N-Acyl Imines and Related Hetero Dienes in [4 + 2]-Cycloaddition Reactions

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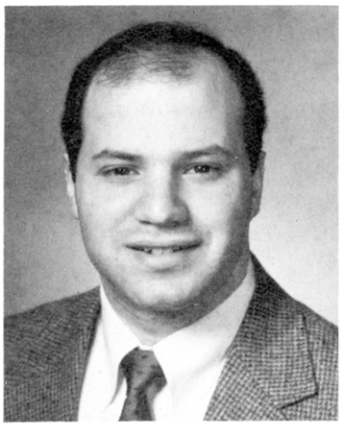

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I. Introduction

N-Acyl imines **1**, and the corresponding positively charged immonium species, are valuable partners in cycloaddition reactions. For example, these compounds can act as dienophiles in [4 + 2]-cycloadditions that produce tetrahydropyridines **2** (Scheme 1).[1] In general, these cycloadditions are both regio- and stereospecific, a feature that has enhanced the value of the methodology as a synthetic tool. This type of hetero Diels–Alder reaction has recently been applied in both the inter- and intramolecular[1b,c] senses to a variety of target structures.

A lesser known feature of *N*-acyl imines and structurally related compounds is their ability to act as 4π components in cycloadditions.[2] These reactions generally constitute a group of inverse electron demand Diels–Alder processes involving the combination of an electron-deficient hetero diene **1** (or more commonly its protonated form) with an electron-rich dienophile to yield a 5,6-dihydro-4*H*-1,3-oxazine **3** (Scheme 1). As in the case of cycloadditions producing adducts **2**, the reactions of **1** as a diene are also regio- and stereospecific in most cases (vide infra). Moreover, both modes of cycloaddition are capable of generating a new carbon–carbon bond. Surprisingly, the Diels–Alder reaction giving dihydrooxazines has found relatively few synthetic applications to date.

It is the intent of this article to survey and update published material on the use of various *N*-acyl imino compounds as hetero dienes in Diels–Alder cycloadditions.[2] Our hope is that this review will help stimulate a wider interest by synthetic chemists in this potentially useful reaction.

II. Mechanistic Aspects

Of the reactions covered in this review, those involving cycloaddition of a cationic *N*-acyl immonium ion with an alkene have been most thoroughly considered from a mechanistic viewpoint.[3] In his pioneering work, Schmidt[4] suggested that these reactions be classified as "polar cycloadditions".[3] A number of facts

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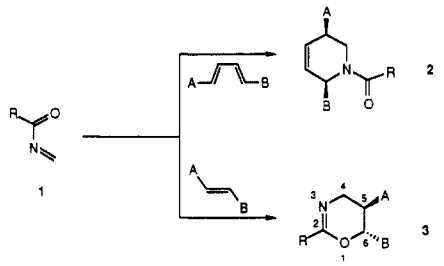
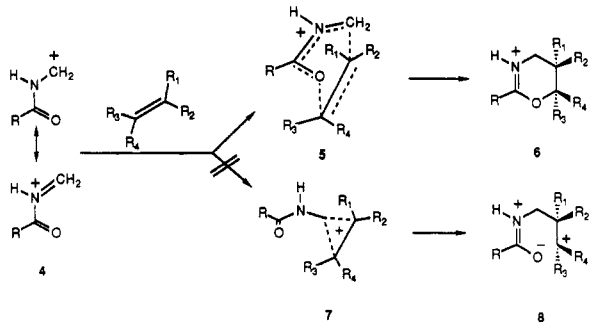


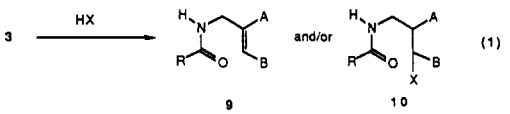
SCHEME 2



suggest that the cycloadditions of 4 occur via a transition state 5 (Scheme 2) involving concerted, but probably not synchronous, bond formation providing dihydrooxazine 6. This orbital symmetry (probably LUMO diene) controlled process is more compatible with experimental observations than a stepwise ionic mechanism via a transition state such as 7 and intermediate 8.[4] For example, the syn stereospecificity in addition to olefins and some of the known regiochemical results are best reconciled by a concerted pericyclic, rather than a stepwise, process. In addition, Schmidt[4d] found that the kinetically controlled addition of an *N*-acyl immonium compound 4 bearing a chiral group R with some alkenes shows facial diastereoselectivity. This result has been analyzed as evidence for a transition state 5 where group R and an alkene substituent (R_3) are close spatially. In the alternative transition state 7, one would not anticipate any significant diastereoselectivity.

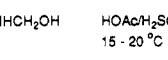
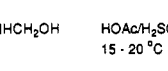
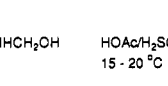
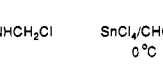
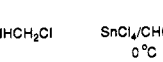
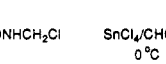
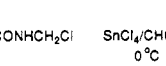
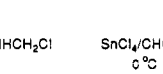
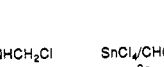
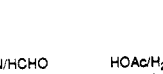
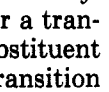
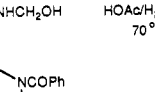
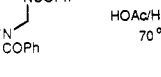
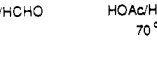
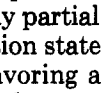
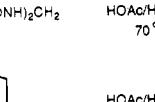
Schmidt[4a] also investigated the cycloaddition of some para-substituted styrenes with immonium ion 4 and found that there is a Hammett $\rho = -1.3$ for the process. This value was taken as being indicative of only partial positive charge formation at C-6 in the transition state for dihydrooxazine generation, once again favoring a concerted cycloaddition mechanism rather than an electrophilic process.

The close relationship between these cycloadditions and the so-called "amidoalkylation" reactions of alkenes should also be noted here.[5] It is probable that most such amidoalkylations involve an initial [4 + 2]-cycloaddition to afford a 5,6-dihydrooxazine 3 and subsequent solvolysis under the reaction conditions, perhaps via an intermediate such as 8 to give products of ring opening such as 9 and 10 (eq 1). In some cases the cycloadduct can, in fact, be isolated,[5] but often it can only be inferred as an intermediate (vide infra).



