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Asymmetric Cascade 1,3-Dipolar Cycloaddition Reactions of Imines.

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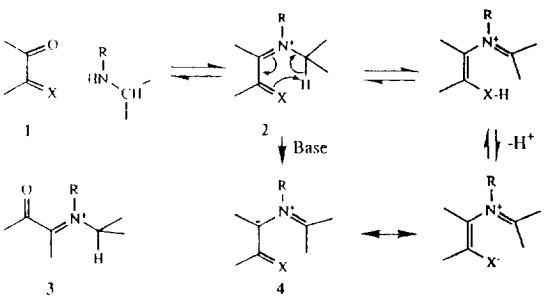
Abstract: Mechanistic and preparative features of a variety of successful approaches to homochiral pyrrolidines based on imine → azomethine ylide → cycloaddition cascades are discussed.

Chiral asymmetric 1,3-dipolar cycloaddition reactions of azomethine ylides can be achieved by three different strategies employing either: (i) chiral azomethine ylides. (ii) chiral dipolarophiles. (iii) chiral catalysts.

All three approaches have been **successfully** implemented by our group. Our work has focused on **cascade processes** and has provided a range of synthetic options for the synthesis of chiral polyfunctional pyrrolidines.

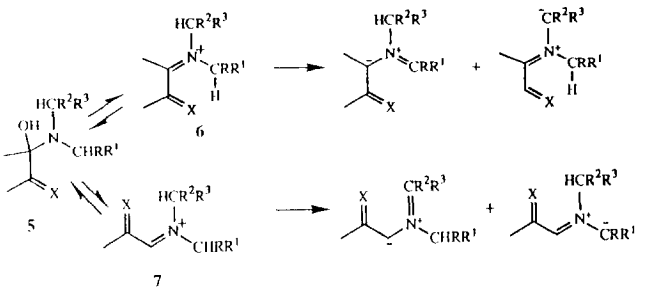
(i) Chiral Azomethine Ylides. A range of chiral cyclic and acyclic azomethine ylides have been developed over the past few years.[1] The general activity in the field caused us to limit our studies in this area to our previously reported iminium ion cascade route to azomethine ylides (Scheme 1)[2]. In this process a bifunctional compound **1** reacts with an amine to produce an iminium species **2** and subsequently an azomethine ylide either via a 1,5-H shift in **2** (Scheme 1) or by intervention of an external base to deprotonate **2**.



Scheme 1

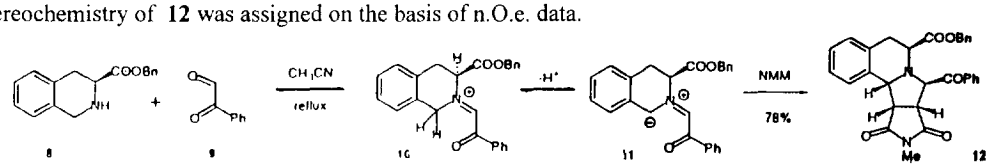
Dedicated to the memory of Professor Hidemasa Takaya, deceased on 5 October 1995

Our previous studies [2] were concerned with substrates in which any α-protons in the group R in iminium ion **2** were kinetically inert. Thus the alternative iminium ion **3** if formed did not exhibit a 1,5-H shift involving R (R = CH<) and no azomethine ylides arising from deprotonation at R in **2** or **3** were observed. Our conclusions in the previous study were that the substrates kinetically favoured iminium ion **2** and, on the data available, external base deprotonation **2** → **4** occurred in certain cases although there was clear evidence of a stereoelectronic interaction between X and CH in **2** [2] in most of the cases studied. It was therefore of interest to study chiral secondary amine substrates in which both amine substituents, upon iminium ion formation would possess kinetically labile protons (Scheme 2). Thus carbinolamine **5** could give rise to iminium ions **6** and **7** and these in turn are each potential precursors of two azomethine ylides depending on the regioselectivity of deprotonation or the operation of a 1,5-H shift (Scheme 2).



