

SYNTHESIS OF NITROGEN-CONTAINING HETEROCYCLES BY THE IMINO DIELS-ALDER
REACTION

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Abstract — This review describes the major advances reported during the past fifteen years on synthesis of heterocyclic compounds using imino dienophiles in the Diels Alder [4+2]-cycloaddition reaction.

CONTENTS

- A. Introduction
- B. Survey of imino dienophiles
 - 1. N-Sulfonyl imines
 - 2. N-Acyl imines
 - a. Acyclic
 - b. Cyclic
 - 3. Iminium salts and imines
 - 4. Miscellaneous imino compounds
 - 5. Intramolecular cycloadditions of imino compounds
- C. Regiochemistry - summary and rationale
- D. Stereochemistry - summary and rationale
- E. Conclusion

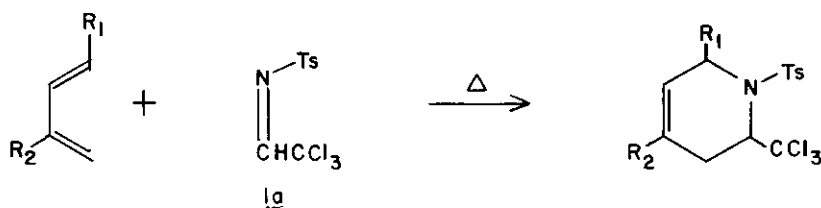
A. INTRODUCTION

The [4+2]-cycloaddition of a conjugated diene with an imine was first reported by Alder in 1943.¹ In 1967 a review covering the literature to 1964 was published on this subject.² In the present review, we describe the work done in this field over the past fifteen years, with particular emphasis on the regiochemical and stereochemical course of the reaction.

A variety of imino compounds are known to undergo the Diels-Alder cycloaddition.² In general, imines bearing electron withdrawing groups are the most effective dienophiles, but simple iminium compounds are occasionally useful. Uncharged alkyl imines are usually unreactive. The

sufficient experimental data is not currently available concerning the reacting geometry (E or Z) of these imines and of the "endo" orienting preferences of tosyl vs trihaloalkyl to fully explain this outcome.^{4,21}

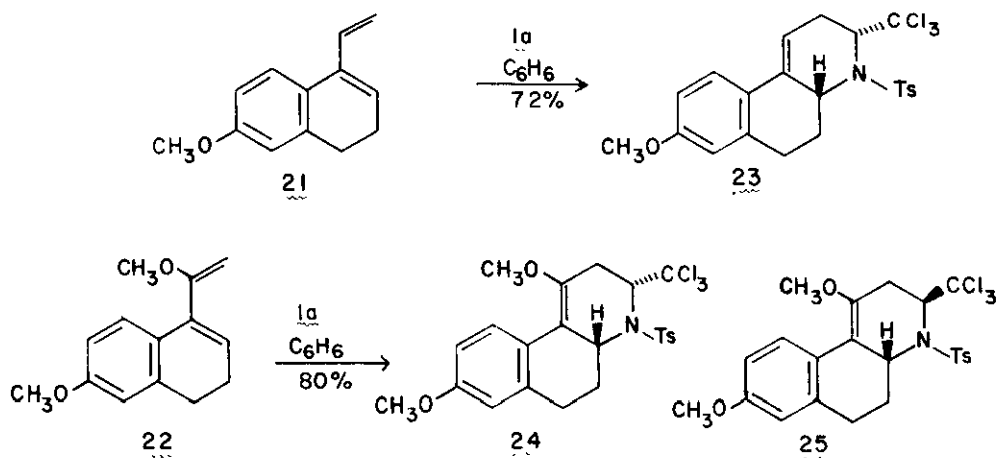
Two groups have examined the thermal cycloaddition of imine 1a with a variety of unsymmetrical acyclic dienes 7-13,^{5,6} and in each case only a single orientational isomer (14-20) was



			Yield %
<u>7</u>	$R_1 = \text{CH}_3, R_2 = \text{H}$	<u>14</u>	72
<u>8</u>	$R_1 = \text{C}_6\text{H}_6, R_2 = \text{H}$	<u>15</u>	70
<u>9</u>	$R_1 = \text{H}, R_2 = \text{CH}_3$	<u>16</u>	82
<u>10</u>	$R_1 = \text{H}, R_2 = \text{C}_6\text{H}_5$	<u>17</u>	86
<u>11</u>	$R_1 = \text{H}, R_2 = \text{C}_6\text{H}_4\text{-p-CH}_3$	<u>18</u>	84
<u>12</u>	$R_1 = \text{H}, R_2 = \text{OCH}_3$	<u>19</u>	unspecified
<u>13</u>	$R_1 = \text{H}, R_2 = \text{C}_6\text{H}_4\text{-p-OCH}_3$	<u>20</u>	unspecified

found. This regioselectivity has been rationalized on the basis of a dipolar transition state for the imino Diels-Alder reaction⁵ (see Section C).

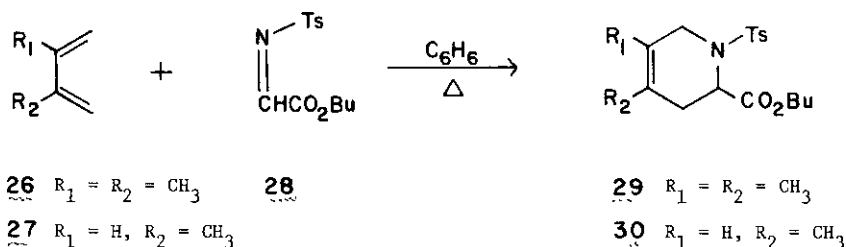
Speckamp and coworkers^{6,7} investigated the addition of imine 1a to the more complicated dienes 21 and 22, and found that with diene 21 only adduct 23 was formed. However, with diene 22,



a 1.5/1 mixture of stereoisomers 24 and 25 was isolated and characterized. In both cases only a

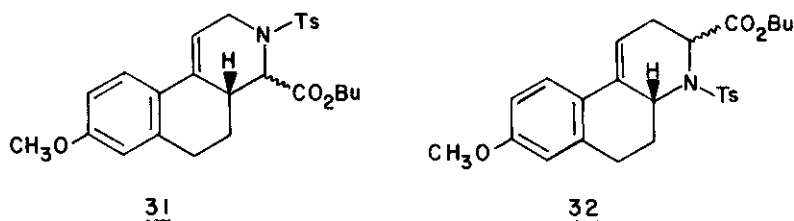
single regioisomeric series was formed. A rationale similar to that first offered by Krow⁴ was proposed to explain the stereochemical outcome of this cycloaddition.⁷

Albrecht and Kresze⁸ have described synthesis of imine 28 and its addition in refluxing



benzene to 2,3-dimethylbutadiene (26) and isoprene (27) to form adducts 29 and 30, respectively, in unspecified yields. Imine 28 was also added successfully to cyclopentadiene and cyclohexadiene, to produce adducts of indeterminate stereochemistry.

Condensation⁹ of diene 21 with imine 28 in benzene at 0° gave a 100% yield of adducts 31 and 32 in a 3/1 ratio. At higher reaction temperatures, the combined yield was lower and double bond

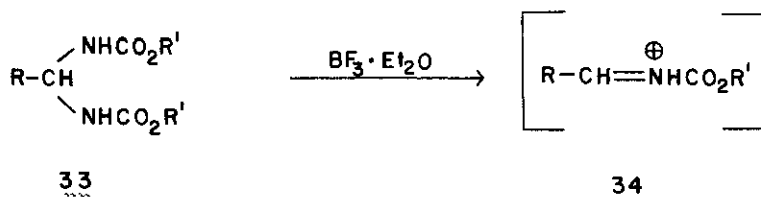


isomers were also formed. Stereochemistry was not elucidated. Adducts such as 29-32 have been converted to pyridines by treatment with base,^{8,9} although yields are not spectacular.

2. N-Acyl imines

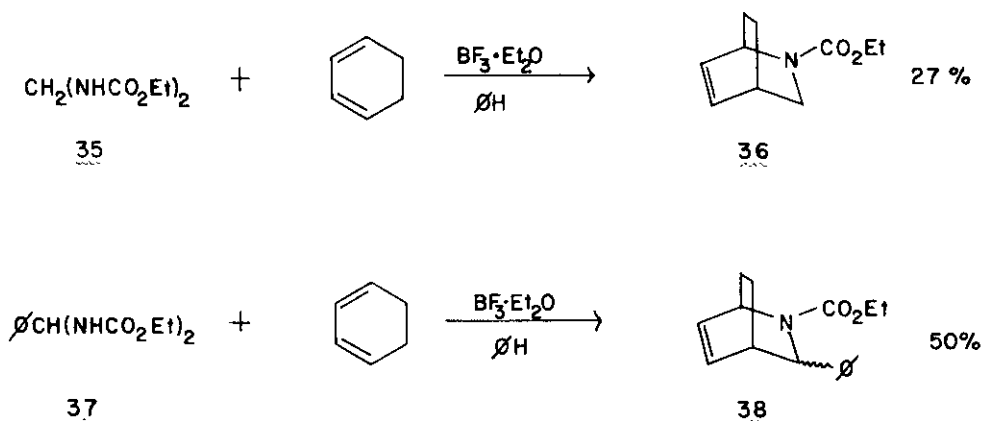
a. Acyclic

Simple acyclic N-acylimino dienophiles, such as 34, first reported by Merten and Müller,^{2,10} have been used extensively during the past fifteen years. These imines are most commonly generated

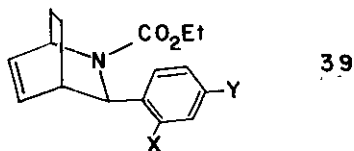


in situ from readily available biscarbamates $\underline{33}$ ¹¹ upon heating with a catalytic amount of boron trifluoride etherate.

