Tetrahedron: *Asymmetry* 23 (2012) 1596–1606

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

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 Ciencias da Saúde, Universidade Federal do Rio de Janeiro, Cidade Universitária, 21941-590 Rio de Janeiro, Brazil*

ARTICLE INFO

Article history:
Received 3 October 2012
Accepted 12 October 2012

ABSTRACT

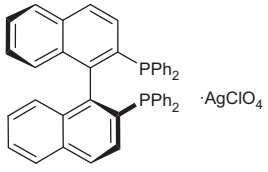
Binap-$AgSbF_6$ catalyzed 1,3-dipolar cycloadditions between azomethine ylides and electrophilic alkenes are described and compared with analogous transformations mediated by other Binap-silver(I) salt complexes. Maleimides and 1,2-bis(phenylsulfonyl)ethylene are suitable dipolarophiles for obtaining very good enantioselectivities, even better values are generated by a multicomponent version. There are some very interesting applications of the disulfonylated cycloadducts in the total synthesis of cis-2,5-disubstituted pyrrolidines, precursors of natural products, or valuable intermediates in the synthesis of antiviral compounds.

© 2012 Elsevier Ltd. All rights reserved.

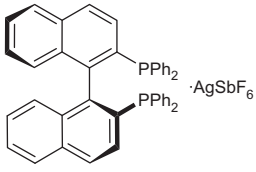
1. Introduction

Privileged chiral ligands[1] are very efficient enantiomerically pure molecules, incorporating a few core structures, and are used as references for chemists working in the field of asymmetric catalysis. Binap is one such example of this concept, which has been used with ruthenium, rhodium, and palladium in many enantioselective organic transformations.[1] This chiral diphosphine was also tested in the catalytic enantioselective 1,3-dipolar cycloaddition[2] (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* values when dipoles derived from imino esters and dimethyl maleate were used (up to 13% *ee*). The change of the counterion of the complex was critical for the success of the reaction. (*S*)-Binap-$AgClO_4$ **1**, a very stable and recyclable complex, is very appropriate for the 1,3-DC of imino esters and maleimides (up to >99% *ee*).[5] In addition to silver(I), copper(I)[6] and (II),[7] gold(I)[8–10] chiral Binap complexes have been studied as catalysts in analogous 1,3-DCs using several dipolarophiles.

The reluctance of chemical companies to use perchlorate salts, prompted us to search another poorly coordinated anion in order to ensure or even improve upon the results obtained from using the (*S*)-Binap-$AgClO_4$ complex. Computational studies of this asynchronous transformation also revealed that in the transition state responsible for the enantiodiscrimination, the perchlorate anion was weakly bonded to the central metal (2.41 Å).[5b] Based on these data, we thought that the weakly coordinating hexafluoroantimonate anion could be used as an alternative to perchlorate as catalyst for this particular cycloaddition. An identical semi-empirical model, but incorporating SbF_6^- instead of ClO_4^-, showed a longer distance (2.46 Å) between the central silver atom and its counterion.[11] Herein we report 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-$AgSbF_6$ catalyst **2** versus other Binap complexes formed with different silver(I) salts.[12]



(S_a)-**1**



(S_a)-**2**

2. Results and discussion

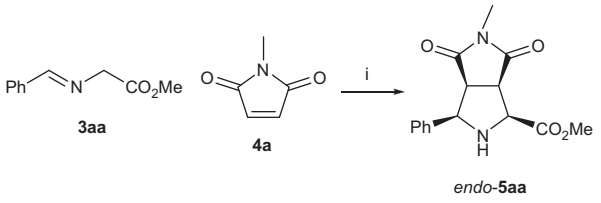
2.1. Optimization of the reaction conditions

The model reaction selected between methyl benzylideneiminoglycinate **3aa** and *N*-methylmaleimide (NMM) **4a** was performed in toluene at room temperature using 5 mol % of

* Corresponding author. Tel./fax: +34 965903549.
E-mail address: jmsansano@ua.es (J.M. Sansano).

0957-4166/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetasy.2012.10.015

(S)-Binap and 5 mol % of Ag^I salt as the catalyst precursor (Scheme 1 and Table 1). The reaction was carried out with equimolar amounts of both (S_a)-Binap and several oxygenated silver(I) salts with a weakly coordinating anion, such as AgOAc, AgOTfa (Tfa = trifluoroacetate), AgOTf (Tf = trifluoromethanesulfonate) $AgNO_3$, or $AgBF_4$, (5 mol %). When AgOAc was used, excellent results for 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 gave excellent results for cycloadduct **5aa**, but again the reaction crude product was slightly impure (^{1}H NMR) (Table 1, entry 3). This chiral catalyst can work as an internal base, with the trifluoroacetate anion being the most effective (Table 1, entry 4). In this case, the enantioselection was excellent, although the reaction was slightly slower and a few impurities were detected in the crude product. The bifunctional behavior of acetate derived catalyst was not as effective as the Tfa complex, affording lower yields 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. $AgBF_4$ and $AgNO_3$ catalyzed the reactions but afforded lower chemical yields, diastereo- and enantioselections (Table 1, entries 6 and 7).



