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Current Topics in Medicinal Chemistry, 2014, *14*, 000-000

Asymmetric 1,3-Dipolar Cycloadditons of Stabilized Azomethine Ylides with Nitroalkenes

Carmen Nájera* and José M. Sansano

Departamento de Química Orgánica and Instituto de Síntesis Orgánica (ISO). Universidad de Alicante, E-03080-Alicante, Spain

Abstract: This review highlights the biological importance of many polysubstituted nitro-prolines and -pyrrolidines. Their preparation using asymmetric 1,3-dipolar cycloadditions of azomethine ylides with nitroalkenes using diastereoselective and enantioselective strategies is described remarking the scope and main features of each one.

Keywords: Antitumoral, asymmetric synthesis, catalysis, cycloaddition, metal, organocatalyst.

1. INTRODUCTION

The relationship between nitrocompounds and explosive agents have been established for ages but during the last two decades many contributions demonstrated the potential interest of those molecules bearing a nitro functional group. From the organic synthetic point of view the utility of these compounds atomic arrangement as building blocks has broadened on the basis of two main features of the nitro-functional group: firstly, its activating effect promotes numerous series of reactions (Henry, Nef, Michael-type additions, cycloadditions, radical denitration, heterocycle formations, etc.), and secondly, its facile transformation into various functional groups [1]. The potential biological activity of the family of nitrocompounds is very interesting, for example, some nitroheterocycles are antibiotic drugs [2], other are genotoxic and several nitrocompounds appear to be well tolerated toxicologically and have enjoyed diverse uses in industrial, cosmetic, and agricultural applications [3]. We have focused our attention on chiral molecules **1**-**5** (Fig. **1**), which have a common structural proline derivative core. Molecules **1** are important inhibitors of $\alpha_4\beta_1$-integrin-mediated hepatic melanoma and in a murine model of colon carcinoma metastasis, as well as potent antiadhesive properties in several cancer cell lines [4, 5]. Bicyclic heterocycles **2**, containing atropane scaffold have been found as novel inhibitors of hedgehog signaling. The deregulation of hedgehog signaling is directly involved in the development of skin cancer [6]. The bioprospection of spirooxindoles **3** has been analyzed following the zebrafish embryo model determining. The LC_{50} values indicated elevated mortality of embryos in several tests [7]. Hybrid molecules **4** with benzopyran skeleton were successfully tested as antimycobacterials against *M.tuberculosis* H37Rv strain [8]. Finally, the most simple proline-*type*-**5** have been recently used as chiral organocatalysts in aldol reactions obtaining good to excellent diastereoselections and high enantiomeric ratios [9]. These applications and properties of the mentioned compounds represent a small part of the enormous interest of prolines and pyrrolidines in many scientific areas [10-12].

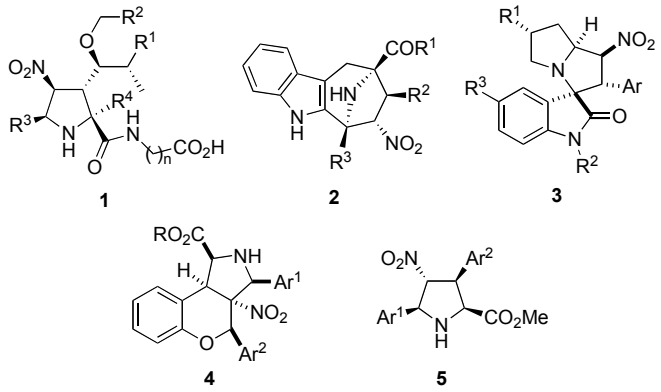

Fig. (1).

All this series of compounds **C**, bearing attached a nitro group, can be prepared in a straightforward manner employing asymmetric 1,3-dipolar cycloadditions (1,3-DC) between stabilized azomethine ylides generated from imino esters **A** or even its corresponding iminium salt **A'** and nitroalkenes **B** [13-20] employing very mild reaction conditions according to the retrosynthetic pathway shown in (Scheme **1**). The most employed 1,3-dipole in the literature is the azomethine ylide [21-27], which can be generated from diverse routes [22]. But the synthesis of the intermediate metalloazomethine ylides acquired more relevance when it was noticed that a high control of the geometry of the intermediate dipole occurred by the metal cation. Firstly, the diastereoselection was excellent [22] and later on, in 2002, a high enantioselection was achieved in the first enantioselective catalyzed processes [28-30]. This last reaction allows creating up to four stereogenic centers in just only one synthetic operation.

The following sections concern the recent advances in the two most frequently employed asymmetric approaches for the synthesis of these nitro-derived prolinates by diastereoselective or enantioselective catalyzed processes.

*Address correspondence to this author at the Departamento de Química Orgánica and Instituto de Síntesis Orgánica (ISO). Universidad de Alicante, E-03080-Alicante, Spain; Tel: +34-965903549; Fax: +34-965903549; E-mail: cnajera@ua.es; jmsansano@ua.es

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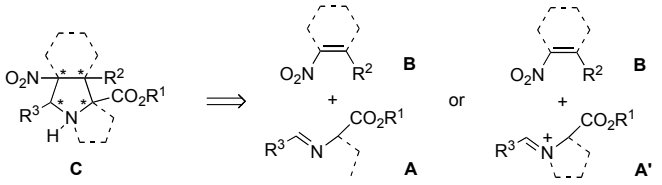
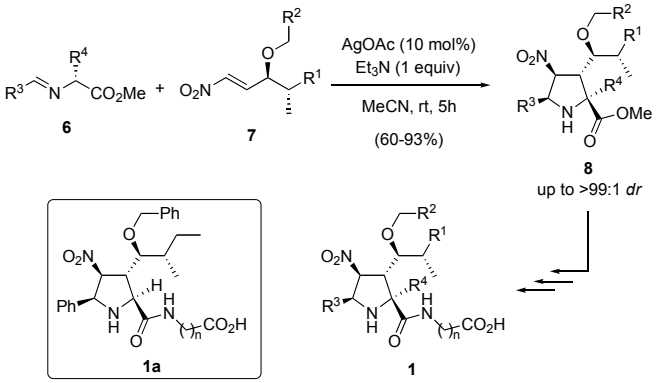


Scheme 1.