Cava, et al.¹² described an approach to isoquinuclidines via BF_3 catalyzed condensation of cyclohexadiene with bis-carbamates $\underline{35}$ and $\underline{37}$ to produce adducts $\underline{36}$ and $\underline{38}$, respectively, in fair



yields. The stereochemistry of $\underline{38}$ was not established at the time, but has been recently reinvestigated in detail by Krow and coworkers,¹³ who found that $\underline{38}$ was actually a mixture of exo and



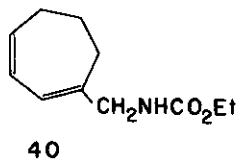
X	Y	% Exo Adduct $\underline{39}$	Total Yield (%)
H	H	80	30-40
H	NO ₂	80	71
H	CH ₃	85	61
CH ₃	H	83	44 (ref. 22)
OCH ₃	OCH ₃	79	64

Scheme I

endo (80/20) stereoisomers. They also prepared some aryl-substituted^{13,20} adducts ($\underline{39}$) via the same cycloaddition and stereochemical results are outlined in Scheme I. In addition, these workers looked at the effects of other Lewis acids upon the exo/endo ratio and the effects of using carbamate esters other than ethyl. In general, the exo products were favored by about 3/4/1. The

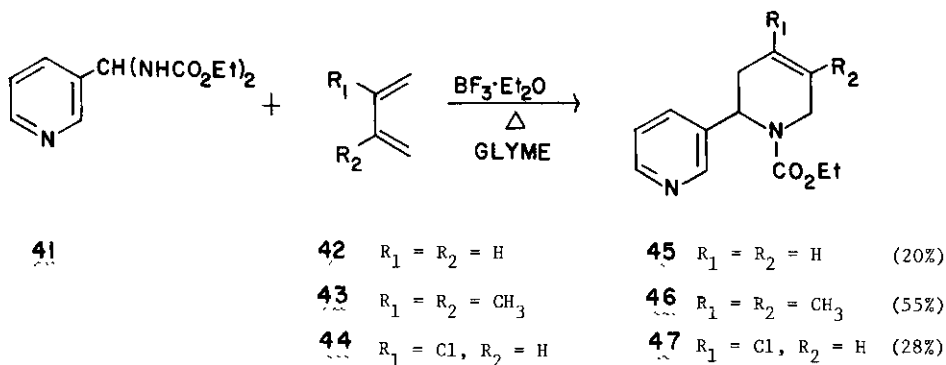
mechanistic rationale(s) given^{13b} to explain these results involves a stepwise cycloaddition of a protonated E-acylimine to the diene.^{13b}

Krow^{14a} and Hobson^{14b} have examined the additions of 35 and 37 to 1,3-cycloheptadiene, and obtained [4+2]-adducts in poor yield along with products of electrophilic substitution of the diene,¹⁷ such as 40. Addition of 35 to cyclopentadiene and 1,3-cyclooctadiene gave no Diels-Alder



products. In addition, the stereochemistry of cycloaddition of 35 and 37 with some menthadienes has been investigated in some detail.¹⁵

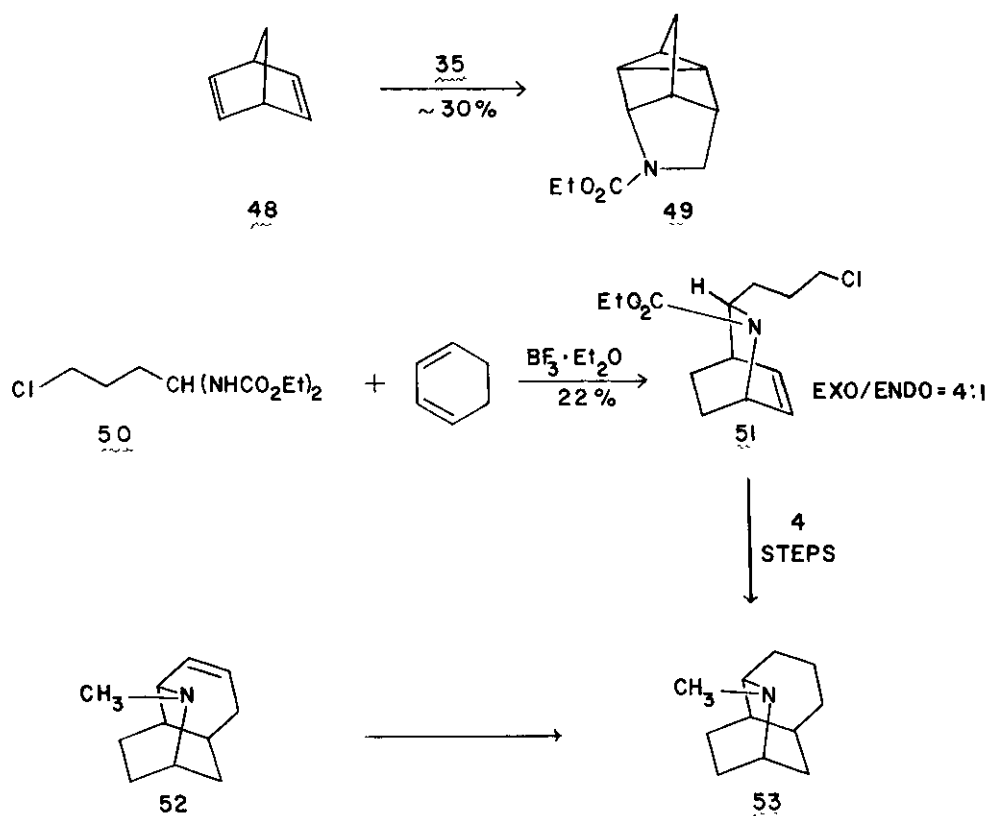
Quan *et al.*¹⁶ reported acid catalyzed addition of the interesting pyridyl-bis-carbamate 41 to butadiene (42), 2,3-dimethylbutadiene (43) and chloroprene (44) to give adducts 45 to 47,



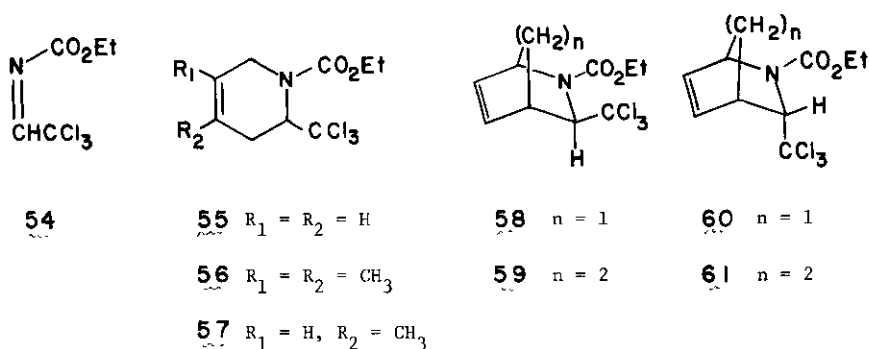
respectively, in mediocre yields. The other possible regioisomer from chloroprene cycloaddition was not detected. Adduct 45 was converted to the tobacco alkaloid anatabine by hydrolytic removal of the carboethoxy group.

Sasaki¹⁸ has described a homo-Diels-Alder reaction of diene 48 with bis-carbamate 35 under Lewis acid catalysis to yield compound 49 in moderate yield. Attempts at similar additions with some other imino dienophiles were unsuccessful.

