# Binap-$AgSbF_6$ *versus* Binap-$AgClO_4$ complexes as catalysts for the enantioselective 1,3-dipolar cycloaddition of azomethine ylides and alkenes

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*Dedicated to Prof. Antonio García Martínez on the occasion of his retirement*

**Abstract**: The employment of $AgSbF_6$ and Binap ligands has been evaluated in the catalyzed enantioselective 1,3-dipolar cycloadditions (1,3-DC) between azomethine ylides and electrophilic alkenes. The results are compared with the analogous ones obtained when using $AgClO_4$. The cycloaddition with maleimides and *trans*-1,2-bis(phenylsulfonyl)ethylene are clearly improved by the $AgSbF_6$ derived catalyst, and its efficiency is crucial for ensure good yields and excellent *ee* in the three-component reaction.

**Key words**: asymmetric catalysis / prolines / silver salts / azomethine ylides / multicomponent reaction

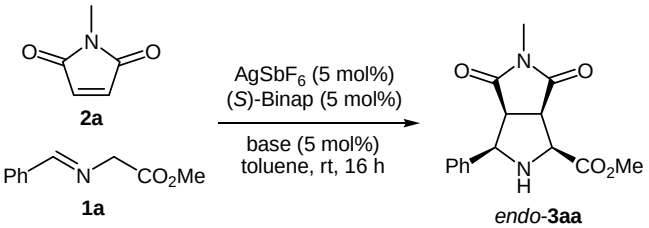
The 1,3-dipolar cycloaddition[1] (1,3-DC) became a very important transformation since the appearance in 2002[2] of the first catalytic enantioselective transformation employing substoichiometric amounts of a silver(I) chiral complex.[3,4] The importance of this reaction is due to the generation of up to four stereogenic centers in the resulting attractive proline derivatives.[5] It is noteworthy that it is produced in only one reaction step using very soft reaction conditions. To date, this regio-, diastereo- and enantioselective transformation becomes more efficient when chiral Lewis acids [obtained from silver(I),[6,7] copper(I),[8] zinc(II),[9] nickel(II)[10], and calcium(II)[11] salts] are employed. For example, the wide scope of both of the iminoesters and dipolarophiles, without structural limitations and the lower catalyst loading employed, are the main advantages of this catalysis *versus* those organocatalysed[12] processes.[13]

In a recent publication, we described the Binap-$AgClO_4$ catalyzed 1,3-DC between azomethine ylides and maleimides.[7] The high stability of the titled catalytic metal-complex to light exposure and its insolubility in toluene made possible its recovery and reutilization. Additionally, it was found that the transition state responsible of the enantiodiscrimination was quite asynchronous, the perchlorate anion being weakly bonded to the central metal.[7b]

According to this precedent, we envisaged that the poorly coordinating anion $SbF_6^-$ would modify the chiral domain of the metal complex vacancy. So, in this communication we will describe the improvements achieved by the use of $AgSbF_6$ in the 1,3-DC of azomethine ylides and alkenes employing (*R*)- or (*S*)-Binap as chiral ligand *versus* the already detailed results obtained with the perchlorate anion.

The standard reaction between methyl benzylideneiminoglycinate **1a** and *N*-methylmaleimide (NMM) **2a** (Table 1) was employed for the optimization tests. Initially, the reaction conditions were identical to those previously described for Binap-$AgClO_4$ (Table 1, entry 1) catalyzed 1,3-DC, that means, 5 mol% of the catalyst (formed with equimolar amounts of chiral Binap and $AgSbF_6$), in toluene at room temperature for 16 h, in the presence of $Et_3N$ as base. Both of the $AgClO_4$ and $AgSbF_6$ catalyzed reactions gave identical results of the cycloadduct *endo*-**3a** (90% yield, >98:2 *endo*:*exo* ratio, and >99% *ee*) (Table 1, entries 1 and 2). Other bases like 1,4-diazabicyclo[2.2.2]octane (DABCO) or diazabicyclo[5.4.0]undec-7-ene (DBU) were evaluated in this reaction affording lower enantioselections with some unidentified secondary products in the crude product (Table 1, entries 3, and 4). As well as described for the catalyst formed from $AgClO_4$,[7] a different stoichiometry such as 2:1 or 1:2 chiral ligand:silver salt, afforded lower enantioselections and larger amounts of the *exo*-diastereoisomer (Table 1, entries 5 and 6). Additionally, other solvents such as THF, DCM, or $Et_2O$ did not improve neither yields nor enantiomeric excesses. In general, a similar behavior was observed for both of the silver complexes for all the experiments summarized on Table 1.