2. DIASTEREOSELECTIVE APPROACHES

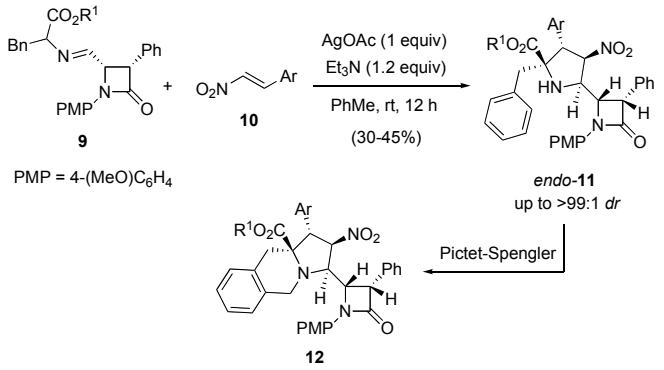
Despite publishing many diasteresoselective 1,3-DC between azomethine ylides and alkenes, a few number of contributions employed nitroolefins as dipolarophile [22, 27]. Such as it was detailed in the previous section, enantiomerically enriched polysubstituted pyrrolydines **1**, with a potent antimetastatic activity, were prepared in twelve preparative steps, the formal [3+2] cycloaddition between imines **6** and nitroalkenes **7** being the key step (Scheme **2**) [4, 5]. The reaction of the silver metallodipole -generated from **6**, AgOAc (10 mol%) and triethylamine- was completely diastereoselective in most of the examples reported (up to >99:1 *dr*) including aliphatic aldimines (R^3 = alkyl). Intermediate proline methyl ester derivatives *endo*-**8** were always isolated as major diastereoisomer [31]. Compound **1a** produces the highest antimetastatic activity on male C57BL/6J mice by measuring the inhibition of adhesion between hepatic sinusoidal endothelial (HSE) cells and B16 melanoma cells.



Scheme 2.

A variety of highly functionalized β-lactam substituted pyrroloisoquinoline and indolizinoindole system was reported. On it, the combination of diastereoselective 1,3-DC involving stabilized azomethine ylides derived from imino esters **9** and β-nitrostyrenes **10** together with a Pictet-Spengler cyclization was successfully implemented. The intermediate cycloadduct *endo*-**11** was obtained by intermediacy of AgOAc (1 equiv) and triethylamine. The conversions were moderate giving yields ranging between 30-45%, and the *dr* were very high (up to >99:1 *dr*) (Scheme **3**). The main goal of the synthesis of final skeletons **12** was their pharmaceutical interest as antiarthritic, antiasthmatic and antiallergenic drugs *via* inhibition of the production of both prostaglandin E2 and intracellular phospholipase A2 [32].

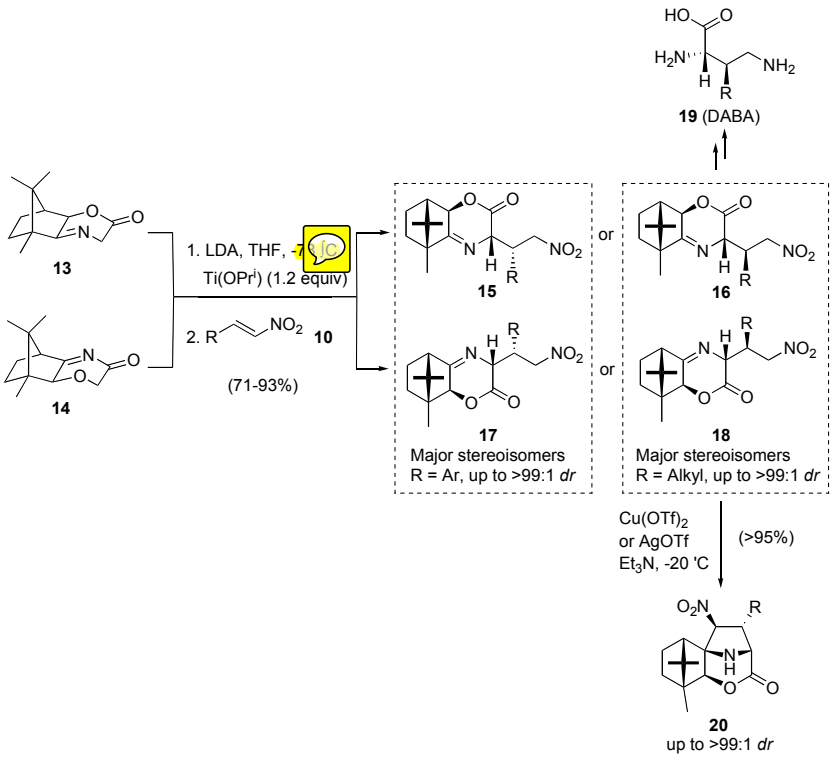
During the synthesis of α,γ-diaminobutyric acids (DABAs) **19**, a series of non proteinogenic amino acids with interesting nutritional, chemical and biomedical properties, optically active polysubstituted pyrrolidines **20** were identified as secondary products when the reaction of oxazinones **13** and **14** were deprotonated with LDA, at -78 ºC in the presence of $Ti(OPr^i)_4$, and treated with aliphatic nitroalkenes **10** (R = alkyl) (Scheme **4**). This reaction afforded diastereoselectively Michael adducts **16** or **18**, respectively. Nitrostyrenes **10** gave very clean crude products **15** or **17** and no cycloaddition products were detected. Several attempts to obtain pyrrolidines **20** were unsuccessfully carried out starting from **13** and **14**. The presumably non-reactive imino group of these oxazinones and **15**-**18** only could be activated by $Cu(OTf)_2$ or by AgOTf as Lewis acids once the Michael adduct (for example **18**) was completely formed. This second step, involving a final metal-catalyzed intramolecular Mannich-type reaction, was completed in almost quantitative yield and excellent diastereoselectivity (>99:1 *dr*) (Scheme **4**) [33].



Scheme 3.