A synthesis of the hydrogenation product 53 of the alkaloid cannivonine (52) has been claimed using the endo adduct 51, formed in minor amount from addition of bis-carbamate 50 to cyclohexadiene.^{19a} However, there is now considerable doubt as to the actual structures of both cannivonine and dihydrocannivonine.^{19b}

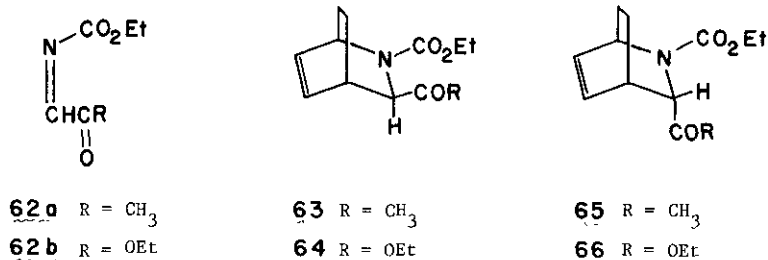


The trichloromethyl imine 54 has been synthesized²⁰ and used^{4b,13b,14a,21} in Diels-Alder reactions. Acid catalyzed addition of 54 to butadiene, 2,3-dimethylbutadiene and isoprene gave

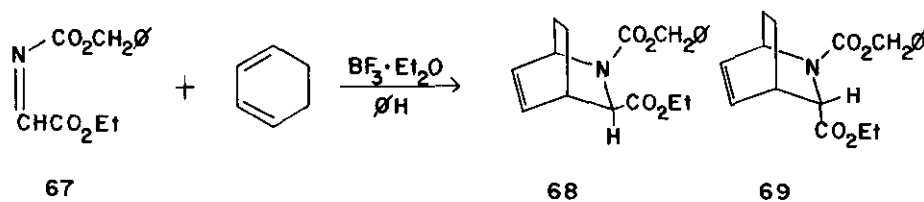


adducts 55-57 in 55, 78 and 75% yields, respectively. Only a single regioisomer was found in the isoprene case. With cyclopentadiene and cyclohexadiene, exo/endo stereoisomeric mixtures are obtained^{4b,21} (58-61), with exact ratios being dependent upon reaction conditions, although endo isomers predominate as in the case of imine 1a,

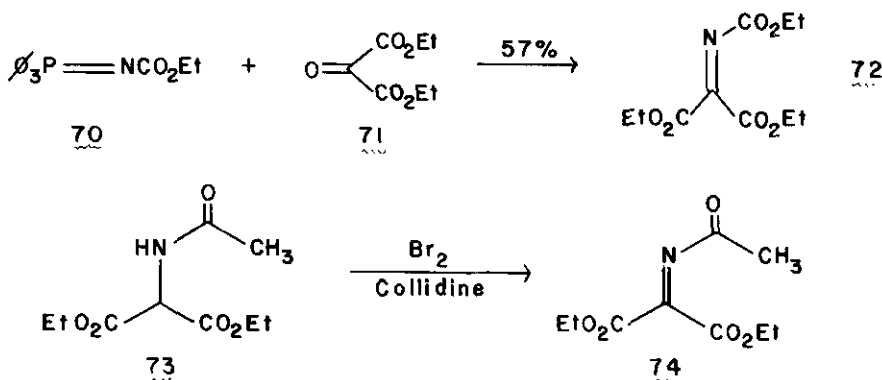
Acylimines of type 62 have found application in cycloaddition reactions.^{13,22,23,25} Imines of this kind are usually generated from methoxyglycinates²⁴ by treatment with $\text{BF}_3 \cdot \text{etherate}$ *in situ*. Addition of 62a and 62b to 1,3-cyclohexadiene produces approximately a 2/1 ratio of *exo* isomers 63 and 64 to *endo* isomers 65 and 66, respectively.^{13b,25}



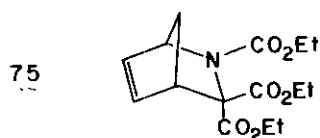
Baxter and Holmes, in an approach to the alkaloid prosopine, have added imine 67 to cyclohexadiene and obtained a 4/1 mixture of *exo/endo* isomers 68 and 69 in a total yield of 35%.²³



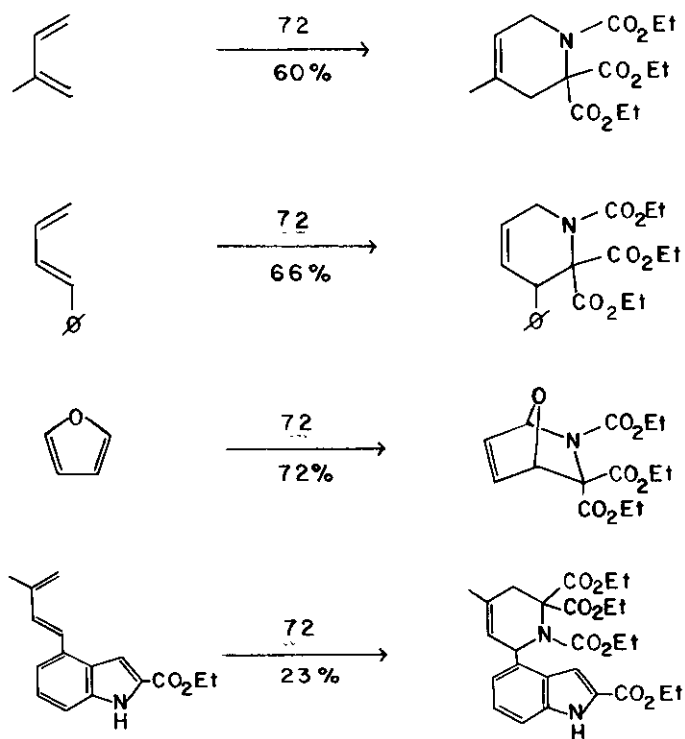
Plieninger, *et al.* have described synthesis of the highly functionalized acylimine 72 by condensation of phosphine imine 70 with diethyl mesoxalate (71).²⁶ A more convenient synthesis of the related imine 74 has been developed by Johnson starting from acetyl amino malonate 73.²⁷



Imine 72 is quite reactive towards cyclopentadiene, producing adduct 75 (62%) on heating in THF. However, other dienes reacted more sluggishly with 72 and required heating at 10^4 atm. Some



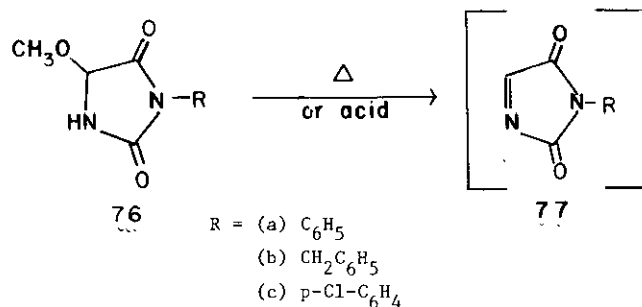
of the cycloadditions reported are outlined below in Scheme II. Cycloadditions with imine 72 reportedly afforded only single regioisomers in those cases where unsymmetrical dienes were used as reacting partners. Imine 74 has also been used successfully in Diels Alder cycloadditions.²⁷



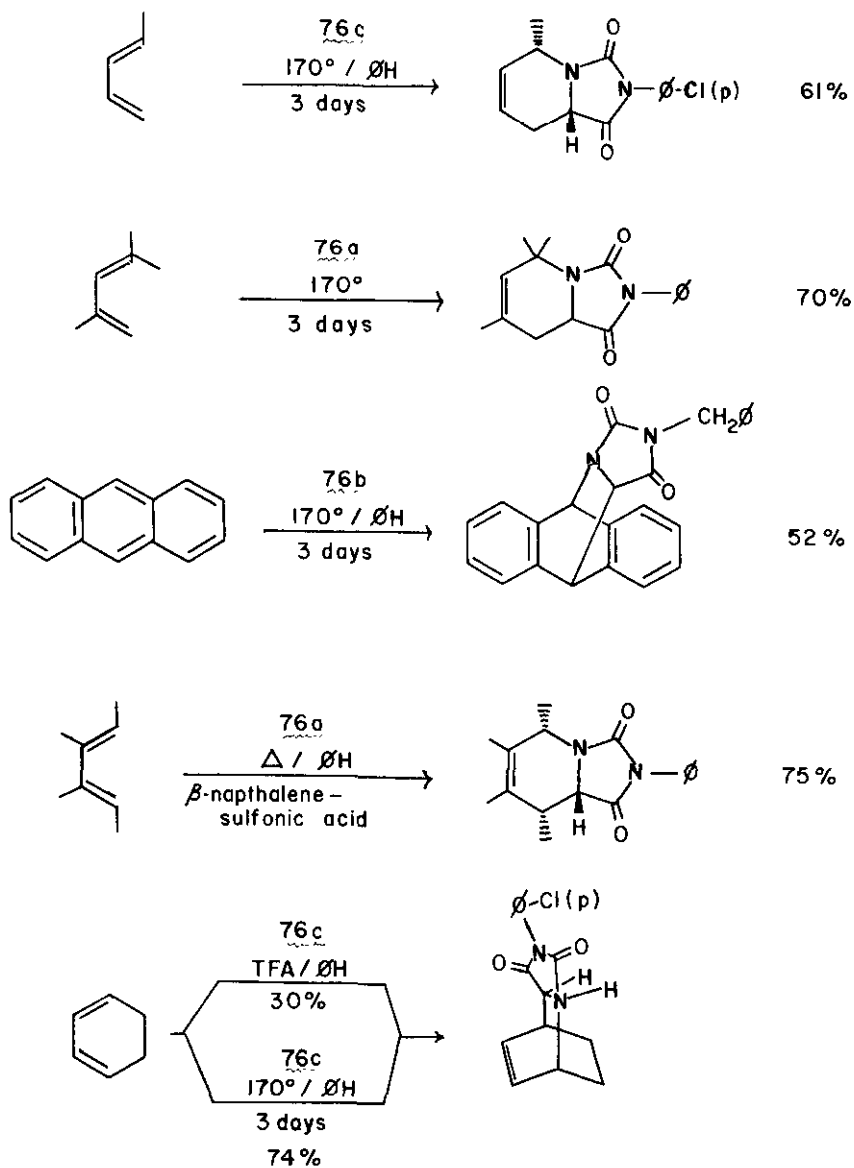
SCHEME II

b. Cyclic

The use of cyclic N-acylimines as dienophiles has received attention recently.²⁸ Readily available methoxyhydantoin (76)²⁹ upon heating or on treatment with an acid lose the elements of