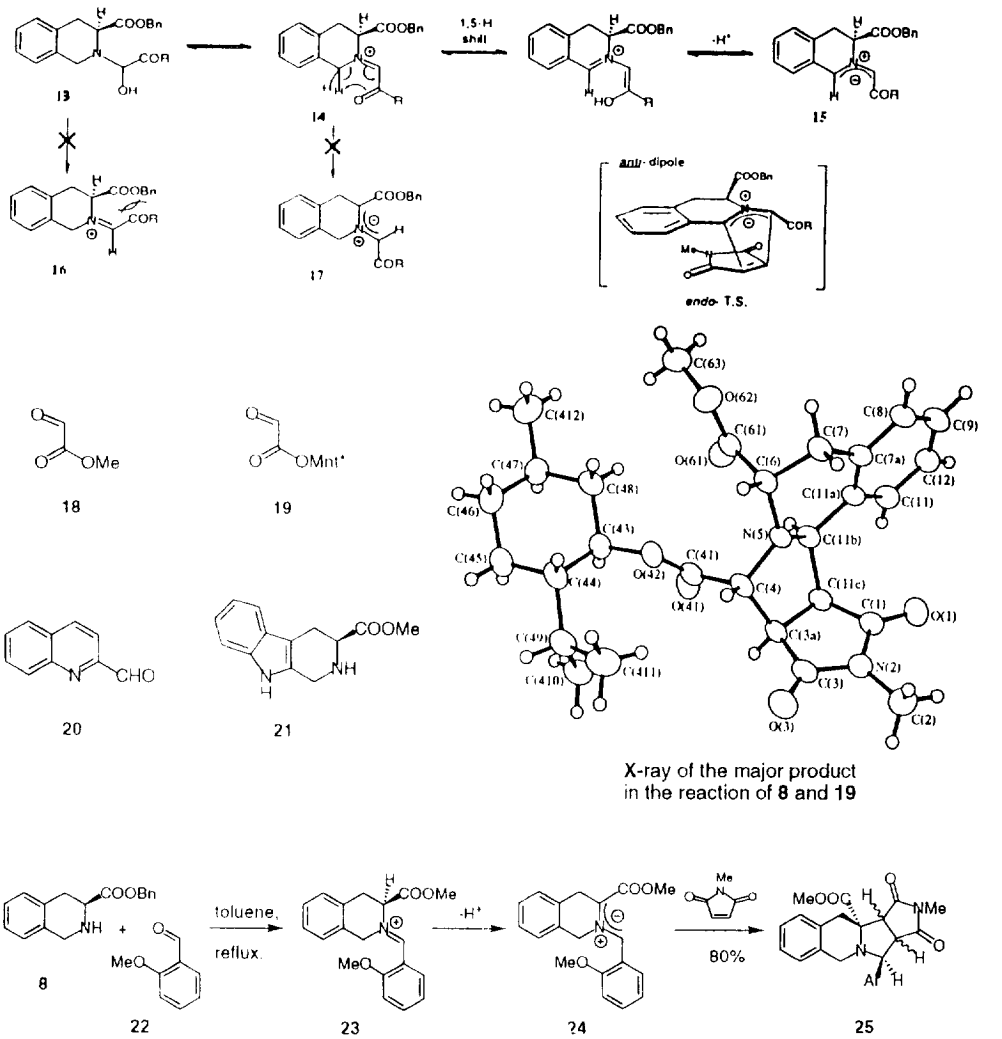
Scheme 2

We observed[3] an unusual and synthetically useful clean regiospecific process in chiral cyclic secondary α-amino esters. Thus benzyl-3-(S)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **8** reacts (MeCN, reflux, 6h) with phenyl glyoxaldehyde **9** and N-methylmaleimide (NMM) to give the azomethine ylide **11** regiospecifically which subsequently undergoes cycloaddition to NMM to afford homochiral cycloadduct **12** (78%, $[\alpha]_D$ +150.5). The stereochemistry of **12** was assigned on the basis of n.O.e. data.



Deprotonation of the iminium species **10** takes place at the benzylic carbon which bears the **less acidic protons**. Stereospecific conversion of carbinolamine **13** [generated in the reaction between **8** and **9**], into the (E)-iminium ion **14** and not (Z)-**16** reflects the higher energy transition state for **13** → **16** as a consequence of the developing $A^{1,3}$-strain[4] between the ester and the carbonyl groups. This process is significantly lower in energy than **14** → **17** since no racemisation occurs.

