Construction of Enantiopure Pyrrolidine Ring System via Asymmetric [3+2]-Cycloaddition of Azomethine Ylides

Ganesh Pandey,* Prabal Banerjee, and Smita R. Gadre

Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411 008, India

Received September 26, 2005

Contents

1. Introduction

1,3-Dipolar cycloaddition reactions are fundamental processes in organic chemistry,[1] and their asymmetric version offers a powerful and reliable synthetic methodology to access five-membered heterocyclic rings in regio- and stereocontrolled fashion.[2−5] In particular, the reaction of azomethine ylides (AMY) with alkenes is a powerful method for the syntheses of substituted and stereoisomerically pure pyrrolidines:[6−10] an important building block in the syntheses of many natural products and pharmaceuticals.[11−20] Although some highlights on the asymmetric cycloadditions of azomethine ylides can be found in a few recent general reviews,[3,5,10] a comprehensive account in this field is lacking despite the substantial development of the field. In this review, we wish to present an exhaustive survey of the published literature, spanning over the past two decades (1985−2005), for accomplishing asymmetric 1,3-dipolar cycloaddition reactions of the azomethine ylides. However, before describing the details of the asymmetric cycloadditions of the azomethine ylides, it is pertinent to append a short and concise description on the structure, mechanism, reactivity, and methods of their generation to put this review in proper perspective, though some aspects of AMY are briefly summarized in a recent review.[21]

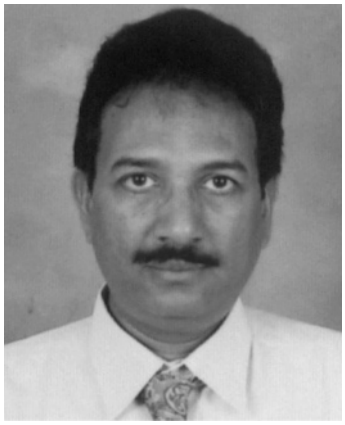
Azomethine ylides can be represented as a zwitterionic form of a C−N−C unit having four electrons in three parallel atomic π orbitals perpendicular to the plane of the dipole, providing a bent-type structure to this allyl anion-type 1,3-dipole.[22] The characteristic stereochemical aspects of AMY cycloadditions are partly accounted for due to this property. Four resonance forms can be drawn for this dipole as shown in Chart 1. In the most common resonance representation, these dipoles have octet structure in which the central N atom is positively charged and the negative charge is distributed over the two terminal carbon atoms. The nature and number of substituents at these carbons determines the degree of negative charge on each carbon atom. In an alternative representation, two of the four allylic π electrons are localized at the central N atom, thereby, canceling the positive charge on it and creating electron sextets at the two terminal carbons.[23]

1,3-Dipolar cycloaddition of AMY with a π system involves a total of six π electrons [π^4s + π^2s] and proceeds through a thermally allowed suprafacial process according to Woodward−Hoffmann rules.[24−26] Although, in general, such cycloadditions are considered to be concerted with both carbon−carbon σ bonds being formed at the same time,[27] involvement of a singlet diradical or zwitterionic intermediates has also been debated.[28] However, strong evidence exists in favor of a concerted mechanism due to the stereospecificity of the cycloadditions in which the relative stereochemistry of the alkene dipolarophile is retained in the pyrrolidine product.

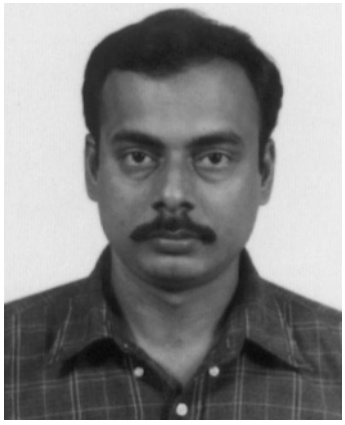
CNDO/2 π calculations of energies of the various orbitals involved have revealed that AMY are all electron-rich species characterized by relatively high-energy HOMOs and LUMOs, preferentially reacting with electron-deficient alkenes due to a narrow $HOMO_{dipole}$−$LUMO_{dipolarophile}$ gap;[29] however, this may not necessarily be obvious, particularly in the intramolecular cycloadditions as reaction can take place even with an unactivated alkene too. Sustman,[30] Houk,[29,31−32] and Bastide[33−35] explained the reactivity and regiochemistry of 1,3-dipolar cycloaddition reactions based on relative FMO energies between the dipole and dipolarophile and classified AMY cycloadditions to a Type I class in which the dominant FMO interaction is of the $HOMO_{dipole}$ with $LUMO_{alkene}$ (HOMO controlled, represented by the solid line) as outlined

* To whom correspondence should be addressed. Phone: +91-20-25902324. Fax: +91-20-25902624. E-mail: gp.pandey@ncl.res.in.

10.1021/cr050011g CCC: $59.00
Published on Web 10/25/2006



Ganesh Pandey (born July 5, 1954) obtained his Ph.D. degree from Banaras Hindu University (under the direction of Professor K. N. Mehrotra) in 1980. Immediately afterward he proceeded to Purdue University for postdoctoral study (from July 1980 to May 1983) in the group of Professor H. A. Morrison. On returning, he first joined (September 1983) Panjab University, Chandigarh, as a "Pool Officer" and within a few months moved to IICT, Hyderabad (May 1984). After establishing his research group at IICT, he once again moved to National Chemical Laboratory, Pune (July 1991), where he is pursuing research in the area of developing new synthetic strategies involving radical ions as reactive species and natural products syntheses.



Prabal Banerjee was born in Burdwan (India) in 1975. He obtained his M.Sc. degree in Organic Chemistry from the University of Burdwan (India) in 1998. He then joined the group of Dr. G. Pandey at National Chemical Laboratory (NCL), Pune (India), to carry out graduate work on the synthesis of Monatanine-type *Amarryllidaceae* alkaloids using intramolecular [3+2]-cycloaddition of azomethine ylide as a key step and obtained his Ph.D. degree in 2005. He now holds a postdoctoral position with Professor H.-J. Gais at the Institut für Organische Chemie, RWTH Aachen, in Germany. His research interests include asymmetric synthesis and synthesis of natural products.

in Chart 2. HOMO-controlled reactions are accelerated by electron-releasing substituents in the dipole and electron-withdrawing groups in the dipolarophiles.[30]

The regioselectivity in the cycloadditions of AMY can be predicted on the basis of the unequal magnitude of the terminal coefficients of the HOMO and the LUMO π orbitals of the dipoles and the direction of the reaction in which maximal FMO overlapping is allowed between the orbitals closest in energy.[36,37] The regioisomeric transition state **A** is more stable than **B** because of its more efficient overlap, Chart 3 , as dictated by the terminal coefficients. The favored regioisomer will be the one formed through the transition state in which atoms with larger coefficients overlap,[36] though there would be very small energy differences (0.1−5 kcal mol^{-1}) between the two transition states. In general, there is overall acceleration of the rate of formation of both the

Smita R. Gadre was born in Pune and studied Organic Chemistry at the University of Pune. She completed her Ph.D. degree in 1994 from NCL under the supervision of Dr. S. Rajappa; since then she has been working in the group of Dr. G. Pandey, and her research interest is in the area of the development of new synthetic methodology.

Chart 1

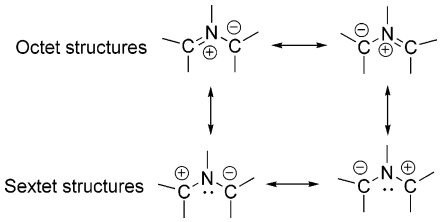


Chart 2

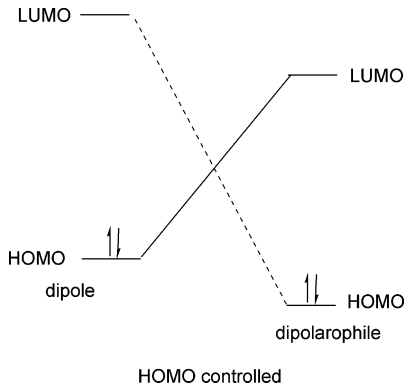
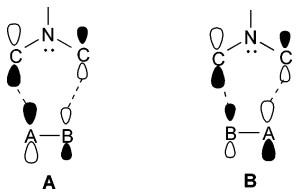


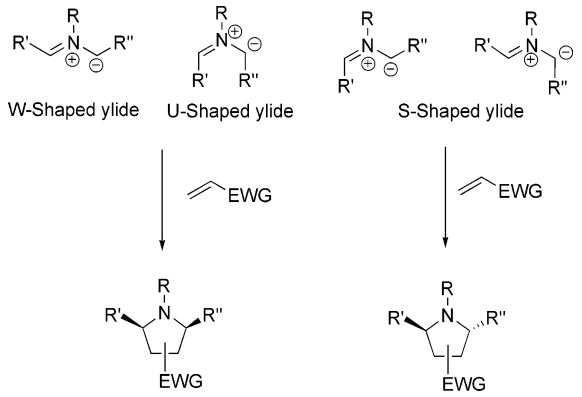
Chart 3



regioisomers in the cycloaddition of the azomethine ylides due to excess negative charge on their terminal atom making double-bonded carbons of the dipolarophile either less negative or more positive. However, in the case of intramolecular cycloadditions, conformational constraints normally dictate that only one particular regioisomer can be formed.

The stereochemical outcome of the cycloaddition of AMY is dependent on the geometries of the dipoles as well as the dipolarophiles. For example, the 2,5-stereochemistry of the resultant pyrrolidine ring emerges from the geometry of the ylide, while 3,4-stereochemistry results from the geometry of the alkene dipolarophile. The 2,5-*cis*-disubstituted pyr-

Chart 4



rolidine results by the involvement of W- and U-shaped dipole, while 2,5-*trans*-disubstituted product emerges from the two possible S-shaped ylides (Chart 4). Mixture of stereoisomers can also result by the isomerization of the ylide. Similarly, 3,4-*cis*-disubstituted pyrrolidine product is derived from the *cis*-disubstituted alkenyl dipolarophiles, and the 3,4-*trans*-disubstituted pyrrolidine products arise from the *trans*-disubstituted alkenyl dipolarophiles due to the concertedness of the cycloaddition reaction. Furthermore, the cycloadditions are normally stereoselective where the substituent(s) on the dipolarophile adopt generally an *endo* orientation analogous to isoelectronic Diels−Alder reaction.

Azomethine ylides can be classified as (a) nonstabilized, (b) stabilized nonmetalated, and (c) stabilized N-metalated depending upon their electronic properties. The important methods of their in situ generation can be summarized schematically as follows: (a) Nonstabilized azomethine ylides (Chart 5), (b) Stabilized nonmetalated azomethine ylides (Chart 6), and (c) Stabilized N-metalated azomethine ylides (Chart 7). Examination of the examples discussed in this review show that most of the methodologies for generating AMY discussed above have been utilized for the asymmetric cycloadditions.

In the last two decades, extensive studies have been performed in the area of asymmetric [3+2]-cycloaddition of azomethine ylides employing all three possible combinations such as (a) chiral dipoles-achiral dipolarophiles, (b) achiral dipole-chiral dipolarophiles, and (c) chiral catalysis. Varying degrees of asymmetric inductions have been recorded from all these combinations, though no definite pattern could be seen emerging. Therefore, the aim of the present review is to compile and categorize the widely scattered results in the area of asymmetric [3+2]-cycloadditions of AMY reported in the literature, so that practicing organic/medicinal chemists may plan to choose a strategy to synthesize highly substituted chiral pyrrolidine moieties of their choice. This review is also intended to inspire further developments in this area.

2. Asymmetric 1,3-Dipolar Cycloaddition Using Nonstabilized AMY

2.1. Chiral Nonstabilized AMY and Achiral Dipolarophiles

Padwa's[51] group was the first to initiate a study designed to examine the extent to which an asymmetric center adjacent to the nitrogen atom of the azomethine ylide controlled diastereoselectivity in the cycloaddition reaction with an achiral dipolarophile. In this context, this group at first studied the cycloaddition of a chiral acyclic nonstabilized AMY **2**, generated by the Ag(I)F-mediated reaction of optically active amine precursor **1a**, using benzaldehyde as a dipolarophile, which gave 1:1 diastereomeric mixtures of corresponding oxazolidines **3**. However, cycloaddition of **2a** to different 1-nitrostyrenes **4** gave **5a** in a maximum of 3:2 diastereomeric ratios (Scheme 1). This group also evaluated the impact on the diastereoselectivity of cycloadducts **5b,c** by increasing the size and changing the electronic character of one of the groups attached to the chiral center of the ylide precursor (e.g., **1b−c)** and noted moderate improvements in it (dr 4:1). This result was explained through a preferred conformer **B** of two possible Felkin−Anh models of the ylide **2** involving *anti*-attack of the alkene on to the opposite face of the dipole due to unfavorable nonbonded interactions in the transition state, Figure 1.

After a gap of several years, cycloaddition of the chiral nonstabilized azomethineylides **7**, derived by treatment of the corresponding chiral amine *N*-oxides (**6a−d**) with LDA at 0 or −78 °C, was studied[52] using several alkenes of the type **8** as the dipolarophile and found to give the corresponding pyrrolidines (**9a**, **9b**, Scheme 2) as a diastereomeric mixture with poor facial selectivities (dr = 57:43 to 80:20). Ylide dimeric product **10** was also isolated in these reactions in a significant amount. The low selectivities observed in these cycloadditions were interpreted by considering the balance of the diastereofacial control with the steric factor due to free rotation of the nitrogen−carbon asymmetric bond.

Almost at the same time Cottrell et al.[53] also showed that 1,3-dipolar cycloaddition of the chiral nonstabilized AMY **2a**, derived from **11**, undergoes cycloaddition to the cyclic dipolarophile **12** resulting a 1:1 mixture of diastereomers **13** and **14** (Scheme 3) without any facial selectivity. Cycloaddition of ylides **2d** and **2e**, having sterically bulky (*S*)-1-naphthyl moiety as an auxiliary, also did not show any appreciable increase in the diastereoselectivity.

In an interesting study aimed at preparing an enantiomerically pure C_2-symmetric fullerene dimer as the new material, ylides **15a−f** having ferrocenyl chiral auxiliary on the carbon atom of the dipole itself was reported[54] to undergo smooth cycloaddition to C_{60} producing the corresponding cycloadducts **16a−f** in >95% de in almost all cases studied (Scheme 4).

2.2. Achiral Nonstabilized AMY and Chiral Dipolarophiles

While asymmetric induction in the 1,3-dipolar cycloaddition of the chiral azomethine ylides with the achiral dipolarophiles was being explored, the study also flourished simultaneously using achiral dipole and chiral dipolarophiles probably due to the invention of several good chiral auxiliaries. In this context, the beginning was made by Wee et al.[55] in 1989 by describing cycloaddition of an achiral nonstabilized AMY **18a** (R = Bn) to a number of enantiopure dipolarophiles **19a−d** (Scheme 5). The reaction with **19a,b** proceeded with high facial selectivity, producing only one diastereomeric cycloadduct (**20a,b)** in each case. Cycloaddition with **19a** was presumed to occur from the side opposite the bulky silyloxymethyl substituents, while in the case of **19b**, it proceeded from the side opposite the anomeric ethoxy group. Interestingly, cycloaddition with α,β-unsaturated esters **19c** and **19d** proceeded with moderate (**20c**, 8.5:1.5) to poor (**20d**, 2:1) π-facial selectivity. The poor diastereo-

Chart 5

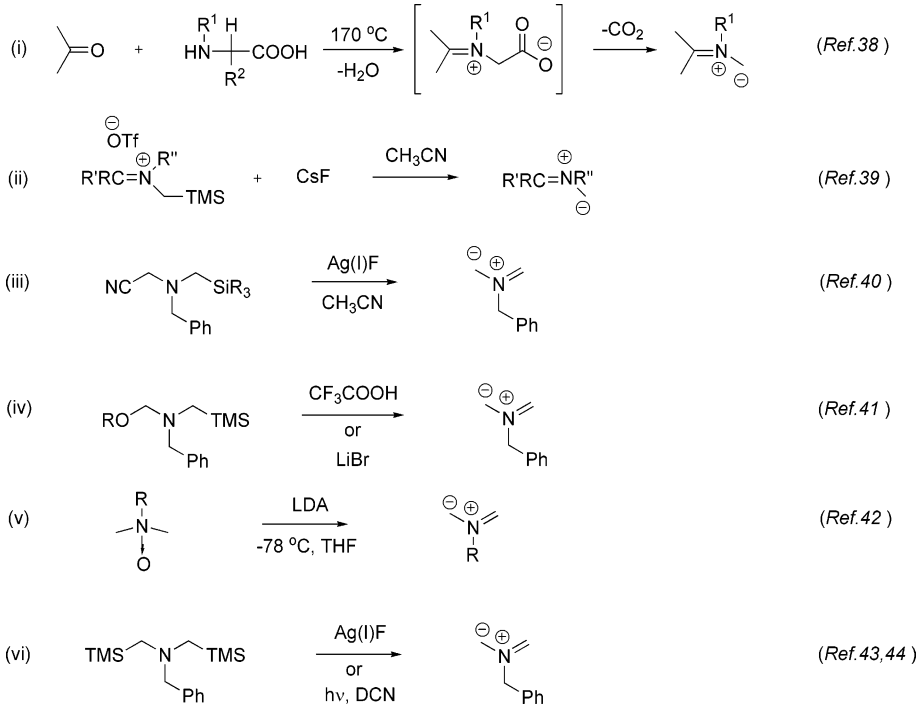


Chart 6

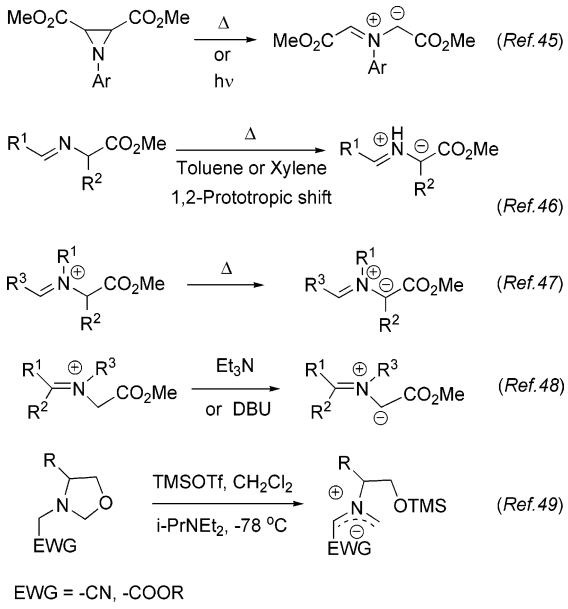
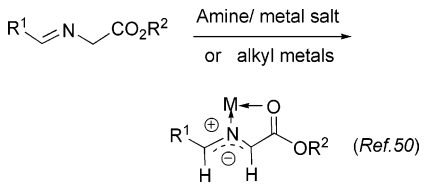


Chart 7



selectivity observed with the *cis*-ester **19c** was explained by considering two reactive conformers **C** and **D** of the dipolarophile (Figure 2). The conformer with the more preferred "inside" alkoxy conformation was considered unstable due to severe nonbonded interactions between the *cis*-methoxycarbonyl group and the dioxolanes ring, and therefore, the *cis*-ester conformer **19c** was forced to react via the "outside" alkoxy conformer **C** to give **20c** as the major product. On the other hand, conformer **D** in which the allylic C−O bond is perpendicular to the plane of the π-bond formed **20c′**. Furthermore, conformer **D** was considered least likely to participate in the 1,3-dipolar cycloaddition reactions as this would have resulted in an unfavorable π, σ^* C−O interaction in the electron-deficient transition state.[56] Recently, Hanessian et al.[57] also reported similar results on the cycloaddition of **18a** to an activated *cis*-olefin having chiral amino acetal auxiliary. This group used this strategy for the stereoselective synthesis of constrained

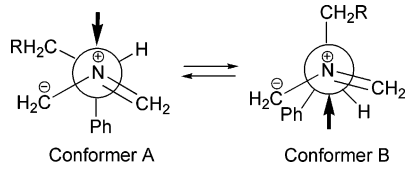
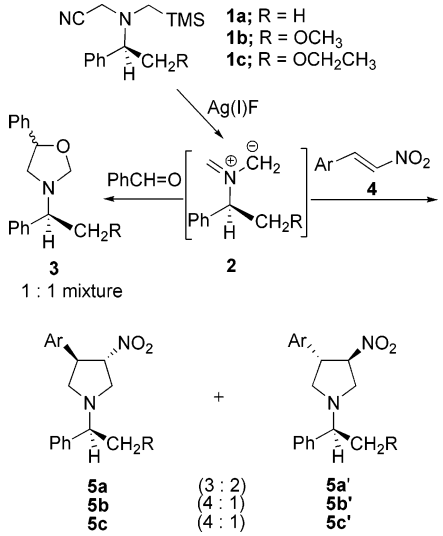
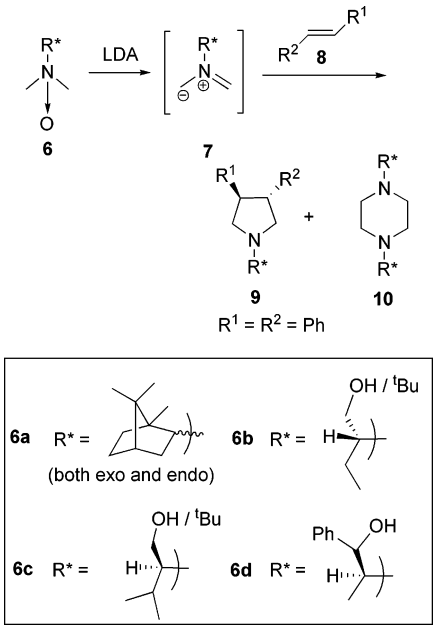


Figure 1. Felkin−Anh model of the ylide **2**.

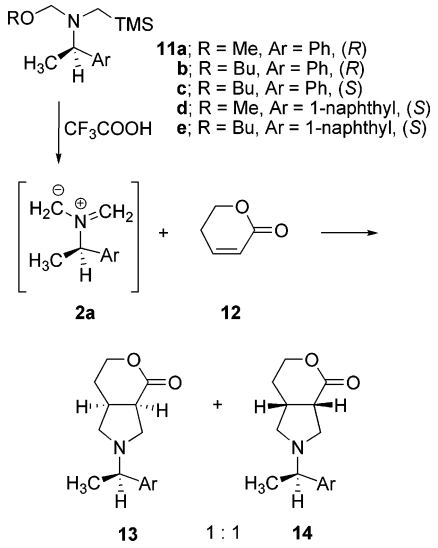
Scheme 1



Scheme 2



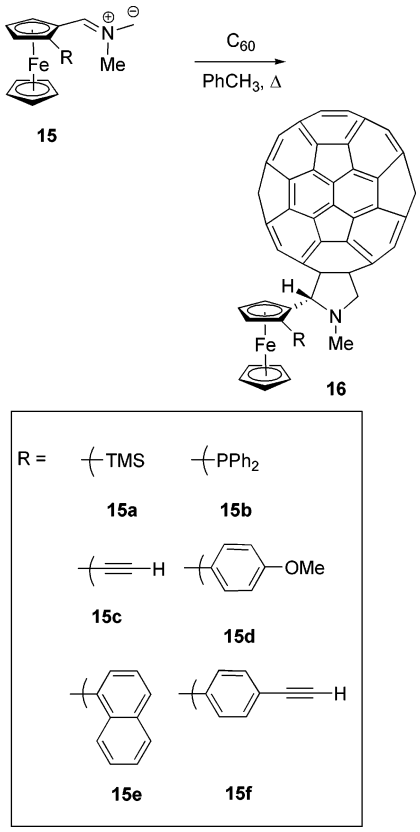
Scheme 3



azacyclic hydroxyethylene isosteres as aspartic protease inhibitors.

