New Twists in Nazarov Cyclization Chemistry

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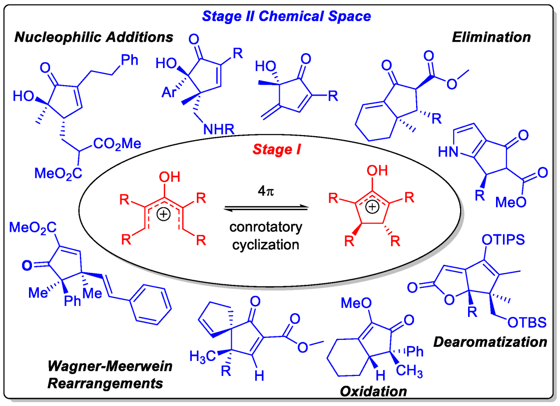
CONSPECTUS



The defining feature of the Nazarov cyclization is a 4π-conrotatory electrocyclization, resulting in the stereospecific formation of functionalized cyclopentanones. The reaction provides access to structural motifs that are found in many natural products and drug targets. Harnessing the full potential of the Nazarov cyclization broadens its utility by enabling the development of new methodologies and synthetic strategies. To achieve these goals through efficient cyclization design, it is helpful to think of the reaction as a two-stage process. The first stage involves a 4π-electrocyclization leading to the formation of an allylic cation and the second stage corresponds to the fate of this cationic intermediate. With a complete understanding of the discrete events that characterize the overall process, one can optimize reactivity and control the selectivity of the different stage 2 pathways.

In this Account, we describe the development of methods that render the Nazarov cyclization catalytic and chemoselective, focusing specifically on advances made in our lab between 2002 and 2015. The initial discovery made in our lab involved reactions of electronically asymmetric ("polarized") substrates, which cyclize efficiently in the catalytic regime using mild Lewis acidic reagents. These cyclizations also exhibit selective eliminative behavior, increasing their synthetic utility. Research directed toward catalytic asymmetric Nazarov cyclization led to the serendipitous discovery of a 4π-cyclization coupled to a well-behaved Wagner-Meerwein rearrangement, representing an underexplored Stage 2 process. With careful choice of promoter and loading, it is possible to access either the rearrangement or the elimination pathway. Additional experimental and computational studies provided an effective model for anticipating migratory behavior of substiutents in the rearrangements. Problem-solving efforts prompted investigation of alternative methods for generating pentadienyl cation intermediates, including oxidation of allenol ethers and addition of nucleophiles to dienyl diketones. These Nazarov cyclization variants afford cyclopentenone products with vicinal stereogenic centers and a different arrangement of substituents around the ring. A nucleophilic addition/cyclization/elimination sequence can be executed enantioselectively using catalytic amounts of a nonracemic chiral tertiary amine.

In summary, the discovery and development of several new variations on the Nazarov electrocyclization are described, along with synthetic applications. This work illustrates how strongly substitution patterns can impact the efficiency of the 4π electrocyclization (stage 1), allowing for mild Lewis acid catalysis. Over the course of these studies, we have also identified new ways to access the critical pentadienyl cation intermediates and demonstrated strategies that exploit and control the different cationic pathways available post-electrocyclization (stage 2 processes). These advances in Nazarov chemistry were subsequently employed in the synthesis of natural product targets such as (±)-merrilactone A, (±)-rocaglamide, and (±)-enokipodin B.

KEY REFERENCES

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by a Wagner/Meerwein rearrangement leads to the formation of highly functionalized cyclopentenones.

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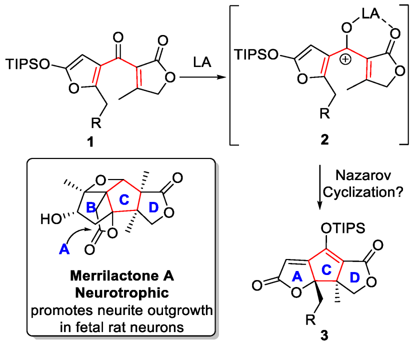
INTRODUCTION

The Nazarov cyclization has undergone several stages of evolution since its discovery in 1940.[5] It has occupied a prominent place in the consciousness of organic chemists since the Woodward/ Hoffman days, when it was highlighted as a textbook example of conrotatory electrocyclization. This early fame was clouded by the poor performance of the reaction as a synthetically useful process. For example, many Nazarov cyclizations only occurred in the presence of stoichiometric amounts of strong acids to give multiple elimination products. Substantial progress was made in the 1980s when Denmark et al. described silicon-directed Nazarov cyclizations which, for the first time, guaranteed regiocontrolled elimination and made the reaction useful in synthetic applications.[6,7] Two research groups, led by West and Tius, were responsible for nearly all progress in Nazarov cyclization chemistry during the 1990s and early 2000s. Tius developed a variant of the Nazarov cyclization which uses alkoxyallenes to obtain functionalized cyclopentanones. This chemistry was applied toward the synthesis of several natural product targets.[8-12] West discovered a series of interrupted Nazarov cyclization processes characterized by cationic reaction cascades capable of generating multiple carbon-carbon bonds initiated by the electrocyclization.[13-18]

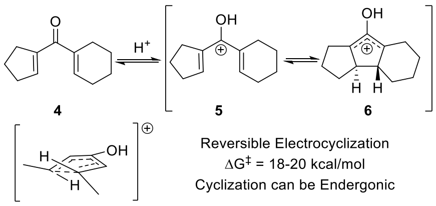
Initial studies in our group were inspired by (±)-merrilactone A, a natural product with a skeletal framework that is uniquely suited for construction using a Nazarov cyclization strategy. Specifically, one can imagine that a substrate like **1** would provide tricycle **3**, in which the stereochemistry in ring C is controlled by conrotatory cyclization (Scheme 1). Unfortunately, there was little precedent for such a transformation. On the other hand, the electron perturbations exerted by the substituents in **1** suggest that the system might exhibit improved reactivity. This led us to the idea that polarized substrates might cyclize more readily than electronically neutral ones and under milder reaction conditions. This study was the beginning of a journey that has exceeded all expectations. This Account will describe the evolution of our thinking and how new methods emerged from our increased understanding of the reaction process. The research described here spans the period 2002 (the start of the program) to 2015 and focuses exclusively on the classical 3-*oxy* pentadienyl cation manifold.