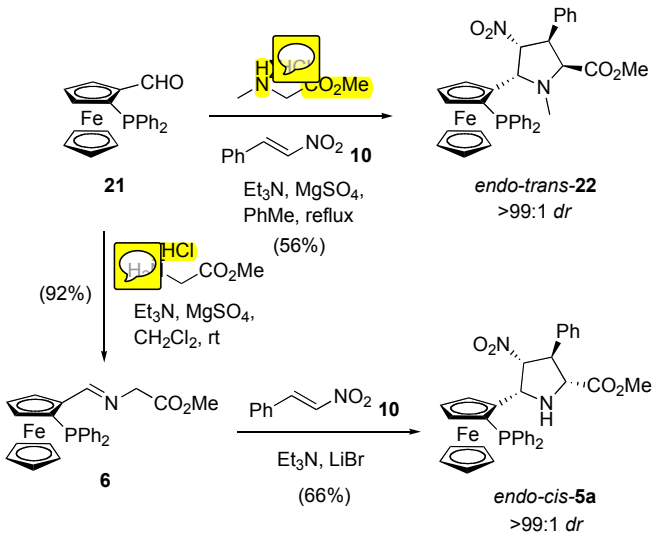
Compounds **5a** [Ar^1 = (diphenylphosphino)ferrocenyl; Ar^2 = Ph] and the *N*-methylated analogue **22** were diastereoselectively prepared taking advantage of the planar chirality of the ferrocenyl scaffold **21**. The thermal 1,3-DC *via* iminium salt between sarcosine methyl ester hydrochloride, aldehyde **21** and nitrostyrene **10** (R = Ph) in refluxing toluene afforded, in moderate chemical yield (52%) and excellent *endo-trans*-diastereoselection (>99:1) enantiomerically enriched nitroproline **22** (Scheme **5**). The absolute stereochemistry of this molecule **22** was not frequently found in the literature, and some stereoelectonic effects can justify the presence of this product at the end of the reaction. The multicomponent reaction employing **21** and glycine methyl ester hydrochloride was not profitable and the imino ester **6** [R^3 = (diphenylphosphino)ferrocenyl; R^4 = H] was prepared and allowed to react with nitrostyrene in the presence of LiBr in THF. Compound *endo-cis*-**5a** [Ar^1 = (diphenylphosphino) ferrocenyl; Ar^2 = Ph] was achieved as sole diastereoisomer in 66% yield (Scheme **5**). Both molecules *endo-trans*-**22** and *endo-cis*-**5a** were immediately tested as chiral ligands in combination with copper(I) salts in the enantioselective catalytic 1,3-DC of imino esters **6** with various dipolarophiles (including nitroalkenes) yielding cycloadducts in very good yields and good enantioselections (see, Scheme **8**) [9].

In general, the synthesis of compounds **5** were previously described using non-asymmetric procedures starting from the corresponding imino ester **6** and nitroalkenes **10** in order to study the origin of the metal effect ($LiClO_4$ or AgOAc) on the stereochemical outcome discovering that the reaction occurred through a two step mechanism [34, 35], and the



Scheme 4.

scope of the reaction employing different dipolarophiles [36]. In addition, analogous multicomponent reactions have been optimized between azomethine ylides and nitroalkenes **10** in the presence of lithium [8], or silver [37] salts and also in the absence of a Lewis acid when thermal processes [7] or dialkyl α-aminomalonates were used [38-41]. Very recently, the use of 3-nitro-2-trihalomethyl-2*H*-chromenes, including 2-unsubstituted derivatives, in 1,3-DC of non-stabilized azomethine ylides allowed the construction of biologically interesting 1-benzopyrano[3,4-*c*]pyrrolidines trough a multicomponent process [42].



Scheme 5.

3. ENANTIOSELECTIVE APPROACHES

Such as it was mentioned before, since 2002 many contributions employing chiral Lewis acids or chiral organocatalysts have been compiled in the literature [13-20]. The number of catalysts and their efficiency contribute to the preparation of multiple and sophisticated molecules with well defined absolute configuration. In general, a wide variety of dipolarophiles have been tested but nitroalkenes, due to their especial coordination ability to the catalyst, offered very interesting diastereoselections. In (Scheme **6**) the general enantioselective process is shown. The main activation of 1,3-dipole precursor occurs when a Lewis acid (**ML$_n$***) is employed ensuring a high rigidity of the resulting metallodipole **F**, however, hydrogen bonding (single or multiple) is the main existing interaction **G** during the activation of the nitroalkene (dipolarophile) by the chiral organocatalyst (**L*—H**).

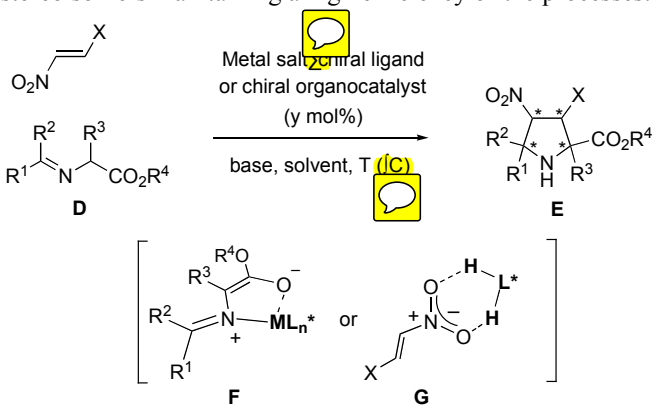
2.1. Chiral Copper Complexes as Catalysts

Chiral copper complexes have been tested in multiple 1,3-DC employing different dipolarophiles [43-49]. They are now the most appropriate catalysts for promoting 1,3-DC between azomethine ylides derived from imino esters **6** and nitroalkenes **10** (Scheme **7**). Copper(I) and copper(II) salts have been used as metal center so they will be discussed in this Section.

(Fig. **2**) contains the bidentate or multidentate chiral ligands employed with copper(I) salts in the catalytic enantioselective 1,3-DC.

It is remarkable the presence of polysubstituted prolines *endo*-**5a** and **22** as chiral ligands (Fig. **2**), which chelated

efficiently $Cu(MeCN)_4PF_6$, in THF. It seems that an autocatalytic process is involved in this transformation. These two catalytic complexes were essayed in the reaction shown in (Scheme **8**) employing a 5 mol% of catalyst loading and triethylamine as base (5 mol%). Under these reaction conditions, *endo*-**5a**·$Cu(MeCN)_4PF_6$ afforded *exo*-cycloadducts **5** in good yield (83-90%), and both high diastereo- (up to 96:4 *dr*) and enantioselectivities (95->99% *ee*) when the reaction was performed at -20 ºC. However, **22**·$Cu(MeCN)_4PF_6$ chiral complex gave the opposite diastereoisomer *endo*-**5** in good yield (79-85%), and not with so high diastereo- (up to 96:4 *dr*) and enantioselectivities (92-94% *ee*) when the reaction was performed at -80 ºC (Scheme **8**) [9]. This is a clear example of fine tuning catalyst in order to obtain different stereoisomers maintaining a high efficiency of the processes.



Scheme 6.

In this work, ONIOM computational studies were performed. Although it is known that the reaction mechanism involving metallodipoles is stepwise, the first step is responsible for the high stereocontrol observed. The nitro group coordinated **5a**·$Cu(MeCN)_4PF_6$ complex because the nitrogen atom of the pyrrolidine did not interact with the metal centre. This allowed the blockage of one of the two prochiral faces of the dipole favoring the mentioned *endo*-cycloadduct **5**. However, this coordination of the nitro group was not available due to the coordination of the nitrogen atom of the pyrrolidine ring furnishing the *exo*-cycloadduct **5** [9].