Asymmetric synthesis of (*S*)-(−)-cucurbitine (**23**) in greater than 98% ee was reported by Williams et al.[58] by employing highly diastereoselective [3+2]-cycloaddition of **18a** to chiral dipolarophile **21**. Cycloadduct **22** was obtained as a single isomer in this cycloaddition reaction (Scheme 6). In another related study,[59] AMY **18a** has been shown to undergo smooth cycloaddition on to the chiral furanone derivative **24** to give diastereomerically pure adduct **25** in 81% yield (Scheme 7). However, the cycloaddition of **18a** as well **2a** and **2a′** to various chiral dipolarophiles of type **26** gave corresponding cycloadducts **27** and **28** in poor (dr 56:44) to modest diastereoselectivity (dr 80:20)[60−62] (Scheme 8, Table 1). In another publication, Karlsson's group has shown,[63] recently, cycloaddition of **2a** to the cyclic five- and six-membered α,β-unsaturated *N*-enoylbornanesultams, and the diastereoselectivities were found to be poor to moderate depending on the solvents used. Slight improvement in the diastereoselectivity was noticed when cycloaddition was

Scheme 4



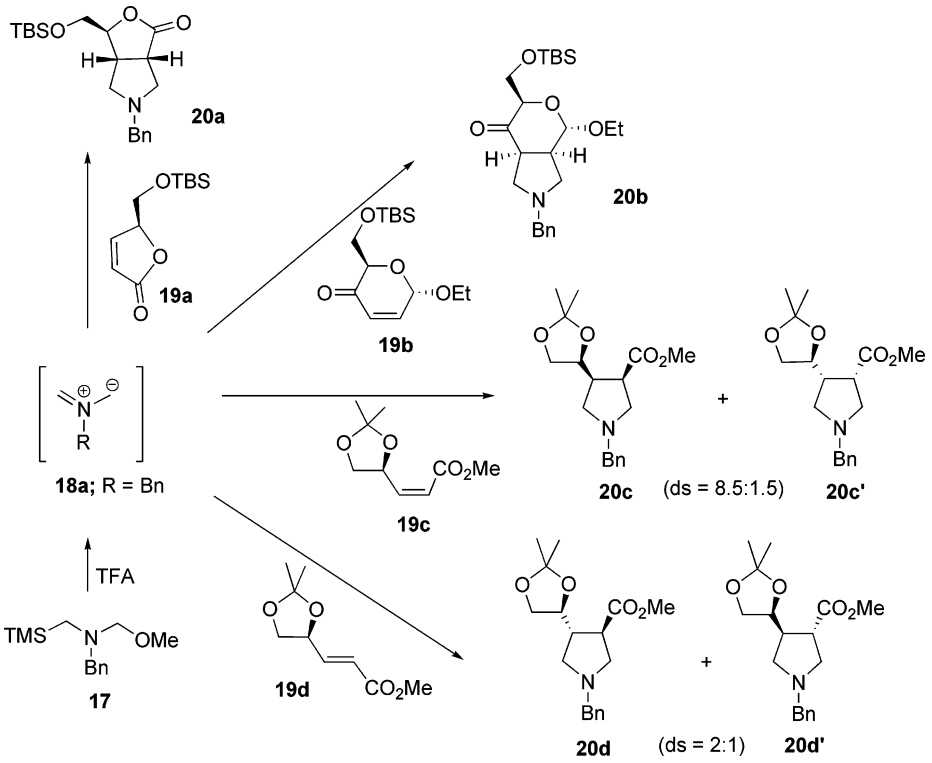
performed in toluene instead of methylene chloride as the solvent.

In related studies,[64,65] cycloaddition of **18a** to (*Z*)-alkenes **29a,b**, (*E*)-alkene **29c** bearing Oppolzer's auxiliary, and alkene **29d** bearing Evans' chiral auxiliary, respectively, were reported to produce corresponding adducts **30a (**dr = 4:1), **30b** (dr = 3.5:1.5) (Scheme 9), and **30c** (dr = 4:1) with significantly good facial selectivity. However, cycloaddition with **29d** produced the corresponding **30d** in reduced diastereomeric ratios (2.6:1.4). The *N*-methylazomethine ylide **18b** (R = Me) upon cycloaddition to isatin-based chiral dipolarophile **31** is reported[66] to produce two oxindole derivatives **32** and **33** in almost equal amounts without any facial selectivity (Scheme 10). These workers also carried forward **32** for the synthesis of (−)-horsfiline. However, significant improvement in the formation of oxindole **38** (single diastereomer) was reported[67] by cycloaddition of ylide **36**, generated by reaction of *N*-phenylisatin (**34**) and L-proline (**35**), using **37** as the dipolarophile (Scheme 11). Furthermore, it has also been established that cycloaddition using **37** attached with Merrifield resin did not change the diastereoselectivity of **38** appreciably.

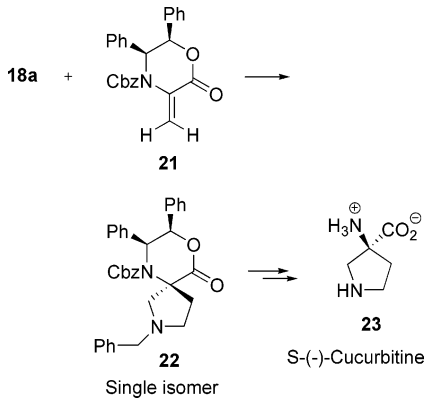
In another publication,[68] cycloaddition of **18b** to **39** bearing various chiral auxiliaries is reported to give the corresponding spiropyrrolidines **40** in varying degrees of diastereoselectivities (Scheme 12). A maximum de of 86% was obtained using **39d** as the substrate.

Single as well as double asymmetric inductions were explored by Meyers et al.[69,70] by carrying out cycloaddition of the chiral AMY **2a** as well as achiral AMY **18a** on to the chiral unsaturated bicyclic lactams **41**. The diastereoselectivities were found to be dependent on the nature of the angular substituents R^1 on **41**. For example, the predominant approach of **41a,b** to the α face of the dipolarophile was

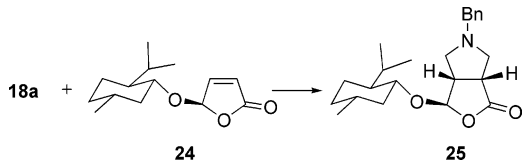
Scheme 5



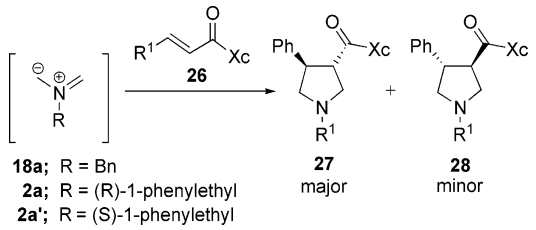
Scheme 6



Scheme 7



Scheme 8



noticed when R^1 = Me, affording a 16:1 mixture of cycloadducts **42** and **43**, whereas with R^1 = H, the approach of the dipole occurred from the β face of **41c**, affording a 5:1 diastereomeric mixture with **43c** predominating the ratio (Scheme 13). Furthermore, cycloaddition of (*R*)-**2a** and (*S*)-**2a** to **41** was also explored by these groups, and it was found that for the cases where R^3 = H (**41a**−**c**), Table 2, the π-facial selectivity was insensitive to the chiral substituents of the dipole. However, wherever R^3 = larger than hydrogen (**41d**−**f**, R^3 = CO_2Me or $CO_2{}^tBu$), significant enhancement

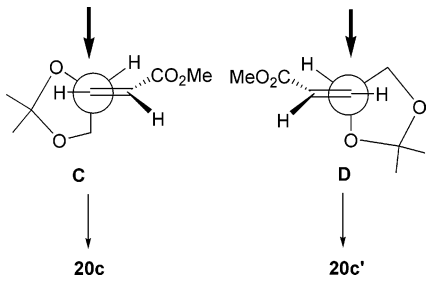


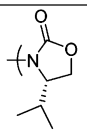
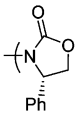
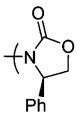
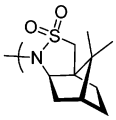
Figure 2. Conformational models of the dipolarophile **19c**.

in the diaselectivities was observed with the dipole (*R*)-**2a** compared with the ratios provided by the achiral **18a** as well as (*S*)-**2a**. On the basis of these experimentally observed results, the transition-state models favoring α approach of the dipole for (*R*)-**2a** as well as achiral **18a** and (*S*)-**2a** were proposed as shown in Figure 3.

More recently Barluenga's group reported[71] highly diastereoselective (dr > 95:5) cycloaddition between AMY **45**, generated from **44** by reaction of CsF, and various (−)-8-phenylmenthol derived Fisher alkoxy alkenyl carbene complexes **46a**−**d** furnishing the corresponding cycloadducts **47** in good yield (Scheme 14). The high diastereoselectivity (dr > 99%) was explained considering the bottom face approach of the dipole **45** to the dipolarophile **46** owing to an effective blocking of the upper face by the phenyl group of the (−)-8-phenylmenthol chiral auxiliary of the dipolarophile due to π-stacking interaction between the phenyl group and the alkene double bond (**TS-1**, Figure 4).

Considering the possibility of better facial selectivity in the cycloaddition of cyclic azomethine ylides due to conforma-

Table 1. Diastereoselectivities between the Cycloaddition of 18 and 26[a]

R	R^1	Xc	Solvent	*dr* (27:28)
Bn	Me		DCM	56:44
			Toluene	60:40
Bn	c-Pr		Toluene	80:20
Bn	c-Pr		Toluene	70:30
Bn	Ph		DCM	74:26
(*R*)-1-phenylethyl				78:22

[a] c-Pr = cyclopropyl.

tional rigidity, Pandey et al.[72] reported a highly diastereoselective asymmetric [3+2]-cycloaddition reaction of cyclic azomethine ylides **49**, generated from **48** by the sequential double desilylation processes using Ag(I)F as one-electron oxidant, to Oppolzer's acryloyl camphor sultam (**50**). The diastereoselectivity was found to depend slightly on the ring size of the cyclic azomethine ylide. Since diastereomeric cycloadducts **51** and **52** were easily separable, the corresponding *X*-aza bicyclo[*m*.2.1]alkane frameworks (**51**, $X = 7$, 8, and 9**)** were obtained in the optically pure form in each case, Scheme 15. This group later demonstrated the application of this strategy for the asymmetric total synthesis of (−)-epibatidine.[73] Subsequently, a similar strategy was also developed by Ashley et al.[74] to prepare the diazabicyclic framework **56** of (−)-lemonomycin (**57**) in excellent enantiomeric purity (94% ee) by cycloaddition of oxidopyrazinium salt **55**, generated by deprotection of **54** with an amine, to **50** followed by reductive removal of the sultam auxiliary, Scheme 16.

3. Asymmetric 1,3-Dipolar Cycloaddition Using Stabilized Nonmetalated AMY

3.1. Acyclic Chiral Azomethine Ylides

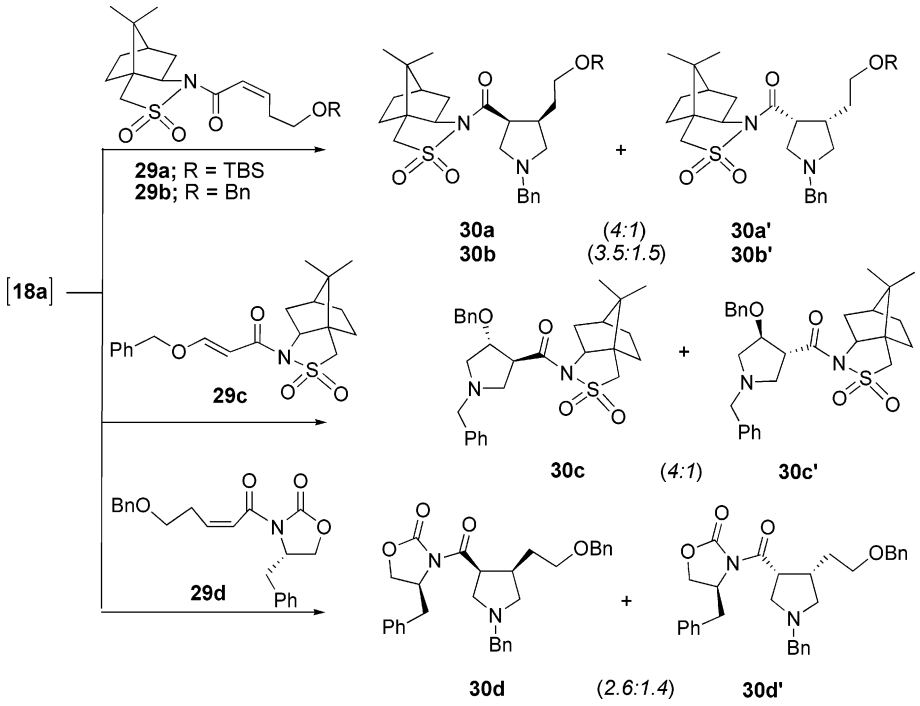
Similar to above studies, extensive research efforts have also been directed to exploring the diastereoselectivities utilizing stabilized chiral azomethine ylides as the dipole. The first paper in this area appeared from the group of Husson et al.,[75] where cycloaddition of the chiral stabilized AMY **59a**, generated by treating the oxazolidine **58a** with TMSOTf in the presence of Hunig base, to the *N*-phenyl maleimide (**60**) was reported to give all four possible isomers of the adducts **61**−**64** in the ratio of 44:32:16:8, respectively. However, with **58b**, the two *exo* isomers (**61b** and **62b**) were formed as major adducts (85% yield) in a 1:1 diastereomeric ratio while the others corresponding to *endo*-**63b** and **64b** (Scheme 17) were formed as minor adducts. The stereochemical outcome of these compounds was explained by an *exo* attack on each side of the stabilized U-shaped ylide **59** without any facial selectivity. In continuation, this group further systematically studied[76] cycloaddition of azomethine ylides **66**, derived from several *N*-methoxycarbonylmethyl oxazolidines **65a**−**e**, to **60**, and the diastereomeric ratios are shown in Table 3. From these results it was concluded that cycloaddition using oxazolidines **65a**−**c** gave two *exo* adducts *exo*-**67** and *exo*-**68** without any facial diastereoselectivity, Scheme 18. This observation was explained by considering the remote position of the chiral center unable to interact with the dipolarophile in this cycloaddition mode. In contrast, cycloaddition using oxazolidine **65d**−**e** gave both *exo* as well as *endo* adducts with excellent diastereoselectivity, which possibly resulted due to *exo*- as well as *endo*-mode addition on the same face of the dipole. This group further explored[77] the diastereofacial selectivity in the cycloaddition of AMY **69**, where chirality was introduced into the ester functionality of the precursor oxazolidine moiety, to **60** (Scheme 19), recording excellent diastereofacial and *endo*/*exo* selectivities. The results with different chiral auxiliaries and substituents are shown in Table 4. The high facial selectivity using 8-phenylmenthol (entry **69e**) is shown to arise due to complete masking of one face of the ylide by the phenyl ring of the 8-phenyl menthyl group involving an *exo* transition state (**TS-2**). In this case, the first chiral center attached to the nitrogen atom forced exclusive *exo* addition of the dipolarophile while the second chiral center on the ester group permitted diastereofacial selectivity.

Takano et al.[78] studied cycloaddition between chiral stabilized AMY **72**, generated by the thermolysis of aziridine **71**, and vinylene carbonate (**73**), but unfortunately the cycloaddition proceeded without much selectivity, producing all four possible diastereo- and enantiomeric cycloadducts such as *exo* (**74** and **77**) and *endo* (**75** and **76**) in a 3:1 ratio (Scheme 20). In another related study,[79,80] ylide **78**, where Oppolzer's chiral sultam was placed on the carbon moiety, is reported to undergo diastereoselective cycloaddition to dimethyl maleate (**79**), producing major adduct **80** via *endo* addition to *Z*-ylide. However, cycloaddition of **78** to the *N*-phenyl maleimide (**60**) gave adducts **81a** and **81a′** in poor *endo*/*exo* selectivity (*endo*:*exo* = 1.8:1). On the other hand, cycloaddition using unsymmetrical dipolarophile methyl acrylate (**82**) produced regioisomers **83a** and **83a′** in a 2:1 ratio (Scheme 21). This group has also shown[80] that the dipolar cycloaddition of the corresponding NH-stabilized azomethine ylide **84**, generated via "imine tautomerization route", to dipolarophiles such as **60**, **79**, and **82** gave all-*cis* adducts via *endo* approach of the dipolarophiles to the *E*,*E*-ylide. In comparison to ylide **78**, the diastereoselectivity observed with **84** was found to be poorer in each case. The facial selectivity of both AMY (**78** as well as **84**) was believed to be controlled by the bulky camphor sultam moiety.

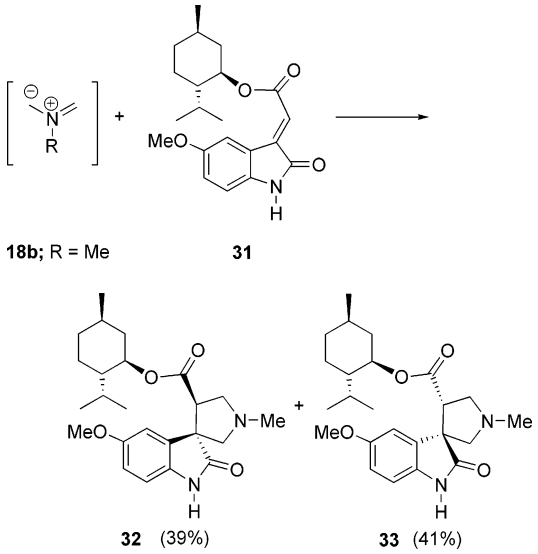
Cycloaddition of the chiral AMY **87**, generated by reaction of ethyl *N*-(1-phenylethyl)glycinecarboxylate (**85**) and ethyl glyoxalate (**86**), to dimethyl fumarate (**88**) was reported[81] to give mixtures of all four possible diastereomers [*exo*(**89a** + **89a′**)/*endo*(**89b** + **89b′**) = 59:41]. The maximum diastereomeric ratio of *exo* adducts **89a**:**89a′** was found to be up to 88:12 (Scheme 22). Similarly, cycloaddition to the maleimides (**60**) was also shown to produce the corresponding pyrrolidines **90** in poor diastereomeric ratios.

Enders et al.[82] have shown that cycloaddition of AMY **92** to several alkenes of type **88** produced mixtures of *exo*/*endo* cycloadducts **93a** and **93b** in poor diastereomeric ratios (Scheme 23, Table 5). It was noted that *endo* adducts dominated in each case except in the case where R^1 = Ph.

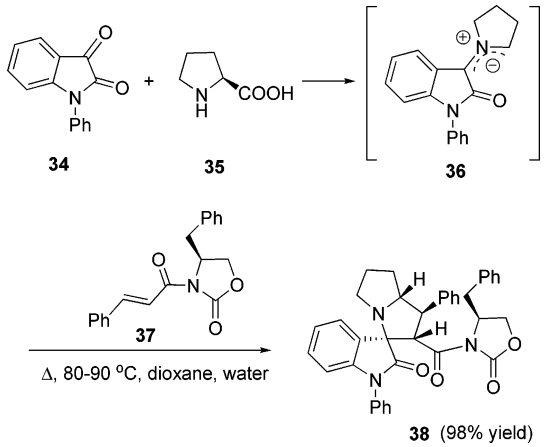
Scheme 9



Scheme 10



Scheme 11

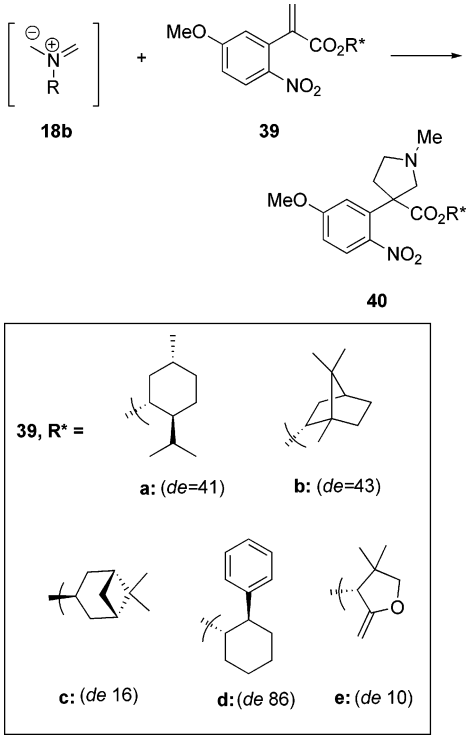


3.2. Cyclic Chiral Stabilized AMY

To develop an azomethine ylide cycloaddition strategy toward the synthesis of the bioactive naphthyridinomycin and quinocarcin alkaloids, Garner et al.[83,84] explored the cycloaddition of the achiral as well as chiral cyclic azomethine ylides **95**, generated by photolysis of the corresponding aziridine **94a**−**d**, to the methyl acrylate **82** (Scheme 24), which produced mixtures of *exo* and *endo* adducts. Cycloaddition of **95a** gave mixtures of *exo*/*endo* adducts in a 5:1 ratio, while reaction of **95b,c** gave the corresponding adducts with very little or no diastereoselectivity. This observation was explained considering the remoteness of the chiral center in **95** from the reacting center of the AMY. To improve diastereoselectivity, this group further studied the cycloaddition of **95d** to a variety of chiral dipolarophiles and found that Oppolzer's chiral acryloyl sultam as well as (+)-**50** is a better auxiliary considering its anticipated *exo*-*re* mode addition due to the conformational biases. Results obtained with various azomethine ylides **95a**−**d** are depicted in Table 6. In fact, the dipolarophile's facial selectivity associated with all the above cycloadditions employing **50** was uniformly excellent (25:1). This cycloaddition strategy has been utilized for the synthesis of (−)-quinocarcin, an antitumor antibiotic.[85,86]

The diastereoselectivities in the cycloaddition[87] of azomethine ylide **124**, derived from (−)-**123** and various aldehydes, to dimethyl maleate (**79**) is shown to depend on the electronic nature of the aldehydes (Scheme 25) used. For example, in the case of the higher aliphatic and aromatic aldehydes, *endo* selectivity was found to be excellent while the stereoselectivity at the C-7 position of **125**, the carbon to which the aldehyde substituents are bound, was generally low, possibly due to the *syn*−*anti* interconversion of the R substituents in (−)-**123**. However, a single isomer of the adduct **125** was formed by cycloaddition of the AMY generated using isobutyraldehyde. Furthermore, this study was extended[88−90] to synthesize (+)- and (−)-spirotryprostatin B by cycloaddition of AMY **127** to **128**, which provided a high degree of *endo* specificity, producing only one

Scheme 12



Scheme 13

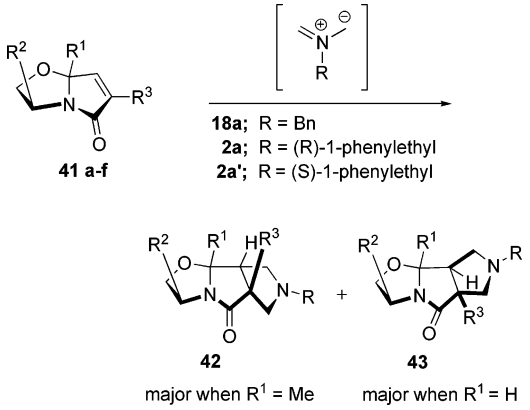


Table 2. Diastereoselectivity in the Cycloaddition of 18a, 2a, and 2a′, and Lactam 41

	lactam **41**				ylide **18a**	ylide (*R*)-**2a**	ylide (*S*)-**2a′**
entry	R^1	R^2	R^3	lactam	(*A*)-**42:43**	(*R*)-**42:43**	(*S*)-**42:43**
1	Me	*i*-Pr	H	41a	91:9	94:6	91:9
2	Me	Ph	H	41b	94:6	91:9	92:8
3	H	Ph	H	41c	17:83	19:81	16:84
4	Me	*i*-Pr	CO_2Me	41d	71:29	87:13	59:41
5	Me	*i*-Pr	$CO_2{}^tBu$	41e	72:28	92:8	51:49
6	Ph	*i*-Pr	CO_2Me	41f	74:26	87:13	69:31

diastereomer **129** in 82% yields (Scheme 26). The high *endo* selectivity was explained by involving a *E*-*β*-*exo*-transition state. These groups also extended this methodology for the stereoselective synthesis of spirotryprostatin-A[91] and ADE fragment of nakadomarin A.[92] Ding et al.[93] also extended the same strategy to prepare a variety of substituted oxiindoles.

Harwood et al.[94−107] explored, in a series of publications, the cycloaddition of various 5-phenylmorpholine-2-one-based chiral azomethine ylides **130** on to a variety of dipolarophiles and under different reaction conditions. The ylides were

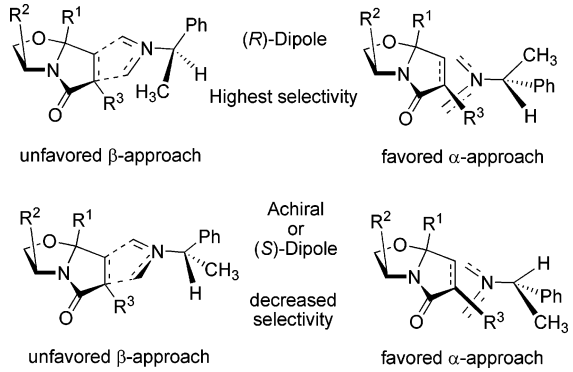


Figure 3. Models to explain the approach of **41** toward dipoles **2** as well as **18**.

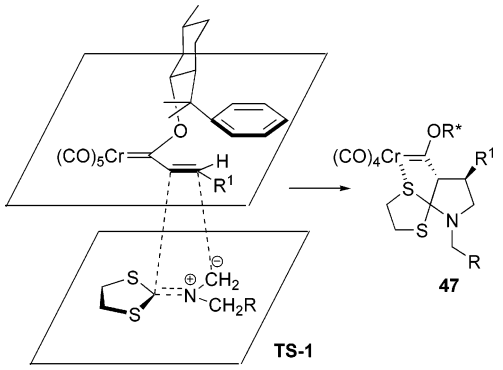
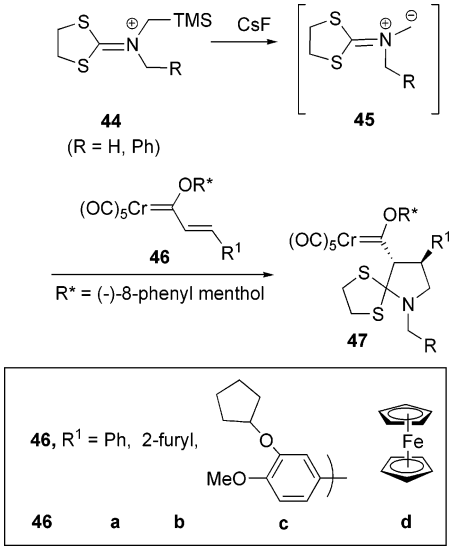


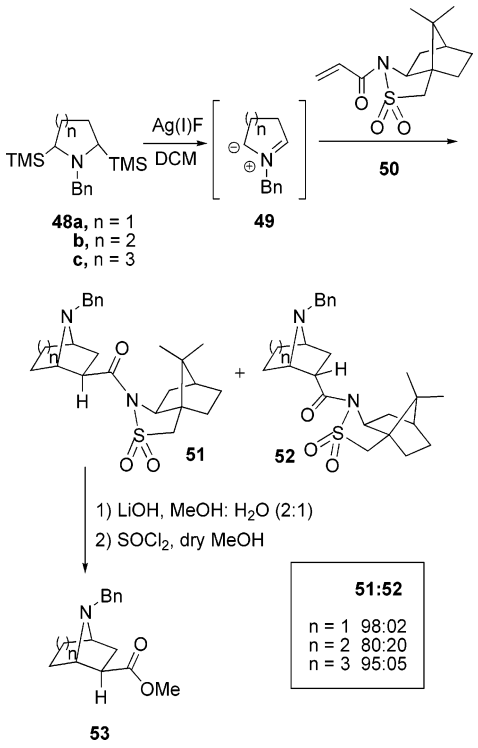
Figure 4. Transition-state model for the stereoselective formation of **47**.

