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Diels–Alder Reactions of 1-Azadienes

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1. Introduction

By virtue of its excellent chemo-, regio- and diastereoselectivity, the Diels–Alder (DA) reaction is one of the most important and elegant methods for the construction of six-membered ring compounds. Since its inception 70 years ago,[1] this reaction has been widely used for the synthesis of a vast number of simple and complex molecules. Although a number of other investigators had reported similar diene-ene addition reactions prior to 1928, Diels and Alder were the first to recognize and report the significance of the reaction in detail.[2,3] In this pericyclic [4+2] cycloaddition reaction, a diene and a dienophile in a single step produce a six-membered ring with up to four new stereo-centers. The synthetic,[4–17] mechanistic,[18–21] and theoretical aspects[18,22,23] of DA reactions have been extensively studied.

The effects of a variety of catalysts,[24–29] solvents[28,30–33] and pressure[28,34] on DA reaction rates have been the subjects of many studies. Substantial advances have been made in asymmetric DA reactions using various catalysts as well as dienes or dienophiles with chiral auxilaries.[4,7,35–44]

2. Mechanism

Diels–Alder reactions can be classified into three types:[6] (I) Normal $HOMO_{diene}$-controlled, (II) Neutral, and (III) $LUMO_{diene}$-controlled or inverse electron demand DA reactions (Fig. 1). This classification is based on the descriptions of both pairs of frontier orbitals in the Huckel molecular orbital (HMO) model.[45,46] In [4+2] cycloaddition reactions, the interaction of occupied orbitals of one reactant with the vacant orbitals of another leads to the formation of the cycloadduct. The efficiency of the two MO's interaction is increased if by some means their energy separation is decreased.[46] As shown in Fig. 1, the electronic character of substituents will affect the HOMO–LUMO energy separation of the MO's of the diene/dienophile. In the normal DA reaction (type I), electron-donating groups (EDG) on the diene and electron-withdrawing groups (EWG) on the dienophile increase the reation rate. In type III DA reactions the electronic effect of the substituents is the reverse of those of type I. A number of mechanisms have been proposed for DA reactions and modeled by ab initio or quantum mechanical calculations. Depending on the nature of the reacting partners, concerted mechanisms with symmetrica1 transition states,[23] or concerted mechanisms with dipolar transition states,[47,48] or even two-step mechanisms[49–51] have been proposed. For hetero Diels–Alder reactions, it has been shown by calculations that the transition structures are usually less symmetrical than for the all-carbon DA

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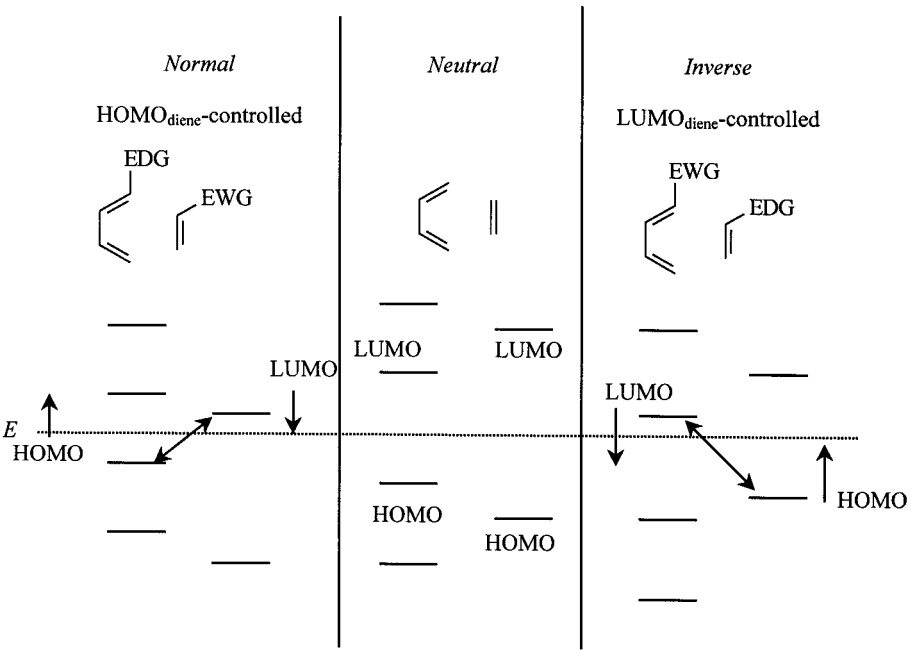


Figure 1.

reactions.[52–54] In addition, a change from a concerted non-synchronous to a stepwise mechanism can occur depending on the electronic character of the substituents.[55–57]

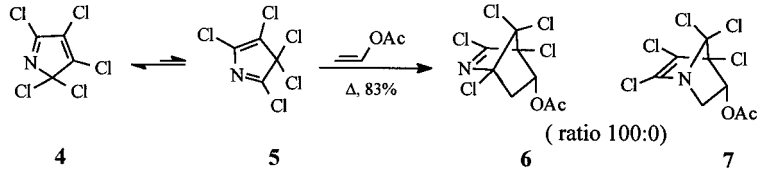
A few experimental observations are in agreement with a two-step mechanism; however, for the majority of the reported results, a concerted mechanism for the reaction via a transition state which has a dipolar character has been proposed.[39,48,50,55–57]

3. Diels–Alder Reactions of 1-Aza-1,3-butadienes

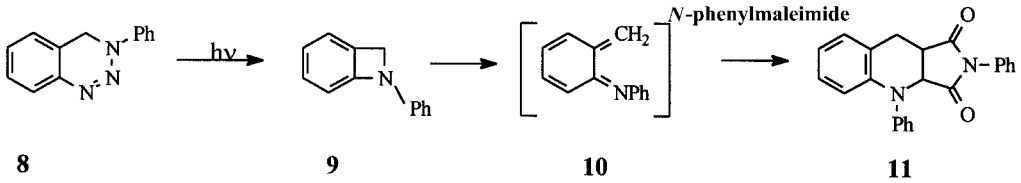
Normal DA reactions, where an electron-rich diene reacts with an electron-deficient dienophile have been the focus of most of the reported synthetic and mechanistic studies. Although, traditionally, the all-carbon normal DA reaction has been the most utilized synthetic method for the preparation of six-membered ring compounds, in recent years the synthetic application of the hetero DA reactions has been significant.[4–7,16,17,58–74] In a hetero DA reaction either diene or dienophile may contain one or more heteroatoms (Eq. (1)). The great potential of the hetero DA reaction for the synthesis of heterocycles can be imagined if in Eq. (1) a combination of C, N, S, O or other atoms are incorporated.

(1)

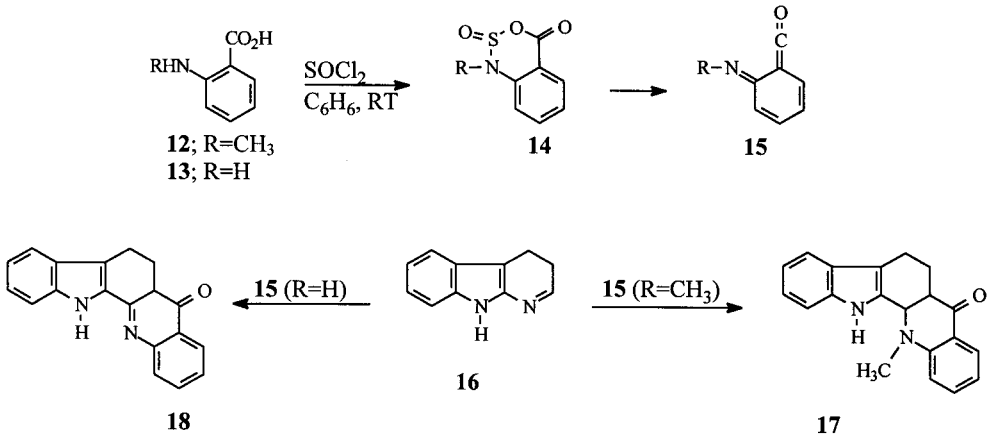
One of the serious limitations of the hetero DA reaction in the synthesis of organic compounds, especially those involving simple 1-azadienes (**1**) has been their low conversions.[6,16,58,66,67,75] The introduction of a nitrogen atom at position 1 of the diene creates a π electron-deficient system and thus lowers its reactivity in the normal HOMO$_{diene}$-controlled DA reactions with electron poor dienophiles.



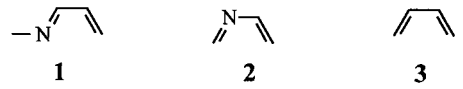
Scheme 1.



Scheme 2.



Scheme 3.



1 **2** **3**

The reluctance of azadiene **1** to undergo a DA reaction is presumably due to the lowering of a thermodynamic driving force by approximately 20 kcal/mol as compared to butadiene **3** or 2-azadiene **2**.[76] The higher reactivity of 2-azadiene compared to 1-azadiene can be seen in Scheme 1.

When 1-azadiene **4** was heated with vinyl acetate the adduct was confirmed to be **6** and not the expected product **7** as reported incorrectly for similar systems by earlier investigators.[77] Under the reaction conditions, 1-azadiene **4** is isomerized to the more reactive 2-azadiene **5** followed by the DA reaction of the latter with the dienophile to produce **6**. Molecular orbital calculations have revealed the low reactivity of the unsubstituted 1-azadienes compared to other dienes. Bachrach has examined the DA reactions of a number of unsubstituted dienes with ethene using ab initio calculations.[47] The calculated energies of activation (E_a) of the reactions are in the following order: 1-azadiene> butadiene> 2-phosphadiene> 2-azadiene> 1-phosphadiene. Experimental ionization potentials,[78] electron affinities,[79] and theoretical energies of HOMO and LUMO orbitals for a number of heterodienes and enol ether dienophiles have been reported and tabulated.[6,80–82]

Due to low reactivity, DA reactions of unactivated 1-azadienes have been sluggish and often of no synthetic significance except when the 1-azadiene has been a part of an *o*-quinone methide imine system[6,66,67,83–96] or it has been used in an intramolecular fashion.[6,66,67,87,89–92,96] Although the main factor responsible for the low efficacy of the 1-azadiene DA reaction is its inherent low reactivity, other factors such as the instability of the enamine product and competitive reactions such as [2+2] imine additions and tautomerization may also contribute to the azadiene's low conversions.[6,66,67,87,89–92,96–98] In recent years the application of this potentially powerful method has been expanded mainly through a change in the electronic character of the diene by means of appropriate substituents.[5,6,16,17,58,75,99–119] Substitution of the diene with electron releasing groups promotes the $HOMO_{diene}$-controlled (normal) reaction,[5,17,58,75,99–105] where electron-withdrawing substituents promote the $LUMO_{diene}$-controlled (inverse) reaction.[6,12,58,75,106–118,120] The rates of DA reactions have also been effected by the electronic nature of the dienophiles. Generally electron-deficient dienophiles increase the rates of normal DA reactions whereas electron rich dienophiles enhance the rates of inverse electron demand DA reactions.[6,16,58,66,98,108,112,113,121–123] To a limited extent catalysis[6,16,57,72,112,124–127] or variation in the reaction conditions[6,16,106,112,128,129] have been shown to improve the reaction efficiency.

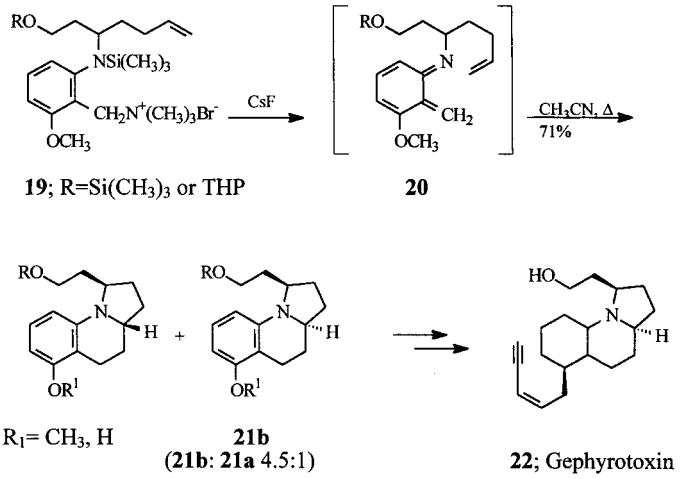
4. Quinone Methide Imines

The application of *o*-quinodimethanes in DA reactions in synthesis has been well documented.[130,131] The first example of the DA reaction of a 1-azadiene was reported in 1966 (Scheme 2).[83] Photolysis of 3-phenyl-4*H*-benzo-1,2,3-triazine (**8**) produced **9** which upon heating in the presence of *N*-phenylmaleimide gave the 1:1 adduct **11**. It appears that **11** is formed by the cycloaddition reaction of the in situ generated *o*-quinone methide imine **10** with *N*-phenylmaleimide.

Heating *N*-methylanthranilic acid (**12**) with thionyl chloride in dry benzene gave an unstable sulfinamide anhydride (**14**). The ketimine **15**, presumably obtained from thermal decomposition of **14**, upon treatment with 3,4-dihydro-β-carboline (**16**) at ambient temperature selectively afforded Evodiamine (**17**) in 65% yield. In a similar manner, Rutecarpine (**18**) was also obtained in one step (Scheme 3).[86]

Narashiman and Kelkar[87] have reported the thermal conversion of the alkaloid (+)-Manahimbine to (±)-Manahimbine and the two related alkaloids curryanine and curryangine. They have postulated the involvement of an *o*-quinone methide imine intermediate in these conversions. A new approach to the synthesis of alkaloid Gephyrotoxin (**22**) has been reported by the application of *o*-quinone methide imine (**20**) DA methodology as shown in Scheme 4.[90]

Acridine alkaloids have been synthesized via the [4+2]



Scheme 4.

cycloaddition of azaxylene **10**. Mild flash vacuum pyrolysis (FVP) of *o*-*N*-phenylaminobenzyl alcohol (**24**) or oxazinone **23** in the presence of Al_2O_3 or SiO_2 at 350°C or molecular sieves at 450°C gives Dihydroacridine (**25**) and Acridine (**26**)[92] (Scheme 5).