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] (%)	*endo*:*exo*[c]	*ee*[d] (%)
1	AgOAc	Et_3N	89	>98:2	99[e]
2	AgOAc	DABCO	85	>95:5	94
3	AgOTfa	Et_3N	89	>98:2	99[e]
4	AgOTfa	—	78	>98:2	99[e]
5	AgOTf	Et_3N	88	90:10	99
6	$AgNO_3$	Et_3N	65	85:11	67
7	$AgBF_4$	Et_3N	77	89:11	72
8	$AgSbF_6$	Et_3N	90 (89)	>98:2 (>98:2)	>99 (>99)
9	$AgSbF_6$[f]	Et_3N	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_3N	90 (90)	90:10 (90:10)	96 (98)[e]
14	$AgSbF_6$[h]	Et_3N	90 (91)	>98:2 (>98:2)	56 (<50)[e]

[a] Conversions were higher than 95% (determined by ^{1}H NMR spectroscopy of the crude product).
[b] Isolated yield after recrystallization. The yields of the analogous reaction performed with $AgClO_4$ are given in parenthesis.[5]
[c] Determined by ^{1}H 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 $AgClO_4$ is given in parenthesis.[5]Identical *ee* values were determined for the purified product in both reaction sets.
[e] Some unidentified impurities were detected in the crude product.
[f] Reaction performed with 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.

Using $AgSbF_6$ and Et_3N as the base, the enantiomerically enriched cycloadduct **5aa** (>99% *ee*) was isolated in very good yield (90%) and with excellent endo-selectivity.[13] This result, and the result obtained when the reaction was performed with $AgClO_4$, were almost identical (Table 1, entry 8). Other solvents, such as Et_2O, DCM, THF, and MeCN, were tested but neither the purity nor the diastereo-/enantioselection of the final product **5aa** were improved upon. The 5 mol % catalyst loading was the most appropriate because the reaction became slower when a 3 mol % charge was used instead (Table 1, entry 9). Bases such as 1,4-diazabicyclo[2.2.2]octane (DABCO) and diazabicyclo[5.4.0]undec-7-ene (DBU) were evaluated in this reaction and afforded lower enantioselections with some unidentified products in the crude mixture (Table 1, entries 10, and 11). However, when the reaction was carried out with *N*,*N*-diisopropylethylamine (DIPEA), it was completely equivalent to the reaction carried out with triethylamine (Table 1, compare entries 8 and 10). Using a 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).

Thus it can be seen that when the reaction is carried out with silver hexafluoroantimonate in the presence of a small amount of thiethylamine, good chemical yields, excellent enantioselection (>99%), and a very clean material that did not require any additional purification were obtained.

2.2. Characterization of the catalytic species

The reaction was also carried out with the isolated complex formed by the addition of equimolar amounts of (*S*)-Binap and $AgSbF_6$; obtaining almost identical results to those described in entry 8 of the Table 1. However, this $AgSbF_6$ derived complex became darker upon standing since it was much more unstable than the identical complex generated by $AgClO_4$. As a result, the in situ generation of the catalytic complex, which avoided light exposure during the whole process was preferred for all of the transformations described herein.

The presumed catalytic monomeric species in the solution were identical to those reported previously with triflate[14] (Fig. 1) 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 et al. These studies revealed that the mixture of structures **6**–**8**

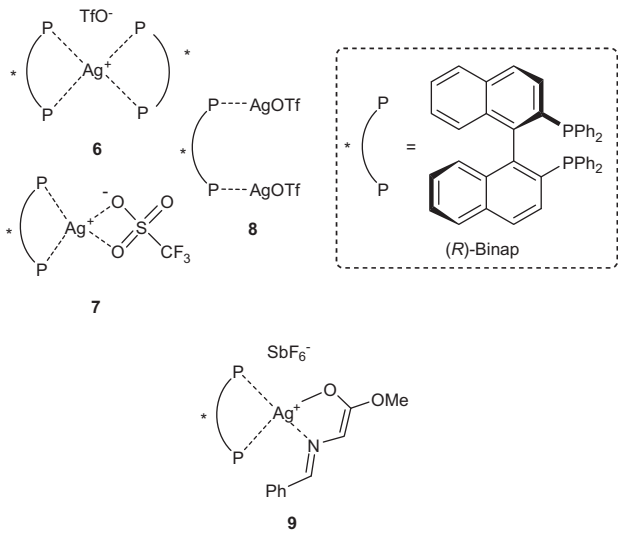


Figure 1. [(*R*)-Binap]AgOTf complexes and catalyst-dipole complex **9**.

