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## The Iso-Nazarov Reaction

Martín J. Riveira,\* Lucía A. Marsili and Mirta P. Mischne\*

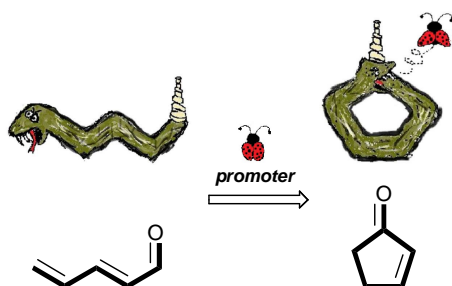
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The acid-promoted cycloisomerization of conjugated dienals and linearly-conjugated dienones for the synthesis of five-membered ring systems is reviewed.

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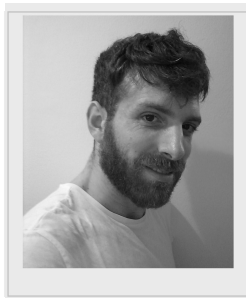
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Martín J. Riveira graduated with a Bachelor's degree in Chemistry in 2009 from Universidad Nacional de Rosario (UNR) and then worked on the development of domino reactions of polyunsaturated carbonyl compounds under the supervision of Prof. Mirta P. Mischne. After earning his Ph. D. degree in 2014, he joined the group of Prof. Ernesto G. Mata as a postdoctoral fellow working on the application of transition-metal-catalyzed reactions to solid-phase organic synthesis. In 2017 he was appointed assistant researcher at CONICET. His research interests gravitate towards the development of new domino reactions based on cycloisomerizations.



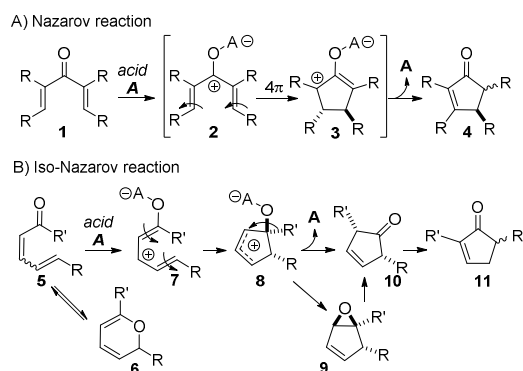
Lucía A. Marsili is an undergraduate student at Facultad de Ciencias Bioquímicas y Farmacéuticas (Universidad Nacional de Rosario). While pursuing her Bachelor's degree in Chemistry, she is now involved in the development of novel variants of the Iso-Nazarov reaction.



**Abstract:** The construction of five-membered rings is essential in organic chemistry. In this context, pentannulation reactions that provide a straightforward access to cyclopentenones are of particular interest, as these structures are not only embedded in important molecules such as some prostaglandins, but also serve as versatile building blocks in organic synthesis. This review documents on the acid-promoted cycloisomerization of conjugated dienals and linearly-conjugated dienones for the construction of cyclopentenones, a transformation that has been largely eclipsed by the well-known Nazarov reaction, *i. e.* the acid-promoted cycloisomerization of cross-conjugated ketones.

## 1. Introduction

Cycloisomerization reactions are undoubtedly attractive atom-economical transformations in synthetic planning.<sup>1</sup> The proper combination of an activator and a suitable polyunsaturated precursor just triggers the fine dancing of atoms and electrons that allows the efficient preparation of complex cyclic and polycyclic frameworks. Naturally, nothing is wasted in these processes and, in some cases, high levels of stereo- and regioselectivity can be attained. In particular, since the pioneering works of I. Nazarov, the cycloisomerization reaction that carries his name has evolved into a well-established methodology for cyclopentannulation.<sup>2,3</sup> Basically, the classic version of this essential reaction involves the initial activation, either by a Brønsted or a Lewis acid, of a cross-conjugated dienone (**1**, Scheme 1A). The pentadienyl cation thus formed (**2**), then undergoes a  $4\pi e^-$  electrocyclic ring-closure to provide a brand new oxyallyl cation (cyclopentenyl cation **3**) that after elimination affords the corresponding conjugated cyclopentenone product (**4**).



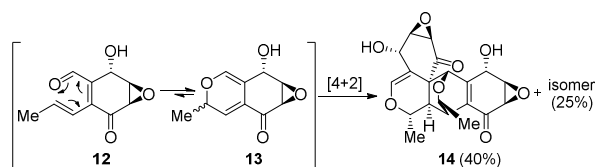
**Scheme 1.** Acid-promoted isomerization of cross- and linearly-conjugated unsaturated carbonyl compounds.

Cyclopentenones are unarguably distinguished structural motifs, not only versatile as synthetic intermediates,<sup>4</sup> but also present in notable natural molecules such as some aflatoxins, prostaglandins, jasmone and phorbol, just to name a few.<sup>5</sup> This importance probably triggered, especially these last decades, continuous efforts on the understanding of the Nazarov reaction by several groups, taking the process to a mature state and rendering this reaction one of the most valuable tools for cyclopentenone construction. Some accomplishments in the field include the application to the total synthesis of natural products,<sup>6</sup> the development of regio- and stereoselective versions,<sup>7</sup> the design of cascade reactions involving the Nazarov cyclization<sup>8</sup> and the extension of the reaction to other substrates capable of providing the key pentadienyl cation intermediates.<sup>9</sup>

Some alternative substrates for the  $4\pi e^-$ -conrotatory electrocyclization comprise  $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds such as dienals and dienyl-ketones (**5**, Scheme 1B). The development of this type of transformation, originally baptized as the anomalous Nazarov reaction by Denmark<sup>10</sup> and then as the iso-Nazarov reaction by Trauner,<sup>11</sup> has been clearly eclipsed by the high popularity of the traditional Nazarov reaction using divinyl ketones. It is the purpose of the present review to document on the state of the art of the hereinafter iso-Nazarov reaction. Presented below is an overview of the literature precedents since its beginning, including our own contributions to the field. These have been organized in five sections and, for the sake of clarity, most sections will be disclosed in chronological order. It should be noted that analogous radical<sup>12</sup> and transition-metal-mediated<sup>13</sup> versions of this cycloisomerization have been developed, but these are outside the scope of the present review.

## 2. Iso-Nazarov Reactions

Along the way to cyclopentenones, an inspection of Scheme 1 reveals there are three main differences when linearly conjugated carbonyl compounds are used as substrates instead of divinyl ketones. First, an interesting feature in the iso-Nazarov pathway is that for cyclopentenones to form, a group migration is required. That is, after  $4\pi$  electrocyclization, migration of group R' in **8** allows for the formation of the carbonyl group. Particularly in the case of dienones, the capability of different alkyl or aryl R' groups to migrate will determine the possibility of forming cyclopentenone products. Secondly, unlike divinyl-ketones, dienals and linearly-conjugated dienones (**5**) are in equilibrium with their *2H*-pyran valence-isomers **6** through an oxa- $6\pi$ -electrocyclic reaction.<sup>14</sup> Whereas in some cases this equilibrium does not limit the pool of substrates available for the iso-Nazarov process, in some others it can also be completely shifted toward reactive pyran isomers that can be trapped in subsequent transformations. For instance, dienal **12** is a putative intermediate in Hayashi's biomimetic synthesis of the angiogenesis inhibitor (+)-epoxyquinol A (**14**) (Scheme 2).<sup>15</sup> Compound **12**, obtained *via* MnO<sub>2</sub> allylic oxidation of the corresponding alcohol, undergoes an oxa- $6\pi$ -electrocyclic ring closure towards *2H*-pyran **13** which readily dimerizes *via* a Diels-Alder-type [4+2] cycloaddition to afford the natural product **14**. Finally, the iso-Nazarov reaction can provide, depending upon the conditions, the thermodynamically less stable 3-cyclopentenones as products (**10**) and not necessarily the conjugated ones commonly obtained by the traditional Nazarov cyclization.

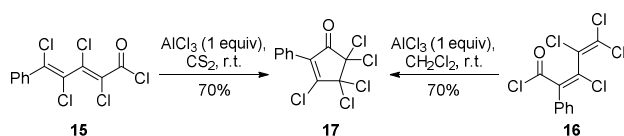


**Scheme 2.** Equilibrium shift in the dienal/*2H*-pyran valence isomerism.

As regards the mechanism of the iso-Nazarov reaction, it should be noted that a non-pericyclic ionic pathway can as well be proposed involving an intramolecular Prins reaction. de Lera and co-workers performed computational studies on this as well as other reactions involving hydroxy-pentadienyl cations as intermediates, e.g. the Nazarov reaction and the Piancatelli rearrangement.<sup>16</sup> His results are in accord with the pericyclic pathway involving the conrotatory electrocyclic ring closure. Notwithstanding this, as shall be seen

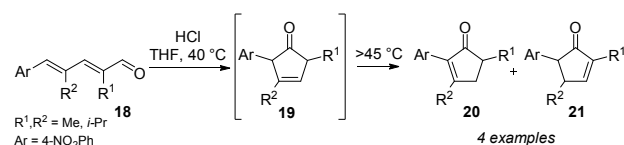
below, several authors have evoked this alternative ionic mechanism to account for certain experimental observations.

Surprisingly, to our knowledge, the first examples on the cycloisomerization of linearly conjugated diene-carbonyl compounds did not involve dienones or dienals but dienoic acid chlorides. In 1962 Märkl *et al.* showed that Lewis acid  $\text{AlCl}_3$  promoted the isomerization of acid chloride **15** at room temperature to afford the 2-cyclopentenone product **17** in good yield (Scheme 3).<sup>17</sup> Many years later, in 1979, the same cyclopentenone product **17** was also obtained by  $\text{AlCl}_3$  treatment of the isomeric dienoyl chloride **16**.<sup>18</sup>



**Scheme 3.** First examples on the cycloisomerization of dienylicarbonyl compounds.

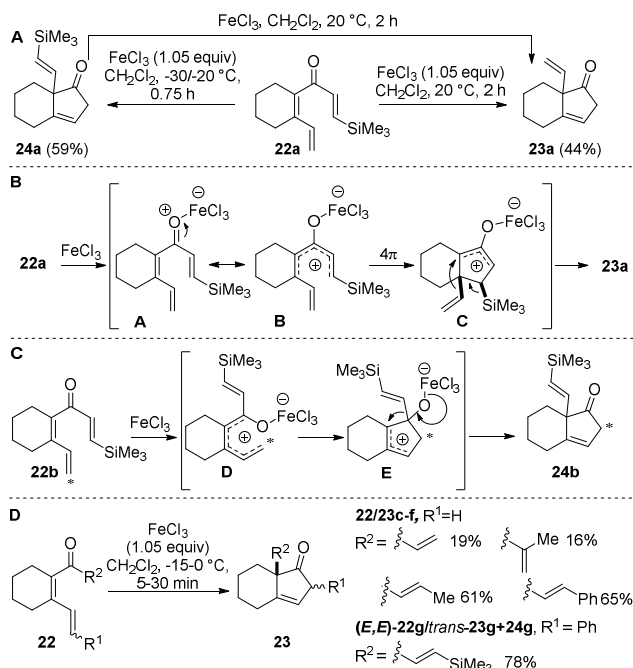
The same year, the group of Ogawa reported the isomerization of conjugated all-*trans*-dienals **18** using concentrated hydrochloric acid in THF at 40 °C (Scheme 4).<sup>19</sup> Consistent with the mechanism depicted in Scheme 1B, the authors stated that non-conjugated cyclopentenones **19** were the initially obtained products of these cycloisomerizations. Instead, if temperature was raised above 45 °C, a ca. 1:1 mixture of isomerized 2-cyclopentenones **20** and **21** was obtained. Unfortunately, no information about yields, stereoselectivity or the amount of acid used is provided in the manuscript and the <sup>1</sup>H NMR data of only one product is reported. Shortly after, the cyclization of 2-methyl-2,4-hexadienal to 2,5-dimethyl-2-cyclopentenone in hot 5% oxalic acid solution was reported as an unwanted side-reaction by the group of Heck.<sup>20</sup>



