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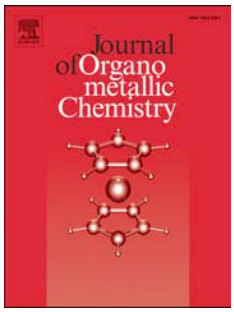

Coinage Metal Complexes as Chiral Catalysts for 1,3-Dipolar Cycloadditions

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GRAPHICAL ABSTRACT

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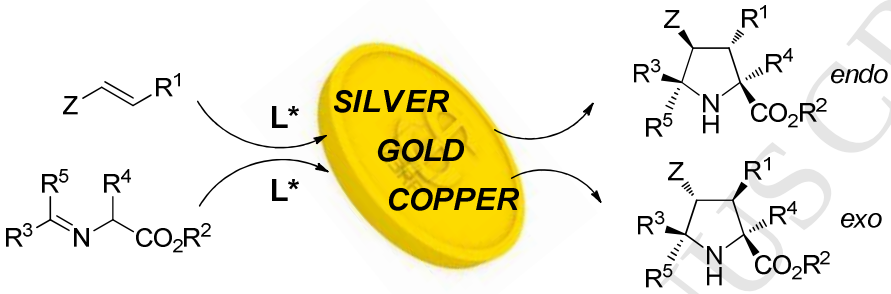

Coinage Metal Complexes as Chiral Catalysts for 1,3-Dipolar Cycloadditions

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Abstract

In this account, we describe the experience of our research group in the implementation of chiral coinage metal complexes into the efficient enantioselective 1,3-DC of azomethine ylides derived from α-amino acids and azlactones with different dipolarophiles. The corresponding chiral metallodipoles were generated *in situ* and next focused on the synthesis of highly substituted prolines. For this purpose, privileged ligands such as phosphoramidites and binap with silver(I), gold(I) and copper(II) salts are described. Depending from the ligand and mainly from the metal salt it can be possible to control the facial *endo/exo*-diasteroselectivity and the enantioselectivity of these types of processes. The synthetic processes are also supported by DFT calculations in order to elucidate the most plausible mechanism and the stereochemical results.

*Keywords:*Gold(I) complexes; Silver salts, Copper(II) triflate, Azomethine ylides, Prolines

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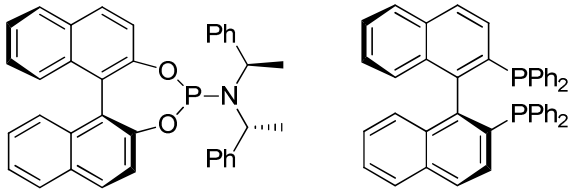
1. Introduction

Coinage metals as salts and complexes attract particular interest from many scientific areas [1,2]. In particular, they can be useful catalysts in synthetic organic chemistry for preparing the core of many important drugs containing heterocyclic structures [3]. Good chemoselectivity, good functional group compatibility, stability, are the main features of noble metal complexes which are crucial for application in complex molecular environments. One of the representative examples concerns the synthesis of enantiomerically enriched prolines [4,5,6] through the catalytic enantioselective 1,3-dipolar cycloadditions (1,3-DC) [7,8,9,10,11,12,13,14]between azomethine ylide and alkenes. In fact, silver and copper catalyzed 1,3-DC are very well known and constitute the most reliable, and direct enantioselective methodology to built up to four stereogenic centers of the resulting proline derivatives [6,15,16,17,18], in only one operation step. In addition, they exhibit more versatility and wider scope than the analogous enantioselective organocatalyzed 1,3-dipolar cycloadditions [19,20,21,22,23,24,25]. However, chiral gold complexes [26,27,28] have not so extensively employed and just a very efficient enantioselective cycloaddition of münchnones with electron-deficient alkenes has been described. In this transformation, followed by an ester/amide formation, Δ^1-pyrrolines were obtained in very high enantioselectivity [29].

In this account, we will describe the experience of our research group in the implementation of chiral coinage metal complexes into the efficient enantioselective 1,3-DC of azomethine ylides derived from α-amino acids with different dipolarophiles. The corresponding chiral metallodipoles were generated *in situ* and next focused on the synthesis of highly substituted prolines. For this purpose, privileged ligands [30] such as and (S_a,*R*,*R*)-phosphoramidite**1**(*R*)- or (*S*)-binap**2**and their enantiomers will be evaluated.

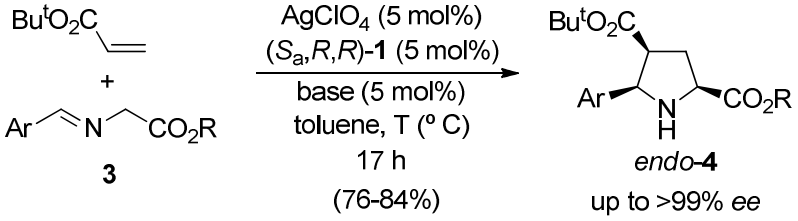


(S_a,*R*,*R*)-Phosphoramidite **1** (*S*)-Binap **2**

2. Silver-catalyzed 1,3-DC of azomethine ylides

Silver-catalyzed enantioselective 1,3-DCsof stabilized azomethine ylides have been demostrated to be very high diastereoselective processes affording mainly *endo*-cycloadducts. Since the pioneering works [31] of Zhang [32] and Jørgensen [33] many examples of chiral silver complexes have been documented [34,35,36,37,38,39] in this silver-mediated asymmetric cycloaddition. In general, chiral bidentate ligands such as bisphosphines, aminophosphines, sulfur-containing phosphines, bisoxazolines and diimines were used as chiral ligands, but not monodentate ligands were tested in this 1,3-DC [40].

Chiral monodentate phosphoramidites were chosen as ligands for silver(I) salts. These complexes were successfully used in the enantioselective 1,3-DC employing azomethine ylides and electrophilic alkenes [41,42]. The new 1:1 and 2:1 complexes of $AgClO_4$ and phosphoramidite (S_a,*R*,*R*)-**1** could be characterized by single crystal X-ray crystallographic diffraction and were tested in the enantioselective 1,3-DC obtaining excelent results when employing the equimolar mixture. The reaction between imino esters **3** derived from glycine (R^1 = H) and *tert*-butyl acrylate occurred at 0 or -20 ºC in the presence of a 5 mol% of (S_a,*R*,*R*)-**1**·$AgClO_4$ complex, giving good yields and very high enantioselections of the exclusive *endo*-cycloadduct **4** (Scheme 1). However, the catalyst formed by 2 equivalents of silver(I) perchlorate and 1 equivalent of chiral ligand gave very poor enantioselections in cycloadducts **4**. The employment of the enantiomeric form of the chiral ligand (R_a,*S*,*S*)-**1** furnished in identical chemical yield, diastereo- and enantioselectivity*ent-endo*-**4**.



Scheme 1

Different dipolarophiles were allowed to react with benzylideneglycine methyl ester modifying the temperature and the base. Triethylamine was the more appropriate base working at -20 ºC with diisopropyl fumarate and chalcone as dipolarophiles (Figure 1, compounds **5** and **7** respectively), but DABCO was a more effective base than triethylamine, at room temperature, in those reactions involving maleimides (for example see Figure 1, compound **6a**). In the case of α-substituted imino esters the reaction with *tert*-butyl acrylate , *N*-methylmaleimide, and chalcone, took place at room temperature giving cycloadducts **8**-**10** in moderate to excellent *ee*'s (Figure 1). These results reflected that a possible steric hindrance at this position of the dipole, which could avoid a perfect enantiodiscrimination in the transition state.

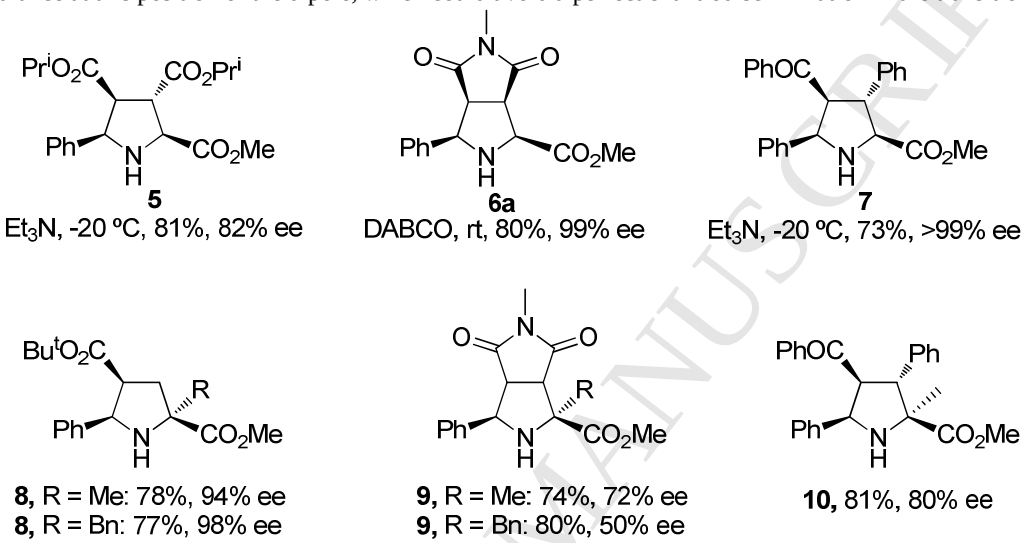


Figure 1

Concerning the most favored transition state the two possible *endo*-**TS1** saddle points were much closer in energy. **TS1-SSR** was calculated to be 1.31 kcal/mol lower in energy than **TS1-RRS**. However, a large energy gap was obtained for **TS1-SRR**(Figure 2). It is observed that the dihedral angle formed by the two naphthyl groups is of *ca.* 57-58 deg. In the case of **TS1-SSR**, this lead to the blockage of the *Re-Si* face of the dipole (Figure 4). These calculations were in good agreement with the experimental results and also support that the whole process occurred through a stepwise mechanism [42].

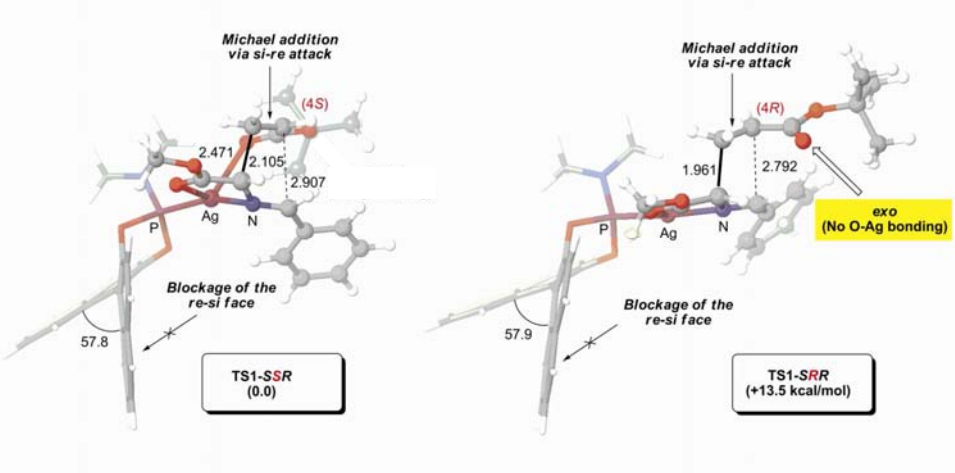
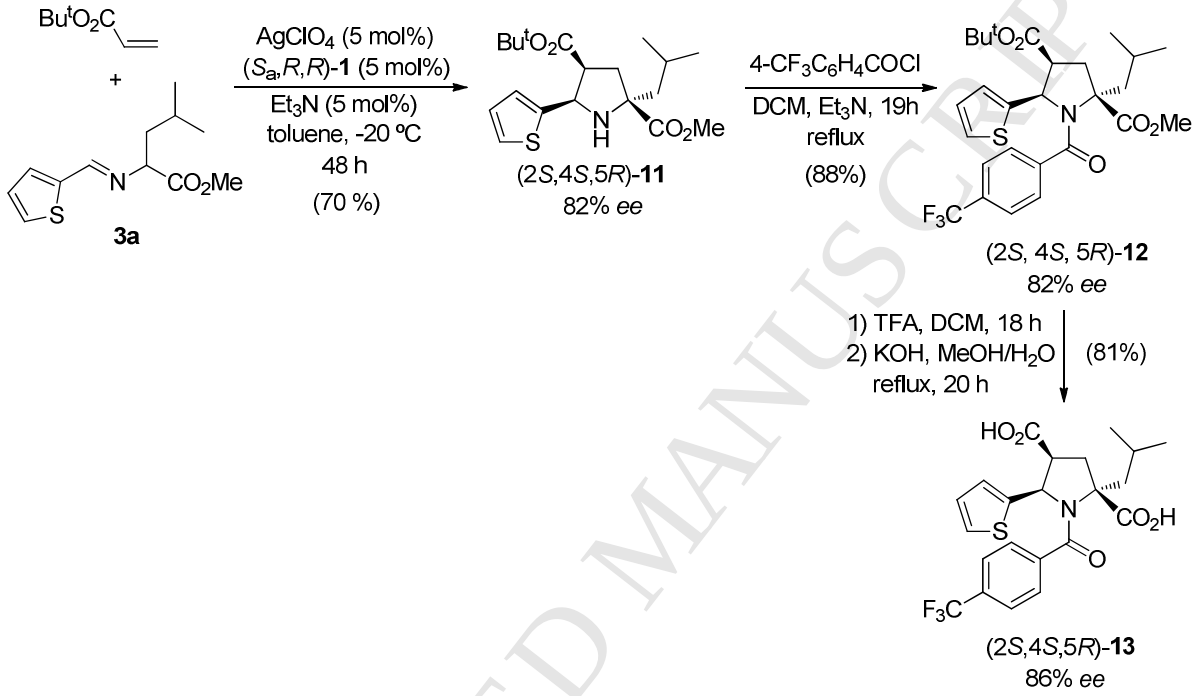