**Table 1**. Reaction conditions study of the reaction of **1a** and **2a** using 1:1 mixture of (*S*)-Binap and $AgSbF_6$ or $AgClO_4$



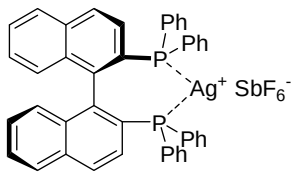

| | (*S*)-Binap: Ag salt | base | product **3aa**[a] yield (%)[b] | $ee_{endo}$ (%)[c] |
|---|---|---|---|---|
| 1 | 1:1 | $Et_3N$ | 90 (89) | >99 (>99) |
| 2 | 1:1[d] | $Et_3N$ | 78 (80) | >99 (>99) |
| 3 | 1:1 | DABCO | 87 (88) | 94[e] (92)[e] |
| 4 | 1:1 | DBU | 87 (80) | 90[e] (91)[e] |

| | | | | |
|---|---|---|---|---|
| 5 | 2:1 | $Et_3N$ | 90 (90) | 96[f] (98)[f] |
| 6 | 1:2 | $Et_3N$ | 90 (91) | 56[e,f] (<50)[e,f] |

[a] The *endo:exo* ratio was always >98:2 ($^1$H NMR spectroscopy, and chiral HPLC).
[b] Isolated after recrystallization using $AgSbF_6$, in brackets the yields of the analogous reaction performed with $AgClO_4$.[7]
[c] Determined by chiral HPLC (Daicel Chiralpak AS) of the crude product, in brackets the *ee* of the analogous reaction performed with $AgClO_4$.[7] Identical *ee* was determined after purification of **3a**.
[d] Reaction performed using 3 mol% of catalyst.
[e] Some unidentified impurities were observed in the crude product.
[f] The *endo*:*exo* ratio was approximately 90:10.

The reaction was also carried out with the isolated complex formed by the addition of equimolar amounts (*S*)-Binap and $AgSbF_6$, obtaining almost identical results to those described in entry 1 of the Table 1. However this $AgSbF_6$ derived complex became darker upon standing being much more unstable than the identical complex generated by $AgClO_4$. So, the *in situ* generation of the catalytic complex, avoiding the light exposure during the whole process was preferred for all the transformations described in the text.

The presumed catalytic monomeric species in solution are identical to those the reported previously with different anions.[7,14] In fact, the 1:1 (*R*)- or (*S*)-Binap 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 Binap-Ag$^I$ complex (*S*)-**4** and a tiny one at 1352 and 1354 corresponding to the 2:1 Binap:$AgSbF_6$.[7,15] The $^{31}$P NMR ($CDCl_3$) spectra of 1:1 (*R*)- or (*S*)-Binap 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). The absence of NLE is another data supporting the existence of a monomeric species in the enantioselective catalytic process in solution.




