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ARTICLE

Nazarov-Like Cyclizations

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The Nazarov cyclization, a well-known method for the formation of cyclopentenones, mechanistically involves the 4π electrocyclization of a 1,4-pentadienyl cation, generated from cross-conjugated divinyl ketones. Recently, advances related to this cyclization, such as the incorporation of heteroatoms as well as the use of cyclopropanes as double bond equivalents have extended the scope of the original reaction. The modifications discussed in this review, which covers the years 2009-2013, have allowed the realization of both heteroatom- and homo-Nazarov cyclizations.

Introduction[1]

The Nazarov cyclization, a well-known method for the formation of cyclopentenones, mechanistically involves the 4π electrocyclization of a 1,4-pentadienyl cation, generated from cross-conjugated divinyl ketones.[2] Due in large part to initially harsh reaction conditions, this cyclization was of limited utility. However, in recent years, numerous groups have reported alternative methods that greatly improved the viability of this reaction.[3] Stimulated by these advances, other researchers have expanded the scope of the original cyclization to a more diverse set of starting materials and these "Nazarov-like" reactions are the subject of this Review.[4] Hetero-Nazarov cyclizations, in which nitrogen or oxygen have been incorporated into the divinyl ketone framework, allow for the synthesis of various heterocycles (see reactions **a** – **d**, Figure 1), and replacement of one of the vinyl moieties with an alternative group such as cyclopropyl provides cyclohexenones via a homo-Nazarov cyclization (reaction **e**, Figure 1).

Before venturing any further, some finer details need to be clarified. The reactions reviewed herein clearly are extensions of the original cyclization conceived by Nazarov. However, in some instances, this connection is merely conceptual, and these reactions do not conform to the same mechanism as the namesake cyclization. Thus, whereas the aza- and imino-Nazarov reactions are likely to be 4π electrocyclizations, the oxa- and homo-Nazarov reactions presumably proceed through ionic intermediates, with the latter being more closely related to a Friedel-Crafts alkylation. These mechanistic differences aside, the use of colloquial terms such as oxa- or homo-Nazarov positions these reactions in an appropriate context with respect to the original transformation.[5]
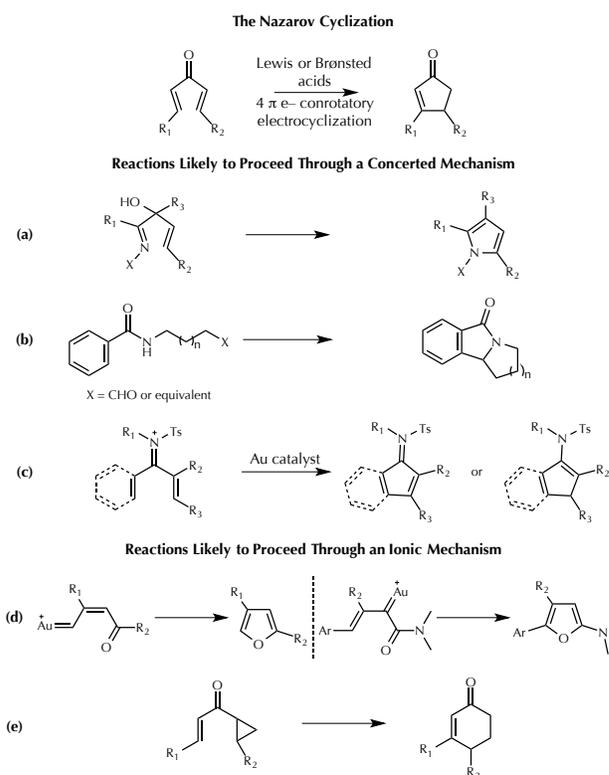
Figure 1 Examples of Nazarov-like reactions described in this Review: reactions **a** and **b** are aza-Nazarov cyclizations; reaction **c** is an imino-Nazarov cyclization; reactions **d** are an oxa-Nazarov cyclizations; and reaction **e** is a homo-Nazarov cyclization.

The Aza-Nazarov Cyclization

The use of imines as aza-Nazarov precursors has allowed for the development of a number of substituted pyrrole syntheses. For instance, in 2012, the Würthwein group disclosed that 1-azapenta-1,4-dien-3-ones undergo a cyclization to pyrroles in the

presence of TfOH (Scheme 1).[6] The requisite starting materials were prepared by first reacting 2,3-butadione *O*-benzyloxime with aryl aldehydes under aldol condensation conditions to give the α-benzyloxyimino enones **2** and then with alkyl- or aryllithium reagents, which selectively added to the ketone to afford the desired allylic alcohols **3**. Subjecting 0.025 M DCM solutions of these compounds to excess TfOH at – 10 °C provided the highly substituted pyrroles **6** in 29-83 % yield. Appropriate choice of starting material allowed for the synthesis of pyrroles with various groups at positions 2 (methyl or phenyl), 3 (alkyl or aryl) and 5 (aryl). Additionally, the reaction was tolerant of electron donating and withdrawing groups on the aryl group at C(5), and worked equally well for *O*-benzyloximes (10 examples) and hydrazones (3 examples; not shown).
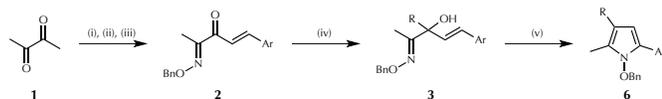
Scheme 1 Synthesis of 1-azapenta-1,4-diene-3-ones **3** and their conversion to pyrroles **6**.
(i) H₂NOH; (ii) K₂CO₃, BnCl; (iii) KOH, ArCHO; (iv) RLi, THF, – 78 °C; (v) TfOH (2 eq), –10 °C

Compounds 3/6	R	Ar	% Yield 6
a	CH₃	Ph	68
b	CH₃	2-H₃CO-Ph	61
c	CH₃	4-Cl-Ph	64
d	CH₃	2-thienyl	63
e	4-H₃CPh	4-Cl-Ph	60