Scheme 14

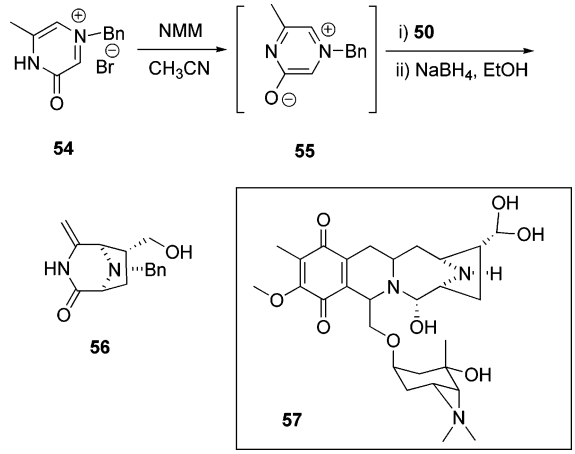


generally generated by condensing chiral 5-phenylmorpholin-2-one and aldehydes, ketones, and/or their derivatives. The results of their various studies are summarized in Table 7. The stereochemical control at C-3 of the morpholin-2-one ring was rationalized[96] by envisaging an axial approach of the dipolarophile to the least hindered face of the ylide **130** held in a chair conformation in which the phenyl group is equatorial (Figure 5). Flipping of the morpholinone ring to a boat conformation, upon completion of the cycloaddition, resulted in all the substituents lying in the sterically least demanding environments. Use of a Lewis acid was initially proposed to change[98] the interaction between **130** and the dipolarophiles from a dominant $HOMO_{dipole}-LUMO_{alkene}$

Scheme 15



Scheme 16



interaction to a $LUMO_{dipole}-HOMO_{alkene}$ interaction, though without much experimental support. However, their recent[108] work on the catalyzed cycloaddition of **157** unequivocally supports such changeovers in FMO interactions.

In contrast to the usual favor of *endo* cycloaddition of **130** to various dipolarophiles reported by Harwood's group,[94−107] Moloney et al.[109] observed the predominance of *exo* adducts in the cycloaddition of (*S*)-**130** to various dipolarophiles as depicted in Scheme 27. Cycloadduct **161** resulted in each case as a byproduct in the cycloaddition of the aldehyde itself used to generate **130**. Surprisingly, in entries 1−4, no *endo* adducts were observed at all. The unactivated alkenes, such as *cis*- and *trans*-stilbene (Table 8, entries 4 and 5) gave particularly low yields of the corresponding adducts. However, these researchers did not provide any suitable explanation for these contrasting observations.

The carboxy-stabilized ylides **172** and **173**, obtained by reaction of paraformaldehyde with corresponding chiral saturated alanine and glycine-derived 6-isopropyl-5-phenylmorpholin-2-ones, **170** and **171**, respectively, are reported[110]

Scheme 17

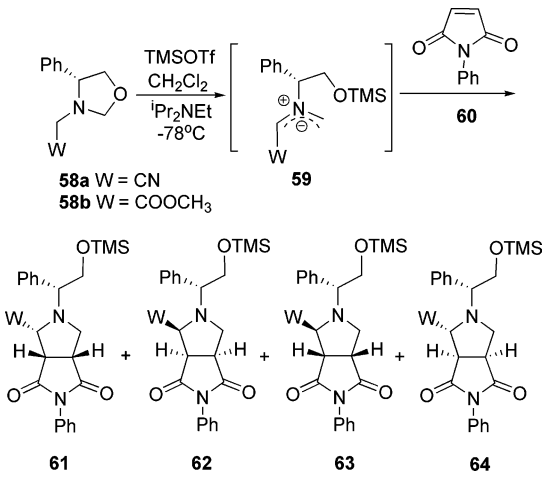
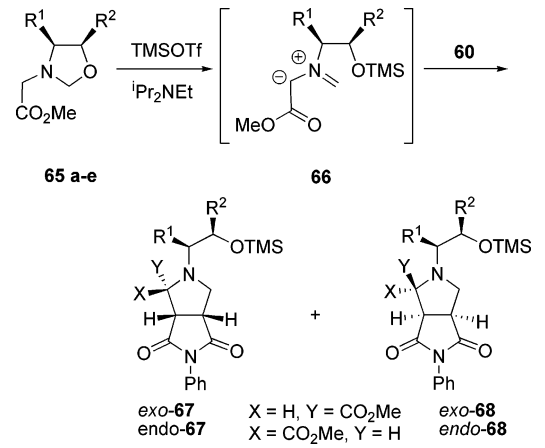


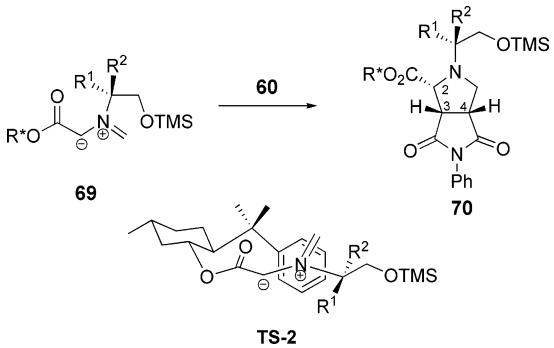
Table 3. Selectivity in the Cycloaddition of 66 with 60

	R^1	R^2	overall yield (%)	*exo*-**67** (%)	*endo*-**67** (%)	*exo*-**68** (%)	*endo*-**68** (%)	de
65a	Ph	Ph	72	52		48		4
65b	i-Pr	H	66	51		49		2
65c	Bn	H	71	55		45		10
65d	H	Ph	62	39			61	>95
65e	Me	Ph	72	42			58	>95

Scheme 18



Scheme 19

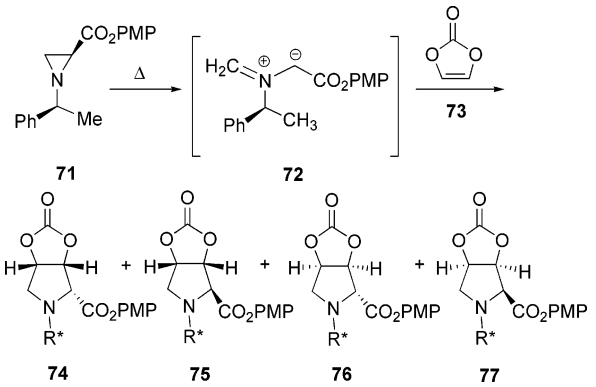


to undergo cycloaddition with various electron-deficient olefins with high *endo* selectivity (Scheme 28). Symmetrically substituted electron-poor olefins such as dimethyl maleate gave high 91:9 *endo*/*exo* diastereoselectivity in comparison with the cyclic dipolarophiles. Cycloaddition of acetylene dicarboxylate with alanine-derived AMY **172**

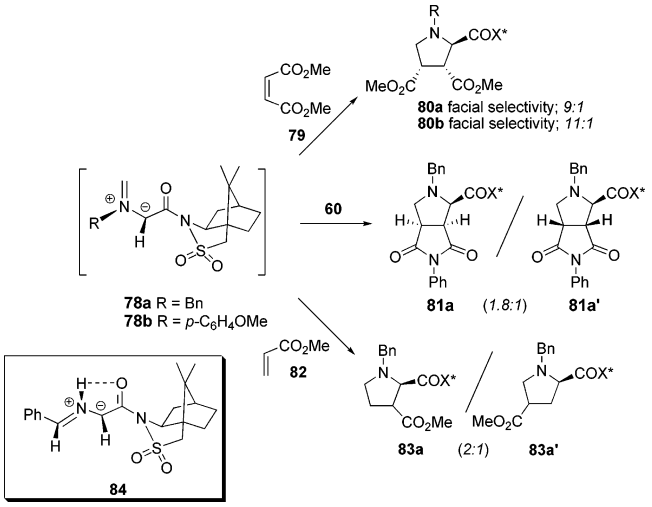
Table 4. Selectivity in the Formation of 70 by the Cycloaddition of 69 with 60

					H-2/H-3 *cis-exo*		H-2/H-3 *trans-endo*			
	R	R^1	R^2	overall yield (%)	**70a**	**70b**	**70c**	**70d**	*exo*/*endo*	de
69a	Me	Ph	H	85	48	52			100:0	4
69b	(+)-menthyl	Me	Me	52	55		45		55:45	
69c	(+)-menthyl	Ph	H	83	84	9	7		93:7	80
69d	(−)-menthyl	Ph	H	79	20	80			100:0	60
69e	(−)-8-phenyl menthyl	Ph	H	86		≥98			100:0	≥95

Scheme 20



Scheme 21



provided exclusively **175d** in 75% yield by attack of the dipolarophile from the less hindered side of the dipole. Detailed results with various dipolarophiles are shown in Table 9.

Similar to Harwood's[94−107] and Najera's[110] study, chiral AMY-template **178**, derived from imidazolidinone **177** and formaldehyde, has also been tested[111] as a chiral controller in the 1,3-dipolar cycloaddition reaction using different electron-deficient alkenes, and the results are depicted in Scheme 29. While cycloaddition with *N*-phenyl maleimide (**60b**) was found to give cycloadducts **179** and **180** in moderate diastereoselectivity (up to 60% de), cycloaddition to **88** gave the corresponding cycloadducts **181** and **182** in poor diastereomeric ratio (de = 20%). The stereochemical outcome of this dipolar cycloaddition was rationalized by envisaging *endo*/*exo* approaches of the dipolarophile to predominantly one face of the essentially planer ylide **178** from the side *anti* to the *t*-Bu group.

Excellent diastereoselectivity was observed with the cycloaddition of homochiral[112,113] 4(*R*)-phenylimidazolinium ylide **184**, where the auxiliary is conformationally restrained by virtue of the heterocyclic ring, to various dipolarophiles **185**, producing a mixture of cycloadducts **186** and **187** (Scheme 30).

However, minor *exo* isomers were also reported to be formed only with the methacrylonitrile as the dipolarophile. Results with both (*R*)- as well as (*S*)-**184** and various dipolarophiles are shown in Table 10. The stereochemical outcome of these cycloadditions was explained by considering the *endo* approach of the dipolarophile (Figure 6) having *anti* geometry where facial selectivity is provided by the 4-phenyl substituents.

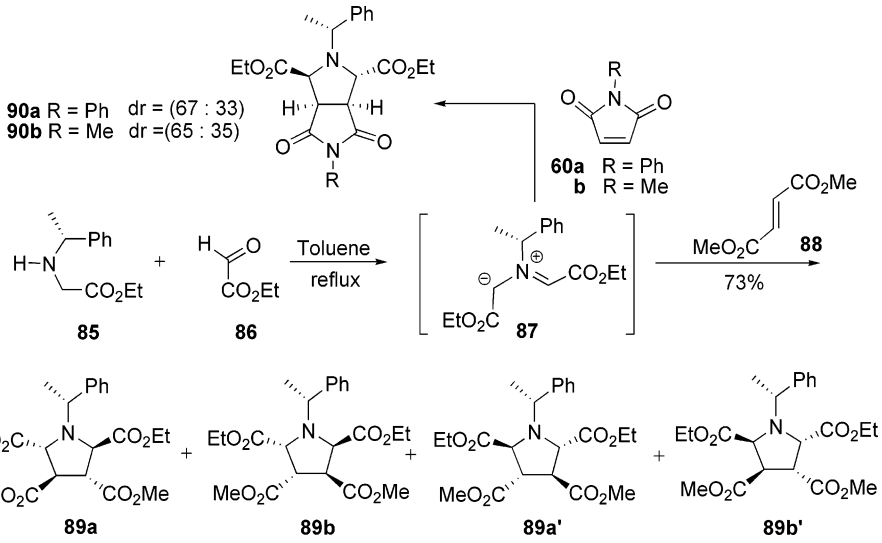
The chiral ylide **188** is reported[114] to undergo cycloaddition to acyclic nitro-olefin **189** exclusively *anti* to the hydroxyl substituents of the ylide, producing **190** as a single diastereomer (Scheme 31). Although cycloaddition with the cyclic nitro-olefins was found to be highly diastereoselective, the regioselectivity was relatively poor. In a few selected cases the authors noted that cycloaddition involved a stepwise mechanism rather than a concerted one.

Grigg et al.[115] reported highly diastereoselective cycloaddition of AMY **192**, derived from isatin (**191**) and L-proline (**35**), to menthyl acrylates, producing **193** in a 9:1 diastereomeric ratio (Scheme 32). The transition-state model **TS-4** was suggested to involve a *s-cis* configuration of the dipolarophile with union occurring between the *re* face of the menthyl acrylate and the *si* face of the dipole, as the carbonyl group of the ester is *syn*-planar with the menthyl C(1)−H and the *si* face of the acrylate is effectively shielded by the C(2) *i*-Pr group. The same group further reported[116] the cycloaddition of nonmetalated **195** as well as metalated azomethine ylide **196**, derived from diazepine-1-carboxylate derivatives **194**, to the *N*-methylmaleimide and ethyl acrylate, respectively, to obtain corresponding spiro-cycloadducts **197** and **198** in a complete regio- and stereoselective manner and in excellent chemical yields (84−93%, Scheme 33). More recently, this group also studied[117] in detail the cycloaddition of uracil polyoxin-derived azomethine ylides **200** and **201** with various maleimides, and the results are summarized in Scheme 34.

3.3. Achiral Stabilized AMY and Chiral Dipolarophile

Apart from these studies, few examples are also found in the literature where cycloaddition of the stabilized nonmetalated achiral azomethine ylides with the chiral dipolarophiles are also studied. One such example[59] concerns with cycloaddition of the stabilized AMY **206** to **24** exhibiting excellent facial selectivity by producing two regioisomers **207** and **208** in a 1:2 ratio (Scheme 35). Furthermore, stabilized AMY **211**, generated in situ from the ethyl pyruvate **209** and alanine **210**, is reported[59] to react with **24** to give **212** (epimeric at C-6) as a diastereomeric mixture in a 23:2 ratio (Scheme 36). The major adduct **212** was formed by an *anti* facial approach of the dipole with *endo*-ester orientation.

Scheme 22



Scheme 23

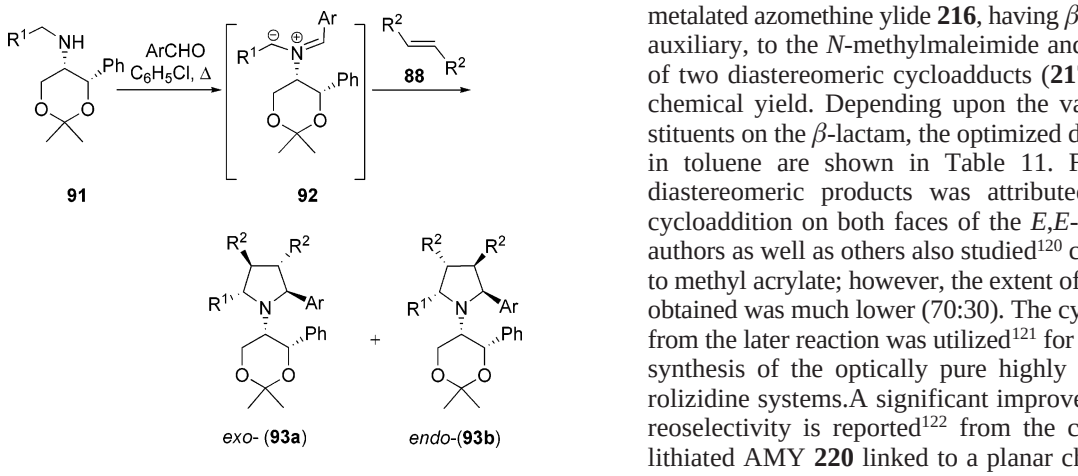


Table 5. Diastereoselectivity Details for the Cycloaddition of 92 onto 88

	R^1	Ar	R^2	**93a**:**93b**
a	CO_2CH_3	C_6H_5	CO_2CH_3	43:57
b	CO_2CH_3	C_6H_5	CN	30:70
c	CO_2CH_3	*p*-FC_6H_4	CO_2CH_3	42:58
d	CO_2CH_3	*p*-FC_6H_4	CN	31:69
e	C_6H_5	C_6H_5	CO_2CH_3	65:35

4. Asymmetric 1,3-Dipolar Cycloaddition Using Stabilized N-Metalated Azomethine Ylides

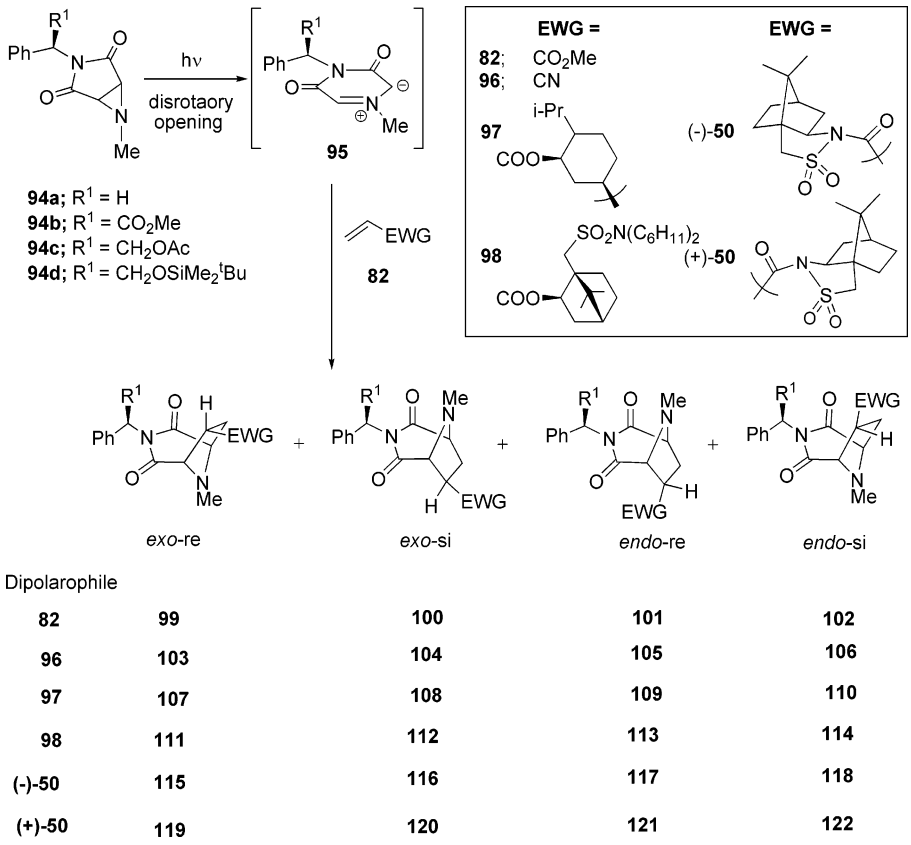
4.1. Chiral N-Metalated Azomethine Ylides and Achiral Dipolarophiles

Husinec et al.[118] explored the cycloaddition of oxazoline-derived stabilized chiral dipole **214**, generated by treating **213** with AgOTf in the presence of Et_3N, to the *N*-methyl maleimide, which produced diastereomerically pure adduct **215**. This high diastereoselectivity was explained by considering the approach of the dipolarophile from the less shielded face of the N-metalated dipole **214**. Monosubstituted dipolarophiles such as methyl acrylate were found to give low diastereoselectivity due to lack of interaction of the dipolarophile with the oxazoline auxiliary (Scheme 37).

Grigg et al.[119] also reported cycloaddition of the N-metalated azomethine ylide **216**, having β-lactam as the chiral auxiliary, to the *N*-methylmaleimide and obtained mixtures of two diastereomeric cycloadducts (**217** and **218**) in good chemical yield. Depending upon the variation of the substituents on the β-lactam, the optimized diastereomeric ratios in toluene are shown in Table 11. Formation of these diastereomeric products was attributed to *endo*-specific cycloaddition on both faces of the *E*,*E*-(*syn*)-dipole. These authors as well as others also studied[120] cycloaddition of **216** to methyl acrylate; however, the extent of diastereoselectivity obtained was much lower (70:30). The cycloaddition product from the later reaction was utilized[121] for the stereocontrolled synthesis of the optically pure highly functionalized pyrrolizidine systems.A significant improvement in the diastereoselectivity is reported[122] from the cycloaddition of N-lithiated AMY **220** linked to a planar chiral arene $Cr(CO)_3$ complex and methyl acrylate. Study with various substituted ylides is shown to produce cycloadduct **221** as a single isomer. The exclusive *syn* and *endo* selectivity was explained by invoking chelation between the lithium, imine nitrogen, and carbonyl oxygen as shown in the transition-state structure **220a**, rendering only opposite face approach of the dipolarophile possible to the chromium tricarbonyl fragment of the AMY. Reversed product regiochemistry in **222** was observed when $TiCl(O^iPr)_3$ was utilized as the Lewis acid. A hypothetical model **220b** was proposed to explain this observation in which the arene−pyrrolidine bond adopted a conformation that minimized $A_{1,3}$-strain between the aryl ortho substituents and the pyrrolidine group (Scheme 39).

Optically pure ferrocenyl-substituted pyrrolidine derivatives **227**−**230** were synthesized by diethylzinc-catalyzed[123] 1,3-dipolar cycloaddition of the chiral azomethine ylide **226** to a number of electron-deficient dipolarophiles (Scheme 40). The chiral azomethine ylide **226** was generated by condensing glycyl sultam **223** with the ferrocenecarboxaldehyde **224** via imine tautomerization and complexation with diethyl zinc. High regio- and diastereoselectivity in the formation of adducts **227**−**230** was explained through a transition-state structure of **227** in which the dipolarophiles approached to the *E*,*E*-ylide in an *endo* mode from the upper face to give the *cis* arrangements of all the substituents. Furthermore, very high diastereofacial selectivity was attributed to the steric bulk imparted by the ferrocenyl group at the *re* face of the

Scheme 24

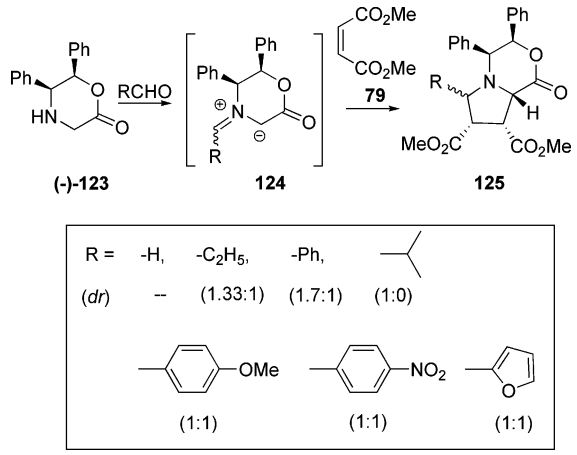


Dipolarophile				
82	**99**	**100**	**101**	**102**
96	**103**	**104**	**105**	**106**
97	**107**	**108**	**109**	**110**
98	**111**	**112**	**113**	**114**
(-)-50	**115**	**116**	**117**	**118**
(+)-50	**119**	**120**	**121**	**122**

Table 6. Cycloaddition Details between Various 95 and Dipolarophiles

entry	aziridine	dipolarophile	*exo* adducts	% yield	ratio (dr)	*endo* adducts	% yield	ratio (dr)
1	94a	82	99a/100a	50		101a/102a	11	
2	94c	82	99c/100c	73	1:1			
3	94a	96	103a/104a	22		105a/106a	36	
4	94a	(−)-97	107a/108a	64	1:1	109a/110a	15	1:1
5	94a	(−)-98	111a/112a	57	1:1			
6	94a	(−)-50	115a/116a	39	>25:1	117a/118a	16	>25:1
7	94b	(−)-50	**[115b** + ent-**120b]/[116b** + ent-**119b]**	61	>25:1			
8	94c	(−)-50	115c/116c	58	>25:1			
9	94c	(+)-50	120c/119c	55	>25:1			
10	94d	(−)-50	115/116d	45	>25:1			
11	94d	(+)-50	120d/119d	46	>25:1			

Scheme 25



ylide, which made the approach of the dipolarophile from this side almost impossible.

