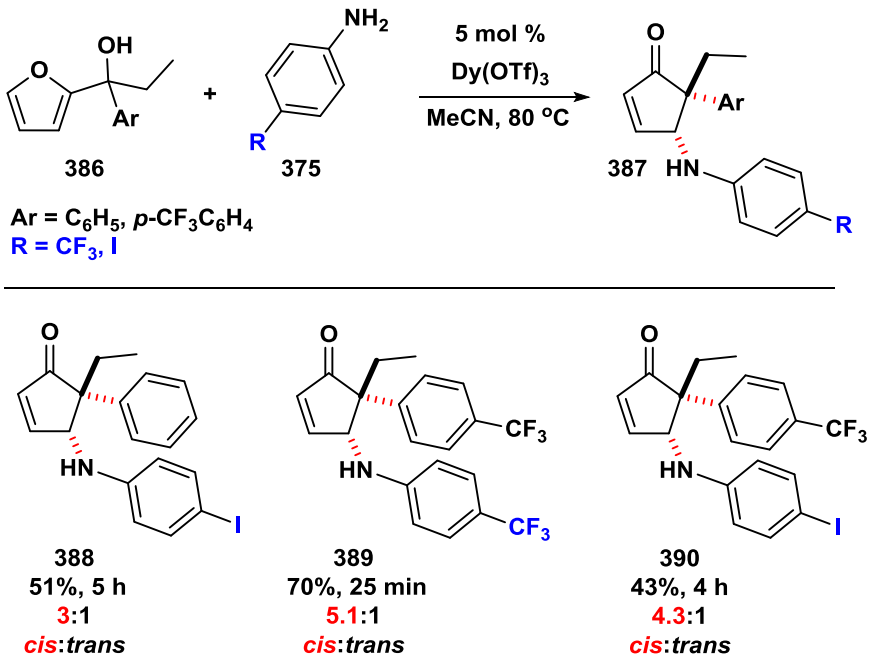


Figure 23. NOESY correlations for 381.

Switching to an intermediately sized ethyl group **386** resulted in a decrease in diastereoselectivity, and produced cyclopentenones **388**, **389** and **390** in moderate yields (Table 17).

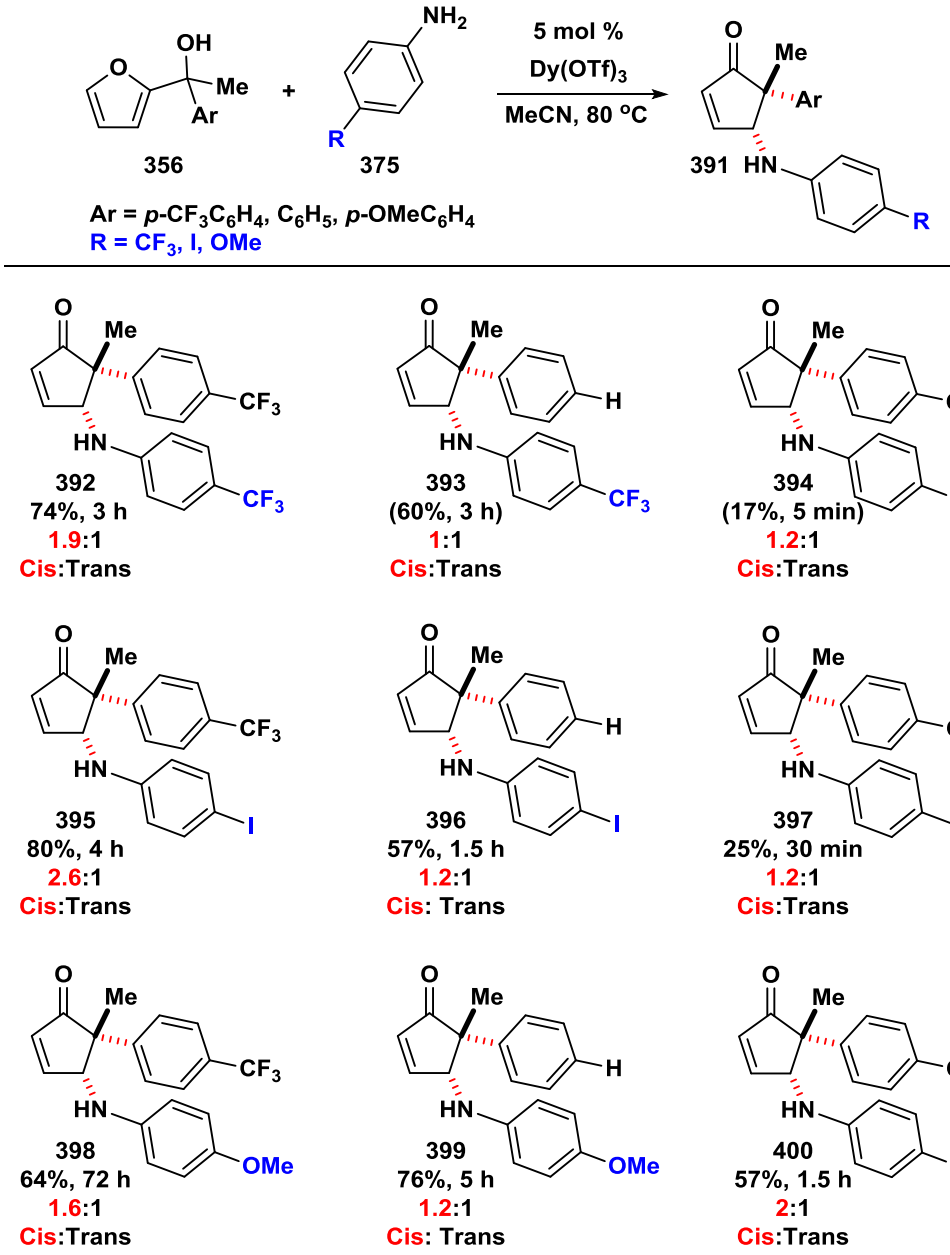
Table 17. Ethyl group decreases diastereoselectivity.



Further reducing the size of the alkyl group to methyl **356** continued to erode the diastereoselectivity to less than 2:1 for most substrates, with modest to poor yields for **392-400** (Table 18). Interestingly, major diastereomer of these cyclopentenones still orients the

methyl group with a *trans* relationship to the aniline, indicating that in our steric model, the methyl group is acting as a larger group than the aryl group. This might be due to the planarity of the aryl group since it can twist out of plane to prevent unfavorable interactions, its ability to participate in π-stacking with the aniline, or other subtle electronic effects the aryl group might impart on the fully conjugated pentadienyl cation intermediate.

Table 18. Investigation using methyl substituted tertiary furylcarbinols.



Piancatelli had observed that tertiary furylcarbinols were prone to eliminating to form terminal olefins, and our results are consistent with this finding. Importaintly, substrates such as bis-phenyl furylcarbinols **401**, **402** and **403** which cannot form products from elimination, produced the desired cyclopentenones in high yield. Interestingly, there seems to be a small electronic component responsible for controlling the diastereoselectivity, since

for substrates **401** and **402**, the cyclopentenones were obtained with a small enrichment of one diastereomer (Figure 24). These results demonstrate that the aza-Piancatelli cascade rearrangement is a viable transformation to form all-carbon quaternary stereocenters but that competitive elimination from the initially formed carbocation is the most significant drawback.

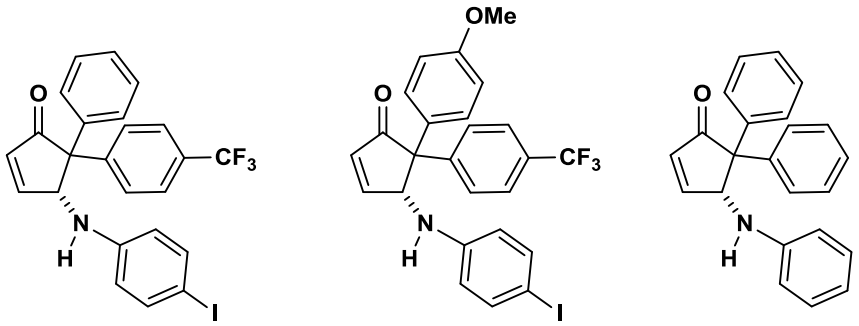


Figure 24. Bis-aryl cyclopentenones.

2.2.3 Conclusion

The Nazarov cyclization using polarized pentadienyl cations is a powerful and versatile method for forming all-carbon quaternary stereocenters. The Piancatelli and aza-Piancatelli rearrangement both cyclize by way of a polarized pentadienyl cation and both are capable of forming an all carbon quaternary stereocenter α to the carbonyl. However, currently the usage of tertiary furylcarbinols to accomplish this task is limited due to competitive elimination reactions and the diastereoselectivity is difficult to control. We have concluded that while the aza-Piancatelli rearrangement has the potential to be rapid way to generate polarized Nazarov substrates, the current method to initiate the rearrangement is limited due to the nature of the newly generated tertiary furylcarbinol. We hypothesize that if we could develop a new method to access the pentadienyl cation intermediate that is not susceptible to

the elimination reaction, that the aza-Piancatelli rearrangement would be a new and potentially powerful way to generate cyclopentenones bearing all-carbon quaternary stereocenters. Providing a solution to this problem is the subject of Chapter 3.

2.3 References

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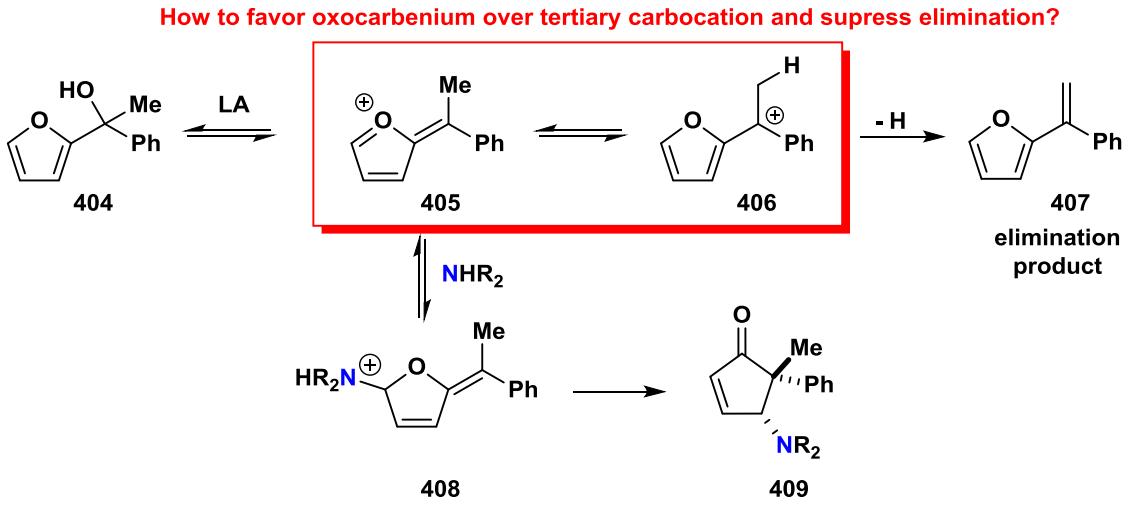
3. Donor-Acceptor Cyclopropanes as a New Activating Group for the aza-Piancatelli Rearrangement

3.1 Introduction

The results from our survey of tertiary furylcarbinols suggest that the traditional mode of activation using a hydroxyl leaving group is limited to secondary furylcarbinols due to the competitive formation of elimination side products and poor diastereochemical control observed using tertiary furylcarbinols. The limitations associated with tertiary furylcarbinols made it clear that a new activating group would be needed in order to utilize an aza-Piancatelli rearrangement to form cyclopentenones bearing all-carbon quaternary stereocenters (Scheme 58). We rationalized that replacing the hydroxyl group with any other leaving group would lead to the formation of a reactive tertiary carbocation, and therefore, an entirely new type of activating group would be needed.

Scheme 58. Problems associated with tertiary furylcarbinols.



Donor-acceptor (D-A) cyclopropanes are known to act as latent carbocations. Due to the inherent ring strain (27.5 kcal/mol) and complimentary push-pull polarization of D-A cyclopropanes, they are prone to ring opening reactions through cleavage of the carbon-carbon bond that connects the donor and acceptor groups.[1] During the course of D-A cyclopropane ring opening reactions, partial positive charge builds up on the carbon adjacent to the donor group and partial negative charge builds up on the acceptor portion (**410**). We hypothesized that a Lewis acid could be used to activate the furyl cyclopropane **410**, leading to either ring opening or buildup of positive charge on the donor carbon, which would activate the furan to nucleophilic attack (Figure 25). Attack by an amine would form the proposed intermediate **411** which would then participate in a series of cascade reactions to ultimately form 4-amino cyclopentenones **412** bearing a fully substituted carbon stereocenter.

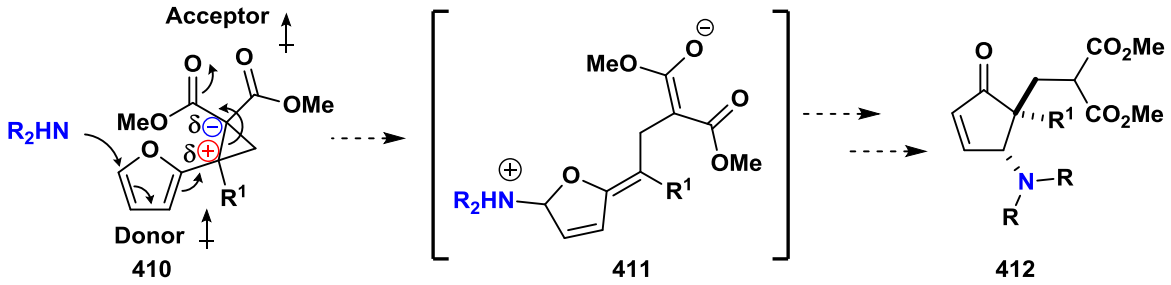
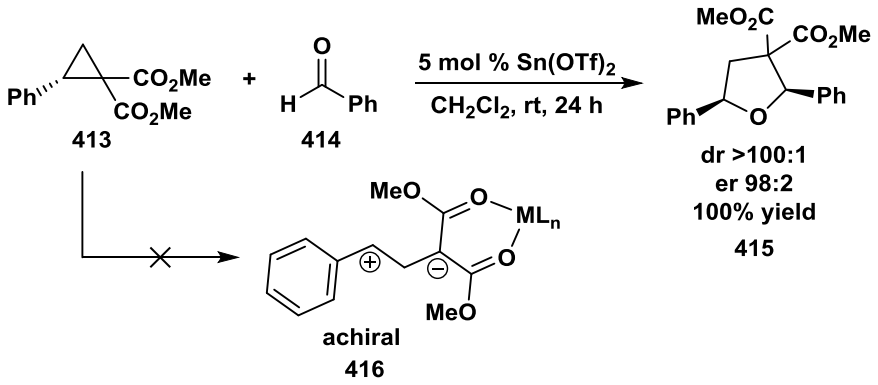


Figure 25. Hypothetical reactivity of furylcyclopropanes.

Work performed by Johnson and co-workers revealed that, under mild conditions, (3+2) cycloaddition reactions with D-A cyclopropanes will retain and transfer the stereochemical information from the starting material **413** to product **415** (Scheme 59).[2] This report was encouraging to us because it indicated that the cyclopropane **413** does not open prematurely and form the achiral zwitterionic species **416** prior to the cycloaddition. Instead, Lewis acid

activation induces polarization and buildup of partial positive and negative charge across the cyclopropane C–C bond which the aldehyde **414** reacts with. Importantly, Johnson's work revealed that the aldehyde reacts prior to cyclopropane ring opening. This was the type of reactivity we hoped to observe by using furyl-substituted D-A cyclopropanes for the aza-Piancatelli rearrangement in order to avoid the formation of a carbocation that would be prone to elimination. However, even in the event that cyclopropane ring opening occurred prior to attack by nitrogen, we hypothesized that the zwitterionic nature of the intermediate would provide a stabilizing effect on the carbocation and help to prevent elimination side products.

Scheme 59. (3+2) Cycloaddition with transfer of stereochemistry from a D-A cyclopropane.



3.2 Tri-Substituted Donor-Acceptor Cyclopropanes

3.2.1 Introduction

While there are a number of methods for synthesizing D-A cyclopropanes, methods to construct tetra-substituted cyclopropanes **418** that would produce cyclopentenones bearing an all-carbon quaternary center are scarce (Figure 26). In order to quickly evaluate the

feasibility of this new activating group we first synthesized the tri-substituted furylcyclopropane **417**, and investigated this substrate with various types of amine nucleophiles.

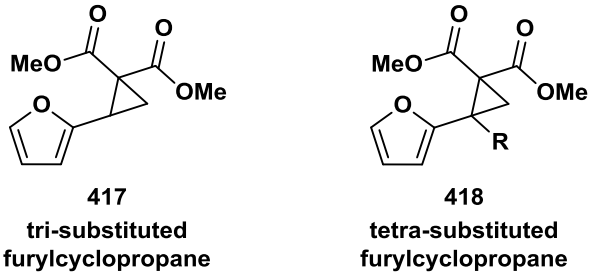
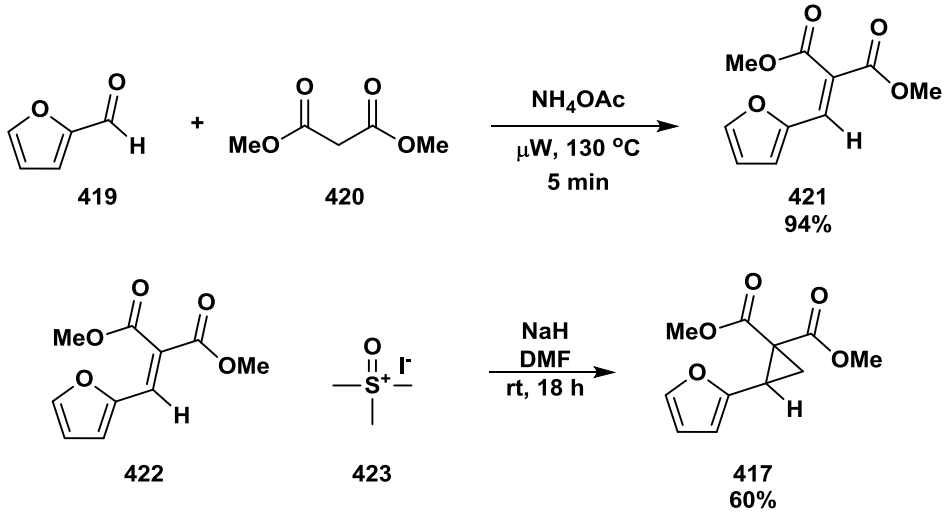


Figure 26. Tri- and tetra-substituted furylcyclopropanes.

The synthesis of tri-substituted cyclopropanes is straightforward. Knoevenagel condensation between furfural **419** and dimethyl malonate **420** afford olefin **421** in high yield (Scheme 60).[3] Corey–Chaykovsky cyclopropanation using trimethylsulfoxonium iodide **423** in the presence of sodium hydride affords the furylcyclopropane **417**.[4]

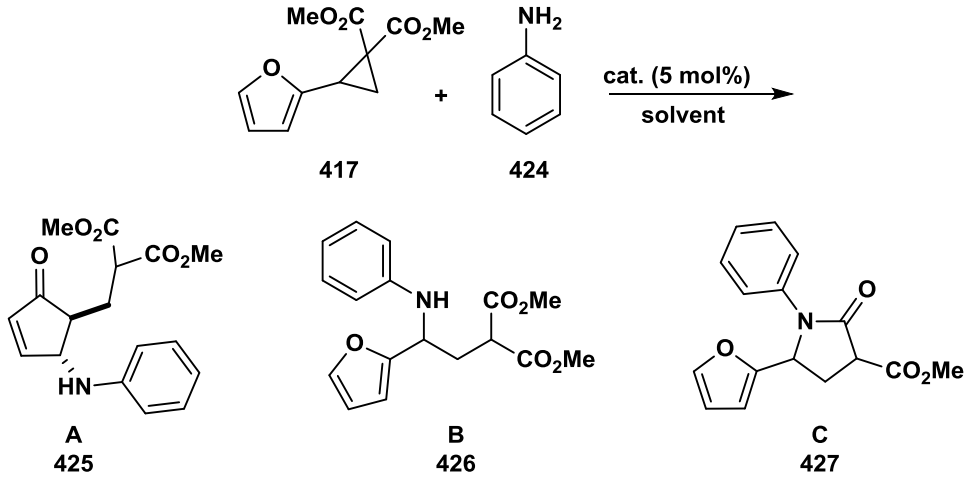
Scheme 60. Synthesis of tri-substituted furylcyclopropanes.



3.2.2 Reaction Optimization

With furyl cyclopropanes in hand, solvent and Lewis acid screens were performed. Reactions using $Dy(OTf)_3$ in methanol (entry 1) and toluene (entry 2) appeared to give only homo-conjugate products **426**, where the amine attacks the electron deficient cyclopropane carbon. These reactions were slow and typically required four days to go to completion. Upon workup we discovered that the product that resulted from these reactions is the corresponding lactam **427**, which results from initial homo-conjugate addition by aniline, followed by intramolecular amidation.[5] In THF, only homo-conjugate addition product **426** was formed in 59% yield (entry 3). Using our previously established conditions employing MeCN, the reaction proceeds by first forming the homo-conjugate addition product **426**, which, over time, rearranges to the desired cyclopentenone **425**. In MeCN, the reaction is complete in 18 hrs and produces 48% of the desired cyclopentenone **425** (entry 4). To our gratification, upon switching to the polar aprotic solvent nitromethane ($MeNO_2$), the reaction is complete in 1 hr and gives cyclopentenone **425** in 77% yield (entry 5). In $MeNO_2$, the reaction still proceeds through the homo-conjugate addition adduct, which is observed by TLC. However, in $MeNO_2$, this addition adduct turns over much more quickly to the desired cyclopentenone. At room temperature, the homo-conjugate addition product **426** is obtained in 98% yield in 10 minutes (entry 6). Other rare earth lanthanide triflates also catalyze the reaction in good yields (entries 7 and 8), but $Dy(OTf)_3$ was chosen because it is inexpensive and due to our long term interest in this Lewis acid.[6]

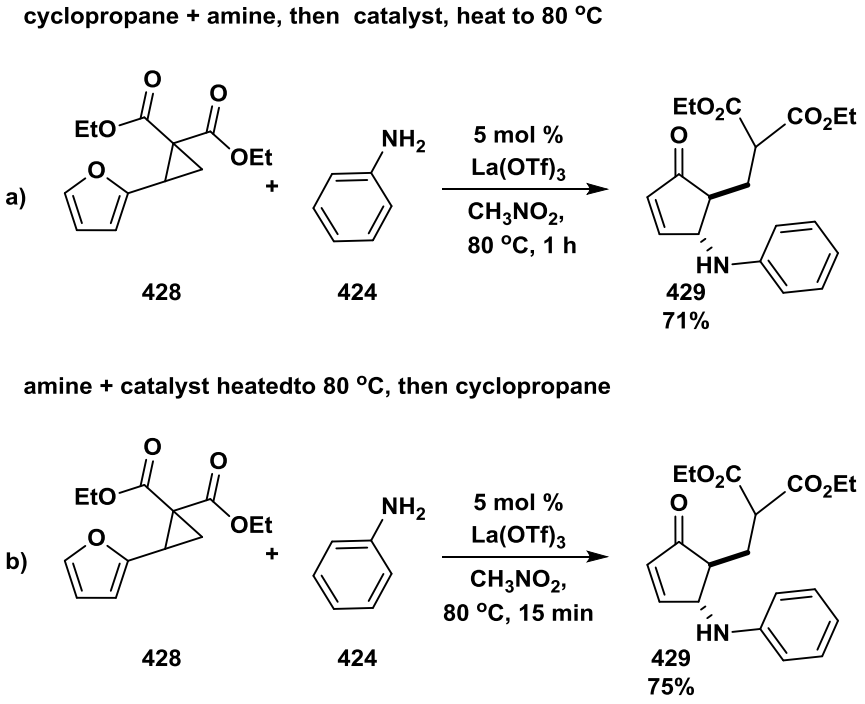
Table 19. Reaction optimization with furylcyclopropanes.



entry	solvent	catalyst (5 mol %)	time	temp (^{o}C)	yield % (A:B:C)
1	MeOH	$Dy(OTf)_3$	4 days	64	0:0:48
2	toluene	$Dy(OTf)_3$	4 days	80	0:0:62
3	THF	$Dy(OTf)_3$	4 days	66	trace:59:trace
4	MeCN	$Dy(OTf)_3$	4 days	80	48:0:0
5	$MeNO_2$	$Dy(OTf)_3$	1 h	80	77:0:0
6	$MeNO_2$	$Dy(OTf)_3$	10 min	23	0:98:0
7	$MeNO_2$	$Yb(OTf)_3$	1 h	80	75:0:0
8	$MeNO_2$	$La(OTf)_3$	1 h	80	60:0:0

The order of addition of reagents into the reaction mixture can affect the rate of the reaction. The standard protocol for setting up the reactions is to premix the furylcyclopropane and the amine in the desired solvent, followed by addition of the catalyst, and then heat the reaction to the desired temperature (Scheme 61, a). When the aniline and catalyst are premixed and heated to 80 ^{o}C followed by the addition of the furylcyclopropane, the reaction was complete in 15 minutes and produced the desired cyclopentenone in good yield (Scheme 61, b).

Scheme 61. The effect of changing the order of reagent addition.

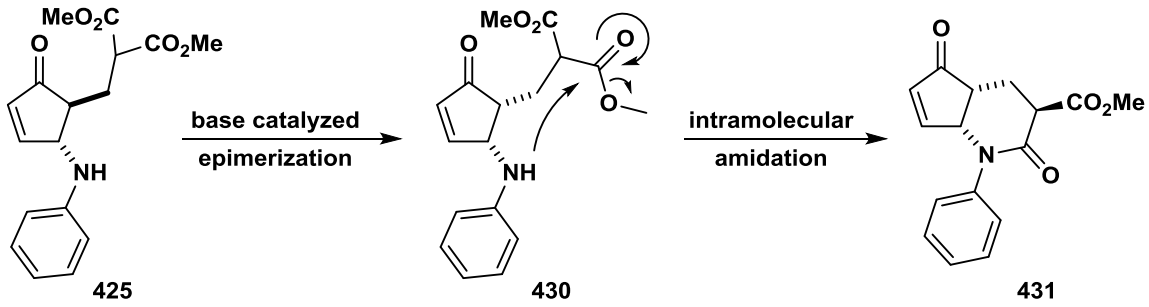


Similarly to what we observed with simple furylcarbinols, the furylcyclopropanes are not stable under the reaction conditions, and in the absence of a nucleophile a mixture of unidentifiable products results. Furylcyclopropanes and amine nucleophiles (4-iodoaniline and piperidine) fail to react in the absence of a Lewis acid catalyst at temperatures up to 100 ^{o}C. Aliphatic amines also failed to give desirable products while attempting to use various Brønsted or Lewis acid catalysts.

We found the intramolecular amidation reaction that forms **427** interesting, and we wondered if we could utilize the reactivity of the pendant malonate and aniline to form fused bicyclic compounds **431** from the 4-amino cyclopentenone **425** (Scheme 62). We hypothesized that the *trans* relationship between the substituents on the cyclopentenone ring **425** would prevent cyclization, but that the cyclization reaction might be possible if we

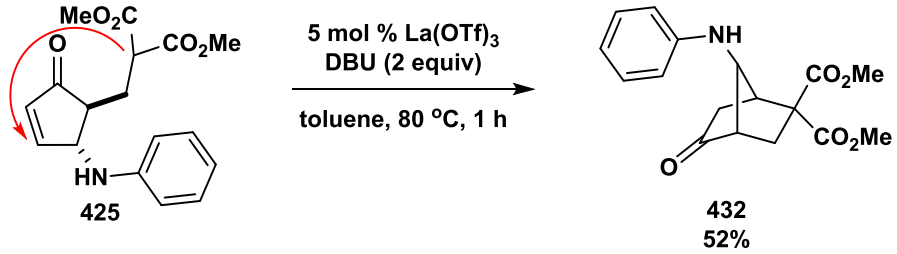
could simultaneously epimerize the stereocenter α to the carbonyl with the addition of an appropriate base.

Scheme 62. Proposed intramolecular amidation reaction.



The 4-amino cyclopentenone **425** was allowed to react with $La(OTf)_3$ and 1,8-diazabicycloundec-7-ene (DBU) in toluene at 80 °C (Scheme 63). Unfortunately, no intramolecular amidation products **431** were detected, and instead only the bicyclic structure 432 was isolated, which results from an intramolecular Michael addition between the malonate group and the enone. With more optimization, this might be a powerful new way to produce highly substituted [2.2.1] bridged systems.

Scheme 63. Intramolecular Michael addition to form bicyclic compounds.



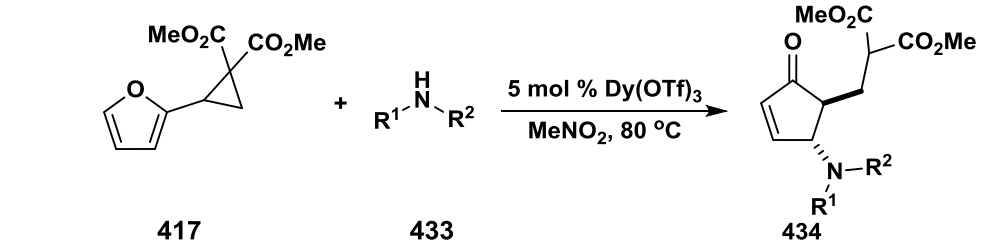
3.2.3 Substrate Scope

With proof that the new D-A cyclopropanes are an effective way to trigger the aza-Piancatelli rearrangement, we set out to explore a range of aniline and hydroxylamine

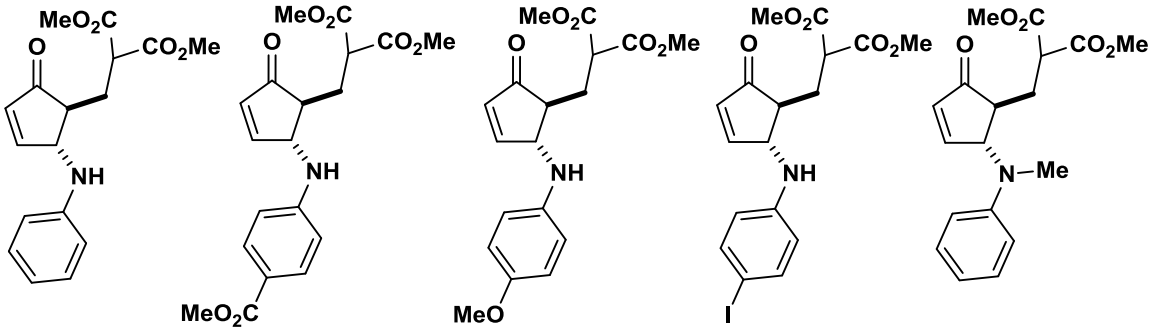
nucleophiles. In general, tri-substituted furylcyclopropanes perform similar to alkyl-substituted furylcarbinols (Table 20). Electron deficient **435** and electron rich **436** anilines give the desired cyclopentenone in good yield. Similarly to what we observed in our original publication utilizing furylcarbinols, slow reacting anilines with an unsubstituted *para* position are susceptible to Friedel–Crafts reactions. Secondary aniline *N*-methylaniline is more prone to Friedel–Crafts reactions and only gave modest yield of the 4-amino cyclopentenone **438**. Bulky 2,6-dimethylaniline is particularly susceptible to Friedel-Crafts reactions and only gave 20% of the desired product **442** due to the increased bulk around nitrogen and an open *para* position on the aromatic ring. Interestingly, reactions with electron deficient secondary *N*-benzyl-4-iodoaniline are very fast and produce the desired product **439** in 89% yield at room temperature in only 3 hrs, whereas electron rich *N*-benzyl-*p*-anisidine **440**, which is much slower to react, requires 7 days at room temperature or 2 hrs at 80 ^{o}C. Surprisingly, bulky 2,4,6-trimethylaniline is reacts quickly and gives cyclopentenone **441** in quantitative yield after 30 minutes at 80 ^{o}C. Unfortunately, cyclic aniline 6-methyl-1,2,3,4-tetrahydroquinoline performs poorly under the current reaction conditions and only produces the desired cyclopentenone **443** in 32% yield. Hydroxylamines **444**-**446** were slow to react and required additional catalyst loading to form cyclopentenones in roughly 60% yield. In general, we found that the performance of anilines explored in Table 20 closely resembles the results obtained for the same anilines when using the traditional furylcarbinol system. This is due to their similar mode of activation, since when using a tri-substituted D-A cyclopropane activating group, we always observe initial attack by aniline on the cyclopropane carbon, forming homo conjugate addition products. The

substituted aniline then acts as a leaving group similar to the hydroxyl group in the traditional furylcarbinol systems, which then continues to rearrange as expected.

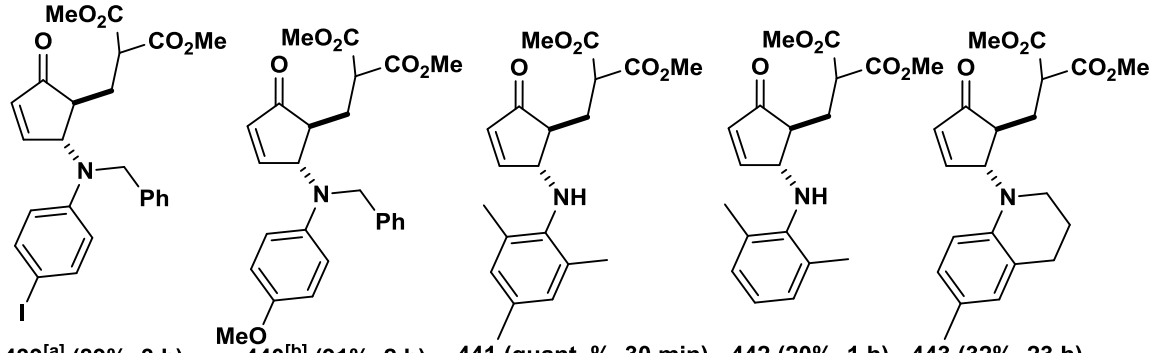
Table 20. Scope of the rearrangement using furylcyclopropanes.



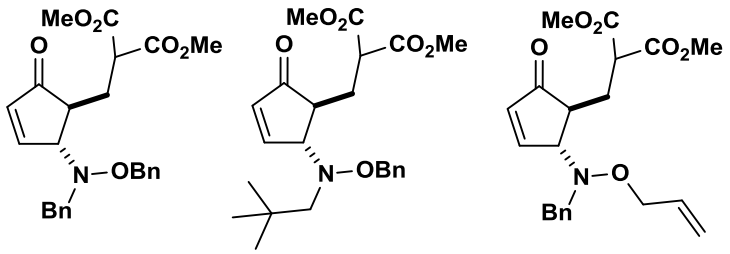
417 433 434



425 (77%, 1 h) 435 (68%, 30 min) 436 (64%, 4 h) 437 (76%, 1 h) 438 (55%, 1 h)



439[a] (89%, 3 h) 440[b] (91%, 2 h) 441 (quant. %, 30 min) 442 (20%, 1 h) 443 (32%, 23 h)

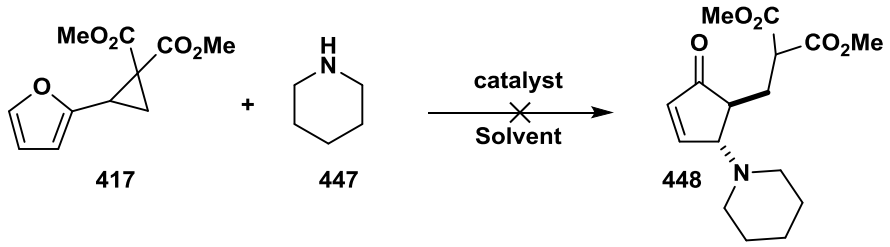


444[c] (59%, 24 h) 445[c] (61%, 24 h) 446[d] (38%, 4 days)

[a] reaction performed at rt [b] 77% after 7 days at rt [c] 10 mol % $Dy(OTf)_3$ [d] 15 mol % $Dy(OTf)_3$

Attempts were made to utilize the aliphatic amine piperidine **447** for the rearrangement by examining a variety of Lewis acid catalysts (Table 21). When the reaction was performed with 5 mol % $Dy(OTf)_3$ at 50 ^oC, only starting materials were recovered from the reaction (entry 1). Milder Lewis acids also failed to catalyze the reaction (entries 2-4). Employing one equivalent of Brønsted acidic HCl (conc.) at rt also only led to the recovery of starting material (entry 5). Employing $Yb(OTf)_3$ in either CH_2Cl_2 or toluene led to the formation of a complex mixture of products by ^1H NMR with no sign of the desired product (entries 6 and 7). Unfortunately, this new activating group still does not enable the usage of more Lewis basic secondary amines.

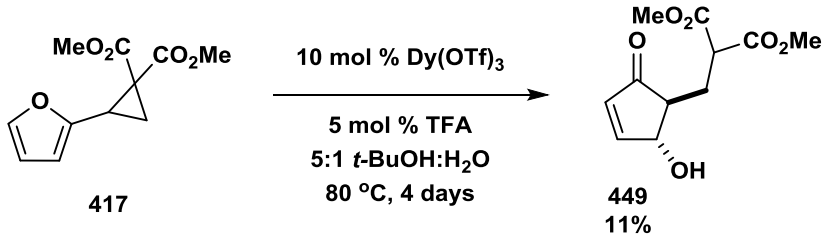
Table 21. Attempts to utilize piperidine in the rearrangement with furylcyclopropanes.



entry	solvent	catalyst	time	temp (^{o}C)	outcome
1	MeCN	$Dy(OTf)_3$ (5 mol %)	2 h	50	no rxn
2	MeCN	MnI_2 (100 mol %)	13 days	rt	no rxn
3	MeCN	$MgCl_2$ (100 mol %)	13 days	rt	no rxn
4	MeCN	MgI_2 (100 mol %)	13 days	rt	no rxn
5	MeCN	HCl (100 mol %)	13 days	rt	no rxn
6	CH_2Cl_2	$Yb(OTf)_3$ (10 mol %)	24 h	rt	Starting material + unknown products
7	toluene	$Yb(OTf)_3$ (10 mol %)	48 h	80	Starting material + unknown products

Our group has recently developed new catalytic conditions for the original Piancatelli reaction with water nucleophiles that employs both Lewis acidic $Dy(OTf)_3$ and Brønsted acidic TFA in the presence of a *t*-BuOH.[7] Attempts were made to utilize these conditions starting from furyl cyclopropane **417**, but unfortunately, the reaction was very low yielding, and only produced 4-hydroxycyclopentenone **449** in 11% yield after reacting for 4 days at 80 ^{o}C (Scheme 64).

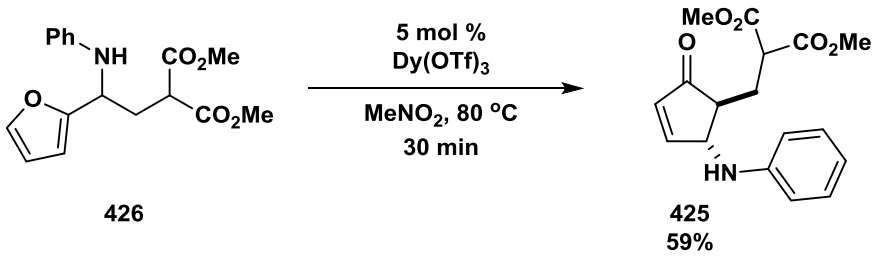
Scheme 64. Attempt to use water as a nucleophile with furyl cyclopropanes.



3.2.4 Rearrangement of Homo-Conjugate Addition Products

It is possible to isolate the homo-conjugate addition products in high yield when the reactions are performed at room temperature. We were interested in studying how these products proceed to form 4-amino cyclopentenones. Subjecting **426** to the reaction conditions produced cyclopentenone **425** in 59% yield after 30 minutes, indicating that an external nucleophile is not required to initiate the reaction that forms cyclopentenones (Scheme 65).

Scheme 65. Rearrangement of homo-conjugate addition products.



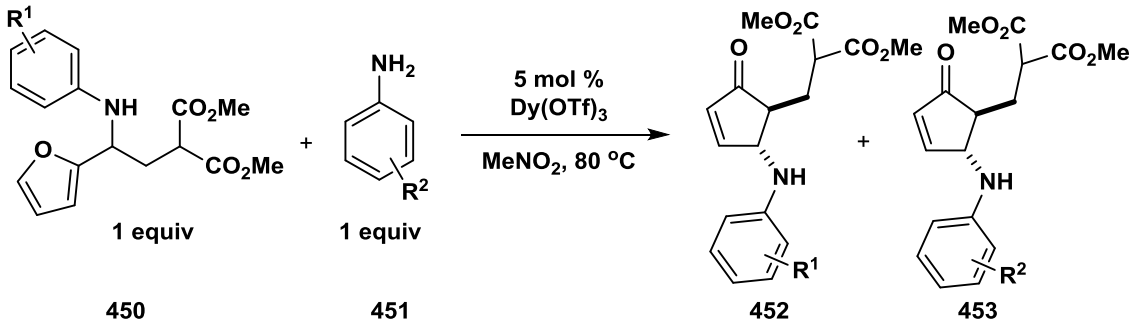
We hypothesized that there are two possible mechanisms that the rearrangement of these aniline-substituted substrates could operate by. The first possible mechanism would be Lewis acid activation of the aniline with complete dissociation from the furan substrate to form the previously proposed oxocarbenium cation. A nucleophile from the bulk solution would then recombine with the oxocarbenium and rearrange as expected. Alternatively, the

rearrangement might proceed through a tight ion pair, where the aniline nitrogen and the furyl cation stay in close proximity as the nitrogen migrates from the alkyl position to the furan ring, then rearrange as expected.

In order to probe the underlying mechanism, crossover experiments were performed utilizing external aniline nucleophiles. If the mechanism involves a tight ion pair, then the presence of a second type of aniline in the reaction mixture should have no effect on the outcome of the rearrangement and 4-amino cyclopentenones would be produced with the sole incorporation of the aniline that was originally present on the starting material. If complete dissociation occurs in the presence of a second aniline nucleophile, we would expect to obtain a mixture of cyclopentenones from the incorporation of both anilines.

The results of the crossover experiments are shown in Table 22. When equimolar amounts of aniline-substituted furan substrates **450** were reacted under the typical reaction conditions with an additional equivalent of 4-iodoaniline, a 1.4:1 ratio of cyclopentenones bearing aniline and 4-iodoaniline were obtained respectively (entry 1). From the reverse scenario, starting with a 4-iodoaniline-substituted furan substrate and 1 equivalent of aniline, we obtained a 1:2.4 mixture of 4-amino cyclopentenones containing 4-iodoaniline and aniline respectively (entry 2). These data indicate the rearrangement is not proceeding through migration of a tight ion pair and that dissociation of the aniline from the furan-substrate results in formation of an oxocarbenium ion that the two anilines compete for. The more nucleophilic aniline is incorporated more readily. Competition experiments using 4-iodoaniline and 2,4,6-trimethoxy aniline produced similar results, where the more nucleophilic 2,4,6-trimethoxy aniline was incorporated more readily into cyclopentenones than 4-iodoaniline (entries 3 and 4).

Table 22. Crossover experiments with aniline-substituted furan substrates.



entry	R^1	R^2	ratio (R^1:R^2)
1	H	4-iodo	1.4 : 1
2	4-iodo	H	1 : 2.4
3	4-iodo	2,4,6-trimethyl	1 : 2.6
4	2,4,6-trimethyl	4-iodo	1.1:1

3.3 Tetra-Substituted Donor-Acceptor Cyclopropanes

3.3.1 Introduction

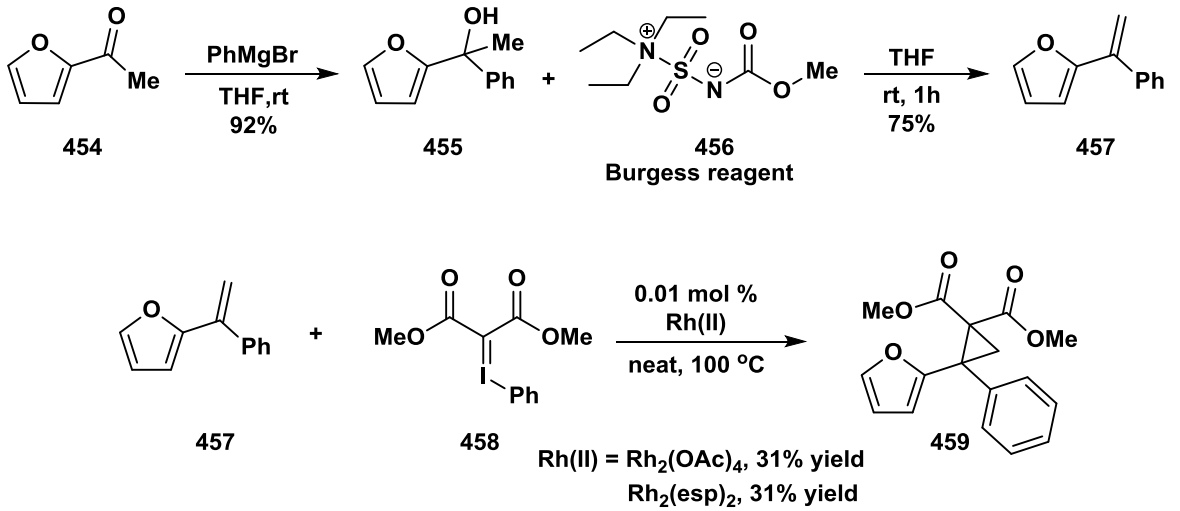
Early efforts to utilize tertiary furylcarbinols as substrates in the aza-Piancatelli rearrangement revealed some critical limitations that would prevent these substrates from being useful as a starting point to access 4-amino cyclopentenones bearing an all carbon quaternary stereocenter α to the carbonyl carbon. The major limitations being their high propensity towards elimination side reactions and the low diastereoselectivity achieved when using alkyl groups smaller than isopropyl. We hypothesized that tetra-substituted furyl donor-acceptor cyclopropanes would be a potential solution to these problems. Following our success using tri-substituted donor-acceptor cyclopropanes as a new activation platform for the aza-Piancatelli rearrangement, we went on to study the behavior of tetra-substituted D-A cyclopropanes.[8]

3.3.2 Synthesis of Tetra-Substituted Donor-Acceptor Cyclopropanes

Tri-substituted cyclopropanes could be easily formed by reacting sulfoxonium ylides with Knoevenagel olefin adducts derived from 2-furaldehyde. Unfortunately, in our hands sulfoxonium ylides gave poor and irreproducible yields when reacted with Knoevenagel adducts derived from furyl ketones.

We decided to pursue a new strategy utilizing rhodium carbenoid cyclopropanation chemistry with phenyliodonium ylides (Scheme 66). Simple Grignard addition into acetyl furan **454** generates the tertiary furylcarbinol **455** in high yield. The Burgess dehydrating agent, methyl N-(triethylammoniumsulfonyl)carbamate **456**, cleanly afforded the terminal olefin **457** in 75% yield.[9] Olefin **457** and phenyl iodonium ylide **458** were combined prior to the addition of a rhodium(II) catalyst, which produced the desired furylcyclopropane **459** in 31% yield.[10] Rhodium catalysts $Rh_2(OAc)_4$, and $Rh_2(esp)_2$, both performed similarly. Attempts to increase the yield of the desired cyclopropanes using other known reaction conditions[11] or by utilizing diazomalonate instead of the iodonium ylide as the carbene source[12] were ineffective at increasing the yields. Although not ideal, we chose to proceed with the unoptimized route shown in Scheme 66.

Scheme 66. Synthesis of tetra-substituted furylcyclopropanes.



Electron rich furylcyclopropane **460**, and electron deficient cyclopropanes **461** and **462** were synthesized in the same way (Figure 27).

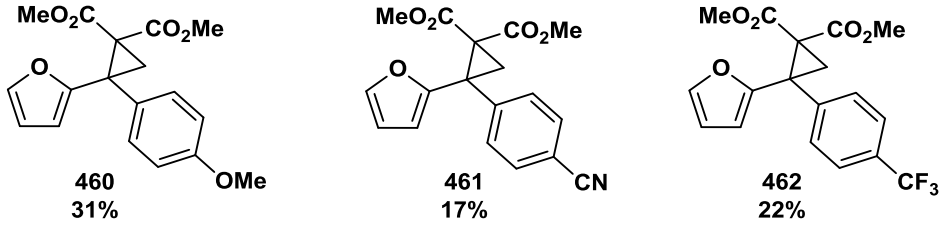


Figure 27. Cyclopropane yields from Rh(II) catalyzed cyclopropanation with phenyl iodonium ylides.

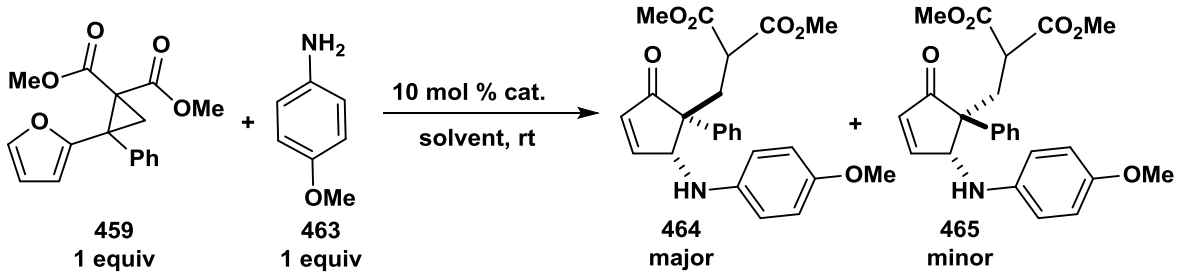
3.3.3 Reaction Optimization

We began our investigations by exploring the reactivity of phenyl furylcyclopropane **459** with a variety of Lewis acids that are known to facilitate ring opening of D-A cyclopropanes (Table 23).[1] To our gratification, $Dy(OTf)_3$ catalyzed the reaction to produce the desired 4-amino cyclopentenones **464** and **465** in a 6:1 diastereomeric ratio, respectively. Moreover, utilization of tetrasubstituted D-A cyclopropanes results in the formation of highly

congested cyclopentenones with vicinal stereocenters in very little time at room temperature. Recall in section **3.2.4** that tri-substituted D-A cyclopropanes activate in less than 10 minutes to form the homo-conjugate addition products at room temperature. We believe that the rate acceleration observed with tetra-substituted D-A cyclopropanes is due to the rapid ring opening of the cyclopropane at room temperature, and that the increased congestion on the cyclopropane blocks homo-conjugate addition, and facilitates direct addition of the aniline into the furan.

In the case of fully-substituted D-A cyclopropanes substrates, the reaction always gives a mixture of cyclopentenones enriched in the *cis* diastereomer with respect to the aryl ring and aniline moiety. Other rare earth triflate Lewis acids also facilitated the rearrangement, but resulted in lower diastereoselectivity (entries 2, 3 and 4). Higher yields and fewer decomposition products were observed when $YbCl_3$ (entry 5) and $ZnBr_2$ (entry 8) were employed at the cost of increased reaction times and reduced diastereoselectivity. Interestingly, an increase in rate and diastereoselectivity was observed when $ZnBr_2$ was heated to 80 ^oC (entry 9). Dichloromethane (CH_2Cl_2) is often used as a solvent in ring opening reactions of D-A cyclopropanes, however, using CH_2Cl_2 with these substrates resulted in increased reaction times and lower diastereoselectivity (entries 10-12). Polar aromatic solvents, such as nitrobenzene and benzonitrile produced cyclopentenones in with low diastereoselectivity (entries 13 and 14).

Table 23. Lewis acid and solvent screen for the rearrangement.

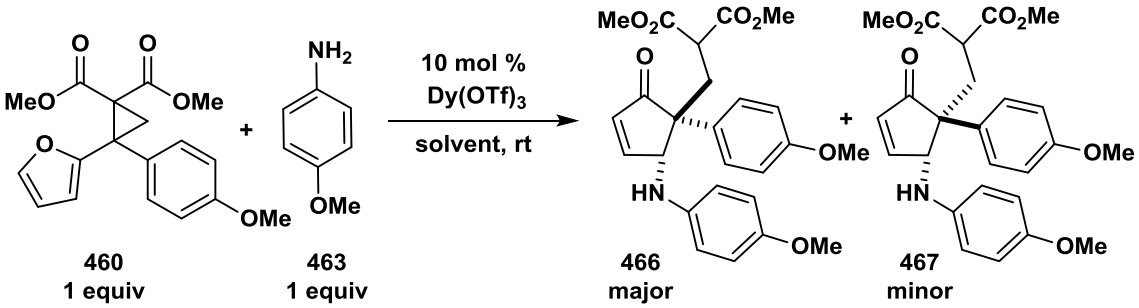


entry	catalyst	solvent	time	yield (%)[a]	ratio[b] (464:465)
1	$Dy(OTf)_3$	MeCN	5 min	57	6:1
2	$La(OTf)_3$	MeCN	5 min	77	1:1
3	$Sc(OTf)_3$	MeCN	5 min	50	5:1
4	$Yb(OTf)_3$	MeCN	5 min	58	2:1
5	$YbCl_3$	MeCN	24 h	80	1:1
6	$Sn(OTf)_2$	MeCN	48 h	<5	n.d.
7	$Cu(OTf)_2$	MeCN	48 h	< 5	n.d.
8[c]	$ZnBr_2$	MeCN	24 h	84	1:1
9[c,d]	$ZnBr_2$	MeCN	2 h	83	2:1
10	$Dy(OTf)_3$	CH_2Cl_2	24 h	58	2:1
11	$Sc(OTf)_3$	CH_2Cl_2	3 h	58	3:1
12	$Sn(OTf)_2$	CH_2Cl_2	48 h	<5	n.d.
13	$Dy(OTf)_3$	nitrobenzene	20 min	n.d.	1:1
14	$Dy(OTf)_3$	benzonitrile	20 min	n.d.	1.5:1

[a] Determined by ^{1}H NMR spectroscopy using dimethyl terephthalate as the internal standard. [b] Determined by ^{1}H NMR spectroscopy.
[c] 1 equiv $ZnBr_2$ was used. [d] Reaction conducted at 80 ºC. n.d. = not determined.

Reactions using *para*-methoxyphenyl substituted furylcyclopropanes **460** and *p*-anisidine **463** are highly diastereoselective in MeCN (Table 24, entry 1). Upon switching to polar aprotic solvent nitromethane, which we found to be the superior solvent for tri-substituted furylcyclopropanes, we saw a drop in selectivity to 15:1 (entry 2). Using ethyl acetate (entry 3) or toluene (entry 4) further reduced the selectivity to around 2:1, and in toluene a large amount of decomposition products were observed in the crude ^{1}H NMR spectrum of the crude material.

Table 24. Solvent screen.



460
1 equiv

463
1 equiv

466
major

467
minor

entry	solvent	time	yield (%)[a]	ratio[b] (466:467)
1	MeCN	5 min	87	25:1
2	$MeNO_2$	5 min	59	15:1
3	EtOAc	5 min	68	1.7:1
4	toluene	24 h	n.d	2:1

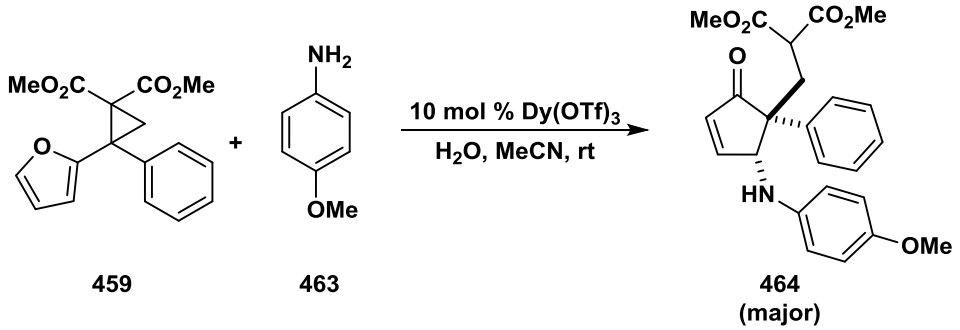
n.d. = not determined

It is important to note that we had some difficulty reproducing the diastereoselectivity values reported in the previous tables using $Dy(OTf)_3$ from different sources and ages (ranging from 1:1 to 6:1 dr). It is known that rare earth Lewis acids are readily hydrated when exposed to air, and that reactions with them can be affected by water.[13] Given the problems we encountered with reproducibility, we investigated the effect that water has on the diastereoselectivity of the rearrangement. We discovered that the hydration state of $Dy(OTf)_3$ was responsible for the irreproducible results. Newly opened bottles of $Dy(OTf)_3$ resulted in lower levels of selectivity, but we found that if we "aged" the $Dy(OTf)_3$, we could reproducibly obtain 6:1 dr and consistent yields. Importantly, "aging" the $Dy(OTf)_3$, only required leaving some in a vial open to air for greater than 24 hrs.

To further examine the effect water has on the reaction, a series of experiments with increasing amounts of water were performed (Table 25). For these experiments, the "aged" catalyst was premixed with water in anhydrous MeCN prior to addition of the cyclopropane **459** and amine **463**. When no water is added, the reaction gives cyclopentenones with a 6:1

dr (entry 1). The addition of 10 mol % H_2O has no effect on the selectivity, but the yield was reduced. Adding more than 10 mol % H_2O gives consistent yields, but the selectivity is reduced (entries 3-6). We sought to try to eliminate all water from the reaction by drying the starting materials under high vacuum for 24h and by generating anhydrous $Dy(OTf)_3$ by heating at 200 ^oC for 48 h under high vacuum.[14] When the rearrangement is conducted under anhydrous conditions under an N_2 atmosphere using dried $Dy(OTf)_3$, the yield and selectivity is comparable to entry 1, (66% yield, 6:1 dr).

Table 25. The role of water in the rearrangement.



459 463 464 (major)

entry	mol % H_2O	time (mins)	yield %	dr (major:minor)
1	0	10	57	6:1
2	10	10	37	6:1
3	30	10	58	1.3:1
4	60	10	60	1.6:1
5	100	10	59	1:1
6	1000	40	55	1.25:1

The relative stereochemistry of **468** was determined by NOESY experiments and x-ray crystal structure analysis of the cyclopentenones (Figure 28).

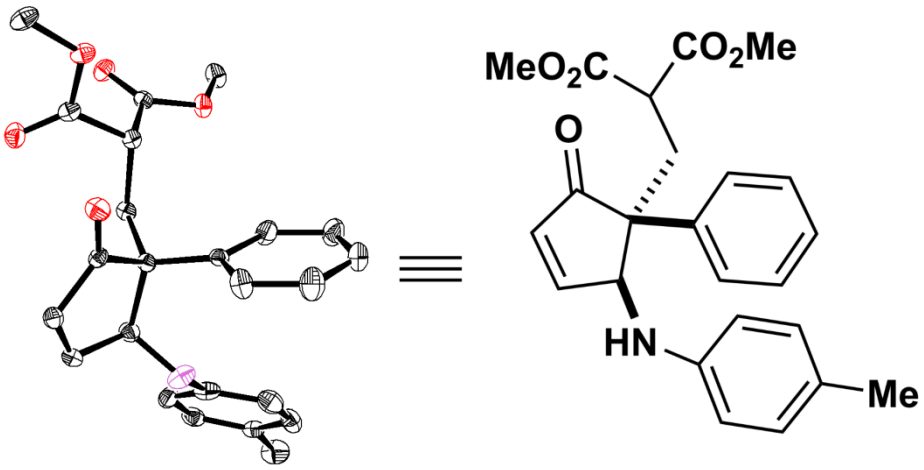


Figure 28. ORTEP drawing of cyclopentenone **468** (left) shown with 50% thermal ellipsoids. Hydrogen atoms have been omitted for clarity. The crystal structure data can be obtained from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. CCDC # 916408

3.3.4 Substrate Scope

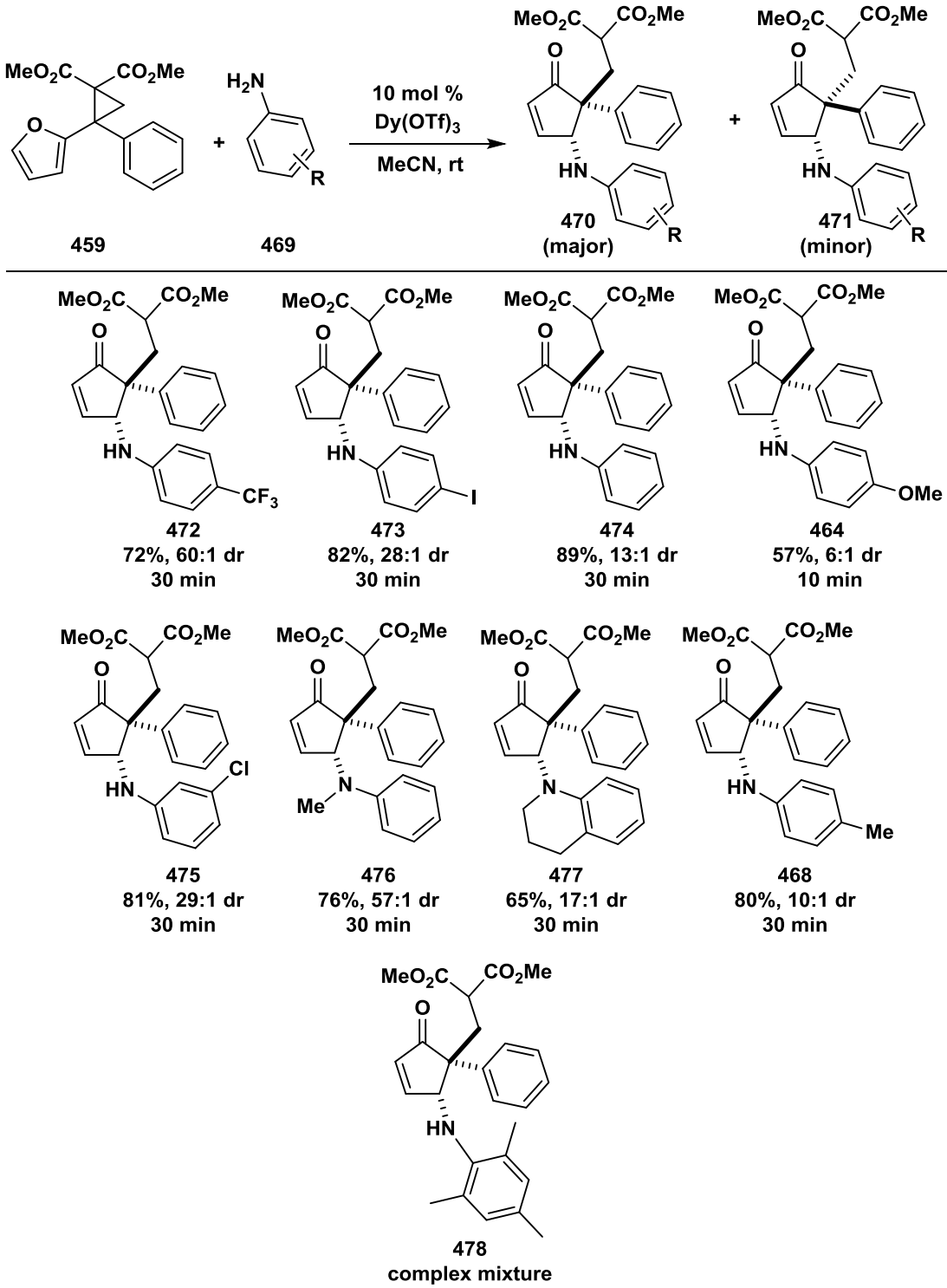
With optimized reaction conditions in hand, we started by examining the reactivity of the standard phenyl furylcyclopropane **459** with a variety of aniline nucleophiles (Table 26). The reaction is very fast at room temperature; most reactions are complete in 30 minutes or less and generally give high yields. Remarkably, electron deficient substrates (**472**,**743** and **475**) and secondary acyclic (**476**) and cyclic (**477**) anilines produce the desired 4-amino cyclopentenones with very high diastereomeric ratios, up to 60:1 However, using more electron rich anilines (**474**, **464** and **468**), we see a loss in selectivity, as low as 6:1 when using *p*-anisidine. Unfortunately, because of the cascade nature of the rearrangement, it is difficult to experimentally determine why the electronics of the aniline affect the selectivity so greatly. This issue is also discussed in sections **3.3.6** and **4.2**. To gain more insight into the selectivity determining processes, we have initiated a collaboration with Prof. Dean

Tantillo at UC Davis, who specializes in computational chemistry. This collaboration is ongoing.

Based on experimental results, it is clear that there are notable reactivity differences between tetra-substituted furylcyclopropanes and all other furan starting materials examined so far. Previously, in collaboration with the Hein group, we reported that the rate determining step is an off-cycle binding event between the aniline and the lanthanide Lewis acid catalyst for reactions between furylcarbinols and anilines.[15] This effect is most pronounced with electron rich anilines due to their higher Lewis basicity and results in longer reaction times (> 18 h). Strangely, using tetra-substituted furylcyclopropanes, we observe the opposite effect: reactions with electron rich anilines are the fastest and electron deficient anilines tend to react slower. Indeed reactions employing *p*-anisidine **464** are complete in as little as 5-10 minutes versus >30 minutes for electron deficient 4-(trifluoromethyl)aniline **472**. It is still unclear what is responsible for this switch in reactivity. Another interesting observation we noted when studying this reaction is that Friedel–Crafts alkylation reactions have not been observed using tetra-substituted cyclopropanes. For example, anilines with an unsubstituted *para* position, which previously lead to Friedel–Crafts products, produce cyclopentenones in high yield. In addition, cyclic aniline 1,2,3,4-tetrahydroquinoline, which is a very poor nucleophile in reactions with furylcarbinols, produces the desired cyclopentenone **477** with good yield (65%) and diastereoselectivity (17:1 dr). Lastly, highly substituted 2,4,6-trimethoxy aniline is one of the fastest and highest yielding anilines in reactions using furylcarbinols and tri-substituted furylcyclopropanes, but with tetra-substituted cyclopropanes, decomposition of the starting

material was observed with no trace of the desired cyclopentenone by ^{1}H NMR of the crude reaction mixture (**478**).

Table 26. Substrate scope using phenyl furylcyclopropane.



472	473	474	464
72%, 60:1 dr	82%, 28:1 dr	89%, 13:1 dr	57%, 6:1 dr
30 min	30 min	30 min	10 min

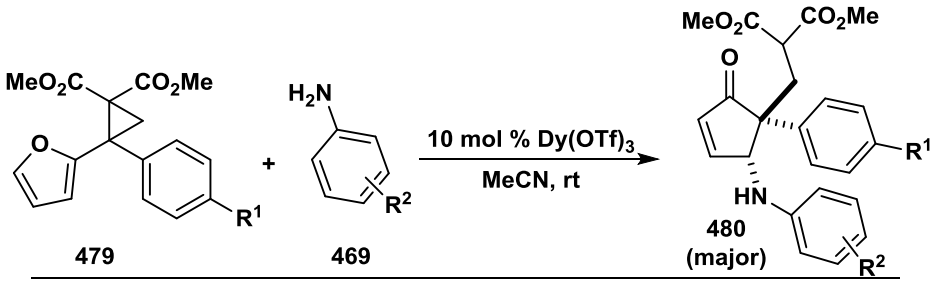
475	476	477	468
81%, 29:1 dr	76%, 57:1 dr	65%, 17:1 dr	80%, 10:1 dr
30 min	30 min	30 min	30 min

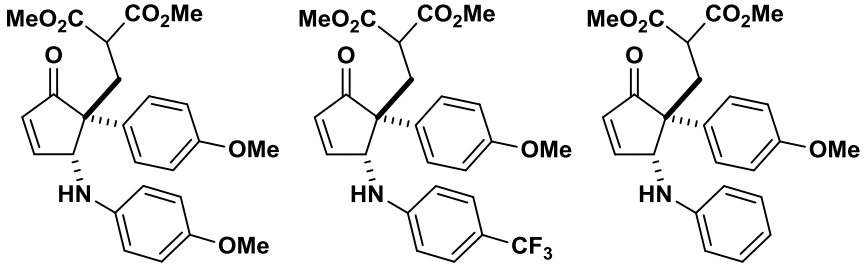
Diastereoselectivity and yield determined by ^{1}H NMR spectroscopy using dimethyl terephthalate as the internal standard. T_1 relaxation time = 40 s

Next, we turned our attention towards examining the electronic effects that the aryl group on the furylcyclopropane might impart on the reaction (Table 27). When electron rich *p*-methoxyphenyl furylcyclopropane was employed, the diastereoselectivity of the rearrangement was high, regardless of the electronic nature of the aniline (**466**, **481** and **482**). In contrast, when electron deficient 4-cyanophenyl furylcyclopropane was utilized, the reaction was slow and the diastereoselectivity was low regardless of the aniline utilized (**483**-**485**). Unfortunately, benzyl substituted tetra-furylcyclopropanes performed poorly and only gave cyclopentenones **486** and **487** in moderate yield with low diastereoselectivity. These results are significant because they demonstrate that the electronic influence of the furylcyclopropane can override the influence imparted by anilines bearing different electronic properties.

It should be noted that in some cases, we had difficulties obtaining isolated yields of the cyclopentenones due to their propensity to undergo an intramolecular Michael addition reaction on silica gel as well as basic and neutral alumina. Cyclopentenones with an electron withdrawing group at the R^1 position are especially prone to this reaction. Because of these difficulties obtaining pure cyclopentenones, we opted to use ^{1}H NMR of the crude reaction mixture to determine reaction yields and diastereoselectivity using dimethyl terephthalate as the internal standard. The T_1 relaxation time was set at 40 seconds to help ensure accurate yields and diastereoselectivities based on peak area integrations.[16]

Table 27. Electronic effects of the furylcyclopropane.

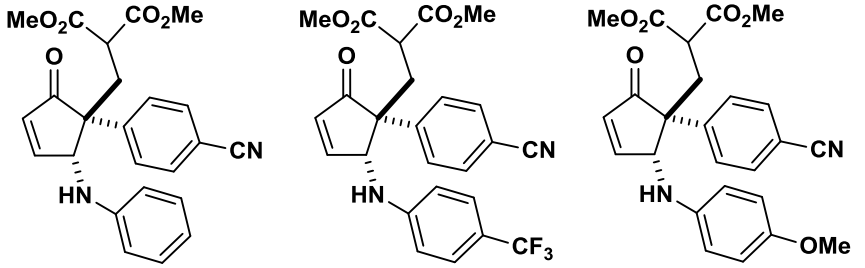




466
87%, 25:1 dr
30 min

481
63%, 22:1 dr
30 min

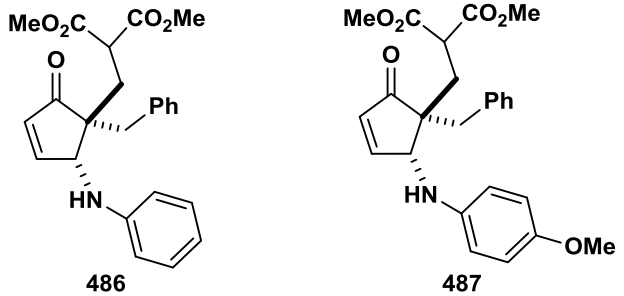
482
84%, 32:1 dr
30 min



483
76%, 1:1 dr
60 min

484
65%, 6:1 dr
60 min

485
58%, 2:1 dr
60 min



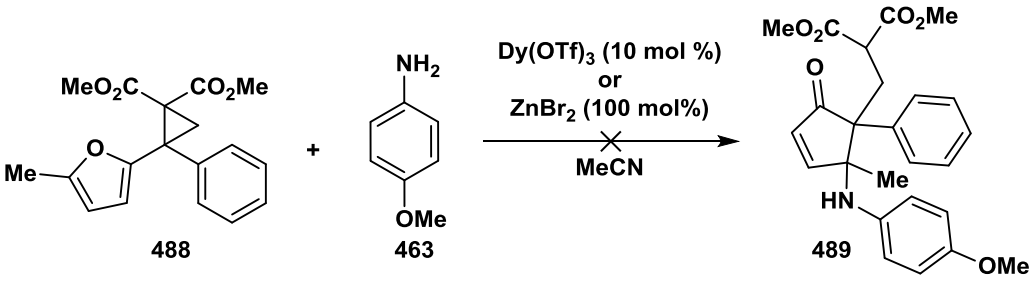
486
56%, 1.3:1 dr
5 h

487
47%, 2:1 dr
40 min

Diastereoselectivity and yield determined by ^{1}H NMR spectroscopy using dimethyl terephthalate as the internal standard. T_1 relaxation time = 40 s

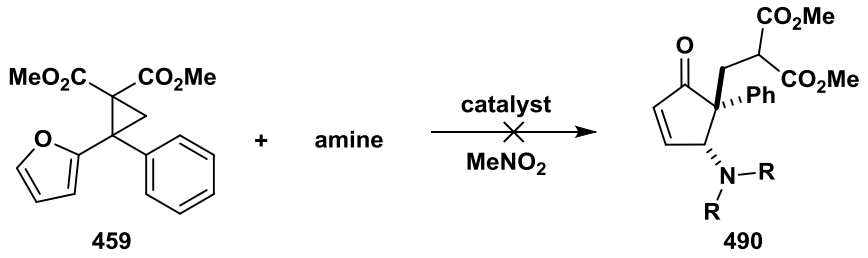
Unfortunately attempts to push this reaction to the most challenging case, using cyclopentenones **488** substituted at the 5 position, that would form cyclopentenones **489** bearing a vicinal fully substituted carbon center, failed to react under reaction conditions employing either $Dy(OTf)_3$ or $ZnBr_2$, and only decomposition products were obtained (Scheme 67).

Scheme 67. Attempts to rearrange 5-methyl furylcyclopropanes.



Encouraged by our success using this new mode of activation, attempts were made to utilize aliphatic amines for the rearrangement of tetra-substituted furylcyclopropanes (Table 28). When pyrrolidine was employed in the reaction with cyclopropane **459** in the presence of 100 mol % $Dy(OTf)_3$ or $ZnBr_2$ only decomposition of the starting materials were observed by ^1H NMR, and none of the desired product was detected (entries 1 and 2). Heating cyclopropane **459** to 100 ^oC in the presence of pyrrolidine or morpholine resulted in recovery of the starting materials (entries 3 and 4). Unfortunately, these reactions were performed during the initial development of tetra-substituted furylcyclopropanes, and were only performed in $MeNO_2$. It would be useful to reinvestigate the usage of aliphatic amines with tetra-substituted cyclopropanes by performing a more exhaustive catalyst and solvent screen.

Table 28. Aliphatic amines in the rearrangement of tetra-substituted furylcyclopropanes.



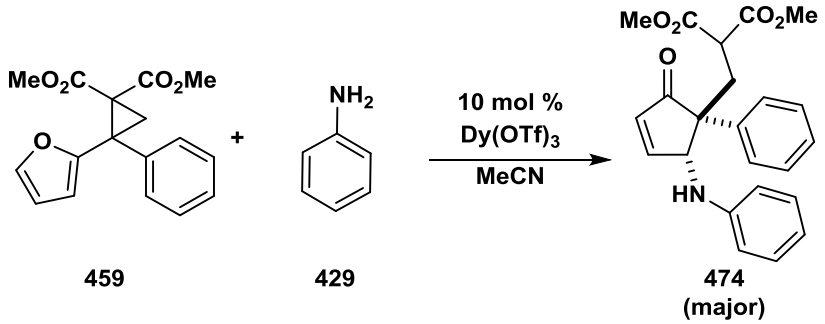
entry	amine	catalyst	temp	time	comment
1	pyrrolidine	$Dy(OTf)_3$ (100 mol %)	rt	18 h	complex mixture
2	pyrrolidine	$ZnBr_2$ (100 mol %)	rt	18 h	complex mixture
3	pyrrolidine	none	100 ^oC	18 h	no reaction
4	morpholine	none	100 ^oC	22 h	no reaction

3.3.5 Effects of Reaction Temperature on the Diastereoselectivity

During our initial solvent screen, we noticed that increasing the temperature to 80 ^oC using $ZnBr_2$, led to an increase in diastereoselectivity, from 1:1 at rt to 2:1 at 80 ^oC. Although modest, this small increase in selectivity caught my attention. While it is certainly more common that the selectivity of reactions increases with decreasing temperatures, reactions that operate with an inverse temperature dependence on selectivity have been documented.[17] Experiments using $Dy(OTf)_3$ and cyclopropane **459** at various temperatures reveal a well defined inverse temperature – selectivity relationship (Table 29). Reactions at -40 ^oC produce a 5.8:1 ratio of cyclopentenone **474** diastereomers. The diastereoselectivity increases as the temperature is raised, and at 80 ^oC we obtained a 30:1 ratio of diastereomers. The reactions at temperatures other than room temperature were performed by premixing the cyclopropane and aniline in anhydrous MeCN, then heating or cooling to the desired temperature, after which, $Dy(OTf)_3$ was added and the reaction was allowed to

react at the target temperature. Reactions at 80 °C were stirred for 90 seconds, and then quickly quenched with H_2O.

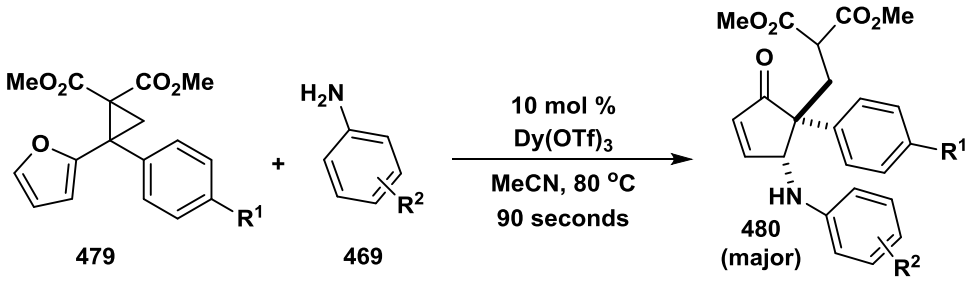
Table 29. Temperature dependence on selectivity.

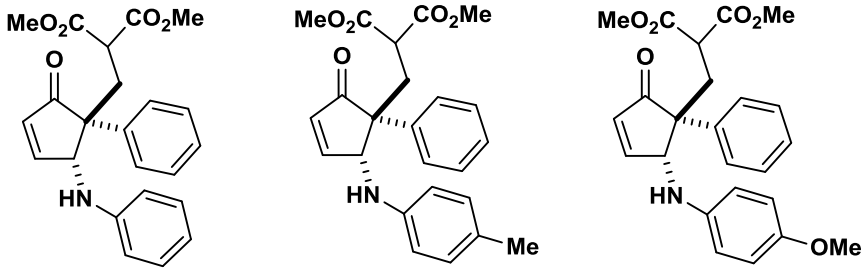


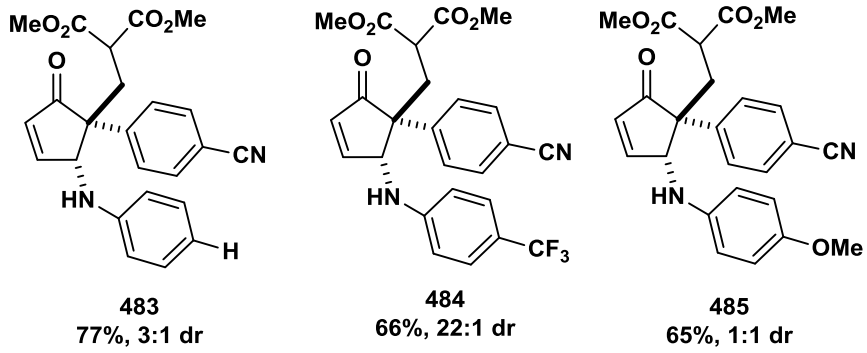
entry	temp (°C)	dr
1	-40	5.8:1
2	0	8.3:1
3	23	13:1
4	60	21:1
5	80	30:1

We were encouraged by these findings and decided to try to increase the diastereoselectivity of substrates that only gave moderate levels of selectivity, below 13:1 dr (Table 30). In most cases, we observed higher diastereoselectivity and higher reaction yields with increasing temperature. At 80 °C, aniline gives cyclopentenone **474** in 87% yield and in 30:1 dr (*cf.*89%, 13:1 dr at rt). More electron rich *p*-toluidine provides cyclopentenone **468** in 87% yield and in 14:1 (*cf.* 80%, 10:1 at rt)., and *p*-anisidine affords cyclopentenone **464** in 82% yield and 16:1 dr (*cf.* 57% yield and 6:1 dr at rt). When R^1 was changed to an electron withdrawing group, poor selectivities are observed at both room temperature and at 80 °C for **483-485**, with the exception of *p*-trifluoromethyl aniline **484**, which increased to 22:1 dr and 66% yield, from 5:1 dr and 65% yield at room temperature.

Table 30. Inverse temperature dependence on diastereoselectivity.





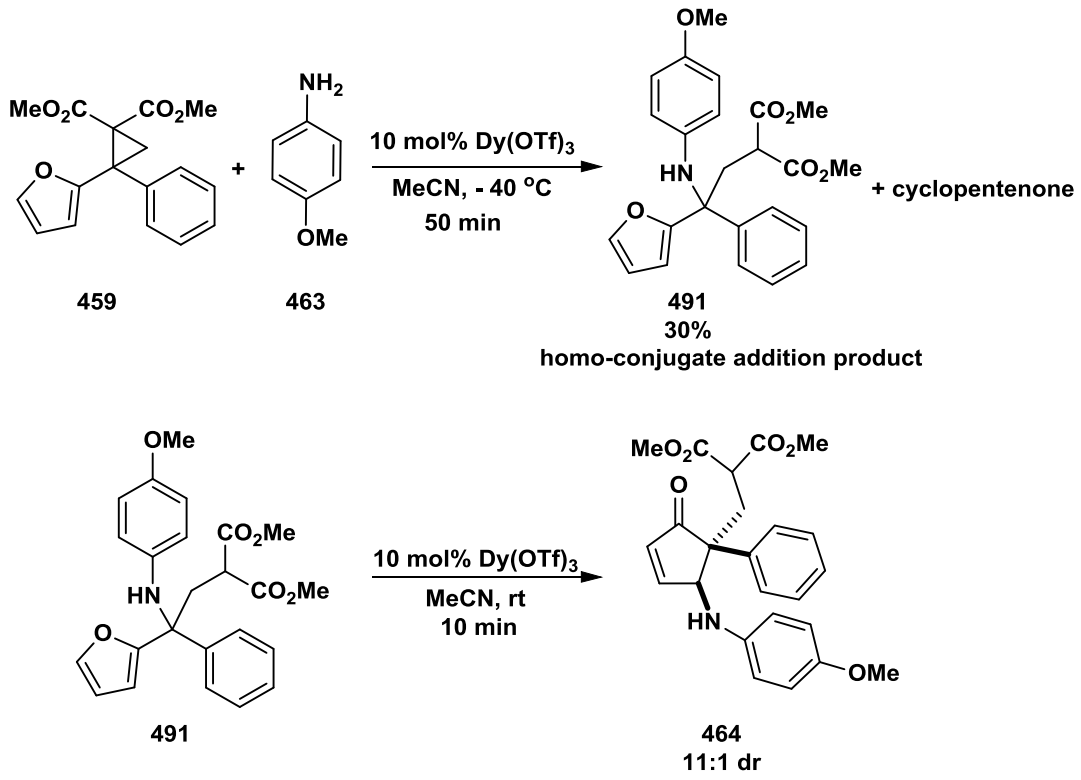


Diastereoselectivity and yield determined by ^{1}H NMR spectroscopy using dimethyl terephthalate as the internal standard. T_1 relaxation time = 40 s

We have never observed homo-conjugate addition products from reactions using tetra-substituted furylcyclopropanes at room temperature, but at -40 ^{o}C, small amounts of **491** can be isolated. When **491** was resubjected to the standard reaction conditions at room temperature, we obtain the expected 4-amino cyclopentenone **464** in 11:1 dr. This is the highest diastereomeric ratio we have observed for reactions between the standard phenyl

furylcyclopropane and electron rich nucleophile *p*-anisidine at room temperature. Indeed, the diastereoselectivity obtained from this reaction more closely resembles reactions performed at 80 ^{o}C (13:1 dr). At this time, we do not have a clear explanation for the dramatic difference in selectivity observed, but hopefully computational studies will help to elucidate this interesting observation.

Scheme 68. Resubjection of homo-conjugate addition products.



3.3.6 Origins of Diastereoselectivity

At this time we can only speculate as to the origin of diastereoselectivity in the reaction. We know that the Lewis acid, solvent, and temperature all have an influence on selectivity. With regards to the Lewis acid, we speculate that the Lewis acid influences the selectivity through coordination to the furan, amine and/or malonate group. Weaker Lewis acids such

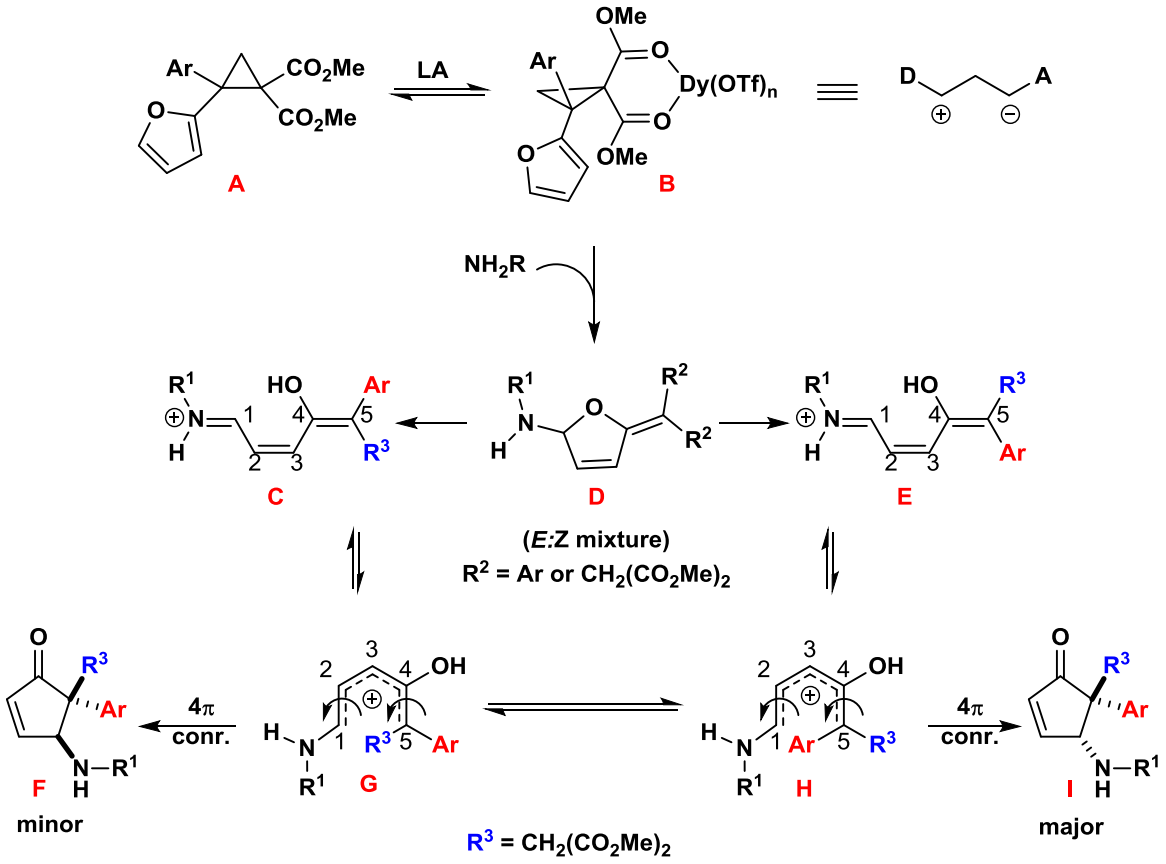
as $ZnBr_2$ result in lower selectivity than lanthanide triflate Lewis acids. From experiments where we incrementally added water to the reaction, we have learned that too much water reduced the selectivity. In addition, before we started using "aged" hydrated $Dy(OTf)_3$, we had difficulties getting repeatable selectivities. It is well known that water is a very good ligand for rare earth Lewis acidic salts, and our observations suggest that reversible coordination of water to the lanthanide salt has an effect on diastereoselectivity.[18] When no water is present, the highly Lewis acidic lanthanide triflate can bind to the substrate to influence the selectivity of the final cyclopentenone. When only a small amount of water is present, the water might disrupt the lanthanide-substrate coordination complex, leading to lower selectivity and irreproducible results. Using fully hydrated lanthanide salts, the coordination environment around the lanthanide might be more homogeneous, which might account for the more reproducible diastereoselectivity observed. Alternative rational cannot be ruled out at this time.

