



HAL
open science

Recent Developments in Asymmetric Nazarov Reactions

Hélène Pellissier

► **To cite this version:**

Hélène Pellissier. Recent Developments in Asymmetric Nazarov Reactions. Current Organic Chemistry, In press, 10.2174/0113852728296619240321060646 . hal-04560123

HAL Id: hal-04560123

<https://hal.science/hal-04560123v1>

Submitted on 26 Apr 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Recent Developments in Asymmetric Nazarov Reactions

Hélène Pellissier*

Aix Marseille Univ, CNRS, Centrale Marseille, iSm2, Marseille, France

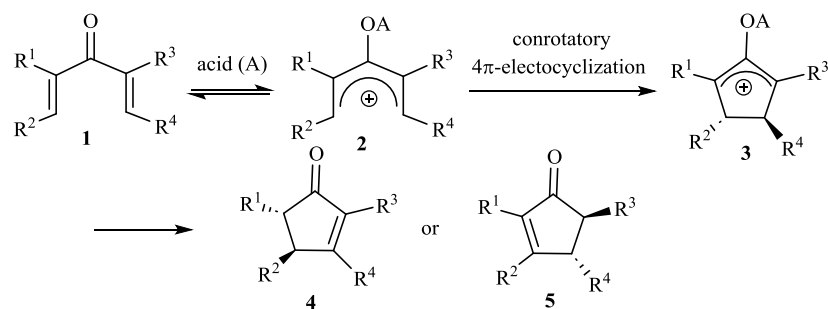
Fax: +33 4 13 94 56 41; e-mail: h.pellissier@univ-amu.fr

Abstract: The Nazarov reaction involves the cyclization of divinyl ketones into cyclopentenones under the influence of strong acids. The prevalence of five-membered carbocycles in a multitude of natural and bioactive products has triggered an intense development of efficient methods for their construction. In particular, asymmetric versions of the Nazarov reaction are achieved by using either a chiral auxiliary or a chiral catalyst which can be an organocatalyst, a metal catalyst, or a multicatalytic system. This review aims to update the field of asymmetric Nazarov reactions published since 2017. It is divided into four sections, dealing successively with Nazarov reactions of chiral auxiliaries; organocatalytic enantioselective Nazarov reactions; metal/boron-catalyzed enantioselective Nazarov reactions; and multicatalytic enantioselective Nazarov reactions. Each section of the review is subdivided into simple asymmetric Nazarov reactions, and Nazarov-based domino/tandem reactions which have allowed numerous more complex functionalized chiral molecules to be synthesized in one-pot procedures.

Keywords: Asymmetric Nazarov reactions; asymmetric cyclizations; chiral auxiliaries; chiral catalysts; asymmetric catalysis; chirality; domino reactions

1. INTRODUCTION

The prevalence of five-membered carbocycles in a multitude of natural and bioactive products has triggered an intense development of efficient methods for their construction [1]. Among them, the original Nazarov reaction reported in 1941 deals with the cyclization of divinyl ketones into cyclopentenones performed in the presence of strong acids [2]. In the 1960s, Woodward and Shoppee established this reaction as a pericyclic electrocyclization reaction [3]. As presented in Scheme 1, the process involves the treatment of a cross-conjugated dienone **1** with a Lewis/Bronsted acid, resulting in the reversible formation of pentadienyl cation **2**. The latter species then undergoes a 4π electron conrotatory cyclization to give an allylic cation **3** bearing the two substituents R^2 and R^4 on opposite sides due to conrotation. Then, allylic cation **3** is submitted to a proton loss, leading to either cyclopentenones **4** or **5**, or to a mixture of both. Thermodynamically more stable products **4** or **5** exhibited a *trans* stereochemistry between respectively R^1 and R^2 in product **4** or between R^3 and R^4 in product **5**. The *trans* relationship between substituents R^2 and R^4 in product **3** can be preserved in the final product if loss of an exocyclic proton from R^1 or R^3 concludes the reaction. In the Nazarov reaction, super-stoichiometric strong acids must be circumvented in order to prevent side reactions, such as Wagner/Meerwein rearrangements. When the process is carried out without any stereochemical control, it proceeds invariantly according to either clockwise or counterclockwise conrotation, which results in the formation of a racemic product. In contrast, a chiral product can be obtained by controlling the conrotation of pentadienyl cation **2** through asymmetric induction arising from the use of a chiral substrate/auxiliary or a chiral catalyst that can be an organocatalyst or a chiral metal complex.



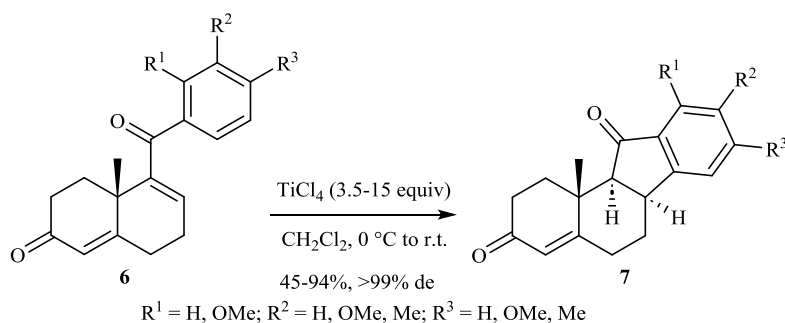
Scheme 1. Conrotatory Nazarov reaction.

This review aims to update the field of asymmetric Nazarov reactions since the beginning of 2017, since the most recent review in this area was published this year by Zlotin and Vinogradov, covering general (racemic and asymmetric) Nazarov reactions up to 2016 [4]. Prior to that, several reviews have been published [5]. It must be noted that in 2018 the special field of metal-catalysed approaches for the synthesis of cyclopenta[b]indoles was reviewed by Ramasastry *et al.* but it included only one reference ≥ 2017 of asymmetric Nazarov reaction [6]. Moreover in 2020, Shirinian and Yadykov published a report focusing on the recent advances in the interrupted Nazarov reaction that contained no reference to asymmetric work ≥ 2017 [7]. In 2021, the special field of transition-metal-catalyzed Nazarov cyclization of alkynes via metal carbenes was reviewed by Shen and Gao albeit with no reference ≥ 2017 dealing with asymmetric Nazarov reaction [8]. In the same year, a report entitled “Advances in organocatalytic asymmetric reactions of vinylindoles: powerful access to enantioenriched indole derivatives” was published by Shi, Liu and Zhang, including only three references ≥ 2017 about Nazarov cyclizations [9]. The present review is divided into four sections dealing successively with Nazarov reactions of chiral auxiliaries; organocatalytic enantioselective Nazarov reactions; metal/boron-catalyzed enantioselective Nazarov reactions; and multicatalytic enantioselective Nazarov reactions. Each part is subdivided into simple asymmetric Nazarov reactions and Nazarov-based domino/tandem reactions.

2. NAZAROV REACTIONS OF CHIRAL AUXILIARIES

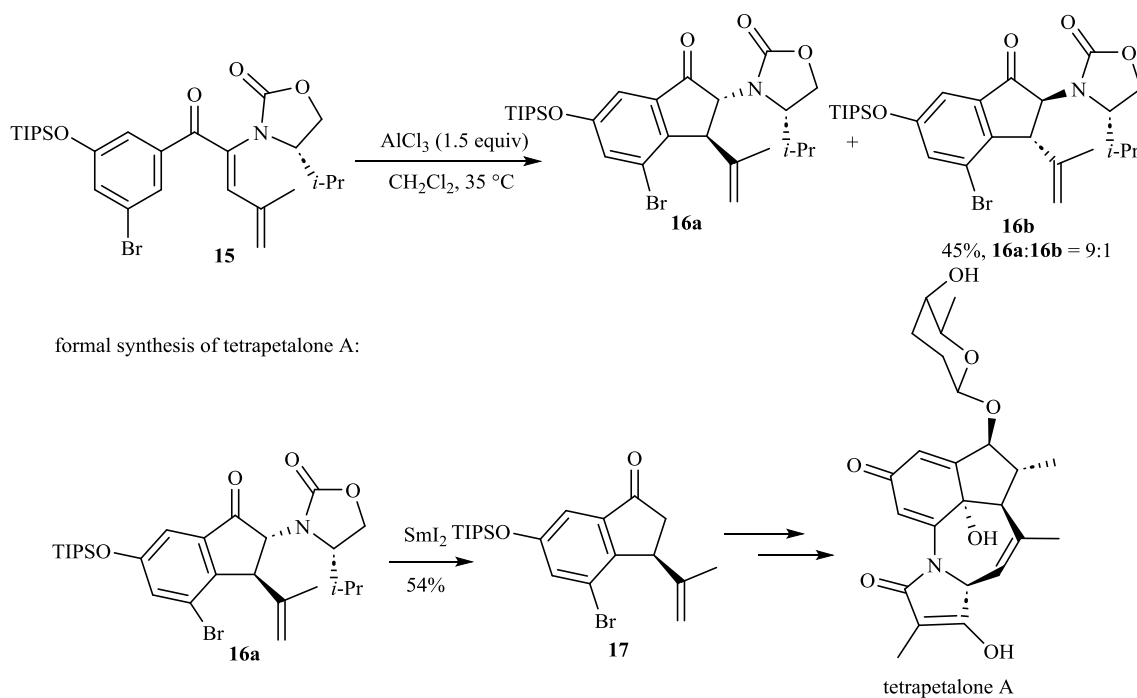
2.1. Nazarov Reactions

In 1999, Pridgen *et al.* described the first asymmetric Nazarov cyclization in the course of synthesizing chiral indanes as potent antagonists of endothelin receptor, such as SB 209670 and SB 217424 [10]. Even since, a multitude of asymmetric Nazarov reactions involving chiral auxiliaries have been developed with many of them applied in total synthesis. Among them, Gianni *et al.* described in 2017 a novel entry to chiral C-nor-D-homo steroids on the basis of the asymmetric Nazarov cyclization of chiral functionalized aryl vinyl ketones **6** derived from (+)-Wieland–Miescher ketone [11]. As shown in Scheme 2, the process was carried out in dichloromethane at 0 °C to room temperature in the presence of 3.5–15 equivalents of TiCl_4 as Lewis acid. It diastereoselectively afforded the desired chiral C-nor-D-homo steroids **7** with 45–94% yields. Notably, this methodology constituted a rare example of Lewis acid-mediated Nazarov reaction of aryl vinyl ketones. Moreover, the thus-formed Nazarov products could be further easily functionalized into novel non-natural C-nor-D-homo steroidal alkaloids.



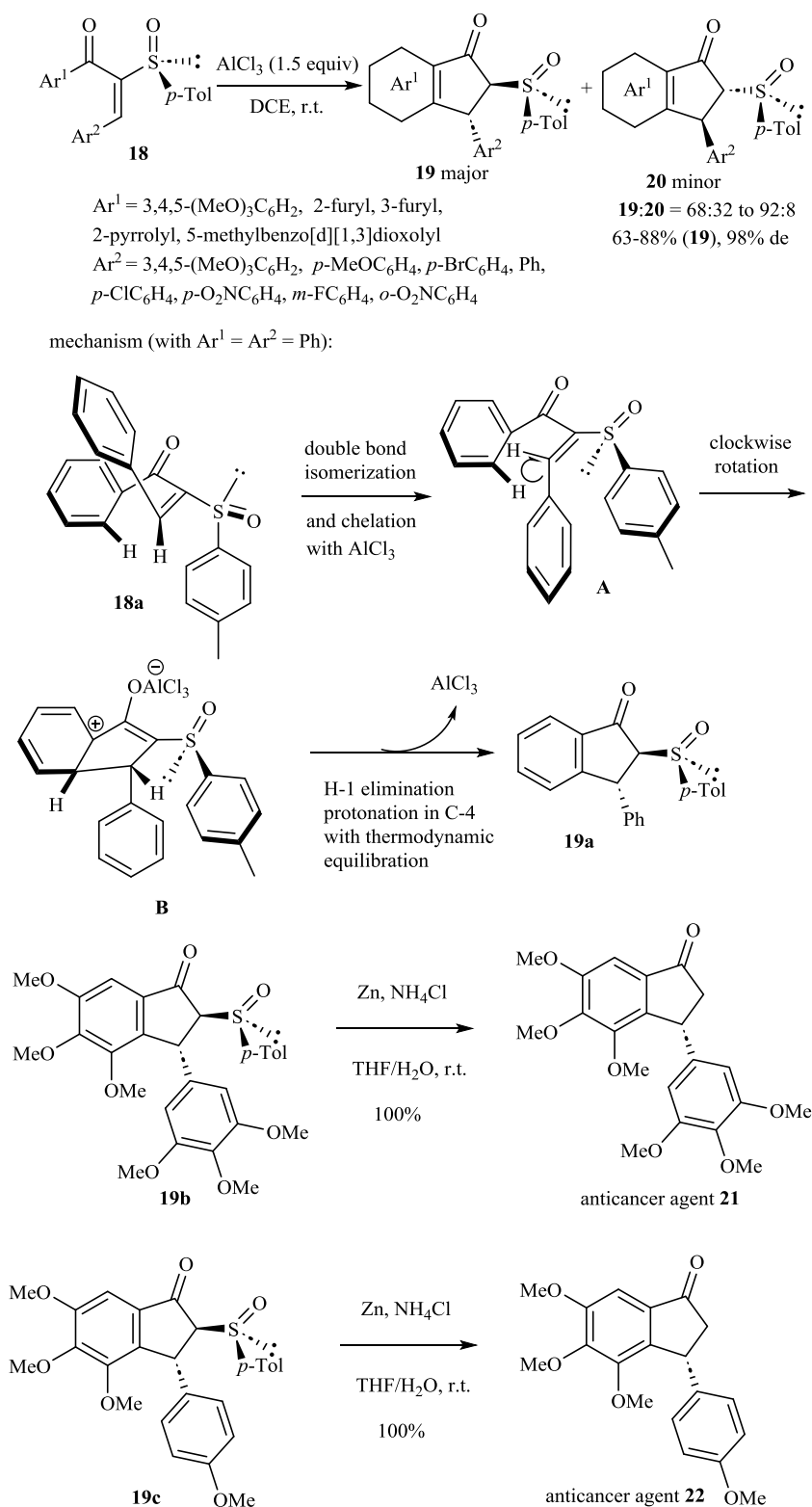
Scheme 2. Nazarov reaction of chiral functionalized aryl vinyl ketones and synthesis of C-nor-D-homo-steroids.

In the same year, Flynn *et al.* identified chiral Evans' oxazolidinone as an excellent activating group in Nazarov substrates **8** through the stabilization of the charge redistribution (δ^+) in the transition state of the conversion of the pentadienyl cation **9** into allylic cation **10** during the Nazarov reaction, thus avoiding [1,2]-sigmatropic shifts of neighboring substituents (Scheme 3) [12]. Indeed, a range of chiral oxazolidinone-activated aryl vinyl and divinyl ketones **8** were found to undergo regio- and diastereoselective oxazolidinone-controlled Nazarov reaction in the presence of 2-10 equivalents of MeSO_3H at room temperature or under heating. Carried out in dichloromethane, DCE or toluene as solvent, the process led to the desired chiral functionalized cyclopentenones **11** as single diastereomers (>90% de) in 25-99% yields, thus demonstrating a strong influence of the chiral oxazolidinone on the torquoselectivity of the Nazarov reaction, resulting in a total diastereoselectivity. The process tolerated variously substituted divinyl ketones and aryl vinyl ketones which generally reacted smoothly with uniformly high yields (76-99%) while a dramatically lower yield (25%) was observed in the Nazarov cyclization of an isopropyl-substituted furanyl vinyl ketone ($\text{R}^1 = i\text{-Pr}$, $\text{R}^2, \text{R}^3 = \text{O-CH=CH}$, $\text{R}^4 = \text{Ph}$, $\text{R}^5 = \text{H}$) which required a higher reaction temperature (refluxing DCE). Later in 2020, the same group investigated the reaction of even more substituted oxazolidinone-activated divinyl and aryl vinyl ketones **12** [13]. In this case, they employed either $\text{BF}_3 \cdot \text{THF}$ (1-3 equivalents) or TfOH (1.2-1.6 equivalent) to promote the Nazarov reaction of these sterically congested substrates in dichloromethane, which afforded chiral cyclopentenones **13** exhibiting a quaternary stereocenter as almost single diastereomers (>90% de) with 45-93% yields, as presented in Scheme 3. The cleavage of the oxazolidinone could be further achieved by treatment with lithium naphthalenide (LiNph) in THF, leading to enantiopure products **14** (>98% ee) with 55-79% yields.



Scheme 4. Nazarov reaction of a chiral oxazolidinone-activated phenyl vinyl ketone and synthesis of tetrapetalone A.

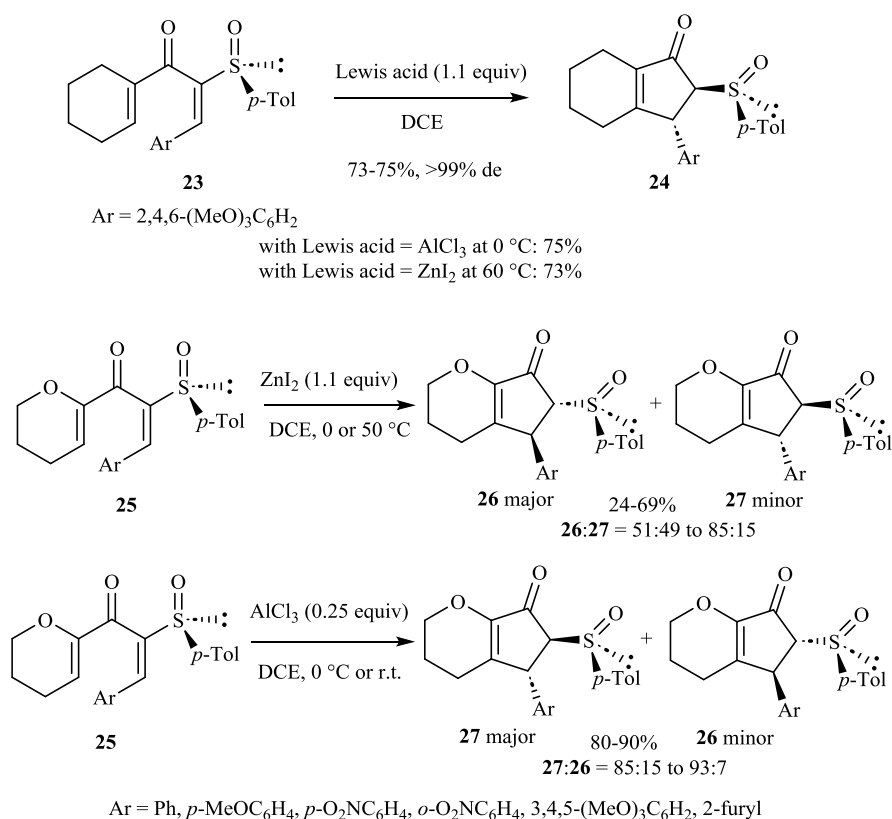
In 2017, chiral sulfoxides were employed as auxiliaries in asymmetric Nazarov reactions by Salom-Roig *et al.* (Scheme 5) [15]. These dienone substrates **18** exhibited an electron-donating (hetero)aromatic moiety (Ar^1) and a chiral sulfoxide acting as both chiral inductor and electron-withdrawing group. The torquoselectivity of the cyclization was directed by the sulfinyl group when 1.5 equivalent of $AlCl_3$ was used as promoter in DCE. Performed at room temperature, the Nazarov cyclization of **18** afforded a mixture of *trans*-stereoisomers **19** and **20** with general excellent *trans*-diastereoselectivity (98% de). Major stereoisomers **19** were obtained with 63–88% yields and low to excellent diastereomeric ratios (**19:20** = 68:32 to 92:8). To explain the stereoselectivity of the reaction, the authors proposed the mechanism as depicted in Scheme 5. $AlCl_3$ formed an O–Al bond with the basic oxygen atom of the sulfinyl group, and then the Al center coordinated with the oxygen atom of the carbonyl group. Simultaneously, the double bond isomerized into intermediate **A**. The *p*-tolyl group directed the sense of rotation, allowing a small amount of clockwise rotation, leading to enolate **B**. Subsequently, the H-1 atom was eliminated and protonation of the enolate with concomitant thermodynamic equilibration yielded stable *trans*-diastereomer **19**, along with regenerated $AlCl_3$. The utility of this methodology was shown in the development of the first synthesis of the two enantiopure anticancer agents **21** and **22** from the two corresponding Nazarov intermediates **19b** and **19c**.



Scheme 5. Nazarov reaction of chiral sulfoxides and synthesis of anticancer agents.

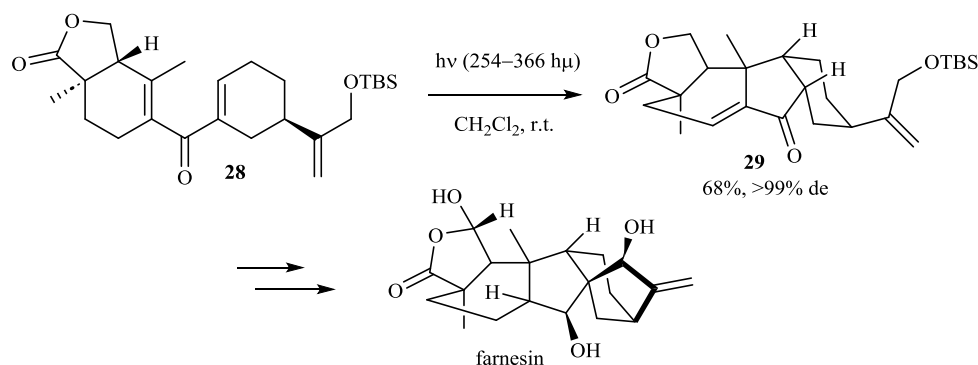
Later in 2022, the same authors investigated other types of chiral sulfoxide auxiliaries, such as cyclohexene derivative **23**, under related reaction conditions [16]. In the presence of 1.1 equivalent of both the same Lewis acid (AlCl_3) and solvent (DCE), this substrate provided at 0°C chiral bicyclic *trans*-product **24** with 75% yield exclusively (Scheme 6). Switching the Lewis acid to ZnI_2 employed at 60°C did not affect the torquoselectivity of the Nazarov reaction since the same single *trans*-product **24** was obtained in comparable yield (73%). In the

same area, the Nazarov cyclization of activated dienones **27** bearing an electron-donating dihydropyran was investigated by these authors, in 2023 (Scheme 6) [17]. The reactions were carried out in DCE in the presence of either 1.1 equivalent of ZnI_2 as promotor or 0.25 equivalent of AlCl_3 , affording a mixture of only two *trans*-diastereomers **26** and **27** from the four possible stereoisomers. Remarkably, changing the Lewis acid allowed to switch the torquoselectivity of the reaction. Indeed, the use of ZnI_2 as promotor at 0 or 50 °C resulted in the privileged formation of diastereomers **26** with 24-69% yields with **26:27** ratios ranging from 51:49 to 85:15. On the other hand, when the reaction was promoted at 0 °C or room temperature by AlCl_3 at only 25 mol% of catalyst loading, it afforded *trans*-diastereomers **27** as major products with 80-90% yields and **27:26** ratios ranging from 85:15 to 93:7. Indeed, the chiral sulfoxide auxiliary directed the asymmetric induction as well as the nature of the Lewis acid employed.