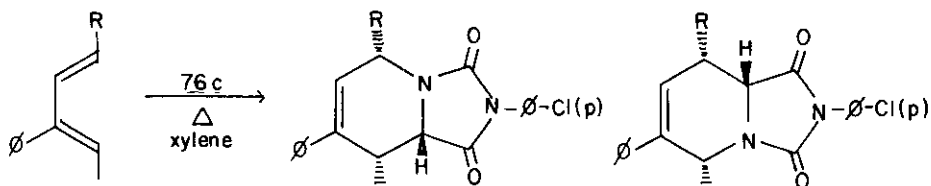


methanol to generate imines such as 77 which can be trapped with conjugated dienes. Ben-Ishai and Goldstein²⁸ have investigated addition of 77 to a large number of dienes and a few representative examples are listed in Scheme III. These cycloadditions were found to be regioselective in those cases tried with unsymmetrical dienes (except for isoprene addition) as can be seen in the Scheme. The addition is also stereoselective and only endo stereoisomers were detected,^{4b} although the hydantoin proton has a tendency to epimerize in some of the adducts after cycloaddition has occurred.²⁸



SCHEME III

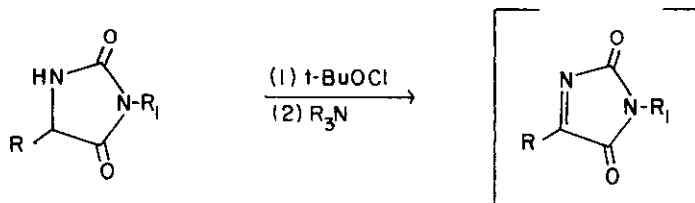
A series of highly substituted unsymmetrical dienes 78 to 82 has been investigated in the thermal reaction with methoxyhydantoin 76c.³⁰ Ratios of the two possible orientational isomers are given in Scheme IV. In all cases, only endo stereoisomers were found as depicted in the structures.



		Product Ratio	
<u>78</u>	R = COOCH ₃	0	100
<u>79</u>	R = H	8	92
<u>80</u>	R = CH ₂ OCOCH ₃	55	45
<u>81</u>	R = CH ₃	67	33
<u>82</u>	R = CH ₂ CH ₃	75	25

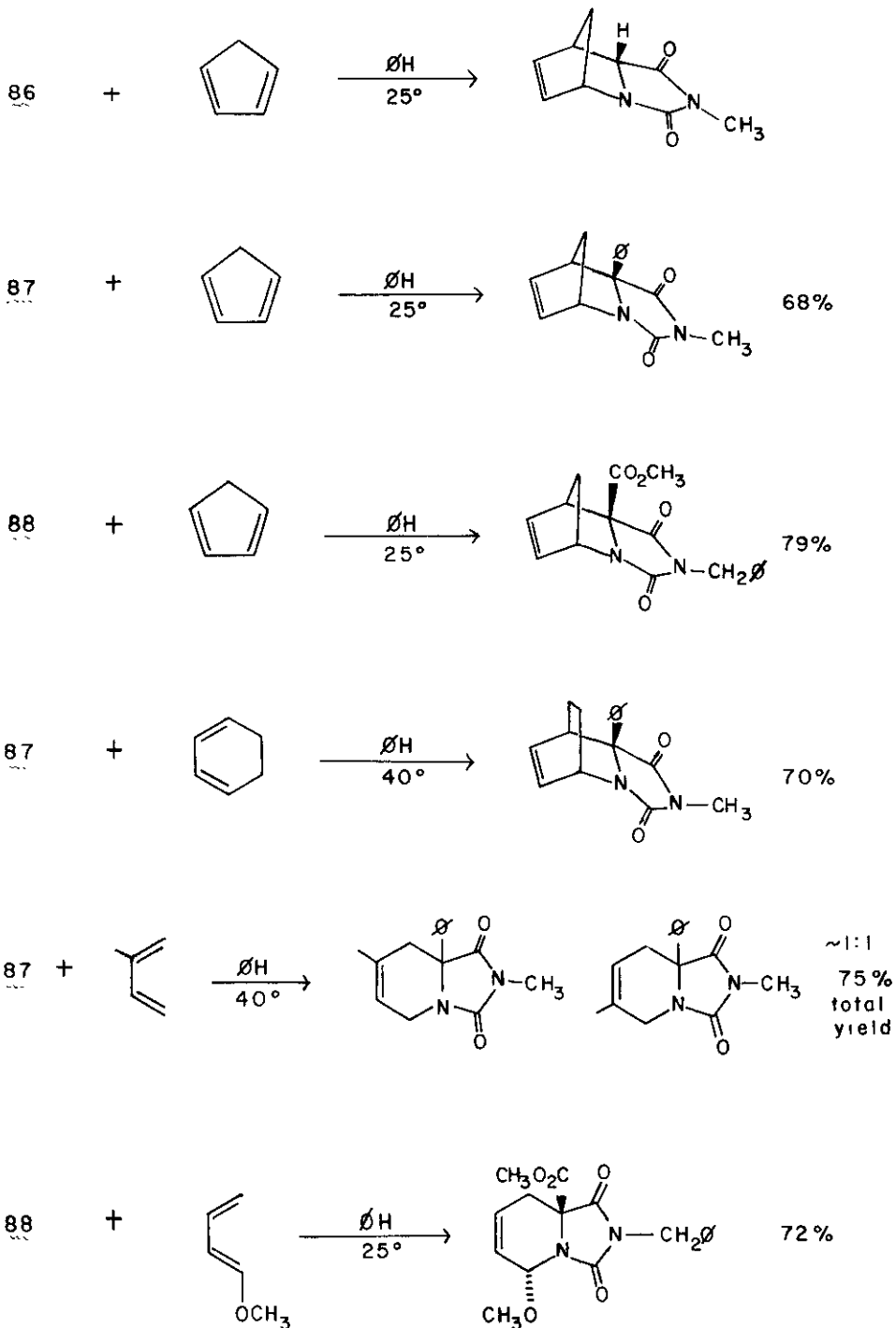
SCHEME IV

In an independent study, Evin, Lam and Blyskal³¹ reported preparation, in situ, of imines 86-88 via chlorination and dehydrochlorination of hydantoin 83-85, respectively. The trapping