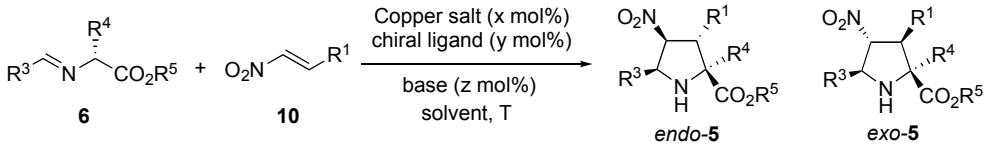
Versatile Fesulphos ligand **23** (3 mol%) (Fig. **2**) and $Cu(MeCN)_4ClO_4$ (3 mol%) as catalytic mixture was employed in the reaction of β-nitrostyrene **10** (R^1 = Ph) and methyl benzylideneaminoglycinate **6** (R^3 = Ph, R^4 = H, R^5 = Me) with triethylamine as base (18 mol%) in dichloromethane at -10 ºC. The corresponding *exo*-cycloadduct **5** was isolated as major diastereoisomer (95:5 *dr*) in moderate yield (61%) and high enantioselection (94% *ee*) following the general reaction shown in (Scheme **7**) [50, 51].

Fesulphos **23**·$Cu(MeCN)_4PF_6$ (5 mol%) was employed as well in the enantioselective 1,3-DC between a non-conventional dipole precursor derived from tryptophan **31** and β-nitrostyrenes **1**[16]. The *exo*-adducts **2** were diastereoselectively obtained (up to >20:1*dr*) using DBU as base (50 mol%) in DCM at -20 ºC. Chemical yields were good (66-92%) and the enantioselections elevated (up to 96% *ee*) (Scheme **9**). Tropane scaffolds have been found as novel inhibitors of hedgehog signaling valuable for the identification of tumor cells such as it was previously mentioned.

Ferrocenyl-oxazoline chiral ligands **24** (11 mol%) (Fig. **2**) were selected to catalyze, together to $CuClO_4$ (10 mol%) the reaction shown in (Scheme **7**). Besides, the optimized reaction conditions included $KOBu^t$ (10 mol%), THF as solvent, 4Å MS, and 0 ºC. Catalyst **24a**·$CuClO_4$ afforded almost exclusively in all of examples the cycloadduct*exo*-**5** (up to >99:1 *dr*) in high chemical yields (73-97%) and high enantioselections (92-99% *ee*). However, the *endo*-selectivity of products **5** was achieved (up to 89:11 *dr*), in very high yields (79-98%) and interesting enantioselections (92-98%) just by employing catalyst **24b**·$CuClO_4$. This behavior can be considered as an exceptional example of how ligands can fine-tune the stereoselectivity in asymmetric catalysis by varying their electronic properties. Computational (DFT) and experimental studies confirm a two-stepwise mechanism and justified the observed enantio- and diastereoselection for each catalytic system [52].

A non-common 1,3-dipole precursor was originally prepared *in situ* starting from imine **32** and further allowed to react with several dipolarophiles, β-nitrostyrene **10** (R^1 = Ph) being one of them (Scheme **10**). The catalytic system comprised bidentate bisoxazolineligand **25** (Fig. **2**) and $Cu(MeCN)_4PF_6$ (10 mol%) and the reaction performed in DCM as solvent and triethylamine (15 mol%) as added base at room temperature. The regioselectivity of the cycloaddition is directed by the electronic charge of the dipole at the γ-position, which seemed much more stabilized for triggering the cycloaddition. Chemical yields and diasteresoselections of the two published examples with β-nitrostyrene **10** (R^1 = Ph) were moderate (53, 57% and 63:37 *dr*, respectively) and the enantioselection was high in both cases (96% *ee*) [53].

Polydentate brucine-derived **26**(Fig. **2**) was initially used for the study of conjugate addition reaction of imino esters **6** onto nitroalkenes **10** giving selectively compounds *anti*-**35** (Scheme **11a**). The resulting nitroimines were cyclized employing DBU as base in DCM at room temperature because the direct 1,3-DC did not occur under these reaction conditions. Benzophenone imine **34** underwent the same Michael-type addition and only a change of the nature of solvent and base was enough to yield the corresponding cycloadduct *endo*-**36** in the same reaction. Thus, when chiral complex **26**·CuCl (10 mol%), triethylamine (10 mol%), ethanol as additive (10 mol%) and trichloroethylene as sol-



Scheme 7.

vent were used polysubstituted proline derivatives **36** were isolated in good yields (63-89%), diastereoselections (up to >99:1) and enantioselectivities (up to 94% *ee*) (Scheme **11b**). These results represented a clear demonstration of the stepwise nature of these 1,3-DC between nitroalkenes and metalloazomethine ylides [54].

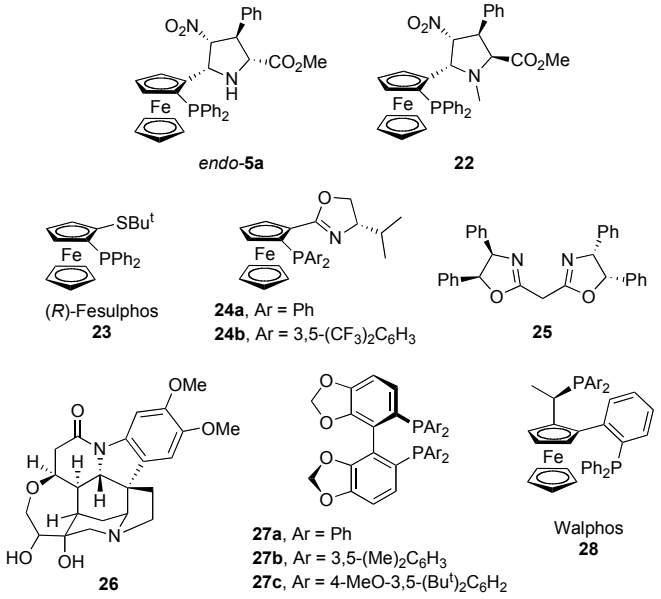


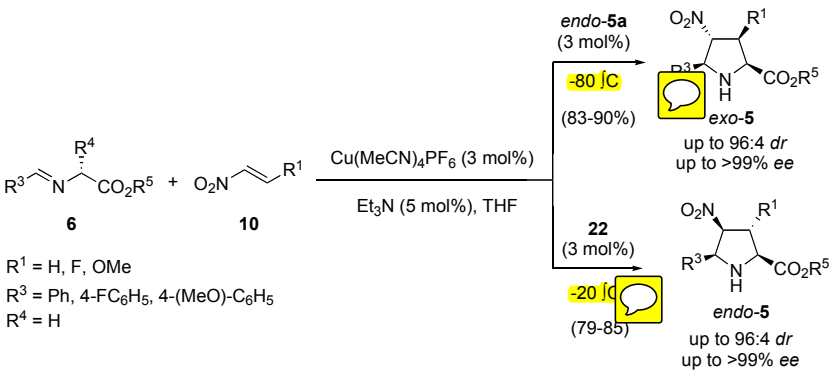
Fig. (2).

