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Recent developments in imino Diels–Alder reactions

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1. Introduction

Hetero Diels–Alder reactions are becoming a mainstay of heterocycle and natural product synthesis.[1] Among these reactions, the imino Diels–Alder provides a rapid means of construction of functionalized heterocyclic rings with control of regio-, diastereo- and enantio-selectivity.[2–13] The key to realizing this potential has been the substantial progress in recent years to activate the imine system toward cycloaddition. The extent of recent advances in imino Diels–Alder reaction methodology suggests that a comprehensive update review of this method is in order.

This review covers three basic variants of the imino Diels–Alder reaction (Fig. 1). In the first and most common method the imine function appears as the dienophile. In

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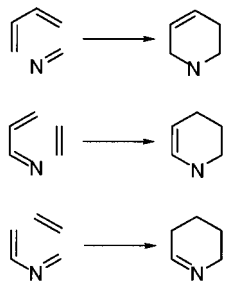


Figure 1.

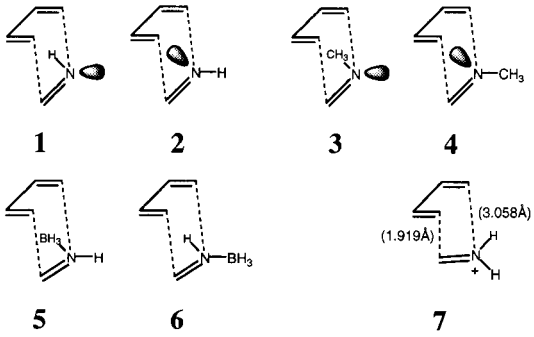


Figure 2.

the second and third variants the imine is found in the diene as either 1-azadiene or 2-azadiene structures.

Imines are readily available from the corresponding aldehydes and ketones. This allows a variety of imine dienophile substrates to be available. The imine dienophile generally needs to be activated or used in conjunction with active dienes.

Of the many heterodienes used in organic synthesis among the most widely used are the azadienes. A limitation to the application of azadienes relative to the more commonly used oxodienes is that azadienes generally require some form of activation to achieve general synthetic utility. The advance of the azadiene imino Diels–Alder reaction to the status of a general synthetic method owes much to the development of methods to activate the azadiene system. With appropriate substitution both 1-aza-1,3-butadienes and 2-aza-1,3-butadienes are reactive as either electron rich or electron deficient Diels–Alder dienes. Reviews featuring the general synthetic utility of azadienes[14] and their utility in the Diels–Alder reaction specifically[15–17] have appeared in recent years.

1.1. Mechanistic aspects

A given Diels–Alder reaction may be described as conforming to one of three general $\pi 4s+2s\pi$ cycloaddition types. These types are the 'normal' $HOMO_{diene}$-controlled reaction, the neutral reaction and the 'inverse electron demand' $LUMO_{diene}$-controlled Diels–Alder reaction.[18–20] The cycloaddition type and corresponding reaction rate correlate with the magnitude of the smallest diene–dienophile HOMO–LUMO energy difference. Electronic and structural features of the reagents determine the size of this energy difference and consequently the nature of the reaction.

The reaction of formaldimine with butadiene has been modeled by ab-initio molecular orbital calculations using the 3-21G and MP2/6-31G* basis sets.[21–25] It was found that having the nitrogen lone pair *exo* in the transition state is 4.3–5.3 kcal/mol more stable than the *endo* orientation (structures **1** vs. **2**, Fig. 2). The *endo*-lone pair is unfavored due to repulsion between lone pair and butadiene π-electrons. In the favored transition state, **1**, the C6–N1 bond formation is more advanced than C2–C3 bond formation, indicating that the dienophile HOMO/diene LUMO interaction is important. The HOMO of formaldimine has a larger coefficient at nitrogen than at carbon. There is also a 20° twist in the C6–N1–C2–C3 dihedral angle, which is believed to be caused by attraction between the imino hydrogen and the butadiene π-electrons at C4 and C5. Modeling of *N*-methylformaldimine shows that the *exo*-lone pair is still favored by 3.3–4.1 kcal mol^{-1} (structures **3** vs. **4**).

Activation of imines by electron withdrawing carbonyl and sulfonyl groups is well known. Ab initio modeling show that carbonyl groups are better activators than sulfonyl groups and that having either on the carbon side of the imine activates the dienophile more than having them on the nitrogen side.[23] An interesting conclusion of these studies is that having the sulfonyl group in the *endo*-position does not seem to stabilize the transition state through secondary overlap or electrostatic interactions, and, therefore, *exo*-cycloaddition may be favored. In reactions involving acylimines, *endo* to N-acyl group is the preferred orientation. When there are acyl groups on carbon and nitrogen, the N-acyl group generally takes the *endo* position.

In contrast to thermal reactions, theoretical examination of the reaction between BH_3-coordinated formaldimine and butadiene shows that C2–C3 bond formation is more advanced than the N1–C6 bond formation (structures **5** vs. **6**). Furthermore, the transition state energy is lower; there is an increase in asynchronicity, and BH_3 in the *exo* position is favored by 3.6–4.4 kcal mol^{-1}. Also, to represent Bronsted acid activation, reaction with formaldiminium ion was calculated. In this case, the asynchronous transition structure shows C2–C3 and N1–C6 bond lengths of 1.919 and 3.058 Å, respectively, essentially indicating a stepwise reaction. For both types of acid activation, solvated systems were modeled and showed little difference in transition state energies or stereochemical preferences as compared to the respective gas-phase reaction models.

Thus, the theoretical and experimental evidence (vide supra) shows that cycloaddition with imino dienophiles can be concerted or stepwise. The stepwise mechanism involves a tandem Mannich–Michael reaction closely related to the aza Diels–Alder reaction and has been included in this review for a more complete coverage.

The most commonly utilized Diels–Alder type in organic synthesis is the $HOMO_{diene}$-controlled 'normal' type in which an electron-deficient dienophile is used (Fig. 3).

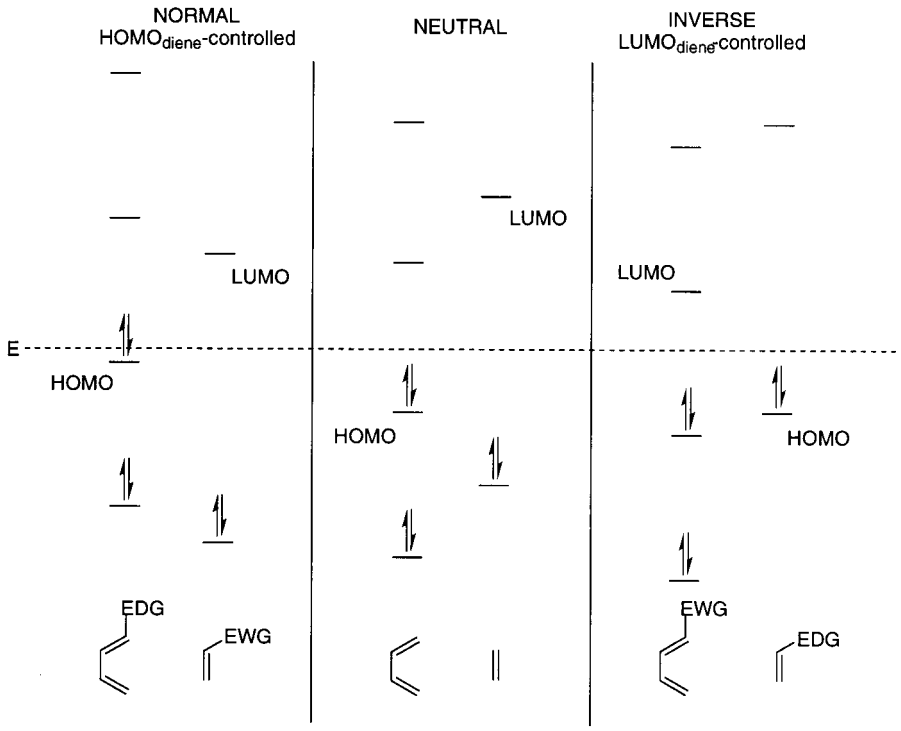


Figure 3.

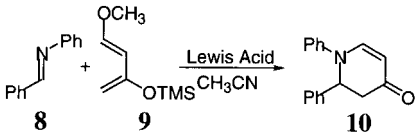
Simple 1- and 2-azadienes, due to their intrinsically electron-deficient nature favor participation in 'inverse electron demand' LUMO$_{diene}$-controlled Diels–Alder reaction.[18–20] By appropriate complementary azadiene and dienophile substitution patterns, however, both 'normal' HOMO$_{diene}$-controlled aza Diels–Alder reactions and 'inverse' LUMO$_{diene}$-controlled aza Diels–Alder reactions have been developed.

Computational studies in ab-initio STO-3G and MP2/6-31G*//MP2/6-31G* and hybrid density functional theory B3LYP/6-31G*//B3LYP/6-31G* of both 1-aza-1,3-butadiene and 2-aza-1,3-butadiene Diels–Alder reactions with ethylene suggest that in both cases the reactions are distinctly concerted and asynchronous.[24,26,27]

2. Imine dienophiles

2.1. Lewis and Bronsted acid catalyzed imino Diels–Alder reactions

Much of the activity in imino Diels–Alder reactions has involved activation by Lewis acids. Rare earth metal triflates have been investigated under various conditions. For example, Yb(OTf)$_3$, Sc(OTf)$_3$, and In(OTf)$_3$ are effective and can tolerate the presence of small amounts of water (Eq. (1), Table 1).[28–32]



(1)

These catalysts have been successful with a variety of substrates. Fig. 4 shows several aldehydes that were used to form imines in situ with aniline or benzylamine for reactions catalyzed by In(OTf)$_3$.[29] Yields were moderate to good, although thiophene derivative **15**, did not react. Interestingly, a competition between carbonyl and imino Diels–Alder reactions showed that In(OTf)$_3$ selectively catalyzed the latter reaction (Eq. (2)).

Table 1. Rare earth metal catalysts for the imino Diels–Alder reaction

Entry	Lewis acid	Reaction conditions	Yield of **10** (%)
1	Yb(OTf)$_3$, (10 mol%)	rt	93
2	Sc(OTf)$_3$, (10 mol%)	rt	99
3	In(OTf)$_3$, (0.5 mol%)	−20°C	93

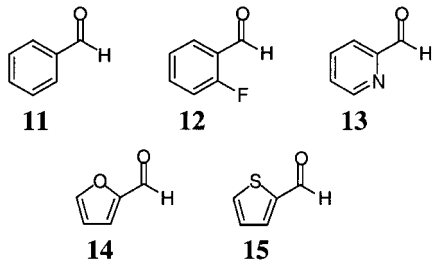
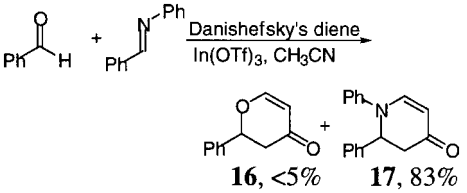


Figure 4. Aldehydes examined in the aza Diels–Alder reactions catalyzed by In(OTf)$_3$.

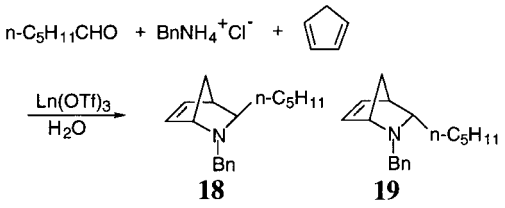


(2)

Lanthanide(III) triflates have been shown to catalyze aza Diels–Alder reactions in water (Eq. (3), Table 2).[32] The reactions were carried out at pH 5–7 and 0.25 M in the presence lanthanide Lewis acids. Praseodymium(III) triflate, niobium-(III) triflate, and neodymium(III) triflate gave the highest yields while gadolinium(III) triflate gave the lowest. Under the same conditions, but in 0.25 M magnesium chloride or lithium chloride, no catalytic effect was found, indicating that the accelerations seen with the lanthanides were not due to salt effects. With the more reactive imines of formaldehyde and methylester of phenylalanine, cycloaddition occurred with acyclic dienes and cyclohexadiene (Table 3).

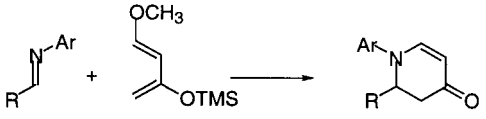
Table 2. Diels–Alder reactions in water catalyzed by $Ln(OTf)_3$

Entry	$Ln(OTf)_3$	**18**:**19**	Yield (%)
1	–	73:27	4
2	$La(OTf)_3$	72:28	47
3	$Pr(OTf)_3$	74:26	68
4	$Nd(OTf)_3$	76:24	57
5	$Gd(OTf)_3$	73:27	19
6	$Dy(OTf)_3$	74:26	49
7	$Er(OTf)_3$	72:28	46
8	$Yb(Otf)_3$	74:26	62



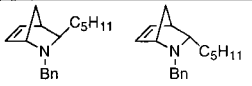
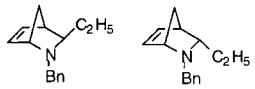
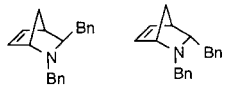
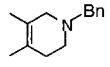
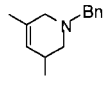
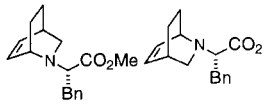
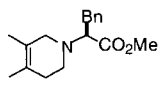
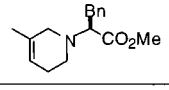
18 **19** (3)

Bronsted acids continue to receive attention.[33] Good yields were obtained with HBF_4, TsOH, and CF_3CO_2H in the cycloaddition of imines and Danishefsky's diene (Eq. (4), Table 4). A survey of solvents including water showed that highest yields were obtained in acetonitrile and methanol. The reactions occurred whether the imine was preformed or generated in situ. Generally, 0.2 equiv. of Bronsted acid and 10 equiv. of water were added. The reaction also worked well in water in the presence of the surfactant sodium dodecyl sulfate/HBF_4.



20 (4)

Table 3. Aqueous aza Diels–Alder reactions catalyzed by lanthanide triflates

Entry	Lewis Acid	Aldehyde	Amine	Diene	Products	Ratio	% Yield[a]
1	$Pr(OTf)_3$	$CH_3(CH_2)_4CHO$	$BnNH_3^+Cl^-$			74:26	68(7)
2	$La(OTf)_3$	CH_3CH_2CHO	$BnNH_3^+Cl^-$			71:29	64(4)
3	$Yb(OTf)_3$	$PhCH_2CHO$	$BnNH_3^+Cl^-$			80:20	72(3)
4	$Yb(OTf)_3$	PhCHO	$BnNH_3^+Cl^-$		No product		7(0)
5	$Ln(OTf)_3$	$CH_3(CH_2)_4CHO$	$BnNH_3^+Cl^-$		No product		
6	$Ln(OTf)_3$	$CH_3(CH_2)_4CHO$	$BnNH_3^+Cl^-$				
7	$Nd(OTf)_3$	CH_2O	$BnNH_3^+Cl^-$				93(23)
8	$Yb(OTf)_3$	CH_2O	$BnNH_3^+Cl^-$				92(54)
9	$Nd(OTf)_3$	CH_2O	L-phenylalanine methyl ester			25:75	84(27)
10	$Nd(OTf)_3$	CH_2O	L-phenylalanine methyl ester				98(58)
11	$Nd(OTf)_3$	CH_2O	L-phenylalanine methyl ester				96(37)

[a] The numbers in parentheses are percent yields for the uncatalyzed reactions. (%)

Table 4. Substituents and conditions for reaction Eq. (4)

Entry	R	Ar	Reaction condition[a]	Yield of **20** (%)
1	Ph	Ph	A	98
2	*p*-$NO_2C_6H_4$	Ph	A	87
3	*p*-$CH_3C_6H_4$	Ph	A	95
4	PhCH=CH	Ph	A	89
5	Ph	*p*-$CH_3OC_6H_4$	A	90
6	Ph	*p*-$CH_3OC_6H_4$	B	88
7	*p*-$CH_3C_6H_4$	*p*-$CH_3OC_6H_4$	B	86
8	PhCH=CH	*p*-$CH_3OC_6H_4$	B	86
9	*c*-C_6H_{11}	*p*-$CH_3OC_6H_4$	B	75

[a] Reaction condition A: HBF_4 (0.1 equiv.), H_2O (10 equiv.), CH_3OH, −40°C, 30 min. Reaction condition B: HBF_4 (0.2 equiv.), sodium dodecylsulfate (0.4 equiv.), H_2O, rt, 1 h.

HCl and trifluoroacetic acid have been used with cyclopentadiene and 2,3-dimethylbutadiene in DMF. Reactions of $PhCH_2N{=}CHCO_2Et$ catalyzed by HCl in DMF are summarized in Table 5.[25] Cyclopentadiene gave good yields while acyclic dienes gave moderate yields. Cyclohexadiene gave low yields of the cycloadduct. Regioselectivity was good for non-symmetrical dienes and the reaction was highly *cis*-selective. It was discovered that 0.1–1 equiv. of water gave the highest yields and that reactions in water solvent gave lower yields. Replacing the small amounts of water with methanol gave high yields, as well. It was proposed that water and methanol activation was due to hydrogen bonding to the imine as shown in Fig. 5. The hydrogen bonding reduces the rotation of the iminium ion about the π bond and increases the effective concentration of the 2π-component or stabilizes the 6π-transition state.[34]

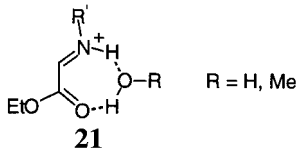
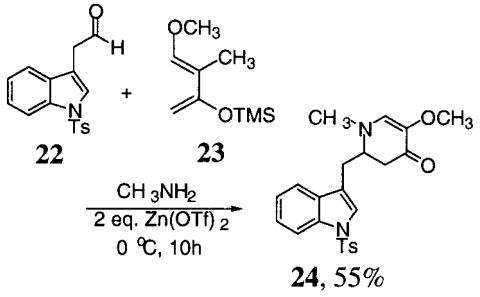


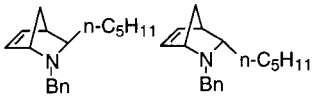
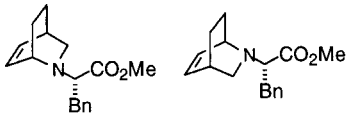
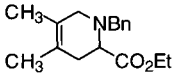
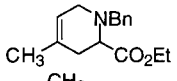
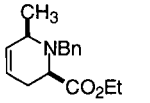
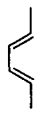
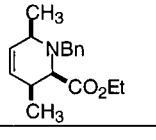
Figure 5. Mode of catalysis with water or methanol under acidic conditions.