Mechanistically, the reaction is believed to proceed via 1-azapentadienyl cation **4-1**, resulting from the loss of water after protonation of the alcohol (equation 1). Subsequent to a requisite conformational change that provides cation **4-2**, 4π conrotatory electrocyclization occurs, a process supported by DFT calculations. The reaction required two full equivalents of a strong acid. Reaction with less than one equivalent of TfOH or the use of weaker acids such as trifluoroacetic acid, resulted in the formation of an adduct in which the desired pyrrole underwent a Friedel-Crafts alkylation with a second equivalent of the open-chain cation **4-2** (equation 2). Presumably, excess acid is required because, in the presence of substoichiometric quantities of acid, both pyrrole **6** and intermediate carbocations **4-1** and **4-2** exist in solution, which allows for Friedel-Crafts alkylation of the pyrrole at C(4).
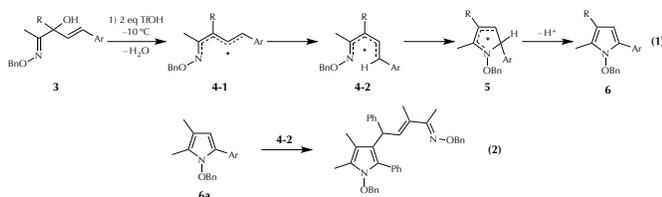
Following this report, the same group disclosed the preparation of substituted NH-pyrroles under related superelectrophilic conditions.[7] A route to starting materials similar to that described above was used (Scheme 2): diacetyl was first converted to its 1-aminoindoline hydrazone, followed by aldol condensation with several substituted benzaldehydes to afford the desired precursors **9a**. Alternatively, for examples in which R was a phenyl ring, a slightly different approach was employed. 1-Aminoindoline was condensed with ethyl 2-oxo-2-phenylacetate (**7**),

followed by reaction with the anion of dimethyl methylphosphonate. The resulting β-ketophosphonate **8** was reacted with substituted benzaldehydes under Horner-Emmons conditions to provide the unsaturated ketones **9b**. In all instances, the C–C double bond was determined by NMR to be of the *E*-configuration.
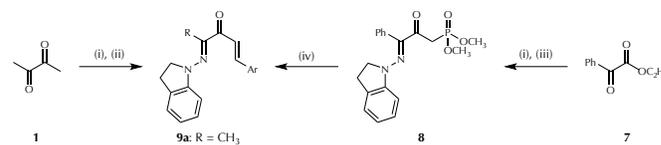
Scheme 2 The synthesis of compounds **9a**,**b**.
(i) 1-aminoindoline; (ii) KOH, ArCHO; (iii)BuLi, (H₃CO)₂P(O)-CH₃; (iv) KOtBu, ArCHO, –78 °C

With a convenient route to starting materials worked out, these reactants were cyclized under two different conditions. The first used high dilution (0.02 M in DCM) and two equivalents of TfOH ("low acid"), which afforded the *N*-substituted pyrrole **12** (Scheme 3), clearly the result of an aza-Nazarov cyclization. The second made use of high concentration conditions (0.2 M in DCM) in the presence of seven equivalents of TfOH ("high acid"), which allowed N–N bond cleavage subsequent to cyclization, producing 3-acetylindole (**16**) and acetylated pyrroles **14**. The resulting 3-hydroxypyrrole products were too unstable to isolate, and therefore the reactions were worked up with acetic anhydride, ultimately providing the peracetylated products shown.

The authors speculated that, since this reaction presumably takes place in two consecutive steps, the second step required "superelectrophilic conditions" to effect N–N bond cleavage, only possible in the presence of a large excess of TfOH. The proposed mechanism shown in Scheme 3 was corroborated by DFT calculations. Based on these data, the carbonyl oxygen represented the most basic site for protonation under low acid concentrations, thus giving rise to the only intermediate (**10**) that could undergo the 4π-electrocyclization reaction to provide **11-1**. In the presence of higher concentrations of TfOH, a second protonation occurs, most likely on the N of the indoline group **11-2**. It is this second protonation, possible only under more acidic conditions, that allows for cleavage of the N–N bond. Deprotonation at C(2) of the indoline releases the protonated heterocycle and the putative pyrrole. Subsequent loss of a proton and acylation with acetic anhydride delivered products **14** and **16**. The reaction was carried out on nine different substrates and was found to be general, allowing for the presence of both electron-donating and electron-withdrawing groups on the Ar group at the end of the enone system. Yields of the acetylated products ranged from 33-60%.
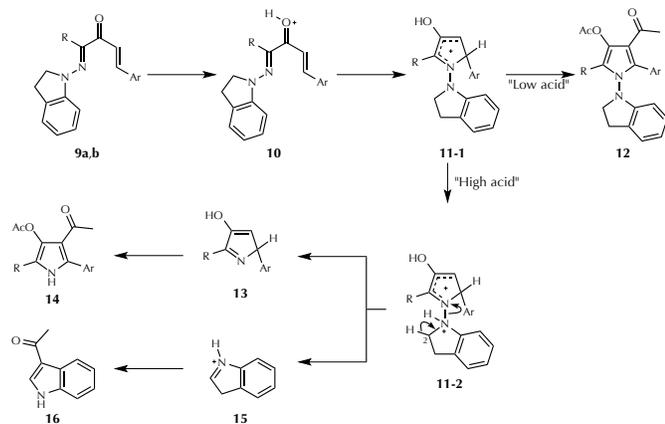
Scheme 3 The mechanism for the conversion of **9a,b** to pyrroles **12** or **14**.

SM	Product 14	R	Ar	% Yield 14
9a	a	CH$_3$	Ph	45
9a	b	CH$_3$	4-Cl-Ph	44
9b	c	Ph	Ph	51
9b	d	Ph	3-F-Ph	60
9b	e	Ph	4-CF$_3$-Ph	45

A slightly different approach to an aza-Nazarov cyclization was reported by Klumpp and coworkers,[8] which is a continuation of earlier work that described reactions of *N*-acyliminium ions in superacid solutions.[9] In the latter publication, excess TfOH induced *N*-acyliminium ions, prepared *in situ* by the reaction of imines with acid chlorides, to cyclize to either 3-oxo-1,2,3,4-tetrahydroisoquinolines or ring-fused isoindolinone products via a dicationic species. The most recent contribution from this group described the reaction of electron-rich arylamides of amino acetals **17** with a large excess of TfOH (25 eq), which effected an aza-Nazarov cyclization to yield **18** (Scheme 4). The group also extended the reaction to include hydroxyamides **19** as substrates. Oxidation of these alcohols with PCC gave the isolable enamine amides **21-2**, which upon exposure to excess TfOH yielded the expected aza-Nazarov cyclization products. Interestingly, with hydroxyamides **19**, demethylation of the aryl substituents occurs in some cases; this side reaction could be suppressed by shortening reaction times.
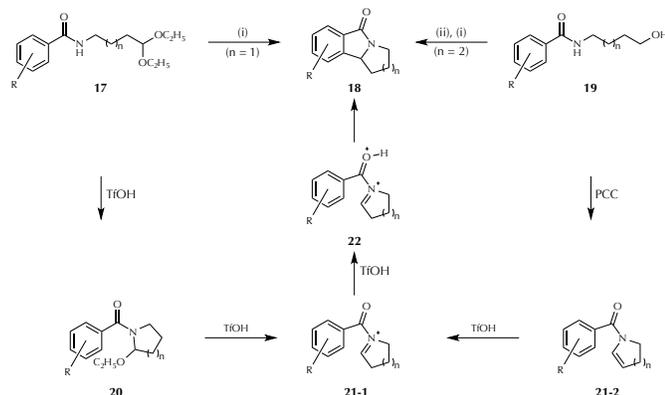
Scheme 4 The preparation of amides **18**.
(i) TfOH (25 eq); (ii) PCC

