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Asymmetric 1,3-dipolar cycloadditions

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Contents

Abbreviations: Ac, acetyl; All, allyl; Ar, aryl; Aux, auxiliary; $BF_3 \cdot Et_2O$, boron trifluoride etherate; BINAP, 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; BINOL, 1,1′-bi-2-naphthol; Bn, benzyl; Boc, *tert*-butoxycarbonyl; Born, borneol; Bz, benzoyl; Bu, butyl; Cbz, benzyloxycarbonyl; Cy, cyclohexyl; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCE, 1,2-dichloroethane; de, diastereomeric excess; DEAD, diethyl azodicarboxylate; DIPT, diisopropyl tartrate; DMAD, dimethyl acetylenedicarboxylate; DMF, dimethylformamide; dr, diastereomeric ratio; E, electrophile; ee, enantiomeric excess; Et, ethyl; Fe, ferrocenyl; Fu, furyl; Hex, hexyl; HMDS, hexamethyldisilazide; HMPA, hexamethylphosphoramide; L, ligand; LDA, lithium diisopropylamide; LHMDS, lithium hexamethyldisilazide; M, metal; MAPh, methylaluminium bis(2,6-diphenylphenoxide); Me, methyl; MPM, 4-methoxyphenylmethyl; Ms, mesyl; MOM, methoxymethyl; Np, naphthyl; Pent, pentyl; Ph, phenyl; Piv, pivaloyl; PMB, *p*-methoxybenzoyl; PMP, *p*-methoxyphenyl; Pr, propyl; *p*-TSA, *p*-toluenesulfonic acid; Py, pyridyl; SEM, [2-(trimethylsilyl)ethoxy]methyl; TBAT, tetrabutylammonium triphenyldifluorosilicate; TBDMS, *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; TES, triethylsilyl; Tf, trifluoromethanesulfonyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; THP, tetrahydropyranyl; TIPS, triisopropylsilyl; TMS, trimethylsilyl; Tol, tolyl; TPP, tetraphenylporphyrin; Ts, 4-toluenesulfonyl (tosyl).

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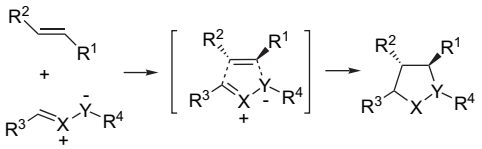
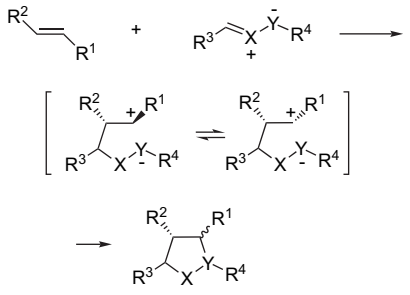
1. Introduction

The preparation of chiral compounds is an important and challenging area of contemporary synthetic organic chemistry.[1] The 1,3-dipolar cycloaddition, also known as the Huisgen cycloaddition,[2] is a classic reaction in organic chemistry consisting of the reaction of a dipolarophile with a 1,3-dipolar compound that allows the production of various five-membered heterocycles. This reaction represents one of the most productive fields of modern synthetic organic chemistry. Most of dipolarophiles are alkenes, alkynes and molecules possessing related heteroatom functional groups (such as carbonyls and nitriles). The 1,3-dipoles can be basically divided into two different types: the allyl anion type such as nitrones, azomethine ylides, nitro compounds, bearing a nitrogen atom in the middle of the dipole, carbonyl ylides, or carbonyl imines, bearing an oxygen atom in the middle of the dipole and the linear propargyl/allenyl anion type such as nitrile oxides, nitrilimines, nitrile ylides, diazoalkanes, or azides. Two π-electrons of the dipolarophile and four electrons of the dipolar compound participate in a concerted, pericyclic shift. The addition is stereoconservative (suprafacial), and the reaction is therefore a $[2_S+4_S]$ cycloaddition (Scheme 1).



Scheme 1. General concerted 1,3-dipolar cycloaddition.

However, the dipole might be stabilised by the adjacent central heteroatom X (nitrogen, oxygen, or sulfur) through resonance, and a non-concerted reaction pathway might also occur. Consequently, in some cases, the original stereochemistry of the alkene is not necessarily conserved, as depicted in Scheme 2.



Scheme 2. Non-concerted 1,3-dipolar cycloaddition.

The transition state of the concerted 1,3-dipolar cycloaddition reaction is controlled by the frontier molecular orbitals of the substrates. Hence, the reaction of dipoles with dipolarophiles involves either a LUMO–dipole/HOMO–dipolarophile reaction or a HOMO–dipole/LUMO–dipolarophile interaction, depending on the nature of the dipole and the dipolarophile. In some cases, when the frontier molecular orbital energies of the dipole and the dipolarophile are very similar, a combination of both modes of interactions can occur. These interactions can also be referred to as either *exo* or *endo*, where the *endo* transition state is stabilised by small secondary π-orbital interactions or via an *exo*-transition state lacking such a stabilisation. However, steric effects can also be important factors for the *endo*/*exo* selectivity and override the secondary orbital interactions.[3] Depending on the substitution pattern in the reacting partners, the stereochemical outcome of the process gives rise to either the *endo*- or *exo*-cycloadducts. Moreover, the presence of a metal, such as a Lewis acid, in 1,3-dipolar cycloaddition reactions can alter both the orbital coefficients of the reacting atoms and the energy of the frontier orbitals of both the 1,3-dipole or the dipolarophile, depending on the electronic properties of these reagents or the Lewis acid. In particular, the coordination of a Lewis acid to one of the two partners of the cycloaddition is of fundamental importance for asymmetric 1,3-dipolar cycloadditions, since the metal can catalyse the reaction. Furthermore, the Lewis acid may also have influence on the selectivity of the cycloaddition reaction, since the regio-, diastereo- and enantioselectivity can all be controlled by the presence of a metal–ligand complex. In recent years, asymmetric 1,3-dipolar cycloadditions have become one of the most powerful tools for the construction of enantiomerically pure five-membered heterocycles. Up to four stereocentres can be introduced in a stereoselective manner in only one single step. In addition, a range of different substituents can be included in the dipole and the dipolarophile, resulting in a broad range of possible cycloadducts, which can serve as useful synthetic building blocks. The enantioselectivity can be controlled by choosing a chiral 1,3-dipole, a chiral dipolarophile, or a chiral catalyst, of which the latter probably has the greatest potential. This review is an update of the recent developments in asymmetric 1,3-dipolar cycloaddition reactions involving a variety of different heteroylides, dipolarophiles and catalysts, covering the literature from 2001 to 2006. The asymmetric 1,3-dipolar cycloadditions were most recently reviewed in 2001 by Karlsson and Högberg.[4] Prior to that survey, these reactions had been reviewed in 1998 by Jorgensen and Gothelf.[5] Moreover, the asymmetric metal-catalysed 1,3-dipolar cycloaddition reactions were reviewed by Kanemasa[6] and Gothelf,[7] covering the literature until the beginning of 2001, whereas the more general transition metal complexation in 1,3-dipolar cycloadditions was updated in 2003 by Zecchi et al.[8] It should also be noted that an in-depth account of stereoselective intramolecular 1,3-dipolar cycloadditions was reported in 2001 by Namboothiri and Hassner.[9]

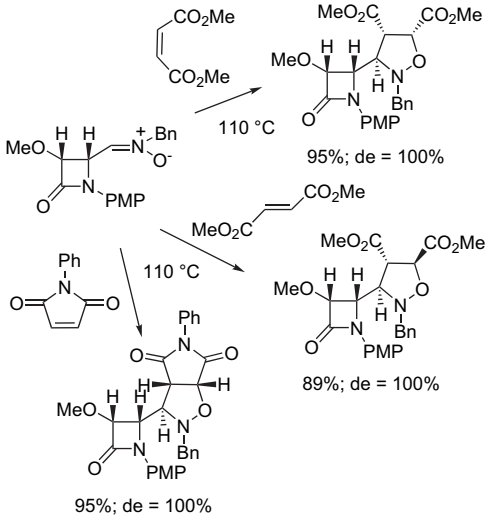
2. Nitrones

The reactions of nitrone dipoles play an important part in the history of cycloaddition reactions. The 1,3-dipolar cycloaddition reaction of nitrones with dipolarophiles such as alkenes has received considerable attention in asymmetric

synthesis over the past 20 years.[4,5,10] Regio- and stereoselective nitrone cycloaddition, followed by reduction of the N–O bond to produce both an amino and a hydroxyl function, allows the synthesis of many products of potential interest. One of the reasons for the success of the synthetic applications of nitrones is that, contrary to the majority of the other 1,3-dipoles, most nitrones are stable compounds that do not require an in situ formation. Another synthetic utility of this reaction is the variety of attractive nitrogenated compounds, which are available from the thus-formed isoxazolidines. In particular, these latter products can be easily reduced under mild conditions to give the corresponding chiral 1,3-amino-alcohols. The absolute majorities of the 1,3-dipolar cycloaddition reactions are diastereoselective and involve chiral alkenes or nitrones, among which are the intramolecular versions. In addition, the catalytic enantioselective 1,3-dipolar cycloaddition reaction of nitrones has gone through rapid developments during the last 12 years.[11]

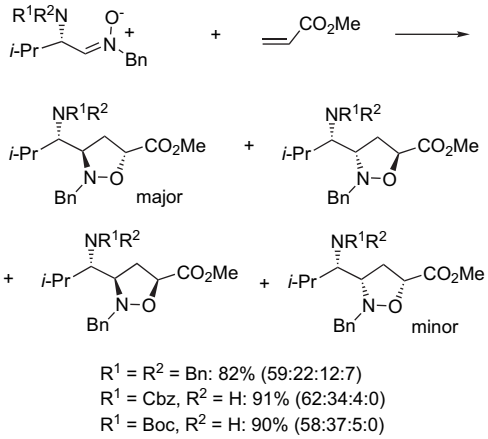
2.1. Chiral nitrones

2.1.1. Acyclic chiral nitrones. In contrast to the cyclic dipoles, acyclic dipoles can undergo *Z*/*E* isomerisation around a double bond. In some cases, this makes it difficult to realise a direct correlation between the product distribution and the *E*/*Z* isomer equilibrium distribution of the starting dipole, since one of the *Z*/*E* isomers can react faster under kinetic control. Various acyclic chiral nitrones have recently been involved in 1,3-dipolar cycloaddition reactions. As an example, Alcaide et al. reported in 2002 an efficient entry to highly functionalised chiral β-lactams by regio- and stereoselective 1,3-dipolar cycloaddition reactions of optically active 2-azetidinone-tethered nitrones with electron-deficient alkenes such as dimethyl fumarate, dimethyl maleate, or *N*-phenylmaleimide (Scheme 3).[12] The stereoselectivity of the reactions was highly dependent on the bulkiness of the N-substituent of the nitrone. Thus, a single diastereoisomer was formed using *N*-benzyl nitrones, whereas the less-hindered *N*-methylhydroxylamine-derived nitrones led to mixtures of diastereoisomers.



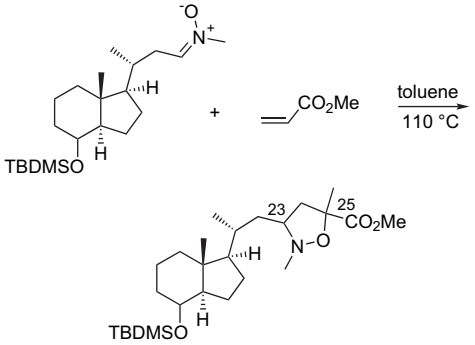
Scheme 3. 1,3-Dipolar cycloadditions of 2-azetidinone-tethered nitrones.

With the goal of developing a simple route for the synthesis of biologically active non-proteinogenic γ-substituted β,γ-diamino acids, Fisera et al. have studied the 1,3-dipolar cycloaddition of chiral nitrones derived from L-valine with methyl acrylate, affording the corresponding diastereomeric 3,5-disubstituted isoxazolidines (Scheme 4).[13] The stereoselectivity of the reaction was dependent on the steric hindrance of the nitrone and the reaction conditions. The major products were found to have the C3/C6 *erythro* and C3/C5 trans relative configuration. These latter products were further converted into the corresponding chiral diaminodiols through an N–O cleavage/deprotection sequence.



Scheme 4. 1,3-Dipolar cycloaddition of L-valine-derived nitrones.

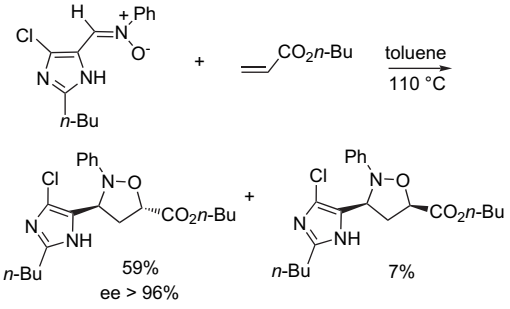
In 2004, Nagasawa et al. reported the synthesis of novel vitamin D_3 analogues on the basis of an asymmetric 1,3-dipolar cycloaddition reaction of a chiral nitrone derived from vitamin D_2 with methyl methacrylate, providing the corresponding isoxazolidine as a mixture of four diastereomers at C3 and C25 (Scheme 5).[14] The subsequent reduction of these latter compounds gave the corresponding lactams, which led to the formation of a novel series of 1α,25-dihydroxyvitamin D_3 antagonists.



Scheme 5. 1,3-Dipolar cycloaddition of a vitamin D_2-derived nitrone.

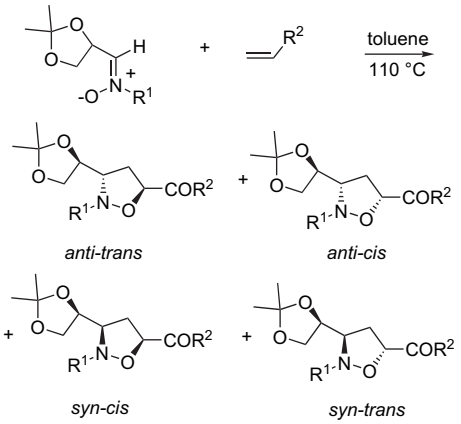
In 2005, the 1,3-dipolar cycloaddition reaction of a chiral nitrone with butyl acrylate was reported as the key step of the synthesis of a novel 5-imidazolyl-substituted isoxazolidine having high antimicrobial activity (Scheme 6).[15]

The stereoselective 1,3-dipolar cycloaddition between D-glyceraldehyde nitrones and acrylates was studied by Merino et al., and applied to a diastereoselective approach to



Scheme 6. 1,3-Dipolar cycloaddition of an imidazolyl-*N*-phenyl nitrone.

4-hydroxypyroglutamic acid derivatives (Scheme 7).[16] In addition, a double chiral induction experiment was performed in the presence of a chiral acrylate, such as Oppolzer's sultam acrylamide, and 2,3-*O*-isopropylidene-D-glyceraldehyde nitrone, providing a higher diastereofacial selectivity [yield= 94% (*anti*-trans/*anti*-cis/*syn*-cis/*syn*-trans)=60:20:20:0].



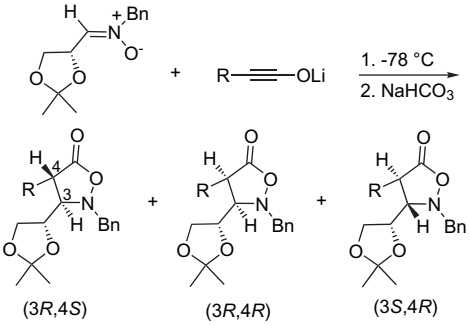
R^1 = Bn, R^2 = OMe: 95%
(*anti-trans:anti-cis:syn-cis:syn-trans*) = 63:23:11:3
R^1 = Bn, R^2 = O*t*-Bu: 66%
(*anti-trans:anti-cis:syn-cis:syn-trans*) = 53:20:16:11
R^1 = (*R*)-CH(Me)Ph, R^2 = OMe: 94%
(*anti-trans:anti-cis:syn-cis:syn-trans*) = 75:15:8:2
R^1 = (*S*)-CH(Me)Ph, R^2 = OMe: 93%
(*anti-trans:anti-cis:syn-cis:syn-trans*) = 25:25:25:25

Scheme 7. 1,3-Dipolar cycloaddition of D-glyceraldehyde nitrones.

In 2003, ynolates were involved, for the first time, in 1,3-dipolar cycloaddition reactions in the presence of chiral nitrones, such as *N*-benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde nitrone, by Shindo et al.[17] The corresponding 5-isoxazolidinones were produced with good diastereoselectivity, and could be readily converted into optically pure β-amino acids and chiral γ-butyrolactones (Scheme 8).

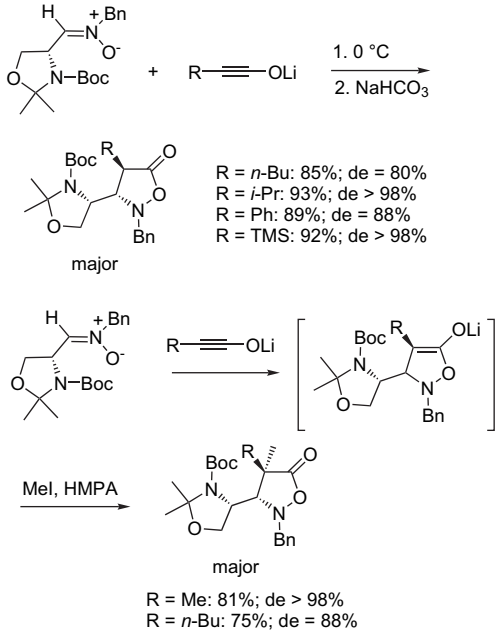
The same methodology was successfully applied to a chiral nitrone derived from L-serine, leading to the corresponding cycloadducts with good yields and good to excellent diastereoselectivities.[18] A further alkylation of the intermediate 5-isoxazolidinone enolates was also achieved with high selectivity, providing the corresponding 2,2-disubstituted products (Scheme 9).

A stereoselective approach towards novel isoxazolidinyl nucleosides was designed by Chiacchio et al., on the basis of a 1,3-dipolar cycloaddition of a chiral nitrone with purine and



R = Me: 91% [(3*R*,4*S*):(3*R*,4*R*):(3*S*,4*R*)] = 84:10:6
R = *n*-Bu: 92% [(3*R*,4*S*):(3*R*,4*R*):(3*S*,4*R*)] = 88:6:6
R = *i*-Pr: 93% [(3*R*,4*S*):(3*R*,4*R*):(3*S*,4*R*)] = 90:5:5
R = Ph: 55% [(3*R*,4*S*):(3*R*,4*R*):(3*S*,4*R*)] = 85:15:0

Scheme 8. 1,3-Dipolar cycloaddition of a D-glyceraldehyde nitrone to ynolates.



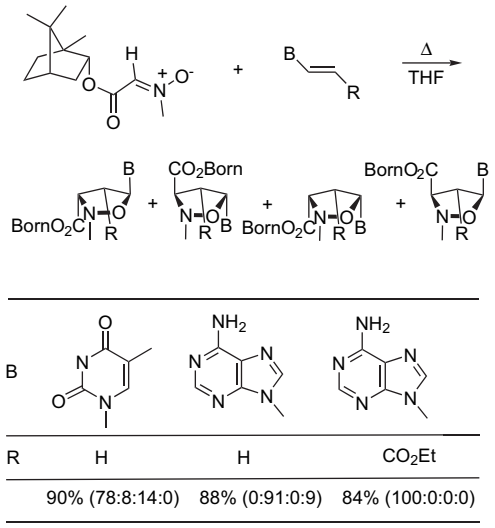
R = *n*-Bu: 85%; de = 80%
R = *i*-Pr: 93%; de > 98%
R = Ph: 89%; de = 88%
R = TMS: 92%; de > 98%

R = Me: 81%; de > 98%
R = *n*-Bu: 75%; de = 88%

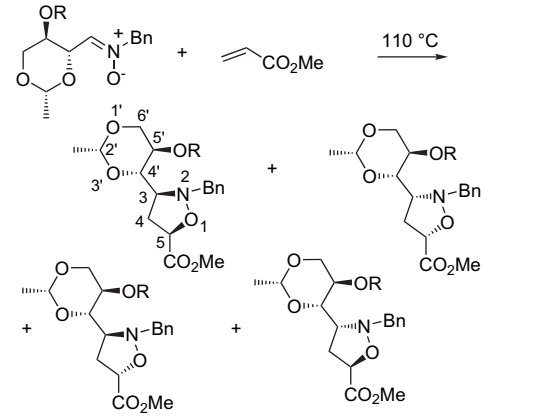
Scheme 9. 1,3-Dipolar cycloaddition of an L-serine-derived nitrone to ynolates.

pyrimidine nucleobases, providing the corresponding chiral thymidine and adenine N,O-nucleosides.[19] In particular, the reaction of ethyl 3-(9-adenyl)acrylate displayed complete regio- and stereoselectivities, affording exclusively the single trans cycloadduct in good yield (Scheme 10).

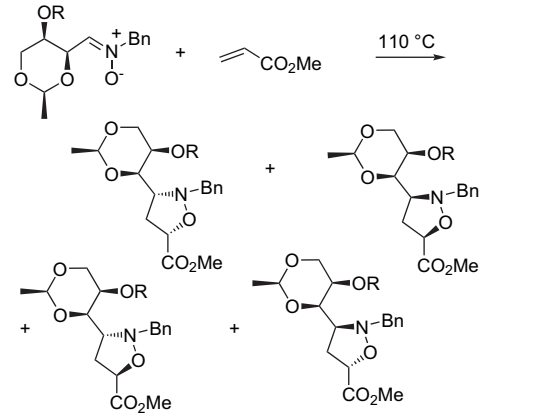
Nitrones, which are derived from, or tethered to, carbohydrates, have proved to be particularly useful for stereoselective entry to stereochemically complex carbocycles and heterocycles. In 2002, Osborn et al. published a review, which detailed the synthesis of 1,3-dipolar cycloaddition reactions of carbohydrate-derived 1,3-dipoles.[20] With the goal of developing a simple route for the synthesis of polyhydroxylated derivatives of pyrrolizidines displaying antiviral activities, Fisera et al. have developed 1,3-dipolar cycloadditions of D-erythrose- and D-threose-derived nitrones with methyl acrylate (Scheme 11).[21] The reactions proceeded in a regiospecific manner to afford the corresponding 3,5-disubstituted diastereomeric isoxazolidines in good yields. The stereoselectivity was dependent on the steric hindrance



Scheme 10. 1,3-Dipolar cycloaddition of a borneol-derived nitrone to vinyl nucleobases.



R = H: 85% (48:18:29:5) *erythro:threo* = 77:23 *cis:trans* = 66:34
R = Ac: 77% (73:3:24:0) *erythro:threo* = 97:3 *cis:trans* = 76:24
R = TBDMS: 82% (87:5:6:2) *erythro:threo* = 93:7 *cis:trans* = 92:8

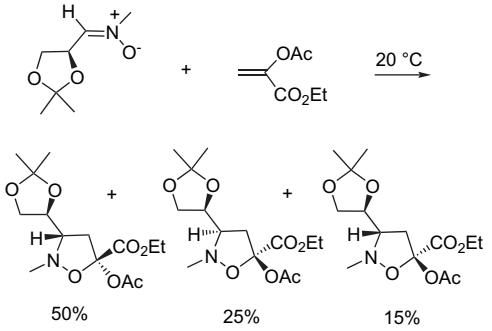


R = H: 68% (62:11:19:8) *erythro:threo* = 81:19 *cis:trans* = 73:27
R = TBDMS: 65% (96:1:3:0) *erythro:threo* = 99:1 *cis:trans* = 97:3

Scheme 11. 1,3-Dipolar cycloadditions of D-erythrose- and D-threose-derived nitrones.

of the nitrone. In all cases, the major products were found to have the C3/C4′ *erythro*- and C3/C5 cis-relative configuration. Their formation could be rationalised by a less-hindered *endo* attack of the *Z*-nitrone in an antiperiplanar manner with respect to the largest group of the cyclic acetal. This methodology was applied for the synthesis of a trihydroxylated pyrrolizidine alkaloid via a sequence involving the cycloaddition of a D-erythrose-derived nitrone followed by an N–O cleavage and recyclisation.[22]

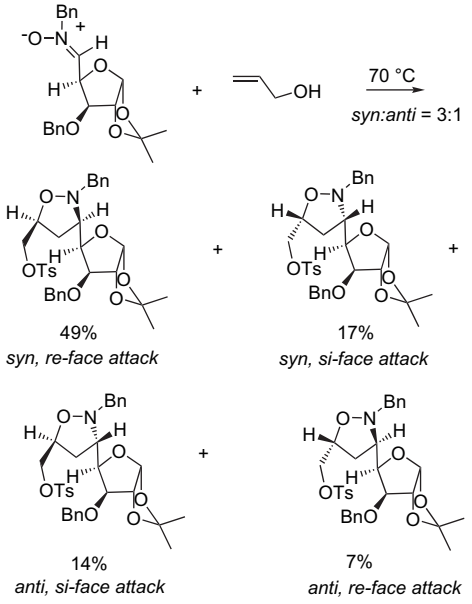
The extension of this methodology to other dipolarophiles such as Baylis–Hillman adducts (β-hydroxy-α-methylene esters) was reported in 2004, affording with complete regioselectivity the corresponding diastereomeric 3,5,5-trisubstituted isoxazolidines.[23] A good stereoselectivity was obtained giving the corresponding C3/C5 *cis*-, C4′/C3 *erythro*-isoxazolidines as the major products. In order to develop a simple route to the synthesis of isoxazolidinyl nucleosides, the same group reported, in 2002, the regioselective 1,3-cycloaddition of new chiral nitrones, readily available from D-xylose, with *N*-vinylated bases derived from uracil and adenine.[24] The attack of the dipolarophile on the *Z*-configuration of the nitrone through *exo* and *endo* transition states from the *si* face of the nitrone (C1′/C3 *erythro*) afforded the C3/C5-*cis* (*exo*) and C3/C5-*trans* (*endo*) isoxazolidines, respectively, as the two major isomers. These latter products were further converted into novel azanucleosides, possessing an ethylene bridge between the anomeric carbon and the nitrogen atom. Natural psicofuranosyl nucleosides, carrying a CH_2OH group at the anomeric carbon atom, are endowed with interesting biological activities. On this basis, Chiacchio et al. have designed an easy route towards chiral modified N,O-psiconucleosides in which the sugar unit was replaced by an isoxazolidine ring (Scheme 12).[25] The reaction of a D-glyceraldehyde-derived nitrone with ethyl 2-acetyloxyacrylate proceeded with a good control of cis/trans diastereoselectivity (5:1) and a moderate *anti*/*syn* diastereofacial selectivity (2.6:1). The major cycloadducts arose from the reaction of the *Z* nitrone through an *endo* transition state. A further Vorbrüggen nucleosidation, followed by removal of the chiral auxiliary, furnished the corresponding β-D and β-L N,O-psiconucleosides.



Scheme 12. 1,3-Dipolar cycloaddition of a D-glyceraldehyde nitrone.

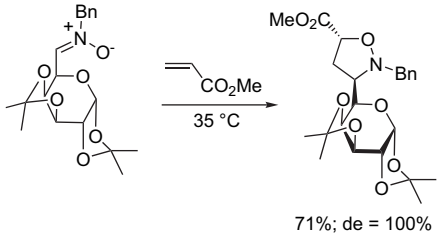
In 2001, Dhavale et al. reported the stereocontrolled 1,3-cycloaddition reaction of a silyl ketene acetal to a D-glucose-derived nitrone, leading to a diastereomeric mixture of the corresponding *O*-silyloxy-β-amino esters with excellent yield and good diastereoselectivity in favour of the L-*ido* isomer (D-*gluco*/L-*ido*=23:77).[26] These latter compounds were successfully used in the synthesis of the glycosidase inhibitors, D-*gluco*-homo-1-deoxynojirimycin and L-*ido*-homo-1-deoxynojirimycin. The applicability of this methodology was demonstrated, in 2005, during the synthesis of

biologically important polyhydroxylated indolizidine alkaloids such as castanospermine derivatives.[27] The key step of the synthesis involved the 1,3-dipolar cycloaddition of a D-glucose-derived nitrone with allyl alcohol followed by tosylation, affording the corresponding tosyloxylated isoxazolidines with complete regioselectivity in high yield (Scheme 13).



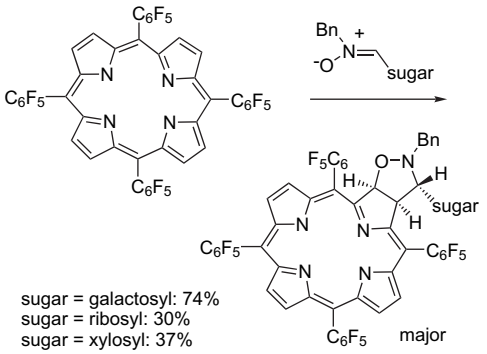
Scheme 13. 1,3-Dipolar cycloaddition of a D-glucose nitrone.

On the other hand, complete regio- and stereoselectivities were observed by Gomez-Guillen et al. in the reaction of a D-galactose-derived nitrone with methyl acrylate, yielding only one of the four possible diastereomeric cycloadducts, which arose from the *endo* attack of methyl acrylate to the *re* face of the nitrone (Scheme 14).[28] The sole isoxazolidine derivative thus formed was further converted into various enantiomerically pure hexahydroxy- and pentahydroxy-perhydroazaazulenes, ring homologues of castanospermine. In the same way, protected C7 and C8 aminodialdoses were stereoselectively prepared from the readily available C5 and C6 monosaccharide *N*-benzyl nitrones, by regio- and diastereoselective 1,3-dipolar cycloaddition reactions with vinyltrimethylsilane, followed by acetyl chloride-mediated cleavage of the 5-(trimethylsilyl)isoxazolidines formed.[29] As shown in Scheme 14, a total *endo* preference was observed for the reaction of the D-galactose-derived nitrone, while a high *endo* preference for the D-*ribo* analogue, and an *exo* preference for the D-*xylo*-configured substrate were observed. However, the attack on the *re* face of the nitrone was predominant in all cases.



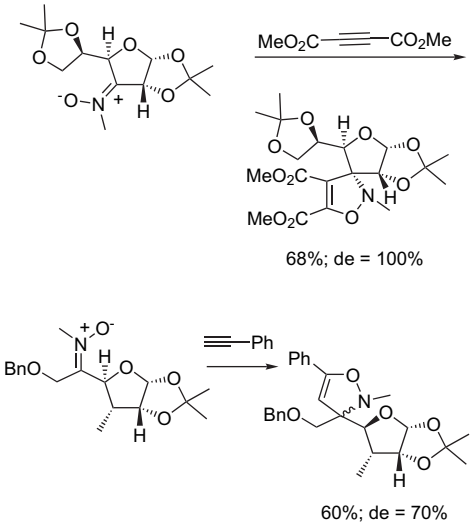
Scheme 14. 1,3-Dipolar cycloaddition of a D-galactose nitrone.

In 2002, Cavaleiro et al. developed the stereoselective synthesis of glycoconjugated isoxazolidine-fused clorins, potential photosensitisers in the photodynamic therapy of cancer, by 1,3-dipolar cycloaddition reactions of *meso*-tetrakis(pentafluorophenyl)porphyrin with glycosyl nitrones.[30] In all cases of sugar moieties, the configuration of the major products indicated an *endo* addition, as shown in Scheme 15.



Scheme 15. 1,3-Dipolar cycloaddition of sugar nitrones to a porphyrin.

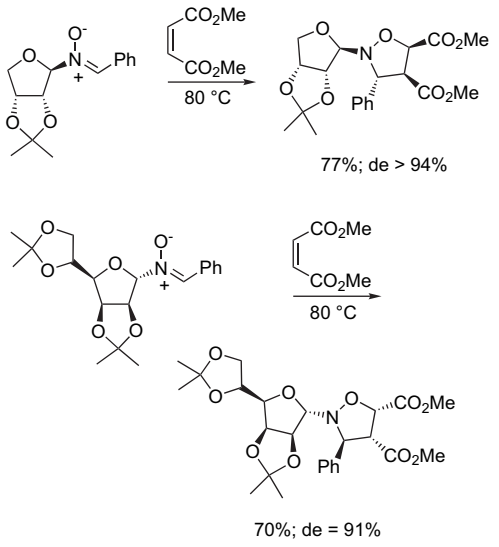
Despite their synthetic potential to build up nitrogenated quaternary centres, the use of ketonitrones has been rare, compared with the extensive studies and broad synthetic applications described for nitrones derived from aldehydes. Cyclic as well as acyclic ketonitrones were reacted with a variety of dipolarophiles such as ethyl vinyl ether, acetylenedicarboxylate, or phenylacetylene, providing the corresponding cycloadducts with moderate to complete stereoselectivities (Scheme 16).[31]



Scheme 16. 1,3-Dipolar cycloadditions of sugar ketonitrones.

In 2003, Goti et al. demonstrated the great potential of cycloaddition reactions applied to *C*-phenyl-*N*-glycosylnitrones. Indeed, *N*-glycosylnitrones underwent highly stereoselective 1,3-dipolar cycloadditions with dimethyl maleate, providing the corresponding 3,4,5-trisubstituted isoxazolidines (Scheme 17).[32]

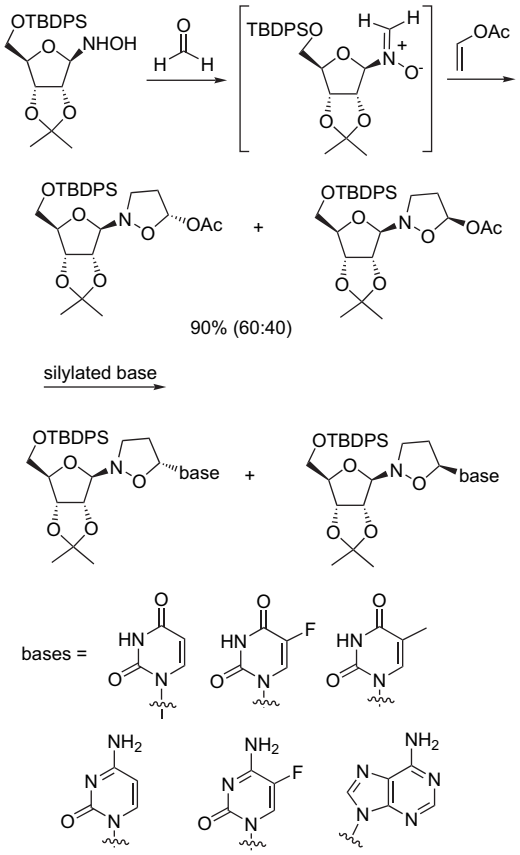
N-Glycosylnitrones have been exploited as versatile building blocks in the preparation of modified nucleosides.[33] A chiral nitrone, as a not-isolated intermediate, was prepared



Scheme 17. 1,3-Dipolar cycloadditions of *N*-glycosylnitrones with dimethyl maleate.

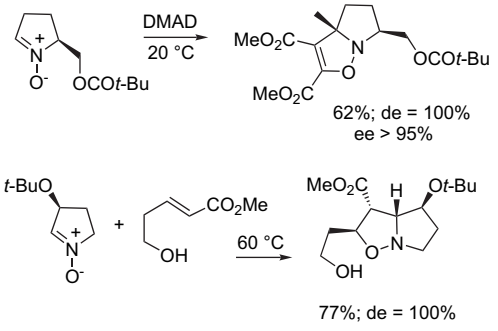
in situ by treatment of the corresponding ribosyl hydroxylamine with formaldehyde, the further reaction of which, with vinyl bases, afforded, regioselectively, a mixture of the two corresponding homochiral isoxazolidines with a modest diastereoselectivity (60:40) and 40% yield. A different synthetic approach to these latter chiral isoxazolidinyl nucleosides was based on the 1,3-dipolar cycloaddition of the same transient nitrone with vinyl acetate, followed by a Vorbrüggen nucleosidation with silylated nucleobases, providing the same diastereoselectivity, but improved yields (Scheme 18).

2.1.2. Cyclic chiral nitrones. 1,3-Dipolar cycloaddition reactions of chiral cyclic nitrones give generally a higher stereoselectivity than their acyclic counterparts, due to a more rigid skeleton, where one face of the molecule is often effectively shielded from attack by the chiral substituent. Moreover, in contrast to the acyclic dipoles, small-ring cyclic dipoles do not suffer from *E*/*Z* isomerism, since one of the isomers is much more thermodynamically stable than the other. Chiral cyclic pyrroline *N*-oxides have been amongst the most-used chiral cyclic nitrones in 1,3-dipolar cycloaddition reactions. As an example, a highly stereoselective synthesis of (*S*)-3,4-dihydro-2-pivaloyloxymethyl-2*H*-pyrrole 1-oxide was reported, in 2002, by Font et al., starting from a chiral nitrone derived from (+)-ethyl L-pyroglutamate and DMAD (Scheme 19).[34] Similarly, the 1,3-dipolar cycloaddition of (3*S*)-3-*tert*-butoxypyrroline *N*-oxide, obtained from L-malic acid, with 5-hydroxypentenoate was performed by Cordero et al. with complete regio- and stereoselectivity, since the corresponding chiral hydroxyindolizidine was isolated as the sole product (Scheme 19).[35] This methodology was applied to the stereoselective synthesis of new chiral bicyclic N,O-*iso*-homonucleoside analogues by the reaction between (*S*)-3,4-dihydro-2-benzyloxy-2*H*-pyrrole 1-oxide and allyl alcohol.[36] In this case of pyrroline *N*-oxide, a lower diastereoselectivity was observed, since a mixture of three diastereomers was quantitatively obtained in a 65:22:13 ratio. In addition, a solid-phase access to chiral polyhydroxypyrrolizidines was achieved by the same group on the basis of a 1,3-dipolar cycloaddition between an



Scheme 18. 1,3-Dipolar cycloadditions of *N*-glycosylnitrones with vinyl acetate.

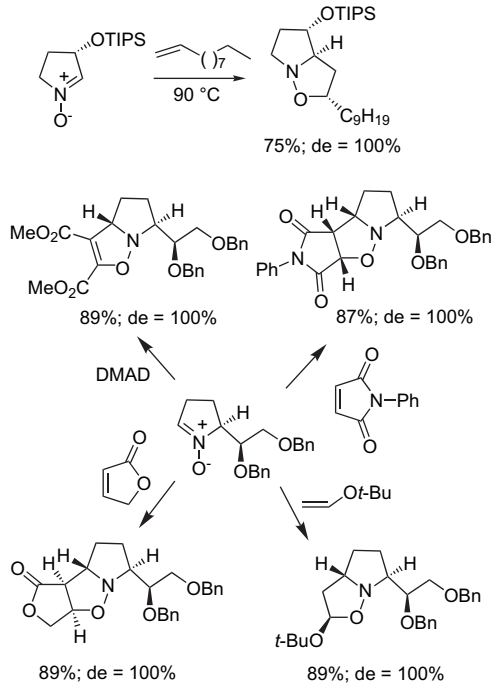
immobilised maleate or 4-hydroxycrotonate and a chiral 3-alkoxypyrroline *N*-oxide.[37]



Scheme 19. 1,3-Dipolar cycloadditions of pyrroline *N*-oxides.