(1)

TABLE 1. Representative Cycloadditions of *N*-Acyl Methylene Immonium Compounds with Alkenes

Entry	N-Acyl Immonium Precursor	Reaction Conditions	Alkene	Cycloadduct (% yield)	Reference
1	$PhCONHCH_2OH$	$HOAc/H_2SO_4$ 15 - 20 °C		 (79)	6
2	$PhCONHCH_2OH$	$HOAc/H_2SO_4$ 15 - 20 °C		 (66)	6
3	$PhCONHCH_2OH$	$HOAc/H_2SO_4$ 15 - 20 °C		 (69)	6,7
4	$PhCONHCH_2Cl$	$SnCl_4/CHCl_3$ 0 °C		 (81)	4a
5	$PhCONHCH_2Cl$	$SnCl_4/CHCl_3$ 0 °C		 (95)	4a
6	$EtOCONHCH_2Cl$	$SnCl_4/CHCl_3$ 0 °C		 (47)	4a
7	$Me_2NCONHCH_2Cl$	$SnCl_4/CHCl_3$ 0 °C		 (91)	4a
8	$PhCONHCH_2Cl$	$SnCl_4/CHCl_3$ 0 °C		 (56)	4a
9	$PhCONHCH_2Cl$	$SnCl_4/CHCl_3$ 0 °C		 (43)	4a
10	MeCN/HCHO	$HOAc/H_2SO_4$ 70 °C		 (45)	8
11	PhCN/HCHO	$HOAc/H_2SO_4$ 70 °C		 (60)	8
12	$PhCONHCH_2OH$	$HOAc/H_2SO_4$ 70 °C		 (75)	8
13		$HOAc/H_2SO_4$ 70 °C		 (73)	8
14	PhCN/HCHO	$HOAc/H_2SO_4$ 70 °C		 (76)	8
15	$(PhCONH)_2CH_2$	$HOAc/H_2SO_4$ 70 °C		 (72)	8
16		$HOAc/H_2SO_4$ 80 °C		 (33)	9

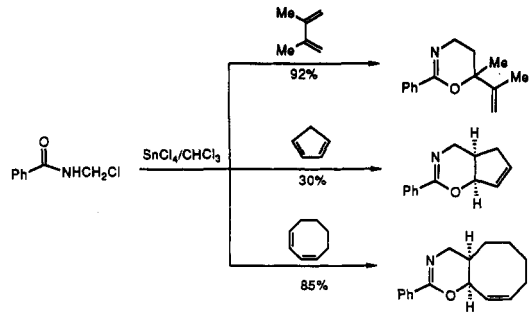
III. Survey of N-Acyl Imino Cycloadditions

A. *N*-Acyl Immonium Compounds

A number of examples have been published of [4 + 2]-cycloadditions of cationic *N*-acyl immonium species with various dienophiles. In general, these *N*-acyl immonium ions are highly electrophilic, unstable intermediates that are generated in situ.[10]

Simple methylene immonium compounds such as 4 have been the most commonly used dienes, and their reactions with substituted alkenes have been described by several groups. Table 1 contains several selected examples of this type of cycloaddition. The various

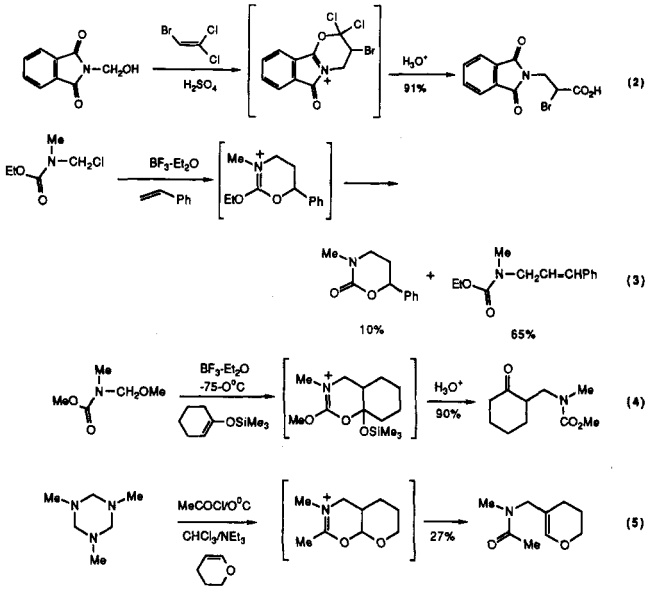
SCHEME 3



methods that have been used to form the *N*-acyl immonium hetero diene are also represented in the table. In addition, a number of examples have been included that show the excellent regioselectivity and syn stereoselectivity of the process. It might be noted that the "reversed" regioselectivity of the cycloaddition of methyl methacrylate (entry 9) has been taken as further evidence for a concerted reaction mechanism.[4a] This example, along with the one shown in entry 8, indicates that electron-deficient alkenes can also add effectively to these reactive *N*-acyl immonium dienes.

An interesting feature of these cycloadditions is shown in Scheme 3. Schmidt found that *N*-acyl immonium ions prefer to react as 4π components with conjugated 1,3-dienes.[4a] In no case here was any tetrahydropyridine detected (cf. Scheme 1). Ben-Ishai suggested that the reason for this preference is that *N*-acyl imines exist in the s-cis conformation (cf. 1), which for steric and perhaps secondary orbital effects favors dihydrooxazine formation.[11]

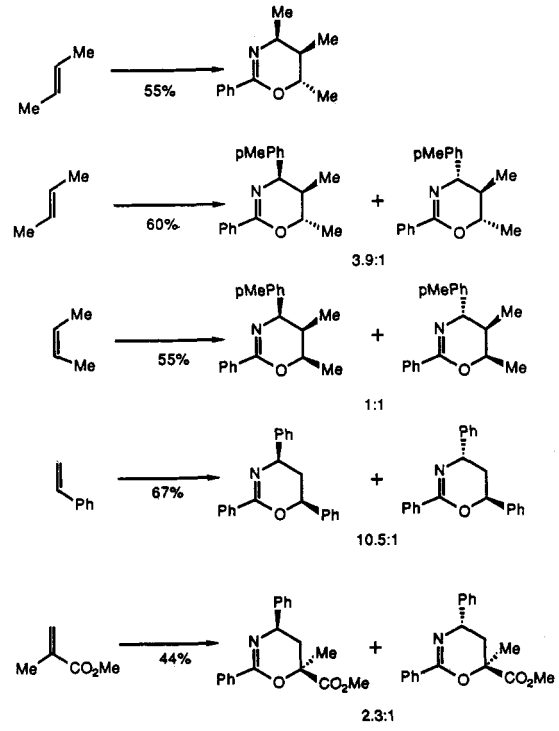
Equations 2,[12] 3,[13] 4,[14] and 5[15] show some examples of reactions that have been classified as amidoalkylations.[1,5] In these cases, an intermediate *N*-acyl