The anti-azomethine ylide **15**, generated from **14** via a 1,5-H shift accelerated by the positive charge on the system, subsequently undergoes endo-specific cycloaddition with the dipolarophile (NMM). Analogous regio- and stereo-selectivity were observed in the reactions of **8** and **21** with other bifunctional carbonyl compounds **18**, **19** and **20**. Thus the α-amino ester stereocentre acts as an efficient chiral control element on the cycloaddition process. The absolute stereochemistry of selected cycloadducts was established by X-ray crystallography (e.g. figure).

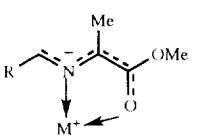


The ortho-methoxy group in **22** is not an effective substitute for the C=O or C=N moieties. Again $A^{1,3}$-strain leads to regiospecific formation of the (E)-iminium ion **23**. However deprotonation of **23** occurs exclusively α- to the ester group resulting in a 1:1.2 mixture of racemic exo- and- endo diastereomeric cycloadducts **25** via the achiral dipole **24**.

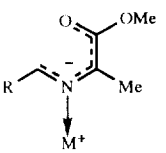
(ii) Chiral Dipolarophiles. a. Reactions with Metallo-azomethine Ylides. To implement chiral dipolarophiles in the broadest way required the extension of our catalytic metallo-azomethine ylide methodology to aliphatic aldimines. This was achieved[5] for a range of imines of general structure RCH=NCH(R^1)EWG (R=alkyl, EWG=2-pyridyl, CO_2Me, CONHR^2, COSR^2). Silver(I) salts in combination with an amine base generate metallo-azomethine ylides stereospecifically from aliphatic aldimines in toluene but **not** in acetonitrile. These 1,3-dipoles undergo regio- and stereo-specific endo-cycloaddition to dipolarphiles. Conditions have also been developed for catalysis by Ti(IV) salts. In this case stereospecific

endo-cycloaddition is again observed but the **regiochemistry of the cycloaddition is reversed** thus providing a precise and powerful synthetic option.

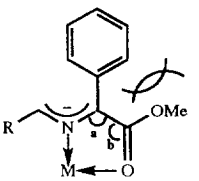
In contrast to aryl imines the aliphatic imines give rise to two metallo-dipoles **26** and **27** in reactions in acetonitrile mediated by Ag(I) salts showing that the two deprotonation transition states are much closer in energy than those of aryl imines which furnish only **26**. In a less polar solvent (toluene), metallo-azomethine ylide **27** which has a greater charge separation is suppressed.



26

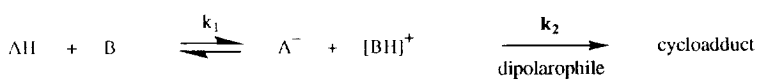


27



28 a. M = Ag(I)

b. M = Li(I)