Both isatoic anhydride (**30**) and benzotriazinone (**31**) (see entry 1, Table 1) decompose in high boiling solvents to produce **32** and then **33** followed by other transformations. When anisaldehyde (**34**; R^1=H, R^2=OMe) is mixed with **31**, a DA reaction occurs and adduct **36** (R^1=H, R^2=OMe) is obtained in 24%. However, in boiling *p*-chloroacetophenone only the dimer **36** (R^1=NH_2, R^2=H) is obtained in 48% yield. While anhydride **30** gives **36** (R^2=H, R^2=CO_2Et, 60%) in hot diethyl phthalate, triazinone **31** only gives the dimer **36** (40%) in this solvent. The reactions of other esters with **30** and **31** are also described. A low yield of **37** was obtained upon heating **31** with diphenyliodonium carboxylate **38**.

Fluoride ion induced elimination of **27** in refluxing acetonitrile selectively produced the tetracyclic **29** in good yield. Similar to the reaction presented in the entry 5 (Table 1), the reaction presumably proceeds via the *N*-substituted *o*-quinone methide intermediate (Scheme 6).[88,89]

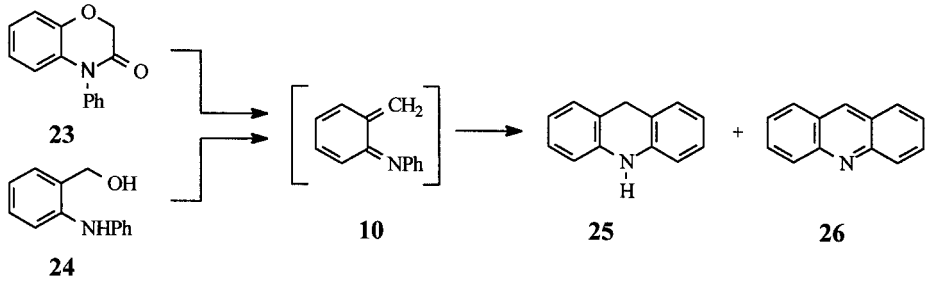
In entry 8 (Table 1), when R^1=Et or Pr and R^2=H or Me, similar product ratios for the *cis* and *trans* isomers **59** and **60** were obtained. It was found that the *cis* isomer **60** was isomerized to the *trans* isomer **59** under the reaction conditions. Table 1 presents the data for a number of other *o*-quinone methide imine Diels–Alder reactions. Entry 11 in Table 1 represents the first example of a 1-azadiene DA reaction with [60] fullerene to produce the fullerene adducts **69**.[132]

5. Intramolecular Diels–Alder Reactions (IMDA) of 1-Azadienes

Among 1-azadiene cycloadditions, IMDA reactions were the first to be applied successfully for the synthesis of a number of alkaloids. A few examples of these syntheses were discussed earlier in the *o*-quinone methide imine section.[86,87,90] Fowler and coworkers reported the synthesis of (−)-Deoxynupharidine (**77**) via the DA reaction of the in situ generated azadiene **74** by flash vacuum pyrolysis of the *N*-acyl derivative **73**.[133] Other investigators have used similar reactions for the synthesis of other alkaloids.[100,103,134–136] The success of intramolecular DA reactions of these unactivated azadienes is attributed to the inability of the diene to tautomerize, the entropic assistance provided by the intramolecular cycloaddition and the relative stability of the product enamines (Scheme 7).[66]

The synthesis of the pyridine alkaloid (±)-Sedridine (**82**) has been reported by Uyehara[134] via a highly diastereoselective DA reaction (Scheme 8). An *exo* transition state has been proposed for the cycloaddition of **80**.[134]

Indolizidine alkaloid (±)-δ-coniceine (**86**) was synthesized



Scheme 5.

Table 1. [4+2] Cycloaddition of *o*-quinone methide imines

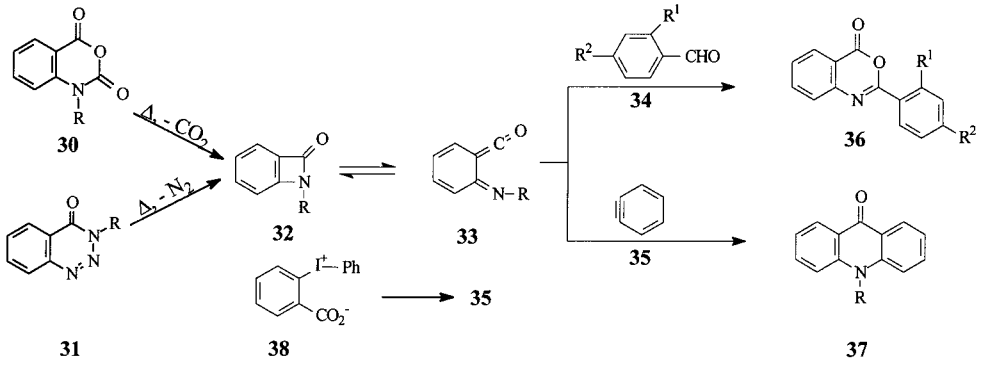
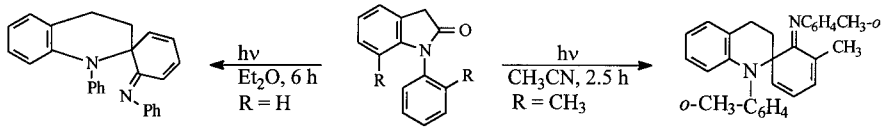
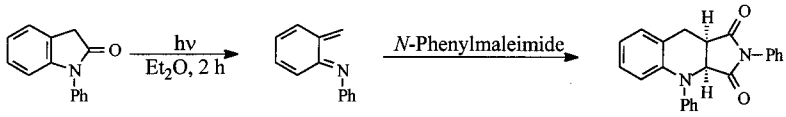
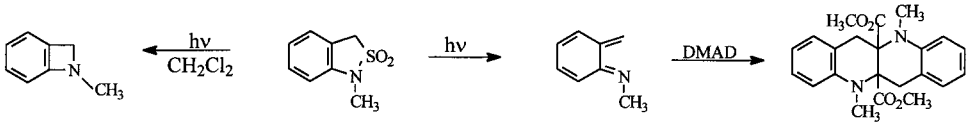
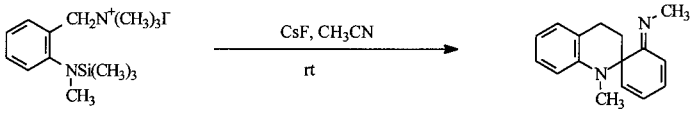
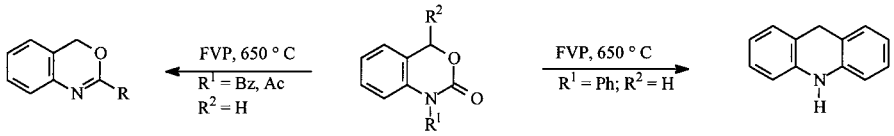
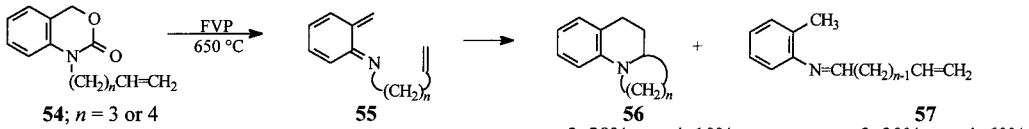
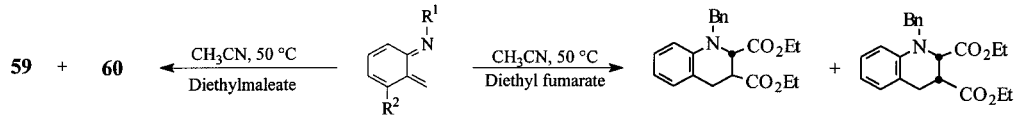
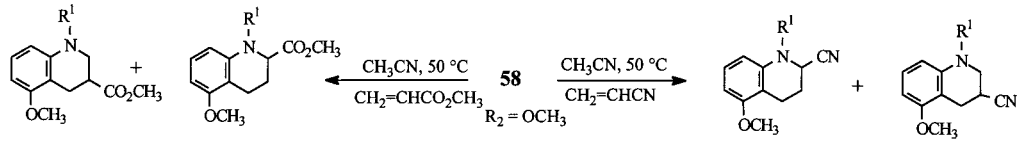
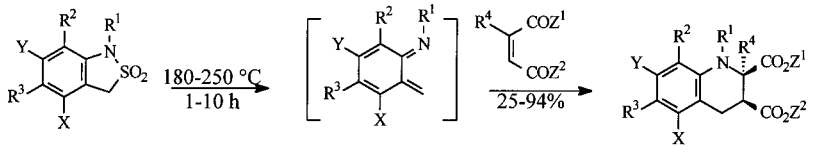
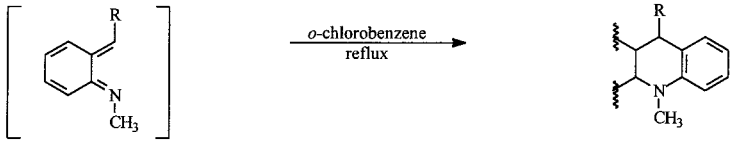
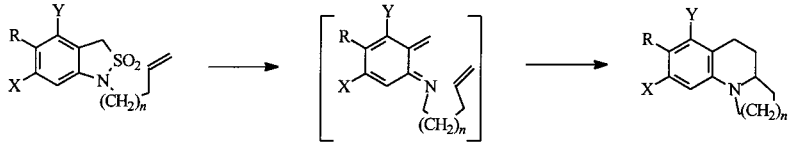
Entry	Diels–Alder Reaction	Ref.
1	 **30** **31** **32** **33** **35** **36** **37** **38**	84
2	 **41**; R = H 98% **38**; R = H **39**; R = Me **40**; 26%	85
3	 **42** **10** **43**; 14%	85
4	 **45**; 62% **44** **46** **47**; 88%	88
5	 **48** **49**; 77%	89
6	 **52**; R = Me 85% **53**; R = Ph 60% **50** **51**; 95%	91
7	 **54**; *n* = 3 or 4 **55** **56** *n* = 3, 29%; *n* = 4 10% **57** *n* = 3, 30%; *n* = 4 60%	91
8	 **59** + **60** 35% 15% **58**; R1 = Bn, R2 = H **59**; 85% **60**; 0%	93
9	 **61**; R1 = Pr, 30% **62**; R1 = *n*-Pr, 20% **63**; R1 = Bn, 50% **64**; R1 = Bn, 9%	93

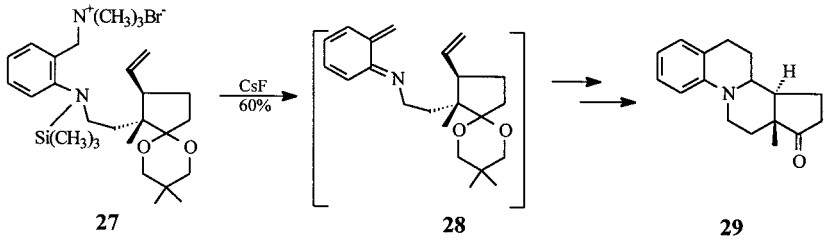
Table 1 (*continued*)

Entry	Diels–Alder Reaction	Ref.
10	 **65** **66** **67** R^1 = Me, Bn or R^1-R^2 = -$(CH_2)_3$-, -$(CH_2)_2O$-; R^2 = H; R^3 = H, Me, OMe, Cl, F; R^4 = H or Me; X = H or NO_2; Y = H or NO_2; Z^1 = Z^2 = OMe; or Z^1-Z^2 = NPh	95,96
11	[60] Fullerene +  **68**: R = Ph, *p*-$H_3CC_6H_4$-, 2-thienyl **69** (25-31%)	132
12	 **70** **71** **72**; 44-82% R = H, Cl; X = H, NO_2; Y = H, NO_2, *n* = 1 or 2	96

by Jung and coworkers by flash pyrolysis of azetine **83** (Scheme 9).[135]

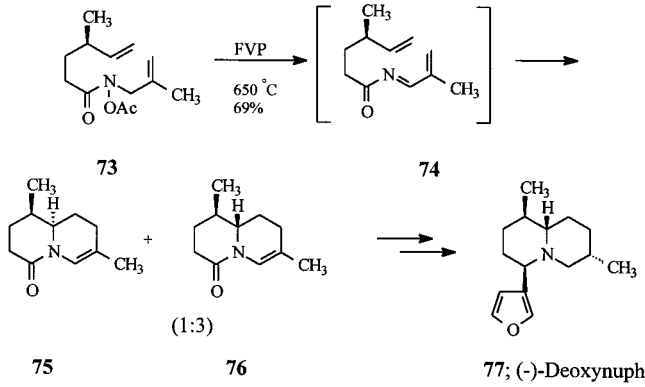
The indolizidine alkaloid (±)-Tylophorine (**90**) has been synthesized by Ihara et al.[136] through the stereoselective annelation of **87** in the presence of *t*-butyldimethylsilyl trifluoromethanesulfonate (Scheme 10).

Similar methodology for the synthesis of quinolizidine alkaloid epilupinine (**94**) through the intramolecular DA



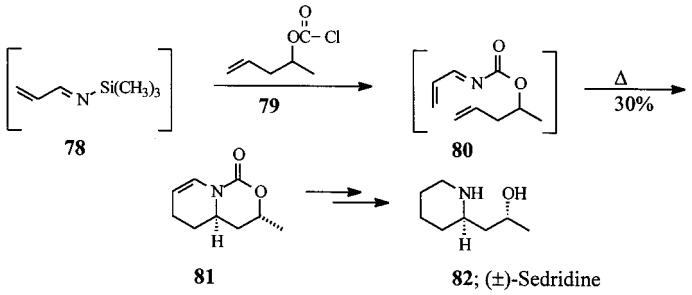
27 **28** **29**

Scheme 6.

