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Stereochemical Diversity in Pyrrolidine Synthesis by Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides

Javier Adrio* and Juan C. Carretero*

The pyrrolidine ring is a privilege structural motif in synthetic and medicinal chemistry. This review aims to highlight the high versatility of the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides for the access to different types of stereochemical patterns in enantioselective pyrrolidine synthesis. Special emphasis will be paid to stereodivergent procedures giving rise to different stereoisomers from the same starting materials.

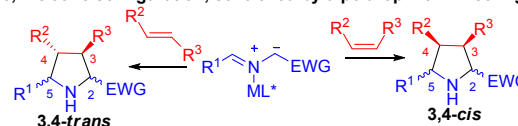
1. Introduction

The pyrrolidine ring has become a privilege structure in synthetic and medicinal chemistry. The great interest of this heterocycle is based on several aspects: a) pyrrolidines constitute the central structure of the proline amino acid and it is present in a plethora of natural products;¹ b) in the last years, chiral pyrrolidines have become leading scaffolds in ligand design either in transition metal mediated or organocatalytic processes;² c) many substituted pyrrolidine derivatives are acknowledged to possess a wide range of bioactivities, such as antibiotic, antibacterial, antifungal and cytotoxic effects, and consequently offer an excellent opportunity for the discovery of new pharmaceutical agents.³ Indeed, there are more than 20 marketed drugs containing the pyrrolidine scaffold in its structure.⁴

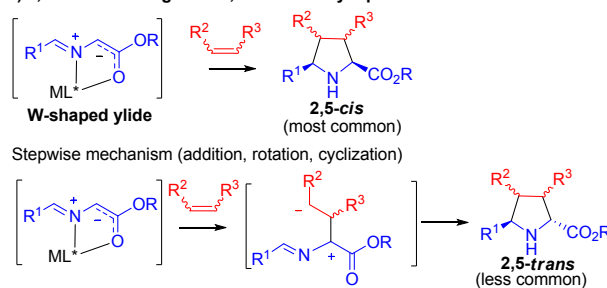
Over the past fifteen years, the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides has emerged as a powerful methodology for the enantioselective convergent preparation of pyrrolidines with an increasing variety of substitution patterns. During this period of time the effort of numerous research groups has been focused on the development of a wide variety of chiral catalysts, both transition metal complexes and small organic molecules (organocatalysts). This pool of new catalysts has also enabled the improvement of the structural scope of this cycloaddition, originally limited to the use of highly activated olefins and α -aminoesters derivatives as azomethine ylide precursors. Thus, less activated dipolarophiles and more challenging 1,3-dipoles have been incorporated to the arsenal of suitable substrates for this transformation. The growing progress in the synthetic interest of this reaction catalytic asymmetric outstanding results has been summarized in several reviews.⁵ In addition, the first examples of higher order cycloadditions of azomethine

ylides (e.g. [3+3] and [6+3] cycloadditions) have been reported in recent years.⁶

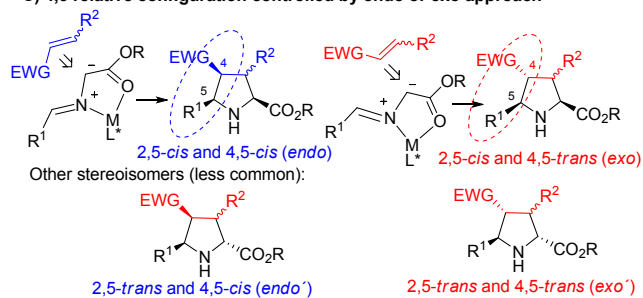
A) 3,4 relative configuration, controlled by dipolarophile E/Z configuration



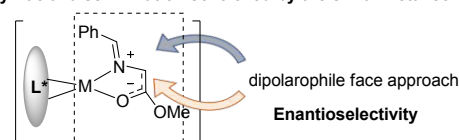
B) 2,5 relative configuration, controlled by dipole conformation



C) 4,5 relative configuration controlled by endo or exo approach



D) Enantioselectivity: facial discrimination controlled by the chiral metal complex



Scheme 1. Controlling factors on the stereochemical outcome of metal-catalyzed asymmetric 1,3-dipolar cycloaddition of stabilized azomethine ylides

1.1. Stereochemical issues

With four sp^3 -hybridized carbon atoms in its structure the pyrrolidine ring can present up to four stereocentres, and

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consequently up to 16 different stereoisomers. Since every stereoisomer can display different biological properties, the development of selective reactions that allow the preparation of pyrrolidines with several stereocenters and complete control of both absolute and relative configuration is crucial in drug discovery.

The catalytic asymmetric 1,3-dipolar cycloaddition can occur either through a concerted (most common) or a stepwise mechanism. Both pathways usually take place with complete or very high stereospecificity. Consequently the 3,4 configuration of the pyrrolidine depends exclusively on the stereochemistry of the dipolarophile (Scheme 1A).

Typically, the 2,5-*cis* diastereoselectivity obtained in this catalyzed cycloaddition is based on the participation of a metal complex by bidentate coordination of the azomethine ylide precursor with the chiral Lewis acid. The formation of this complex facilitates the deprotonation of the iminoester and the transmission of the chiral information from the chiral ligand. The coordination with the nitrogen and oxygen atoms of the azomethine precursor also fix the *W*-conformation of the 1,3-dipole, which determines the usual 2,5-*cis* configuration of the final pyrrolidine (Scheme 1B). Although less common 2,5-*trans* pyrrolidines have been also prepared. This stereochemical result has been justified by a stepwise mechanism involving a Michael addition, a rotation of the C-N bond, and a Mannich reaction to afford the 2,5-*trans* adduct (see section 2.4).

The 4,5-configuration of the pyrrolidine depends on the *exo* or *endo* approach of the dipolarophile to the dipole (Scheme 1C), whereas the control of the enantioselectivity is based on the ability of the chiral ligand to promote a good discrimination between both faces of the metallo-dipole (Scheme 1D).

Finally, in the goal of developing more stereochemically efficient methodologies catalytic stereodivergent procedures are extremely appealing. In these processes the judicious choice of the catalytic system could enable a controllable access to more than one diastereoisomer from the same starting materials.⁷ In the last years, several examples of catalytic asymmetric stereodivergent 1,3-dipolar cycloadditions of azomethine ylides have been developed, facilitating the preparation of structurally diverse small-molecule libraries.

1.2 Organization of the review

Due to the ongoing progress in the stereochemical control of the metal catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides, the aim of this review is focused on the stereochemical diversity achievable by this reaction rather than its structural scope, summarized in other reviews.⁵ Our goal is to provide the readers with an overview on the impact of the structure of the catalyst, starting materials and reaction conditions on the stereoselectivity of the cycloaddition, with main focus on recent developments. A selection of representative examples to illustrate this stereochemical diversity will be presented, starting with a selected historic compilation of the most frequent and well developed pyrrolidine configurations. In the second part a special attention will be devoted to stereodivergent procedures.⁷ In addition, some mechanistic aspects will be presented highlighting the

relationships between catalyst structure and diastereoselectivity.

2. Endo/exo selectivity

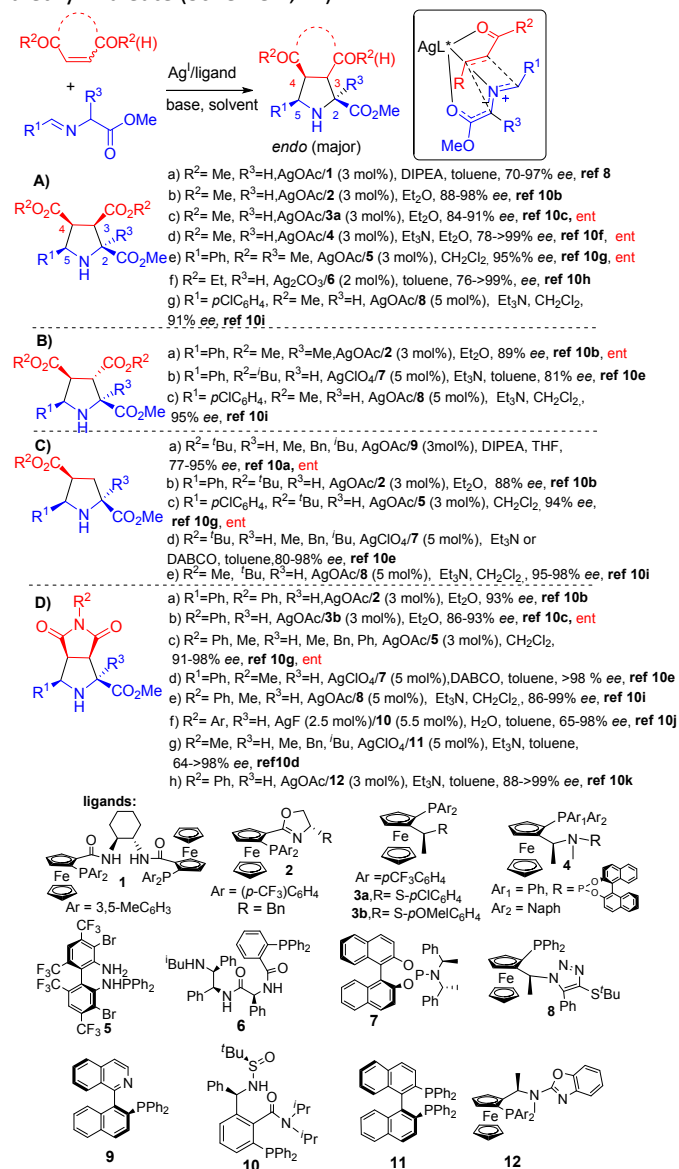
As it is shown in Scheme 1 in the 1,3 dipolar cycloaddition with azomethine ylides two possible diastereomeric cycloadducts can be formed as result of the *endo* or *exo* approach of the 1,3-dipole and dipolarophile. In principle, the *endo* approach would be favoured by secondary orbital interaction, in a similar way as in the Diels-Alder reaction. However, in 1,3-dipolar cycloadditions this stabilizing orbital interaction is usually much smaller and the unfavourable steric effects can play a major role in the observed diastereoselectivity. Therefore, the *endo/exo* selectivity of the reaction depends frequently on the steric hindrance and electronic nature of the substitution at both reaction partners, as well as the metal complex used as catalyst. As a general trend, It is worth mentioning that the silver-catalyzed 1,3-dipolar cycloadditions are typically more *endo* selective than the corresponding copper-catalyzed processes. In the latter case the *endo/exo* highly depends on the ligand and dipolarophile.

