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ABSTRACT

In this account, Diels-Alder reactions of different 1-amino-1,3-dienes with dienophiles are considered. As 1-amino-1,3-dienes, dienamines, dienamides, 1,2-dihydropyridines, 2-pyridones and vinylic heterocycles, such as vinyl-pirroles, pyrazoles, imidazoles, indoles, tetrahydropyridines and dihydropyridones are studied. As dienophiles, enals, acrylic, maleic and fumaric derivatives, quinones, tetracyanoethylene, dialkyl acetylenedicarboxylates, nitroolefines, nitrosobenzene and azocompounds play an important role. Synthetic applications of these inter or intramolecular, racemic or enantioselective reactions in order to prepare polycyclic nitrogen-containing heterocycles, are pointed out, especially in the preparation of naturally occurring and biologically active compounds specially alkaloids. The most significant feature of the chemistry described in this account is the fact that this methodology represents a simple and selective way to get mainly nitrogen-containing heterocyclic compounds in only one reaction step, creating at least two carbon-carbon bonds in a regio-, diastereo- and enantioselective fashion.

Keywords:

Diels-Alder
1-amino-1,3-dienes
1,2-dihydropyridines
2-pyridones
vinylic heterocycles

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1. Introduction

1-Amino-1,3-dienes have been widely used as electron-rich dienes in inter and intramolecular Diels-Alder [4+2] cycloadditions [1-5]. In this review, different types of 1-amino-1,3-dienes are considered according to their acyclic **1** or cyclic **2** structures, as well as heterocyclic systems such as dihydropyridines **3**, 2-pyridones **4**, and alkenyl substituted nitrogenated heterocycles, mainly compounds **5-9** (Figure 1). Their synthesis and reactivity in Diels-Alder reactions and the corresponding applications to the synthesis of natural products and biologically active compounds will be summarized.
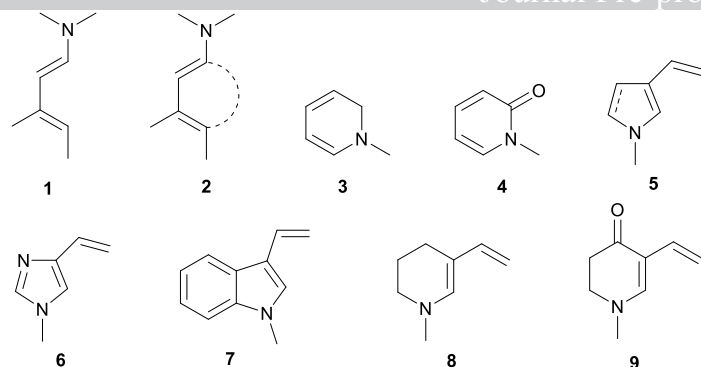
Figure 1. 1-Amino-1,3-dienes.

2. Acyclic 1-amino-1,3-dienes

2.1. Dienamines

In 1939 it was described the *in situ* generation of a dienamine of the type **1** derived from 2-ethyl-2-hexenal and aniline by isomerization of the corresponding aldimine, which was trapped by maleic anhydride [6]. In general, dienamines derived from secondary amines are prepared by this condensation-isomerization process using unsaturated aldehydes [7].
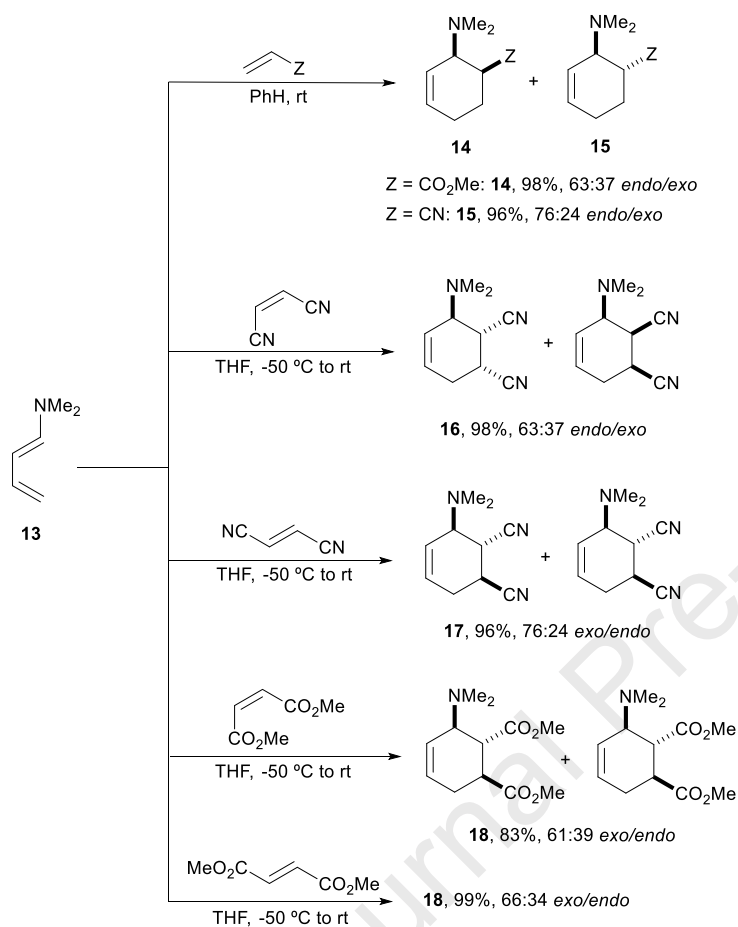
Madsen and Lawesson described the Diels-Alder (DA) cycloaddition of *N*-morpholino-1,3-butadiene (**10**) with α-chloroacrylonitrile [8]. The corresponding adduct **11** eliminates under heating hydrogen cyanide and hydrogen chloride giving *N*-phenylmorpholine hydrochloride **12** (Scheme 1).
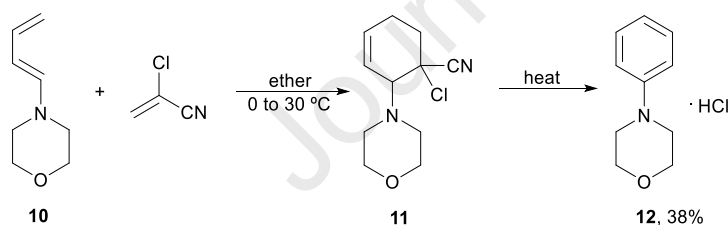
Scheme 1. DA reaction of *N*-morpholino-1,3-butadiene and α-chloroacrylonitrile.

Langenbeck and co-workers [9] reported the cycloaddition of 1-(diethylamino)- and 1-piperidino-1,3-butadiene with acrolein and crotonaldehyde. Later on Hünig and Kahanek [10] carried out the reaction of 1-(dimethylamino)-1,3-butadiene with methyl acrylate, methyl vinyl ketone, acroleins and acrylonitrile. Also Satzinger [11] studied some more cycloadditions of 1-(dialkylamino)-1,3-dienes. In these reports only the 'ortho'-regioselectivity in the obtained disubstituted cyclohexenes was confirmed. The *endo/exo* diastereoselectivity in the cycloaddition of 1-(dimethylamino)-1,3-butadiene (**13**) with different dienophiles was established by Sutsmann and co-workers [12]. This aminodiene **13** was prepared in 46% yield by reaction of crotonaldehyde with dimethylamine. Methyl acrylate and acrylonitrile gave products **14** and **15** in 98 and 96% yield, respectively, as 63:37 and 76:24 mixtures of *endo/exo* diastereomers (Scheme 2). Maleonitrile adducts **16** were isolated as 63:37 *exo/endo* mixture in 98% yield, whereas fumaronitrile afforded compounds **17** as a 76:24 mixture of *exo/endo* diastereomers. However, dimethyl maleate and fumarate provided almost the same mixture 61:39 and 63:34 of *endo/exo*

diastereomers **18** in 83 and 99% yield, respectively. These results supported a concerted cycloaddition with maleonitrile and fumaronitrile, while stepwise reactions, presumably proceeding *via* zwitterions were proposed in the case of dimethyl maleate and fumarate.

Z = CO₂Me: **14**, 98%, 63:37 *endo/exo*
Z = CN: **15**, 96%, 76:24 *endo/exo*

16, 98%, 63:37 *endo/exo*

17, 96%, 76:24 *exo/endo*

18, 83%, 61:39 *exo/endo*

18, 99%, 66:34 *exo/endo*

Scheme 2. DA reaction of 1-(dimethylamino)-1,3-butadiene (**13**) with different dienophiles.

Snowden's group [13-17] studied the DA reaction of (*E*)-dienamines with different dienophiles as strategy for the synthesis of decalines and drimanes. In Scheme 3 is described the thermal cycloaddition of dienamine **19** with dimethyl fumarate to provide diastereoselectively a ≥20:1 mixture of adducts **20**, which under heating eliminates dimethylamine to provide mainly decaline **21** precursor of drimane sesquiterpenes [17].
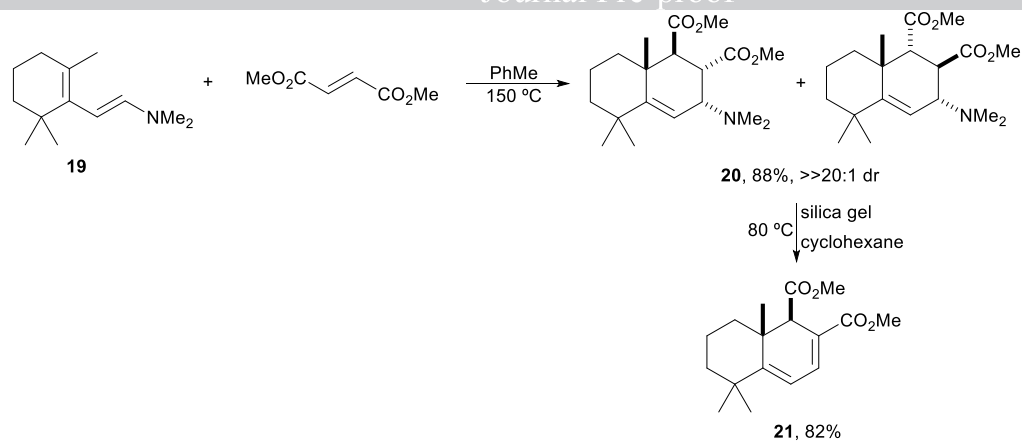
Scheme 3. DA reaction of dienamine **19** and dimethyl fumarate.

Wu and Houk [18] reported an intramolecular Diels-Alder reaction (IMDA) of dienamines **22** to provide mainly *trans*-adduct **23** for n = 3, whereas the decatriene (n = 4) afforded a *ca.* 1:1 mixture of *trans/cis* diastereomers **24** (yields not reported) (Scheme 4). According to MM2 calculations the group proposed a twist-asynchronous model for this IMDA [19].
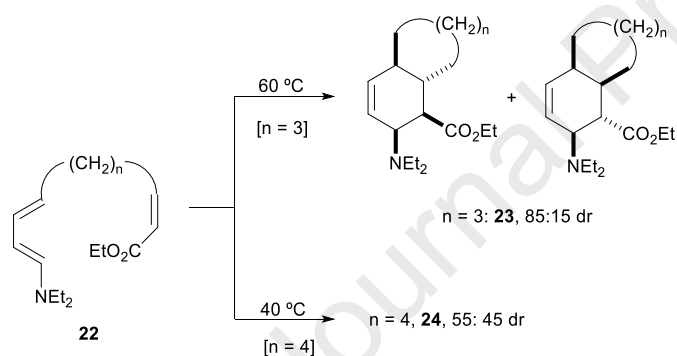
Scheme 4. Intramolecular DA reaction of dienamines **22**.

Dienamines **25** reacted with *N*-phenylmaleimide (NPM) in refluxing DMF through a [4+2] cycloaddition to provide cycloadducts **26**, which evolved to xanthones **27** (Scheme 5) [20]. However, dimethyl acetylenedicarboxylate (DMAD) gave xanthones **30** through a [2+2] cycloaddition to give adducts **28**, which isomerized to **29** by ring opening of the cyclobutene unit. Electrocyclization of **29** and subsequent elimination of dimethylamine afforded products **30**.
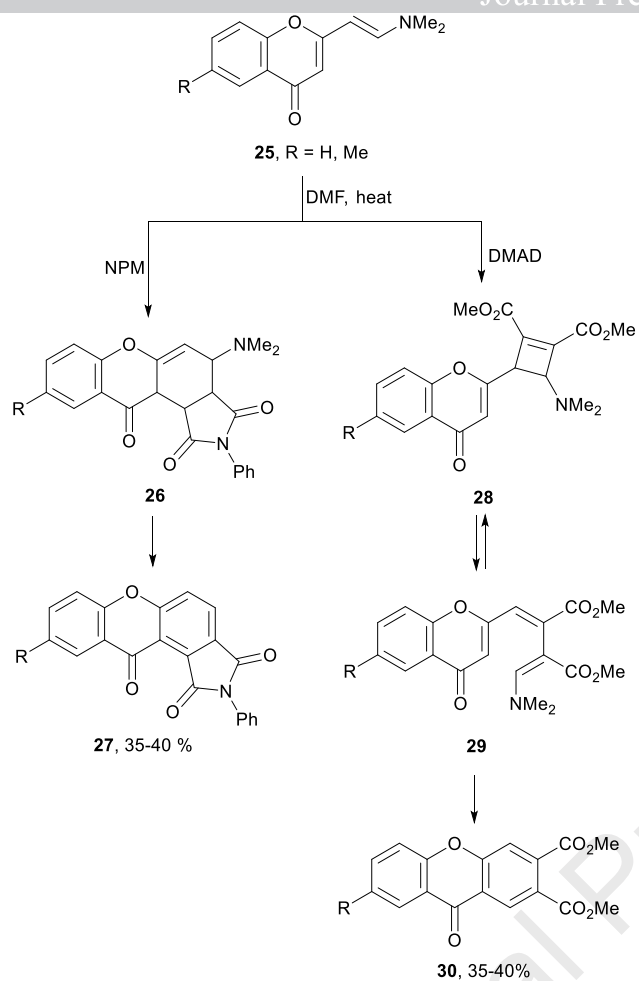
Scheme 5. DA reactions of dienamines **25** with NPM and DMAD.

Dienamine **32** [21] is a push-pull diene which has been prepared by reaction of 1,1,5,5-tetramethyl-1,5-diazapentadienium chloride **31** with the enolate of cyclopentenone [22] in 88% yield. Under thermal conditions reacted with DMAD, NPM and ethyl propiolate to give the corresponding spiranic cycloadducts **33-35** (Scheme 6).
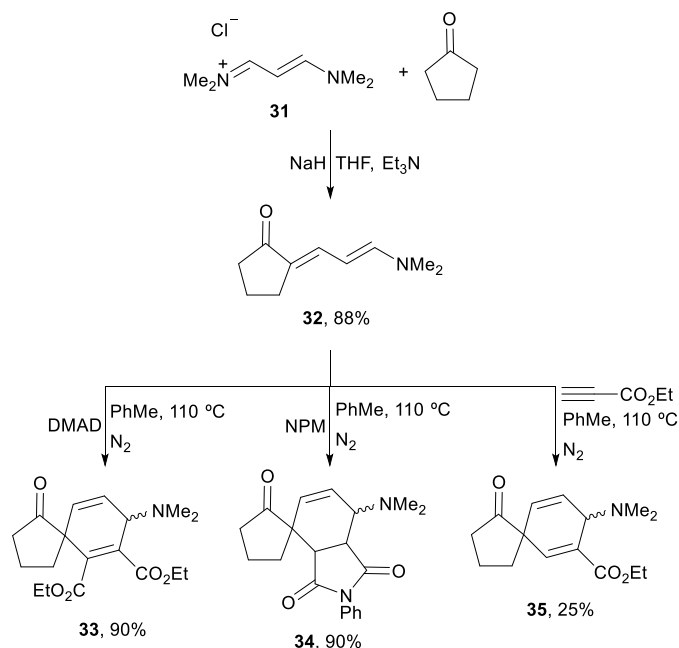
Scheme 6. DA reactions of dienamine **32** with DMAD, NPM and ethyl propiolate.

An inverse electron demand DA reaction has been described by Smith and co-workers [23] working with 1-amino-2-methylpenta-1,3-dienes **36** and dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **37**. The process gave tricyclic diesters (**38**) using acetonitrile at room temperature through intermediates **I** and **II** (Scheme 7).
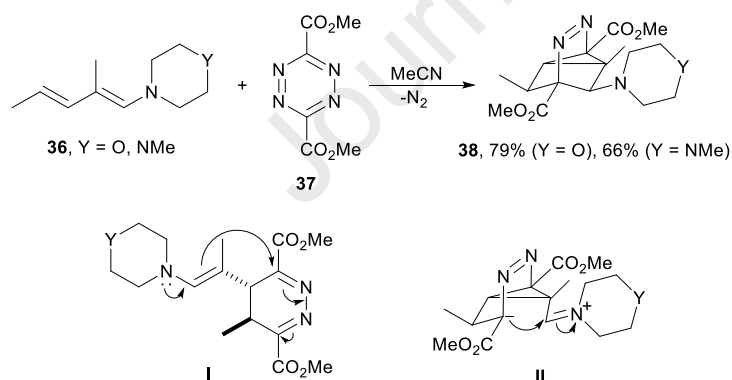

Scheme 7. Inverse electron-demand DA reaction of dienamines **36** and tetrazine **37**.

The stereoselective 1,4-elimination reaction of 1-amino-4-methoxy-(2*Z*)-alkenes promoted by *n*BuLi to give (1*E*,3*E*)-1-amino-1,3-dienes has been described by Tayama and Sugai [24]. For instance, dienamine **40** has been prepared by treatment of **39** with *n*BuLi in ether at 0 ºC to room temperature in 96% yield as a mixture 96:4 of diastereomers. After reaction with NPM in benzene at room temperature the corresponding cycloadduct **41** was stereoselectively obtained in 79% yield (Scheme 8). This procedure has been also used for the preparation of Boc-derived dienamides.
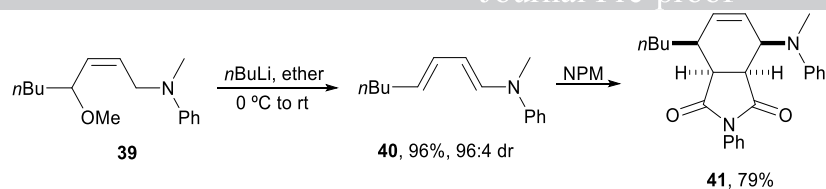
Scheme 8. Preparation of dienamine **40** by 1,4-elimination of **39** followed by DA reaction with NPM.

Katritzky and co-workers [25] studied the synthesis and transformations of 1-(1,3-butadienyl)benzotriazoles **43** (Scheme 9). Starting from 1-[α-(phenylsulphanyl)alkyl]benzotriazoles **42** after allylation and treatment with potassium *tert*-butoxide a 1,4-elimination gave rise to pure (*E*)-dienyl benzotriazoles **43**. DA reaction with NPM, maleic anhydride and ethyl acrylate provided the corresponding diastereomeric cyclohexenes **44-46** in *ca.* 1:1.2 ratio. Hetero DA reaction with nitroso benzene and Eschenmoser's salt afforded the dihydro-1,2-oxazine **47** and 1,2,5,6-tetrahydropyridinium salt **48** in 90 and 77% yield, respectively.
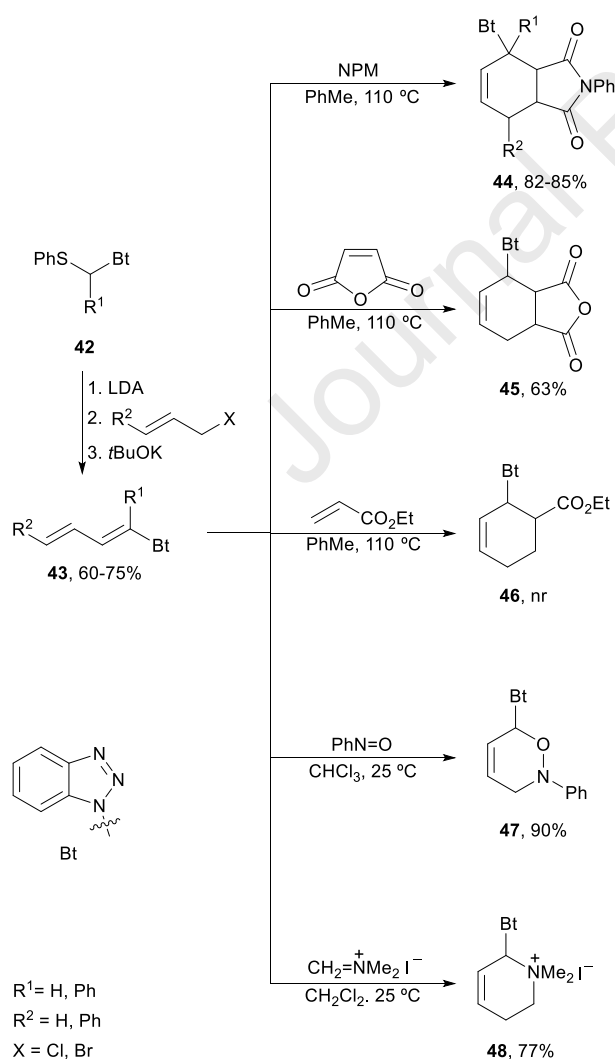
Scheme 9. Synthesis and DA reactions of 1-(1,3-butadien-1-yl)benzotriazoles **43**.

Substituted dienamines with an amino group at positions 1 and 4 have been described by Sustmann and co-workers. 1,1-Bis(dimethylamino)-1,3-butadiene **49** [26,27] a strong donor diene, was prepared from crotonic acid dimethylamide and tetrakis(dimethylamino)titanium in 41% yield [28]. Cycloaddition reaction of **49** with acrylonitrile took place at 85 ℃ with elimination of dimethylamine giving cyclohexadiene **50** in 69% yield (Scheme 10). However, the reaction with tetracyanoethylene (TCNE) at -45 ℃ was very fast leading to compound **51**, which at -20 ℃ evolved to merocyanine **52**. In the case of dimethyl dicyanofumarate a crystalline compound **53** was obtained in 86% yield. These compounds **51** and **53** are formed by a Michael addition of the olefin at the *s-trans* form of **49** and cannot be converted into cycloadducts. The tendency to react *via* zwitterions increases with growing difference in electronic polarization of diene and dienophile.
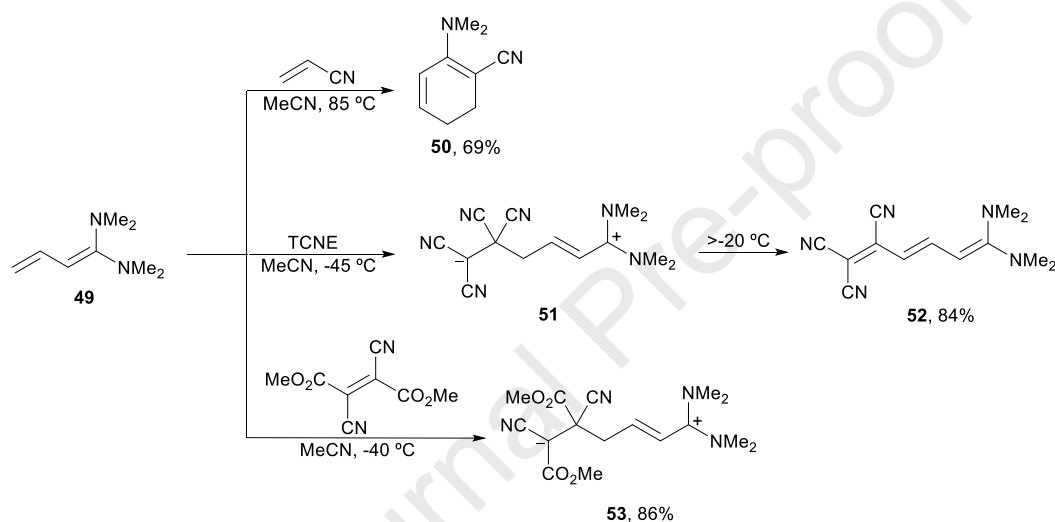
Scheme 10. Reaction of 1,1-bis(dimethylamino)-1,3-butadiene **49** with dienophiles.

The introduction of a second dimethylamino unit at the four position of 1-(dimethylamino)-1,3-butadiene can favor electron-transfer reactions depending on the dienophile. Sustmann's group studied [4+2] cycloadditions of different 1,4-bis(dimethylamino)dienes **54** and **55** [29-31]. Diastereomeric dienes **54** and **55** reacted with fumaric dinitrile to produce the same cycloadduct **56** in 96% crude yield (Scheme 11). Diene **55** was prepared by isomerization of 1,4-bis(dimethylamino)-2-butyne [32] and compound **54** by isomerization of **55** in the presence of catalytic amount of acetic acid. It has been shown that **54** isomerizes quantitatively to **55** at 35 ℃. If the cycloaddition of **54** was carried out at 50 ℃, compound **57** was obtained in 95% yield. Formation of **56** from **55** and **57** from **54** can be rationalized in terms of concerted cycloadditions. Maleic dinitrile reacted with **54** or **55** at 35 ℃ within 23 days to give in both cases a mixture of 86:14 of adducts **58** and **59** in 96% yield. However, methyl acrylate, acrylonitrile and dimethyl fumarate did not form cycloadducts with **55** at 35 ℃ in six weeks and isopropylidenemalononitrile underwent dimerization. Dimethyl maleate isomerized to dimethyl fumarate and reacted with **55** to provide **60** in 97% yield and with *N*-methylmaleimide (NMM) to cycloadduct **61** in 86% yield. In the case of 1,1,2-tris(methoxycarbonyl)ethane and 2-cyano-1,1-bis(methoxycarbonyl)ethene, addition to C−2 of **55** formed the corresponding zwitterions which stabilized by a 1,3-hydrogen shift to **62** and **63** in 99 and 95% yield, respectively. Dimethyl dicyanomaleate and fumarate

reacted with both dienes **54** and **55** at -50 ºC to give only one of the six possible cycloadducts, presumably compound **64** in 97% yield. The reduction potentials of these alkenes and the oxidation potentials of **54** and **55** showed that electron-transfer was possible when they are close together. The authors conclude that the loss of stereochemistry during the cycloadduct formation of these last cases is due to the electron-transfer process.
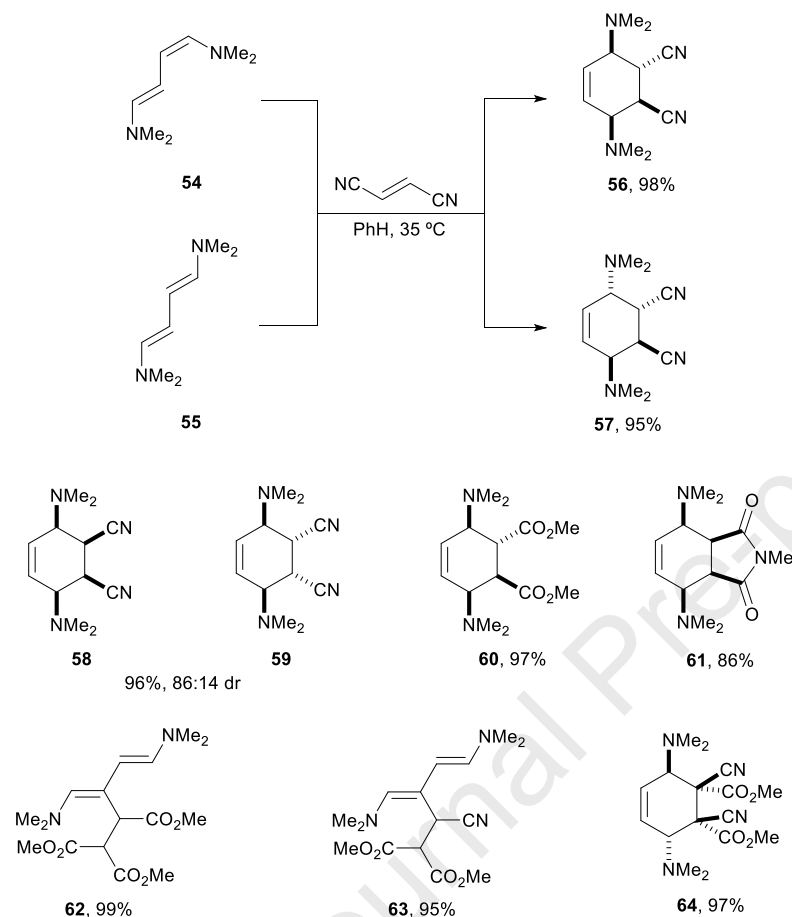

Scheme 11. Cycloaddition reactions of 1,4-bis(dimethylamino)-1,3-dienes **54** and **55** with electron-deficient alkenes.

3-Siloxy substituted 1-amino-1,3-dienes **65** and **66** were described by Smith III and Rawal groups, respectively. Smith III and co-workers [33,34] employed diene **65** for the synthesis of bicyclic enones *via* a DA-like reaction with methyl acrylate and methacrylate (Scheme 12). These cycloadditions took place at 50 ºC in benzene in the case of methyl acrylate and under toluene reflux for methyl methacrylate to provide the expected adducts, which were treated *in situ* with methyl iodide giving intermediates **I**. After elimination, the corresponding enones **67** were isolated in 45 and 63%, respectively. In particular, enone **67a** (R = H) is an intermediate in the total synthesis of cyclopentanoid sesquiterpenes (±)-modhephene and (±)-epimodhephene. 1-(Dimethylamino)-3-siloxy-1,3-butadienes **66** were prepared by Rawal and co-workers [35,36] from 4-(dimethylamino)-3-buten-2-one. These dienes showed higher reactivity than Danishefsky's diene in DA cycloadditions giving the corresponding adducts **68-71** in very good yields (Scheme 12). Other dienophiles such as methyl acrylate and crotonate, acrylonitrile, diethyl fumarate and dimethyl maleate reacted at 20 ºC giving the corresponding cycloadducts **72-76** in good yields (81-100%) and moderate to good *exo*-diastereoselectivity (4.5:1-15:1), except for diethyl fumarate which gave 1.4:1 *endo/exo* diastereoselectivity. Desilylation to the corresponding enones has been

performed with 10% HF [36]. Different 1-amino-3-silyloxy-1,3-butadienes derived from other aliphatic amines such as diisopropylamine, pyrrolidine and dihydroindole have been prepared by reaction of 4-methoxy-3-buten-2-one with the amine followed by deprotonation of the ketone with KHMDS at

-78 ºC and final silylation [36].
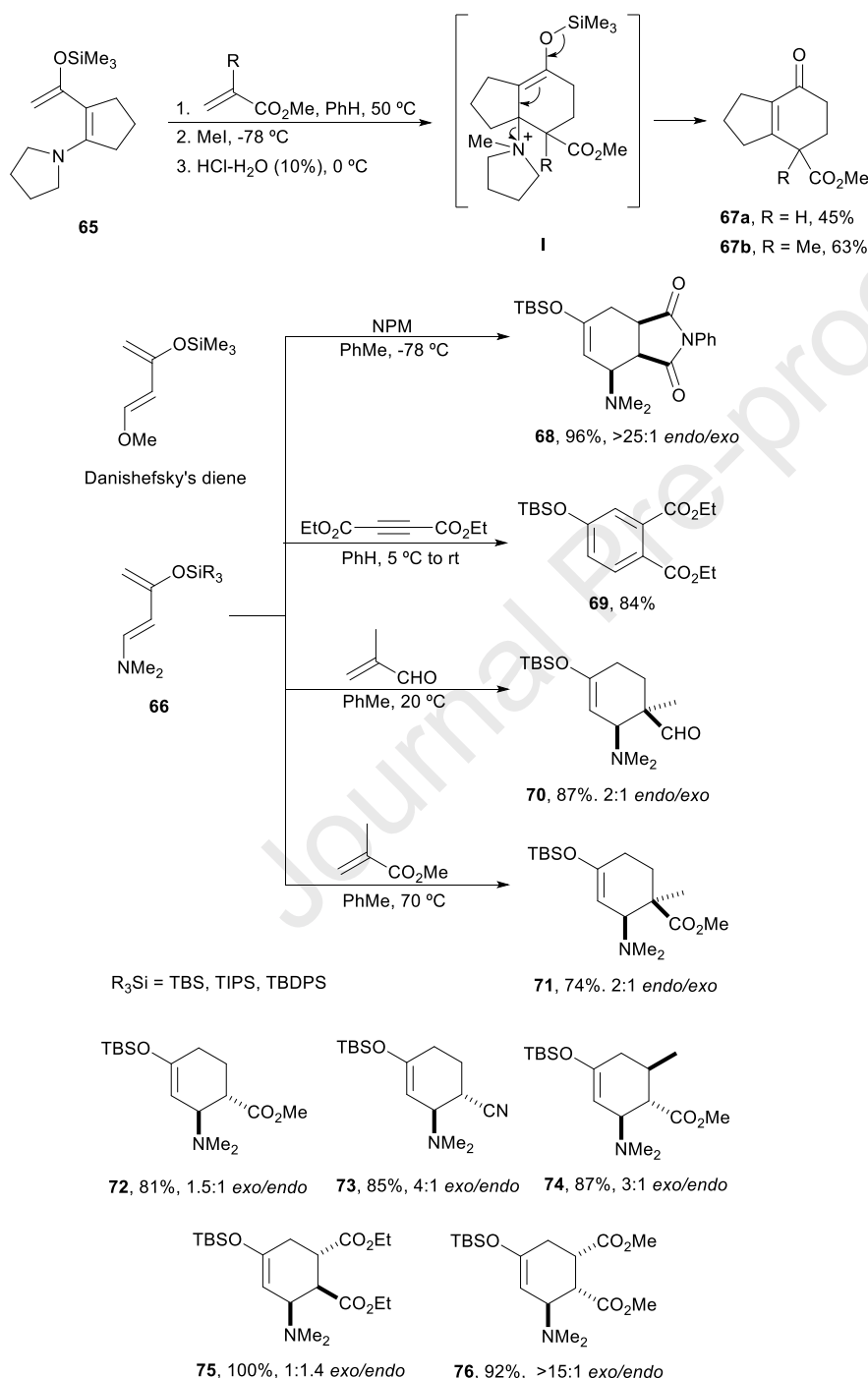
Scheme 12. DA reactions of 1-amino-3-siloxy-1,3-dienes **65** and **66**.

Chiral-modified aminosiloxydienes bearing   different chiral pyrrolidines **77-79** have been used for the asymmetric synthesis of cyclohexenones by Kozmin and Rawal (Scheme 13) [37,38].

The aminosilyloxydiene **79**, derived from the C_2-symmetric 2,5-diphenylpyrrolidine, provided the highest diastereofacial control at lower temperatures giving the corresponding cyclohexenones **80** with ee ranging from 85 to >98%, through cycloadduct **I**. The absolute configuration of the newly formed quaternary stereocenter was determined using methacrolein as dienophile to give after subsequent Wittig methylenation compound **81** and enone **82** after hydrolysis. This enone **82** was further transformed into (−)-α-elemene in 88% ee. The asymmetric induction observed in this cycloaddition with methacrolein was rationalized by the two *endo* transition states **II** and **III** in which the larger group (Me) is placed in the open pocket of the chiral pyrrolidine.
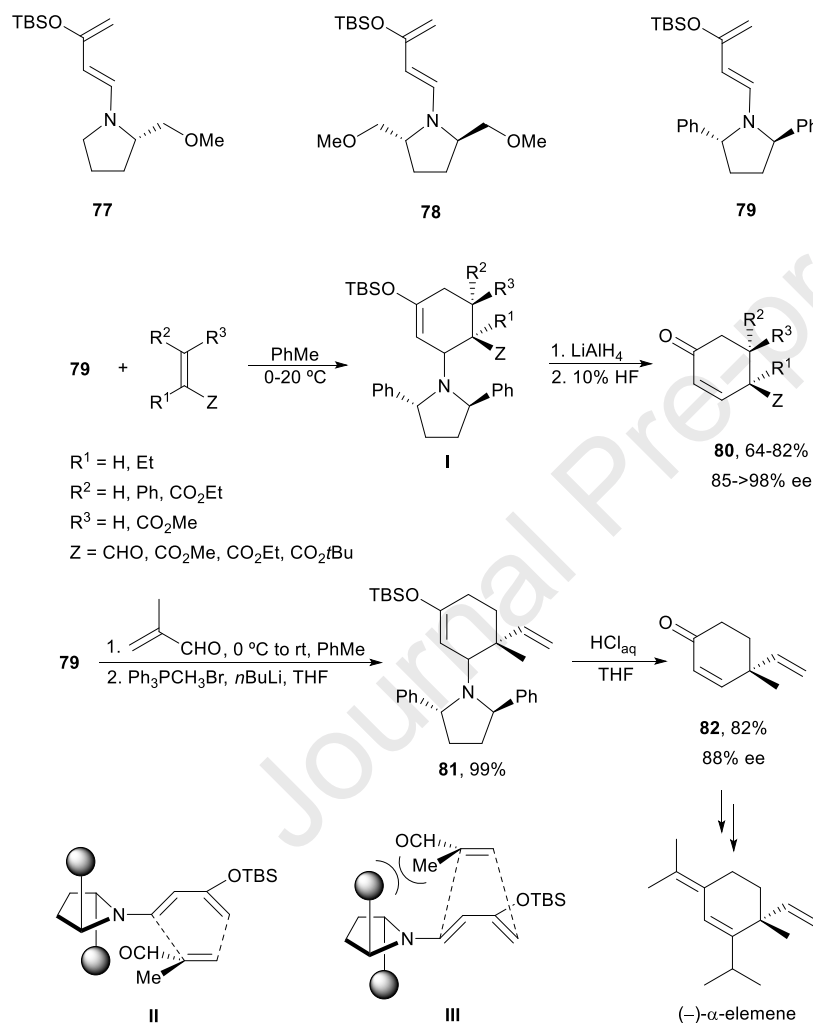
Scheme 13. Asymmetric DA reactions of chiral 1-amino-3-silyloxy-1,3-butadiene **79**.

Rawal and co-workers described the enantioselective DA of aminosilyloxydiene **66** catalyzed by hydrogen bond donor [39,40]. TADDOL **83** catalyzed the cycloaddition of **66** with α,β-unsaturated aldehydes in toluene at -80 ºC for 2 days to furnish adducts **84**, which were further treated with HF in acetonitrile to provide cyclohexenones **85** (Scheme 14). By *in situ* treatment of intermediate **84** with LiAlH$_4$ and subsequent acidic hydrolysis enones **86** were obtained in good yields and enantioselectivities. In the proposed model **I**, methacrolein is expected to complex with TADDOL **83** through a two-point interaction. First, the free hydroxy group on TADDOL could form a strong intermolecular hydrogen bond to the carbonyl group of the dienophile lowering the LUMO energy. Second, the C=C of the dienophile could be stabilized through a π-π donor-aceptor

interaction with the equatorial naphthyl moiety, which would shield one face of the dienophile. In this model **I**, the *Si* face of the aldehyde is accessible to diene **66** predicting the observed absolute configuration of the cycloadduct [40].
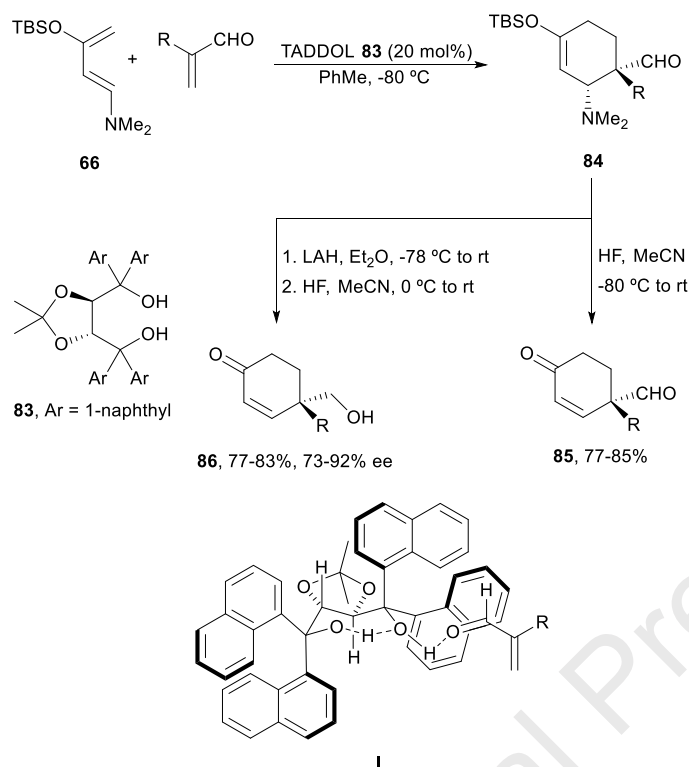
Scheme 14. Enantioselective DA reactions of 1-(dimethylamino)-3-silyloxydiene **66** with α,β-unsaturated aldehydes catalyzed by TADDOL **83**.

Hetero DA reactions of diene **66** (R$_3$Si = TBS) with unactivated aldehydes proceeded under very mild reaction conditions and in the absence of a Lewis acid as catalyst [41]. The resulting cycloadducts were directly transformed into dihydro-4-pyrones **87** using acetyl chloride or HCl/THF (Scheme 15). Methyl pyruvate and aldimines were also reactive with this diene. Unactivated ketones can be efficiently used in these hetero DA reactions in hydrogen-bonding solvents [42]. Using 2-butanol as solvent diene **66** reacted with cyclic ketones to give after treatment with AcCl the corresponding enones **87** in moderate to good yields (35-82%). Organocatalyzed asymmetric DA reactions of aminosiloxydiene **66** with aldehydes has been carried out using TADDOL **83** (Scheme 15) [42]. The corresponding cycloadducts were transformed into dihydropyrones **87** by treatment with acetyl chloride at -78 ºC in high yields and enantioselectivities. Jensen and Sigman [43] described that the catalyst **88** gave dihydro-4-pyrone **87** in 91% ee (Scheme 15). The cycloaddition took place by hydrogen bonding with the organocatalyst **88**.
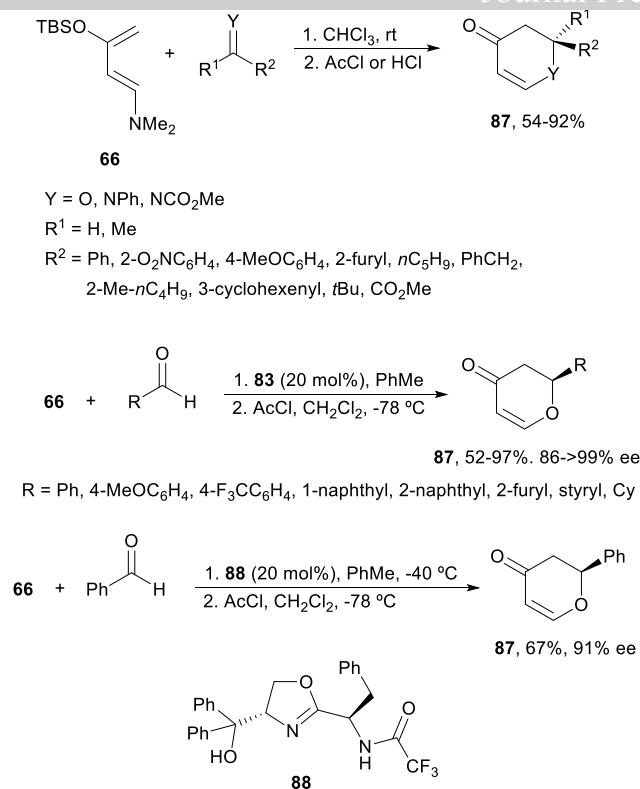
Scheme 15. Hetero DA reactions of 4-(dimethylamino)-3-(*tert*-butyldimethylsilyloxy)-1,3-butadiene **66**.

