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Beyond the Divinyl Ketone: Innovations in the Generation and Nazarov Cyclization of Pentadienyl Cation Intermediates

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Abstract

The requirement for new strategies for synthesizing five-membered carbocycles has driven an expansion in the study of the Nazarov cyclization. This renewed interest in the reaction has led to the discovery of several interesting new methods for generating the pentadienyl cation intermediate central to the cyclization. Methods reviewed include carbon-heteroatom ionization, functionalization of a double bond, nucleophilic addition, or electrocyclic ring opening. Additional variations employ unconventional substrates to produce novel pentacycles, such as the iso- and imino-Nazarov. Herein, we provide an overview of these unconventional, yet highly useful versions of the Nazarov cyclization.

Keywords

Nazarov; electrocyclization; carbocation; cyclopentane; synthesis

Introduction

Since its initial discovery over 60 years ago,[1] the Nazarov cyclization has evolved to become a primary tool for the of cyclopentenones. The classical version (Scheme 1) is triggered by the Lewis- or Brønsted-acid activation of a divinyl ketone (**1**), which forms a pentadienyl cation (**2**). Electrocyclization produces an oxyallyl cation (**3**) which may eliminate or undergo trapping by a nucleophile to yield the product cyclopentenone (**4** and **5**). The characteristic diastereospecificity[2] of the cyclization is a consequence of orbital symmetry rules, which dictate an antarafacial overlap of the two cyclization termini in the transition state, leading to stereospecific conrotatory cyclization.

These powerful attributes have stimulated the extensive development and expansion of the reaction.[2,3] In recent years, this expansion has included the use of unconventional substrates or transformations to generate the requisite pentadienyl cation. In this microreview, we provide an overview of select examples of these methods.

We have organized them according to two defining features: 1) the reaction that generates the pentadienyl cation, and 2) the structure of the pentadienyl cation. There are several approaches which may fall under more than one classification, and in these instances we have used our discretion.

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1. Formation of Pentadienyl Cations Through Ionization of a Carbon-Heteroatom Bond

Ionizing the C–O bond of an alcohol or ether is an effective way to initiate a Nazarov cyclization when the resulting carbocation is capable of conjugating with two double bonds, thus providing a straightforward route to cyclopentenes and cyclopentadienes.

Alcohol Ionization

An increasingly common method for constructing such 5-membered carbocycles by means of the Nazarov cyclization is through the ionization of a divinyl carbinol substrate.[4] This is illustrated by the $Sc(OTf)_3$-catalyzed ionization of alkenyl aryl carbinols (**6**) to form [6,6,5,6] and [6,6,5,5] heterocyclic ring systems (**8**, Scheme 2).[5] The cyclization efficacy was highest when the participating aromatic ring was electron-rich, with yields ranging from good-to-excellent. 2-Thienyl, 3-furyl, or 3-benzo[*b*]thienyl aryl groups resulted in decomposition.

Ether Ionization

Ionization of an ether has also found application in several contexts. One that exemplifies the potent synthetic potential of this approach is demonstrated in Scheme 3. After C–O bond cleavage of dihydrofuran **9** by $BF_3{\cdot}OEt_2$, a Nazarov cyclization interrupted by intramolecular alkoxide trapping occurs to form [6,5] ring system **13** which is hydrolyzed during workup to furnish lactone **14**.[6] A related ether ionization–intramolecular trapping method uses an allene as one of the π components.[7]

Quite recently, Romo has employed such a tactic to construct the C ring of Agelastatin A (Scheme 4).[8] Treatment of **15** with trifluoroacetic acid at low temperature yielded **18**, presumably through removal of ethoxide in **15** to form pentadienyl cation **16** and subsequent water trapping of the stabilized allylic cation **17**. The cyclization was notably complete within 5 minutes.

2. Formation of Pentadienyl Cations Through Activation of a C=C Bond

Pentadienyl cation generation is also possible through activation of a conjugated or cross-conjugated triene with a Lewis or Brønsted acid.

Protonation of Alkoxytrienes

Alkoxytrienes can be excellent divinyl ketone surrogates. They undergo facile Nazarov cyclization immediately following protonation, under conditions which are too mild for the analogous divinyl ketone substrates to cyclize.[9] The erudite study of this reaction by Occhiato and Prandi has established a framework for several aspects of the reaction including torquoselectivity, size of the heterocyclic ring component, and regioselectivity. The latter parameter was found to be controlled primarily by substitution at the exocyclic triene terminus (Scheme 5): when R^1 and/or R^2 are unsubstituted, fused [6,5] ring system **22** was obtained (Path a), while Me or Et mono- or di-substitution allowed competition with spirocyclic [6,5] products **24** and **25** (Path b).

3. Formation of Pentadienyl Cations Through Activation of an Allene

The reactivity of the allene double bond, driven in part by the relief of allenic strain, has been harnessed to effect Nazarov cyclizations prompted by exposure to various electrophilic species such as oxidants, transition metal complexes, and Brønsted acids.[10]

Oxidation-Initiated Nazarov Cyclization

This approach was demonstrated recently when Frontier and Spencer[11] found that exposure of vinyl alkoxyallenes to dimethyldioxirane (DMDO) initiated a Nazarov cyclization that produced cyclopentenones with adjacent stereocenters at C_4 and C_5 in high diastereoselectivity (Scheme 6).[12] A mechanistic rationale based on the results of several informative experiments was proposed which elucidates the observed diastereochemical outcomes of the reaction: when a vinylalkoxyallene substituted with a large group (R_L) and a small group (R_S) at the allene terminus reacts with DMDO, epoxidation occurs away from R_L. When $R_L >> R_S$, the diastereoselectivity of this epoxidation is complete, resulting in allene oxide **29**. When $R_L > R_S$, epoxidation is less diastereoselective, resulting in a mixture of allene oxide diastereomers (**29**'). Epoxide ring opening of **29** results in pentadienyl cation **30**/**31**, which after electrocyclization yields a single diastereomer of the product cyclopentenone (**32**). The analogous process which occurs on diastereomeric allene oxide mixture **29**' results in cyclopentenone **32**' as a mixture of diastereomers. This transformation was used in a total synthesis of (±)-Rocaglamide.[13]

Activation using transition metal catalysts

Toste and coworkers activated vinylallenes (**33**) with cationic Au(I), resulting in cyclopentadienes **34** (Scheme 7).[14] The group proposes the following catalytic cycle: activation of the allene produces pentadienyl cation **36**, which undergoes electrocyclization to give allylic cation **37**/**38**. A hydride shift then occurs (H_a shifts to the Au *ipso* position), followed by elimination to regenerate the active catalyst and yield a molecule of cyclopentadiene product **34**. A similar variant initiated by platinum activation was published back-to-back with this work,[15] and an additional gold-catalyzed variant which generates a cyclopentadiene with different double bond regioselectivity was recently disclosed.[16]

Cationic gold(I) activation of a phenylallene bonded with a homopropargylic moiety (**39**, Scheme 8) resulted in carbocyclic [6,5,6] systems (**44**).[17] Deuterium-labeling experiments supported an initial coordination of $[AuPPh_3]^+$ to the alkyne, followed by 6-*endo*-*dig* cyclization to form pentadienyl cation **41**/**42**. Subsequent electrocyclization forms **43**, which undergoes protonolysis of the C-Au bond to furnish polycycle **44**.

When allenes of type **45** were treated with $PtCl_2$ under an atmosphere of CO,[18] an unexpected double Nazarov cyclization occurred (Scheme 9).[19] The proposed mechanism starts with the Pt(II)-catalyzed ionization of methoxide to give pentadienyl cation **46**, which after a first Nazarov cyclization generates pentadienyl cation **47**. A second Nazarov cyclization followed by methoxide trapping yields the product carbocycle **49**.

4. Formation of Pentadienyl Cations Through 1,6-Conjugate Addition

Frontier, Brooks, and Caruana[20] recently found that various carbon and nitrogen nucleophiles undergo a 1,6-conjugate addition on α-diketone substrates (**50**, Scheme 10). A subsequent Nazarov cyclization occurs to provide α-hydroxycyclopentenones (**51**),[21] which in the presence of $Y(OTf)_3$ are isolated as a single diastereomer. If a catalytic amount of nucleophile is employed, exo-cyclopentadienones **58** are isolated instead of cyclopentenones **56**. It is proposed that under the basic reaction conditions, γ-deprotonation of cyclopentenone **56** produces **57**, which expels the nucleophile to form diene **58**. This hypothesis was supported by the observation that when stoichiometric nucleophile was employed, extended reaction times led to epimerization of **56**, presumably via either deprotonation/reprotonation (**56**/**57**) or retro-1,6-addition/ 1,6- addition (**57**/**58**).

Extension to substrates containing a substituent R^1 (**59**, Scheme 11) enabled the synthesis of products containing adjacent quaternary centers (**60**).[22] When R^1 was a pendant acetate group ($R^1 = (CH_2)_nCHR^2OAc$) and exposed to conditions incorporating 1,4-diazabicyclo[2.2.2]octane (DABCO), diastereopure bicycle **61** was unexpectedly obtained. This result was rationalized by the conjugate addition of DABCO to dienyl ketones of type **62** to form zwitterion **65**, which then undergoes an intramolecular S_N2 reaction to form 7-membered intermediate **66** (Scheme 12). A Nazarov cyclization, torquoselective through the steric influence of the R^2-substituted stereocenter, results in **68**. A final S_N2 displacement restores charge neutrality by forming bicycle **69**.

5. Pentadienyl Cations from Transition Metal Catalyzed Rearrangements of Propargyl Acetates

The ability of propargylic alkanoates to undergo rearrangement chemistry with transition metals has been capitalized upon to generate pentadienyl cations when this moiety is appropriately substituted with a vinyl group.

Toste and coworkers found that when propargylic pivalates (**70**) are substituted with a vinyl group at the propargylic position, they undergo a rearrangement under gold(I) catalysis to produce cyclopentenones **71**,[23] in what is effectively a gold-catalyzed Rautenstrauch cyclization (Scheme 13).[24]

The utility of the cyclization was further augmented when a series of chiral, enantiopure substrates yielded the corresponding cyclopentenone products enantioselectively. According to DFT calculations,[25] initial catalyst coordination to the triple bond of propargylic acetate **72** occurs, followed by intramolecular 1,2-addition of the ester onto the alkyne to form **74**. Fragmentation then leads to a helically chiral pentadienyl cation **75**, which undergoes electrocyclization faster than racemization to form **76**. Elimination of **76** affords cyclopentenone surrogate **77** and regenerates the active catalyst. There is only one additional example[26] to our knowledge of memory of chirality[27] in the electrocyclization of a pentadienyl cation. Closely related versions of this cyclization using ruthenium[28] and palladium[29] catalysis have also been explored recently.

Remarkably, placement of the vinyl group at the alkyne terminus results in an entirely different mode of reactivity (Scheme 14).[30] Exposure of vinyl propargylic acetate of type **78** to catalytic $AuPPh_3Cl/AgSbF_6$ results in conversion to cyclopentenones of type **87**. DFT calculations[31] suggest a formal 3,3-rearrangement of **78** to form allene **79**, which is activated by the gold complex to form pentadienyl cation **80**. Electrocyclization forms an allylic cation (**81**/**82**) which is converted to cyclopentadiene **85** in two ways. In dry CH_2Cl_2, the primary pathway is a 1,2-hydride shift to form **83**, which eliminates to give **85**. In wet CH_2Cl_2 however, **85** is formed through a two-step water-catalyzed deprotonation-protonation process in which water aggregates, stabilized by the acetoxy carbonyl, serve to shuttle protons. This water-catalyzed hydrogen transfer mechanism is lower in energy than the 1,2-hydride shift, supporting experimental observations demonstrating that the reaction is faster in wet CH_2Cl_2. A similar rearrangement was studied by Malacria and coworkers, involving a cyclopropanation of the intermediate gold alkylidene species with a pendant olefin.[32]

6. Tautomerization / Nazarov Cyclization Sequences

The Nazarov cyclization of α-diketones was first noted in 1965 by Muxfeldt[33] and then used by Weinreb in 1975 to synthesize Cephalotaxine.[34] Later, in an extension of his earlier studies on the palladium(II)-catalyzed cyclizations of α-alkoxydienes, Tius and

coworkers explored the scope of the cyclization under both basic conditions using LiTMP and Lewis acidic conditions using $Yb(OTf)_3$.[35] Shortly afterwards, they made the striking discovery that the reaction could simply be performed on activated silica in the absence of any other reagents or solvents (Scheme 15),[36] although triethylamine increased the reaction rate. The Tius group later developed asymmetric versions using a diamine promoter[37] and a bifunctional organocatalyst, allowing access to highly functionalized chiral cyclopentenones such as **90a** and **90b**.[38] Lewis-acid catalyzed variants have been used by Williams in the synthesis of Fusicoauritone[39] and by Harmata for preparation of an advanced intermediate in a synthetic strategy targeting Hamigeran B.[40]

7. Electrocyclic Ring Opening / Nazarov Cyclization Sequences

An elegant and novel means to generate Nazarov substrates *in situ* is through a 4π or 6π electrocyclic ring opening. Subsequent Nazarov cyclization occurs under the same conditions to form the cyclopentenone product.

Hetero-enyne metathesis

The use of a catalyst which plays dual roles in activating alkyne π bonds and carbonyl lone pairs has allowed the development of a tandem alkyne-aldehyde metathesis–Nazarov cyclization (Scheme 16).[41] Using a substrate containing both functional groups bridged by an appropriately sized tether, an initial metathesis enables formation of divinyl ketone substrate **94**, which under the same catalytic conditions undergoes a Nazarov cyclization to regioselectively produce cyclopentenones of type **95**, containing two new rings. An intermolecular version of the reaction in which the alkyne and aldehyde are in separate reactants has also been developed.[42]

Treatment of squarate esters of type **96** at −78°C with two equivalents of vinylmagnesium bromide followed by quenching with a proton source at the same temperature allows regioselective formation of cyclopentenones **100** (Scheme 17).[43] The mechanism was proposed to initiate with a regioselective double 1,2–1,4 addition of vinylmagnesium bromide to form cyclobutadiene **97**, which undergoes an electrocyclic ring opening to give tetraene **98**. Regioselective protonation at the methylene terminus with the highest coefficient and electronic density occurs to yield divinyl ketone **99**, which undergoes a 4π electrocyclization to furnish cyclopentenone **100** as a single diastereomer. DFT calculations show a transition state geometry and orbital topology compatible with a 4π conrotatory electrocyclization. Related cyclizations have been reported but whether or not these cyclopentannelations occur by a conrotatory electrocyclization is unclear.[44]

Sarpong and coworkers[45] have shown that propargylic acetates of type **101** undergo a $PtCl_2$-catalyzed rearrangement to form cyclopentenones of type **102**. DFT calculations[46] indicate the mechanism initiates with Pt-catalyzed formation of oxacycle **104**. Electrocyclic ring opening of **104** leads to formation of pentadienyl cation **106**, which undergoes a Pt-catalyzed Nazarov and acyl shift to form cyclopentenone **108** diastereospecifically in moderate-to-good yields (Scheme 18).