Compound 17/18	R	% Yield	Compound 19/18	R	% Yield
a	3,4,5-(OCH$_3$)$_3$	69	a	2-benzothiophene	40
b	3,5-(OCH$_3$)$_2$	76	b	3,4,5-(OCH$_3$)$_3$	43*
c	3,4-(OCH$_3$)$_2$	71	c	3,5-(OCH$_3$)$_2$	81
d	3-OCH$_3$	66			

*Mono demethylation observed

Putatively the reaction of acetals proceeds through an amide hemiaminal **20**, which on exposure to TfOH loses a molecule of ethanol to generate *N*-acyliminium ion **21-1** *in situ*. Likewise, enamide **21-2** presumably progresses to product via this same intermediate. The carbonyl oxygen is then protonated a second time to yield a superelectrophile **22**, which undergoes an aza-Nazarov cyclization. Yields were generally good (40-81%) and most of the aryl groups incorporated one or more electron releasing groups. In two instances, when extension to alkenes such as indene **23** was attempted, 1,6-cyclization via dienol **25** onto the iminium carbon lead to six membered rings, a process corroborated by DFT calculations (equation 3).
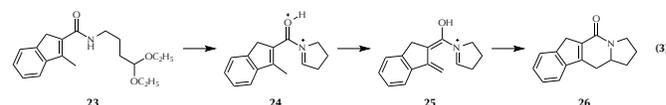
In 2010, Tius, et al. reported a catalytic asymmetric aza-Nazarov cyclization reaction that involved an azirine starting material (Scheme 5).[10] When allylic alcohol **28** was oxidized with MnO$_2$, rather than the expected α-aminodienone **29**, azirine **30** was isolated in a capricious 37 % yield. Probing the synthesis of this compound further identified a two step procedure, sulfur trioxide oxidation to enone **29** followed by treatment with PhI(OAc)$_2$, that provided the desired azirine **30** with greater reproducibility. The structure was confirmed by HRMS, IR, ^{1}H and ^{13}C NMR.
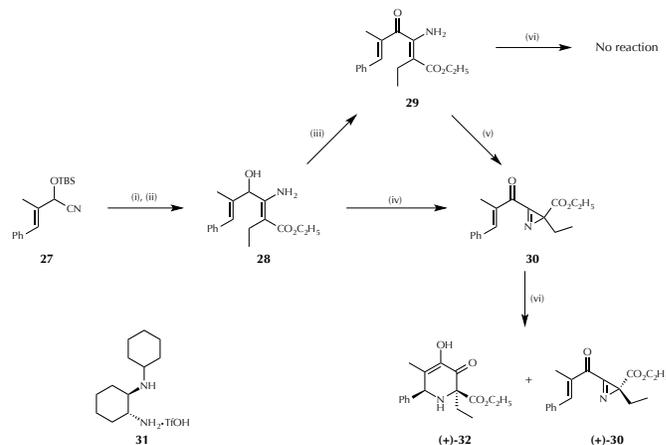
Scheme 5 The synthesis of chiral tetrahydropyridine **32**.
(i) EtCHBrCO$_2$C$_2$H$_5$, Zn dust; (ii) TBAF, THF; (iii) SO$_3$•pyr, Hünigs base, DMSO; (iv) MnO$_2$, DCM, RT; (v) PhI(OAc)$_2$, DCE, 0 °C; (vi) 20 mol % **31**, MeCN

When azirine **30** was treated with the chiral diamine monotriflate salt **31**, cyclization to tetrahydropyridine **32** was noted. This reaction proved to be very intriguing in that firstly, enone **29** failed to react under identical conditions, and secondly, both recovered azirine **30** and the cyclic product **32** were found to be optically active, indicating the cyclization involved a kinetic resolution. Mechanistically, the authors proposed enantioselective formation of the imine **33** followed by an aza-Nazarov cyclization to generate cation **34** (equation 4). Quenching of this intermediate with water and subsequent ring expansion produces **32**. Given that enone **29** failed to react under identical conditions indicated that ring strain relief is likely to be the driving force for this reaction.

(4)
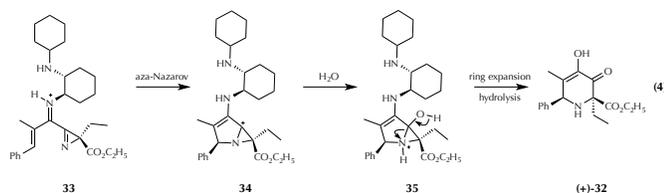
The Oxa-Nazarov Cyclization

Several accounts of oxa-Nazarov cyclizations have been published recently. Skrydstrup reported in 2012 the regioselective reaction of stabilized sulfur ylides **37** with Au(I)-activated alkynes **36** that afforded a vinyl gold intermediate, which, upon loss of the sulfur leaving group, provided the "oxa-Nazarov" cation intermediate that cyclized directly to 2,4-disubstituted furans **38** in moderate to good yields (30-82%; Scheme 6).[11] The reaction, which required a terminal alkyne, was tolerant of a wide variety of alkyl groups (R_1) on the alkyne, and worked well with both electron rich (R_2 = PhCH$_3$; not shown in the accompanying table) and electron deficient aromatic rings (cf, **38b-d, f-h**). One example demonstrated the ylide need not be derived from an aryl ketone (**38i**) and the presence of a minor amount of isomeric 2,5-disubstituted product was noted in only one example (**38f**).
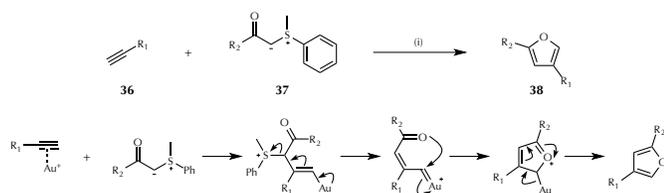
Scheme 6 The preparation of subsituted furans **38** from alkynes **36** and ylides **37**. (i) 5 mol % [(Ph$_3$P)AuNTf$_2$], DCE, 60 ºC

Compound 38	R$_1$	R$_2$	% Yield
a	nC$_6$H$_{13}$	Ph	63
b	nC$_6$H$_{13}$	4-Cl-Ph	65
c	nC$_6$H$_{13}$	4-NO$_2$-Ph	57
d	nC$_6$H$_{13}$	4-H$_3$CO$_2$C-Ph	73
e	nC$_4$H$_9$	2-Naphthyl	62
f	cyclohexyl	4-Br-Ph	61*
g	(CH$_2$)$_2$OCH$_2$Ph	4-Br-Ph	78
h	(CH$_2$)$_3$Cl	4-Br-Ph	30
i	nC$_6$H$_{13}$	C(CH$_3$)$_3$	51

