Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Binap-silver salts as chiral catalysts for the enantioselective 1,3-dipolar cycloaddition of azomethine ylides and alkenes

Juan Mancebo-Aracil^a, María Martín-Rodríguez^a, Carmen Nájera^a, José M. Sansano^{a*}, Paulo R. R. Costa^b, Evanoel Crizanto de Lima^b, Ayres G. Dias^b
^a *Departamento de Química Orgánica e Instituto de Síntesis Orgánica (ISO), Facultad de Ciencias, Universidad de Alicante, E-03080-Alicante (Spain).*
^b *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.*

Leave this area blank for abstract info.

Stereochemistry Abstract

To create your abstract, type over the instructions in the template box below.

Fonts or abstract dimensions should not be changed or altered. You may insert more abstracts by copying this box or by using the menu option to insert a stereochemistry abstract.

J. Mancebo-Aracil , M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{15}H_{16}N_2O_4$

Methyl (1S,3R,3aS,6aR)-5-methyl-3-phenyl-4,6-dioxooctahydro pyrrolo[3,4-c]pyrrole-1-carboxylate

Source of chirality: (S_a)-Binap

$[\alpha]_D^{20} = +140^\circ$ (c 0.5, $CHCl_3$, >99% *ee* from HPLC)

Absolute configuration: (1S,3R,3aS,6aR)

J. Mancebo-Aracil , M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{16}H_{18}N_2O_4$

Ethyl (1S,3R,3aS,6aR)-5-methyl-3-phenyl-4,6-dioxooctahydro pyrrolo[3,4-c]pyrrole-1-carboxylate

Source of chirality: (S_a)-Binap

$[\alpha]_D^{20} = +74^\circ$ (c 1, $CHCl_3$, 92% *ee* from HPLC)

Absolute configuration: (1S,3R,3aS,6aR)

J. Mancebo-Aracil , M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{17}H_{20}N_2O_4$

Isopropyl (1S,3R,3aS,6aR)-5-methyl-3-phenyl-4,6-dioxooctahydro pyrrolo[3,4-c]pyrrole-1-carboxylate

Source of chirality: (S_a)-Binap

$[\alpha]_D^{20} = +63^\circ$ (c 1, $CHCl_3$, 87% *ee* from HPLC)

Absolute configuration: (1S,3R,3aS,6aR)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

C₁₈H₂₂N₂O₄

tert-Butyl (1S,3R,3aS,6aR)-5-methyl-3-phenyl-4,6-dioxoocta hydropyrrolo[3,4-c]pyrrole-1-carboxylate

Source of chirality: (*S_a*)-Binap

[α]_D²⁰ = +33.9° (c 0.8, CHCl₃, 91% *ee* from HPLC)

Absolute configuration: (1*S*,3*R*,3*aS*,6*aR*)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

C₁₉H₁₈N₂O₄

Methyl (1S,3R,3aS,6aR)-5-methyl-3-(2-naphthyl)-4,6-dioxoocta hydropyrrolo[3,4-c]pyrrole-1-carboxylate

Source of chirality: (*S_a*)-Binap

[α]_D²⁰ = +109.4 (c 1, CHCl₃, >99% *ee* from HPLC)

Absolute configuration: (1*S*,3*R*,3*aS*,6*aR*)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

C₁₆H₁₈N₂O₄

Methyl (1S,3R,3aS,6aR)-5-methyl-4,6-dioxo-3-o-tolyl-octa hydropyrrolo[3,4-c]pyrrole-1-carboxylate

Source of chirality: (*S_a*)-Binap

[α]_D²⁰ = +50.8° (c 0.6, CHCl₃, 70 % *ee* from HPLC)

Absolute configuration: (1*S*,3*R*,3*aS*,6*aR*)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

C₁₅H₁₅ClN₂O₄

Methyl (1S,3R,3aS,6aR)-3-(2-chlorophenyl)-5-methyl-4,6-dioxoocta hydropyrrolo[3,4-c]pyrrole-1-carboxylate

Source of chirality: (*S_a*)-Binap

[α]_D²⁰ = +27.1 (c 1, CHCl₃, >99% *ee* from HPLC)

Absolute configuration: (1*S*,3*R*,3*aS*,6*aR*)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{16}H_{18}N_2O_4$

Methyl (1S,3R,3aS,6aR)-5-methyl-3-(4-methylphenyl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate

Source of chirality: (*S_a*)-Binap

$[\alpha]_D^{20} = +89^\circ$ (*c* 0.4, $CHCl_3$, 99% *ee* from HPLC)

Absolute configuration: (1*S*,3*R*,3*aS*,6*aR*)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{15}H_{15}ClN_2O_4$

Methyl (1S,3R,3aS,6aR)-3-(4-chlorophenyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate

Source of chirality: (*S_a*)-Binap

$[\alpha]_D^{20} = +39^\circ$ (*c* 0.8, $CHCl_3$, 94% *ee* from HPLC)

Absolute configuration: (1*S*,3*R*,3*aS*,6*aR*)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{14}H_{15}N_3O_4$

Methyl (1S,3R,3aS,6aR)-3-(3-pyridyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate

Source of chirality: (*S_a*)-Binap

$[\alpha]_D^{20} = +8^\circ$ (*c* 0.5, $CHCl_3$, 40% *ee* from HPLC)

Absolute configuration: (1*S*,3*R*,3*aS*,6*aR*)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{13}H_{14}N_2O_4S$

Methyl (1S,3R,3aS,6aR)-5-methyl-4,6-dioxo-3-(2-thienyl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate

Source of chirality: (*S_a*)-Binap

$[\alpha]_D^{20} = +48^\circ$ (*c* 0.6, $CHCl_3$, 93% *ee* from HPLC)

Absolute configuration: (1*S*,3*R*,3*aS*,6*aR*)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{15}H_{18}N_2O_4$

Methyl (1S,3R,3aS,6aR)-5-ethyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate

Source of chirality: (*S_a*)-Binap

$[\alpha]_D^{20} = +58.7^\circ$ (*c* 0.5, $CHCl_3$, 99% *ee* from HPLC)

Absolute configuration: (1*S*,3*R*,3*aS*,6*aR*)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{15}H_{16}N_2O_4$

Methyl (1S,3R,3aS,6aR)-4,6-dioxo-3,5-diphenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate

Source of chirality: (*S_a*)-Binap

$[\alpha]_D^{20} = +40.2^\circ$ (*c* 0.5, $CHCl_3$, 82% *ee* from HPLC)

Absolute configuration: (1*S*,3*R*,3*aS*,6*aR*)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{21}H_{20}N_2O_4$

Methyl (1S,3R,3aS,6aR)-5-benzyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate

Source of chirality: (*S_a*)-Binap

$[\alpha]_D^{20} = +69.4^\circ$ (*c* 1, $CHCl_3$, 98% *ee* from HPLC)

Absolute configuration: (1*S*,3*R*,3*aS*,6*aR*)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{16}H_{18}N_2O_4$

Methyl (1S,3R,3aS,6aR)-1,5-dimethyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate

Source of chirality: (*S_a*)-Binap

$[\alpha]_D^{20} = +108.6$ (*c* 1, $CHCl_3$, 99% *ee* from HPLC)

Absolute configuration: (1*S*,3*R*,3*aS*,6*aR*)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{17}H_{22}N_2O_4S$

Methyl (1S,3R,3aS,6aR)-1-isobutyl-5-methyl-4,6-dioxo-3-(2-thienyl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate

Source of chirality: (*S_a*)-Binap

$[\alpha]_D^{20} = +24.7^\circ$ (*c* 1, $CHCl_3$, 91% *ee* from HPLC)

Absolute configuration: (1*S*,3*R*,3*aS*,6*aR*)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{22}H_{22}N_2O_4$

Methyl (1S,3R,3aS,6aR)-1-benzyl-5-methyl-4,6-dioxo-3-phenyl octahydropyrrolo[3,4-c]pyrrole-1-carboxylate

Source of chirality: (*S_a*)-Binap

$[\alpha]_D^{20} = -75.8$ (*c* 0.8, $CHCl_3$, 99% *ee* from HPLC)

Absolute configuration: (1*S*,3*R*,3*aS*,6*aR*)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{24}H_{23}NO_6S_2$

Methyl (2R,3R,4R,5S)-5-phenyl-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate

Source of chirality: (*S_a*)-Binap

$[\alpha]_D^{20} = +1.2^\circ$ (*c* 1, $CHCl_3$, 90% *ee* from HPLC)

Absolute configuration: (2*R*,3*R*,4*R*,5*S*)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{28}H_{25}NO_6S_2$

Methyl (2R,3R,4R,5S)-5-(naphth-2-yl)-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate

Source of chirality: (*S_a*)-Binap

$[\alpha]_D^{20} = +17.1^\circ$ (*c* 0.5, $CHCl_3$, 92% *ee* from HPLC)

Absolute configuration: (2*R*,3*R*,4*R*,5*S*)

J. Mancebo-Aracil , M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

C₂₉H₂₅NO₆S₂

Methyl (2R,3R,4R,5S)-2-methyl-5-(naphth-2-yl)-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate

Source of chirality: (*S_a*)-Binap

[α]_D²⁰ = +5.2° (*c* 1, CHCl₃, 24% *ee* from HPLC)

Absolute configuration: (2*R*,3*R*,4*R*,5*S*)

J. Mancebo-Aracil , M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

C₂₅H₂₅NO₆S₂

Methyl (2R,3R,4R,5S)-3,4-bis(phenylsulfonyl)-5-(o-tolyl)pyrrolidine-2-carboxylate

Source of chirality: (*S_a*)-Binap

[α]_D²⁰ = +1.7° (*c* 0.8, CHCl₃, 18% *ee* from HPLC)

Absolute configuration: (2*R*,3*R*,4*R*,5*S*)

J. Mancebo-Aracil , M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

C₂₅H₂₅NO₆S₂

Methyl (2R,3R,4R,5S)-3,4-bis(phenylsulfonyl)-5-(p-tolyl)pyrrolidine-2-carboxylate

Source of chirality: (*S_a*)-Binap

[α]_D²⁰ = +2.3° (*c* 1, CHCl₃, 88% *ee* from HPLC)

Absolute configuration: (2*R*,3*R*,4*R*,5*S*)

J. Mancebo-Aracil , M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

C₂₅H₂₅NO₇S₂

Methyl (2R,3R,4R,5S)-5-(4-methoxyphenyl)-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate

Source of chirality: (*S_a*)-Binap

[α]_D²⁰ = -4.5° (*c* 1, CHCl₃, % *ee* from HPLC)

Absolute configuration: (2*R*,3*R*,4*R*,5*S*)

J. Mancebo-Aracil , M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{24}H_{22}ClNO_6S_2$

Methyl (2R,3R,4R,5S)-5-(4-chlorophenyl)-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate

Source of chirality: (*S_a*)-Binap

$[\alpha]_D^{20} = +91.6^\circ$ (*c* 1, $CHCl_3$, 45% *ee* from HPLC)

Absolute configuration: (2*R*,3*R*,4*R*,5*S*)

J. Mancebo-Aracil , M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{26}H_{26}ClNO_6S_2$

Isopropyl (2R,3R,4R,5S)-5-(4-chlorophenyl)-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate

Source of chirality: (*S_a*)-Binap

$[\alpha]_D^{20} = +37.0^\circ$ (*c* 0.7, $CHCl_3$, 40% *ee* from HPLC)

Absolute configuration: (2*R*,3*R*,4*R*,5*S*)

J. Mancebo-Aracil , M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{23}H_{22}N_2O_6S_2$

Methyl (2R,3R,4R,5S)-3,4-bis(phenylsulfonyl)-5-(pyrid-3-yl)pyrrolidine-2-carboxylate