Ultimately, because the rearrangement terminates with a stereospecific 4π conrotatory electrocyclization, the geometry of the pentadienyl cation just prior to cyclization will control the final stereochemical outcome (Scheme 69). Alternatively, if the reaction is reversible, then the diastereoselectivity might be set after the electrocyclization due to a thermodynamic equilibrium. However, we do not believe this to be the case based on reversibility studies, which for clarity, are discussed in section **3.3.8**.

We postulate that intermediates **G** and **H** are the most likely pentadienyl cation geometries because isomers that place the amine terminal group inward would induce unfavorable steric interactions (not shown). At this time, it is unclear what factors control the geometry of **G** and **H**, or when these geometries are set. It is conceivable that the

pentadienyl cation geometry is set during ring opening of the cyclopropane **B**, forming differing *E*/*Z* geometries of intermediate **D**, which then forms isomers **C** and **E**. Because the reaction produces a mixture of diastereomers, this assumption would mean that **C** and **E**, or **G** and **H** can interconvert, however, the energy barrier for interconversion between **C** and **E** or **G** and H should be higher than the 4π electrocyclization. A computational study of the Piancatelli reaction and a related study of the Nazarov cyclization suggest that the energetic barrier for interconversion of the *E/Z* geometric isomers is higher than the energy barrier for the electrocyclization.[19] However, *E*/*Z* interconversion of **C** and **E** or **G** an **H** prior to electrocyclization is not out of the question. Frontier and co-workers have shown that changes to the electronic nature of the aryl group at the termini of polarized pentadienyl cations in the Nazarov reaction can assist in lowering the activation energy required for the isomerization process that is associated with diastereomutation.[20]

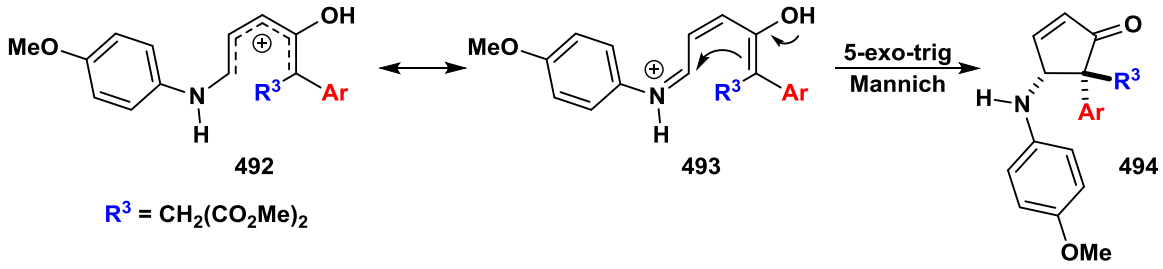
Scheme 69. Origins of diastereoselectivity.



Departing from the geometrical isomerization hypothesis, Tius has suggested that the cyclization of polarized pentadienyl cations with electron rich groups at the termini might actually cyclize through a 5-exo-trig aldol-like process rather than from a conrotatory ring closure.[21] This process is shown in Scheme 70. An electron rich amine might stabilize the carbocation in a way that more resembles the iminium **493**, which is then susceptible to attack by way of a process more resembling a 5-exo-trig Mannich cyclization. This might explain why we observe poorer selectivity when electron rich anilines are employed, since the Mannich cyclization is not a stereospecific process. This would also help to explain why electron deficient anilines result in higher diastereoselectivity, since destabilization of the

iminium cation would facilitate more pentadienyl cation-like behavior (**492**), which would cyclize through a stereospecific 4π conrotatory electrocyclization.

Scheme 70. Possible 5-exo-trig Mannich-like reaction using electron rich anilines.



In order to probe these possible mechanisms, we examined whether or not specific cyclopropane enantiomers might lead to different stereochemical outcomes. We were able to separate the two enantiomers of the standard phenyl furylcyclopropane using HPLC with a10mm CHIRALPAK® OJ-H column. We did not identify the absolute configuration of the each enantiomer and they will be referred to by their retention time on the HPLC column.

The reaction between racemic phenyl furylcyclopropane and *p*-anisidine at -40 ^{o}C produced cyclopentenone **464** in a 2:1 mixture of diastereomers. When enantiomer 1 (first elution from the HPLC column) of cyclopropane **459** was subjected to the reaction conditions at -40 ^{o}C, cyclopentenones with a 5.7:1 dr were obtained. The second to elute, enantiomer 2, was subjected to the reaction conditions and gave cyclopentenones in a 1:1.4 ratio of diastereomers. This is a striking difference, and can be clearly seen by comparing the ^{1}H NMR spectra in Figure 29 that shows the integration values of both diastereomers from the crude reaction mixtures. Interestingly, if we combine the dr values for each enantiomer, we obtain a 6.7:2.4 dr, or a 2.8:1 dr, which resembles the selectivity of the racemic sample at -40 ^{o}C. Reactions of individual enantiomers of cyclopropane **459** at room temperature result in 5:1 dr for enantiomer 1 and a 2:1 dr for enantiomer 2. Combining the

dr values from enantiomer 1 and 2 at room temperature results in a 3.5:1 dr, compared to the 6:1 ratio that we see from the racemic reaction at room temperature. We do not have a good explanation for these results at this time since, by definition, the reaction profile of each enantiomer should behave the same. Further experiments are needed to verify the reproducibility of these results and to gain a better understanding of this observed effect. However, it is important to note that the 4 reactions in Figure 29 using enantiomerically pure cyclopropanes were conducted on the same day using "aged" hydrated $Dy(OTf)_3$ from the same source and performed in dry acetonitrile in an attempt to limit as much experimental error as possible.

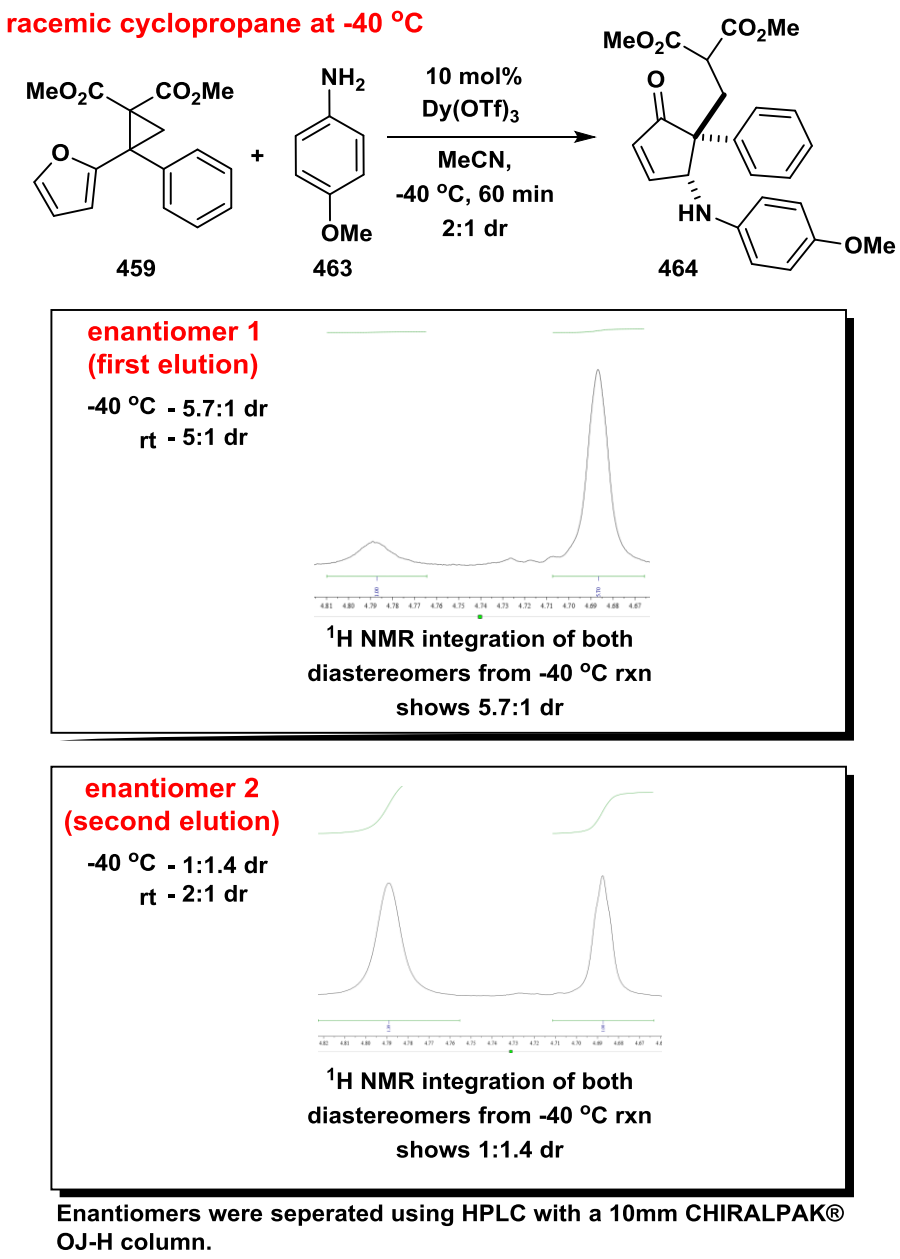


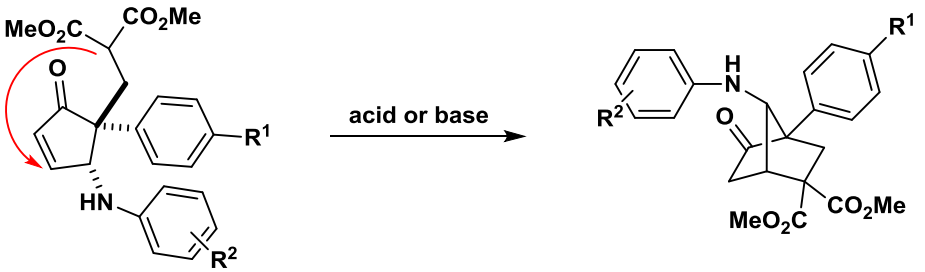
Figure 29. Separation and rearrangement of enantiomerically pure cyclopropanes.

3.3.7 Intramolecular Michael Addition

It was noted earlier that we had difficulties obtaining isolated yields of the cyclopentenones due to the propensity for the tethered malonate group to undergo intramolecular Michael addition into the enone (Scheme 71). This reaction occurs under

basic or acidic reaction conditions and can make purification of the cyclopentenones challenging. Attempts to purify the crude reaction mixtures using untreated silica gel, silica gel treated with 2% triethyl amine, and both neutral and basic alumina all formed small amounts of the bicyclic structures **495** during purification attempts.

Scheme 71. Intramolecular Michael addition.

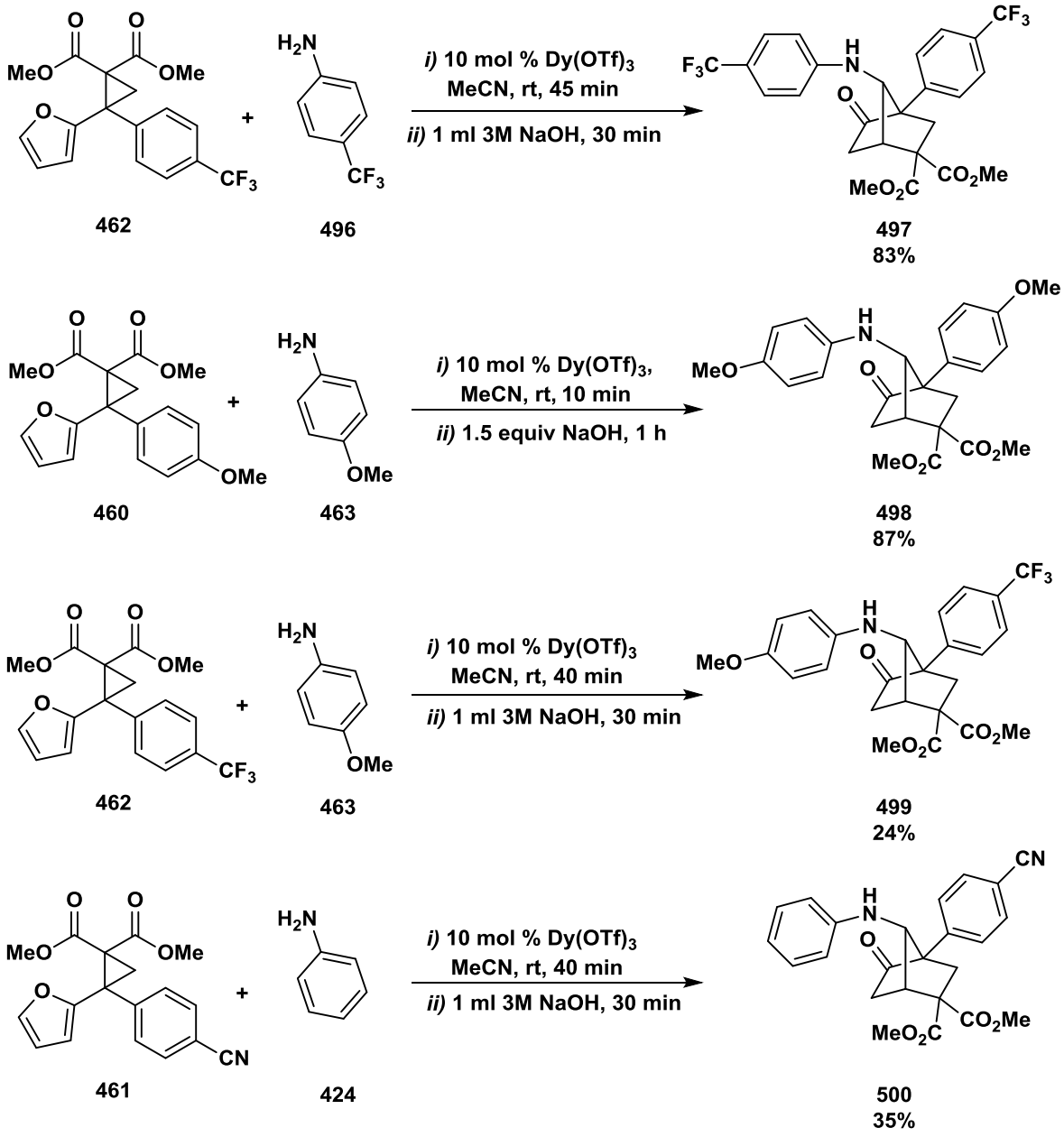


In all cases, only one diastereomer of the bicyclic products have been observed. The bicyclic products are a result of the intramolecular reaction from only the major cyclopentenone diastereomer, where the malonate group is *trans* to the aniline. This is presumably due to increased steric interactions between the amine and malonate nucleophile in the minor diastereomer.

We found that we could obtain the bicyclic compounds in good yield in one pot by simply adding 3M NaOH to the reaction mixture after the formation of the cyclopentenone (as indicated by TLC) (Scheme 72). A range of substituted cyclopentenones and anilines were tested. Strangely, we obtained higher than expected yield of the bicyclic products **497** and **498**. Only a single diastereomer of the bicyclic compounds is obtained. The bicyclic compound that is isolated results from intramolecular reaction from the major *cis* cyclopentenone diastereomer, which should leave the minor diastereomer unchanged, and should be recoverable. However, inspection of the crude reaction mixture with ^{1}H NMR

shows no sign of the minor diastereomer in all cases where NaOH was used, even in cases such as **499** and **500** that gave lower yields of the bicycle.

Scheme 72. NaOH induced intramolecular Michael addition.



X-ray crystal structure analysis confirmed the bicyclic structure and relative stereochemistry of the products (Figure 30).

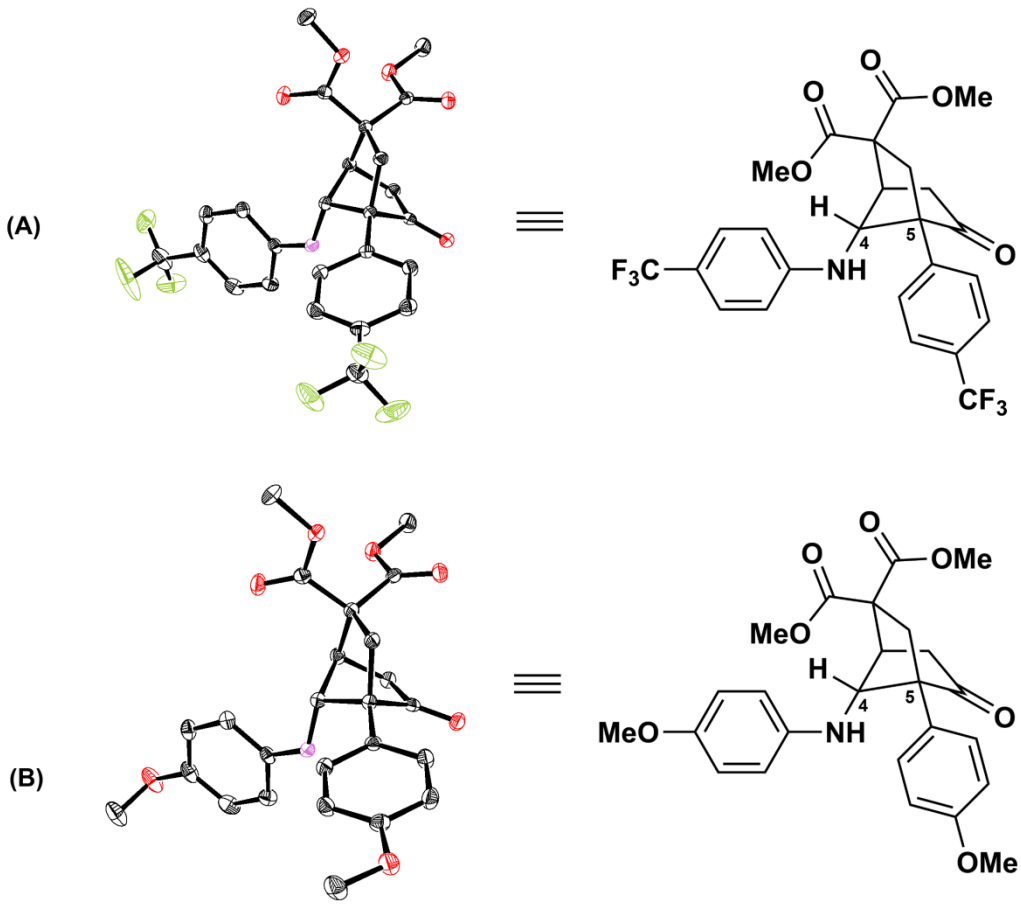
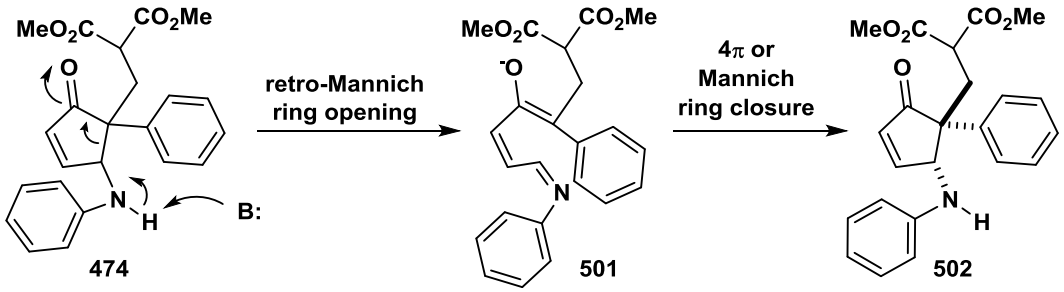


Figure 30. ORTEP drawings of bicyclic intramolecular Michael adducts of **497** (A) and **498** (B) (left) shown with 50% thermal ellipsoids. Hydrogen atoms have been omitted for clarity. The crystal structure data can be obtained from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. CCDC # (A) 901791, (B) 913832.

The higher than expected yields might be due to a base catalyzed ring opening reaction. We presume that the deprotonation of the amine **474** could induce ring opening of the 4-aminocyclopentenone to form enolate **501**, which could re-cyclize by way of an intramolecular Mannich reaction or a 4π electrocyclization (Scheme 73). In this way, NaOH might facilitate a dynamic kinetic resolution of the cyclopentenones through *in situ* epimerization to the *cis* diastereomer that then further cyclize to from the bicyclic

compounds. This would also explain why there is no minor cyclopentenone diastereomer present after treatment with NaOH, since cyclopentenone ring opening might only lead to bicyclic products or other decomposition products.

Scheme 73. Possible base catalyzed ring opening of 4-amino cyclopentenones.

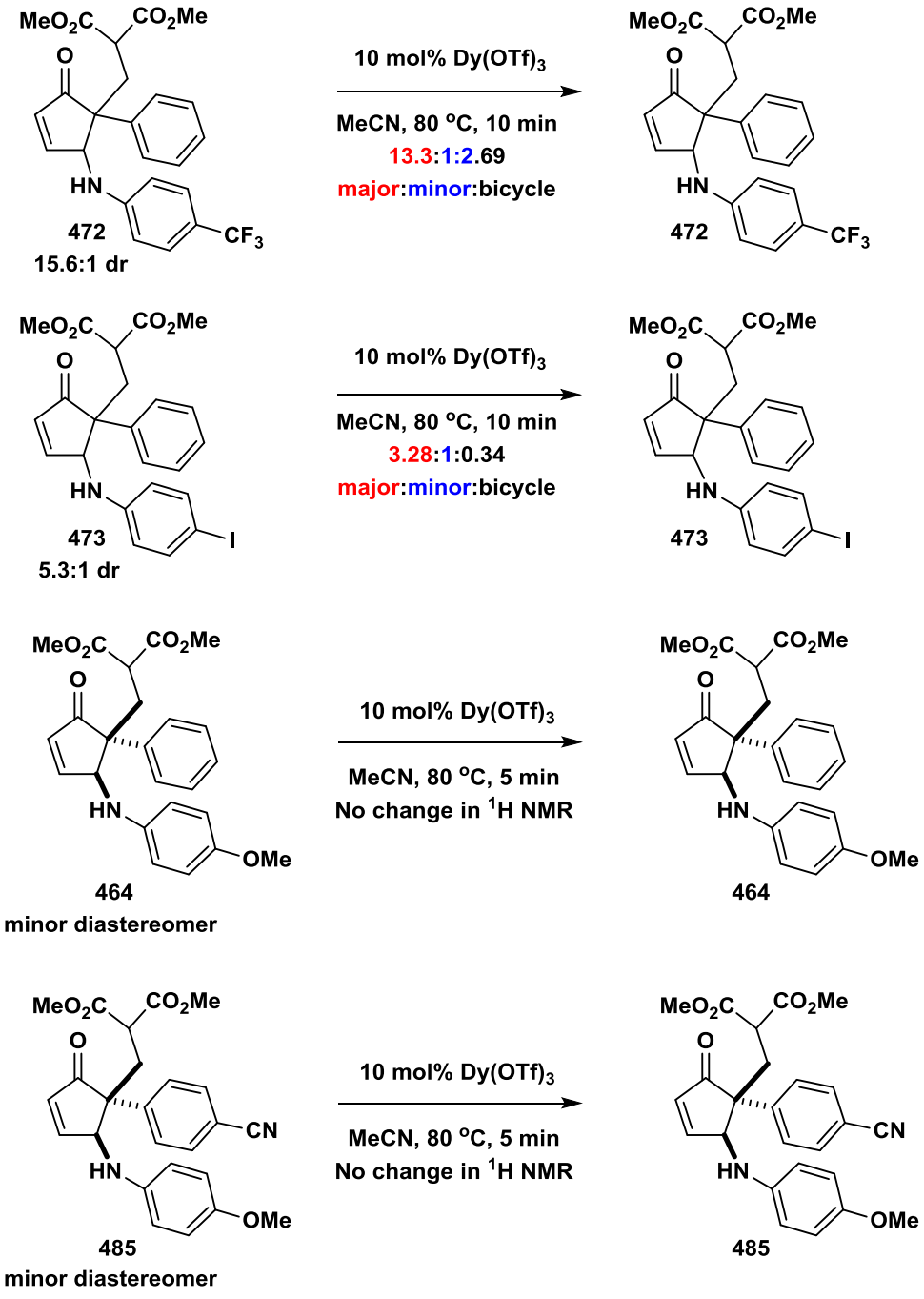


3.3.8 Reversibility Studies

We were interested in understanding why higher temperatures lead to an increase in diastereoselectivity for the rearrangement. In order to study the origin of the selectivity for the rearrangement, we performed experiments that would reveal if the cyclopentenone formation is reversible under the Lewis acid catalyzed reaction conditions. We hypothesized that if the reaction is reversible, the *cis* diastereomer is the more thermodynamically stable since we always observe this to be the major diastereomer, and that at higher temperatures the reversible reaction would lead to enrichment in the *cis* diastereomer. We found that when cyclopentenones comprised of a mixture of diastereomers **472** and **473**, were heated to 80 ^{o}C in the presence of 10 mol % $Dy(OTf)_3$, the ratio of diastereomers remained largely unchanged after accounting for the formation of the bicyclic products. Resubjecting the minor *trans* diastereomer to the reaction conditions at 80 ^{o}C produces no change in the ^{1}H NMR using either the phenyl substituted cyclopentenone **464** or the electron deficient cyclopentenone **485**, which we know to be more prone to the intramolecular Michael

addition under the reaction conditions. This data indicates that under acidic conditions, the formation of the 4-amino cyclopentenone is not reversible and only the major diastereomer can react to form the bicyclic compounds.

Scheme 74. Reversibility studies.



3.4 Conclusion

In conclusion, we have shown that donor-acceptor cyclopropanes can function as a distinctly new and effective activation group for the aza-Piancatelli rearrangement. We have shown that tri-substituted donor-acceptor cyclopropanes perform similarly to alkyl substituted furylcarbinols due to the initial formation of aniline substituted homo-conjugate addition products. Tri-substituted furyl cyclopropanes are compatible with a range of aniline and N,O-substituted hydroxylamine nucleophiles. Competition experiments reveal that the homo-conjugate addition products react by way of Lewis acid activation that facilitates dissociation of the aniline from the furan-substrate to form a reactive oxocarbenium cation, which nucleophiles in the bulk solution compete to react with.

In addition, we have discovered that tetra-substituted furyl cyclopropanes are capable of overcoming the limitations inherent to tertiary furylcarbinols and are capable of forming 4-amino cyclopentenones bearing an all-carbon quaternary stereocenter in high yield and with high diastereoselectivity. The new tetra-substituted activation group exhibits behavior unique to these substrates. The reactions can be performed at very low temperatures, but also benefit from elevated reaction temperatures. Additionally, in contrast to our previous observations for other furan activating groups, electron rich anilines nucleophiles are faster to react than electron deficient anilines. The mechanism of the rearrangement is still not well understood and there are a number of factors that influence the diastereoselectivity of reactions using tetra-substituted furyl cyclopropanes. Further work is warranted to uncover the unique underlying mechanism.

3.5 References

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4. Aliphatic Amine Nucleophiles and Computational Studies

4.1. Attempts to Utilize Aliphatic Amines for the Rearrangement

4.1.1 Introduction

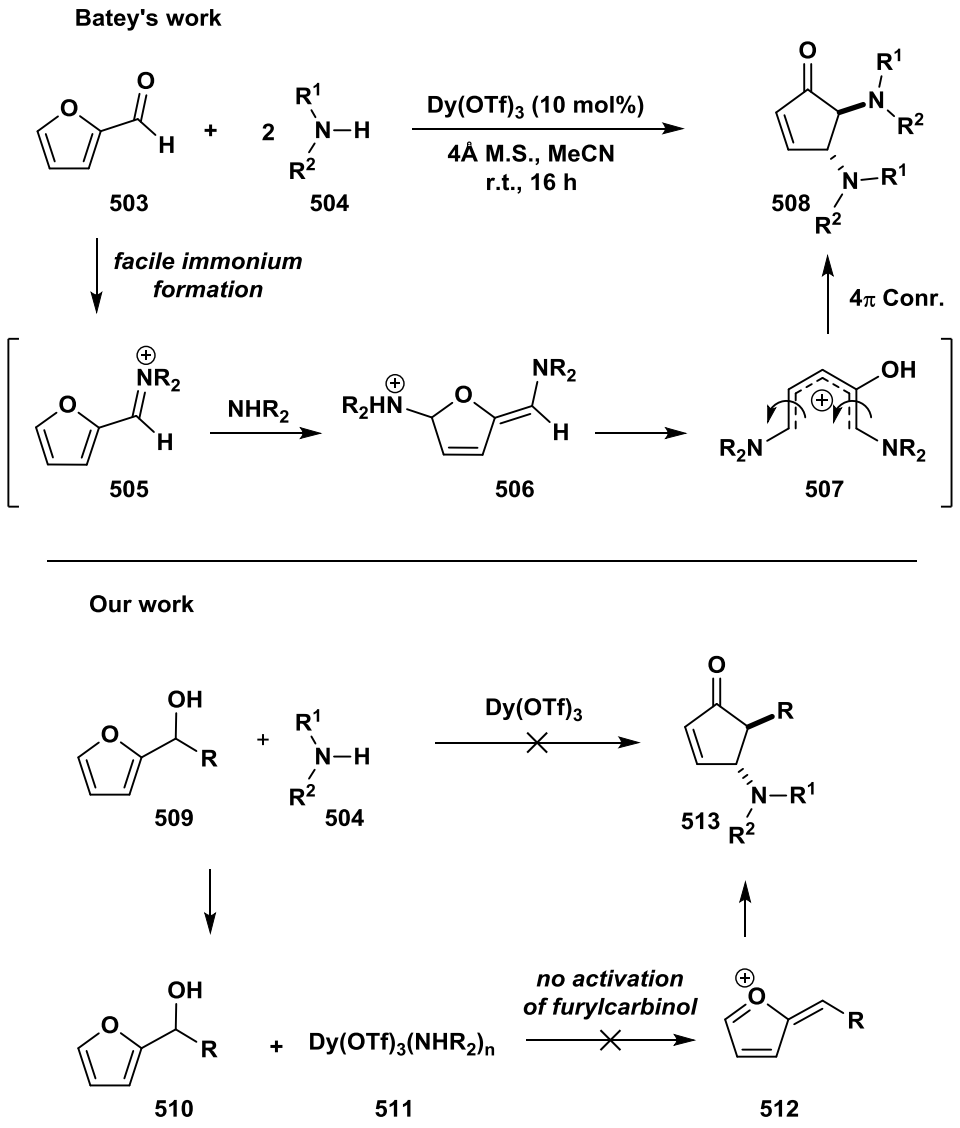
Throughout the development of the aza-Piancatelli rearrangement, we have been interested in expanding the scope of amine nucleophiles to include primary and secondary aliphatic amines because this would be the most attractive solution for applications in natural product synthesis and it would provide a useful starting point for forming a variety of nitrogen containing functional groups.

We were initially inspired by Batey's report on the ability utilize lanthanide triflate Lewis acids for the rearrangement of furfural in the presence of either aniline or aliphatic amine nucleophiles.[1] Unfortunately, under similar conditions but using furylcarbinols instead of furfural for the aza-Piancatelli rearrangement, only aniline nucleophiles were found to be effective, and attempts to use aliphatic amines resulted in no reaction and recovery of starting materials. We believe that the major difference between our furylcarbinol system (**509**) and Batey's usage of furfural (**503**), is the nature of the furan activation. Using furfural, condensation to form the immonium **505** is more facile, which, once formed, activates furan to nucleophilic attack by another equivalent of amine (**504**), to form **505** (Scheme 75).

In collaboration with the Hein group, we have determined that that a coordination complex forms between aniline and $Dy(OTf)_3$, and that the rate limiting step of the aza-Piancatelli rearrangement is the dissociation of an aniline from the catalyst.[2] Dissociation of an aniline ligand frees a coordination site on the Lewis acid and provides the ability for the

furylcarbinol to coordinate and initiate the cascade sequence. This effect is stronger for electron rich anilines, and results in longer reaction times. Overall, this is consistent with predicted Lewis acid / Lewis base chemistry, where, more Lewis basic amines coordinate more strongly and reduce the catalytic activity of the Lewis acid. It is plausible that the barrier for the activation of the cascade rearrangement using furylcarbinols is higher than for furfural, which would explain why Batey is able to utilize aliphatic amines with furfural, and due to the reduced catalytic activity of the Lewis acid in the presence of aliphatic amines, furylcarbinols fail to activate. Another possible explanation for the observed lack of catalytic activity when using aliphatic amines with lanthanide triflate Lewis acids is that when the two compounds are combined, often we observe the formation of a white precipitate. This might be due to the formation of an insoluble Lewis acid-base complex between the amine and lanthanide cation, or through the formation of insoluble lanthanide hydroxide species, which could be formed under slightly basic conditions – a result of the amine functional group.[3]

Scheme 75. Activation of furfural and furylcarbinols.

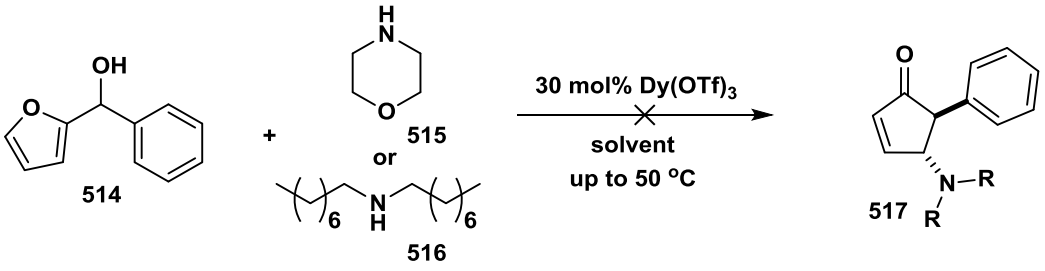


4.1.2 Aliphatic Amines for the aza-Piancatelli Rearrangement

We investigated why aliphatic amines failed to react with furylcarbinols by performing a solvent screen with two different amines either as the free base or as the HCl acid salt. Morpholine and dioctylamine were chosen because they could be easily handled as either the free base or as the HCl salt.

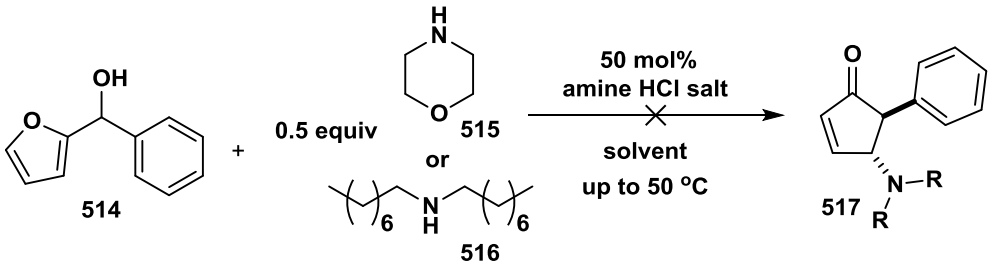
Investigations began by attempting to use the free base of amines **515** and **516**. The reaction conditions using the free base amines were standardized to be one equivalent of phenyl furylcarbinol, one equivalent of the amine, and 30 mol % $Dy(OTf)_3$ in the selected solvent at reflux or up to 50 ^oC (Scheme 76). Unfortunately, the solvent screen did not produce any positive results with either morpholine or dioctylamine, and all reactions resulted in recovery of starting materials after >3 days.

Scheme 76. Solvent screen with aliphatic amines as their free base.



By utilizing amine acid salts we also explored the possibility of catalyzing the reaction using a Brønsted acid by employing 0.5 equivalents of the amine free base and 0.5 equivalents of the same amine as its HCl acid salt (Scheme 77). Unfortunately testing these conditions in a variety of solvents also lead to the recovery of starting materials after >3 days.

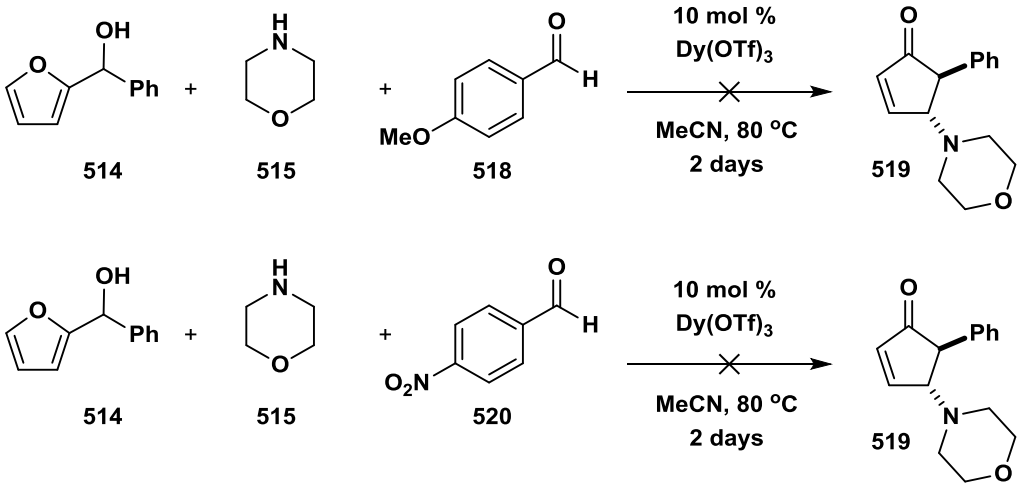
Scheme 77. Solvent screen with aliphatic amines and their HCl salt.



Trying to induce the rearrangement thermally at high temperatures (100 ^{o}C in toluene or $MeNO_2$) using morpholine and phenyl furylcarbinol in the absence of catalyst was also unsuccessful and only starting materials were recovered.

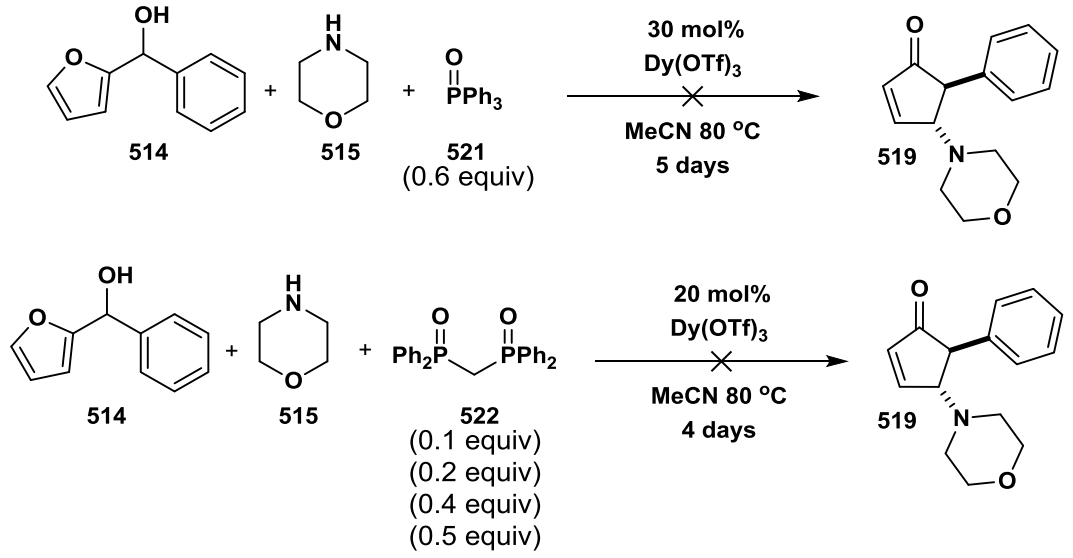
Throughout the development of the aza-Piancatelli rearrangement, we have occasionally investigated the utilization of aliphatic amines based on the hypothesis that the Lewis acid-amine complex is responsible for inhibiting the reaction. To evaluate this scenario, we have tried various ways to try and disrupt the proposed Lewis acid-amine complex. We hypothesized that one way to do this would be to utilize a reversible condensation into an aldehyde to slowly release the amine into solution. Phenyl furylcarbinol **514**, morpholine **515**, and either an electron rich aldehyde **518** or electron deficient aldehyde **520** were combined in MeCN, then $Dy(OTf)_3$ was added and the reaction heated at 80 ^{o}C for 2 days (Scheme 78). Unfortunately, only starting materials were recovered from the reactions.

Scheme 78. Attempts to use aldehyde condensations to control the release of amine.



We have also tried disrupting the Lewis acid-amine complex through a series of experiments where we added phosphorous Lewis bases in various amounts to attempt to competitively bind to the lanthanide Lewis acid and help to displace the amine ligands. Unfortunately, these efforts were also unsuccessful and also led to recovery of starting materials (Scheme 79).

Scheme 79. Attempts to use phosphorous ligands to displace amine ligands on the Lewis acid.

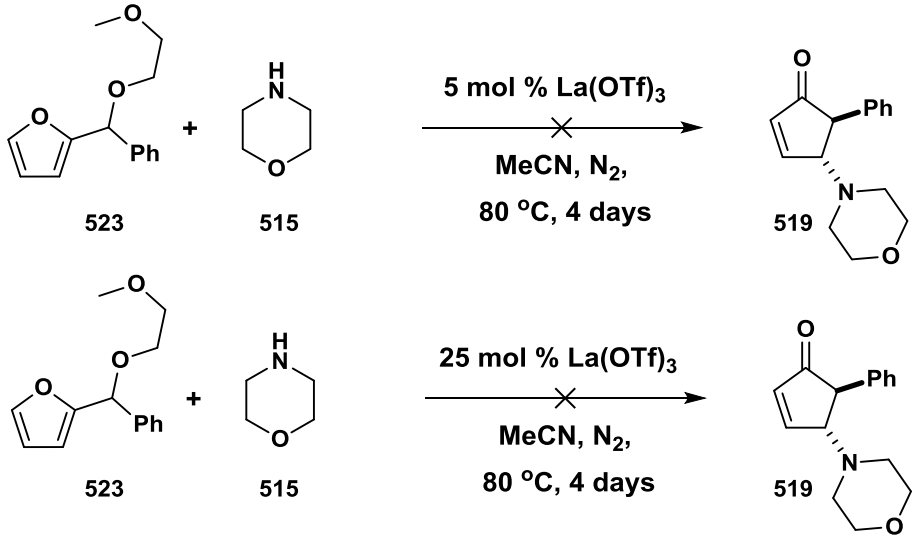


Since we often observed a precipitate form after adding the catalyst, we wondered if we were forming an insoluble lanthanide hydroxide complex due to water present in the reaction mixture, and that this is responsible deactivation of the catalyst. We hypothesized that water might be problematic due to the possible formation of insoluble lanthanide hydrate complexes. Unfortunately, using standard furylcarbinols, it is not possible to perform the reactions under strictly anhydrous conditions due to the loss of water during the activation step. Attempts were made to add desiccants such as $MgSO_4$ or $NaSO_4$ to the reaction mixture, but these experiments simply resulted in recovery of the starting materials.

In order to obtain strictly anhydrous conditions, we opted to use the ether based leaving group **523** instead of the hydroxyl leaving group. Lanthanum triflate was selected for these experiments since it is the least Lewis acidic lanthanide triflate complex.[3] The catalyst was dried by heating the powder to 200 ^oC for 24 h under high vacuum, and was stored under N_2 in a glovebox. Morpholine was distilled from sodium metal, and the furyl ether starting

material was dried under high vacuum for 24 h. The reactions were performed in flame dried glassware under N_2 atmosphere. These reactions were very slow and we still recovered mostly starting materials, but the ^{1}H NMR of these two reactions showed trace amounts of material that might be the desired cyclopentenone. This observation encouraged us to continue pursuing the usage of different types of leaving groups.

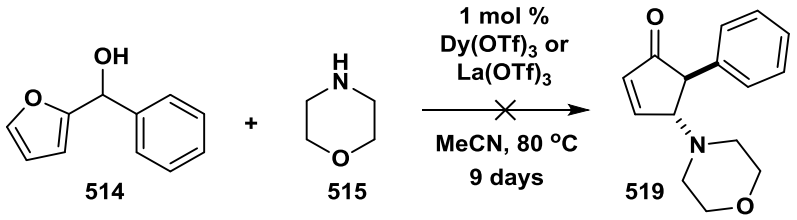
Scheme 80. Anhydrous conditions using ether leaving groups gave recovery of starting materials and trace amounts of unknown products.



A report by Forsberg suggests that when utilizing lanthanide (Ln^{3+}) triflate Lewis acids for reactions involving aliphatic amines, that a low amine:Ln^{3+} ratio is important to enhance reaction rates.[4] Forsberg studied the effect of catalyst to Ln^{3+} ratios and found that a 50:1 ratio of amine to La^{3+} in MeCN gave the highest reaction turnover rates, and the shortest reaction times. The reasoning behind this finding is that with lower catalyst loading, more free amine exists in the bulk solution that is not coordinated to the Lewis acid, and when association between the Lewis acid and substrate take place, there are amine nucleophiles available to react, rather than being sequestered due to coordination to the Lewis acid. Based

on this finding, we reduced the catalyst loading to 1 mol % $Dy(OTf)_3$ or $La(OTf)_3$ (which is known to be the least Lewis acidic lanthanide triflate) (Scheme 81).[3] Unfortunately, again, no reaction was observed and only starting materials were recovered. We have attempted to use less Lewis acidic lanthanide catalysts such as $DyCl_3$ and $YbCl_3$, also with no success.

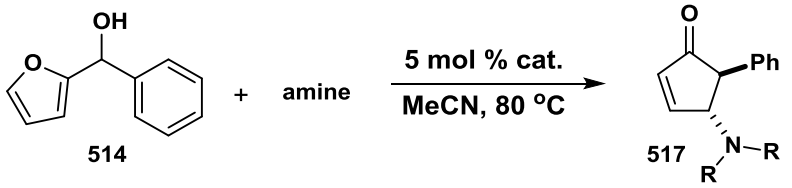
Scheme 81. Attempts to use aliphatic amines with low catalyst loading.

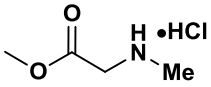
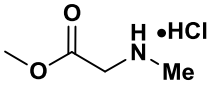
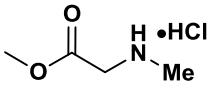
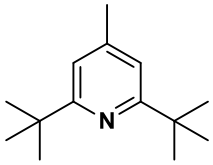
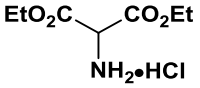
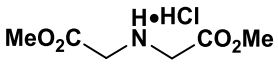
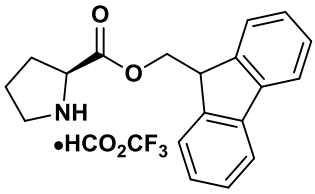


We were curious about exploring the electronic nature of the amine. Investigations using anilines and hydroxylamines indicate that a balance between Lewis basicity and nucleophilicity must be struck in order for the amine to be an effective nucleophile. We hypothesized that electron withdrawing groups close to the amine might help to reduce the Lewis basicity of the nitrogen and allow it to participate in the rearrangement. A number of amines bearing electron withdrawing ester groups were examined with mixed amounts of success (Table 31). When sarcosine methyl ester hydrochloride was subjected to the standard reaction conditions, a mixture of products was formed. We were able to isolate an inseparable mixture of what we have tentatively identified as a 2.3:1 mixture of 4-amino cyclopentenone to 4-hydroxy cyclopentenone (the standard Piancatelli product from the addition of water rather than amine) (entry 1). Unfortunately, sarcosine methyl ester is volatile as its free base and difficult to handle. Attempts were made to generate the free base *in situ* by addition of either $NaHCO_3$ (entry 2) or the bulky base 2,6-di-tert-butyl-4-methylpyridine (entry 3), but both reactions only produced a complex mixture of products

with no sign of the desired 4-amino cyclopentenone. Additionally, we tried to free base sarcosine methyl ester hydrochloride in MeCN using K_2CO_3, followed by filtration using a 0.2 μm syringe filter to remove solid K_2CO_3. Addition of the furylcarbinols and $Dy(OTf)_3$ to the MeCN that presumably contained the free amine only resulted in the recovery of starting materials. When a primary amine HCl salt with two adjacent electron withdrawing groups was employed, we were able to isolate a 15% yield of the desired 4-amino cyclopentenone (entry 4), with no additional water addition products detected. Unfortunately, a similar but secondary amine only gave a complex mixture of products (entry 5). A proline derived amine as the TFA salt was employed to examine the affect of the nature of the Brønsted acid, but again only gave a complex mixture of products (entry 6).

Table 31. Attempts to utilize electron deficient aliphatic amines.



entry	amine	catalyst	additive	time	yield %
1		$Dy(OTf)_3$	-	1 h	2.3:1 amine:H_2O product
2		$Dy(OTf)_3$	1 equiv $NaHCO_3$	14 days	complex mixture
3		$Dy(OTf)_3$	1 equiv 	8 h	complex mixture
4		$Dy(OTf)_3$	-	2 h	15 %
5		$La(OTf)_3$	-	4 h	complex mixture
6		$La(OTf)_3$	-	7 h	complex mixture

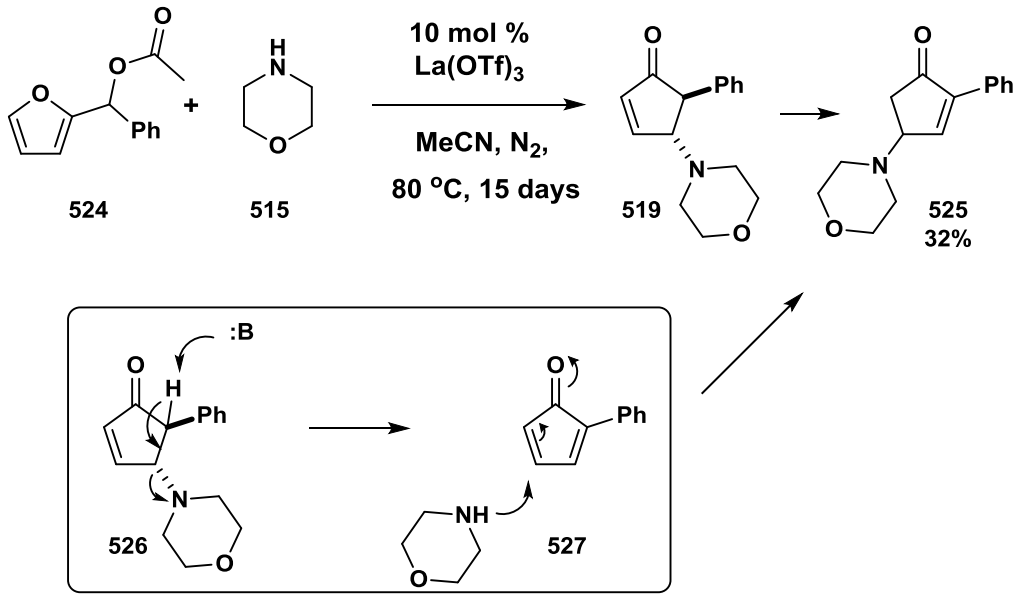
The results from experiments utilizing aliphatic amines with adjacent electron withdrawing groups are intriguing, because for the first time, using the standard reaction conditions, we have been able to form small amounts of 4-amino cyclopentenone products, and in the case of bis(2-chloroethyl)amine form 4-amino cyclopentenones in quantitative yield. In addition, these reactions are distinct from our attempts to utilize aliphatic amines such as morpholine. In our attempts to utilize morpholine, we always observed catalyst

inhibition and no reaction progress, while this class of amines leads to decomposition of the starting materials, indicating that an active catalyst remains present.

4.1.3 Acetate as a Leaving Group Compatible with Aliphatic Amines

We hypothesized that furylcarbinols are not activated enough to be able to utilize more Lewis basic aliphatic amines, so we sought to investigate utilizing more labile activating groups to facilitate the rearrangement. Utilizing acetylated furylcarbinol **524**, morpholine **515** and 10 mol % $La(OTf)_3$ under anhydrous conditions and N_2 atm, we were pleasantly surprised to isolate the fully rearranged 4-amino cyclopentenone **525** in 32% yield (Scheme 82). This type of fully rearranged cyclopentenone has been observed by Piancatelli under basic conditions,[5] but until now, had never been observed during the aza-Piancatelli rearrangement. Based on Piancatelli's finding, we presume that the continued rearrangement of 4-aminocyclopentenone **519** to **525** is base catalyzed. We speculate that the basic aliphatic amine can deprotonate α to the carbonyl (**526**) to form the elimination product **527**, which is susceptible to nucleophilic attack by the amine and ultimately forms 4-amino cyclopentenone **525**.

Scheme 82. aza-Piancatelli rearrangement using morpholine.



Encouraged by this initial result, we continued to study the rearrangement using acylated furylcarbinols (Table 32). Taking no precautions to exclude air or water, experiments using acylated furylcarbinol **524** with 10 mol % $Dy(OTf)_3$ resulted in the formation of cyclopentenone **525** as well as the substitution product **528** in a 1:1.6 ratio, respectively (entry 1). In our previous work, we have observed that substitution products from aniline or hydroxylamine nucleophiles are labile enough to act as a leaving group and continue to turn over to form cyclopentenones. However, we have not been successful in turning over morpholine substitution products to the cyclopentenone by resubjecting them to the reaction conditions. When $Sc(OTf)_3$ was employed, a 1:2 ratio of cyclopentenone**525** to substitution product **528** was obtained (entry 2). Using $La(OTf)_3$, a 1:1 ratio of products was obtained (entry 3). Employing $La(OTf)_3$ with the addition of the weakly coordinating anion $NaBAr^F$ (Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) reduced the reaction time to 11 h, but still produced a 1:1 mixture of cyclopentenone and substitution products (entry 4).

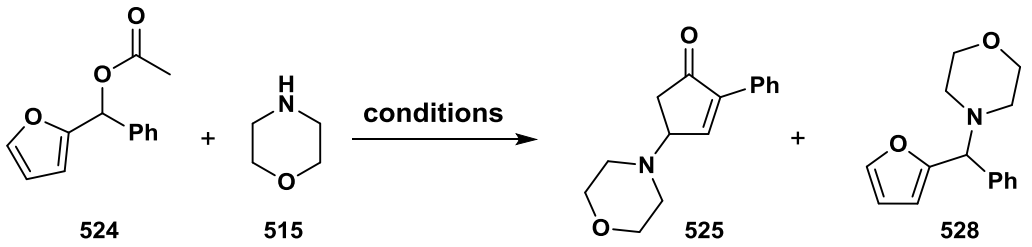
Tius and co-workers have published an interesting interrupted Nazarov reaction using primary and secondary aliphatic amines catalyzed solely by silica gel with no solvent.[6] Due to the problems we faced with catalyst inhibition when using aliphatic amines, we hypothesized that silica gel could be an alternative catalyst for the aza-Piancatelli rearrangement, and might still be active when using aliphatic amine nucleophiles.

Unfortunately, simple phenyl furylcarbinol failed to react with morpholine when stirred in silica gel; however we had some success when using acylated phenyl furylcarbinols. The experiments were performed by placing the solid furylcarbinol into a round bottom flask and crushing it with a spatula, then silica gel was added (20 equivalents based on a 60 g/mol molecular weight) followed by addition of morpholine, then stirred with a magnetic stirrer. The reactions were worked up by adding ~5 ml EtOAc then filtering off the silica gel (3x) followed by removal of the solvent. Using EMD Geduran® silica gel and acylated phenyl furylcarbinol **524** resulted in the recovery of starting material after stirring for 2 days (entry 5). However, after switching to a different brand of silica gel, (Silicycle SiliaFlash® F60) we were able to obtain a 4:1:1.4 ratio of cyclopentenone, substitution and starting material, respectively (entry 6). We speculate that the Silicycle silica gel is more acidic than the EMD silica gel.

We sought to experiment more with the EMD silica gel to get a better understanding of the dramatic differences between the two brands. First, we activated the EMD silica gel at 160 ^{o}C for 24 h under high vacuum. Activation in this way helps to drive off water from the micro-capillaries in the silica gel and increase the available surface area. The activated silica gel was more active, but even after stirring at rt for 5 days, a 2.5:1:8 ratio of cyclopentenone, substitution and starting material, respectively was obtained (entry 7). Heating reactions

using activated EMD silica gel to 80 ^{o}C produced mostly substitution products (entry 8). We explored adding a Lewis acid to the activated EMD silica gel. After 5 days stirring at room temperature with 10 mol % $Sc(OTf)_3$ we obtained a 3.7:1:3 cyclopentenone, substitution and starting material, respectively, which is closer to the results we observed with the unaltered Silicycle silica gel. Unfortunately, heating the reaction to 80 ^{o}C in the presence of $Sc(OTf)_3$ lowers the amount of cyclopentenone product formed compared to reactions at rt (cf. entries 9 and 10). Addition of 5 mol % TFA resulted in closer to a 1:1 ratio of cyclopentenone to substitution products after 9 days at room temperature (entry 11).

Table 32. Reactions between acylated furylcarbinols and morpholine.



524 515 525 528

cyclopentenone substitution

entry	solvent		time	temp	cyclopent : sub
1	MeCN	10 mol % $Dy(OTf)_3$	42 h	80	1 : 1.6
2	MeCN	10 mol % $Sc(OTf)_3$	40 h	80	1 : 2
3	MeCN	10 mol % $La(OTf)_3$	62 h	80	1 : 1
4	MeCN	10 mol % $La(OTf)_3$, $NaBAr^F$	11 h	80	1 : 1
	no solvent Silica Gel	**additive**	**time**	**temp**	**cyclopent : sub : S.M.**
5	EMD		2 days	rt	recovered S.M.
6	Silicycle		3 days	rt	4 : 1 : 1.4
7	EMD*		5 days	rt	2.5 : 1 : 8
8	EMD*		22 h	80	0.1 : 1 : 0.14
9	EMD*	10 mol % $Sc(OTf)_3$	5 days	rt	3.7 : 1 : 3
10	EMD*	10 mol % $Sc(OTf)_3$	2 h	80	1 : 1 : 0.2
11	EMD*	5 mol % TFA	9 days	rt	1.2 : 1 : 4.2

*Silica gel activated at 160 ^oC under vacuum for 24h. S.M. = starting material
EMD = EMD Geduran® Silica Gel 60 11567 40-63µm
Silicycle = SiliaFlash® F60 40-63µm (230-400 mesh) 60Å Irregular Silica Gels (R10030B)

4.1.4 Conclusion

Throughout the development of the aza-Piancatelli rearrangement, we have been uncertain as to why the more Lewis basic aliphatic amines do not participate in the rearrangement. From our extensive experiments using aliphatic amines, we can speculate

that the poor reactivity that is observed is due to the coordination complex that forms between the Lewis acid and Lewis basic amine. The coordination complex either does not undergo ligand exchange at an appreciable rate, which would lead to extremely long reaction times, or the amine influences the effective Lewis acidity of the catalyst in such a way that the catalyst is only mildly active and only able to have an effect on more sensitive systems, such as Batey's imine or the acetylated furylcarbinols. Indeed, the usage of the more labile acetylated furylcarbinols shows promise towards a more general method to utilize basic amines for the aza-Piancatelli rearrangement. However, unfortunately at this point, using acetylated furylcarbinols is still limited due to the formation of large amounts of irreversible substitution adducts. In the future we are optimistic that further modifications to the leaving group or the addition of electron donating or electron withdrawing groups to the furan will help to overcome these limitations.

4.2 Using a Computational Approach to Investigate the Origins of Diastereoselectivity

4.2.1 Introduction

When the aza-Piancatelli rearrangement is performed using tertiary furylcarbinols, which cyclize to form all carbon quaternary centers, we often obtain cyclopentenones as a mixture of diastereomers (Figure 31).

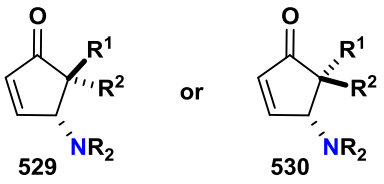


Figure 31. 4-Amino cyclopentenone diastereomers.

We know that the ratio of diastereomers can be influenced by a number of factors. Some of the factors that have an influence on the stereochemical outcome of the reaction are steric interactions, as well as electronic factors such as the nature of the aniline or aryl group pendant to the furylcarbinol. In addition, we know that employing Lewis or Brønsted acids result often will lead to differences in the stereochemical outcome of the rearrangement. Furthermore, our studies utilizing tetra-substituted donor-acceptor cyclopropanes show that in addition to the type of Lewis acid, the hydration state of lanthanide Lewis acids can influence the diastereomeric outcome. Indeed, there are a number of factors in a delicate balance that influence the final outcome of the rearrangement. Unfortunately, it is still unclear as to which step, or intermediates in the mechanism give rise to diastereoselectivity, or how each of these factors, and in particular, electronics and differences in Lewis acids, influence the key diastereodetermining step.

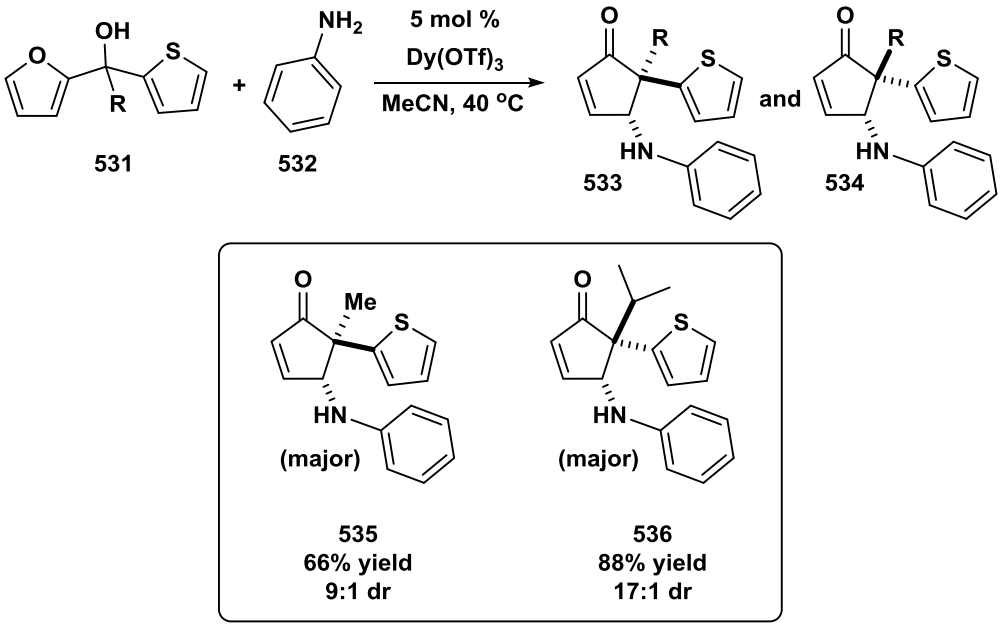
In order to gain a better understanding of the underlying mechanism, we established a collaboration with the Tantillo group at UC Davis to utilize a computational approach to help understand the nature of the intermediates that govern the stereochemical outcome of the rearrangement. Through this collaboration, I had the opportunity to travel to UC Davis and learn about computational chemistry using the Gaussian computational package. After my trip to Davis, I was able to utilize the Knot computer cluster in the Center for Scientific Computing at UCSB to calculate rotational energy barriers for a number of reaction intermediates. This is a freely available cluster open to all users at UCSB and is supported by the NSF Grant CNS-0960316.

We were primarily interested in understanding the nature of the diastereodetermining event in the rearrangement of tetra-substituted donor-acceptor furyl cyclopropanes.

Unfortunately, calculations using density functional theory (DFT) at the B3LYP/6-31G* level where prohibitively time consuming for furyl cyclopropanes due to the large molecular size and lack of conformational rigidity of the systems (often taking over one week per computation). In order to study the origin of diastereoselectivity, we sought to use a simpler system that is also known to give mixtures of diastereomeric products.

In our laboratory, we have studied the rearrangement of another class of tertiary furylcarbinols bearing a thiophene group **531** that produces cyclopentenones **533** and **544** in a mixture of diastereomers (Scheme 83).[7] Previously we have studied the diastereomeric outcome of tertiary furylcarbinols bearing both an alkyl group and a phenyl group. When the alkyl group was a small methyl group, the selectivity was never higher than 2.6:1 dr (see section 2.2.2). Interestingly, tertiary furylcarbinols bearing a small methyl group and a thiophene group produce cyclopentenones **235** in higher diastereomeric ratios (9:1 dr), and with the major diastereomer having opposite relative stereochemistry to that observed when using methy- phenyl-substituted furylcarbinols. We speculated that coordination between the acid, sulfur and hydroxyl group directs the formation of the major diastereomer. As expected, furylcarbinols bearing an isopropyl group and a thiophene group produced cyclopentenones **536** with high diastereoselectivity (17:1 dr), with the major diastereomer having a *trans* relationship between the isopropyl group and the aniline, which is in agreement with our previous studies employing tertiary furylcarbinols.

Scheme 83. Thiophene bearing tertiary furylcarbinols.



In an attempt to better understand the nature of the origin of diastereoselectivity in the rearrangement reaction, we decided to study the thiophene-containing tertiary furylcarbinol system computationally, since this simpler system would require substantially less processing time than the donor-acceptor cyclopropane systems. Due to our limited knowledge in this area, the system was only studied using a Brønsted acid (H^+) rather than metallic Lewis acids.

4.2.2. Probing the Mechanism

A thorough examination of the mechanism is needed to help understand where the origin of diastereoselectivity might arise throughout the course of the rearrangement (Figure 32). If the ring closing step is a stereospecific 4π conrotatory electrocyclization, then intermediates **G** and **H** are ultimately responsible for the formation of either diastereomers **F** and **I**. Moving backwards from the ring forming step to the initial activation of the furylcarbinol reveals that the olefin geometry of intermediates **A** and **C** could ultimately be parlayed into

the final diastereomer by way of intermediates **G** and **H**. However, it is uncertain as to whether the elimination step that forms **B** and **C** is the diastereodetermining event, or if **B** and **C**, or **D** and **E** can interconvert through an isomerization pathway prior to electrocyclization. We hypothesized that a computational approach could help us to understand whether or not it is energetically favorable to interconvert between the olefin geometries **B** and **C** or **D** and **E** prior to electrocyclization, which, would in turn help to reveal the origin of the stereoselectivity.

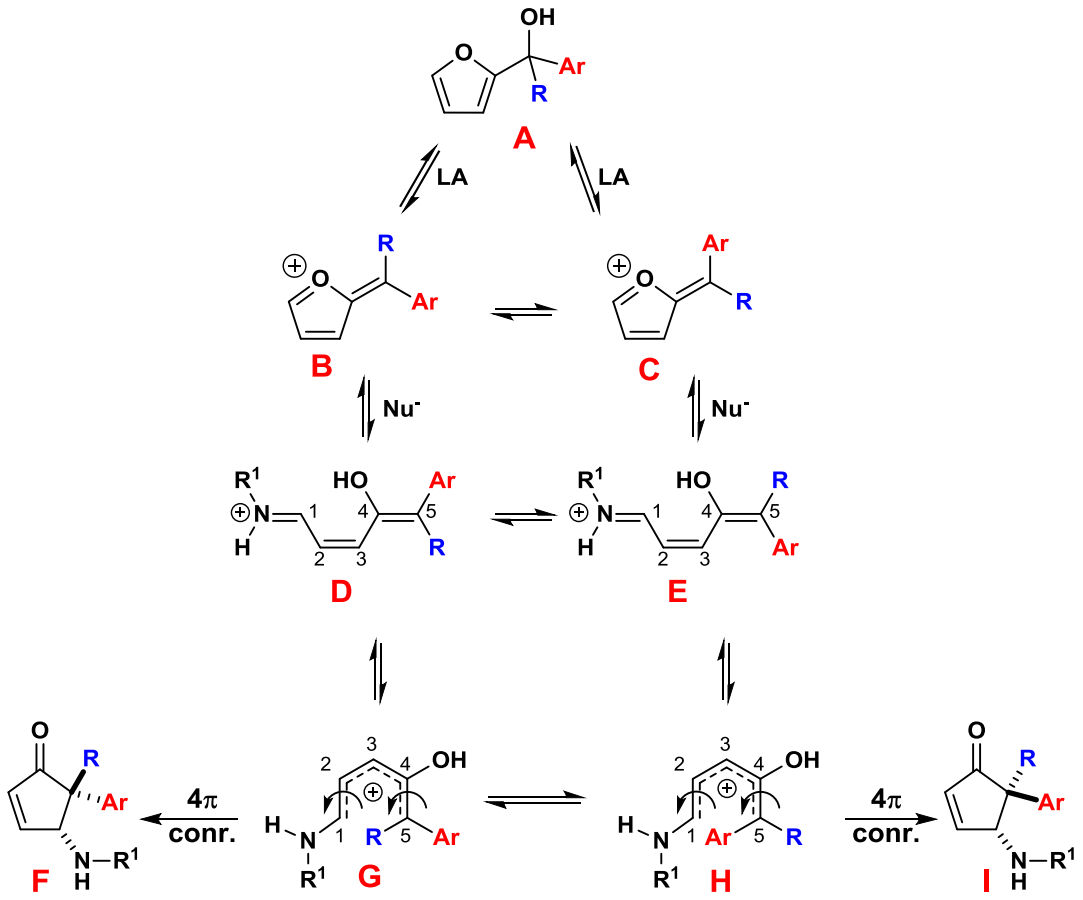


Figure 32. Examination of the mechanism that gives rise to diastereoselectivity.

We started our computational study by first computing the relative energies of intermediates from secondary furylcarbinols in order to establish a basis for comparison

later against tertiary furylcarbinol intermediates. All calculations were performed at the B3LYP/6-31G* (d,p) level of theory unless stated. Starting from phenyl furylcarbinol, dehydration leads to fully conjugated cationic intermediates **537** and **539**. The relative energies of the two possible olefin geometries and the barrier for interconversion between them were determined by calculating the energy of minimized intermediates through a 360^{o} rotational scan at 10^{o} intervals. The conversion between the *cis* **537** and *trans* **539** cation must pass through a 24.7 kcal/mol energy barrier. The *trans* cation **539** was calculated to be 2.8 kcal/mol higher in energy than the *cis* cation, which is an interesting observation, because if this geometry is conserved throughout the rearrangement, then the lower energy *cis* isomer **537** would lead to *trans* substituted cyclopentenones as the major product, which we observe as the major product in all examples that we have studied to date.

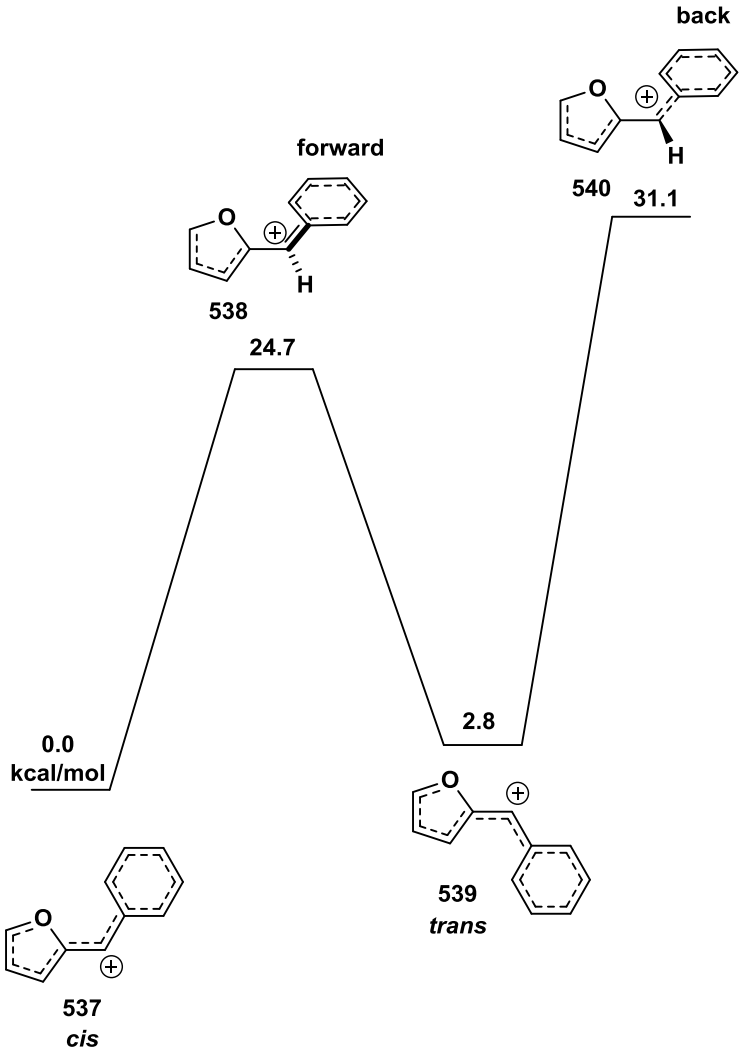


Figure 33. Relative energies of cationic intermediates. Rotational scan calculated using B3LYP/6-31G* (d,p) with 10^{o} intervals. All values in kcal/mol.

We examined a variety of computational methods using identical conditions by performing the same coordinate scan in order to compare their predicted energy differences (Figure 34). Interestingly, every method examined predicted that the *trans* cation **539** is at least 2 kcal/mol higher in energy than the *s-cis* cation **537**.

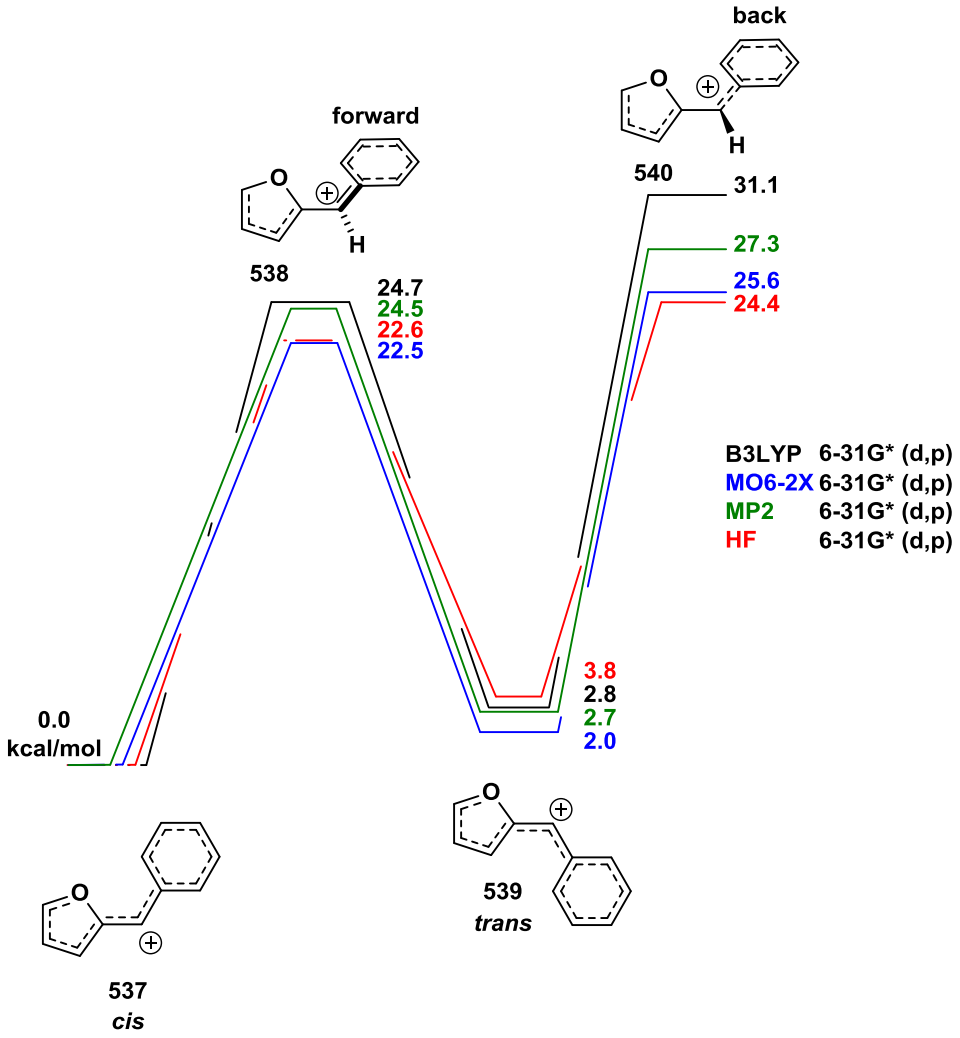


Figure 34. Comparison of computational methods. All values in kcal/mol.

For another point of comparison, we also performed a 360° rotational scan at 10° intervals using the electron rich *para*-methoxy phenyl group (Figure 35). Again, the *cis* cation isomer **541** is predicted to be lower in energy than the *trans* cation isomer **543**. These calculations suggest that the there is an energetic preference for the formation of the *cis* cation isomer over the *trans*, and that the energy for interconversion between the two cation isomers is high.

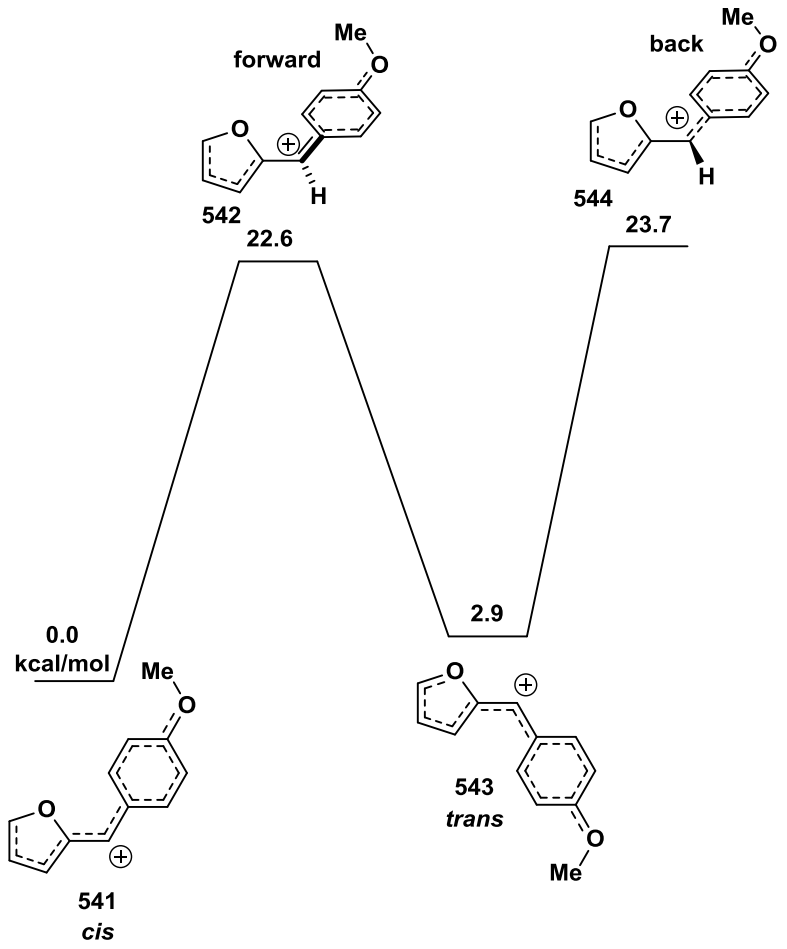


Figure 35. Relative energies of cationic intermediates. Rotational scan calculated using B3LYP/6-31G* (d,p) with 10^{o} intervals. All values in kcal/mol.

Next we sought to determine the energetic differences between the possible pentadiene geometries that would lead to the ring closing electrocyclization and their barriers for interconversion. First, let's examine the possible intermediates that form throughout the course of the rearrangement to help understand which are important for helping to control the diastereoselectivity. Nucleophilic addition by aniline into the oxocarbenium **548** derived from phenyl furylcarbinol and proton transfer gives rise to the possibilty of forming either of the two fully conjugated ring opened intermediates **546** (*cis*) or **550** (*trans*) (Figure 36). The stereospecific nature of the 4π conrotatory electrocyclization dictates that in order to form

cyclopentenones bearing a *trans* configuration, the electrocyclization must take place from pentadienyl cations **545** or **551**, that place the amine and phenyl group on opposing, or inward faces of the pentadienyl cation terminus. We hypothesize that electrocyclization from the *in-in* pentadienyl cation **551** would be energetically unfavorable due to strong steric interactions, which if true, would mean that the precursor to the electrocyclization must be **545** in all cases.

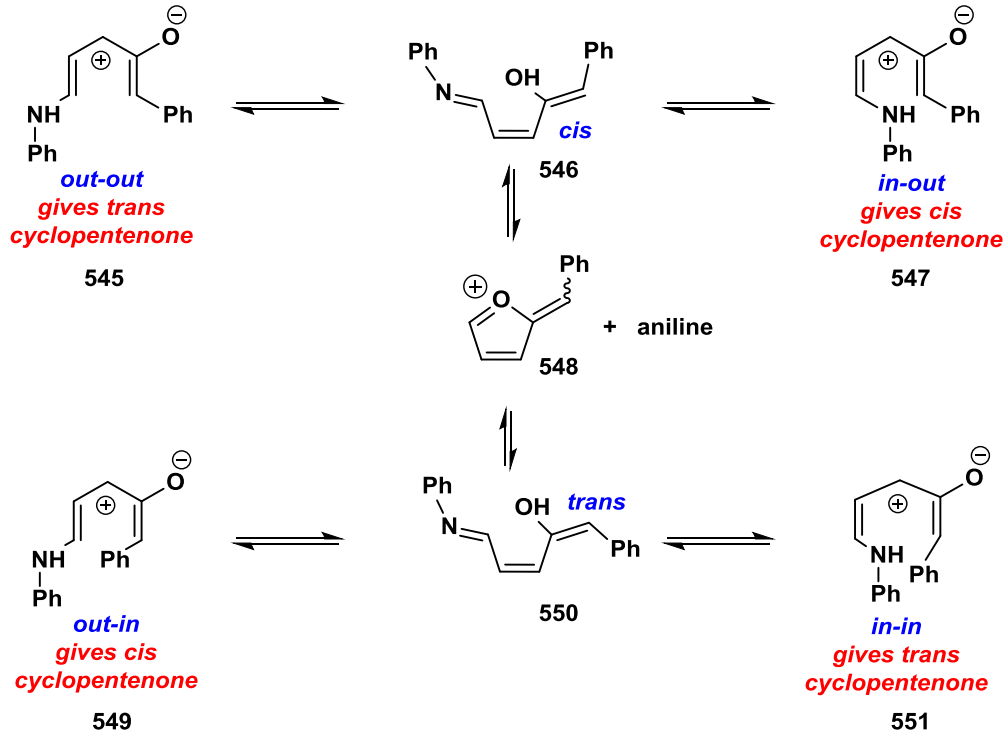


Figure 36. Possible pentadienyl cation geometries.

We have calculated the relative energies of the *cis* (**A**) and *trans* (**E**) ring opened intermediates and the rotation barriers that allow them to adopt the four possible pentadienyl cation geometries by starting from either the *cis* or *trans* intermediates and performing a rotational scan at 10^{o} intervals around atoms 1 - 2 and 3 - 4 at the B3LYP/6-31G* (d,p) level of theory (Figure 37). In corroboration with the cation energies in Figure 33, *cis*

intermediate **A** was calculated to be lower in energy (5.1 kcal/mol) than *trans* intermediate **E**. Starting from *cis* intermediate **A**, bond rotation around atoms 3 and 4 leads to the *out-out* geometry **B**, which we predicted would be the most favorable geometry that leads to *trans* substituted cyclopentenones. Indeed, **B** has the lowest relative energy of the 4 possible pentadiene geometries (**B**, **D**, **F** and **H**), and also passes through the smallest energy barrier of all four possible geometries while adopting geometry **B**. Starting at *cis* intermediate **A** and rotating around atoms 1 and 2 leads to a lower energy configuration **C**, which sits in an energy well and has to pass through a large energy barrier in order to rotate in either direction.

The *trans* intermediate **E**, displays a similar, albeit higher, rotational energy profile to the *cis* geometry. From **E**, the only geometry would lead to a *trans* cyclopentenone is **H**, but as we would expect, is the highest energy configuration due to the *in-in* terminal group geometry. These data suggest that under Brønsted acidic conditions, that the formation of *trans*-4-amino cyclopentenones likely proceeds through the formation of *cis* intermediate **A,** which undergoes bond rotation around 3 - 4 to adopt geometry **B,** which cyclizes to form the expected *trans* product. The barrier for olefin isomerization between **A** and **E** was not calculated at this time, but would be informative for future work.

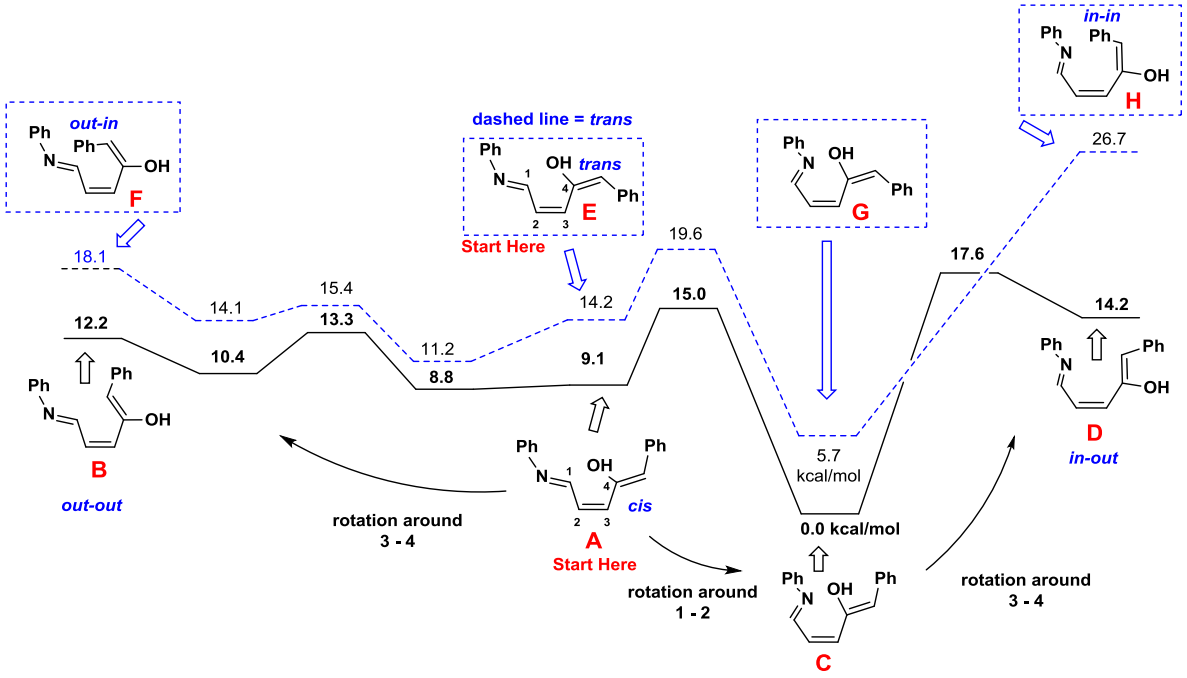


Figure 37. Energy barriers for rotation of the ring opened intermediate derived from phenyl furylcarbinol. Rotational scans calculated using B3LYP/6-31G* (d,p) with 10^{o} intervals. All values in kcal/mol.

Next, we turned our attention towards thiophene-substituted tertiary furylcarbinols. Energies of the cation geometries were calculated for the methyl-, thiophene-substituted cation (Figure 38). The *cis* geometry **552** was calculated to be 2.4 kcal/mol lower in energy than the *trans* cation geometry **554**.

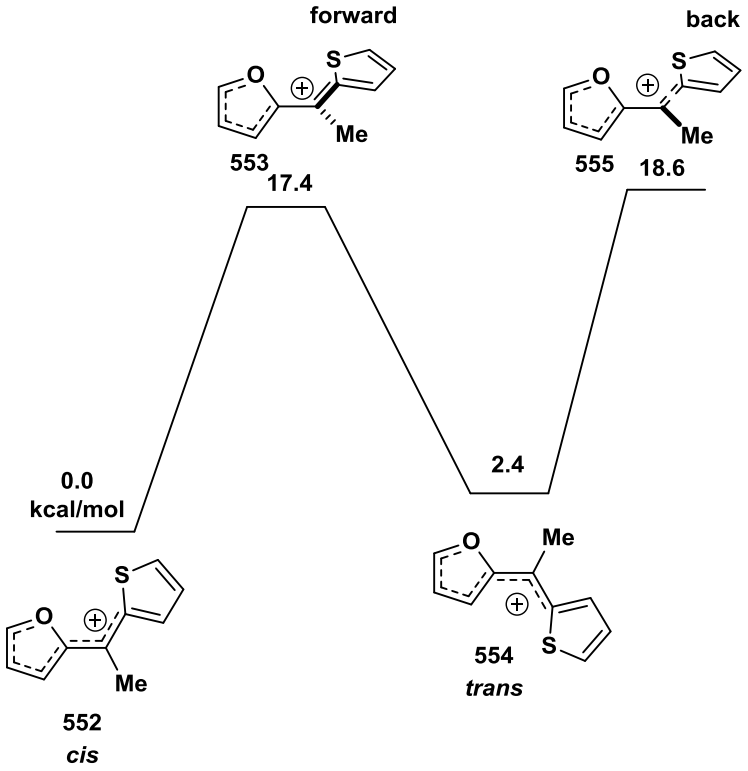


Figure 38. Methyl-, thiophene-substituted furyl carbocation geometries. Rotational scan calculated using B3LYP/6-31G* (d,p) with 10^{o} intervals. All values in kcal/mol.