While screening propargylic derivatives for their reactivity toward *N*-tosylimines in the presence of gold catalysts, a $IPrAuCl/AgBF_4$ catalyzed rearrangement using propargylic tosylates was found to completely reorganize both reactants into product carbocycle **111** (Scheme 19).[47] The reaction has a wide scope for variable propargylic tosylate and imine substitution. The mechanistic proposal involves an initial rearrangement of propargylic tosylate **112** to diene **113**, which serves as a nucleophile for addition to activated imine **114**. The resulting adduct (**115**) collapses to azetidine **116**, which eliminates to form azete **117**. Electrocyclic ring opening forms imino-Nazarov intermediate **118**, which undergoes

Nazarov cyclization to form cyclopentenone imine **120**. Subjection of diene **113** to the reaction conditions resulted in **120**, supporting this mechanistic hypothesis.

West and co-workers found that pentadienyl cation generation is possible through electrocyclic ring opening of a dichlorocyclopropane substituted with a vinyl group (**121**, Scheme 20).[48] An oxygen-containing substituent at the same position not only enables the formation of cyclopentenones after pentadienyl cation electrocyclization,[49] but according to computations enhances the rate of cyclization. The reaction is initiated by Ag(I), which ionizes a chloride to trigger electrocyclic ring opening. Substitution at R^1 or R^3 with a pendant aryl group allowed trapping of the oxyallyl cation to form fused or bridged tricyclic compounds such as **127** and **128**.

8. Formation of 1-Oxo-Pentadienyl Cations (Iso-Nazarov Cyclization)

4π electrocyclizations involving 1-oxo-pentadienyl cation intermediates, rather than the more typical 3-oxo-pentadienyl cation species, are sometimes termed “iso-Nazarov cyclizations.” Recently, some interesting strategies for generating and cyclizing 1-oxo-pentadienyl cation intermediates have been developed. Selected examples are described below.

In the presence of an external nucleophile, $AuPPh_3SbF_6$ catalyzes a deoxygenative iso-Nazarov cyclization of dienals of type **129** with concomitant nucleophile trapping (Scheme 21).[50]

Extension to vinyl and aryl nucleophiles allowed the construction of polycyclic frameworks, some of which are shown in Scheme 22. The mechanism is proposed to occur by an initial trapping of allylic cation **134** formed from the Nazarov cyclization by an allylic alcohol or allylic silane, followed by ionization of the oxygen to form a second allylic cation (**137** and **139**). A subsequent intramolecular trapping by the double bond of each intermediate occurs, leading to fused ring system **138** or bridged ring system **141**.

An iso-Nazarov-type cyclization was used in an expedient formal synthesis of the potent antileukemic natural product (±)-Cephalotaxine (Scheme 23).[51] Reduction of the ester carbonyl of dioxolanone **142** formed putative oxonium intermediate **143**, which underwent facile electrocyclization to yield **145** as a single diastereomer. The cyclization was found to work on a number of additional substrates, including a torquoselective example.

9. Formation of 1-Amino-Pentadienyl Cations (Imino-Nazarov Cyclization)

The canonical form of the imino-Nazarov cyclization has been determined by ab initio molecular orbital studies to be energetically disfavored due to stabilization of the pentadienyl cation (**147**) over the oxyallyl cation (**148**, Scheme 24).[52] However, 1-amino-pentadienyl cations have been shown to cyclize given a sufficient driving force.

Li employed a novel 1-imino-type Nazarov cyclization to construct the E ring of (±)-Cephalotaxine (Scheme 25).[53] Exposure of enamine **149** to acetic acid and $FeSO_4$ in air ensues an acid-catalyzed autoxidation process forming conjugated system **150**. Acid-catalyzed tautomerization allows the formation of **151**, in resonance with pentadienyl cation **152**. Nazarov cyclization yields key intermediate **153**.

Over 36 years ago, Piancatelli noted that in the presence of water and an acid catalyst, 2-hydroxymethyl furans rearrange to 4-hydroxycyclopentenones.[54] Recently, Read de Alaniz and co-workers augmented the power of this cyclization by performing it in the presence of catalytic $Dy(OTf)_3$ and an amine instead of water to produce the corresponding 4-amino-5-

aryl/alkyl cyclopentenones (**156**) in excellent diastereoselectivity (Scheme 26).[55] The mechanism is thought to occur by the $Dy(OTf)_3$-catalyzed ionization of hydroxide from **155**, followed by trapping at the 5-position of resulting furyl cation **157** with an amine. Proton transfer and ring opening produce iminium ion **159**, which is a resonance form of pentadienyl cation **160**. Electrocyclization occurs to form **161**, which yields cyclopentenone **156** upon elimination. The methodology was quite general for multiple variations of R^1 and a variety of mono- and di-substituted aryl and alkylamines. It was later extended to the synthesis of spirocycles of type **163** by simple addition of a pendant amine to the furan α-position.[56] Batey and coworkers have studied a closely related cyclization that produces diastereopure 4,5-diamino cyclopentenones.[57]

10. Conclusions

We hope this microreview on some of the recent unconventional extensions of the Nazarov cyclization offers perspective on the wealth of methods available for the generation of well-behaved pentadienyl cations. In particular, these advances demonstrate that if a pentadienyl cation can be generated, in most cases it will undergo efficient electrocyclization. Furthermore, pentadienyl cations with many different substitution patterns can be generated and cyclized, using the novel methods described in this review. for this reason, the cyclization has become appealing to chemists interested in many different chemical questions, ranging from catalysis to cationic reactivity to natural product synthesis. We expect that as the field continues to evolve, the versatility, generality and applicability that the Nazarov cyclization will achieve will further increase its synthetic utility.

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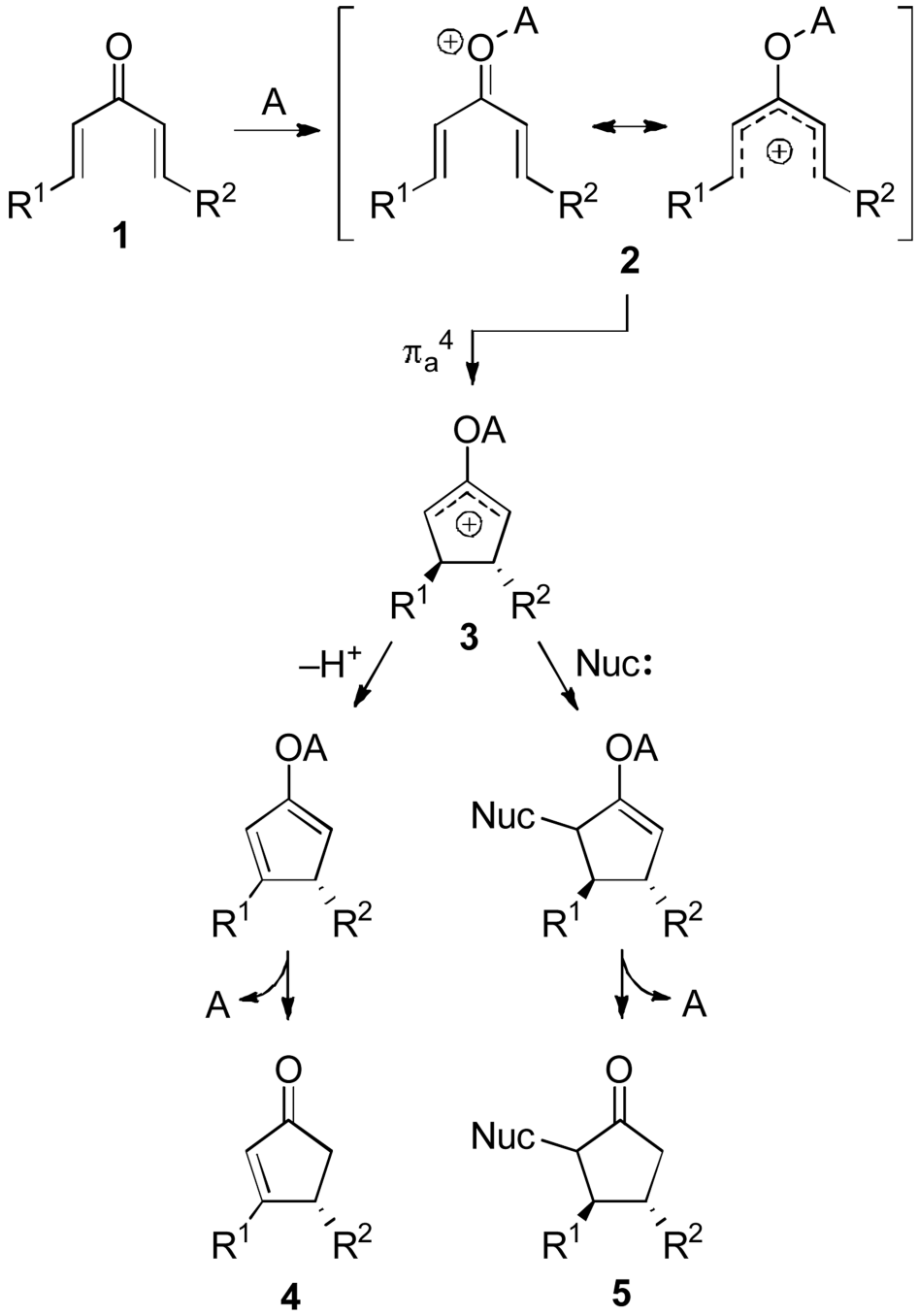
Biographies

William T. Spencer III was born in Poughkeepsie, NY (United States) in 1979. He graduated with a Bachelor’s degree in chemistry from Rensselaer Polytechnic Institute in 2001, after which he held a position as a Research Scientist at AMRI, Inc. synthesizing small molecule analogs for biological testing until 2006. He then returned to academia to obtain his Master’s in chemistry from Rochester Institute of Technology under the direction of Professor Chrisitna G. Collison. After graduating in 2008, he enrolled in the Ph.D. program at the University of Rochester, where he earned his degree in 2012 under the supervision of Professor Alison J. Frontier performing methodology studies and natural product synthesis. He is currently a postdoctoral fellow at the same university in the laboratory of Professor Robert K. Boeckman synthesizing enzyme inhibitors for antifungal SAR.

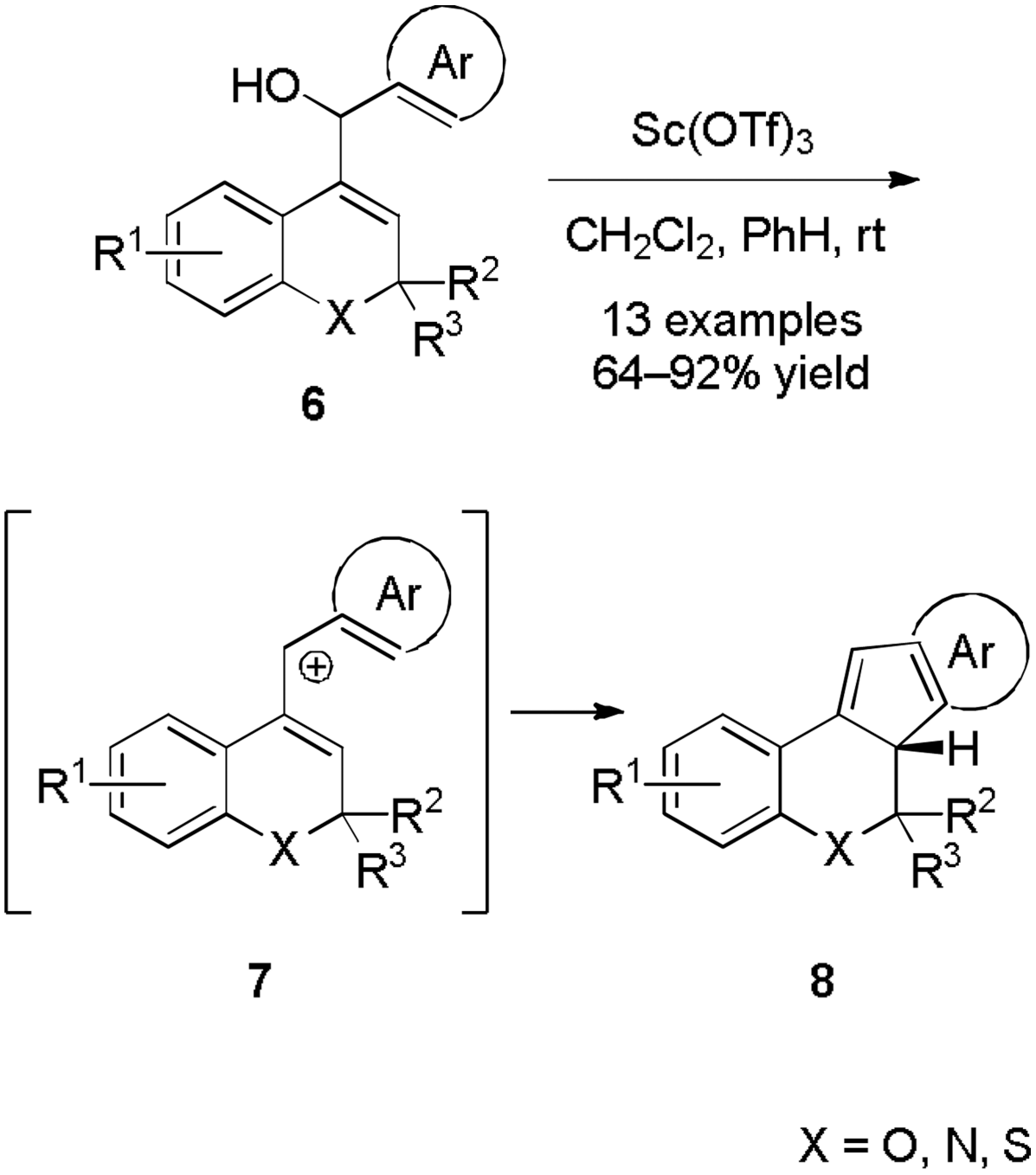
Tulaza Vaidya is a native of Kathmandu, Nepal. She graduated with a Bachelor’s degree in Chemistry in 2007 from Lake Forest College, Lake Forest, IL, where she pursued research in palladium-catalyzed cross-coupling reactions under the direction of Professor William B. Martin. She joined the University of Rochester, Rochester, NY in 2007 and worked on electrophilicly-driven annulations of polarized Nazarov precursors using iridium and gold catalysts underthe joint supervision of Professor Alison J. Frontier and Professor Richard Eisenberg. After earning a Ph.D. degree in 2012, she moved to Cornell University, Ithaca, NY to explore polymer chemistry. She is currently a postdoctoral fellow working on olefin polymerization under the supervision of Professor Geoffrey W. Coates.