Scheme 1. (±)-Merrilactone A Inspiration



After studying the "Nazarov Cyclization" for fifteen years, we began to realize that the name of the reaction actually works to obscure its full potential. Considering it a simple cyclization suggests that one can only create one new bond and nothing else. While the reaction involves several discrete events, we find it helpful to think about it as a two-stage process. This analysis unifies the different variants and gives us a better appreciation of the synthetic capabilities of the process (Schemes 2 and 3). Stage one involves a conrotatory 4π-electrocyclization as dictated by the Woodward-Hoffman rules governing orbital symmetry. This process ensures the stereospecific installation of two stereogenic centers at the carbon termini. Some general observations: the barrier for electrocyclization of a simple 3-oxypentadienyl cation **5** is estimated at 18-20 kcal mol^{-1}, depending on the method used for the calculation. Furthermore, as is typical for pericyclic processes, the electrocyclization is reversible, and can be either endergonic or exergonic.[19,20] The case shown in Scheme 2 is representative: the barrier for cyclization of **5** to **6** is estimated to be 18 kcal mol^{-1}, and endergonic by 1.3 kcal mol^{-1}.[21] In addition, electrocyclization does not lead directly to a stable product, but rather to a new high energy cationic intermediate **6**. The fate of the oxyallyl cation **6** constitutes Stage 2 of the "Nazarov Cyclization." Therefore, focusing attention on the electrocyclization alone overlooks the factors driving the conclusion of the process, which are equally important to consider when designing and executing synthetically useful Nazarov cyclizations.

Scheme 2. Stage 1 of Nazarov Cyclization: Electrocyclization

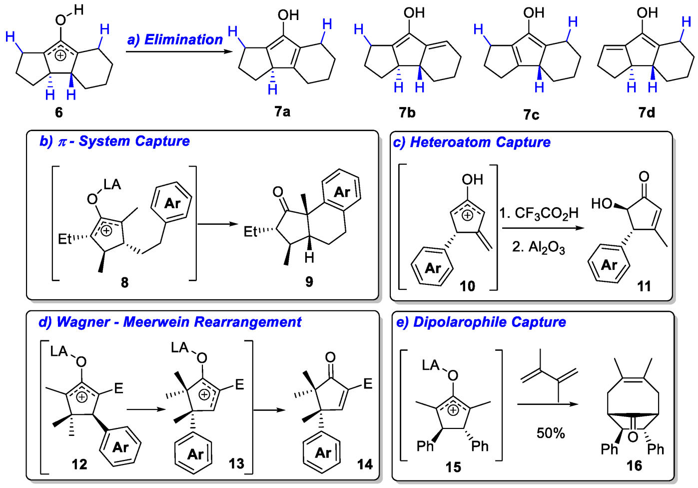


Reversible Electrocyclization
ΔG‡ = 18-20 kcal/mol
Cyclization can be Endergonic

Challenge: Control Equilibrium in Electrocyclization

While Stage 1 requires overcoming kinetic barriers in a process that is reversible and not necessarily thermodynamically favorable, Stage 2 poses a selectivity challenge. Depending on the reactant and reaction conditions, an oxyallyl cation generated from a Stage 1 electrocyclization may have access to several different reaction pathways (Scheme 3). In a routine case, elimination occurs to afford enone products after tautomerization of the enol **7a-d**. Typically, more than one proton is available for elimination, leading to mixtures from that pathway alone. However, intermolecular or intramolecular capture of oxyallyl cation **6** with a nucleophile is more favorable than elimination (Scheme 3b-e). These reaction sequences have been collectively referred to as “interrupted Nazarov cyclizations” by West.[18] The nucleophilic partners that participate in these cascades range from electron-rich aromatic systems (Scheme 3b),[16,17,22] to alkenes,[23] heteroatoms (Scheme 3c),[24-29] or hydrides.[30] These oxyallyl cation intermediates have also been captured by dipolarophiles in [4+3] and [3+2] cycloaddition processes to get products like **16** (Scheme 3e).[31] A third Stage 2 pathway, also dominant over elimination, is Wagner-Meerwein rearrangements (Scheme 3d).[32,33]

Scheme 3. Stage 2 of Nazarov Cyclization: Fate of Oxyallyl Cation



Challenge: Control Cation Behavior

In order to achieve a synthetically useful Nazarov cyclization, the different Stage 2 pathways must be controlled. Even for simple (symmetric) substrates, complex mixtures of products can be obtained from elimination at different sites. Additionally, elimination pathways pose the risk of losing one of the newly installed stereogenic centers. In more complex systems, rearrangement pathways become competitive, as well as pathways involving intramolecular or intermolecular cation capture.

Given all of these challenges, one could argue that historically, the primary drawback for chemists wishing to use the Nazarov cyclization for synthetic applications was poor selectivity in Stage 2. In support of this statement, the synthetic breakthroughs in the 80s and 90s all represented solutions to this selectivity problem. Silicon-directed Nazarov cyclizations allowed for a controlled elimination, preventing formation of complex mixtures.[6] Addition of different nucleophiles that can trap the oxyallyl cation effectively minimized or completely suppressed the elimination pathway. However, Nazarov cyclization methodology had other shortcomings that limited its utility at the time. Most significantly, the cyclization was not catalytic and stoichiometric amounts of strong Brønsted or Lewis acid were typically required to promote the reaction. In our work, we have found that both Stage 1 and Stage 2 behavior is strongly impacted by substrate design. We have come to appreciate that if one considers the factors that drive each step of the reaction then the overall transformation can be improved, thus overcoming limitations on synthetic utility. Going a step further, we have also employed this two-stage logic to design variants of the reaction that take full advantage of its potential to construct highly functionalized cyclopentanoid systems.

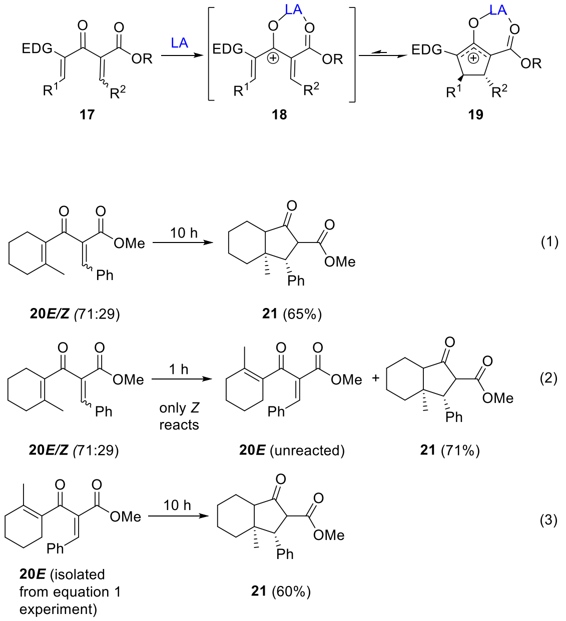
RESULTS AND DISCUSSION

Using Polarized Substrates, Electrocyclization Becomes Catalytic and Thermodynamically Favorable.