2.1 Silver-catalyzed cycloadditions

2.1.1. Endo-selective cycloadditions (4,5-*cis* pyrrolidines)

The first examples of transition metal catalyzed 1,3-dipolar cycloadditions of azomethine ylides were reported by the groups of Zhang⁸ and Jorgensen⁹ in 2002, both procedures afforded the corresponding *endo* pyrrolidines in the reaction of α,β -unsaturated esters with excellent enantioselectivity. From these findings, a set of asymmetric procedures were described for the *endo* selective cycloaddition of α,β -unsaturated carboxylic acid derivatives using different transition metal complexes and chiral ligands. In this arena, chiral silver complexes have afforded excellent results, becoming the most used catalysts for the preparation of *endo*-pyrrolidines under different reaction conditions.¹⁰ A highly stabilizing bonding interaction between the carbonyl group of the dipolarophile and the silver centre has been proposed to explain the excellent observed *endo* diastereoselectivity.¹¹ In Scheme 2 the most relevant results obtained in silver catalyzed cycloaddition are summarized using maleates, fumarates, acrylates and maleimides as dipolarophiles. In 2002, Zhang and co-workers⁷ reported the *endo* selective cycloaddition between iminoesters and dimethyl fumarate using the complex Ag^I/xilyl-FAP (**1**) as catalysts (Scheme 2, Aa). The Ag^I/Quinap (**9**) catalytic system developed by Schreiber and co-workers enlarged the substrate scope of the reaction by the use of other iminoesters different from glycinates ($R^3 \neq H$).^{10a} The *endo* pyrrolidines were obtained with excellent diastereo and enantioselectivity in the reaction with acrylates (Scheme 2, Ca). Ferrocenyloxazoline **2**^{10b} and Ugi-amine derived ferrocenyl ligands such as **3**,^{10c} **4**,^{10f} **8**¹⁰ⁱ and **12**^{10k} afforded the *endo* adducts with high enantiocontrol in the silver catalyzed cycloaddition with maleates (Scheme 2, Ab, Ac, Ad, Ag),^{10b,c,f,i} fumarates (Ba, Bc)^{10b,i} acrylates, (Cb, Ce)^{10b,i} and maleimides (Da, Db, De, Dh).^{9b,c,i,k} Ligands with axial chirality

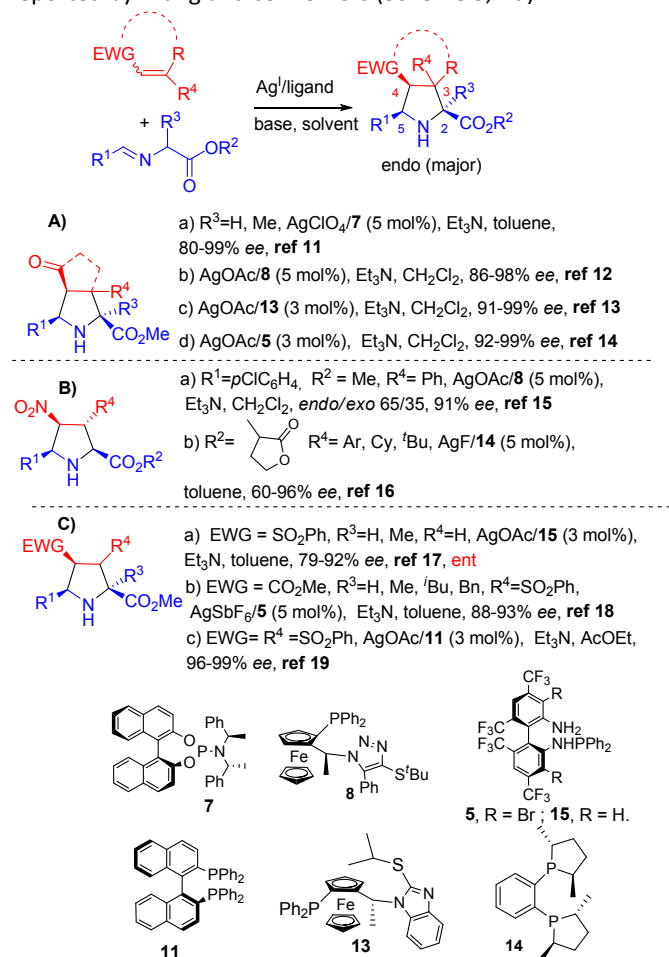
such as BINAP (**11**)^{10d} and BiphamPhos (**5**)^{10g} have been also successfully applied in this transformation (Scheme 2, Ae, Cc, Dc, Dg). Particularly, the BiphamPhos family of ligands developed by Wang and co-workers showed a wide scope regarding both the dipole and dipolarophile partner.^{10g} In 2008 Najera and co-workers^{10e} described that the combination of the phosphoramidite monodentate ligand **7** and a silver salt was an excellent catalytic system for the *endo* selective cycloaddition of azomethine ylides with acrylates and fumarates (Scheme 2, Bb, Cd, Dd). A sulfonamide derived non-biaryl atropoisomer ligand **10** was a very efficient ligand in the silver catalyzed cycloaddition with maleimides (Scheme 2, Df).^{10j} Finally, the chiral secondary amine-amidophosphane **6** in combination with Ag₂CO₃ served as an efficient catalyst in the reaction with diethyl maleate (Scheme 2, Af).^{10h}



Scheme 2. Silver-catalyzed *endo* selective cycloaddition of azomethine ylides with α,β -unsaturated carboxylic acid derivatives

Since 2005 enones, nitroalkenes and vinylsulfones have been incorporated to the arsenal of suitable dipolarophiles (Scheme

3). In 2009 Najera and co-workers reported the first examples of silver catalyzed *endo* selective cycloaddition of azomethine ylides with acyclic and cyclic enones using phosphoramidite **7** as ligand (Scheme 3, Aa).¹¹ Later Fukuzawa¹² and Zheng¹³ groups developed a couple of catalytic systems for this transformation based on the ferrocenyl ligands **8** and **13** (Scheme 3, Ab, Ac). An efficient silver/TF biphamPhos **5** catalyzed the asymmetric desymmetrization of prochiral cyclopentenediones was also reported by Wang and co-workers (Scheme 3, Ad).¹⁴



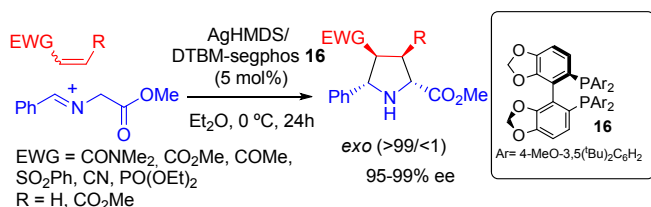
Scheme 3. Silver-catalyzed *endo*-selective cycloaddition of azomethine ylides with enones, nitroalkenes and vinyl sulfones