**4**

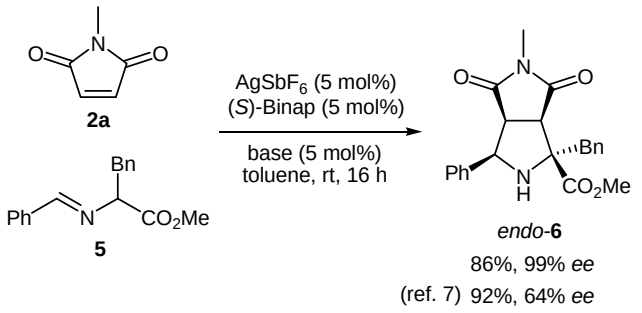
The reaction of several azomethine ylides, generated from the corresponding methyl arylideneiminoglycinates **1**, and maleimides in toluene employing a 5 mol% of a equimolar mixture of (*S*)-Binap and $AgSbF_6$ was studied and compared with the analogous results obtained with (*S*)-Binap-$AgClO_4$ complex[7] (Table 2). In general, we can observe that isolated chemical yields of compounds **3** are identical to each other finding a higher enantioselection in those reactions promoted by the complex formed by (*S*)-Binap and $AgSbF_6$. This is more noticeable when the aromatic moiety was substituted at different positions as, for example, cycloadducts **3ba**, **3ca**, **3da**, and **3ea** (Table 2, entries 3-6). Whilst the reaction with *N*-ethylmaleimide (NEM) do not represent any difference with respect to those results obtained in the (*S*)-Binap-$AgClO_4$ (Table 2, entry 7), the reaction carried out with *N*-phenylmaleimide (NPM) was much more enantioselective in the presence of (*S*)-Binap-$AgSbF_6$ complex (82% *ee*, *vs* 62% *ee* obtained with perchlorate derived chiral complex) and >98:2 *endo*:*exo* ratio was obtained (Table 2, entry 8). Computational calculations have revealed the existence of steric hindrance between the phenyl group of the NPM and the Binap-$AgClO_4$ catalyst.[7b] However, in the case of Binap-$AgSbF_6$ catalyzed process seems that the less coordinating anion decreases the steric congestion of the transition state.

**Table 2.** 1,3-DC of maleimides and several iminoglycinates **1**.


| | Ar | R | **3**[a] | yield (%)[b,c] | $ee_{endo}$ (%)[c,d] |
|---|---|---|---|---|---|
| 1 | Ph | Me | **3aa** | 90 (90) | >99 (>99) |
| 2 | Ph[e] | Me | *ent*-**3aa** | 90 (90) | >99 (>99) |
| 3 | 2-$MeC_6H_4$ | Me | **3ba** | 85 (85) | 99 (70) |
| 4 | 2-$ClC_6H_4$ | Me | **3ca** | 82 (82) | >99[f] (85)[f] |
| 5 | 4-$MeC_6H_4$ | Me | **3da** | 85 (88) | 99 (88) |
| 6 | 4-$MeOC_6H_4$ | Me | **3ea** | 85 (85) | 99 (80) |
| 7 | Ph | Et | **3ab** | 84 (91) | 99 (99) |
| 8 | Ph | Ph | **3ac** | 86 (86) | 82 (62)[g] |

[a] The *endo:exo* ratio was always >98:2 ($^1$H NMR spectroscopy, and chiral HPLC).
[b] Isolated after flash chromatography.
[c] In brackets the result obtained previously with (*S*)-Binap-$AgClO_4$ complex.[7]
[d] Determined by chiral HPLC of the crude product. Identical *ee* was determined after purification of **3**.
[e] Reaction performed with (*R*)-Binap-$AgSbF_6$.
[f] Reaction performed at –20 ºC.
[g] For the $AgClO_4$-catalyzed process, the *endo*:*exo* ratio was approximately 90:10.