* Yield is for a 96:4 mixture of 2,4/2,5 regioisomers

The Liu group reported another gold activation of enyne sulfonamides **39** to produce trisubstituted furans **40** (Scheme 7).[12] Upon formation of a resonance stabilized gold complex *in situ*, addition of a one-atom donor (e.g., **A**), was proposed to yield a vinyl Au species **41**, which led to formation of the oxa-Nazarov intermediate **42**, after expulsion of the quinoline leaving group. Cyclization, rearomatization, and protodeauration provided the C(2) amino substituted furans **40** in good to excellent yields (56-91%). The amine was required to carry an electron-withdrawing group, which was a sulfonamide in all cases reported. The best choice of catalyst was a mix of P(tBu)$_2$(o-biphenyl)AuCl/AgSbF$_6$. Other catalysts did not provide the necessary chemoselectivity and 8-methylquinoline oxide was the oxide of choice. The aromatic group attached to the vinyl portion of the starting material could carry both electron-donating and withdrawing groups (**39f,g**), or could be replaced by a variety of heterocycles (**39h-j**).
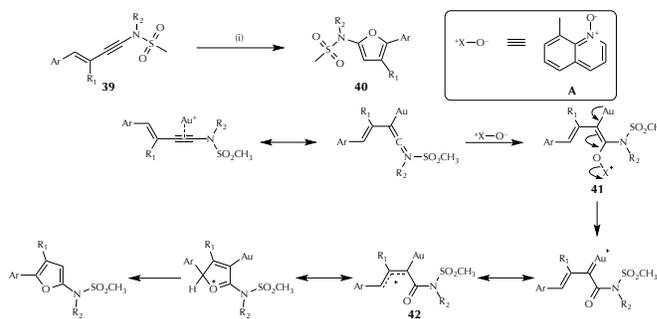
Scheme 7 The preparation of 2-aminofurans **40** from sulfonamides **39**. (i) 5 mol % (tBu)$_2$(o-biphenyl)AuCl/AgSbF$_6$, DCE, RT to 80 ºC

Compound 39/40	R$_1$	R$_2$	Ar	% Yield 40
a	CH$_3$	nC$_4$H$_9$	Ph	81
b	CH$_3$	CH$_2$Ph	Ph	86
c	CH$_3$	Ph	Ph	78
d	CH$_3$	cyclopropyl	Ph	91
e	nC$_3$H$_7$	CH$_3$	Ph	56
f	CH$_3$	CH$_3$	4-F-Ph	76
g	CH$_3$	CH$_3$	4H$_3$CO-Ph	76
h	CH$_3$	CH$_3$	2-thiophene	67
i	CH$_3$	CH$_3$	2-benzothiophene	74
j	CH$_3$	CH$_3$	2-benzofuran	71

The Imino-Nazarov Reaction

This section will cover Nazarov reactions that employ divinyl imines as Nazarov cyclization precursors rather than the traditional divinyl ketones. The issue with this variation is that *ab initio* calculations[13] suggest that, relative to their oxygen counterparts, the requisite 3-amino-1,4-pentadienyl cations are likely to resist cyclization, due in part to the conformational preference for this amino cation and the result of enhanced stabilization by nitrogen.[14] Nevertheless, since the first report of an imino-Nazarov cyclization by Tius,[15] several additional examples have been published.

González reported the reaction of propargyl tosylates **43** with N-tosylimines **44** in the presence of a Au(I) carbene catalyst (Scheme 8) provided the N-tosyl cyclopentenylimines **45** in good to high yields.[16] This disclosure is in stark contrast to an earlier report,[17] in which α-acetoxyalkynes failed to react with tosylimines in the presence of a Au(III) carbene catalyst, and instead underwent acyl migration to afford Knoevenagel products. For the reactions presented in Scheme 8, the best counterion for the catalyst was found to be either BF$_4^-$ or SbF$_6^-$. The R$_3$ group on the imine could be an electron-rich or moderately electron-deficient aryl group as well as alkyl and cycloalkyl without any negative effect on yield. Strong deactivating groups (i.e., **45d**) on the aryl substituent did adversely affect yield (34 %) however. If R$_1$ was CH$_3$, the reaction pathway usually involved a methyl group migration, prior to the imino-Nazarov cyclization step. However, for compound **43i**, ring expansion occurred preferentially to methyl migration to yield ring fused product **45i**. Alternatively, if the group attached to the propargylic carbon was secondary, such as in **43j**, the reaction allowed for the synthesis of some interesting spiro ring structures (i.e., **45j**). Primary alkyl groups did not work in this protocol.
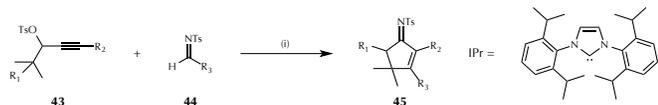
Scheme 8 Synthesis of N-tosylimino cyclopentenones
(i) 5 mol % IPrAuCl/AgBF$_4$, DCM or DCE, 40 to 70 °C

Compound 45	R$_1$	R$_2$	R$_3$	% Yield
a	CH$_3$	C$_4$H$_9$	Ph	86
b	CH$_3$	C$_4$H$_9$	4-H$_3$CO-Ph	77
c	CH$_3$	C$_4$H$_9$	4-Cl-Ph	64
d	CH$_3$	C$_4$H$_9$	4-NO$_2$-Ph	34
e	CH$_3$	CH$_2$Ph	Ph	76
f	CH$_3$	(CH$_2$)$_4$OCH$_2$Ph	Ph	64
g	H	C$_4$H$_9$	Ph	68
h	CH$_3$	4-NO$_2$-Ph	Ph	59
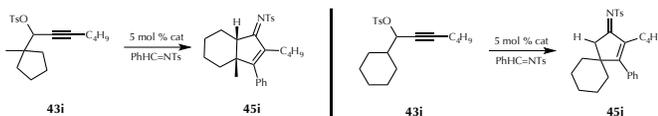
The presence of a tosyl group and Au-coordination to this nitrogen likely prevented donation of the nitrogen lone pair to the cation. Thus, the adverse effects of nitrogen on a 3-amino-1,4-pentadienyl cation are presumably minimized in this process, allowing the imino-Nazarov cyclization to take place. The authors proposed a complex mechanism (equation 5) that involved several rearrangements, including the formation of a 1,3-diene system, and azetidine synthesis, before the metal-activated imino Nazarov intermediate cyclized to the product.