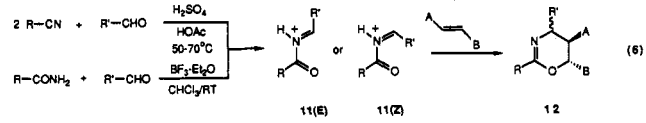
immonium compound probably undergoes initial [4 + 2]-cycloaddition with an alkene to afford a solvolytically unstable dihydrooxazinium intermediate. Therefore, in these cases only further transformation products of the Diels–Alder adducts were isolated. A more detailed compilation of reactions of this type can be found in Zaugg's reviews.[5]

It is also possible to effect [4 + 2]-cycloadditions of *N*-acyl immonium ions that are substituted on the

SCHEME 4

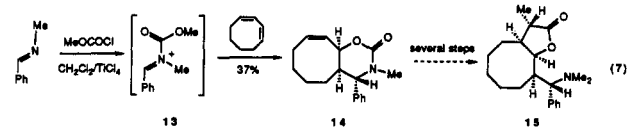


methylene carbon. In a study of such reactions, Giordano and Abis found that immonium compounds of type 11 could be generated in situ by the two methods shown in eq 6.[16] Trapping of the hetero diene by al-



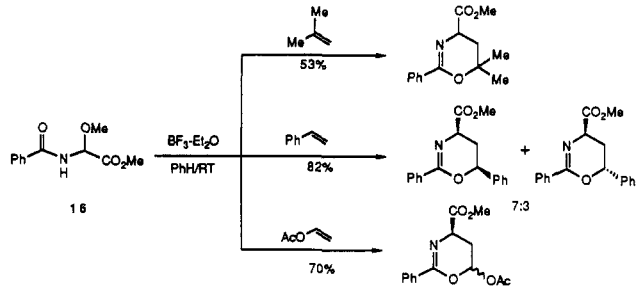
kenes yielded 4-substituted dihydrooxazines 12. These reactions showed the same regiospecificity and *syn*-alkene stereospecificity as the simpler cases in Table 1. The cycloadditions also showed varying degrees of kinetic diastereoselectivity with respect to C-4. Scheme 4 shows several representative examples. There is some ambiguity in interpreting these results since the acyl immonium components are not isolable, and it is unclear whether they react in the *E* or the *Z* form. It would seem reasonable that the selectivity in these reactions is due primarily to steric factors (cf. *cis*- and *trans*-2-butene) although electronic effects may play a role. If one assumes that the cycloadditions occur via the (*E*)-*N*-acyl immonium compounds, the reactions of styrene and methyl methacrylate may indicate a preference for π substituents to be endo to the hetero diene. Some further work in this area would be useful in order to fully elucidate the stereochemical features of the cycloaddition.

In a recent study of the synthesis of peptide β-turn mimics, Kahn and Chen found that *N*-acyl immonium ion 13 reacted stereospecifically with 1,3-cyclooctadiene to afford adduct 14 (eq 7).[17] If one again assumes that



13 reacts as the *E* isomer, formation of 14 requires an

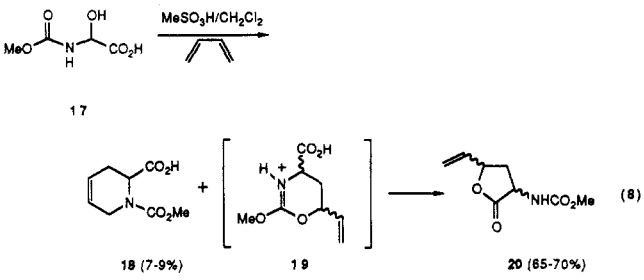
SCHEME 5



exo transition state, perhaps favored here for steric reasons. Compound 14 was subsequently converted into the desired amino γ-lactone 15.

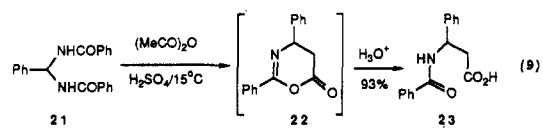
Ben-Ishai and co-workers[11,18] reported that under appropriate reaction conditions the *N*-acyl immonium compound derived from glyoxylate 16 adds to alkenes to afford 5,6-dihydrooxazines (Scheme 5). In the case of styrene the reaction showed modest diastereoselectivity. The adducts from vinyl acetate equilibrated under the reaction conditions, and it was therefore not possible to establish the kinetic stereochemical preference in this case.

As part of a related study, Ben-Ishai and Hirsch[11,18d] found that glyoxylic acid derivative 17 reacts with 1,3-butadiene in the presence of methanesulfonic acid to give a small amount of tetrahydropyridine 18 along with a mixture of stereoisomeric γ-lactones 20 as the major products (eq 8). This lactone presumably arises via



rearrangement of Diels–Alder adduct 19. Similar results were found with a number of other conjugated dienes. These reactions again reveal the propensity of *N*-acyl immonium compounds to act as dienes rather than as dienophiles.