For comparison, we also calculated the cation geometry for the phenyl-, thiophene-substituted furyl cation (Figure 39). Interestingly, again, the *cis* cation geometry **556** is lower in energy (1.7 kcal/mol) than the *trans* geometry **558**.

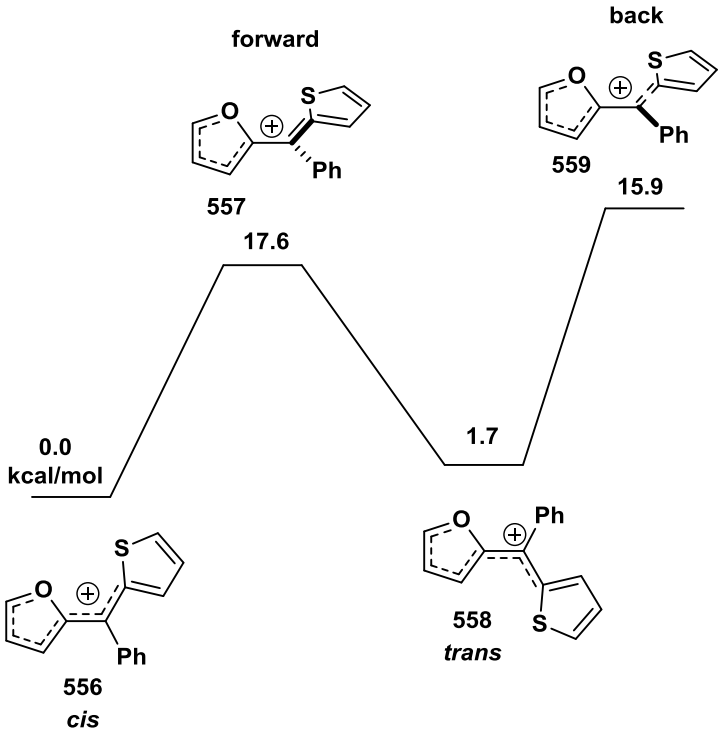


Figure 39. Phenyl-, thiophene-substituted furyl carbocation geometries. Rotational scan calculated using B3LYP/6-31G* (d,p) with 10^{o} intervals. All values in kcal/mol.

Calculations were performed to determine the relative energies of the *cis*(**A**) and *trans* (**E**) methyl-, thiophene-substituted ring opened intermediates and the rotational barriers around the bonds that allow them to adopt different pentadienyl geometries (Figure 40). The calculations started from both *cis* and *trans* intermediates and rotational scans at 10^{o} intervals about atoms 1 - 2 and 3 - 4 at the B3LYP/6-31G* (d,p) level of theory were performed. The energy profiles resemble those from the simpler phenyl furylcarbinol derived system in Figure 37. Interestingly, the energy difference between the *cis* **A** and *trans* **E** is only 0.3 kcal/mol, which is much lower than in the phenyl furylcarbinol system, and might provide a hint as to why the diastereoselectivity is generally low for this system. Moving towards right of the figure and rotating around atoms 1 and 2 lead to a lower energy

intermediate **C**, but this intermediate must pass through a high barrier in order to adopt the possible geometries **D** or **H** that could cyclize to form cyclopentenones. Conversely, moving to the left of the figure from **A** and **E**, and rotating around atoms 3 and 4, the *cis* and *trans* intermediates have the possibility of adopting either **B** or **F** after passing through only a modest energy barrier, however the *out-out* geometry **B** still remains lower in energy than *out-in* **F**. (Scheme 83). Indeed, geometry **B** leads to the major diastereomer observed experimentally. The small calculated energy difference in energy between **A** and **E**, might explain the modest selectivity observed experimentally (9:1 dr). If this is the case, then the elimination step that precedes the formation of intermediates **A** and **E** might be the diastereodetermining event.

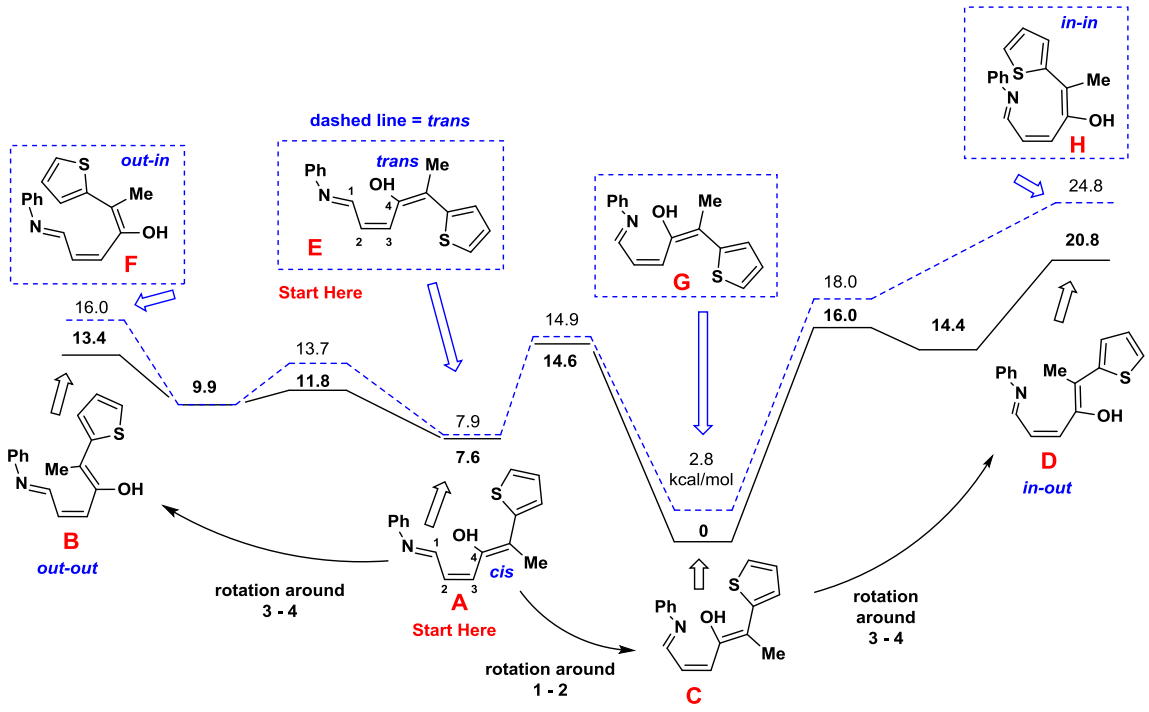


Figure 40. Energy barriers for rotation of the ring opened intermediate derived from methyl-, thiophene-substituted furylcarbinol. Rotational scans calculated using B3LYP/6-31G* (d,p) with 10° intervals. All values in kcal/mol.

Finally, we calculated the relative energies for intermediates resulting from isopropyl-, thiophene-substituted tertiary furyl carbinols (Figure 41). Calculating the energies of the carbocation generated after dehydration also results in the *cis* cation geometry **560** being lower in energy than the *trans* geometry **562**. This is interesting because the *cis* geometry in this case would lead to the minor diastereomer of the final cyclopentenone. This is the first time that the lower energy cation geometry does not agree with the experimentally observed major diastereomer. We cannot directly compare the energies from charged species to neutral species, but this might suggest that the dehydration step might not be the diastereodetermining event in this case.

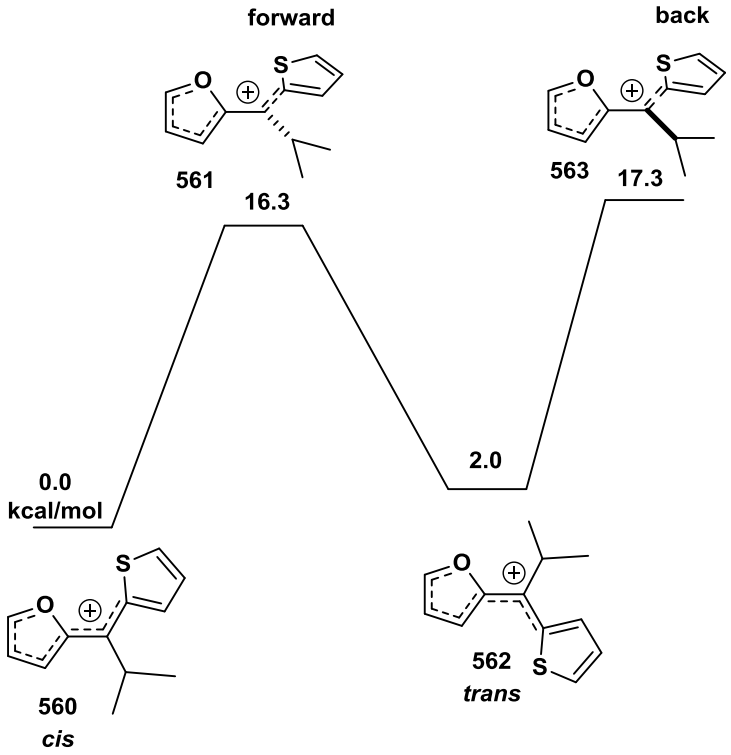


Figure 41. Isopropyl-, thiophene-substituted furyl carbocation geometries. Rotational scan calculated using B3LYP/6-31G* (d,p) with 10^{o} intervals. All values in kcal/mol.

We calculated the relative energies of the *cis* (**A**) and *trans* (**E**) ring opened intermediates of the isopropyl-, thiophene-substituted system and the rotation energy barriers around the bonds that allow them to adopt the possible pentadiene geometries (Figure 42). Intermediate **A** and **E** result from ring opening of furan after nucleophilic attack by aniline. In this case the *trans* geometry **A** is lower in energy than the *cis* geometry **E**. From **A**, rotation around atoms 3 and 4 result in the *out*-out geometry **B** which would cyclize to form the experimentally observed major diastereomer. In the energy barrier to rotate **E** about atoms 3 - 4 to form **F** is 11.5 kcal/mol, which is much higher than the rotation from **A** to **B** (6.9 kcal/mol). Both intermediates **A** and **E** have the possibility to rotate about atom 1 and 2 to form **C** or **G** by passing through a modest energy barrier. However, the energy

barriers from **C** or **G** to **D** or **H** are high and we would expect reversion back to **A** and **E** to be more likely. From these data, we can hypothesize that the diastereodetermining event is taking place prior to the formation of **B** and **F** due to their large energy differences. It would be convenient if formation of **A** or **E** from the oxocarbenium intermediate is the diastereodetermining event, but unfortunately, we cannot rule out possible olefin isomerization between **A** and **E** at this time.

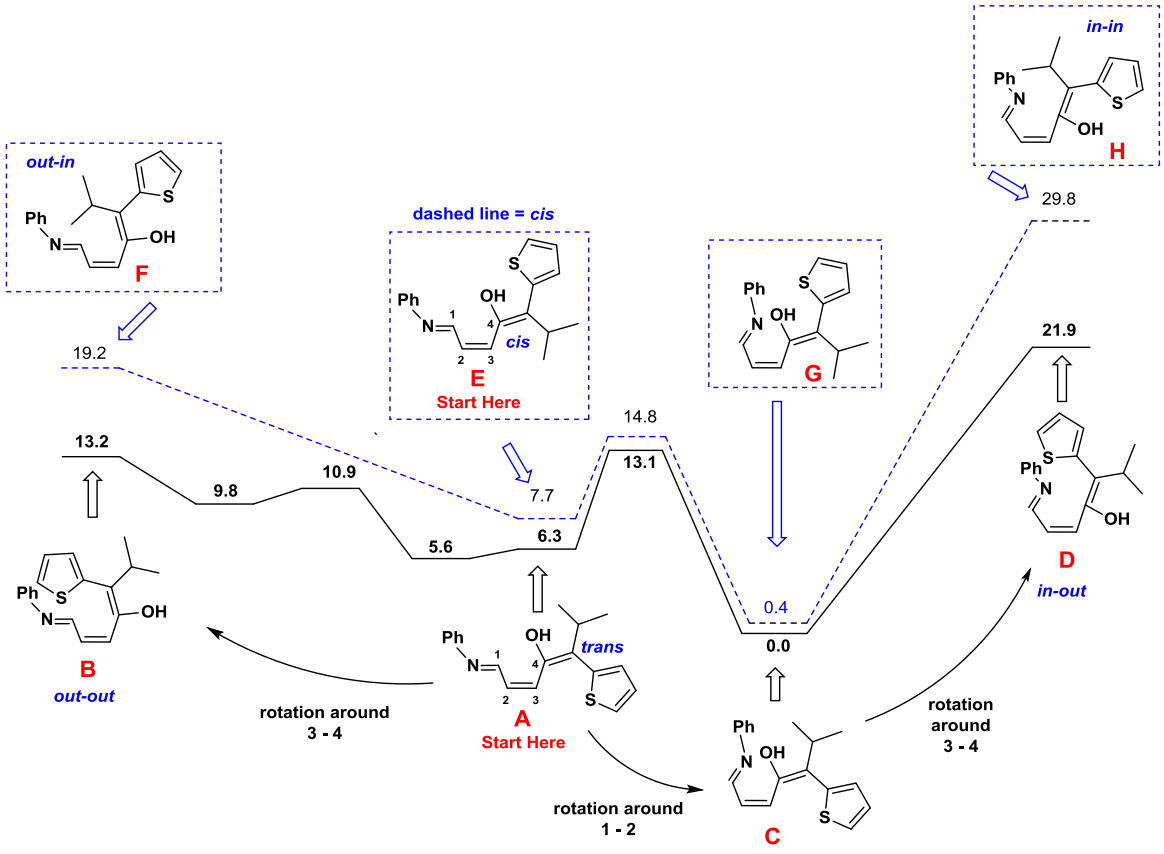


Figure 42. Energy barriers for rotation of the ring opened intermediate derived from isopropyl-, thiophene-substituted furylcarbinol. Rotational scans calculated using B3LYP/6-31G* (d,p) with 10^{o} intervals. All values in kcal/mol.

4.2.3 Conclusion

Using computational chemistry we have been able to get a better understanding of the energy profile and barriers that the reaction intermediates must pass through for conversion between many of the possible intermediates for the rearrangement. At this time, the calculations support our experimental observations since the *out-out* geometry that leads to consistently experimentally observed major diastereomer is always calculated to have the lowest energy of the four possible pentadienyl geometries. However, at this point we cannot definitively conclude which intermediate is the diastereodetermining step since the scope of these calculations is limited to Brønsted acids, and olefin isomerization energies of the ring opened intermediates were not determined. Future calculations should also compare the energy required to isomerize between the *cis* and *trans* olefin geometries. In addition, using tetr-substituted furyl cyclopropanes, we have observed experimentally that the nature of the Lewis acid has a large influence on the diastereoselectivity of the rearrangement and future work should also focus on the nature and influence of the Lewis acid.

4.3 References

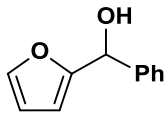
[1] Li, S.-W.; Batey, R. a. *Chem. Commun.* **2007**, *8*, 3759.
[2] Yu, D.; Thai, V. T.; Palmer, L. I.; Veits, G. K.; Cook, J. E.; Read de Alaniz, J.; Hein, J. E. *J. Org. Chem.* **2013**, *78*, 12784.
[3] Cotton, S. In *Lanthanide and Actinide Chemistry*; John Wiley & Sons, Ltd: 2006, p 35.
[4] Forsberg, J. H.; Spaziano, V. T.; Balasubramanian, T. M.; Liu, G. K.; Kinsley, S. A.; Duckworth, C. A.; Poteruca, J. J.; Brown, P. S.; Miller, J. L. *J. Org. Chem.* **1987**, *52*, 1017.
[5] **(a)** Piancatelli, G.; Scettri, A. *Synthesis* **1977**, *1977*, 116; **(b)** Scettri, A.; Piancatelli, G.; D'Auria, M.; David, G. *Tetrahedron* **1979**, *35*, 135.
[6] Dhoro, F.; Tius, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 12472.
[7] Work performed by Gesine Veits, Dr. Leoni Palmer, David Fisher, John Cook and Jessica Davis.

5. Experimental Procedures

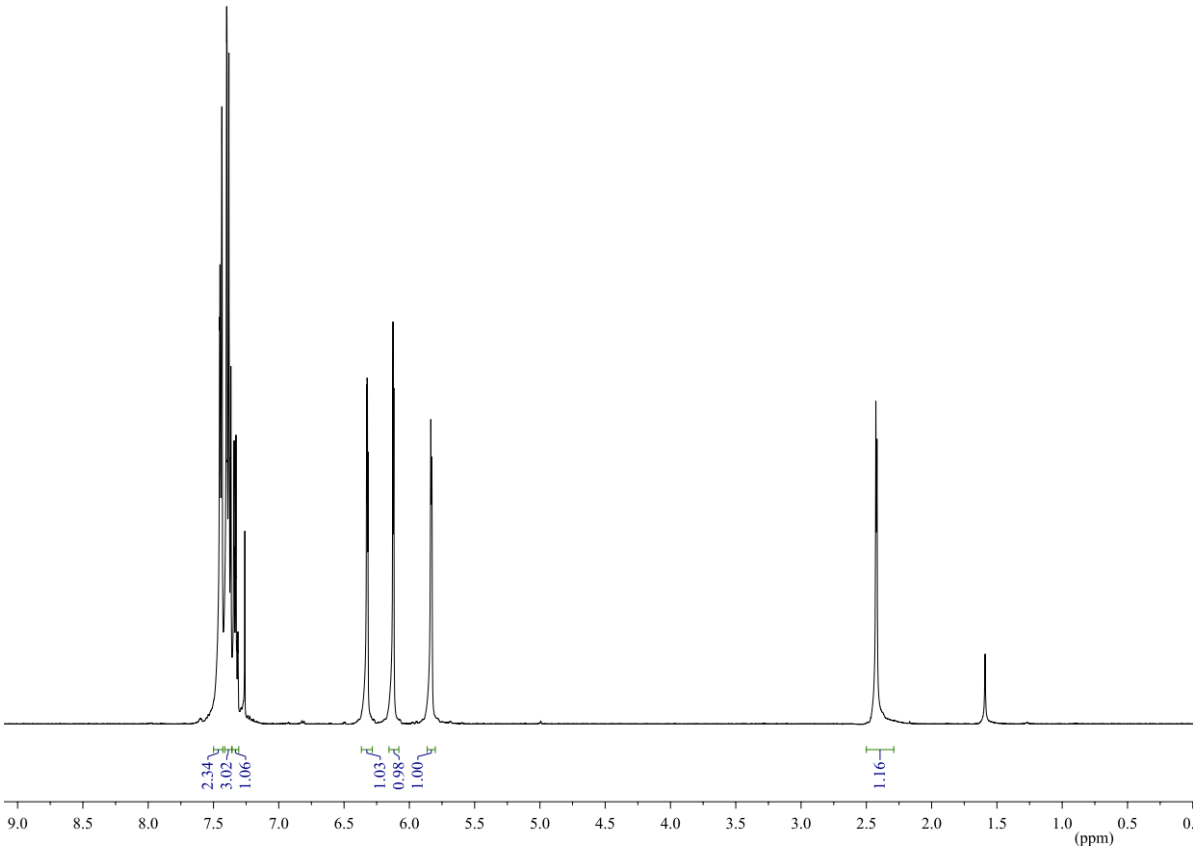
Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of air using reagent grade solvents. All commercially obtained reagents were used as received. Reaction temperatures were controlled using an Heidolph temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 ºC). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized by exposure to UV light (254 nm) or stained with anisaldehyde and potassium permanganate. Flash column chromatography was performed using normal phase silica gel (60 Å, 0.040 – 0.063 mm, Geduran). ^{1}H NMR spectra were recorded on Varian spectrometers (at 500 or 600 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Varian Spectrometers (125 or 150 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ ppm), multiplicity, coupling constant (Hz). IR spectra were recorded on a Perkin Elmer Spectrum 100 FT/IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the UC Santa Barbara Mass Spectrometry Facility on a (Waters Corp.) Micromass QTOF2 with an electrospray ionization source. X-ray data were obtained from the UC Santa Barbara X-ray Facility.

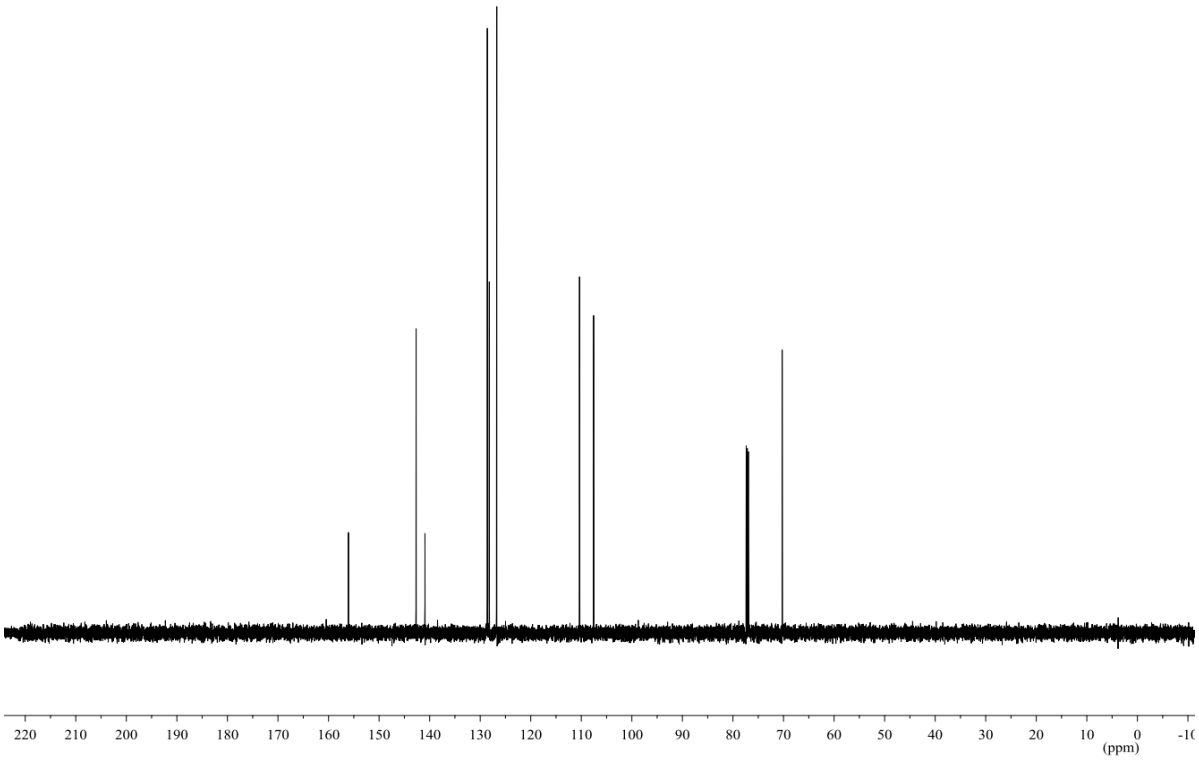
5.1.1 Chapter 1.1

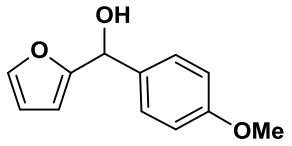
Furylcarbinols were prepared according to literature precedent by reacting furfural with the corresponding Grignard reagent.[1] Furylcarbinol 1-(furan-2-yl)ethan-1-ol was used as received.



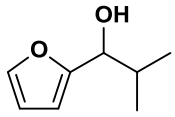
Furan-2-yl(phenyl)methanol (131): Light yellow oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 – 7.43 (m, 2H), 7.42 – 7.36 (m, 3H), 7.36 – 7.30 (m, 1H), 6.32 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.12 (d, *J* = 3.3 Hz, 1H), 5.83 (d, *J* = 4.0 Hz, 1H), 2.42 (d, *J* = 4.3 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 156.1, 142.7, 140.9, 128.6, 128.2, 126.7, 110.4, 107.6, 70.3 ppm; **IR** (thin film) 3362, 3063, 3031, 2897, 1957, 1888, 1810, 1602, 1492, 1452, 1141, 1007 cm^{-1}; **MS** (EI^+) *m/z* 174.0685 (174.0681 calcd. for $C_{11}H_{10}O_2^+$ $[M]^+$).


2.34
3.02
1.06
1.03
0.98
1.00
1.16
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

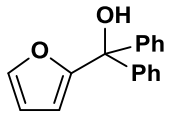

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)



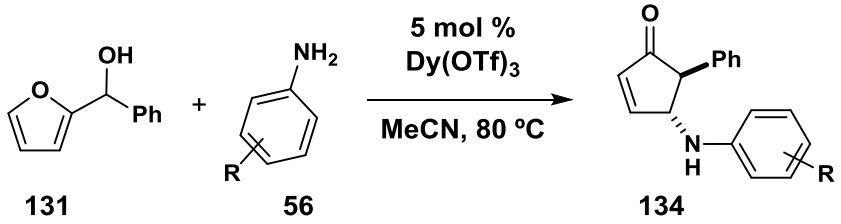
Furan-2-yl(4-methoxyphenyl)methanol (E-1): Yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 0.8 Hz, 1H), 7.34 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.31 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.11 (d, *J* = 3.2 Hz, 1H), 5.76 (s, 1H), 3.80 (s, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.5, 156.3, 142.5, 133.2, 128.1, 113.9, 110.3, 107.3, 69.9, 55.4 ppm; **IR** (thin film) 3402, 3001, 2957, 2935, 2910, 2837, 1610, 1586, 1510 cm^{-1}; **MS** (EI) *m/z* 204.0776 (204.0786 calcd for $C_{12}H_{12}O_3^+$ $[M]^+$).



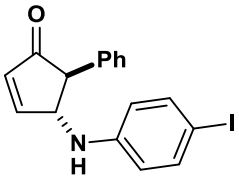
1-(Furan-2-yl)-2-methylpropan-1-ol (E-2): Yellow oil; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.33 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.23 (d, *J* = 3.2 Hz, 1H), 4.38 (d, *J* = 7.0 Hz, 1H), 2.11 (h, *J* = 6.8 Hz, 1H), 1.84 (s, 1H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 156.3, 141.8, 110.2, 106.6, 73.7, 33.5, 18.9, 18.4 ppm; **IR** (thin film) 3392, 2961, 2933, 2873, 1665, 1505, 1468 cm^{-1}; **MS** (EI) *m/z* 140.0840 (140.0837 calcd for $C_8H_{12}O_2^+$ $[M]^+$).



Furan-2-yldiphenylmethanol (E-3): Yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.40 – 7.27 (m, 10H), 6.34 (d, *J* = 1.5 Hz, 1H), 5.94 (d, *J* = 3.2 Hz, 1H), 3.11 (s, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 158.0, 144.7, 142.8, 128.1, 127.8, 127.3, 110.2, 109.8, 78.1 ppm; **IR** (thin film) 3410, 3061, 3028, 1957, 1888, 1813, 1725, 1675, 1598, 1554, 1490, 1447 cm^{-1}; **MS** (EI) *m/z* 250.0991 (250.0994 calcd for $C_{17}H_{14}O_2^+$ $[M]^+$).

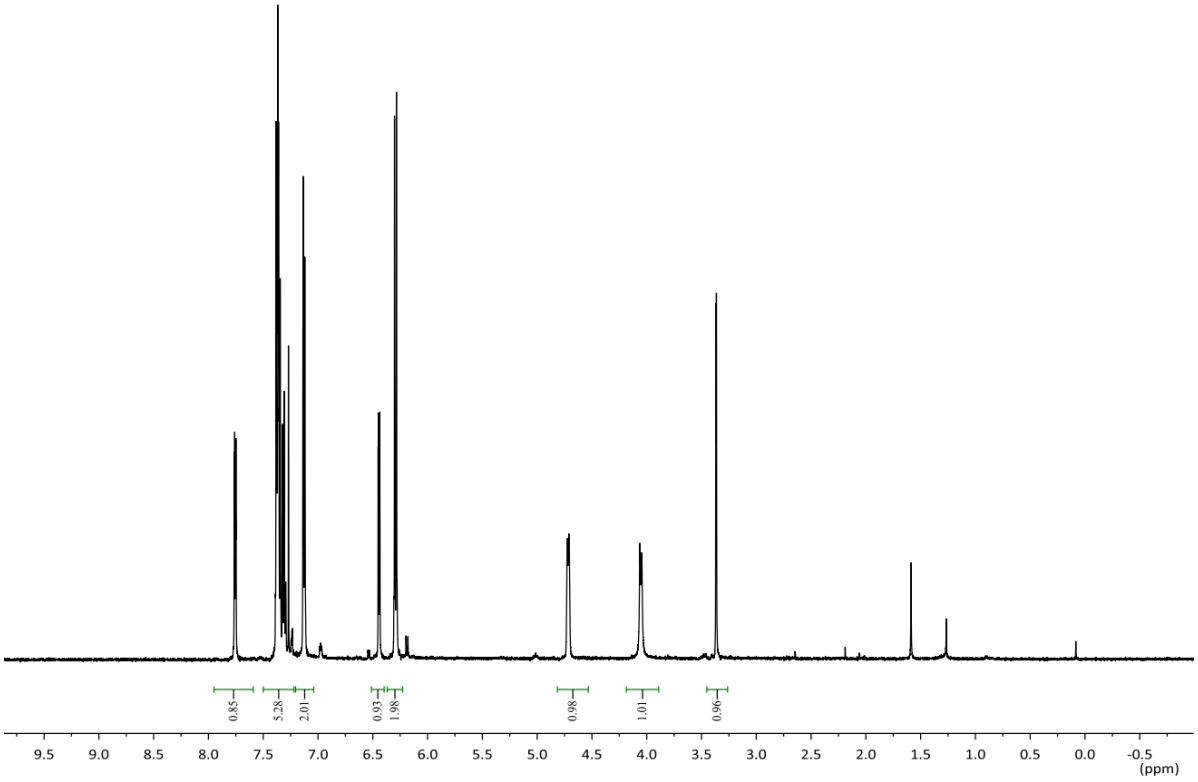


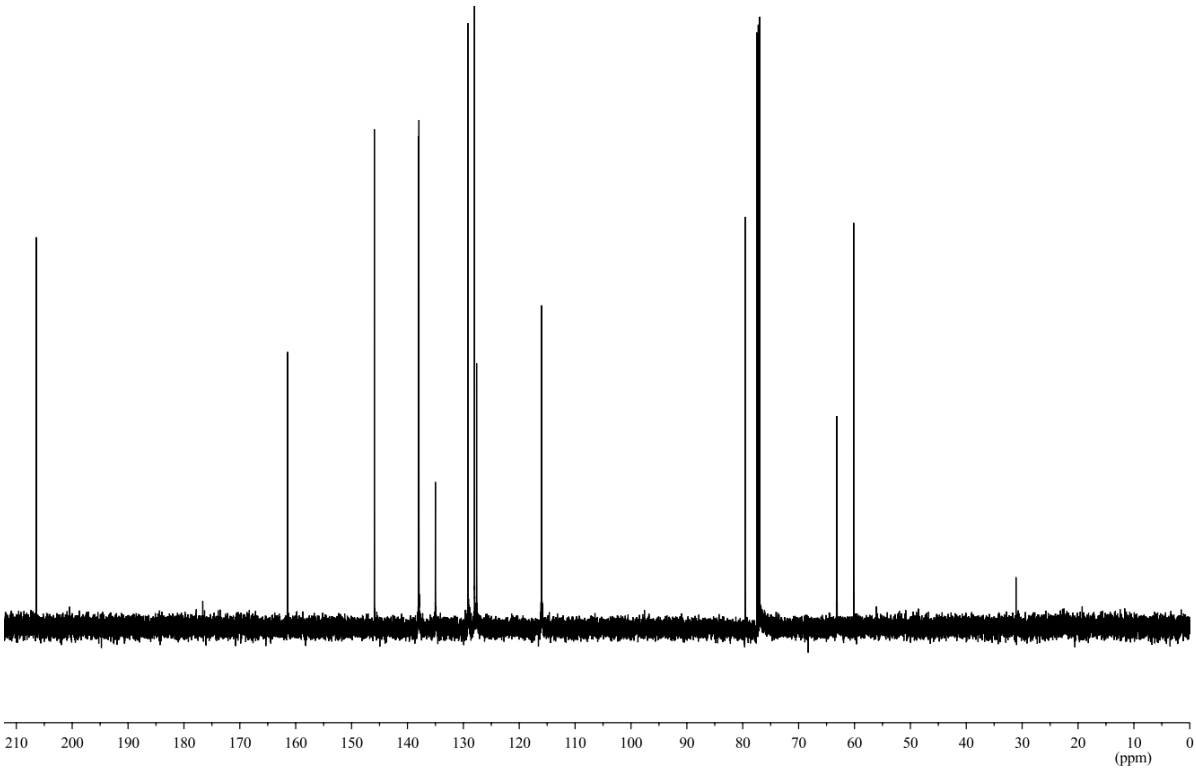
General procedure for the rearrangement: Furan-2-yl(phenyl)methanol and aniline were dissolved in MeCN. To the reaction mixture at 23 ºC was added 5 mol % of $Dy(OTf)_3$. The reaction mixture was immediately fitted with a reflux condenser and placed in an oil bath pre-heated to 80 ºC. The reaction was monitored by TLC. Upon completion, the reaction was then quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **134**.

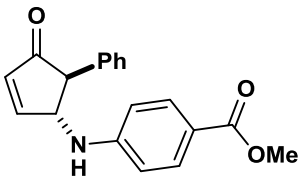


4-((4-Iodophenyl)amino)-5-phenylcyclopent-2-enone (133): According to the general procedure $Dy(OTf)_3$ (23 mg, 0.038 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol (128 mg, 0.74 mmol, 1 equiv) and 4-iodoaniline (162 mg, 0.74 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 30 minutes. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **133** (255 mg, 92%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.72 (dd, J = 5.7, 2.4 Hz, 1H), 7.40 – 7.28 (m, 5H), 7.15 – 7.09 (m, 2H), 6.40 (dd, J = 5.7, 1.7 Hz, 1H), 6.27 (dddd, J = 9.8, 2.0, 2.0, 2.0 Hz, 2H), 4.69 (dd, J = 8.2, 1.7 Hz, 1H), 4.19 (d, J = 8.3 Hz,

1H), 3.35 (d, J = 2.6 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.4, 161.5, 145.9, 138.0, 137.9, 135.0, 129.2, 128.0, 127.6, 116.0, 79.6, 63.2, 60.1 ppm; **IR** (thin film) 3776, 3026, 1704, 1588, 1496, 1316 cm^{-1}; **HRMS** (ESI) *m/z* 398.0022 (398.0012 calcd for $C_{17}H_{14}INONa^+$ $[M + Na]^+$). The crystal structure date for 4-((4-iodophenyl)amino)-5-phenylcyclopent-2-enone **133** can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. CCDC 769123.

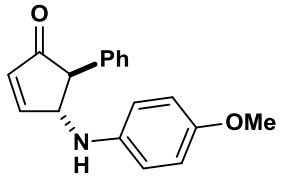




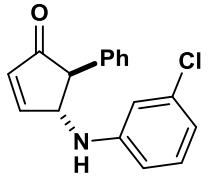


Methyl 4-((4-oxo-5-phenylcyclopent-2-en-1-yl)amino)benzoate (135): According to the general procedure $Dy(OTf)_3$ (17 mg, 0.028 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol (97 mg, 0.56 mmol, 1 equiv) and methyl 4-aminobenzoate (84 mg, 0.56 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 1 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **135** (148 mg, 86%) as a solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83 – 7.77 (m, 2H), 7.75 (dd, J = 5.7, 2.3 Hz, 1H), 7.41 – 7.29 (m, 3H), 7.16 – 7.10 (m, 2H), 6.49 – 6.42 (m, 3H), 4.82 (dddd, J = 8.1, 2.2, 2.2, 2.2 Hz, 1H), 4.63 (d,

J = 8.3 Hz, 1H), 3.84 (s, 3H), 3.39 (d, J = 2.6 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.2, 167.2, 161.0, 150.3, 137.8, 135.3, 131.7, 129.3, 128.1, 127.8, 119.8, 112.6, 62.8, 60.3, 51.8 ppm; **IR** (thin film) 3359, 3023, 2950, 1705, 1604, 1280 cm^{-1}; **HRMS** (ESI) *m/z* 330.1106 (330.1101 calcd for $C_{19}H_{17}NO_3Na^+$ $[M + Na]^+$).

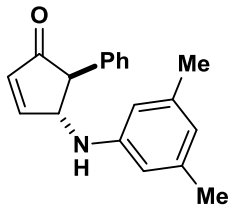


4-((4-Methoxyphenyl)amino)-5-phenylcyclopent-2-enone (136): According to the general procedure $Dy(OTf)_3$ (69 mg, 0.114 mmol, 0.2 equiv) was added to furan-2-yl(phenyl)methanol (100 mg, 0.57 mmol, 1 equiv) and 4-methoxyaniline (78 mg, 0.57 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 18 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **136** (99 mg, 62%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.78 (dd, J = 5.7, 2.3 Hz, 1H), 7.38 – 7.24 (m, 3H), 7.12 (d, J = 7.2 Hz, 2H), 6.72 (d, J = 8.9 Hz, 2H), 6.51 (d, J = 8.9 Hz, 2H), 6.39 (dd, J = 5.7, 1.5 Hz, 1H), 4.67 (d, J = 1.7 Hz, 1H), 3.73 (s, 3H), 3.38 (d, J = 2.5 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.9, 162.3, 153.2, 140.2, 138.3, 134.8, 129.1, 128.2, 127.5, 115.8, 115.1, 64.6, 60.1, 55.8 ppm; **IR** (thin film) 3363, 3031, 2935, 2835, 1709, 1593, 1512, 1242 cm^{-1}; **HRMS** (ESI) *m/z* 302.1154 (302.1151 calcd for $C_{18}H_{17}NO_2Na^+$ $[M + Na]^+$).



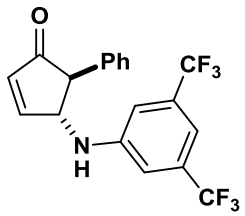
4-((3-Chlorophenyl)amino)-5-phenylcyclopent-2-enone (137): According to the general procedure $Dy(OTf)_3$ (18 mg, 0.029 mmol, 0.05

equiv) was added to furan-2-yl(phenyl)methanol (100 mg, 0.58 mmol, 1 equiv) and 3-chloroaniline (73 mg, 0.58 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 20 minutes. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **137** (134 mg, 82%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 5.7, 2.3 Hz, 1H), 7.40 – 7.29 (m, 3H), 7.16 – 7.12 (m, 2H), 7.03 (t, *J* = 8.1 Hz, 1H), 6.74 – 6.69 (m, 1H), 6.49 (t, *J* = 2.1 Hz, 1H), 6.44 (dd, *J* = 5.7, 1.7 Hz, 1H), 6.38 (dd, *J* = 8.2, 2.3 Hz, 1H), 4.72 (dddd, *J* = 8.3, 2.1, 2.1, 2.1 Hz, 1H), 4.16 (d, *J* = 8.5 Hz, 1H), 3.38 (d, *J* = 2.7 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.4, 161.3, 147.5, 137.9, 135.3, 135.2, 130.6, 129.3, 128.1, 127.7, 118.7, 113.8, 112.1, 63.3, 60.3 ppm; **IR** (thin film) 3376, 3062, 3029, 1704, 1596, 1327 cm^{-1}; **HRMS** (ESI) *m/z* 306.0656 (306.0656 calcd for $C_{17}H_{14}ClNONa^+$ $[M + Na]^+$).

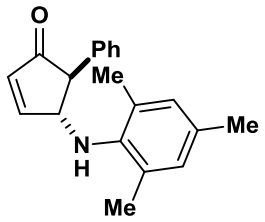


4-((3,5-Dimethylphenyl)amino)-5-phenylcyclopent-2-enone (138): According to the general procedure $Dy(OTf)_3$ (18 mg, 0.029 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol (100 mg, 0.58 mmol, 1 equiv) and 3,5-dimethylaniline (70 mg, 0.58 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 3 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **138** (130 mg, 81%) as a solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 5.7, 2.2 Hz, 1H), 7.43

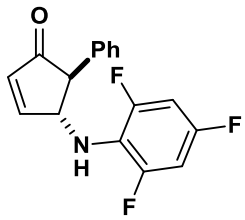
– 7.29 (m, 3H), 7.17 (d, J = 7.2 Hz, 2H), 6.47 – 6.39 (m, 2H), 6.16 (s, 2H), 4.75 (d, J = 1.6 Hz, 1H), 3.94 (bs, 1H), 3.40 (d, J = 2.5 Hz, 1H), 2.17 (s, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.9, 162.1, 146.3, 139.3, 138.5, 134.8, 129.1, 128.3, 127.5, 120.8, 112.1, 63.7, 60.5, 21.6 ppm; **IR** (thin film) 3375, 3028, 2916, 2858, 1709, 1600, 1492, 1338 cm^{-1}; **HRMS** (ESI) *m/z* 300.1359 (300.1359 calcd for $C_{19}H_{19}NONa^+$ $[M + Na]^+$).



4-((3,5-Bis(trifluoromethyl)phenyl)amino)-5-phenylcyclopent-2-enone (139): According to the general procedure $Dy(OTf)_3$ (18 mg, 0.029 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol (103 mg, 0.592 mmol, 1 equiv) and 3,5-bis(trifluoromethyl)aniline (97 mg, 0.8 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 24 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **139** (171 mg, 75%) as a solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 (dd, J = 5.7, 2.4 Hz, 1H), 7.40 – 7.28 (m, 3H), 7.17 (s, 1H), 7.14 – 7.08 (m, 2H), 6.80 (s, 2H), 6.49 (dd, J = 5.7, 1.8 Hz, 1H), 4.78 (dddd, J = 8.2, 2.3, 2.3, 2.3 Hz, 1H), 4.60 (d, J = 8.2 Hz, 1H), 3.34 (d, J = 2.6 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.0, 160.2, 147.1, 137.6, 135.9, 132.8 (q, J = 32.9 Hz), 129.5, 128.1, 128.0, 123.4 (q, J = 272.8 Hz), 113.1 (d, J = 2.9 Hz), 111.7 (dddd, J = 3.8, 3.8, 3.8, 3.8 Hz), 63.3, 60.8 ppm; **IR** (thin film) 3375, 3055, 2908, 1705, 1600, 1315 cm^{-1}; **HRMS** (ESI) *m/z* 408.0799 (408.0794 calcd for $C_{19}H_{13}F_6NONa^+$ $[M + Na]^+$).

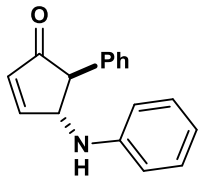


4-(Mesitylamino)-5-phenylcyclopent-2-enone (140): According to the general procedure $Dy(OTf)_3$ (20 mg, 0.033 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol (114 mg, 0.66 mmol, 1 equiv) and 2,4,6-trimethylaniline (92µl, 0.66 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 4 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **140** (175 mg, 91%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 5.7, 2.2 Hz, 1H), 7.33 – 7.21 (m, 3H), 7.06 – 7.00 (m, 2H), 6.81 (bs, 2H), 6.34 (dd, *J* = 5.7, 1.4 Hz, 1H), 4.43 (s, 1H), 3.40 (d, *J* = 2.9 Hz, 1H), 3.17 (bs, 1H), 2.23 (s, 3H), 2.10 (s, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.1, 163.1, 140.9, 138.1, 133.7, 132.5, 130.0, 129.9, 128.9, 128.1, 127.3, 67.7, 60.6, 20.8, 18.8 ppm; **IR** (thin film) 3359, 2920, 1708, 1589, 1485, 1230 cm^{-1}; **HRMS** (ESI) *m/z* 314.1512 (314.1515 calcd for $C_{20}H_{21}NONa^+$ $[M + Na]^+$).

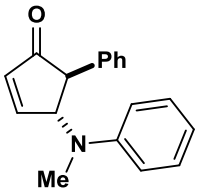


5-Phenyl-4-((2,4,6-trifluorophenyl)amino)cyclopent-2-enone (141): According to the general procedure $Dy(OTf)_3$ (21 mg, 0.035 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol (120 mg, 0.69 mmol, 1 equiv) and 2,4,6-trifluoroaniline (304 mg, 2.1 mmol, 3 equiv) in 6 mL of MeCN. The resulting reaction mixture was allowed to proceed at rt for 3 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column

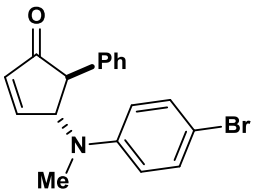
chromatography to afford cyclopentenone **141** (155 mg, 74%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 5.8, 2.2 Hz, 1H), 7.32 – 7.20 (m, 3H), 7.04 – 6.93 (m, 2H), 6.64 – 6.56 (m, 2H), 6.37 (dd, *J* = 5.8, 1.7 Hz, 1H), 4.85 – 4.74 (m, 1H), 3.56 (d, *J* = 10.0 Hz, 1H), 3.34 (d, *J* = 3.0 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.0, 161.7, 156.3 (ddd, *J* = 243.9, 15.0, 15.0 Hz), 154.5 (ddd, *J* = 244.1, 14.5, 9.0 Hz), 137.3, 134.6, 128.9, 128.0, 127.4, 120.4 (ddd, *J* = 15.1, 15.1, 4.7 Hz), 100.6 (dddd, *J* = 26.2, 26.2, 20.5, 8.6 Hz), 66.1 (dd, *J* = 2.9, 2.9 Hz), 61.2 ppm; **IR** (thin film) 3344, 3070, 1712, 1612, 1508, 1442 cm^{-1}; **HRMS** (ESI) *m/z* 326.0782 (326.0763 calcd for $C_{17}H_{12}F_3NONa^+$ $[M + Na]^+$).



5-Phenyl-4-(phenylamino)cyclopent-2-enone (142): According to the general procedure $Dy(OTf)_3$ (18 mg, 0.029 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol (100 mg, 0.58 mmol, 1 equiv) and aniline (54 mg, 0.58 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 1.5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **142** (124 mg, 86%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 5.7, 2.3 Hz, 1H), 7.41 – 7.30 (m, 3H), 7.20 – 7.12 (m, 4H), 6.78 (dd, *J* = 10.6, 4.1 Hz, 1H), 6.57 – 6.51 (m, 2H), 6.41 (dd, *J* = 5.7, 1.6 Hz, 1H), 4.76 (bs, 1H), 4.11 (bs, 1H), 3.41 (d, *J* = 2.6 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.7, 162.0, 146.3, 138.1, 134.7, 129.5, 129.1, 128.1, 127.5, 118.7, 113.9, 63.4, 60.1 ppm; **IR** (thin film) 3374, 3053, 3027, 1708, 1601, 1497, 1314 cm^{-1}; **HRMS** (ESI) *m/z* 272.1049 (272.1046 calcd for $C_{17}H_{15}NONa^+$ $[M + Na]^+$).

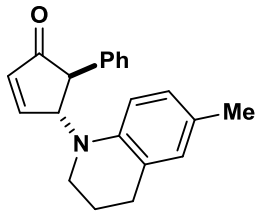


4-(Methyl(phenyl)amino)-5-phenylcyclopent-2-enone (143): According to the general procedure $Dy(OTf)_3$ (18 mg, 0.029 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol (100 mg, 0.57 mmol, 1 equiv) and 2,6-dimethyl aniline (61 mg, 0.57 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 2.5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **143** (111 mg, 74%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 5.8, 2.3 Hz, 1H), 7.35 – 7.24 (m, 3H), 7.13 (t, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 7.2 Hz, 1H), 6.74 (t, *J* = 7.3 Hz, 1H), 6.64 (d, *J* = 8.3 Hz, 2H), 6.48 (dd, *J* = 5.8, 2.0 Hz, 1H), 5.16 – 5.12 (m, 1H), 3.53 (d, *J* = 2.9 Hz, 1H), 2.86 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.7, 163.5, 149.4, 138.5, 135.3, 129.4, 129.2, 128.3, 127.4, 118.6, 114.6, 70.1, 56.3, 33.5 ppm; **IR** (thin film) 3059, 2916, 2812, 1709, 1597, 1500, 1377 cm^{-1}; **HRMS** (ESI) *m/z* 286.1199 (286.1202 calcd for $C_{18}H_{17}NONa^+[M + Na]^+$).



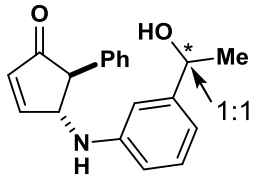
4-((4-Bromophenyl)(methyl)amino)-5-phenylcyclopent-2-enone (144): According to the general procedure $Dy(OTf)_3$ (21 mg, 0.034 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol (119 mg, 0.68 mmol, 1 equiv) and 4-bromo-N-methylaniline (127 mg, 0.68 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 45 minutes. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl

acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **144** (205 mg, 88%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 5.8, 2.4 Hz, 1H), 7.37 – 7.24 (m, 3H), 7.24 – 7.15 (m, 2H), 7.10 – 7.04 (m, 2H), 6.51 – 6.43 (m, 3H), 5.13 – 5.04 (m, 1H), 3.48 (d, *J* = 3.0 Hz, 1H), 2.82 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 206.3, 162.8, 148.4, 138.2, 135.5, 132.0, 129.3, 128.3, 127.5, 115.9, 110.4, 69.8, 56.4, 33.3 ppm; **IR** (thin film) 3062, 2896, 2815, 1712, 1589, 1496, 1311 cm^{-1}; **HRMS** (ESI) *m/z* 364.0306 (364.0307 calcd for $C_{18}H_{16}BrNONa^+$ $[M + Na]^+$).

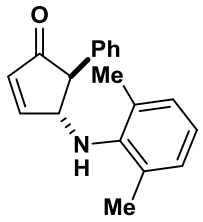


4-(6-Methyl-3,4-dihydroquinolin-1(2H)-yl)-5-phenylcyclopent-2-enone (145): According to the general procedure $Dy(OTf)_3$ (18 mg, 0.03 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol (105 mg, 0.6 mmol, 1 equiv) and 6-methyl-1,2,3,4-tetrahydroquinoline (87 mg, 0.6 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 18 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **145** (122 mg, 67%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 5.7, 2.2 Hz, 1H), 7.33 – 7.21 (m, 3H), 7.06 – 7.00 (m, 2H), 6.81 (s, 2H), 6.34 (dd, *J* = 5.7, 1.4 Hz, 1H), 4.43 (s, 1H), 3.40 (d, *J* = 2.9 Hz, 1H), 3.17 (bs, 1H), 2.23 (s, 3H), 2.10 (s, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.8, 164.2, 142.4, 138.8, 135.1, 130.3, 129.2, 128.2, 127.5, 127.3, 126.6, 123.9,

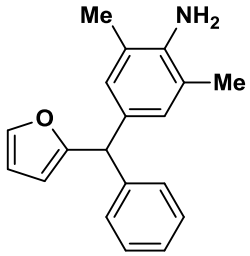
112.5, 68.7, 55.9, 44.5, 28.1, 22.9, 20.3 ppm; **IR** (thin film) 3020, 2931, 2854, 1709, 1504, 1296 cm^{-1}; **HRMS** (ESI) *m/z* 326.1524 (326.1515 calcd for $C_{21}H_{21}NONa^+$ $[M + Na]^+$).



4-((4-(1-Hydroxyethyl)phenyl)amino)-5-phenylcyclopent-2-enone (146): According to the general procedure $Dy(OTf)_3$ (23 mg, 0.038 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol (130 mg, 0.75 mmol, 1 equiv) and 1-(4-aminophenyl)ethanol (103 mg, 0.75 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 2 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **146** (193 mg, 88%) as an oil. **^{1}H NMR** of 1:1 mixture of diastereomers (500 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 5.7, 2.3 Hz, 1H), 7.39 – 7.28 (m, 3H), 7.17 – 7.06 (m, 3H), 6.71 (dd, *J* = 7.4, 3.5 Hz, 1H), 6.50 (d, *J* = 9.6 Hz, 1H), 6.46 – 6.37 (m, 2H), 4.78 (s, 1H), 4.67 (dddd, *J* = 6.4, 6.4, 6.4, 1.9 Hz, 1H), 4.14 (bs, 1H), 3.36 (d, *J* = 2.5 Hz, 1H), 1.94 (bs, 1H), 1.35 (dd, *J* = 6.3, 5.3 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.8, 206.8, 162.0, 161.9, 147.5, 147.5, 146.5, 146.5, 138.3, 138.3, 134.8, 134.8, 129.6, 129.62, 129.1, 129.1, 128.2, 128.2, 127.5, 115.9, 115.8, 113.1, 113.0, 110.9, 110.8, 70.3, 63.5, 63.4, 60.6, 60.5, 25.1, 25.0 ppm; **IR** (thin film) 3375, 3032, 2970, 2920, 1705, 1601, 1489, 1331 cm^{-1}; **HRMS** (ESI) *m/z* 316.1309 (316.1308 calcd for $C_{19}H_{19}NO_2Na^+$$[M + Na]^+$).

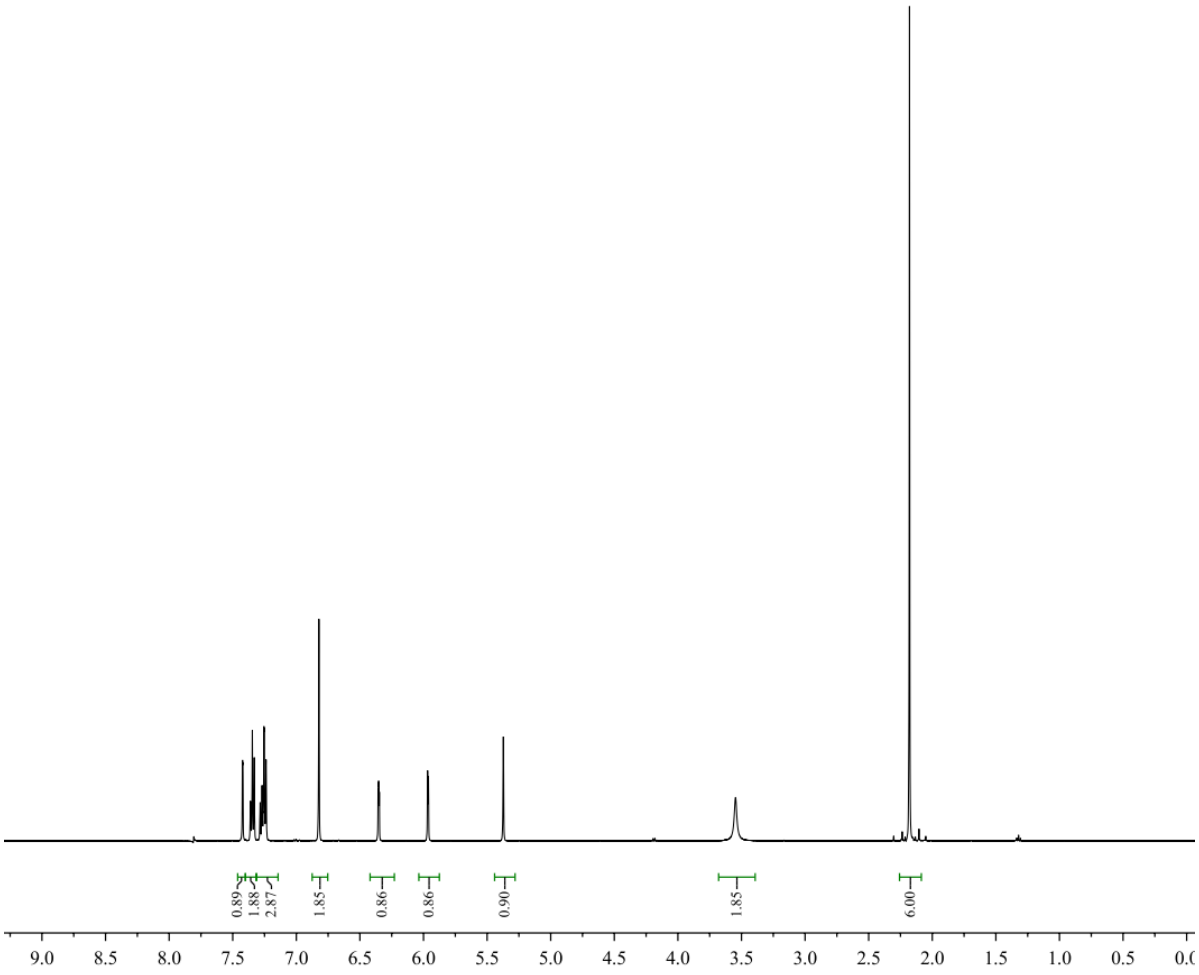


4-((2,6-Dimethylphenyl)amino)-5-phenylcyclopent-2-enone (147): According to the general procedure $Dy(OTf)_3$ (20 mg, 0.03 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol (115 mg, 0.66 mmol, 1 equiv) and 2,6-dimethylaniline (82 µl, 0.66 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 3 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **147** (60 mg, 33%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 5.7, 2.3 Hz, 1H), 7.31 – 7.22 (m, 4H), 7.02 – 6.95 (m, 4H), 6.90 – 6.83 (m, 1H), 6.36 (dd, *J* = 5.7, 1.6 Hz, 1H), 4.50 – 4.47 (m, 1H), 3.39 (d, *J* = 2.9 Hz, 1H), 2.13 (s, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.1, 163.0, 143.6, 138.1, 134.0, 129.9, 129.3, 129.0, 128.1, 127.4, 123.2, 67.4, 60.7, 19.0 ppm; **IR** (thin film) 3359, 3032, 2927, 1709, 1469, 1219 cm^{-1}; **HRMS** (ESI) *m/z* 300.1358 (300.1359 calcd for $C_{19}H_{19}NONa^+$ $[M + Na]^+$).



4-(Furan-2-yl(phenyl)methyl)-2,6-dimethylaniline (149): According to the general procedure $Dy(OTf)_3$ (22 mg, 0.036 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-2-methylpropan-1-ol (100 mg, 0.71 mmol, 1 equiv) and 2,6-dimethylaniline (91 mg, 0.71 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 24 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **149**

(60 mg, 38%) as a solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 1.0 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.30 – 7.21 (m, 3H), 6.82 (s, 2H), 6.35 (dd, *J* = 3.0, 1.9 Hz, 1H), 5.96 (d, *J* = 3.2 Hz, 1H), 5.37 (bs, 1H), 3.55 (s, 2H), 2.18 (s, 6H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.8, 142.7, 141.8, 141.6, 131.2, 128.8, 128.7, 128.5, 126.6, 121.8, 110.1, 108.0, 50.4, 17.9 ppm; **IR** (thin film) 3473, 3114, 3025, 1624, 1599 cm^{-1}; **HRMS** (ESI) *m/z* 278.1536 (278.1467 calcd for $C_{17}H_{23}NOH^{+}$ $[M + H]^{+}$).


0.89
1.88
2.87
1.85
0.86
0.86
0.90
1.85
6.00
9.0
8.5
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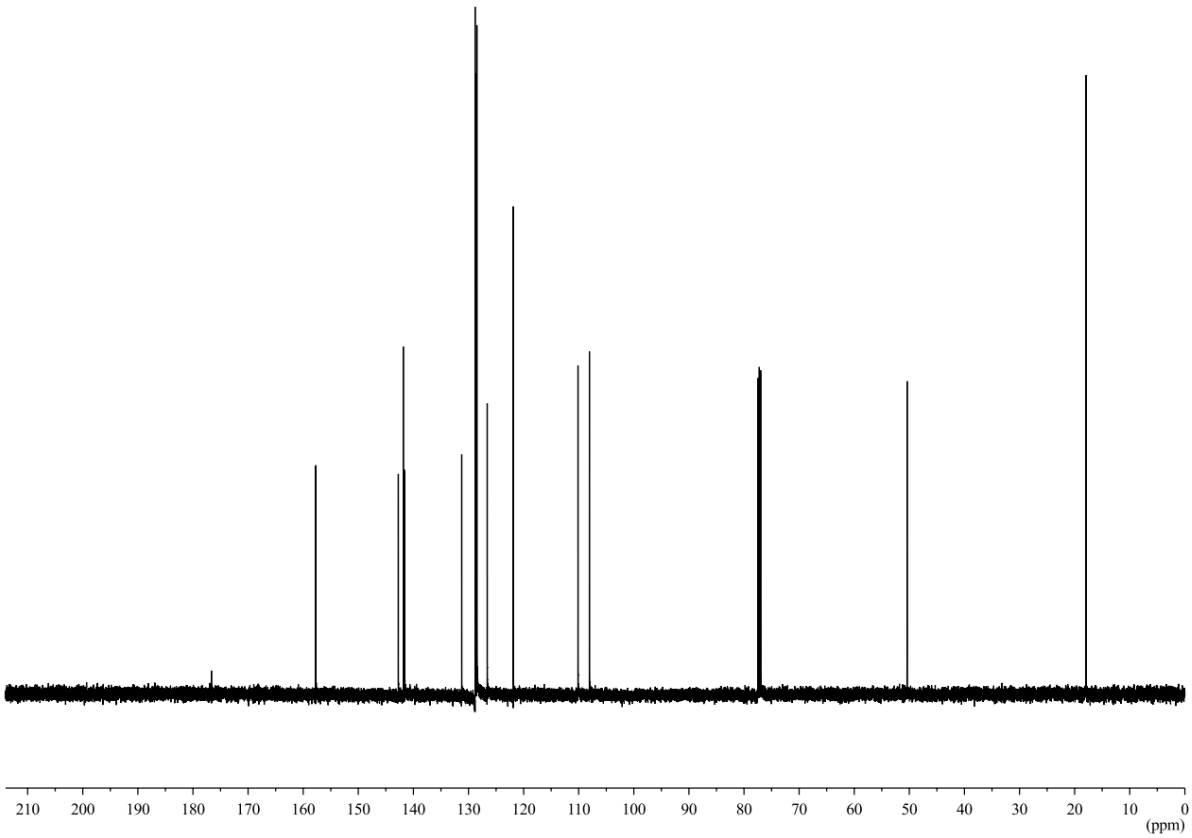
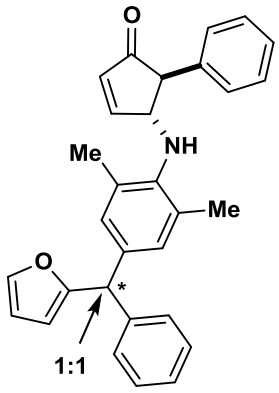
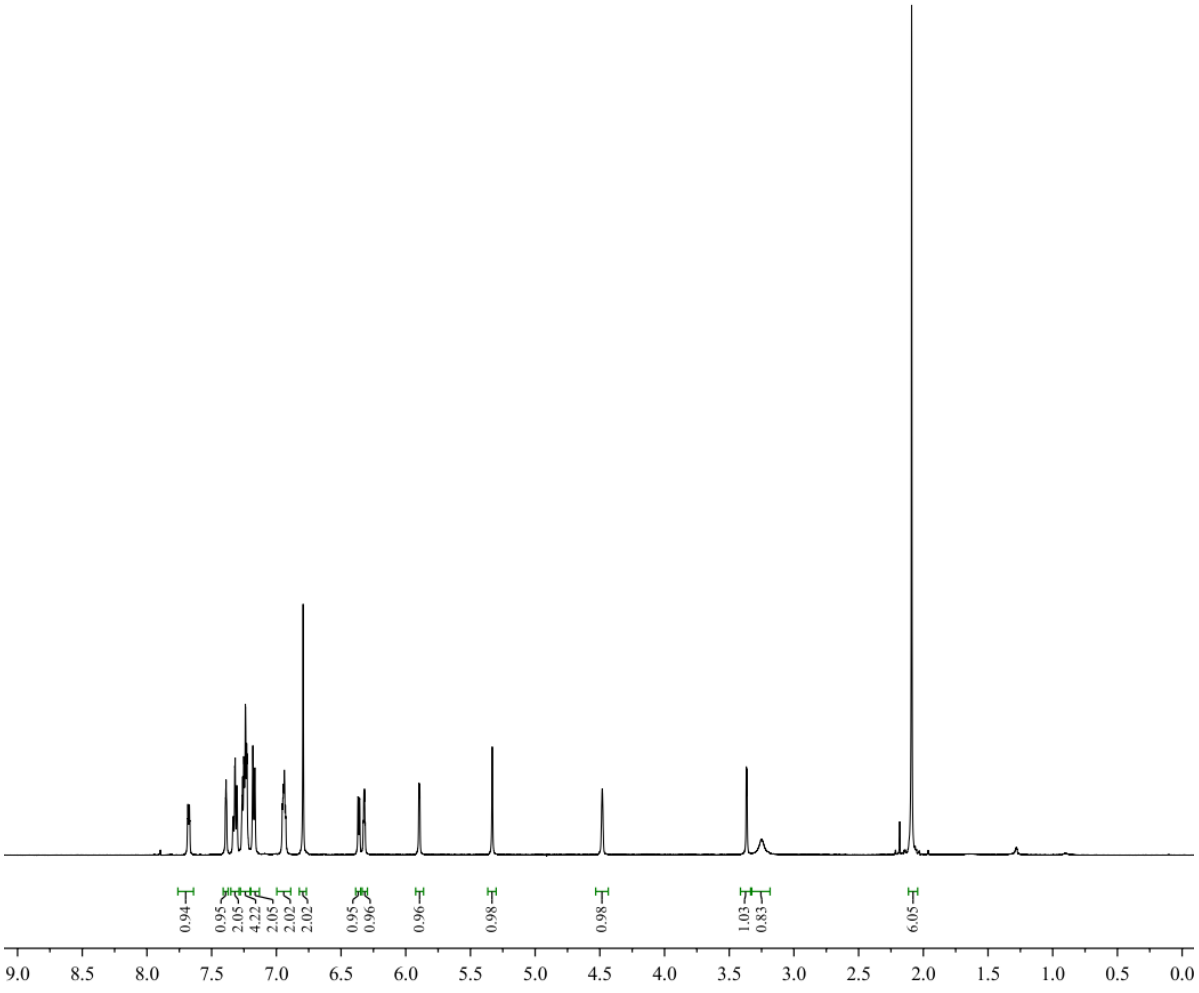
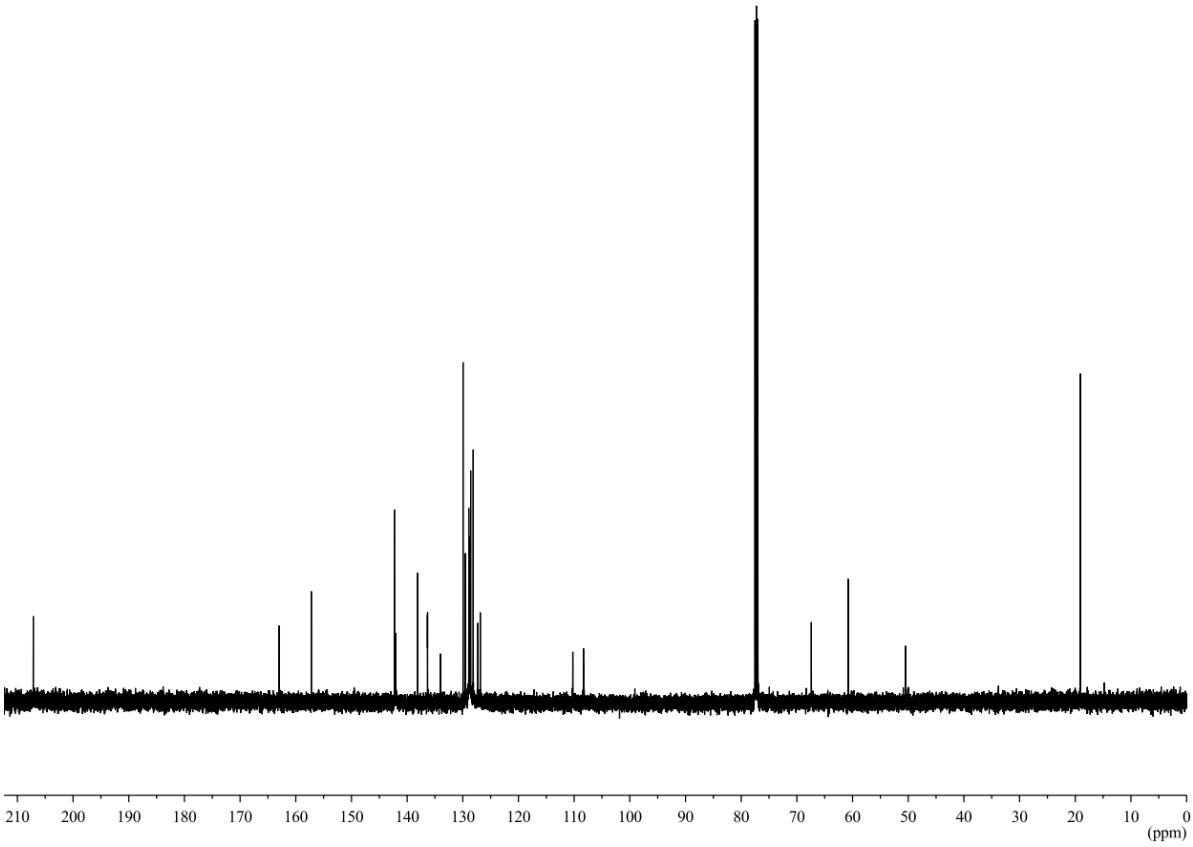


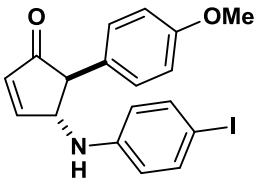


((4-(Furan-2-yl(phenyl)methyl)-2,6-dimethylphenyl)amino)-5-phenylcyclopent-2-enone (150): According to the general procedure $Dy(OTf)_3$ (22 mg, 0.036 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-2-methylpropan-1-ol (100 mg, 0.71 mmol, 1 equiv) and 2,6-dimethylaniline (91 mg, 0.71 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 24 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **150** (37 mg, 15%) as a solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69 (dd, J = 5.7, 1.8 Hz, 1H), 7.41 – 7.39 (m, 1H), 7.35 – 7.31 (m, 2H), 7.28 –

7.23 (m, 4H), 7.20 – 7.16 (m, 2H), 6.98 – 6.92 (m, 2H), 6.80 (s, 2H), 6.37 (dd, *J* = 5.7, 0.7 Hz, 1H), 6.34 – 6.32 (m, 1H), 5.90 (d, *J* = 2.5 Hz, 1H), 5.34 (s, 1H), 4.49 (s, 1H), 3.38 (d, *J* = 2.7 Hz, 1H), 3.26 (bs, 1H), 2.10 (s, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.1, 163.0, 157.2, 142.3, 142.0, 138.1, 136.3, 134.0, 123.0, 129.6, 129.5, 128.9, 128.8, 128.6, 128.1, 127.3, 126.9, 110.3, 108.3, 67.4, 60.8, 50.5, 19.1 ppm; **HRMS** (ESI) *m/z* 456.19 (456.20 calcd for $C_{30}H_{27}NO2Na^+$ $[M + Na]^+$).

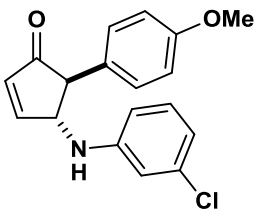




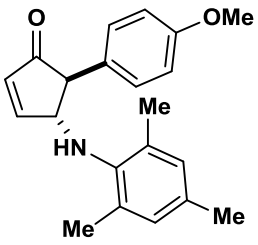


4-((4-Iodophenyl)amino)-5-(4-methoxyphenyl)cyclopent-2-enone (152): According to the general procedure $Dy(OTf)_3$ (15 mg, 0.025 mmol, 0.05 equiv) was added to furan-2-yl(4-methoxyphenyl) methanol (100 mg, 0.49 mmol, 1 equiv) and 4-iodoaniline (107 mg, 0.49 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was allowed to react at rt for 1.5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **152** (135 mg, 68%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.72 (dd, J = 5.7, 2.2 Hz, 1H), 7.37 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.6 Hz,

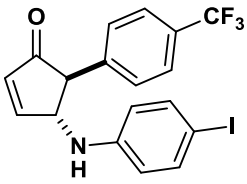
2H), 6.88 (d, J = 8.6 Hz, 2H), 6.41 (dd, J = 5.7, 1.5 Hz, 1H), 6.29 (d, J = 8.7 Hz, 2H), 4.66 (s, 1H), 4.10 (bs, 1H), 3.81 (s, 3H), 3.30 (d, J = 2.5 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.7, 161.2, 159.1, 146.0, 138.1, 135.2, 130.0, 129.1, 116.1, 114.7, 79.7, 63.3, 59.5, 55.5 ppm; **IR** (thin film) 3374, 2931, 2839, 1709, 1589, 1504, 1300 cm^{-1}; **HRMS** (ESI) *m/z* 428.0118 (428.0118 calcd for $C_{18}H_{16}INO_2Na^+$ $[M + Na]^+$).



4-((3-Chlorophenyl)amino)-5-(4-methoxyphenyl)cyclopent-2-enone (153): According to the general procedure $Dy(OTf)_3$ (15 mg, 0.025 mmol, 0.05 equiv) was added to furan-2-yl(4-methoxyphenyl) methanol (100 mg, 0.49 mmol, 1 equiv) and 3-chloroaniline (63 mg, 0.49 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was allowed to react at rt for 6.5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **153** (126 mg, 82%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.74 (dd, J = 5.7, 2.3 Hz, 1H), 7.09 – 7.00 (m, 3H), 6.92 – 6.87 (m, 2H), 6.73 – 6.69 (m, 1H), 6.51 (t, J = 2.0 Hz, 1H), 6.44 (dd, J = 5.8, 1.6 Hz, 1H), 6.40 (dd, J = 8.2, 1.8 Hz, 1H), 4.68 (dd, J = 8.4, 1.8 Hz, 1H), 4.06 (bs, 1H), 3.81 (s, 3H), 3.34 (d, J = 2.7 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.6, 161.1, 159.2, 147.5, 135.4, 135.3, 130.6, 129.9, 129.2, 118.8, 114.8, 113.9, 112.1, 63.5, 59.6, 55.5 ppm; **IR** (thin film) 3371, 2927, 1708, 1597, 1512, 1250 cm^{-1}; **HRMS** (ESI) *m/z* 336.0757 (336.0762 calcd for $C_{18}H_{16}ClNO_2Na^+$ $[M + Na]^+$).

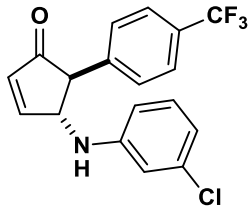


4-(mesitylamino)-5-(4-methoxyphenyl)cyclopent-2-enone (153): According to the general procedure $Dy(OTf)_3$ (30 mg, 0.05 mmol, 0.1 equiv) was added to furan-2-yl(4-methoxyphenyl)methanol (100 mg, 0.49 mmol, 1 equiv) and 2,4,6-trimethylaniline (66 mg, 0.49 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was allowed to react at rt for 5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **154** (140 mg, 89%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 (ddd, *J* = 5.7, 2.0, 2.0 Hz, 1H), 6.98 – 6.92 (m, 2H), 6.89 – 6.79 (m, 4H), 6.33 (ddd, *J* = 5.7, 1.5, 1.5 Hz, 1H), 4.39 (s, 1H), 3.80 (d, *J* = 1.8 Hz, 3H), 3.35 (d, *J* = 2.8 Hz, 1H), 3.16 (s, 1H), 2.24 (s, 3H), 2.12 (s, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.5, 163.0, 158.8, 141.0, 133.7, 132.5, 130.1, 130.0, 129.9, 129.2, 114.4, 67.7, 59.9, 55.4, 20.8, 18.9 ppm; **IR** (thin film) 3357, 2996, 2915, 2835, 1713, 1612, 1513, 1250 cm^{-1}; **HRMS** (ESI) *m/z* 344.1618 (344.1621 calcd for $C_{21}H_{23}NO_2Na^+$ $[M + Na]^+$).



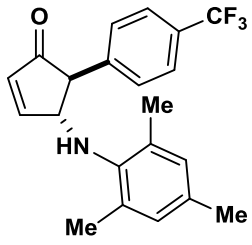
4-((4-iodophenyl)amino)-5-(4-(trifluoromethyl)phenyl)cyclopent-2-enone (155): According to the general procedure $Dy(OTf)_3$ (13 mg, 0.020 mmol, 0.05 equiv) was added to furan-2-yl(4-(trifluoromethyl) phenyl)methanol (100 mg, 0.41 mmol, 1 equiv) and 4-iodoaniline (90 mg, 0.41 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 4.5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over

$MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **155** (151 mg, 83%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 5.8, 2.4 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.43 – 7.35 (m, 2H), 7.29 – 7.23 (m, 2H), 6.46 (dd, *J* = 5.8, 1.7 Hz, 1H), 6.33 – 6.25 (m, 2H), 4.73 (bs, 1H), 4.08 (bs, 1H), 3.44 (d, *J* = 2.6 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 205.2, 161.4, 145.6, 141.9, 138.3, 135.2, 130.0 (q, *J* = 32.6 Hz), 128.5, 126.2 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272.2 Hz), 116.1, 80.2, 63.0, 59.9 ppm; **IR** (thin film) 3379, 3062, 2924, 1712, 1589, 1496, 1327 cm^{-1}; **HRMS** (ESI) *m/z* 444.0062 (444.0067 calcd for $C_{18}H_{13}F_3INOH^+$ $[M + H]^+$).

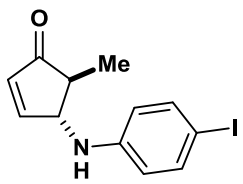


4-((3-chlorophenyl)amino)-5-(4-(trifluoromethyl) phenyl)cyclopent-2-enone (156): According to the general procedure $Dy(OTf)_3$ (14 mg, 0.024 mmol, 0.05 equiv) was added to furan-2-yl(4-(trifluoromethyl)phenyl)methanol (115 mg, 0.47 mmol, 1 equiv) and 3-chloroaniline (61 mg, 0.47 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 2 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **156** (144 mg, 87%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 5.7, 2.3 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.05 (t, *J* = 8.1 Hz, 1H), 6.74 (ddd, *J* = 7.9, 1.9, 0.8 Hz, 1H), 6.50 – 6.46 (m, 2H), 6.38 (ddd, *J* = 8.2, 2.3, 0.7 Hz, 1H), 4.75 (bs, 1H), 4.08 (bs, 1H), 3.47 (d, *J* = 2.8 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 205.1, 161.3, 147.1, 141.9, 135.5, 135.3, 130.7, 130.1 (d, *J* = 32.7 Hz), 128.6, 126.3 (q, *J* = 3.8 Hz), 119.2, 112.2, 63.2, 60.1 ppm; **IR** (thin film)

3375, 3070, 2924, 1712, 1597, 1508, 1327 cm^{-1}; **HRMS** (ESI) *m/z* 374.0538 (374.0530 calcd for $C_{18}H_{13}ClF_3NONa^+$ $[M + Na]^+$).

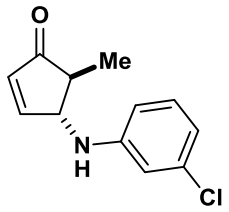


4-(mesitylamino)-5-(4-(trifluoromethyl)phenyl)cyclopent-2-enone (157): According to the general procedure $Dy(OTf)_3$ (25 mg, 0.041 mmol, 0.1 equiv) was added to furan-2-yl(4-(trifluoromethyl) phenyl)methanol (100 mg, 0.41 mmol, 1 equiv) and 2,4,6-trimethylaniline (56 mg, 0.41 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 8 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **157** (115 mg, 78%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 5.6, 1.4 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.82 (s, 2H), 6.37 (d, *J* = 5.6 Hz, 1H), 4.44 (bs, 1H), 3.46 (d, *J* = 2.6 Hz, 1H), 3.20 (bs, 1H), 2.24 (s, 3H), 2.11 (s, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ δ 206.0, 163.1, 142.1, 140.6, 133.7, 132.9, 129.9, 129.6 (q, *J* = 32.5 Hz), 128.6, 125.9 (q, *J* = 3.7 Hz), 124.3 (q, *J* = 272.0 Hz), 67.4, 60.4, 20.8, 18.8 ppm; **IR** (thin film) 3359, 2924, 2858, 1712, 1616, 1481, 1326 cm^{-1}; **HRMS** (ESI) *m/z* 382.1405 (382.1389 calcd for $C_{21}H_{20}F_3NONa^+$ $[M + Na]^+$).



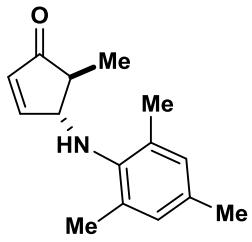
4-((4-iodophenyl)amino)-5-methylcyclopent-2-enone (158): According to the general procedure $Dy(OTf)_3$ (27 mg, 0.045 mmol, 0.05 equiv) was added to 1-(furan-2-yl)ethanol (100 mg, 0.89 mmol, 1

equiv) and 4-iodoaniline (195 mg, 0.89 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 2.5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **158** (190 mg, 68%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 5.8, 2.2 Hz, 1H), 7.49 – 7.46 (m, 2H), 6.50 – 6.47 (m, 2H), 6.28 (dd, *J* = 5.8, 1.6 Hz, 1H), 4.34 – 4.29 (m, 1H), 3.83 (d, *J* = 8.8 Hz, 1H), 2.22 (dddd, *J* = 7.4, 7.4, 7.4, 2.9 Hz, 1H), 1.33 (d, *J* = 7.4 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 208.7, 160.4, 146.4, 138.3, 134.4, 115.9, 79.6, 61.9, 49.1, 14.6 ppm; **IR** (thin film) 3367, 3062, 2970, 1709, 1589, 1496, 1315 cm^{-1}; **HRMS** (ESI) *m/z* 335.9860 (335.9856 calcd for $C_{12}H_{12}INONa^+$ $[M + Na]^+$).

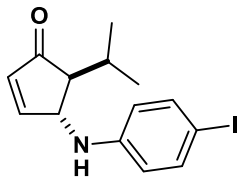


4-((3-chlorophenyl)amino)-5-methylcyclopent-2-enone (159): According to the general procedure $Dy(OTf)_3$ (60 mg, 0.1 mmol, 0.05 equiv) was added to 1-(furan-2-yl)ethanol (222 mg, 1.98 mmol, 1 equiv) and 3-chloroaniline (253 mg, 1.98 mmol, 1 equiv) in 15 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 3 h. The reaction was then quenched with 10 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **159** (44 mg, 10%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 5.7, 1.9 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.68 (s, 1H), 6.60 – 6.52 (m, 1H), 6.29 (d, *J* = 5.7 Hz, 1H), 4.33 (d, *J* = 8.0 Hz, 1H), 3.86 (d, *J* = 8.8 Hz, 1H), 2.23 (dddd, *J* = 7.4, 7.4, 7.4, 2.8 Hz,

1H), 1.35 (d, J = 7.4 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 208.7, 160.4, 147.9, 135.5, 134.4, 130.8, 118.7, 113.4, 112.0, 61.9, 49.1, 14.6 ppm; **IR** (thin film) 3367, 2968, 2930, 1709, 1598, 1483, 1324 cm^{-1}. **HRMS** (ESI) *m/z* 244.0505 (244.0505 calcd for $C_{14}H_{12}ClNONa^+$ $[M + Na]^+$).

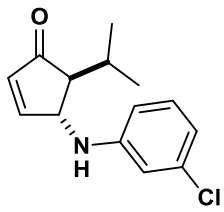


4-(mesitylamino)-5-methylcyclopent-2-enone (160): According to the general procedure $Dy(OTf)_3$ (27 mg, 0.45 mmol, 0.05 equiv) was added to 1-(furan-2-yl)ethanol (100 mg, 0.89 mmol, 1 equiv) and 2,4,6-trimethylaniline (125 µl, 0.89 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 3.5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **160** (151 mg, 74%) as a solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 (dd, J = 5.7, 1.9 Hz, 1H), 6.88 (s, 2H), 6.19 (d, J = 5.7 Hz, 1H), 4.00 – 3.98 (m, 1H), 2.98 (bs, 1H), 2.29 (s, 6H), 2.26 (s, 3H), 2.24 (dddd, J = 7.4, 7.4, 7.4, 2.9 Hz, 1H), 1.26 (d, J = 7.4 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, CDC_3) δ 209.3, 162.5, 141.2, 133.1, 132.4, 129.9, 129.9, 66.3, 49.6, 20.8, 18.8, 13.9 ppm; **IR** (thin film) 3356, 2927, 1712, 1481, 1234 cm^{-1}; **HRMS** (ESI) *m/z* 252.1364 (252.1359 calcd for $C_{15}H_{19}NONa^+$ $[M + Na]^+$).



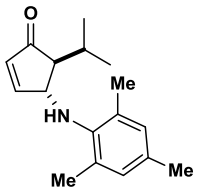
4-((4-iodophenyl)amino)-5-isopropylcyclopent-2-enone (161): According to the general procedure $Dy(OTf)_3$ (22 mg, 0.036 mmol,

0.05 equiv) was added to 1-(furan-2-yl)-2-methylpropan-1-ol (100 mg, 0.71 mmol, 1 equiv) and 4-iodoaniline (156 mg, 0.71 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **161** (176 mg, 73%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 5.7, 2.1 Hz, 1H), 7.51 – 7.41 (m, 2H), 7.27 (s, 1H), 6.54 – 6.42 (m, 2H), 6.20 (dd, *J* = 5.8, 1.4 Hz, 1H), 4.48 (d, *J* = 8.8 Hz, 1H), 3.84 (d, *J* = 8.6 Hz, 1H), 2.43 – 2.25 (m, 1H), 2.16 (dd, *J* = 4.1, 3.1 Hz, 1H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 208.3, 161.3, 146.2, 138.3, 134.9, 115.8, 79.3, 59.1, 56.4, 28.1, 20.6, 18.6 ppm; **IR** (thin film) 3371, 3062, 2958, 2877, 1589, 1496, 1319 cm^{-1}; **HRMS** (ESI) *m/z* 364.0168 (364.0169 calcd for $C_{14}H_{16}INONa^+$ $[M + Na]^+$).

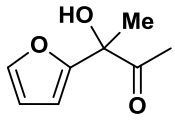


4-((3-chlorophenyl)amino)-5-isopropylcyclopent-2-enone (162): According to the general procedure $Dy(OTf)_3$ (22 mg,0.036 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-2-methylpropan-1-ol (100 mg, 0.71 mmol, 1 equiv) and 3-chloroaniline (91 mg, 0.71 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 6 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **162** (92 mg, 52%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 5.8, 2.1 Hz, 1H), 7.13

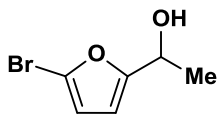
(dd, J = 8.0 Hz, 1H), 6.79 – 6.73 (m, 1H), 6.69 (dd, J = 2.0 Hz, 1H), 6.56 (dd, J = 8.2, 2.3 Hz, 1H), 6.24 (dd, J = 5.7, 1.3 Hz, 1H), 4.51 (d, J = 7.1 Hz, 1H), 3.77 (d, J = 7.8 Hz, 1H), 2.41 – 2.31 (m, 1H), 2.20 – 2.14 (m, 1H), 1.05 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 208.2, 161.2, 147.7, 135.6, 135.1, 130.8, 118.6, 113.3, 112.0, 59.2, 56.4, 28.2, 20.7, 18.6 ppm; **IR** (thin film) 3377, 2958, 2926, 1703, 1598, 1483, 1323 cm^{-1}. **HRMS** (ESI) *m/z* 272.0824 (272.0818 calcd for $C_{14}H_{16}ClNONa^+$ $[M + Na]^+$).



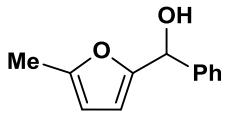
5-isopropyl-4-(mesitylamino)cyclopent-2-enone (163): According to the general procedure $Dy(OTf)_3$ (22 mg, 0.036 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-2-methylpropan-1-ol (100 mg, 0.71 mmol, 1 equiv) and 2,4,6-trimethylaniline (91 mg, 0.71 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 24 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **163** (163 mg, 89%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 (dd, J = 5.7, 2.2 Hz, 1H), 6.86 (s, 2H), 6.16 (dd, J = 5.7, 1.1 Hz, 1H), 4.21 (d, J = 1.0 Hz, 1H), 2.91 (bs, 1H), 2.35 – 2.23 (m, 11H), 2.17 (dd, J = 3.6, 2.6 Hz, 1H), 0.98 (d, J = 7.0 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 209.7, 163.8, 141.2, 134.17, 132.3, 130.0, 129.9, 60.4, 59.9, 28.4, 20.8, 20.5, 19.1, 18.6 ppm; **IR** (thin film) 3352, 2958, 1704, 1589, 1481, 1230 cm^{-1}; **HRMS** (ESI) *m/z* 258.1863 (258.1852 calcd for $C_{17}H_{23}NOH^+$ $[M + H]^+$).



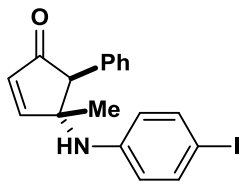
3-(Furan-2-yl)-3-hydroxybutan-2-one (166): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (dd, J = 1.8, 0.9 Hz, 1H), 6.40 (dd, J = 3.3, 0.9 Hz, 1H), 6.37 (dd, J = 3.3, 1.8 Hz, 1H), 4.46 (s, 1H), 2.16 (s, 3H), 1.73 (s, 4H) ppm.