AH = imine metal complex

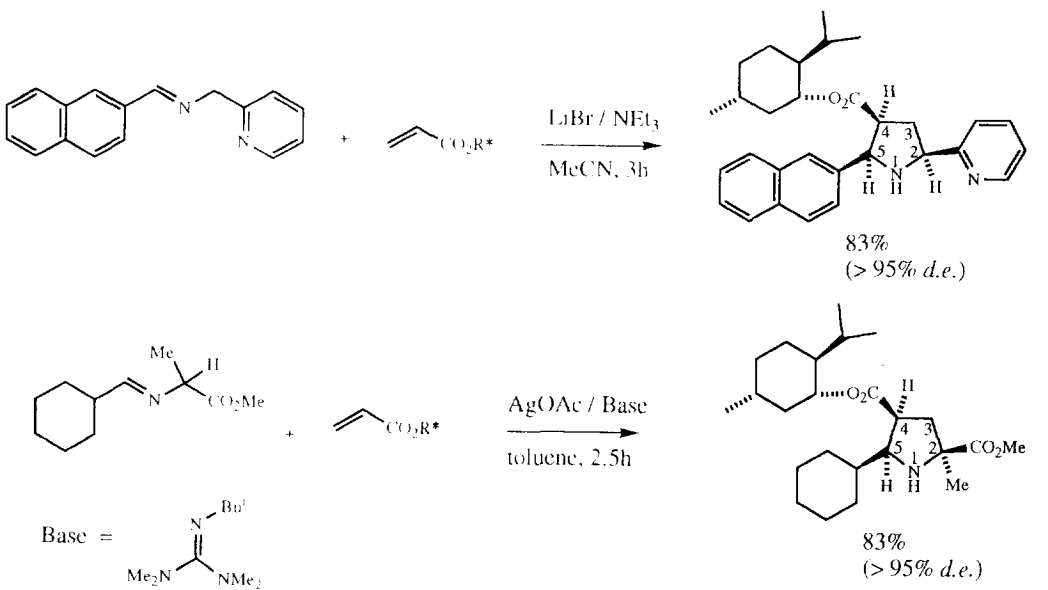
Scheme 3

A further practical feature that emerged is that Ag(I) salts are invariably much more effective catalysts then Li(I) salts which give variable amounts of Michael adducts in most cases. However, Li(I) salts are the most effective catalysts for cycloadditions involving phenylglycine imines. This switch in effectiveness of the metal salt catalysts is ascribed to steric factors arising in formation of the metal coordinated azomethine ylides. The silver cation (ionic radius 1.26Å) is considerably larger than the lithium cation (ionic radius 0.68Å) and when chelated causes the angles a and b in **28** to increase resulting in increased steric compression between the phenyl and methoxy moieties which is relieved by twisting of the phenyl group out of plane of the azomethine ylide. This both disrupts conjugation (effect on the pka of chelated imine) and sterically hinders the cycloaddition. The much smaller lithium cation allows the steric compression between the phenyl and methoxy moieties in **28** to be accommodated by a decrease in the angles a and b, whilst the bulky phenyl substituent impedes Michael addition in this case.

Menthyl acrylate has been implemented as an effective dipolarophile giving **homochiral cycloadducts in all cases**[6]. Two typical examples are shown in Scheme 4. Absolute stereochemistries of the cycloadducts was established by X-ray crystallography and was independent of the C(2)-substituents. Thus 1R, 2S, 5R-menthyl acrylate gives the 2S, 4S, 5R-cycloadducts[6]. A key advantage of using the menthyl group as a chiral auxiliary is that both enantiomers are available commercially, the auxiliary is cheap and is recyclable if required.

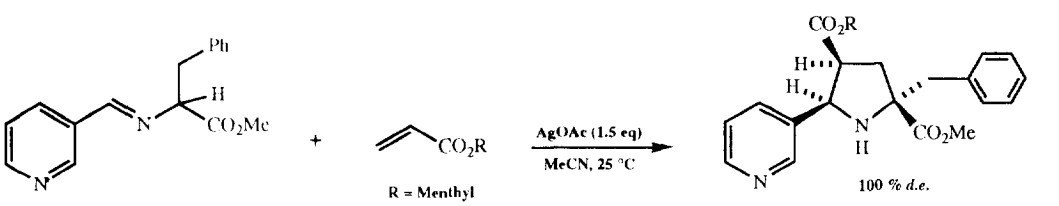
A key practical feature to note is that cycloadditions employing menthyl acrylate are considerably slower than those employing methyl acrylate. This often results in substantially lower yields due to slow metal ion induced hydrolysis of the imine by traces of water. However, this can be overcome by using a stronger base. The stronger the base, the faster the cycloaddition and the greater the yield with 2-t-butyl-1,1,3,3-

tetramethyl guanidine > DBU > NEt_3[6]. A typical set of data is shown below. The results accord with Scheme 3 in which k_2 is rate limiting. The concentration of the dipole obviously depends on the base strength [NEt_3,pka 10.8; DBU, pka 12; guanidine pka 14.3] whilst the sensitivity of the rate to the structure of the dipolarophile also accords with cycloaddition (k_2) as the rate limiting step. It is apparent that the reactive metallodipole could be either **29** or **30**. At present we have no definitive evidence on this point although use of homochiral tertiary bases cinchonidine and sparteine, in combination with silver acetate, for the cycloaddition of imines and methyl acetate results in cycloadducts exhibiting low enantiomeric excess (13 - 18%) and the solvent effects on the configuration of metallo-dipoles **26/27** derived from aliphatic aldimines implicate **30**. Clearly a more detailed study of chiral bases is imperative as is a study of the effect of solvent on the % ee. It is pertinent to reflect that chiral amines **may** exert their effect by complexing to **29**.