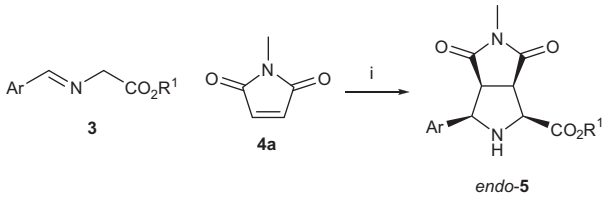
were in equilibrium, and at room temperature, the 1:1 complex **7** was the most abundant system (Fig. 1).[14]

The 1:1 (*R*)- or (*S*)-Binap and $AgSbF_6$ complexes were characterized by ESI-MS experiments and ^{31}P NMR. ESI-MS showed an 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:$AgSbF_6$ (similar to complex **6**). The ^{31}P NMR ($CDCl_3$) spectra of 1:1 (*R*)- or (*S*)-Binap and $AgSbF_6$ (using 10% aqueous polyphosphoric acid as an internal reference) afforded signals at 15.31 ppm and 15.45 ppm (2d, J = 242 Hz) (15.26, and 15.35 ppm for the Binap-$AgClO_4$ complex).

Calculations performed with the Binap-$AgClO_4$ model, which were comparable with the Binap-$AgSbF_6$ model, supported the idea that NMM was the best dipolarophile due to coordination of the nitrogen atom to the metal center. The TS responsible for the enantiodiscrimination was as expected, asynchronous. The steric interaction between one of the phenyl groups of the phosphine moiety of the chiral ligand and the dipolarophile can be considered to be 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-$AgSbF_6$ 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 5 mol % of an equimolar mixture of (*S*)-Binap and $AgSbF_6$ in the presence of toluene as a solvent and a catalytic amount of triethylamine (5 mol %) were compared directly with the analogous results obtained with the (*S*)-Binap-$AgClO_4$ complex[5] (Scheme 2, and Table 2).

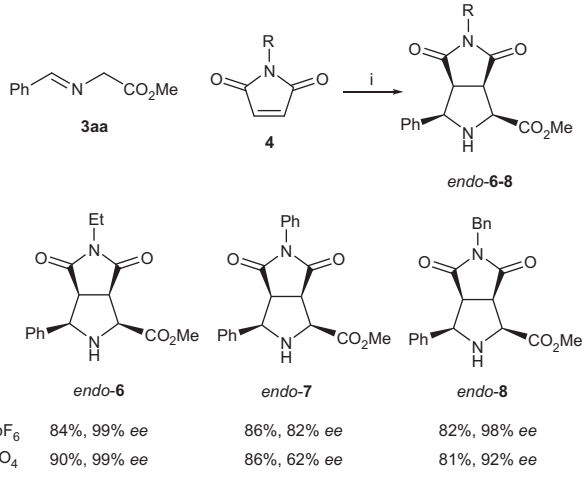


Scheme 2. Reagents and conditions: (i) (S_a)-Binap (5 mol %), Ag^I salt (5 mol %), Et_3N (5 mol %), toluene, 25 °C, 16 h.

In general, we observed that the isolated chemical yields of compounds **5** were 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; similar enantioselections and lower chemical yields of slightly unpurified cycloadducts *endo*-**5** (not shown in Table 2) were obtained. 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). Modification of the alkyl moiety of the ester group caused a decrease of the diastereoselection, (Table 2, entries 3–5). In all of these cases, the enantioselectivity was lower than that obtained for the methyl ester. For substituted aromatic imino esters, the enantioselection was always higher when $AgSbF_6$ was selected as the 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 a 2-thienyl derivative furnished **5ha** with very good enantioselection, 3-pyridyl derivative **3ga** was not suitable for this particular transformation (Table 2, entries 11 and 12). Presumably, the basic character of the nitrogen heterocycle promoted the non-asymmetric process.

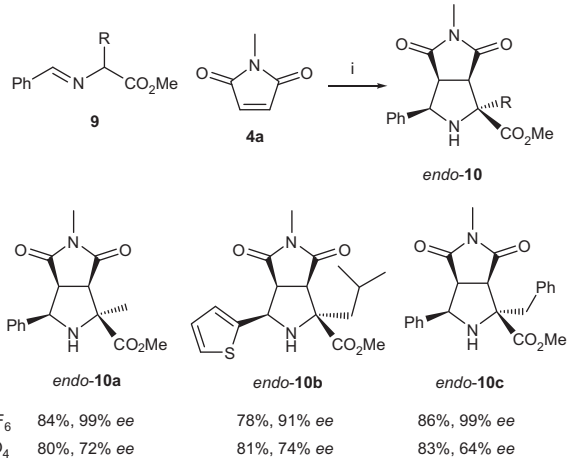
The absolute configuration of these products **5**, as well as all of the compounds described herein, was determined by comparison with the known data reported in the literature for identical molecules.

When different N-substituted maleimides were compared, we found that *N*-ethylmaleimide (NEM) did not give any difference with respect to those results obtained with the (*S*)-Binap-$AgClO_4$. However, when the reaction was carried out with *N*-phenylmaleimide (NPM), it was much more enantioselective in the presence of (*S*)-Binap-$AgSbF_6$ complex than that obtained with a 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-$AgClO_4$ catalyst.[5b] The less coordinating anion in the catalyst Binap-$AgSbF_6$ released the steric congestion of the transition state. In the examples carried out with *N*-benzylmaleimide, the differences in the ee values of the product *endo*-**8** were not important (Scheme 3). Products *endo*-**6**, *endo*-**7**, and *endo*-**8** were isolated in more than a 98:2 *endo*:*exo* ratio independent of the chiral catalyst employed.



