Binap-AgSbF₆ versus Binap-AgClO₄ complexes as catalysts for the enantioselective 1,3-dipolar cycloaddition of azomethine ylides and alkenes

María Martín-Rodríguez, Carmen Nájera, José M. Sansano, Paulo R. R. Costa, Evanoel Crizanto, Ayres G. Dias

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

Laboratório de Química Biorgânica, Núcleo de Pesquisas de Produtos Naturais, Centro de Ciências da Saúde, Universidade Federal do Rio de Janeiro, Cidade Universitária, 21941-590, Rio de Janeiro, Brazil.

Fax: +34-965903549

e-mail: jmsansano@ua.es

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

Abstract: The employment of AgSbF₆ 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 AgClO₄. The cycloaddition with maleimides and trans-1,2-bis(phenylsulfonyl)ethylene are clearly improved by the AgSbF₆ 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 cycloaddition¹ (1,3-DC) became a very important transformation since the appearance in 2002² 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 iminoester and dipolarophiles, without structural limitations and the lower catalyst loading employed, are the main advantages of this catalysis versus those organocatalysed¹² processes.

In a recent publication, we described the Binap-AgClO₄ catalyzed 1,3-DC between azomethine ylides and maleimides.¹³ 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.¹³

According to this precedent, we envisaged that the poorly coordinating anion Sbf₆⁻ would modify the chiral domain of the metal complex vacancy. So, in this communication we will describe the improvements achieved by the use of AgSbF₆ 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 benzyldeineiminoglycinate 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-AgClO₄ (Table 1, entry 1) catalyzed 1,3-DC, that means, 5 mol% of the catalyst (formed with equimolar amounts of chiral Binap and AgSbF₆), in toluene at room temperature for 16 h, in the presence of Et₃N as base. Both of the AgClO₄ and AgSbF₆ 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 AgClO₄, a different stoichiometry such as 2:1 or 1:2 chiral ligand:silver salt, afforded lower enantioselectivities and larger amounts of the exo-diastereoisomer (Table 1, entries 5 and 6). Additionally, other solvents such as THF, DCM, or Et₂O 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 AgSbF₆ or AgClO₄

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₃N</td>
<td>90</td>
<td>&gt;99 (&gt;99)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Et₃N</td>
<td>78</td>
<td>&gt;99 (&gt;99)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>DABCO</td>
<td>87</td>
<td>94 (92)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>DBU</td>
<td>87</td>
<td>90 (91)</td>
<td></td>
</tr>
</tbody>
</table>
The reaction was also carried out with the isolated complex formed by the addition of equimolar amounts (S)-Binap and AgSbF₆, obtaining almost identical results to those described in entry 1 of the Table 1. However this AgSbF₆ derived complex became darker upon standing being much more unstable than the identical complex generated by AgClO₄. 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 reported previously with different anions. In fact, the 1:1 (R)- or (S)-Binap and AgSbF₆ complexes were characterized by ESI-MS experiments and ³¹P NMR. ESI-MS revealed a M⁺+1 signal at 730, and 732 corresponding to the monomeric Binap-Ag⁺ complex (S)-4, and a tiny one at 1352 and 1354 corresponding to the 2:1 Binap:AgSbF₆. The ³¹P NMR (CDCl₃) spectra of 1:1 (R)- or (S)-Binap and AgSbF₆ (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-AgClO₄ complex). The absence of NLE is another data supporting the existence of steric hindrance between the phenyl group of the NPM and the Binap-AgClO₄ catalyst. However, in the case of Binap-AgSbF₆ catalyzed process seems that the less coordinating anion decreases the steric congestion of the transition state.

The reaction of several azomethine ylides, generated from the corresponding methyl aryldieneiminoglycinates 1, and maleimides in toluene employing a 5 mol% of a equimolar mixture of (S)-Binap and AgSbF₆ was studied and compared with the analogous results obtained with (S)-Binap-AgClO₄ complex (Table 2). In general, we can observe that isolated chemical yields of compounds 3 are identical to each other finding a higher enantioselective in those reactions promoted by the complex formed by (S)-Binap and AgSbF₆. 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-AgClO₄ (Table 2, entry 7), the reaction carried out with N-phenylmaleimide (NPM) was much more enantioselective in the presence of (S)-Binap-AgSbF₆ 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-AgClO₄ catalyst. However, in the case of Binap-AgSbF₆ catalyzed process seems that the less coordinating anion decreases the steric congestion of the transition state.

The incorporation of a bulky substituent at the a-position of the 1,3-dipole precursor as occurred in the methyl benzylidenemino phenylalaninate 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-AgSbF₆ 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.
Acrylates, maleates and fumarates were not suitable dipolarophiles neither for the (S)-Binap-AgSbF₆ (<30% ee and <40% ee, respectively) nor for (S)-Binap-AgClO₄ 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. 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-AgSbF₆ 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 AgSbF₆ 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 8 endo-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.

The high enantioselectivity observed for the reaction using different maleimides, and 1,2-bis(phenylsulfonyl)ethylene as dipolarophiles with (S)-Binap-AgSbF₆ catalytic complex suggest a weaker coordination of the SbF₆ 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 AgSbF₆ derived chiral complex and very good yields and with identical enantioselections than that reported for the examples run with iminooesters as starters. Evaluating all

\[ \text{Scheme 1} \]

\[ \text{Scheme 2} \]

Table 3. 1,3-DC of (E)-1,2-bis(phenylsulfonyl)ethylene 7 and iminoglycinates 1.
of these results, it was demonstrated how important resulted to be the anion in this sensitive enantioselective process, which is controlled by many parameters.

**Acknowledgements**

This work has been supported by the DGES of the Spanish Ministerio de Educación y Ciencia (MEC) (Consolider INGENIO 2010 CSD2007-00006, CTQ2007-62771/BQU, and the Hispano-Brazilian project PHB2008-0037-PC and CNPq-2878), Generalitat Valenciana (PROMETEO/2009/039), and by the University of Alicante. MM-R thanks MEC for a predoctoral fellowship. EC thanks CNPq for a predocotor Doutorado Sanduche study.

**References and Notes**


(7) For a recent review about Lewis acid versus organocatalytic asymmetry 1,3-DC, see: Nájera, C.; Sansano, J. M.; Yis, M. Braz. Chem. Soc. 2009, in press.


(9) The 2:1 Binap:AgSbF 6 chiral cluster was not characterized because it afforded low endo-exo-diastereoselectivity, such as occurred in the previously reported chiral Binap:AgClO 4 catalyzed 1,3-DC (ref. 7).

(10) General procedure for the catalytic enantioselective 1,3-DC using silver salts: A solution of the imino ester (1 mmol) and the dipolarophile (1 mmol), and triethylamine (0.05 mmol) in toluene (5 mL). The mixture was stirred at room temperature and in the absence of 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.

(11) General procedure for the three-component catalytic enantioselective 1,3-DC using silver salts: A suspension containing (R)- or (S)-Binap (0.05 mmol, 31 mg) and silver(I) salt (0.05 mmol) in toluene (5 mL). The resulting suspension triethylamine (0.05 mmol, 7 μL) was added and the mixture stirred at room temperature and in the absence of 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.