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Chiral catalysts in the stereoselective synthesis of pyrrolidine derivatives via metallo-azomethine ylides

Suren Husinec[a] and Vladimir Savic[b,*]

[a]*Institute of Chemistry, Technology and Metallurgy, Centre for Chemistry, PO Box 815, Njegoseva 12, 11000 Belgrade, Serbia and Montenegro*
[b]*Department of Organic Chemistry, Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, 11000 Belgrade, Serbia and Montenegro*

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1. Introduction

Although 1,3-dipoles have been known for more than a century, intensive research in this area was initiated in the 1960s. Since then, numerous methods have been developed for the generation of various types of these reactive species. Their cycloaddition reactions have become powerful synthetic tools, providing access to highly functionalised O-, S- and N-containing heterocycles. The synthetic utility of these cycloadditions has been expanded further by developing tandem processes, which allow the preparation of complex molecules starting from relatively simple starting materials.[1]

In recent years, azomethine ylides have become one of the most investigated classes of 1,3-dipoles. Based on their cycloaddition chemistry, various methods for the synthesis of pyrrolidine derivatives have been developed. In addition, the most recent advances, particularly, in the area of metallo-azomethine ylides provide highly stereoselective methodologies for the preparation of this important class of compounds.

2. Azomethine ylides

Azomethine ylides, represented by the general structure **1**, are planar 1,3-dipoles composed of one nitrogen and two terminal sp^2 carbon atoms. Their cycloaddition reactions, to olefinic dipolarophiles, provide a direct and general way for the synthesis of pyrrolidine derivatives (Scheme 1).[2] This cycloaddition approach to the

* Corresponding author. Tel.: +381(0)11 3970 379x643; fax: +381 (0)11 3972 840; e-mail: vladimir.savic@pharmacy.bg.ac.yu

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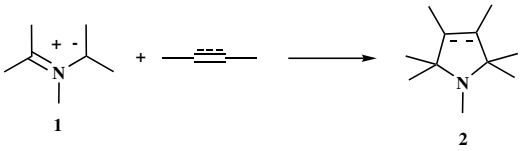


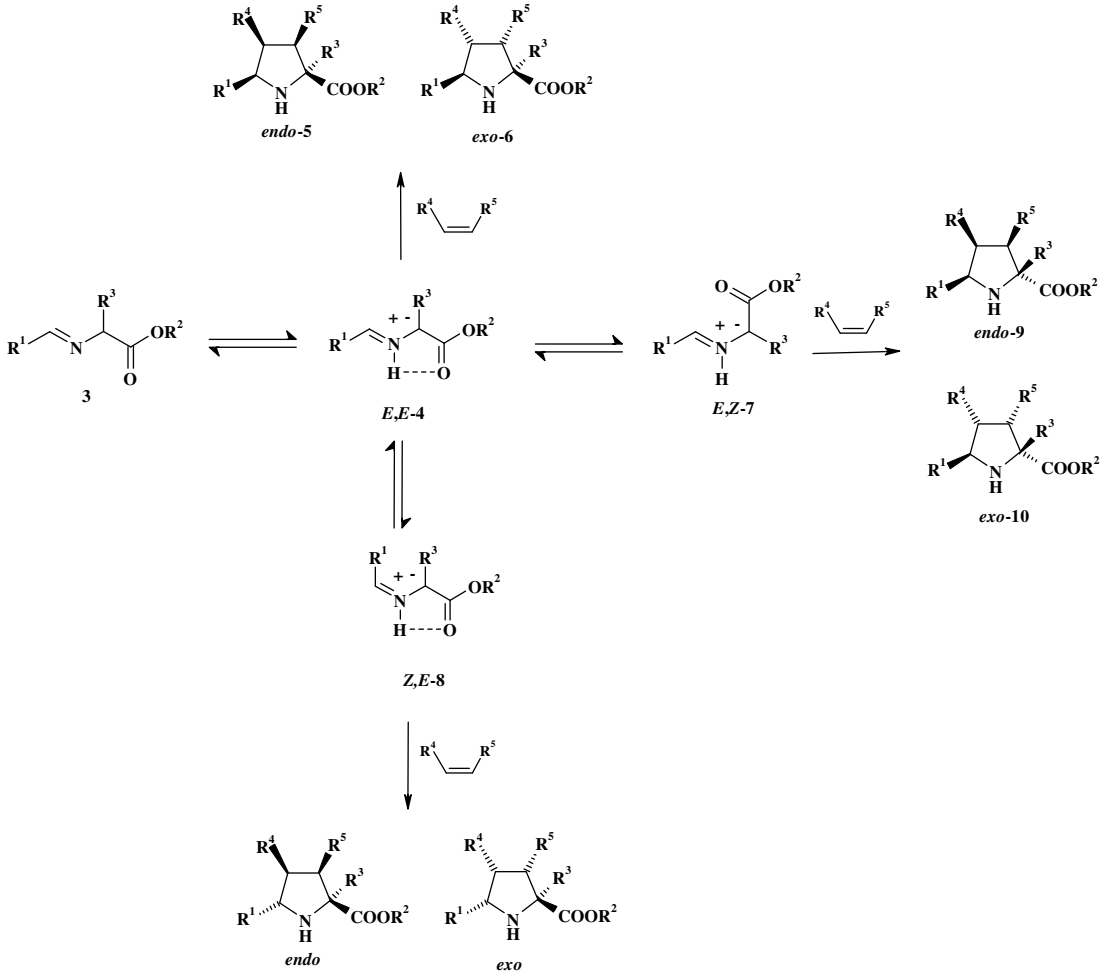
Scheme 1.

pyrrolidine synthesis allows the formation of two bonds and up to four stereogenic centres in a single operation.

Although there are examples of stable, isolable azomethine ylides,[3] they are normally generated in situ and trapped by almost any multiple C–C or C–X (X = heteroatom) bond. Since the first report[4] on these reactive intermediates, a number of methods have been developed for their generation. These include processes such as ring opening of aziridines,[5] desylylation of various silylamino derivatives,[6] 1,2-prototropy/metallo-azomethine ylides of amino acids derived imines,[7] decarboxylative condensation of amino acids,[8] deprotonation of iminium salts[9] and others.[10] Advances made in this area over the last few decades have made cycloaddition reactions of azomethine ylides a powerful synthetic tool, extensively used in the synthesis of natural products as well as other products.[11]

3. 1,2-Prototropy and metallo-azomethine ylides

Amino acid derived imines undergo 1,2-prototropy under thermal conditions to produce, in a kinetically controlled process, *E*,*E*-azomethine ylide **4** (Scheme 2).[12] In the presence of the dipolarophile, this ylide takes part in the cycloaddition reaction, which may or may not be the rate determining step, to often afford a mixture of cycloadducts **5** and **6**, obtained via an *endo* and an *exo* transition state, respectively. Formation of azomethine ylides is sensitive to the pK_a of the α-hydrogen and the basicity of the imine nitrogen, which in turn depend on the imine structure.[13] The initially formed *E*,*E*-ylide, although rarely, may undergo stereomutation to produce either *E*,*Z*-**7** or *Z*,*E*-**8** ylides, which then undergo the cycloaddition reaction. Further progression of the kinetic ylide **4** is generally controlled by a number of factors such as the imine structure, solvent, reaction temperature and reactivity of the dipolarophile used in the subsequent cycloaddition step.[13,14]