**Scheme 4.** First examples on the cycloisomerization of dienals.

In the course of their studies on silicon-directed Nazarov reactions,<sup>21</sup> Hite and Denmark reported an anomalous cyclization of dienylic vinyl ketones (Scheme 5A).<sup>10</sup> As shown, the cyclization of substrate **22a** using iron chloride as promoter in dichloromethane at room temperature provided non-conjugated cyclopentenone **23a** in 44% yield. Although this transformation could be explained by a classic Nazarov pathway followed by cationic migrations (Scheme 5B), this mechanism could not account neither for the formation of **24a** at lower temperatures, nor the outcome of <sup>13</sup>C-isotopic labeling studies (see Schemes 5A and 5C). In this manner, the authors introduced the mechanism of the iso-Nazarov reaction involving hydroxy-pentadienyl cation **D** that, after cyclization and 1,2-group migration provides the same product **24b** (*i.e.* <sup>13</sup>C-labeled **24a**). Scheme 5D exhibits other dienylic vinyl ketones that also underwent this iso-Nazarov cyclization. In particular, styryl-side-chain bearing substrate **22g** provided a mixture of both cyclopentenone products **24g** and protodesilylated **23g** (ratio 0.77:1, 78% combined yield). Surprisingly, other substrates lacking the cross-conjugated motif (for example substrates **22** with  $\text{R}^2 = \text{Me}, t\text{-Bu}, \text{Ph}$ ) did not undergo the discovered process. Since  $\text{R}^2$  is the group that migrates, this failure was unsettling as for instance phenyl groups are well-known to participate in pinacol

rearrangements. In addition, the transformation proved to be stereospecific: the use of pure (*E,E*)-**22g** provided the corresponding products **23** and **24** as single diastereoisomers (*trans*). On the other hand, the use of a mixture of (*E,E*)-**22g** and (*E,Z*)-**22g** provided both *cis* and *trans* isomers of **24g**. Since at that time other authors had already dealt with “normal” Nazarov reactions of dienyl vinyl ketones,<sup>22</sup> the success of the devised iso-Nazarov pathway was attributed to the *Z*-geometry of the  $\alpha,\beta$ -unsaturation of the reacting dienone moiety.

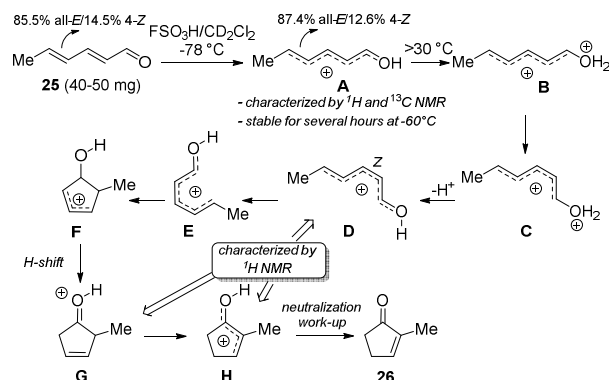


**Scheme 5.** First examples of the iso-Nazarov cyclization of dienyl vinyl ketones.

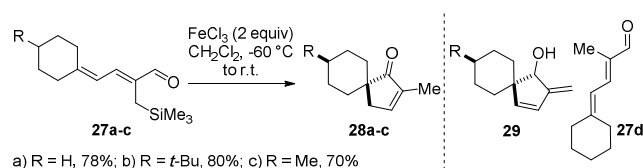
The isomerization of aldehyde 2,4-hexadienal (**25**) to 2-methyl-2-cyclopentenone (**26**) in  $\text{FSO}_3\text{H}/\text{CD}_2\text{Cl}_2$  was reported by Elia *et al.* in 1991 (Scheme 6).<sup>23</sup> Protonated **25** (**A**), initially formed at  $-78^\circ\text{C}$ , was shown to be stable for several hours at  $-60^\circ\text{C}$  and could also be characterized by  $^1\text{H}$  and  $^{13}\text{C}$  NMR. When temperature was increased above  $30^\circ\text{C}$ , however, **A** cycloisomerized into cation **H**, *i. e.* protonated **26**. Cyclopentenone **26** could be retrieved by neutralization of **H** and its identification was confirmed *via* an independent synthesis. Due to the large negative entropy of activation measured for the isomerization of **A** to **H**, a dication was proposed as intermediate (**B**). On the other hand, the key role of intermediate **D**, which could also be characterized by NMR, was also established. Irradiation of **A** in a quartz Dewar ( $\lambda_{\text{max}} = 338\text{ nm}$ ) provided a 7:3 mixture of **A** and **D** that already underwent isomerization to **G** at  $-40^\circ\text{C}$ . Upon heating to  $-10^\circ\text{C}$  this cation, also identified by NMR, was found to further rearrange to **H**. No yield for the production of **26** was reported.

In 2000, Kuroda and Koshio reported the cycloisomerization of dienals **27a-c** bearing a trimethylsilylmethyl group at the  $\alpha$  carbon (Scheme 7).<sup>24</sup> The reaction was promoted by anhydrous  $\text{FeCl}_3$  (2 equiv) and provided the spirocyclic products **28a-c** in good yields. Other Lewis acids such as  $\text{BF}_3\cdot\text{OEt}_2$ ,  $\text{AlCl}_3$  and  $\text{Et}_2\text{AlCl}$  were also tested but without success. In particular, for substrates **27b-c**, the reaction was found to proceed stereoselectively, affording the corresponding cyclopentenones as single diastereoisomers. This was

rationalized by a preferential equatorial attack of the  $\gamma,\delta$ -double bond. Although a complete mechanistic scenario was not provided, cycloalkenol **29** was proposed as key intermediate of the reaction (see Scheme 1B, protonated **8**). The authors found that the silyl group may play an important role in stabilizing cationic intermediates of the reaction since analogous substrate **27d** did not participate in the cyclization.



**Scheme 6.** NMR studies on the isomerization of 2,4-hexadienal in  $\text{FSO}_3\text{H}$ .



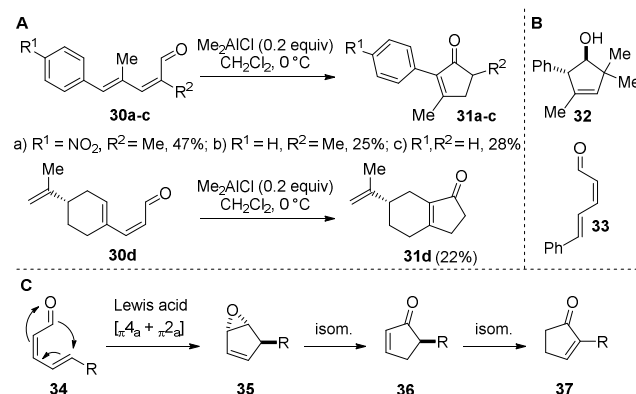
**Scheme 7.** Isomerization of 2-(trimethylsilylmethyl)-pentadienals for the synthesis of spirocyclic cyclopentenones.

In 2003, Trauner's group introduced the Lewis-acid catalyzed cycloisomerization of (*Z*)-dienals that they named the iso-Nazarov cyclization (Scheme 8A).<sup>11</sup> 2-Cyclopentenones **31a-d** were obtained as single regioisomers using a catalytic amount of  $\text{Me}_2\text{AlCl}$  as Lewis acid. Indeed, one of these cyclopentenones (**31a**) had been prepared by Ogawa and co-workers using concentrated HCl and an all-*trans*-dienal (**20**, Scheme 4). Interestingly, product **31b** was found to be accompanied by side-product **32**, the formation of which can be explained by an interrupted iso-Nazarov reaction involving the trapping of a cyclopentenyl cation intermediate (such as **8**) by the catalyst (Scheme 8B). The pattern of substituents in the dienal substrates seemed to play a major role as extended cinnamaldehyde **33** only underwent *E-Z* isomerization under the reaction conditions employed for the isomerization. Apart from the iso-Nazarov pathway involving the conrotatory  $4\pi$  electrocyclicization, the authors proposed yet another mechanism involving a pericyclic [ $\pi 4_a + \pi 2_a$ ] cycloaddition (Scheme 8C). The epoxide thus formed would then isomerize in the presence of acid to the obtained cyclopentenone product.

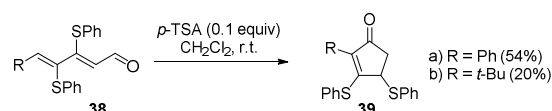
As an application of their studies on pentadienylations of aldehydes using 4-ethoxy-1,2-bis(sulfonyl)-buta-1,3-dienes, the same year, Yoshimatsu and co-workers reported the cyclization of aldehydes **38a** and **38b** (Scheme 9).<sup>25</sup> The only two substrates tested were found to be quite reactive, probably due to the presence of the cation-stabilizing heteroatoms, and the cyclizations only took 30 minutes using *p*-TSA (0.1



equiv) as additive at room temperature. The carbonyl-ene type mechanism was proposed to account for the formation of cyclopentenone products **39**. It should be noted that the stereochemistry of the starting materials could not be unambiguously determined by NOE experiments and it was only established by comparison with other dienals prepared.



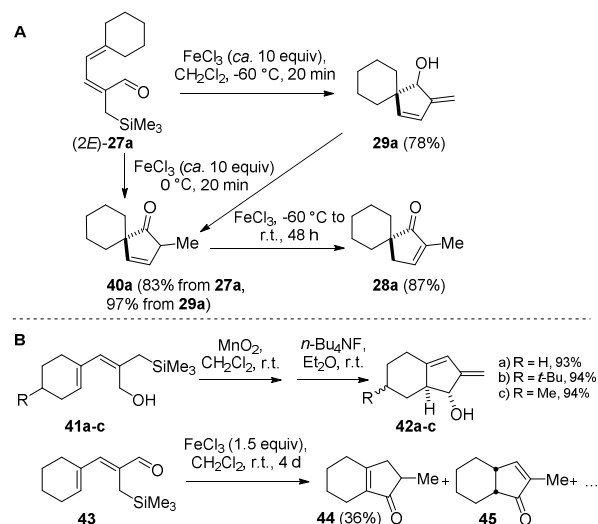
**Scheme 8.** Catalytic iso-Nazarov cyclization of (2Z,4E)-dienals.



**Scheme 9.** Catalytic iso-Nazarov cyclization of (2Z,4Z)-dienals.

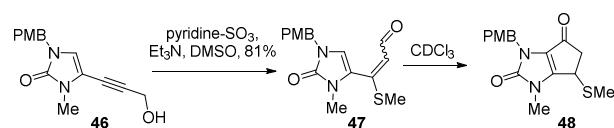
A few years later after their first report, Kuroda and collaborators reported an extension of their work in order to gain more insight into the iso-Nazarov reaction (Scheme 10).<sup>26</sup> By evaluating isomers of the original starting materials **27** and other reaction conditions, a complete picture of the mechanism was gathered. When substrate (2E)-**27a** was treated with  $\text{FeCl}_3$  at 0 °C, cyclopentenone **40a** was obtained within only 20 min in 41% yield. A two fold increase in yield was obtained when 10 equiv. of the acid were added (Scheme 10A). If temperature was kept at -60 °C, originally expected cyclopentenol **29a** was the product of the cycloisomerization. The previously obtained conjugated 2-cyclopentenone **28a** was produced as a result of a slow isomerization process of **40a** at -60 °C. The diastereoisomers of substrates **27b** and **27c** (Scheme 7) were also evaluated with similar results except for the fact that cyclopentenol isomers were either not isolated or found to be unstable. Other 2-trimethylsilylmethyl-dienals were evaluated as well. In an attempt to oxidize allylic alcohols **41a-c** to the corresponding dienals using  $\text{MnO}_2$ , it was found that the reaction conditions already promoted the iso-Nazarov rearrangement to deliver the cyclopentenols **42a-c** in good yields. Since the dienols **42a-c** were originally obtained as mixtures with their corresponding trimethylsilyl ethers, the crude reaction mixtures were treated with *n*- $\text{Bu}_4\text{NF}$ . The cyclization was found to be stereoselective featuring a *cis*-relationship between the hydroxyl group and the  $\alpha$ -hydrogen. Notwithstanding this, the incorporation of a substituent in the cyclohexane ring in **41b,c** did not impair any effect and products **42b,c** were isolated as 1:1 mixtures of diastereoisomers. Along with the finding of cyclopentenol **32** by Trauner's group, these represent the first examples of cascade processes based on the iso-Nazarov reaction (see next section). Dienal **43** could

indeed be obtained *via* oxidation of the corresponding alcohol but behaved differently than the putative diastereoisomeric dienal. Upon treatment with FeCl<sub>3</sub>, a complex mixture of at least seven compounds, including oxidation products, was obtained. Among these, conjugated cyclopentenone **44** was found as the major product and could be isolated in ca. 36% yield.