Segphos chiral ligand **27a** and derivatives **27b** and **27c** (Fig. **2**) were selected for the formation of chiral complexes with $Cu(MeCN)_4PF_6$ (only in a 1 mol% loading) in the survey of the general scope of imino amides **37**. Particularly, in the 1,3-DC of **37** and β-nitrostyrene only was effective complex **27a**·$Cu(MeCN)_4PF_6$. The diastereo- (up to 88:12 *dr*) and the enantioselectivity (up to 91% *ee*) were not so high than in precedent reactions, but the chemical yields of the major *exo*-stereoisomers **38** were high (80-87%) (Scheme **12**) [55].

The same *exo*-diastereoselectivity was obtained during the synthesis of fluorinated proline derivatives **5**. Catalytic system Walphos **28**·$CuClO_4$ (10 mol%) (Fig. **2**), LiHMDS (10 mol%) in DCM at 0 ºC were the optimum reaction conditions to perform the 1,3-DC of imino esters **6** (R^3 = Ar, R^4 = H, R^5 = Me) with fluorinated nitroalkenes **10** (R^1 = CF_3, CF_2H,CF_2Cl, CF_2Br) (Scheme **13**). Cycloadducts *exo*-**5** were isolated in moderate to good diastereoselections and yields (up to 27:1, and 47-88%, respectively) and high enantioselectivities (up to 97% *ee*) [56] (Scheme **13**). The main goal of this methodology was the production of 4-amino-3-(trifluoromethyl)proline, a molecule with potential biological activity, after reduction of the nitro functional group without epimerization.

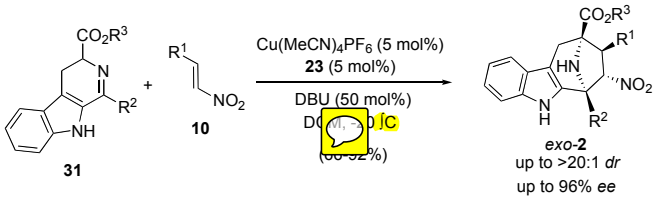
The chiral ligands employed with more stable and easily handle copper(II) salts are depicted (Fig. **3**). A couple of examples were recorded in the literature with different results in terms of diastereoselectivity. Thus, PyBidine **39** (Fig. **3**), easily prepared by condensation of 2,4-pyridyldicarbaldehyde and *N*-benzyl (*S*,*S*)-diphenylethylenediamine, (5 mol%) and copper(II) triflate (5 mol%) formed a chiral complex able to promote the reaction shown (Scheme 7) in the presence of 1,4-dioxane as solvent and cesium carbonate or triethylamine as base (10 mol%). Unlike the other copper(I) and copper(II) chiral complexes, in which the general trend was the diastereoselective generation of *exo*-compounds, *endo*-cycloaducts **5** were selectively obtained (95:5 to >99:1 *dr*) in good yields (60-99%) and excellent enantioselections (93-99%). The authors justified these results on the basis of a concerted mechanism, where the negative charge of the nitro group interacted with the copper atom. This hypothesis was not confirmed for any theoretical study until date [57].

The title reaction has been catalyzed mainly with the combination of poly- or bidentate chiral ligands and copper(I) salts. Next, the unique example of monodentate chiral phosphoramidite ligand **40**·$Cu(OTf)_2$ reported until now (Fig. **3**) was exploited in the asymmetric synthesis of *exo*-prolines **5**. The successful reaction conditions required 5 mol% of catalyst loading, triethylamine (10 mol%), toluene and 25 ºC. The resulting major *exo*-diastereoisomers **5** were isolated in good *exo/endo* ratio (up to 99:1), moderate to good chemical yields (44-79%) and excellent enantioselections (up to >99% *ee*). In this contribution the effects of substituents of the nitroalkene **10** (R^1), and substituents of the imino ester **6** (R^3, R^4, and R^5) were evaluated together for the first time. Actually, dipole precursors derived from α-substituted α-amino acids such as leucine and phenylalanine afforded under the already described conditions compounds *endo*-**5** in more than 99% *ee*. Such as occurred in precedent examples, here the experimental results of the reactions carried out at lower temperatures (-80ºC) giving also Michael adducts **41** supported the existence of a stepwise mechanism (Scheme **14**)

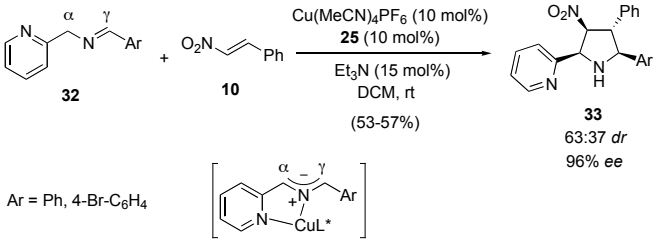


Scheme 8.

[58]. The isolation of equimolecular quantities of *exo*-cycloadduct **5** and non-characterized *syn*-imine **41** followed by acidic work up allowed to obtain α-amino ester **42** in 40% yield, 98:2 *dr*, and 94% *ee* (Scheme **14**).



Scheme 9.



Scheme 10.

In addition, DFT calculations and parallel theoretical studies confirmed the low energy barrier for the previous transition state to the generation of this major *exo*-isomer **5** [59]. The mechanism of these metal catalyzed 1,3-DC can be exemplified by DFT calculations on the **30**·$Cu(OTf)_2$ catalyzed reaction to obtain *exo*-**5** (R^1 = Ph, R^3 = Ph, R^4 = H, R^5 = Me). This model shown a single interaction Lewis acid imino ester **6** and that the coordination sphere of Cu(II) atom is saturated by an OTf moiety (note the importance of the anion to block the access of the nitroalkene). The most stable transition structures located are depicted in (Fig. **4**). Thus, *exo*-**TS1** was found to be about 1.5 kcal mol^{-1} more stable than its enantiomeric counterpart. New carbon-carbon bond distances were very different to each other demonstrating the already mentioned asynchronous cyclization [59].