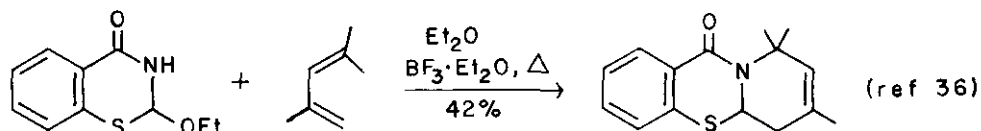
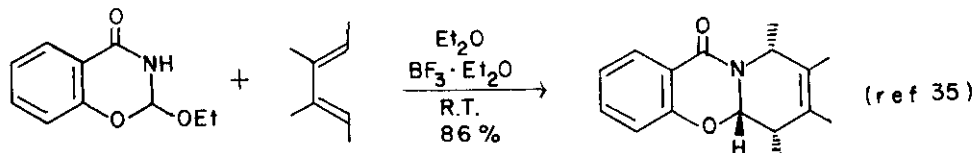
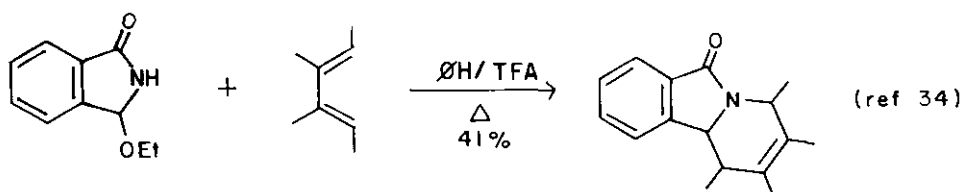
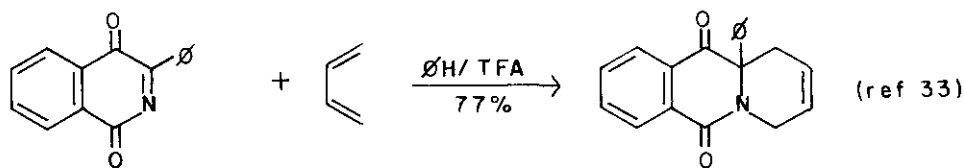
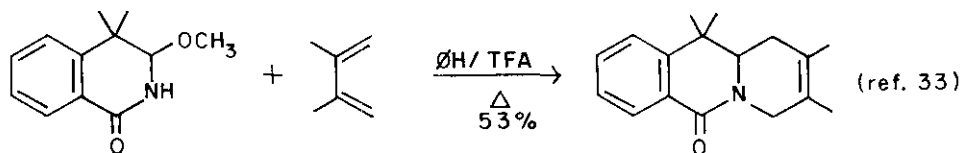
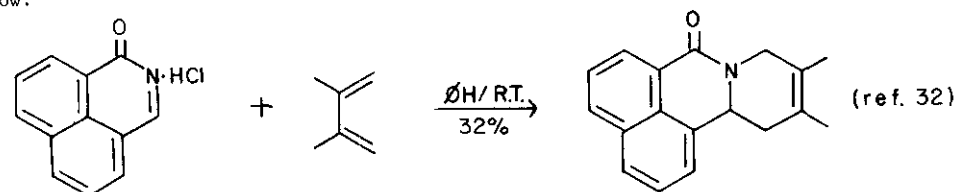
<u>83</u>	R = H, R ₁ = CH ₃	<u>86</u>
<u>84</u>	R = C ₆ H ₅ , R ₁ = CH ₃	<u>87</u>
<u>85</u>	R = CO ₂ CH ₃ , R ₁ = CH ₂ C ₆ H ₅	<u>88</u>

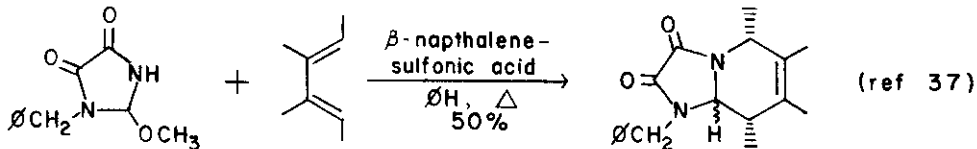
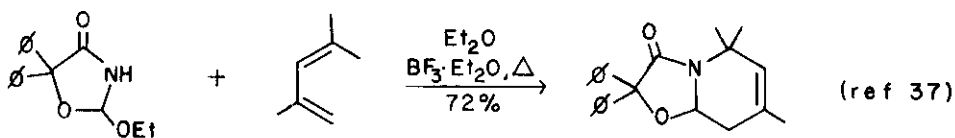
of these imines with several dienes was investigated, and some of the results are outlined below:



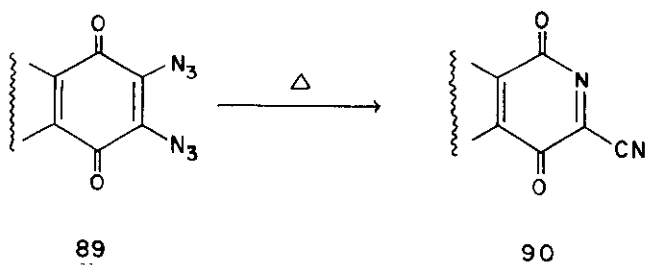
As in the cases reported by Ben-Ishai,²⁸ these cycloadditions show excellent regio- and stereo-selectivity in all cases except those using isoprene as the diene component. The regiochemical results in these hydantoin cycloadditions have been rationalized on the basis of the involvement of a dipolar transition state^{30,31} (see Section C).

In a series of several papers, Ben-Ishai and coworkers have looked at the Diels-Alder cycloadditions of many different types of cyclic acylimines.³²⁻³⁶ Some representative examples are outlined below:

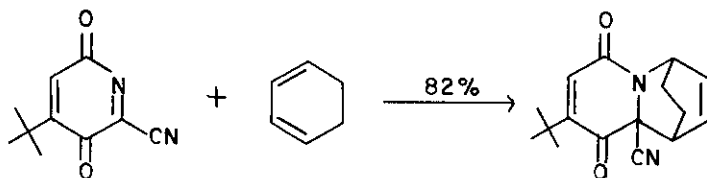
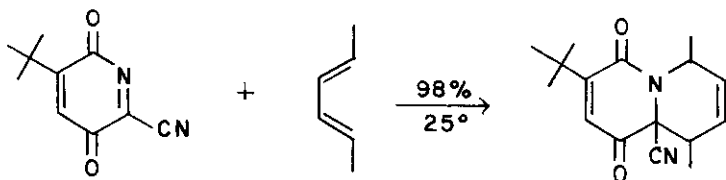
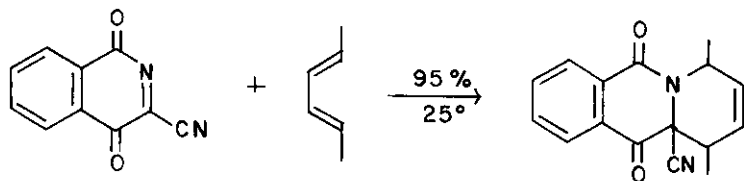


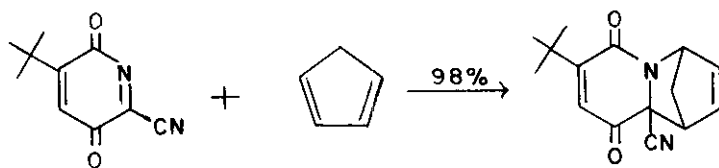


More recently, azaquinones³⁷ have received additional attention as Diels-Alder dienophiles (see entry 3 above). Compounds of type 90, generated by thermal rearrangement of 1,2-bis-azidoquinones 89, react rapidly with a number of dienes to produce [4+2]-adducts in high yield.



Some representative examples of this cycloaddition are outlined below. Stereochemistry was not determined in these cases, nor were unsymmetrical dienes tried. Interestingly, the rate of addition of azaquinones to dienes is about 10 times faster than the analogous addition of dehydrohydantoin (77).

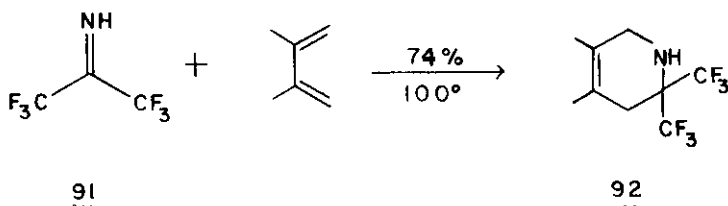




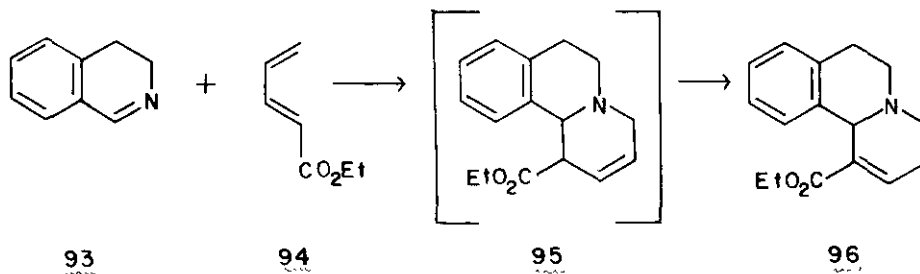
3. Iminium salts and imines

The cycloaddition of conjugated dienes with simple alkyl imines and iminium salts has received no systematic investigation to date and only a few isolated examples have been reported since the last review.²

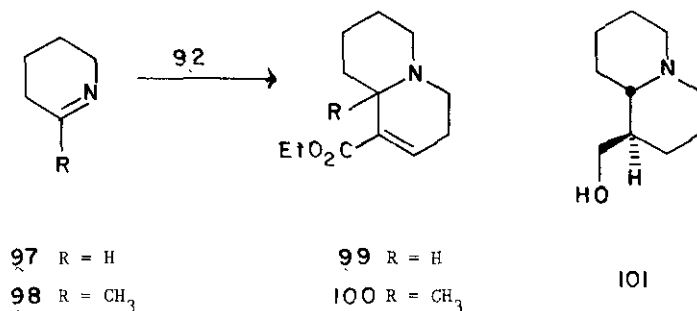
Middleton and Krespan³⁸ described cycloaddition of hexafluoroacetone imine (91) to 2,3-dimethylbutadiene (100°/18 hr) to produce adduct 92 in good yield. Apparently the free base is the reactive species in this case.