During the initial studies inspired by (±)-merrilactone A, we hypothesized (rather naively) that a divinyl ketone with complementary electron-donating and electron-withdrawing groups might accelerate cyclization. The idea was that polarized substrates like **17** contain a nucleophilic and an electrophilic half (Scheme 4). The substitution pattern would create electronic asymmetry in the oxyallyl cation intermediate, improving chemoselectivity in Stage 2 processes. In addition, the alkylidene β-dicarbonyl moiety can readily complex to a Lewis acid catalyst and preorganize the system before cyclization. These polarized substrates prove to be more reactive, making mild Lewis acid catalysis possible, and exhibiting predictable behavior in the eliminative regime.[1,34-39]

The isomerization behavior of the polarized systems added a dimension to the study that we did not anticipate. Specifically, *in situ* interconversion of *E/Z* divinyl ketones is facilitated by the electron-withdrawing group resulting in stereoconvergent cyclization (Scheme 4, equation 1; product **21** is derived from conrotatory cyclization of the minor *Z* isomer). Additional experiments revealed that the *Z* isomer generates **21** in 1 hour (Scheme 4, equation 2), while it takes the *E* isomer 10 hours to isomerize to the *Z* isomer and cyclize to afford **21** (Scheme 4, equation 3).

Scheme 4. For Divinyl Ketones with an Electron-Withdrawing Group, Electrocyclization is Stereoconvergent.



In the years since these initial reports, other researchers have demonstrated that as long as the substrate is polarized with an electron-donating substituent, many different catalysts will promote the reaction.[40-42] Further investigation into the substituent effects revealed the true impacts of the polarized substrate design on the Stage 1 electrocyclization process, as discussed in later sections of this Account.

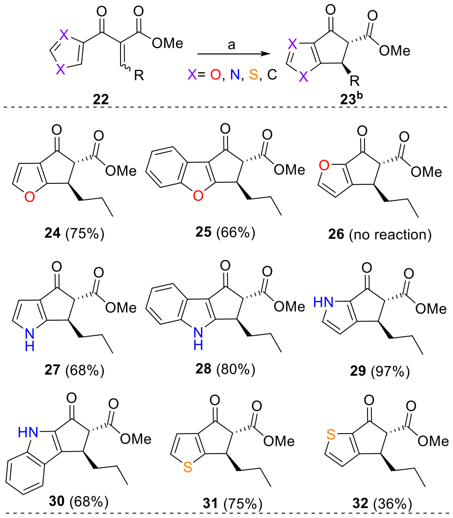
Nazarov Cyclization of Heteroaryl Vinyl Ketones

Once we established that polarized aliphatic systems cyclize smoothly using mild Lewis acids as catalysts, our next goal was to identify a method for achieving cyclization of polarized heteroaromatic substrates **22** under catalytic conditions (Scheme 5a).[38] It was disappointing to find that cyclization only occurs slowly (over several days) under the typical conditions for polarized cyclization (2-10 mol% of Lewis acids like scandium(III) triflate and copper(II) triflate). This was resolved when 1 equivalent of lithium perchlorate was added to 5 mol% of scandium triflate (this combination was employed in our synthesis of the roseophilin core).[43] Efficient catalysis of the cyclizations is also possible using 5 mol% of copper and scandium perchlorate salts.

In addition to the simple heteroaromatic rings shown in Scheme 5a, we examined silyloxyfuran reactants of type **33** (Scheme 5b) in the context of the (±)-merrilactone A synthetic strategy (see Schemes 1 and 5b). Successful execution of the cyclization of **1** to **3** not only demands electrocyclization of an especially hindered system (fully substituted at both termini of the pentadienyl cation **2**), but also requires dearomatization of a silyloxyfuran **1**. Experimentation quickly revealed that **1** does not undergo the desired cyclization.[44] This observation inspired us to examine the reactivity of a series of silyloxyfuran enones **33** (Scheme 5b). It was rewarding to find that these are viable substrates for the cyclization. We were able to identify two catalysts that could convert **33** to **34**. Ir(III) complexes, developed in collaboration with the Eisenberg group, turned out to be the only transition metal Lewis acids we tested that are capable of initiating the cyclization. These complexes made it possible to use loadings as low as 2 mol%. Triisopropylsilyl triflimide is also effective in catalyzing these cyclizations with just 1 mol% loading. This suggests that once initiated, the cyclizations occur through an autocatalytic process.[44]

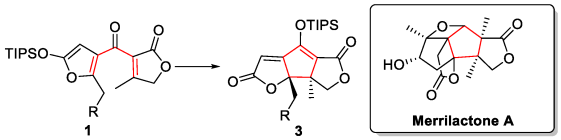
Scheme 5. Heteroaromatic Systems in the Polarized Nazarov Cyclization

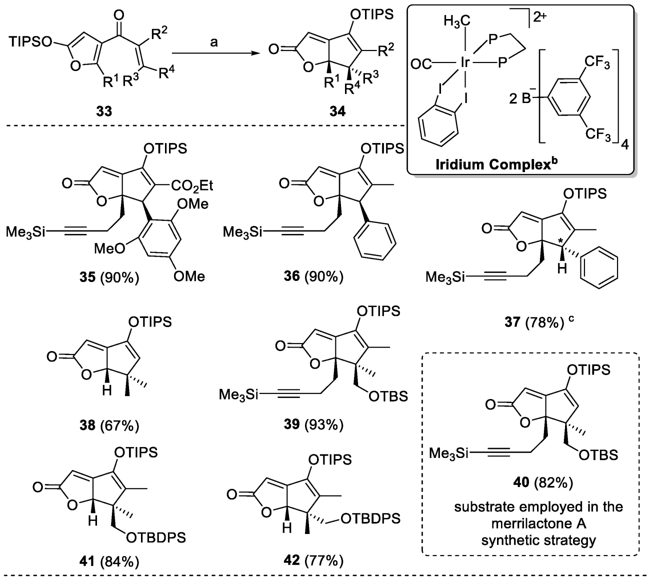
a) Catalytic Nazarov Cyclization of Simple Heteroarenes



a) Reaction conditions: 5 mol% $Sc(OTf)_3$, 1.0 equivalent of $LiClO_4$, DCE, 80°C b) All products were isolated as single diastereomers.

b) Catalytic Nazarov Cyclizations of Silyloxyfurans (Synthesis of (±)-Merrilactone A)





a)Reaction conditions: Ir[(dppe)(CO)(DIB)(CH$_3$)]$^{2+}$ 2BAr$^{F}{}_4{}^{-}$ (2 mol%), CH$_2$Cl$_2$, room temperature. b) Phenyl groups on phosphorous omitted for clarity c)3:1 mix of diastereomers (from 3:1 *E/Z* mix of **33**)