Regarding the use of nitroalkenes (Scheme 3, B), in 2010 Fukuzawa and co-workers¹⁵ reported that with the system AgOAc/ClickFerrophos **8**, the reaction with *p*-chlorobenzylidene methyl glycinate occurred with high enantioselectivity (91% ee) but with low yield and diastereoselectivity (Scheme 3, Ba). The synthesis of spiro-prolinates was described by Sansano, Cossio and co-workers by the AgF/Me-DuPhos-**14** catalyzed cycloaddition of α -imino- γ -lactones and nitroalkenes (Scheme 3, Bb).¹⁶ In 2008 Wang and co-workers reported the first examples of *endo* selective silver catalyzed cycloaddition of vinyl phenyl sulfone using TF-BiphamPhos **15** as ligand (Scheme 3, Ca).¹⁷ The scope of the sulfonyl dipolarophile was later expanded to β -sulfonylacrylates (Scheme 3, Cb)¹⁸ and 1,2-bis-phenylsulfonyl ethylene (Scheme 3, Cc).¹⁹

Although α -iminoglycinates are the standard, typically used, azomethine precursors ($R=H$), substituted α iminoesters derived from other aminoacids, such as alanine, phenylalanine, valine, etc. have been also successfully applied in some cases.^{10a,d,e, 11,17,18}

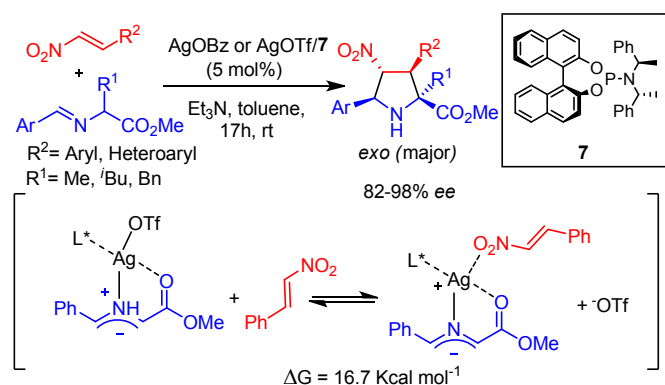
2.1.2. *Exo*-selective silver-catalyzed cycloadditions (4,5-*trans* pyrrolidines)

As previously mentioned the examples of silver catalyzed *exo* selective cycloadditions are very rare: in 2011, Kobayashi and co-workers²⁰ reported the first examples of 1,3-dipolar cycloaddition of azomethine ylides and diverse olefins, catalyzed by AgHMDS/DTBM-segphos ligand (**16**) leading to the corresponding pyrrolidines with excellent *exo* diastereoselectivity and enantioselectivity (Scheme 4). As it will be empathised throughout this review the very bulky DTBM-segphos ligand typically leads to the formation of the *exo* adducts with high selectivity due to the destabilizing steric interaction between the substituents of the phosphine and the dipolarophile in the *endo* approach.



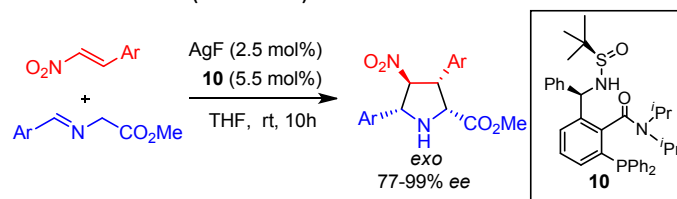
Scheme 4. AgHMDS/DTBM-segphos catalyzed *exo*-selective asymmetric 1,3-dipolar cycloaddition of azomethine ylides.

An unusual *exo*-selective 1,3-dipolar cycloaddition between iminoesters and nitroalkenes using silver triflate or silver benzoate phosphoramidite **7** complexes was reported by Nájera, Sansano, Cossío and co-workers.²¹ DFT calculations demonstrated the crucial role of the counteranion: the OTf anion remained coordinated to the silver atom along the reaction pathway avoiding the stabilizing *endo* interaction between the metal and the nitro group of the dipolarophile (Scheme 5).



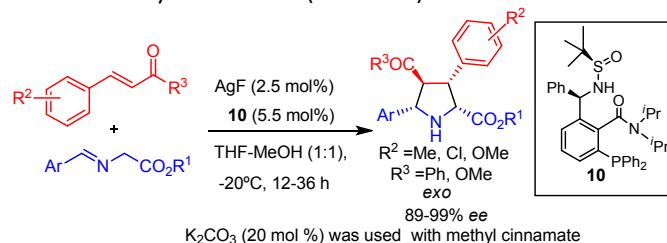
Scheme 5. Ag/phosphoramidite catalyzed *exo* selective asymmetric 1,3-dipolar cycloaddition of azomethine ylides with nitroalkenes.

In 2005, Xia, Xu and co-workers described the synthesis of a new family of non-biaryl atropoisomers chiral ligands. These sulfinyl phosphine ligands afforded excellent levels of *exo* diastereoselectivity and enantioselectivity in the silver catalyzed *exo*-selective 1,3-dipolar cycloaddition of iminoesters and nitroalkenes (Scheme 6).²²



Scheme 6. *Exo*-selective cycloaddition of azomethine ylides with nitroalkenes catalyzed by Xing-Phos/Ag complex.

The applicability of Xing-Phos ligand (**10**) was efficiently extended to other dipolarophiles such as chalcones and the less reactive methyl cinnamates (Scheme 7).²³



Scheme 7. Xing-Phos/Ag *exo*-selective cycloaddition of azomethine ylides with chalcones.

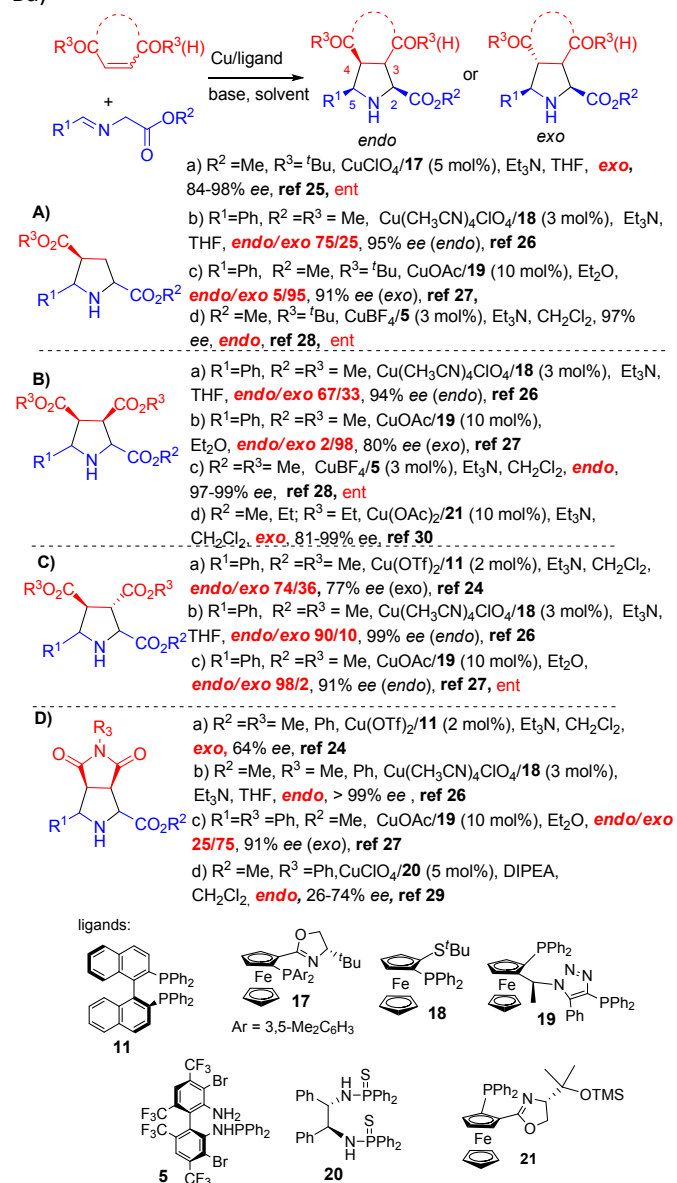
2.2 Copper-catalyzed cycloadditions

Together with silver based catalyst, copper(I) complexes are the most widely employed catalysts in asymmetric 1,3-dipolar cycloadditions of azomethine ylides.

The first examples of chiral copper complexes were reported by Komatsu and co-workers in 2003.²⁴ The reaction with maleimide or fumarate, catalyzed by BINAP (**11**)/Cu(OTf)₂ complexes, afforded mainly the *exo* adducts albeit with modest enantioselectivities (Scheme 8, Ca, Da). Two years later, the first copper catalyzed highly *exo*-selective cycloadditions were reported by Zhang and co-workers:²⁵ the reaction of azomethine ylides with acrylates in the presence of Cu/ferrocenyl P,N-ligand **17** provided the *exo* pyrrolidines in up to 98% ee (Scheme 8, Aa). The same year, our research group²⁶ described a general protocol involving Cu/Fesulphos **18** as catalyst, providing high levels of diastereo and enantioselectivity with a wide variety of iminoesters and dipolarophiles (Scheme 8, Ab, Ba, Cb, Db). The *endo/exo* selectivity proved to be highly dependent on the dipolarophile. Thus, whereas the *endo* adduct was exclusively obtained from maleimide the diastereoselectivity was much poorer with fumarate, maleate and acrylates (*endo/exo*: 90/10, 67/33 and 75/25, respectively). Similarly, the CuOAc/ClickFerrophos **19** complex developed by Fukuzawa and co-workers provided good results in the reaction with acrylates, maleates, fumarates and maleimides. Except in the case of the fumarate (Scheme 8, Cc),

the *exo* adducts were predominantly formed with high enantioselectivity (Scheme 8, Ac, Bb, Dc).²⁷ Alternatively, the *endo* adducts were selectively prepared using the Cu^I/TF-BiphamPhos **5** complex.²⁸ Excellent enantioselectivity was also observed in the reaction with acrylates and maleates (Scheme 8, Ad, Bc), and different types of iminoesters.