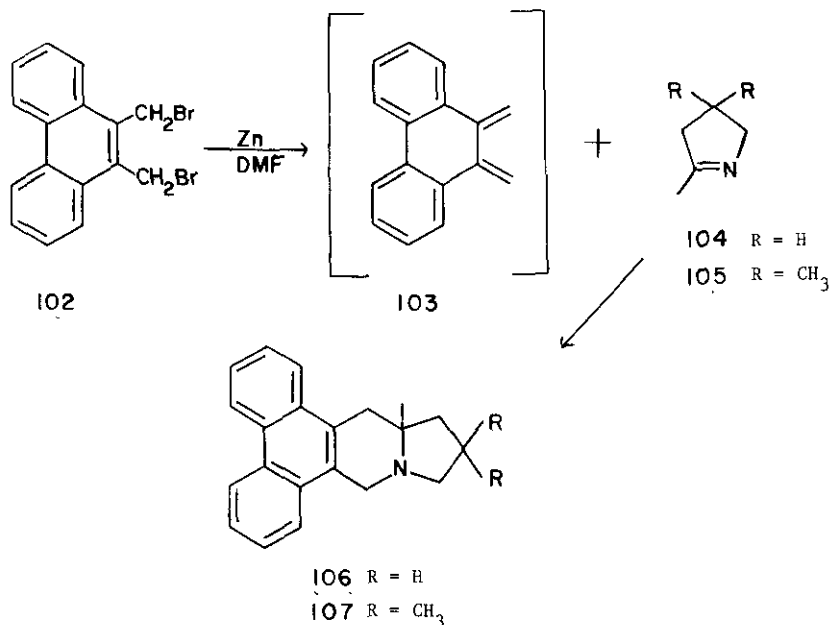
Bohlmann and coworkers³⁹ have added several imines to ethyl 2,4-pentadienoate (94). Thus, dihydroquinoline 93 and diene 94 on heating at 130° produced tricyclic compound 96, presumably



via the unconjugated intermediate 95. Similarly, imines 97 and 98 added to diene 94 to afford adducts 99 and 100, respectively, in fair yields. However, some other substituted imines were found to react as enamines with diene 94. Adduct 99 was further transformed into the quinolizidine alkaloid lupinine (101).

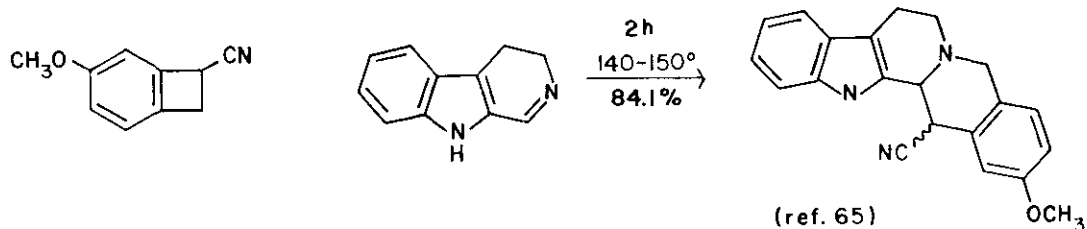
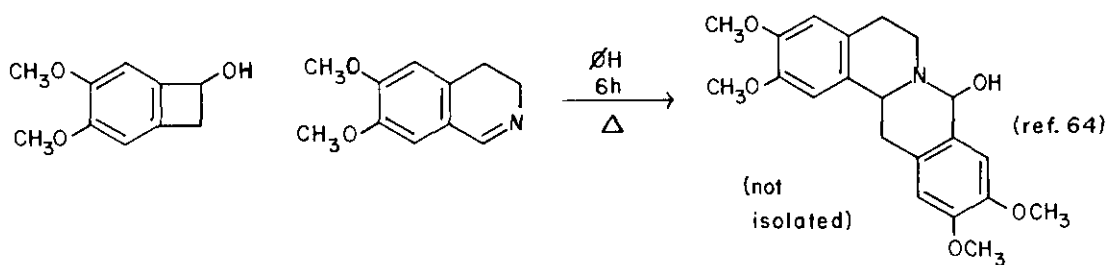
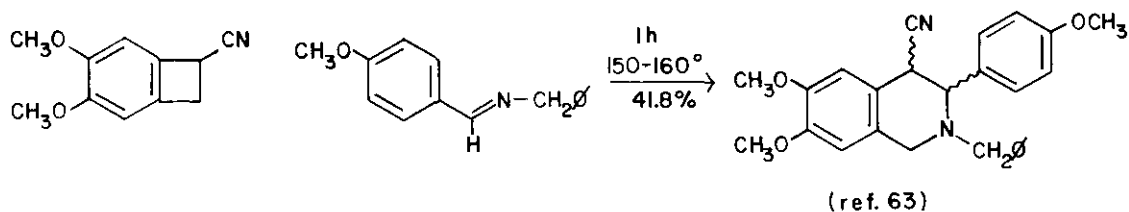
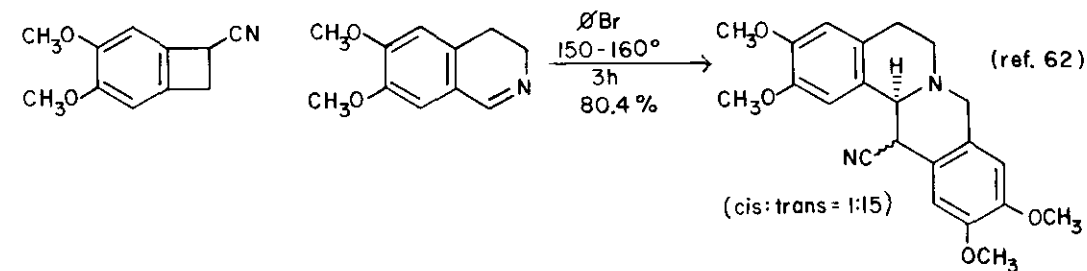


Wiegrebe⁴⁰ has condensed diene 103, generated in situ from the dibromomethylphenanthrene 102, with imines 104 and 105 to produce adducts 106 and 107, respectively, in 10% yields.

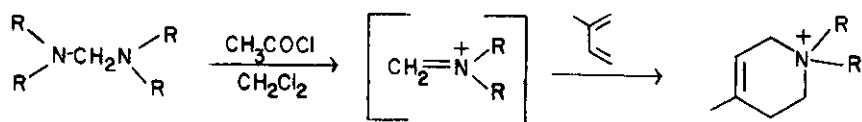


In the above two investigations, it is not completely clear from the experimental conditions described whether the reacting dienophile is in the iminium form or is the free base.

Kametani and coworkers have examined the thermolytic cycloaddition reactions of several imines with *o*-quinodimethanes, produced in situ from substituted benzocyclobutenes.⁶²⁻⁶⁵ These reactions proceeded with a high degree of regioselectivity and in good yield. Some examples follow:



In work similar to that originally described by Bohme, *et al.*,⁴¹ Russian workers⁴² found that iminium salts, generated from ainals 108-111 by treatment with acetyl chloride, added to isoprene to afford adducts 112-115. These adducts were not characterized but were directly rearranged with base to dienes of type 116, and it appears that the cycloadditions are regioselective since only one diene was isolated in each case.



108

R = CH₃

112

109

R = CH₂CH₃

113

110

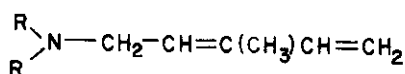
R = (CH₂)₅

114

111

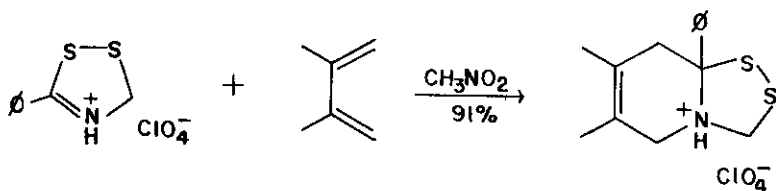
R = C₄H₉

115



116

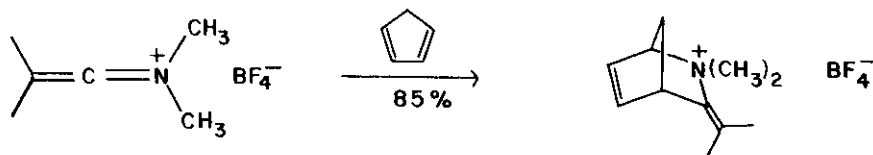
The rather exotic iminium salt 117 has been added to 2,3-dimethylbutadiene to afford adduct 118 in excellent yield.⁴³ The free base corresponding to 117 was unreactive toward cycloaddition.