Scheme 26

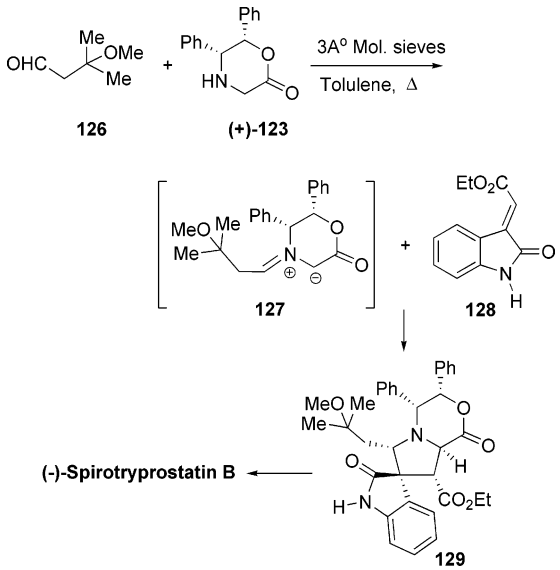


Table 7. Cycloaddition Details of Various Chiral Oxazine-Based Azomethine Ylides and Dipolarophiles

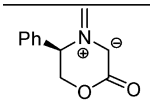
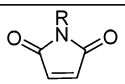
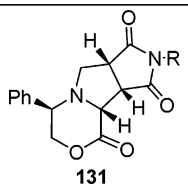
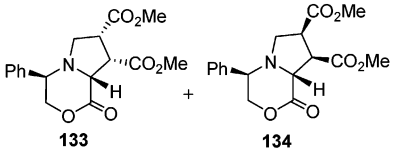
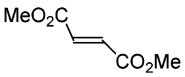
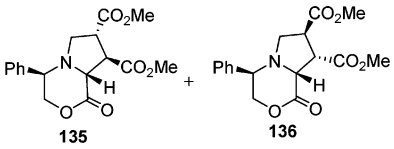
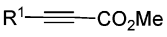
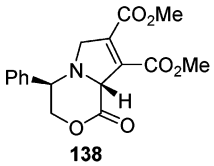
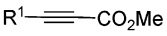
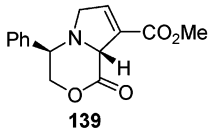
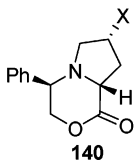
Dipole	Dipolarophiles	Addends	Cycloadducts (%)		*Ref.*
					*94-96*
***(R)*-130**	**60**		**131**	**132**	
			endo	*exo*	
	a, R = Ph	Nil	45	13	
	b, R = Me		41	19	
	c, R = H		54	14	
	60a	$MgBr_2$.	9	54	*98*
	60b	Et_2O	<1	80	
					*94-96*
	79		**133**	**134**	
		Nil	20	6	
		$MgBr_2$.	40	20	
		Et_2O			
					*94-95*
	88		**135**	**136**	
		Nil	0	0	
		$MgBr_2$.	0	56	
		Et_2O			
					*94, 95*
	137	Nil	**138**		
	$R^1 = CO_2Me$				
					*94, 95*
	137	Nil	**139**		
	$R^1 = H$				
					*98*
	82b, X = SO_2Ph	Nil	**140**		

Table 7 (Continued)

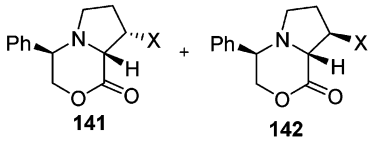
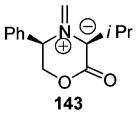
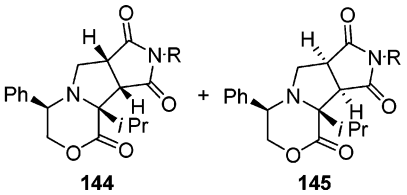
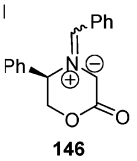
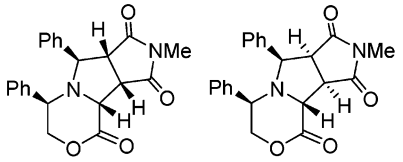
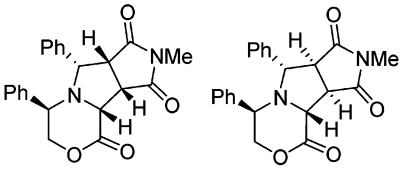
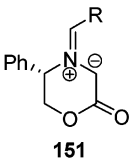
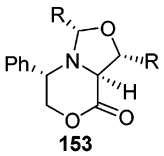
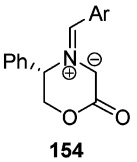
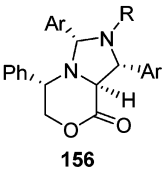
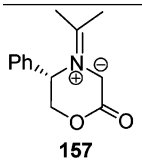
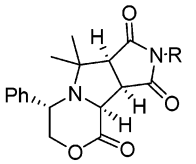
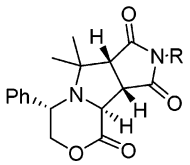
Dipole	Dipolarophiles	Addends	Cycloadducts (%)	*Ref.*
	82c, X = CN **82a**; X = CO_2Me	$MgBr_2$. Et_2O	 **141** + **142** *dr*-1:1	*98*
 **143**		Nil	 **144** + **145**	*95*
	60b		34 7	
	60c		46 -	
 **146**	**53b**	Nil	 **147** 38 **148** 13	*96*
			 **149** 11 **150** 9	
 **151**	RCH=O **152**	Nil	 **153**	*97, 105, 106*
			R = Ph 69	
			R = Cyclohexyl 69	
 **154**	ArCH=NR **155**	Nil	 **156**	*104*
			Ar = Ph, R = Me, 56	
			Ar = *p*-F C_6H_4, R = Bn, 70	

Table 7 (Continued)

Dipole	Dipolarophiles	Addends	Cycloadducts (%)		*Ref.*
 **157**		$MgBr_2$. Et_2O	 **158** +  **159**		*106*
	60b		43	30	
	60c		33	28	

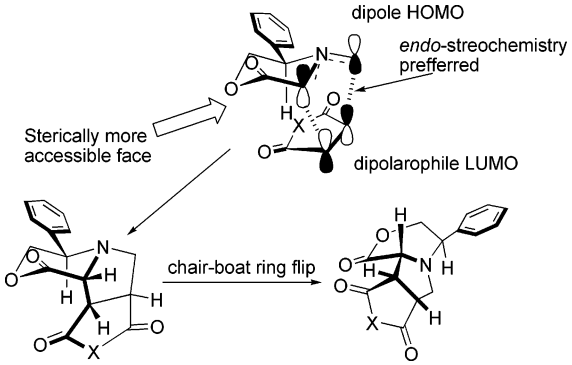
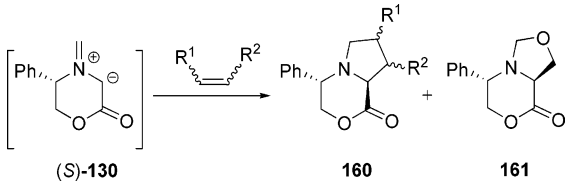


Figure 5. $HOMO_{dipole}-LUMO_{dipolarophile}$ interaction to explain stereoselectivities.

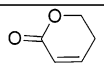
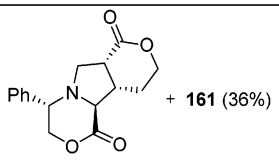
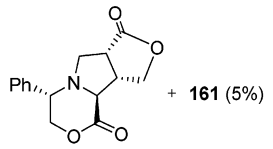
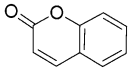
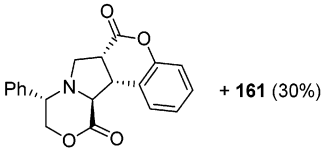
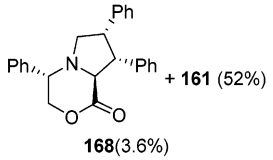
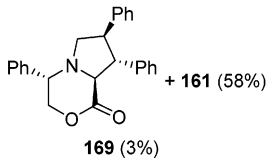
Scheme 27



4.2. Achiral N-Metalated AMY and Chiral Dipolarophiles

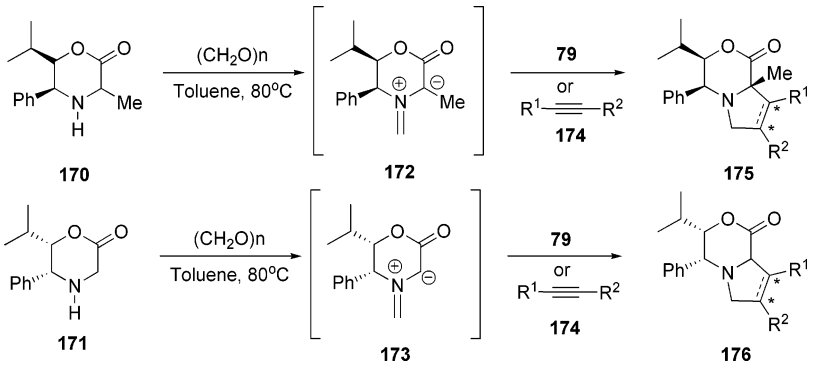
Although cycloaddition of the N-metalated-azomethine ylides with both acyclic as well as cyclic dipolarophiles is explored extensively, its asymmetric version was first reported by Kanemasa et al.[124,125] by studying cycloaddition of a highly reactive *N*-lithiated AMY **231** (M = Li) at −78 °C to α,β-unsaturated esters bearing a methyl (*E*)-3-[(3*R*,-7a*S*)-2-phenylperhydropyrrolo-[1,2-c]imidazol-3-yl]propenoate [**232**, mixture of 2,4-*trans* and 2,4-*cis* (86:14)] and chiral 2-oxazolidinyl (**233**) moieties as chiral controllers at their β positions. In each case, the corresponding cycloadducts **234** and **235** were isolated in excellent yields (80−85%) and diastereoselectivities. Formation of **234a,b** in a diastereomeric ratio of 75:25 was explained considering the isomeric ratio of the dipolarophile **232** since **233** produced only **235** as a single diastereomer. It was also noted that the temperature (−78 °C to room temperature), metals (Li or Mg), and size of R^3 in the dipole (Me vs *t*-butyl) did not alter the diastereoselectivity (Scheme 41). The *endo* specificity together with excellent diastereoselectivity for these cycloadditions was explained by considering transition-state models **TS-5** to **TS-6** (Figure 7). The diastereoselectivity for formation of **234a** was explained by invoking predominant involvement of thermodynamically more stable C(2)−C(β)

Table 8. Diastereoselectivity in the Cycloaddition of (*S*)-130 with Various Dipolarophiles

Entry	Dipolarophile	Isolated yield of major cycloadduct
1	 **12**	 + **161** (36%) **162** (53 %)
2	 **163**	 + **161** (5%) **164**(27%)
3	 **165**	 + **161** (30%) **166** (28%)
4	 **167**	 + **161** (52%) **168**(3.6%)
5	 **8**	 + **161** (58%) **169** (3%)

anti-periplanar conformer (*ap*) **TS-5** instead of *syn*-periplanar conformer (*sp*) in which the *si*(Cα) face is open to attack by the dipole because of the critical steric hindrance caused by the *N*-phenyl substituents. Similarly, exclusive attack of the ylide at the *re* (Cα)-face of C(2)−C(β) involving *anti*-periplanar conformer of **TS-6** produced cycloadduct **234b**. On the other hand, formation of cycloadduct **235** involved transition state **TS-7**, where ylide **231** attacked the *si* face (C2) of the thermodynamically less favored 3H/3′-H *syn*-periplanar conformer rather than *anti*-periplanar conformer

Scheme 28



TS-8. Existence of serious steric hindrance between the ester moiety of **231** and 7a′-H of **233** or between the ester moiety and the bridgehead hydrogen was considered a major contributor to the stereoselectivity determining factor.

Kanemasa's group further explored[126] cycloaddition of **231** (M = Li, −78 °C) to α,*β*-unsaturated methyl ester having C_2-symmetric 1,2-diamine-based chiral auxiliaries (**236a** and **236b**) and reported formation of the homochiral pyrrolidines **237** and **238** in a maximum optimized diastereomeric ratio of 96:4 (Scheme 42). Interestingly, it was also noted that diastereoselectivity depends very much on the nature of the R^3 of the dipole and R of the dipolarophile. For example, cycloaddition of (−)- and/or (+)-**236a** (R = Ph) to **231** (R^3 = Me) produced corresponding **237** and **238** in a 96:4 ratio, whereas the ratio was reversed (4:96) using **236b** (R = Me) and **231** (R^3 = *tert*-butyl). This observation was explained considering the attack of the methyl ester ylide (R^3 = Me) and *tert*-butyl ester ylide (R^3 = *t*-Bu) from the opposite diastereotopic faces, *si* (*β*) and *re* (*β*) faces, respectively, of **236**. Furthermore, it was also noticed that cycloaddition of **231**, irrespective of the nature of the R^3 group (R^3 = Me or *t*-Bu), to **236b** always produced **238** as the major diastereomer, indicating that both types of the dipole attacked **236b** from the same diastereotopic faces.

Simultaneous to Kanemasa's[124−126] result, Grigg et al.[127,128] also reported independently complete diastereo- as well as *endo*-selective cycloaddition of several Ag-metalated ylides **231a**−**c** onto (+)-menthyl acrylate (**239**) producing only one adduct **240** in each case with a maximum yield of 50% (Scheme 43). This group further evaluated the effect of different metal salts on the diastereo- and regioselectivities of the cycloaddition reaction and reported that metal salts such as LiBr and $Tl(NO_3)_2$ gave only **240** whereas $Ti(O^iPr)_2$ led to the reversal of regioselectivity, producing homochiral cycloadduct **241**. Successful isolation of **243** by cycloaddition of **242** to **239** demonstrated that the ester moiety in the ylide structure **231** can be replaced with any other electronegative group.

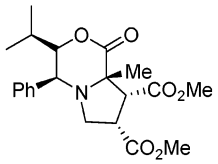
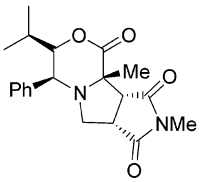
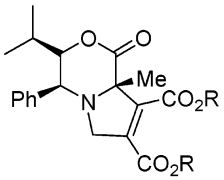
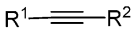
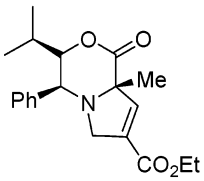
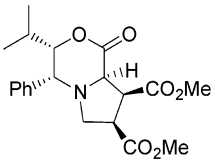
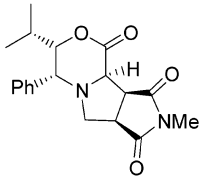
The regio- and *endo*-specificity in the formation of **240** was explained through a transition-state model **TS-9** where a facial shielding effect of the isopropyl moiety of the menthyl moiety is accommodated. This model involved addition of 1-*si*,3-*re* face of the dipole to the *re* face of the *s*-*cis* acrylate. The isopropyl group effectively shielded the *si* face of the *s*-*cis* acrylate. The C(6) equatorial hydrogen atom of the menthyl moiety was believed to infringe slightly on the *π* cloud of any C(3)-aryl substituent on the dipole (Figure 8). The generality of the regio- and *endo*-mode cycloaddition of various dipoles of type **231** to optically active furanone and pyrrolone derivatives was further[129] established by these workers.

In contrast to Grigg's[127−129] observation that the cycloaddition of various dipoles of type **231** with several optically pure acrylates or equivalents gave diastereomerically pure cycloadduct, a report highlighted[130] that cycloaddition of **231** to acyclic chiral dipolarophiles **244** produced two diastereomeric cycloadducts (**245** and **246**, de = 95:5, under optimized reaction condition) presumably via *endo* addition of a W-shaped dipole (Scheme 44). However, cycloaddition with **247** gave *anti*-selective cycloadducts **248** and **249** largely depending on the nature of the R of O-protecting group**.** The diastereomeric ratio of **248**:**249** increased with the increase in the size of the R group **(**R = Bn, 78:22; R = TBDMS, 90:10), which was interpreted by proposing three transition-state models (**TS-10** and **TS-11** or **TS-12**) as shown in Figure 9. To explain the formation of **248**, it was proposed that the ylide attacked the *re*/*re* face of the ester away from the bulky alkyl residue at the stereocenter as shown in **TS-10**. This attack led to a transition state where the −OR allylic substituents occupied a stereoelectronically favored "inside" position and small H group, the more sterically demanding "outside" position, closer to the incoming dipole. Similarly, for the formation of **249**, transition-state **TS-11** was invoked, featuring attack at the *si*/*si* face *anti*-periplanar to small H group with the alkoxy group "inside" and an unfavorable steric interaction between the ylide −OMe group and the allylic R group in the "outside" region. The model **TS-12** was believed to be energetically less favorable as the steric interaction between the "outside" −OR group and the methoxy residue on the ylide destabilizes this transition structure with respect to **TS-10** (Figure 9). The highest dr (96:4), obtained when R = H, was explained by considering the hydrogen bonding between the −OH of the dipolarophile and the dipole oxygen. Similar results were also reported,[131] subsequently, using chiral nitroalkene **250**, which produced a diastereomeric mixture of the corresponding cycloadducts **251** and **252**, de mostly depending on the nature of the metal used. This strategy was, recently,[132] utilized for the preparation of inhibitors of $\alpha_4\beta_1$-integrin-mediated hepatic melanoma metastasis.

Patzel et al.[133,134] also described a highly regio- as well as diastereoselective cycloaddition between **231** (M = Ag, −78 °C) and different chiral enones **253a**−**e**, producing the corresponding adducts **254** in more than **a** 95:5 ratio in each case under optimized reaction conditions. A substantially lower de was recorded when M = Li and at room temperature (Scheme 45).

Waldmann et al.[135,136] accomplished almost complete *endo*/*exo* selectivity (**256a**:**256b**, 99:1) in the cycloaddition of **231** (M = Li,) to *N*-acryloyl-(*S*)-proline benzyl ester (**255**) at a temperature range from −78 to 25 °C (Scheme 46). The almost complete *endo*/*exo* selectivity and face selectivity was

Table 9. *Exo/Endo* Selectivity in the Formation of 175 and 176

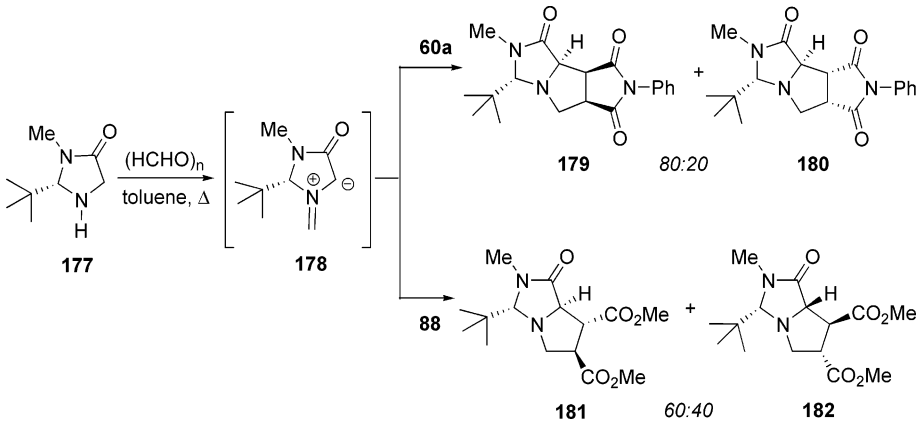
Entry	Dipole	Dipolarophile	Time (h)	*endo*/*exo* ratio	Major adduct	
					Structure	Yield (%)
1	**172**	**79**	24	91:9	 **175a**	33
2	**172**	**60b**; R = Me	6	75:16	 **175b**	32
3	**172**	 **174a**; $R^1 = R^2$ = -COOEt	3	-[a]	 **175c**	75
4	**172**	 **174b;** R^1 = H, R^2 = -COOEt	3	-[b]	 **175d**	44
5	**173**	**79**	3	85:8	 **176a**	34
6	173	**60b;** R = Me	6	55:25	 **176b**	58

[a] dr = 99:1. [b] dr = 96:4.

explained by invoking highly ordered *endo* transition states **TS-13** and **TS-14** (Figure 10) in which the lithium cation is coordinated to the azomethine ylide and to the dipolarophile in such a way that a compact and efficient ordering of the reaction partners results. Of the two *endo* transition states proposed, **TS-13** is energetically more favorable because in **TS-14** the R^1 group of the dipole lies close to the −COOBn group of the proline benzyl ester while in **TS-13** only an interaction with the sterically undemanding α-hydrogen of the proline needs to be considered (Figure 10).

It has also been shown by Nyerges et al.[137,138] that the diastereoselectivity in the cycloaddition of **231** (M = Ag, room temperature) to various chiral acrylamides **257** depends on the nature of the chiral auxiliary utilized. For example, ylide **231** added on to the acrylamides **257a,b**, producing adducts with only poor to low diastereoselectivity (**258**:**259**,

Scheme 29



Scheme 30

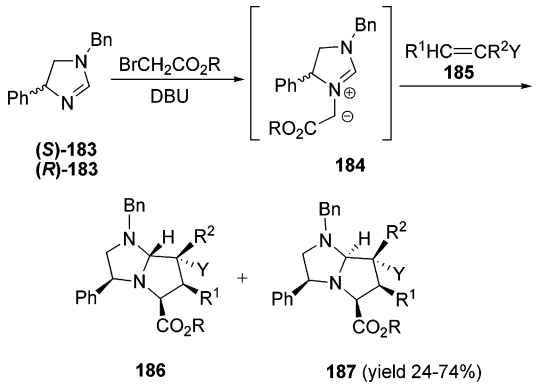


Table 10. Diastereoselectivity in the Cycloaddition of 184 to 185

dipole	dipolarophile **185**			cycloadducts	
R	R^1	R^2	Y	**186**[a] (%)	**187**[a] (%)
Me	H	Me	CO_2Me	53 (55)	
Me	H	Me	CN	24 (41)	3 (5)
t-Bu	H,	Me	CO_2Me	61 (62)	
t-Bu	H	Me	CN	27 (22)	4 (3)
t-Bu	H	H	CO_2Me	59 (49)	3 (2)
t-Bu	Me	H	CO_2Me	46 (26)	
t-Bu	H	H	SO_2Ph	33	
t-Bu	H	H	COMe	71	

[a] Value in brackets indicates the yield of the corresponding *R* isomer of the dipole.

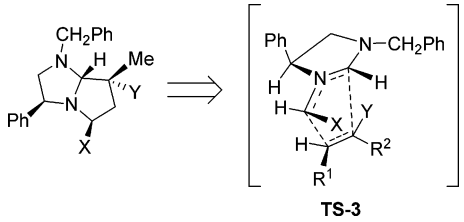
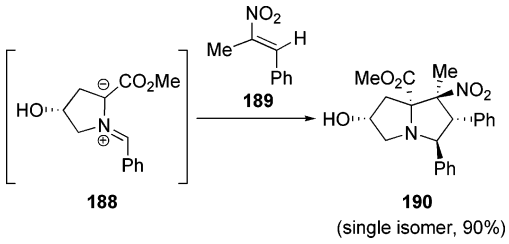


Figure 6. Model showing *endo* approach of **184** to explain the facial selectivity.

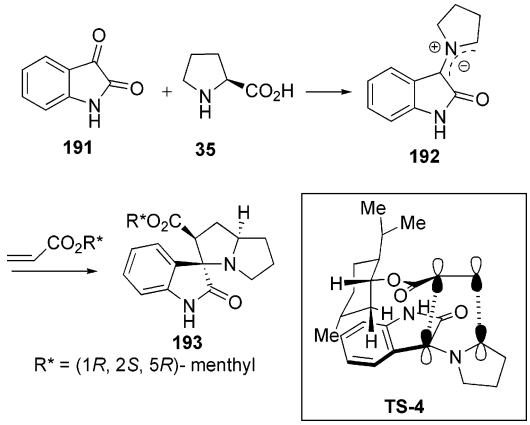
1:1 to 1.8:1); however, C_2-symmetric acrylamides **257c**−**e** reacted with complete diastereoselectivity in all cases, producing only one adduct **258** (Scheme 47).