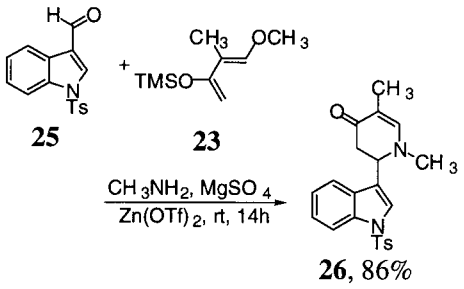
One of the potential problems of imino cycloaddition occurs when the imine has acidic α-hydrogens. In this case, Lewis acid catalysts may promote enamine formation rather than cycloaddition. However, mild Lewis acids, such as $Zn(OTf)_2$ and TMSOTf have been found to minimize this difficulty. Eq. (5) shows that indole acetaldehyde derived imine, **22**, gives a moderate yield of the cycloaddition product with $Zn(OTf)_2$ as catalyst. In contrast, Eq. (6) shows that reaction with indole derived imine **25**, which lacks α-hydrogens, gives higher yield.[35,36]



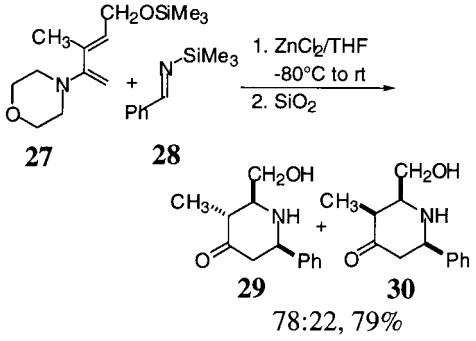
(5)

Table 5. HCl catalyzed reactions of $PhCH_2N{=}CHCO_2Et$ with various dienes in DMF

Entry	Diene	Products	Ratio (exo:endo)	Yield(%)
1			69:31	89
2			27:73	21
3				47
4				43
5				38
6				36



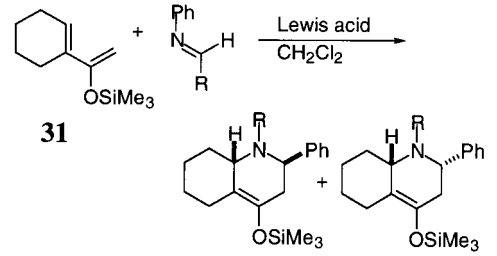
(6)



(7)

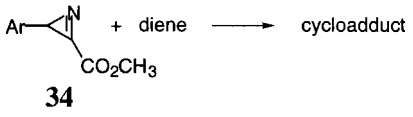
Another potential weakness of the imino Diels–Alder reaction is the difficulty removing unwanted nitrogen substituents after cycloaddition. Benzyl groups can be removed by hydrogenation, but this is not always trivial. The problem can be avoided by using silylimines and activated dienes. In this case, the silyl group is removed by filtration through a short silica gel column following cycloaddition, (Eq. (7)).[37]

Choice of Lewis acid can have a strong influence on the *endo–exo* selectivity of the reaction. For substrate **31**, the cycloaddition catalyzed by aluminum chloride was *endo*-selective and with *t*-dimethylsilyl triflate, *exo*-selective (Eq. (8)).[38]



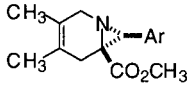
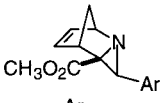
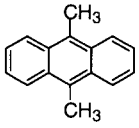
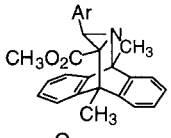
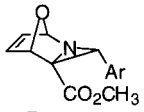
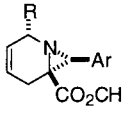
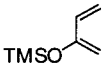
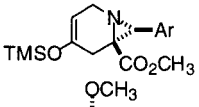
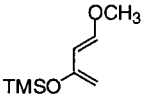
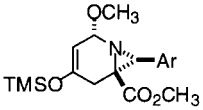
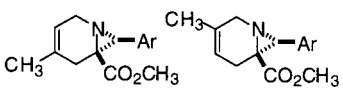
Lewis Acid	exo:endo	Yield (%)
1 eq. $AlCl_3$	2:>98	71
0.1 eq. TBDMSOTf	>98:2	84

(8)



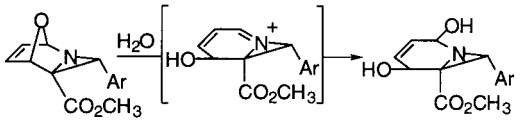
(9)

Table 6. Azirine Diels–Alder cycloadditions

Entry	Diene	Cycloadduct	Yield(%)
1			40
2			65
3			60
4			100
5	 R=OAc OCH_3 CH_3		48 60-63 46-78
6			42
7			25-65
8			69 2.7:1

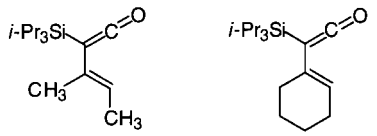
Azirines continue to be developed as useful dienophiles. The strain of the ring increases the reactivity of this system. In **34** which undergoes cycloaddition with a number of dienes there is an additional activation by the ester group (Eq. (9), Table 6).[39,40]

The reaction with cyclopentadiene and azirine **34** was *endo*-selective with respect to the methine carbon, whereas with furan, the cycloaddition was *exo*-selective (entries 2 and 4, respectively). Anthracene did not undergo cycloaddition with azirine, but the more electron-rich 9,10-dimethylanthracene gave 60% of the cycloadduct. The unstable cycloadduct from furan underwent ring opening when exposed to water (Fig. 6). High stereo- and regioselectivities were observed with unsymmetrical dienes with the exception of isoprene, which gave a 2.7:1 ratio of regioisomers (entry 8).



35 **36** **37**

Figure 6. Ring opening of unstable aziridine/furan cycloadduct **2**.



38 **39**

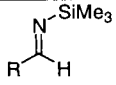
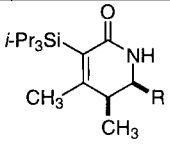
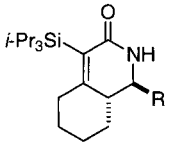
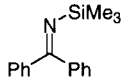
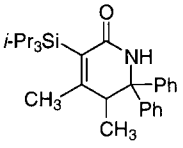
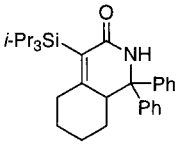
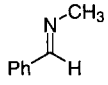
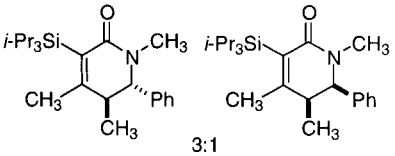
Figure 7.

Silyl vinylketenes have been shown to undergo imino Diels–Alder cycloadditions with nonenolizable imines (Fig. 7, Table 7).[41] It was found that Lewis acid activation was not necessary. Silylimines and alkylamines gave good yields of the cycloadduct, whereas enolizable imines and sterically demanding imines derived from substituted amines gave no cycloaddition. The reactions involving silylimines were highly stereoselective. Acyclic silyl vinylketene **38** gave *cis*-substituted cycloadducts with silylimines via *endo*-approach while cyclic silyl vinylketene **39** gave *trans* substitution via *exo*-approach. In contrast, the reaction of alkylimine with the acyclic silyl vinylketene **38** gave a 3:1 ratio of *cis–trans* isomers. The carbon–silicon bond in the cycloadducts was cleaved with methanesulfonic acid.

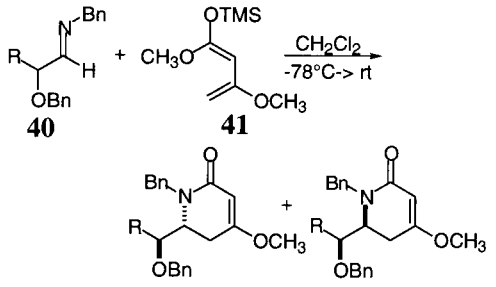
2.2. Stereoselective cycloaddition

2.2.1. Imines derived from chiral aldehydes. Stereoselective cycloadditions of imines and dienes have been extensively investigated recently. Some of the first stereoselective cycloadditions were of imines derived from α-alkoxyaldehydes.[42,43] Cycloaddition of α-alkoxy imine **40** with diene **41** gave the best selectivities when promoted by Et_2AlCl (Eq. (10)). Two equivalents of Et_2AlCl gave the highest ratios of stereoisomers. The *tert*-butyl group gave the highest selectivity. With α-siloxy imine **44**, $Zn(OTf)_2$ and TMSOTf gave the cycloadduct **47** as the major isomer, whereas $TiCl_4$ gave the reverse selectivity (Eq. (11)).[44,45] With diene **48**, similar selectivity was observed with $TiCl_4$, but poor selectivities were seen with $Zn(OTf)_2$ and TMSOTf (Eq. (12)).

Table 7. Imino Diels–Alder reactions with vinylketenes **38** and **39**

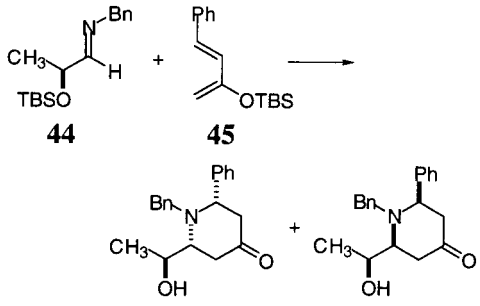
Entry	Imine	Ketene	Product(s)	Yield(%)
1	 R = Ph	**38**		79-83
2	= CH=CHPh			78
3	R = Ph			91
4	= CH=CHPh	**39**		73
5	= *t*-Bu			56
6		**38**		79
7		**39**		66
8		**38**	 3:1	71

Reaction conditions: ketene and 1.5 equiv. of imine in refluxing acetonitrile or at room temperature with no solvent.



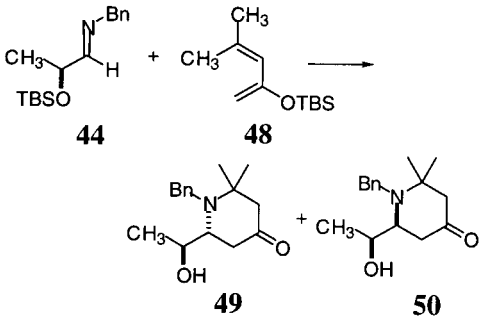
(10)

2.eq. Et_2AlCl	R = *n*-pentyl	10:90	55%
2.eq. Et_2AlCl	R = *i*-propyl	40:60	58%
2.eq. Et_2AlCl	R = *t*-butyl	1:99	75%



(11)

TMSOTf/tol	78:22	97%
$Zn(OTf)_2$/*n*-hexane	89:11	93%
$TiCl_4$/*i*-PrCN	<2:>98	87%



(12)

1 eq. TMSOTf/CH_2Cl_2	43:57	80%
1 eq. $Zn(OTf)_2$/*n*-hexane	43:57	75%
1 eq. $TiCl_4$/*i*-PrCn	9:91	65%

Chelation and non-chelation control models can be used to rationalize the selectivity of many of these cycloadditions (Fig. 8). Nonchelation control structure **52** gives *anti*-product **51** whereas chelation control structure **53** gives the *syn*-cycloadduct **54**.

The reaction of dibenzyloxy glyceraldehyde *N*-benzylimine, **55**, and Danishefsky's diene gave good selectivities in the presence of ZnI_2 (Eq. (13)).[46] The acetonide-protected compound, **58**, gave low selectivity under the same conditions (Eq. (14)). Acetonide imine **61** gave high diastereoselectivity with Et_2AlCl.[41] In this case, a more reactive diene was used at a lower temperature (Eq. (15)).

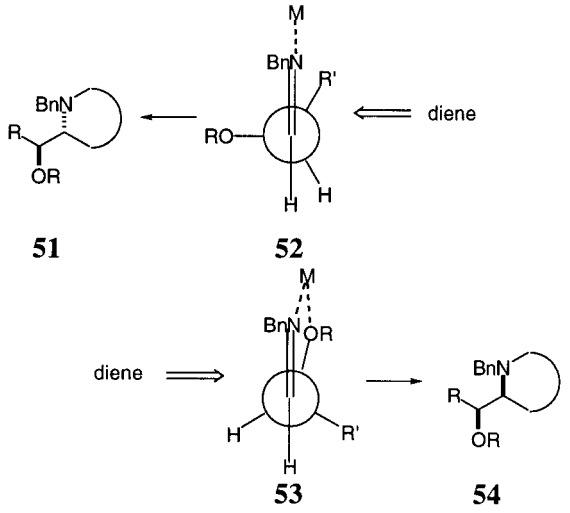
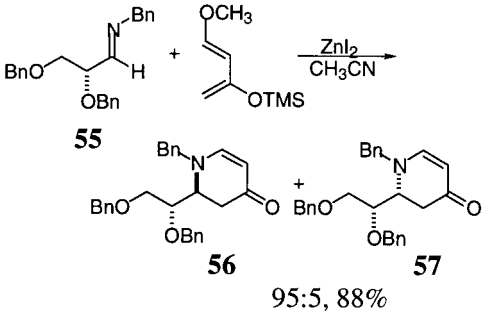
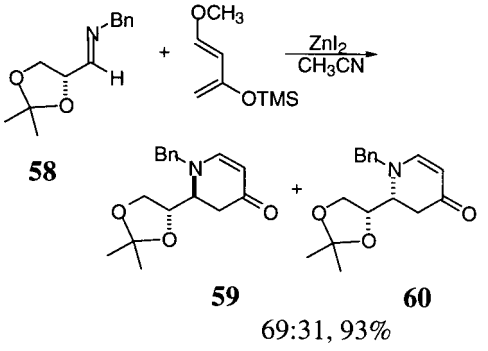


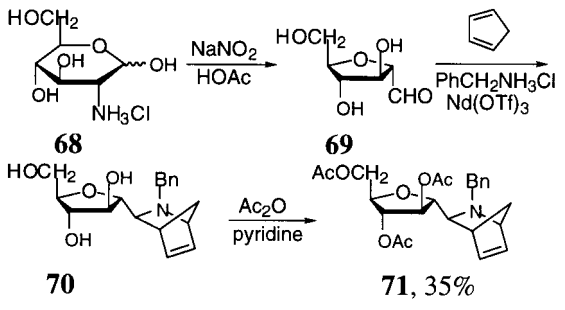
Figure 8.



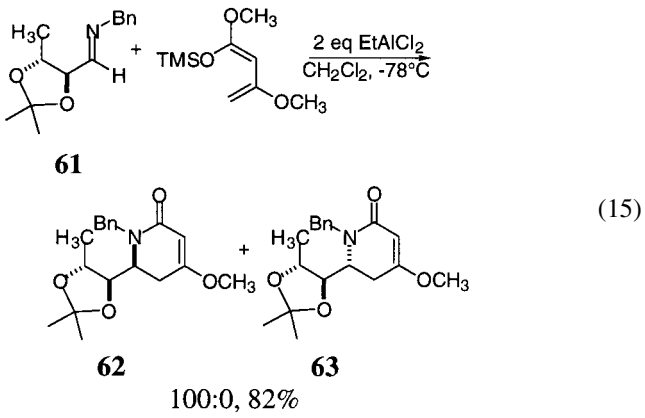
(13)



(14)

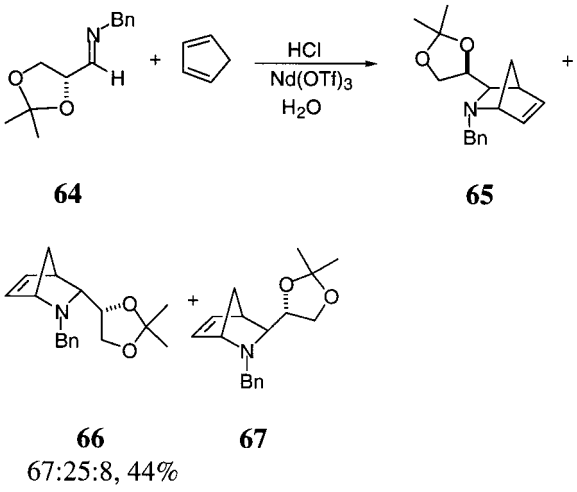


Scheme 1. Synthesis of aza-sugar **71**.



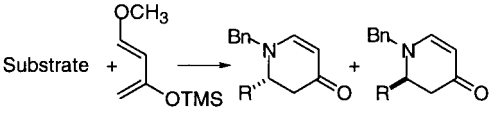
(15)

The iminium ion of acetonide protected imine **64**, undergoes $Nd(OTf)_3$ catalyzed cycloaddition in water to give three diastereomers in moderate selectivity and yield (Eq. (16)).[47] This approach was successful in the synthesis of aza-sugars. Aza-sugar **71**, for example, was synthesized in 35% yield from **68** (Scheme 1).



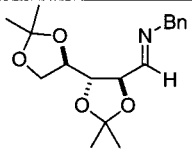
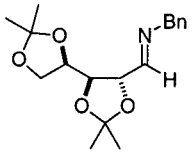
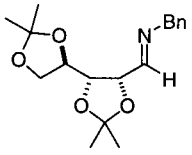
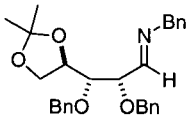
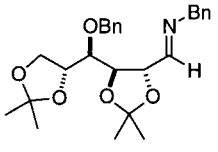
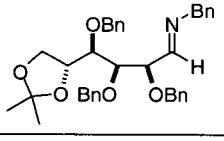
(16)

Imines derived from a variety of protected forms of pentose and hexose also undergo cycloaddition (Eq. (17), Table 8).[48–50] Good to excellent diastereoselectivities were



(17)

Table 8. Imino cycloadditions with protected pentose and hexose substrates

Entry	Substrate	Reaction Conditions	Product Ratio	Yield(%)
1		$ZnCl_2$/THF	6:94	79
2		$ZnCl_2$/dioxane	67:33	65
3		$ZnCl_2$/THF	90:10	61
4		$ZnCl_2$/CH_3CN	95:5	76
5		$ZnCl_2$/THF	92:8	72
6		$ZnCl_2$/THF	0:100	76

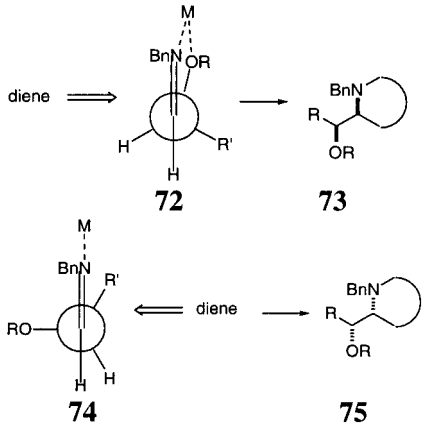
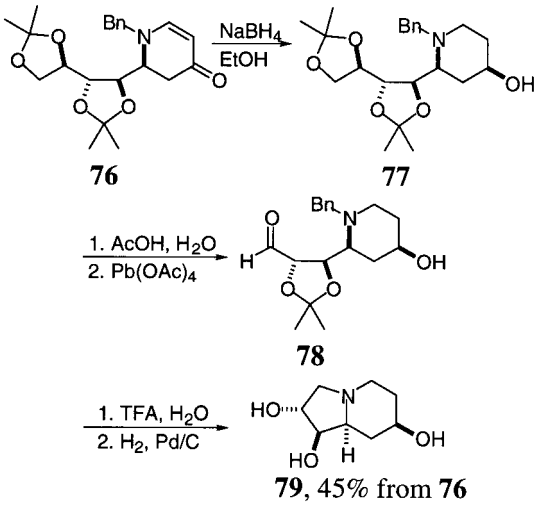
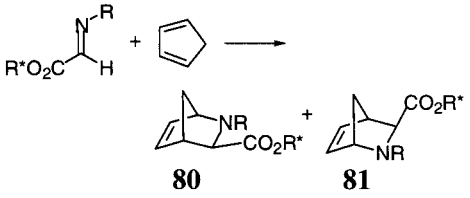


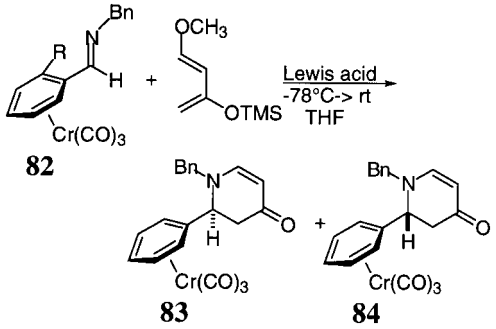
Figure 9.



Scheme 2.



(18)



(19)

Table 10. Chiral tricarbonyl(η^6arene) chromium(0) complexes as chiral auxiliaries for imino Diels–Alder reactions (Eq. (19))

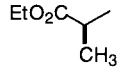
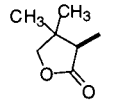
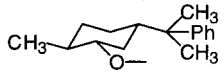
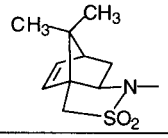
Entry	R	Lewis acid	**83**:**84**	Yield (%)
1	OCH_3	$ZnCl_2$	83:17	82
2		$SnCl_4$	86:14	82
3		$TiCl_4$	87:13	57
4		$MgBr_2$	87:13	24
5		Et_2AlCl	85:15	88
6	Cl	$ZnCl_2$	89:11	88
7		$SnCl_4$	>98:<2	98
8	F	$SnCl_4$	98:2	89
9	CH_3	Et_2AlCl	>98:<2	82

observed. The selectivities can be rationalized by chelation control of the α-alkoxy oxygen (Fig. 9). Other oxygens may play a minor role as shown by the difference in selectivity between entries 2 and 3. There seems to be a slight increase in selectivities when the α-alkoxy group is protected as an acyclic benzyl rather than a cyclic acetonide (entries 3 and 4). The cycloadduct **76** has been converted to indolizidines as well as quinolizidines as exemplified by Scheme 2.

Chiral auxiliaries (substrate control) have been tested using imines derived from glyoxylates.[51–53] Moderate ratios and yields have been obtained with lactate, pantolactone, and 8-phenylmenthol auxiliaries (Eq. (18), Table 9). The chiral auxiliaries can be removed by mild hydrolysis (LiOH, $THF–H_2O$) or with excess Grignard reagents.

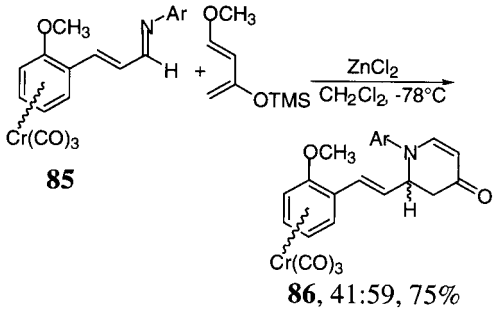
Chiral tricarbonyl (η^6Arene) chromium(0) complexes have been found to undergo selective imine cycloaddition (Eq. (19), Table 10).[54,55] Moderate to excellent ratio and yields

Table 9. Cycloaddition of chiral imines of glyoxylates (Eq. (18))

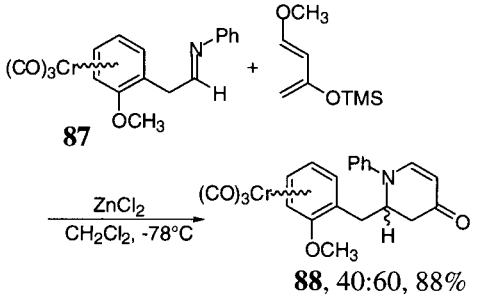
Entry	R*	R	Reaction Conditions	**80**:**81**	Yield(%)
1		Ts	0.1-0.3 eq. Et_2AlCl/tol, -78°C	12:88	50-60
2		Ts	0.1-0.3 eq. Et_2AlCl/tol, -78°C	85:15	50-60
3		CH_2Ph	TFA, $BF_3.Et_2O$ CH_2Cl_2, -78°C	12:88[a]	81
4		Ts	0.5 eq. TiCl4/tol, tol, -78°C	80:20	38

[a] *Exo*:*endo*, 91:9.