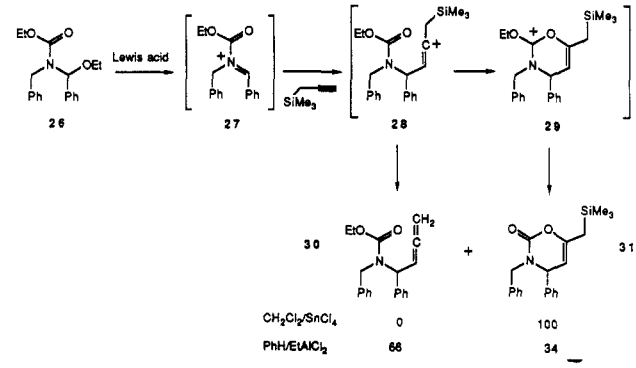
In an interesting reaction that appears to involve a [4 + 2] *N*-acyl immonium ion cycloaddition, Giordano reported the reaction of bisamide 21 with symmetrical acid anhydrides in the presence of strong acid yields lactone 22 and/or amide acid 23, depending upon reaction conditions (eq 9).[19] This transformation may



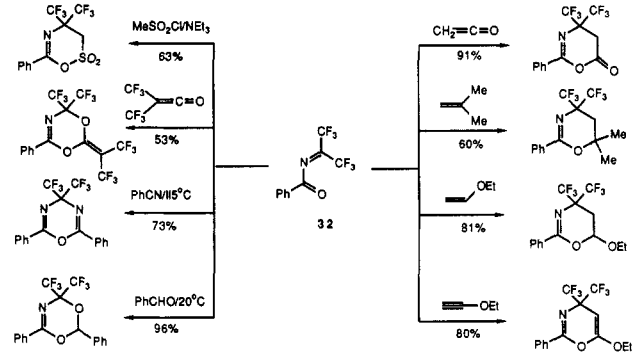
involve cycloaddition of the *N*-acyl immonium compound derived from 21 with the enol form of the anhydride (or perhaps with the corresponding ketene), leading to adduct 22.

Relatively few examples have been reported to date of alkynes acting as dienophiles in Diels–Alder reactions of *N*-acyl immonium compounds. An early example was described by Schmidt,[20] who found that hetero

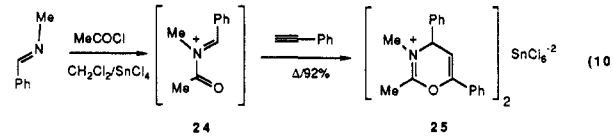
SCHEME 6



SCHEME 7



diene 24 reacts with phenylacetylene to afford isolable adduct 25 in good yield (eq 10).



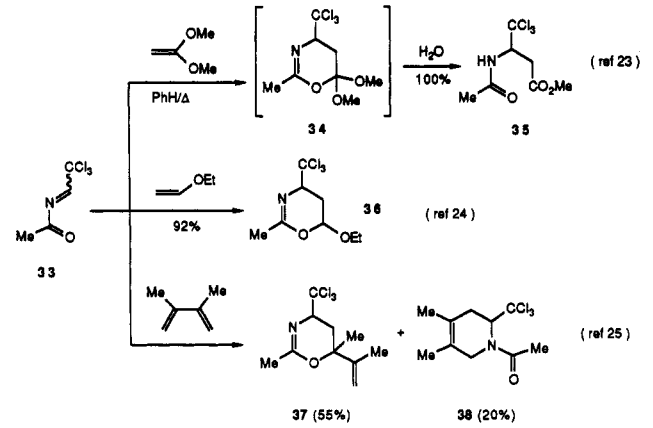
In 1988, Speckamp and co-workers reported the reaction of propargyltrimethylsilane with *N*-acyl immonium compounds such as 27, which were generated from precursors such as 26 (Scheme 6).[21] Depending upon the immonium compound and the Lewis acid that was employed, either oxazinone 31 or mixtures of 31 and allene 30 were obtained. Based upon the fact that allene 30 was produced in the reaction, a stepwise mechanism was proposed involving cations 28 and 29. Further support for this mechanism was the observation that 1-pentyne, which lacks the β-cation stabilizing silicon group, is unreactive with immonium ion 27.

B. Neutral *N*-Acyl Imines

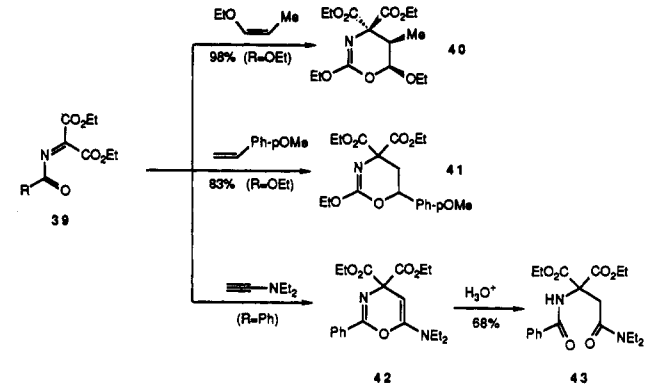
N-Acyl imines, like the corresponding immonium compounds, are usually highly reactive, unstable species that are ordinarily generated in situ. However, if the amino carbon bears one or two strongly electronwithdrawing groups, it is sometimes possible to actually isolate the compound.[10] Several widely scattered examples are known of these neutral *N*-acyl imines acting as hetero dienes in [4 + 2]-cycloadditions.

Some of the earliest reported cases of this type involved isolable bis(trifluoromethyl) *N*-acyl imine 32.[22] Scheme 7 contains a number of examples of [4 + 2]-cycloadditions of diene 32 with both C–C and hetero

SCHEME 8



SCHEME 9

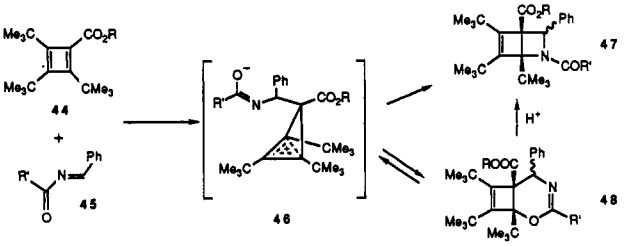


dienophiles. As can be seen, the cycloadditions of this diene with a structurally diverse range of dienophiles are regiospecific. Interestingly, **32** shows opposite regiochemistry with ketene and bis(trifluoromethyl)ketene. Desimoni and Tacconi rationalized this difference in terms of frontier molecular orbital theory.[2d] They suggested that the dominant interaction with ketene and **32** is between the hetero diene LUMO and dienophile HOMO. Since the methylene carbon of ketene has the larger coefficient, attack occurs here. The trifluoromethyl groups of the substituted ketene lower both the HOMO and LUMO. Cycloaddition may now involve the hetero diene HOMO and ketene LUMO, leading to the observed regiochemistry.