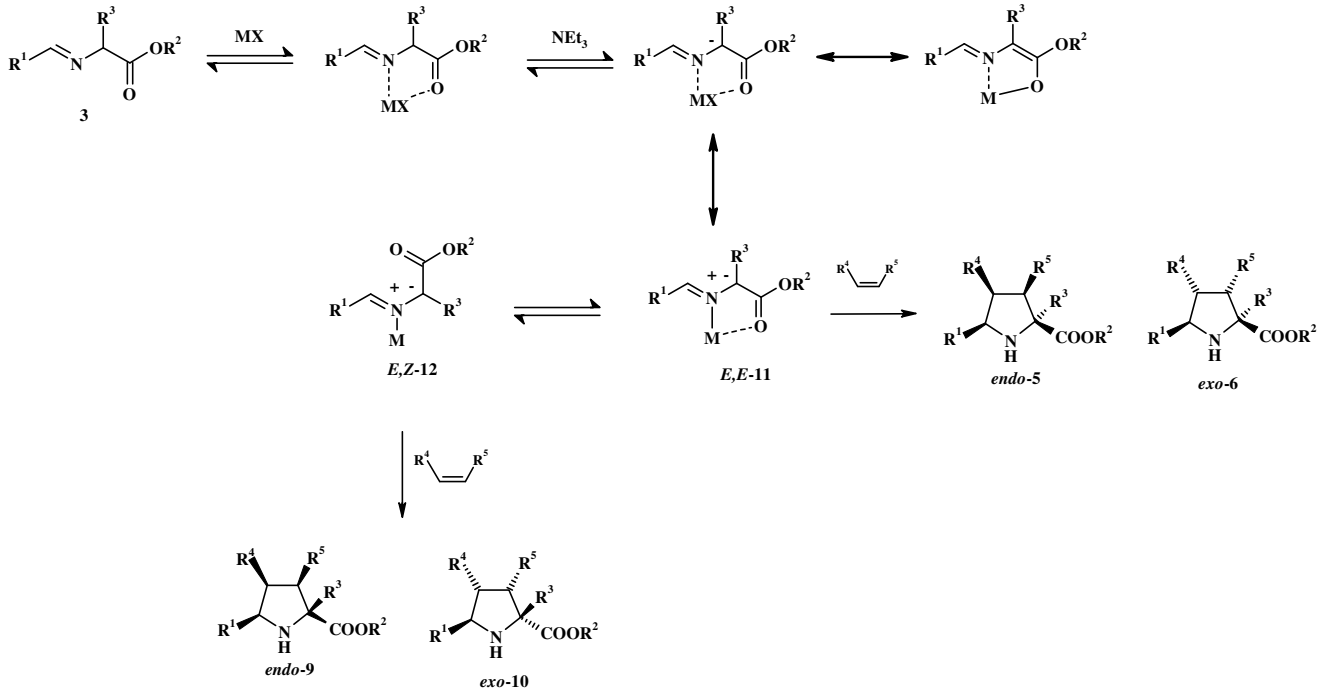
Scheme 2.

Related to the 1,2-prototropy processes, which lead to the formation of azomethine ylides, are processes in which metallo-azomethine ylides are formed.[15] Essentially, in these transformations the hydrogen atom in the above processes is replaced by a metal ion. One of the first examples of transformations potentially involving metallo-azomethine ylides was reported in the '70s.[16] It was shown that the metal complexes of imines, derived from the α-amino acids and ketones possessing an additional coordinating group, reacted with activated alkenes to afford the pyrrolidine products. Although a mixture of diastereoisomers was formed in this reaction, suggesting a stepwise mechanism such as double Michael reactions, further investigation in this area supported a concerted 4π + 2π process.[16c] Reports following these initial findings demonstrated that α-amino esters or α-aminonitrile derived imines produced pyrrolidine products in the presence of activated alkenes when treated with strong bases, such as NaOMe, BuLi, LDA, *t*-BuMgCl and NaH.[17] In addition, Lewis and Bronsted acids were shown to promote the same process.[18]

All these efforts culminated in the development of a very mild and efficient method for the generation of metallo-azomethine ylides employing Lewis acids in conjunction with a weak base.[15] Reactions of amino acid derived imines or related compounds and activated alkenes promoted by Lewis acid/base afford pyrrolidine products often in very high yields and with a high level of stereoselectivity. The proposed mechanism for this transformation is outlined in Scheme 3.[19]

The coordination of the metal ion by the imine/ester moieties increases the acidity of the α-CH and facilitates the deprotonation step promoted by a weak base. This leads to the initial formation of the kinetically favoured *E*,*E* azomethine ylide. Various Lewis acids can be used for this purpose, such as Ag^{I}, Tl^{I}, Li^{I}, Mg^{II}, Co^{II}, Ti^{IV}, Zn^{II}, Cu^{II} and Sn^{IV} in conjunction with bases such as Hunig's base, Et_3N, DBU, TMEDA, guanidine derived bases and phosphazanes.[19] The reaction can proceed without the presence of a base but is generally much slower, even at higher temperatures. The regiochemistry of the cycloaddition step can be controlled by Lewis acid.[20] The exact nature of the metallo-azomethine ylide is not known. The coordination chemistry and properties of Lewis acids used vary widely, suggesting that different species are present and can contribute to the metallo-azomethine ylide structure.

The major difference and advantage of the metallo-azomethine over the related 1,2-prototropy route towards pyrrolidine derivatives lies in its stereoselectivity. The kinetic *E*,*E* ylide **4**, generated via thermally induced 1,2-prototropy, may undergo stereomutation processes, while two modes of the cycloaddition step, *endo* and *exo*, contribute further to the complexity of the reaction sequence (Scheme 2). As a result, in many transformations of this type, a mixture of products is obtained. This is not the case in the cycloaddition reactions involving metallo-azomethine ylides. They are generated under milder conditions and often the only species formed, particularly from imines of aromatic aldehydes and amino ester derivatives, is *E*,*E*-ylide **11**. The following cycloaddition step is highly *endo* selective but can be influenced by the dipolarophile structural properties. The stereomutation of ylide **11** is observed in case of the metallo-ylides generated from imines of aliphatic aldehydes.[21] These processes can be suppressed by a Lewis acid and solvent selection. Very mild conditions used to generate



Scheme 3.

metalloazomethine ylides provide the opportunity to use imines obtained from aliphatic aldehydes. These imines under the thermal conditions of the 1,2-prototropy method undergo the imine–enamine isomerisation and often afford the final product in low yields.

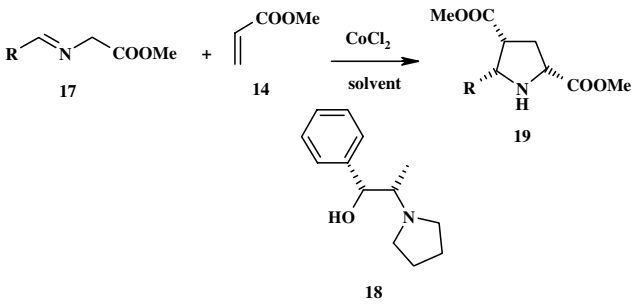
4. Metallo-azomethine ylides in the stereoselective synthesis of pyrolidine derivatives

Stereoselectivity in the 1,3-dipolar cycloaddition reactions of metallo-azomethine ylides can be achieved in various ways.[17b,20b,22] The chiral auxiliary approach is based on the presence of a removable chiral moiety as part of either the azomethine ylide or the dipolarophile structure. Both of these strategies were extensively investigated, with the reactions being performed under both 1,2-prototropy and the metallo-azomethine ylide conditions.[22] An alternative and perhaps more desirable methodology employs chiral Lewis acids, in most cases generated in situ, which promote reactions between prochiral reactants to afford the final product in a stereoselective manner. Although this is a well established and widely applied strategy, only in recent years has this approach been investigated in the area of azomethine ylide cycloadditions. The current status in this field will be discussed further in this text.

4.1. Co^{II} catalysed reactions

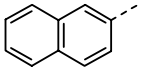
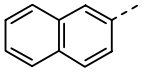
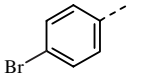
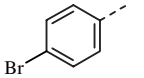
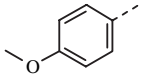
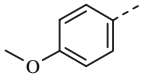
The first example of stereoselective cycloadditions of the azomethine ylides mediated by a chiral Lewis acid complex appeared in the literature in 1991.[23] It was reported that the reaction of imine **13** and acrylate **14** in the presence of $CoCl_2$ and ephedrine derived ligand **15** afforded pyrrolidine product **16** in 45% yield with 80% ee (Scheme 4). The product was isolated as a single diastereoisomer, arising from *E*,*E*-dipole via an *endo* transition state.

The moderate yield was likely to be caused by the imine hydrolysis promoted by Lewis acid or Bronsted acid generated from the metal salt. Neither the reaction time (16 h) nor the enantioselectivity was significantly affected by other solvents (CH_2Cl_2, MeCN, PhCN and THF), but further improvement of the ee was achieved by using the dipolarophile as a solvent (Scheme 5, Table 1). All pyrrolidine products, under the conditions using methyl acrylate **14** as a solvent, were isolated as a single



Scheme 5.

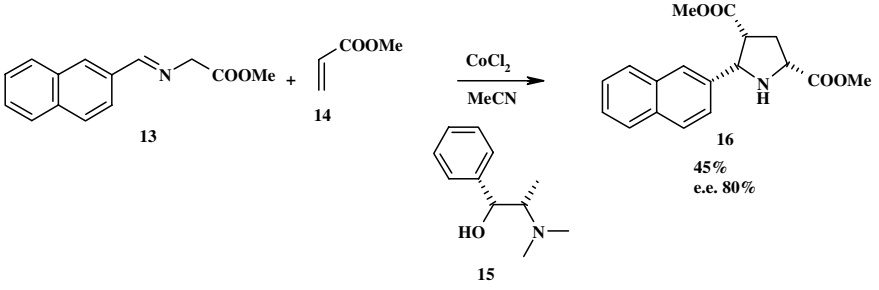
Table 1. Enantioselective 1,3-dipolar cycloadditions in the presence of $CoCl_2$ and (1*R*,2*S*)-**18**[a]

Entry	R	Solvent	Time (h)	Yield, **19** (%)	ee, **19** (%)[b]
1		MeCN	16	55	84
2		Methylacrylate	0.7	84	96
3		MeCN	24	45	80
4		methylacrylate	0.5	67	96
5		MeCN	24	—	
6		Methylacrylate	0.7	83	96

[a] $CoCl_2$, 1 mol; ligand **18**, 2 mol, reactions carried out at 25 °C.
[b] Ee determined by ^1H NMR and HPLC.

diastereoisomers in good yields and with excellent ee (Table 1, entries 2, 4 and 6). As in the case above, they were obtained from *E*,*E*-ylide via an *endo* transition state.