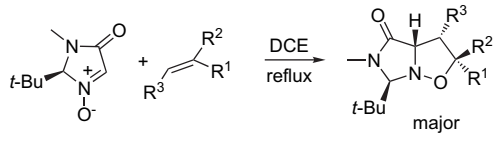
In 2002, Nagasawa et al. accomplished the first total synthesis of crambescidin 359, a novel biologically active pentacyclic guanidine alkaloid, on the basis of a 1,3-dipolar cycloaddition reaction between (*S*)-3,4-dihydro-2-hydroxy-2*H*-pyrrole 1-oxide and (2*R*)-2-*tert*-butyldimethylsilyloxy-6-heptene, giving stereoselectively the corresponding isoxazolidine as a single diastereomer in 67% yield.[38] Similarly, the stereoselective reaction of the corresponding TIPS-protected pyrroline *N*-oxide with 1-undecene was the key step of the total syntheses of (+)-batzelladine A and (−)-batzelladine D (Scheme 20).[39] On the other hand, the 1,3-dipolar cycloaddition strategy was exploited, in 2005, by Figueredo et al., in order to develop a new approach for the construction of the azabicyclic core of the *Stemona* alkaloids.[40] In this

context, the 1,3-dipolar cycloadditions of a new chiral 5-substituted pyrroline *N*-oxide derived from D-glyceraldehyde, to various dipolarophiles, were investigated, with the aim of determining the scope of this chiral nitrone as an asymmetric inductor (Scheme 20). Almost all of the dipolarophiles used in this study led to a total diastereoselectivity. In the same context, Chmielewski et al. have investigated the 1,3-dipolar cycloadditions of similar chiral nitrones, derived from (*S*)-malic acid and tartaric acid, with α,β-unsaturated δ-lactones, providing the corresponding chiral cycloadducts with high stereoselectivity, according to a sole *exo* approach of reactants, thus offering an easy access to the swainsonine-related indolizidines.[41] In addition, Goti et al. have observed total diastereoselectivities and good yields (56–78%) in the 1,3-dipolar cycloadditions of a new chiral trisubstituted pyrroline *N*-oxide with maleic and acrylic acid derivatives, occurring according to an exclusive *anti–exo* approach.[42] The thus-formed cycloadducts were further converted into potent glycosidase inhibitors such as hyacinthacine A_2 and 7-deoxycasuarine.



Scheme 20. Further 1,3-dipolar cycloadditions of pyrroline *N*-oxides.

In 2004, Baldwin and Long reported the cycloaddition reactions of a new chiral imidazolone-derived nitrone with a variety of alkenes, affording the corresponding chiral isoxazolidine cycloadducts in high yields and with high *exo* stereoselectivities (Scheme 21).[43] These latter products

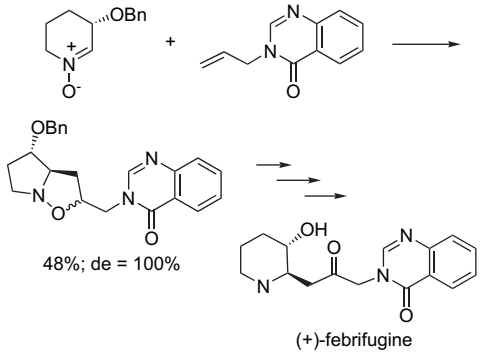


$R^1 = R^3 = H$, R^2 = Ph: 89%; de = 82%
$R^1 = R^3 = H$, R^2 = *p*-(*t*-Bu)C_6H_4: 95%; de = 90%
$R^1 = R^3 = H$, R^2 = cy: 86%; de = 82%
$R^1 = CO_2Me$, $R^2 = Me$, $R^3 = H$: 98%; de = 90%
$R^1 = H$, $R^2 = Me$, $R^3 = CO_2Me$: 98%; de = 90%

Scheme 21. 1,3-Dipolar cycloaddition of an imidazolone-derived nitrone.

were readily transformed into the corresponding α-amino-γ-lactones, which were then easily converted into the corresponding γ-hydroxy-α-amino acids.

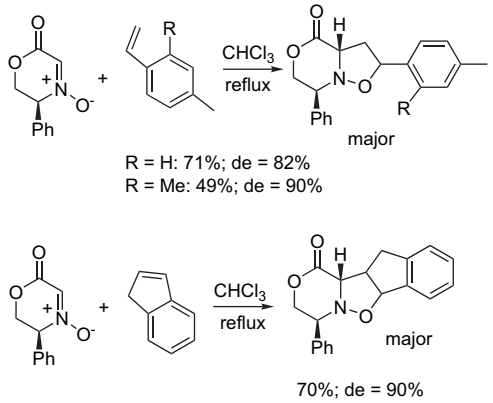
Another class of chiral cyclic nitrones, chiral 3-substituted 3,4,5,6-tetrahydropyridine *N*-oxides, have been submitted to the 1,3-dipolar cycloaddition reaction with dipolarophiles such as *N*-allylquinazolone (Scheme 22). The process was regio- and diastereoselective, leading to a single product (NMR analysis did not allow the unambiguous assignment of one carbon's stereochemistry), which was further converted into (+)-febrifugine, a potent antimalarial alkaloid.[44]



Scheme 22. 1,3-Dipolar cycloaddition of 3-benzyloxy-3,4,5,6-tetrahydropyridine *N*-oxide.

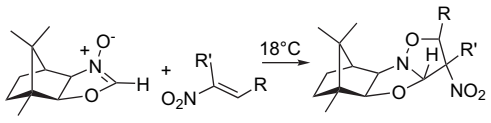
In 2001, some uncommon derivatives of homophenylalanine were prepared via the cycloaddition of a chiral cyclic nitrone glycine template with various styrene derivatives with good yields and diastereoselectivities of up to 90% de (Scheme 23).[45] A subsequent one-step hydrogenolysis (three bonds) afforded the corresponding chiral α-amino acids related to homophenylalanine.

In 2001, a new and practical synthesis of both enantiomers of protected 4-oxopipecolic acid was achieved through the 1,3-dipolar cycloaddition of *C*-ethoxycarbonyl *N*-(1*R*)-phenylethyl nitrone to but-3-en-1-ol.[46] Moreover, a camphor-derived oxazoline *N*-oxide has been submitted to the 1,3-dipolar cycloaddition in the presence of a variety of cyclic and acyclic dipolarophiles, providing, with almost complete regio- and *endo* stereoselectivity, depending on the substitution patterns of the dipolarophiles, the corresponding chiral cycloadducts.[47] In particular, a remarkable



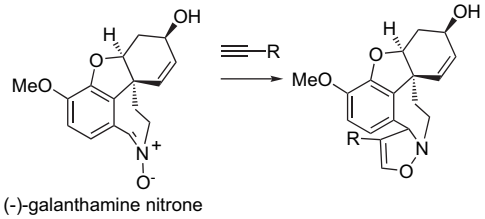
Scheme 23. 1,3-Dipolar cycloadditions of a nitrone glycine template.

reactivity of nitroalkenes in the cycloaddition is illustrated in Scheme 24, showing that a great variety of substitution onto the double bond was allowed, in that case of dipolarophiles, without any loss of regio- or stereoselectivity.[48]



Scheme 24. 1,3-Dipolar cycloadditions of a camphor-derived oxazoline *N*-oxide.

With the aim of developing a strategy towards isoxazole annellated galanthamine derivatives as novel potential acetylcholine inhibitors for anti-Alzheimer therapy, Fröhlich et al. demonstrated, in 2004, that more complex nitrones could be involved in the asymmetric 1,3-dipolar cycloaddition reaction.[49] Hence, (−)-galanthamine nitrone, prepared from (−)-norgalanthamine, was submitted to cycloaddition with alkynyl dipolarophiles, giving rise quantitatively to the corresponding isoxazole annellated compounds with complete diastereoselectivity (Scheme 25).

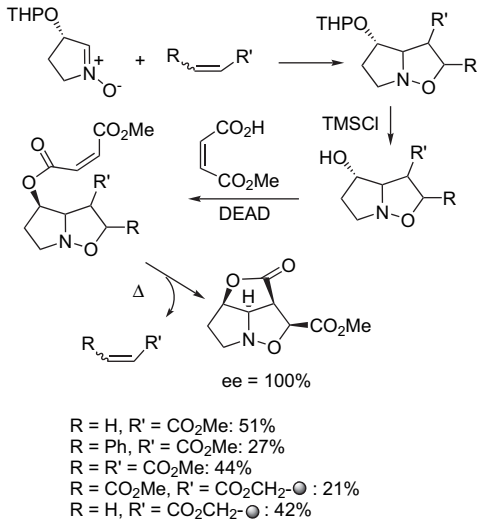


Scheme 25. 1,3-Dipolar cycloaddition of (−)-galanthamine nitrone.

In 2003, Brandi et al. reported the first examples of the successful protection of the functionality of a chiral cyclic nitrone, using a solid-supported dipolarophile and the solid-phase elaboration of the cycloadducts.[50] Hence, acrylate- and maleate-functionalised resins were used to mask the nitrone moiety of a chiral pyrroline *N*-oxide, to prevent the racemisation at the C3 stereogenic centre, and to link them to a solid phase. After the elaboration of the linked cycloadducts, the product was disconnected from the resin through a 1,3-dipolar cycloreversion/intramolecular cycloaddition domino process (Scheme 26).

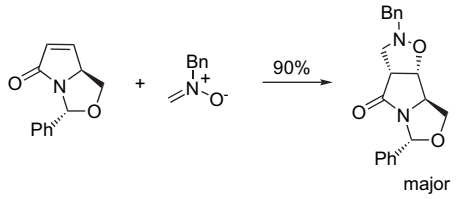
2.2. Chiral dipolarophiles

In recent years, several chiral dipolarophiles have been successfully involved in the 1,3-dipolar cycloaddition reaction with nitrones. As an example, Langlois et al. have used an (*S*)-pyroglutaminol derivative as chiral material in the cycloaddition with *N*-benzylnitrone, leading to excellent yield of a major diastereomer, as depicted in Scheme 27.[51] This product was further converted into various highly functionalised piperidines by a ring enlargement of five- to the



Scheme 26. Resin-linked dipolarophiles to mask nitrones.

corresponding six-membered nitrogen heterocycles. More recently, the [3+2]-nitrone-mediated cycloaddition reaction of (*S*)-(−)-4-benzyl-*N*-methacryloyl-2-oxazolidinone has been applied to the synthesis of highly substituted isoxazolidines with highly controlled stereochemistry.[52]

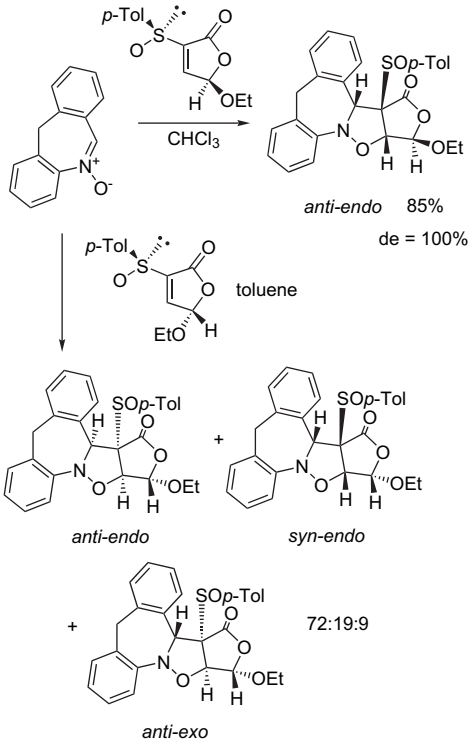


Scheme 27. 1,3-Dipolar cycloaddition of an (*S*)-pyroglutaminol derivative.

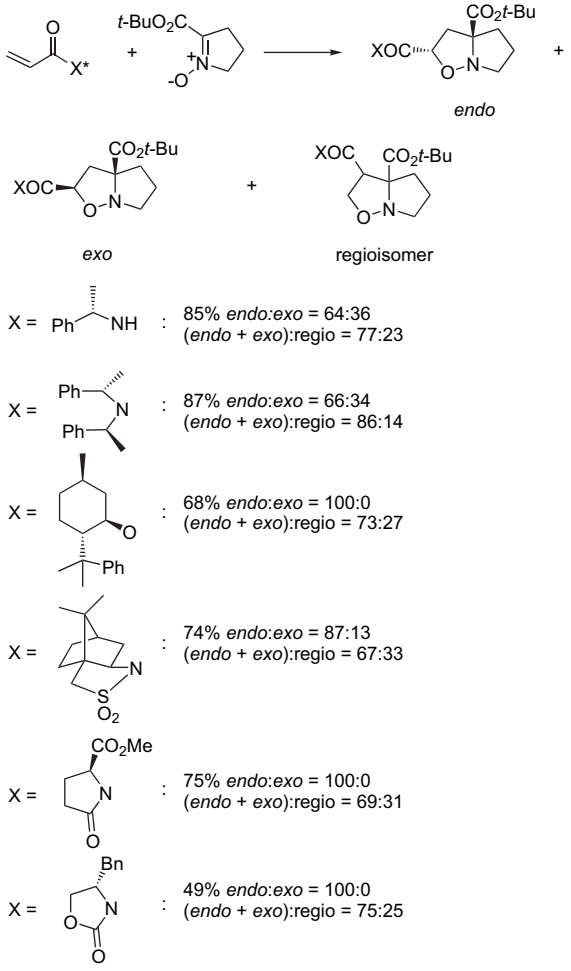
A few chiral sultams have been investigated as chiral auxiliaries in the 1,3-dipolar cycloaddition reaction. As an example, Chan et al. have reported the asymmetric cycloaddition of nitrones with chiral α,β-unsaturated-γ-sultams, providing the corresponding bicyclic chiral sultams with modest diastereoselectivities.[53] The biological activity of molecules containing a modified azepine ring has been intensively tested against various diseases. In the course of preparing new chiral pyrrolo- and isoxazoloazepines, Rosario Martin et al. have developed asymmetric 1,3-dipolar reactions of 3-sulfinylfuran-2(5*H*)-ones with 11*H*-dibenzo-[*b*,*e*]azepine 5-oxide, affording the corresponding furo-isoxazoloazepines (Scheme 28).[54] In one case, the regio-, π-facial and *endo*-selectivities were complete, yielding only one diastereoisomer.

In 2006, Brandi et al. studied the 1,3-dipolar cycloadditions of a series of chiral acrylates and acrylamides with 2-*tert*-butoxycarbonyl-1-pyrroline *N*-oxide.[55] In some cases, total diastereoselectivities were observed, as depicted in Scheme 29.

In addition, Faita et al. have developed a soluble polymer-supported chiral oxazolidinone (Evans' chiral auxiliary), which was reacted with diphenylnitrone, leading to the corresponding cycloadducts in high purities and fair yields after reductive cleavage.[56]

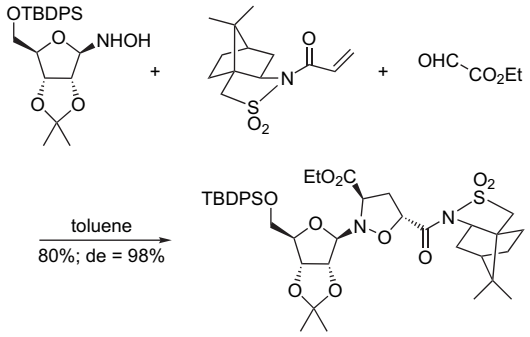


Scheme 28. 1,3-Dipolar cycloadditions of 3-sulfinylfuran-2(5*H*)-ones.



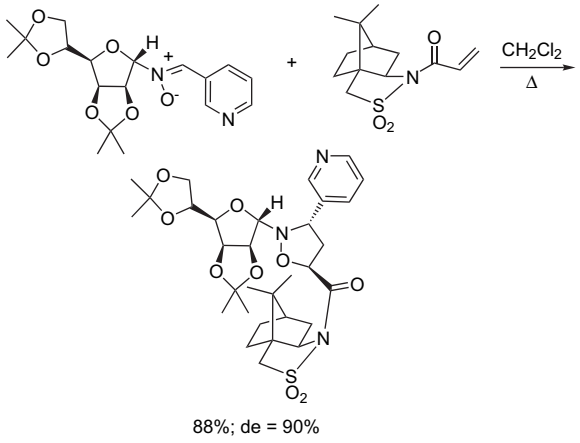
Scheme 29. 1,3-Dipolar cycloadditions of chiral acrylates and acrylamides.

An interesting example of double asymmetric induction was reported by Merino et al., in 2002, involving the asymmetric 1,3-dipolar cycloaddition between Oppolzer's sultam acrylamide and 2,3-*O*-isopropylidene-D-glyceraldehyde nitrone, providing a mixture of three cycloadducts in a 60:20:20 ratio and 94% yield.[16] The cycloadducts were further used for the stereoselective synthesis of various protected 4-hydroxypyroglutamic acids. The same group has developed a multicomponent reaction including an asymmetric 1,3-dipolar cycloaddition between a chiral nitrone derived from glyoxylic acid and protected D-ribosyl hydroxylamine with Oppolzer's sultam acrylamide, providing the corresponding N,O-nucleoside precursors (Scheme 30).[57]



Scheme 30. 1,3-Dipolar multicomponent reaction with double asymmetric induction.

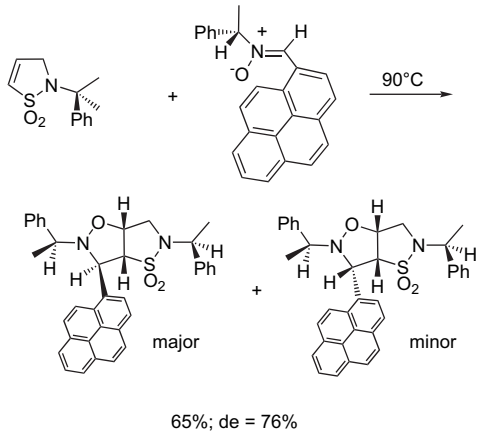
In order to develop the synthesis of (3′*R*,5′*S*)-3′-hydroxycotinine, one of the main metabolites of nicotine, the same chiral sultam as that depicted in Scheme 30 was reacted with an L-glucose-derived nitrone, providing the expected cycloadduct in 90% de (Scheme 31).[58]



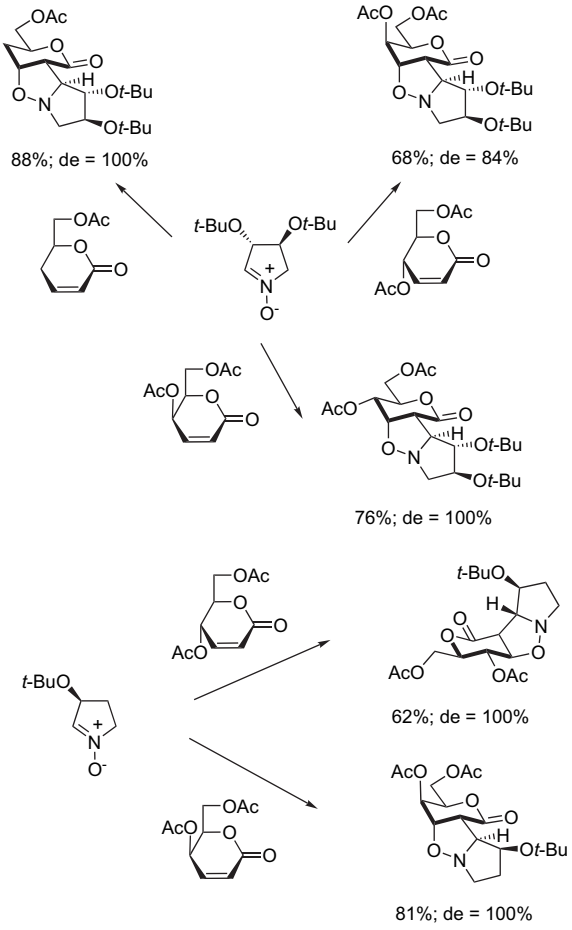
Scheme 31. 1,3-Dipolar cycloaddition with double asymmetric induction.

The double asymmetric induction strategy was also applied by Chan et al., in 2004, to the 1,3-dipolar cycloaddition of a chiral α,β-unsaturated-γ-sultam with a chiral nitrone, providing the corresponding chiral cycloadducts in an 88:12 diastereomeric ratio (Scheme 32).[59]

Another interesting example of double asymmetric induction in 1,3-dipolar cycloadditions was developed by Chmielewski et al., involving chiral five-membered cyclic nitrones and chiral 2,3-unsaturated sugar 1,5-lactones, proceeding exclusively in an *exo* mode (Scheme 33).[60] The high preference



Scheme 32. 1,3-Dipolar cycloaddition with double asymmetric induction.

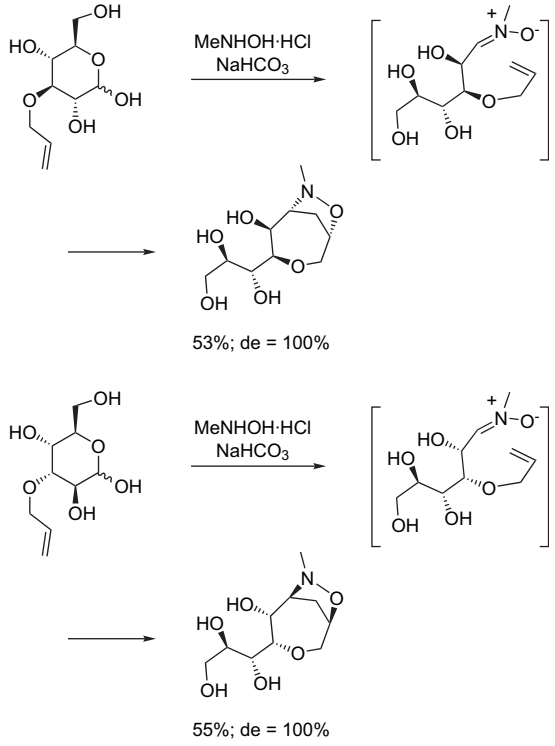


Scheme 33. 1,3-Dipolar cycloadditions with double asymmetric induction.

for *anti* addition of the nitrones to the terminal acetoxymethyl group in the lactones could be explained in terms of the axial approach of the nitrogen oxygen atom, the 3-*tert*-butoxy group of the nitrone playing a similar role. In almost all cases, the formation of a single diastereomer was observed.

2.3. Intramolecular reactions

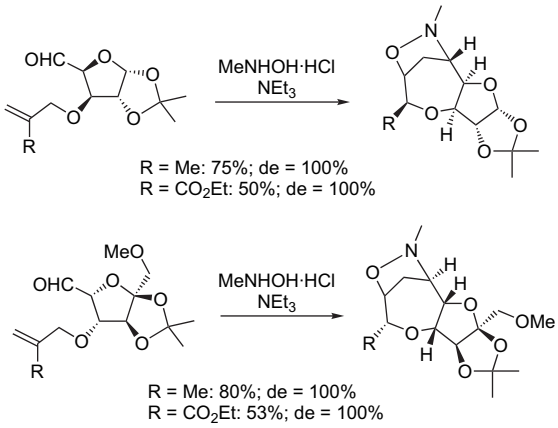
Asymmetric intramolecular 1,3-dipolar cycloadditions constitute an effective approach for the synthesis of enantiopure polycyclic compounds in a single step. Intramolecular 1,3-dipolar cycloaddition reactions have several advantages over the corresponding intermolecular reactions.[9] Hence, in most cases, the asymmetric intramolecular 1,3-dipolar cycloadditions are known to proceed with higher diastereoselectivities than those of the intermolecular variant, because the flexibility of the reactant is much more restricted. Moreover, due to entropy factors, the activation barrier for the reaction is lower, allowing lower reaction temperatures and the use of dipoles and dipolarophiles of lower reactivity. The degree of spatial freedom in the transition state of an intramolecular reaction is, of course, limited, compared with the intermolecular reactions. Hence, a higher degree of regioselectivity, *endo*/*exo* selectivity and diastereofacial selectivity is usually observed in intramolecular 1,3-dipolar cycloaddition reactions. A number of 1,3-dipolar intramolecular cycloaddition reactions involving chiral nitrones derived from sugars are present in the literature. As an example, intramolecular nitrone cycloadditions have been performed by Shing and Zhong, with the aim of developing the ring-selective synthesis of *O*-heterocycles from acyclic 3-*O*-allyl-monosaccharides.[61,62] Hence, nitrones, generated in situ from 3-*O*-allyl-D-glucose and D-altrose, afforded, highly stereoselectively, the corresponding chiral oxepanes (Scheme 34), whereas the similar reaction of nitrones derived from 3-*O*-allyl-D-allose and D-mannose gave the corresponding chiral tetrahydropyrans as mixtures of two diastereomers. In the same context, the reaction of 3-*O*-benzyl-1,2-*O*-isopropylidene-1,5-pentadialdo-α-D-xylofuranose with *N*-(1,1-dimethylbut-3-enyl)-hydroxylamine, followed by intramolecular 1,3-dipolar cycloaddition, yielded the corresponding chiral 7-oxa-1-azabicyclo[2.2.1]heptane



Scheme 34. 1,3-Dipolar intramolecular cycloadditions of D-glucose- and D-altrose-derived nitrones.

derivative, which was further easily converted into novel chiral polyhydroxylated derivatives of quinolizidine and indolizidine.[63] In 2003, the syntheses of various chiral oxepanes and pyrans were developed by Bhattacharjya et al., starting from 3-*O*-allyl-carbohydrate nitrones.[64] In this work, it was demonstrated that the regioselectivity of the cycloaddition was dependent on the skeletal nature of the carbohydrate backbone of the nitrone, the substitution at C3, the stereochemistry at C3, and the substitution at the allyl terminus of the *O*-allyl moiety.

In 2003, Sharma et al. reported the highly stereoselective synthesis of chiral furano-oxepanes via intramolecular nitrone cycloaddition reactions on sugar-derived 2-substituted allylic ethers (Scheme 35).[65] It was clearly demonstrated that the substituent on the 2-position of the allylic group had a prominent role in defining the regiochemical outcome, thus resulting in seven-membered oxepane ring systems as the exclusive products.

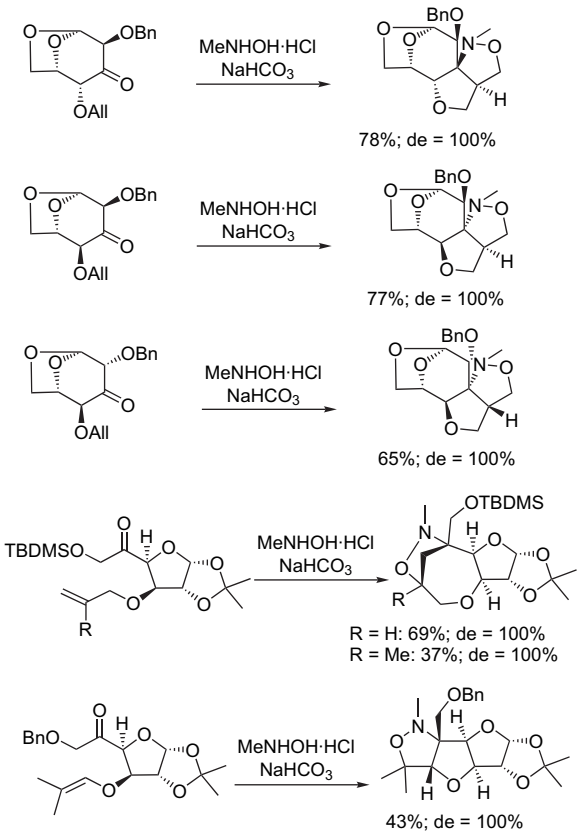


Scheme 35. 1,3-Dipolar intramolecular cycloadditions of sugar-derived 2-substituted allylic ethers.

These methodologies were extended to much less common chiral nitrones such as those derived from ketones, e.g., ketopyrano- and ketofuranonitrones, which led to the corresponding cycloadducts in good yields and as a single stereoisomer from each of the ketosugars (Scheme 36).[31]

In 2001, Dhavale et al. reported the 1,3-dipolar intramolecular cycloaddition reaction of a chiral nitrone generated in situ from a sugar-derived α,β-unsaturated ester by treatment with *N*-benzylhydroxylamine hydrochloride (Scheme 37).[66] This latter nitrone spontaneously underwent a diastereo- and regioselective intramolecular cycloaddition to afford a chiral hydroxyl-functionalised 4-*exo*-ethoxycarbonyl-3-oxa-2-azabicyclo[3.3.0]octane system, a precursor to a hitherto unknown aminocyclopentitol derivative.

In 2005, Kovacs et al. studied the intramolecular 1,3-dipolar cycloaddition of unsaturated nitrones derived from methyl α-D-glucopyranoside with 2-furaldehyde, affording a mixture of three 9-oxa-1-azabicyclo[4.2.1]nonane diastereomers in a 3:1:1 ratio.[67] On the other hand, the intramolecular nitrone strategy was applied by Mandal et al. to the simple syntheses of chiral spironucleosides and spirobisnucleosides.[68] Hence, the reaction of D-glucose-derived precursors

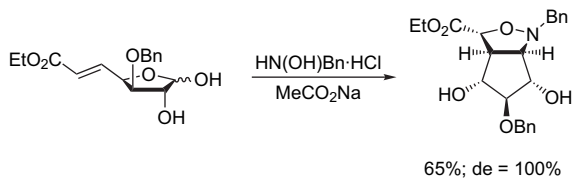


Scheme 36. 1,3-Dipolar intramolecular cycloadditions of ketonitrones.

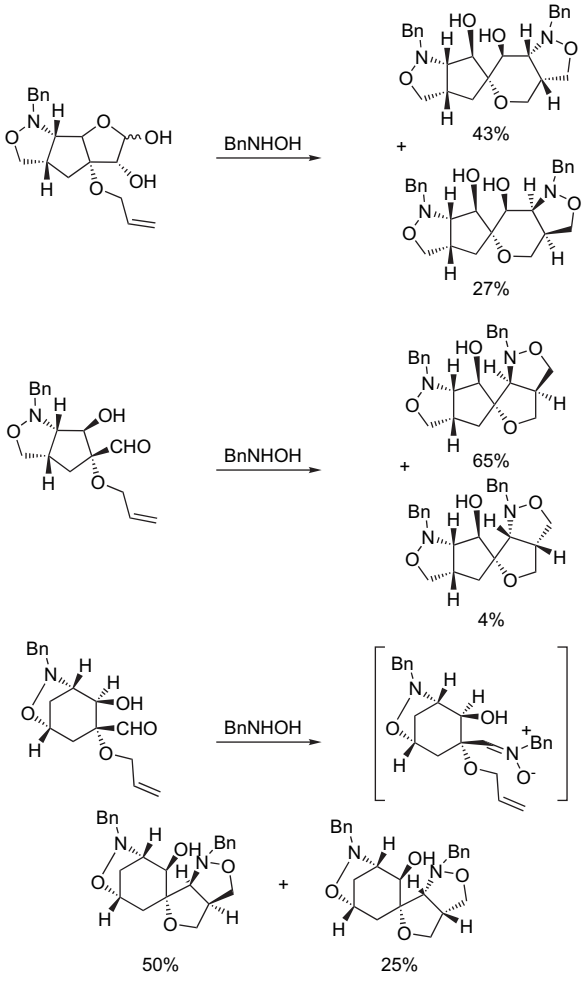
having an olefin at C3 and a nitrone at C5, C1, or C2 (in nor-series) furnished the corresponding bisisoxazolidinospirocycles in good yields as mixtures of two diastereomers (Scheme 38).

Very recently, Bhattacharya et al. have demonstrated that highly stereoselective syntheses of chiral oxepanes and pyrans were possible through intramolecular nitrone cycloadditions performed in organised aqueous media.[69] A much improved stereoselectivity relative to that observed in conventional organic solvents was observed, since the exclusive formation of a single isomer was observed in all cases with yields up to 85%.

A number of chiral nitrones, which are not derived from sugars, have been involved in 1,3-dipolar cycloaddition reactions. In this context, an efficient and simple method for the synthesis of functionalised azaoxobicycloalkane amino acids has been devised by Manzoni et al. in 2005.[70] The key step was an intramolecular cycloaddition on 5-allyl- or

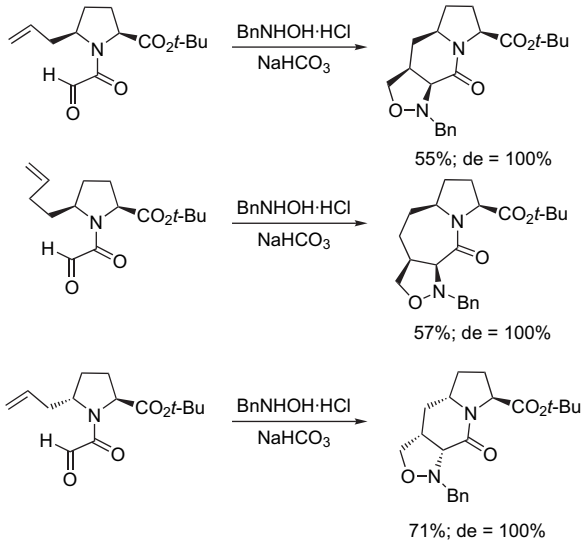


Scheme 37. 1,3-Dipolar intramolecular cycloaddition of a sugar-derived α,β-unsaturated ester.



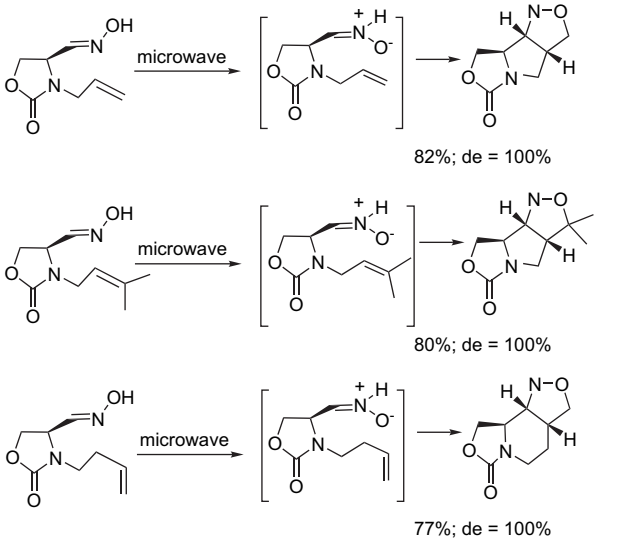
Scheme 38. 1,3-Dipolar intramolecular cycloadditions of D-glucose-derived nitrones.

5-homoallylproline, which was found to be completely regio- and stereoselective (Scheme 39).



Scheme 39. 1,3-Dipolar intramolecular cycloadditions of proline-derived nitrones.

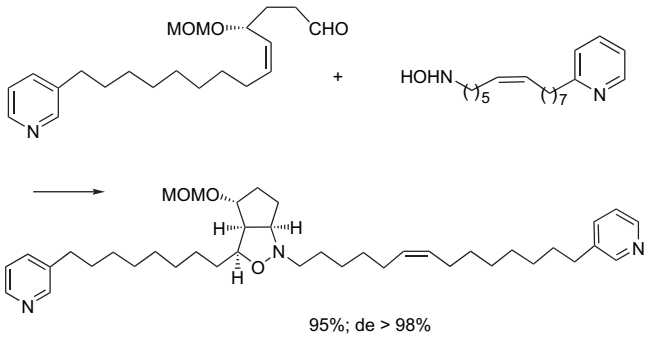
The total highly stereoselective synthesis of (−)-rosmarinecine, a pyrrolizidine alkaloid, was reported by Goti et al., in 2001, on the basis of an intramolecular cycloaddition of (*S*)-malic acid-derived pyrroline *N*-oxide, occurring with complete stereoselectivity.[71] On the other hand, the chiral preparation of functionalised tricyclic isoxazolidines fused with a pyrrolidine or piperidine ring was reported by Cheng et al., who demonstrated that highly stereoselective 1,3-dipolar intramolecular cycloadditions of chiral nitrones derived from L-serine could be induced on the surface of silica gel without the presence of a solvent and under microwave irradiation (Scheme 40).[72]



Scheme 40. Microwave-induced 1,3-dipolar intramolecular cycloadditions of L-serine-derived nitrones.

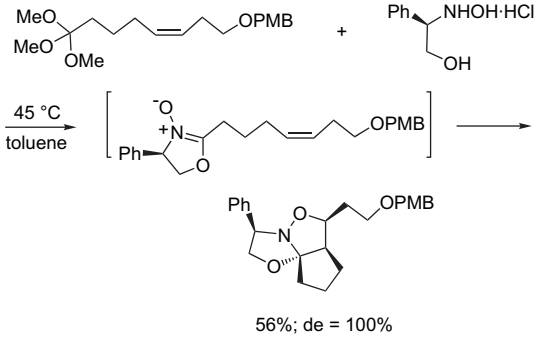
In 2004, Williams and Looper reported a concise asymmetric synthesis of the marine hepatotoxin, 7-epicylindrospermopsin, on the basis of a stereoselective intramolecular cycloaddition of a chiral allyl oxazinone *N*-oxide, which gave, in 78% yield, the corresponding tricyclic isoxazolidine as a 91:9 diastereomeric mixture, with the major product assumed to arise from an *exo* approach of the alkene to the nitrone.[73] A similar methodology was applied by the same group, in 2006, in the course of developing the syntheses of the cylindrospermopsin alkaloids, giving a similar diastereoselectivity.[74] Chiral nitrones derived from thiophene-2-carboxylic acids were submitted to intramolecular cycloaddition by Zecchi et al., in order to provide the new isoxazolo[3,4-*d*]thieno[2,3-*b*]pyridine system.[75] The regioselectivity of the reaction was complete, whereas the diastereoselectivity was modest with des up to 34%. In 2003, Morimoto et al. accomplished the first asymmetric total synthesis of a structurally novel *cis*-cyclopent[*c*]isoxazolidine alkaloid, (−)-pyrinodemin A, exhibiting a potent cytotoxicity (Scheme 41).[76] The key step was a highly diastereoselective intramolecular cycloaddition reaction of an alkenylnitrone derived from a hydroxylamine and a chiral aldehyde, providing the corresponding bicyclic product in high yield and excellent diastereoselectivity (>98% de). On the other hand, a synthetic sequence, involving a stereocontrolled intramolecular nitrone-olefin dipolar cycloaddition, has been developed for the preparation of

enantioenriched 2-formyl-4-phenyl-1-aminocyclopentanes from a β-allyl-substituted aldehyde.[77] Further manipulations allowed access to a chiral β-lactam. In 2005, White and Hansen reported the total synthesis of (−)-7-epicylindrospermopsin, a toxic metabolite of the freshwater cyanobacterium, *Aphanizomenon ovalisporum*, involving an intramolecular dipolar cycloaddition of a chiral nitrone, leading to substituted 1-aza-7-oxobicyclo[2.2.1]heptanes in a diastereomeric ratio of 2:1.[78] In this case, the nitrone was not formed in situ during the reaction, but was previously prepared from the condensation of the corresponding aldehyde with a chiral hydroxylamine. On the other hand, modest stereoselectivities were observed by Chiacchio et al. for the intramolecular cycloaddition of an unisolated chiral α-allyloxycarbonylnitrone derived from glyoxylic acid, providing a 1:1 diastereomeric mixture of furoisoxazolidines in 40–50% yield.[79]



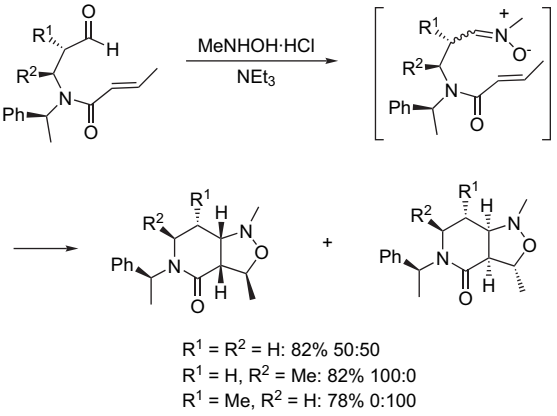
Scheme 41. 1,3-Dipolar intramolecular cycloaddition of an alkenylnitrone.