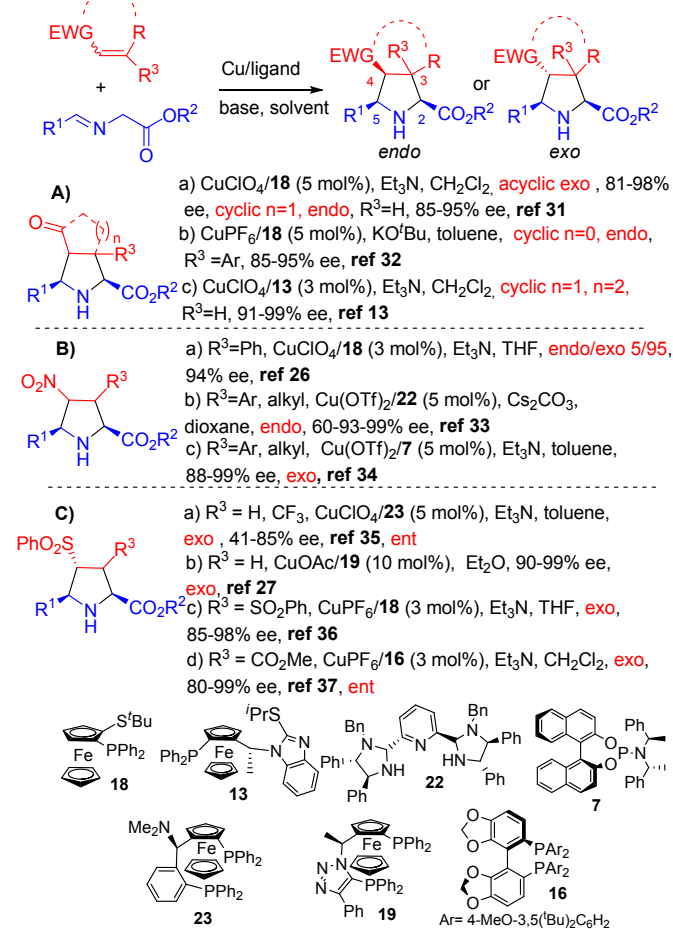
Shi and co-workers reported a new thiophosphoramidate ligand (**20**) for the Cu^I-promoted cycloaddition with maleimides, leading to the *endo* adducts with moderate enantioselectivities (Scheme 8, Dd).²⁹ The P,N-ferrocenyl ligand (**21**) developed by Bdiri³⁰ and co-workers afforded excellent results in the *exo*-selective Cu^{II}-catalyzed cycloaddition with maleates (Scheme 8, Bd)



Scheme 8. Copper catalyzed 1,3-dipolar cycloaddition of azomethine ylides with α,β -unsaturated carboxylic acid derivatives.

Copper catalysts have been also widely employed in the reaction with enones, nitroalkenes, and vinylsulfones. The first procedure for the catalytic enantioselective cycloaddition of

azomethine ylides with enones was reported by our research group in 2009 using the Cu^I/Fesulphos **18** complex (Scheme 9, Aa). The *endo/exo* diastereoselectivity proved to be highly dependent on the E/Z configuration of the enone. Thus, acyclic *trans*-enones led to the formation of the *exo* adducts, whereas cyclopentenone provided the *endo* pyrrolidines.³¹ We have recently reported that the same catalytic system afforded excellent results in the reaction with cyclobutenones.³² In this case, taking advantage of the ring strain of the dipolarophile sterically demanding substrates including β -substitution at the cyclobutenone unit, provided the *endo* adducts with excellent diastereo and enantioselectivity (Scheme 9, Ab).³² Zhang and co-workers extended the scope of the reaction to cyclohexenones with ImiFerroS **13** as ligand (up to 99% ee, Scheme 9, Ac).¹³



Scheme 9. Copper-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with enones, nitroalkenes and vinylsulfones.

In 2005, our research group reported the catalytic asymmetric cycloaddition of methyl glycinate with nitrostyrene. The use of Cu^I/Fesulphos **18** as catalytic system enabled the formation of the *exo* pyrrolidine with excellent diastereo and enantioselectivity (Scheme 9, Ba).²⁶ In 2010 Arai and co-workers described the copper (II)/PyBidine **22** catalyzed *endo*-selective version of this reaction (Scheme 9, Bb).³³ Later, a Cu^{II} *exo*-selective cycloaddition was reported by Sansano and co-workers³⁴ with the phosphoramidite ligand **7** (Scheme 9, Bc).

The first catalytic asymmetric cycloaddition of vinyl sulphones was described by our research group.³⁵ Almost complete *exo* selectivity and excellent enantioselectivities were obtained using CuClO₄/Taniaphos **23** as catalyst system (Scheme 9, Ca). The Cu/ClickFerrophos **19** combination also provided excellent results in this cycloaddition (Scheme 9, Cb).²⁷ Later, our research group extended the scope of the reaction to novel sulfonyl dipolarophiles such as bis-sulfonyl ethylenes³⁶ (Scheme 9, Cc, ligand **18**), and sulfonylacrylates (Scheme 9, Cd, ligand **16**).³⁷

2.3 Other metal-catalyzed cycloadditions

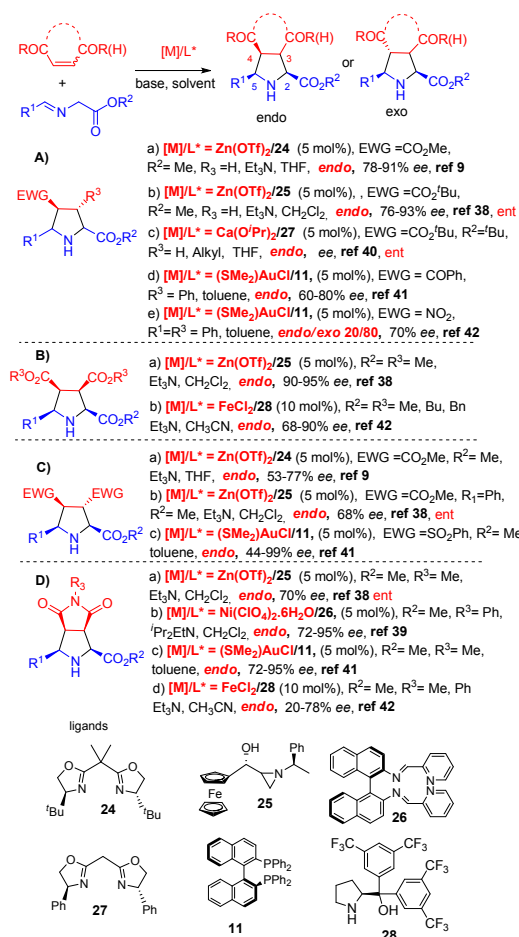
As previously mentioned,⁹ in 2002 Jorgensen and co-workers described that the combination of Zn(OTf)₂ with BOX ligand **24** was very effective for the *endo* selective cycloaddition of azomethine ylides with acrylate and fumarate (Scheme 10, Aa, Ca). Later, Dogan, Garner and co-workers developed a chiral ferrocenyl aziridino ligand **25** for Zn-catalyzed cycloadditions: the *endo* adducts were obtained with high ee's in the reaction with acrylates, maleates or maleimides³⁸ (Scheme 10, Ab, Ba, Cb). In 2008 Shi and co-workers³⁹ demonstrated the feasibility of Ni complexes, excellent *endo* and enantioselectivities were obtained in the reaction with maleimides catalysed by Ni(ClO₄)₂/BINIM **26** (Scheme 10, Db). On the other hand, chiral calcium complexes were reported by Kobayashi and co-workers in 2008.⁴⁰ The catalytic system prepared from Ca(iPrO)₂ and bisoxazoline **27** afforded the *endo* adducts with very high diastereo and enantioselectivities in the reaction with crotonates and alkenyl amides (Scheme 10, Ac).

The *endo* selective cycloadditions of iminoesters with maleimides, bis-sulfonylethylene, chalcone and nitrostyrene were also efficiently catalyzed by the Au-BINAP **11** complex (Scheme 10, Cc, Dc).⁴¹

In 2011 Wang and co-workers reported the Fe^{II}/diaryl prolinol **28** catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with maleates and maleimides providing the *endo* adducts with modest enantioselectivities (Scheme 10, Bb, Dd).⁴² Interestingly, except the case of the gold catalyzed reaction with nitrostyrene (Scheme 10, Ae), all the reactions summarized in Scheme 10 led to the formation of the *endo* isomers.