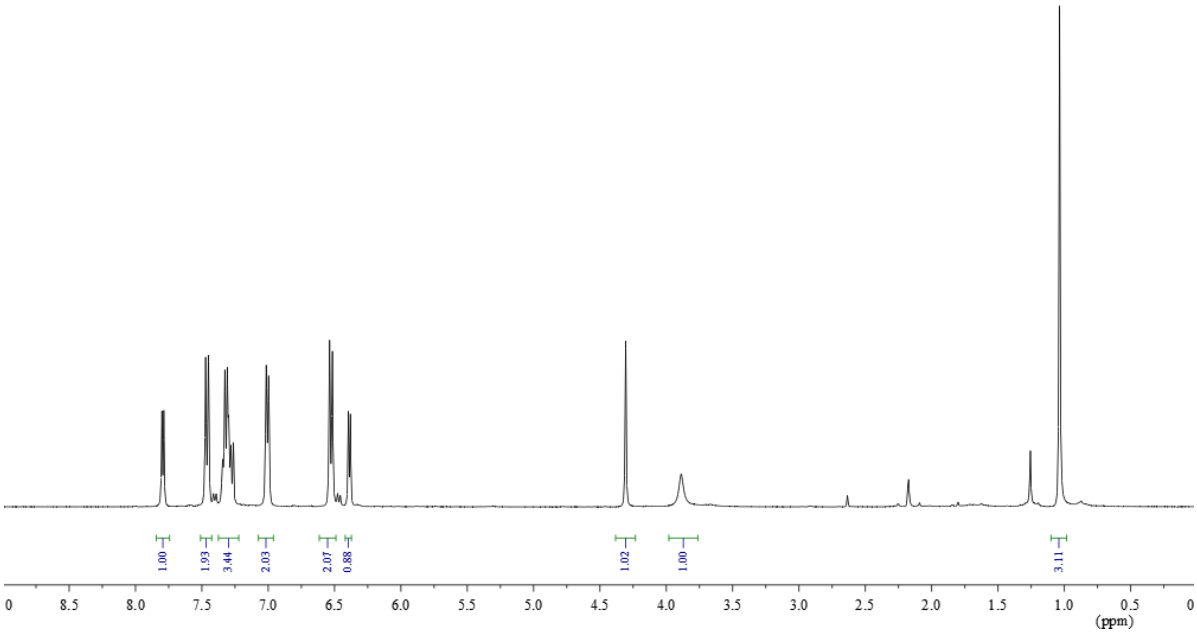
1-(5-Bromofuran-2-yl)ethan-1-ol (174): ^{1}H NMR (400 MHz, CDCl3) δ 6.24 (d, J = 3.3 Hz, 1H), 6.20 (dd, J = 3.3, 0.7 Hz, 1H), 4.83 (q, J = 6.6 Hz, 1H), 1.52 (d, J = 6.6 Hz, 3H) ppm.

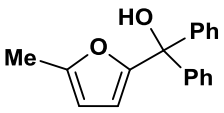


(5-methylfuran-2-yl)(phenyl)methanol (177): **^{1}H NMR** (400 MHz, CDCl3) δ 7.47 – 7.42 (m, 2H), 7.41 – 7.35 (m, 2H), 7.35 – 7.29 (m, 1H), 5.94 (d, J = 3.1 Hz, 1H), 5.91 – 5.87 (m, 1H), 5.79 – 5.74 (m, 1H), 2.43 (d, J = 3.7 Hz, 1H), 2.28 (d, J = 1.0 Hz, 3H) ppm.

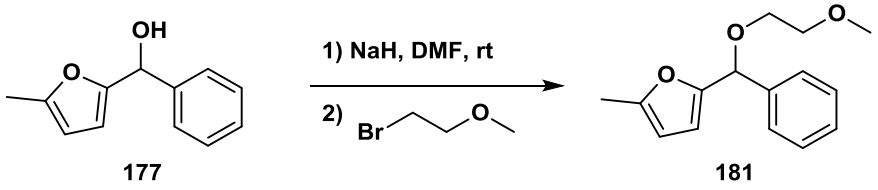


(5-methylfuran-2-yl)(phenyl)methanol (178): **^{1}H NMR** (400 MHz, CDCl3) δ 7.79 (d, J = 5.9 Hz, 1H), 7.46 (d, J = 8.3 Hz, 2H), 7.38 – 7.22 (m, 3H), 7.07 – 6.96 (m, 2H), 6.53 (d, J = 8.3 Hz, 2H), 6.39 (d, J = 5.8 Hz, 1H), 4.31 (s, 1H), 3.89 (s, 1H), 1.04 (s, 3H) ppm.



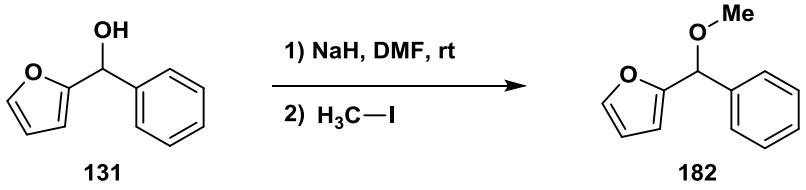


(5-methylfuran-2-yl)(phenyl)methanol (179): **^{1}H NMR** (400 MHz, CDCl3) δ 7.35 – 7.27 (m, 11H), 5.91 – 5.86 (m, 1H), 5.73 (d, J = 3.1 Hz, 1H), 2.29 (s, 3H) ppm.



2-((2-Methoxyethoxy)(phenyl)methyl)-5-methylfuran (181): Furylcarbinol **177** (219.4 mg, 1.167 mmol, 1 equiv) was added slowly to a suspension of NaH (121.1 mg, 3.03 mmol, 1.5 equiv) in 3 mL anhydrous DMF under an atmosphere of N_2 and stirred for 30 mins.

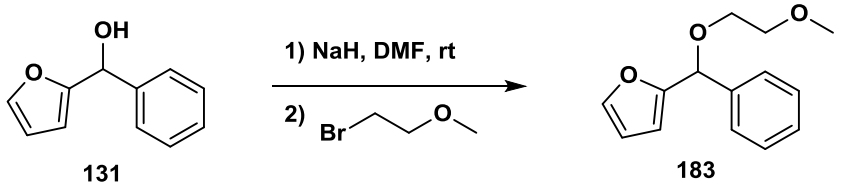
Subsequently, 1-bromo-2-methoxyethane (121.1 mg, 3.03 mmol, 1.5 equiv) was added to the solution and the reaction was stirred at 23 °C for 20 h. The reaction was quenched with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over $MgSO_4$, filtered and reduced *in vacuo*, then purified by flash column chromatography to afford **181** (259.1 mg, 55%) as an oil. **^{1}H NMR** (400 MHz, CDCl3) δ 7.48 – 7.43 (m, 2H), 7.40 – 7.33 (m, 2H), 7.33 – 7.27 (m, 1H), 5.98 (d, J = 3.1 Hz, 1H), 5.91 – 5.84 (m, 1H), 5.41 (s, 1H), 3.71 – 3.57 (m, 4H), 3.39 (s, 3H), 2.27 (d, J = 1.1 Hz, 3H).



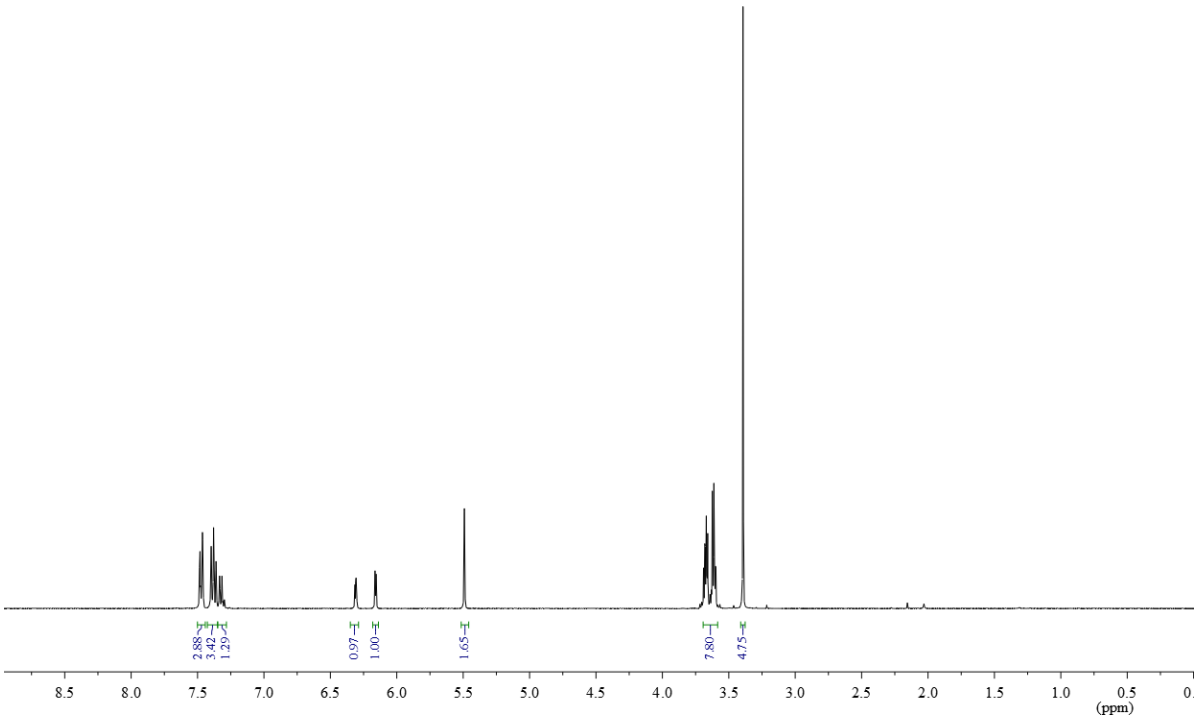
131 182

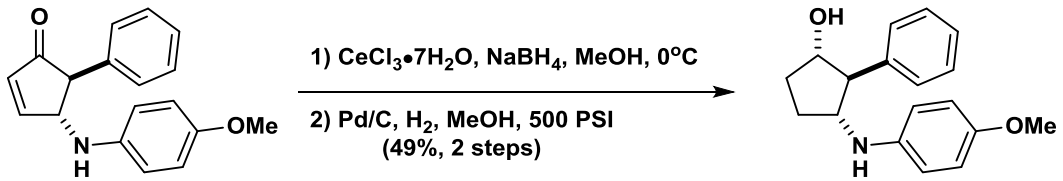
2-(methoxy(phenyl)methyl)furan (182): Furylcarbinol **131** (210.0 mg, 1.207 mmol, 1 equiv) was added slowly to a suspension of NaH (62.8 mg, 1.568 mmol, 1.3 equiv) in 3 mL anhydrous DMF under an atmosphere of N_2 and stirred for 30 mins. Subsequently, methyliodide (171.3 mg, 1.207 mmol, 1 equiv) was added to the solution and the reaction was stirred at 23 °C for 20 h. The reaction was quenched with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over $MgSO_4$, filtered and reduced *in vacuo*, then purified by flash column chromatography to afford **182** (214.8 mg, 95%) as an oil. **^{1}H NMR** (400 MHz, CDCl3) δ 7.50 – 7.45 (m, 2H), 7.45 – 7.38 (m, 3H),

7.38 – 7.32 (m, 1H), 6.34 (dd, J = 3.3, 1.8 Hz, 1H), 6.16 (dt, J = 3.2, 0.8, 0.8 Hz, 1H), 5.32 (s, 1H), 3.42 (s, 3H).



2-((2-Methoxyethoxy)(phenyl)methyl)furan (183): Furylcarbinol **131** (351.3 mg, 2.019 mmol, 1 equiv) was added slowly to a suspension of NaH (121.1 mg, 3.03 mmol, 1.5 equiv) in 3 mL anhydrous DMF under an atmosphere of N_2 and stirred for 30 mins. Subsequently, 1-bromo-2-methoxyethane was added to the solution and the reaction was stirred at 23 °C for 20 h. The reaction was quenched with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over $MgSO_4$, filtered and reduced *in vacuo*, then purified by flash column chromatography to afford **183** (259.1 mg, 55%) as an oil. **^{1}H NMR** (600 MHz, CDCl3) δ 7.50 – 7.44 (m, 2H), 7.43 – 7.35 (m, 3H), 7.35 – 7.28 (m, 1H), 6.31 (dd, J = 3.2, 1.8 Hz, 1H), 6.16 (dt, J = 3.2, 0.8 Hz, 1H), 5.49 (s, 1H), 3.69 – 3.58 (m, 4H), 3.39 (s, 3H).

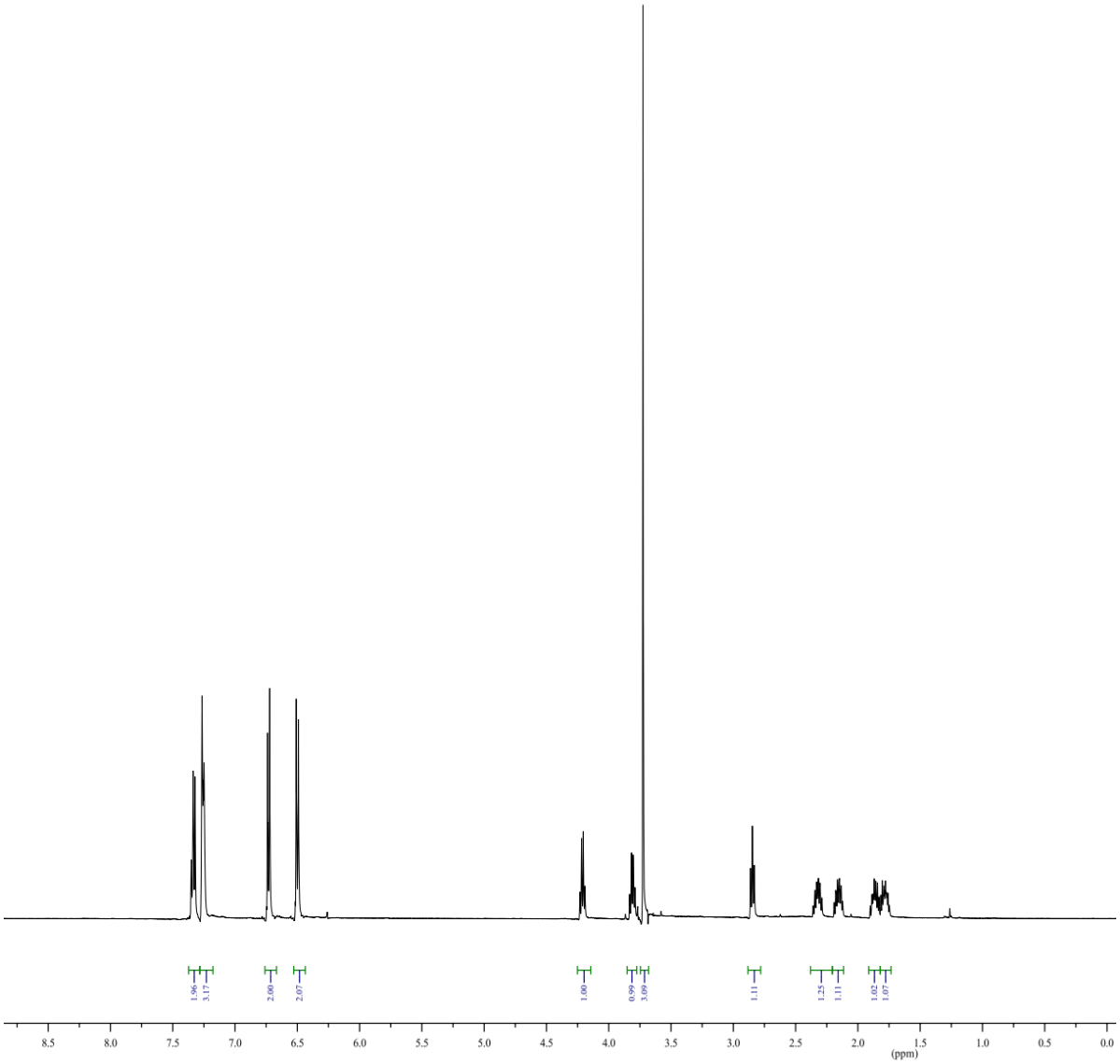




137 188

3-((4-methoxyphenyl)amino)-2-phenylcyclopentanol (188): 4-((4-methoxyphenyl)amino)-5-phenylcyclopent-2-enone **137** (399 mg, 1.43 mmol, 1 equiv) and $CeCl_3 \bullet 7H_2O$ (745 mg, 2.00 mmol, 1.4 equiv) were combined in 16 mL MeOH at 23 °C. After 20 min, the solution was cooled to 0 °C and $NaBH_4$ (76 mg, 2.0 mmol, 1.4 equiv) was added in several portions. Upon completion, the reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic

layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The material was purified by flash column chromatography, eluted with 4:1 hexanes/EtOAc, to give the reduced product as a 2:1 mixture of diastereomers of the allylic alcohol that were not separated. This mixture of diastereomers (347 mg, 1.23 mmol, 1 equiv) was added to a suspension of Pd/C (10%) (131 mg, 1.23 mmol, 0.1 equiv) in 14 mL MeOH and placed under an atmosphere of H_2 at 500 psi for 16 h. The solution was filtered through Celite®, washed with EtOAc (3 × 15 mL) and the combined organic phases were reduced *in vacuo*. Purification by flash column chromatography, eluting with 4:1 hexanes/EtOAc, afforded cyclopentanol **188** (350 mg, 76% 2:1 mixture) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 2H), 7.28 – 7.19 (m, 3H), 6.77 – 6.66 (m, 2H), 6.55 – 6.46 (m, 2H), 4.21 (ddd, *J* = 13.4, 6.7, 6.7 Hz, 1H), 3.81 (ddd, *J* = 13.5, 7.5, 7.5 Hz, 1H), 3.73 (s, 3H), 2.85 (dd, *J* = 7.4, 7.4 Hz, 1H), 2.32 (dddd, *J* = 13.8, 7.4, 7.4, 7.4, Hz, 1H), 2.20 – 2.11 (m, 1H), 1.92 – 1.82 (m, 1H), 1.82 – 1.72 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 152.4, 141.9, 141.1, 128.9, 127.8, 127.1, 115.4, 114.9, 78.9, 61.5, 60.4, 55.9, 32.5, 30.8 ppm; **IR** (thin film) 3377, 3028, 2952, 1602, 1512, 1237 cm^{-1}; **MS** (ESI) *m/z* 306.18 (306.15 calcd for $C_{18}H_{21}NO_2Na^+$ $[M + Na]^+$).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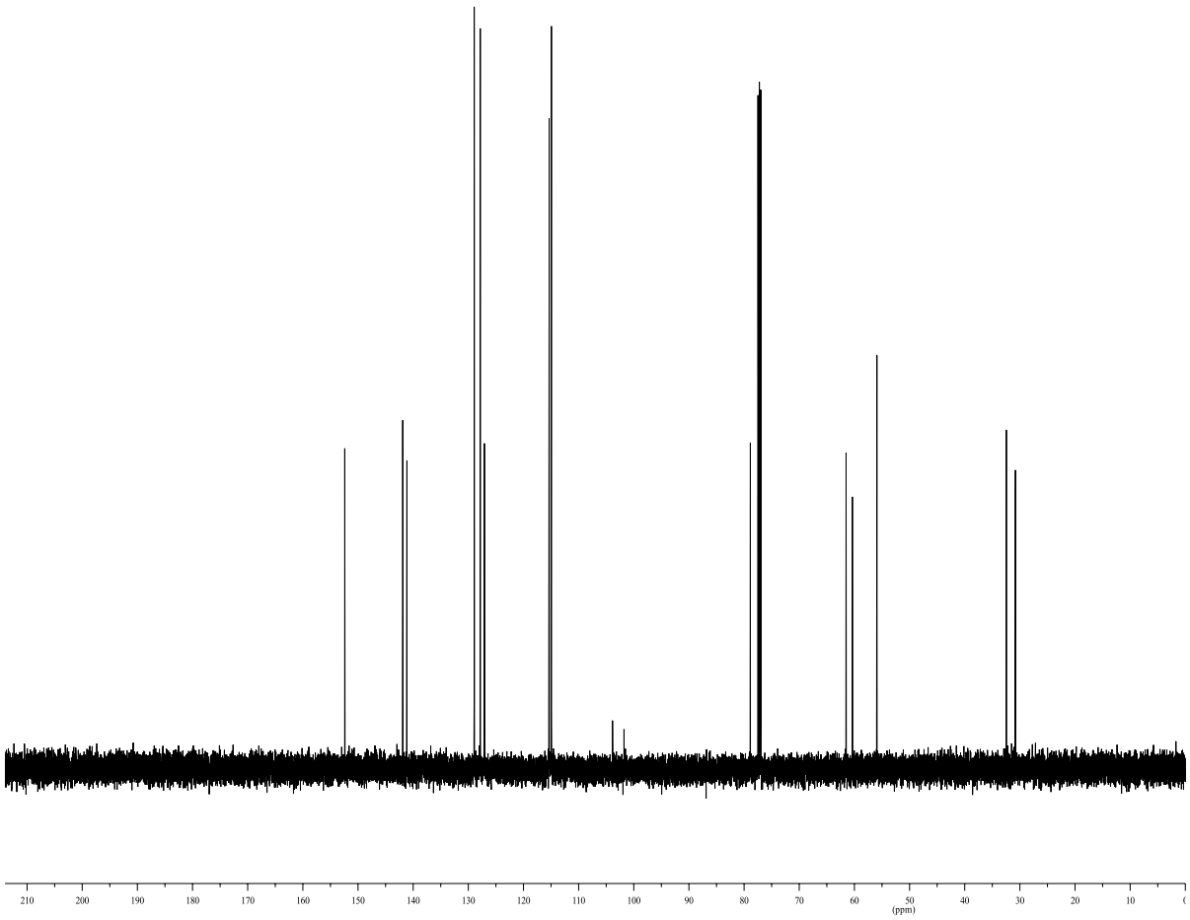
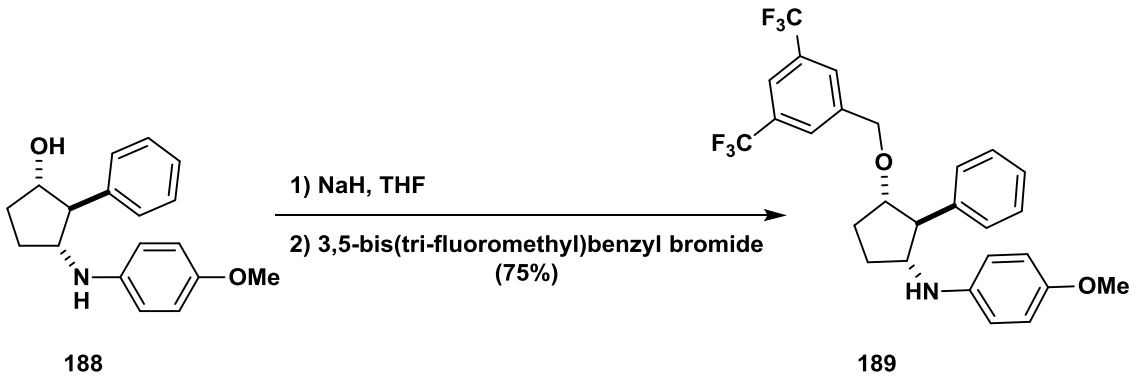
3.17
2.00
2.07
1.00
0.99
3.09
1.11
1.25
1.11
1.02
1.07
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

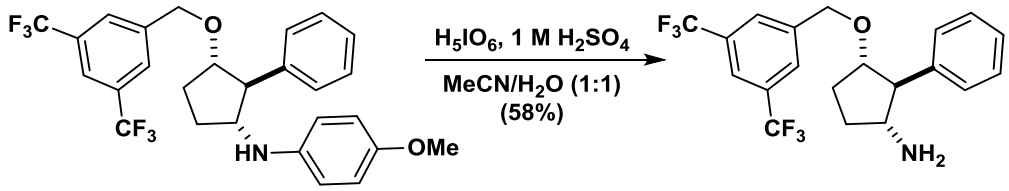




188 189

N-3-((3,5-bis(trifluoromethyl)benzyl)oxy)-2-phenylcyclopentyl)-4-methoxyaniline (189): Cyclopentanol **188** (111 mg, 0.39 mmol, 1 equiv) was added slowly to a suspension of NaH (168 mg, 7 mmol, 18 equiv) in 11 mL anhydrous THF under an atmosphere of N_2

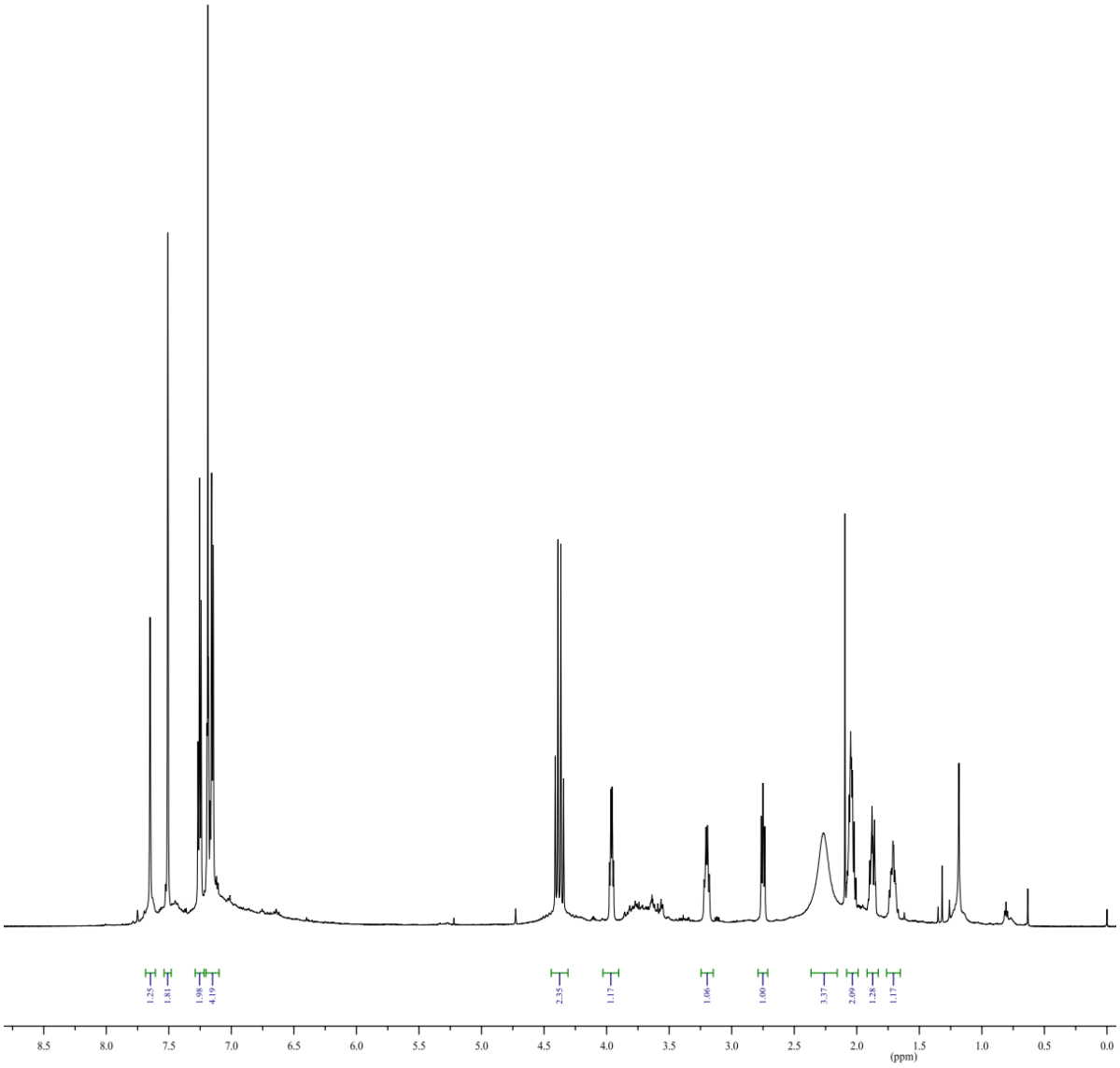
and stirred for 1 h. Subsequently, 3,5-*bis*-trifluoromethylbenzyl bromide was added to the solution and the reaction was stirred at 23 °C for 16 h. The reaction was quenched with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over $MgSO_4$, filtered and reduced *in vacuo*, then purified by flash column chromatography, eluting with 9:1 hexanes/EtOAc, to afford **189** (149 mg, 75%) as a yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.66 (s, 2H), 7.36 – 7.31 (m, 2H), 7.28 – 7.24 (m, 3H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.48 (d, *J* = 8.8 Hz, 2H), 4.53 (dd, *J* = 31.5, 12.8 Hz, 2H), 4.06 (ddd, *J* = 12.0, 6.1, 6.1 Hz, 1H), 3.80 (ddd, *J* = 14.3, 7.1, 7.1 Hz, 1H), 3.73 (s, 3H), 3.08 (ddd, *J* = 6.7, 6.7 Hz, 1H), 2.36 (dddd, *J* = 13.3, 7.0, 7.0, 7.0 Hz, 1H), 2.18 (dddd, *J* = 14.8, 7.6, 7.6, 7.6 Hz, 1H), 2.1 – 1.99 (m, 1H), 1.87 – 1.80 (dddd, *J* = 15.1, 7.5, 7.5, 7.5 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 152.5, 141.9, 141.9, 141.4, 131.8 (q, *J* = 33.2 Hz), 129.0, 127.7, 127.4 (m), 127.2, 123.5 (q, *J* = 272.2 Hz), 121.57 (ddd, *J* = 3.8, 3.8, 3.8 Hz),115.3, 115.0, 86.7, 70.1, 61.4, 59.6, 56.0, 31.3, 30.3 ppm; **IR** (thin film) 3030, 2937, 2834, 1622, 1512, 1352, 1280 cm^{-1}; **HRMS** (ESI) *m/z* 510.1844 (510.1868 calcd for $C_{27}H_{25}F_6NO_2H^+$ $[M + H]^+$).



189 190

3-((3,5-bis(trifluoromethyl)benzyl)oxy)-2-phenylcyclopentanamine (190): To a solution of cyclopentane **189** (103 mg, 0.203 mmol, 1 equiv) in 4.4 mL MeCN/H_2O (1:1), H_5IO_6 (46.3 mg, 0.203 mmol, 1 equiv) and 1 M H_2SO_4 (203 μL, 0.203 mmol, 1 equiv) were added

sequentially. The reaction mixture was stirred for 6 h at 23 °C. Upon completion, the solution was extracted with CH_2Cl_2 (3 × 10 mL). The aqueous phase was then adjusted to pH 10/11 using 5 M KOH and extracted with EtOAc (4 × 10 mL). The combined organic layers were acidified to pH 1 with HCl/EtOAc, dried over $MgSO_4$, filtered and reduced *in vacuo*. The material was then purified by flash column chromatography, eluting with a gradient hexanes/EtOAc to 9:1 CH_2Cl_2/MeOH, to afford 3-((3,5-bis(trifluoromethyl) benzyl)oxy)-2-phenylcyclopentanamine **190** (47.5 mg, 58%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.59 (s, 2H), 7.36 – 7.31 (m, 2H), 7.29 – 7.21 (m, 3H), 4.46 (dd, *J* = 26.9, 12.8 Hz, 2H), 4.04 (ddd, *J* = 12.3, 7.1, 7.1 Hz, 1H), 3.28 (ddd, *J* = 15.7, 9.2, 9.2 Hz, 1H), 2.83 (dd, *J* = 7.5, 7.5 Hz, 1H), 2.54 – 2.19 (bs, 2H), 2.17 – 2.07 (m, 2H), 2.00 – 1.92 (m, 1H), 1.85 – 1.73 (m, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 141.4, 141.2, 131.8 (q, *J* = 33.3 Hz), 129.1, 127.8, 127.4 (m), 127.3, 123.5 (q, *J* = 272.4 Hz), 121.5 (dddd, *J* = 7.7, 3.7, 3.7, 3.7 Hz), 86.2, 69.9, 62.2, 59.1, 32.3, 29.8 ppm; **IR** (thin film) 3062, 3030, 2933, 1624, 1510, 1376, 1280, 1173 cm^{-1}; **HRMS** (ESI) *m/z* 404.1434 (404.1449 calcd for $C_{20}H_{19}F_6NOH^+$ [M + H]$^+$).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1.17
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2.69
1.28
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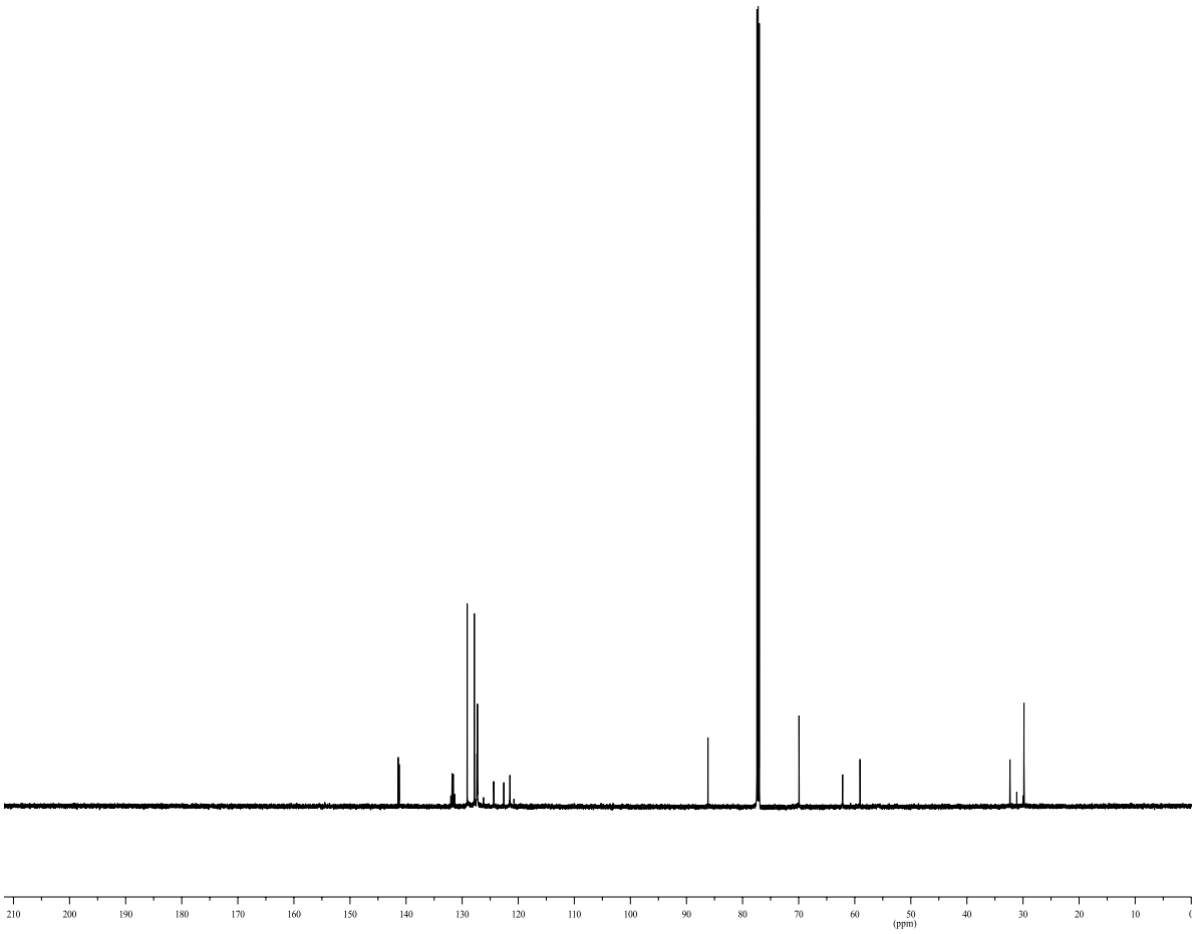
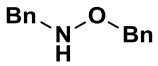
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

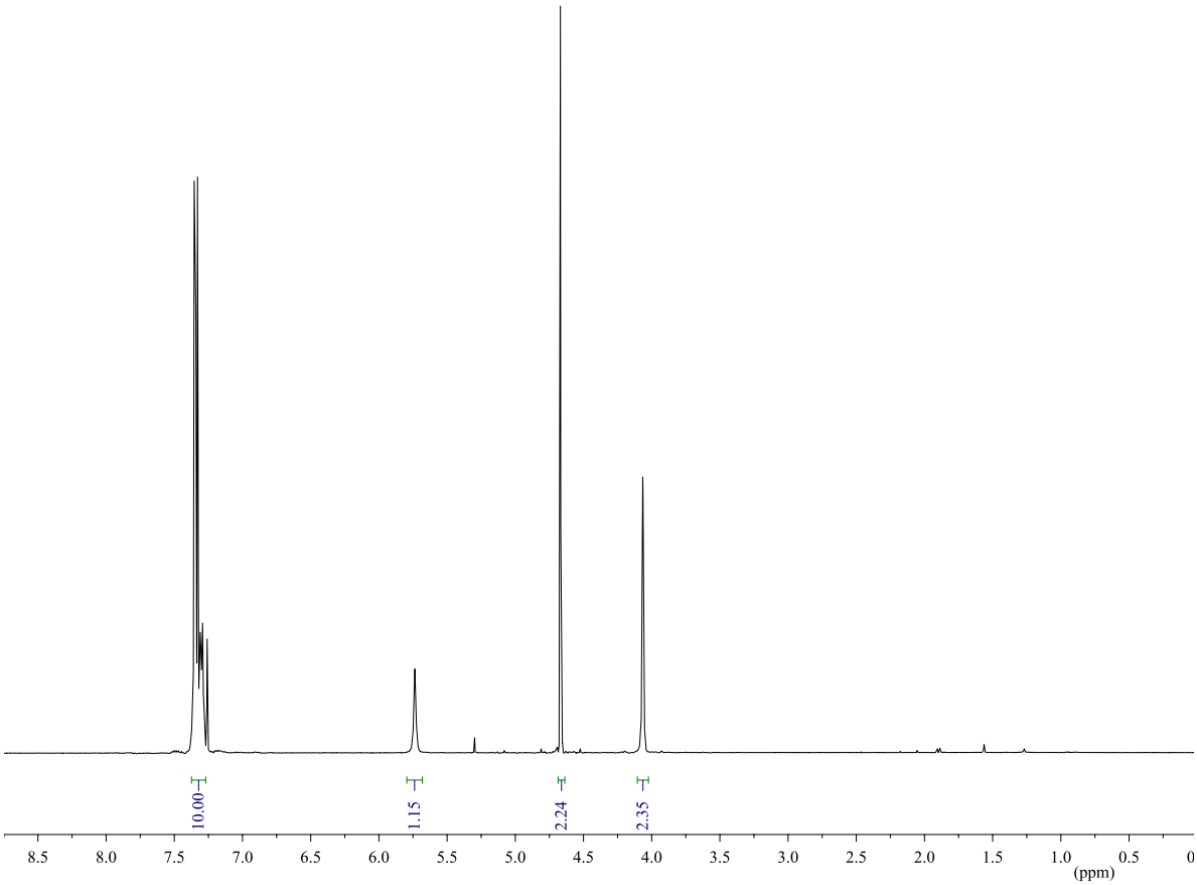


5.1.2 Chapter 1.2

General Procedure for the Synthesis of Hydroxylamines: Hydroxylamines were synthesized following published procedures.[2]



***N*,*O*-Dibenzylhydroxylamine (201):** Colorless oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 10H), 5.74 (s, 1H), 4.67 (s, 2H), 4.07 (s, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.0, 137.7, 129.1, 128.6, 128.5, 128.5, 127.9, 127.6, 76.5, 56.7 ppm; **IR** (thin film) 3260, 3087, 3019, 2912, 2858, 1895, 1877, 1810, 1604, 1495, 1453, 1275, 1260, 988 cm^{-1}; **MS** (ESI) *m/z* 214.1219 (214.1232 calcd for $C_{14}H_{16}NO^{+}$ $[MH]^{+}$).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1.15
2.24
2.35
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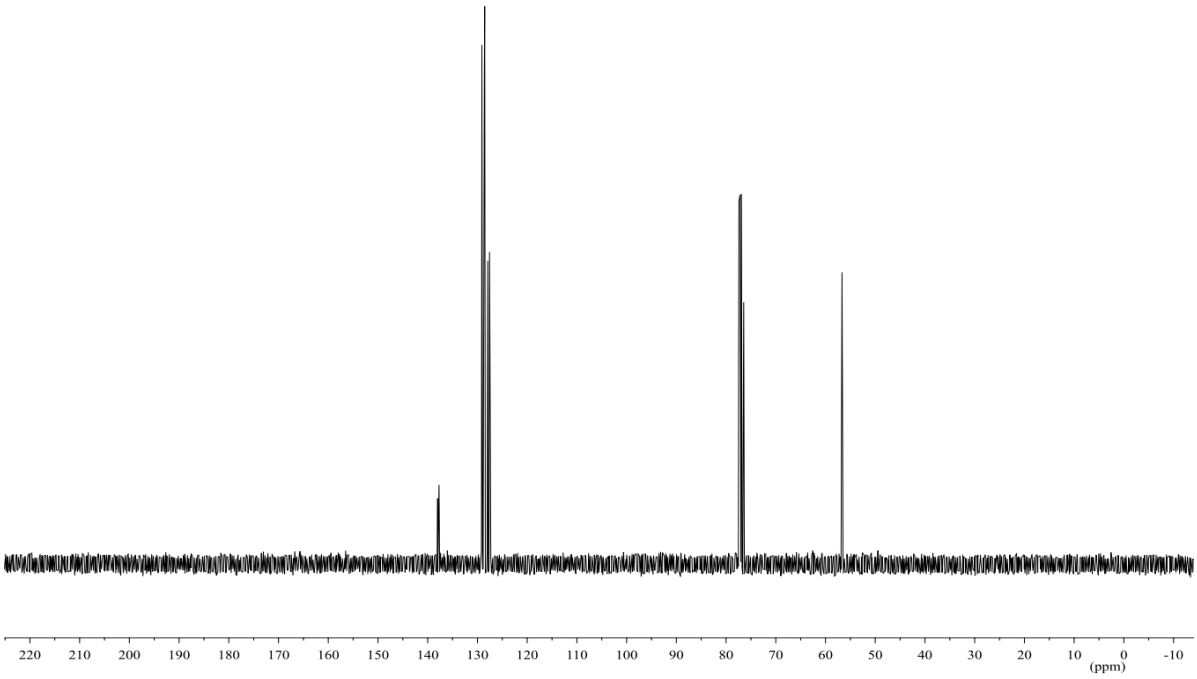
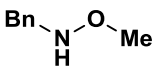
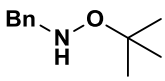
(ppm)

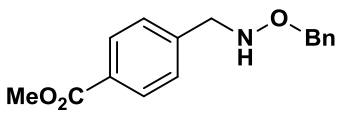

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)



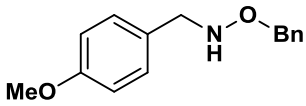
***N*-Benzyl-*O*-methylhydroxylamine (E-4):** Colorless oil; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 4H), 7.31 – 7.27 (m, 1H), 5.73 (s, 1H), 4.06 (s, 2H), 3.52 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 137.7, 129.0, 128.6, 127.6, 62.0, 56.4 ppm; **IR** (thin film) 3259, 3030, 2937, 2894, 2808, 1604, 1454, 1275, 1260, 992 cm^{-1}; **MS** (ESI) *m/z* 160.0737 (160.0738 calcd for $C_8H_{11}NNaO^+$ $[MNa]^+$).



***N*-Benzyl-*O*-(tert-butyl)hydroxylamine (E-5):** Colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 4.00 (s, 2H), 1.18 (s, 9H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 129.4, 128.5, 127.6, 57.8, 26.9 ppm; **IR** (thin film) 3255, 2975, 2929, 2863, 1947, 1876, 1806, 1603, 1454, 1360 cm^{-1}; **MS** (ESI) *m/z* 180.1362 (180.1383 calcd for $C_{11}H_{18}NO^+$ $[MH]^+$).

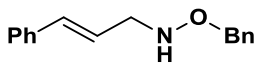


Methyl 4-(((benzyloxy)amino)methyl)benzoate (E-6): Colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.38 – 7.27 (m, 5H), 4.63 (s, 2H), 4.09 (s, 2H), 3.92 (s, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 167.1, 143.3, 137.8, 129.8, 129.4, 128.9, 128.6, 128.5, 128.0, 76.6, 56.3, 52.2 ppm; **IR** (thin film) 3267, 3031, 2951, 1937, 1721, 1612 cm^{-1}; **MS** (ESI) *m/z* 294.1096 (294.1106 calcd for $C_{16}H_{17}NNaO_3^+$ $[MNa]^+$).

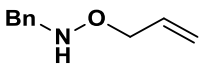


***O*-Benzyl-*N*-(4-methoxybenzyl)hydroxylamine (E-7):** Colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 3.0 Hz, 4H), 7.35 – 7.32 (m, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 5.68 (bs, 1H) 4.70 (s, 2H),

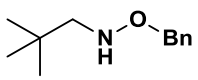
4.03 (s, 2H), 3.83 (s, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.1, 138.0, 130.3, 129.7, 128.5, 128.4, 127.8, 113.9, 76.3, 56.0, 55.3 ppm; **IR** (thin film) 3261, 3031, 2910, 2859, 2060, 1883, 1612, 1513 cm^{-1}; **MS** (ESI) *m/z* 244.1319 (244.1332 calcd for $C_{15}H_{18}NO_2^+$ $[MH]^+$).



***O*-Benzyl-*N*-cinnamylhydroxylamine (E-8):** Colorless oil; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 9H), 7.27 – 7.21 (m, 1H), 6.58 (d, *J* = 16.0 Hz, 1H), 6.30 (dt, *J* = 15.9, 6.6 Hz, 1H), 5.61 (s, 1H), 4.76 (s, 2H), 3.72 (dd, *J* = 6.6, 1.3 Hz, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.0, 137.1, 133.3, 128.7, 128.6, 128.5, 128.0, 127.7, 126.5, 125.7, 76.5, 54.6 ppm; **IR** (thin film) 3258, 3061, 3028, 2910, 2853, 1877, 1598, 1494, 1453, 1361, 1275, 1260, 965^{-1}; **MS** (ESI) *m/z* 240.1381 (240.1388 calcd for $C_{16}H_{18}NO^+$ $[MH]^+$).

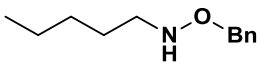


***O*-Allyl-*N*-benzylhydroxylamine (E-9):** Colorless oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 4H), 7.32 – 7.25 (m, 1H), 5.91 (ddt, *J* = 17.3, 10.4, 5.9 Hz, 1H), 5.72 (s, 1H), 5.26 (ddt, *J* = 17.3, 1.6, 1.6 Hz, 1H), 5.18 (ddt, *J* = 10.4, 2.0, 1.2 Hz, 1H), 4.17 (ddd, *J* = 6.0, 1.3, 1.3 Hz, 2H), 4.07 (s, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 137.6, 134.6, 129.1, 128.5, 127.6, 117.7, 75.2, 56.7 ppm; **IR** (thin film) 3254, 3065, 3030, 2907, 2858, 1807, 1645, 1454, 1421, 1343, 1239, 988, 923 cm^{-1}; **MS** (ESI) *m/z* 186.0873 (186.0895 calcd for $C_{10}H_{13}NNaO^+$ $[MNa]^+$).

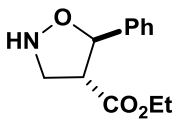


***O*-Benzyl-*N*-neopentylhydroxylamine (E-10):** Colorless oil; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 4H), 7.32 – 7.28 (m, 1H), 5.60 (s,

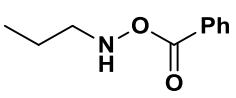
1H), 4.70 (s, 2H), 2.75 (s, 2H), 0.93 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.1, 128.6, 128.4, 127.8, 75.9, 63.6, 31.1, 28.3 ppm; **IR** (thin film) 3276, 3031, 2953, 2906, 2865, 1476, 1454, 1363, 1275, 1259, 978 cm^{-1}; **MS** (ESI) *m/z* 194.1523 (194.1545 calcd for $C_{12}H_{20}NO^+$ $[MH]^+$).



***O*-Benzyl-*N*-pentylhydroxylamine (E-11):** Colorless oil; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 4H), 7.32 – 7.27 (m, 1H), 5.54 (s, 1H), 4.71 (s, 2H), 2.93 (dd, *J* = 7.3, 7.3 Hz, 2H), 1.52 (dddd, *J* = 7.4, 7.4, 7.4, 7.4 Hz, 2H), 1.36 – 1.25 (m, 4H), 0.90 (dd, *J* = 6.8, 6.8 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.2, 128.5, 128.5, 127.9, 76.3, 52.4, 29.5, 27.2, 22.7, 14.2 ppm; **IR** (thin film) 3265, 3031, 2955, 2930, 1857, 1454, 1362, 1275, 1206, 998 cm^{-1}; **MS** (ESI) *m/z* 194.1535 (194.1545 calcd for $C_{12}H_{20}NO^+$ $[MH]^+$).

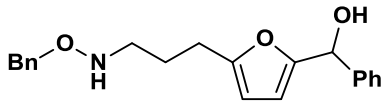


Ethyl (*trans*)-5-phenylisoxazolidine-4-carboxylate (E-12): Prepared according to literature procedure.[3] Colorless oil. **^{1}H NMR** (600 MHz, Chloroform-d) δ 7.39 – 7.32 (m, 4H), 7.32 – 7.28 (m, 1H), 5.72 (s, 1H), 5.08 (d, J = 5.7 Hz, 1H), 4.27 – 4.12 (m, 2H), 3.57 (dd, J = 11.8, 3.3 Hz, 1H), 3.47 (dd, J = 11.8, 8.4 Hz, 1H), 3.35 – 3.20 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H) ppm; **^{13}C NMR** (151 MHz, Chloroform-d) δ 173.2, 139.2, 128.7, 128.3, 126.2, 86.8, 61.4, 56.6, 53.7, 14.2 ppm; **IR** (thin film) 3229, 3065, 3034, 2983, 2942, 2906, 1886, 1813, 1729 cm^{-1}; **MS** (ESI) *m/z* 244.0942 (244.0950 calcd for $C_{12}H_{15}NO_3^+$ $[MH]^+$).

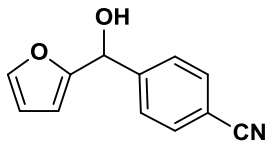


***O*-Benzoyl-*N*-propylhydroxylamine (E-13):** Colorless oil. **^{1}H NMR**

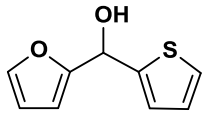
(600 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.5, 1.4 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 3.12 (t, *J* = 7.1 Hz, 2H), 1.66 (h, *J* = 7.4 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 167.1, 133.4, 129.5, 128.7, 128.6, 54.5, 20.7, 11.7 ppm; **IR** (thin film) 3239, 2963, 2936, 2876, 1765, 1716 cm^{-1}; **MS** (ESI) *m/z* 180.0997 (180.1019 calcd for $C_{10}H_{14}NO_2^+$ $[MH]^+$).



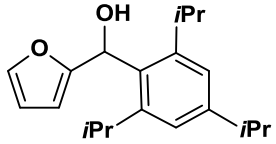
(5-(3-((Benzyloxy)amino)propyl)furan-2 yl)(phenyl) methanol (E-14): Light yellow oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 2H), 7.39 – 7.28 (m, 8H), 5.94 (d, *J* = 3.1 Hz, 1H), 5.90 (d, *J* = 3.1 Hz, 1H), 5.76 (s, 1H), 4.70 (s, 2H), 2.95 (t, *J* = 7.0 Hz, 2H), 2.65 (t, *J* = 7.5 Hz, 2H), 1.85 (tt *J* = 7.3, 7.3 Hz, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 156.0, 154.5, 141.1, 138.0, 128.5, 128.5, 128.5, 128.0, 127.9, 126.7, 108.4, 105.8, 76.4, 70.2, 51.5, 25.8 ppm; **IR** (thin film) 3382, 3087, 3062, 3030, 2910, 2858, 1955, 1885, 1453, 1190, 1010, 961 cm^{-1}; **MS** (ESI) *m/z* 360.1574 (360.1576 calcd for $C_{21}H_{23}NNaO_3^+$ $[MNa]^+$).



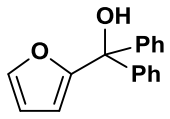
4-(Furan-2-yl(hydroxy)methyl)benzonitrile (E-15): Yellow solid; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 2H), 7.59 – 7.54 (m, 2H), 7.42 – 7.38 (m, 1H), 6.36 – 6.31 (m, 1H), 6.15 (d, *J* = 3.3 Hz, 1H), 5.88 (s, 1H), 2.69 (s, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 154.7, 146.0, 143.2, 132.4, 127.3, 118.8, 111.8, 110.6, 108.1, 69.4 ppm; **IR** (thin film) 3418, 3122, 2879, 2228, 1927, 1808, 1609, 1504, 1410, 1141, 1009 cm^{-1}; **MS** (EI^+) *m/z* 199.0628 (199.0633 calcd for $C_{12}H_9O_2^+$ $[M]^+$).



Furan-2-yl(thiophen-2-yl)methanol (E-16): Yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 3.3 Hz, 1H), 7.38 (dd, *J* = 1.5, 0.7 Hz, 1H), 7.32 (d, *J* = 3.2 Hz, 1H), 6.35 – 6.30 (m, 2H), 6.08 (s, 1H), 4.79 (s, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 171.7, 153.3, 143.1, 142.3, 119.9, 110.6, 108.4, 67.6 ppm; **IR** (thin film) 3119, 2852, 1766, 1621, 1503, 1432 cm^{-1}; MS (EI) *m/z* 180.0247 (180.0245 calcd for $C_9H_8O_2S^+$ $[M]^+$).

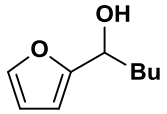


Furan-2-yl(2,4,6-triisopropylphenyl)methanol (E-17): Brown solid; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 (ddd, *J* = 1.8, 0.8, 0.8 Hz, 1H), 7.05 (s, 2H), 6.41 (d, *J* = 2.9 Hz, 1H), 6.31 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.00 (ddd, *J* = 3.3, 1.1, 1.1 Hz, 1H), 3.35 (hept, *J* = 6.8 Hz, 2H), 2.89 (hept, *J* = 6.9 Hz, 1H), 2.32 (d, *J* = 3.5 Hz, 1H), 1.26 (d, *J* = 6.9 Hz, 6H), 1.20 (d, *J* = 6.8 Hz, 6H), 1.15 (d, *J* = 6.8 Hz, 6H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 156.4, 148.8, 142.0, 131.7, 122.2, 110.5, 106.6, 65.8, 34.3, 29.8, 25.1, 24.1, 24.1 ppm; IR (thin film) 3408, 2959, 2928, 2868, 1768, 1607, 1460, 1362, 1142, 1004 cm^{-1}; **MS** (EI^+) *m/z* 300.2096 (300.2089 calcd for $C_{20}H_{28}O_2^+$ $[M]^+$).



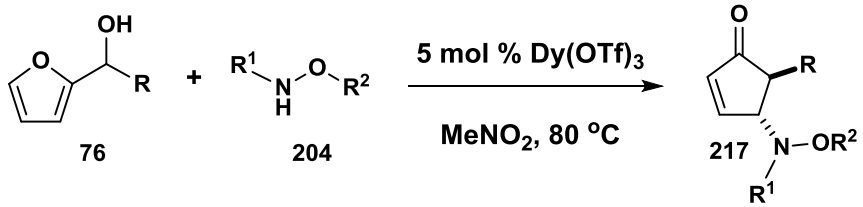
Furan-2-yldiphenylmethanol (E-3): Yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.40 – 7.27 (m, 10H), 6.34 (d, *J* = 1.5 Hz, 1H), 5.94 (d, *J* = 3.2 Hz, 1H), 3.11 (s, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 158.0, 144.7, 142.8, 128.1, 127.8, 127.3, 110.2, 109.8, 78.1 ppm; **IR** (thin film) 3410, 3061, 3028, 1957, 1888,

1813, 1725, 1675, 1598, 1554, 1490, 1447 cm^{-1}; **MS** (EI) *m/z* 250.0991 (250.0994 calcd for $C_{17}H_{14}O_2^+$ $[M]^+$).

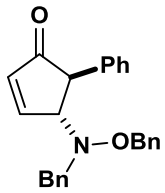


1-(Furan-2-yl)pentan-1-ol (E-18): Colorless oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (m, 1H), 6.32 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.22 (d, *J* = 3.2 Hz, 1H), 4.66 (td, *J* = 6.7, 3.8 Hz, 1H), 1.91 (s, 1H), 1.88 – 1.80 (m, 2H), 1.47 – 1.23 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.1, 142.0, 110.2, 105.9, 68.0, 35.4, 27.8, 22.6, 14.1 ppm; **IR** (thin film) 3360, 2956, 2932, 2861, 1597, 1505, 1466, 1149, 1007 cm^{-1}; **MS** (EI^+) *m/z* 154.0998 (154.0994 calcd for $C_9H_{14}O_2^+$ $[M]^+$).

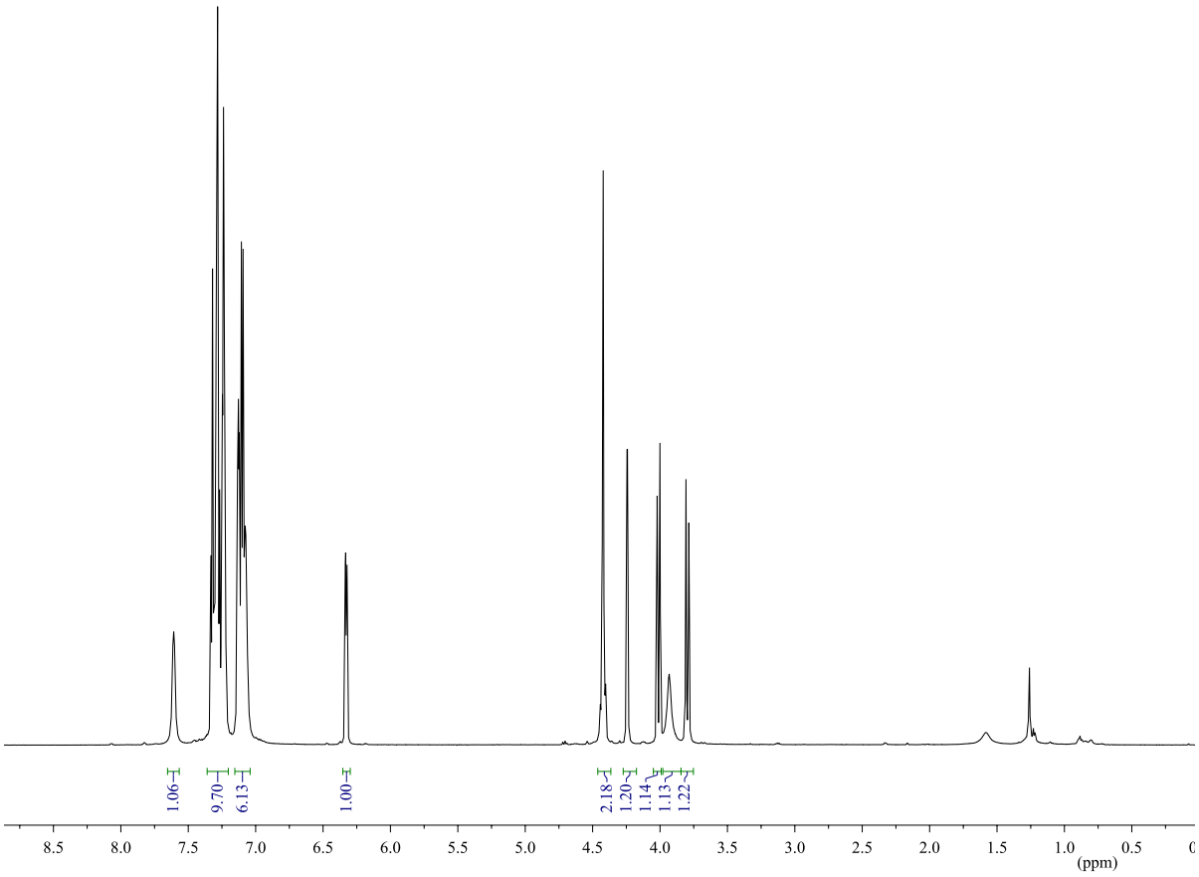
Synthesis of Substituted Cyclopentenones:

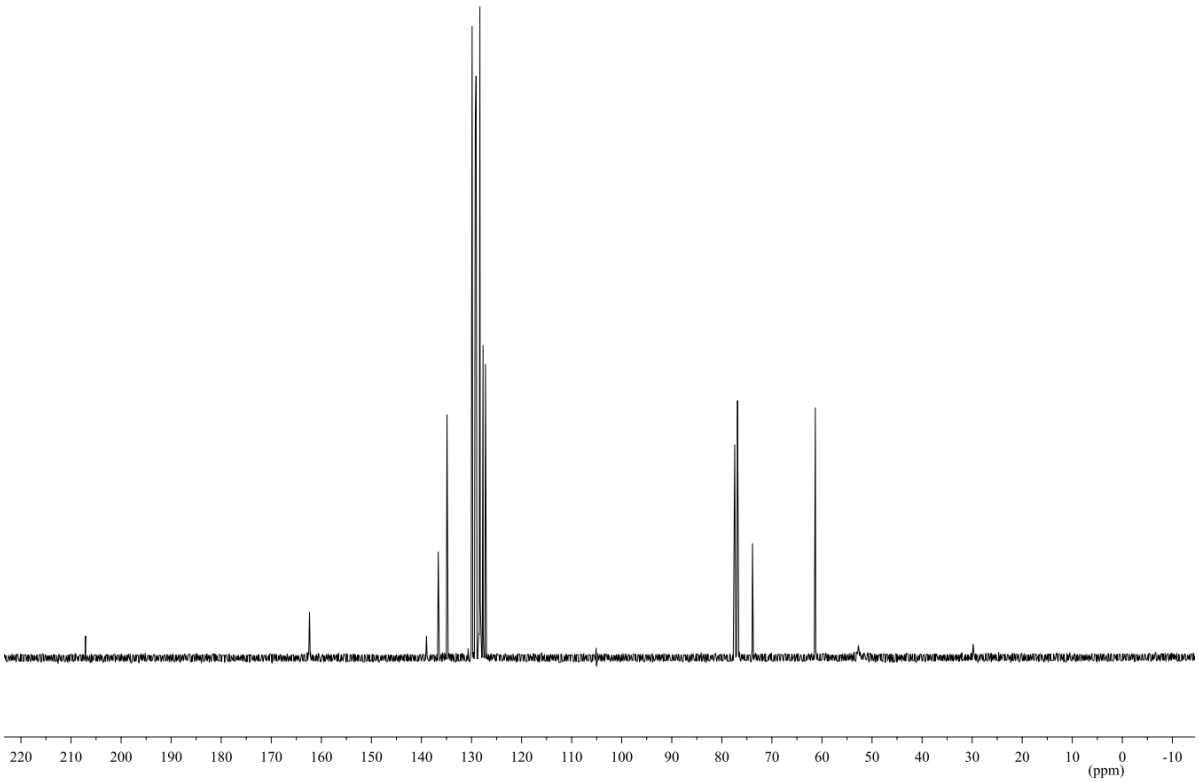


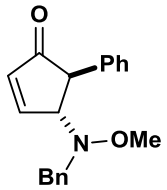
General Procedure for the Synthesis of Substituted Cyclopentenones: Furylcarbinol (**76**) and hydroxylamine (**204**) were stirred as a solution in $MeNO_2$ at rt. 5-10 mol % $Dy(OTf)_3$ was added to the reaction mixture, and the flask placed in an oil bath pre-heated at 80 °C. The reactions were monitored by TLC. Upon completion, the reaction was quenched with saturated $NaHCO_3$ at rt and extracted with EtOAc (3x). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenones (**217**).



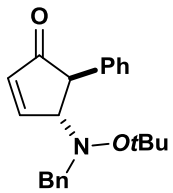
4-(Benzyl(benzyloxy)amino)-5-phenylcyclopent-2-en-1-one (202): According to the general procedure, furan-2-yl(phenyl)methanol (38.2 mg, 0.220 mmol) and *N*,*O*-dibenzylhydroxylamine (46.8 mg, 0.220 mmol) were treated with $Dy(OTf)_3$ (6.7 mg, 0.011 mmol) in $MeNO_2$ (2.2 mL). The resulting reaction mixture was heated to 80 ºC for 30 min. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **202** (71.6 mg, 88%) as a light orange/yellow solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.36 – 7.20 (m, 9H), 7.15 – 7.04 (m, 6H), 6.33 (dd, *J* = 5.8, 1.9 Hz, 1H), 4.43 (d, *J* = 11.9 Hz, 1H), 4.41 (d, *J* = 10.2 Hz, 1H), 4.24 (ddd, *J* = 2.3, 2.3, 2.3 Hz, 1H), 4.01 (d, *J* = 12.6 Hz, 1H), 3.93 (s, 1H), 3.80 (d, *J* = 12.6 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.1, 162.4, 139.0, 136.7, 136.6, 134.9, 129.9, 129.2, 129.1, 128.5, 128.4, 128.3, 128.3, 127.7, 127.2, 76.9, 73.9, 61.3, 52.7 ppm; **IR** (thin film) 3063, 3031, 2919, 1709, 1595, 1454, 1265, 1029, 975 cm^{-1}; **MS** (ESI) *m/z* 392.1636 (392.1626 calcd for $C_{25}H_{23}NNaO_2^+$ $[MNa]^+$).


1.06
9.70
6.13
1.00
2.18
1.20
1.14
1.13
1.22
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

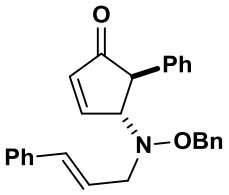


4-(Benzyl(methoxy)amino)-5-phenylcyclopent-2-en-1-one (206): According to the general procedure, furan-2-yl(phenyl)methanol (30.0 mg, 0.172 mmol) and *N*-benzyl-*O*-methylhydroxylamine (23.6 mg, 0.172 mmol) were treated with $Dy(OTf)_3$ (5.2 mg, 0.0086 mmol) in $MeNO_2$ (1.8 mL). The resulting reaction mixture was heated to 80 ºC for 30 min. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **206** (46.2 mg, 91%) as an orange/brown solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 5.7, 2.3 Hz, 1H), 7.33 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.29 – 7.24 (m, 1H), 7.23 – 7.21 (m, 3H), 7.12 (d, *J* = 7.2 Hz, 2H), 7.08 (s, 2H), 6.36 (dd, *J* = 5.7, 1.9 Hz, 1H), 4.21 (ddd, *J* = 2.3, 2.3, 2.3 Hz, 1H), 3.99 (d, *J* = 12.7 Hz, 1H), 3.87 (s, 1H), 3.74 (d, *J* = 12.7 Hz, 1H), 3.32 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.1, 162.1, 138.9, 136.7, 135.0, 129.7, 129.1, 128.5, 128.3, 127.6, 127.2, 73.9, 62.4, 60.9, 52.9 ppm; **IR** (thin film) 3062, 3030, 2934, 2812, 1709, 1595, 1454, 1266, 1040, 978 cm^{-1}; **MS** (ESI) *m/z* 316.1309 (316.1313 calcd for $C_{19}H_{19}NNaO_2^+$ $[MNa]^+$).



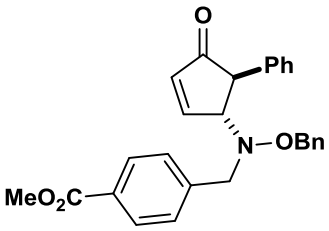
4-(Benzyl(tert-butoxy)amino)-5-phenylcyclopent-2-en-1-one (207): According to the general procedure, furan-2-yl(phenyl)methanol (31.7 mg, 0.182 mmol) and *N*-benzyl-*O*-(*tert*-butyl)hydroxylamine (32.7 mg, 0.182 mmol) were treated with $Dy(OTf)_3$ (5.54 mg, 0.0091 mmol) in $MeNO_2$ (1.8 mL). The

resulting reaction mixture was heated to 80 ºC for 1 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **207** (46.2 mg, 76%) as a colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.68 – 7.63 (m, 1H), 7.35 – 7.25 (m, 3H), 7.19 – 7.03 (m, 5H), 6.79 (d, *J* = 7.5 Hz, 2H), 6.28 (d, *J* = 3.6 Hz, 1H), 4.19 – 4.08 (m, 3H), 3.80 (d, *J* = 12.7 Hz, 1H), 1.22 (s, 9H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 207.9, 164.9, 140.0, 136.9, 134.1, 129.4, 129.1, 128.7, 128.3, 127.5, 127.1, 78.0, 72.0, 62.8, 51.1, 28.1 ppm; **IR** (thin film) 3062, 3029, 2975, 2928, 2867, 1712, 1602 cm^{-1}; **MS** (ESI) *m/z* 358.1774 (358.1783 calcd for $C_{22}H_{25}NNaO_2^+$ $[MNa]^+$).



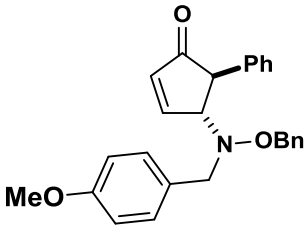
4-((Benzyloxy)(cinnamyl)amino)-5-phenylcyclopent-2-en-1-one (208): According to the general procedure, furan-2-yl(phenyl)methanol (15.0 mg, 0.086 mmol) and *O*-benzyl-*N*-cinnamylhydroxylamine (20.6 mg, 0.086 mmol) were treated with $Dy(OTf)_3$ (5.2 mg, 0.0086 mmol) in $MeNO_2$ (1.8 mL). The resulting reaction mixture was heated to 80 ºC for 1.5 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **208** (29.3 mg, 86%) as a light orange oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.35 – 7.19 (m, 11H), 7.16 (d, *J* = 7.4 Hz, 2H), 7.11 (d, *J* = 7.2 Hz, 2H), 6.33 (dd, *J* = 5.8, 2.0 Hz, 1H), 6.12 (ddd, *J* = 14.7, 6.6, 6.6 Hz, 1H), 5.90 (d, *J* = 15.9 Hz, 1H), 4.69 (d, *J* = 10.7 Hz, 1H), 4.63 (d, *J* = 10.8 Hz, 1H), 4.37 (s, 1H), 3.87 (s, 1H), 3.69 (dd, *J* =

12.8, 6.1 Hz, 1H), 3.48 (dd, J = 13.0, 8.1 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.1, 162.5, 139.0, 136.8, 136.7, 134.9, 134.9, 129.2, 129.1, 128.6, 128.6, 128.5, 128.3, 127.9, 127.2, 126.5, 123.9, 76.8, 73.6, 59.3, 52.4 ppm; **IR** (thin film) 3061, 3029, 2822, 2854, 1950, 1709, 1495, 1453, 1165, 1028, 968 cm^{-1}; **MS** (ESI) *m/z* 418.1766 (418.1783 calcd for $C_{27}H_{25}NNaO_2^+$ $[MNa]^+$).

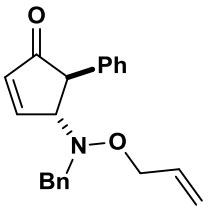


Methyl 4-(((benzyloxy)(4-oxo-5-phenylcyclopent-2-en-1-yl)amino)methyl)benzoate (209): According to the general procedure, furan-2-yl(phenyl)methanol (28.8 mg, 0.166 mmol) and methyl 4-(((benzyloxy)amino)methyl)benzoate (44.9 mg, 0.166 mmol) were treated with $Dy(OTf)_3$ (5.1 mg, 0.0084 mmol) in $MeNO_2$ (1.6 mL). The resulting reaction mixture was heated to 80 ºC for 1 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **209** (57.4 mg, 82%) as a white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.92 (d, J = 7.8 Hz, 2H), 7.62 (s, 1H), 7.33 (t, J = 7.3 Hz, 2H), 7.31 – 7.27 (m, 4H), 7.18 – 7.13 (m, 2H), 7.13 – 7.08 (m, 4H), 6.35 (dd, J = 5.8, 1.9 Hz, 1H), 4.47 – 4.37 (m, 2H), 4.24 (d, J = 2.3 Hz, 1H), 4.04 (d, J = 12.8 Hz, 1H), 3.94 (s, 1H), 3.91 (s, 3H), 3.84 (d, J = 12.8 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 206.8, 167.0, 162.0, 141.9, 138.8, 136.5, 135.1, 129.8, 129.6, 129.6, 129.2, 129.2, 128.5, 128.5, 128.4, 127.3, 77.0, 74.1, 61.0, 52.7, 52.2 ppm; **IR** (thin film)

3084, 3031, 2950, 2910, 2874, 2275, 1738, 1718, 1701 cm^{-1}; **MS** (ESI) *m/z* 450.1665 (450.1682 calcd for $C_{27}H_{25}NNaO_4^+$ $[MNa]^+$).

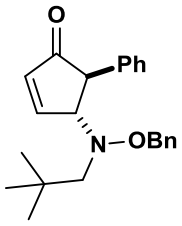


4-((Benzyloxy)(4-methoxybenzyl)amino)-5-phenylcyclopent-2-en-1-one (210): According to the general procedure, furan-2-yl(phenyl)methanol (19.7 mg, 0.113 mmol) and *O*-benzyl-*N*-(4-methoxybenzyl)hydroxylamine (27.6 mg, 0.113 mmol) were treated with $Dy(OTf)_3$ (3.4 mg, 0.0057 mmol) in $MeNO_2$ (1.1 mL). The resulting reaction mixture was heated to 80 ºC for 2h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **210** (34.4 mg, 76%) as a white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.36 – 7.26 (m, 6H), 7.20 – 7.14 (m, 2H), 7.11 (d, *J* = 7.5 Hz, 2H), 6.95 (s, 2H), 6.76 (d, *J* = 8.1 Hz, 2H), 6.33 (dd, *J* = 5.8, 2.1 Hz, 1H), 4.44 (s, 2H), 4.24 (d, *J* = 2.5 Hz, 1H), 3.96 (d, *J* = 12.5 Hz, 1H), 3.94 (s, 1H), 3.78 (s, 3H), 3.74 (d, *J* = 12.6 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 207.2, 162.6, 159.2, 139.1, 136.8, 134.9, 131.1, 129.3, 129.1, 128.7, 128.6, 128.4, 128.3, 127.2, 113.7, 76.8, 73.6, 60.6, 55.4, 52.8 ppm; **IR** (thin film) 3030, 2930, 2837, 1884, 1712, 1611, 1513 cm^{-1}; **MS** (ESI) *m/z* 422.1716 (422.1732 calcd for $C_{26}H_{25}NNaO_3^+$ $[MNa]^+$).



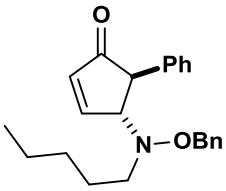
4-((Allyloxy)(benzyl)amino)-5-phenylcyclopent-2-en-1-one (211): According to the general procedure, furan-2-yl(phenyl)methanol (100.0

mg, 0.57 mmol) and *O*-allyl-*N*-benzylhydroxylamine (93.8 mg, 0.57 mmol) were treated with $Dy(OTf)_3$ (17.5 mg, 0.029 mmol) in $MeNO_2$ (5.7 mL). The resulting reaction mixture was heated to 80 ºC for 45 min. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **211** (173.5 mg, 95%) as an orange oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 6.0, 2.5 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.29 – 7.24 (m, 1H), 7.23 – 7.18 (m, 3H), 7.12 (d, *J* = 7.3 Hz, 2H), 7.07 (s, 2H), 6.36 (dd, *J* = 5.8, 2.0 Hz, 1H), 5.70 (dddd, *J* = 16.8, 10.3, 6.2, 6.2 Hz, 1H), 5.15 – 5.07 (m, 2H), 4.25 – 4.19 (m, 1H), 4.02 (d, *J* = 12.7 Hz, 1H), 4.00 – 3.89 (m, 3H), 3.78 (d, *J* = 12.7 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 207.1, 162.3, 138.9, 136.6, 135.0, 133.5, 129.8, 129.1, 128.5, 128.3, 127.6, 127.2, 118.3, 75.9, 73.8, 61.4, 52.8 ppm; **IR** (thin film) 3063, 3029, 2916, 2858, 1708, 1495, 1454, 1165, 1029, 980 cm^{-1}; **MS** (ESI) *m/z* 342.1466 (342.1470 calcd for $C_{21}H_{21}NNaO_2^+$ $[MNa]^+$).



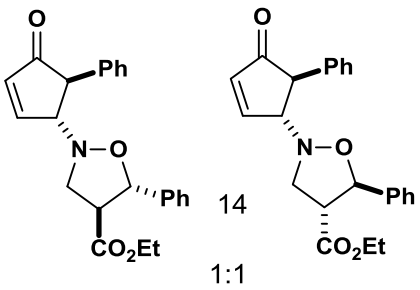
4-((Benzyloxy)(neopentyl)amino)-5-phenylcyclopent-2-en-1-one (212): According to the general procedure, furan-2-yl(phenyl)methanol (30.0 mg, 0.172 mmol) and *O*-benzyl-*N*-neopentylhydroxylamine (33.3 mg, 0.172 mmol) were treated with $Dy(OTf)_3$ (5.2 mg, 0.0085 mmol) in $MeNO_2$ (1.8 mL). The resulting reaction mixture was heated to 80 ºC for 45 min. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford

cyclopentenone **212** (52.6 mg, 81%) as an orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 5.8, 2.3 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.30 – 7.22 (m, 4H), 7.17 – 7.09 (m, 4H), 6.40 (dd, *J* = 5.8, 1.9 Hz, 1H), 4.70 (d, *J* = 10.5 Hz, 1H), 4.62 (d, *J* = 10.5 Hz, 1H), 4.38 (ddd, *J* = 2.3, 2.3, 2.3 Hz, 1H), 3.72 (d, *J* = 2.8 Hz, 1H), 2.65 (d, *J* = 14.1 Hz, 1H), 2.58 (d, *J* = 14.1 Hz, 1H), 0.94 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.3, 162.2, 139.2, 136.6, 135.4, 129.0, 128.7, 128.5, 128.3, 128.1, 127.1, 76.5, 75.1, 67.8, 53.5, 31.7, 28.5 ppm; **IR** (thin film) 3063, 3030, 2952, 2866, 1711, 1601, 1453, 1362, 1026, 981 cm^{-1}; **MS** (ESI) *m/z* 372.1932 (372.1939 calcd for $C_{23}H_{27}NNaO_2^+$ $[MNa]^+$).



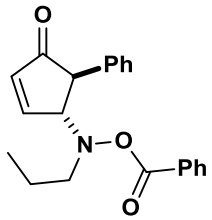
4-((Benzyloxy)(pentyl)amino)-5-phenylcyclopent-2-en-1-one (213): According to the general procedure, furan-2-yl(phenyl)methanol (15.0 mg, 0.086 mmol) and *O*-benzyl-*N*-pentylhydroxylamine (16.7 mg, 0.086 mmol) were treated with $Dy(OTf)_3$ (5.2 mg, 0.0086 mmol) in $MeNO_2$ (0.9 mL). The resulting reaction mixture was heated to 80 ºC for 1 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **213** (22.8 mg, 76%) as an orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 5.8, 2.3 Hz, 1H), 7.32 (ddd, *J* = 7.7, 4.1 Hz, 5H), 7.27 – 7.22 (m, 3H), 7.13 – 7.08 (m, 2H), 6.36 (dd, *J* = 5.8, 1.9 Hz, 1H), 4.69 (d, *J* = 10.6 Hz, 1H), 4.64 (d, *J* = 10.7 Hz, 1H), 4.27 (ddd, *J* = 2.3, 2.3, 2.3 Hz, 1H), 3.77 (s, 1H), 2.87 (ddd, *J* = 12.5, 8.9, 5.6 Hz, 1H), 2.67 (ddd, *J* = 12.5, 8.8, 5.9 Hz, 1H), 1.57 – 1.41 (m, 2H), 1.29 – 1.20 (m, 4H), 0.89 – 0.81 (m, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.3, 162.2, 139.1, 136.8, 135.0, 129.1, 128.9, 128.5, 128.3, 128.3, 127.1,

77.2, 75.1, 57.4, 52.8, 29.5, 27.1, 22.6, 14.1 ppm; **IR** (thin film) 3062, 3029, 2954, 2982, 2858, 1711, 1496, 1453, 1165, 1029, 982 cm^{-1}; **MS** (ESI) *m/z* 372.1937 (372.1939 calcd for $C_{23}H_{27}NNaO_2^+$ $[MNa]^+$).



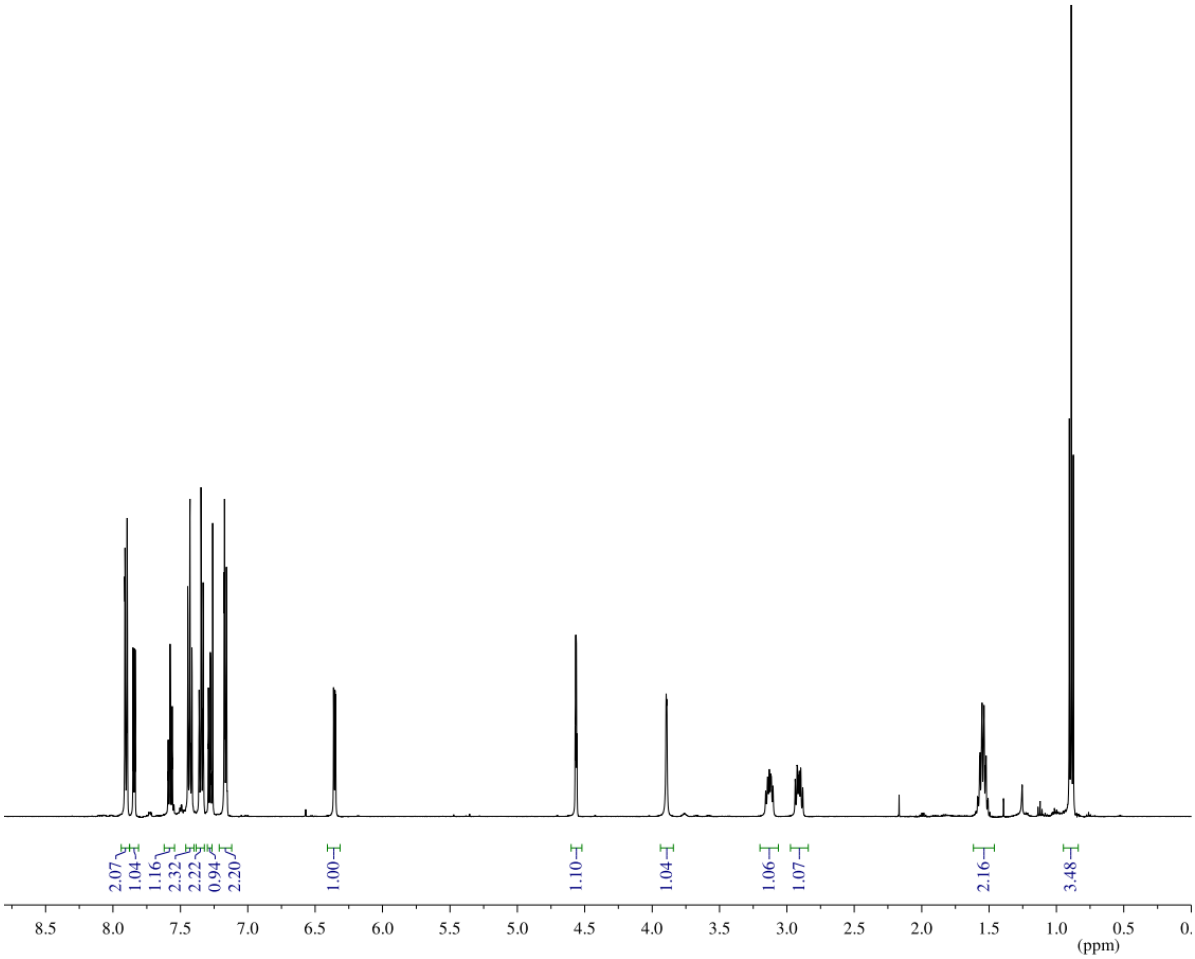
Ethyl 2-(4-oxo-5-phenylcyclopent-2-en-1-yl)-5-phenylisoxazolidine-4-carboxylate (214): According to the general procedure, furan-2-yl(phenyl)methanol (33.7 mg, 0.194 mmol) and ethyl 5-phenylisoxazolidine-4-carboxylate (made according to literature procedure)[3] (42.9 mg, 0.194 mmol) were treated with $Dy(OTf)_3$ (5.9 mg, 0.0097 mmol) in $MeNO_2$ (1.9 mL). The resulting reaction mixture was heated to 80 ºC for 1.25 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **214** (46.0 mg, 63%, 1:1 mixture of diastereomers) as a brown oil. Higher RF diastereomer **^{1}H NMR** (500 MHz, Toluene-d_8, 90 ºC) δ 7.45 – 7.30 (m, 3H), 7.21 – 6.94 (m, 8H), 6.02 (d, J = 5.8 Hz, 1H), 5.33 (d, J = 5.9 Hz, 1H), 4.09 (s, 1H), 3.94 – 3.75 (m, 2H), 3.52 (s, 1H), 3.19 – 3.08 (m, 2H), 3.08 – 3.00 (m, 1H), 3.04 (t, J = 8.1 Hz, 1H), 0.88 (t, J = 7.1 Hz, 3H) ppm; **^{13}C NMR** (200 MHz, Toluene-d_8, 70 ºC) 204.0, 171.6, 170.0, 159.8, 135.4, 129.2, 129.1, 128.6, 127.5, 126.8, 125.7, 81.8, 74.3, 61.3, 60.2, 57.0, 56.8, 56.1, 14.3 ppm; **IR** (thin film) 3063, 3030, 2981, 2927, 2852, 1714, 1597 cm^{-1}; **MS** (ESI) *m/z* 400.1516 (400.1525 calcd for $C_{23}H_{23}NNaO_4^+$ $[MNa]^+$).

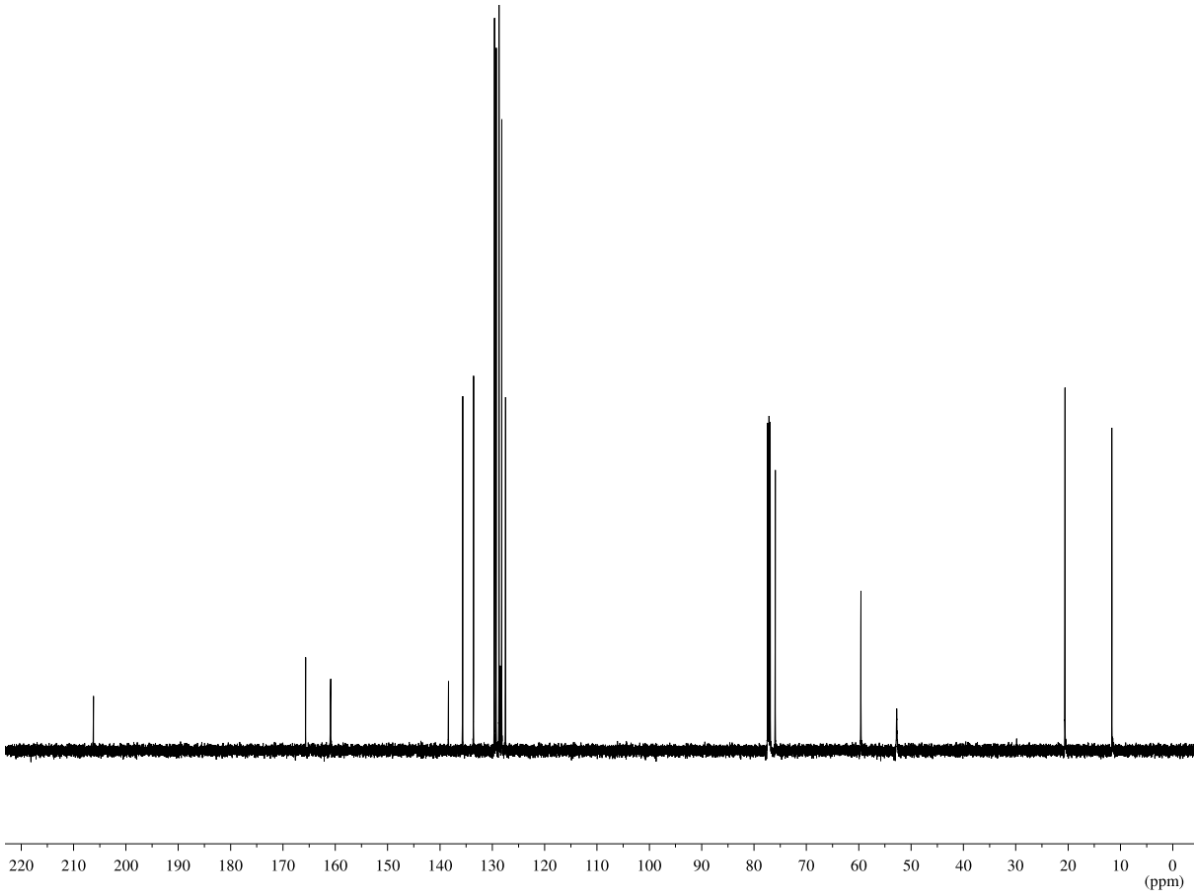
Lower RF diastereomer **^{1}H NMR** (500 MHz, Toluene-d_8, 90 ºC) δ 7.32 (d, J = 7.1 Hz, 3H), 7.19 – 7.10 (m, 2H), 7.10 – 6.95 (m, 6H), 6.02 (dd, J = 5.8, 1.6 Hz, 1H), 5.18 (d, J = 6.5 Hz, 1H), 4.06 (q, J = 2.5 Hz, 1H), 3.90 (dddd, J = 17.9, 10.8, 7.1, 3.7 Hz, 2H), 3.58 (d, J = 3.1 Hz, 1H), 3.37 (dd, J = 9.4, 5.2 Hz, 1H), 3.06 (ddd, J = 8.7, 6.5, 5.1 Hz, 1H), 2.78 (t, J = 9.1 Hz, 1H), 0.92 (t, J = 7.1 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, Toluene-d_8, 90 ºC) 203.9, 171.5, 159.5, 159.3, 141.2, 139.4, 135.6, 135.6, 127.4, 127.0, 100.8, 82.1, 74.9, 61.3, 57.0, 56.5, 56.2, 24.5, 14.4 ppm; **IR** (thin film) 3063, 3030, 2981, 2925, 2852, 1714, 1597 cm^{-1}; **MS** (ESI) *m/z* 400.1508 (400.1525 calcd for $C_{23}H_{23}NNaO_4^+$ $[MNa]^+$).