Scheme 3. Reagents and conditions: (i) (S_a)-Binap (5 mol %), Ag^I salt (5 mol %), Et_3N (5 mol %), toluene, 25 °C, 16 h.

The effect of 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, requiring 48 h to reach complete conversions (Scheme 4). Cycloadducts

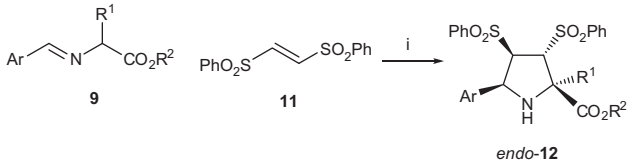


Scheme 4. Reagents and conditions: (i) (S_a)-Binap (5 mol %), Ag^I salt (5 mol %), Et_3N (5 mol %), toluene, 25 °C, 48 h.

endo-**10** were obtained in good yields when both chiral catalysts were used, but the enantioselectivity achieved by (S_a)-Binap-$AgSbF_6$ was noticeably higher. This is further evidence of the ease of the hexafluoroantimonate salt to perform cycloadditions with sterically hindered components.

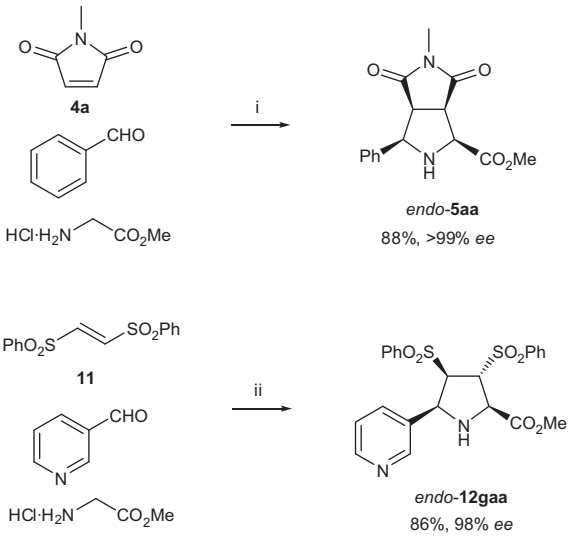
We also found that dipolarophiles such as alkyl acrylates, dialkyl fumarates, dimethyl maleate, and acrylonitrile exhibited identical behavior with both silver salts, that is, very low enantioselections and good chemical yields were obtained. More polar solvents, such as acetone, acetonitrile, diethyl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

Large differences were detected when 1,2-bis(phenylsulfonyl)ethylene was employed as low-LUMO alkene (Scheme 5 and Table 3). Although toluene was used as the solvent, the reactions could also be carried out in THF because we observed a very clean reaction mixture, and the crude products *endo*-**12** did not require additional purification. When the reaction was performed with (S)-Binap-$AgClO_4$, we saw no improvement in the results generated by intermediacy of (S)-Binap-$AgSbF_6$. Phenyl- and 2-naphthyl substituents bonded to the imino group afforded high enantioselections of the products **12aaa** and **12baa**, respectively (Table 3, entries 1–4). The effect of the methyl group in the azomethine ylide caused lower enantioselections in the 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 the cycloadducts was very low, except in the case of *para*-methyl substituted derivatives (Table 3, entries 7–14). The presence of an isopropyl ester instead of a methyl group also gave poor enantioselection in heterocycle **12fab** (Table 3, entries 15 and 16). The 3-pyridyl group was the most appropriate heterocycle (Table 3, entries 17 and 18) since the 2-thienyl and 2-thiazolyl imino esters did not afford very high enantioselections despite producing excellent yields (Table 3, entries 19–22). Sterically hindered imino esters such as *ortho*-substituted arylinenes, isopropyl esters, and α-branched amino acid derivatives (alanine and leucine) furnished lower *endo*:*exo* ratios, and this was more pronounced when (S)-Binap-$AgClO_4$ 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 %), Et_3N (5 mol %), toluene or THF, 25 °C, 48 h.

Multicomponent reactions were attempted using the best results obtained in Tables 2 and 3. Thus, benzaldehyde/NMM **4a** or 3-pyridinecarbaldehyde/disulfone **11**, 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 25 °C for 48 h. The results obtained for compound *endo*-**5aa** or *endo*-**12gaa** were good (88% yield, >99% *ee*, or 86% yield, 98% *ee*, respectively, Scheme 6). However, analogous reac-



Scheme 6. Reagents and conditions: (i) (S_a)-Binap (5 mol %), $AgSbF_6$ (5 mol %), Et_3N (5 mol %), toluene, 25 °C, 16 h. (ii) (S_a)-Binap (5 mol %), $AgSbF_6$ (5 mol %), Et_3N (5 mol %), toluene, 25 °C, 48 h.