Source of chirality: (*S_a*)-Binap

$[\alpha]_D^{20} = -63.9^\circ$ (*c* 1.2, CH_2Cl_2 , 93% *ee* from HPLC)

Absolute configuration: (2*R*,3*R*,4*R*,5*S*)

J. Mancebo-Aracil , M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{22}H_{20}NO_6S_3$

Methyl (2R,3R,4R,5S)-2-isobutyl-3,4-bis(phenylsulfonyl)-5-(thien-2-yl)pyrrolidine-2-carboxylate

Source of chirality: (*S_a*)-Binap

$[\alpha]_D^{20} = +7.1^\circ$ (*c* 1, $CHCl_3$, 70% *ee* from HPLC)

Absolute configuration: (2*R*,3*R*,4*R*,5*S*)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{21}H_{19}N_2O_6S_3$

Methyl (2R,3R,4R,5S)-2-isobutyl-3,4-bis(phenylsulfonyl)-5-(thiazol-2-yl)pyrrolidine-2-carboxylate

Source of chirality: (S_a)-Binap

$[\alpha]_D^{20} = +4.1^\circ$ (c 1, CH_2Cl_2 , 10% ee from HPLC)

Absolute configuration: (2R,3R,4R,5S)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{12}H_{15}NO_2$

Methyl (2S,5R)-5-phenylpyrrolidine-2-carboxylate

Source of chirality: (S_a)-Binap

$[\alpha]_D^{20} = +19.0$ (c 1, CH_2Cl_2 , 90% ee from HPLC)

Absolute configuration: (2S,5R)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{30}H_{33}NO_{10}S_2$

Methyl (2R,3S,4S,5S)-5-[2-(2-acetoxyethyl)-4,5-dimethoxyphenyl]-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate

Source of chirality: (S_a)-Binap

$[\alpha]_D^{20} = -25.3^\circ$ (c 1, $CHCl_3$, 50% ee from HPLC)

Absolute configuration (2R,3S,4S,5S)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{40}H_{46}N_2O_9S_3Si$

Methyl (2R,3R,4R,5S)-5-{3-[2-((tert-butyl)dimethylsilyl)oxy]ethyl}-1-(phenylsulfonyl)-1H-indol-2-yl}-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate

Source of chirality: (S_a)-Binap

$[\alpha]_D^{20} = -4.5^\circ$ (c 1, $CHCl_3$, 12% ee from HPLC)

Absolute configuration: (2R,3S,4S,5S)

J. Mancebo-Aracil, M. Martín-Rodríguez, C. Nájera, J. M. Sansano*, P. R. R. Costa, E. Crizanto de Lima, A. G. Dias

$C_{18}H_{28}N_2O_4S$

tert-Butyl methyl (2S,4S,5R)-2-isobutyl-5-(thiazol-2-yl)pyrrolidine-2,4-dicarboxylate

Source of chirality: (*S_a*)-Binap

$[\alpha]_D^{20} = +38.0^\circ (c\ 1, CH_2Cl_2, 88\%\ ee\ \text{from HPLC})$

Absolute configuration: (2*S*,4*S*,5*R*)

Binap-silver salts as chiral catalysts for the enantioselective 1,3-dipolar cycloaddition of azomethine ylides and alkenes

Juan Mancebo-Aracil^a, María Martín-Rodríguez^a, Carmen Nájera^a, José M. Sansano^{a*}, Paulo R. R. Costa^b, Evanoel Crizanto de Lima^b, and Ayres G. Dias^b

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

^b 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.

ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

ABSTRACT

Binap-AgSbF₆ catalyzed 1,3-dipolar cycloaddition between azomethine ylides and electrophilic alkenes is described and compared with the analogous transformations mediated by other Binap-silver(I) salt complexes. Maleimides and 1,2-bis(phenylsulfonyl)ethylene, are suitable dipolarophiles to obtain very good enantioselections, even better enantioselections are generated by the multicomponent version. Some very interesting applications of disulfonylated cycloadducts into the total synthesis of *cis*-2,5-disubstituted pyrrolidines, precursors of natural products, or valuable intermediates in the synthesis of antiviral compounds.

2009 Elsevier Ltd. All rights reserved.

* Corresponding author. Tel.: +34-965903549; fax: +34-965903549; jmsansano@ua.es

1. Introduction

Privileged chiral ligands¹ are the most efficient enantiomerically pure molecules, incorporating few core structures, which are taking as reference for every chemist working in the field of asymmetric catalysis. Binap is a clear cut example of this concept, which has been used together with ruthenium, rhodium, and palladium in many organic enantioselective transformations.¹ This chiral diphosphane was also tested in the catalytic enantioselective 1,3-dipolar cycloaddition² (1,3-DC) of azomethine ylides (derived from imino esters) and electrophilic alkenes.³ In the first substoichiometric catalytic enantioselective 1,3-DC of azomethine ylides reported by Zhang *et al.*,⁴ the combination of (*S*)-Binap-AgOAc (3 mol%) showed low *ee* when dipoles derived from imino esters and dimethyl maleate (up to 13% *ee*). The change of the counterion of the complex by our group was critical for the reaction success. In this way, (*S*)-Binap-AgClO₄ **1**, a very stable and recyclable complex, resulted to be very appropriate in the 1,3-DC of imino esters and maleimides (up to >99% *ee*).⁵ Apart from silver(I), copper(I)⁶ and (II),⁷ and gold(I)^{8,9,10} chiral Binap complexes have been studied as catalysts in analogous 1,3-DCs using several dipolarophiles.

Reluctance of chemical companies to perchlorate salts moved us to search another poorly coordinated anion in order to ensure or even improve the results obtained from (*S*)-Binap-AgClO₄ complex. Computational studies of this asynchronous transformation also revealed that in the transition state, responsible of the enantiodiscrimination, the perchlorate anion was weakly bonded to the central metal (2.41 Å).^{5b} Based on this data, we thought that weakly coordinating hexafluoroantimonate anion would be an alternative to perchlorate as catalyst of this particular cycloaddition. An identical semi-empirical model to the already described, but incorporating SbF₆⁻ instead of ClO₄⁻, shown a longer distance (2.46 Å) between silver central atom and its counterion.¹¹ In this article, we will search how important this small distance difference is during the enantioselective catalyzed 1,3-DC between imino esters and electron-deficient alkenes, and the scope of (*S*)-Binap-AgSbF₆ catalyst **2** vs. other Binap complexes formed with different silver(I) salts.¹²

2. Discussion

2.1. Optimization of the reaction conditions.

The selected model reaction between methyl benzylideneiminoglycinate **3aa** and *N*-methylmaleimide (NMM) **4a** was performed in toluene at room temperature using 5 mol % of (*S*)-Binap and 5 mol% of Ag^I salt as catalyst precursor (Scheme 1 and Table 1). The reaction run with

equimolar amount of both (*S*_a)-Binap and several oxygenated silver(I) salts with a weak coordinating anion, such as AgOAc, AgOTf (Tf = trifluoromethanesulfonyl), AgOTf (Tf = trifluoromethanesulfonyl), AgNO₃, and AgBF₄, (5 mol%) were compared. When AgOAc was used excellent results of the compound **5aa** were obtained by using triethylamine rather than DABCO (Table 1, entries 1 and 2), but the crude reaction product was not very clean. Silver trifluoroacetate also yields an excellent result of cycloadduct **5aa**, but again the reaction crude product was slightly unpurified (¹H NMR) (Table 1, entry 3). This chiral catalyst can work as an internal base, the trifluoroacetate anion being the most effective (Table 1, entry 4). In this case, the enantioselection was excellent, the reaction slightly slower and a few impurities in the crude product were detected. The bifunctional behavior of acetate derived catalyst was not as effective as Tfa complex did, affording lower yield of the cycloadduct **5aa**. Silver triflate afforded excellent enantioselection (99% *ee*) but with a higher amount of the *exo*-diastereoisomer (Table 1, entry 5). The rest of the silver salts described in Table 1 were not able to promote the 1,3-DC in the absence of an external base. AgBF₄ or AgNO₃ catalyzed reactions affording lower chemical yields, diastereo- and enantioselections (Table 1, entries 6 and 7).

Using AgSbF₆ and Et₃N as base, enantiomerically enriched cycloadduct **5aa** (>99% *ee*) was isolated in very good yield (90%) and with an excellent *endo*-selectivity.¹³ This result, and the obtained when the reaction was performed with AgClO₄, were almost identical (Table 1, entry 8). Other solvents, such as Et₂O, DCM, THF, and MeCN, were tested but neither the purity nor diastereo-/enantioselection of the final product **5aa** were improved. The 5 mol% catalyst loading was the most appropriate because the reaction became slower when a 3 mol% charge was placed instead (Table 1, entry 9). 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 products in the crude mixture (Table 1, entries 10, and 11). However, the reaction run with *N,N*-diisopropylethylamine (DIPEA) was completely equivalent to the reaction done with triethylamine (Table 1, compare entries 8 and 10). Different stoichiometry to 1:1 (*S*_a)-Binap:silver salt, such as 2:1 or 1:2, afforded lower enantioselections and larger amounts of the *exo*-diastereoisomer in both situations (Table 1, entries 13 and 14).

So, the reaction involving silver hexafluoroantimonate in the presence of a tiny amount of triethylamine ensures a good chemical yield, an excellent enantioselection (>99%) and a very clean material that did not require any additional purification.

Scheme 1. Reagents and conditions: i) (*S_a*)-Binap (5 mol%), Ag^I salt (5 mol%), base (5 mol%), toluene, 25 °C, 16 h.

Table 1. Optimization of the reaction of imino esters **3aa** with NMM (**4a**).

	Ag ^I salt	Base	Product 5aa ^a		
			Yield (%) ^b	<i>endo:exo</i> ^c	<i>ee</i> (%) ^d
1	AgOAc	Et ₃ N	89	>98:2	99 ^e
2	AgOAc	DABCO	85	>95:5	94
3	AgOTfa	Et ₃ N	89	>98:2	99 ^e
4	AgOTfa	—	78	>98:2	99 ^e
5	AgOTf	Et ₃ N	88	90:10	99
6	AgNO ₃	Et ₃ N	65	85:11	67
7	AgBF ₄	Et ₃ N	77	89:11	72
8	AgSbF ₆	Et ₃ N	90 (89)	>98:2 (>98:2)	>99 (>99)
9	AgSbF ₆ ^f	Et ₃ N	78 (80)	>98:2 (>98:2)	>99 (>99)
10	AgSbF ₆	DIPEA	89 (89)	>98:2 (>98:2)	>99 (>99)
11	AgSbF ₆	DABCO	87 (88)	>90:10 (>90:10)	94 (92) ^e
12	AgSbF ₆	DBU	87 (80)	>90:10 (>90:10)	90 (91) ^e
13	AgSbF ₆ ^g	Et ₃ N	90 (90)	90:10 (90:10)	96 (98) ^e
14	AgSbF ₆ ^h	Et ₃ N	90 (91)	>98:2 (>98:2)	56 (<50) ^e

^a Conversions were higher than 95% (determined by ¹H NMR spectroscopy of the crude product).

^b Isolated yield after recrystallization. The yields of the analogous reaction performed with AgClO₄ are given in parenthesis.⁵

^c Determined by ¹H NMR spectroscopy of the crude product.

^d Determined by HPLC of the crude product employing chiral columns (Daicel Chiralpak AS). The *ee* of the analogous reaction performed with AgClO₄ are given in parenthesis.⁵ Identical *ee* was determined for the purified product in both reaction sets.

^e Some unidentified impurities were detected in the crude product.

^f Reaction performed with a 3 mol% of the catalyst.

^g Reaction performed with 2 equiv. of Binap and 1 equiv. of Ag^I salt.

^h Reaction performed with 1 equiv. of Binap and 2 equiv. of Ag^I salt.