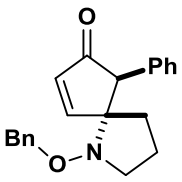


4-((Benzoyloxy)(propyl)amino)-5-phenylcyclopent-2-en-1-one (215): According to the general procedure, furan-2-yl(phenyl)methanol (28.3 mg, 0.163 mmol) and *O*-benzoyl-*N*-propylhydroxylamine (29.1 mg, 0.163 mmol) were treated with 30 mol % $Dy(OTf)_3$ (29.8 mg, 0.0489 mmol) in MeCN (1.6 mL). The resulting reaction mixture was stirred at room temperature for 58 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **215** (27.1 mg, 50%) as a yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.3, 1.4 Hz, 2H), 7.84 (dd, J = 5.8, 2.4 Hz, 1H), 7.58 (dddd, J = 7.1, 7.1, 1.3, 1.3 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.38 – 7.31 (m, 2H), 7.31 – 7.25 (m, 1H), 7.20 – 7.14 (m, 2H), 6.36 (dd, J = 5.8, 1.9 Hz, 1H), 4.56 (dd, J = 4.6, 2.3 Hz, 1H), 3.89 (d, J = 2.8 Hz, 1H), 3.16 – 3.09 (m, 1H), 2.91 (ddd, J = 12.7, 8.2, 6.8 Hz, 1H), 1.61 – 1.48 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.2, 165.7,

160.9, 138.4, 135.7, 133.6, 129.6, 129.3, 128.7, 128.5, 128.2, 127.5, 76.0, 59.6, 52.7, 20.6, 11.6 ppm; **IR** (thin film) 3063, 3030, 2964, 2935, 2876, 1743, 1712 cm^{-1}; **MS** (ESI) *m/z* 358.1406 (358.1419 calcd for $C_{21}H_{21}NNaO_3^+$ $[MNa]^+$).

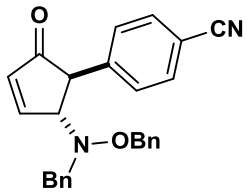




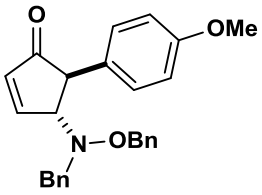


1-(Benzyloxy)-6-phenyl-1-azaspiro[4.4]non-8-en-7-one (216): According to the general procedure, (5-(3-((benzyloxy)amino)propyl)furan-2-yl)(phenyl)methanol (240 mg, 0.71 mmol) was treated with $Dy(OTf)_3$ (21.6 mg, 0.036 mmol) in $MeNO_2$ (7 mL). The resulting reaction mixture was heated to 80 ºC for 1 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **216** (185.6 mg, 82%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (d, J = 5.8 Hz, 1H), 7.38 – 7.21 (m, 8H), 7.06 – 7.00 (m, 2H),

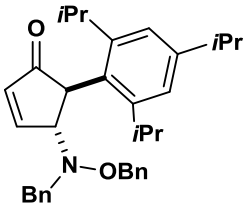
6.34 (d, J = 5.8 Hz, 1H), 4.73 (d, J = 11.4 Hz, 1H), 4.70 (d, J = 11.4 Hz, 1H), 4.00 (s, 1H), 3.28 – 3.20 (m, 1H), 3.10 (ddd, J = 10.2, 8.0, 4.3 Hz, 1H), 1.71 – 1.59 (m, 2H), 1.60 – 1.50 (m, 1H), 1.28 – 1.13 (m, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 208.2, 165.5, 137.8, 137.6, 134.5, 130.2, 129.0, 128.6, 128.5, 128.2, 127.1, 78.5, 76.8, 56.6, 53.5, 29.5, 18.9 ppm; **IR** (thin film) 3061, 3029, 2940, 2865, 1707, 1594, 1496, 1453, 1342, 1208, 1032, 977, 918 cm^{-1}; **MS** (ESI) *m/z* 342.1477 (342.1470 calcd for $C_{21}H_{21}NNaO_2^+$ $[MNa]^+$).



4-(2-(Benzyl(benzyloxy)amino)-5-oxocyclopent-3-en-1-yl)benzonitrile (218): According to the general procedure, 4-(furan-2-yl(hydroxy)methyl)benzonitrile (34.4 mg, 0.172 mmol) and *N*,*O*-dibenzylhydroxylamine (36.8 mg, 0.172 mmol) were treated with $Dy(OTf)_3$ (5.2 mg, 0.0086 mmol) in $MeNO_2$ (1.8 mL). The resulting reaction mixture was heated to 80 ºC for 17 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **218** (57.0 mg, 84%) as an orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 – 7.56 (m, 3H), 7.32 – 7.22 (m, 6H), 7.16 (d, J = 8.1 Hz, 2H), 7.15 – 7.10 (m, 2H), 7.07 (s, 2H), 6.32 (dd, J = 5.8, 2.0 Hz, 1H), 4.45 (d, J = 10.9 Hz, 1H), 4.43 (d, J = 10.9 Hz, 1H), 4.22 (ddd, J = 2.3 Hz, 1H), 4.00 (d, J = 12.6 Hz, 1H), 3.95 (s, 1H), 3.78 (d, J = 12.5 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 205.3, 162.3, 144.3, 136.5, 136.2, 134.7, 132.7, 129.6, 129.4, 129.4, 128.5, 128.5, 128.4, 128.0, 118.8, 111.1, 76.8, 73.1, 61.1, 52.6 ppm; **IR** (thin film) 3063, 3031, 2919, 2866, 2227, 1708, 1607, 1454, 1276, 1163, 1028, 972 cm^{-1}; **MS** (ESI) *m/z* 417.1573 (417.1579 calcd for $C_{26}H_{22}N_2NaO_2^+$ $[MNa]^+$).

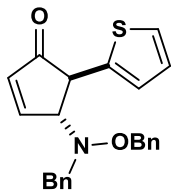


4-(Benzyl(benzyloxy)amino)-5-(4-methoxyphenyl)cyclopent-2-en-1-one (219): According to the general procedure, furan-2-yl(4-methoxyphenyl)methanol (23.1 mg, 0.113 mmol) and *N*,*O*-dibenzylhydroxylamine (24.1 mg, 0.113 mmol) were treated with $Dy(OTf)_3$ (3.4 mg, 0.0057 mmol) in $MeNO_2$ (1.1 mL). The resulting reaction mixture was heated to 80 ºC for 30 min. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **219** (36.7 mg, 81%) as a yellow waxy solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.31 – 7.27 (m, 3H), 7.28 – 7.23 (m, 3H), 7.15 – 7.09 (m, 4H), 7.02 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.32 (dd, *J* = 5.8, 1.9 Hz, 1H), 4.41 (s, 2H), 4.21 (dd, *J* = , 4.2, 2.1 Hz, 1H), 4.01 (d, *J* = 12.6 Hz, 1H), 3.88 (s, 1H), 3.81 (d, *J* = 12.6 Hz, 1H), 3.80 (s, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 207.4, 162.2, 158.8, 136.7, 136.7, 134.9, 130.9, 130.0, 129.5, 129.3, 128.4, 128.4, 128.3, 127.7, 114.6, 77.0, 73.9, 61.4, 55.5, 52.0 ppm; **IR** (thin film) 3030, 2921, 2854, 1883, 1708, 1611, 1511 cm^{-1}; **MS** (ESI) *m/z* 422.1717 (422.1732 calcd for $C_{26}H_{25}NNaO_3^+$ $[MNa]^+$).



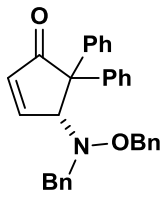
4-(Benzyl(benzyloxy)amino)-5-(2,4,6-triisopropylphenyl) cyclopent-2-en-1-one (220): According to the general procedure, furan-2-yl(2,4,6-triisopropylphenyl)methanol (32.0 mg, 0.105 mmol) and *N*,*O*-dibenzylhydroxylamine (22.5 mg, 0.105 mmol) were treated with $Dy(OTf)_3$ (3.2 mg, 0.0053 mmol) in $MeNO_2$ (1.0 mL). The resulting reaction mixture was heated to 80 ºC

for 40 min. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **220** (41.7 mg, 80%) as a white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 4H), 7.28 (d, *J* = 7.3 Hz, 2H), 7.17 – 7.13 (m, 1H), 7.11 (t, *J* = 7.4 Hz, 2H), 7.07 (d, *J* = 1.9 Hz, 1H), 6.90 (d, *J* = 1.9 Hz, 1H), 6.67 (s, 2H), 6.31 (d, *J* = 4.7 Hz, 1H), 4.66 (d, *J* = 11.2 Hz, 1H), 4.63 – 4.53 (m, 2H), 4.03 (s, 1H), 3.99 (d, *J* = 12.2 Hz, 1H), 3.65 (d, *J* = 12.2 Hz, 1H), 3.57 (p, *J* = 6.8 Hz, 1H), 2.91 (hept, *J* = 6.9 Hz, 1H), 1.83 (hept, *J* = 6.7 Hz, 1H), 1.44 (d, *J* = 6.6 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 6H),z 1.25 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.65 (d, *J* = 5.6 Hz, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 207.4, 160.9, 147.9, 147.7, 137.3, 136.3, 134.4, 130.7, 129.7, 129.2, 128.4, 128.3, 128.2, 127.5, 122.5, 121.4, 76.2, 72.6, 60.1, 48.3, 34.4, 30.7, 30.3, 29.9, 26.5, 24.4, 24.3, 24.2, 24.1, 22.2 ppm; **IR** (thin film) 3063, 3032, 2960, 2926, 2868, 1710, 1607 cm^{-1}; **MS** (ESI) *m/z* 518.3011 (518.3035 calcd for $C_{34}H_{41}NNaO_2^+$ $[MNa]^+$).



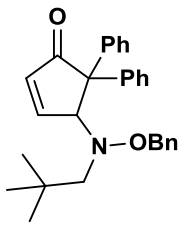
4-(Benzyl(benzyloxy)amino)-5-(thiophen-2-yl)cyclopent-2-en-1-one (221): According to the general procedure, furan-2-yl(thiophen-2-yl)methanol (31.1 mg, 0.172 mmol) and *N*,*O*-dibenzylhydroxylamine (36.8 mg, 0.172 mmol) were treated with $Dy(OTf)_3$ (5.2 mg, 0.0086 mmol) in $MeNO_2$ (1.8 mL). The resulting reaction mixture was heated to 80 ºC for 30 min. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then

concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **221** (59.2 mg, 92%) as a brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.32 – 7.27 (m, 6H), 7.25 – 7.19 (m, 3H), 7.14 – 7.10 (m, 2H), 7.00 – 6.96 (m, 1H), 6.90 (d, *J* = 3.3 Hz, 1H), 6.31 (dd, *J* = 6.0, 1.8 Hz, 1H), 4.43 (d, *J* = 10.6 Hz, 1H), 4.40 (d, *J* = 10.6 Hz, 1H), 4.34 (ddd, *J* = 2.4, 2.4, 2.4 Hz, 1H), 4.20 (s, 1H), 4.06 (d, *J* = 12.7 Hz, 1H), 3.95 (d, *J* = 12.7 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 204.7, 161.4, 140.1, 136.7, 136.5, 134.1, 129.9, 129.2, 128.6, 128.4, 128.3, 127.8, 127.2, 125.9, 124.7, 77.0, 74.1, 61.4, 47.6 ppm; **IR** (thin film) 3064, 3030, 2919, 2867, 1954, 1712, 1454, 1343, 1167, 1028, 972 cm^{-1}; **MS** (ESI) *m/z* 398.1188 (398.1191 calcd for $C_{23}H_{21}NNaO_2S^+$ $[MNa]^+$).

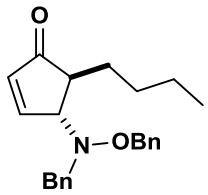


4-(Benzyl(benzyloxy)amino)-5,5-diphenylcyclopent-2-en-1-one (222): According to the general procedure, furan-2-yldiphenylmethanol (43.2 mg, 0.173 mmol) and *N*,*O*-dibenzylhydroxylamine (36.8 mg, 0.173 mmol) were treated with $Dy(OTf)_3$ (5.3 mg, 0.0087 mmol) in $MeNO_2$ (1.7 mL). The resulting reaction mixture was heated to 80 ºC for 4 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **222** (58.4 mg, 76%) as a yellow oil. **^{1}H NMR** (500 MHz, Toluene-d_8, 90 °C) δ 7.58 (dd, *J* = 6.1, 2.8 Hz, 1H), 7.43 – 7.35 (m, 2H), 7.30 – 7.19 (m, 2H), 7.13 – 7.09 (m, 2H), 7.08 – 6.89 (m, 11H), 6.79 (d, *J* = 6.7 Hz, 2H), 6.32 (s, 1H), 6.02 (dd, *J* = 6.0, 1.4 Hz, 1H), 4.96 (s, 1H), 3.95 (d, *J* = 11.0 Hz, 1H), 3.76 (d, *J* = 10.9 Hz, 1H), 3.49 (dd, *J* = 20.3, 12.9 Hz, 2H) ppm; **^{13}C NMR** (125 MHz, Toluene-d_8, 90 °C) δ 205.0, 143.5, 142.1, 138.3, 135.3, 132.0, 131.8, 130.5,

130.4, 130.4, 128.7, 128.6, 128.5, 128.1, 128.0, 127.9, 127.3, 127.0, 75.8, 75.5, 63.6, 60.7 ppm; **IR** (thin film) 3087, 3060, 3030, 2922, 2858, 1952, 1883, 1808, 1709 cm^{-1}; **MS** (ESI) *m/z* 468.1920 (468.1940 calcd for $C_{31}H_{27}NNaO_2^+$ $[MNa]^+$).

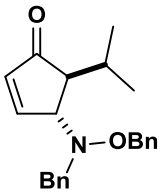


4-((Benzyloxy)(neopentyl)amino)-5,5-diphenylcyclopent-2-en-1-one (223): According to the general procedure, furan-2-yldiphenylmethanol (100.0 mg, 0.40 mmol) and *O*-benzyl-*N*-neopentylhydroxylamine (77.2 mg, 0.40 mmol) were treated with $Dy(OTf)_3$ (12.2 mg, 0.020 mmol) in $MeNO_2$ (4.0 mL). The resulting reaction mixture was heated to 80 ºC for 18 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **223** (142.0 mg, 83%) as a brown/orange solid. **^{1}H NMR** (500 MHz, toluene-d_8, 80 °C) δ 7.58 (dd, *J* = 6.1, 2.7 Hz, 1H), 7.54 – 7.50 (m, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.03 (m, 11H) 6.02 (dd, *J* = 6.0, 1.4 Hz, 1H), 4.92 (s, 1H), 4.28 (d, *J* = 11.1 Hz, 1H), 3.86 (s, 1H), 2.55 (d, *J* = 13.9 Hz, 1H), 2.25 (d, *J* = 13.8 Hz, 1H), 0.71 (s, 9H) ppm; **^{13}C NMR** (125 MHz, toluene-d_8, 80 °C) δ 204.5, 158.1, 143.9, 141.3, 138.0, 135.0, 131.8, 131.6, 128.5, 128.4, 128.2, 127.6, 126.9, 126.7, 77.2, 73.2, 67.7, 62.9, 31.7, 28.7, 24.2 ppm; **IR** (thin film) 3059, 2953, 2868, 1707, 1494, 1444, 1265, 1037, 1029, 949 cm^{-1}; **MS** (ESI) *m/z* 448.2231 (448.2252 calcd for $C_{29}H_{31}NNaO_2^+$ $[MNa]^+$).



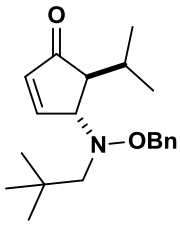
4-(Benzyl(benzyloxy)amino)-5-butylcyclopent-2-en-1-one (224): According to the general procedure, 1-(furan-2-yl)pentan-1-ol (26.5 mg,

0.172 mmol) and *N*,*O*-dibenzylhydroxylamine (36.7 mg, 0.172 mmol) were treated with $Dy(OTf)_3$ (10.5 mg, 0.0172 mmol) in $MeNO_2$ (1.8 mL). The resulting reaction mixture was heated to 80 ºC for 48 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **224** (31.8 mg, 53%) as a dark yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 5.9, 2.0 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.35 – 7.31 (m, 1H), 7.29 – 7.24 (m, 3H), 7.11 – 7.05 (m, 2H), 6.26 (dd, *J* = 5.8, 1.4 Hz, 1H), 4.34 (s, 2H), 3.98 (d, *J* = 12.9 Hz, 1H), 3.95 (d, *J* = 13.1 Hz, 1H), 3.91 (s, 1H), 2.53 (s, 1H), 1.76 – 1.65 (m, 1H), 1.63 – 1.51 (m, 1H), 1.35 – 1.23 (m, 4H), 0.88 (dd, *J* = 6.9 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 209.9, 160.8, 137.4, 136.7, 135.7, 129.8, 129.1, 128.5, 128.4, 128.2, 127.8, 76.9, 71.7, 60.7, 47.2, 30.0, 28.9, 23.0, 14.0 ppm; **IR** (thin film) 3063, 3031, 2955, 2928, 2858, 1707, 1454, 1359, 1176, 1028, 976 cm^{-1}; **MS** (ESI) *m/z* 372.1941 (372.1939 calcd for $C_{23}H_{27}NNaO_2^+$ $[MNa]^+$).



(4-(Benzyl(benzyloxy)amino)-5-isopropylcyclopent-2-en-1-one (225): According to the general procedure, 1-(furan-2-yl)-2-methylpropan-1-ol (12.1 mg, 0.086 mmol) and *N*,*O*-dibenzylhydroxylamine (18.4 mg, 0.086 mmol) were treated with $Dy(OTf)_3$ (5.2 mg, 0.0086 mmol) in $MeNO_2$ (0.9 mL). The resulting reaction mixture was heated to 80 ºC for 24 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone

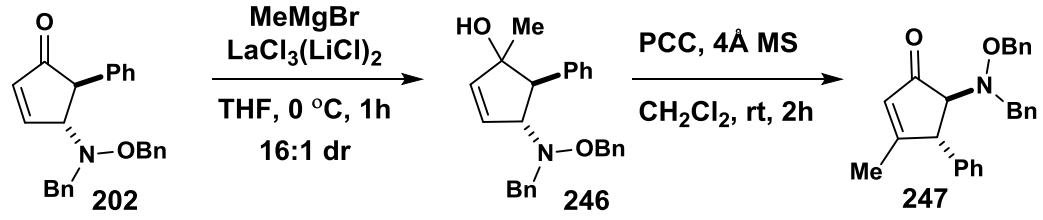
225 (14.4 mg, 50%) as a light orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 5.7, 2.1 Hz, 1H), 7.36 (m, 5H), 7.28 – 7.22 (m, 3H), 7.09 – 7.01 (m, 2H), 6.26 (dd, *J* = 5.8, 1.3 Hz, 1H), 4.33 (s, 2H), 4.00 – 3.87 (m, 3H), 2.41 (s, 1H), 2.19 (dqq, *J* = 13.9, 6.9, 4.5 Hz, 1H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 209.7, 160.8, 137.5, 136.7, 136.6, 129.8, 129.1, 128.5, 128.4, 128.2, 127.8, 77.0, 68.9, 60.5, 52.9, 29.0, 20.2, 18.8 ppm; **IR** (thin film) 3063, 3031, 2957, 2928, 2872, 1703, 1454, 1367, 1181, 1028, 963 cm^{-1}; **MS** (ESI) *m/z* 358.1787 (358.1783 calcd for $C_{22}H_{25}NNaO_2^+$ $[MNa]^+$).



4-((Benzyloxy)(neopentyl)amino)-5-isopropylcyclopent-2-en-1-one (226): According to the general procedure, 1-(furan-2-yl)-2-methylpropan-1-ol (20.0 mg, 0.140 mmol) and *O*-benzyl-*N*-neopentylhydroxylamine (27.6 mg, 0.140 mmol) were treated with $Dy(OTf)_3$ (8.7 mg, 0.014 mmol) in $MeNO_2$ (1.4 mL). The resulting reaction mixture was heated to 80 ºC for 96 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **226** (22.6 mg, 51%) as an orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 5.8, 2.1 Hz, 1H), 7.36 – 7.27 (m, 5H), 6.27 (dd, *J* = 5.9, 1.6 Hz, 1H), 4.79 (d, *J* = 10.6 Hz, 1H), 4.73 (d, *J* = 10.6 Hz, 1H), 4.15 (s, 1H), 2.55 (d, *J* = 14.3 Hz, 1H), 2.34 (d, *J* = 14.0 Hz, 1H), 2.27 (dqq, *J* = 13.8, 6.9, 4.1 Hz, 1H), 2.15 (s, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.97 (s, 9H), 0.87 (d, *J* = 6.8 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 209.5, 161.9, 137.0, 136.8, 128.6, 128.5, 128.1, 74.6, 69.1, 66.0, 53.4, 31.6, 28.8, 28.6, 20.5, 18.6 ppm; **IR**

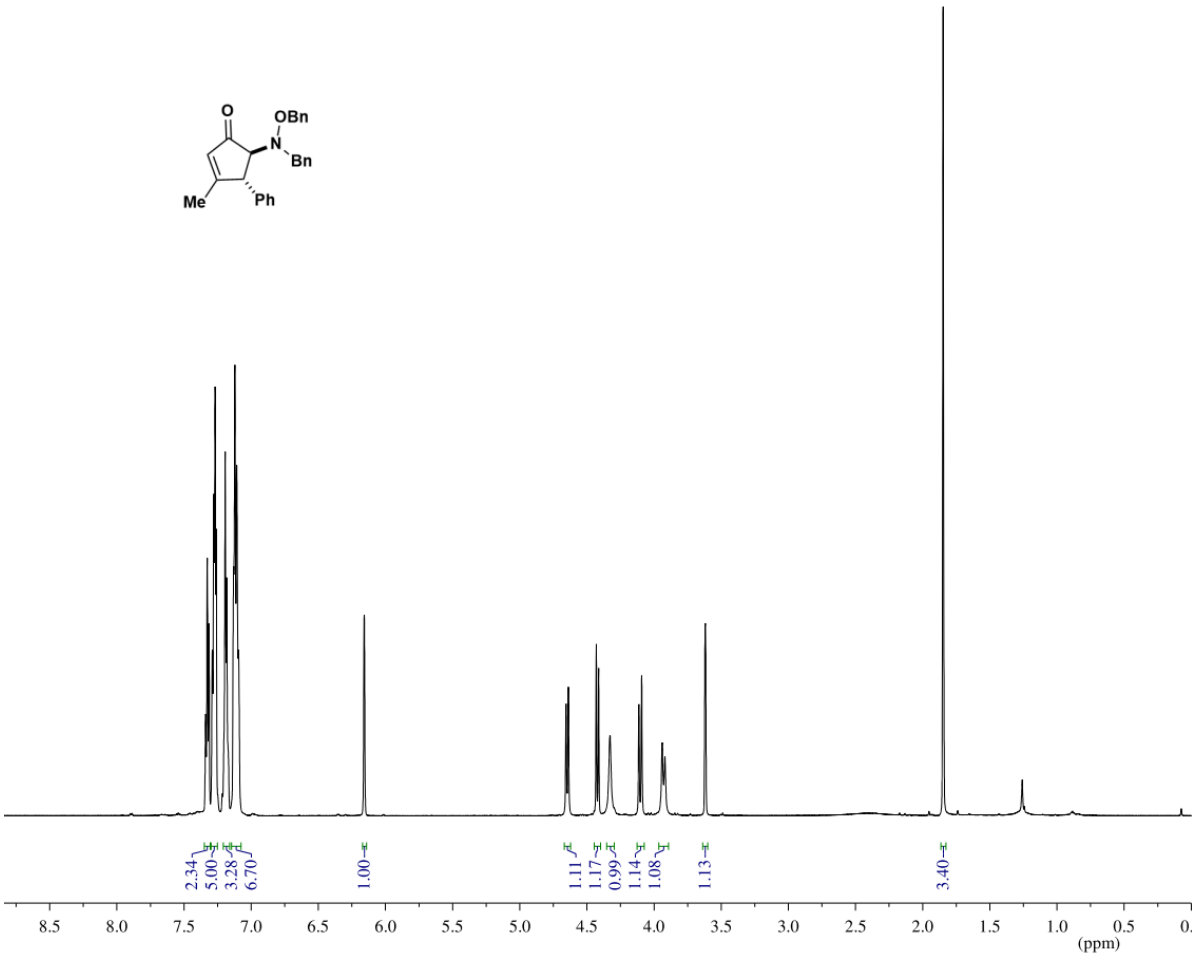
(thin film) 3065, 3032, 2955, 2870, 1705, 1463, 1362, 1027, 976 cm^{-1}; **MS** (ESI) *m/z* 338.2093 (338.2096 calcd for $C_{20}H_{29}NNaO_2^+$ $[MNa]^+$).

Selected Functionalization of the Cyclopentenone Scaffold:



5-(Benzyl(benzyloxy)amino)-3-methyl-4-phenylcyclopent-2-en-1-one (247): Adapted from literature procedure.[4] In a flame dried round bottom flask with magnetic stirrer under N_2 atmosphere, 4-(benzyl(benzyloxy)amino)-5-phenylcyclopent-2-en-1-one **202** was dissolved in 0.5 mL dry THF followed by the addition of 0.6 M $LaCl_3(LiCl)_2$ in THF (0.0939 mmol, 157 µL) and stirring at room temperature for 1 hour. The reaction mixture was cooled to 0 ºC and 3.0 M methylmagnesium bromide in diethyl ether (0.188 mmol, 63 µL) was added. Stirring at 0 ºC continued until complete as determined by thin layer chromatography. Upon completion, the reaction was quenched with saturated aqueous NH_4Cl (5 mL) then extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The crude reaction mixture contained allylic alcohol **246** in 16:1 dr as determined by ^1H NMR spectroscopy**.** The crude reaction mixture was passed through a silica gel plug using 3:1 hexanes : ethyl acetate and used as is for the subsequent reaction. 80% Yield of crude material.

Adapted from literature procedure.[5] In a 10 mL round bottom flask containing a magnetic stir bar under N_2 atmosphere, 4Å mol sieves (500 mg) and pyridinium chlorochromate (PCC) (27.2 mg, 0.126 mmol) were added to anhydrous CH_2Cl_2 (1 mL) followed by addition of 4-(benzyl(benzyloxy)amino)-1-methyl-5-phenylcyclopent-2-en-1-ol **246** (24.3 mg, 0.063 mmol). The reaction was stirred until complete (2 h) as determined by thin layer chromatography. Upon completion, 5 mL Et_2O was added, and the residual solids were decanted off (3 x). The decanted liquid was transferred to a separatory funnel containing 5 mL 2M NaOH and extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography (1% EtOAc in toluene) to afford cyclopentenone **247** (18.4 mg, 70%) (56% yield over 2 steps) as a colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 2H), 7.31 – 7.24 (m, 3H), 7.21 – 7.16 (m, 3H), 7.14 – 7.08 (m, 7H), 6.16 (s, 1H), 4.65 (d, J = 10.3 Hz, 1H), 4.42 (d, J = 10.3 Hz, 1H), 4.33 (s, 1H), 4.10 (d, J = 12.4 Hz, 1H), 3.93 (d, J = 12.4 Hz, 1H), 3.62 (d, J = 2.7 Hz, 1H), 1.85 (s, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 205.3, 179.1, 141.0, 137.0, 136.5, 130.7, 130.0, 129.3, 129.3, 128.4, 128.2, 128.1, 128.1, 127.6, 127.4, 76.5, 76.5, 60.8, 51.4, 18.2 ppm; **IR** (thin film) 3405, 3063, 3030, 2924, 2857, 1953, 1880, 1810, 1711, 1623 cm^{-1}; **MS** (ESI) *m/z* 406.1795 (406.1783 calcd for $C_{26}H_{25}NNaO_2^+$ $[MNa]^+$).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Bn
Me
Ph
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1.08
1.13
3.40
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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2.0
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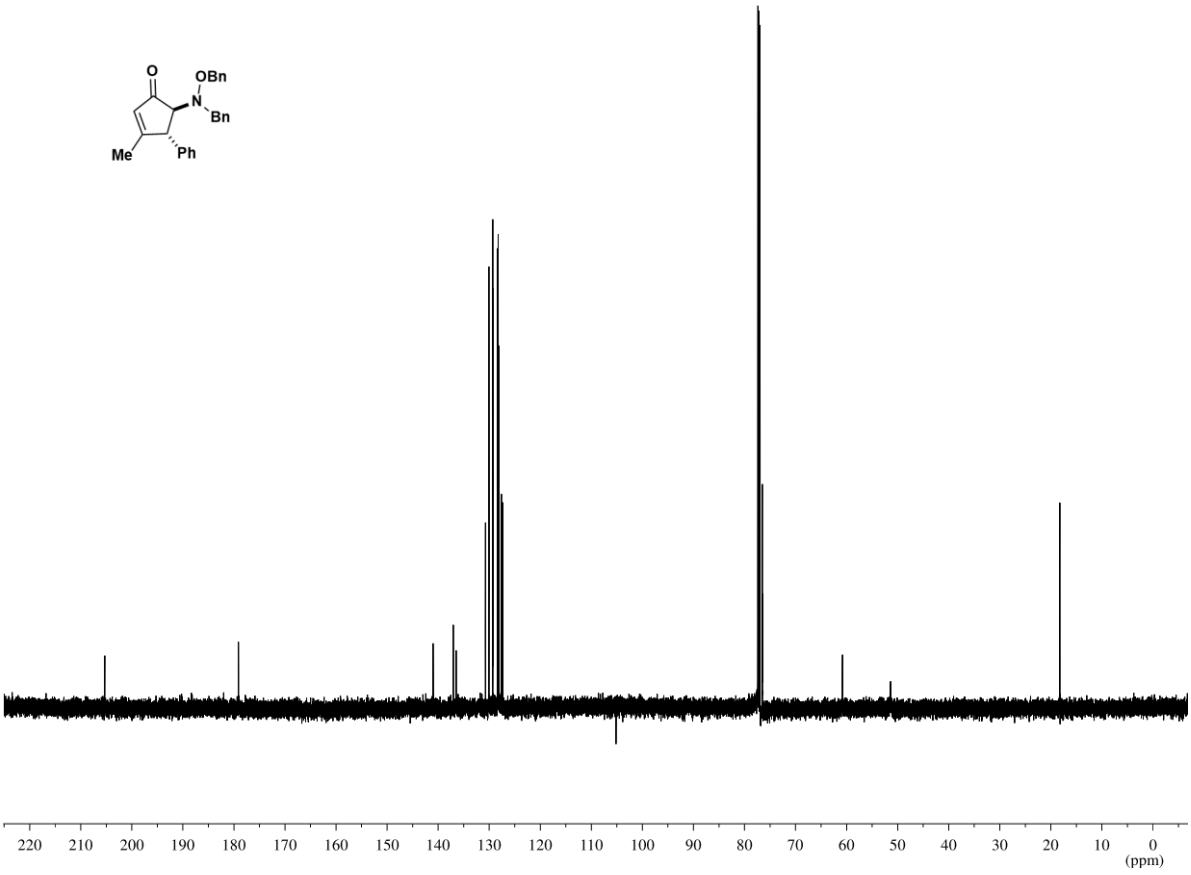
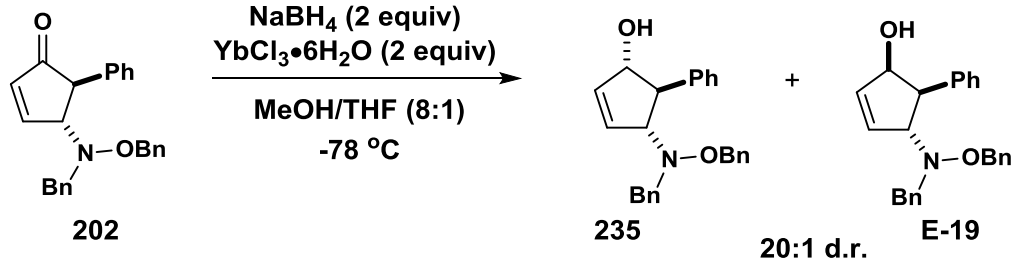
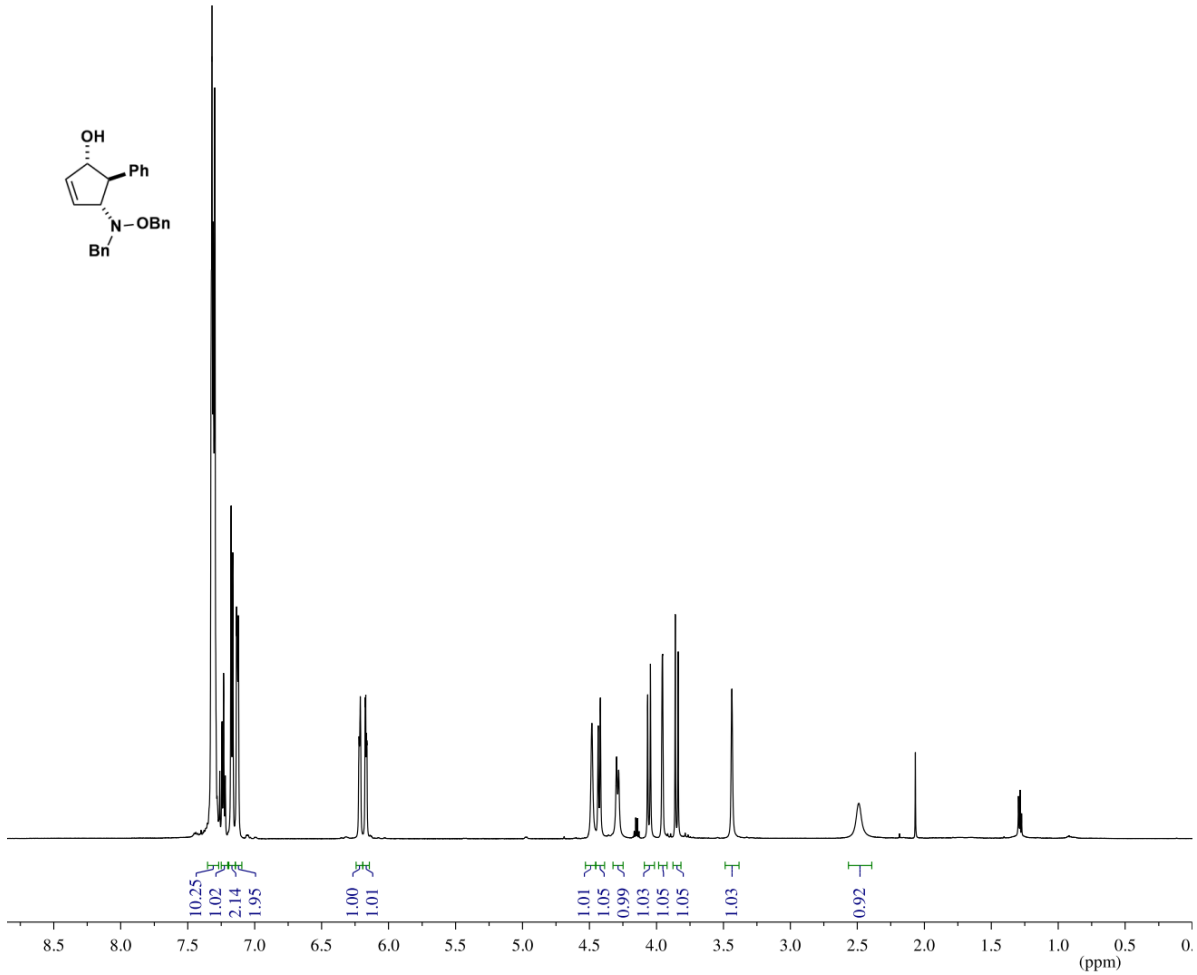
(ppm)





4-(Benzyl(benzyloxy)amino)-5-phenylcyclopent-2-en-1-ol (235 and E-19): 4-(Benzyl (benzyloxy)amino)-5-phenylcyclopent-2-en-1-one (**202**) (231 mg, 0.63 mmol) and $YbCl_3 \cdot 6H_2O$ (387.5 mg, 1.25 mmol) was dissolved in 3 mL THF, then 23 mL MeOH was added and the solution stirred while cooling to -78 ºC. $NaBH_4$ (47.3 mg, 1.25 mmol) was added in one portion and the reaction was stirred at -78 ºC until complete (1 h) as determined by thin layer chromatography (2:1 hexanes:ethyl acetate, stained with

anisaldehyde). The reaction was then quenched with saturated aqueous NH_4Cl (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue (20:1 dr as determined by ^1H NMR of crude mixture) was purified by flash column chromatography (15:1 → 9:1 → 6:1 hexanes:ethyl acetate) to afford cyclopentenone **235** and **E-19** (174 mg, 78%, 20:1 dr) as a colorless oil. *Major Diastereomer:* **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 10H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 2H), 7.15 – 7.09 (m, 2H), 6.24 – 6.19 (m, 1H), 6.19 – 6.14 (m, 1H), 4.48 (s, 1H), 4.43 (d, *J* = 9.8 Hz, 1H), 4.29 (d, *J* = 9.8 Hz, 1H), 4.06 (d, *J* = 12.7 Hz, 1H), 3.96 (q, *J* = 2.1 Hz, 1H), 3.85 (d, *J* = 12.7 Hz, 1H), 3.44 (s, 1H), 2.49 (s, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 144.5, 137.4, 137.0, 136.1, 134.4, 130.1, 129.5, 128.9, 128.5, 128.4, 128.3, 127.6, 127.0, 126.4, 83.4, 78.2, 77.3, 61.4, 53.1 ppm; **IR** (thin film) 3414, 3062, 3030, 2878, 1602, 1495, 1454 cm^{-1}; **MS** (ESI) *m/z* 394.1785 (394.1783 calcd for $C_{25}H_{25}NNaO_2^+$ $[MNa]^+$).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1.03
0.92
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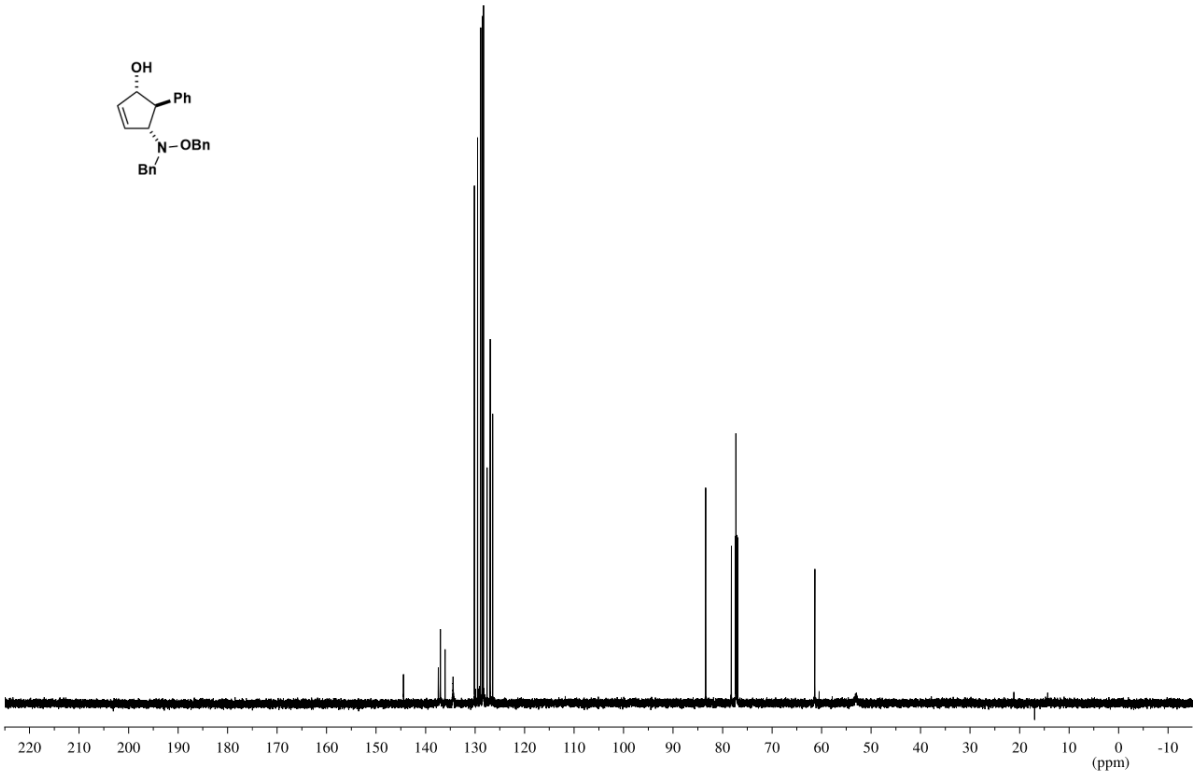
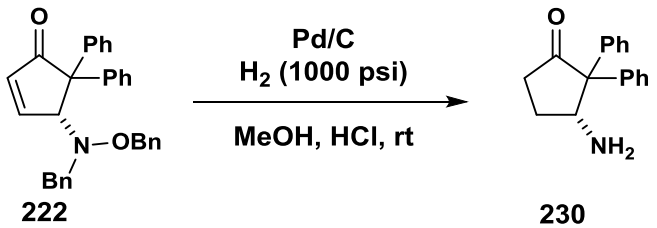
(ppm)

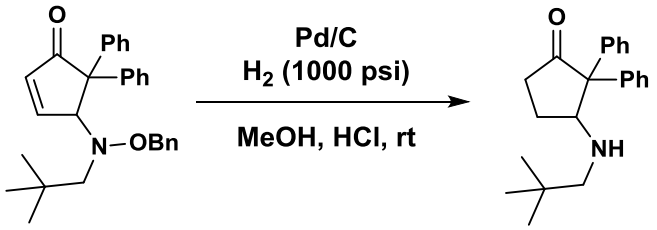


Minor Diastereomer: **^{1}H NMR** (600 MHz, Chloroform-d) δ 7.37 – 7.31 (m, 2H), 7.32 – 7.21 (m, 12H), 7.03 (s, 2H), 6.31 (d, J = 6.4 Hz, 1H), 6.12 (d, J = 5.8 Hz, 1H), 4.96 (d, J = 6.8 Hz, 1H), 4.49 – 4.40 (m, 1H), 4.40 – 4.24 (m, 2H), 3.89 (d, J = 12.9 Hz, 1H), 3.82 – 3.71 (m, 2H). ppm; **^{13}C** NMR (150 MHz, Chloroform-d) δ 139.0, 137.0, 135.8, 135.4, 130.0, 129.4, 129.1, 128.8, 128.3, 128.2, 128.0, 127.4, 127.1, 77.7, 77.0, 76.5, 61.6 ppm; **IR** (thin film) 3413, 3062, 3003, 2919, 1602, 1495, 1454, 1361 cm^{-1}; **MS** (ESI) *m/z* 394.1769 (394.1783 calcd for $C_{25}H_{25}NNaO_2^+$ $[MNa]^+$).



222 **230**

3-Amino-2,2-diphenylcyclopentan-1-one (230): In a 20 mL vial, 4-(benzyl (benzyloxy)amino)-5,5-diphenylcyclopent-2-en-1-one **222** (13.4 mg, 0.0301 mmol) was dissolved in MeOH (1.5 mL), followed by addition of Palladium on carbon (10 wt%) (1.6 mg, 0.0015 mmol). One drop of 12M HCl from an 18 gauge needle was added prior to placing the vial into the pressure vessel. The reaction mixture was placed under H_2 gas at 70 bar for 48h. The reaction mixture was filtered over Celite. The Celite pad was rinsed with ethyl acetate (3 x 5mL). The organic layer was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 x 5 ml). The combined organic layers were dried with Na_2SO_4, filtered and then concentrated *in vacuo* to afford **230** (7.6 mg, quantitative yield) as a clear oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41 (d, J = 7.6 Hz, 2H), 7.36 – 7.31 (m, 2H), 7.29 – 7.24 (m, 3H), 7.24 – 7.19 (m, 1H), 7.11 (d, J = 8.0 Hz, 2H), 4.37 (t, J = 4.5 Hz, 1H), 2.75 – 2.60 (m, 1H), 2.46 – 2.29 (m, 2H), 1.83 – 1.74 (m, 1H), 1.69 (bs, 2H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 216.3, 140.5, 139.8, 129.7, 128.8, 128.6, 128.2, 127.3, 127.0, 66.7, 56.4, 36.0, 27.5 ppm; **IR** (thin film) 3372, 3302, 3086, 3057, 3032, 2925, 2855, 1763, 1672 cm^{-1}; **MS** (EI) *m/z* 251.1305 (251.1310 calcd for $C_{17}H_{17}NO^+$ $[M]^+$).

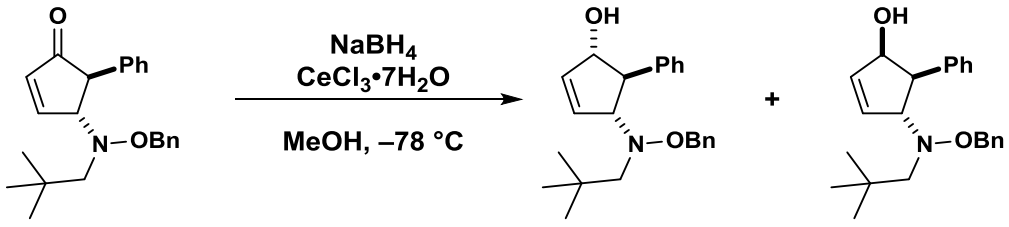


223 231

3-(Neopentylamino)-2,2-diphenylcyclopentan-1-one (231): In a 20 mL vial, 4-((benzyloxy)(neopentyl)amino)-5,5-diphenylcyclopent-2-en-1-one **223** (41.5 mg, 0.098 mmol) was dissolved in MeOH (1.5 mL), followed by addition of Palladium on carbon (10

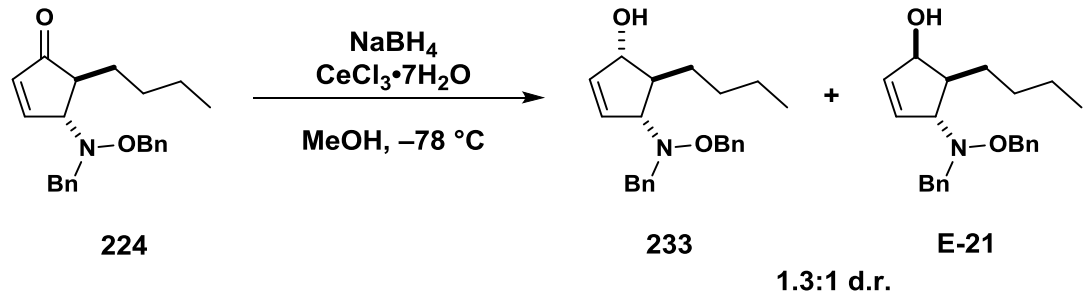
wt%) (5.2 mg, 0.0049 mmol). One drop of 12M HCl from an 18 gauge needle was added prior to placing the vial into the pressure vessel. The reaction mixture was placed under H_2 gas at 70 bar for 48h. The reaction mixture was filtered over Celite. The Celite pad was rinsed with ethyl acetate (3 x 5mL). The organic layer was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and then concentrated *in vacuo* to afford **231** (31.3 mg, quantitative yield) as a brown oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45 (d, J = 7.3 Hz, 2H), 7.31 (t, J = 7.8 Hz, 2H), 7.28 – 7.21 (m, 3H), 7.20 (d, J = 7.5 Hz, 3H), 3.94 (t, J = 4.3 Hz, 1H), 2.63 (ddd, J = 18.9, 9.0, 7.2 Hz, 1H), 2.46 (d, J = 11.1 Hz, 1H), 2.28 (ddd, J = 18.8, 9.1, 4.5 Hz, 1H), 2.22 (d, J = 11.0 Hz, 1H), 2.19 (dddd, J = 11.5, 9.1, 5.9, 3.5 Hz, 1H), 1.89 (dddd, J = 13.4, 9.1, 4.4, 4.4 Hz, 1H), 1.29 (s, 1H), 0.76 (s, 9H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 216.6, 140.4, 140.0, 66.3, 63.4, 59.8, 35.5, 31.7, 29.8, 27.7, 23.8 ppm; **IR** (thin film) 3347, 3087, 3058, 3031, 2951, 2864, 1737, 1599 cm^{-1}; **MS** (EI) *m/z* 321.2096 (321.2093 calcd for $C_{22}H_{27}NO^+$ $[M]^+$).

Synthesis of Allylic Alcohols:



4-((Benzyloxy)(neopentyl)amino)-5-phenylcyclopent-2-en-1-ol (232 and E-20): A solution of **212** (52.6 mg, 0.15 mmol) in MeOH (3.6 mL) was treated with $CeCl_3$•$7H_2O$ (61.7 mg, 0.17 mmol) and stirred at rt for 20 min. The solution was cooled to –78 °C and

subsequently treated with $NaBH_4$ (7.4 mg, 0.20 mmol) and stirred at this temperature until the reaction was complete as judged by TLC. The reaction was quenched with H_2O and allowed to come to rt before extracting with EtOAc (3x 6 mL). The combined organic phases were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. ^{1}H NMR analysis of the crude reaction mixture indicated a 2:1 mixture of diastereomers. The residue was purified by flash column chromatography to afford the separated allylic alcohols **232** and **E-20** (37.1 mg, 70% combined yield, 2:1 dr) as yellow oils. *Major diastereomer*: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 5H), 7.23 – 7.19 (m, 3H), 7.16 – 7.11 (m, 2H), 6.18 (dd, *J* = 5.7, 2.1 Hz, 1H), 6.15 (ddd, *J* = 5.7, 1.8, 1.8 Hz, 1H), 4.76 (d, *J* = 10.0 Hz, 1H), 4.58 (d, *J* = 9.9 Hz, 1H), 4.45 (s, 1H), 3.95 (s, 1H), 3.25 (dd, *J* = 2.6, 2.6 Hz, 1H), 2.82 (d, *J* = 14.1 Hz, 1H), 2.60 (d, *J* = 14.1 Hz, 1H), 2.33 (s, 1H), 0.95 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 144.9, 136.7, 136.2, 134.6, 129.1, 128.9, 128.6, 128.3, 127.0, 126.3, 83.3, 80.9, 75.6, 69.0, 53.9, 31.7, 28.7 ppm; **IR** (thin film) 3408, 3086, 3061, 3029, 2951, 2903, 2866, 1945, 1804, 1602, 1453, 1360, 1209, 1020, 1011, 909 cm^{-1}; **MS** (ESI) *m/z* 374.2069 (374.2096 calcd for $C_{23}H_{29}NNaO_2^+$ $[MNa]^+$). *Minor Diastereomer*: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.5 Hz, 2H), 7.30 – 7.24 (m, 6H), 7.14 (d, *J* = 6.0 Hz, 2H), 6.30 (d, *J* = 5.6 Hz, 1H), 6.13 – 6.04 (m, 1H), 4.92 (d, *J* = 6.5 Hz, 1H), 4.66 – 4.60 (m, 2H), 4.56 (s, 1H), 3.53 (dd, *J* = 6.2 Hz, 1H), 2.61 (d, *J* = 14.2 Hz, 1H), 2.48 (d, *J* = 14.2 Hz, 1H), 1.25 (s, 1H), 0.89 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 139.3, 137.2, 136.1, 135.5, 129.4, 128.8, 128.6, 128.4, 127.9, 127.0, 78.4, 77.4, 74.8, 67.6, 50.4, 31.6, 28.6 ppm; **IR** (thin film) 3412, 3086, 3061, 3030, 2951, 2904, 2865, 1947, 1807, 1602, 1453, 1361, 1208, 1027, 910 cm^{-1}; **MS** (ESI) *m/z* 374.2097 (374.2096 calcd for $C_{23}H_{29}NNaO_2^+$ $[MNa]^+$).

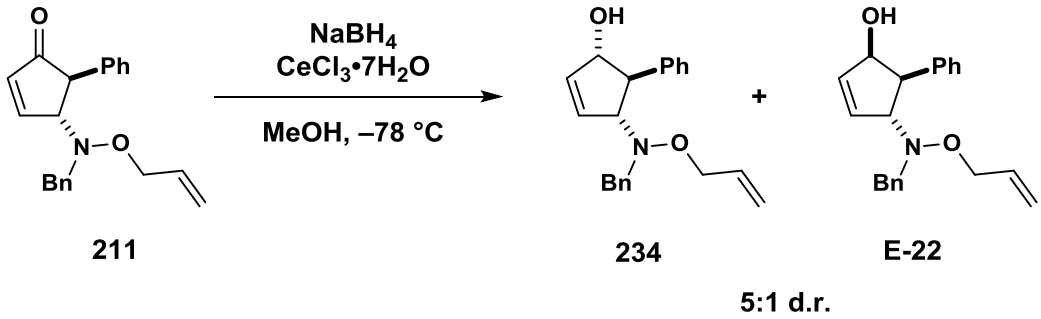


224 **233** **E-21**

1.3:1 d.r.

4-(Benzyl(benzyloxy)amino)-5-butylcyclopent-2-en-1-ol (233 and **E-21):** A solution of **224** (145.5 mg, 0.42 mmol) in MeOH (10 mL) was treated with $CeCl_3 \bullet 7H_2O$ (170.6 mg, 0.45 mmol) and stirred at rt for 20 min. The solution was cooled to –30 °C and subsequently treated with $NaBH_4$ (20.5 mg, 0.54 mmol) and stirred at this temperature until the reaction was complete by TLC. The reaction was quenched with H_2O and allowed to come to rt before extracting with EtOAc (3x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. ^{1}H NMR analysis of the crude reaction mixture indicated a 1.3:1 mixture of diastereomers. The residue was purified by flash column chromatography to afford the separated allylic alcohols **233** and **E-21** (132.6 mg, 90% combined yield) as a yellow oil (major) and light orange solid (minor). *Major diastereomer*: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.43 (d, J = 7.2 Hz, 2H), 7.36 (t, J = 7.4 Hz, 2H), 7.31 (t, J = 7.3 Hz, 1H), 7.25 (d, J = 5.9 Hz, 3H), 7.08 – 7.05 (m, 2H), 6.03 (d, J = 5.3 Hz, 1H), 5.99 – 5.95 (m, 1H), 4.35 (d, J = 9.7 Hz, 1H), 4.24 – 4.18 (m, 1H), 4.15 (d, J = 8.4 Hz, 1H), 3.96 (d, J = 12.8 Hz, 1H), 3.86 (d, J = 12.8 Hz, 1H), 3.51 (s, 1H), 2.28 (s, 1H), 2.15 (s, 1H), 1.42 – 1.27 (m, 6H), 0.90 (dd, J = 7.0, 7.0 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 137.9, 136.7, 136.1, 133.0, 130.0, 129.5, 128.5, 128.4, 128.3, 127.6, 80.9, 77.2, 76.1, 61.3, 46.9, 33.6, 30.1, 23.0, 14.2 ppm; **IR** (thin film) 3422, 3087, 3062, 3031, 2955, 2926, 2856, 1496, 1454, 1359, 1209, 1028, 1000 cm^{-1}; **MS** (ESI) *m/z* 374.2101 (374.2096 calcd for $C_{23}H_{29}NNaO_2$ $[MNa]^+$). *Minor Diastereomer*: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39

(d, J = 7.2 Hz, 2H), 7.33 (t, J = 7.3 Hz, 2H), 7.29 (d, J = 7.2 Hz, 1H), 7.28 – 7.21 (m, 3H), 7.11 – 7.02 (m, 2H), 6.24 (d, J = 5.2 Hz, 1H), 6.06 (ddd, J = 5.8, 2.1, 2.1 Hz, 1H), 4.78 (d, J = 5.6 Hz, 1H), 4.34 (s, 2H), 3.93 (d, J = 13.0 Hz, 1H), 3.85 (d, J = 13.0 Hz, 1H), 3.80 (s, 1H), 2.13 (dddd, J = 12.5, 6.1, 6.1, 6.1 Hz, 1H), 1.64 – 1.54 (m, 1H), 1.52 – 1.45 (m, 1H), 1.45 – 1.38 (m, 1H), 1.37 – 1.28 (m, 3H), 1.14 (s, 1H), 0.91 (dd, J = 7.1, 7.1 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.3, 137.2, 136.0, 134.7, 129.8, 129.1, 128.3, 127.9, 127.4, 76.7, 76.2, 76.1, 60.3, 44.6, 31.0, 27.5, 23.2, 14.3 ppm; **IR** (thin film) 3376, 3089, 3064, 3033, 2956, 2930, 2872, 2859, 1606, 1496, 1454, 1362, 1265, 1210, 1028, 906 cm^{-1}; **MS** (ESI) *m/z* 374.2087 (374.2096 calcd for $C_{23}H_{29}NNaO_2$ $[MNa]^+$).

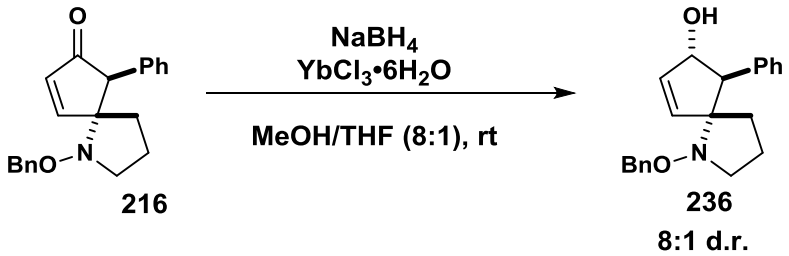


211 **234** **E-22**

5:1 d.r.

4-((Allyloxy)(benzyl)amino)-5-phenylcyclopent-2-en-1-ol (234 and E-22): A solution of **211** (300.0 mg, 0.94 mmol) in MeOH (22 mL) was treated with $CeCl_3$•$7H_2O$ (384.9 mg, 1.03 mmol) and stirred at rt for 20 min. The solution was cooled to –78 °C and subsequently treated with $NaBH_4$ (46.2 mg, 1.22 mmol) and stirred at this temperature until the reaction was complete by TLC. The reaction was quenched with H_2O, and allowed to come to rt before removal of the solvent and extracting with EtOAc (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. ^{1}H NMR analysis of the crude reaction mixture indicated a 5:1 mixture of diastereomers. The residue

was purified by flash column chromatography to afford the separated allylic alcohols **234** and **E-22** (286.8 mg, 95% combined yield, 5:1 dr) as yellow oils. *Major diastereomer*: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.27 – 7.24 (m, 5H), 7.25 – 7.18 (m, 1H), 7.18 – 7.13 (m, 2H), 6.19 (ddd, *J* = 5.7, 1.9, 1.9 Hz, 1H), 6.11 (dd, *J* = 5.7, 2.3 Hz, 1H), 5.70 (dddd, *J* = 16.8, 10.3, 6.3, 6.3 Hz, 1H), 5.17 – 5.08 (m, 1H), 5.13–5.11 (m, 1H), 4.48 (d, *J* = 6.1 Hz, 1H), 4.04 (d, *J* = 12.7 Hz, 1H), 3.96 – 3.90 (m, 1H), 3.90 – 3.83 (m, 2H), 3.81 (d, *J* = 12.8 Hz, 1H), 3.43 (s, 1H), 2.65 (s, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 144.4, 137.3, 137.1, 134.4, 133.0, 130.0, 128.9, 128.3, 127.5, 127.0, 126.5, 119.0, 83.3, 78.0, 76.0, 61.4, 53.3 ppm; **IR** (thin film) 3413, 3061, 3029, 2918, 2851, 1601, 1494, 1453, 1344, 1080, 1027, 995, 925 cm^{-1}; **MS** (ESI) *m/z* 344.1605 (344.1626 calcd for $C_{21}H_{23}NNaO_2$ $[MNa]^+$). *Minor diastereomer*: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.5 Hz, 2H), 7.29 – 7.18 (m, 8H), 6.27 (d, *J* = 4.3 Hz, 1H), 6.11 – 6.05 (m, 1H), 5.63 (dddd, *J* = 16.7, 10.4, 6.3, 6.3 Hz, 1H), 5.07 – 5.00 (m, 2H), 4.92 (d, *J* = 5.9 Hz, 1H), 4.40 – 4.36 (m, 1H), 3.90 – 3.82 (m, 3H), 3.76 – 3.68 (m, 2H), 1.25 (d, *J* = 12.8 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CHCl_3$) δ 139.0, 137.7, 135.9, 135.2, 133.8, 129.8, 129.4, 128.8, 128.2, 127.4, 127.1, 117.9, 77.6, 76.2, 75.9, 61.6, 50.8 ppm; **IR** (thin film) 3425, 3061, 3029, 2917, 2865, 1602, 1494, 1453, 1342, 1069, 1029, 994 $^{-1}$; **MS** (ESI) *m/z* 344.1636 (344.1626 calcd for $C_{21}H_{23}NNaO_2$ $[MNa]^+$).

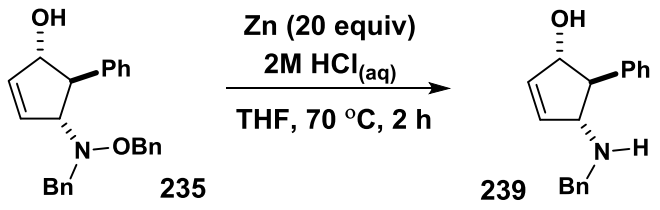


216 **236**

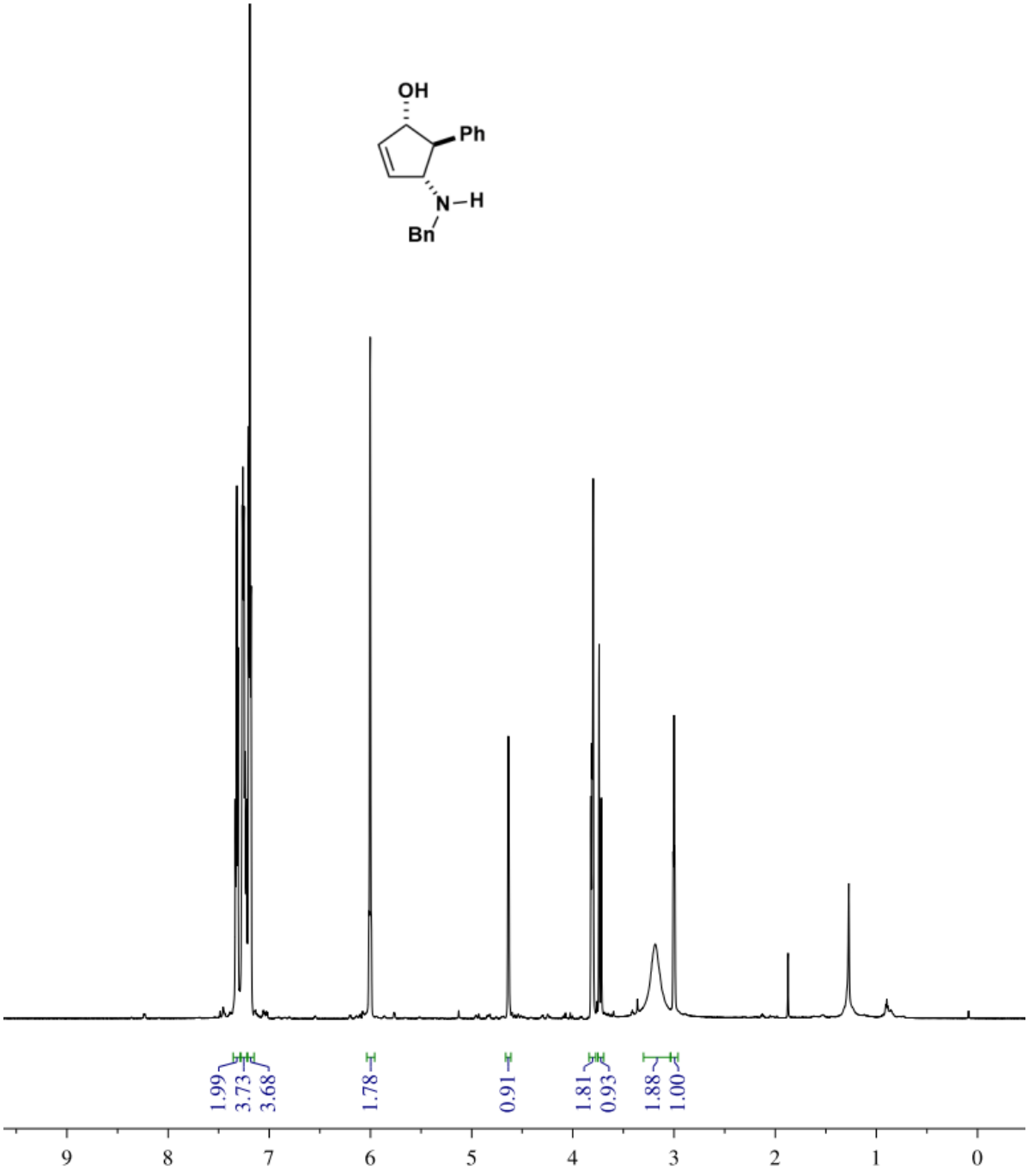
8:1 d.r.

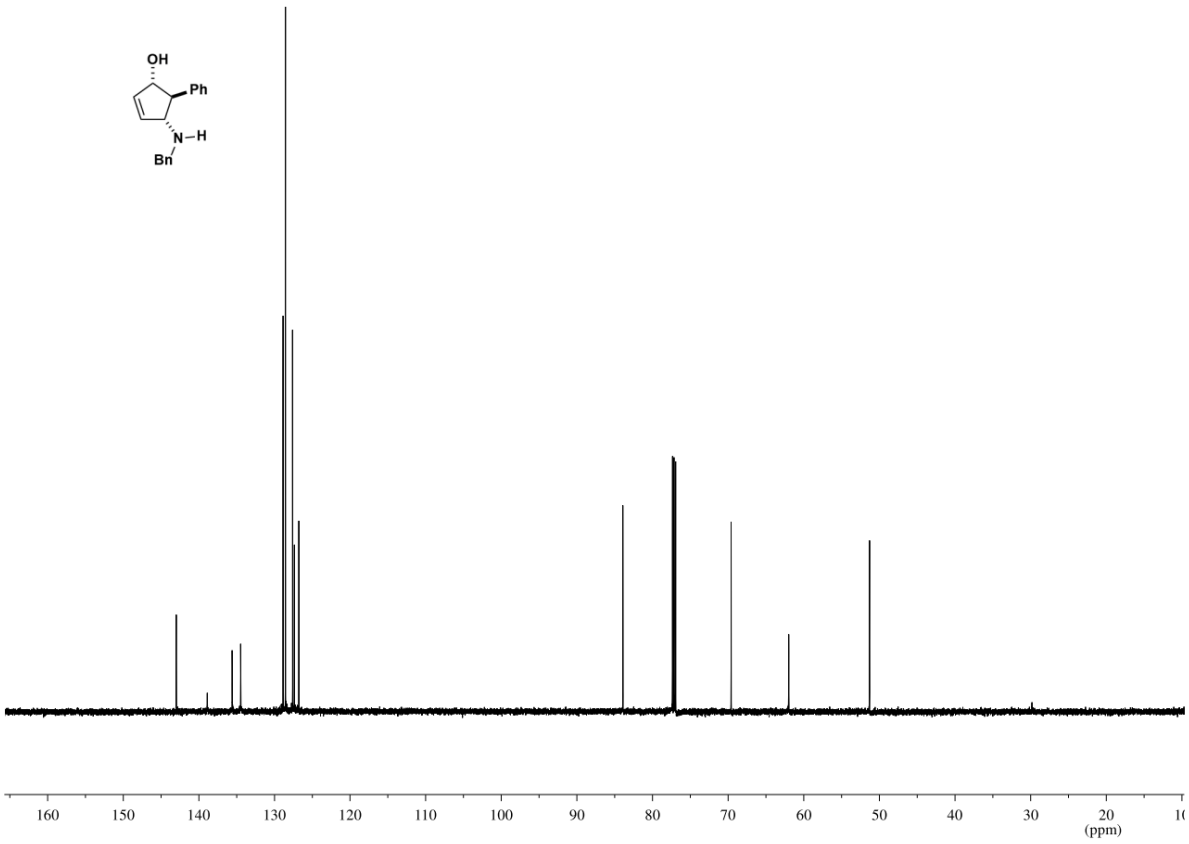
1-(Benzyloxy)-6-phenyl-1-azaspiro[4.4]non-8-en-7-ol (236): A solution of **216** (85.0 mg, 0.27 mmol) in MeOH (3.6 mL) and THF (0.4 mL) was treated with $YbCl_3 \bullet 6H_2O$ (206.4 mg, 0.53 mmol) and stirred at rt for 20 min. The solution was subsequently treated with $NaBH_4$ (20.1 mg, 0.53 mmol) and stirred at this temperature until the reaction was complete by TLC. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford allylic alcohol **236** (66.5 mg, 77%, isolated as an inseparable mixture of diastereomers with 8:1 dr) as a light yellow oil. *Major*: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 8H), 7.27 – 7.22 (m, 2H), 6.18 (dd, *J* = 5.7, 1.9 Hz, 1H), 6.02 (d, *J* = 5.3 Hz, 1H), 5.19 (dd, *J* = 6.3, 6.3 Hz, 1H), 4.80 – 4.67 (m, 2H), 3.68 (d, *J* = 7.0 Hz, 1H), 3.17 – 2.99 (m, 2H), 1.70 – 1.60 (m, 2H), 1.59 – 1.49 (m, 1H), 1.49 – 1.38 (m, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ138.2, 137.9, 137.6, 137.2, 130.6, 128.9, 128.5, 128.4, 127.9, 127.1, 83.0, 78.3, 76.6, 54.7, 53.3, 30.6, 19.3 ppm; **IR** (thin film) 3413, 3086, 3059, 3029, 2940, 2866, 1601, 1494, 1453, 1362, 1208, 1080, 1026, 974 cm^{-1}; **MS** (ESI) *m/z* 344.1640 (344.1626 calcd for $C_{21}H_{23}NNaO_2$ $[MNa]^+$).

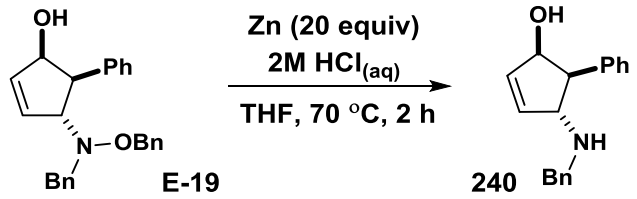
Reductive N–O bond cleavage:



4-(Benzylamino)-5-phenylcyclopent-2-en-1-ol (239): 4-(Benzyl(benzyloxy)amino)-5-phenylcyclopent-2-en-1-ol **235** (13.3 mg, 0.036 mmol) was dissolved in 0.5 mL THF, followed by addition of 6-9 micron Zn powder (46.8 mg, 0.716 mmol). Next, 2M HCl (1 mL) in H_2O was added and the solution was heated to 70 ºC. Reaction was stirred until complete (2 h) as determined by thin layer chromatography. The reaction was then quenched by the addition of 4M $NaOH_{(aq)}$ until pH 14 was reached and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to afford the free amine **239** (9.5 mg, quantitative yield) as a colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.5 Hz, 2H), 7.28 – 7.22 (m, 4H), 7.19 (t, *J* = 7.2 Hz, 4H), 6.00 (t, *J* = 7.0 Hz, 2H), 4.64 (d, *J* = 4.5 Hz, 1H), 3.84 – 3.77 (m, 2H), 3.73 (d, *J* = 13.1 Hz, 1H), 3.18 (s, 2H), 3.00 (t, *J* = 4.9 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 143.0, 138.9, 135.6, 134.5, 128.9, 128.6, 127.6, 127.4, 126.8, 83.9, 69.6, 62.0, 51.3 ppm; **IR** (thin film) 3294, 3061, 3028, 2922, 2854, 1951, 1877, 1810, 1734, 1602, 1495 cm^{-1}; **MS** (ESI) *m/z* 288.1371 (288.1371 calcd for $C_{18}H_{19}NNaO^+$ $[MNa]^+$).

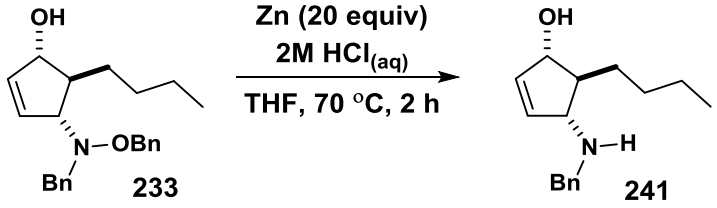

OH
Ph
N–H
Bn
1.99
3.73
3.68
1.78
0.91
1.81
0.93
1.88
1.00
9
8
7
6
5
4
3
2
1
0





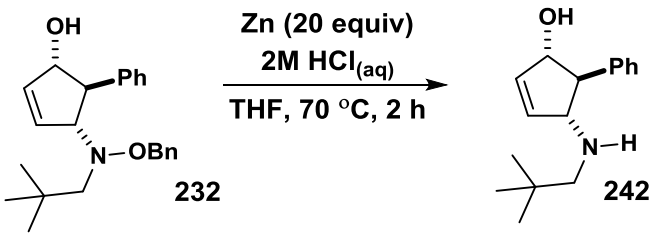
4-(Benzylamino)-5-phenylcyclopent-2-en-1-ol (240): A solution of **E-19** (20.0 mg, 0.062 mmol) in THF (1.9 mL) was treated with Zn (81.4 mg, 1.2 mmol), followed by slow addition of 3.7 mL 2M HCl. The reaction was placed in an oil bath at 70 °C and stirred until no starting material was observed by TLC. The reaction was then cooled to rt, quenched with saturated $NaHCO_3$, then the pH was adjusted to 9 using 3 M NaOH before extraction with EtOAc (3 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and solvent removed *in vacuo*. The residue was purified by flash column chromatography to

afford **240** (11.7 mg, 98%) as a light yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.31 – 7.27 (m, 3H), 7.27 – 7.24 (m, 2H), 7.24 – 7.18 (m, 3H), 6.21 (dd, *J* = 5.8, 1.7 Hz, 1H), 6.04 (ddd, *J* = 5.8, 2.2, 2.2 Hz, 1H), 4.84 (ddd, *J* = 6.3, 2.1, 2.1 Hz, 1H), 4.31 (dddd, *J* = 6.6, 1.8, 1.8, 1.8 Hz, 1H), 3.77 (s, 2H), 3.23 (dd, *J* = 6.4, 6.4 Hz, 1H), 1.57 (s, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 140.1, 138.7, 138.2, 133.2, 129.4, 128.8, 128.5, 128.3, 127.2, 127.2, 77.3, 67.2, 57.8, 52.4 ppm; **IR** (thin film) 3302, 3059, 3027, 2901, 2851, 1601, 1553, 1493, 1453, 1319, 1094, 1070, 1028 cm^{-1}; **MS** (ESI) *m/z* 288.1354 (288.1364 calcd for $C_{18}H_{19}NNaO$ $[MNa]^+$).

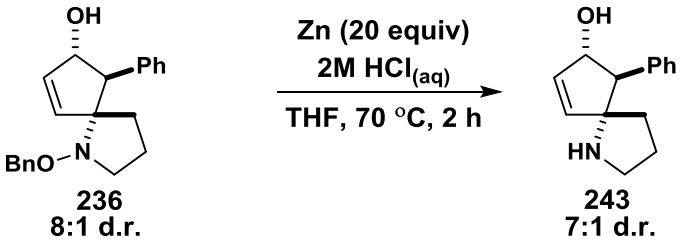


4-(Benzylamino)-5-butylcyclopent-2-en-1-ol (241): A solution of **233** (30.2 mg, 0.086 mmol) in THF (2.6 mL) was treated with Zn (112.4 mg, 1.7 mmol), followed by slow addition of 5.2 mL 2M HCl. The reaction was placed in an oil bath at 70 °C and stirred for 40 min, until no starting material was observed by TLC. The reaction was then cooled to rt, quenched with saturated $NaHCO_3$, then the pH was adjusted to ~10 using 3 M NaOH before extraction with EtOAc (3 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and solvent removed *in vacuo*. The residue was purified by flash column chromatography to afford **241** (17.3 mg, 82%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 4H), 7.28 – 7.23 (m, 1H), 5.97 – 5.91 (m, 1H), 5.89 (ddd, *J* = 5.7, 1.7, 1.7 Hz, 1H), 4.32 – 4.27 (m, 1H), 3.84 (d, *J* = 2.0 Hz, 2H), 3.34 – 3.28 (m, 1H), 2.53 (s, 2H),

1.79 (dddd, J = 10.0, 3.6, 3.6, 3.6 Hz, 1H), 1.56 – 1.28 (m, 6H), 0.91 (dd, J = 7.1, 7.1 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 139.5, 135.7, 134.4, 128.6, 128.5, 127.4, 81.6, 67.9, 54.7, 51.8, 33.1, 30.1, 23.1, 14.2 ppm; **IR** (thin film) 3290, 3059, 2039, 2955, 2924, 2855, 1454, 1354, 1073, 1027, 996 cm^{-1}; **MS** (ESI) *m/z* 268.1662 (268.1677 calcd for $C_{16}H_{23}NNaO$ $[MNa]^+$).

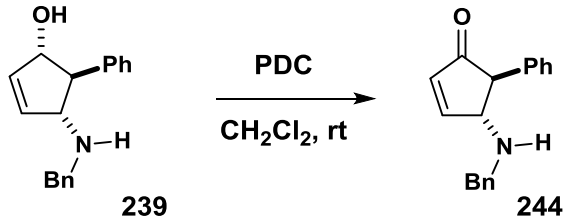


4-(Neopentylamino)-5-phenylcyclopent-2-en-1-ol (242): A solution of **232**(7.6 mg, 0.022 mmol) in THF (0.7 mL) was treated with Zn (28.3 mg, 0.43 mmol), followed by slow addition of 1.3 mL 2M HCl. The reaction was placed in an oil bath at 70 °C and stirred until no starting material was observed by TLC. The reaction was then cooled to rt, quenched with saturated $NaHCO_3$, then the pH was adjusted to ~10 using 3 M NaOH before extraction with EtOAc (3 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and solvent removed *in vacuo*. The residue was purified by flash column chromatography to afford **242** (3.1 mg, 58%) as a yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.32 (t, J = 7.3 Hz, 2H), 7.27 – 7.20 (m, 3H), 6.08 (d, J = 5.7 Hz, 1H), 6.01 (d, J = 5.2 Hz, 1H), 4.68 (s, 1H), 3.80 – 3.75 (m, 1H), 2.99 – 2.94 (m, 1H), 2.39 (s, 2H), 1.28 (s, 1H), 1.25 (s, 1H), 0.89 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.0, 136.7, 133.9, 129.0, 127.4, 126.9, 84.1, 71.4, 59.2, 31.4, 29.9, 27.9 ppm; **IR** (thin film) 3293, 3061, 3028, 2953, 2926, 2855, 1555, 1467, 1453, 1363, 1079, 1013, 906 cm^{-1}; **MS** (ESI) *m/z* 246.1853 (246.1858 calcd for $C_{16}H_{24}NO$ $[MH]^+$).

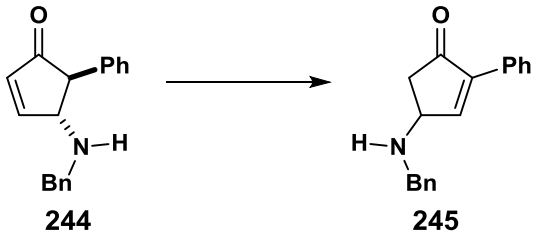


6-Phenyl-1-azaspiro[4.4]non-8-en-7-ol (243): A solution of (**236**) (66.5 mg, 0.21 mmol, as an 8:1 mixture of diastereomers) in 6.4 mL THF was treated with zinc (274.7 mg, 4.2 mmol), followed by dropwise addition of 2M HCl (12.7 mL). The reaction was placed in an oil bath heated to 70 °C and stirred for 2 hours. The reaction was then cooled to rt, quenched with saturated $NaHCO_3$, then the pH was adjusted to ~10 using 3M NaOH before extraction with EtOAc (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and solvent removed *in vacuo*. The residue was purified by flash column chromatography to afford **243** (34.3 mg, 77%) as a yellow oil and an inseparable 7:1 mixture of diastereomers. *Major diastereomer*: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 5H), 6.04 (d, J = 5.8 Hz, 1H), 6.01 (dd, J = 5.8, 1.9 Hz, 1H), 5.13 (ddd, J = 6.4, 1.6, 1.6 Hz, 1H), 3.37 (d, J = 6.4 Hz, 1H), 2.94 (ddd, J = 10.4, 7.9, 5.0 Hz, 1H), 2.84 (ddd, J = 10.6, 6.8, 6.8 Hz, 1H), 2.14 (bs, 3H), 1.73 – 1.46 (m, 5H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 140.6, 138.0, 134.7, 130.7, 128.4, 127.2, 77.7, 76.6, 61.0, 45.7, 34.8, 25.7 ppm; **IR** (thin film) 3363, 3060, 3029, 2922, 2852, 1600, 1554, 1455, 1387, 1104, 1083, 1033 cm^{-1}; **MS** (ESI) *m/z* 216.1393 (216.1388 calcd for $C_{14}H_{18}NO$ $[MH]^+$).

Allylic Oxidation:

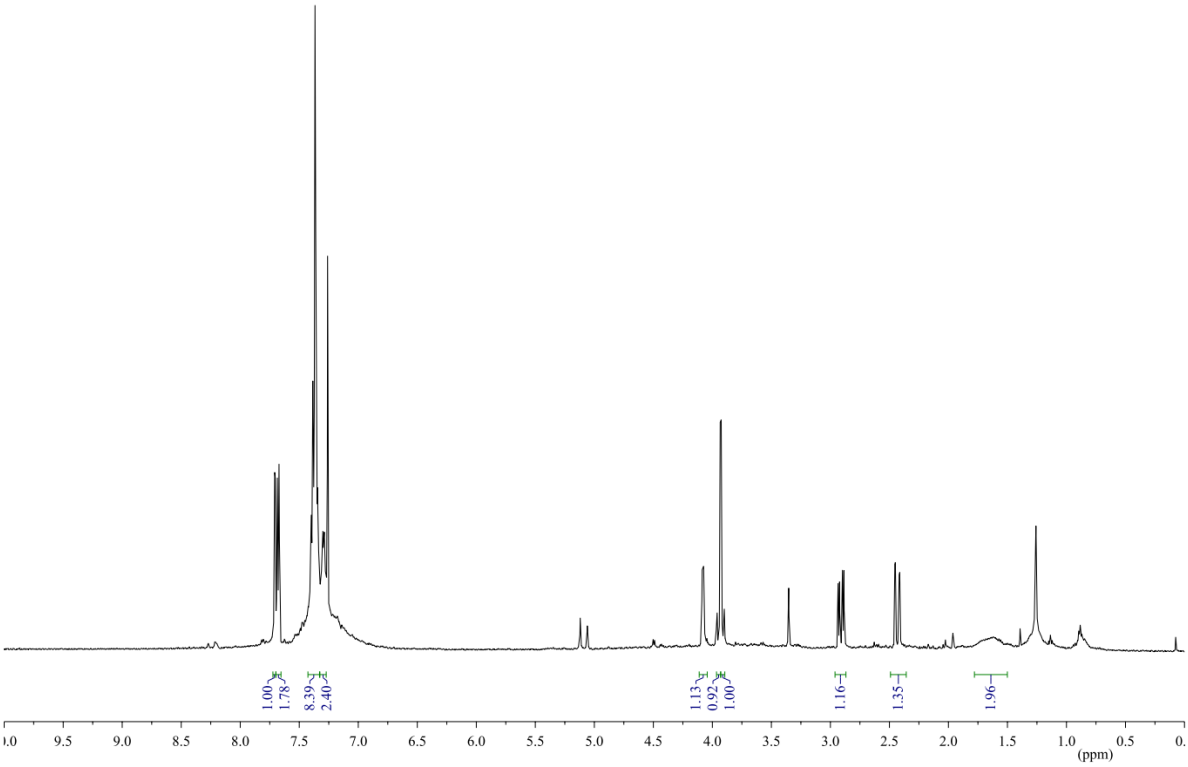


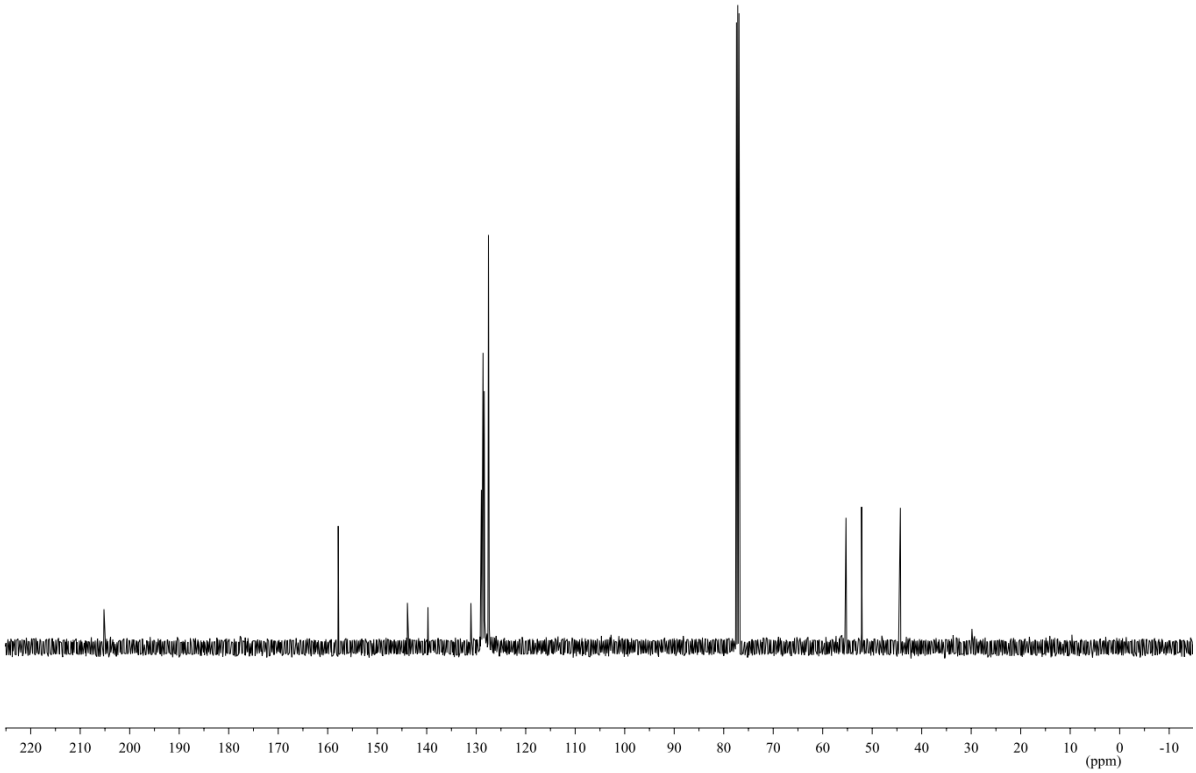
4-(Benzylamino)-5-phenylcyclopent-2-en-1-one (244): A solution of (**239**) (50.0 mg, 0.19 mmol) in 1.9 mL dry DMF was treated with pyridinium dichromate (PDC) (354 mg, 0.94 mmol) and stirred at rt for 2 h. The reaction was quenched with water (20 mL) and diluted with EtOAc (5 mL). The phases were separated, and the aqueous phase extracted with EtOAc (3 x 5 mL). Subsequently, the combined organic phases were washed with H_2O (5 x 5 mL) and brine (2 x 5 mL). The organic layer was dried over $MgSO_4$, filtered and solvent removed *in vacuo* to give the crude, desired product **244** (35 mg, 70%) as a yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.42 – 7.03 (m, 10H), 6.31 (s, 1H), 4.13 (s, 1H), 3.91 (d, J = 12.8 Hz, 1H), 3.82 (d, J = 12.3 Hz, 1H), 3.41 (s, 1H), 2.19 (bs, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.1, 163.3, 139.4, 138.4, 134.0, 129.0, 128.6, 128.3, 127.4, 127.3, 67.3, 60.6, 51.9 ppm; **IR** (thin film) 3085, 3061, 3029, 2925, 2853, 1705, 1494, 1453, 1265 cm^{-1}; **MS** (ESI) *m/z* 264.1376 (264.1388 calcd for $C_{18}H_{18}NO$ $[MH]^+$).