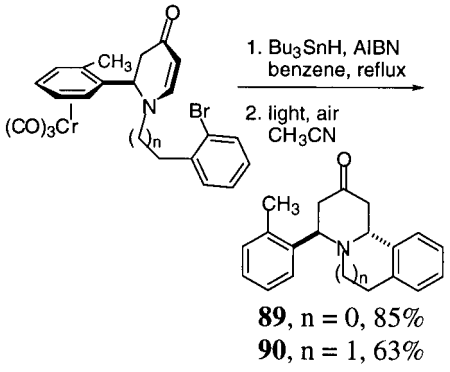
were found. Having a methoxy-group in the *ortho*-position of the aryl ring seemed to lower the selectivity slightly. Extending the distance between the arene chromium group and imine by a methylene or ethenylene group significantly lowered the selectivity (Eqs. (20) and (21), respectively). The cycloadduct can be cyclized via radical reaction to give the *trans* 6,5- and 6,6-ring junction in high selectivity leading to the heterocyclic compounds **89** and **90** (Eq. (22)).



(20)

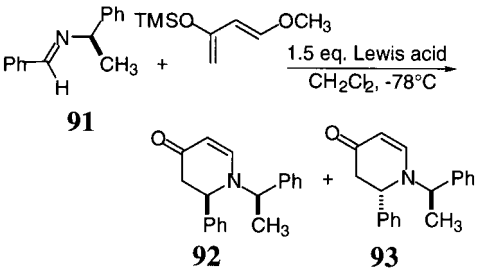


(21)



(22)

2.2.2. Imines derived from chiral amines. Simple chiral imines derived from α-phenylethylamine and alkyl or aryl aldehydes can give high selectivities and moderate yields.[56–58] Several Lewis acid catalysts have been examined with these substrates. Boron, titanium, and zinc Lewis acids gave the highest selectivities and yields (Eq. (23), Table 11). The chiral phenylethyl group was removed by hydrogenation. Acyl-activated chiral imine **94**, derived from alkyl glyoxylate, gave better selectivities and allowed less reactive dienes to undergo cycloaddition (Fig. 10, Table 12).[34,58–61] Cyclopentadiene gave the best ratios and yields. Cyclohexadiene and the acyclic dienes gave moderate ratios and yields. Of note was that under reaction conditions A, high *exo–endo* ratios of cycloadducts of cyclopentadiene and cyclohexadiene were obtained. The mechanistic details of the face-selectivity of these reactions have yet to be determined. The nitrogen can be deprotected with loss of the auxiliary chiral center by hydrogenolysis.



(23)

Table 11. Cycloadditions with α-phenylethylimine (Eq. (23))

Entry	Lewis acid	**92**:**93**	Yield (%)
1	BF_3Et_2O	94:6	41
2	$B(Oph)_3$	96:4	61
3	$MeAl(OPh)_3$	90:10	23
4	$ZnCl_2$	96:4	75
5	$TiCl_2(O\text{-}I\text{-}Pr)_2$	95:5	56

Another strategy was to use an amine with a second Lewis basic site.[57,58,62,63] This approach has been tested using alkoxy, siloxy, ester, and alcohol functionalities as part of the auxiliary (Eq. (24), Fig. 11, Table 13). A variety of Lewis acids were examined. The selectivities for substrates **98**, **99**, **101**, and **102** can be rationalized by the chelation controlled conformation (Structure **103**, Fig. 12). On the other hand, the selectivities for aminoester derived imines **100** seem more complicated. There is evidence that this type of cycloaddition is predominantly a tandem Mannich–Michael reaction. The working model proposed for $BF_3{\cdot}Et_2O$ and $EtAlCl_2$ promoted reactions is represented by **104**. The Lewis acid coordinates only to the imine and not a cyclic chelation with the carbonyl group giving a Felkin–Anh type conformation. Unexpectedly, $ZnCl_2$ and $TiCl_4$ gave the same major isomers. The working model **105** was proposed. Here, the cyclic chelation is in effect; however, there is evidence that on coordination, the imine double bond undergoes isomerization to the *cis*-form. On the other hand, two equivalents of $ZnCl_2$ give the opposite selectivity. This is rationalized by the acyclic complex **106**. The imine and carbonyl are coordinated by two separate $ZnCl_2$ molecules, a Felkin–Anh conformation is formed, and the imine is in the *cis*-geometry. There has been extensive investigation of cycloaddition of imines derived from aminoesters. The ester chiral auxiliary can be removed in several steps with the loss of the original chiral center (Eq. (25)).[62]

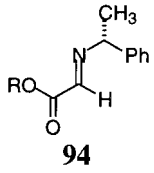
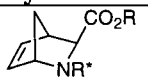
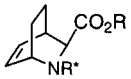
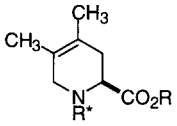
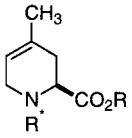
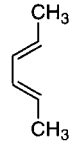
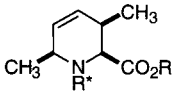
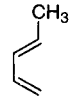
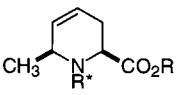


Figure 10.

Table 12. Cycloadditions with chiral alkyl glyoxylate substrates (**94**)

Entry	Diene	Major Product	Conditions	Diastereoselectivity	Endo:Exo	% Yield
1			A	95:5	3:97	82
2			B	>98:<2	2:98	94
3			A	92:8	8:92	31
4			B	88:12	22:78	50
5			A	86:14	-	69
6			B	95:5	-	30
7			A	85:15	-	44
8			B	68:32	-	86
9			A	62:38	-	55
10			A	69:31	-	35

R=CH_3 or CH_2CH_3; R*=(*R*)-PhCHCH$_3$ or (±)-was used; Condition A: 2 equiv. diene, 1 equiv. TFA, 0.03 equiv. H_2O, DMF, rt; Condition B: TFA, $BF_3{\cdot}Et_2O$, CH_2Cl_2.

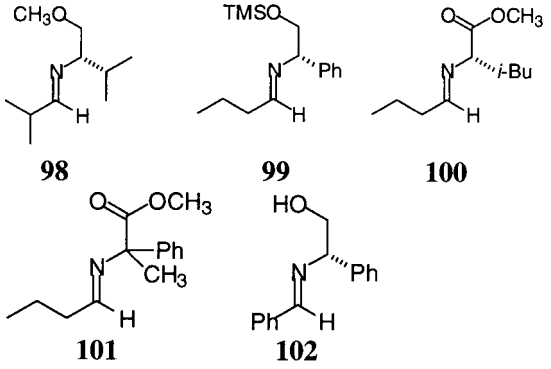
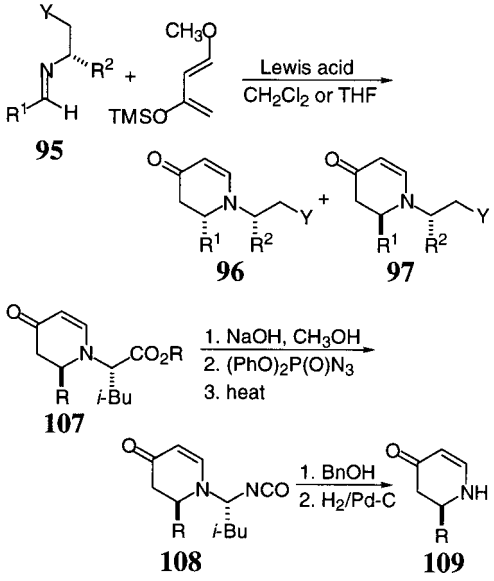


Figure 11.



(24)

(25)

Table 13.

Entry	Imine	Lewis acid	**96**:**97**	Yield (%)
1	**98**	$Zn(OTf)_2$	87:13	67
2	**98**	$SnCl_2$	83:17	66
3	**99**	$Zn(OTf)_2$	58:42	45
4	**100**	$ZnCl_2$	10:90	65
5	**100**	2 equiv. $ZnCl_2$	15:85	11
6	**100**	$TiCl_4$	9:91	37
7	**100**	$EtAlCl_2$	6:94	80
8	**100**	$BF_3{\cdot}Et_2O$	20:80	64
9	**101**	$Zn(OTf)_2$	>95:5	60
10	**102**	$BF_3{\cdot}Et_2O$	>95:5	60

The 5-phenyl-3,4-dehydromorpholin-2-one **111** was synthesized from **110** (Scheme 3). Stereoselectivity of the cycloaddition step was excellent.[64] Reaction with acyclic 2,3-dimethylbutadiene gave one detectable isomer. The cycloadduct of **111** and isoprene gave only one stereoisomer and regioisomer **117** (Fig. 13). Cyclopentadiene also gave only one detectable isomer **115**.

Imines derived from the carbohydrate auxiliary, 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine **116**, gave

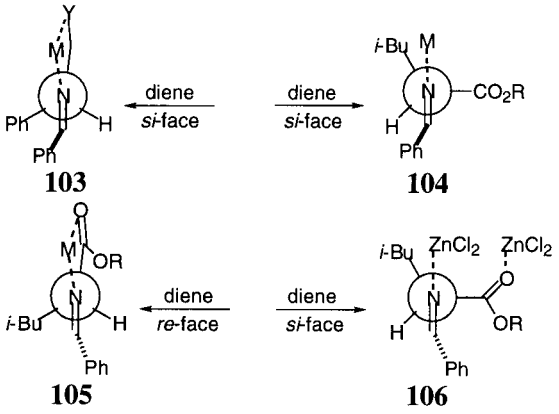
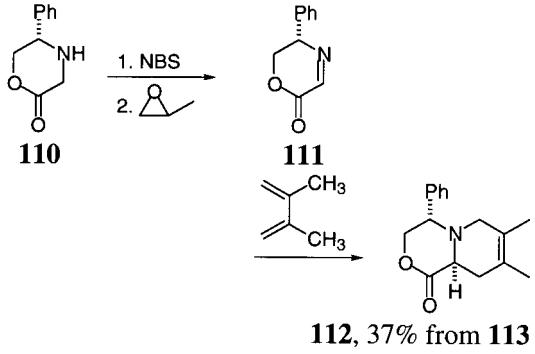


Figure 12.



Scheme 3.

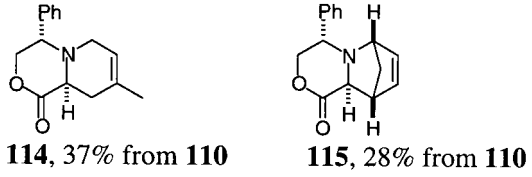
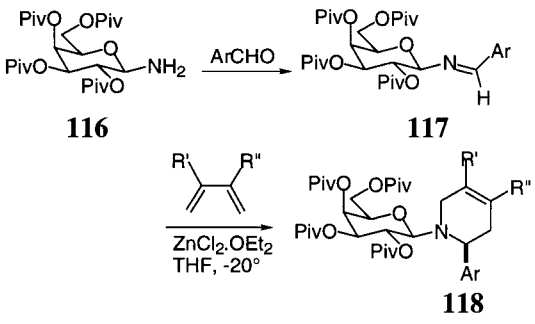


Figure 13.

high selectivities and yields (Scheme 4).[65–67] In this system, the aromatic imino group is in the *exo*-position and in *trans*-configuration. The reactivity of the imine substrates was low, but with $ZnCl_2$ etherate as catalyst isoprene and 2,3-dimethylbutadiene undergo cycloaddition. Various aromatic imines gave products in high yields and moderate

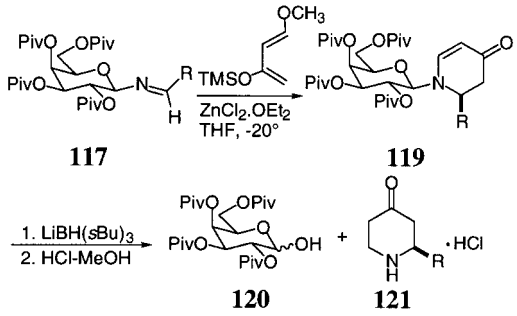


Scheme 4.

Table 14.

Entry	Ar	R′	R″	Diastereomeric ratio of **118**	Yield (%)
1	Furan	H	CH_3	79:21	98
2	Thiophene	H	CH_3	85:15	95
3	3-Pyridyl	H	CH_3	69:31	98
4	4-Cl-Ph	H	CH_3	85:15	95
5	4-Cl-Ph	CH_3	CH_3	87:13	96

ratios of anomeric isomers (Table 14). These reactions were proposed to be concerted. Aliphatic imines undergo anomerization and gave rise to complex mixtures of products under the same reaction conditions. However, both aromatic and aliphatic imines undergo cycloaddition with the more reactive Danishefsky's diene to give high selectivities and yields (Scheme 5, Table 15). These reactions were believed to proceed in tandem Mannich–Michael addition reaction.



Scheme 5.

Table 15.

Entry	R	Diastereomeric ratio of **119**	Yield (%)
1	Propyl	97:3	96
2	3-Propyl	97:3	90
3	*i*-Propyl	97:3	58
4	4-CN-Phenyl	95:5	71

The chiral auxiliary could be removed from the pyridone products and reused. The selectivity in these reactions is rationalized by chelation of the zinc to carbonyl oxygen and the imine nitrogen, with the pivoyol group blocking the *re*-face of the imine (Fig. 14).

An N-(1*R*)-camphorsulfonyl auxiliary derived sulfonylimine gave low selectivity (Eq. (26)).[68,69] The reaction occurred at room temperature without a catalyst or with catalyst at −78°C. The $TiCl_4$ gave the same major isomer **124** as the reaction without a catalyst while the aluminum

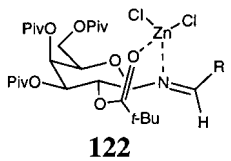
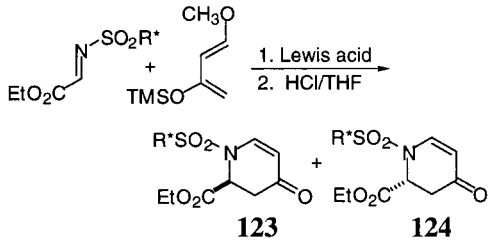
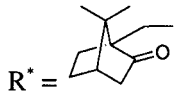


Figure 14.

Lewis acid gave isomer **123** as the major isomer.



(26)



Lewis Acid	Temp. (°C)	**123**:**124**	% Yield
None	rt	35:65	58
0.25 eq. $TiCl_4$	-78	30:70	25
0.25 eq. Et_2AlCl	-78	59:41	45

2.2.3. Double asymmetric induction. Imines derived from chiral amines and chiral aldehydes. Imines derived from chiral glyoxylate esters and chiral phenylethylamine allowed for the study of double asymmetric induction. The imines derived from the chiral glyoxylate esters of borneol, pantolactone, and 8-phenylmenthol were tested (Fig. 15).[70] Chiral phenylethylamine in conjuction with the glyoxylates of borneol and pantolactone gave low selectivities. However, the auxiliaries of phenylethylamine and 8-phenylmenthol of matching stereoselectivity, gave products in excellent selectivity and in moderate yields (Table 16). The mismatching set gave selectivities lower than when the chiral glyoxylate of 8-phenylmenthol and achiral benzyl amine was used.

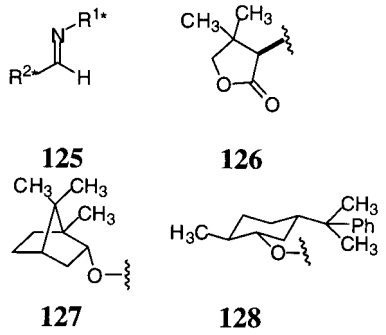
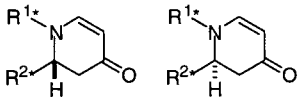
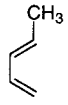
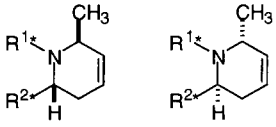
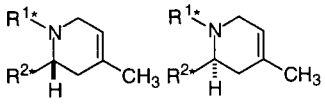
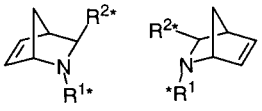
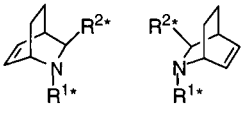
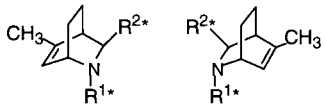


Figure 15.

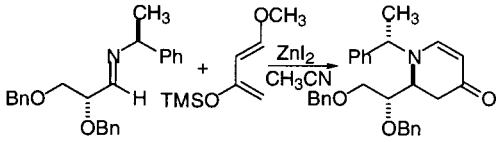
The same approach was used with imines derived from chiral phenylethylamine and dibenzyl protected glyceraldehyde.[71] With the matching auxiliaries, only one stereoisomer was detected (Eq. (27)). The mismatching auxiliaries gave

Table 16. Double asymmetric induction with 8-phenylmenthol and phenylethylamine auxiliaries (structure **125**, R^{1*}=(*R*)- or (*S*)-phenylethyl, R^{2*}=8-phenylmenthol)

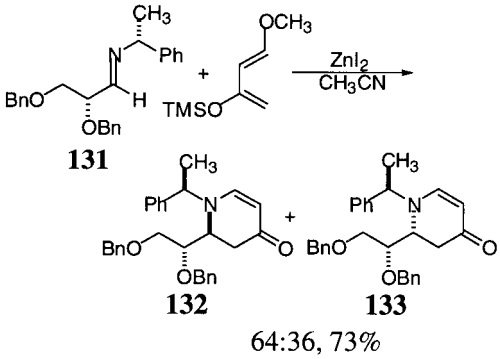
Entry	Diene	Products	Match[a]	Yield	Mismatch[b]	Yield
1			>97.5:<2.5	54%	62:38	54%
2			>97.5:<2.5	53	91:9	49
3			>97.5:<2.5	48	74:6	61
4			>97.5:<2.5	69	59:41	48
5			>97.5:<2.5	51	50:50	38
6			>97.5:<2.5	40	-	-

[a] R^{1*}=(*R*)-phenylethyl, R^{2*}=8-phenylmenthol.
[b] R^{1*}=(*S*)-phenylethyl, R^{2*}=8-phenylmenthol.

low selectivity (Eq. (28)).

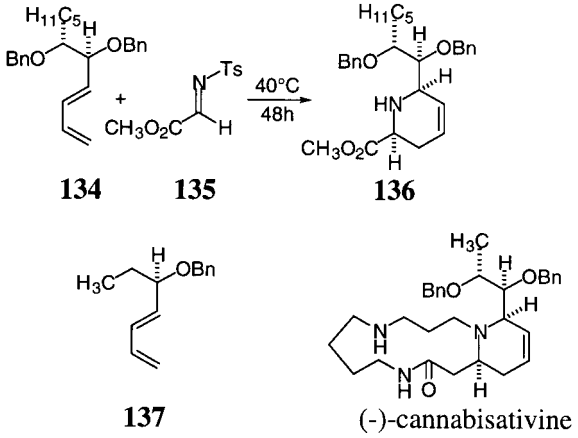


(27)



(28)

2.2.4. Chiral dienes. Cycloaddition of chiral diene **134** and imine **135** gave only one detectable cycloadduct **136** (Eq. (29)).[72,73] Chiral diene **137** also gave one detectable isomer with imine **135** in 74% (Fig. 16). This approach was used to synthesize (−)-cannabisativine. With this type of diene, the chiral centers of the diene are incorporated into the product.



(29)

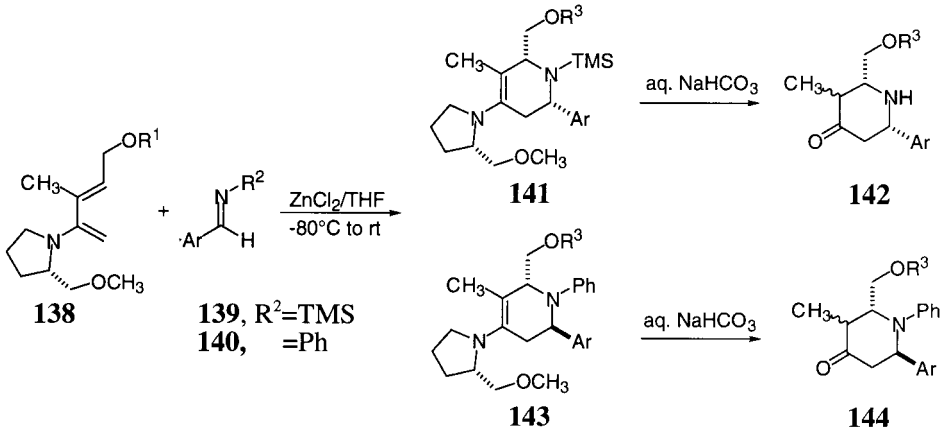
Figure 16.