2.2. Chiral Silver(I) and Gold(I) Complexes as Catalysts

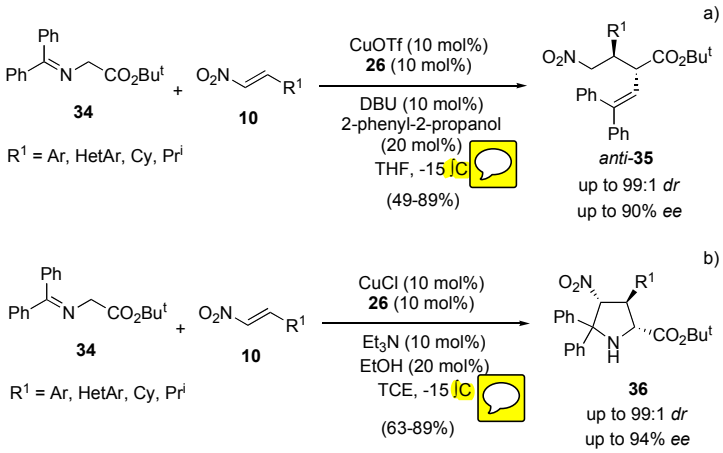
Chiral silver(I) complexes are very suitable for the control of the geometry of the 1,3-dipole furnishing mainly *endo*-cycloadducts. A large series of dipolarophiles have been successfully tested demonstrating the wide scope (higher than the analogous for the chiral copper-catalyzed cycloadditions) exhibited by the employment of this cation [60-70]. Despite the versatility shown by these metal the employment of nitroalkenes **10** was very scarce. In (Fig. **5**) chiral ligands used in enantioselective silver(I) promoted 1,3-DC are illustrated.

Following the model reaction shown in (Scheme **15**), chiral bipyrrolidine ligand **43**(Fig. **5**) and AgOTf (both in 5 mol% loadings) promoted the reaction of imino ester **6** (R^3 = Ph, R^4 = H, R^5 = Me) and β-nitrostyrene **10** (R^1 = Ph) in the presence of potassium carbonate (10 mol%) in DCM at room temperature giving the *endo*-cycloadduct**5** as major isomer in modest results such as 45% yield, 1.8:1 *dr* and 42% *ee* [71].

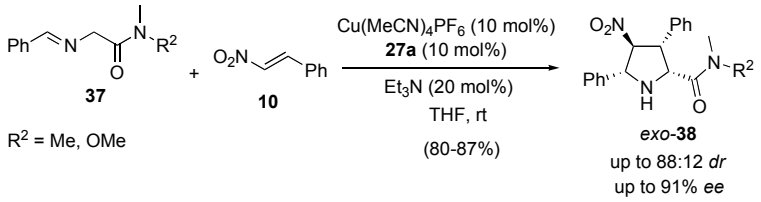
By contrast, ThioClickFerrophos **45** (5 mol%), rather than ClickFerrophos **44**(Fig. **5**), as ligand and AgOAc as salt (5 mol%) gave a complex that afforded the *endo*-cycloadduct **5** as major stereoisomer in poor yield (36%), low diastereoselection (65:35 *dr*) and good enantioselectivity (91% *ee*). The only difference with respect to the last example was the R^3 substituent of the starting imino ester **6** (4-ClC_6H_4 instead of Ph) (Scheme **15**) [72].

The same research group studied the reaction between benzophenone imine **34** and nitrostyrenes **10** (R^1 = Ar, Scheme **11b**). The *ent*-cycloadducts **36** were isolated as pure reaction product, or with some impurities derived from Michael type addition compounds (up to 99:1 cycle:open chain), when the reactions were carried out at room temperature in THF in the absence of base and using ThioClickFerrophos **40**·AgOAc chiral complex (5 mol%). The enantioselectivities of compounds *ent*-**36** were very high (up to 98%) [73].

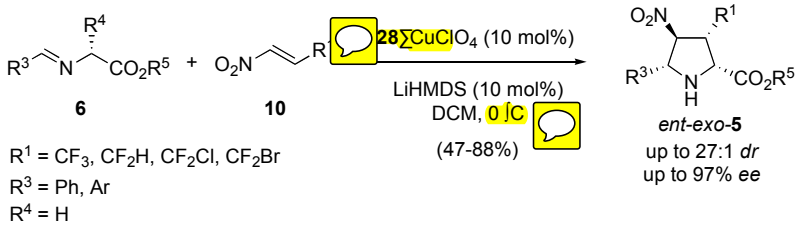
Privileged ligand Binap **46** (Fig. **5**) was also evaluated as complex with silver(I) salts and with gold(I) salts. Whilst the reaction shown in (Scheme **15**) completely failed in the presence of Binap **46**·AgTfa (Tfa = $CF_3CO_2^-$, 5 mol%), the reaction of imino ester **6** (R^3 = Ph, R^4 = H, R^5 = Me) and β-nitrostyrene **10** (R^1 = Ph) using triethylamine (10 mol%) in toluene at room temperature catalyzed by dimeric [(*S*)-Binap **46**·AuTfa]$_2$ (5 mol%) gave compound *exo*-**5** in 78% yield, 80:20 diastereomeric ratio and 70% *ee* [74].



Scheme 11.



Scheme 12.



Scheme 13.

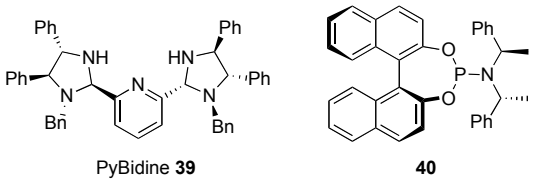


Fig. (3).

2.3. Nickel Chiral Metal Complexes as Catalysts

Another *exo*-selective 1,3-DC of imino esters with nitroalkenes has been described employing chiral ligand **47** (imidazoline-aminophenol scaffold, Fig. **6**) together with $Ni(OAc)_2$.The s[illegible]tion of this ligand obeyed to a previous screening of th[illegible]action employing solid-phase supported imidazoline-aminophenol·$(NiOAc)_2$ catalysts. Only glycine derived imino esters **6** (R^3 = Ar, R^4 = H, R^5 = Me) and nitroalkenes **10** (R^1 = Ar or alkyl) were essayed using 10 mol% of catalyst loading in the presence of potassium carbonate at -10 ºC in acetonitrile as solvent. Non conventional *exo'*-**5**cycloadducts [illegible]e obtained (corresponds with structure *endo*-**5** epimer[illegible] position, R^3 is in *trans*-relative position with respect to the nitro group, Scheme **16**) as major stereoisomers in good yields (64-99%), with variable diastereoselectivity (two or three stereoisomers could be identified) and high enantioselections (91-99% *ee*) [75].