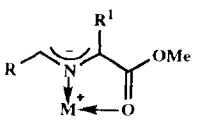


Scheme 4

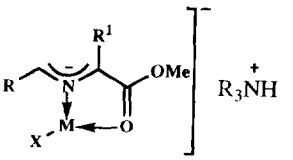
EFFECT OF BASE



BASE(1eq)	TIME (h)	YIELD (%)
NEt_3	24	51
DBU	6	76
Me_2N, Me_2N, =N, Bu^t	0.5	78

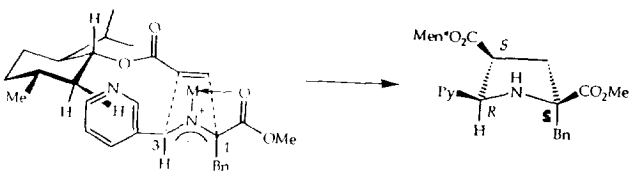


29



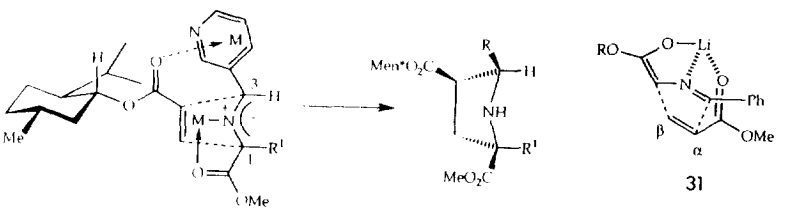
30

Cycloaddition Transition State. The regio- and endo-specificity of the cycloaddition together with the established absolute configuration of the cycloadducts and the facial shielding effect of the menthyl isopropyl moiety are accommodated in the transition state shown in Scheme 5. This involves addition of the 1-si, 3-re-face of the dipole to the re-face of the s-cis acrylate. The menthyl isopropyl group effectively shields the si-face in the s-cis acrylate. In this transition state the C(6) equatorial hydrogen atom of the menthyl moiety infringes slightly on the π-cloud of any C(3)-aryl substituent on the dipole.



Scheme 5

Coordination of the acrylate to a Lewis acid favours cycloaddition via the s-trans acrylate. However, addition of the metallodipole to the Li(I) or Ag(I) complexed s-trans acrylate (or the non-Lewis acid coordinated s-trans acrylate) would require attack of the 1-re, 3-si face of the E,E-dipole on the acrylate si-face due to steric blockade of the re-face by the menthyl isopropyl group. This transition state (Scheme 6) would lead to the opposite enantiomer to that observed i.e. would produce the 2R, 4R, 5S-cycloadduct.



31

Scheme 6

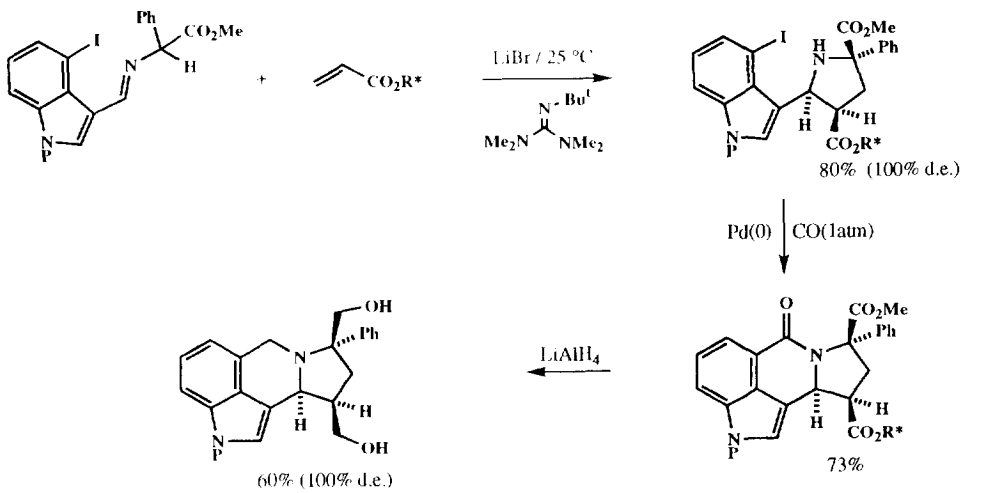
Both Ag(I) and Li(I) catalysed reactions give rise to cycloadducts with the same absolute stereochemistry even though these metal ions have different coordination numbers/geometry and donor atom preferences and substantially different ionic radii (vide infra). Moreover, particularly with lithium salts, polymeric species may be involved so that transition state representations such as **31** must be treated with due caution. Furthermore substantial amounts of silver acetate remain undissolved in acetonitrile whilst lithium bromide is completely soluble. Several authors have reported results of LiBr catalysed cycloadditions with non-chiral acrylates and enones in which both dipole and dipolarophile are considered to be coordinated to the same Li(I) cation and which are postulated to involve the Li(I)-complexed s-cis dipolarophile (e.g. **31**)[7].