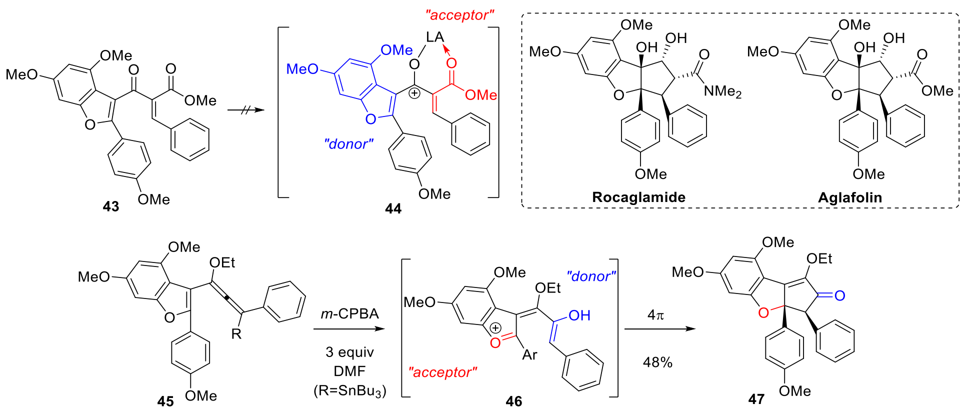
Synthesis of (±)-Aglafolin and (±)-Rocaglamide

The successful cyclization of a series of heteroaromatic systems encouraged us to apply the strategy to the synthesis of (±)-rocaglamide (Scheme 6a), a complex molecule with antiproliferative, and insecticidal properties.[45] Unfortunately, despite our successful preparation of benzofuran **35**, and the smooth dearomatization behavior observed in the Scheme 5b systems, benzofuran **43** did not produce the target **44** when subjected to the usual cyclization conditions.[46] This failure inspired us to re-evaluate the system. With related work by Magnus as context, we realized that the benzofuran component of the molecule should be considered electron-deficient, rather than electron-donating in this case (compare **44** and **46**). This analysis encouraged us to target intermediate **46**, with an electron-rich enol moiety to match the electron-deficient benzofuran subunit. We identified allenol ether **45** as an appropriate precursor,[47] poised to undergo oxidation with generation of polarized intermediate **46**, and subsequent cyclization to afford **47**. The product would then contain both stereogenic centers present in the core of the rocaglate natural product family.

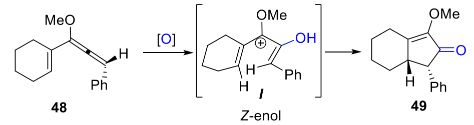
This strategy was ultimately successful. Treatment of **45** (R=$SnBu_3$) with *m*-CPBA (3 equiv) delivers **47** in 48% yield as a single diastereomer.[48,49] This intermediate was critical to our strategy for the total synthesis of rocaglate natural products including (±)-rocaglamide and (±)-aglafolin. The stannane was employed because it was not possible to build allenol ether **45** (R=H). The tributylstannyl group is cleaved under the cyclization conditions, presumably before the electrocyclization step. In a later study, we tested this assumption by oxidizing simple allenol vinyl systems without the stannane substituent. The stereochemistry observed corresponds to the cyclization of an intermediate enol analogous to **46** (Scheme 6b).[2] Interestingly, the Nazarov cyclization is diastereoselective. The selectivity can be rationalized as follows: a diastereoselective oxidation (facial selectivity on the allenol ether)[50] produces a cationic intermediate (**I**, Scheme 6b) as the *Z*-isomer, which cyclizes to give the observed diastereomer. The minor diastereomer is generated from cyclization of the *E*-isomer, which can result from oxidation of the more hindered face of the allenol (or through *Z*/*E* isomerization post oxidation).

Scheme 6. Nazarov Cyclization Triggered by Oxidation:

a) Strategy for the Synthesis of (±)-Aglafolin and (±)-Rocaglamide



b) Simple Allenol Ethers



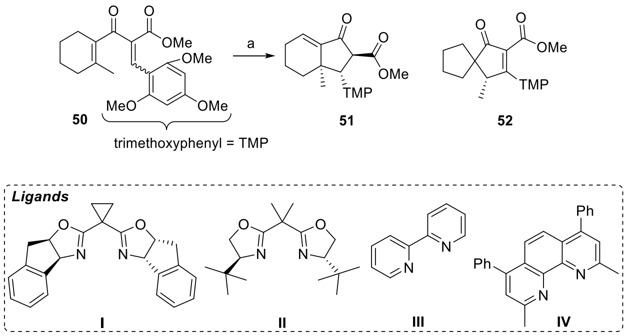
Nazarov Cyclization/ Wagner-Meerwein Rearrangement Sequences

During efforts to develop methods for catalytic asymmetric Nazarov cyclizations, we observed the formation of an unexpected product that proved to arise from an atypical Stage 2 process: a Wagner-Meerwein shift. The initial result was obtained upon exposure of **50** to a stoichiometric amount of copper(II) bisoxazoline complex I (Scheme 7). We were astonished to find that precursor **50**, which had always reacted smoothly to produce fused system **51**, had suddenly delivered compound **52** instead. The reaction conditions for each result differed in only two ways: the identity and the loading of the catalyst. This inspired us to investigate further in order to identify which factors were responsible for selective generation of **51** (Cu(OTf)$_2$, 2 mol%) or **52** (Cu(box)(SbF$_6$)$_2$, 1 equiv).[32]

We reasoned that there were three variables that could alter the reaction pathway: the ligand, the counterion, or the copper(II) loading. Using stoichiometric loadings, we tested copper(II) hexafluoroantimonate complexes with bidentate bisoxazoline (entries 6-7) and bipyridine ligands (entries 9-10), as well as a promoter generated from counterion exchange of copper(II) chloride

(1 equiv) with silver hexafluoroantimoate in acetonitrile (entry 8). All of these promoters produced the spirocyclic product **52** exclusively, which indicated that the ligand has no effect on the product distribution.[51] It is important to note that, for the cases where enantiopure chiral ligands were used (entries 3-7), the ee observed was poor (less than 45% ee for most cases).[51]

Scheme 7. Nazarov Cyclization/Wagner-Meerwein Sequences.[52]