2.2. Dienamides

N-Dienyl amides and lactams [1-5] are more stable than dienamines and are prepared by: (a) acylation of α,β-unsaturated imines derived from crotonaldehyde and amines (Oppolzer method) [44,45], (b) Curtius rearrangement from azides of 1,3-dienoic acids (Overman method) [46,47], (c) thermal rearrangement of propargyl trichloroacetimidic esters also by Overman and co-workers [48-50], (d) gold-catalyzed isomerization of ynamides and allenamides [51], (e) metal-catalyzed amidation of dienyl halides with primary amides [52] and (f) metal-catalyzed cross-coupling reactions [53]. These dienes have been used extensively in synthesis of natural products and biologically active molecules.

2.2.1. Intermolecular DA reactions

Intermolecular DA reaction of acyclic dienamides were initially described by Overman and co-workers [48,49,54] using trichloroacetamido-1,3-dienes. (*E*)-Dienamide **89** reacted regiospecifically with acrolein at 110 ℃ to give **90** in 46% yield as a 3:1 mixture of *cis* and *trans* stereoisomers (Scheme 16). With maleic anhydride **89** reacted at 80 ℃ to provide **91** in 80% yield and with methyl acrylate at 110 ℃ giving a 3:1 mixture of *endo/exo* diastereomers **92**. (*Z*)-Dienamide **89** isomerizes during the last cycloaddition in dioxane or in toluene in the presence of Et$_3$N affording the same diastereomeric adducts **92** [48].
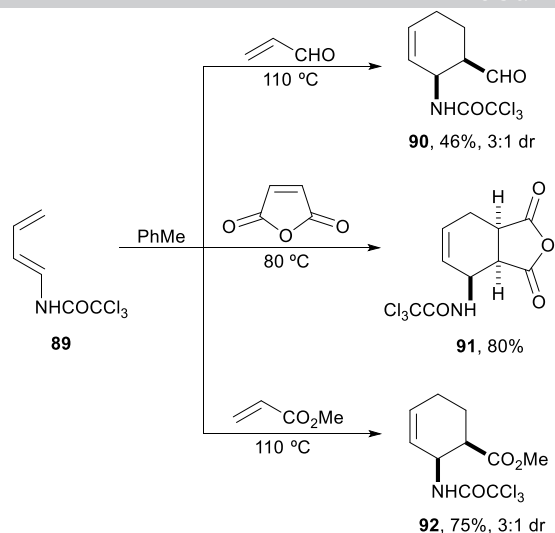
Scheme 16. DA reactions of dienamide **89** with dienophiles.

Overman and co-workers [46,54] studied the reactivity of different amidodienes **93** with methyl acrylate. Carbamate **93a** (X = OEt) reacted at 110 °C giving the adduct **94a** as a 5.4:1 *cis/trans* mixture in 78% yield (Scheme 17). The urea derivative **93b** [X = N(CH$_2$)$_4$] provided at 80 °C the adduct **94b** in 80% yield as 6:1 mixture of *cis/trans* isomers. Overman and Houk [54] showed that the *endo*-selectivity increases with faster rate of reaction. Oppolzer and co-workers [55] prepared a *N*-benzyl benzamide derivative **95**, which also showed *endo*-selectivity with different monosubstituted dienophiles (Scheme 17). Adducts **96** were obtained at temperatures in the range of 80 to 110 °C to furnish mainly *endo*-cycloadducts in good yields.
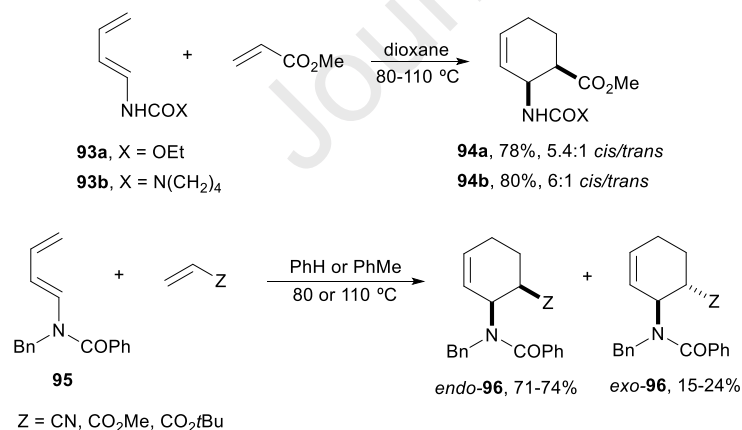
Scheme 17. DA reaction of dieniamides **93** and **95** with acrylic systems.

Overman and Jessup [56,57] have applied this type of DA reaction to the synthesis of the alkaloid (±)-pumiliotoxin C (**98**) in four steps and greater than 50% overall yield. The reaction of amidodiene **93** (R^1 = H; R^2 = EtO) with neat crotonaldehyde at 110 °C gave, after purification *endo*-adduct **97** (R^1 = H; R^2 = EtO) in 61% yield (Scheme 18). After Wittig olefination, hydrogenation, cyclization with HBr in AcOH and final hydrogenation provided the alkaloid. This strategy has been applied to the synthesis of dialkyl *cis*-decahydroquinolines [57]. Using **93** (R^1 = H; R^2 = BnO) and 2-octenal the resulting *endo*-cycloadduct has been used in the total synthesis of

(±)-perhydrogephyrotoxin also isolated from the tropical poison frogs of the genus *Dendrobates* [58]. The analgesic tilidine has been synthesized starting by cycloaddition of different amidodienes **89** and **93** (R^1 = H; R^2 = BnO) with ethyl atropate to provide the cycloadduct at 80 and 110 ºC, respectively [59]. The best results were obtained with **89** giving exclusively the corresponding *endo*-cyclohexene in 84% yield. A comprehensive study from Overman's group about the DA reaction of eight 1-(arylamino)-1,3-dienes with thirteen dienophiles has been reported [60]. In general, good *endo*-selectivity was observed in the DA reaction of dienes **89** and **93** with acrolein, methyl acrylate, crotonaldehyde and methyl crotonoate. Total regioselectivity was observed with all amidodienes with unsymmetrical dienophiles. Dienes **93** reacted efficiently with poor dienophiles such as 2-cyclohexenone, styrene and 3,4-methylenedioxystyrene.
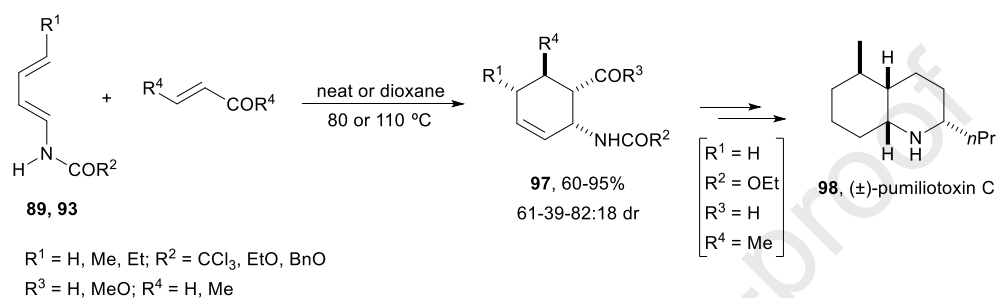
Scheme 18. DA reaction of dienic carbamates **89** and **93** with dienophiles.

Cycloadditions of dienamides **93** (R^1 = H; R^2 = BnO) [61] and **95** with quinones have been considered by Fillion and co-workers [62,63]. Tetrahydronaphthoquinones **99** and anthraquinones **100** have been prepared by DA reaction with benzoquinone and 5-substituted naphthoquinones, respectively (Scheme 19). *In vitro* cytotoxicity assays showed that naphthoquinones had significant activities towards tumor cells. Mancini and co-workers [64] described the DA reaction of *N*-tosyl-3-nitroindole (**102**) with dienamides **95** and **101** (Scheme 19). The corresponding adducts **103** were obtained regioselectively in good yields, being advanced intermediates for the synthesis of *Aspidosperma* alkaloids.
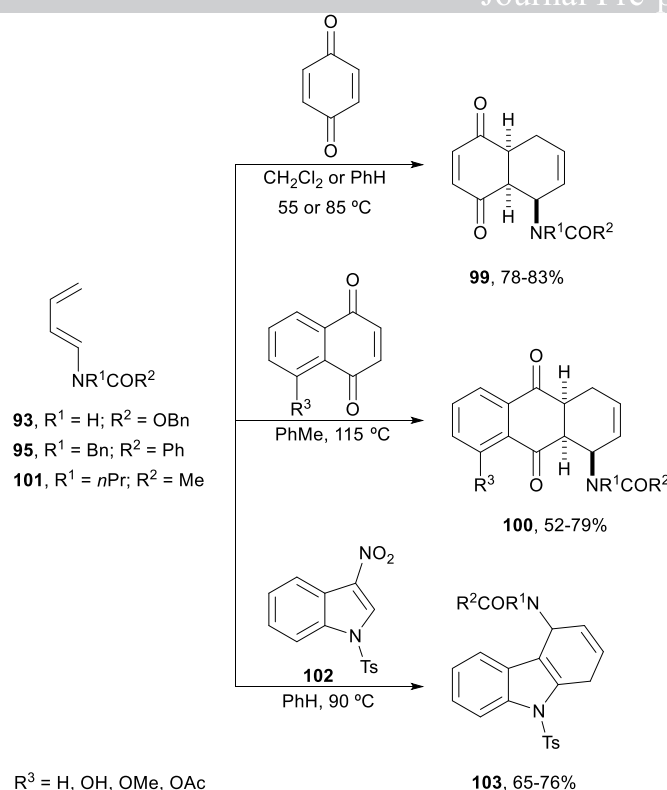
Scheme 19. DA reactions of dienamides **93**, **95** and **101** with dienophiles.

The nitroso DA reaction with dienamides has been reported by Masson and co-workers [65]. Arylhydroxylamines **104** generate *in situ* nitrosoarenes under visible light catalytic aerobic conditions and blue LED irradiation using a 5 mol% of Ru(bpy)$_3$PF$_6$ as photocatalyst. The DA reaction with dienamides of type **93** took place at room temperature in trifluoroethanol (TFE) to provide *cis*-3,6-dihydro-1,2-oxazines **105** in good yields and excellent diastereoselectivity (Scheme 20). Hydroxylamines were oxidized by Ru(bpy)$_3{}^{2+}$ in its triplet state and the Ru(bpy)$_3{}^+$ was reoxidized by O$_2$ to generate the catalyst and superoxide radical anion O$_2{}^{\cdot-}$. Subsequently ArNHOH$^{+\cdot}$ was deprotonated by lutidine giving the radical ArN$^\cdot$OH which underwent a single electron transfer with O$_2{}^{\cdot-}$ to produce the nitroso compound ArNO.

R^1 = OBn, OCH$_2$CH=CH$_2$, OCH$_2$CCH, SBn
R^2 = H, F, Cl, Br, I, Me
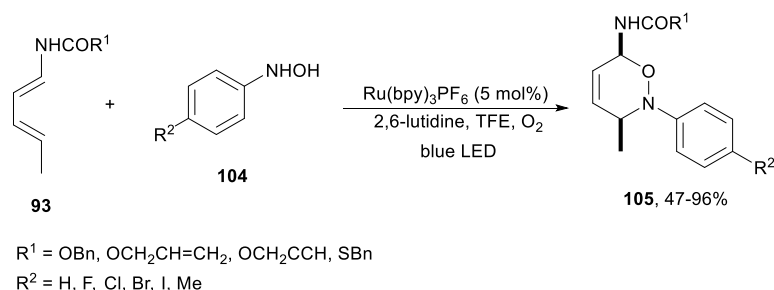
Scheme 20. Nitroso DA reactions of dienamides **93** under visible light photoredox conditions.

Asymmetric intermolecular DA reactions of dienamides were initially performed using chiral auxiliaries. Smith and co-workers [66,67] used ethyl *N*-dienyl pyroglutamate **106** as chiral

diene with ethyl acrylate and methyl vinyl ketone as dienophiles to provide adducts **107** regio- and diastereoselectively mainly with excellent *endo*-selectivity (Scheme 21).
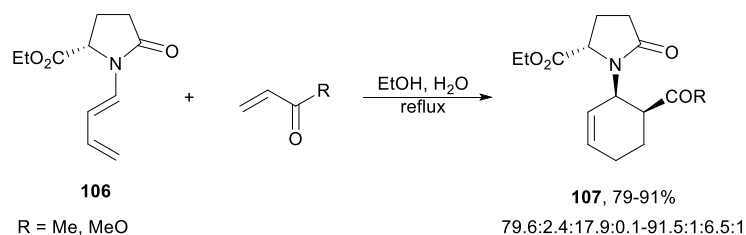
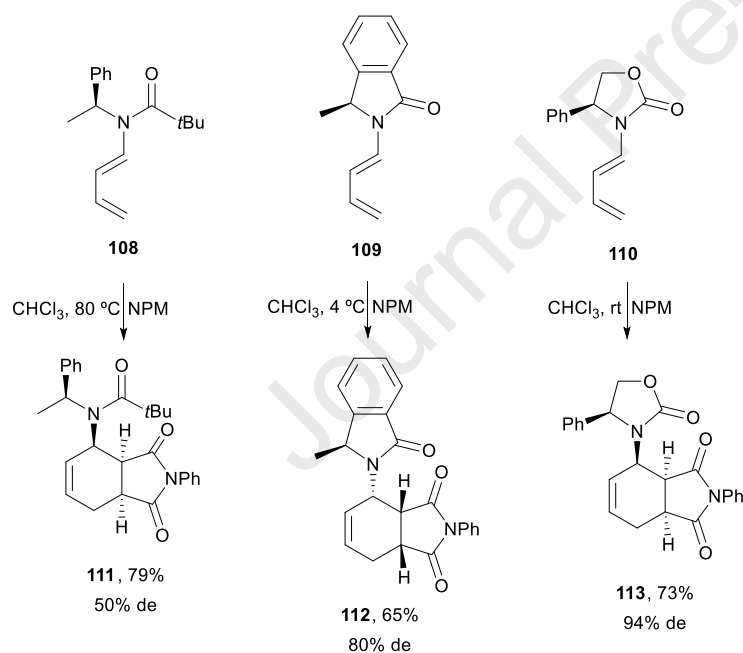

Scheme 21. Asymmetric DA reactions of ethyl *N*-dienylpyroglutamate **106**.

Stevenson and co-workers [68,69] used chiral dienamides derived from a chiral amine **108**, lactam **109** and oxazolidinone **110**. These dienic systems reacted with dienophiles such as NPM to give the corresponding cyclohexenes **111-113** with complete regio- and *endo*-selectivity and high diastereoselectivity in the case of **113** (Scheme 22).

Scheme 22. Asymmetric DA reactions of chiral dienamides **108-110** with NPM.

DA reactions of *N*-(butadienyl)-4-phenyloxazolidin-2-one **110** and thione **114** with different dienophiles have been reported by Marchand-Bryanert and co-workers [70,71]. Chiral 4-phenyloxazolidin-2-thione auxiliary provided better facial selectivity than oxazolidinone due to steric hindrance between the sulfur atom and the substituent in the *exo*-transition state. Methyl acrylate, a vinyl phosphonate and *N*-methylmaleimide (NMM) gave the best results affording the corresponding adducts **115** (Scheme 23).
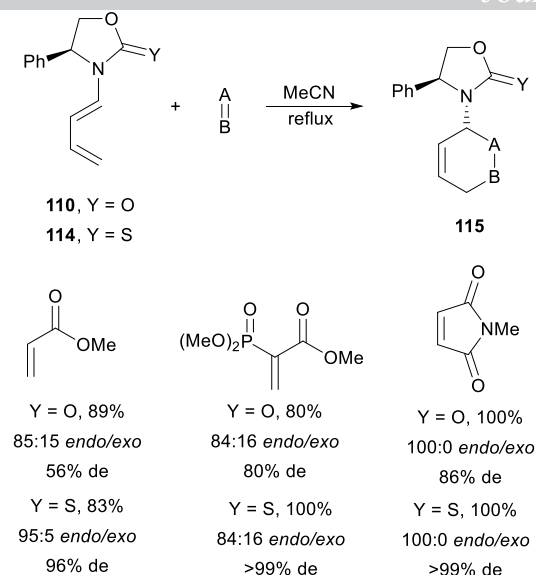
Scheme 23. Asymmetric DA reactions of chiral dienamides **110** and **114**.

Calmiès and co-workers [72] used as strategy for the asymmetric DA reaction of dienyl carbamate **93** (R^1 = H; R^2 = BnO) [61], the use of a chiral acrylate **116** (Scheme 24). This cycloaddition proceeded with total *endo*-diastereoselectivity and good facial control to give mainly adduct **117** in 85:15 dr, which was isolated in 30% yield and 99% de and transformed into (1*R*,2*S*)-*cis*-2-aminocyclohexane carboxylic acid. An enantioselective catalyzed method was described by Wipf and Wang [73] using carbamate **93** (R^1 = H; R^2 = BnO) and *N*-acryloyloxazolidinone **118** using as chiral catalyst Kobayashi's scandium (*R*)-BINOL complex as Lewis acid [74] (Scheme 24). The corresponding *endo*-adduct **119** was obtained in 92% yield and ee, whereas the *exo*-product was isolated in 6% yield. This product **119** was further transformed into the dihydroxylated β-amino ester **120** in 74% overall yield.
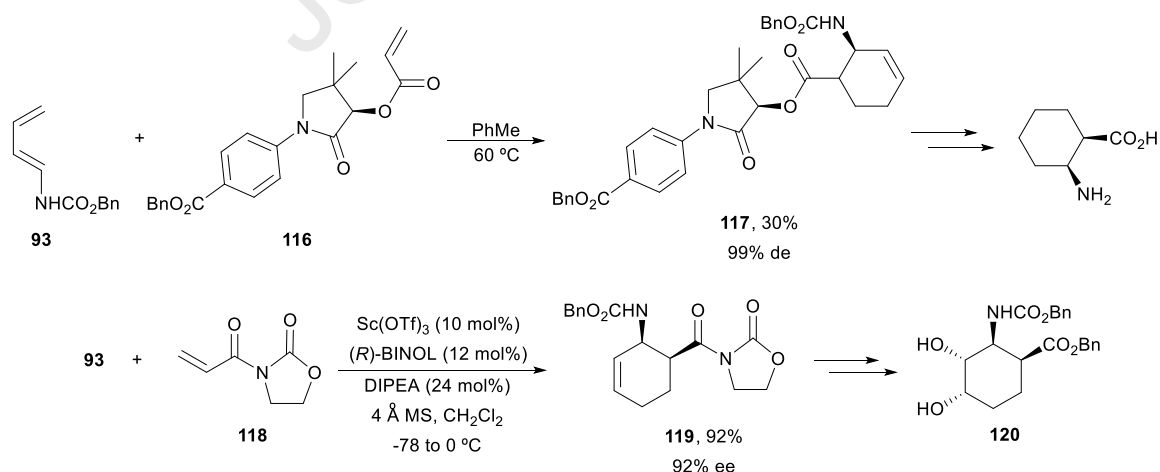
Scheme 24. Asymmetric DA reaction of dienyl carbamate **93** with chiral **116** and with **118** using a chiral catalyst.

Asymmetric DA reactions of dienamides **93** with methyleneindolinones **121** catalyzed by *N,N'*-dioxide/Ni(II) complex with ligand **122** provided spirooxindole-cyclohexaneamides **123**

with high diastereo- and enantioselectivities (Scheme 25) [75]. Taking into account control experiments and spectral data simplified TSI was proposed. The tetradentate ligand **122** and the bidentate dienophile **121** are coordinated with Ni(II) to form an octahedral geometry. The *Si*-face of the methyleneindolinone is shielded by the amide group of the ligand and the dienamide attacks from the *Re*-face.
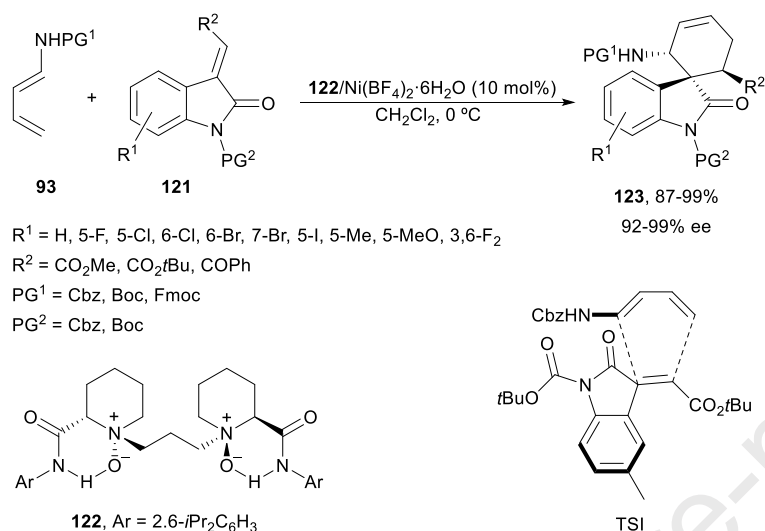
Scheme 25 Enantioselective Ni-catalyzed DA reaction of dienyl carbamates **93** with methyleneindolinones **121**.

Chiral phosphoric acids have been employed as catalysts in the enantioselective DA reaction of dienamides **99** and α,β-unsaturated aldehydes by Terada's group [76] (Scheme 26). This Brønsted acid catalysis provided the best results using diphosphoric acid **124** to provide *endo*-products (1*S*,6*R*)-**125** in good yields and excellent enantioselectivities. They also used a new C1-symmetric chiral bis-phosphoric acid **126** for the cycloaddition of dienamides **99** with acroleins, methacrolein and α-haloacroleins to provide adducts **127** in good yields and enantioselectivities [77].
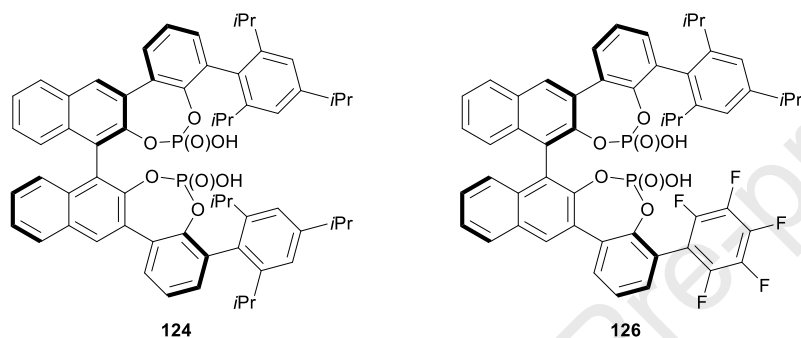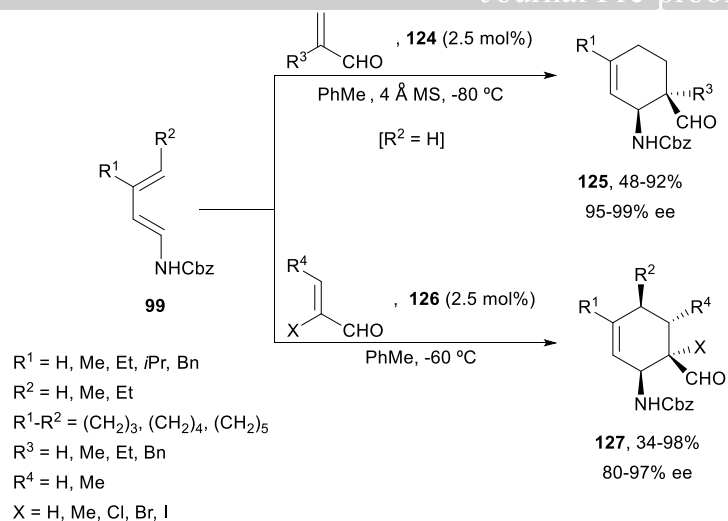
Scheme 26. Enantiocatalyzed DA reactions of dienyl carbamates **99** with α,β-unsaturated aldehydes using the chiral diphosphoric acids **124** and **126**.

Chiral phosphoramide **128** was the appropriate Brønsted acid catalyst for the enantioselective cycloaddition of **99** with aryl vinyl ketones. Jiao and co-workers [78] reported this DA reaction which took place with *endo*-selectivity giving adducts **129** in good yields and enantioselectivities (Scheme 27). DFT calculations supported the stereochemical results.
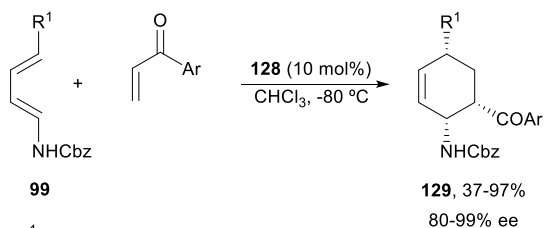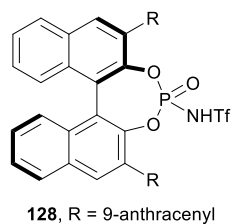
Scheme 27. Enantiocatalyzed DA reactions of dienyl carbamates **99** with aryl vinyl ketones using the chiral phosphoramide **128**.

Nishikawa, Hara and co-workers [79] used a chiral pyridinium phosphoramide **130** as a dual Brønsted acid catalyst for the enantioselective DA reaction of dienamides **99** with maleimides and benzoquinones. In the case of maleimides, adducts **131** were obtained with *endo*-selectivity, high yields and enantioselectivities (Scheme 28). Benzoquinones provided chiral dihydronaphthalenes **132** after acetylation with Ac_2O of the unstable cycloadducts.
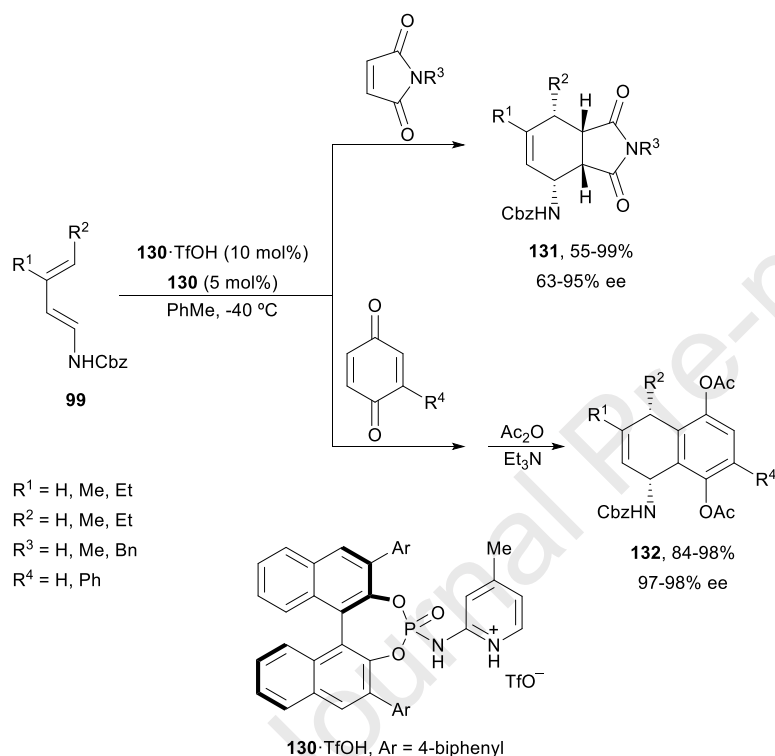
Scheme 28. Enantiocatalyzed DA reactions of dienyl carbamates **99** with maleimides and quinones using a chiral pyridinium phosphoramide **130**·TfOH.

Chiral phosphoric acid-catalyzed asymmetric hetero-DA reactions of nitrosoarenes with different substituted dienyl carbamates **99** was described by Masson and co-workers [80]. The cycloaddition afforded *cis*-3,6-disubstituted dihydro-1,2-oxazines **133** in excellent regio-, diastereo and enantioselectivities (Scheme 29). Regioselectivity, which is reversed compared to Masson previous work (Scheme 20) [65], was explained by protonation of the nitrogen of the nitroso group both by experimental and theoretical studies. According to this mechanism a highly asynchronous concerted cycloaddition process was proposed. The obtained chiral oxazines can be converted into valuable chiral 1,4-amino alcohols such as **134** by N−O cleavage.
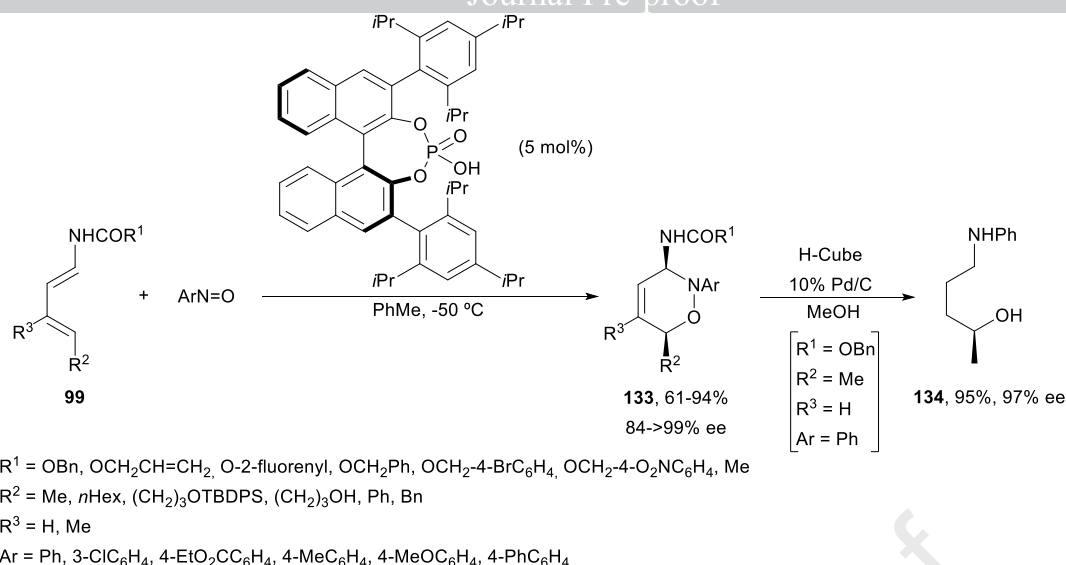
Scheme 29. Chiral phosphoric acid-catalyzed nitroso DA reactions of dienyl carbamates **99**.

Terada's group [81] designed a chiral phosphoric acid **136** for the hetero-Diels-Alder reaction of azopyridine carboxylates **135** with amidodienes **99** to give stereoselectively substituted 1,2,3,6-tetrahydropyridazines **137** (Scheme 30). From DFT calculations the multipoint hydrogen-bonding interactions among the carboxylic acid, monophosphoric acid, 2-azopyridinecarboxylate and NH-aminodiene moieties in *endo*-TSI is depicted in Scheme 30.

endo-TSI
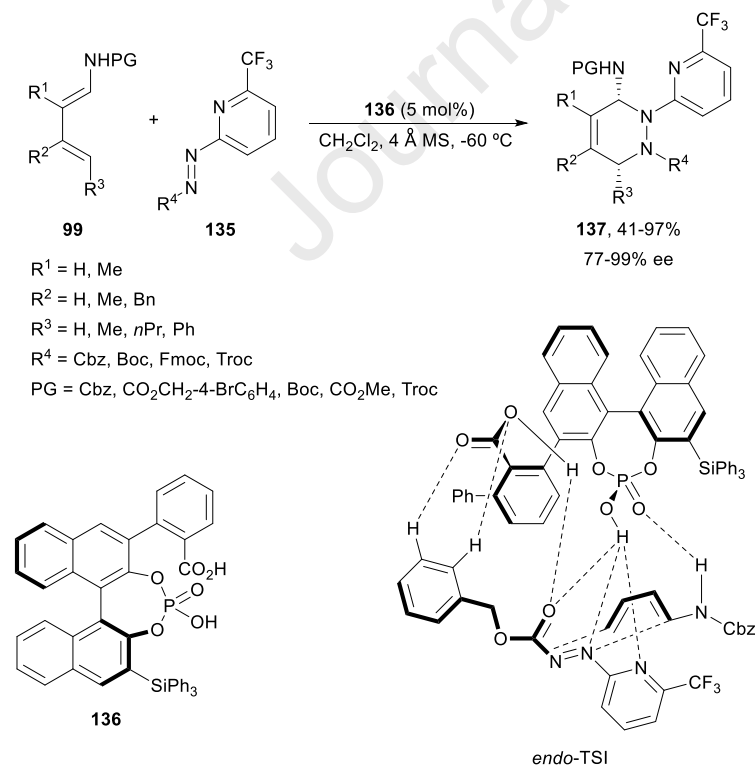
Scheme 30. Chiral phosphoric acid-catalyzed hetero-DA reactions of dienyl carbamates **99** with azopyridinecarboxylates **135**.

Biological catalysts such as proteins have been used in cycloaddition reactions namely antibody catalysts [82]. Schultz [83,84] and Janda [85-87] groups have reported DA reactions of dienamides **138** and **139** with a maleimide **140** and *N,N*-dimethylacrylamide, respectively. In the case of the DA reaction of **138** and **140** only one diastereomer **141** was formed using antibody 39-A11 as catalyst [83] (Scheme 31). The energy of the LUMO becomes closer to the HOMO of the diene because of hydrogen bonding of the dienophile. However, a low effective molarity (0.35 M) was a major drawback of this catalyst. Antibody 39-A11 was modified by site-directed mutagenesis to improve the packing interactions with the diene affording a 10-fold increase in catalytic rate [84]. Janda and co-workers [85] prepared a pair of antibodies which generated the *endo* and *exo*-adducts **142** in greater than 98% ee, whereas the uncatalyzed reaction gave a racemic mixture of 85:15 *endo:exo* adducts (Scheme 31).
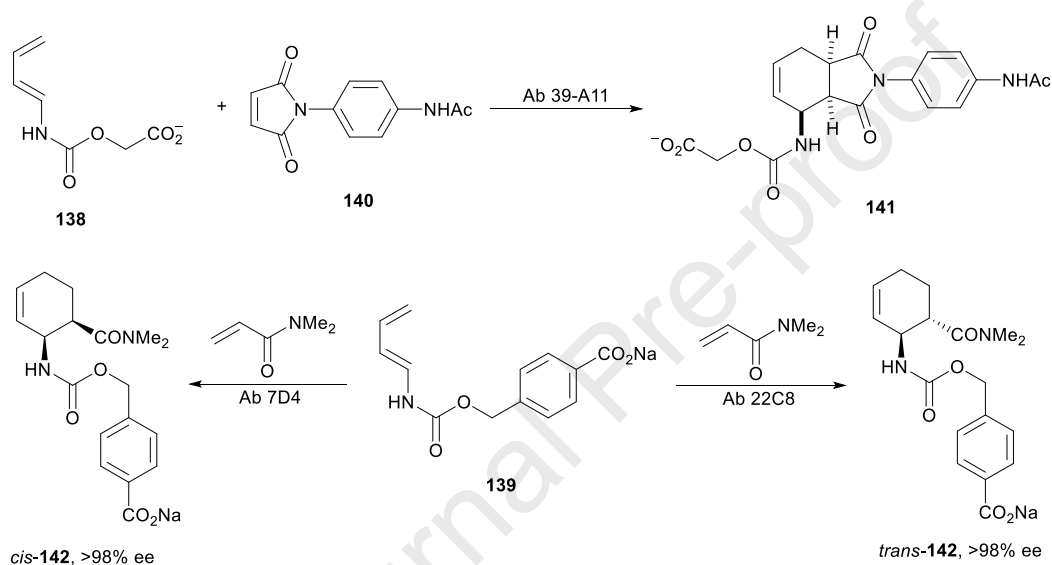
Scheme 31. Antibody-catalyzed DA reactions of dienamides **138** and **139**.

Functionalized dienamides bearing a sulfur substituent at 4-position were described by Overman and co-workers [88]. The regioselectivity of these dienes **143** with dienophiles was controlled by the carbamate group giving products **144-146** (Scheme 32). In the case of the thioether derivative **143a** *endo*-cycloaddition occurred with NPM and phenyl vinyl ketone, whereas with acrolein a 4:1 mixture of *end/exo* diastereomers was obtained. The mixture of diastereomers **146a** was treated with DBU in refluxing methanol to give the *exo* product in 83% yield. Sulfone diene carbamate **143b** reacted with acroleins at 56 ℃ to provide a 7:1 mixture of adducts **146b** in 78% yield and the sulfoxide **143c** reacted with phenyl vinyl ketone at room temperature to give adduct **145c** in 85% yield as 1:1 mixture of diastereomers and with acrolein at 56 ℃ a 10:10 (*endo*):1:1 (*exo*) mixture of cycloadducts **146c** were formed.
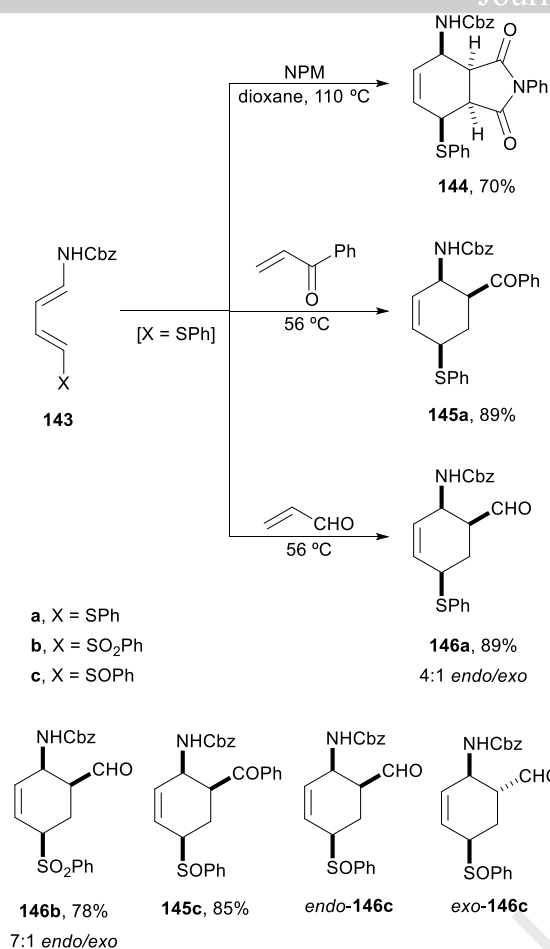
Scheme 32. DA reactions of sulfur substituted amidodienes **143**.

Jaeger and co-workers [89] studied DA reactions of a sulfone diene **147** bearing an ammonium substituent in the carbamate (Scheme 33). This surfactant diene **147** in micelle concentration (7×10^{-4} M) in water reacted at 50 °C with aryl vinyl ketones to furnish mainly *endo*-adducts **148** without influence of the orientation in the aggregates.
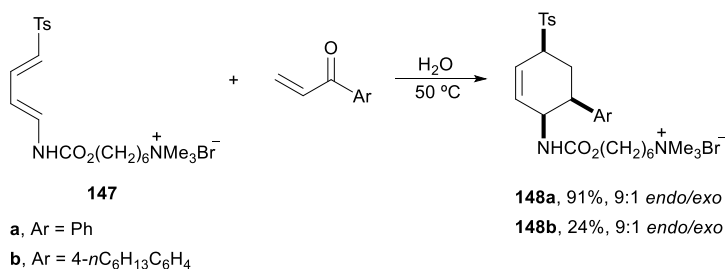
Scheme 33. DA reactions of a sulfactant 4-tosyl dienyl carbamate **147** with aryl vinyl ketones.

Cascade reactions were observed by Neier and co-workers [90] when the silyl acetal of *N*-isopropyl-*N*-propanoyl-1-amino-1,3-butadiene **149** was allowed to react with NPM and acryloyl chloride. In the case of α,β-unsaturated acyl chlorides, after the DA reaction an intramolecular acylation took place giving bicyclic products **150** (Scheme 34) [91].
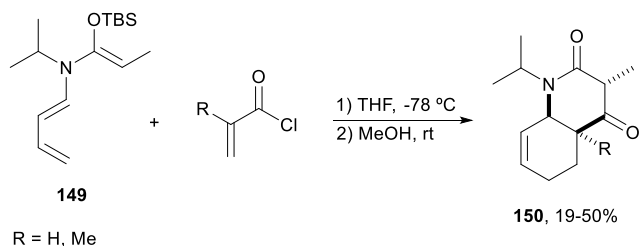
Scheme 34. DA reaction-acylation of diene **149** with α,β-unsaturated acyl chlorides.

1-Hydrazinodiene **151** has been used in a Lewis acid catalyzed DA reaction by Sorensen and co-workers [92]. These dienes underwent DA reactions with a range of dienophiles using Sc(OTf)$_3$ to furnish adducts **152** with good diastereoselectivities (Scheme 35). These products **152** were submitted to a reductive 1,5-sigmatropic rearrangement with 1,3-transfer of stereochemistry giving cyclohexenes **153** in three steps.
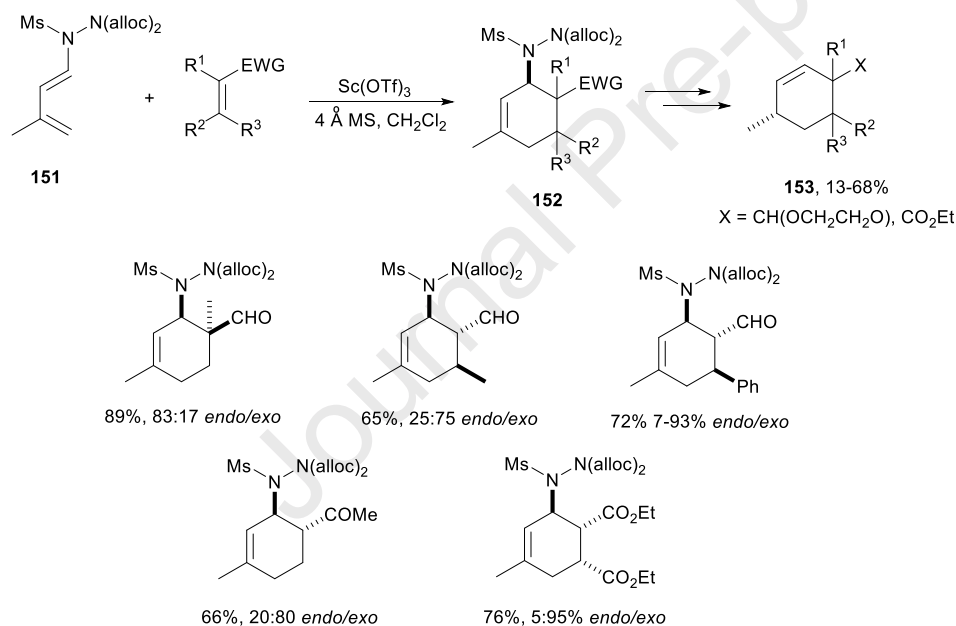
Scheme 35. DA reactions of 1-hydrazinodiene **151**.