Alison J. Frontier grew up in Farmington, Michigan, a suburb of Detroit. She received her AB from Harvard in 1992, and then took a two-year position as an Associate Chemist at the

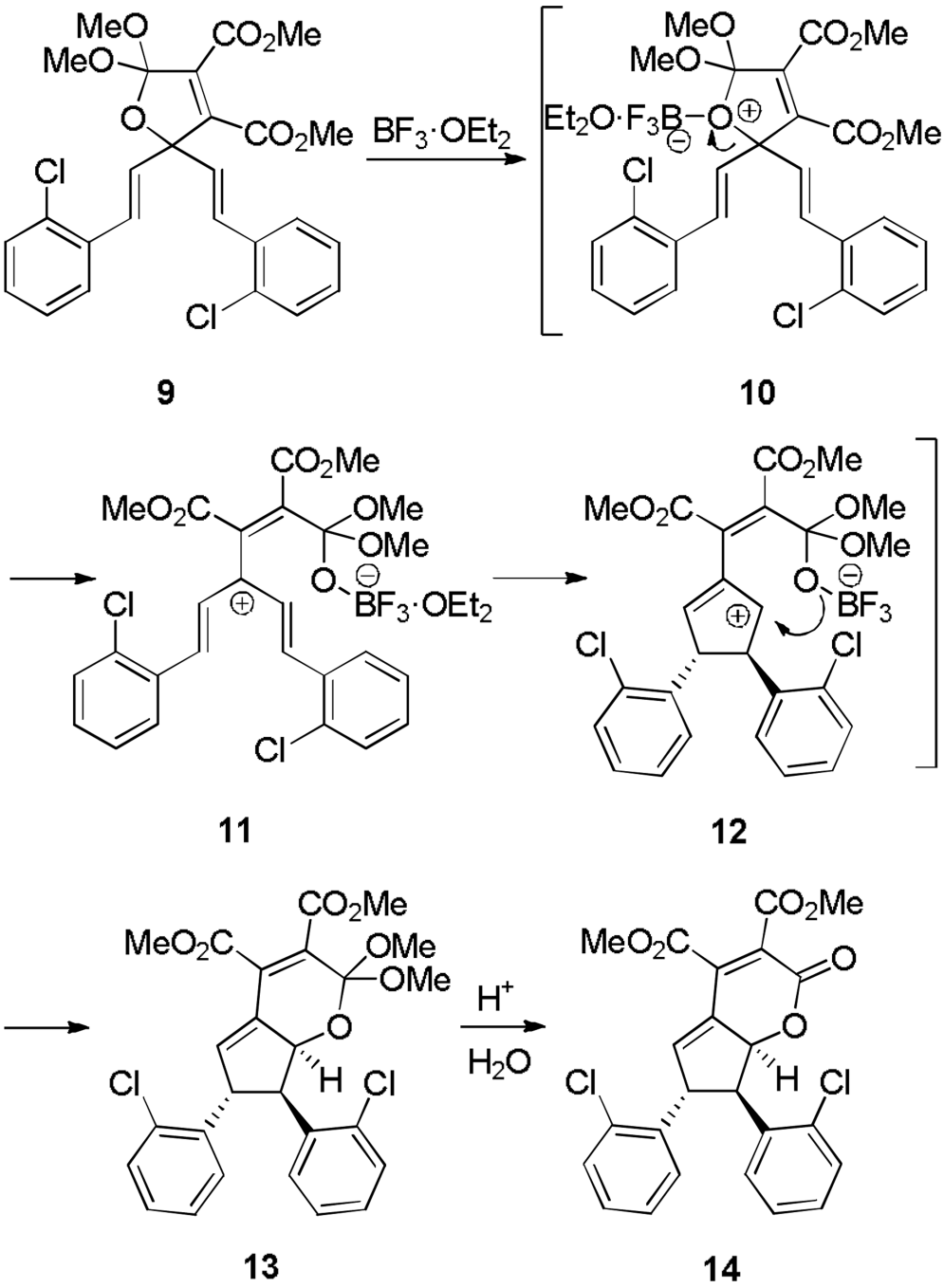
Merck Research Laboratories in Rahway, NJ. She earned her PhD in 1999 from Columbia University, where she studied with Samuel Danishefsky, and then she did postdoctoral work with Barry Trost at Stanford University. She has been on the faculty at the University of Rochester since 2002. Her research interests focus on target molecule synthesis and reaction development using novel catalytic methods. Students in her research group are pursuing novel strategies for the synthesis of bioactive, structurally interesting natural products, as well as the development of cationic and neutral pericyclic reactions and multistep cyclization cascades.



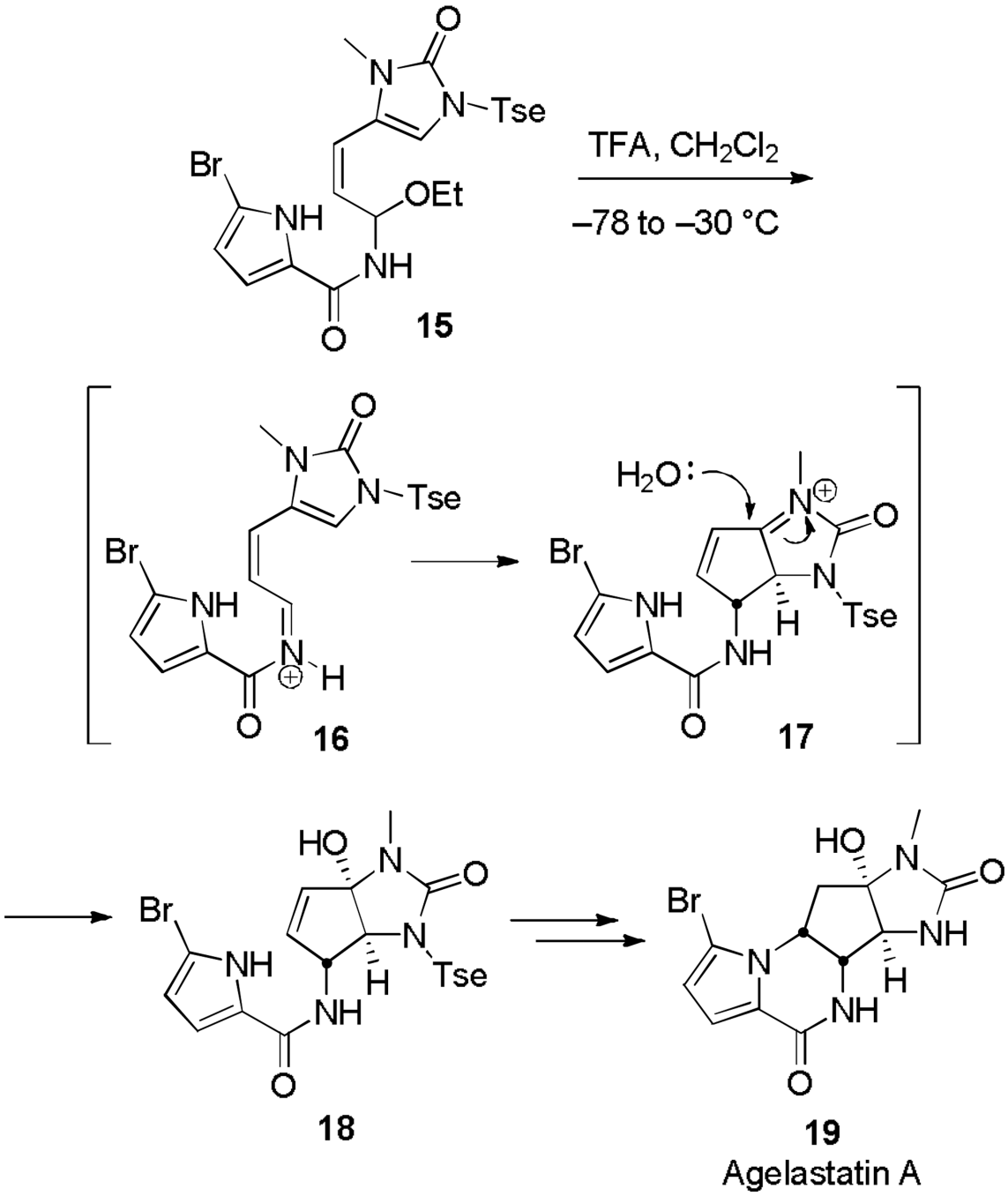
Scheme 1.
The Prototypical Nazarov Cyclization.



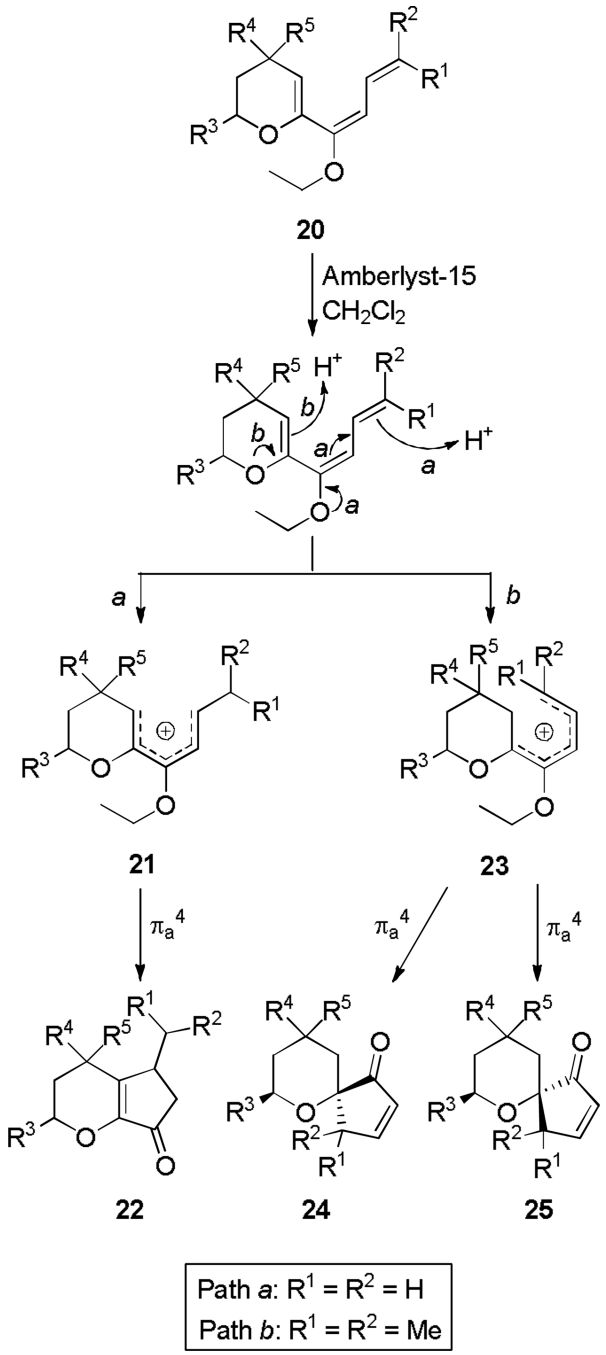
Scheme 2.
Nazarov Cyclization Triggered by Ionization of Alkenyl Aryl Carbinols.



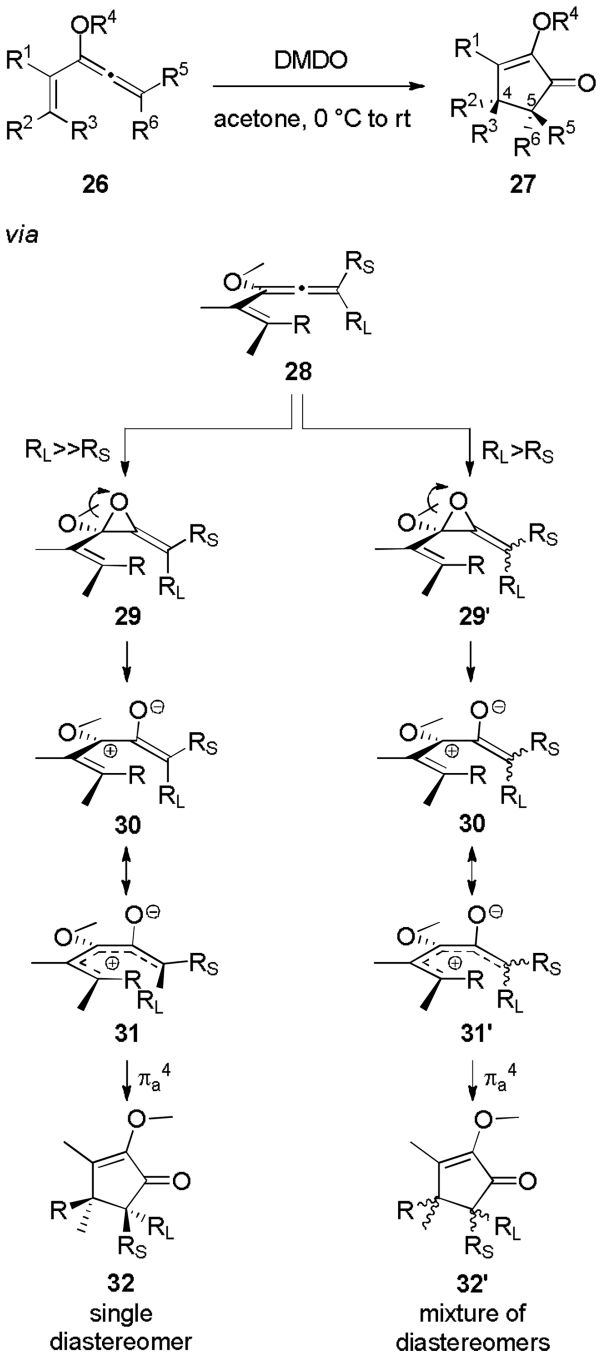
Scheme 3.
Nazarov Cyclization Triggered by Ether Ionization Followed by Trapping.