Furthermore, under the above conditions, the reaction time was significantly decreased (Table 1, entry 1 vs entry 2). Performing the reaction in MeCN and replacing



Scheme 4.

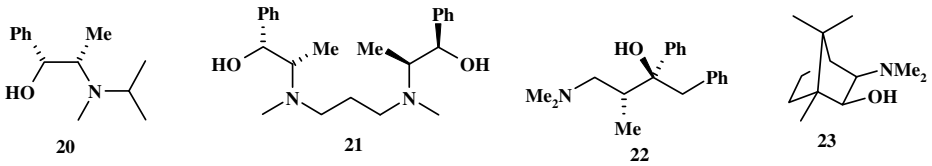


Figure 1.

$CoCl_2$ with $CoBr_2$ resulted in a shorter reaction time (4 h) but lower ee (45%), whilst the use of CoF_2 resulted in a very slow reaction and little chiral induction.

Several additional ligands, compounds **20**–**23**, were investigated in this transformation but were shown to be less efficient than ligand **18** (Fig. 1).

To address the origin of the observed enantioselectivity, a model of the transition state was proposed (Fig. 2). It was assumed that Co^{II} forms an octahedral complex, involving both the ligand and the imine, in which one face of the imine was effectively blocked by the phenyl group of the ligand. The proposed arrangement around the metal may be additionally stabilised by the π–π interactions of the aromatic substituents. It is likely that the acrylate dipolarophile is coordinated to the metal centre during the cycloaddition step.

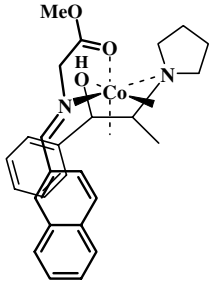


Figure 2.

Although highly enantioselective, this method suffers from several drawbacks. As shown, in order to obtain a synthetically useful ee, the use of a dipolarophile as a solvent is essential. Application of a large excess of the reactant may not always be convenient, particularly in case of complex dipolarophiles which require a multi-step synthesis. In addition, Lewis acid is used in an equimolar amount and for optimal results requires 2 equiv of the ligand. Even so, this first example of the enantioselective cycloaddition reactions of azomethine ylides demonstrated the potential of this methodology and opened a new field in the synthesis of pyrrolidine derivatives.

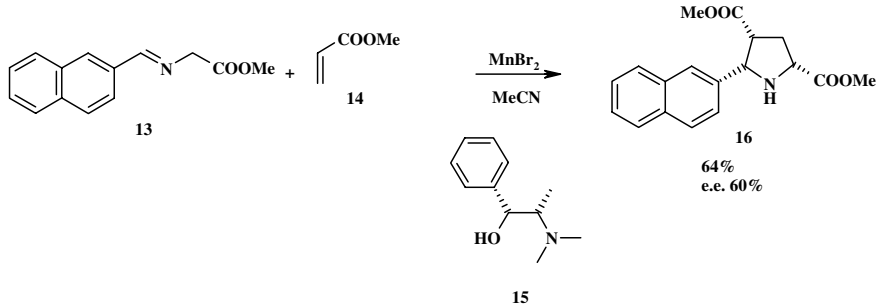
4.2. Mn^{II} catalysed reactions

Attempts have been made to use $MnBr_2$ in the processes discussed above, but this Lewis acid was shown to be less efficient than Co^{II} salts.[23] Under the same conditions, using an equimolar amount of $MnBr_2$ and 4 equiv of ligand **15**, pyrrolidine product **16** was isolated in 64% yield with 60% ee (Scheme 6). As before, the product was obtained from the *E*,*E*-dipole via an *endo* transition state. The use of other investigated ligands **20**–**23** in conjunction with Mn^{II} salts did not result in improvement of this initial result.

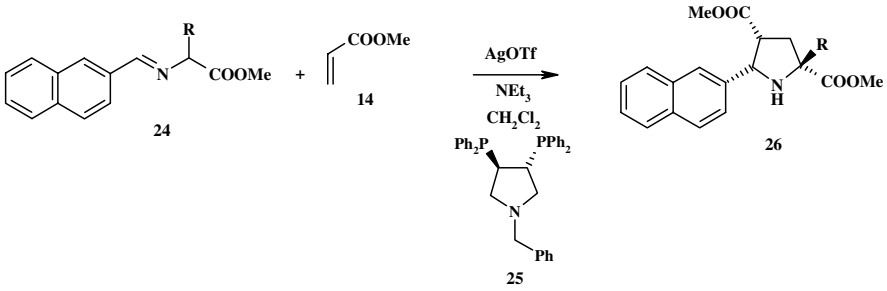
4.3. Ag^{I} catalysed reactions

The most effective Lewis acids in the cycloaddition reactions of metallo-azomethine ylides are arguably Ag^{I} salts. The reaction times in these cases are generally short, requiring no more than a few hours, and the products are normally isolated in very high yields. A further benefit of the short reaction time is that the imine hydrolysis, often observed in the reactions catalysed by some other Lewis acids, is not a significant side reaction.

Based on the reactivity and stability of its complexes, the Ag^{I} ion was characterised as a 'soft' acid for which the following ligand stability order is observed $N \ll P > As > Sb$; $O \ll S$.[24] One of the first examples of stereoselective cycloaddition reactions of azomethine ylides in the presence of an Ag^{I} salt employed



Scheme 6.

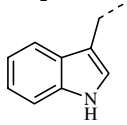


Scheme 7.

bisphosphine ligand **25**.[25] Results from the initial set of experiments are outlined in Scheme 7, Table 2.

The reactions were performed with 1 equiv of AgOTf and an equimolar amount of the ligand, using an excess of Et_3N as a base in CH_2Cl_2 as a solvent. Various aminoester derived imines were used to afford the pyrrolidine products in good yields with a moderate level of enantioselectivity (49–71%). The cycloadducts were derived from *E*,*E*-dipole via an *endo* transition state. Incorporation of the α-substituent in the imine structure had a moderate impact on the enantioselectivity (Table 2, entry 1 vs entry 2). Surprisingly, variation of this substituent did not influence the ee further (Table 2, entries 2/3, 4 and 5). These puzzling similarities between the imines possessing different α-substituents suggest that this moiety is not directly involved in factors controlling the enantioselectivity but its precise role is unclear.

Table 2. Enantioselective 1,3-dipolar cycloadditions in the presence of AgOTf and (3*R*,4*R*)-**25**[a]

Entry	R	Temperature (°C)	Yield, **26** (%)	ee, **26** (%)[b]
1	H	rt	69	49
2	Me	rt	72	64
3	Me	−20	78	71
4	CH_2Ph	rt	80	66
5		rt	80	67

[a] AgOTf, 1 mol; ligand **25**, 1 mol; Et_3N 1.5 mol; reactions carried out at 25 °C.
[b] Ee determined by ^1H NMR using $Eu(hfc)_3$.

Performing the reaction at a lower temperature improved enantioselectivity but by only a small amount (Table 2, entry 2 vs entry 3). Further study focused on the base showed that under the same conditions, the use of a stronger base than Et_3N, such as DBU or a substituted guanidine, produced lower levels of enantioselectivity (ee ~ 57%).

Replacing methylacrylate with *N*-methyl maleimide **27**, under otherwise the same conditions, afforded the cycloadducts in good yields but with a poor ee (Scheme 8). The absolute stereochemistry of the product **28** was not established but was assumed to be the outcome, as in the previous cases, of the cycloaddition involving *E*,*E*-ylide via an *endo* transition state.