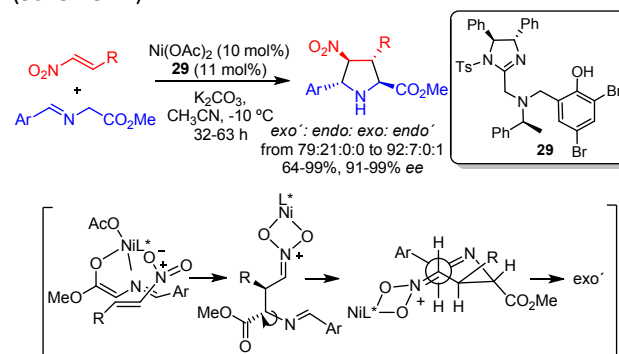
2.4 *Exo'*/*endo'* isomers: Pyrrolidines with 2,5-*trans* configuration

Unlike pyrrolidines with 2,5-*cis* configuration, the enantioselective access to the 2,5-*trans* diastereomers has been described much later and it is yet underdeveloped. In 2010 Arai and co-workers reported the first metal-catalyzed *exo'*-selective (2,5-*trans* configuration) cycloaddition of azomethine ylides,⁴³ which differs with all the precedents described to that date via W-shaped azomethine metal complexes and consequent formation of 2,5-*cis* substituted pyrrolidines. This unusual stereochemistry was obtained in the Ni/imidazoline-



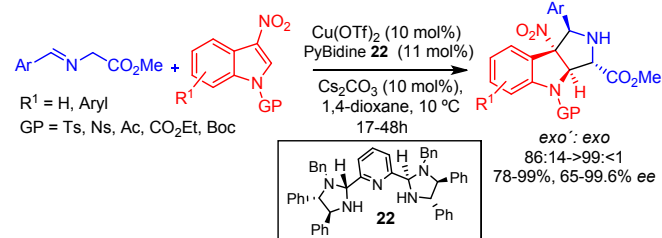
Scheme 10. Zn-, Ni-, Ca-, Au- and Fe-catalyzed 1,3-dipolar cycloadditions of azomethine ylides

aminophenol **29** catalyzed reaction of iminoesters with nitroalkenes. This stereochemical outcome suggested that the cycloaddition takes place through a stepwise mechanism.⁴⁴ Thus, the proposed mechanism would involve an initial anti selective Michael addition of the metallo-dipole to the corresponding nitroalkene controlled by the interaction of the nitro group with the nickel centre. The subsequent coordination of the Ni atom to the nitronate would allow the rotation of the C-N bond before the Mannich reaction, which would afford the *exo'* adduct. DFT calculations confirmed that the *exo'*-cycloadduct is the most stable of the four possible pyrrolidines (Scheme 11).



Scheme 11. Ni-catalyzed *exo'*-selective 1,3-dipolar cycloaddition of azomethine ylides with nitroalkenes

More recently, the Arai group has extended this methodology to the use of 3-nitroindoles as dipolarophiles using Copper (II) as metal.⁴⁵ The Cu^I/PyBidine **22** complex enabled the dearomative cycloaddition process leading to the corresponding *exo'* pyrroloindoline compounds with high diastereo and enantioselectivity (Scheme 12).



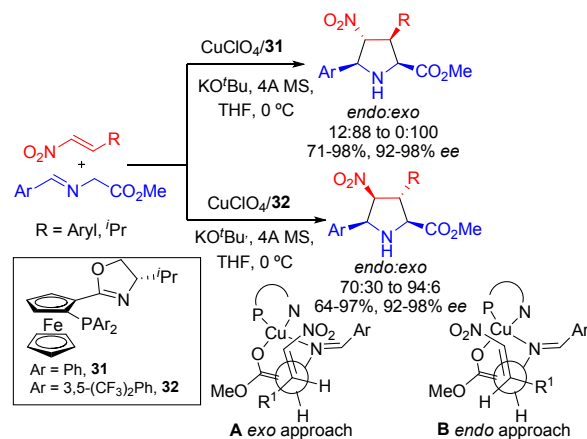
Scheme 12. Cu^I-catalyzed *exo'* selective 1,3-dipolar cycloaddition of azomethine ylides with 3-nitroindoles.

3. Stereodivergent reactions

As pointed out above, the metal catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides has experienced an outstanding progress and a diversity of highly diastereo and enantioselective procedures have been developed.⁵ However, most of these methods are oriented to the selective synthesis of either the *endo* or the *exo* diastereoisomer. Only in recent years a special focus has been applied to the stereodivergent preparation of several diastereomers from the same starting materials, which significantly improves the synthetic efficiency of this reaction.⁷ As described below this stereodivergence can be addressed using either ligand-controlled or metal-controlled cycloadditions.

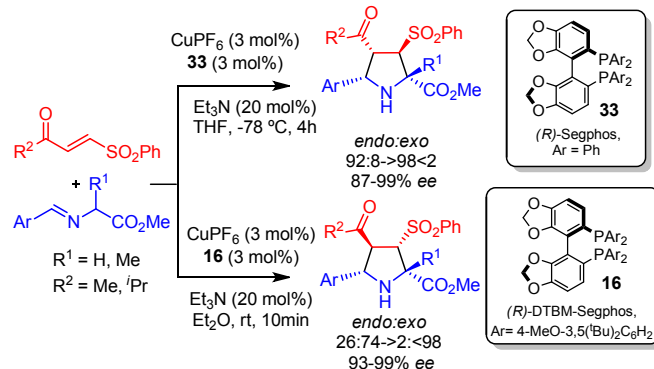
3.1. Ligand-controlled diastereodivergent reactions

The first example of catalytic asymmetric diastereodivergent 1,3-dipolar cycloaddition of iminoesters with nitroalkenes was reported by Hou and co-workers in 2006.⁴⁶ By proper choice of electron rich or electron deficient aryl groups on the phosphorous atom of the ferrocenyl phosphine oxazoline ligand a reversal in the *exo/endo* diastereoselectivity was observed. Thus, the cycloaddition in the presence of ligand **31** provided the *exo* adduct as major isomer, whereas with ligand **32** the *endo*-diastereomers were selectively obtained. Computational studies suggested that the transition state models **A** and **B** were the most favourable approaches for the formation of *exo* and *endo* adducts, respectively (Scheme 13). In structure **A** the nitro group is far from the aromatic groups of the ligand, while in structure **B** it lies between the two aromatic substituents of the phosphine. Thus, the transition structure **A** which would lead to the *exo* product is expected to be more stable with electron rich aryl groups. Conversely, the approach **B** is stabilized by electrostatic interactions when the aryl groups are electron deficient.



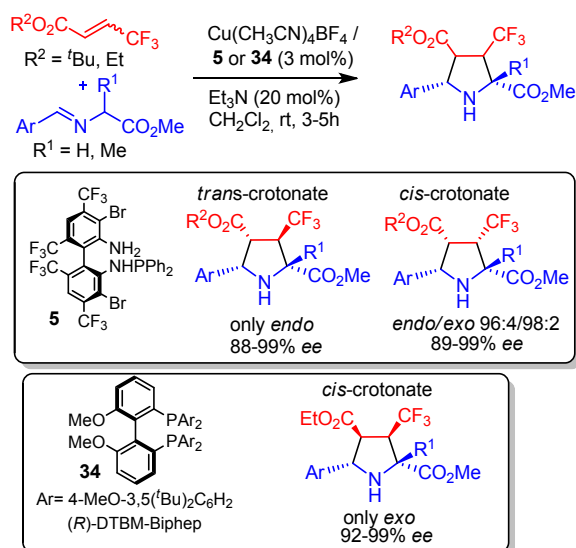
Scheme 13. Diastereodivergent cycloaddition of α -iminoesters with nitroalkenes.

In 2010 our research group described the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with β -sulfonylenones.⁴⁷ The regioselectivity of the reaction catalyzed by Cu^I/Segphos-type ligands was mainly controlled by the carbonyl group, leading to 4-acetyl pyrrolidines as major products. Interestingly, the *endo/exo* selectivity could be controlled by the substitution on the phosphorous atoms of the segphos-type ligands. Thus, the use of the segphos ligand **33** (Ar=Ph) afforded the *endo* isomers while the sterically hindered and electron rich DTBM-segphos **16** led to the *exo* isomers with high selectivity (Scheme 14).