117

118

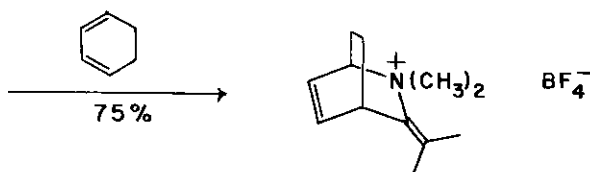
Cycloaddition of cumulene 119 to several conjugated dienes has been described.⁴⁴ Cyclic dienes such as cyclopentadiene and cyclohexadiene give good yields of [4+2]-adducts 120 and 121,



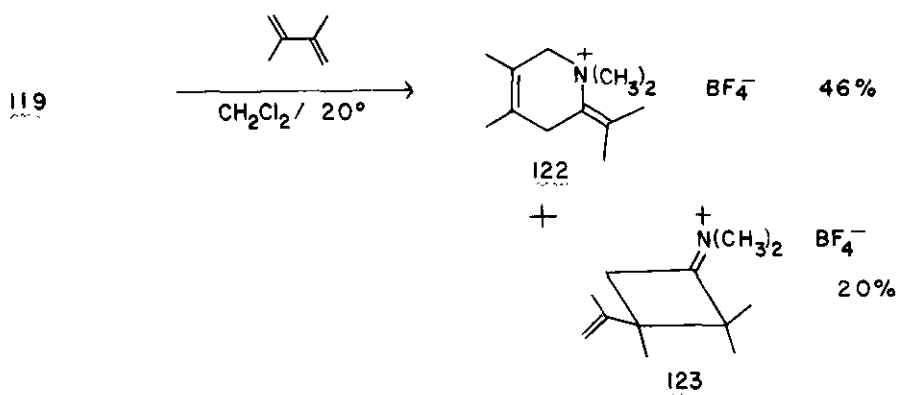
119

120

119



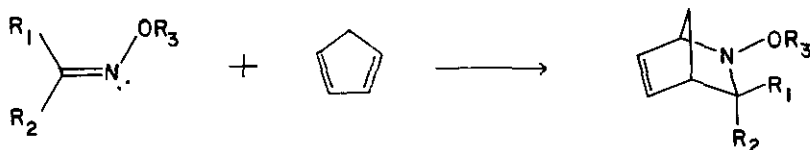
121



respectively. 2,3-Dimethylbutadiene and 119 yields a mixture of [4+2]-adduct 122 and [2+2]-adduct 123. However, with butadiene, piperylene and isoprene only [2+2]-adducts were formed from cumulene 119.

4. Miscellaneous imino compounds

The synthesis, configuration and reactivity of isonitroso malonate derivatives 124-141 have been investigated extensively by Fleury and coworkers.⁴⁵⁻⁵⁰ Scheme V shows the results of the [4+2]-cycloadditions of these dienophiles to cyclopentadiene.⁴⁸ In general, the adducts formed have



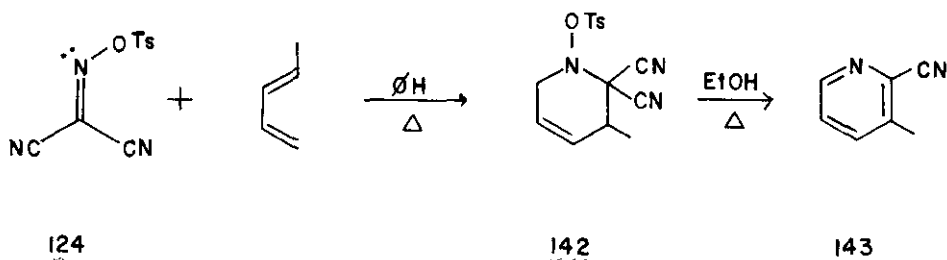
	R ₁	R ₂	R ₃	Yield of Adduct	t °C	Reaction Time (h)	Solvent
<u>124</u>	CN	CN	SO ₂ C ₇ H ₇	88	20	12	Et ₂ O
<u>125</u>	CN	CN	COC ₆ H ₄ pNO ₂	90	20	24	Et ₂ O
<u>126</u>	CN	CN	COC ₆ H ₅	80	20	48	Et ₂ O
<u>127</u>	CN	CO ₂ Et	SO ₂ C ₇ H ₇	55	80	3	C ₆ H ₆
<u>128</u>	CN	CO ₂ Et	SO ₂ CH ₃	51	80	3	C ₆ H ₆
<u>129</u>	CN	CO ₂ Et	COC ₆ H ₄ pNO ₂	65	80	4	C ₆ H ₆
<u>130</u>	CN	CO ₂ Et	COC ₆ H ₅	0	80	8	C ₆ H ₆
<u>131</u>	CN	CO ₂ Me	SO ₂ C ₇ H ₇	57	80	4	C ₆ H ₆
<u>132</u>	CN	CO ₂ Me	SO ₂ CH ₃	50	80	4	C ₆ H ₆
<u>133</u>	CN	CO ₂ Me	COC ₆ H ₄ pNO ₂	62	80	4	C ₆ H ₆
<u>134</u>	CN	CO ₂ Me	COC ₆ H ₅	0	80	8	C ₆ H ₆
<u>135</u>	CN	CONH ₂	SO ₂ C ₇ H ₇	42	60	20	acetone
<u>136</u>	CN	CONH ₂	SO ₂ CH ₃	39	70	36	dioxane

	R ₁	R ₂	R ₃	Yield of Adduct	t°C	Reaction Time (h)	Solvent
<u>137</u>	CN	CONH ₂	COC ₆ H ₄ pNO ₂	20	70	48	dioxane
<u>138</u>	CN	CONH ₂	COC ₆ H ₅	0	80	48	dioxane
<u>139</u>	CO ₂ Et	CO ₂ Et	SO ₂ C ₇ H ₇	0	60	72	acetone
<u>140</u>	CO ₂ Et	CO ₂ Et	SO ₂ CH ₃	0	60	72	acetone
<u>141</u>	CO ₂ Et	CO ₂ Et	COC ₆ H ₄ pNO ₂	0	60	72	acetone

Scheme V

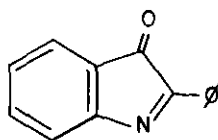
group R₂ endo (OR₃ is exo in the transition state, presumably) although endo-exo equilibration does often occur. The reactivity sequence for R₁, R₂ = -CN >> CO₂R > CONH₂ and for R₃ = -SO₂C₇H₇ > -SO₂CH₃ > COC₆H₄pNO₂ > COC₆H₅.

Other dienes have not been investigated as thoroughly as has cyclopentadiene, but it has been reported⁵⁰ that piperylene adds to 124 to afford 142. Of potential synthetic utility is the thermal



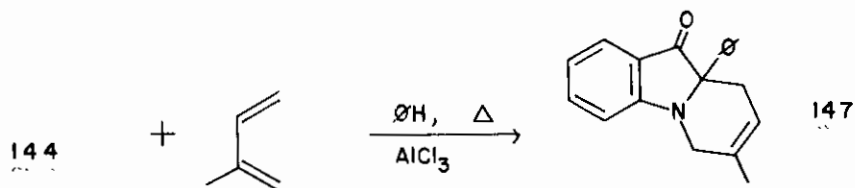
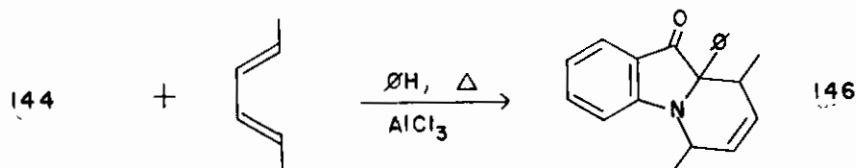
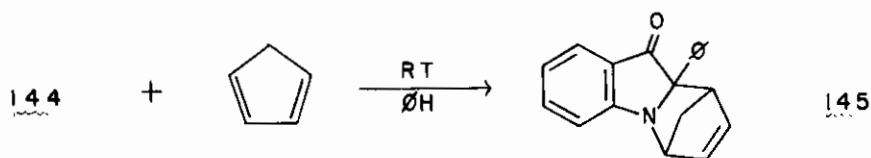
elimination of HCN and p-toluenesulfonic acid from 142 to yield cyanopyridine 143. Compound 124 also adds to cyclohexadiene and 2,3-dimethylbutadiene,⁴⁶ but is unreactive towards 3-vinylindene.⁵¹

Indolones of type 144 add readily to dienes to afford adducts of the Diels-Alder variety.⁵²



144

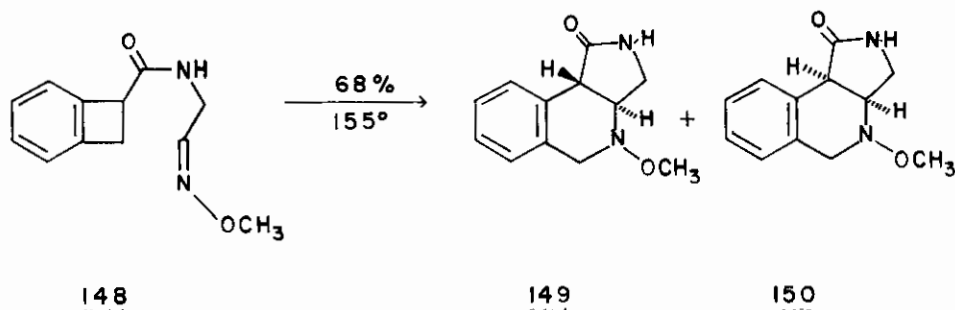
Addition of 144 to cyclopentadiene and 1,4-dimethylbutadiene gave compounds 145 and 146, respectively, in unspecified yields. Stereochemistry was not determined. Addition of isoprene to



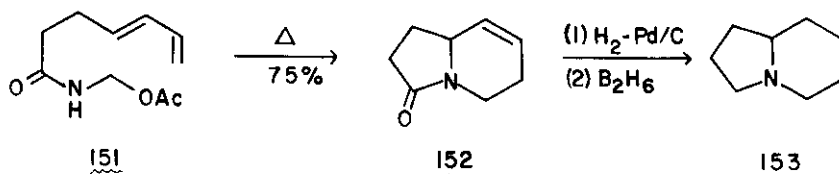
$\underline{144}$ gave only a single adduct for which structure $\underline{147}$ was suggested solely on mechanistic grounds.