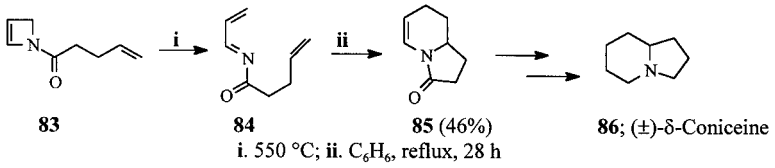


73 **74** **75** **76** (1:3) **77**; (-)-Deoxynupharidine

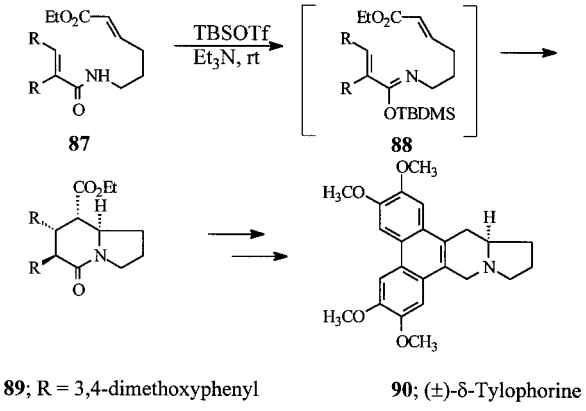
Scheme 7.



Scheme 8.



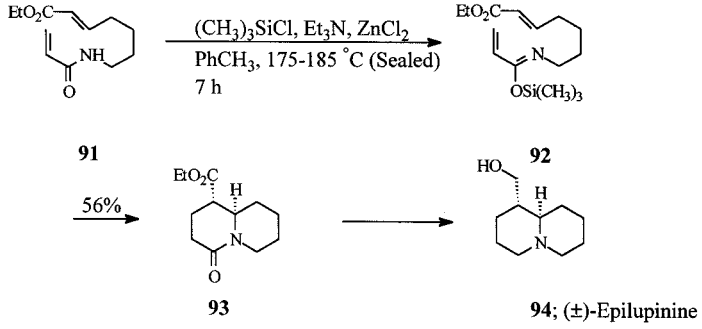
Scheme 9.



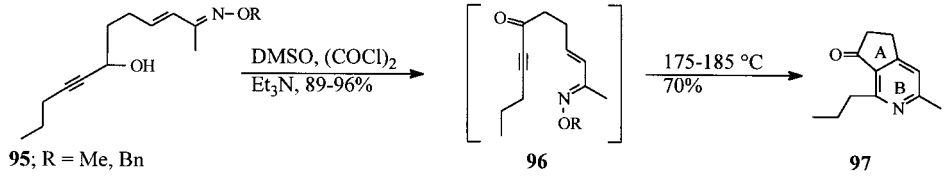
Scheme 10.

reaction of 1-azadiene **92** has been reported by Fukomoto and coworkers (Scheme 11).[103]

Boger has reported an efficient intramolecular DA reaction of an electron rich 1-azadiene tethered to an electron-deficient ynone in the construction of the AB ring system of Rubrolone (**97**) as presented in Scheme 12.[100] This is an $HOMO_{diene}$-controlled reaction in contrast to $LUMO_{diene}$-controlled DA reactions described earlier for the synthesis of the alkaloids deoxynupharidine,[133] sedridine,[134] and δ-coniceine.[135] The IMDA reactions described previously for the synthesis of **90**[136] and **94**[103] may also be of the $HOMO_{diene}$-controlled cycloaddition type. A number of other intramolecular DA reactions have been schematically presented in Table 2.



Scheme 11.



Scheme 12.

Table 2. Intramolecular Diels–Alder reaction of 1-azadienes

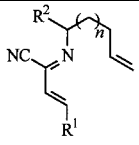
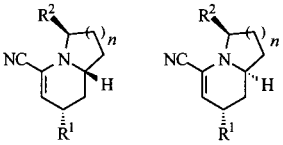
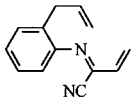
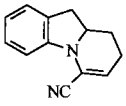
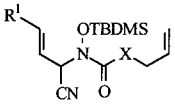
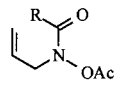
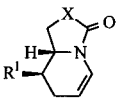
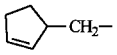
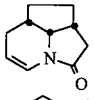
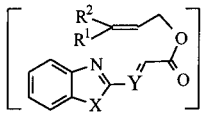
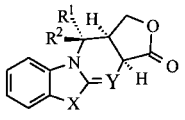
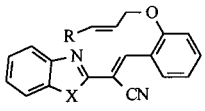
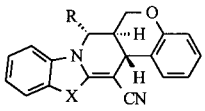
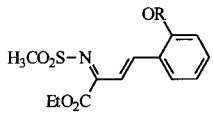
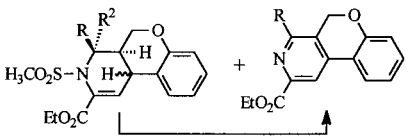
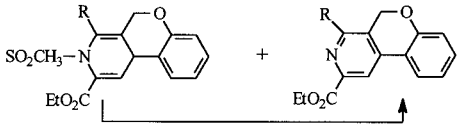
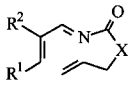
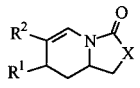
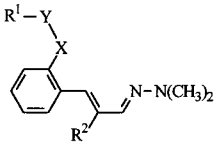
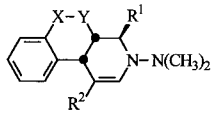
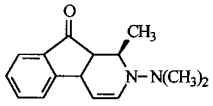
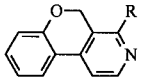
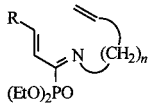
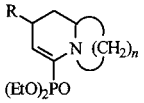
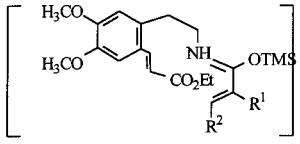
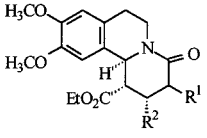
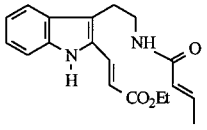
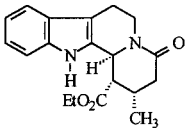
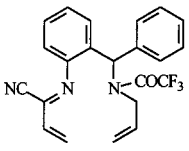
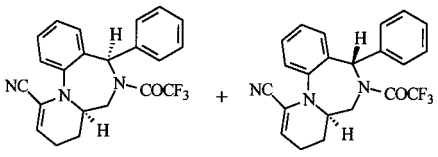
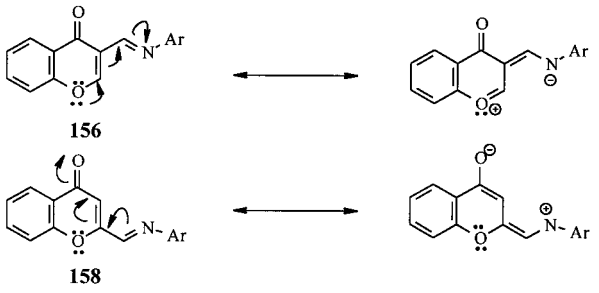
Entry	Substrate	Conditions/Reagents	Products			% Yield	Ref.
1							
	98a; R^1 = H, R^2 = Ph, n = 1	470 °C	**99a**	3:1	**100a**	60	106
	98b; R^1 = Ph, R^2 = CH_3, n = 1	110 °C, 26 h	**99b**	3:2	**100b**	73	107
	98c; R^1 = H, R^2 = CH_3, n = 1	110 °C, 24 h	**99c**	4:1	**100c**	94	107
		14 minutes microwave	**99c**	4:1	**100c**	94	106
	98d; R^1 = H, R^2 = CH_3, n = 2	110 °C, 48 h	**99d**	1:4	**100d**	86	107
2	 **101**	C_6H_6, reflux, 1 h	 **102**			74	137
3							
	103; R^1 = Ph, Me; X = O, CH_2, $(CH_2)_2$	C_6H_6, reflux	**104** (major)	(8-25:1)	**105** (minor)	32-61	113, 116
4		650 °C, 1 μs					
	106; R = -$(CH_2)_2CH=CH_2$, -$(CH_2)_3CH=CH_2$, (*E*)$(CH_2)_2CH=CHPh$, -$OCH_2CH=CH_2$		**107**; R^1 = H, Ph; X = O, CH_2, $(CH_2)_2$			69-75	118, 120
	108; R = 	650 °C, 1 μs	**109** 			69	118, 120
	110; R = -$CH_2CH_2C{\equiv}CH$	650 °C, 1 μs	**111** 			90	118
5	 **112**		 **113**				138
	X = S, Y = CCN, N; R^1 = H, Ph, *p*-$MeOC_6H_4$- R^2 = H, Ph, *p*-$MeOC_6H_4$-	Xylenes, reflux	X = S, Y = CCN, N; R^1 = H,Ph, *p*-$MeOC_6H_4$- R^2 = H, Ph, *p*-$MeOC_6H_4$-			35-84	
	X = O, Y = N, CCN, R^1 = H, Ph, *p*-$MeOC_6H_4$- R^2 = H,Ph,*p*-$MeOC_6H_4$-	Toluene, rt	X = O, Y = N, CCN, R^1 = H,Ph,*p*-$MeOC_6H_4$- R^2 = H,Ph,*p*-$MeOC_6H_4$-			28-80	
6	 **114**	*o*-dichlorobenzene 20-40 minutes reflux	 **115**				139
	X = O, S; R = Me, Ph		X = O, S R = Me, Ph			62-90	
7							109
	116a; R = $CH_2CH=CH_2$	PhMe, 108 °C, 40 h	**117a** R^1 = R^2 = H (1:1 cis:*trans*)		**118a**; R^1 = H	68:21	
		1,3,5-*i*$Pr_3C_6H_3$, 150 °C, 60 h				10:47	
	116b; R = (Z) $CH_2CH=CHPh$	PhMe, 108 °C, 23 h	**117b** R^1 = H, R^2 = Ph (1:20 cis:*trans*)		**118b**; R^1 = Ph	58:12	
		i. MeSOCl, Et_3N, CH_2Cl_2, 40 °C, 64 h **ii.** DBU, THF, or DDQ, CH_2Cl_2, 25 °C				0:66	
	116c; R = $CH_2CH=C(Me)_2$	PhMe, 108 °C, 22 h	**117c**; R^1 = R^2 = Me (1:1 cis:*trans*)			66:0	

Table 2 (*continued*)

Entry	Substrate	Conditions/Reagents	Products	% Yield	Ref.
					
	119a; R = $CH_2C{\equiv}CH$	PhMe, 108 °C, 44 h	**120a**; R^1 = H	**121a**; R^1 = H	24:36
		1,3,5-$iPr_3C_6H_3$, 150 °C, 24 h			0:56
	119b; R = $CH_2C{\equiv}CPh$	PhMe, 108 °C, 40 h	**120b**; R^1 = Ph	**121b**; R^1 = Ph	39:30
		PhMe, 108 °C, 66 h			56:41
		1,3,5-$iPr_3C_6H_3$, 150 °C 24 h			0:43
		i. MeSOCl, Et_3N, CH_2Cl_2, 40 °C, 67 h **ii**. DBU, THF, 0 °C			0:45
8					140
	122		**123**		
	X = O, CH_2, $(CH_2)_2$ R^1 = H, Ph; R^2 = H, Ph			38-65	
9					101
	124		**125**		
	X = O, NH; Y = CO, CH_2, R^1 = (E) CH=CHPh, CH = CCl_2, -CH = CH_2 R^2 = H, Me		X = O, NH; Y = CO, CH_2, R^1 = H, Cl, Ph, R^2 = H, Me	12-80	
	126; X = CO			35	
	Y-R^1 = (E)-CH=CHCH$_3$, R^2 = H	162 °C, 48 h	**127**		
	128a; X = O, Y = CH_2, R^1 = -C≡CH	138 °C, 18 h		58	
	R^2 = H		**129a** R = H		
	128b;X = O, Y = CH_2, R = -C≡CPh, R^2 = H	138 °C, 18 h	**129b** R = Ph	74	
10					141
	130		**131**		
	n = 3,4; R = Ph, Me, *p*-$O_2NC_6H_4$	PhMe, 18 h, reflux		30-63	
11		PhMe, 170-180 °C (sealed) or *o*-$Cl_2C_6H_4$, reflux			103
	132; R^1 = H, CH_3; R^2 = H, CH_3, Ph		**133**	25-52	
12		PhMe, 170-180 °C (sealed)			103
	134		**135**	58	
13		PhMe, 180 °C 5.5 h		74	142
	136		**137** **138**		



Scheme 13.

