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X=Y-ZH SYSTEMS AS POTENTIAL 1,3-DIPOLES. PART 14.[1] BRONSTED AND LEWIS ACID CATALYSIS OF CYCLOADDITIONS OF ARYLIDENE IMINES OF α-AMINO ACID ESTERS.[2]

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Abstract - Cycloadditions of arylidene imines of α-amino acid esters to a range of dipolarophiles show substantial rate enhancements in the presence of Bronsted and Lewis acids. For Bronsted acids the rate is related to the pK_a of the acid and cycloadditions to reactive dipolarophiles occur at room temperature. For the Lewis acids studied the rate acceleration decreases in the order $Zn(OAc)_2$ > AgOAc > LiOAc > $MgOAc_2$ but is also anion dependent with LiBr > LiOAc and AgOAc > AgOTs. The Lewis acid catalysed processes are believed to be examples of cycloadditions of metallo-1,3-dipoles. In both Bronsted and Lewis acid catalysed processes the cycloadditions are regio- and stereo-specific.

Proton transfer processes are particularly common in X=Y-ZH systems in which the formal 1,3-proton transfer from Z to X is termed prototropy.[3] Depending on the nature of X, Y and Z such prototropy may involve proton transfer from a carbon atom to a carbon atom (e.g. imines)[4], from a carbon atom to a heteroatom or the reverse (e.g. keto ⇌ enol)[5], or from a heteroatom to a heteroatom (e.g. triazene isomerisation)[6]. Enolisation is historically the preeminent example of those prototropic rearrangements in which a proton is transferred from a carbon atom to a heteroatom. We have shown that the three types of formal 1,3-proton transfer encountered in X=Y-ZH systems are complemented by two related types of formal 1,2-proton transfers (carbon atom to heteroatom, and heteroatom to heteroatom) when the central Y atom in X=Y-ZH is nitrogen. Such formal 1,2-proton transfers lead to the formation of novel types of 1,3-dipoles.[7] In this latter process imines (Scheme 1a) parallel carbonyl compounds (Scheme 1b) in that proton transfer occurs from a carbon atom to a heteroatom and, of course, both give 4π-anions on base catalysed deprotonation.

The analogy between carbonyl compounds and imines is particularly useful in suggesting suitable methods for generating either the 1,2-prototropy product (an azomethine ylide) or the 4π-azaallyl anion (Scheme 1a) from imines. We have shown that imines of α-amino acids and their esters (1) generate azomethine ylides (2) stereospecifically (Scheme 2) on heating in a range of solvents and that these ylides can be trapped by a wide range of dipolarophiles in regiospecific and stereospecific or highly stereoselective 1,3-dipolar cycloaddition reactions.[7-9] Anionic 4π + 2π cycloadditions of azaallyl anions (Scheme 1a) were first reported by Kauffmann[10] although there is a distinct possibility that these reactions involve a lithiated azaallyl species(6)(lithium

alkyl or lithium diisopropylamide are used to generate the azaallylanions) and are examples of metallo-1,3-dipoles. We subsequently showed (1, R^1=Me) undergoes a regio- and stereo-specific sodium methoxide catalysed cycloaddition to methyl acrylate, via (4, M=Na^+) (Scheme 2)[15] and reported related amine catalysed anionic cycloadditions of 4π-sulphinylaminomethamide species[16] and of α-amino acid ester derivatives.[12] Others have extended Kauffmann's methodology to (1).[17] The reactive intermediate in this case must be (4, M=Li) and it seems unlikely that simple azaallyl anions (5) (Scheme 2), derived from imines of α-amino esters, have been prepared. The precise nature of the azaallyl anion will be a function of the base used and this will be discussed more fully in a subsequent paper. The analogy between imines and carbonyl compounds is further emphasised by the report that the addition of metallated carboxylic acids (7) to aldehydes involves a 4π + 2π transition state (8) similar to that of a 1,3-dipolar cycloaddition.[18]

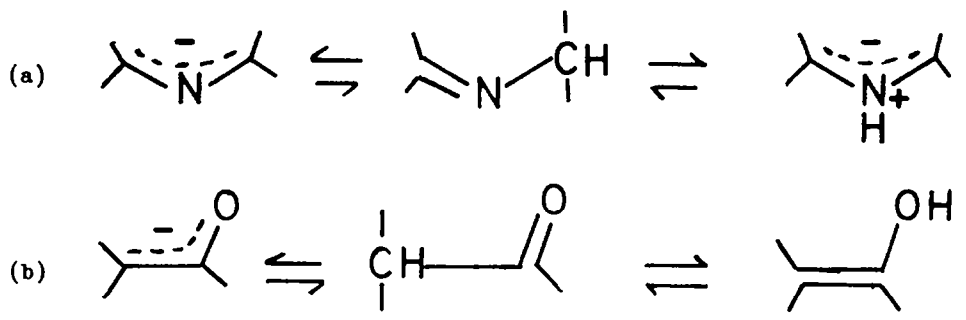
Bronsted Acid Catalysis. Cycloadditions of arylidene imines of α-amino acid esters show substantial rate enhancements in the presence of Bronsted acids. Thus cycloadditions of (9a-c) with N-phenylmaleimide (NPM) in the presence of acids occur stereospecifically and yield cycloadducts (10a) identical to those obtained in the absence of added acid.[19] The rates of the cycloaddition reactions are dependant on the pK_a of the added acid (Tables 1 and 2).≠

The fastest cycloaddition in Table 1 is observed with 2,4-dinitrophenol, the strongest acid, whilst the slowest rate is observed with 2-pyridone, the weakest acid studied. An analogous trend is reproduced in Table 2 for carboxylic acids with o-nitrobenzoic acid giving the fastest rate and acetic acid the slowest rate. From our brief survey it appears that acids capable of bifunctional catalysis such as 2-pyridone[20] or acetic acid[21] [e.g. via (11), arrows] do not give rise to unusually high rates indicating such effects are not important. These acid mediated cycloadditions involve stereospecific generation of the azomethine ylide (3) (Scheme 2) in a kinetically controlled process[8,9], followed by cycloaddition to NPM via an endo transition state. Initial protonation of the imine(1) nitrogen atom results in a substantial lowering of the pK_a of H_A leading to deprotonation and dipole formation (Scheme 2). Hydrogen bonding (2) bridging the imine nitrogen atom and the ester group (Scheme 2) results in a kinetic preference for the azomethine ylide with configuration (3). Enhanced rates of cycloaddition (9)⟶(10) in the absence of added acid are observed when [$^2H_8$]toluene is replaced by [$^2H_3$]nitromethane as solvent. Thus $t_{½}$ values of (9a) (60min.), (9b,160min.), and (9c,175min.) were substantially less in [$^2H_3$]nitromethane compared to [$^2H_8$]toluene (Table 1) In apportioning this rate enhancement between the effects of increased solvent polarity and the ability of [$^2H_3$]nitromethane to act as a weak acid (pK_a 10.6) reference to Table 1 suggests that the weak acid effect alone is sufficient to account for the rate enhancement.