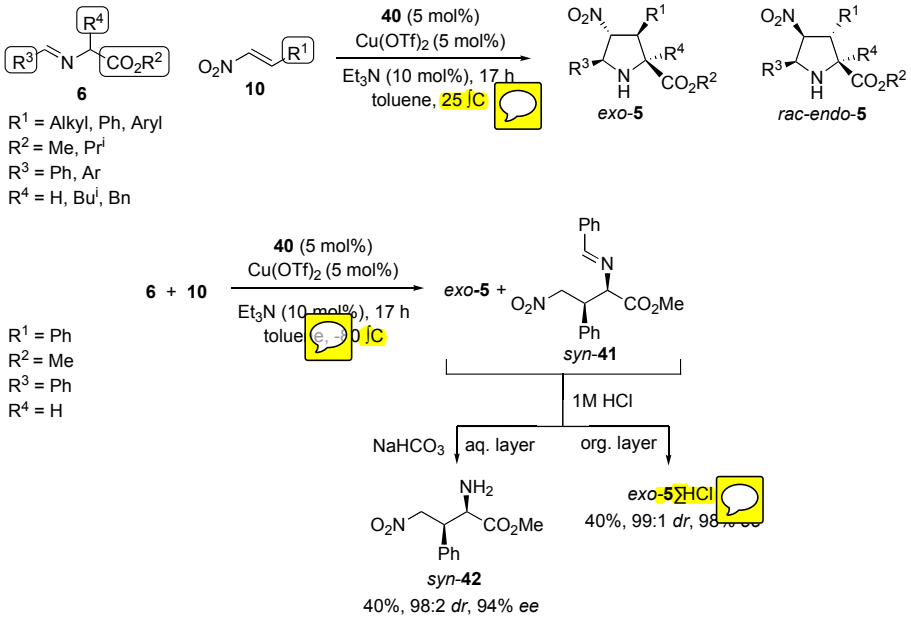
2.3. Chiral Organocatalysts

Asymmetric organocatalysis is a topic of great interest due to the conceptual importance and environmentally benign feature [76-79]. However, to date, the number of reported examples about organocatalytic 1,3-DC is very low in comparison with all those involving chiral Lewis acids [80-86]. Several chiral bifunctional organocatalysts bearing a tertiary amino group and a thiourea or a squaramide, able to form hydrogen bonding with the nitro group have been essayed (Fig. **7**). The original structural limitations and inconveniences found with an organocatalyzed cycloaddition (only aminomalonate derived 1,3-dipoles were employed, or the large amount of the organocatalysts required, etc.) have been overcome with the incorporation of new organic catalysts.

The first organocatalytic enantio- and diastereoselective 1,3-dipolar cycloaddition of azomethine ylides and nitroalkenes occurred in the presence of the organocatalyst **48** (Fig. **7**). The reaction of *tert*-butyl diphenylmethyleneaminoglycinate **34** and nitroalkenes **10** (R^1 = Ar, HetAr) was run in cyclohexane at 40 ºC and a catalyst loading of 10 mol% (Scheme **17**). Under these particular conditions, products *ent*-**36** were obtained as major stereoisomers (up to >99:1 *dr*), moderate to good yields (49-77%) and moderate enantioselection (46-65% *ee*) [87].

Thiourea **49** (Fig. **7**) (10 mol%) efficiently catalyzed the reaction of reactive imino esters **6** derived from diethyl aminomalonate (R^3 = Ar, R^4 = CO_2Et, R^5 = Et) and nitroalkenes **10** (R^1 = Ar, HetAr) in toluene at 0 ºC. The presence of 2,2,2-trifluorethanol (TFE) as additive would activate the imino group after a weak protonation of the nitrogen atom increasing the reaction rate[illegible] conversions. The resulting polysubstitutedpyrrolidines [illegible]were isolated between 52 and 86% yields, high diastereoselections (up to 98:2*dr*) [illegible]notable enantioselectivities (up to 92% *ee*) (Scheme **18**) [88].

A very interesting enantioselectively catalyzed multicomponent reaction successfully established a direct route to biologically important spiro[pyrrolidin-3,2'oxindole] scaffolds **54** (very similar to biologically active molecules **3**, Fig. **1**) with four contiguous stereogenic centers. Chiral squaramide **50** (5 mol%, Fig. **7**) in DCM at 40 ºC allowed the 1,3-DC of the *in situ* prepared imine from isatin derivative **52** and amine **53** with nitroalkenes **10** (R^1 = Ph, Ar). Yields of spirocycle **54** were good (58-77%) and also high diastereoselections (up to 10:1) and good enantiomeric excesses (up to 87% *ee*) were obtained (Scheme **19**) [89]. A plausible explanation of the activation for this, and for the organocatalyzed cycloadditions described before, starts from the double hydrogen bonding of the diamide with nitro group. Nucleophile can be also activated through a second interaction with the quinuclidine nucleus. The approach can also be facilitated by a presumed π-stacking interaction according to **II** (Scheme **19**).



Scheme 14.

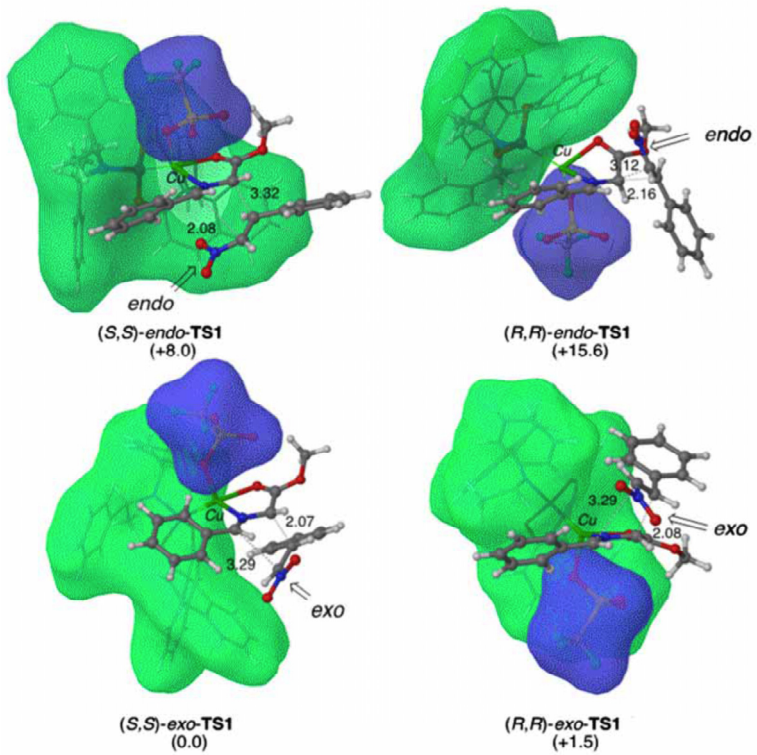


Fig. (4).