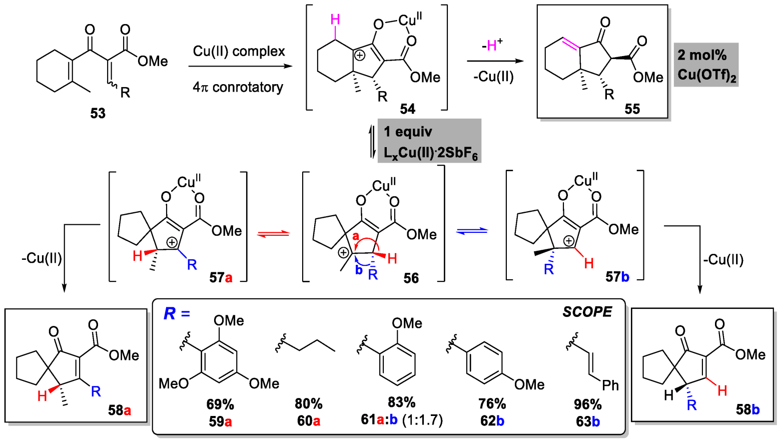
Entry	L	Cu(II) Anion	Cat. (mol%)	Ratio (**51**:**52**)	% Yield (**51**+**52**)
1	-[b]	OTf	2	100:0	95[c]
2	-[b]	OTf	100	7:1	89
3	I	OTf	10	100:0	66[d]
4	I	ClO_4	100	~1:1	90[d]
5	I	SbF_6	10	4:1	62[d]
6	I	SbF_6	100	0:100	69[c]
7	II	SbF_6	100	0:100	85[d]
8	(CN)x	SbF_6	100	0:100	76[c]
9	III	SbF_6	100	0:100	76[d]
10	IV	SbF_6	100	0:100	91[d]

a) Reaction conditions: Substrate **50** in CH_2Cl_2 (0.03M), ligand and promoter added at 25°C. b) No added ligand. c) From Ref. 3. d) From Ref. 51

Additional experiments were conducted to examine the effect of catalyst loading and the counterion associated with the copper(II) promoter. 1 equivalent of copper(II) triflate (no ligand) gives a 7:1 ratio of Nazarov products **51** and **52** (entry 2). The copper(II) box complex prepared with a perchlorate counterion gives no selectivity for one Nazarov product over the other. These experiments indicate that, as the counterion becomes more noncoordinating and less basic, the rearranged product **52** becomes dominant. Experiments examining the effects of catalyst loading on the process were also illuminating. When the copper(II) hexafluoroantimonate complex with ligand **I** is used in substoichiometric amount (10 mol%, entry 5), product **51** is formed preferentially over **52** (4:1 ratio). These observations suggest that the use of stoichiometric amounts of a promoter with a non-coordinating counterion maximizes the formation of rearranged product **52**.[32]

From this data, we formulated the mechanistic hypothesis presented in Scheme 8. Using either catalytic or stoichiometric amounts of any promoter, oxyallyl cation intermediate **54** is formed. At this point, two different reactions can occur: elimination to produce **55**, or Wagner-Meerwein shift to generate intermediate **56**. The elimination pathway is expected to occur more slowly in the presence of non-basic counterions, allowing the rearrangement pathway (via **56**) to become competitive. Under conditions employing a 1:1 ratio of substrate and promoter elimination will be even slower, since all the basic carbonyl groups are engaged in coordination to the Lewis acidic center. Therefore, this mechanism (with branch point at intermediate **54**) is consistent with the observation that complete suppression of the elimination pathway is observed under the optimized conditions.

Scheme 8. Wagner-Meerwein Rearrangement Pathways[52]

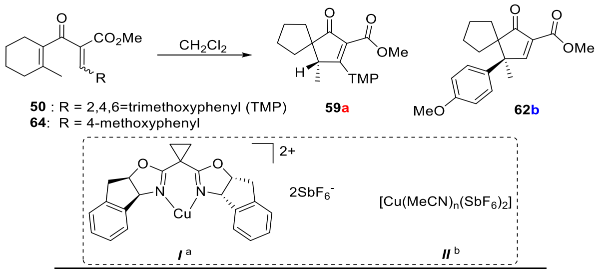


Also relevant is the observation that two different types of products (spirocycles **58a** and **58b**) can be obtained depending on the R substituent in substrate **53**. If intermediate **56** undergoes a hydride shift, product **58a** is obtained, while migration of the R group (a second Wagner-Meerwein shift) leads to product **58b**. Remarkably, most reactions are selective for either **58a** or **58b** and do not produce a mixture of the two.[51]

The finding that stoichiometric copper(II) salts are optimal for effecting clean cyclization/ rearrangement (Scheme 9) did not bode well for achieving catalytic enantioselective reactions. When our experiments suggested that the salts are critical for complexation of the carbonyl oxygen, we began to search for surrogates that could act in combination with a catalytic amount of a chiral copper(II) complex. Subjecting **64** to 1.0 equivalent of $[Cu(box)(SbF_6)_2]$ with no additive gives 76% of spirocycle **62b**.[51] Using a combination of 10 mol% $[Cu(MeCN)_n(SbF_6)_2]$ and 90 mol% of a second additive (including $Zn(OAc)_2$, $Mn(acac)_2$, $Fe(acac)_2$, $LiClO_4$, $Mg(OTf)_2$, $NaSbF_6$, and $NaBPh_4$) leads to longer reaction times and mixtures of products.

Ultimately, we found that copper(II) loading can be reduced significantly when $NaBAr^F{}_4$ is employed as a stoichiometric additive. We hypothesize that the sodium atom serves to coordinate with the ketone oxygen, which must be the basic species that is responsible for facilitating the competing elimination step. Subjecting substrate **64** to 90 mol% of $NaBAr^F{}_4$ in combination with 10 mol% of $[Cu(MeCN)_n(SbF_6)_2]$ gives 78% of spirocycle **62b**.[53] Switching to the Cu(II) box complex results in 88% yield of **62b** (enantiomeric excess was not measured, since it was known to be low from previous findings).[33] Lowering the catalyst loading to 5 mol% and increasing the amount of $NaBAr^F{}_4$ to 95 mol% leads to a slight drop in the yield of **62b**. Subjecting **50** to 10 mol% of $[Cu(MeCN)_n(SbF_6)_2]$ and 90 mol% of additive gives 90% yield of spirocycle **59a**. As expected, adding no copper(II) catalyst and 100 mol% of the additive leads to no reaction.[53]

Scheme 9. Cyclization/ rearrangement using catalytic Copper(II)[52]

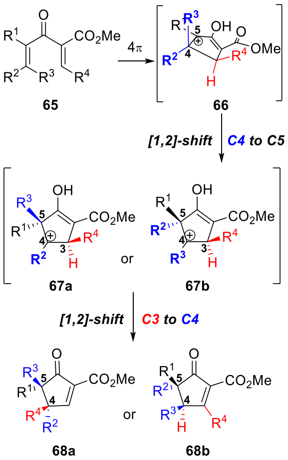


Entry	SM	Cat. (mol%)	$NaBAr^{F}_{4}$ (mol%)	Prod. (%yield)
1	**64**	I (100)	0	**62b**(76)[d]
2	**64**	II (10)	90	**62b**(78)[c]
3	**64**	I (10)	90	**62b**(88)
3	**64**	I (5)	95	**62b**(82)
6	**50**	II (10)	90	**59a**(90)[b]
7	**50**	-	100	NR