Utilising these observations, we have developed a method for conducting cycloadditions with reactive dipolarophiles at room temperature in acetic anhydride containing acetic acid (~6%). Cycloadducts usually crystallise from the reaction medium in good yield (Table 3).

Acid catalysis does not require the presence of an α-ester group on the imine as shown by the catalysis of the cycloaddition of the fluorenylimine (12) with NPM to give (13),[22] i.e. bifurcated hydrogen bonding (Scheme 2) is not a prerequisite for catalysis. Acid catalysis is also effective for alkylamino acid

≠ Rate studies were carried out in toluene in which the pK_a's of the acids will be markedly different from those noted in Tables 1 and 2.



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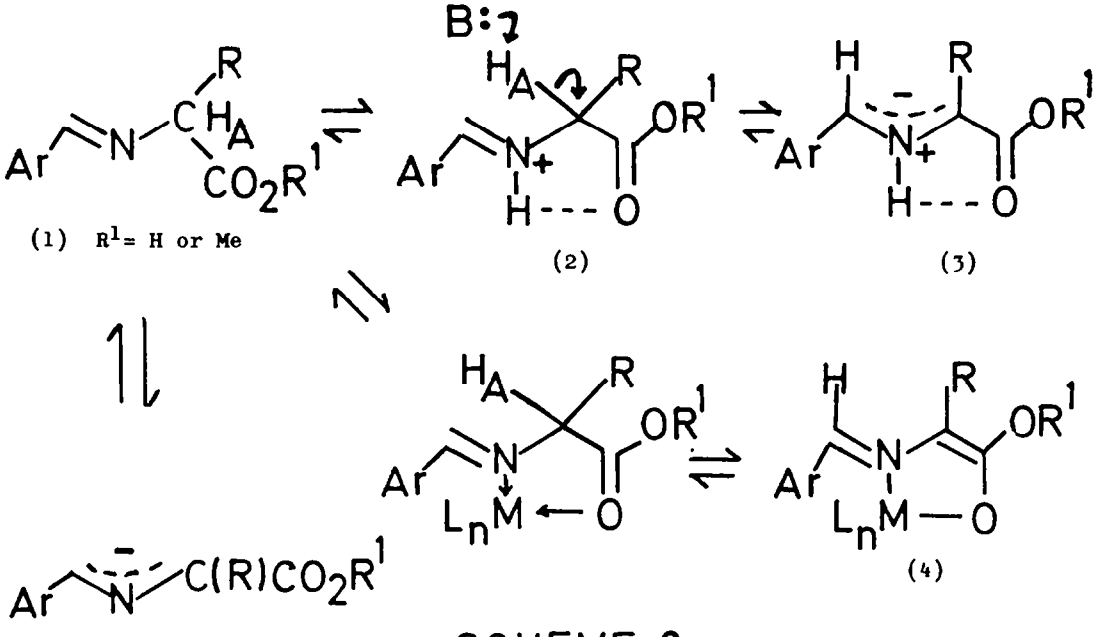

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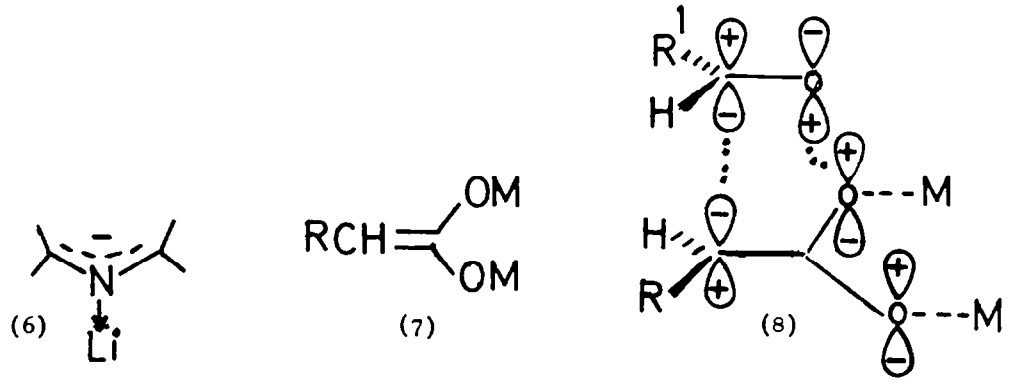
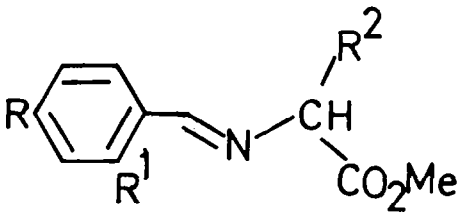
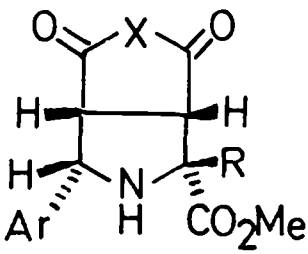
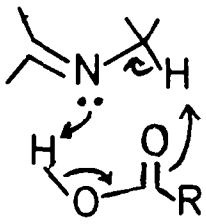




(9) a. R=R^1=H, R^2=Ph
b. R=NO$_2$, R^1=H, R^2=Ph
c. R=CN, R^1=H, R^2=Ph
d. R=H, R^1=OMe, R^2=Ph
e. R=OMe, R^1=H, R^2=Ph
f. R=R^1=H, R^2=Me
g. R=R^1=R^2=H
h. R=H, R^1=OH, R^2=Ph



(10) a. X=NPh, R=Ph
b. X=O, R=Ph
c. X=NPh, R=Me
d. X=NPh, R=H



(11)

Table 1. Half lives of the cycloaddition of imines (9a-c) and NPM to give (10a) in the presence of acids.[a]