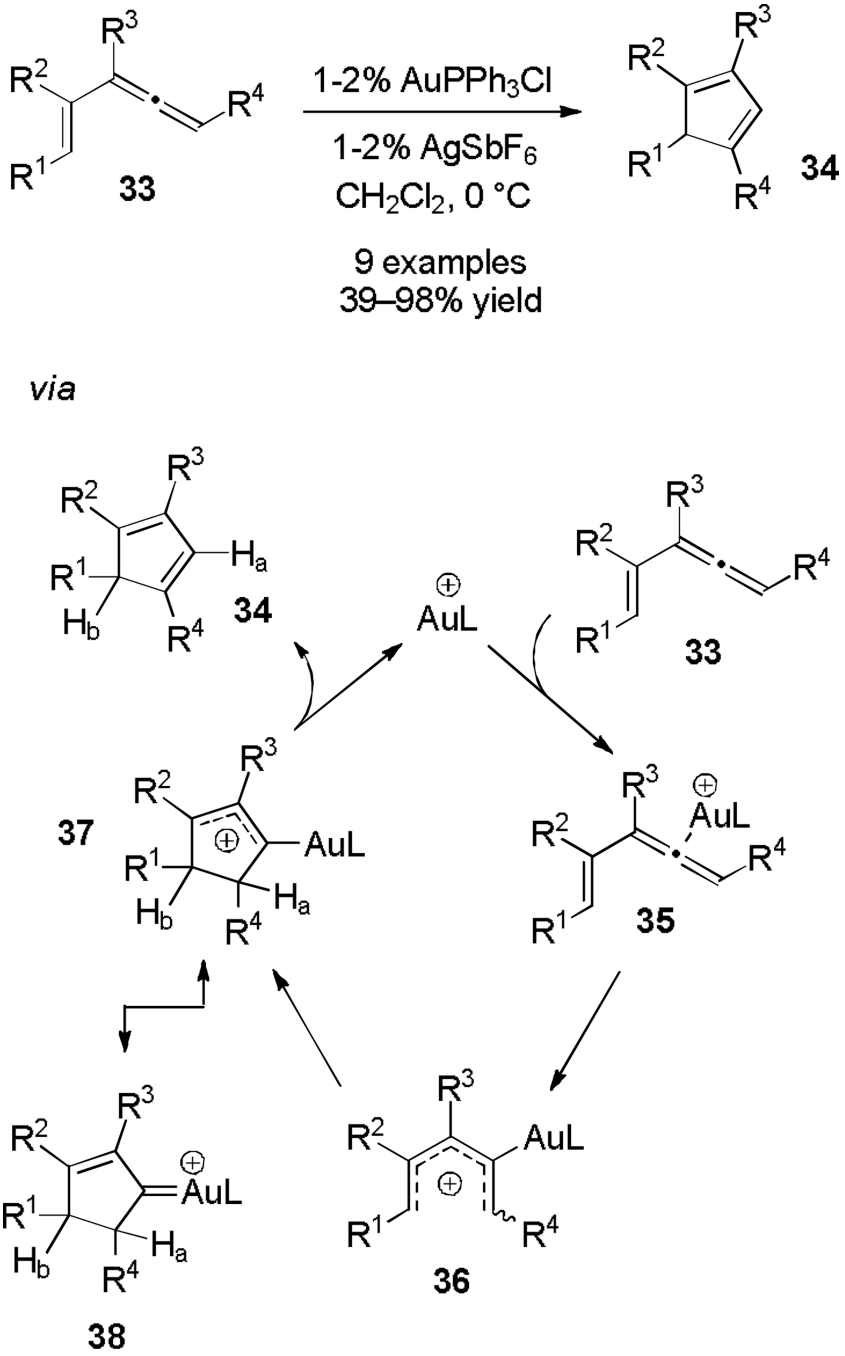
Scheme 4.
Nazarov Cyclization in the Synthesis of Agelastatin A.



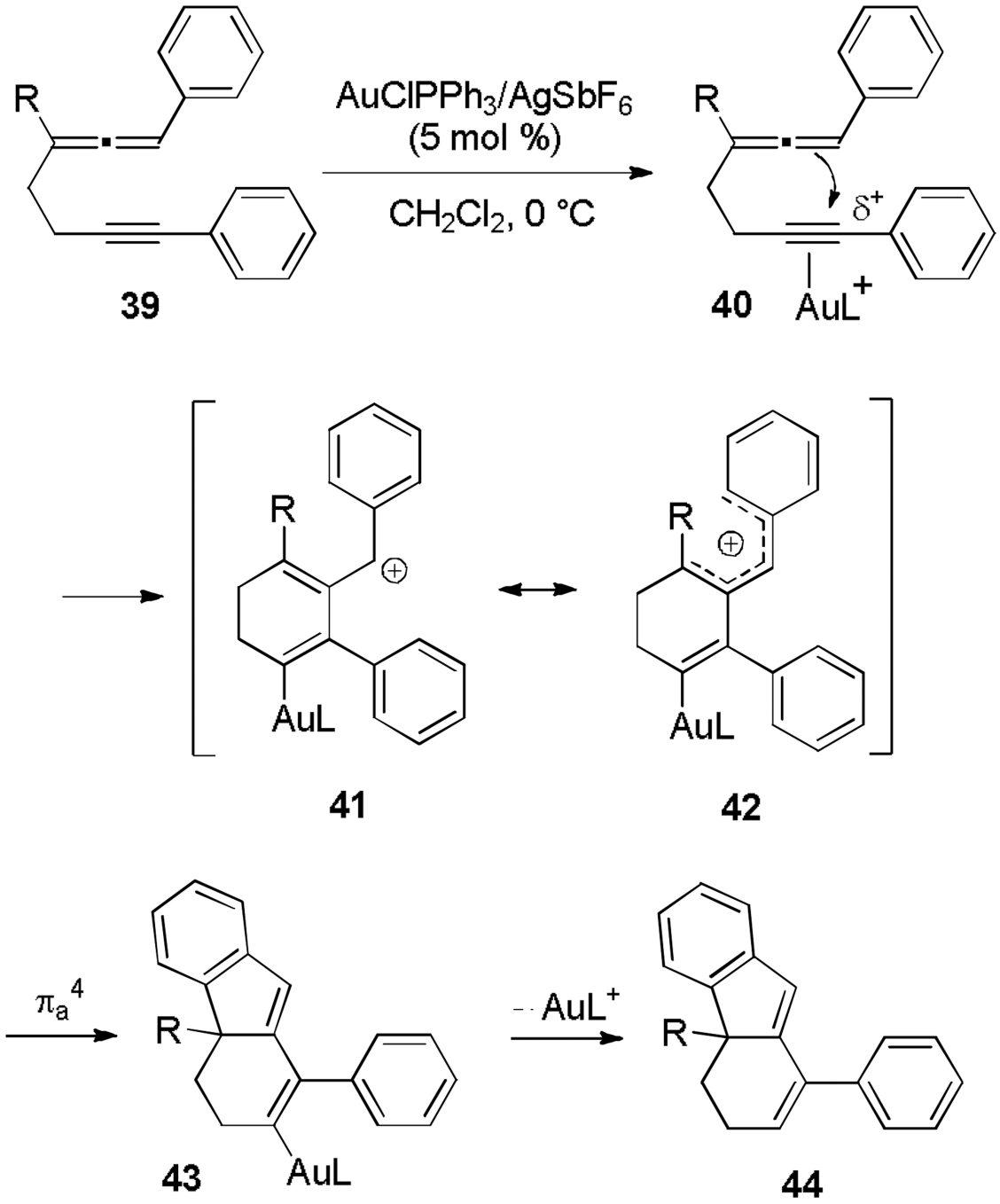
Scheme 5.
Regioselectivity in the Nazarov Cyclization of Conjugated Alkoxytrienes.



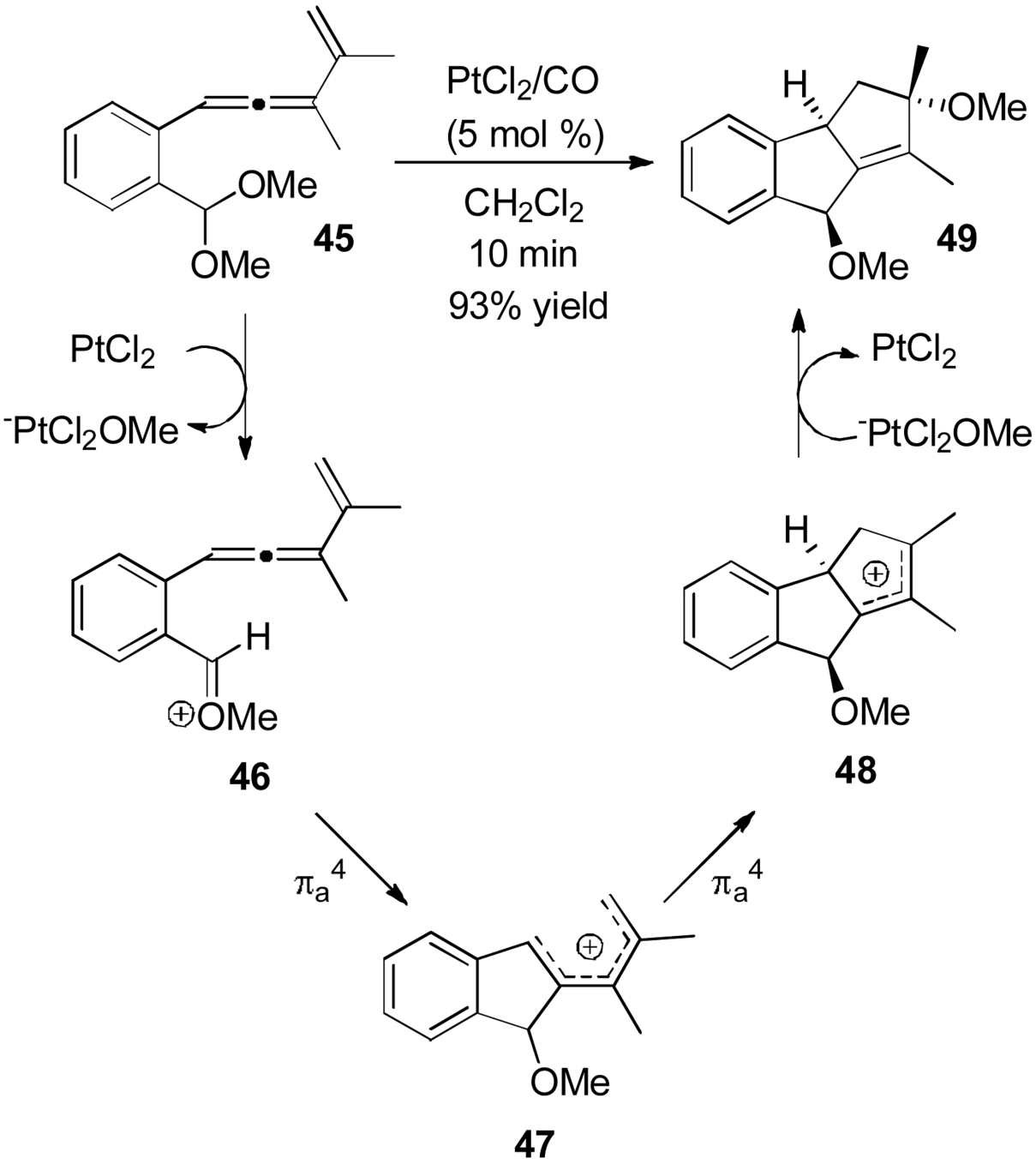
Scheme 6.
The Oxidation-Initiated Nazarov Cyclization.



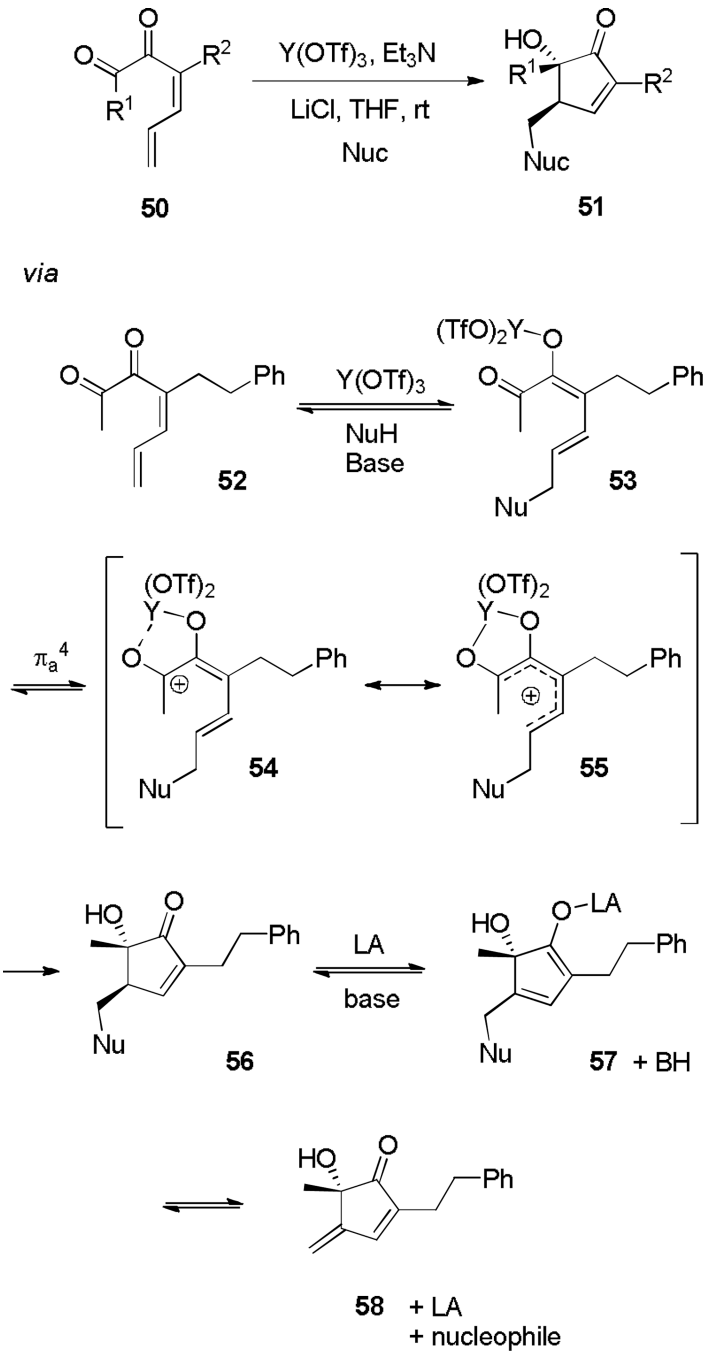
Scheme 7.
Gold-catalyzed conversion of Vinylallenes to Cyclopentadienes.