2.2. Characterization of the catalytic species.

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 8 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 triflate¹⁴ (Figure 2) or perchlorate anions.^{5b} Complexes formed from silver triflate and (*R*) or (*S*)-Binap, were isolated at different temperatures and further characterized by X-ray diffraction analysis by Yamamoto's group. These studies revealed that mixture of structures **6-8** are in equilibrium, and at room temperature, being the 1:1 complex **7** the most abundant system (Figure 2).

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^I complex (*S_a*)-**2** and a tiny one at 1352 and 1354 corresponding to the 2:1 Binap:AgSbF₆ (similar to complex **6**). 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).

Figure 1. [(*R*)-Binap]AgOTf complexes and catalyst-dipole complex **9**.

Calculations performed with Binap-AgClO₄ model, which are comparable with Binap-AgSbF₆ model, supported that NMM was the best dipolarophile due to the coordination of the nitrogen atom to the metal centre. The TS responsible of the enantiodiscrimination is, as expected, quite asynchronous. On it a very important steric interaction between one of the phenyl groups of the phosphine moiety of chiral ligand and the dipolarophile can be considered crucial for explaining the experimental findings and providing a rationale for the observed excellent asymmetric induction.

2.3. General scope of the (*S_a*)-Binap-AgSbF₆ catalyzed 1,3-DC.

The optimized reaction conditions were employed in the diastereo- and enantioselective transformation of several azomethine ylides, generated from the corresponding methyl arylideneiminoglycinates **3**, and maleimides into the corresponding cycloadducts *endo*-**5**. Reactions employing a 5 mol% of an equimolar mixture of (*S*)-Binap and AgSbF₆ in the presence of toluene as solvent and a catalytic amount of triethylamine (5 mol%) were directly compared with the analogous results obtained with (*S*)-Binap-AgClO₄ complex⁵ (Scheme 2, and Table 2).

In general, we can observe that isolated chemical yields of compounds **5** are identical to each other. For example, for Ar = Ph, 2-naphthyl, and 2-thienyl, there was no difference in terms of enantioselection between both catalytic complexes (Table 2, entries 1, 6 and 12). These three entries were also repeated employing (*S*)-Binap-AgTfa with no added base, finding similar enantioselections and lower chemical yields of slightly unpurified cycloadducts *endo*-**5** (not shown in Table 2). When the reaction was performed with (*R*)-Binap the corresponding enantiomer of *endo*-**5aa** was isolated in good yield and excellent enantioselectivity (Table 2, entry 2). A modification of the alkyl moiety of the ester group produced a drop of the diastereoselection, higher when the *tert*-butyl ester was tested (Table 2, entries 3-5). In all these cases the enantioselectivity was lower than the obtained one for the methyl ester. For substituted aromatic imino esters, the enantioselection was always higher when AgSbF₆ was selected as co-catalyst, except when *o*-tolyl derivative **3ca** was used (Table 2, entries 7-10). Heteroaromatic groups, attached to the 1,3-dipole precursor, influenced the reaction course. Whereas 2-thienyl derivative furnished **5ha** with very good enantioselection, 3-pyridyl derivative **3ga** is not suitable for this particular transformation (Table 2, entries 11 and 12). Presumably, the basic character of the nitrogenated heterocycle promoted the non-asymmetric process.

The absolute configuration of these products **5**, as well as all compounds described along the text, was determined by comparison of known data reported in the literature for identical molecules.

When different *N*-substituted maleimides were compared, it was detected that *N*-ethylmaleimide (NEM) did not represent any difference with respect to those results obtained in the (*S*)-Binap-AgClO₄. However, the reaction carried out with *N*-phenylmaleimide (NPM) was much more enantioselective in the presence of (*S*)-Binap-AgSbF₆ complex than that obtained with perchlorate derived chiral complex (82% *ee*, vs. 62% *ee*). Computational calculations justified this difference because of the existence of steric hindrance between the phenyl group of the NPM and the Binap-AgClO₄ catalyst.^{5b} Less coordinating anion in the catalyst Binap-AgSbF₆ released the steric congestion of the transition state. In the examples run with *N*-benzylmaleimide the difference of *ee* in product *endo*-**8** was not so important (Scheme 3). Products *endo*-**6**, *endo*-**7**, and *endo*-**8** were isolated as more than 98:2 *endo:exo* ratio independently of the chiral catalyst employed.

Scheme 2. Reagents and conditions: i) (*S_a*)-Binap (5 mol%), Ag^I salt (5 mol%), Et₃N (5 mol%), toluene, 25 °C, 16 h.

Table 2. 1,3-DC of iminoglycinates **3** and NMM **4a**.

Entry	N°	Ar	R ¹	Product <i>endo</i> - 5			
				No.	Yield (%) ^{a,b}	<i>endo:exo</i> ^{b,c}	<i>ee</i> _{endo} (%) ^{b,d}
1	3aa	Ph	Me	5aa	90 (90)	>98:2	>99 (>99)
2	3aa^e	Ph	Me	<i>ent</i> - 5aa	90 (90)	>98:2	>99 (>99)
3	3ab	Ph	Et	5ab	81 (78)	95:5 (90:10)	92 (91)
4	3ac	Ph	Pr ⁱ	5ac	80 (81)	90:10	87 (72)
5	3ad	Ph	Bu ^t	5ad	81 (79)	80:20 (75:25)	91 (92)
6	3ba	2-naphthyl	Me	5ba	89 (80)	>98:2	>99 (>99)
7	3ca	2-CH ₃ C ₆ H ₄	Me	5ca	85 (85)	>98:2	70 (75)
8	3da	2-ClC ₆ H ₄ ^f	Me	5da	85 (88)	>98:2	>99 (85)
9	3ea	4-CH ₃ C ₆ H ₄	Me	5ea	85 (85)	>98:2	99 (80)
10	3fa	4-ClC ₆ H ₄	Me	5fa	84 (87)	>98:2	94 (65)
11	3ga	3-Pyridyl	Me	5ga	77 (81)	80:20	40 (10)

^a Isolated yield after flash chromatography.

^b In brackets the result obtained previously with (*S*)-Binap-AgClO₄ complex.⁵

^c Determined by chiral ¹H NMR of the crude product.

^d Determined by HPLC of the crude product using chiral columns. Identical *ee* was determined after purification of **5**.

^e Reaction performed with (*R*)-Binap-AgSbF₆.

^f Reaction performed at -20 °C.

Scheme 3. Reagents and conditions: i) (*S_a*)-Binap (5 mol%), Ag^I salt (5 mol%), Et₃N (5 mol%), toluene, 25 °C, 16 h.

The effect of the α -substitution in the 1,3-dipole precursor was next evaluated. Alanine, leucine and phenylalaninates **9** were allowed to react with NMM under the typical reaction conditions taking 48 h to reach complete conversions (Scheme 4). Cycloadducts *endo*-**10** were obtained in good yields when both chiral catalysts were used, but the enantioselectivity achieved by (*S_a*)-Binap-AgSbF₆ was noticeably higher. This is another evidence of the facility of the hexafluoroantimonate salt to perform cycloadditions with sterically hindered components.

Scheme 4. Reagents and conditions: i) (*S_a*)-Binap (5 mol%), Ag^I salt (5 mol%), Et₃N (5 mol%), toluene, 25 °C, 48 h.

We have also found that dipolarophiles such as alkyl acrylates, dialkyl fumarates, dimethyl maleate and acrylonitrile exhibited exactly identical behavior with both silver salts, that means very low enantioselections and good chemical yields were obtained. Also more polar solvents, such as acetone, acetonitrile, diethyl ether, ethanol, and water were essayed but cycloaddition was not completed at all and the crude reaction mixtures were notably impurified. When small amounts of cycloadducts were isolated the enantioselections were almost zero.

However, big differences were detected when 1,2-bis(phenylsulfonyl)ethylene was employed as low-LUMO alkene (Scheme 5 and Table 3). 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*-**12** did not require additional purification. The reaction performed with (*S*)-Binap-AgClO₄ never improved the results generated by intermediacy of (*S*)-Binap-AgSbF₆. Phenyl- and 2-naphthyl substituents bonded to the imino group afforded high enantioselections of the product **12aaa** and **12baa**, respectively (Table 3, entries 1-4). The effect of the methyl group in the azomethine ylide caused lower enantioselections in final products **12bba** (Table 3, entries 5 and 6). The introduction of a substituent in the arylidene moiety of the imino ester was not very profitable because the *ee* of cycloadducts were very low, except in the case of *para*-methyl substituted derivative (Table 3, entries 7-

14). The presence of an isopropyl ester instead of the methyl one also gave a disappointing enantioselection of heterocycle **12fab** (Table 3, entries 15 and 16). 3-Pyridyl group was the most appropriate heterocycle (Table 3, entries 17 and 18) because 2-thienyl and 2-thiazolyl imino esters, present in antiviral agents, did not afford very high enantioselections in spite of producing an excellent yield (Table 3, entries 19-22). Sterically hindered imino esters furnished lower *endo:exo* ratio such as occurred in *ortho*-substituted arylamines, isopropyl esters, and α -branched amino acid derivatives (alanine and leucine), and far more when (*S*)-Binap-AgClO₄ was employed (Table 3, entries 5-8, 15, 16, and 19-22).

Scheme 5. Reagents and conditions: i) (*S_a*)-Binap (5 mol%), Ag^I salt (5 mol%), Et₃N (5 mol%), toluene or THF, 25 °C, 48 h.

Table 3. 1,3-DC of iminoglycinates **9** and disulfone **11**.

Entry	Ar	R ¹	R ²	Solvent	Product <i>endo</i> - 12			
					No.	Yield. (%) ^{a,b}	<i>endo:exo</i> ^{b,c}	<i>ee</i> _{endo} (%) ^{b,d}
1	Ph	H	Me	PhMe	12aaa	81 (80)	>98:2	90 (88)
2	Ph	H	Me	THF	12aaa	82	>98:2	90
3	2-Naphthyl	H	Me	PhMe	12baa	91 ^e (88)	>98:2	92 (80)
4	2-Naphthyl	H	Me	THF	12baa	90	>98:2	80
5	2-Naphthyl	Me	Me	PhMe	12bba	95 ^e (82)	90:10	24 (10)
6	2-Naphthyl	Me	Me	THF	12bba	91 ^e	90:10	12
7	2-CH ₃ C ₆ H ₄	H	Me	PhMe	12caa	63 (79)	90:10	18 (16)
8	2-CH ₃ C ₆ H ₄	H	Me	THF	12caa	68	90:10	6
9	4-CH ₃ C ₆ H ₄	H	Me	PhMe	12daa	91 ^e (78)	>98:2	88 (28)
10	4-CH ₃ C ₆ H ₄	H	Me	PhMe	12daa	78	>98:2	82
11	4-MeOC ₆ H ₄	H	Me	PhMe	12eaa	58 (60)	>98:2	38 (28)
12	4-MeOC ₆ H ₄	H	Me	THF	12eaa	78	>98:2	12
13	4-ClC ₆ H ₄	H	Me	PhMe	12faa	81 (85)	>98:2	45 (27)
14	4-ClC ₆ H ₄	H	Me	THF	12faa	79	>98:2	42
15	4-ClC ₆ H ₄	H	Pr ⁱ	PhMe	12fab	64 (71)	80:20	40 (30)
16	4-ClC ₆ H ₄	H	Pr ⁱ	THF	12fab	93 ^e	80:20	30
17	3-Pyridyl	H	Me	PhMe	12gaa	83 (82)	>98:2	93 (78)
18	3-Pyridyl	H	Me	THF	12gaa	92 ^e	>98:2	90
19	2-Thienyl	Bu ⁱ	Me	PhMe	12hca	92 (<50)	90:10 (75:25)	70 (12)
20	2-Thienyl	Bu ⁱ	Me	PhMe	12hca	95 ^e	90:10 (75:25)	58
21	2-Thiazolyl	Bu ⁱ	Me	PhMe	12ica	92 ^e (<50)	90:10 (75:25)	10 (8)
22	2-Thiazolyl	Bu ⁱ	Me	PhMe	12ica	93 ^e	90:10 (75:25)	4

^a Isolated yield after flash chromatography.