Imine		pK$_a$ of acid	t$_{\frac{1}{2}}$ (min)[b]
9a	-	-	120 ± 4
9a	2-pyridone	11.99	88 ± 6
9a	MeCO$_2$H	4.75	6[c]
9a	Meldrum's acid[d]	5.1	5[c]
9a	2,4-dinitrophenol	4.0	3[c]
9b	-	-	668 ± 8
9b	MeCO$_2$H	4.75	56 ± 4
9c	-	-	583 ± 7
9c	MeCO$_2$H	4.75	50 ± 6

a. Reactions were performed at 105-± 0.5°C in sealed n.m.r. tubes with equimolar amounts (0.4M) of imines (9a-c), NPM, and acid in [$^2H_8$]toluene. Kinetics were measured in the probe of a Bruker WH90 spectrometer, spectral width 1000Hz, 4K data points.

b. Errors refer to statistical errors.

c. Approximate values.

d. 2,2-Dimethyl-1,3-dioxan-4,6-dione.

esters such as (9f), (9g) and (14) (Table 3) and yields are good to excellent. When p-benzoquinone is used as the dipolarophile, the initial adduct (16)[9] is not isolated but undergoes enolisation and acetylation giving (17). Acid catalysis is not effective with unactivated dipolarophiles where cycloaddition is the rate determining step, i.e. the rate enhancement arises from catalysis of the dipole forming step and the dipole reactivity is not increased. Thus (18) fails to undergo intramolecular cycloaddition[23] in acetic anhydride-acetic acid at room temperature but does react with NPM under the same conditions (Table 2) to give (19). Similarly (9a) did not react with either dimethyl maleate or dimethyl fumarate when kept in acetic anhydride-acetic acid for 5 dy at room temperature. A 10% v/v solution of acetic acid in acetonitrile is also an effective catalyst/reaction medium. Thus (9c) reacts with NPM in 10% acetic acid-acetonitrile at room temperature to give an immediate precipitate of the crystalline cycloadduct

Table 2. Pseudo first order rate constants (k_1) for the cycloaddition of imine (9a) and NPM to give (10a) in the presence of acids.[a]

Acid catalyst	pK_a	Temp.(°C)	$k_1(sec^{-1}) \times 10^5$	r[b]
	-	50	0.169 ± 0.03	0.999
$MeCO_2H$	4.75	50	4.41 ± 0.05	0.999
$PhCO_2H$	4.2	40	9.06 ± 0.60	0.995
$PhCO_2H$		50	8.44 ± 0.20	0.998
$PhCO_2H$		60	32.5 ± 0.50	0.999
$ClCH_2CO_2H$	2.8	50	15.9 ± 0.09	0.996
o-$O_2NC_6H_4CO_2H$	2.17	50	22.1 ± 0.10	0.996

a. Reactions were performed in sealed n.m.r. tubes with equimolar amounts (0.05M) of imine and NPM and 0.025M in acid, in [$^2H_8$]-toluene. Kinetics were measured in the probe of a Bruker WH90 spectrometer, spectral width 1000Hz, 4k data points.

b. Correlation coefficient.

Table 3. Cycloaddition of imines to reactive dipolarophiles at 25°C in acetic anhydride containing 6% acetic acid.[a]

Imine	Dipolarophile	Time(h)	Product	Yield(%)[b]
9d	NPM	0.75	10a, Ar=2-$MeOC_6H_4$	88
9d	MA[c]	0.5	10b, Ar=2-$MeOC_6H_4$	85
9a	NPM	12	10a, Ar=Ph	81
9e	NPM	12	10a, Ar=4-$MeOC_6H_4$	79
12	NPM	12	13	76
14	NPM	12	15	78
9d	p-benzoquinone	15	16	68
18	NPM	1	19	57
9f	NPM	24	10c, Ar=Ph	68
9g	NPM	24	10d, Ar=Ph	62

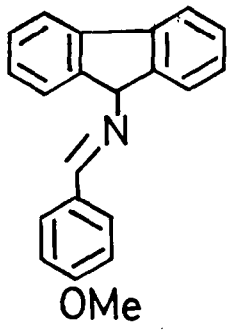
a. The general procedure is given in the experimental section.

b. Isolated yields.

c. Maleic anhydride.

(10a, Ar=o-$MeOC_6H_4$). Attempts were made to observe intramolecular acid catalysis by incorporating an ortho-carboxyl group into the imine. The imine (20) of 2-carboxybenzaldehyde and phenylglycine methyl ester exists in the cyclic form (21). However ring-chain tautomerism followed by cycloaddition occurs on heating (21) with NPM (toluene, 110°C, 6h) to give (22, 78%). Cycloaddition is thus not greatly accelerated. The salicylidene imine (9h) was prepared and reacted with NPM. Cycloaddition in toluene (no added acid) at 110°C took approximately 5dy (n.m.r. monitoring) and gave (10a, Ar=o-HOC_6H_4). A similar reaction of (9a) and NPM was complete in 10h at 105°C and (9d) reacted completely with NPM after heating for 3h at 85°C. Thus intramolecular catalysis by the ortho-hydroxy group is not observed, rather it dramatically inhibits the reaction. This suggests that the well known strong intramolecular hydrogen bond (23)[24] present in salicylidene imines renders the imino-nitrogen atom unavailable for functioning as a base and suggests an important role for the imino-nitrogen atom as a base in dipole formation in the absence of added catalysts. Steric effects can be discounted as the cause of the slow cycloaddition of (9h) since the corresponding o-methoxy derivative (9d) undergoes facile cycloaddition.

Lewis Acid Catalysis. Catalysis of 4π + 2π cycloadditions by complex formation between a Lewis acid and the dienophile (Diels-Alder)[25] or enophile



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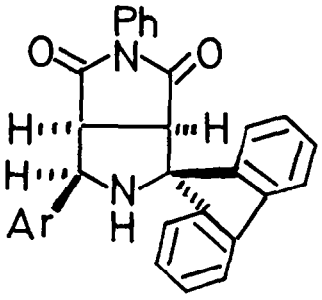
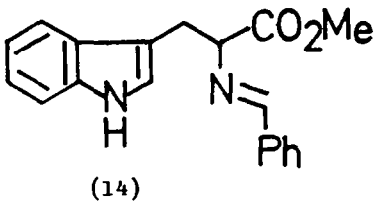


(13) Ar=p-$MeOC_6H_4$



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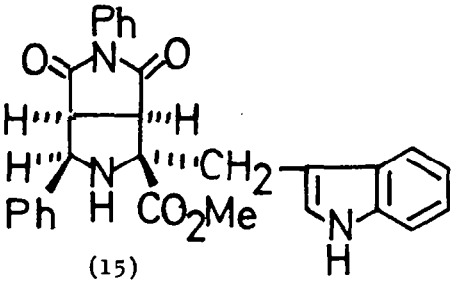