CONCLUSIONS

The increasing applications of nitro-substituted prolines in many scientific areas demand new and versatile methodologies to prepare them in optically enriched manner. Chiral metal complexes, acting as Lewis acids, are able to form the corresponding chiral metallodipole and induce high diastereo- and enantioselectivities. Non-racemic copper(I) or (II) complexes favor, in general, the generation of the *exo*-cycloadducts although it has been published examples where a switchable or tunable ligands allow the formation of the *endo*-isomer. Another metal cations, such as silver(I), gold(I) and nickel(II) coordinated to chiral ligands represent a low number of examples in the literature with different diastereoselections between them. Recently, asymmetric organocatalysis have been applied to this 1,3-DC but did not improve the general scope and versatility of the already mentioned metal catalysis. The general mechanism of this cycloaddition is not concerted such as it has been demonstrated in many contributions but takes place in a sequential 1,4-Michael type addition followed by an intramolecular Mannich cyclization.

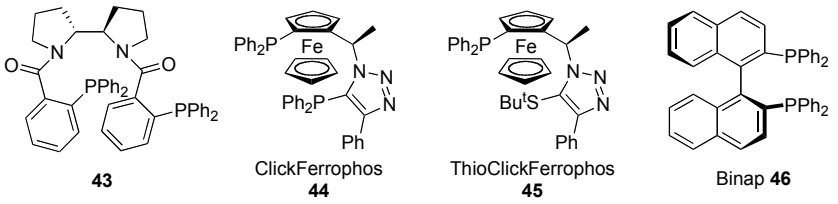
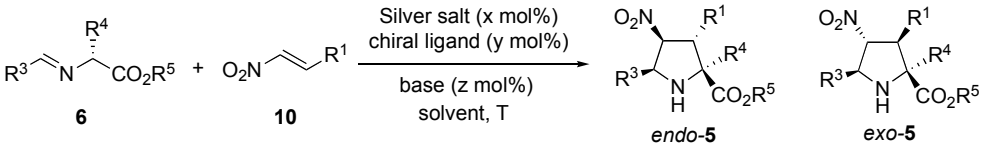


Fig. (5).



Scheme 15.

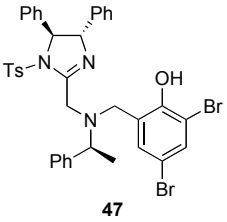
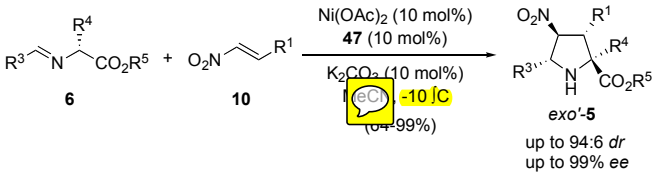


Fig. (6).



Scheme 16.

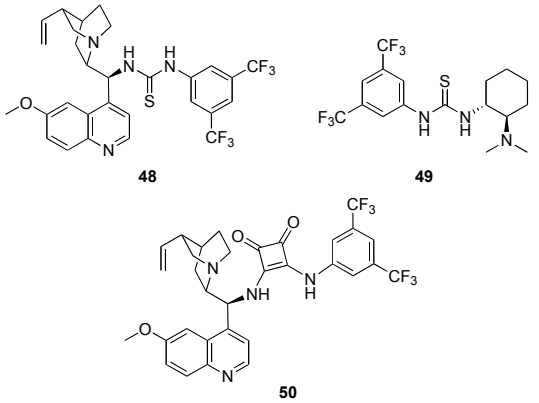
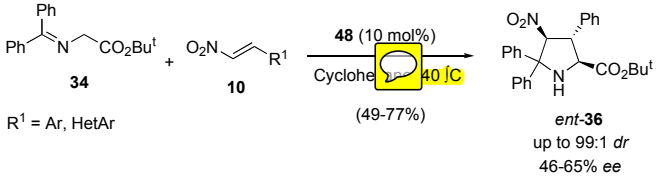
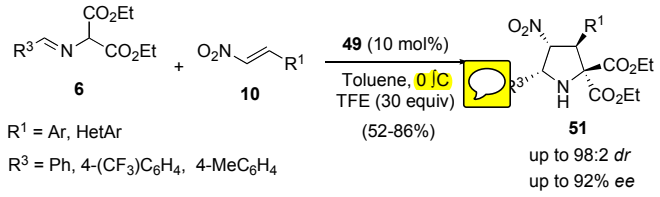


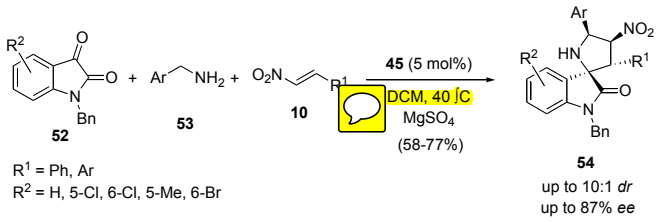
Fig. (7).

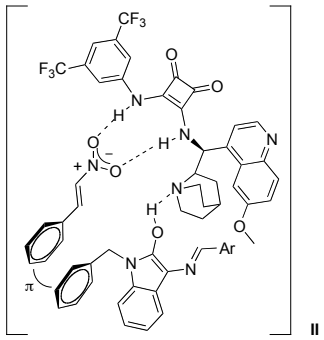


Scheme 17.



Scheme 18.





Scheme 19.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

This work has been supported by the Spanish Ministerio de Economía y Competitividad (MINECO) (Consolider INGENIO 2010 CSD2007-00006, CTQ2010-20387), FEDER, Generalitat Valenciana (PROMETEO/2009/039), and by the University of Alicante.

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Received: December 21, 2013 Revised: February 28, 2014 Accepted: February 28, 2014