^b In brackets the result obtained previously with (*S*)-Binap-AgClO₄ complex.

^c Determined by chiral ¹H NMR of the crude product.

^d Determined by HPLC of the crude product using chiral columns. Identical *ee* was determined after purification of **12**.

^e No additional purification was required.

Multicomponent reactions were attempted using the best result depicted in Tables 2 and 3. Thus, benzaldehyde/NMM **4a** or 3-pyridinecarbaldehyde/disulfone **11**, glycine methyl ester hydrochloride, triethylamine (1.05 equiv), (*S*)-Binap-AgSbF₆ (5 mol%), were put together in toluene and the resulting mixture was allowed to react at 25 °C for 48 h. The results obtained for compound *endo*-**5aa** or *endo*-**12gaa** were impressive (88% yield, >99% *ee*, or 86% yield, 98% *ee*, respectively, Scheme 6). However, analogous reactions carried out in the presence of (*S*)-Binap-AgClO₄ complex failed. Although very activated aminomalonates have been involved as one of the three components of the enantioselective organocatalyzed 1,3-DC, this was the first occasion that a three-component transformation is enantioselectively performed in the presence of a chiral Lewis acid. Disappointingly, the employment of other substrates with these two dipolarophiles did not afford neither the expected enantioselections nor even good chemical yields. The introduction of the free α -amino ester instead of the corresponding hydrochloride did not represent any improvement.

Scheme 6. Reagents and conditions: i) (*S_a*)-Binap (5 mol%), AgSbF₆ (5 mol%), Et₃N (5 mol%), toluene, 25 °C, 16 h. ii) (*S_a*)-Binap (5 mol%), AgSbF₆ (5 mol%), Et₃N (5 mol%), toluene, 25 °C, 48 h.

2.4. Applications of (*S_a*)-Binap-AgX catalyzed 1,3-DC.

As masked acetylene equivalent, disulfone **11** has been used in this 1,3-DC for the preparation of very interesting Schramm's C-azanucleoside,¹⁵ which is a promising trypanosomal nucleoside hydrolase inhibitor. In this work the enantioselective synthesis of the *exo*-cycloadduct (type **12**) was the key step of the total process, and next the methoxycarbonyl group was reduced with lithium aluminum hydride (LAH) followed by the complete desulfonylation with sodium amalgam. In our case, when the enantiomerically enriched *endo*-**12aaa** was allowed to undergo this double reduction protocol (LAH plus amalgam) a very complex reaction mixture was obtained, pyrrole being the major product observed. In spite of several conditions essayed the behavior of the *endo*-diastereoisomer is very different to the *exo* one, even in terms of stability upon flash chromatography.

The synthesis of 5-substituted prolines can be another interesting application because gives access to biologically active compounds, such as nonpeptide cholecystokinin antagonist (+)-RP 66803 **13**.¹⁶ The 5-phenylproline fragment was prepared according to the route described in Scheme 7. Isomers **14** and **15** 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 **16** was 47 (Scheme 7). This low yield could be justified by the formation of significant amounts of pyrrole derivative after the desulfonylation step.

Scheme 7. Reagents and conditions: i) Na(Hg), 10%, MeOH/THF (3/1), from 0 to 25 °C, 1h. ii) Pt/C (10%), H₂ (1 atm), MeOH, 48 h, 25 °C.

(*R*)-(+)-Crispine A **17** and (*R*)-(+)-harmicine **18** are naturally occurring molecules employing in traditional medicine. The anticancer properties of the former and the anti-leishmaniasis effects of the latter have attracted the attention of many scientists.^{17,18} Following the approach of Coldham's group, inspired in a 1,3-DC using disulfone **11** (Scheme 8),¹⁹ new starting -suitably protected- aromatic precursors **19** and **20** were prepared.

Scheme 8. Retrosynthetic analysis of natural products **19** and **20**.

The reaction of the imine **21** (obtained from the corresponding aldehyde²⁰ and methyl glycinate) and disulfone **11** was accomplished at 20-25 °C in toluene as solvent and a 10 mol% of catalyst loading (formed by chiral Binap and a silver salt) and in the presence of a base or not (Scheme 9 and Table 4). AgSbF₆,

AgTfa, and AgOAc were tested obtaining best results when the trifluoroacetate salt was combined with triethylamine (10 mol%) as base (Table 4, entries 1-3). Other different bases such as DIPEA, DABCO, or DBU were essayed finding a very noticeable increment of the enantioselection with AgTfa/DABCO mixture (up to 50% *ee*) (Table 4, entries 4-7). Quinuclidine based alkaloids were next tested in a double chiral induction, but the results never overtook 40% *ee* (Table 4, entries 8-11). Also unfruitful were the transformations carried out with these silver salts in the absence of base. Poor enantioselection of cycloadduct **19** (up to 32% *ee*) was isolated in moderate chemical yields (55-65%).

Scheme 9. Reagents and conditions: i) (*S_a*)-Binap (10 mol%), Ag^I salt (10 mol%), base (10 mol%), toluene, 20-25 °C, 48 h.

Table 4. Optimization of the reaction of imino ester **21** with **11**.

	Ag ^I salt	Base	Product 19	
			Yield (%) ^{a,b}	<i>ee</i> (%) ^c
1	AgSbF ₆	Et ₃ N	55	32
2	AgOAc	Et ₃ N	45	30
3	AgTfa	Et ₃ N	55	35
4	AgTfa	DIPEA	80	30
5	AgTfa	DABCO	59	50
6	AgSbF ₆	DABCO	50	30
7	AgTfa	DBU	63	24
8	AgTfa	Cinchonine	87	40
9	AgTfa	Cinchonidine	81	40
10	AgTfa	Quinine	71	45
11	AgTfa	Quinidine	77	-12

^a Isolated yield of the *endo*-product after flash chromatography.

^b The *endo/exo* ratio could not be determined from the crude product.

^c Determined by HPLC of the crude product employing chiral column (Daicel Chiralpak AD).

Under the best reaction conditions described in Table 4 imino ester **22** was submitted to the cycloaddition with disulfone **11** affording cycloadduct **20** in 60% chemical yield and a very poor enantioselectivity (12% *ee*)

Scheme 10. Reagents and conditions: i) (*S_a*)-Binap (10 mol%), AgTfa (10 mol%), DABCO (10 mol%), toluene, 25 °C, 48 h.

In spite of the low enantioselections registered in the reaction performed between imino ester **3aa** and acrylates, the 1,3-DC of the heterocyclic imino ester **23** and *tert*-butyl acrylate was attempted (Scheme 11 and Table 6). Such as it has been reported in previous works by our group, molecule **24** is the key intermediate in the elaboration of 2nd generation GSK inhibitors of the virus causing hepatitis C **25**.^{9,21} AgClO₄, AgTfa, and AgSbF₆ were tested (Table 6), and unexpectedly the reactions afforded good chemical yields at 25 °C, for 48 h and with high enantioselections, especially for the reaction carried out with silver perchlorate (88% *ee*) (Table 6, entry 1). The reaction needed a 10 mol% of both of the catalyst loading and triethylamine to occur. The lowering of the temperature, the use of different solvents from toluene, and several bases did not ameliorate the results described in Table 6.

Scheme 11. Reagents and conditions: i) (*S_a*)-Binap (10 mol%), AgX (10 mol%), Et₃N (10 mol%), toluene, 25 °C, 48 h.

Table 6. Synthesis of antiviral agent precursor **24**.

Entry	AgX	Product 24	
		Yield (%) ^{a,b}	<i>ee</i> (%) ^c
1	AgClO ₄	78	88
2	AgTfa	75	88
3	AgSbF ₆	79	72

^a Isolated yield of the *endo*-product after flash chromatography.

^b The *endo/exo* ratio was >98:2 (¹H NMR).

^c Determined by HPLC of the crude product employing chiral column (Daicel Chiralpak AD).

We can conclude once more that a minimum variation in structures of dipole-dipolarophile or in the reaction parameters can origin a dramatic change in the final enantioselection of the chiral Binap-silver(I) complexes when they catalyze enantioselective 1,3-dipolar cycloadditions between azomethine ylides and electrophilic alkenes. The importance of replacing perchlorate salts by other different anions is also desirable since the industrial point of view. Silver hexafluoroantimonate catalyze efficiently cycloadditions dealing with maleimides and 1,2-bis(phenylsulfonyl)ethylene obtaining best results when sterically hindered dipole precursors are employed, improving the published results using silver(I) perchlorate as co-catalyst. Also noticeable are multicomponent transformations run in the presence of AgSbF₆ whilst the analogous reaction, mediated by silver(I) perchlorate, completely failed. However, silver trifluoroacetate was much more effective, or as effective as silver(I) perchlorate, in the applications of this methodology into the synthesis of natural (crispine or harmicine precursors) or biologically attractive compounds (antiviral precursors).

Experimental part

1. General

All reactions were carried out in the absence of light. Anhydrous solvents were freshly distilled under an argon atmosphere. Aldehydes were also distilled prior to use for the elaboration of the imino esters. Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. Only the structurally most important peaks of the IR spectra (recorded on a Nicolet 510 P-FT) are listed. ¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra were obtained on a Bruker AC-300 using CDCl₃ as solvent and TMS as internal standard, unless otherwise stated. Optical rotations were measured on a Perkin Elmer 341 polarimeter. HPLC analyses were performed on a JASCO 2000-series equipped with a chiral column (detailed for each compound in the main text), using mixtures of n-hexane/isopropyl alcohol as mobile phase, at 25 °C. Low-resolution electron impact (EI) mass spectra were obtained at 70eV on a Shimadzu QP-5000 and high-resolution mass spectra were obtained on a Finnigan VG Platform. HRMS (EI) were recorded on a Finnigan MAT 95S. Microanalyses were performed on a Perkin Elmer 2400 and a Carlo Erba EA1108. Analytical TLC was performed on Schleicher & Schuell F1400/LS silica gel plates and the spots were visualized under UV light (λ=254 nm). For flash chromatography we employed Merck silica gel 60 (0.040-0.063 mm).

2. 1,3-Dipolar cycloaddition of imino esters 3, 9, 21, 22, or 23 and dipolarophiles. General procedure.

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 AgX (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 precipitate was filtered and the complex was recovered. The organic filtrate was directly evaporated and the residue was purified by recrystallization or by flash chromatography yielding pure *endo*-cycloadducts.