In order to develop a new access to a bicyclic isoxazolidine related to the pyrinodemin family of alkaloids, Kouklovsky et al. developed, in 2005, the intramolecular dipolar cycloaddition of a chiral nitrone arising from the hydroxyamino-alcohol hydrochloride derived from 1-phenylglycinol and an unsaturated trimethylorthoester (Scheme 42).[80] The reaction gave a single cycloadduct arising from an *exo*-transition state, in which the dipolarophile approached the dipole from the face opposite to the phenyl substituent on the oxazoline ring. The *endo* transition state was destabilised by torsion of the chain and steric repulsions between the OPMB group and the oxazoline ring hydrogens.



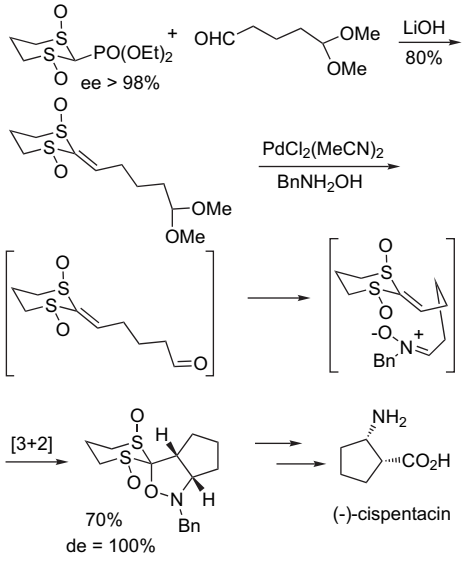
Scheme 42. 1,3-Dipolar intramolecular cycloaddition of an oxazoline *N*-oxide.

In 2005, Romeo et al. developed a synthetic approach to chiral bicyclic isoxazolidinylpyridin-4(1*H*)-ones through intramolecular cycloadditions of nitrones prepared from chiral β-amino acids (Scheme 43).[81] A complete diastereoselectivity was observed when a stereocentre was present at the α position with respect to the amido group, or at the α position with respect to the nitrone group, otherwise the process was found to be stereospecific, but lacking in any diastereofacial selectivity.



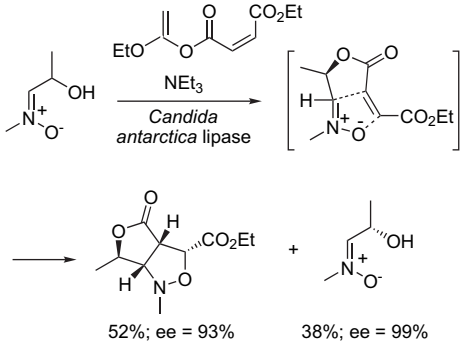
Scheme 43. 1,3-Dipolar intramolecular cycloadditions of β-amino acid-derived nitrones.

In 2003, Aggarwal et al. reported the intramolecular 1,3-dipolar nitrone cycloaddition onto an enantiomerically pure ketene dithioacetal dioxide using a three-carbon tether, providing the corresponding 5,5-disubstituted isoxazolidine as a single diastereomer (Scheme 44).[82] In fact, such a process was the first example of an intramolecular cycloaddition in which a chiral ketene equivalent was employed. This reaction has been used as the key step in an asymmetric synthesis of the naturally occurring antibiotic, (−)-cispentacin. In addition, the first asymmetric synthesis of 4-amino-pyrrolidine-3-carboxylic acid has also been carried out, using the intramolecular nitrone cycloaddition as the stereocontrolling step. In 2001, Chiacchio et al. developed the stereoselective synthesis of a variety of chiral annulated sultams via intramolecular cycloaddition reactions of nitrones derived from L-amino acids.[83]



Scheme 44. 1,3-Dipolar intramolecular cycloaddition of a chiral ketene dithioacetal bis(sulfoxide).

In 2001, Tamura et al. investigated the diastereofacial selectivity of the intramolecular cycloaddition of chiral α-allyloxycarbonylnitrones by employing a tandem process.[84] It was found that the factors governing diastereofacial selection were highly dependent on the geometries of the precursor allylic alcohols. In addition, in the course of developing a concise asymmetric total synthesis of (−)-rosmarinecine, Kita et al. developed, in 2005, a lipase-catalysed domino kinetic resolution of an α-hydroxynitrone/intramolecular 1,3-dipolar cycloaddition reaction (Scheme 45).[85]

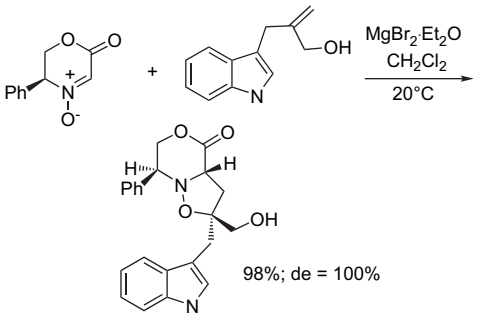


Scheme 45. Lipase-catalysed domino kinetic resolution of an α-hydroxynitrone/intramolecular 1,3-dipolar cycloaddition reaction.

2.4. Metal-catalysed reactions

Metal-catalysed asymmetric 1,3-dipolar cycloadditions have only recently become an important research field.[6,7,86] The efficiency of chiral catalysts relies not only on the capability of the enantiopure catalyst to help discriminate between the two π-faces of the dipolarophile, but also on its ability to control both the *exo*/*endo* selectivity and the regiochemistry as well as the yield. When coordinating to the dipole or the dipolarophile, the Lewis-acid catalysts lower the energy difference between the LUMO–HOMO of the reacting species. The result is that the LUMO energy of one of the reacting species is lowered. This decreases the energy gap between the HOMO and the LUMO of the dipole and the dipolarophile, leading to an increased reactivity. Effective catalysis by the use of a wide variety of chiral Lewis-acid catalysts has been reported for the nitrone cycloaddition reactions using both electron-deficient and rich alkene dipolarophiles. This section has been organised according to the nature of the metal catalysts. Catalysts containing Mg^{2+} such as $MgBr_2$ have recently been employed by several groups for the chelation-controlled nitrone cycloaddition. As an example, Tamura et al. developed, in 2003, this methodology for the key step of a highly stereoselective synthesis of (−)-monatin, a high-intensity sweetener.[87] Hence, the cycloaddition of a chiral six-membered cyclic nitrone with an allylic alcohol in the presence of $MgBr_2$ yielded the corresponding cycloadduct with complete stereoselectivity (Scheme 46). This latter product was further elaborated to (−)-monatin in three steps.

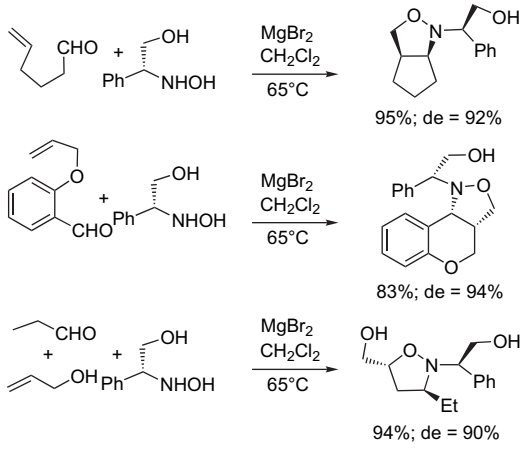
Similar conditions have been applied to several chiral acyclic nitrones. Hence, chiral isoxazolidines have been synthesised in diastereomeric excesses of up to 94% via an $MgBr_2$-induced chelation-controlled 1,3-dipolar cycloaddition reaction with *N*-hydroxyphenylglycinol and as a chiral



Scheme 46. $MgBr_2$-induced cycloaddition of a six-membered cyclic nitrone.

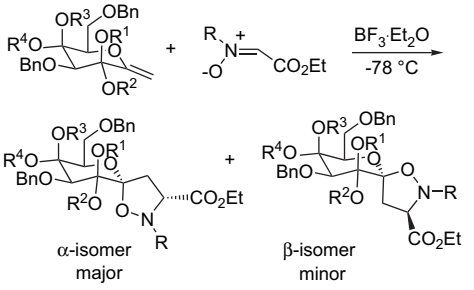
auxiliary (Scheme 47).[88] In 2001, Faita et al. evaluated 1,3-dipolar cycloadditions of supported Evans' chiral auxiliary with diphenylnitrone in the presence of the Mg(II) cation as the catalyst.[89] The presence of acetonitrile, and the use of catalytic amounts of the Mg(II) cation in the solid-phase protocol, allowed the corresponding chiral cycloadducts to be obtained with an excellent control of the diastereoselectivity (up to 90% de).

In 2002, Schneider et al. reported the intramolecular 1,3-dipolar cycloaddition reaction of a nitrone derived from secoestrone aldehyde, induced by $BF_3 \cdot Et_2O$, giving access to novel chiral heterocyclic estrone derivatives in high yields and with total chemo-, regio- and diastereoselectivities.[90] In order to provide a new access to *C*-glycosyl amino acids, Ikegami et al. developed, in 2003, the α-stereoselective synthesis of spiro ketosyl isoxazolidines by 1,3-dipolar cycloadditions of 1-methylene-sugars with nitrones under the catalysis of $BF_3 \cdot Et_2O$ (Scheme 48).[91] In 2005, Pellegrinet et al. reported a computer-assisted design of asymmetric 1,3-dipolar cycloadditions between dimethylvinylborane and a variety of chiral nitrones, with the aim of identifying the requisite structural features to achieve high levels of selectivity.[92] Excellent regioselectivities towards the formation of the 5-borylisoxazolidines were computed in all cases, due to the presence of a strong secondary orbital interaction between the boron of the vinylborane and the oxygen atom of the nitrones. It was shown that *endo* transition structures, leading to the favoured products, adopted chair-like



Scheme 47. $MgBr_2$-induced cycloadditions of an *N*-hydroxyphenylglycinol-derived acyclic nitrone.

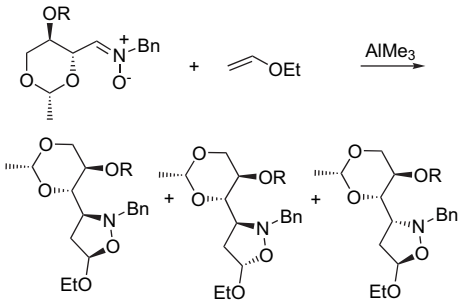
conformations only, unlike their *exo* counterparts, which exhibited either boat or twist-boat structures. Placing a stereocentre adjacent to the nitrone nitrogen atom appeared to be an effective strategy to stereodiscriminate the *anti* and *syn* approaches of the dipolarophile.



R = Bn, $R^1 = R^3 = H$, $R^2 = R^4 = Bn$: 72% + 6%
R = Bn, $R^1 = R^4 = H$, $R^2 = R^3 = Bn$: 73% + 5%
R = Bn, $R^1 = R^4 = Bn$, $R^2 = R^3 = H$: 58% + 11%
R = Me, $R^1 = R^3 = H$, $R^2 = R^4 = Bn$: 70% + 8%
R = Me, $R^1 = R^4 = H$, $R^2 = R^3 = Bn$: 69% + 8%
R = Me, $R^1 = R^4 = Bn$, $R^2 = R^3 = H$: 54% + 29%

Scheme 48. $BF_3 \cdot Et_2O$-catalysed cycloadditions of acyclic nitrones to 1-methylene-sugars.

In 2005, diastereoselective 1,3-dipolar cycloadditions of chiral sugar-derived nitrones with enol ethers were performed under $AlMe_3$ catalysis by Fisera et al.[93] The corresponding chiral products were obtained as mixtures of only two diastereomers, and were further converted through oxidative ring opening of the oxazolidines into a new class of β-amino acid esters. The diastereoselectivity of the reaction was reversed when the nitrone was substituted with TBDPS (Scheme 49).

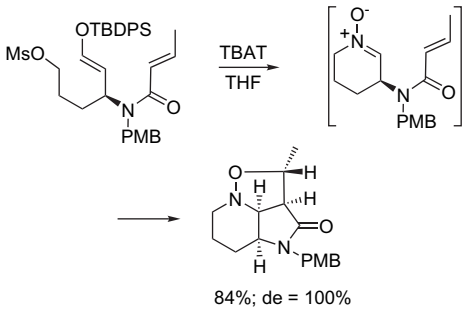


R = H: 76% (83:0:17)
R = TBDPS: 74% (11:89:0)

Scheme 49. $AlMe_3$-catalysed cycloadditions of nitrones to an enol ether.

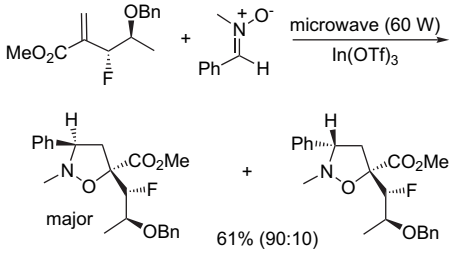
Tetrabutylammonium triphenyldifluorosilicate (TBAT) has proved to be very efficient for mediating the nitrone formation of ω-mesyloxy-*O*-*tert*-butyldiphenylsilyloximes.[94] In some cases, such as that depicted in Scheme 50, a sequential nitrone formation and intramolecular cycloaddition occurred in a highly stereoselective manner. The cycloadduct possessed a backbone close to the alkaloid, laccarin, showing phosphodiesterase inhibitory activity.

The first 1,3-dipolar cycloaddition using allylic fluorides was reported, in 2004, by Comes-Franchini et al.[95] This reaction, performed in the presence of *Z*-α-phenyl-*N*-methylnitrone and a chiral allylic fluoride, was catalysed by a Lewis acid



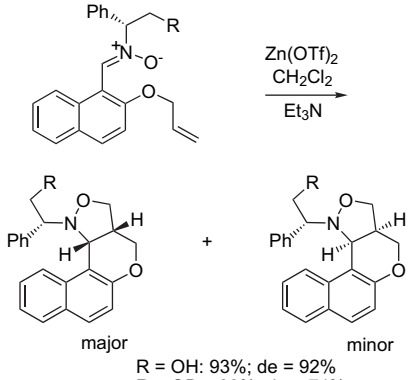
Scheme 50. TBAT-mediated nitrone formation cycloaddition reaction of an ω-mesyloxy-*O*-*tert*-butyldiphenylsilyloxime.

such as $In(OTf)_3$ under solvent-free conditions and microwave irradiation, giving the corresponding unknown chiral fluorinated isoxazolidines as a mixture of two diastereomers in a 90:10 ratio (Scheme 51). A subsequent reductive opening of these cycloadducts allowed the chiral amino polyols to be obtained. In addition, Hultin et al. reported, in 2005, the nitrone cycloaddition of a fluorous oxazolidinone chiral auxiliary, catalysed by a variety of catalysts such as $Yb(OTf)_3$ or $Sc(OTf)_3$, providing yields and selectivities comparable with the conventional Evans-type auxiliaries.[96]



Scheme 51. $In(OTf)_3$-catalysed cycloaddition of *Z*-α-phenyl-*N*-methylnitrone to a chiral allylic fluoride.

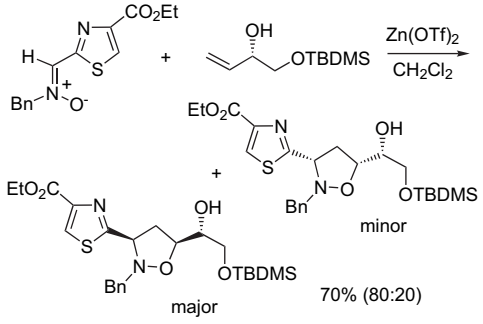
The use of the Zn(II) cation to mediate 1,3-dipolar cycloadditions was reported by Romero et al., in 2002, in the course of developing a stereoselective synthesis of chiral substituted chromanes.[97] The key to the success of this highly stereoselective intramolecular cycloaddition was the choice of the chiral nitrone bearing a pendant coordinating group, and $Zn(OTf)_2$ as the Lewis acid, which allowed diastereoselectivities of up to 92% de to be obtained (Scheme 52).



R = OH: 93%; de = 92%
R = OBn: 93%; de = 74%
R = OMe: 90%; de = 82%
R = H: 92%; de = 20%

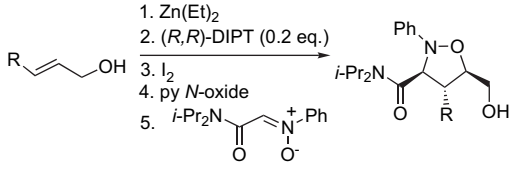
Scheme 52. $Zn(OTf)_2$-catalysed intramolecular cycloadditions of nitrones.

The same Lewis acid was recently employed by Chiacchio et al., in order to control 1,3-dipolar cycloadditions of *C*-(2-thiazolyl) nitrones with chiral allylic alcohols (Scheme 53).[98] The reaction occurred with a total regioselectivity and 80% diastereofacial selectivity, according to an exclusive *exo* approach. Application of this methodology allowed the synthesis of a new chiral isoxazolidinyl analogue of the antitumour C-nucleoside, tiazofurin.



Scheme 53. $Zn(OTf)_2$-mediated cycloaddition of a *C*-(2-thiazolyl) nitrone.

On the other hand, Inomata et al. have found that diisopropyl (*R*,*R*)-tartrate [(*R*,*R*)-DIPT] could serve as an efficient chiral catalyst together with $ZnEt_2$ in the highly diastereo- and enantioselective 1,3-dipolar cycloaddition of nitrones bearing a bulky amide moiety to γ-substituted allylic alcohols, furnishing the corresponding chiral 3,4,5-trisubstituted isoxazolidines with excellent enantioselectivities of up to over 99% ee (Scheme 54).[99]



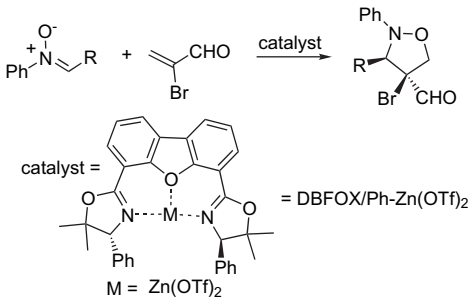
R = Me: 64%; ee > 99%
R = *n*-Pr: 48%; ee > 99%
R = CO_2Me: 63%; ee = 97%
R = CO_2Et: 61%; ee = 92%
R = CO_2*i*-Pr: 37%; ee = 94%

Scheme 54. $ZnEt_2$-[(*R*,*R*)-DIPT]-catalysed cycloadditions of a nitrone.

Metal complex catalysts such as DBFOX/Ph–$Zn(OTf)_2$ have been successfully applied by Kanemasa et al. to the nitrone cycloadditions to a variety of α,β-unsaturated aldehydes, providing excellent enantioselectivities of up to 99% ee at room temperature with a catalytic loading of 2 mol % (Scheme 55).[100]

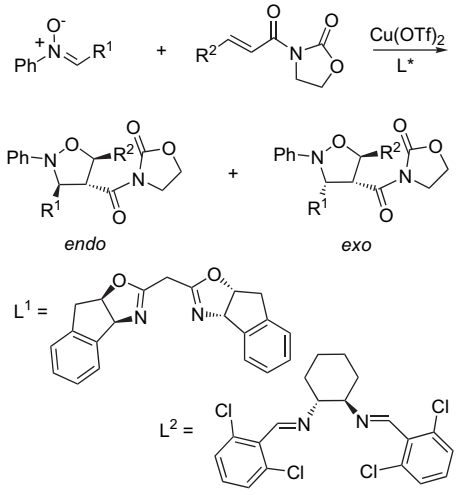
Several groups have reported very efficient $Cu(OTf)_2$-catalysed nitrone cycloadditions performed in the presence of chiral ligands. As an example, Saito et al. have used chiral bis(oxazoline) and bis(imine) ligands to catalyse the reaction of nitrones with electron-deficient dipolarophiles, which occurred with extremely high enantioselectivity in both cases (Scheme 56).[101]

In the same context, Palomo et al. reported, in 2005, the catalytic enantioselective 1,3-dipolar cycloadditions of nitrones with α′-hydroxy enones carried out in the presence of the



R = Ph: 100%; de > 98%; ee = 97%
R = *p*-Tol: 94%; de = 98%; ee = 94%
R = *p*-BrC_6H_4: 89%; de > 98%; ee = 98%
R = *p*-$NO_2C_6H_4$: 88%; de > 98%; ee > 99%
R = 2-Fu: 67%; de = 90%; ee = 97%
R = 1-Np: 98%; de > 98%; ee > 99%
R = 2-Np: 96%; de > 98%; ee = 98%

Scheme 55. DBFOX/Ph–$Zn(OTf)_2$-catalysed cycloadditions of nitrones.



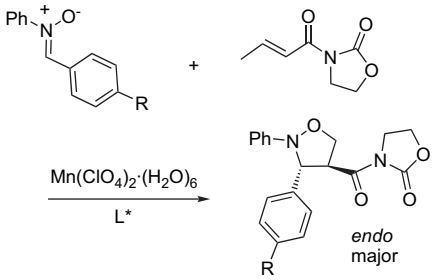
with L* = L^1:
R^1 = Ph, R^2 = Me: 99% (70:30) ee (*endo*) > 99%
R^1 = *p*-FC_6H_4, R^2 = Me: 89% (80:20) ee (*endo*) = 95%
R^1 = *p*-$CF_3C_6H_4$, R^2 = Me: 99% (86:14) ee (*endo*) = 95%
R^1 = *p*-NCC_6H_4, R^2 = Me: 86% (83:17) ee (*endo*) = 99%
R^1 = 2-Fu, R^2 = Me: 90% (91:9) ee (*endo*) = 96%
with L* = L^2:
R^1 = Ph, R^2 = Me: 94% (91:9) ee (*endo*) = 90%
R^1 = *p*-FC_6H_4, R^2 = Me: 96% (92:8) ee (*endo*) = 95%
R^1 = *p*-$CF_3C_6H_4$, R^2 = Me: 99% (> 99:1) ee (*endo*) = 92%
R^1 = *p*-NCC_6H_4, R^2 = Me: 87% (97:3) ee (*endo*) > 99%
R^1 = *p*-$NO_2C_6H_4$, R^2 = Me: 99% (97:3) ee (*endo*) = 98%
R^1 = 2-Fu, R^2 = Me: 99% (99:1) ee (*endo*) = 98%
R^1 = 2-Np, R^2 = Me: 90% (92:8) ee (*endo*) = 97%

Scheme 56. $Cu(OTf)_2$-catalysed cycloadditions of nitrones with chiral bis(oxazoline) and bis(imine) ligands.

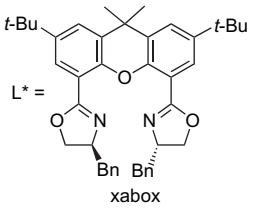
Evans bis(oxazoline)/Cu(II) complex (*t*-BOX/Cu), which provided the corresponding chiral cycloadducts with very high stereoselectivity (*endo*/*exo* ratios≥98:2 and up to 99% ees) and with regioisomeric ratios≥90:10.[102] The same group also reported the diastereoselective cycloaddition of camphor-derived α′-hydroxy enones with nitrones catalysed by $Cu(OTf)_2$, which allowed excellent combined levels of regio- and *endo*/*exo*-stereoselectivities.[102] Other chiral bis(oxazolines) have been successfully involved to catalyse the enantioselective cycloaddition of nitrones with α,β-disubstituted acrylimides in the presence of $Cu(OTf)_2$.[103] In

each case, the regioselectivity was very high, the diastereoselectivity was outstanding, strongly favouring the *exo*-products, and the enantioselectivity was consistently excellent.

In 2004, Iwasa et al. developed catalytic 1,3-dipolar cycloadditions between nitrones and 3-crotonoyl-2-oxazolidinone in the presence of a bis(2-oxazolinyl)xanthene (xabox)/Mn(II) complex as a chiral Lewis-acid catalyst, providing the corresponding cycloadducts ranging from a 96:4 to 98:2 *endo*/*exo* ratio and 91–95% ee for the *endo*-adduct (Scheme 57).[104]

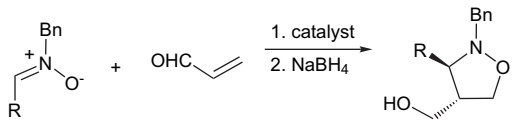


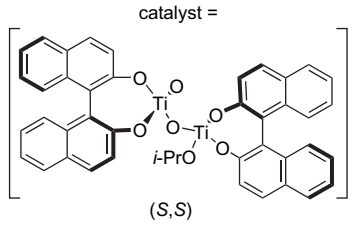
R = H: 85%; de = 92%; ee (*endo*) = 95%
R = Me: 90%; de = 92%; ee (*endo*) = 94%
R = OMe: 95%; de = 94%; ee (*endo*) = 95%
R = Br: 81%; de = 96%; ee (*endo*) = 91%



Scheme 57. Mn(II)-catalysed cycloadditions of nitrones with (*S*,*S*)-xabox ligand.

Chiral bis-metal Lewis acids often exhibit a unique reactivity and selectivity in several asymmetric reactions. In this context, Maruoka et al. developed, in 2005, asymmetric 1,3-dipolar cycloaddition reactions between various nitrones and acrolein catalysed by a μ-oxo-type chiral bis-Ti(IV) oxide, which gave rise to the corresponding isoxazolidines with high to excellent enantioselectivities (Scheme 58).[105]

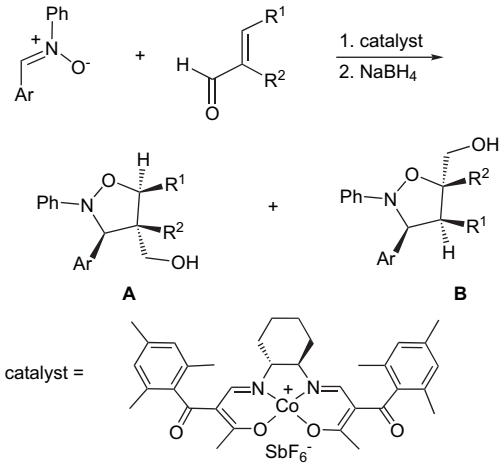




R = Ph: 94%; ee = 93%
R = *p*-Tol: 81%; ee = 94%
R = *p*-MeOC$_6$H$_4$: 76%; ee = 88%
R = *p*-ClC$_6$H$_4$: 85%; ee = 88%
R = 2-Np: 92%; ee = 93%
R = *t*-Bu: 90%; ee = 97%

Scheme 58. Bis-titanium-catalysed cycloadditions of nitrones.

A variety of enantioselective reactions have successfully used chiral cationic cobalt(III) complexes as chiral catalysts. Hence, Yamada et al. have employed these efficient Lewis-acid catalysts for the enantioselective 1,3-dipolar cycloaddition reaction of α,β-unsaturated aldehydes with nitrones.[106] Even in the case of α-substituted α,β-unsaturated aldehydes, the corresponding cycloadducts were obtained completely regioselectively, *endo* selectively and in good to high enantioselectivities (Scheme 59).

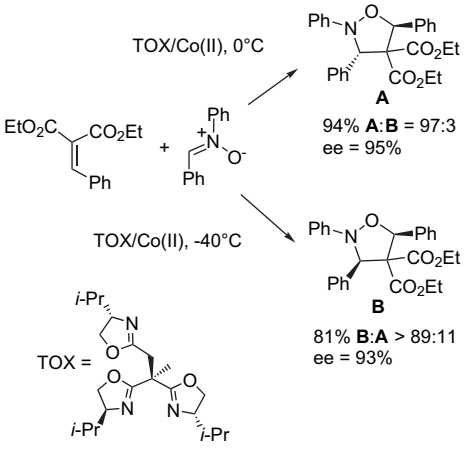


Ar = Ph, R^1,R^2 = (CH$_2$)$_3$: 100% **A**:**B** > 99:1 ee (**A**) = 87%
Ar = *p*-Tol, R^1,R^2 = (CH$_2$)$_3$: 91% **A**:**B** > 99:1
Ar = *p*-MeOC$_6$H$_4$, R^1,R^2 = (CH$_2$)$_3$: 82% **A**:**B** = 99:1
Ar = *p*-ClC$_6$H$_4$, R^1,R^2 = (CH$_2$)$_3$: 83% **A**:**B** = 99:1
Ar = *m*-ClC$_6$H$_4$, R^1,R^2 = (CH$_2$)$_3$: 94% **A**:**B** > 99:1
Ar = *o*-BrC$_6$H$_4$, R^1,R^2 = (CH$_2$)$_3$: 85% **A**:**B** = 99:1
Ar = 1,2-(Cl)$_2$C$_6$H$_3$, R^1 = H, R^2 = Me: 100% **A**:**B** = 6:94
Ar = 1,2-(Cl)$_2$C$_6$H$_3$, R^1 = H, R^2 = (CH$_2$)$_5$Me: 80% **A**:**B** = 3:97
Ar = 1,2-(Cl)$_2$C$_6$H$_3$, R^1 = H, R^2 = Bn: 93% **A**:**B** = 1:99
Ar = 1,2-(Cl)$_2$C$_6$H$_3$, R^1 = H, R^2 = (CH$_2$)*p*-Tol: 100% **A**:**B** > 1:99

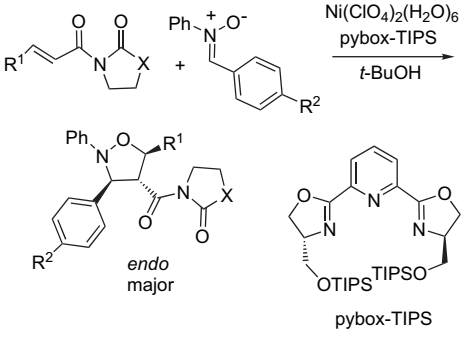
Scheme 59. Co(III)-catalysed cycloadditions of nitrones.

Similar excellent results were obtained, in 2004, by Tang et al. by employing a trisoxazoline/Co(II) complex, (TOX)/Co(ClO$_4$)$_2$·6H$_2$O, for the enantioselective 1,3-dipolar cycloaddition of nitrones to alkylidene malonates.[107] The expected chiral isoxazolidines were formed with both high enantioselectivity and high *exo* selectivity, but, when the reaction temperature was lowered from 0 to −40 °C, the same cycloaddition afforded the *endo*-isomers as the major products with good to high enantioselectivity (Scheme 60).

A combination of the Ni(ClO$_4$)$_2$ aqua complex with a chiral pybox–TIPS ligand has been successfully used by Iwasa et al. as a chiral catalyst for asymmetric 1,3-dipolar cycloaddition reactions of nitrones with alkenoyl oxazolidinone and pyrrolidinone derivatives in *t*-BuOH, providing the corresponding cycloadducts ranging from a 90:10 to >99:1 *endo*/*exo* ratio and 90–98% ee for the *endo*-adduct (Scheme 61).[108]



Scheme 60. (TOX)/$Co(ClO_4)_2 \cdot 6H_2O$-catalysed cycloadditions of a nitrone.

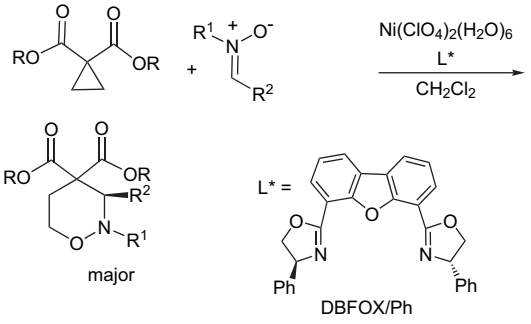


R^1 = H, X = O, R^2 = Me:
95% *endo*:*exo* = 92:8 ee (*endo*) = 95%
R^1 = H, X = CH_2, R^2 = Me:
96% *endo*:*exo* > 99:1 ee (*endo*) = 97%
R^1 = H, X = CH_2, R^2 = OMe:
85% *endo*:*exo* > 99:1 ee (*endo*) = 96%
R^1 = Me, X = O, R^2 = H:
89% *endo*:*exo* > 99:1 ee (*endo*) = 93%
R^1 = Me, X = O, R^2 = Me:
87% *endo*:*exo* > 99:1 ee (*endo*) = 90%
R^1 = Me, X = CH_2, R^2 = Me:
79% *endo*:*exo* > 99:1 ee (*endo*) = 96%
R^1 = Me, X = CH_2, R^2 = OMe:
81% *endo*:*exo* > 99:1 ee (*endo*) = 95%

Scheme 61. Ni(II)–pybox–TIPS-catalysed cycloadditions of nitrones.

The first examples of chiral Lewis-acid catalysis in the formation of chiral tetrahydro-1,2-oxazines with very high enantioselectivity were reported by Sibi et al., in 2005, by way of the enantioselective cycloaddition of nitrones to activated cyclopropanes.[109] A highly effective chiral Lewis-acid system, derived from nickel perchlorate and a chiral ligand, DBFOX/Ph, depicted in Scheme 62, allowed excellent yields and selectivities to be obtained.

The same chiral catalyst was previously used by Kanemasa et al. to catalyse enantioselective nitrone cycloadditions to α-alkyl- and α-arylacroleins, producing the corresponding sterically controlled isoxazolidine-5-carbaldehydes with enantioselectivities of up to 99.5% ee at room temperature.[110] In addition, Suga et al. have developed enantioselective 1,3-dipolar cycloadditions of a variety of nitrones, catalysed by a chiral binaphthyldiimine/Ni(II) complex,



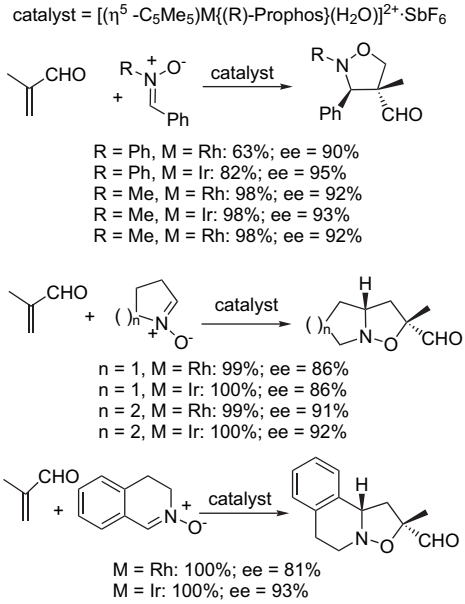
R^1 = R = Me, R^2 = Ph: 96%; ee = 89%
R = Et, R^1 = Me, R^2 = Ph: 99%; ee = 92%
R = Et, R^1 = R^2 = Ph: 99%; ee = 94%
R = Et, R^1 = Me, R^2 = *p*-BrC_6H_4: 99%; ee = 95%

Scheme 62. Ni(II)-catalysed cycloadditions of nitrones to activated cyclopropanes.

prepared from *N*,*N*′-bis(2,6-dichlorobenzylidene)-1,1′-binaphthyl-2,2′-diamine and $Ni(ClO_4)_2 \cdot 6H_2O$, allowing significant levels of *exo* selectivity and enantioselectivity to be obtained with both 3-crotonoyl-2-oxazolidinones and 3-(2-alkenoyl)-2-thiazolidinethiones used as dipolarophiles.[111] Furthermore, only a catalyst loading as small as 5–10 mol % was active in most cases.

In 2004, Carmona et al. reported enantioselective 1,3-dipolar cycloadditions of nitrones with methacrolein catalysed by a chiral rhodium- or iridium-based system $[(\eta^5\text{-}C_5Me_5)M\{(R)\text{-Prophos}\}(H_2O)]^{2+} \cdot SbF_6$ [(*R*)-Prophos=1,2-bis(diphenylphosphino)propane].[112] The reactions occurred with perfect *endo* selectivity and with enantiomeric excesses of up to 96% (Scheme 63). Similar results were previously reported by Kündig et al. by using chiral ruthenium complexes.[113]

With the aim of finding an *exo* selective catalyst for the enantioselective 1,3-dipolar cycloaddition between an

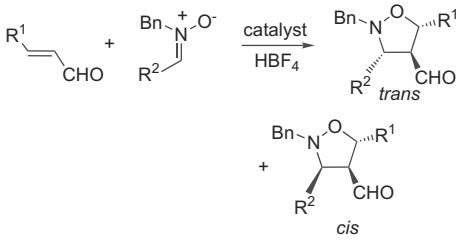


Scheme 63. Rhodium- and iridium-catalysed cycloadditions of nitrones.

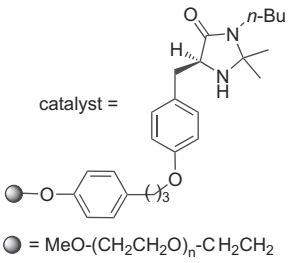
acryloyloxazolidinone and a diphenylnitrone, Desimoni et al. have screened several complexes of (4*R*)-phenylbis(oxazolines), either 5-unsubstituted, or 4,5-*cis*- and *trans*-diphenyl-substituted.[114] The expected *endo*-selectivities were obtained with Mg(II) and Ni(II) catalysts, whereas Co(II) and Zn(II) catalysts gave good levels of *exo* selectivity. Hence, the flexibility of the catalysts was remarkable, since a change in the cation allowed the *endo*-cycloadducts or the *exo*-cycloadducts to be obtained, enantioselectively, with ees in a range 84–99%.