Fowler and coworkers demonstrated [107,113,116] that a cyano group at C-2 of 1-azadienes is sufficient to activate the dienes in their DA reactions to produce high to fair yields for compounds shown in entries 1 and 3 (Table 2). It has been proposed that the 2-cyano group enhances the DA reaction in several ways: (a) It lowers the diene LUMO energy level and increases its interaction with the HOMO of the dienophile; (b) It stabilizes the azadiene and diminishes its reactivity toward nucleophiles and thus decreases the amount of side products; (c) In cases where the azadiene is generated in situ, it lowers the activation energy of the elimination reaction necessary for the formation of the azadiene.[107,113,116]

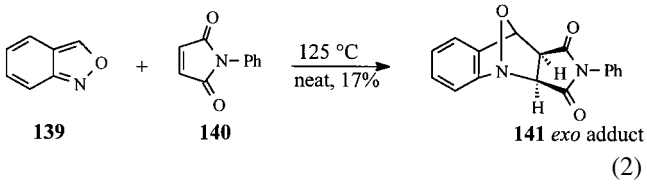
A high degree of stereospecificity occurs in these reactions with high preference for the *exo* (*anti*) products as seen in entries 3 and 6, Table 2.[113,139] This is also true for the intramolecular DA reactions of *N*-acylazadienes with no α-cyano groups, as presented in entries 4 and 8, Table 2.[116,118,140] In contrast, the inverse electron demand DA reactions, shown in entry 5, Table 2, proceed with *endo* selectivity.[138, 141]

Boger reported that in the intramolecular DA reactions of *N*-sulfonylazadienes with unactivated dienophiles a strong *endo* diastereoselectivity was observed for **116b** and not for **116a** and **116c** (entry 7, Table 2). Boger attributes the difference to a combination of a strong, stabilizing secondary orbital interaction and preferred cycloaddition through a stable *anti-endo* transition state in which the nitrogen lone pair and the C-aryl bond of the dienophile lie *trans* periplanar to one another.[109]

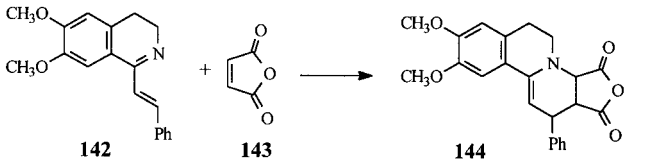
In Table 2, entry 5, higher yields (69–80%) obtained for derivatives with R^1=H, R^2=Ar, compared with R^1=Ar, R^2=H (28–44%), have been attributed to the enhanced stabilization of the corresponding DA reaction transition states through secondary orbital interactions.[138] A new approach to the synthesis of the tricyclic 1,4-benzodiazepines **137** and **138** using the IMDA reaction of **136** has been reported[142] (entry 13; Table 2).

6. Intermolecular Diels–Alder Reactions of 1-Azadienes

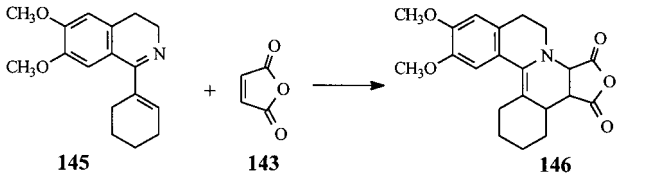
Early examples of successful 1-azadiene intermolecular DA reactions include those presented by Eqs. (2)–(4).[66,143–146]



(2)

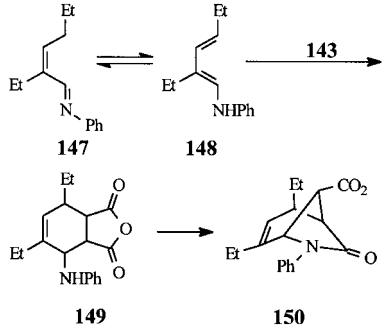


(3)



(4)

The above reactions represent the early exceptions to the general observations that such systems fail to undergo [4+2] cycloaddition. Simple unactivated 1-aza-1,3-butadienes undergo intermolecular DA reaction with electron-deficient dienophiles preferentially through their enamine tautomer (Eq. (5)).[66,143,147]

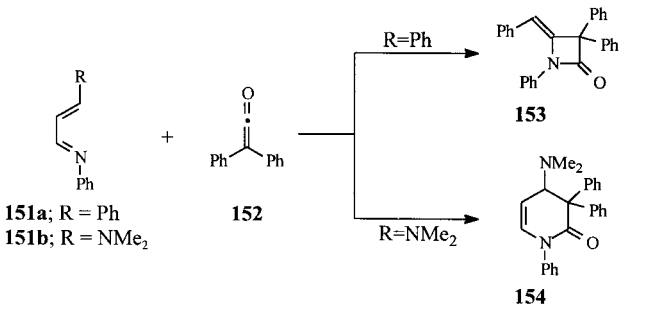


(5)

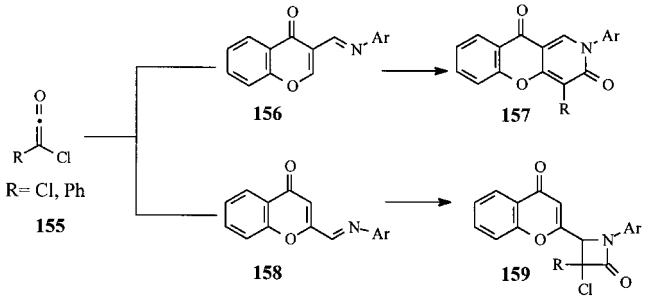
This DA reaction of the carbodiene tautomer may be due to the fact that tautomer **148** is more stable than 1-azadiene **147**. Furthermore, the reactivity of **148** is accentuated by the overlap of the nitrogen lone pair with the diene system. This phenomenon is similar in nature to that of the 1-azadiene **4** in Scheme 1, which upon treatment with vinyl acetate first isomerizes to the more reactive 2-azadiene **5** and then undergoes the DA reaction to produce the cycloadduct **6**.

The structure and the electronic nature of the dienes dictate the direction in which the reaction will take place. Eq. (6)[108,119,148] and Eq. (7)[149] represent examples of both [2+2] and [4+2] cycloaddition reactions. The oxygen lone pair electrons enhance the electron density of the azabutadiene moiety in compound **156**. On the other hand, the electron density is decreased in **158** by the electronic effect of the carbonyl group (Scheme 13 and Eq. (7)). The difference in the electron density of the azabutadienes could perhaps explain the difference in the outcome of the cycloaddition reactions of the two isomers (Eq. (7)). This factor elevates the diene HOMO energy level and facilitates its reaction with **155** to produce the adduct **157**. A similar

argument is valid for the activation of **151b** through sharing of the nitrogen electron pair with the diene system (Eq. (6)).

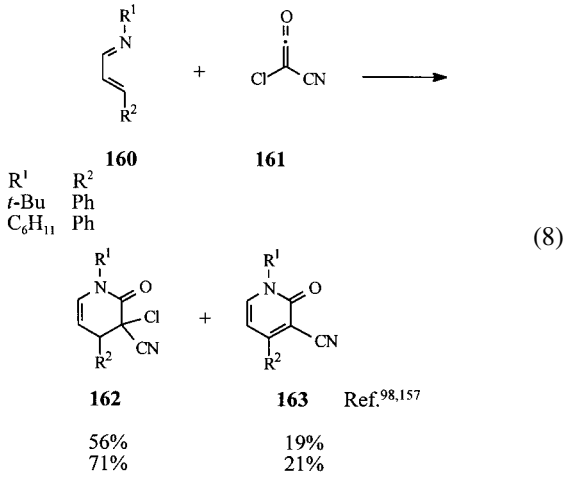


(6)



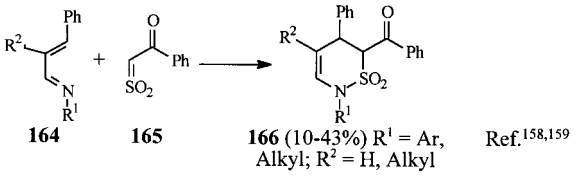
(7)

This interpretation is in sharp contrast to the earlier explanations that systems such as azadienes **151a** and **152** undergo the [2+2] rather than the [4+2] cycloaddition reactions because of their inability to tautomerize.[66,119,148–150] Similar [4+2] cycloadditions with dichloroketene,[66,119,148–156] chlorocyanoketene,[98,157] benzoylsulfene,[158,159] maleic acid,[160] and (*Z*)-3-phenyl-3-trimethylsilyloxyacrylonitrile,[94,161] or with in situ generated ketene,[162] have also been reported. Eqs. (8)–(10) represent examples of these transformations.

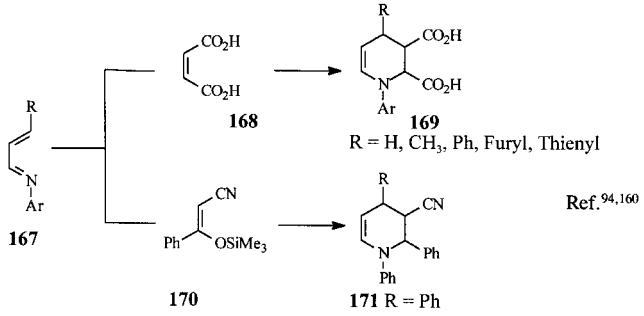


(8)

It should be noted that if in Eq. (6), R is a phenyl group, a mixture of [4+2] and [2+2] cycloadducts are obtained and in some instances only the latter occurs.[98,119,148,157] The formation of the [2+2] cycloadducts have been attributed to the steric effects of the large phenyl groups that inhibit the [4+2] cycloaddition and directs the reaction toward the [2+2] reactions.[119,148]



(9)

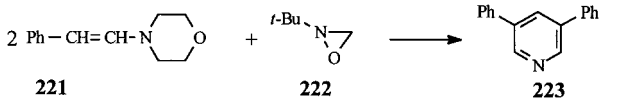


(10)

Table 3 lists DA reactions of unsaturated heterocyclic 1-azadienes. It should be noted that in entry 16 (Table 3), as expected the yields of the DA reactions of the unactivated azadienes **211** with electron-rich dienophiles **212** ($LUMO_{diene}$-controlled) are high compared to the yield of the reaction of **211** with the electron-deficient dienophiles **212**. The results also show the regio- and stereoselectivity (*endo*) of the reactions. In nearly all cases the *cis* isomer is either the major or the only product.

In entry 17 (Table 3) the existence and reactivity of an azadiene such as **214** has been established by Gavina and coworkers by heating a mixture of polymeric 5-sulfonate of 3-pyrrolin-2-one with trapping dienophiles **215** and **218**.[171]

In recent years the application of both normal ($HOMO_{diene}$-controlled) and inverse electron demand ($LUMO_{diene}$-contolled) 1-azadiene DA reactions in synthesis has increased significantly due to the modification of the electronic characters of the diene and the dienophile. In a normal DA reaction where an electron-rich diene reacts with an electron-deficient dienophile the reaction rates have been enhanced by electron releasing groups on the diene and/or electron-withdrawing groups on the dienophile. On the other hand in an inverse electron demand DA reaction, where an electron deficient diene reacts with an electron-rich dienophile, the reaction rates have been increased by electron withdrawing groups on the diene and/or electron releasing groups on the dienophile. In 1976 Komatsu reported[172] the synthesis of 3,5-diphenylpyridine **223** by heating the electron-rich dienophile **221** with oxaziridine **222** as shown in Eq. (11).



(11)

In these reactions a reactive dienophile is required. Pyridine yields in these reactions were improved significantly by acid

Table 3. Diels–Alder reactions of unsaturated heterocyclic 1-azadienes

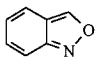
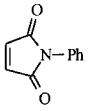
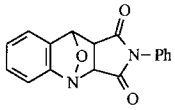
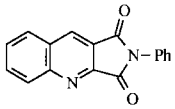
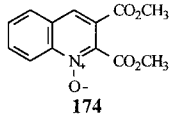
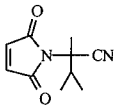
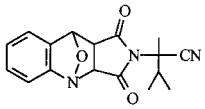
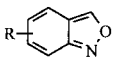
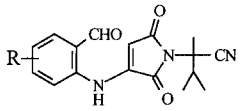
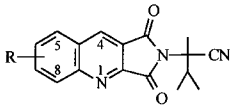
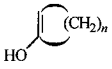
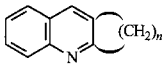
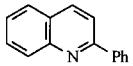
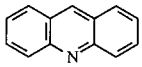
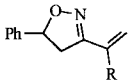
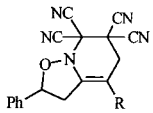
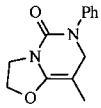
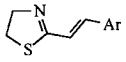
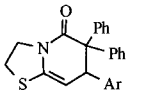
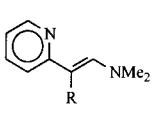
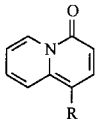
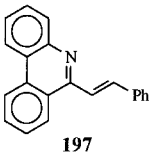
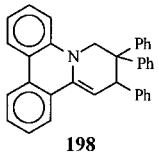
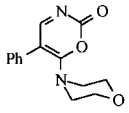
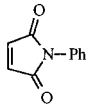
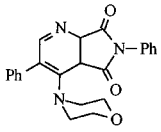
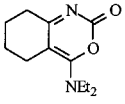
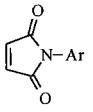
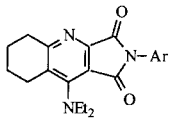
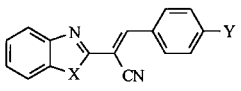
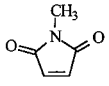
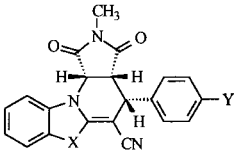
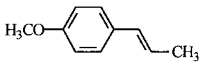
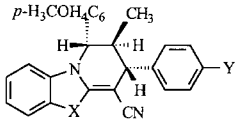
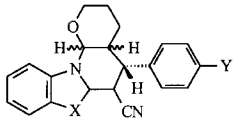
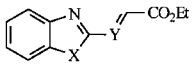
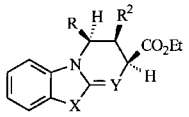
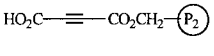
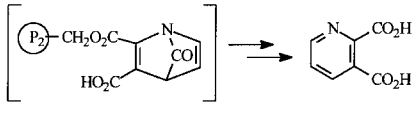
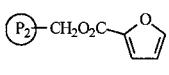
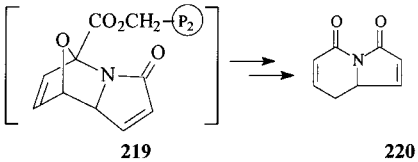
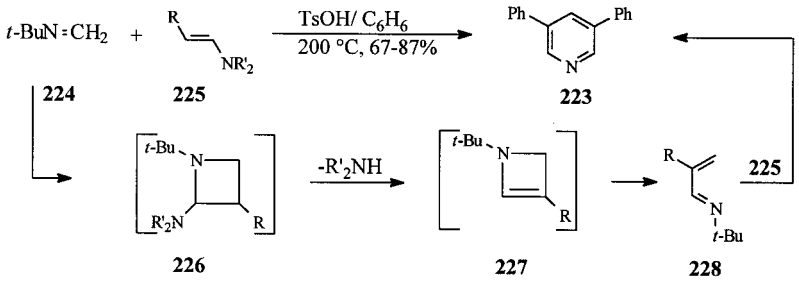
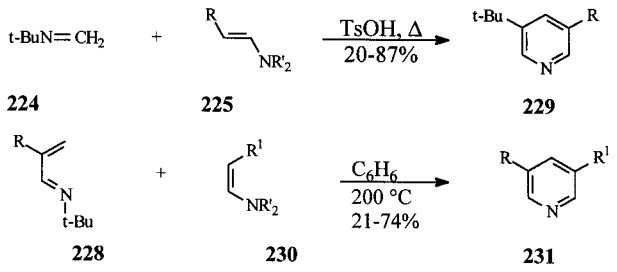
Entry	1-Azadiene	Dienophile	Conditions	Product	% Yield	Ref.
1	 **139**	 **140**	Neat, 125-130 °C, 1 h	 **141**	17%	143, 163, 164
			Xylene, reflux, 20 h	 **172**	--	143, 164
2	**139**	$H_3CO_2C-\equiv-CO_2CH_3$ **173**	--	 **174**		143, 164
3	**139**	 **175**	58 °C	 **176**		66
	 **177**	**175**	Xylene, 138 °C	 **178**	37%	66
	177; R= 5-, 6-, 8-Cl, 6-, 7-NO_2, 6-OCH_3		*o*-$Cl_2C_6H_4$, 180 °C, 41h	 **179**	75% 20-54%	66
4	**139**	 **180**	Xylene, 140-150 °C	 **181** (n = 3-6)	11-25%	165
5	**139**	 **182**	Xylene, 150 °C	n = 3 n = 4	19% 6%	165
6	**139**	Phenylacetylene **183**	Xylene, 140 °C	 **184**	11%	165
7	**139**	Benzyne (**35**)	--	 **185**	5%	166
8	 **186**	 **187**	Neat, 140 °C 4-15 min, reversible	 **188a**; R = H **188b**; R = Ph	33% 52%	102
9	 **189**	 **190**	--	 **191**	--	167
10	 **192**	 **152**	Xylene, reflux, 10 h	 **193**; Ar = C_6H_5; *p*-C_6H_4, *p*-ClC_6H_4	39-78%	168