Scheme 6. Nazarov reactions of chiral sulfoxides bearing a cyclohexene/dihydropyran moiety.

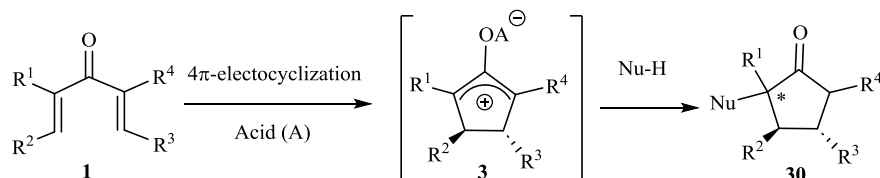
In some rare cases, the Nazarov reaction may be induced by UV irradiation. These photochemical Nazarov cyclizations occurred through an electronically excited state arising from disrotation. An example was applied by Gao *et al.* in 2020 in the first total synthesis of farnesin, a chiral rearranged *ent*-kaurenoid [18]. As presented in Scheme 7, the photoinitiated Nazarov reaction of chiral non-aromatic dicyclic divinyl ketone **28** performed at room temperature under UV light ($\lambda = 254\text{-}366$ nm) in dichloromethane as solvent afforded chiral tetracyclic product **29** as a single diastereomer with 68% yield. This chiral product was further converted into expected farnesin through fourteen supplementary steps.



Scheme 7. Photochemical Nazarov reaction of a chiral non-aromatic bicyclic divinyl ketone and synthesis of farnesin.

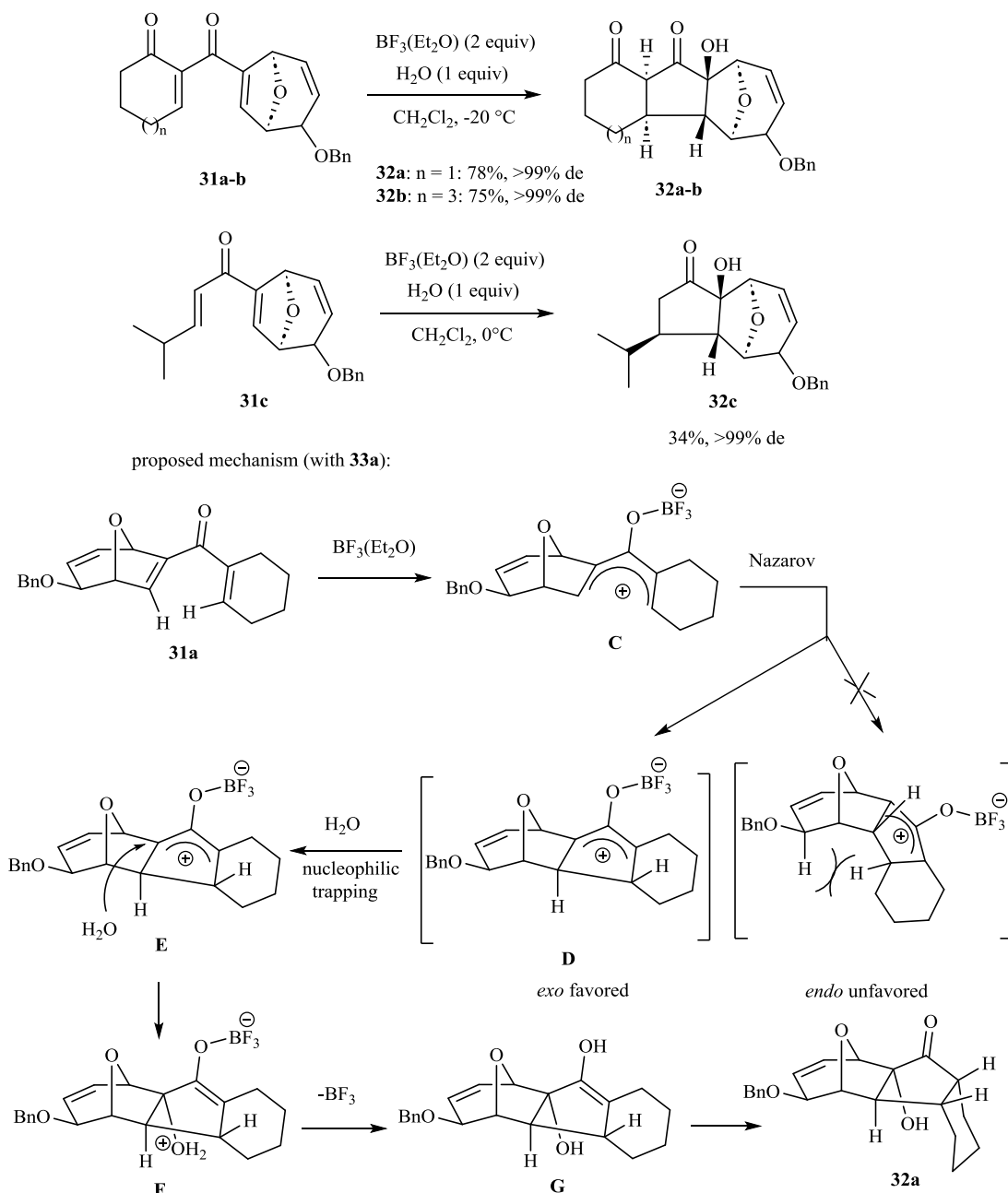
2.2. Nazarov-Based Domino/Tandem Reactions

The concept of domino reactions was introduced by Tietze in 1990s, dealing with one-step transformations occurring under strictly the same reaction conditions [19]. These economic reactions have allowed many natural and bioactive products to be easily synthesized without cost purification of intermediates [20]. Among domino reactions, interrupted Nazarov reactions [7] constitute one of the latest important achievements of the Nazarov cyclization, which has widely expanded the scope of the original process [21]. Indeed, this methodology, consisting of a domino Nazarov/nucleophilic trapping reaction, is useful for the stereoselective construction of polycyclic molecules by a cascade polycyclization process initiated by a 4π -electrocyclic ring closure. As presented in Scheme 8, the interrupted Nazarov reaction is a domino reaction beginning with the electrocyclic ring closure of dienone **1** into cyclopentenyl cation **3**. In a second step, this intermediate undergoes a nucleophilic attack, leading to substituted cyclopentanone **30** bearing up to four new stereocenters. Various olefins, dienes, (hetero)arenes, alkylaluminum reagents, nitrogen and oxygen compounds and halogens among others have been successfully used as nucleophiles.



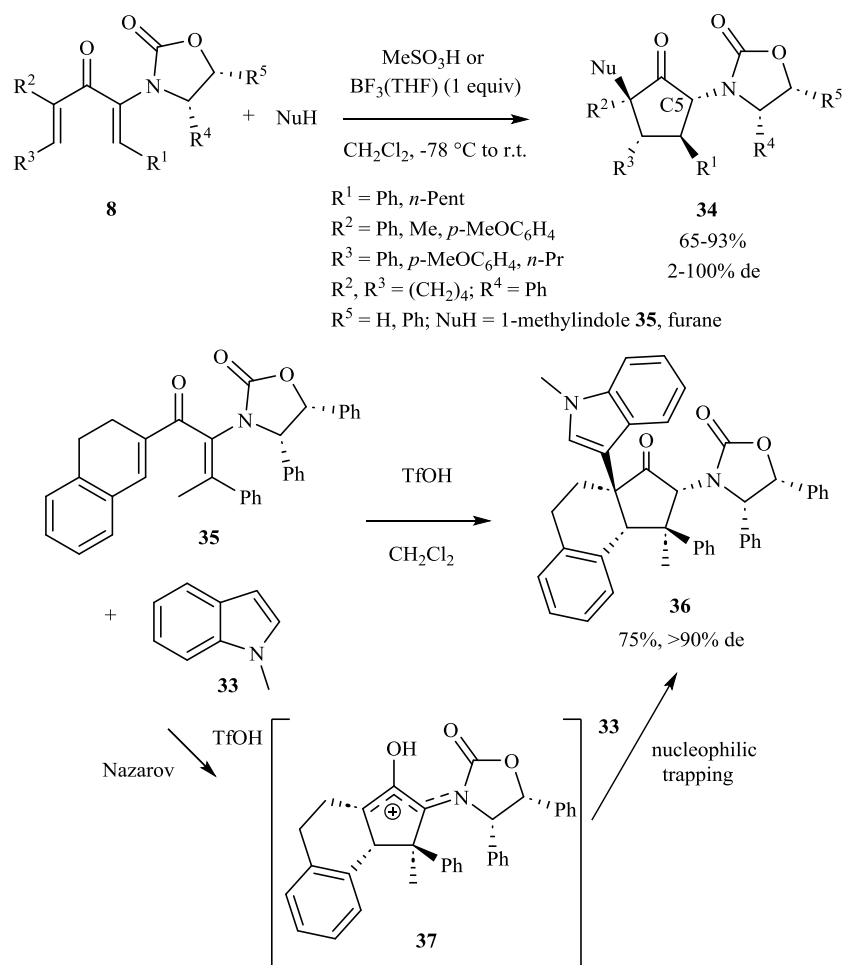
Scheme 8. Interrupted Nazarov reaction (domino Nazarov/nucleophilic trapping reaction).

In 2017, Liu *et al.* developed asymmetric interrupted Nazarov reactions of chiral 8-oxabicyclo[3.2.1]octanes **31** (Scheme 9) [22]. The latter arose from a gold-catalyzed tandem 1,3-acyloxy migration/Ferrier rearrangement of the corresponding glycal-derived propargylic esters. When 8-oxabicyclo[3.2.1]octanes **31** were submitted to two equivalents of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in dichloromethane as solvent, they underwent domino Nazarov/nucleophilic trapping reaction to give chiral 11-oxatricyclo[5.3.1.0]-undecanes **32** as single diastereomers with moderate to good yields (34-78%). The importance of this process was related to the fact that these molecules constitute the skeletons of numerous natural products and biologically active ones. The reaction tolerated cyclohexenyl as well as cyclooctenyl ketones **31a-b**, which afforded at $-20\text{ }^\circ\text{C}$ polycyclic products **32a-b** with 75-78% yields. Moreover, β -substituted ketone **31c** was compatible, leading at $0\text{ }^\circ\text{C}$ to product **32c** with 34% yield, which constitutes the core structure of natural product homalomenol C. To explain the high torquoselectivity of 11-oxatricyclo[5.3.1.0]undecanes **32**, a mechanism is proposed in Scheme 9. Activated by the Lewis acid, the starting 8-oxabicyclo[3.2.1]octane **31** led to pentadienyl cation **C**, which further underwent a conrotatory 4π -electrocyclization, affording intermediate **D** with complete *exo* stereoselectivity. Subsequently, stoichiometric additive H_2O trapped species **D** from the less-bulky *endo* face of the polycyclic system to give intermediate **F**. Then, the latter species was converted into the final product through hydrogen shift and enol/ketone tautomerism.



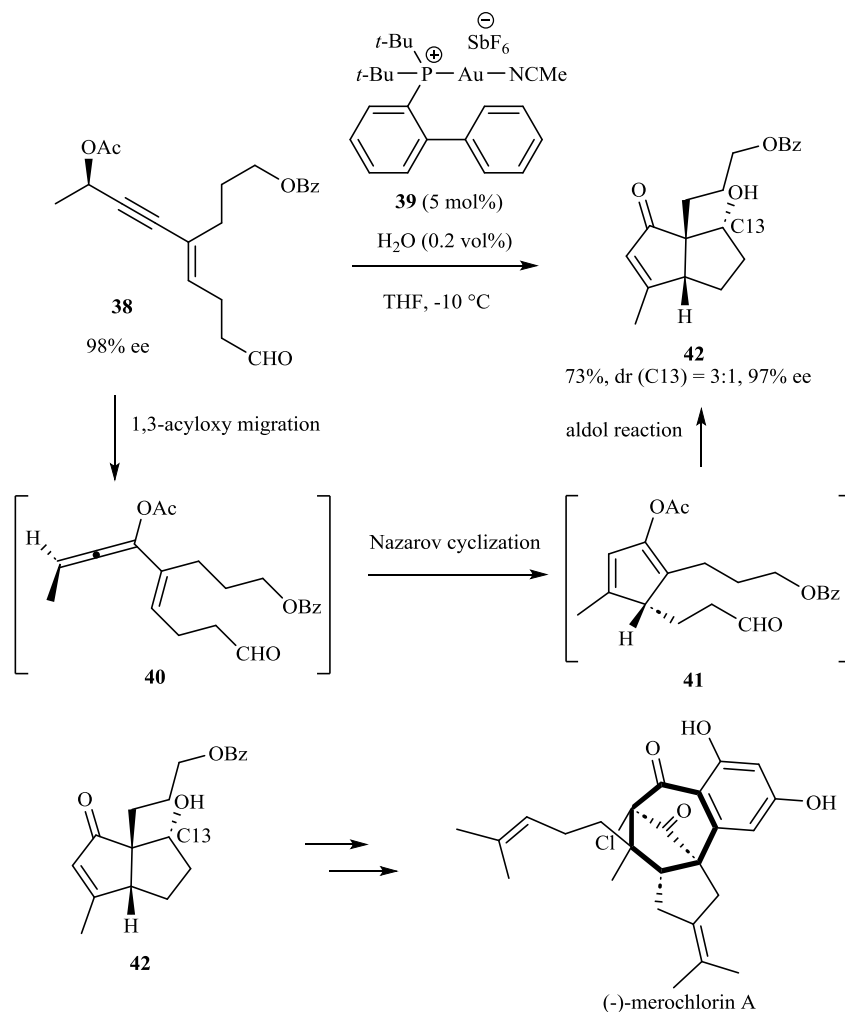
Scheme 9. Domino Nazarov/nucleophilic trapping reactions of 8-oxabicyclo[3.2.1]octanes.

Chiral oxazolidinone-activated divinyl ketones **8** were investigated by Flynn *et al.* in interrupted Nazarov reactions, in 2017 [12]. The Nazarov intermediates, generated in the presence of one equivalent of MeSO_3H or $\text{BF}_3 \cdot \text{THF}$ as promotor, could be regio- and stereoselectively trapped by nucleophiles in dichloromethane as solvent, such as 2-furane and 1-methylindole **33**, to afford products **34** with 65-93% yields (Scheme 10). In general, a single diastereomer was obtained except in one case ($\text{R}^1 = \text{Ph}$, $\text{R}^2, \text{R}^3 = (\text{CH}_2)_4$, $\text{R}^4 = \text{R}^5 = \text{Ph}$, $\text{Nu} = 1\text{-furyl}$) which provided a product as a 51:49 mixture of two C5-epimers. Later in 2020, these authors described the same reaction between chiral oxazolidinone-activated divinyl ketone **35** and 1-methylindole **33** as nucleophile, which allowed complex chiral tricyclic product **36** to be achieved as an almost single diastereomer (>90% de) with 75% yield by treatment with TfOH in dichloromethane. The latter was formed by nucleophilic trapping of the Nazarov intermediate oxyallyl cation **37** [13].



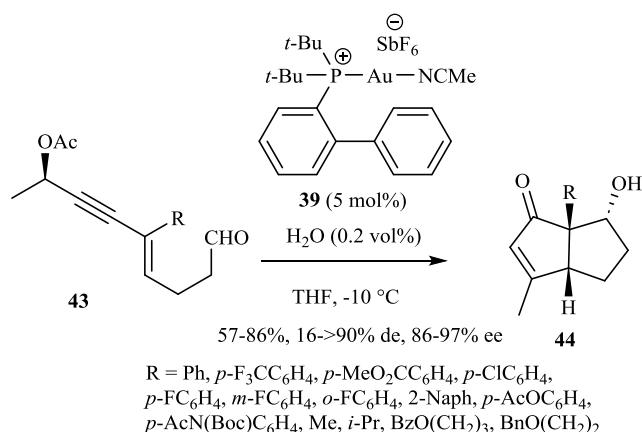
Scheme 10. Domino Nazarov/nucleophilic trapping reactions of chiral oxazolidinone-activated divinyl ketones with furane and 1-methylindole.

In 2019, the first asymmetric total synthesis of antibiotic (-)-merochlorin A was reported by Carreira *et al.* [23]. The key step of this synthesis was a diastereoselective gold-catalyzed Nazarov-based domino reaction of almost enantiopure (98% ee) linear enyne aldehyde **38**. As illustrated in Scheme 11, the authors showed that when substrate **38** was submitted at -10°C to only 5 mol% of Echavarren's catalyst **39** in THF as solvent in the presence of water, it underwent a cascade of three reactions beginning with a 1,3-acyloxy migration to give intermediate **40**. Then, the latter species evolved through a Nazarov cyclization into cyclopentadiene **41**, which finally underwent an aldol reaction to afford domino bicyclic product **42** with 73% yield. This key product was obtained as a 3:1 diastereomeric mixture at C(13). Remarkably, the domino product **42** was obtained with a high degree of chirality transfer (97% ee) from the corresponding acyclic precursor **38** (98% ee). Product **42** was further converted into expected (-)-merochlorin A through fifteen additional steps.



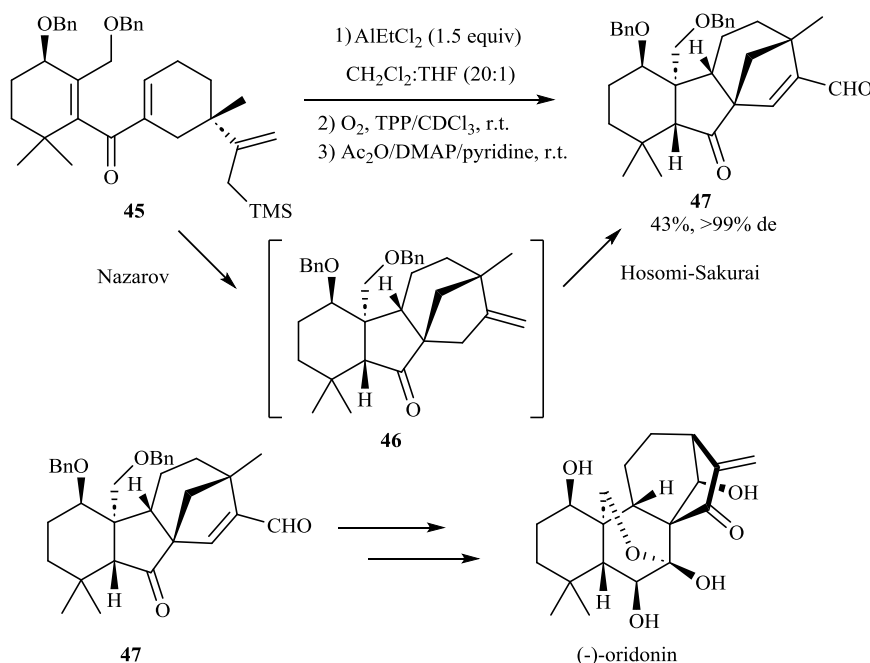
Scheme 11. Domino 1,3-acyloxy migration/Nazarov/aldol reaction of a chiral linear enyne aldehyde and synthesis of (-)-merochlorin A.

Soon later, this highly efficient domino 1,3-acyloxy migration/Nazarov/aldol reaction was extended to a series of other chiral acyclic propargylic enynes **43** exhibiting a pendant aldehyde [24]. Indeed, the same reaction conditions allowed the synthesis of chiral bicyclo[3.3.0]octanes **44** with 57-86% yields in moderate to high diastereoselectivities (16->90% de) and excellent enantioselectivities (86-97% ee), as presented in Scheme 12. Various aromatic as well as aliphatic substituents were tolerated with the lowest diastereoselectivity (15% de) obtained in the reaction of the methyl-substituted substrate (R = Me). It must be noted that these chiral fused five-membered rings bearing three contiguous stereogenic centers constitute the skeletons of many natural products.



Scheme 12. Domino 1,3-acyloxy migration/Nazarov/aldol reaction of other chiral acyclic enyne aldehydes.

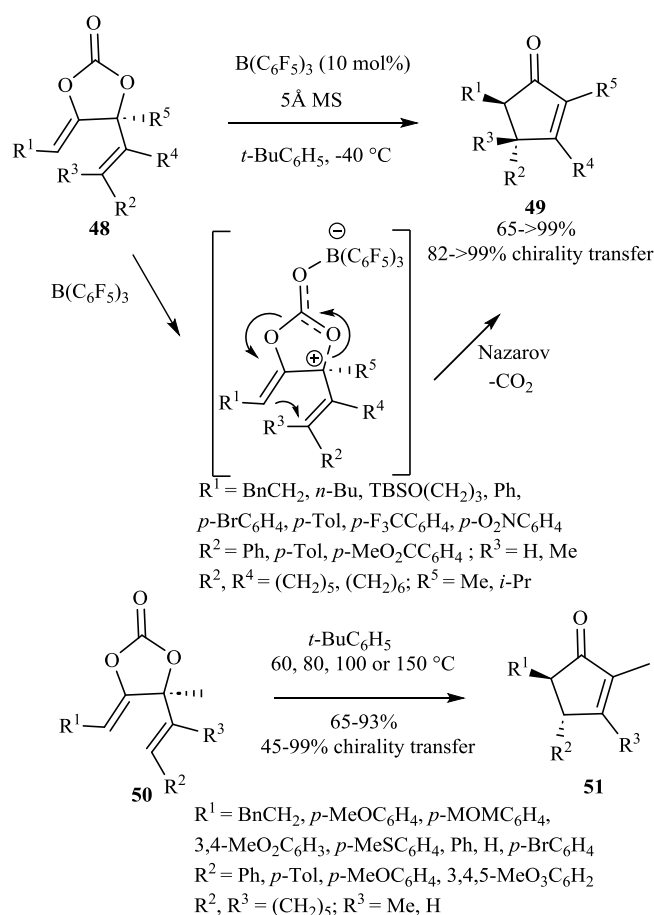
In 2019, Luo *et al.* described the first total synthesis of anti-cancer agent (–)-oridonin, the key step of which was an interrupted asymmetric Nazarov reaction (Scheme 13) [25]. This consisted of an asymmetric tandem Nazarov/Hosomi–Sakurai reaction of chiral functionalized ketone **45**. In the presence of 1.5 equivalent of AlEtCl_2 as promotor, this ketone underwent a Nazarov cyclization in a 20:1 mixture of dichloromethane and THF as solvent to give chiral intermediate **46**, which was directly submitted to singlet oxygen followed by acetate anhydride to provide through Hosomi–Sakurai reaction chiral product **47** with 43% yield. This complex multifunctionalized product was further converted into desired (–)-oridonin through thirteen additional steps.