Rawal and co-workers prepared 1-amido-3-silyloxy-1,3-butadienes to control the reactivity of 1-amino-3-silyloxy-1,3-butadienes **66** in DA reactions. For the synthesis of a key intermediate for the synthesis of tabersonine, an *Aspidosperma* alkaloid, diene **154** was prepared and submitted to the DA reaction with ethacrolein (Scheme 36) [93]. The corresponding adduct **155** was obtained in 97% yield with complete regiocontrol and excellent *endo*-selectivity.
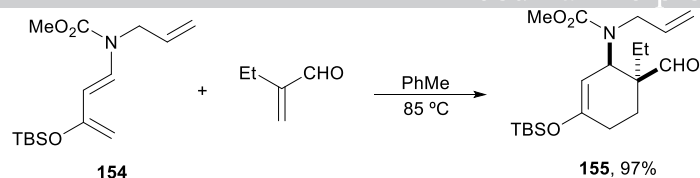
Scheme 36. DA reaction of 3-silyloxydienamide **154** with ethacrolein.

Asymmetric DA reactions of 3-silyloxydienamides were initially performed using oxazolidinones as chiral auxiliaries by Rawal group [94]. The reactivity of achiral oxazolidinone diene **156** was firstly explored with three different dienophiles. In the case of NPM the cycloaddition took place at -20 ºC to room temperature giving *endo*-**157** in 78% yield (Scheme 37). With methacrolein the reaction occurred at 55 ºC giving *endo*-**158** in 99% yield and methyl acrylate reacted at 60 to 70 ºC giving in 88% yield a 3:1 mixture of *endo/exo* diastereomers **159**. Considering different chiral oxazolidinone dienes **160-162**, the best results were obtained with **162**, which reacted with different dienophiles, such as methacrolein, ethacrolein, ethyl fumarate and maleate, maleic anhydride and NPM in good yields and modest to high *endo*-selectivity. Upon reduction of cycloadducts **163** and hydrolysis, substituted cyclohexenones **164** were obtained with ee ranging from 22 to >98%.
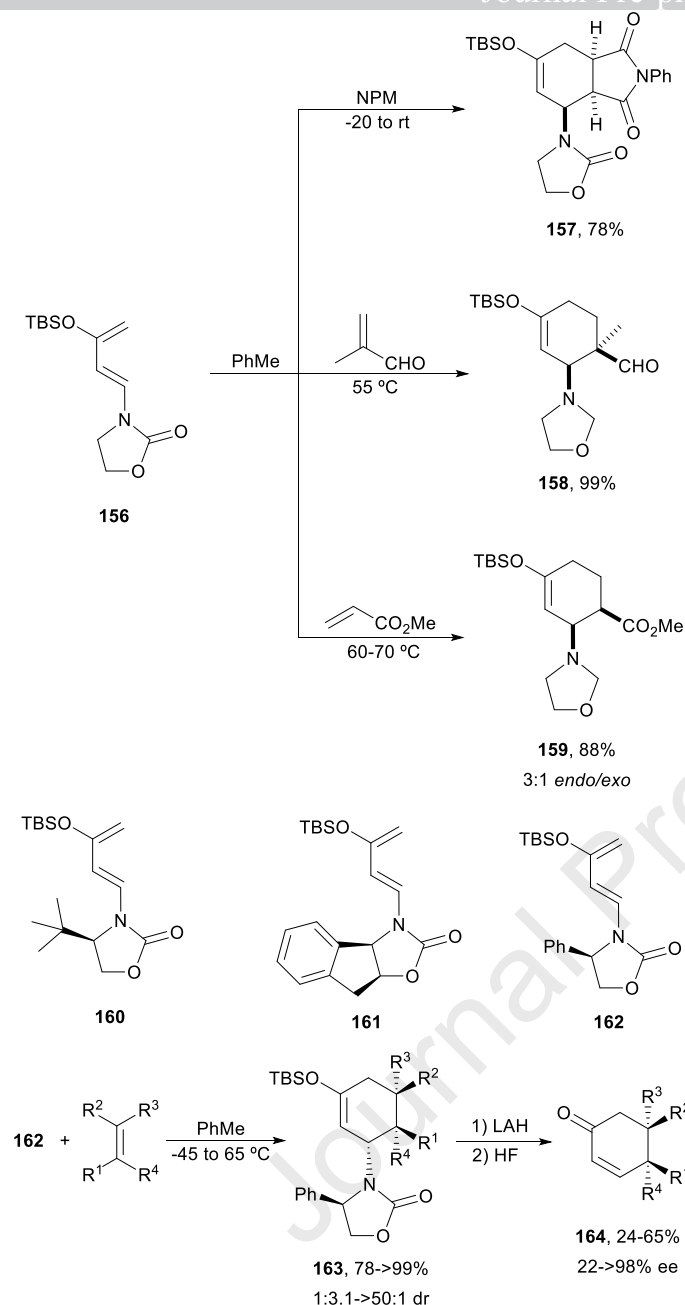
Scheme 37. DA reactions of 3-silyloxy dienamides **156**, **160-162**.

Rawal and co-workers [95-98] reported enantioselective DA reactions of dienamides **154** with α,β-unsaturated aldehydes in the presence of 5 mol% of Jacobsen chiral salen-Cr(III) complex **165** (Scheme 38). High *endo*-selectivity was observed with *N*-benzyl carbamate **154** (R^1 = Bn) at -40 ºC in dichloromethane. Based on X-ray analysis of the salen-Co(III) complex a model for the cycloaddition has been proposed [97]. The favored TSI toward TSII for the salen-Cr(III) explain the observed asymmetric induction of the obtained products **166**. The same catalyst has been used in the enantioselective DA reaction of dienamides **99** with methacrolein [96]. In the case of α,β-unsaturated aldehydes [97] the salen-Co(III) complex gave the corresponding cycloadducts with total *endo*-diastereoselectivity in 100% yield and 85-98% ee. The cycloaddition of **154** (R^1 = allyl) with ethacrolein catalyzed by Jacobsen chiral Cr(III) complex **165** gave the corresponding cycloadduct **166** (R^1 = allyl, R^2 = Et) in 91% yield and 96% ee. This methodology has been used as key step toward the synthesis of (+)-tabersonine, (+)-16-methoxytabersonine,

(+)-aspidospermidine and (−)-quebrachamine [98]. The Co-catalyzed reaction was applied by Nicolaou and co-workers to the synthesis of (−)-platencin [99].
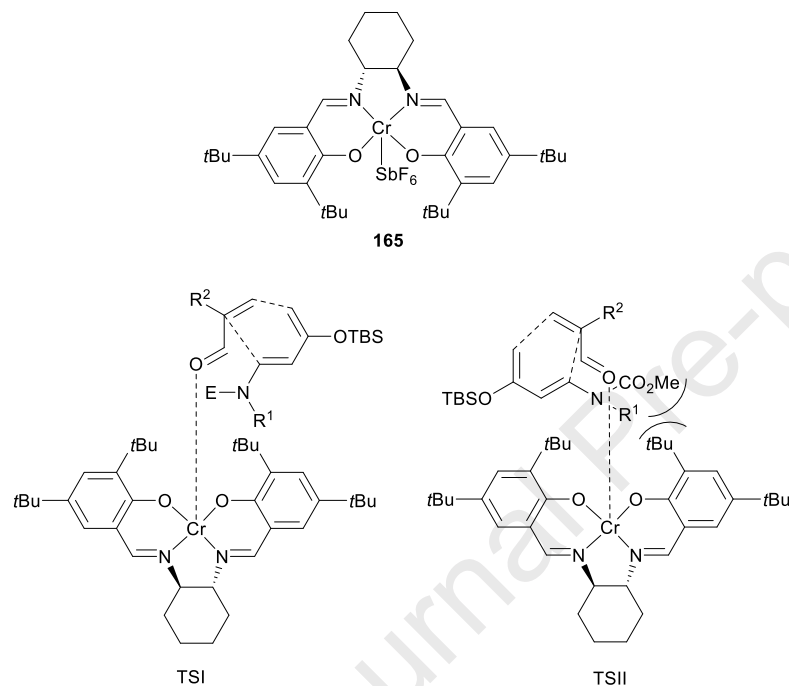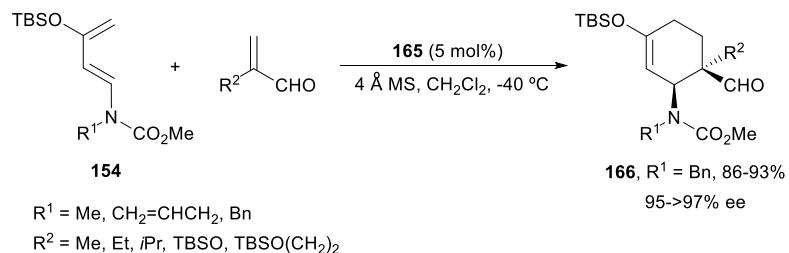
Scheme 38. Enantioselective DA reactions of dienes **154** (R^1 = Bn) with α,β-unsaturated aldehydes catalyzed by Cr(III)-salen complex **165**.

1-Formamido-2-silyloxy-1,3-butadienes **167** have been prepared by Tomé and co-workers [100] from 1,3-dichloroacetone by means of phosphorane formation, formamide substitution, Wittig olefination and silylation. The DA reaction with NMM was carried out under toluene reflux providing cycloadducts **168** in good yields and diastereoselectivities (Scheme 39).
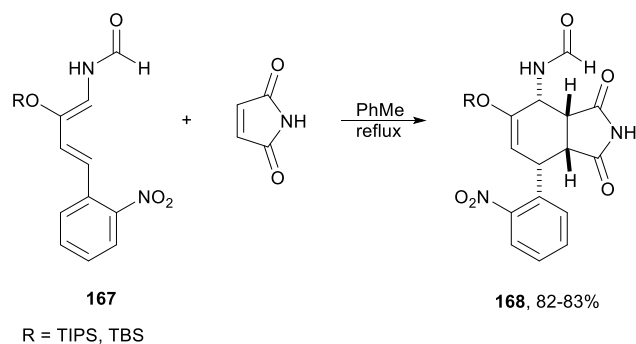
Scheme 39. DA reactions of 2-silyloxy dienamides **167** with NMM.

2.2.2. Intramolecular DA reactions

Intramolecular DA cycloadditions [1-5,101-103] of dienamides were initially reported by Oppolzer's group. Dienyl carbamate **169a** cyclized under thermal conditions giving stereoselectively octahydroquinoline **170a** in 84% yield [104] (Scheme 40). However, low yield was observed in the cycloaddition of **169b** to product **170b**, precursor of (±)-pumiliotoxin C (**98**), which was obtained in only 25% yield [105]. Witiak and co-workers [106] used a similar methodology for the synthesis of *cis*-decahydroquinoline-5-carboxylic acids which contain the γ-aminobutyric acid (GABA) moiety. Dienyl carbamate **171** was heated at 200-210 ℃ also in a sealed tube giving mainly the *cis*-isomer **172** in 60% yield (Scheme 40).
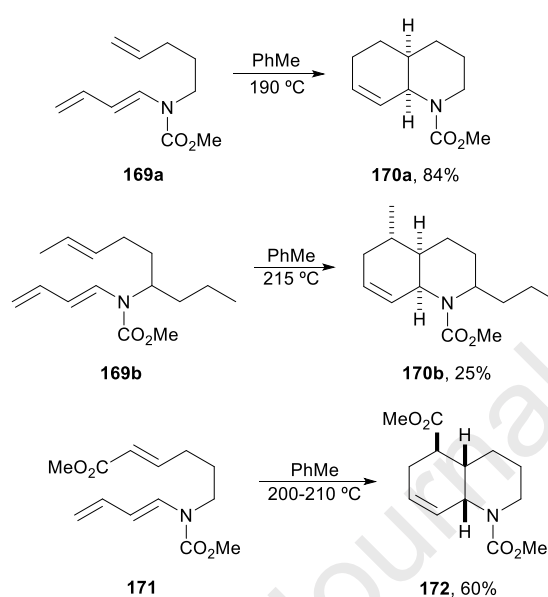
Scheme 40. Intramolecular DA reactions of dienyl carbamates **169** and **171**.

Natural pumiliotoxin C [(*R*)-**98**] was prepared from chiral dienamide **173** by Oppolzer's group [107]. Starting from (*R*)-norvaline, the corresponding amide **173** was heated at 230 ℃ in the presence of bis(trimethylsilyl)acetamide to furnish mainly **174** in 60% yield (Scheme 41). This cycloadduct was further transformed into the antipode (*R*)-pumiliotoxin C (**98**), therefore the synthetic process was further carried out starting from (*S*)-norvaline in order to prepare natural (*S*)-pumiliotoxin C [108].
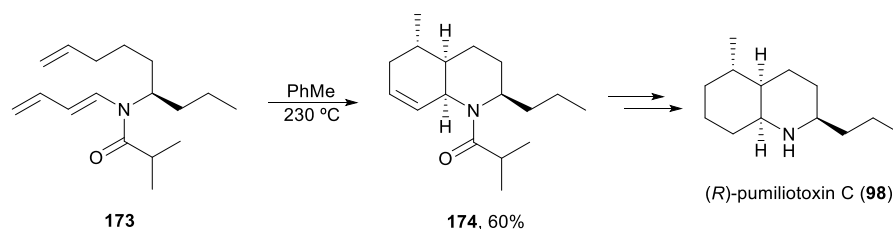
Scheme 41. Intramolecular DA reaction of dienamide **173** precursor of (*R*)-pumiliotoxin C (**98**).

An efficient indole synthesis *via* intramolecular DA reaction of dienyl carbamate bearing an allene was developed by Kanematsu and co-workers [109]. Allenic dienyl carbamates **175** cyclized under thermal conditions to provide cycloadducts **176**, which were oxidized with DDQ or activated MnO$_2$ in benzene at room temperature to the corresponding indole derivative **177** (Scheme 42).

R^1, R^3 = H, Et; R^2 = H, Me; R^4 = H, Bn; R^1-R^2 = (CH$_2$)$_4$
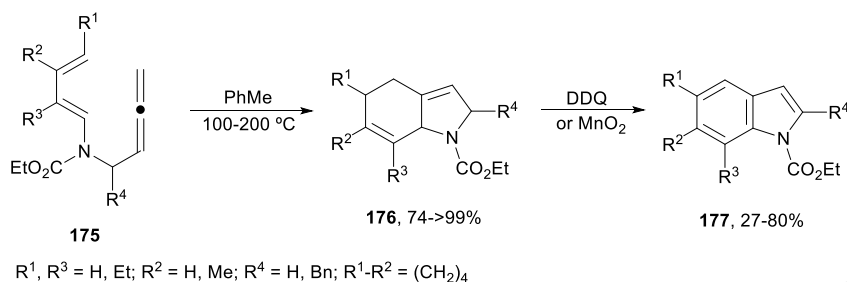
Scheme 42. Intramolecular DA reactions of allenic dienyl carbamates **175**.

Allenic dienamide **178** was employed by Kanematsu and co-workers [110] to perform the enantioselective total synthesis of polyalkylindole alkaloid *cis*-trikentrin B. Intramolecular DA reaction of **178** proceeded at 160 °C in a sealed tube to give compound **179** in 88% yield (Scheme 43).
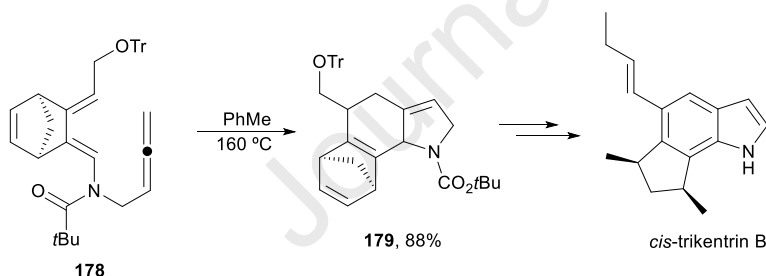
Scheme 43. Intramolecular DA reaction of allenic dienamide **178**.

Martin and Li [111] prepared a tricyclic enone **182**, key intermediate in the total synthesis of the alkaloid (±)-dendrobine from the cycloadduct **181** starting from a olefinic dienamide **180** (Scheme 44). Compound **180** was submitted to thermolysis in xylenes at 180 °C to provide a 55% yield of a 8:1 mixture of cycloadducts which after separation **181** was isolated. The isopropyl group in **180** favors the *s-cis*-conformation facilitating the DA reaction and the *endo*-cycloadduct. Compound **181** was further transformed into the key intermediate **182**. A short synthesis of strychnine was reported by Rawal and Iwasa [112] involving a reaction of aminodiene **183** (Scheme 44). Upon heating **183** in benzene in a sealed tube at 185-200 °C product **184** was obtained diastereoselectively in quantitative yield with three of strychnine stereocenters already set.
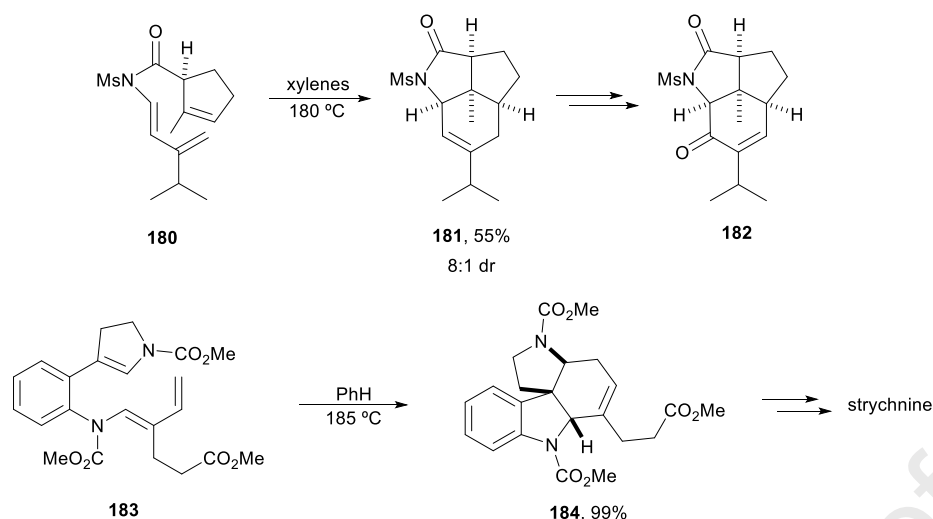
Scheme 44. Intramolecular DA reaction of alkene dienamides **180** and **183**.

Oppolzer [113,114] described the thermal rearrangement of 1-aminobenzocyclobutene **185** to provide a transitory dienamide **186** diastereoselectively, which cyclized to furnish a 4.7:1 mixture of *cis* and *trans* benzo[*g*]indoles **187** in 96% yield (Scheme 45). This synthetic procedure has been applied as key step in the synthesis of the racemic alkaloid chelidonine using **188** as starting carbamate [115]. This acetylene **188** rearranged smoothly in *o*-xylene at 120 ºC to give crystalline tetrahydrobenzo[*c*]phenanthridine **189**, which was further transformed into chelidonine. They observed different stereochemical results using amide **190** or its methyl carbamate **192**. In the case of the amide the *trans*-product **191** was formed in 90% yield, whereas the carbamate gave the *cis*-adduct **193** in 78% yield due to the higher flexibility of **192** (Scheme 45).
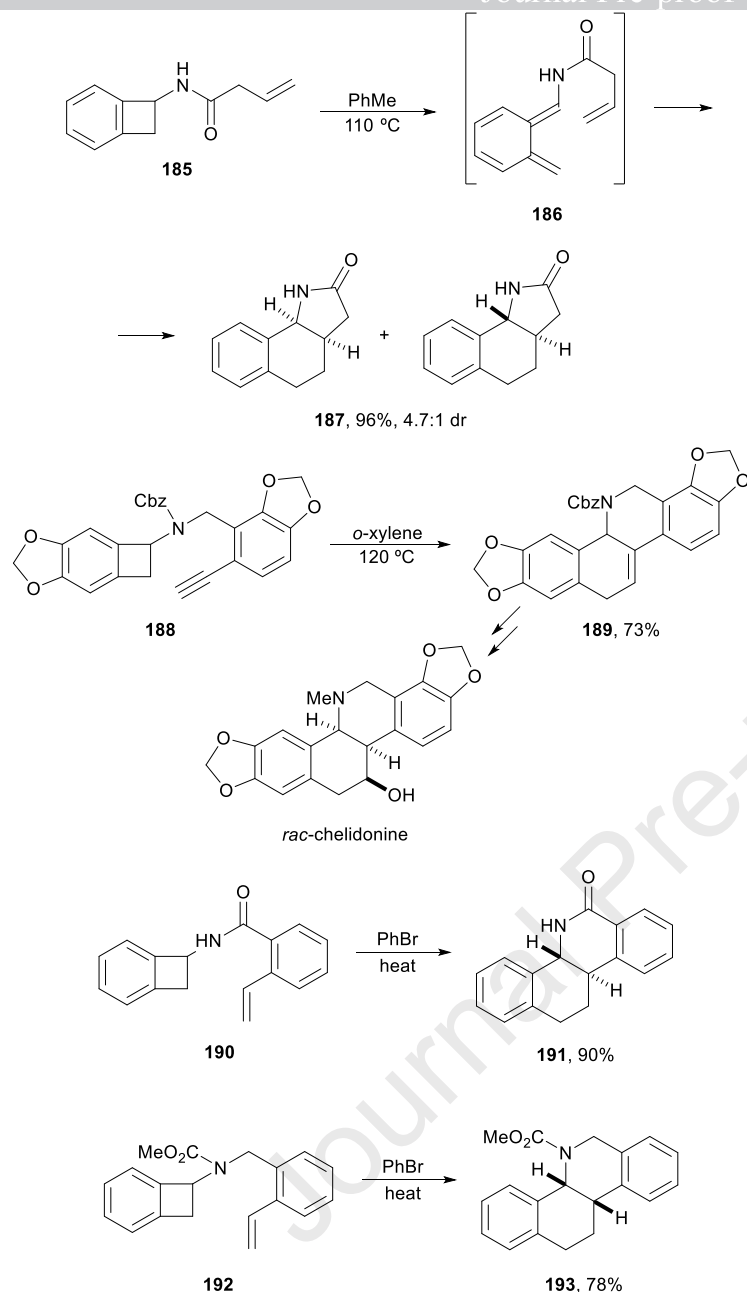
Scheme 45. Intramolecular *ortho*-quinodimethane cycloaddition of 1-amidobenzocyclobutenes **185**, **188**, **190** and **192**.

The synthesis of amido substituted benzocyclobutenes was carried out by an enamide-benzyne [2+2] cycloaddition by Hsung and co-workers [116]. A tandem [2+2] cycloaddition of benzyne formed from **194** followed by pericyclic ring-opening and intramolecular [4+2] cycloaddition provided *cis*-products **195** (Scheme 46). By using a chiral enamide derived from (*S*)-aspartic acid the corresponding product **196** was obtained by intermediacy of the amido benzocyclobutenes in a high stereoselective manner. In both cases TSI and TSII have been proposed to explain the stereochemical results.
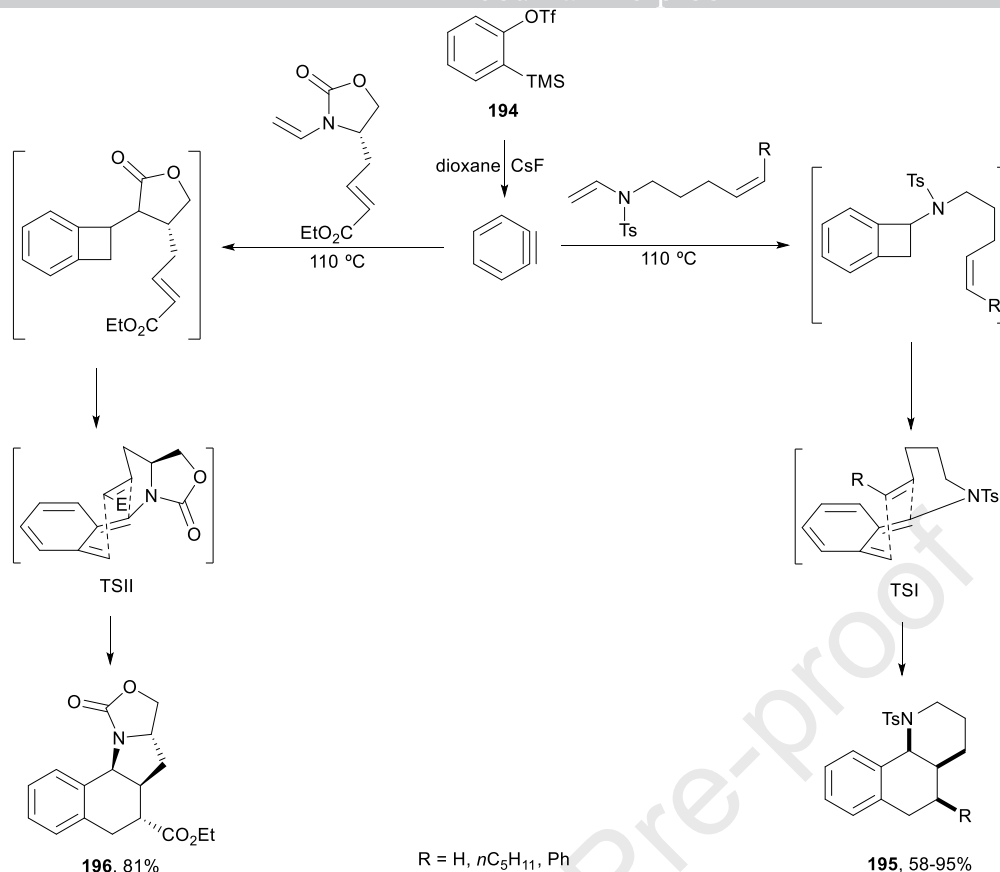
Scheme 44. Tandem [2+2]-[4+2] cyclizations of amido benzocyclobutenes.

Gauvry and Huet [117] prepared dienamides from cyclobutene compounds, which were allowed to react with dienophiles to give the corresponding cyclohexenes by an electrocyclic ring opening-[4+2] cycloaddition. This strategy has been applied to the preparation of a new cyclohexene nucleoside. Starting from bicyclic lactam **197** methanolysis gave dienyl carbamate **198**, which reacts with maleic anhydride to provide **199** (Scheme 47). Further transformations provided the nucleoside analogue **200**.
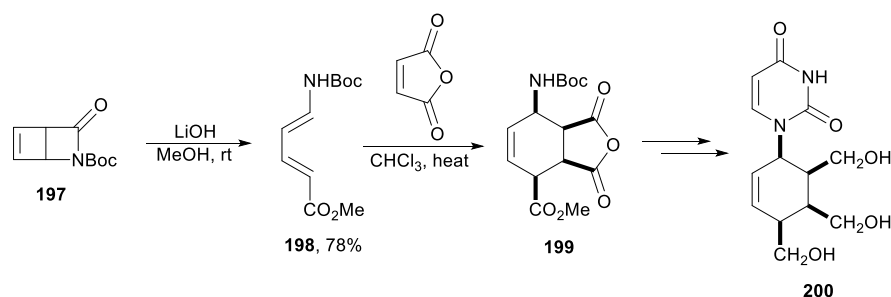
Scheme 47. Synthesis of dienyl carbamate **198** from lactam **197** and DA reaction.

Another Oppolzer-type IMDA reaction was carried out through γ-isomerization of allenamides **201** followed by IMDA [118]. Hsung and co-workers [119] previously reported the γ-isomerization of allenamides to provide 1-amido-1,3-dienes. The tandem process was carried out by treatment of compound **201** with 10 mol% of camphorsulfonic acid (CSA) to give **202**

followed by treatment with Et$_3$N (or a proton sponge) at 165 ºC, so the bicyclic amine **203** was obtained in 76% yield (Scheme 48).
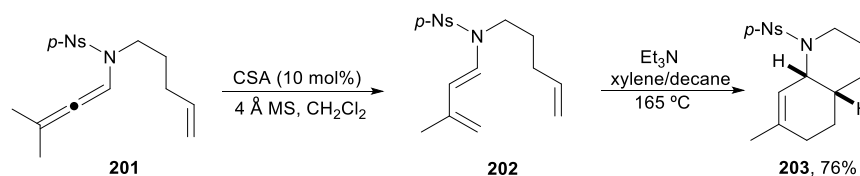
Scheme 48. Tandem γ-isomerization-IMDA of allenamide **201**.

3. Acyclic 1-amino-1,3-dienes: Multicomponent reactions

3.1. Amides-aldehydes-dienophiles (AAD) reactions

Beller and co-workers [120] described in 2001 a multicomponent reaction (MCR) [121] in which Amides-Aldehydes-Dienophiles (AAD reaction) are involved to afford expeditious preparation of multisubstituted cyclohexene and cyclohexadiene derivatives. This strategy allows the *in situ* generation of the dienamide **I**, from amide-aldehyde condensation-isomerization, which is trapped by the dienophile present in the reaction medium. Cycloadducts **204-207** were obtained by reaction of amides or 1,1-dimethylurea with aldehydes and maleimides, acetylenedicarboxylates, acrylonitrile and maleic anhydride as dipolarophiles using acetic anhydride, a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) in *N*-methylpyrrolidone (NMP) or DMF as solvents (Scheme 49). Reactions with maleimides gave *endo*-adducts **204** verifying that only *s-cis*-1*E*,3*E*-dienamides are involved in the intermolecular DA reaction. Dialkyl acetylenedicarboxylates afforded cyclohexadienes **205** by concomitant double bond shift to give a conjugate diene moiety. Acrylonitrile provided the *ortho*-cyano substituted product **206**. In the case of maleic anhydride rearranged cyclic products **207** were obtained [120,122]. The formation of these 1-amido-1,3-dienes is due to the initial aldol condensation of the aldehyde to give a α,β-unsaturated aldehyde followed by condensation with the amide [123]. Beller's group improved the protocol of these AAD reactions using toluene as solvent and acetic anhydride or a Dean-Stark apparatus for water removal giving tetrahydroisoindole-1,3-dione derivatives **204** in higher yields (40-88%) [124]. Under these reaction conditions, maleic anhydride adducts **208**, instead of 7-oxo-6-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid derivatives **207** were obtained in good yields (72-76%) [124]. Alternatively α,β-unsaturated aldehydes have been used in the AAD reaction of carboxamides, bezenesulfonamide, *N,N*-dimethylurea and maleimide to give amino functionalized tetrahydroisoindole-1,3-dione derivatives **204** in 48-91% yields [125], but other dienophiles gave lower yields. However, under microwave (MW) heating the Beller reaction of amides, α,β-unsaturated aldehydes and *N*-substituted maleimides took place during 8 minutes in NMP giving products **204** in higher yields (80-95%) [126]. Under solvent-free conditions and MW heating this AAD reaction proceeded in good yields with *N*-methylmaleimide (NMM) (52-96%) and maleic anhydride gave **208** (R^1 = NHCbz; R^2 = Me) in 71% yield [127]. In addition, the reaction with diethyl acetylenedicarboxylate (DEAD) provided **205** (R^1 = Ph) in 26% yield and with acrylonitrile **206** (R^1 = Ph) in 31% yield.
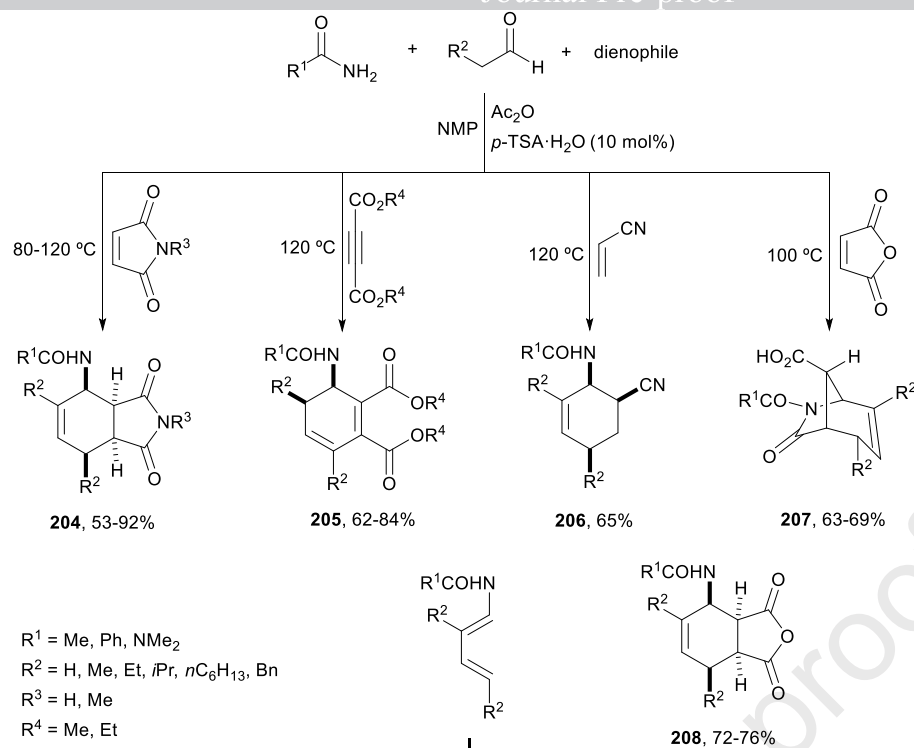
Scheme 49. AAD reactions of carboxamides and dimethylurea with aliphatic aldehydes and dienophiles.

The AAD reaction of acetamide with α,β-unsaturated aldehydes and DEAD in NMP at 120 ºC catalyzed by *p*-TSA provided substituted phthalic acid derivatives **209** by intermediacy of cyclohexadienes **205**, which underwent *in situ* acetamide elimination (Scheme 50) [128]. When intermediates aminocyclohexadienes **205** were reluctant to eliminate acetamide the process was carried out at 160 ºC. Parallelization and automation techniques were implemented for the rapid screening of reaction conditions and composition. All the above mentioned processes were summarized by Beller and co-workers [129].
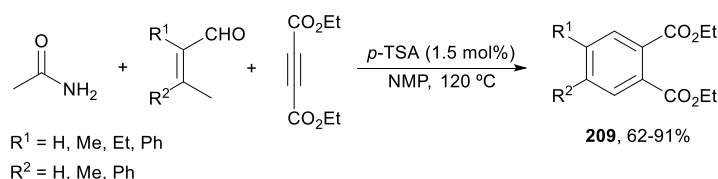
Scheme 50. Synthesis of ethyl phthalates **209** by AAD reactions.

Polysubstituted anilines have been prepared by Beller and co-workers [130] from *O*-benzyl carbamate, aldehydes and different dipolarophiles, mainly NMM but also acrylonitrile and diethyl fumarate. This AAD reaction was carried out with aliphatic aldehydes using Ac$_2$O, *p*-TSA in NMP at 120 ºC, whereas with α,β-unsaturated aldehydes reactions were run without Ac$_2$O to give products **212** (Scheme 51). After the AAD reaction the resulting adducts **210** were treated with 10% Pd/C (8 mol%) in triglyme at 140 ºC to provide anilines **211** in good yields. When NMM was used as dipolarophile the resulting anilines **211** were treated with hydrazine hydrate in a pressure tube at 110 ºC to furnish the corresponding luminols **212** [131]. On the other hand, when

compounds **211** were treated with *n*-hexylmagnesium bromide, regioselective addition to one of the carbonyl groups took place giving *syn/anti* mixtures of *N*-analogous corollosporines **213** [132]. These products were tested in several biological assays to evaluate their antimicrobial activity.

R^1 = H, Me, Et, *i*Pr, Bn, Ph
R^2 = H, Me, Ph
R^3 = H, Me, Et, *i*Pr, Bn, Ph
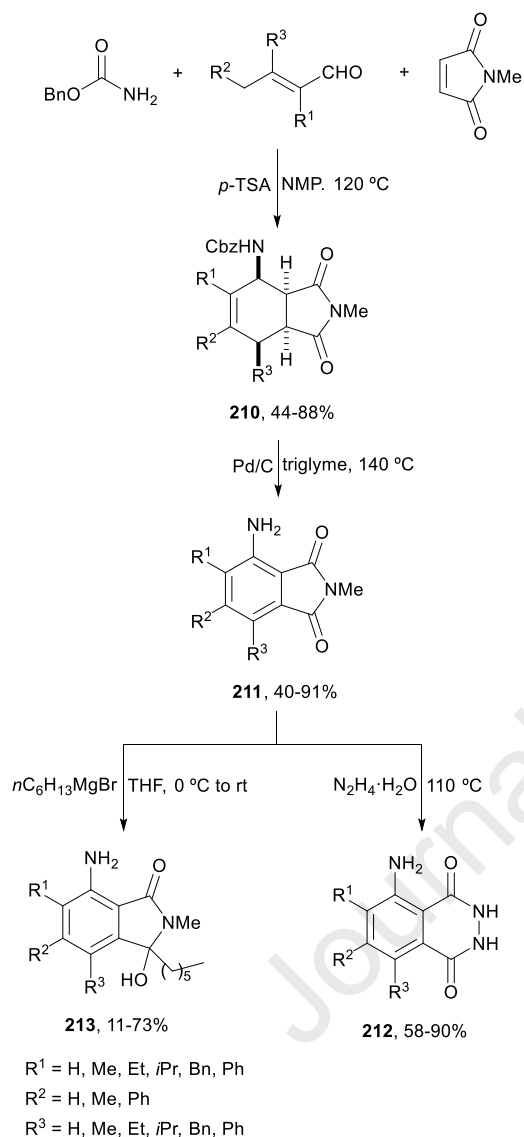
Scheme 51. Synthesis of anilines, luminols and corollosporine analogues.

A sequential AAD and Heck reactions have been employed by Beller and co-workers [133] for the synthesis of phenanthridone derivatives. The corresponding adducts **214** resulting from the AAD reaction of *o*-bromobenzamides with crotonaldehyde and different dipolarophiles, such as NMM, acrylonitrile and dimethyl maleate, were submitted to Pd-catalyzed intramolecular 6-*exo* Heck cyclization to provide phenanthridones **216** (Scheme 52). For the Heck reaction two protocols were employed: (a) high temperature (140 ºC) in DMF, and (b) lower temperature (100 ºC) in dioxane. In the case of using maleic anhydride as dipolarophile resulted bicyclic derivatives **215**, after thermal skeletal rearrangement and ethanolysis. After subsequent intramolecular Heck reaction on compounds **215**, tricyclic compounds **217** were obtained.
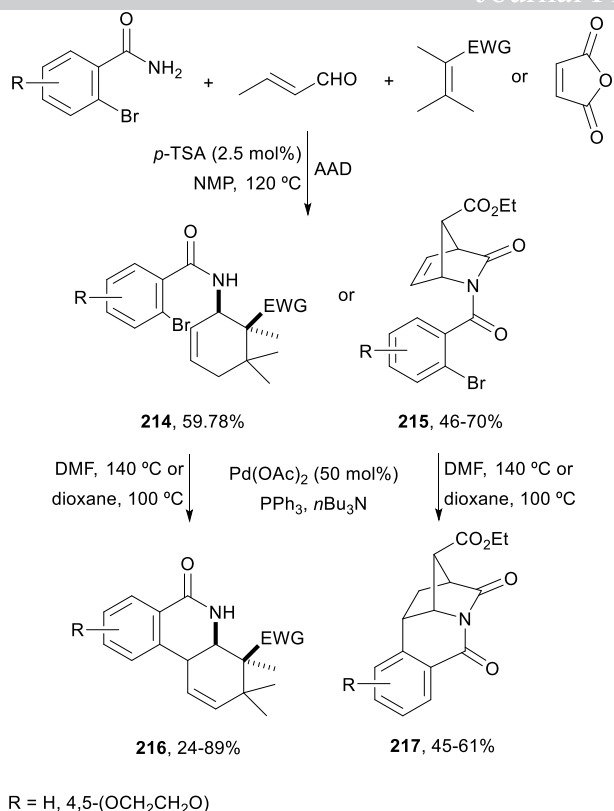
Scheme 52. Sequential AAD-Heck reactions.

The synthesis of cyclohexenes bearing a tethered alkyne moiety has been carried out by Beller and co-workers [134] using amides derived from acetylenic carboxylic acids. These enynes resulting from an AAD reaction were converted *via* intramolecular catalytic Pauson-Khand and Alder-ene reactions in di-, tri- and tetracyclic lactams [135]. As represented for NMM adducts **218**, the Pauson-Khand reaction was carried out with 10 mol% of $Co_2(CO)_8$ in THF at 80 ºC to give tetracyclic lactams **219** (Scheme 53). For the Alder-ene reaction, $Pd(OAc)_2$ and dppb as ligand in toluene at 60 ºC gave tricyclic lactams **220**.
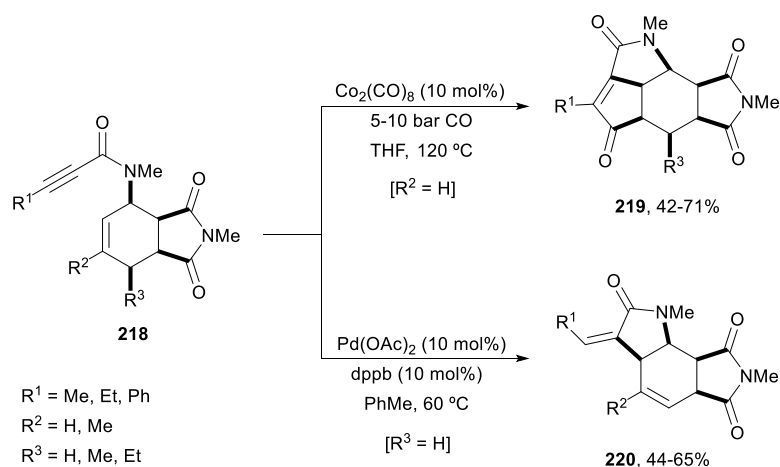
Scheme 53. Pauson-Khand and Alder-ene reactions of AAD cycloadducts **218**.

When α-bromo α,β-unsaturated aldehydes were allowed to react with carboxamides, lactams, oxazolidinone, methanesulfonamide and phenyl carbamate in the presence of NMM and under MW heating the corresponding cycloadducts **221** were obtained (Scheme 54) [136]. The presence of a bromine atom in the cycloadduct allows further elaboration of these products. One example has been also reported using β-bromocrotonaldehyde, acetamide and NMM affording the corresponding adduct **222** in 53% yield.
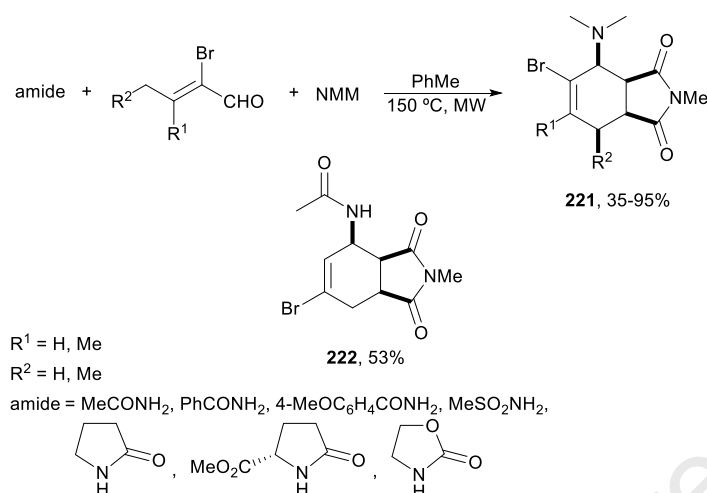
Scheme 54. AAD reactions with α- and β-bromo α,β-unsaturated aldehydes.