4-(Benzylamino)-2-phenylcyclopent-2-en-1-one (245): Upon purification on silica, exposure to base, or standing at rt, **244** isomerizes to the more thermodynamically stable cyclopentenone **245**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 (d, J = 2.6 Hz, 1H), 7.71 – 7.65

(m, 2H), 7.41 – 7.32 (m, 7H), 7.32 – 7.27 (m, 1H), 4.08 (ddd, J = 5.9, 2.5, 2.5 Hz, 1H), 3.95 (d, J = 13.0 Hz, 1H), 3.91 (d, J = 13.0 Hz, 1H), 2.91 (dd, J = 18.5, 6.2 Hz, 1H), 2.43 (dd, J = 18.5, 2.4 Hz, 1H), 1.63 (bs, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 205.2, 157.9, 143.9, 139.7, 131.1, 129.0, 128.8, 128.6, 128.4, 127.5, 55.3, 52.1, 44.3 ppm; **IR** (thin film) 3086, 3059, 3029, 2925, 2851, 1704, 1598, 1577, 1494, 1452, 1265 cm^{-1}; **MS** (ESI) *m/z* 264.1374 (264.1388 calcd for $C_{18}H_{18}NO$ $[MH]^+$).



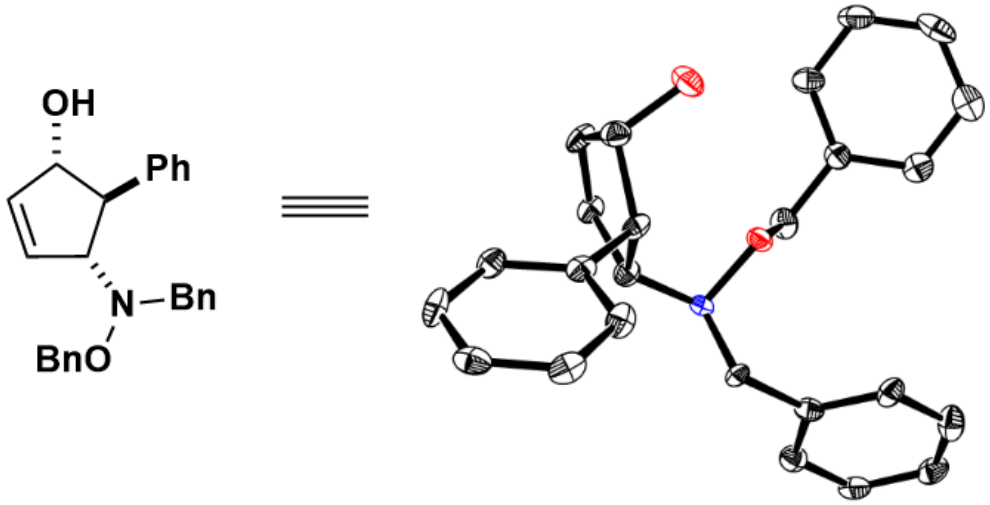


Crystallographic Experimental Section

A colorless crystal of approximate dimensions 0.3*0.1*0.1 mm was mounted on a glass fiber and transferred to a Bruker Kappa Apex II diffractometer. The APEX2 program was used to determine the unit cell parameters and data collection (15 sec / frame, 0.3 deg. /frame).[2] The data were collected at 100K. The raw frame data were processed using APEX2 program.[2] The absorption correction was applied using program SADABS.[3] Subsequent calculations were carried out using SHELXTL program.[4] The structure was solved by direct methods and refined on F^2 by full-matrix least-squares techniques. Hydrogen atomic positions were theoretically calculated. At convergence, wR2= 0.1517 and GOF = 0.957 for 274 variables refined against 4375 reflections, while R1= 0.0620 for 3625 reflections with $I>2\sigma(I)$. All ORTEP diagrams have been drawn with 50% probability ellipsoids.

Crystals were prepared by slow vapor diffusion using hexanes and ethyl acetate. The crystal structure data can be obtained free of charge from the Cambridge Crystallographic Data Centre www.ccdc.cam.ac.uk/data_request/cif

Compound # 235 CCDC 986010

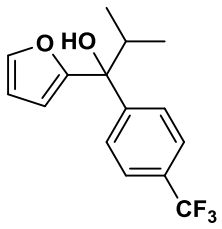


5.1.3 References

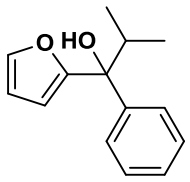
[1] Csákÿ, A. G.; Mba, M.; Plumet, J. *Synlett* **2003**, *13*, 2092.
[2] **(a)** Grierson, L.; Perkins, M. J. *Tetrahedron Lett.* **1993**, *34*, 7463; **(b)** Keck, G. E.; Wager, T. T.; McHardy, S. F. *Tetrahedron* **1999**, *55*, 11755; **(c)** Davies, S. G.; Goodwin, C. J.; Hepworth, D.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2010**, *75*, 1214.
[3] Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.
[4] Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 497.
[5] Jones, R. S.; Sutherland, J.; Weaver, D. F. *Synth. Commun.* **2003**, *33*, 43.

5.2.1 Chapter 2

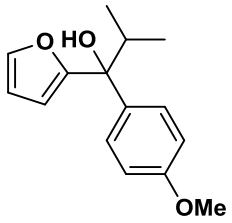
Furylcarbinols were prepared according to literature precedent by reacting furfural with the corresponding Grignard reagent,[1] followed by oxidation by MnO_2,[2] and subsequent second Grignard addition.



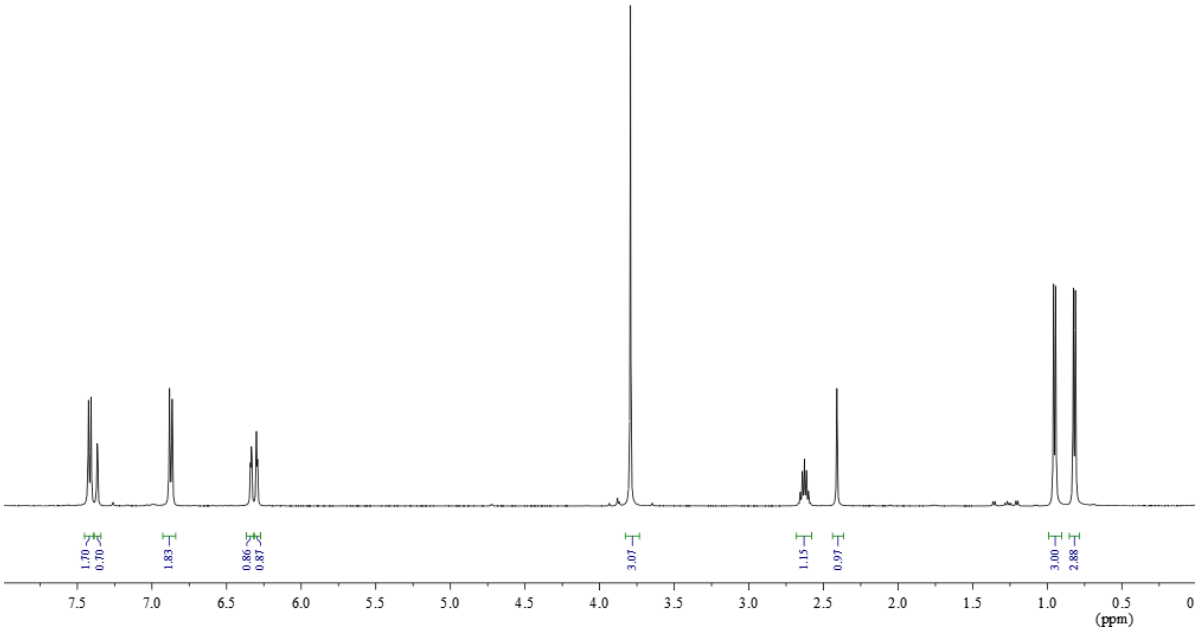
1-(Furan-2-yl)-2-methyl-1-(4-(trifluoromethyl)phenyl)propan-1-ol (E-23): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7.9 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.40 – 7.34 (m, 1H), 6.36 – 6.32 (m, 2H), 2.68 (dq, J = 6.8, 6.8, 6.8, 6.8, 6.8, 6.8 Hz, 1H), 2.54 (s, 1H), 0.96 (d, J = 6.8 Hz, 3H), 0.77 (d, J = 6.9 Hz, 4H).

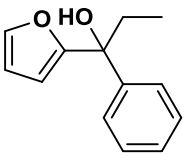


1-(Furan-2-yl)-2-methyl-1-phenylpropan-1-ol (E-24): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.46 (m, 2H), 7.37 – 7.29 (m, 3H), 7.26 – 7.21 (m, 1H), 6.33 – 6.31 (m, 1H), 6.31 – 6.28 (m, 1H), 2.64 (dq, J = 6.8, 6.8, 6.8, 6.8, 6.8, 6.8 Hz, 1H), 2.31 (s, 0H), 0.94 (dd, J = 6.8, 2.2 Hz, 3H), 0.78 (dd, J = 6.9, 2.2 Hz, 3H).

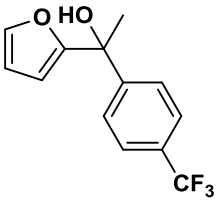


1-(Furan-2-yl)-1-(4-methoxyphenyl)-2-methylpropan-1-ol (E-25): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 7.37 (s, 0H), 6.93 – 6.84 (m, 2H), 6.37 – 6.31 (m, 1H), 6.32 – 6.27 (m, 1H), 3.79 (s, 3H), 2.63 (dq, J = 6.8, 6.8, 6.8, 6.8, 6.8, 6.8 Hz, 1H), 2.41 (s, 1H), 0.95 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H).

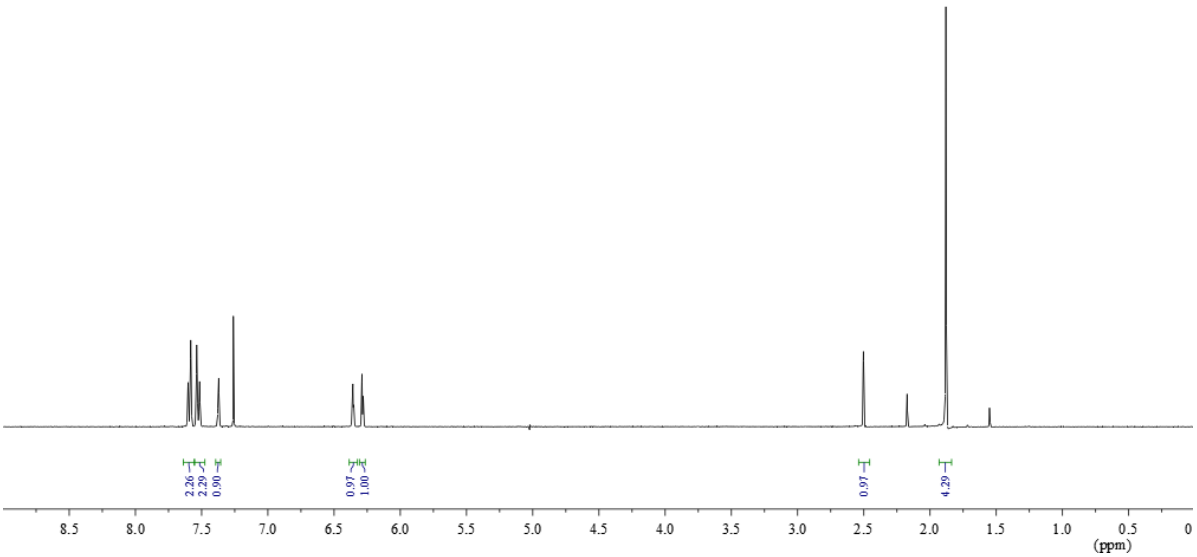


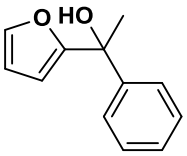


1-(Furan-2-yl)-1-phenylpropan-1-ol (E-26): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 2H), 7.38 – 7.30 (m, 3H), 7.30 – 7.23 (m, 1H), 6.34 (dd, J = 3.2, 1.8 Hz, 1H), 6.27 (dd, J = 3.3, 0.9 Hz, 1H), 2.56 (s, 1H), 2.30 (dq, J = 14.6, 7.4, 7.4, 7.4 Hz, 1H), 2.17 (dq, J = 14.5, 7.4, 7.4, 7.4 Hz, 1H), 0.88 (t, J = 7.4 Hz, 3H).

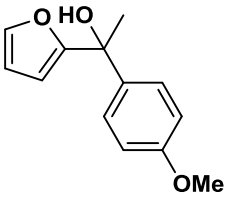


1-(Furan-2-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-ol (E-27): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 8.9 Hz, 2H), 7.40 – 7.34 (m, 1H), 6.36 (dd, J = 3.4, 1.8 Hz, 1H), 6.29 (dd, J = 3.3, 0.8 Hz, 1H), 2.50 (s, 1H), 1.88 (s, 3H).

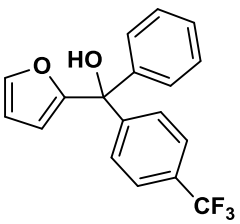




1-(Furan-2-yl)-1-phenylethan-1-ol (356): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 5H), 7.30 – 7.22 (m, 1H), 6.33 (dd, J = 3.3, 1.8 Hz, 1H), 6.24 (dd, J = 3.2, 0.9 Hz, 1H), 2.49 (d, J = 3.1 Hz, 1H), 1.87 (s, 3H).

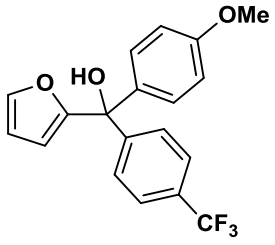


1-(Furan-2-yl)-1-(4-methoxyphenyl)ethan-1-ol (E-28): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.35 (m, 1H), 7.34 – 7.29 (m, 2H), 6.88 – 6.83 (m, 2H), 6.34 (dd, J = 3.3, 1.8 Hz, 1H), 6.23 (dd, J = 3.3, 0.9 Hz, 1H), 3.80 (s, 3H), 1.86 (s, 3H).

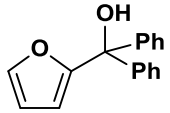


Furan-2-yl(phenyl)(4-(trifluoromethyl)phenyl)methanol (E-29): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.3 Hz, 2H), 7.51 (d, J = 8.2 Hz, 2H), 7.44 (dd, J = 2.0, 0.9 Hz, 1H), 7.39 – 7.27 (m, 5H), 6.35 (dd, J

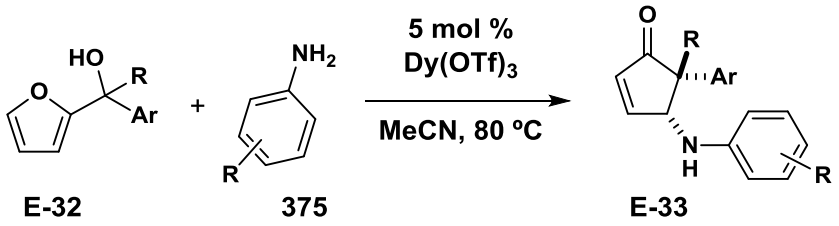
= 3.3, 1.8 Hz, 1H), 5.98 (dd, J = 3.3, 0.9 Hz, 1H), 3.65 (s, 1H).



Furan-2-yl(4-methoxyphenyl)(4-(trifluoromethyl) phenyl)methanol (E-30): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H), 7.45 (dd, J = 1.9, 1.0 Hz, 1H), 7.25 – 7.17 (m, 2H), 6.93 – 6.82 (m, 2H), 6.36 (dd, J = 3.3, 1.8 Hz, 1H), 6.02 – 5.94 (m, 1H), 3.80 (s, 3H), 3.50 (d, J = 6.9 Hz, 1H).

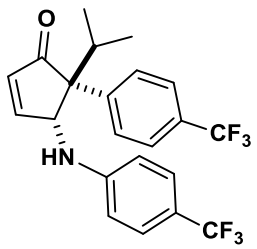


Furan-2-yldiphenylmethanol (E-31): Yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.40 – 7.27 (m, 10H), 6.34 (d, *J* = 1.5 Hz, 1H), 5.94 (d, *J* = 3.2 Hz, 1H), 3.11 (s, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 158.0, 144.7, 142.8, 128.1, 127.8, 127.3, 110.2, 109.8, 78.1 ppm; **IR** (thin film) 3410, 3061, 3028, 1957, 1888, 1813, 1725, 1675, 1598, 1554, 1490, 1447 cm^{-1}; **MS** (EI) *m/z* 250.0991 (250.0994 calcd for $C_{17}H_{14}O_2^+$ $[M]^+$).



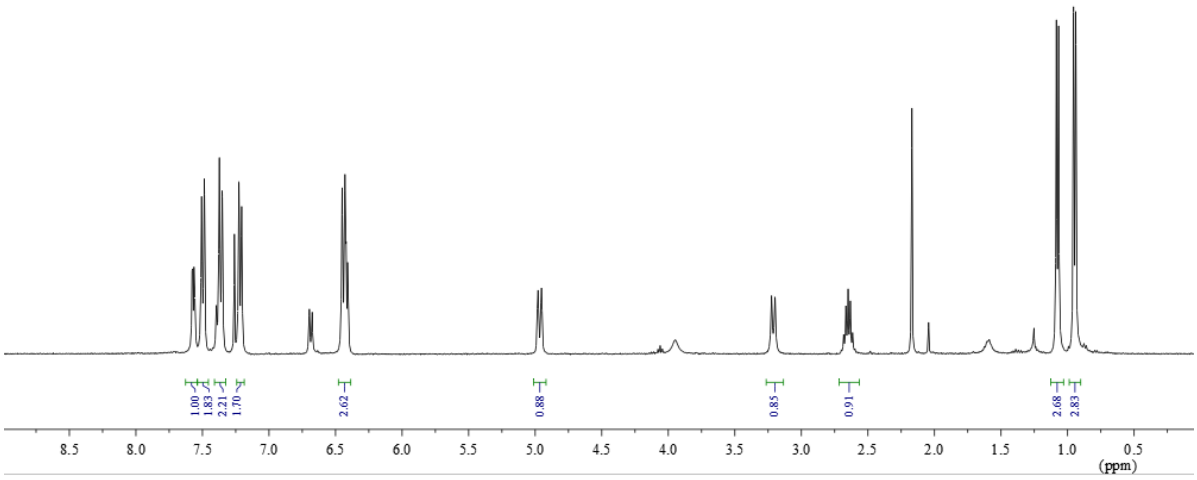
E-32 375 E-33

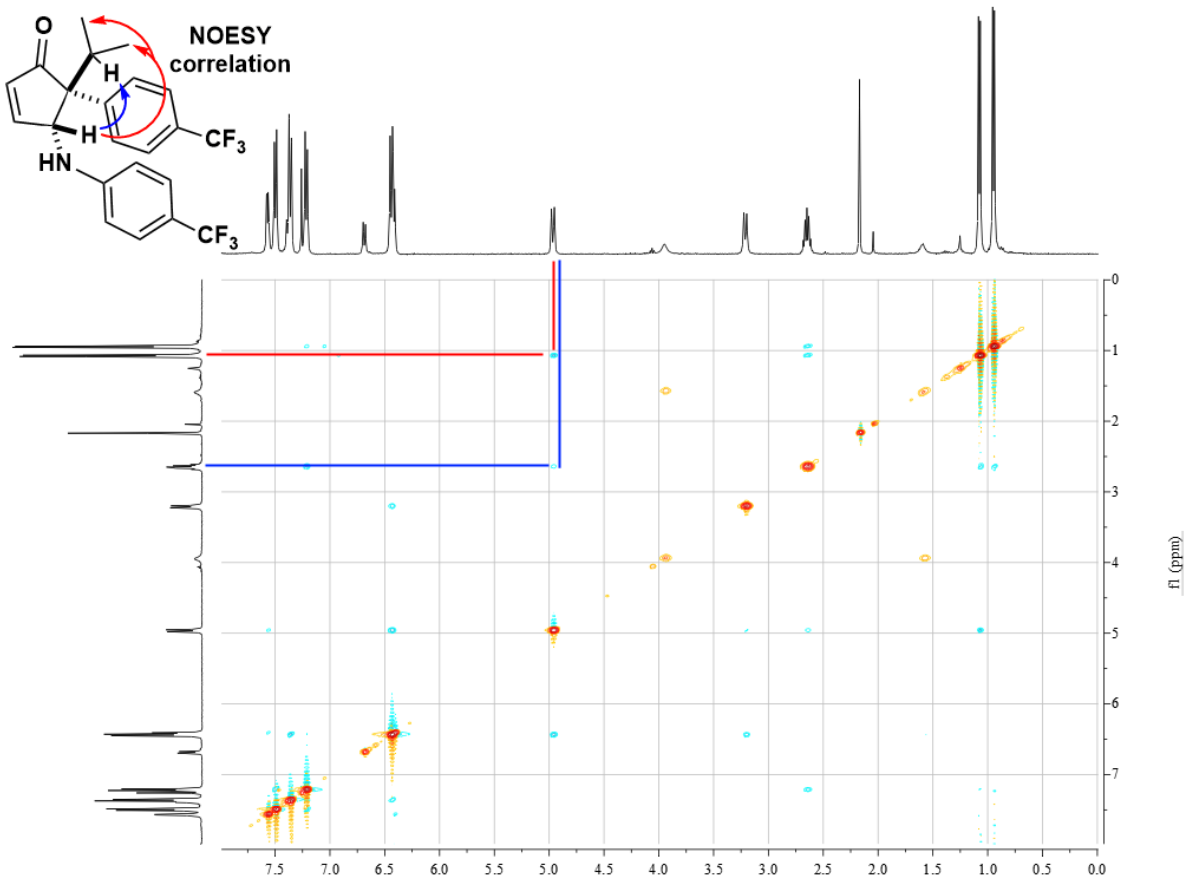
General procedure for the rearrangement: The tertiary furylcarbinol **E-32** and aniline **375** were dissolved in MeCN. To the reaction mixture at 23 ºC was added 5 mol % of $Dy(OTf)_3$. The reaction mixture was immediately fitted with a reflux condenser and placed in an oil bath pre-heated to 80 ºC. The reaction was monitored by TLC. Upon completion, the reaction was then quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **E-33**.

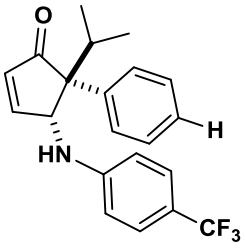


5-Isopropyl-5-(4-(trifluoromethyl)phenyl)-4-((4-(trifluoromethyl) phenyl)amino)cyclopent-2-en-1-one (377): According to the general procedure $Dy(OTf)_3$ (2.7 mg, 0.00445 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-2-methyl-1-(4-(trifluoromethyl)phenyl)propan-1-ol (22.1 mg, 0.089 mmol, 1 equiv) and 4-trifluoromethylaniline (11.2 µL, 0.089 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 2 h. The reaction was then quenched with 1 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over

$MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **377** (27.9 mg,73%, >20:1 dr) as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (dd, J = 5.8, 2.4 Hz, 1H), 7.50 (d, J = 8.2 Hz, 2H), 7.41 – 7.32 (m, 2H), 7.22 (d, J = 8.2 Hz, 2H), 6.48 – 6.39 (m, 3H), 4.97 (ddd, J = 10.4, 2.2, 2.2 Hz, 1H), 3.21 (d, J = 10.4 Hz, 1H), 2.65 (p, J = 6.8 Hz, 1H), 1.08 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.7 Hz, 3H).

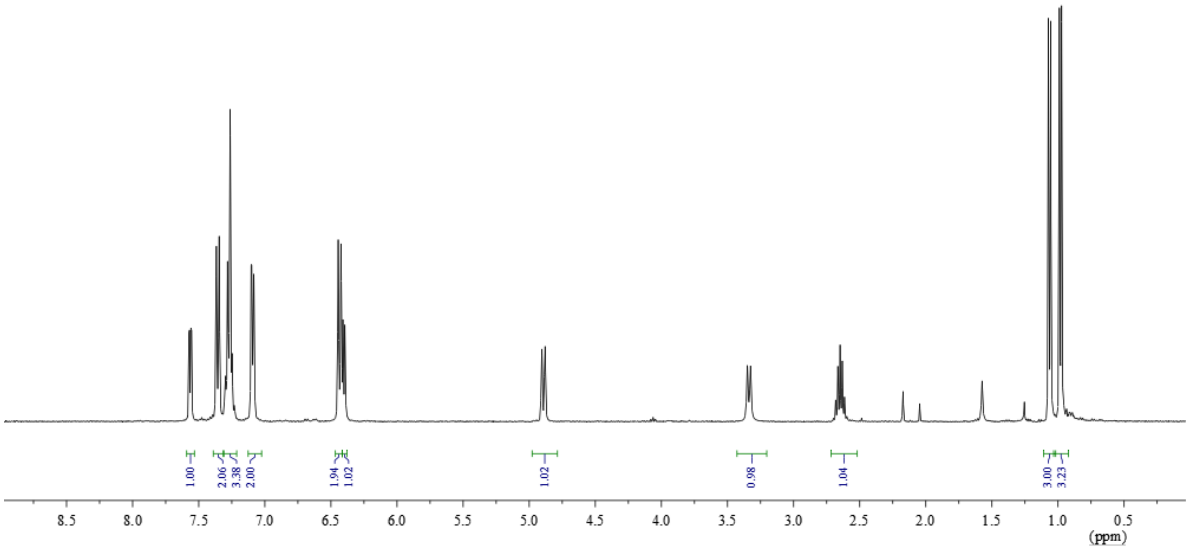


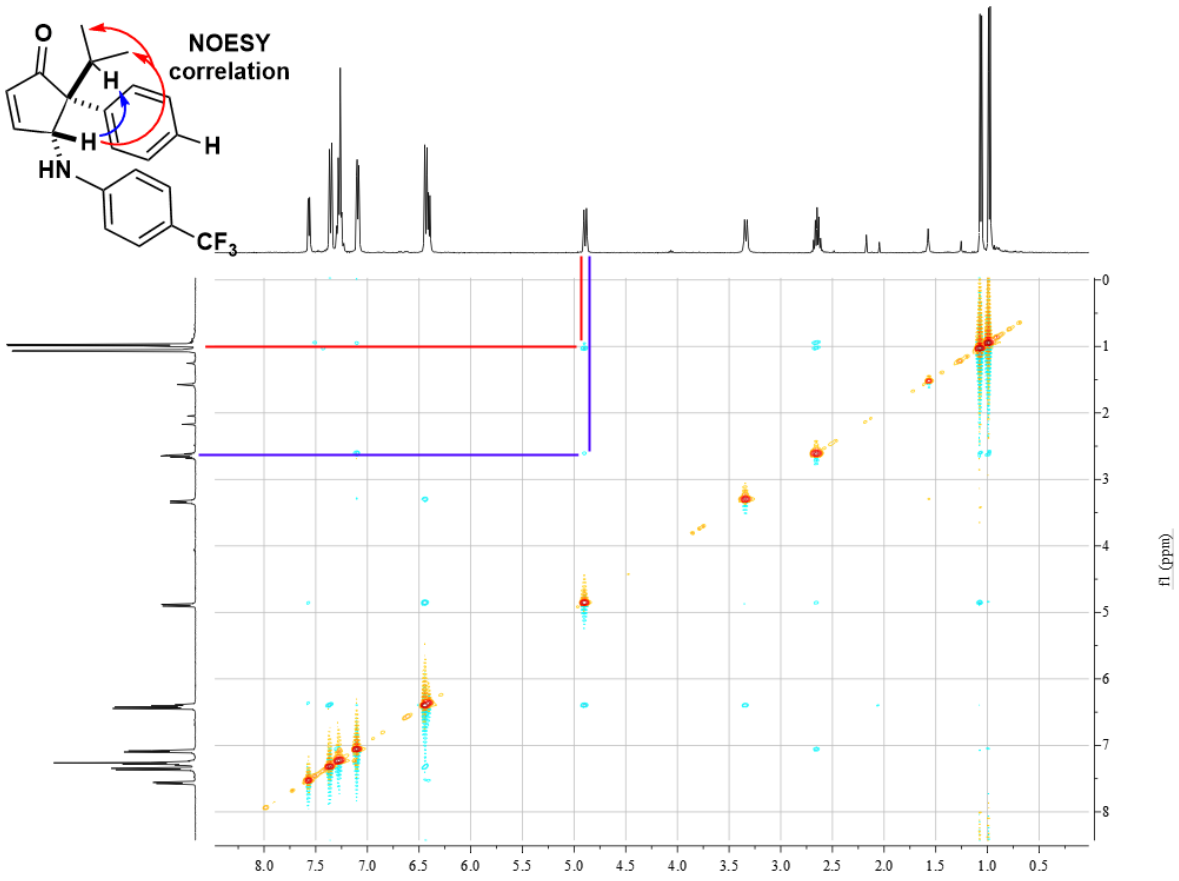


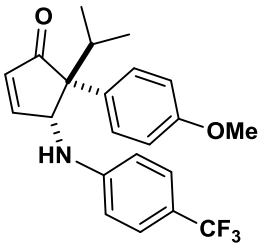


5-isopropyl-5-phenyl-4-((4-(trifluoromethyl)phenyl) amino)cyclopent-2-en-1-one (378): According to the general procedure $Dy(OTf)_3$ (2.8 mg, 0.0046 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-2-methyl-1-phenylpropan-1-ol (20.0 mg, 0.0926 mmol, 1 equiv) and 4-trifluoromethylaniline (11.7 µL, 0.089 mmol, 1 equiv) in 1 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 30 min. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford

cyclopentenone **378** (19.5 mg, 69%, >20:1 dr) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 5.9, 2.3 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.31 – 7.21 (m, 3H), 7.13 – 7.02 (m, 2H), 6.43 (d, J = 8.3 Hz, 2H), 6.40 (dd, J = 5.8, 1.8 Hz, 1H), 4.89 (ddd, J = 9.8, 2.0, 2.0 Hz, 1H), 3.34 (d, J = 9.7 Hz, 1H), 2.65 (p, J = 6.8 Hz, 1H), 1.06 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H).

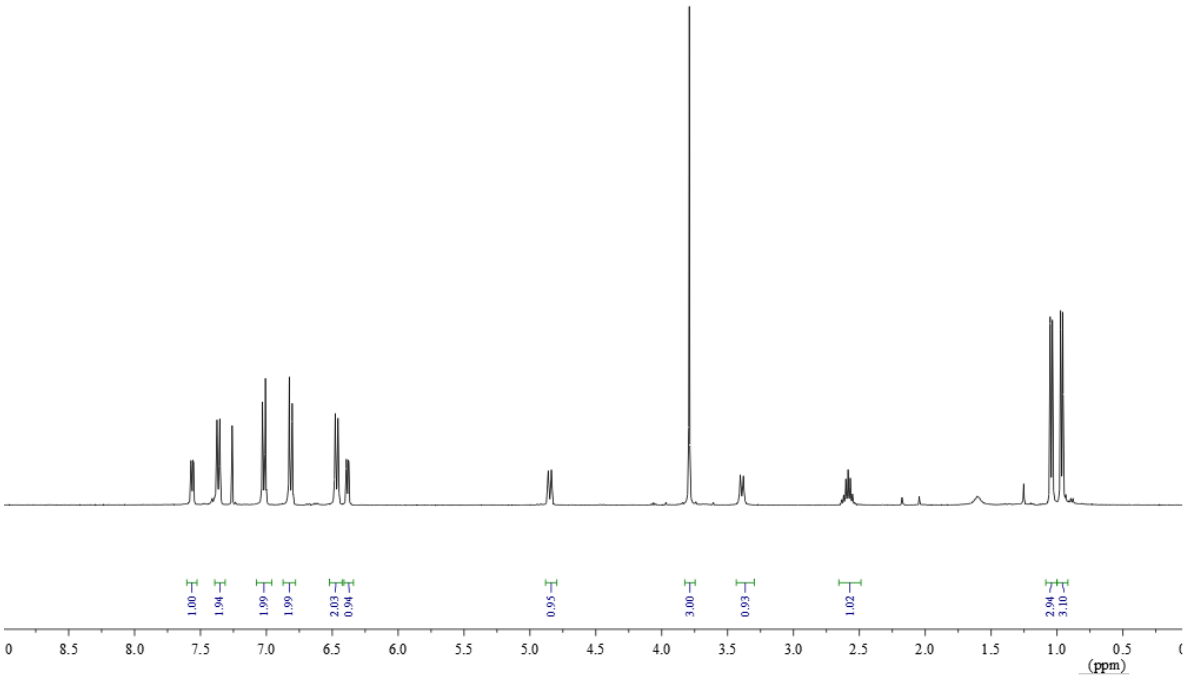


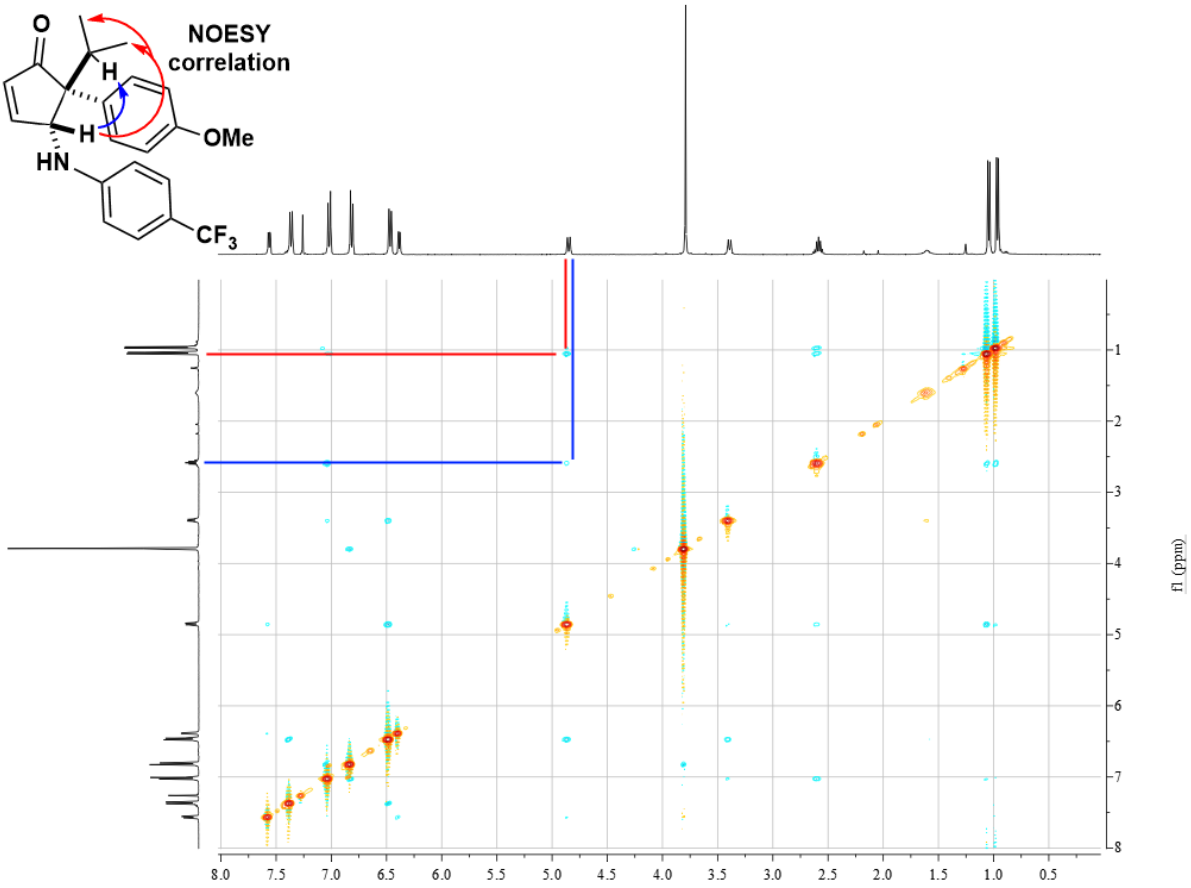


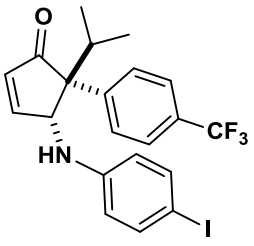


5-Isopropyl-5-(4-methoxyphenyl)-4-((4-(trifluoromethyl) phenyl)amino)cyclopent-2-en-1-one (379): According to the general procedure $Dy(OTf)_3$ (2.5 mg, 0.00406 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-1-(4-methoxyphenyl)-2-methylpropan-1-ol (20.0 mg, 0.0812 mmol, 1 equiv) and 4-trifluoromethylaniline (10.2 µL, 0.0812 mmol, 1 equiv) in 1 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 10 min. The reaction was then quenched with 1 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford

cyclopentenone **379** (21.8 mg, 69%, >20:1 dr) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 5.8, 2.2 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.08 – 6.96 (m, 2H), 6.87 – 6.78 (m, 2H), 6.47 (d, J = 8.4 Hz, 2H), 6.38 (dd, J = 5.8, 1.8 Hz, 1H), 4.85 (ddd, J = 9.6, 2.1 Hz, 1H), 3.79 (s, 3H), 3.39 (d, J = 9.5 Hz, 1H), 2.59 (hept, J = 6.3, 6.3, 6.8, 6.8, 6.8, 6.8 Hz, 1H), 1.04 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H).

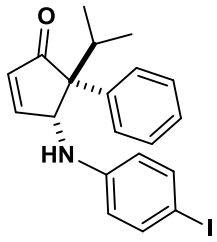




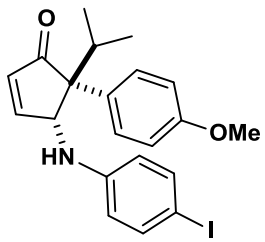


4-((4-iodophenyl)amino)-5-isopropyl-5-(4-(trifluoromethyl) phenyl)cyclopent-2-en-1-one (380): According to the general procedure $Dy(OTf)_3$ (5.4 mg, 0.0088 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-2-methyl-1-(4-(trifluoromethyl)phenyl)propan-1-ol (50.0 mg, 0.179 mmol, 1 equiv) and 4-iodoaniline (38.5 mg, 0.179 mmol, 1 equiv) in 2 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 3 h. The reaction was then quenched with 1 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **380** (44.6 mg, 52%, >20:1 dr) as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56

(dd, J = 5.8, 2.4 Hz, 1H), 7.50 (d, J = 8.2 Hz, 2H), 7.43 – 7.34 (m, 2H), 7.21 (d, J = 8.1 Hz, 2H), 6.38 (dd, J = 5.8, 1.9 Hz, 1H), 6.26 – 6.14 (m, 2H), 4.87 (ddd, J = 11.4, 2.4, 2.4 Hz, 1H), 2.92 (d, J = 10.2 Hz, 1H), 2.71 – 2.54 (m, 1H), 1.06 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H). **MS** (ESI) *m/z* 486.09 (486.05 calcd for $C_{21}H_{19}F_3INOH^+$ $[M + H]^+$).

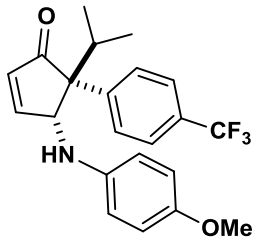


4-((4-Iodophenyl)amino)-5-isopropyl-5-phenylcyclopent-2-en-1-one (381): According to the general procedure $Dy(OTf)_3$ (2.6 mg, 0.00421 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-2-methyl-1-phenylpropan-1-ol (22.1 mg, 0.0926 mmol, 1.1 equiv) and 4-iodoaniline (18.4 mg, 0.0842 mmol, 1 equiv) in 1 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 1 h. The reaction was then quenched with 1 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **381** (15.2 mg, 43%, >20:1 dr) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (dd, J = 5.8, 2.3 Hz, 1H), 7.40 – 7.33 (m, 2H), 7.31 – 7.21 (m, 3H), 7.13 – 7.04 (m, 2H), 6.37 (dd, J = 5.8, 1.8 Hz, 1H), 6.24 – 6.17 (m, 2H), 4.80 (ddd, J = 9.8, 2.1, 2.1 Hz, 1H), 3.06 (d, J = 9.8 Hz, 1H), 2.62 (p, J = 6.7, 6.7, 6.7, 6.7 Hz, 1H), 1.04 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H).



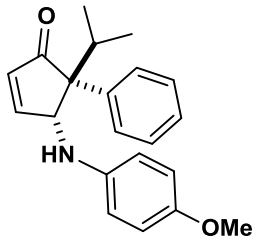
4-((4-Iodophenyl)amino)-5-isopropyl-5-(4-methoxyphenyl) cyclopent-2-en-1-one (382): According to the general procedure $Dy(OTf)_3$ (2.5 mg, 0.00406 mmol, 0.05 equiv) was added to 1-(furan-

2-yl)-1-(4-methoxyphenyl)-2-methylpropan-1-ol (20.0 mg, 0.0812 mmol, 1 equiv) and 4-iodoaniline (17.8 mg, 0.0812 mmol, 1 equiv) in 1 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 15 min. The reaction was then quenched with 1 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **382** (15.3 mg, 42%, >20:1 dr) as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (dd, J = 5.9, 2.2 Hz, 1H), 7.44 – 7.33 (m, 5H), 7.05 – 6.97 (m, 2H), 6.87 – 6.76 (m, 2H), 6.35 (dd, J = 5.8, 1.7 Hz, 1H), 6.28 – 6.20 (m, 2H), 4.76 (ddd, J = 9.7, 2.1, 2.1 Hz, 1H), 3.79 (s, 3H), 3.10 (d, J = 9.6 Hz, 1H), 2.55 (h, J = 6.7, 6.7, 6.7, 6.7, 6.7, 6.7, 6.7 Hz, 1H), 1.02 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.7 Hz, 3H).

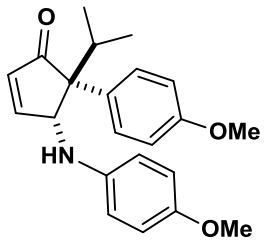


5-Isopropyl-4-((4-methoxyphenyl)amino)-5-(4-(trifluoromethyl) phenyl)cyclopent-2-en-1-one (383): According to the general procedure $Dy(OTf)_3$ (2.5 mg, 0.00413 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-2-methyl-1-(4-(trifluoromethyl)phenyl)propan-1-ol (23.5 mg, 0.0827 mmol, 1 equiv) and *p*-anisidine (10.2 mg, 0.0827 mmol, 1 equiv) in 1 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 15 min. The reaction was then quenched with 1 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **383** (5.3 mg, 16%, >20:1 dr) as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (dd, J = 5.9, 2.2 Hz, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.74 – 6.69 (m,

2H), 6.37 – 6.31 (m, 2H), 4.84 (d, J = 9.6 Hz, 1H), 3.80 (s, 1H), 3.75 (d, J = 4.1 Hz, 3H), 2.63 (p, J = 6.7, 6.7, 6.7, 6.7 Hz, 2H), 1.05 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H).

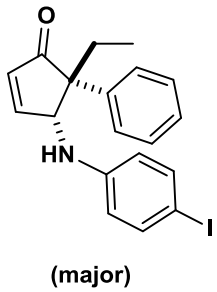


5-Isopropyl-4-((4-methoxyphenyl)amino)-5-phenylcyclopent-2-en-1-one (384): According to the general procedure $Dy(OTf)_3$ (2.8 mg, 0.0046 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-2-methyl-1-phenylpropan-1-ol (20.0 mg, 0.0926 mmol, 1 equiv) and *p*-anisidine (11.4 mg, 0.0926 mmol, 1 equiv) in 1 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 72 h. The reaction was then quenched with 1 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **384** (20.4 mg, 69%, >20:1 dr) as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (dd, J = 5.8, 2.3 Hz, 1H), 7.32 – 7.20 (m, 2H), 7.15 – 7.04 (m, 2H), 6.77 – 6.65 (m, 2H), 6.42 – 6.29 (m, 3H), 4.78 (d, J = 8.2 Hz, 1H), 3.74 (s, 3H), 2.79 (d, J = 10.0 Hz, 1H), 2.63 (h, J = 6.7, 6.7, 6.7, 6.7, 6.7, 6.7, 6.7 Hz, 1H), 1.04 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H).



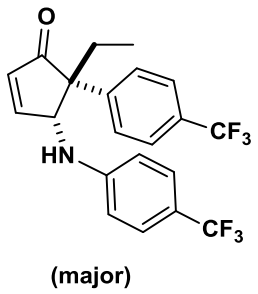
5-Isopropyl-5-(4-methoxyphenyl)-4-((4-methoxyphenyl) amino)cyclopent-2-en-1-one (385): According to the general procedure $Dy(OTf)_3$ (2.5 mg, 0.00406 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-1-(4-methoxyphenyl)-2-methylpropan-1-ol (20.0 mg, 0.0812 mmol, 1 equiv) and *p*-anisidine (10.0 mg, 0.0812 mmol, 1 equiv) in 1 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 5 h. The reaction was then

quenched with 1 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **385** (22.4 mg, 79%, >20:1 dr) as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (dd, J = 5.9, 2.2 Hz, 1H), 7.06 – 7.00 (m, 2H), 6.85 – 6.78 (m, 2H), 6.75 – 6.69 (m, 2H), 6.44 – 6.38 (m, 2H), 6.33 (dd, J = 5.8, 1.7 Hz, 1H), 4.82 – 4.65 (m, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 2.83 (d, J = 9.6 Hz, 1H), 2.57 (hept, J = 6.8, 6.8, 6.8, 6.8, 6.8, 6.8 Hz, 1H), 1.03 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.7 Hz, 3H).



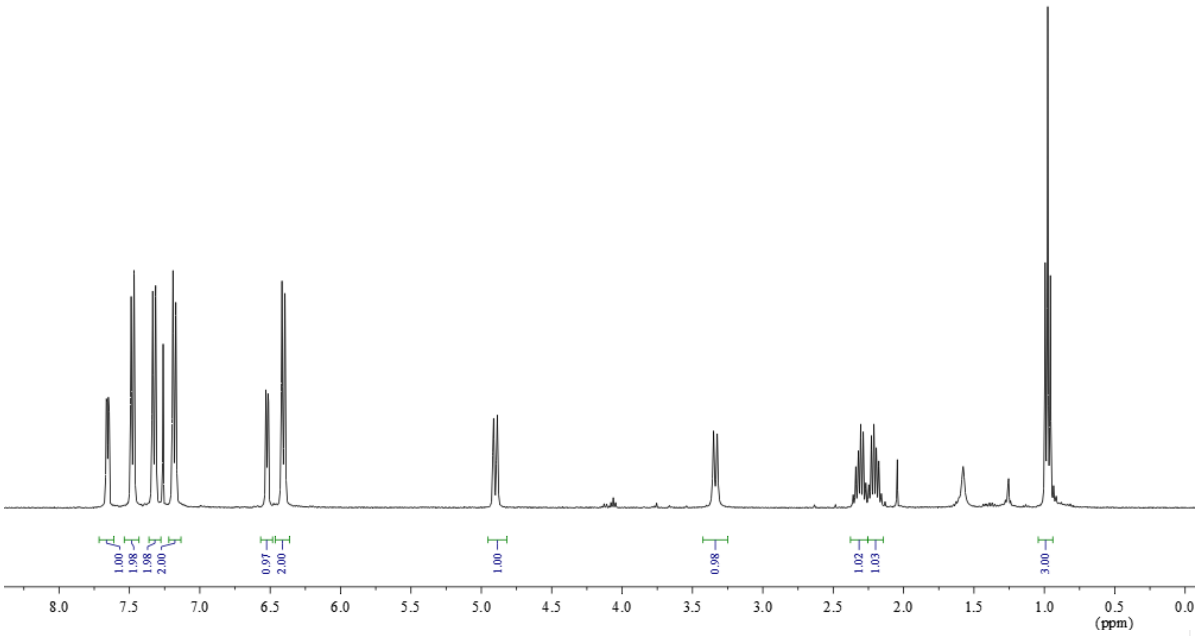
(major)

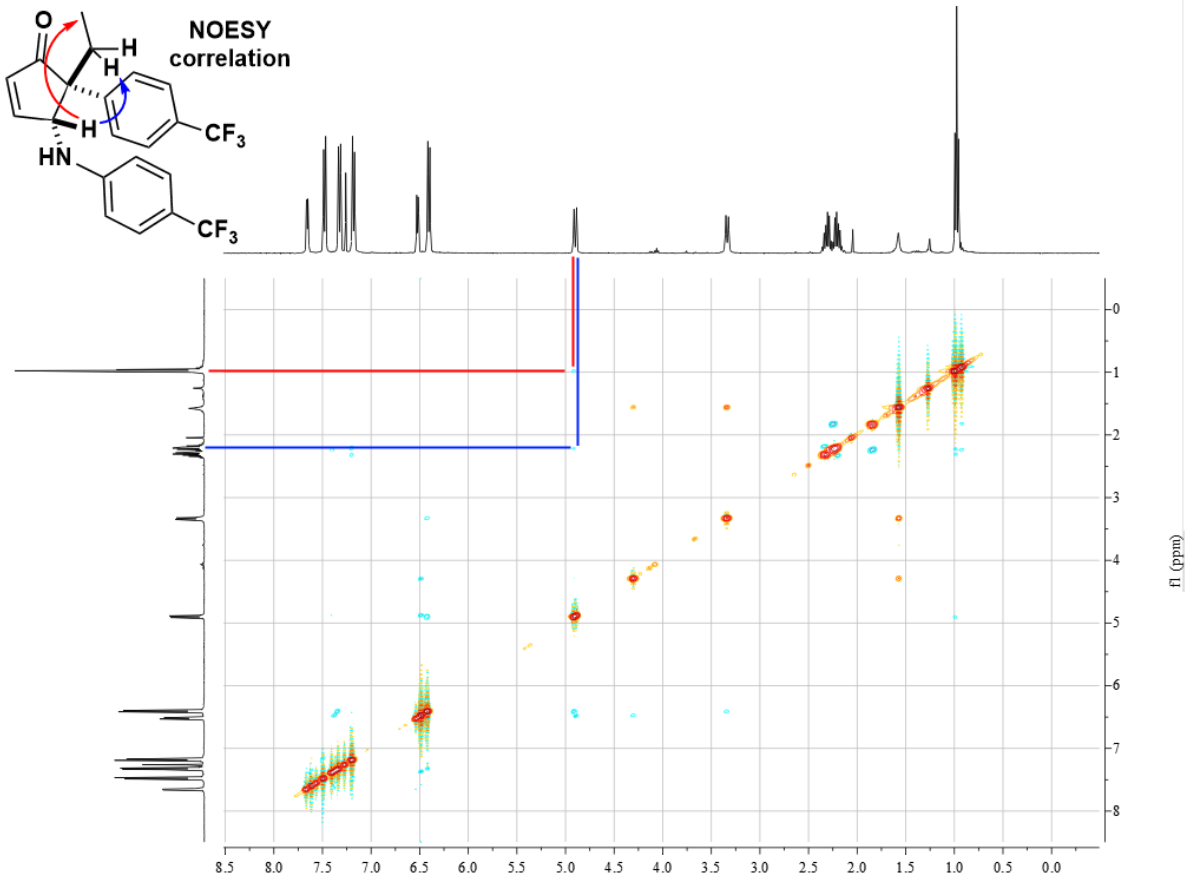
5-Ethyl-4-((4-iodophenyl)amino)-5-phenylcyclopent-2-en-1-one (388): According to the general procedure $Dy(OTf)_3$ (18.4 mg, 0.030 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-1-phenylpropan-1-ol (122.3 mg, 0.605 mmol, 1 equiv) and 4-iodoaniline (132.5 mg, 0.605 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 5 h. The reaction was then quenched with 1 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **388** (122.0 mg, 51%, 3:1 dr) as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (dd, J = 5.8, 2.3 Hz, 1H), 7.37 – 7.30 (m, 2H), 7.28 – 7.22 (m, 3H), 7.10 – 7.00 (m, 2H), 6.48 (dd, J = 5.9, 1.9 Hz, 1H), 6.21 – 6.14 (m, 2H), 4.75 (ddd, J = 10.3, 2.1, 2.1 Hz, 1H), 3.15 (d, J = 10.2 Hz, 1H), 2.27 (dq, J = 14.7, 7.3, 7.3, 7.3 Hz, 1H), 2.17 (dq, J = 14.2, 7.3, 7.3, 7.3 Hz, 1H), 0.96 (t, J = 7.4 Hz, 3H). **MS** (ESI) *m/z* 404.09 (404.09 calcd for $C_{19}H_{18}INOH^+$ $[M + H]^+$).



(major)

5-Ethyl-5-(4-(trifluoromethyl)phenyl)-4-((4-(trifluoromethyl) phenyl)amino)cyclopent-2-en-1-one (389): According to the general procedure $Dy(OTf)_3$ (2.8 mg, 0.00463 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-1-(4-(trifluoromethyl)phenyl)propan-1-ol (25.0 mg, 0.0925 mmol, 1 equiv) and 4-trifluoromethylaniline (11.6 µL, 0.0925 mmol, 1 equiv) in 1 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 25 min. The reaction was then quenched with 1 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **389** (27.6 mg, 70%, 5:1 dr) as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 (dd, J = 5.8, 2.3 Hz, 1H), 7.48 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.2 Hz, 2H), 6.52 (dd, J = 5.8, 1.9 Hz, 1H), 6.41 (d, J = 8.4 Hz, 2H), 4.90 (ddd, J = 10.6, 2.1, 2.1 Hz, 1H), 3.34 (d, J = 10.5 Hz, 1H), 2.31 (dddd, J = 14.8, 7.4, 7.4, 7.4 Hz, 1H), 2.20 (dddd, J = 14.4, 7.3, 7.3, 7.3 Hz, 1H), 0.98 (t, J = 7.4 Hz, 3H).


1.00
1.98
1.98
2.00
0.97
2.00
1.00
0.98
1.02
1.03
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


O
H
H
H
HN
CF3
CF3
NOESY
correlation
f1 (ppm)
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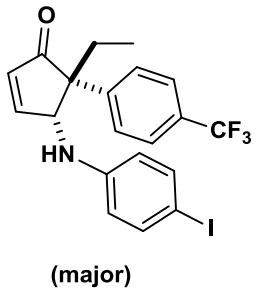
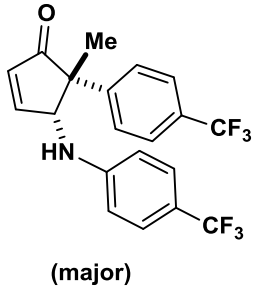
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0



(major)

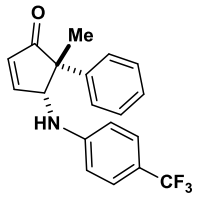
5-Ethyl-4-((4-iodophenyl)amino)-5-(4-(trifluoromethyl) phenyl)cyclopent-2-en-1-one (390): According to the general procedure $Dy(OTf)_3$ (2.8 mg, 0.00463 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-1-(4-(trifluoromethyl)phenyl)propan-1-ol (25.0 mg, 0.0925 mmol, 1 equiv) and 4-iodoaniline (20.3 mg, 0.0925 mmol, 1 equiv) in 1 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 3 h. The reaction was then quenched with 1 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **390** (18.7 mg, 43%, 4.3:1 dr) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 (dd, J = 5.8, 2.4 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.38 – 7.31 (m, 2H), 7.18 (d, J = 8.1 Hz, 2H), 6.49 (dd, J = 5.8, 1.9 Hz, 1H), 6.21 – 6.11 (m, 2H), 4.81 (ddd, J = 10.7, 2.2, 2.2 Hz, 1H), 3.04 (d, J = 10.6 Hz, 1H), 2.29 (dddd, J = 14.7, 7.4, 7.4, 7.4 Hz, 1H), 2.18 (dddd, J = 14.8, 7.3, 7.3, 7.3 Hz, 1H), 0.96 (t, J = 7.4 Hz, 3H).



(major)

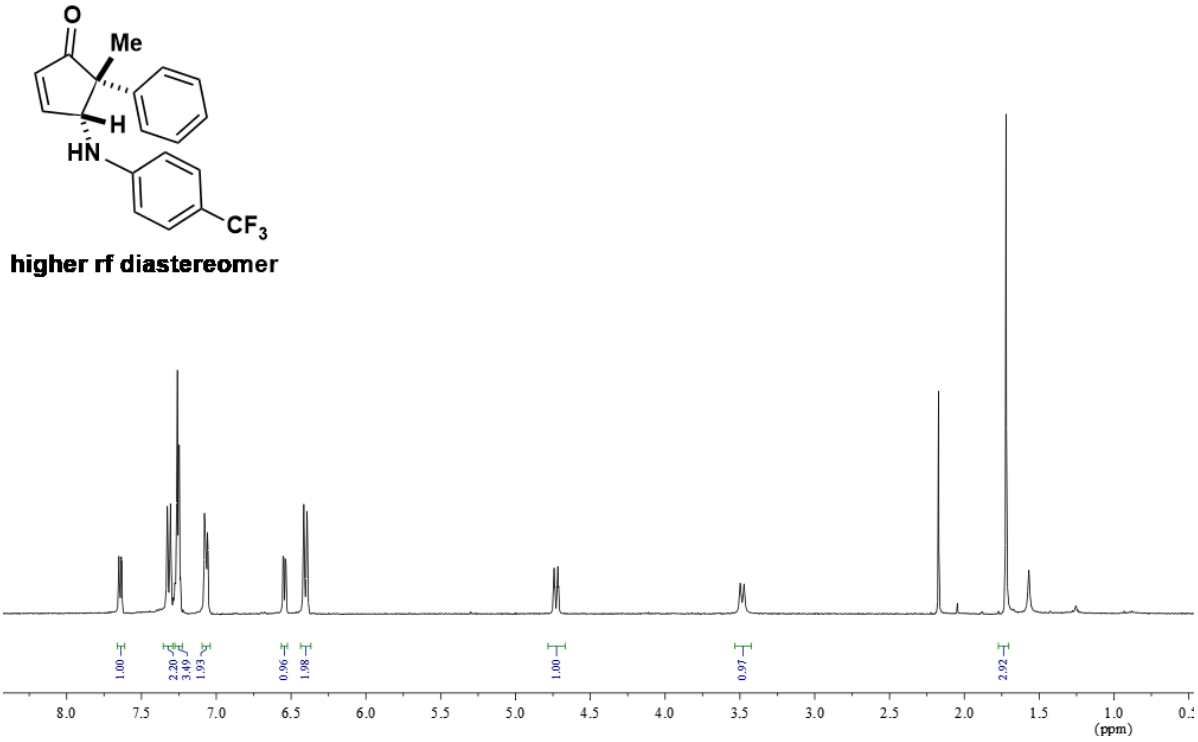
5-Methyl-5-(4-(trifluoromethyl)phenyl)-4-((4-(trifluoromethyl) phenyl)amino)cyclopent-2-en-1-one (392): According to the general procedure $Dy(OTf)_3$ (2.5 mg, 0.00412 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-ol (21.1 mg, 0.0824 mmol, 1 equiv) and 4-trifluoromethylaniline (10.3 µL, 0.0824 mmol, 1 equiv) in 1 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 3 h. The reaction was then quenched with 1 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over

$MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **392** (31.1 mg, 74%, 1.9:1 dr) as an oil. **^{1}H NMR (major diastereomer)** (400 MHz, $CDCl_3$) δ 7.66 (dd, J = 5.7, 2.3 Hz, 1H), 7.48 (d, J = 8.2 Hz, 2H), 7.35 – 7.28 (m, 2H), 7.18 (d, J = 8.2 Hz, 2H), 6.56 (dd, J = 5.8, 2.0 Hz, 1H), 6.45 – 6.34 (m, 2H), 4.81 (ddd, J = 10.5, 2.1, 2.1 Hz, 1H), 3.46 (d, J = 10.5 Hz, 1H), 1.76 (d, J = 1.9 Hz, 3H). **^{1}H NMR (minor diastereomer)** (400 MHz, $CDCl_3$) δ 7.67 (dd, J = 5.8, 2.4 Hz, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.36 – 7.27 (m, 4H), 6.51 (dd, J = 5.8, 2.1 Hz, 1H), 6.37 (d, J = 8.4 Hz, 2H), 4.88 (ddd, J = 9.5, 2.3, 2.3 Hz, 1H), 4.28 (d, J = 9.4 Hz, 1H), 1.46 (s, 3H).



higher rf diastereomer

5-Methyl-5-(4-(trifluoromethyl)phenyl)-4-((4-(trifluoromethyl) phenyl)amino)cyclopent-2-en-1-one (393): According to the general procedure $Dy(OTf)_3$ (3.8 mg, 0.0063 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-1-phenylethan-1-ol (23.8 mg, 0.126 mmol, 1 equiv) and 4-trifluoromethylaniline (15.9 µL, 0.126 mmol, 1 equiv) in 1 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 3 h. The reaction was then quenched with 1 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **393** (25.1 mg, 60%, 1:1 dr) as an oil. **^{1}H NMR (higher rf diastereomer)** (400 MHz, Chloroform-d) δ 7.64 (dd, J = 5.9, 2.2 Hz, 1H), 7.32 (d, J = 8.6 Hz, 2H), 7.28 – 7.23 (m, 3H), 7.09 – 7.04 (m, 2H), 6.54 (dd, J = 5.9, 1.9 Hz, 1H), 6.40 (d, J = 8.4 Hz, 2H), 4.73 (ddd, J = 10.1, 2.1 Hz, 1H), 3.49 (d, J = 10.0 Hz, 1H), 1.72 (s, 3H).


O
Me
H
HN
CF3
higher rf diastereomer
1.00
2.20
3.49
1.93
0.96
1.98
1.00
0.97
2.92
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7.5
7.0
6.5
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3.0
2.5
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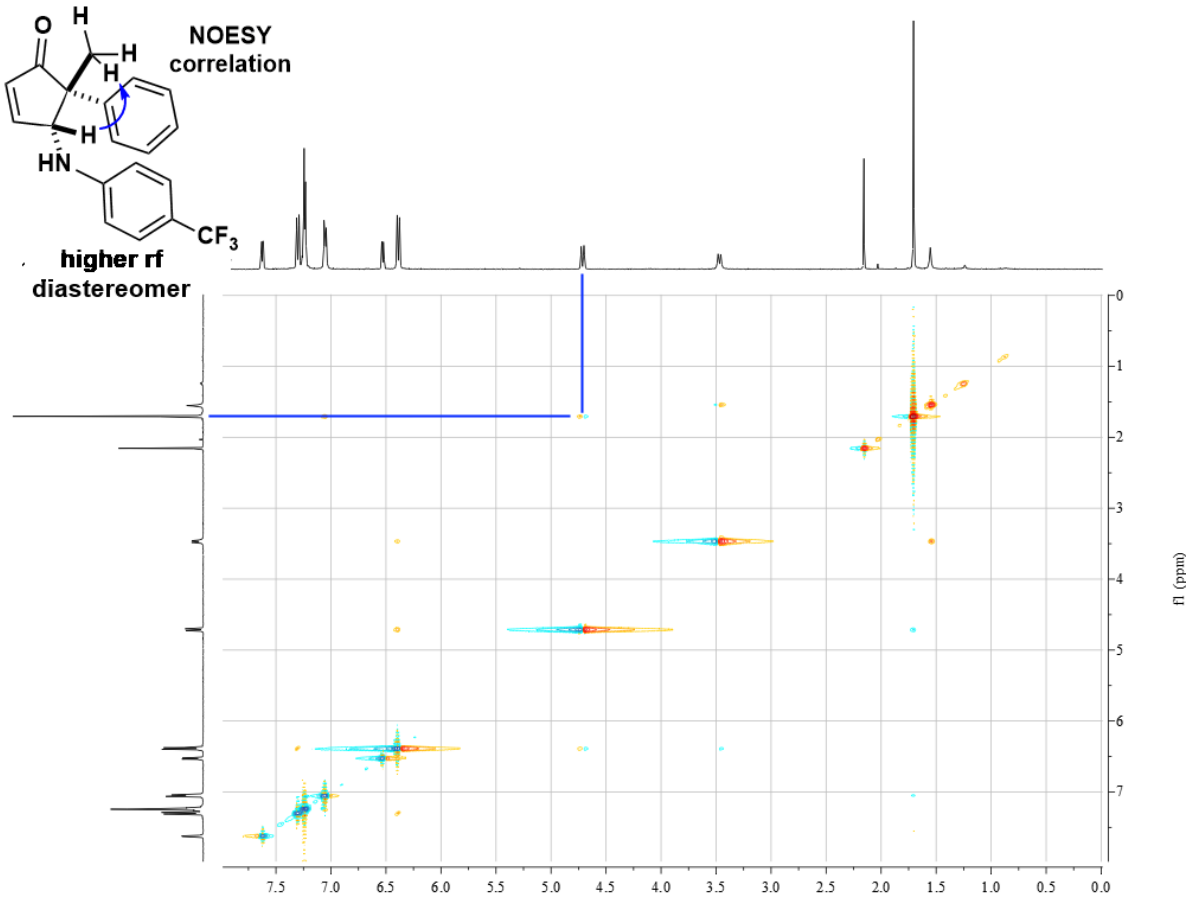
(ppm)


O
H
H
H
HN
CF3
NOESY
correlation
higher rf
diastereomer
0
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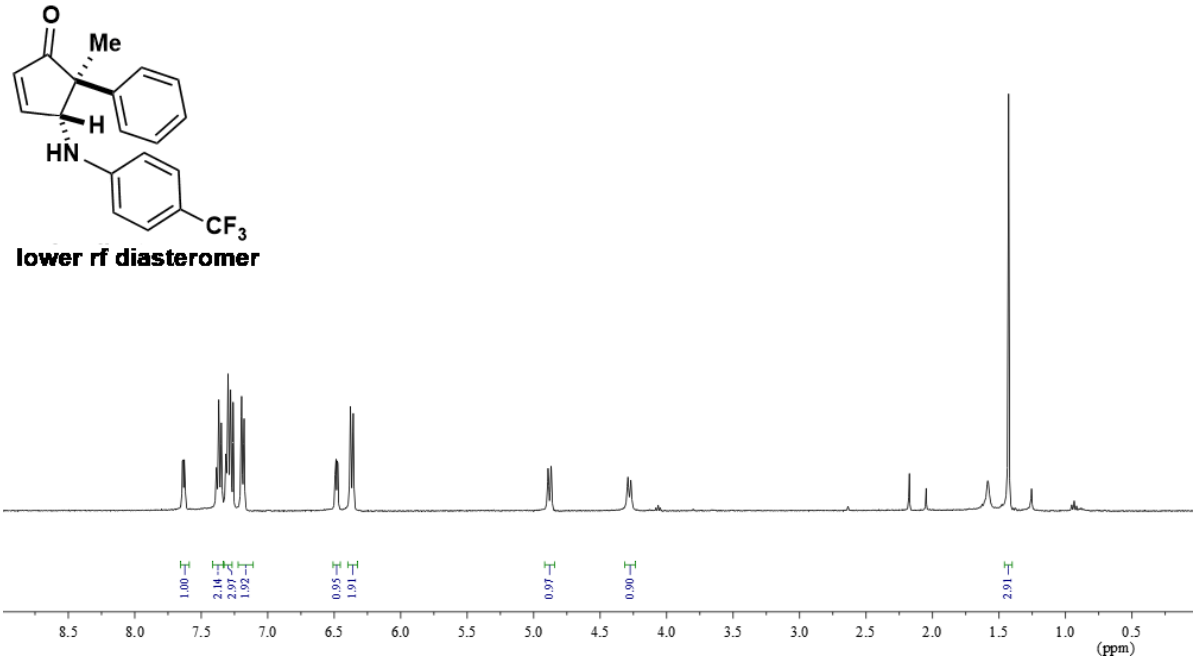
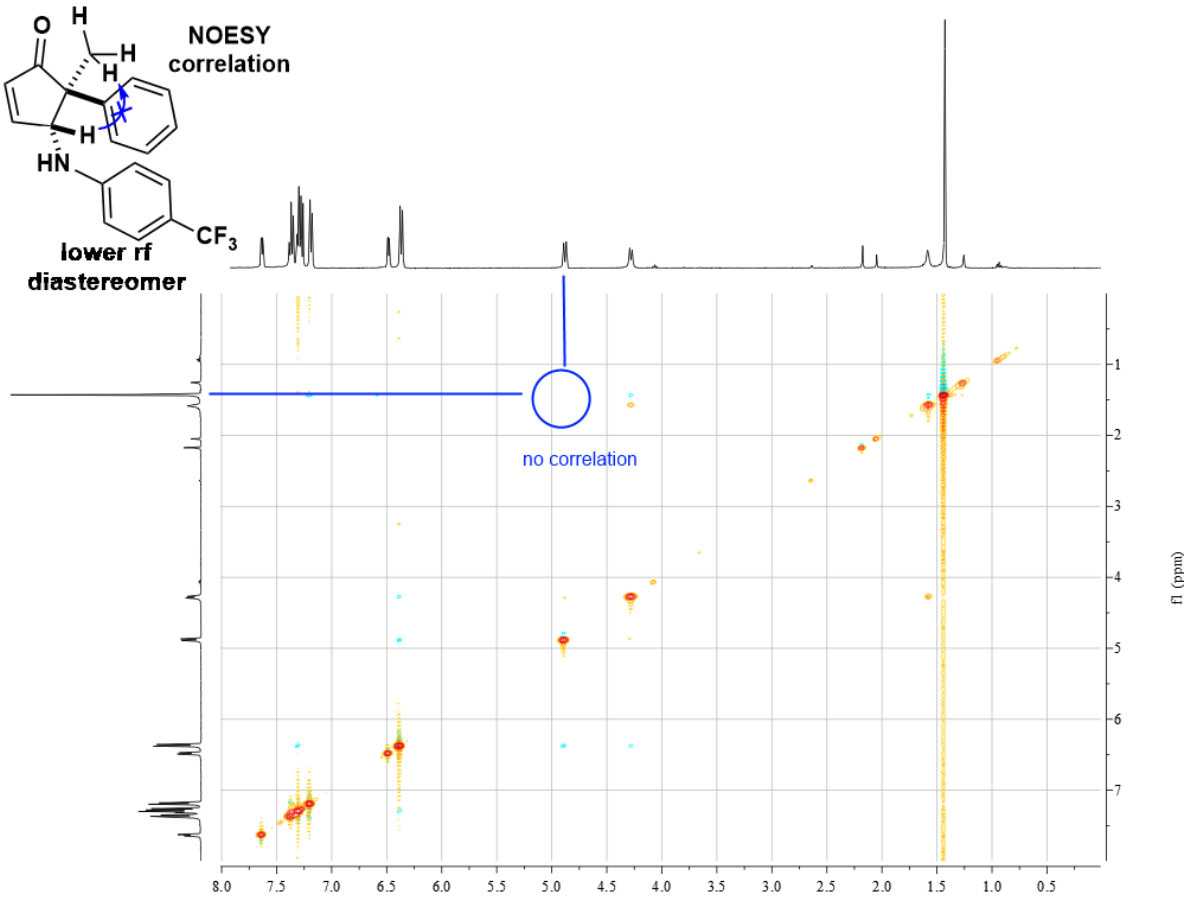
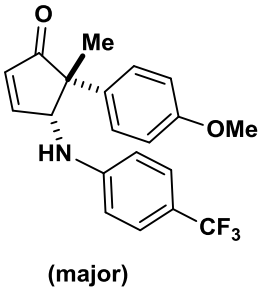
2
3
4
5
6
7
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

^{1}H NMR (lower rf diastereomer) (400 MHz, $CDCl_3$) δ 7.63 (dd, J = 5.8, 2.4 Hz, 1H), 7.37 (dd, J = 8.3, 6.6 Hz, 2H), 7.30 (dd, J = 8.0, 6.6 Hz, 3H), 7.19 (dd, J = 7.5, 1.8 Hz, 2H), 6.48 (dd, J = 5.8, 2.1 Hz, 1H), 6.37 (d, J = 8.4 Hz, 2H), 4.88 (ddd, J = 9.4, 2.3, 2.3 Hz, 1H), 4.28 (d, J = 9.3 Hz, 1H), 1.43 (s, 3H).

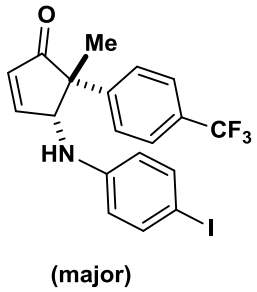






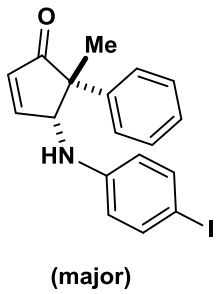
5-(4-Methoxyphenyl)-5-methyl-4-((4-(trifluoromethyl)phenyl)amino)cyclopent-2-en-1-one (394): According to the general procedure $Dy(OTf)_3$ (2.8 mg, 0.0046 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-1-(4-methoxyphenyl)ethan-1-ol (20.0 mg, 0.0917 mmol, 1 equiv) and 4-trifluoromethylaniline (11.5 µL, 0.0917 mmol, 1 equiv) in 1 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 10 min. The reaction was then quenched with 1 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was

purified by column chromatography to afford cyclopentenone **394** (5.6 mg, 17%, 1.2:1 dr) as an oil. **^{1}H NMR (major diastereomer)** (400 MHz, $CDCl_3$) δ 7.63 (dd, J = 5.9, 2.1 Hz, 1H), 7.36 – 7.29 (m, 2H), 6.99 (dd, J = 8.6, 1.6 Hz, 2H), 6.82 – 6.75 (m, 2H), 6.53 (dd, J = 5.9, 1.9 Hz, 1H), 6.47 – 6.37 (m, 2H), 4.68 (ddd, J = 9.8, 2.1, 2.1 Hz, 1H), 3.78 (d, J = 1.4 Hz, 3H), 3.50 (d, J = 9.9 Hz, 1H), 1.69 (d, J = 1.4 Hz, 3H). **^{1}H NMR (minor diastereomer)** (400 MHz, Chloroform-d) δ 7.61 (dd, J = 5.8, 2.3 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.14 – 7.07 (m, 2H), 6.92 – 6.87 (m, 2H), 6.47 (dd, J = 5.8, 2.1 Hz, 1H), 6.39 (d, J = 8.4 Hz, 2H), 4.85 (ddd, J = 9.3, 2.3, 2.3 Hz, 1H), 4.25 (d, J = 9.3 Hz, 1H), 3.82 (s, 3H), 1.40 (s, 3H).



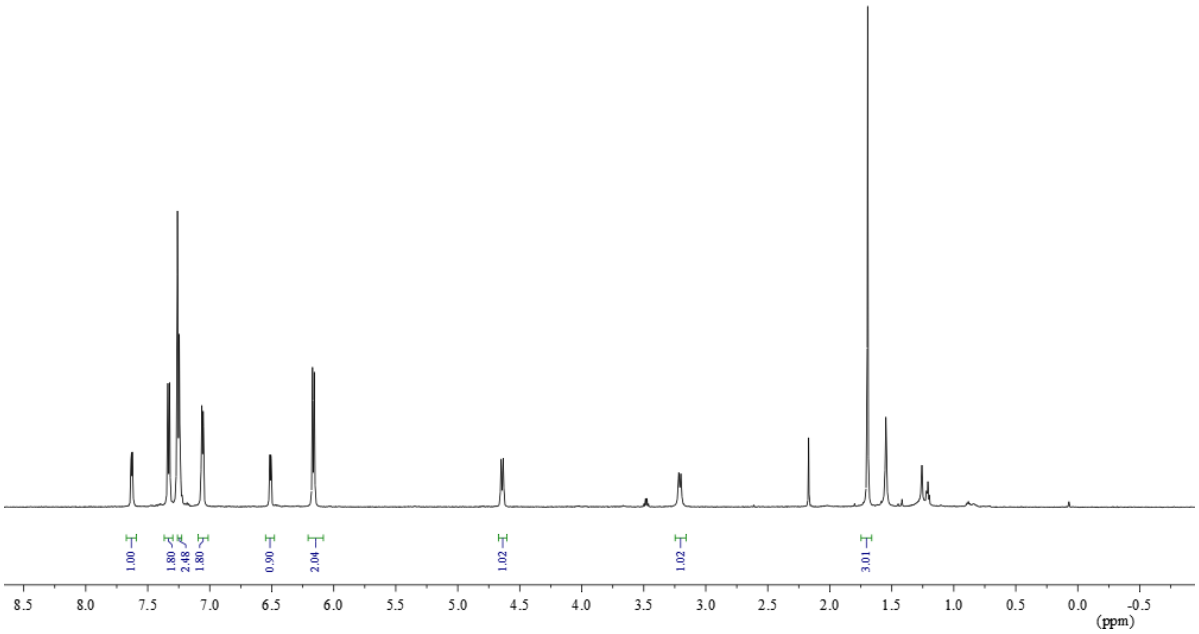
(major)

4-((4-Iodophenyl)amino)-5-methyl-5-(4-(trifluoromethyl) phenyl)cyclopent-2-en-1-one (395): According to the general procedure $Dy(OTf)_3$ (7.2 mg, 0.0118 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-ol (60.4 mg, 0.236 mmol, 1 equiv) and 4-iodoaniline (51.7 mg, 0.236 mmol, 1 equiv) in 1 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 4 min. The reaction was then quenched with 1 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **395** (86.4 mg, 80%, 2.6:1 dr) as an oil. **^{1}H NMR (major diastereomer)** (400 MHz, $CDCl_3$) δ 7.65 (dd, J = 5.8, 2.3 Hz, 1H), 7.50 – 7.45 (m, 2H), 7.35 – 7.30 (m, 2H), 7.19 – 7.12 (m, 2H), 6.52 (dd, J = 5.8, 1.9 Hz, 1H), 6.19 – 6.13 (m, 2H), 4.72 (ddd, J = 10.5, 2.2 Hz, 1H), 3.18 (d, J = 10.6 Hz, 1H), 1.72 (s, 3H). **MS** (EI^+) *m/z* 480.07 (480.01 calcd. for $C_{19}H_{15}F_3INNaO^+$ $[M+Na]^+$).



(major)

4-((4-Iodophenyl)amino)-5-methyl-5-phenylcyclopent-2-en-1-one (396): According to the general procedure $Dy(OTf)_3$ (16.2 mg, 0.0266 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-1-phenylethan-1-ol (100.0 mg, 0.532 mmol, 1 equiv) and 4-iodoaniline (116.5 mg, 0.532 mmol, 1 equiv) in 5 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 1.5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **396** (103.6 mg, 57%, 1.2:1 dr) as an oil. **^{1}H NMR (major diastereomer)** (600 MHz, $CDCl_3$) δ 7.63 (dd, J = 5.9, 2.2 Hz, 1H), 7.37 – 7.30 (m, 2H), 7.27 – 7.23 (m, 4H), 7.09 – 7.01 (m, 2H), 6.51 (dd, J = 5.9, 1.9 Hz, 1H), 6.21 – 6.08 (m, 2H), 4.64 (ddd, J = 10.4, 2.3, 2.3 Hz, 1H), 3.21 (d, J = 10.3 Hz, 1H), 1.69 (s, 3H). **MS** (ESI) *m/z* 390.08 (390.03 calcd for $C_{18}H_{16}INOH^+$ $[M + H]^+$).


1.00
1.80
2.48
1.80
0.90
2.04
1.02
1.02
3.01
8.5
8.0
7.5
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6.5
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5.5
5.0
4.5
4.0
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2.5
2.0
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1.0
0.5
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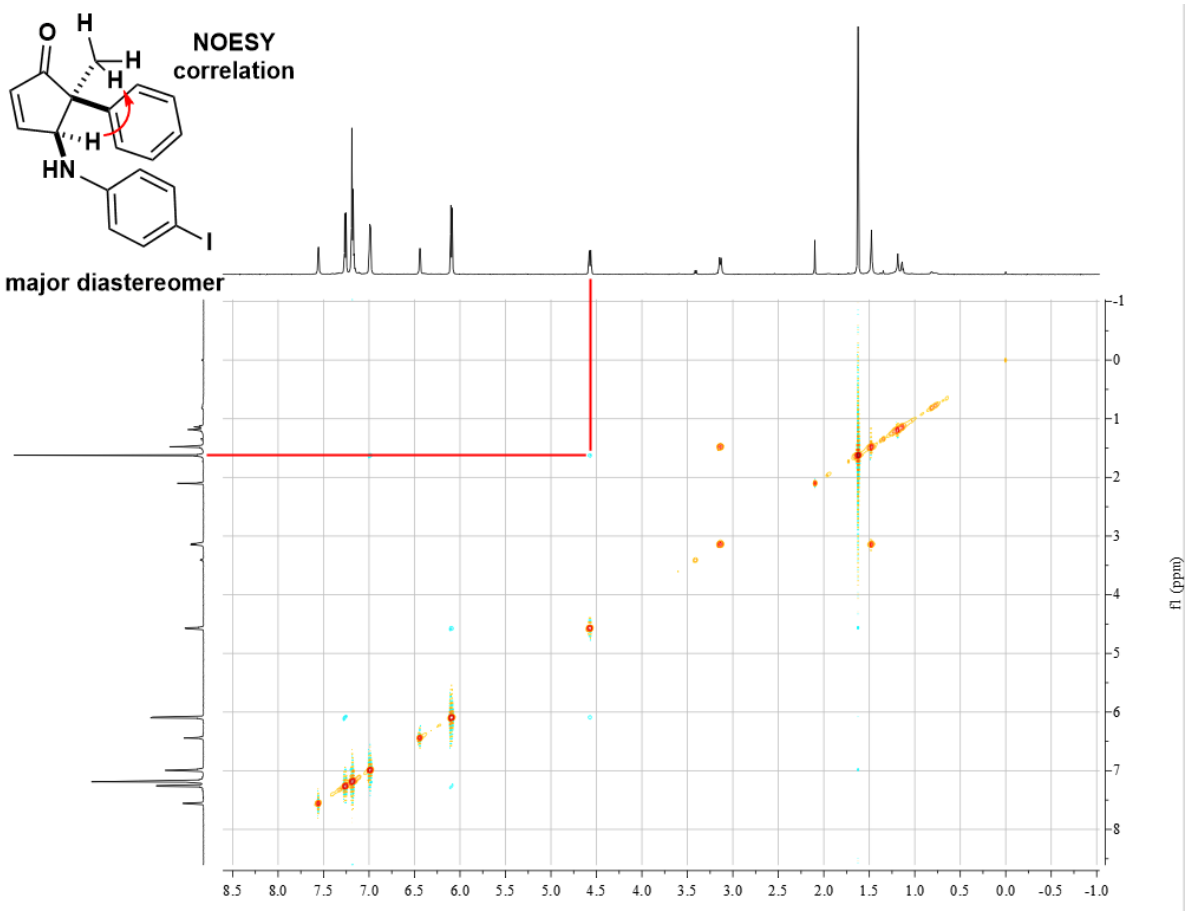
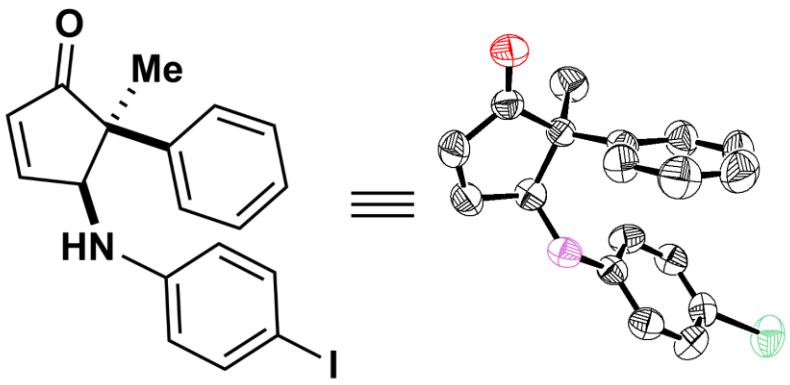
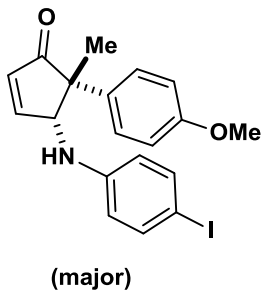
-0.5
(ppm)





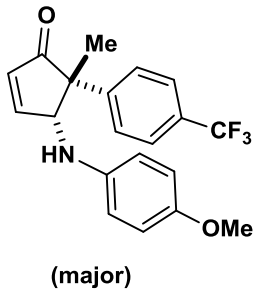
Crystals were prepared by slow vapor diffusion using hexanes as the outer layer and ethyl acetate as the inner layer. ORTEP drawing of cyclopentenone **396** (left) shown with 50% thermal ellipsoids. Hydrogen atoms have been omitted for clarity. The crystal structure

data can be obtained from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. **CCDC # 1015523**



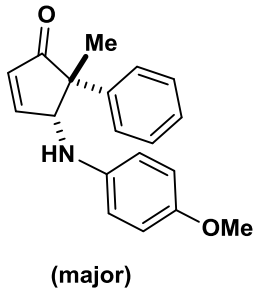
(major)

4-((4-Iodophenyl)amino)-5-(4-methoxyphenyl)-5-methylcyclopent-2-en-1-one (397): According to the general procedure $Dy(OTf)_3$ (23.4 mg, 0.0417 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-1-(4-methoxyphenyl)ethan-1-ol (181.9 mg, 0.833 mmol, 1 equiv) and 4-iodoaniline (182.4 mg, 0.833 mmol, 1 equiv) in 8 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 30 min. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **397** (73.4 mg, 21%, 1.2:1 dr) as an oil. **^{1}H NMR (major diastereomer)** (400 MHz, $CDCl_3$) δ 7.62 (dd, J = 5.9, 2.0 Hz, 1H), 7.38 – 7.31 (m, 2H), 7.01 – 6.94 (m, 2H), 6.83 – 6.71 (m, 2H), 6.49 (dd, J = 5.7, 1.7 Hz, 1H), 6.25 – 6.16 (m, 2H), 4.60 (ddd, J = 9.7, 2.0, 2.0 Hz, 1H), 3.78 (s, 2H), 3.22 (d, J = 9.7 Hz, 1H), 1.66 (s, 3H). **^{1}H NMR (minor diastereomer)** (400 MHz, $CDCl_3$) δ 7.59 (dd, J = 5.8, 2.3 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.12 – 7.06 (m, 2H), 6.90 – 6.85 (m, 2H), 6.43 (dd, J = 5.8, 2.1 Hz, 1H), 6.18 – 6.14 (m, 2H), 4.77 (ddd, J = 9.2, 2.1, 2.1 Hz, 1H), 4.03 – 3.93 (m, 1H), 3.81 (s, 3H), 1.38 (s, 3H).



(major)

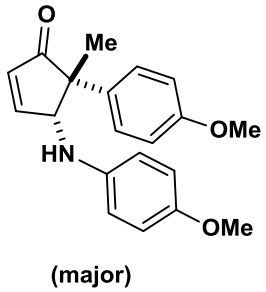
4-((4-Methoxyphenyl)amino)-5-methyl-5-(4-(trifluoromethyl) phenyl)cyclopent-2-en-1-one (398): According to the general procedure $Dy(OTf)_3$ (2.8 mg, 0.00454 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-ol (23.3 mg, 0.0909 mmol, 1 equiv) and *p*-anisidine (11.2 mg, 0.0.0909 mmol, 1 equiv) in 1 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 72 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **398** (21.0 mg, 64%, 1.6:1 dr) as an oil. **^{1}H NMR (inseparable mixture of diastereomers)** (400 MHz, $CDCl_3$) δ 7.68 (dd, J = 14.1, 4.7 Hz, 3H), 7.60 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.1 Hz, 3H), 7.32 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 8.1 Hz, 3H), 6.66 (dd, J = 11.9, 8.6 Hz, 5H), 6.53 – 6.47 (m, 1H), 6.43 (dd, J = 5.7, 2.1 Hz, 1H), 6.34 (d, J = 8.6 Hz, 2H), 6.28 (d, J = 8.5 Hz, 3H), 4.77 (s, 1H), 4.70 (s, 1H), 3.72 (s, 7H), 2.93 (s, 1H), 1.71 (s, 4H), 1.46 (s, 3H).