Methyl (1S,3R,3aS,6aR)-5-methyl-3-phenyl-4,6-dioxooctahydro pyrrolo[3,4-c]pyrrole-1-carboxylate endo-5aa.5^b

Ethyl (1S,3R,3aS,6aR)-5-methyl-3-phenyl-4,6-dioxooctahydro pyrrolo[3,4-c]pyrrole-1-carboxylate endo-5ab.5^b

Isopropyl (1S,3R,3aS,6aR)-5-methyl-3-phenyl-4,6-dioxooctahydro pyrrolo[3,4-c]pyrrole-1-carboxylate endo-5ac.5^b

tert-Butyl (1S,3R,3aS,6aR)-5-methyl-3-phenyl-4,6-dioxooctahydro pyrrolo[3,4-c]pyrrole-1-carboxylate endo-5ad.5^b

Methyl (1S,3R,3aS,6aR)-5-methyl-3-(2-naphthyl)-4,6-dioxooctahydro pyrrolo[3,4-c]pyrrole-1-carboxylate endo-5ba.5^a

Methyl (1S,3R,3aS,6aR)-5-methyl-4,6-dioxo-3-o-tolyl-octahydro pyrrolo[3,4-c]pyrrole-1-carboxylate endo-5ca.5^b

Methyl (1S,3R,3aS,6aR)-3-(2-chlorophenyl)-5-methyl-4,6-dioxooctahydro pyrrolo[3,4-c]pyrrole-1-carboxylate endo-5da.5^a

Methyl (1S,3R,3aS,6aR)-5-methyl-3-(4-methylphenyl)-4,6-dioxooctahydro pyrrolo[3,4-c]pyrrole-1-carboxylate endo-5ea.5^a

Methyl (1S,3R,3aS,6aR)-3-(4-chlorophenyl)-5-methyl-4,6-dioxooctahydro pyrrolo[3,4-c]pyrrole-1-carboxylate endo-5fa.5^a

Methyl (1S,3R,3aS,6aR)-3-(3-pyridyl)-5-methyl-4,6-dioxooctahydro pyrrolo[3,4-c]pyrrole-1-carboxylate endo-5ga.5²²

Methyl (1S,3R,3aS,6aR)-5-methyl-4,6-dioxo-3-(2-thienyl)octahydro pyrrolo[3,4-c]pyrrole-1-carboxylate endo-5ha.5^a

Methyl (1S,3R,3aS,6aR)-5-ethyl-4,6-dioxo-3-phenyloctahydro pyrrolo[3,4-c]pyrrole-1-carboxylate endo-6.5²³

Methyl (1S,3R,3aS,6aR)-4,6-dioxo-3,5-diphenyloctahydro pyrrolo[3,4-c]pyrrole-1-carboxylate endo-7.

Methyl (1S,3R,3aS,6aR)-5-benzyl-4,6-dioxo-3-phenyloctahydro pyrrolo[3,4-c]pyrrole-1-carboxylate endo-8. Pale yellow oil; [α]_D²⁰ = +69.4° (c 1, CHCl₃, 98% *ee* from HPLC); IR ν_{max} 1740-1705, 3260 cm⁻¹; ¹H NMR δ_H: 2.10 (s, 1H, NH), 3.33, 3.58 (2xdeform. d, J = 7.0, Hz, 2H, CH₂Ph), 3.40 (d, J = 7.5 Hz, 1H, CCH), 3.58 (dd, J = 9.1, and 7.6 Hz, 1H, CHCHCO₂CH₃), 3.76 (s, 3H, CO₂Me), 3.58 (d, J = 7.1 Hz, 1H, CHCO₂CH₃), 4.25 (d, J = 6.8 Hz, 1H, CHAr), 7.27-7.48 (m, 10H, ArH); ¹³C RMN δ_C: 46.2 (CH₂Ph), 47.1, 48.9 (2xCHCON), 51.9 (CH₃), 61.4, 66.2 (2xCHN), 128.1, 128.5, 125.9, 140.5, 126.9, 128.6, 126.7, 136.5 (ArC), 176.4, 176.0, 171.6 (3xCO); MS (EI-GC) m/z: 364 (M⁺+1, 2%), 273 (100), 91 (47), 68 (11); HRMS calculated for C₂₁H₂₀N₂O₄: 364.1423, found: 364.1430; HPLC (Chiralpak AS, 1 mL/min, n-hexane/i-PrOH: 20/80, λ 225 nm), t_{Rmaj} = 10.5 min, t_{Rmin} = 26.7 min.

Methyl (1S,3R,3aS,6aR)-1,5-dimethyl-4,6-dioxo-3-phenyloctahydro pyrrolo[3,4-c]pyrrole-1-carboxylate endo-10a.5^b

Methyl (1S,3R,3aS,6aR)-1-isobutyl-5-methyl-4,6-dioxo-3-(2-thienyl)octahydro pyrrolo[3,4-c]pyrrole-1-carboxylate endo-10b.5^b

Methyl (1S,3R,3aS,6aR)-1-benzyl-5-methyl-4,6-dioxo-3-phenyloctahydro pyrrolo[3,4-c]pyrrole-1-carboxylate endo-10c.5^b

Methyl (2R,3R,4R,5S)-5-phenyl-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate endo-12aaa. Sticky oil, [α]_D²⁰ = +1.2° (c 1, CH₂Cl₂, 90% *ee* from HPLC); IR (neat) ν_{max}: 3311, 1753 cm⁻¹; ¹H RMN δ_H: 2.80 (br. s, 1H, NH), 3.68 (s, 3H, CO₂Me), 4.33 (m, 1H, PhCHCHSO₂Ph), 4.41 (dd, J = 2.4, 6.3 Hz, 1H, NCCCHSO₂Ph), 4.47 (dd, J = 2.4, 6.0 Hz, 1H, CHCO₂Me), 4.64 (m, 1H, PhCHN), 7.28-7.26 (m, 2H, ArH), 7.34-7.32 (m, 2H, ArH), 7.46-7.42 (m, 2H, ArH), 7.61-7.52 (m, 3H, ArH), 7.72-7.65 (m, 6H, ArH); ¹³C RMN δ_C: 38.3 (Me), 48.6 (CHCO₂Me), 49.1, 52.7 (2xCHS), 56.0 (CHPh), 112.3, 112.9, 113.2, 113.3, 113.7, 113.9, 114.1, 114.2, 119.2, 121.9, 122.8, 123.1 (ArC), 152.4 (CO); MS (EI) m/z (%): 485 (M⁺, <1%), 284 (11), 203 (15), 202 (100), 170 (18), 144 (27), 143 (60), 115 (14), 77 (14); HRMS calculated for C₂₄H₂₃NO₆S₂: 485.0967, found: 485.0990; HPLC (Chiralpak IA, 1 mL/min, n-hexane/i-PrOH: 80/20, λ 224 nm), t_{Rmaj} = 50.23 min, t_{Rmin} = 30.92 min.

Methyl (2R,3R,4R,5S)-5-(naphth-2-yl)-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate endo-12baa. Sticky oil, [α]_D²⁰ = +17.1° (c 0.5; CH₂Cl₂, 92% *ee* from HPLC); IR (neat) ν_{max}: 1741, 3340 cm⁻¹; ¹H RMN δ_H: 2.20 (br. s, 1H, NH), 3.69 (s, 3H, CO₂Me); 4.38 (m, 1H, ArCHCHSO₂Ph), 4.45 (dd, J = 2.4, 6.4 Hz, 1H, NCCCHSO₂Ph), 4.49 (dd, J = 2.4, 6.0 Hz, 1H, CHCO₂Me), 4.79 (m, 1H, CHAr), 7.39-7.35 (m, 2H, ArH), 7.56-7.45 (m, 6H, ArH), 7.72-7.60 (m, 7H, ArH), 7.81-7.77 (m, 2H, ArH); ¹³C RMN δ_C: 38.5 (Me), 48.6 (CHCO₂Me), 49.1, 52.7 (2xCHSO₂), 55.9 (ArCH), 109.3, 111.2, 111.3, 112.0, 112.4, 112.5, 112.9, 113.0, 113.3, 113.4, 113.5, 113.8, 114.2, 114.3, 119.2, 120.0, 121.1, 121.3 (ArC), 152.5 (CO); MS (EI) m/z (%): 535 (M⁺, <1%), 394 (26), 392 (11), 391 (35), 359 (28), 268 (21), 267 (19), 266 (17), 253 (19), 252 (100), 251 (31), 250 (13), 220 (31), 219 (31), 194 (35), 193 (62), 192 (22), 191 (31), 190 (41), 167 (15), 166 (11), 165 (47), 164 (13), 163 (15), 155 (11), 153 (11), 152 (22), 142 (11), 127 (17), 125 (14), 78 (20), 77 (46), 51 (15); HRMS calculated for C₂₈H₂₅NO₆S₂: 535.1123; found: 535.1110; HPLC (Chiralpak AD, 1 mL/min, n-hexane/i-PrOH: 75/25, λ 227 nm), t_{Rmaj} = 57.01 min, t_{Rmin} = 51.97 min.

Methyl (2R,3R,4R,5S)-2-methyl-5-(naphth-2-yl)-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate endo-12bba. Colorless oil, [α]_D²⁰ = +5.2° (c 1; CH₂Cl₂, 24% *ee* from HPLC); IR (neat) ν_{max}: 1748 3341 cm⁻¹; ¹H RMN δ_H: 1.80 (s, 3H, CH₃), 3.79 (s, 3H, CO₂Me), 3.46-3.43 (m, 1H, NH), 4.48 (d, J = 3.9 Hz, 1H, ArCHCHSO₂Ph), 4.61 (dd, J = 3.9, 7.2 Hz, 1H, NCCCHSO₂Ph), 4.83-4.77 (m, 1H, ArCH), 7.28-7.12 (m, 5H, ArH), 7.51-7.43 (m, 5H, ArH), 7.73-7.57 (m, 6H, ArH), 7.90-7.87 (m, 1H, ArH); ¹³C RMN δ_C: 25.2 (CH₃), 39.2 (CO₂Me), 49.0, 52.1 (2xCHSO₂), 56.9 (ArCH), 73.5 (CMe),

111.7, 112.0, 112.5, 112.9, 113.0, 124.0, 126.3, 126.4, 127.5, 127.6, 128.0, 128.2, 128.8, 129.0, 129.1, 129.4, 134.1, 134.4 (ArC), 171.0 (CO); MS (EI) m/z (%): 549 (M^+ , < 1%), 408 (22), 348 (15), 267 (20), 266 (100), 234 (31), 208 (39), 207 (91), 206 (27), 193 (19), 165 (20), 77 (14). HRMS required for $C_{29}H_{27}NO_6S_2$: 549.1280; found: 549.1301; HPLC (Chiralpak AD, 1 mL/min, *n*-hexane/*i*-PrOH: 60/40, λ 227 nm), t_{Rmaj} = 18.21 min, t_{Rmin} = 39.37 min.

Methyl (2R,3R,4R,5S)-3,4-bis(phenylsulfonyl)-5-(*o*-tolyl)pyrrolidine-2-carboxylate endo-12caa: Colourless sticky oil, $[\alpha]_D^{20}$ = +1.7° (c 0.9; CH_2Cl_2 , 18% *ee* from HPLC); IR (neat) ν_{max} : 1749, 3341 cm^{-1} ; 1H RMN δ_H : 2.42 (s, 3H, ArCH₃); 2.90 (br. s, 1H, NH), 3.64 (s, 3H, CO₂Me), 4.32 (s, 1H, ArCHCHSO₂Ph), 4.48 (dd, J = 2.7, 6.2 Hz, 1H, NCCHSO₂Ph), 4.65 (dd, J = 2.7, 6.9 Hz, 1H, CHCO₂Me), 4.97 (s, 1H, ArCH), 7.25-7.16 (m, 2H, ArH), 7.41 (t, J = 7.6 Hz, 8.0 Hz, 2H, ArH), 7.58-7.54 (m, 5H, ArH), 7.71-7.67 (m, 5H, ArH), ^{13}C RMN δ_C : 37.4 (OMe), 44.3 (ArMe), 50.0 (CHCO₂Me), 53.0, 55.5 (2xCHSO₂), 57.8 (ArCH), 110.9, 111.9, 113.1, 113.3, 114.2, 114.3, 115.5, 119.1, 119.2, 120.8, 122.0, 122.1, 123.1, 124.6, (ArC), 152.3 (CO); MS (EI) m/z (%): 499 (M^+ , < 1%), 298 (10), 217 (16), 216 (100), 184 (18), 158 (29), 157 (49), 156 (20), 143 (12), 129 (11), 77 (23); HRMS calculated for $C_{25}H_{25}NO_6S_2$: 499.1123; found: 499.1134; HPLC (Chiralpak AD, 1 mL/min, *n*-hexane/*i*-PrOH: 80/20, λ 227 nm), t_{Rmaj} = 35.89 min, t_{Rmin} = 43.91 min.