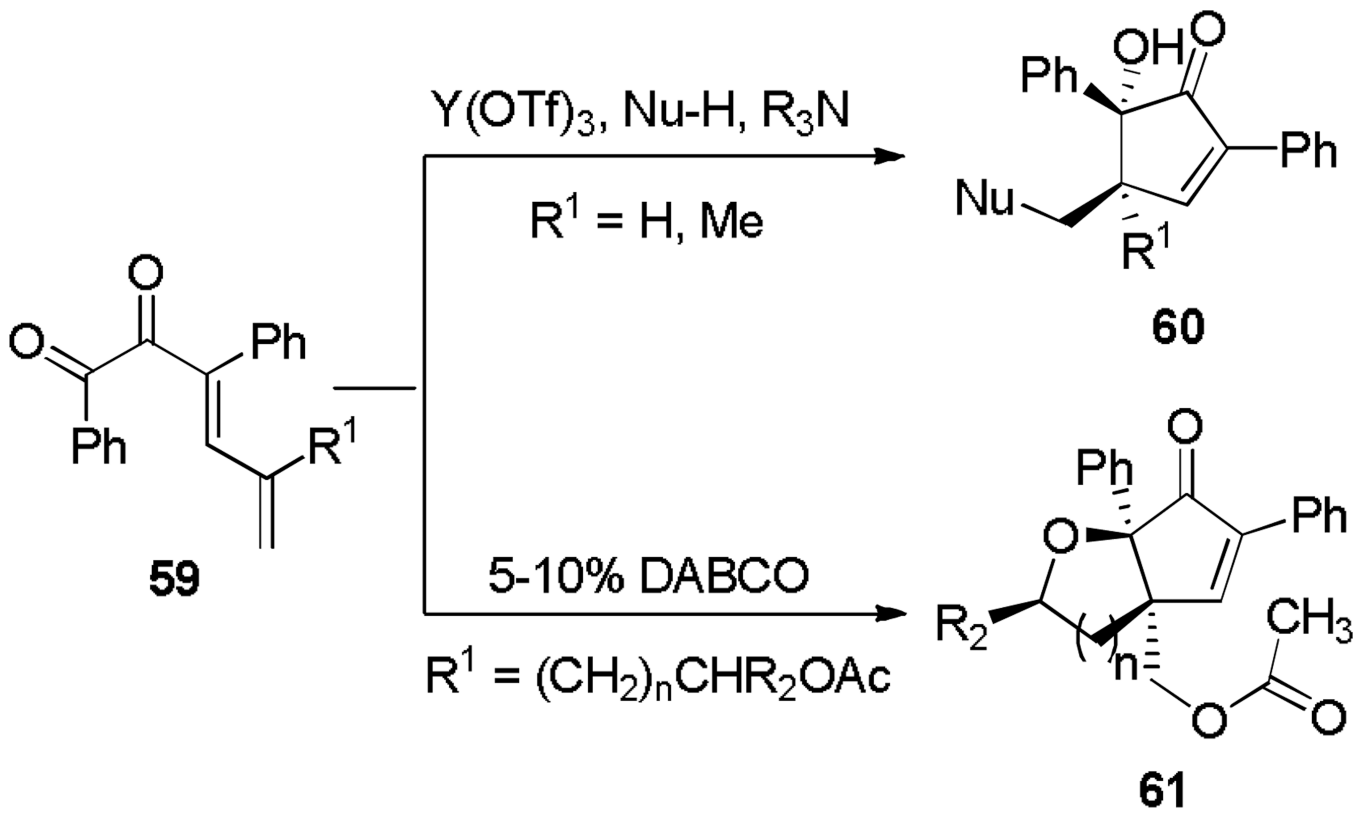
Scheme 8.
6-*endo-dig*–Nazarov Cyclization to Form Tricycles.



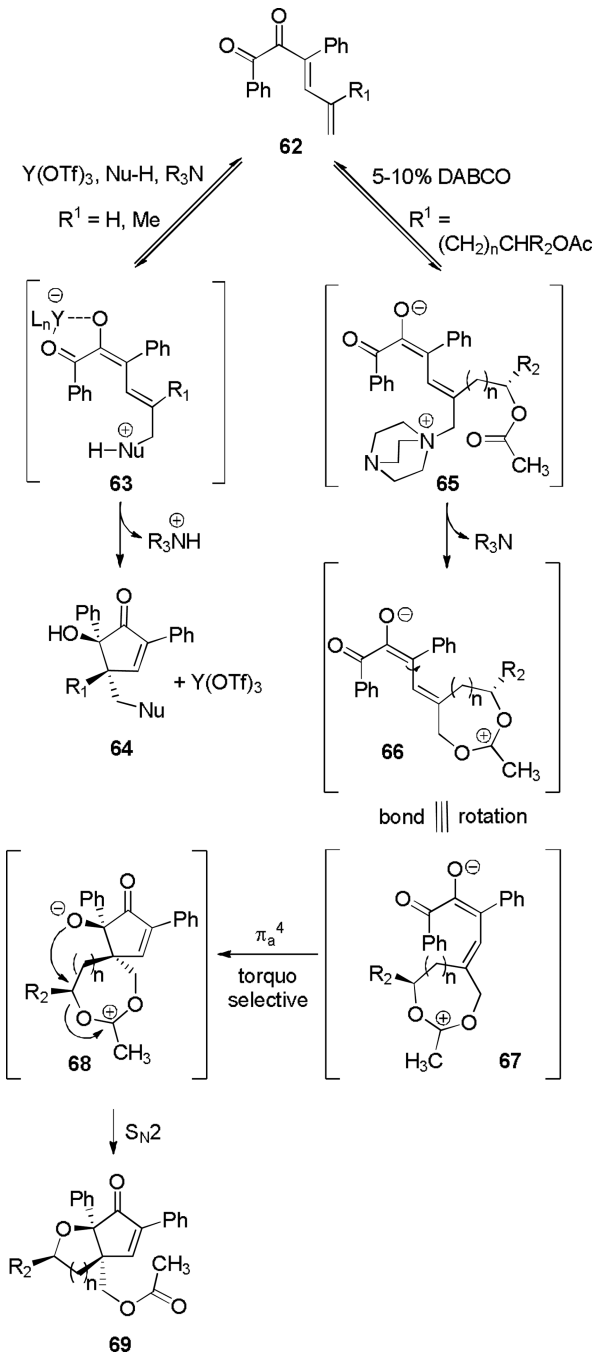
Scheme 9.
Tandem Double Nazarov Cyclization to Form Tricycles.



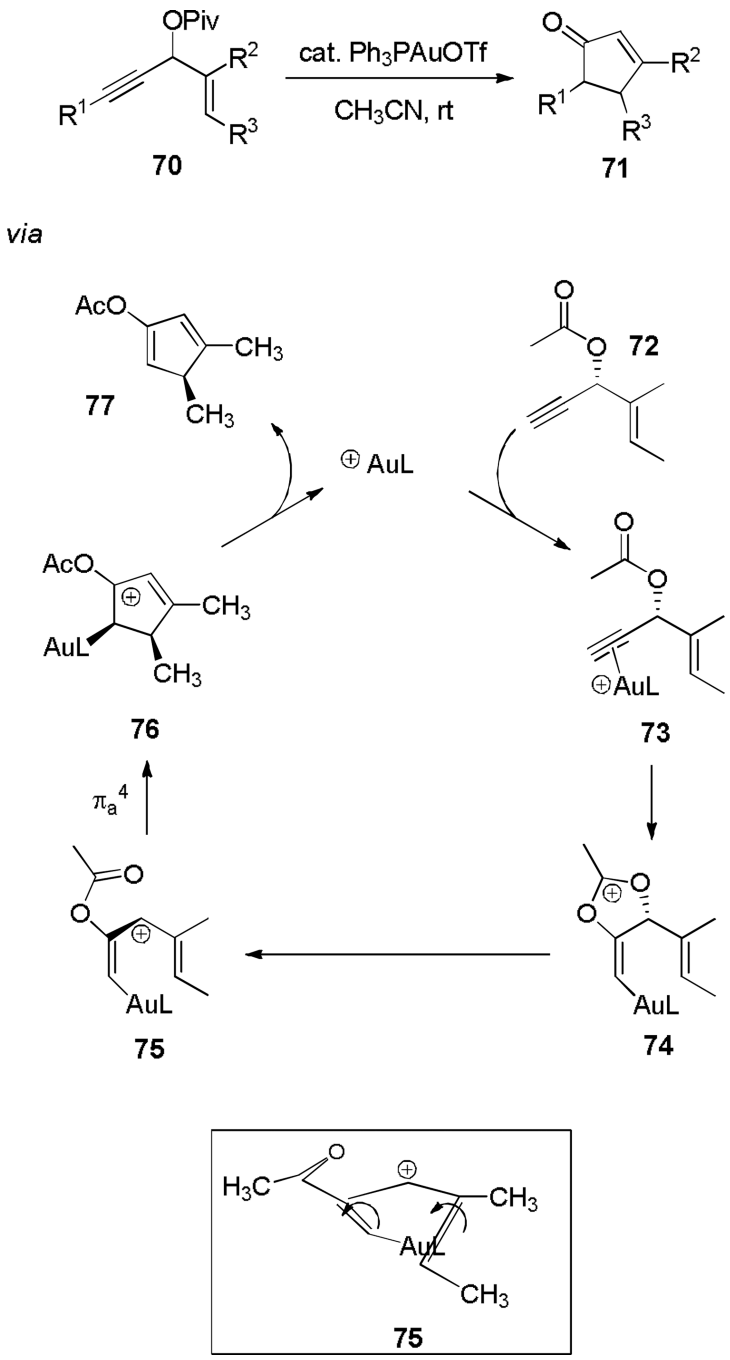
Scheme 10.
Conjugate-Addition Initiated Nazarov Cyclization.



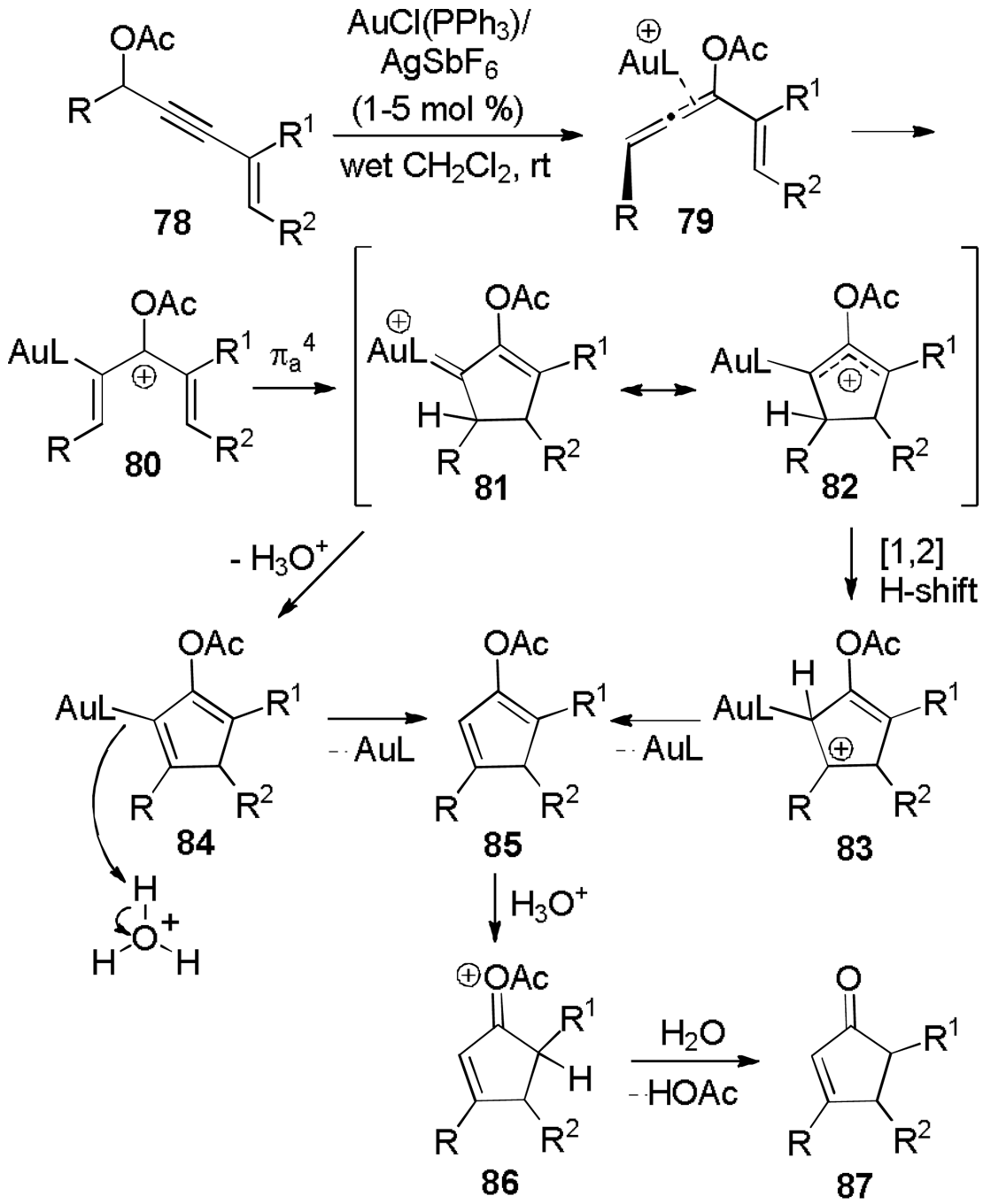
Scheme 11.
Divergent Cyclization Pathways of Dienyl α-Diketones.