Table 17. Imino Diels–Alder reaction with chiral diene **138**

Entry	R^1	Ar	R^2	R^3	ee of **142**	Yield (%)
1	TMS	3-Fu	TMS	H	>98	51
2	CH_3	3-Fu	TMS	CH_3	86	23
3	MOM	3-Fu	TMS	MOM	82	33
4	TBDMS	3-Fu	TMS	TBDMS	77	30
5	TMS	*p*-CH_3OPh	TMS	H	90	43
6	TBDMS	*p*-CH_3OPh	TMS	TBDMS	86	29
7	TMS	Ph	TMS	H	95	65
8	MOM	Ph	TMS	MOM	87	35
9	TBDMS	Ph	TMS	TBDMS	84	28
10	CH_3	*o*-BrPh	TMS	CH_3	86	63
11	TBDMS	*o*-BrPh	TMS	TBDMS	53	32
12	CH_3	Ph	Ph	CH_3	35 (**144**)	45

Chiral 2-aminobutadiene **138** was found to undergo cycloaddition with high stereoselectivity (Scheme 6).[74,75] The chiral pyrrolidine auxiliary activates the diene and can easily be removed. The cycloadditions were promoted by 2 equiv. of $ZnCl_2$ in THF, and the products were hydrolyzed during aqueous work-up to piperidones. Moderate to high selectivities with moderate yields were observed (Table 17). The R^1-group on the diene seemed to have some influence on the selectivities. The nitrogen substituent on the imine played a more important role. TMS substitution on the imine nitrogen gave *cis*-2,6-piperidones, while the phenyl substituted imine gave the *trans*-2,6 isomers as products. Based on these stereoselectivities, *exo*-approach of the TMS-group and *endo*-approach of the N-phenyl group to the diene were inferred. In the *endo* approach, the Ar-group of the imine is further removed from the chiral auxiliary of the diene, which is consistent with the low selectivity seen (Table 17, entry 12). This approach has been applied for the syntheses fo pipecolic acid derivatives and (−)-nupharamine.[76,77]

2.2.5. Chiral Lewis acids. Chiral Lewis acids have been used for highly selective carbon Diels–Alder reactions.[78,79] Recently, this approach has been applied to aza Diels–Alder reactions. Although initial works tended to rely on stoichiometric amounts of chiral catalysts, more recently there has been success using catalytic amounts of the chiral reagents. The first successful results were obtained with boron Lewis acids.[57,58,80,81] Chiral Lewis acids **145** and **146**, gave good enantio- and diastereoselectivity with imine **148** (Fig. 17,



Scheme 6.

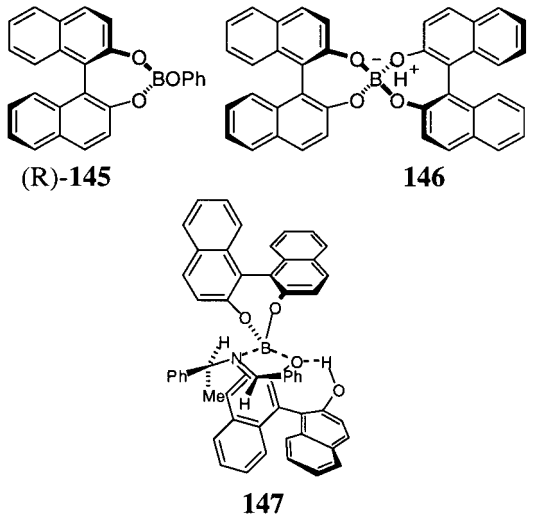


Figure 17.

Table 18. Catalytic asymmetric cycloadditions of imine **148**

Entry	Ar	R	Lewis acid	de (%)	Yield (%)
1	Ph	H	(*R*)-**145**	82	75
2	*c*-Hexyl	H	(*R*)-**145**	76	45
3	Ph	H	**146**	86	78
4	Ph	CH_3	$B(OPh)_3$	92	57
5	Ph	CH_3	(*R*)-**145**	98	61
6	Ph	CH_3	(*S*)-**145**	86	30
7	3-Pyridyl	CH_3	$B(OPh)_3$	78	53
8	3-Pyridyl	CH_3	(*R*)-**145**	98	63
9	3-Pyridyl	CH_3	(*S*)-**145**	72	35
10	*c*-Hexyl	CH_3	$B(OPh)_3$	80	40
11	*c*-Hexyl	CH_3	(*R*)-**145**	98	31
12	*c*-Hexyl	CH_3	(*S*)-**145**	78	20
13	*n*-Propyl	CH_3	$B(OPh)_3$	82	59
14	*n*-Propyl	CH_3	(*R*)-**145**	90	49
15	*n*-Propyl	CH_3	(*S*)-**145**	82	31

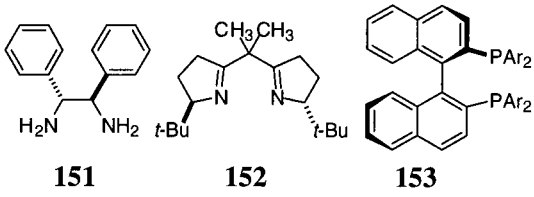
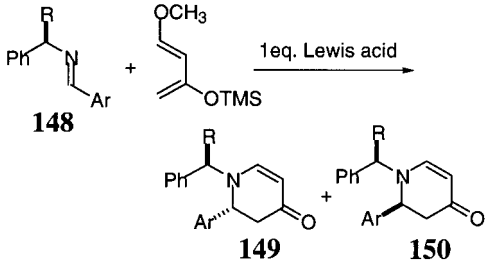


Figure 18.

Eq. (30), Table 18). Double asymmetric induction using chiral imines gave excellent selectivities for the matching auxiliaries (*R*)-imine **146** and chiral Lewis acid (*R*)-**145**. Mismatched auxiliaries gave lower selectivities than the reaction of (*R*)-imine and achiral Lewis acid $B(OPh)_3$. X-Ray crystal structures and NMR nOe studies supported the proposal than complex **147** was responsible for the observed selectivities. In this complex, the *si*-face of the (*E*)-imine is blocked and the diene must approach the *re*-face.



(30)

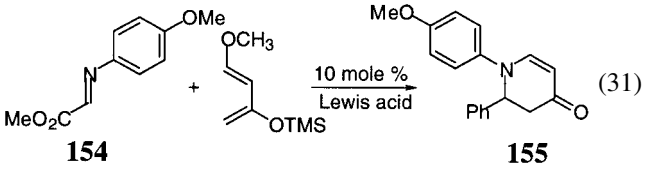
Ligands **151** and **152** derived chiral Lewis acids gave successful cycloaddition with imines derived from methyl glyoxylate and anisidine (Fig. 18, Eq. (31), Table 19).[82] Several Lewis acids were examined with these ligands and in some cases, 2,6-lutidine ligand or molecular sieves were necessary.

The binaphthyl phosphine ligand **153** modified Lewis acids gave high enantioselectivities with tosylimine of methylglyoxylate and $CuClO_4$ (Eq. (32), Table 20).[83] High enantioselectivities were obtained with as low as 1 mol% catalyst loading (Table 20, Entry 5).

Chiral Lewis acid **158**, derived from zirconium, hafnium and titanium and modified with chiral binaphthol derivates showed good enantioselectivities (Fig. 19, Eq. (33), Table 21).[84,85] 2-Aminophenol was used as the nitrogen source in the imine. Of the several ligands examined, *N*-methylimidazole (NMI) gave the best results. For the same imino Diels–Alder reaction, asymmetric catalyst **159** was optimized in terms of R^1-, Ar-, and ligand X. High selectivities were obtained with R=Br or H, Ar=*p*-CF_3, and X=CN.[86]

2.3. Cycloaddition of imines derived from ketones

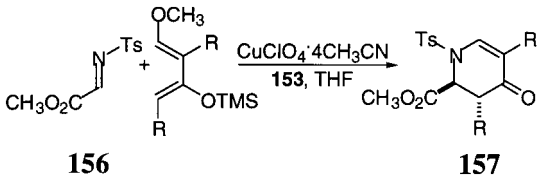
There are few new examples of cycloadditions with imines derived from ketones. Oximinoacetate **162** derived from Meldrum's acid undergoes cycloaddition with dienes under high-pressure (Eq. (34)).[87] The oximinosulfonate **165** also undergoes cycloaddition (Eq. (35)). The low yields were obtained initially due to decomposition of the products



(31)

Table 19. Asymmetric cycloadditions catalyzed by **151** and **152** modified chiral Lewis acids (Eq. (31))

Entry	Lewis acid/solvent	Ligand	Additive	ee **155** (%)	Yield (%)
1	MgI_2	**151**	2,6-Lutidine	97	64
2	$Yb(OTf)_3$/toluene	**151**	2,6-Lutidine	87	60
3	$Cu(OTf)_2/CH_3CN$	**151**	None	86	58
4	$FeCl_3/CH_2Cl_2$	**152**	4 Å MS	92	67

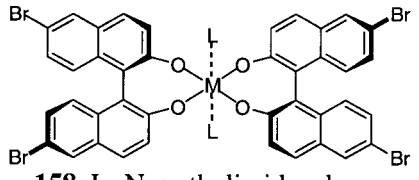


(32)

Table 20. Catalytic asymmetric cycloadditions with phospine ligand **153** modified Lewis acids (Eq. (32))

Entry	Mol (%)	Alkene R	ee **157** (%)	Yield (%)
1	10	H	67	78
2	10	H	80	68
3	10	CH_3	94	67
4	5	CH_3	94	70
5	1	CH_3	96	70
6	10	CH_3	81	70

under the reaction conditions. Dimethylaluminum chloride Lewis acid allows the reaction to occur at a lower temperature in higher yields. It was found that 2 equiv. of Lewis acid were necessary suggesting complex **170** (Fig. 20). The second equivalent serves to promote ionization of chloride.



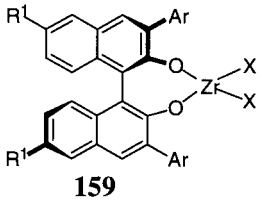
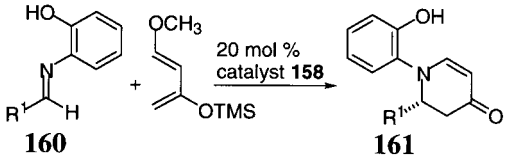


Figure 19.

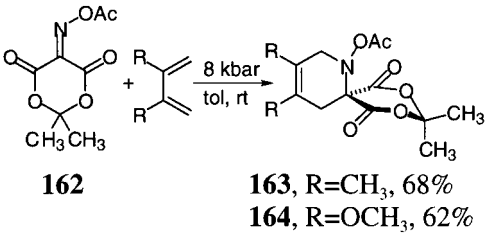


(33)

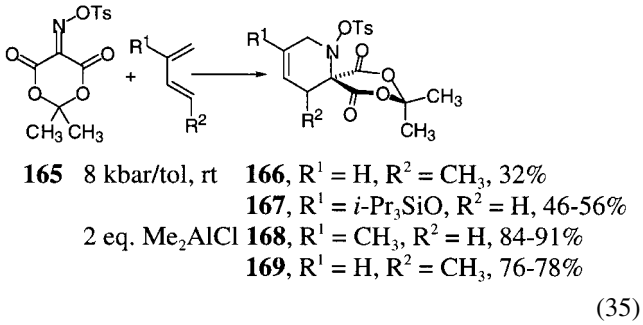
Table 21. Catalytic asymmetric cycloadditions with zirconium, hafnium, and titanium based catalyst (Eq. (33))

Entry	R^1	Metal	ee **161** (%)	Yield (%)
1	CH_3	Zr	82	94
2	2-Thiophene	Zr	86	74
3	*c*-C_6H_{11}	Zr	81	64[a]
4	α-Naphthyl	Zr	88	96
5	α-Naphthyl	Hf	84	96
6	α-Naphthyl	Ti	62	70

[a] 3-Amino-2-methylphenol was used.



(34)



(35)

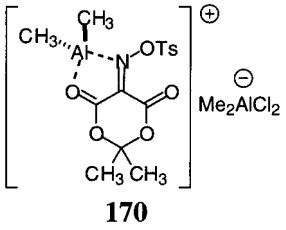


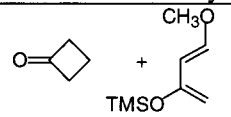
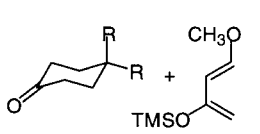
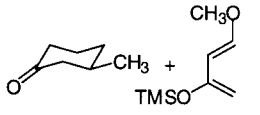
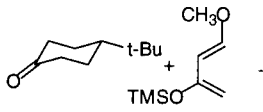
Figure 20. Possible mode of complexation between substrate **165** and two equivalents of dimethylaluminum chloride.

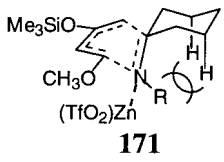
Unactivated imines from cyclic ketones undergo $Zn(OTf)_2$ promoted cycloaddition with Danishefsky's diene.[88] Imines of cyclobutanone gave only 18% cycloadduct (Table 22, Entry 1). Imines derived from cyclohexanones and methylamine gave moderate to good yields. Substitutions on the 3- or 4-positions gave only one detectable isomer and no cycloaddition was observed for 2-substituted cyclohexanones. It was found that more sterically demanding substituents on the nitrogen gave lower yields. The stereoselectivities can be rationalized by transition state **171** in which the diene approaches from the less hindered equatorial position and the N-R group initially develops axially causing a 1,3-diaxial interaction (Fig. 21). For the more hindered amines, this can become significant enough to prevent the cycloaddition.

2.4. Intramolecular imino cycloaddition

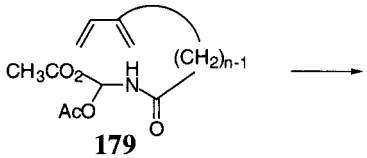
In an effort to synthesize imino tricyclic compound **174** by intramolecular imino Diels–Alder reaction, Grieco synthesized substrate **172** and **173** (Eq. (36)).[89] Heating **172** and **173** in water gave imino tricyclic compounds **174** and **175** in 55 and 80% yield, respectively. Interestingly, treatment of substrate **173** in 5.0 M lithium perchlorate in diethyl ether gave only 13% cycloadduct **175**. Substrate **176**, on the other hand, under the same conditions undergoes initial diene isomerization followed by cycloaddition to give **178** in 26% yield (Eq. (37)).

Table 22. $Zn(OTf)_2$ promoted cycloadditions of imines derived from ketones

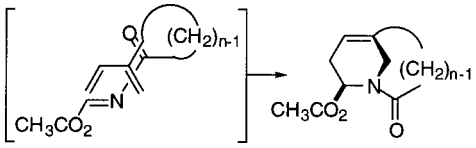
Entry	Cycloaddition	Yield (%)
1		18
2	 R = H	51-64
3	R = $OCH_2CH_2OCH_3$	84
4		76
5		49



171



179

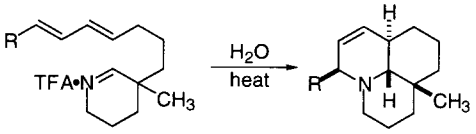


180

181, n=3, 29%
182, n=4, 82%
183, n=5, 76%
184, n=6, 9%

Scheme 7.

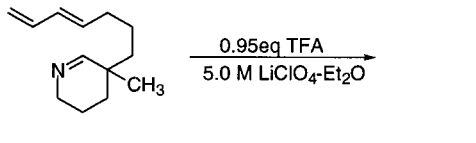
Figure 21. Proposed transition state for cycloaddition of imines derived from ketones and Danishefsky's diene.



172, R=H
173, R=CH_3

174, R=H, 55%
175, R= CH_3, 80%

(36)



176

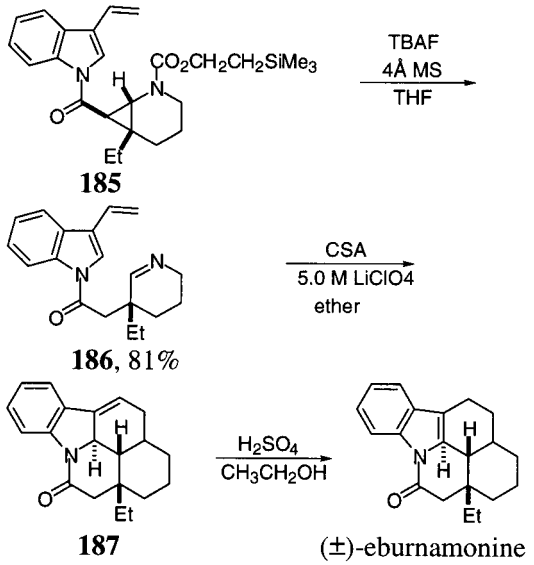
177

178, 26%

(37)

As part of a study investigating bridgehead olefin and bridgehead amide, type 2 intramolecular imino cycloaddition was investigated (Scheme 7).[90] Under thermolysis conditions the bridgehead products formed. The yields were low for the 3- and 4-carbon tethered compound but high for substrates with the 4- and 5-carbon tether.

Grieco has used the intramolecular imino Diels–Alder strategy as key steps for the synthesis of indole alkaloids.



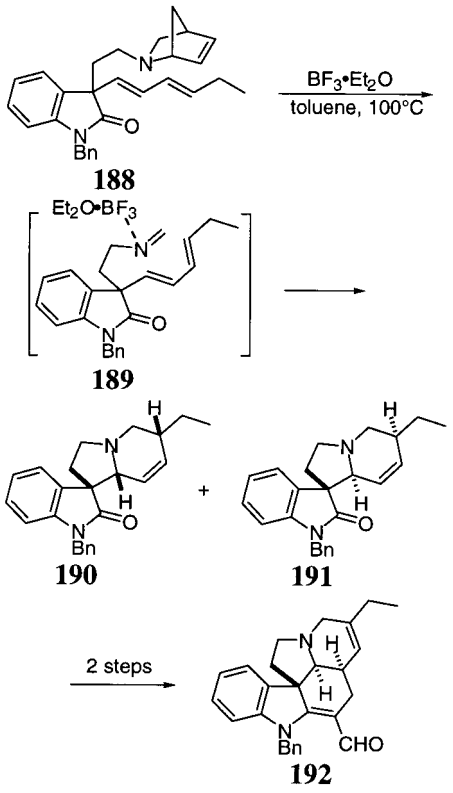
185

186, 81%

187

(±)-eburnamonine

Scheme 8.



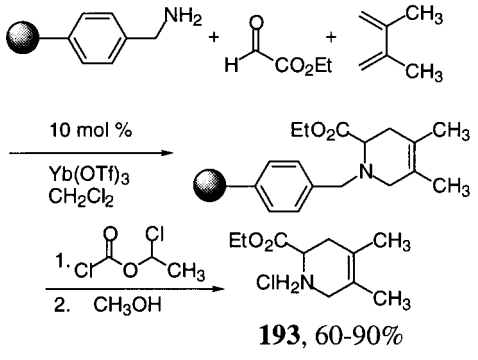
Scheme 9.

He has developed a novel approach of unmasking cyclopropanecarboxamide **185** to generate substrate **186** for the cycloaddition (Scheme 8).[91,92] Under the condition of camphorsulfonic acid and 5.0 M lithium perchlorate, **186** undergoes cycloaddition to give cycloadduct **187**. Double bond isomerization gave (±)-eburnamonine.

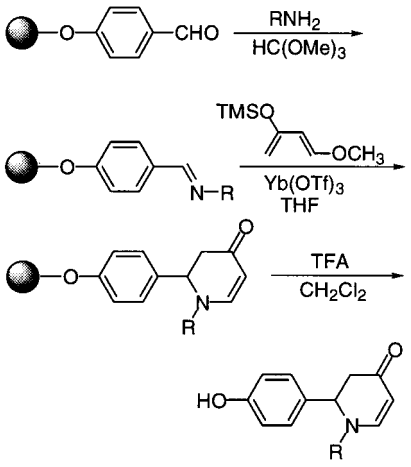
The synthesis of aspidosperma alkaloid structures involve unmasking the imine from substrate **188** (Scheme 9).[93] When **188** was heated with $BF_3{\cdot}Et_2O$ in toluene, compounds **190** and **191** were generated in 1.5:1 ratio. Both compounds can be taken on to compound **192** in two steps.

2.5. Polymer-supported cycloaddition

2.5.1. Solid phase substrate. Imines supported on polymers undergo cycloaddition. The imine has been generated from polymer supported aldehyde[94] or amines.[95] Survey of Lewis



Scheme 10.



Scheme 11.

acids showed that $Yb(OTf)_3$ gave the highest yields (Schemes 10 and 11). The resulting cycloadducts were removed from the bead. In the case of imines derived from polymer bound aldehydes, the product cleavage incorporated the aromatic group from the polymer. In the case of imines derived from polymer bound amine, the cycloadduct cleavage took place at the nitrogen atom of the cycloadduct.

2.5.2. Solid phase catalysts. Polymer supported binaphthol based catalyst **194** gave excellent selectivities (Fig. 22).[95] The highest selectivities were obtained by adding a mixture of imine and diene to the catalyst over an hour period. The catalyst was recovered by filtration and reused up to 3 times with high yields and selectivities.

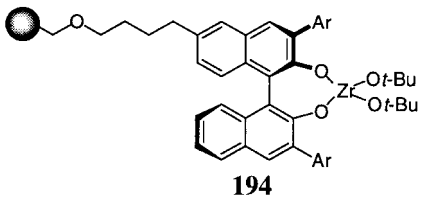


Figure 22.

3. Imino dienes

3.1. 1-Azabutadienes (enimine dienes)

Owing to their electron-deficient character simple 1-azadienes are less reactive toward standard electron deficient dienophiles. They therefore tend to undergo inverse electron demand Diels–Alder reactions when they do react. In many early studies the electrophilic nature of nitrogen compromised the utility of simple 1-azadienes as Diels–Alder dienes due to competitive self-condensation, dimerization, imine addition, and/or imine tautomerization.[2a,96]

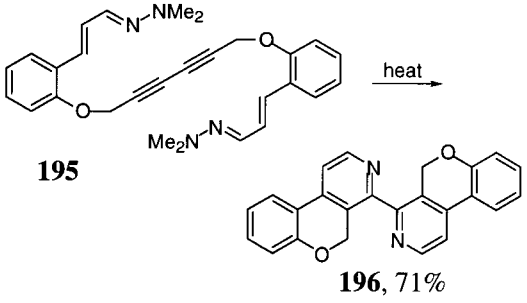
Theoretical studies of the transition state for the Diels–Alder reactions of unsubstituted 1-azabutadienes support the conclusion that the terminal nitrogen lowers the LUMO of the diene to allow for an inverse electron demand type reaction.[18] In accord with expectations, FMO (MP2/6-31G*) and DFT (B3LYP/6-13G*) analysis of the

*endo*1-aza-1,3-butadiene shows that the C4–C6 bond (FMO 2.079, DFT 2.066) is shorter than the N1–C5 (2.278, 2.284) bond in the Diels–Alder transition state. The *exo* form transition state is more synchronous with a transition state C4–C6 bond length (2.159, 2.163) and an N1–C5 bond length (2.209, 2.193). The calculated activation energy for the *exo* is lower by about 4 kcal mol^{-1}.