A number of conceptional problems arise with such transition states: (i) for dipolarophiles lacking β-substituents [cf **31**] coordination to a metal ion via a carbonyl oxygen lone pair should result in steric exclusion of the s-cis acrylate conformer (ii) the carbonyl oxygen lone pair electrons in the dipolarophile have the wrong

geometry for coordination to the Li(I) ion in the manner depicted in **31**. However, coordination of Li(I) to carbonyl groups may have substantial ion-dipole character which effectively relaxes geometrical constrains (iii) the transition state for the cycloaddition is expected, by analogy with the Diels-Alder reaction, to be asynchronous and to have an "open-jaw" geometry in which the four centres involved in bond formation comprise the narrow end of the "open jaw". In this situation the dipolarophile carbonyl group is at too great a distance from the Li(I) ion to be coordinated unless it rotates out of the plane of the dipolarophile π-bond thereby deactivating the dipolarophile. Thus the postulated transition states for metalloazomethine ylide cycloadditions reactions offer an expedient interpretation rather than an accurate one.

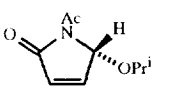
The stereospecificity observed in the metallo-azomethine ylide-menthyl acrylate cycloaddition reactions contrasts with the moderate diastereomeric excesses observed for the Diels-Alder reactions of Lewis acid complexed menthyl acrylate. This is believed to be due to the accentuated steric interactions in the 5- versus 6-membered transition states.

We have achieved the combination of sequential and cascade metallo-azomethine ylide cycloaddition and Pd(0) catalysed carbonylation (e.g. Scheme 7),[8] and the combination of cycloaddition and Pd catalysis, both core reaction resources, offer tremendous future synthetic possibilities.



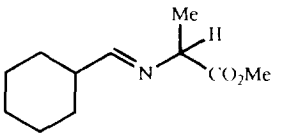
Scheme 7

32 R = menthyl

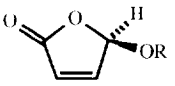


33

Homochiral room temperature cycloaddition of metallo-azomethine ylides with the cyclic dipolarophiles **32** and **33** have also been implemented in excellent yield[9] and absolute stereochemistries of the cycloadducts established by X-ray crystallography. These reactions display the same trend of increased rate and yield as the base strength of the amine co-catalyst is increased. A typical data set is shown below.

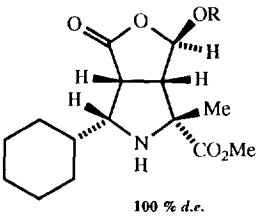


R = 1R, 2S, 5R- menthyl

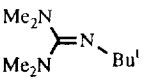


AgOAc (1.5mol)

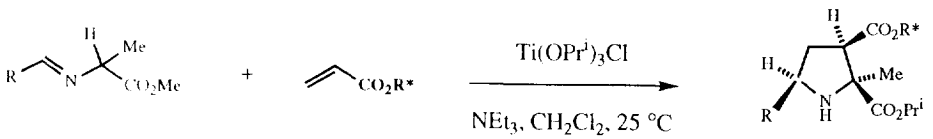
MeCN, 25 °C



100 % *d.e.*

BASE	TIME (h)	YIELD (%)
NEt_3	14	81
DBU	7	87
	1.7	91

Use of Ti(IV) salts as catalysts again results in homochiral cycloadducts with reversed regiochemistry for both aryl and aliphatic aldimines e.g. Scheme 8 (unpublished). Cycloadducts have been obtained from **32** by analogous Ti(IV) catalysed processes.