Table 3 (*continued*)

Entry	1-Azadiene	Dienophile	Conditions	Product	% Yield	Ref.
11	 **194**	 **195**	--	 **196**; R = CN, CO_2Et	--	169
12	 **197**	**152**	--	 **198**	28%	168
13	 **199**	 **140**	--	 **200**	--	170
14	 **201**	 **202**	--	 **203a**; Ar = C_6H_5 49% **203b**; Ar = *p*-ClC_6H_4 38%		170
15	 **204** X=O, S; Y=H, NO_2, CH_3, OCH_3	 **205**	120 °C	 **206**	35-85%	139
	204	 **207**	120 °C	 **208** X=O, S Y= H, NO_2, OCH_3	42-82%	
	204	 **209**	190 °C (Sealed)	 **210a**; X = S, Y = H *endo:exo 1.3:1* **210b**; X = S, Y = CH_3 *endo:exo 1:1.15* **210c**; X = O, Y = H *endo:exo 1.3:1*	39% 49% 56%	
16	 **211**; X= O, S; Y = N, C-CN	 **212** R^1 = OEt, -OCH_2CH_2-, CH:CHC_6H_4OMe-*p*, CH_3CH:CHC_6H_4OMe-*p*, CO_2CH_3 R^2 = H, -OCH_2CH_2-		 **213**	35-98%	121
17	 **214**	 **215**		 **216** **217**		
		 **218**		 **219** **220**		171



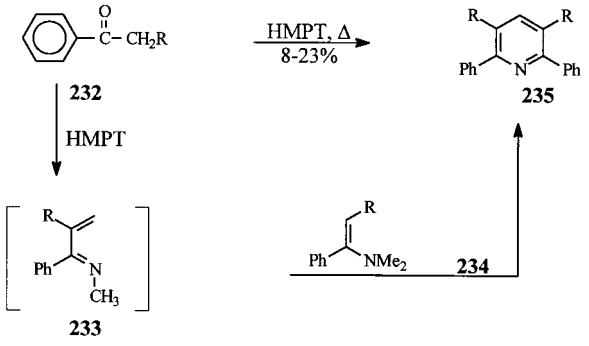
Scheme 14. R=CH_3, C_2H_5, *i*-Pr, cyclohexyl, Ph, PhS; NR'_2=piperidino, morpholino.



Scheme 15.

catalysis.[173] The in situ generated azadiene **228** was proposed to be involved in these reactions as presented in Scheme 14.

This cycloaddition was further investigated and a general method for the preparation of 1-azadienes **228** and their use in the synthesis of 3,5-disubstituted pyridines was reported (Scheme 15).[174]



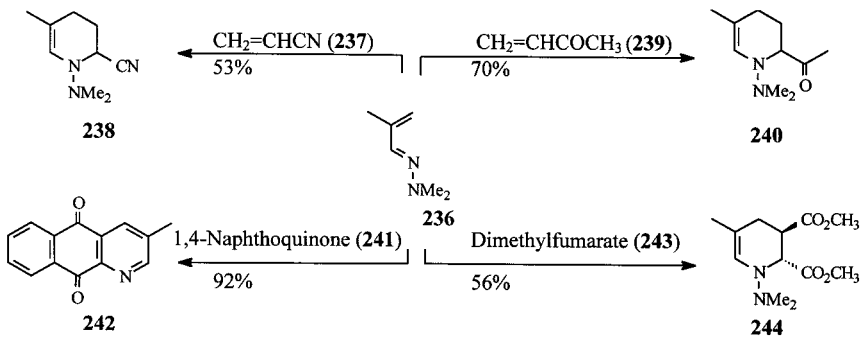
Scheme 16.

A polar DA mechanism is proposed for these [4+2] cycloadditions.[174] Similar methodology has been reported by Vijn et al. for preparation of di- and trisubstituted pyridines including 5,6,7,8-tetrahydroquinolines.[97] Reaction between alkylphenones **232** (other than acetophenone) and hexamethylphosphoric triamide generates the azadiene **233** which upon addition to the enamine **234** produces 3,5-dialkyl-2,6-diphenylpyridines **235**[175] as presented in Scheme 16.

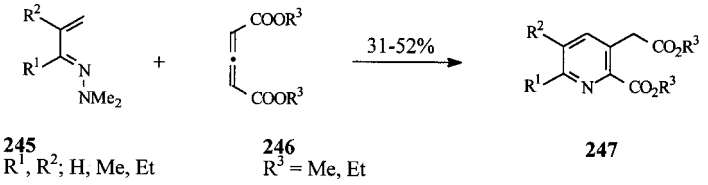
Ghosez and coworkers have demonstrated that a dimethylamino group on the *N*-1 position of a simple 1-azadiene activates the diene enough to undergo normal ($HOMO_{diene}$-controlled) DA reactions with a series of electron-deficient dienophiles and produce tetrahydropyridines in fair to good yields (Scheme 17).[75,105]

Upon treatment with Zn/HOAc these adducts can be converted to the corresponding piperidines via concurrent double bond reduction and dimethylamine elimination. Azadiene **236** produced the *trans*-adduct **244** with either fumarate or maleate methyl esters.[105] It was found that the formation of **244** in the DA reaction of methyl maleate is due to the isomerization of maleate to fumarate under the reaction conditions.[75] These DA reactions are regioselective and exclusively produce the expected regioisomers. Diels–Alder reactions of azadiene **236** and similar systems (**245**) with allene dicarboxylates have produced homophthalic acid derivatives **247** (Scheme 18).[176]

The preparation of quinolinedione **250b**, an intermediate in the total synthesis of the antibiotic Lavendamycin methyl ester (**251**) analogs via Diels–Alder reaction of azadiene **248** with bromoquinone **249**[99] (Scheme 19) was attempted by Behforouz and coworkers. Although **248** failed to



Scheme 17.

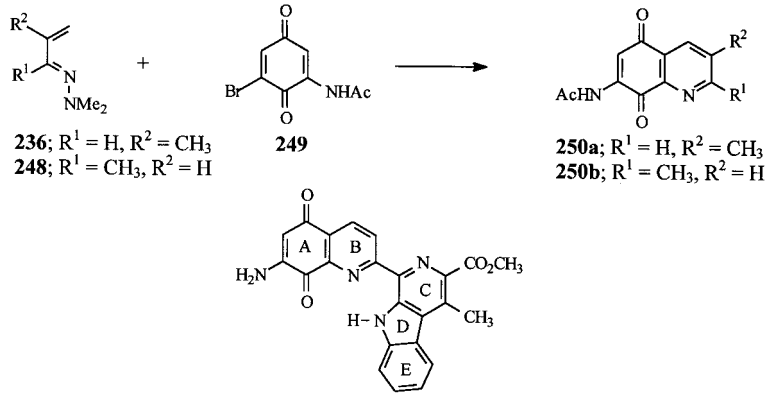


245
R^1, R^2; H, Me, Et

246
R^3 = Me, Et

247

Scheme 18.



236; R^1 = H, R^2 = CH_3
248; R^1 = CH_3, R^2 = H

249

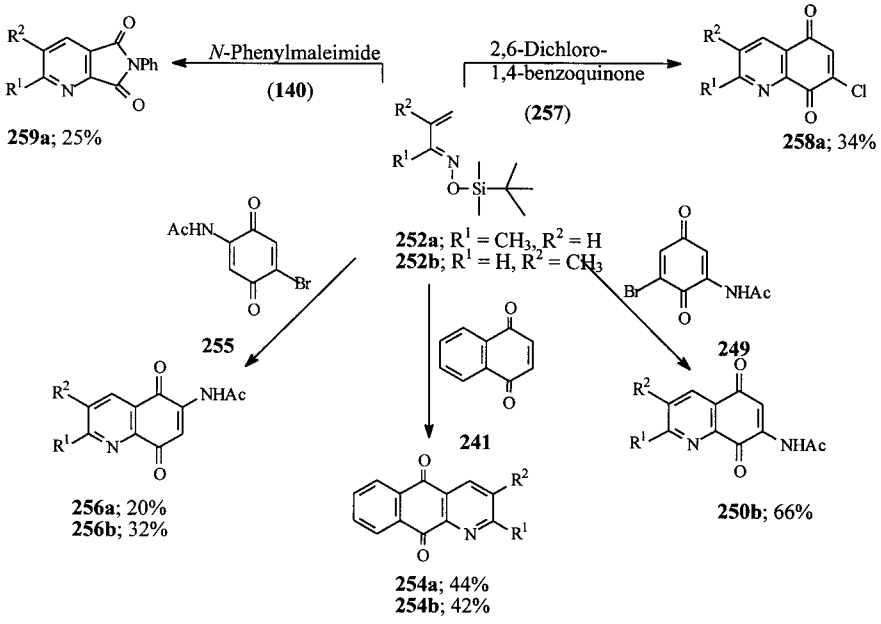
250a; R^1 = H, R^2 = CH_3
250b; R^1 = CH_3, R^2 = H

251; Lavendamycine Methyl Ester

Scheme 19.

undergo [4+2] cycloaddition, 3-methyl-1-azabutadiene **236** regioselectively gave the corresponding cycloadduct **250a** in 64% yield. It appears that the steric interference of the C-2 and N-1 methyl groups twists the nitrogen electron pair out of conjugation and diminishes its ability to activate the diene. The synthesis of dione **250b** (and subsequently lavendamycin methyl ester) was accomplished via the DA reaction of the novel *N*-silyloxy derivative 1-azadiene **252a** with bromoquinone **249**.[99,177]

Scheme 20 shows a number of transformations using the DA reactions of azadiene **252a** and its isomer **252b** with a series of electron-deficient dienophiles.[177] Although **252b** is the azadiene of choice for the synthesis of 2-methyl substituted quinolinedione and their derivatives, the synthetic potential of its Diels–Alder reaction and that of its isomer **252b** is limited because of their low conversions. More work is needed to improve the DA reaction yields of these azadienes. DA reactions of α,β-unsaturated dimethylhydrazones and similar azadienes with electron-deficient dienophiles ($HOMO_{diene}$-controlled) have been applied by a number of investigators for the synthesis of a variety of



259a; 25%

258a; 34%

252a; R^1 = CH_3, R^2 = H
252b; R^1 = H, R^2 = CH_3

256a; 20%
256b; 32%

254a; 44%
254b; 42%

250b; 66%

Scheme 20.