Scheme 13. Tandem Nazarov/Hosomi–Sakurai reaction of a chiral divinyl ketone and synthesis of (–)-oridonin.

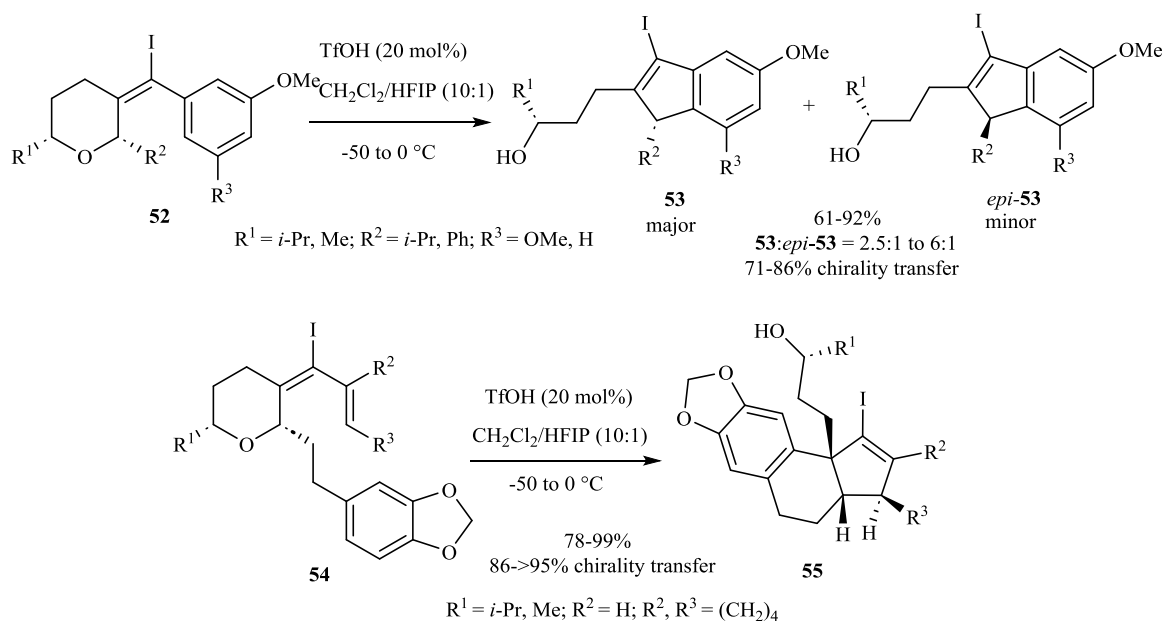
Another type of chirality transfer was disclosed in 2019 by Yamada *et al.* in a decarboxylative Nazarov reaction of chiral cyclic enol carbonates **48** catalyzed by only 10 mol% of $\text{B}(\text{C}_6\text{F}_5)_3$ (Scheme 14) [26]. The process evolved at $-40\text{ }^\circ\text{C}$ in *t*-butylbenzene to give chiral cyclopentenones **49** with both good to excellent yields (65–>99%) and chirality transfer (82–>99%). Interestingly, even substrates bearing seven- and eight-membered cyclic olefins ($\text{R}^2, \text{R}^4 = (\text{CH}_2)_5, (\text{CH}_2)_6$) were transformed into bicyclic fused-ring structures in good to high yields (65–99%) and excellent chiral transfer (95–>99%). Later in 2020, these authors developed a thermal

version of the same methodology (Scheme 14) [27]. Indeed, in the absence of a Lewis acid, a range of chiral cyclic enol carbonates **50** underwent under heating at 60, 80, 100 or 150 °C in *t*-butylbenzene as solvent decarboxylative Nazarov cyclization to give variously substituted chiral 2-cyclopentenones **51** with 65-93% yields and generally high chirality transfer (45-99%). This novel catalyst-free version extended the substrate scope of the original domino reaction.

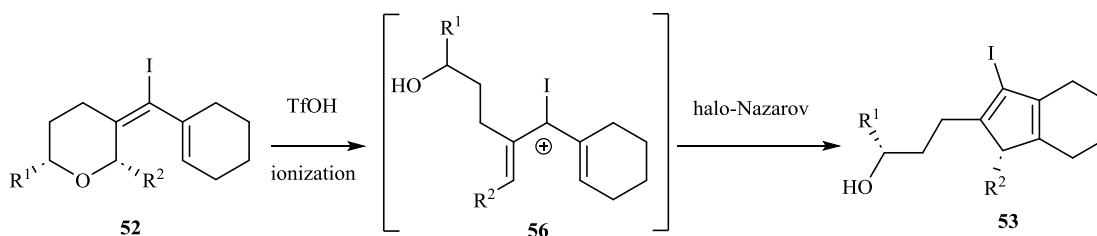


Scheme 14. Boron-catalyzed and thermal decarboxylative Nazarov reactions of chiral cyclic enol carbonates.

Asymmetric domino ionization/halo-Nazarov reactions of a series of chiral dihydropyrans were reported by Frontier *et al.*, in 2020 [28]. For example, dihydropyrans **52** submitted to only 20 mol% of TfOH at -50 to 0 °C in a 10:1 mixture of dichloromethane and HFIP led to chiral haloindenes **53** as major products along with epimers *epi*-**53** in 2.5:1 to 6:1 ratio with 61-92% yields, as illustrated in Scheme 15. The chirality transfer was evaluated to 71-86%. The latter was improved to up to >95% by changing the type of dihydropyran substrates involved. Under the same reaction conditions, dihydropyrans **54** underwent the domino ionization/halo-Nazarov reaction which was followed in this case by an arylation to give chiral products **55** as single diastereomers with 86->95% of chirality transfer and 78-99% yields. As presented in Scheme 15, the mechanism of the first domino process resulting in the formation of **53** involved that starting dihydropyran **52** underwent ionization in the presence of TfOH to give 3-halopentadienyl cation **56**, which further cyclized to afford the final product.

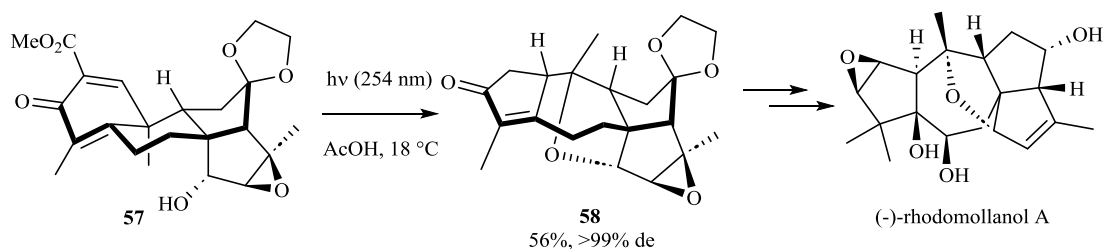


mechanism (for 53):



Scheme 15. Domino ionization/halo-Nazarov reactions of chiral dihydropyrans.

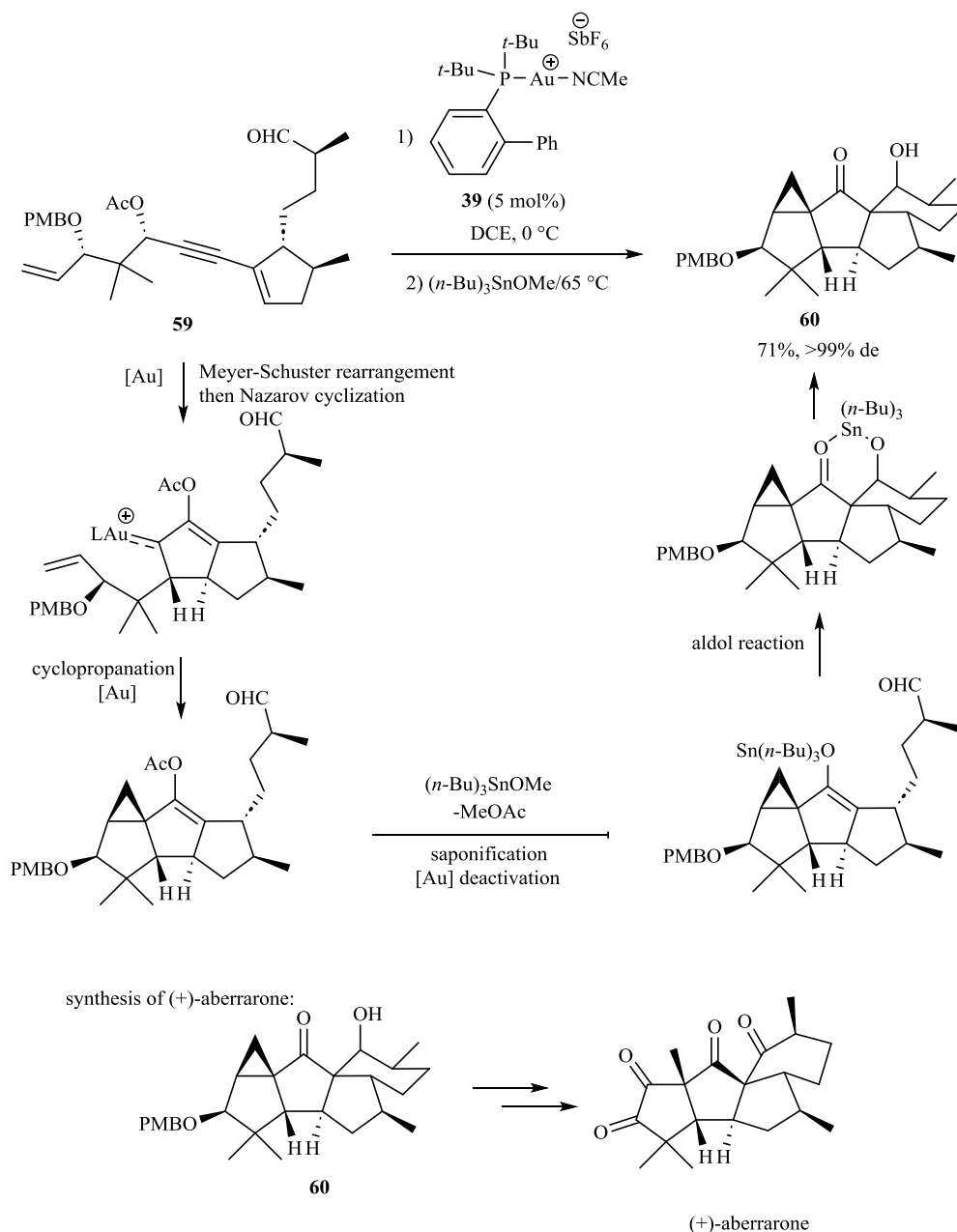
The first total synthesis of (–)-rhodomollanol A was disclosed in 2020 by Ding *et al.* on the basis of a domino photo-Nazarov/intramolecular cycloetherification reaction of chiral cyclohexadienone **57** [29]. As presented in Scheme 16, irradiation (254 nm) of this substrate at 18 °C in AcOH resulted in the formation of product **58** exhibiting the 7-oxabicyclo[4.2.1]nonane core structure of desired (–)-rhodomollanol A. Indeed, chiral domino product **58** obtained in 56% yield was further converted through twelve additional steps into desired (–)-rhodomollanol A.



Scheme 16. Domino photo-Nazarov/cycloetherification reaction of a chiral cyclohexadienone and synthesis of (–)-rhodomollanol A.

In 2022, Carreira and Amberg reported the first total synthesis of natural product (+)-aberraronone, the key step of which consisted in a gold-catalyzed cyclization cascade reaction of chiral functionalized alkyne **59** [30]. When this substrate was submitted to as low as 5 mol% of Echavarren's catalyst **39** in DCE at 0 °C followed by adding (*n*-Bu)₃SnOMe and then heating at 65 °C, it afforded chiral pentacyclic product **60** as a single

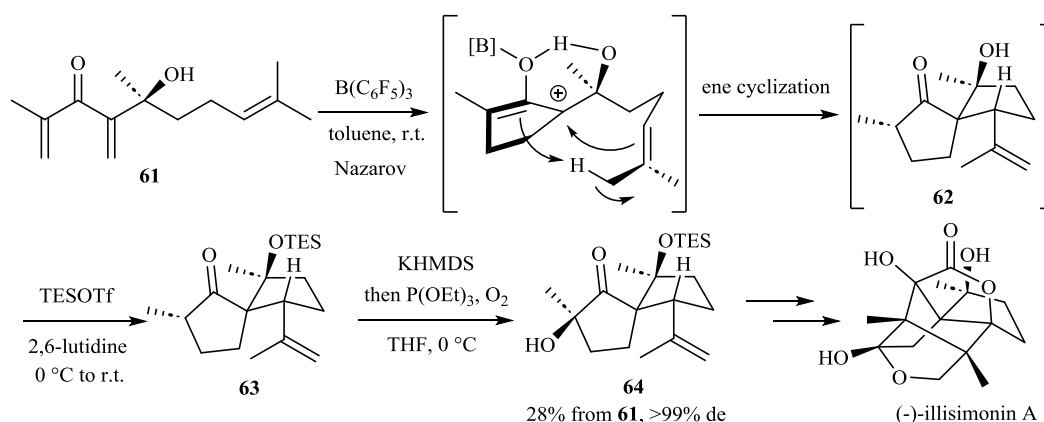
diastereomer in 71% yield (Scheme 17). Actually, this complex product arose from successive Meyer–Schuster rearrangement, Nazarov cyclization, cyclopropanation and aldol condensation, as detailed in Scheme 17. Through five additional steps, product **60** was further converted into desired (+)-aberrarone.



Scheme 17. Tandem Meyer–Schuster rearrangement/Nazarov/cyclopropanation/aldol reaction of a chiral alkyne and synthesis of (+)-aberrarone.

In 2023, the first asymmetric total synthesis of the natural product (–)-illisimonin A, exhibiting neurotrophic properties, was reported by Kalesse *et al.* on the basis of an asymmetric domino Nazarov/ene cyclization reaction catalyzed by $\text{B}(\text{C}_6\text{F}_5)_3$ (Scheme 18) [31]. The sequence, carried out at room temperature in toluene, involved chiral tertiary alcohol **61** as starting material, which afforded diastereoselectively in the presence of the Lewis acid chiral domino spirocyclic product **62**. However, the latter was unstable, and a subsequent TES protection of the alcohol moiety by treatment with TESOTf was performed to give the more stable

corresponding TES-protected congener **63**. Since this product was found inactive for the next step of the synthesis, it was submitted to α -oxidation with oxygen to provide chiral α -hydroxy ketone **64**, which was obtained with 26% yield starting from precursor **61**. This tertiary alcohol could be further converted into desired (-)-illisimonin A through seventeen additional steps.

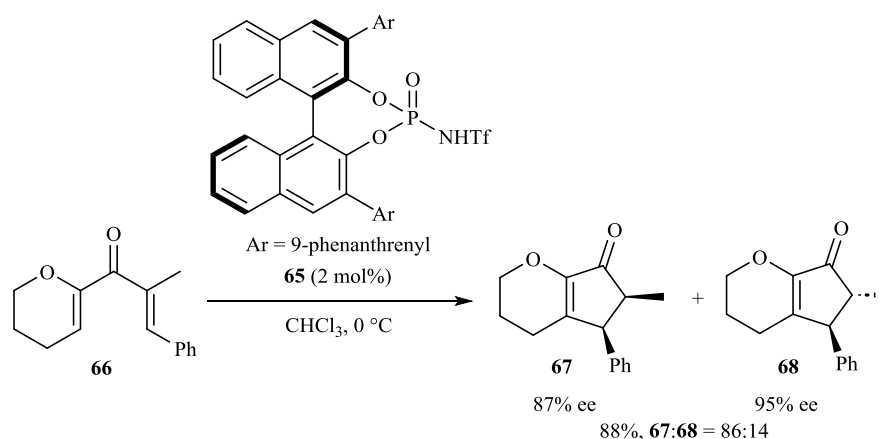


Scheme 18. Domino Nazarov/ene cyclization reaction of a chiral tertiary alcohol and synthesis of (-)-illisimonin A.

3. ORGANOCATALYTIC ENANTIOSELECTIVE NAZAROV REACTIONS

3.1. Nazarov Reactions

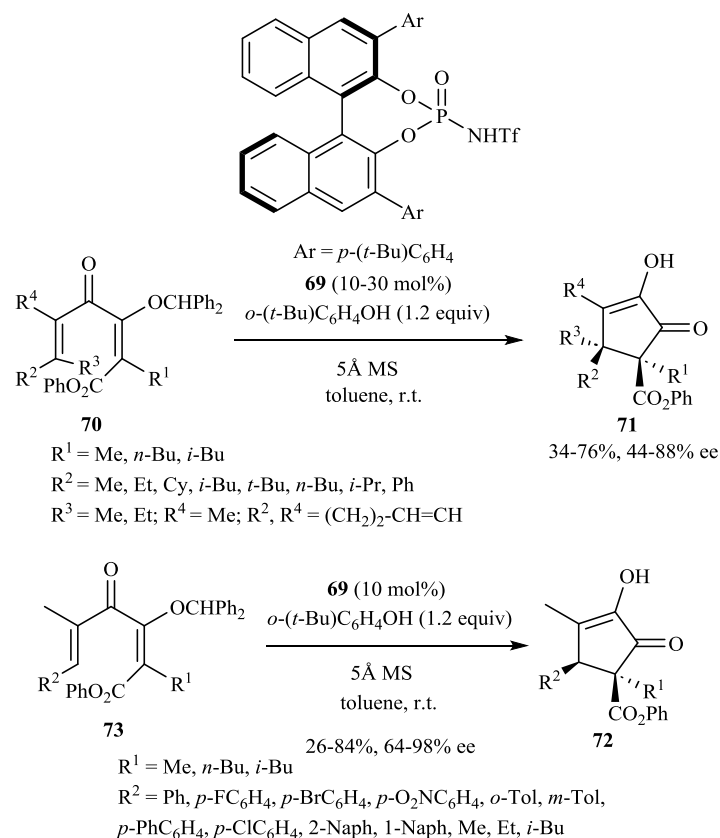
In contrast with toxic and often expensive metal catalysts [32] organocatalysts are non-toxic, robust, cheaper, and inert to moisture [33]. In 2007, the first enantioselective organocatalytic Nazarov cyclization was described by Rueping *et al.* [34]. It was promoted by 2 mol% of chiral BINOL-derived *N*-triflylphosphoramidate **65** in chloroform at 0 °C. As remembered in Scheme 19, the enantioselective Nazarov cyclization of dienone **66** resulted in the formation of a 86:14 mixture of the corresponding chiral *cis*- and *trans*-cyclopentenones **67** and **68** with 88% yield and excellent enantioselectivities (87% and 95% ee, respectively). The preponderance of the *cis*-product **67** over the *trans*-one **68** showed that the reaction took place under kinetic control. The configuration of the phenyl-bearing β -carbon atom was fixed by the absolute sense of conrotation, while the stereochemistry at the α -carbon atom was directed during the final proton transfer step.



Scheme 19. First organocatalytic Nazarov reaction reported by Rueping *et al.* in 2007.

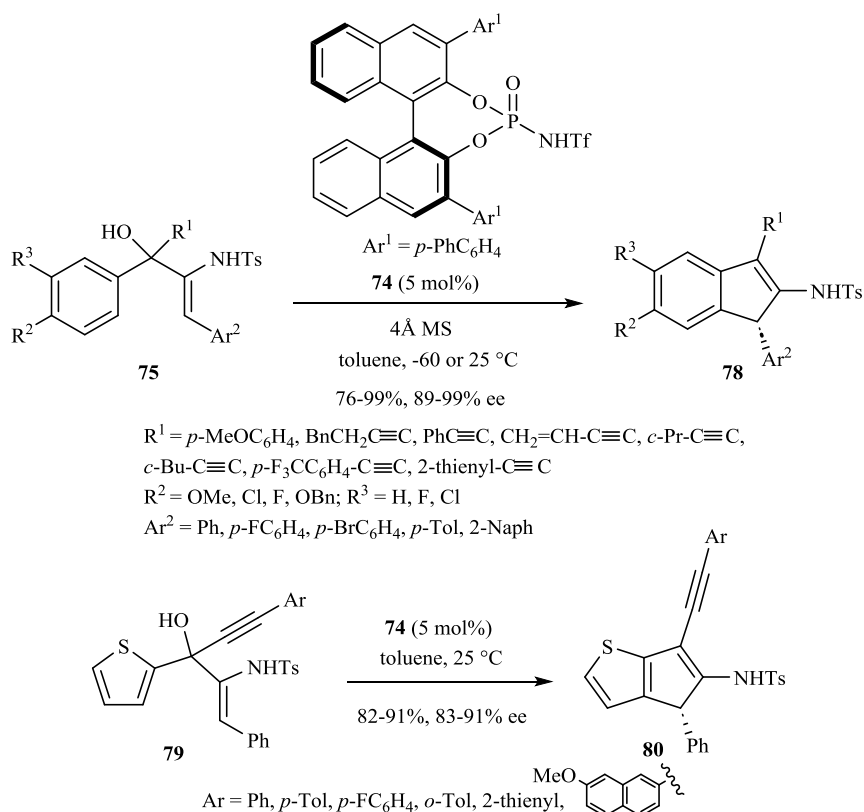
By using a related chiral BINOL-derived *N*-triflylphosphoramidate **69**, Tius *et al.* developed in 2017 asymmetric Nazarov cyclization of challenging divinyl ketones **70** not activated toward cyclization by an aryl group [35]. Indeed, a wide range of chiral aliphatic C-1,C-2-tetrasubstituted cyclopentenones **70** could be synthesized as single diastereomers from the corresponding dienones **70** with both moderate to high yields (34–76%) and enantioselectivities (44–88% ee), as shown in Scheme 20. The reaction was performed at room

temperature in toluene as solvent with 10-30 mol% of organocatalyst **69** in the presence of 1.2 equivalent of 2-*tert*-butylphenol. The reaction conditions could also be applied to the synthesis of a series of chiral all-aliphatic C-1,C-5-trisubstituted cyclopentenones **72** as single diastereomers with variable yields (26-84%) and moderate to excellent ee values (64-98% ee) starting from the corresponding divinyl ketones **73**. This methodology presented the advantage of allowing the asymmetric synthesis of single diastereomers of all-aliphatic cyclopentenones starting from challenging dienone substrates not activated by an aryl group. Furthermore, it offered a novel solution to the enduring challenge that is the stereoselective construction of adjacent, all-carbon quaternary centers.