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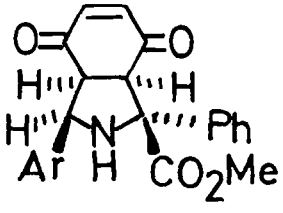

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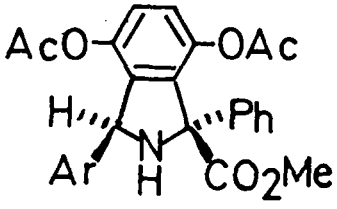
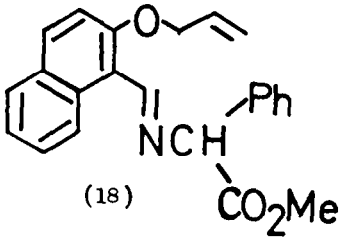


(17) Ar=o-$MeOC_6H_4$



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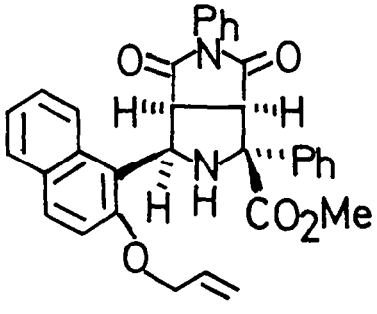

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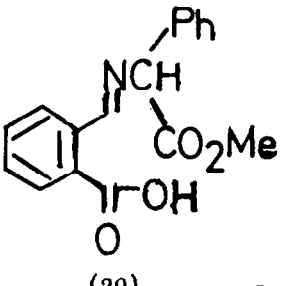

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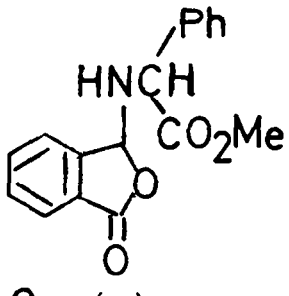

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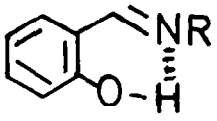

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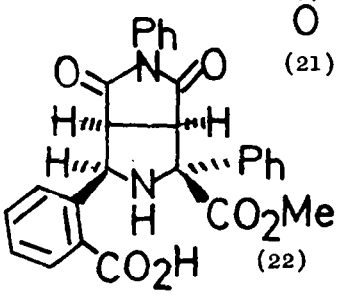

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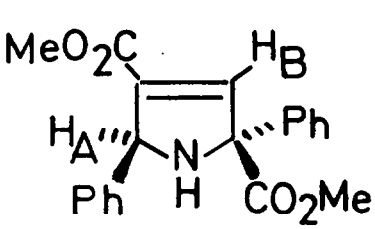
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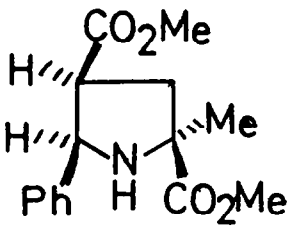
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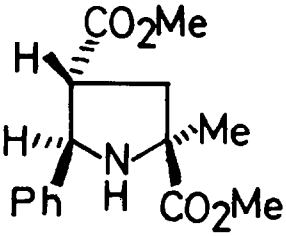
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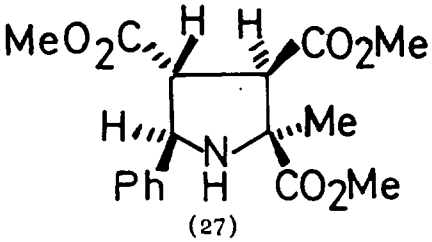
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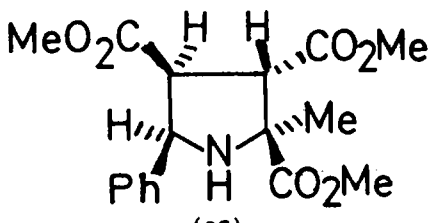
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Table 4. Effect of Lewis acids on the half life for the cycloaddition of imine (9a) and methyl propiolate.[a]

Lewis Acid[b]	$t_{\frac{1}{2}}$(h)	Yield(%)[c]
-	38	94
$MeCO_2H$	1.8	-
$Zn(OAc)_2.2H_2O$	3.0	88
AgOAc	3.25	95
$LiOAc.2H_2O$	5.5	93
$Mg(OAc)_2$	8.75	-

a. Reactions were run in $[^2H_8]$toluene in a thermostatted oil bath at 80 ± 0.5°C using 0.4M solutions of the three reactants.

b. The metal salts only partially dissolved in the hot solvent.

c. Estimated by n.m.r. spectroscopy using hexamethylbenzene as internal standard.

(ene-reaction)[26], i.e. the 2π-component, is well known. Lewis acid complexation of dienophiles results in increased rates of cycloaddition,[27] enhanced or reversed regio-selectivity[28] and enhanced stereoselectivity (endo:exo ratio).[29] In the present context, however, the Lewis acids coordinate with the 1,3-dipole (Scheme 2), the 4π-component, to form metallo-1,3-dipoles (4).

The effect of some weak Lewis acids on the cycloaddition of (9a) and methyl propiolate to give (24) is shown in Table 4.

The cycloaddition (9a)→(24) is regiospecific with or without added Lewis acid. Regiochemistry is assigned on the basis of the small coupling constant between H_A and H_B (J 1.95Hz).[30] Use of stronger Lewis acids such as aluminium chloride tends to divert the reaction to pyrrole formation. A similar quantitative and essentially regiospecific cycloaddition of (9f) to methyl acrylate giving (25) is observed in acetonitrile (80°C) in the presence of 1mol. of either silver acetate, lithium bromide or lithium acetate. The reactions take approximately 12h, 13.5h, and 15h, for completion respectively. Adventitious water in the presence of lithium bromide results in slight hydrolysis of the imine and in this latter case a minor amount (< 5%) of a second isomer (26) is detected (n.m.r.). This minor isomer probably arises from (25) by an acid catalysed epimerisation similar to that noted previously.[13] When the reactions of (9f) with methyl acrylate was repeated with silver tosylate