Methyl (2R,3R,4R,5S)-3,4-bis(phenylsulfonyl)-5-(*p*-tolyl)pyrrolidine-2-carboxylate (12daa): Colourless sticky oil, $[\alpha]_D^{20}$ = +2.3° (c 1; CH_2Cl_2 , 88% *ee* from HPLC); IR (neat) ν_{max} : 1747, 3341 cm^{-1} ; 1H RMN δ_H : 2.30 (s, 3H, ArCH₃); 2.20 (br. s, 1H, NH), 3.66 (s, 3H, CO₂Me), 4.31-4.27 (m, 1H, ArCHCHSO₂Ph), 4.35 (dd, J = 2.4, 6.4 Hz, 1H, NCCHSO₂Ph), 4.41 (dd, J = 2.4, 6.0 Hz, 1H, CHCO₂Me), 4.61-4.57 (m, 1H, ArCH), 7.06 (d, J = 8.1 Hz, 1H, ArH), 7.20 (d, J = 8.1 Hz, 1H, ArH), 7.54-7.40 (m, 6H, ArH), 7.64-7.57 (m, 2H, ArH), 7.70-7.66 (m, 4H, ArH), ^{13}C RMN δ_C : 21.2 (CH₃Ar), 53.6 (OMe), 63.5, 64.2 (2xCHSO₂), 67.9 (CHCO₂Me), 71.2 (ArCH), 127.3, 128.5, 128.6, 129.1, 129.3, 129.4, 129.5, 134.3, 135.0, 138.2, 138.3 (ArC), 167.6 (CO); MS (EI) m/z (%): 499 (M^+ , < 1%), 358 (24), 217 (15), 216 (100), 184 (22), 158 (22), 157 (48), 156 (14), 77 (15); HRMS required for $C_{25}H_{25}NO_6S_2$: 499.1123; found: 499.1122; HPLC (Chiralpak AD, 1 mL/min, *n*-hexane/*i*-PrOH: 75/25, λ 220 nm), t_{Rmaj} = 50.08 min, t_{Rmin} = 26.11 min.

Methyl (2R,3R,4R,5S)-5-(4-methoxyphenyl)-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate endo-12eaa: Colourless sticky oil, $[\alpha]_D^{20}$ = -4.5° (c 1; CH_2Cl_2 , 38% *ee* from HPLC); IR (neat) ν_{max} : 1747, 3341 cm^{-1} ; 1H RMN δ_H : 2.70 (br. s, 1H, NH), 3.68, 3.80 (2xs, 6H, CO₂Me); 4.31 (s, 1H, ArCHCHSO₂Ph), 4.35 (dd, J = 2.4, 6.4 Hz, 1H, NCCHSO₂Ph), 4.44 (dd, J = 2.4, 6.0 Hz, 1H, CHCO₂Me), 4.61 (s, 1H, ArCH), 7.29-7.24 (m, 2H, ArH), 7.47-7.43 (m, 2H, ArH), 7.63-7.52 (m, 5H, ArH), 7.72-7.66 (m, 5H, ArH); ^{13}C RMN δ_C : 37.4, 40.1 (2xOMe), 45.3 (CHCO₂Me), 49.0, 52.7 (2xCHSO₂), 56.0 (ArCH), 99.0, 113.4, 113.5, 114.2, 114.3, 119.2, 119.5, 120.8, 121.9, 122.2, 123.0, 144.4 (ArC), 152.4 (CO); MS (EI) m/z (%): 515 (M^+ , < 1%), 375 (17), 374 (77), 233 (17), 232 (100), 231 (14), 200 (31), 199 (16), 174 (27), 173 (46), 172 (11), 159 (11), 158 (23), 130 (11), 78 (10), 77 (29); HRMS required for $C_{25}H_{25}NO_7S_2$: 515.1072; found: 515.1082; HPLC (Chiralpak AD, 1 mL/min, *n*-hexane/*i*-PrOH: 70/30, λ 230 nm), t_{Rmaj} = 38.85 min, t_{Rmin} = 43.96 min.

Methyl (2R,3R,4R,5S)-5-(4-chlorophenyl)-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate endo-12faa: Colourless viscous oil, $[\alpha]_D^{20}$ = +91.6° (c 1; CH_2Cl_2 , 45% *ee* from HPLC); IR (neat) ν_{max} : 1750, 3341 cm^{-1} ; 1H RMN δ_H : 2.40 (br. s, 1H, NH), 3.67 (s, 3H, CO₂Me); 4.30 (dd, J = 2.3, 6.3 Hz, 1H, ArCHCHSO₂Ph), 4.34 (m, 1H, NCCHSO₂Ph), 4.38 (dd, J = 2.3, 5.9 Hz, 1H, CHCO₂Me), 4.66-4.61 (m, 1H, ArCH), 7.30-7.21 (m, 3H, ArH), 7.53-7.43 (m, 4H, ArH), 7.71-7.59 (m, 7H, ArH); ^{13}C RMN δ_C : 37.5 (Me); 45.2 (CHCO₂Me), 48.9, 52.6 (2xCHSO₂), 55.9 (ArCH), 113.2, 113.5, 113.8, 113.9, 114.2, 114.3, 114.5, 114.8, 119.2, 119.5, 121.7, 123.0 (ArC), 152.3 (CO); MS (EI) m/z (%): 519 (M^+ , < 1%), 238 (32), 237 (17), 236 (100), 235 (12), 204 (19), 203 (15), 179 (17), 178 (19), 177 (48), 143 (21), 140 (14), 125 (16), 115 (13), 77 (29), 152 (13); HRMS required

for $C_{24}H_{22}ClNO_6S_2$: 519.0577; found: 519.0585; HPLC (Chiralpak AD, 1 mL/min, *n*-hexane/*i*-PrOH: 70/30, λ 220 nm), t_{Rmaj} = 41.08 min, t_{Rmin} = 34.69 min.

Isopropyl (2R,3R,4R,5S)-5-(4-chlorophenyl)-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate endo-12fab: Colourless needles, mp 178 °C (CH_2Cl_2 /*n*-hexane); $[\alpha]_D^{20}$ = +37.0° (c 0.7, $CHCl_3$, 40% *ee* from HPLC); IR (KBr) ν_{max} : 1735, 3328 cm^{-1} ; 1H RMN δ_H : 1.33, 1.41 [2xd, J = 6.2 Hz, 6H, CO₂CH(CH₃)₂], 2.42 (br. s, 1H, NH), 4.30 (dd, J = 2.3, 6.3 Hz, 1H, ArCHCHSO₂Ph), 4.34 (m, 1H, NCCHSO₂Ph), 4.38 (dd, J = 2.3, 5.9 Hz, 1H, CHCO₂Me), 4.66-4.61 (m, 1H, ArCH), 5.20 (m, 1H, CHMe₂); 7.21-7.81 (m, 7Hz, 14H, ArH); ^{13}C RMN δ_C : 21.6, 21.9 [CH(CH₃)₂], 45.2 (CHCO₂), 47.5, 48.9 (2xCHSO₂), 55.9 (ArCH), 62.0 [CH(CH₃)₂], 113.2, 113.5, 113.7, 113.9, 114.0, 114.1, 114.5, 114.6, 119.4, 119.5, 121.7, 123.0 (ArC), 152.3 (CO); MS (EI) m/z (%): 513 (M^+ , 2%), 229 (100), 140 (14); HRMS calculated for $C_{17}H_{20}N_2O_4$: 513.11280; found: 513.11289; Microanalysis for $C_{26}H_{27}NO_6S_2$: C, 60.8; H, 5.3; N, 2.8%, found: C, 60.5; H, 5.3; N, 2.5; HPLC (Chiralpak OD-H, 1 mL/min, *n*-hexane/*i*-PrOH: 80/20, λ 215 nm), t_{Rmaj} = 20.5 min, t_{Rmin} = 38.4 min.

Methyl (2R,3R,4R,5S)-3,4-bis(phenylsulfonyl)-5-(pyrid-3-yl)pyrrolidine-2-carboxylate endo-12gaa: Colourless sticky oil, $[\alpha]_D^{20}$ = -63.9° (c 1.2; CH_2Cl_2 , 92% *ee* from HPLC); IR (neat) ν_{max} : 1753, 3310 cm^{-1} ; 1H RMN δ_H : 2.25 (br. s, 1H, NH), 3.68 (s, 3H, Me); 4.33 (dd, J = 2.3, 6.4 Hz, 1H, ArCHCHSO₂Ph), 4.35 (s, 1H, NCCHSO₂Ph), 4.43 (dd, J = 2.3, 5.9 Hz, 1H, CHCO₂Me), 4.66 (d, J = 6.4 Hz, 1H, ArCH), 7.46 (t, J = 7.7 Hz, 8.0 Hz, 2H, ArH), 7.53 (t, J = 7.4 Hz, 2H, ArH), 7.61-7.65 (m, 3H, ArH), 7.70 (t, J = 7.4 Hz, 5H, ArH), 8.36 (s, 1H, ArH), 8.52 (s, 1H, ArH); ^{13}C RMN δ_C : 34.6, 37.5 (CHCO₂Me), 48.9, 52.4 (2xCHSO₂), 55.7 (ArCH), 108.7, 113.3, 113.4, 114.3, 114.6, 119.3, 119.6, 119.8, 120.1, 121.5, 122.5, 134.0, 134.7 (ArC), 152.3 (CO); MS (EI) m/z (%): 289 (M^+ , 18%); HRMS calculated for $C_{23}H_{22}N_2O_6S_2$: 289.1062; found: 289.1064; HPLC (Chiralpak AD, 1 mL/min, *n*-hexane/*i*-PrOH: 50/50, λ 222 nm), t_{Rmaj} = 15.05 min, t_{Rmin} = 7.91 min.

Methyl (2R,3R,4R,5S)-2-isobutyl-3,4-bis(phenylsulfonyl)-5-(thien-2-yl)pyrrolidine-2-carboxylate endo-12hca: Pale yellow oil, $[\alpha]_D^{20}$ = 7.1° (c 1; CH_2Cl_2 , 70% *ee* from HPLC); IR (neat) ν_{max} : 1779, 3338 cm^{-1} ; 1H RMN δ_H : 0.88 [d, J = 6.7 Hz, 3H, CH(CH₃)₂], 1.08 [d, J = 6.4 Hz, 3H, CH(CH₃)₂], 1.84-1.74 [m, 1H, CH(CH₃)₂], 1.98 [dd, J = 6.4, 14.6 Hz, 1H, CH₂CH(CH₃)₂], 2.22 [dd, J = 5.7 Hz, 14.6 Hz, 1H, CH₂CH(CH₃)₂], 3.10 (br. s, 1H, NH), 3.82 (s, 3H, CO₂Me), 4.40 (d, J = 3.9 Hz, 1H, ArCHCHSO₂Ph), 4.46 (dd, J = 3.9 Hz, 7.2 Hz, 1H, NCCHSO₂Ph), 4.88 (m, 1H, ArCH), 7.21-7.13 (m, 2H, ArH), 7.36-7.26 (m, 4H, ArH), 7.54-7.45 (m, 4H, ArH), 7.65-7.61 (m, 1H, ArH), 7.76-7.23 (m, 1H, ArH), 7.90 (d, J = 7.3 Hz, 1H, ArH); ^{13}C RMN δ_C : 24.4, 24.6 [CH(CH₃)₂], 28.4 [CH(CH₃)₂], 37.7 (CH₂), 39.5, 43.7, 57.8 (OMe and 2xCHSO₂), 58.4, 58.9 (CCO, NCH), 110.2, 110.5, 111.1, 111.7, 113.0, 114.0, 114.2, 118.9, 119.2, 123.2, 123.3, 125.7, (ArC), 155.2 (CO). MS (EI) m/z (%): 547 (M^+ , < 1%), 488 (13), 406 (13), 348 (28), 346 (22), 317 (12), 316 (66), 265 (16), 264 (100), 232 (22), 208 (26), 207 (25), 206 (26), 205 (57), 176 (26), 175 (12), 162 (43), 150 (13), 149 (30), 121 (14), 77 (20); HRMS calculated for $C_{26}H_{29}NO_6S_3$: 547.1157; found: 547.1151. HPLC (Chiralpak AD, 1 mL/min, *n*-hexane/*i*-PrOH: 70/30, λ 233 nm), t_{Rmaj} = 19.67 min, t_{Rmin} = 23.43 min.