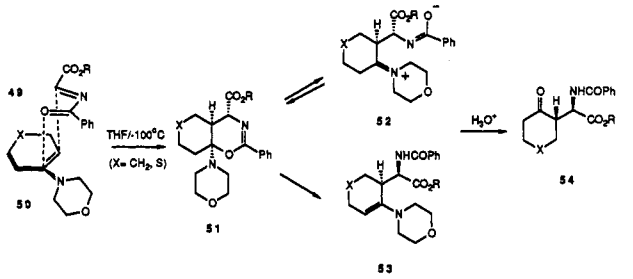
Another moderately stable *N*-acyl imine is **33**, which is prepared from chloral. This compound has been used in Diels–Alder cycloadditions with a few different dienophiles (Scheme 8). For instance, **33** reacts with ketene acetals to give an unstable intermediate **34**, which could be detected spectroscopically.[23] Upon hydrolysis adduct **34** afforded amide ester **35** in high yield. Hetero diene **33** also reacts with vinyl ethers to give stable adducts **36**.[24] The stereochemistry of this process has apparently not been investigated. Finally, **33** can act as both diene and dienophile in its reactions with 1,3-dienes.[25] With 2,3-dimethylbutadiene imine **33** afforded predominantly dihydrooxazine **37** along with some tetrahydropyridine **38**. Once again, information regarding the stereochemistry of **37** was not provided.

Imino malonate derivatives **39** have also been used occasionally as hetero dienes (Scheme 9). Addition of **39** (R = OEt) to vinyl ethers occurs rapidly to afford cycloadducts. With ethyl vinyl ether the reaction is syn

SCHEME 10



SCHEME 11



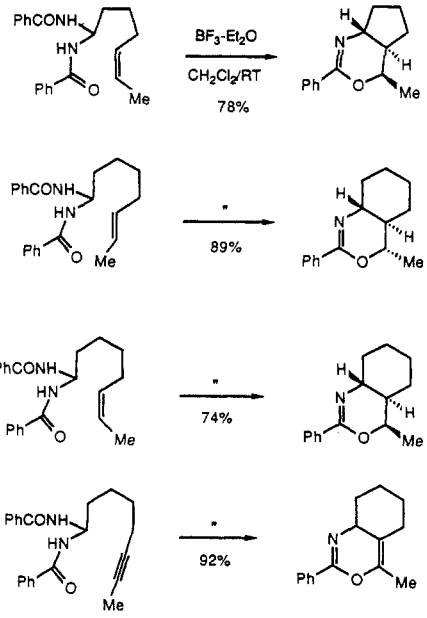
stereospecific and gives only regioisomer **40**.[26] The cycloaddition also occurs regiospecifically with styrenes, although much more sluggishly, to yield adduct **41**. Moreover, Steglich and co-workers found that **39** (R = Ph) reacts with an ynamine to give **42**, which can be hydrolyzed to diamide **43**.[27]

In a recent study to determine whether *N*-acyl imine **45** reacts as a diene or dienophile with a cyclobutadiene, Regitz and co-workers treated this compound with **44** and found that adducts **47** and/or **48** were produced (Scheme 10).[28] It was suggested that these cycloadducts result not from a concerted pericyclic process but rather probably involve intermediate zwitterion **46**. It was also found that adduct **48** can be isomerized to **47** by acid, perhaps via **46**. Thus, although adducts **47** and **48** are formally products of imine **45** acting as both diene and dienophile, mechanistically this process may differ from the other reactions of *N*-acyl imines and dienes discussed above.

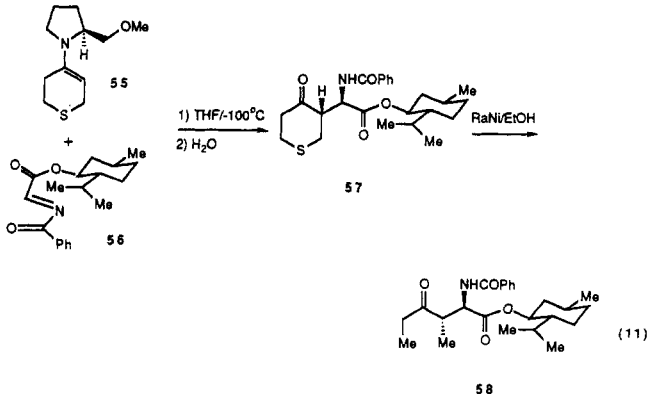
Steglich, Enders, and co-workers devised an interesting route for the diastereo- and enantioselective syntheses of γ-oxo-α-amino acid derivatives based upon *N*-acyl imine Diels–Alder chemistry.[29] Thus, treatment of *N*-acyl imine **49** (R = Me, Et) with enamine **50** at very low temperature, followed by acidic hydrolysis, yielded **54** with >96% diastereomeric excess of the isomer shown (Scheme 11). It is believed that this reaction occurs via an initial [4 + 2]-cycloaddition of the *E* form of acyl imine **49** in an exo transition state to afford intermediate adduct **51**. This compound then opens to zwitterion **52** and/or enamine **53**, which upon hydrolysis gives **54**.

Several reactions were also described using *N*-acyl imines **49** bearing chiral auxiliaries in the ester moiety (e.g., menthyl, 8-phenylmenthyl). In these cases diastereoselectivity was still high, but only modest (27–67% ee) enantioselectivity was achieved. However, if the principle of double stereodifferentiation was applied, it was possible to achieve high enantiomeric excesses. Therefore, combining (*S*)-enamine **55** with (+)-menthyl ester **56** (eq 11) gave adduct **57** with complete diastereo- and enantioselectivity. Using the (−)-menthyl ester of **56** along with (*S*)-**55** gave only 45%

SCHEME 12

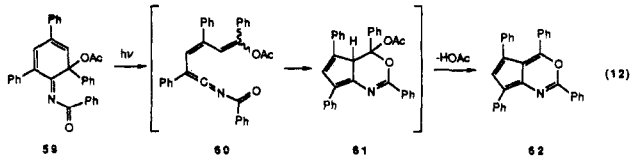


ee in the adduct. Raney nickel desulfurization of **57** yielded acyclic amino acid derivative **58**.

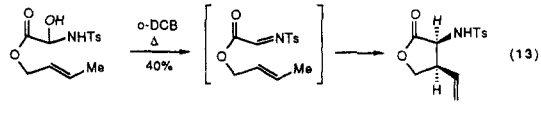


C. Intramolecular Cycloadditions

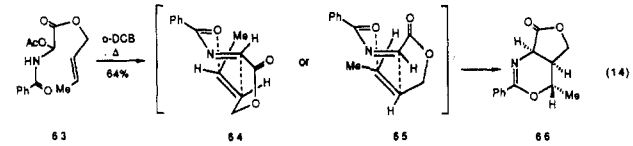
During the past few years the first examples of intramolecular Diels–Alder reactions of *N*-acyl imino hetero dienes have been described. In what is probably the initial example of such a process, Eckhardt and Perst found that photolysis of acyl imine **59** afforded fulvene derivative **62** (eq 12).[30] It was proposed that **59** rearranges to imine **60**, which undergoes an intramolecular [4 + 2]-cycloaddition, yielding oxazine **61**. Loss of acetic acid from **61** would give the observed product **62**.