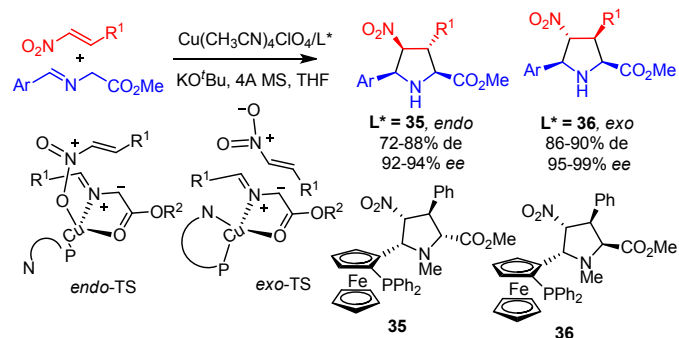
Scheme 14. Catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with β -sulfonylenones

In 2011 Wang and co-workers developed a new methodology for the enantioselective synthesis of 3-trifluoromethylated pyrrolidines from (*Z*) or (*E*)-4,4,4-trifluorocrotonates.⁴⁸ The catalyst Cu^I/(*S*)-TF-BiphamPhos **5** led to the *endo* isomers with high enantioselectivity regardless of the (*Z*) or (*E*) configuration of the trifluorocrotonate. The *exo*-selective cycloaddition was later developed using the bulky electron rich biphosphine ligand DTBM-Biphep **34** (Scheme 15).⁴⁹



Scheme 15. Cu(I)/(S)-TF-BiphamPhos catalyzed cycloaddition with trifluorocrotonates

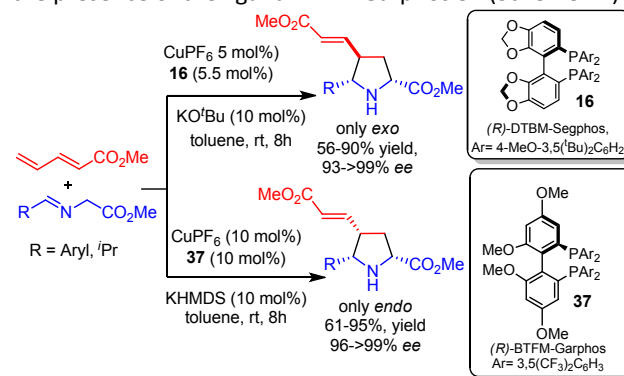
A new family of hybrid pyrrolidine ferrocene ligands, developed by Cossio and co-workers, enabled the diastereodivergent cycloaddition of azomethine ylides with nitroolefins.⁵⁰ The *endo* cycloadducts were obtained in high yield and enantioselectivity using Cu^I/ligand **35** complex, whereas the combination of Cu^I and ligand **36** afforded selectively the *exo* pyrrolidines. DFT calculations indicated that in the *endo* transition state the metallated azomethine ylide is only coordinated to the phosphorous atom of the ligand and, consequently, the Cu atom has a vacant orbital to coordinate the nitro group. However, ligand **36** showed a bidentate coordination, where the copper atom was bound to the phosphorous and nitrogen atoms. Therefore, the nitro group of the dipolarophile was not available to coordinate the metal and the *exo* pyrrolidines were formed (Scheme 16).



Scheme 16. Cu(I)-catalyzed diastereodivergent cycloaddition of azomethine ylides and nitroalkenes

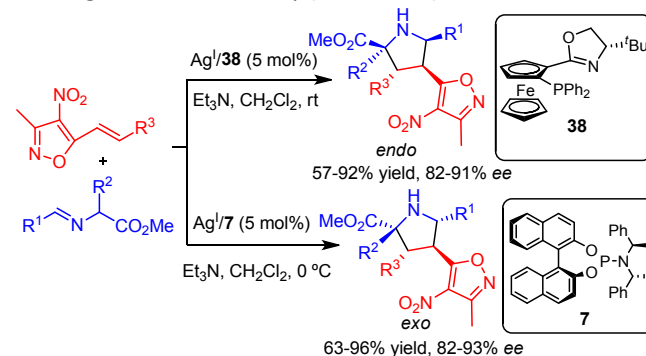
In 2015 our research group reported the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with acyclic electron-poor 1,3-dienes and 1,3-enynes.⁵¹ The combination of a Cu^I salt and a bidentate axial chiral phosphine allowed to control the regio, diastereo and enantioselectivity of the process. The reaction occurred regioselectively in the γ,δ -double bond of the dipolarophile. The *exo* isomers were

obtained with excellent diastereo and enantioselectivities using Cu^I/DTBM-Segphos **16** as catalyst and K^tBuO as base. A complete reversal on the diastereoselectivity was achieved in the presence of the ligand BTFM-Garphos **37** (Scheme 17).



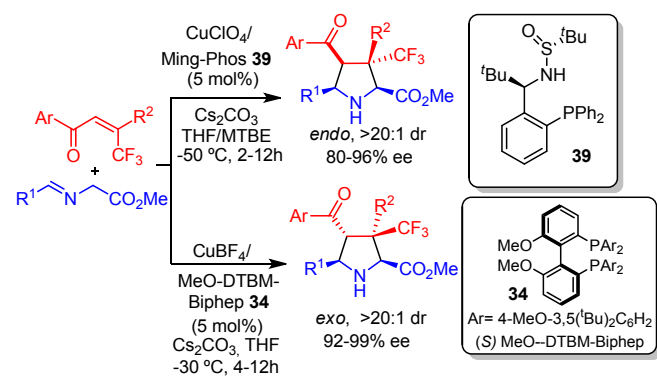
Scheme 17. Cu^I/DTBM-Segphos catalyzed 1,3-dipolar cycloaddition of azomethine ylides and 1,3-dienes.

Shortly after, Wang and co-workers developed an Ag^I-catalyzed diastereodivergent 1,3-dipolar cycloaddition of azomethine ylides with 3-methyl-4-nitro-5-styrylisoxazoles.⁵² The reaction using Phosferrox ligand **38** afforded the expected *endo* adduct with almost complete diastereoselectivity and good enantioselectivity. Interestingly, the monodentate phosphoramidite ligand **7** led selectively to the *exo* adducts also with high enantioselectivity (Scheme 18).



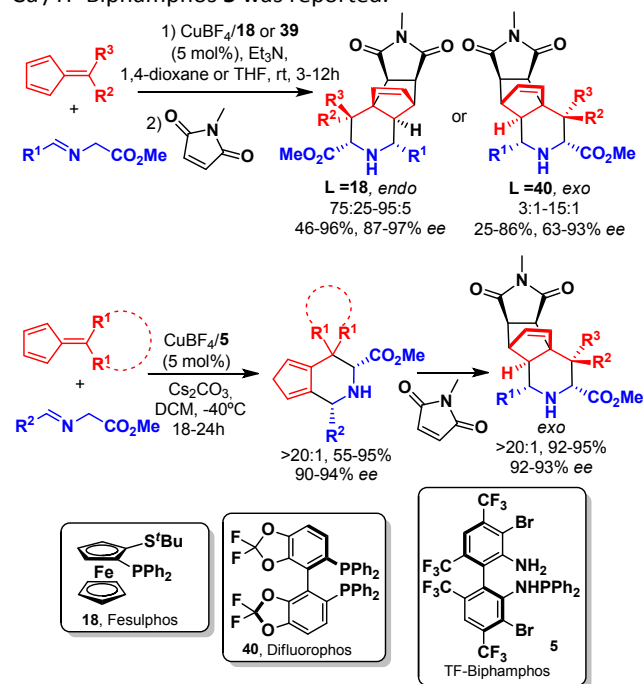
Scheme 18. Diastereodivergent cycloaddition with methyl-4-nitro-5-styrylisoxazoles.

In 2016, Zhang and co-workers described the enantioselective preparation of pyrrolidines bearing a quaternary stereocenter at C-3 by a Cu^I-catalyzed [3+2] cycloaddition of azomethine ylides with β -CF₃- β,β -disubstituted enones. The sulfonamide monophosphine (Ming-Phos) ligand **39** afforded the *endo* pyrrolidines with high diastereoselectivity and enantioselectivity.⁵³ This research group later described the *exo* selective version of the cycloaddition using (S)-MeO-DTBM-Biphep **34** as ligand (Scheme 19).⁵⁴



Scheme 19 [3+2] cycloaddition of azomethine ylides with β -CF₃- β,β -substituted enones

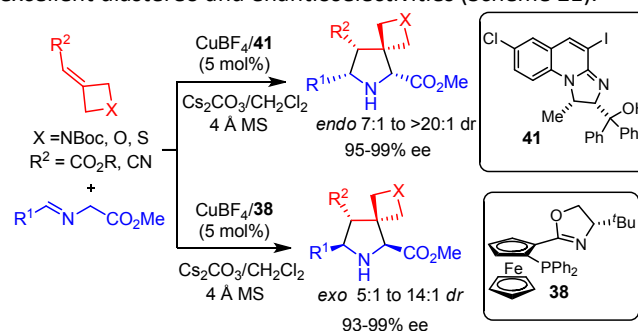
In 2012 Antonchick and Waldmann⁵⁵ reported the enantioselective Cu-catalyzed [6+3] cycloaddition of iminoesters with fulvenes. The best results were obtained using the catalyst combination Cu(CH₃CN)₄BF₄ and Fesulphos ligand **18**. Due to the instability of the products a subsequent Diels-Alder reaction with maleimide was performed, affording the *endo* adducts with high enantioselectivity (Scheme 20). In a later work the diastereodivergent version, which provided the *exo*-adducts, was performed using difluorophos ligand **40**.⁵⁶ Almost simultaneously, a similar cycloaddition catalyzed by Cu^I/TF-Biphosphos **5** was reported.⁵⁷