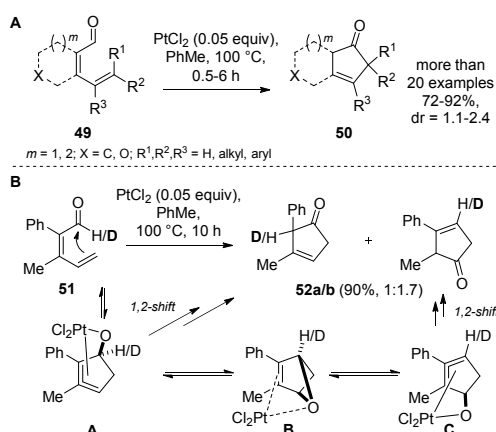
**Scheme 10.** Iso-Nazarov cyclization of 2-(trimethylsilylmethyl)-pentadienals.

In an attempt to oxidize propargylic alcohol **46** under Parikh-Doering conditions, Porter and co-workers obtained an unexpected conjugate addition product (**47**, Scheme 11).<sup>27</sup> This dienal **47**, obtained as a 10:1 mixture of *E:Z* isomers, underwent a smooth iso-Nazarov cyclization when dissolved in CDCl<sub>3</sub>. The facile cycloisomerization was attributed to the assistance of the  $\gamma$ -nitrogen atom and to the presence of traces of acid in the deuterated solvent. A Nazarov pathway as well as a carbonyl-ene type mechanism were proposed to account for the spontaneous transformation which led to a single regioisomer of **48**. No yield was reported for the iso-Nazarov step.



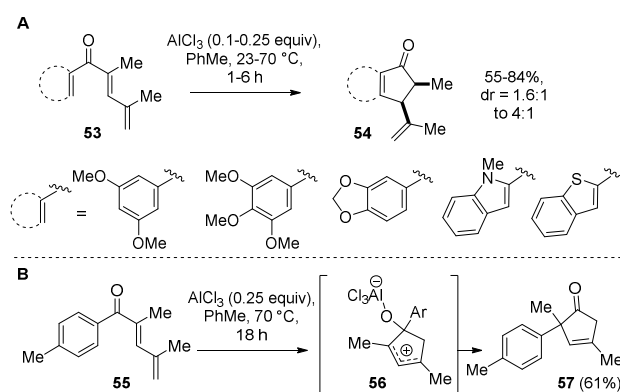
**Scheme 11.** Iso-Nazarov cyclization of a dienal in CDCl<sub>3</sub>.

In 2006 the group of Liu reported the iso-Nazarov cyclization of both monocyclic and acyclic *cis*-2,4-dienals **49** (Scheme 12).<sup>28</sup> The process was catalyzed by PtCl<sub>2</sub> (5 mol%), leading to the corresponding 3-cyclopentenones (**50**) in high yields. Since some substrates bearing a bulky substituent at the  $\alpha$ -carbon (*t*-Bu or Ph) underwent skeletal rearrangement (Scheme 12B), an alternative mechanism to that involving the  $4\pi e^-$  electrocycloisomerization was proposed. This proposal features an initial carbonyl-ene type reaction and a bicyclic epoxide as intermediate (**B**). In addition, both <sup>2</sup>H- and <sup>13</sup>C-labeling studies were performed in order to validate the mechanistic proposal.



**Scheme 12.** Iso-Nazarov cyclization of *cis*-dienals.

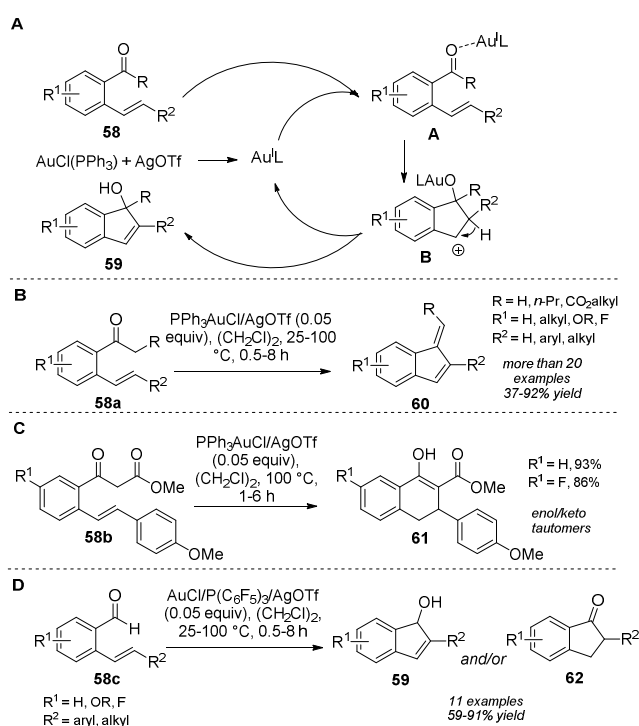
Since the work of Denmark, the next example of an iso-Nazarov reaction involving a dienyl-ketone was provided by Sarpong, Tantillo and co-workers.<sup>29</sup> As a means to access natural product tetrapetalone A, the researchers studied the Nazarov cyclization of aryl dienyl ketones for the synthesis of indanones. As shown in Scheme 13A, many substrates succumbed to this cycloisomerization upon treatment with Lewis acid  $\text{AlCl}_3$ , provided steric and electronic effects were carefully controlled. For example, the presence of the  $\alpha$ -methyl substituent at the dienyl moiety was mandatory for the success of the process. Surprisingly, analogous substrate **55** which does not bear an electron-rich aromatic group exclusively underwent an iso-Nazarov reaction with migration of the tolyl group to afford 3-cyclopentenone **57** (Scheme 13B).



**Scheme 13.** Iso-Nazarov cyclization of an aryl dienyl ketone promoted by  $\text{AlCl}_3$ .

Jagdale and Youn reported the catalytic iso-Nazarov cyclization of 2-alkenylphenyl carbonyl compounds (**58**) including aldehydes, ketones and  $\beta$ -ketoesters (Scheme 14A).<sup>30</sup> The process was found to be catalyzed by  $\text{Au}^I$  catalysts and this was unexpected since these species are well known to act as soft  $\pi$ -philic activators. Indeed, several Lewis acidic metal salts as well as many Brønsted acids were tested without success. Ag, Cu and Pt salts did promote the cyclization. Depending on the nature of the substrates, different classes of products were obtained including indenenes, indenols and indanones. Ketones and  $\beta$ -ketoesters

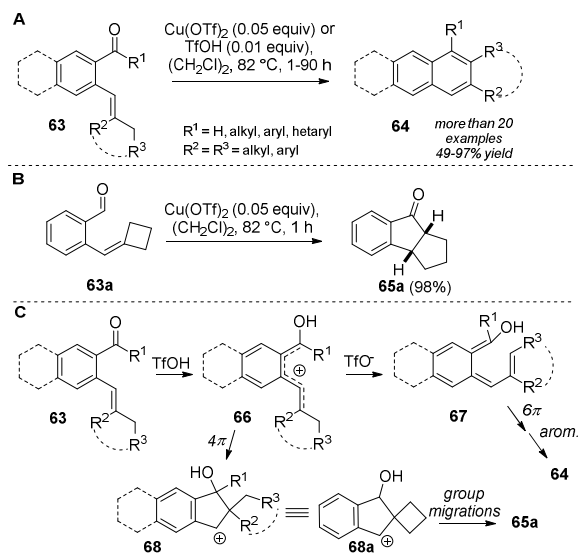
delivered indene-type products **60** after dehydration of the corresponding indenol intermediates of type **59** (Scheme 14B). The reactions were in general stereoselective affording in most cases products **60** as the *E* isomers only. Interestingly, substrates bearing an electron-rich alkenyl side-chain indeed underwent the originally expected transformation involving the activation of the olefin moiety followed by C-attack from the dicarbonyl nucleophilic group (Scheme 14C). Tetralones **61** thus obtained were isolated as mixtures of keto- and enol-tautomers. Benzaldehydes in general required harsh reaction conditions and this was circumvented by using an electron deficient ligand for the catalyst (Scheme 14D). Alkenols **59** were obtained as products except when electron-rich alkenyl side-chains were present. For these substrates **58c**, alkenols **59** underwent partial or complete isomerization to the corresponding cyclopentenones **62**. In these cases it is clear that the presence of the aromatic ring next to the carbonyl group prevents any 1,2-group migration (compare cation **B** in Scheme 14A with cation **8** in Scheme 1B).



**Scheme 14.** Au(I)-catalyzed cyclization of 2-alkenylphenyl carbonyl compounds.

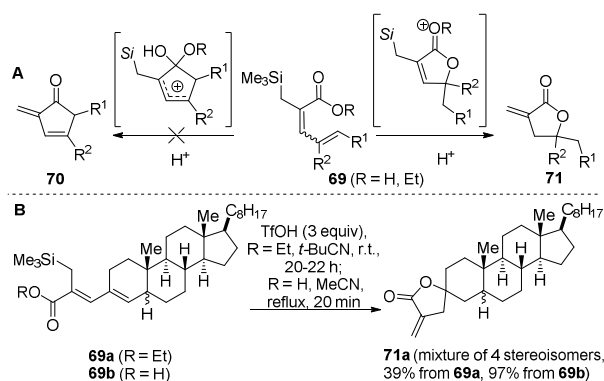
The group of Narasaka also employed 2-alkenylphenyl ketones and aldehydes (**63**) as substrates of a recently reported catalytic transformation in which polycyclic arenes (**64**) are prepared (Scheme 15A).<sup>31</sup> Both Cu(OTf)<sub>2</sub> and triflic acid were found to achieve best results unlike BF<sub>3</sub>·OEt<sub>2</sub> or SnCl<sub>4</sub> that only provided the desired products in less than 10% yields. Interestingly, while 2-cyclohexylidenemethyl-benzaldehyde [ $R^1=H$ ;  $R^2, R^3=(CH_2)_4$ ] provided the corresponding polycyclic product of type **64** in 60% yield (not shown), 2-cyclobutylidenemethyl-benzaldehyde (**63a**) failed to undergo such transformation (Scheme 15B). Instead, indanone **65a** was obtained in almost quantitative yield. The unexpected result was interpreted as arising from an iso-Nazarov reaction of **63a** followed by group migrations promoted by strain release (Scheme 15C). The

developed transformation towards **64** relies instead on the formation of trienes **67** that undergo a  $6\pi$ -electrocyclization and an eventual aromatization.