Methyl (2R,3R,4R,5S)-2-isobutyl-3,4-bis(phenylsulfonyl)-5-(thiazol-2-yl)pyrrolidine-2-carboxylate endo-12ica: Sticky oil, $[\alpha]_D^{20}$ = +4.1° (c 1; CH_2Cl_2 , 10% *ee* from HPLC); IR (neat) ν_{max} : 1735, 3328 cm^{-1} ; 1H RMN δ_H : 0.87, 1.07 [2xd, J = 6.7 Hz, 6H, CH(CH₃)₂], 1.86-1.73 [m, 1H, CH(CH₃)₂], 1.98 (dd, J = 6.4 Hz, 14.6 Hz, 1H, CH₂), 2.22 (dd, J = 5.7 Hz, 14.6 Hz, 1H, CH₂), 3.79 (s, 3H, OMe), 4.40 (d, J = 4.1 Hz, 1H, ArCHCHSO₂Ph), 4.97 (dd, J = 7.1 Hz, 12.2 Hz, 1H, NCCHSO₂Ph), 5.11 (dd, J = 4.1 Hz, 7.1 Hz, 1H, ArCH), 7.26-7.19 (m, 3H, ArH), 7.38-7.33 (m, 2H, ArH), 7.62-7.50 (m, 5H, ArH), 7.74-7.68 (m, 1H, ArH), 7.88-7.85 (m, 2H, ArH); ^{13}C RMN δ_C : 24.5, 24.7 [CH(CH₃)₂], 28.0 [CH(CH₃)₂], 37.9 (CH₂), 39.9, 43.9, 57.2 (OMe and 2xCHSO₂), 58.4, 58.4 (CCO, NCH), 110.2, 110.5, 111.7,

113.4, 114.4, 114.2, 118.4, 119.2, 123.1, 123.3, 125.9, (ArC), 155.8 (CO); MS (EI) m/z (%): 548 (M^+ , < 1%), 491 (26), 489 (19), 407 (13), 351 (13), 347 (28), 317 (53), 266 (15), 265 (87), 233 (50), 221 (12), 209 (35), 208 (71), 207 (52), 206 (100), 205 (10), 178 (11), 177 (79), 176 (13), 164 (13), 163 (65), 151 (19); 150 (17), 141 (11), 125 (16), 123 (17), 122 (13), 94 (10), 86 (10), 80 (12), 78 (13), 77 (44), 59 (11); HRMS calculated for $C_{25}H_{28}N_2O_6S_2$: 548.1109; found: 548.1118. HPLC (Chiralpak AD, 1 mL/min, *n*-hexane/*i*-PrOH: 70/30, λ 220 nm), t_{Rmaj} = 21.63 min, t_{Rmin} = 12.69 min.

3. Multicomponent 1,3-Dipolar cycloaddition of glycine methyl ester hydrochloride. General procedure.

To a suspension containing (*R*)- or (*S*)-Binap (0.05 mmol, 31 mg) and AgSbF₆ (17 mg, 0.05 mmol) in toluene (3 mL), triethylamine (6.6 μ L, 0.05 mmol), the corresponding dipolarophile (1 mmol) and glycine methyl ester hydrochloride (126 mg, 1 mmol) were added in this order at 25 °C. The reaction mixture was then stirred at the same temperature 16 or 48h (see Scheme 6). The solvent was evaporated under vacuo and the residue was purified by flash chromatography yielding products *endo*-5aa or *endo*-12gaa.

4. Synthesis of pyrrolidine 16.

To a solution of methyl (2*R*, 3*S*, 4*S*, 5*S*)-5-phenyl-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate *endo*-12aaa, (22.0 mg, 0.04 mmol), in a 3:1 mixture of MeOH/THF (3ml), 10% Na(Hg) (69.3 mg) and Na₂HPO₄ (22.4 mg, 0.16 mmol) were sequentially added at 0 °C. After stirring for 1h at room temperature, ethyl acetate (10 ml) was added, and the resulting suspension was filtered and washed with water (2x5 ml). The aqueous phase was extracted with ethyl acetate (2x5 ml) and the combined organic phases were washed with brine (5 ml), dried and concentrated. The residue (7:5 mixture of **14** and **15**) was next dissolved in methanol (3mL) and Pt/C (10%) (30 mg) was added. The reaction was stirred for 48h under an hydrogen atmosphere (1 atm) at 25 °C and the final mixture filtered over a celite pad. The remaining solution was evaporated under vacuo and the residue was purified by flash chromatography yielding product **16a** in 47% overall yield.

Methyl 5-phenylpyrrolidine-2-carboxylate 16a.

5. Synthesis of imine 21.

To a solution of 3,4-dimethoxyphenethyl alcohol (3.0 g, 16.6 mmol) in pyridine (4 mL) Ac₂O (1.6 mL, 16.6 mmol), DMAP (0.040 g, 0.33 mmol) and Et₃N (2.35 mL, 16.6 mmol) were added in this order. The mixture was stirred for 4h. Water (5 mL) and ethyl acetate (3 x 6 mL) were added, and the resulting organic layers were washed with brine. The crude product was employed in the next step without purification. This aldehyde [2-(2-acetoxyethyl)-4,5-dimethoxybenzaldehyde] (252 mg, 1 mmol), glycine methyl ester hydrochloride (126 mg, 1 mmol), Et₃N (1.1 mmol) and MgSO₄ (100 mg) were suspended in chloroform and the mixture refluxed during 16 h. The mixture was then filtered and the resulting organic phase washed with water (2x5 mL). The organic layer was dried (MgSO₄) and evaporated under vacuo obtaining imine **21** in 96% crude pure yield.

Methyl (E)-2-[(2-(2-acetoxyethyl)-4,5-dimethoxybenzylidene)amino]acetate 21: Pale yellow oil; IR (neat) ν_{max} : 1741, 1731, 1634 cm⁻¹; ¹H-RMN δ_H : 1.96 (s, 3H, CH₃CO₂), 3.05 (t, J = 7.3 Hz, 2H, AcOCH₂), 3.61 (s, 3H, CO₂CH₃), 3.84, 3.85 (2xs, 6H, 2xOCH₃), 4.16 (t, J = 7.3 Hz, 2H, PhCH₂), 4.36 (s, 2H, NCH₂), 6.61 (s, 1H, ArH), 7.46 (s, 1H, ArH), 8.48 (s, 1H, NCH); ¹³C-RMN δ_C : 20.9 (CH₃CO), 31.3 (CH₂Ar), 52.0, 55.8, 56.0 (3xOMe), 62.1, 65.0 (CH₂CO, CH₂O), 109.7, 112.8, 126.5, 131.3, 148.1, 151.4 (ArC), 162.9 (CN), 170.7, 170.9 (2xCO); MS (EI) m/z (%): 323.2 (M^+ , 5%), 264 (21), 263 (26), 262 (100), 190 (13), 176 (14), 175 (59); HRMS calculated for C₁₆H₂₁NO₆: 323.1369; found: 323.1361.

6. Synthesis of cycloadduct 19.

A suspension of silver(I) salt (0.01 mmol), and (*S*)-Binap (6 mg, 0.01 mmol) in toluene was stirred at 25 °C for 30 min avoiding the light exposure. Then, imine **21** (32 mg, 0.1 mmol), 1,2-bis(phenylsulfonyl)ethylene (31 mg, 0.1 mmol) and the

corresponding base (0.01 mmol, see Table 4) were added in this order. The reaction was stirred 48 h at 25 °C and water (5 mL) and the aqueous phase extracted with ethyl acetate (2x5 mL). The organic layer was dried (MgSO₄) and evaporated under vacuo obtaining cycloadduct **19**.

*Methyl (2*R*,3*S*,4*S*,5*S*)-5-[2-(2-acetoxyethyl)-4,5-dimethoxyphenyl]-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate 19:* Colourless needles, mp 92-94 °C (*n*-hexane/ethyl acetate); $[\alpha]_D^{20}$ = -25.3° (*c* 1, CHCl₃, 50% *ee* from HPLC); IR (KBr) ν_{max} : 1148, 1309, 1738, 3306 cm⁻¹; ¹H-RMN δ_H : 2.05 (s, 3H, CH₃CO₂), 2.30 (br. s, 1H, NH), 2.85, 3.18 (2m, 2H, PhCH₂), 3.60 (s, 3H, CO₂CH₃), 3.88, 3.91 (2s, 6H, 2xOCH₃), 4.25-4.28 (m, 4H, AcOCH₂, CHS, CHCO₂Me), 4.60 (dd, J = 6.3, 1.9 Hz, 1H, CHS), 5.04 (d, J = 6.3 Hz, 1H, PhCH), 6.63 (s, 1H, ArH), 7.31 (s, 1H, ArH), 7.43-7.74 (m, 10H, ArH); ¹³C-RMN δ_C : 21.0 (CH₃CO), 31.9 (CH₂Ar), 45.6, 49.9, 52.4, 55.9, 56.1, 58.6 (CHCO₂Me 3xOMe and 2 CHS), 64.4, 64.8 (CH₂CO, CH₂O), 68.5 (ArCH), 109.8, 112.8, 128.1, 128.4, 129.1, 129.3, 129.5, 134.2, 135.5, 137.3, 137.4, 137.5, 138.3, 148.7 (ArC), 167.4, 171.0 (2xCO); MS (EI) m/z (%): 631.1 (M^+ , 0.1%), 348 (16), 347 (79), 272 (13), 256 (17), 255 (25), 254 (21), 229 (17), 228 (100), 227 (55), 215 (17), 214 (11), 213 (11), 212 (16), 200 (14), 197 (12), 196 (13), 184 (13); Microanalysis for C₃₀H₃₃NO₁₀S₂: C, 57.0; H, 5.3; N, 2.2%, found: C, 57.3; H, 5.3; N, 2.5; HPLC (Chiralpak AD, 1mL/min, *n*-hexane/*i*-PrOH: 70/30, λ 217nm), t_{Rmaj} = 28.20 min, t_{Rmin} = 21.53.

7. Synthesis of imine 22.²⁴

To a cooled solution (0 °C) of tryptophol (0.5 g, 3.1 mmol) and imidazole (0.46 g, 6.8 mmol) in DMF (3 mL) TBDMCl (0.51 g, 3.4 mmol) was added, and the reaction mixture stirred for 16 h at 26 °C. Ethyl acetate was added (10 mL) and the organic phase was washed with brine (3x4 mL). The organic phase was dried with MgSO₄ and evaporated under vacuo and the residue purified by flash chromatography obtaining the silyl-protected derivative (0.84 g, 99 %). A solution of it (0.84 g, 3.1 mmol) in anhydrous DMF (3 mL) was slowly added, at 0 °C, to a suspension of 60% NaH (0.19 g, 9.5 mmol) in anhydrous DMF (2 mL) and stirring continued at 25 °C during 30 min. Then, PhSO₂Cl (0.53 mL, 4 mmol) was added in one portion and the reaction was maintained at the same temperature for another 19 h. A saturated solution of ammonium chloride was poured out (10 mL) and the aqueous phase was extracted with diethyl ether (3x15 mL) and the combined organic phases were dried with MgSO₄ and evaporated under vacuo and the residue purified by flash chromatography obtaining the *N*-phenylsulfonyl derivative (0.79 g, 81%). The final formylation was achieved by preparing a solution of the last compound (0.79 g, 1.90 mmol) in anhydrous THF (2 mL), which was cooled to -78 °C and treated with 1.6 M solution of BuLi in hexanes (2.14 mL). After 2 h, the temperature was slowly increased to get 25 °C and immediately cooled to -78 °C. At that time DMF (0.77 mL, 1mmol) was added and the temperature again was allowed to rise to 25 °C. A saturated solution of ammonium chloride was poured out (10 mL) and the aqueous phase was extracted with ethyl acetate (3x15 mL) and the combined organic phases were dried with MgSO₄ and evaporated under vacuo and the residue purified by flash chromatography obtaining the desired aldehyde (0.63 g, 75%).^{24b}

The imine **22** was prepared in 95% pure crude yield such as it was described for **21** (see above).