5. Intramolecular cycloadditions of imino compounds

Only a single published example of this sort of reaction exists to date.⁵³ Oppolzer has described thermal cyclization of oxime $\underline{148}$ to form a mixture of stereoisomeric products $\underline{149}$ and $\underline{150}$, presumably occurring via an intermediate *o*-quinodimethane.⁵⁴

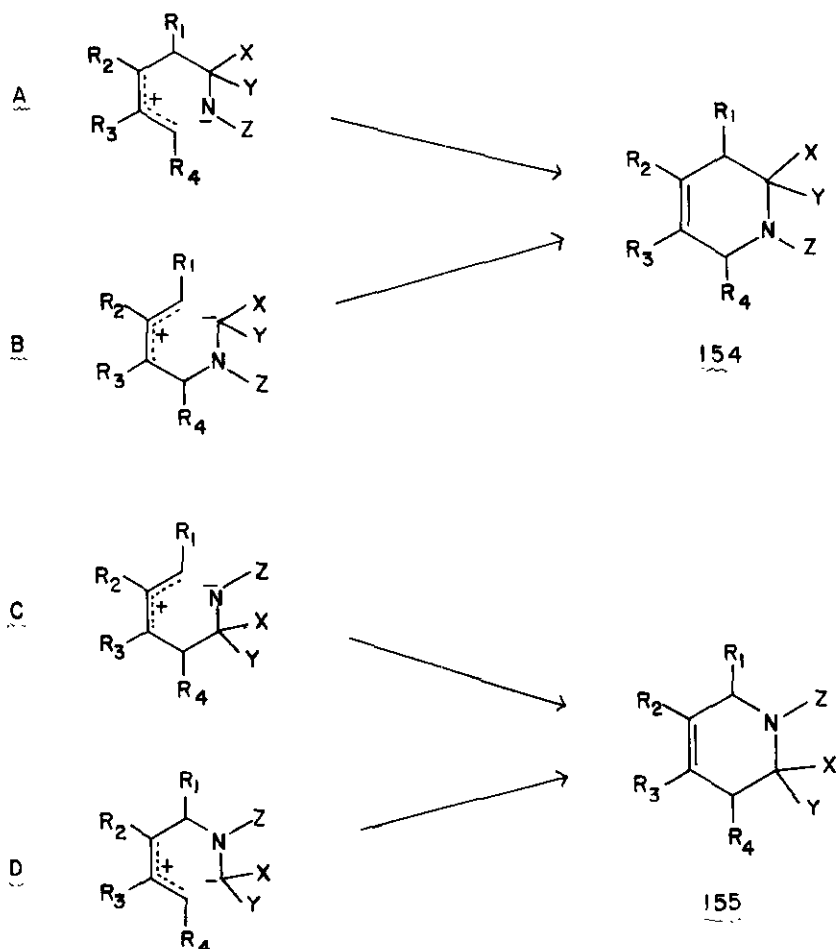


In recent work,⁵⁵ diene $\underline{151}$ has been thermally cyclized to the indolizidine lactam $\underline{152}$, which was converted to the alkaloid δ -coniceine ($\underline{153}$).



C. Regiochemistry - Summary and Rationale

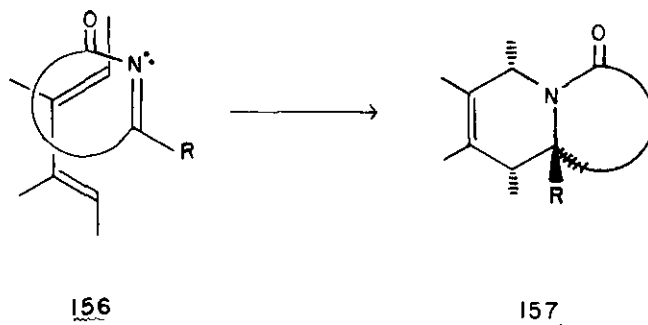
Unlike the "all carbon" Diels-Alder reaction,⁵⁶ no systematic study exists concerning the regiochemistry of the imino cycloaddition. However, there is enough fragmentary information now available about these additions with unsymmetrical dienes to make a few reasonable generalizations, particularly in the cases of N-sulfonyl and N-acyl imines. Although mechanistic information is scarce, several authors have suggested^{5,13b,30,31} that the regiochemical outcome for these cyclizations, whether thermal or acid catalyzed, can be rationalized most satisfactorily by invoking a polar reaction transition state or intermediate. For example, in thermal reactions one can consider four possible forms A-D. Forms A and B would lead to regioisomer 154, and C and D would afford the alternative regioisomer 155. From the available data, it appears that B and D are only applicable in those cases where groups X and Y are both electron withdrawing (i.e., imines 72, 74, 124 to 141, and perhaps 90). In virtually all other cases discussed in Part B, only pair A and C need be considered when rationalizing product regiochemistry. One must next consider the carbonium ion stabilizing ability of diene substituents R₁, R₂, R₃ and R₄. It is known that C-1 and C-4 diene substituents have a greater accelerating effect on [4+2]-cycloadditions than do C-2 and C-3 substituents.⁵⁷ There is some hint from the available data that this effect may be magnified in imino Diels-Alder additions.^{30,58} Thus for any given cycloaddition, one can readily identify the form (A-D) from which the major product is best derived.⁵⁹ A similar model would seem to hold for prediction of the major product in acid catalyzed cycloadditions.



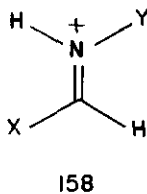
D. Stereochemistry - Summary and Rationale

As pointed out by Krow^{13-15,25} lone pair inversion in both reactant imines and in the Diels-Alder adducts of these imines introduces stereochemical problems not found in the "all carbon" [4+2]-cycloaddition. For example, when using acyclic imines, one cannot a priori be sure whether the reacting dienophile has the E or Z geometry and thus predictive application of the "Alder rule of endo-addition"⁶⁰ becomes difficult. Although data is still quite sparse, a few generalizations can be made regarding the stereochemistry of the imino Diels-Alder reaction.

Cyclic N-acyl imines (e.g., 77, 86-88) cannot undergo nitrogen lone pair inversion and thus the endo-addition rule⁶⁰ is easy to apply. A transition state model such as 156 would reasonably explain the observed high endo stereoselectivity (157) observed in these examples.^{28,30,31}



In general, acyclic imino compounds do not show quite the same high degree of stereoselectivity as do the cyclic compounds, and exo/endo mixtures are usually formed. Available evidence points towards a protonated (or Lewis acid complexed) E-imine 158 as the reacting species in acid catalyzed cycloadditions of imines of type 1, 28, 34, 54 and 62.^{13b,25} In general, the group (Y)



attached to nitrogen seems to act most effectively as the endo director, thus leaving group X as the exo substituent in the cycloaddition product. Two exceptions to this generalization are imines 1a and 54 (X = CCl₃) where endo products predominate. A rationale based upon steric arguments has been postulated for these last cases.^{4b,7}

A complete and detailed understanding of the mechanism of the imino Diels-Alder reaction is still lacking and the above generalizations should be considered strictly empirical at this time.

E. Conclusion

Although the imino Diels-Alder reaction has been known for over thirty-five years, it has received only a fraction of the attention paid to the "all carbon" cycloaddition.⁶¹ This neglect is somewhat surprising considering that the cycloaddition is a method for carbon-carbon bond formation which shows good regio- and stereoselectivity. Clearly, this reaction has the potential for construction of a variety of nitrogenous heterocycles, but has not yet found wide application. Perhaps the increased understanding of the parameters governing the reaction which has developed during the past fifteen years will correct this situation.

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