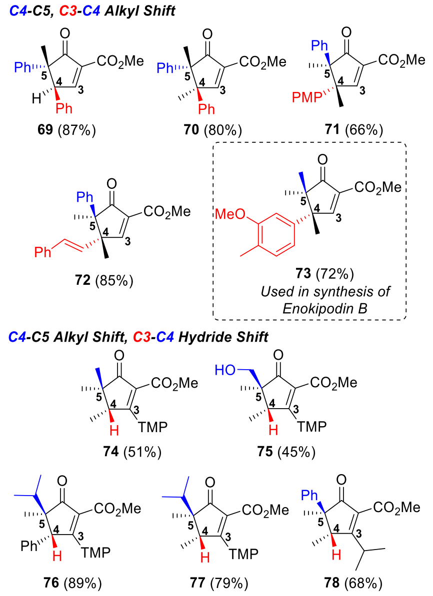
a) Procedure for preparation of catalyst: To BOX I and $CuCl_2$ in DCM add $2AgSbF_6$ and isolate Cu(II) BOX hexafluoroantimonate complex. b) Procedure for preparation of catalyst: $CuCl_2$ and $2AgSbF_6$ in acetonitrile; isolate Cu(II) acetonitrile hexafluoroantimonate complex, then add BOX. c) From Ref. 55 d) From Ref. 51

We next sought to examine whether the cyclization/rearrangement chemistry would occur selectively in acyclic systems, to produce cyclopentenones containing vicinal stereogenic centers at C4 and C5 (Scheme 10). We appreciated that the success of this venture would hinge upon the chemoselectivity of the initial Wagner-Meerwein shift since two different substituents are poised to migrate from C4 to C5. The second [1,2]-shift, (C3 to C4) was expected to be well-behaved, based on the experiments on the spirocycle formation (Scheme 7).

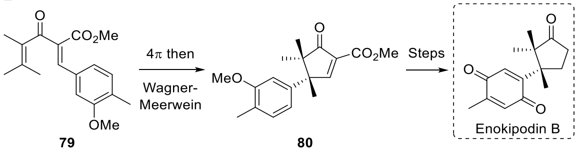
Scheme 10. Cyclization/ Rearrangement of Acyclic Dienones



a) Products of cyclization/ rearrangement



b) Synthesis of (±)-Enokipodin B

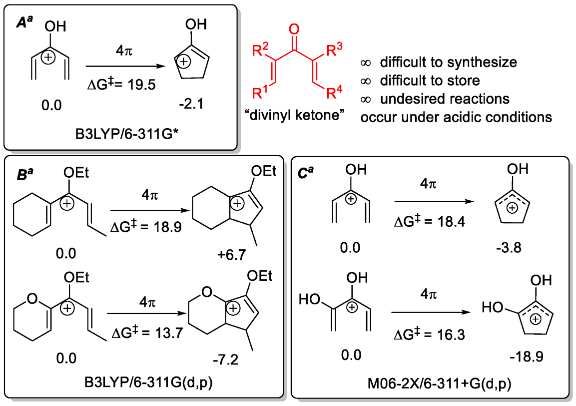


Our studies demonstrate that chemoselective [1,2]-shifts occur for a variety of acyclic substrates **65**. C4 to C5 migrations are colored blue in Scheme 10a, while C3 to C4 migrations are colored red.[53] This methodology was employed toward the synthesis of (±)-enokipodin B from divinyl ketone **79**, which cyclizes to give Nazarov product **80** (Scheme 10b).[54] When the C4 substituents have different migratory aptitudes, single diastereoisomers are obtained from the cyclization/rearrangement. In **74-77**, migration of the sterically bulky 2,4,6-trimethoxyphenyl group from C3 to C4 does not occur, and a chemoselective hydride shift is observed instead. A C3 to C4 hydride shift is also observed when a bulky alkyl group (having low migratory aptitude) is present on C3 (see **78**). In collaboration with Prof. Gandon (ICMMO, France), DFT calculations were executed which accurately predict the dominant rearrangement pathways in cases influenced by either migratory aptitudes and/or steric effects within the molecule.[3,55]

Shortcomings of Divinyl Ketones as Pentadienyl Cation Precursors

After studying the classical Nazarov for several years, we came to realize two different limitations that significantly impact the utility of the reaction as a synthetic method. The first limitation is the need to use divinyl ketones as reactants. These can be difficult to synthesize, have limited shelf life, and can react in undesired ways under acidic conditions. The second limitation lies in the energetics of the reaction (Scheme 11).[56] Formation of the oxyallyl cation can be thermodynamically favorable (Scheme 11, boxes A, C)[57] or endergonic (box B, top; see also Scheme 2). Polarizing the system improves the energetic profile (boxes B, C),[57] but the barrier is still relatively high.[19,20] Upon gaining these new perspectives on the reaction, the focus of our research program shifted toward discovery and development of alternative ways to access pentadienyl cations, to achieve a more efficient electrocyclization processes.

Scheme 11. Shortcomings of Divinyl Ketones and 3-Oxypentadienyl Cation Intermediates

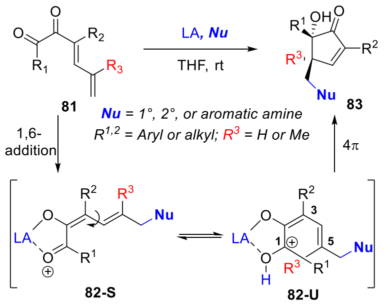


a)All energies given in kcal mol^{-1}

Alternative Pentadienyl Cation Precursors

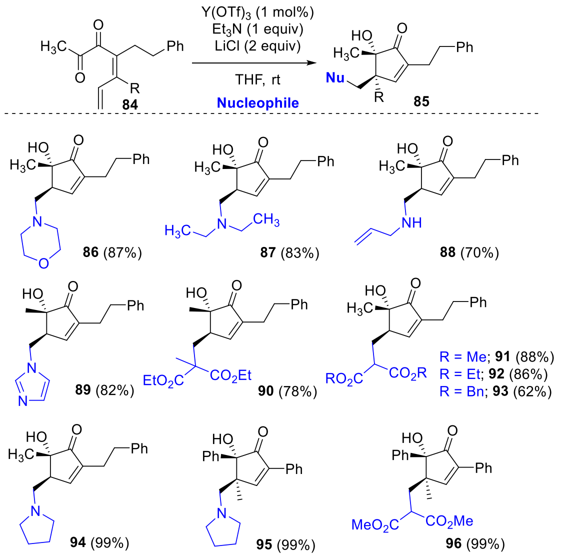
During the (±)-rocaglamide study, we generated 3-oxypentadienyl cation **46** from an allenyl ether and later explored the scope and limitations of this approach (Scheme 7).[2] This piqued our interest in alternative methods for generating pentadienyl cation intermediates for the Nazarov cyclization. In a different study, we found that generating pentadienyl cations of type **82** (3-alkyl or -aryl) is possible from the 1,6-addition of a nucleophile to a dienyl diketone (Scheme 12).[58-61] Activation of the dienyl diketone with a Lewis acid facilitates addition of nucleophiles to generate intermediate **82**. This intermediate presumably forms in the S-conformation but can then isomerize (through σ-bond rotation) to the U-shape necessary for cyclization.