Figure 2. Chief geometric features saddle relative energies (in kcal/mol) of the two transition structures associated with the first step in the reaction between *t*-butyl acrylate and complex formed by (S_a)-Monophos and imine **3aa**. Bond distances and angles are given in Å and deg, respectively. These fully optimized structures were computed at the

B3LYP/LanL2DZ&6-31G* level. The energies were computed at the B3LYP/ LanL2DZ &6-31G*+ΔZPVE level of theory

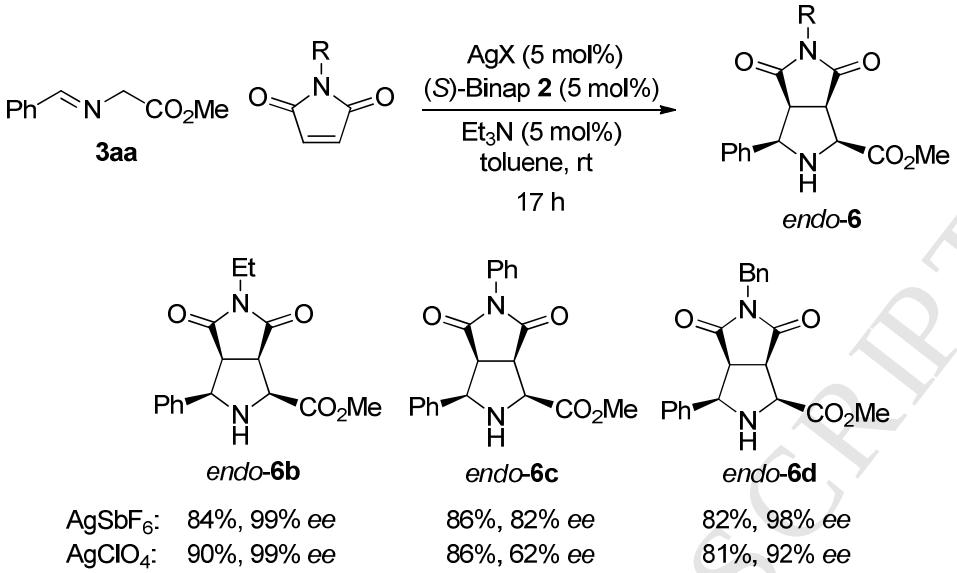
It has been demonstrated that enantiomerically pure proline derivative **11** is the key precursor to a series of antiviral agents inhibitors of the hepatitis C virus (HCV) polymerase [18,43,44] such as prolinamide**13** [45,46]. The intermediate prolinamide**12** was synthesized in 88% yield (estimated by ^{1}H NMR) from enantiomerically enriched **11** by a simple amidation reaction with 4-(trifluoromethyl)benzoyl chloride in refluxing dichloromethane during 19 h. After subsequent hydrolysis, the resulting dicarboxylic acid **13**(a first generation GSK-antiviral agent) was finally obtained in 81% yield (50% overall yield from iminoester**11**) in 86% *ee* (Scheme 2).



Scheme 2

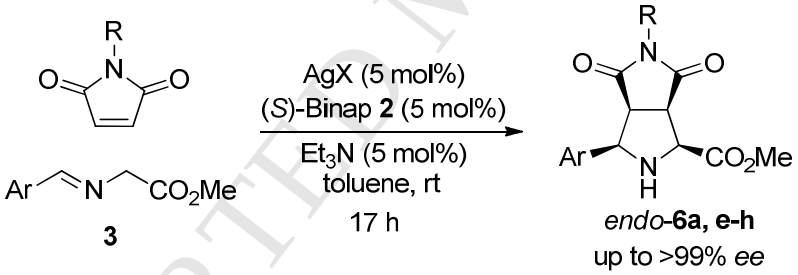
This type of phosphoramidite-silver complexes opened new perspectives in this and other reactions because is capable to perform cycloadditions involving sterically hindered components with moderate enantioselections, the fine-tuning being achieved by modification of the temperature, base and ester substituent. Besides, the catalytic complex could not be recovered and reused in additional catalytic processes. An interesting alternative solution to these problems was found in parallel studies carried out with another privileged ligand such as chiral binap **2** [47,48,49,50].

The first attempt reported using a 3 mol% of (S_a)-Binap **2** and AgOAc and Et_3N as base gave very poor results of the 1,3-DC of azomethine ylides with dimethyl maleate was described in 2002 by Zhang and co-workers [32]. However, our results of 1,3-DC between imino esters and *N*-methylmaleimide (NMM) catalyzed by 1:1 molar ratio of (S_a)-Binap **2**·$AgClO_4$(5 mol%) [51], were excellent in terms of both diastereo- and enantioselectivity (>98:2 *endo/exo* ratio and 99% *ee*). The easy separation of the silver complex (S_a)-Binap **2** ·$AgClO_4$ [52] was a very important feature to apply in a larger scale process. So, a series of cycles (up to five) were run employing the same catalytic mixture, which was recovered and reused without any additional purification giving pyrrolidine*endo*-**6a** in excellent enantioselections. Due to the reluctance to operate with perchlorate salts by chemists, other silver salts were essayed, silver hexafluoroantimonate being the more suitable substitute, but the corresponding chiral complex could not be recovered after reaction completion. The first comparison was done in the 1,3-DC between imino ester **3aa** and maleimides. The presence of bulkier substituents in the maleimide (phenyl or benzyl groups) was more tolerated by the hexafluoroantimonate complex due possibly to its less coordinative character. Cycloadducts *endo*-**6** were obtained in good chemical yields and higher enantioselections than the corresponding ones generated by intermediacy of silver perchlorate [47,48].



Scheme 3

The comparative study of the aryl substituent in the imino group was also carried out (Scheme 4 and Table 1). In general, chemical yields were almost identical to each other but the highest enantioselections were achieved by using (S_a)-Binap **2**·$AgSbF_6$ complex. The biggest difference was noticed in the examples run with imino esters bearing hindered *ortho*-substituted aryl imines, with 4-methoxyphenyl imino group and with *N*-phenylmaleimide (NPM) (Table 1, Scheme 4) [47,48].



Scheme 4

Table 1

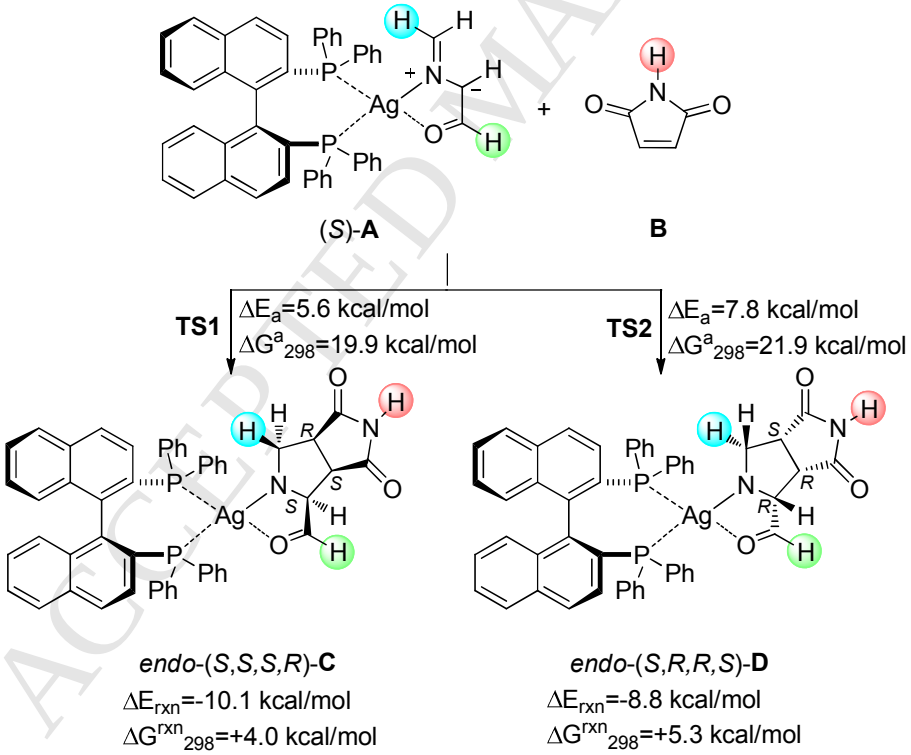
Comparative study of 1,3-DC of glycine derived imino esters **3** and maleimides using (*S*)-Binap **2**·$AgSbF_6$ or (*S*)-Binap **2**·$AgClO_4$ complexes.

			Product *endo*-**6**		
Ar	R	AgX	Yield (%)	*endo*:*exo*	ee_{endo} (%)
Ph	Me	$AgSbF_6$	90	>98:2	99
Ph	Me	$AgClO_4$	90	>98:2	99
2-$CH_3C_6H_4$	Me	$AgSbF_6$	85	98:2	99
2-$CH_3C_6H_4$	Me	$AgClO_4$	85	95:5	70
2-ClC_6H_4	Me	$AgSbF_6$	82	>98:2	99
2-ClC_6H_4	Me	$AgClO_4$	82	>98:2	85

4-(MeO)C_6H_4	Me	$AgSbF_6$	85	>98:2	99
4-(MeO)C_6H_4	Me	$AgClO_4$	82	>98:2	80
Ph	Ph	$AgSbF_6$	86	>98:2	82
Ph	Ph	$AgClO_4$	86	>98:2	62

DFT calculations performed onto a reduced iminoglycinate model (Scheme 5 and Figure 3) revealed, as expected, that both **TS1** and **TS2** are quite asynchronous, **TS1** being ca. 2 kcal/mol more stable than **TS2**. In this latter transition structure there was an appreciable steric clash between one of the phenyl groups of the phosphine moiety and the dipolarophile **B**. As a result, exclusive formation of *endo*-(*S*,*S*,*S*,*R*)-**C** was predicted, in full agreement with the experimentally observed formation of cycloadducts *endo* described across the text. The same trend was found for the cycloadducts *endo*-(*S*,*S*,*S*,*R*)-**C** and *endo*-(*S*,*R*,*R*,*S*)-**D**, the latter being ca. 1.3 kcal/mol less stable than the former. Moreover, the slightly positive values of the Gibbs reaction energies associated with the formation of these catalyst-bound cycloadducts were compatible with the catalyst turnover since there was no inhibition of the catalyst by the product of the cycloaddition step [48].