Table 4. Normal intermolecular Diels–Alder reactions of 1-aza-1,3-butadienes

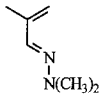
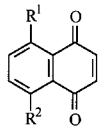
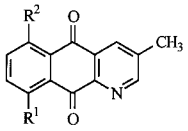
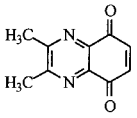
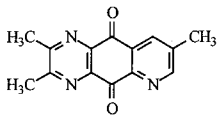
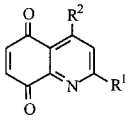
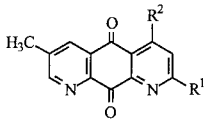
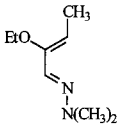
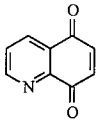
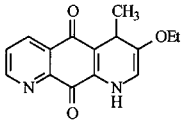
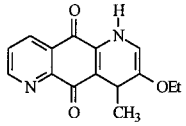
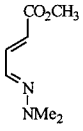
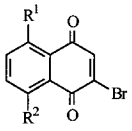
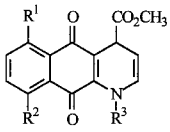
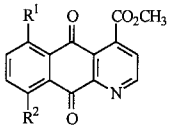
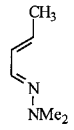
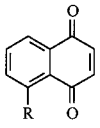
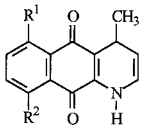
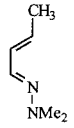
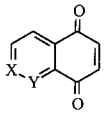
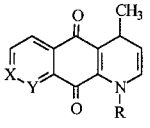
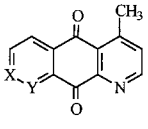
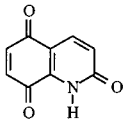
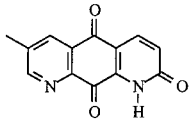
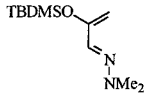
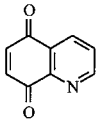
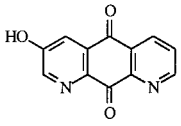
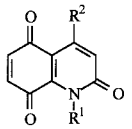
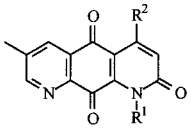
Entry	Substrate	Reagents/Conditions	Products	% Yield	Ref.
1					178,189
	236	**264a**; R^1 = OH, R^2 = H **264b**; R = OMe, R^2 = H	**265a**; R^1 = OH, R^2 = H **265b**; R^1 = H, R^2 = OMe	83% 62%	
				75%	178
		266	**267**		
					
		268a; R^1 = H, R^2 = H **268b**; R^1 = Cl, R^2 = CH_3	**269a**; R^1 = H, R^2 = H **269b**; R^1 = Cl, R^2 = CH_3	73% --	
2			 		179
	270	**271**	**272** 6: 4 **273**	63%	
3			 		180
	275	**276a**; R^1 = H, OH, OCH_3 **276b**; R^2 = H, OH, OCH_3	**277** R^3 = H, NMe_2	**278**	37-67%
4					183
	281	**282a**; R = OH, rt **282b**; R = OCH_3, 100 °C **282c**; R = $OCOCH_3$, rt	**283a**; R^1 = H, R^2 = H (*Claistopholine*) **283b**; R^1 = H, R^2 = OH **283c**; R^1 = OCH_3, R^2 = H **283d**; R^1 = H, R^2 = $OCOCH_3$	50% 50% 70%	
5			 		128,181, 182
	281	**284**; X = N, Y= CH **271**; X= CH, Y = N	**285a**; X = N, Y= CH,R=H & NMe_2 **285b**; X= CH, Y = N,R=H & NMe_2	**286a**; X = N, Y= CH **286b**; X= CH, Y = N	14-52%
6				68%	190
	236	**287**	**288**		
7				43%	190
	289	**271**	**290**		
8	**236**				122
		291a; R^1 = Me, R^2 = H THF, N_2, 50°C 3 days **291b**; R^1 = H, R^2 = Me THF, N_2, dark 3 days	**292**	40% 48%	

Table 4 (*continued*)

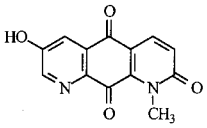
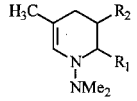
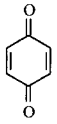
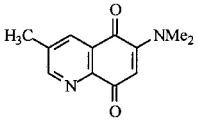
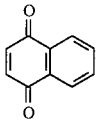
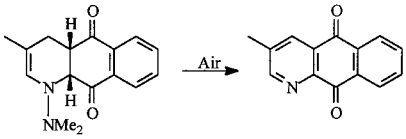
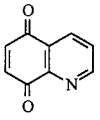
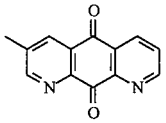
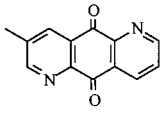
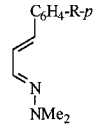
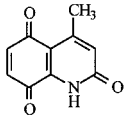
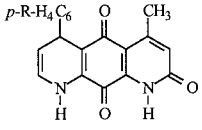
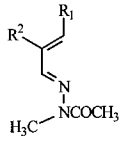
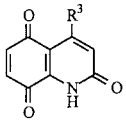
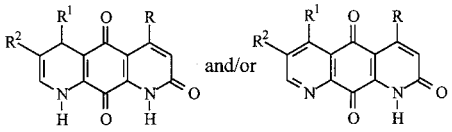
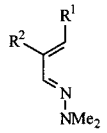
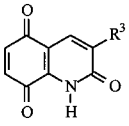
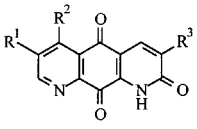
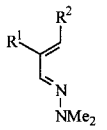
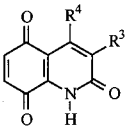
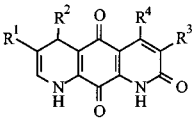
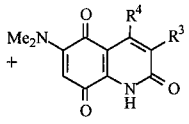
Entry	Substrate	Reagents/Conditions	Products	% Yield	Ref.
9	**289**	**291a** THF, N_2, rt, 24 h	 **293**	28%	
10	**236**	 Neat, 50 °C,Ultrasound **294**; R^1 = CN, CO_2Me R^2 = H, CO_2CH_3	 **295**	35-60%	184
11	**236**	 **296**	 **297**	50%	184
	236	 **241**	 **298** **242**	92%	
	236	 **271**	 **269a**	67%	
	236	**271** $CDCl_3$, 1 h, Air, rt, Sonication	**299** 	33%	
12	 **300**; R = H, NMe_2	 **291b**	 **301**; R = H	35 & 56%	
13	 **302**; R^1, R^2 = H, Me, Et, Ph	 R^3 = H, CH_3 (**287**, **291b** resp.)	 **303** **304**	44-84%	185
14	 **281**; R^1 = CH_3, R^2 = H **236**; R^1 = H, R^2 = CH_3	 **305**; R^3 = CH_3, C_2H_5, Ph, CHO, CN, CO_2H, CO_2Et, $COCH_3$	 **306**	40-66%	186
15	 **307** R^1 = H, CH_3 R^2 = H,CH_3,C_2H_5	 **308** R^3 = H, Ph R^4=CH_3,C_2H_5, C_3H_7	 **309** Standard Conditions 32-52% SiO_2 Support 70-92%	 **310** 35-59% 0-10%	127

Table 4 (*continued*)

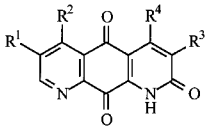
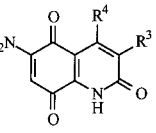
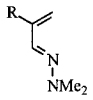
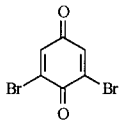
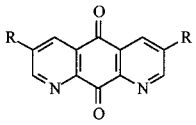
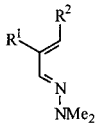
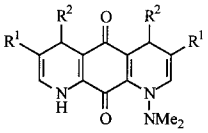
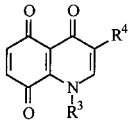
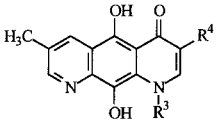
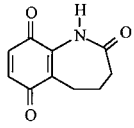
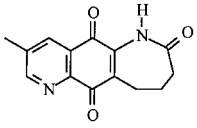
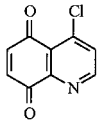
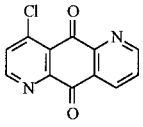
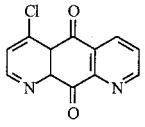
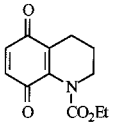
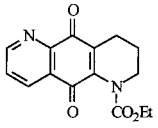
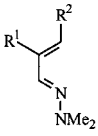
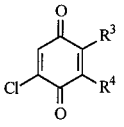
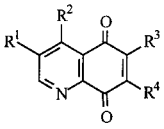
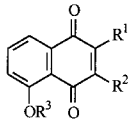
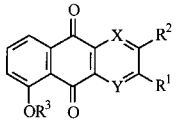
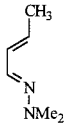
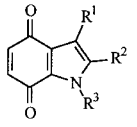
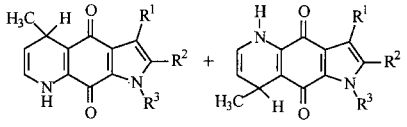
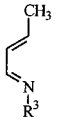
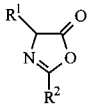
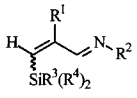
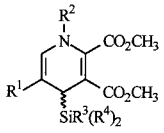
Entry	Substrate	Reagents/Conditions	Products	% Yield	Ref.
	307	R^3 = H, Ph; R^4 = Me, $Ph(CH_2)_2$	 + 		127
			311 **312**		
			Standard Conditions 40-79% 15-33%		
			SiO_2 Support 57-89% 0-7%		
16					191
	313; R = H, Me, Et	**314**	CH_2Cl_2, rt, 1 min **315**	66-94%	
17		**314**			191
	281; R^1= H, R^2= CH_3	CH_2Cl_2, Et_3N, rt, 15 min.	**317**	96%	
	316; R^1= Et, R^2= Me			100%	
18	**236**				187
		318	**319**		
		R^3 = Me, Et, R^2 = H, CO_2Me		26-56%	
19	**236**			56%	192
		CH_2Cl_2, rt, 1 h			
		320	**321**		
20			 + 		188
	322	**323**	**324** **325**		
		1. CH_3CN, rt, 1 h	12% 43%		
		2. SiO_2, *p*-Chloranil, reflux, 3 h			
21	**322**				188
		326	**327**		
		1. CH_3CN, rt, 1 h			
		2. SiO_2, *p*-Chloranil, reflux, 3 h		52%	
22					193
	236; R^1 = CH_3, R^2 = H	**328a**; R^3 = H, Cl, OCH_3 R^4 = H, Cl, OCH_3	**329**	56-73%	
	281; R^1 = H, R^2 = CH_3	**328b**; R^3 = OCH_3, H, R^4 = H, OCH_3		17-42%	
	322; R^1 = H, R^2 = H	**328c**; R^3 = H, Cl, OCH_3, R^4 = H, Cl, OCH_3		17-36%	

Table 4 (*continued*)

Entry	Substrate	Reagents/Conditions	Products	% Yield	Ref.
23					
	236	**330;** R^1= H, Cl, R^2= H, Cl; R^3= H, CH_3	**331**; X= N, CH; Y=N, CH	66-92%	
24				25-54%	
		$R^1 = R^2 = H$; $R^1,R^2 = (CH_2)_4$, CO_2Et, R^3 = H, $PhSO_2$, TsO, CO_2Me	15:85 to 100:0		
	281	**332**	**333** **334**		
25				65-90%	194
	335; $R^3 = C_6H_{11}$, iPr	**336**; R^1 = Ph, Me, R^2 =Ph, *p*-$NO_2C_6H_4$, *p*-ClC_6H_4, *p*-MeC_6H_4, Bn, *t*-Bu	**337**		
26		$MeO_2CC{\equiv}CCO_2Me$		33-51%	195
	338 R^1 = Ph, Bu; R^2= i-Pr R^3 = Ph, Et; R^4 = Me, Et	Xylene or acetonitrile, reflux	**339**		

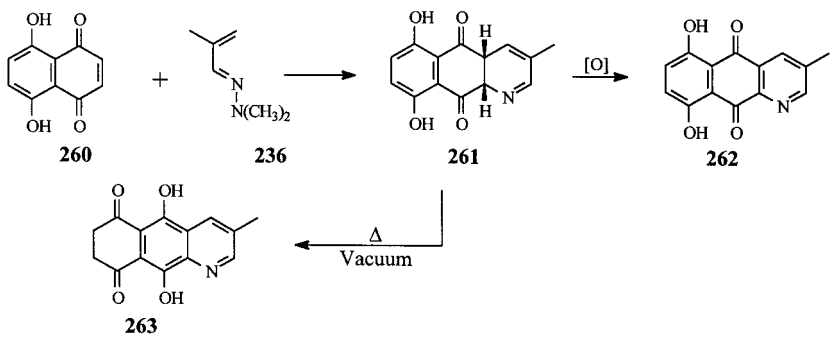
natural products and biologically active molecules. Table 4 summarizes a series of these reactions.[189–192,195]

Upon the reaction of azadiene **236** with hydroxyquinone **260**, Potts and coworkers isolated the intermediate **261** as dark blue needles which was oxidized to quinone **262** or isomerized to the hydroquinone **263** by heat at low pressure (Scheme 21).[178]

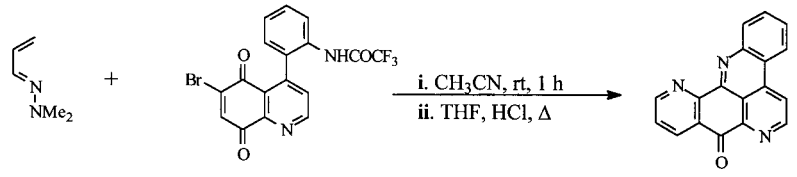
Entry 2 in Table 4 shows the formation of the desired [4+2] cycloadducts **272** and **273** when azadiene **270** was treated with dione **271** or its 2-methyl substituted derivative. However, when the reactions were carried out in the presence of trifluoroacetic acid a [3+2] cycloaddition process occurred and the furan derivative **274** was obtained.[179]

The Diels–Alder reactions presented in entry 3 (Table 4) were performed under reflux (100 or 140°C) in a nitrogen atmosphere in the presence or absence of sodium bicarbonate. Depending on the method used, mixtures of products **277** and **278** were obtained. In some instances dimethylamine derivatives **279** and **280** were also formed.[180]

Entries 4 and 5 (Table 4) describe the synthesis of analogs of alkaloid Claistopholine (**283a**), a natural 1-azaanthraquinone,[181,182] by Fillion et. al. using the DA reactions of azadiene **281** and Juglones **282**[183] or azadiene **281** and quinolinedione **271** or isoquinolinedione **284**.[128,181,182] The overall yields of **285** and **286** were low,[128,181,182] however, yields were significantly increased when reactions were carried out under sonication or pressure. In addition to the cycloadducts **285** and **286** quinoline-, or isoquinolinedione



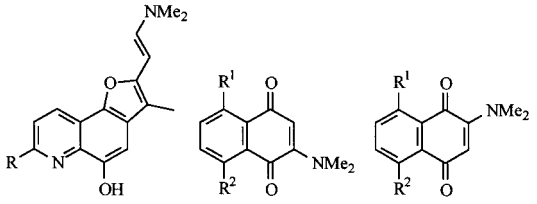
Scheme 21.