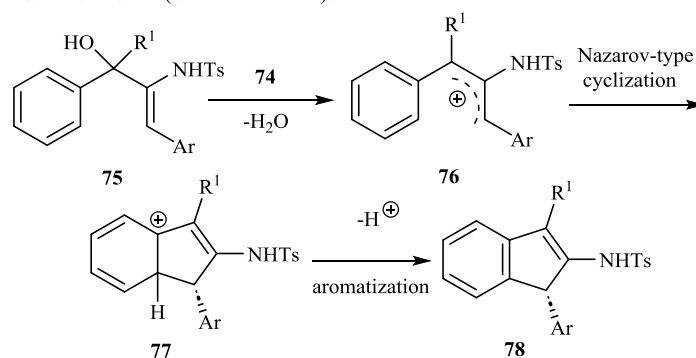


Scheme 20. Nazarov reactions of aliphatic divinyl ketones.

In 2018, Chan *et al.* employed 5 mol% of related chiral Brønsted acid catalyst **74** to develop a novel enantioselective Nazarov-type electrocyclization of α -hydroxy enamides **75** [36]. The mechanism illustrated in Scheme 21 proposes that the catalyst mediates the dehydration of the substrate to generate intermediate **76**. Then, the latter species undergoes a conrotatory 4π -electrocyclization to give chiral intermediate **77**. Finally, hydrogen abstraction and aromatization deliver product **78** along with regenerated chiral catalyst. The reaction of α -aryl α -hydroxyenamides **75** exhibiting various types of electron-rich aryl groups and substituted alkynyl groups afforded at 25 or -60 °C in toluene as solvent chiral 1H-indenes **78** with both uniformly high yields (76-99%) and enantioselectivities (89-99% ee). The scope of the process could be even more extended to α -thienyl α -hydroxyenamides **79** which provided chiral 4H-cyclopenta[b]thiophenes **80** with comparable excellent yields (82-91%) and ee values (83-91% ee).

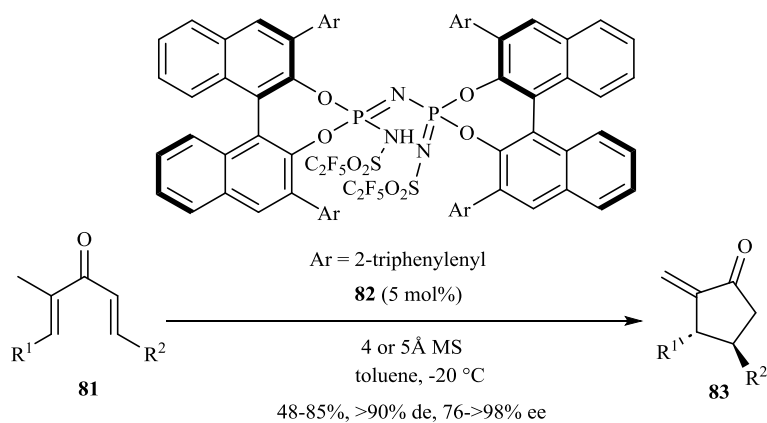


mechanism for **78** (with $\text{R}^2 = \text{R}^3 = \text{H}$):



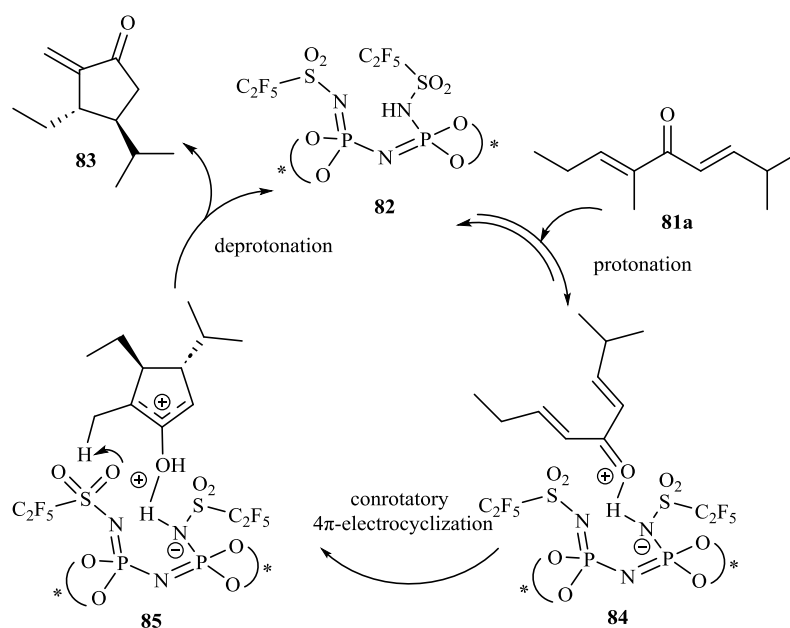
Scheme 21. Nazarov-type reactions of α -aryl and α -thienyl α -hydroxyenamides.

In 2019, List *et al.* developed a powerful enantioselective Nazarov cyclization of challenging simple, acyclic, aliphatic substituted divinyl ketones **81** using a strong Brønsted acid, such as imidodiphosphorimidate **82** (Scheme 22) [37]. In the presence of only 5 mol% of this catalyst in toluene at -20 °C, simple divinyl ketones **81** underwent regio-, diastereo- and enantioselective Nazarov reaction to give chiral cyclopentenones **82** as almost single diastereomers (>90% de) with good to high yields (48-85%), high regioselectivity (82->90% rr) and in most cases very high enantioselectivities (76->98% ee). Various types of substituents (R^2) were well tolerated, including linear, branched and cyclic aliphatic groups, all reacting with excellent regio-, diastereo- and enantioselectivities. To explain the stereochemical outcome of the reaction, a mechanism is shown in Scheme 22, beginning with the coordination of the chiral catalyst to the substrate to form intermediate complex **84** in which the reactive divinyl ketone exhibited a *s-trans/s-trans* conformation. Then, a conrotatory 4π -electrocyclization occurred to give intermediate **85**. The latter species subsequently underwent deprotonation induced by the O atoms of the sulfonyl group, thus releasing the product along with the regenerated catalyst. This novel remarkable methodology allowed the asymmetric Nazarov cyclization of simple, acyclic, aliphatic-substituted divinyl ketones with enantioselectivities of up to >98% ee by using a strong and confined Brønsted acid.



R¹ = Et, *n*-Bu, Cl(CH₂)₄, BnCH₂, Me; R² = *i*-Pr, *n*-Pr, *i*-Bu, *i*-Pent, *c*-Pr, *c*-Bu, *c*-Pent, Cy, *t*-Bu, *o*-BrC₆H₄

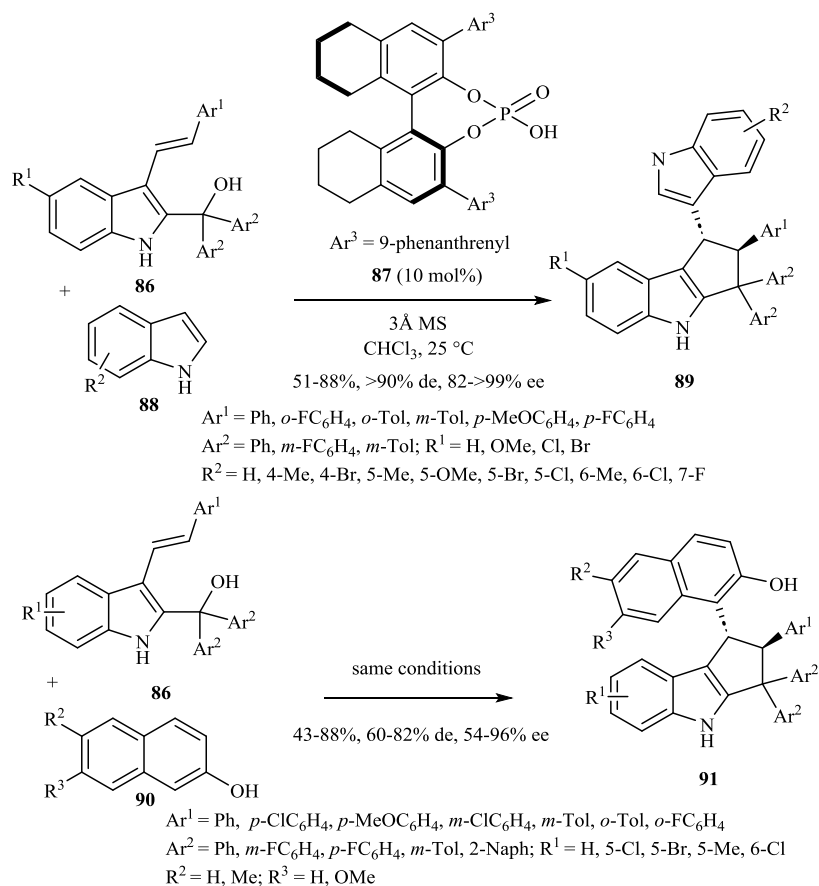
proposed mechanism (with R¹ = Et, R² = *i*-Pr):



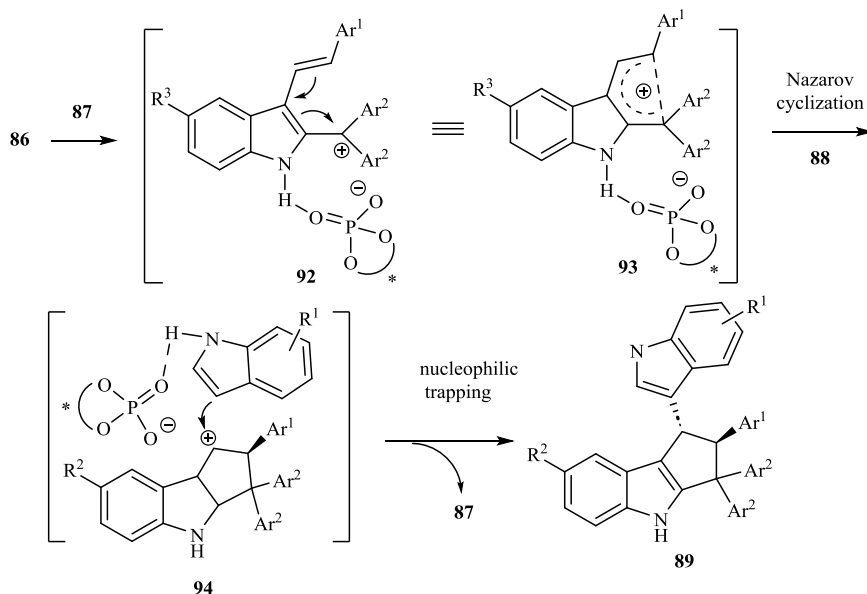
Scheme 22. Nazarov reaction of aliphatic divinyl ketones.

3.2. Nazarov-Based Domino Reactions

In 2018, Shi *et al.* designed C3-alkenyl-substituted 2-indolylmethanols **86** as novel substrates to be used in enantioselective interrupted Nazarov-type reactions with nucleophiles [38]. In the presence of 10 mol% of chiral phosphoric acid **87**, the interrupted Nazarov-type cyclization of a wide range of C3-alkenyl-substituted 2-indolylmethanols **86** with indoles **88** as nucleophiles occurred smoothly to afford chiral cyclopenta[b]indoles **89** as almost single diastereomers (>90% de) in moderate to quantitative yields (51-88%) and generally very high enantioselectivities (82->99% ee), as illustrated in Scheme 23. Along with variously substituted indoles **88**, substituted 2-naphthols **90** were found to be other compatible nucleophiles to react with C3-alkenyl-substituted 2-indolylmethanols **86** under the same reaction conditions. Indeed, the enantioselective domino Nazarov/nucleophilic trapping reaction led to chiral products **91** with moderate to high yields (43-88%), moderate to good diastereoselectivities (60-82% de) and uniformly excellent enantioselectivities (54-96% ee) [39]. As illustrated in Scheme 23, the authors proposed that the chiral catalyst reacted with the C3-alkenyl-substituted 2-indolylmethanol **86** to generate carbocation **92** via dehydration. Then, 4π carbocation **93** was generated, undergoing the Nazarov reaction controlled by hydrogen-bonding and ion pair interaction, thus affording cyclic carbocation **94**. Subsequently, both the nucleophile and carbocation **94** were activated by the anion of catalyst **87** via ion pair and hydrogen-bonding interaction, which induced the nucleophilic substitution to give the final product **89**.

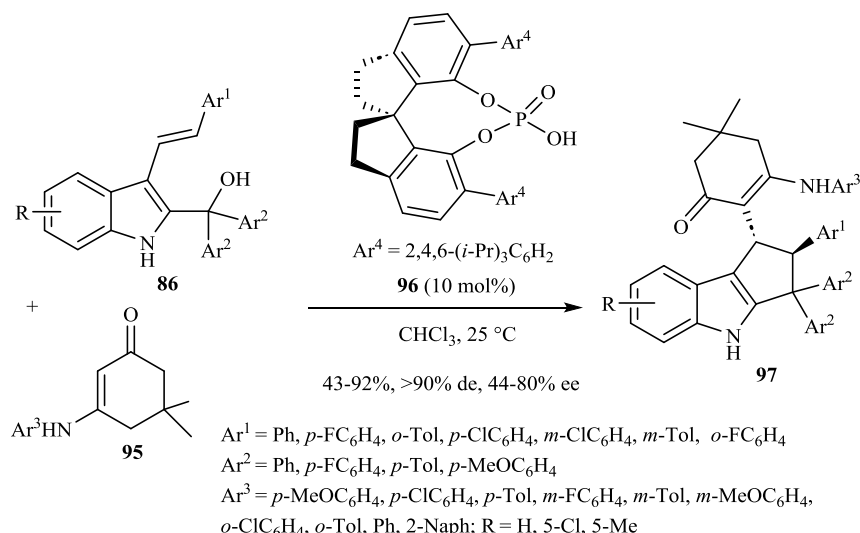


proposed mechanism (with **88**):



Scheme 23. Domino Nazarov/nucleophilic trapping reactions of C3-alkenyl-substituted 2-indolylmethanols with indoles/2-naphthols.

The extension of the precedent methodology to other nucleophiles, such as dimedone-derived enaminones **95**, was achieved [40]. In this case, the optimal chiral catalyst was chiral spirocyclic phosphoric acid **96** employed at 45 °C at 10 mol% of catalyst loading in chloroform as solvent (Scheme 24). The interrupted Nazarov reaction of these nucleophiles with a variety of C3-alkenyl-substituted 2-indolylmethanols **86** afforded chiral cyclopenta[b]indole derivatives **97** as almost single diastereomers (>90% de) with 43-92% yields and 44-80% ee.

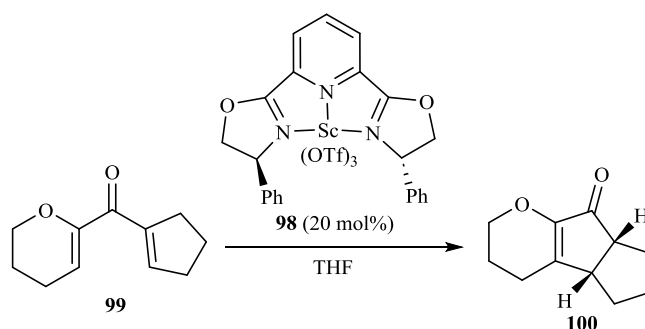


Scheme 24. Domino Nazarov/nucleophilic trapping reactions of C3-alkenyl-substituted 2-indolylmethanols with dimedone-derived enaminones.

4. METAL-/BORON-CATALYZED ENANTIOSELECTIVE NAZAROV REACTIONS

4.1. Nazarov Reactions

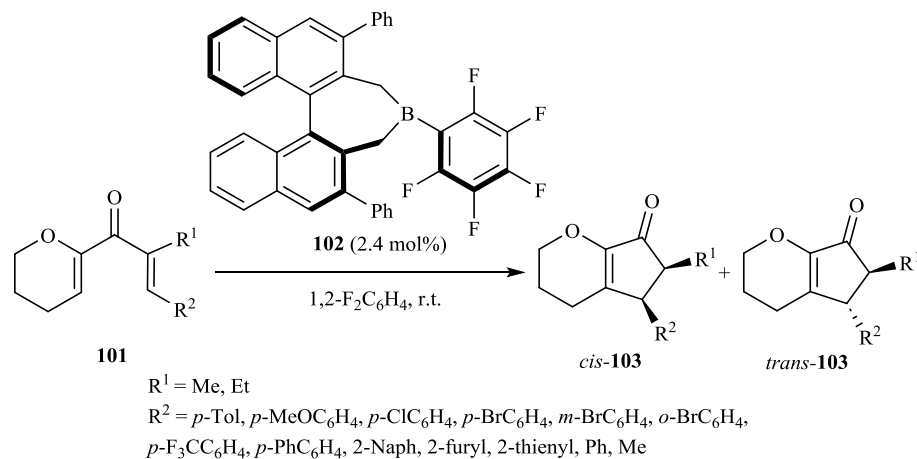
In 2003, Trauner *et al.* disclosed the first enantioselective version of the Nazarov reaction [41]. It was achieved by employing 20 mol% of chiral scandium triflate pybox complex **98** as Lewis acid in THF as solvent, as remembered in Scheme 25. Under these conditions, alkoxyalkoxydienone **99** underwent a Nazarov cyclization to afford chiral tricyclic product **100** with both moderate yield (53%) and enantioselectivity (61% ee).



Scheme 25. First catalytic asymmetric Nazarov reaction reported by Trauner *et al.* in 2003.

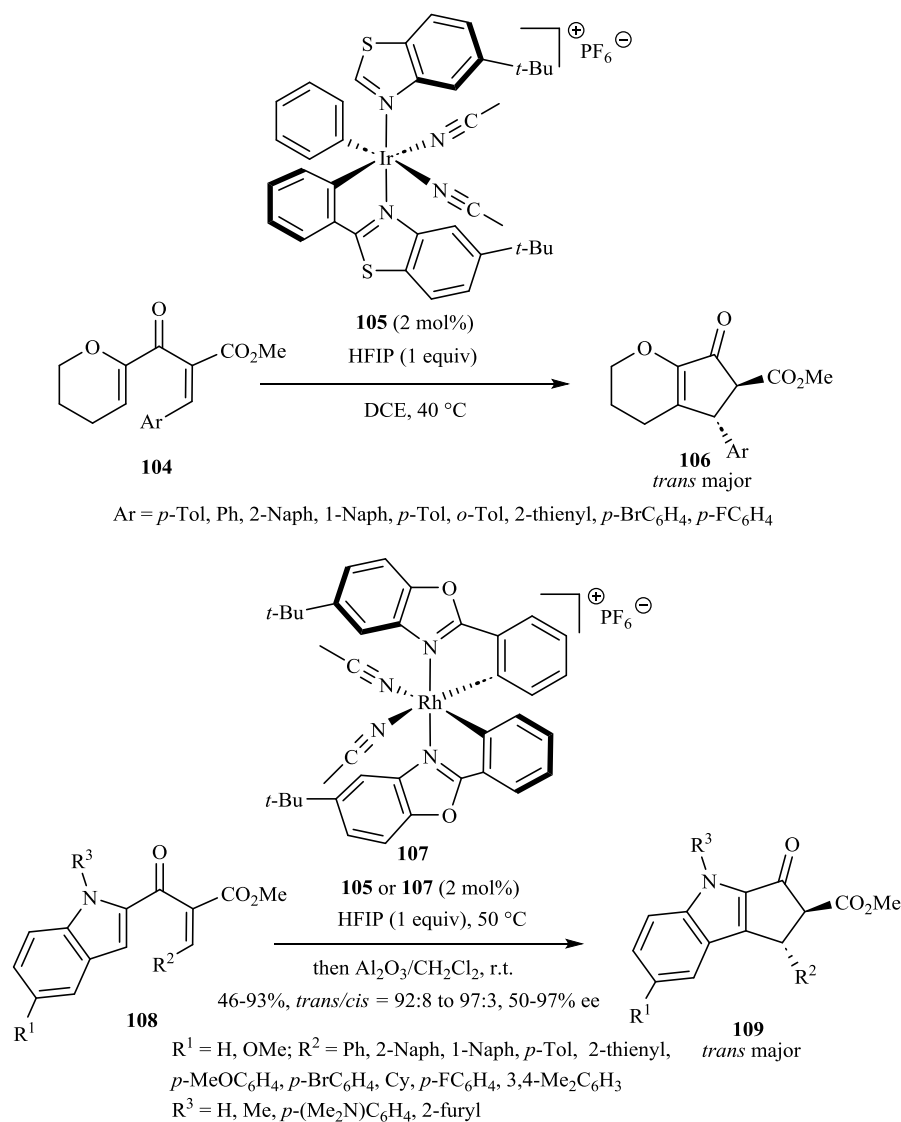
Concomitantly, Aggarwal *et al.* demonstrated that a copper complex derived from a chiral bisoxazoline ligand could catalyze the enantioselective Nazarov cyclization of divinyl ketones bearing α -ester or α -amide groups with enantioselectivities of up to 88% ee [42]. Later, other chiral bisoxazoline ligands were successfully applied in these reactions associated with different metals, such as scandium, copper, and cobalt. In addition, other metal catalysts, including chiral nickel and salen chromium complexes among others, also found success. Along with metals, chiral boron Lewis acids were employed for the first time in 2018 by Oestreich *et al.* to promote enantioselective Nazarov cyclizations [43]. They involved precisely alkoxy-activated divinyl ketones **101** as substrates which were submitted to only 2.4 mol% of a chiral sterically hindered boron catalyst **102** bearing a 3,3'-disubstituted binaphthyl backbone derived from $\text{B}(\text{C}_6\text{F}_5)_3$. The reaction carried out at room temperature in 1,2-difluorobenzene led to chiral bicyclic cyclopentenones as mixtures of *cis*- and *trans*-diastereomers **103** with 75-97% yields. The major *cis*-diastereomers were generally obtained in good *cis/trans* ratios (57:43 to 92:8) and moderate to excellent enantioselectivities (64-96% ee), as presented in Scheme 26. The

catalyst system tolerated a wide variety of (hetero)aromatic groups at R² while the presence of a methyl group at this position resulted in no diastereocontrol (*cis/trans* = 53:47). Moreover, replacing the methyl with an ethyl group at R¹ had a dramatic effect on both the enantio- and diastereoselectivities of the reaction since the ethyl-substituted corresponding product was obtained with both diminished ee values (79% ee vs 90% ee) and *cis/trans* ratios (63:37 vs 88:12). In this work, the steric hindrance exerted by the 3,3'-disubstituted binaphthyl backbone of the boron Lewis acid was found crucial for achieving a high level of enantioselectivity. Moreover, this methodology presented the advantage to involve a low quantity of catalyst (2.4 mol%).