*(E)-Methyl 2-[[3-(2-[(tert-butyl)dimethylsilyloxy]ethyl)-1-(phenylsulfonyl)-1*H*-indol-2-yl]methylene]aminoacetate 22:* Orange sticky oil; IR (neat) ν_{max} : 1747, 1631, 1371, 1170 cm⁻¹; ¹H-RMN δ_H : -0.17, 0.02 (2xs, 6H, 2xSiCH₃), 0.87 [s, 9H, SiC(CH₃)₃], 2.88 (t, J = 6.7 Hz, 2H, CCH₂), 3.31 (t, J = 6.7 Hz, 2H, OCH₂), 3.81 (s, 3H, CO₂CH₃), 4.53 (s, 2H, NCH₂), 7.41-8.00 (m, 9H, ArCH), 8.84 (s, 1H, NCH); ¹³C-RMN δ_C : -2.8, -2.6, 18.2, 25.8, 28.5, 52.0, 62.5, 63.2, 113.6, 115.3, 119.5, 120.3, 121.3, 123.0, 124.1, 124.5, 126.6, 128.9, 129.1, 133.5, 158.6, 170.9; MS (EI) m/z (%): 514 (M^+ , 1%), 359 (16), 358 (59), 233 (11), 217 (11), 216 (51), 200 (16), 199 (100). HRMS calculated for C₂₆H₃₄N₂O₅SSi: 514.1958; found: 514.1967.

8. Synthesis of cycloadduct 20.

A suspension of silver(I) trifluoroacetate (3 mg, 0.01 mmol), and (S)-Binap (6 mg, 0.01 mmol) in toluene was stirred at 25 °C for 30 min avoiding the light exposure. Then, imine **22** (51 mg, 0.1 mmol), 1,2-bis(phenylsulfonyl)ethylene (31 mg, 0.1 mmol) and DABCO corresponding base (2 mg, 0.01 mmol) were added in this order. The reaction was stirred 48 h at 25 °C and water (5 mL) and the aqueous phase extracted with ethyl acetate (2x5 mL). The organic layer was dried (MgSO₄) and evaporated under vacuo obtaining cycloadduct **20**.

Methyl (2R,3R,4R,5S)-5-{3-[2-((tert-butyldimethylsilyl)oxy)ethyl]-1-(phenylsulfonyl)-1H-indol-2-yl]-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate **20**: Colourless needles, mp 155 °C (*n*-hexane/ethyl acetate); [α]_D²⁰ = -4.5° (*c* 1; CHCl₃, 12% *ee* from HPLC); IR (KBr) ν_{max}: 1142, 1309, 1765, 3286 cm⁻¹; ¹H-RMN δ_H: -0.137, -0.04 (2xs, 6H, 2xSiCH₃), 0.79 [s, 9H, SiC(CH₃)₃], 2.81 (t, *J* = 6.6 Hz, 2H, OTBDMSCH₂), 3.02 (td, *J* = 6.6, 1.9 Hz, 2H, CCH₂), 3.76-3.79 (m, 5H, CO₂CH₃, SCH, CHCO₂CH₃), 4.26 (d, *J* = 7.1 Hz, 1H, NCH₂), 4.87 (dd, *J* = 7.1, 4.7 Hz, 1H, CHN), 5.40 (s, 1H, NH), 7.07-8.01 (m, 19H, ArCH); ¹³C-RMN δ_C: -5.5, -5.3, 18.0, 29.9, 30.0, 30.6, 48.4, 51.9, 52.5, 62.5, 64.1, 108.7, 115.8, 115.9, 116.8, 116.9, 117.6, 125.6, 125.7, 126.9, 127.0, 128.00, 128.46, 128.73, 129.13, 129.86, 133.59, 134.09, 134.92, 136.96, 140.37, 171.5; MS (ESI) *m/z* (%): 822 (M⁺, 2%). Microanalysis for C₄₀H₄₆N₂O₉S₃Si: C, 58.4; H, 5.6; N, 3.4%, found: C, 58.3; H, 5.3; N, 3.5; HPLC (Chiralpak OD-H, 1 mL/min, *n*-hexane/*i*-PrOH: 93/7, λ 222nm), t_{Rmaj} = 24.5 min, t_{Rmin} = 27.8 min.

9. Synthesis of the antiviral precursor **24**.²⁵

Compound **24** was prepared according to the procedure described before (see section 2).

tert-Butyl methyl (2S,4S,5R)-2-isobutyl-5-(thiazol-2-yl)pyrrolidine-2,4-dicarboxylate **24**: [α]_D²⁰ = +38° (*c* 1, CH₂Cl₂, 99% *ee* by HPLC) Lit. [α]_D²⁰ = +43° (*c* 1, CH₂Cl₂, 99% *ee* by HPLC).

Acknowledgments

This work has been supported by the Spanish Ministerio de Ciencia e Innovación (MICINN) through the Hispano-Brazilian project PHB2008-0037-PC and CNPq-2878, Consolider INGENIO 2010 CSD2007-00006, CTQ2010-20387, FEDER, Generalitat Valenciana (PROMETEO/2009/039), and by the University of Alicante. MM-R thanks MEC for a predoctoral fellowship. EC thanks CNPq for a predoctoral Doutorado Sanduiche stay.

References and notes

1. Privileged Chiral Ligands and Catalysts Qi-Lin Zhou Ed, Wiley-VCH Verlag, New York, 2011
2. The pioneering catalytic enantioselective 1,3-DC was reported by Grigg and co-workers: a) Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, 32, 5817-5820. (b) Grigg, R. *Tetrahedron: Asymmetry* **1995**, 6, 2475-2486.
3. The enantioselective 1,3-DC of azomethine ylides is a prolific area in organic synthesis and it is frequently being reviewed. For selected recent examples, see: a) Pellissier, H. *Tetrahedron* **2007**, 63, 3235-3285; b) Nájera, C.; Sansano J. M. in *Topics in Heterocyclic Chemistry*, A. Hassner, Ed. Springer-Verlag Berlin-Heidelberg, 2008, vol. 12, pp. 117-145; c) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, 108, 2887-2902; d) Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I. *Chem. Rev.* **2008**, 108, 3174-3198; e) Naodovic, M.; Yamamoto, H. *Chem. Rev.* **2008**, 108, 3132-3148; f) Nájera, C.; Sansano, J. M.; Yus, M. *J. Braz. Chem. Soc.* **2010**, 21, 377-412; g) Kissane, M.; Maguire, A. R. *Chem. Soc., Rev.* **2010**, 39, 845-883; h) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, 47, 6784-6794.
4. Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, 124, 13400-13401.

5. a) Nájera, C.; Retamosa, M. G.; Sansano, J. M. *Org. Lett.* **2007**, 9, 4025-4028. b) Nájera, C.; Retamosa, M. G.; Sansano, J. M.; de Cózar, A.; Cossío, F. P. *Tetrahedron: Asymmetry* **2008**, 19, 2913-2923.
6. (R)-Binap-Cu(MeCN)₄ClO₄ catalyzed the reaction with phenyl vinyl sulfone (up to 26% *ee*). Llamas, T.; Gómez-Arrayás, R.; Carretero, J. C. *Org. Lett.* **2006**, 8, 1795-1798.
7. (R)-Binap-Cu(OTf)₂ catalyzed the reaction with maleimides (up to 64-65% *ee* of the corresponding *exo*-adduct). Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, 5, 5043-5046.
8. [(S₂)-Binap-AuTFA]₂ catalyzed the reaction with maleimides, maleates, acrylates, vinylic sulfones, etc. (up to 99% *ee*). a) Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M.; Wu, F. L. *Tetrahedron: Asymmetry* **2010**, 21, 1184-1186, and corrigendum **2010**, 21, 2559; b) Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M.; de Cózar, A.; Cossío, F. P. *Chem. Eur. J.* **2011**, 17, 14224-14233.
9. The reactivity of the dimeric gold complex [(S₂)-Binap-AuTFA]₂ has been studied and compared with several silver complexes in the elaboration of the key precursor of the 2nd generation GSK-inhibitors of the virus responsible of hepatitis C: Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M.; de Cózar, A.; Cossío, F. P. *Beilstein J. Org. Chem.* **2011**, 7, 988-996.
10. For the enantioselective gold(I)-catalyzed cycloaddition dealing with azlactones see: a) Melhado, A. D.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, 129, 12638-12639; b) Melhado, A. D.; Amarante, G. W.; Wang, Z. J.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, 133, 3517-3527; c) Martín-Rodríguez, M.; Nájera, C.; Sansano J. M. *Synlett* **2012**, 62-65.
11. Unpublished estimated data calculated by F. P. Cossío and A. de Cózar (University of the Basque Country).
12. For a preliminary communication, see: Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M.; Costa, P. R. R.; de Lima, E. C.; Dias, A. G. *Synlett* **2010**, 962-967.
13. The *endo* descriptor refers the approach of the electron-withdrawing group to the metalodipole before the cycloaddition.
14. Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, 126, 5360-5361.
15. López-Pérez, A.; Adrio, J.; Carretero, J. C. *J. Am. Chem. Soc.* **2008**, 130, 10084-10085.
16. See, for example: van Esseveldt, B. C. J.; Vervoort, P. W. H.; van Delft, F. L.; Rutjes, P. J. T. *J. Org. Chem.* **2005**, 70, 1791-1795.
17. Zhang, Q.; Tu, G.; Zhao, Y.; Cheng, T. *Tetrahedron* **2002**, 58, 6795-6798.
18. Kam, T.; Sim, K. *Phytochemistry* **1997**, 47, 145-147.
19. Coldham, I.; Jana, S.; Watson, L.; Martin, N. G. *Org. Biomol. Chem.* **2009**, 7, 1674-1679.
20. Ammendola, S.; Mosca, L.; Bovicelli, P. *Arkivoc* **2008**, VIII, 105-115.
21. Nájera, C.; Sansano, J. M. *Org. Biomol. Chem.* **2009**, 7, 4567-4581.
22. Nájera, C.; Retamosa, M. G.; Martín-Rodríguez, M.; Sansano, J. M.; de Cózar, A.; Cossío, F. P. *Eur. J. Org. Chem.* **2009**, 5622-5634.
23. a) Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, 5, 5043-5046. b) Dogan, Ö.; Koyuncu, H.; Garner, P.; Bulut, A.; Youngs, W. J.; Panzner, M. *Org. Lett.* **2006**, 8, 4687-4690.
24. a) Hirschmann, R.; Nicolau, K.; Pietranico, S.; Leahy, E.; Salvino, J.; Arison, B.; Cichy, M.; Spoors, P.; Shakespeare, W.; Sprengeler, P.; Hamley, P.; Smith, A.; Reisine, T.; Raynor, K.; Maechler, L.; Donaldson, C.; Vale, W.; Freidinger, R.; Cascieri, M.; Strader, C. *J. Am. Chem. Soc.* **1993**, 115, 12550-12568. b) Kuethe, J.; Davies, I.; Dormer, P.; Reamer, R.; Mathre, D.; Reider, P.; *Tetrahedron Lett.* **2002**, 43, 29-32.
25. Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M.; de Cózar, A.; Cossío F. P. *Beilstein J. Org. Chem.* **2011**, 7, 988-996.