(1 mole) as the Lewis acid the reaction was slower than that observed with silver acetate. Thus after 13h p.m.r. monitoring showed the solution to contain a 4.3:1:1 mixture of product, starting material and benzaldehyde. The product consisted of a 6.3:1 mixture of (25) and (26). Adventitious water is again responsible for, and consumed in, the formation of benzaldehyde apparently via formation of small amounts of p-toluenesulphonic acid which also effects the epimerisation of (25) to (26). The cycloaddition of (9f) and dimethyl fumarate (acetonitrile, 80°C, 1 mol. LiOAc.$2H_2O$), gives a 2:1 mixture of (27) and (28) after 16h in quantitative yield. This ratio compares with a 2.3:1 ratio of (27) and (28) obtained from reaction of (9f) and dimethyl fumarate in toluene (110°C, 48h) in the absence of base.[8]

These Lewis acid catalysed cycloadditions are apparently the result, at least partially, of traces of Bronsted acids produced from the reaction of the Lewis acids with adventitious water. Nevertheless it is probable that the metallo-1,3-dipoles (4; M=Li^+, Ag^+, or Zn^{2+})(Scheme 2) make a major contribution to cycloadduct formation. These metallodipoles, if involved, arise by initial coordination of the metal ion to the nitrogen atom and the carboxylate group of the imine (1) followed by deprotonation, with the metal counterion, adventitious water, or uncomplexed imine, acting as the base.[31,32] Metal coordination (Scheme 2) ensures the formation of only one dipole configuration. The metallo-1,3-dipoles (4) (Scheme 2) differ electronically from the azomethine ylides (3) in that the metal ion will perturb the frontier orbitals of (4) possibly conferring modified reactivity with respect to (3), in cycloaddition reactions.[32]

Experimental. General experimental details were as previously noted.[19] Imines were prepared as previously described,[8,9,19] except as noted below. N-Phenylmaleimide was recrystallised three times from cyclohexane. The commercial material as supplied contains acidic impurities which result in enhanced rates of cycloaddition. 2-Pyridone, Meldrum's acid and 2,4-dinitrophenol were crystallised and dried before use. Acetic acid was distilled with 5% acetic anhydride and stored over 4A molecular sieves. Analytical grade zinc, silver, lithium and magnesium acetates were used without further purification. Petroleum ether refers to the fraction with b.p. 60-80°C.

Imines

Methyl N-o-methoxybenzylidene phenylglycinate (9d). A mixture of phenylglycine methyl ester hydrochloride (5.0g, 0.025mole), o-methoxybenzaldehyde (3.4g, 0.025mole) and anhydrous magnesium sulphate (10g) were stirred in dry methylene chloride (50ml) and triethylamine (15.2g, 0.15mole, 6-fold excess) was added dropwise. Stirring was continued for 18h and the mixture was then filtered and the filtrate washed with water until neutral, dried (Na_2SO_4) and the solvent evaporated to leave a viscous oil which crystallised on standing. Recrystallisation from ether-petroleum ether afforded the product (4.8g, 68%) as colourless prisms, m.p. 86-88°C (Found: C, 72.10; H, 6.00; N, 4.85. $C_{17}H_{17}NO_3$ requires C, 72.05; H, 6.05; N, 4.95%); δ 8.70 (s, 1H,CH=N), 8.18-6.68 (m, 9H, ArH), 5.16 (s, 1H, CH), and 3.80 and 3.70 (2 x s, 2 x 3H, 2 x OMe); m/z(%) 283 (M^+, 1), 224(100), 209(10), 106(7), 91(12) and 77(6); ν_{max} 1745 and 1630 cm^{-1}.
Methyl o-hydroxybenzylidene phenylglycinate (9h). Sodium metal (0.107mole) was dissolved in dry methanol (150ml) and phenylglycine methyl ester hydrochloride (0.107mole) added. The mixture was stirred at room temperature until the amino acid ester hydrochloride had dissolved when salicylaldehyde (0.107mole) was added and the stirring continued for a further 12h. Work-up as above afforded a yellow solid which was crystallised from methanol to afford the product (88%) as bright

yellow needles, m.p. 101°C (Found: C, 71.45; H, 5.80; N, 5.10. $C_{16}H_{15}NO_3$ requires C, 71.35; H, 5.60; N, 5.20%); δ 13.13 (br, s, 1H, OH), 8.37 (s, 1H, CH=N), 7.48-6.85 (m, 9H, ArH), 5.18 (s, 1H,CH), and 3.75 (s, 3H, OMe); m/z(%) 269 (M^+,45) 210(100), 121(7), 91(16), and 77(14); ν_{max} 3425, 1740 and 1625 cm^{-1}.

N-p-Methoxybenzylidene-9-aminofluorene (12). Prepared from 9-aminofluorene hydrochloride (2.17g, 0.01mole) and p-methoxybenzaldehyde (1.36, 0.01moles) by the method used for (9h). The product (2.72g, 91%) crystallised from methanol as colourless needles, m.p. 134-135°C (Found: C, 84.40; H, 5.75; N, 4.65. $C_{21}H_{17}NO$ requires C, 84.25; H, 5.70; N, 4.70%); δ 8.71 (s, 1H, CH=N), 7.78-7.90 (m, 12H, ArH), 5.37 (s, 1H, CH) and 3.82 (s, 3H, OMe); m/z(%) 299 (M^+, 56), 191(4), 166(17), 165(100), and 164(6).

1-Oxo-3-N(methyl phenylglycinyl)phthalan (21). Phenylglycine methyl ester hydrochloride (10.0g, 0.05mole) and sodium carbonate (5.3g, 0.05mole) were dissolved in water (ca. 200ml) and 2-carboxybenzaldehyde (7.5g, 0.05mole) added. The mixture was stirred at 40°C for 45 min. and then for 16h. at room temperature. The mixture was then extracted with chloroform (3 x 75ml) and the combined organic extracts washed with water, dried (Na_2SO_4) and evaporated to leave a colourless solid. Crystallisation from ethanol afforded the product (13.4g, 91%) as colourless rods, m.p. 154°C (Found: C, 64.45; H, 5.05; N, 4.65. $C_{17}H_{15}NO_4.H_2O$ requires C, 64.75; H, 5.40; N, 4.65%); δ 8.00-7.18 (m,9H,ArH) 6.00 (br s, 1H, NCHO), 5.02 (br s, 1H, NCH), and 3.71 (s, 3H, OMe); m/z(%) 298 (M + 1, 1), 253(1), 239(10), 238(61), 194(15), 133(100), 105(13), and 77(20); ν_{max} 3340, 1740 and 1725 cm^{-1}.

Bronsted and Lewis acid catalysed cycloadditions

General Procedure for half-life studies. Equimolar amounts (0.4M) of imine, dipolarophile and Bronsted or Lewis acid were accurately weighed into an n.m.r. tube and [$^2H_8$]toluene added. The mixture was flushed with argon and the n.m.r. tube sealed. Liquid acids were measured using a microsyringe.