The ability of the optically pure vinyl sulfoxides in controlling the π-facial selectivity led Ruano et al.[139] to evaluate the degree of diastereoselectivity in the cycloaddition of azomethine ylide **231** (M = Ag, room temperature) to optically pure vinyl sulfoxides **260**. The cycloaddition proceeded with complete regio- and *endo*- selectivity,

Scheme 31



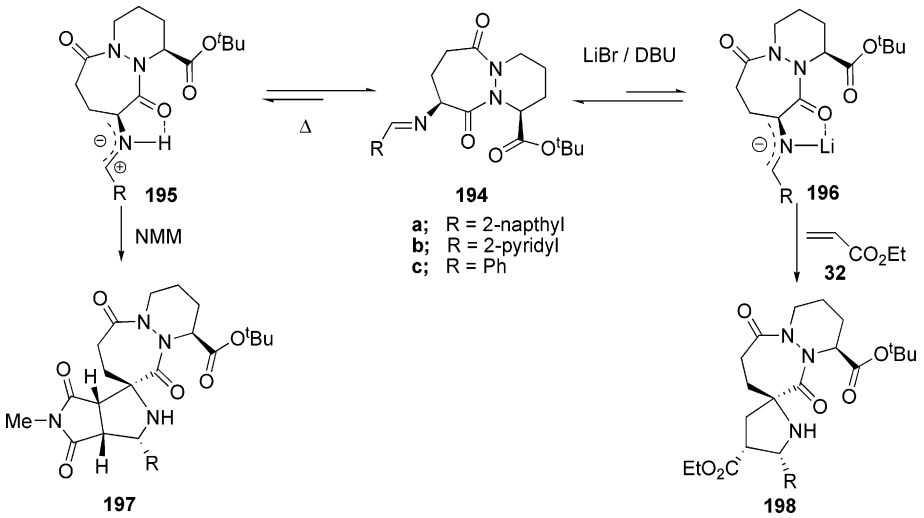
Scheme 32



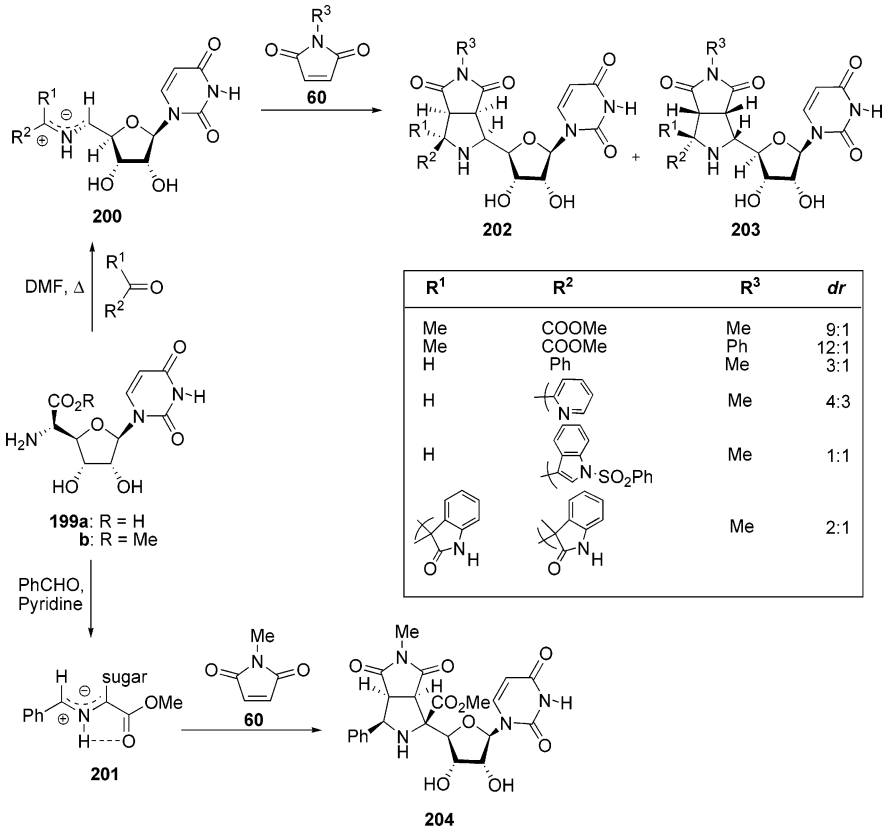
producing mixtures of the two diastereomers **261a** and **261a′**, resulting from the *anti*-dipole/*s-cis* dipolarophile and *syn*-dipoles/*s-trans*-dipolarophiles approaches, respectively. Under optimized reaction conditions, a maximum diastereoselectivity of 90:10 was obtained for **231a**. Use of α-alkyl substituents on the dipole **231b** did not influence either the reactivity or the diastereoselectivity. However, use of MeCN instead of THF as the reaction medium in the case of **231c** reversed the stereoselectivity completely (**261c**/**261c′** = 20/80). Surprisingly, the stereoselectivity of **261d**/**261d′** was found re-reversed (94:06) again in refluxing MeCN (Scheme 48).

This interesting dependence of stereoselectivity on relative solvent polarity between THF and MeCN was explained through a more dominant conformer **A** in polar MeCN than conformer **B** in THF where the sulfinyl oxygen in a *s-cis* arrangement minimized the electrostatic repulsion between the two oxygen atoms due to higher ability of THF to stabilize the metal (Figure 11). The same group further reported[140] an interesting observation of low diastereoselectivity (**263a**:**263a′**, maximum 55:45) between the cycloaddition of **231** (M = Ag, room temperature) and tolylsulfi-

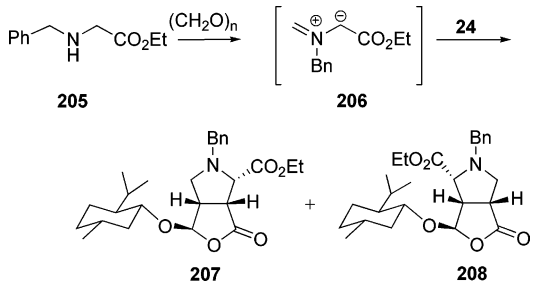
Scheme 33



Scheme 34

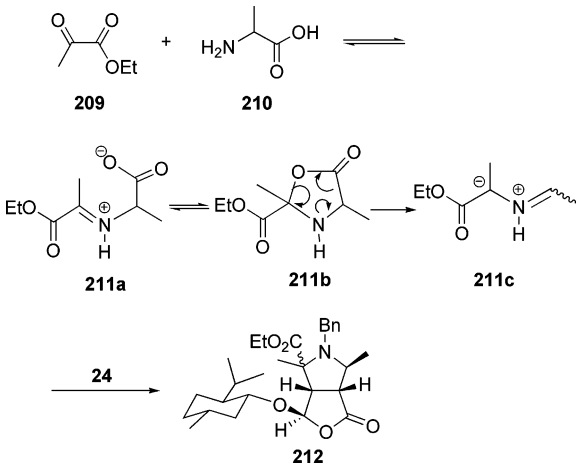


Scheme 35



nylcyclopentenone **262** in MeCN. THF solvent was not found to influence the ratio of **263a**:**263a′** (52:48) to any significant extent. However, the corresponding Li-metalated AMY **231** (M = Li, −78 °C, THF) produced **263a** exclusively (Scheme 49). These results were explained by assuming that the reaction occurs via a nucleophilic addition/ring-closure (NARC) mechanism in which the lithium acts as a tether between the reagent and the substrate (Figure 12). In the first step, the lithium of the dipole gets associated with the sulfinyl oxygen of the electrophile, evolving a 1,4-addition product through two transition states **TS-15** and **TS-16** which results from the approach of the nucleophile to each face of the sulfinylcyclopentenone. The strong steric interaction produced by the *p*-tolyl group on approach of the nucleophile to the upper face of the cyclopentenone (**TS-16**) explained that compounds **263a**−**263a′**, resulting from **TS-15**, were clearly favored. After formation of the C−C bond, the stereochemistry of the ring closure (second step of the

Scheme 36



Scheme 37

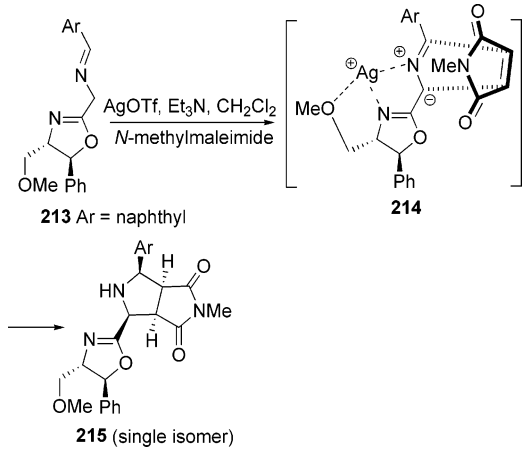


Table 11. Diastereoselectivity in the Cycloaddition of 216 to 60

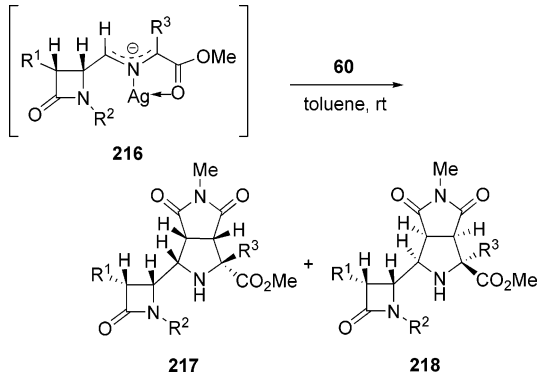
R^1	R^2	R^3	**217**:**218**
Et	PMP	Me	1:1
BnO	PMP	Me	1:3
Phth	PMP	Me	>30:1
BnO	PMP	H	1:7
Phth	PMP	H	24:1
t-Bu	PMP	Me	9:1
BnO	Allyl	Me	1.5:1
BnO	$CH_2CH(OMe)_2$	Me	2:1

process) was imposed by the rigidity of the system (only *cis* fusion is possible) and the stereochemistry of the C=N (*E* in all cases).

Cycloaddition of **231** (M = Li) is reported[141,142] to proceed in a highly regioselective and *exo*-diastereoselective fashion to chiral lactone **264**. Temperature was found to have a profound effect on the diastereoselectivity. Silver-metalated ylide **231** (M = Ag) gave poor diastereoselectivity in comparison to lithiated AMY **231** (Scheme 50). The preference for *exo* cycloadducts was rationalized by assuming chelation between the lithium cation and the *N*-benzoyl carbonyl group of the dipolarophile as shown in the possible transition state (**TS-17**).

Most recently, Bashiardes et al.[143] reported a highly regio- and stereoselective cycloaddition between **231** (M = Ag, room temperature) and various chiral carbohydrate-derived enones **266** to obtain a single enantiomeric compound **267** in almost all cases (Scheme 51). It was suggested that the

Scheme 38



newly formed pyrrolidine unit is created by exclusive addition of the dipole from the face opposite that of the anomeric aglycone ethoxide group. In case of the ylide **231** (R^2 = H), the conformation of the approaching ylide is such that the carboxyl group is opposite the carbohydrate moiety (Figure 13). Thus, in compound **267a** the resulting *syn*-ring junction is of *endo* configuration and the carboxyl group is *anti* with respect to the α-ethoxy group. In a similar manner, with other ylides **231** (R^2 = *t*-Bu and Ph) the bulkier groups are oriented farthest from the carbohydrate moiety to give **267b,c**.

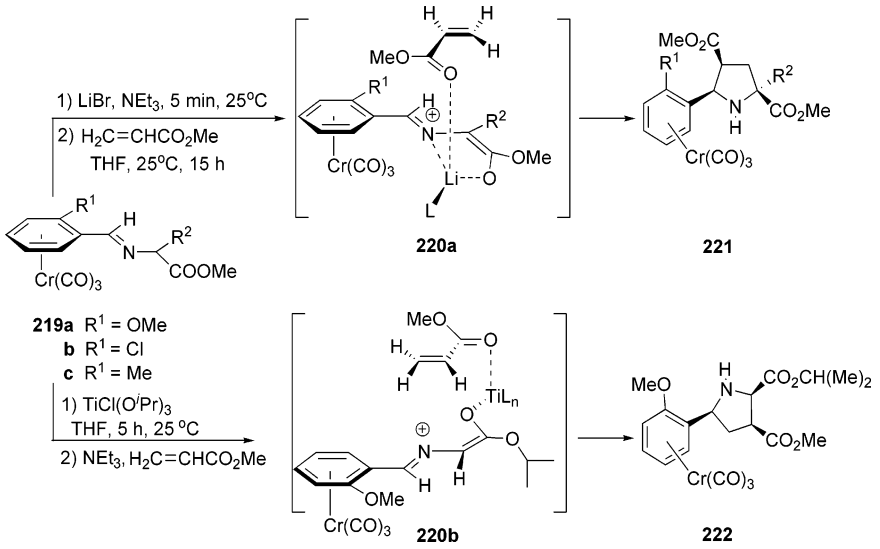
In addition to the studies concerning cycloaddition of **231** to various chiral olefinic dipolarophiles, highly diastereoselective cycloaddition has also been reported[144,145] between **231** (M = Li, −78 °C) and enantiopure sulfinimines **268**, known to display facial selectivity. Cycloaddition of **231a,b** on **268a** gave the corresponding *N*-sulfinyl imidazolidines **269** and **270** (dr = 95:5) in moderate yield (∼55%). More reactive sulfinimines **268b** was found to react with **231c,d**, producing the corresponding imidazolidines in excellent yields (∼80%) and practically as a single isomer (Scheme 52). The stereochemical outcome of this cycloaddition reaction was explained in terms of the predominant *endo* approach of the ylide (relative to Ar group) to the less hindered *β*-face of the sulfinimines.

Unlike most other reports where *endo* selectivity predominated in the cycloaddition of the ylide of type **231**, Barluenga et al.[146] reported exceptionally high *exo* diastereoselectivity (**272** > 9:1) between cycloaddition of **231** (M = Li) and chiral alkoxy alkenylcarbene complexes of chromium **271** derived from (−)-8-phenylmenthol (Scheme 53). However, considering the nature of the highly *π*-deficient alkenyl carbene complex (**271**), a concerted [3+2]-cycloaddition has been ruled out; instead, a stepwise Michael addition of **231** with **271** as shown in Scheme 54 was suggested.

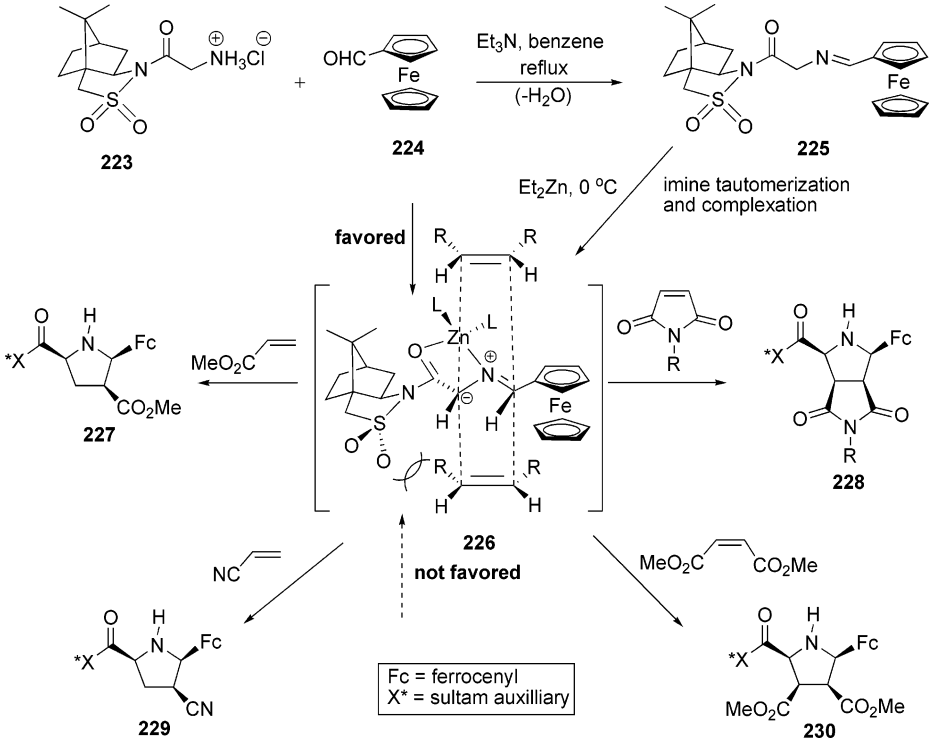
5. Intramolecular Asymmetric Cycloaddition of AMY

Intermolecular cycloaddition of an azomethine ylide with a dipolarophile leads to the formation of one new ring only. However, the intramolecular version of this reaction is amenable to construction of inherently more complex products than intermolecular cycloadditions. The greater steric constraint associated with these cycloadditions often affords high diastereofacial discrimination, exhibiting very high stereoselectivity. On the basis of these facts, there are some very interesting synthetic designs which involve highly diastereofacial intramolecular cycloadditions of chiral azo-

Scheme 39



Scheme 40



methine ylides tethered to an appropriate dipolarophile. Although this subject was reviewed recently[21] in general, examples pertaining to intramolecular asymmetric cycloadditions are not discussed in detail. Therefore, considering the general theme of the subject, we illustrate this aspect here again in detail. The first example related to an asymmetric intramolecular cycloaddition of the chiral nonstabilized azomethine ylide may be traced to cycloaddition of the dipole **278**, generated by thermolysis of **277a**, which produced diastereomerically pure cycloadduct **281**, out of four possible isomers, with all *syn* stereochemistry. The extremely high diastereofacial selectivity for cycloaddition of **278** was in best accord with the *anti*-azomethine ylide as the reactive conformer in which the bulky benzyloxymethyl group took the most stable six-membered chairlike arrangements to give all *syn*-**281**. This strategy was utilized effectively for the synthesis of acromelic acid-A (**282**),[147] (−)-kainic acid (**283**),[148] (−)-mesembrine (**284**),[149] and (−)-dihydroxyheliotridane (**285**)[150] (Scheme 55). Furthermore, these groups noted that diastereoselectivity in such cycloadditions depends on the length of the tether between the dipole and the dipolarophile. While cycloaddition of **278** produced **281** exclusively, reaction of **279** gave **280** with reversal of the stereochemistry at the 2,3-ring junction in a 3:1 diastereomeric ratio.

Asymmetric entry to the 3,8-diazabicyclo[3.2.1]octane nucleus **288** of naphthyridinomycin was reported[151] by the stereospecific intramolecular cycloaddition of the chiral nonstabilized azomethine ylide **287** equipped with the tethered dipolarophile with an acetal linkage (Scheme 56). In this cycloaddition, *si*-diastereofacial preference is forced by the steric repulsion between the aromatic ring and one of the amide carbonyl in the *endo* transition state **287**. Furthermore, this group also reported[152] a novel strategy of control-

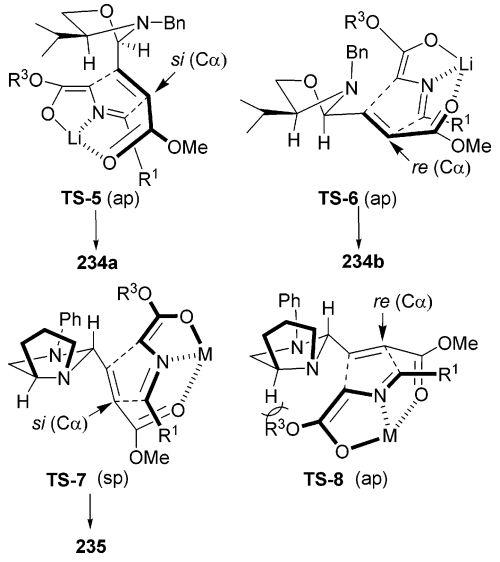
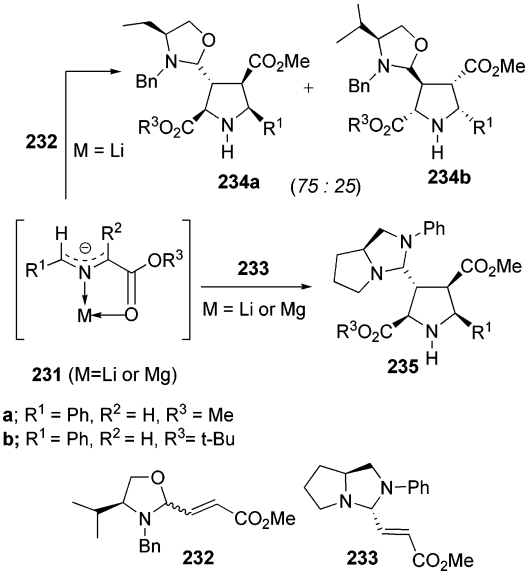
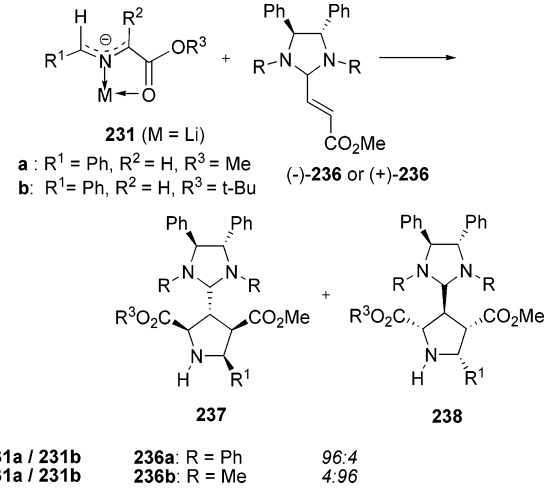


Figure 7. Transition-state models to explain the stereoselective formation of **234a** and **235**.

Scheme 41



Scheme 42



ling the diastereofacial selectivity in the intramolecular dipolar cycloaddition of the azomethine ylides generated from **289**−**291** by varying the structure of the silicon-based

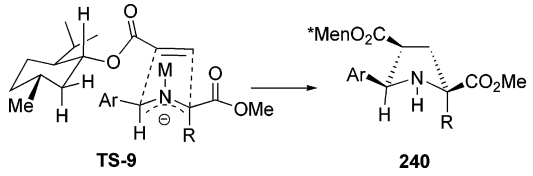
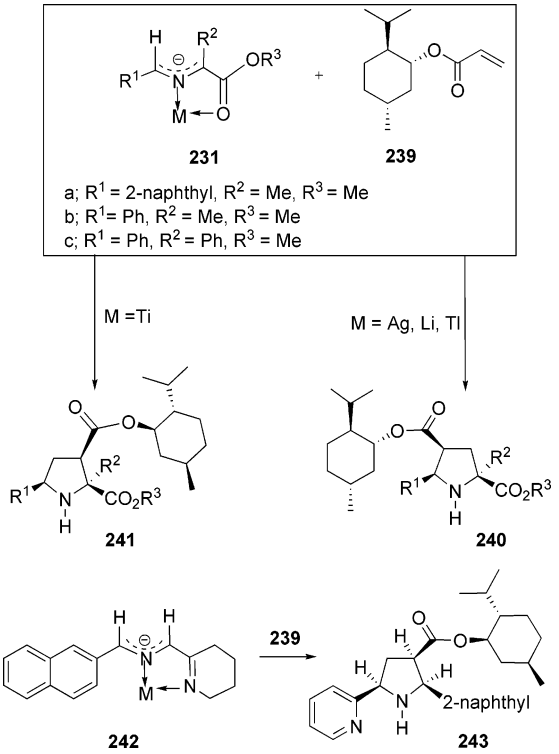


Figure 8. Transition-state model for the regio- and stereoselective formation of **240**.

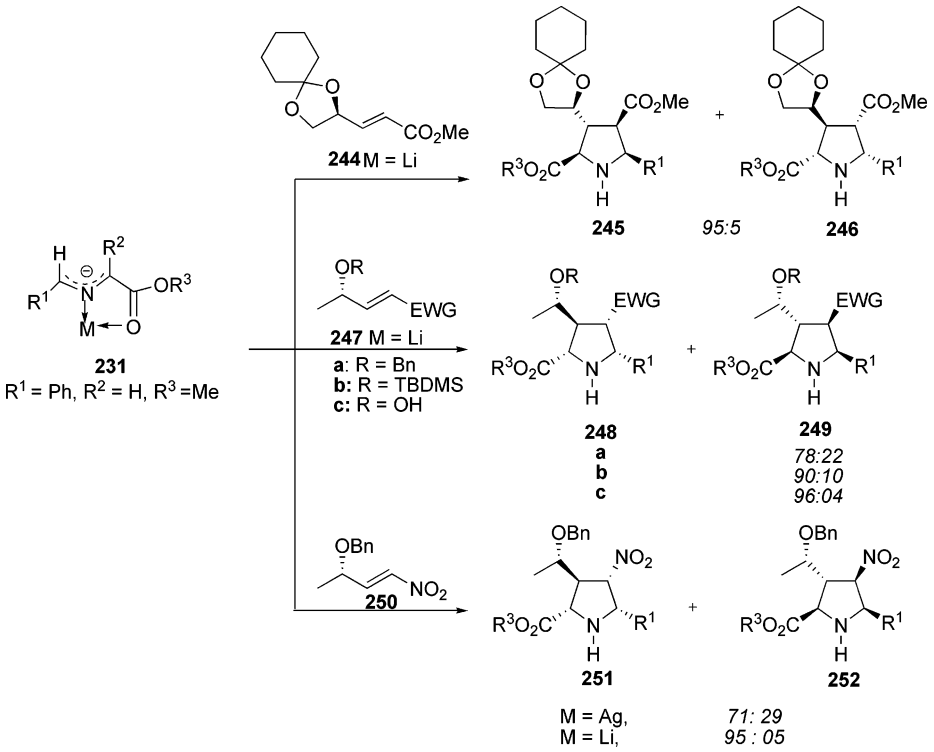
Scheme 43



tether. A correlation was found between the lengths of the tether dipolarophile conjugate (TDC) and the observed sense of diastereocontrol. For example, the azomethine ylides incorporating longer TDC such as **290a,b** favored *endo-si* attack (**293**), while shorter TDC **291** led to the reversal of selectivity producing *endo-re* product **294** (Scheme 57). This group also recently reported[153] intramolecular cycloaddition of the chiral α-amino azomethine ylide **296**, derived from **295** by the catalytic reaction of AgOAc and Ph_3P, to produce highly functionalized pyrrolidine derivatives **297a** and **297b** in a 1.3:1 ratio (Scheme 58). The minor adduct **297b** was believed to be formed by either cycloaddition of isomerized **296** or epimerization of **297a**. Formation of imidazolidine byproduct **298** was explained by the competitive intermolecular cycloaddition of the azomethine ylide to the imine double bond.

Although most of the above-discussed approaches for the asymmetric variants of the intramolecular cycloaddition of aziridine-derived azomethine ylides utilized a localized chiral center contained within the olefin tether to invoke a degree of asymmetry, Dogan et al.[154] used an alternative strategy of attaching the chiral auxiliary onto one of the carbon atoms of the aziridine framework itself to influence the stereochemical outcome of the cycloaddition onto an achiral alkene. For example, intramolecular cycloaddition of camphorsultam-derived azomethine ylide **300**, generated by heating *cis*- as well as *trans*-aziridines **299**, furnished fused bicycles **301** (Scheme 59), albeit in relatively poor diastereoselectivity (de

Scheme 44



= 50%). Complete diastereoselectivity was also reported[155] in the formation of **306** by the intramolecular cycloaddition of ylide **304**. The observed stereochemistry of **306** was explained by involving a preferred *Z*-configuration of benzylidene azomethine ylide **304** producing *endo*-phenyl adduct selectively instead of *exo*-phenyl adduct **305** via an alternative *E*-ylide **303**, presumably due to steric congestion (Scheme 60).