The key to a successful azadiene Diels–Alder strategy is to decrease the HOMO–LUMO energy difference by matching the 1-azadiene to the dienophile and stabilizing the transition state. A number of investigators have been able to facilitate the aza-Diels–Alder reaction by introducing electron-donating or withdrawing substituents to the nitrogen atom of the diene to increase its activity with a selected dienophile.

3.1.1. Enhydrazones. The introduction of electron donor groups to the imine nitrogen reverses the natural electron-deficient character of the 1-azadienes. Sufficient donation raises the HOMO of the azadiene and causes the reaction to proceed through the $HOMO_{diene}$-controlled manifold.

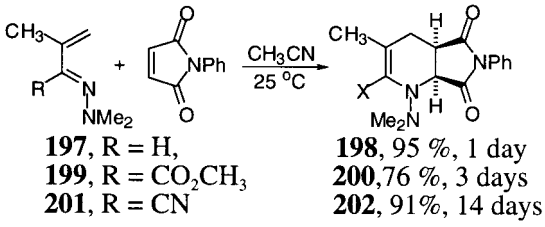
Ghosez et al. demonstrated the utility of 1-dimethylamino-1-azadienes in some of the earliest examples of the addition of electron donor groups to facilitate normal electron demand Diels–Alder reactions (Eq. (38)).[97,98] In these reactions the conjugative interaction between the lone pair of the amine nitrogen with the enimine system is critical to the activation. The importance of interaction of the tertiary nitrogen lone pair with the azadiene is manifested in the yields of the intramolecular double Diels–Alder reaction of compound **195**.



(38)

Even with the introduction of the electron releasing dimethylamino group the necessary conditions for reactions to simple dienophiles are generally relatively harsh. Reactions in sealed tubes at temperatures of 100–200°C for times as long as 220 h are not unusual. The use of additional donating groups or activated dienophiles is necessary to obtain synthetically useful processes.

The introduction of substituent groups may be used to attenuate the reactivity of azadienes. Alkyl groups in the C-2 position renders the azadiene unreactive.[99] The reduced reactivity is proposed to be due to steric hindrance between the hydrazone N-methyl and the alkyl C-2 substituents, which forces the amine lone pair out of plane with the imine. The introduction of electron withdrawing carboxylate or nitrile groups as C-2 substituents are tolerated, allowing the reaction to proceed. The reaction rate of the carboxyl or nitrile C-2 substituted systems is substantially reduced relative to the unsubstituted cases due to the more electron deficient nature of the azadiene (Eq. (39)).



(39)

Substitution of an electron-releasing group at C-3 has also been shown to enhance the reaction rate for the cycloadditions of 1-azadienes.[97,98,100] The 3-ethoxy azadiene **204** for example adds regioselectively and in high yield to 5-hydroxynaphthoquinone (Fig. 23).[101]

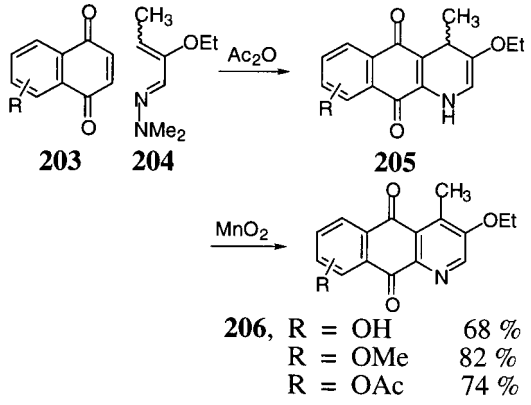
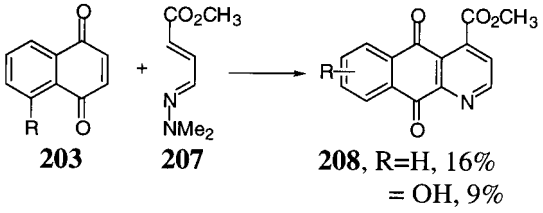


Figure 23.

The chemical yield and regioselectivity in Diels–Alder reactions of enhydrazones with substitution at the C-4 position is subject to a combination of steric and electronic factors. The presence of electron-withdrawing methoxycarbonyl functionality resulted in low yields upon addition to naphthoquinone or juglone in refluxing toluene (Eq. (40)).[102] In the latter case no regioselectivity was observed.



(40)

Conversely adding an activating substituent such as the tributylstannyl group at the C-4 position allows for aza Diels–Alder synthesis in good to excellent yields with a number of dienophiles (Fig. 24).[103]

The reversal of the normal 'polarity' of the enimine system is manifested in the regiochemistry of the reaction. In accord with expectation from FMO theory, only the regioisomer that places the most electron deficient end of the dienophile closest to the diene nitrogen is observed.[98]

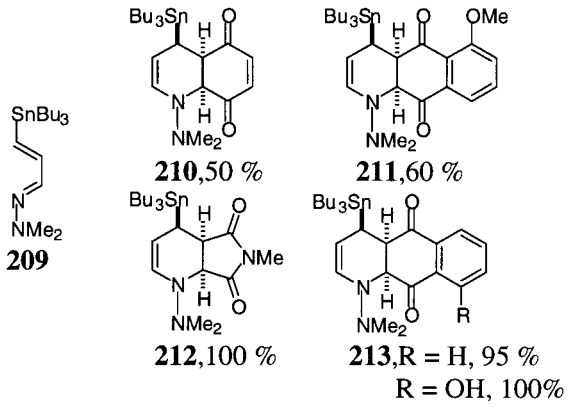
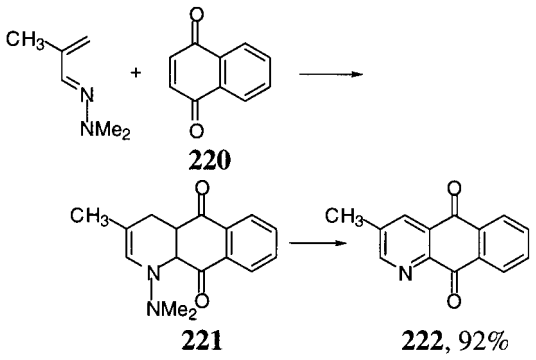


Figure 24.



Scheme 12.

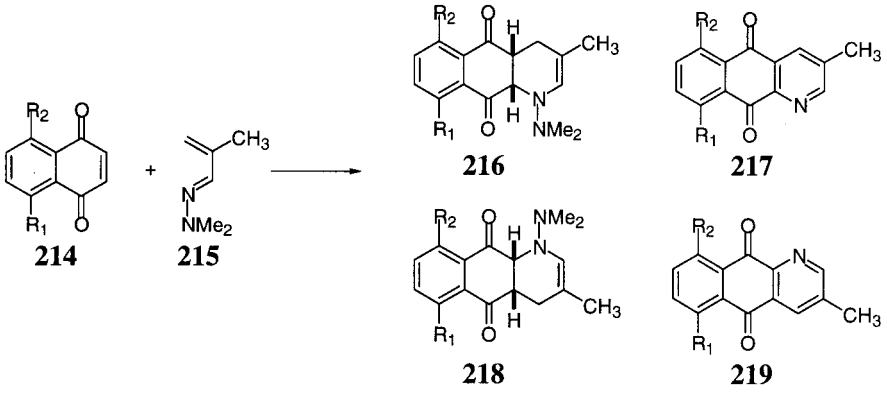


Figure 25.

Table 23.

Quinone	R_1	R_2	Time	Products	Ratio	Yield (%)
214a	OH	NH_2	20 days	**217a**		93
214b	OH	NHAc	8 h	**217b+219**	4:1	88
214c	OAc	NHAc	36 h	**216+218**	1:9	79

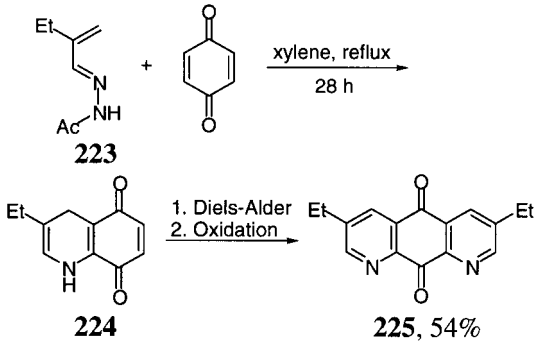
An interesting study is provided in the work of Parades et al., where acylation of the hydroxyl and amino substituents on the quinone results in reversal of the expected regiochemistry (Fig. 25, Table 23).[104] The authors postulate that hydrogen bonding between the dimethylamino group of the diene and the acetamide is the reason for this result.

The enhydrazones have been utilized in numerous syntheses involving quinone dienophiles. In the majority of these cases, the Diels–Alder products undergo in situ elimination to 1,4-dihydropyridines, or oxidation to the corresponding fused pyridine framework (Scheme 12).[105–109]

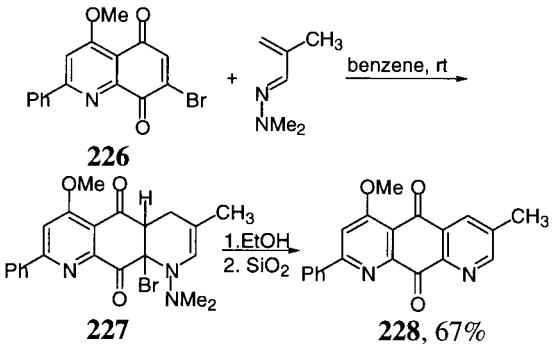
To avoid competitive nucleophilic addition of liberated dimethylamide to the quinone several procedures have been employed. One method has been the modification of the hydrazone to produce a less nucleophilic species. *N*-Acyl-enhydrazones have been applied but have found limited use. They suffer from lower cycloaddition reaction rates and yields due to the less electron rich nature of the 1-acylamino-1-azadiene (Scheme 13).[110–114] However, they do have the advantage of high regioselectivity upon double aza-Diels–Alder reaction.[115]

The basis for the improved regioselectivity lies with the lower oxidation rate of the initial Diels–Alder adduct as compared to that of the corresponding *N*,*N*-dimethylhydrazone based diene. In the unoxidized intermediate **224**, conjugation between the nitrogen and the C-5 carbonyl results in C-6 being the electrophilic end of a relatively isolated $C_6{=}C_7{-}C_8{=}O$ dienophile. This dienophile undergoes Diels–Alder cycloaddition prior to oxidation.

The more typical means of circumventing the nucleophilic addition of liberated dimethylamide has involved sweeping the reaction medium with an inert gas to remove dimethylamine,[102,114] or introducing some type of amine scavenger species such as acetic anhydride,[101] silica gel,[101,116] or an electrophilic scavenger resin.[117]



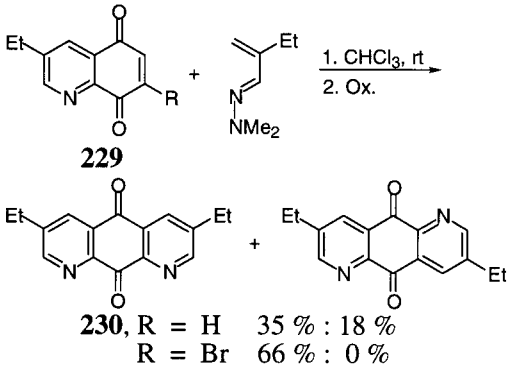
Scheme 13.



Scheme 14.

The use of halo-dienophiles has provided at least a partial solution to the problem of dimethylamine elimination and subsequent nucleophilic attack on the quinone starting material and the cycloaddition products.[102] The cycloaddition reaction is followed by liberation of hydrobromic acid, which traps the amine eliminated as the product is aromatized (Scheme 14). While thermal aromatization of **227** produced both **228** and the retro Diels–Alder product, chromatography over SiO_2 produced only **228**.[106]

An additional advantage of the application of haloquinone dienophiles is an improvement in the regioselectivity of the cycloaddition reaction with the halogenated carbon acting as the more nucleophilic end of the dienophile (Eq. (41)).[102,115,117–120]



(41)

Substitution at C-4 of the aza-diene resulted in the isolation of 1,8-bis-(dimethylamino)-1,4,5,8-tetrahydro derivative, **235** (Fig. 26). Presumably steric interactions between the alkyl groups and the carbonyl prevented spontaneous aromatization. Heating **236** under vacuum allowed for the aromatization.

There are relatively few examples of the use of chiral 1-azadienes in asymmetric aza-Diels–Alder reactions. In one of the earliest examples, the chiral dienophile **237** was utilized to provide compound **238** regioselectively, in 85% yield, and in >98% de (Eq. (42)).

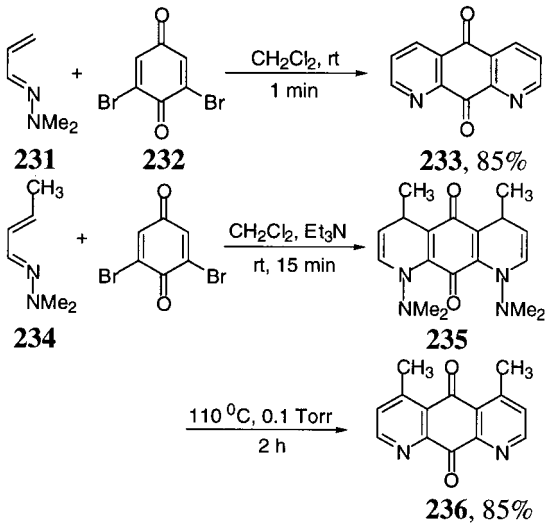
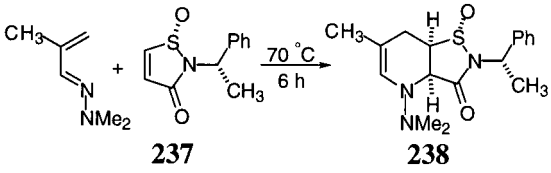


Figure 26.



(42)

Ghosez et al. have observed high levels of diastereoselectivity through the use of Enders' hydrazones (Fig. 27, Table 24, Eq. (43)).[121] The selectivity has been rationalized

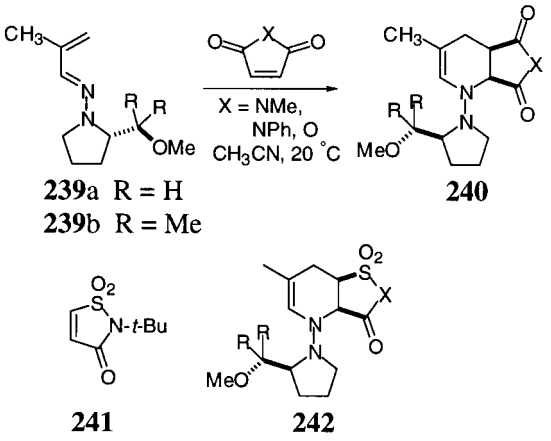
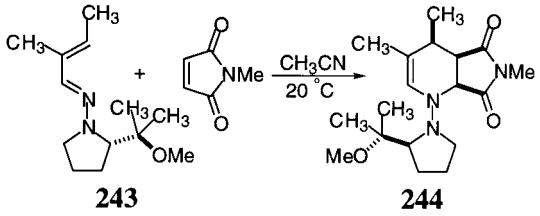


Figure 27.

Table 24.

Dienophile	Diene	Yield (%)	de (%)
N-Methylmaleimide	**239a**	81	85
	239b	68	98
N-Phenylmaleimide	**239a**	75	76
	239b	70	98
Maleic anhydride	**239a**	58	80
	239b	61	96
Isothiazol-3-(2*H*)-one **241**	**239a**	51	73

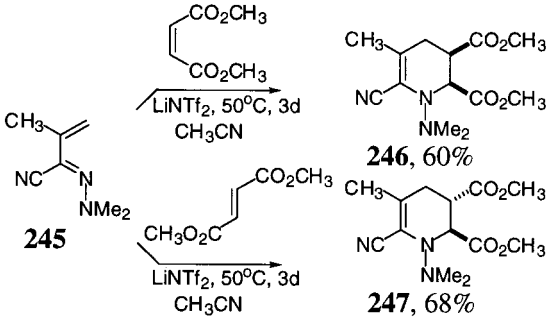
by invoking the conformational bias provided by the hydrazone, which favors β-face dienophile attack.



243 **244** (43)

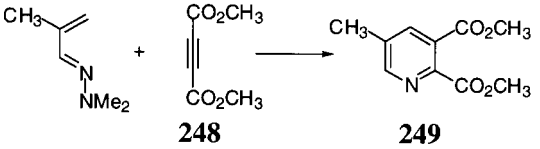
The electronic complementarity of the diene and dienophile are critical to the success of the aza-Diels–Alder cycloaddition. While high temperatures or pressures are often used to overcome larger HOMO–LUMO energy differences, the addition of catalysts or modification of the reaction conditions can also improve reaction yields.

In their study incorporating electron-withdrawing substituents on the C-2 position of **245** Ghosez et al. noted a decrease in reaction rate, but were able to overcome this difficulty by performing the reaction in 2.5 M $LiNTf_2$-acetonitrile.[99] While the reaction in toluene proceeded to a yield of 86% in 14 days, the lithium containing solvent reaction reached 82% yield in 3 h. The enhancement in reactivity was sufficient to allow cycloadditions with less reactive dienophiles such as fumaric and maleic esters (Scheme 15).



Scheme 15.

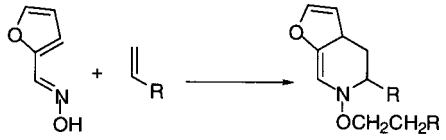
Both ultrasonic[110,112,113] and microwave[114] techniques have been used to provide acceleration of the aza-Diels–Alder reaction. Contrast is provided in evaluating the reaction of **248** with acetylenedicarboxylate. These reagents are not reported to react under thermal conditions,[97] however, under ultrasonic irradiation (50 h, 50°C) without solvent, a 60% cycloaddition yield was obtained (Eq. (44)).[122] Microwave irradiation of the same reagents on a graphite support for 10 min produced **249** in 50% yield after chromatography.[123]



248 **249** (44)

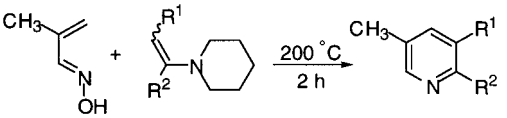
3.1.2. Enoximes and enoxime ethers. Few successful [4+2] cycloaddition reactions of α,β-unsaturated oximes have been reported, although several authors have reported various competing reactions with these dienes.[124] The weak electron donor character of the hydroxyl group does not sufficiently reduce the HOMO–LUMO energy difference. In those few cases where successful reactions have been reported additional electron-donating groups have been present on the azadiene.

One such case is the earliest example of the cycloaddition of the oxime of 2-furfural with electron-deficient dienophiles including acrylonitrile, maleic anhydride, and acrylic esters (Eq. (45)).[125] The observed regiochemistry is consistent with FMO considerations. The diastereoselectivity was not reported.



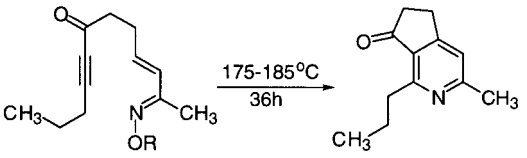
250 **251**, R = CN, 76%
= CO_2Et
= CO_2Me (45)

To circumvent the difficulty associated with the low reactivity of the enoxime dienes, their addition to electron rich enimines has been tested by Vijn et al.[126] Even under conditions of 200°C heating in a sealed tube for two hours the unoptimized yields of pyridines were low (Eq. (46)).



R_1= CH_3 R_2= H 9 %
R_1= CO_2Et R_2= CH_3 10 %
R_1,R_2 = -$(CH_2)_4$- 13 %
R_1,R_2 = -$(CH_2)_3$- 17 % (46)

The ethers of α,β-unsaturated oximes provide sufficient electron donation to the nitrogen to promote the normal $HOMO_{diene}$-controlled Diels–Alder reaction. Such reactions generally require considerable thermal activation (Eq. (47)).[127] In intramolecular cycloadditions temperatures as high as 170–200°C may be required. Another limitation of the reaction is that the initial cycloaddition products are prone to oxidation through the loss of the ether –OR functionality under the harsh reaction conditions used.