Cycloadditions in acetic acid-acetic anhydride. General procedure. Imine (1mmole) and the appropriate dipolarophile (1mmole) were dissolved in 6% v/v acetic acid-acetic anhydride (2ml) and stirred at room temperature for the required length of time. The products normally crystallised from the reaction mixture and were filtered off and washed with ether. Yields and reaction times are collected in Table 2.

Methyl c-4 (o-methoxyphenyl)-2,7-diphenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane-r-2-carboxylate (10a, Ar=2-$MeOC_6H_4$). Colourless needles from chloroform-methanol, m.p. 235-237°C (Found: C, 71.15; H, 5.35; N, 6.00. $C_{27}H_{24}N_2O_5$ requires C, 71.10; H, 5.30; N, 6.15%); δ 7.71-6.84 (m, 14H, ArH), 4.54 (d, 1H, J 9.0Hz, 4-H), 4.26 (d, 1H, J 7.5Hz, 1-H), 3.80 and 3.76 (2 x s, 2 x 3H, 2 x OMe), and 3.66 (dd, 1H, 5-H); m/z(%) 456 (M^+, 1), 398(13), 397(46), 284(23), 283(100), 250(9), 224(11), 223(40), 208(12) and 91(9); ν_{max} 3410, 3045, 2940, 2820, 1770, 1735, 1705, 1590, 1370, 755 and 730 cm^{-1}.

Methyl c-4 (o-methoxyphenyl)-2-phenyl-6,8-dioxo-7-oxa-3-azabicyclo[3.3.0]octane-2-carboxylate (10b, Ar=2-$MeOC_6H_4$). Colourless prisms from acetic anhydride, m.p. 220-222°C (Found: C, 65.45; H, 5.00; N, 3.70. $C_{21}H_{19}NO_6$ requires C, 66.05; H, 5.00; N, 3.65%); δ 7.69-6.89 (m, 9H, ArH), 4.40 (2 x overlapping d, 2H, J 11.0 and 8.3Hz, 4-H and 1-H), 3.82 and 3.80 (2 x s, 2 x 3H, 2 x OMe), and 3.64 (dd, 1H, 5-H); m/z(%) 381 (M^+, 1), 368(6), 322(56), 284(27), 283(100), 224(24), 223(52), 118(15), 91(16) and 77(14); ν_{max} 3340, 2995, 2900, 1850, 1780, 1740, 1600, 1499, 1200, 860, 800, 760, 730 and 695 cm^{-1}.

Methyl 2,c-4,7-triphenyl-6,8-dioxo-3,7-diazobicyclo[3.3.0]octane-r-2-carboxylate (10a, Ar=Ph). Colourless prisms from dichloromethane-petroleum ether, m.p. 237-239°C (lit.[19] 238-240°); δ 7.63-7.10 (m, 15H, ArH), 4.41 (d, 1H, J 9.2Hz, 4-H), 4.25 (d, 1H, J 7.3Hz, 1-H), 3.79 (s, 3H, OMe) and 3.51 (dd, 1H, 5-H).

Methyl c-4(p-methoxyphenyl)-2,7-diphenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane-r-2-carboxylate (10a, Ar=4-$MeOC_6H_4$). Obtained as colourless needles from dichloromethane-petroleum ether, m.p. 184-186°C (lit.[19] 184-186°C); δ 7.62-6.82 (m, 14H, ArH), 4.36 (d, 1H, J 9.0Hz, 4-H), 4.24 (d, 1H, J 7.3Hz, 1-H), 3.79 (s, 6H,2 x OMe) and 3.46 (dd, 1H, 5-H).

2,2-(Spiro-9,9-fluorenyl)-4(p-methoxyphenyl)-7-phenyl-6,8-dioxo-3,7-diazabicyclo [3.3.0]octane (13). The product crystallised from toluene as colourless prisms, m.p. 290°C (Found: C, 77.40; H, 5.25; N, 5.70. $C_{31}H_{24}N_2O_3$ requires C, 78.80; H, 5.10; N, 5.95%); δ 7.76-6.90 (m, 17H, ArH), 5.51 (d, 1H, J 8.5Hz, 4-H), 4.02 (t, 1H, 5-H), 3.81 (s, 3H, OMe), and 3.63 (d, 1H, J 8.1Hz, 1-H); m/z(%) 472 (M^+, 38), 471(21), 455(14), 307(20), 299(14), 205(18), 176(38), 165(10) and 134(8)

Methyl 2-(3-indolylmethyl)-4,7-diphenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane-2-carboxylate (15). The product crystallised from methylene chloride-petroleum ether as colourless prisms, m.p. 281-283°C (lit.[9] 282-284°C).

1-Carbomethoxy-1-phenyl-3-(o-methoxyphenyl)-4,7-diacetoxyisoindoline (17). The product crystallised from methanol as colourless prisms, m.p. 200-201°C (Found: C, 68.10; H, 5.20; N, 2.80. $C_{27}H_{25}NO_7$ requires C, 68.20; H, 5.30; N, 2.95%); δ 7.84-6.70 (m, 11H, ArH), 6.33 (s, 1H, CH), 4.09 and 4.08 (2 x s, 2 x 3H, OMe) and 2.23 (s, 6H, 2 x COMe); m/z(%) 475 (M^+, 1), 433(35), 391(14), 390(47), 374(24), 333(29), 332(100), 331(25) and 43(81); ν_{max} 3390, 1735, 1690, and 1620 cm^{-1}.

Methyl 4-[1-(2-allyloxynaphthyl)]-2-phenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane -2-carboxylate (19). The product crystallised from methanol as colourless needles, m.p. 182-184°C (Found: C, 74.70; H, 5.20; N, 5.00. $C_{33}H_{28}N_2O_5$ requires C, 74.40; H, 5.30; N, 5.25%); δ 7.90-7.22 (m, 16H, ArH), 6.00 (m, 1H, $CH=CH_2$), 5.85 (d, 1H, NH), 5.22 (m, 3H, $CH=CH_2$ and 4-H), 4.68 (m, 2H, OCH_2),

4.32 (d, 1H, J 7.7Hz, 1-H), 3.82 (s, 3H, OMe) and 3.61 (dd, 1H, H-5); m/z(%) 532 (M^+, 1), 473(4), 359(53), 318(100), 300(20), 258(63) and 77(16).

Methyl 2-methyl-c-4,7-diphenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane-r-2-carboxylate (10c, Ar=Ph). The product crystallised from methylene chloride-ether as colourless needles, m.p. 219-221°C (lit.[9] 220-222°C).