Kanemasa et al.[156] found excellent stereoselectivity in the intramolecular cycloaddition of an *in-situ*-generated azomethine ylide **309** by reaction of methyl 2-phenyl-4-thiazolidine-carboxylate (**307**) and enones **308a,b**, producing the corresponding cycloadducts **310a,b** (Scheme 61). Similar diastereoselectivity was also recorded by Jones et al.[157] in

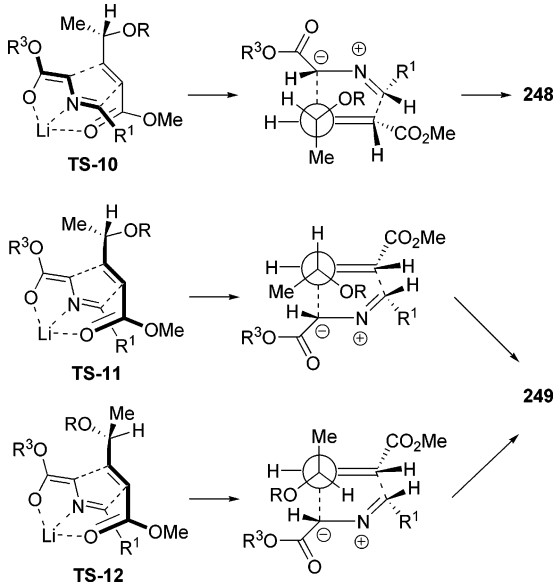
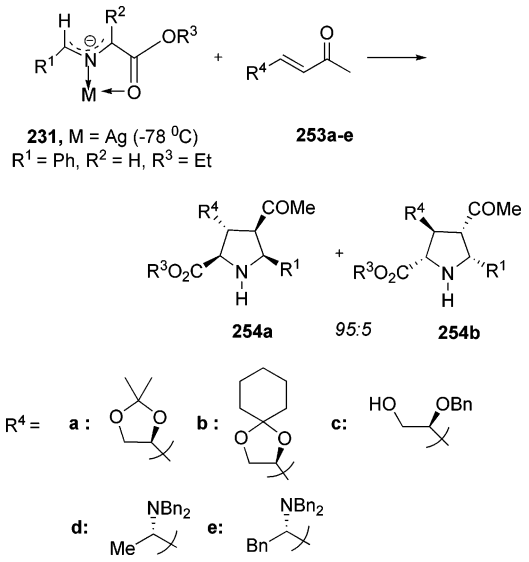


Figure 9. Transition-state models depicting the direction of attack of the dipole toward the dipolarophile.

Scheme 45



an intramolecular cycloaddition of **313**, generated by reaction of **311** and **312a** (X = O) in the presence of DBU as a base, which produced **314** as the only product (yield 40%; Scheme 62). However, this group also noted that AMY of type **313**,

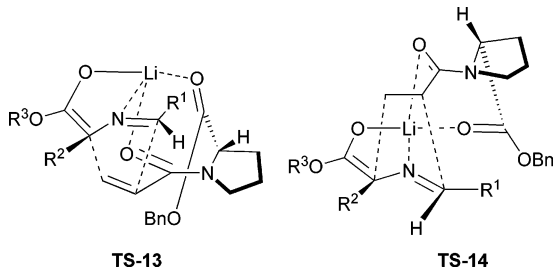
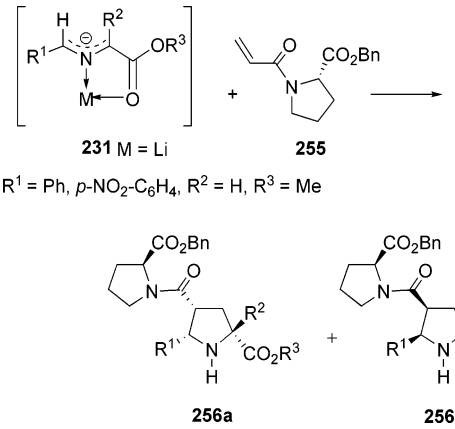
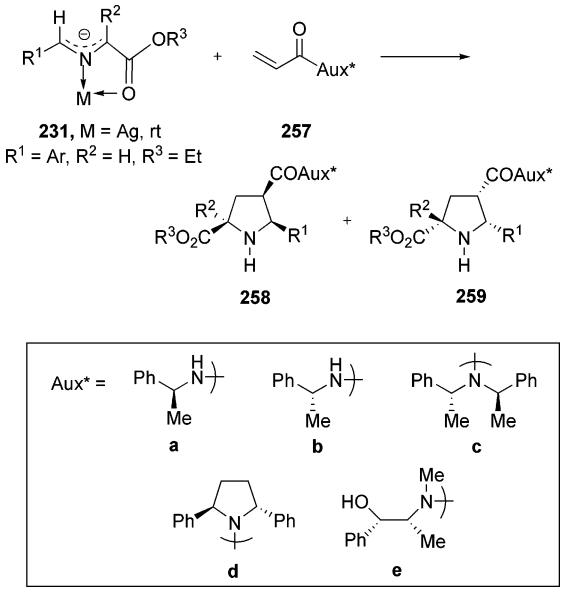


Figure 10. Transition-state models to explain the *endo*/*exo* as well as face selectivity for formation of **236**.

Scheme 46



Scheme 47



derived from reaction of **311** and β-haloketone **312b** (X = $-CH_2$), failed to undergo cycloaddition reaction.[158] The stereochemical results in these cycloadditions were explained by considering the identical transition-state model as described earlier[110,111] for the intermolecular cycloadditions.

Harwood et al.[159−162] also showed excellent diastereoselectivity in an intramolecular cycloaddition of in-situ-generated azomethine ylide **317**, produced by reaction of **315** and an aldehyde **316** (Scheme 63), producing **318** as the only product. On the basis of semiempirical and ab initio quantum mechanical calculations it was suggested that the most favorable transition state involved an *anti* addition of the dipolarophile to the *E*-ylide ($E_{act} \approx 12$ kcal/mol). This group also reported recently[163] the generation of unsymmetrical ketone-derived chiral stabilized azomethine ylides and their intra- as well as intermolecular cycloadditions to synthesize both enantiomerically pure bicyclic proline derivatives and β-hydroxy-α-amino acids, respectively. Excellent diastereoselectivity was also reported[164] from cycloaddition of **321** (Scheme 64), producing **322** as the only product.

Stereospecific cycloaddition leading to formation of a single diastereomeric octahydropyrrolo[3,4]pyrrole derivative **326** is reported[165] by intramolecular cycloaddition of an azomethine ylide **325**, generated by reaction of the N-substituted glycines **324**, to chiral perhydro-1,3-benzoxazines

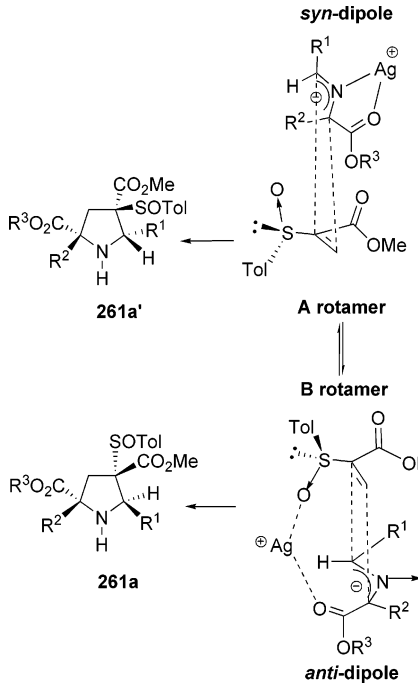
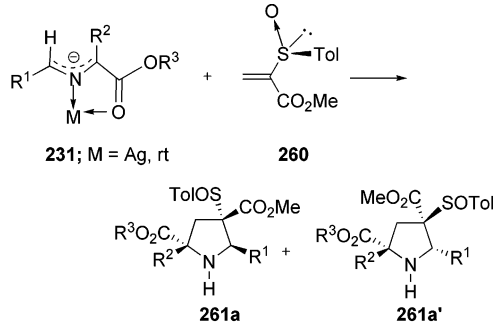
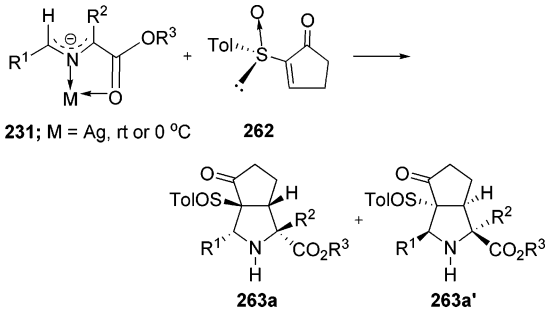


Figure 11. Models to explain the dependence of diastereoselectivity of **261** on solvent polarity.

Scheme 48



Scheme 49



323 (Scheme 65). The chemical yields of the cycloadducts were found to be dependent on the reaction temperature and the presence or absence of a base.

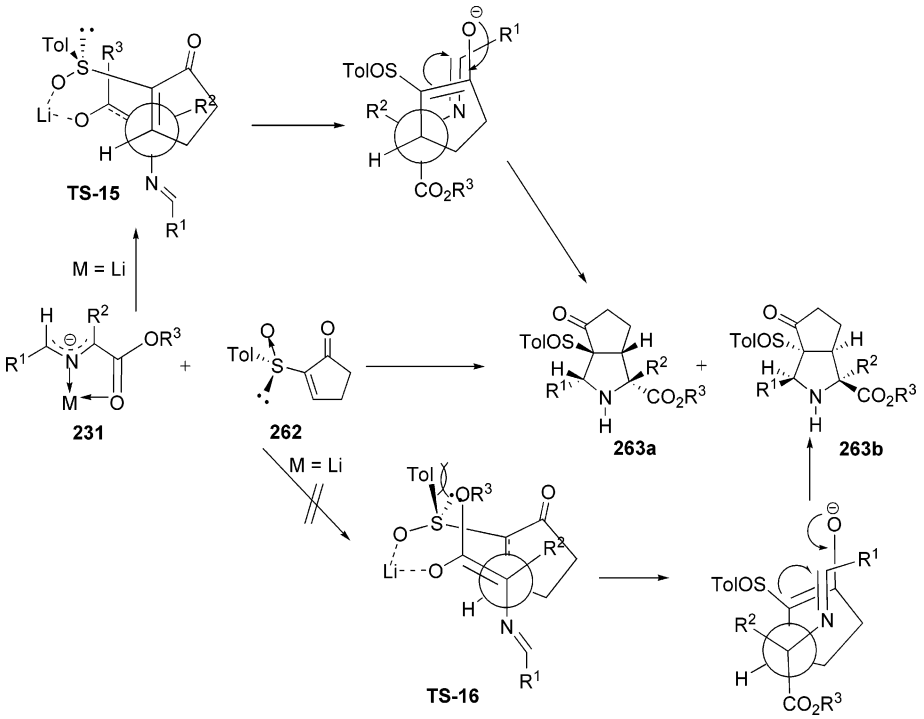
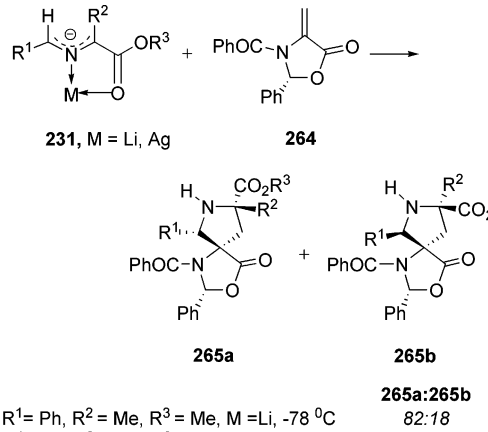
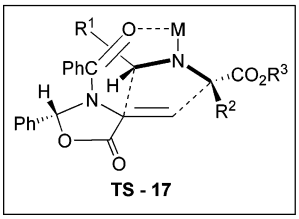


Figure 12. NARC mechanism showing stereoselectivity for the formation of **263**.

Scheme 50



	265a:265b
231 a; R^1= Ph, R^2 = Me, R^3 = Me, M =Li, -78 ^{0}C	*82:18*
b; R^1= Ph, R^2 = Me, R^3 = Me, M =Ag, rt	*58:42*
c; R^1= Ph, R^2 = CH_2Pr-i, R^3 = Me, M = Li, -20 ^{0}C	*94:06*
d; R^1= Ph, R^2 = Ph, R^3 = Me, M = Li, 0 ^{0}C	*93:07*



An enantioselective synthetic route was developed[166] for construction of bridged pyrrolizidine core structure **330** of asparagamine-A[167] by intramolecular cycloaddition of an azomethine ylide **329**, generated by treating vinylogous amide **328** with triflic anhydride followed by desilylation with tetrabutylammonium triphenyldifluorosilicate. The cycloadduct **330 (**Scheme 66) was obtained in this reaction as a mixture of *E* and *Z* isomers (ratio 6:1).

Although most of the above examples pertaining to intramolecular cycloaddition reactions involved chiral ylides in the cycloaddition processes, a lone report in which the

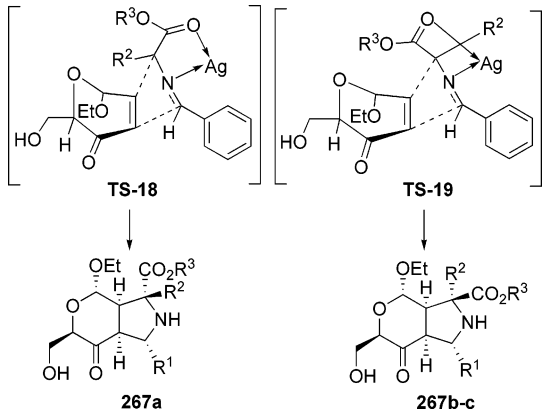
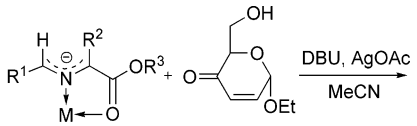
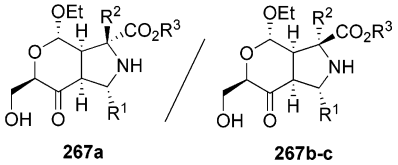


Figure 13. Transition-state model depicting the facial approach of the dipole.

Scheme 51

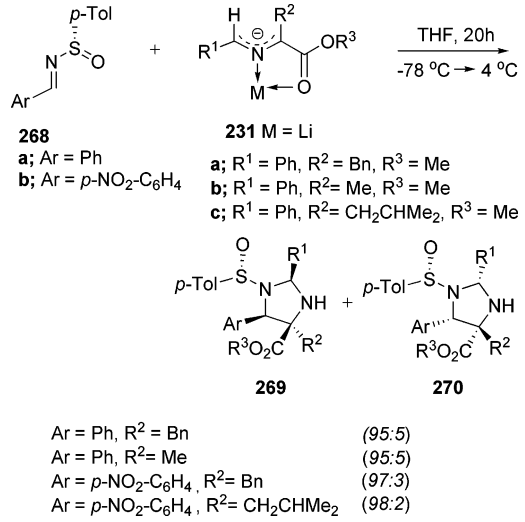


231a; R^1= Ph, R^2 = H, R^3 = Me,
b; R^1= Ph, R^2 = t-Bu, R^3 = Me,
c; R^1= Ph, R^2 = Ph, R^3 = Me

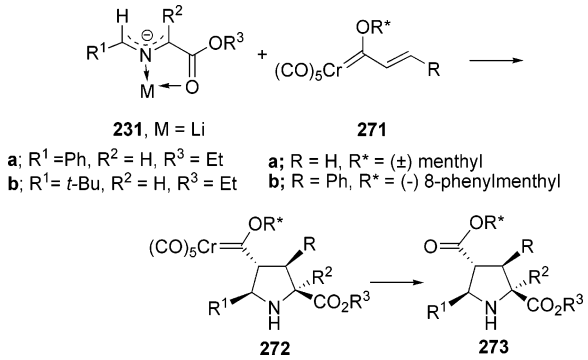


chiral auxiliary was remotely placed on the dipolarophile unit was also reported. The Abbot research group[168] synthesized analogues of antibacterial agent Cethromycin[169] by carrying out the intramolecular cycloaddition of the azomethine ylide **331** for construction of a pyrrolidine ring

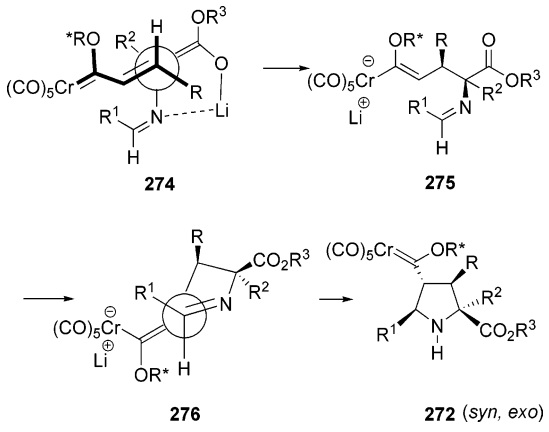
Scheme 52



Scheme 53



Scheme 54



system at C11 and C12 of the macrolide core. However, formation of the two nonseparable isomers **332** and **333** in a ratio of 10:1 restricted its merit to (Scheme 67) a great extent.

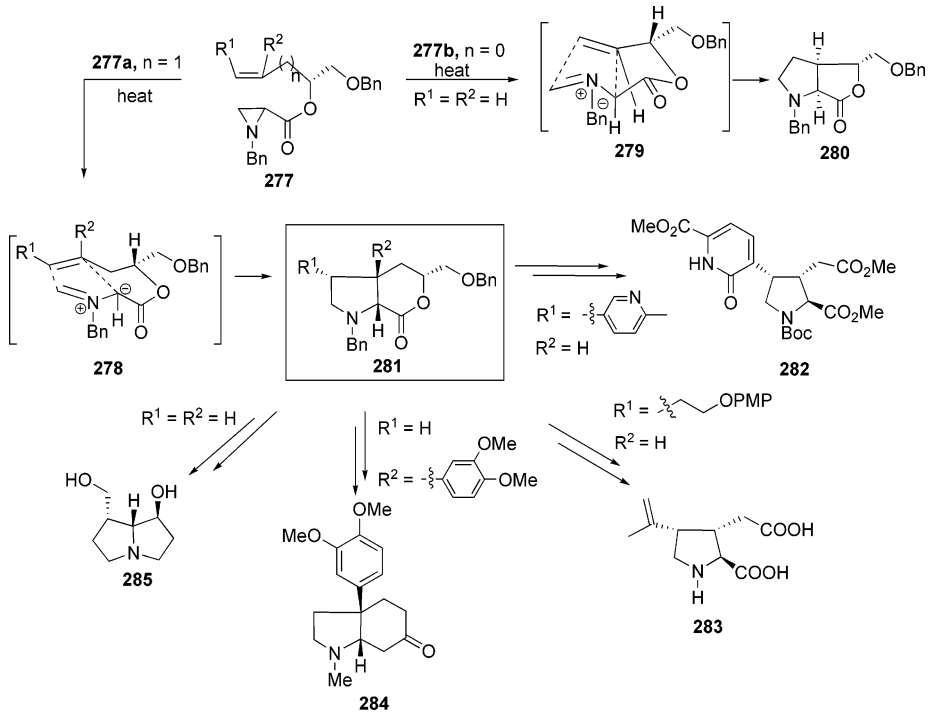
6. Asymmetric 1,3-Dipolar Cycloaddition of AMY Using Chiral Catalyst

Although asymmetric 1,3-dipolar cycloaddition using either chiral AMY or chiral dipolarophiles has been studied exhaustively, use of chiral catalysts for optical induction in such types of dipolar cycloadditions is still in the developmental stage.[170,171] Grigg et al.[172,173] were the first one to attempt the use of chiral Mn(II) complex of ephedrine derivative **335a** in a stoichiometric amount as catalyst for studying the enantioselective 1,3-dipolar cycloaddition reaction of the N-metalated AMY **231** with methyl acrylates (metal salt to ligand ratio 1:4) (Scheme 68). The corresponding pyrrolidines **334** were obtained in 64% yield and 60% ee. A reduced amount of ligand **335a** lowered the ee, while an increased amount slowed the reaction dramatically. Using a molar equivalent of the anhydrous $CoCl_2$ in the presence of 2 mol of **335a** gave cycloadduct **334** (45% yield, 80% ee) accompanied by a substantial amount of imine hydrolysis product. The ligand **335a** was found to be a less efficient ligand for Co(II) salt than **335b** (80% yield, 80% ee). The role of various solvents (CH_2Cl_2, MeCN, PhCN, THF) was found to have a negligible effect on the rate of the reaction and on the ee of the product. However, when methyl acrylate was used as the solvent, the maximum ee of 96% was recorded. Use of Ag(I) salt has also been found to catalyze the reaction; however, the best ee obtained was only 70%. A working transition-state model **336**, in which *cis* arrangement of the methyl and phenyl groups of the ligand led to pseudoequatorial conformation of the phenyl group and effective blockage of one face of the dipole, was proposed to explain the chiral induction.

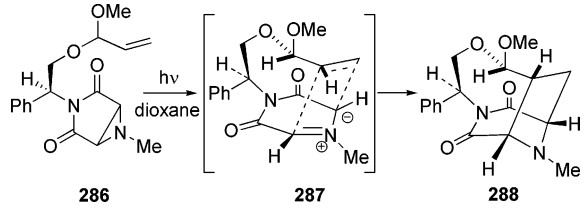
Karlsson et al.[174] later described the use of a chiral Lewis acid **337** and **338** for catalyzing asymmetric cycloaddition between nonstabilized AMY **18a** and a variety of α,β-unsaturated dipolarophiles **26** which proceeded with low enantioselectivity (Scheme 69). The cycloaddition reaction of **26a** using 1 equiv of Cu(II)−PYBOX **338** as the catalyst furnished (3*S*,4*R*)-**27a** in just 8% ee. However, the same reaction with oxazolidinone-derived dipolarophile **26b** in the presence of Cu(II)−isopropylidinebis(4-phenyloxazoline) [Ph-BOX] **337a** as the catalyst gave **27b** in 2% ee. Further study using **26c** as the dipolarophile and **337a** and **337b** as the catalysts also gave poor (20−22% ee) enantiomeric ratios.

Zhang et al.[175] reported a highly enantioselective Ag(I)-catalyzed [3+2]-cycloaddition of **231** (M = Ag) with dimethyl maleate in the presence of various chiral phosphine ligands (**340**−**346**). The cycloaddition reaction in toluene using 3 mol % AgOAc, 3.3 mol % ligand, and 10 mol % *i*-Pr_2NEt at room temperature was found to be the ideal reaction conditions (Scheme 70). With the exception of BINAP (**340**), all other ligands (**341**−**345**) gave only *endo* diastereomers. The BINAP and Me-DuPhos (**342**) ligands gave poor enantioselectivity (13% ee with **340** and 23% ee with **342**), and poor diastereoselectivity was observed in the case of BINAP (*endo*/*exo* = 3:1). The PennPhos (**343**) and BIOP (**344**) ligands also provided poor ee (27% ee with **343** and 13% ee with **344**). Trost's ligand (59% ee) and bis-ferrocenyl amide phosphine ligands (FAP **345a** 76% ee and with **345b** 97% ee) gave considerably high ee. Using ligand **345b** a number of ylides of the type **231** were cyclized with dimethyl maleimide in good yields and high enantioselectivities (up to 97% ee). The details are presented in Table 12. By studying the cycloaddition with a variety of dipolarophiles, it was established that only *endo* products were obtained in each case. The high enantioselectivity observed was explained by considering the effective blocking of one of the enantiotopic faces of the metal bound dipole **231** with the chiral ligand due to steric interactions. The improved enantioselectivity observed with xylyl-FAP (**345b**) as compared to FAP (**345a**) explained this hypothesis. This group also achieved,[176] recently, up to 98/2 *exo*/*endo* selectivity and up to 98% enantiomeric excess in the

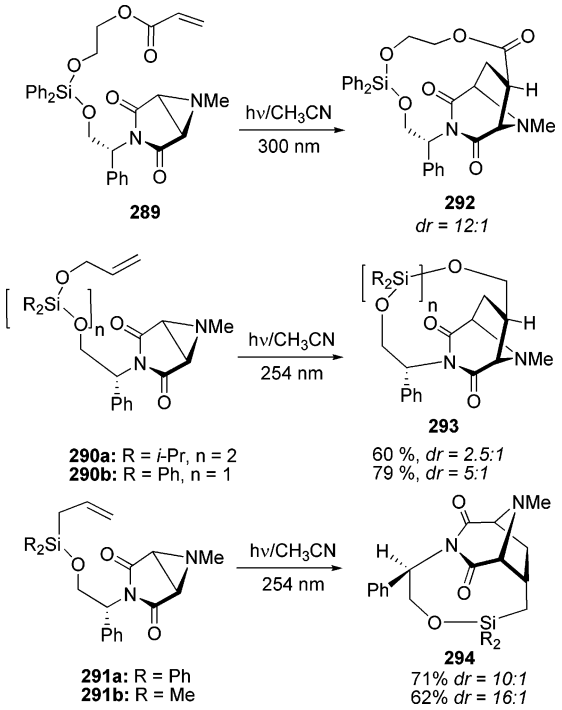
Scheme 55



Scheme 56

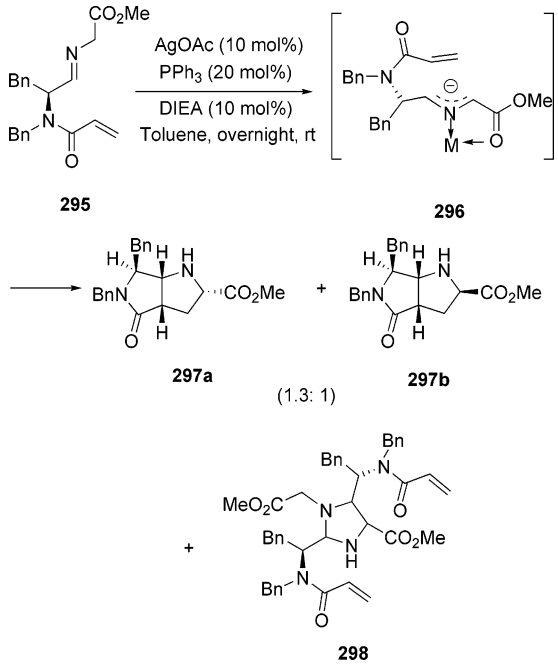


Scheme 57



cycloaddition of **231** with various acrylates using a Cu(I) complex of **346** ligand.