252 **253**, R = Me, 70%
= Bn, 70% (47)

A limitation of the dimethylhydrazone azadiene was observed in an attempt to generate the quinolinedione. Behforouz et al. noted that, while reaction of the dimethylhydrazone **254** yields the aromatized adduct **256** in 64% yield, reaction with **257** fails to produce **258** (Fig. 28).[128] It was postulated that the steric interference of the

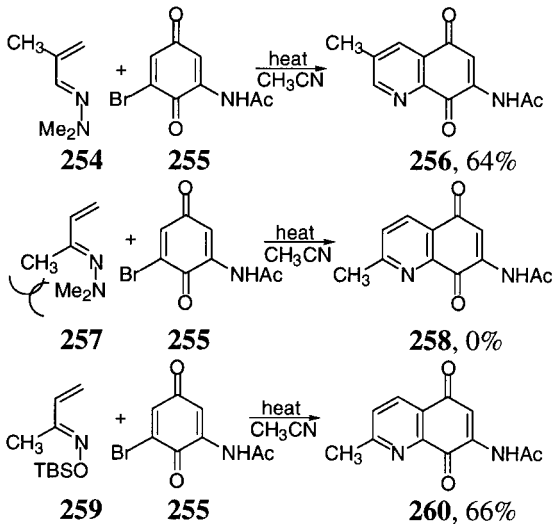
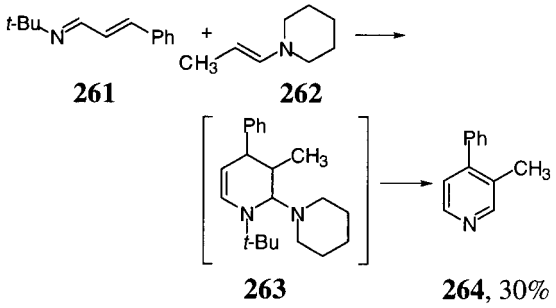


Figure 28.

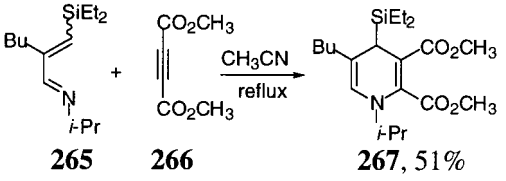
hydrazone and C2 methyl groups interrupts conjugation between the hydrazone nitrogen lone pair and the diene. Such interaction mitigates the donor ability of the hydrazone leading to an increase in the HOMO–LUMO energy difference. The use of the trialkysilyloxyazadiene circumvented the steric interference problem. In general the yields of these reactions are low to moderate, somewhat limiting the utility of the trialkysilyloxyazadienes.[129]

3.1.3. *N*-Alkyl and *N*-aryl enimines. To avoid competitive self-condensation and enamine dimerization processes observed in the reactions involving pure isolated *N*-alkyl enimines, researchers have frequently chosen to generate the desired heterodienes in situ. Even with in situ generation, however, Diels–Alder product yields tend to be relatively low (Scheme 16).[126] Given the mildly electron donating properties of the N-alkyl enimines, it has been postulated that the undesirable yields may be attributed to an unfavorable energy barrier in these LUMO diene controlled Diels–Alder reactions.



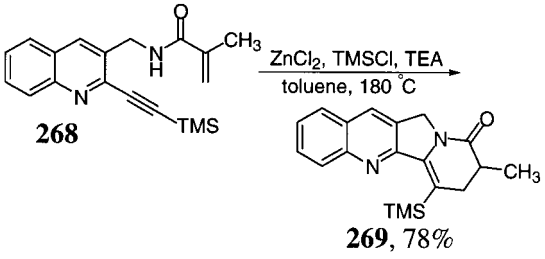
Scheme 16.

The concept of matching the electronic properties of the diene to the dienophile is demonstrated in the case of the Diels–Alder reaction of **265** (Eq. (48)).[130] While cycloaddition is not observed when refluxing a mixture of 4-silylated-1-azadienes **265** with phenylethyne, 1-hexyne, or 1-butyne, the more reactive dimethyl acetylene-dicarboxylate does undergo Diels–Alder reaction in low to moderate yields.



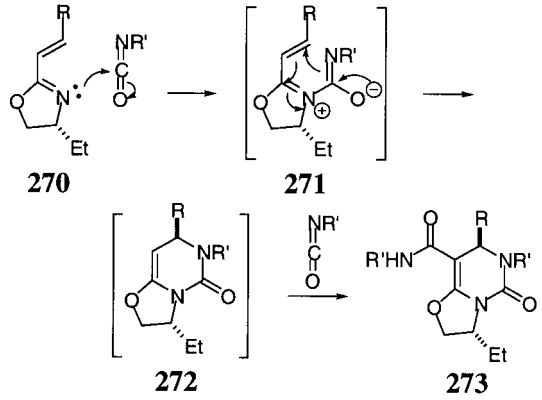
(48)

Substitution at the C-2 position can modify the electronic nature of the *N*-alkyl-1-azadiene to facilitate the cycloaddition reaction. With regard to electron-donating groups, the intramolecular Diels–Alder reaction of **268** proceeds in 78% yield when performed at 180°C in a sealed tube (Eq. (49)).[131] Even in cases where an electron-deficient alkyne dienophile was used high temperature and pressure were required to obtain synthetically useful yields.



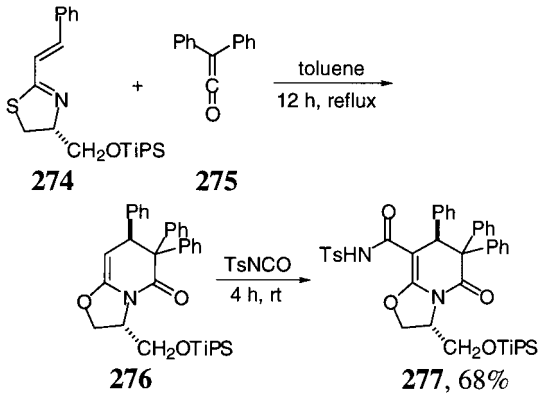
(49)

Elliot et al. have attempted to exploit the cycloaddition potential of the chiral alkenyloxazolines and alkenylthiazolines with ketene and aryl and arylsulfonyl isocyanate dienophiles (Scheme 17).[132–135] These diastereoselective reactions undergo a stepwise rather than a synchronous process however. Alkenyloxazoline ketene cycloadditions also form a 2:1 adduct with both isocyanate and diphenylketene dieneophiles. The second addition is believed to proceed via either a $2\pi_s+2\pi_a$ cycloaddition or an enamine acylation.



Scheme 17.

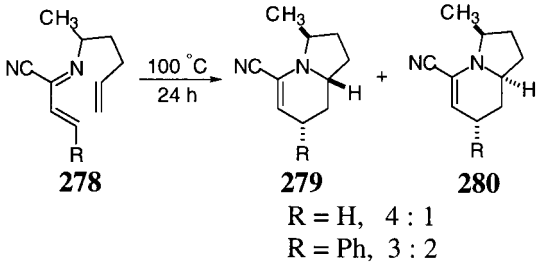
The alkenylthiazolines produce 1:1 adducts on reaction with diphenyl ketene and one equivalent of isocyanate (Scheme 18). In the isocyanate case the single adduct proved unstable and prone to retro-Diels–Alder reaction. The addition of a second equivalent of isocyanate produced a stable product.



Scheme 18.

Tandem reaction of alkenylthiazolines with isocyanates and diphenylketene has recently allowed for the controlled introduction of two different heterocumulenes.

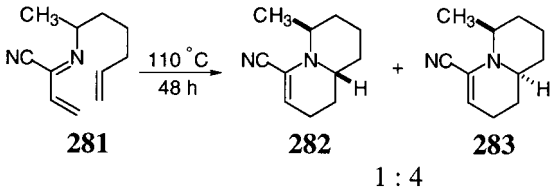
Complementary to the addition of electron donating substituents to the C-2 position of the diene are studies in which the nitrile group is used as an electron-withdrawing-group at C-2. The nitrile group is believed to lower the LUMO of the diene and stabilize the developing bonds in the transition state (Eq. (50)).[136] Whereas simple 1-aza-1,3-butadienes have not been reported to undergo intramolecular Diels–Alder reactions, the C-2 nitrile substituted azadiene underwent reaction at 110°C in 24 h in a sealed tube to produce a 94% yield.[137]



(50)

The diastereoselectivity of the reaction was investigated through a study of the intramolecular Diels–Alder reaction of **278**, which produced a 3:2 ratio of diastereomers. Based on this result it could be concluded that the reaction proceeds primarily through an *endo* transition state.

The stereochemistry of the intramolecular reaction is reversed upon homologation of the linking chain (Eq. (51)). It has been proposed that the reversal reflects a change to an *exo* dominated reaction mechanism.



(51)

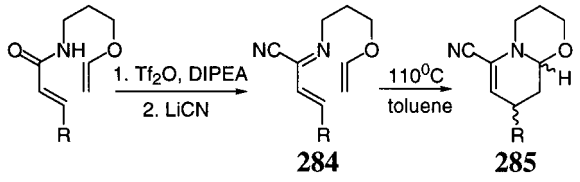
Similar reactions incorporating vinyl ether dienophiles have allowed for the production of cyanoenamine precursors to 2-cyano-6-oxazolopiperidines in 59–80% yield (Eq. (52)).[138] Under the conditions employed in the initial report (toluene, 110–130°C, 24 h) partial thermal degradation of the cycloaddition products was also observed.

Consequently, studies of Lewis acid catalysis were undertaken in an effort to reduce the reaction temperature.[139] The results (Table 25) indicate that in the presence of 10 mol% copper triflate or bismuth trichloride Lewis acid the reaction proceeds at temperatures as low as −20°C. The diastereoselectivity of the reactions was comparable to the analogous thermal process. The marked improvement in the catalyzed yield in the C-4 substituted cases has been attributed to the stabilization of the azadiene–copper complex and of the reaction products.

N-Aryl substituted enimines have been utilized in the aza-Diels–Alder reaction in a limited number of studies in which other functionality present in the diene also influences the reactivity of the system.

Bazureau et al. expanded the range of azadiene carbon substituted aza-Diels–Alder reactions to the pyrimidine system.[140] The aza-diene, in this case, contains a carboxylic ester as the C-2 electron-withdrawing group (Scheme 19). Using ethyl propiolate and but-3-yn-2-one as the dienophiles in the intermolecular process at 78°C afforded the desired products, albeit with some retro-addition which compromised the yields. The application of focused microwaves under solvent-free conditions allowed the reaction to proceed in near quantitative yield.

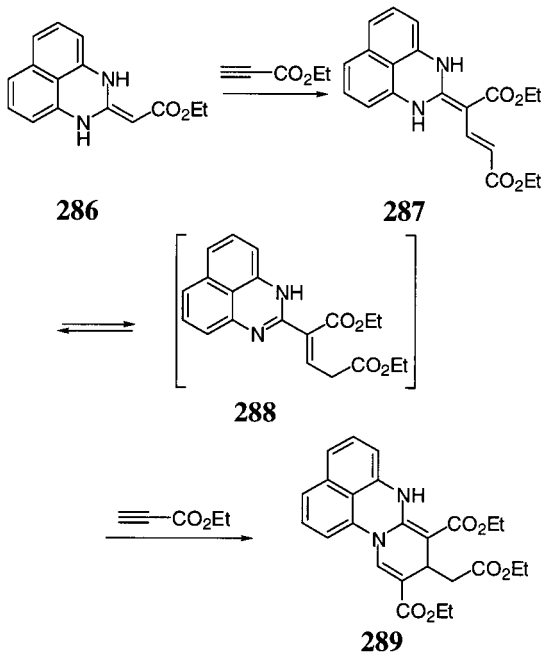
The addition of electron-withdrawing substituents to the



(52)

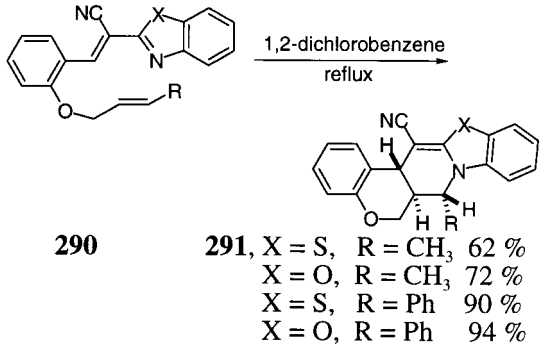
Table 25.

R	Catalyst	Temperature (°C)	Time	Yield (%)	*cis:trans*
Me	$Cu(OTf)_2$	−20	38	60	1:3.7
Ph	$Cu(OTf)_2$	−20	12	71	1:6.4
Me	$BiCl_3$+MS 3A	0	72	69	1:4.8
Ph	$BiCl_3$	rt	30	82	1:8.3
Me	$TiCl_4$	−20	10	32+amide	1:4.7
Me	$Cu(oxaz)_2OTf)_2$	rt	18	61+10 amide	1:3.6



Scheme 19.

C-3 position of the benzylidine(cyano)methyl-1,3-benzooxazoles and benzylidine(cyano)methyl-1,3-benzothiazoles has been undertaken by Sakamoto et al. (Eq. (53)).[141–144] The combination of donor and withdrawing substituents produces a system that reacts with both electron-rich and electron-deficient dienophiles. In general electron-withdrawing substituents increase the reactivity of the diene, suggesting an inverse-electron demand type reaction.

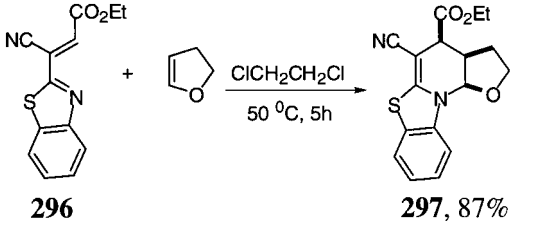


(53)

The intermolecular reactions display a bias toward regiospecific and *endo* selective reaction in the cycloadditions to succinimide and anethole to produce **293** and **295**, respectively (Fig. 29, Table 26). The yields in the latter case were notably higher and the reaction times at 120°C shorter. On cycloaddition with dihydropyran the regiospecificity was maintained although the *endo–exo* selectivity was compromised.

Yields for the intramolecular variant of the above process were generally low, and alkynyl dienophiles failed to react altogether. The lower reactivity of the alkynyl system was attributed to a lower energy HOMO–dienophile than in the vinyl case. The vinyl systems showed *exo*-selectivity presumably due to secondary orbital interactions.

In subsequent studies, an electron-withdrawing carboxylic ester functionality replaced the aromatic ring at C-4. This species proved to be a highly reactive azadiene with cycloadditions to electron-rich dienophiles proceeding in good to excellent regio- and *endo*-selective yield at ambient temperatures to 50°C (Eq. (54)). Reactions with electron-poor dienophiles proved much less facile, suggesting that the reaction proceeds through an inverse-electron demand manifold.



(54)

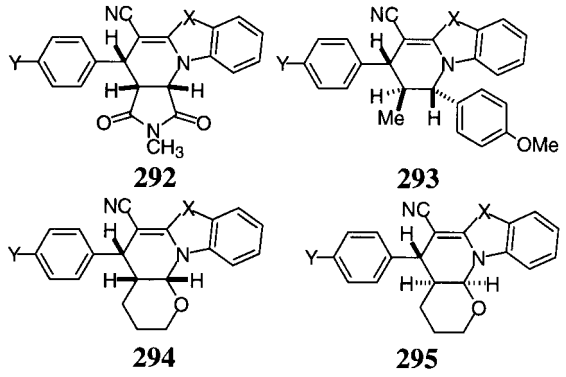


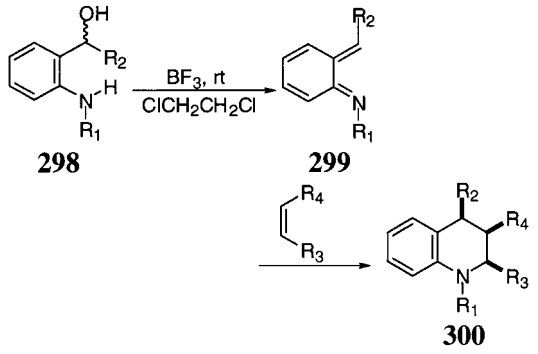
Figure 29.

Table 26. Formation of **292–295**

Entry	X	Y	Product	Yield	*endo*:*exo*
1	S	OCH_3	**292**	33	
2	S	H	**292**	52	
3	S	NO_2	**292**	85	
4	S	OCH_3	**293**	42	
5	S	H	**293**	77	
6	S	NO_2	**293**	75	
7	S	OCH_3	**294,295**	34	1:1
8	S	H	**294,295**	39	1.3:1
9	S	NO_2	**294,295**	46	1:1.6
10	O	OCH_3	**292**	14	
11	O	H	**292**	18	
12	O	NO_2	**292**	71	
13	O	OCH_3	**293**	45	
14	O	OCH_3	**294,295**	30	2:1
15	O	H	**294,295**	56	1.3:1
16	O	NO_2	**294,295**	30	1:2

3.1.4. *o*-Quinone methide imines. The *o*-quinone methide imines are highly reactive intermediates, which have been successfully utilized in several syntheses of nitrogen heterocycles. Several methods have been developed to synthesize *o*-quinone methide imines. Among these are thermal extrusions of carbon dioxide, sulfur dioxide or water and by treatment of *o*-amino benzylic alcohols with Lewis acids.[145]

Both intra- and intermolecular Diels–Alder cycloadditions have been observed in the in situ generation of the

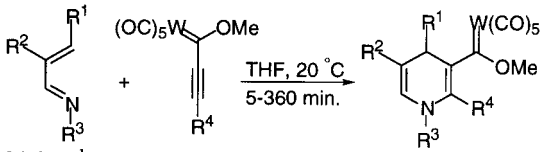


Scheme 20.

o-quinone **299** by BF_3 etherate addition to *o*-amino benzylic alcohols (Scheme 20).[146] The reactions were shown to be both regio- and stereoselective.

In another example of the in situ synthesis of *N*-alkyl-enimines, the *N*-methyl-*o*-Quinone methide imines have been successfully applied to hetero-Diels–Alder reaction with C_{60} (Scheme 21).[147]

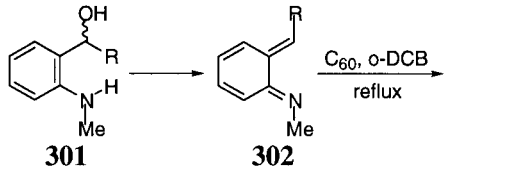
A variety of alkynyl Fischer carbene–carbodiene Diels–Alder cycloadditions have been reported in the literature. Following this lead Barluenga et al. have demonstrated that alkynyl Fischer carbenes may also participate in [4+2] cycloadditions with *N*-alkyl enimines.[148] These reactions have the advantage of proceeding at room temperature, in relatively short reaction times and in superior yields to the typical *N*-alkyl enimine cycloaddition (Eq. (55)).

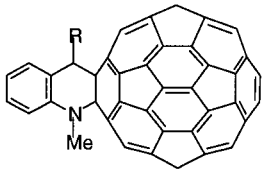


304, R^1 = Ph, CH_3, H
R^2 = H, CH_3
R^3 = alkyl, vinyl
R^4 = Ph, CH_3, TMS, vinyl

305, 65 - 89% (55)

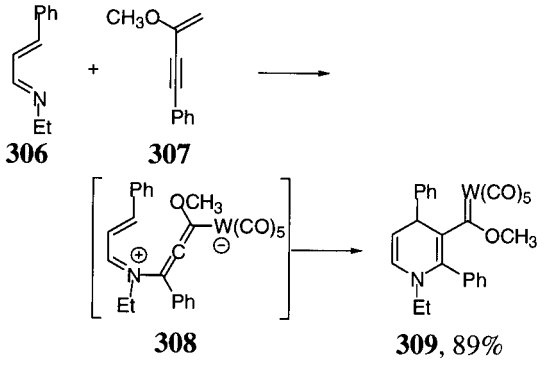
The regiospecificity of the reaction can be accounted for by the formation of the allenic intermediate **308** (Scheme 22), which has been unequivocally characterized from its NMR spectral data. The use of azadiene containing a chiral center





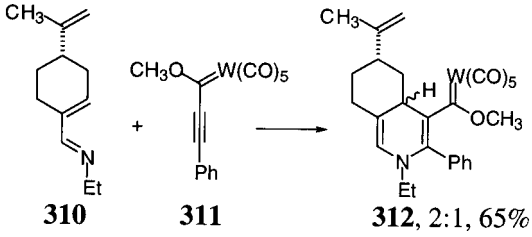
303, 25-31%

Scheme 21.



Scheme 22.

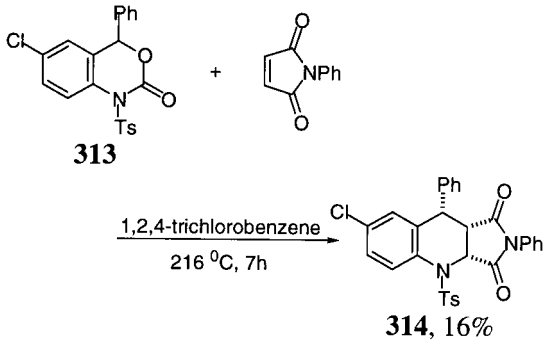
has allowed for the observation of 1,3 asymmetric induction in the cycloaddition reaction (Eq. (56)).



(56)

Reductions in the HOMO–LUMO separation substantially increase the rate of reaction. Introduction of electron withdrawing substituents to the N-1 and/or C-3 positions enhances the reactivity of the 1-azadiene through an inverse electron demand Diels–Alder manifold. To date *N*-acyl- and *N*-sulfonyl groups have been successfully applied.