(major)

4-((4-Methoxyphenyl)amino)-5-methyl-5-phenylcyclopent-2-en-1-one (399): According to the general procedure $Dy(OTf)_3$ (5.6 mg, 0.0092 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-1-phenylethan-1-ol (34.7 mg, 0.184 mmol, 1 equiv) and *p*-anisidine (22.7 mg, 0.184 mmol, 1 equiv) in 2 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic

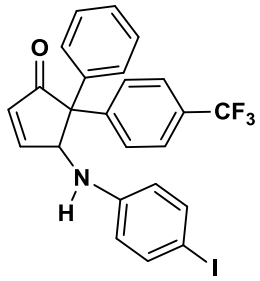
layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **399** (41.0 mg, 76%, 1.2:1 dr) as an oil. **^{1}H NMR (major diastereomer)** (400 MHz, $CDCl_3$) δ 7.69 (dd, J = 5.8, 2.2 Hz, 1H), 7.25 – 7.21 (m, 2H), 7.09 – 7.03 (m, 2H), 6.70 – 6.63 (m, 2H), 6.49 (dd, J = 5.8, 2.0 Hz, 1H), 6.33 – 6.27 (m, 2H), 4.67 – 4.60 (m, 1H), 3.72 (s, 3H), 3.06 – 2.86 (m, 1H), 1.68 (s, 3H). **^{1}H NMR (minor diastereomer)** (400 MHz, $CDCl_3$) δ 7.64 (dd, J = 5.8, 2.3 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.29 – 7.25 (m, 1H), 7.23 – 7.15 (m, 2H), 6.69 – 6.62 (m, 2H), 6.41 (dd, J = 5.8, 2.1 Hz, 1H), 6.39 – 6.31 (m, 2H), 4.79 (d, J = 6.3 Hz, 1H), 3.71 (s, 4H), 1.44 (s, 3H).



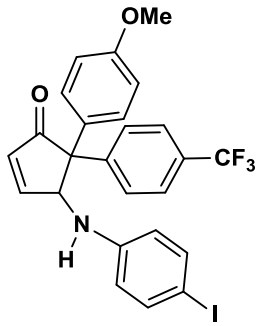
(major)

5-(4-Methoxyphenyl)-4-((4-methoxyphenyl)amino)-5-methylcyclopent-2-en-1-one (400): According to the general procedure $Dy(OTf)_3$ (2.8 mg, 0.0046 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-1-(4-methoxyphenyl)ethan-1-ol (20.0 mg, 0.0917 mmol, 1 equiv) and *p*-anisidine (11.3 mg, 0.0917 mmol, 1 equiv) in 2 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 1.5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **400** (16.8 mg, 57%, 1.2:1 dr) as an oil. **^{1}H NMR (inseparable mixture of diastereomers)** (400 MHz, $CDCl_3$) δ 7.68 (dd, J = 5.8, 2.2 Hz, 1H), 7.62 (dd, J = 5.8, 2.3 Hz, 2H), 7.14 – 7.05 (m, 6H), 7.02 – 6.96 (m, 4H), 6.93 – 6.83 (m, 11H), 6.83 –

6.72 (m, 18H), 6.72 – 6.62 (m, 17H), 6.62 – 6.45 (m, 7H), 6.45 – 6.33 (m, 8H), 4.76 (s, 2H), 4.59 (s, 1H), 3.82 – 3.68 (m, 56H), 1.64 (s, 3H), 1.50 (s, 3H), 1.42 (d, J = 4.4 Hz, 9H).

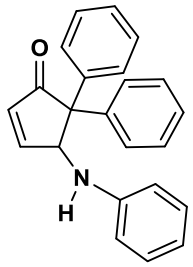


4-((4-iodophenyl)amino)-5-phenyl-5-(4-(trifluoromethyl) phenyl)cyclopent-2-en-1-one (401): According to the general procedure $Dy(OTf)_3$ (7.5 mg, 0.0123 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)(4-(trifluoromethyl)phenyl)methanol (78.6 mg, 0.247 mmol, 1 equiv) and 4-iodoaniline (54.1 mg, 0.247 mmol, 1 equiv) in 2.5 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 4.5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **401** (102.7 mg, 92%, 1.5:1 dr) as an oil. **^{1}H NMR (inseparable mixture of diastereomers)** (400 MHz, $CDCl_3$) δ 7.78 – 7.71 (m, 2H), 7.45 (d, J = 8.2 Hz, 3H), 7.42 – 7.34 (m, 8H), 7.34 – 7.28 (m, 4H), 7.28 – 7.21 (m, 3H), 7.11 (d, J = 8.1 Hz, 3H), 6.96 – 6.88 (m, 2H), 6.50 (dd, J = 5.9, 1.9 Hz, 1H), 6.48 – 6.42 (m, 2H), 6.24 – 6.19 (m, 2H), 6.19 – 6.12 (m, 3H), 5.55 (ddd, J = 10.5, 2.2, 2.2 Hz, 1H), 5.47 (ddd, J = 10.2, 2.1, 2.1 Hz, 1H), 3.68 (s, 1H), 3.35 (d, J = 10.1 Hz, 1H), 3.21 (d, J = 10.5 Hz, 1H).



4-((4-iodophenyl)amino)-5-(4-methoxyphenyl)-5-(4-(trifluoromethyl)phenyl)cyclopent-2-en-1-one (402): According to the general procedure $Dy(OTf)_3$ (4.7 mg, 0.00775 mmol, 0.05 equiv)

was added to furan-2-yl(4-methoxyphenyl)(4-(trifluoromethyl)phenyl)methanol (54.0 mg, 0.155 mmol, 1 equiv) and 4-iodoaniline (33.4 mg, 0.155 mmol, 1 equiv) in 1.5 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 1 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **402** (82.5 mg, 97%, 1.5:1 dr) as an oil. **^{1}H NMR (inseparable mixture of diastereomers)** (400 MHz, $CDCl_3$) δ 7.73 (ddd, J = 5.9, 2.4, 1.0 Hz, 3H), 7.46 – 7.40 (m, 3H), 7.40 – 7.34 (m, 2H), 7.34 – 7.24 (m, 7H), 7.14 – 7.08 (m, 3H), 6.90 – 6.85 (m, 3H), 6.85 – 6.74 (m, 4H), 6.48 (dd, J = 5.9, 1.6 Hz, 1H), 6.43 (dd, J = 5.8, 1.5 Hz, 1H), 6.28 – 6.22 (m, 2H), 6.20 – 6.12 (m, 3H), 5.49 (s, 1H), 5.43 (s, 1H), 3.79 (s, 3H), 3.77 (s, 2H).



4-((4-iodophenyl)amino)-5-(4-methoxyphenyl)-5-(4-(trifluoromethyl)phenyl)cyclopent-2-en-1-one (403): According to the general procedure $Dy(OTf)_3$ (7.2 mg, 0.0118 mmol, 0.05 equiv) was added to furan-2-yldiphenylmethanol (59.0 mg, 0.236 mmol, 1 equiv) and aniline (21.5 μL, 0.236 mmol, 1 equiv) in 1.5 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 2 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **403** (72.8 mg, 95%) as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (dd, J = 5.9, 2.3 Hz, 1H), 7.57 – 7.46 (m, 2H), 7.40 – 7.29 (m, 3H), 7.29 – 7.24 (m, 3H), 7.19 – 7.09 (m, 2H), 7.06 – 6.98 (m, 2H), 6.74 (ddd, J =

7.4, 1.0, 1.0 Hz, 1H), 6.53 – 6.43 (m, 3H), 5.59 (ddd, J = 10.0, 2.1, 2.1 Hz, 1H), 3.34 (d, J = 10.0 Hz, 1H).

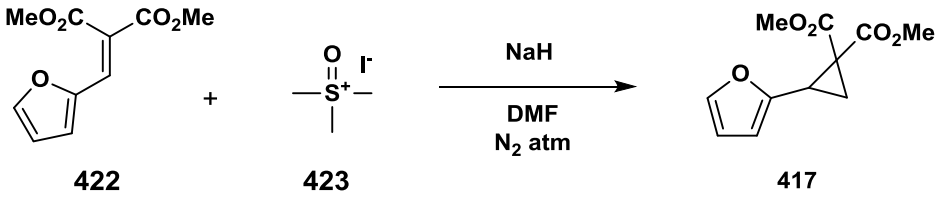
5.2.2 References

[1] Csákÿ, A. G.; Mba, M.; Plumet, J. *Synlett* **2003**, *13*, 2092.
[2] Trost, B. M.; Kunz, R. A. *J. Am. Chem. Soc.* **1975**, *97*, 7152.

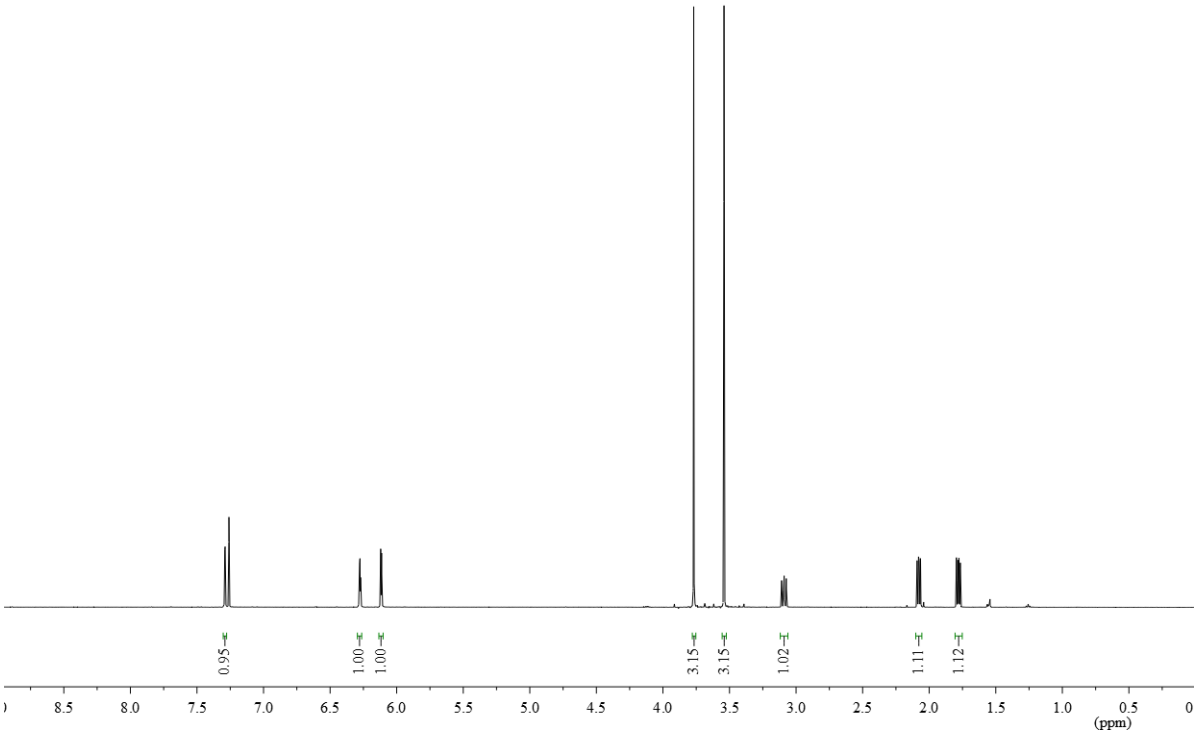
5.3.1 Chapter 3.1

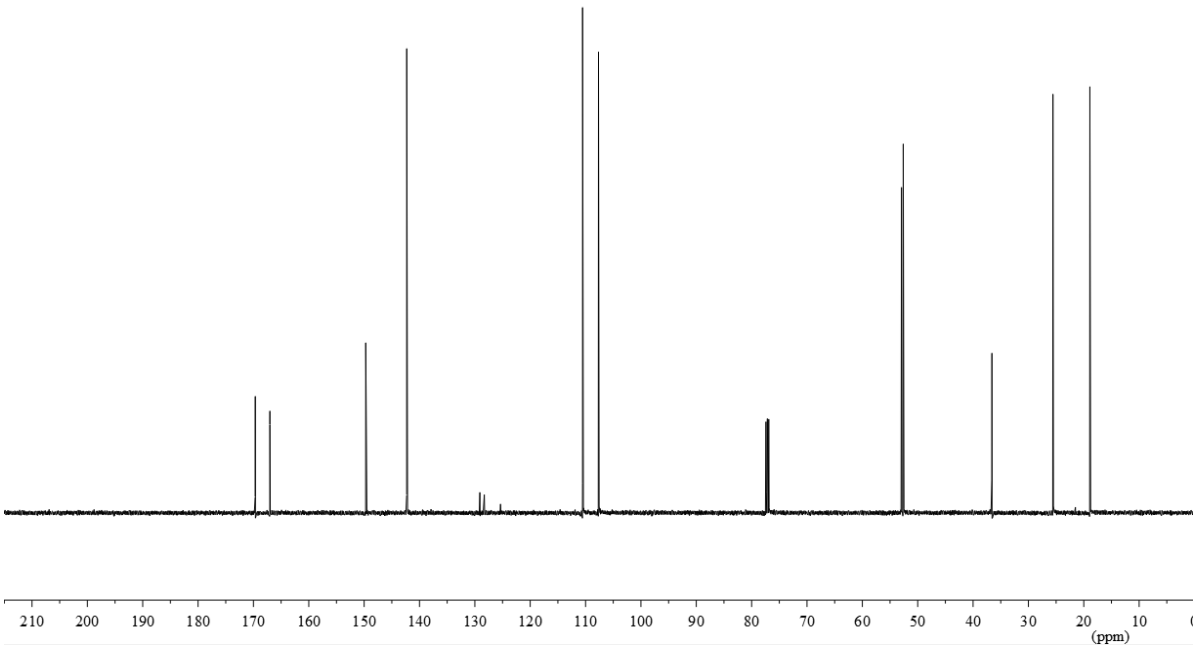
419 420 421

Dimethyl 2-(furan-2-ylmethylene)malonate (421): Prepared according to modified literature procedure.[1] Furan-2-carbaldehyde **419** (1921.6 mg, 20 mmol), dimethyl malonate (2.06 ml, 18 mmol) and ammonium acetate (1541.6 mg, 20 mmol) were added to a 5 ml sealable microwave vial with stir bar and then sealed. The mixture was stirred and heated to 130 ^{o}C for 5 minutes in a Biotage microwave reactor. Upon completion, the mixture was allowed to cool to room temperature. The reaction was quenched H_2O (25 mL) and brine (10 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford dimethyl 2-(furan-2-ylmethylene)malonate **421** (3784 mg, 94%) as a reddish brown oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 (dd, J = 1.8, 0.6 Hz, 1H), 7.38 (s, 1H), 6.68 (dd, J = 3.5, 0.7 Hz, 1H), 6.40 (dd, J = 3.5, 1.8 Hz, 1H), 3.81 (s, 3H), 3.71 (s, 3H)ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.5, 164.3, 148.7, 146.3, 128.0, 121.1, 118.2, 112.6, 52.4, 52.3 ppm; **IR** (thin film) 3585, 3130, 3003, 2955, 2903, 2848, 2046, 1971, 1729, 1634, 1553 cm^{-1}; **HRMS** (ESI) *m/z* 233.0423 (233.0426 calcd for $C_{10}H_{10}NaO_5^+$ $[MNa]^+$).

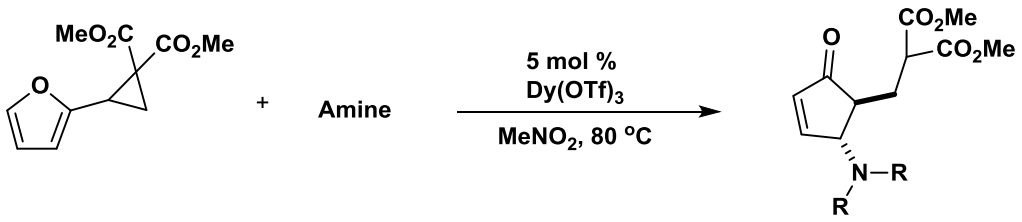


Dimethyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (417): Prepared according to modified literature procedure.[2] A flame dried 100 mL round bottom flask under N_2 atm was charged with anhydrous DMF (25 mL). Trimethyl sulfoxonium iodide (1546 mg, 7.02 mmol) was added followed by addition of NaH (60% dispersion in mineral oil, 281 mg, 7.02 mmol). The reaction was stirred at room temperature for 15 minutes then cooled to 0 ^{o}C. Dimethyl 2-(furan-2-ylmethylene)malonate **422** (1477 mg, 7.02 mmol) was added at 0^{o}C then allowed to warm to room temperature and stirred for 18 hours. The reaction was then quenched at 23 ºC with saturated aqueous NH_4Cl (15 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with H_2O (3x 30 mL), then the organic layer was dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopropane **417** (1052.4 mg, 67%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 (dd, J = 1.9, 0.8 Hz, 1H), 6.28 (dd, J = 3.3, 1.9 Hz, 1H), 6.12 (d, J = 3.3 Hz, 1H), 3.77 (s, 3H), 3.54 (s, 3H), 3.09 (dd, J = 9.4, 7.8 Hz, 1H), 2.08 (dd, J = 7.7, 5.1 Hz, 1H), 1.78 (dd, J = 9.5, 5.1 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 169.7, 167.0, 149.7, 142.3, 110.5, 107.7, 52.9, 52.6, 36.6, 25.6, 18.9 ppm; **IR** (thin film) 3647, 3585, 3152, 3123, 3005, 2956, 2906, 2849, 1733, 1438 cm^{-1}; MS (ESI) *m/z* 247.0593 (247.0583 calcd for $C_{11}H_{12}NaO_5^+$ $[MNa]^+$).


0.95
1.00
1.00
3.15
3.15
1.02
1.11
1.12
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

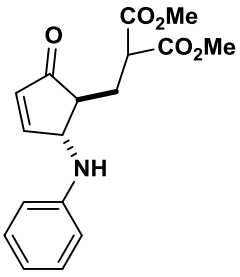

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

General procedure for the rearrangement.



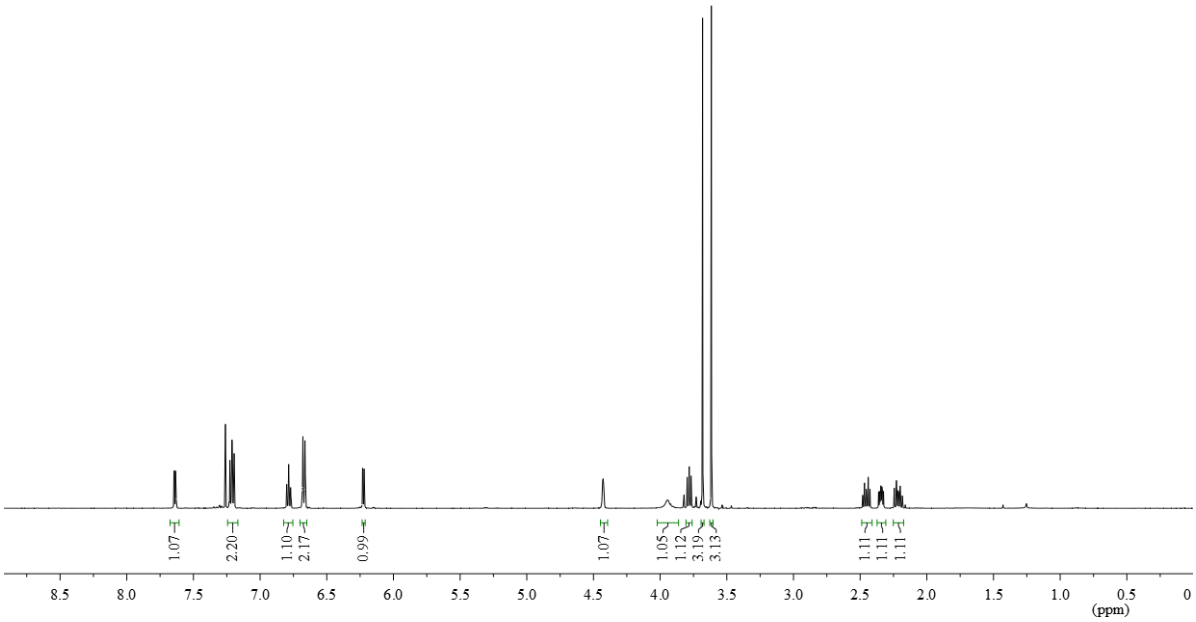
417 434

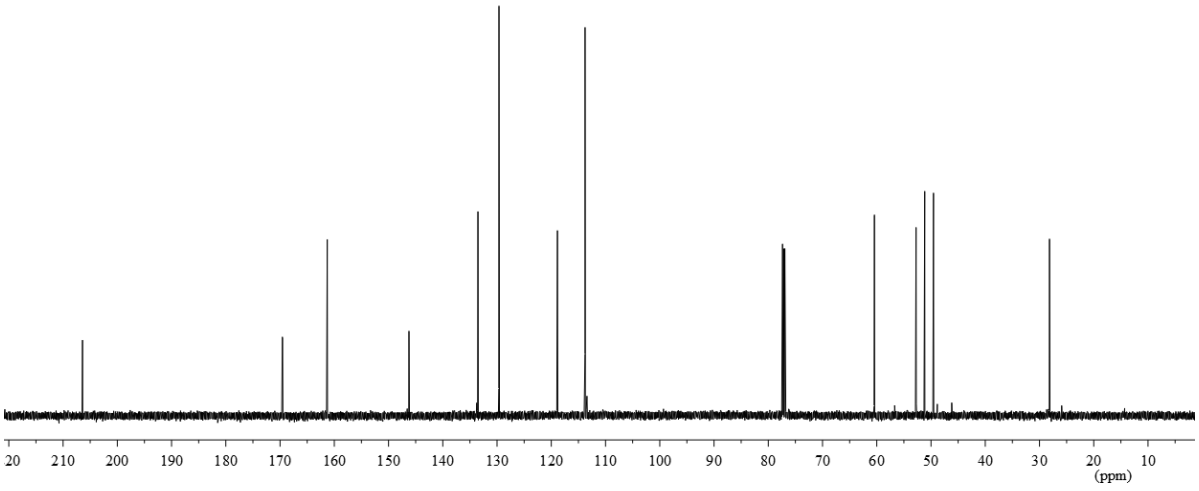
Donor-Acceptor cyclopropane (**417**) and the amine nucleophile were stirred as a solution in nitromethane at 23 ºC. Next, 5 mol % of $Dy(OTf)_3$ was added and the reaction flask was immediately placed in an aluminium heating block pre-heated to 80 ºC. The reaction was monitored by TLC. Upon completion, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and then concentrated in vacuo. The residue was purified by flash column chromatography to afford cyclopentenones (**434**).

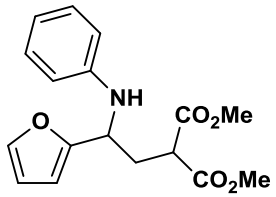


Dimethyl 2-((-2-oxo-5-(phenylamino)cyclopent-3-en-1-yl) methyl)malonate (425): According to the general procedure, dimethyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (50.9 mg, 0.227 mmol) and aniline (21 µL, 0.113 mmol) were treated with $Dy(OTf)_3$ (6.9 mg, 0.0113 mmol , 0.05 equiv) in $MeNO_2$ (2.3 mL). The resulting reaction mixture was heated to 80 ºC for 1 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **425** (55.1 mg, 77%) as a yellow

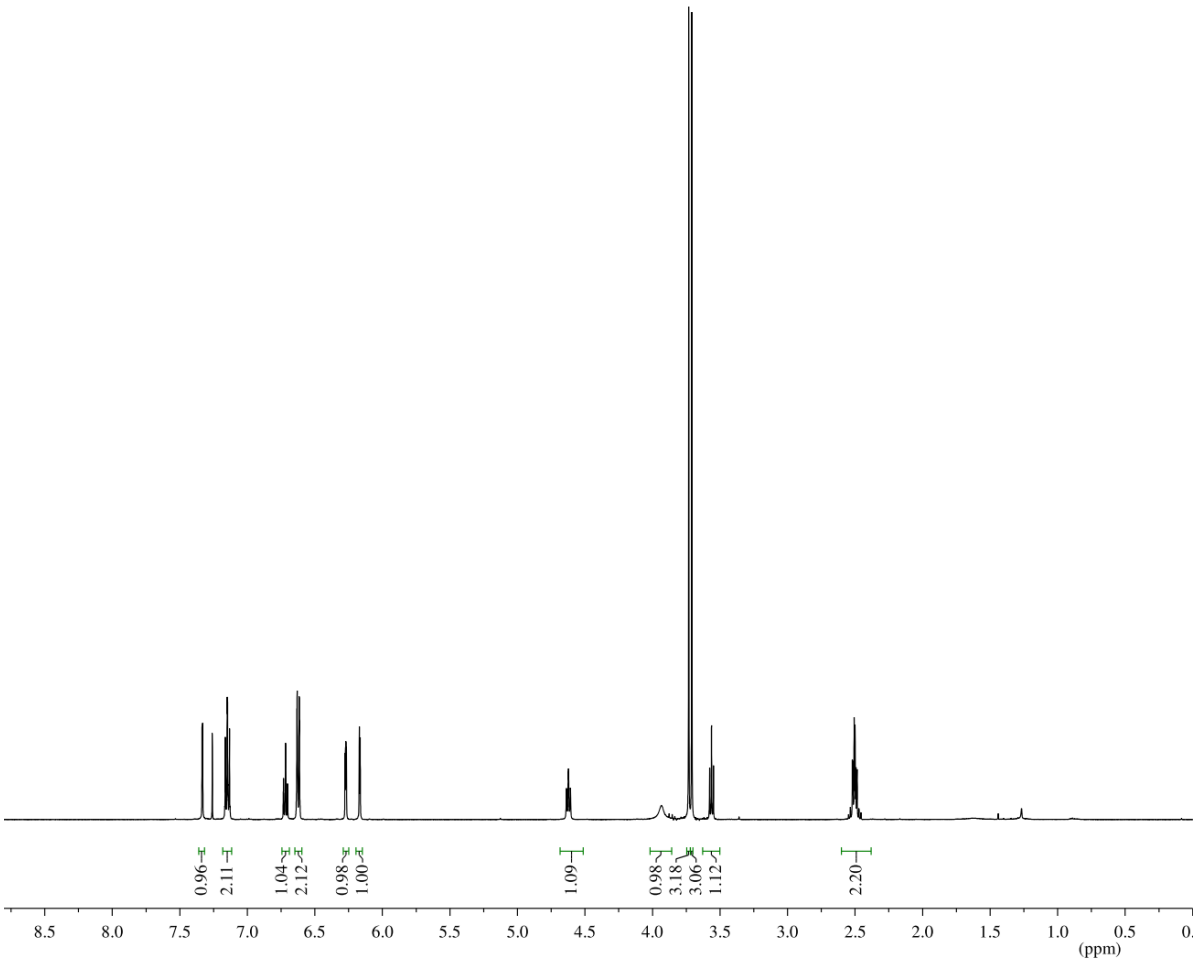
oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 (dd, J = 5.8, 1.9 Hz, 1H), 7.25 – 7.17 (m, 2H), 6.82 – 6.75 (m, 1H), 6.67 (dd, J = 8.7, 1.1 Hz, 2H), 6.22 (dd, J = 5.8, 1.5 Hz, 1H), 4.43 (ddd, J = 3.2, 1.3, 1.3 Hz, 1H), 3.95 (s, 1H), 3.78 (dd, J = 7.7, 6.7 Hz, 1H), 3.68 (s, 3H), 3.62 (s, 3H), 2.45 (ddd, J = 14.0, 6.5, 6.5 Hz, 1H), 2.34 (ddd, J = 8.4, 6.3, 3.7 Hz, 1H), 2.21 (ddd, J = 14.1, 8.1, 8.1 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 206.4, 169.6, 169.5, 161.3, 146.2, 133.5, 129.6, 118.9, 113.8, 60.4, 52.8, 52.8, 51.2, 49.5, 28.2 ppm; **IR** (thin film) 3380, 3055, 3027, 2955, 1931, 1733, 1603 cm^{-1}; **HRMS** (ESI) *m/z* 340.1167 (340.1161 calcd for $C_{17}H_{19}NNaO_5^+$ $[MNa]^+$).

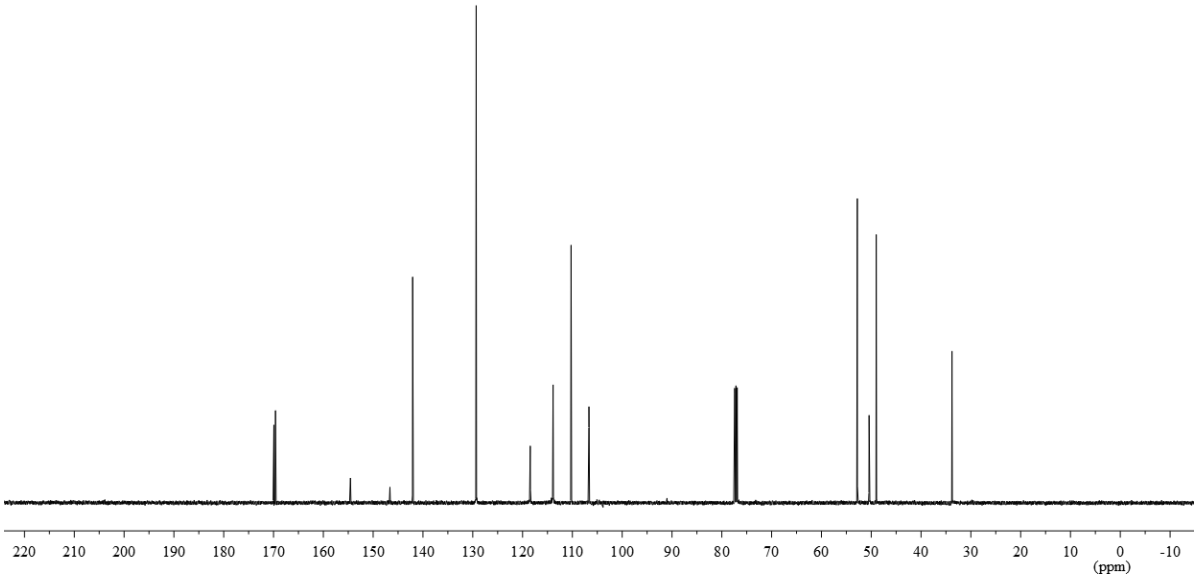


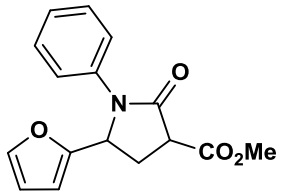




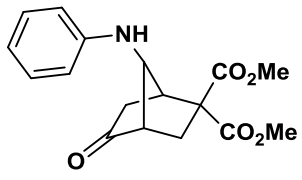
Dimethyl 2-(2-(furan-2-yl)-2-(phenylamino)ethyl)malonate (426): Prepared according to the general procedure, but performed at room temperature and quenched after 10 minutes. Yellow oil, 68.1 mg, 98% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 (dd, J = 1.8, 0.8 Hz, 1H), 7.18 – 7.12 (m, 2H), 6.74 – 6.69 (m, 1H), 6.65 – 6.60 (m, 2H), 6.27 (dd, J = 3.2, 1.8 Hz, 1H), 6.17 (d, J = 3.2 Hz, 1H), 4.62 (dd, J = 7.2, 7.2 Hz, 1H), 3.93 (s, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.56 (dd, J = 7.1, 7.1 Hz, 1H), 2.50 (ddd, J = 7.7, 7.2, 3.3 Hz, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 169.9, 169.6, 154.6, 146.6, 142.1, 129.3, 118.5, 113.9, 110.3, 106.7, 77.4, 52.8, 50.4, 49.0, 33.8 ppm; **IR** (thin film) 3392, 3054, 3024, 2955, 2848, 1750, 1733, 1604 cm^{-1}; **HRMS** (ESI) *m/z* 340.1162 (340.1161 calcd for $C_{17}H_{19}NNaO_5^+$ $[MNa]^+$).


0.96
2.11
1.04
2.12
0.98
1.00
1.09
0.98
3.18
3.06
1.12
2.20
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)



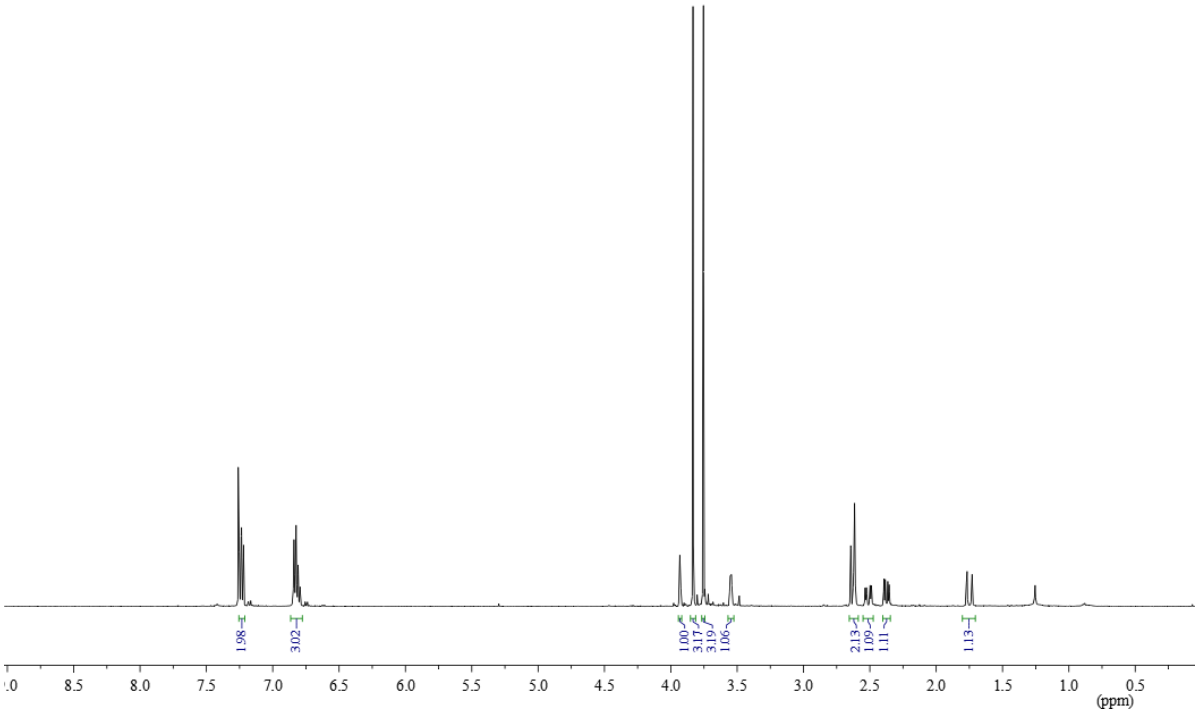


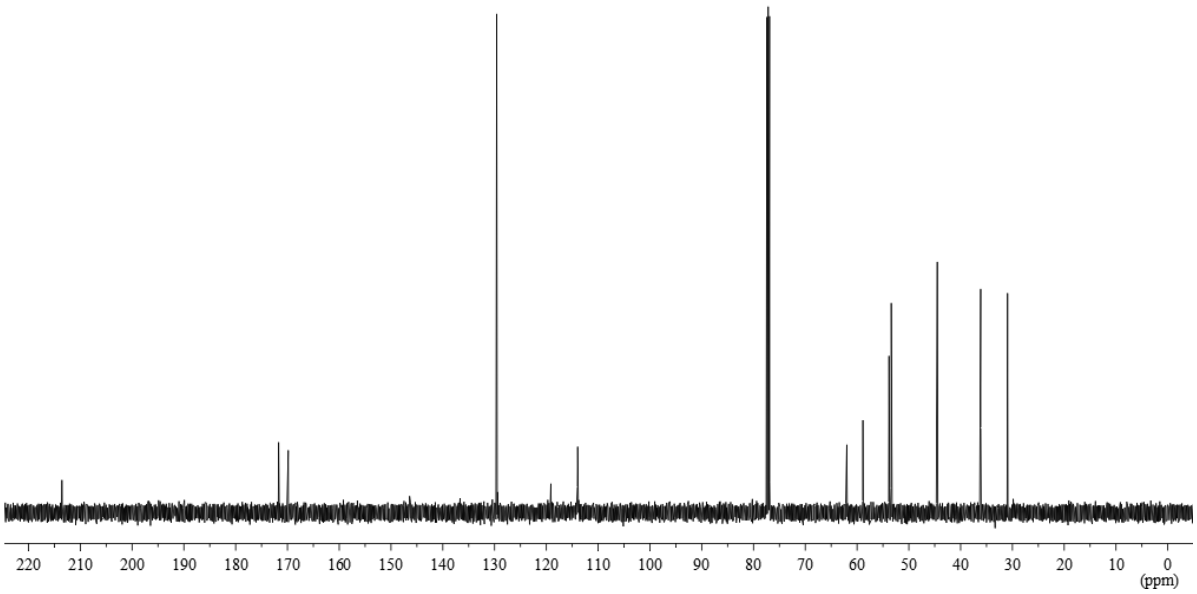
Methyl 5-(furan-2-yl)-2-oxo-1-phenylpyrrolidine-3-carboxylate (427): Prepared according to the general procedure, but performed in toluene or MeOH instead of $MeNO_2$. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.22 (m, 4H), 7.15 (tdd, J = 7.0, 3.2, 1.6 Hz, 1H), 6.25 (dd, J = 3.3, 1.9 Hz, 1H), 6.15 (d, J = 3.3 Hz, 1H), 5.31 (dd, J = 8.2, 3.7 Hz, 1H), 3.92 (t, J = 8.5 Hz, 1H), 3.82 (s, 3H), 2.90 (ddd, J = 12.9, 8.2, 8.2 Hz, 1H), 2.77 (qdd, J = 13.2, 13.2, 13.2 9.2, 7.4 Hz, 1H), 2.50 (ddd, J = 12.7, 8.8, 3.7 Hz, 1H).; **HRMS** (ESI) *m/z* 308.07 (308.08 calcd for $C_{16}H_{15}NNaO_4^+$ $[MNa]^+$).

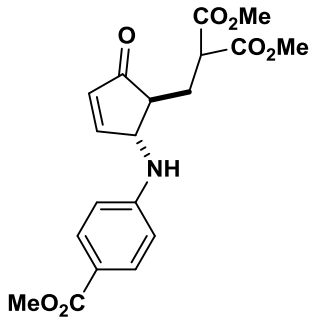


dimethyl 5-oxo-7-(phenylamino)bicyclo[2.2.1]heptane-2,2-dicarboxylate (432): Dimethyl 2-((-2-oxo-5-(phenylamino) cyclopent-3-en-1-yl) methyl)malonate (26.8 mg, 0.0845 mmol)

and 1,8-diazabicycloundec-7-ene (12.6 µL, 0.0145 mmol) were treated with $La(OTf)_3$ (2.5 mg, 0.00423 mmol, 0.05 equiv) in toluene (1 mL). The resulting reaction mixture was heated to 80 ºC for 1 h. The reaction was then quenched with saturated aqueous NH_4Cl (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford bicycle **432** (14.0 mg, 52%) as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26 – 7.21 (m, 2H), 6.86 – 6.78 (m, 3H), 3.93 (ddd, J = 1.9, 1.9, 1.9 Hz, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 3.55 (ddd, J = 4.4, 1.8, 1.8 Hz, 1H), 2.65 – 2.59 (m, 2H), 2.51 (dd, J = 18.7, 5.0 Hz, 1H), 2.37 (dd, J = 14.5, 5.1 Hz, 1H), 1.77 (d, J = 2.2 Hz, 1H).ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 213.6, 171.7, 169.8, 129.6, 119.2, 113.9, 62.0, 58.8, 53.8, 53.4, 53.4, 44.5, 36.1, 30.9 ppm.

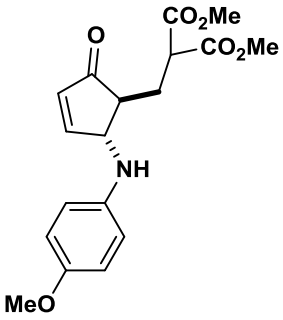




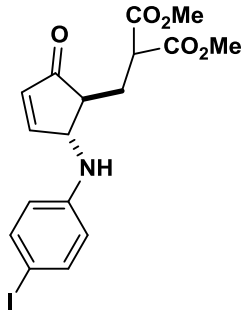


Dimethyl 2-((-2-((4-(methoxycarbonyl)phenyl)amino)-5-oxocyclopent-3-en-1-yl)methyl)malonate (435): According to the general procedure, dimethyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (54.9 mg, 0.245 mmol) and methyl 4-aminobenzoate (37.0 mg, 0.245 mmol) were treated with $Dy(OTf)_3$ (7.5 mg, 0.0123 mmol, 0.05 equiv) in $MeNO_2$ (2.5 mL). The resulting reaction mixture was heated to 80 ºC for 30 min. The reaction was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **435** (62.6 mg, 68%) as a yellow oil. **^{1}H NMR** 1H NMR (500 MHz, $CDCl_3$) δ 7.93 – 7.85 (m, 2H), 7.60 (dd, J = 5.8, 1.9 Hz, 1H), 6.68 – 6.58 (m, 2H), 6.25 (dd, J = 5.8, 1.5 Hz, 1H), 4.57 (d, J = 7.9 Hz, 1H), 4.49 (ddd, J = 7.5, 3.6, 1.7 Hz, 1H), 3.85 (s, 3H), 3.76 (dd, J = 7.6, 6.4 Hz, 1H), 3.65 (s,

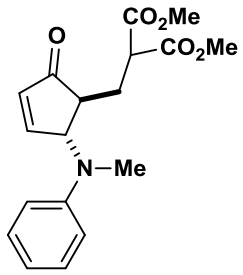
3H), 3.61 (s, 3H), 2.48 – 2.36 (m, 2H), 2.22 (ddd, J = 13.7, 7.9, 7.9 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 205.7, 169.5, 169.4, 167.1, 160.4, 150.2, 133.9, 131.8, 120.0, 112.4, 59.7, 52.9, 52.8, 51.8, 51.0, 49.4, 27.9 ppm; **IR** (thin film) 3531, 3371, 3002, 2955, 2848, 1748, 1709, 1606 cm^{-1}; **HRMS** (ESI) *m/z* 398.1197 (398.1216 calcd for $C_{26}H_{25}NNaO_3^+$ $[MNa]^+$).



Dimethyl 2-((-2-((4-methoxyphenyl)amino)-5-oxocyclopent-3-en-1-yl)methyl)malonate (436): According to the general procedure, dimethyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (56.6 mg, 0.252 mmol) and *p*-anisidine (31.1 mg, 0.252 mmol) were treated with $Dy(OTf)_3$ (7.7 mg, 0.0126 mmol, 0.05 equiv) in $MeNO_2$ (2.5 mL). The resulting reaction mixture was heated to 80 ºC for 4 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **436** (56.4 mg, 64%) as an orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 (dd, J = 5.8, 1.9 Hz, 1H), 6.83 – 6.78 (m, 2H), 6.67 – 6.62 (m, 2H), 6.21 (dd, J = 5.8, 1.5 Hz, 1H), 4.34 (ddd, J = 3.5, 1.7, 1.7 Hz, 1H), 3.78 (dd, J = 7.8, 6.7 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.63 (s, 3H), 2.44 (ddd, J = 14.0, 6.5, 6.5 Hz, 1H), 2.30 (ddd, J = 8.5, 6.2, 3.6 Hz, 1H), 2.20 (ddd, J = 14.0, 8.1, 8.1 Hz, 1H), 1.63 (s, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.7, 169.7, 169.6, 161.5, 153.3, 140.2, 133.5, 115.7, 115.2, 61.8, 55.9, 52.9, 52.8, 51.2, 49.6, 28.3 ppm; **IR** (thin film) 3613, 3364, 3002, 2955, 2837, 1713, 1733, 1514 cm^{-1}; **HRMS** (ESI) *m/z* 370.1257 (370.1257 calcd for $C_{18}H_{21}NNaO_6^+$ $[MNa]^+$).

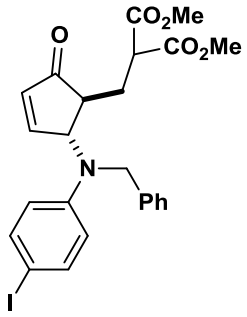


Dimethyl 2-((-2-((4-iodophenyl)amino)-5-oxocyclopent-3-en-1-yl) methyl)malonate (437): According to the general procedure, dimethyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (48.2 mg, 0.215 mmol) and 4-iodoaniline (47.1 mg, 0.215 mmol) were treated with $Dy(OTf)_3$ (6.5 mg, 0.0108 mmol, 0.05 equiv) in $MeNO_2$ (2.2 mL). The resulting reaction mixture was heated to 80 ºC for 1 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **437** (72.0 mg, 76%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.59 (dd, J = 5.8, 1.9 Hz, 1H), 7.49 – 7.42 (m, 2H), 6.49 – 6.42 (m, 2H), 6.23 (dd, J = 5.8, 1.5 Hz, 1H), 4.40 – 4.32 (m, 1H), 4.05 (d, J = 8.2 Hz, 1H), 3.75 (dd, J = 7.7, 6.6 Hz, 1H), 3.67 (s, 3H), 3.63 (s, 3H), 2.43 (ddd, J = 14.1, 6.5, 6.5 Hz, 1H), 2.32 (ddd, J = 8.4, 6.2, 3.7 Hz, 1H), 2.19 (ddd, J = 14.1, 8.1, 8.1 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 206.0, 169.6, 169.5, 160.6, 145.8, 138.3, 133.8, 115.9, 79.8, 60.3, 52.9, 52.8, 51.0, 49.5, 28.1 ppm; **IR** (thin film) 3620, 3381, 3061, 3024, 3005, 2954, 1729, 1589 cm^{-1}; **HRMS** (ESI) *m/z* 466.0121 (466.0128 calcd for $C_{17}H_{18}INNaO_5^+$ $[MNa]^+$).



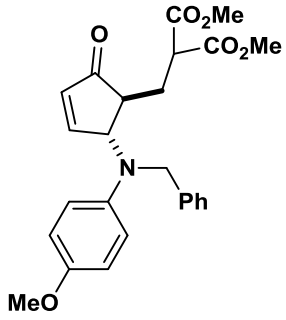
Dimethyl 2-((-2-(methyl(phenyl)amino)-5-oxocyclopent-3-en-1-yl)methyl)malonate (438): According to the general procedure, dimethyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (51.2 mg, 0.228 mmol) and *N*-methylaniline (24.7 μL, 0.228 mmol) were treated with $Dy(OTf)_3$ (6.9 mg, 0.0114 mmol, 0.05 equiv) in $MeNO_2$ (2.3 mL). The resulting

reaction mixture was heated to 80 ºC for 1 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **438** (41.5 mg, 55%) as a yellow wax. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 (dd, J = 5.8, 2.2 Hz, 1H), 7.31 – 7.26 (m, 2H), 6.90 – 6.85 (m, 2H), 6.85 – 6.80 (m, 1H), 6.32 (dd, J = 5.8, 2.0 Hz, 1H), 4.83 (ddd, J = 3.7, 2.1, 2.1 Hz, 1H), 3.73 (dd, J = 7.5, 7.5 Hz, 1H), 3.67 (s, 3H), 3.61 (s, 3H), 2.71 (s, 3H), 2.57 (ddd, J = 7.5, 7.5, 3.4 Hz, 1H), 2.36 (ddd, J = 14.4, 7.3, 7.3 Hz, 1H), 2.12 (ddd, J = 14.2, 7.6, 7.6 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 206.8, 169.6, 169.5, 162.6, 149.4, 135.2, 129.5, 118.9, 114.7, 66.9, 52.7, 52.7, 49.2, 46.8, 32.9, 28.6 ppm; **IR** (thin film) 3635, 3463, 3405, 3004, 2955, 2815, 1751, 1734, 1599, 1505 cm^{-1}; **MS** (ESI) *m/z* 354.1312 (354.1318 calcd for $C_{18}H_{21}NNaO_5^+$ $[MNa]^+$).



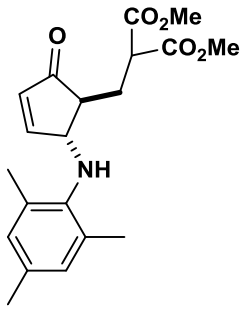
Dimethyl 2-((-2-(benzyl(4-iodophenyl)amino)-5-oxocyclopent-3-en-1-yl)methyl)malonate (439): According to the general procedure, dimethyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (30.2 mg, 0.135 mmol) and N-benzyl-4-iodoaniline (41.6 mg, 0.135 mmol, 0.05 equiv) were treated with $Dy(OTf)_3$ (4.1 mg, 0.00675 mmol) in $MeNO_2$ (1.4 mL). The resulting reaction mixture was stirred at rt for 3 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **439** (63.8 mg, 89%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (dd, J = 5.8, 2.1 Hz,

1H), 7.48 – 7.43 (m, 2H), 7.36 – 7.27 (m, 2H), 7.29 – 7.23 (m, 1H), 7.26 – 7.20 (m, 3H), 6.67 – 6.60 (m, 2H), 6.30 (dd, J = 5.8, 1.8 Hz, 1H), 4.92 (dd, J = 2.4, 2.4 Hz, 1H), 4.37 – 4.25 (m, 2H), 3.86 (dd, J = 7.3, 7.3 Hz, 1H), 3.70 (s, 3H), 3.60 (s, 3H), 2.49 (ddd, J = 7.4, 3.2, 3.2 Hz, 1H), 2.30 (dd, J = 7.3, 7.3 Hz, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.6, 169.5, 169.4, 161.3, 147.7, 138.1, 138.0, 135.7, 128.9, 127.4, 126.5, 117.6, 81.0, 66.4, 52.8, 52.7, 50.9, 49.0, 47.5, 28.9 ppm; **IR** (thin film) 3063, 3031, 3004, 2953, 2850, 1750, 1733, 1710, 1584 cm^{-1}; **HRMS** (ESI) *m/z* 556.0593 (556.0597 calcd for $C_{24}H_{24}INNaO_5^+$ $[MNa]^+$).

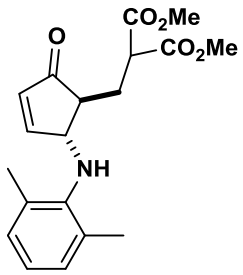


Dimethyl 2-((-2-(benzyl(4-methoxyphenyl)amino)-5-oxocyclopent-3-en-1-yl)methyl)malonate (440): According to the general procedure, dimethyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (38.0 mg, 0.169 mmol) and N-benzyl-4-methoxyaniline (36.2 mg, 0.169 mmol) were treated with $Dy(OTf)_3$ (5.1 mg, 0.00845 mmol, 0.05 equiv) in $MeNO_2$ (1.7 mL). The resulting reaction mixture was stirred at 80 ^oC for 2 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **440** (67.6 mg, 91%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.62 (dd, J = 5.8, 2.1 Hz, 1H), 7.29 (d, J = 4.4 Hz, 4H), 7.25 – 7.18 (m, 1H), 6.93 – 6.84 (m, 2H), 6.81 – 6.74 (m, 2H), 6.22 (dd, J = 5.8, 1.9 Hz, 1H), 4.61 (dd, J = 2.3, 2.3 Hz, 1H), 4.27 (s, 2H), 3.91 (dd, J = 7.3, 7.3 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.64 (s, 3H), 2.45 (ddd, J = 7.4, 7.4, 3.1 Hz, 1H), 2.33 – 2.17 (m, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.4, 169.7, 169.6, 162.5, 154.3, 142.0, 139.1, 134.9, 128.7, 127.3,

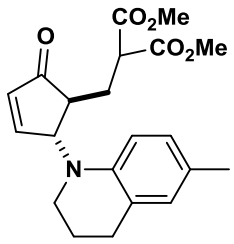
127.2, 120.4, 114.6, 68.5, 55.6, 52.9, 52.7, 52.7, 49.1, 47.0, 29.0 ppm; **IR** (thin film) 3062, 3030, 3003, 2954, 2838, 1751, 1734, 1709, 1512 cm^{-1}; **HRMS** (ESI) *m/z* 460.1740 (460.1735 calcd for $C_{25}H_{27}NNaO_6^+$ $[MNa]^+$).



Dimethyl 2-((-2-(mesitylamino)-5-oxocyclopent-3-en-1-yl)methyl)malonate (441): According to the general procedure, dimethyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (52.7 mg, 0.235 mmol) and 2,4,6-trimethylaniline (33 μL, 0.235 mmol) were treated with $Dy(OTf)_3$ (7.2 mg, 0.0118 mmol, 0.05 equiv) in $MeNO_2$ (2.4 mL). The resulting reaction mixture was heated to 80 ºC for 30 min. The reaction was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **441** (84.9 mg, quantitative yield) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 (dd, J = 5.8, 2.1 Hz, 1H), 6.85 (s, 1H), 6.14 (dd, J = 5.8, 1.5 Hz, 1H), 4.10 – 4.03 (m, 1H), 3.94 (dd, J = 7.0, 7.0 Hz, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 2.95 (s, 1H), 2.37 – 2.27 (m, 2H), 2.25 (s, 7H), 2.24 (s, 3H), 2.20 – 2.09 (m, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.6, 169.7, 169.6, 162.5, 140.7, 133.0, 132.6, 130.1, 129.9, 64.5, 52.7, 52.7, 51.5, 49.0, 28.8, 20.7, 18.9 ppm; **IR** (thin film) 3357, 3000, 2954, 2920, 2860, 1751, 1734, 1710 cm^{-1}; **HRMS** (ESI) *m/z* 382.1639 (382.1631 calcd for $C_{20}H_{25}NNaO_5^+$ $[MNa]^+$).

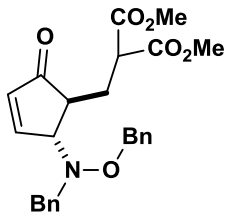


Dimethyl 2-((-2-((2,6-dimethylphenyl)amino)-5-oxocyclopent-3-en-1-yl)methyl)malonate (442): According to the general procedure, dimethyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (49.3 mg, 0.220 mmol) and 2 ,6-dimethylaniline (27 μL, 0.220 mmol , 0.05 equiv) were treated with $Dy(OTf)_3$ (6.7 mg, 0.0110 mmol, 0.05 equiv) in $MeNO_2$ (2.2 mL). The resulting reaction mixture was heated to 80 ºC for 1 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **442** (15 mg, 20%) as a yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.44 (dd, J = 5.9, 2.2 Hz, 1H), 7.04 (d, J = 7.5 Hz, 2H), 6.95 – 6.86 (m, 1H), 6.17 (d, J = 5.7 Hz, 1H), 4.15 (s, 1H), 3.93 (dd, J = 7.4, 7.4 Hz, 1H), 3.72 (d, J = 6.3 Hz, 6H), 2.43 – 2.35 (m, 1H), 2.35 – 2.26 (m, 7H), 2.16 (ddd, J = 14.4, 7.3, 7.3 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.6, 169.8, 169.6, 162.4, 143.4, 133.2, 130.1, 129.3, 123.2, 103.9, 64.3, 52.8, 52.7, 51.7, 49.0, 28.8, 19.1 ppm; **IR** (thin film) 3359, 2954, 2926, 2854, 2280, 1751, 1734, 1710 cm^{-1}; **HRMS** (ESI) *m/z* 368.1468 (368.31474 calcd for $C_{19}H_{23}NNaO_5^+$ $[MNa]^+$).



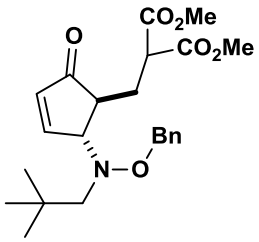
Dimethyl 2-((-2-(6-methyl-3,4-dihydroquinolin-1(2H)-yl)-5-oxocyclopent-3-en-1-yl)methyl)malonate (443): According to the general procedure, dimethyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (48.2 mg, 0.217 mmol) and 6-methyl-1,2,3,4-tetrahydroquinoline (32.0 mg, 0.217 mmol) were treated with $Dy(OTf)_3$ (6.6 mg, 0.0109 mmol, 0.05 equiv) in $MeNO_2$ (2.2 mL). The resulting reaction mixture was stirred at 80 ^oC

for 23 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **443** (26.0 mg, 32%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (dd, J = 5.8, 2.1 Hz, 1H), 6.90 – 6.86 (m, 1H), 6.84 (s, 1H), 6.69 (d, J = 8.3 Hz, 1H), 6.30 (dd, J = 5.8, 2.0 Hz, 1H), 4.84 (ddd, J = 3.0, 1.8, 1.8 Hz, 1H), 3.81 (dd, J = 7.5, 7.5 Hz, 1H), 3.69 (s, 3H), 3.61 (s, 3H), 3.08 (ddd, J = 11.6, 7.8, 4.0 Hz, 1H), 2.97 (ddd, J = 11.1, 7.0, 3.9 Hz, 1H), 2.73 (dd, J = 5.9, 5.9 Hz, 2H), 2.66 (ddd, J = 7.5, 7.5, 3.5 Hz, 1H), 2.42 (ddd, J = 14.3, 7.2, 7.2 Hz, 1H), 2.24 – 2.16 (m, 4H), 1.96 – 1.80 (m, 2H)ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.8, 169.6, 169.5, 163.0, 142.2, 135.1, 130.6, 127.7, 126.9, 124.5, 111.9, 65.3, 52.7, 49.3, 46.5, 43.8, 28.8, 28.1, 22.6, 20.3 ppm; **IR** (thin film) 3067, 3016, 2953, 2845, 1751, 1731, 1710, 1602, 1497 cm^{-1}; **HRMS** (ESI) *m/z* 394.1622 (394.1631 calcd for $C_{21}H_{25}NNaO_5^+$ $[MNa]^+$).



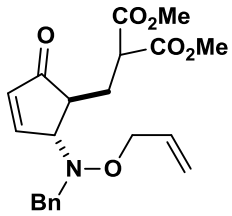
Dimethyl 2-((-2-(benzyl(benzyloxy)amino)-5-oxocyclopent-3-en-1-yl)methyl)malonate (444): According to the general procedure, dimethyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (59.9 mg, 0.249 mmol) and *N,O*-dibenzylhydroxylamine (53.2 mg, 0.249 mmol) were treated with $Dy(OTf)_3$ (15.2 mg, 0.0249 mmol, 0.1 equiv) in $MeNO_2$ (2.5 mL). The resulting reaction mixture was heated to 80 ºC for 24 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **444**

(64.6 mg, 59%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 – 7.54 (m, 1H), 7.47 – 7.40 (m, 2H), 7.40 – 7.30 (m, 3H), 7.30 – 7.18 (m, 3H), 7.15 – 7.03 (m, 2H), 6.21 (dd, J = 5.9, 1.8 Hz, 1H), 4.38 – 4.30 (m, 2H), 4.07 – 3.95 (m, 3H), 3.85 (q, J = 2.4 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 2.64 (ddd, J = 9.5, 6.8, 2.3 Hz, 1H), 2.23 – 2.05 (m, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 208.2, 169.8, 169.7, 160.4, 137.0, 136.6, 135.1, 129.9, 129.1, 128.6, 128.4, 128.2, 127.8, 77.0, 72.1, 60.4, 52.8, 52.7, 49.0, 44.3, 29.4 ppm; **IR** (thin film) 3088, 3064, 3032, 3007, 2954, 2927, 2872, 1750, 1734, 1710 cm^{-1}; **HRMS** (ESI) *m/z* 460.1736 (460.1736 calcd for $C_{25}H_{27}NNaO_6^+$ $[MNa]^+$).

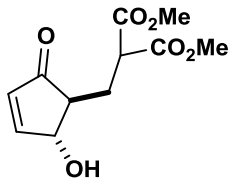


Dimethyl 2-((-2-((benzyloxy)(neopentyl)amino)-5-oxocyclopent-3-en-1-yl)methyl)malonate (445): Prepared According to the general procedure, dimethyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (29.4 mg, 0.131 mmol) and *O*-benzyl-*N*-neopentylhydroxylamine (25.3 mg, 0.131 mmol) were treated with $Dy(OTf)_3$ (8.0 mg, 0.0131 mmol, 0.1 equiv) in $MeNO_2$ (1.3 mL). The resulting reaction mixture was heated to 80 ºC for 24 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **445** (33.4 mg, 61%) as a yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.71 (dd, J = 5.9, 2.2 Hz, 1H), 7.35 – 7.24 (m, 5H), 6.24 (dd, J = 5.9, 1.7 Hz, 1H), 4.74 (d, J = 10.5 Hz, 1H), 4.69 (d, J = 10.5 Hz, 1H), 4.02 (dd, J = 7.3, 7.3 Hz, 1H), 3.99 (dd, J = 2.1, 2.1 Hz, 1H), 3.71 (d, J = 2.2 Hz, 6H), 2.56 (d, J = 14.1 Hz, 1H), 2.43 (d, J = 14.1 Hz, 1H), 2.40 – 2.32 (m, 1H), 2.28 (ddd, J = 14.0, 8.1, 6.9 Hz, 1H), 2.16 (ddd, J = 14.3, 7.4, 7.4 Hz, 1H),

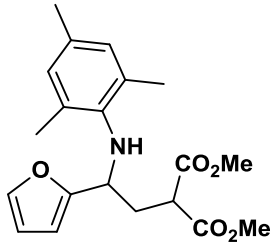
0.96 (s, 9H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 207.9, 169.8, 169.6, 161.0, 136.6, 135.4, 128.6, 128.6, 128.2, 74.9, 73.6, 66.7, 52.8, 52.7, 49.1, 45.1, 31.6, 29.4, 28.6 ppm; **IR** (thin film) 3140, 3033, 2955, 2870, 1753, 1736, 1712 cm^{-1}; **HRMS** (ESI) *m/z* 440.2040 (440.204 calcd for $C_{23}H_{31}NNaO_6^+$ $[MNa]^+$).



Dimethyl 2-((-2-((allyloxy)(benzyl)amino)-5-oxocyclopent-3-en-1-yl)methyl)malonate (446): Prepared According to the general procedure, dimethyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (55.1 mg, 0.246 mmol) and *O*-allyl-*N*-benzylhydroxylamine (40.1 mg, 0.246 mmol) were treated with $Dy(OTf)_3$ (22.5 mg, 0.0368 mmol, 0.15 equiv) in $MeNO_2$ (2.5 mL). The resulting reaction mixture was heated to 80 ºC for 24 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **446** (36.6 mg, 38%) as a yellow oil.**^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68 (dd, J = 5.9, 2.3 Hz, 1H), 7.42 – 7.38 (m, 2H), 7.36 – 7.31 (m, 2H), 7.31 – 7.27 (m, 1H), 6.23 (dd, J = 5.9, 1.7 Hz, 1H), 5.64 (dddd, J = 16.8, 10.4, 6.1, 6.1 Hz, 1H), 5.10 – 5.02 (m, 2H), 4.06 (dd, J = 7.3, 7.3 Hz, 1H), 4.03 – 3.96 (m, 2H), 3.86 (ddd, J = 6.1, 4.0, 1.5 Hz, 2H), 3.84 (dd, J = 2.3, 2.3 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 2.61 (ddd, J = 7.8, 7.8, 2.8 Hz, 1H), 2.17 (dd, J = 7.4, 7.4 Hz, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 208.2, 169.9, 169.7, 160.3, 137.0, 135.1, 133.3, 129.8, 128.5, 127.8, 118.3, 75.9, 72.1, 60.4, 52.8, 52.7, 49.0, 44.5, 29.3 ppm; **IR** (thin film) 3066, 3008, 2954, 2924, 2854, 2924, 2853, 1751, 1735, 1710 cm^{-1}; **HRMS** (ESI) *m/z* 410.1565 (410.1580 calcd for $C_{21}H_{25}NNaO_6^+$ $[MNa]^+$).

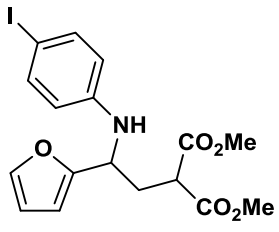


Dimethyl 2-((-2-hydroxy-5-oxocyclopent-3-en-1-yl)methyl)malonate (449): Dimethyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (50.1 mg, 0.223 mmol) was dissolved in 1.8 mL *t*-BuOh and 0.37 mL H_2O (5:1 ratio) followed by addition of $Dy(OTf)_3$ (13.6 mg, 0.0223 mmol, 0.1 equiv) and then TFA (0.1 μL, 0.0112 mmol, 0.05 equiv). The resulting reaction mixture was heated to 80 ºC for 4 days. The reaction was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **449** (6.1 mg, 11%) as an oil.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.52 (dd, J = 5.8, 2.1 Hz, 1H), 6.22 (dd, J = 5.9, 1.4 Hz, 1H), 4.70 (dt, J = 3.4, 1.7 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.74 (d, J = 1.3 Hz, 2H), 2.85 – 2.82 (m, 1H), 2.50 (ddd, J = 14.5, 6.5, 5.0 Hz, 1H), 2.30 – 2.25 (m, 1H), 2.02 (ddd, J = 14.5, 9.2, 7.7 Hz, 1H).



Dimethyl 2-(2-(furan-2-yl)-2-(mesitylamino)ethyl)malonate (E-32): Prepared according to the general procedure, but performed at room temperature and quenched after 10 minutes. Yellow oil, 61.5 mg, quantitative yield. **^{1}H NMR** (600 MHz, Chloroform-d) δ 7.33 – 7.32 (m, 1H), 6.74 (s, 2H), 6.21 (dd, J = 3.2, 1.8 Hz, 1H), 5.87 (d, J = 3.1 Hz, 1H), 4.13 (dd, J = 7.8, 7.8 Hz, 1H), 3.73 (d, J = 1.8 Hz, 6H), 3.65 (dd, J = 8.3, 6.2 Hz, 1H), 2.68 (ddd, J = 14.1, 8.2, 8.2 Hz, 1H), 2.52 (ddd, J = 13.9, 6.9, 6.9 Hz, 1H), 2.19 (s, 3H), 2.04 (s, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 169.9, 169.8, 141.9, 130.4, 129.5, 110.5, 107.3, 53.7, 52.8, 52.8, 49.3, 33.4, 20.7, 18.1 ppm; **IR** (thin film) 3465, 3361, 3118, 2999, 2954, 2920, 2860,

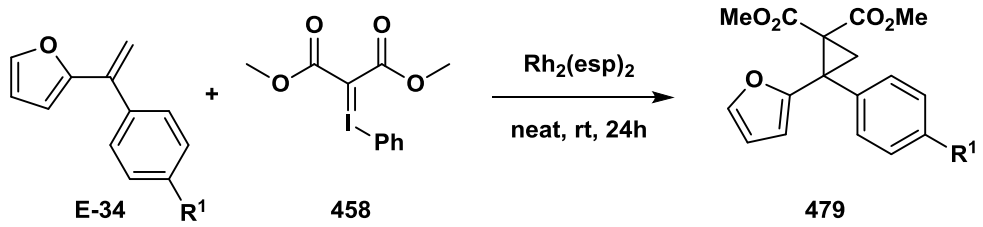
2282, 1752, 1737 cm^{-1}; **HRMS** (ESI) *m/z* 382.1610 (382.1631 calcd for $C_{20}H_{25}NNaO_5^+$ $[MNa]^+$).



Dimethyl 2-(2-(furan-2-yl)-2-((4-iodophenyl)amino)ethyl) malonate (E-33): Prepared according to the general procedure, but performed at room temperature and quenched after 10 minutes. Yellow oil, 54.4 mg, 77% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 2H), 7.33 (dd, J = 1.9, 0.8 Hz, 1H), 6.45 – 6.37 (m, 2H), 6.27 (dd, J = 3.2, 1.8 Hz, 1H), 6.16 (d, J = 3.2 Hz, 1H), 4.56 (dd, J = 7.2, 7.2 Hz, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.51 (dd, J = 7.1, 7.1 Hz, 1H), 2.53 – 2.43 (m, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 169.8, 169.5, 153.9, 146.2, 142.3, 137.9, 116.1, 110.3, 106.9, 79.5, 52.9, 52.9, 50.4, 48.9, 33.6 ppm; **IR** (thin film) 3391, 3149, 3119, 3003, 2953, 2847, 1749, 1733, 1591 cm^{-1}; **HRMS** (ESI) *m/z* 466.0129 (466.0128 calcd for $C_{17}H_{18}INNaO_5^+$ $[MNa]^+$).

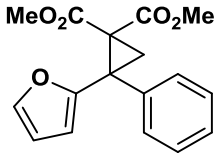
5.3.1 Chapter 3.2

Synthesis of Cyclopropanes: General Procedure A

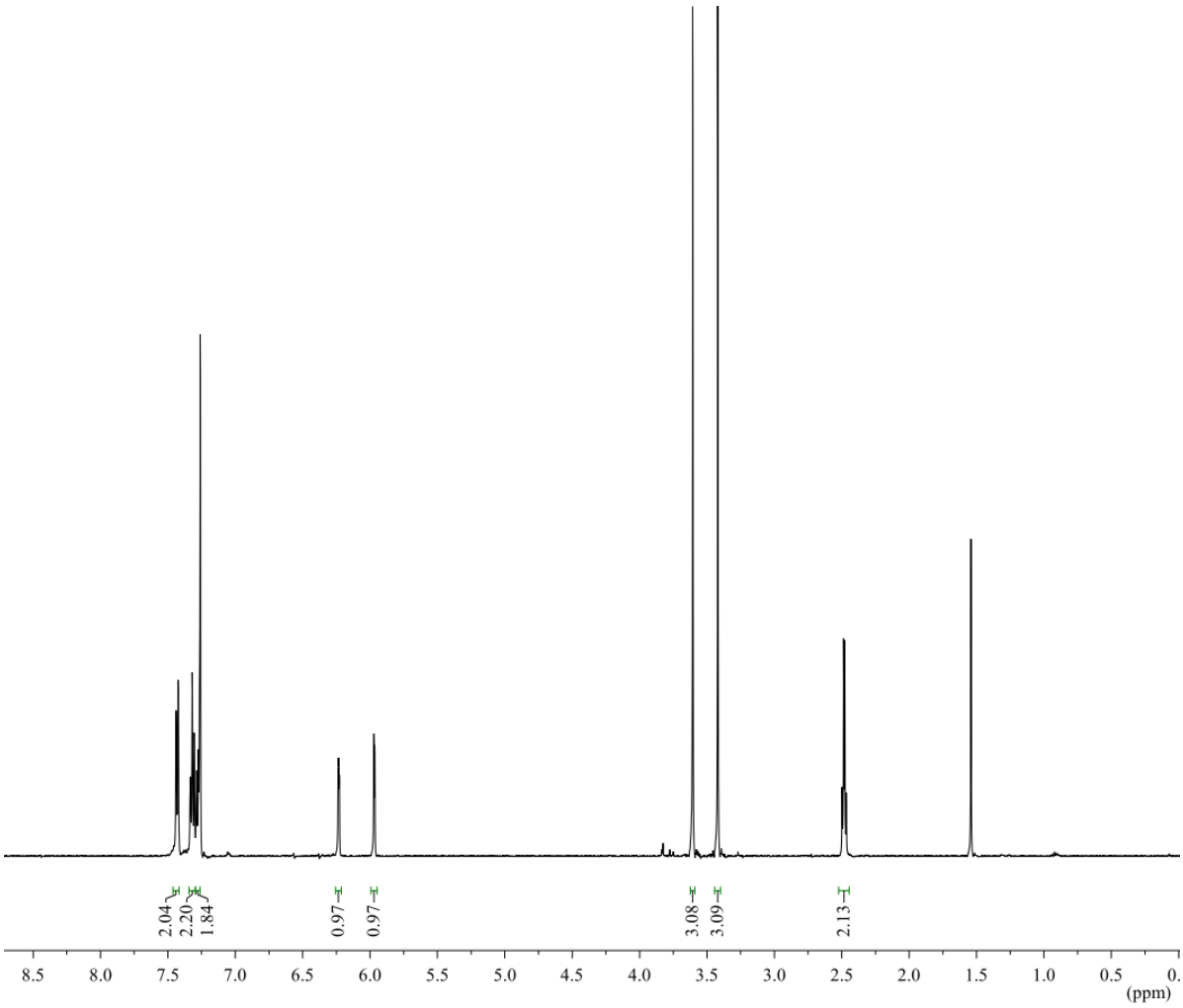


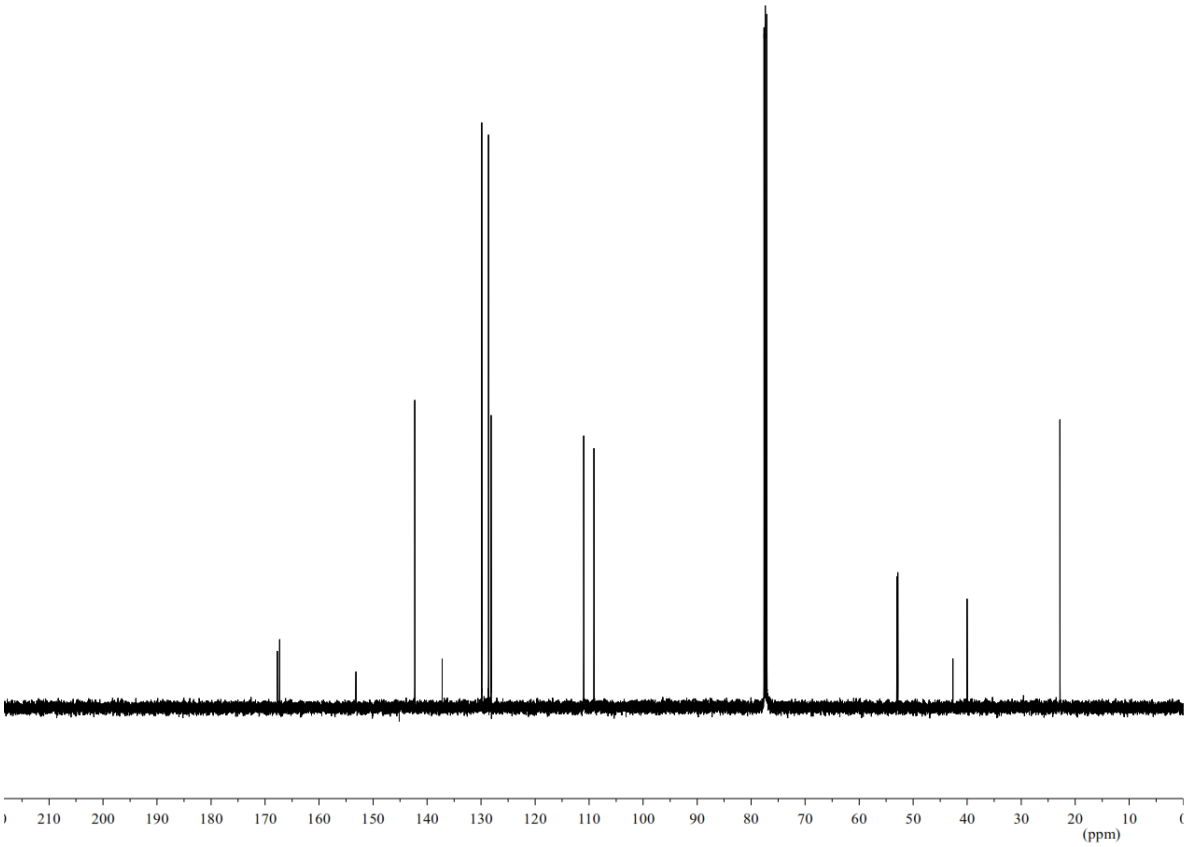
Cyclopropane dicarboxylates (**479**) were prepared using an adapted literature procedure.[3] In a flame dried flask with stirrer under N_2 atmosphere, $Rh_2(esp)_2$ (0.0005 equiv) was added to 2-(1-phenylvinyl)furan (**E-34**) (1 equiv) followed by addition of

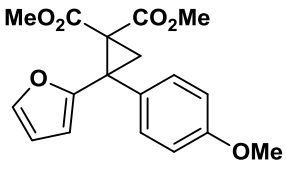
phenyliodonium bis(carbomethoxy)methylide (**458**) (1.2 equiv) and stirred at room temperature for 24 hours. After complete consumption of starting material, as judged by TLC analysis, the reaction was taken up in 10 mL ethyl acetate and washed with saturated aqueous thiourea. Brine was added to break up any resulting emulsion. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). Organic layers were combined, dried over $MgSO_4$, then filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (2% EtOAc/toluene) to give cyclopropane dicarboxylates (**479**).



Dimethyl 2-(furan-2-yl)-2-phenylcyclopropane-1,1-dicarboxylate (459): The title compound was prepared according to General Procedure A using $Rh_2(esp)_2$ (0.0020 g, 0.0029 mmol, 0.0005 equiv), 2-(1-phenylvinyl)furan (1.0 g, 5.8 mmol, 1 equiv), and phenyliodonium bis(carbomethoxy)methylide (2.3 g, 7.0 mmol, 1.2 equiv). After workup, the residue was purified by flash column chromatography (2% EtOAc/toluene) to afford **459** (0.56 g, 32% yield) as a pale yellow waxy solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 – 7.39 (m, 2H), 7.34 – 7.30 (m, 2H), 7.30 – 7.26 (m, 2H), 6.23 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.97 (dd, *J* = 3.3, 0.8 Hz, 1H), 3.61 (s, 3H), 3.42 (s, 3H), 2.48 (dd, *J* = 9.8, 5.6 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.7, 167.3, 153.2, 142.3, 137.2, 129.9, 128.6, 128.1, 111.0, 109.1, 53.0, 52.8, 42.6, 40.0, 22.8; **IR** (thin film, cm^{-1}) 3120, 3030, 2953, 2846, 1739, 1119; **HRMS** (ESI) *m/z* 323.0893 (323.0896 calcd for $C_{17}H_{16}NNaO_5^+$ $[MNa]^+$).

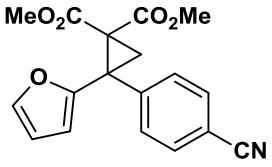

2.04
2.20
1.84
0.97
0.97
3.08
3.09
2.13
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)



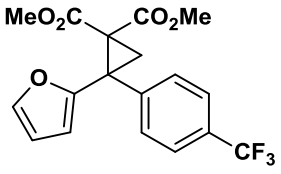


Dimethyl 2-(furan-2-yl)-2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (460). The title compound was prepared according to General Procedure A using $Rh_2(esp)_2$ (0.0030 g, 0.0037 mmol, 0.0005 equiv), 2-(1-(4-methoxyphenyl)vinyl)furan (1.5 g, 5.8 mmol, 1 equiv), and phenyliodonium bis(carbomethoxy)methylide (3.0 g, 9.0 mmol, 1.2 equiv). After workup, the residue was purified by flash column chromatography (2% EtOAc/toluene) to afford **460** (0.76 g, 31% yield) as a pale yellow waxy solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 2H), 7.26 – 7.25 (m, 1H), 6.86 – 6.82 (m, 2H), 6.23 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.96 (d, *J* = 3.2 Hz, 1H), 3.79 (s, 3H), 3.60 (s, 3H), 3.46 (s, 3H), 2.45 (dd, *J* = 5.5 Hz, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 167.8, 167.4, 159.4, 153.5, 142.2, 131.0, 129.2, 114.0, 111.0, 108.9,

55.5, 53.0, 52.9, 42.7, 39.4, 23.0; **IR** (thin film, cm^{-1}) 3993, 2954, 2925, 2849, 1734, 1247; **HRMS** (ESI) *m/z* 353.0997 (353.1001 calcd for $C_{18}H_{18}NaO_6^+$ $[MNa]^+$).

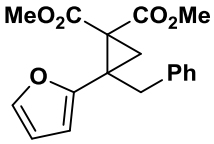


Dimethyl 2-(4-cyanophenyl)-2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (461). The title compound was prepared according to General Procedure A using $Rh_2(esp)_2$ (0.0040 g, 0.0050 mmol, 0.0005 equiv), 4-(1-(furan-2-yl)vinyl)benzonitrile (1.9 g, 9.9 mmol, 1 equiv), and phenyliodonium bis(carbomethoxy)methylide (4.3 g, 13 mmol, 1.3 equiv). After workup, the residue was purified by flash column chromatography (2% EtOAc/toluene) to afford **461** (0.536 g, 17% yield) as a pale yellow waxy solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.1 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.28 (s, 1H), 6.25 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.97 (d, *J* = 3.3 Hz, 1H), 3.60 (s, 3H), 3.48 (s, 3H), 2.47 (dd, *J* = 62.5, 5.8 Hz, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.8, 166.7, 151.2, 142.6, 142.1, 132.1, 130.4, 118.5, 111.7, 110.7, 109.0, 52.8, 52.8, 42.2, 39.1, 22.6; **IR** (thin film, cm^{-1}) 3005, 2955, 2850, 2230, 1738, 1251; **HRMS** (ESI) *m/z* 348.0841 (348.0848 calcd for $C_{18}H_{15}NNaO_5^+$ $[MNa]^+$).

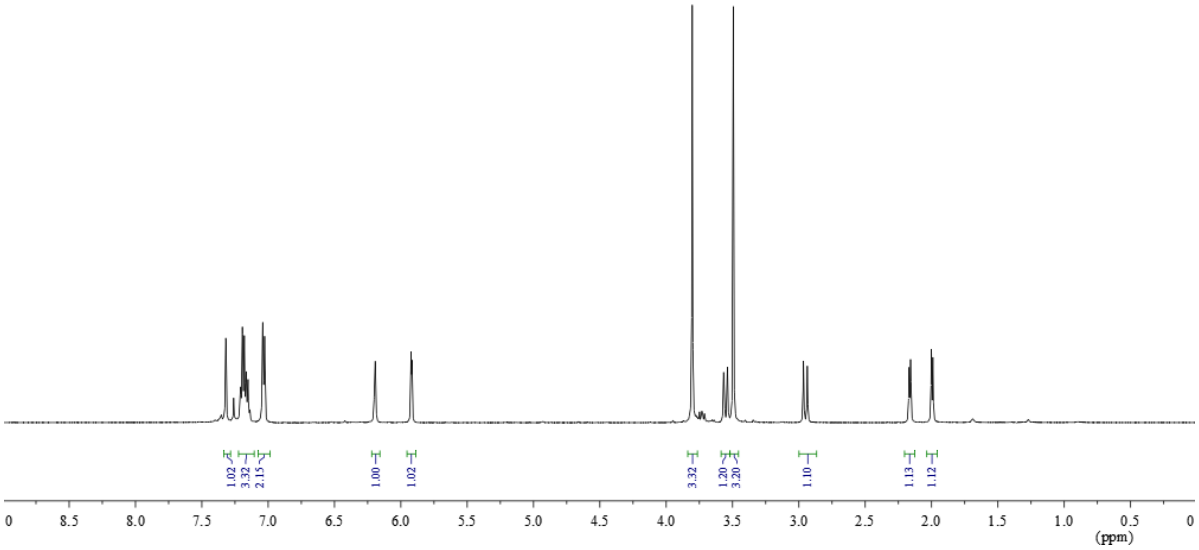


Dimethyl 2-(furan-2-yl)-2-(4(trifluoromethyl)phenyl) cyclopropane-1,1-dicarboxylate (462). The title compound was prepared according to General Procedure A using $Rh_2(esp)_2$ (0.0010 g, 0.0018 mmol, 0.0005 equiv), 2-(1-(4-(trifluoromethyl)phenyl)vinyl)furan (0.87 g, 3.7 mmol, 1 equiv), and phenyliodonium bis(carbomethoxy)methylide (1.5 g, 4.4 mmol, 1.2 equiv). After workup, the residue was purified by flash column chromatography (2% EtOAc/toluene) to afford **462** (0.298 g, 22% yield) as a pale yellow waxy solid. **^{1}H NMR**

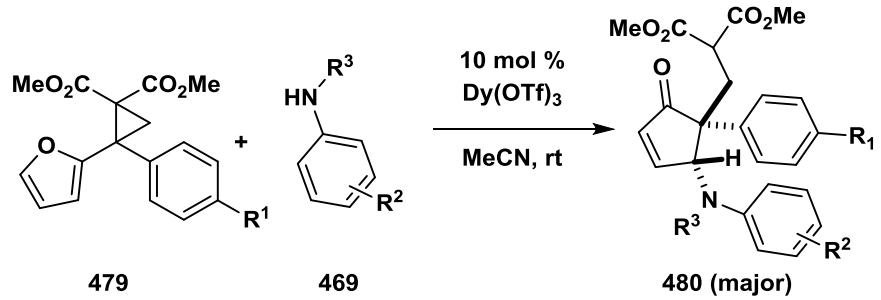
(600 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.4 Hz, 4H), 7.28 (d, *J* = 0.9 Hz, 1H), 6.24 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.99 – 5.96 (m, 1H), 3.61 (s, 3H), 3.46 (s, 3H), 2.49 (dd, *J* = 42.9, 5.7 Hz, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 167.3, 167.2, 152.1, 142.7, 141.2, 141.2, 130.3, 125.6 (q, *J* = 3.8 Hz), 124.3 (q, *J*= 272 Hz), 111.1, 109.3, 53.1, 53.0, 42.6, 39.5, 22.9; **IR** (thin film, cm^{-1}) 3005, 2956, 2850, 1739, 1438, 1327; **HRMS** (ESI) *m/z* 391.0776 (391.0770 calcd for $C_{18}H_{15}F_3NaO_5^+$ $[MNa]^+$).



Dimethyl 2-benzyl-2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (**E-35**)**.** The title compound was prepared according to General Procedure A using $Rh_2(esp)_2$ (1.2 mg, 0.00159 mmol, 0.0005 equiv), 2-(3-phenylprop-1-en-2-yl)furan (587.9 mg, 3.19 mmol, 1 equiv), and phenyliodonium bis(carbomethoxy)methylide (1279 mg, 3.82 mmol, 1.2 equiv). After workup, the residue was purified by flash column chromatography (2% EtOAc/toluene) to afford **E-35** (131.3 mg, 13% yield) as a pale yellow waxy solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 (d, J = 2.0 Hz, 1H), 7.22 – 7.11 (m, 3H), 7.08 – 6.98 (m, 2H), 6.19 (dd, J = 3.4, 1.9 Hz, 1H), 5.92 (d, J = 3.3 Hz, 1H), 3.80 (s, 3H), 3.55 (d, J = 14.5 Hz, 1H), 3.49 (s, 3H), 2.95 (d, J = 14.4 Hz, 1H), 2.16 (d, J = 5.6 Hz, 1H), 2.00 (d, J = 5.7 Hz, 1H) ppm.



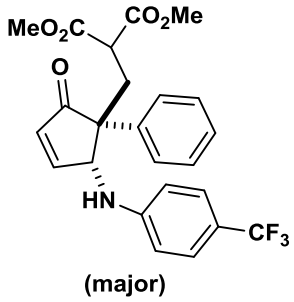
Experimental Procedures



Rearrangement Reaction, General Procedure B: Dimethyl 2-(furan-2-yl)-2-phenylcyclopropane-1,1-dicarboxylate (**479**) (1 equiv) and aniline (**469**) (1 equiv) were dissolved in anhydrous MeCN. To the reaction mixture at room temperature was added 10 mol % of hydrated $Dy(OTf)_3$ ($Dy(OTf)_3$ had been left open to air for >24 h). The reaction mixture was left to stir open to air while being monitored by TLC (3:1 hexanes:ethyl acetate, staining with anisaldehyde). Upon completion, the reaction was quenched with water (5 ml)

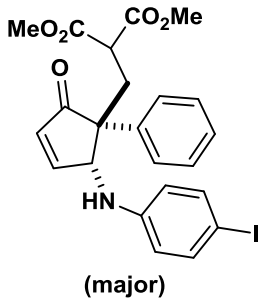
and saturated aqueous NaCl (2 ml), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, then concentrated in *vacuo*. The residue was purified by column chromatography (9:1 → 6:1 → 3:1 hexanes/EtOAc) to afford 4-amino cyclopentenones (**480**). Yields and diastereomeric ratios are an average of 2-3 runs and were determined by ^{1}H NMR spectroscopy using dimethyl terephthalate as the internal standard. T_1 relaxation time set at 40 seconds.

Water plays a significant role in the selectivity of the rearrangement. Initial studies of the rearrangement conducted with commercially available $Dy(OTf)_3$, as received from Strem, gave irreproducible diastereoselectivities. We found that using commercially available $Dy(OTf)_3$ that had been left open to air for greater than 24 hours gave the most reproducible results and highest diastereoselectivities.