Table 2
1.3-DC of iminoglycinates **3** and NMM **4a**

Entry	N°	Ar	R^1	Product *endo*-**5**			
				No.	Yield[a,b] (%)	*endo*:*exo*[b,c]	ee_{endo}[b,d] (%)
1	**3aa**	Ph	Me	**5aa**	90 (90)	>98:2	>99 (>99)
2	**3aa**[e]	Ph	Me	*ent*-**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-$CH_3C_6H_4$	Me	**5ca**	85 (85)	>98:2	70 (75)
8	**3da**	2-ClC_6H_4 [f]	Me	**5da**	85 (88)	>98:2	>99 (85)
9	**3ea**	4-$CH_3C_6H_4$	Me	**5ea**	85 (85)	>98:2	99 (80)
10	**3fa**	4-ClC_6H_4	Me	**5fa**	84 (87)	>98:2	94 (65)
11	**3ga**	3-Pyridyl	Me	**5ga**	77 (81)	80:20	40 (10)
12	**3ha**	2-Thienyl	Me	**5ha**	84 (87)	>98:2 (90:10)	93 (92)

[a] Isolated yield after flash chromatography.
[b] In brackets the result obtained previously with (S)-Binap-$AgClO_4$ 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-$AgSbF_6$.
[f] Reaction performed at −20 °C.

Table 3
1.3-DC of iminoglycinates **9** and disulfone **11**

Entry	Ar	R^1	R^2	Solvent	No	Product *endo*-**12**		
						Yield[a,b] (%)	*endo*:*exo*[b,c]	ee_{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-$CH_3C_6H_4$	H	Me	PhMe	**12caa**	63 (79)	90:10	18 (16)
8	2-$CH_3C_6H_4$	H	Me	THF	**12caa**	68	90:10	6
9	4-$CH_3C_6H_4$	H	Me	PhMe	**12daa**	91[e] (78)	>98:2	88 (28)
10	4-$CH_3C_6H_4$	H	Me	PhMe	**12daa**	78	>98:2	82
11	4-$MeOC_6H_4$	H	Me	PhMe	**12eaa**	58 (60)	>98:2	38 (28)
12	4-$MeOC_6H_4$	H	Me	THF	**12eaa**	78	>98:2	12
13	4-ClC_6H_4	H	Me	PhMe	**12faa**	81 (85)	>98:2	45 (27)
14	4-ClC_6H_4	H	Me	THF	**12faa**	79	>98:2	42
15	4-ClC_6H_4	H	Pr^i	PhMe	**12fab**	64 (71)	80:20	40 (30)
16	4-ClC_6H_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 an (*S*)-Binap–$AgClO_4$ 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.

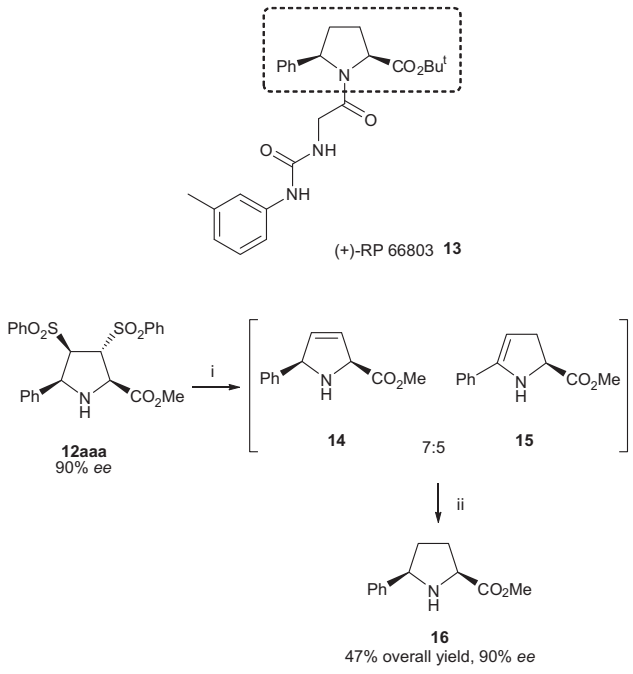
tions carried out in the presence of the (*S*)-Binap-$AgClO_4$ complex were unsuccessful. Although very activated aminomalonates have been used as one of the three components of enantioselective organocatalyzed 1,3-DC, this was the first occasion in which a three-component transformation was performed enantioselectively in the presence of a chiral Lewis acid.[12] However, the employment of other substrates with these two dipolarophiles did not afford either the expected enantioselections or good chemical yields. The introduction of the free α-amino ester instead of the corresponding hydrochloride did not improve the results.