$$(5)$$
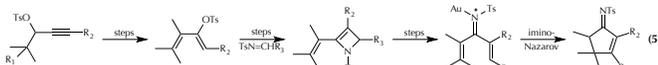
A few years later, Hsung demonstrated the use of the same mixed gold catalyst (chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] Au(I)/AgSbF$_6$) to induce the formation of 3-amino-1,4-pentadienyl cation system **48** from allenamides **46** (equation 6).[18] The key to this reaction was the use of an electron-withdrawing group (Ts) on the N atom to reduce its ability to donate into the cation, thus enhancing the reactivity of the key cationic intermediate. The phenyl group could bear electron donating or moderately electron withdrawing groups, and substituents larger than CH$_3$ (C$_4$H$_9$, CH$_2$Ph) on nitrogen were tolerated, though these reactions were typically sluggish but nonetheless provided product in excellent yields. Additionally, for compounds in which a 6π-electron electrocyclization could conceivably compete with the imino-Nazarov cyclization, only the latter was observed. This chemistry allowed for the synthesis of substituted aromatic systems with fused aminocyclopentene rings (i.e., **49**).

$$(6)$$
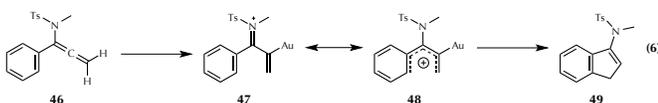
The third example of an imino-Nazarov cyclization was contributed by the West group, in which 2,2-dichloroaminocyclopropanes **51**, available in two steps from enynes **50**, were employed as imino-Nazarov cyclization precursors (Scheme 9).[19] Treating these compounds with silver triflimide (AgNTf$_2$) opened the strained ring to reveal a 3-aminopenta-1,4-dienyl cation (**52**) that underwent subsequent electrocyclization to

afford iminocyclopentenones **53**. While the iminium products could be identified by NMR, stereoselective reduction of the crude mixture with NaBH$_4$ afforded better-behaved aminocyclopentane products **54**. Overall yields for the two-step conversion were modest (48-50 %), but in certain instances, such as the last two entries in the table, poor yields of cyclized products and recovered starting cyclopropanes were reported. The authors speculated the cause for the inferior conversion was the presence of the strong acid, HNTf$_2$. Indeed when starting material was first exposed to this acid and then AgNTf$_2$ for an extended period, none of the imino-Nazarov cyclized product was isolated. Recovered starting material accounted for more than 80% of the mass balance. Furthermore, addition of a hindered base such as 2,4,6-tri-*tert*-butylpyridine permitted rapid consumption of starting material but failed to yield imino-Nazarov cyclization products.
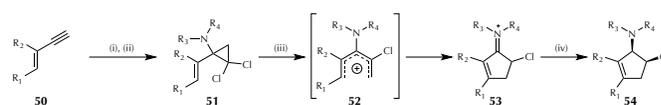
Scheme 9 The preparation of aminocyclopropanes **51** and their conversion to aminocyclopentanes **54**.
(i) HgF, TEA, R$_3$R$_4$NH, THF, 0.01 eq AlCl$_3$; (ii) 50% NaOH, CHCl$_3$, BnEt$_3$NCl; (iii) AgNTf$_2$, CH$_3$CN, Δ; (iv) NaBH$_4$, MeOH, RT

Compounds 53/54	R$_1$	R$_2$	R$_3$	R$_4$	% Yield
a	Ph	CH$_3$	PhCH$_2$	CH$_3$	50
b	Ph	CH$_3$	(CH$_2$)$_2$O(CH$_2$)$_2$		50
c	Ph	CH$_3$	Ph	CH$_3$	48
d	H	CH$_3$	(CH$_2$)$_2$O(CH$_2$)$_2$		22
e	(CH$_2$)$_4$		(CH$_2$)$_2$O(CH$_2$)$_2$		12

Interestingly, reducing the donating ability of the nitrogen substituent, such as replacing it with an acetyl group (R$_3$ = Ac) in cyclopropane **51**, yielded no reaction at room temperature and decomposition upon exposure to higher temperatures. Thus, cyclopropanes bearing an electron-rich nitrogen were necessary for this reaction, contrary to the previous report in which only amines bearing electron-withdrawing groups successfully underwent Au(I) induced cyclization. The method was expanded to substrates that contained aromatic rings tethered to the cyclopropyl group (i.e., **55**), affording imino-Nazarov cyclized tricyclic systems such as **56a**,**b** (65%) with modest diastereoselectivity (1.4:1/**56a**:**56b**; Scheme 10).
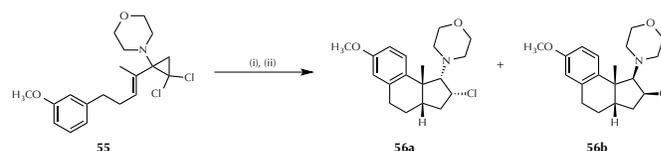
Scheme 10 The preparation of diastereomers **56a**,**b**.
(i) AgNTf$_2$, CH$_3$CN, Δ; (ii) NaBH$_4$, MeOH, RT

The Homo-Nazarov Cyclization[20]

Given that cyclopropyl groups can often mimic double bonds in terms of reactivity,[21] extension of the Nazarov to vinyl cyclopropyl ketones is compelling. There were several early reports by Wattanasin[22a,b] and Tsuge[22c] of successful application of the homo-Nazarov, which provided substituted cyclohexenones, but further investigation into this methodology was minimal until it was revisited by Yadav[23], Waser[24], and France.[25]

Yadav reported the cyclization of *t*-butyldiphenylsilyl (TBDPS) substituted cyclopropyl heteroaryl ketones **57** and **58**

under Lewis acid conditions (SnCl$_4$) in DCE at 80 ºC to yield 2,3-heteroaromatic ring-fused cyclohexanones **59** and **60**, respectively (equation 7).[23] Other combinations of solvents and Lewis acids were less efficacious. The reaction was general, providing products in good to excellent yields (70-85%), regardless of the substitution pattern of the original five-membered heterocycles. Additionally, the reaction also tolerated the presence of electron deficient aryl groups at position 5 of the heterocycle (i.e., **57d**) and the reaction with other groups capable of stabilizing the developing positive charge at the β position of the cyclopropyl ketone (equations 8, 9) were equally proficient.