2.5. Organo-catalysed reactions

Organic catalysts, especially chiral organic catalysts,[115] can be regarded as minimalist versions of enzymes, from which they are derived conceptually and to which they are often compared. Even though they rarely display the remarkable selectivity that is characteristic of enzymes, organic catalysts are generally more stable than biocatalysts, and enjoy a wider application under a variety of conditions that are unsustainable for enzymes. In principle, organic catalysts are more readily amenable than metal-based catalysts to anchoring on a support with the aim of facilitating the separation of the product from the catalyst and the recovery and recycling of the latter.[116] Indeed, it has been shown repeatedly that the use of a metal-based catalyst immobilised on a support is often affected by extensive metal leaching and requires catalyst regeneration by metal replenishment before recycling. In this context, Benaglia et al. have developed enantioselective 1,3-dipolar cycloadditions of nitrones with unsaturated aldehydes promoted by a poly(ethylene glycol)-supported organic catalyst.[117] The cycloadducts were obtained as mixtures of trans- (major) and cis-isomers with diastereoisomeric excesses of up to 86% and enantiomeric excesses for the trans-isomer of up to 87% (Scheme 64).



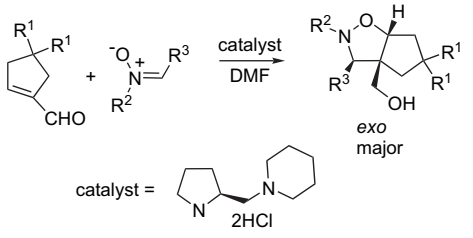
R^1 = H, R^2 = Ph: 71% (86:14) ee = 87%
R^1 = H, R^2 = *p*-MeOC_6H_4: 64% (90:10) ee = 84%
R^1 = H, R^2 = *p*-ClC_6H_4: 60% (85:15) ee = 60%
R^1 = H, R^2 = Cy: 41% (90:10) ee = 80%
R^1 = Me, R^2 = Ph: 59% (93:7) ee = 87%



= MeO-$(CH_2CH_2O)_n$-CH_2CH_2

Scheme 64. 1,3-Dipolar cycloadditions promoted by a poly(ethylene glycol)-supported organic catalyst.

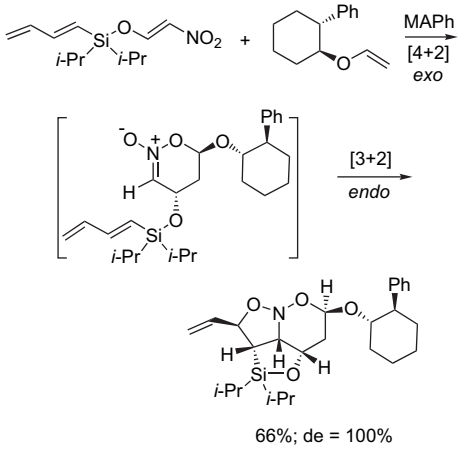
In 2002, Karlsson and Högberg reported the enantioselective 1,3-dipolar cycloaddition of nitrones to 1-cycloalkene-1-carboxaldehydes by using chiral pyrrolidinium salts as catalysts.[118] In this study, the organocatalyst worked in the absence of metals, because the catalytic effect was due to the activation of the α,β-unsaturated aldehyde by iminium salt formation between the catalyst and the starting aldehyde, resulting in a decrease in the LUMO energy of the alkene moiety. The predominant *exo*-bicyclic isoxazolidine was obtained in both high enantio- and diastereoselectivity (Scheme 65).



R^1 = H, R^2 = Me, R^3 = Ph: 49%; de = 94%; ee = 92%
R^1 = H, R^2 = Me, R^3 = *c*-C_5H_7: 68%; de = 96%; ee = 99%
R^1 = H, R^2 = Me, R^3 = *n*-Pr: 76%; de > 98%; ee = 57%
R^1 = H, R^2 = Me, R^3 = *c*-C_3H_5: 58%; de > 98%; ee = 41%
R^1 = R^2 = Me, R^3 = *c*-C_3H_5: 38%; de > 98%; ee = 37%

Scheme 65. Pyrrolidinium salt-catalysed cycloadditions of nitrones.

To the best of the author's knowledge, only one example of asymmetric 1,3-dipolar cycloadditions involving a chiral nitronate has been reported in the literature since 2001 and it was decided to include this single result, depicted in Scheme 66, in this part dealing with nitrones. This reaction was actually a tandem intermolecular [4+2]/intramolecular [3+2] nitroalkene cycloaddition reaction, involving a dienylsilyloxy nitroalkene and a chiral vinyl ether.[119] The Diels–Alder reaction between these two compounds produced a chiral intermediate nitronate, which underwent an intramolecular 1,3-dipolar cycloaddition upon catalysis with methylaluminium bis(2,6-diphenylphenoxide) (MAPh), providing a 66% yield of the expected cycloadduct.



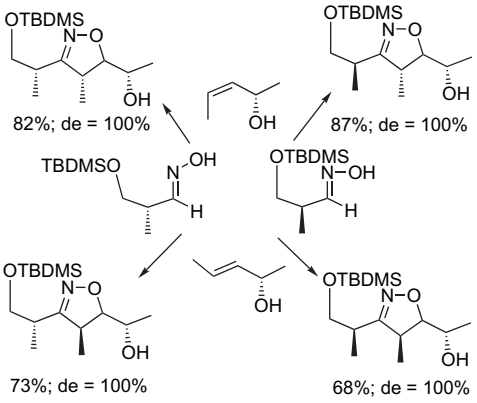
Scheme 66. MAPh-mediated intramolecular [3+2] cycloaddition of a nitronate.

3. Nitrile oxides

Nitrile oxides are reactive, relatively unstable, linear molecules, which may be generated from nitro compounds by treatment with aromatic isocyanates, or from aldoximes by halogenation followed by an in situ dehydrohalogenation using a base. It is important to note that nitrile oxides are prone to dimerisation or polymerisation, especially upon heating. In order to avoid the dimerisation process, nitrile oxides are usually generated in situ.

3.1. Chiral nitrile oxides

In 2001, Carreira et al. reported a general, stereo- and regioselective cycloaddition of in situ generated chiral nitrile oxides with allylic alcohols to provide enantiomerically pure isoxazolines.[120] This strategy has permitted the modular preparation of all possible protected dipropionate diastereomers, isolated as single compounds in each case, with the same set of reagents and a single reaction protocol, affording complex, densely functionalised polyketide building blocks (Scheme 67). In 2005, these chiral isoxazolines were used as the key intermediates of a succinct synthesis of β-amino acids.[121]

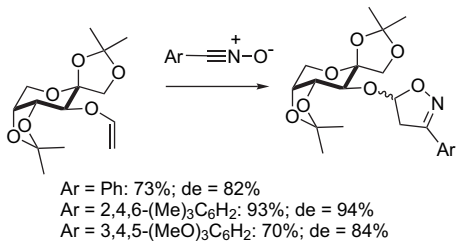


Scheme 67. Hydroxy-directed nitrile oxide cycloadditions.

In order to prepare new chiral macrocyclic barbiturate receptors, Skrydstrup et al. have developed 1,3-cycloadditions between various arylnitrile oxides and cinnamate conjugates in the presence of a chiral receptor, affording two regioisomeric isoxazolines. The cycloadducts arising from the reaction of 2-naphthyl-nitrile oxide were obtained in 75% yield and with a 79:21 diastereomeric ratio, with an enantiomeric excess of 30% for the major product.[122] In 2005, Jurczak et al. reported the synthesis of new chiral oximes and nitroalkanes, which were converted into nitrile oxides and subjected to 1,3-dipolar cycloaddition with 3-*E*-hexene, giving the corresponding 2-isoxazolines in fair yields, but only with moderate stereoselectivities.[123] As an example, the reaction of the aldoxime derived from Oppolzer's (2*R*)-bornane-10,2-sultam with 3-*E*-hexene yielded the corresponding 2-isoxazolines in 58% yield and 15% de.

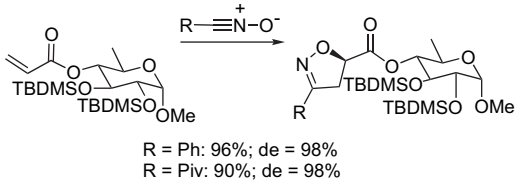
3.2. Chiral dipolarophiles

In 2003, Gallos and Koumbis reviewed the 1,3-dipolar cycloadditions of nitrile oxides in the synthesis of carbohydrate mimics.[124] The use of selected sugar-derived chiral dipolarophiles in the [3+2] cycloaddition with nitrile oxides is a supplementary example of the importance of sugars as a tool for asymmetric synthesis.[125] As an example, Rollin et al. have reported the 1,3-dipolar cycloaddition of sugar-based ethenyl ethers with nitrile oxides, providing the corresponding isoxazolines.[126] Impressive properties in terms of stereoselective induction were obtained in the D-fructo series (Scheme 68), whereas its epimeric β-D-psico counterpart was significantly less effective (up to 66% des), and the D-galactose-derived adduct gave no diastereoselectivity.



Scheme 68. 1,3-Dipolar cycloadditions of nitrile oxides to a sugar-based ethenyl ether.

Another example of a 1,3-dipolar cycloaddition performed with a sugar-derived chiral dipolarophile was reported by Tadano et al. in 2003.[127] Benzonitrile oxide and pivalonitrile oxide were reacted with methyl 4-*O*-acryloyl-6-deoxy-2,3-di-*O*-(*tert*-butyldimethylsilyl)-α-D-glucopyranoside, providing the respective cycloadducts in excellent yields, each as a single diastereomer (Scheme 69).

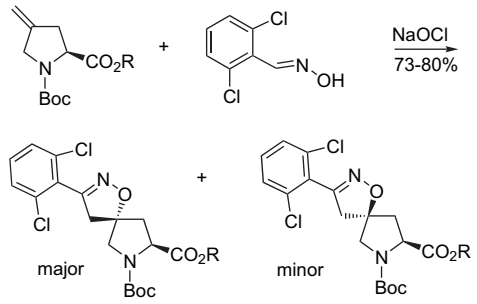


Scheme 69. 1,3-Dipolar cycloadditions of nitrile oxides to a D-glucose-derived dipolarophile.

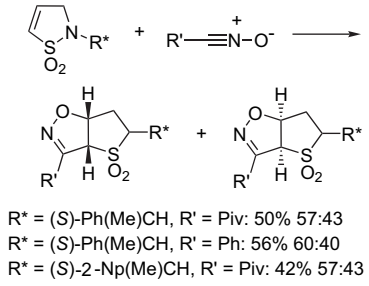
On the other hand, several chiral dipolarophiles, which were not derived from sugars, have been involved in 1,3-dipolar cycloadditions with nitrile oxides. As an example, the reaction of L-proline esters has allowed the stereoselective synthesis of spiroisoxazolinoprolinates, further converted into the corresponding unnatural spiroisoxazolinoproline-based amino acids.[128] In particular, the *tert*-butyl spiroisoxazolinoprolinates were obtained in good yields with an 80:20 trans/cis ratio (Scheme 70).

In 2004, Chan et al. investigated the scope and limitations of 1,3-dipolar cycloaddition reactions between chiral α,β-unsaturated-γ-sultams and nitrile oxides, but only very marginal diastereoselectivities were observed (Scheme 71).[59,53]

The nitrile oxide methodology was applied, in 2004, to a one-pot diastereoselective synthesis of new chiral spiro-1,4,2-oxathiazoles from the reaction between (1*R*)-thiocamphor and arylonitrile oxides, in situ generated from the corresponding arylhydroximinoyl chlorides.[129] In each case

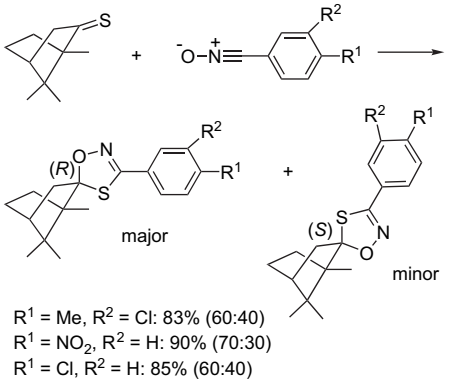


Scheme 70. 1,3-Dipolar cycloadditions of a nitrile oxide to L-proline esters.



Scheme 71. 1,3-Dipolar cycloadditions of nitrile oxides to α,β-unsaturated-γ-sultams.

of the nitrile oxide, a mixture of two diastereomers was obtained with moderate diastereoselectivities (Scheme 72).

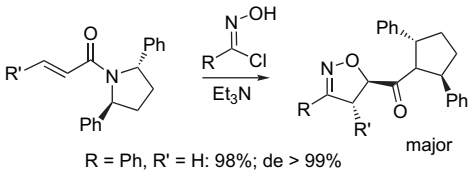


Scheme 72. 1,3-Dipolar cycloadditions of nitrile oxides to (1*R*)-thiocamphor.

In 2005, Lassaletta et al. reported the highly stereoselective 1,3-dipolar cycloaddition of a variety of aromatic and aliphatic nitrile oxides to 2,5-*trans*-2,5-diphenylpyrrolidine-derived acrylamide and cinnamamide, affording the corresponding 4,5-dihydroisoxazole-5-carboxamides as single diastereomers in almost all cases (Scheme 73).[130]

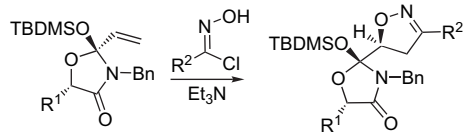
Chiral oxyoxazolidinones have been successfully used as chiral dipolarophiles with a variety of nitrile oxides, producing stereoselectively the corresponding chiral 4,5-dihydroisoxazoles with good diastereoselectivity (Scheme 74).[131]

On the other hand, disappointing diastereoselectivities were obtained by Molteni and Del Buttero for the 1,3-dipolar

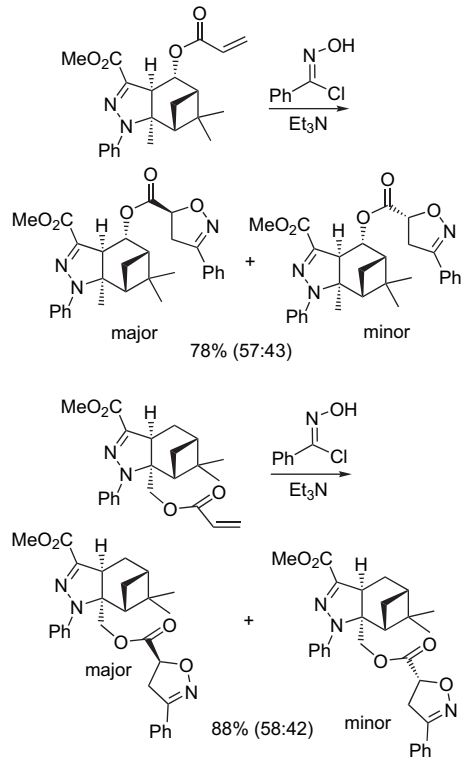


Scheme 73. 1,3-Dipolar cycloadditions of nitrile oxides to 2,5-*trans*-2,5-diphenylpyrrolidine derivatives.

cycloadditions of benzonitrile with chiral bicyclo[3.1.1]heptano[4,3-*c*]pyrazoles, whereas complete regioselectivity and good yields were observed (Scheme 75).[132]



Scheme 74. 1,3-Dipolar cycloadditions of nitrile oxides to oxyoxazolidinones.

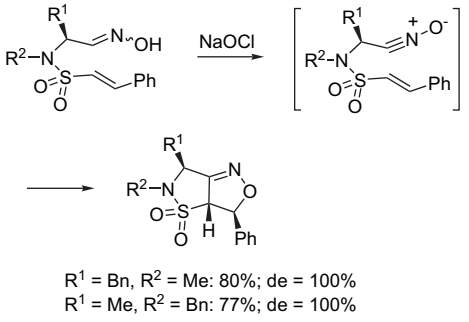


Scheme 75. 1,3-Dipolar cycloadditions of benzonitrile to bicyclo[3.1.1]-heptano[4,3-*c*]pyrazoles.

In addition, Chai et al. have developed 1,3-dipolar cycloadditions of chiral methylidene piperazine-2,5-diones with mesitonitrile oxide, providing the corresponding cycloadducts as mixtures of two diastereomers in ratios of up to 83:17 in some cases.[133] In 2002, Ma et al. reported the regioselective synthesis of bifunctional macrolides for probing ribosomal binding.[134] The key step was a 1,3-dipolar cycloaddition process between a chiral 6,11-*cis*-butenylene-bridged compound with in situ generated 3-quinolyl nitrile oxide, the regioselectivity of which was controlled by the remote cladinose group attached to the C3 position. The thus-formed conformationally constrained molecules were employed as molecular probes to study the ribosomal binding sites of bifunctional macrolide antibiotics. Furthermore, a theoretical investigation of the nitrile oxide cycloaddition to chiral allylic fluorides was reported by Grée et al., in 2003, indicating that both steric and electronic effects have important influences on the stereoselectivities of these reactions.[135]

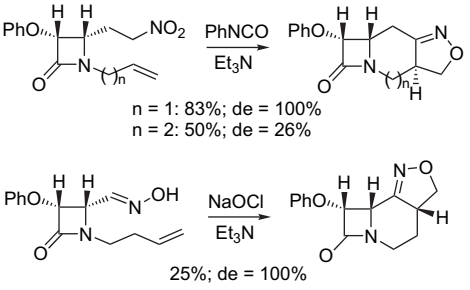
3.3. Intramolecular reactions

Enantiomerically pure annulated sultams have been stereoselectively synthesised on the basis of an intramolecular 1,3-dipolar cycloaddition of chiral nitrile oxides in situ generated from the corresponding oximes by oxidation (Scheme 76).[83] A total stereoselectivity was observed, since only one of the eight possible stereoisomers was produced.



Scheme 76. Intramolecular 1,3-dipolar cycloadditions of nitrile oxides bearing a sulfonamido group.

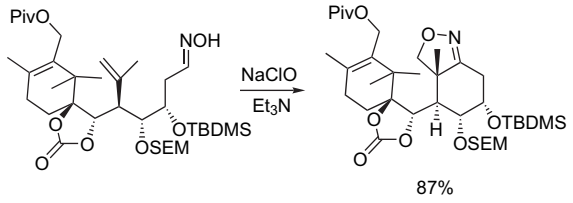
In 2004, Alcaide et al. reported the regio- and stereoselective intramolecular 1,3-dipolar cycloaddition of novel chiral 2-azetidinone-tethered alkenyl nitrile oxides, providing the corresponding chiral fused tricyclic β-lactams (Scheme 77).[136]



Scheme 77. Intramolecular 1,3-dipolar cycloadditions of 2-azetidinone-tethered alkenyl nitrile oxides.

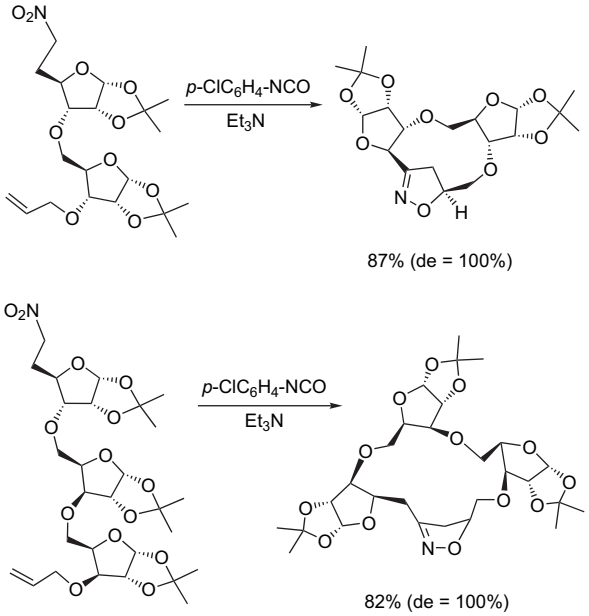
It was demonstrated that the process was more efficient when the nitrile oxide moiety was separated by a methylene group, rather than being directly linked to the C4 position of the four-membered ring.

With the aim of developing a novel and efficient synthesis of paclitaxel, having strong antitumour activity, Takahashi et al. reported, in 2005, the construction of the C-ring of this latter biologically active compound, using an intramolecular nitrile oxide cycloaddition with a precursor containing the A ring (Scheme 78).[137]



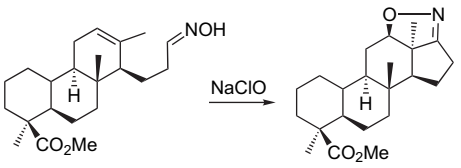
Scheme 78. Synthesis of the C-ring of paclitaxel via intramolecular nitrile oxide cycloaddition.

On the other hand, Bhattacharjya et al. have applied the nitrile oxide methodology to 3,5′-ether-linked pseudo-oligopentose derivatives, allowing an approach to chiral macro-oxacycles.[138] Hence, the intramolecular cycloaddition of the nitrile oxides, derived from these pseudo-oligosaccharide derivatives, led to the diastereoselective formation of chiral isoxazolines fused to 10- to 16-membered oxacycles (Scheme 79).



Scheme 79. Intramolecular nitrile oxide cycloadditions of 3,5′-ether-linked pseudo-oligopentose derivatives.

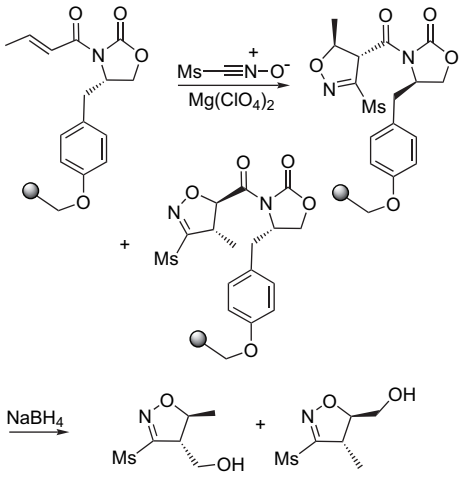
In addition, Fernandez-Mateos et al. have recently developed a total stereoselective synthesis of a 12-acetoxyazadiradione analogue based on an intramolecular 1,3-dipolar cycloaddition of a nitrile oxide, in situ generated from the corresponding hydroxylamine (Scheme 80).[139]



Scheme 80. Intramolecular nitrile oxide cycloaddition of an azadiradione-derivative.

3.4. Metal-catalysed reactions

In 2001, Faita et al. studied the 1,3-cycloadditions of supported Evans' chiral auxiliary with nitrile oxides in the presence of the Mg(II) cation as the catalyst.[89] It was shown that the regio- and stereochemical outcomes of the nitrile oxide cycloadditions were influenced by near-stoichiometric quantities of the cation, since the diastereoselectivity of the reaction was reversed according to whether the amounts of catalyst were catalytic or stoichiometric (Scheme 81).

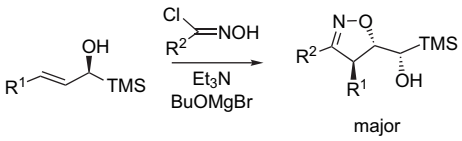


Scheme 81. $Mg(ClO_4)_2$-induced nitrile oxide cycloadditions of resin-bound oxazolidinones.

The magnesium ion-induced nitrile oxide cycloaddition to chiral α-silylallyl alcohols examined by Kamimura et al., has provided excellent yields and *syn* diastereoselectivities with a variety of in situ generated nitrile oxides (Scheme 82).[140]

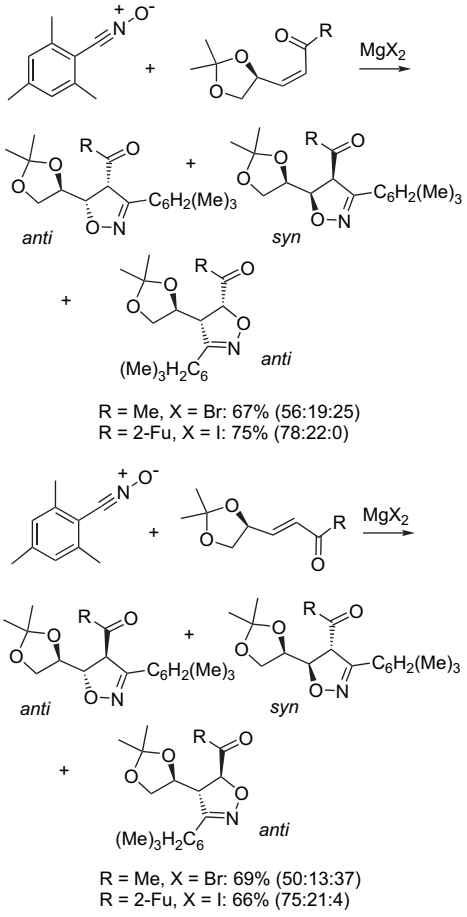
In 2005, Jedlovska et al. demonstrated that the use of MgX_2 (X=Br or I) in 1,3-dipolar cycloadditions of mesityl nitrile oxide to chiral α,β-unsaturated enones (both *E* and *Z* isomers) improved the regio- and stereoselective outcome of these reactions.[141] Predominantly 4-acyl-substituted C5/C6 *anti* isoxazolines were formed (Scheme 83).

With the aid of the magnesium chelation effect, Kim et al. developed, in 2005, the diastereoselective synthesis of chiral 3-diphenylmethyl-5-(1,2-dihydroxy-3-butenyl)isoxazoline



R^1 = *i*-Pr, R^2 = Ph: 75%; de = 92%
R^1 = *i*-Pr, R^2 = *p*-ClC_6H_4: 52%; de = 94%
R^1 = *i*-Pr, R^2 = *p*-$CF_3C_6H_4$: 32%; de = 96%
R^1 = *i*-Pr, R^2 = $BnCH_2$: 40%; de = 98%
R^1 = Me, R^2 = Ph: 59%; de = 88%
R^1 = Me, R^2 = *p*-ClC_6H_4: 58%; de = 90%
R^1 = Me, R^2 = *p*-$CF_3C_6H_4$: 45%; de = 98%

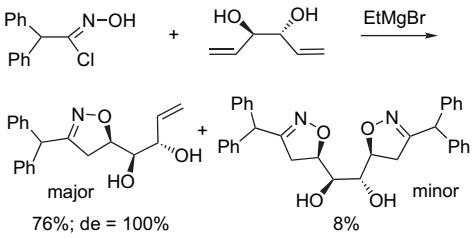
Scheme 82. BuOMgBr-induced nitrile oxide cycloadditions of α-silylallyl alcohols.



Scheme 83. MgX_2-induced mesityl nitrile oxide cycloadditions of α,β-unsaturated enones.

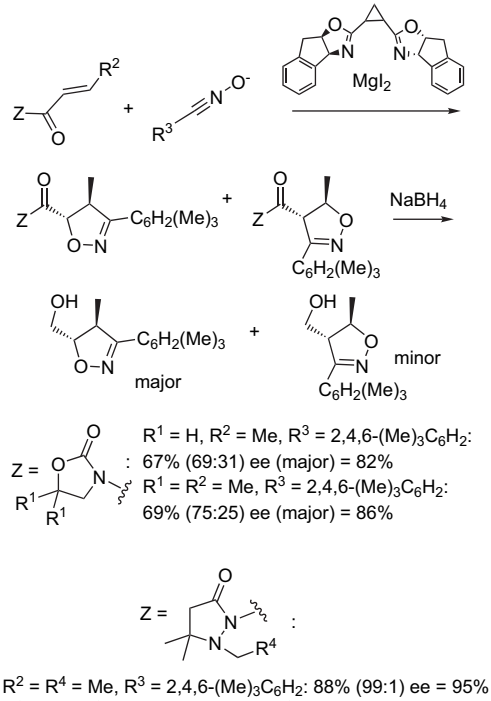
by 1,3-dipolar cycloaddition of diphenylacetoxyhydroximic chloride with (3*R*,4*R*)-1,5-hexadiene-3,4-diol, giving access to highly substituted chiral tetrahydrofurans (Scheme 84).[142] A single diastereomer was obtained along with a small amount of diadduct.

An enantioselective variant of the 1,3-dipolar cycloaddition, using a chiral Lewis acid prepared from magnesium iodide and a chiral bisoxazoline derived from amino indanol, was reported by Sibi et al. in 2004.[143] The reaction of preformed mesityl nitrile oxide with dipolarophiles such as oxazolidinone crotonates proceeded with low regioselectivity and



Scheme 84. EtMgBr-induced diphenylacetonitrile oxide cycloaddition of (3*R*,4*R*)-1,5-hexadiene-3,4-diol.

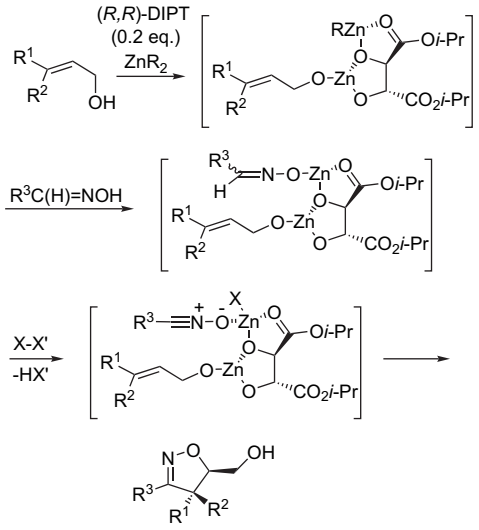
varying enantioselectivity, whereas the use of achiral pyrazolidinone templates containing a fluxional nitrogen atom gave both highly regio- and enantioselectivities, providing the C-adducts exclusively (Scheme 85). This methodology was successfully extended, in 2005, to the cycloaddition with α,β-disubstituted acrylimides, providing regioselectively the corresponding C-adducts in high yields and good stereoselectivities (up to 77% ee).[103b]



$R^2 = R^4$ = Me, R^3 = 2,4,6-$(Me)_3C_6H_2$: 88% (99:1) ee = 95%
R^2 = Me, R^3 = 2,4,6-$(Me)_3C_6H_2$, R^4 = Ph: 84% (99:1) ee = 99%
R^2 = Me, R^3 = 2,4,6-$(Me)_3C_6H_2$, R^4 = 1-Np: 98% (99:1) ee = 99%
R^2 = Et, R^3 = 2,4,6-$(Me)_3C_6H_2$, R^4 = Ph: 86% (99:1) ee = 99%
$R^2 = R^4$ = Ph, R^3 = 2,4,6-$(Me)_3C_6H_2$: 85% (99:1) ee = 99%
$R^2 = CO_2Et$, R^3 = 2,4,6-$(Me)_3C_6H_2$, R^4 = Ph: 75% (99:1) ee = 99%
R^2 = Me, $R^3 = R^4$ = Ph: 75% (99:1) ee = 99%
R^2 = Me, R^3 = *o*-ClC_6H_4, R^4 = Ph: 78% (99:1) ee = 86%
R^2 = Me, R^3 = *p*-ClC_6H_4, R^4 = Ph: 70% (99:1) ee = 96%
R^2 = Me, R^3 = *t*-Bu, R^4 = Ph: 44% (99:1) ee = 92%

Scheme 85. MgI_2-catalysed mesityl nitrile oxide cycloadditions.

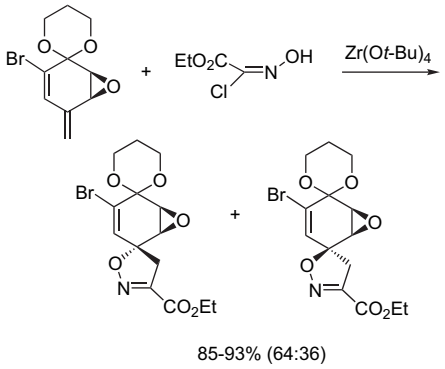
In 2003, Inomata et al. employed a dialkylzinc derivative as a catalyst of the nitrile oxide cycloaddition to allylic alcohols in the presence of diisopropyl (*R*,*R*)-tartrate [(*R*,*R*)-DIPT].[99c,144] The nitrile oxide, generated in situ by direct oxidation of the corresponding aldoxime, coordinated to zinc metal of a zinc-bridging intermediate before giving, via cycloaddition, the corresponding chiral isoxazoline (Scheme 86). Catalytic amounts of (*R*,*R*)-DIPT (0.2 equiv) were sufficient to provide high enantioselectivities.



R = Et, $R^1 = R^2$ = H, R^3 = Ph: 87%; ee = 84%
R = Et, $R^1 = R^2$ = H, R^3 = *p*-$MeOC_6H_4$: 98%; ee = 90%
R = Et, $R^1 = R^2$ = H, R^3 = *p*-ClC_6H_4: 91%; ee = 90%
R = Et, $R^1 = R^2$ = H, R^3 = *t*-Bu: 91%; ee = 93%
R = *i*-Pr, $R^1 = R^2$ = H, R^3 = *p*-$MeOC_6H_4$: 77%; ee = 92%

Scheme 86. (*R*,*R*)-DIPT-ZnR_2-catalysed nitrile oxide cycloadditions.

In 2006, Porco et al. reported the use of Zr(IV) alkoxides to mediate a nitrile oxide cycloaddition, which constituted the key step of a total synthesis of the spiroisoxazoline natural product, (+)-calafianin.[145] The nitrile oxide was generated in situ from the corresponding ethyl chloro-oximinoacetate and diisopropylethylamine, and reacted with a chiral exocyclic vinyl epoxide in the presence of $Zr(Ot\text{-}Bu)_4$ to give the corresponding spiroisoxazoline as a mixture of two diastereomers (Scheme 87).



Scheme 87. $Zr(Ot\text{-}Bu)_4$-mediated nitrile oxide cycloaddition.

4. Azomethine ylides

In recent years, azomethine ylides have become one of the most investigated classes of 1,3-dipoles and, based on their cycloaddition chemistry, various methods for the synthesis of pyrrolidine derivatives have been developed. Azomethine ylides are planar 1,3-dipoles composed of one nitrogen and two terminal sp^2 carbon atoms. Their cycloadditions to

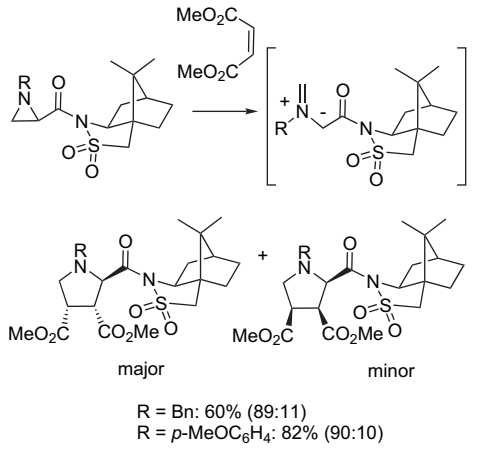
olefinic dipolarophiles provide a direct and general method for the synthesis of pyrrolidine derivatives. Although there are examples of stable, isolable azomethine ylides, they are normally generated in situ and trapped by almost any multiple C–C or C–X (X=heteroatom) bond. A number of methods have been developed for their generation, including the ring opening of aziridines, the desilylation of various silylamino derivatives, the decarboxylation condensation of amino acids, the 1,2-prototropy/metallo-azomethine ylides of amino acid-derived imines and the deprotonation of iminium salts. Advances in this area, over the last few decades, have made cycloaddition reactions of azomethine ylides a powerful synthetic tool, extensively used in the synthesis of natural products as well as other biologically interesting compounds.[146]

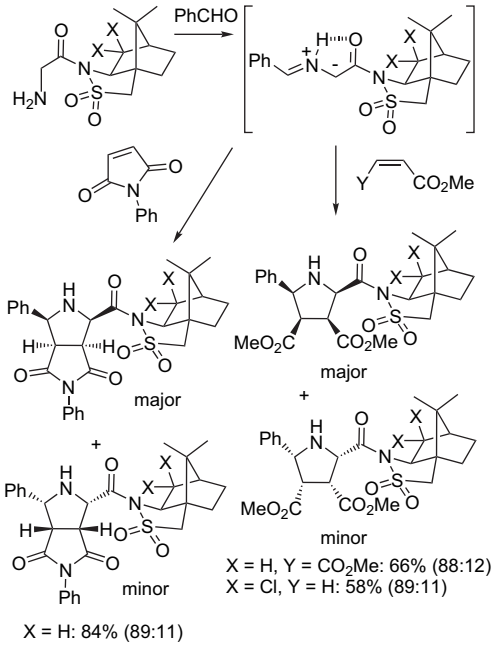
4.1. Chiral azomethine ylides

In 2001, Garner et al. reported that Oppolzer's sultam could serve as an effective, recoverable chiral auxiliary for stabilised azomethine ylides, generated either by aziridine thermolysis or by imine tautomerisation.[147] These chiral azomethine ylides underwent 1,3-dipolar cycloadditions with a variety of dipolarophiles to give good yields of the diastereomerically enriched cycloadducts (Scheme 88). The subsequent removal of the chiral auxiliary provided access to a variety of enantiomerically pure pyrrolidine derivatives.

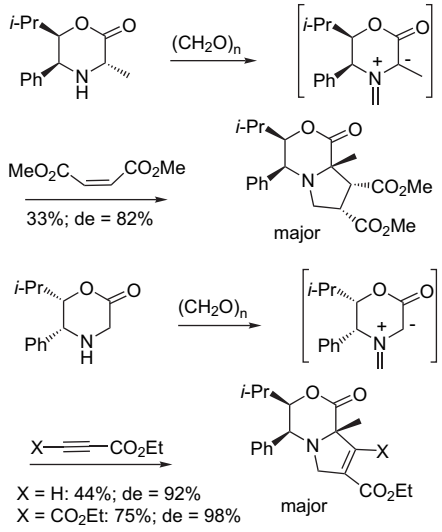
Nàjera et al. have shown that chiral 2,3,5,6-tetrahydro-6-isopropyl-5-phenyl-1,4-oxazin-2-ones derived from glycine and alanine were useful systems for the generation of chiral carboxy-stabilised ylides after reaction with formaldehyde.[148] These ylides could be used for the thermally induced 1,3-dipolar cycloaddition reaction to electron-deficient olefins and acetylenes, giving the corresponding cycloadducts mainly with *endo* selectivity (Scheme 89). The diastereoselectivity of the reaction proved to be high, and a superior reactivity towards acetylenic compounds, compared to the related oxazin-2-one-derived ylides, has been observed. The products were employed for the preparation of highly substituted enantiomerically pure proline derivatives. In 2002, the scope of this reaction was extended by Williams and Sebahar to azomethine ylides derived from chiral 5,6-diphenylmorpholin-2-one and a variety of aldehydes.[149] The corresponding cycloadducts were obtained in moderate to excellent regio- and diastereoselectivities (up to 90% de).