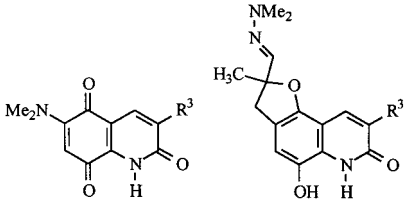
322 342 343

Scheme 22.

dimethylamino adducts were also formed. The reaction efficacy, when the reactants were used neat, were low in the absence (14%) or the presence of ultrasound (15%).

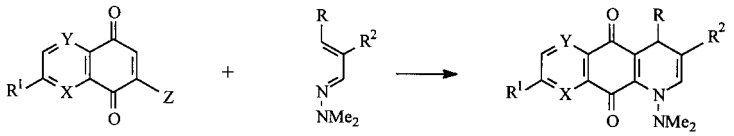


274 279 280



340 341

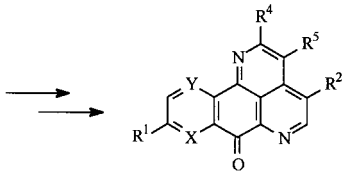
Avendano and coworkers (entries 10–12, Table 4) have found that in most cases ultrasound irridation accelerates the DA reactions of methacroleine dimethylhydrazone **236** with electron-deficient dienophiles. Besides the lower reaction times and higher yields, other advantages of the sonicated method is the decrease in side reactions and the possibility of isolating previously unknown adducts due to the milder reaction conditions.[184] In entry 12, in addition to the products **301**, reactions of **300** and **291b** also produced the corresponding 6-dimethylamino- adduct of the quinolinetrione.[184] In an effort to decrease the addition of the liberated dimethylamine to the starting quinones, *N*-acetyl-*N*-methylhydrazones have been prepared and employed in place of dimethylhydrazones.[185] Although acetylhydrazones are less reactive than the corresponding *N*,*N*-dimethylhydrazones, their DA reaction yields are comparable to those of the latter. Entry 13 presents the data for the DA reactions of acetylhydrazones **302** with 2,5,8(1*H*)-quinolinetriones (**287** or **291b**) to produce 1,8-diazaanthracene-2,9,10-triones **304** and/or its dihydro derivative **303**. No products were obtained when azadiene **302** (R^1=Ph, R^2=H) was used.[185] The DA reaction of the 3-substituted azadiene **236** with quinolinetriones **305** unlike those of the 4-substituted azadiene **281** gives no trace of the corresponding 6-dimethylamino adduct **340** (entry 14). In cases where R^3 is a strong electron-withdrawing group (R^3=CHO, CO_2H, NO_2, CN, COMe) the formation of furo[2,3-*f*]quinolin-7-one derivative **341**, through an ionic mechanism, competes with the formation of the [4+2] cycloaddition product **306**.[186] Excellent yields of the cycloadducts 5,8-dihydro-1,8-diazaanthracene-2,9,10-triones **309** or 1,8-diazoanthracene-2,9,10-triones **311**



344; R^1 = H, OCH_3, X = CH, C-Cl Y = CH, C-Cl; Z = H, Br

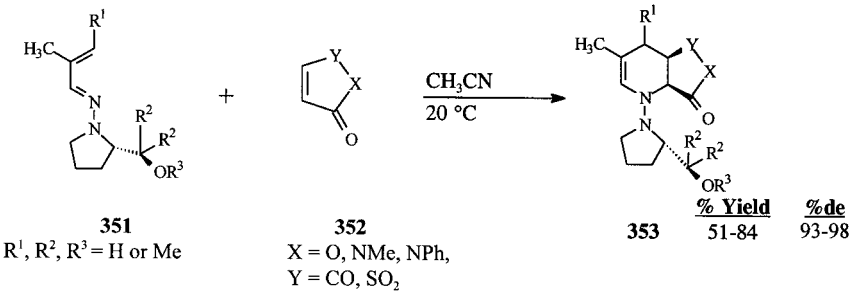
345c; R = CH_3, *o*-$C_6H_4NO_2$, R^2 = H, OCH_3

346



347a; X = Y = CH, R^1 = OCH_3, R^2 = R^4 = R^5 = H (*Eupomatidine 1*)
347b; X = Y = CH, R^1 = H, R^2 = OCH_3, R4 = R^5 = H (*Eupomatidine 2*)
347c; X = Y = CH, R^1 = R^2 = OCH_3, R^4 = R^5 = H (*Eupomatidine 3*)
347d; X = N, Y = CCl, R^1 = R^2 = H, R^4,R^5 = -CH:CH-CH:C(NO_2)- (*Cystodamine*)
347e; X = CH, Y = N, R^1 = R^2 = H, R^4,R^5 = -CH:CH-CH:C(NO_2)- (*Cystodamine isomer)*

Scheme 23.



351 R^1, R^2, R^3 = H or Me

352 X = O, NMe, NPh, Y = CO, SO_2

353

Scheme 24.

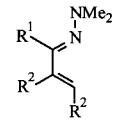
were obtained by the DA reactions of silica gel supported quinolinetriones and azadienes (entry 15).[127] This procedure minimizes or completely prevents the formation of the side product **310**.

N-Substituted 4,5,8(1*H*)-quinolinetriones react with 1-azadienes to give a range of products depending on the nature of the azadiene and the substituent on the nitrogen of the quinolinetriones. The regioselectivity of the reaction, although it is high, it is not as good as those of the DA reactions of 2,5,8(1*H*)-quinolinetriones with the same dienes.[187] Although the DA reaction of methacrolein dimethylhydrazone (**236**) with quinolinediones is regioselective[178] that of **322** with quionlindione **323** is not (entry 20).[188]

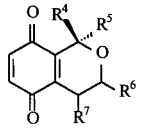
Brassard has studied the regiochemistry of chloroquinone DA reactions and concluded that the position of the chlorine atom is the sole determinant of the product's regiochemistry (see entry 22).[193] Indoloquinones (entry 24) have been treated with azadienes to produce regioisomers **333** and **334**. When R^1,R^2=H or $(CH_2)_4$ the major product was **333** (**333**:**334** ratio is equal to 65:35 and 100:0, respectively), when R^3 or R^2 were electron-withdrawing groups, the major regioisomer was **334**.[196,197]

Echavarren has applied the azadiene DA reaction to the synthesis of Isoascididemin (**343**) a regioisomer of the marine alkaloid Ascididemin (Scheme 22).[194]

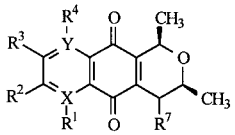
Kubo has reported the synthesis of alkaloids; Eupomatidines 1, 2, 3 (**347a**, **b**, **c**)[198] and Cystodamine (**347d**, **e**)[199] through the DA reactions of the α,β-unsaturated dimethylhydrazones (Scheme 23). Lackner has employed the DA reactions of substituted isochromanquinones (**349**) with structurally modified 1-aza-1,3-dienes **348** to synthesize a number of benzisochromanquinone antibiotics (**350**).[200] Application of this methodology proved to be a flexible strategy for the synthesis of *6-aza* regio isomers of benzisochromanquinones.



348; R^1= H, CH_3; R^2=H, CH_3, OTBDMS; R^3=H, CH_3



349; R^4=CH_3, R^5=H, CH_3; R^6=CH_3 (3R), CH_2CO_2Me (3S), -CH2CO_2-; R^7=H, -CH2CO_2-

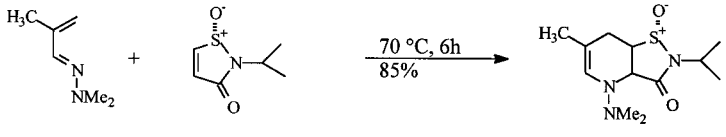


350

Asymmetric intermolecular DA reaction of 1-azadienes in which chiral auxiliaries are present on the dienes or dienophiles have been applied to the diastereoselective synthesis of a number of dihydropyridines.[201,202] Ghosez has reported a very high degree of diastereoselectivity in the reactions of chiral azadienes **351** with reactive dienophiles **352** to produce dihydroxypyridines as presented in Scheme 24.[201]

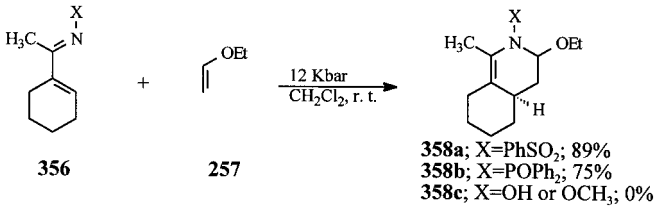
It should be noted that the values for diastereomeric excess (de) are given for the purified products and are lower (73–85%) for the crude products obtained from the less hindered diene **351**.

Waldner has synthesized tetrahydropyridine **355** with an excellent diastereoselectivity by the reaction of azadiene **236** with chiral dienophile **354** (Scheme 25).[202]



236 **354** **355**; >96% de

Scheme 25.

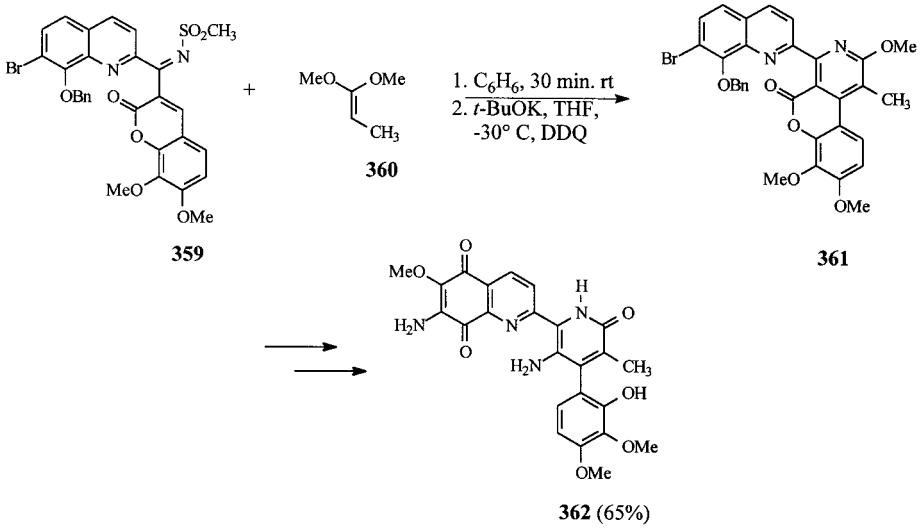


Scheme 26.

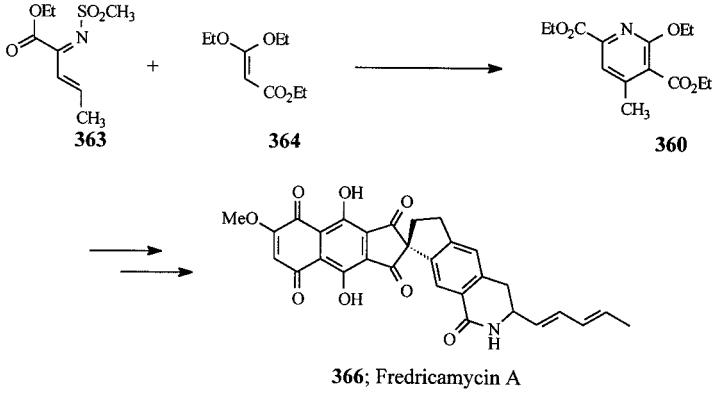
7. Inverse Electron Demand Intermolecular Diels–Alder Reactions of 1-Azadienes

The inverse electron demand ($LUMO_{diene}$-controlled) 1-azadiene DA reactions have been successfully used by Boger[58,203] and Fowler[108] for the synthesis of a variety of pyridine molecules including some natural products. In his elegant and extensive studies, Boger has demonstrated that *N*-sulfonyl and *N*-phosphinyl α,β-unsaturated imines constitute stable and easily accessible 1-aza-1,3-butadienes for use in well-behaved intra- or intermolecular [4+2] cycloaddition reactions.[100,109,112,115,117,203,204] Boger has shown that while *N*-benzenesulfonylimine and *N*-diphenylphosphinylimine give 75–89% of the cycloadduct **358**, the corresponding oxime and *O*-methyloxime do not give any product (Scheme 26).[117]

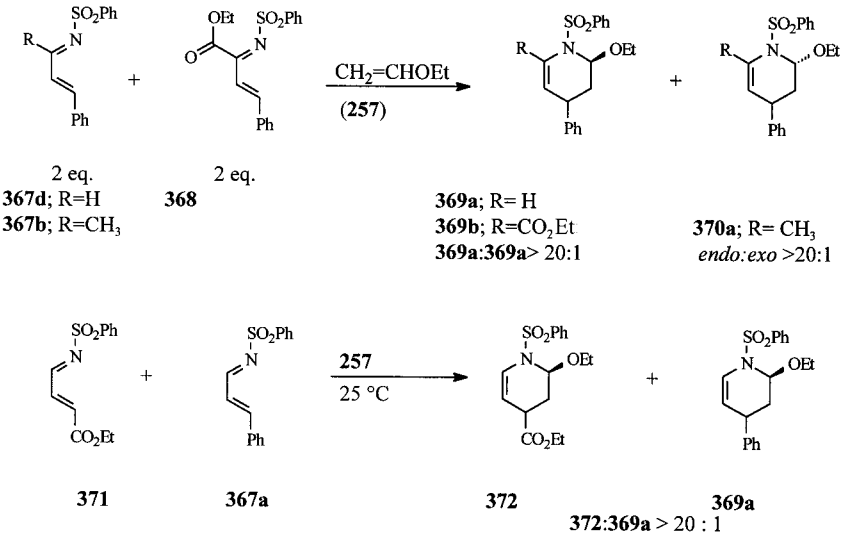
Boger has successfully applied the inverse electron demand methodology in the total synthesis of a number of complex natural products such as Streptonigrone (**362**)[205,206] and Fredricamycin A (**366**)[111,207–209] (Schemes 27 and 28). The reactivity of the diene **359** is enhanced by the complementary effect of the C-3 substituent and reactivity of diene **363** is enhanced via the noncomplementary effect of the electron-withdrawing group at the C-2 position.[41] Using similar methodologies, the syntheses of natural product Nothapodytine B and (−)-Mappiline were also reported.[216]



Scheme 27.