R* = menthyl

R = 2-naphthyl 80% 100%*d.e.*
R = c-C_6H_{11} 94% 100%*d.e.*

Scheme 8

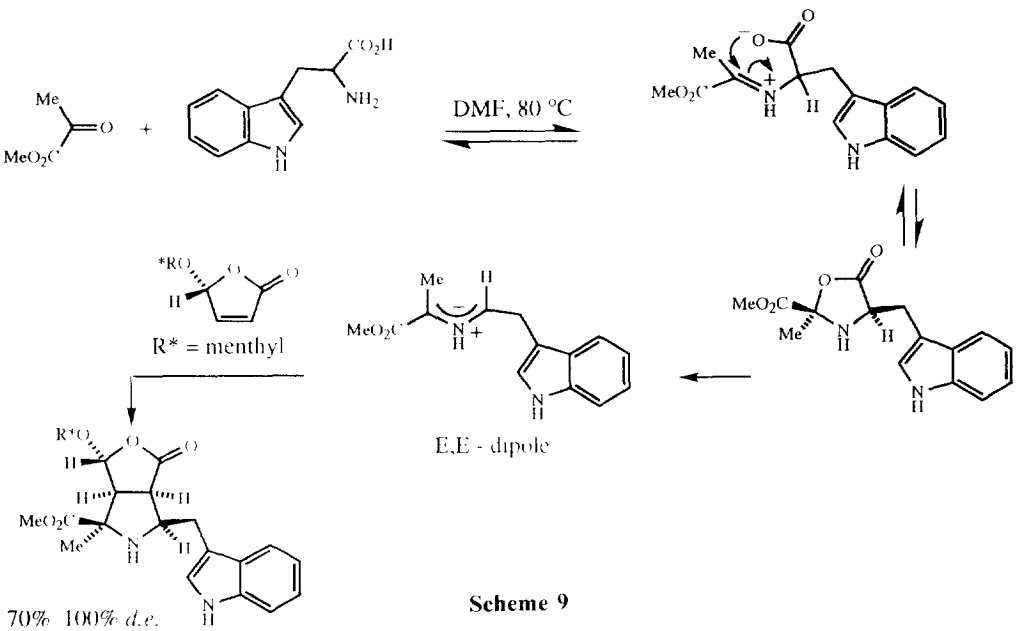
Proposals for the transition states for the Ti(IV) catalysed processes await assignment of the absolute stereochemistries of cycloadducts. The relevant X-ray structures are currently being determined.

Other workers have also reported the successful implementation of both acyclic and cyclic dipolarophiles for azomethine cycloaddition reactions.[10]

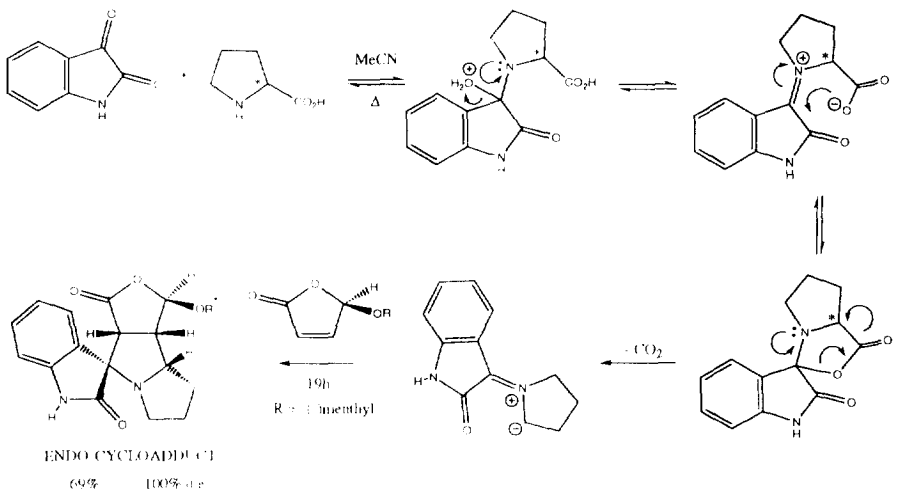
(b) Reactions with Azomethine Ylides Generated by the Decarboxylative Route. We have continued to develop our decarboxylative route to azomethine ylides and have demonstrated their presence as intermediates in the Strecker Degradation and related reactions and have used this approach to provide a facile entry to medium sized heterocycles via a 3-carbon ring expansion.[11]

The decarboxylative methodology has now been implemented for the cycloaddition of azomethine ylides derived from primary and secondary α-amino acids to both menthyl acrylate[12] and the lactone **32** (unpublished). A typical primary α-amino acid example is provided in Scheme 9 whilst Scheme 10 illustrates the reaction with secondary α-amino acids.