In 2002, Williams et al. reported the total synthesis of (+)- and (−)-spirotryprostatin B on the basis of a diastereoselective 1,3-dipolar cycloaddition reaction of an azomethine ylide, generated from 3-methoxy-3-methylbutanal and (5*R*,6*S*)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-2-one, with ethyl oxindolylidene acetate.[150] The reaction, performed in the presence of molecular sieves in toluene, resulted in the formation of the desired *exo*-cycloadduct, along with another compound resulting from elimination of methanol from this desired product (Scheme 90). This key spiro-tetracyclic intermediate was further converted into the natural specimens of (−)-spirotryprostatin B, whereas its antipode was synthesised similarly, but starting with the opposite antipode of the oxazinone. In 2004, the same group applied this methodology to a concise total



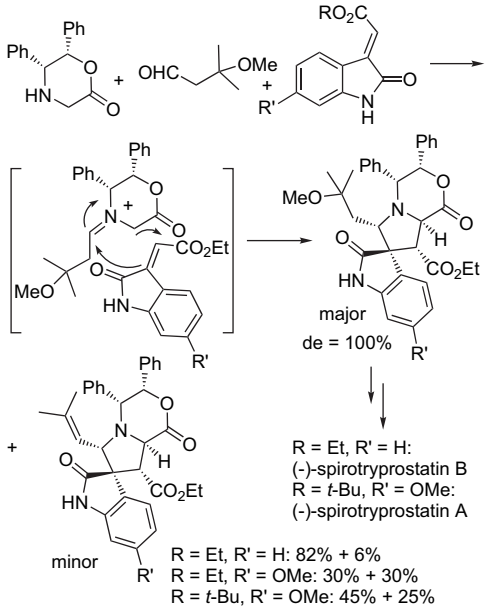


Scheme 88. 1,3-Dipolar cycloadditions of Oppolzer's sultam-derived azomethine ylides.



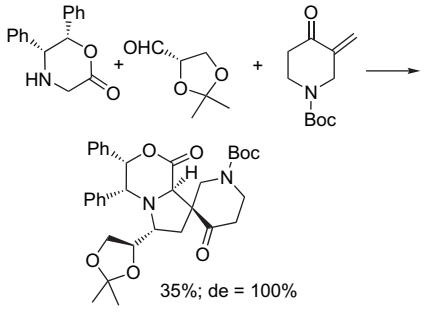
Scheme 89. 1,3-Dipolar cycloadditions of azomethine ylides from chiral 6-isopropyl-5-phenylmorpholin-2-ones.

synthesis of spirotryprostatin A starting from the same chiral morpholinone (Scheme 90).[151]



Scheme 90. 1,3-Dipolar cycloaddition of an azomethine ylide from a chiral oxazinone.

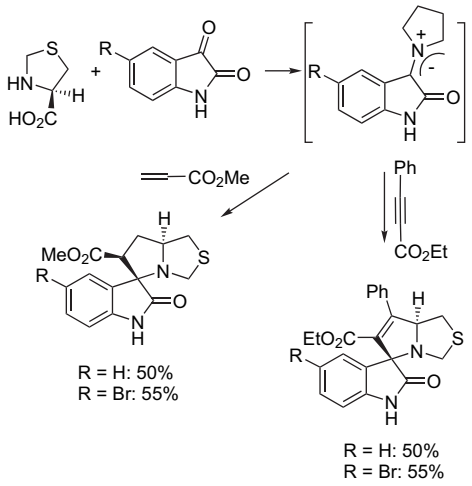
In 2005, using the preceding methodology, chiral 2′-alkyl-4′-aryl-1*H*-spiro[indole-3,3′-pyrrolidin]-2-ones were efficiently synthesised by Wang et al., as a novel class of potential inhibitors of the p53-MDM2 interaction.[152] In addition, the application of the Williams' methodology has allowed the total synthesis of the ADE fragment of nakadomarin A, a potent cytotoxic agent.[153] The three-component condensation reaction of the same chiral morpholinone, as depicted in Scheme 90, with a chiral aldehyde and an enone led to the formation of the corresponding 2,5-*trans*-cycloadduct as a single diastereomer (Scheme 91).



Scheme 91. 1,3-Dipolar cycloaddition of an azomethine ylide from a chiral oxazinone.

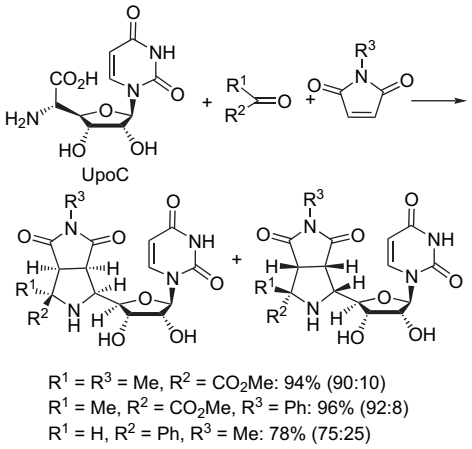
On the other hand, Pardasani et al. have shown that the reaction of imines, formed from a secondary cyclic amino acid such as (*S*)-(−)-thiazolidine-4-carboxylic acid and isatins gave, via a decarboxylative azomethine ylide formation followed by a subsequent 1,3-dipolar cycloaddition, a single cycloadduct in good yield (Scheme 92).[154]

In 2004, Grigg et al. reported cascade thermal and decarboxylative cycloaddition reactions of uracil polyoxin C (UpoC)



Scheme 92. 1,3-Dipolar cycloadditions of azomethine ylides from (*S*)-(−)-thiazolidine-4-carboxylic acid and isatins.

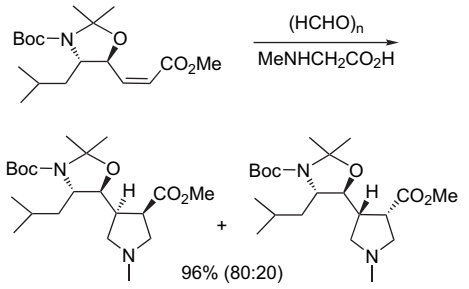
with mono- and di-carbonyl compounds in the presence of a dipolarophile (Scheme 93).[155] These processes led, via stabilised and non-stabilised azomethine ylides, respectively, to a series of polyoxin cycloadducts related to nikkomycin B, a nucleoside antibiotic, in good to excellent yields and high diastereoselectivity.



Scheme 93. 1,3-Dipolar cycloadditions of azomethine ylides from uracil polyoxin C.

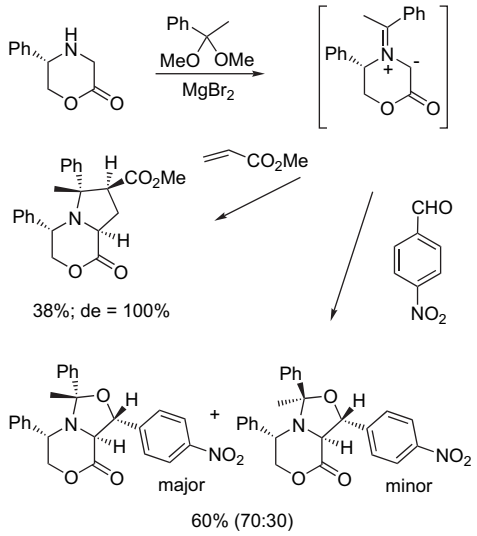
The azomethine ylide methodology was used by Hanessian et al., in 2005, in the course of developing a stereoselective synthesis of constrained azacyclic hydroxyethylene isosteres as aspartic protease inhibitors.[156] The key step was the treatment of an *N*-Boc-leucinal derivative with *N*-methyl glycine and formaldehyde, affording the azomethine ylide cyclisation product and its diastereomer as an 80:20 mixture, as depicted in Scheme 94. The major isomer was further elaborated into a desired pseudopeptide inhibitor.

In 2005, Harwood et al. reported the first generation of unsymmetrical ketone-derived chiral stabilised azomethine ylides,[157] the 1,3-dipolar cycloaddition reactions of which have been used to prepare enantiomerically pure bicyclic proline derivatives and enantiomerically pure β-hydroxy-α-amino acids. Hence, the reaction of the azomethine ylide



Scheme 94. 1,3-Dipolar cycloaddition of an azomethine ylide from an *N*-Boc-leucinal derivative.

generated from (5*S*)-phenylmorpholin-2-one and acetophenone dimethyl acetal with dipolarophiles such as methyl acrylate or *p*-nitrobenzaldehyde furnished the corresponding cycloadducts as a single isomer, or as a 70:30 mixture of diastereomers, respectively (Scheme 95).

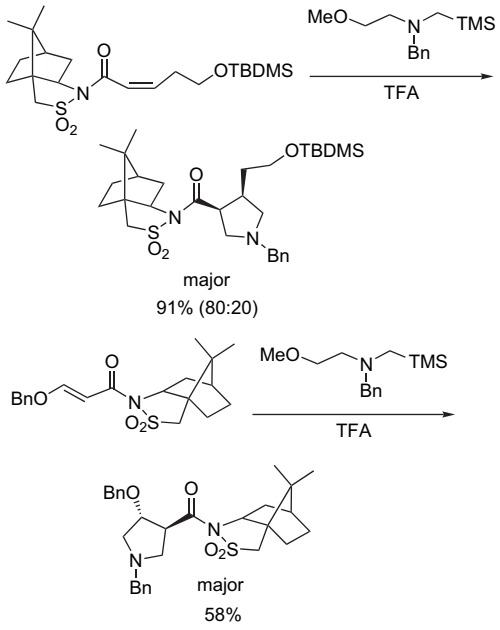


Scheme 95. 1,3-Dipolar cycloadditions of azomethine ylide from (5*S*)-phenylmorpholin-2-one.

4.2. Chiral dipolarophiles

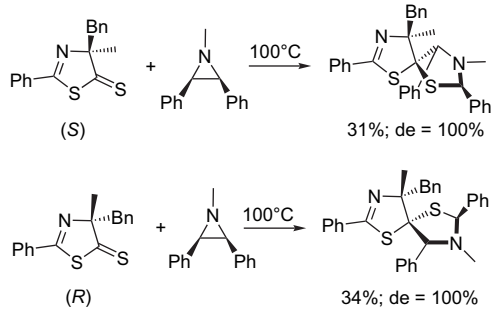
In 2001, Carey reported the 1,3-dipolar cycloaddition of a chiral (*Z*)-alkene with an azomethine ylide performed in the presence of a catalytic quantity of TFA, providing an 80:20 mixture of diastereomers (Scheme 96).[158] The absolute stereochemistry was controlled by the use of the chiral (2*R*)-bornane-2,10-sultam moiety. The cycloaddition of (*E*)-3-benzyloxypropenoyl-(2′*S*)-bornane-10,2-sultam with the same azomethine ylide was investigated by Chand et al., in 2005, using the same conditions, leading to the corresponding cycloadduct in 58% yield (Scheme 96).[159]

In 2002, Heimgartner and Gebert studied the 1,3-dipolar cycloaddition reactions of azomethine ylides with the C=S group of chiral substituted 1,3-thiazole-5(4*H*)-thiones.[160] Hence, the reaction of the azomethine ylide generated in situ from *N*-(benzylidene)[(trimethylsilyl)methyl]amine with (*R*)-4-benzyl-4-methyl-2-phenyl-1,3-thiazole-5(4*H*)-thione gave a mixture of four chiral spirocyclic cycloadducts



Scheme 96. 1,3-Dipolar cycloadditions of an azomethine ylide to chiral alkenic sultams.

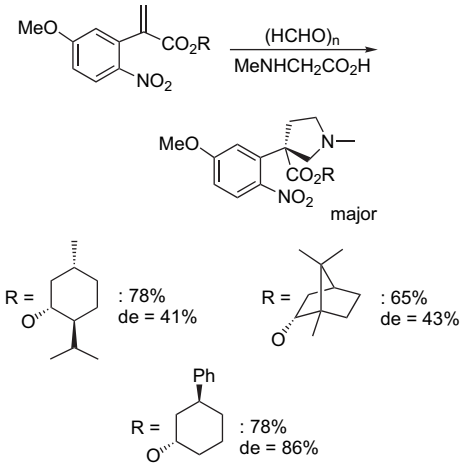
with a low regioselectivity (62:38). In contrast, the analogous reactions of (*R*)- or (*S*)-4-benzyl-4-methyl-2-phenyl-1,3-thiazole-5(4*H*)-thione performed in the presence of the thermally generated azomethine ylide from *cis*-*N*-methyl-2,3-diphenylaziridine provided, in each case, a single cycloadduct (Scheme 97).



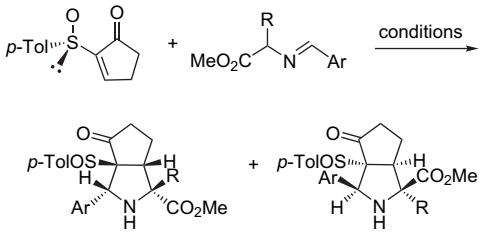
Scheme 97. 1,3-Dipolar cycloadditions of an azomethine ylide to chiral 4-benzyl-4-methyl-2-phenyl-1,3-thiazole-5(4*H*)-thiones.

With the aim of developing an approach to oxindole alkaloids such as (−)-horsfiline, Palmisano et al. have investigated the 1,3-dipolar cycloaddition of the azomethine ylide derived from *N*-methyl glycine and paraformaldehyde with a variety of chiral 2-(2-nitrophenyl)acrylates (Scheme 98).[161] The corresponding cycloadducts were obtained in modest to good diastereoselectivity (up to 86% de) and were then converted by reductive heterocyclisation into various spiro-(indole-pyrrolidine) ring systems.

Garcia Ruano et al. have studied the condensation of azomethine ylides generated from iminoesters in the presence of a base such as LHMDS on (*S*)-2-*p*-tolylsulfinyl-2-cyclopentenone. Complete regio- and *endo*-selectivities were observed, since only one diastereoisomer was systematically obtained in almost quantitative yield (Scheme 99).[162]



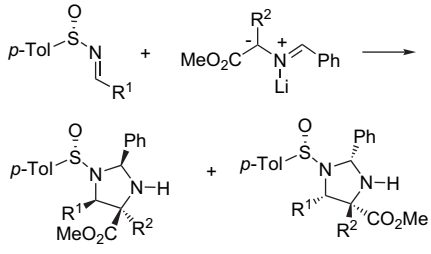
Scheme 98. 1,3-Dipolar cycloadditions of an azomethine ylide to chiral 2-(2-nitrophenyl)acrylates.



Ar	R	Conditions	Yield (%)
2-Np	Me	LHMDS/THF	91% + < 2%
Ph	H	LHMDS/THF	89% + < 2%
Ph	Me	LHMDS/THF	91% + < 2%
2-Np	H	LHMDS/THF	93% + < 2%

Scheme 99. 1,3-Dipolar cycloadditions of azomethine ylides to (*S*)-2-*p*-tolylsulfinyl-2-cyclopentenone.

In the same context, Viso et al. have developed highly diastereoselective 1,3-dipolar cycloadditions between chiral *p*-tolylsulfinimines and azomethine ylides generated in situ from α-iminoesters and LDA, producing the corresponding enantiopure *N*-sulfinylimidazolidines with a high degree of stereocontrol (Scheme 100).[163] These latter products could

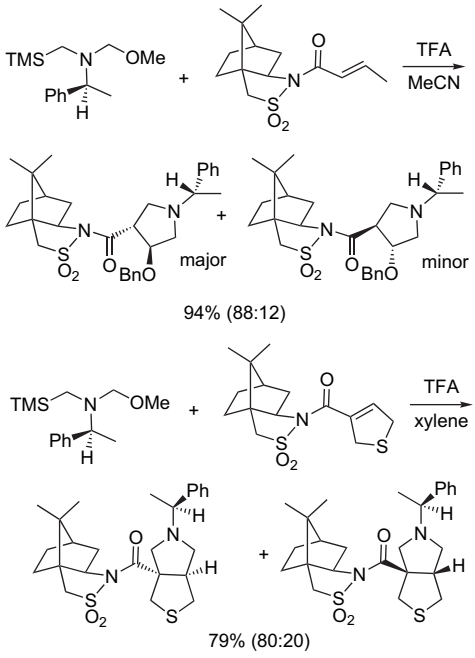


R^1 = Ph, R^2 = Bn: 55% (95:5)
R^1 = Ph, R^2 = Me: 53% (95:5)
R^1 = *p*-$NO_2C_6H_4$, R^2 = Bn: 80% (97:3)
R^1 = *p*-$NO_2C_6H_4$, R^2 = *i*-Bu: 70% (98:2)
R^1 = 3-py, R^2 = Bn: 80% (99:1)
R^1 = 2-Fu, R^2 = Bn: 37% (98:2)

Scheme 100. 1,3-Dipolar cycloadditions of azomethine ylides to *p*-tolylsulfinimines.

be converted into a variety of chiral differentially protected vicinal diamines.

Doubly diastereoselective 1,3-dipolar cycloadditions of chiral azomethine ylides to 3-benzyloxy-substituted alkenoylcamphorsultams have been reported by Karlsson and Högberg, furnishing the corresponding *trans*-3,4-disubstituted pyrrolidines containing a protected hydroxyl group at C4 of the pyrrolidine ring in high diastereomeric ratios (Scheme 101).[164] The best diastereoselectivities (up to 76% de) were obtained when polar solvents such as MeCN were employed. These products were used as starting materials in a short synthetic route to a known glycosidase inhibitor, (3*R*,4*R*)-4-(hydroxymethyl)pyrrolidin-3-ol, and its enantiomer. This double asymmetric induction methodology could be extended to the use of cyclic five-membered α,β-unsaturated *N*-enoylbornanesultams, affording the corresponding fused bicyclic adducts in good diastereoselectivities (Scheme 101).[165]



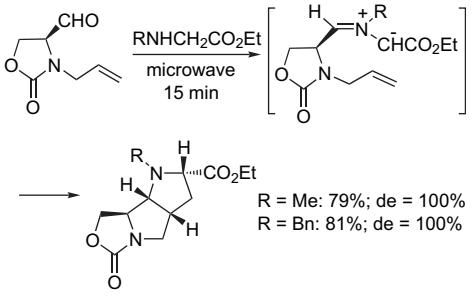
Scheme 101. 1,3-Dipolar cycloadditions of a chiral azomethine ylide to chiral *N*-enoylbornanesultams.

Several other asymmetric multicomponent reactions based on 1,3-dipolar cycloadditions have been recently developed using chiral amines as the chiral auxiliaries.[151,155,166] Not only chiral amines, but also chiral hydroxylamines, have been involved in this type of reaction. Excellent results have been obtained with chiral dipolarophiles such as a cinnamyl derivative in the presence of *N*-phenyl isatin and proline, which yielded the corresponding chiral spirooxindole derivative.[167]

4.3. Intramolecular reactions

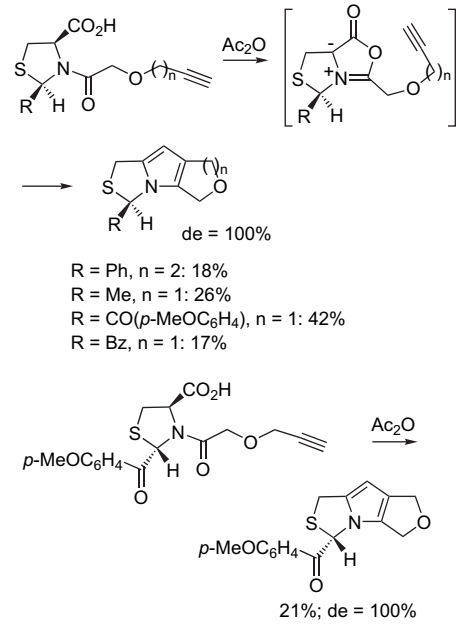
The general intramolecular dipolar cycloaddition reaction of azomethine ylides was reviewed by Coldham and Hufton, in 2005, demonstrating the significant progression of these reactions since the first report nearly 30 years ago.[168] An asymmetric example of an intramolecular 1,3-dipolar

cycloaddition involving chiral azomethine ylides was reported by Cheng et al., in 2001.[72] The highly stereoselective reaction of in situ generated azomethine ylides was induced by microwave irradiation on the surface of silica gel, leading, in a short time, to the corresponding cycloadducts in good yields (Scheme 102).



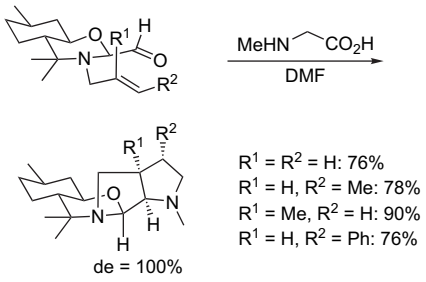
Scheme 102. 1,3-Dipolar intramolecular cycloadditions of *N*-substituted azomethine ylides.

In 2002, Pinho e Melo et al. reported the intramolecular dipolar cycloaddition of bicyclic münchnones derived from the cyclodehydration of 2-substituted-*N*-acylthiazolidine-4-carboxylic acids.[169] A range of new chiral pyrrolo[1,2-*c*]thiazole derivatives were obtained as single enantiomers from 2-phenylthiazolidines, 2-benzoylthiazolidines and 2-methylthiazolidine-4-carboxylates (Scheme 103).



Scheme 103. 1,3-Dipolar intramolecular cycloadditions of bicyclic münchnones.

A novel synthesis of enantiopure octahydropyrrolo[3,4-*b*]-pyrroles was accomplished by Pedrosa et al., in 2002, on the basis of an intramolecular dipolar cycloaddition performed on chiral perhydro-1,3-benzoxazines.[170] Hence, the condensation of *N*-substituted glycines with chiral 3-allyl-2-formyl-perhydro-1,3-benzoxazines formed the corresponding azomethine ylides, which cyclised to give stereoselectively the corresponding octahydropyrrolo[3,4-*b*]pyrrole derivatives as single diastereomers (Scheme 104). The cis,*syn*-stereochemistry of the cycloadducts could be explained by the fact that the reaction occurred only in an *endo* mode and with total diastereofacial selectivity.



Scheme 104. 1,3-Dipolar intramolecular cycloadditions of perhydro-1,3-benzoxazines.

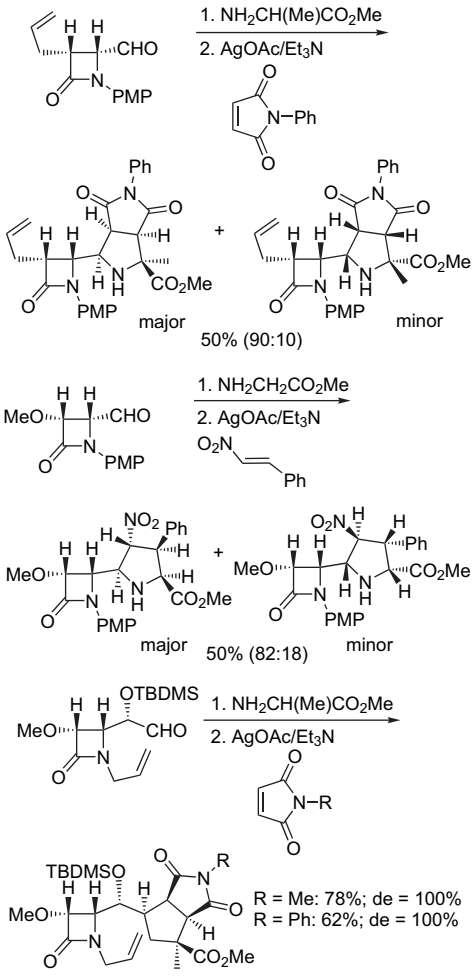
4.4. Metal-catalysed reactions

Although a variety of Lewis acids have provided excellent results in the stereoselective metal-catalysed dipolar cycloaddition of azomethine ylides, the Ag(I)-based processes stand out as the most used. As an example, Alcaide et al. reported, in 2001, the 1,3-dipolar cycloaddition of 4-oxo-azetidine-2-carbaldehyde-derived azomethine ylides with a variety of dipolarophiles in the presence of AgOAc/Et_3N, affording the corresponding chiral pyrrolidinyl-β-lactams with reasonable diastereoselectivities and moderate to good yields (Scheme 105).[171] In order to improve the stereoselectivity of this methodology, the installation of an extra stereocentre in the starting material was undertaken in 2005 (Scheme 105). Hence, the scope of this methodology was extended to the cycloaddition of α-alkoxy β-lactam acetaldehyde-derived azomethine ylides, providing the corresponding cycloadducts with diastereoselectivities ranging from good (90:10) to complete (single isomer).[172]

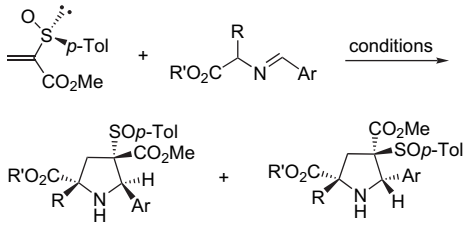
In 2002, Garcia Ruano et al. reported the AgOAc-catalysed dipolar cycloaddition of azomethine ylides to vinyl sulfoxides such as methyl (*S*)-2-(*p*-tolylsulfinyl)acrylate (Scheme 106).[173] The reaction evolved with complete regio- and *endo*-selectivities, but, nevertheless, mixtures of two diastereoisomers (75–88% des) resulting from the *anti* dipole/*s*-cis dipolarophile and *syn* dipole/*s*-trans dipolarophile approaches, respectively, were obtained. The stereoselectivity could, however, be controlled by using THF or MeCN as solvents. This new methodology represented a new entry into the synthesis of highly substituted pyrrolidines, which constitute the main building blocks of many alkaloids and pharmacologically active compounds.

A total synthesis of epibatidine, an important analgesic having an 8-azabicyclo[3.2.1]octane skeleton, was developed by Pandey et al., in 2002, on the basis of a dipolar cycloaddition of a cyclic azomethine ylide with Oppolzer's sultam acrylamide catalysed by AgF, giving rise to the corresponding cycloadducts with a very good *exo*/*endo* selectivity (Scheme 107).[174]

The AgOAc-catalysed 1,3-dipolar cycloadditions of arylidene glycine imines and a variety of chiral acrylamides have been studied by Nyerges et al.[175] Complete



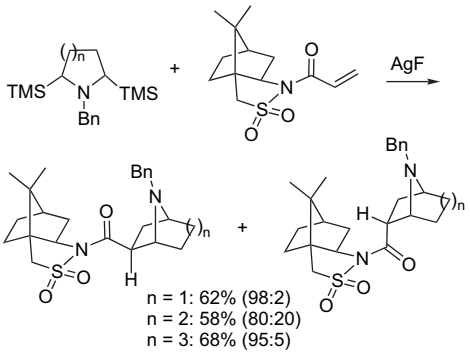
Scheme 105. Ag(I)-catalysed 1,3-dipolar cycloadditions of β-lactam aldehyde-derived azomethine ylides.



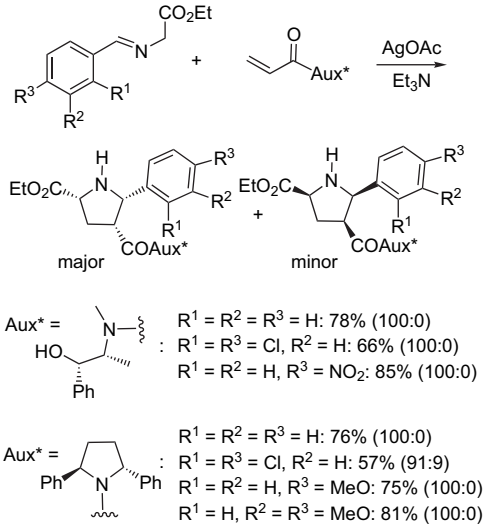
Ar	R	R'	Conditions	Yield (%)
Ph	H	Me	AgOAc/DBU/MeCN	3% + 36%
Ph	H	Me	AgOAc/DBU/THF	32% + 13%
Np	H	Me	AgOAc/DBU/THF	50% + 8%
Np	H	Me	AgOAc/DBU/MeCN	12% + 51%
Np	Me	Me	AgOAc/DBU/MeCN	51% + 6%
Np	Me	Et	AgOAc/DBU/MeCN	50% + 3%
Np	Me	Et	AgOAc/DBU/THF	44% + 9%
Np	Me	Et	AgOAc/NEt_3/MeCN	11% + 48%

Scheme 106. Ag(I)-catalysed 1,3-dipolar cycloadditions of azomethine ylides to a sulfinyl acrylate.

diastereoselectivities were obtained by using a cyclic C_2-symmetric pyrrolidine, as depicted in Scheme 108, and (1*R*,2*S*)-ephedrine as the chiral auxiliaries.



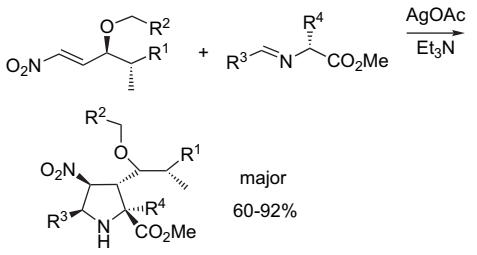
Scheme 107. AgF-catalysed 1,3-dipolar cycloadditions of cyclic azomethine ylides with Oppolzer's sultam.



Scheme 108. AgOAc-catalysed 1,3-dipolar cycloadditions of imines with chiral acrylamides.

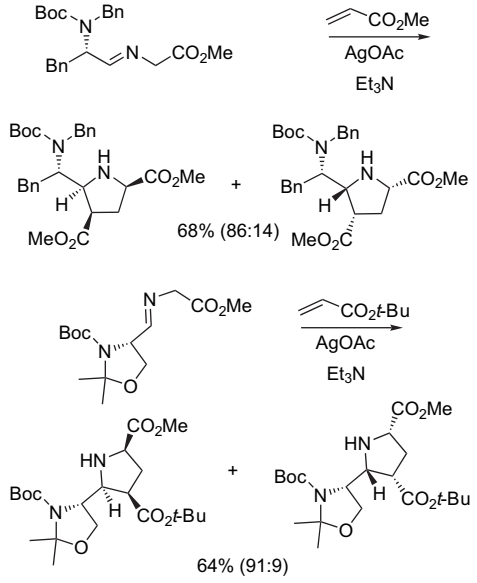
Similar conditions were applied to the cycloaddition between imines and *E*-nitroalkenes, which constituted the key step in the synthetic route to a new family of inhibitors of α_4,β_1-integrin-mediated hepatic melanoma metastasis.[176] It was shown that the reaction took place through a stepwise, and not a concerted mechanism, to give the [3+2] cycloadduct. The first step comprised a Michael-type nucleophilic attack of the α carbon atom of the azomethine ylide, which formed in situ, on the β carbon atom of the nitroalkene. The cyclisation step took place by means of an intramolecular Henry-type reaction between the intermediate nitronate moiety and the iminic fragment of the zwitterionic intermediate (Scheme 109). A complete stereoselectivity was systematically observed when R^3 was a phenyl group.

In 2005, Garner and Kaniskan reported stereoselective AgOAc-catalysed dipolar cycloadditions of chiral α-amino azomethine ylides applied to a new approach to the bioxalomycin family of antibiotics.[177] The reaction of a phenylalanine-derived α-amino imine and methyl acrylate gave an 86:14 ratio of two diastereomers, whereas that of an *N*-Boc-serinal acetonide imine with *tert*-butyl acrylate gave a 91:9 ratio of the corresponding diastereomeric cycloadducts (Scheme 110).



R^1 = Me, R^2 = R^3 = Ph, R^4 = H: de = 100%
R^1 = Me, R^2 = *o*-FC_6H_4, R^3 = Ph, R^4 = H: de = 100%
R^1 = Et, R^2 = R^3 = Ph, R^4 = H: de = 100%
R^1 = Me, R^2 = 2,6-$F_2C_6H_4$, R^3 = Ph, R^4 = H: de = 100%
R^1 = Et, R^2 = 3,5-$F_2C_6H_4$, R^3 = Ph, R^4 = H: de = 100%
R^1 = Et, R^2 = 2,3-$F_2C_6H_4$, R^3 = Ph, R^4 = H: de = 100%
R^1 = Et, R^2 = R^3 = Ph, R^4 = Me: de = 100%
R^1 = Me, R^2 = R^3 = Ph, R^4 = H: de > 98%
R^1 = Et, R^2 = Ph, R^3 = *c*-Hex, R^4 = H: de = 82%

Scheme 109. AgOAc-catalysed 1,3-dipolar cycloadditions of imines with *E*-nitroalkenes.

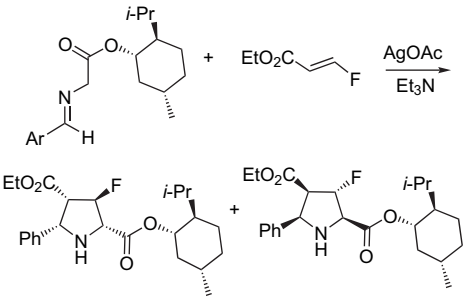


Scheme 110. AgOAc-catalysed 1,3-dipolar cycloadditions of α-amino azomethine ylides.

In 2006, Comes-Franchini et al. developed the first 1,3-dipolar cycloaddition of chiral azomethine ylides with (*E*)-ethyl 3-fluoroacrylate performed in the presence of AgOAc, allowing the efficient regio- and stereoselective synthesis of enantiopure pharmacologically important 3F-substituted prolines (Scheme 111).[178]

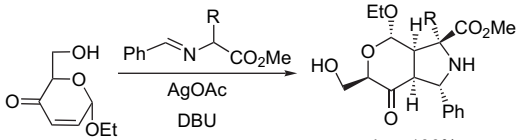
The same catalyst as that used in the above examples was involved by Bashiardes in a highly selective dipolar cycloaddition of various azomethine ylides with a chiral carbohydrate-derived enone.[179] The reaction proved to be extremely regio- and stereoselective, giving rise to single enantiomeric pyranopyrrolidines in all cases (Scheme 112).

The most recent advance in the chemistry of azomethine ylides is the use of chiral catalysts in the stereoselective synthesis of pyrrolidine derivatives via metallo-azomethine ylides,[180] which was reviewed by Savic and Husinec, covering the literature until the beginning of 2005.[181] The most



Ar = Ph: 86% (90:10)
Ar = *p*-CNC_6H_4: 90% (90:10)

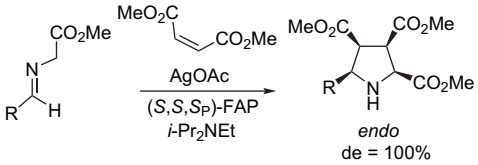
Scheme 111. AgOAc-catalysed 1,3-dipolar cycloadditions of chiral azomethine ylides with (*E*)-ethyl 3-fluoroacrylate.



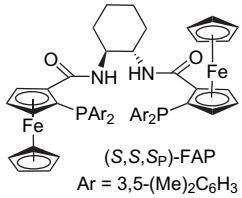
de = 100%
R = *i*-Bu: 65%
R = Ph: 66%

Scheme 112. AgOAc-catalysed 1,3-dipolar cycloadditions of azomethine ylides with a carbohydrate-derived enone.

effective Lewis acids in the cycloaddition reactions of metallo-azomethine ylides are arguably Ag(I) salts. The reaction times in these cases are generally short, requiring no more than a few hours, and the products are normally isolated in very high yields. Several chiral ligands have been involved in the catalytic asymmetric silver-catalysed cycloaddition of azomethine ylides. As an example, Zhang et al. have shown that high enantioselectivities could be achieved by using a new bis-ferrocenyl amide phosphine (FAP) as the ligand in highly enantioselective AgOAc-catalysed 1,3-dipolar cycloadditions of α-iminoesters with dimethyl maleate (Scheme 113).[182] Only the *endo*-products were isolated in all cases.



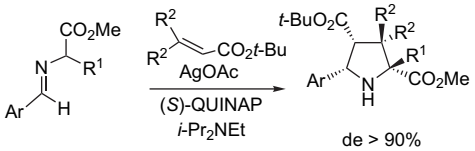
R = Ph: 87%; ee = 87%
R = *p*-Tol: 93%; ee = 88%
R = *p*-ClC_6H_4: 96%; ee = 92%
R = *p*-NCC_6H_4: 90%; ee = 96%
R = *p*-FC_6H_4: 96%; ee = 90%
R = 2-Np: 98%; ee = 97%
R = *o*-Tol: 97%; ee = 90%



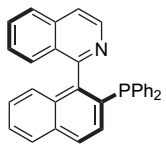
(*S*,*S*,*S*P)-FAP
Ar = 3,5-$(Me)_2C_6H_3$

Scheme 113. Enantioselective 1,3-dipolar cycloadditions in the presence of AgOAc and FAP ligand.

In the same context, (*S*)-QUINAP was successfully used by Schreiber et al., in 2003, in the dipolar cycloaddition of azomethine ylides derived from α-iminoesters with various α,β-unsaturated esters, giving excellent levels of diastereoselectivity (>90% de) and enantioselectivity (up to 96% ee) (Scheme 114).[183] In 2004, Carreira et al. reported the use, in a similar reaction, of new readily available atropisomeric P,N chiral ligands (PINAP) that were structurally similar to QUINAP and have parallel reactivity.[184] These latter ligands, in combination with AgOAc, gave very close results in terms of reactivity, diastereoselectivity and enantioselectivity, compared with those obtained with the QUINAP ligand.



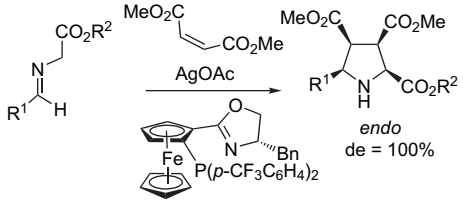
Ar = *p*-MeOC$_6$H$_4$, R^1 = R^2 = H: 93%; ee = 95%
Ar = *p*-BrC$_6$H$_4$, R^1 = R^2 = H: 89%; ee = 95%
Ar = *p*-NCC$_6$H$_4$, R^1 = R^2 = H: 92%; ee = 96%
Ar = 2-Np, R^1 = R^2 = H: 89%; ee = 94%
Ar = *o*-Tol, R^1 = R^2 = H: 95%; ee = 89%
Ar = Ph, R^1 = H, R^2 = Me: 97%; ee = 84%
Ar = Ph, R^1 = Me, R^2 = H: 98%; ee = 80%



(*S*)-QUINAP

Scheme 114. Enantioselective 1,3-dipolar cycloadditions in the presence of AgOAc and (*S*)-QUINAP.

More recently, a chiral ferrocenyloxazoline-derived N,P ligand, depicted in Scheme 115, was found to be an efficient chiral catalyst in the presence of AgOAc to perform similar reactions to those described above. An extra base such as a tertiary amine was not necessary in this case, since the reactive metal-bound azomethine ylide dipole was formed by deprotonation with acetate that played the role of base.[185] Indeed, it was postulated that AgOAc, bearing a weakly basic

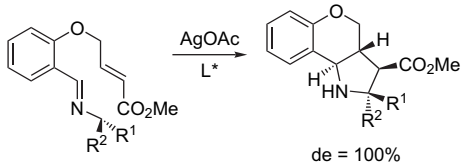


R^1 = *p*-ClC$_6$H$_4$, R^2 = Et: 98%; ee = 98%
R^1 = Ph, R^2 = Me: 85%; ee = 97%
R^1 = *p*-ClC$_6$H$_4$, R^2 = Me: 99%; ee = 97%
R^1 = *p*-FC$_6$H$_4$, R^2 = Me: 96%; ee = 97%
R^1 = *p*-NCC$_6$H$_4$, R^2 = Me: 91%; ee = 97%
R^1 = *o*-ClC$_6$H$_4$, R^2 = Me: 98%; ee = 97%
R^1 = *o*-Tol, R^2 = Me: 99%; ee = 98%
R^1 = 1-Np, R^2 = Me: 85%; ee = 98%
R^1 = 2-Np, R^2 = Me: 95%; ee = 98%

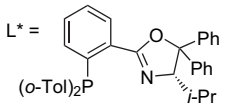
Scheme 115. Enantioselective 1,3-dipolar cycloadditions in the presence of AgOAc and a ferrocenyloxazoline-derived N,P ligand.

charged acetate ligand, facilitated the deprotonation of iminoesters to generate the azomethine ylides. This method provided a total *endo* diastereoselectivity in all cases, furnishing enantiopure highly substituted pyrrolidine derivatives.