Methyl c-4,7-diphenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane-r-2-carboxylate (10d, Ar=Ph). The product crystallised from chloroform-ether as colourless plates, m.p. 213-215°C (Found: C, 68.60; H, 5.05; N, 8.05. $C_{20}H_{18}N_2O_4$ requires C, 68.55; H, 5.20; N, 8.00%); δ 7.45-7.10 (m, 10H, ArH), 4.54 (d, 1H, J 8.7Hz, 4-H), 4.07 (d, 1H, J 6.6Hz, 2-H), 3.84 (s, 3H, OMe), 3.67 (dd, 1H, J 7.8 and 6.8Hz, 1-H) and 3.51 (dd, 1H, 5-H).

Methyl 2,7-diphenyl-c-4-(o-carboxyphenyl)-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane-r-2-carboxylate (22). A solution of 1-oxo-3-N-(methyl phenylglycinyl)phthalan (2.96g, 1mmol) and N-phenylmaleimide (1.73g, 1mmol) in dry toluene (80ml) was boiled under reflux for 6h. On cooling the product (3.66g, 78%) crystallised as colourless needles, m.p. 245-247°C (Found: C, 68.900; H, 4.55; N, 5.95. $C_{27}H_{22}N_2O_6$ requires C, 68.95; H, 4.70; N, 5.95%); δ ([$^2H_5$]-pyridine + 1 drop D_2O) 7.99-6.81 (m, 14H, ArH), 5.28 (d, 1H, J 9.3Hz, 4-H), 4.34 (d, 1H, J 7.3Hz, 1-H), 4.16 (dd, 1H, 5-H) and 3.38 (s, 3H, OMe).

Methyl 2,7-diphenyl-c-4-(o-hydroxyphenyl)-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane-r-2-carboxylate (10a, Ar=o-HOC_6H_4). A solution of methyl o-hydroxybenzylidene phenylglycinate (54mg, 0.2mmole) and N-phenylmaleimide (37mg, 0.22mmole) in [$^2H_8$]toluene (0.5ml) was sealed in an n.m.r. tube under an argon atmosphere and heated for 5dy at 110°C, at which time all the imine had been consumed. The product (63mg, 71%) crystallised from toluene as colourless prisms, m.p. 264-266°C (Found: C, 70.35; H, 5.10; N, 6.20. $C_{26}H_{22}N_2O_5$ requires C, 70.60; H, 5.00; N, 6.35%); δ ($CDCl_3$ + 1 drop TFA) 7.60-7.68 (m, 14H, ArH), 5.29 (d, 1H, J 10.7Hz, 4-H), 4.69 (d, 1H, J 8.8Hz, 1-H), 4.36 (dd, 1H, 5-H) and 3.97 (s, 3H, OMe);; m/z(%) 442 (M^+, 5), 383(33), 270(13), 269(63), 235(14), 211(17),, 210(100), 209(31), 173(62), 91(20) and 77(20); ν_{max} 3430, 3310, 1780, 1740 and 1715 cm^{-1}.

Dimethyl 2,5-diphenyl-3-pyrroline-2,4-dicarboxylate (24).

A solution of methyl N-benzylidene phenylglycinate (759mg, 3 mmole) and methyl propiolate (504mg, 6mmole) were dissolved in dry toluene (10ml) and heated in a sealed tube at 100°C for 24h. The solvent was then evaporated under reduced pressure and the residue crystallised from ether-petroleum ether to afford the product (700mg, 69%), m.p. 121°C (Found: C, 71.00; H, 5.60; N, 4.20. $C_{20}H_{19}NO_4$ requires C, 71.20; H, 5.70; N, 4.15%); δ 7.56-7.24 (m, 11H, ArH and CH=C), 5.29 (br s, 1H, 5-H), 3.79 (s, 1H, NH) and 3.63 (s, 3H, OMe); m/z(%) 381 (M-1, 0.5) 324(21), 323(100), 291(36), 264(16), 218(15), 77(17) and 59(17); ν_{max} 3340, 3020, 1725, 1715 and 1635 cm^{-1}.

Dimethyl 2-methyl-c-5-phenyl-r-2,c-4-pyrrolidine-dicarboxylate (25) and Dimethyl 2-methyl-c-5-phenyl-r-2,t-4-pyrrolidine-dicarboxylate (26). A solution of methyl N-benzylidenealaninate (19mg, 0.01mmole), the appropriate Lewis acid (LiOAc.$2H_2O$, 10mg; AgOAc, 16.5mg; LiBr, 8.5mg; 0.01mmole), and methyl acrylate (10.5mg, 0.01mmole in [$^2H_3$]acetonitrile was sealed in an n.m.r. tube and heated at 80°C. Periodic monitoring by n.m.r. showed the cycloaddition to be complete in 15h (LiOAc) 12h (AgOAc) and 13.5h(LiBr) respectively in essentially quantitative yield. Reactions in the presence of lithium or silver acetate gave only product (25). Reaction in the presence of lithium bromide gave a trace (<5%) of (26). A scaled up experiment using lithium bromide gave samples of both isomers.

(25). Colourless prisms from petroleum ether at -20°C, m.p. 26-28°C (Found: C, 64.90; H, 6.65; N, 4.95. $C_{15}H_{19}NO_4$ requires C, 65.00; H, 6.85; N, 5.05%); δ 7.28 (s, 5H, ArH), 4.65 (d, 1H, 5-H), 3.83 and 3.20 (2 x s, 2 x 3H, OMe), 3.38 (m, 1H, 4-H), 2.73 (dd, 1H, 3-H), 2.06 (dd, 1H, 3-H) and 1.53 (s, 3H, Me); m/z(%) 218(100), 191(17), 186(8), 158(25), and 131(40).

(26). δ 7.35 (m, 5H, ArH), 4.47 (d, 1H, 5-H), 3.72 and 3.55 (2 x s, 2 x 3H, OMe), 2.96 (m, 1H, 4-H), 2.68 (dd, 1H, 3-H), 2.07 (dd, 1H, 3-H), and 1.5 (s, 3H, Me).

Trimethyl 2-methyl-c-5-phenylpyrrolidine-r-2, c-3, t-4-tricarboxylate (27) and trimethyl 2-methyl-c-5-phenylpyrrolidine-r-, t-3, c-4-tricarboxylate (28). A solution of methyl N-benzylidenealaninate (19mg, 0.01mmole), lithium acetate dihydrate (10mg, 0.01mmole) and dimethyl fumarate (14.5mg, 0.01mmole) in [$^2H_3$] acetonitrile (1ml) was sealed in an n.m.r. tube and heated at 80°C for 15h monitoring by n.m.r. The n.m.r. showed a quantitative reaction had occurred giving a 2:1 mixture of (27) and (28). A larger scale reaction provided pure samples of the two products.