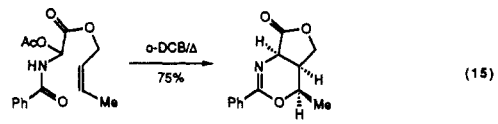
In some work from these laboratories, we found that it was possible to effect the intramolecular *N*-sulfonyl imine ene reaction shown in eq 13.[31] An attempt was



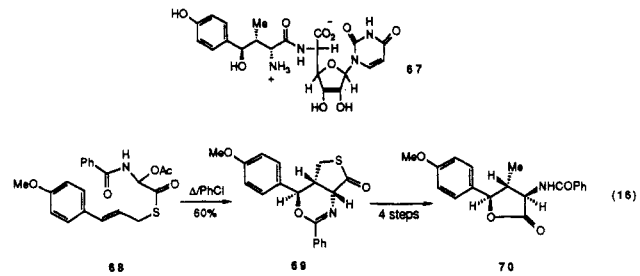
made to effect the analogous ene reaction with the corresponding *N*-acyl imine. However, when amide acetate **63** was heated, bicyclic dihydrooxazine **66** was obtained instead (eq 14). This reaction undoubtedly



involves elimination of acetic acid from **63** to form an acyl imine that undergoes an intramolecular [4 + 2]-cycloaddition, giving the cis-fused system **66** as the only isolable product. Although cyclization of an (*E*)-*N*-acyl imine via transition state **64** seems most reasonable, the alternative (*Z*)-imine cyclizing as in **65** cannot be ruled out. It is also possible that **66** is not the kinetic product of cycloaddition since it contains a relatively acidic angular proton potentially capable of epimerization under the reaction conditions. The syn stereospecificity of the process with respect to the dienophile was confirmed by the cyclization of the corresponding *cis*-alkene as shown in eq 15.[32] Again in this case, only the cis-fused ring system was found.



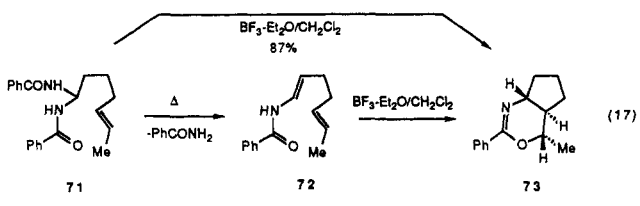
We have used this methodology in an approach to the "left-hand" α-amino acid component of the nucleoside antibiotic nikkomycin B (**67**).[32] Compound **68**, pre-



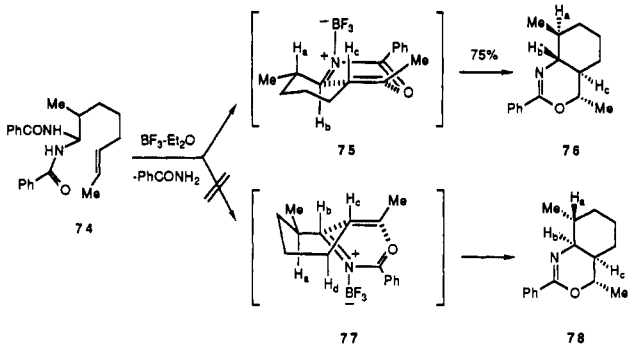
pared in a few steps from simple starting materials, was heated in the absence of oxygen to afford cycloadduct **69** stereospecifically (eq 16). It was then possible to convert **69** to lactone **70**, which contains all of the functionality and relative stereochemistry needed for the nikkomycin B amino acid.

In an extension of this work, we were interested in determining if it is possible to effect intramolecular Diels–Alder reactions of *N*-acyl imines or immonium compounds that are capable of tautomerization (i.e., imino compounds derived from enolizable carbonyl compounds). Interestingly, only one example of an intermolecular [4 + 2]-cycloaddition of this type has been reported[16] (first entry, Scheme 4).

We therefore prepared bisamide **71** but found that it gave only enamide **72** upon heating (eq 17).[33] Ap-



SCHEME 13

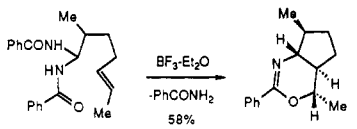


parently, tautomerization of the *N*-acyl imine is more rapid than cyclization. However, if enamide **72** was treated with boron trifluoride, cyclization occurred smoothly to afford trans-fused dihydrooxazine **73**. Similarly, bisamide **71** could be cyclized directly to **73** with BF_3 in excellent yield.

As can be seen in Scheme 12, this reaction is quite general. Both [6,6]- and [6,5]-fused systems can be prepared in good yields. The reactions were all found to give trans-fused systems and were syn specific with respect to the alkene. The intramolecular cycloaddition could also be effected with an alkyne dienophile. Another stereochemical feature of the process is that if there is a chiral center in the chain connecting diene and dienophile, only a single stereoisomeric bicyclic dihydrooxazine is produced. Thus, treatment of bisamide **74** with boron trifluoride etherate gave only adduct **76** (Scheme 13).

We believe all of these cyclizations involve a BF_3-complexed *N*-acyl immonium ion intermediate and have rationalized the stereochemistry of the process as outlined in Scheme 13. Adduct **76** probably arises via a transition state such as **75** in which the connecting chain assumes a chairlike conformation with the methyl group pseudoequatorial. The alternative transition state **77** that leads to the cis-fused isomer **78** may be destabilized relative to **75** due to a nonbonded steric interaction between the complexed Lewis acid and H_d.

Interestingly, the cycloaddition is stereospecific even when there is a chiral center in a shorter bridging chain. For example, the reaction leading to a [6,5]-fused system in eq 18 gives only the single stereoisomer shown.