Scheme 12. Generation of 3-Alkyl/ 3-Aryl Pentadienyl Cations by 1,6-Conjugate Addition to Dienyl Diketones



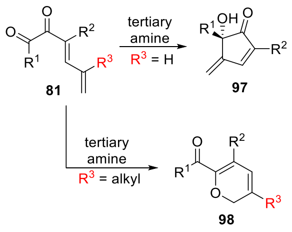
Cyclization generates 5-hydroxyketone products **83** as single diastereoisomers. Cyclizations triggered by 1,6-addition of amine and malonate nucleophiles have been demonstrated with both unsubstituted (R^3 = H, **86-94**)[58] and substituted (R^3 = methyl, **95** and **96**)[59,60] dienones (Scheme 13). Strangely, if R^3 is any larger than methyl, electrocyclization is thwarted and a different reaction pathway is observed (vide infra). A wide variety of amines can initiate cyclization, including primary and secondary amines, aniline derivatives, and aromatic amines. With many amine nucleophiles, aryl dienones (R^3 = aryl) can be induced to cyclize smoothly even in the absence of a Lewis acid reagent.[4] In cyclizations of unsubstituted dienones (R^3 = H) reactions must be halted as soon as the cyclization is complete, as longer reaction times lead to decreased diastereoselectivities. This gradual erosion of diastereoselectivity is thought to occur through a post-cyclization isomerization (details provided in Scheme 15 below).

Scheme 13. Scope of the Nazarov Cyclization of Unsubstituted Dienones with Different Nucleophiles

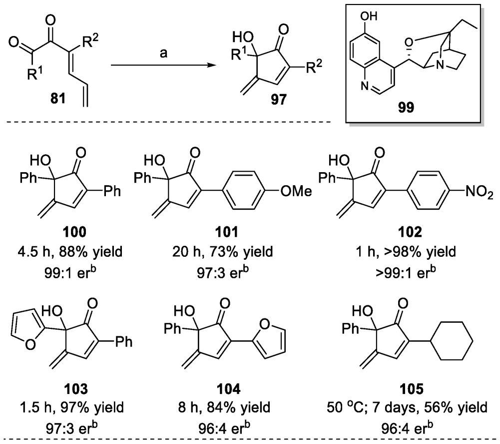


Tertiary amines (DABCO, Cinchona alkaloids) are also competent nucleophiles for the 1,6-addition/cyclization sequence, but the ultimate outcomes of these reactions are different. In unsubstituted dienones (R^3 = H), *exo*-methylene enones **97** are obtained (Scheme 14a).[62] Having established that trisubstituted amines do promote the cyclization, we carried on with addition of DABCO to substituted dienones (R^3 = Me) and found that these reactions do not produce cyclopentenones at all, but rather dihydropyrans **98** (Scheme 14b).[59,60]

Scheme 14: Nazarov Cyclization of Dienones with Tertiary Amine Nucleophiles

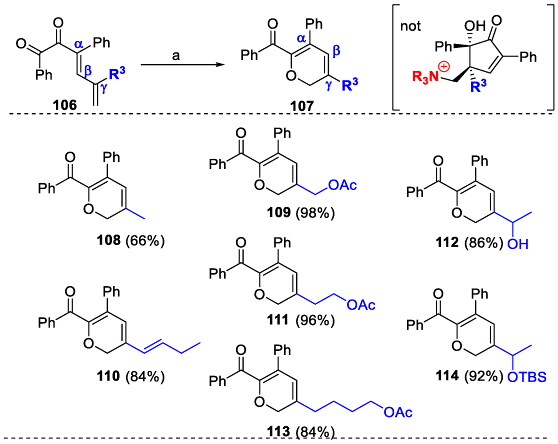


a) Enantioselective Cyclization/Elimination using Cinchona alkaloid derivative as nucleophile (R^3 = H)



a)Reaction conditions: **81** (1 equiv), **99** (3 mol%), DMF (0.1 M). b) Enantioselectivities determined by Super-Critical Fluid Chromatography (SFC)

b) Dihydropyrans Isolated from Reaction of DABCO with γ-substituted Dienone (R^3 = Alkyl)

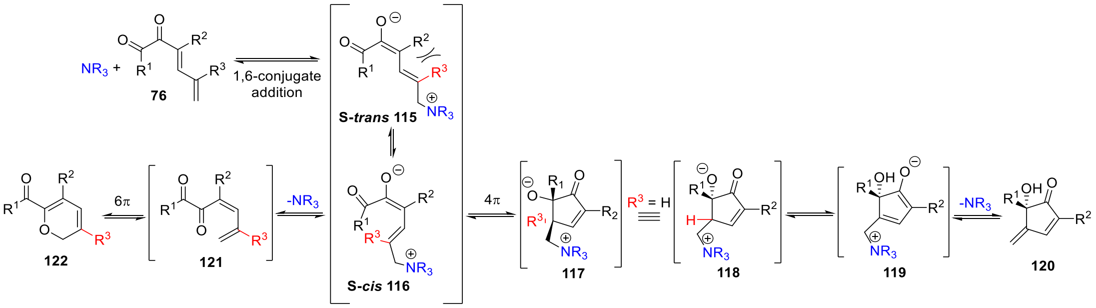


a)Reaction conditions: Diene **106** (1 equiv) in THF (1 M), DABCO (10 mol%) added. Stir at rt

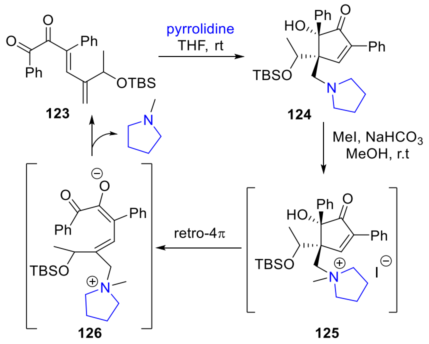
The mechanism for the formation of different products from dienones is shown in Scheme 15. Addition of a tertiary amine to dienone **81** generates an intermediate species **117** which cannot deprotonate at nitrogen to afford products like **85**. Longer reaction times lead to erosion of the diastereomeric ratio due to enolization of **118** under the reaction conditions, ablating the *γ*-stereocenter generated during cyclization. Tautomerization then occurs with poor facial selectivity.[58] The cyclic dienones **120** are generated from 1,6-addition, cyclization, and then elimination of the amine from the enol tautomer **119** of intermediate **118**.