A proposed transition state for the above cycloaddition reactions mediated by Ag^I is shown in Figure 3 (the pyrrolidine rings of the ligand are omitted for clarity). d^{10}, Ag^I ion is assumed to adopt a square planar geometry

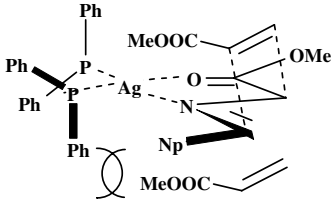
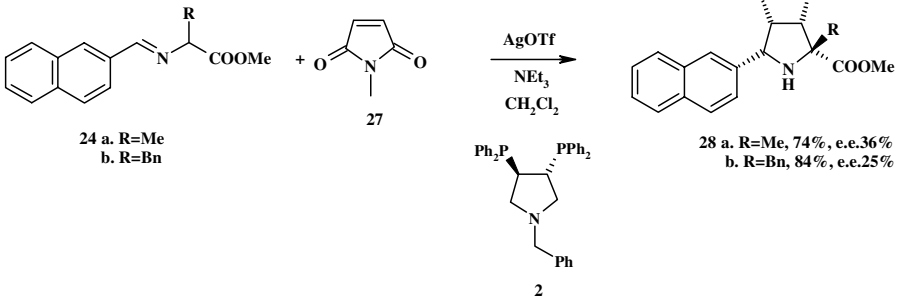


Figure 3.



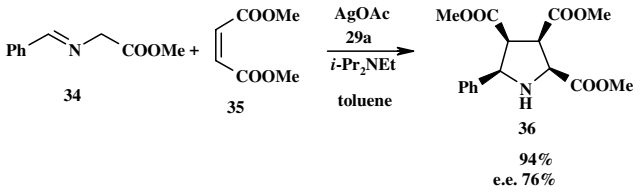
Scheme 8.

with the ligand and the imine occupying the coordination sphere of the metal. The dipolarophile orientation to the metallo-azomethine ylide is controlled by the regiochemistry of the cycloaddition step while the chiral ligand controls the facial selectivity. Access to the *Re* face of the ylide via an *endo* transition state is less favoured due to the development of steric interactions between the *pseudo*-axial phenyl group on the phosphorus and the ester group on the dipolarophile. The *Si* face of the ylide is less shielded due to *pseudo*-equatorial orientation of the phenyl group. To challenge this model further, it would be of interest to study, for example, the effect of the steric factors controlled by the dipolarophile ester moiety on the enantio- and the *exo*/*endo*-selectivity.

Further advances in the stereoselective Ag^{I} catalysed cycloaddition reactions of azomethine ylides were reported recently.[26] It was shown that a very efficient catalyst for the cycloaddition reactions of azomethine ylides is AgOAc (1 mol %) in combination with PPh_3 (2 mol %). Although AgOAc is insoluble in most organic solvents, addition of phosphine promotes the formation of a highly soluble and efficient catalyst. As a result, a number of chiral bisphosphine ligands were screened with the intention of developing an enantioselective process (Fig. 4). The most efficient amongst them was shown to be ligand **29**.

The reaction between imine **34** and methyl maleate, carried out in toluene using AgOAc (3 mol %), ligand **29a** (3.3 mol %) and Hunig's base (10 mol %) at room temperature afforded pyrrolidine **36** as a single diastereoisomer in 94% yield with 76% ee (Scheme 9). Further improvement in the enantioselectivity, to 86%, was achieved with ligand **29b**. The isomerisation maleate–fumarate, which is often observed and leads to a mixture of products under the thermal 1,2-prototropy conditions, was not promoted by the conditions used.

All other ligands were less efficient, affording the product with significantly lower ee and often as a mixture of diastereoisomers.

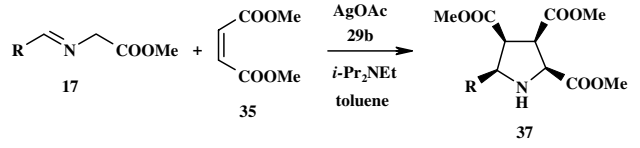


Scheme 9.

In order to investigate the scope of this transformation a range of imines were used under the above-described conditions (Scheme 10, Table 3).

As in the above discussed cases, all products were isolated as single diastereoisomers in good yields and were obtained from the *E*,*E*-dipole via an *endo* transition state. Generally, arylidene imines afforded the products with better enantioselectivity than alkylidene (Table 3, entries 12 and 13), which also required longer reaction times. The best results were obtained with 2-naphthylidene imine (Table 3, entry 10), which yielded the product in an almost quantitative yield and excellent enantioselectivity (ee 97%). Small variations in ee were observed in the case of substituted benzylidene imines although the origin of it is not clear at the moment (Table 3, entries 3–8).

The authors further studied various dipolarophiles with the results summarised in Table 4. They showed that there were significant differences between the maleate/fumarate and between *tert*-butyl acrylate/methyl acrylate. The maleate and *tert*-butyl acrylate afforded the products with significantly better ees (Table 3, entry 1,



Scheme 10.

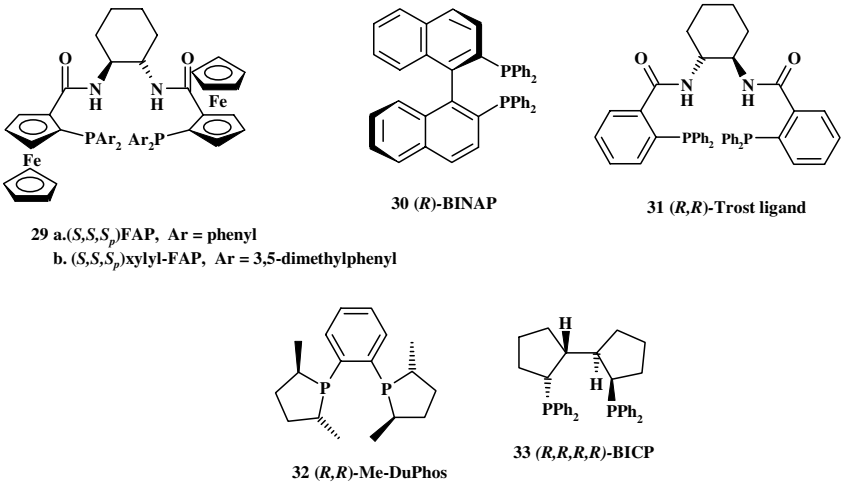
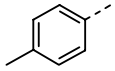
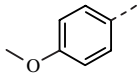
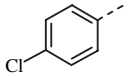
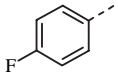
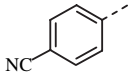
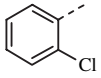
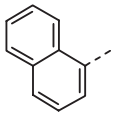
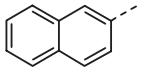


Figure 4.

Table 3. Enantioselective 1,3-dipolar cycloadditions in the presence of AgOAc and (*S*,*S*,*Sp*)-xylyl-FAP **29b**[a]

Entry	R	Time (h)	Yield, **37** (%)	ee, **37** (%)[b]
1		7	87	87
2		7	93	88
3		7	98	92
4		7	96	92
5		7	96	90
6		7	96	96
7		7	92	86
8		7	97	90
9		7	73	85
10		14	98	97
11		7	98	84
12		48	82	70
13		48	82	71

[a] AgOAc, 3 mol %; ligand **29b**, 3.3 mol % 1 mol; *i*-PrNEt$_2$ 10 mol %; reactions carried out at room temperature.
[b] Ee determined by HPLC.

87% ee vs Table 4, entry 1, 52% ee and Table 4, entry 3, 60% ee vs 4, 93% ee).

The transition state model for the reactions involving Ag^I and ligand **29b** may be related to the model proposed in Figure 3, but an additional steric factor was introduced by the ferocene moiety of ligand **29b**. As a result, the use of dipolarophiles with sterically more demanding substituents, such as *tert*-butyl acrylate, may result in a better enantiodiscrimination. This may also explain an improved enantioselectivity obtained with ligand **29b** compared to that of **29a**, which possesses bulkier P-substituents.

A study was carried out with (*S*)-QUINAP ligand **39** which is related to the above investigation.[27] The results showed that this ligand performed in a comparable manner to ligand **29b**, showing a high degree of diastereo (>20:1) and enantioselectivity (>89%) (Scheme 11, Table 5). The reactions were performed with 3 mol % catalyst loading at −45 °C and all products were isolated in excellent yields. Once again, the electronic effects controlled by the phenyl substituents of the arylidene imine did not affect the enantioselectivity significantly (Table 5, entries 2–4).

Apart from the *tert*-butyl acrylate, some other dipolarophiles were also studied (Scheme 12, Table 6). While maleate (Table 6, entry 1) and crotonate (Table 6, entry 2) esters showed excellent levels of diastereoselectivity, cinnamate (Table 6, entry 3) afforded a 2:1 mixture of the *endo* and *exo* cycloadducts. On the other hand, enantioselectivity in the reaction with maleate was considerably lower than that with the other two dipolarophiles.

Comparison of the results obtained for ligands (*S*,*S*,*Sp*)-xylyl-FAP **29b** and (*S*)-QUINAP **39** shows that **29b** is much more efficient in the cycloaddition reactions employing maleate esters (87% ee, Table 3, entry 1 and 60% ee, Table 6, entry 1) while results obtained with acrylate are comparable (93% ee, Table 4, entry 4 and 91% ee, Table 5, entry 1).