(7)
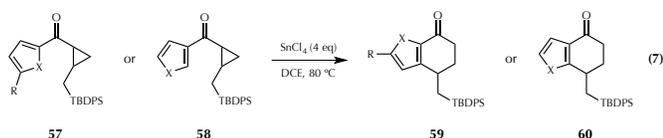
Compound	X	R	% Yield 59/60
57a	O	H	80
57b	S	H	80
57c	O	Br	80
57d	S	2,4-Cl$_2$Ph	85
58a	O	—	85
58b	S	—	80

(8)

(9)
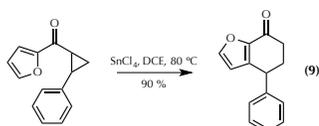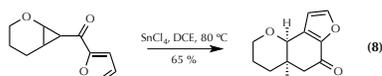
Waser was the first to report a catalytic homo-Nazarov cyclization (Scheme 11) on a vinyl ether cyclopropyl ketone substrate.[24] A quick two-step sequence to the requisite precursors started with cyclopropanation of α,β-unsaturated Weinreb amides **61**, followed by treatment with lithiated vinyl ethers. Several acids were screened for activity: Lewis acid catalysts led to mostly polymerization, but sulfuric acid and TsOH were found to efficiently catalyze the desired reaction. Acetonitrile as the solvent offered the best compromise in terms of reaction time and suppressing polymerization. At least one electron-donating group was required on the aromatic ring (Ar), and in one instance furan was tolerated. In another example (i.e., **62f**), the cyclopropane carried an additional methyl group (R = CH$_3$), which caused a substantial rate increase with some diastereoselectivity (5:1, stereochemistry not defined). In total, ten examples (nine with R = H) were reported with yields ranging from 15 % to quantitative. The authors postulated that after protonation of the carbonyl oxygen and rate-limiting cyclopropane ring cleavage, the resulting carbocation **64** undergoes an intramolecular Friedel-Crafts reaction followed by the loss of a proton to yield the cyclohexenone products.
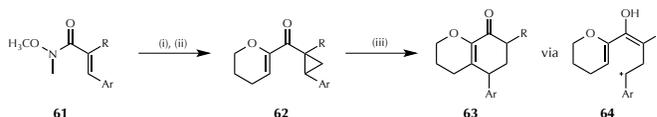
Scheme 11 The preparation cyclohexenones **63**.
(i) (CH$_3$)$_2$S(O)=CH$_2$, THF; (ii) 3,4-dihydro-2H-pyran, tBuLi, THF; (iii) 20 mol % TsOH, CH$_3$CN

Compound	Ar	R	% Yield
62a/63a	4-H$_3$CO-Ph	H	70
62b/63b	Ph	H	NR
62c/63c	3,4-(H$_3$CO)$_2$-Ph	H	100
62d/63d	2,4-(H$_3$CO)$_2$-Ph	H	100
62e/63e	2-furan	H	50
62f/63f	4-H$_3$CO-Ph	CH$_3$	100

Building on this methodology, with an eye toward a formal total synthesis of aspidospermidine, the Waser group next prepared 2-ketoindolyl cyclopropylamine **65** in eight steps from 2-piperidinone,[26] with the expectation that this system would undergo a diastereoselective homo-Nazarov cyclization to yield a final product consisting of four of the five rings found in the natural product (equation 10). However, since the indole nitrogen was not protected, cyclization (TsOH, CH$_3$CN) gave a product that, by NMR analysis, was a 1.6:1 mixture of C(3) to N(1) cyclized products (**68** and **70**, respectively). Fortunately, conditions were identified that allowed either regioisomer to be isolated as the major product. The use of Cu(OTf)$_2$ in DCM afforded the desired carbon-cyclized product **68** (91 %, 8:1 dr), whereas treatment with TsOH in DCM favored indole nitrogen participation to give **70** (89 %, 21:1 dr). Moreover, the N(1) product could be converted to the C(3) product upon exposure to copper triflate, identifying the former as the kinetic product. To explain the excellent observed diastereoselectivity, the authors proposed structures **67**/**69**. Analysis of the alternative transition state structures that lead to *trans*-ring fusion could only be generated from an energetically less favorable boat-like conformation. With a route to the Cbz protected intermediate **68** successfully achieved, the formal total synthesis of aspidospermidine was completed by N-deprotection, yielding a Wenkert intermediate en route to the natural product.[27]

(10)
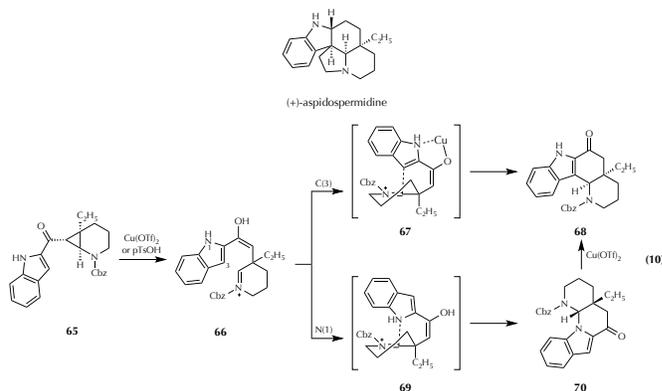
In the latest contribution from this group,[28] an attempt was made to address some shortcomings of this chemistry, most notably, the requirement of electron-rich donor groups on the cyclopropane and the lack of asymmetric induction in the presence of chiral catalysts. As a result, the original route was modified to incorporate

an α-carbomethoxy group, which would not only further polarize the labile C–C bond of the cyclopropane but also offer an additional binding site for catalytic cations, a concept first exploited by the France group (*vide infra*).

After generating the requisite substituted dimethyl cyclopropane-1,1-dicarboxylate, selective hydrolysis of the less-hindered methyl ester afforded monoacid **72**, which was then treated sequentially with the vinyllithium reagent derived from 3,4-dihydro-2*H*-pyran and methyl iodide in the presence of potassium carbonate to provide the final targets **73** ($R_1 = CO_2CH_3$) in good overall yield (Scheme 12).
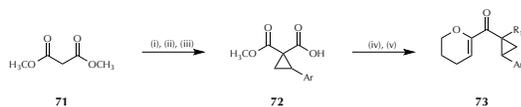
Scheme 12 Preparation of cyclopropyl ketones **73**.
(i) TsN_3, TES; (ii) Rh(esp)_2, H_2C=CHAr; iii) NaOH, MeOH, RT; (iv) 3,4-dihydro-2*H*-pyran, tBuLi, THF, –90 °C; (v) K_2CO_3, CH_3-I, DMF
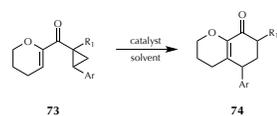
Compound 73/74	R_1	Ar	Cat (mol %)	Time (h)	Solvent	% Conversion
a	H	4-H₃CO-Ph	pTsOH (20)	18	CH₃CN	100
b	CO₂CH₃	4-H₃CO-Ph	pTsOH (20)	0.25	CH₃CN	100
c	CO₂CH₃	Ph	pTsOH (20)	19	CH₃CN	0
d	CO₂CH₃	Ph	Ni(ClO₄)₂•6H₂O (20)	26	DCM	100
e	CO₂CH₃	Ph	BF₃•OEt₂ (10)	3	DCM	100