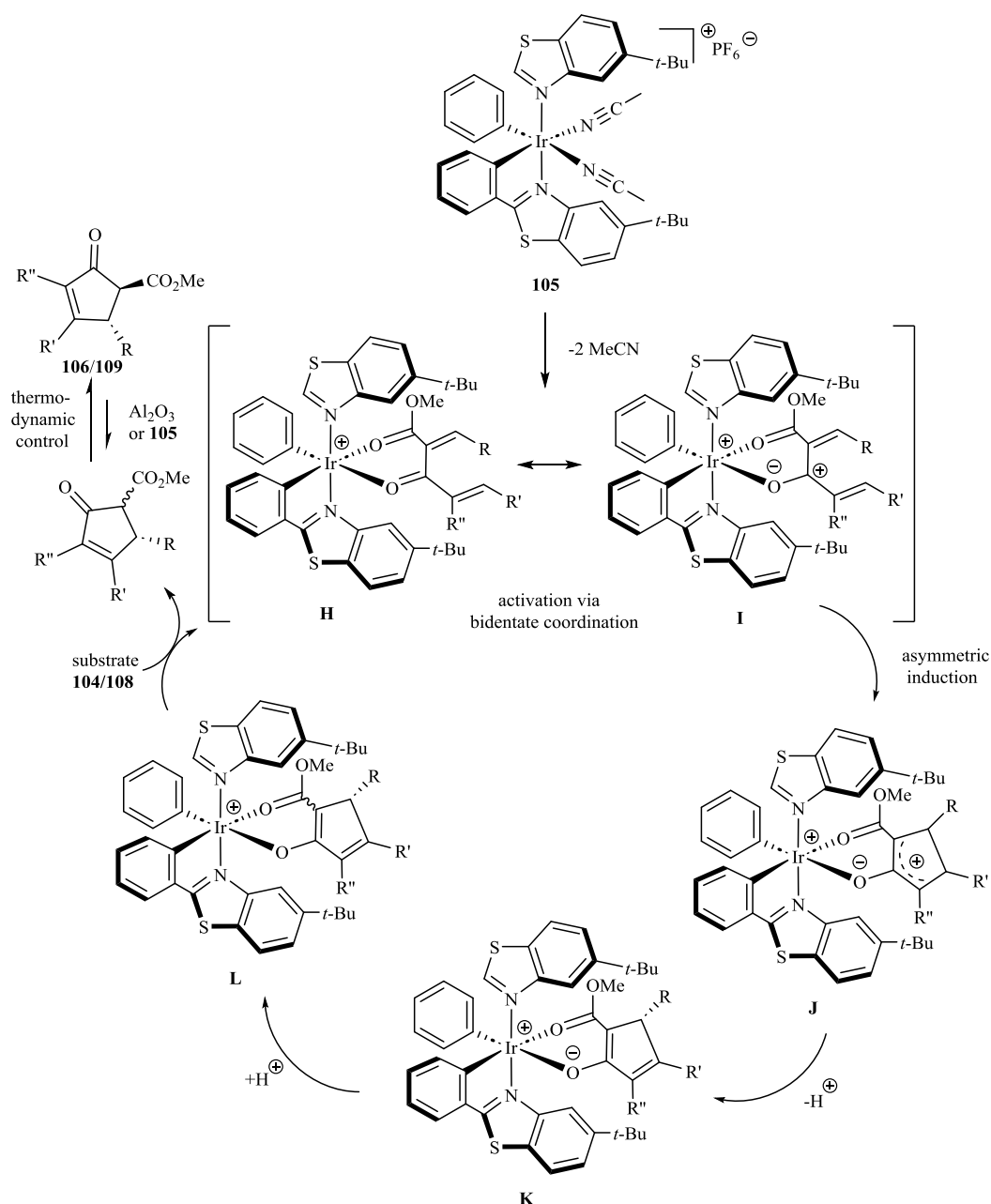
Scheme 26. Boron-catalyzed enantioselective Nazarov reaction of alkoxy-activated divinyl ketones.

Hexacoordinated octahedral iridium(III) and rhodium(III) chiral complexes recently introduced by Meggers *et al.* as a novel class of chiral catalysts, were investigated in 2018 by these authors as promoters of enantioselective Nazarov cyclizations [44]. These reactions involved a wide variety of dihydropyran- and indole-functionalized α -unsaturated β -ketoesters as substrates. In spite of the fact that all ligands were achiral, the chirality was generated through the asymmetric assembly of the cyclometalated ligands around the stereogenic metal center. These monocationic catalysts with an hexafluorophosphate ion as counterion were remarkably efficient at as low as 2 mol% of catalyst loading (Scheme 27). The enantioselective Nazarov cyclization of 9 dihydropyran-functionalized α -unsaturated β -ketoesters **104** carried out at 40 °C in DCE in the presence of HFIP as stoichiometric additive and only 2 mol% of iridium catalyst **105** led to chiral bicyclic products **106** with remarkable yields (85-98%), *trans*-diastereoselectivities (*trans/cis* = 94:6 to 98:2) and enantioselectivities (89->99% ee). Using the same catalyst or in some cases rhodium catalyst **107** at 2 mol% of catalyst loading at 50 °C allowed the enantioselective Nazarov reaction of indole-functionalized α -unsaturated β -ketoesters **108** to give chiral tricyclic products **109** with moderate to high yields (46-93%), generally excellent *trans*-diastereoselectivities (*trans/cis* = 92:8 to 97:3) and moderate to excellent ee values (50-97% ee). This novel methodology presented the advantage of a low catalyst loading (2 mol%) which should offset the high cost for iridium and rhodium. Furthermore, although the requirement for a bidentate coordination of the substrate to the catalyst limited the substrate scope to divinyl and aryl vinyl ketones exhibiting an additional coordinating ester group in β -position, the versatility of the ester group for further functionalization in combination with the observed high stereoselectivities rendered this novel procedure attractive.



Scheme 27. Iridium- and rhodium-catalyzed Nazarov reactions of dihydropyran- and indole-functionalized α -unsaturated β -ketoesters.

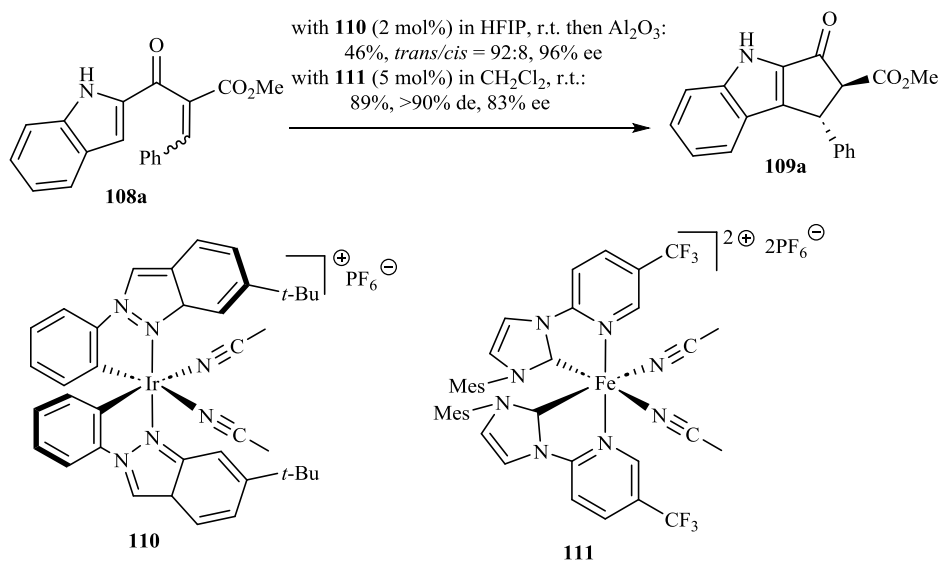
A plausible mechanism is proposed in Scheme 28, beginning with the formation of complex **H** from the O,O-bidentate coordination of the α -unsaturated β ketoester **104/108** to the iridium- or rhodium-based Lewis acid. This intermediate led to an electronic activation resonance structure **I** which underwent a conrotatory 4π -electrocyclization to afford a catalyst-bound cyclopentadienyl cation intermediate **J**, in which the asymmetric induction was provided by the helical chirality of the C₂-symmetrical Lewis acid. Subsequent deprotonation afforded intermediate **K** which upon reprotonation generated intermediate **L**. Finally, the latter released the product. In the cases of indole substrates **108**, the kinetic product was the *cis*-diastereomer, which then either slowly epimerized to the thermodynamic *trans*-diastereomer under the reaction conditions or faster in the presence of a base such as Al₂O₃.



Scheme 28. Mechanism for iridium-catalyzed Nazarov reaction of dihydropyran/indole-functionalized α -unsaturated β -ketoesters.

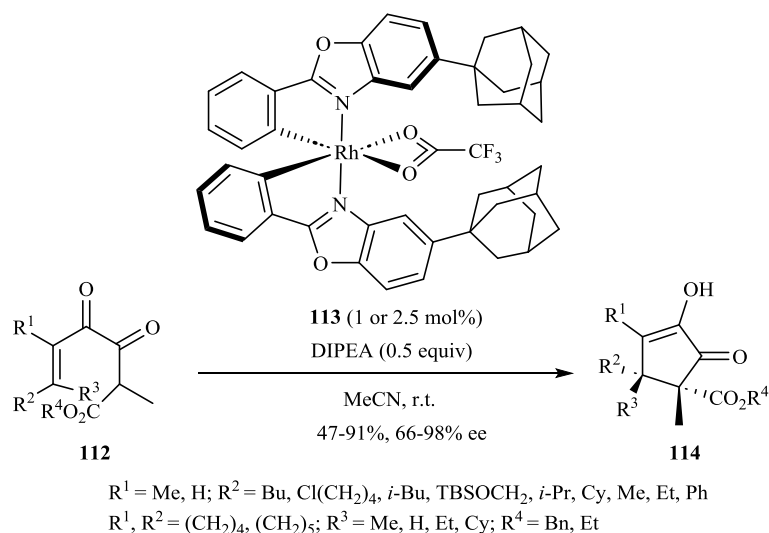
Since the nature of the ligands was demonstrated in the precedent work to affect the reactivity and stereoselectivity of the cyclometalated complexes during the catalysis, the same authors introduced in 2021 a related novel chiral iridium complex containing two inert 6-*tert*-butyl-2-phenyl-2*H*-indazole bidentate ligands in addition to two monodentate labile acetonitriles [45]. Investigated at 2 mol% of catalyst loading to promote the enantioselective Nazarov reaction of indole-functionalized α -unsaturated β -ketoester **108a**, catalyst **110** allowed chiral tricyclic product **109a** to be obtained as major *trans*-diastereomer (*trans/cis* = 92:8) with 46% yield and 96% ee (Scheme 29). Earlier in 2019, these authors introduced related chiral iron catalysts the chirality of which arisen from stereogenic iron center and not from chiral ligands, once again [46]. For example, in dicationic catalyst **111**, iron(II) was *cis*-coordinated to two achiral *N*-(2-pyridyl)-substituted *N*-heterocyclic carbene ligands through a bidentate fashion in addition to two monodentate acetonitriles. The lability of the two acetonitriles allowed asymmetric transition metal catalysis to be achieved as for iridium and rhodium complexes of the precedent studies (Schemes 27-28). This more economic iron catalyst **111** was successfully applied at 5 mol% of catalyst loading to promote at room temperature in dichloromethane as solvent the enantioselective Nazarov

cyclization of indole-functionalized α -unsaturated β -ketoester **108a** into chiral Nazarov product **109a** obtained as single *trans*-diastereomer (>90% de) in 89% yield and 83% ee (Scheme 29).

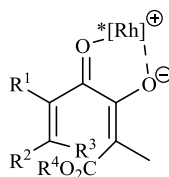


Scheme 29. Iridium/iron-catalyzed Nazarov reaction of an indole-functionalized α -unsaturated β -ketoester.

To develop a novel and rare access to chiral cyclopentenones exhibiting vicinal all-carbon quaternary stereocenters, Tius *et al.* described in 2023 an asymmetric rhodium-catalyzed Nazarov reaction of simple diketoesters **112** (Scheme 30) [47]. The methodology employed chiral rhodium catalyst **113** at generally only 1 mol% of catalyst loading in acetonitrile or 3.6:1 mixture of acetonitrile and DMSO at room temperature and required the use of a substoichiometric quantity (0.5 equiv) of a tertiary base such as DIPEA. Under these conditions, the Nazarov cyclization of a wide range of α -ketoenones **112** led to chiral cyclopentenones **114** bearing either vicinal quaternary stereocenters or contiguous quaternary and tertiary stereocenters. These functionalized cyclic products were obtained with 47-91% yields and in most cases high ee values (66-98% ee). The authors proposed the formation of a bidentate rhodium enolate that is depicted in Scheme 30. In addition to involving an extremely low catalyst loading (1 mol%), this novel methodology constituted a very rare example of a catalytic asymmetric Nazarov cyclization generating two contiguous all-carbon quaternary stereocenters with high levels of enantioselectivity.



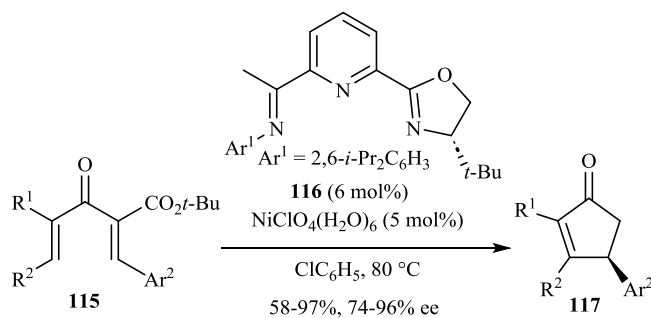
bidentate rhodium intermediate:



Scheme 30. Rhodium-catalyzed Nazarov reaction of diketoesters in the presence of DIPEA.

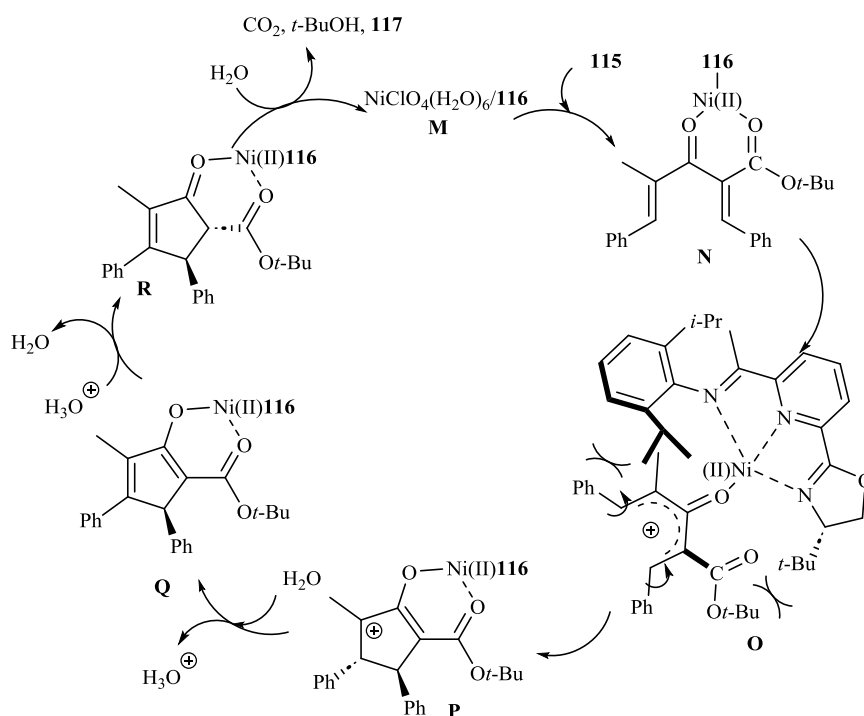
4.2. Nazarov-Based Domino Reactions

In 2018, Lu and Zhang developed enantioselective nickel-catalyzed domino Nazarov/decarboxylation reactions of divinyl ketones **115** bearing an α -*tert*-butyl ester [48]. Along with Pybox ligands, chiral oxazoline iminopyridine **116** was selected as optimal in combination with $\text{NiClO}_4 \cdot 6\text{H}_2\text{O}$ as precatalyst when employed at 6 mol% and 5 mol% of respective catalyst loadings. Performing the reaction at 80 °C in chlorobenzene as solvent, the one-pot process afforded chiral cyclopentenones **117** with 58-97% yields and generally high enantioselectivities (74-96% ee), as illustrated in Scheme 31. Indeed, the catalyst system tolerated a wide variety of (hetero)aromatic substituents at R^2 , allowing the desired products to be obtained in uniformly high ee values (81-96% ee) while the reaction of a cyclic vinyl alkyl ketone ($\text{R}^1, \text{R}^2 = (\text{CH}_2)_4$) afforded the corresponding product with a lower enantioselectivity (74% ee). A possible mechanism is depicted in Scheme 31 in which the divinyl ketone ($\text{R}^1 = \text{R}^2 = \text{Ph}$) coordinated to the chiral nickel catalyst **M** to give intermediate **N** which converted to its resonance structure **O**. The latter presented a steric hindrance between the *tert*-butyl or isopropyl group of the ligand and the alkene substituted phenyl rings which determined the stereochemical outcome of the following Nazarov cyclization leading to intermediate **P**. With the assistance of water, **P** was subsequently submitted to deprotonation to give complex **Q** which could transform into **R** through protonation. Finally, decarboxylation in the presence of water afforded the product.



$R^1 = \text{Me, Ph}$; $R^1, R^2 = (\text{CH}_2)_4$; $R^2 = \text{Ph, } p\text{-Tol, } p\text{-PhC}_6\text{H}_4, 3,4,5\text{-(MeO)}_3\text{C}_6\text{H}_3,$
 $p\text{-O}_2\text{NC}_6\text{H}_4, 2\text{-thienyl}$; $\text{Ar}^2 = \text{Ph, } p\text{-Tol, } p\text{-MeOC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4,$
 $p\text{-F}_3\text{CC}_6\text{H}_4, p\text{-MeO}_2\text{CC}_6\text{H}_4, p\text{-Et}_2\text{NOCC}_6\text{H}_4, p\text{-AcOC}_6\text{H}_4, p\text{-O}_2\text{NC}_6\text{H}_4, p\text{-NCC}_6\text{H}_4,$
 $2\text{-Naph, } m\text{-Tol, } m\text{-ClC}_6\text{H}_4, o\text{-Tol, } o\text{-MeOC}_6\text{H}_4, o\text{-FC}_6\text{H}_4, 1\text{-Naph, } \text{MeO-N}$

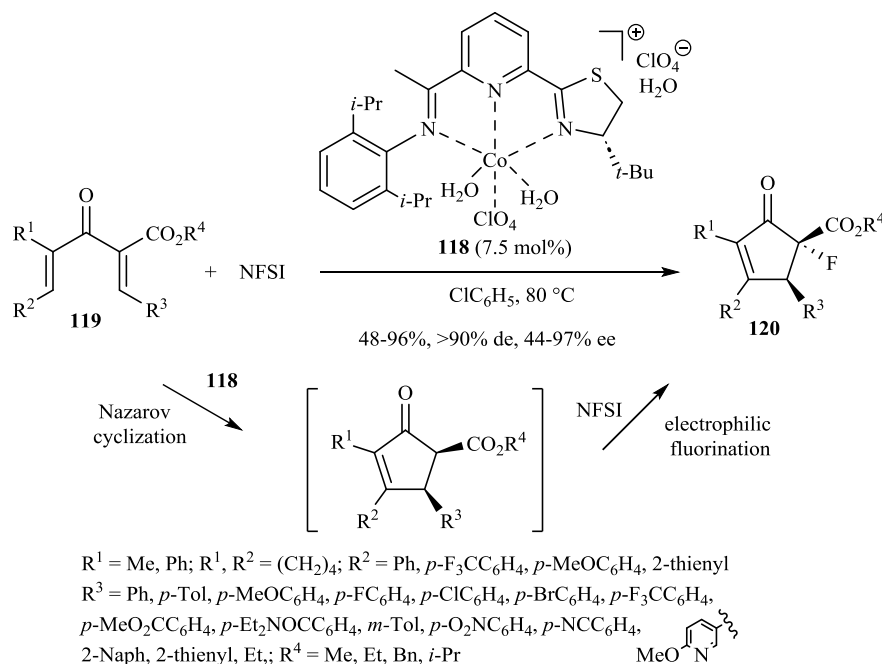
proposed mechanism (with $R^1 = \text{Me, } R^2 = \text{Ar}^2 = \text{Ph}$):



Scheme 31. Nickel-catalyzed domino Nazarov/decarboxylation reaction of divinyl ketones bearing an α -*tert*-butyl ester.

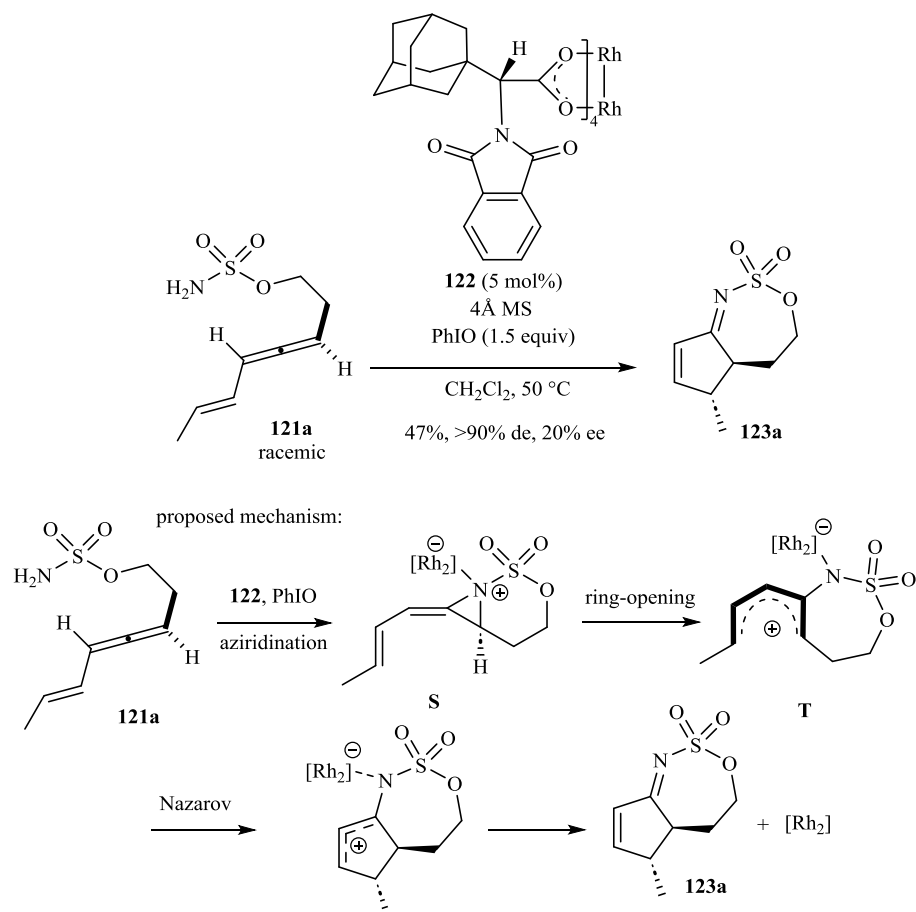
The same authors also designed a novel related chiral thiazoline iminopyridine ligand which was reacted in THF at room temperature with $\text{Co}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ as precatalyst to prepare chiral cobalt catalyst **118** [49]. The latter complex was demonstrated as an efficient promoter of a novel enantioselective domino Nazarov/electrophilic fluorination reaction of α -alkyl ester divinyl ketones **119** with *N*-fluorobenzenesulfonimide (NFSI) as fluorinating agent (Scheme 32). Carried out at 80 °C in chlorobenzene in the presence of 7.5 mol% of catalyst **118**, the one-pot reaction afforded a wide range of chiral α -fluorocyclopentenones **120** bearing a fluorine-substituted quaternary stereocenter as almost single diastereomers (>90% de) with 48-96% yields and 44-97% ee. Notably, this study represented the first asymmetric fluorination of cyclopentenone derivatives. The catalyst loading was compatible with aromatic groups at R^3 exhibiting various substituents on the phenyl ring regardless of their position and electronic properties, which provided the products with 91-96% yields and 81-97% ee. In addition, heterocycles and polycycle, such as 2-thienyl, 3-pyridyl, and 2-naphthyl groups, were also well tolerated. Interestingly, substrates bearing cyclohexyl ($R^1, R^2 = (\text{CH}_2)_4$) and ethyl ($R^3 = \text{Et}$) groups could

afford the desired products in moderate yields (50 and 48%, respectively) with decreased enantioselectivities (73 and 44% ee, respectively).



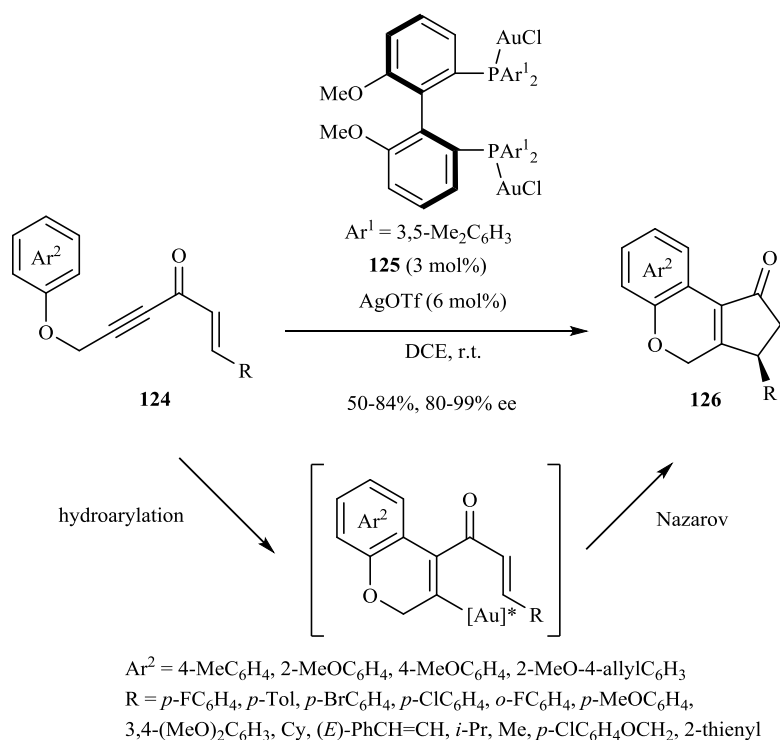
Scheme 32. Cobalt-catalyzed domino Nazarov/fluorination reaction of α -alkyl ester divinyl ketones.

In 2020, Schomaker and Fernandez described stereocontrolled rhodium-catalyzed domino allene aziridination/ring-opening/Nazarov reactions of racemic eneallenes **121** in the presence of PhIO [50]. The authors developed an enantioselective version by promoting the reaction at 50 °C in dichloromethane as solvent with 5 mol% of chiral dinuclear rhodium catalyst **122** (Scheme 33). The reaction of racemic eneallene **121a** afforded enantio-enriched α,β -iminocyclopentene **123a** as an almost single diastereomer (>90% de) in a moderate yield (47%) and a low enantioselectivity (20% ee). The authors suggested the formation of strained methyleneaziridine intermediate **S** which was further submitted to ring-opening to give 2-amidopentadienyl cation **T**. The latter species subsequently underwent a Nazarov reaction to furnish the final bicyclic product. In spite of its low enantioselectivity, this novel strategy presented the advantages to allow improved reactivity compared to 3-pentadienyl cations, control over the ultimate position of the alkene, and high diastereoselectivity.



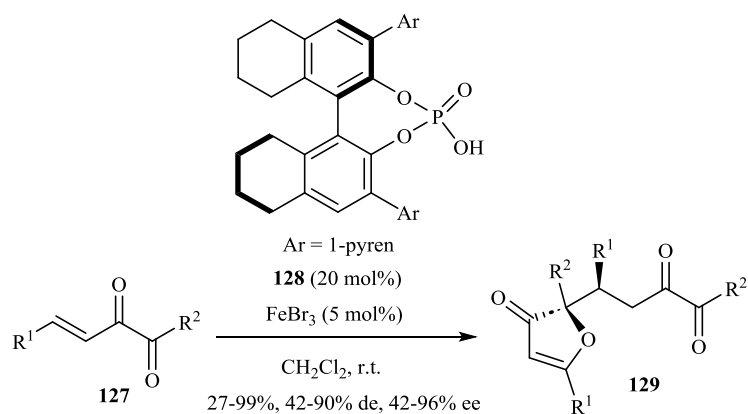
Scheme 33. Rhodium-catalyzed domino allene aziridination/ring-opening/Nazarov reaction of a racemic eneallene.

In 2022, an enantioselective gold-catalyzed domino hydroarylation/Nazarov reaction of alkenynones **124** was disclosed by Sanz *et al.* [51]. The reaction was promoted at room temperature by 3 mol% of chiral dinuclear gold catalyst **125** in DCE in the presence of AgOTf as an additive. Successive hydroarylation and Nazarov cyclization allowed a series of chiral cyclopentenones **126** to be synthesized with 50-84% yields and 80-99% ee (Scheme 34).



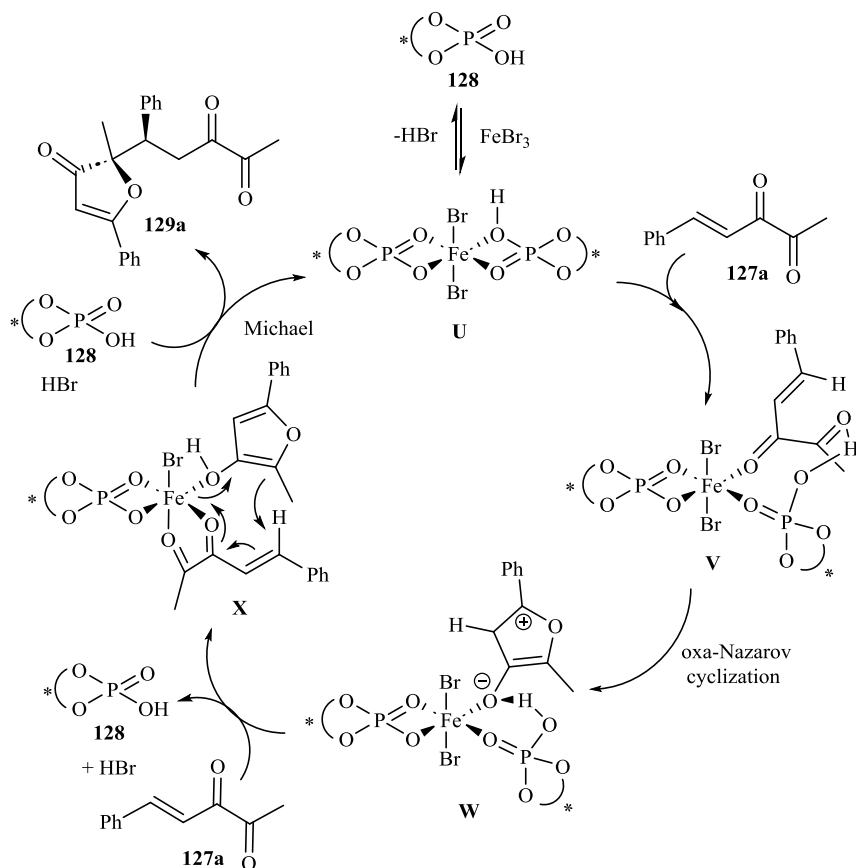
Scheme 34. Gold-catalyzed domino hydroarylation/Nazarov reaction of alkenynes.

In 2023, Lv *et al.* described the first enantioselective domino oxa-Nazarov/Michael reaction of conjugated 1,2-diketones **127** based on an asymmetric binary-acid catalysis with FeBr_3 and a chiral phosphoric acid (Scheme 35) [52]. Indeed, in the presence of 5 mol% of FeBr_3 and 8 mol% of chiral phosphoric acid **128** in dichloromethane as solvent, a range of conjugated 1,2-diketones **127** underwent regioselectively at room temperature an asymmetric iron-catalyzed domino oxa-Nazarov/Michael reaction which afforded chiral 3(2H)-furanones **129** as major *syn*-diastereomers with 27-99% yields, and generally both high diastereo- (42-90% de) and enantioselectivities (42-96% ee). Actually, γ -aryl α -diketones all reacted with good to excellent yields (63-99%) while a γ -alkyl α -diketone ($\text{R}^1 = \text{Cy}$) provided the corresponding product in only 27% yield combined with 64% ee. The products were obtained with uniformly high ee values (84-96% ee) except that derived from the reaction of (*E*)-1,4-diphenylbut-3-ene-1,2-dione ($\text{R}^1 = \text{R}^2 = \text{Ph}$) which was obtained with only 42% ee probably due to the bulky phenyl substituent. A mechanism is illustrated in Scheme 35, beginning with the formation of iron complex **U** from FeBr_3 and chiral phosphoric acid **128**. In the presence of iron complex **U**, the α -diketone is activated to form iron complex **V**, which underwent a 4π electrocyclicization and 1,2-H shift to give the carbocationic enolate intermediate **W**. The latter was subsequently treated with a second equivalent of α -diketone to form intermediate **X** through dissociation of the phosphoric acid and HBr. In the presence of these two free Brønsted acids, the Michael addition occurred to afford the final domino product along with regeneration of the active binary acid catalyst **U**.



$\text{R}^1 = \text{Ph}, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4,$
 $p\text{-Tol}, p\text{-MeOC}_6\text{H}_4, p\text{-PhC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, m\text{-F}_3\text{CC}_6\text{H}_4,$
 $m\text{-Tol}, m\text{-MeOC}_6\text{H}_4, o\text{-FC}_6\text{H}_4, o\text{-ClC}_6\text{H}_4, o\text{-Tol}, o\text{-MeOC}_6\text{H}_4,$
 $3,5\text{-Me}_2\text{C}_6\text{H}_3, 2\text{-thienyl}, 1\text{-Naph}, \text{Cy}; \text{R}^2 = \text{Me}, \text{Et}, n\text{-C}_{10}\text{H}_{21}, i\text{-Pr}, \text{Ph}$

proposed mechanism (with $\text{R}^1 = \text{Ph}, \text{R}^2 = \text{Me}$):

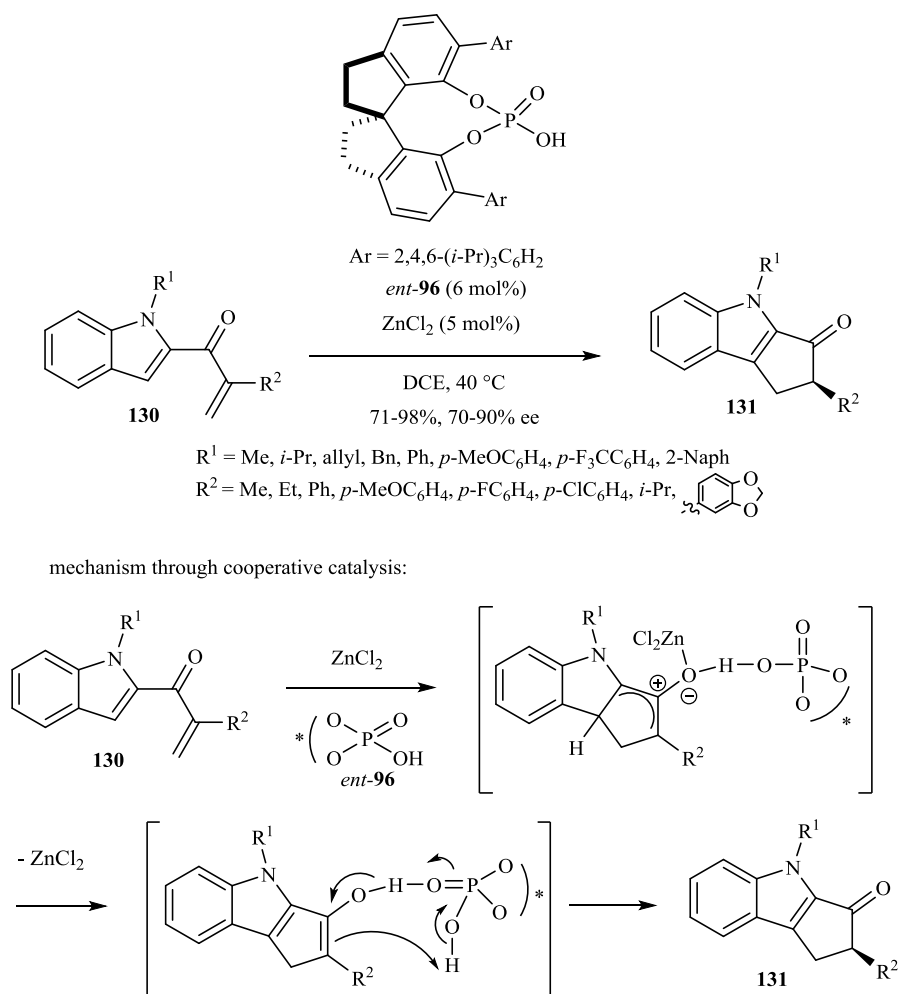


Scheme 35. Iron-catalyzed domino oxa-Nazarov/Michael reaction of conjugated 1,2-diketones.

5. MULTICATALYTIC ENANTIOSELECTIVE NAZAROV REACTIONS

5.1. Nazarov Reactions

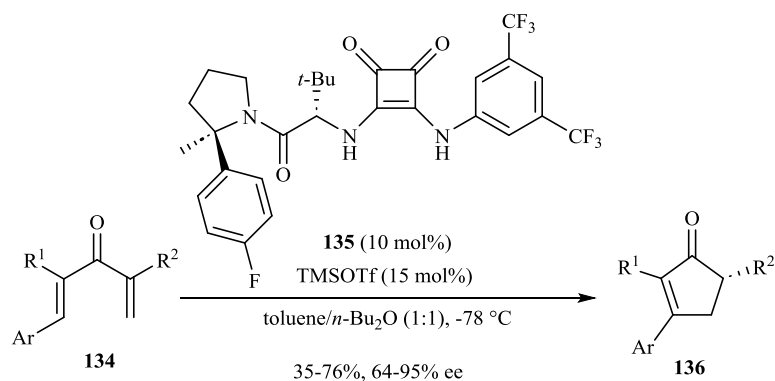
The combination of different catalysts, such as chiral organocatalysts with metal catalysts, attracts great attention from chemists [53]. In 2017, this methodology was applied by Zhou and Zhu to promote enantioselective Nazarov cyclizations of indole enones **130** (Scheme 36) [54]. A combination of 5 mol% of ZnCl_2 with 6 mol% of chiral spirocyclic phosphoric acid *ent*-**96** cooperatively catalyzed these reactions at 40 °C in DCE to afford chiral cyclopenta[b]indoles **131** in 71-98% yields and 70-90% ee. The cooperative catalysis with chiral phosphoric acid *ent*-**96** as Brønsted acid and ZnCl_2 as Lewis acid is illustrated in this Scheme. This study constituted a rare example of cooperative catalysis involving zinc and a chiral organocatalyst. Furthermore, this procedure constituted the first enantioselective construction of cyclopenta[b]indoles with chiral tertiary α -carbons *via* Nazarov cyclization of indole enones with only one coordinating site.



Scheme 36. Nazarov reaction of indoles in the presence of a cooperative dual Zn/phosphoric acid catalysis.

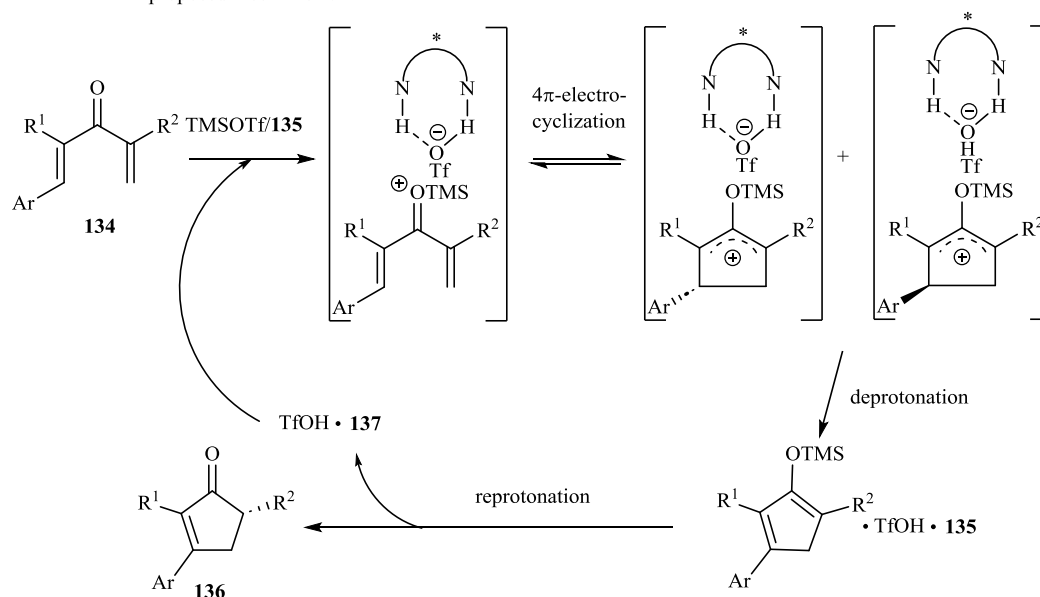
To avoid unselective placement of the cyclopentenone double bond and cationic rearrangements often observed in Nazarov reactions, Denmark *et al.* described in the 1980s a variation of the Nazarov reaction based on the use of silyl substituted divinyl ketones as substrates [55]. The placement of the double bond in the thermodynamically less stable position in the final product was controlled by the stabilization associated with a positive charge β to the silicon atom. Furthermore, side reactions of the cationic intermediates, such as rearrangements, were avoided thanks to the ability of silicon to serve as an electrofugal leaving group. In 2021, Zhu *et al.* reported the first highly enantioselective silicon-directed Nazarov reaction which was cooperatively catalyzed by a Lewis acid and a chiral Brønsted acid (Scheme 37) [56]. Indeed, the Nazarov cyclization of

variously substituted β -silyl dienones **132** catalyzed by a combination of 6 mol% of chiral spirocyclic phosphoric acid *ent*-**96** and 5 mol% of $\text{Zn}(\text{OTf})_2$ afforded at 40 or 50 °C in DCE in the presence of 1.1 equivalent of phenol as a superstoichiometric additive the desired chiral multifunctionalized cyclopentenones **133** with 47-97% yields and 65-98% ee. The position of the double bond in the product was found to be directed by the stabilization of the β -carbocation of the intermediate by the silicon group in the dienone substrate. Brønsted and Lewis acids synergistically activated the dienone, and the enantioselectivity of the reaction arose from a chiral Brønsted acid-promoted proton shift of the enol intermediate, as shown in the mechanism depicted in Scheme 37. The substrate activated by $\text{Zn}(\text{OTf})_2$ and PhOH underwent a 4π -electrocyclization reaction to give two possible carbocationic enol intermediates **Y** and **AA** exhibiting the TMS group in respective *cis* or *trans* configuration toward the coordinated phenol. In the *cis*-configured intermediate **Y**, an intramolecular attack of the phenol to the TMS group occurred to give a free enol intermediate **Z**. Then, protonation of the latter species by the chiral phosphoric acid catalyst through transition state **TS-1** generated the final cyclopentenone. However, in the case of the *trans*-configured intermediate **AA**, elimination of the TMS group most likely assisted with another phenol generated zinc enolate intermediate **AB** and an oxonium of phenol. Because of the high acidity of the latter species, it could protonate the zinc enolate without the assistance of the chiral phosphoric acid catalyst as in transition state **TS-1'**, which provided a low enantioselectivity. Since different silyl groups as well as their initial configurations could lead to different ratios of **Y** to **AA**, the two possible pathways a and b could explain the significant silyl effect on the enantioselectivity of the reaction.



$R^1 = \text{Me, Et}$; $\text{Ar} = \text{Ph, } p\text{-Tol, } m\text{-Tol, } p\text{-FC}_6\text{H}_4, m\text{-FC}_6\text{H}_4, o\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, m\text{-MeOC}_6\text{H}_4, 2\text{-Naph}$; $R^2 = \text{Ph, } p\text{-FC}_6\text{H}_4, o\text{-FC}_6\text{H}_4, p\text{-Tol, } m\text{-Tol, Me}$

proposed mechanism:

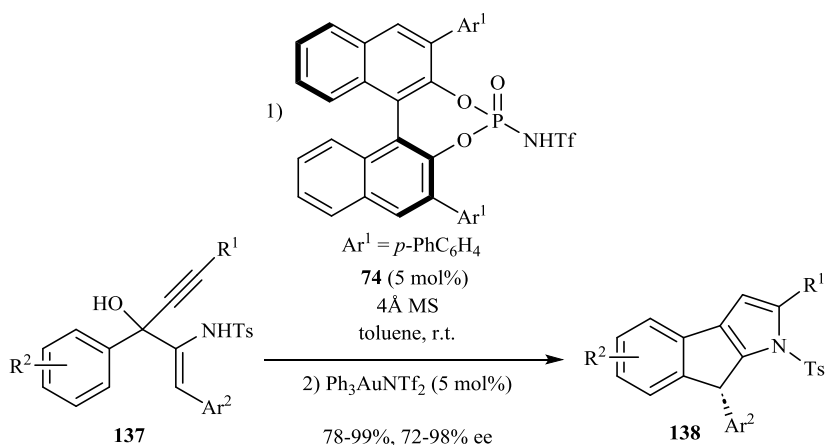


Scheme 38. Nazarov reaction of unactivated divinyl ketones in the presence of a cooperative dual squaramide/TMSOTf catalysis.

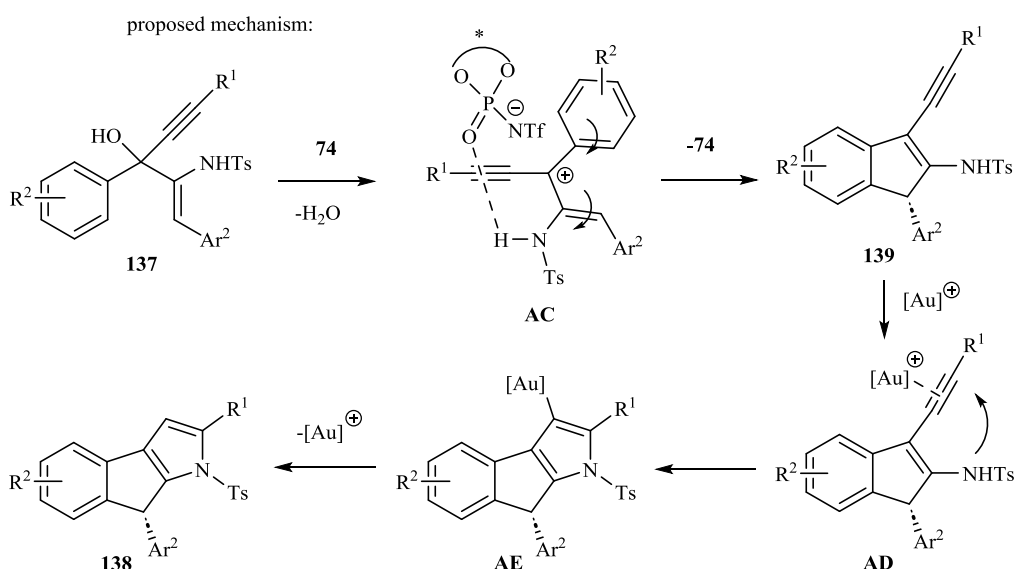
5.2. Nazarov-Based Domino/Tandem Reactions

In 2018, Chan *et al.* described an enantioselective tandem dehydrative Nazarov-type electrocyclization/hydroamination reaction of electron-rich β -amino-1,4-enyols **137**, which was sequentially promoted by a chiral Brønsted acid and a gold catalyst (Scheme 39) [58]. When these substrates were submitted at room temperature to 5 mol% of chiral BINOL-derived *N*-triflylphosphoramidate **74** in toluene as solvent, they underwent a Nazarov-type cyclization which generated chiral 1H-indene product **138**. Then, the latter was treated with 5 mol% of $\text{Ph}_3\text{PAuNTf}_2$ which triggered an hydroamination to afford final chiral 1,8-dihydroindeno[2,1-b]pyrroles **139** with 78-99% yields and 72-98% ee. This novel class of products exhibiting both the privileged pyrrole and 1H-indene scaffolds constitute potential molecules for medicinal chemistry. Comparable results were achieved whatever the nature of the substituents, spanning from (hetero)aryl to aliphatic ones (R^1). A plausible mechanism is depicted in Scheme 39, beginning with the formation of the chiral ion-pair intermediate **AC** exhibiting hydrogen bonding interactions between the catalyst anion and the amino group of the substrate cation. This arose from the dehydration of the substrate in the presence of the organocatalyst and combination of the *N*-triflyl phosphoramidate anion with the ensuing carbocation species. Then, a Nazarov-type cyclization occurred to give chiral 1H-indene adduct **139**. Subsequent activation of the

alkyne moiety with gold(I) salt generated intermediate **AD**, which further underwent hydroamination to give intermediate **AE**. Final protodeauration of the latter species delivered the final product.



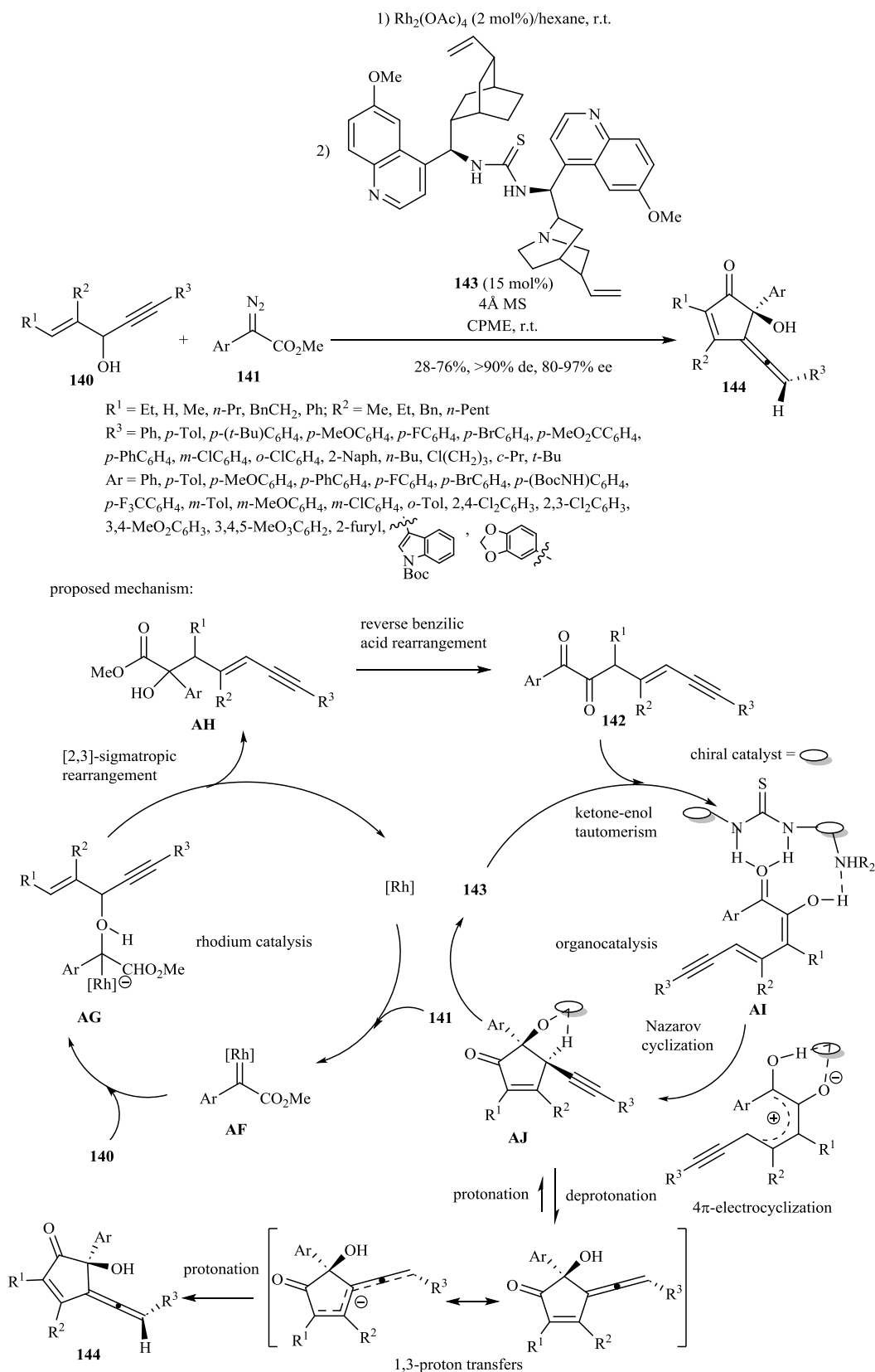
$\text{R}^1 = o\text{-Tol}, m\text{-Tol}, p\text{-Tol}, p\text{-FC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-PentC}_6\text{H}_4, n\text{-Bu}, c\text{-Pr}, c\text{-Pent}, \text{CH}_2=\text{C}(\text{Me}), 2\text{-cyclohexenyl}, 2\text{-thienyl}, \text{Ph}, \text{BnCH}_2$
 $\text{R}^2 = 6\text{-OMe}, 6\text{-Me}, 6\text{-OBn}, 6\text{-Cl}, 6\text{-F}, 5\text{-Cl}, 4\text{-F}, 5\text{-F}$
 $\text{Ar}^2 = \text{Ph}, o\text{-Tol}, p\text{-Tol}, p\text{-BrC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, 1\text{-Naph}, 2\text{-thiophenyl}$



Scheme 39. Tandem dehydrative Nazarov/hydroamination reaction of β -amino-1,4-enynols in the presence of a sequential dual *N*-triflylphosphoramidate/Au catalysis.

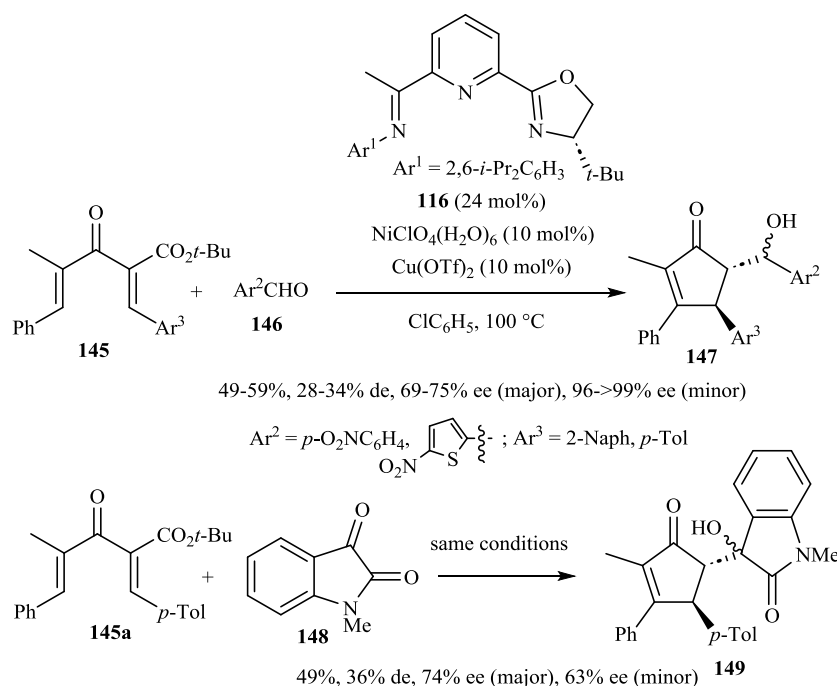
With the aim of developing novel classes of substrates to be used in enantioselective Nazarov reactions, Tang, Sun *et al.* investigated for the first time in 2022 1,4-enyne alcohols **140** (Scheme 40) [59]. Under a metal/organocatalyst relay catalyst system, these substrates were found to react with diazo compounds, such as diazoacetates **141**, through a tandem rhodium-catalyzed rearrangement/organocatalyzed-Nazarov reaction. The first reaction was catalyzed in hexane at room temperature by 2 mol% of $\text{Rh}_2(\text{OAc})_2$ to give the real Nazarov candidates that were enyne diketone intermediates **142**. The latter species were then treated in CPME as solvent by 15 mol% of cinchona-alkaloid-derived chiral thiourea **143** which triggered the final Nazarov cyclization, thus affording chiral allene cyclopentenones **144** as almost single diastereomers (>90% de) in variable yields (28-76%) combined with uniformly high enantioselectivities (80-97% ee). The mechanism of the tandem process is detailed in Scheme 40, beginning with the generation of rhodium carbene species **AF** from the reaction between $\text{Rh}_2(\text{OAc})_2$ and diazoacetate **141**. Subsequent nucleophilic addition of 1,4-enyne alcohol **140** to intermediate **AF** resulted in the formation of ylide intermediate **AG**, which then underwent a [2,3]-sigmatropic rearrangement to give intermediate **AH**. The latter generated 1,2-diketone-enyne **142** via reverse benzylic acid rearrangement. Exposing **142** to the organocatalyst produced intermediate **AI** via hydrogen-bonding and keto-enol tautomerism

Then, intramolecular Nazarov cyclization delivered the cyclopentenone alkyne intermediate **AJ**. Finally, an alkyne-to-allene isomerization occurred to give the final product.



Scheme 40. Tandem rearrangement/Nazarov reaction of 1,4-enyne alcohols with diazoacetates in the presence of a sequential dual Rh/thiourea catalysis.

The combined use of two metal catalysts still remains generally less developed in organic chemistry than the combination of organocatalysts with metal catalysts [60]. In particular, asymmetric dual metal catalysis is still not widely developed, probably owing to the fact that the presence of multiple metal catalysts leads to the competitive coordination of metals with the chiral ligand used, which makes the chiral environment unpredictable. In 2018, Lu and Zhang reported a diastereoselective nickel/copper cocatalyzed domino Nazarov/decarboxylative aldol reaction of α -*tert*-butyl ester divinyl ketones **145** with aldehydes **146** to deliver racemic β -hydroxycyclopentenones **147** with three contiguous stereocenters with 38-74% yields and 75->90% de [61]. This process was performed in chlorobenzene at 100 °C with 24 mol% of a racemic oxazoline iminopyridine combined with 10 mol% of Cu(OTf)₂ and the same quantity of Ni(ClO₄)₄·6H₂O as catalyst system. An asymmetric version of this domino reaction was developed in a second time by using enantiopure ligand **116** under the same reaction conditions (Scheme 41). However, poor diastereoselectivities (28-34% de) combined with moderate to good yields (49-59%) were observed in this enantioselective reaction of α -*tert*-butyl ester divinyl ketones **145** with aldehydes **146** to give **147** as a mixture of two diastereomers. Additionally, the chiral major diastereomers were obtained with moderate enantioselectivities (69-75% ee). Surprisingly, the corresponding minor diastereomers were obtained with 96->99% ee. This phenomenon could reflect the fact that the enantioselectivity was determined in the Nazarov cyclization, and that there was a strong mismatched effect for the decarboxylative aldol step. The scope of the reaction was extended to isatin derivative **148** which reacted with α -*tert*-butyl ester divinyl ketone **145a**, leading to product **149** with 49% yield, 36% de, and 74% ee and 63% ee for the major and minor diastereomers, respectively. This study represented a very rare example of domino Nazarov-based reactions promoted by a dual metal catalysis.



Scheme 41. Domino Nazarov/decarboxylative aldol reactions of α -*tert*-butyl ester divinyl ketones with aldehydes/isatin derivative in the presence of a sequential dual Ni/Cu catalysis.

CONCLUSION

As demonstrated in this review, a range of interesting developments have been achieved in the last seven years in the field of asymmetric Nazarov reactions, such as many applications of various types of chiral auxiliaries especially in the total synthesis of important natural and bioactive products. In the context of enantioselective catalyzed reactions, the requirement of using activated dienones as substrates could be avoided in a Nazarov cyclization of challenging simple, acyclic, aliphatic substituted divinyl ketones published by List *et al.*, which employed a confined imidodiphosphorimidate organocatalyst, allowing the corresponding chiral cyclopentenones to be obtained as single diastereomers with up to 98% ee. Along with organocatalyzed

reactions, the first enantioselective boron-catalyzed Nazarov reaction was described by Oestreich *et al.* with up to 96% ee. In the area of enantioselective metal-catalyzed Nazarov reactions, Meggers *et al.* described enantioselectivities of >99% ee by using a novel type of chiral iridium/rhodium catalysts bearing achiral benzoxazole/benzothiazole/indazole ligands the chirality of which being the result of a stereogenic metal center and not from chiral ligands. Comparable and more economic iron complexes bearing achiral N-heterocyclic carbene ligands were also successfully applied to promote these reactions with up to 83% ee. Furthermore, several types of dual catalysis were found to be efficient catalyst systems. For example, the Nazarov cyclization of indoles was achieved by Zhou and Zhu in the presence of a cooperative dual Zn/phosphoric acid catalysis with up to 90% ee. Moreover, a cooperative dual squaramide/TMSOTf catalysis was successfully applied by Jacobsen *et al.* to promote the Nazarov reaction of unactivated divinyl ketones with 95% ee. In addition to simple Nazarov cyclizations, a wide diversity of asymmetric domino/tandem Nazarov-based reactions have been developed, allowing more complex chiral molecules to be synthesized in one-pot procedures. In spite of these recent successes, it must be recognized that a truly general asymmetric Nazarov methodology, either chiral auxiliary-controlled or catalytic, is still missing. In most cases, the requirement of using activated dienones constitutes a limitation in the procedures. Finally, more efforts in the future will focus on the development of novel catalytic systems for the sake of atom economy, since chiral auxiliary-controlled reactions still remain the more employed.

LIST OF ABBREVIATIONS

Ar = Aryl
BINOL = 1,1'-bi-2-naphthol
Bn = Benzyl
Boc = *tert*-butoxycarbonyl
Bz = Benzoyl
CPME = Cyclopentyl Methyl Ether
Cy = Cyclohexyl
DCE = 1,2-dichloroethane
de = Diastereomeric Excess
DIPEA = Diisopropylethylamine
DMAP = 4-dimethylaminopyridine
ee = Enantiomeric Excess
Hex = Hexyl
HFIP = Hexafluoro-2-propanol
HMDS = Hexamethyldisilazane
Mes = Mesityl
MOM = Methoxymethyl
MS = Molecular Sieves
Naph = Naphthyl
NFSI = *N*-fluorobenzenesulfonimide
Nph = Naphthalimide
Nu = Nucleophile
Pent = Pentyl
PMB = *para*-methoxybenzyl
r.t. = Room Temperature
TBS = *tert*-butyldimethylsilyl
TES = Triethylsilyl
Tf = Trifluoromethanesulfonyl
THF = Tetrahydrofuran
TIPS = Triisopropylsilyl
TMS = Trimethylsilyl
Tol = Tollyl
TPP = Triphenylphosphonium
Ts = 4-toluenesulfonyl (tosyl)

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

Dr. Helene Pellissier is on the Editorial Advisory Board of the journal COC.

ACKNOWLEDGEMENTS

This work was supported by the National Centre for Scientific Research: CNRS.