Further study of the (*S*)-QUINAP ligand was performed using substituted imine derivatives (Scheme 13, Table 7). Interestingly, the enantioselectivity (77–81% ee) was not significantly influenced by varying the α-substituent although conversion/yields were very much dependent on this moiety. In addition, it seems that the absence of this group is crucial for achieving a high level of enantioselectivity (compare Table 5, entry 1 and Table 7, entry 1).

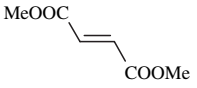
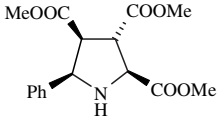
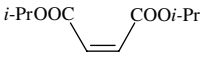
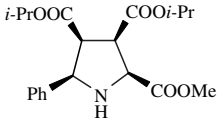
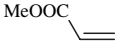
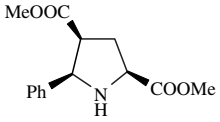
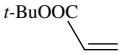
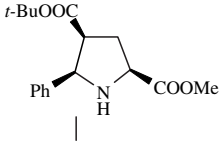
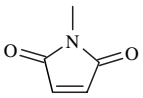
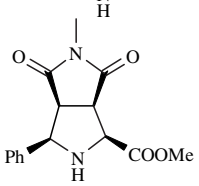
It was further demonstrated that the methodology based on the application of the Ag^I/(*S*)-QUINAP catalytic system could be efficiently performed on polystyrene macrobeads. The pyrrolidine product was isolated in 79% overall yield (over three steps), >20:1 de and 90% ee.

4.4. Cu^{II} catalysed reactions

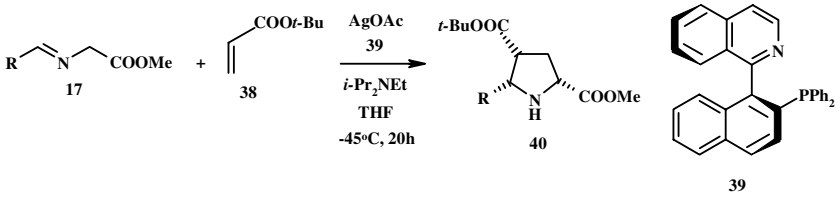
Methodologies utilising Cu-based reagents or Lewis acids are valuable synthetic tools with a wide application in the synthesis of complex molecules. It is not just the efficiency, but also the diversity of these methods that make copper one of the most important transition metals in organic synthesis. In recent years, Cu-Lewis acids in combination with some bis-phosphine ligands have been evaluated in the stereoselective cycloadditions of azomethine ylides.[28]

The studied ligands, outlined in Figure 5, have been used in conjunction with $Cu(OTf)_2$ and the reactions performed in CH_2Cl_2 at −40 °C, using Et_3N as a base (Scheme 14, Table 8). It is worth noting that the major products of the reactions were obtained from the *E*,*E*-dipol, as in all the above discussed processes, but via an

Table 4. Enantioselective 1,3-dipolar cycloadditions in the presence of AgOAc and (*S*,*S*,*Sp*)-xylyl-FAP **29b**[a] (study of dipolarophiles)

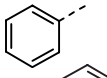
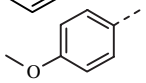
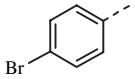
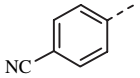
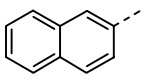
Entry	Imine	Dipolarophile	Product	Yield (%)	ee (%)[b]
1	**34**			88	52
2	**34**			85	87
3	**34**			90	60
4	**34**			85	93
5	**34**			87	79

[a] AgOAc, 3 mol %; ligand **29b**, 3.3 mol % 1 mol; *i*-PrNEt$_2$ 10 mol %; reactions carried out at room temperature.
[b] Ee determined by HPLC.



Scheme 11.

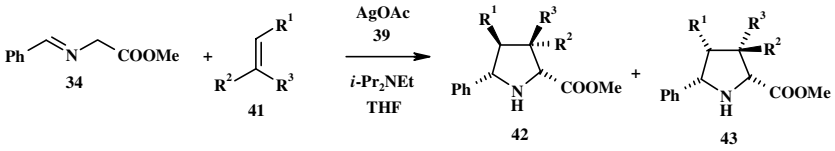
Table 5. Enantioselective 1,3-dipolar cycloadditions in the presence of AgOAc and (*S*)-QUINAP **39**[a]

Entry	R	Yield, **40** (%)	ee, **40** (%)[b]
1		84	91
2		93	95
3		89	95
4		92	96
5		89	94
6		95	89

[a] Catalyst loading 3 mol %.
[b] Ee determined by HPLC.

exo mode of the cycloaddition step. As discussed previously and suggested by the above examples, the cycloaddition reactions of metallo-azomethine ylides usually yield the product via an *endo* transition state. This *endo*/*exo* switch using different catalysts may allow further rational control of the stereochemistry of the final product, providing wider synthetic utility of the cycloaddition reactions of azomethine ylides. The best initial enantioselection for the *exo* cycloadduct was obtained with (*R*)-SEGPHOS **47** (Table 8, entry 4 vs entries 1–3). Further study was carried out only with two ligands **46a** (*R*)-BINAP and **47** (*R*)-SEGPHOS and Cu(OTf)$_2$ as Lewis acid, which were used in the reactions of various imines under the same conditions.

Preferences for the *exo* mode of the cycloaddition step were observed in all reactions with both ligands, while (*R*)-BINAP **46a** generally afforded the products with better enantioselectivity (Table 8). However, in the case of *p*-chlorobenzylidene imine (Table 8, entries 9 and 10) the reaction involving (*R*)-SEGPHOS **47** proceeded in higher yield and with better enantioselectivity.

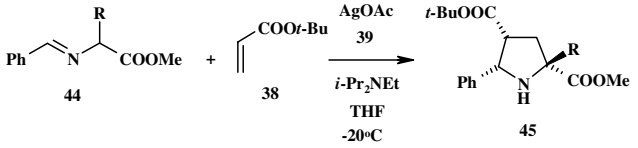


Scheme 12.

Table 6. Enantioselective 1,3-dipolar cycloadditions in the presence of AgOAc and (*S*)-QUINAP **39**[a] (study of dipolarophiles)

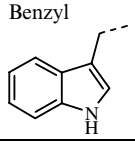
Entry	R^1	R^2	R^3	Temp (°C)	Time (h)	*endo* (**43**)/*exo* (**42**)	Yield, **43** (%)	ee, **43** (%)[c]
1[a]	COOMe	H	COOMe	−60	48	>20:1	88	60
2[b]	COO*t*-Bu	Me	H	−20	85	>20:1	97	84
3[b]	COO*t*-Bu	Ph	H	−20	85	2:1	62	81(50[d])

[a] Catalyst loading 3 mol %.
[b] Catalyst loading 10 mol%.
[c] Ee determined by HPLC.
[d] Ee of *exo* product 50%.



Scheme 13.

Table 7. Enantioselective 1,3-dipolar cycloadditions in the presence of AgOAc and (*S*)-QUINAP **39**[a] (study of substituted imines[a])

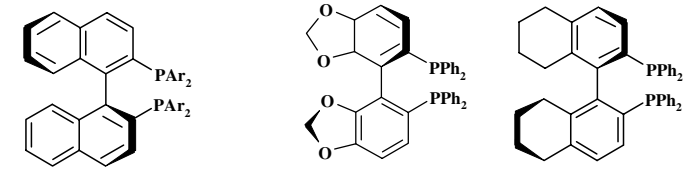
Entry	R	Time (h)	Yield, **45** (%)	ee, **45** (%)[b]
1	Me	24	98	80
2	*i*-Bu	48	77[c]	80
3	Benzyl	48	93	77
4		96	47[d]	81

[a] Catalyst loading 10 mol %.
[b] Ee determined by HPLC.
[c] Conversion 85%.
[d] Conversion 50%.

The investigation of other dipolarophiles showed similar results (Table 9). *N*-Methyl maleimide (Table 9, entries 3 and 4) showed preferences for *exo* selectivity, although this selectivity is lower compared to the *N*-phenyl derivative (Table 9, entries 1 and 2 vs entries 3 and 4). In the case of maleimides, the enantioselectivity was generally moderate, with (*R*)-SEGPHOS **47** giving slightly better selectivity. The situation is more complex with *trans* dipolarophiles such as fumarates, where there are two possible but related modes of the cycloaddition step. When diethyl fumarate was used as dipolarophile (Table 9, entries 5 and 6) cycloadducts were obtained only when (*R*)-BINAP **46a** was used as a ligand. Two diastereoisomeric products **52** and **53** were obtained in a ~1:2 ratio and 81% and 77% ee, respectively. The major product was the compound with cis orientation of the phenyl at C(5) and ester functionalities on C(4). These results contradict previous observations that the dominant interactions in the transition state of these cycloadditions employing fumarate ester are the ester–ester rather than the phenyl–ester interactions.[29]

Contrary to ethyl fumarate, fumaronitrile afforded cycloadducts **54** and **55** under the conditions employing both ligands (Table 9, entries 7 and 8). Interestingly, the ratio of two diastereoisomeric products is completely opposite and ligand dependant while the reaction using (*R*)-SEGPHOS **47** showed slightly better enantioselectivity (Table 9, entry 8).