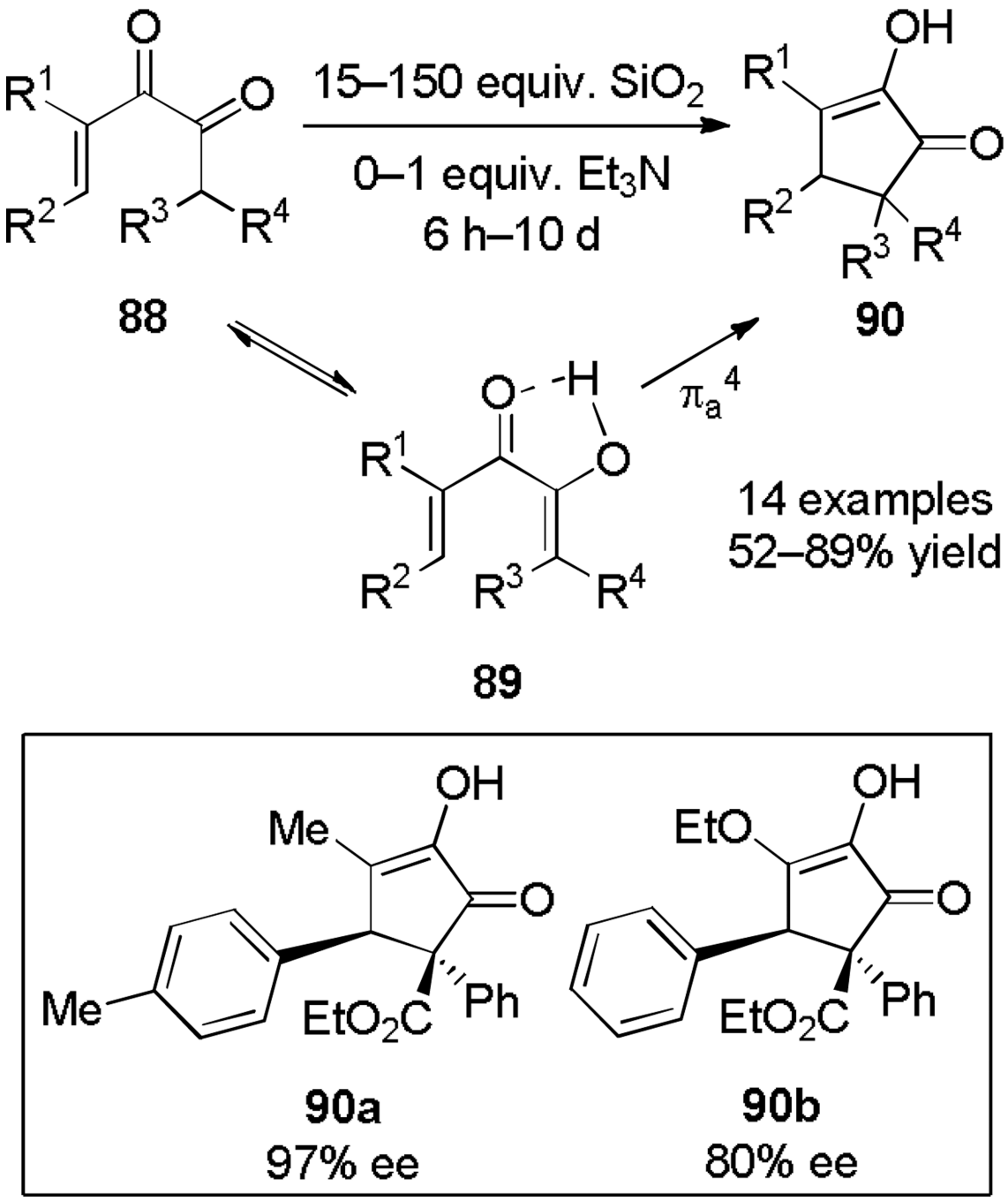
Scheme 12.
Mechanistic Proposal for Bicycle Formation.



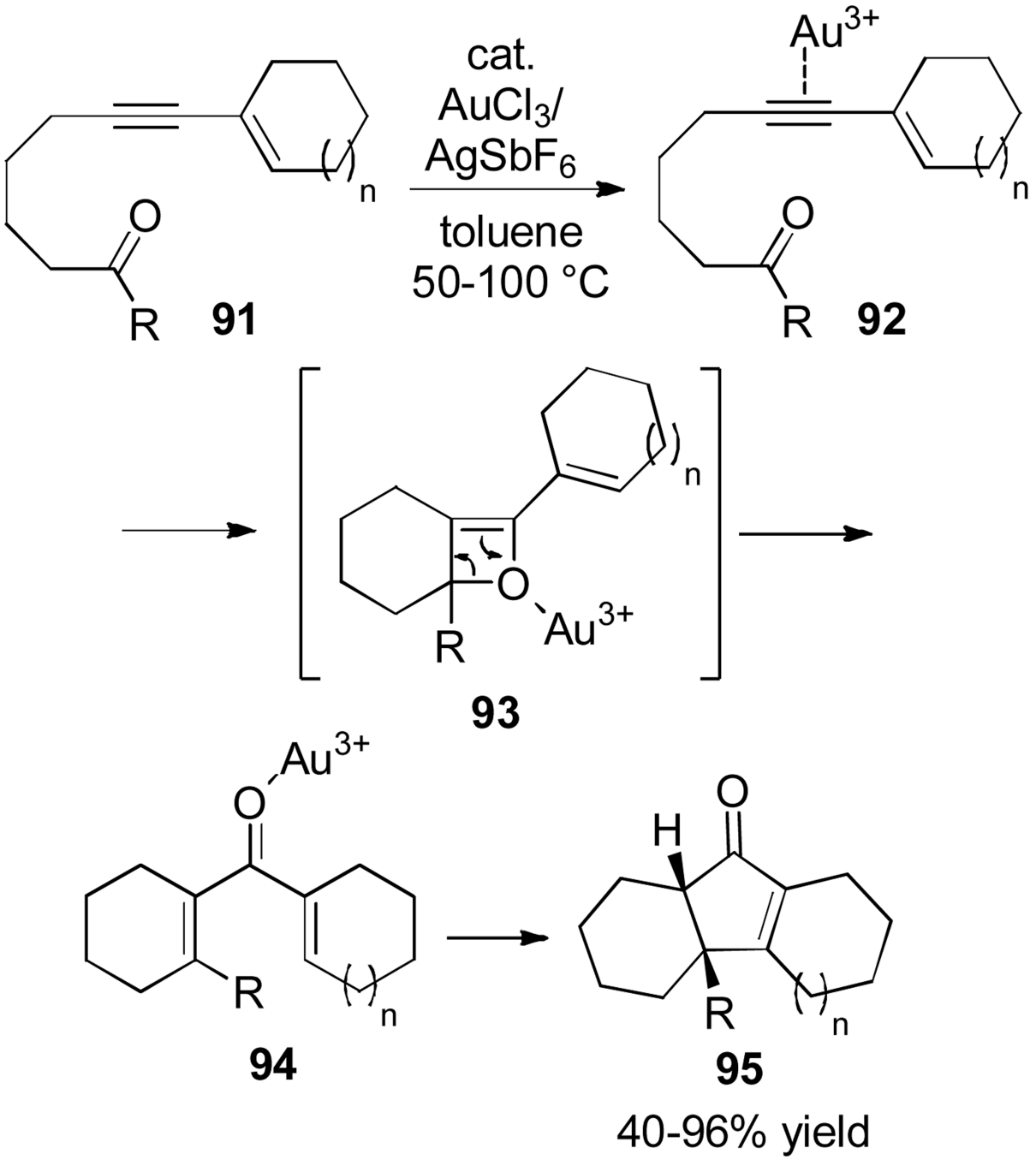
Scheme 13.
Gold-Catalyzed Rautenstrauch Cyclization.



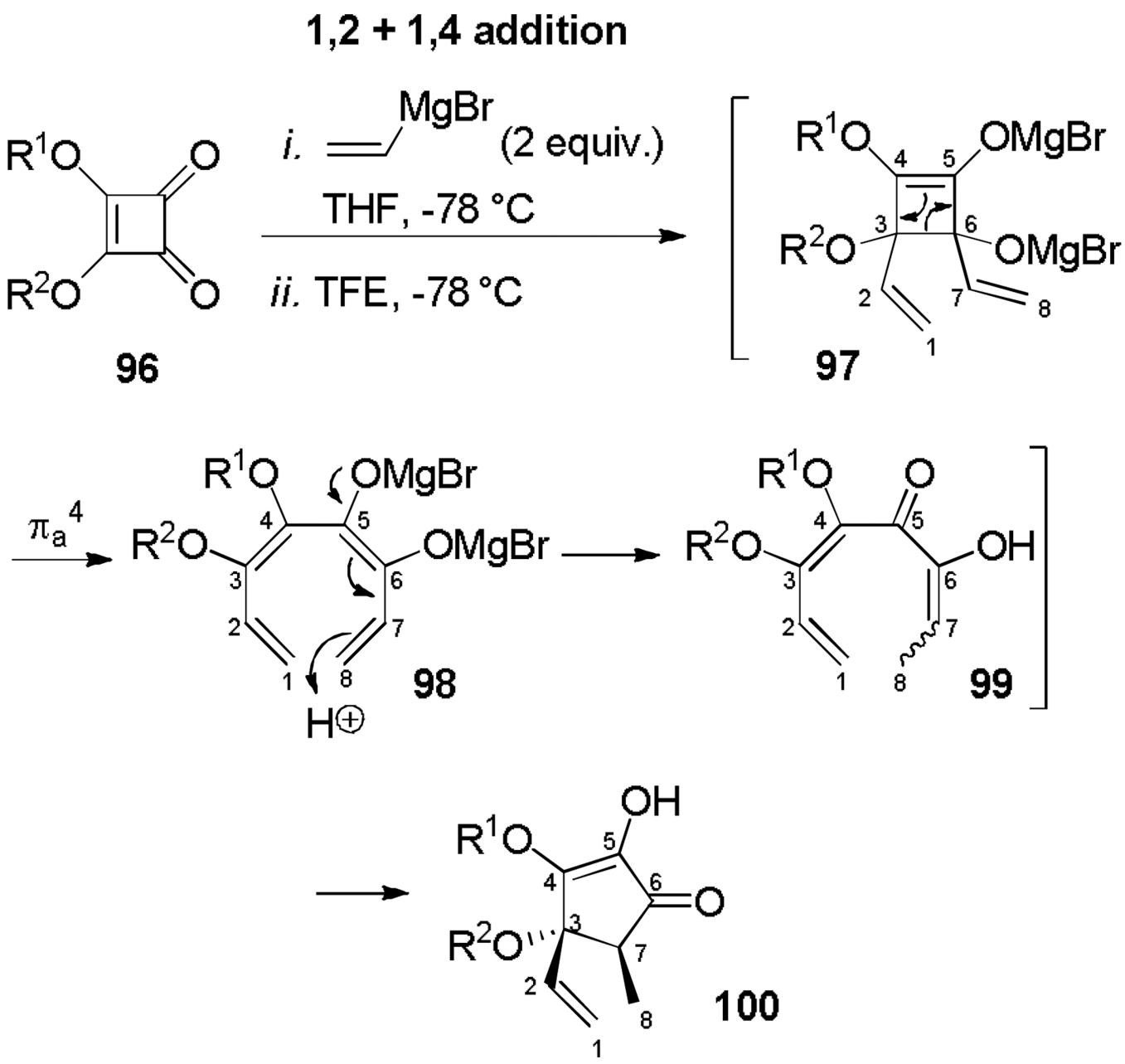
Scheme 14.
Tandem Gold(I)-Catalyzed 3,3-Rearrangement Followed by a Nazarov Cyclization.



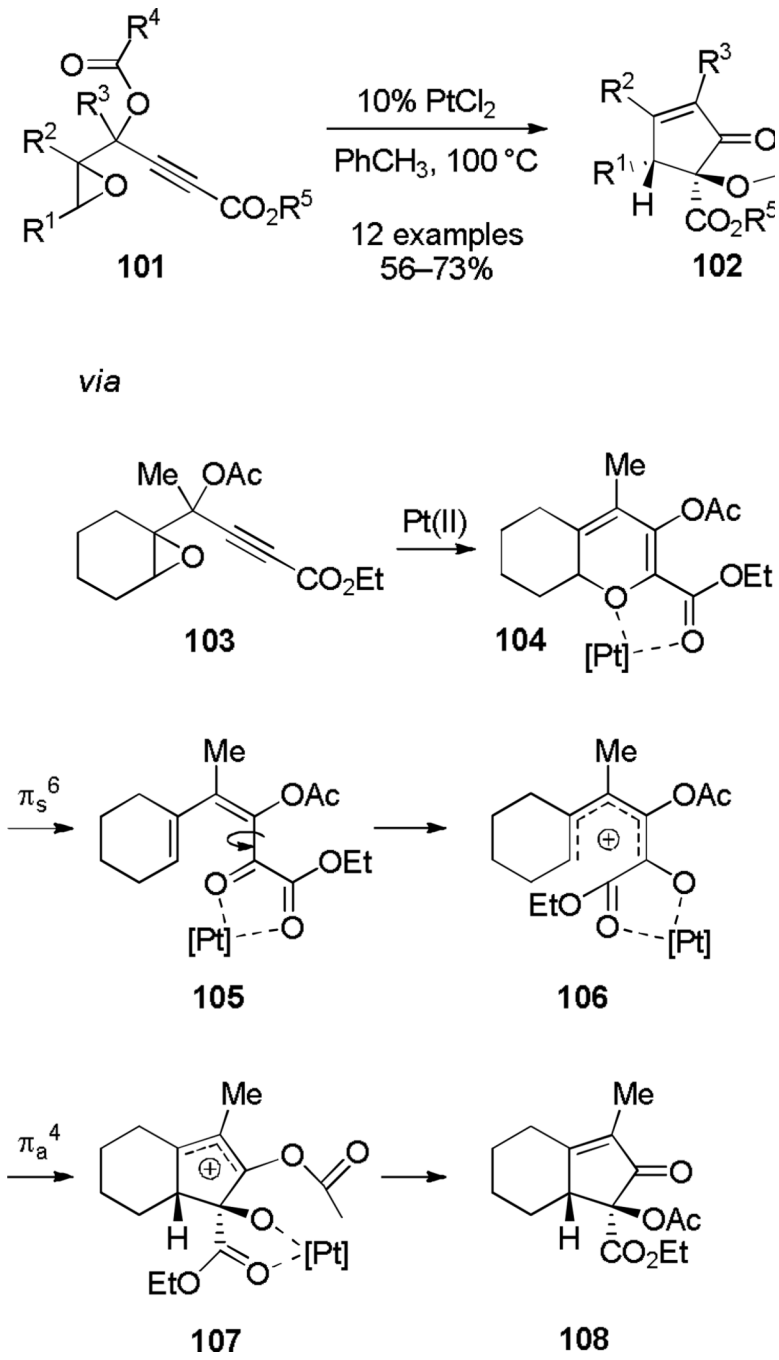
Scheme 15.
Nazarov Cyclization of α-Ketoenones.