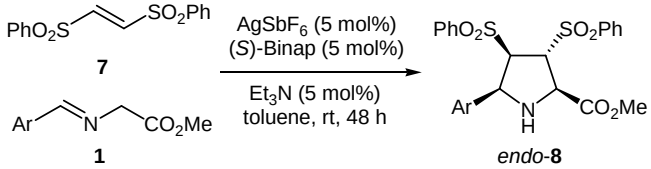
The incorporation of a bulky substituent at the α-position of the 1,3-dipole precursor as occurred in the methyl benzylideneiminophenylalaninate **5** was successfully overcome using the standard reaction conditions. Here, the *endo*-adduct **6** was obtained as a single enantiomer (99% *ee*) in very good chemical isolated yield (86%). Clearly this reaction promoted by (*S*)-Binap-$AgSbF_6$ complex improve the results obtained in the reaction performed with the perchlorate salt (Scheme 1), when steric problems are presented in the 1,3-DC.




**Scheme 1**

Acrylates, maleates and fumarates were not suitable dipolarophiles neither for the (*S*)-Binap-$AgSbF_6$ (<30% *ee* and <40% *ee*, respectively) nor for (*S*)-Binap-$AgClO_4$[7] catalysed processes. However *trans*-1,2-bis(phenylsulfonyl)ethylene **7** afforded very interesting results of *endo*-cycloadducts **8**. 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 Fesulphos-copper(I) complex following similar reaction conditions.[8d] The reaction operates under the standard conditions but taking 48 h to complete. This 1,3-DC, not evaluated previously with the chiral perchlorate complex, was performed using both silver salts (Table 3). The four methyl iminoglycinates **1** tested in this reaction under the control of (*S*)-Binap-$AgSbF_6$ catalytic complex afforded *endo*-cycloadducts **8** in good chemical yields (80-91%) and very high enantioselectivities (88-92% *ee*) (Table 3). The enantioselection was higher for $AgSbF_6$ by the chiral silver complex in all of the entries described in Table 3, especially in the reaction of *p*-tolyliminoester (Table 3, entry 3). This is the first synthesis of the disulfonyl *endo*-**8** cycloadducts, whose absolute configuration was determined by NOESY experiments, and indirectly by comparison of the corresponding HPLC analysis with those described in the literature for the *exo*-cycloadducts.[8d]

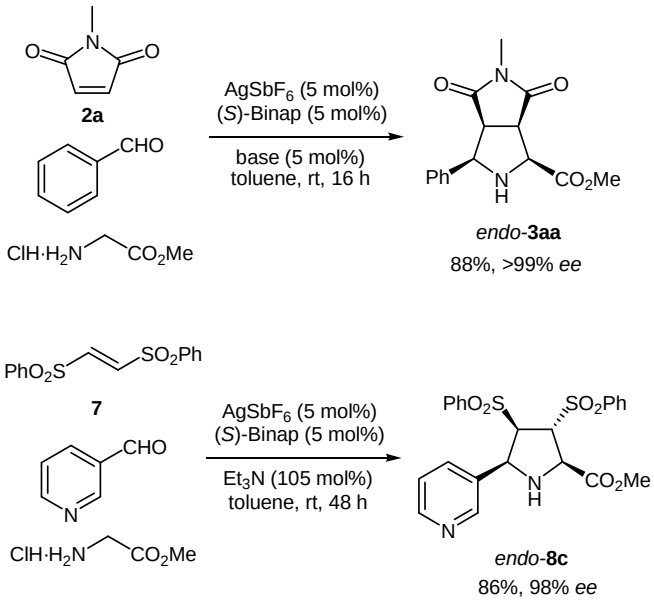
**Table 3.** 1,3-DC of (*E*)-1,2-bis(phenylsulfonyl)ethylene **7** and iminoglycinates **1**.




| | Ar | **8**[a] | yield (%)[b,c] | $ee_{endo}$ (%)[c,d] |
|---|---|---|---|---|
| 1 | Ph | **8a** | 81 (80) | 90 (88) |
| 2 | Ph[e] | *ent*-**8a** | 80 (80) | 90 (88) |
| 3 | 4-$MeC_6H_4$ | **8b** | 91[f] (85) | 88 (28) |
| 4 | 3-Pyridyl | **8c** | 83 (82) | 93 (78) |
| 5 | 2-Naphthyl | **8d** | 91[f] (88) | 92 (80) |

[a] The *endo:exo* ratio was >98:2 ($^1$H NMR spectroscopy, and chiral HPLC).
[b] Isolated after column chromatography.
[c] In brackets the result obtained with (*S*)-Binap-$AgClO_4$ complex.
[d] Determined by chiral HPLC of the crude product. Identical *ee* was determined after purification of **8**.
[e] Reaction performed with (*R*)-Binap-$AgSbF_6$.
[f] Pure crude yields.