On the other hand, dihydropyrans **122** are not products of the 1,6-addition/cyclization sequence yet are obtained in good yields. In these cases, with tertiary amine nucleophiles, the usual conjugate addition/cyclization is unproductive and indeed must be reversible. This reversibility was unanticipated and led us to misassign structures at first.[59,60] Later experiments designed to explore the feasibility of this pathway provided strong support for this hypothesis (Scheme 15a). Methylation of the amine in Nazarov product **124** leads to quaternary ammonium intermediate **124**, which is analogous to the zwitterion **117** formed when a tertiary amine is used. Intermediate **125** can then undergo retro-4π to give **123** via **126**.[4]

Scheme 15. Mechanistic Proposal for Reactions of Tertiary Amines with Dienones



a) Evidence for Retro-4π Electrocyclization Pathway

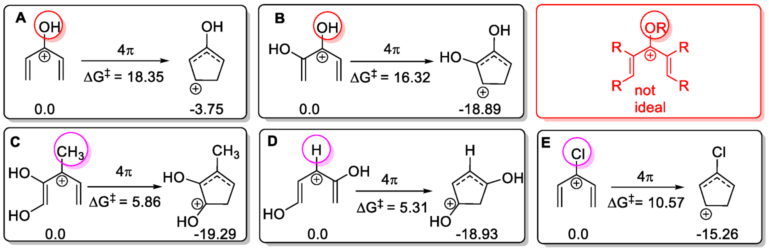


Is this cyclization a true cationic electrocyclization, or does it have some ionic character? Stereochemical data is consistent with conrotatory cyclization for all the examples studied. Interestingly however, this is not conclusive evidence of an electrocyclic mechanism.[63] As a result, we cannot rule out the possibility that the reaction is ionic and geometrically predisposed to occur diastereoselectively in what is apparently a conrotatory sense. A better understanding of the intricacies of the mechanism will require further analysis using both experimentation and computational methods.

Moving Away from 3-*Oxy* Nazarov Substrates

Over the course of these studies along with concurrent research on the Piancatelli version of the Nazarov cyclization, it was becoming clear that the central 3-substituent on the pentadienyl cation, in combination with the adjacent substituents, has an enormous influence on the cyclization rate and efficiency.[20] To understand the kinetic and thermodynamic profiles of the different variants, we applied the M06-2X/6-311+G(d,p) basis set to the simplified systems A-D.[56] Scheme 16 shows data for the Nazarov cyclization (A; **3-*oxy***), polarized Nazarov cyclization (B; 2,**3**-di**oxy**), nucleophilic Nazarov cyclization (C; 1,4 dioxy-***3-alkyl***), and Piancatelli cyclization (D; 1,4 dioxy ***3-hydrido***).

Scheme 16. Calculated Impact of Pentadienyl Cation 3-substituents on Reaction Energetics (M062X/6-311+G(d,p)) (Energy values given in kcal mol^{-1})



Most striking is the low electrocyclization barriers calculated when the 3-position is hydrogen or carbon (~ 5 kcal mol^{-1}), compared to oxygen (>16 kcal mol^{-1}). A confluence of research projects underway in our group[64] led us to consider strategies for generating and cyclizing a 3-halopentadienyl cation, an underexplored reaction manifold.[65] Computational analysis on the proposed *chloro*-Nazarov cyclization intermediate in box E (***3-chloro*** pentadienyl cation, Scheme 16) predicts barriers lower than the 3-oxy analogs but higher than the 3-hydrido and 3-alkyl analogs.[66] The thermodynamic profile of this *chloro*-Nazarov reaction is predicted to be similar to the polarized systems (Scheme 16, boxes B, C and D). This encouraging data led to our current studies of cascade cyclizations that are predicated on *halo*-Nazarov electrocyclizations.[67] These studies are ongoing and will not be discussed in this Account.

In summary, the research program that began in our lab in 2002 first interrogated substitution patterns and their impact on electrocyclization behavior. Over the course of these studies, including the quest to achieve enantioselective catalysis and apply these methods to natural product synthesis, we developed an appreciation for the two-stage nature of the Nazarov cyclization and an aversion to divinyl ketones as reactants. These new perspectives led to the discovery and characterization of a rearrangement sequence influenced by both sterics and migratory aptitudes, which launched a search for alternative methods for the generation of pentadienyl cation intermediates. Two new variants of the Nazarov electrocyclization emerged from these studies, one initiated by allenol ether oxidation and another triggered by 1,6-addition of nucleophiles to dienyl diketones. Ultimately, we were able to complete formal or total syntheses of four natural products using the methods uncovered in our lab: (±)-merrilactone A, (±)-roseophilin, (±)-rocaglamide and (±)-enokipodin B.

The studies also led us full circle in our evaluation of the electronic impact of pentadienyl cation substituents during the Nazarov cyclization. This work began in 2002, with studies focused on the advantages of polarization in 3-oxy pentadienyl cation systems and ended in 2015, with the rejection of 3-oxy systems *in general.* Experimentation has revealed that when the 3-position is substituted with a hydrogen, carbon, or a halide (rather than oxygen) reactions are more efficient and a wider range of product scaffolds can be obtained. Following this lead, research directions focused on 3-*halo*-Nazarov cyclizations are currently being pursued in the lab. Some of this work has been disclosed already,[67-70] and new findings will be reported in due course.

BIOGRAPHICAL INFORMATION

Professor Alison J. Frontier

Professor Frontier was born in Royal Oak, Michigan on November 23rd, 1970. She received her AB from Harvard in 1992, then spent two years as an Associate Chemist at Merck Research Laboratories in Rahway, NJ. She earned her PhD in 1999 with Professor Danishefsky (Columbia University) and trained as a postdoc with Professor Trost (Stanford University) before joining the faculty at the University of Rochester, where she is now Professor of Chemistry. Her research focuses on devising novel strategies for the synthesis of bioactive, structurally interesting natural products, as well as the development of pericyclic reactions and multistep cationic cyclization cascades.

Jackson J. Hernandez

Jackson was born in Cuba on February 14th, 1997. He moved to the United States in 2012 as a High School student, then received his BS in chemistry from the University at Buffalo in 2018. While at UB, he worked with Dr. Bing Gong on the synthesis of unnatural foldamers. Jackson began his graduate studies in 2018 at the University of Rochester, where he joined the research of Dr. Alison Frontier. His work is focused on the development of new *halo-aza*-Prins/*halo*-Nazarov methodologies for the synthesis of bioactive alkaloids.

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