**Scheme 15.** Iso-Nazarov cycloisomerization of 2-cyclobutylidene-methyl-benzaldehyde (**63a**).

Due to the importance of five-membered rings, the iso-Nazarov reaction is more than attractive and many more striking examples will be discussed in the following sections. Notwithstanding this, it is clear that the reaction has not reached a mature state. Whereas *cis*-dienals were found to react more readily than their corresponding isomers, it is not wholly understood whether this is a strict structural requirement. This is important considering all-*trans*-dienals are synthesized more easily. The reasons to why many substrates do not engage in the process also remain unclear (for example **22** with  $\text{R}^2 = \text{Me}$  or  $\text{Ph}$ , **27d** and **33**). 2-Cyclopentenones seem to be the ultimate thermodynamic products and still in some cases these do not form (even at  $100^\circ\text{C}$  for many hours). A thorough survey of catalysts as well as a strict exploration of structural and electronic requirements is lacking. More importantly, it would be priceless to test if these reactions can be rendered enantioselective by the evaluation of chiral Lewis acids. As shown, examples of dienates suffering this type of cyclization have not been reported so far. In this context, Kuroda and co-workers found that upon treatment with triflic acid, both  $\alpha$ -trimethylsilylmethyl-dienoates and -dienoic acids (**69**) do not give rise to cyclopentenones (**70**) but to  $\alpha$ -methylene- $\gamma$ -lactones (**71**, Scheme 16A).<sup>32</sup> The reaction was proposed to proceed *via* initial protonation of the  $\gamma,\delta$ -olefin moiety followed by intramolecular attack of the carbonyl oxygen atom.



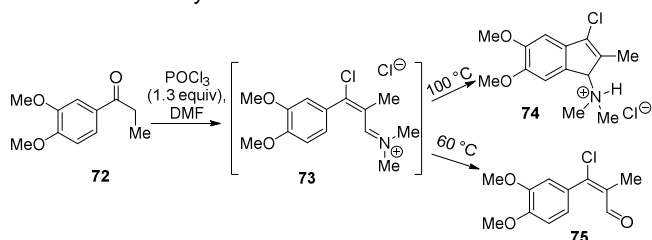
**Scheme 16.** Cyclization of dienoates and dienoic acids.

### 3. Domino or Cascade Processes Involving Iso-Nazarov Reactions

A domino reaction has been defined by Tietze as a process involving two or more bond-forming or breaking transformations which take place under the same reaction conditions, without any further addition of reagents or catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in each previous step.<sup>33</sup> Basically, the essence of this class of chemical transformation is to provide molecular complexity in an operationally simple and environmentally friendly fashion; pretty much the way Nature conceives its precious molecules.

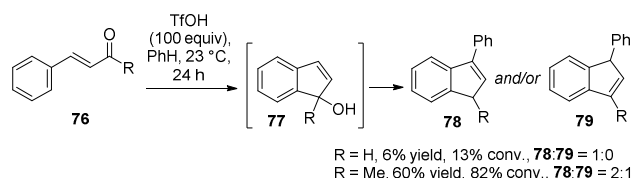
It is somewhat extraordinary to find that there have been more examples of domino reactions involving iso-Nazarov processes than pure iso-Nazarov transformations themselves. Whereas some examples have already been disclosed, many more will be depicted here and some will be specially discussed in the following sections.

As early as in 1964, Bodendorf and Mayer reported that under Vilsmeier-Haack reaction conditions at 100 °C, ketone **72** was converted to hydrochloride **74** in 75% yield (Scheme 17).<sup>34</sup> The originally expected cinnamaldehyde **75** was isolated as product as long as the reaction was kept at 60 °C. The formation of **74** can be explained by an iso-Nazarov cyclization of intermediate chloroiminium salt **73**. The cyclization can intuitively be regarded as an electrophilic aromatic substitution. More recently, Fan and co-workers explored the FeCl<sub>3</sub> catalyzed iso-Nazarov cyclization of iminium ions of type **73** prepared by condensation of sulfonamides and unsaturated aldehydes.<sup>35</sup>



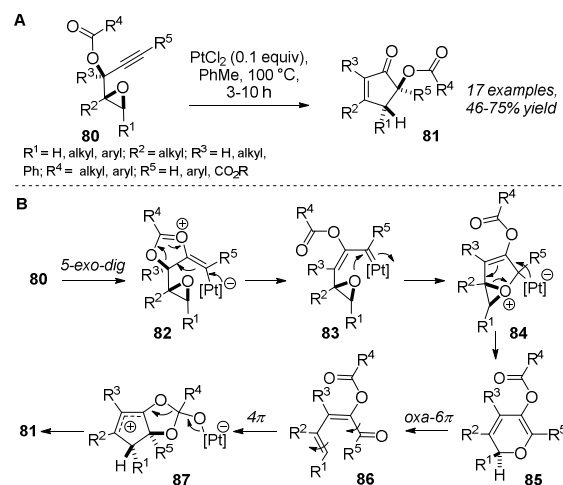
**Scheme 17.** Cyclization of a cinnamaldehyde derivative.

Shudo and co-workers reported a domino iso-Nazarov-type cyclization/arene trapping reaction also involving cinnamaldehydes and related chalcones.<sup>36</sup> As shown in Scheme 18, cinnamaldehyde and 4-phenyl-3-buten-2-one were converted to the corresponding phenyl-indenes (**78** and/or **79**) upon treatment with triflic acid in benzene.



**Scheme 18.** Domino iso-Nazarov/arene trapping sequence.

In 2006, Sarpong's group reported an impressive Pt-catalyzed rearrangement of epoxy-propargylic esters **80** to cyclopentenones **81** involving an iso-Nazarov reaction (Scheme 19A).<sup>37</sup> The mechanistic proposal is depicted in Scheme 19B and begins with a Pt-catalyzed 5-exo-dig cyclization to afford intermediate **82** which delivers metalcarbenoid **83** after rearrangement. Attack by the epoxide produces a labile intermediate (**84**) that upon ring-opening delivers 2*H*-pyran **85**. Isomerization by means of a oxa-6 $\pi$  electrocyclic reaction would then provide dienone **86** prone to an iso-Nazarov cycloisomerization upon activation by the Lewis acid thus forming products **81** stereoselectively. Intermediates **85** and **86** could be isolated in some cases which supports the devised mechanism. More recently, the developed cascade was further investigated by Nieto Faza and de Lera both experimentally and computationally.<sup>38</sup>

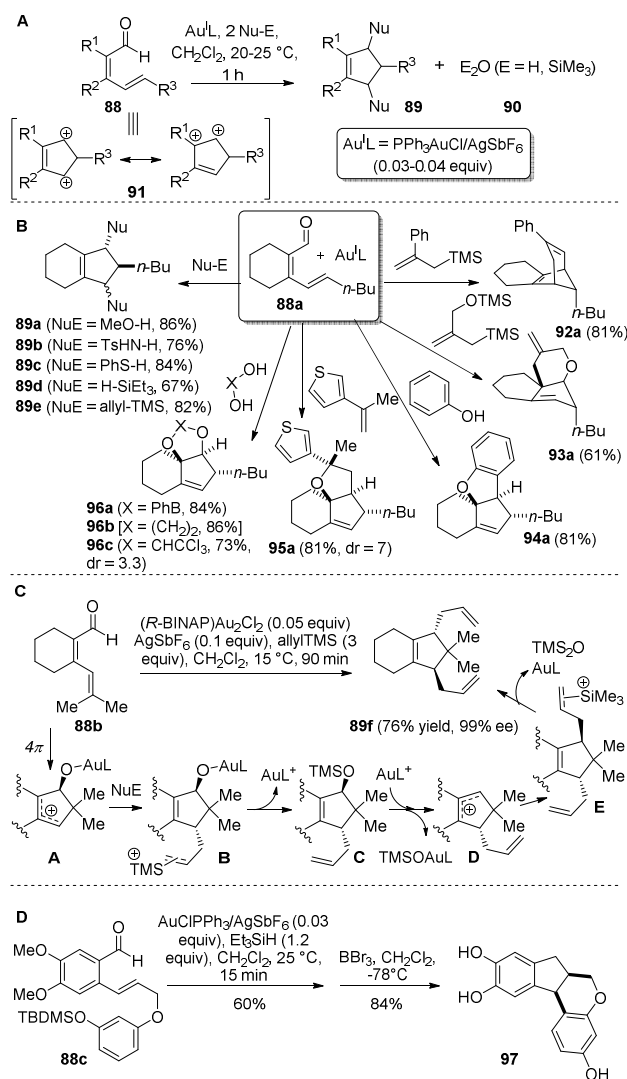


**Scheme 19.** Rearrangement of oxyranalpropargylic esters to cyclopentenones.

After their original report on the cyclization of *cis*-dienals to cyclopentenones (Scheme 12), the group of Liu then published a spectacular domino reaction initiated by an iso-Nazarov process (Scheme 20A).<sup>39,40</sup> More than 80 complex cyclopentene systems were prepared *via* this interesting transformation baptized as the deoxygenative-iso-Nazarov reaction and which relies on Au<sup>I</sup> to allow the sequential generation of two allylic carbocations that can be trapped by a plethora of different nucleophiles. As shown in Scheme 20B, for example, aldehyde **88a** can engage in different modes of cyclization such as [4+2], [4+3] and [3+2]-annulations

as well as in the construction of C-N, C-S, C-O, C-H bonds leading to diverse and complex systems. The enantioselective version of the process was also demonstrated and as shown in Scheme 20C substrate **88b** gave rise to product **89f** which was obtained with excellent ee provided a chiral ligand was used in the catalytic system. The proposed mechanism for this transformation, which can also be applied to the other modes of cyclization, begins with a Au<sup>I</sup> catalyzed iso-Nazarov reaction (Scheme 20C). Cation **A** thus formed then suffers a stereoselective attack by allylsilane to afford intermediate **B**. After metal exchange by the olefin coordinated SiMe<sub>3</sub> cation, deoxygenation follows thus releasing a brand new allylic cation **D**.<sup>41</sup> A second nucleophilic attack by allylsilane from the less-hindered face provides access to the cyclopentene product **89f** and the active catalyst *via* generation of by-product (Me<sub>3</sub>Si)<sub>2</sub>O.

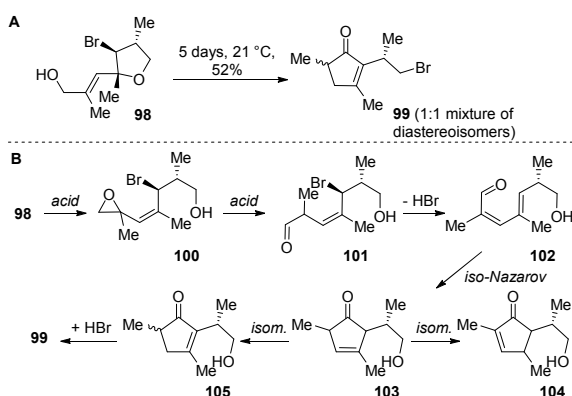
As a proof of the versatility of the methodology, some members of the brazilane family of natural products were also synthesized (Scheme 20D). For instance, brazilane (**97**) could be prepared *via* the deoxygenative iso-Nazarov reaction, one of the nucleophiles being Et<sub>3</sub>SiH and the other being already present in the conveniently functionalized starting dienal **88c**, *i.e.* the electron-rich aromatic nucleus. Final removal of protecting groups by BBr<sub>3</sub> furnishes natural product **97** in 50% overall yield.



**Scheme 20.** Domino gold-catalyzed deoxygenative iso-Nazarov reaction of 2,4-dienals.



During their studies on the preparation of the antitumor agents tedanolides, Jung and Yoo prepared tetrahydrofuran **98** as a potential intermediate in their synthesis (Scheme 21A).<sup>42</sup> To the surprise of the researchers, this intermediate proved to be unstable and after standing in the absence of solvent for five days it rearranged to cyclopentenone product **99**. The transformation was proposed to be caused by traces of acid or aluminum salts present in the sample since **98** had been prepared by DIBAL reduction of the corresponding ester. The proposed mechanism for the transformation is depicted in Scheme 21B and involves an iso-Nazarov reaction as key step. *cis*-Dienal **102** is produced *via* rearrangement of substrate **98** and loss of hydrogen bromide. After iso-Nazarov cycloisomerization and further isomerization to the stable cyclopentenone **105** (tetra-substituted alkene isomer), HBr converts the primary alcohol to the final bromide **99**. Interestingly, the transformation also took place when compound **98** was treated with Lewis acid Me<sub>2</sub>AlCl at 23 °C for 5 days, albeit a lower yield of the dehydration product **99** was obtained (30%). Moreover, when pure **98** was treated with a catalytic amount of DIBAL, cyclopentenone product **99** could be obtained in 50% yield. Stopping the reaction before completion allowed the group to find small amounts of intermediates **104** and **105**.