Scheme 28.



Scheme 29.

The complementary effects of N-1 and C-3 electron-withdrawing substituents of 1-azadienes accentuate their electron-deficiency and accelerate their reactivity with electron-rich dienophiles. These reactions exhibit characteristics of concerted [4+2] cycloaddition reactions in that they are solvent independent and show high degrees of regio- and *endo*-diastereoselectivity (Scheme 29 and entries 1-4 in Table 5). The unusually high level of diastereoselectivity (⩾20:1 *endo*/*exo*) may be attributed to two complementary features of the reaction. The first is the *endo* transition state stability due to the orbital interaction of the diene C-2 and the dienophile OR group. The second is the stabilization of an *endo* boat transition state due to an anomeric effect of a *trans* periplanar nitrogen lone pair electrons and the electron-rich enol ether σ bond.[114] The latter feature which is absent in the *exo* transition state and in the all-carbon DA reactions may be responsible for the high degree of the *endo* selectivity.

Electron-withdrawing substituents at the C-3 position of the 1-azadiene complement the effect of the *N*-1 sulfonyl group in lowering the $LUMO_{diene}$ energy level to an extent that the azadiene [4+2] cycloadditions are performed at room or even lower temperatures and maintain their high degree of endoselectivity and exclusive regioselectivity. Non-complementary electron-withdrawing groups at C-2 and C-4 of the *N*-sulfonylazadienes by virtue of their lowering of the $LUMO_{diene}$ energy level accelerate the rates of inverse electron demand DA reactions without decreasing the regioselectivity (compare the data of reactions in entry 2 with those of similar systems in entries 4, 5 and 6, Table 5).[112,114,115,117] Boger has also demonstrated the C-2, C-4 noncomplementary azadiene rate enhancement by a comparison of the yields obtained when azadienes **368**, **367d**,**b** competed for the dienophile **257** or azadienes **371** and **367a** competed for the same dienophile as shown in Scheme 29.

Table 5 is a summary of inverse electron demand intermolecular DA reactions. It should be noted that the yields of adduct **383** (entry 4, Table 5) were significantly lower when R^2=*n*-C_6H_{13} or CH_3. Overall, in entries 4 and 5 the yields of DA reactions of *trans*-1,2-disubstituted dienophiles are higher than those of their corresponding *cis* isomers, and the latter exhibit a preferential pressure-induced rate acceleration.[112,114]

Fowler and coworkers, through a series of studies, have demonstrated that a 2-cyano substituent on a 1-azadiene molecule activates the system enough to undergo efficient intra-[106,107,113,116,121,137,139] or intermolecular[108,110,113,137] DA reactions. The intermolecular DA reactions of the 2-cyano-azadienes gave fair to excellent yields with a range of electron rich, electron-deficient and neutral dienophiles under mild thermal conditions (90–120°C).[108,110,113,137]

Calculation of the frontier orbital energies and coefficients, as well as the transition state geometries for the [4+2] cycloaddition of *N*-phenyl-2-cyano-1-azadiene (**386**, entry 6, Table 5) reveal that the DA reaction of **386** with methyl vinyl ether is a $LUMO_{diene}$-controlled reaction, whereas that of methyl vinyl ketone preferably occurs as a $HOMO_{diene}$-controlled reaction.[108] The $LUMO_{diene}$-controlled reactions are *endo*- and regioselective affording α-cycloadducts while the $HOMO_{diene}$-controlled reactions give a mixture of α/β adducts with an approximate ratio of α:β=4–5:1. A concerted mechanism with a transition state possessing a high degree of diradical character has been proposed for these reactions.[113] An unusually high yield of 95% was reported for the reaction of azadiene **390** with norbornene.[113] It should be noted that entries 6–8, Table 5 include some normal DA reactions. In entry 7, Table 5, α isomers were the only products in nearly all cases involving electron-rich dienophiles while electron-deficient dienophiles gave mixture of α and β iosmers with α isomer as the major product.

8. Catalysis

The rate enhancements of 1-azadiene DA reactions by Lewis or Bronsted acids has not been significant, although in certain cases some improvements of product yields have been reported. Avendano and coworkers have obtained high

Table 5. Inverse electron demand intermolecular Diels–Alder reactions

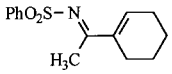
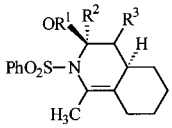
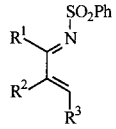
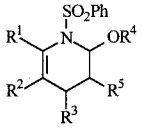
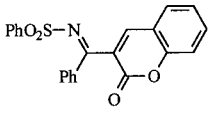
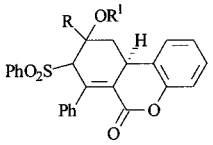
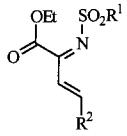
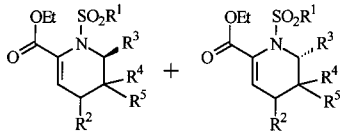
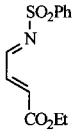
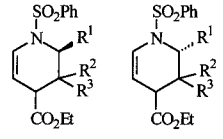
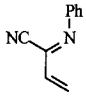
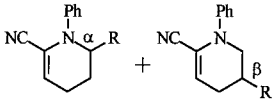
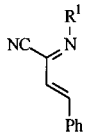
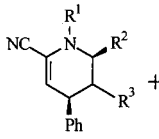
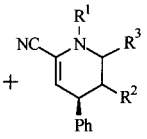
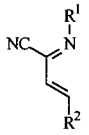
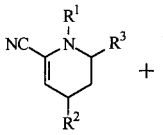
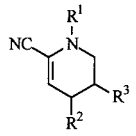
Entry	Substrate	Reagents/Conditions	Products	% Yield	Ref.
1				*endo:exo* >20:1	117
	356	**373**; R^1 = Me, Et, Bn; R^2 = H, Me, OMe; R^3 = H, Me, [C=CH_2]	CH_2Cl_2, rt, 12 kbar or Neat, rt, 12 kbar or PhMe or mesitylene, reflux	**374** 28-89%	
2				*endo:exo*	112,117
	375; R^1 = H, Me, Ph; R^2 = H, Me; R^3 = H, Ph	**376**; R^4 = Et, Bn; R^5 = H, Me	Neat, 60 °C; or CH_2Cl_2, rt, 12 kbar or CH_2Cl_2, 40 °C	**377** 52-82%	> 20 : 1
3					112,117, 205
	378	**379a**; R^1 = Et, R^2 = H (5 eqiv., Dioxane, 100 °C, 12 h)		**380a** *Yield* 56%	*endo : exo* >20 : 1
		(10 eqiv., Dioxane, 100 °C, 12 h)		**380a** 89%	>20 : 1
		379b; R^1 = R = OCH_3 (10 eqiv., CH_2Cl_2, 25 °C, 72 h)		**380b** 79%	>20 : 1
4			CH_2Cl_2, rt, or CH_2Cl_2, rt, 6 kbar		114
	381a; R^1, Ph, Me; R^2 = Ph, Me	**382**; R^3 = OEt, OBn; R^4 = H, Me, OAc; R^5 = H, Me, OAc		**383** 50-80% *endo:exo* > 20:1	
5			CH_2Cl_2, (21, or 10 or 40 °C) or C_6H_6, 80 °C	 major minor	112,115
	371	**384** R^1 = OMe, OEt, OBn, Ph, *p*-$H_3CC_6H_4$; R^2 = H, Me, Ph, OAc; R^3 = H, Me, Ph, OAc, R^2R^3 = [C=CH_2]		*Endo* **385** *exo* 42-91%	*endo : exo ratio* >20:1 for most cases
6			Neat, 90 °C or C_6H_6, 90 °C	 **388** (α) major **(389)**β minor	137
	386	**387**; R = OEt, Ph, $COCH_3$, CO_2CH_3		75% 1 : 0	

Table 5 (*continued*)

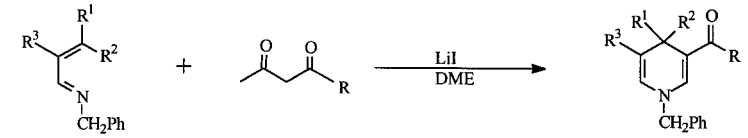
Entry	Substrate	Reagents/Conditions	Products	% Yield	Ref.
7		 Neat, rt, or C_6H_6, reflux or PhMe, reflux	 α  β	*cis* + *trans* 25-92%	110, 113
	390 R^1 = OAc, Ph, CO_2Et	**391** R^2 = *n*-Bu, Ph, OEt, CO_2Me; R^3 = H, Me, Ph	**392**		
8		 Closed Conditions: 75 , 90, 120 °C or C_6H_6, 90 °C	 major  minor	36-91%	108,137
	393 R^1 = Ph, *p*-MeC_6H_4; R^2 = H, Me	**394** R^3 = OEt, Ph, *n*-Bu, $COCH_3$, CO_2CH_3, *p*-BrC_6H_4, *p*-$O_2NC_6H_4$; or **394** = 2,3-dihydrofuran; 3,4-dihydro-2*H*-pyran; *trans*-β-methylstyrene; *cis*-β-methylstyrene	**395**		

yields of products in the DA reactions of quinolinetriones with 1-azadienes on silica gel.[127] *p*-Toluenesulfonic acid has been used in the preparation of 3,5-disubstituted pyridines via 1-azadiene DA reactions.[97,173,174] Lithium iodide has been successfully used as a catalyst in the preparation of 1,4-dihydropyridines **398** by the reaction of azadienes **396** with β-dicarbonyl systems **397** (Scheme 30).[210,211]

Often Lewis acids have promoted the [3+2] cycloaddition processes of 1-azadienes over their corresponding DA reactions. Echavarren has reported the formation of the [3+2] cycloadduct **400** when azadiene **399** was treated with benzoquinone in the presence of BF_3.[126] High yields of the [3+2] cycloadducts have been obtained by Fillion upon the reaction of α,β-unsaturated dimethylhydrazones with benzoquinone or quinoline-5,8-diones in the presence of boron trifluoride or trifluoroacetic acid (Scheme 31).[179]

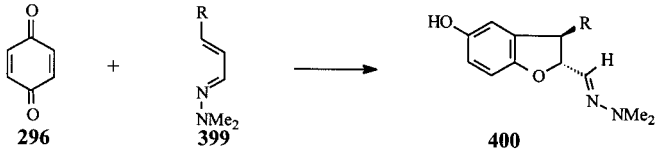
The [3+2] cycloadduct was the major product observed by Avendano in the reaction of methacrolein dimethylhydrazone with 3-nitroquinolinetrione when the reaction solvent was changed from THF to the more polar CH_3CN–H_2O mixture.[186] The DA reaction rates have been increased when transition metals such as copper[212] or tungsten[124] have complexed with diene[213] or dienophiles.[124] The use of ultrasound[128,181,182,184] or microwave[106] in promoting [4+2] cycloaddition reactions have been reported. A number of investigators have used irridation to generate 1-azadienes and facilitate their DA reactions.[83,85,88,212,214]

The application of flash vacuum pyrolysis either in the absence or the presence of catalysts have been used in 1-azadiene DA reactions.[101,215] Recently Blechert and coworkers have introduced cationic radicals such as **402**, an elegant alternative to the classical 1-azadiene system. The species such as **402** act as an azadiene and are generated through a single electron transfer (SET) process either by anodic oxidation or by treatment with photochemically excited triarylpyrylium tetrafluoroborate. Cycloaddition of



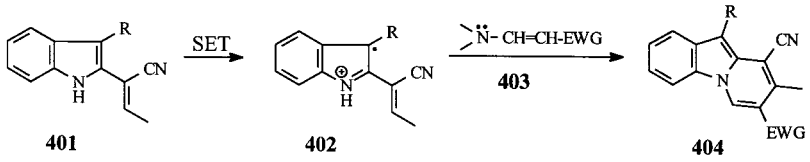
396; R^1 = Me, Et, Ph; R^2 = H, Me; R^3 = H, Me — **397** R = Me, OCH_3, NHR — **398** 27-72%

Scheme 30.



296 **399** **400**

Scheme 31.



Scheme 32.

402 with dienophiles produces adducts **404** in 22–52% yield (Scheme 32).[125,129]

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Biographical sketch

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Mohammad Ahmadian was born in Damghan, Iran. He received his BS degree in chemistry from Pars College, Tehran in 1980. After four years of work in the pharmaceutical industry, he returned to school and in 1986 he received his MS degree in organic chemistry from Tehran Teachers Training University. After teaching chemistry at Kaashaan University in Iran for four years, he began his graduate studies at Ball State University in Indiana where he received his MS degree in organic chemistry under the supervision of Professor M. Behforouz in 1992. He then attended Purdue University and completed his PhD degree in organic chemistry in 1997 under the direction of Professor Donald E. Bergstrom in the Department of Medicinal Chemistry, School of Pharmacy. After two years of a postdoctoral fellowship with Dr John A. Secrist III at The Southern Research Institute in Birmingham, AL, he moved to CERUS Corporation in Concord, CA, where he is now working as a Research Chemist. His research interest is in the area of heterocyclic chemistry including nucleic acids and Diels–Alder reactions of azadienes.