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

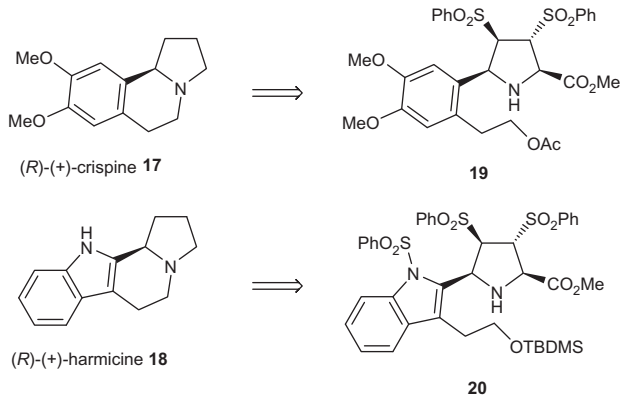
As a masked acetylene equivalent, disulfone **11** has been used in this 1,3-DC for the preparation of Schramm's C-azanucleoside,[15] which is a promising trypanosomal nucleoside hydrolase inhibitor. Herein the enantioselective synthesis of the *exo*-cycloadduct (of type **12**) was the key step of the total process, after which the methoxycarbonyl group was reduced with lithium aluminum hydride (LAH) followed by 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, with pyrrole being the major product observed. Several conditions were tested and we found that the behavior of the *endo*-diastereoisomer was very different to the *exo* one, even in terms of stability upon flash chromatography.

The synthesis of 5-substituted prolines is another interesting application because it gives access to biologically active compounds, such as the nonpeptide cholecystokinin antagonist (+)-RP 66803 **13**.[16] The 5-phenylprolinate 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 the pyrrole derivative after the desulfonylation step.

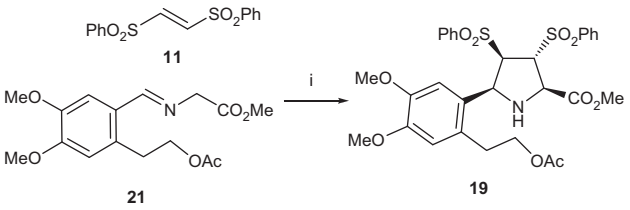
(*R*)-(+)-Crispine A **17** and (*R*)-(+)-harmicine **18** are naturally occurring molecules that are employed in traditional medicine. The anticancer properties of the former and the anti-leishmaniasis effects of the latter have attracted the attention of many scientists.[17,18] Following the approach of Coldham et al., which used a 1,3-DC with disulfone **11** (Scheme 8),[19] new starting aromatic precursors **19** and **20**, that were suitably protected, were prepared.



Scheme 7. Reagents and conditions: (i) Na(Hg), 10%, MeOH/THF (3/1), from 0 to 25 °C, 1 h. (ii) Pt/C (10%), H_2 (1 atm), MeOH, 48 h, 25 °C.



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



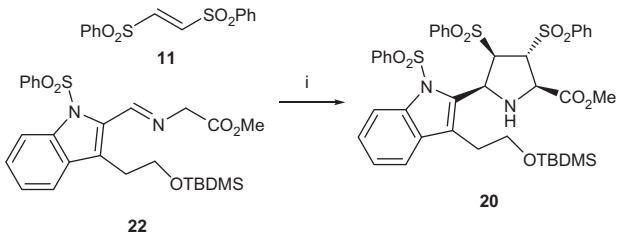
Scheme 9. Reagents and conditions: (i) (S_a)-Binap (10 mol %), Ag^I salt (10 mol %), base (10 mol %), toluene, 20–25 °C, 48 h.

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

	Ag^I salt	Base	Product **19**	
			Yield[a,b] (%)	*ee*[c] (%)
1	$AgSbF_6$	Et_3N	55	32
2	AgOAc	Et_3N	45	30
3	AgTfa	Et_3N	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).

The reaction of imine **21** (obtained from the corresponding aldehyde[20] and methyl glycinate) and disulfone **11** was accomplished at 20–25 °C using toluene as the solvent with 10 mol % of catalyst loading (formed by chiral Binap and a silver salt) and in the presence or absence of a base (Scheme 9 and Table 4). $AgSbF_6$, AgTfa, and AgOAc were tested and the best results were obtained when the trifluoroacetate salt was combined with triethylamine (10 mol %) as the base (Table 4, entries 1–3). Other bases such as DIPEA, DABCO, or DBU were tested and we found a noticeable increase in the enantioselection with AgTfa/DABCO mixture (up to 50% *ee*) (Table 4, entries 4–7). Quinuclidine based alkaloids were tested next for double chiral induction, but the results never overtook 45% *ee* (Table 4, entries 8–11). The transformations carried out with these silver salts in the absence of base were unsuccessful. Cycloadduct **19** (up to 32% *ee*) was obtained with poor enantioselections and in moderate chemical yields (55–65%).



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

Under the best reaction conditions described in Table 4, imino ester **22** was submitted to cycloaddition with disulfone **11** to afford cycloadduct **20** in 60% chemical yield with very poor enantioselectivity Scheme 10 (12% *ee*).