Scheme 20. [6+3] cycloaddition of iminoesters with fulvenes

Very recently, Xu, Deng and co-workers have described a catalytic asymmetric cycloaddition with four membered rings decorated with an exocyclic double bond.⁵⁸ The *endo* or *exo* spirocyclic pyrrolidines were selectively prepared depending exclusively on the ligand. Thus, the Cu^I/Phosferrox **38** complex afforded the *exo* adduct whereas the Cu^I/N,O-ligand **41**

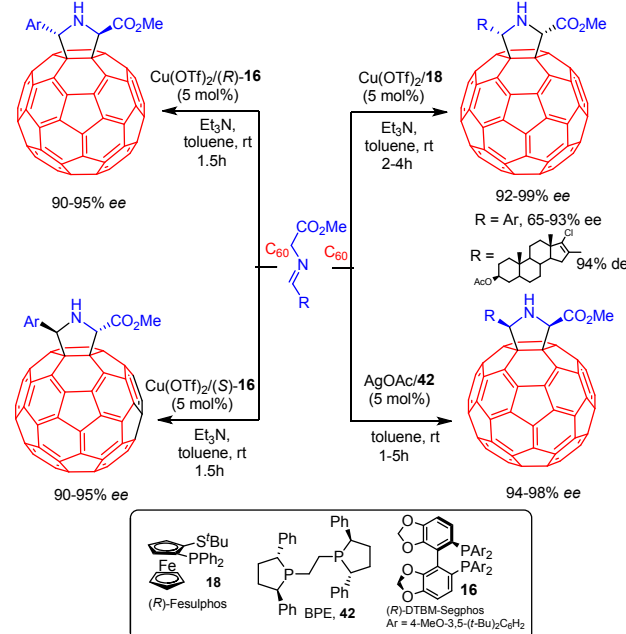
complex gave rise the *endo* pyrrolidine, in both cases with excellent diastereo and enantioselectivities (Scheme 21).



Scheme 21. Diastereodivergent synthesis of spirocyclic pyrrolidines.

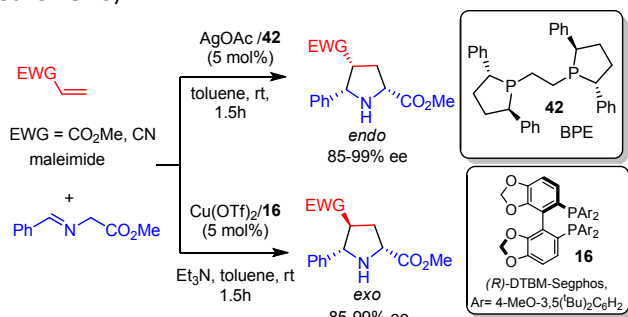
3.2. Metal-controlled diastereodivergent reactions

In 2009 Martín and co-workers reported the first catalytic asymmetric methodology for obtaining pyrrolidino fullerenes. The 1,3-dipolar cycloaddition of azomethine ylides derived from iminoesters using Cu^{II}/Fesulphos **18** or Ag^I/BPE **42** as catalysts enabled the preparation of *cis* C₆₀/pyrrolidine adducts with high yield and enantioselectivity.⁵⁹ The *trans* adducts were selectively obtained using the combination of Cu(OTf)₂ and DTBM-segphos **16**.⁶⁰ This diastereodivergent methodology was also successfully applied to the preparation of C₇₀⁶¹ and *endohedral* H₂@C₆₀ derivatives.⁶² These catalytic systems provided excellent diastereocontrol in the cycloaddition of C₆₀ with varied azomethine ylides including steroid substitution: the catalytic combinations Cu^{II}/Fesulphos **18** and Ag^I/BPE afforded the *cis* adducts, while the Cu(OTf)₂/DTBM-segphos complex provided *trans*-pyrrolidino fullerenes (Scheme 22).⁶³



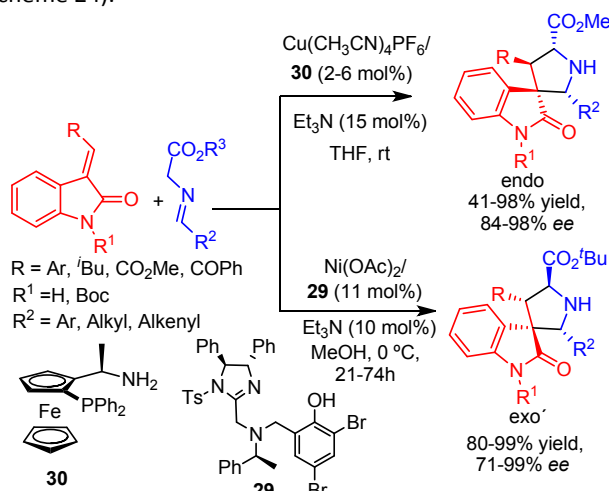
Scheme 22. Fullerenes as dipolarophiles

This diastereodivergent methodology was extended to activated olefins such as acrylates and acrylonitriles. In this case only the formation of pyrrolidines with 2,5-*cis* configuration was observed. The combination of $\text{Cu}(\text{OTf})_2$ and DTBM-segphos **16** afforded the *exo* adducts, whereas the AgOAc/BPE **42** complex gave rise the *endo* pyrrolidines. Excellent diastereo and enantioselectivities were obtained for both diastereomers (Scheme 23).⁶⁰



Scheme 23. Diastereodivergent 1,3-dipolar cycloadditions of azomethine ylides with acrylates and acrylonitriles.

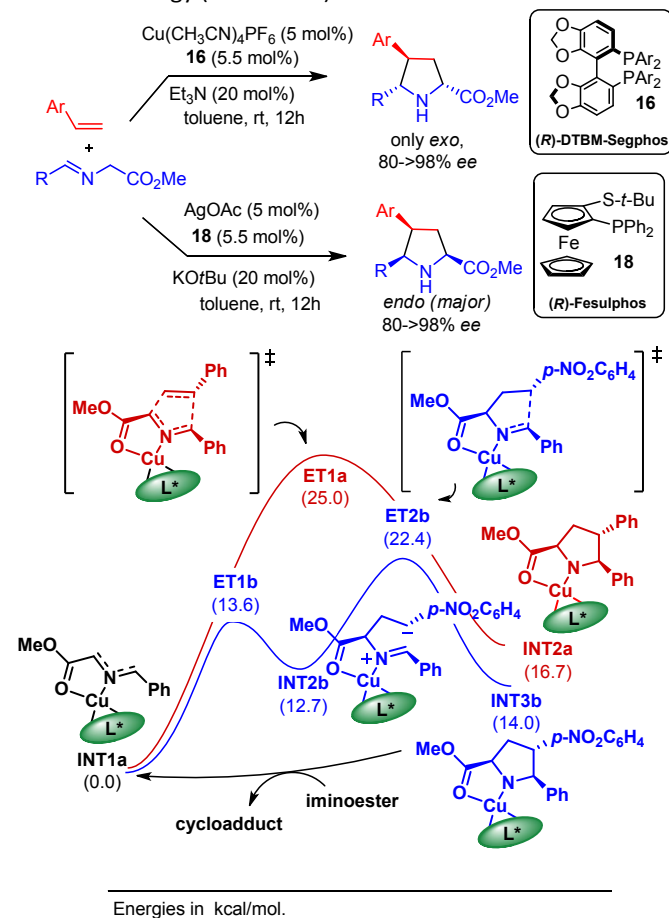
In 2010 Waldmann and co-workers reported the preparation of 3,3-pyrrolidinyl spirooxindoles via Cu-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with 3-methylen-2-oxindoles.⁶⁴ The combination of $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$ and ferrocenyl ligand **30** afforded the *exo* cycloadducts with excellent diastereo and enantioselectivities. Shortly after, Wang and co-workers described the silver catalyzed version of this reaction.⁶⁵ As a stereochemical complementary protocol, Arai, and co-workers published the *exo* selective cycloaddition by using the Ni-imidazoline-aminophenol **29** complex, providing the 2,5-*trans* configured spirooxindoles with high enantioselectivity (Scheme 24).⁶⁶



Scheme 24. Synthesis of *endo* and *exo* 3,3-pyrrolidinyl spirooxindoles

In 2016 our research group reported the feasibility of vinylarenes as dipolarophiles in catalytic asymmetric [3+2] cycloaddition of azomethine ylides.⁶⁷ The reaction catalyzed by $\text{Cu}^I/\text{DTBM-Segphos}$ **16** led to the formation of *exo* 4-

arylprrrolidines with high enantioselectivity. Interestingly, the complementary *endo* adducts were enantioselectively prepared using silver catalysis ($\text{AgOAc}/\text{Fesulphos}$ **18**). The presence of electron-withdrawing substitution at the aryl group of the alkenyl arene was crucial for the reaction to occur. Vinyl heteroarenes bearing pyridyl, quinolyl or thiazolyl moieties were also suitable dipolarophiles in this cycloaddition. DFT calculations on the reaction with styrene and *p*-nitrostyrene catalysed by $\text{Cu}^I/\text{DTBM-Segphos}$ **16** were performed: the cycloaddition with styrene suggested a concerted pathway with a high activation barrier (25 Kcal/mol), whereas the reaction with *p*-nitrostyrene was stepwise and with significant lower activation energy (Scheme 25).