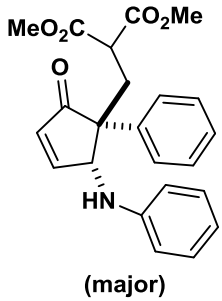
Dimethyl 2-((2-oxo-1-phenyl-5-((4-(trifluoromethyl) phenyl)amino)cyclopent-3-en-1-yl)methyl)malonate (**472**): According to General Procedure B, $Dy(OTf)_3$ (7.2 mg, 0.012 mmol, 0.1 equiv) was added to dimethyl 2-(furan-2-yl)-2-phenylcyclopropane-1,1-dicarboxylate (36 mg, 0.12 mmol, 1 equiv) and 4-(trifluoromethyl)aniline (15 µL, 0.12 mmol, 1 equiv) in 3 mL anhydrous MeCN. The resulting mixture was stirred at room temperature for 30 minutes. The reaction was quenched with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, then concentrated *in vacuo* (72% yield; 60:1 dr as determined by ^{1}H NMR of the crude reaction mixture). The residue was purified by column chromatography to afford

cyclopentenone **472** as a pale yellow solid. Analytical data for major diastereomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 5.8, 2.3 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.30 – 7.24 (m, 3H), 7.12 – 7.06 (m, 2H), 6.46 – 6.39 (m, 3H), 4.82 (ddd, *J* = 10.0, 2.0, 2.0 Hz, 1H), 3.75 (s, 3H), 3.64 (dd, *J* = 6.7, 4.2 Hz, 1H), 3.57 (s, 3H), 3.37 (d, *J* = 10.2 Hz, 1H), 3.01 (dd, *J* = 14.9, 4.2 Hz, 1H), 2.81 (dd, *J* = 15.0, 6.7 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 209.2, 170.3, 170.1, 161.0, 148.9, 148.9, 136.9, 135.1, 129.0, 128.2, 127.1 (q, J = 4 Hz), 125.0 (q, J = 271 Hz), 120.4 (q, J = 33 Hz), 112.8, 64.1, 59.3, 53.1, 48.2, 35.3; **IR** (thin film, cm^{-1}) 3389, 2957, 1733, 1709, 1615, 1532; **HRMS** (ESI) *m/z* 484.1326 (484.1348 calcd for $C_{24}H_{22}F_3NNaO_5^+$ $[MNa]^+$).



Dimethyl 2-((-2-((4-iodophenyl)amino)-5-oxo-1-phenylcyclopent-3-en-1-yl)methyl)malonate (**473**): According to General Procedure B, $Dy(OTf)_3$ (8.2 mg, 0.014 mmol, 0.1 equiv) was added to dimethyl 2-(furan-2-yl)-2-phenylcyclopropane-1,1-dicarboxylate (41 mg, 0.14 mmol, 1 equiv) and 4-iodoaniline (30 mg, 0.14 mmol, 1 equiv) in 4 mL anhydrous MeCN. The resulting mixture was stirred at room temperature for 30 minutes. The reaction was quenched with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, then concentrated *in vacuo* (82% yield; 28:1 dr as determined by ^{1}H NMR of the crude reaction mixture). The residue was purified by column chromatography to afford cyclopentenone **473** as a yellow waxy solid. Analytical data for major diastereomer: **^{1}H NMR** ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 5.9, 2.3 Hz, 1H), 7.36 (d, *J* = 8.6 Hz, 2H), 7.30 – 7.23 (m, 3H), 7.08 (dd, *J* = 7.5, 1.8 Hz, 2H), 6.42 (dd, *J* = 5.9, 1.8 Hz, 1H), 6.18

(d, J = 8.5 Hz, 2H), 4.72 (d, J = 9.9 Hz, 1H), 3.74 (s, 3H), 3.64 (dd, J = 6.8, 4.1 Hz, 1H), 3.57 (s, 3H), 3.09 (d, J = 10.2 Hz, 1H), 2.99 (dd, J = 14.9, 4.2 Hz, 1H), 2.79 (dd, J = 15.0, 6.7 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 209.4, 170.4, 170.2, 161.49, 146.0, 138.3, 137.0, 134.8, 129.0, 129.0, 128.1, 115.9, 79.5, 64.4, 59.3, 53.2, 53.1, 48.2, 35.3; **IR** (thin film, cm^{-1}) 3392, 2951, 1748, 1732, 1707, 1589, 1495; **HRMS** (ESI) *m/z* 542.0445 (542.0441 calcd for $C_{23}H_{22}INNaO_5^+$ $[MNa]^+$).

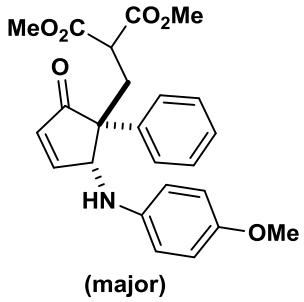


(major)

Dimethyl 2-((-2-oxo-1-phenyl-5-(phenylamino)cyclopent-3-en-1-yl)methyl)malonate (474): Reaction Performed at room temperature: According to General Procedure B, $Dy(OTf)_3$ (7.4 mg, 0.012 mmol, 0.1 equiv) was added to dimethyl 2-(furan-2-yl)-2-phenylcyclopropane-1,1-dicarboxylate (37 mg, 0.12 mmol, 1 equiv) and aniline (11 μL, 0.12 mmol, 1 equiv) in 3 mL anhydrous MeCN. The resulting mixture was stirred at room temperature for 30 minutes. The reaction was quenched with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, then concentrated *in vacuo* (89% yield; 13:1 dr as determined by ^{1}H NMR of the crude reaction mixture). The residue was purified by column chromatography to afford cyclopentenone **474** as a yellow oil:

Reaction performed at 80 ^{o}C: Dimethyl 2-(furan-2-yl)-2-phenylcyclopropane-1,1-dicarboxylate (25 mg, 0.083 mmol, 1 equiv) and aniline (7.6 μL, 0.083 mmol, 1 equiv) were dissolved in 2 mL anhydrous MeCN then placed in an oil bath at 80 ^{o}C for 2 minutes. Next, $Dy(OTf)_3$ (5.1 mg, 0.0083 mmol, 0.01 equiv) was added to the reaction mixture and stirred at 80 ^{o}C for 90 seconds, then quickly removed and quenched with H_2O (5 mL). The

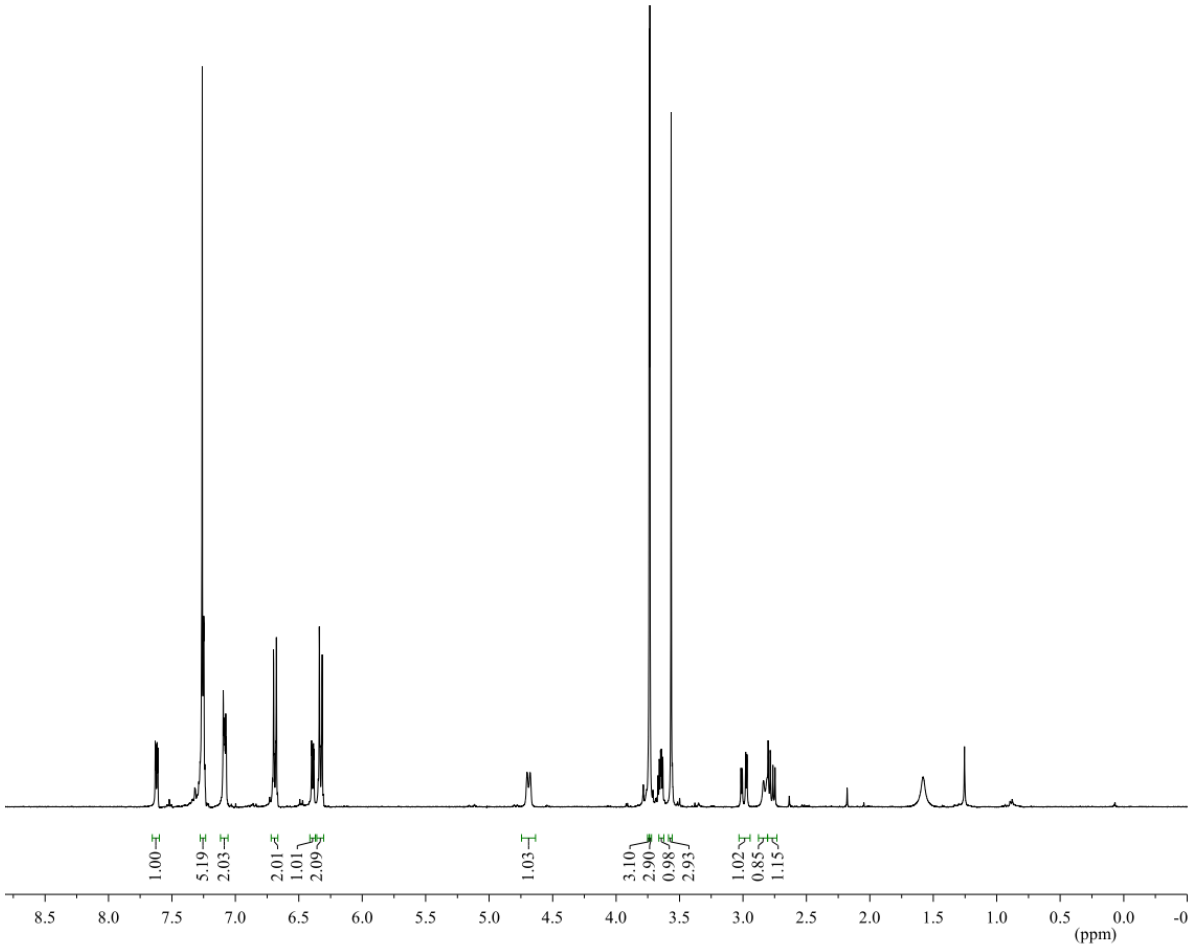
reaction mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* (87% yield; 30:1 dr as determined by ^{1}H NMR of the crude reaction mixture). The residue was purified by column chromatography to afford cyclopentenone **474** as a yellow oil. Analytical data for major diastereomer: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 5.9, 2.2 Hz, 1H), 7.29 – 7.22 (m, 3H), 7.15 – 7.07 (m, 4H), 6.70 (t, *J* = 7.2 Hz, 1H), 6.42 – 6.37 (m, 3H), 4.78 (t, *J* = 2.0 Hz, 1H), 3.74 (s, 3H), 3.65 (dd, *J* = 6.6, 4.3 Hz, 1H), 3.55 (s, 3H), 3.01 (dd, *J* = 14.9, 4.3 Hz, 1H), 2.80 (dd, *J* = 15.0, 6.7 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 209.7, 170.4, 170.2, 162.2, 146.2, 137.1, 134.5, 129.7, 129.1, 128.8, 128.0, 118.8, 113.7, 64.5, 59.3, 53.1, 53.1, 48.2, 35.3; **IR** (thin film, cm^{-1}) 3397, 2953, 1750, 1733, 1707, 1602; **HRMS** (ESI) *m/z* 416.1471 (416.1474 calcd for $C_{23}H_{23}NNaO_5^+$ $[MNa]^+$).



Dimethyl 2-((-2-((4-methoxyphenyl)amino)-5-oxo-1-phenylcyclopent-3-en-1-yl)methyl)malonate (464): Reaction performed at room temperature: According to General Procedure B, $Dy(OTf)_3$ (6.5 mg, 0.011 mmol, 0.1 equiv) was added to dimethyl 2-(furan-2-yl)-2-phenylcyclopropane-1,1-dicarboxylate (32 mg, 0.11 mmol, 1 equiv) and *p*-anisidine (13 mg, 0.11 mmol, 1 equiv) in 3 mL anhydrous MeCN. The resulting mixture was stirred at room temperature for 30 minutes. The reaction was quenched with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, then concentrated *in vacuo* (57% yield; 6:1 dr as determined by ^{1}H NMR of

the crude reaction mixture). The residue was purified by column chromatography to afford cyclopentenone **464** as a yellow oil.

Reaction performed at 80 ^{o}C: Dimethyl 2-(furan-2-yl)-2-phenylcyclopropane-1,1-dicarboxylate (26 mg, 0.087 mmol, 1 equiv) and *p*-anisidine (11 mg, 0.087 mmol, 1 equiv) were dissolved in 2 mL anhydrous MeCN then placed in an oil bath at 80 ^{o}C for 2 minutes. Next, $Dy(OTf)_3$ (5.3 mg, 0.0087 mmol, 0.1 equiv) was added to the reaction mixture and stirred at 80 ^{o}C for 90 seconds, then quickly removed and quenched with H_2O (5 mL). The reaction mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* (82% yield; 16:1 dr as determined by ^{1}H NMR of the crude reaction mixture). The residue was purified by column chromatography to afford cyclopentenone **464** as a yellow oil. Analytical data for major diastereomer: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 5.8, 2.2 Hz, 1H), 7.27 – 7.24 (m, 3H), 7.16 – 6.96 (m, 2H), 6.78 – 6.60 (m, 2H), 6.39 (dd, *J* = 5.8, 1.8 Hz, 1H), 6.42 – 6.25 (m, 2H), 4.69 (d, *J* = 9.5 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.65 (dd, *J* = 6.7, 4.1 Hz, 1H), 3.57 (s, 3H), 2.99 (dd, *J* = 14.9, 4.2 Hz, 1H), 2.87 – 2.81 (m, 1H), 2.77 (dd, *J* = 15.0, 6.8 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 209.9, 170.5, 170.2, 162.6, 153.0, 140.3, 137.3, 134.4, 129.1, 128.8, 128.0, 115.2, 115.2, 65.8, 59.4, 56.1, 53.1, 53.1, 48.3, 35.3; **IR** (thin film, cm^{-1}) 3392, 2953, 2923, 1750, 1733, 1706, 1512; **HRMS** (ESI) *m/z* 446.1566 (446.1580 calcd for $C_{24}H_{25}NNaO_6^{+}$ $[MNa]^{+}$).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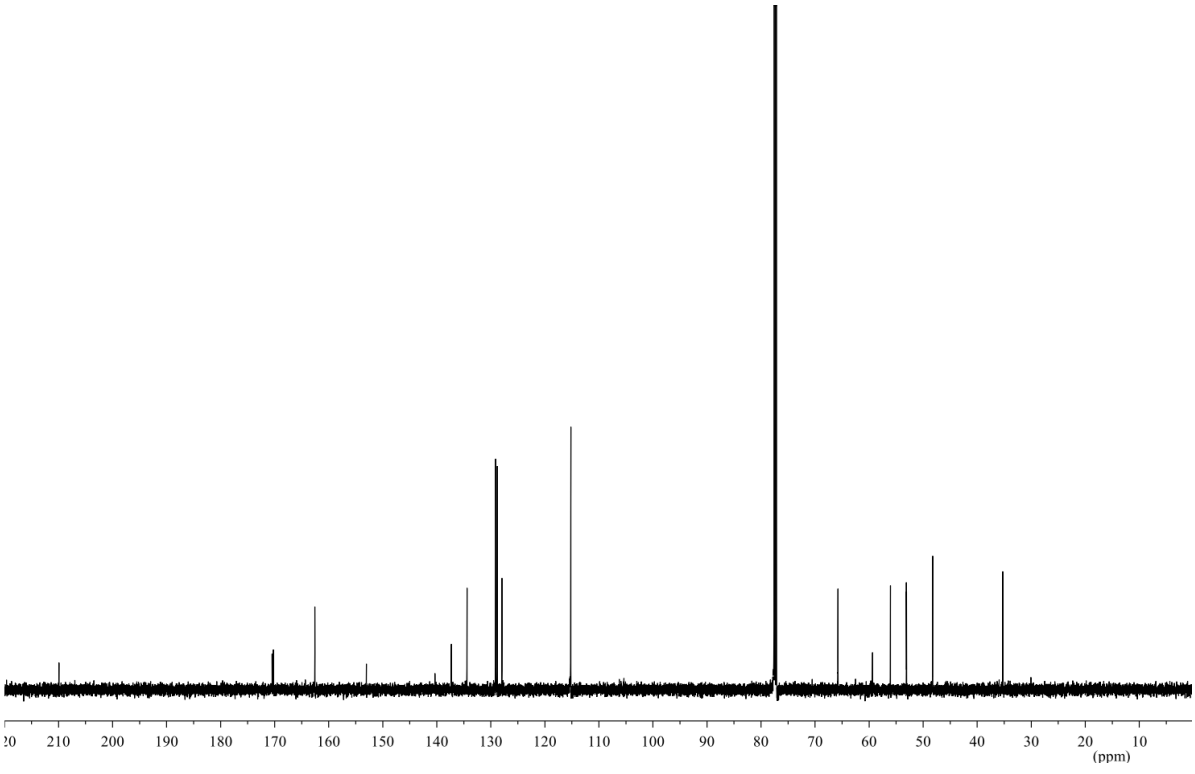
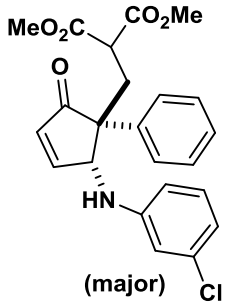
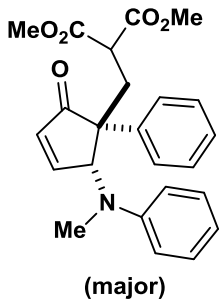
5.19
2.03
2.01
1.01
2.09
1.03
3.10
2.90
0.98
2.93
1.02
0.85
1.15
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
(ppm)


20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

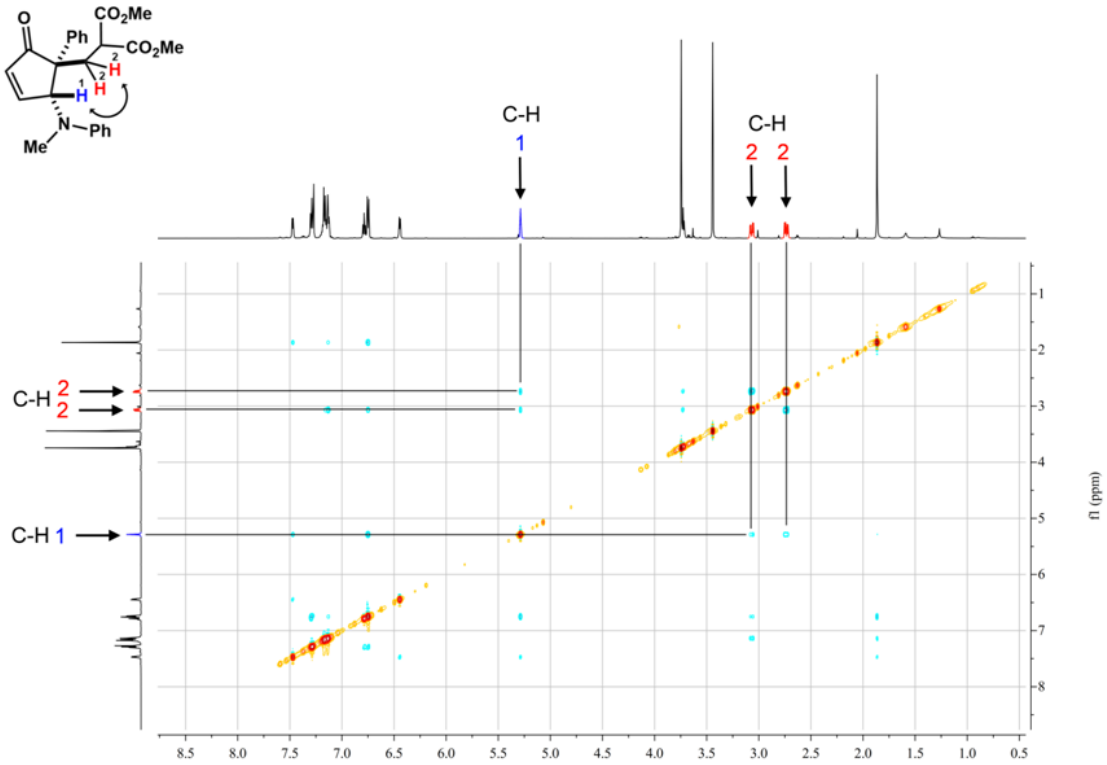


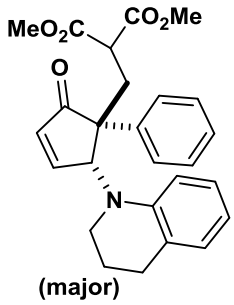
Dimethyl 2-((-2-((3-chlorophenyl)amino)-5-oxo-1-phenylcyclopent-3-en-1-yl)methyl)malonate (**475**): According to General Procedure B, $Dy(OTf)_3$ (6.3 mg, 0.010 mmol, 0.1 equiv) was added to dimethyl 2-(furan-2-yl)-2-phenylcyclopropane-1,1-dicarboxylate (31 mg, 0.10 mmol, 1 equiv) and 3-chloroaniline (11 μL, 0.10 mmol, 1 equiv) in 3 mL anhydrous MeCN. The resulting mixture was stirred at room temperature for 30 minutes. The reaction was quenched with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, then concentrated *in vacuo* (81% yield; 29:1 dr as determined by ^{1}H NMR of the crude reaction mixture). The residue was purified by column chromatography to afford cyclopentenone **475** as a yellow oil. Analytical data for major diastereomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 5.8, 2.3 Hz, 1H), 7.31 – 7.22 (m, 3H), 7.14 – 7.06 (m, 2H), 7.01 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.67 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.42 (dd, *J* = 5.8, 1.8 Hz, 1H), 6.35 (dd, *J* = 2.1, 2.1 Hz, 1H), 6.27 (dd, *J* = 8.3, 2.2 Hz, 1H), 4.72 (ddd, *J* = 10.3, 2.1, 2.1 Hz, 1H), 3.74 (s, 3H), 3.63 (dd, *J* = 6.7, 4.2 Hz, 1H), 3.57 (s, 3H), 3.11 (d, *J* = 10.2 Hz, 1H), 3.00 (dd, *J* = 15.0, 4.2 Hz, 1H), 2.79 (dd, *J* = 15.0, 6.7 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 209.2, 170.2, 170.0, 161.3, 147.4, 136.8, 135.3, 134.7, 130.6, 128.9, 128.8, 128.1, 118.6, 113.5, 111.7, 64.3, 59.1, 53.0, 48.1, 35.1; **IR** (thin film, cm^{-1}) 3393, 2953, 1749, 1732, 1708, 1598; **HRMS** (ESI) *m/z* 450.1094 (450.1085 calcd for $C_{23}H_{22}ClNNaO_5^+$ $[MNa]^+$).



(major)

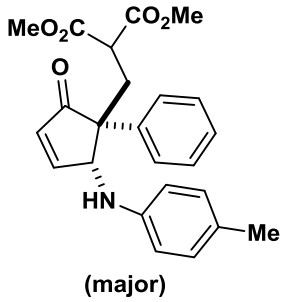
Dimethyl 2-((-2-(methyl(phenyl)amino)-5-oxo-1-phenylcyclopent-3-en-1-yl)methyl)malonate (**476**): According to General Procedure B, $Dy(OTf)_3$ (8.5 mg, 0.014 mmol, 0.1 equiv) was added to dimethyl 2-(furan-2-yl)-2-phenylcyclopropane-1,1-dicarboxylate (42 mg, 0.14 mmol, 1 equiv) and N-methylaniline (15 µL, 0.14 mmol, 1 equiv) in 4 mL anhydrous MeCN. The resulting mixture was stirred at room temperature for 30 minutes. The reaction was then quenched with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, then concentrated *in vacuo* (76% yield; 57:1 dr as determined by ^{1}H NMR of the crude reaction mixture). The residue was purified by column chromatography to afford cyclopentenone **476** as a yellow oil. Analytical data for major diastereomer: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 5.9, 2.5 Hz, 1H), 7.28 (dd, *J* = 7.8, 7.8 Hz, 2H), 7.19 – 7.10 (m, 5H), 6.78 (dd, *J* = 7.3, 7.3 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 2H), 6.44 (dd, *J* = 5.9, 2.1 Hz, 1H), 5.28 (s, 1H), 3.73 (s, 3H), 3.72 (dd, *J* = 5.4, 5.4 Hz, 1H), 3.43 (s, 3H), 3.06 (dd, *J* = 14.6, 5.2 Hz, 1H), 2.73 (dd, *J* = 14.6, 5.8 Hz, 1H), 1.86 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 209.6, 170.5, 170.2, 161.5, 149.1, 136.9, 134.7, 129.9, 129.4, 128.3, 127.5, 117.5, 112.3, 70.8, 58.6, 53.1, 52.9, 47.9, 38.2, 33.3; **IR** (thin film, cm^{-1}) 2953, 1750, 1733, 1704, 1599, 1504; **HRMS** (ESI) *m/z* 430.1640 (430.1631 calcd for $C_{24}H_{25}NNaO_5^+$ $[MNa]^+$).





Dimethyl 2-((-2-(3,4-dihydroquinolin-1(2H)-yl)-5-oxo-1-phenylcyclopent-3-en-1-yl)methyl)malonate (**477**): According to General Procedure B, $Dy(OTf)_3$ (9.0 mg, 0.015 mmol, 0.1 equiv) was added to dimethyl 2-(furan-2-yl)-2-phenylcyclopropane-1,1-dicarboxylate (44 mg, 0.15 mmol, 1 equiv) and 1,2,3,4-tetrahydroquinoline (19 µL, 0.15 mmol, 1 equiv) in 4 mL anhydrous MeCN. The resulting mixture was stirred at room temperature for 30 minutes. The reaction was quenched with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, then concentrated *in vacuo* (65% yield; 17:1 dr as determined by ^1H NMR of the crude reaction mixture). The

residue was purified by column chromatography to afford cyclopentenone **477** as a yellow oil. Analytical data for major diastereomer: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 5.9, 2.6 Hz, 1H), 7.24 – 7.12 (m, 6H), 6.92 (dd, *J* = 26.3, 7.7 Hz, 2H), 6.63 (t, *J* = 7.3 Hz, 1H), 6.41 (dd, *J* = 5.9, 2.0 Hz, 1H), 5.21 (s, 1H), 3.73 (s, 3H), 3.70 (dd, *J* = 5.4, 5.4 Hz, 1H), 3.44 (s, 3H), 3.07 (dd, *J* = 14.6, 5.2 Hz, 1H), 2.72 (dd, *J* = 14.6, 5.8 Hz, 1H), 2.63 (ddd, *J* = 11.7, 8.4, 3.2 Hz, 1H), 2.53 (ddd, *J* = 14.8, 8.8, 5.1 Hz, 1H), 2.35 (ddd, *J* = 15.8, 5.8, 5.8 Hz, 1H), 1.97 (ddd, *J* = 11.0, 6.7, 3.4 Hz, 1H), 1.33 (ddd, *J* = 12.1, 5.9, 3.3 Hz, 1H), 0.81 (dddd, *J* = 12.9, 8.8, 4.6, 4.6 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 209.6, 170.5, 170.1, 161.6, 145.0, 137.0, 134.7, 130.1, 129.5, 128.2, 127.8, 127.4, 123.0, 116.8, 110.9, 70.2, 58.0, 53.1, 52.9, 47.9, 45.0, 38.6, 28.3, 21.3; **IR** (thin film, cm^{-1}) 2951, 1750, 1733, 1704, 1601, 1496; **HRMS** (ESI) *m/z* 456.1764 (456.1787 calcd for $C_{26}H_{27}NNaO_5^+$ $[MNa]^+$).

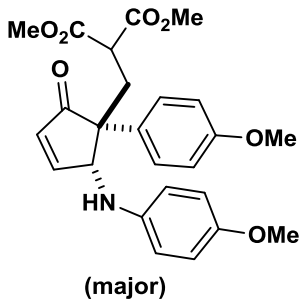


(major)

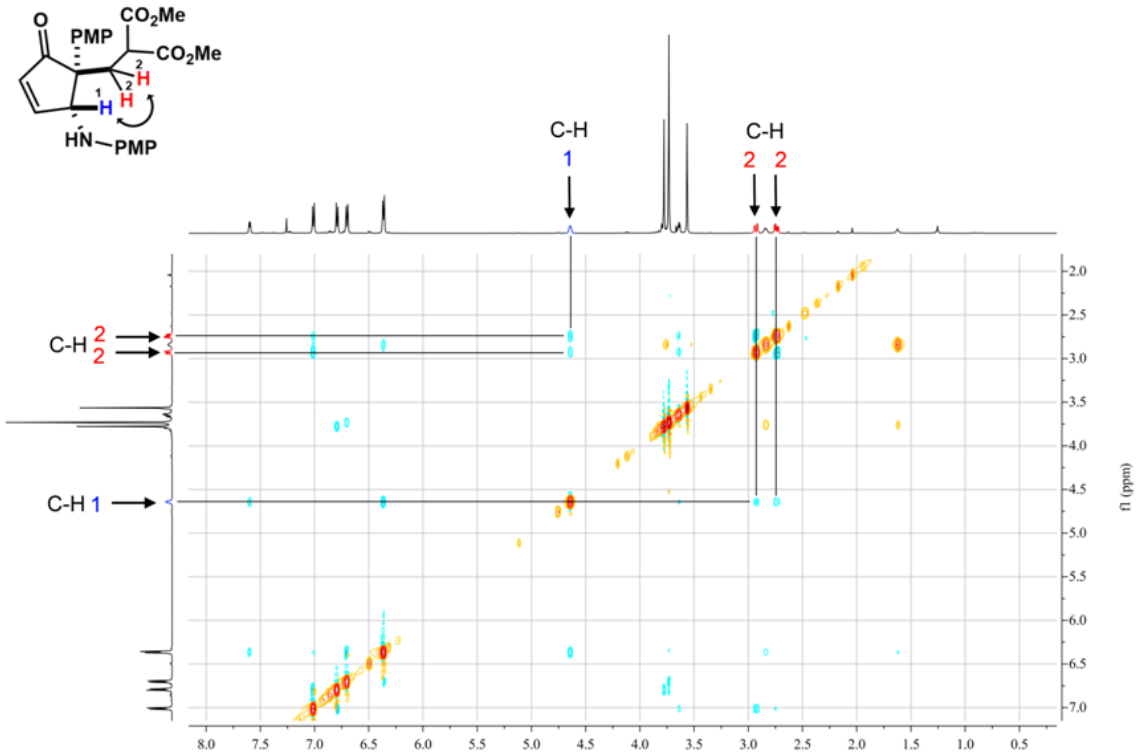
Dimethyl 2-((-2-oxo-1-phenyl-5-(p-tolylamino)cyclopent-3-en-1-yl)methyl)malonate (468): Reaction Performed at room temperature: According to General Procedure B, $Dy(OTf)_3$ (7.8 mg, 0.013 mmol, 0.1 equiv) was added to dimethyl 2-(furan-2-yl)-2-phenylcyclopropane-1,1-dicarboxylate (38 mg, 0.13 mmol, 1 equiv) and *p*-toluidine (**S-12**) (14 mg, 0.13 mmol, 1 equiv) in 4 mL anhydrous MeCN. The resulting mixture was stirred at room temperature for 30 minutes. The reaction was quenched with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, then concentrated *in vacuo* (80% yield; 10:1 dr as determined by ^{1}H NMR of the crude reaction

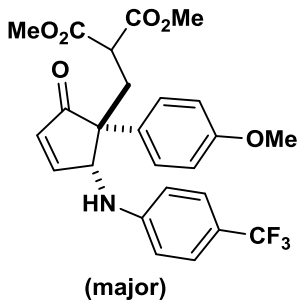
mixture). The residue was purified by column chromatography to afford cyclopentenone **468** as a white solid.

Reaction performed at 80 ^{o}C: Dimethyl 2-(furan-2-yl)-2-phenylcyclopropane-1,1-dicarboxylate (23 mg, 0.080 mmol, 1 equiv) and *p*-toluidine (8.1 mg, 0.080 mmol, 1 equiv) were dissolved in 2 mL anhydrous MeCN then placed in an oil bath at 80 ^{o}C for 2 minutes. Next, $Dy(OTf)_3$ (4.6 mg, 0.0080 mmol, 0.1 equiv)was added to the reaction mixture and stirred at 80 ^{o}C for 90 seconds, then removed and quickly quenched with H_2O (5 mL). The reaction mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* (87% yield; 14:1 dr as determined by ^{1}H NMR of the crude reaction mixture). The residue was purified by column chromatography to afford cyclopentenone **468** as a white solid. Analytical data for major diastereomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 5.8, 2.2 Hz, 1H), 7.30 – 7.24 (m, 3H), 7.15 – 7.08 (m, 2H), 6.92 (d, *J* = 7.6 Hz, 2H), 6.39 (dd, *J* = 5.8, 1.8 Hz, 1H), 6.32 (d, *J* = 8.4 Hz, 2H), 4.75 (d, *J* = 9.3 Hz, 1H), 3.74 (s, 3H), 3.66 (dd, *J* = 6.7, 4.3 Hz, 1H), 3.56 (s, 3H), 3.00 (dd, *J* = 15.0, 4.3 Hz, 1H), 2.94 (d, *J* = 10.2 Hz, 1H), 2.79 (dd, *J* = 15.0, 6.7 Hz, 1H), 2.22 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 209.8, 170.5, 170.2, 162.4, 143.9, 137.3, 134.4, 130.2, 129.1, 128.8, 128.1, 128.0, 113.9, 65.0, 59.3, 53.1, 53.1, 48.3, 35.3, 20.7; **IR** (thin film, cm^{-1}) 3401, 2953, 1751, 1734, 1701, 1616, 1519; **HRMS** (ESI) *m/z* 430.1613 (430.1631 calcd for $C_{24}H_{25}NNaO_5^{+}$ $[MNa]^{+}$).



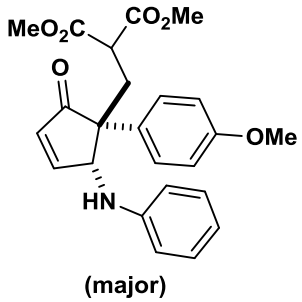
Dimethyl 2-((-1-(4-methoxyphenyl)-2-((4-methoxyphenyl) amino)-5-oxocyclopent-3-en-1-yl)methyl)malonate (**466**): According to General Procedure B, $Dy(OTf)_3$ (4.3 mg, 0.0071 mmol, 0.1 equiv) was added to dimethyl 2-(furan-2-yl)-2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (23 mg, 0.071 mmol, 1 equiv) and *p*-anisidine (8.7 mg, 0.071 mmol, 1 equiv) in 2 mL anhydrous MeCN. The resulting mixture was stirred at room temperature for 30 minutes. The reaction was quenched with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, then concentrated *in vacuo* (87% yield; 25:1 dr as determined by ^{1}H NMR of the crude reaction mixture). The residue was purified by column chromatography to afford cyclopentenone **466** as a yellow oil. Analytical data for major diastereomer: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 5.9, 2.2 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 6.34 (d, *J* = 8.6 Hz, 3H), 4.61 (s, 1H), 3.75 (s, 3H), 3.71 (s, 6H), 3.61 (dd, *J* = 6.7, 4.1 Hz, 1H), 3.54 (s, 3H), 2.90 (dd, *J* = 14.9, 4.2 Hz, 1H), 2.81 (s, 1H), 2.71 (dd, *J* = 15.0, 6.7 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 210.0, 170.5, 170.3, 162.5, 159.1, 153.0, 140.5, 134.3, 130.3, 129.1, 115.2, 115.2, 114.2, 65.7, 58.8, 56.1, 55.6, 53.1, 53.0, 48.3, 35.5; **IR** (thin film, cm^{-1}) 3392, 2954, 1749, 1733, 1708, 1610, 1513; **HRMS** (ESI) *m/z* 476.1663 (476.1686 calcd for $C_{25}H_{27}NNaO_7^+$ $[MNa]^+$).





Dimethyl 2-((-1-(4-methoxyphenyl)-2-oxo-5-((4-(trifluoromethyl)phenyl)amino)cyclopent-3-en-1-yl)methyl)malonate (**481**): According to General Procedure B, $Dy(OTf)_3$ (9.4 mg, 0.016 mmol, 0.1 equiv) was added to dimethyl 2-(furan-2-yl)-2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (51 mg, 0.16 mmol, 1 equiv) and 4-(trifluoromethyl)aniline (19 µL, 0.16 mmol, 1 equiv) in 2 mL anhydrous MeCN. The resulting mixture was stirred at room temperature for 30 minutes. The reaction was quenched with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* (63% yield; 22:1 dr as

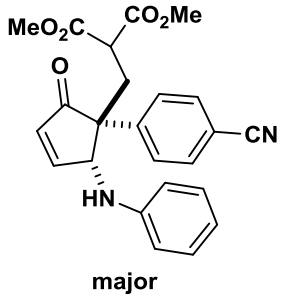
determined by ^{1}H NMR of the crude reaction mixture). The residue was purified by column chromatography to afford cyclopentenone **481** as a yellow oil. Analytical data for major diastereomer: **^{1}H NMR** (600 MHz, CD_3CN) δ 7.44 (dd, *J* = 5.9, 2.6 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.54 (d, *J* = 8.8 Hz, 2H), 6.34 (d, *J* = 8.5 Hz, 2H), 6.17 (dd, *J* = 5.8, 1.8 Hz, 1H), 4.66 (dd, *J* = 10.2, 2.2 Hz, 1H), 4.26 (d, *J* = 10.2 Hz, 1H), 3.52 (s, 3H), 3.46 (s, 3H), 3.38 (s, 3H), 3.30 (dd, *J* = 6.8, 4.0 Hz, 1H), 2.75 (dd, *J* = 15.0, 4.1 Hz, 1H), 2.51 (dd, *J* = 15.0, 6.9 Hz, 1H); **^{13}C NMR** (150 MHz, CD_3CN) 211.0, 170.9, 170.4, 162.4, 159.6, 151.0, 134.7, 131.2, 129.9, 127.1 (q, *J* = 4 Hz), 114.1, 113.2, 64.8, 59.4, 55.8, 53.3, 53.1, 48.9, 36.1; **IR** (thin film, cm^{-1}) 3391, 2955, 1749, 1733, 1710, 1615, 1515; **HRMS** (ESI) *m/z* 514.15 (514.15 calcd for $C_{25}H_{24}F_3NNaO_6^+$ $[MNa]^+$).



(major)

Dimethyl 2-((-1-(4-methoxyphenyl)-2-oxo-5-(phenylamino) cyclopent-3-en-1-yl)methyl)malonate (**482**): According to General Procedure B, $Dy(OTf)_3$ (5.1 mg, 0.0083 mmol, 0.1 equiv) was added to dimethyl 2-(furan-2-yl)-2-(4-methoxyphenyl) cyclopropane-1,1-dicarboxylate (27 mg, 0.083 mmol, 1 equiv) and aniline (7.5 µL, 0.083 mmol, 1 equiv) in 3 mL anhydrous MeCN. The resulting mixture was stirred at room temperature for 30 minutes. The reaction was quenched with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, then concentrated *in vacuo* (84% yield; 32:1 dr as determined by ^{1}H NMR of the crude reaction mixture). The residue was purified by column chromatography to afford cyclopentenone **482** as a yellow oil. Analytical data for major diastereomer: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 5.8, 2.2 Hz, 1H),

7.15 – 7.08 (m, 2H), 7.03 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 6.71 (t, J = 7.3 Hz, 1H), 6.43 (d, J = 7.3 Hz, 2H), 6.38 (dd, J = 5.8, 1.8 Hz, 1H), 4.74 (t, J = 2.1 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.65 (dd, J = 6.6, 4.3 Hz, 1H), 3.55 (s, 3H), 2.95 (dd, J = 15.0, 4.3 Hz, 1H), 2.76 (dd, J = 15.0, 6.7 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 209.8, 170.5, 170.2, 162.1, 159.2, 146.3, 134.4, 130.3, 129.7, 128.9, 118.8, 114.2, 113.7, 64.5, 58.7, 55.6, 53.1, 53.1, 48.2, 35.5; **IR** (thin film, cm^{-1}) 3395, 2953, 1749, 1733, 1707, 1601, 1514; **HRMS** (ESI) *m/z* 446.1585 (446.1580 calcd for $C_{24}H_{25}NNaO_6^+$ $[MNa]^+$).

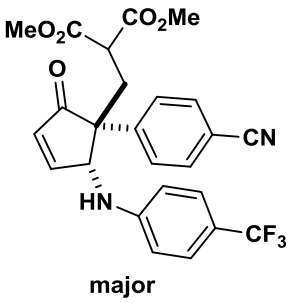


major

Dimethyl 2-((-1-(4-cyanophenyl)-2-oxo-5-(phenylamino) cyclopent-3-en-1-yl)methyl)malonate (483): Reaction performed at room temperature: According to General Procedure B, $Dy(OTf)_3$ (3.7 mg, 0.0062 mmol, 0.1 equiv) was added to dimethyl 2-(4-cyanophenyl)-2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (20 mg, 0.062 mmol, 1 equiv) and aniline (5.6 µL, 0.062 mmol, 1 equiv) in 2 mL anhydrous MeCN. The resulting mixture was stirred at room temperature for 60 minutes. The reaction was quenched with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a crude mixture of **483**. (76 % yield; 1:1 dr as determined by ^{1}H NMR of the crude reaction mixture). **Reaction performed at 80 ^{o}C:** Dimethyl 2-(4-cyanophenyl)-2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (26 mg, 0.080 mmol, 1 equiv) and aniline (7.2 µL, 0.080 mmol, 1 equiv) were dissolved in 2 mL anhydrous MeCN then placed in an oil bath at 80 ^{o}C for 2 minutes. Next, $Dy(OTf)_3$ (4.8 mg, 0.0080 mmol, 0.1 equiv) was added to the reaction mixture and stirred at 80 ^{o}C for 90 seconds, then removed

and quickly quenched with H_2O (5 mL). The reaction mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a crude mixture of **483**. (77% yield; 3:1 dr as determined by ^{1}H NMR of the crude reaction mixture).

Due to the difficulties of product isolation identified in the manuscript, full characterization data of **483** was not obtained.

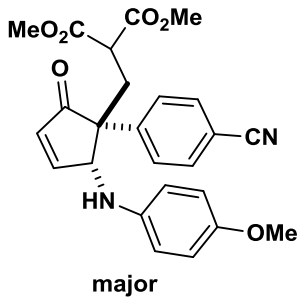


major

Dimethyl 2-((-1-(4-cyanophenyl)-2-oxo-5-((4-(trifluoromethyl) phenyl)amino)cyclopent-3-en-1-yl)methyl)malonate (484): **Reaction performed at room temperature:** According to General Procedure B, $Dy(OTf)_3$ (4.9 mg, 0.0081 mmol, 0.1 equiv) was added to dimethyl 2-(4-cyanophenyl)-2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (26 mg, 0.081 mmol, 1 equiv) and 4-(trifluoromethyl)aniline (10 μL, 0.081 mmol, 1 equiv) in 2 mL anhydrous MeCN. The resulting mixture was stirred at room temperature for 60 minutes. The reaction was quenched with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a crude mixture of **484**. (65% yield; 5:1 dr as determined by ^{1}H NMR of the crude reaction mixture). **Reaction performed at 80 ^{o}C:** Dimethyl 2-(4-cyanophenyl)-2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (26 mg, 0.080 mmol, 1 equiv) and 4-(trifluoromethyl)aniline (10 μL, 0.080 mmol, 1 equiv) were dissolved in 2 mL anhydrous MeCN then placed into an oil bath at 80 ^{o}C for 2 minutes. Next, $Dy(OTf)_3$ (5.0 mg, 0.0080 mmol, 0.1 equiv) was added to the reaction mixture and stirred at 80 ^{o}C for 90 seconds, then removed and quickly quenched

with H_2O (5 mL). The reaction mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a crude mixture of **484**. (66% yield; 22:1 dr as determined by ^{1}H NMR of the crude reaction mixture).

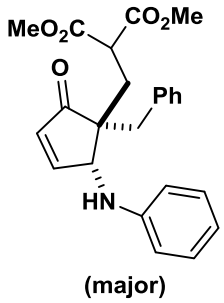
Due to the difficulties of product isolation identified in the manuscript, full characterization data of **484** was not obtained.



Dimethyl 2-((-1-(4-cyanophenyl)-2-((4-methoxyphenyl)amino)-5-oxocyclopent-3-en-1-yl)methyl)malonate (485): Reaction performed at room temperature: According to General Procedure B, $Dy(OTf)_3$ (3.9 mg, 0.0064 mmol, 0.1 equiv) was added to dimethyl 2-(4-cyanophenyl)-2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (21 mg, 0.064 mmol, 1 equiv) and anisidine (57.8 mg, 0.064 mmol, 1 equiv) in 2 mL anhydrous MeCN. The resulting mixture was stirred at room temperature for 60 minutes. The reaction was quenched with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a crude mixture of **485**. (58% yield; 2:1 dr as determined by ^{1}H NMR of the crude reaction mixture). **Reaction performed at 80 ^{o}C:** Dimethyl 2-(4-cyanophenyl)-2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (24 mg, 0.074 mmol, 1 equiv) and anisidine (9.1 mL, 0.074 mmol, 1 equiv) were dissolved in 2 mL anhydrous MeCN then placed in an oil bath at 80 ^{o}C for 2 minutes. Next, $Dy(OTf)_3$ (4.5 mg, 0.0074 mmol, 0.1 equiv) was added to the reaction mixture and stirred at 80 ^{o}C for 90 seconds, then removed and quickly quenched with H_2O (5 mL). The reaction mixture was

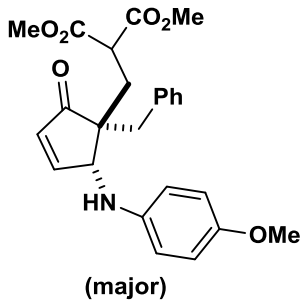
extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a crude mixture of crude **485**. (65% yield; 1:1 dr as determined by ^1H NMR of the crude reaction mixture).

Due to the difficulties of product isolation identified in the manuscript, full characterization data of **485** was not obtained.

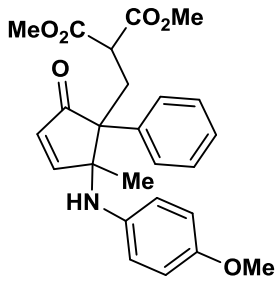


Dimethyl 2-((-1-benzyl-2-oxo-5-(phenylamino)cyclopent-3-en-1-yl)methyl)malonate (**486**): According to General Procedure B, $Dy(OTf)_3$ (9.1 mg, 0.0149 mmol, 0.1 equiv) was added to dimethyl 2-benzyl-2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (46.9 mg, 0.149 mmol, 1 equiv) and aniline (13.6 µL, 0.149 mmol, 1 equiv) in 1.5 mL anhydrous MeCN. The resulting mixture was stirred at room temperature for 5 h. The reaction was quenched with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, then concentrated *in vacuo* (56% yield; 1.3:1 dr as determined by ^1H NMR of the crude reaction mixture). The residue was purified by column chromatography to afford cyclopentenone **486** as a yellow oil. Analytical data for the mixture of diastereomers: **^1H NMR** (600 MHz, $CDCl_3$) δ 7.44 (dd, J = 5.8, 2.2 Hz, 1H), 7.31 (dd, J = 5.9, 2.2 Hz, 1H), 7.28 – 7.17 (m, 20H), 7.17 – 7.04 (m, 6H), 6.78 (dq, J = 15.4, 7.9 Hz, 3H), 6.73 (d, J = 8.0 Hz, 1H), 6.68 (dd, J = 15.7, 7.8 Hz, 3H), 6.62 (d, J = 7.9 Hz, 2H), 6.24 (dd, J = 5.9, 2.0 Hz, 1H), 6.13 (dd, J = 5.9, 2.0 Hz, 1H), 4.72 (d, J = 9.2 Hz, 1H), 4.64 (s, 1H), 4.12 (q, J = 7.2 Hz, 1H), 4.07 (t, J = 6.7 Hz, 0H), 3.95 (s, 2H), 3.90 (t, J = 5.7 Hz, 2H), 3.78 – 3.69 (m, 15H), 3.57 (s, 3H), 3.31 (d, J = 13.6 Hz, 1H), 3.13 (d, J = 13.8 Hz, 1H), 3.00 – 2.86 (m, 1H),

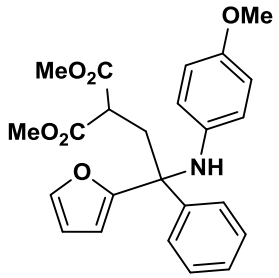
2.79 (d, J = 13.8 Hz, 1H), 2.71 (d, J = 13.7 Hz, 1H), 2.54 – 2.40 (m, 3H), 2.37 – 2.30 (m, 2H), 2.01 (d, J = 14.4 Hz, 1H), 1.85 (dd, J = 18.5, 2.4 Hz, 1H), 1.61 (p, J = 7.0 Hz, 1H), 1.38 (dt, J = 14.9, 7.5 Hz, 1H).



Dimethyl 2-(((1R,2R)-1-benzyl-2-((4-methoxyphenyl)amino)-5-oxocyclopent-3-en-1-yl)methyl)malonate (**487**): According to General Procedure B, $Dy(OTf)_3$ (4.6 mg, 0.00757 mmol, 0.1 equiv) was added to dimethyl 2-benzyl-2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (23.8 mg, 0.0757 mmol, 1 equiv) and *p*-anisidine (9.3 mg, 0.0757 mmol, 1 equiv) in 1 mL anhydrous MeCN. The resulting mixture was stirred at room temperature for 40 mins. The reaction was quenched with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, then concentrated *in vacuo* (47% yield; 2:1 dr as determined by ^1H NMR of the crude reaction mixture). The residue was purified by column chromatography to afford cyclopentenone **487** as a yellow oil. Analytical data for the mixture of diastereomers: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 (dd, J = 5.8, 2.2 Hz, 1H), 7.25 – 7.18 (m, 3H), 7.12 – 7.07 (m, 2H), 6.82 – 6.76 (m, 2H), 6.61 – 6.54 (m, 2H), 6.11 (dd, J = 5.8, 1.9 Hz, 1H), 4.57 – 4.47 (m, 1H), 3.91 (t, J = 5.6 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 3.30 (d, J = 13.6 Hz, 1H), 2.69 (d, J = 13.6 Hz, 1H), 2.34 (d, J = 5.7 Hz, 2H) ppm.

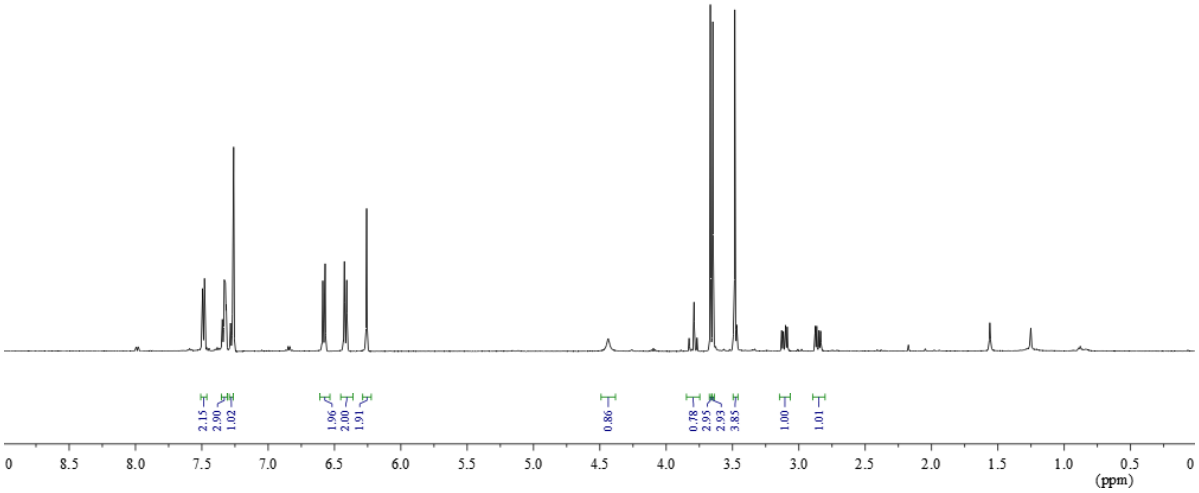


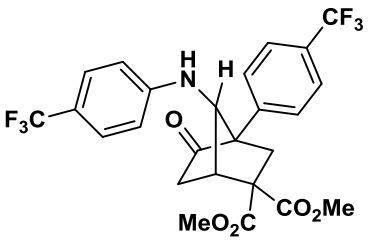
Dimethyl 2-((2-((4-methoxyphenyl)amino)-2-methyl-5-oxo-1-phenylcyclopent-3-en-1-yl)methyl)malonate (489): Appears to be an inseparable mixture of diastereomers (1.2:1 dr) **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.48 – 7.37 (m, 7H), 7.37 – 7.27 (m, 7H), 6.85 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 8.5 Hz, 2H), 6.28 (dd, J = 7.5, 3.1 Hz, 2H), 5.93 (d, J = 3.2 Hz, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H), 3.44 (s, 3H), 3.40 (t, J = 5.8 Hz, 1H), 3.32 – 3.23 (m, 2H), 3.16 (dd, J = 14.9, 5.0 Hz, 1H), 3.11 (s, 3H), 3.08 (s, 3H), 2.82 (dd, J = 14.8, 6.6 Hz, 1H), 2.67 (dd, J = 14.2, 3.7 Hz, 1H), 2.23 (s, 3H), 2.21 (s, 3H) ppm. **MS** (ESI) *m/z* 460.17 (460.16 calcd for $C_{25}H_{27}NO_6Na^+$ $[MNa]^+$).



Dimethyl 2-(2-(furan-2-yl)-2-((4-methoxyphenyl)amino)-2-phenylethyl)malonate (491): According to General Procedure B, $Dy(OTf)_3$ (3.4 mg, 0.00563 mmol, 0.1 equiv) was added to dimethyl 2-(furan-2-yl)-2-phenylcyclopropane-1,1-dicarboxylate (16.9 mg, 0.0563 mmol, 1 equiv) and *p*-anisidine (6.9 mg, 0.0.0563 mmol, 1 equiv) in 1 mL anhydrous MeCN. The resulting mixture was stirred at -40 ^oC for 50 minutes. The reaction was quenched with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, then concentrated *in vacuo* (30% isolated yield). The residue was purified by column chromatography to afford cyclopentenone **491** as an oil: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 – 7.46 (m, 2H), 7.35 – 7.31 (m, 3H), 7.29 – 7.26 (m, 1H), 6.61 – 6.53 (m, 2H), 6.45 – 6.36

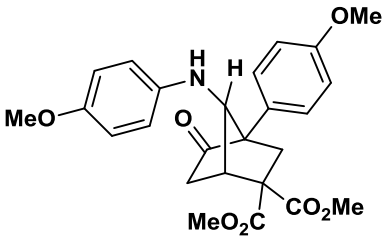
(m, 2H), 6.26 (d, J = 1.3 Hz, 2H), 4.44 (s, 1H), 3.85 – 3.75 (m, 1H), 3.67 (s, 3H), 3.65 (s, 3H), 3.48 (s, 3H), 3.11 (dd, J = 14.7, 6.4 Hz, 1H), 2.86 (dd, J = 14.7, 5.9 Hz, 1H) ppm.





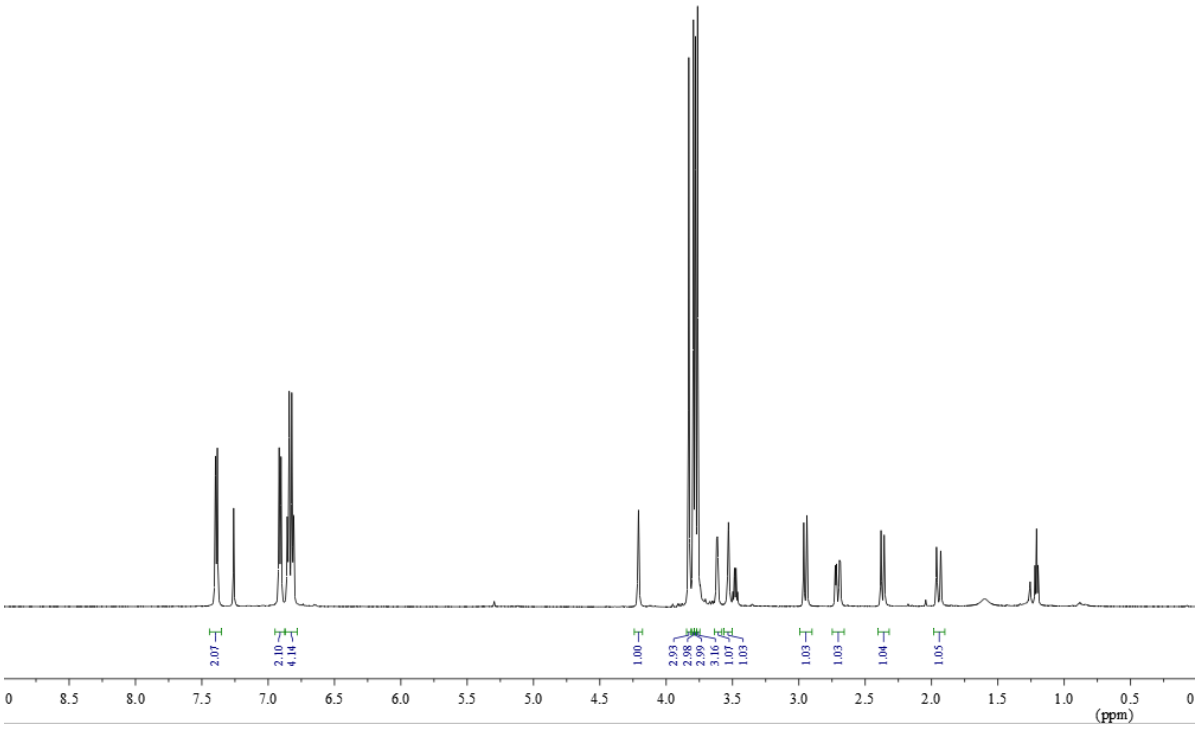
Dimethyl 5-oxo-4-(4-(trifluoromethyl)phenyl)-7-((4-(trifluoromethyl)phenyl)amino)bicycle [2.2.1]heptanes-2,2-dicarboxylate (**497**): $Dy(OTf)_3$ (11 mg, 0.018 mmol, 0.1 equiv) was added to dimethyl 2-(furan-2-yl)-2-(4-(trifluoromethyl)phenyl)cyclopropane-1,1-dicarboxylate (66 mg, 0.18 mmol, 1 equiv) and 4-(trifluoromethyl)aniline (23 μL, 0.18 mmol, 1 equiv) in 6 mL anhydrous MeCN. The resulting mixture was stirred at room temperature for 45 minutes, after which, 3M NaOH (1 mL) was added and stirred for 25 minutes. The reaction was worked up with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, then concentrated *in vacuo*. The residue was purified by column chromatography to afford bicycle **497** as a white solid (83%

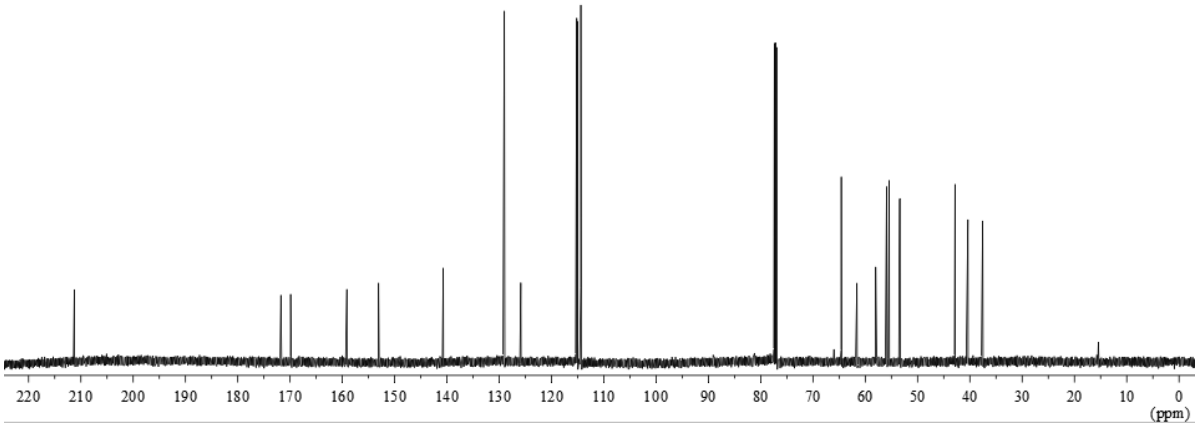
isolated yield; as a single diastereomer as determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 4.45 (s, 1H), 4.03 (d, *J* = 3.9 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.66 (d, *J* = 3.8 Hz, 1H), 3.05 (d, *J* = 14.5 Hz, 1H), 2.64 (dd, *J* = 18.8, 5.1 Hz, 1H), 2.33 (d, *J* = 14.6 Hz, 1H), 2.03 (dd, *J* = 18.8, 2.3 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 206.7, 168.7, 166.7, 146.1, 134.9, 134.9, 127.5 (q, J = 33 Hz), 125.6, 124.3 (q, J = 3.8 Hz), 123.1 (q, J = 3.8 Hz), 122.1 (q, J = 271 Hz), 121.3 (q, J = 272 Hz), 118.3 (q, J = 33 Hz), 110.5, 60.4, 59.1, 54.9, 50.9, 50.8, 39.8, 37.7, 34.7; **IR** (thin film, cm^{-1}) 3392, 2959, 1732, 1618, 1533; **HRMS** (ESI) *m/z* 552.1220 (552.1222 calcd for $C_{25}H_{21}F_6NO_5^+$ [MNa]$^+$).

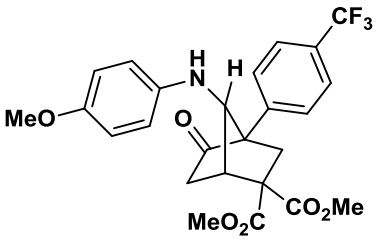


Dimethyl-4-(4-methoxyphenyl)-7-((4-methoxyphenyl)amino)-5-oxobicyclo[2.2.1]heptane-2,2-dicarboxylate (**498**): $Dy(OTf)_3$ (3.4 mg, 0.00605 mmol, 0.1 equiv) was added to dimethyl 2-(furan-2-yl)-2-(4-methoxyphenyl) cyclopropane-1,1-dicarboxylate (20.0 mg, 0.0605 mmol, 1 equiv) and *p*-anisidine (7.5 mg, 0.0605 mmol, 1 equiv) in 2 mL anhydrous MeCN. The resulting mixture was stirred at room temperature for 10 minutes, after which, 3M NaOH (1 mL) was added and stirred for 3 h. The reaction was worked up with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, then concentrated *in vacuo*. The residue was purified by column chromatography to afford bicycle **498** (87% isolated yield; as a single diastereomer as determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.44 – 7.35 (m, 2H), 6.95 – 6.87

(m, 2H), 6.87 – 6.76 (m, 4H), 4.21 (s, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.62 (dd, J = 5.2, 2.1 Hz, 1H), 3.53 (s, 1H), 2.95 (d, J = 14.5 Hz, 1H), 2.71 (dd, J = 18.5, 5.0 Hz, 1H), 2.37 (d, J = 14.6 Hz, 1H), 1.95 (dd, J = 18.6, 2.2 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 211.3, 171.8, 169.9, 159.1, 153.1, 140.7, 129.0, 125.9, 115.2, 115.0, 114.4, 64.6, 61.6, 58.0, 55.9, 55.4, 53.5, 53.4, 42.8, 40.4, 37.6 ppm.

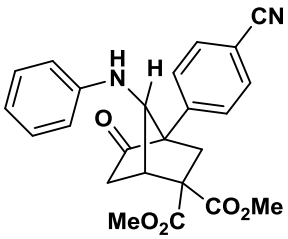






Dimethyl-7-((4-methoxyphenyl)amino)-5-oxo-4-(4-(trifluoromethyl)phenyl)bicyclo[2.2.1]heptane-2,2-dicarboxylate (**499**): $Dy(OTf)_3$ (7.7 mg, 0.0127 mmol, 0.1 equiv) was added to dimethyl 2-(furan-2-yl)-2-(4-(trifluoromethyl)phenyl)cyclopropane-1,1-dicarboxylate (46.7 mg, 0.127 mmol, 1 equiv) and *p*-anisidine (15.6 mg, 0.127 mmol, 1 equiv) in 1 mL anhydrous MeCN. The resulting mixture was stirred at room temperature for 45 minutes, after which, 3M NaOH (1 mL) was added and stirred for 25 minutes. The reaction was worked up with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, then concentrated *in vacuo*. The residue was purified by column chromatography to afford bicycle **499** (24%yield as a single diastereomer as determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.70 – 7.51 (m, 4H), 6.91 – 6.73 (m, 4H), 4.32 (d, J = 3.0 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H),

3.69 – 3.61 (m, 1H), 3.52 – 3.44 (m, 1H), 3.01 (d, J = 14.5 Hz, 1H), 2.72 (dd, J = 18.6, 5.1 Hz, 1H), 2.36 (d, J = 14.5 Hz, 1H), 2.04 – 1.93 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 209.9, 171.5, 169.7, 153.3, 140.2, 138.1, 128.4, 125.8, 125.8, 115.3, 115.1, 107.7, 64.2, 62.0, 57.9, 55.9, 53.6, 53.5, 42.9, 40.4, 37.4 ppm.



Dimethyl 4-(4-cyanophenyl)-5-oxo-7-(phenylamino) bicyclo[2.2.1]heptane-2,2-dicarboxylate (**500**): According to General Procedure B, $Dy(OTf)_3$ (9.0 mg, 0.015 mmol, 0.1 equiv) was added to dimethyl 2-(4-cyanophenyl)-2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (48 mg, 0.15 mmol, 1 equiv) and aniline (13 μL, 0.15 mmol, 1 equiv) in 4 mL anhydrous MeCN. The resulting mixture was stirred at room temperature for 45 minutes, after which, 3M NaOH (1 mL) was added and stirred for 25 minutes. The reaction was worked up with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, then concentrated *in vacuo*. The residue was purified by column chromatography to afford bicycle **500** as a white solid (81% isolated yield; as a single diastereomer as determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.68 – 7.64 (m, 2H), 7.60 – 7.57 (m, 2H), 7.29 – 7.25 (m, 2H), 6.87 – 6.82 (m, 3H), 4.41 (t, J = 2.2 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.68 (dd, J = 4.7, 1.1 Hz, 1H), 3.01 (d, J = 14.5 Hz, 1H), 2.70 (dd, J = 18.8, 5.1 Hz, 1H), 2.34 (d, J = 14.5 Hz, 1H), 2.02 (dd, J = 18.8, 2.2 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 209.7, 171.6, 169.8, 146.2, 139.6, 132.8, 130.0, 129.1, 119.5, 118.9, 114.0, 112.0, 63.6, 62.2, 57.9, 53.9, 53.8, 42.9, 40.6, 37.7; **IR** (thin film, cm^{-1}) 3392, 2956,

2926, 2230, 1734, 1280, 1254; **HRMS** (ESI) *m/z* 441.1423 (441.1427 calcd for $C_{24}H_{22}N_2NaO_5^+$ $[MNa]^+$).

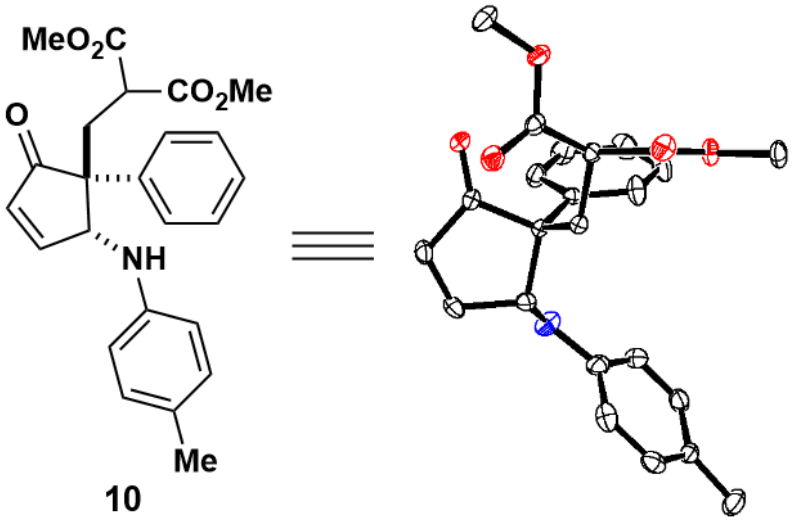
Crystallographic Experimental Section

A colorless crystal of approximate dimensions 0.3*0.1*0.1 mm was mounted on a glass fiber and transferred to a Bruker Kappa Apex II diffractometer. The APEX2 program was used to determine the unit cell parameters and data collection (15 sec / frame, 0.3 deg. /frame). The data were collected at 100K. The raw frame data were processed using APEX2 program. The absorption correction was applied using program SADABS. Subsequent calculations were carried out using SHELXTL program. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares techniques. Hydrogen atomic positions were theoretically calculated. At convergence, wR2= 0.1517 and GOF = 0.957 for 274 variables refined against 4375 reflections, while R1= 0.0620 for 3625 reflections with $I>2\sigma(I)$. All ORTEP diagrams have been drawn with 50% probability ellipsoids.

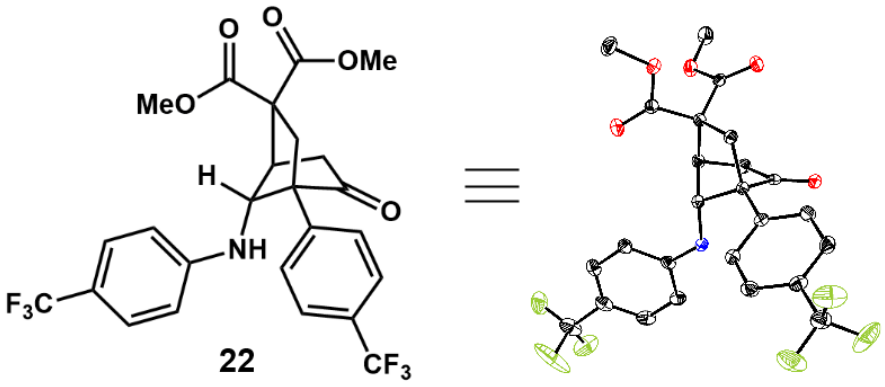
Crystals were prepared by slow vapor diffusion using hexanes as the outer layer and ethyl acetate as the inner layer.

The crystal structure data can be obtained free of charge from the Cambridge Crystallographic Data Centre www.ccdc.cam.ac.uk/data_request/cif

Compound 468: CCDC 916408



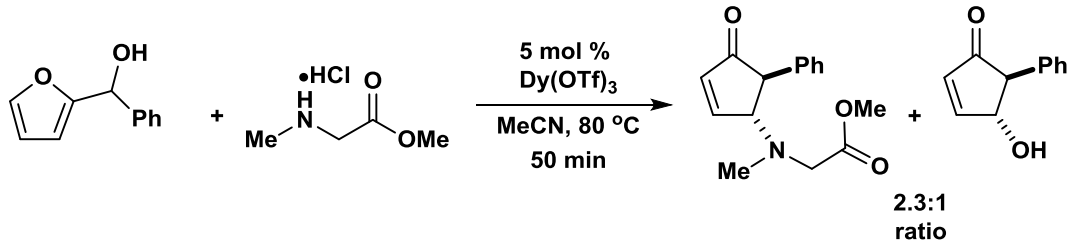
Compound 497: CCDC 901791



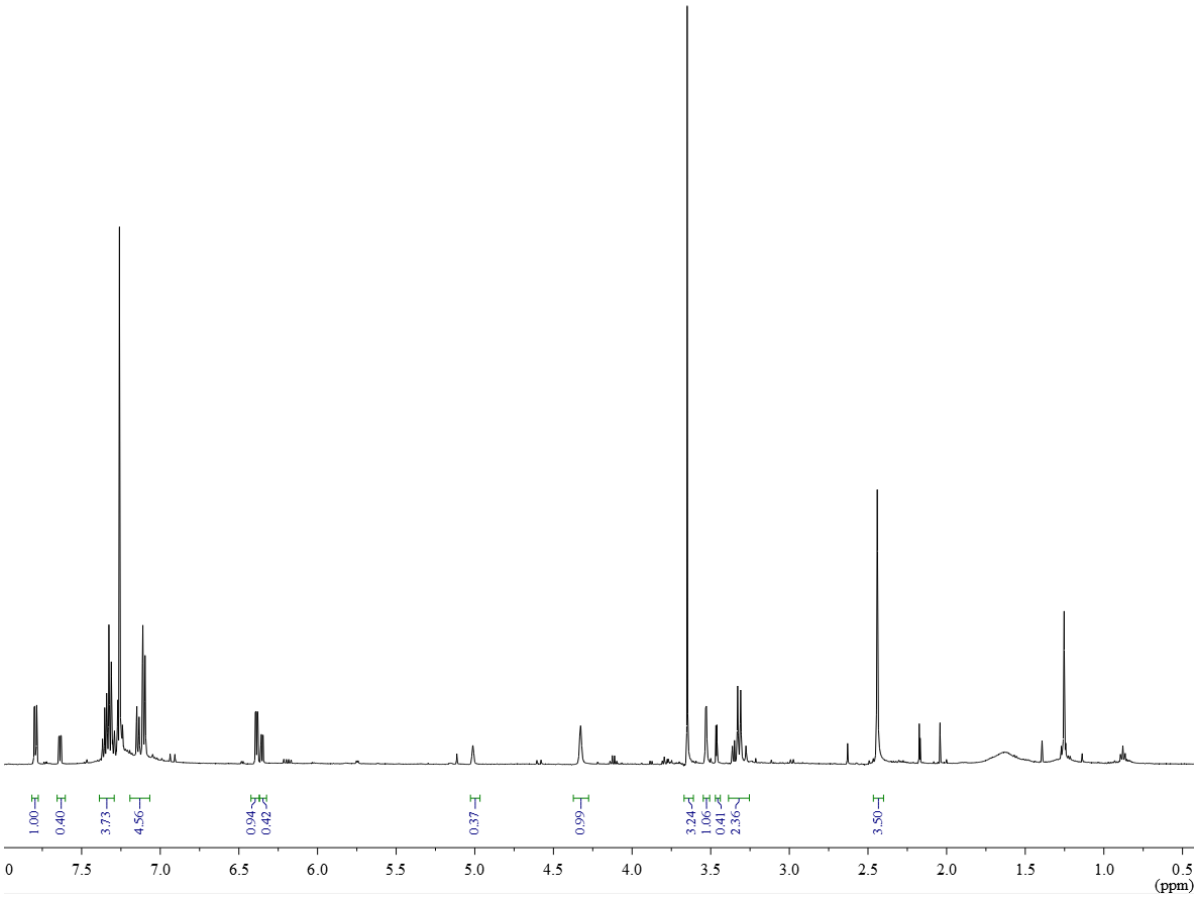
5.3.3 References

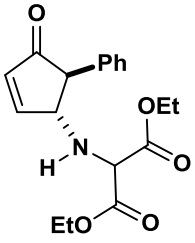
[1] Mitra, A. K.; De, A.; Karchaudhuri, N. *Synth. Commun.* **1999**, *29*, 2731.
[2] Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
[3] Charette, A. B. *Org. Syn.* **2010**, *87*, 115.

5.4.1 Chapter 4.1



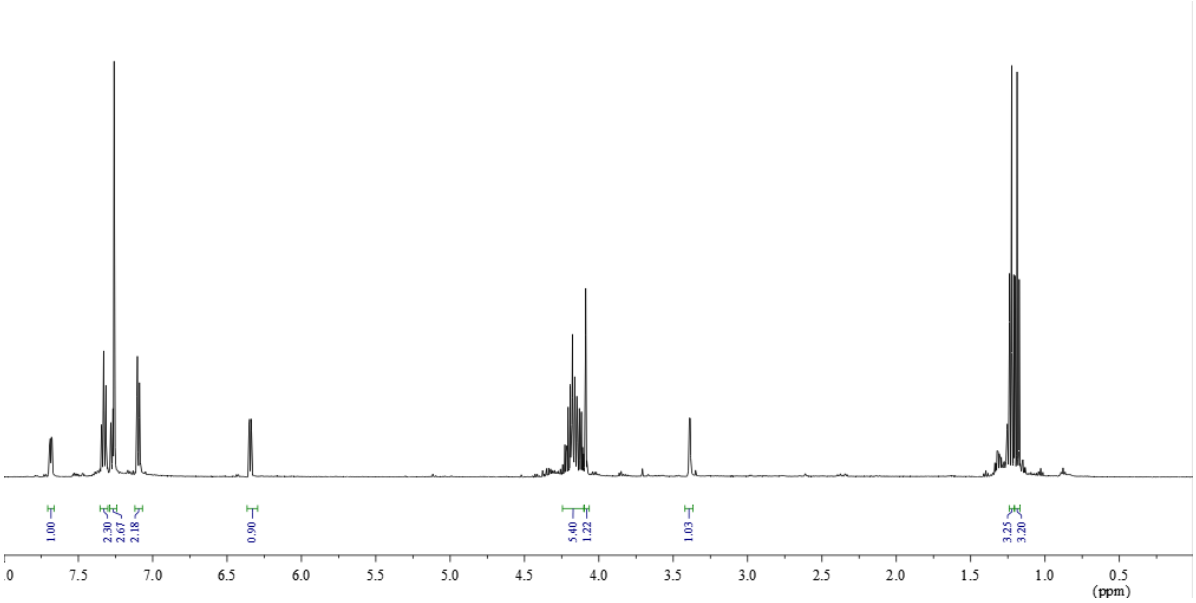
Diethyl 2-((-4-oxo-5-phenylcyclopent-2-en-1-yl)amino)malonate (**E-36**): $Dy(OTf)_3$ (5 mg, 0.012 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol (28.6 mg, 0.164 mmol, 1 equiv) and sarcosine methyl ester•HCl (34.8 mg, 0.164 mmol, 1 equiv) in 1.6 mL MeCN. The resulting mixture was stirred at 80 ^{o}C for 2 h. The reaction was quenched with H_2O (5 mL) and saturated aqueous $NaHCO_3$ (5 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, then concentrated *in vacuo.* The residue was purified by column chromatography to afford cyclopentenone **E-36** as a pale yellow solid. (8.0 mg, 15% isolated yield). ^{1}H NMR pictured below is a mixture of inseparable products.

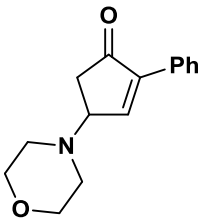




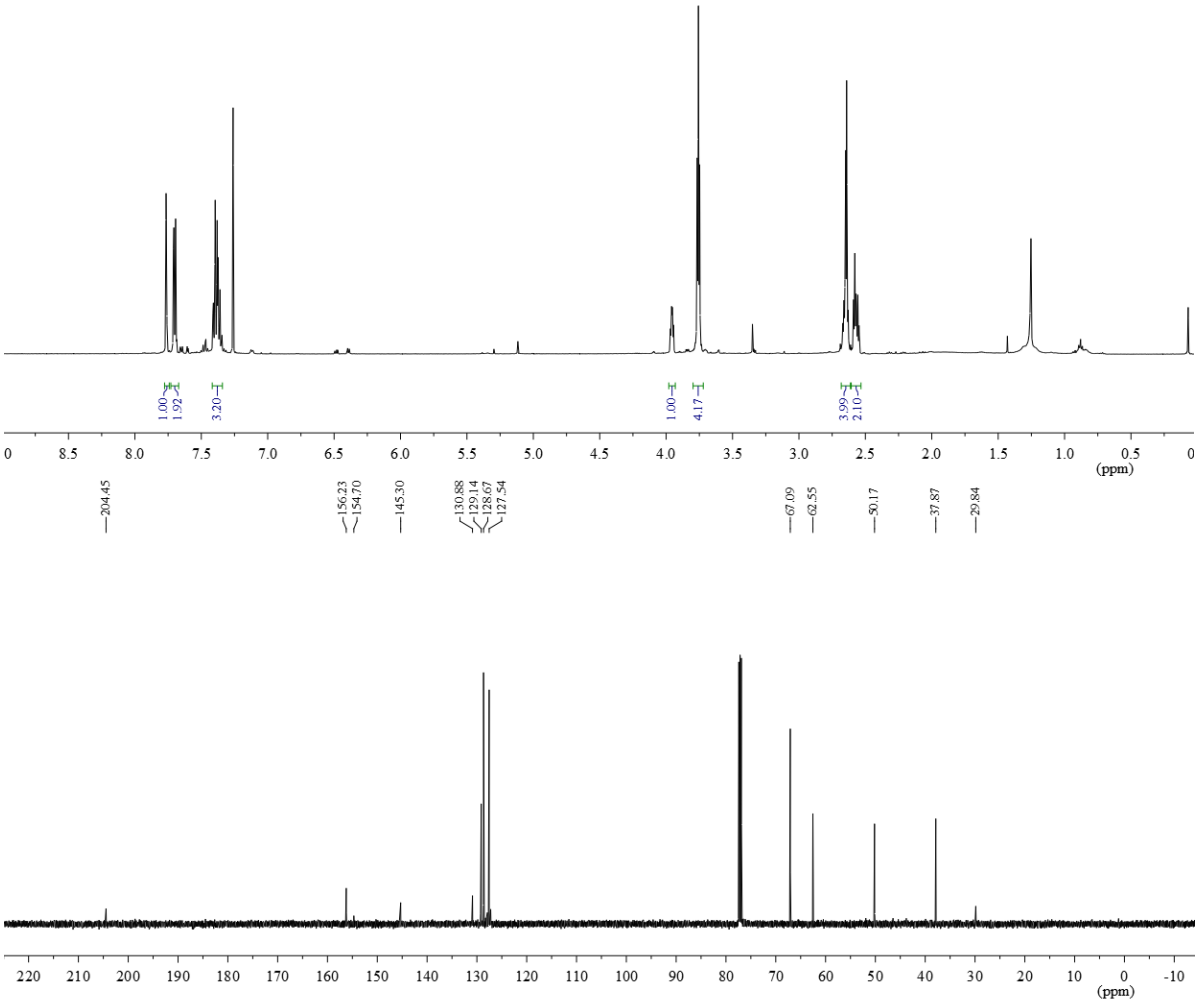
Diethyl 2-((-4-oxo-5-phenylcyclopent-2-en-1-yl)amino)malonate (**E-37**): $Dy(OTf)_3$ (5 mg, 0.012 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol (28.6 mg, 0.164 mmol, 1 equiv) and diethyl 2-aminomalonate•HCl (34.8 mg, 0.164 mmol, 1 equiv) in 1.6 mL MeCN. The resulting mixture was stirred at 80 ^{o}C for 2 h. The reaction was quenched with H_2O (5 mL) and saturated aqueous NaCl (2 mL), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, then concentrated *in vacuo.* The residue was purified by column chromatography to afford cyclopentenone **E-37** as a pale yellow solid. (8.0 mg, 15% isolated yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68 (dd, J = 5.8,

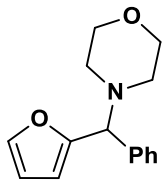
2.3 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.29 – 7.24 (m, 1H), 7.12 – 7.07 (m, 2H), 6.34 (dd, J = 5.8, 1.8 Hz, 1H), 4.24 – 4.10 (m, 5H), 4.09 (d, J = 3.5 Hz, 1H), 3.39 (d, J = 3.0 Hz, 1H), 1.22 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H) ppm.



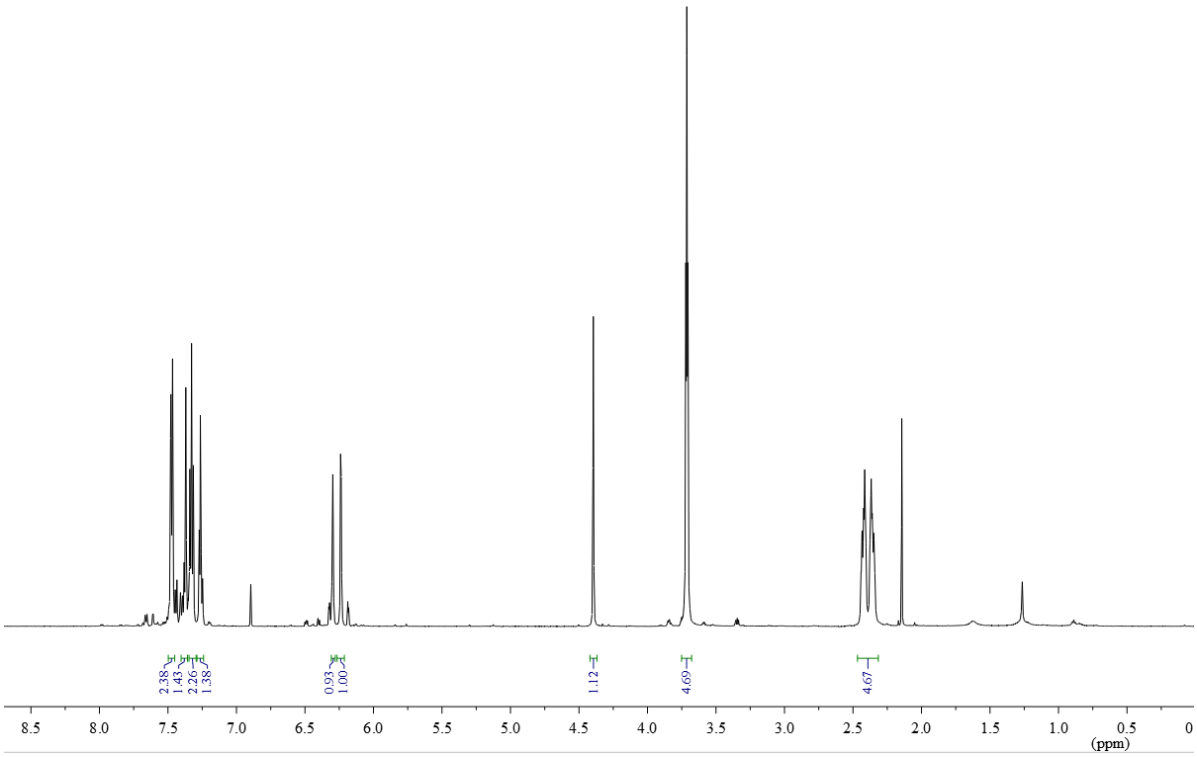


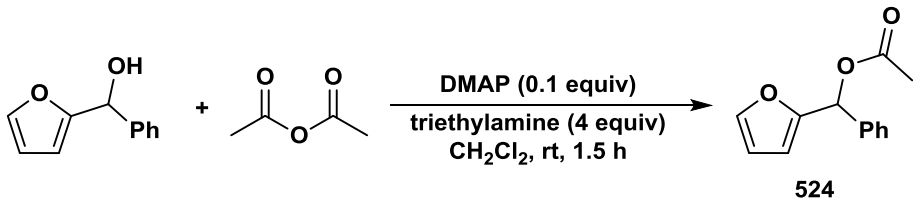
4-Morpholino-2-phenylcyclopent-2-en-1-one (**525**): Yellow oil **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.76 (d, J = 2.6 Hz, 1H), 7.73 – 7.67 (m, 2H), 7.42 – 7.34 (m, 3H), 3.96 (ddd, J = 5.0, 3.9, 2.6 Hz, 1H), 3.76 (t, J = 4.7 Hz, 4H), 2.70 – 2.61 (m, 4H), 2.57 (ddd, J = 11.2, 4.7, 4.7 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 204.5, 156.2, 154.7, 145.3, 130.9, 129.1, 128.7, 127.5, 67.1, 62.6, 50.2, 37.9, 29.8 ppm. **MS** (ESI) *m/z* 244.13 (244.13 calcd for $C_{15}H_{17}NO_2H^+$ $[MH]^+$).





4-Morpholino-2-phenylcyclopent-2-en-1-one (**528**): Yellow oil **^{1}H NMR** (600 MHz, CDCl3) δ 7.50 – 7.45 (m, 2H), 7.40 – 7.36 (m, 1H), 7.33 (d, J = 15.1 Hz, 1H), 7.30 – 7.23 (m, 2H), 6.30 (dd, J = 3.3, 1.8 Hz, 1H), 6.24 (d, J = 3.2 Hz, 1H), 4.40 (s, 1H), 3.71 (t, J = 4.7 Hz, 4H), 2.39 (dddd, J = 39.9, 11.2, 4.8, 4.8 Hz, 5H) ppm.





524

Furan-2-yl(phenyl)methyl acetate (**524**): Furan-2-yl(phenyl)methanol (722.3 mg, 4.15 mmol, 1 equiv), 4-dimethylaminopyridine (DMAP) (50.7 mg, 0.415 mmol, 0.1 equiv), and triethylamine (2.3 mL, 16.6 mmol, 4 equiv) were dissolved in 30 mL CH_2Cl_2 and cooled to 0 ^oC. Next, acetic anhydride (1.2 mL, 12.4 mmol, 3 equiv) was added slowly dropwise. The resulting mixture was stirred at 0 ^oC for 1.5 h. The reaction was quenched with H_2O (5 mL)

and saturated aqueous $NHCO_3$ (2 mL), then extracted with CH_2Cl2 (3 x 10 mL). The combined organic layers were dried over $NaSO_4$, filtered, then concentrated *in vacuo.* The residue was purified by column chromatography using 2% EtOAc in hexanes to afford acetylated furylcarbinol **524** as a pale yellow solid. (803.5 mg, 90% isolated yield). Yellow solid **^{1}H NMR** (500 MHz, CDCl3) δ 7.46 – 7.31 (m, 6H), 6.89 (s, 1H), 6.32 (dd, J = 3.3, 1.8 Hz, 1H), 6.18 (ddd, J = 3.3, 0.8, 0.8 Hz, 1H), 2.14 (s, 3H) ppm.