With these starting materials in hand, catalysts were screened for efficacy. A host of Brønsted and Lewis acids failed to generate homo-Nazarov products, and equally ineffective was TsOH when the aryl group was devoid of an activating group, as was observed earlier (see the reaction of **62b** in Scheme 11). Fortunately, the use of nickel(II) perchlorate hexahydrate or boron trifluoride etherate overcame this limitation in good yields (63 % and 83 % isolated yields, respectively). In addition, having identified a Lewis acid catalyst and incorporating the ester moiety had other noteworthy benefits: reaction times were reduced more than 70-fold when compared to the original 20 mol % TsOH/acetonitrile conditions, and the reaction was more tolerant of less reactive aromatic components. For instance, the reaction of **73** bearing a 4-Cl phenyl group ($R_1 = CO_2CH_3$, Ar = 4-Cl-Ph; not shown) performed admirably (85%). These researchers also demonstrated that the added carboxylate group could be removed post-cyclization via Krapcho dealkoxycarbonylation (NaCl, DMSO, 150 °C) but an attempt to make use of chiral PYBOX Lewis acids to generate chiral cyclohexenones **74** ($R_1 = H$) was disappointing, as only low % ee values (11–25%) were noted. This paper also includes full experimental details of the approach described above *en route* to cyclohexylamine-containing natural products such as aspidospermidine.

France and coworkers were the first take advantage of donor-acceptor-acceptor cyclopropanes and to make use of an ester group as an additional coordinating site for Lewis acids to effect a homo-Nazarov cyclization.[25] In essence, by correctly positioning electron donating (e.g., 4-methoxyphenyl) and withdrawing (e.g., β-ketoester) groups within the cyclopropane framework, the key C–C bond becomes rather polarized, thus facilitating ring opening. The

required starting materials were rapidly prepared by effecting a diazo transfer reaction on the Weinreb amide **75**. Subsequent rhodium-catalyzed cyclopropanation with several styrenes, and addition of vinyl Grignard reagents provided, in short order and good yields, vinyl cyclopropyl ketones **76** (Scheme 13). Screening a variety of Lewis acids and solvents identified In(OTf)₃ (30 mol %) as the best catalyst of those studied and DCM as the solvent of choice. Although most catalysts did provide homo-Nazarov products, all except In(OTf)₃ either gave complex product mixtures, which included the desired cyclohexenone **77-1**, its isomeric conjugated β-dienol (**77-2**), and/or dihydrofuran **78**, or failed to go to completion, even after extended reaction times. Substrates bearing less effective donating groups, such as phenyl (**76c**) or even 4-F-phenyl (**76d**), did give cyclization products but failed to go to completion after 24 h. Overall, the yields for the combined homo-Nazarov products ranged from 29-93%, with the lower yielding reactions representing those that returned starting material.
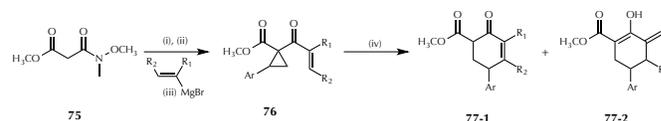
Scheme 13 Preparation of enones **77-1**.
(i) TsN₃, TEA; (ii) Rh₂(oct)₄, H₂C=CHAr; (iii) Grignard reagent; (iv) 30 mol % In(OTf)₃, DCM, RT
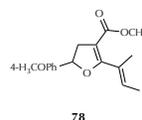
Compound 76/77	Ar	R_1	R_2	% Combined Yield 77-1/77-2
a	4-H₃CO-Ph	CH₃	CH₃	75
b	4-H₃CO-Ph	CH₃	H	77
c	Ph	CH₃	H	46
d	4-F-Ph	CH₃	H	55
e	4-H₃CO-Ph	CH₂TMS	H	92

The next phase of this project involved the application of this protocol to the synthesis of heteroaromatic ring-fused cyclohexenones.[29] The route to the requisite precursors started with a variety of heteroaryl β-ketoesters **79** and utilized the same sequence of reactions to arrive at cyclopropanes **80** (Scheme 14). Due to the enhanced reactivity of the heterocycles, lower catalyst loading (5 mol %) was tolerated (86% yield vs 88% yield at 30 mol %), though the reaction time increased (2.5 h vs 5 h). Unfortunately, the diastereoselectivity of the cyclization (i.e., *trans/cis* ratios) was generally low (1.2-1.7:1), but the chemistry was tolerant of a wide variety of heterocycles. Cyclopropanes that lacked electron donating aryl substituents (i.e., compounds **80i**,**j**), required elevated temperatures (80 °C in DCE) to achieve successful reactions.
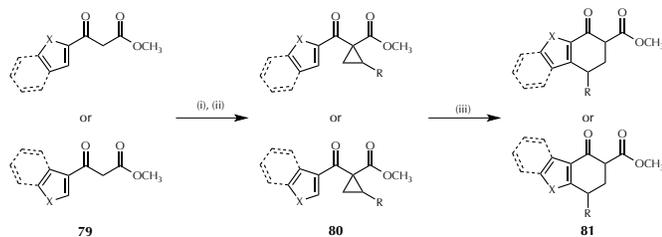
Scheme 14 Preparation of heterocyclic cyclohexanones **81**.
(i) TsN₃, TEA; (ii) Rh(esp)₂, H₂C=CHR; (iii) 5 mol % In(OTf)₃

Compound	Heterocycle	R	% Yield	*trans/cis* ratio
80a	2-thiophene	4-H₃CO-Ph	86	1.5/1
80b	2-furan	4-H₃CO-Ph	67	1.1/1
80c	3-thiophene	4-H₃CO-Ph	73	1.7/1
80d	3-furan	4-H₃CO-Ph	73	1.1/1
80e	N-methyl-2-indole	4-H₃CO-Ph	63	1.2/1
80f	2-benzofuran	4-H₃CO-Ph	91	1.4/1
80g	N-methyl-3-indole	4-H₃CO-Ph	61	1.2/1
80h	3-benzofuran	4-H₃CO-Ph	71	1.2/1
80i	2-thiophene	Ph	81*	2.3/1
80j	3-furan	Ph	83*	1.2/1

* These reactions required elevated reaction temperatures.