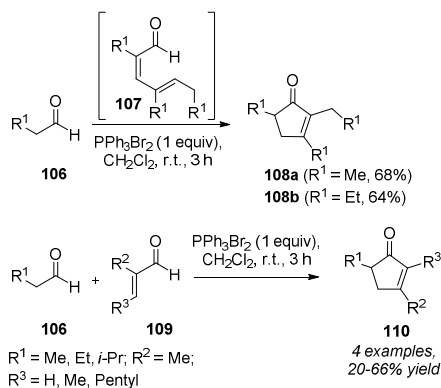


**Scheme 21.** A rearrangement involving an iso-Nazarov reaction.

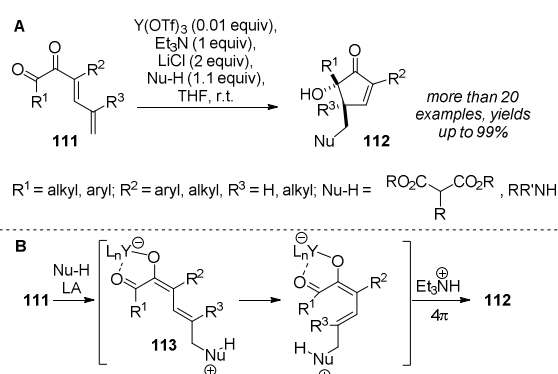
Heck and co-workers developed a domino double-aldol-condensation/iso-Nazarov cycloisomerization for the synthesis of cyclopentenones (Scheme 22).<sup>43,44</sup> Both propionaldehyde and butyraldehyde (**106** with R<sup>1</sup> = Me and Et, respectively) were found to undergo self-trimerization when treated with equimolar amounts of dibromotriphenylphosphorane reagent (PPh<sub>3</sub>Br<sub>2</sub>) to afford the corresponding cyclopentenones **108a/b** in moderate yields. As a mechanistic rationale, an initial double aldol condensation was proposed to provide the corresponding dienal intermediates **107** which under the reaction conditions would undergo an Iso-Nazarov reaction. The process was then extended to a domino cross-aldol condensation/iso-Nazarov process in order to provide structural diversity. Hence, aliphatic aldehydes (**106**) and  $\alpha,\beta$ -unsaturated aldehydes (**109**) were subjected to the same reaction conditions to provide other cyclopentenone products (**110**). In every case, the cyclopentenone products obtained were those bearing the double bonds with the highest degree of substitution arising from isomerization under the reaction conditions.

The group of Frontier developed a riveting iso-Nazarov domino process initiated by 1,6-conjugate addition that provides access to 5-hydroxycyclopentenones (Scheme 23A).<sup>45-47</sup> Upon 1,6-conjugate addition of a nucleophile (malonates, primary and secondary amines), dienyl diketones **111** furnish intermediates **113** bearing a linearly-conjugated dienone motif prone to  $4\pi$ -electrocyclization (Scheme 23B). This stereoselective process, catalyzed by minimal amounts of Lewis acid, delivers valuable  $\alpha$ -hydroxycyclopentenone products

**112** in high yields. Further studies revealed that in most cases the reaction could even work in the absence of any acid catalyst or additive.<sup>48</sup>



**Scheme 22.** Domino aldol condensation/iso-Nazarov reaction of aldehydes promoted by  $\text{PPh}_3\text{Br}_2$ .

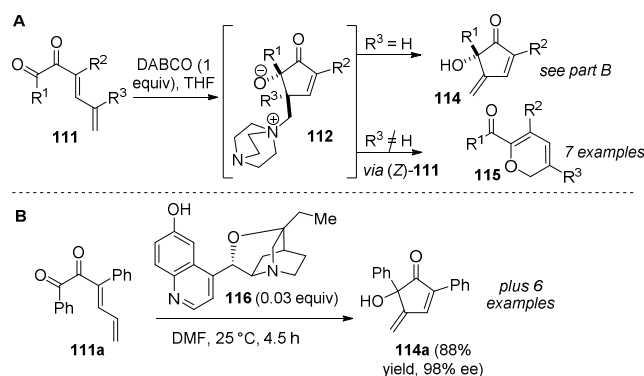


**Scheme 23.** A 1,6-conjugate addition-initiated domino iso-Nazarov reaction.

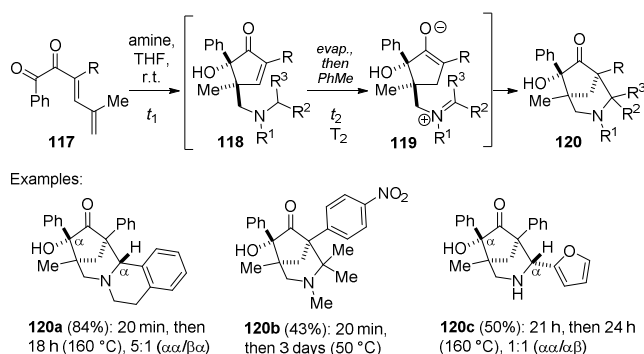
In addition, the authors found that by using a tertiary amine such as DABCO for the nucleophilic role, the process can deliver either the  $\gamma$ -methylene cyclopentenone isomers of the starting substrates (**114**) or the corresponding  $2H$ -pyran isomers (**115**, Scheme 24).<sup>48</sup> The former products are formed as a result of an elimination step in now zwitterionic intermediates **112** formed after initial conjugate addition and ensuing  $4\pi$  cyclization. When no hydrogen atom can be eliminated then retro-electrocyclization can provide  $Z$ -isomers of the starting dienyl-diketones **111** which can undergo an oxa- $6\pi$  cyclization to provide the  $2H$ -pyran products **115**. In particular, the domino conjugate addition/iso-Nazarov cyclization/elimination sequence could be rendered enantioselective by using a chiral tertiary amine (Scheme 24B).<sup>49</sup> For example, under optimized conditions using Hatakeyama's cinchona alkaloid **116**, cyclopentenone **114a** was obtained in 88% yield and with excellent enantiomeric excess.

The same group recently expanded their original domino sequence to provide access to complex  $N$ -containing bicyclic systems.<sup>50</sup> By using  $\alpha$ -methylene or  $\alpha$ -methine amines as nucleophiles, diketones **117** yield the corresponding cyclopentenone products **118** that can still engage in a thermal redox cyclization upon thermal treatment (Scheme 25). This intramolecular final annulation sequence would comprise a hydride

transfer step (**118** to **119**) followed by a Mannich ring-closure (**119** to **120**) and in this manner the whole transformation installs two cycles and up to four stereogenic centers. In some cases, the use of Lewis acid  $Y(\text{OTf})_3$  and an amine base was necessary to trigger this fascinating sequence.

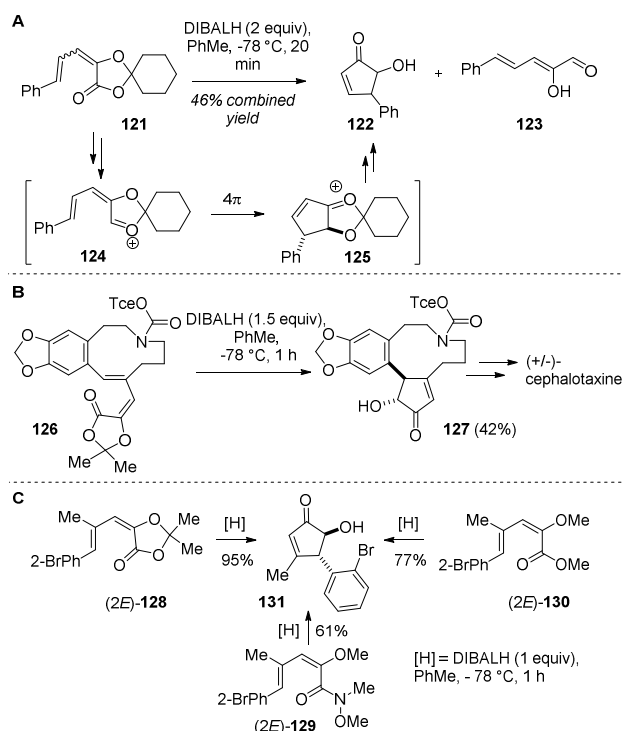


**Scheme 24.** Alternative 1,6-conjugate addition-initiated domino processes.



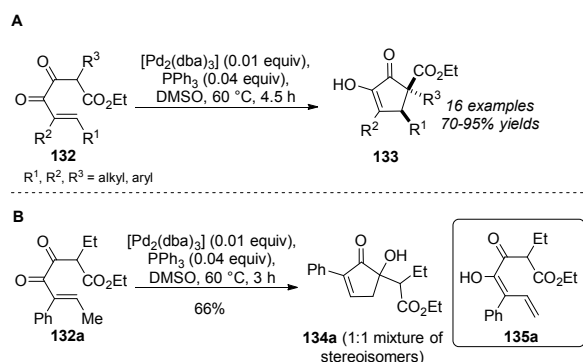
**Scheme 25.** Domino 1,6-conjugate addition/iso-Nazarov/internal redox cyclization sequence.

In 1984, during their studies on the chemistry of 5-ylidene-1,3-dioxolan-4-ones, the group of Ramage obtained the cyclopentenone product **122** and the expected aldehyde **123** upon DIBALH reduction of substrate **121** (Scheme 26A).<sup>51</sup> Whereas no interpretation was given at the time, the formation of **122** can be understood as a result of a domino reduction/iso-Nazarov reaction of an oxocarbenium intermediate derived from the reduction of (*E*)-**121** (**124**).<sup>52</sup> Many years later, this process was studied by Li and co-workers who elegantly applied it to the synthesis of notable alkaloid cephalotaxine as well as many interesting 5-hydroxycyclopentenones (Scheme 26B).<sup>53</sup> Not only dioxolanones were prone to the developed cascade but also other substrates such as Weinreb amides (e.g. **129**) and  $\alpha$ -alkoxydienoates (e.g. **130**, Scheme 26C).<sup>54</sup> Notwithstanding this, in all cases best results were obtained starting from dioxolanones such as **128**, supporting the intermediacy of cationic species of type **124** in a facilitated iso-Nazarov cyclization. The stereochemistry of the substrates was crucial for the success of the devised process, named by the research group as the reductive oxy-Nazarov cyclization, since the use of (*2Z*)-**128** and (*2Z*)-**129** only delivered the corresponding dienal upon reduction with DIBALH and the use of ester (*2Z*)-**130** led to the formation of the corresponding dienyl alcohol.