Jacobi von Wangelin and co-workers [137] reported a practical synthesis of crowded arenes by a two steps procedure based on AAD-oxidation reactions. For instance, by AAD reaction of aliphatic aldehydes or enals with carboxamides and dimethyl acetylenedicarboxylate or NMM the resulting adducts **223** or **224**, respectively, were oxidized with MnO_2 in refluxing toluene to provide arenes **225** or **226** (Scheme 55).
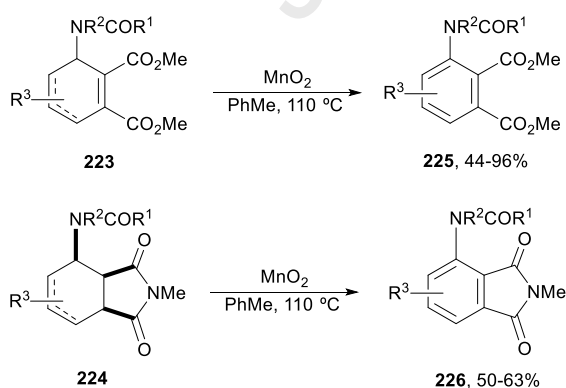
R^1 = Me, Ph, $BrCH_2$, $4-BrC_6H_4$, BnO
R^2 = H; R^1-R^2 = $(CH_2)_3$
R^3 = H, 6-Me, 5-Me, 4-Me, 4,6-Me_2, 4,6-Et_2, 4,6-Ph_2, 4-*i*Pr-6-Ph,
     4-prenyl-5-Me, 4-Et-6-Ph, 4-Et-6-Br, 6-Br-4-Me, 6-Br-5-Me

Scheme 55. Oxidation reactions of AAD cycloadducts **223** and **224**.

A sequential one-pot hydroformylation of acetylenes to α,β-unsaturated aldehydes followed by AAD reaction allows the synthesis of polysubstituted cyclohexenes, cyclohexadienes and phthalates [138]. Beller and co-workers [139] described previously that Pd(acac)$_2$ and heterocyclic phosphine ligands (L) catalyzed the hydroformylation of internal alkynes to enals with syngas. Then, methanesulfonamide, NMM and *p*-TsOH were added and the reaction mixture heated at 110 °C to furnish cycloadducts **227** in good yields (Scheme 56). This process has been also performed with acetamide, oxazolidinone and benzyl carbamate and different dipolarophiles, such as acrylonitrile, β-nitrostyrene and DMAD under the same reaction conditions. Using acetamide and DMAD it was possible to generate phthalates performing the AAD reaction at 160 °C.
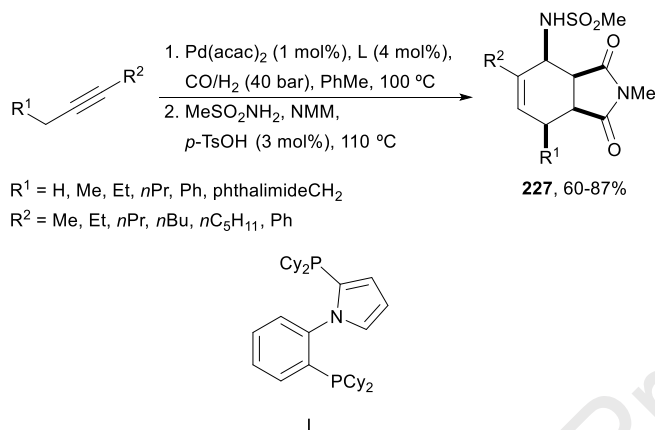
Scheme 56. Sequential hydroformylation of acetylenes and AAD reactions.

Enzymatic kinetic resolution of *N*-(phenylacetamido)cyclohexene derivatives **228** and **229**, obtained in good yields (55-70%) by AAD reaction of phenylacetamide, aliphatic or α,β-unsaturated aldehydes with NMM and acrylonitrile, were carried out by Kragl and co-workers [140] using penicillin G amilase (PGA, penicillin G acylase, EC 3.5.1.11) from *Escherichia coli* (Scheme 57). The enantioselective hydrolysis of the amido group in the cyclohexene derivatives **228** gave amines **230** and the remaining enantiomers *ent*-**228** with ee values from 30 to 70% at 50% conversion. In the case of cycloadducts **229** the same process gave amines **231** and its enantiomer *ent*-**229** in 65 to >99% ee.
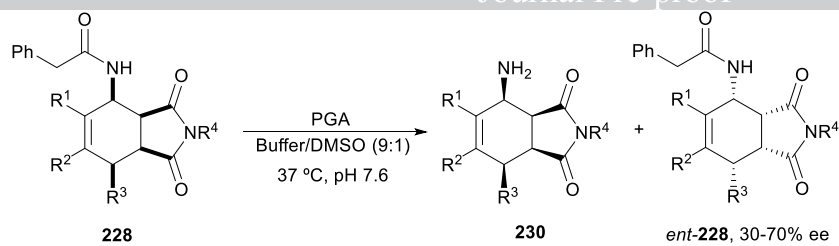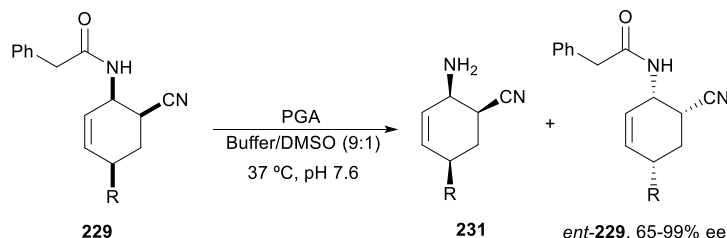
Scheme 57. PGA-catalyzed kinetic resolution of cycloadducts **228** and **229** obtained by an AAD reactions.

Initial studies by Beller and co-workers [141] on enantioselective AAD reactions were carried out with oxazolidinones as chiral auxiliaries and as amide components. Intermediate chiral *N*-dienyl lactams have been previously mentioned in Section 2.2.1, which were prepared by multistep synthesis [68-71]. The highest facial selectivity in the DA reaction was achieved with the phenyl substituted oxazolidinone giving adduct **113** in 94% yield and 90% de (Scheme 58). DFT calculations were performed to explain the observed stereoselectivities.

113, 94%. 90% de
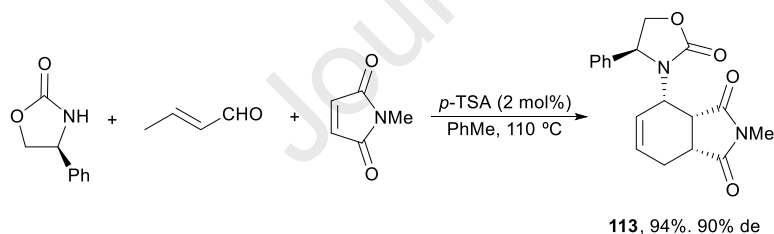
Scheme 58. Asymmetric AAD reaction of (*S*)-4-phenyloxazolidinone with crotonaldehyde and NMM.

The same group [142] also studied the AAD of (*S*)-methyl pyroglutamate as chiral auxiliary as it was described by Smith and co-workers [66,67] preparing the *N*-dienyl derivative **106** (Scheme 21). The scope of this AAD reaction using (*S*)-methyl pyroglutamate was performed with different α,β-unsaturated aldehydes and NMM, maleic anhydride, acrylonitrile and DEAD (Figure 2). Major diastereomeric products **232** derived from NMM were obtained in good yields and de. In the case of maleic anhydride, compound **233** was isolated in 82% yield, and DEAD provided product **234** in 65% yield. However, acrylonitrile reacted with crotonaldehyde and (*S*)-methyl pyroglutamate giving **235** in lower yield. In all cases the shown *endo*-products were the major or exclusive ones, the other diastereomer being the other *endo*-compounds **236** resulting form the less favored approach of the dienophile to the diene. DFT calculations revealed that the diastereoselectivity is due to both kinetic and thermodynamic control.

232a, 77%, 74% de   **232b**, 48%, de nd   **232c**, 82%, 67% de

232d, 78%, 82% de   **232e**, 72%, only   **232f**, 76%, only

233, 82% only   **234**, 65%, only   **235**, 35%, only

236
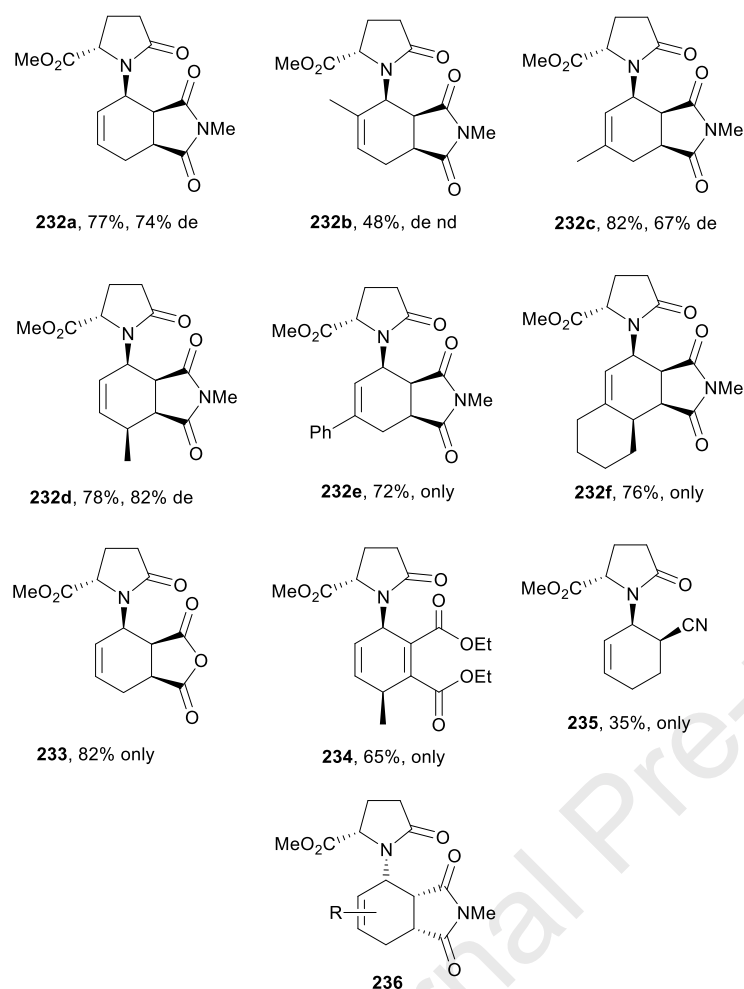
Figure 2. Major AAD *endo*-products derived from (*S*)-methyl pyroglutamate, α,β-unsaturated aldehydes and dienophiles.

Diethyl phosphoramidate, enals and maleimides have been used for the synthesis of polysubstituted cyclohex-2-enylamine derivatives **237** (Scheme 59) [143]. This multicomponent phosphoramidate-aldehyde-dienophile (PAD) has to be performed in the presence of acetic anhydride and TsOH in toluene reflux giving the corresponding products in 40-88% yield. It has been proposed that Ac_2O activates diethyl phosphoramidate by acetylation, which was observed in the absence of the dienophile. In addition, TsOH activates the starting enal by protonation. By using (*R*)-*N*-(1-phenylethyl)maleimides product **238** was obtained in 82:18 dr. The major diastereomer could be isolated by flash chromatography in 54% yield.

237, 44-88%, >99:1

238, 54%, 82:18 dr
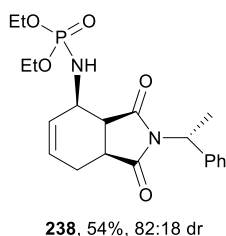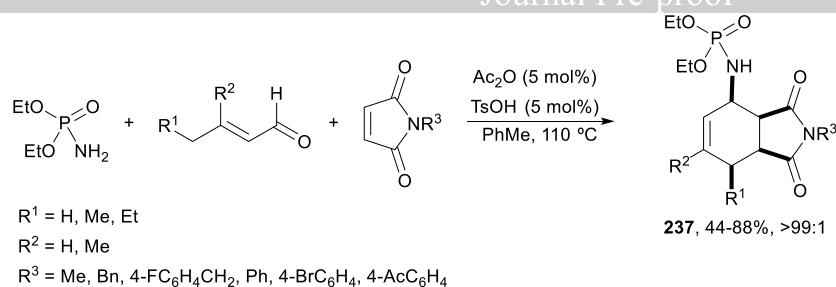
Scheme 59. PAD reactions of diethyl phosphoramidate with α,β-unsaturated aldehydes and maleimides.

3.2. Amines-aldehydes-dienophiles (AAD) reactions

These multicomponent reactions [144] have been less studied than the previously described amides-aldehydes-dienophiles. Working with two mol% of *p*-TSA in dioxane at 110 °C, different α,β-unsaturated aldehydes and dienophiles the corresponding adducts **239** and **240** (in the case of maleic anhydride) were isolated in good yields (Scheme 60). Intermediate **I** (to give intermediate **III**) and **II** (by decarboxylation) have been alternatively proposed to to be involved before the DA reaction. This process took place with total diastereoselectivity using NMM, maleic anhydride and acrylonitrile. The reaction failed with aliphatic isocyanates. On the other hand, the direct use of aniline gave <3% yield.

239, 51-75%

240, 76%

I

II

III
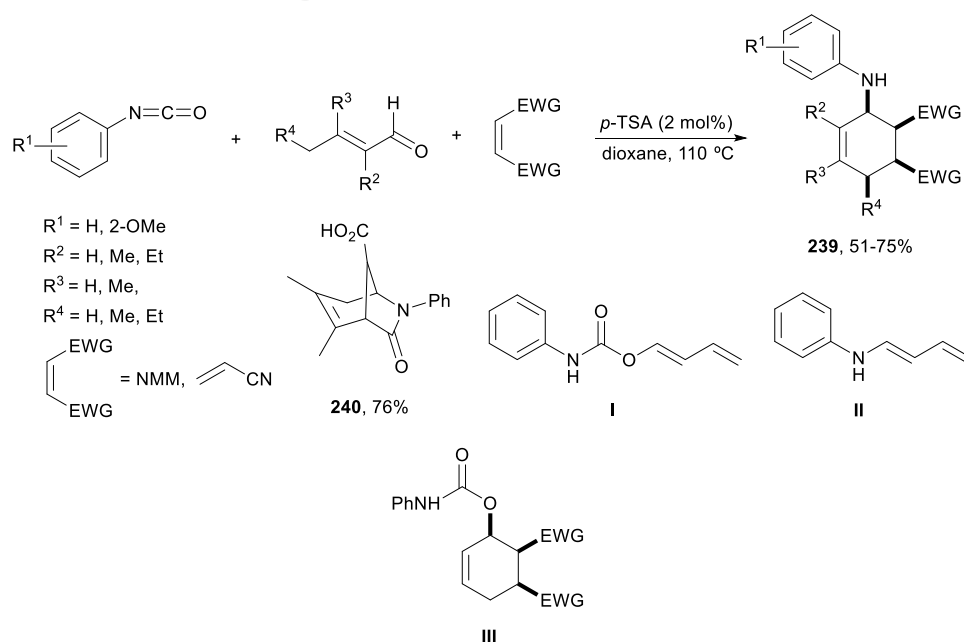
Scheme 60. AAD reaction using aryl isocyanates, α,β-unsaturated aldehydes and dipolarophiles.

AAD reactions using secondary aliphatic amines, enals and nitroalkenes were described by Jacobi von Wangelin and co-workers [145]. *trans,trans*-Nitrocyclohexenylamines **241** were obtained in moderate yield and diastereoselectivity working in toluene at 30 ºC (Scheme 61). The three-component reaction was also carried out with chiral prolinols to provide enantioenriched cycloadducts in good yields and moderate to high diastereoselectivity. Some cycloadducts **242** derived from *O*-trimethylsilyl diaryl prolinol [146,147] were transformed under acidic conditions into chiral nitrocyclohexadienes **243**. The oxidation of products **241** with MnO$_2$ afforded 2-nitrobiaryls **244**. In addition, adducts **241** were allowed to react with dissolving metals to provide *trans*-1,2-diaminocyclohexenes **245**. On the other hand, using carboxamides in toluene at 100 ºC *cis,trans*-nitrocyclohexenyl amides were obtained as the major diastereomer.

R^1 = (CH$_2$)$_4$, CH$_2$CH$_2$OCH$_2$CH$_2$, CH$_2$=CHCH$_2$
R^2 = H, Me
R^3 = H, Me, CO$_2$Me, Me$_2$C=CH(CH$_2$)$_2$
R^4 = H, Me
R^5 = Ph, 2-FC$_6$H$_4$, 2,3-(MeO)$_2$C$_6$H$_3$, 3,4-(OCH$_2$O)C$_6$H$_3$, 2,4-Cl$_2$C$_6$H$_3$, 2-O$_2$NC$_6$H$_4$, 2-furyl

trans,trans-**241**, 16-94%
2:1-35:1 dr

242
R^1 = H, Me
R^2 = H, Me
R^3 = Ph, 2-FC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$, 2-furyl

243, 29-60%
82-94% ee

244, 48->99%

245, 48-50%

R^2 = R^4 = H
R^3 = Me
R^5 = Ph, 2-FC$_6$H$_4$, 2-O$_2$NC$_6$H$_4$, 3,4-(OCH$_2$O)C$_6$H$_3$,
2,4-Cl$_2$C$_6$H$_3$, 2,6-Cl$_2$C$_6$H$_3$
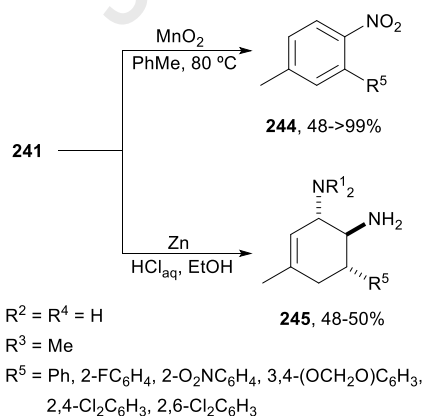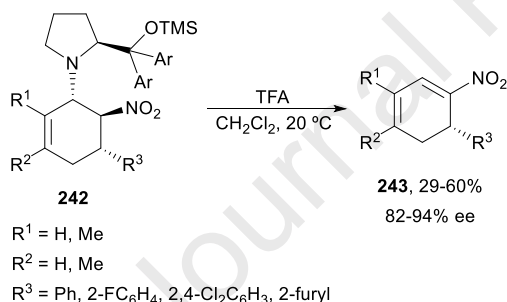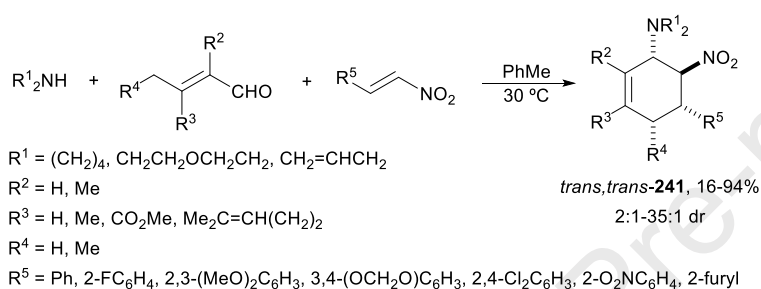
Scheme 61. AAD reactions of secondary amines, enals and nitrostyrenes and further transformations.

Dienals **246** reacted with primary and secondary amines in the presence of different dienophiles to give cycloadducts **248** by intermediacy of trienamines **247** (Scheme 62) [148]. These products **248** can react with another dienophile in a one-pot process to provide compounds

249. Dendralenes **247** could not be isolated due to their instability. Chiral derivatives *syn*-**250** can be trapped by a double DA reaction to give in the case of *O*-trimethylsilyldiphenylprolinol [146,147] adduct **251** with total diastereoselectivity. Tethering the dienophile to the amine as in **252** allowed after the AAD reaction an intramolecular second DA reaction by intermediacy of compounds **253** using NMM, which provide products **254** resulting from an *endo*-IMDA reaction (Scheme 62) [148].
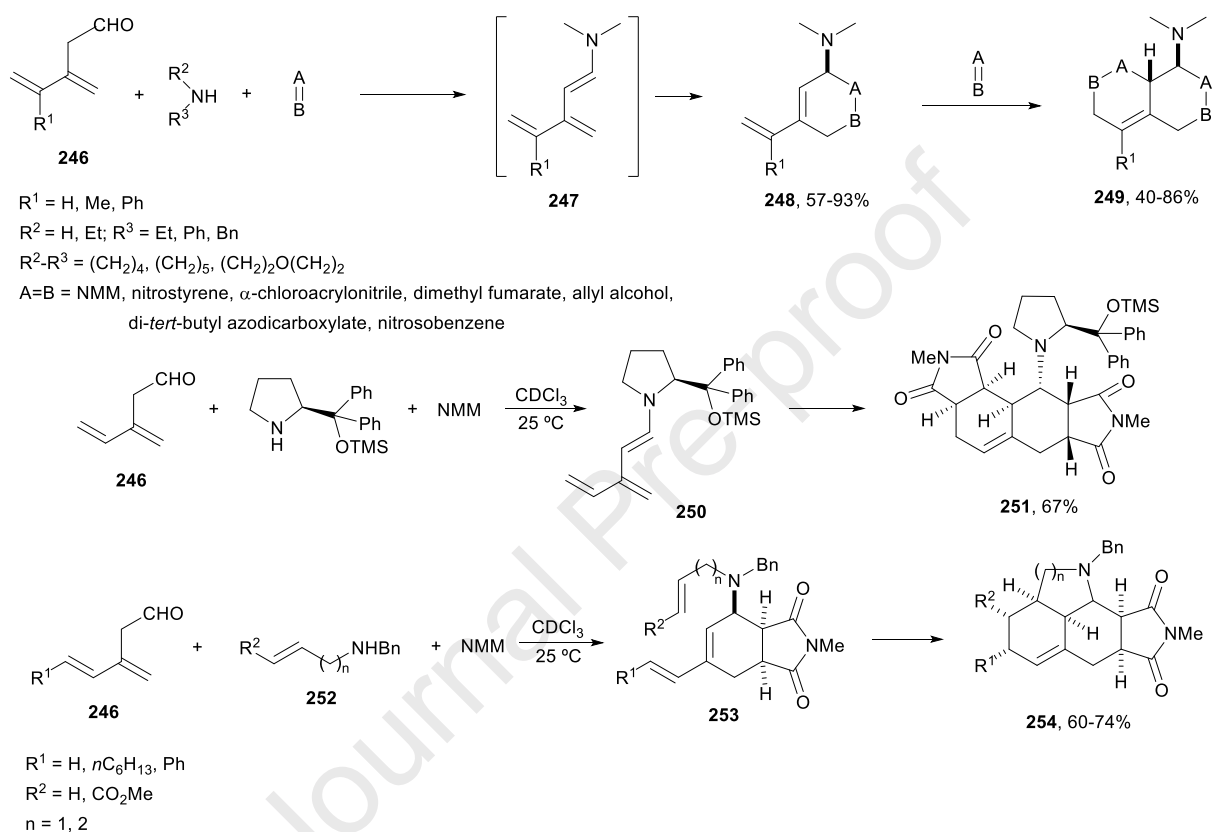
Scheme 62. AAD-DA reactions of dienals **246** with amines and dienophiles.

Our group has described the diastereoselective AAD reaction of a chiral nitroprolinate **255** with enals and different dienophiles (Scheme 63) [149]. The nitroprolinate **255** was prepared by 1,3-dipolar cycloaddition of methyl benzylideneglycinate and β-nitrostyrene catalyzed by chiral phosphoramidite (Feringa's ligand) and copper or silver complexes [150-152]. Products **257** were obtained working at room temperature in good yields and total diastereoselectivity using maleimides, *p*-benzoquinone, (*E*)-1,2-(benzenesulfonyl)ethylene and diisopropyl azodicarboxylate as dienophiles. Only maleic anhydride provided a 63:27 mixture of diastereomers. Chiral dienamides **256** in the major *s-cis*-conformation explain the observed facial *endo*-diastereoselectivity.
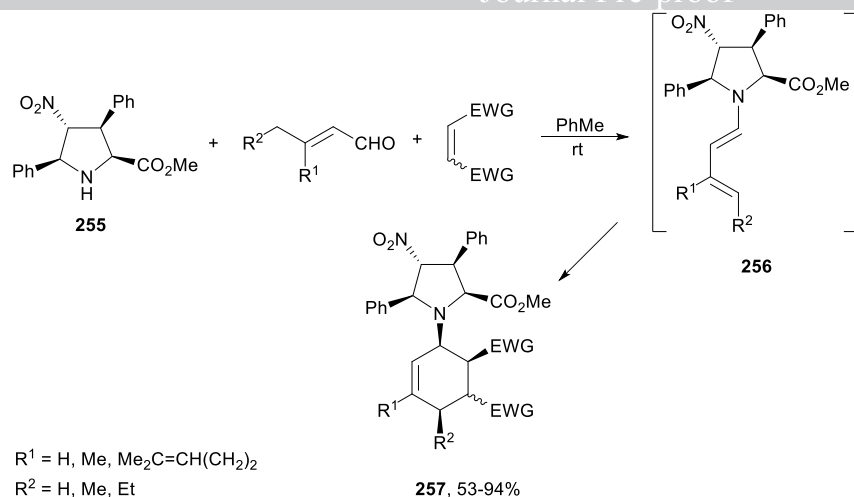
Scheme 63. AAD reactions of chiral nitroprolinate **255** with enals and dienophiles.

In order to prepare aminocyclohexenes, the AAD reaction with primary benzylamines has been developed [153]. In the presence of Et$_3$N and toluene as solvent at 70 ℃ the cycloaddition using enals and maleimides gave the corresponding adducts **258** in good yields with *endo*-selectivity (Scheme 64). For the synthesis of enantiomerically enriched cyclohex-2-en-1-amines, chiral benzylamines and chiral (*R*)-*N*-(1-phenylethyl)maleimide were assayed to provide products **259** and **260**, respectively. The best diastereoselectivity was obtained using (*R*)-*N*-(1-phenylethyl)maleimide and the chiral maleimide providing products **260** up to 95:5 dr, which were isolated by column chromatography.
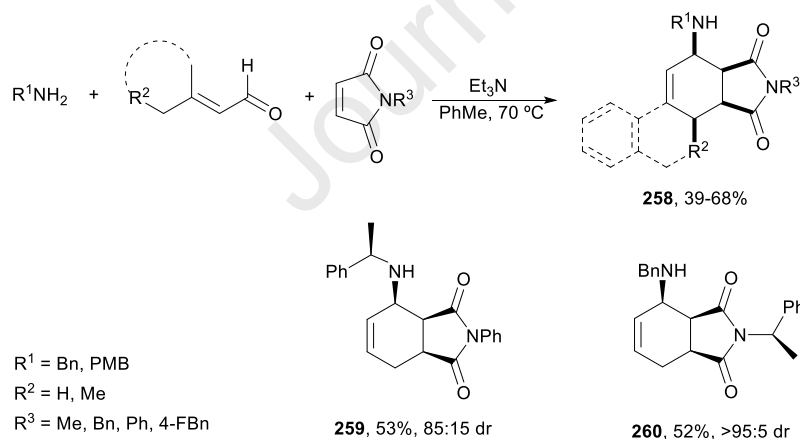
Scheme 64. AAD reactions of benzylamines, enals and maleimides.

The use of chiral amines as organocatalysts is the basis of asymmetric DA reactions and are not considered in this review article [154,155].

4. Cyclic 1-amino-1,3-dienes

Aminodienes of the type **2** with an *exo*-cyclic amino or amido group have been less studied than the acyclic derivatives. Initial studies of isophorone dienamines **261** showed that under

thermal conditions the reaction with acrylonitrile, methyl vinyl ketone and methyl acrylate gave mixtures of bicyclic cycloadducts due to isomerization of the linear and cross-conjugated forms [156,157]. Dauben and Kozikowski [158] reported later that using high pressure products **262** were exclusively obtained as mixture of *endo/exo* isomers (Scheme 65).

Y = O, CH$_2$
Z = CN, CO$_2$Me
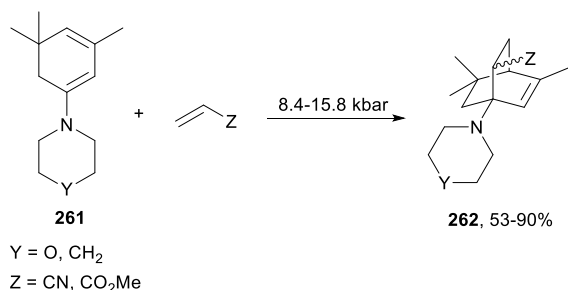
Scheme 65. DA reactions of isophorone dienamines **261** under high pressure.

A solvent-dependent regioselective DA reaction of $\Delta^{1,8a}$-2-octalone dienamine **263** with methyl vinyl ketone was observed by Hickmott and Simpson [159,160]. In boiling MeOH **263** reacts as linear dienamine at the δ-position to provide mainly products **264** and **265** in 12% and 9% yield, respectively (Scheme 66). However, under toluene reflux compound **267** resulted, by participation of the cross-conjugated dienamine **266**, in 28% yield.
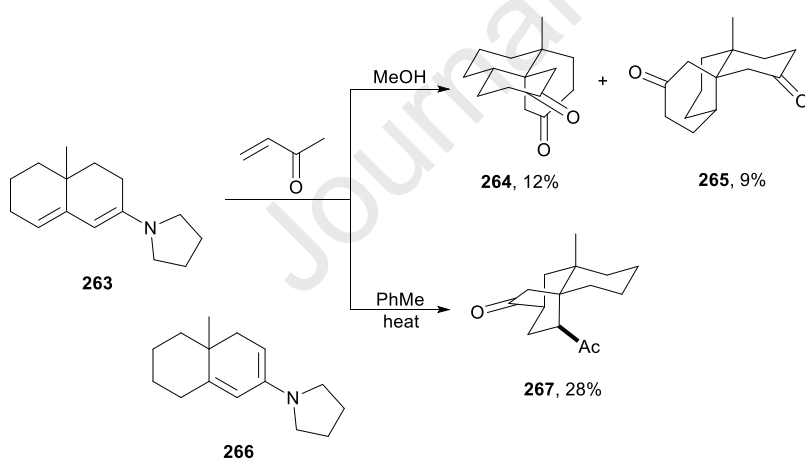
Scheme 66. DA reactions of dienamine **263** with methyl vinyl ketone in different solvents.

(*R*)-9-(2-Phenylethyl)aminoanthracene (**268**) has been used as a chiral template for the synthesis of α,β-unsaturated lactams and α,β-butenolides by Snyder and co-workers [161]. The DA reaction of **268** with maleic anhydride and maleimides at room temperature provided cycloadducts **269** in good to excellent yields and with high diastereoselectivity (Scheme 67). These products were further elaborated by functional group transformations and a final retro-DA reaction into enantiomerically pure unsaturated lactams and α,β-butenolides. Aminoanthracene **268** was obtained by Pd-catalyzed amination of 9-bromoanthracene with (*R*)-1-phenylethylamine, which should be trapped by the dienophile immediately after preparation. The same process was carried out by Jones and co-workers [162] who established that the correct configuration for the

major adduct was **270** and was explained due to a favorable combination of electrostatic and hydrogen bonding effects.

Y = O, NMe, NCH$_2$CH=CH$_2$
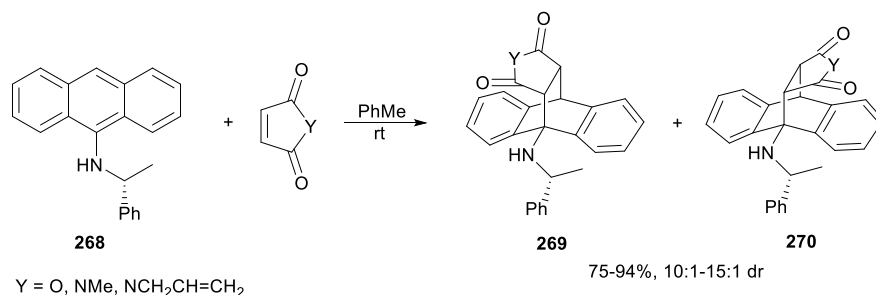
Scheme 67. DA reaction of chiral aminoanthracene **268**.

2-Amino substituted furan **271** withx a methoxycarbonyl group reacted easily with dienophiles to give unstable adducts **272**, which suffered spontaneous ring opening to give cyclohexadienols **273** (Scheme 68) [163]. The cycloaddition with methyl acrylate, acrylonitrile, methyl vinyl ketone and phenyl vinyl sulfone proceeded with high stereoselectivity and the resulting products **273** can be transformed into anilines **274** by treatment with BF$_3$. Other substituted 2-aminofurans such as the morpholine-substituted nitrofuran **275** reacted with NPM to provide phenol **276**, and *N*-protected 2-aminofuran **277** gave the *exo*-cycloadduct **278**. The oxa-bridged compound **278** underwent thermal dehydration to the corresponding aniline **279**.
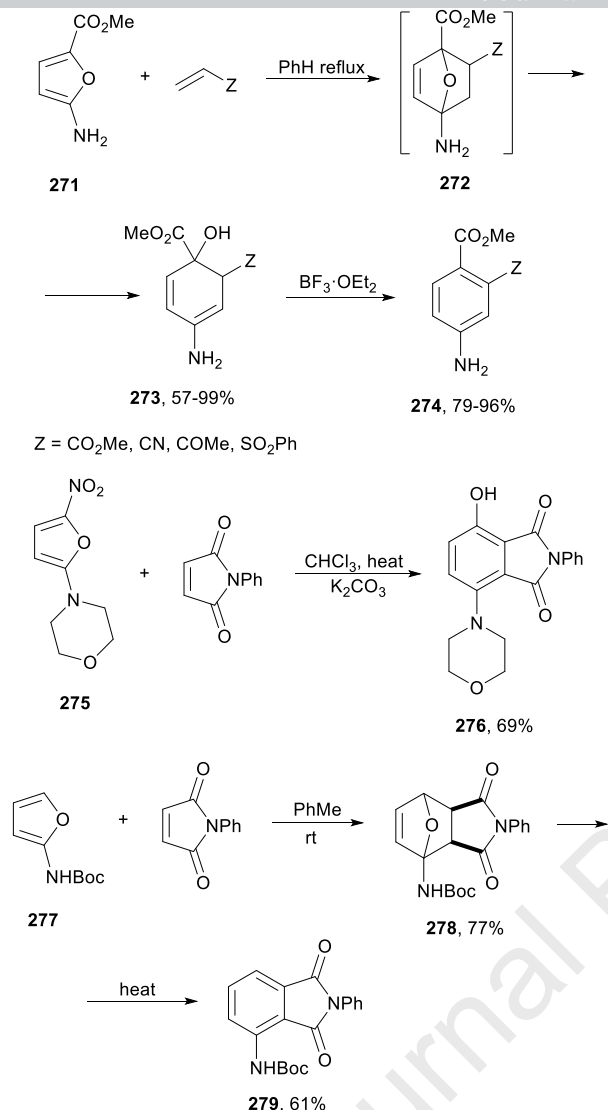
Scheme 68. DA reactions of 2-amino substituted furans **271**, **275** and **277**.

Padwa's group [164,165] also studied inter- and intramolecular DA reactions of 2-amidofurans. In the case of the fused amidofuran **280** the DA reaction with NPM gave a 1:3 mixture of cycloadduct **281** and indoline **282** in 95% yield (Scheme 69). Treatment of the 7-oxabicyclo[2.2.1]heptene **281** with acid provided indoline **282** in high yield. On the other hand, by heating a toluene solution of amidofuran **283** the cycloadduct **284** was obtained in 70% overall yield from the starting diazoimide.
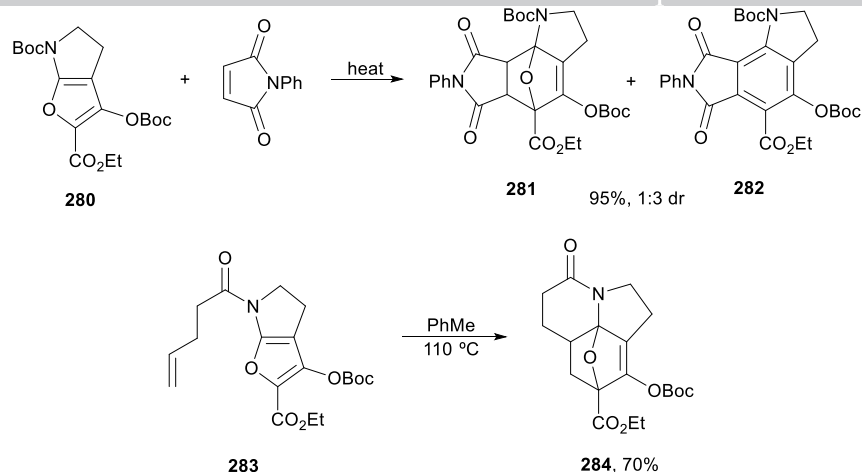
Scheme 69. Inter- and intramolecular DA reactions of cyclic 2-amidofurans **280** and **283**.

Schlessinger's group [166] reported intermolecular DA reactions of the chiral 3-aminofuran **285** with α,β-unsaturated esters, nitriles, sulfones and imides. For instance, the cycloaddition with methyl acrylate gave rise, working at room temperature, to adduct **286** isolated as a 10:1 mixture of *endo/exo* diastereomers in 93% yield (Scheme 70). The major *endo*-diastereomer *endo*-**286** was further transformed into bicyclic ketone **287**, butenolides **288** and vinylogous amide **289**. The same group [167] studied the intramolecular cycloaddition of an allenyl substituted 3-aminofuran for the enantioselective synthesis of (+)-cyclophellitol.
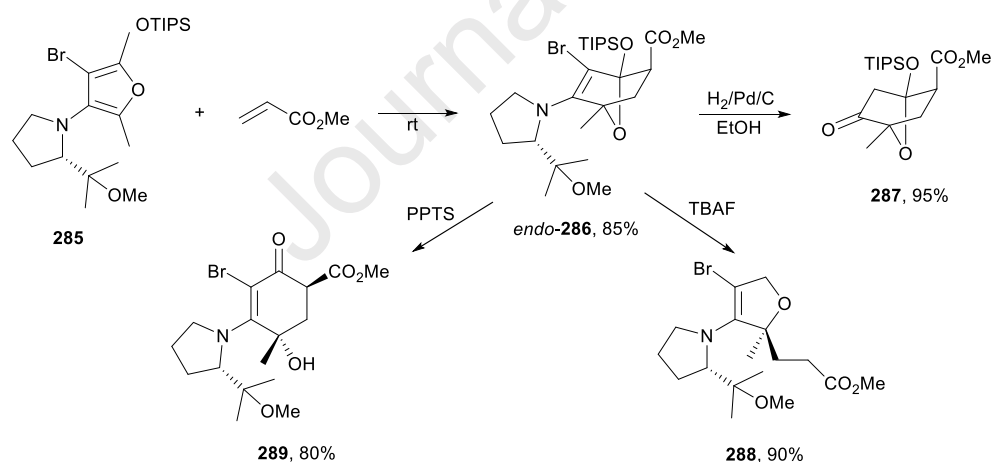
Scheme 70. DA reaction of 3-aminofuran **285** with methyl acrylate and further transformations.

Chen and Beak [168,169] reported the DA reaction of 1-aminoisobenzofuran **291** prepared from *o*-diazomethylbenzamide **290**. Cycloadditions with methyl acrylate, dimethyl fumarate, dimethyl maleate, cyclohexenone, dimethyl acetylenedicarboxylate and phenyl vinyl sulfone gave regioselectively the corresponding products **293** with variable stereochemistry by ring opening of cycloadducts **292** (Scheme 71). The sequence took place in the presence of Cu(acac)$_2$ or Rh$_2$(OAc)$_4$ as catalysts for the formation of the 1-aminoisobenzofurans, which are trapped *in situ* by the dienophile. Other alternative routes can be also employed for the generation of 1-

aminoisobenzofurans species. The annelated products have been further reduced to tetrahydronaphthalenes with Zn/AcOH or oxidized to the aromatic systems.
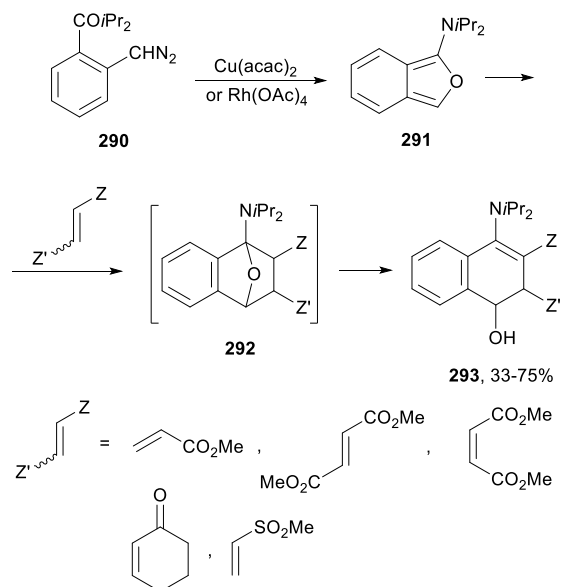
Scheme 71. Preparation and DA reactions of 1-aminoisobenzofuran **291**.

Amino-2*H*-pyran-2-ones also behave as electron-rich cyclic 1-aminodienes in DA reactions. The preparation and DA reactions of α-amino-2*H*-pyran-2-ones have been studied by Kočevar's group extensively [170-183]. Fused 2*H*-pyran-2-ones **294** reacted with maleimides in boiling decalin during *ca.* 9 hours providing fused isoindole derivatives **297** (Scheme 72) [175]. These compounds were formed by a DA reaction of the pyranone unit giving adducts **295** followed by CO$_2$ extrusion to **296** and aromatization in the presence of a dehydrogenation agent. When the DA reaction of **294** (Y = CO) was stopped after 15 hours of reflux, bicyclo[2.2.2]octene derivatives **298** were isolated by a second DA reaction of intermediates **296** with a second molecule of maleimide. These compounds **298** underwent a retro DA reaction to give products **297**. In the absence of a dehydrogenation agent, such as Rh/C, products **298** can be isolated [171].
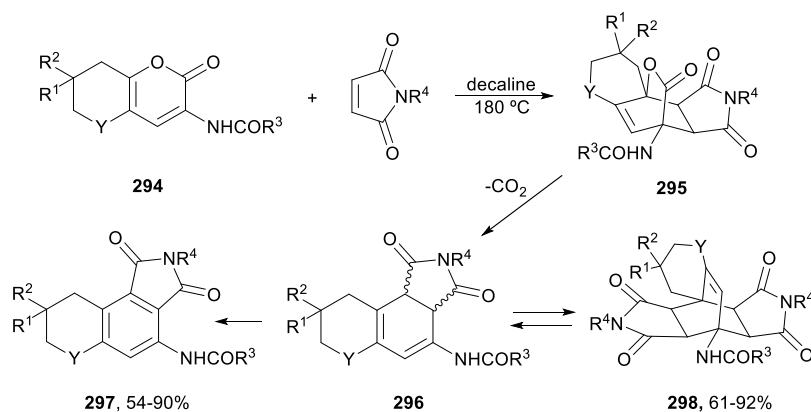
R^1 = H, Me; R^2 = H, Me; R^3 = Ph, 4-Py; R^4 = Me, Et, Ph; Y = CH$_2$, (CH$_2$)$_2$, C=O

Scheme 72. DA reactions of fused α-amino-2*H*-pyran-2-ones **294** with maleimides.