Cu^{II}/(*R*)-SEGPHOS **47** or (*R*)-BINAP **46a** catalytic system, as discussed above, showed preferences for the *exo* mode of the cycloaddition step of metallo-azomethine

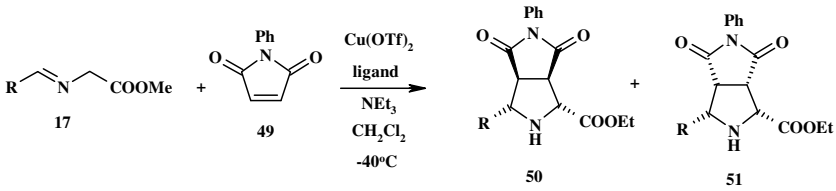


46 a. (*R*)-BINAP, Ar = Ph
b. (*R*)-*tol*-BINAP, Ar = *p*-tolyl

47 (*R*)-SEGPHOS

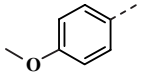
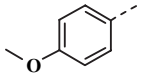
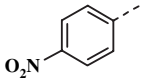
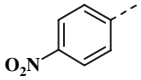
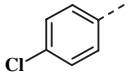
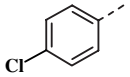
48 (*R*)-H_8-BINAP

Figure 5.



Scheme 14.

Table 8. Enantioselective 1,3-dipolar cycloadditions in the presence of $Cu(OTf)_2$ and ligands **46**–**48**[a]

Entry	R	Ligand	Time (h)	*exo*-**50**/*endo*-**51**[d]	Yield, **50** (%)	ee, **50** (%)
1		**46a**	24	>95/5	71	64[b]
2		**46b**	24	>95/5	40	47[b]
3		**48**	48	>93/7	25	60[b]
4		**47**	48	>85/15	78	72[b]
5		**46a**	48	>95/5	83	87[c]
6		**47**	48	—	0	—
7		**46a**	24	>95/5	77	62[c]
8		**47**	24	>95/5	32	19[c]
9		**46a**	48	>95/5	83	65[c]
10		**47**	48	>95/5	94	75[c]

[a] $Cu(OTf)_2$, 2 mol %; ligand, 2.2 mol %; Et_3N 4 mol %.
[b] Determined by HPLC.
[c] Determined by ^1H NMR in the presence of $Eu(hfc)_3$.
[d] Determined by ^1H NMR.

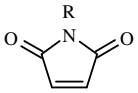
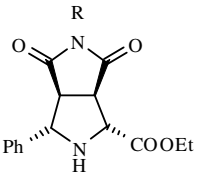
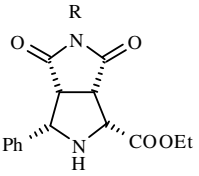
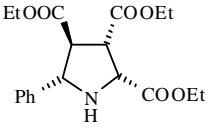
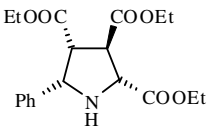
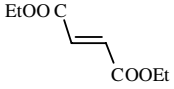
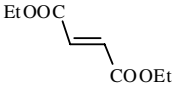
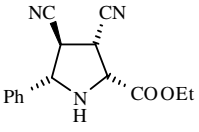
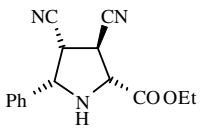
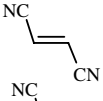
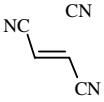
ylides. In an attempt to rationalise this observation, the transition state shown in Figure 6 was proposed. The *endo* approach of the dipolarophile to the Cu-complex incorporating both the ligand and imine was less favoured due to steric interactions caused by the *N*-phenyl substituent of the dipolarophile and the ligand moiety. Further support of this model was provided by the results obtained for *N*-methyl maleimide. This dipolarophile possesses a sterically less demanding *N*-methyl functionality and consequently showed lower *exo*/*endo* selectivity. Although a similar rationale can be used for Ag^I catalysed reactions (see Fig. 3) this *exo* switch was not observed, reflecting differences in the coordination chemistry of Cu^{II} and Ag^I. The results clearly show potential to rationally control the stereochemical outcome of these cycloadditions simply by a selection of Lewis acid, and establish further synthetic potential of the methodology.

The use of $Cu(OTf)_2$ in combination with the chiral bis-oxazoline ligands **56** was briefly investigated but did not show any enantioselectivity.[30] In addition, it was found that the conversion is significantly dependant on the ligand used.

4.5. Zn^{II} catalysed reactions

Oxazoline derivatives are versatile and widely used ligands in various metal-based stereoselective methodologies.[31] They are easily accessible from amino alcohols, of which many are commercially available or can be prepared from α-amino acids.

Table 9. Enantioselective 1,3-dipolar cycloadditions in the presence of $Cu(OTf)_2$ and ligands (*R*)-BINAP **46a** and (*R*)-SEGPHOS **47**[a] (study of dipolarophiles)

Entry	Dipolarophile	Ligand	Time (h)	Cycloadduct[d]	Yield (%)	Ee *exo* (%)
			 *exo*-**50**	 *endo*-**51**		
1	R = Ph	**46a**	24	95 : 5	71	64 (*exo*)[b]
2	R = Ph	**47**	48	89 : 11	78	72 (*exo*)[b]
3	R = Me	**46a**	24	72 : 28	64	55 (*exo*)[b]
4	R = Me	**47**	24	86 : 14	64	62 (*exo*)[b]
			 **52**	 **53**		
5		**46a**	48	36 : 64	80	81(52), 77(53)[b]
6		**47**	60	-	0	-
			 **54**	 **55**		
7		**46a**	24	14 : 86	57	75(54), 82(55)[c]
8		**47**	24	63 : 37	54	92(54), 83(55)[c]

[a] $Cu(OTf)_2$, 2 mol %; ligand, 2.2 mol %; Et_3N 4 mol %.
[b] Determined by HPLC.
[c] Determined by ^1H NMR in the presence of $Eu(hfc)_3$.
[d] Determined by ^1H NMR.

The oxazoline ligands have been used in stereoselective cycloadditions of the metallo-azomethine ylides in conjunction with Zn^{II} Lewis acids.[30] Of the investigated ligands (Fig. 7) the most efficient was shown to be **56a**.

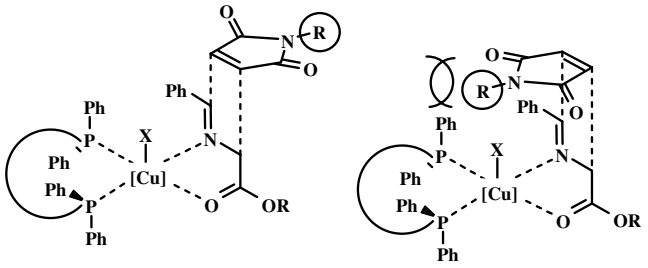
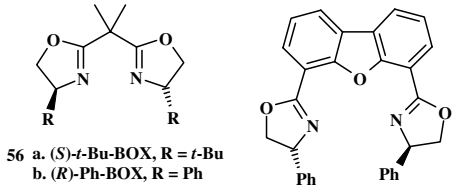


Figure 6.



56 a. (*S*)-*t*-Bu-BOX, R = *t*-Bu
b. (*R*)-Ph-BOX, R = Ph

57 (*R*,*R*)-Ph-DBFOX

Figure 7.

Reaction of imine **34** and methyl acrylate **14** in the presence of $Zn(OTf)_2$, ligand **56a** and Et_3N (10 mol % each) afforded cycloadduct **60a** with 78% ee (Scheme 15, Table 10).

The reaction conditions were studied in more detail and it was found that the use of a less polar solvent, such as Et_2O or toluene, resulted in a lower ee, ~25%, while in CH_2Cl_2 or MeCN the ee (~65%) was comparable to that observed in THF. Performing the reaction at −20 °C further improved the enantioselectivity (Table 10, entry 2 vs entry 1) while varying the amount of Et_3N did not have any influence.