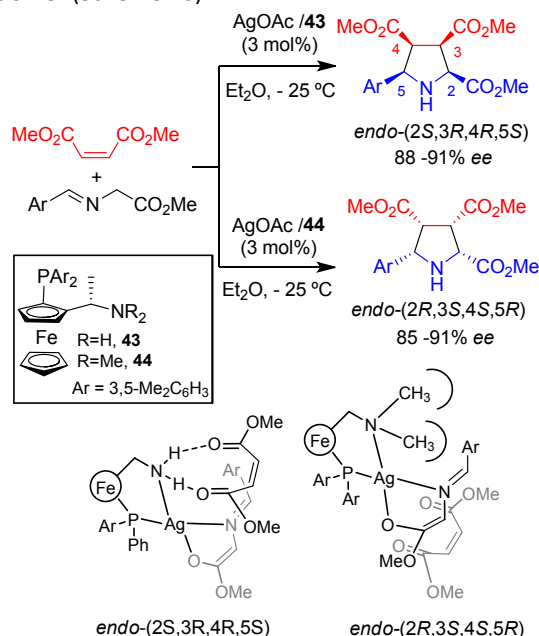


Scheme 25. 1,3-dipolar cycloaddition of azomethine ylides with vinylarenes

3.3. Ligand-controlled enantiodivergent reactions

A ligand controlled enantiodivergent cycloaddition of iminoesters with dimethyl maleate was reported by Li and co-workers in 2007.⁶⁸ The use of AgOAc and the Ugi amine derived ligand **43** containing a primary amine afforded exclusively the *endo* cycloadducts with high *ee*'s (Scheme 26). A complete inversion of the enantioselectivity was achieved varying the substitution on the nitrogen atom of the ligand. Thus, using dimethyl amino derived ligand **44** the *endo* enantiomer was obtained with similar enantioselectivity. DFT calculations were carried out to shed some light to this unusual enantiodivergent

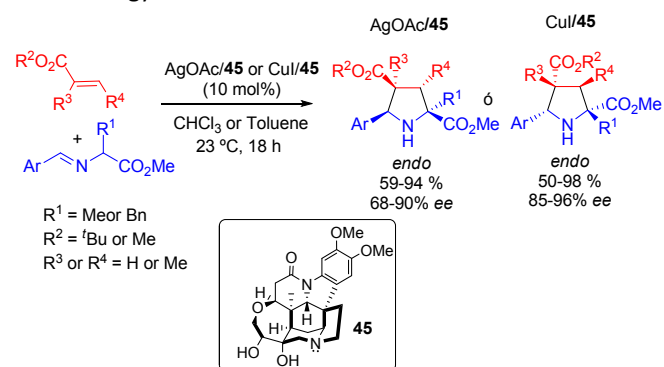
process: with ligand **43** the two carbonyl groups of the dipolarophile could form two hydrogen bonds with the NH₂ of the ligand, which favours the approach from the top face. However, from ligand **44**, having a NMe₂ group (which cannot form this hydrogen bonding), the maleate was coordinated to the silver atom and would approach from the less hindered bottom face, leading to the formation of the opposite enantiomer (Scheme 26).



Scheme 26. Ligand-controlled enantiodivergent cycloaddition of iminoesters with dimethyl maleate

3.4. Metal-controlled enantiodivergent reactions

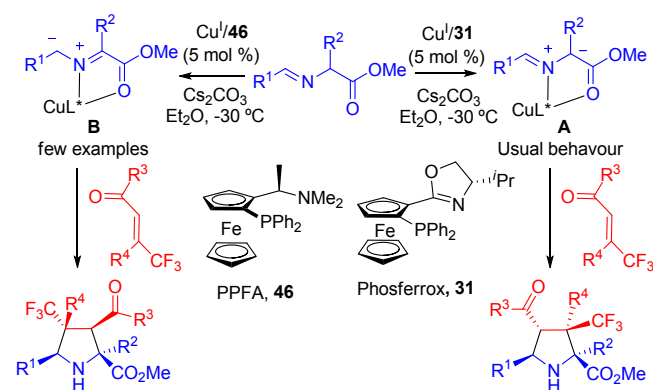
In 2009 Oh and co-workers⁶⁹ described a metal-controlled enantiodivergent cycloaddition between azomethine ylides and acrylates by using a brucine derived amino alcohol ligand **45** in combination with silver or copper salts. The inversion on the enantioselectivity was based on the different coordination modes of Cu^I and Ag^I with the ligand. Both catalytic systems afforded excellent results with a variety of iminoesters, allowing the preparation of pyrrolidines with quaternary stereocentres in C-2 or C-4 positions (Scheme 27). Later, this enantiodivergent methodology was extended to chalcones.⁷⁰



Scheme 27. Metal controlled enantiodivergent 1,3-dipolar cycloaddition of azomethine ylides with acrylates

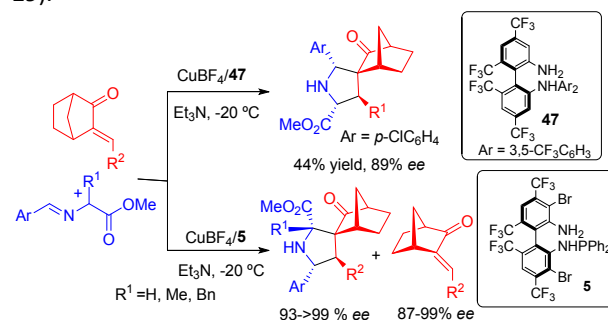
3.5. Regiodivergent reactions

The usual regioselectivity found in the 1,3-dipolar cycloaddition of iminoesters is controlled by the higher stability of resonance form **A** where the negative charge was at the α -position of the ester group. The first examples of regioversed catalytic asymmetric [3+2] cycloaddition of iminoesters, involving an umpolung of the azomethine ylide, were developed using organocatalytic approaches.⁷¹ Very recently, Liu, Zhang and co-workers⁷² have developed a Cu^I-catalyzed asymmetric regiodivergent 1,3-dipolar cycloaddition of iminoesters with β -trifluoromethyl enones (Scheme 28). The regioselectivity of the cycloaddition was controlled by the chiral ligand. DFT calculations revealed that using Phosferrox ligand **31** the usual catalytic pathway where the P and N atoms of the ligand were coordinated to the copper atom led to the expected regioisomer with excellent diastereo and enantioselectivity. A switch in the regioselectivity was observed with PPFA **46** that acted as a pseudobidentate ligand. The dissociation of the nitrogen from copper and subsequent formation of a Cu-O bond with the carbonyl oxygen atom of the dipolarophile would explain the formation of the opposite regioisomer.



Scheme 28. Cu^I-catalyzed regiodivergent 1,3-dipolar cycloaddition of iminoesters with β -trifluoromethyl enones

Very recently, Wang and co-workers⁷³ have reported a very efficient kinetic resolution of alkylidene norcamphors via Cu-catalyzed 1,3-dipolar cycloaddition of azomethine ylides, providing spiro-pyrrolidines with high levels of diastereo and enantioselectivity. The regiochemistry of the reaction could be controlled by the chiral ligand: the BiphamPhos ligand **47** afforded the expected regioisomer while the unconventional regioisomer was effectively obtained using ligand **5** (Scheme 29).



Scheme 29. Cu-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with alkyldiene norcamphors

Conclusions

In conclusion this feature article summarizes the great progress achieved in the diastereoselective and enantioselective synthesis of varied stereochemical patterns in substituted pyrrolidines by metal-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides. Not only a wide variety of highly enantioselective *endo* or *exo* [3+2] cycloadditions have been developed, but also the access to less common configurations such as 2,5-*trans* pyrrolidines (*endo'* and *exo'* isomers).

Interestingly, a significant effort has been recently made to develop stereodivergent versions of this process, providing the enantioselective preparation of two different pyrrolidine stereoisomers from the same reaction partners. In this regard efficient procedures have been recently described using either ligand-controlled or metal controlled cycloadditions. All these advances have substantially improved the state of the art in the enantioselective stereocontrolled access to pyrrolidines on demand.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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The aim of this Feature Article is to show the stereochemical versatility of the metal-catalyzed asymmetric 1,3-dipolar dipolar cycloaddition of azomethine ylides.