Several researchers have reported intramolecular cycloadditions of N-acyl-1-aza-1,3-butadienes over the last fifteen years.[149–152] Intermolecular variants on the other hand are rare. Ferraccioli et al. reported low yields of **314** from the cycloaddition of **313** formed by in situ CO_2 extrusion (Eq. (57)).[153]



(57)

Steinhagen and Corey successfully generated *o*-azaxylxyene by base induced elimination of hydrogen chloride and trapping with methyl vinyl ether to produce **316** in synthetically useful yields (Fig. 30).[154] The intramolecular version proceeded via a suprafacial (*cis*) cycloaddition to give compound **318**. Analogous substrates gave **319** and **320** stereospecifically under mild conditions.

Recently, Boruah et al. reported the conversion of

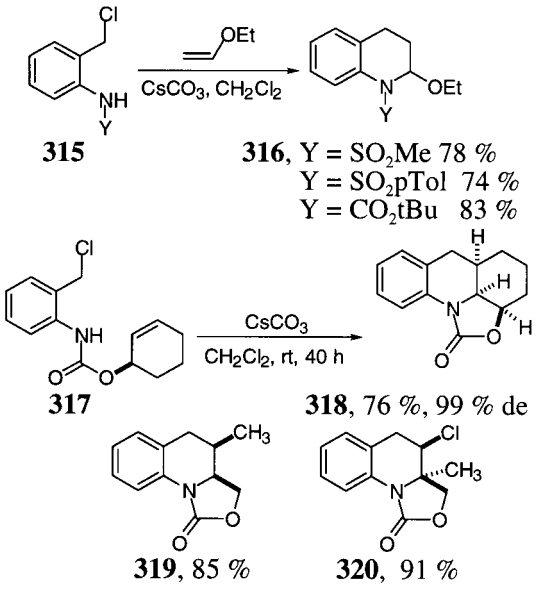
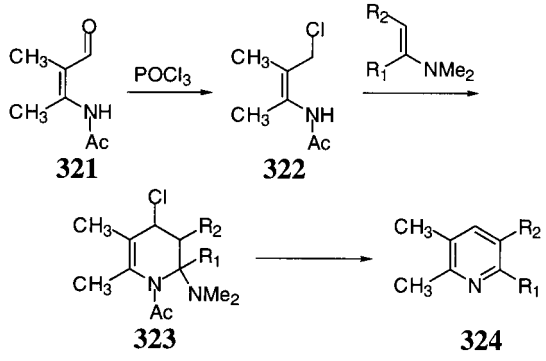


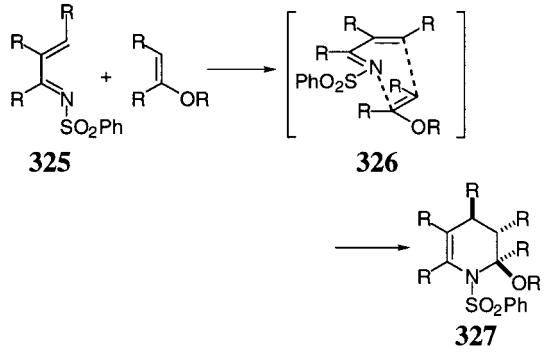
Figure 30.

β-formylenamides to *N*-acyl-1-aza-1,3-dienes, by treatment with $POCl_3$ (Scheme 23).[155] The reaction presumably proceeds through intermediate **323**. Addition of Lewis acids, $TiCl_4$ and BF_3 etherate enhanced the yield of pyridine products. It was hypothesized that the Lewis acid forms a complex with the acetyl oxygen enhancing the electron-deficient nature of the diene.

N-Sulfonylenimines react as electron-deficient dienes in the aza-Diels–Alder reaction. Boger et al. have thoroughly



Scheme 23.



Scheme 24.

investigated these inverse Diels–Alder cycloadditions with electron-rich olefins.[156–161] The empirical and computational data support the argument that the reactions proceed through a concerted $LUMO_{diene}$-controlled process.[26] These reactions are substantially regioselective and have typically >95% diastereoselectivity, preferring the *endo* product.[162] The high *endo*-alkoxy selectivity can be ascribed to an anomeric-like effect in the transition state (Scheme 24).

The introduction of electron-withdrawing substituents at the 2, 3, or 4 positions of the 1-azadiene may further accelerate reaction rates. The complementarity of the substituent groups influences both the regio- and diastereoselectivity of the reactions (Fig. 31).

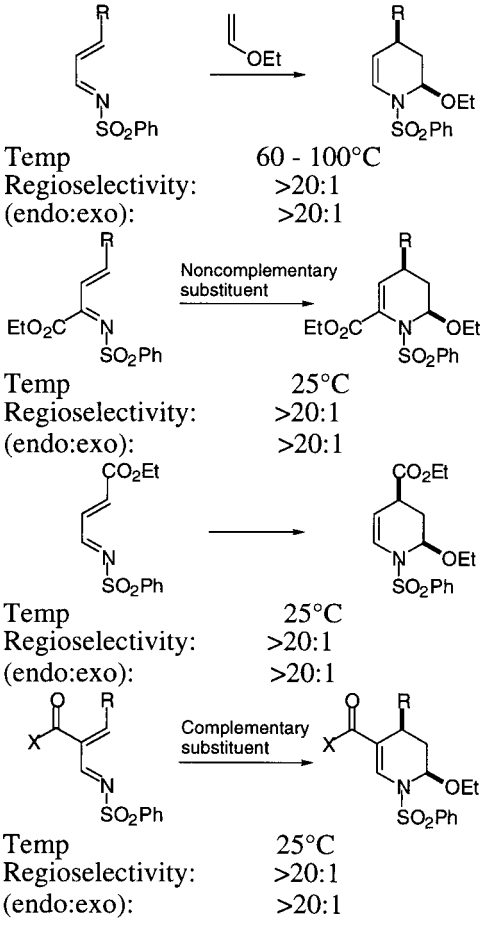


Figure 31.

3.2. 2-Azabutadienes

Like the 1-aza-1,3-butadienes, 2-aza-1,3-butadienes have proven to be useful reagents for the Diels–Alder based synthesis of pyridones, isoquinolones and pyrimidones of defined substitution patterns. While generally more reactive they mirror the behavior of the 1-aza-1,3-butadienes in that appropriate substitution renders them electron-rich or electron-deficient.

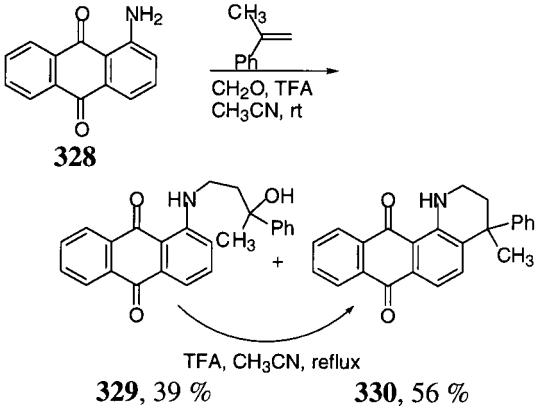
A major difference between the two systems is the efficacy of Lewis acid catalysis in the 2-azadiene cycloadditions. The success of Lewis acid mediated cycloadditions depends

on the identification of a Lewis acid which, by complexing an appropriate functional group, activates the dienophile and does not irreversibly complex the azadiene nitrogen.

3.2.1. Mechanistic aspects. Computational analysis of the activation energies and asynchronicities of 2-azadiene reactions with alkene and alkyne carbon dienophiles have been shown at the HF/3-21G* level of theory to follow the same trends as the corresponding reactions of 1,3-butadiene.[163] The influence of the diene nitrogen was predicted to be small. Catalysis by Lewis acids causes the transition state to become more asynchronous, although the change in geometry was calculated to be less dramatic than in the corresponding reactions using all carbon dienes.

Studies using ab-initio and density functional methods have also been applied to cycloaddition reactions with formaldehyde.[164] At the CASPT2F/6-31G*//CASSCF/6-13G* theory level the cycloaddition is predicted to proceed by a concerted rather than stepwise mechanism. The regioselectivity of the reaction, which favors formation of the 1,3 oxazine, can be rationalized in terms of FMO theory.

Based on semiempirical calculations of their LUMO energies and p-orbital coefficients cationic 2-azabutadienes have been shown to be more reactive and selective than the neutral analogs.[165,166] Empirical evidence suggests that non-concerted mechanisms play a significant role in systems with dienophiles that may stabilize an intermediate cation.[167,168] The domino reaction of **328** with formaldehyde and α-methylstyrene produced both the desired cycloadduct **330** and the side-product **329** (Eq. (58)). The latter is presumably produced through the intermediacy of the cationic species. Compound **329** may be converted to **330** by refluxing with TFA.



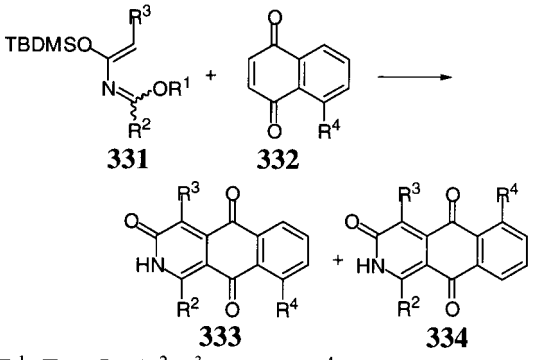
(58)

Cycloaddition between 2-azadienes and aldehydes requires Lewis acid catalysis. HF/6-31G*, MP2/6-31G*, and Becke3LYP/6-31G* theory levels all suggest that the catalyst lowers the aldehyde-LUMO increasing the charge transfer from the diene to the aldehyde in the transition state. The *anti* coordination of the Lewis acid to the aldehyde and the electrostatic interaction between the Lewis acid and the diene nitrogen lone pair are responsible for the *exo*-coordination of the catalyst in the transition state.

3.2.2. Non-catalyzed reactions. The Diels–Alder reaction of *N*-arylimines has a relatively long history in the synthesis of pyridine and quinoline derivatives.[169–171] Both intra- and intermolecular cycloadditions have been developed taking advantage of the electron-deficient nature of the 2-azadiene to perform cycloadditions with electron-rich alkene, alkyne, cyclopentadiene, enamine, vinylether, and vinylsulfide dienophiles. Recent developments center largely on improvements in the protocol and applications to synthesis.

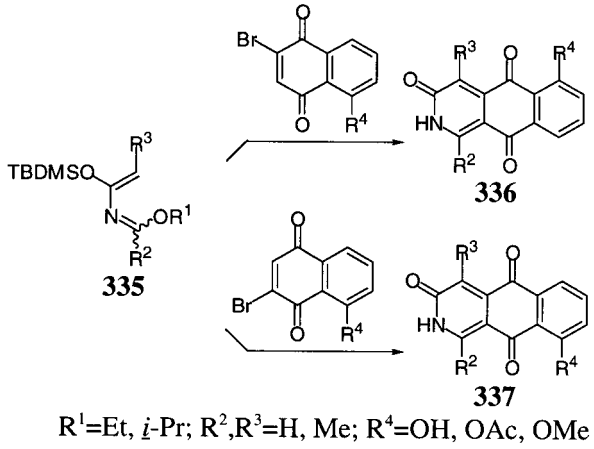
Sufficiently electron-donating substituents placed at the C-1 and/or C-3 position in the 2-azadiene can enhance the Diels–Alder reactivity through the $HOMO_{diene}$-controlled normal electron demand process. While silyloxy groups are the most commonly utilized donor functionality, amino, alkoxy and thioether groups have also been utilized in cycloadditions with electron-poor dienophiles.

The cycloaddition of 3-siloxy-2-azadienes to 5-substituted naphthoquinones produces the biologically interesting 2-azaanthraquinon-3-ones (Eq. (59)).[172] As in the cycloadditions to 1-azadienes, the regiochemistry of the addition is subject to the directing effect of the C-5 group. Substituent groups that are not sufficiently electron donating often lead to the formation of mixtures of products that are difficult to separate.

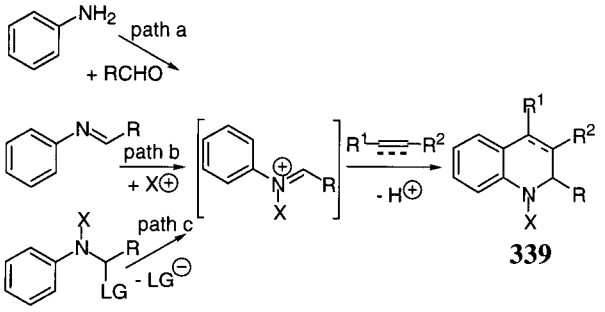


(59)

As with the 1-azadienes, the introduction of a C-2 or C-3 bromine atom to the dienophile produces a more electron-deficient, and consequently more reactive, dienophile. In addition, the bromine atom exerts regiochemical control over the reaction. Regardless of the C-5 substituent the



Scheme 25.

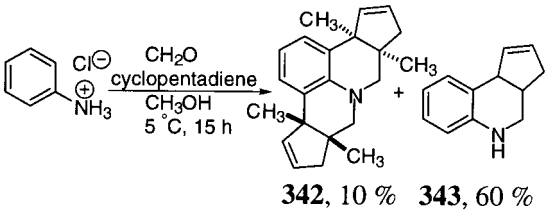


Scheme 26.

electron-rich end of the diene adds exclusively to the unsubstituted carbon of the bromonaphthoquinone (Scheme 25).

3.2.3. Cationic 2-azabutadienes. Cationic 2-azabutadienes may be generated by several means (Scheme 26). In pathway A, the in situ condensation of arylamines with carbonyl compounds especially formaldehyde and other aldehydes in the presence of a proton source forms the dienophile. In an example, cationic 2-azadiene iminium species generated from anilines or tetrahydroquinolines and formaldehyde have recently been shown to undergo cycloaddition with cyclopentadiene to produce cyclopenta[*c*]quinoline derivatives (Fig. 32).[173] The high degree of regioselectivity is paired with an equally high degree of diastereoselectivity.

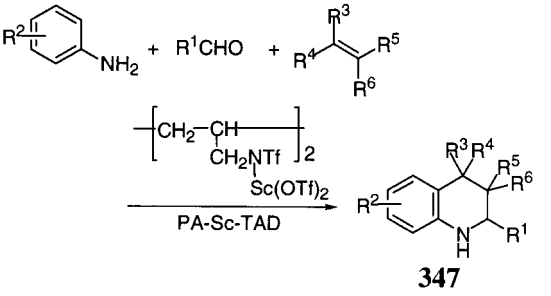
The pathway A method suffers from competition with double cycloaddition in which the initial product condenses with additional aldehyde and participates in a second cycloaddition.[174] This problem is particularly prevalent when the formaldehyde is used (Eq. (60)).



(60)

Such domino imine condensation-intramolecular cycloaddition reactions are highly diastereoselective and have been utilized to produce octahydroacridines with five stereocenters (Scheme 27).[175] The best yields are observed when substoichiometric quantities of Lewis acids are present in the reaction medium. In the cycloaddition of **344** the diastereomeric ratio of the starting materials (approximately 1.3:1.0) is maintained in the products as is the *E*-stereochemistry of the dienophilic olefin. AM1 calculations support the author's conclusions that the cycloaddition is kinetically controlled.

In pathway B a preformed imine is treated with a protic or Lewis acid. The maturity of the Lewis acid catalyzed quinoline derivative aza-Diels–Alder synthesis method is well demonstrated in the development of the polymer-supported scandium catalyst, PA-Sc-TAD (Eq. (61)).[176] Using a three-component coupling strategy Kobayashi and Nagayama created a library of 1,2,3,4-tetrahydroquinolines from a variety of aromatic amines, aldehydes, and olefins, vinyl ethers, vinyl sulfides, and alkynes. The yields and diastereoselectivities of these reactions were good to excellent.



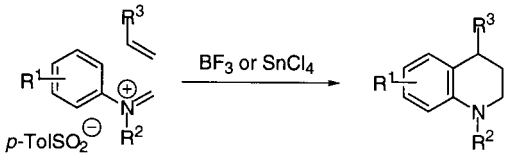
(61)

In pathway C, the in situ loss of an ionizable leaving group produces the iminium ion. Beifuss et al. have demonstrated

Figure 32.

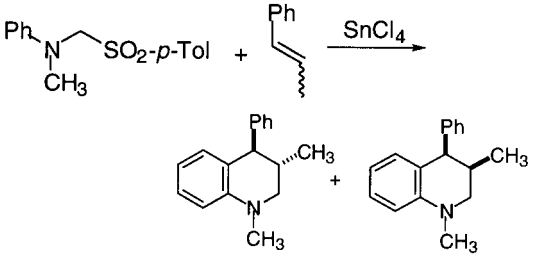
Scheme 27.

the viability of this methodology utilizing α-arylamino-sulfones and α-arylaminonitriles (Eq. (62)).[177,178] The addition of $SnCl_4$, $TiCl_4$ or BF_3 etherate Lewis acids initiates the heterolytic cleavage to generate the cationic 2-azabutadiene, which subsequently undergoes cyclo-addition.



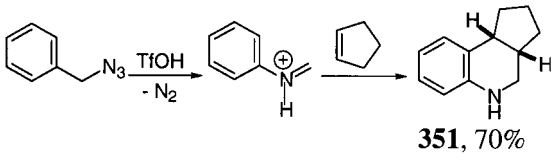
(62)

Here, both AM1 and PM3 analysis suggest a concerted mechanism of reaction. This is supported by empirical evidence from the reactions of the *E*-and *Z*-isomers of methylstyrene. The *E*-isomer cycloaddition yields exclusively **349** while the *Z*-isomer gives a 98.4:1.6 ratio of **350** to **349** (Eq. (63)).



(63)

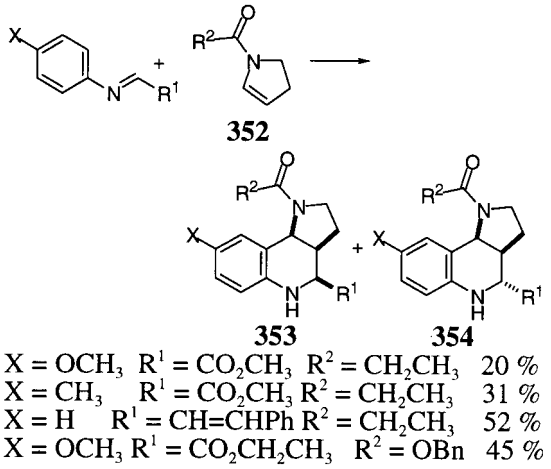
A fourth method involves the formation of the iminium ion by rearrangement of an azide (Scheme 28).[179] The acid promoted decomposition of azides involves rearrangement of aminodiazonium ions, whereas the Schmidt reaction of azides with carbocations involves rearrangement of the aminodiazonium ions.



Scheme 28.

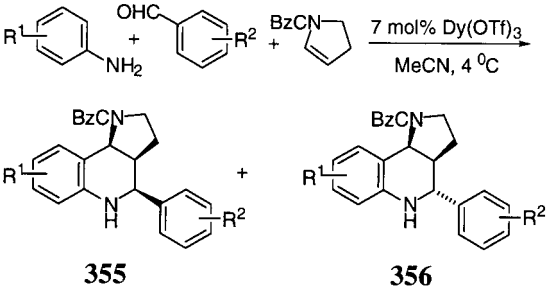
3.2.4. Catalyzed reactions. Two avenues of study that have earned considerable attention are the tandem (domino) processes[180] and Lewis acid catalysis.[181,182] While Lewis acids are useful in promoting 2-azadiene cycloadditions super-stoichiometric quantities of the acid are often required to overcome the substantial coordination of the acid to the nitrogen atom.[2a] In contrast sub-stoichiometric quantities of anhydrous indium trichloride can catalyze the same reactions.[183]

As components of independent efforts directed toward the synthesis of martinelline, Stevenson and Batey have studied the cycloaddition of *N*-arylimines with enamines in acetonitrile. In the report by Stevenson et al. indium trichloride catalysis of the cycloaddition of preformed *N*-arylimines and enamide **352** was studied (Eq. (64)).[184] Dienes derived from simple aliphatic amines failed to react and those derived from methyl glyoxylate (R=CO_2Me) underwent cycloaddition in low yields. Aliphatic amine derived *N*-arylamines underwent reaction in moderate yields and with *endo–exo* selectivity that did not exceed 2:1. The application of a CBz protected enamide produced the desired adduct in 45% yield in a 1:1 *endo–exo* ratio.



(64)

Batey et al. also utilized the CBz protected enamide as the dienophile in their study.[185] Rather than $InCl_3$ catalyst, they used $Dy(OTf)_3$ as the catalyst, and they also employed in situ generation of the *N*-arylimine (Eq. (65)). Using a variety of aromatic aldehydes the cycloaddition yields in acetonitrile were moderate to excellent. The diastereoselectivity of these examples was on par with that reported by Stevenson.



(65)

The diastereoselectivity proved to be strongly solvent dependent. With water as a co-solvent it was markedly improved, although the yields were reduced (Fig. 33, Table 27). The source of the increased diastereoselectivity was suggested to be due to the hydrophobic effect by which a more compact transition state induces *endo*-selectivity.

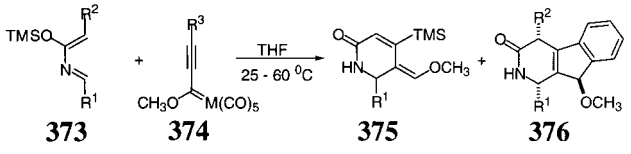
Mixed donor acceptor substituents have been observed and studied by several groups. Hajos et al, produced a 4-(1-pyrrolidino-1-([1,2,3triazol-5-yl)-2-aza-1,3-butadiene **359** via a pyrrolidine induced ring opening of the 1,3-disubstituted-[1,2,3]triazolo[1,5-a]pyrazinium salt **358**

(Scheme 29).[186] This compound underwent Diels–Alder cycloaddition with *N*-phenylmaleinimide producing compounds **361** and **362** via a presumed oxidation of the initial cycloadduct. Bubbling air through the mixture completed the oxidation producing **362** as the sole product.