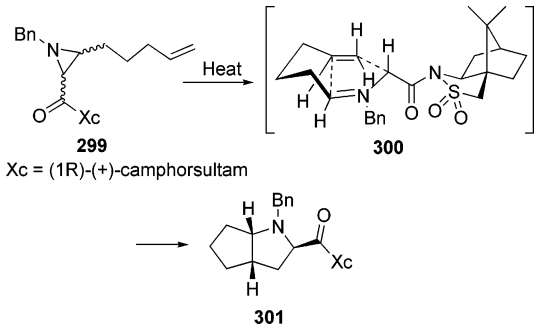
Scheme 58



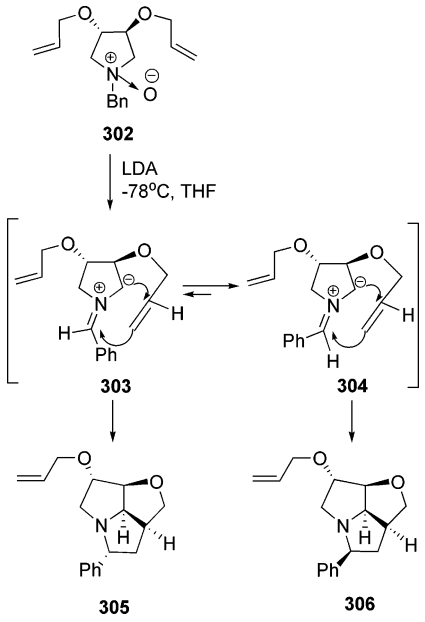
Recently, Jørgensen et al.[177] described their results on the catalytic asymmetric dipolar cycloaddition reaction of ylide **231** [(M = Cu(II) and zinc(II)] in combination with the chiral bisoxazoline(BOX) ligands **337a,b** and **349** (Scheme 71). Out of these three ligands screened with Cu(II) and Zn(II) metal salts, the Zn(II)−*t*-Bu-BOX complex (Zn(II)−**337b**,-10 mol %) gave good enantiomeric excess. The results with various substituents on dipole, dipolarophiles, and reaction conditions are summarized in Table 13. Reaction at low temperature (−20 °C) slightly improved the ee.

More recently, Schreiber et al.[178] reported catalytic asymmetric dipolar cycloaddition of **231** (M = Ag) with *tert*-butyl acrylate in the presence of six different chiral phosphine ligands **341** and **351**−**355**, available in both enantiomeric

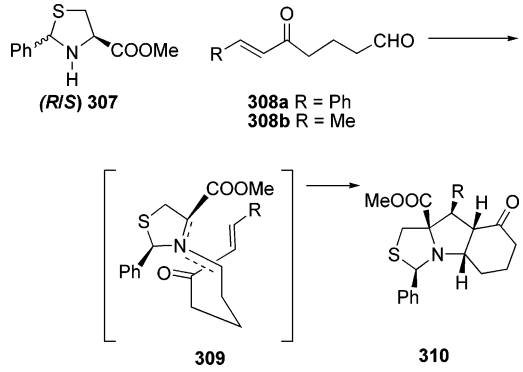
Scheme 59



Scheme 60

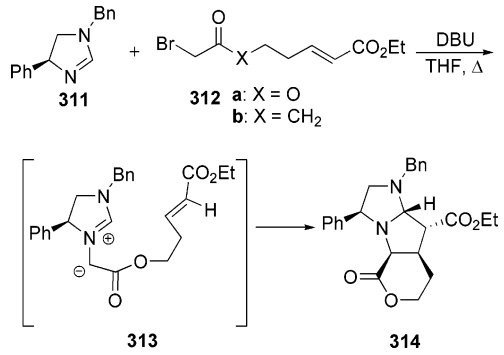


Scheme 61

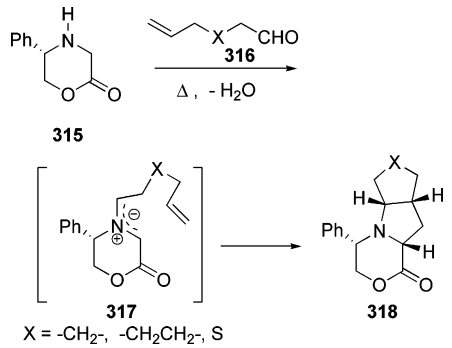


forms (Scheme 72). With 3 mol % catalyst loading, cycloaddition of azomethine ylide **231** using ligands **341** and **351** while ligands **352**−**355** gave low conversion at 4 °C, while ligands **352**−**355** showed excellent reactivity. With the exception of ligand **351**, the diastereoselectivity was in general high. The P,N-ligand QUINAP **353** showed an excellent level of both diastereo- and enantioselectivity even at a reduced catalyst loading of 1%. The results of the cycloaddition with various ylides **231** and with 3 mol % Ag(I) acetate/QUINAP-based catalyst showed excellent diastereoselectivity (>20:1) and enantioselectivity (94−96%) (Table 14) regardless of the electronic property of the aromatic ring, although specifically hindered ylide (entry 5) resulted in slightly lower enantioselectivity (89%, ee).

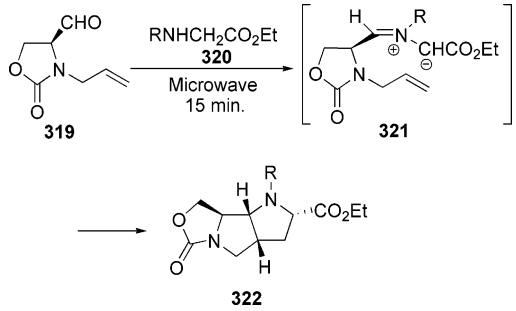
Scheme 62



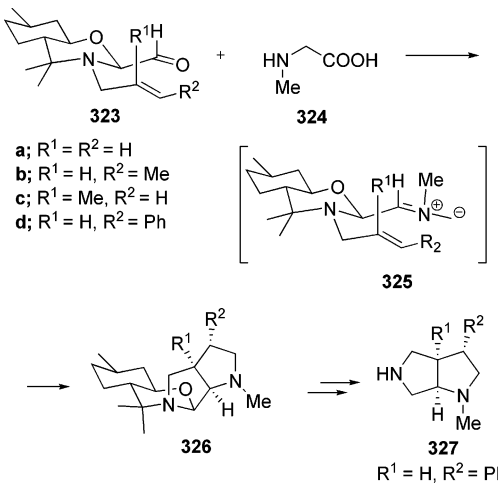
Scheme 63



Scheme 64



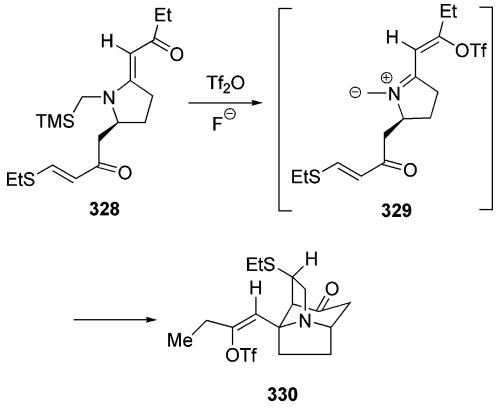
Scheme 65



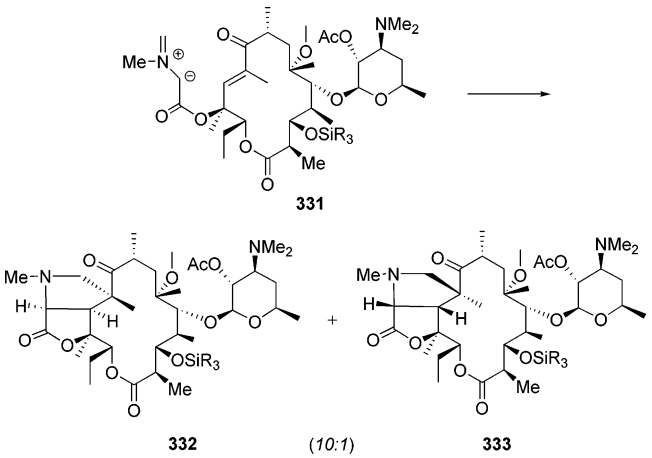
Intramolecular cycloaddition of the azomethine ylides using Ag(I) complexes of QUINAP (1−3 mol %) was also recently reported,[179] virtually with complete diastereocontrol and enantiomeric excess of up to 99%.

Although most of the cycloadditions of AMY catalyzed by chiral metal complexes show *endo* selectivity, Komatsu

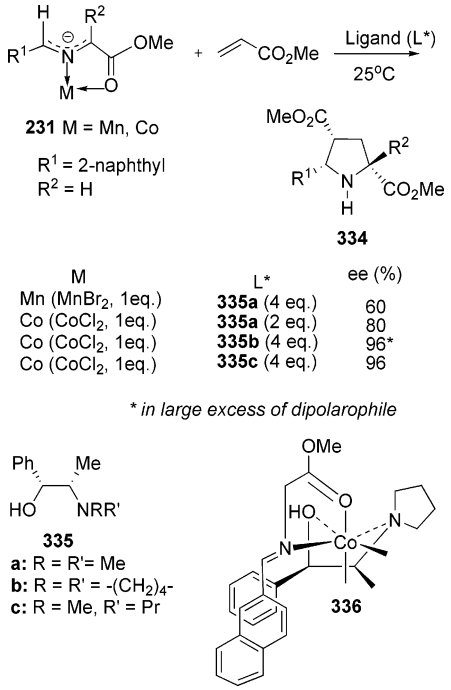
Scheme 66



Scheme 67

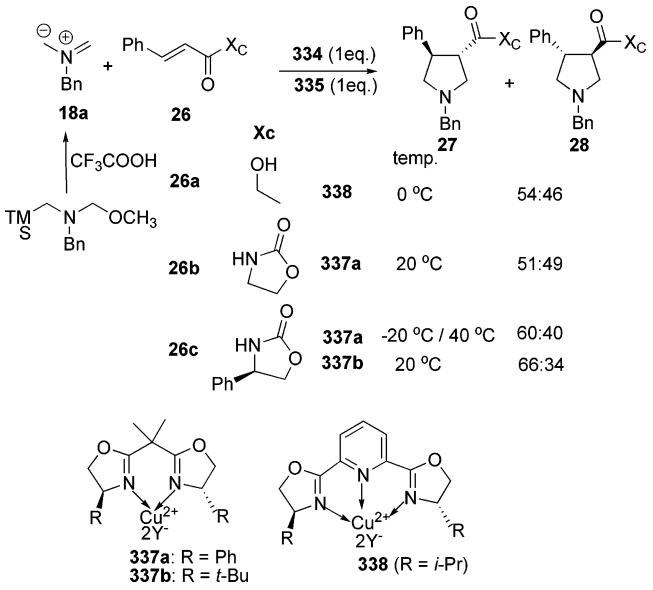


Scheme 68

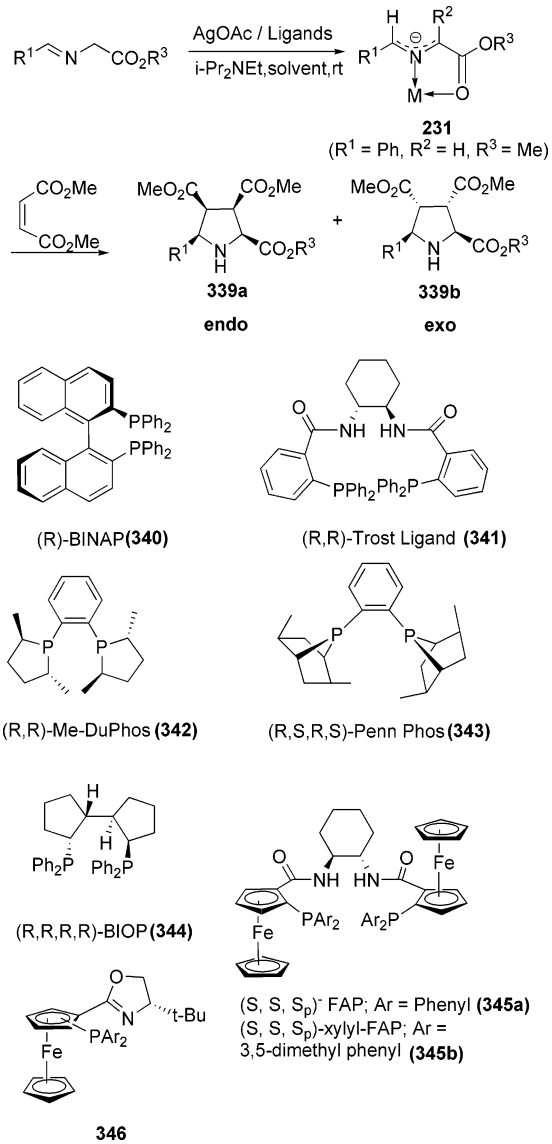


et al.[180] reported *exo*-selective cycloaddition reaction between various N-metalated azomethine ylides **231** and N-phenylphthalimides (**60a**) catalyzed by $Cu(OTf)_2$ in combination with the chiral phosphine ligands (**340** and **358**−**363**, Scheme 73). Use of 20 mol % $Cu(OTf)_2$ and 10 mol % BINAP **340** gave best *exo*- and enantioselectivity (*exo*/*endo* = 87/13; ee

Scheme 69



Scheme 70



of *exo* adduct = 34%). Both *exo* addition and enantioselectivities were improved at low temperature employing BINAP

Scheme 71

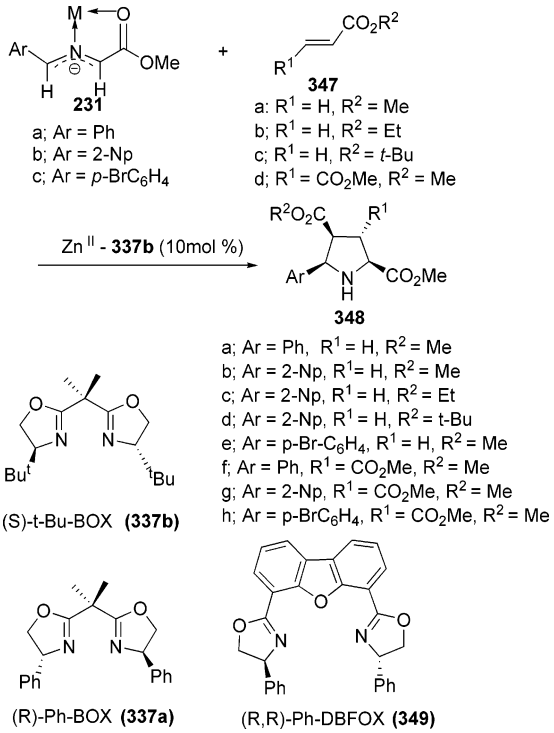


Table 12. Enantioselectivity in the Cycloaddition of 231 Using Ligand 345b

			endo product	
entry	R	time (h)	% yield	% ee
1	Ph	7	87	87
2	*p*-tolyl	7	93	88
3	*p*-anisolyl	7	98	92
4	4-chlorophenyl	7	96	92
5	4-fluorophenyl	7	96	90
6	4-cyanophenyl	7	90	96
7	2-chlorophenyl	7	96	86
8	*o*-tolyl	7	97	90
9	1-naphthyl	7	73	85
10	2-naphthyl	14	98	97
11	3-pyridyl	7	98	84
12	*i*-Pr	48	82	70
13	Cyclohexyl	48	82	81

Table 13. Enantioselectivity in the Cycloaddition of 231 in the Presence of 337b

entry	AMY (**213**)	dipolarophile	product (yield %)	ee (%)
1	231a	347a	**348a** (>95)	78
2[a]	231a	347a	**348a** (80)	88
2	231b	347a	**348b** (93)	78
4[a]	231b	347a	**348b** (84)	91
5[a,b]	231b	347a	**348b** (86)	87
6	231b	347a	**348c** (76)	68
7	231b	347b	**348d** (12)	<5
8	231c	347a	**348e** (89)	61
9[a]	231c	347a	**348e** (89)	94
10[a]	231a	347d	**348f** (78)	76
11	231b	347d	**348g** (84)	90
12	231c	347d	**348h** (87)	68

[a] Reaction temperature = 20 °C. [b] Reaction in the absence of solvent.

and BINAP derivatives (2.2 mol %) and $Cu(OTf)_2$ (2.0 mol %) (Scheme 72). The highest *exo* selectivity (*exo*/*endo* = 99/1) was reported using BINAP−Cu(II) complex. In the case of SEGPHOS (**363**), the reaction afforded the highest ee of the *exo* adduct (72% ee). Reaction with several other

Scheme 72

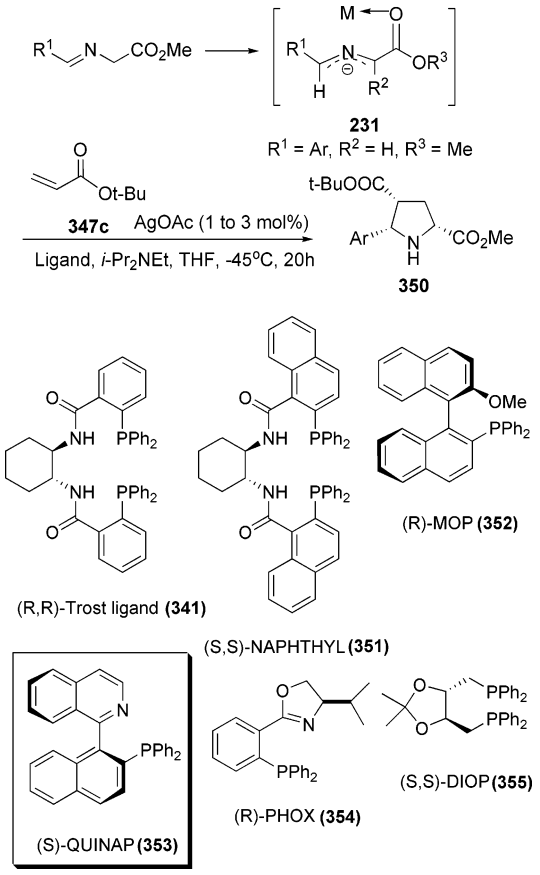


Table 14. Enantioselectivity *i*n the Formation of 350 Using Ligand 353

entry	Ar	pyrrolidine	yield (%)	ee (%)
1	4-methoxyphenyl	350a	93	95
2	4-bromophenyl	350b	89	95
3	4-cyanophenyl	350c	92	96
4	2-naphthyl	350d	89	94
5	2-tolyl	350e	95	89

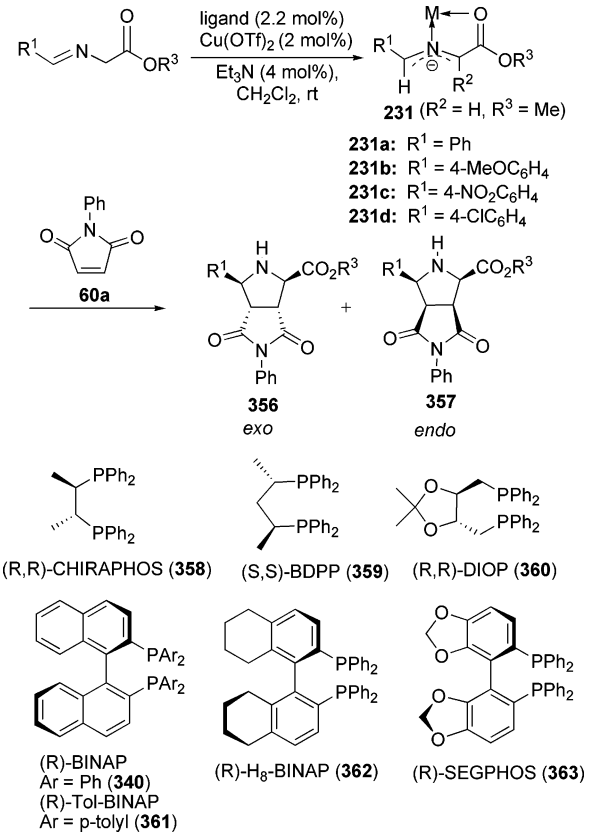
dipolarophiles gave similar results. The authors gave a plausible mechanism, as shown in Scheme 74, for the cycloaddition reaction in which coordinated chiral phosphine−Cu(II) complexes are shown to participate. The *exo* and *endo* selectivity was explained with the help of transition-state models **TS-20** and **TS-21** (Figure 14).

More recently,[181,182] cycloaddition of extremely electron-poor azomethine ylide **369**, generated by reaction of aziridine **367** with the chiral Lewis acid **368** at 45 °C in CH_2Cl_2, onto norbornene (**370**) was reported to produce adduct **372** in modest (dr = 6:1) diastereoselectivity (Scheme 75). However, cycloaddition of the same ylide with 2-methoxypropene (**371**) produced adduct **373** in poor (dr = 1.3:1) diastereoselectivity.

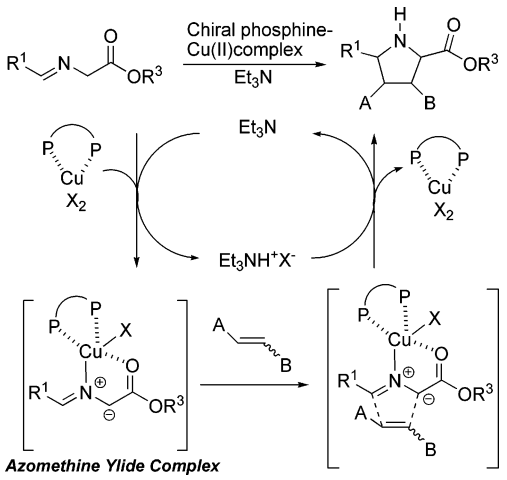
7. Conclusion

As highly substituted pyrrolidines are an integral part of numerous biologically active alkaloids and pharmaceuticals, their syntheses in optically pure form via asymmetric [3+2]-cycloaddition of azomethine ylides, which allows simultaneous construction of up to four stereocenters, is increasingly becoming an important strategy. All three possible approaches, such as use of (a) chiral azomethine ylides, (b)

Scheme 73



Scheme 74



chiral dipolarophiles, and (c) chiral catalysts, have been extensively evaluated as stereodirecting reagents in these cycloaddition reactions. Studies concerning the cycloaddition of chiral nonstabilized azomethine ylides have generally given poor diastereoselectivity; however, reaction employing achiral nonstabilized AMY and chiral dipolarophiles has given poor to excellent diastereofacialselectivity. The cycloadditions with stabilized, both nonmetalated as well as metalated, azomethine ylides have attracted greater attention in this area of research, though reaction of chiral acyclic azomethine ylides with both acyclic as well as cyclic olefins have shown poor to moderate diastereoselectivity. However, cycloaddition utilizing chiral cyclic stabilized AMY, on the other hand, has provided relatively better diastereoselectivity in comparison to their acyclic counterpart. Most of the studies related to stabilized N-metalated AMY have generally used

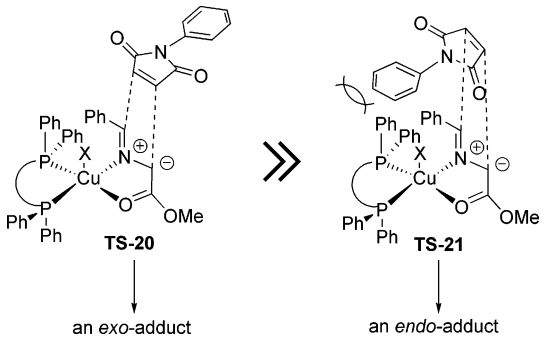
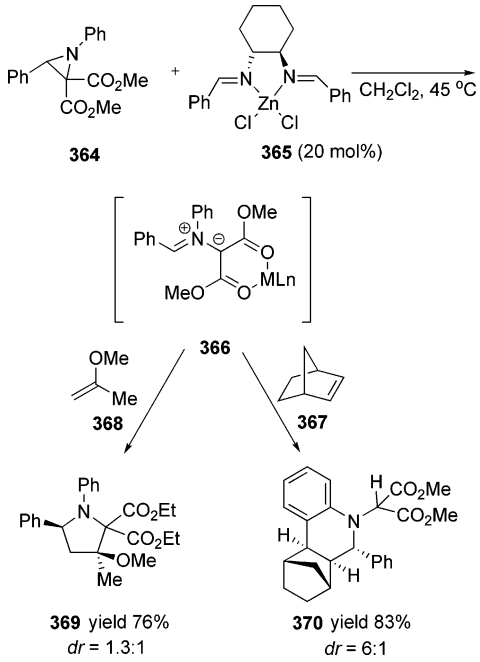


Figure 14. Transition-state models depicting addition of coordinated chiral phosphine−Cu(II) ylide complex toward dipolarophile.