Further experimentation highlighted other facets of this chemistry. For instance, when C(2) was blocked, as shown in equation 11, the heterocycle was forced to cyclize onto C(4) (56 % yield as a 2:1 mixture of keto and enol tautomers). Additionally, the cyclopropane also tolerated higher substitution with little impact on yield (equation 12; 71% yield). Lastly, in an impressive display of the power of this chemistry, the diazoketone shown in equation 13 was subjected to a *one-pot* homo-Nazarov cyclization, using substantially lower catalyst loading. The yield for this one step sequence was 56%, which compared very favorably to the two-step procedure (73% for each step, 53% overall).

(11)

(12)

(13)
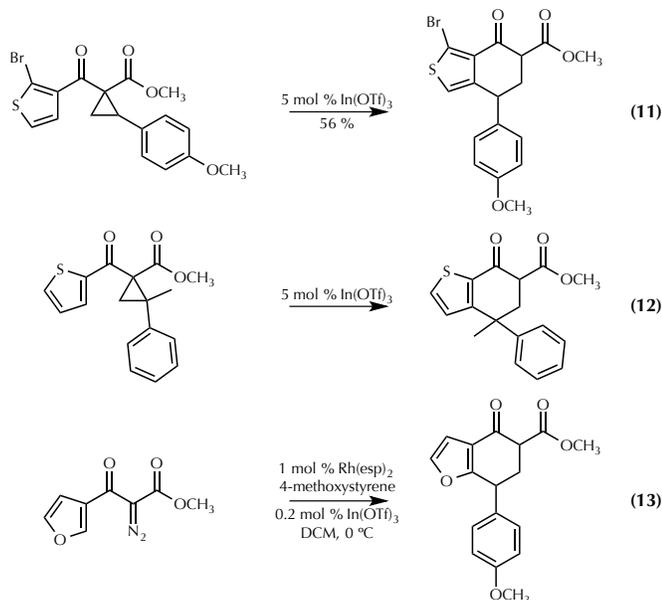
Recognizing that extension of this protocol to acylated indoles[30] could potentially open a route to the numerous natural products bearing a common hydropyrido-[1,2-*a*]indole-6(7*H*)-one core, the France group next prepared N-acyl-3-methylindolyl cyclopropanes **83** (Scheme 15).[31] With these precursors in hand, In(OTf)₃–induced cyclization afforded the desired tricyclic heterocycles in good to excellent yields (48-99 %) for a selection of

compounds. The only substrate that failed to yield cyclized product in good yield carried the strongly deactivated 4-NO₂-phenyl ring on the cyclopropane (**83e**). Other substrates with less deactivating groups such as **83d** worked well but did require elevated temperatures. Also not surprising was the fact that substrates bearing alkyl groups (i.e., **83h**,**i**) on the cyclopropane likewise required elevated temperatures, but these reactions were nonetheless successful. Overall, the diastereoselectivity ranged from moderate to high. Only a single diastereomer was observed for spiro products **84h**,**i**.
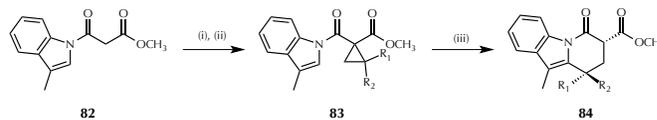
Scheme 15 The preparation of lactams **84**.
(i) TsN₃, TEA, CH₃CN; (ii) Rh₂esp₂, H₁C=CHR, 0 °C; (iii) 30 mol % In(OTf)₃, DCM, RT

Compound 83/84	R₁	R₂	% Yield	*trans/cis* ratio
a	H	4-H₃CO-Ph	99	2.6/1
b	H	2-H₃CO-Ph	95	3.2/1
c	H	Ph	52*	2.6/1
d	H	4-F-Ph	48*	2.6/1
e	H	4-NO₂-Ph	31	—
f	H	2-furyl	99	4.5/1
g	CH₃	Ph	94	1.1/1
h	–(CH₂)₄–		88*	**
i	–(CH₂)₅–		79*	**
j	H	SPh	83	6.3/1

* Reaction performed in DCE at 80 °C; ** only a single diastereomer was observed by NMR

The last series of compounds reported in this paper tested the structural requirements of the acylated indole (equation 14). In particular, the C(3) position was varied to prove that no alkyl group was required (R = H) and further that the reaction tolerated an assortment of functional groups (R = -CH₂CH₂Br, -CH₂CH₂NPhth, -CH₂CO₂CH₃), with little-to-no effect on yield (76-99%).

(14)

This methodology was then applied toward a short, diastereoselective total synthesis of (±)-deethyleburnamonine (**86b**), a member of the *eburnan* alkaloids (Scheme 16).[32] Exposing cyclopropyl acylindole **84** to catalytic In(OTf)₃ in DCM at RT afforded the tetracyclic core structure **85** as the major product in 71 % (3:1 dr). A two-step sequence (TFA induced removal of the Boc group with concomitant cyclization and Krapcho demethoxycarbonylation with NaCl in hot DMSO) afforded the natural product in 18% overall yield in six steps.
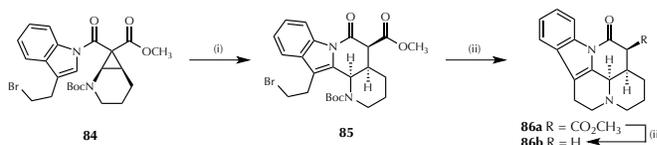
Scheme 16 Preparation of (±)-deethyleburnamonine (**86b**).
(i) 30 mol % In(OTf)₃, DCM, RT; (ii) TFA; (iii) NaCl, DMSO, Δ

Conclusion

The Nazarov cyclization has captured the imagination of many an organic chemist, and the ingenuity and creativity of these scientists continues to expand upon this idea. These inspirations, whether related mechanistically or merely conceptually, have significantly augmented the general applicability of the original concept. Whereas the Nazarov cyclization affords cyclopentenones, the modifications discussed in this Review have broadened its scope to include a) the synthesis of highly substituted pyrroles and furans via the aza- and oxa-Nazarov cyclizations; b) extension to imino substrates, which allows for the construction of aminocyclopentanes; c) and lastly, under appropriate conditions, access to substituted cyclohexenone products via cyclopropyl vinyl ketones. In many instances, these transformations were accomplished in high yield, and with a good degree of regio- and stereocontrol. These features, in combination with a general tolerance for additional functional groups, greatly add to the synthetic utility of these Nazarov-like cyclizations and further extension to the synthesis of complex molecules, in addition to the natural products referenced herein, is anticipated.

Notes and references

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1 List of abbreviations: TfOH = triflic acid; DFT = density functional theory; DCM = dichloromethane; DCE = 1,2-dichloroethane; TsOH = p-toluenesulfonic acid.

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5 Despite being potentially misleading, the author does not refrain from using terms such oxa-Nazarov, homo-Nazarov, etc. The reader is once again reminded of the "formal" connection to the original cyclization.

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