Under microwave heating, different α-amino-2*H*-pyran-2-ones **299** were transformed into bicyclo[2.2.2]oct-7-ene derivatives **300** of the type **298** using water as solvent (Scheme 73) [174,175]. These cycloadducts **300** were further hydrogenated using ionic-immobilized Rh ligand complexes on layered double hydroxide (LDH) supports as recoverable catalyst. Under microwave irradiation using neat conditions in the presence of a minor amount of butanol higher yields (85-98%) and shorter reaction times were observed with pyranones **294** [176] and **299** [177]. When acetylenes were used as dienophiles, 3-benzamido-2*H*-pyran-2-ones **299** gave under pressure at room temperature highly substituted *N*-benzoylanilines **301** in good yields (62-98%) (Scheme 73) [178,179]. On the other hand, in neat conditions under MW irradiation and in the presence or absence of butanol for 30 minutes the corresponding anilines **301** were obtained in high yield (82-95%) [176] The observed regioselectivity was explained on the basis of electron demand and also by the formation of zwitterionic intermediates [179]. The application of activated carbon (Darco® KB) in the DA reaction of pyranones **299** with maleimides allowed the synthesis of isoindoles **302** (Scheme 73) [180]. This catalyst mainly influenced the dehydrogenation step which is essential to avoid the formation of the bicyclo[2.2.2]octenes **300**. Using decalin as solvent in a closed pressure tube at 180 ℃ products **302** were isolated in good yields.

R^1 = COMe, CO$_2$Et, 4-MeC$_6$H$_4$
R^2 = Me, CH$_2$CO$_2$Me
R^3 = H, Me, Et, Ph

300, 81-94%

R^1 = H, COMe, COPh, CO$_2$Et, 4-MeOC$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_3$
R^2 = Me, CH$_2$CO$_2$Me
R^3 = H, CO$_2$Me, CO$_2$Et
R^4 = CO$_2$Me, CO$_2$Et, Ph, 4-MeC$_6$H$_4$

301, 62-98%

R^1 = H, Me
R^2 = H, COMe, COPh, CO$_2$Me, CO$_2$Et
R^3 = Me, Ph, 2-furyl, 2-thienyl, 2-Py, CH$_2$CO$_2$Me, CH$_2$CO$_2$Et
R^4 = Me, Et, Ph

302, 41-87%
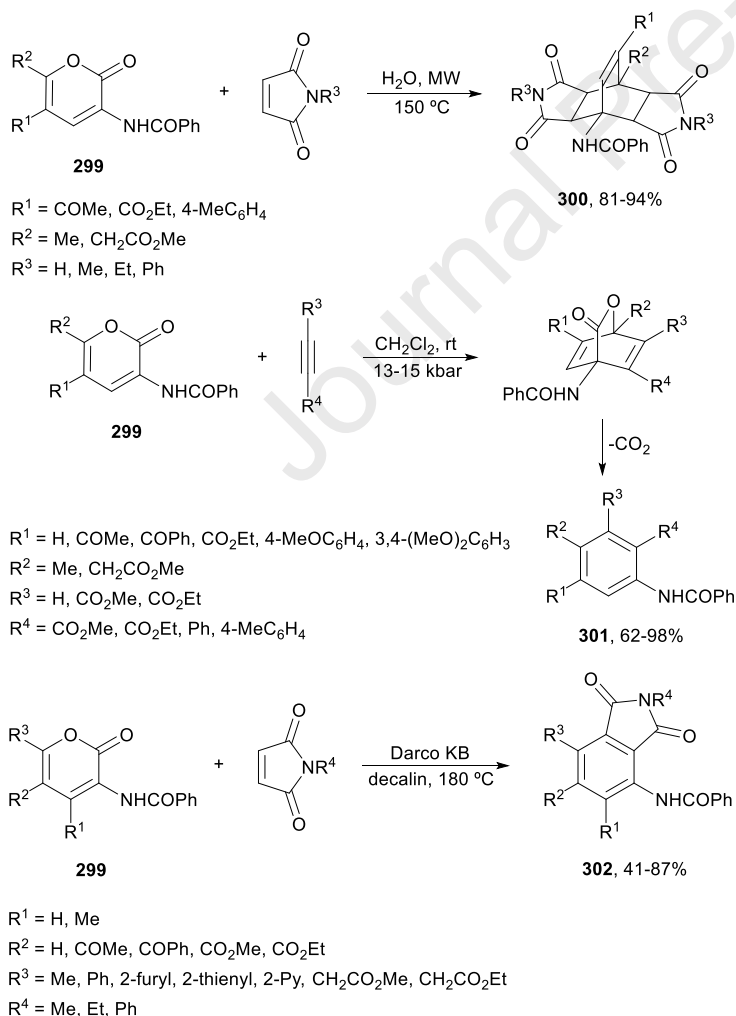
Scheme 73. DA reactions of α-amino-2*H*-pyran-2-ones **299** with dienophiles.

When the cycloaddition of pyranones **299** was carried out with styrenes in the presence of chloranil as oxidant under MW irradiation or activated carbon as dehydrogenation catalyst under conventional heating the corresponding boscalid derivatives **303** were obtained (Scheme 74) [181,182]. Styrenes acted as synthetic equivalents of phenylacetylenes in this method for the synthesis of derivatives of the fungicide boscalid.
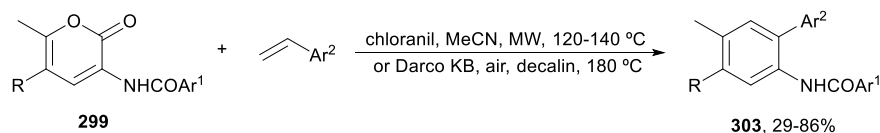
R = H, COMe, CO₂Et, 4-MeOC₆H₄

Ar¹ = Ph, 4-FC₆H₄, 4-O₂NC₆H₄, 3,4,5-(MeO)₃C₆H₂, 2-furyl, 2-Clnicotinoyl, 6-Clnicotinoyl

Ar² = Ph, 4-ClC₆H₄

Scheme 74. DA reactions of 3-benzamido-2*H*-pyran-2-ones **299** with styrenes.

The use of a double dienophile 1,1'-(hexane-1,6-diyl)bis(1*H*-pyrrole-2.5-dione) (**305**) and pyranone **304** afforded the macrocycle **306** by two consecutive DA reactions (Scheme 75) [183]. Under MW irradiation at 150 ºC and under solvent-free conditions just adding a small amount of butanol the symmetric 26-membered product *exo,exo*-**306** was obtained in 34% yield.
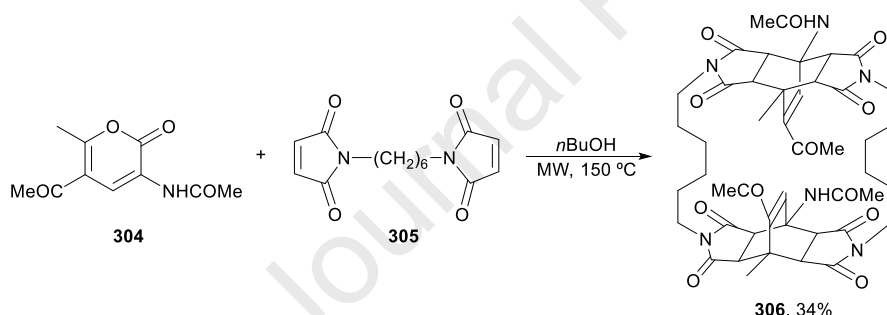
Scheme 75. DA reaction of 3-acetamido-2*H*-pyran-2-one **304** with bismaleimide **305**.

Cho and co-workers [184] have studied the cycloaddition of 3-phenylamino-5-bromo-2*H*-pyran-2-one **307** with different dienophiles such as methyl acrylate, methyl vinyl ketone, acrylonitrile, *N*-ethylmaleimide, methyl methacrylate, methyl crotonoate, 4-bromostyrene, dimethyl fumarate and maleate. This pyrone was prepared by regioselective Pd-catalyzed amination of 3,5-dibromo-2*H*-pyran-2-one. The cycloaddition reaction took place in CH₂Cl₂ at 100 ºC in a sealed tube giving the cycloadducts in 10:90 to 76:24 *endo/exo* diastereomers and with excellent yields (81-95%). In Scheme 76 are depicted compounds **308** resulting from some selected dienophiles. Lactone ring opening of the *endo*-adducts with NaOMe gave carboxylic amino acid methyl esters **309**, whereas the *exo*-adducts were transformed into diastereomeric amino esters **310**.
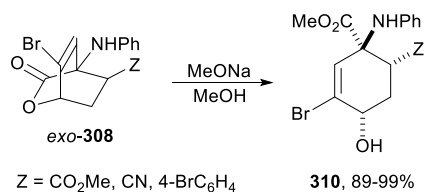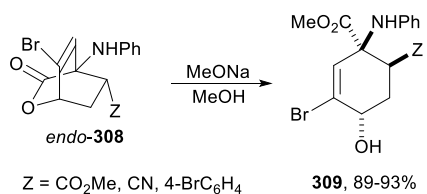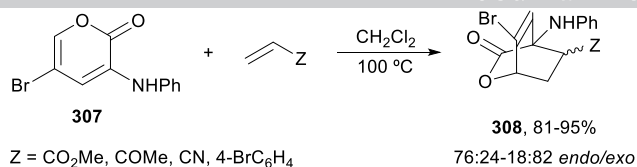
Scheme 76. DA reactions of 3-phenylamino-3-bromo-2*H*-pyran-2-one (**307**) with dienophiles and subsequent ring opening.

Khatri and Samant [185] reported the DA reaction of 6-amino-2*H*-pyran-2-ones **311** with diethyl acetylenedicarboxylate, 1,4-naphthoquinone and NPM (Scheme 77). These cycloaddition took place under refluxing toluene giving the corresponding products **312**-**314** in good yields.
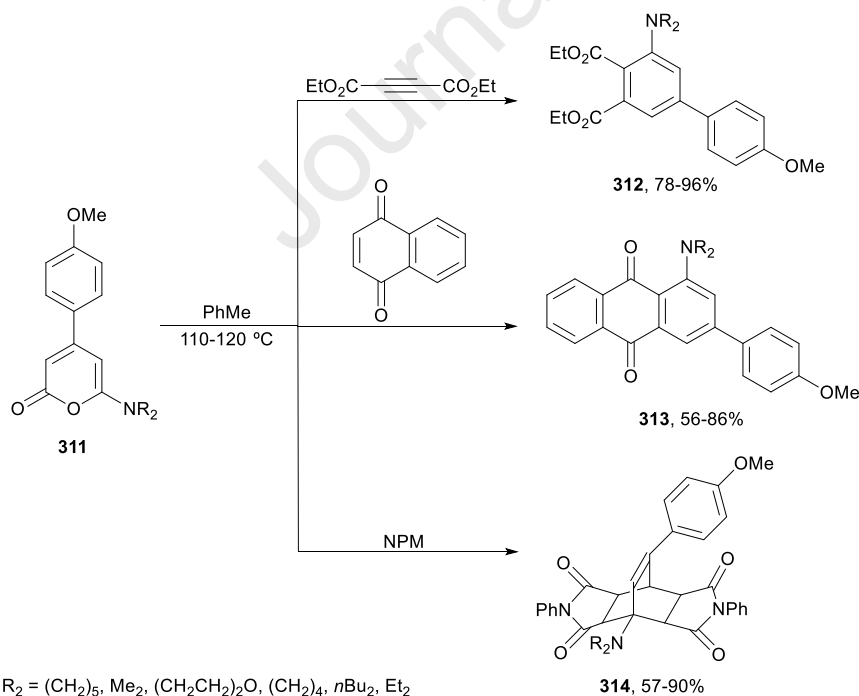
Scheme 77. DA reactions of 6-amino-2*H*-pyran-2-ones **311** with dienophiles.

5. Heterocyclic 1-amino-1,3-dienes

In this section 1,2-dihydropyridines **3** and 2-pyridones **4** will be considered as heterocyclic dienic systems in DA reactions.

5.1. 1,2-Dihydropyridines

DA reactions of 1,2-dihydropyridines (1,2-DHPs) have been extensively used in the synthesis of the isoquinuclidine scaffold found in numerous biologically active natural and unnatural products [186,187]. The most common methods for the synthesis of 1,2-DHPs [188-192] involve (a) regioselective reduction of pyridines and pyridinium salts or nucleophilic addition of Grignard or other organometallic reagents at the 2-position, (b) condensation reactions and (c) pericyclic reactions. Recent methods for the synthesis of racemic 1,2-DHPs such as a three-component reaction of arynes, pyridines and terminal alkynes [193], electrocyclization of unsaturated imines [194-197], Rh-catalyzed reaction of *N*-sulfonyl-1,2,3-triazoles with 2-siloxyfurans [198] and of 4-allyltriazoles [199] have been described. Asymmetric reactions, such as Reissert reaction to pyridines [200], addition of acetylenes to pyridinium salts [201,202], boronic acids [203] and organozinc bromides [204], and cycloadditions of dienes and sulfonimines [205] and glutaraldehyde with imines [206] have been also recently reported.

5.1.1. Racemic DA reactions

Initial studies on DA reactions used *N*-substituted 1,2-DHPs with electron-withdrawing groups, which possess an attenuate nucleophilicity [4]. Fowler and co-workers [207] initially studied the reactivity of *N*-methyl-1,2-dihydropyridines with electron-deficient alkenes demonstrating its behavior as an enamine rather than a diene with methyl acrylate, dimethyl acetylenedicarboxylate, methtyl vinyl ketone and α-(*N*-methylindol-2-yl)acrylate.

Wender and co-workers [208,209] performed the synthesis of reserpine starting from *N*-(methoxycarbonyl)-1,2-dihydropyridine **315** [210] and methyl α-acetoxyacrylate **316** giving mainly the cycloadduct azabicyclo[2.2.2]octane **317**, an isoquinuclidine precursor, by heating at 120 ºC during 56 hours in toluene (Scheme 78). Isoquinuclidines have been used as intermediates in the preparation of tetrahydroisoquinoline alkaloids, piperidines, *Iboga* alkaloids and *Cantharanthus* alkaloids [211,212]. For instance, a formal synthesis of deserpidine has been carried out by Mariano and co-workers [213]. In this case, the first step is the cycloaddition of 1,2-DHP **318** and 1-cyanovinyl acetate **319** to furnish the isoquinuclidine **320** as a mixture of diastereomers in 40% yield, which were transformed into the corresponding ketone (Scheme 78). Krow and co-workers [214,215] and other groups [216-219] have studied the cycloaddition of *N*-alkoxycarbonyl-1,2-dihydropyridines such as **315** with phenyl vinyl sulfone, acrylates, acrolein, methyl vinyl ketone and styrenes giving isoquinuclidine adducts **321** with moderate *endo*-selectivity (Scheme 78). These DA reactions were also described using 3-, 4-, 5- and 6-substituted 1,2-DHPs and styrenes or methyl vinyl ketone as dienophiles affording mainly 7-*endo*-cycloadducts **321** (51-96%, ≥ 89% *endo*) [215]. Isoquinuclidine **324**, a possible intermediate for the synthesis of the *Iboga* alkaloid catharanthine, has been prepared by DA reaction of *N*-methoxycarbonyl-5-ethyl-1,2-dihydropyridine **322** with dimethyl methylenemalonate (**323**) (Scheme 78) [220]. The cycloaddition was carried out under CCl$_4$ reflux giving **324** in 68% yield. Krow and co-workers [221,222] have studied the DA reaction of different substituted *N*-ethoxycarbonyl-1,2-dihydropyridines with maleimides, which gave *endo*-cycloadducts.
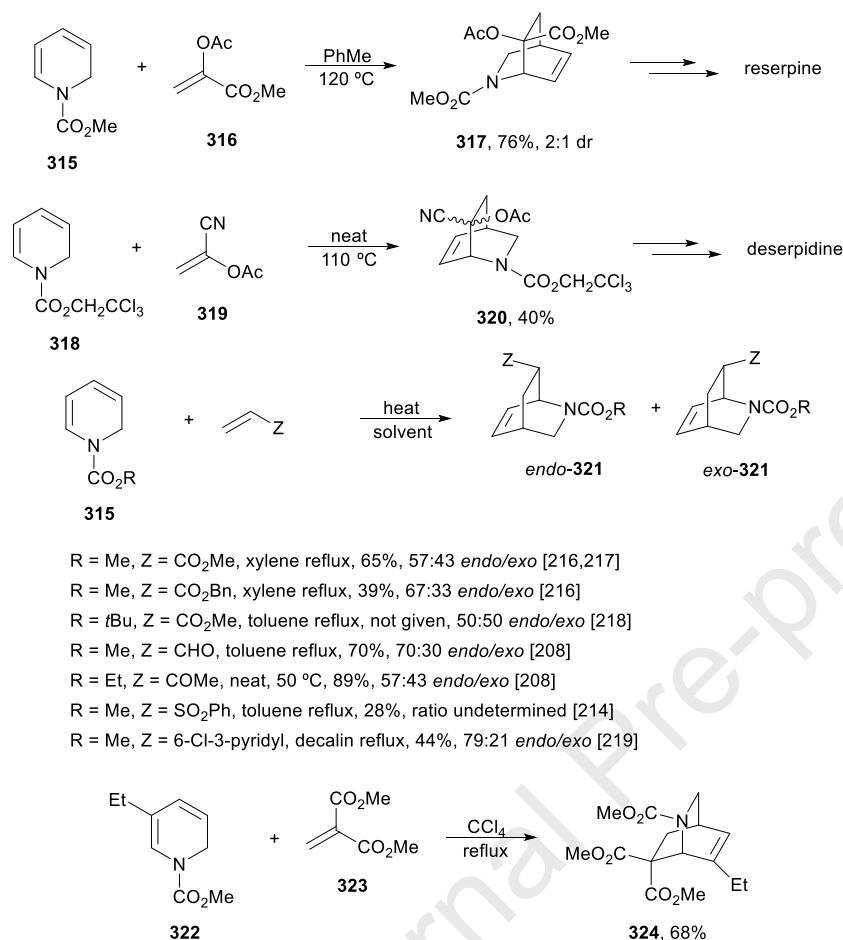
Scheme 78. DA reactions of 1,2-DHP **315**, **318** and **322** with dienophiles.

By heating the tetrahydropyridine **325** in the presence of methyl acrylate and *N*-benzylmaleimide the corresponding cycloadducts **326** and **327** were obtained, respectively (Scheme 79) [223]. Under heating, this precursor **325** eliminates MeOH to give a mixture of 1,4- and 1,2-dihydropyridines in a 4:1 ratio. However, only the 1,2-DHP underwent a DA reaction in the presence of the dienophile to provide isoquinuclidines **326** and **327**.
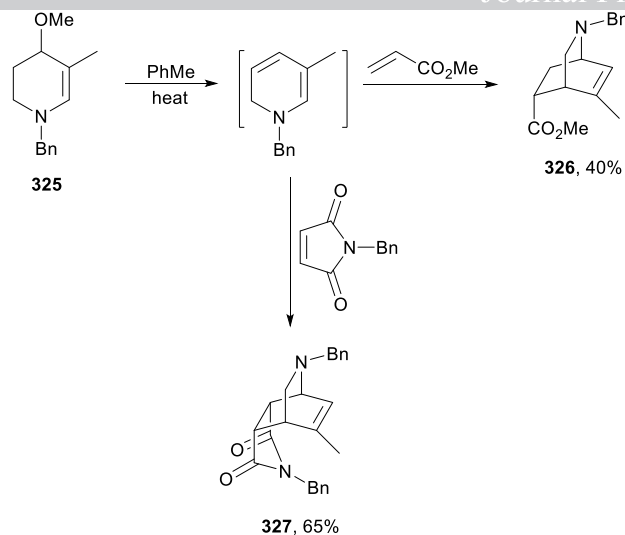
Scheme 79. DA reactions of compound **325** precursor of *N*-benzyl-5-methyl-1,2-dihydropyridine.

Resin-bound *N*-acyl-2-substituted 1,2-DHPs **328** have been submitted to DA reactions with different dienophiles such as NPM, nitrostyrene and diethyl azodicarboxylate to provide after hydrolysis 5-oxo-2-azabicyclo[2.2.2]octanes **329-331** in modest to good yields (Scheme 80) [224].
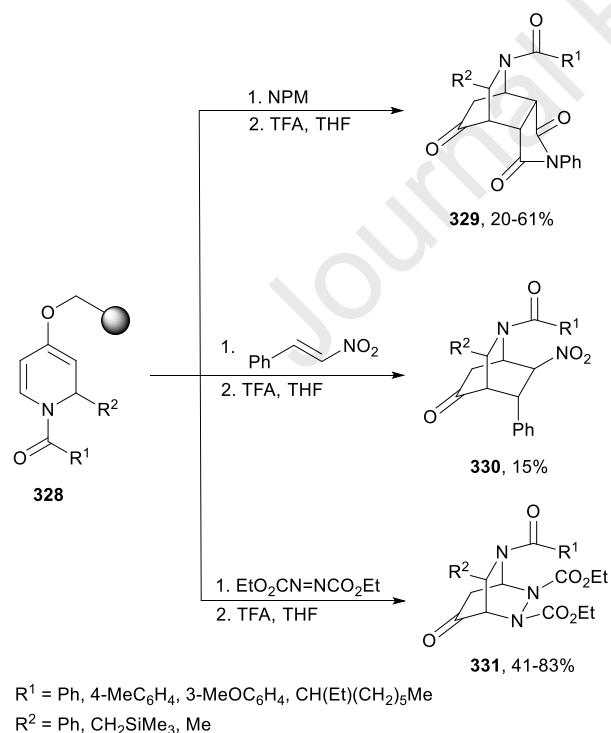
Scheme 80. DA reactions of 1,2-DHPs bounded to the Wang resin **328**.

Highly substituted *N*-methyl 1,2-DHPs **332** underwent DA reactions with maleic anhydride, dimethyl fumarate and methyl acrylate to provide the corresponding isoquinuclidines **333-335** in moderate to low yields (Scheme 81) [225].
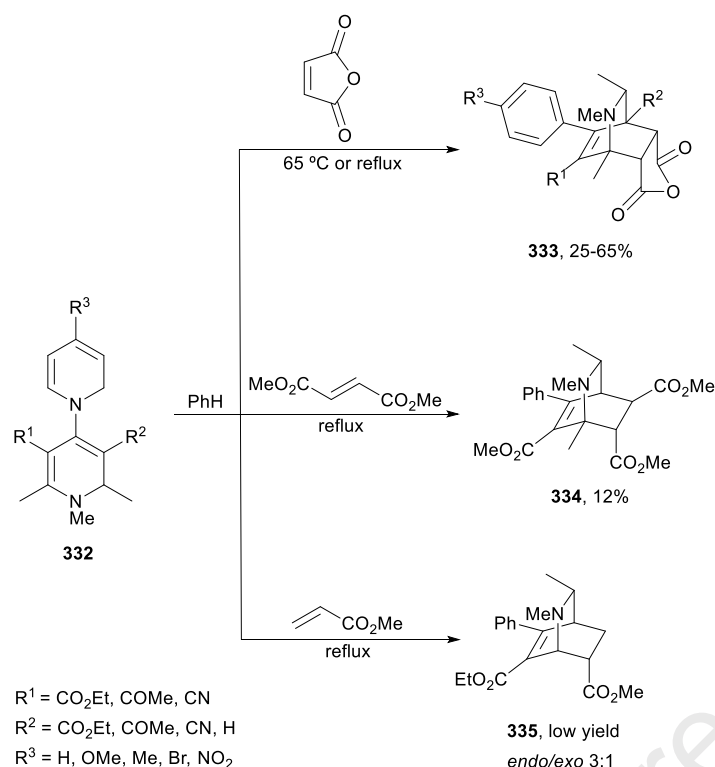
Scheme 81. DA reactions of highly substituted 1,2-DHPs **332**.

Arakawa and co-workers [216,226] performed the DA reaction of 1,2-DHP **315** with dimethyl maleate, maleic anhydride and acrylates. The corresponding cycloadducts, such as **336** and **321**, were transformed by RuO$_4$ oxidation into 2,3,4,5-piperidinetetracarboxylic and 2,3,5-piperidinetricarboxylic acids, respectively. Selected examples are depicted in Scheme 82 for the stereospecific synthesis of tetraester **337** and triester **338**. In the case of acrylates, *ca.* 1:1 mixtures of *endo/exo* diastereomers were obtained.
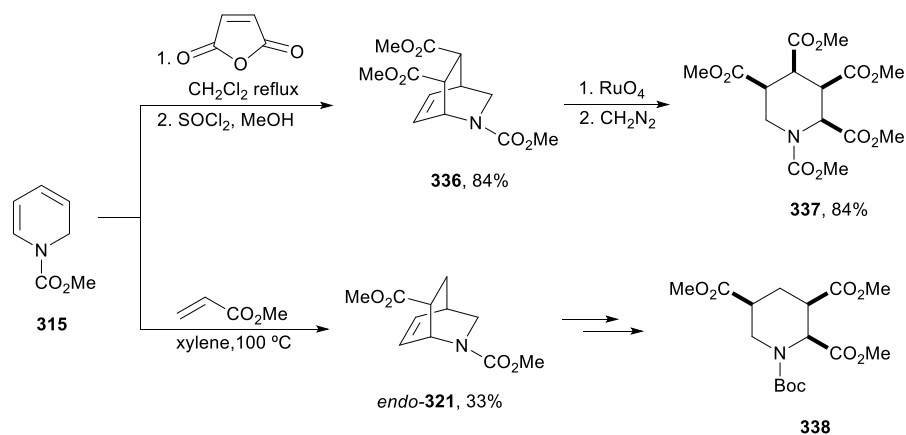
Scheme 82. DA reactions of 1,2-DHP **315** and further transformation into piperidinetetra and tricarboxylic acid esters.

Solid-supported 1,2-DHP **339** reacted with *N*-benzylmaleimide to provide bicyclic compound **340** as a single diastereomer in 54% yield after cleavage with HF-pyridine (Scheme 83). This synthetic strategy developed by Schreiber and co-workers [227] allowed the generation of reactive 1,2-DHP and dihydroisoquinoline as well as using macrobeads (silicon-functionalized 500-600 μm polystyrene).
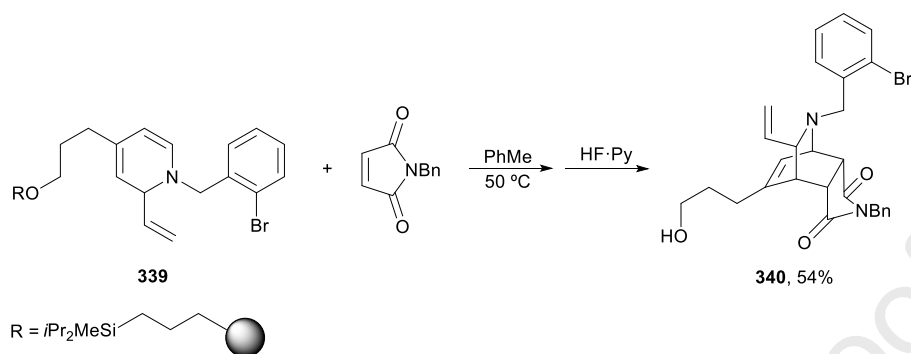
Scheme 83. DA reaction of macrobeads-supported 1,2-DHP **339** with *N*-benzylmaleimide.

Cheng and co-workers [193] studied the DA reaction of *N*-phenyl-2-phenylethynyl-1,2-dihydropyridine (**341**) with NPM in toluene at 80 ℃ (Scheme 84). The resulting isoquinuclidine derivative **342** was isolated in 87% yield as a unique diastereomer.
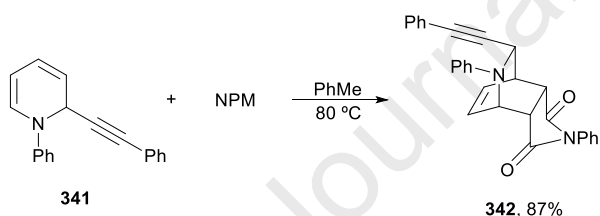
Scheme 84. DA reaction of 1,2-DHP **341** with NPM.

1,2-DHP complexes **343** of TpW(NO)(PMe₃) undergo [4+2] cyclocondensation with enones, enals, nitrosobenzene and isocyanates to form diazabicyclo[2.2.2]octenes **344-346** (Scheme 85) [228]. These reactions have been performed in the presence of a Lewis acid, namely BF₃·OEt₂ and 2,6-di-*tert*-butylpyridine (DTBP), when enones and enals are used as electron-deficient alkenes, giving products **344**. In the case of nitrosobenzene the hetero-DA reaction occurs in the absence of a Lewis acid to provide compounds **345**. The reaction with tosyl isocyanate (TsICN) gave the corresponding [4+2] cycloadducts **346**. Oxidative decomplexation of compounds **344** and **346** was achieved with cerium ammonium nitrate (CAN) to furnish products **347** and **348**, respectively. Compound **348** possess a diazabicyclooctene core similar to that of brevianamides and related compounds [229].
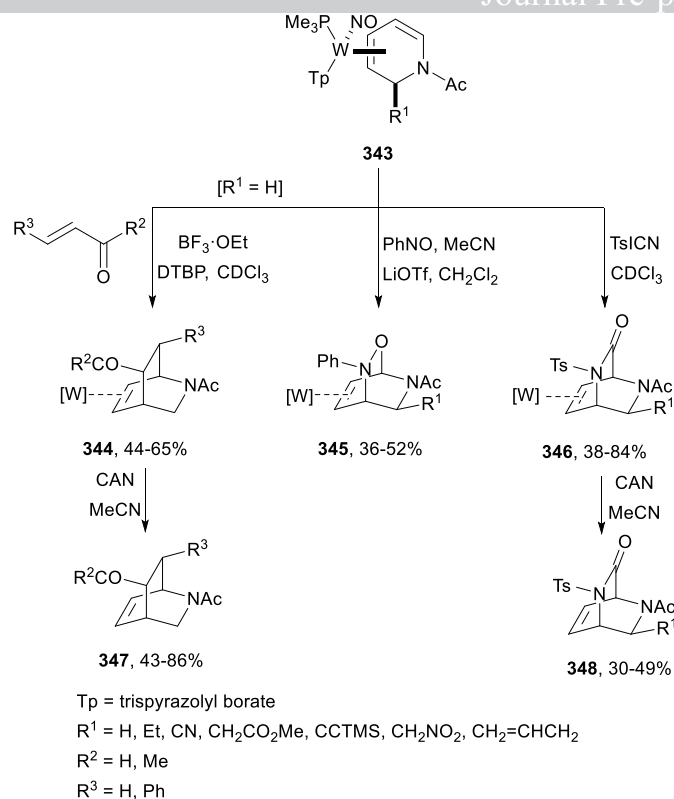
Scheme 85. DA reactions of W-DHP complexes **343**.

The addition of pinacolborane (HBpin) to pyridines in the presence of a Rh catalyst gave *N*-boryl-1,2-dihydropyridines **349** (Scheme 86) [230]. These compounds **349** can be converted into *N*-acyl-1,2-DHPs by reaction with acetyl or pivaloyl chlorides in 54-73% yield. DA reactions with NMM took place at room temperature to give *N*-borylated isoquinuclidines, which were treated with pivaloyl chloride to provide products **350**. Highly substituted 1,2-DHPs **351** [194] react with NPM at room temperature whereas methyl acrylate and acrylonitrile required heating at 105 ºC under neat conditions. The resulting isoquinuclidines **352** and **353** were obtained regio and stereoselectively as *endo*-products (Scheme 86). In the case of crotonaldehyde the DA reaction took place in CH_2Cl_2 at 0 ºC using $ZnCl_2$ as Lewis acid giving the corresponding adduct **354** in 59% yield.
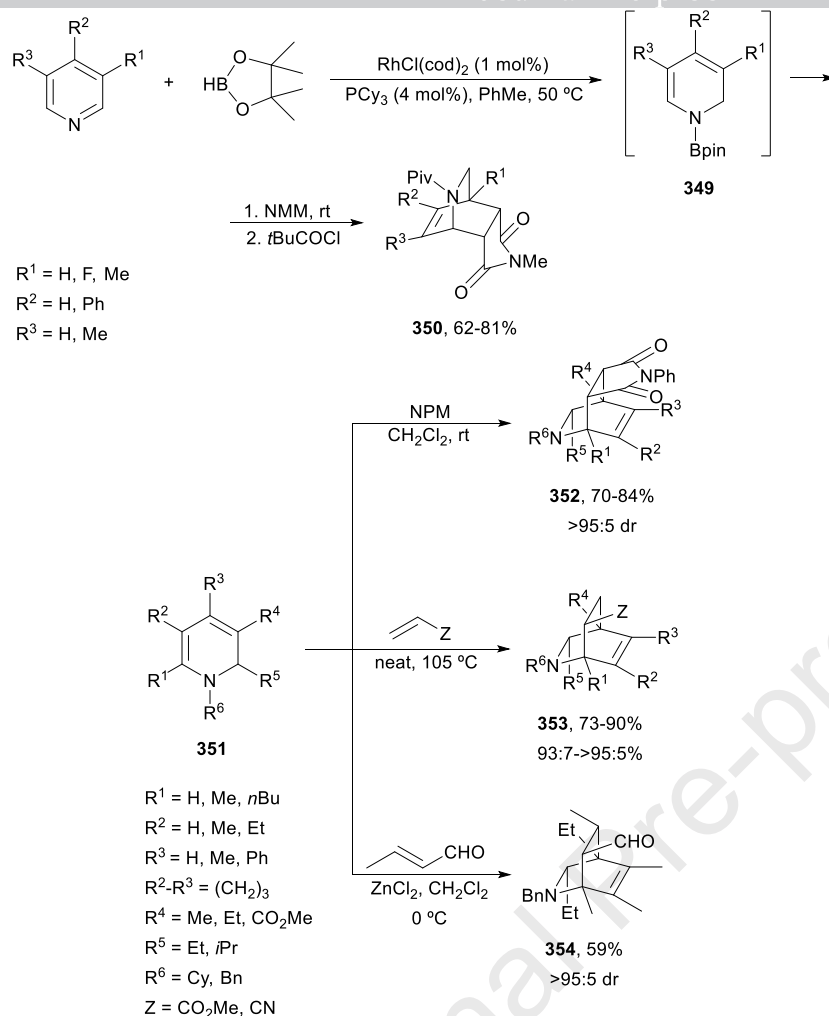
Scheme 86. Synthesis and DA reactions of 1,2-DHPs **349** and **351**.

Under thermal DA conditions 1,2-DHPs **356** [197] showed degradation and therefore the electrocyclization of starting (*E*,*E*)-cinnamylacetophenone **355** with amines in the presence of TiCl$_4$ followed by cycloaddition with NMM was performed in an one-pot procedure (Scheme 87). The resulting isoquinuclidines **357** were obtained as *endo*-diastereomers using different amines in moderate yields.
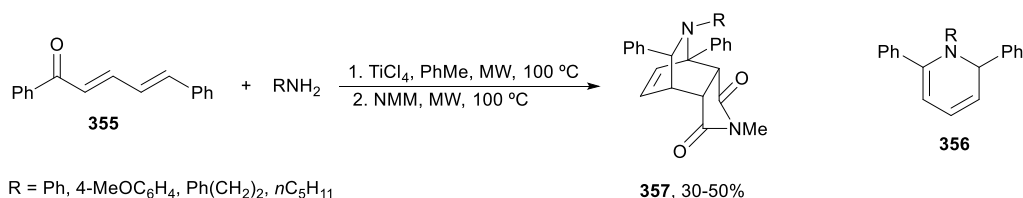
Scheme 87. One-pot electrocyclization-DA reaction of (*E*,*E*)-cinnamaldehydeacetophenone **355** with amines and NMM .

Intramolecular DA reactions of *N*-acyl-1,2-dihydropyridines bearing an acrylate unit were described by Comins and co-workers [231] to provide under heating in refluxing decalin

polycyclic products. This strategy has been applied to the synthesis of compound **359** by heating at 190 ºC 1,2-DHP **358** (Scheme 88). This adduct was further transformed into the *cis*-decahydroquinoline **360** precursor of the alkaloid gephirotoxin. Model studies toward the preparation of *cis*-decahydroquinoline derivatives precursors of *Lycopodium* alkaloids have been performed by the same group [232]. More recently, the AB ring fragment of spirolucidine has been also prepared [233].
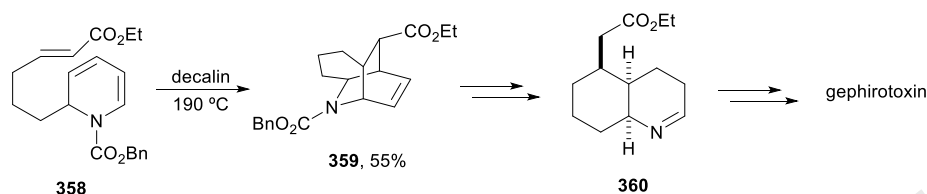
Scheme 88. Intramolecular DA reaction of 1,2-DHP **358**.

5.1.2. Asymmetric DA reactions

Chiral isoquinuclidines have been prepared using three main strategies for the asymmetric DA reactions, by the use of a chiral 1,2-DHP, chiral dienophiles and chiral catalysts. These methodologies have been reviewed [211,212] partially and here a brief comprehensive summary will be discussed.

Chiral 1,2-DHPs such as **362** bearing a *N*-glycopyranosyl group was generated *in situ* by reduction of the pyridinium salt **361** giving after cycloaddition to methyl acrylate isoquinuclidine *endo*-**321** up to 84% ee (Scheme 89) [234].
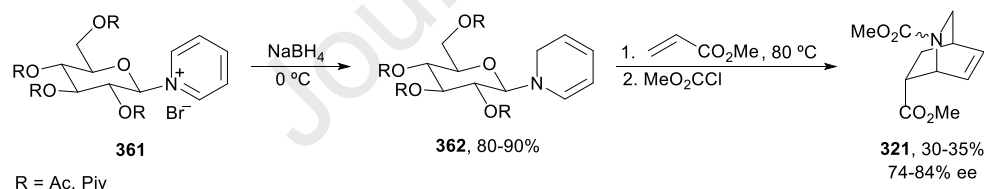
Scheme 89. Asymmetric DA reactions of *N*-glycopyranosyl-1,2-dihydropyridines **362** with methyl acrylate.

The same group [235] prepared chiral 1,2-DHPs **363** and **364**, which by reaction with methyl acrylate provided isoquinuclidines **365** and **366**, respectively. Compound **365** was obtained in 62:38 dr and 55% overall yield, while **366** was isolated in 65:35 dr and 60% overall yield (Scheme 90). These two types of chiral 1,2-DHPs developed by Marazano and co-workers [234,235] used chiral auxiliaries bonded at the nitrogen atom easily removed. Matsumura and co-workers [236] prepared the chiral 1,2-DHP **367**, which reacts with *N*-acryloyloxazolidinone **118** in the presence of one equivalent of AlCl₃ to give *endo*-cycloadduct **368** in 98.4:1.6 dr (Scheme 90). This product was further transformed into isoquinuclidine **369** in 96.8% ee. The diastereoselective synthesis of tetra and pentasubstituted pyridines has been reported by Charettes's group using *N*-protected 1,2-DHPs with a chiral auxiliary [237,238] This methodology has been applied to the total synthesis of (+)-lepadin B [238] belonging to the family of lepadins natural products with significant *in*

vitro cytotoxicity. The synthesis begins using chiral 1,2-DHP **370** which reacted with methyl acrylate in the presence of $BF_3 \cdot OEt_2$ at 50 ºC to provide *endo*-**371**, which was reduced to **372** in 47% overall yield (Scheme 90).
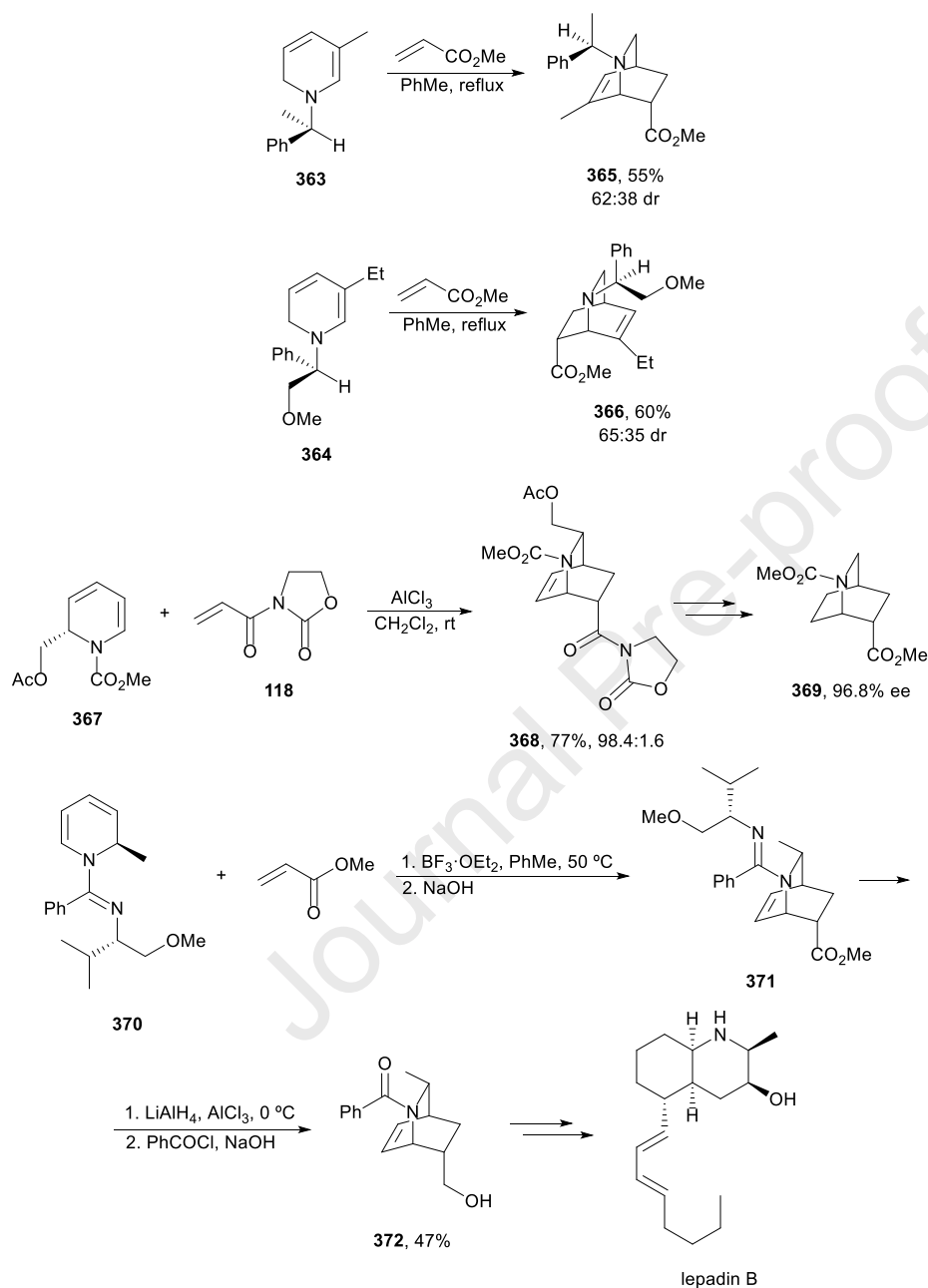
Scheme 90. Asymmetric DA reactions of chiral 1,2-DHPs **363**, **364**, **367** and **370** with dienophiles.