The multicomponent reactions were attempted using the best result depicted in Tables 2 and 3. Thus, benzaldehyde/NMM or 3-pyridinecarbaldehyde/disulfone **7**, glycine methyl ester hydrochloride, triethylamine (1.05 equiv), (*S*)-Binap-$AgSbF_6$ (5 mol%), were put together in toluene and the resulting mixture was allowed to react at rt for 48 h. The results obtained for compound *endo*-**3aa** or *endo*-**8c** were impressive (88% yield, >99% *ee*, or 86% yield, 98% *ee*, respectively, Scheme 2). However, taking in account that the analogous reactions in the presence of (*S*)-Binap-$AgClO_4$ complex failed. Although very activated aminomalonates have been involved as one of the three components of the enantioselective organocatalyzed 1,3-DC,[12c,i,j,k] this is the first occasion that a three-component transformation is enantioselectively performed in the presence of a chiral Lewis acid.




**Scheme 2**

The high enantioselectivity observed for the reaction using different maleimides, and 1,2-bis(phenylsulfonyl)ethylene as dipolarophiles with (*S*)-Binap-$AgSbF_6$ catalytic complex[16] suggest a weaker coordination of the $SbF_6$ anion to the metal centre. The enantioselections, in general, are higher with this novel chiral catalyst constituting this study a clear example of fine tuning of the catalyst for the obtention of highly enantiomerically enriched *endo*-cycloadducts. In addition the multicomponent process only succeeded with $AgSbF_6$ derived chiral complex and very good yields and with identical enantioselections than that reported for the examples run with iminoesters as starters. Evaluating all

of these results, it was demonstrated how important resulted to be the anion in this sensitive enantioselective process, which is controlled by many parameters.

## Acknowlwdgements

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(15) The 2:1 Binap:$AgSbF_6$ chiral cluster was not characterized because it afforded lower *endo*:*exo*-diastereoselectivity, such as occurred in the previously reported chiral Binap:$AgClO_4$ catalyzed 1,3-DC (ref. 7).

(16) **General procedure for the catalytic enantioselective 1,3-DC using silver salts**: A solution of the imino ester (1 mmol) and dipolarophile (1 mmol) in toluene (5 mL) was added to a suspension containing (*R*)- or (*S*)-Binap (0.05 mmol, 31 mg) and silver(I) salt (0.05 mmol) in toluene (5 mL). To the resulting suspension triethylamine (0.05 mmol, 7 μL) was added and the mixture stirred at room temperature and in the absence of the light for 16-48 h (see main text). The reaction was filtered and the organic filtrate was directly evaporated and the residue was purified by recrystallization or by flash chromatography yielding pure *endo*-cycloadducts.
**General procedure for the three-component catalytic enantioselective 1,3-DC using silver salts**: To a suspension containing (*R*)- or (*S*)-Binap (0.05 mmol, 31 mg) and $AgSbF_6$ (0.05 mmol, 17 mg) in toluene (10 mL) was added the freshly distilled aldehyde (1 mmol), glycine methyl ester hydrochloride (1 mmol) , the dipolarophile (1 mmol), and triethylamine (140 μL, 1.05 mmol). The mixture was stirred at room temperature and in the absence of the light for 16-48 h (see main text). Following the same work-up than that described previously (above) final cycloadducts **3aa**, and **8c** were obtained.