The potential of the Zn^{II}/bis-oxazoline ligand was explored in the reactions of various glycine derived imines and several dipolarophiles. Under the above conditions, in most cases, the cycloadducts were isolated in excellent yields and with ees ranging from 61% to 94%. Interestingly, it was found that the yield and enantioselectivity were strongly dependant on the acrylate ester. Methyl acrylate **14** in the reaction with naphthylidene imine **13** afforded the product in 93% yield with 78% ee (Table 10, entry 3 or entry 4, 91% ee at −20 °C). On the other hand, when ethyl acrylate was used for the same reaction, the yield dropped to 76% and the ee to 68% (Table 10, entry 6), while *tert*-butyl acrylate proved completely inefficient, yielding the product in only 12% yield with <5% ee (Table 10, entry 7). These results are completely opposite to the related Ag^{I} catalysed cycloadditions in the presence of (*S*,*S*,*Sp*)-xylyl-FAP **29b** or (*S*)-QUINAP **39** ligands. Dimethyl fumarate reacted highly diastereo- and enantioselectively and again when the reaction was carried out at −20 °C, it afforded the product with improved ee (Table 10, entries 10–12).

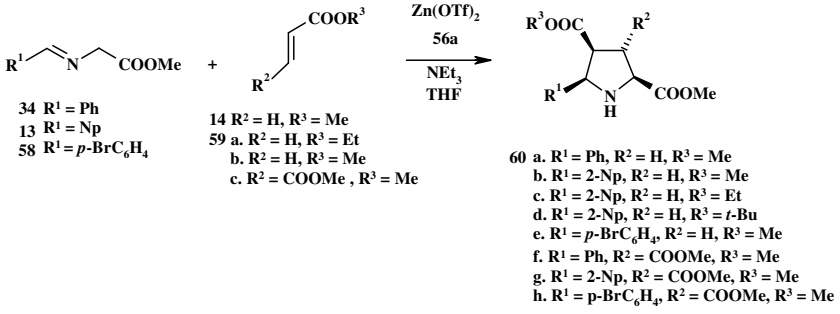
Table 10. Enantioselective 1,3-dipolar cycloadditions in the presence of $Zn(OTf)_2$ and (*S*)-*t*-Bu-BOX **56a**[a]

Entry	Imine	Dipolarophile	Product/yield (%)	ee (%)[b]
1	34	14	60a(>95)[c]	78
2[d]	34	14	60a(80)	88
3	13	14	60b(93)	78
4[d]	13	14	60b(84)	91
5[d,e]	13	14	60b(86)	87
6	13	59a	60c(76)	68
7	13	59b	60d(12)	<5
8	58	14	60e(89)	61
9[d]	58	14	60e(89)	94
10[d]	34	59c	60f(78)	76
11[d]	13	59c	60g(84)	90
12	58	59c	60h(87)	68

[a] $Zn(OTf)_2$, 10 mol %, (*S*)-*t*-Bu-BOX **56a**, 10 mol %, Et_3N, 10 mol %.
[b] Determined by HPLC.
[c] Conversion.
[d] Reaction temperature −20 °C.
[e] No solvent.

The absolute stereochemistry of the product was established by X-ray analysis and based on it a transition state was proposed. To account for the observed stereochemistry, Zn^{II} was suggested to form the trigonal bipyramid intermediate, which involves coordination of the dipolarophile as well (Fig. 8). The dipolarophile coordination was proposed based on the fact that acrylonitrile did not undergo the cycloaddition reaction, whereas acrylate esters did.

In the proposed transition state, the *Re* face of the coordinated dipolarophile approaches the *Re* face (*lk* approach) of the metallo-ylide to afford the product. The proposed transition state may provide an explanation for the lower reactivity of the *tert*-butyl acrylate. In this case, the coordination of the dipolarophile is likely to be more difficult due to a steric clash between the *tert*-butyl



34 R^1 = Ph
13 R^1 = Np
58 R^1 = *p*-BrC_6H_4

14 R^2 = H, R^3 = Me
59 a. R^2 = H, R^3 = Et
b. R^2 = H, R^3 = Me
c. R^2 = COOMe , R^3 = Me

60 a. R^1 = Ph, R^2 = H, R^3 = Me
b. R^1 = 2-Np, R^2 = H, R^3 = Me
c. R^1 = 2-Np, R^2 = H, R^3 = Et
d. R^1 = 2-Np, R^2 = H, R^3 = *t*-Bu
e. R^1 = *p*-BrC_6H_4, R^2 = H, R^3 = Me
f. R^1 = Ph, R^2 = COOMe, R^3 = Me
g. R^1 = 2-Np, R^2 = COOMe, R^3 = Me
h. R^1 = p-BrC_6H_4, R^2 = COOMe, R^3 = Me

Scheme 15.

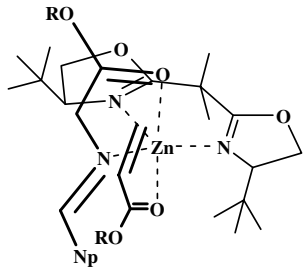


Figure 8.

ester group and the *tert*-butyl group of the coordinated ligand. Since, as it was demonstrated in this study, the dipolarophile coordination is essential to obtain a good yield of the cycloadduct, non-coordinated *tert*-butyl acrylate does not afford the product in a synthetically acceptable yield.

4.6. Summary and outlook[32]

Intensive research over the last few decades in the area of the cycloaddition reactions of metallo-azomethine ylides has resulted, in recent years, in the development of a number of highly diastereo- and enantioselective processes. From the atom economic point of view, of particular interest are those employing catalytic quantities of chiral Lewis acid complexes. Indeed, several of these have been developed allowing the synthesis of pyrrolidine derivatives in good yields with a high level of stereoselectivity. The scope of these methodologies have been investigated regarding both the 1,3-dipole (imine) and the dipolarophile (alkene). The results suggested quite good tolerance towards different structural properties of both the components. Currently, for the stereoselective synthesis of substituted pyrrolidine derivatives via 1,3-dipolar cycloaddition reactions, the Ag^{I} based processes stand out as more efficient, but other Lewis acids certainly provide an additional synthetic value. The Ag^{I}-methodologies are highly *endo*- and stereoselective, affording the products in excellent yields. An additional interesting feature of these processes is the potential to control the *endo*/*exo* selectivity of the cycloaddition step by the choice of the catalytic system. As discussed above and contrary to other related methods, Cu^{II}-based catalysts allow access to the pyrrolidine cycloadducts derived via an *exo* transition state.

Although significant progress has been made in this area, further work is necessary to explore the full potential of the stereoselective synthesis of pyrrolidine derivatives via metallo-azomethine ylide chemistry. Investigation of other Lewis acids known to promote the ylide formation and the subsequent cycloaddition reactions may be of great importance, particularly those identified to reverse the regioselectivtity of the cycloaddition step. Lewis acids/ligand complexes are also likely to provide an opportunity to influence the stereochemistry of the ylide in a rational manner, which, in turn would allow access to various pyrrolidine stereoisomers.

Based on the current results, it is likely that the stereoselective synthesis using metallo-azomethine ylides will attract more attention in the near future and provide further excitement in the synthesis of the pyrrolidine derivatives.