The intramolecular version of the enantioselective silver-catalysed 1,3-dipolar cycloaddition performed in the presence of a chiral ligand was reported by Pfaltz et al., in 2005, involving a phosphino-oxazoline (PHOX) as the chiral ligand, giving access to chiral tricyclic compounds with perfect diastereoselectivity and high levels of enantiocontrol (Scheme 116).[186]

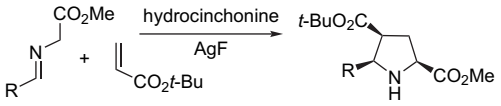


R^1 = CO$_2$Me, R^2 = H: 74%; ee = 96%
R^1 = CO$_2$*t*-Bu, R^2 = H: 66%; ee = 99%
R^1 = CO$_2$Me, R^2 = Me: 61%; ee = 96%
R^1 = py, R^2 = H: 70%; ee = 83%



Scheme 116. Enantioselective intramolecular 1,3-dipolar cycloadditions in the presence of AgOAc and PHOX ligand.

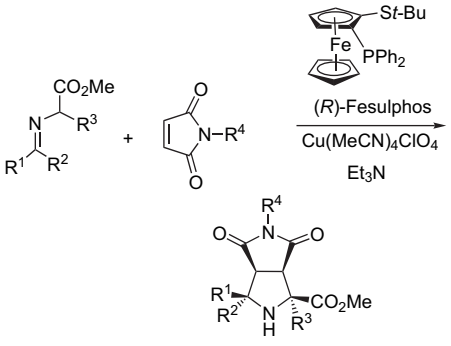
Although some of the preceding procedures afford the corresponding cycloadducts in good yields and high enantioselectivities, they normally require preformation of the catalysts, dry and deoxygenated solvents, and glovebox techniques. In addition, the reactions must be carried out under an inert atmosphere, which may limit their application from a practical point of view. In 2005, Jorgensen et al. reported a new convenient catalytic procedure for the enantioselective 1,3-dipolar cycloaddition of azomethine ylides, generated from *N*-alkylidene glycine esters, and acrylates to give the corresponding *endo*-products, which did not require special precautions with regard to drying, degasifying solvents, or using an inert atmosphere.[187] In this method, involving silver fluoride and cinchona alkaloids as the catalyst system, it was envisioned that chelation of the metal to the iminoester followed by deprotonation by a cinchona alkaloid acting as the chiral base would form a metallo-azomethine ylide-chiral base ion pair. This species would then react with the dipolarophile in a chiral environment to afford the expected cycloadduct stereoselectively (Scheme 117).



R = *p*-Tol: 89%; ee = 70%
R = *p*-MeOC$_6$H$_4$: 93%; ee = 70%
R = *p*-Me$_2$NC$_6$H$_4$: 86%; ee = 67%
R = *p*-BrC$_6$H$_4$: 88%; ee = 66%
R = *p*-NCC$_6$H$_4$: 86%; ee = 70%
R = 2-Fu: 86%; ee = 73%

Scheme 117. Enantioselective intramolecular 1,3-dipolar cycloadditions in the presence of AgF and hydrocinchonine.

Methodologies using Cu-based reagents or Cu–Lewis acids are valuable synthetic tools with a wide application in the synthesis of complex molecules. It is not just the efficiency, but also the diversity, of these methods that make copper one of the most important transition metals in organic synthesis. In recent years, Cu–Lewis acids in combination with a variety of chiral ligands have been evaluated in the enantioselective cycloadditions of azomethine ylides. As an example, Carretero et al. demonstrated, in 2005, that the combination of copper(I) salts and a Fesulphos ligand resulted in a highly reactive catalyst system, displaying exceptional enantioselectivities and a broad scope in the asymmetric 1,3-dipolar cycloaddition of azomethine ylides generated from iminoesters and maleimide dipolarophiles (Scheme 118).[188] In order to explore more deeply the scope and generality of this new methodology, other dipolarophiles of a varied nature such as dimethyl maleate, dimethyl fumarate and fumarodinitrile were also examined, proving to be excellent substrates for this reaction, since they provided high asymmetric inductions (76–99% ee), although the *endo*/*exo* selectivity was poorer than that of the maleimide dipolarophiles. In 2003, Komatsu et al. studied the same reaction, but in the presence of $Cu(OTf)_2$, and BINAP derivatives as chiral ligands, providing, in this case, an *exo* selectivity (up to 90% de) and high enantioselectivity (up to 87% ee).[189]

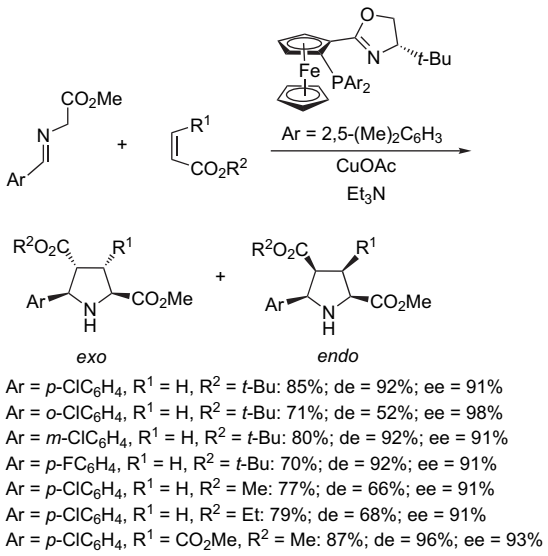


R^1	R^2	R^3	R^4	Yield (%)	de (%)	ee (%)
Ph	H	H	Ph	86	94	>99
2-Np	H	H	Ph	81	94	>99
p-FC_6H_4	H	H	Ph	82	> 96	>99
p-$MeOC_6H_4$	H	H	Ph	85	> 96	>99
o-Tol	H	H	Ph	85	> 96	>99
Ph	H	H	Me	97	> 96	>99
2-Np	H	Me	Ph	78	> 96	92
p-ClC_6H_4	Me	H	Ph	80	> 96	>99

Scheme 118. Enantioselective intramolecular 1,3-dipolar cycloadditions in the presence of Cu(I)–Fesulphos catalyst system.

The Cu(I)-catalysed enantioselective 1,3-dipolar cycloaddition of azomethine ylides with acrylates was also developed by Zhang et al., in 2005, in the presence of a chiral phosphino-oxazoline ligand in combination with CuOAc (Scheme 119).[190] Excellent *exo*/*endo*-selectivities were obtained, combined with high levels of enantioselectivity (up to 98% ee).

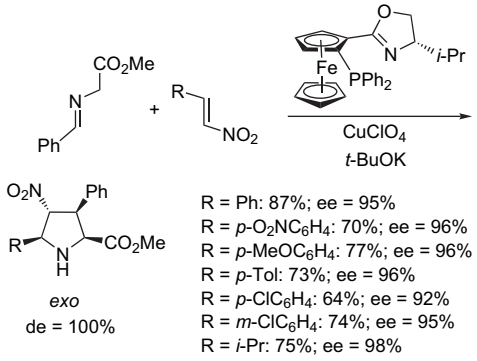
In 2006, Hou et al. extended the scope of this reaction to the use of nitroalkenes in the presence of a $CuClO_4$-P,N-ferrocene catalyst, providing exclusively the *exo*-adducts in



Ar = *p*-ClC_6H_4, R^1 = H, R^2 = *t*-Bu: 85%; de = 92%; ee = 91%
Ar = *o*-ClC_6H_4, R^1 = H, R^2 = *t*-Bu: 71%; de = 52%; ee = 98%
Ar = *m*-ClC_6H_4, R^1 = H, R^2 = *t*-Bu: 80%; de = 92%; ee = 91%
Ar = *p*-FC_6H_4, R^1 = H, R^2 = *t*-Bu: 70%; de = 92%; ee = 91%
Ar = *p*-ClC_6H_4, R^1 = H, R^2 = Me: 77%; de = 66%; ee = 91%
Ar = *p*-ClC_6H_4, R^1 = H, R^2 = Et: 79%; de = 68%; ee = 91%
Ar = *p*-ClC_6H_4, R^1 = CO_2Me, R^2 = Me: 87%; de = 96%; ee = 93%

Scheme 119. Enantioselective intramolecular 1,3-dipolar cycloadditions in the presence of CuOAc and a phosphino-oxazoline ligand.

high yields and with ee values ranging from 92 to 98% (Scheme 120).[191] In addition, a general protocol for the enantioselective catalytic 1,3-dipolar cycloaddition of azomethine ylides with aryl vinyl sulfones was reported, in 2006, by Carretero et al.[192] Near-complete *exo* selectivity and enantioselectivities of up to 85% ee were attained using $Cu(MeCN)_4ClO_4$/Taniaphos as the catalyst system.

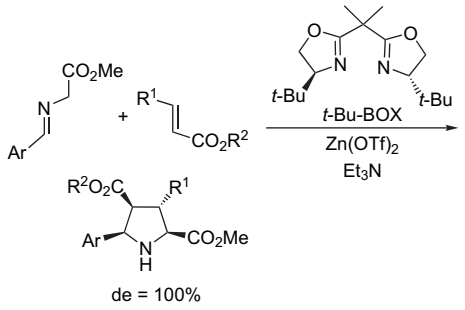


R = Ph: 87%; ee = 95%
R = *p*-$O_2NC_6H_4$: 70%; ee = 96%
R = *p*-$MeOC_6H_4$: 77%; ee = 96%
R = *p*-Tol: 73%; ee = 96%
R = *p*-ClC_6H_4: 64%; ee = 92%
R = *m*-ClC_6H_4: 74%; ee = 95%
R = *i*-Pr: 75%; ee = 98%

Scheme 120. Enantioselective intramolecular 1,3-dipolar cycloadditions of an azomethine ylide to nitroalkenes in the presence of $CuClO_4$ and a phosphino-oxazoline ligand.

On the other hand, chiral oxazoline ligands have been used in asymmetric 1,3-dipolar cycloadditions of azomethine ylides in conjunction with Zn(II) Lewis acids. Hence, Jorgensen et al. have shown that the use of $Zn(OTf)_2$ in combination with a chiral bisoxazoline ligand (BOX), for the 1,3-dipolar cycloaddition of a series of imines of glycine methyl ester with different electron-deficient alkenes, allowed the corresponding diastereomerically pure products to be obtained with up to 94% ee (Scheme 121).[193]

In 2002, the asymmetric syntheses of ferrocenyl-substituted pyrrolidine derivatives were successfully achieved by $ZnEt_2$-mediated 1,3-dipolar cycloaddition reactions of chiral azomethine ylides derived from camphor with a number of electron-deficient dipolarophiles.[194] The chiral azomethine



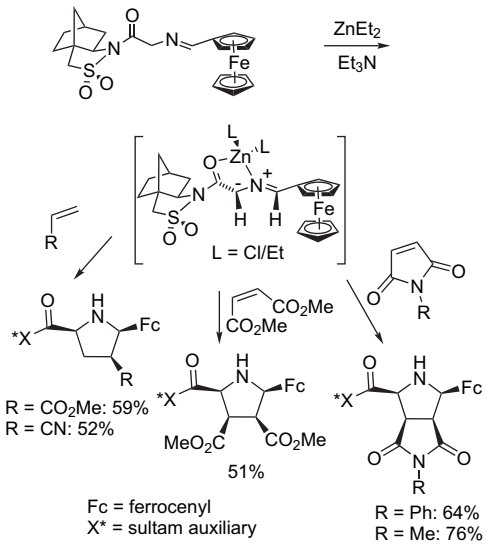
Ar = Ph, R^1 = H, R^2 = Me: 80%; ee = 88%
Ar = 2-Np, R^1 = H, R^2 = Me: 84%; ee = 91%
Ar = *p*-BrC_6H_4, R^1 = H, R^2 = Me: 89%; ee = 94%
Ar = 2-Np, R^1 = CO_2Me, R^2 = Me: 84%; ee = 90%
Ar = 2-Np, R^1 = H, R^2 = Et: 76%; ee = 68%

Scheme 121. Enantioselective 1,3-dipolar cycloadditions of azomethine ylides to alkenes in the presence of $Zn(OTf)_2$ and *t*-Bu-BOX ligand.

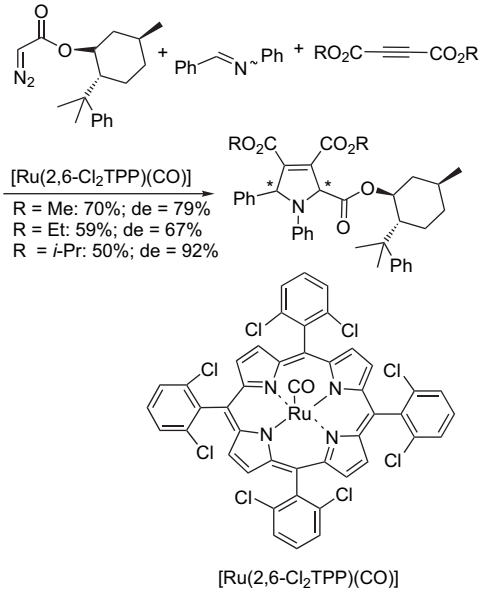
ylides were formed by condensing glycyl sultam with ferrocenecarboxaldehyde via imine tautomerisation and complexation with $ZnEt_2$. All the cycloadditions gave the corresponding ferrocenyl-substituted pyrrolidine derivatives with very high regio- and diastereoselectivities in reasonable yields (Scheme 122).

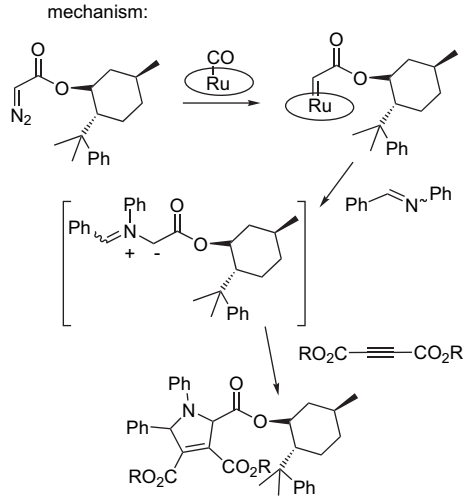
In 2005, Che et al. developed the first asymmetric synthesis of chiral pyrrolines based on a ruthenium porphyrin-catalysed three-component coupling process.[195] In this process, it was demonstrated that ruthenium porphyrins catalysed the decomposition of chiral 8-phenylmenthol α-diazo esters to give metallocarbenoids that reacted with imines to afford chiral azomethine ylides (Scheme 123). Subsequently, these chiral azomethine ylides underwent 1,3-dipolar cycloaddition reactions with dipolarophiles to afford chiral pyrrolines in good yields and high diastereoselectivities (up to 92% de).

In addition, Riant and Mamane have developed the 1,3-dipolar cycloaddition of chiral ferrocenyl-substituted azomethine ylides, generated in situ by the reaction of the



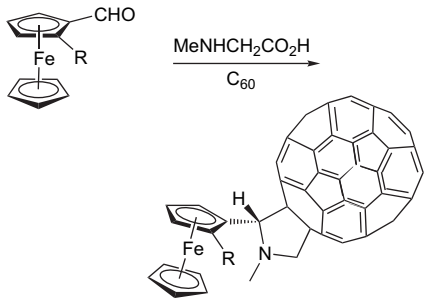
Scheme 122. $ZnEt_2$-mediated 1,3-dipolar cycloadditions of a camphor-derived azomethine ylide to alkenes.





Scheme 123. Ruthenium porphyrin-catalysed three-component coupling process.

corresponding aldehydes with sarcosine, to C_{60}, leading to the corresponding fulleropyrrolidines with high diastereoselectivities (Scheme 124).[196] This methodology has been



R = TMS: 23%; de > 95%
R = *p*-$MeOC_6H_4$: 24%; de > 95%
R = Np: 40%; de > 95%
R = *p*-(H-C≡C)-C_6H_4: 15%; de > 95%

Scheme 124. 1,3-Dipolar cycloadditions of chiral ferrocenyl azomethine ylides to C_{60}.

applied to the preparation of a C_2-symmetric enantiopure fullerene dimer.

5. Diazoalkanes

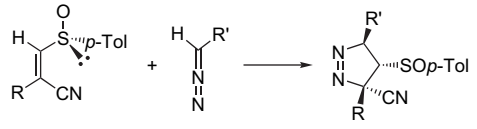
In the last five years, only the 1,3-dipolar cycloadditions of diazoalkanes with chiral dipolarophiles, and the metal-catalysed reactions of diazoalkanes have been reported in the literature, both resulting in the formation of chiral 1-pyrazoline derivatives.

5.1. Chiral dipolarophiles

The dipolarophilic reactivity of chiral (*Z*)-3-*p*-tolylsulfinylacrylonitriles has been evaluated with diazoalkanes, providing a new entry into chiral Δ^1-cyanopyrazolines, the structures of which are much less frequently reported in the literature than those of their corresponding Δ^2-analogues (Scheme 125).[197] Moreover, the asymmetric synthesis of pyrazolines has been studied mainly from cyclic and much less from acyclic alkenes. In each case, only one cycloadduct was formed in high yield under mild conditions, therefore evidencing a complete control of the regioselectivity and the *endo*/*exo* and π-facial selectivities.

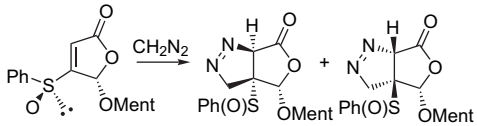
Diazoalkanes have also been submitted to asymmetric 1,3-dipolar cycloaddition in the presence of (5*S*,S_S)-5-[(1*R*)-methyloxy]-4-phenylsulfinylfuran-2(5*H*)-ones, providing the corresponding pyrazolines resulting from the approach of the dipole to both diastereotopic faces of the dipolarophile (Scheme 126).[198] The reactions were completely regioselective, yielding only the adduct resulting from the formation of the N_{dipole}–$C(3)_{furanone}$ bond.

The role of steric and electronic interactions in the stereocontrol of the asymmetric 1,3-dipolar reaction of 5-alkoxy-3-*p*-(*S*)-tolylsulfinylfuran-2(5*H*)-ones with diazoalkanes was studied in 2003 (Scheme 127).[199] It was demonstrated that



R = *n*-Bu, R' = H: > 93%; de = 100%
R = *t*-Bu, R' = H: > 93%; de = 100%
R = Bn, R' = H: > 93%; de = 100%
R = *n*-Bu, R' = Me: > 93%; de = 100%
R = *t*-Bu, R' = Me: > 93%; de = 100%
R = Bn, R' = Me: > 93%; de = 100%

Scheme 125. 1,3-Dipolar cycloadditions of chiral (*Z*)-3-*p*-tolylsulfinylacrylonitriles to diazoalkanes.

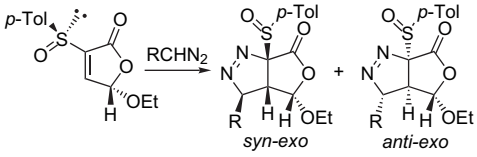


80%; de = 70%
with $ZnBr_2$: 79%; de = 100%

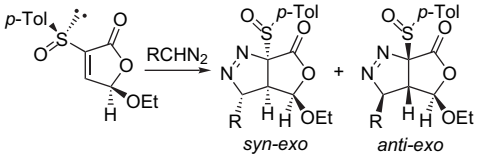
Scheme 126. 1,3-Dipolar cycloaddition of (5*S*,S_S)-5-[(1*R*)-methyloxy]-4-phenylsulfinylfuran-2(5*H*)-one to diazomethane.

these reactions evolved in high yields under mild conditions, affording bicyclic pyrazolines with complete regioselectivity, which could be modulated, becoming almost complete, with the solvent polarity. Electrostatic interactions between dipoles and the alkoxy group at C5 were, however, also significant in apolar solvents. The steric interactions between the substituents at diazoethane and at C4 of the furanone rings were the main reasons for the observed *exo* selectivity.

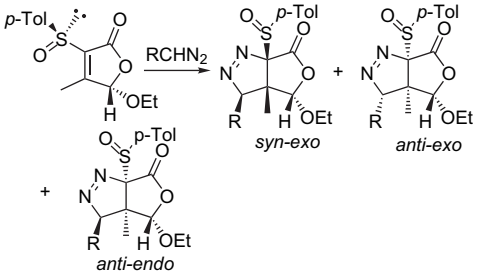
In 2005, the same group reported the 1,3-dipolar cycloaddition of 2-*p*-tolylsulfinyl 3-alkyl cyclopentenones with diazomethane, affording the corresponding pyrazolines in moderate to high diastereoselectivities (up to 96% de without 3-alkyl substitution).[200] The scope of this methodology was



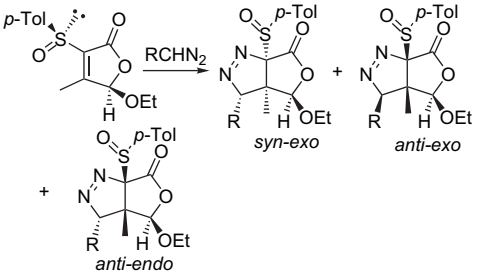
R = Me, solvent = Et_2O: *syn*:*anti* = 95:5
R = Me, solvent = MeCN/Et_2O: *syn*:*anti* = 60:40
R = H, solvent = MeCN/Et_2O: *syn*:*anti* = 40:60
R = H, solvent = Et_2O: *syn*:*anti* = 100:0



R = Me, solvent = Et_2O: *syn*:*anti* = 7:93
R = Me, solvent = MeCN/Et_2O: *syn*:*anti* = 5:95
R = H, solvent = Et_2O: *syn*:*anti* = 7:93
R = H, solvent = MeCN/Et_2O: *syn*:*anti* = 9:91

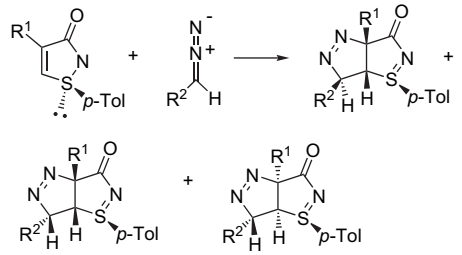


R = Me, solvent = Et_2O: *syn*:*anti* = 100:0
R = Me, solvent = MeCN/Et_2O: *syn*:*anti* = 84:16
R = H, solvent = Et_2O: *syn*:*anti* = 100:0
R = H, solvent = MeCN/Et_2O: *syn*:*anti* = 75:25



R = Me, solvent = Et_2O: *syn*:*anti* = 0:100
R = Me, solvent = MeCN/Et_2O: *syn*:*anti* = 0:100
R = H, solvent = Et_2O: *syn*:*anti* = 0:100
R = H, solvent = MeCN/Et_2O: *syn*:*anti* = 5:95

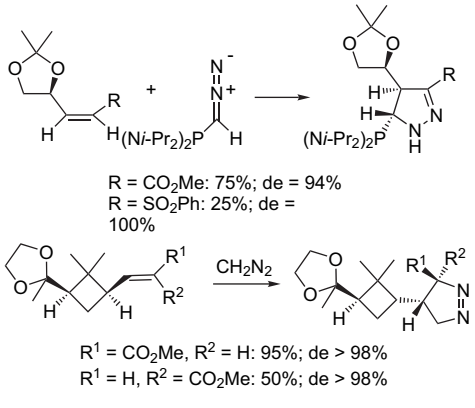
Scheme 127. 1,3-Dipolar cycloadditions of chiral 5-ethoxy-3-*p*-(*S*)-tolylsulfinylfuran-2(5*H*)-ones to diazoalkanes.



Scheme 128. 1,3-Dipolar cycloadditions of chiral cyclic vinyl *p*-tolyl sulfilimines to diazoalkanes.

also extended to the use of chiral cyclic vinyl *p*-tolyl sulfilimines with diazoalkanes, producing the corresponding Δ^1-pyrazolines in a highly stereoselective manner (Scheme 128).[201]

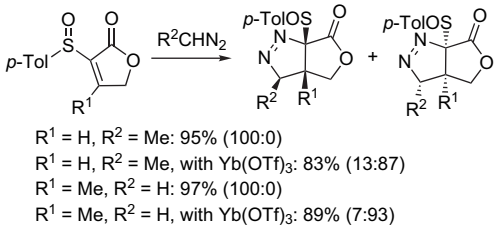
In 2001, Ohkata et al. reported the 1,3-dipolar cycloaddition of diazoalkanes with (−)-8-phenylmenthyl (*E*)-3-aryl-2-phosphonoacrylates, affording the corresponding Δ^1-pyrazolines with high stereoselectivity (up to 100% de) and high yields.[202] These latter compounds were further converted into the corresponding cyclopropane derivatives via photolysis. In 2002, Branchadell et al. studied the first 1,3-dipolar cycloaddition of bis(diisopropylamino)phosphinodiazomethane and diazomethane with chiral electron-deficient olefins derived from D-glyceraldehyde acetonide and (−)-verbenone (Scheme 129).[203] In the reactions of diazomethane, it was shown that the diastereoselectivity was not dependent on the *Z*/*E* stereochemistry of the starting material, but the reactivity was lower for (*Z*)-cyclobutyl derivatives than for their *E* isomers. On the other hand, in the reactions between bis(diisopropylamino)phosphinodiazomethane and the glyceraldehyde derivatives, the *E* isomers were less reactive than the *Z* isomers, giving high diastereoselectivities, and afforded adducts with poor facial diastereoselectivities.



Scheme 129. 1,3-Dipolar cycloadditions of bis(diisopropylamino)phosphinodiazomethane and diazomethane to electron-deficient olefins.

5.2. Metal-catalysed reactions

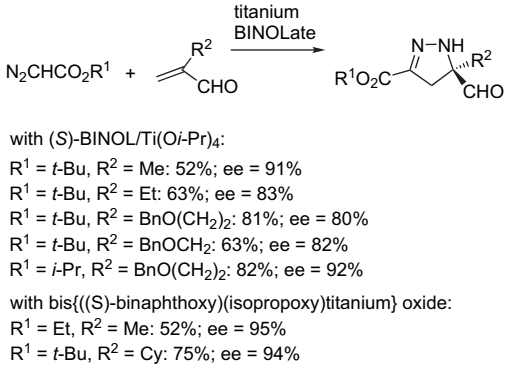
In 2005, Garcia Ruano et al. studied the 1,3-dipolar cycloaddition of diazoalkanes to activated sulfoxides such as chiral



Scheme 130. $Yb(OTf)_3$-catalysed 1,3-dipolar cycloadditions of diazoalkanes to sulfinyl furanones.

sulfinyl furanones in the presence or absence of Lewis acids.[204] It was demonstrated that the sulfinyl group was able to completely control the π-facial selectivity in the absence of Lewis acids. Furthermore, the use of some Lewis acids as the catalysts, such as $Yb(OTf)_3$, substantially inverted the selectivity, making possible the stereodivergent synthesis of chiral pyrazolines. In all cases, excellent yields and almost complete stereoselectivity were obtained, as shown in Scheme 130.

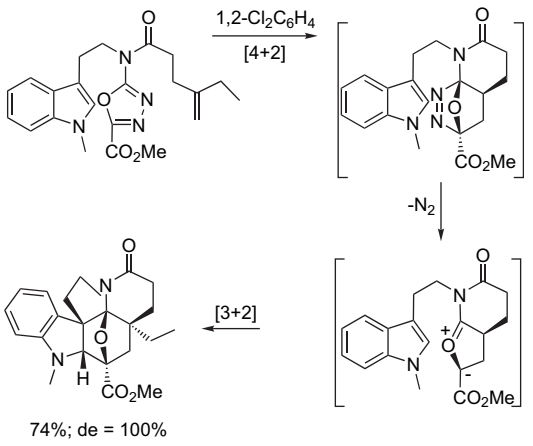
In 2006, Maruoka et al. developed enantioselective 1,3-dipolar cycloadditions between diazoacetates and α-substituted acroleins catalysed by chiral titanium BINOLate Lewis acids such as (*S*)-BINOL/Ti(O*i*-Pr)$_4$ complex and bis{((*S*)-binaphthoxy)(isopropoxy)titanium} oxide, providing the corresponding 2-pyrazolines bearing an asymmetric tetrasubstituted carbon centre (Scheme 131).[205] This methodology was successfully applied to the short synthesis of manzacidin A.



Scheme 131. Titanium BINOLate-catalysed 1,3-dipolar cycloadditions of diazoacetates to α-substituted acroleins.

6. Carbonyl ylides

In 2005, Boger et al. reported a total synthesis of both enantiomers of the Aspidosperma alkaloids, 4-desacetoxy-6,7-dihydrovindorosine, vindorosine and minovine.[206] The key step was a tandem intramolecular [4+2]/[3+2] cycloaddition reaction of a 1,3,4-oxadiazole in which three new rings were stereoselectively formed, since only a single diastereomer was isolated in excellent yield (Scheme 132). In this sequence, an olefinic dienophile tethered to a 2-amino-1,3,4-oxadiazole reacted to form the initial [4+2] cycloadduct that lost N_2 to generate a carbonyl ylide, which was trapped by a tethered indole. The relative stereochemistry was set by

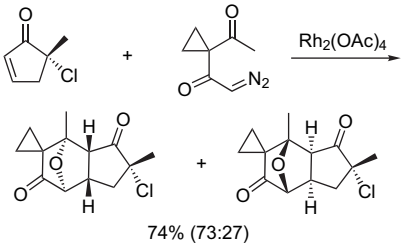


Scheme 132. Tandem [4+2]/[3+2] cycloaddition reaction of a 1,3,4-oxadiazole.

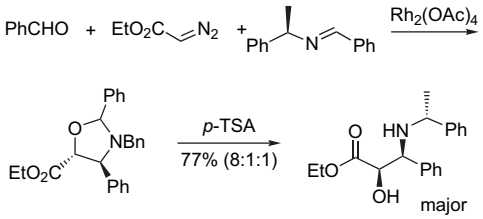
a combination of the dienophile geometry and the exclusive indole *endo* [3+2] cycloaddition sterically directed to the face opposite to the fused lactam. Impressively, the tandem reaction set all five stereocentres about the central six-membered ring in a single step.

It should be noted that the catalytic enantioselective rearrangements and cycloadditions involving ylides from diazo compounds were reviewed in 2001 by Hodgson et al.[207] Rhodium catalysts have been involved in a number of catalysed 1,3-dipolar cycloadditions of carbonyl ylides generated from diazocarbonyl derivatives. As an example, a stereoselective synthesis of the antitumour agent, (−)-irofulven, was achieved by McMorris et al., in 2004, on the basis of the 1,3-dipolar cycloaddition of (*S*)-5-chloro-5-methyl-2-cyclopentenone to the dipolar intermediate from 1-acetyl-1-(diazoacetyl)cyclopropane, performed in the presence of a catalytic amount of $Rh_2(OAc)_4$.[208] A mixture of two diastereomers was obtained in good yield, but moderate diastereoselectivity, as depicted in Scheme 133.

In 2005, a highly diastereoselective Rh(II)-catalysed three-component coupling of imines, benzaldehyde and ethyl diazoacetate was reported by Somfai et al., providing an efficient protocol for the synthesis of *syn*-α-hydroxy-β-amino esters.[209] When an enantiomerically pure imine derived from (+)-α-methylbenzylamine was used, the reaction led to the corresponding chiral *syn*-amino alcohol in good yield and selectivity (Scheme 134). This latter compound was further converted in two steps into the taxol C13 side chain.



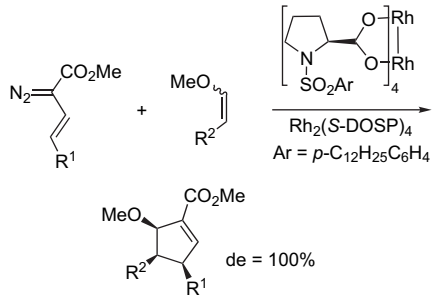
Scheme 133. Rh(II)-catalysed 1,3-dipolar cycloaddition of 1-acetyl-1-(diazoacetyl)cyclopropane to (*S*)-5-chloro-5-methyl-2-cyclopentenone.



Scheme 134. Rh(II)-catalysed 1,3-dipolar cycloaddition of a carbonyl ylide to a chiral imine.

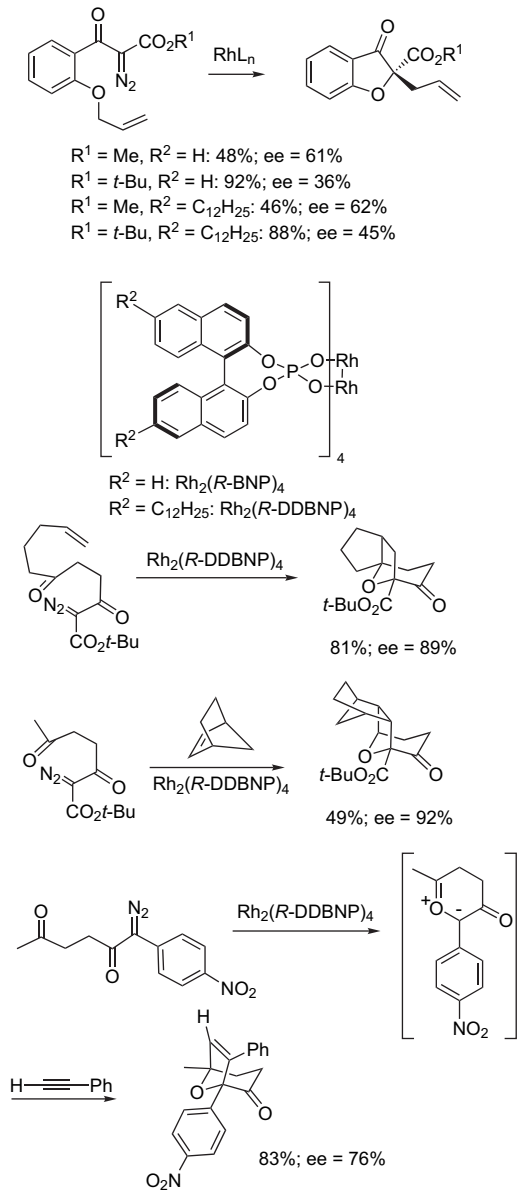
Davies et al. have developed the Rh_2(*S*-DOSP)$_4$-catalysed decomposition of vinyldiazocarbonyl derivatives in the presence of vinyl ethers.[210] The corresponding chiral cyclopentenecarboxylates were formed in 79–99% ees with full control of the relative stereochemistry at up to three contiguous stereogenic centres, as depicted in Scheme 135.

In 2001, Rh(II)-binaphthol phosphate catalysts were used by Hodgson and Petroliagi in the enantioselective intramolecular oxonium ylide 1,3-dipolar cycloaddition of α-diazo-β-ketoesters.[211] Hence, the reaction of α-diazo-β-ketoesters, depicted in Scheme 136, led to the formation of the corresponding benzofuranones in the presence of catalytic dirhodium tetrakisbinaphthol phosphate catalysts with enantiomeric excesses of up to 62%. When the reaction was applied to a 2-diazo-3,6-diketoester, it led to the corresponding cycloadduct with a rise in the ee (Scheme 136).[212] This methodology was extended by the same group to an intermolecular version of the reaction performed between diazodiones and arylacetylenes, providing the corresponding cycloadducts with enantioselectivities of up to 76% ee (Scheme 136).[213] In addition, norbornadiene also proved to be a viable dipolarophile with *tert*-butyl 2-diazo-3,6-dioxoheptanoate, affording the corresponding cycloadduct with up to 92% ee, as depicted in Scheme 136.[214] In 2004, the same group also applied this methodology to the enantioselective synthesis of chiral nemorensic acids by using 6-diazoheptane-2,5-dione in a carbonyl ylide cycloaddition, performed in the presence of DMAD and a chiral rhodium catalyst, Rh_2(*S*-BPTV)$_4$.[215] On the other hand, the application of this methodology to the enantioselective intramolecular 1,3-dipolar cycloaddition of diazocarbonyl-



R^1 = Me, R^2 = Ph: 79%; ee = 98%
R^1 = Me, R^2 = *p*-BrC_6H_4: 71%; ee > 99%
R^1 = Me, R^2 = *E*-CH=CHEt: 49%; ee = 99%
R^1 = *n*-Bu, R^2 = Ph: 55%; ee > 94%
R^1 = H, R^2 = Ph: 61%; ee = 82%
R^1 = H, R^2 = *E*-CH=CHEt: 74%; ee = 79%

Scheme 135. Rh_2(*S*-DOSP)$_4$-catalysed 1,3-dipolar cycloadditions of vinyldiazocarbonyl derivatives to vinyl ethers.

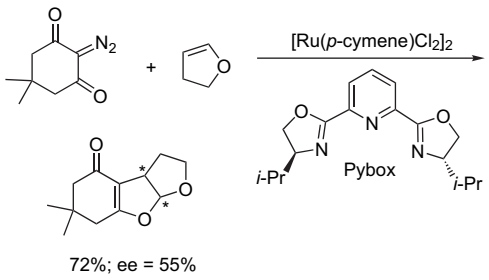


Scheme 136. Rh(II)-binaphthol phosphate-catalysed-1,3-dipolar cycloadditions of α-diazo-β-ketoesters and diazodiones.

derived oxidopyryliums gave, however, lower enantioselectivities (up to 19% ee).[216]

In 2003, Müller et al. studied the enantioselectivity of the transition metal-catalysed 1,3-dipolar cycloaddition of 2-diazocyclohexane-1,3-diones to acyclic and cyclic enol ethers in the presence of Rh(II) catalysts to afford dihydrofurans.[217] In some cases, excellent diastereoselectivities were observed, while no significant enantioselectivity was observed in general. In 2005, however, the same group re-investigated this reaction in the presence of Ru(II) catalysts containing chiral ligands, which allowed a better enantioselectivity to be obtained (Scheme 137).[218]

In 2005, the scope of this reaction was extended to the use of alkyl diazopyruvates, which provided in the presence of [$RuCl_2$(Pybox)] catalysts and enol ethers the corresponding chiral dihydrofurans (Scheme 138).[218,219] The best result

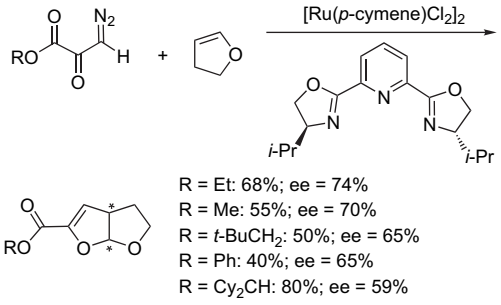


Scheme 137. Ru(II)–Pybox-catalysed 1,3-dipolar cycloaddition of 2-diazocyclohexane-1,3-dione to 2,3-dihydrofuran.