García Mancheño and co-workers [239] performed an asymmetric synthesis of chiral 1,2-DHP **375** by nucleophilic dearomatization of pyridines. Using an anion-binding organocatalyst **373**, silyl ketene acetal **374** was enantio- and regioselectively added at the 2-position of pyridines (Scheme 91). The resulting chiral 1,2-DHP **375** (R = 6-Me) was allowed to react with NMM to provide isoquinuclidine **376**.
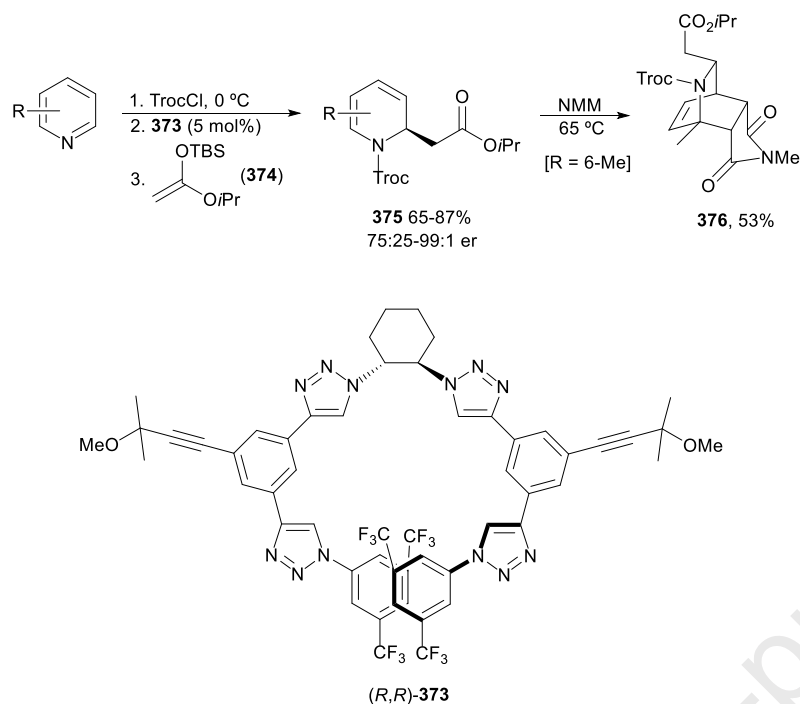
Scheme 91. Enantiocatalyzed synthesis of 1,2-DHP **375** and DA reaction with NMM.

A five steps one-pot synthesis of isoquinuclidines has been carried out in an enantio- and diastereoselective manner by Kumar and co-workers [206,240]. The proline-catalyzed Mannich reaction-cyclization-IBX oxidation and NaBH$_4$ reduction sequences between glutaraldehyde and imines gave enantioenriched 1,2-DHPs **377**. These 1,2-DHPs were extracted and without purification allowed to react with *N*-aryl maleimides furnishing isoquinuclidines **378** in excellent diastereo- and enantioselectivities (Scheme 92). DFT calculations support the high diastereoselectivity.
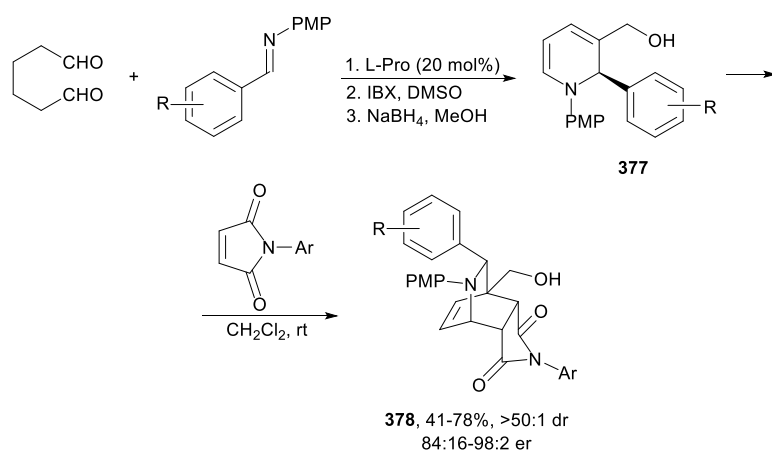
R = H, 3-NO$_2$, 4-NO$_2$, 3-F, 4-F, 2-Cl, 3-Cl, 4-Cl, 3-Br, 4-Br, 3-CN, 4-CN, 3-Br-4-F, 3,4-Cl$_2$,
    3-Py, 4-Py, 2-thienyl
Ar = Ph, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$

Scheme 92. Synthesis of enantioenriched 1,2-DHPs **377** and DA reactions with maleimides.

5.2. 2-Pyridones

2-(1H)-Pyridones are heterocyclic dienyl lactams which can be prepared mainly by (a) oxidation of pyridinium salts and (b) acylation of pyridine N-oxides [4]. DA reactions of N-substituted 2-pyridones can be performed easier than unsubstituted ones and have been mainly applied to the synthesis of isoquinuclidine derivatives and has been reviewed by Posner and co-workers in 1992 [241].

Nucleophilic N-tosyl 2-pyridones **379** substituted at the 3-position by alkoxy, TBSO and TolS groups showed good reactivity with electrophilic alkenes under mild thermal conditions (Scheme 93) [242]. The resulting bicyclic lactams **380** were formed with complete regio and stereocontrol. Hongo and co-workers [243] reported DA cycloadditions of N-unsubstituted 2-pyridones **381** having a methoxycarbonyl group as electron-withdrawing substituent. Using NPM the corresponding cycloadducts **382** were obtained by heating at 110 ºC for 3 days (Scheme 93). Only the 3-monosubstituted pyridine gave the Michael adduct instead of the DA one. Mixture of 22:10 of *endo/exo* cycloadducts were obtained with $R^3 = CO_2Me$ and $R^1 = R^2 = H$.

X = OMe, OBn, OTBS, STol
Z = NO₂, CHO, CO₂Me, COMe

R^1 = H, CO₂Me
R^2 = H, CO₂Me
R^3 = H, CO₂Me
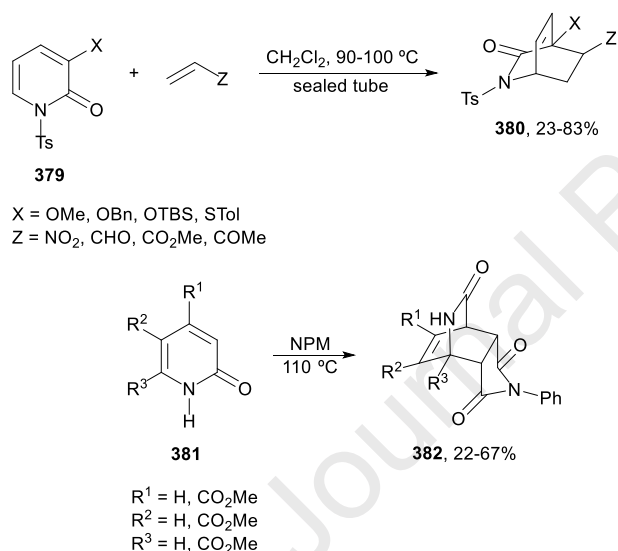
Scheme 93. DA reactions of compounds **379** and **381** with dienophiles.

The influence of the N-sulfonyl substituent in DA reactions of 2-pyridones with methyl acrylate, acrylonitrile, maleic anhydride and NMM has been studied by Afarinkia and Mahmood [244]. Significantly improved yields were obtained with bulky N-2,4,6-triisopropylbenzenesulfonyl-2-pyridones **383** providing cycloadducts **384** at 90-100 ºC in toluene and in a sealed tube (Scheme 94). Okamura and co-workers [245] reported the base-mediated DA reaction of N-tosyl-3-hydroxy-2-pyridone **379** (X = OH) with electron-deficient dienophiles to provide adducts **380** (Scheme 94). These reactions were performed at room temperature using one equivalent of Et₃N as base or with 0.1 equivalent of alkali metal derivatives such as nBuLi, MeONa and tBuOK in the case of using NMM as dienophile. In all cases no Michael adducts were observed and the stereospecificity of cycloadditions suggested that proceed *via* a concerted DA reaction mechanism. The cycloadduct derived from methyl acrylate was used for the synthesis of (±)-validamine and its epimers [246] and also for the synthesis of Corey's Tamiflu intermediate [247].
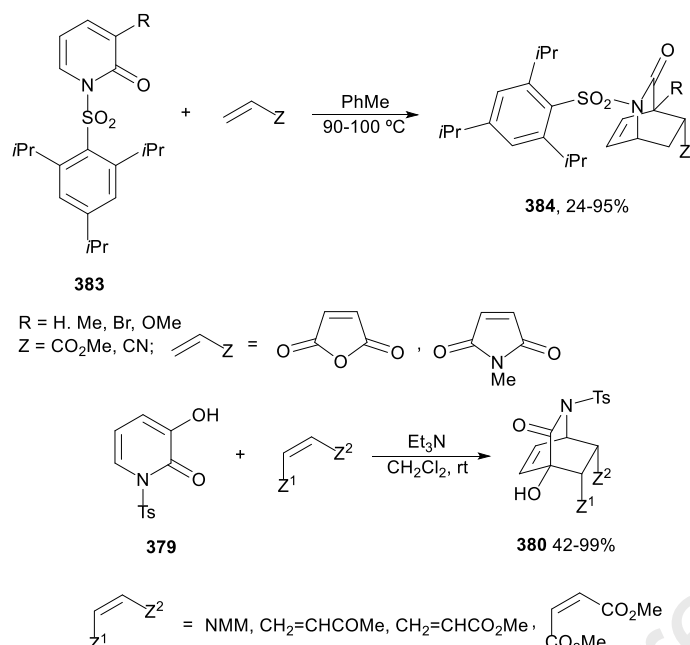
Scheme 94. DA reactions of *N*-sulfonyl-2-pyridones **383** and **379**.

Fujita's group [248] studied the reactivity of *N*-methyl-2-pyridones bearing a methoxy or a chloro substituent with NPM at atmospheric and high pressure (10 kbar) at 110 and 90 ℃, respectively, to give the corresponding *endo*-isoquinuclidine derivatives in 36-93% and 18-80% yield, respectively. In general, *endo*-adducts were exclusively obtained. The same cycloaddition was also carried out with *N*-methyl-2-pyridones bearing a benzoyl or a cyano group at the 3,4 and 5 positions [249]. The reactions gave the *endo*-adducts in 13-99% yields at 110 ℃ in a sealed tube and in 3-65% yields at 90 ℃ under 10 kbar.

Cycloadditions of 4-(phenylthio)- and 4-(phenylsulfonyl)-2-pyridones **385** substituted at the nitrogen atom by tosyl and alkyl groups have been reported by Chou and co-workers [250]. Maleimides and methyl acrylate gave mainly *endo*-isoquinuclidines **386** working at 100 or 150 ℃ in moderate yields (Scheme 95). Several other dienophiles such as dimethyl acetylenedicarboxylate, methyl vinyl ketone and methyl methacrylate failed. Asymmetric DA reactions of 3-hydroxy-2-pyridones **379** with (−)-8-phenylmenthyl acrylate (**387**) using quinine as catalyst have been reported by Vasella and co-workers (Scheme 95) [251]. A single diastereomer **388** was obtained in high yield, which was further transformed into enantiomerically pure D-*mano*-isoquinuclidines with good glycosidase inhibitory activity.
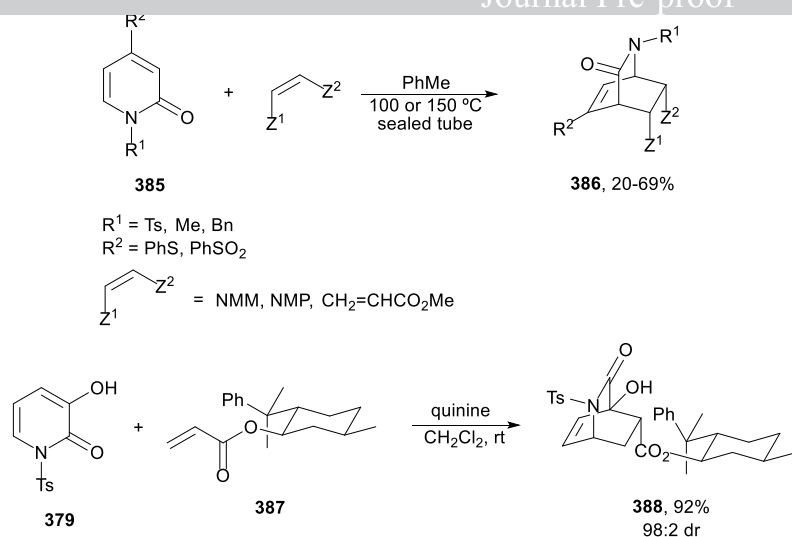
Scheme 95. DA reactions of 2-pyridones **385** and **379** with dienophiles.

The aminoindanol **390** catalyzed enantioselective DA reactions of 3-hydroxy-2-pyridones **389** have been studied by Soh and Tan (Scheme 96) [252]. This amine-organocatalyzed cycloadditions were carried out with maleimides at -50 °C giving the corresponding *endo*-isoquinuclidines **391** in high yields and enantioselectivities. Other dienophiles such as vinyl ketones and β-nitrostyrenes were also employed. Nakano and co-workers [253] reported the same asymmetric DA reaction using *N*-tosyl-3-hydroxy-2-pyridone (**379**) and different chiral primary β-amino alcohols as organocatalysts. The best result with NMM was obtained using **392** which gave the corresponding cycloadduct **393** in 95% yield and 98% ee (Scheme 96). The *endo*-adduct **393** might be formed through the transition state TS in which the pyranone could be fixed by two hydrogen bonds between the ammonium site of the catalyst and the carbonyl and hydroxy groups of the pyranone. Then, the maleimides might approach by one of the reaction sites of the coordinate pyridone.
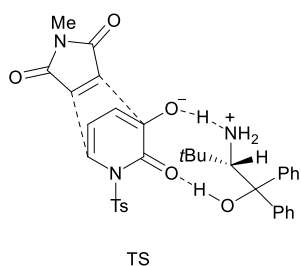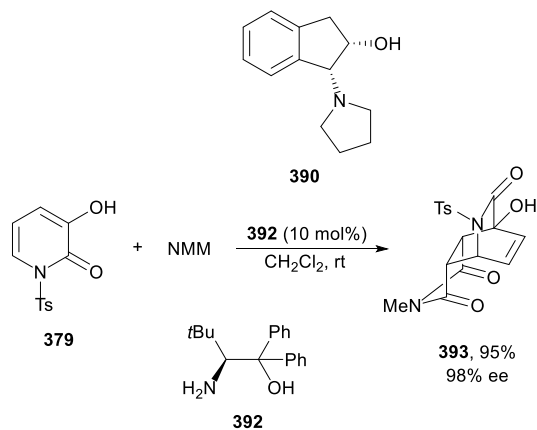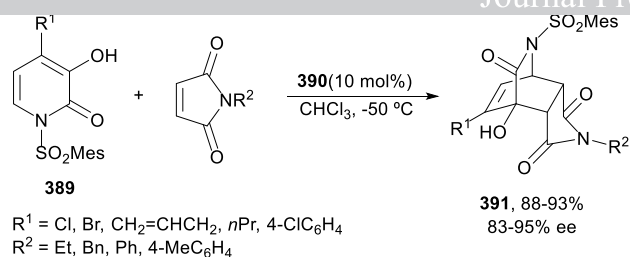
Scheme 96. Enantiocatalyzed DA reactions of 3-hydroxy-2-pyridones **389** and **379** with maleimides.

An organocatalyst bearing a chiral β-amino alcohol and a squaramide **394** has been also used for the enantioselective DA reaction of 3-hydroxy-2-pyrones **379** and **389** with maleimides by Nakano and co-workers [254] (Scheme 97). The corresponding *endo*-4-hydroxy-2-azabicyclo[2.2.2]octanes **391** were obtained in excellent yields and moderate to high enantioselectivities. In these cases TSI was proposed as a model in which three hydrogen bondings between the catalyst and the 3-hydroxy-2-pyranone were involved.
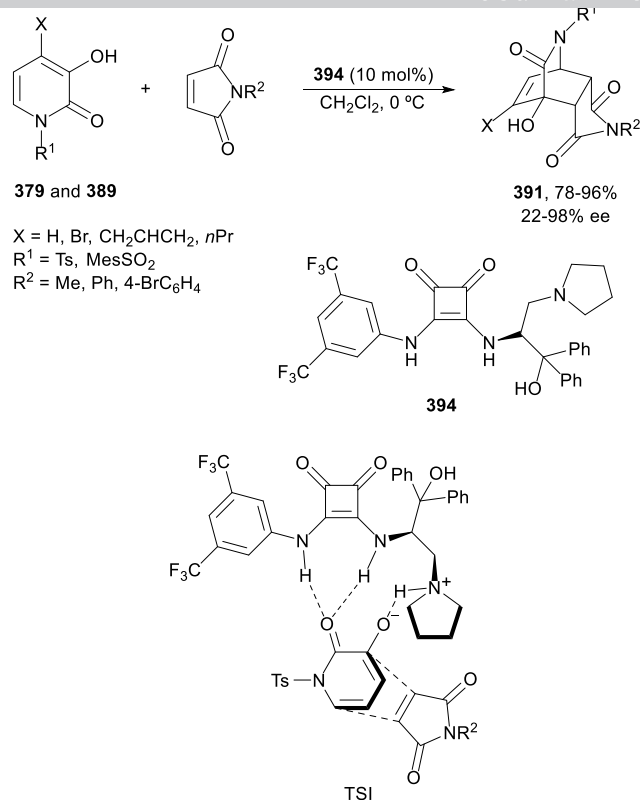
Scheme 97. Enantiocatalyzed DA reactions of 3-hydroxy-2-pyridones **379** and **389** with maleimides.

The quinolizidine alkaloid (−)-cytisine [255] is a partial agonist of nicotinic acetylcholine receptor (nAChR). In order to increase the affinity to nAChR, Tsypysheva and co-workers [256-260] have performed DA reactions of *N*-methylcytisine (**395**), (−)-leontidine (**396**) and (−)-thermopsine (**397**) with NPM [256] to give adducts **398-400** with the same diastereoselectivity (Scheme 98). Cycloadditions of *N*-methylcytisine with maleic anhydride, 1,4-benzoquinone, tetracyanoethylene and methyl acrylate were performed in boiling toluene giving the corresponding adducts in 2.5:1 dr [257]. DA reaction of *N*-substituted (−)-cytisine with NPM under high pressure gave mainly the other diastereomers in 63-90% yields and 1:3 to 1:6 dr [258,259]. A library of diastereomeric DA adducts of *N*-substituted (−)-cytisine and maleimides were synthesized and their anti-influenza A virus activity studied [260]. The virus-inhibitory activity of the *endo*-adducts was higher than the hit compound.
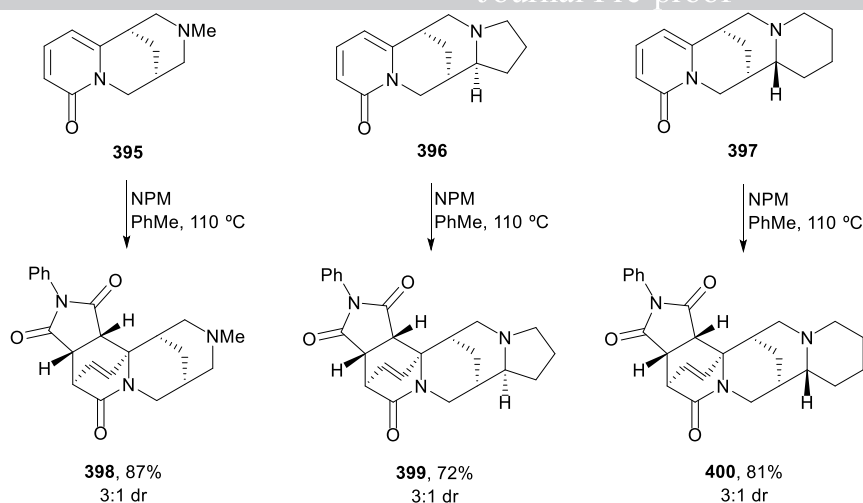
Scheme 98. DA reactions of *N*-methylcytisine (**395**), leontidine (**396**) and thermopsine (**397**) with NMP.

6. Alkenyl-substituted nitrogenated heterocycles

Nitrogen-containing heterocycles bearing a vinyl or alkenyl substituent conjugated with an internal double bond and the nitrogen **5-9** such as five-membered Δ^2-pyrrolines, pyrroles, pyrazoles, imidazoles and indoles, and six-membered tetrahydropyridines and 5-vinyl-2,3-dihydro-4-pyridones have been employed as 1-amino-1,3-dienes in DA reactions [261]. The reactivity of these heterocyclic dienes is determined by the number of heteroatoms and other substituents, and in the case of heteroaromatic compounds also by their aromatic character.

6.1. 3-Vinyl-Δ^2-pyrrolines

3-Vinyl-Δ^2-pyrroline **401** was used by Stork and Morgans Jr. [262] for the synthesis of the skeleton of lycorine alkaloids. Compound **401** underwent an intramolecular DA reaction to provide *exo*-**402**, which was further transformed into α-lycorane (Scheme 99). A similar strategy was employed by Boeckman Jr. [263,264] using the Δ^2-pyrroline **403** for the synthesis of tetracycle **404** precursor of lycorine. The cycloaddition took place under toluene reflux giving **404** in 64% yield (Scheme 99).
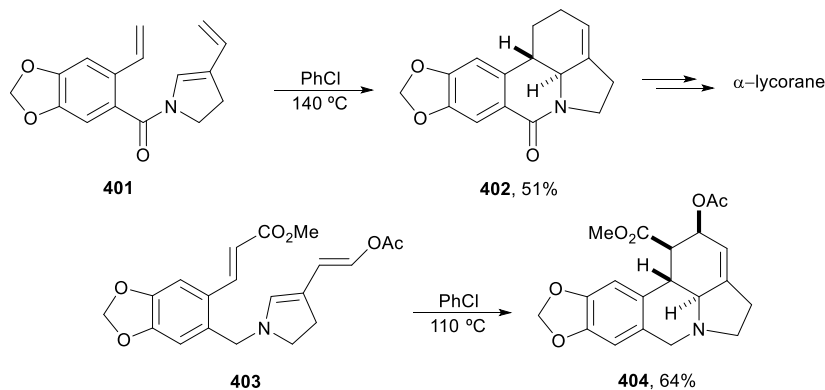
Scheme 99. Intramolecular DA reactions of vinyl Δ^2-pyrroline **401** and **403**.

The same group [265] developed a general synthesis of 3-alkenyl Δ^2-pyrrolines by a tandem cyclopropyliminium ion rearrangement-Hofmann elimination. For instance, α-aminonitrile **405** gave by treatment with AgOTf and LiBr the enamonium salt **406** in 85-95% yield (Scheme 100). After treatment with DBU or basic ion exchange resin (IRA 400), elimination of ethyl acrylate took place giving the 3-alkenyl-Δ^2-pyrroline **407** in 90% yield. This dienic system underwent DA reaction with dienophiles to provide the corresponding cycloadducts **408**.

EWG = CO$_2$Me, SO$_2$Ph, COMe, CHO
Z = H, Me
X^1 = H, CO$_2$Me
X^2 = H, Me, CO$_2$Me, SO$_2$Ph
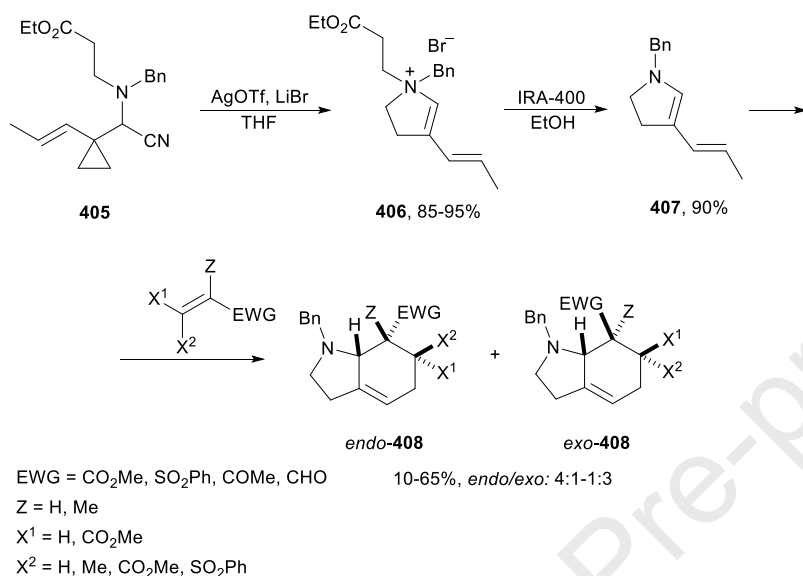
Scheme 100. Synthesis of alkenyl Δ^2-pyrroline **407** and intermolecular DA reactions.

During synthetic studies and *in vitro* evaluation of SG3227, a pyrrolobenzodiazepine dimer antibody-drug conjugate payload based on sibiromycin, Tiberghein, Howard and co-corkers [266] found out that intermediate **409** underwent an intermolecular DA reaction with NMM within 6 hours at room temperature to give **410**. However, the intermolecular reaction of the ring-open intermediate **411** needed one week to react with NMM to provide compound **412** (Scheme 101).
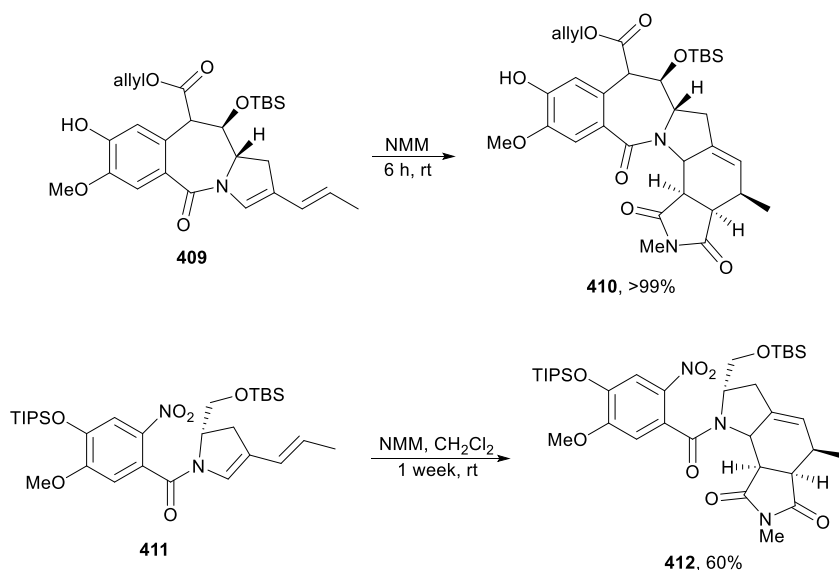
Scheme 101. DA reactions of alkenyl Δ^2-pyrrolines **409** and **411** with NMM.

6.2. 3-Vinylpyrroles

DA reactions of 3-vinylpyrroles have been mainly used for the synthesis of indoles. DA reactions of vinylpyrroles substituted at the 2-position by electron-withdrawing groups **413** with dimethyl acetylenedicarboxylate (DMAD) gave 4,5-dihydroindoles **414** (Scheme 102) [267]. Subsequent aromatization was accomplished with DDQ under benzene reflux to furnish indoles **415**. For the cycloaddition high temperatures were needed with or without solvent in a sealed steel reaction vessel. Compounds **413** were prepared using Wittig olefination of the corresponding formyl pyrroles [267]. Salvadori and co-workers [268] reported the synthesis of unsubstituted 3-alkenylpyrroles by acylation of *N*-tosylpyrrole followed by reduction, dehydration and desulfonylation. Harman and co-workers [269,270] reported the DA reaction of osmium complexed *N*-methyl-3-vinylpyrroles **416** with NPM, 4-cyclopentene-1,3-dione, DMAD, dimethyl fumarate and methyl acrylate to give tetrahydroindoles **417**, which were oxidized with DDQ to the corresponding indoles **418** (Scheme 102).

R = CHO, CO$_2$Me, CN

Alkenes: NPM, 4-cyclopentene-1,3-dione, DMAD, dimethyl fumarate, methyl acrylate
R^1 = H, Me, 3,5-dimethylbenzyl
R^2 = H, Me, Et, Ph, OMe, CO$_2$Me
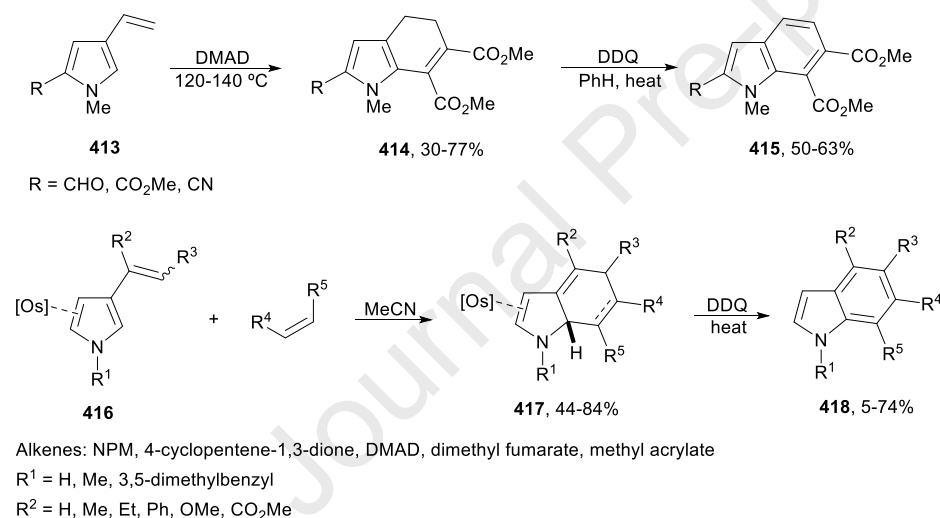
Scheme 102. DA reactions of 2-substituted 4-vinylpyrroles **413** and Os-complexes **416**.

N-Phenylsulfonyl-3-vinylpyrrole **419** reacted with maleic anhydride and NPM in refluxing toluene giving after spontaneous [1,3] sigmatropic hydrogen rearrangement rearomatized pyrroles **420** and **421**, respectively (Scheme 103) [271]. However, the cycloaddition with methyl acrylate failed.
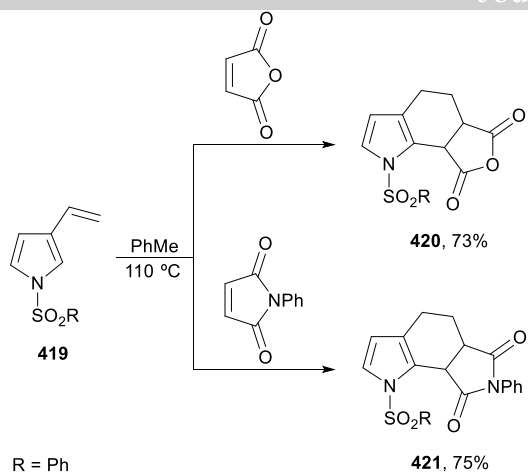
Scheme 103. DA reactions of *N*-phenylsulfonyl-3-vinylpyrrole **419**.

Noland and Lanzatella [272] applied the former methodology to the synthesis of indoles **424** and **425**. The corresponding adducts **422** and **423** from *N*-tosyl-3-vinylpyrrole **419** (R = 4-Tol) were aromatized with MnO$_2$ under toluene reflux and detosylated with Mg powder and Na$_2$CO$_3$, respectively (Scheme 104).
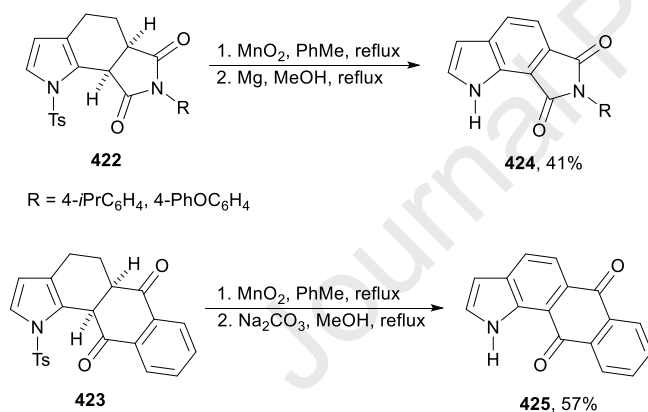
Scheme 104. Synthesis of indoles **424** and **425** from DA adducts **422** and **423**.

6.3. 4-Vinylpyrazoles

Synthetic applications of 4-vinylpyrazoles have been focusing on the synthesis of tetrahydroindazoles precursors of indazoles, which showed important pharmaceutical activities as well as herbicides, bactericides, fungicides and plant growth inhibitors and many other properties [273].

N-Phenyl-4-vinylpyrazole (**426**, R = Ph) reacted with DMAD in a sealed vessel at high temperature to give the corresponding indazole derivatives. In the case of using methyl propiolate and NPM at 150 ºC resulted DA adducts **427** and **428**, respectively in very poor yields and also other products resulting from an ene-reaction (Scheme 105) [274]. The same group [275] reported cycloaddition reactions of 1-*tert*-butyl-4-vinylpyrazole (**426**, R = *t*Bu) with DMAD, methyl propiolate and NPM giving the corresponding products in poor yields (4-15%).
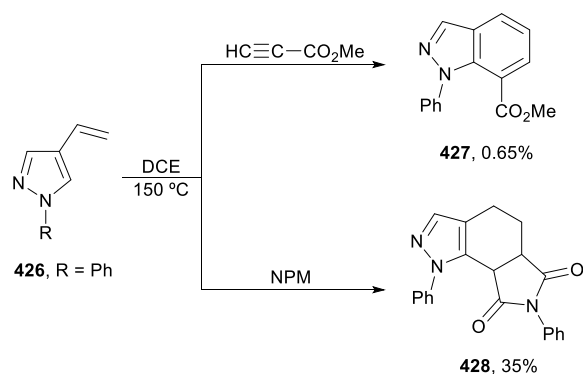
Scheme 105. DA reactions of *N*-phenyl-4-vinylpyrazole (**426**) with methyl propiolate and NPM.

Silva and co-workers [276] reported an efficient microwave-assisted DA reactions of *N*-acetylstyrylpyrazoles **429** with NMM under solvent-free conditions to give tetrahydroindazoles **430** in good yields (Scheme 106). However, under conventional heating these reactions do not occur or afford only traces of cycloadducts. Oxidation with DDQ provided the corresponding indazoles **431** with concomitant deacylation. Diastereomeric *Z*- and *E*-**429** were independently submitted to DA reaction to give *cis*- and *trans*-**430** in 32-54% yield and 68-95% yield, respectively. The same procedure was performed with NPM to provide the corresponding 1*H*-indazoles after oxidation [277].

R = H, Cl, OEt, NO$_2$
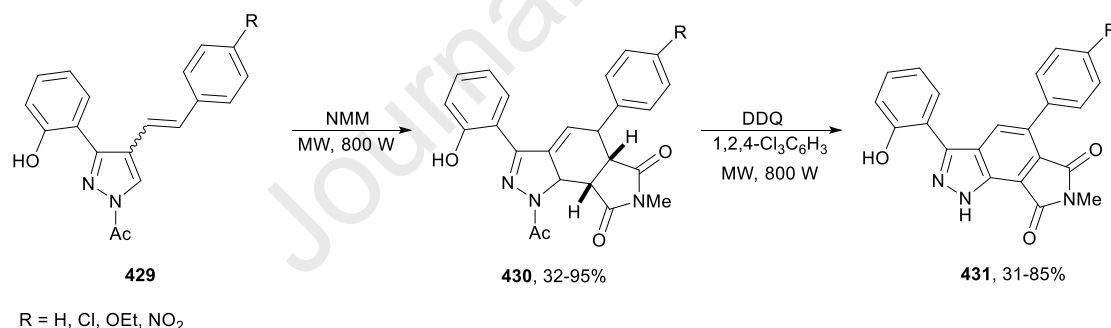
Scheme 106. DA reaction of 4-styrylpyrazoles **429** with NMM.

6.4. 4-Vinylimidazoles

For the preparation of *N*-substituted 4-vinylimidazoles **432** in multigram scale the corresponding 4-imidazole carbaldehyde was submitted to a Wittig olefination [278]. Lovely and co-workers [279-282] synthesized compounds **432** by Stille reaction of 4-iodoimidazoles with tributylvinylstannane. DA reactions of these 4-vinylimidazoles **432** with NPM under dichloromethane reflux provided the corresponding cycloadducts **433** without isomerizing to the thermodynamically more stable imidazoles (Scheme 107). The same group prepared *N*-alkyl 4-vinylimidazoles, which also with NPM gave mainly products **433** (R = Me, Bn) in 21-80% yields [280]. When other dienophiles such as methyl acrylate and acrylonitrile were used, the corresponding imidazole derivatives **434** and **435** were obtained regioselectively [281]. Maleic anhydride gave cycloadduct **436** as in the case of NPM. Hall and co-workers [283] found out that

N-trityl-4-vinylimidazole **432** (R = Tr) underwent 1,3-trityl migration during cycloaddition reactions with NPM (Scheme 107). Under thermal conditions in toluene for 1 or 3 hours, compound **433** was exclusively formed, whereas after prolonged reaction times (5 hours) resulted the *N-N* trityl migrated product **437**.
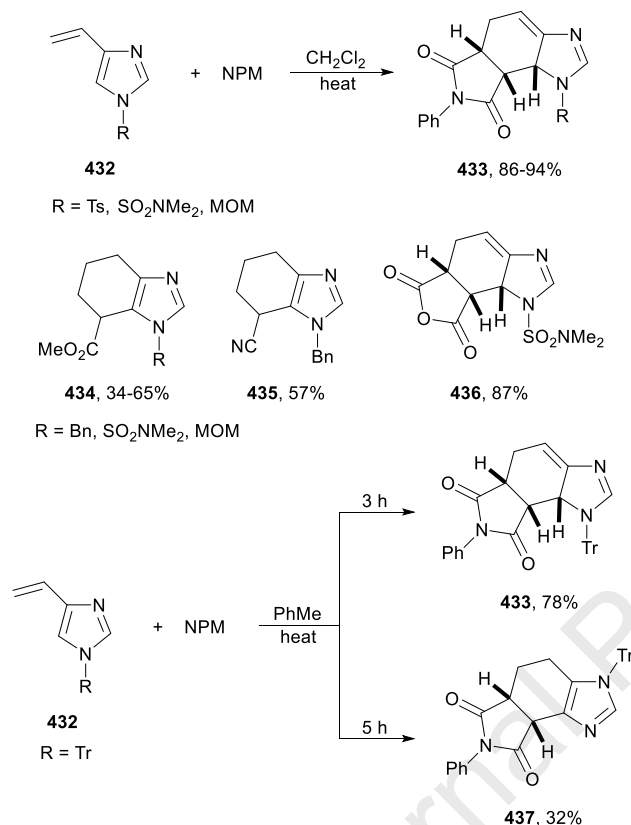
Scheme 107. DA reactions of 4-vinylimidazoles **432** with dienophiles.

Lovely and co-workers [281] reported the synthesis and DA reactions of 2-substituted *N*-benzyl-4-vinylimidazoles **438**. 2-Methyl-4-vinylimidazole **438** (X = Me) reacted with methyl acrylate at 140 ºC to provide imidazole **439** (Scheme 108). 2-Amino-4-vinylimidazole **438** (X = NHBoc) and NPM underwent also a DA reaction at 60 ºC to provide product **440**, whereas **438** (X = NPhth) needed to be heated at 120 ºC to furnish product **441** after DA/1,3-H shift reactions.
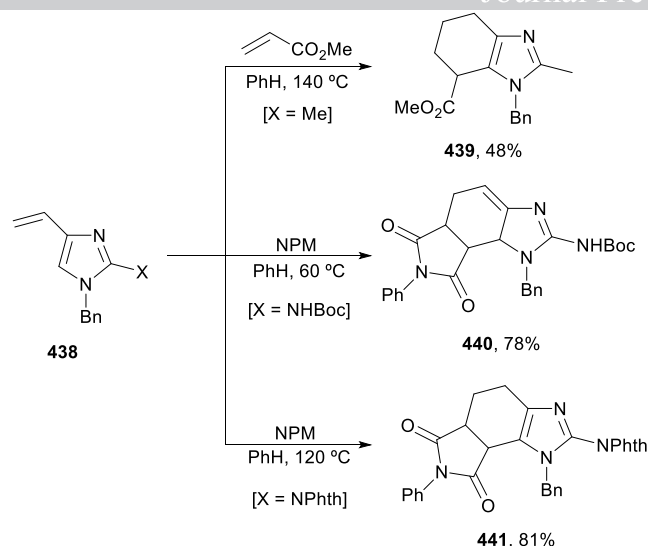
Scheme 108. DA reactions of 2-substituted *N*-benzyl-4-vinylimidazolea **438**.

When the substituents are incorporated in the vinyl moiety such as **442** (X = OTBS) the reaction with NPM afforded at 55 ºC cycloadduct **443**, whereas under benzene reflux product **444** was obtained (Scheme 109) [281]. On the other hand, when **442** (X = NBnBoc) was allowed to react with NPM at 100 ºC resulted imidazole **445** in 80% yield. In the case of silylated allylic alcohol with a *N*-trityl group **446** the reaction with NPM gave mainly product **447** arising from an *endo*-DA/[1,3]-H migration/[1,3]-Tr migration domino sequence (Scheme 109) [283].
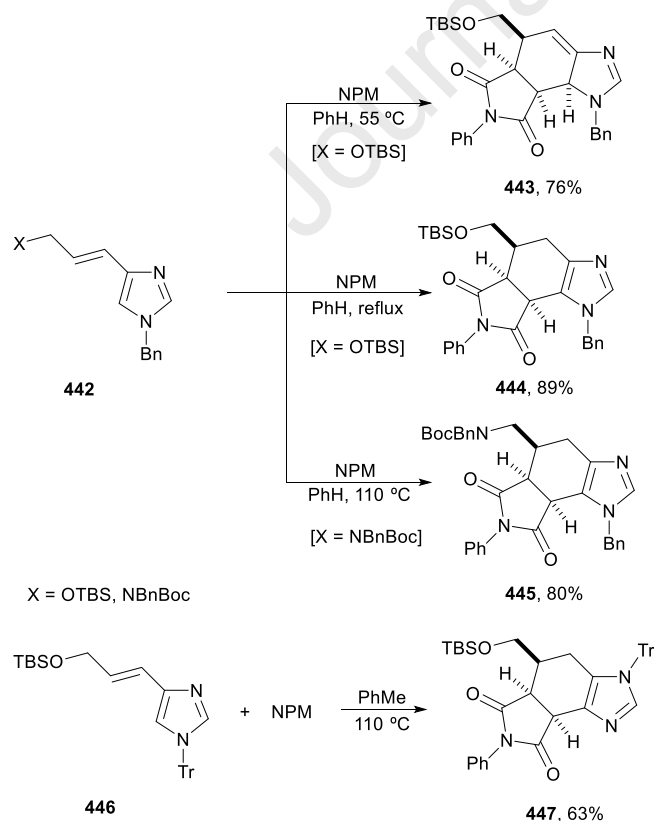
Scheme 109. DA reactions of substituted *N*-benzyl-4-alkenylimidazoles **442** and **446** with NPM.