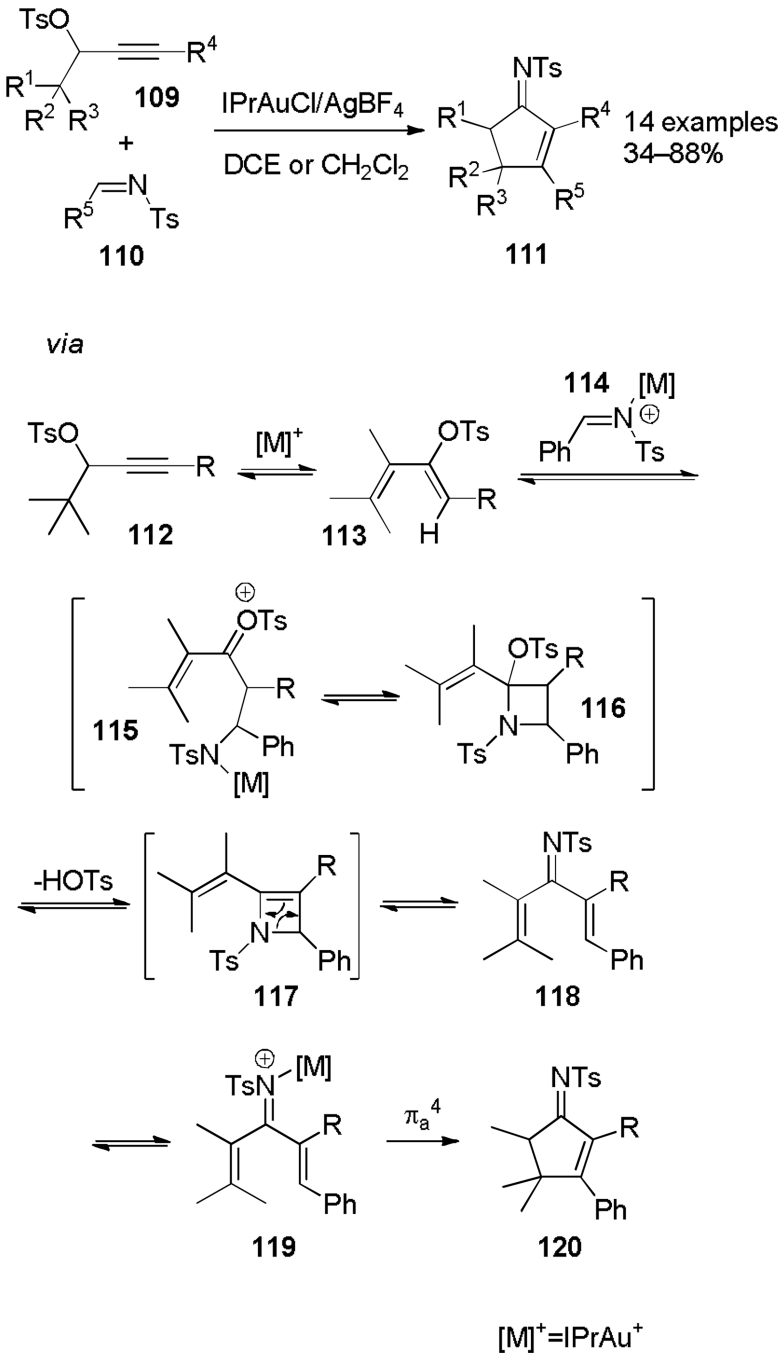
Scheme 16.
Tandem Alkyne-Aldehyde Metathesis–Nazarov Cyclization.



Scheme 17.
Formation of Cyclopententones Through Regioselective 1,2 ,4 Addition of Vinylmagnesium Bromide to Squarate Esters

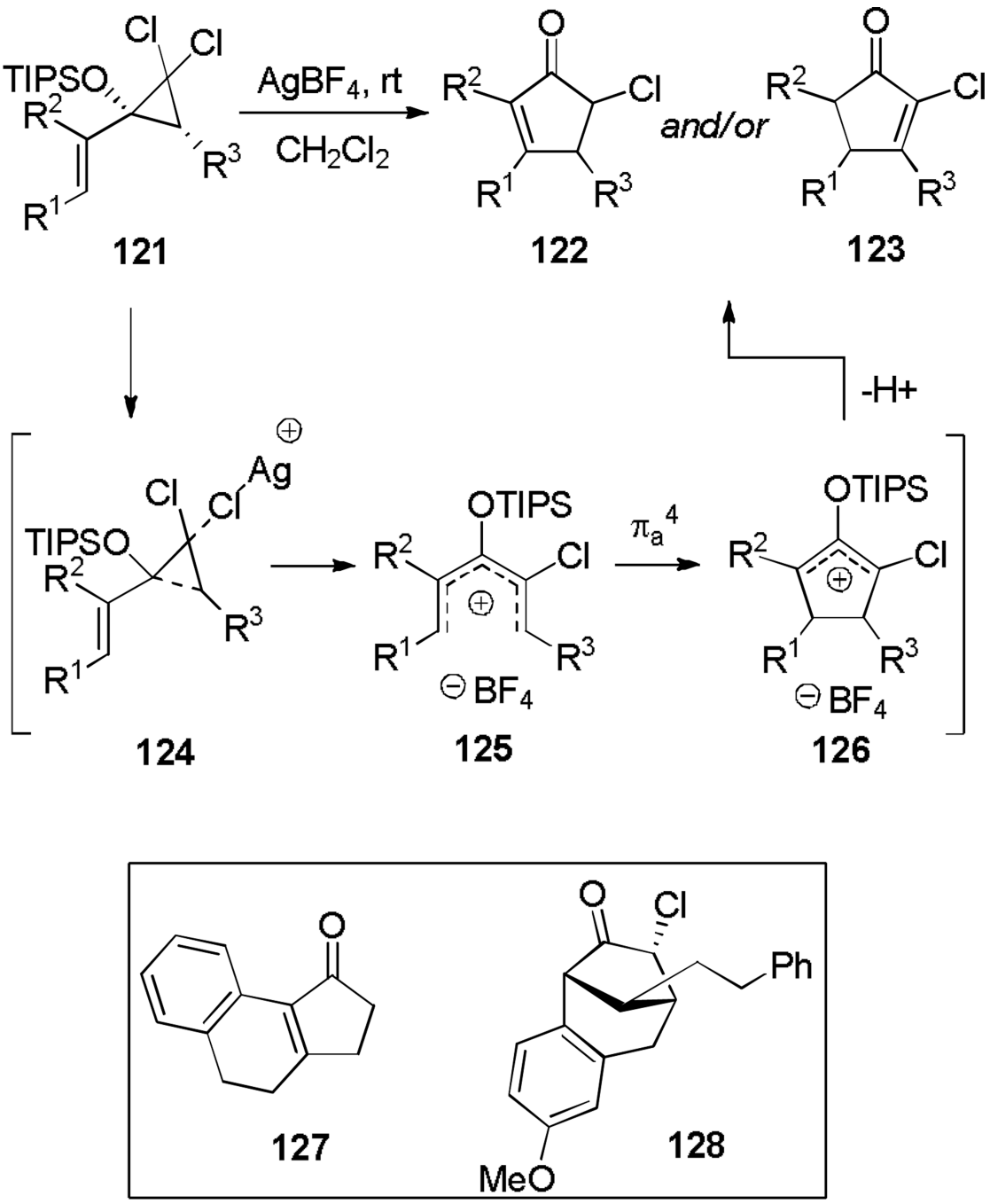


Scheme 18.
Oxa-6π Electrocyclic Ring Opening–Nazarov Cyclization.

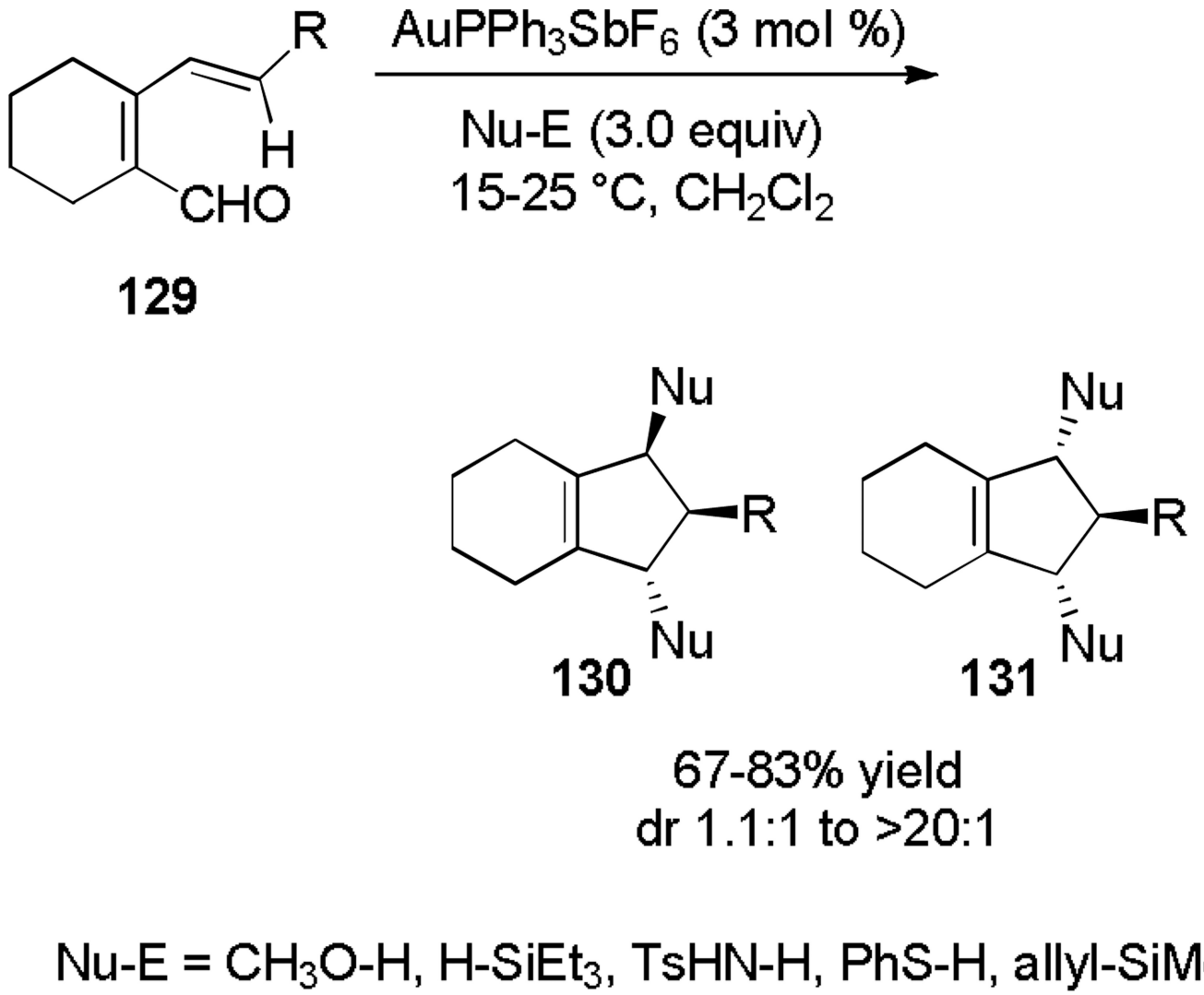


Scheme 19.

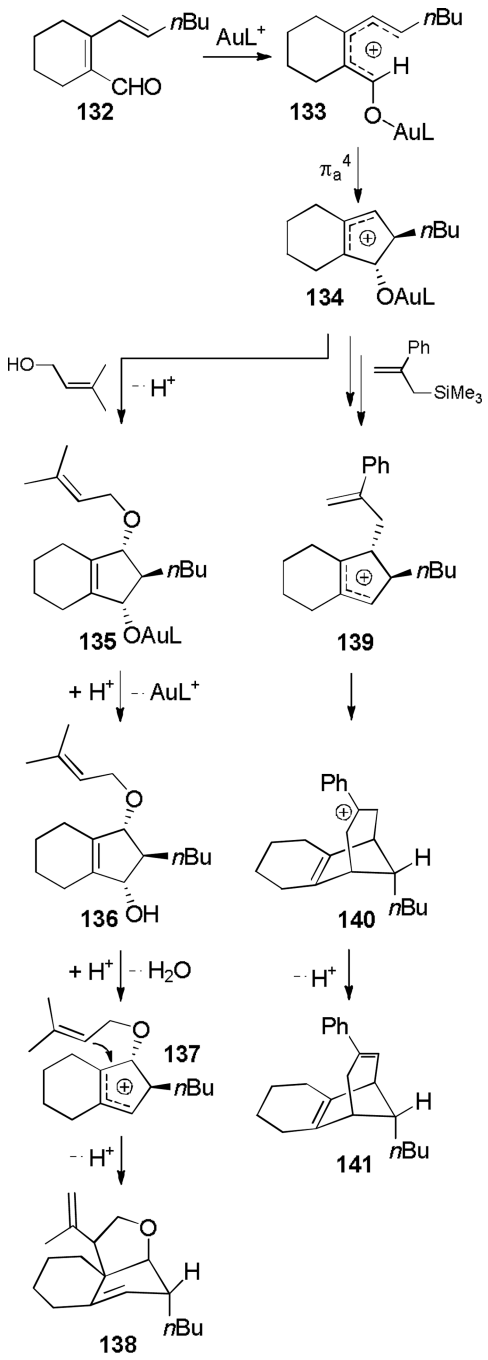
Rearrangement of Propargylic Tosylates and Imines to Form Cyclopentenone Imines.