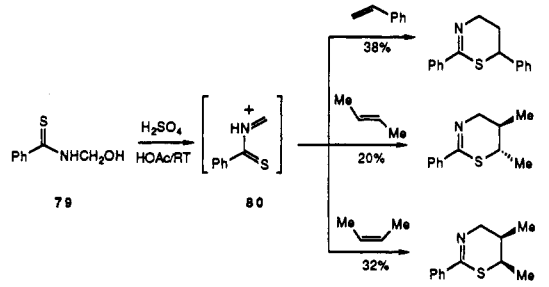
(18)

IV. N-Thioacyl Imine Cycloadditions

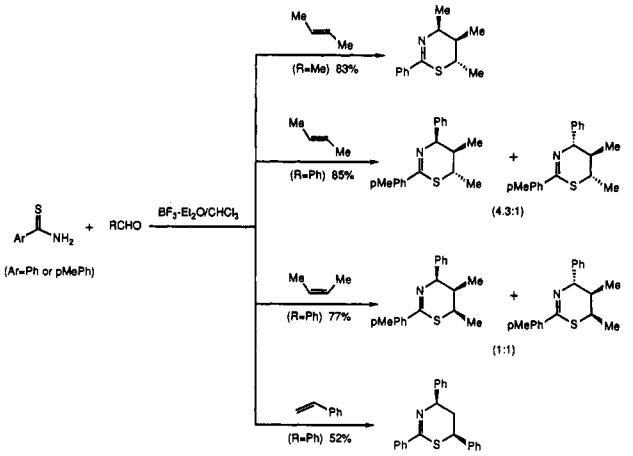
A. Cationic Hetero Dienes

Even less known to synthetic chemists than the cycloadditions of *N*-acyl imines as hetero dienes are the reactions of the corresponding thiocarbonyl compounds. Giordano reported the first examples of this type of cycloaddition in 1972.[34a] Treatment of amide methylol **79** with strong acid generates the transient *N*-thioacyl immonium ion **80**, which can be trapped in Diels–Alder fashion by alkenes to give 5,6-dihydrothiazines (Scheme 14). These reactions, like the corresponding *N*-acyl immonium cyclizations (cf. Table 1), are both regio- and

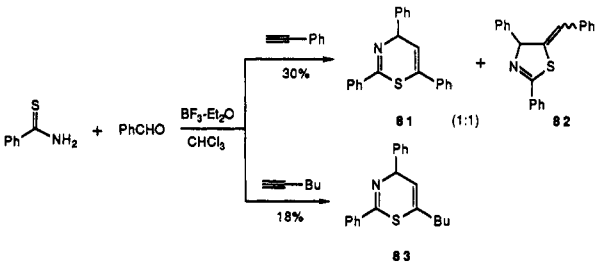
SCHEME 14



SCHEME 15



SCHEME 16



stereospecific. The product yields, however, under Giordano's reaction conditions are not impressive.

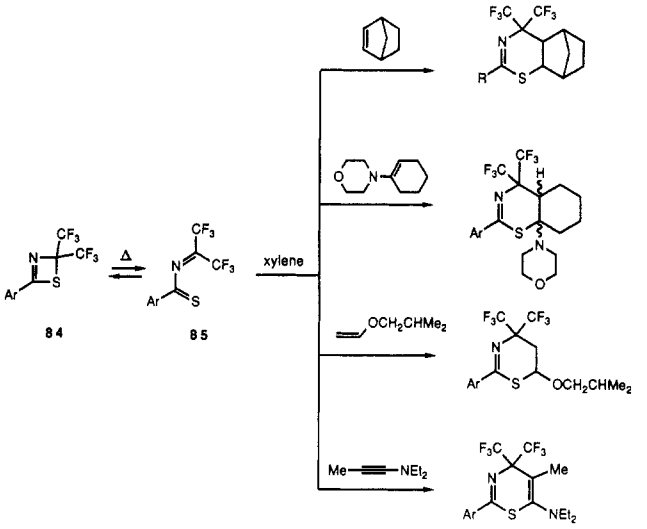
In subsequent work, Abis and Giordano looked at cycloadditions of *N*-thioacyl imines derived from higher aldehydes with alkenes.[16,34b] The immonium compounds were prepared from thioamides and aldehydes as shown in Scheme 15. Under these conditions yields of cycloadducts were higher than in the previous examples. Interestingly, the regiochemical and stereochemical outcome of these reactions was nearly identical with that of the *N*-acyl immonium cases (cf. Scheme 4), suggesting identical mechanisms for the two processes.[16]

Giordano also found that a similar Diels–Alder reaction can be effected with alkynes as dienophiles.[35] When arylacetylenes were used, approximately a 1:1 mixture of dihydrothiazine **81** and thiazole **82** was produced (Scheme 16). On the other hand, with alkyl-substituted alkynes only [4 + 2]-cycloadducts such as **83** were formed, but only in poor yield.

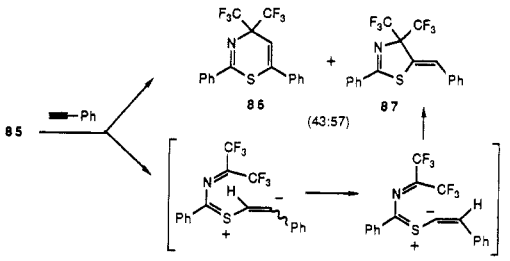
B. Neutral Hetero Dienes

A limited number of examples exist of [4 + 2]-cycloadditions of substituted neutral *N*-thioacyl imino compounds. Burger and co-workers found that al-

SCHEME 17



SCHEME 18



though 2*H*-1,3-thiazetes **84** exist in the cyclic form at room temperature, upon heating they are in equilibrium with *N*-thioacyl imines **85**.[36] This latter compound, which is the thiocarbonyl analogue of imine **32** (Scheme 7), undergoes smooth cycloadditions with a number of electron-rich alkenes as shown in Scheme 17. The reaction has also been effected with an ynamine.