Calculations also located and characterized the four possible transition *endo/exo* structures. The less energetic saddle points are those that exhibit the *t*-butoxycarboxyl group in an *endo*-relationship with respect to the phenyl group of **4aa**. Both **TS1-SRR** and **TS1-RSS** lack the highly stabilizing bonding interaction between the *tert*-butoxycarbonyl moiety and the metallic centre. As a consequence, these transition structures are *ca.* 10 kcal/mol less stable than their *endo*-analogues. These calculations support that NMM is the best dipolarophile due to the coordination of the nitrogen atom to the metal centre. On the other hand, the presence of a bulkier substituent in this nitrogen atom blocks the *endo*-approach reducing the enantioselectivity, such as occurred with NPM [48].



Scheme 5. Model reaction used in the computational studies. The hydrogen atoms highlighted in blue, green and red correspond to a phenyl, a methoxy and a methyl group, respectively.

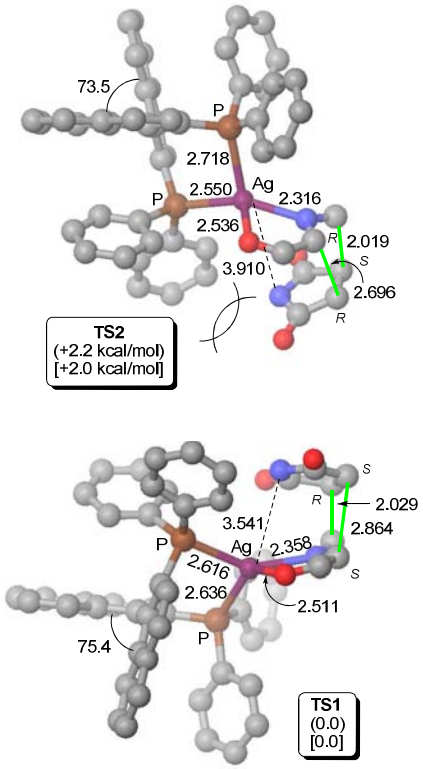
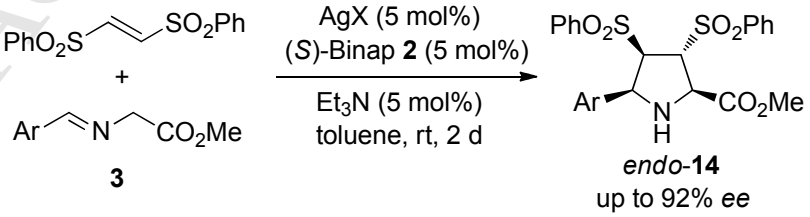


Figure 3. Fully optimized structure (B3LYP/LANL2DZ&6-31G* level) of **TS1** and **TS2**, leading to *endo*-(*S,S,R*)-**C** and *endo*-(*S,R,R,S*)-**D**, respectively. The hydrogen atoms have been omitted for clarity. Bond distances and dihedrals are given in Å and deg., respectively. Numbers in parentheses and in square brackets are the relative total and Gibbs free energies respectively, computed at the B3LYP/LANL2DZ&6-31G*+ΔZPVE level.

Methyl *N*-arylideneglycinates **3** also reacted with 1,2-bis(phenylsulfonyl)ethylene (BPSE) under the standard reaction conditions catalyzed by (S_a)-Binap **2**·$AgSbF_6$ or (S_a)-Binap **2**·$AgClO_4$ complexes (Scheme 6 and Table 2). This acetylene equivalent afforded *endo*-cycloadducts as major compounds in good yields and high diastereo- and enantioselections. (S_a)-Binap **2**·$AgSbF_6$ resulted to be the most efficient catalytic system, which improved the enantiodiscrimination exhibited by the analogous transformations run with (S_a)-Binap **2**·$AgClO_4$ complex (Table 2) [50].



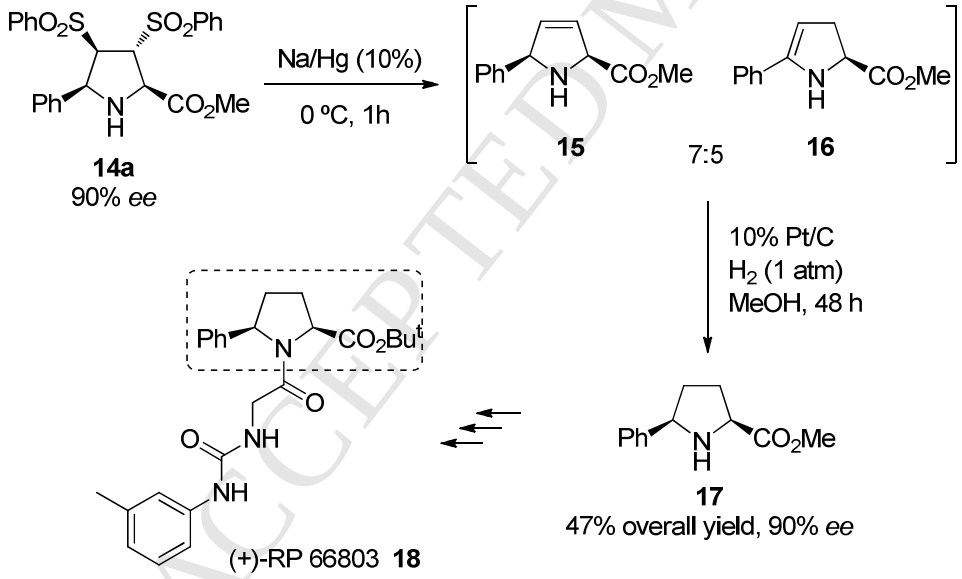
Scheme 6

Table 2

Comparative study of 1,3-DC of glycine derived imino esters **3** and maleimides using (S_a)-Binap **2**·$AgSbF_6$ or (S_a)-Binap **2**·$AgClO_4$ complexes.

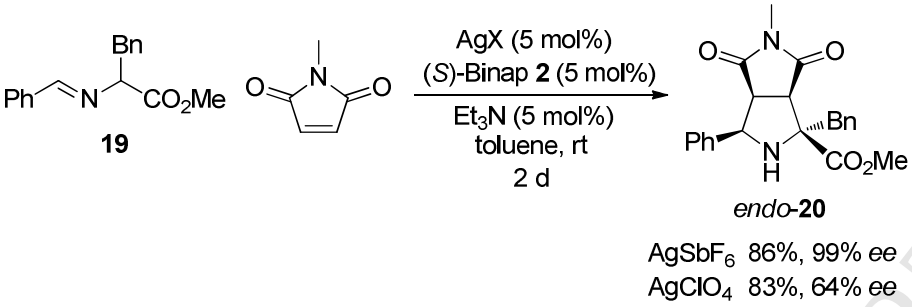
		Product *endo*-**14**		
Ar	AgX	Yield. (%)	*endo*:*exo*	ee_{endo} (%)
Ph	$AgSbF_6$	91	>98:2	90
Ph	$AgClO_4$	80	>98:2	88
4-$CH_3C_6H_4$	$AgSbF_6$	91	>98:2	88
4-$CH_3C_6H_4$	$AgClO_4$	85	95:5	28
3-Pyridyl	$AgSbF_6$	83	>98:2	93
3-Pyridyl	$AgClO_4$	82	>98:2	78
2-Naphthyl	$AgSbF_6$	91	>98:2	82
2-Naphthyl	$AgClO_4$	88	>98:2	80

The cycloaddition with BPSE [53] was applied to the enantioselective synthesis of compound **17,**which is a key intermediate in the total synthesis of bioactive nonpeptide cholecystokinin antagonist (+)-RP 66803 **18** [54]. The synthesis of the 5-phenylprolinate fragment was performed according to the route described in Scheme 7. Isomers **15** and **16**were obtained after desulfonylation with 10% sodium amalgam in MeOH/THF and the crude mixture, without purification, was submitted to hydrogenation with Pt/C (10%). The enantiomeric excess of prolinate**17** remained unaltered with respect to the starting disulfonylatedheterocycle**14a**, being 47% the overall yield of **17** (Scheme 7) [50].



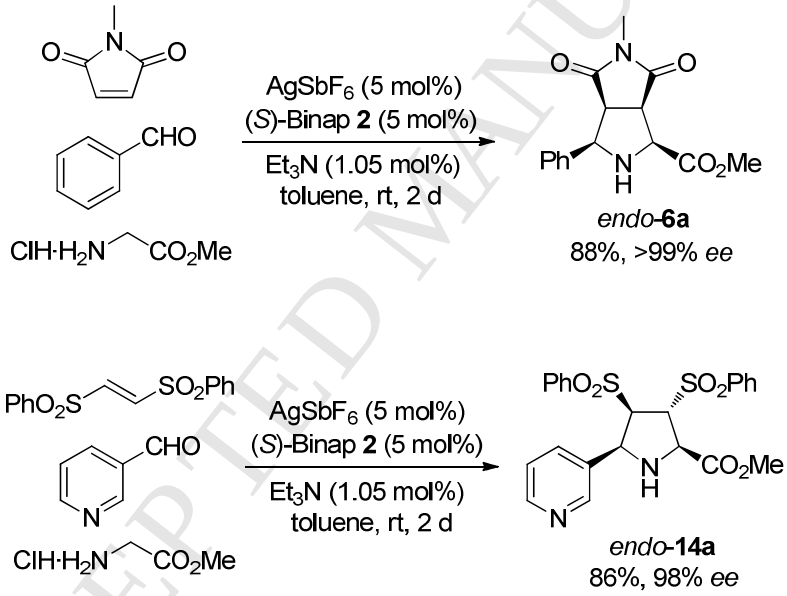
Scheme 7

α-Substituted α-imino esters were tested in both silver-catalyzed 1,3-DC. As representative example, phenylalaninate **19** was allowed to react with NMM under the typical reaction conditions taking 48 h to reach complete conversions (Scheme 8). Cycloadduct *endo*-**20** was obtained in good yields when both chiral catalysts were used, but the enantioselectivity achieved by (S_a)-Binap-$AgSbF_6$ was noticeably higher. This was another evidence of the facility of the hexafluoroantimonate salt to perform cycloadditions with sterically hindered components [50].



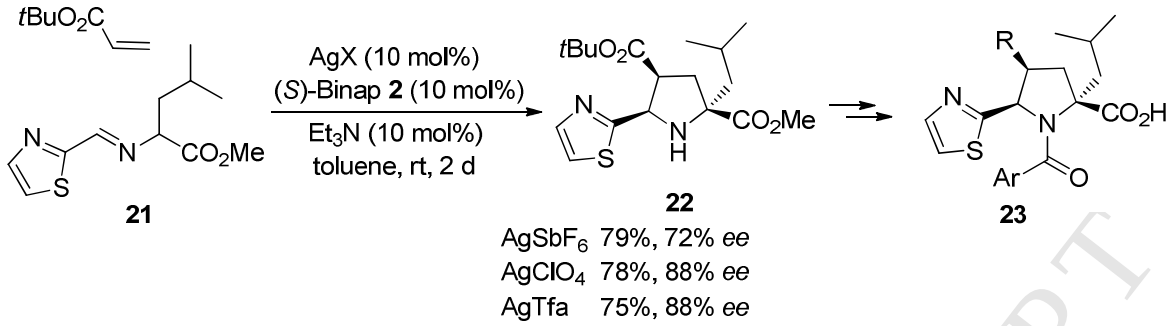
Scheme 8

An unexpected and selective result was detected in the multicomponent 1,3-DC version. Benzaldehyde/NMM or 3-pyridinecarbaldehyde/disulfone, glycine methyl ester hydrochloride, triethylamine (1.05 equiv), (*S*)-Binap**2**·$AgSbF_6$ (5 mol%), were put together in toluene and the resulting mixture was allowed to react at 25 ºC for 48 h. The results obtained for compound *endo*-**6a** or *endo*-**14a**were impressive 88% yield, >99% *ee*, or 86% yield, 98% *ee*, respectively, (Scheme 9). However, analogous reactions carried out in the presence of (*S*)-Binap**2**·$AgClO_4$ complex failed. This was the first occasion that a three-component transformation is enantioselectively performed in the presence of a chiral Lewis acid [50].