Scheme 75



achiral ylides and chiral dipolarophiles, and due to the conformational rigidity acquired by these ylides, the diastereoselectivities recorded have been generally good to excellent. The nature of the metal, solvent, and reaction temperature have played decisive roles on the outcome of the diastereoselectivities. Although there are only a few reports on the cycloaddition of chiral N-metalated AMY, the diastereoselectivities are found to be excellent. Due to greater steric constraints, intramolecular cycloaddition of chiral azomethine ylides has provided only one diastereomer in almost all studies reported in this area. Asymmetric cycloaddition of AMY using chiral Lewis acid catalysts, which is also the current emerging field of research in this area, has shown interesting results, producing good to excellent enantioselectivity depending upon the structure of the ligands and the metal salts utilized.

8. Acknowledgments

We are grateful to the Department of Science and Technology, New Delhi, for generously funding our research program in this area. P.B. is thankful to the CSIR, New Delhi, for providing research fellowships.

9. References

(1) (1)Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. 2, p 277.

(2) Harwood, L. M.; Vickers, R. J. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: New York, 2002; p 169.
(3) (a) Gothelf, K. V. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2002; Chapter 6, p 211. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.
(4) Karlsson, S.; Högberg, H. E. *Org. Prep. Proceed. Int.* **2001**, *33*, 103−172.
(5) Najera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105.
(6) Kanemasa, S.; Tsuge, O. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 3, p 99.
(7) Grigg, R.; Sridharan, V. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 3, p 161.
(8) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 4, p 1069.
(9) Wade, P. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 4, p 1111.
(10) Pearson, W. H.; Stoy, P. *Synlett* **2003**, 903.
(11) Obst, U.; Betschmann, P.; Lerner, C.; Seiler, P.; Diederich, F. *Helv. Chim. Acta* **2000**, *83*, 855.
(12) Alvarez-Ibarra, C.; Csákÿ, A. G.; Lüpez, I.; Quiroga, M. L. *J. Org. Chem.* **1997**, *62*, 479.
(13) Waid, P. P.; Flynn, G. A.; Huber, E. W.; Sabol, J. S. *Tetrahedron Lett.* **1996**, *37*, 4091.
(14) Bianco, A.; Maggini, M.; Scorrano, G.; Toniolo, C.; Marconi, G.; Villani, C.; Prato, M. *J. Am. Chem. Soc.* **1996**, *118*, 4072.
(15) Kolodziej, S. A.; Nikiforovich, G. V.; Skeean, R.; Lignon, M. F.; Martinez, J.; Marshall, G. R. *J. Med. Chem.* **1995**, *38*, 137.
(16) Pearson, W. H. In *Studies in Natural Product Chemistry*; Atta-Ur-Rahman, Ed.; Elsevier: New York, 1998; Vol. 1, p 323.
(17) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666.
(18) Denhart, D. J.; Griffith, D. A.; Heathcock, C. H. *J. Org. Chem.* **1998**, *63*, 9616.
(19) Overman, L. E.; Tellew, J. E. *J. Org. Chem.* **1996**, *61*, 8338.
(20) Sisko, J.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4945.
(21) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765.
(22) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565.
(23) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, p 1.
(24) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, Germany, 1970.
(25) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976.
(26) Houk, K. N.; Yamaguchi, K. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, p 407.
(27) Huisgen, R.; Scheer, W.; Huber, H. *J. Am. Chem. Soc.* **1967**, *89*, 1753.
(28) Houk, K. N.; González, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81.
(29) Sustmann, R. *Tetrahedron Lett.* **1971**, *12*, 2717.
(30) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361.
(31) Houk, K. N.; Sims, J.; Duke, R. E.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287.
(32) Houk, K. N. *J. Am. Chem. Soc.* **1972**, *94*, 8953.
(33) Bastide, J.; El Ghandour, N.; Henri-Rousseau, O. *Tetrahedron Lett.* **1972**, *13*, 4225.
(34) Bastide, J.; El Ghandour, N.; Henri-Rousseau, O. *Bull. Soc. Chim. Fr.* **1973**, 2290.
(35) Bastide, J.; Henri-Rousseau, O. *Bull. Soc. Chim. Fr.* **1973**, 2294.
(36) Fukui, K. *Fortschr. Chem. Forsch* **1970**, *15*, 1.
(37) Fukui, K. *Acc. Chem. Res.* **1971**, *4*, 57.
(38) Rizzi, G. P. *J. Org. Chem.* **1970**, *35*, 2069.
(39) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 6452.
(40) Padwa, A.; Chen, Y.-Y. *Tetrahedron Lett.* **1983**, *24*, 3447.
(41) Padwa, A.; Dent, W. *J. Org. Chem.* **1987**, *52*, 235.
(42) Beugelmans, R.; Negron, G.; Roussi, G. *J. Chem. Soc., Chem. Commun.* **1983**, 31.
(43) Pandey, G.; Lakshmaiah, G.; Kumaraswamy, G. *J. Chem. Soc., Chem. Commun.* **1992**, 1313.
(44) Pandey, G.; Lakshmaiah, G. *Tetrahedron Lett.* **1993**, *34*, 4861.
(45) (a) Lown, J. W.; Smalley, R. K.; Dallas, G. *J. Chem. Soc., Chem. Commun.* **1968**, 1543. (b) Lown, J. W.; Smalley, R. K. *Tetrahedron Lett.* **1969**, *10*, 169.
(46) (a) Grigg, R.; Kemp, J.; Sheldrick, G.; Trotter, J. *J. Chem. Soc., Chem. Commun.* **1978**, 109 (b) Grigg, R.; Gunaratne, H. Q. N.; Kemp, J. J. *Chem. Soc., Perkin Trans 1* **1984**, 41 (c) Joucla, M.; Hamelin, J. *Tetrahedron Lett.* **1978**, *19*, 2885.
(47) (a) Confalone, P. N.; Huie, E. M. *J. Org. Chem.* **1983**, *48*, 2994 (b) Confalone, P. N.; Huie, E. M. *J. Am. Chem. Soc.* **1984**, *106*, 7175 (c) Confalone, P. N.; Earl, R. A. *Tetrahedron Lett.* **1986**, *27*, 2695.
(48) (a) Kraus, G. A.; Nagy, J. O. *Tetrahedron Lett.* **1981**, *22*, 2727 (b) Kraus, G. A.; Nagy, J. O. *Tetrahedron Lett.* **1983**, *24*, 3427 (c) Tsuge, O.; Kanemasa, S.; Takenaka, S. *J. Org. Chem.* **1986**, *51*, 1853.
(49) (a) Rouden, J.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1989**, *30*, 5133 (b) Deprez, P.; Royer, J.; Husson, H.-P. *Synthesis* **1991**, 759.
(50) (a) Grigg, R.; Gunaratne, H. Q. N. *J. Chem. Soc., Chem. Commun.* **1982**, 384 (b) Grigg, R.; Kemp, J., Malone, J.; Tangthongkum, A. *J. Chem. Soc., Chem. Commun.* **1980**, 648.
(51) Padwa, A.; Chen, Y.-Y.; Chiacchio, U.; Dent, W. *Tetrahedron* **1985**, *41*, 3529.
(52) Negron, G.; Roussi, G.; Zhang, J. *Heterocycles* **1992**, *34*, 293.
(53) Cottrell, I. F.; Hands, D.; Kennedy, D. J.; Paul, K. J.; Wright, S. H. B.; Hoogsteen, K. *J. Chem. Soc., Perkin. Trans I* **1991**, 1091.
(54) Mamane, V.; Riant, O. *Tetrahedron* **2001**, *57*, 2555.
(55) Wee, A. G. H. *J. Chem. Soc., Perkin. Trans. I* **1989**, 1363.
(56) (a) Houk, K. N.; Duh, H.-Y.; Wu, Y.-D.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754. (b) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronc Zek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880.
(57) Hanessian, S.; Yun, H.; Hou, Y.; Tintelnot-Blomley, M. *J. Org. Chem.* **2005**, *70*, 6746.
(58) Williams, R. M.; Fegley, G. J. *Tetrahedron Lett.* **1992**, *33*, 6755.
(59) Rispens, M. T.; Keller, E.; de Lange, B.; Zijlstra, R. W. J.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 607.
(60) Ma, Z.; Wang, S.; Cooper, C. S.; Fung, A. K. L.; Lynch, J. K.; Plagge, F.; Chu, D. T. W. *Tetrahedron: Asymmetry* **1997**, *8*, 883.
(61) Karlsson, S.; Högberg, H.-E. *Tetrahedron: Asymmetry* **2001**, *12*, 1975.
(62) Karlsson, S.; Högberg, H.-E. *Tetrahedron: Asymmetry* **2001**, *12*, 1977.
(63) Karlsson, S.; Högberg, H.-E. *J. Chem. Soc., Perkin Trans. I* **2002**, 1076.
(64) Carey, J. S. *J. Org. Chem.* **2001**, *66*, 2526.
(65) Kotian, P. L.; Lin, T.-H.; El-Kattan, Y.; Chand, P. *Org. Proc. Res. Dev.* **2005**, *9*, 193.
(66) Palmisano, G.; Annunziata, R.; Papeo, G.; Sisti, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1.
(67) Ganguly, A. K.; Seah, N.; Popov, V.; Wang, C. H.; Kuang, R.; Saksena, A. K.; Pramanik, B. N.; Chan, T. M.; McPhail, A. T. *Tetrahedron Lett.* **2002**, *43*, 8981.
(68) Cravotto, G.; Giovenzana, G. B.; Pilati, T.; Sisti, M.; Palmisano, G. *J. Org. Chem.* **2001**, *66*, 8447.
(69) Fray, A. H.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 3362.
(70) Meyers, A. I.; Fray, A. H. *Bull. Soc. Chim. Fr.* **1997**, *134*, 283.
(71) Barluenga, J.; Fernández-R, M. A.; Aguilar, E.; Fernández-M, F.; Salinas, A.; Olano, B. *Chem.−Eur. J.* **2001**, *7*, 3533.
(72) Pandey, G.; Laha, J. K.; Mohanakrishnan, A. K. *Tetrahedron Lett.* **1999**, *40*, 6065.
(73) Pandey, G.; Laha, J. K.; Lakshmaiah, G. *Tetrahedron* **2002**, *58*, 3525.
(74) Ashley, E. R.; Cruz, E. G.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 15000.
(75) Rouden, J.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1989**, *30*, 5133.
(76) Deprez, P.; Rouden, J.; Chiaroni, A.; Riche, C.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1991**, *32*, 7531.
(77) Deprez, P.; Royer, J.; Husson, H.-P. *Tetrahedron: Asymmetry* **1991**, *2*, 1189.
(78) Takano, S.; Moriya, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1992**, *3*, 681.
(79) Garner, P.; Dogan, Ö. *J. Org. Chem.* **1994**, *59*, 4.
(80) Garner, P.; Dogan, Ö.; Youngs, W. J.; Kennedy, V. O.; Protasiewicz, J.; Zaniewski, R. *Tetrahedron* **2001**, *57*, 71.
(81) Wittland, C.; Flörke, U.; Risch, N. *Synthesis* **1997**, 1291.
(82) Enders, D.; Meyer, I.; Runsink, J.; Raabe, G. *Tetrahedron* **1998**, *54*, 10733.
(83) Garner, P.; Sunitha, K.; Shanthilal, T. *Tetrahedron Lett.* **1988**, *29*, 3525.
(84) Garner, P.; Ho, W. B.; Grandhee, S. K.; Youngs, W. J.; Kennedy, V. O. *J. Org. Chem.* **1991**, *56*, 5893.
(85) Garner, P.; Ho, W. B. *J. Org. Chem.* **1990**, *55*, 3973.
(86) Garner, P.; Ho, W. B.; Shin, H. *J. Am. Chem. Soc.* **1993**, *115*, 10742.
(87) Williams, R. M.; Zhai, W.; Aldous, D. J.; Aldous, S. C. *J. Org. Chem.* **1992**, *57*, 6527.
(88) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666.
(89) Sebahar, P. R.; Hiroyuki, O.; Usui, T.; Williams, R. M. *Tetrahedron* **2002**, *58*, 6311.
(90) Sebahar, P. R.; Williams, R. M. *Heterocycles* **2002**, *58*, 563.
(91) Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135.
(92) Ahrendt, K. A.; Williams, R. M. *Org. Lett.* **2004**, *6*, 4539.
(93) Parrish, D. A.; Wang, S.; Ding, K.; Wang, G.; Deschamps, J. R. *Tetrahedron Lett.* **2005**, *46*, 5949.
(94) Anslow, A. S.; Harwood, L. M.; Phillips, H.; Watkin, D. *Tetrahedron: Asymmetry* **1991**, *2*, 169.

(95) Anslow, A. S.; Harwood, L. M.; Phillips, H.; Watkin, D. *Tetrahedron: Asymmetry* **1991**, *2*, 997.
(96) Anslow, A. S.; Harwood, L. M.; Phillips, H.; Watkin, D.; Wong, L. F. *Tetrahedron: Asymmetry* **1991**, *2*, 1343.
(97) Harwood, L. M.; Macro, J.; Watkin, D.; Williams, C. E.; Wong, L. F. *Tetrahedron: Asymmetry* **1992**, *3*, 1127.
(98) Harwood, L. M.; Manage, A. C.; Robin, S.; Hopes, S. F. G.; Watkin, D.; Williams, C. E. *Synlett* **1993**, 777.
(99) Anslow, A. S.; Cox, G. G.; Harwood, L. M. *Chem. Heterocycl. Compd.* **1995**, *31*, 1222.
(100) Anslow, A. S.; Harwood, L. M.; Lilley, I. A. *Tetrahedron: Asymmetry* **1995**, *6*, 2465.
(101) Harwood, L. M.; Lilley, I. A. *Tetrahedron: Asymmetry* **1995**, *6*, 1557.
(102) Alker, D.; Harwood, L. M.; Williams, C. E. *Tetrahedron* **1997**, *53*, 12671.
(103) Alker, D.; Harwood, L. M.; Williams, C. E. *Tetrahedron Lett.* **1998**, *39*, 475.
(104) Harwood, L. M.; Robertson, S. M. *Chem. Commun*. **1998**, 2641.
(105) Alker, D.; Hamblett, G.; Harwood, L. M.; Robertson, S. M.; Watkin, D. J.; Williams, C. E. *Tetrahedron* **1998**, *54*, 6089.
(106) Aldous, D. J.; Drew, M. G. B.; Hamelin, E. M.-N.; Harwood, L. M.; Jahans, A. B.; Thurairatnam, S. *Synlett* **2001**, 1836.
(107) Aldous, D. J.; Hamelin, E. M.-N.; Harwood, L. M.; Thurairatnam, S. *Synlett* **2001**, 1841.
(108) Draffin, W. N.; Harwood, L. M. *Synlett* **2006**, *6*, 857.
(109) Baldwin, J. E.; MacKenzie, T. S. C.; Moloney, M. G. *Synlett* **1994**, 925.
(110) Chinchilla, R.; Falvello, L. R.; Galindo, N.; Nájera, C. *Eur. J. Org. Chem.* **2001**, 3133.
(111) Peyronel, J.-F.; Grisoni, S.; Carboni, B.; Courgeon, T.; Carrie, R. *Tetrahedron* **1994**, *50*, 189.
(112) Jones, R. C. F.; Howard, K. J.; Snaith, J. S. *Tetrahedron Lett.* **1996**, *37*, 1707.
(113) Jones, R. C. F.; Howard, K. J.; Snaith, J. S. *Tetrahedron Lett.* **1996**, *37*, 1711.
(114) Felluga, F.; Pitacco, G.; Visintin, C.; Valentin, E. *Helv. Chim. Acta* **1997**, *80*, 1457.
(115) Coulter, T.; Grigg, R.; Malone, J. F.; Shridharan, V. *Tetrahedron Lett.* **1991**, *32*, 5417.
(116) Dondas, H. A.; Grigg, R.; Kilner, C. *Tetrahedron* **2003**, *59*, 8481.
(117) Dondas, H. A.; Fishwick, C. W. G.; Grigg, R.; Kilner, C. *Tetrahedron* **2004**, *60*, 3473.
(118) Husinec, S.; Savic, V. *J. Serb. Chem. Soc*. **1998**, *63*, 921.
(119) Grigg, R.; Thornton, P. M.; Xu, J.; Xu, L.-H. *Tetrahedron* **1999**, *55*, 13841.
(120) Alcaide, B.; Almendros, P.; Alonso, J. M.; Redondo, M. C. *J. Org. Chem.* **2003**, *68*, 1426.
(121) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Chem. Commun*. **2000**, 485.
(122) Schnell, B.; Bernardinelli, G.; Kündig, E. P. *Synlett* **1999**, 348.
(123) Dogan, Ö.; Öner, I.; Ülkü, D.; Arici, C. *Tetrahedron: Asymmetry* **2002**, *13*, 2099.
(124) Kanemasa, S.; Yamamoto, H. *Tetrahedron Lett.* **1990**, *31*, 3633.
(125) Kanemasa, S.; Yamamoto, H.; Wada, E.; Sakurai, T.; Urushido, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2857.
(126) Kanemasa, S.; Hayashi, T.; Tanaka, J.; Yamamoto, H.; Sakurai, T. *J. Org. Chem.* **1991**, *56*, 4473.
(127) Barr, D. A.; Dorrity, M. J.; Grigg, R.; Malone, J. F.; Montgomery, J.; Rajviroongit, S.; Stevenson, P. *Tetrahedron Lett.* **1990**, *31*, 6569.
(128) Barr, D. A.; Dorrity, M. J.; Grigg, R.; Hargreaves, S.; Malone, J. F.; Montgomery, J.; Redpath, J.; Stevenson, P.; Thronton, P. M. *Tetrahedron* **1995**, *51*, 273.
(129) Cooper, D. M.; Grigg, R.; Hargreaves, S.; Kennewell, P.; Redpath, J. *Tetrahedron* **1995**, *51*, 7791.
(130) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Pilati, T. *Tetrahedron: Asymmetry* **1991**, *2*, 1329.
(131) Ayerbe, M.; Arrieta, A.; Cossío, F. P. *J. Org. Chem.* **1998**, *63*, 1795.
(132) Zubia, A.; Mendoza, L.; Vivanco, S.; Aldaba, E.; Carrascal, T.; Lecea, B.; Arrieta, A.; Zimmerman, T.; Vidal-Vanaclocha, F.; Cossio, F. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 2903.
(133) Pätzel, M.; Galley, G.; Jones, P. G.; Chrapkowsky, A. *Tetrahedron Lett.* **1993**, *34*, 5707.
(134) Galley, G.; Liebscher, J.; Pätzel, M. *J. Org. Chem.* **1995**, *60*, 5005.
(135) Waldmann, H.; Bläser, E.; Jansen, M.; Letschert, H.-P. *Angew. Chem. Int. Ed*. **1994**, *33*, 683.
(136) Waldmann, H.; Bläser, E.; Jansen, M.; Letschert, H. P. *Chem.—Eur. J.* **1995**. *1*, 150.
(137) Nyerges, M.; Bendell, D.; Arany, A.; Hibbs, D. E.; Coles, S. J.; Hursthouse, M. B.; Groundwater, P. W.; Meth-Cohn, O. *Synlett* **2003**, 947.
(138) Nyerges, M.; Bendell, D.; Arany, A.; Hibbs, D. E.; Coles, S. J.; Hursthouse, M. B.; Groundwater, P. W.; Meth-Cohn, O. *Tetrahedron* **2005**, *61*, 3745.
(139) Ruano, J. L. G.; Tito, A.; Peromingo, M. T. *J. Org. Chem.* **2002**, *67*, 981.
(140) Ruano, J. L. G.; Tito, A.; Peromingo, M. T. *J. Org. Chem.* **2003**, *68*, 10013.
(141) Pyne, S. G.; Safaei, G. J.; Koller, F. *Tetrahedron Lett.* **1995**, *36*, 2511.
(142) Pyne, S. G.; Safaei, G. J.; Javidan, A.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1998**, *51*, 137.
(143) Bashiardes, G.; Cano, C.; Mauzé, B. *Synlett* **2005**, 587.
(144) Viso, A.; Fernández de la Pradilla, R.; Guerrero-Strachan, C.; Alonso, M.; Martínez-Ripoll, M.; André, I. *J. Org. Chem.* **1997**, *62*, 2316.
(145) Viso, A.; Fernández de la Pradilla, R.; Garcia, A.; Alonso, M.; Guerrero-Strachan, C.; Fonseca, I. *Synlett* **1999**, 1543.
(146) Merino, I.; Santosh Laxmi, Y. R.; Flórez, J.; Barluenga, J. *J. Org. Chem.* **2002**, *67*, 648.
(147) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Am. Chem. Soc.* **1987**, *109*, 5523.
(148) a) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1204. (b) Takano, S.; Tomita, S.; Iwabuchi, Y.; Ogasawara, K. *Heterocycles* **1989**, *29*, 1473.
(149) Takano, S.; Samizu, K.; Ogasawara, K. *Chem. Lett.* **1990**, 1239.
(150) Hashimura, K.; Tomita, S.; Hiroya, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1995**, 2291.
(151) Garner, P. P.; Sunitha, K.; Ho, W.-B.; Youngs, W. J.; Kennedy, V. O.; Djebli, A. *J. Org. Chem.* **1989**, *54*, 2041.
(152) a) Garner, P. P.; Cox, P. B.; Anderson, J. T.; Protasiewicz, J.; Zaniewski, R. *J. Org. Chem.* **1997**, *62*, 493. (b) Garner, P. P.; Cox, P. B.; Klippenstein, S. J.; Youngs, W. J.; McConville, D. B. *J. Org. Chem.* **1994**, *59*, 6510.
(153) Garner, P.; Kaniskan, H. U. *Tetrahedron Lett.* **2005**, *46*, 5181.
(154) Dogan, Ö.; Garner, P. *Turk. J. Chem.* **2000**, *24*, 59.
(155) Takano, S.; Sugihara, Y.; Ogasawara, K. *Heterocycles* **1992**, *34*, 1519.
(156) Kanemasa, S.; Doi, K.; Wada, E. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2866.
(157) Jones, R. C. F.; Howard, K. J.; Snaith, J. S. *Tetrahedron Lett.* **1997**, *38*, 1647.
(158) Jones, R. C. F.; Iley, J. N.; Lory, P. M. J.; Coles, S. C.; Light, M. E.; Hursthouse, M. B. *Tetrahedron Lett.* **2001**, *42*, 3951.
(159) Harwood, L. M.; Lilley, I. A. *Tetrahedron Lett.* **1993**, *34*, 537.
(160) Harwood, L. M.; Kitchen, L. C. *Tetrahedron Lett.* **1993**, *34*, 6603.
(161) Harwood, L. M.; Lilley, I. A. *Synlett* **1996**, 1010.
(162) Drew, M. G. B.; Harwood, L. M.; Price, D. W.; Choi, M.-S.; Park, G. *Tetrahedron Lett.* **2000**, *41*, 5077.
(163) Aldous, D. J.; Drew, M. G. B.; Draffin, W. N.; Hamelin, E. M.-N.; Harwood, L. M. *Synthesis* **2005**, *19*, 3271.
(164) Cheng, Q.; Zhang, W.; Tagami, Y.; Oritani, T. *J. Chem. Soc., Perkin Trans. I* **2001**, 452.
(165) Pedrosa, R.; Andrés, C.; Heras, L. de las; Nieto, J. *Org. Lett.* **2002**, *4*, 2513.
(166) Epperson, M. T.; Gin, D. Y. *Angew. Chem., Int. Ed*. **2002**, *41*, 1778.
(167) Sekine, T.; Fukasawa, N.; Kashiwagi, Y.; Ruangrungsi, N.; Murakoshi, I. *Chem. Pharm. Bull*. **1994**, *42*, 1360.
(168) Gu, Y. G.; Zhang, X.; Clark, R. F.; Djuric, S. W.; Ma, Z. *Tetrahedron Lett*. **2004**, *45*, 3051.
(169) Ma, Z.; Nemoto, P. A. *Curr. Med. Chem.: Anti-infective Agents* **2002**, *1*, 15.
(170) Husinec, S.; Savic, V. *Tetrahedron: Asymmetry* **2005**, *16*, 2047.
(171) Nájera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6272.
(172) Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 5817.
(173) Grigg, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2475.
(174) Karlsson, S.; Han, F.; Högberg, H.-E.; Caldirola, P. *Tetrahedron: Asymmetry* **1999**, *10*, 2605.
(175) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400.
(176) Gao, W.; Zhang, X.; Raghunath, M. *Org. Lett.* **2005**, *7*, 4241.
(177) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236.
(178) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174.
(179) Stohler, R.; Wahl, F.; Pfaltz, A. *Synthesis* **2005**, 1431.
(180) Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, *5*, 5043.
(181) Pohlhaus, P. D.; Bowman, R. K.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2294.
(182) Bowman, R. K.; Johnson, J. S. *J. Org. Chem.* **2004**, *69*, 8537.

CR050011G