**Scheme 26.** Domino reduction/iso-Nazarov process. Tce = 2,2,2-trichloroethyl.

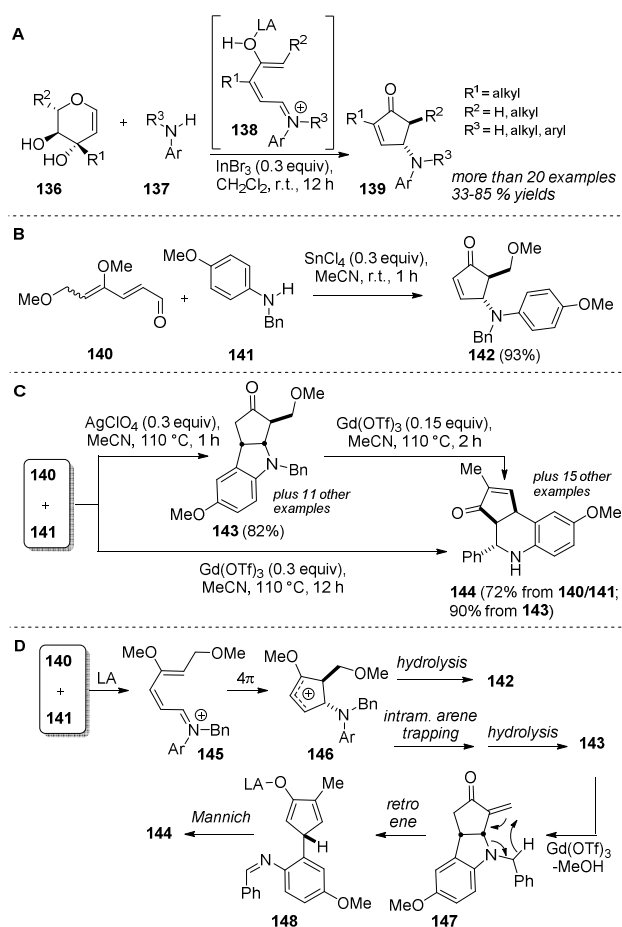
A neutral Nazarov reaction catalyzed by Pd(0) was recently reported by Tius and co-workers.<sup>55</sup> Treatment of diketones **132** with small amounts of the Pd<sub>2</sub>(dba)<sub>3</sub>/PPh<sub>3</sub> catalytic system affords cyclopentenones **133** in good yields and with complete diastereoselectivity (Scheme 27A). Substrate **132a**, in particular, did not participate in the developed process but underwent an iso-Nazarov reaction towards cyclopentenone **134a** presumably *via* the intermediacy of tautomeric dienol **135a** (Scheme 27B). Since another substrate with both R<sup>1</sup> and R<sup>2</sup> as methyl groups underwent the “expected” Nazarov mode of cyclization, the authors considered the phenyl group to be responsible for the unexpected outcome of the reaction of **132a**. The reaction can as well be viewed as an intramolecular vinylogous aldol reaction on intermediate **135a**.



**Scheme 27.** Pd-catalyzed iso-Nazarov reaction of diketone **132a**.

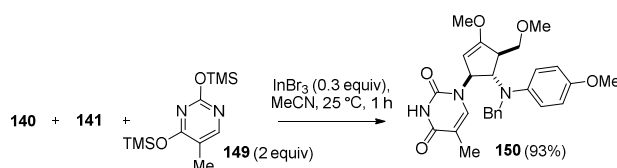
The group of Zhang recently reported the synthesis of 4-aminocyclopentenones from glycals and aryl- or heteroaryl amines (Scheme 28A).<sup>56-57</sup> These particular cyclopentenone scaffolds are not only attractive due

to their antiviral properties but also because they serve as building blocks for the construction of 4-aminocarbocyclic nucleosides as analogues of some antiviral drugs. The research group proposed 1-aminopentadienyl cation **138** as key intermediate that would deliver products **139** after  $4\pi$ -conrotatory ring closure.<sup>58</sup> Based on these and other observations, the group of Liu later introduced the imino-iso-Nazarov reaction (Scheme 28B).<sup>59</sup> Lewis acid  $\text{SnCl}_4$  (30 mol%) promotes the condensation of dienal **140** and aniline **141** to provide, after iso-Nazarov cyclization, 4-amino-cyclopentenone **142**. Product **142**, which is obtained in excellent yield, is found as a single diastereoisomer although a mixture of *E* and *Z* isomers of dienal **140** is used in the reaction, suggesting the sole intermediacy of an *out, out*-U-shaped cyclopentadienyl cation of type **138** due to isomerization. Interestingly, by careful control of the reaction conditions the process can be tamed and further transformations result in novel domino processes (Scheme 28C). By running the reaction at higher temperatures and using silver perchlorate as catalyst, **140** and **141** engage in an interrupted imino-iso-Nazarov reaction to provide cyclopentaindole products of type **143** diastereoselectively. Surprisingly, in the presence of lanthanide metal catalysts such as  $\text{Gd}(\text{OTf})_3$ , tetrahydroquinoline-fused cyclopentenones are obtained instead (e.g. **144**). As shown in Scheme 28D, after condensation and  $4\pi$ -electrocyclization, diastereoselective intramolecular arene trapping on intermediate **146** delivers product **143** after hydrolysis. The formation of **144** from **143** (Scheme 28C) along with deuterium labeling studies prompted the authors to propose an elimination/retro-ene/stereoselective Mannich sequence as mechanistic rationale for the formation of the tetrahydroquinoline products of type **144**.

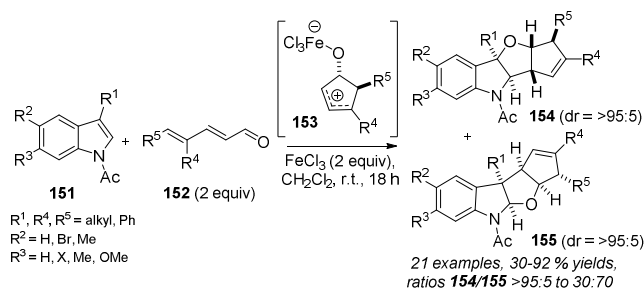


**Scheme 28.** Imino iso-Nazarov domino processes.

Shortly after their report, and encouraged by the importance of carbocyclic nucleosides, the group of Liu then became interested in intercepting the oxyallyl cation **146** with an external amine nucleophile. These studies gave birth to the intermolecular interrupted imino-iso-Nazarov reaction (Scheme 29).<sup>60</sup> For example, InBr<sub>3</sub> catalyzed coupling of **140** and **141**, in the presence of silylated nucleobase **149**, led to the formation of highly functionalized cyclic enol ether **150**. The methodology was found to be versatile allowing the preparation of several derivatives with excellent yields. In all cases, the carbocyclic nucleoside analogues were obtained as single diastereoisomers arising from selective nucleophilic attack by the silylated nucleobases on the opposite side of that occupied by the amino group at C-4.

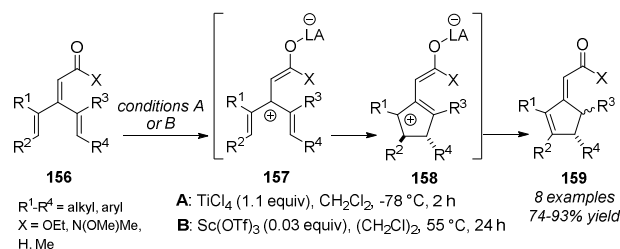
**Scheme 29.** Intermolecular interrupted imino iso-Nazarov domino process.

Another example of an interrupted iso-Nazarov reaction was recently provided by the groups of Moreau and Vincent.<sup>61</sup> Cyclic oxyallyl cations (**153**) obtained *via* iso-Nazarov cyclization of the corresponding dienals (**152**) can be intercepted by different *N*-acetyl indoles (**151**) in a dearomative [3 + 2] cycloaddition that provides indoline-based complex architectures with high diastereoselectivities (**154** and **155**, Scheme 30). The process was found to be promoted by inexpensive and environmentally benign ferric chloride and in most cases major products were those arising from a reversal of the classical polarity of the C2 and C3-positions on the indoles (**154**) as a consequence of Lewis acid activation of *N*-Ac indoles. Curiously enough, unbranched dienals **152** (R<sup>4</sup> = H) did not participate in the reaction with substrates **151**.

**Scheme 30.** Intermolecular interrupted iso-Nazarov domino process.**4. Vinylogous Iso-Nazarov Reactions**

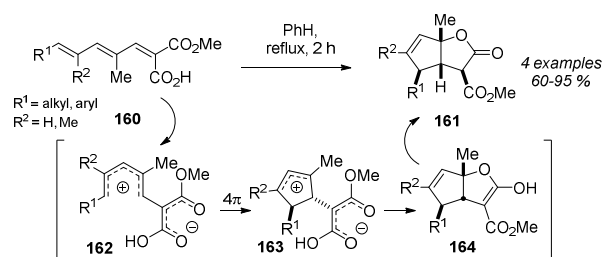
The group of West recently introduced the vinylogous Nazarov reaction (Scheme 31).<sup>62</sup> The acid activation of cross-conjugated trienes of type **156** leads to the formation of the corresponding cyclic isomers **159** *via* 4 $\pi$ -electrocyclization at the end of the polyene-carbonyl chain. In an analogous fashion, cycloisomerization processes of linearly-conjugated triene-carbonyl compounds have been as well developed

by the groups of Valla, Trauner and ours. As shall be seen below, all studies have in common the fact that the  $4\pi e^-$  cyclization takes place at the end of the polyene chain and this is consistent with computational studies on 1-hydroxyheptatrienyl cations carried out by de Lera's group.<sup>63</sup>



**Scheme 31.** The vinylogous Nazarov reaction.

Valla and Giraud were the first to report the spectacular cycloisomerization of all-*E* 2,4,6-trienoic acids **160** to  $\gamma$ -lactones **161** under neutral conditions (Scheme 32).<sup>64</sup> At the time, the authors proposed zwitterion **162** as intermediate, which undergoes cyclization to cyclopentenyl cation **163** via a U-form conformation. Trapping of this cation by the carboxylate moiety then furnishes the bicyclic products **161** which were described as single diastereoisomers. Almost a decade after their original study the authors further developed the reaction expanding its synthetic scope.<sup>65-67</sup>

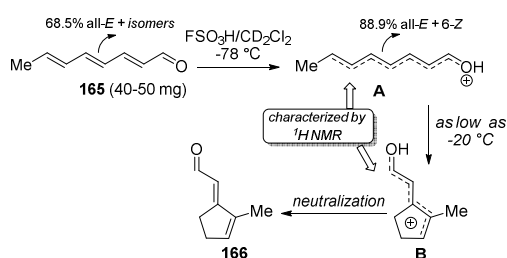


**Scheme 32.** Formation of  $\gamma$ -lactones via cycloisomerization of trienoic acids.

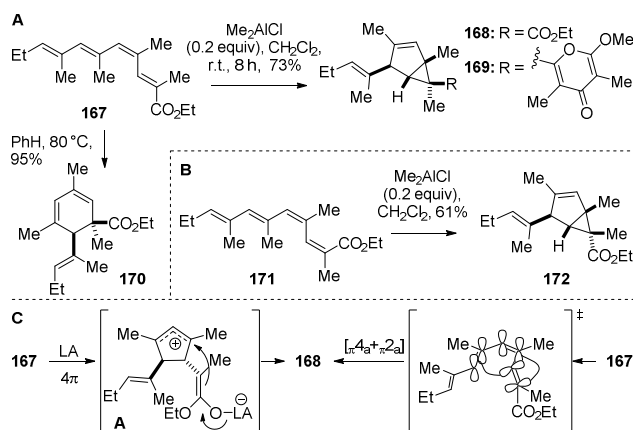
Soon after Valla's report on the vinylogous iso-Nazarov transformation of trienoic acids **160**, Elia and co-workers reported NMR studies on the isomerization of 2,4,6-octatrienal (**165**) in  $\text{FSO}_3\text{H}$ , which can be regarded as the first example of a non-interrupted vinylogous iso-Nazarov process (Scheme 33).<sup>23</sup> Protonated 2,4,6-octatrienal (**A**) undergoes quantitative cycloisomerization to cation **B** at temperatures as low as  $-20^\circ\text{C}$ . Cation **B** formed as a single stereoisomer according to NOE experiments, delivered dienal **166** upon neutralization. Although a pure sample of **166** could not be obtained (yield not reported either), its identity could be confirmed by comparison of  $^1\text{H}$  NMR data with reported literature data. A dication intermediate was also proposed as intermediate towards **166**.