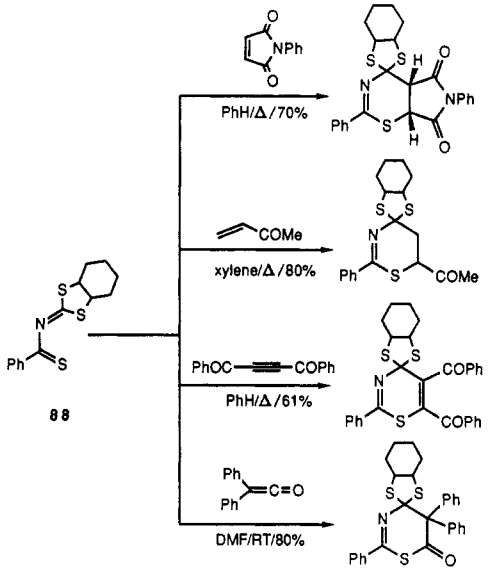
When diene **85** (Ar = Ph) was treated with phenylacetylene, a mixture of Diels–Alder adduct **86** and thiazole **87** was formed. It was suggested that **87** is produced via the mechanism shown in Scheme 18. Presumably the thiazole **82** (Scheme 16) of Giordano[34] is generated by a similar route.

Inamoto and co-workers reported that *N*-thioacyl dithioimidocarbonates undergo [4 + 2]-cycloadditions with several different dienophiles.[37] Scheme 19 contains some examples of these reactions. The cycloadditions with methyl vinyl ketene, as well as with acrylates, acrylonitrile, and acrylamide, were regiospecific. Similarly, the process was regiospecific with diphenylketene, although it was proposed that this particular reaction occurs via a zwitterionic intermediate.

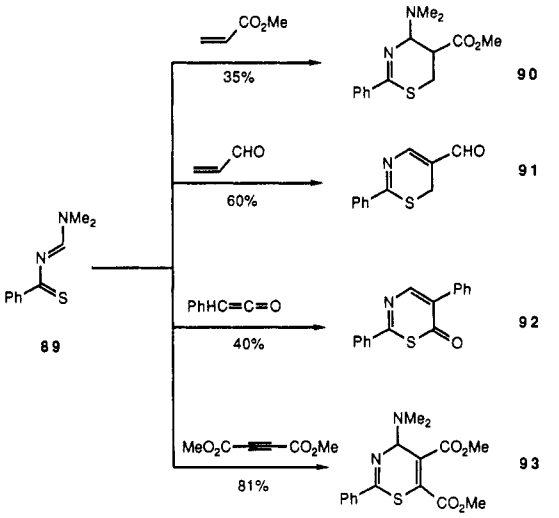
In an extensive series of publications, Quiniou and co-workers investigated the Diels–Alder reactivity of *N'*-thioaroyl-*N*,*N*-dimethylformamidines such as **89** with electron-deficient dienophiles (Scheme 20).[38] Depending upon the dienophile used and the reaction conditions, a [4 + 2]-cycloadduct such as **90** or a dimethylamine elimination product **91** could be obtained regioselectively. The cycloaddition was also successful with various ketenes (cf. **92**) and electron-deficient alkynes (cf. **93**).

It is also possible to prepare and cycloadd more highly substituted versions of hetero diene **89**. An interesting approach to cephem systems has been developed by

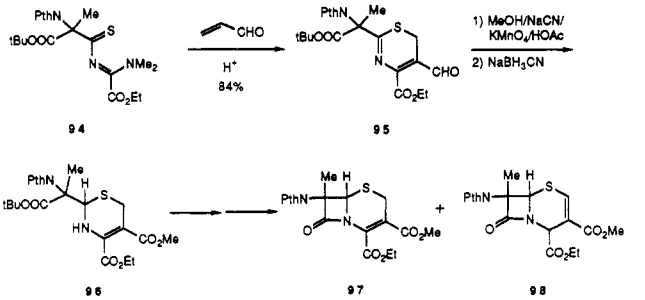
SCHEME 19



SCHEME 20



SCHEME 21

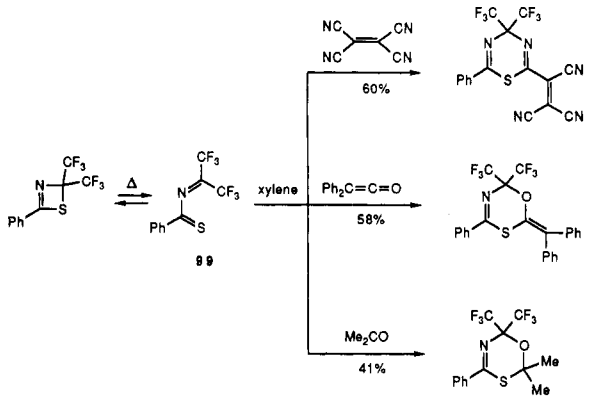


using this methodology (Scheme 21). For example, *N*-thioacyl imine **94** added regioselectively to acrolein under acid catalysis to afford thiazine **95** in good yield. It was then possible to oxidize the formyl group of **95** and selectively reduce the imine double bond to produce **96** as a mixture of stereoisomers. Cyclization of **96** led to a mixture of cephems **97** and **98**.

C. Cycloadditions with Hetero Dienophiles

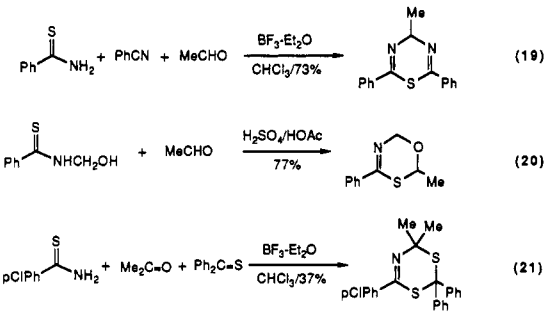
Although perhaps not of wide interest to the general practitioner of organic synthesis, it is possible to effect

SCHEME 22



[4 + 2]-cycloadditions of *N*-thioacyl imino compounds with various hetero dienophiles.[36b,39,40] These reactions do generate some interesting, if unusual, heterocycles that may be of value to medicinal chemists.

Giordano and co-workers investigated a number of assorted cycloadditions of *N*-thioacyl immonium compounds (cf. **80**) with hetero dienophiles.[39] A selection of these reactions is shown in eq 19,[39a] 20,[39b] and 21.[39d,e]



In general, moderate yields of cyclization products could be achieved by these methods.

Another thioacyl imine that smoothly undergoes cycloaddition with hetero dienophiles is compound **99**.[36b,40] Scheme 22 contains some instances of this type of reaction. Interestingly, the reaction of TCNE with **99** involves one of the cyano groups rather than the carbon–carbon double bond.[41]

V. Acknowledgment

We are grateful to the National Institutes of Health (Grant CA 34303) for support of the research from our laboratory cited in this article.

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