(27) Colourless prisms from ether-petroleum ether, m.p.79-81°C (lit.[9] 78-81°C) (Found: C, 60.95; H, 6.25; N, 4.15. Calc. for $C_{17}H_{21}NO_6$ C, 60.9; H, 6.3; N, 4.2%); δ 7.35 (m, 5H, ArH), 4.5 (d, 1H, J 6.8Hz, 5-H), 3.5 (dd, 1H, 4-H), 3.45 (d, 1H, J 2.5Hz, 3-H), 3.7 (s, 6H, 2 x OMe), 3.6 (s, 3H, OMe) and 1.5 (s, 3H, Me).

(28) The minor isomer was not isolated in pure form and its structure is assigned on the basis of its p.m.r. spectrum admixed with some of the major isomer (above). δ 7.4 (m, 5H, ArH), 4.85 (d, 1H, J 8.5Hz, 5-H), 4.0 (d, 1H, J 9.3Hz, 3-H), 3.85 (s, 3H, OMe), 3.8 (dd, 1H, 4-H), 3.7 (s, 3H, OMe), 3.15 (s, 3H, OMe), and 1.4 (s,3H,Me)

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References

1. Part 13. R. Grigg, M. Dowling, M.W. Jordan, J. Kemp and V. Sridharan, Tetrahedron, submitted.
2. Preliminary communication: R. Grigg and H.Q.N. Gunaratne, J. Chem. Soc., Chem. Commun., 1982, 384.
3. C.K. Ingold, 'Structure and Mechanism in Organic Chemistry', G. Bell and Sons, London, 1953,, Chapt.10.
4. R.D. Guthrie and J.L. Hendrick, J. Am. Chem. Soc., 1973, 95, 2971; D.H. Hunter and R.P. Steiner, Can. J. Chem., 1975, 53, 355.
5. R.P. Bell, 'The Proton in Organic Chemistry', Cornell University Press, New York, 2nd edn., 1973; G.E. Lienhard and T.C. Wang, J. Am. Chem. Soc., 1969, 91, 1146.
6. K. Vaughan, J. Chem. Soc.,Perkin Trans. 2, 1977, 17; L. Lunazzi, G. Panciera and M. Guerra, ibid, 1980, 52.
7. R. Grigg, Chem. Soc. Rev., 1987, 16, 89.
8. R. Grigg, J. Kemp and W. Warnock, J. Chem. Soc., Perkin Trans. 1, in press.
9. K. Amornraksa, R. Grigg, H.Q.N. Gunaratne, J. Kemp, and V. Sridharan, J. Chem. Soc., Perkin Trans. 1, in press.
10. For reviews see T. Kauffmann, Angew. Chem., Int. Ed. Engl., 1974, 13. 627; idem, Top. Curr. Chem., 1980, 92, 109.
11. R. Grigg and J. Kemp, Tetrahedron Lett., 1978, 2823.
12. R. Grigg and T. Mongkolaussavaratana, J. Chem. Soc., Perkin Trans. 1, in press.
13. R. Grigg and J. Devlin, J. Chem. Soc., Chem. Commun., 1986, 631.
14. R. Grigg, V. Sridharan and S. Thianpatanagul, J. Chem. Soc., Perkin Trans. 1, 1986, 1669.
15. R. Grigg, J. Kemp, J. Malone and A. Tangthongkum, J. Chem. Soc., Chem. Commun., 1980, 648.
16. R. Grigg, M. Dowling and V. Sridharan, J. Chem. Soc., Chem. Commun., 1986, 1777
17. M. Joucla, B. Fouchet and J. Hamelin, Tetrahedron, 1985, 41, 2707.
18. J. Mulzer, G. Bruntrup, J. Finke and M. Zippel, J. Am. Chem. Soc., 1979, 101, 7723; J. Mulzer, M. Zippel, G. Bruntrup, J. Segner and J. Finke, Ann. Chemie, 1980, 1108.
19. R. Grigg, H.Q.N. Gunaratne and J. Kemp, J. Chem. Soc., Perkin Trans. 1, 1984, 41.
20. K.- A. Engdahl, H. Bivehed, P. Ahlberg and W.H. Saunders, J. Chem. Soc., Chem. Commun., 1982, 423.
21. R. Grigg, J. Trocha-Grimshaw, L. Waring, D. Leeworthy and P. Regan, J. Chem. Soc., Chem. Commun., 1979, 557.

22. R. Grigg, H.Q.N. Gunaratne, V. Sridharan and S. Thianpatanagul, Tetrahedron Lett., 1983, 24, 4363.

23. P. Armstrong, R. Grigg, M.W. Jordan, and J.F. Malone, Tetrahedron, 1985, 41, 3547.

24. J.W. Ledbetter, J. Phys. Chem., 1967, 71, 2351; 1968, 72, 4111; 1982, 86, 2449.

25. K.N. Houk and R.W. Strozier, J. Am. Chem. Soc., 1973, 95, 4094; T. Inukai and T. Kojima, Can. J. Chem., 1971, 36, 924; A.W. McCulloch and A.G. McInnes, ibid, 1971, 49, 3152.

26. B.B. Snider, J. Org. Chem., 1981, 46, 3155; M.J. Begley, J.P. Benner, and G.B. Gill, J. Chem. Soc., Perkin Trans. 1, 1981, 1112; M. Orfanopoulos and L.M. Stephenson, J. Org. Chem., 1981, 46, 2201.

27. T. Inukai and T. Kojima, J. Org. Chem., 1967, 32, 869.

28. J.S. Tou and W. Reusch, J. Org. Chem., 1980, 45, 5013.

29. P.C. Jain, Y.N. Mukerjee and N. Anand, J. Am. Chem. Soc., 1974, 96, 2996.

30. Coupling constants for CH-CH= are 6.5-11.5Hz. Four bond W coupling constants for CH-C=CH are 1.5-2.5Hz and are dependant on the angle between the protons: A.J. Gordon and R.A. Fond, 'The Chemists Companion', Wiley-Interscience, New York, 1972, p273.

31. This suggested that the weak Lewis acids would form metallo-1,3-dipoles more efficiently in the presence of a weak base, e.g. t-amines.

32. This will be explored more fully in a subsequent paper on amine catalysed cycloadditions.