Electron-deficient 2-azadienes, in spite of being good potential substrates for inverse demand Diels–Alder reactions, have received relatively little attention. In recent contributions, Palacios et al. have studied the cycloaddition of the dienes **363** (Scheme 30).[187] The cycloadditions with *cis*- and *trans*-cyclooctene formed product consistent with the maintenance of the configuration of the olefin starting material.

Less strained olefins failed to react with **366**, with the exception of norbornadiene under lithium perchlorate catalysis (Fig. 34). Cycloaddition with enamines such as **366** initially give products that undergo loss of amine to yield compounds **367** and **370** and pyridines **372**.

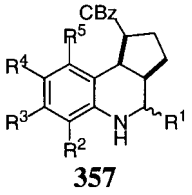
As in the case of 1-azadienes, cycloadditions of 2-azadienes with alkynyl Fischer carbene complexes have been studied by Barluenga et al.[188] While 3-siloxy-2-azadiene **373** was found to be unreactive toward methyl phenylpropiolate after 7 days in refluxing toluene, the (trimethylsilyl)-ethynyl carbene **374** proved reactive at room temperature (Eq. (66)). The pyridone cycloadduct was produced in 92% yield and was subsequently converted to **375** by heating at 60°C.



373 374 375 376

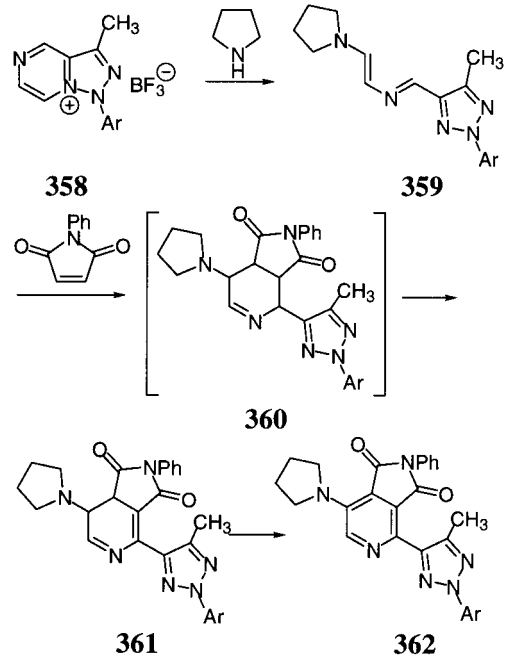
R^1 = *t*-Bu	R^2 = H	R^3 = TMS	82 %	
R^1 = 2-furyl	R^2 = H	R^3 = TMS	71%	
R^1 = *t*-Bu	R^2 = H	R^3 = Ph	76 %	
R^1 = Ph	R^2 = H	R^3 = Ph		84%
R^1 = *t*-Bu	R^2 = Me	R^3 = Ph		62%

(66)



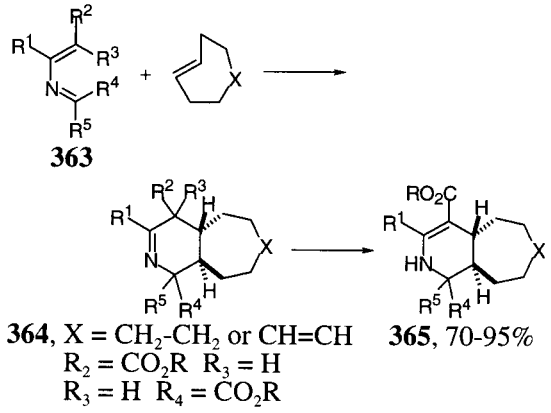
357

Figure 33.



358 359 360 361 362

Scheme 29.



363

364, X = CH_2-CH_2 or CH=CH; R_2 = CO_2R R_3 = H; R_3 = H R_4 = CO_2R 365, 70-95%

Scheme 30.

In an attempt to achieve an asymmetric cycloaddition of 3-siloxy-2-azadienes to olefinic dienophiles, Ghosez et al. have utilized Evans' copper(II) triflate-bis(oxazoline) ligand complex as the Lewis acid system (Eq. 67).[189] An advantage of this system is that the catalyst activates the dienophile without irreversibly complexing the diene nitrogen. Increases in diastereo- and enantio-selectivity and rate

Table 27.

R^1	R^2	R^3	R^4	R^5	Yield (%)	*endo*:*exo*
Ph	H	H	H	H	91	51:49
3,4-$Cl_2C_6H_3$	H	H	H	H	93	57:43
4-$MeOC_6H_4$	H	H	H	H	84	50:50
2-MeC_6H_4	H	H	H	H	96	42:58
4-$O_2NC_6H_4$	H	H	H	H	96	53:47
Ph	H	H	CO_2Me	H	61	50:50
3,4-$Cl_2C_6H_3$	Cl	H	Cl	Cl	47	40:60
3,4-$Cl_2C_6H_3$	H	NO_2	H	H	65	55:45
3,4-$Cl_2C_6H_3$	–N=CHCH=CH–		H	H	78	63:37

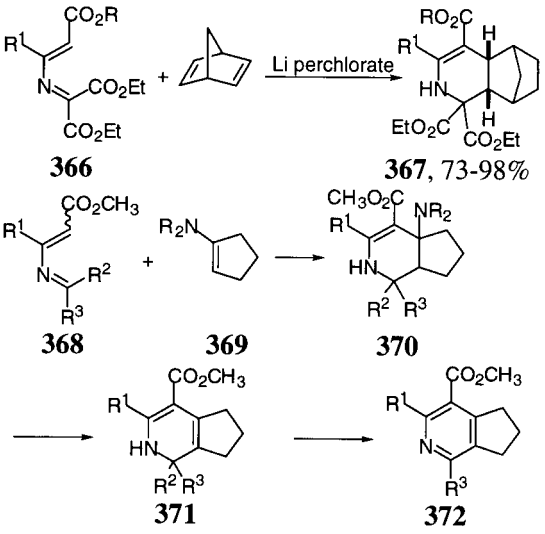
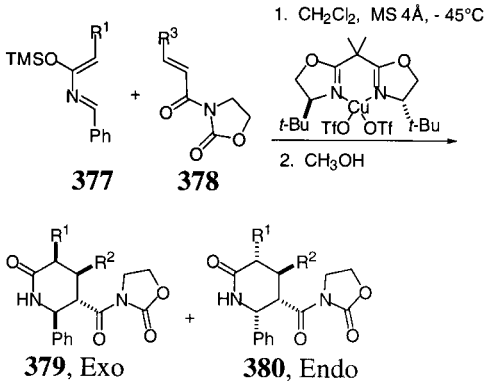


Figure 34.

were reported for reactions proceeding between −45°C and room temperature.



$R^1 = CH_3$ $R^2 = CH_3$ Yield 80 %, exo:endo >99:1, ee 95 %
$R^1 = CH_3$ $R^2 = H$ Yield 96 %, exo:endo >99:1, ee 98 %
$R^1 = H$ $R^2 = H$ Yield 83 %, exo:endo 6:1, ee 98 %

(67)

The configuration of the new stereogenic centers is accurately predicted by Evans' transition state model, previously proposed for application of the identical catalyst (Fig. 35). The predicted *exo*-selectivity was excellent with the exception of the 4-unsubstituted azadiene.

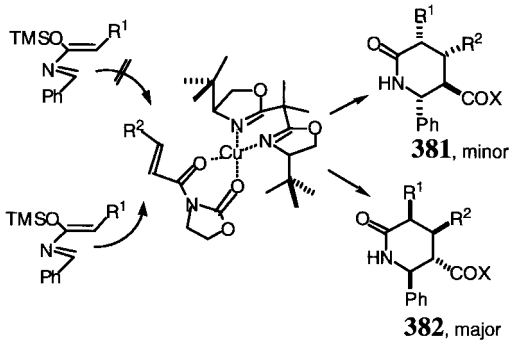


Figure 35.

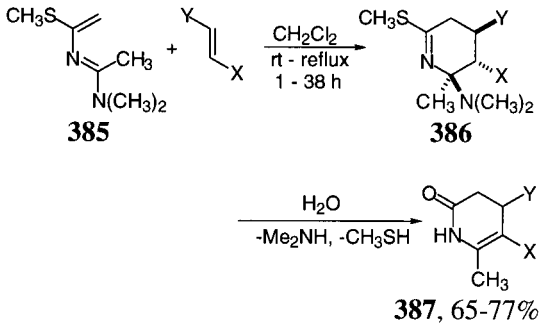
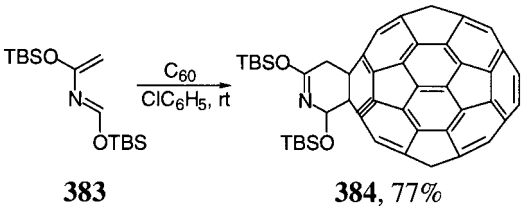


Figure 36.

The presence of a second alkylsilyloxy functionality on the 2-azadiene produces a significantly electron rich diene. By taking advantage of the low lying LUMO of C_{60} and the electron rich 1,3-bis(*tert*-butyldimethylsilyoxy)-2-azadiene **383** a room temperature cycloaddition was achieved which upon acid hydrolysis allowed for the production of the d-valerolactam derivative of C_{60} (Eq. (68)).[190]



(68)

Substituted 2-aza-1-(dimethylamino-3-(methylthio)dienes **385** have been demonstrated to react readily with electron-deficient dienophiles to produce pyridines and pyrimidines (Fig. 36).[191] The reactions are regioselective and in the cases of dimethylfumarate and acrylonitrile proceeded with *exo*-selectivity.

In the cycloadditions with alkyne dienophiles rearrangement of the initial cycloadduct resulted in the formation of multiple products via spontaneous allylic rearrangement followed by dimethylamine or methanethiol extrusion (Fig. 37). The resulting pyridines accounted for the major portion of the conversion.

In C-4 substituted systems the cycloaddition yield and product distribution is dependent on steric factors. The *E*,*E*-diene is unreactive toward the olefin dienophiles tested.

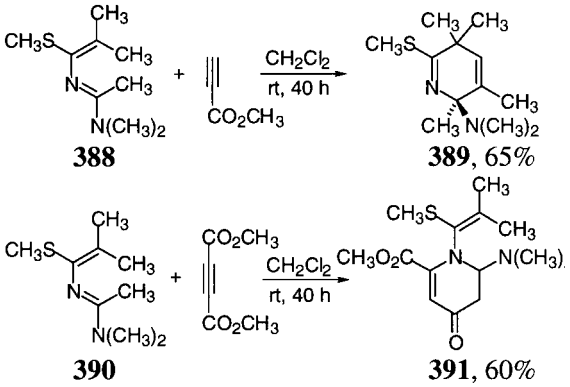


Figure 37.

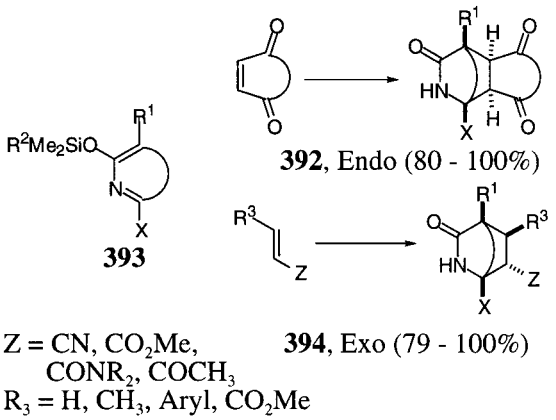


Figure 38.

The *E*,*Z*-isomer undergoes cycloaddition to produce the tetrahydropyridine in high yield. Dimethylacetylene-dicarboxylate (DMAD) reaction produces only the pyridine **391** from elimination of dimethylamine. Loss of methanethiol was not observed in this case.

3.2.5. Stereoselective cycloaddition. Cycloadditions of 2-azadienes with electron-deficient olefins show an interesting stereoselctivity.[192] In the reactions with cyclic dienophiles *endo*-selectivity is observed, while with acyclic dienophiles *exo*-selectivity predominates (Fig. 38).

The selectivity has been attributed to the reacting conformations. The *endo*-transition state stabilized by secondary orbital interactions and lacking electrostatic repulsion between the heteroatoms would be preferred over the *exo*-transition state in reactions of cyclic dienophiles constrained to the s-*trans* conformation (Fig. 39). In the acyclic case reaction would proceed through the s-*cis* conformation. The *exo*-transition state is preferred largely due to electrostatic repulsion between the heteroatoms, which would overcome the stabilization due to secondary orbital interactions in the *endo*-transition state.

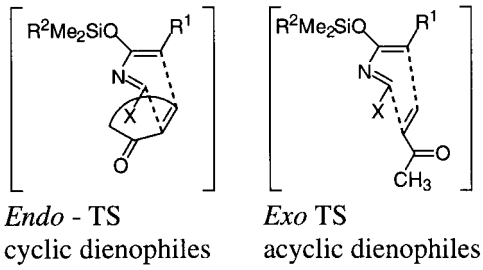
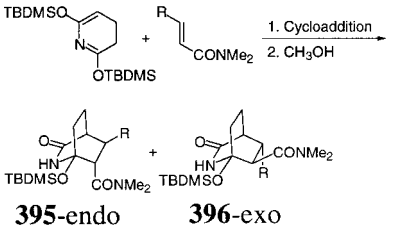


Figure 39.

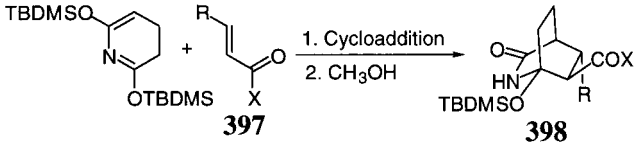
Ghosez et al. reasoned that the addition of a Lewis acid, which would generate an iminium ion dienophile, would replace the electrostatic repulsion of the diene nitrogen, to the carbonyl group with a coulombic attraction between the diene nitrogen and a positively charged species. The addition of *t*-butyldimethylsilyl triflate provided the desired *endo*-product, but only in the case in which R=H (Eq. (69)). In 4-substituted α,β-unsaturated amides the *exo*-products were observed exclusively, as was also observed with the addition of $Eu(fod)_3$.



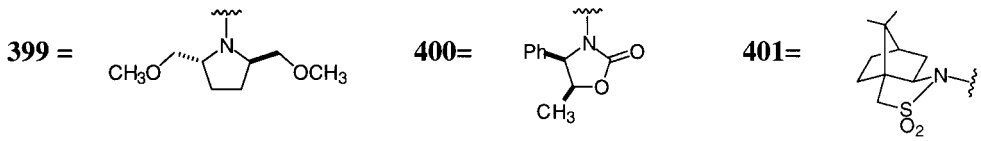
		Endo:exo	Yield(%)
R = H	no Catalyst, benzene, heat	15:85	53
	0.1 equiv. TBDMSOTf, benzene, rt	84:16	92
	0.1 equiv. TBDMSOTf, CH_3CN, rt	<1:>99	40
	0.1 equiv. $Eu(fod)_3$, benzene, 80°C	<3:>97	80
R = CH_3	0.2 equiv. TBDMSOTf, toluene, 60°C	<1:>99	77
R = Ph	0 .2 equiv. TBDMSOTf, toluene, 60°C	<1:>99	73

(69)

Utilizing non-racemic α,β-unsaturated amide dienophile **397** Ghosez et al. observed high levels of *exo*- and facial selectivity (Eq. (70), Fig. 40). With Evans' and Oppolzer's dienophiles less satisfactory results were obtained.

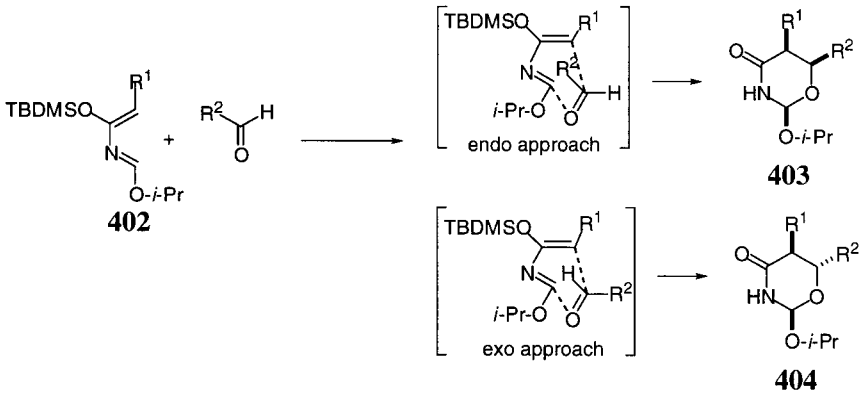


(70)



			Yield	Exo	(de)
399	R = H	0.1 equiv. TBDMSOTf, toluene, rt	84	87	>98
399	R = H	0.1 equiv. $Eu(fod)_3$, toluene, 60°C	96	>98	>98
399	R = CH_3	0.5 equiv. TBDMSOTf, 1,2-DCE, 80°C	59	>98	>98
399	R = Ph	0.5 equiv. TBDMSOTf, 1,2-DCE, 80°C	73	>98	>98
400	R = CH_3	1.4 equiv, Et_2AlCl, CH_2Cl_2, -78°C	45	100	>80
400	R = Ph	1.4 equiv, Et_2AlCl, CH_2Cl_2, -78°C	57	100	>80
401	R = CH_3	1.4 equiv, Et_2AlCl, CH_2Cl_2, -78°C	70	90	~0, endo (de>95%)
401	R = CH_3	1.4 equiv, $TiCl_4$, CH_2Cl_2, -78°C	90	81	~0, endo (de >95%)
401	R = Ph	No adducts with Et_2AlCl or $TiCl_4$			

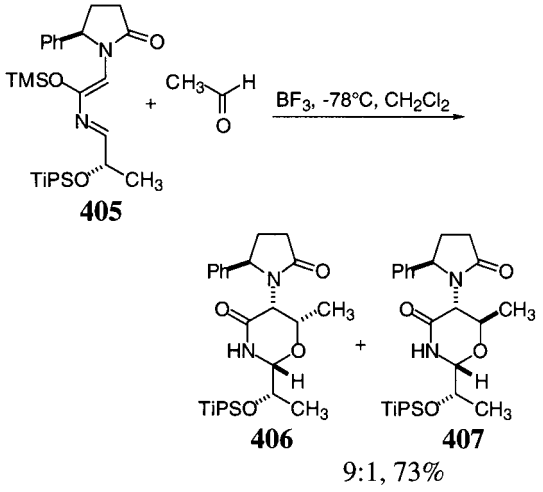
Figure 40.



Scheme 31.

Asymmetric Diels–Alder reactions of electron-rich 3-silyloxy-2-azadienes and aldehydes have been studied.[193] These azadienes are more reactive toward aldehydes than the Danishefsky's diene counterparts, and therefore do not require Lewis acid catalysis. The reactions are predominately *endo*-selective in accord with the general trend of cycloadditions to aldehydes (Scheme 31).

Panunzio et al. have demonstrated that the introduction of a chiral center to 2-azadiene may allow for the enantioselective cycloaddition reaction with aldehydes (Eq. (71)).[194] This reaction required addition of BF_3 as catalyst. The product mixture contained a 9:1 ratio of diastereomers.



(71)

While cycloadditions to aldehydes show marked *endo*-selectivity, additions to ketones range from marginal to moderate.[195] The cycloaddition of the homochiral azadiene **408** with the symmetrical ketones acetone and cyclohexanone resulted in the formation of racemic mixtures of the diastereomers **409** and **410** (Fig. 41). The use of (−)-menthone as the dienophile has been reported to give a 91:9 ratio of diastereomers.

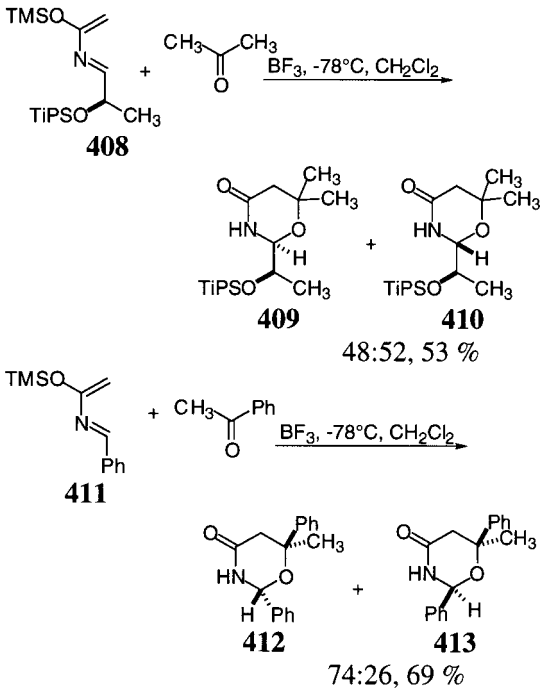


Figure 41.

4. Conclusions

There has been progress in imino Diels–Alder chemistry to the point where high selectivities and versatility allow for its application to the synthesis of complex natural products. However, the variety of piperidine based natural products is wide, and so the development of the imino Diels–Alder will continue in order to make this reaction even more useful to the synthetic organic chemist.

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