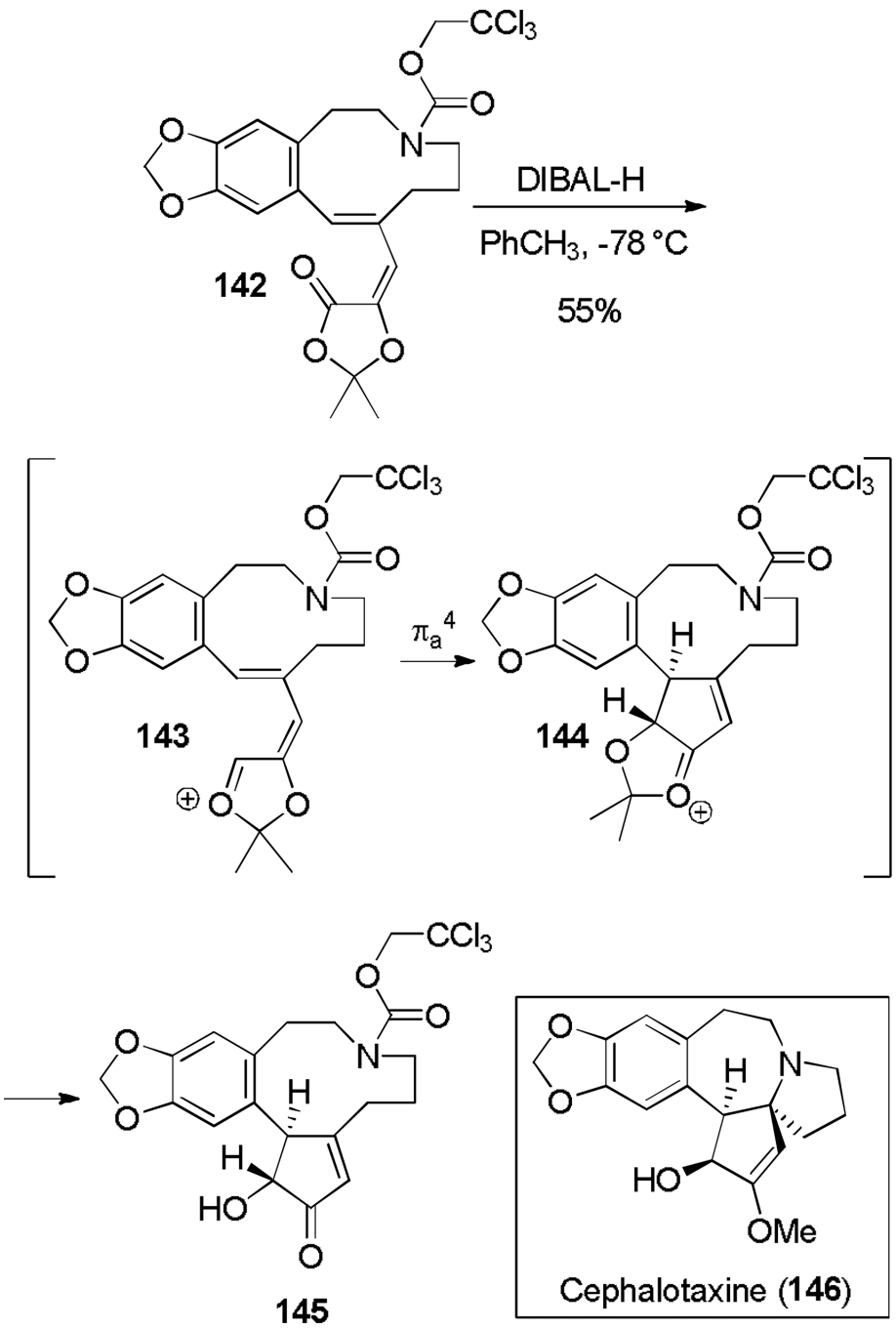
Scheme 20.
Dichloropropane Ring Opening Nazarov Cyclization.



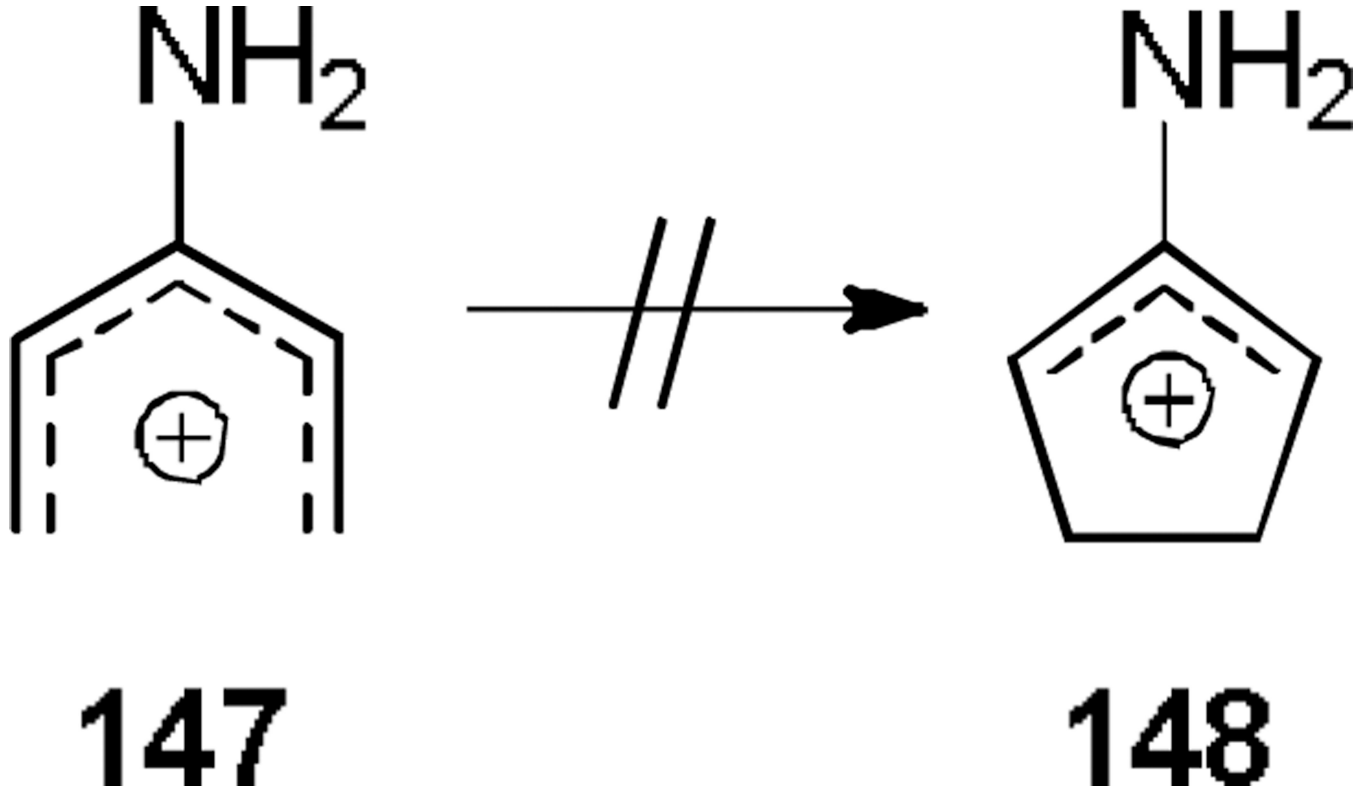
Scheme 21.
Deoxygenative Iso-Nazarov Cyclization.



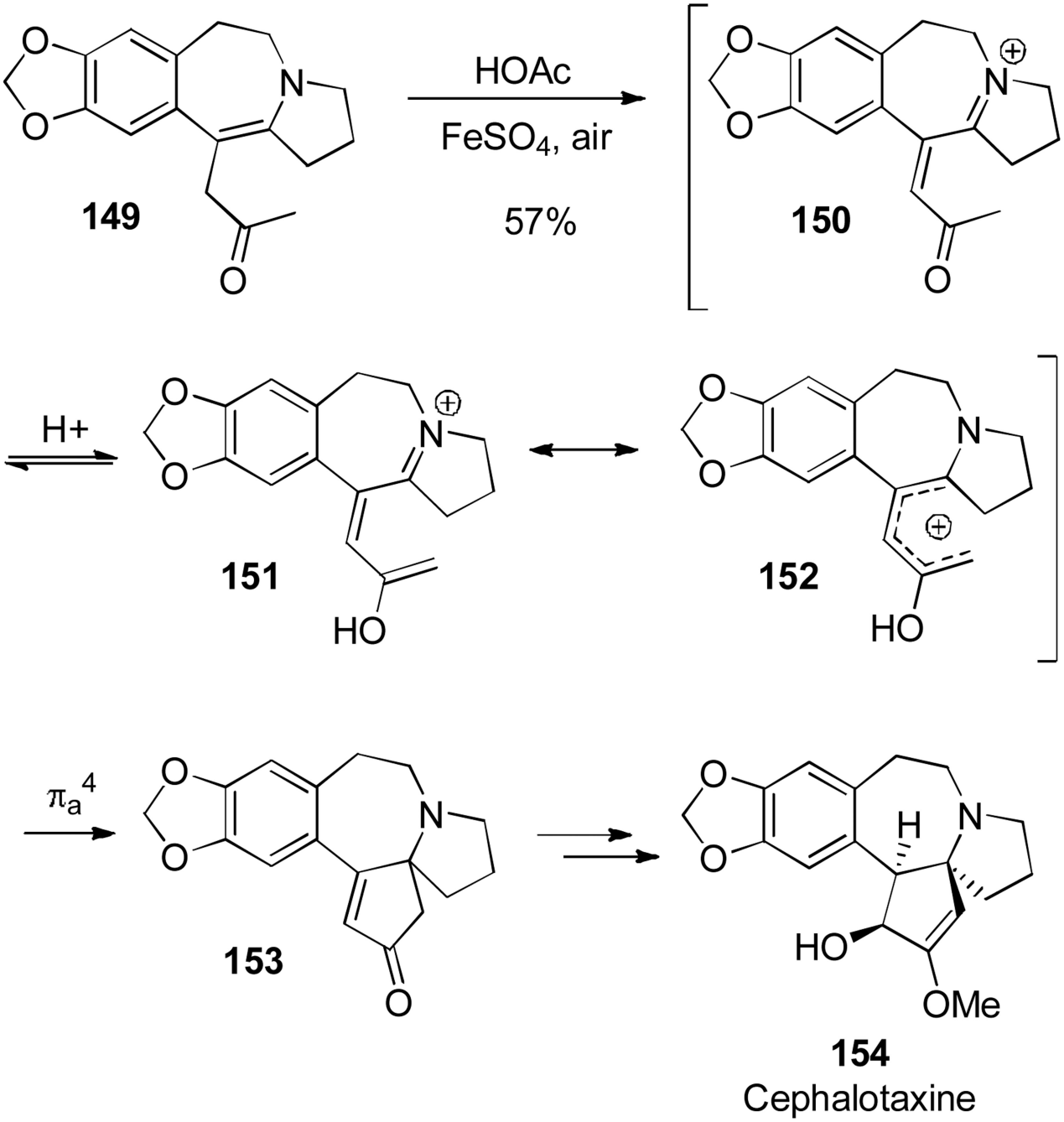
Scheme 22.
Assembly of Polycyclic Frameworks.



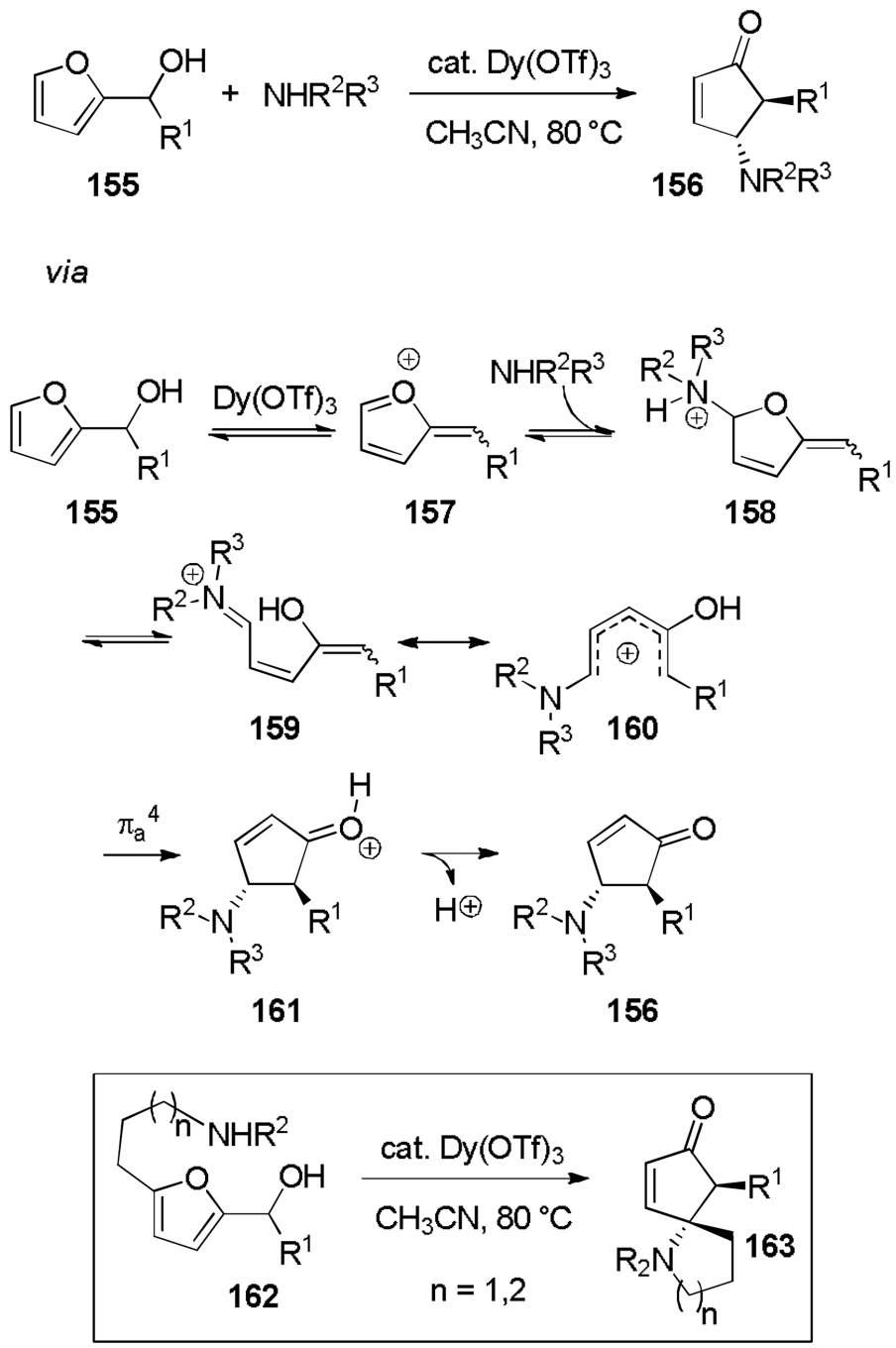
Scheme 23.
Reductive Oxy-Nazarov Cyclization in the Formal Synthesis of (±)-Cephalotaxine



Scheme 24.
Unfavorable Electrocyclization of 3-Amino Pentadienyl Cations.



Scheme 25.
Synthesis of the E ring of (±)-Cephalotaxine.



Scheme 26.
Aza-Piancatelli Electrocyclization.