References

1. For some recent examples see: Qing Yuan, Z.; Ishikawa, H.; Boger, D. L. *Org. Lett.* **2005**, *7*, 741–744; Denmark, S. E.; Gomez, L. *J. Org. Chem.* **2003**, *68*, 8015–8024; Grigg, R.; Millington, E.; Thornton-Pett, M. *Tetrahedron Lett.* **2002**, *43*, 2605–2608.
2. Gribble, G. W. In *Comprehensive Heterocyclic Chemistry I*; Katrityky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 2, pp 207–257; Lown, J. W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons, 1984; Vol. 1, pp 653–732.
3. Grigg, R.; Malone, J. F.; Mongkolaussavaratana, T.; Thianpatanagul, S. *Tetrahedron* **1989**, *45*, 3849–3862; Fleury, J. P.; Schoeni, J. P.; Clerin, D.; Fritz, H. *Helv. Chim. Acta* **1975**, *58*, 2018–2026; Seidl, H.; Huisgen, R.; Knorr, R. *Chem. Ber.* **1969**, *102*, 904–914.
4. Krohnke, F. *Angew. Chem.* **1953**, *65*, 605–626.
5. Huisgen, R.; Scheer, W.; Huber, H. *Tetrahedron Lett.* **1966**, *7*, 397–404; Huisgen, R.; Scheer, W.; Huber, H. *J. Am. Chem. Soc.* **1967**, *89*, 1753–1755; Garner, P.; Dogan, O. *J. Org. Chem.* **1994**, *59*, 4–6; DeShong, P.; Kell, D. A. *Tetrahedron Lett.* **1986**, *27*, 3979–3982.
6. Vedejs, E.; West, F. G. *Chem. Rev.* **1986**, *86*, 941–955; Padwa, A.; Fryxell, G. E.; Gasdaska, J. R.; Venkatramanan, M. K.; Wong, G. S. K. *J. Org. Chem.* **1989**, *54*, 644–653; Wee, A. G. H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1363–1364; Komatsu, M.; Okada, H.; Yokoi, S.; Minakata, S. *Tetrahedron Lett.* **2003**, *44*, 1603–1606.
7. Grigg, R.; Kemp, J. *J. Chem. Soc., Chem. Commun.* **1978**, 109–111; Grigg, R.; Donegan, G.; Gunaratne, H. Q. N. *Tetrahedron* **1989**, *45*, 1723–1746; Grigg, R.; Sridharan, V. In *Advances in Cycloaddition*; JAI Press: Greenwich, 1993; Vol. 3, pp 161–204; Tsuge, O.; Kanemasa, S.; Yoshioka, M. *J. Org. Chem.* **1988**, *53*, 1384–1391.
8. Dondas, A. H.; Fishwick, C. W. G.; Grigg, R.; Kilner, C. *Tetrahedron* **2004**, *60*, 3473–3485; Grigg, R.; Savic, V.; Thornton-Pett, M. *Tetrahedron* **1997**, *53*, 10633–10642; Brown, G. A.; Martel, S. R.; Wisedale, R.; Charmant, J. P. H.; Hales, N. J.; Fishwick, C. W. G.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1281–1289; Joucla, M.; Mortier, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1566–1567; Tsuge, O.; Kanemasa, S.; Ohe, M.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4079–4089; Smith, R.; Livinghouse, T. *Tetrahedron* **1985**, *41*, 3559–3568.
9. Huisgen, R.; Grashey, R. *Tetrahedron Lett.* **1963**, *4*, 1441–1445; Kraus, G. A.; Nagy, J. O. *Tetrahedron Lett.* **1983**, *24*, 3427–3430.
10. Chapman, O. L.; Eian, G. L. *J. Am. Chem. Soc.* **1968**, *90*, 5329–5330; Padwa, A.; Austin, D. J.; Precedo, L.; Zhi, L. *J. Org. Chem.* **1993**, *58*, 1144–1150; Pearson, W. H.; Stoy, P.; Mi, Y. *J. Org. Chem.* **2004**, *69*, 1919–1939; Pearson, W. H.; Clark, R. B. *Tetrahedron Lett.* **1999**, *40*, 4467–4471; Reinhoudt, D. N.; Viser, G. V.; Verboom, W.; Benders, P. H.; Pennings, M. L. M. *J. Am. Chem. Soc.* **1983**, *105*, 4775–4781; Vedejs, E.; Piotrowski, D. W. *J. Org. Chem.* **1993**, *58*, 1341–1348; Negron, G.; Roussi, G.; Zhang, J. *Heterocycles* **1992**, *34*, 293–301.
11. Harwood, L. M.; Vickers, R. J. In *The Chemistry of Heterocyclic Compounds: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley & Sons: New York, 2002, pp 169–252.

12. Grigg, R.; Kemp, J. *J. Chem. Soc., Chem. Commun.* **1978**, 109–111; Grigg, R. *Chem. Soc. Rev.* **1987**, *16*, 89–121; Tsuge, O.; Ueno, K.; Oe, K. *Chem. Lett.* **1979**, 1407–1410; Tsuge, O.; Ueno, K. *Heterocycles* **1982**, *19*, 1411–1414; Joucla, M.; Hamelin, J. *Tetrahedron Lett.* **1978**, *19*, 2885–2888.
13. Grigg, R.; Donegan, G.; Gunaratne, H. Q. N.; Kenedy, D. A.; Malone, J. F.; Sridharan, V.; Thianpatanagul, S. *Tetrahedron* **1989**, *45*, 1723–1746.
14. Van Es, J. J. G. S.; Jarrsveld, K.; van der Gen, A. J. *J. Org. Chem.* **1990**, *55*, 4063–4069; Van Es, J. J. G. S.; Wolde, A.; van der Gen, A. J. *J. Org. Chem.* **1990**, *55*, 4069–4079; Grigg, R.; Jordan, M. W.; Malone, J. F.; Armstrong, P. *Tetrahedron* **1985**, *41*, 3547–3558; Grigg, R.; Kemp, J. *Tetrahedron Lett.* **1980**, *21*, 2461–2464; Tsuge, O.; Ueno, K.; Kanemasa, S.; Yorozu, K. *Bull. Chem. Soc. Jpn.* **1986**, 1809–1824.
15. Barr, D.; Grigg, R.; Gunaratne, H. Q. N.; Kemp, J.; McMeekin, P.; Sridharan, V. *Tetrahedron* **1988**, *44*, 557–570; Tsuge, O.; Kanemasa, S.; Yoshioka, M. *J. Org. Chem.* **1988**, *53*, 1384–1391.
16. (a) Casella, L.; Gulloti, M.; Pasini, A.; Pasaro, R. *Synthesis* **1979**, 150–151; (b) Casella, L.; Gulloti, M.; Melani, E. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1827–1831; (c) Grigg, R.; Sridharan, V.; Thianpatanagul, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1669–1675.
17. (a) Grigg, R.; Kemp, J.; Malone, J.; Tangthongkum, A. *J. Chem. Soc., Chem. Commun.* **1980**, 648–650; (b) Kanemasa, S.; Hayashi, T.; Tanaka, J.; Yamamoto, H.; Sakurai, T. *J. Org. Chem.* **1991**, *56*, 4473–4481; (c) Kanemasa, S.; Uchida, O.; Wada, E. *J. Org. Chem.* **1990**, *55*, 4411–4417; (d) Kanemasa, S.; Yamamoto, H. *Tetrahedron Lett.* **1990**, 3633; Kanemasa, S.; Tsuge, O. In *Advances in Cycloaddition*; Curran, D., Ed.; JAI Press: Greenwich, 1993; Vol. 3, pp 99–159.
18. Grigg, R.; Gunaratne, H. Q. N. *J. Chem. Soc., Chem. Commun.* **1982**, 384–386; Grigg, R.; Gunaratne, H. Q. N.; Sridharan, V. *Tetrahedron* **1987**, *43*, 5887–5898.
19. Kanemasa, S. *Synlett* **2002**, 1371–1387, and references cited therein; Grigg, R.; Sridharan, V. In *Advances in Cycloaddition*; JAI Press: Greenwich, 1993; Vol. 3, pp 161–204, and references cited therein.
20. (a) Barr, D. A.; Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1989**, *30*, 4727–4730; (b) Grigg, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2475–2486; (c) Kanemasa, S.; Uchida, O.; Wada, E.; Yamamoto, H. *Chem. Lett.* **1990**, 105–108.
21. Grigg, R.; Montgomery, J.; Somasunderam, A. *Tetrahedron* **1992**, *48*, 10431–10442.
22. for some examples see: Ahrendt, K. A.; Williams, R. M. *Org. Lett.* **2004**, *69*, 8537–8540; Gu, Y. G.; Zhang, X.; Clark, R. F.; Djuric, S. W.; Ma, Z. *Tetrahedron Lett.* **2004**, *45*, 3051–3053; Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135–3137; Ruano, J. L. G.; Tito, A.; Peromingo, T. M. *J. Org. Chem.* **2003**, *68*, 10013–10019; Karlsson, S.; Hoegberg, H. E. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1076–1082; Patzel, M.; Galley, G.; Jones, P. G.; Chrapkovsky, A. *Tetrahedron Lett.* **1993**, *34*, 5707–5710; Waldman, H.; Blaser, E.; Jansen, M.; Letschert, H. P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 150–154; Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Pilati, T. *Tetrahedron: Asymmetry* **1991**, *2*, 1329–1342; Keller, E.; deLange, B.; Rispens, M. T.; Feringa, B. L. *Tetrahedron* **1993**, *49*, 8899–8910; Kim, B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293–318.
23. Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 5817–5820.
24. Lancashire, R. J. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon Press: Oxford, 1987; Vol. 5, pp 775–851.
25. Savic, V. Ph.D. Thesis, University of Leeds (UK), 1994; For the synthesis of the ligand see: Nagel, U.; Kinzel, E. *Chem. Ber.* **1986**, *119*, 3326–3343.
26. Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400–13401.
27. Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174–10175.
28. Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, *4*, 1441–1445.
29. Grigg, R.; Kemp, J.; Warnock, W. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2275–2284.
30. Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236–4238.
31. For some recent examples see: Langner, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 5984–5987; Lu, S. H.; Du, D. M.; Zhang, S. W.; Xu, J. *Tetrahedron: Asymmetry* **2004**, *15*, 3433–3441; Le, J. C. D.; Pagenkopf, B. L. *Org. Lett.* **2004**, *6*, 4097–4099; Trifonova, A.; Diesen, J. S.; Chapman, C. J.; Andersson, P. G. *Org. Lett.* **2004**, *6*, 3825–3827.
32. A single example of an enantioselective cycloaddition of the metallo-azomethine ylide using Mg^{II}-bis-imine complex was reported recently (ee 7%): Kbowman, R.; Johnson, J. S. *J. Org. Chem.* **2004**, *69*, 8537–8540.