Despite the low enantioselections obtained in the reaction performed between imino ester **3aa** and acrylates, the 1,3-DC of the heterocyclic imino ester **23** and *tert*-butyl acrylate were attempted (Scheme 11 and Table 5). As reported in previous works, molecule **24** is the key intermediate in the elaboration of 2nd generation GSK inhibitors of the virus causing hepatitis C **25**.[9,21] $AgClO_4$, AgTfa, and $AgSbF_6$ were tested (Table 5), and 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 5, entry 1). The reaction needed 10 mol % of both catalyst loading and triethylamine to occur. Lowering the temperature and using different solvents, bases did not improve upon the results described in Table 5.

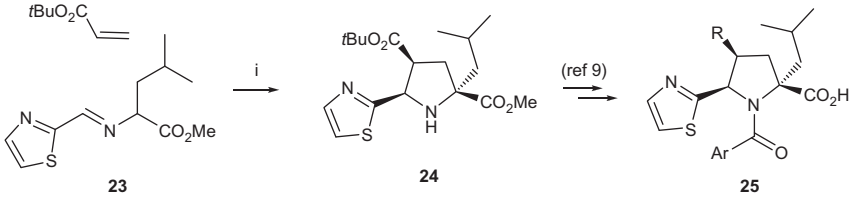
3. Conclusion

We conclude that a small variation in the structure of the dipole-dipolarophile or in the reaction parameters can cause 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. Replacing perchlorate salts with other different anions is also desirable from an industrial point of view. Silver hexafluoroantimonate can efficiently catalyze cycloadditions dealing with maleimides and 1,2-bis(phenylsulfonyl)ethylene and the best results were obtained when using sterically hindered dipole precursors. It should be noted that multicomponent transformations could be carried out in the presence of $AgSbF_6$ while the analogous reaction, mediated by silver(I) perchlorate, was unsuccessful. However, silver trifuoroacetate 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 (e.g. antiviral precursors).

4. Experimental

4.1. 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 ^{13}C NMR (75 MHz) spectra were obtained on a Bruker AC-300 using $CDCl_3$ as the solvent and TMS as the internal standard, unless otherwise stated. Optical rotations were measured on a Perkin Elmer 341 polarimeter. HPLC analyses were performed on a JASCO 2000-



Scheme 11. Reagents and conditions: (i) (S_a)-Binap (10 mol %), AgX (10 mol %), Et_3N (10 mol %), toluene, 25 °C, 48 h.

Table 5
Synthesis of antiviral agent precursor **24**

Entry	AgX	Product **24**	
		Yield[a,b] (%)	*ee*[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 (^{1}H NMR).
[c] Determined by HPLC of the crude product employing chiral column (Daicel Chiralpak AD).

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 70 eV 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).

4.2. 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 was 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 (1*S*,3*R*,3a*S*,6a*R*)-5-methyl-3-phenyl-4,6-dioxooctahydro pyrrolo [3,4-*c*]pyrrole-1-carboxylate *endo*-**5aa**.[5b]

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

Isopropyl (1*S*,3*R*,3a*S*,6a*R*)-5-methyl-3-phenyl-4,6-dioxoocta hydropyrrolo[3,4-*c*]pyrrole-1-carboxylate *endo*-**5ac**.[5b]

tert-Butyl (1*S*,3*R*,3a*S*,6a*R*)-5-methyl-3-phenyl-4,6-dioxoocta hydropyrrolo[3,4-*c*]pyrrole-1-carboxylate *endo*-**5ad**.[5b]

Methyl (1*S*,3*R*,3a*S*,6a*R*)-5-methyl-3-(2-naphthyl)-4,6-dioxoocta hydropyrrolo[3,4-*c*]pyrrole-1-carboxylate *endo*-**5ba**.[5a]

Methyl (1*S*,3*R*,3a*S*,6a*R*)-5-methyl-4,6-dioxo-3-o-tolyloctahydro pyrrolo[3,4-*c*]pyrrole-1-carboxylate *endo*-**5ca**.[5b]

Methyl (1*S*,3*R*,3a*S*,6a*R*)-3-(2-chlorophenyl)-5-methyl-4,6-dioxo octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate *endo*-**5da**.[5a]

Methyl (1*S*,3*R*,3a*S*,6a*R*)-5-methyl-3-(4-methylphenyl)-4,6-dioxo octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate *endo*-**5ea**.[5a]

Methyl (1*S*,3*R*,3a*S*,6a*R*)-3-(4-chlorophenyl)-5-methyl-4,6-dioxo octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate *endo*-**5fa**.[5a]

Methyl (1*S*,3*R*,3a*S*,6a*R*)-3-(3-pyridyl)-5-methyl-4,6-dioxoocta hydropyrrolo[3,4-*c*]pyrrole-1-carboxylate *endo*-**5ga**.[22]

Methyl (1*S*,3*R*,3a*S*,6a*R*)-5-methyl-4,6-dioxo-3-(2-thienyl)octa hydropyrrolo[3,4-*c*]pyrrole-1-carboxylate *endo*-**5ha**.[5a]