Another dazzling cycloisomerization was later disclosed by Miller and Trauner.<sup>68</sup> Lewis acid  $\text{Me}_2\text{AlCl}$  was found to promote a novel Lewis acid-catalyzed process involving the isomerization of trienoates to bicyclo[3.1.0]hex-2-enes, a process we later categorized as an interrupted vinylogous iso-Nazarov reaction.<sup>69</sup> As shown in Scheme 34A for the synthesis of *rac*-photodeoxytridachione, polyene precursor **167** delivers

product **168** as a single stereoisomer. Further elaboration, *i.e.* the installment of the pyrone moiety, eventually provided natural product **169**. In stark contrast to Valla's iso-Nazarov process (Scheme 32), under neutral conditions, *i.e.* in the absence of  $\text{Me}_2\text{AlCl}$ , substrate **167** was found to undergo a thermal disrotatory  $6\pi$  electrocyclicization and thus cyclohexenes such as **170** were obtained. The newly discovered process which involves the formation of a strained bicyclic system with four contiguous stereocenters was found to be stereospecific and, for instance, diastereoisomeric **171** provided epimeric **172** as product (Scheme 34B). Shortly after, the reaction was extended to the synthesis of natural (-)-crispatene and biosynthetic implications on these polyketide-derived molluscan natural products were considered.<sup>70,71</sup> The authors provided two mechanistic scenarios for their fascinating transformation (Scheme 34C). The stepwise mechanism involves initial regioselective  $4\pi$ -electrocyclic ring-closure to deliver cation **A** that is subsequently trapped in a stereoselective fashion. In this case, rotation about C2-C3 bond is supposed to be slow enough so that the reaction is stereospecific as exemplified for the outcome of using stereoisomeric precursor **171**. The concerted version, on the other hand, is based on the dissection of the polyene chain into tethered diene and dienophile moieties that engage in an intramolecular  $[\pi_4s+\pi_2a]$  cycloaddition. Computational studies on this reaction by de Lera *et al.* suggest the transformation does not strictly follow neither a concerted nor a stepwise reaction mechanism.<sup>72</sup> No intermediate is found and the reaction would proceed through initial five-membered ring formation followed by a barrierless creation of the cyclopropane system.



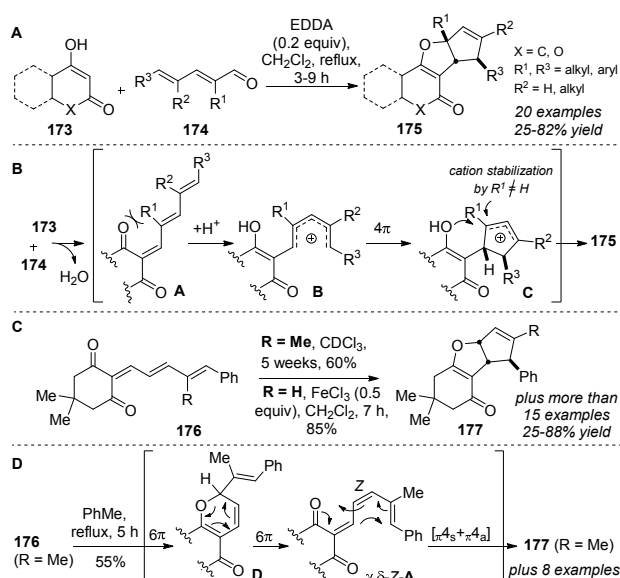
**Scheme 33.** Regio- and stereoselective cyclization of 2,4,6-octatrienal.



**Scheme 34.** Lewis acid-catalyzed isomerization of trienoates to bicyclo[3.1.0]hex-2-enes.

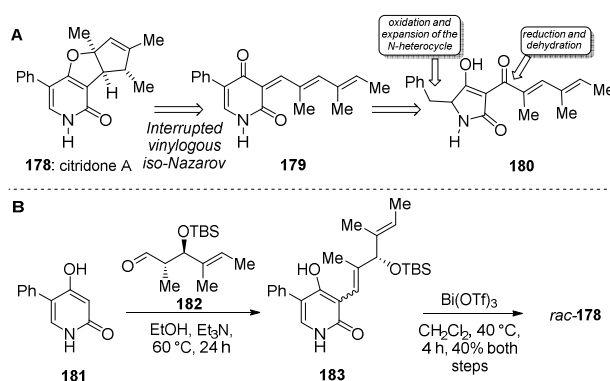


We came across an iso-Nazarov process analogous to the one portrayed above during our studies on the Knoevenagel condensation between dicarbonyl compounds and unsaturated aldehydes.<sup>73,74</sup> Different cyclic 1,3-dicarbonyl compounds (**173**) and dienals (**174**) were found to engage in a cascade process that provides cyclopenta[*b*]furan derivatives **175** as products (Scheme 35A). Diverse experimental observations led us to propose a domino Knoevenagel/vinylogous-iso-Nazarov pathway to account for the stereoselective formation of products **175** (Scheme 35B). Thus, after condensation and mild-acid activation, conrotatory  $4\pi e^-$  ring closure at the end of the polyene chain provides cyclopentenyl cation **C** ready for intramolecular capture. In contrast with Trauner's process, in this case, cyclopentenyl cation **C** is intramolecularly trapped by enol oxygen atom leading to heterocycle construction instead of carbon-carbon bond formation. Substituents on the polyene chain played a crucial role and mostly  $\alpha$ -substituted dienals only participated in the reaction. This structural feature was not only supportive of a requirement for instability of the conjugated polyene chain but also seemed to play a cation-stabilizing role. Indeed, the use of  $\alpha$ -unsubstituted dienals on these condensations delivered classical Knoevenagel products isolated as colorful crystals (e.g. **176**, Scheme 35C). Notwithstanding this, the system could have such a fine tuning that for instance branching at the  $\epsilon$ -position was enough perturbation to provoke slow cycloisomerization in, for instance, deuterated chloroform (**176**, R = Me). Whereas this rearrangement was attributed to acid traces present within the deuterated solvent, the cationic Nazarov pathway was later cleanly supported by the finding that stable trienediketones such as **176** (R = H) rearranged to their polycyclic isomers **177** upon Lewis or Brønsted acid activation (Scheme 35C).<sup>69</sup> Since we later found that the process could be rendered possible also under neutral conditions (refluxing toluene) we departed from the classical cationic point of view and a pericyclic cascade was elaborated and supported computationally.<sup>75</sup> This proposal involves an initial isomerization *via* well-known oxa- $6\pi$  processes to deliver a reactive intermediate ( $\gamma,\delta$ -Z-**A**) that undergoes an intramolecular  $[\pi_4s+\pi_4a]$  cycloaddition (Scheme 35D). Indeed, a stable 2*H*-pyran substrate similar to proposed intermediate **D** was found to undergo cycloisomerization towards its cyclopenta[*b*]furan isomer upon both thermal and Lewis-acid treatment.



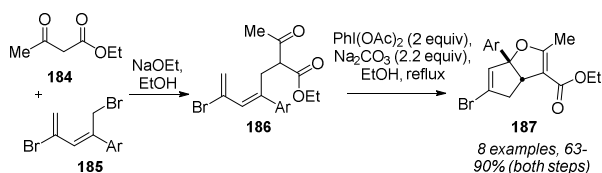
**Scheme 35.** Interrupted vinylogous iso-Nazarov process for the synthesis of cyclopenta[*b*]furan derivatives.

We were somehow pretty sure that, based on the ease with which these polyenes undergo neat and precise polycyclizations, this cascade had to be traced in Nature. In this context, we proposed that citridone A (**178**), a furopyridone belonging to a new family of natural products recently presented by Nobel Laureate S. Ōmura and co-workers,<sup>76-78</sup> could be naturally produced *via* an interrupted vinylogous iso-Nazarov cascade (Scheme 36A). Previous biosynthetic studies on tetramic acid derived natural products suggest that a suitable polyunsaturated precursor such as **179** could be produced from a less-elaborated acyl-tetramic intermediate **180** derived, at the same time, from amino acid phenylalanine and a proper polyketide derivative. The closest solution to this puzzle was provided by Zografos and Fotiadou who carried out the Knoevenagel reaction between phenylpyridone **181** and chiral aldehyde **182** (Scheme 36B).<sup>79</sup> This condensation led to an unwieldy mixture of products **183** that upon treatment with Lewis acid bismuth triflate provided *rac*-**178** presumably *via* an intermediate of type **B** (Scheme 35B).



**Scheme 36.** Possible biosynthetic pathway for alkaloid **178** involving an interrupted vinylogous iso-Nazarov process and synthesis of **178** by Zografos and Fotiadou.

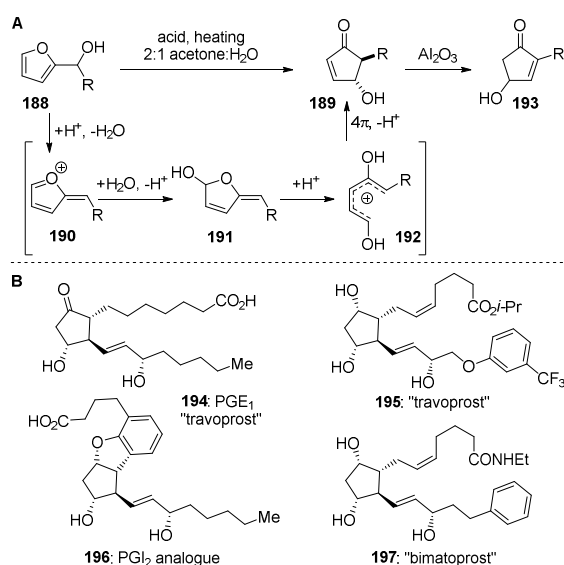
More recently, Lin *et al.* devised another domino reaction involving a vinylogous iso-Nazarov process that also provides cyclopenta[*b*]furans as products (Scheme 37).<sup>80</sup> Alkylation of ethyl acetoacetate with different dienylyl bromides (**185**) provides intermediates **186** that upon dehydrogenation with diacetoxyiodobenzene deliver cyclopenta[*b*]furan derivatives **187** as products. According to the authors, at ambient temperature the conjugated trienedicarbonyl intermediates can be intercepted.