Scheme 9

Despite the low enantioselections registered in the reaction performed between imino ester **3aa** and acrylates [up to 30% *ee* with (*S*)-Binap**2**·$AgSbF_6$, and up to 36% *ee* with (*S*)-Binap**2**·$AgClO_4$], the 1,3-DC of the heterocyclic imino ester **21** and *tert*-butyl acrylate was attempted (Scheme 10). Such as it has been reported in previous works by our group, molecule **22** is the key intermediate in the elaboration of 2nd generation GSK inhibitors of the virus causing hepatitis C of the type **23** [55]. When $AgClO_4$, $AgSbF_6$, and AgTfa were tested, unexpectedly, the reactions afforded good chemical yields at 25 ºC, for 48 h and with high enantioselections, especially for the reaction carried out with silver perchlorate (88% *ee*) [50].



Scheme 10

3. Gold-catalyzed 1,3-DC of azomethine ylides

The sensitivity to the presence of bulky substituents in both components (dipole and dipolarophile) of the 1,3-DC observed in some examples described in the previous section encouraged our group to check another cationic metal with different coordinative features. Very close to silver in the periodic table is gold. Gold-catalyzed transformations employing mild reaction conditions appeared during the last twelve years [26,27,28]. Initially, coordination arrangements of chiral gold complexes avoided high enantiodiscriminations but, recently, it has been demonstrated that chiral bis-gold complexes type **24** (Figure 4) are very efficient in asymmetric catalysis [56,57]. However, classical 1,3-dipolar cycloaddition of iminoesters and electrophilic olefins was not described using gold complexes. Only Toste´s group published an efficient 1,3-DC employing alanine, phenylalanine and allylglycine derived azlactones with maleimides and acrylates in the presence of dimetallic type **24** (*S*)-Cy-Segphos $(AuOBz)_2$ complex as catalyst (2 mol%) in the absence of base [29,58].

The gold(I) cation has only two coordination sites and its linear geometry makes asymmetric catalysis extremely difficult [[59]]. Fortunately, a key to the successful enantioselecive gold(I)-catalyzed 1,3-DC of imino esters **3** and alkenes by our group was the identification of enantiomerically pure bis(gold)-chiral diphosphine complexes of the form $[(AuX)_2(P\text{-}P)^*]$ as catalysts for enantioselective transformations. A clear and recent example of the isolation, identification, and characterization of two chiral Binap-gold(I) complexes **25** and **26**, bearing trifluoroacetate as counteranion, have been reported by Puddephatt *et al.*[60].

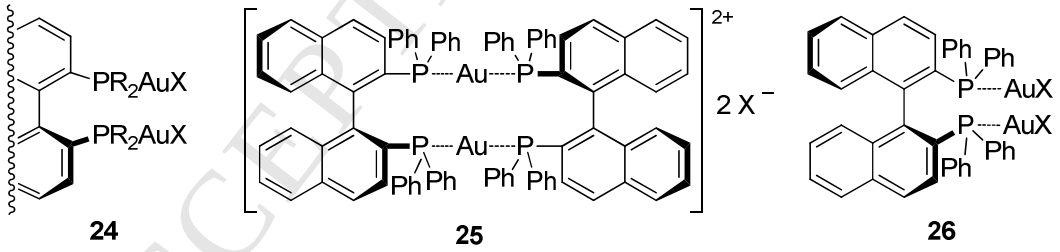
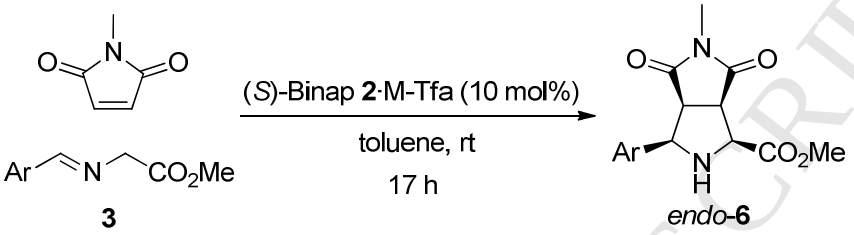


Figure 4

These cationic complexes bearing different counter anions (X) were prepared according the literature (above) and tested in the catalytic enantioselective 1,3-DC of the imino ester **3a** (Ar = Ph) and NMM in toluene at rt (Scheme 11), Tfa derived complex being the most effective in terms of both diastereo- and enantioselections [61,62]. Whilst the reaction catalyzed by dimeric complex **25** (X = Tfa) took place with an excellent enantioselection, a racemic cycloadduct was isolated when catalytic chiral dimetallic complex **26** (X = Tfa) was used instead.

The scope of this reaction was surveyed by modifying the arylidene moiety of the imino ester and compared with the results obtained in the analogous reactions performed with chiral (*S*)-Binap**2**·AgTfa (Scheme 11 and Table 3). Thus, the difference of reactivity between the two metals was more evident, especially when bulky substituents were present in whatever of the two reaction components. The first detail to notice is the evolution of the reaction without an added base. The weak basicity of the Tfa anion was enough to promote by itself the cycloadditions in toluene at rt for 16 h.

The dipole precursors containing an *ortho*-substituent in the aryl moiety, were appropriate sterically hindered starters in the gold(I)-catalyzed 1,3-DC with NMM affording *endo*-compounds with high *ee* (Scheme 11, and Table 3). In both examples the resulting enantioselections induced with the corresponding chiral silver(I) complex were clearly lower. The *para*-substituted methyl iminoglycinate underwent the gold(I) and the silver(I)- mediated 1,3-DC obtaining identical both chemical yields and enantioselections (Table 3). Nevertheless, the reaction dealing with 2-naphthyl derived precursor was much more efficient by using chiral silver(I) catalyst rather than chiral gold(I) complex. This reaction completely failed when chiral phosphoramidite (S_a,*R*,*R*)-phosphoramidite **1**·gold(I) complexes acted as catalysts [62].



Scheme 11

Table 3

Comparative study of 1,3-DC of glycine derived imino esters **3** and NMM using (S_a)-Binap **2**·M-Tfa complexes.

		Product *endo*-**6**		
Ar	M	Yield. (%)	*endo*:*exo*	ee_{endo} (%)
2-$CH_3C_6H_4$	Ag	90	>98:2	70
2-$CH_3C_6H_4$	Au	86	>98:2	88
2-ClC_6H_4	Ag	92	>98:2	85
2-ClC_6H_4	Au	88	>98:2	99
4-$(CH_3O)C_6H_4$	Ag	99	>98:2	99
4-$(CH_3O)C_6H_4$	Au	95	>98:2	99
2-Naphthyl	Ag	99	>98:2	99
2-Naphthyl	Au	94	>98:2	91

The observed strong positive NLE in the reaction of iminoester **3a** (R = Ph) with NMM employing different enantiomeric purity of the catalytic chiral complex **25** (X = TFA) was, presumably originated by a generation of a reservoir of unproductive non-chiral heterodimer complex [63] increasing the concentration of the chiral catalytic active species in solution. It was calculated the geometries of the most stable (S)-Binap–silver(I) or –gold(I) ylide **I** reactive complexes (Figure 5). As expected, in the case of the silver complex (Figure 5A), the metallic centre adopted a tetrahedral environment. This Ag^I centre was surrounded by both phosphorous atoms of the ligand and by the nitrogen and oxygen atoms of the ylide (Figure 5A). Due to this coordination pattern, the proximity of the chiral ligand and the prochiral faces allows an efficient stereoselction, only the (2*Si*,5*Re*) face of the ylide can react. This was in good agreement with the experimental evidence of the major formation of the (*S*,*S*,*S*,*R*) cycloadducts [62].In the case of monomeric (S_a)-Binap-Au-ylide**I** complex (Figure 5B), the gold atom presented a linear coordination and it was surrounded only by one phosphorous atom of the ligand and the nitrogen atom of the ylide. In this case, the carboxy-gold distance is *c.a.* 0.3 Å larger than the carboxy-silver distance as one may expect from the known low oxophilicity of the gold(I) cation. This geometry made the two prochiral faces approximately equivalent. Therefore, no significant enantioselection should be expected in the [3+2] reaction [62].

We also considered the existence of (S_a)-Binap-Au dimeric units as the actual catalytic complex (Figures 5B and 5C). Under these conditions only two significant conformations were energetically accessible. In $[(S_a)$-Binap-$Au]_2$-ylide-**I** only the (2*Si*,5*Re*) face is accessible. By contrast, in $[(S_a)$-Binap-$Au]_2$-ylide-**I-b** the accessible face is the opposite one [named (2*Re*,5*Si*)]. *endo*-Saddle points corresponding to the reaction of the dipolarophile through the

hindered (2*Re*,5*Si*) face of ylide [(S_a)-BinapAu]$_2$-**I** are of much lower energy (6 kcal mol^{-1}) than the obtained from suprafacial approach through (2*Si*,5*Re*) of ylide [(S_a)-BinapAu]$_2$- **I-b** in solution at room temperature [62].

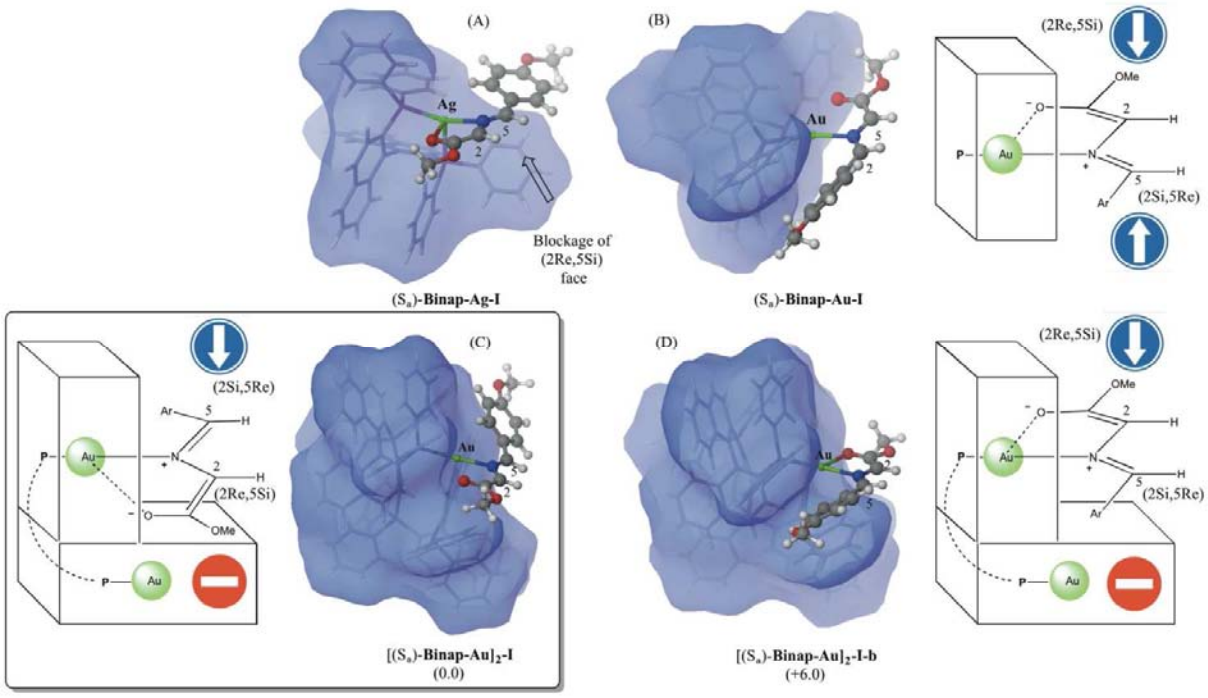
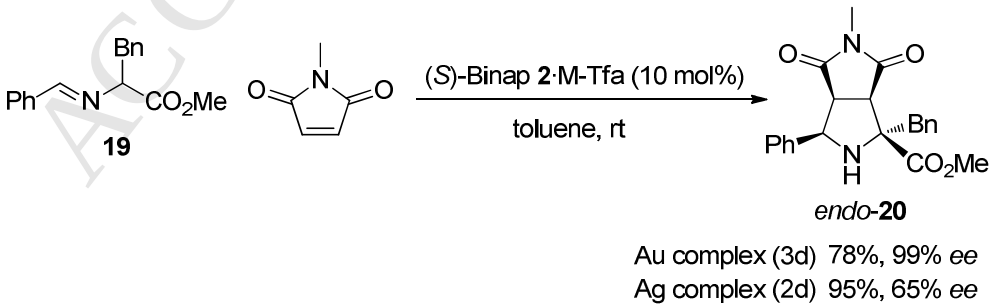


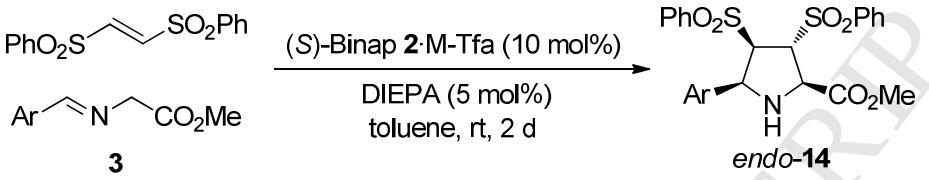
Figure 5. Geometry of the most stable (S_a)-BinapAg(I) or Au(I) complexes computed at ONIOM(B3LYP/LanL2DZ:UFF) level of theory. The B3LYP/LanL2DZ and UFF levels in the ONIOM calculation are depicted in ball & stick and tube representations respectively. Number in parentheses correspond to the relative Gibbs free energies at 298K and are given in kcal mol^{-1}. Surfaces represent e solvent accessible surface with a probe radius of 1.9 Å. For panels (B), (C) and (D) a schematic cartoon of the possible stereochemical course of the corresponding (3+2) cycloaddition is also displayed.

The insertion of a substituent at the α position of the 1,3-dipole precursor was evaluated. When methyl benzylidenephenylalaninate **19** was allowed to react with NMM under the previously shown reaction conditions, the reaction performed with the gold(I) complex needed 24 h more than the corresponding reaction that used the analogous silver(I) complex to achieve almost total conversion (Scheme 12). Besides, enantioselectivity achieved by the [(*S*)-Binap**2**–AuTfa)]$_2$ complex(99% *ee*) was higher than that obtained by using silver catalyst (65% *ee*) (Scheme 12). The *endo*-diastereoselectivity (>98:2) was determined in both examples.



Scheme 12

Such as it was mentioned in section 2, BPSE was another interesting dipolarophile to evaluate. The reaction, performed with 5 mol % of the dimeric gold(I) **25** (X = TFA) catalyst, afforded cycloadducts **14** in the absence or in the presence of diisopropylethylamine (DIPEA) (10 mol%) as base. In general, the reaction products were diastereoselectively obtained with both chiral catalysts, whilst a lower or equal enantiomeric excess were obtained when (S_a)-Binap **2**-AgTfa was used as catalyst. Better results were obtained in the absence of base (Scheme 13, Table 4) [61,62].



Scheme 13

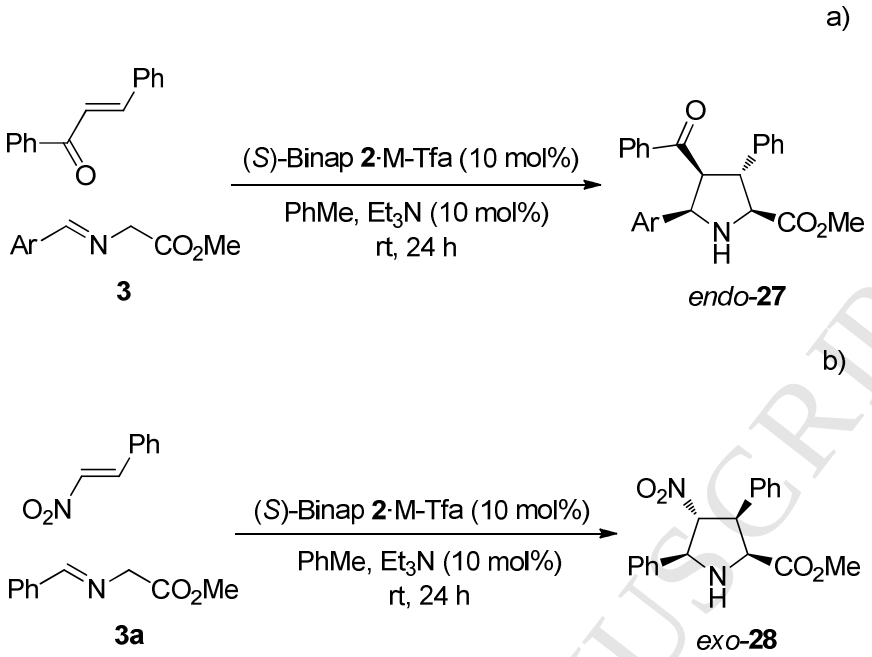
Table 4

Comparative study of 1,3-DC of glycine derived imino esters **3** and BPSE using (S_a)-Binap **2**·M-Tfa complexes.

		Product *endo*-**14**		
Ar	M	Yield. (%)	*endo*:*exo*	ee_{endo} (%)
Ph	Ag	80 (81)	>98:2	86 (96)
Ph	Au	81 (74)	>98:2	80 (99)
4-$CH_3C_6H_4$	Ag	90 (75)	>98:2	96 (96)
4-$CH_3C_6H_4$	Au	91 (67)	>98:2	88 (99)
3-Pyridyl	Ag	70 (70)	>98:2	92 (96)
3-Pyridyl	Au	73 (73)	>98:2	96 (96)

In brackets results obtained without DIPEA.

Another appropriate dipolarophiles for this enantioselective catalyzed 1,3-DC of azomethine ylides resulted to be chalcone and β-nitrostyrene. As well as occurred in the 1,3-DC catalyzed by chiral phosphoramidites and silver perchlorate, chalcones reacted efficently affording exclusively very clean *en*do-cycloadducts**27** after 24 h, at room temperature and in the presence of Et_3N (10 ml%) as base. The most important difference consisted of the enantioselection achieved. Whilst chiral dimeric gold catalyst furnished very high *ee* of *endo*-product **27**, silver complex gave always lower enantiodiscriminations (Scheme 14a, and Table 5). The reaction between iminoester**3a** and β-nitrostyrene afforded very complex mixtures of diastereoisomers when chiral silver complex was employed. However, very clean crude reaction products were obtained when dimeric [(*S*)-Binap **2**-AuTFA]$_2$ was used (Scheme 14b, and Table 5). The diastereoselectivity was not as high as usual, with 20:80 *endo*:*exo* mixtures of **28** formed despite of runnig the reaction at ⁻20 ºC. The lowering of the temperature in the reactions involving chalcone or β-nitrostyrene did not improve the enantioselectivity furnished at room temperature [61,62].



Scheme 14

Table 5

Comparative study of 1,3-DC of glycine derived imino esters **3** and chalcone or β-nitrostyrene as dipolarophiles using (S_a)-Binap **2**·M-Tfa complexes.

			Product *endo*-**27**		
Dipolarophile	M	Ar	Yield. (%)	*endo*:*exo*	ee_{endo} (%)
Chalcone	Ag	Ph	80	>98:2	20
	Au	Ph	95	>98:2	80
	Ag	4-$CH_3C_6H_4$	80	>98:2	74
	Au	4-$CH_3C_6H_4$	80	>98:2	80
	Ag	2-Naphthyl	81	>98:2	50
	Au	2-Naphthyl	90	>98:2	60
			Product *endo*-**28**		
Dipolarophile	M	Ar	Yield. (%)	*endo*:*exo*	ee_{exo} (%)
Nitrostyrene	Ag	Ph	—	—	—
	Au	Ph	78	20:80	70
	Ag[a]	Ph	—	—	—
	Au[a]	Ph	77	20:80	60

[a]Reaction performed at -20 ºC

Turning back to the enantioselective synthesis of intermediate compounds in the synthesis of hepatitis C virus (HCV) inhibitors (compound **13** was already isolated in Scheme 2), compound **22**, direct precursor of 2nd generation GSK-antiviral agents (Figure 6), was obtained in 88%*ee* (Scheme 10). So and additional effort was dedicated in order to increase the enantioselection of the process [44,64].Triethylamine promoted the reaction affording good yield and important enantioselection for whatever silver(I) salt essayed. However, [(*S*)-Binap**2**·AuTfa]$_2$ was able to provide a 78% *ee* at room temperature. Unlike the results obtained with silver(I) catalytic complexes at lower temperatures (0 or ⁻20 ºC), the gold(I) catalyzed cycloaddition could be successfully carried out at 0 ºC obtaining an excellent 99% *ee* in detriment of the reaction time, which had to be increased till 3 d (Table 6). The result obtained in this last entry of Table

6 was excellent but the enantiomeric excess achieved at room temperature in the reaction performed with (*S*)-Binap **2**·$AgClO_4$ complex of 88% *ee* is also valuable (Table 6, first entry).

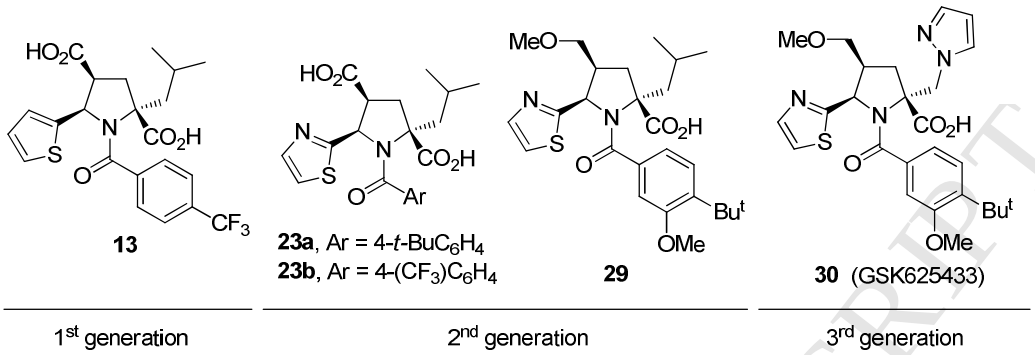
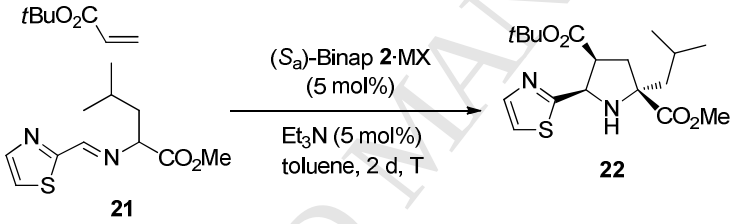


Figure 6. More active GSK HCV inhibitors.



Scheme 15

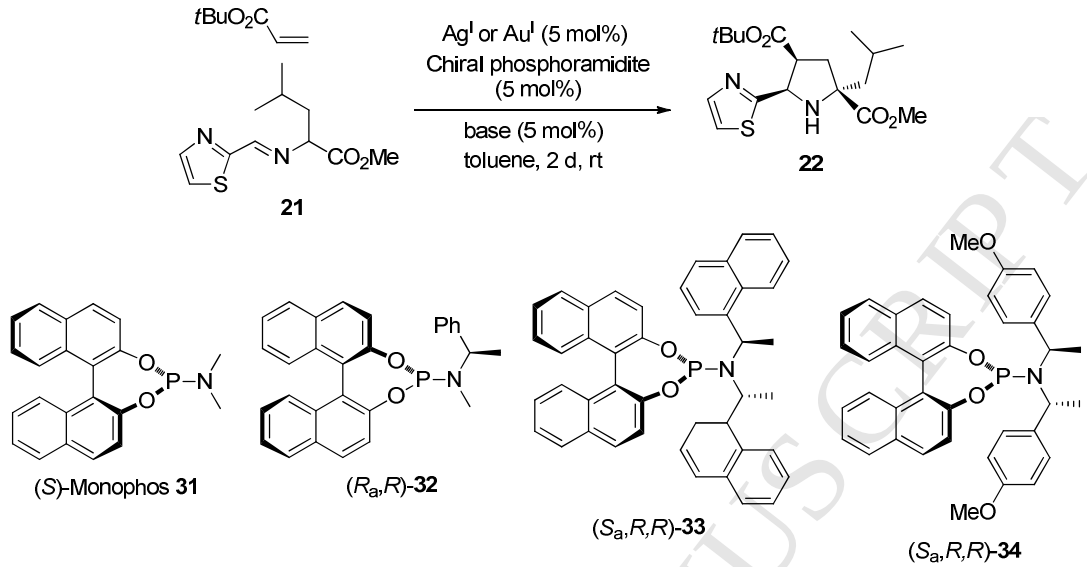
Table 6

Comparative study of 1,3-DC of imino ester **21**and *tert*-butyl acrylate using (S_a)-Binap**2**·M-Tfa complexes.

	Product *endo*-**22**		
MX	Yield. (%)	*endo*:*exo*	ee_{endo} (%)
$AgClO_4$	78	>98:2	88
$AgClO_4$[a]	75	>98:2	85
$AgSbF_6$	79	>98:2	72
AgTfa	82	>98:2	40
AuTfa	90	>98:2	78
AuTfa[a,b]	92	>95:5	99

[a]Reaction performed at 0 ºC. [b]3 d.

A screening of several chiral ligands [(S_a,*R*,*R*)-**1**, and **31**-**34**] and the most representative and more frequently used silver(I) and gold(I) salts was done for the synthesis of cycloadduct **22** [Scheme 16]. Monophos **31** and chiral phosphoramidites **33** and **34** afforded very disappointing enantioselections, as well as the reaction promoted by any chiral phosphoramidite·gold(I) complex where no product was identified from the crude reaction mixture (^{1}H NMR). Particularly (S_a,*R*,*R*)-**1** induced a promising moderate enantioselection using AgOTfa in good yields (50% *ee*, Scheme 16, Table 7). Perhaps the most impactant result was the obtained one employing $AgSbF_6$, Et_3N, toluene and the chiral phosphoramidite (R_a,*R*)-**32** (Table 7, 82% and 99% *ee*) [65].



Scheme 16

Table 7

Comparative study of 1,3-DC of imino ester **21** and *tert*-butyl acrylate in the presence of (S_a)-Binap **2**·MX complexes.

			Product *endo*-**22**		
Phosphoramidite	MX	Base	Yield. (%)	*endo*:*exo*	ee_{endo} (%)
(S_a,*R*,*R*)-**1**	$AgClO_4$	DIPEA	86	>98:2	30
	$AgSbF_6$	DIPEA	82	>98:2	40
	AgTfa	Et_3N	80	>98:2	50
	AuTfa	DIPEA	—	—	—
			Product *endo*-**22**		
Phosphoramidite	MX	Base	Yield. (%)	*endo*:*exo*	ee_{endo} (%)
(R_a,*R*)-**32**	$AgClO_4$	Et_3N	82	>98:2	20
	$AgSbF_6$	Et_3N	82	>98:2	99
	AgTfa	DIPEA	82	>98:2	64
	AuTfa	DIPEA	—	—	—

Despite the published DFT calculations appeared in this research group account, an explanation for the excellent results obtained employing the gold complex [(*S*)-Binap **2**·AgTfa]$_2$ (Scheme 15, Table 6 last entry) was needed. In a previous work, we demonstrated that the stereoselectivity of the 1,3-DC employing chiral-metallic Lewis basis arises from the blockage of one of the prochiral faces [66]. In this way, our results (in terms of DFT calculations) show that there is only one energetically accessible conformation due to the high substitution of the leucine-derived ylide (Figure 7). In this reactive complex there is an effective blockage of the (2*Re*,5*Si*) prochiral face of the ylide in **I**. Therefore, the predicted stereochemical outcome corresponds to the exclusive formation of cycloadduct (2*S*,4*S*,5*R*)-**22**, the same as obtained experimentally. Such as it is shown in Figure 7, the reaction proceeded to a concerted but highly asynchronous cycloaddition in which the *endo*-approach of the dipolarophile is favored due to a stabilizing interaction of the carboxylic group and the metallic centre. It is worth to note that there is a stabilizing coulombic interaction between the

nitrogen atom of the thiazole moiety (N_7) and one of the gold atoms of the catalyst both in the TS and the ylide complex. This interaction fixes the planar conformation of the ylide moiety and minimizes the possible steric hindrance with the bulky *tert*-butyl group of the dipolarophile [65].

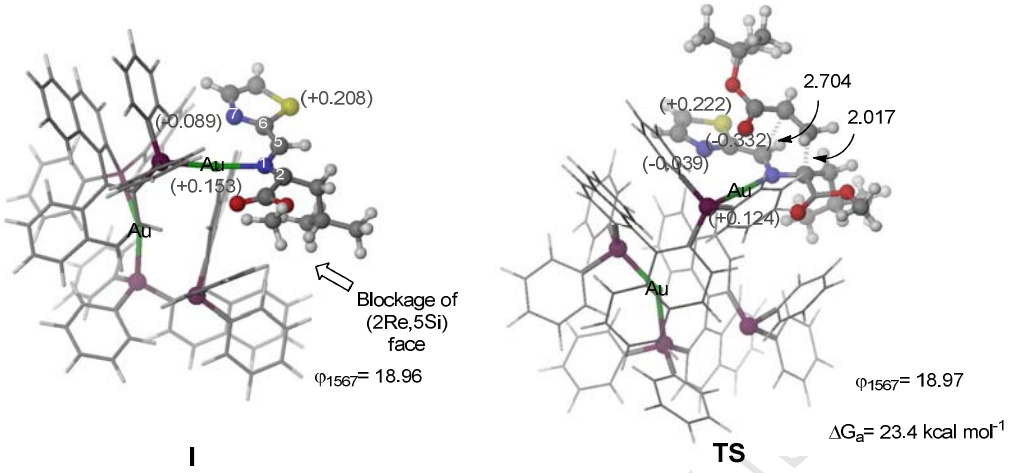
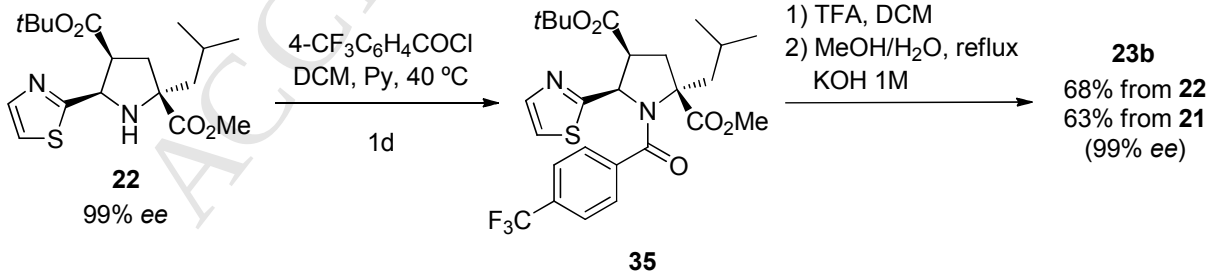


Figure 7. Gibbs activation energy and main geometrical features of the computed ylide and transition structures corresponding of the 1,3-DC of Au(I) ylide complex and *tert*-butyl acrylate computed at ONIOM(B3LYP/LanL2DZ:UFF) level of theory. High level and low-level layers were represented as ball & stick and wireframe models respectively. Grey numbers in parentheses represent Mulliken charges. Distances are in Å.

With the best enantiomerically enriched cycloadduct **22**, that means the product obtained at 0 ºC using [(*S*)-Binap **2**·AuTfa]$_2$ as catalyst, the synthesis of the antiviral agent **23b** could be accomplished in two conventional steps involving an amidation reaction and a double ester hydrolysis.The latter consisted on a first TFA-mediated hydrolysis of the *tert*-butyl ester and a basic one employing a refluxing solution of KOH/MeOH (Scheme 17). The final product **23b** was finally isolated in 68% overall yield (from pyrrolidine **22b**) and with 99% *ee*, or in 63% overall yield from iminoester **21**. Unfortunately, the reaction to give **22** did not work when phosphoramidite·AgX complexes were employed.At this moment, studies concerning the synthesis of the most active third generation antiviral agent **30** (GSK625433) are underway using imino ester **36** as starting precursor of the corresponding azomethine ylide (Figure 8) [65].



Scheme 17

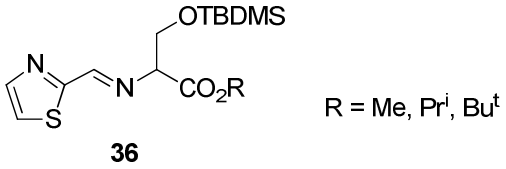
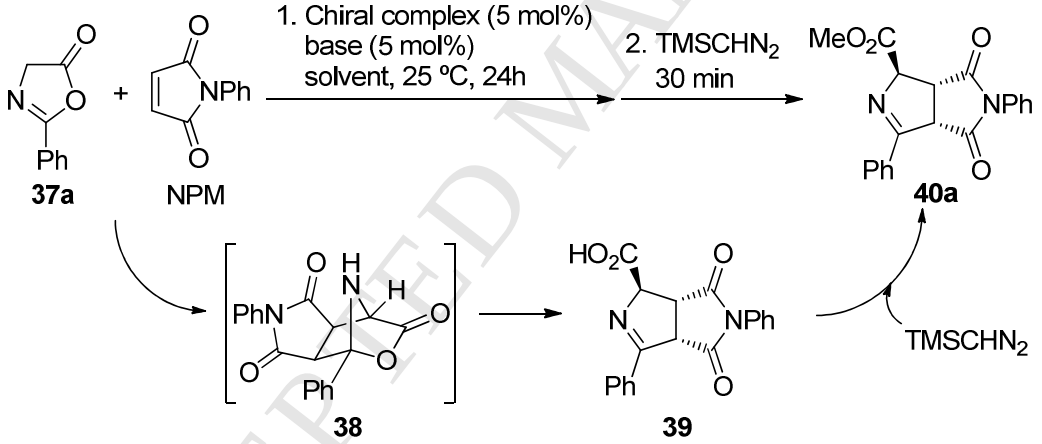


Figure 8

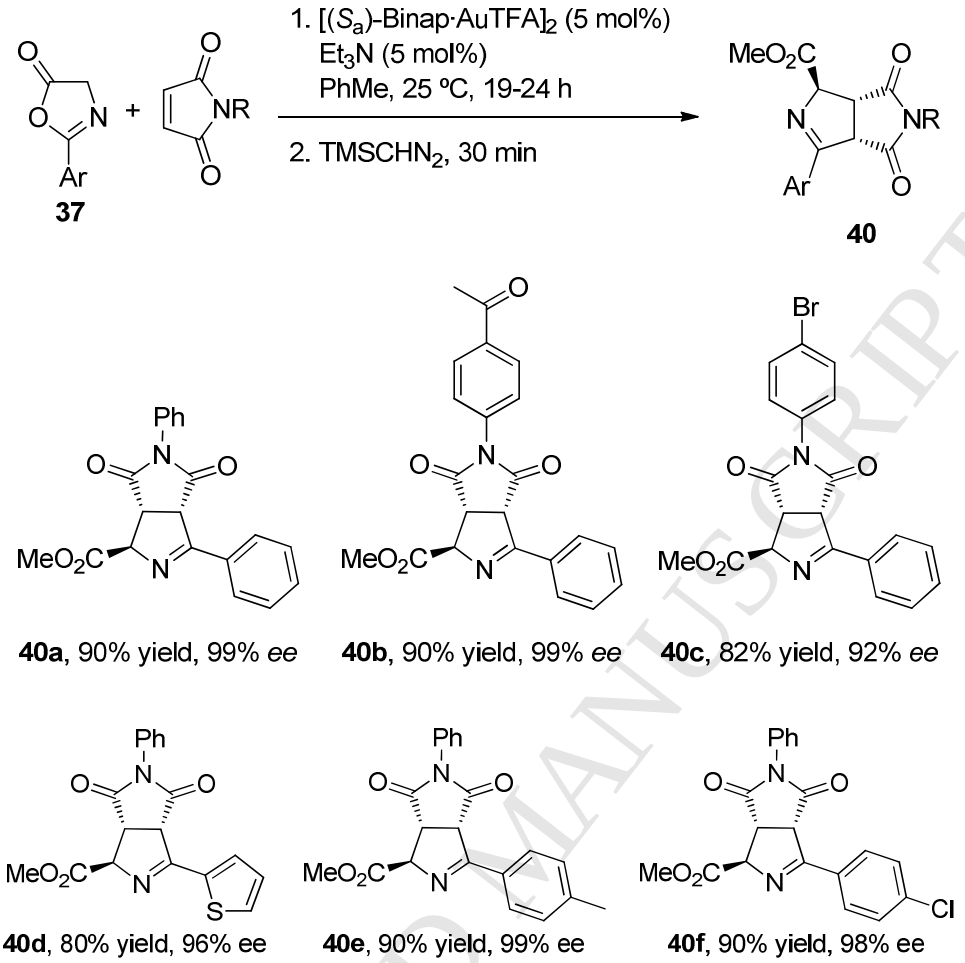
Such as it was described at the beginning of this section, oxazol-5-(4*H*)-ones (azlactones) are suitable heterocycles to perform this C-C bond generation based strategy affording both quaternized and non quaternized α-amino acid derivatives [67,68,69,70]. These substrates can be easily transformed in münchnones, which are potential 1,3-dipoles, after deprotonation and imine-activation with a chiral Lewis acid. Despite of the easy access to this mesoionicheterocycles their enantioselectivecycloadditions with electrophilic alkenes have not been exploited. Toste´s group published an efficient 1,3-dipolar cycloaddition (1,3-DC) between alanine, phenylalanine and allylglycine derived azlactones with maleimides and acrylates employing dimetallic (*S*)-Cy-Segphos $(AuOBz)_2$ complex type **24** (Figure 4) as catalyst (2 mol%) in the absence of base [58].

Oxazolone derived from glycine **37a** was allowed to react with *N*-phenylmaleimide (NPM) at room temperature using a 5 mol% of the chiral catalytic complex and a 5 mol% of base (Scheme 18) [71,72]. After completion, a large excess of trimethylsilyldiazomethane was added to obtain the methyl ester of intermediate carboxylic acid **39** (30 min), resulting from ring opening of the biciclic transient species **38**. Compound **40a** was obtained diastereoselectively (>98:2, by ^{1}H NMR spectroscopy) after purification and its absolute configuration was established according to the literature.



Scheme 18

Following the results achieved in the 1,3-DC of imino esters and alkenes using [(*S*)-Binap **2**·AuTfa]$_2$ catalyst, this complex was successfully tested and the optimization of the solvent, temperature, and base was completed. Thus, azlactones**37** were allowed to react with several maleimides (Scheme 19). *N*-Substituted methyl, and ethyl maleimides did not afford compounds **40** with so high enantioselections (60 and 70% *ee*, respectively), however *N*-phenyl or *N*-arylmaleimides gave very good enantioselections of compounds **40a**-**40c** in high chemical yields (Scheme 19). The variation of the arene substituent of the azlactones (even working with an heteroaromatic substituent, such as 2-thienyl) promoted also excellent to good enantioselections in compounds **40d**-**40f** (Scheme 19) [71,72].



Scheme 19

Refined computational results showed the *exo*-approach is the preferred one. In this analysis, only that approach was considered. The less energetic computed TS are depicted on Figure 9 where the gold atom is coordinated only to the azlactone by the nitrogen atom. This reaction completely failed when chiral silver(I) complexes were attempted [72].

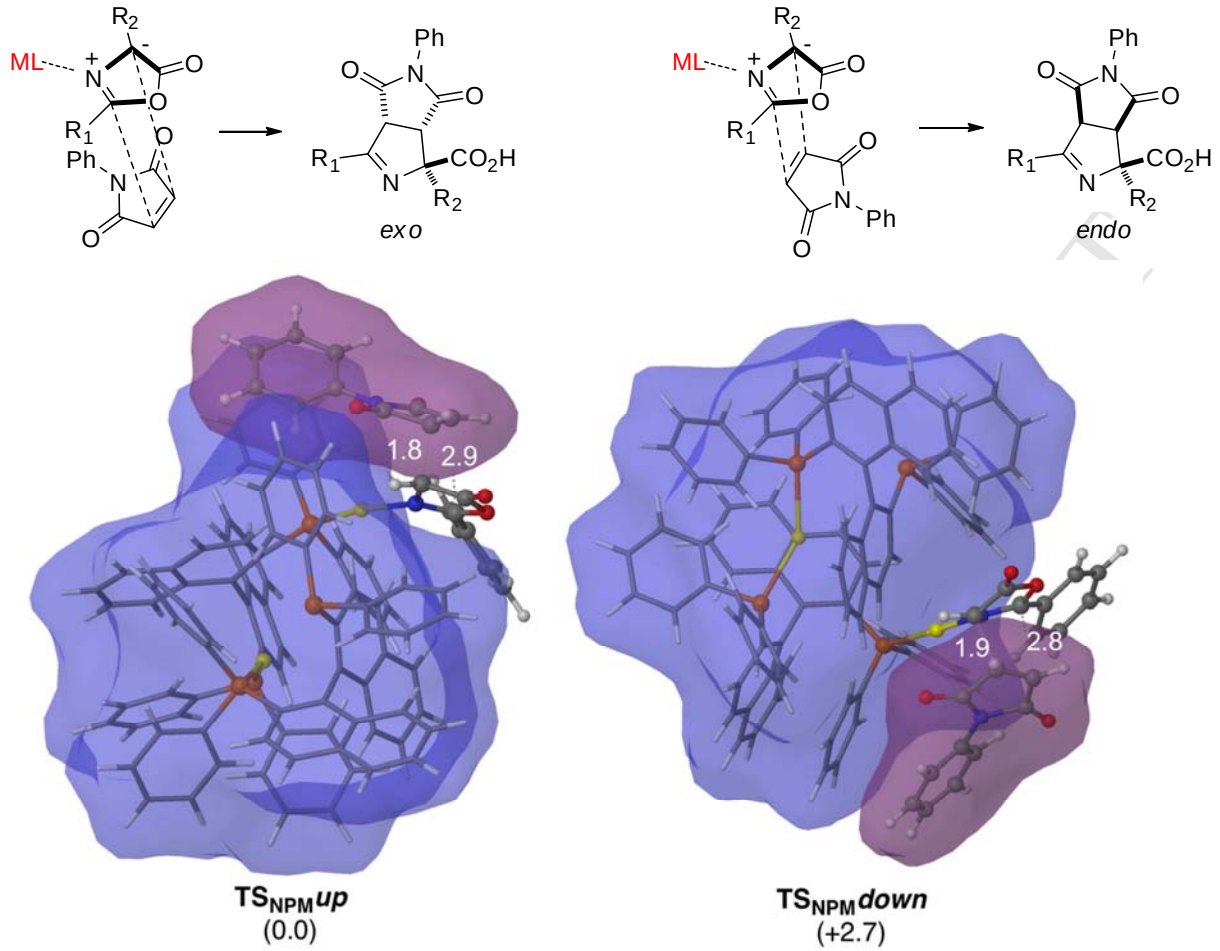
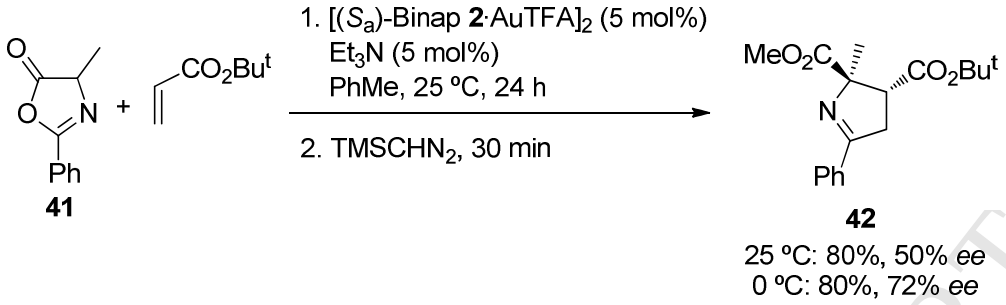


Figure 9. Main geometrical features and relative Gibbs free energies (in kcal mol^{-1}) of the less energetic transition states associated with the 1,3-DC of **37a** and NPM catalyzed by (S_a)-Binap gold dimers computed at M06/Lanl2dz//ONIOM(b3lyp/Lanl2dz:UFF) level of theory. High-level and low level layers are represented as ball & stick and wireframe models, respectively. Distances are in Å. Blue and purple surfaces representsthe solvent-accessible surface of the catalyst and NPM with a probe radius of 1.9 Å.

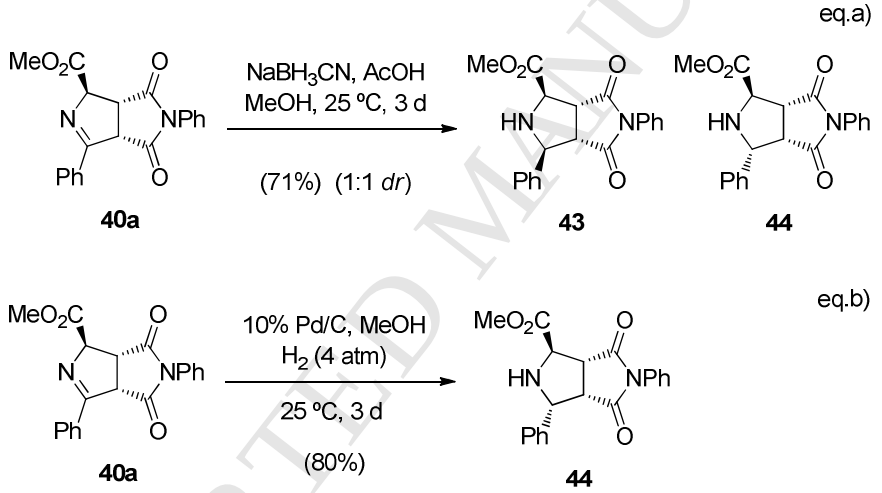
The less reactive alanine-derived 4-methyloxazole-5-one **41** under these reaction conditions only reacted at 25 and at 0 ºC with *tert*-butyl acrylate yielding cycloadduct **42** in good yields and moderate to good enantioselections (Scheme 20). If we compare these results with previous ones obtained using α-imino esters, this last diastereoselective cycloaddition exhibited an opposite regioselection. Besides, the resulting relative configuration of Δ^1-pyrroline **42** is equivalent to the *exo*-approach of the dipolarophile when an *endo*-transition state was the most favourable in the gold(I)-catalyzed 1,3-DC with α-imino esters and alkenes [72].

To gain more insight into the unexpected regioselectivity of the 1,3-DC depicted in Scheme 20, calculations within the DFT framework were performed but this anomalous behavior could not be explained. So, alternative Natural Resonance Theory Analysis (NRT) [73,74,75] had to be employed. It demosntrated that the negative charge in the Lewis structure of the ylide is mainly placed on C5. The importance of these electronic distributions was verified by Nucleus Independent Chemical Shifts (NICS) calculations in the ring point of the oxazoline [76]. The NICS value of -7.3 ppm pointed to the aromaticity of that ring in the ylide. These results explain the existence of different regioselectivities for both possible ylides (Scheme 20) [71,72].



Scheme 20

As a possible application of the resulting pyrrolines (for example pyrroline **40a**), it could be reduced to the corresponding pyrrolidines employing sodium cyanoborohydride in acidic media. In this reaction, a 1:1 mixture of 2,5-*cis*pyrrolidine **43** and its 5-epimer **44** (2,5-*trans*) was isolated in good chemical yield (71%) (Scheme 21, eq. a). Fortunately, 5-epimer **44** (2,5-*trans*) was diastereoselectively generated through a 10% Pd/C catalyzed hydrogenation using 4 atmospheres of hydrogen during three days at 25 ºC (Scheme 21, eq. b) [71,72]. This *trans*- arrangement in molecule **44** is not very easy to built because several steps were needed using other synthetic strategies [77].



Scheme 21

4. Copper-catalyzed 1,3-DC of azomethine ylides and nitroalkenes

Substituted prolinates **45** (Figure 10), obtained from the corresponding 1,3-DC between glycine imino esters and nitroalkenes, are important inhibitors of $\alpha_4\beta_1$-integrin-mediated hepatic melanoma metastasis [78]. The most simple proline*exo*-**46** have been recently used as chiral organocatalysts in aldol reactions [79]. In particular, for the asymmetric 1,3-DC of nitroalkenes as dipolarophiles chiral copper(I) complexes, formed from ferrocenyl-type phosphanes, have been mainly used as catalysts [80,81,82,83,84,85].Copper(I) complexes **47** [80,82], **48** [81,83], and **49** [79], generally afforded *exo*-cycloadducts, whereas the corresponding *endo*-diastereomers have been prepared using complex **50** [79]. On the other hand, when copper(II) triflate and chiral ligand PyBidine [86] were combined the resulting catalyst **51**afforded mainly *endo*-cycloadducts. In the case of 1,3-DC of glycinamides and nitrostyrene (*R*)-Segphos and $Cu(CH_3CN)_4PF_6$ as catalytic mixture, furnished *exo*-cycloadducts in good yields (up to 76%) and up to 96:4 *er*[87]. A 5-position epimer (called *exo*'-diastereoisomer) was mainly obtained when a solid-phase imidazolidine-aminophenol/$Ni(OAc)_2$was employed [88].Other chiral metal complexes such as $[BinapAuTFA]_2$ afforded modest results for the cycloaddition of methyl benzylideneglycinate and nitrostyrene (up to 80:20 *dr* and 85:15 *er*) [62]. The benzophenone-derived *N*-(diphenylmethylene)glycinates have also been employed as azomethine ylide precursors in the presence of chiral silver catalysts [89],and organocatalysts [90,91].

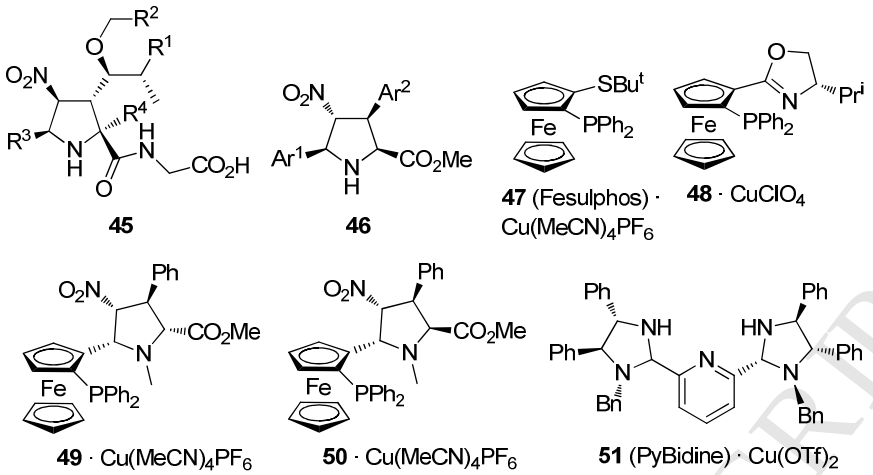
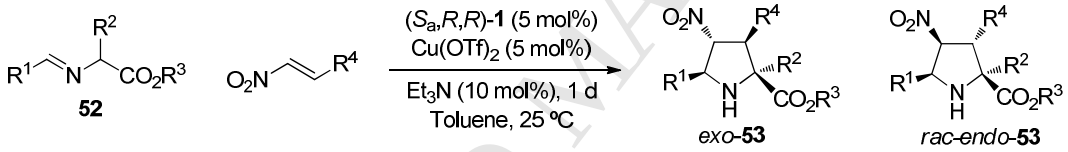


Figure 10

We used chiral phosphoramidites**1**and **31** [30,40], as monodentate privileged ligands in the general asymmetric 1,3-DC of azomethine ylides, derived from α-amino acids, and nitroalkenes [92]. The best *exo*-diastereo- and enantioselections were achieved using chiral ligand (S_a,*R*,*R*)-**1** (5 mol%), $Cu(OTf)_2$ (5 mol%) [93], triethylamine (10 mol%), in toluene at room temperature for 1 d (Scheme 22) [94].



Scheme 22

The stereochemical course of the reaction was clearly influenced by the aryl substituent of the imino ester (Scheme 22 and Table 8). The 2-naphthyl derivative gave a 86/14 *exo:endo* diasteromeric ratio with a good *er* of product **53**. The *p*-substitution increased these two parameters up to 93/7 *exo/endo* ratio with higher enantioselections (up to >99 *ee* after recrystallization) [94].

Table 8

1,3-DC of imino ester **52** (R^1 = Ar, R^2 = H, R^3 = Me) and nitrostyrene (R^4 = Ph)

	Product *exo*-**53**		
R^1	Yield. (%)	*exo*:*endo*	ee_{exo} (%)
2-Naphthyl	70	86:14	88
4-MeC_6H_5	59 (46)[a]	80:20	88 (98)[a]
4-BrC_6H_5	76 (69)[a]	89:11	90 (98)[a]
4-ClC_6H_5	70 (62)[a]	93:7	98 (>99)[a]

[a] After recrystallization

The insertion of an α-substituent in the dipole precursor afforded different behavior depending on the alkyl substituent. Whilst the alanine derivative afforded mainly the *endo*-stereosisomer**53** as a racemic form, leucine and

phenylalanine derivatives gave a high *exo*-diastereoselection and excellent enantioselectivities (>99% *ee*) (Scheme 22 and Table 9).

Table 9

1,3-DC of imino ester **52** (R^1 = Ph, R^2 = Alkyl, R^3 = Me) and nitrostyrene (R^4 = Ph)

	Product *exo*-**53**		
R^2	Yield. (%)	*exo*:*endo*	ee_{exo} (%)
Me	61	13:87	0[a]
Bu[i]	60	92:8	>99
$PhCH_2$	65 (51)[b]	75:25	>99

[a] For *endo*-compound. [b] After recrystallization

Several β-arylnitroalkenes were allowed to undergo this 1,3-DC employing imino ester **52** (R^1 = Ph, R^2 = H, R^3 = Me). The *o*- and *m*-substituted aryl groups afforded very good enantioselection with variable *endo/exo* ratio. Again, the *p*-substitution resulted to be most favorable for this transformation such as it was exemplified in Table 10 and Scheme 22. Higher diastereoselections were achieved in these examples together with excellent enantioselectivities [94].

Table 10

1,3-DC of imino ester **52** (R^1 = Ph, R^2 = H, R^3 = Me) and nitrostyrenes (R^4 = Ar)

	Product *exo*-**53**		
R^4	Yield. (%)	*exo*:*endo*	ee_{exo} (%)
2-BrC_6H_5	56 (46)[a]	73:27	92 (96)[a]
3-BrC_6H_5	61 (52)[a]	90:10	88 (96)[a]
4-BrC_6H_5	70 (64)[a]	87:13	90 (88)[a]
4-MeC_6H_5	48 (40)[a]	87:13	98 (98)[a]
4-$(MeO)C_6H_5$	68 (63)[a]	74:26	96 (98)[a]
4-FC_6H_5	73 (70)[a]	85:15	92 (98)[a]

[a]After recrystallization

DFT calculations on the (S_a,*R*,*R*)-**1**·$Cu(OTf)_2$ catalyzed reaction to obtain **53** (R^1 = Ph, R^2 = H, R^3 = Me, R^4 = Ph), showed that the coordination sphere of copper(II) atom is saturated by a OTf moiety. Therefore, no extra coordination with the nitro group took place favoring the *exo*-approach. The most stable transition structures located are depicted in Figure 11. (*S*,*S*)-*exo*-**TS1**-**53** was found to be about 1.5 kcal mol^{-1} more stable than its enantiomeric counterpart. These calculations support a computed er_{exo} of about 92%, in good agreement with the experimental results [94].

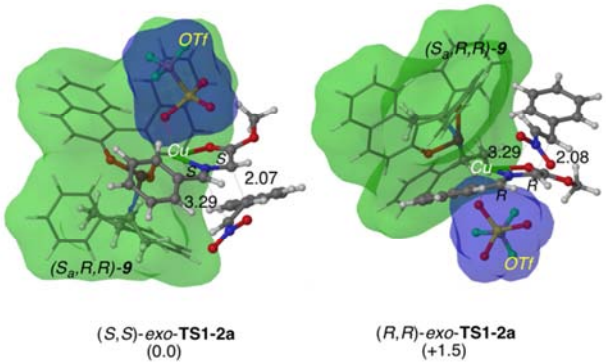


Figure 11. Main geometric features and relative energies (in kcal mol^{-1}) of the computed transition structures associated with the first step of the reaction between **11a** and (S_a,*R*,*R*)-**9**·CuOTf-**II** with **10a** computed at M06/LANL2DZ//ONIOM (B3LYP/LANL2DZ:UFF) + ΔZPCE level of theory. Bond-lengths are given in Å. The chiral ligand and OTf moiety are highligted in green and blue, respectively.

5. Conclusions

According to all these experimental and theoretical data we have demonstrated the high modulation or fine tuning of catalysts derived from coinage metals in the 1,3-DC reaction involving azomethine ylides and alkenes. The appropriate combination of the ligand and the metal salt plays an important role. Thus, phosphoramidites and silver salts represent general catalysts for different dipolarophiles, with wider scope than the corresponding binap·silver(I) complexes. Binap·gold(I) complexes are the catalysts of choice for almost all possible combinations of the dipole and the dipolarophile. In all these cases the *endo*-adducts have been diastereoselectively obtained with high *ee*'s. On the other hand, phosphoramidite·$Cu(OTf)_2$ is the adequate catalyst for the diastereo- and enantioselective preparation of *exo*-polysubstitutednitroprolines through a 1,3-DC between imino esters and nitroalkenes. Azlactone derived from glycine reacts as dipole precursor only in the presence of the dimeric binap·gold(I) complex giving good results when working with maleimides as dipolarophiles. However, alanine derived oxazolone only reacts with *tert*-butyl acrylate furnishing the corresponding cycloadduct with the opposite regiochemistry. In many occasions, applications of the final products are found, prolines acting as inhibitors HCV being the most interesting and promising research line.
All experimental data are supported by computational studies in order to clarify the mechanism involved in the reaction. Maleimides follow a concerted asynchronous mechanism in both silver(I) and gold(I) catalyzed processes. In contrast, a stepwise mechanism is preferred by acrylates and nitroalkenes. The calculations support all the highest values of enantiomeric excesses as well as the more abundant formed diastereoisomer.

Acknowledgments

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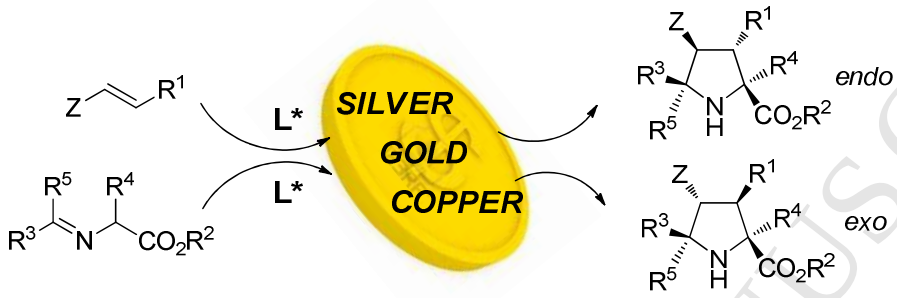
Graphical Abstract



Coinage Metal Complexes as Chiral Catalysts for 1,3-Dipolar Cycloadditions

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Chiral coinage metal complexes of privileged ligands such as phosphoramidites and binap with silver(I), gold(I) and copper(II)salts catalyzed efficiently the enantioselective 1,3-DC of azomethine ylides derived from α-amino acids and azlactones with different dipolarophiles affording enantioenriched highly substituted prolines. DFT calculations supported all the experimental results and stereochemical outcomes.

- Highly diastereo- and enantioselective 1,3-dipolar cycloadditions are described.
- Chiral complexes of coinage metals are excellent catalysts.
- Fine tunable chiral complexes allow the synthesis of a single steroisomer.
- Up to four stereogenic centres are unambiguously generated.
- A set of enantiomerically enriched prolines are inhibitors of hepatitis C virus.