Recently, Lovely and co-workers [284] reported a DA reactions of 1',2'-disubstituted-4-vinylimidazoles **448** with NPM (Scheme 110). The corresponding tetrahydrobenzimidazole derivatives **449** (R = SO$_2$NMe$_2$) were obtained in good yields in the case of silylated and stannylated compounds. However, in the case of silylated *N*-benzylimidazole **448** (R = Bn, X = PhMe$_2$Si) the subsequent [1,3]-H shift provided product **450** as 1:0.6 mixture of diastereomers. Starting imidazoles **448** with X = Br, I gave very low yields and the X = Cl derivatives failed.
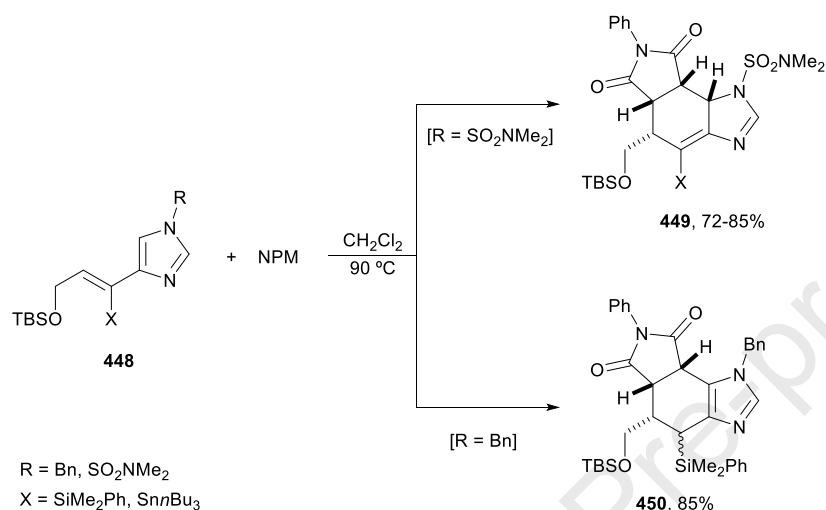
Scheme 110. DA reaction of imidazoles **448** with NPM.

3-Amino-1-(2-aminoimidazoyl)prop-1-ene (AAPE), isolated as a natural product [285], has an extended π-system and presents several tautomers [286]. This imidazole is a precursor of the pyrrole-imidazole alkaloid family from marine sponges such as palau'amines, styloguanidines, oroidin, hymenidin, clathrodin, giroline, axinellamine A and massadine [287]. Lindel and co-workers [288] studied DA reaction of AAPE derivatives **451** with NPM as model studies. The corresponding adducts **452** were obtained in good yields working at room temperature (Scheme 111). Oroidinium formate **453** reacted with maleimide and NPM already at room temperature. However, addition of Y(OTf)$_3$ accelerates the DA reaction giving products **454** (Scheme 111).
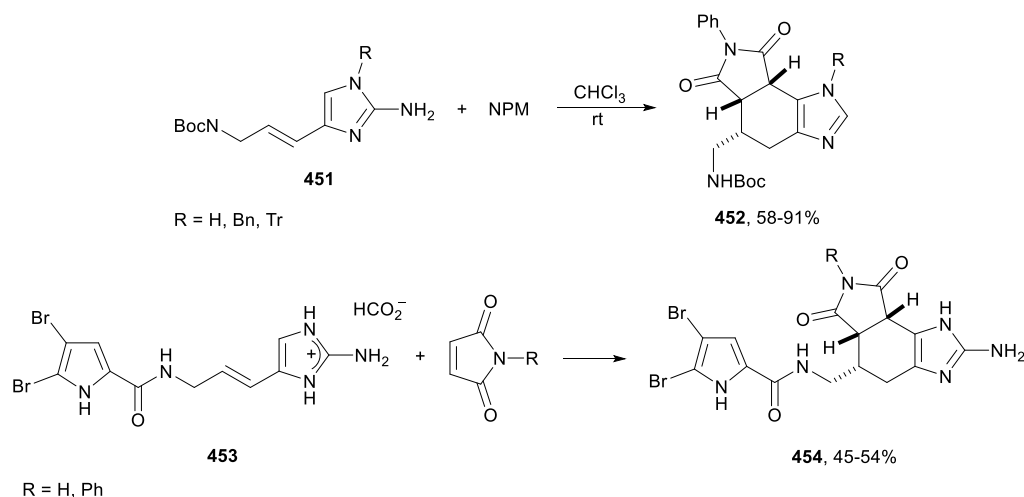
Scheme 111. DA reactions of imizazoles **451** and **453** with maleimides.

Intramolecular DA reactions of 4-vinylimidazoles have been studied by Lovely and co-workers [289-293] to access the polysubstituted carbocycles from marine natural products of the oroidin family [287]. Initial studies were carried out with several urocanic acid derivatives at 95 ºC in benzene [289,290]. Propargyl ethers and esters gave the corresponding cycloadducts in low yields. In the case of urocanic acid amide derivatives the cycloaddition took place at 68 to 130 ºC to provide the corresponding *trans*-ring fused tricyclic products *via endo*-transition states. In Scheme 112 it has been depicted the example of the dimeric AAPE-urocanic acid substrate **455**, which is the model approach to ageliferin. Under thermal conditions a mixture of regioisomeric products **456** and **457** were obtained diastereoselectively by an intramolecular DA reaction.
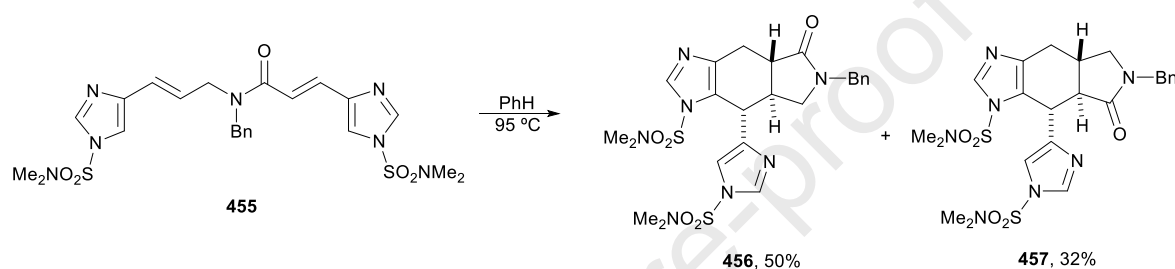
Scheme 112. Intramolecular DA reaction of dimeric imidazolyl derivative **455**.

Synthetic approach to the imidazole fragment of the dimeric pyrrole-imidazole alkaloids axinellamine A and massadine involves intramolecular DA reaction of several N−O linked 4-vinylimidazoles **458** (Scheme 113) [291]. These compounds were subjected to DA reaction in toluene at 150 ºC (sealed tube) giving mixtures of the normal **459** and inverse electron demand products **460**. Oxidative rearrangement of cycloadducts **459** provided spiro imidazoles **461** in 47-81% yields.
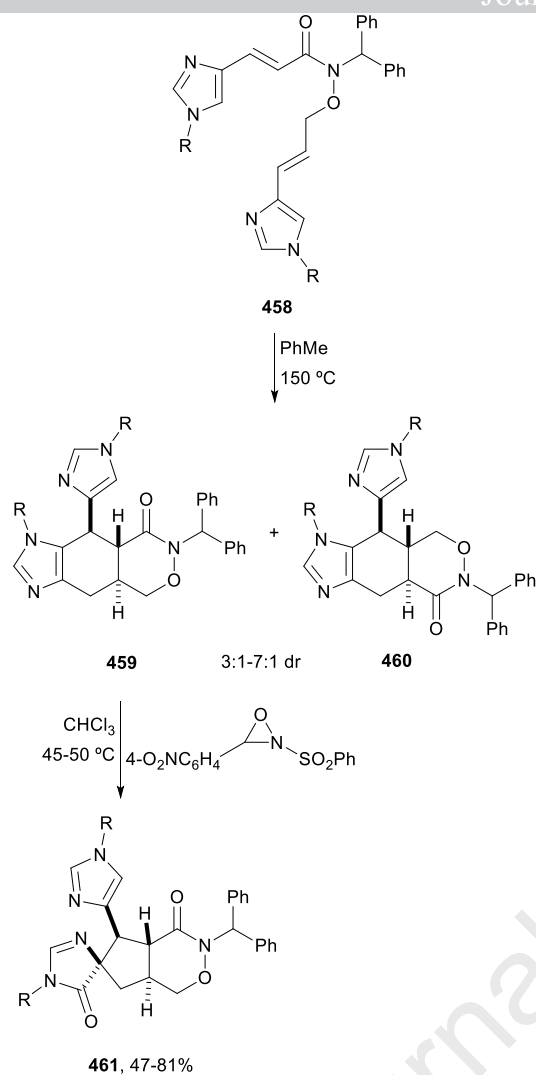
Scheme 113. Intramolecular DA reaction-oxidative rearrangement of N−O linked 4-vinylimidazoles **458**.

A DA-rearrangement sequence of oroidin dimers **462** has been described for the construction of the core ring systems of ageliferin and palau'amine [292]. The intramolecular cycloaddition of compounds **462** took place at 130 ºC in a sealed tube to furnish products **463** (Scheme 114). Intramolecular DA reaction of the imidazole-containing enyne **464** has been used as key step for the total synthesis of 7'-desmethylkealiiquinone an analogue of the marine alkaloid kealiiquinone [293]. The resulting cycloadduct **465** was obtained under toluene reflux (Scheme 114).
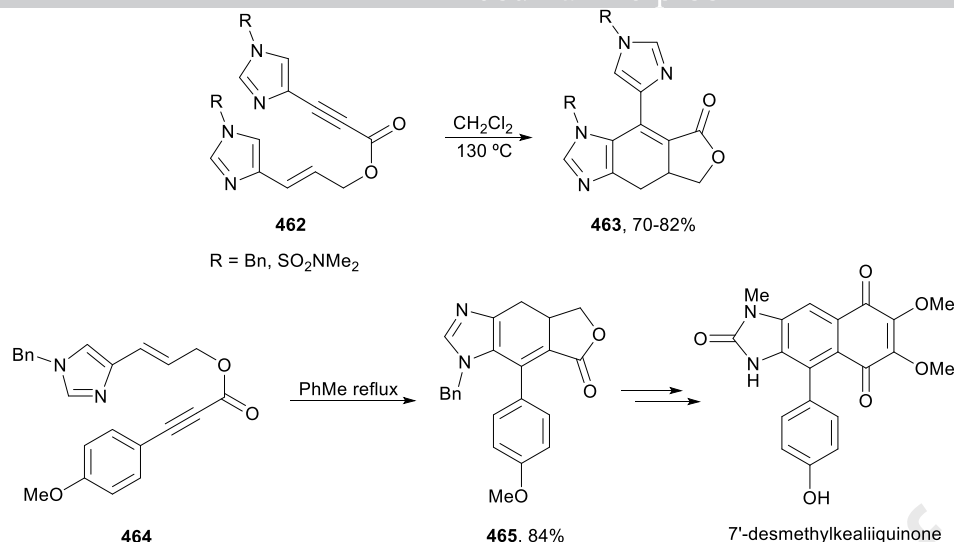
Scheme 114. Intramolecular DA reactions of compounds **462** and **464**.

For the enantioselective synthesis of the spirocyclic core of palau'amine and related bisguanidine marine alkaloids Romo and co-workers [294-296] based their strategy on a biosynthetic proposal [286,297]. The initial DA reaction was carried out with imidazolidinone **466** [298] and the pyroglutamic acid derived lactam **467** under thermal conditions to furnish mainly the desired cycloadduct **468** and regioisomer **469** after isomerization of the double bond (Scheme 115). In order to improve the regioselectivity of this cycloaddition different protecting groups at the nitrogen atoms of the imidazolidinone were used. The DA reaction of imidazolidinone **470** with lactam **467** provided, in the presence of 2,6-lutidine, cycloadduct **471**.
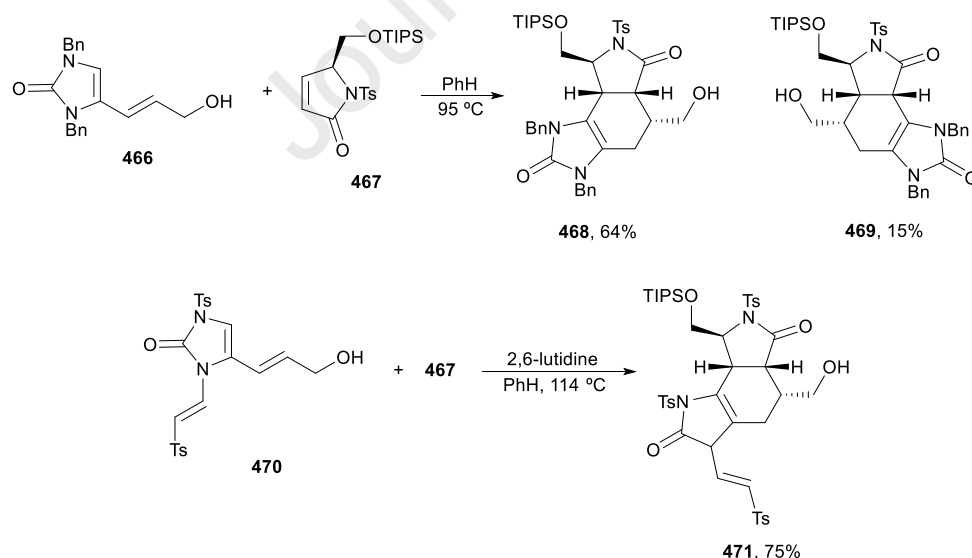
Scheme 115. DA reactions of imidazolidinones **466** and **470** with lactam **467**.

6.5. 3-Vinylindoles

Inter and intramolecular DA reactions of 3-vinylindoles **7** led to the synthesis of carbazoles and polycyclic indole derivatives [261]. For the synthesis of 3-vinylindoles, Wittig olefination has

been widely employed, Recently, Peterson olefination and the use of Nysted reagent have been described [299].

For the synthesis of the carbazole alkaloid carbazomycin B, an inhibitor of 5-lipoxygenase, the vinylindole **472** [300] was allowed to react with DMAD at 125 ºC in a sealed tube to form carbazole **473** (Scheme 116) [301]. Using **473**, carbazomycin B was obtained in three steps in 50% overall yield from **472**.
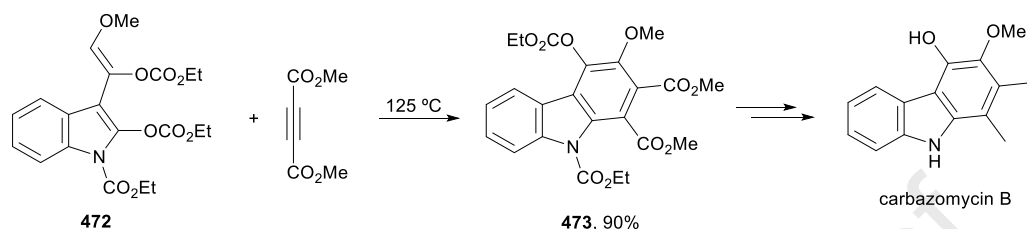
Scheme 116. DA reaction of 3-vinylindole **472** with DMAD.

DA reactions of differently substituted 3-vinylindoles **474** at the olefinic moiety with benzyne have been described by Pindur and co-workers [302]. Benzyne was generated *in situ* from benzene diazonium-2-carboxylate, prepared by nitrosation of anthranilic acid. Dehydrogenated benzo[*a*]carbazoles **475** were obtained in modest yields (Scheme 117).
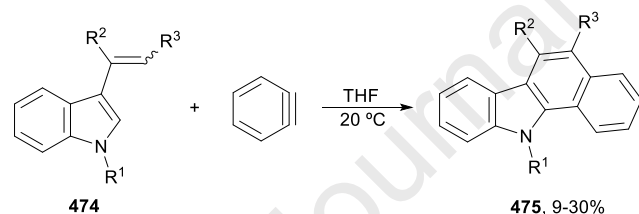
R^1 = Me, SO$_2$Ph; R^2 = H, Me, Ph; R^3 = H, CO$_2$Me

Scheme 117. DA reactions of 3-vinylindoles **474** with benzyne.

Starting from the 2-iodoanilines derivative **476**, prepared by alkylation of *N*-Boc-2-iodoaniline with a propargyl bromide, the halogen-lithium exchange triggers an intramolecular addition on the triple bond according to a 5-*exo-dig* cyclization followed by a β-elimination of LiOEt to give 3-vinylindole **477** (Scheme 118) [303]. This indole **477** reacted with methyl acrylate under thermal conditions (A) to give cycloadduct **478** regioselectively in 61% yield and 27:73 *endo/exo* mixture, whereas at 12 kbar (B) a 70% yield and 70:30 *endo/exo* mixture was obtained. Regioisomeric *N*-tosyl-3-(1-methoxyvinyl)indoles of **477** (**479**) reacted with maleimides at room temperature in toluene to afford pyrrolo[3,4-*a*]carbazoles **480** in modest yields (Scheme 118) [304]. However, *N*-Boc protected indoles **479** gave under the same reaction conditions the corresponding ketones **481**.
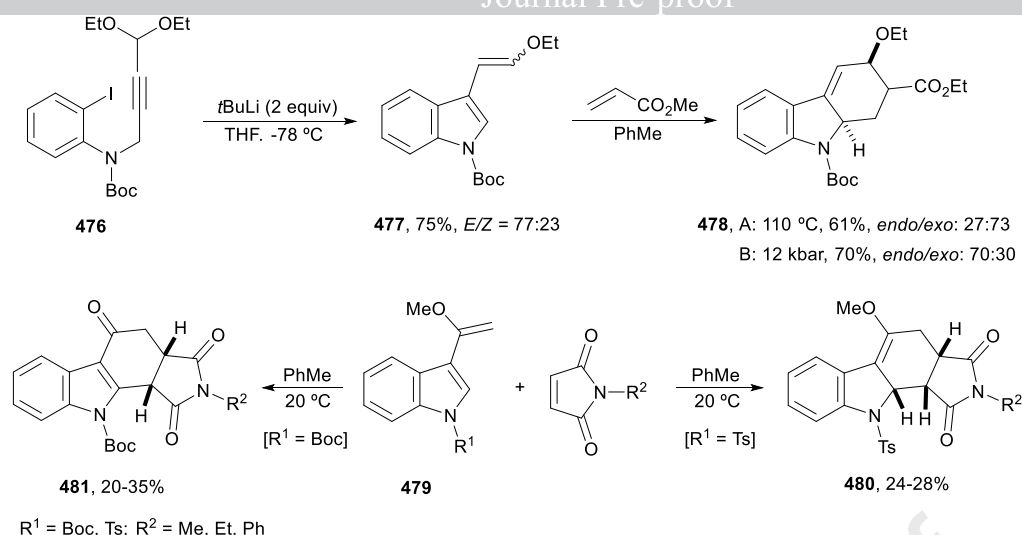
Scheme 118. Synthesis and DA reactions of índole **477** and **479** with dienophiles.

6-(3-Indolyl)quinolinequinone **483** gave regioselectively DA reactions with different dienophiles such as NMM, DMAD, 6-chloro-3-methylquinolinequinone and 4-methyl-2,5,8'(1*H*)-quinolinetrione [305]. The one-pot reaction was performed starting from indoles and quinolinetriones **482** to give after regioselective Michael and DA reactions polycyclic carbazole derivatives **484** (Scheme 119). Indolylmaleimides **485** were prepared in two steps by Michael addition of indoles to maleimides followed by dehydrogenation using DDQ [306-308]. Prudhomme and co-workers [306-315] have studied the synthesis of bis-imide granulatimide analogues in order to evaluate *in vitro* antiproliferative activities and ChK1 inhibitory properties. DA reactions of compounds **485** with maleimide gave a compound, which after oxidation gave bis-imide granulatimide analogues **486** (Scheme 119) [306-310]. Similar DA reaction has been performed with lactam derivatives **487** and **488** by reaction with maleimides providing products **489** and **490**, respectively [309]. All the tested compounds proved to be potent ChK1 inhibitors and to have cytotoxicity toward different tumor cell lines [310,311].
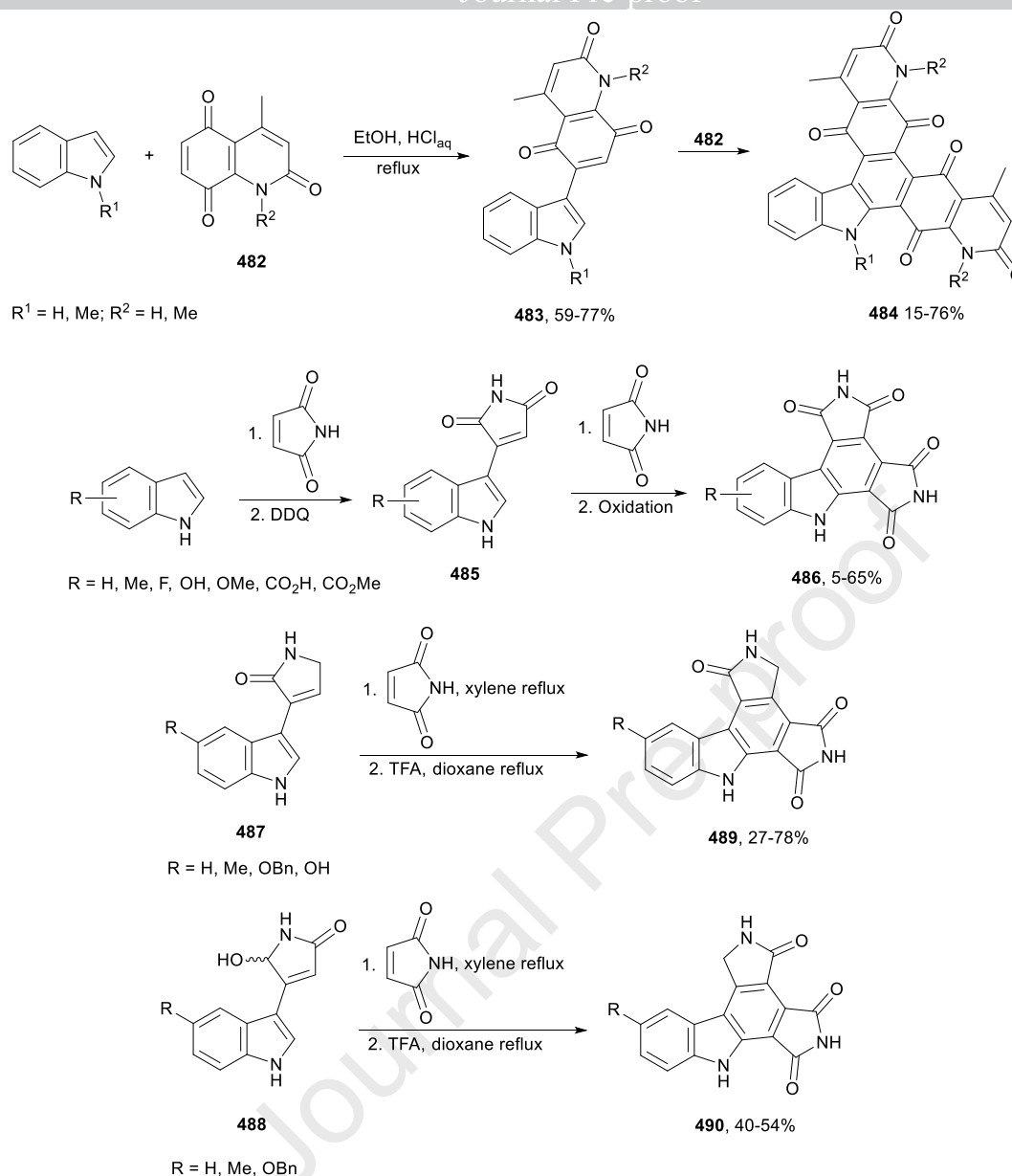
Scheme 119. Synthesis and DA reaction of índoles **483**, indolylmaleimide **485** and lactams **487** and **488** with dienophiles.

The same group performed DA reactions of 3-indolylmaleimides **485** with cyclohex-2-enone, cyclopent-2-enone and benzoquinone followed by DDQ oxidation in the two first cases to give products **491-493** in good yields (Scheme 120) [312]. Among these compounds, **493** (R = OH) and its reduced derivative **494** were the most potent ChK1 inhibitors of this series. In the case of using ethyl *cis*-β-cyanoacrylate followed by DDQ oxidation compound **495** was prepared in 22% overall yield, which was further transformed into lactam **496** [313]. In addition, the reaction of **487** (R = H) with 2,2-dimethylcyclopent-4-en-1,3-dione gave adduct **497**, which provided after treatment with TFA product **498** [313]. The strongest ChK1 inhibitor was compound **496**.
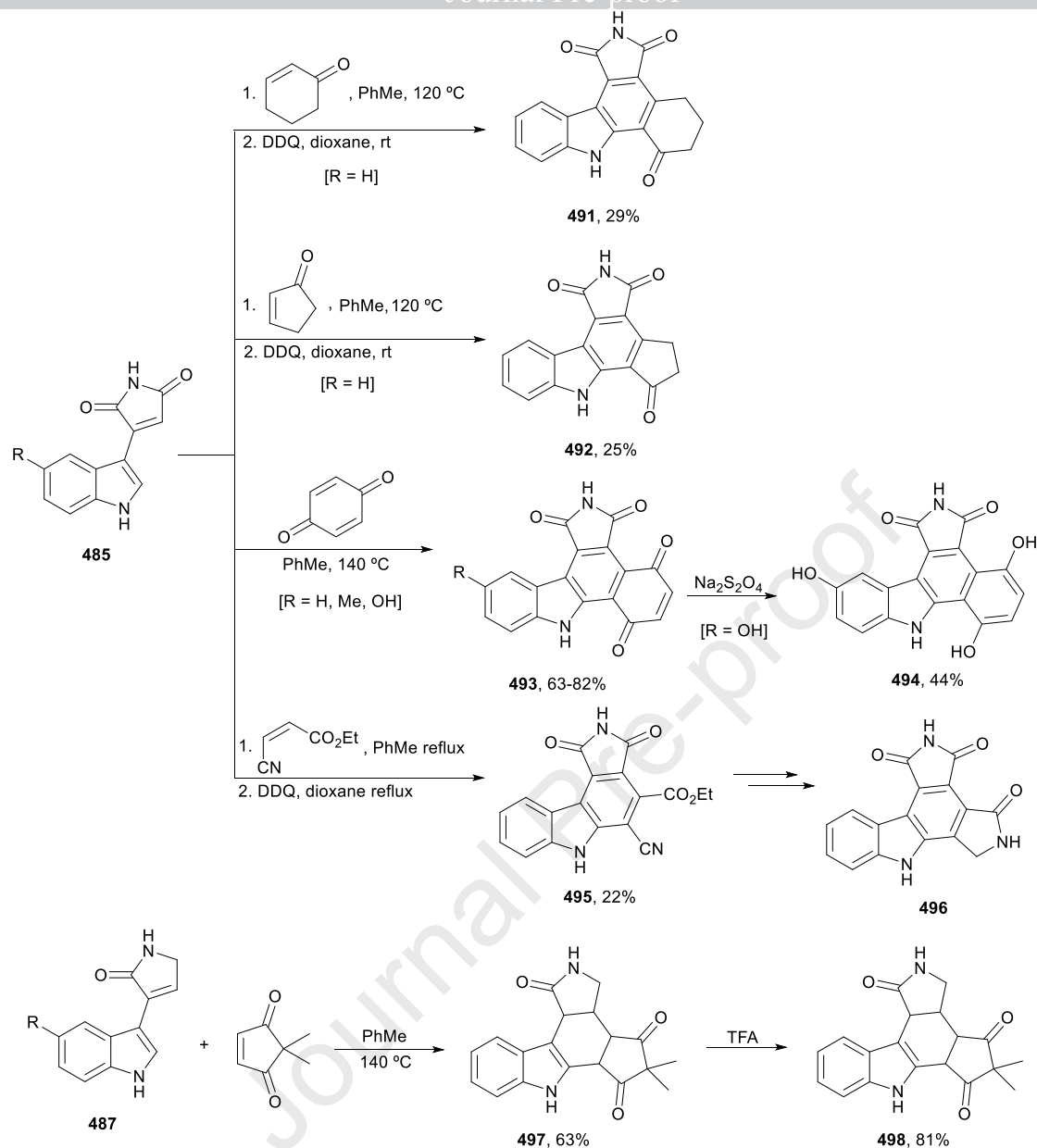
Scheme 120. Products prepared by DA reactions of 3-indolylmaleimides **485** and lactam **487**.

DA reaction of the vinylic indole **499** with maleimide gave product **500**, which was further transformed into compounds **501** and **502** (Scheme 121) [314]. In addition, the reaction of **485** (R = H) with ethyl acrylate followed by oxidation and *N*-protection with a hydroxymethyl group provided **503** as a minor product [314]. This last compound showed the most potent activity for ChK1 inhibition.
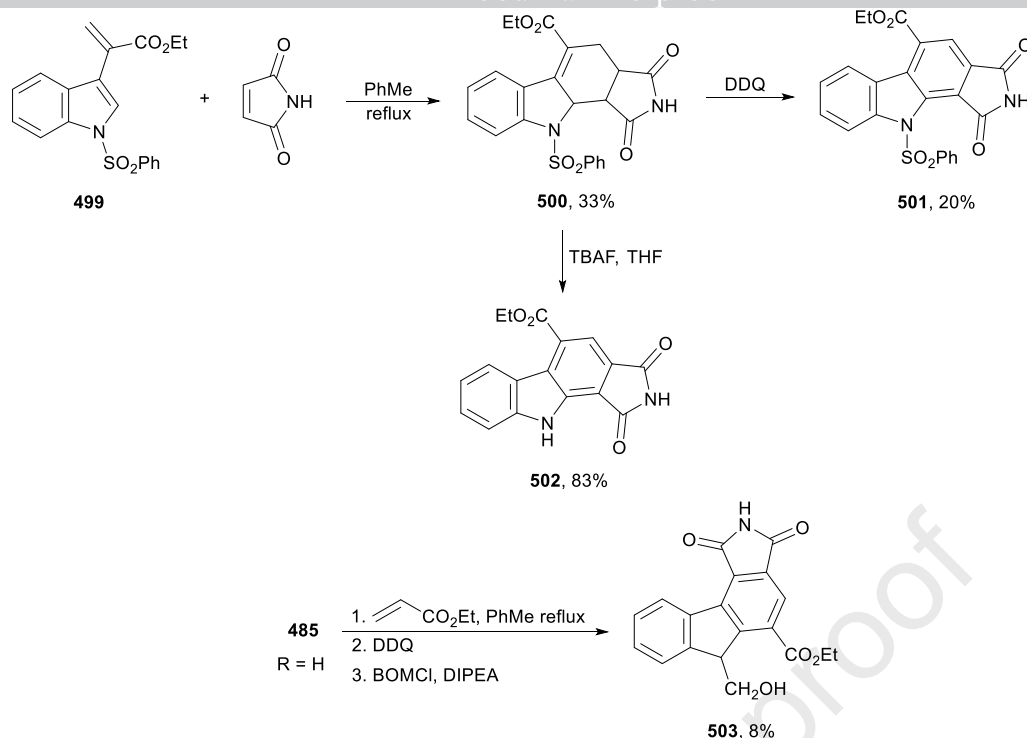
Scheme 121. DA reactions of **499** with maleimide and **485** (R = H) with ethyl acrylate.

More recently, Prudhomme's group reported that when indolylmaleimide **485** (R = H) was allowed to react with pyridones an unexpected dimerization was observed to give products **504** and **505** (Scheme 122) [315]. It was found that the same dimerization also occurred using organic bases such as DIPEA and piperidine providing *endo*-**504** and *exo*-**505**, respectively. Compound **504** inhibited protein kinase *in vitro* in the sub-micromolecular range.
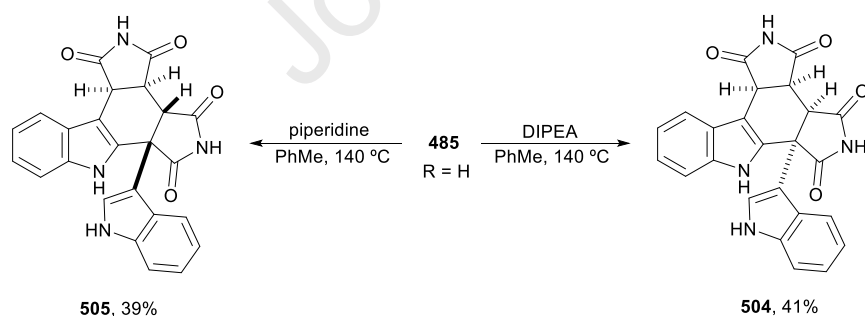
Scheme 122. DA dimerization of indolylmaleimide **485** (R = H).

Working under MW conditions *N*-phenylsulfonyl 3-alkenylindoles reacted with methyl acrylate and NPM to furnish regio and diastereoselectively tetrahydrocarbazoles in good yields [316]. Hall and co-workers [317] have performed DA reactions of *N*-tosyl-3-vinylindole **474** with NMM and 4-phenyl-1,2,4-trizole-3,5-dione (PTAD, **506**) the corresponding cycloadducts **507** and **508** were obtained, respectively (Scheme 123). In addition, ethyl 3-indolepent-4-enoate **509** gave products **510** in good yields using 2 equivalents of Me$_2$AlCl and maleimides. These cycloadducts were submitted to an ene reaction in two steps one-pot procedures giving high functionalized carbazoles. In the case of (*Z*)-3-alkenylindoles **511** the corresponding cycloadducts **512** derived

from NMM, working in the presence of Me₂AlCl, were transformed into aldehydes **513** and after further intramolecular carbonyl-ene reaction the corresponding pentacyclic compounds **514** were obtained (Scheme 123) [318].
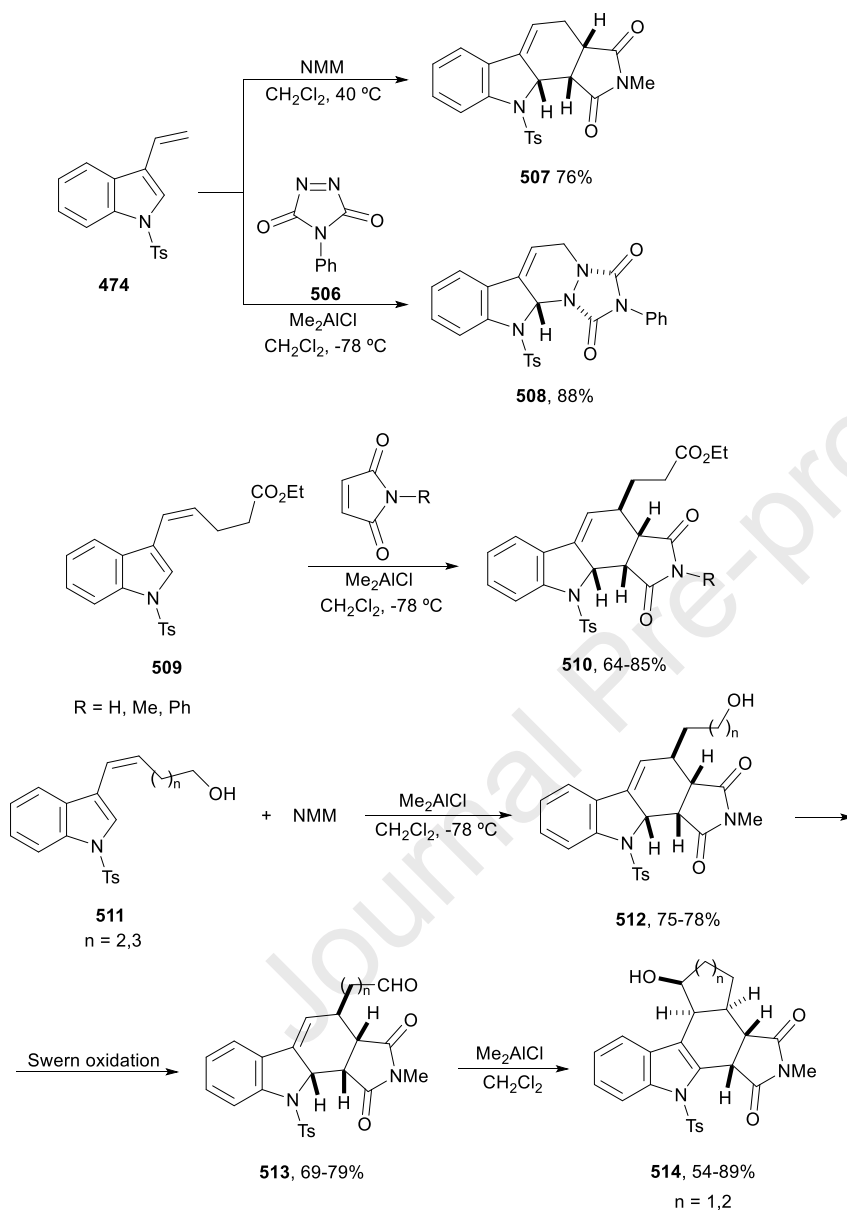
Scheme 123. DA reaction of *N*-tosyl-3-alkenylindoles **474**, **509** and **511** with dienophiles.

A three-component synthesis of carbazoles was developed by Kotha and co-workers [319]. By reaction of indoles, cyclohexanone and DMAD the corresponding products **515** were obtained in toluene at 130 ºC in good yields (Scheme 124). This multicomponent method was also carried out with naphthoquinone giving products **516**. The intermediacy of the 3-alkenylindole intermediate **I** was postulated, which after DA reaction and aromatization gave products **515** and **516**.
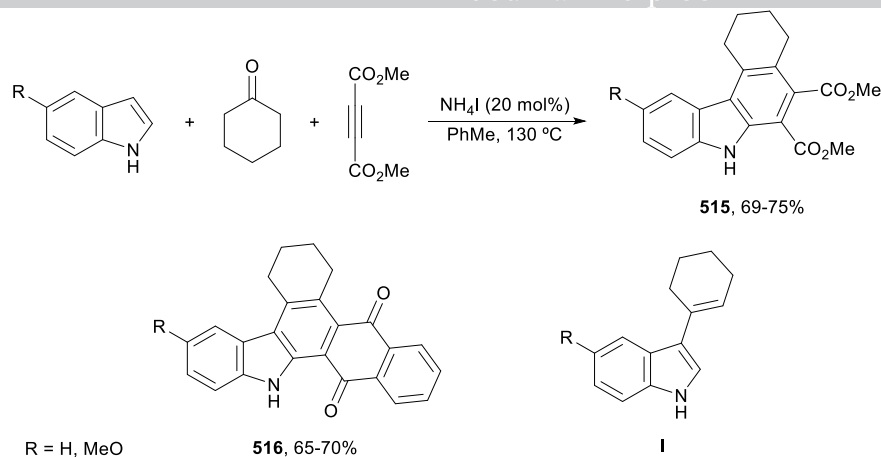
Scheme 124. Three-component reaction of indoles with cyclohexanone and DMAD.

3-Vinylpyrrolo[2,3-*b*]pyridine derivatives **517** (R = Me) underwent DA reaction with DMAD under toluene reflux to provide pyrido[2,3-*b*]indole derivative **518** in 40% yield (Scheme 125) [320]. Kusurkar and co-workers [321] performed the cycloaddition of *N*-phenylsulfonyl **517** with maleimides absorbed in silica gel under MW irradiation to give *endo*-tetrahydrocarbolines **519** in 81-88% yields. These cycloadducts could not be dehydrogenated to the corresponding α-carbolines. However, starting from compounds **520** the resulting cycloadducts were dehydrogenated using Pd/C under xylene reflux to provide α-carbolines **521**.
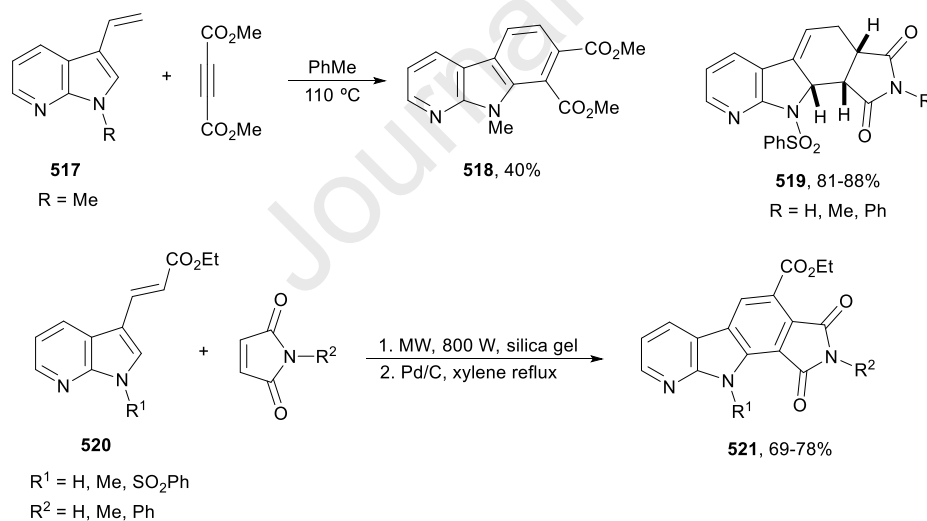
Scheme 125. DA reactions of 3-alkenylpyrrolo[2,3-*b*]pyridines **517** and **520**.

A nucleobase, 7-vinyl-7-deazaguanine (^VG) **522** reacted smoothly with NMM in MeOH to give cycloadduct **523** after subsequent [1,3]-H shift identified by MALDI-TOF (Scheme 126). This method has been used by Saito and co-workers [322] with other *N*-substituted maleimides for the post-synthesis modification to oligonucleotides with diverse functionalities introduced in the nitrogen of maleimides.
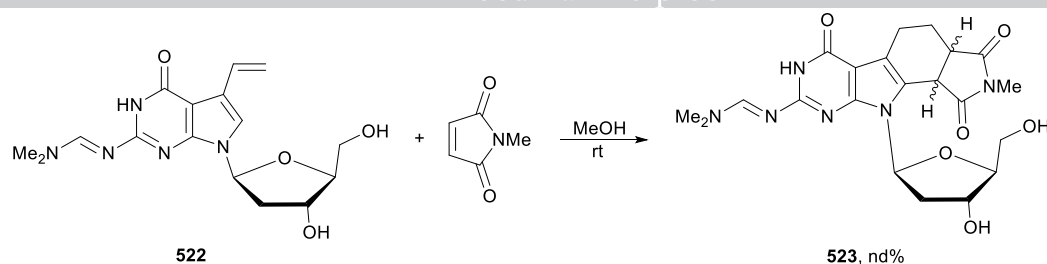
Scheme 126. DA reaction of 7-vinyl-7-deazaguanine **522** with NMM.

Intramolecular DA reaction of a 3-vinylindole **524** has been employed by Kaufman and Grieco [323,324] as key step for the total synthesis of the alkaloid (±)-eburnamonine. The cycloaddition was performed using Florisil as catalyst to provide the pentacyclic adduct **525** in 82% yield, which by treatment with 6 M H_2SO_4 in ethanol at reflux underwent [1,3]-H shift to provide the alkaloid in 80% yield and total enantioselectivity (Scheme 127) [324].
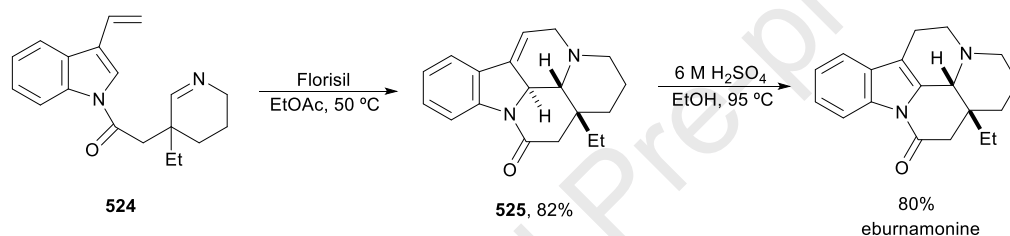
Scheme 127. Total synthesis of (±)-eburnamonine.