REFERENCES

- [1] Simeonov, S. P.; Nunes, J. P. M.; Guerra, K.; Kurteva, V. B.; Afonso, C. A. M. Synthesis of Chiral Cyclopentenones. *Chem. Rev.*, **2016**, *116*, 5744–5893.
- [2] Nazarov, I.N.; Zaretskaya, I.I. Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya. *Izv. Akad. Nauk. SSSR, Ser. Khim.*, **1941**, 211–224.
- [3] (a) Woodward, R. B. *Chem. Soc. Special Publication N°21*, **1967**, 237–239. (b) Shoppee, C. W.; Lack, R. E. *J. Chem. Soc.* **1969**, 1346–1349. (c) Shoppee, C. W.; Cooke, B. J. A. *J. Chem. Soc., Perkin Trans. I* **1972**, 2271–2276. (d) Shoppee, C. W.; Cooke, B. J. A. *J. Chem. Soc., Perkin Trans. I* **1973**, 1026–1032.
- [4] Vinogradov, M. G.; Turova, O. V.; Zlotin, S. G. Nazarov reaction: current trends and recent advances in the synthesis of natural compounds and their analogs. *Org. Biomol. Chem.*, **2017**, *15*, 8245–8269.
- [5] (a) Santelli-Rouvier, C.; Santelli, M. The Nazarov Cyclization. *Synthesis*, **1983**, 429–442. (b) Denmark, S. E. *Comprehensive Organic Synthesis*, Vol. 5, Paquette, L. A., Ed., Pergamon Press, Oxford, **1991**, pp. 751–784. (c) Habermas, K. L.; Denmark, S. E. *Org. React.* **1994**, *45*, 11971, p. 1–158. (d) Pellissier, H. Recent developments in the Nazarov process. *Tetrahedron*, **2005**, *61*, 6479–6517. (e) Grant, T. N.; Rieder, C. J.; West, F. G. Interrupting the Nazarov reaction: domino and cascade processes utilizing cyclopentenyl cations. *Chem. Commun.*, **2009**, 5676–5688. (f) Shimada, N.; Stewart, C.; Tius, M. A. Asymmetric Nazarov Cyclizations. *Tetrahedron*, **2011**, *67*, 5851–5870. (g) Vaidya, T.; Eisenberg, R.; Frontier, A. J. Catalytic Nazarov Cyclization: The State of the Art. *ChemCatChem*, **2011**, *3*, 1531–1548. (h) Di Grandi, M. J. Nazarov-like cyclization reactions. *Org. Biomol. Chem.*, **2014**, *12*, 5331–5345. (i) Tius, M. A. Allene ether Nazarov cyclization. *Chem. Soc. Rev.*, **2014**, *43*, 2979–3002. (j) Wenz, D. R.; de Alaniz, J. R. The Nazarov Cyclization: A Valuable Method to Synthesize Fully Substituted Carbon Stereocenters. *Eur. J. Org. Chem.*, **2015**, 23–37.
- [6] Vivekanand, T.; Satpathi, B.; Bankar, S. K.; Ramasastry, S. S. V. Recent metal-catalysed approaches for the synthesis of cyclopenta[b]indoles. *RSC Adv.*, **2018**, *8*, 18576–18588.
- [7] Yadykov, A. V.; Shirinian, V. Z. Recent Advances in the Interrupted Nazarov Reaction. *Adv. Synth. Catal.*, **2020**, *362*, 702–723.
- [8] Ru, G.-X.; Zhang, T.-T.; Zhang, M.; Jiang, X.-L.; Wan, Z.-K.; Zhu, X.-H.; Shen, W.-B.; Gao, G.-Q. Recent progress towards the transition-metalcatalyzed Nazarov cyclization of alkynes via metal carbenes. *Org. Biomol. Chem.*, **2021**, *19*, 5274–5283.
- [9] Tu, M.-S.; Chen, K.-W.; Wu, P.; Zhang, Y.-C.; Liu, X.-Q.; Shi, F. Advances in organocatalytic asymmetric reactions of vinylindoles: powerful access to enantioenriched indole derivatives. *Org. Chem. Front.*, **2021**, *8*, 2643–2672.
- [10] Pridgen, L. N.; Huang, K.; Shilcrat, S.; Tickner-Eldridge, A.; DeBrosse, C.; Haltiwanger, R. C. An Unprecedented Asymmetric Nazarov Cyclization for the Synthesis of Nonracemic Indanes as Endothelin Receptor Antagonists. *Synlett*, **1999**, *10*, 1612–1614.
- [11] Krieger, J.; Smeilus, T.; Schackow, O.; Giannis, A. Lewis Acid Mediated Nazarov Cyclization as a Convergent and Enantioselective Entry to C-nor-D-homo-Steroids. *Chem. Eur. J.*, **2017**, *23*, 5000–5004.
- [12] Manchala, N.; Law, H. Y. L.; Kerr, D. J.; Volpe, R.; Lepage, R. J.; White, J. M.; Krenske, E. H.; Flynn, B. L. Multistereocenter-Containing Cyclopentanoids from Ynamides via Oxazolidinone-Controlled Nazarov Cyclization. *J. Org. Chem.*, **2017**, *82*, 6511–6527.
- [13] Volpe, R.; Lepage, R. J.; White, J. M.; Krenske, E. H.; Flynn, B. L. Asymmetric synthesis of multiple quaternary stereocenter-containing cyclopentyls by oxazolidinone-promoted Nazarov cyclizations. *Chem. Sci.*, **2020**, *9*, 4644–4649.
- [14] Carlsen, P. N.; Stoutenburg, E. G.; Frontier, A. J. SYNTHESIS–SYNLETT Lecture: Toward the Asymmetric Synthesis of Tetrapetalone A: Preparation of an Enantioenriched Indane Intermediate and Strategy for Endgame Glycosylation. *Synthesis*, **2018**, *50*, 1238–1245.
- [15] Grenet, E.; Martinez, J.; Salom-Roig, X. J. Torquoselective Nazarov Cyclization Mediated by a Chiral Sulfoxide: First Enantioselective Synthesis of two Known Anticancer Agents. *Asian J. Org. Chem.*, **2017**, *6*, 189–198.
- [16] Grenet, E.; Robidas, R.; van der Lee, A.; Legault, C. Y.; Salom-Roig, X. J. Mechanistic Insights into Lewis Acid-Controlled Torquoselective Nazarov Cyclization of Activated Dienones Bearing a Chiral Sulfoxide. *Eur. J. Org. Chem.*, **2022**, e202200828.

- [17] Greneta, E.; van der Leeb, A.; Salom-Roig, X. J. Doubly Switchable Diastereodivergent Strategy Mediated by a Chiral Sulfoxide to Access Disubstituted Tetrahydrocyclopentapyranone and Hexahydrocyclopentapyranol Scaffolds via Nazarov Cyclization. *Synthesis*, **2023**, *55*, 580–597.
- [18] Que, Y.; Shao, H.; He, H.; Gao, S. Total Synthesis of Farnesin through an Excited-State Nazarov Reaction. *Angew. Chem., Int. Ed.*, **2020**, *20*, 7444–7449.
- [19] (a) Tietze, L. F.; Beifuss, U. Sequential Transformations in Organic Chemistry: A Synthetic Strategy with a Future. *Angew. Chem., Int. Ed.*, **1993**, *32*, 131–163. (b) Tietze, L. F. Domino Reactions in Organic Synthesis. *Chem. Rev.*, **1996**, *96*, 115–136.
- [20] (a) Tietze, L. F. *Domino Reactions - Concepts for Efficient Organic Synthesis*, Wiley-VCH: Weinheim, **2014** (b) Pellissier, H. Recent Developments in Enantioselective Metal-Catalyzed Domino Reactions. *Adv. Synth. Catal.*, **2016**, *358*, 2194–2259. (c) Snyder, S. A. *Science of Synthesis. Applications of Domino Transformations in Organic Synthesis*, Thieme Verlag: Stuttgart, **2016**, Vols 1–2. (d) Pellissier, H. Recent developments in enantioselective metal-catalyzed domino reactions. *Adv. Synth. Catal.*, **2019**, *361*, 1733–1755. (e) Pellissier, H. *Asymmetric Metal Catalysis in Enantioselective Domino Reactions*. Wiley: Weinheim, **2019**. (f) Westphal, R.; Filho, E. V.; Medici, F.; Benaglia, M.; Greco, S. J. Stereoselective Domino Reactions in the Synthesis of Spiro Compounds. *Synthesis*, **2022**, *54*, 2927–2975. (g) Pellissier, H. Recent Developments in Enantioselective Domino Reactions. Part A: Noble Metal Catalysts. *Adv. Synth. Catal.*, **2023**, *365*, 620. (h) Pellissier, H. Recent Developments in Enantioselective Domino Reactions. Part B: First Row Metal Catalysts. *Adv. Synth. Catal.*, **2023**, *365*, 768–819.
- [21] (a) Bender, J. A.; Blize, A. E.; Browder, C. C.; Giese, S.; West, F. G. Highly Diastereoselective Cycloisomerization of Acyclic Trienones. The Interrupted Nazarov Reaction. *J. Org. Chem.*, **1998**, *63*, 2430–2431. (b) Zuev, D.; Paquette, L. A.; Browder, C. C.; Giese, S.; West, F. G.; Wang, Y.; Arif, A. M. First examples of the interrupted Nazarov reaction. *Chemtracts*, **1999**, *12*, 1019–1025.
- [22] Liao, H.; Leng, W.-L.; Le Mai Hoang, K.; Yao, H.; He, J.; Ying Hui Voo, A.; Liu, X.-W. Asymmetric syntheses of 8-oxabicyclo[3.2.1]octane and 11-oxatricyclo[5.3.1.0]undecane from glycals. *Chem. Sci.*, **2017**, *8*, 6656–6661.
- [23] Brandstätter, M.; Freis, M.; Huwyler, N.; Carreira, E. M. Total Synthesis of (-)-Merochlorin A. *Angew. Chem., Int. Ed.*, **2019**, *58*, 2490–2494.
- [24] Brandstätter, M.; Huwyler, N.; Carreira, E. M. Gold(I)-catalyzed stereoselective cyclization of 1,3-enyne aldehydes by a 1,3-acyloxy migration/Nazarov cyclization/aldol addition cascade. *Chem. Sci.*, **2019**, *10*, 8219–8223.
- [25] Kong, L.; Su, F.; Yu, H.; Jiang, Z.; Lu, Y.; Luo, T. Total Synthesis of (-)-Oridonin: An Interrupted Nazarov Approach. *J. Am. Chem. Soc.*, **2019**, *141*, 20048–20052.
- [26] Komatsuki, K.; Kozuma, A.; Saito, K.; Yamada, T. Decarboxylative Nazarov Cyclization-Based Chirality Transfer for Asymmetric Synthesis of 2- Cyclopentenones. *Org. Lett.*, **2019**, *21*, 6628–6632.
- [27] Kozuma, A.; Komatsuki, K.; Saito, K.; Yamada, T. Thermal Decarboxylative Nazarov Cyclization of Cyclic Enol Carbonates Involving Chirality Transfer. *Chem. Lett.*, **2020**, *49*, 60–63.
- [28] Alachouzos, G.; Holt, C.; Frontier, A. J. Stereochemical Relay through a Cationic Intermediate: Helical Preorganization Dictates Direction of Conrotation in the halo-Nazarov Cyclization. *Org. Lett.*, **2020**, *22*, 4010–4015.
- [29] (a) Gao, J.; Rao, P.; Xu, K.; Wang, S.; Wu, Y.; He, C.; Ding, H. Total Synthesis of (-)-Rhodomollanol A. *J. Am. Chem. Soc.*, **2020**, *142*, 4592–4597. (b) Gao, K.; Hu, J.; Ding, H. Tetracyclic Diterpenoid Synthesis Facilitated by ODI-Cascade Approaches to Bicyclo[3.2.1]octane Skeletons. *Acc. Chem. Res.*, **2021**, *54*, 875–889.
- [30] Amberg, W. M.; Carreira, E. M. Enantioselective Total Synthesis of (+)-Aberrarone. *J. Am. Chem. Soc.*, **2022**, *144*, 15475–15479.
- [31] Etling, C.; Tedesco, G.; Di Marco, A.; Kalesse, M. Asymmetric Total Synthesis of Illisimonin A. *J. Am. Chem. Soc.*, **2023**, *145*, 7021–7029.
- [32] (a) Beller, M.; Bolm, C. *Metals for Organic Synthesis*, second ed., Wiley-VCH: Weinheim, **2004**. (b) Tietze, L. F.; Hiriyakkanavar, I.; Bell, H. P. Enantioselective Palladium-Catalyzed Transformations. *Chem. Rev.*, **2004**, *104*, 3453–3516. (c) Ramon, D. J.; Yus, M. In the Arena of Enantioselective Synthesis, Titanium Complexes Wear the Laurel Wreath. *Chem. Rev.*, **2006**, *106*, 2126–2208. (d) Pellissier, H. Enantioselective Silver-Catalyzed Transformations. *Chem. Rev.*, **2016**, *116*, 14868–14917. (e) Pellissier, H. Enantioselective Magnesium-Catalyzed Transformations. *Org. Biomol. Chem.*, **2017**, *15*, 4750–4782. (f) Pellissier, H. Recent Developments in enantioselective cobalt-catalyzed transformations. *Coord. Chem. Rev.*, **2018**, *360*, 122–168. (g) Pellissier, H. Recent Developments in Enantioselective Vanadium-Catalyzed Transformations. *Coord. Chem. Rev.*, **2020**, *418*, 213395. (p) Pellissier, H. Enantioselective Indium-Catalyzed Transformations. *Synthesis*, **2021**, *53*, 1379–1395. (h) Pellissier, H. Recent developments in enantioselective zinc-catalyzed transformations. *Coord. Chem. Rev.*, **2021**, *439*, 213926. (i) Pellissier, H. Recent developments in enantioselective titanium-catalyzed transformations. *Coord. Chem. Rev.*, **2022**, *463*, 214537. (j) Pellissier, H. Enantioselective nickel(II)-catalyzed conjugate additions. *Org. Chem. Front.*, **2022**, *9*, 6717–6748.
- [33] (a) Doyle, A. G.; Jacobsen, E. N. Small-Molecule H-Bond Donors in Asymmetric Catalysis. *Chem. Rev.*, **2007**, *107*, 5713–5743. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. Asymmetric Enamine Catalysis. *Chem. Rev.*, **2007**, *107*, 5471–5569. (c) Dondoni, A.; Massi, A. Asymmetric Organocatalysis: From Infancy to Adolescence. *Angew. Chem., Int. Ed.*, **2008**, *47*, 4638–4660. (d) Pellissier, H. *Recent Developments in Asymmetric Organocatalysis*, Royal Society of Chemistry: Cambridge, **2010**. (e) Volla, C. M. R.; Atodiresi, I.; Rueping, M. Catalytic C–C Bond-Forming Multi-Component Cascade or Domino Reactions: Pushing the Boundaries of Complexity in Asymmetric Organocatalysis. *Chem. Rev.*, **2014**, *114*, 2390–2431 (f) Tian, L.; Luo, Y.-C.; Hu, X.-Q.; Xu, P.-F. Recent Developments in the Synthesis of Chiral Compounds with Quaternary Centers by Organocatalytic Cascade Reactions. *Asian J. Org. Chem.*, **2016**, *5*, 580–607. (g) Chanda, T.; Zhao, J. C.-G. Recent Progress in Organocatalytic Asymmetric Domino Transformations. *Adv. Synth. Catal.*, **2018**, *360*, 2–79. (h) Guo, H.; Fan, Y. C.; Sun, Z.; Wu, Y.; Kwon, O. Phosphine Organocatalysis. *Chem. Rev.*, **2018**, *118*, 10049–10293. (i) Sahoo, B. M.; Banik, B. K. Organocatalysis: Trends of Drug Synthesis in Medicinal Chemistry. *Current Organocatalysis*, **2019**, *6*, 92–105.

- [34] Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. Chiral Brønsted Acids in the Catalytic Asymmetric Nazarov Cyclization—The First Enantioselective Organocatalytic Electrocyclic Reaction. *Angew. Chem., Int. Ed.*, **2007**, *46*, 2097–2100.
- [35] Jolit, A.; Dickinson, C. F.; Kitamura, K.; Walleiser, P. M.; Yap, G. P. A.; Tius, M. A. Catalytic Enantioselective Nazarov Cyclization. *Eur. J. Org. Chem.*, **2017**, 6067–6076.
- [36] Jin, J.; Zhao, Y.; Gouranourimi, A.; Ariafard, A.; Chan, P. W. H. Chiral Brønsted Acid Catalyzed Enantioselective Dehydrative Nazarov-Type Electrocyclization of Aryl and 2-Thienyl Vinyl Alcohols. *J. Am. Chem. Soc.*, **2018**, *140*, 5834–5841.
- [37] Ouyang, J.; Kennemur, J. L.; Kanta De, C.; Farès, C.; List, B. Strong and Confined Acids Enable a Catalytic Asymmetric Nazarov Cyclization of Simple Divinyl Ketones. *J. Am. Chem. Soc.*, **2019**, *141*, 3414–3418.
- [38] Wang, C.-S.; Wu, J.-L.; Li, C.; Li, L.-Z.; Mei, G.-J.; Shi, F. Design of C3-Alkenyl-Substituted 2-Indolylmethanols for Catalytic Asymmetric Interrupted Nazarov-Type Cyclization. *Adv. Synth. Catal.*, **2018**, *360*, 846–851.
- [39] Wu, J.-L.; Wang, J.-Y.; Ping Wu, Wang, J.-R.; Mei, G.-J.; Shi, F. Diastereo- and enantioselective construction of chiral cyclopenta[b]indole framework via a catalytic asymmetric tandem cyclization of 2-indolylmethanols with 2-naphthols. *Org. Chem. Front.*, **2018**, *5*, 1436–1445.
- [40] Wu, J.-L.; Wang, C.-S.; Wang, J.-R.; Mei, G.-J.; Shi, F. A catalytic asymmetric interrupted Nazarov-type cyclization of 2-indolylmethanols with cyclic enamines. *Org. Biomol. Chem.*, **2018**, *16*, 5457–5464.
- [41] Liang, G.; Gradl, S. N.; Trauner, D. Efficient Nazarov Cyclizations of 2-Alkoxy-1,4-pentadien-3-ones. *Org. Lett.*, **2003**, *5*, 4931–4934.
- [42] Aggarwal, V. K.; Belfield, A. J. Catalytic Asymmetric Nazarov Reactions Promoted by Chiral Lewis Acid Complexes. *Org. Lett.*, **2003**, *5*, 5075–5078.
- [43] Süsse, L.; Vogler, M.; Mewald, M.; Kemper, B.; Irran, E.; Oestreich, M. Enantioselective Nazarov Cyclizations Catalyzed by an Axial Chiral C₆F₅-Substituted Boron Lewis Acid. *Angew. Chem., Int. Ed.*, **2018**, *57*, 11441–11444.
- [44] Mietke, T.; Cruchter, T.; Larionov, V. A.; Faber, T.; Harms, K.; Meggers, E. Asymmetric Nazarov Cyclizations Catalyzed by Chiral-at-Metal Complexes. *Adv. Synth. Catal.*, **2018**, *360*, 2093–2100.
- [45] Brunen, S.; Grell, Y.; Steinlandt, P. S.; Harms, K.; Meggers, E. Bis-Cyclometalated Indazole and Benzimidazole Chiral-at-Iridium Complexes: Synthesis and Asymmetric Catalysis. *Molecules*, **2021**, *26*, 1822–1834.
- [46] Hong, Y.; Jarrige, L.; Harms, K.; Meggers, E. Chiral-at-Iron Catalyst: Expanding the Chemical Space for Asymmetric Earth-Abundant Metal Catalysis. *J. Am. Chem. Soc.*, **2019**, *141*, 4569–4572.
- [47] Dickinson, C. F.; Yap, G. P. A.; Tius, M. A. Anion-accelerated asymmetric Nazarov cyclization: access to vicinal all-carbon quaternary stereocenters. *Org. Biomol. Chem.*, **2023**, *21*, 5014–5020.
- [48] Zhang, H.; Lu, Z. Nickel-catalyzed enantioselective sequential Nazarov cyclization/decarboxylation. *Org. Chem. Front.*, **2018**, *5*, 1763–1767.
- [49] Zhang, H.; Cheng, B.; Lu, Z. Enantioselective Cobalt-Catalyzed Sequential Nazarov Cyclization/Electrophilic Fluorination: Access to Chiral α -Fluorocyclopentenones. *Org. Lett.*, **2018**, *20*, 4028–4031.
- [50] Corbin, J. R.; Ketelboeter, D. R.; Fernández, I.; Schomaker, J. M. Biomimetic 2- Imino-Nazarov Cyclizations via Eneallene Aziridination. *J. Am. Chem. Soc.*, **2020**, *142*, 5568–5573.
- [51] Solas, S.; Suárez-Pantiga, S.; Sanz, R. Asymmetric Gold(I)-Catalyzed Tandem Hydroarylation–Nazarov Cyclization: Enantioselective Access to Cyclopentenones. *Angew. Chem., Int. Ed.*, **2022**, *61*, e202207406.
- [52] Tian, Y.; Tang, M.; Lian, C.; Song, R.; Yang, D.; Lv, J. Asymmetric binary-acid catalysis: a diastereo- and enantioselective oxo-Nazarov cyclization-Michael addition of conjugated 1,2-diketones. *Org. Chem. Front.*, **2023**, *10*, 3039–3044.
- [53] (a) Pellissier, H. Recent Developments in Enantioselective Multicatalysed Tandem Reactions. *Tetrahedron*, **2013**, *69*, 7171–7210. (b) Pellissier, H. *Enantioselective Multicatalysed Tandem Reactions*, Royal Society of Chemistry: Cambridge, **2014**. (c) Lohr, T. L.; Marks, T. J. Orthogonal tandem catalysis. *Nature Chem.*, **2015**, *7*, 477–608. (d) Zhou, J. *Multicatalyst System in Asymmetric Catalysis*, Wiley: Weinheim, **2015**. (e) S. Afewerki, S.; Cordova, A. Combinations of Aminocatalysts and Metal Catalysts: A Powerful Cooperative Approach in Selective Organic Synthesis. *Chem. Rev.*, **2016**, *116*, 13512–13570. (f) Pellissier, H. Recent developments in enantioselective multicatalysed tandem reactions. *Adv. Synth. Catal.*, **2020**, *362*, 2289–2325.
- [54] Wang, G.-P.; Chen, M.-Q.; Zhu, S. F.; Zhou, Q.-L. Enantioselective Nazarov cyclization of indole enones cooperatively catalyzed by Lewis acids and chiral Brønsted acids. *Chem. Sci.*, **2017**, *8*, 7197–7202.
- [55] (a) Denmark, S.; Jones, T. Silicon-Directed Nazarov Cyclization. *J. Am. Chem. Soc.*, **1982**, *104*, 2642–2645. (b) Jones, T. K.; Denmark, S. E. Silicon-Directed Nazarov Reactions II. Preparation and Cyclization of β -Silyl-substituted Divinyl Ketones. *Helv. Chim. Acta*, **1983**, *66*, 2377–2396. (c) Jones, T. K.; Denmark, S. E. Silicon-Directed Nazarov Reactions III. Stereochemical and Mechanistic Considerations. *Helv. Chim. Acta*, **1983**, *66*, 2397–2411. (d) Denmark, S. E.; Klix, R. C. Silicon-directed nazarov cyclizations VII: Linearly-fused tricyclics. *Tetrahedron*, **1988**, *44*, 4043–4060. (e) Denmark, S. E.; Wallace, M. A.; Walker, C. B. Silicon-directed Nazarov cyclizations. 8. Stereoelectronic control of torquoselectivity. *J. Org. Chem.*, **1990**, *55*, 5543–5545.
- [56] (a) Cao, J.; Hu, M.-Y.; Liu, S.-Y.; Zhang, X.-Y.; Zhu, S.-F.; Zhou, Q.-L. Enantioselective Silicon-Directed Nazarov Cyclization. *J. Am. Chem. Soc.*, **2021**, *143*, 6962–6968. (b) Cao, J.; Zhu, S.-F. Chiral Proton-Transfer Shuttle Catalysts Promoted Enantioselective Nazarov Cyclization. *Synlett*, **2023**, *34*, 29–39.
- [57] Metternich, J. B.; Reiterer, M.; Jacobsen, E. N. Asymmetric Nazarov Cyclizations of Unactivated Dienones by Hydrogen-Bond-Donor/Lewis Acid Co-Catalyzed, Enantioselective Proton-Transfer. *Adv. Synth. Catal.*, **2020**, *362*, 4092–4097.

-
- [58] Jin, J.; Zhao, Y.; Ling Sze, E. M.; Kothandaraman, P.; Chan, P. W. H. Chiral Brønsted Acid and Gold Catalyzed Enantioselective Synthesis of 1,8-Dihydroindeno[2,1-b]pyrroles. *Adv. Synth. Catal.*, **2018**, *360*, 4744–4753.
- [59] Tang, S.; Zhang, P.; Shao, Y.; Sun, J. Enyne diketones as substrate in asymmetric Nazarov cyclization for construction of chiral allene cyclopentenones. *Nature Chem.*, **2022**, *3*, 3146–3156.
- [60] Mankad, N. P. Selectivity Effects in Bimetallic Catalysis. *Chem. Eur. J.*, **2016**, *22*, 5822–5829.
- [61] Zhang, H.; Lu, Z. Nickel/Copper Dual Catalysis for Sequential Nazarov Cyclization/Decarboxylative Aldol Reaction. *Org. Lett.*, **2018**, *20*, 5709–5713.