The absolute stereochemistry of the cycloadducts generated by the decarboxylative route is currently awaiting assignment by X-ray crystallography.



Scheme 9

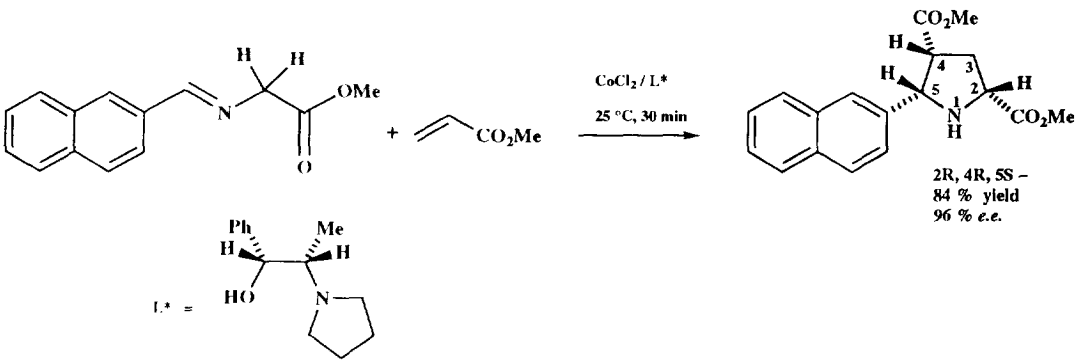


Scheme 10

(iii) Chiral Catalysts. Our previous work demonstrated the potential of chiral metal catalysts for imine → metallo-azomethine → cycloaddition cascades when we showed that Mn(II) and Co(II) salts in combination with chiral ligands gave cycloadducts with moderate to excellent (96%) % ee.[13] A typical example is shown in Scheme 11.[13] In this example the pre-transition state chelate (figure 1) results in effective shielding of one face of the putative metallo-dipole. These first generation catalysts suffered from a lack of flexibility with respect to the dipolarophile.

A series of second generation Ag(I) catalysts (unpublished) is currently being developed. A very wide

range of chiral ligands, some novel others previously described, have been evaluated in combination with Ag(I) salts. The Ag(I) catalysts accept a range of dipolarophiles and the reactions occur in good chemical yield. However, the % ee with these catalysts is ca 70% at present and thus further exploratory work is required. Some typical examples (unpublished) are shown below:



Scheme 11

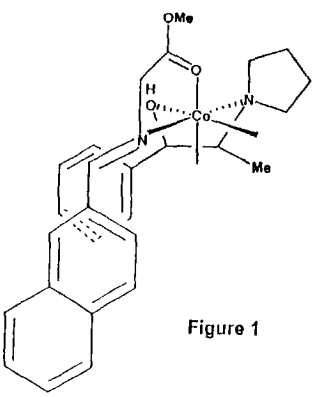
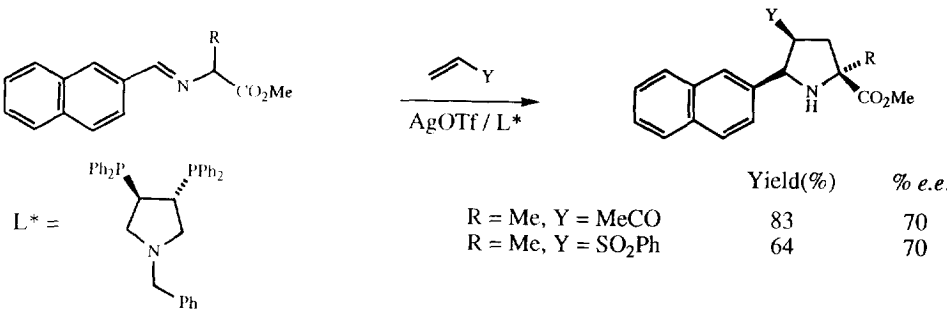


Figure 1



	Yield(%)	% *e.e.*
R = Me, Y = MeCO	83	70
R = Me, Y = SO_2Ph	64	70

Much of the foregoing chemistry is ideally suited to applications in combinatorial chemistry and this aspect is being actively pursued by ourselves and others. For example a mercaptoacylproline library has recently been reported which led to the identification of a potent inhibitor of angiotensin converting enzyme (ACE).[14]

References.

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