**Scheme 37.** A domino oxidation-vinylogous iso-Nazarov process for the synthesis of cyclopenta[*b*]furan derivatives.

## 5. The Piancatelli Reaction

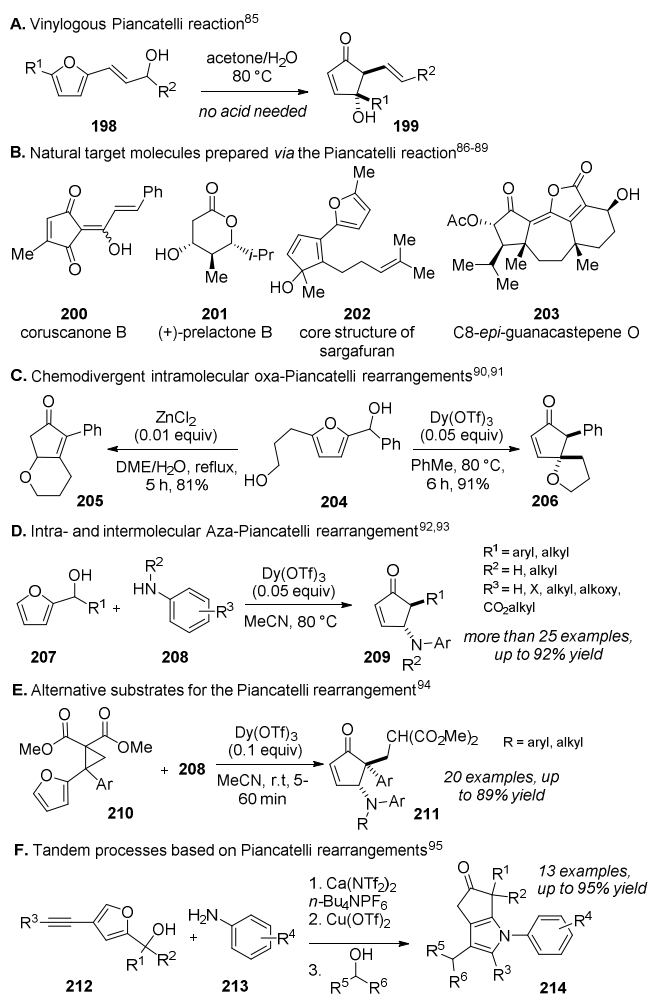
As the preceding pages show, the number of domino or cascade reactions involving iso-Nazarov steps is large and growing. Notwithstanding this, there is one particular domino iso-Nazarov reaction that has received considerable attention and that is actually a named reaction, *i.e.* the Piancatelli rearrangement. In 1976, Piancatelli and co-workers reported the acid-catalyzed isomerization of 2-furylcarbinols (**188**) to 4-hydroxycyclopentenones (**189**, Scheme 38A).<sup>81</sup> According to the research group, a possible mechanism to explain this transformation begins with the protonation of starting alcohol **188** followed by loss of water. Oxocarbenium ion **190** thus formed is then trapped by water and this leads to intermediate **191** which gives rise to *out,out*-cation **192** after acid-promoted ring-opening. Hydroxy-pentadienyl cation **192** would finally undergo  $4\pi$ -conrotatory ring closure towards product **189**. It should be noted that although other mechanisms have been as well proposed, computational studies support this iso-Nazarov mechanistic scenario.<sup>16a</sup> In addition, Piancatelli and co-workers also observed further rearrangement of products **189** to cyclopentenones **193** during chromatography purification using neutral or basic alumina (Scheme 38A).<sup>82</sup> Much of the interest in the Piancatelli reaction has lain on the fact that it is a versatile platform for prostaglandin synthesis.<sup>83</sup> Many members of this class of fatty acid-derived natural bioactive molecules have been prepared *via* this methodology including analogues commercialized as drugs (Scheme 38B). It is not the purpose of this chapter to cover all the work done on this transformation but to only present its most recent advances. The interested reader should consult some previous reviews available on the subject.<sup>84</sup>



**Scheme 38.** The Piancatelli rearrangement and some natural prostaglandins or derivatives prepared using this reaction.

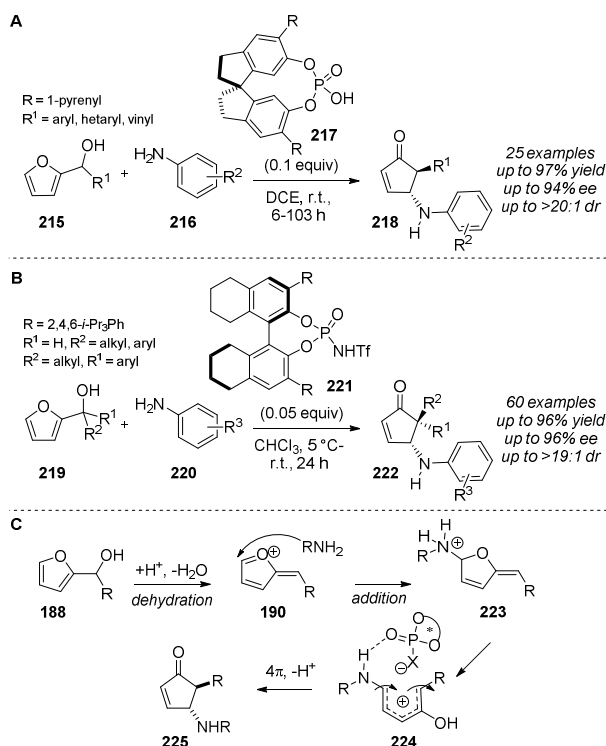
Several variants of the reaction including domino and tandem processes based on the Piancatelli reaction have materialized over the past decades (Scheme 39).<sup>85-95</sup> These include, for example, the application to natural product synthesis other than prostaglandins and the development of both inter- and intramolecular

interrupted processes based on the trapping of key intermediate **190** by C-, N-, and O-nucleophiles other than water.



**Scheme 39.** Some developments on the Piancatelli rearrangement since its discovery.

Most recent breakthrough contributions to the field came to light in 2016 when the groups of Sun<sup>96</sup> and Rueping<sup>97</sup> almost simultaneously reported the asymmetric variants of the aza-Piancatelli rearrangement (Schemes 40A and 40B, respectively). Both strategies rely on the use of chiral Brønsted acids **217** and **221** as catalysts to provide priceless enantioenriched 4-aminocyclopentenones (**218/222**). As shown in Scheme 40C, in the aza-Piancatelli reaction, once key cation intermediate **190** is formed after dehydration of starting 2-furylcarbinol **188**, intermolecular attack by an amine nucleophile provides hemiaminal **223**. This species evolves into 1-amino-pentadienyl cation **224** that after 4 $\pi$ -electrocyclic ring closure affords 4-aminocyclopentenone product **225**. By using these chiral acids, hydrogen bonding on intermediates **224** would allow for counter ion/asymmetric induction to operate.<sup>98</sup>



**Scheme 40.** Catalytic asymmetric aza-Piancatelli rearrangements.

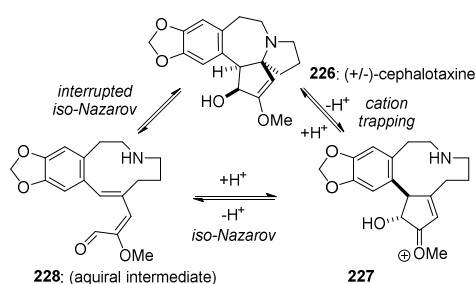
## 6. The Iso-Nazarov Reaction in Nature

Since both polyunsaturated carbonyl compounds and cyclopentenones are common structural motifs amid natural substances, it would not be surprising to find the iso-Nazarov process operates in Nature. Over the years, many pericyclic reactions such as cycloadditions have indeed been found to be part of biosynthetic pathways.<sup>99</sup> Apart from citridone A (**178**, Scheme 36), for which a vinylogous iso-Nazarov reaction can be proposed to account for its biomimetic synthesis, some more examples can be advanced.

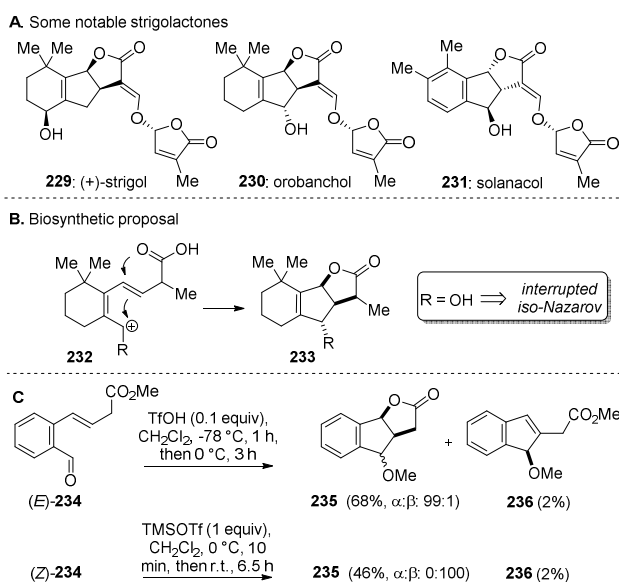
Cephalotaxine ester derivatives are an important class of alkaloids that have aroused considerable attention due to their potent antileukemic activity, one of these, harringtonine, being approved by the FDA in 2012. An intriguing issue with parent natural product cephalotaxine (**226**) is the lability of its enantiomeric purity. Heating its hydrochloric salt or formation of a quaternary ammonium salt have been found to proceed with racemization. As shown in Scheme 41, an iso-Nazarov process was invoked by Liang as well as by other authors to account for this behavior.<sup>100</sup>

Strigolactones are carotenoid-derived plant hormones that play several roles in plant life and thus have triggered considerable research studies (Scheme 42A).<sup>101</sup> Whereas a lot of knowledge as regards biological intermediates and enzymes involved in their biosynthesis has been gathered, the exact mechanism for their formation remains unclear. The group of Aponick recently reported a biosynthetic proposal based on a cation-initiated cascade that seems to match all the biosynthetic studies performed to date.<sup>102</sup> As shown in

Scheme 42B, a 4 $\pi$ -electrocyclization process on stabilized cation **232** followed by intramolecular trapping by the carboxylic acid moiety would provide the parent tricyclic core present in these natural cyclopentafuranones. In order to test their hypothesis, the group prepared diastereomeric esters **234** and submitted them to acid treatment. Indeed, *trans*-olefin (*E*)-**234** underwent cyclization under TfOH catalysis to deliver lactone **235** almost free from diastereomeric product. A small amount of side-product **236** arising from a non-interrupted cyclization was also isolated. Diastereomeric precursor (*Z*)-**234** required harsher conditions, *i. e.* prolonged reaction time and stoichiometric acid. In this case, best selectivity was achieved using trimethylsilyl triflate as promoter. Interestingly, no interconversion between products **238** was observed upon acid treatment and the compounds were produced as methyl ethers. It should be noted that the use of a suitable **234** analogue precursor in combination with Liu's gold-catalyzed deoxygenative iso-Nazarov reaction using a silane as external nucleophile (see Scheme 20C) could provide a straightforward entry to strigol's tricyclic core.



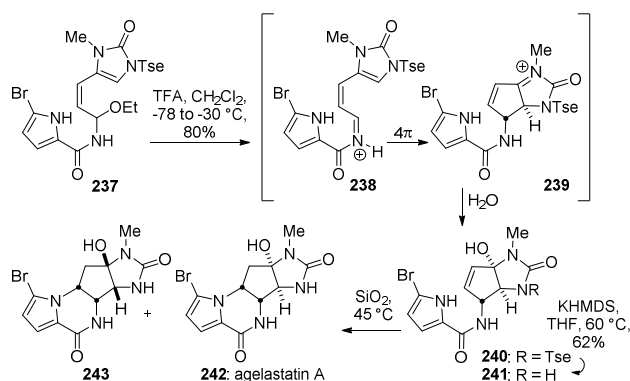
**Scheme 41.** Iso-Nazarov process proposed to account for the optical lability of cephalotaxine (**226**).



**Scheme 42.** Interrupted iso-Nazarov reaction for the synthesis of strigolactone analogues.

Reyes and Romo also reported a bioinspired approach featuring an iso-Nazarov reaction (Scheme 43).<sup>103</sup> En route towards anticancer natural product agelastatin A (**242**), Brønsted acid treatment of

intermediate **237** promotes the formation of iminium key species **238** that undergoes conrotatory cyclization towards cyclopentene **239** which is finally trapped by water. Deprotection of the cyclic urea in **240** delivered a flexible intermediate **241** that on silica gel and under mild heating already underwent formation of the last ring. Isomer **243** was also found in the reaction mixture and a hypothesis for its formation was elaborated.



**Scheme 43.** Bioinspired total synthesis of agelastatin A based on an interrupted imino-iso-Nazarov reaction. Tse = *p*-toluenesulfonylethyl.

## 7. Conclusions and Future Perspectives

The history of the Iso-Nazarov reaction has been presented for the first time. This variant of the remarkable Nazarov cyclization employs linearly-conjugated dienones and dienals to provide valuable 2- and 3-cyclopentenones as well as other five membered-ring systems with ease. Whereas it can still be considered an immature transformation, the number of processes in which it is involved is overwhelming and it has not only been applied to the synthesis of various natural products but also has provided a straightforward access to densely decorated polycyclic frameworks when involved in domino cascades. We expect future studies on this process will result in novel applications and simple enantioselective protocols will emerge that will drive the reaction through the path of fame.

### Conflicts of interest

There are no conflicts to declare.

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**Keywords:** cycloisomerization reactions • cyclopentenones • dienals • Nazarov • pentadienyl cation

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