Asymmetric DA reactions of silyloxyvinylindole **526** with electron-deficient alkenes **527** bearing a oxazolidinone unit has been carried out using a novel holmium complex derived from bis-thiourea **528** as chiral ligand by Nishida and co-workers (Scheme 128) [325]. The resulting hydrocarbazoles **529** were obtained up to 92% yield and can be converted into the corresponding alkylated products **530** bearing a chiral stereocenter.

R^1 = CO_2Me, COSPh, COMe, CN, CF_3, Ph, $ClCH_2$, $BnOCH_2$, Me. nPr. H
R^2X = MeI, $CH_2=CHCH_2Br$, $NCCH_2I$
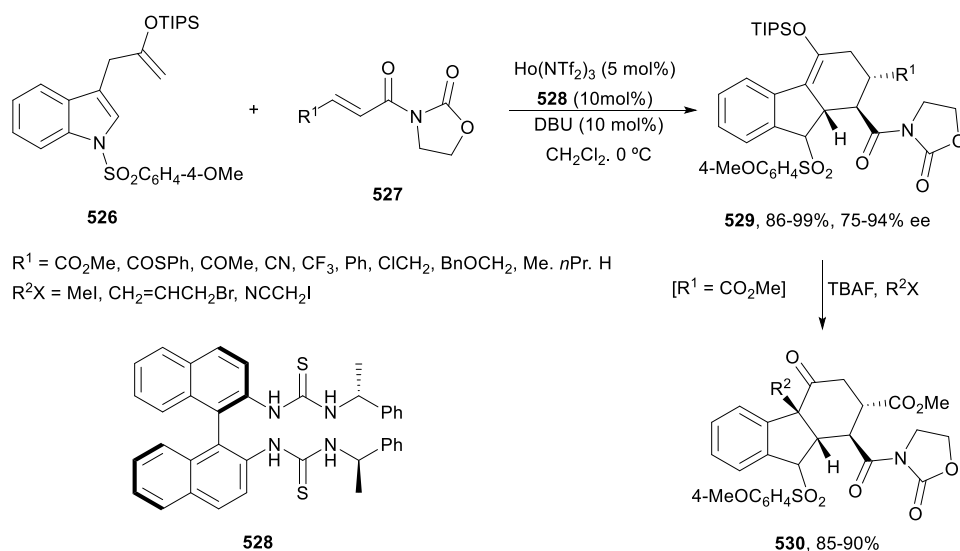
Scheme 128. Asymmetric DA reactions of silyloxyvinylindole **526** with dienophiles **527** catalyzed by Ho(NTf$_2$)$_3$/**528**.

Feng and co-workers [326] accomplished the symmetric [4+2] cycloaddition of silyloxyvinylindoles **526** with β,γ-unsaturated-α-ketoesters **531** catalyzed by a *N,N'*-dioxide **532**/ytrium triflate complex (Scheme 129). The corresponding hydrocarbazoles **533** were obtained up to 98% yield and 99% ee. A possible transition state model TSI was proposed in which the yrtrium complex activates the dienophile **531** in a bidentate manner. The *Si*-face of **531** is shielded by the 2,4,6-triisopropylaniline group of the ligand **532** leading to the formation of (1*R*,2*S*,9a*S*)-**533** preferably.

R^1 = H, 5-MeO, 5-Br

R^2 = Ph, 4-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 3,4-(OCH$_2$O)C$_6$H$_3$, 4-PhC$_6$H$_4$, 4-FC$_6$H$_4$, 3-ClC$_6$H$_4$,
4-ClC$_6$H$_4$, 3,4-Cl$_2$C$_6$H$_3$, 2-naphthyl, (*E*)-PhCH=CH, 2-thienyl, 3-thienyl, Cy, *n*Pr
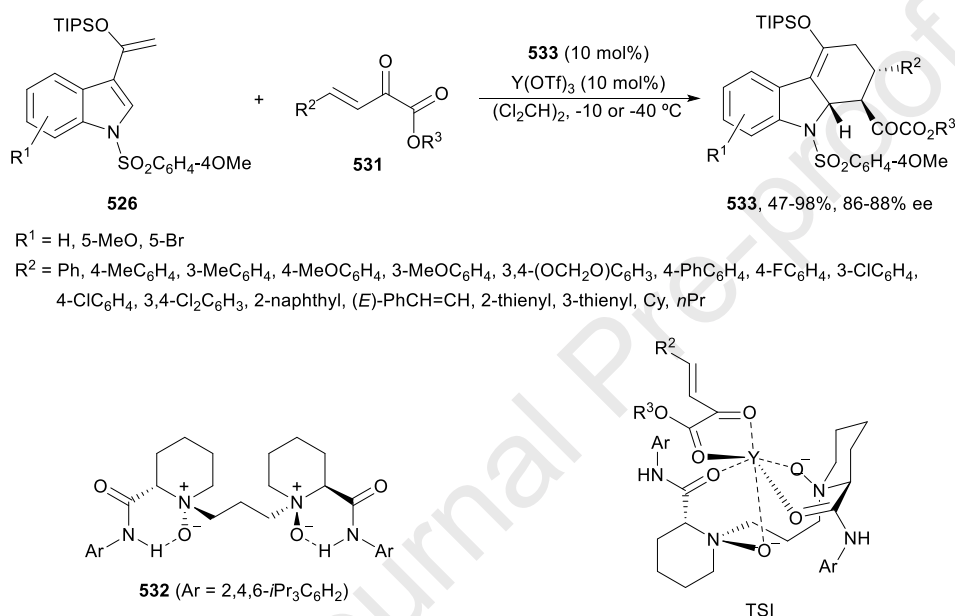
Scheme 129. Asymmetric DA reactions of silyloxyvinylindoles **526** with dienophiles **531** catalyzed by Y(OTf)$_3$/**532**.

Ricci and co-workers [327,328] performed the asymmetric DA reaction of 3-vinylindoles **474** with maleimides and quinones using chiral bifunctional organocatalysts. Thioureas **534** or **535** were the best catalysts working at -55 ºC to give after treatment of cycloadducts with trifluoroacetic anhydride (TFAA), tetrahydrocarbazoles **536** and **537** in good yields and enantioselectivities (Scheme 130). In the proposed working model for the catalyst **534** the NH of the diene and the basic moiety of the catalyst interact through a hydrogen bonding and the dienophile maleimides is activated by the thiourea unit by hydrogen bonding as well.
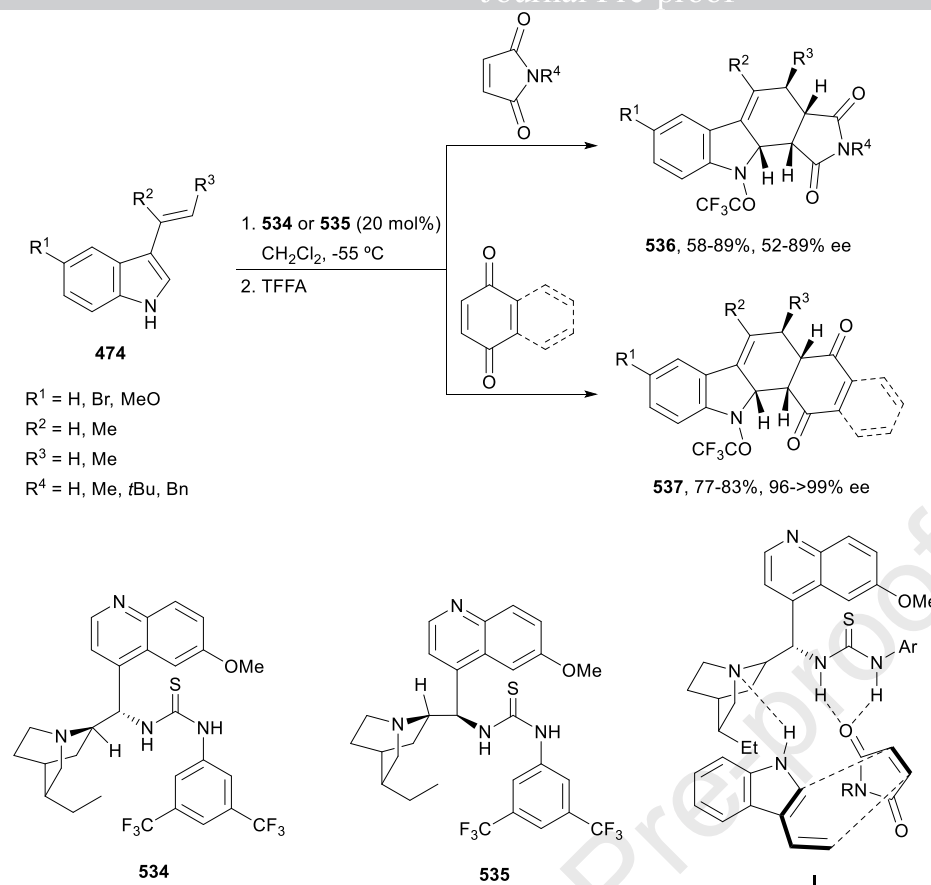
Scheme 130. Asymmetric DA reactions of 3-vinylindoles with maleimides and quinones catalyzed by ureas **534** and **535**.

The former hydrogen-bonding catalysis has been applied to the DA reaction of 3-vinylindoles with methyleneindolinones **538** using the C2-symmetric thiourea **539** as chiral organocatalyst by Barbas III and co-workers (Scheme 131) [329]. This cycloaddition took place at room temperature in only 10 minutes to provide carbazolespirooxindoles **540** with high yields, diastereo- and enantioselectivities. The organocatalyst **539** could be recovered by filtration and reused during five cycles and the process was scale up to gram quantities. It has been proposed that the vinylindole must be oriented by interaction between the NH group of the diene unit and the Boc group of the dienophile *via* π-π and weak H-bonding interactions prior to C–C bond formation.
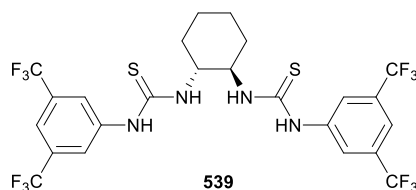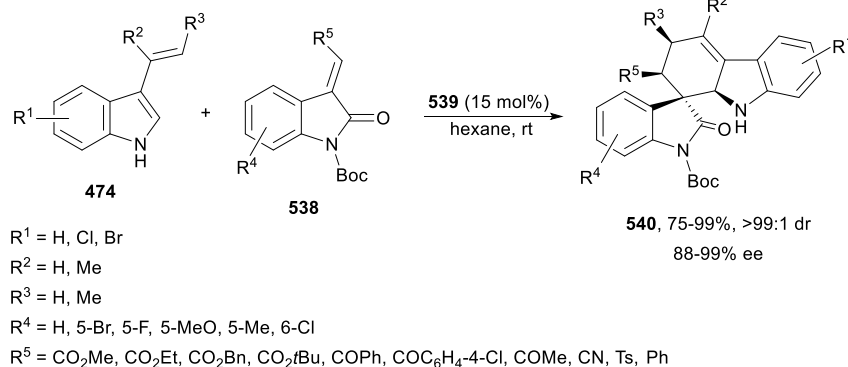
Scheme 131. Asymmetric DA reactions of 3-vinylindoles **474** with methyleneindolinones **538** catalyzed by thiourea **539**.

Hall and co-workers [330] performed the asymmetric DA reaction of 3-vinyl-1H-indole with NMM using organocatalyst **534** to provide products of the type **536** acylated at the N by Boc, Ac and Ts followed by an ene reaction to provide enantioenriched tetrahydrocarbazoles.

6.6. 3-Vinyltetrahydropyridines

3-Vinyltetrahydropyridines have been used as 1-aminodienes **8**, for the synthesis of polyhydroquinolines. N-Acyl 3-vinyltetrahydropyridines **541** were initially reported by Ludwig and Wistrand [331] and used as 1-aminodienes **8** for the synthesis of hydrogenated quinolines (Scheme 132). The DA reaction with methyl acrylate provided regioselectively products **542** as *endo/exo* mixture of diastereomers. N-Alkyl 3-vinyltetrahydropyridines **544**, prepared by alkylation of 1-azapentadienyl anions of α,β-unsaturated imines **543**, reacted with NPM under THF reflux to give stereoselectively *endo*-octahydro-1H-pyrrolo[3,4-h]quinoline-1,3-diones **545** (Scheme 132) [332].
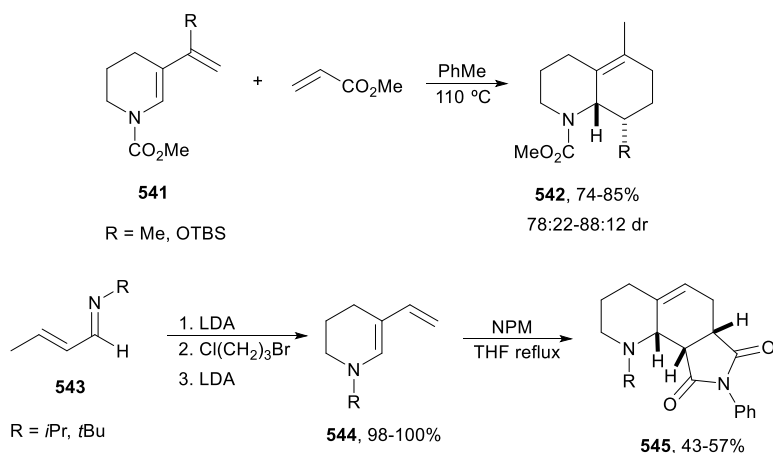
Scheme 132. DA reactions of 3-vinyltetrahydropyridines **541** and **544** with dienophiles.

Overman and co-workers [333] applied the intramolecular DA reaction of a 3-alkenyltetrahydropyridine as key step for the total synthesis of the lupinine alkaloid (+)-aloperine and derivatives. From initial studies performed with different 3-alkenyltetrahydropyridines it was found that the silyl-tethered chiral derivative **547**, prepared from (*R*)-pipecolinic acid derivative **546**, furnished DA products **548** and **549** as a 5:1 mixture of diastereomers (Scheme 133). These cycloadducts were not isolated and further transformed into (+)-aloperine in gram quantities.
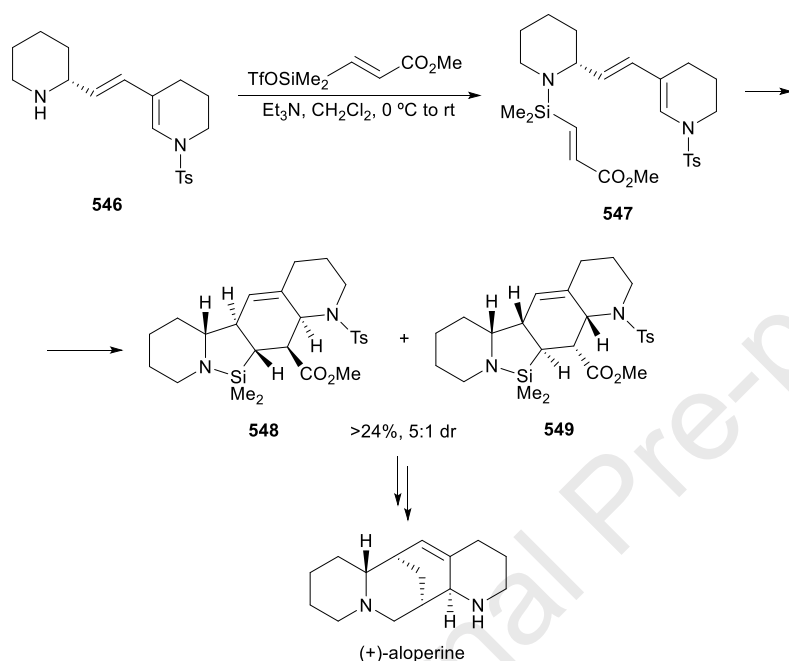
Scheme 133. Asymmetric intramolecular DA reaction of 3-alkenyltetrahydropyridine **547** toward the total synthesis of (+)-aloperine.

Craig and co-workers [334] prepared 3-alkenyltetrahydropyridines **550** by Stille and Suzuki cross-coupling of the corresponding 3-iododerivatives. Dienes **550** participated in homo- and hetero DA reactions with unsaturated carbonyl compounds and nitroso compounds to lead to the formation of products **551**, **552** and **553**, respectively (Scheme 134). The reaction with acrolein gave a 82:18 mixture of diastereomers, which were transformed into benzoate **552** after chromatographic separation. However, maleic anhydride gave *endo*-, *syn*-selectivity to provide after esterification diester **551**. In the case of nitroso dienophiles generated *in situ* by oxidation of hydroxylamines, products **553** were obtained at room temperature.
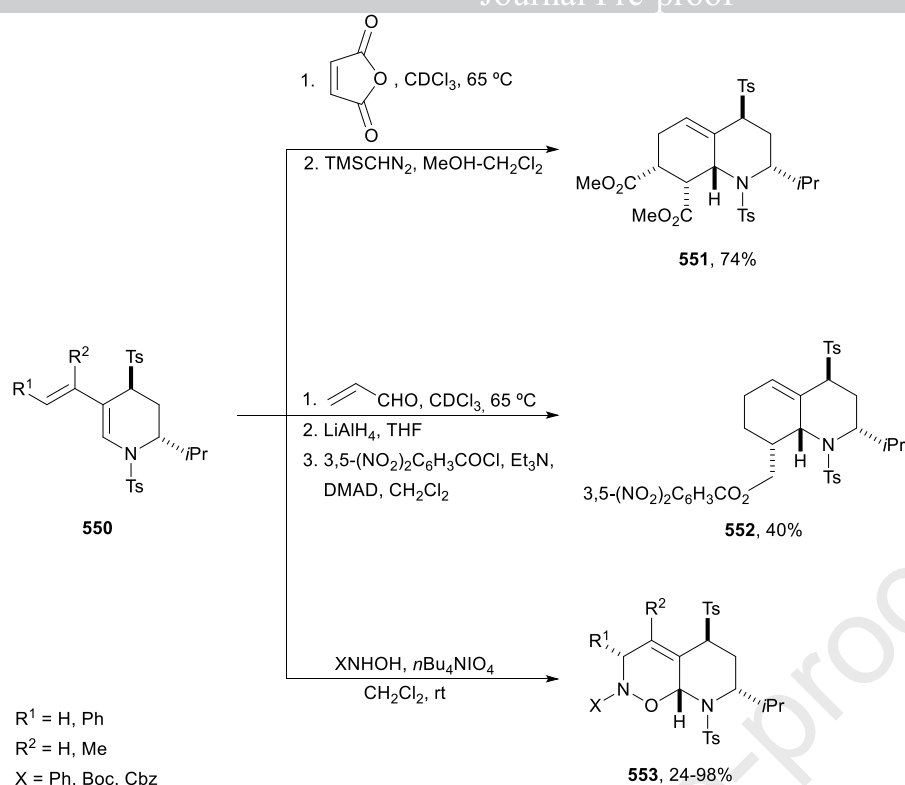
Scheme 134. DA reactions of 3-alkenylpiperidines **550** with maleic anhydride, acrolein and nitroso compounds.

By direct C3 alkenylation of tetrahydropyridines through Pd-catalyzed Fujiwara-Moritani oxidative cross-coupling the corresponding 3-vinyltetrahydropyridines were obtained [335]. Tetrahydroquinoline derivatives **555** and **556** were obtained under toluene reflux using **554** as diene and maleimides and maleic anhydride as dienophiles, respectively (Scheme 135).
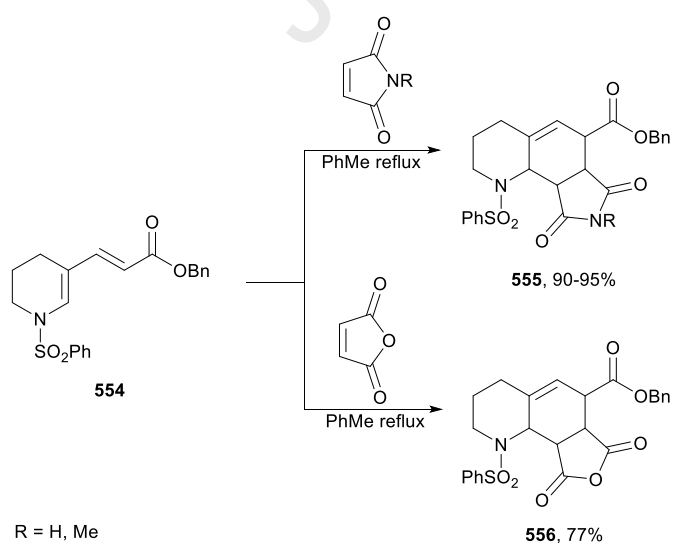
Scheme 135. DA reactions of 3-alkenyltetrahydropyridine **554** with maleimides and maleic anhydride.

An inverse electron-demand (IED) diene-transmissive hetero-DA reaction of *N*-sulfonyl-[3]-1-azadendralenes **557** has been used for the synthesis of polyhydroquinolines [336]. The first IED takes place between the cross-conjugate carbotrienes **557** and ethyl vinyl ether or thioether to provide mainly *endo*-3-vinyltetrahydropyridines **558** (Scheme 136). Subsequent DA reaction of dienes **558** with TCNE, NPM and methyl vinyl ketone gave rise to polysubstituted polyhydroquinolines **559-561**.
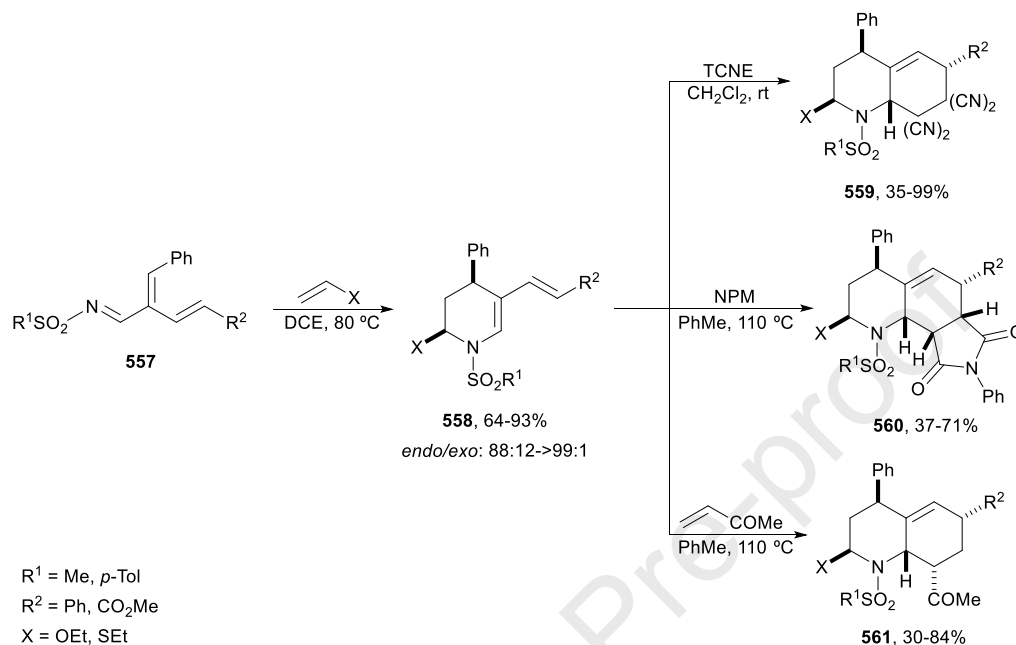
Scheme 136. IED DA reactions of azadendralenes **557** to give 3-alkenyltetrahydropyridines **558** followed by DA reactions with dienophiles.

The diene-transmissive hetero-DA reaction of azatrienes **563**, prepared from 2-vinyl α,β-unsaturated aldehydes **562**, with tosyl isocyanate afforded alkenyl tetrahydropyridines **544** (Scheme 137) [337,338]. The second DA reaction with the same previously mentioned dienophiles gave diastereoselectively hexahydroquinazolin-2(1*H*)-ones **565-567**. In the case of methyl vinyl ketone the DA reaction was performed using TMSOTf (20 mol%) as catalyst. The reaction of azatrienes **563** with aryl isothiocyanates allowed the synthesis of hexahydrobenzothiazine-2-imines [338].
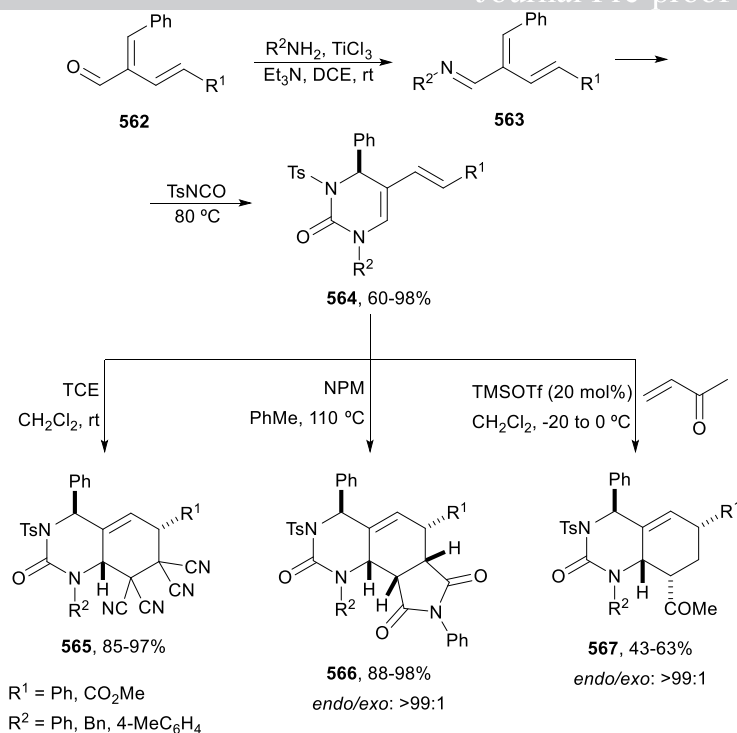
Scheme 137. Hetero-DA reaction of azatrienes **563** with tosyl isocyanate followed by DA reactions of dihydropyrimidinones **564** with dienophiles.

6.7. 5-Vinyldihydropyridin-2-ones

This type of heterocyclic compounds have been used as dienic systems in DA reactions. Passarella and co-workers [339] reported the cycloaddition of 5-ethenyldihydro-2-pyridinones **567** for the synthesis of advanced intermediates toward the synthesis of the indole alkaloid (±)-andranginine. The reaction of compounds **567** with the vinylindole **568** took place regio and stereoselectively in toluene at room temperature to furnish products **569** in modest yields (Scheme 138).
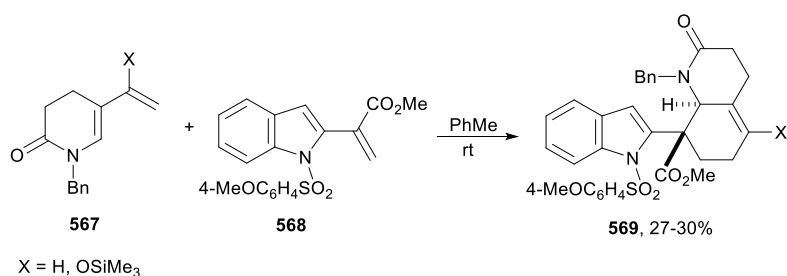
Scheme 138. DA reactions of 5-ethenyldihydro-2-pyridinones **567** with **568**.

Comins and co-workers [340,341] have studied the reactivity of 5-vinyl-2,3-dihydro-4-pyridone **570** as diene with dienophiles. The DA reactions with NPM, maleic anhydride, (*Z*)-1,2-bis(phenylsulfonyl)ethylene, cyclopentenoene, diethyl azodicarboxylate, dimethyl maleate and fumarate, and methyl acrylate, acrylonitrile and phenylsulfonylethylene gave the corresponding cycloadducts under toluene reflux (Scheme 139). In the case of *cis*-substituted dienophile

cycloadducts **571-576** were obtained as single diastereomers in good yields. Dimethyl fumarate gave a 1:1 mixture of diastereomers **577**. Monosubstituted dienophiles gave regioselectively mainly *endo*-cycloadducts **578-580**.
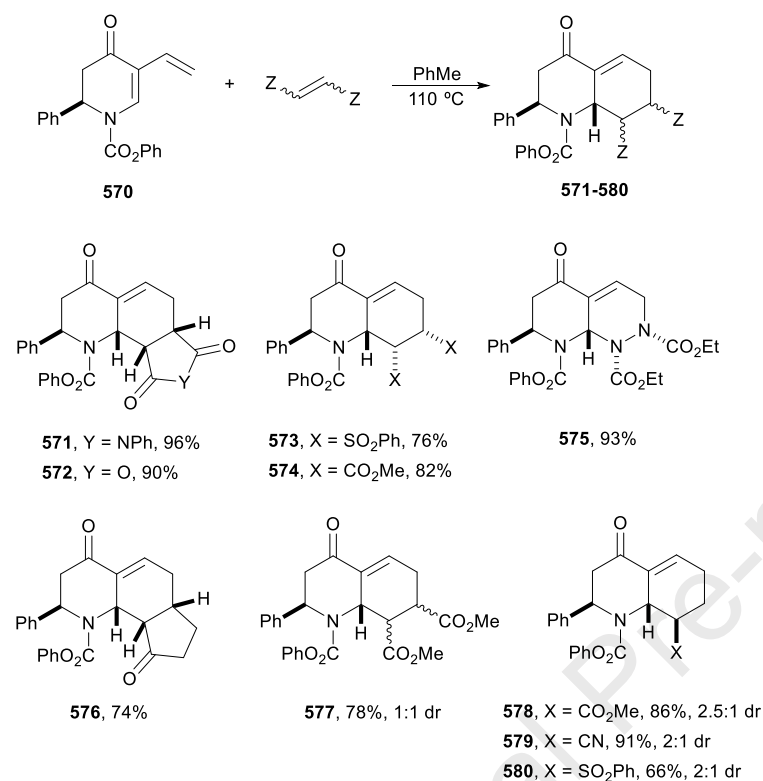
Scheme 139. DA reactions of 5-vinyl-2,3-dihydro-4-pyridone **570** with dienophiles.

The same group studied the reactivity of *cis*- and *trans*-4-hydroxy derivatives **581**, which reacted with NPM in refluxing toluene to give diastereoselectively octahydroquinolines **582** and **583**, reapectively (Scheme 140) [340,341]. By using this methodology a potential route to gephyrotoxin has been developed.
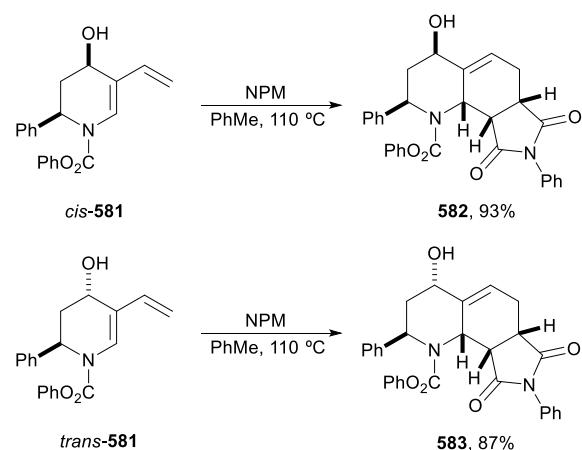
Scheme 140. DA reactions of *cis*- and *trans*-dienes **581** with NPM.

Tandem DA-aromatization reactions of pyridone **570** have been reported by the same group [341,342]. The resulting cycloadducts underwent elimination-aromatization to provide β-amino ketones. In Scheme 141 the cycloaddition of **570** and 1,4-naphthoquinone in refluxing toluene occurred to provide cycloadduct **584** in 84% yield as a single diastereomer. During silica gel purification the corresponding amino ketone **585** was isolated in 88% yield. This methodology has been applied to the synthesis of unnatural amino acids.
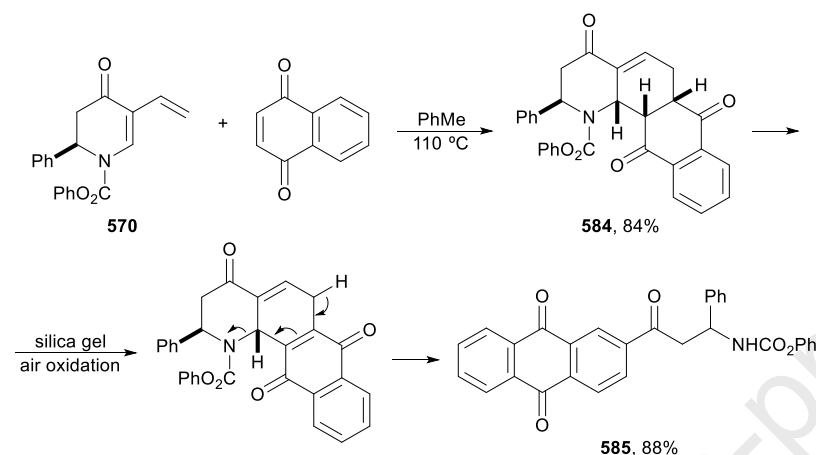
Scheme 141. DA reaction-aromatization of 5-vinylpyridone **570** with 1,4-naphthoquinone.

7. Conclusions

1-Amino-1,3-dienes and related systems have played an important role in synthetic organic chemistry as dienic components in normal electron-demand Diels-Alder (DA) reactions with dienophiles. Acyclic dienamines showed higher reactivity than dienamides and carbamates. However, the later have been used more extensively in synthesis due to their higher stability and therefore more preparation methods have been developed. In fact, dienyl carbamates have been used for the synthesis of amidocyclohexane precursors, such as alkaloids pumiliotoxin and perhydrogephyrotoxin, *Aspidosperma* alkaloids, palmerolide A, chelidonine, *cis*-trikentin B and 2-aminocyclohexane carboxylic acids. 1-Amino or amido 3-sililoxy-1,3-butadienes showed excellent regio and diastereoselectivity under milder reaction conditions and were applied to the synthesis of terpenes such as α-elemene, and the alkaloids (+)-tabersonine, (+)-16-methoxytabersonine, (+)-aspidospermidineand (−)-quebrachamine. The three-component amides or amines-aldehydes-dienophiles (AAD) reaction has demonstrated a wider applicability under more simple reaction conditions and has been applied to the synthesis of aminocyclohexenes but also of phthalic acid derivatives, anilines, luminals and corollosporines. In the case of cyclic 1-amino-1,3-dienes, they allowed the synthesis of bicyclic derivatives.

Heterocyclic 1-amino-1,3-dienes such as 1,2-dihydropyridines (DHPs) gave isoquinuclidine derivatives found in numerous biologically active natural and unnatural products in reacemic and enantioselective manners. Some selected applications of 1,2-DHPs are tetrahydroisoquinoline alkaloids, piperidines, *Iboga* and *Cantharantus* alkaloids. 2-Pyridones showed higher stability but lower reactivity than 1,2-DHPs and have been applied in the synthesis of validamine and its epimers, Corey's Tamiflu intermediate and (−)-cytisine derivatives.

Alkenyl-substituted nitrogenated five- and six-membered heterocycles such as 3-vinyl-Δ^2-pyrrolines, 3-vinylpyrroles, 4-vinylimidazoles, 3-vinylindoles, 3-vinyltetrahydropyridines and pyridines have demonstrated good reactivity as 1-amino-1,3-dienes in DA reactions under thermal conditions. Intramolecular cycloadditions of Δ^2-pyrroline derivatives have been applied to the synthesis of α-lycorane and lycorine. 3-Vinylpyrroles allowed the synthesis of indoles and 3-vinylpyrazoles or indazoles. The most interesting derivatives of 4-vinylimidazoles are those bearing a 3-aminoallyl substituent which have been applied to the synthesis of marine origin products such as Palau's amines, styloguanidines, oroidin, hymenidin, clathrodin, giroline, axinellamine A, massadine and kealiquinone using intramolecular DA reactions. The heterocyclic systems, 3-vinylindoles have been employed in the synthesis of carbazoles and polycyclic indole derivatives with biological activity and also natural products. 3-Vinyltetrahydropyridines and 5-vinyldihydropyridinones allowed the synthesis of polyhydroquinolines such as (−)-aloperine and (±)-androginine, respectively.

Abbreviations

AAAP: 3-Amino-1-(2-aminoimodazoyl)prop-1-ene

Ab: Antibody

Ac: Acetyl

acac: Acetylacetate

adm: Adamantyl

alloc: Allyloxycarbonyl

aq: Aqueous

Ar: Aryl

BARF: Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

BINAP: 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl

BINOL: 1,1′-Bi-2-naphthol

BIPHEP: 5,5",6,6"-Tetramethyl-3,3"-di-t-butyl-1,1"-biphenyl-2,2"-diol

Bn: Benzyl

Boc: *tert*-Butoxycarbonyl

bpy: 2,2'-Bipyridine

Bt: Benzotriazolyl

BTBP: 2,6-di-*tert*-Butylpyridine

CAN:	Cerium ammonium nitrate
Cbz:	Benzyloxycarbonyl
chloranyl:	Tetrachlorobenzoquinone
Clnicotinoyl:	Nicotinoyl chloride
cod:	1,5-Cyclooctadiene
coe:	Cyclooctene
conc:	Concentrated
CSA:	Camphorsulfonic acid
Cy:	Cyclohexyl
DA:	Diels-Alder
Darco KB:	Activated Carbon
DBU:	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCE:	1,2-Dichloroethane
DDQ:	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD:	Diethyl azadicarboxylate
DFT:	Density-functional theory
DHP:	Dihydropyridine
DIPEA:	Diisopropylethylamine
DMAD:	Dimethyl acetylenedicarboxylate
DMF:	Dimethylformamide
DMSO:	Dimethylsulfoxide
DPP:	Diphenyphosphoric acid
dr:	Diastereomeric ratio
DTBP:	2,6-di-*tert*-Butylpyridine
ee:	Enantiomeric excess
esp:	$\alpha,\alpha,\alpha',\alpha'$-Tetramethtyl-1,3-benzenedipropionate
ESR:	Electron spin resonance

EWG:	Electron withdrawing group
Florosil:	Powdered magnesium silica gel
GABA:	Gamma aminobutyric acid
Hex:	Hexyl
HOMO:	Highest occupied orbital
IBX:	2-Iodoxybenzoic acid
IED:	Inverse electron demand
IMDA:	Intramolecular Diels-Alder
IPA:	Isopropanol
IRA 400:	Basic ion exchange resin
KHMDS:	Potassium hexamethyldisilazane
L:	Ligand
LAH:	Lithium aluminum hydride
LDA:	Lithium diisopropylamide
LDH:	Layered doublé hydroxide
LED:	Light emitting diode
LUMO:	Lowest unoccupied molecular orbital
MALDI-TOF:	Matrix-Assisted Laser Desorption/Ionization-Time of Flight
MCR:	Multicomponent reactions
Mes:	Mesityl, 2,4,6-trimethylphenyl
MOM:	Methoxymethyl
Ms:	Mesyl, methanesulfonyl
MS:	Molecular sieves
nAChR:	Neuronal nicotine acetylcholine receptor
NMM:	*N*-Methylmaleimide
NMR:	Nuclear magnetic resonance
NPM:	*N*-Phenylmaleimide

Ns:	2-Nitrobenzenesulfonyl
NTTL:	Naphthoyl-*tert*-leucinate
Oct:	Octyl
Piv:	Pivaloyl
PPTS:	Pyridinium *p*-toluenesulfonate
prenyl:	3-Methylbut-2-en-1-yl
Pro:	Proline
PTAD:	4-Phenyl-1,2,4-triazole-3,5-dione
Py:	Pyridyl
rac:	Racemic
rt:	Room temperature
sc:	Supercritical conditions
SEM:	[2-(Trimethylsilyl)ethoxy]methyl acetal
TADDOL:	α,α,α',α'-Tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAF:	Tetrabutylammonium fluoride
TBDPS:	*tert*-Butyldiphenylsilyl
TBS:	*tert*-Butyldimethylsilyl
TCNE:	Tetracyanoethylene
Tf:	Triflic, trifluoromethylsulfonyl
TFA:	Trifluoroacetic acid
TFAA:	Trifluoroaetic anhydride
TFE:	Trifluoroethanol
THF:	Tetrahydrofuran
TIPS:	Trisisopropylsilyl
TMS:	Trimethylsilyl
Tol:	Tolyl, 4-methylphenyl
Tp:	Trispyrazolyl borate

Tr: Trityl, triphenylmethyl

Troc: Trichloromethyloxycarbonyl

Ts: Tosyl, 4-methylphenylsulfonyl

TS: Transition state

TsICN: Tosyl isocyanate

^{v}G: 7-Vinyl-7-deazagucanine

XPhos: 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

Declaration of competing interest

Acknowledgements

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Biographical sketchs

Carmen Nájera was born in Nájera (La Rioja) in 1951 and was graduated from the University of Zaragoza in 1973, obtaining her doctorate in chemistry from the University of Oviedo in 1979. She spent postdoctoral stays at the ETH (Zurich), the Dyson Perrins Laboratory (Oxford), Harvard University, and Uppsala University. She became Associate Professor in 1985 at the University of Oviedo and Full Professor in 1993 at the University of Alicante. She is coauthor of more than 400 papers (more than 20.000 citations, h 70), 6 patents and 30 book chapters and has supervised more than 45 PhD students, belonging also to the Editorial Board of several international journals. She has been awarded with the 2006 Organic Chemistry Prize from the Spanish Royal Chemical Society of Chemistry, the 2006 Rosalind Franklin International Lectureship from the English Royal Society, the SCF 2010 French-Spanish Prize from the Société Chimique de France, the IUPAC 2015 Distinguished Women in Chemistry or Chemical Engineering Award and the 2018 Serratosa lectureship. In 2012 she was named full Member of the Royal Spanish Academy of Sciences and was appointed as Active Member of the European Academy of Sciences and Arts. Professor Nájera has been in the Advisory Board of several international journals and in 2016-2017 was named ChemPubSoc Europe Fellow

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Miguel Yus was born in Zaragoza (Spain) in 1947, and received his BSc (1969), MSc (1971) and PhD (1973) degrees from the University of Zaragoza. After spending two years as a postdoctoral fellow at the Max Planck Institut für Kohlenforschung in Mülheim a.d. Ruhr he returned to Spain to the University of Oviedo where he became associate professor in 1977, being promoted to full professor in 1987 at the same university. In 1988 he moved to a chair in Organic Chemistry at the University of Alicante. Professor Yus has been visiting professor at different institutions and universities among them ETH-Zentrum, Oxford, Harvard, Uppsala, Marseille, Tucson, Okayama, Paris, Strasbourg, Bolonia, Sassari, Tokyo and Kyoto. He is co-author of more than 600 papers (and six patents) and has supervised 62 Doctoral Theses, and delivered about 250 lectures, most of them abroad. His bibliometric data are more than 28.000 citations and h-index 77. He has received several international awards being also named Active Academician from the European Academy of Sciences and Arts, and Academic Member of the Athens Institute for Education and Research. Professor Yus has been in the Advisory Board of more than 30 international journals. Professor Yus founded in 2002 the new chemical company MEDALCHEMY S.L. to commercialize fine chemicals.

Graphical abstract
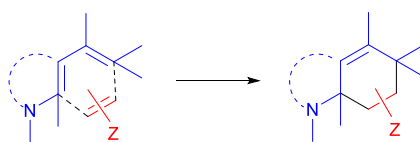
Starting dienes: dienamines, dienamides, 1,2-dihydropyridines, 2-pyridones, vinylheterocycles
Dienophiles: acrylic, maleic and fumaric derivatives, quinones, nitrosobenzene, TNC, DMAC, nitroolefines

Declaration of interests

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: