Binap and phosphoramidites as privileged chiral ligands for the metal-catalyzed enantioselective 1,3-dipolar cycloaddition of azomethine ylides and dipolarophiles

Carmen Nájera,*[a] and José M. Sansano*[b]

Dedication ((optional))

((Insert Picture for Frontispiece here [18.0×18.0 cm]))

Abstract: Binap and phosphoramidites are privileged chiral ligands which have been tested in the coinage metal-catalyzed 1,3-dipolar cycloadditions of metalloazomethine ylides and electrophilic alkenes. Silver(I), copper(II) and gold(I) salts have been evaluated in all these reactions. Maleimides, acrylates, fumarates, 1,2-bis(phenylsulfonyl)ethylene and enones reacted with imino esters giving the corresponding *endo*-prolinates such as HCV inhibitors in high diastereo- and enantioselectivity. In the case of nitroalkenes *exo*-4-nitroprolinates were obtained. Azlactones reacted with maleimides and acrylates to give pyrrolines only in the presence of binap-gold(I) complexes. The observed enantioselectivity and the mechanism of these 1,3-DC was studied by means of DFT calculations.

1. Introduction

Rolf Huisgen introduced and defined the 1,3-dipolar cycloaddition (1,3-DC) by first time in 1963.[1] The main features of this reaction are the high number of functional groups tolerated, the complete atom economy from the dipole and dipolarophile structures, the final product obtained (most of them heterocycles) which are very difficult to obtain using other routes, and up to four stereogenic centers can be generated. The high utility of these processes spreads in chemistry, synthesis of natural products, material science, medicinal chemistry, pharmacy, agriculture, etc. The main interest of the scientific community in 1,3-DC[2] started with the first publications concerning catalytic enantioselective processes. Azomethine ylides are one of the most frequently employed dipoles and they can be easily prepared following different routes, activation of imino esters being the most widely employed. Since the pioneering works[3] of Zhang[4] and Jørgensen[5] in 2002 many examples of enantioselective 1,3-DC[6] have been published using imino esters as precursors of stabilized azomethine ylides. Despite of the utility of chiral organocatalysts, they performed 1,3-DC with some limitations since the structural point of view. However, chiral metal complexes not only overcome these difficulties but also they can be tuned in order to control the dipole geometry to improve the diastereoselectivity of the process.[6k]

During the last decade we have been working in 1,3-DC of stabilized azomethine ylides and alkenes focusing on our effort in the metal-catalyzed enantioselective processes using chiral privileged ligands[7] as (*R*)- or (*S*)-binap **1**, monophos **2**, and phosphoramidite **3** (Figure 1). So in this personal account we will describe our experience in this enantioselective cycloaddition starting from enolizable substrates **I** and electron-deficient alkenes **III** promoted by coinage metals and the named chiral ligands on the basis of the dipolarophile employed (Scheme 1). Rigid chiral metallodipoles **II** control of the final absolute configuration of the up to four stereogenic centers of polysubstituted proline derivatives **IV**.

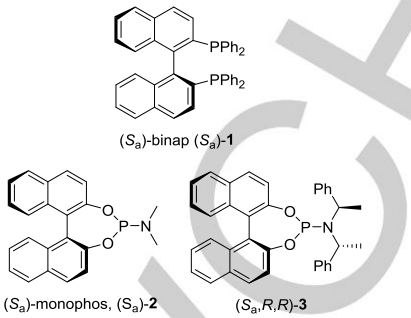
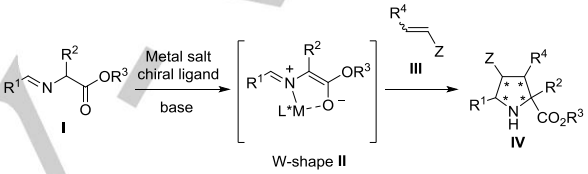


Figure 1. Chiral privileged ligands used in this account.



Scheme 1. General 1,3-DC reaction discussed in this work.

[a] Prof. Dr. C. Nájera
Department of Organic Chemistry and Centro de Innovación en Química Avanzada (ORFEO-CINQA).
Faculty of Sciences, University of Alicante,
E-03080 Alicante, Spain
Fax: +34 965903549
E-mail: cnajera@ua.es

[b] Prof. Dr. José M. Sansano
Department of Organic Chemistry, Instituto de Síntesis Orgánica and Centro de Innovación en Química Avanzada (ORFEO-CINQA).
Faculty of Sciences, University of Alicante,
E-03080 Alicante, Spain
E-mail: jmsansano@ua.es

Carmen Nájera was born in Nájera (La Rioja) and was graduated from the University of Zaragoza in 1973, obtaining her doctorate in chemistry from the University of Oviedo in 1979. She spent postdoctoral stays at the ETH (Zurich), the Dyson Perrins Laboratory (Oxford), Harvard University, and Uppsala University. She became Associate Professor in 1985 at the University of Oviedo and Full Professor in 1993 at the University of Alicante. She is coauthor of more than 350 papers and book chapters and has supervised more than 40 PhD students. She has been awarded with the 2006 Organic Chemistry Prize from the Spanish Royal Chemical Society of Chemistry, the 2006 Rosalind Franklin International Lectureship from the English Royal Society, the SCF 2010 French-Spanish Prize from the Société Chimique de France and the IUPAC 2015 Distinguished Women in Chemistry or Chemical Engineering Award. In 2012 she was named full Member of the Royal Spanish Academy of Sciences, and was appointed as Active Member of the European Academy of Sciences and Arts.

José Miguel Sansano was born in Rojales (Alicante), studied chemistry at the University of Alicante, where he obtained his B.Sc. and Ph.D. degrees in 1988 and 1994, respectively. His Thesis was supervised by Prof. C. Nájera and dealt about sulfone chemistry. After spending a two-year postdoctoral stay at the University of Leeds (U.K.) with Prof. R. Grigg, he joined the University of Alicante in 1996, where he was appointed Associate Professor in 2001. In 2010 he was promoted to Full Professor in 2010 in the same University. He is coauthor of more than 90 articles and has supervised 10 PhD students.

2. Enantioselective 1,3-DC of stabilized azomethine ylides and dipolarophiles

There are many routes to prepare an azomethine ylide being the stabilized metallo-dipoles generated in situ from imino esters the most employed one in synthesis due to its mild and easy manipulation conditions. According to precedent publications, the most efficient $HOMO_{azomethine\ ylide}$ -$LUMO_{dipolarophile}$ interaction is produced when electron-poor alkenes are used, so a high regioselectivity is ensured. This orbital arrangement also benefits a stereoelectronic interaction of the metal with the dipolarophile affording *endo*-products as major diastereoisomers. Taking in account all these general features plus the high control of the geometry exhibited by W-shaped metallo-azomethine ylides **II** (Scheme 1) it is possible to justify the high 2,5-*cis*-stereoselection observed. Chiral metal complexes have been successfully implemented as catalyst giving rise to enantiomerically enriched proline derivatives **IV**.[6] The most efficient processes involved silver(I) and copper(I) chiral metallodipoles allowing the generation of mainly *endo*-4,5-*cis* and *exo*-4,5-*trans*-cyloadducts,[8] respectively. Maleimides, acrylates, maleates, fumarates, α.β-unsaturated ketones, nitroalkenes, and vinyl sulfones, are the most typical dipolarophiles.

2.1. 1,3-DC involving maleimides

Maleimides **5** resulted to be one of the most reactive dipolarophiles in 1,3-DC dealing with azomethine ylides and are frequently selected for the long optimization process. Too many parameters can be modified the cycloaddition being sensitive to all of them. For example, our first successful 1,3-DC attempt was achieved employing *N*-methylmaleimide (NMM) **5a**, glycine imino ester **4a** in toluene at room temperature in the presence of 5 mol% of an equimolar mixture of (S_a)-binap **1** and silver perchlorate (Scheme 2)[9] In this example, product *endo*-**6aa** was isolated in 90% yield, >98:2 *endo*:*exo* ratio and >99% *ee*.[10,11] When the enantiomer (R_a)-binap **1** and silver perchlorate was tested in the same reaction *ent*-*endo*-**6aa** was isolated in analogous yield and *ee*. This effect was observed in all of the examples described along this account.

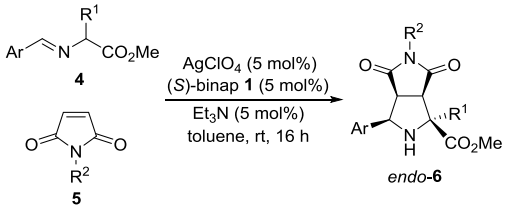
Scheme 2. Optimized reaction conditions using (S_a)-binap **2** and $AgClO_4$.

An important feature of this transformation was the easy separation of the catalytic species from the reaction mixture. In fact, when the process was judged complete, the separation of the catalytic complex (*S*)-binap **1**·$AgClO_4$ (insoluble in toluene) from the reaction mixture was achieved in 95-90% yield by simple filtration. A series of four cycles were run employing the same recovered catalyst [(*S*)-binap] **1**·$AgClO_4$ used without any further purification obtaining excellent results of *endo*-**6aa**. Several stable silver triflate complexes with (*R*)-binap as ligand have been isolated and characterized by X-ray diffraction analysis by Yamamoto's group.[12] So, we prepared and crystallized the 1:1 complex [(*S*)-binap] **1**·$AgClO_4$ and was further characterized by ESI-MS experiments and ^{31}P NMR spectra (see below) being stable to light exposure and high temperatures.

Despite perchlorates are classified as low order explosives and not excessively sensitive to rubbing, the thermogravimetric (TG) and differential thermal analysis (DTA) of the stable species (*S*)-binap **1**·$AgClO_4$ revealed that the loss of water of the sample occurred from 50 to 180 ºC without any variation of the heat of the system. The melting point of this complex is located in the range of 209-211 ºC. The three most important exothermic decomposition processes occurred approximately at 300, 550 and 860 ºC.

The scope of this reaction was studied with methyl esters **4** and it was found that *N*-methyl and *N*-ethylmaleimides afforded good enantioselections (Table 1, entry 1). However, this catalytic system resulted to be very sensitive to bulky substituents. Thus, for example, working with α-branched α-amino acid derived imino esters **4** (R^1 = alkyl, benzyl) or with 2-substituted aromatic groups in the imino moiety, lower enantioselections were obtained (Table 1, entries 2 and 3, respectively). Some of the 4-substituted arylideneglycinates (Table 1, entry 4) afforded very good results when employing glycine derivative together with NMM. Very high enantiodiscrimination occurred with the 2-naphthyl derivative (Table 1, entry 5) and the employment of the 2-thienyl surrogate afforded good enantioselections (Table 1, entry 6). In general chemical yields were good in all cases as well as the *endo*:*exo* diastereoselection (>98:8 in most reactions). Nevertheless, *N*-phenylmaleimide (NPM) and glycine derived imino ester **4** furnished lower *ee* (62%) and lower diastereoselectivity (90:10 *endo*:*exo* ratio) of *endo*-**6** (Table 1, entry 7).

Table 1. Scope of the (*S*)-binap **1**·$AgClO_4$ catalyzed 1,3-DC between **4** and maleimides **5**.



Entry	Ar	R^1	R^2	Yield (%)[a]	*ee* (%)
1	Ph	H	Me or Et	90-91	>99
2	Ph	Me, Pr^i, Bn	Me	80-83	64-74
3	2-R-C_6H_4[b]	H	Me	82-85	72-82
4	4-R-C_6H_4[b]	H	Me	83-88	74-98
5	2-Naph	H	Me	89	99
6	2-Thienyl	H	Me	87	90
7	Ph	H	Ph	86	62[c]

[a] Isolated yield after column chromatography or by recrystallization, with >98:2 *endo*:*exo* ratio. [b] R = Me or Cl. [c] 90:10 *endo*:*exo* ratio

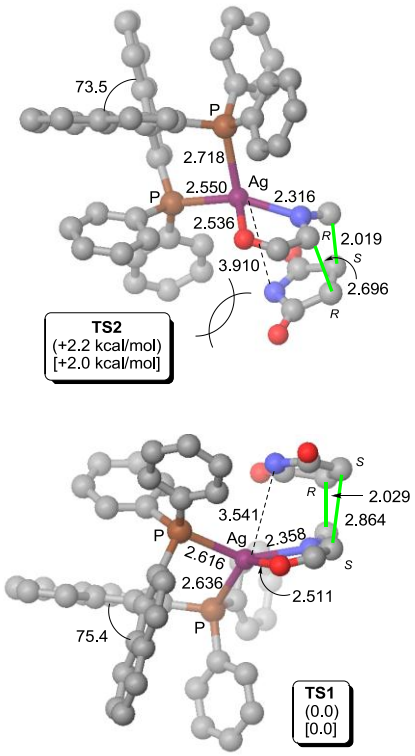


Figure 2. Fully optimized structure (B3LYP/LANL2DZ&6-31G* level) of **TS1** and **TS2**, leading to both *endo*-diastereoisomers. Bond distances and dihedrals are given in Å and deg., respectively. Numbers in parentheses and in square brackets are the relative total and Gibbs free energies respectively, computed at the B3LYP/LANL2DZ&6-31G*+ΔZPVE level..

The diastereomeric *endo*-cycloadducts were originated via transition structures **TS1** and **TS2** using a basic reaction of maleimide and imino ester derived from formaldehyde. The main geometric features and the relative energies of these transition structures are reported in Figure 2. As expected both **TS1** and **TS2** were quite asynchronous but concerted, **TS1** being ca. 2 kcal/mol more stable than **TS2**.[11,13] It was also observed that the metallic centre is coordinated to the two phosphorus atoms of the catalysts and to the oxygen and nitrogen atoms of the azomethine ylide. 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. In summary, our calculations were in full agreement with the experimental findings and provide a rationale for the excellent asymmetric induction and catalytic efficiency. Although perchlorate anion formed a covalent bond with silver it was not considered in this calculations.

Although this perchlorate complex resulted to be very stable, another poorly coordinated anions were explored in order to ensure or even improve the results obtained from (*S*)-binap **1**-$AgClO_4$ complex. After testing several oxygenated silver(I) salts, with a weak coordinating anion, such as AgOAc, AgOTf (Tf = trifluoromethanesulfonate) $AgNO_3$, and $AgBF_4$, in the model reaction described in Scheme 2, it was found that the combination (*S*)-binap **1** and $AgSbF_6$ afforded excellent enantioselection of cycloadduct *endo*-**6aa** (90% yield, >98:2 *endo*:*exo* ratio, and >99% *ee*).[14,15]

The presumed catalytic monomeric species in solution are identical to those the reported previously with the perchlorate anion. The 1:1 (*S*)-binap **1** and $AgSbF_6$ complexes were characterized by ESI-MS experiments and ^{31}P NMR. ESI-MS reveled a M^++1 signal at 730, and 732 corresponding to the monomeric (*S*)-binap **1**-Ag^I complex. The ^{31}P NMR ($CDCl_3$) spectra of 1:1 (*S*)-Binap **1** and $AgSbF_6$ (10% aqueous polyphosphoric acid as internal reference) afforded signals at 15.31 ppm and 15.45 ppm (2d, *J* = 242 Hz) (15.26, and 15.35 ppm for Binap-$AgClO_4$ complex).[15]

The scope of the reaction with maleimides was next evaluated (Table 2 and Scheme of Table 1) and compared with the results shown in Table 1. Entries 1, 5 and 6 of Table 2 afforded similar

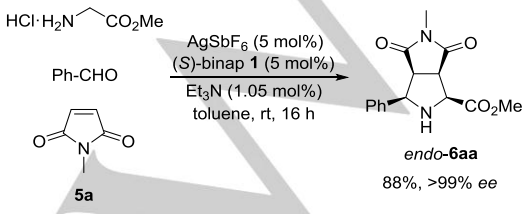
results that the reactions performed with silver perchlorate.[16] However, the most relevant results were obtained when sterically hindered dipoles were employed. Thus, in the case of α-branched azomethine ylides and 2-substituted arenes in the imino moiety the reactions employing catalyst (*S*)-binap **1**·$AgSbF_6$ gave excellent enantioselections (Table 2, entries 2 and 3). Besides, 4-substituted arenes were more appropriate precursors for this catalytic system giving 94-99% *ee* of *endo*-**6** products. Such as ocurred in Table 1, all compounds **6** obtained *via* catalysis of (*S*)-binap **1**·$AgSbF_6$ were isolated as unique diastereoisomers (>98:2 *dr*) and good to excellent chemical yields. In this line, the reaction between NPM and glycine-derived imino ester gave both higher enantio- and diastereoselection (>98:2) than the analogous reaction performed with [(*S*)-binap] **1**·$AgClO_4$.

Table 2. Scope of the (*S*)-binap **1**·$AgSbF_6$ catalyzed 1,3-DC between **4** and maleimides **5**.[a]

Entry	Ar	R^1	R^2	Yield (%)[b]	*ee* (%)
1	Ph	H	Me, Et	90	>99
2	Ph	Me, Pr^i, Bn	Me	78-86	91-99
3	2-R-C_6H_4[c]	H	Me	85	70->99
4	4-R-C_6H_4[c]	H	Me	84-85	94-99
5	2-Naph	H	Me	89	99
6	2-Thienyl	H	Me	84	93
7	Ph	H	Ph	86	82

[a] Reaction conditions: (*S*)-binap **1**·$AgSbF_6$ (5 mol%), Et_3N (5 mol%), toluene, rt, 16 h. [b] Isolated yield after column chromatography or by recrystallization with >98:2 *endo*:*exo* ratio. [c] R = Me or Cl.

Using (*S*)-binap **1**·$AgSbF_6$ the multicomponent version could be performed. Benzaldehyde glycine methyl ester hydrochloride, benzaldehyde, NMM and triethylamine (1.05 equiv), were put together at room temperature to yield compound *endo*-**6aa** in 88% yield, and >99% *ee* (Scheme 3).[17] However, the same reaction promoted by (*S*)-binap **1**·$AgClO_4$ failed. It can be concluded that $AgSbF_6$ is better salt than $AgClO_4$ due to the lower coordination of the counteranion with the silver cation.



Scheme 3. (*S*)-binap **1**·$AgSbF_6$ catalyzed enantioselective multicomponent 1,3-DC.

Later, in other different studies using gold(I) trifluoroacetate we needed to assay the effect of the [(*S*)-binap] **1**·AgTFA in the cycloaddition involving maleimides **5** and imino esters **4** (Table 3 and Scheme of Table 1).[18,19] In this case we observed that the chiral complex could act as a bifunctional catalyst because no external base was required for achieving good conversions. In this case, the counterion acted as base. However, the enantioselections were not so predictable such as occurred in the two previous results (see Tables 2 and 3). Imino ester **4a** (R^1 = H, Ar = Ph) and NMM and NEM afforded excellent *ee* of cycloadduct *endo*-**6** as well as the 2-naphthyl surrogate with NMM (Table 3, entries 1, 2, and 5). This catalytic system was very sensitive to bulky substituents at the α-position of the iminoester **4a** giving low enantioselection (65% *ee*, Table 3, entry 3). Not consistent results were detected when imino esters with 2-aryl or 4-arylsubstituents at the imino moiety were used. Substituent at the *ortho*-position furnished low enantioselections as well (Table 3, entry 3). Surprisingly, *p*-chloroarene gave a racemic product under the same conditions (Table 3, entry 4). In addition, NPM afforded racemic cycloadduct **6** (Table 3, entry 6).

Table 3. Scope of the (*S*)-binap **1**·AgTFA catalyzed 1,3-DC between **4** and maleimides **5**. [a]

Entry	Ar	R^1	R^2	Yield (%)[b]	*ee* (%)
1[c]	Ph	H	Me, Et	86	99
2[d]	Ph	H	Me, Et	80	99
3[d,e]	Ph	Bn	Me	95	65
3[d]	2-R-C_6H_4[f]	H	Me	89-92	50-60
4[d]	4-R-C_6H_4[f]	H	Me	88-91	99-*rac*
5[d]	2-Naph	H	Me	88	99
6[d]	Ph	H	Ph	80	*rac*

[a] Reaction conditions: (*S*)-binap **1**·AgTFA (5 mol%), DIPEA (5 mol%) or without base, toluene, rt, 16 h. [b] Isolated yield after column chromatography or by recrystallization with >98:2 *endo*:*exo* ratio. [c] With DIPEA. [d] Without base. [e] The reaction time was 2 days. [f] R = Me or Cl.

We envisaged that the use of a monodentate phosphorous such as a phosphoramidite would favor the formation of very hindered transition states. Thus, we reported the first enantioselective 1,3-DC induced by a phosphoramidite and a silver salt.[20,21] ^{31}P NMR experiments revealed a wide band centered at 126.9 ppm when a 1:1 mixture of (S_a,*R*,*R*)-**3**·$AgClO_4$ was formed in solution, which corresponded to its polymeric character detected by X-ray diffraction analysis (Figure 3a).[20] The complex **3** formed crosslinked sheets, or polymeric assemblies, which are typical of Ag-complexes, independently of the mono- or bidentate character of the corresponding ligand. The responsible of this crosslink was a π-interaction between an aromatic ring of the phenyl ring of de amino moiety of the phosphoramidite and the

silver atom (Figure 3b). Here, the perchlorate anion was covalently bonded to the complex.

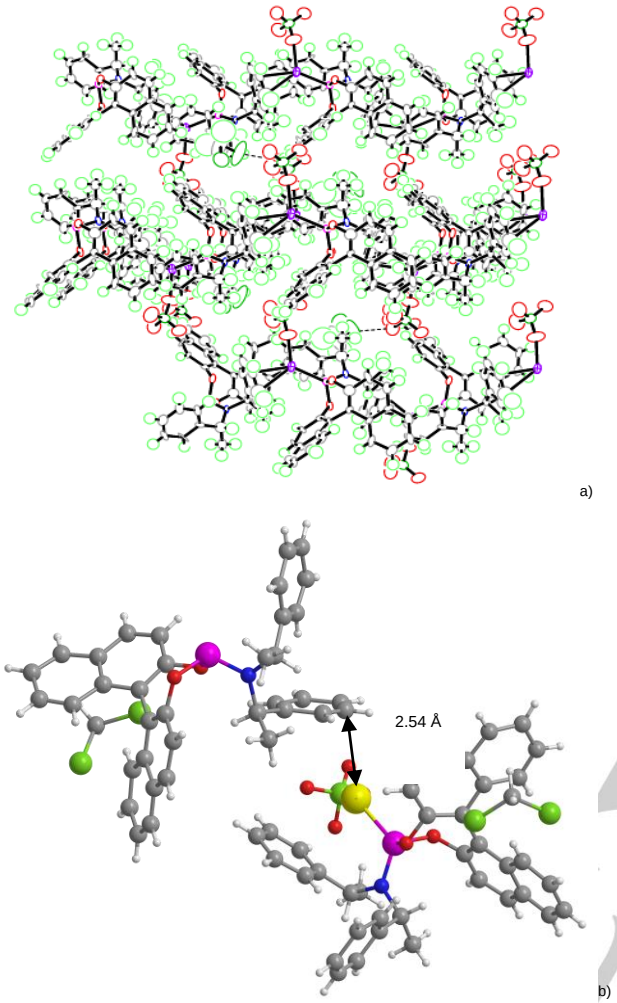
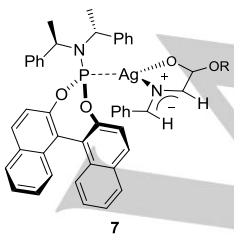


Figure 3. a) Crosslinked sheets of 1:1 mixture of (S_a,*R*,*R*)-**3**·$AgClO_4$ obtained after X-ray diffraction analysis; b) Reproduction of the main intermolecular π-interaction silver atom-aromatic ring.

However, two separated bands were observed at 124.9 and 132.0 ppm in the case of a 2:1 ligand:$AgClO_4$ mixture as a consequence of the partial disaggregation. The complete disaggregation of the polymeric sheets of the 1:1 complex was achieved with the addition of 1 equiv. of the 1,3-dipole generate from **4aa** and triethylamine. The result was the transformation of the original ^{31}P NMR band into two perfectly defined doublets at 125.1 ($J_{P\text{-}Ag(109)}$ = 76 Hz) and 133.61 ppm ($J_{P\text{-}Ag(107)}$ = 73 Hz), which corresponded to the phosphorous atom of the complex **7** (Figure 4) according to ESI-MS experiments.



7

Figure 4. Presumed structure of complex **7** in solution.

The optimization sequence revealed that privileged ligand (S_a)-monophos (**2**) and $AgClO_4$ also promote the enantioselective 1,3-DC between NMM and **4a** (Ar = Ph, R = H). Chemical yield of *endo*-**6aa** was quantitative but only a 60% *ee* was achieved (Table 4, entry 1). In contrast, the analogous 1,3-DC catalyzed by chiral phosphoramidite (S_a,*R*,*R*)-**3**·$AgClO_4$ afforded *endo*-**6aa** with excellent enantioselections at room temperature in shorter reaction times (6 h, Table 4, entry 2). The reaction carried out with NEM afforded 88% *ee* (Table 4, entry 3). In addition, this catalytic system did not resulted to be very sensitive to substituents at the α-position of the iminoester **4a**. For example, the reaction involving alanine derivative and NMM afforded the corresponding compound **6**, with 72% *ee*, after 48 h at -20 ºC. Even a 90% *ee* was determined when the phenylalanine surrogate was allowed to react under the same reaction conditions.[21] NPM did not afford the expected product but a complex reaction crude.

Table 4. Scope of the (S_a,*R*,*R*)-**3**·$AgClO_4$ catalyzed 1,3-DC between **4** and maleimides **5**.[a]

Entry	Ar	R^1	R^2	Yield (%)[b]	*ee* (%)
1[c]	Ph	H	Me	95	60
2[d]	Ph	H	Me	80	>99:1
3	Ph	H	Et	78	88
4[e,f]	Ph	Me	Me	74	72
5[f,g]	Ph	Bn	Me	71	90

[a] Reaction conditions: (S_a,*R*,*R*)-**3**·$AgClO_4$ (5 mol%), Et_3N (5 mol%) toluene, rt, 6 h. [b] Isolated yield after column chromatography or by recrystallization with >98:2 *endo*:*exo* ratio. [c] Reaction performed with (S_a)-**2**·$AgClO_4$. [d] DABCO was used instead of triethylamine. [e] Reaction run at -20 ºC. [f] 48 h were needed. [g] Reaction run at 0 ºC.

Looking for a catalyst showing a different coordination pattern with longer distances metal-dipole to run the reactions with very hindered substrates a gold(I) catalyst was designed (Figure 5). A key to the development of enantioselecive gold(I)-catalyzed transformations has been the identification of enantiomerically pure (gold)-chiral diphosphine complexes of the form [$(AuX)_2$(P-P)*] as catalysts for enantioselective transformations. In this sense, a clear and recent example of the isolation, identification, and characterization of two chiral Binap-gold(I) complexes (*S*)-binap **1**·$(AuX)_2$ and [(*S*)-binap **1**·AuX]$_2$, bearing trifluoroacetate as counteranion, have been reported by Puddephatt *et al.*[22] These complexes were prepared by mixing (Me_2S)AuCl and the corresponding amount of the chiral binap ligand. The resulting gold(I) chloride complexes were treated with different silver salts for 1 h in toluene and the suspension was filtered through a celite plug. The remaining solution was evaporated obtaining the corresponding complexes in 89-96% yields, respectively. These cationic complexes were immediately employed without any other purification in the catalytic enantioselective 1,3-DC. The reaction involving gold complexes derived from binap (**1**) was studied. When this cycloaddition was performed in the presence

of 10 mol% of DIPEA and 10 mol% of complexes (*S*)-binap **1**·$(AuX)_2$ (X = Cl or TFA), product *endo*-**6aa** was obtained with high conversion but in racemic form. However, dimeric complexes type [(*S*)-binap **1**·$AuX]_2$ resulted to be the appropriate catalysts. Thus, in the case of the chiral complex (X = OAc) product *endo*-**6aa** was obtained with high conversion and 60% *ee* in the presence of DIPEA. Interestingly, in the absence of base a 70% *ee* for *endo*-**6aa** was obtained working with [(*S*)-binap **1**·$AuOAc]_2$ complex as a bifunctional catalyst. Better results were achieved when using complex [(*S*)-binap **1**·$AuOBz]_2$ in the presence of DIPEA or in the absence of added base affording cycloadduct *endo*-**6aa** in 74% and 94% *ee*, respectively. When the gold(I) trifluoroacetate complex [(*S*)-binap **1**·$AuTFA]_2$ was used as catalyst, 74% *ee* of compound *endo*-**6aa** was obtained in the presence of DIPEA, whereas without base, 99% *ee* was obtained.

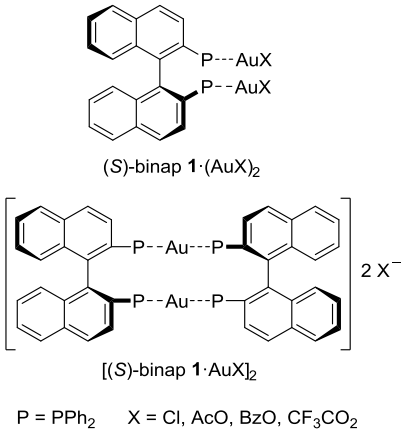


Figure 5. (*S*)-binap **1**·$(AuX)_2$ and [(*S*)-binap **1**·$AuTFA]_2$ catalytic complexes.

In general, if we compare Tables 2, 3 and 5, the results of the general scope were similar for the reactions run with (*S*)-binap **1**·$AgSbF_6$ and with [(*S*)-binap **1**·$AuTFA]_2$ (entries 1, 2, 4 of Tables 2 and 5). The reactions performed with (*S*)-binap **1**·AgTFA were always improved by [(*S*)-binap **1**·$AuTFA]_2$ catalyst. Small differences were observed in the 1-naphthyl derivative [better *ee* was achieved with (*S*)-binap **1**·$AgSbF_6$ (entries 5 of Tables 2 and 5)] and in the imino esters bearing an aromatic group with a substituent in position 2 (entries 3 of Tables 2 and 5). In these last examples dimeric gold complexes gave the highest enantioselections. In addition, the reaction of imino ester **4a** with NPM afforded the corresponding cycloadduct *endo*-**6** in 80% yield and 81% *ee* (Table 5, entry 6). This reaction with chiral silver catalysts did not give high enantioselectivities.

Table 5. Scope of the [(*S*)-binap **1**·$AuTFA]_2$ 1,3-DC between **4** and maleimides **5**.

Entry	Ar	R^1	R^2	Yield (%)[b]	*ee* (%)
1	Ph	H	Me, Et	75-98	99
2	Ph	Bn	Me	78	99
3	2-R-C_6H_4[c]	H	Me	85	88-99
4	4-R-C_6H_4[c]	H	Me	80-90	88-99
5	2-Naph	H	Me	87	90
6	Ph	H	Ph	80	81

[a] Reaction conditions: [(*S*)-binap **1**·$AuTFA]_2$ (5 mol%), toluene, rt, 6 h. [b] Isolated yield after column chromatography or by recrystallization. [c] R = Me or Cl.

It was observed a strong positive NLE (Figure 6) when the reaction of iminoester **4a** was allowed to react with NMM employing different enantiomeric purity of the catalytic chiral complex [(*S*)-binap **1**·$AuTFA]_2$. This behavior could be justified by a generation of a reservoir of unproductive non-chiral heterodimer complex,[23] increasing the concentration of the chiral catalytic active species in solution. This NLE observed in was theoretically calculated, detecting that there was only one energetically feasible geometry for the [(*S*)-Binap **1**,(*R*)-binap **1**-Au_2]-dipole reactive complex and this complex is much more stable than the possible homodimeric species.[13] To the best of our knowledge it was the first work in which NLE was analyzed using computational tools.[19]

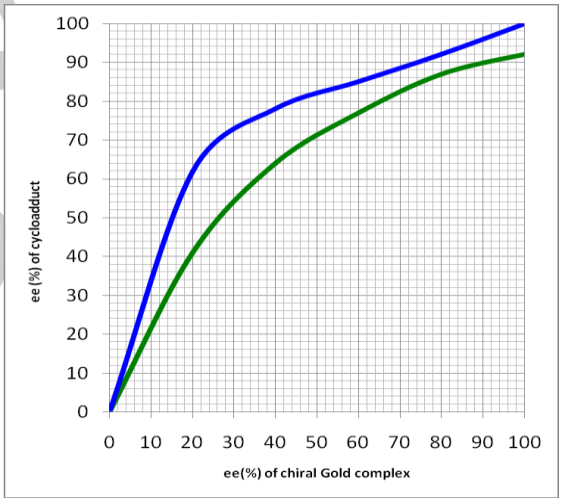


Figure 6. Experimental (blue line) and theoretical (green line) NLE observed in the chiral complex [(*S*)-binap **1**·$AuTFA]_2$ 1,3-DC between the iminoester **4a** and NMM.

The origin of the enantioselection was confirmed by DFT calculations, revealing very interesting geometric data of the transition states.[13,19] Gold atom was exclusively coordinated to nitrogen atom of the imino group. Surprisingly, the second unit of binap-Au is blocking the approach of the dipolarophile through the other face of the metallo-dipole. The reaction of the dipolarophile through the hindered (2*Re*,5*Si*) face of ylide [(S_a)-$binapAu]_2$ were of much higher energy than the obtained from suprafacial approach through (2*Si*,5*Re*) of ylide (Figure 7). Calculations also indicated that the reaction presents a concerted but slightly asynchronous transition structure in which the critical distance of the forming C2-C_{NMM} bond is shorter than that associated with formation of the C5-C'_{NMM} bond. Gold atom

was exclusively coordinated to the nitrogen atom of the imino ester meanwhile silver is coordinated by the iminic nitrogen and by the enolate oxygen atom. If we compared the distance metal-nitrogen $atom_{dipole}$ in binap complexes, for silver a 2.32 Å could be measured whilst a 2.22 Å was determined for gold complex. This relatively close distances together with the higher coordination of the silver cation, supported the high versatility exhibited for [(*S*)-binap 1·AuTFA]$_2$ in the 1,3-DC between imino esters **4** and maleimides **5** incorporating one of both of them a steric hindrance.

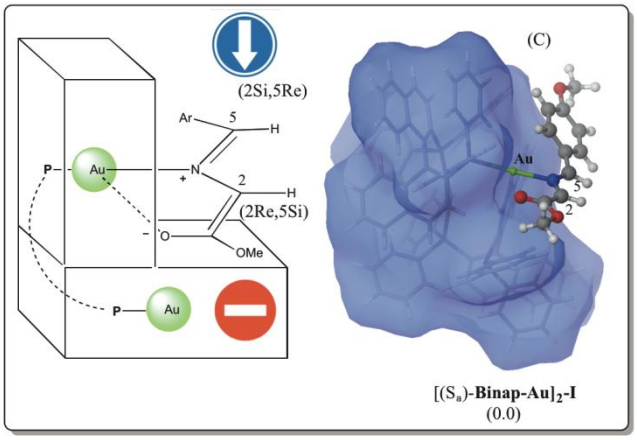
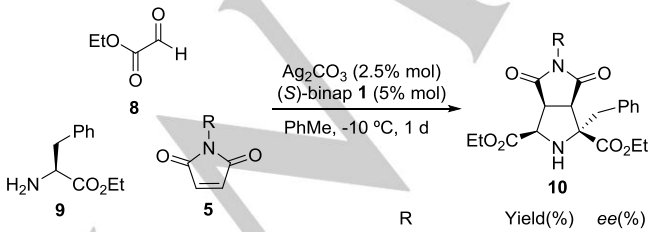


Figure 7. Geometry of the most stable conformation of [(*S*)-binap **1**·AuTFA]$_2$ catalytic complex-dipole.

The enantioselective binap **1**-silver catalyzed multicomponent 1,3-dipolar cycloaddition using ethyl glyoxylate **8**, phenylalanine ethyl ester **9** and maleimides **5** was successfully implemented after a comprehensive optimization work. The employment of the basic silver carbonate allowed the reaction in the absence of an extra base giving high yields and *ee* of compounds **10** (Scheme 4). The study of the scope of this multicomponent reaction in toluene at -10 ºC revealed that *N*-alkyl maleimides **5** (R = Me, Et, Bn) gave high yields of **10** with high enantioselectivities (90, 88, and 80% *ee*, respectively). However, the best results were achieved when NPM and *N*-(4-bromophenyl)maleimide offering 90 and 92% *ee*, respectively.[24] Here, monophos ligand **2** and phosphoramidite ligand **3** were not appropriate for this transformation. Glycine, alanine, and phenylglycine gave good yields and enantioselectivities under this reaction conditions.



R	Yield(%)	*ee*(%)
Me	94	90
Et	96	88
Bn	95	80
Ph	95	90
4-Br-C$_6$H$_4$	98	92

Scheme 4. Scope of the multicomponent (*S*)-binap **1**·Ag_2CO_3 catalyzed 1,3-DC between **9**, ethyl glyoxylate **8** and maleimides **5**.

The presence of a monomeric (ligand-metal) structure (Figure 8) justified the high enantioselectivity observed just with the phenylalanine derivative. A possible favorable π-stacking interaction between the phenyl ring of the amino ester and the phenyl group of a phosphorous atom was observed.[24]

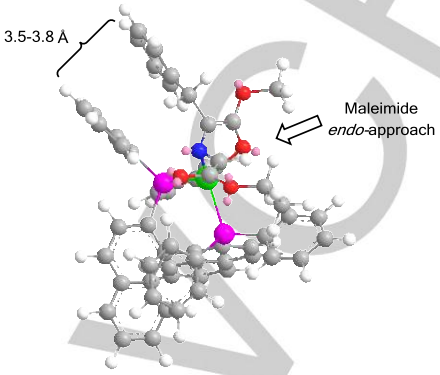
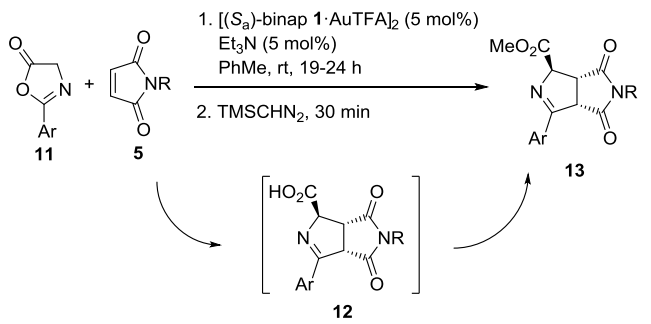


Figure 8. Geometry optimization of the most stable (*S*)-binap **1**·Ag_2CO_3-dipole TS.

Apart from imino esters (previously prepared or generated in situ) oxazol-5-(4*H*)-ones (azlactones) were suitable heterocycles to perform this 1,3-DC.[25] The preparation of azlactones is very simple and their reactivity is very diverse due to their functional groups. These substrates can be easily transformed in münchnones after deprotonation and imine-activation with a chiral Lewis acid. These mesoionic heterocycles are potential 1,3-dipoles. Oxazolone derived from glycine **11** was allowed to react with maleimides at room temperature using a 5 mol% of the chiral catalytic complex [(*S*)-binap **1**·AuTFA]$_2$ and a 5 mol% of base (Table 6). After completion, a large excess of trimethylsilyldiazomethane was added to obtain the methyl ester of intermediate carboxylic acids **12** (30 min). Compounds **13** were obtained diastereoselectively (>98:2, by ^{1}H NMR spectroscopy) after purification and its absolute configuration was established according to the retention times of signals observed after HPLC analysis and by comparison with the previously reported data.[26,27] This reaction was not produced in the presence of any chiral ligands **1**, **2**, and **3** complexed with silver(I) salts.

Following this reaction pattern a set of maleimides were attempted. *N*-Substituted methyl, ethyl and benzylmaleimides did not afford compounds **13** with so high enantioselections despite performing the reaction at -20 ºC (Table 6, entries 1-3). NPM and *N*-(4-acetoxyphenyl)maleimide were the best examples of this series affording almost enantiomerically pure bicyclic products **13** at room temperature (Table 6, entries 4 and 5). In the case of *N*-(4-bromophenyl)maleimide a good enantioselection was observed when the reaction was run at -20 ºC furnishing enantiomerically pure cycloadduct **13** in good chemical yield (Table 6, entry 6). The variation of the arene substituent of the azlactones promoted also excellent to good enantioselections in compounds **13** (Table 6, entries 7 and 8). Even working with a heteroaromatic substituent, such as 2-thienyl, the result was very satisfactory (95% *ee*, Table 6, entry 9).

Table 6. Scope of the [(*S*)-binap **1**·AuTFA]$_2$ 1,3-DC between **11** and maleimides **5**.

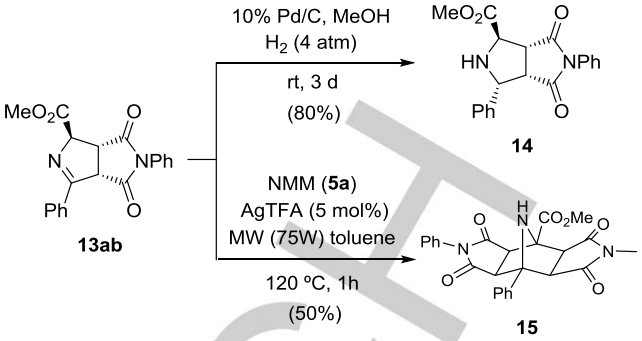


Entry	Ar	R	Yield (%)[a]	*ee* (%)
1	Ph[b]	Me	90	60
2	Ph[b]	Et	70	70
3	Ph[b]	Bn	83	71
4	Ph	Ph	90	99
5	Ph	4-(AcO)C_6H_4	90	99
6	Ph[b]	4-BrC_6H_4	84	99
7	4-MeC_6H_4	Ph	78	99
8	4-ClC_6H_4	Ph	83	98
9	2-Thienyl	Ph	80	95

[a] Isolated yield after column chromatography or by recrystallization. [b] Reaction run at -20 ºC.

As possible applications of the resulting pyrrolines **13**, it was found that 5-epimer **14** (2,5-*trans*) was diastereoselectively generated through a 10% Pd/C catalyzed hydrogenation (4 atm) of **13ab** during three days at room temperature (Scheme 5). This *trans*-arrangement in molecule **14** is not very easy to built because several steps were needed using other synthetic strategies.[28] This result is opposite to the 2,5-*cis*-arrangement generated by a typical W-shape dipole from imino esters **4**.

In addition, pyrrolines **13** also possess a 1,3-dipole precursor structure (azomethine ylide), so a second cycloaddition was attempted with a new equivalent of NMM. The reaction took place under a microwave assisted heating (1 h, 75 W) using triethylamine as base and toluene as solvent at 120 ºC. Polycyclic compound **15** was finally obtained in 50% yield as a single diastereoisomer (Scheme 5).



Scheme 5. Applications of the enantiomerically enriched pyrroline **13ab**.

As a brief summary of this section, all of the processes evaluated were concerted but asynchronous. Complexes (*S*)-binap **1**·AgSbF$_6$ and [(*S*)-binap **1**·AuTFA]$_2$ were more efficient, affording the best enantioselections in the reaction of imino esters **4** and maleimides. Oxazolone reacted with maleimides at room temperature using exclusively a 5 mol% of the chiral catalytic complex [(*S*)-binap **1**·AuTFA]$_2$ whilst silver chiral complexes with phosphoramidites completely failed.

2.2. 1,3-DC involving acrylates

Alkyl acrylates are very frequently used for the optimization and evaluation of the efficiency of many 1,3-DC using several dipoles. In our research concerning the scope of the reaction between acrylates and imino esters **4** we found it very interesting because it was the key to access the synthesis of a family of pyrrolidines active against viruses responsible of the hepatitis C (Figure 9).[29,30] The enantioselective synthesis of these interesting drugs developed by GSK[31] represented a big challenge. The retrosynthetic analysis (Scheme 6) clearly shows the main objective of this particular 1,3-DC involving acrylates.

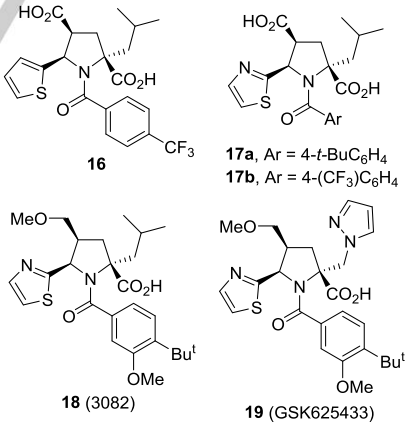
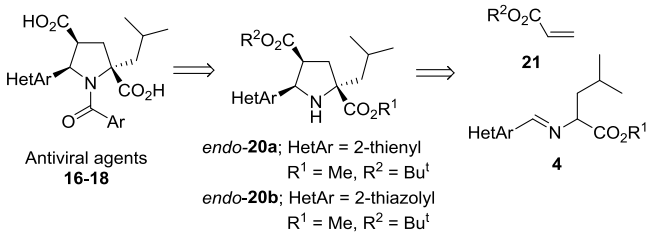
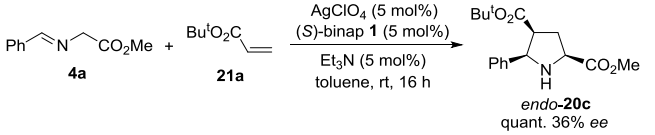


Figure 9. Antiviral agents developed by GSK for the treatment of hepatitis C.



Scheme 6. Retrosynthetic analysis for the construction of the antiviral skeletons **16**-**18**.

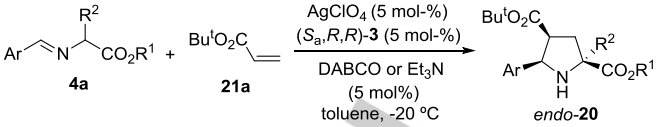
Following with the chronology of this report we initially search the enantioselective synthesis of first generation GSK antiviral agent **16**. Thus, catalytic complex (*S*)-binap **1**·$AgClO_4$ was attempted in the reaction of **4a** and *tert*-butyl acrylate **21a** obtaining compound *endo*-**20c** (>98:2 *endo*/*exo* ratio) quantitatively but with very low enantioselection (36% *ee*) (Scheme 7).[11]



Scheme 7. 1,3-DC of **4a** and *tert*-butyl acrylate **21a** catalyzed by (*S*)-binap **1**·$AgClO_4$ complex.

This disappointed result was overcome by the employment of (S_a,*R*,*R*)-**3**·$AgClO_4$ complex. In this case, under the optimized reaction conditions, the synthesis of *endo*-cycloadducts **20** was achieved using DABCO or triethylamine as base in a range of temperatures between 0 and -20 ºC. Isolated chemical yields of pure stereoisomers *endo*-**20** were high but the enantioselections were excellent (Table 7).[10,11] The reaction with *tert*-butyl acrylate **21a** afforded better *ee* than the analogous reaction run in the presence of methyl acrylate **21b**. Monophos **2**·$AgClO_4$ complex was allowed to catalyze the same reaction obtaining in 95% yield the corresponding cycloadduct *endo*-**20** with a low 52% *ee*. For example, isopropyl ester of compound **4** is more appropriate for reactions of **21a** with phenyl or with 4-substituted aryl imino esters (Table 7, entries 2 and 4). In both cases, the best base was DABCO. Methyl ester of **4** (Ar = Ph) afforded lower *ee* (88%, Table 7, entry 1). However it was selected for reactions of **4** (Ar = 4-RC_6H_4) and **21a** (Table 7, entry 4). For 2-naphthyl-substituted imino ester **4**, the combination of methyl ester and triethylamine gave the highest *ee* (92%, Table 7, entry 5). The reactions with α-substituted imino esters **4** derived from alanine, phenylalanine and leucine afforded *endo*-cycloadducts **20** with high enantioselections and good chemical yields (Table 7, entries 6-9). The example recorded in the last entry of Table 7, using the 2-thienyl group bonded to the leucine dipole precursor encourage us to prepare the corresponding HCV inhibitor **16**.
The higher performance of **3** than **1** in the reaction of acrylates could be due to a better electrostatic secondary interaction between the metal center and the carbonyl group of the dipolarophile in a less congested transition state.

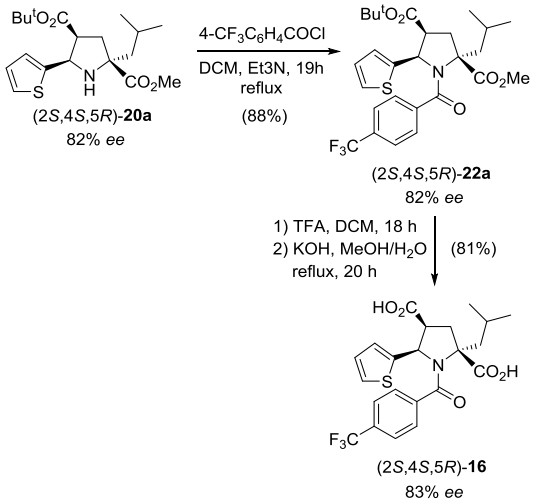
Table 7. Scope of the (S_a,*R*,*R*)-**3**·$AgClO_4$ catalyzed 1,3-DC between **4** and *tert*-butyl acrylate **21a**.



Entry	Ar	R^1	R^2	Yield (%)[a]	*ee* (%)
1	Ph[b]	Me	H	80	88
2	Ph[c]	Pr^i	H	83	>99
3	2-RC_6H_4[b,d]	Me	H	80-83	>99
4	4-RC_6H_4[b,d]	Pr^i	H	76-80	90-94
5	2-Naph[c]	Me	H	84	92
6	Ph[c]	Me	Me	78	94
7	2-Thienyl[c]	Me	Me	78	92
8	Ph[c]	Me	Bn	77	98
9	2-Thienyl[c]	Me	Bu^i	70	82

[a] Isolated yield after column chromatography or by recrystallization. [b] Reaction run with DABCO. [c] Reaction run with triethylamine. [d] R = Me, Cl.

For the synthesis of the HCV inhibitor **16** the reaction affording heterocycle **20a** took place in 70% yield and 82% *ee*. The intermediate prolinamide **22** was synthesized in 88% yield (estimated by ^{1}H NMR) from enantiomerically enriched **20a** by a simple amidation reaction with 4-(trifluoromethyl)benzoyl chloride in refluxing dichloromethane during 19 h. The crude product was submitted, in a second step, to a hydrolysis of the *tert*-butyl ester with trifluoroacetic acid followed by the methyl ester hydrolysis using a 1M aqueous solution of KOH in methanol for 16 h. The first enantioselective synthesis of dicarboxylic acid **16** was finally accomplished in 81% yield from compound **22** (50% overall yield from iminoester **4**) in 83% *ee* (Scheme 9).[11]



Scheme 9. Enantioselective synthesis of the first generation GSK HCV inhibitor **16**.

The origin of this high enantioselection was studied through DFT calculations. It was observed that the dihedral angle formed by the two naphthyl groups is of *ca.* 57-58 deg. In the case of the most stable stepwise transition state (Figure 10), this lead to the blockage of the *Re-Si* face of the dipole. Since there is a stronger steric congestion between one naphthyl group and the *tert*-butyl group of the dipolarophile. These results were in good agreement with the experimental ones because they supported a preferential generation of the *endo*-(2*S*,4*S*,5*R*)-**20**. Note the interaction of the silver atom with the dipole and also a weaker one with the carbonyl group of the dipolarophile was estimated.[11,13] For comparison, the other diastereomeric *endo*-TS was less favorable in around 1.3 kcal·mol^{-1}. However, higher energy values (9.7-10.0 kcal·mol^{-1}) were registered for the *exo*-TS. According to these DFT calculations these 1,3-DC occurred through a stepwise mechanism being the first Michael type addition step the responsible of the enantiocontrol of the process.

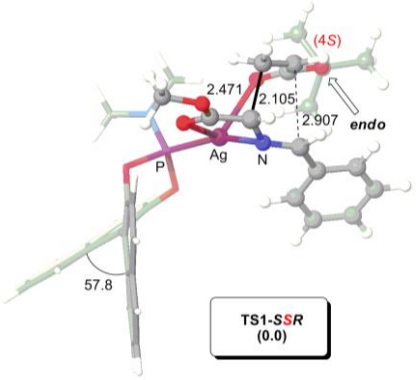


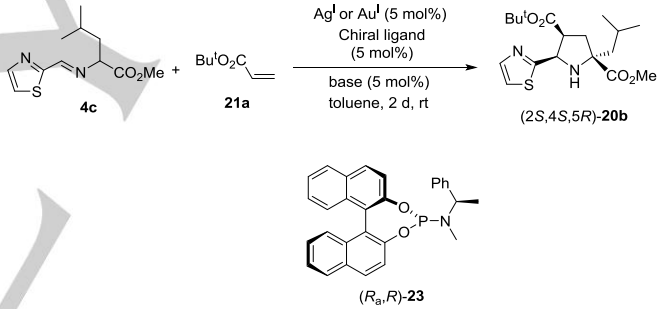
Figure 10. Chief geometric features of the most stable transition structure associated with the first step in the reaction between *t*-butyl acrylate **21a** and complex by (*S*$_a$)-monophos **2** and imine **4aa**. These fully optimized structures were computed at the B3LYP/LanL2DZ&6-31G* level. The energies were computed at the B3LYP/ LanL2DZ &6-31G*+ΔZPVE level of theory.

According to all these results, the synthesis of second generation GSK antivirals **17** and **18** only would be possible using (*S*$_a$,*R*,*R*)-**3**·AgClO$_4$ as catalyst. Once iminoester **4c** was prepared the 1,3-DC was essayed finding the best enantioselection for cycloadduct **20b** in the presence of DIPEA as base after 2 d at room temperature (Table 8, entry 1). Other silver salts were not appropriate for this purpose employing chiral phosphoramidite **3** (Table 8, entries 2 and 3).

At this point a very important feature regarding all these enantiocontrolled 1,3-DC was confirmed. They are extremely sensitive to structural modifications and reaction conditions. So, we performed a comprehensive screening employing silver(I) and gold(I) salts[15,19] ligands **1**, **3** and **23** being the most appropriate (Table 8).

Despite low enantioselections registered in the reaction performed between conventional imino esters **4** and acrylates using binap-derived catalytic silver(I) or gold(I) complexes, the 1,3-DC of the heterocyclic imino ester **4c** and *tert*-butyl acrylate was very efficient with ligand **23** together with AgSbF$_6$ rather than with AgTFA (Table 8, entries 4 and 5). Surprisingly, (*S*)-binap **1** combined with AgClO$_4$ or AgTFA afforded very important enantioselections of cycloadduct **20b** in good chemical yields (Table 4, entries 6-8). These results could not be improved by lowering the temperature, but with dimeric chiral gold(I) catalyst [(*S*$_a$)-binap **1**·AuTFA]$_2$ the process was very efficient at 0 ºC (92% yield and 99% *ee*) rather that at room temperature (Table 8, entries 9 and 10).

Table 8. Optimization of the synthesis of intermediate **20b**.



Ent.	Ag^I or Au^I	Ligand	Base	Yield (%)[a]	*ee* (%)
1	AgClO$_4$	**3**	DIPEA	86	30
2	AgTFA	**3**	Et$_3$N	72	50
3	AgSbF$_6$	**3**	Et$_3$N	82	40
4	AgTFA	**23**	DIPEA	82	64
5	AgSbF$_6$	**23**	Et$_3$N	82	99
6	AgClO$_4$	**1**	Et$_3$N	78	88
7	AgTFA	**1**	Et$_3$N	75	88
8	AgSbF$_6$	**1**	Et$_3$N	79	72
9	[(*S*)-binap **1**·AuTFA]$_2$		Et$_3$N	90	78

10	[(*S*)-binap **1**·AuTFA]$_2$	Et_3N[b]	92	99

[a] Isolated yield after column chromatography or by recrystallization. [b] Reaction performed at 0 ºC for 3 d.

This final result was analyzed using DFT calculations obtaining that there was only one energetically accessible conformation due to the high substitution of the leucine-derived ylide (Figure 11).[13,27] In this reactive gold complex there is an effective blockage of the (2*Re*,5*Si*) prochiral face of the ylide. Therefore, the predicted stereochemical outcome corresponds to the exclusive formation (2*S*,4*S*,5*R*)-**20b** cycloadduct, the same as obtained experimentally. The planarity of the whole dipole would also increase the reaction rate of the process, even at 0 ºC. 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. Again the iminic nitrogen is directly coordinate to the gold(I) atom and with the nitrogen atom of the thiazole ring rather than with the sulfur atom.

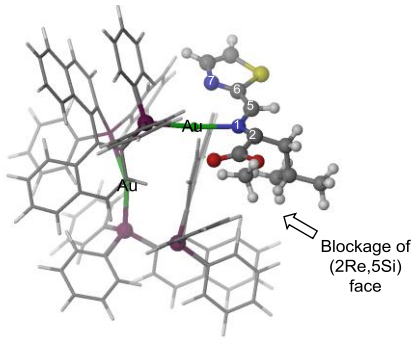
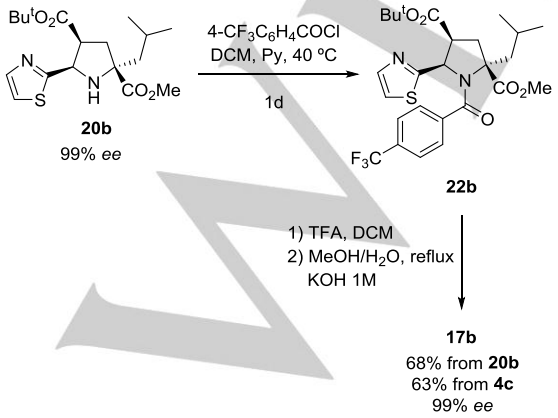


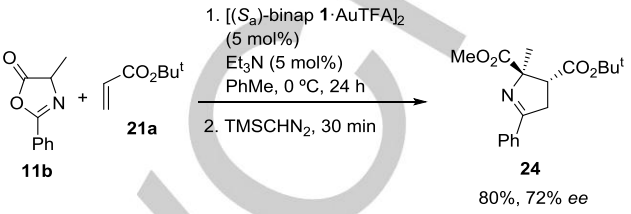
Figure 10. Lower energy transition state structure corresponding of the 1,3-DC of Au(I) ylide complex and dipole generated from **20b** computed at ONIOM(B3LYP/LanL2DZ:UFF) level of theory.

With the best enantiomerically enriched cycloadduct **20b**, the synthesis of the second generation antiviral agent **17b** could be accomplished in two conventional steps such as it was indicated in Scheme 10. The final product **17b** was finally isolated in 68% overall yield (from pyrrolidine **20b**) and with 99% *ee*, or in 63% overall yield from iminoester **4c** (Scheme 18).



Scheme 10. Total enantioselective synthesis of the second generation GSK antiviral agent **17b**.

When *tert*-butyl acrylate was allowed to react with azlactones **11** but the unique productive transformation was when the alanine-derived 4-methyloxazole-5-one **11b** was employed as dipole precursor at 0 ºC using [(*S*)-binap **1**·AuTFA]$_2$ as catalyst. Compound **24** was isolated in high yield (80%) and relatively good enantioselection (72% *ee*, Scheme 11).



Scheme 11. Enantioselective synthesis of pyrroline **24**.

If we compare this result with previous ones derived from lineal imino esters (see scheme of Table 7) this last diastereoselective cycloaddition exhibited an opposite regioselection, which 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. To gain more insight into the unexpected regioselectivity of the 1,3-DC depicted in Scheme 19, results obtained using Natural Resonance Theory (NRT) analysis were crucial. The most stable Lewis structures of the ylides obtained shown that the negative charge in the Lewis structure of the corresponding ylide is mainly placed on C5 atom.[13,27]

As conclusion, acrylates reacted with azlactones **11** and imino esters **4** through a concerted but asynchronous process. For imino esters the presence of phosphoramidite **3**·$AgClO_4$ ensured the widest scope. This reaction resulted to be the key step for the access to a family of HCV inhibitors developed by GSK. For this purpose, the better catalyst for the synthesis of the first generation GSK HCV inhibitor **16** was formed by the named phosphoramidite **3**·$AgClO_4$ whilst both phosphoramidite **23**·$AgSbF_6$ or [(*S*)-binap **1**·AuTFA]$_2$ were appropriate for the preparation of the second generation GSK HCV inhibitor **17b**.

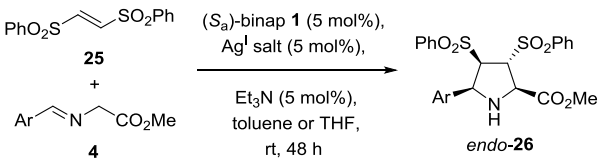
2.3. 1,3-DC involving vinyl sulfones

One of the featuring properties of vinylic sulfones is their ability to act as Michael type acceptors. They have been used in enantioselective 1,3-DC employing mostly chiral copper(I) complexes.[6] In our research regarding vinyl sulfones the scope of enantioselective 1,3-DC was reduced to the employment of *trans*-1,2-bis(phenylsulfonyl)ethylene (BPSE) **25**. This electrophilic alkene is a synthetic equivalent of acetylene and has been employed in the synthesis of the corresponding *exo*-cycloadducts in the presence of chiral copper(I) complex.[32] This electron-poor alkene was tested in the presence of chiral phosphoramidites **2** or **3** and the corresponding silver(I) or gold(I) salt. Simply, no reaction was observed when chiral phosphoramidites were used independently of the metal introduced for the generation of the catalytic complex.

However, (*S*)-binap **1**·AgX complexes allowed the enantioselective reaction with different results in terms of enantiodiscriminations. Despite toluene was used as the

selected solvent, the reactions run in THF were also compared because it was observed a very clean reaction mixture, and crude products *endo*-**26** did not require additional purification. In general, the reaction performed with (*S*)-binap **1**·$AgClO_4$ never improved the results generated by intermediacy of (*S*)-binap-$AgSbF_6$ (Table 9). As representative examples, phenyl- and 2-naphthyl substituents bonded to the imino group afforded high enantioselections of the product **26** (Table 9, entries 1-4). Methyl substituent at the *para*-position of the imino ester also gave good enantioselections (Table 9, entries 5 and 6). The 3-pyridyl group was the most appropriate heterocycle (Table 9, entries 7 and 8). Sterically hindered α-alkyl substituted imino esters furnished lower *endo:exo* ratio and lower enantioselections.[14,15]

Table 9. Synthesis of compounds *endo*-**26** using $AgSbF_6$ or $AgClO_4$ and (*S*)-binap **1** as catalyst.



Ent.	Ar	Solvent	Yield (%)[a][b]	*endo*:*exo*	*ee* (%)[b]
1	Ph	PhMe	81 (80)	>98:2	90 (88)
2	Ph	THF	82	>98:2	90
3	2-Naphthyl	PhMe	91 (88)	>98:2	92 (80)
4	2-Naphthyl	THF	90	>98:2	80
5	4-MeC_6H_4	PhMe	91 (78)	>98:2	88 (28)
6	4-MeC_6H_4	THF	78	>98:2	82
7	3-Pyridyl	PhMe	83 (82)	>98:2	93 (78)
8	3-Pyridyl	THF	92	>98:2	90

[a] Isolated yield after column chromatography or by recrystallization. [b] In brackets the result obtained with (*S*)-binap **1**-$AgClO_4$ complex.

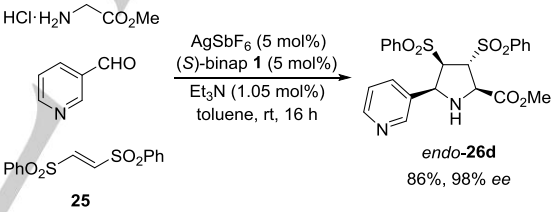
Binap-gold(I) trifluoroacetate complex dimer [(*S*)-binap **1**·AuTFA]$_2$ was next tested in the enantioselective cycloaddition of azomethine ylides and BPSE **25** and compared with the same reactions catalyzed by (*S*)-binap **1**·AgTFA complex (Table 10). The reaction, performed with both catalysts (5 mol % of metal) operated with higher enantioselections in the absence of base. In all cases, silver catalysis did not improve the effectiveness of gold(I) catalysis. For aromatic and heteroaromatic imino moieties no added base was needed for achieving high *ee* (Table 10, entries 1, 3 and 4), but in the case of 2-naphthyl derivative DIPEA (10 mol%) was needed. In its absence a racemic mixture was obtained in both examples (Table 10, entry 2).[19]

Table 10. Synthesis of compounds *endo*-**26** using [(*S*)-binap **1**·AuTFA]$_2$ as catalyst.[a]

Ent.	Ar	Yield (%)[b][c]	*endo*:*exo*	*ee* (%)[c]
1	Ph	81 (81)	>98:2	99 (96)
2	2-Naphthyl[d]	91 (90)	>98:2	88 (64)
3	4-MeC_6H_4	67 (75)	>98:2	99 (96)
4	3-Pyridyl	73 (69)	>98:2	96 (96)

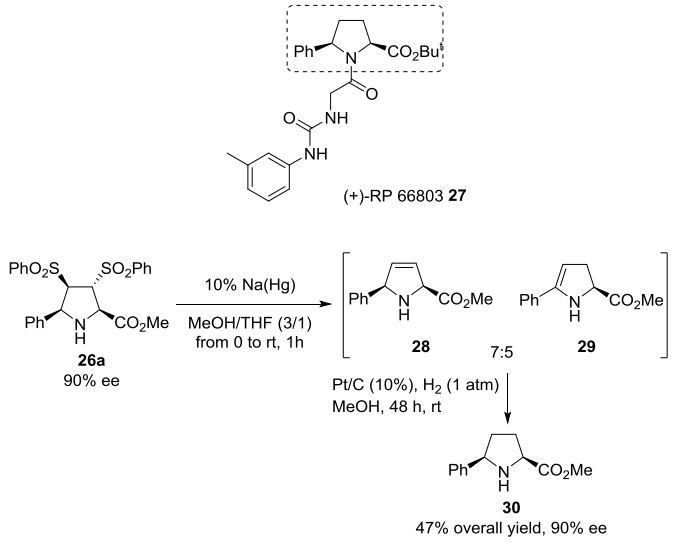
[a] Reaction conditions: [(*S*)-binap **1**·AuTFA]$_2$ (5 mol%), Et_3N (5 mol%) toluene, rt, 48 h. [b] Isolated yield after column chromatography or by recrystallization. [c] In brackets results obtained with (*S*)-binap **1**-AgTFA complex. [d] DIPEA (10 mol%) was used.

This gold(I) catalysis afforded higher *ee* of cycloadducts *endo*-**26** than the reaction catalyzed by (*S*)-binap **1**·$AgSbF_6$. In fact, the dimeric species [(*S*)-binap **1**·AuTFA]$_2$ can act as bifunctional catalysts employing its trifluoroacetate anion as internal base. However, (*S*)-binap **1**·$AgSbF_6$ was able to promote the multicomponent 1,3-DC between glycine methyl ester hydrochloride, 3-pyridinecarbaldehyde and **25** giving compound *endo*-**26d** in 86% yield and 98% *ee* (Scheme 12), whilst no reaction occurred in the presence of [(*S*)-binap **1**·AuTFA]$_2$.



Scheme 12. (*S*)-Binap **1**·$AgSbF_6$ catalyzed enantioselective multicomponent 1,3-DC.

A direct application of using BPSE was envisaged. The synthesis of 5-substituted prolines gave access to biologically active compounds, such as nonpeptide cholecystokinin antagonist (+)-RP 66803 **27**.[33] The 5-phenylprolinate fragment was prepared according to the route described in Scheme 13. Isomers **28** and **29** were obtained after desulfonylation with sodium amalgam (10%) and the crude mixture, without purification, was submitted to hydrogenation with Pt/C (10%). The enantiomeric excesses of both prolinates remained unaltered with respect to the starting disulfonylated heterocycle ones. The overall yield of **30** was 47%, and could be justified by the formation of significant amounts of pyrrole derivative after the desulfonylation step.[19]



Scheme 13. Synthesis of enantiomerically enriched *trans*-2,5-disubstituted proline **30**.

Following the approach of Coldham's group, inspired in a 1,3-DC using disulfones,[34] new starting -suitably protected- aromatic precursors **26e** and **26f** were prepared (Figure 12). These molecules are direct precursors of natural (*R*)-(+)-crispine A **31** and (*R*)-(+)-harmicine **32**, which are natural products used as antitumoral agent and anti-leishmaniasis drug, respectively.[35,36]

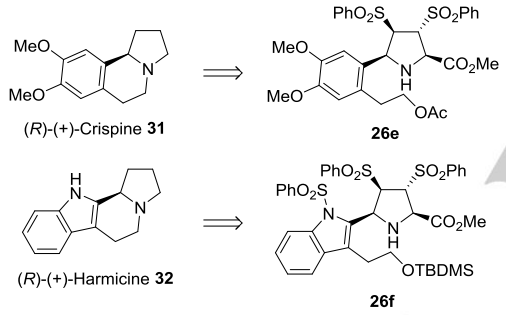
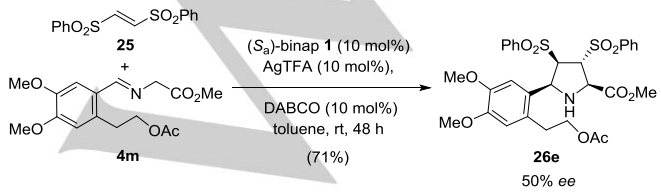


Figure 12. Retrosynthetic analysis of natural compounds **31** and **32**.

The reaction of the imine **4m** (obtained from the corresponding aldehyde[37] and methyl glycinate) and disulfone **25** was accomplished at room temperature in toluene as solvent and a 10 mol% of catalyst loading (formed by chiral binap and silver trifluoroacetate). The best result (71% yield and 50% *ee*) was achieved adding DABCO (10 mol%) to the reaction mixture (Scheme 14).[15]



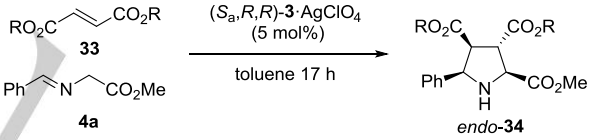
Scheme 14. Enantioselective synthesis of **26e**.

Unfortunately, following the best reaction conditions described in Scheme 24 and other different modifications, compound **26f** was obtained from the corresponding imine in 60% chemical yield and a very poor enantioselectivity (up to 12% *ee*).[15]

With all these results BPSE **25** and imino esters **4** afforded very good enantioselections using (*S*)-binap **1** with $AgSbF_6$ rather than with $AgClO_4$, and several examples were improved by the employment of dimeric [(*S*)-binap **1**·AuTFA]$_2$ complex.

2.4. 1,3-DC involving fumarates

Fumarates **33** are considered very useful dipolarophiles and they are frequently employed in cycloaddition reactions. During our studies of enantioselective 1,3-DC we tried to perform it using silver(I) and gold(I) complexes derived from chiral ligand (*S*)-binap **1**. The reaction was successful in terms of chemical yields, employing several silver(I) salts and even the dimeric [(*S*)-binap **1**·AuTFA]$_2$ complex but none of these processes afforded *endo*-**34** with more than 30% *ee*.
However, (S_a,*R*,*R*)-**3**·$AgClO_4$ complex was much more effective for this particular transformation obtaining compound *endo*-**34** (>98:2 *endo*/*exo* ratio) in good chemical yields (79-81%) and high *er* (91:9). The reaction conditions were variable, thus diisopropyl fumarate required triethylamine as base, at -20 ºC for 17 h, and diisobutyl fumarate reacted in the presence of DABCO at 0 ºC for 17 h as well (Scheme 15).[20,21]



R	base (5 mol%)	T (ºC)	Yield(%)	*er*
Pr^i	Et_3N	-20	81	91:9
Bu^i	DABCO	0	79	91:9

Scheme 15. Enantioselective synthesis of *endo*-**34**.

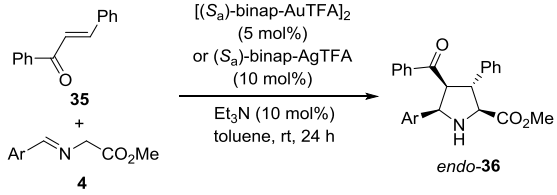
In this section the summary is very clear because (S_a,*R*,*R*)-**3**·$AgClO_4$ complex is the unique to yield high *ee* (82%) in spite of trying different conditions and catalysts.

2.5. 1,3-DC involving α,β-unsaturated ketones

Conjugated aldehydes did not react at all using the reaction conditions of the metal-catalyzed 1,3-DC described along the previous sections of this report. However, the not so polymerizable α,β-unsaturated ketones could be trapped with high enantioselectivies. The first attempt was carried out between **4** and chalcone **35**, evaluating the effectiveness of (*S*)-binap **1**·AgTFA and [(*S*)-binap **1**·AuTFA]$_2$ complexes. Their reactivities were compared to each other employing a 10 mol% of base at room temperature (Table 11). In all cases, the

diastereoselection was very high and the best enantioselectivities in **36** were induced by [(*S*)-binap **1**·AuTFA]$_2$ (Table 11).[19]

Table 11. Synthesis of compounds *endo*-**36** using [(*S*)-binap **1**·AuTFA]$_2$ or (*S*)-binap **1**·AgTFA complexes as catalysts.

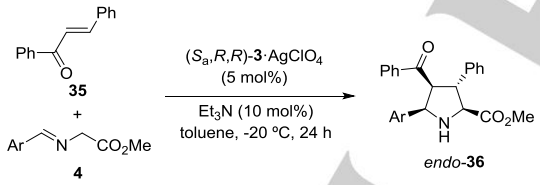


Ent.	Ar	Yield (%)[a][b]	*endo*:*exo*	*ee* (%)[b]
1	Ph	95 (80)	>98:2	80 (20)
2	2-Naphthyl	90 (81)	>98:2	60 (50)
3	4-MeC$_6$H$_4$	80 (80)	>98:2	80 (74)

[a] Isolated yield after column chromatography or by recrystallization. [b] In brackets the result obtained with (*S*)-binap **1**·AgTFA complex.

Excellent results were obtained when chiral phosphoramidite (*S*$_a$,*R*,*R*)-**3** and AgClO$_4$. Chalcone **33** reacted with imino esters **4** smoothly giving at -20 ºC product *endo*-**36** (Table 12).[21] These results improved the enantioselections described for the reaction run with [(*S*)-binap **1**·AuTFA]$_2$ or (*S*)-binap **1**·AgTFA complexes as catalysts (compare Tables 11 and 12).

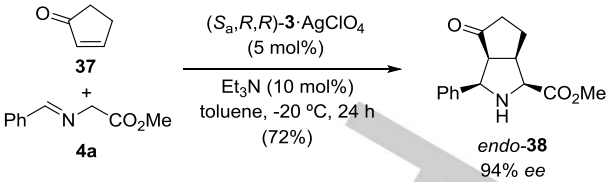
Table 12. Synthesis of compounds *endo*-**36** using (*S*$_a$,*R*,*R*)-**3**·AgClO$_4$ complex as catalysts.[a]



Ent.	Ar	Yield (%)[b]	*endo*:*exo*	*ee* (%)
1	Ph	80	>98:2	>99
2	2-MeC$_6$H$_4$	70	>98:2	98
3	4-MeC$_6$H$_4$	75	>98:2	94

[a] Reaction conditions: (*S*$_a$,*R*,*R*)-**3** and AgClO$_4$ (5 mol%), Et$_3$N (10 mol%) toluene, -20 ºC, 24 h. [b] Isolated yield after column chromatography or by recrystallization.

Cyclohex-2-enone **37** was another good candidate to test furnishing *endo*-**38** (72% yield, and 94% *ee*) under the same reaction conditions promoted by chiral (*S*$_a$,*R*,*R*)-**3**·AgClO$_4$ complex (Scheme 16).[19] This transformation could not be performed in the presence of binap **1** complexes.



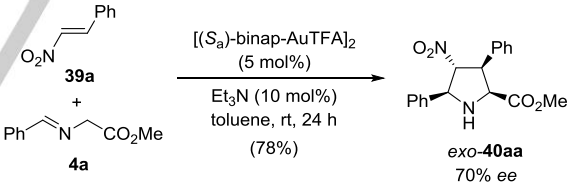
Scheme 16. Enantioselective synthesis of *endo*-**38** using (*S*$_a$,*R*,*R*)-**3**·AgClO$_4$ complex.

Reaction conditions promoted by the chiral phosphoramidite (*S*$_a$,*R*,*R*)-**3**·AgClO$_4$ complex must be taken in consideration whether a highly enantioselective transformation involving imino esters **4** and conjufated ketones is desired.

2.6. 1,3-DC involving nitroalkenes

Substituted 4-nitroprolinates obtained from the corresponding 1,3-dipolar cycloadditions (1,3-DC) between glycine ester aldimines and nitroalkenes,[38] are important inhibitors of $\alpha_4\beta_1$-integrin-mediated hepatic melanoma metastasis.[39] The most simple nitroprolines have been recently used as chiral organocatalysts in aldol reactions.[40] Silver(I) complexes (perchlorate and hexafluoroantimoniate) derived from chiral binap **1** or chiral phosphoramidites **2** or **3** afforded very complex reaction mixtures.

However, the reaction between iminoester **4a** and β-nitrostyrene **39a** afforded a very clean crude reaction product when dimeric [(*S*)-binap-AuTFA]$_2$ was used as catalyst. The diastereoselectivity was not as high as in previous cycloadditions, generating a 20:80 *endo*:*exo* mixture of crude **40aa** despite running the reaction at –20 ºC (Scheme 17).[19]



Scheme 17. Enantioselective synthesis of *exo*-**40a** using [(*S*)-binap-AuTFA]$_2$ complex.

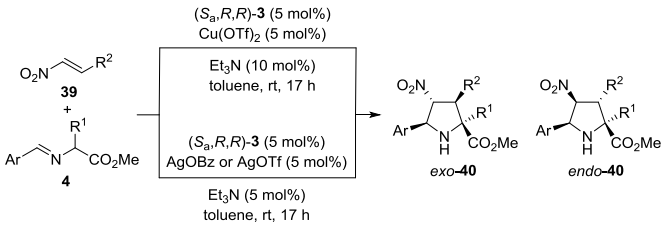
However, phosphoramidites were the ligands of choice for this 1,3-DC.[41] The scope of the reaction took place with different nitroalkenes **39**, employing various arylideneimino esters **4** under the control of: a) the catalyst formed by phosphoramidite (*S*$_a$,*R*,*R*)-**3** and Cu(OTf)$_2$[42] or by the catalyst originated by (*S*$_a$,*R*,*R*)-**3** and AgOTf[43] or the combination of phosphoramidite (*S*$_a$,*R*,*R*)-**3** with AgOBz.[43] The whole study was carried out methyl α-imino esters as metallo-azomethine ylide precursors because the presence of other different esters did not improve the results (Scheme 18).

The study of the influence of the aryl substituent of the nitroalkene **39** for the 1,3-DC with methyl benzylidene glycinate revealed that, in general, higher chemical yields, *exo*-diastereoselectivties and enantioselections in products *exo*-**40** were observed when the reactions occurred in the presence of

(S_a,*R*,*R*)-**1**·AgOBz rather than with the silver(I) or copper(II) triflates (61-92% yield, and up to >99% *ee*).

When alanine, leucine, and phenylalanine derived imino esters **4** were used as azomethine ylide precursors, an increment of the *endo*-diastereoisomers **40** was observed. Surprisingly this diastereoisomer was always obtained as a racemic mixture. The corresponding quaternized pyrrolidines *exo*-**40** were satisfactorily isolated (>99:1 *er*) by employing (S_a,*R*,*R*)-**3**·Cu(OTf)$_2$ catalysis.

With respect to the reaction of different methyl arylideneimino glycinates **4** with nitrostyrene **39a**, the more sterically hindered *o*-tolyl imino group also favoured the generation of the *endo*-isomer **40** but in less proportion in the case of AgOBz. For different aryl-substituted imino esters better results for compounds **40** were observed when (S_a,*R*,*R*)-**3**·AgOTf was the selected catalyst, rather than the processes mediated by the silver benzoate (70-81% yield, >99:1 *ee*).



Scheme 18. Enantioselective synthesis of *exo*-**40** using silver(I) or copper(II) and chiral phosphoramidite **3** complex.

In Figure 13 we can observe a summary of the most important features of each catalytic complexes during their evaluation in 1,3-DC between stabilized azomethine ylides obtained from **4** and nitroalkenes **39**.

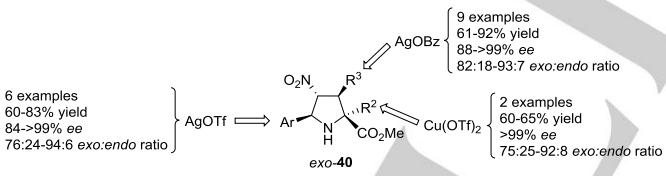


Figure 13. Recommended salts for the enantioselective synthesis of cycloadducts *exo*-**40** in the presence of chiral phosphoramidite ligand **3**.

In general, for silver(I) or copper(II) catalysis the computed transition structures correspond to a stepwise mechanism,[44] in which the first step consists in a Michael addition of the enolate moiety in the *N*-metallated azomethine ylide to β-nitrostyrene forming a zwiterionic intermediate that undergoes an intramolecular Mannich-like reaction to yield the final cycloadduct. Our results showed the predicted preference of the *exo*-approaches over the *endo*-ones due to the presence of OTf on the silver coordination sphere. It is noticeable that in all of the *endo*-approaches, their corresponding energies were higher.

DFT calculations[13] on the (S_a,*R*,*R*)-**3**·Cu(OTf)$_2$ catalyzed reaction to obtain **40a**, showed that the coordination sphere of Cu(II) atom is saturated by a OTf moiety. The most stable transition structures located are depicted in Figure 14. (*S*,*S*)-*exo*-**TS1** 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. It is noticeable that the anion is blocking one of the enantiotopic faces of the dipole.[42]

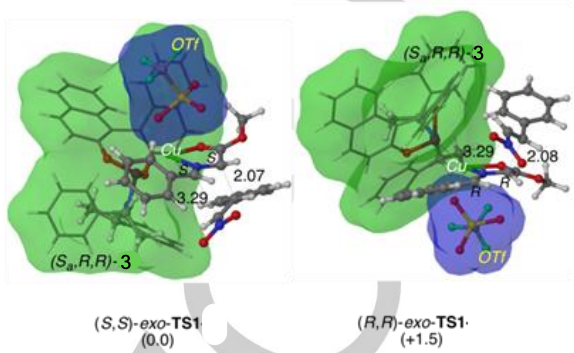


Figure 14. Main geometric features and relative energies (in kcal mol^{-1}) of the computed transition structures associated with the first step of the reaction between **4a** and (S_a,*R*,*R*)-**3**·CuOTf-**II** with nitrostyrene **39a** computed at M06/LANL2DZ//ONIOM (B3LYP/LANL2DZ:UFF) + ΔZPCE level of theory. Bond-lengths are given in Å. The chiral ligand and OTf moiety are highligted in green and blue, respectively.

In the example run with AgOTf the effective blockage of one prochiral face by the (S_a,*R*,*R*)-**3**·AgOTf catalytic system is pointed out by the energetic difference of 3.8 kcal mol^{-1} between (*S*,*S*)-**TS1-*exo*** and (*R*,*R*)-**TS1-*exo*** in favor to the former one. This energetic difference means a theoretical ee_{exo} of about 99%, in good agreement with the experimental results. Here, the presence of the anion is not so crucial than in the example of the catalysis in presence of copper(II) metal. Here, the aromatic moieties of the ligand were blocking one of the two accessible fases (Figure 15).

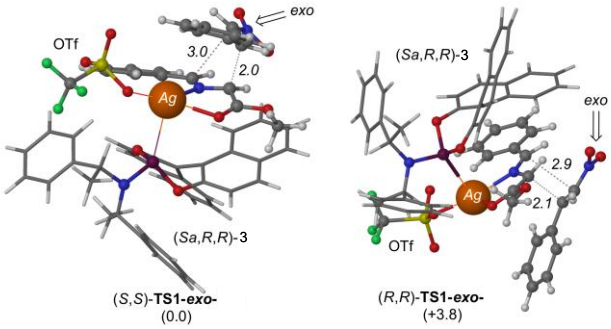
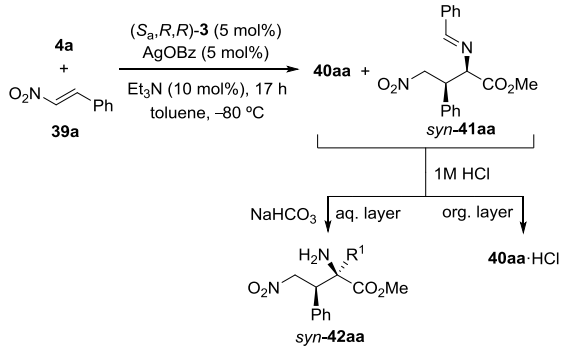


Figure 15. Main geometrical features and relative energies (in kcal mol^{-1}) of transition structures associated with the first step of the 1,3-DC reaction of imine **4a** and β-nitrostyrene **39a** catalyzed by (S_a,*R*,*R*)-**3**·AgOTf. Distances are in Å.

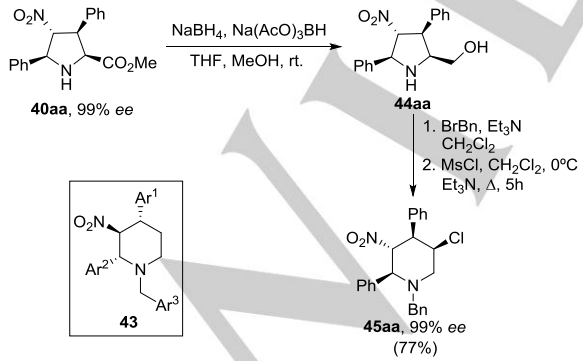
The influence of the benzoate anion *vs.* triflate anion can be explained by the assumption that benzoate (bulkier group than triflate) is oriented along the arylidene moiety of the dipole. Thus, a small π-stacking interaction is observed when **4a** (R = H, Ar = Ph) is computed so, we think that a variation of this aromatic group implies that triflate anion is much less sensitive than the benzoate one.[45]

The existence of a stepwise mechanism moved us to search for the selective isolation of Michael-type addition compound **41aa**. It was possible by performing the reaction at lower temperatures followed by an acidic-basic treatment. The *syn*-diastereoselection was observed when silver benzoate was employed whilst the reaction in the presence of silver triflate failed. At -80 ºC equimolar amounts of compounds **40aa** and *syn*-**41aa** were generated. Cyclic product **40aa** was obtained in 91:9 *exo:endo* ratio and 98% *ee* in 40% yield and the desired Michael-type adduct *syn*-**42aa** was isolated in 40% yield as unique diastereoisomer and with a 98:2 *er* (Scheme 19).[43]



Scheme 19. Enantioselective isolation of *syn*-**42aa** using chiral phosphoramidite **3**·AgOBz complex.

We envisaged that products **43** (a series of nitropiperidines which are potent farnesyl-transferase inhibitors with promising antitumoral activity)[46] can be accessed through the enantiomerically enriched proline derivatives **40** by a ring-expansion of their cyclic β-amino alcohol derivatives following the methodology developed by Cossy's group.[47] Thus, crude nitroalcohol **44aa** was obtained as optically pure compoud, in almost quantitative yield, after reduction with $NaBH_4$/$NaBH(AcO)_3$.[48] Finally, product **45aa** could be synthesized in 77% overall yield by forming the tertiary amine with benzyl bromide and mesylation of the primary alcohol, taking place the corresponding ring expansion with complete retention of the configuration (Scheme 20).[43]



Scheme 20. Synthetic approach to the potential farnesyltransferase inhibitor **45aa** from enantiomerically enriched *exo*-nitroprolinate **40aa**.

Further studies of many other applications of the nitroprolinates, different enantioselective 1,3-DC and the development of efficient chiral complexes are currently underway.

3. Conclusions

The appropriate chiral metal Lewis acid using binap and phosphoramidites as privileged ligands in 1,3-DC involving azomethine ylides was studied. According to the structure of this work, and starting from the reaction of maleimides **5** and imino eters **4**, (*S*)-binap **1** is the most appropriate ligand together with $AgClO_4$, or with $AgSbF_6$ and even when [(*S*)-binap-AuTFA]$_2$. In general the last two catalysts are much more useful for sterically hindered components giving *endo*-prolinates. By contrast the 1,3-DC involving azlactones and maleimides is exclusively promoted by [(*S*)-binap **1**-AuTFA]$_2$. The employment of phosphoramidite (S_a,*R*,*R*)-**3** together with $AgClO_4$, was recommended for cycloadditions regarding acrylates. These reaction conditions were used to prepare the first generation GSK inhibitor of HCV. In addition, [(*S*)-binap-AuTFA]$_2$ complex was the catalyst of choice for the synthesis of the second generation GSK inhibitor of HCV. BPSE **25** and imino esters **4** afforded the best *endo*-enantioselections using (*S*)-binap **1** with $AgSbF_6$ rather than with $AgClO_4$, and several examples were improved by the employment of dimeric [(*S*)-binap **1**·AuTFA]$_2$. Both fumarates and enones could be successfully employed in the 1,3-DC with imino esters **4** in the presence of chiral phosphoramidite (S_a,*R*,*R*)-**3** complex. Nitroalkenes deserved special attention because they could be efficiently transformed in enantiomerically enriched *exo*-nitroprolinates. Chiral phosphoramidite (S_a,*R*,*R*)-**3** was the best chiral ligand modulating its activity employing several metal salts such as: a) AgOBz, appropriate for different substituents bonded at the β-position of the nitrostyrene; b) AgOTf, suitable when the aryl substituent (5 position) was modified; c) Cu(OTf)$_2$, adequate when α-substituted imino esters were involved in the cycloaddition. The final and noticeable aspect of this tunable methodology was the valuable applications found in the synthesis of important biologically active compounds. Thus, the already mentioned enantioselective synnthesis of GSK antiviral agents against HCV were described for the first time. In addition, the preparation of a potentially active farnesyl transferase inhibitor as well as several alkaloid skeletons were reported. Experimental results matched with the corresponding computational data obtained. The processes were in general concerted with variable asynchrony, except the examples performed with acrylates and nitroalkenes, which operated via a stepwise mechanism. As main conclusion, chiral ligand (S_a,*R*,*R*)-**3** offered, in general the wider scope. Silver(I) cation was the most appropriate to carry on the control of the geometry of the dipole favoring secondary interactions with the dipolarophiles except for the nitroalkenes. The anion played also a very important role and should be optimized for each dipolarophile.

Acknowledgements

Our work has been supported by the Spanish Ministerio de Ciencia e Innovación (MICINN) (Consolider INGENIO 2010

CSD2007-00006, CTQ2004-00808/BQU, CTQ2007-62771/BQU, CTQ2010-20387 and the Hispano-Brazilian project PHB2008-0037-PC), the Spanish Ministerio de Economia y Competitividad (MINECO) (projects CTQ2013-43446-P and CTQ2014-51912-REDC) FEDER, Generalitat Valenciana (PROMETEO/2009/039, and PROMETEOII/2014/017), and by the University of Alicante. We thank Prof. F. P. Cossío's group for the big effort and important contributions of concerning computational studies.

Keywords: asymmetric catalysis • binap • phosphoramidites • dipolar cycloadditions • azomethine ylides • silver • copper

Entry for the Table of Contents (Please choose one layout)

Layout 1:

PERSONAL ACCOUNT

Text for Table of Contents

((Insert TOC Graphic here))

Page No. – Page No.

Title

Layout 2:

PERSONAL ACCOUNT

Carmen Nájera, and José M. Sansano**

Page No. – Page No.

Binap and phosphoramidites as privileged chiral ligands for the enantioselective 1,3-dipolar cycloaddition of azomethine ylides and dipolarophiles

Versatile and fine tuning enantioselective 1,3-DC

References

[1] a) R. Huisgen *Angew. Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565-598; b) R. Huisgen *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 633-645.

[2] a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, A. Padwa, W. H. Pearson, Eds., John Wiley & Sons: New Jersey, **2003**; b) C. Nájera, J. M. Sansano, *Curr. Org. Chem*. **2003**, *7*, 1105-1150; c) W. Eberbach, In *Sci. Synth., Houben-Weyl Methods of Molecular Transformations*; A. Padwa, D. Bellus, Eds.; Thieme Verlag: Stuttgart, **2004**; Vol. 27, chp. 11, pp 441-498; d) I. Coldham, R. Hufton, *Chem. Rev.* **2005**, *105*, 2765-2810; e) V. Nair, T. D. Suja, *Tetrahedron* **2007**, *63*, 12247-12275; f) A. Padwa, S. K. Bur, *Tetrahedron* **2007**, *63*, 5341-5378; g) T. Hashimoto,; K. Maruoka, *Handbook of Cyclization Reactions*, Ma, S. Ed. Wiley-VCH: Weinheim, 2010; h) Kanemasa, S. *Heterocycles* ***2010***, *82*, *87-200;* i) Han, M.-Y.; Jia, J.-Y.; Wang, W. *Tetrahedron Lett.* **2014**, *55*, 784-794; j) H. Suga,; K. Itoh, in *Methods and Applications of Cycloaddition Reactions in Organic Syntheses*, Nishiwaki, N. Ed., Wiley: Weinheim, **2014**, pp. 175-204.

[3] R. Grigg *et al.* pioneered the catalytic enantioselective 1,3-DC employing stoichiometric amounts of chiral cobalt complexes. P. Allway, R. Grigg, *Tetrahedron Lett.* **1991**, *32*, 5817-5820.

[4] J. M. Longmire. B. Wang, X. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13400-13401.

[5] A. S. Gothelf, K. V. Gothelf, R. G. Hazell, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2002**, *41*, 4236-4238.

[6] For recent reviews of asymmetric 1,3-DC, see: a) H. Pellissier, *Tetrahedron* **2007**, *63*, 3235-3285; b) C. Nájera, J. M. Sansano in *Topics in Heterocyclic Chemistry*, A. Hassner, Ed., Springer-Verlag: Berlin-Heidelberg, 2008, vol. 12, pp. 117-145; c) L. M. Stanley, M. P. Sibi, *Chem. Rev.* **2008**, *108*, 2887-2902; d) M. Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García, *Chem. Rev*. **2008**, *108*, 3174-3198; e) M. Naodovic, H. Yamamoto, *Chem. Rev*. **2008**, *108*, 3132-3148; f) C. Nájera, J. M. Sansano, M. Yus, *J. Braz. Chem. Soc.* **2010**, *21*, 377-412; g) M. Kissane, A. R. Maguire, *Chem. Soc. Rev*. **2010**, *39*, 845-883; h) J. Adrio, J. C. Carretero, *Chem. Commun*. **2011**, *47*, 6784-6794; i) J. Adrio, J. C. Carretero, *Chem. Commun.*, **2014**, *50*, 12434-12446; j) C. Nájera, J. M. Sansano, *J. Organomet. Chem*. **2014**, *771*, 78-92; k) T. Hashimoto, K. Maruoka, *Chem. Rev.* **2015**, *115*, 5366-5412.

[7] a) *Privileged Chiral Ligands and Catalysts*, Qi-Lin Zhou, Ed.; Wiley-VCH: New York, 2011; b) J. F. Teichert, B. L. Feringa, *Angew. Chem. Int. Ed.* **2010**, *49*, 2486–2528.

[8] The *endo*-descriptor reffers to the result of the approach of the dipolarophile in such way that its electron-withdrawig is orientated towards the metal sphere.

[9] Although the combination (*S*)-binap-AgOAc has shown low *ee* in 1,3-DCRs using dipoles derived from imino esters and dimethyl maleate (up to 13% *ee*) or phenyl vinyl sulfone (up to 26% *ee*) as dipolarophiles, our findings in a similar reaction but employing NMM as dipolarophile were very promising. J. M. Longmire, B. Wang, X. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13400-13401.

[10] a) C. Nájera, M. G. Retamosa, J. M. Sansano, *Org. Lett.* **2007**, *9*, 4025–4028.

[11] C. Nájera, M. G. Retamosa, J. M. Sansano, A. de Cózar, F. P. Cossío, *Tetrahedron*: *Asymmetry* **2008**, *19*, 2913-2923.

[12] Mixtures of several aggregrates Binap·silver salts were identified. N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5360-5361.

[13] All calculations were performed by the group of Prof. F. P. Cossío. University of the Basque Country, Donostia Campus, Spain.

[14] M. Martín-Rodríguez, C. Nájera, J. M. Sansano, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias*, Synlett* **2010,** 962-966.

[15] J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias, *Tetrahedron: Asymmetry* **2012,** *23*, 1596-1606.

[16] The reaction with *N*-phenylmaleimide (NPM) afforded the corresponding *endo*-**6** adduct in 86% yield and 82% *ee*, whilst a 62% *ee* and the same chemical yield was isolated when the reaction was performed with (*S*)-binap **1**·$AgClO_4$.

[17] This was the first successful chiral complex-catalyzed enantioselective multicomponent 1,3-DC published in the literature.

[18] M. Martín-Rodríguez, C. Nájera, J. M. Sansano, F.-L. Wu, *Tetrahedron: Asymmetry* **2010**, *21*, 1184-1886.

[19] M. Martín–Rodríguez, C. Nájera, J. M. Sansano, A. de Cózar, F. P. Cossío, *Chem. Eur. J.* **2011**, *17*, 14224–14233.

[20] C. Nájera, M. G. Retamosa, J. M. Sansano, *Angew. Chem. Int. Ed.* **2008**, *47*, 6055-6058.

[21] C. Nájera, M. G. Retamosa*,* M. Martín-Rodríguez, J. M. Sansano*,* A. de Cózar, F. P. Cossío, *Eur. J. Org. Chem.* **2009**, 5622-5634.

[22] C. A. Wheaton, M. C. Jennings, R. J. Puddephatt, *Z. Naturforsch* **2009**, *64b*, 1569-1477.

[23] H. B. Kagan, *Synlett* **2001**, 888-899 and references cited therein.

[24] J. Mancebo-Aracil, C. Nájera, J. M. Sansano, *Tetrahedron: Asymmetry* **2015,** *26*, 674-678. *Synfacts* **2015**, *11*, 1065

[25] For previous contributions, see: a) A. D. Melhado, M. Luparia, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 12638-12639; b) A. D. Melhado, G. W. Amarante, J. Wang, M. Luparia, F. D. Toste, *J. Am. Chem. Soc.* **2011**, *133*, 3517-3527

[26] M. Martín-Rodríguez, C. Nájera, J. M. Sansano, *Synlett* **2012**, 62–65.

[27] M. Martín-Rodríguez, L. M. Castelló, C. Nájera, J. M. Sansano, O. Larrañaga, A. de Cózar, F. P. Cossío *Beilstein J. Org. Chem.* **2013,** *9,* 2422–2433.

[28] See, for example: M. Lee, Y.-J. Lee, E. Park, Y. Park, M. W. Ha, S. Hong, Y. J. Lee, T.-S. Kim, M. Kim, H. Park, *Org. Biomol. Chem.* **2013**, *11*, 2039-2046.

[29] C. Nájera, J. M. Sansano, *Org. Biomol. Chem.* **2009**, *7*, 4567-4581.

[30] C. Nájera, J. M. Sansano, *L'Actualité Chimique* **2013**, *370*, 28-30.

[31] a) G. Burton, T. W. Ku, T. J. Carr, T. Kiesov, R. T. Sarisky, J. Lin-Goerke, G. A. Hofmann, M. J. Slater, D. Haigh, D. Dhanak, V. K. Johnson, N. R. Parry, P. Thomes, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1930-1933; b) M. J. Slater, E. M. Amphlett, D. M. Andrews, G. Bravi, G. Burton, A. G. Cheasty, J. A. Corfield, M. R. Ellis, R. H. Fenwick, S. Fernandes, R. Guidetti, D. Haigh, C. D. Hartley, P. D. Howes, D. L. Jackson, R. L. Jarvest, V. L. H. Lovegrove, K. J. Medhurst, N. R. Parry, H. Price, P. Shah, O. M. P. Singh, R. Stocker, P. Thommes, C. Wilkinson, A. Wonacott, *J. Med. Chem.* **2007**, *50*, 897-900; c) A. A. Agbodjan, B. E. Cooley, R. C. B. Copley, J. A. Corfield, R. C. Flanagan, B. N. Glover, R. Guidetti, D. Haigh, P. D. Howes, M. M. Jackson, R. T. Matsuoka, K. J. Medhurst, A. Millar, M. J. Sharp, M. J. Slater, J. F. Toczko, S. Xie, *J. Org. Chem.* **2008**, *73*, 3094-3102; d) R. C. Flanagan, S. Xie, A. Millar, *Org. Process. Res. Develop.* **2008**, *12*, 1307-1312; e) D. Haigh, E. M. Amphlett, G. S. Bravi, H. Bright, V. Chung, C. L. Chambers, A. G. Cheasty, M. A. Convey, A. Maire, M. R. Ellis, R. Fenwick, D. F. Gray, C. D. Hartley, P. D. Howes, R. L. Jarvest, K. J. Medhurst, A. Mehbob, D. Mesogiti, F. Mirzai, F. Nerozzi, N. R. Parry, N. R. Roughley, T. Skarynzski, M. J. Slater, S. A. Smith, R. Stocker, C. J. Theobald, P. J. Thomas, P. A. Thommes, J. H. Thorpe, C. S. Wilkinson, E. W. Williams, w.w.w.CEN-ONLINE ORG, **2007**:*295448*, 56-59.

[32] T. Llamas, R. Gómez-Arrayás, J. C. Carretero, *Org. Lett.* **2006**, *8*, 1795-1798.

[33] See, for example: van B. C. J. Esseveldt, P. W. H. Vervoort, F. L. van Delft, P. J. T. Rutjes, *J. Org. Chem.* **2005**, *70*, 1791-1795.

[34] I. Coldham, S. Jana, L. Watson, N. G. Martin, *Org. Biomol. Chem.* **2009**, *7*, 1674-1679.

[35] Q. Zhang, G. Tu, Y. Zhao, T. Cheng, *Tetrahedron* **2002**, *58*, 6795–6798.

[36] T. Kam, K. Sim, *Phytochemistry* **1997**, *47*, 145-147.

[37] S. Ammendola, L. Mosca, P. Bovicelli, *Arkivoc* **2008**, *VIII*, 105-115.

[38] C. Nájera, J. M. Sansano, *Curr. Top. Med. Chem*. **2014**, *14*, 1271-1282.

[39] A. Zubia, L. Mendoza, S. Vivanco, E. Aldaba, T. Carrascal, B. Lecea, A. Arrieta, T. Zimmerman, F. Vidal-Vanaclocha, F. P. Cossío, *Angew. Chem. Int. Ed*. **2005**, *44*, 2903-2905.

[40] E. Conde, D. Bello, A. de Cózar, M. Sánchez, M. A. Vázquez, F. P. Cossío, *Chem. Sci.* **2012**, *3*, 1486-1491.

[41] L. M. Castelló, C. Nájera, J. M.; Sansano, O. Larrañaga, A. de Cózar, F. P. Cossío, *Synthesis* **2015**, *47*, 934-943.

[42] L. M. Castelló, C. Nájera, J. M. Sansano, O. Larrañaga, A. de Cózar, F. P. Cossío, *Org. Lett.* **2013**, *15*, 2902-2905.

[43] L. M. Castelló, C. Nájera, J. M. Sansano, O. Larrañaga, A. de Cózar, F. P. Cossío, *Adv. Synth. Catal.* **2014**, *356*, 3861-3870.

[44] A. de Cózar, F. P. Cossío, *Chem Phys. Phys. Chem.***2011**, *13*, 10858-10868.

[45] A. de Cózar, Private communication.

[46] R. Tanaka, A. Rubio, N. K. Harn, D. Gernert; T. A. Grese, J. Eishima, M. Hara, N. Yoda, R. Ohashi, T. Kuwabara, S. Soga, S. Akinaga, S. Nara, Y. Kanda, *Bioorg. Med. Chem.* **2007**, *15*, 1363-1382.

[47] a) B. Anxionat, B. Robert, P. George, G. Ricci, M.-A. Perrin, D. Gómez-Pardo, J. Cossy, *J. Am. Chem. Soc.* **2012**, *77*, 6087-6099; b) A. Cochi, D. Gómez-Pardo, J. Cossy, *Eur. J. Org. Chem.* **2012**, 2023-2040.

[48] A similar reduction was performed in the presence of $NaBH_4$/$Na(MeO)_3BH$ instead of $NaBH_4$/$Na(AcO)_3BH$: J. A. Gálvez, M. D. Díaz-de Villegas, M. Alías, R. Badorrey, *J. Org. Chem.* **2013**, *78*, 11404-11413.