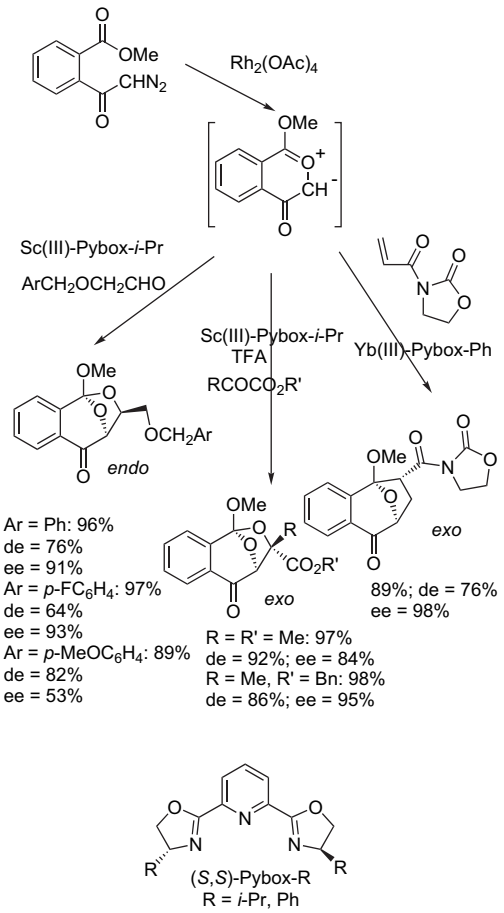
was obtained by using ethyl diazopyruvate, giving an enantiomeric excess of up to 74%.

Suga et al. have used chiral 2,6-bis(oxazolinyl)pyridine–rare earth-metal complexes as catalysts for the highly enantioselective 1,3-dipolar cycloaddition reaction of 2-benzopyrylium-4-olate.[220] Significant levels of enantioselectivity were obtained in the 1,3-dipolar cycloaddition of 2-benzopyrylium-4-olate generated from the $Rh_2(OAc)_4$-catalysed decomposition of *o*-methoxycarbonyl-α-diazoacetophenone. This reaction involved chiral 2,6-bis(oxazolinyl)pyridine (Pybox)–rare earth-metal triflate complexes as chiral Lewis-acid catalysts. The reactions involving several benzyloxyacetaldehyde derivatives, catalysed by a Sc(III)–Pybox–*i*-Pr complex, proceeded smoothly to yield the *endo*-adducts selectively with high enantioselectivity (up to 93% ee). For the reaction with benzyl pyruvate, the Sc(III)–Pybox–*i*-Pr complex catalysed the reaction effectively in the presence of trifluoroacetic acid, yielding an *exo*-adduct with both high diastereo- and enantioselectivities (94% ee). Furthermore, this catalytic system was efficiently applied to the reactions involving several other α-keto esters with high *exo*- and enantioselectivities (up to 95% ee). In contrast to the reaction with carbonyl compounds, a Yb(III)–Pybox–Ph complex was found to be effective to obtain high enantioselectivity (96% ee) of the diastereoselectively produced *exo*-cycloadduct in the reaction with 3-acryloyl-2-oxazolidinone (Scheme 139).

In this context, Suga et al. have demonstrated that the 1,3-dipolar cycloaddition reaction of the same carbonyl ylide as that depicted in Scheme 139, generated by the $Rh_2(OAc)_4$-catalysed decomposition of *o*-(methoxycarbonyl)-α-diazoacetophenone, with *N*-substituted maleimides in the presence of a catalytic amount of $Yb(OTf)_3$, showed a high *endo*



Scheme 138. Ru(II)–Pybox-catalysed 1,3-dipolar cycloadditions of alkyl diazopyruvates to 2,3-dihydrofuran.



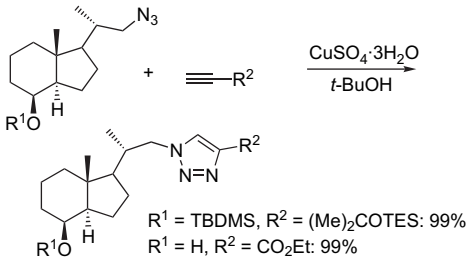
Scheme 139. Sc(III)–Pybox-catalysed 1,3-dipolar cycloadditions of 2-benzopyrylium-4-olate.

selectivity.[221] When the reaction was performed in the presence of chiral catalysts, prepared from Cu(I) or Cu(II) and 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] as the ligand, a moderate enantioselectivity was observed.

7. Azides

Azides react with dipolarophiles to form triazolines, which may be stable, or decompose to aziridines or imines, for example. In particular, the 1,3-dipolar cycloaddition of azides to alkynes is one of the most important and efficient routes to triazoles. The intermolecular variant of the azide 1,3-dipolar cycloaddition is not common, because the reaction is generally very slow, whereas the intramolecular variant has been more frequently employed. Only a few examples of intermolecular reactions have been reported in recent years. As an example, Fall et al. reported, in 2004, an intermolecular 1,3-dipolar cycloaddition in the course of developing a stereoselective route to vitamin D analogues bearing triazole rings in their side chains.[222] The methodology was based on a 1,3-dipolar cycloaddition of a vitamin D side chain terminal azide with a terminal acetylene, leading to the formation of the expected triazolines (Scheme 140).

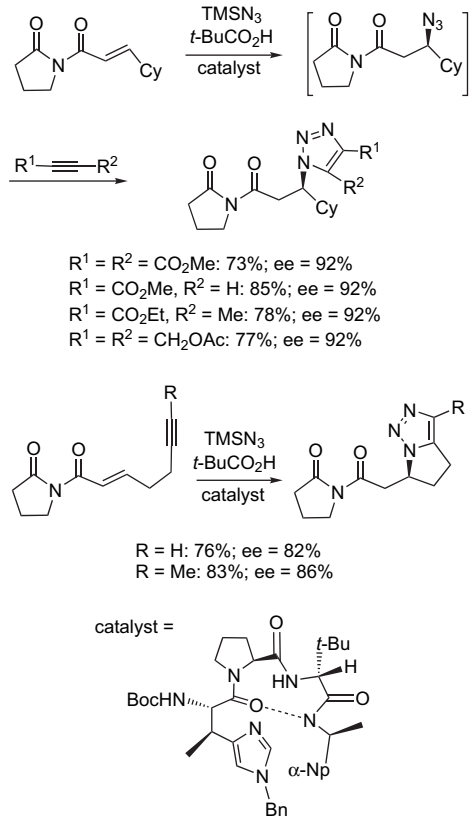
In 2002, Miller and Guerin reported asymmetric tandem azidation/1,3-dipolar cycloaddition reactions catalysed by open-chain peptide-based catalysts.[223] For the first time,



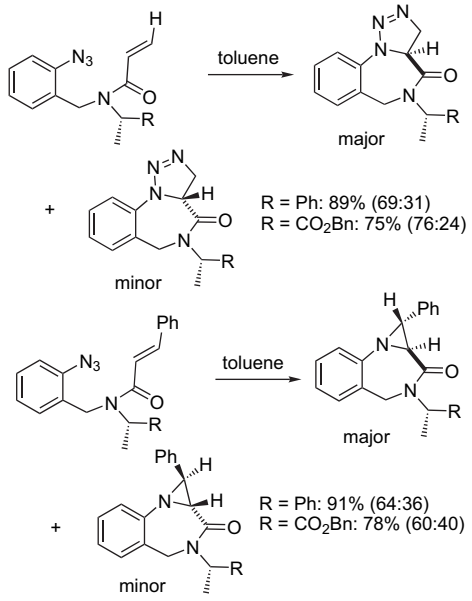
Scheme 140. 1,3-Dipolar cycloadditions of vitamin D side chain terminal azides to terminal acetylenes.

an asymmetric azidation according to the Evans procedure proceeded with complete diastereocontrol to afford the corresponding α-azido imide, which was further submitted to a 1,3-dipolar cycloaddition in the presence of a dipolarophile, providing the corresponding chiral triazole in high enantioselectivity (Scheme 141). The intramolecular version of this reaction was successfully applied to pendant alkynes, as depicted in Scheme 141.

Several groups have described intramolecular 1,3-dipolar cycloadditions, such as Garanti's group, who reported the cycloaddition of *N*-alkenoyl aryl azides.[224] The reaction of unsubstituted *N*-alkenoyl aryl azides gave the corresponding enantiopure 3,3a-dihydro-1,2,3-triazolo[1,5-*a*][1,4]benzodiazepine-4(6*H*)-ones as a mixture of two diastereomers, whereas phenyl-substituted *N*-alkenoyl aryl azides gave the corresponding enantiopure 1,1a-dihydro-2*H*-azirino[2,1-*c*][1,4]benzodiazepine-4(6*H*)-ones as a diastereomerically enriched mixture of diastereomers (Scheme 142).



Scheme 141. Tandem azidation/1,3-dipolar cycloaddition reactions.

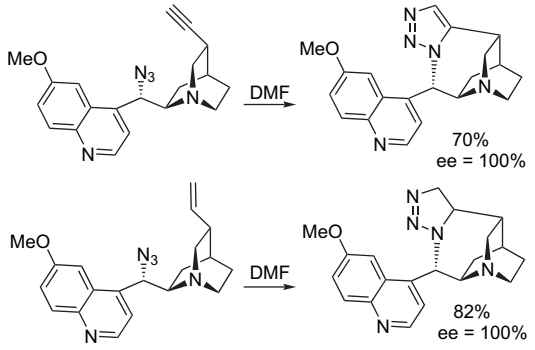


Scheme 142. Intramolecular 1,3-dipolar cycloadditions of *N*-alkenoyl aryl azides.

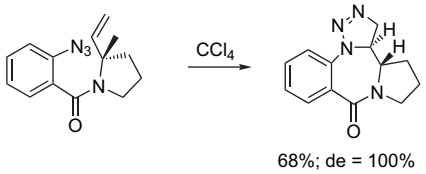
In 2003, Hoffmann et al. reported the intramolecular 1,3-dipolar cycloadditions of cinchona azides to the C10–C11 alkyne and C10–C11 olefin unit of the alkaloid, giving access to a variety of fused triazoles and triazolines, both possessing a bis-azahomotwistane skeleton (Scheme 143).[225]

The synthesis of the new pyrrolo[2,1-*c*][1,2,3]triazolo[1,5-*a*][1,4]benzodiazepine skeleton was reported by Broggini et al., in 2004, involving a totally diastereoselective intramolecular azide cycloaddition as the key step (Scheme 144).[226]

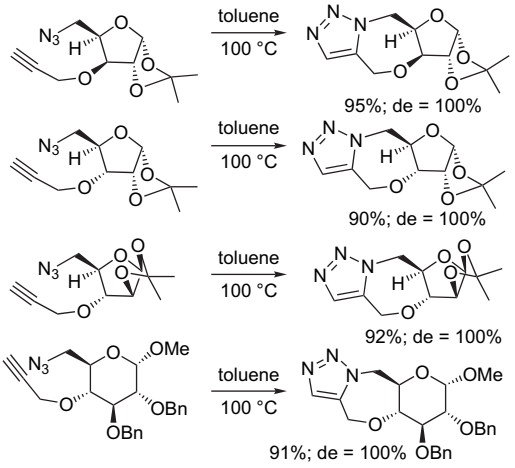
In addition, the azide methodology was also applied, in 2005, to carbohydrate-derived azido-alkynes, allowing an



Scheme 143. Intramolecular 1,3-dipolar cycloadditions of activated cinchona alkaloids with azide ion.



Scheme 144. Intramolecular 1,3-dipolar cycloaddition of an *o*-azidobenzamide.

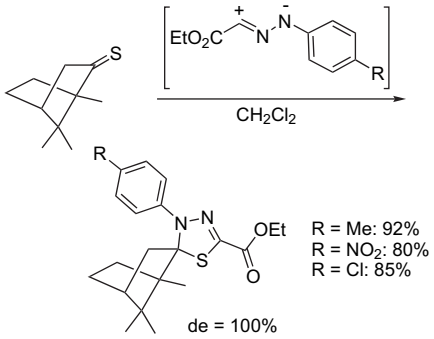


Scheme 145. Intramolecular 1,3-dipolar cycloadditions of carbohydrate-derived azido-alkynes.

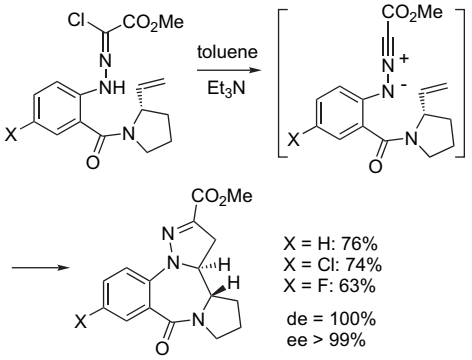
expedient synthesis of 1,2,3-triazole-fused tetracyclic compounds (Scheme 145).[227] The versatility of the current protocol was demonstrated using a range of substrates comprising *gluco*-, *allo*-, *xylo*-, *ribo*- and *arabino*-derived azido-alkynes, which gave, in all cases, a single product.

8. Nitrilimines

The stereoselective cycloadditions of nitrilimines as a source of enantiopure heterocycles were reviewed by Molteni, in 2005, covering the literature until the beginning of 2005.[228] Consequently, this section will be limited to updating this preceding review. The 1,3-dipolar cycloadditions of nitrilimines, most conveniently generated from the dehydrohalogenation of hydrazidic halides, with olefins and acetylenes result in the formation of pyrazolines and pyrazoles, respectively. Despite the utility of enantiopure heterocycles such as pyrazolines in organic synthesis, the stereoselective cycloadditions of nitrilimines have become useful only in the last few years. A one-pot diastereoselective synthesis of new chiral spiro-1,3,4-thiadiazoles has been developed by Daran et al., on the basis of a 1,3-dipolar cycloaddition of *N*-aryl-*C*-ethoxycarbonyl nitrilimines, generated in situ from ethyl *N*-arylhydrazo-α-bromoglyoxalates and triethylamine, to (1*R*)-thiocamphor.[129] The reaction was revealed to be highly diastereoselective, as all the new 1,3,4-thiadiazoles were isolated as pure diastereoisomers (Scheme 146).



Scheme 146. 1,3-Dipolar cycloadditions of *N*-aryl-*C*-ethoxycarbonyl nitrilimines to (1*R*)-thiocamphor.

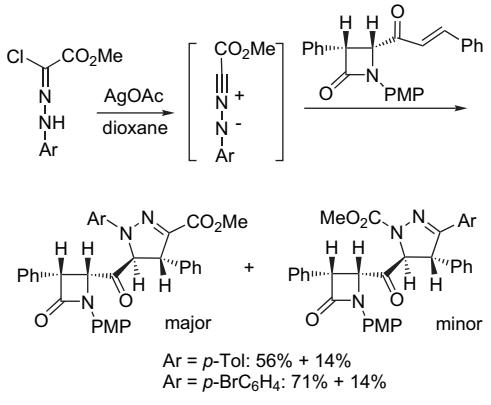


Scheme 147. Intramolecular 1,3-dipolar cycloadditions of L-proline-derived nitrilimines.

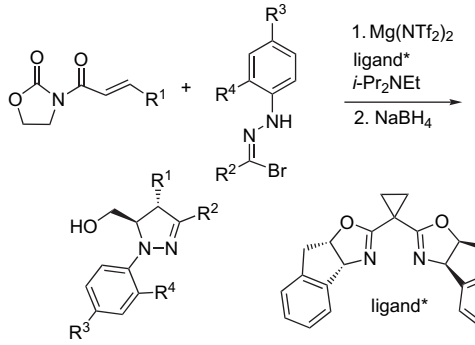
In 2005, Broggini et al. reported an effective synthesis of a new class of enantiopure tetracyclic compounds, namely pyrazolo[1,5-*a*]-pyrrolo[2,1-*c*][1,4]benzodiazepines, by a totally diastereoselective intramolecular nitrilimine cycloaddition (Scheme 147).[229] These latter 1,4-benzodiazepinonic systems were formed by the 1,3-dipolar cycloaddition of nitrilimines, generated in situ from the corresponding hydrazonyl chlorides derived from *N*-Boc-L-proline by treatment with Et_3N. The exclusive formation of the trans diastereoisomers was explained by the fact that the bulky and rather rigid pyrrolidine moiety worked against the intramolecular approach of the dipole to the *re* face of the ethylenic bond.

In 2005, Buttero et al. studied the silver acetate-promoted nitrilimine cycloaddition onto 2-azetidinones bearing alkenyl dipolarophiles.[230] The generation of the nitrilimine intermediate, as depicted in Scheme 148, was accomplished in situ by treatment of the corresponding hydrazonoyl chloride with an equimolecular amount of silver acetate in the presence of the dipolarophile, 3(*R*)-phenyl-4(*S*)-cinnamoyl-2-azetidinone. The reaction led to the formation of a mixture of two regioisomeric cycloadducts, both detected as single stereoisomers, thus making the cycloaddition fully stereoselective.

The first successful examples of highly regio- and enantioselective additions of nitrilimines to olefins, using 10 mol %



Scheme 148. AgOAc-promoted 1,3-dipolar cycloadditions of nitrilimines to a chiral 4-cinnamoyl-2-azetidinone.



R^1 = Me, R^2 = Ph, R^3 = Br, R^4 = H: 91%; ee = 99%
R^1 = Et, R^2 = Ph, R^3 = Br, R^4 = H: 93%; ee = 99%
R^1 = R^2 = Ph, R^3 = Br, R^4 = H: 95%; ee = 97%
R^1 = OBz, R^2 = Ph, R^3 = Br, R^4 = H: 97%; ee = 96%
R^1 = 2-Fu, R^2 = Ph, R^3 = Br, R^4 = H: 94%; ee = 99%
R^1 = Me, R^2 = *i*-Pr, R^3 = Br, R^4 = H: 98%; ee = 99%
R^1 = Me, R^2 = Ph, R^3 = OMe, R^4 = Br: 96%; ee = 96%

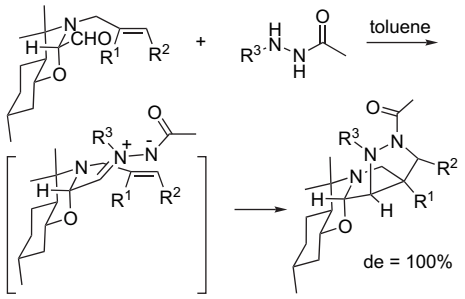
Scheme 149. Mg(II)-catalysed enantioselective nitrilimine 1,3-dipolar cycloadditions.

chiral Lewis-acid catalysts, were reported by Sibi et al., in 2005.[231] The nitrilimine was generated in situ by dehydrohalogenation of the corresponding hydrazonyl bromide in the presence of a compatible amine base (*i*-Pr_2NEt)-chiral Lewis acid [$Mg(NTf_2)_2$-chiral ligand] combination, and an oxazolidinone crotonate as the dipolarophile (Scheme 149). In all cases, the diastereoselectivity was total, providing a versatile strategy to access dihydropyrazoles in a highly enantioenriched form.

9. Other types of 1,3-dipoles

There are a few reports concerning the asymmetric 1,3-dipolar cycloaddition of azomethine imines resulting in chiral pyrazolines, which can be further converted into interesting functionalised optically active diamines. The ylides are most commonly prepared via the reaction of *N*-acyl-*N*′-alkylhydrazines with aldehydes and ketones. The intramolecular version of this reaction results in the formation of new fused or bridged diazabicyclic systems, and takes place easily, even with unactivated dipolarophiles such as terminal alkenes, and often turns out with excellent diastereofacial discrimination, exhibiting high stereoselectivity. As an example, Pedrosa et al. reported, in 2003, the synthesis of enantiopure perhydropyrrolo[3,4-*c*]pyrazole derivatives by the stereoselective intramolecular 1,3-dipolar cycloaddition of azomethine imines with unactivated alkenes positioned on a chiral perhydro-1,3-benzoxazine moiety (Scheme 150).[232] The condensation took place at the more basic *N*-alkyl- or *N*-phenyl-substituted, rather than at the acyl-substituted, nitrogen atom and the cyclisation afforded, with total regioselectivity, the 5,5-fused bicyclic and no bridged products.

In 2004, Micouin et al. studied the reactivity of a chiral glyoxylic azomethine imine generated in situ from the condensation of a chiral cyclic hydrazine with ethyl glyoxylate through a cycloreversion reaction.[166] This species reacted with a wide range of dipolarophiles, with a complete regio- and facial stereoselectivity. The glyoxylic ylide led to a lower *endo* selectivity with dipolarophiles bearing



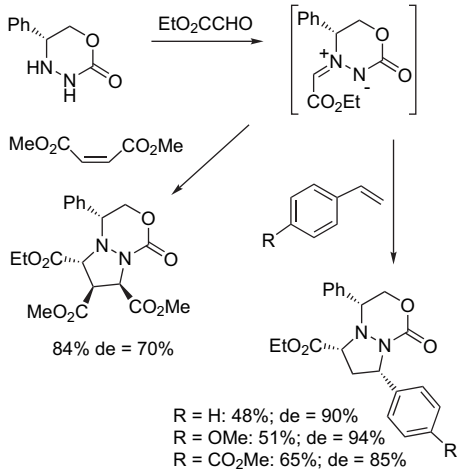
$R^1 = R^2 = H$, $R^3 = Me$: 94%
$R^1 = H$, $R^2 = R^3 = Me$: 80%
$R^1 = H$, $R^2 = Ph$, $R^3 = Me$: 92%
$R^1 = Me$, $R^2 = R^3 = Me$: 90%
$R^1 = R^2 = H$, $R^3 = Ph$: 82%
$R^1 = H$, $R^2 = R^3 = Ph$: 78%

Scheme 150. 1,3-Dipolar intramolecular cycloadditions of azomethine imines.

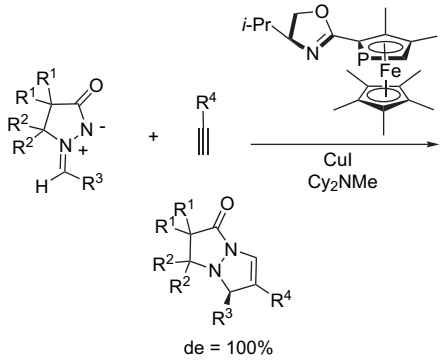
electron-withdrawing groups, but an improved *exo* selectivity with styrene derivatives, allowing des of up to 94% (Scheme 151).

The reactivity towards azomethine imines of another type of dipolarophiles such as terminal alkynes was investigated by Fu and Shintani.[233] The catalyst system, constituted by CuI and a chiral phosphaferrocene-oxazoline, furnished the corresponding products in excellent yields, with total diastereoselectivity and with high ees for a range of substitution patterns (Scheme 152). The scope of this process, based on kinetic resolutions of azomethine imines via copper-catalysed 1,3-dipolar cycloadditions, was successfully extended, in 2005, to a variety of *N*- and *C*-substituted dipoles.[234]

In 2002, Kobayashi et al. developed the first example of enantioselective intramolecular 1,3-dipolar cycloaddition of olefinic hydrazones using a chiral zirconium catalyst.[235] Excellent yields and selectivities were observed in the formation of the corresponding chiral pyrazolidine derivatives, which could be readily converted by cleavage of the N–N bonds into various chiral diamine derivatives (Scheme 153). The intermolecular version of this reaction was reported, in 2004, by the same group.[236] Hence, hydrazones



Scheme 151. 1,3-Dipolar cycloadditions of a glyoxylic azomethine imine.



$R^1 = R^2 = H$, $R^3 = Ph$, $R^4 = CO_2Et$: 98%; ee = 90%
$R^1 = R^2 = H$, $R^3 = o\text{-}FC_6H_4$, $R^4 = CO_2Et$: 99%; ee = 81%
$R^1 = R^2 = H$, $R^3 = m\text{-}BrC_6H_4$, $R^4 = CO_2Et$: 99%; ee = 86%
$R^1 = R^2 = H$, $R^3 = p\text{-}CF_3C_6H_4$, $R^4 = CO_2Et$: 99%; ee = 95%
$R^1 = R^2 = H$, $R^3 = Cy$, $R^4 = CO_2Et$: 94%; ee = 97%
$R^1 = R^2 = H$, $R^3 = Ph$, $R^4 = Ac$: 98%; ee = 90%
$R^1 = R^2 = H$, $R^3 = Ph$, $R^4 = CONMePh$: 100%; ee = 94%
$R^1 = H$, $R^2 = Me$, $R^3 = Ph$, $R^4 = CO_2Et$: 99%; ee = 98%
$R^1 = Me$, $R^2 = H$, $R^3 = Ph$, $R^4 = CO_2Et$: 100%; ee = 96%

Scheme 152. Enantioselective 1,3-dipolar cycloadditions of azomethine imines to alkynes in the presence of CuI and a phosphaferrocene-oxazoline.

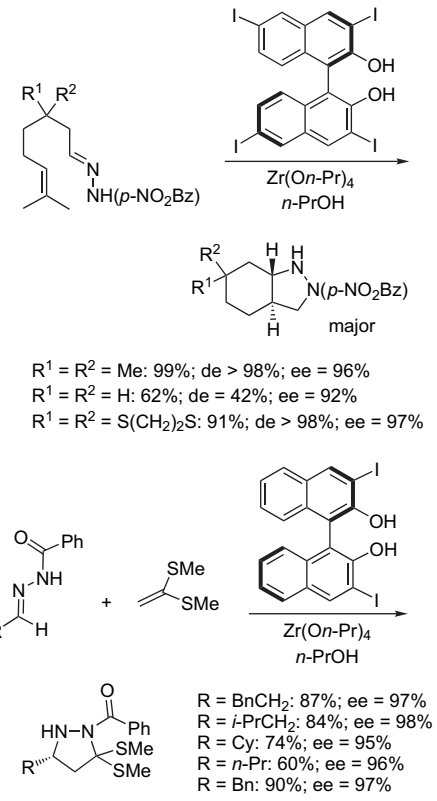
were successfully added onto external olefins such as ketene dimethyl dithioacetal or vinyl ethers, leading to the corresponding optically active pyrazolidine cycloadducts in high yields with high enantioselectivities (Scheme 153).

In addition, Leighton et al. developed, in 2005, highly diastereo- and enantioselective 1,3-dipolar cycloadditions of acylhydrazones to enol ethers catalysed by a chiral silicon Lewis acid (Scheme 154).[237]

A series of other dipoles have been studied such as a chiral mesoionic acyclic C-nucleoside derived from δ-gluconolactone, which has served as the chiral core to construct a series of functionalised nucleosides bearing 2-aza-7-thiabicyclo[2.2.1]heptane or 2-(1*H*)-pyridone moieties as the aglycon.[238] The key step involved a 1,3-dipolar cycloaddition of the dipolar mesoionic acyclic C-nucleoside with several electron-deficient dipolarophiles such as *N*-phenylmaleimide, methyl vinyl ketone, methyl acrylate and acrylonitrile, but no appreciable facial diastereoselectivity was observed in all cases.

A range of 3-oxidopyridinium betaines bearing various substituents on the nitrogen atom were found to react with the C_2-symmetric vinyl sulfoxide, *trans*-2-methylene-1,3-dithiolane 1,3-dioxide, with total diastereoselectivity in the case of simple 3-oxidopyridinium betaines (Scheme 155).[239] These reactions were under kinetic control, although, over longer periods of time, the ratio of regioisomers changed, on account of the reversibility of the reaction. The regioselectivity in these reactions was moderate, although this could be improved by placing an additional substituent at the 2-position of the betaine.

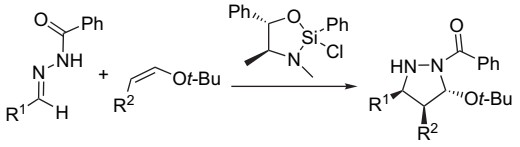
In the same context, Stoltz et al. have reported the dipolar 1,3-cycloaddition of an in situ generated oxidopyrazinium salt with Oppolzer's sultam-derived acrylamide in the presence of *N*-methyl morpholine as a base, producing an



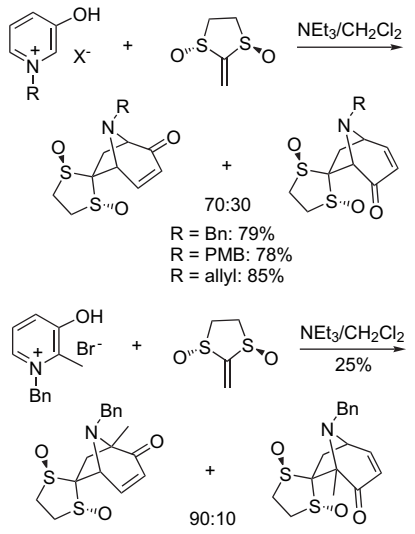
Scheme 153. Zr-catalysed enantioselective 1,3-dipolar cycloadditions of hydrazones.

enantiopure single cycloadduct, which was used in a total synthesis of (−)-lemonomycin, an antitumour antibiotic (Scheme 156).[240]

An intramolecular version of the oxidopyridinium dipolar cycloaddition methodology was reported by Gin and Peese, in 2005, allowing the formation of the 3-methyl-1-aza-tricyclo[5.2.1.0^{3,8}]decane core of the hetisine alkaloids.[241] In addition, the first application of such methodology to the cycloaddition of a chiral 3-oxidopyridinium betaine was reported, in 2006, by Curtis et al.[242] 8-Azabicyclo[3.2.1]oct-3-en-2-ones were thus prepared with excellent diastereofacial selectivity for the major 6-*exo*-cycloadducts (Scheme 157).



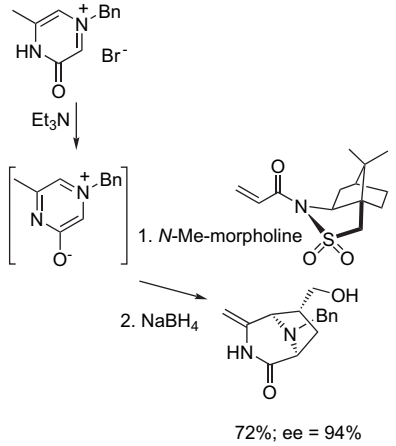
Scheme 154. Silane Lewis acid-catalysed enantioselective 1,3-dipolar cycloadditions of hydrazones to enol ethers.



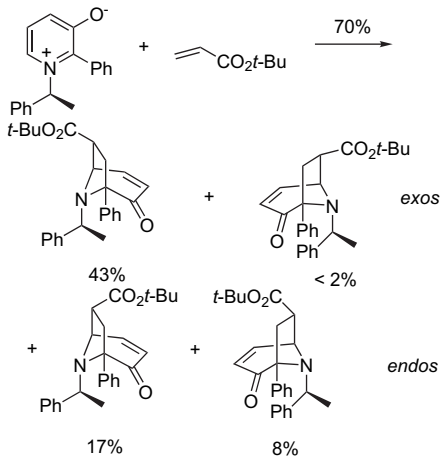
Scheme 155. 1,3-Dipolar cycloadditions of 3-oxidopyridinium betaines to chiral *trans*-2-methylene-1,3-dithiolane 1,3-dioxide.

On the other hand, a phosphine-catalysed 1,3-dipolar cycloaddition strategy was employed, in 2003, for the first total synthesis of (−)-hinesol, an important biologically active *cis*-spirovetivane.[243] Hence, a dipole, generated in situ by the reaction of *tert*-butyl 2-butynoate with a catalytic amount of tributylphosphine, was added to a chiral electron-deficient alkene such as (*S*)-3-methyl-2-methylenecyclohexenone, leading to the formation of a single enantiopure cycloadduct (Scheme 158). More recently, this methodology was applied by Pyne et al. to a chiral 2-methylene γ-lactam, producing, in the presence of ethyl 2-butynoate and tributylphosphine, three cycloadducts in a ratio of 63:17:30.[244] The corresponding cycloaddition reaction of an ethyl 2-(2-nitrophenyl)propenoate with a chiral alkyne derived from Oppolzer's (1*S*)-sultam was shown to give a 77:23 mixture of the corresponding diastereomeric cycloadducts, which were further converted by reductive cyclisation into the corresponding spiro-heterocyclic products (Scheme 158).

The concept of vicinally substituted donor–acceptor cyclopropanes as ring-opened 1,3-zwitterionic equivalents



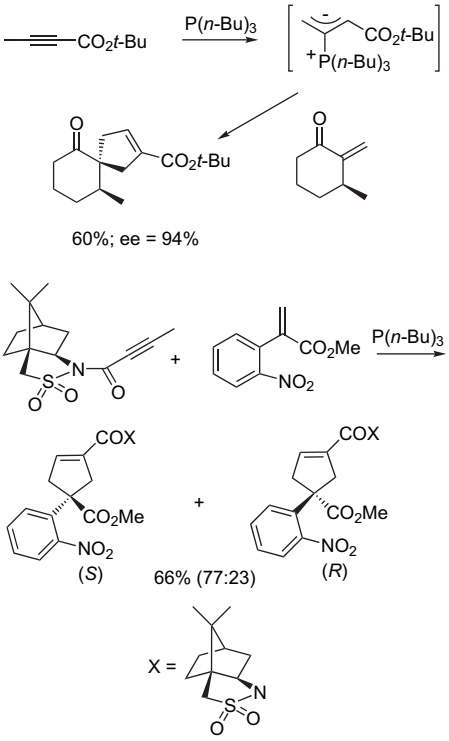
Scheme 156. 1,3-Dipolar cycloaddition of an oxidopyrazinium salt to Oppolzer's sultam-derived acrylamide.



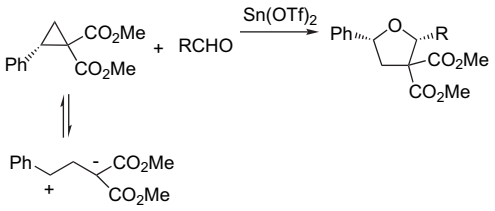
Scheme 157. 1,3-Dipolar cycloaddition of a chiral pyridinium betaine.

implies chirality loss concurrent with reaction progress. In 2005, Johnson and Pohlhaus demonstrated, however, the unexpected preservation of optical activity in a new family of Lewis acid-catalysed cyclopropane/aldehyde cycloadditions.[245] Hence, a chiral cyclopropane, depicted in Scheme 159, reacted with a range of aldehydes in the presence of a catalytic amount of $Sn(OTf)_2$, affording the corresponding chiral substituted tetrahydrofurans in excellent yields and diastereoselectivities, combined with a very high degree of absolute stereochemical control.

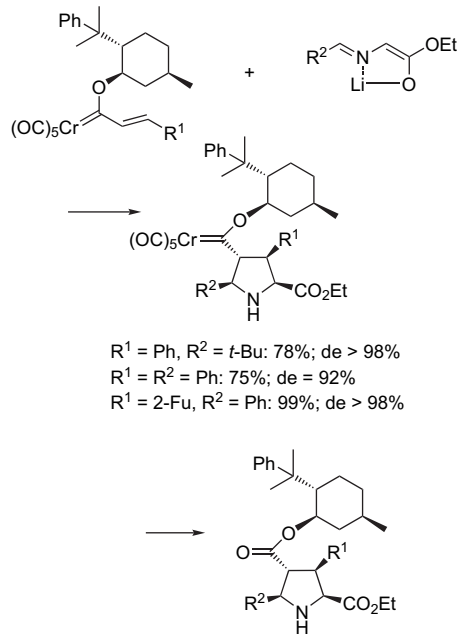
In addition, Barluenga et al. reported, in 2002, the stereoselective formal [3+2] cycloadditions of *N*-alkylidene glycine ester anions to chiral Fischer alkenylcarbene complexes, allowing the synthesis of chiral 3,4,5-trisubstituted prolines.[246] The enolate appeared to behave in this type of reactions as a formal azomethine ylide dipole, and the carbine complex to act as a formal dipolarophile, giving rise to the corresponding [3+2] cycloadduct (Scheme 160).



Scheme 158. Phosphine-catalysed 1,3-dipolar cycloadditions.



Scheme 159. $Sn(OTf)_2$-catalysed 1,3-dipolar cycloadditions of a chiral cyclopropane to aldehydes.



Scheme 160. [3+2] Cycloadditions of *N*-alkylidene glycine ester anions to chiral Fischer alkenylcarbene complexes.

10. Conclusions

Heterocyclic compounds, which represent almost two-thirds of all the known organic compounds, include some of the most significant for human beings. It is not surprising, therefore, that this class of compounds has received special attention by chemists to provide selective synthetic access to the enormous variety of structural features typical of this class. The asymmetric 1,3-dipolar cycloaddition reaction is undoubtedly one of the most important methods for the construction of chiral five-membered rings. The stereocontrol of 1,3-dipolar cycloadditions is extremely important for

constructing heterocyclic compounds from the viewpoint of the synthesis of biologically active compounds. The versatility of 1,3-dipoles and dipolarophiles, the regio- and stereoselectivity during the reaction, and the scope for further transformation of the cycloadducts to a variety of multifunctional molecules have elevated the asymmetric 1,3-dipolar cycloaddition reaction to an enviable methodology, not only for the construction of chiral functionalised normal-ring carbocycles, but also for the synthesis of complex natural products. This review has concentrated on the new developments achieved since 2001, and the asymmetric 1,3-dipolar cycloaddition reaction is therefore well represented as an important tool for organic synthesis. Steady progress has been made in the last few years in expanding the metal-catalysed asymmetric 1,3-dipolar cycloadditions.

References and notes

1. Nogradi, M. *Stereoselective Synthesis*; VCH: Weinheim, 1995.
2. Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *10*, 565–598.
3. Rastelli, A.; Gandolfi, R.; Amadè, M. S. *Adv. Quantum Chem.* **1999**, *36*, 151–167.
4. Karlsson, S.; Högberg, H.-E. *Org. Prep. Prod. Int.* **2001**, *33*, 103–172.
5. Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909.
6. Kanemasa, S. *Synlett* **2002**, 1371–1387.
7. Gothelf, K. V. *Synthesis* **2002**, 211–247.
8. Broggini, G.; Molteni, G.; Terraneo, A.; Zecchi, G. *Heterocycles* **2003**, *59*, 823–858.
9. Namboothiri, I. N. N.; Hassner, A. *Top. Curr. Chem.* **2001**, *216*, 1–49.
10. Frederickson, M. *Tetrahedron* **1997**, *53*, 403–425.
11. Gothelf, K. V.; Jorgensen, K. A. *Chem. Commun.* **2000**, 1449–1458.
12. Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F.; Pardo, C.; Saez, E.; Torres, M. R. *J. Org. Chem.* **2002**, *67*, 7004–7013.
13. Blanarikova-Hlobilova, I.; Kubanova, Z.; Fisera, L.; Cyranski, M. K.; Salanski, P.; Jurczak, J.; Pronayova, N. *Tetrahedron* **2003**, *59*, 3333–3339.
14. Kato, Y.; Nakano, Y.; Sano, H.; Tanatani, A.; Kobayashi, H.; Shimazawa, R.; Koshino, H.; Hashimoto, Y.; Nagasawa, K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2579–2583.
15. Sadashiva, M. P.; Mallesha, H.; Karunakara Murthy, K.; Rangappa, K. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1811–1814.
16. Merino, P.; Mates, J. A.; Revuelta, J.; Tejero, T.; Chiacchio, U.; Romeo, G.; Iannazzo, D.; Romeo, R. *Tetrahedron: Asymmetry* **2002**, *13*, 173–190.
17. Shindo, M.; Itoh, K.; Ohtsuki, K.; Tsuchiya, C.; Shishido, K. *Synthesis* **2003**, *9*, 1441–1445.
18. Shindo, M.; Ohtsuki, K.; Shishido, K. *Tetrahedron: Asymmetry* **2005**, *16*, 2821–2831.
19. Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Piperno, A.; Procopio, A.; Rescifina, A.; Romeo, G.; Romeo, R. *Eur. J. Org. Chem.* **2001**, 1893–1898.
20. Osborn, H. M. I.; Gemmell, N.; Harwood, L. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2419–2438.
21. Kuban, J.; Kolarovic, A.; Fisera, L.; Jäger, V.; Humpa, O.; Pronayova, N.; Ertl, P. *Synlett* **2001**, 1862–1865.
22. Kuban, J.; Kolarovic, A.; Fisera, L.; Jäger, V.; Humpa, O.; Pronayova, N. *Synlett* **2001**, 1866–1868.
23. Dugovic, B.; Fisera, L.; Hametner, C.; Cyranski, M. K.; Pronayova, N. *Monatsh. Chem.* **2004**, *135*, 685–696.
24. Fischer, R.; Druckova, A.; Fisera, L.; Rybar, A.; Hametner, C.; Cyranski, M. K. *Synlett* **2002**, 1113–1117.
25. (a) Saita, M. G.; Chiacchio, U.; Iannazzo, D.; Corsaro, A.; Merino, P.; Piperno, A.; Previtera, T.; Rescifina, A.; Romeo, G.; Romeo, R. *Nucleosides Nucleotides* **2003**, *22*, 739–742; (b) Chiacchio, U.; Borrello, L.; Iannazzo, D.; Merino, P.; Piperno, A.; Rescifina, A.; Richichi, B.; Romeo, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2419–2425.
26. Saha, N. N.; Desai, V. N.; Dhavale, D. D. *Tetrahedron* **2001**, *57*, 39–46.
27. Karanjule, N. S.; Markad, S. D.; Sharma, T.; Sabharwal, S. G.; Puranik, V. G.; Dhavale, D. D. *J. Org. Chem.* **2005**, *70*, 1356–1363.
28. Torres-Sanchez, M. I.; Borrachero, P.; Cabrera-Escribano, F.; Gomez-Guillen, M.; Angulo-Alvarez, M.; Dianez, M. J.; Estrada, M. D.; Lopez-Castro, A.; Perez-Garrido, S. *Tetrahedron: Asymmetry* **2005**, *16*, 3897–3907.
29. Borrachero, P.; Cabrera-Escribano, F.; Dianez, M. J.; Estrada, M. D.; Gomez-Guillen, M.; Castro, A. L.; Perez-Garrido, S.; Torres, M. I. *Tetrahedron: Asymmetry* **2002**, *13*, 2025–2038.
30. Silva, A. M. G.; Tome, A. C.; Neves, M. G. P. M. S.; Silva, A. M. S.; Cavaleiro, J. A. S.; Perrone, D.; Dondoni, A. *Tetrahedron Lett.* **2002**, *43*, 603–605.
31. Torrente, S.; Noya, B.; Branchadell, V.; Alonso, R. *J. Org. Chem.* **2003**, *68*, 4772–4783.
32. Cicchi, S.; Marradi, M.; Corsi, M.; Faggi, C.; Goti, A. *Eur. J. Org. Chem.* **2003**, 4152–4160.
33. (a) Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Piperno, A.; Pistara, V.; Rescifina, A.; Romeo, R.; Sindona, G.; Romeo, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2717–2723; (b) Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Piperno, A.; Pistara, V.; Rescifina, A.; Romeo, R.; Valveri, V.; Mastino, A.; Romeo, G. *J. Med. Chem.* **2003**, *46*, 3696–3702.
34. Busqué, F.; de March, P.; Figueredo, M.; Font, J.; Gallagher, T.; Milan, S. *Tetrahedron: Asymmetry* **2002**, *13*, 437–445.
35. Cordero, F. M.; Pisaneschi, F.; Gensini, M.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **2002**, 1941–1951.
36. Richichi, B.; Cicchi, S.; Chiacchio, U.; Romeo, G.; Brandi, A. *Tetrahedron* **2003**, *59*, 5231–5240.
37. Pisaneschi, F.; Della Monica, C.; Cordero, F. M.; Brandi, A. *Tetrahedron Lett.* **2002**, *43*, 5711–5714.
38. Nagasawa, K.; Georgieva, A.; Koshino, H.; Nakata, T.; Kita, T.; Hashimoto, Y. *Org. Lett.* **2002**, *4*, 177–180.
39. (a) Shimokawa, J.; Shirai, K.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1559–1562; (b) Shimokawa, J.; Ishiwata, T.; Shirai, K.; Koshino, H.; Tanatani, A.; Nakata, T.; Hashimoto, Y.; Nagasawa, K. *Chem.—Eur. J.* **2005**, *11*, 6878–6888.
40. Alibés, R.; Blanco, P.; Casas, E.; Closa, M.; de March, P.; Figueredo, M.; Font, J.; Sanfeliu, E.; Alvarez-Larena, A. *J. Org. Chem.* **2005**, *70*, 3157–3167.
41. (a) Socha, D.; Jurczak, M.; Frelek, J.; Klimek, A.; Rabiczko, J.; Urbanczyk-Lipkowska, Z.; Suwinska, K.; Chmielewski, M.; Cardona, F.; Goti, A.; Brandi, A. *Tetrahedron: Asymmetry* **2001**, *12*, 3163–3172; (b) Socha, D.; Jurczak, M.; Chmielewski, M. *Carbohydr. Res.* **2001**, *336*, 315–318.
42. Cardona, F.; Faggi, E.; Liguori, F.; Cacciarini, M.; Goti, A. *Tetrahedron Lett.* **2003**, *44*, 2315–2318.

43. Baldwin, S. W.; Long, A. *Org. Lett.* **2004**, *6*, 1653–1656.
44. (a) Ashoorzadeh, A.; Caprio, V. *Synlett* **2005**, 346–348; (b) Ooi, H.; Urushibara, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2001**, *3*, 953–955.
45. Long, A.; Baldwin, S. W. *Tetrahedron Lett.* **2001**, *42*, 5343–5345.
46. Machetti, F.; Cordero, F. M.; De Sarlo, F.; Brandi, A. *Tetrahedron* **2001**, *57*, 4995–4998.
47. Collon, S.; Kouklovsky, C.; Langlois, Y. *Eur. J. Org. Chem.* **2002**, 3566–3572.
48. Voituriez, A.; Moulinas, J.; Kouklovsky, C.; Langlois, Y. *Synthesis* **2003**, 1419–1433.
49. Hemetsberger, M.; Treu, M.; Hametner, C.; Jordis, U.; Mereiter, K.; Fröhlich, J. *Heterocycles* **2004**, *63*, 2217–2224.
50. Pisaneschi, F.; Cordero, F. M.; Brandi, A. *Synlett* **2003**, 1889–1891.
51. Deyine, A.; Delcroix, J.-M.; Langlois, N. *Heterocycles* **2004**, *64*, 207–214.
52. Tyrrell, E.; Allen, J.; Jones, K.; Beauchet, R. *Synthesis* **2005**, 2393–2399.
53. Zhang, H.-K.; Chan, W.-H.; Lee, A. W. M.; Wong, W.-Y.; Xia, P.-F. *Tetrahedron: Asymmetry* **2005**, *16*, 761–771.
54. (a) Garcia Ruano, J. L.; Andrés Gil, J. I.; Fraile, A.; Martin Castro, A. M.; Rosario Martin, M. *Tetrahedron Lett.* **2004**, *45*, 4653–4656; (b) Garcia Ruano, J. L.; Fraile, A.; Martin Castro, A. M.; Rosario Martin, M. *J. Org. Chem.* **2005**, *70*, 8825–8834.
55. Pisaneschi, F.; Gensini, M.; Salvati, M.; Cordero, F. M.; Brandi, A. *Heterocycles* **2006**, *67*, 413–420.
56. Desimoni, G.; Faita, G.; Galbiati, A.; Pasini, D.; Quadrelli, P.; Rancati, F. *Tetrahedron: Asymmetry* **2002**, *13*, 333–337.
57. Merino, P.; Revuelta, J.; Tejero, T.; Chiacchio, U.; Rescifina, A.; Piperno, A.; Romeo, G. *Tetrahedron: Asymmetry* **2002**, *13*, 167–172.
58. Tamura, O.; Kanoh, A.; Yamashita, M.; Ishibashi, H. *Tetrahedron* **2004**, *60*, 9997–10003.
59. Zhang, H.; Chan, W. H.; Lee, A. W. M.; Xia, P.-F.; Wong, W. Y. *Lett. Org. Chem.* **2004**, *1*, 63–66.
60. (a) Pasniczek, K.; Socha, D.; Jurczak, M.; Frelek, J.; Suszczynska, A.; Urbanczyk-Lipkowska, Z.; Chmielewski, M. *J. Carbohydr. Chem.* **2003**, *22*, 613–629; (b) Stecko, S.; Pasniczek, K.; Jurczak, M.; Urbanczyk-Lipkowska, Z.; Chmielewski, M. *Tetrahedron: Asymmetry* **2006**, *17*, 68–78.
61. Shing, T. K. M.; Zhong, Y.-L. *Tetrahedron* **2001**, *57*, 1573–1579.
62. Shing, T. K. M.; Zhong, Y.-L. *Synlett* **2006**, 1205–1208.
63. Gebarowski, P.; Sas, W. *Chem. Commun.* **2001**, 915–916.
64. Bhattacharjee, A.; Datta, S.; Chattopadhyay, P.; Ghoshal, N.; Kundu, A. P.; Pal, A.; Mukhopadhyay, R.; Chowdhury, S.; Bhattacharjya, A.; Patra, A. *Tetrahedron* **2003**, *59*, 4623–4639.
65. Sharma, G. V. M.; Begum, A.; Ravinder Reddy, K.; Ravi Sankar, A.; Kunwar, A. C. *Tetrahedron: Asymmetry* **2003**, *14*, 3899–3905.
66. Jachak, S. M.; Karche, N. P.; Dhavale, D. D. *Tetrahedron Lett.* **2001**, *42*, 4925–4928.
67. Padar, P.; Hornyak, M.; Forgo, P.; Kele, Z.; Paragi, G.; Howarth, N. M.; Kovacs, L. *Tetrahedron* **2005**, *61*, 6816–6823.
68. Singha, K.; Roy, A.; Dutta, P. K.; Tripathi, S.; Sahabuddin, Sk.; Achari, B.; Mandal, S. B. *J. Org. Chem.* **2004**, *69*, 6507–6510.
69. Chatterjee, A.; Bhattacharya, P. K. *J. Org. Chem.* **2006**, *71*, 345–348.
70. Manzoni, L.; Arosio, D.; Belvisi, L.; Bracci, A.; Colombo, M.; Invernizzi, D.; Scolastico, C. *J. Org. Chem.* **2005**, *70*, 4124–4132.
71. Goti, A.; Cacciarini, M.; Cardona, F.; Cordero, F. M.; Brandi, A. *Org. Lett.* **2001**, *3*, 1367–1369.
72. Cheng, Q.; Zhang, W.; Tagami, Y.; Oritani, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 452–456.
73. Looper, R. E.; Williams, R. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2930–2933.
74. Looper, R. E.; Runnegar, M. T. C.; Williams, R. M. *Tetrahedron* **2006**, *62*, 4549–4562.
75. Broggini, G.; Chiesa, K.; De Marchi, I.; Martinelli, M.; Pilati, T.; Zecchi, G. *Tetrahedron* **2005**, *61*, 3525–3531.
76. Morimoto, Y.; Kitao, S.; Okita, T.; Shoji, T. *Org. Lett.* **2003**, *5*, 2611–2614.
77. Whisler, M. C.; Beak, P. *J. Org. Chem.* **2003**, *68*, 1207–1215.
78. White, J. D.; Hansen, J. D. *J. Org. Chem.* **2005**, *70*, 1963–1977.
79. Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Piperno, A.; Procopio, A.; Rescifina, A.; Romeo, G.; Romeo, R. *J. Org. Chem.* **2002**, *67*, 4380–4383.
80. Amado, A. F.; Kouklovsky, C.; Langlois, Y. *Synlett* **2005**, 103–106.
81. Romeo, R.; Iannazzo, D.; Piperno, A.; Chiacchio, M. A.; Corsaro, A.; Rescifina, A. *Eur. J. Org. Chem.* **2005**, 2368–2373.
82. (a) Aggarwal, V. K.; Roseblade, S.; Alexander, R. *Org. Biomol. Chem.* **2003**, *1*, 684–691; (b) Aggarwal, V. K.; Roseblade, S.; Barrell, J. K.; Alexander, R. *Org. Lett.* **2002**, *4*, 1227–1229.
83. Chiacchio, U.; Corsaro, A.; Rescifina, A.; Bkaithan, M.; Grassi, G.; Piperno, A.; Privitera, T.; Romeo, G. *Tetrahedron* **2001**, *57*, 3425–3433.
84. Tamura, O.; Mita, N.; Okabe, T.; Yamaguchi, T.; Fukushima, C.; Yamashita, M.; Morita, Y.; Morita, N.; Ishibashi, H.; Sakamoto, M. *J. Org. Chem.* **2001**, *66*, 2602–2610.
85. Akai, S.; Tanimoto, K.; Kanao, Y.; Omura, S.; Kita, Y. *Chem. Commun.* **2005**, 2369–2371.
86. Gothelf, K. V.; Jörgensen, K. A. *Acta Chem. Scand.* **1996**, *50*, 652–660.
87. Tamura, O.; Shiro, T.; Toyao, A.; Ishibashi, H. *Chem. Commun.* **2003**, 2678–2679.
88. Hanselmann, R.; Zhou, J.; Ma, P.; Confalone, P. N. *J. Org. Chem.* **2003**, *68*, 8739–8741.
89. Faita, G.; Paio, A.; Quadrelli, P.; Rancati, F.; Seneci, P. *Tetrahedron* **2001**, *57*, 8313–8322.
90. Frank, E.; Wölfling, J.; Aukszi, B.; König, V.; Schneider, T. R.; Schneider, G. *Tetrahedron* **2002**, *58*, 6843–6849.
91. Li, X.; Takahashi, H.; Ohtake, H.; Ikegami, S. *Heterocycles* **2003**, *59*, 547–571.
92. Diaz, J.; Silva, M. A.; Goodman, J. M.; Pellegrinet, S. C. *Tetrahedron* **2005**, *61*, 10886–10893.
93. Dugovic, B.; Wiesenganger, T.; Fisera, L.; Hametner, C.; Pronayova, N. *Heterocycles* **2005**, *65*, 591–605.
94. Tamura, O.; Toyao, A.; Ishibashi, H. *Synlett* **2002**, 1344–1346.
95. Bernardi, L.; Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Folegatti, M.; Grilli, S.; Mazzanti, A.; Ricci, A. *Tetrahedron: Asymmetry* **2004**, *15*, 245–250.
96. Hein, J. E.; Hultin, P. G. *Tetrahedron: Asymmetry* **2005**, *16*, 2341–2347.
97. Zha, Q.; Han, F.; Romero, D. L. *J. Org. Chem.* **2002**, *67*, 3317–3322.

98. Chiacchio, U.; Rescifina, A.; Saita, M. G.; Iannazzo, D.; Romeo, G.; Mates, J. A.; Tejero, T.; Merino, P. *J. Org. Chem.* **2005**, *70*, 8991–9001.
99. (a) Ding, X.; Taniguchi, K.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2001**, 468–469; (b) Ding, X.; Ukaji, Y.; Fujinami, S.; Inomata, K. *Chem. Lett.* **2002**, 302–303; (c) Ukaji, Y.; Inomata, K. *Synlett* **2003**, 1075–1087.
100. Shirahase, M.; Kanemasa, S.; Hasegawa, M. *Tetrahedron Lett.* **2004**, *45*, 4061–4063.
101. (a) Saito, T.; Yamada, T.; Miyazaki, S.; Otani, T. *Tetrahedron Lett.* **2004**, *45*, 9581–9584; (b) Saito, T.; Yamada, T.; Miyazaki, S.; Otani, T. *Tetrahedron Lett.* **2004**, *45*, 9585–9587.
102. Palomo, C.; Oiarbide, M.; Arceo, E.; Garcia, J. M.; Lopez, R.; Gonzalez, A.; Linden, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6187–6190.
103. (a) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718–719; (b) Sibi, M. P.; Ma, Z.; Itoh, K.; Prabagaran, N.; Jasperse, C. P. *Org. Lett.* **2005**, *7*, 2349–2352.
104. Iwasa, S.; Ishima, Y.; Setyo Widagdo, H.; Aoki, K.; Nishiyama, H. *Tetrahedron Lett.* **2004**, *45*, 2121–2124.
105. Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 11926–11927.
106. (a) Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Org. Lett.* **2002**, *4*, 2457–2460; (b) Kezuka, S.; Ohtsuki, N.; Mita, T.; Kogami, Y.; Ashizawa, T.; Ikeno, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2197–2207; (c) Ohtsuki, N.; Kezuka, S.; Kogami, Y.; Mita, T.; Ashizawa, T.; Ikeno, T.; Yamada, T. *Synthesis* **2003**, *9*, 1462–1466.
107. Huang, Z.-Z.; Kang, Y.-B.; Zhou, J.; Ye, M.-C.; Tang, Y. *Org. Lett.* **2004**, *6*, 1677–1679.
108. (a) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron Lett.* **2001**, *42*, 6715–6717; (b) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 227–232; (c) Iwasa, S.; Maeda, H.; Nishiyama, K.; Tsushima, S.; Tsukamoto, Y.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 8281–8287.
109. Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 5764–5765.
110. Shirahase, M.; Kanemasa, S.; Oderaotoshi, Y. *Org. Lett.* **2004**, *6*, 675–678.
111. (a) Suga, H.; Kakehi, A.; Ito, S.; Sugimoto, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 327–334; (b) Suga, H.; Nakajima, T.; Itoh, K.; Kakehi, A. *Org. Lett.* **2005**, *7*, 1431–1434.
112. (a) Carmona, D.; Lamata, M. P.; Viguri, F.; Rodriguez, R.; Oro, L. A.; Balana, A. I.; Lahoz, F. J.; Tejero, T.; Merino, P.; Franco, S.; Montesa, I. *J. Am. Chem. Soc.* **2004**, *126*, 2716–2717; (b) Carmona, D.; Lamata, M. P.; Viguri, F.; Rodriguez, R.; Oro, L. A.; Lahoz, F. J.; Balana, A. I.; Tejero, T.; Merino, P. *J. Am. Chem. Soc.* **2005**, *127*, 13386–13398.
113. Viton, F.; Bernardinelli, G.; Kündig, E. P. *J. Am. Chem. Soc.* **2002**, *124*, 4968–4969.
114. Desimoni, G.; Faita, G.; Mella, M.; Boiocchi, M. *Eur. J. Org. Chem.* **2005**, 1020–1027.
115. Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726–3748.
116. Benaglia, M.; Puglisi, A.; Cozzi, F. *Chem. Rev.* **2003**, *103*, 3401–3429.
117. Puglisi, A.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Celentano, G. *Eur. J. Org. Chem.* **2004**, 567–573.
118. (a) Karlsson, S.; Högberg, H.-E. *Tetrahedron: Asymmetry* **2002**, *13*, 923–926; (b) Karlsson, S.; Högberg, H.-E. *Eur. J. Org. Chem.* **2003**, 2782–2791.
119. Denmark, S. E.; Cottell, J. J. *J. Org. Chem.* **2001**, *66*, 4276–4284.
120. Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2082–2084.
121. Fuller, A. A.; Chen, B.; Minter, A. R.; Mapp, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 5376–5383.
122. Rasmussen, B. S.; Elezcano, U.; Skrydstrup, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1723–1733.
123. Kudyba, I.; Jozwik, J.; Romanski, J.; Raczko, J.; Jurczak, J. *Tetrahedron: Asymmetry* **2005**, *16*, 2257–2262.
124. Gallos, J. K.; Koumbis, A. E. *Curr. Org. Chem.* **2003**, *7*, 397–425.
125. Totani, K.; Takao, K.-i.; Tadano, K.-i. *Synlett* **2004**, 2066–2080.
126. Desroses, M.; Chéry, F.; Tatibouët, A.; De Lucchi, O.; Rollin, P. *Tetrahedron: Asymmetry* **2002**, *13*, 2535–2539.
127. Tamai, T.; Asano, S.; Totani, K.; Takao, K.-i.; Tadano, K.-i. *Synlett* **2003**, 1865–1867.
128. Cheng, W.-C.; Liu, Y.; Wong, M.; Olmstead, M. M.; Lam, K. S.; Kurth, M. J. *J. Org. Chem.* **2002**, *67*, 5673–5677.
129. Feddouli, A.; Ait Itto, M. Y.; Hasnaoui, A.; Villemin, D.; Jaffrès, P.-A.; Sopkova-De Oliveira Santos, I.; Riahi, A.; Huet, F.; Daran, J.-C. *J. Heterocycl. Chem.* **2004**, *41*, 731–735.
130. Ros, A.; Alvarez, E.; Dietrich, H.; Fernandez, R.; Lassaletta, J. M. *Synlett* **2005**, 2899–2904.
131. Kamimura, A.; Omata, Y.; Kakehi, A.; Shirai, M. *Tetrahedron* **2002**, *58*, 8763–8770.
132. Molteni, G.; Del Buttero, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 1983–1987.
133. Chai, C. L. L.; Edwards, A. J.; Wilkes, B. A.; Woodgate, R. C. J. *Tetrahedron* **2003**, *59*, 8731–8739.
134. Ma, Z.; Li, L.; Rupp, M.; Zhang, S.; Zhang, X. *Org. Lett.* **2002**, *4*, 987–990.
135. Prakesch, M.; Grée, D.; Grée, R.; Carter, J.; Washington, I.; Houk, K. N. *Chem.—Eur. J.* **2003**, *9*, 5664–5672.
136. Alcaide, B.; Almendros, P.; Sàez, E. *Arkivoc* **2004**, *IV*, 137–152.
137. Nakai, K.; Doi, T.; Takahashi, T. *Synlett* **2005**, 866–868.
138. Sengupta, J.; Mukhopadhyay, R.; Bhattacharjya, A.; Bhadbhade, M. M.; Bhosekar, G. V. *J. Org. Chem.* **2005**, *70*, 8579–8582.
139. Fernandez-Mateos, A.; Coca, G. P.; Rubio Gonzalez, R. *Tetrahedron* **2005**, *61*, 8699–8704.
140. Kamimura, A.; Kaneko, Y.; Ohta, A.; Matsuura, K.; Fujimoto, Y.; Kakehi, A.; Kanemasa, S. *Tetrahedron* **2002**, *58*, 9613–9620.
141. Fischer, R.; Jedlovska, E.; Solcaniova, E. *Arkivoc* **2005**, *V*, 103–115.
142. Seo, M. J.; Son, B. S.; Song, B. G.; Song, B. J.; Lee, S. D.; Kim, J. Y.; Kim, H. D.; No, Z.; Kim, H. R. *Bull. Korean Chem. Soc.* **2005**, *26*, 1597–1599.
143. Sibi, M. P.; Itoh, K.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 5366–5367.
144. Tsuji, M.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2002**, 1112–1113.
145. Bardhan, S.; Schmitt, D. C.; Porco, J. A. *Org. Lett.* **2006**, *8*, 927–930.
146. Nàjera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105–1150.
147. Garner, P.; Dogan, O.; Youngs, W. J.; Kennedy, V. O.; Protasiewicz, J.; Zaniewski, R. *Tetrahedron* **2001**, *57*, 71–85.

148. Chinchilla, R.; Falvello, L. R.; Galindo, N.; Nàjera, C. *Eur. J. Org. Chem.* **2001**, 3133–3140.
149. Sebahar, P. R.; Williams, R. M. *Heterocycles* **2002**, *58*, 563–575.
150. Sebahar, P. R.; Osada, H.; Usui, T.; Williams, R. M. *Tetrahedron* **2002**, *58*, 6311–6322.
151. (a) Onishi, T.; Sebahar, P. R.; Williams, R. M. *Tetrahedron* **2004**, *60*, 9503–9515; (b) Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135–3137.
152. Ding, K.; Wang, G.; Deschamps, J. R.; Parrish, D. A.; Wang, S. *Tetrahedron Lett.* **2005**, *46*, 5949–5951.
153. Ahrendt, K. A.; Williams, R. M. *Org. Lett.* **2004**, *6*, 4539–4541.
154. Pardasani, P.; Pardasani, R. T.; Sherry, D.; Chaturvedi, V. *Synth. Commun.* **2002**, *32*, 435–441.
155. Dondas, H. A.; Fishwick, C. W. G.; Grigg, R.; Kilner, C. *Tetrahedron* **2004**, *60*, 3473–3485.
156. Hanessian, S.; Yun, H.; Hou, Y.; Tintelnot-Blomley, M. *J. Org. Chem.* **2005**, *70*, 6746–6756.
157. (a) Aldous, D. J.; Drew, M. G. B.; Draffin, W. N.; Hamelin, E. M.-N.; Harwood, L. M.; Thurairatnam, S. *Synthesis* **2005**, 3271–3282; (b) Draffin, W. N.; Harwood, L. M. *Synlett* **2006**, 857–860.
158. Carey, J. S. *J. Org. Chem.* **2001**, *66*, 2526–2529.
159. Kotian, P. L.; Lin, T.-H.; El-Kattan, Y.; Chand, P. *Org. Process Res. Dev.* **2005**, *9*, 193–197.
160. (a) Gebert, A.; Heimgartner, H. *Helv. Chim. Acta* **2002**, *85*, 2073–2082; (b) Gebert, A.; Linden, A.; Mloston, G.; Heimgartner, H. *Heterocycles* **2002**, *56*, 393–402.
161. Cravotto, G.; Giovenzana, G. B.; Pilati, T.; Sisti, M.; Palmisano, G. *J. Org. Chem.* **2001**, *66*, 8447–8453.
162. Garcia Ruano, J. L.; Tito, A.; Peromingo, M. T. *J. Org. Chem.* **2003**, *68*, 10013–10019.
163. Viso, A.; Fernandez de la Pradilla, R.; Garcia, A.; Guerrero-Strachan, C.; Alonso, M.; Tortosa, M.; Flores, A.; Martinez-Ripoll, M.; Fonseca, I.; Andre, I.; Rodriguez, A. *Chem.—Eur. J.* **2003**, *9*, 2867–2876.
164. (a) Karlsson, S.; Högberg, H.-E. *Tetrahedron: Asymmetry* **2001**, *12*, 1975–1976; (b) Karlsson, S.; Högberg, H.-E. *Tetrahedron: Asymmetry* **2001**, *12*, 1977–1982.
165. Karlsson, S.; Högberg, H.-E. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1076–1082.
166. Chung, F.; Chauveau, A.; Seltki, M.; Bonin, M.; Micouin, L. *Tetrahedron Lett.* **2004**, *45*, 3127–3130.
167. 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*, 8981–8983.
168. Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765–2809.
169. Pinho e Melo, T. M. V. D.; Soares, M. I. L.; Rocha Gonsalves, A. M. d'A.; Paixao, J. A.; Beja, A. M.; Ramos Silva, M.; da Veiga, L. A.; Pessoa, J. C. *J. Org. Chem.* **2002**, *67*, 4045–4054.
170. Pedrosa, R.; Andrés, C.; de las Heras, L.; Nieto, J. *Org. Lett.* **2002**, *4*, 2513–2516.
171. Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *J. Org. Chem.* **2001**, *66*, 1351–1358.
172. Alcaide, B.; Almendros, P.; Redondo, M. C.; Ruiz, M. P. *J. Org. Chem.* **2005**, *70*, 8890–8894.
173. Garcia Ruano, J. L.; Tito, A.; Peromingo, M. T. *J. Org. Chem.* **2002**, *67*, 981–987.
174. Pandey, G.; Laha, J. K.; Lakshmaiah, G. *Tetrahedron* **2002**, *58*, 3525–3534.
175. (a) Nyerges, M.; Bendell, D.; Arany, A.; Hibbs, D. E.; Coles, S. J.; Hursthouse, M. B.; Groundwater, P. W.; Meth-Cohn, O. *Synlett* **2003**, 947–950; (b) Nyerges, M.; Bendell, D.; Arany, A.; Hibbs, D. E.; Coles, S. J.; Hursthouse, M. B.; Groundwater, P. W.; Meth-Cohn, O. *Tetrahedron* **2005**, *61*, 3745–3753.
176. Zubia, A.; Mendoza, L.; Vivanco, S.; Aldaba, E.; Arrascal, T.; Lecea, B.; Arrieta, A.; Zimmerman, T.; Vidal-Vanaclocha, F.; Cossio, F. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 2903–2907.
177. Garner, P.; Kaniskan, H. U. *Tetrahedron Lett.* **2005**, *46*, 5181–5185.
178. Bonini, B. F.; Boschi, F.; Comes-Franchini, M.; Fochi, M.; Fini, F.; Mazzanti, A.; Ricci, A. *Synlett* **2006**, 543–546.
179. Bashiardes, G.; Cano, C.; Mauzé, B. *Synlett* **2005**, 587–590.
180. Nàjera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6272–6276.
181. Husinec, S.; Savic, V. *Tetrahedron: Asymmetry* **2005**, *16*, 2047–2061.
182. Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400–13401.
183. Chen, C.; Li, X.; Schreiber, S. *J. Am. Chem. Soc.* **2003**, *125*, 10174–10175.
184. Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971–5973.
185. Zeng, W.; Zhou, Y.-G. *Org. Lett.* **2005**, *7*, 5055–5058.
186. Stohler, R.; Wahl, F.; Pfaltz, A. *Synthesis* **2005**, *9*, 1431–1436.
187. Alemparte, C.; Blay, G.; Jorgensen, K. A. *Org. Lett.* **2005**, *7*, 4569–4572.
188. Cabrera, S.; Gomez Arrayas, R.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394–16395.
189. Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, *5*, 5043–5046.
190. Gao, W.; Zhang, X.; Raghunath, M. *Org. Lett.* **2005**, *7*, 4241–4244.
191. Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979–1983.
192. Llamas, T.; Gomez Arrayas, R.; Carretero, J. C. *Org. Lett.* **2006**, *8*, 1795–1798.
193. Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236–4238.
194. Dogan, O.; Oner, I.; Ulku, D.; Arici, C. *Tetrahedron: Asymmetry* **2002**, *13*, 2099–2104.
195. Xu, H.-W.; Li, G.-Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2005**, *7*, 5349–5352.
196. Mamane, V.; Riant, O. *Tetrahedron* **2001**, *57*, 2555–2561.
197. (a) Garcia Ruano, J. L.; Alonso de Diego, S. A.; Blanco, D.; Martin Castro, A. M.; Rosario Martin, M.; Rodriguez Ramos, J. H. *Org. Lett.* **2001**, *3*, 3173–3176; (b) Garcia Ruano, J. L.; Alonso de Diego, S. A.; Martin, M. R.; Torrente, E.; Martin Castro, A. M. *Org. Lett.* **2004**, *6*, 4945–4948.
198. Garcia Ruano, J. L.; Bercial, F.; Gonzalez, G.; Martin Castro, A. M.; Rosario Martin, M. *Tetrahedron: Asymmetry* **2002**, *13*, 1993–2002.
199. Garcia Ruano, J. L.; Fraile, A.; Gonzalez, G.; Rosario Martin, M.; Clemente, F. R.; Gordillo, R. *J. Org. Chem.* **2003**, *68*, 6522–6534.
200. Garcia Ruano, J. L.; Alonso, M.; Fraile, A.; Martin, R.; Peromingo, M. T.; Tito, A. *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, *180*, 1441–1442.
201. Garcia Ruano, J. L.; Gonzalez Gutiérrez, L.; Torrente, E.; Yuste, F.; Martin Castro, A. M. *Arkivoc* **2005**, *IX*, 146–158.
202. Takagi, R.; Nakamura, M.; Hashizume, M.; Kojima, S.; Ohkata, K. *Tetrahedron Lett.* **2001**, *42*, 5891–5895.

203. Illa, O.; Muray, E.; Amsallem, D.; Moglioni, A. G.; Gornitzka, H.; Branchadell, V.; Baceiredo, A.; Ortuno, R. *Tetrahedron: Asymmetry* **2002**, *13*, 2593–2603.
204. Garcia Ruano, J. L.; Peromingo, M. T.; Alonso, M.; Fraile, A.; Martin, M. R.; Tito, A. *J. Org. Chem.* **2005**, *70*, 8942–8947.
205. Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174–2175.
206. (a) Yuan, Z. Q.; Ishikawa, H.; Boger, D. L. *Org. Lett.* **2005**, *7*, 741–744; (b) Elliott, G. I.; Velcicky, J.; Ishikawa, H.; Li, Y.; Boger, D. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 620–622.
207. Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50–61.
208. McMorris, T. C.; Staake, M. D.; Kelner, M. J. *J. Org. Chem.* **2004**, *69*, 619–623.
209. Torssell, S.; Kienle, M.; Somfai, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 3096–3099.
210. Davies, H. M.; Xiang, B.; Kong, N.; Stafford, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 7461–7462.
211. Hodgson, D. M.; Petroliagi, M. *Tetrahedron: Asymmetry* **2001**, *12*, 877–881.
212. (a) Hodgson, D. M.; Stupple, P. A.; Pierard, F. Y. T. M.; Labande, A. H.; Johnstone, C. *Chem.—Eur. J.* **2001**, *7*, 4465–4476; (b) Hodgson, D. M.; Labande, A. H.; Pierard, F. Y. T. M. *Synlett* **2002**, 59–62; (c) Hodgson, D. M.; Labande, A. H.; Pierard, F. Y. T. M.; Exposito Castro, M. A. *J. Org. Chem.* **2003**, *68*, 6153–6159.
213. (a) Hodgson, D. M.; Glen, R.; Grant, G. H.; Redgrave, A. J. *J. Org. Chem.* **2003**, *68*, 581–586; (b) Hodgson, D. M.; Glen, R.; Redgrave, A. J. *Tetrahedron Lett.* **2002**, *43*, 3927–3930.
214. Hodgson, D. M.; Labande, A. H.; Glen, R.; Redgrave, A. J. *Tetrahedron: Asymmetry* **2003**, *14*, 921–924.
215. Hodgson, D. M.; Le Strat, F.; Avery, T. D.; Donohue, A. C.; Brückl, T. *J. Org. Chem.* **2004**, *69*, 8796–8803.
216. Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Arkivoc* **2003**, *VII*, 49–58.
217. Müller, P.; Allenbach, Y. F.; Bernardinelli, G. *Helv. Chim. Acta* **2003**, *86*, 3164–3178.
218. Müller, P.; Chappellet, S. *Helv. Chim. Acta* **2005**, *88*, 1010–1021.
219. Chappellet, S.; Müller, P. *Synlett* **2004**, 2573–2575.
220. (a) Suga, H.; Inoue, K.; Inoue, S.; Kakehi, A. *J. Am. Chem. Soc.* **2002**, *124*, 14836–14837; (b) Suga, H.; Inoue, K.; Inoue, S.; Kakehi, A.; Shiro, M. *J. Org. Chem.* **2005**, *70*, 47–56.
221. Suga, H.; Kakehi, A.; Ito, S.; Inoue, K.; Ishida, H.; Ibata, T. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1115–1121.
222. Suarez, P. L.; Gandara, Z.; Gomez, G.; Fall, Y. *Tetrahedron Lett.* **2004**, *45*, 4619–4621.
223. Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134–2136.
224. Broggini, G.; Garanti, L.; Molteni, G.; Pilati, T. *Tetrahedron: Asymmetry* **2001**, *12*, 1201–1206.
225. Röper, S.; Franz, M. H.; Wartchow, R.; Hoffmann, H. M. R. *Org. Lett.* **2003**, *5*, 2773–2776.
226. Broggini, G.; De Marchi, I.; Martinelli, M.; Paladino, G.; Penoni, A. *Lett. Org. Chem.* **2004**, *1*, 221–223.
227. Hotha, S.; Anegundi, R. I.; Natu, A. A. *Tetrahedron Lett.* **2005**, *46*, 4585–4588.
228. Molteni, G. *Heterocycles* **2005**, *65*, 2513–2537.
229. Broggini, G.; De Marchi, I.; Martinelli, M.; Paladino, G.; Pilati, T.; Terraneo, A. *Synthesis* **2005**, *13*, 2246–2252.
230. Buttero, P. D.; Molteni, G.; Pilati, T. *Tetrahedron* **2005**, *61*, 2413–2419.
231. Sibi, M. P.; Stanley, L. M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 8276–8277.
232. Pedrosa, R.; Andres, C.; Maestro, A.; Nieto, J. *Synthesis* **2003**, *9*, 1457–1461.
233. Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778–10779.
234. Suarez, A.; Downey, C. W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11244–11245.
235. Kobayashi, S.; Shimizu, H.; Yamashita, Y.; Ishitani, H.; Kobayashi, J. *J. Am. Chem. Soc.* **2002**, *124*, 13678–13679.
236. Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 11279–11282.
237. Shirakawa, S.; Lombardi, P. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 9974–9975.
238. Arévalo, M. J.; Avalos, M.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; Palacios, J. C. *Tetrahedron: Asymmetry* **2002**, *13*, 223–226.
239. Aggarwal, V. K.; Grainger, R. S.; Newton, G. K.; Spargo, P. L.; Hobson, A. D.; Adams, H. *Org. Biomol. Chem.* **2003**, *1*, 1884–1893.
240. Ashley, E. R.; Cruz, E. G.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 15000–15001.
241. Peese, K. M.; Gin, D. Y. *Org. Lett.* **2005**, *7*, 3323–3325.
242. Curtis, N. R.; Ball, R. G.; Kulagowski, J. J. *Tetrahedron Lett.* **2006**, *47*, 2635–2638.
243. Du, Y.; Lu, X. *J. Org. Chem.* **2003**, *68*, 6463–6465.
244. Yong, S. R.; Williams, M. C.; Pyne, S. G.; Ung, A. T.; Skelton, B. W.; White, A. H.; Turner, P. *Tetrahedron* **2005**, *61*, 8120–8129.
245. Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014–16015.
246. Merino, I.; Laxmi, Y. R. S.; Florez, J.; Barluenga, J. *J. Org. Chem.* **2002**, *67*, 648–655.

Biographical sketch

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