Methyl (1*S*,3*R*,3a*S*,6a*R*)-5-ethyl-4,6-dioxo-3-phenyloctahydro pyrrolo[3,4-*c*]pyrrole-1-carboxylate *endo*-**6**.[23]

Methyl (1*S*,3*R*,3a*S*,6a*R*)-4,6-dioxo-3,5-diphenyloctahydro pyrrolo[3,4-*c*]pyrrole-1-carboxylate *endo*-**7**.[23]

Methyl (1*S*,3*R*,3a*S*,6a*R*)-5-benzyl-4,6-dioxo-3-phenyloctahydro pyrrolo[3,4-*c*]pyrrole-1-carboxylate *endo*-**8**. Pale yellow oil; $[\alpha]_D^{20} = +69.4$ (*c* 1, $CHCl_3$) 98% *ee* from HPLC; IR ν_{max} 1740–1705, 3260 cm^{-1}; ^{1}H NMR δ_H: 2.10 (s, 1H, NH), 3.33, 3.58 (2×deform. d, *J* = 7.0, Hz, 2H, C*H*$_2$Ph), 3,40 (d, *J* = 7,5 Hz, 1H, CCH), 3,58 (dd, *J* = 9.1, and 7.6 Hz, 1H, C*H*CHCO$_2$CH$_3$), 3.76 (s, 3H, CO_2Me), 3.58 (d, *J* = 7.1 Hz, 1H, C*H*CO$_2$CH$_3$), 4.25 (d, *J* = 6.8 Hz, 1H, C*H*Ar), 7.27–7.48 (m, 10H, Ar*H*); ^{13}C NMR δ_C: 46.2 (C*H*$_2$Ph), 47.1, 48.9 (2 × CHCON), 51.9 (CH_3), 61.4, 66.2 (2 × CHN), 128.1, 128.5, 125.9, 140.5, 126.9, 128.6, 126.7, 136.5 (ArC), 176.4, 176.0, 171.6 (3 × CO); MS (EI-GC) *m*/*z*: 364 (M^++1, 2%), 273 (100), 91 (47), 68 (11); HRMS calculated for $C_{21}H_{20}N_2O_4$: 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 (1*S*,3*R*,3a*S*,6a*R*)-1,5-dimethyl-4,6-dioxo-3-phenyloctahydro pyrrolo[3,4-*c*]pyrrole-1-carboxylate *endo*-**10a**.[5b]

Methyl (1*S*,3*R*,3a*S*,6a*R*)-1-isobutyl-5-methyl-4,6-dioxo-3-(2-thienyl) octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate *endo*-**10b**.[5b]

Methyl (1*S*,3*R*,3a*S*,6a*R*)-1-benzyl-5-methyl-4,6-dioxo-3-phenyl octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate *endo*-**10c**.[5b]

Methyl (2*R*,3*R*,4*R*,5*S*)-5-phenyl-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate *endo*-**12aaa**. Sticky oil, $[\alpha]_D^{20} = +1.2$ (*c* 1, CH_2Cl_2) 90% *ee* from HPLC; IR (neat) ν_{max}: 3311, 1753 cm^{-1}; ^{1}H NMR δ_H: 2.80 (br s, 1H, NH), 3.68 (s, 3H, CO_2*M*e), 4.33 (m, 1H, PhCHC*H*SO$_2$Ph), 4.41 (dd, *J* = 2.4, 6.3 Hz, 1H, NCC*H*SO$_2$Ph), 4.47 (dd, *J* = 2.4, 6.0 Hz, 1H, C*H*CO$_2$Me), 4.64 (m, 1H, PhC*H*N), 7.28–7.26 (m, 2H, Ar*H*), 7.34–7.32 (m, 2H, Ar*H*), 7.46–7.42 (m, 2H, Ar*H*), 7.61–7.52 (m, 3H, Ar*H*), 7.72–7.65 (m, 6H, Ar*H*); ^{13}C NMR δ_C: 38.3 (Me) 48.6 (*C*HCO$_2$Me), 49.1, 52.7 (2 × CHS), 56.0 (*C*HPh), 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 $C_{24}H_{23}NO_6S_2$: 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 (2*R*,3*R*,4*R*,5*S*)-5-(naphth-2-yl)-3,4-bis(phenylsulfonyl) pyrrolidine-2-carboxylate *endo*-**12baa**. Sticky oil, $[\alpha]_D^{20} = +17.1$ (*c* 0.5; CH_2Cl_2) 92% *ee* from HPLC; IR (neat) ν_{max}: 1741, 3340 cm^{-1}; ^{1}H NMR δ_H: 2.20 (br s, 1H, NH), 3.69 (s, 3H, CO_2*M*e); 4.38 (m, 1H, ArCHC*H*SO$_2$Ph), 4.45 (dd, *J* = 2.4, 6.4 Hz, 1H, NCC*H*SO$_2$Ph), 4.49 (dd, *J* = 2.4, 6.0 Hz, 1H, C*H*CO$_2$Me), 4.79 (m, 1H, C*H*Ar), 7.39–7.35 (m, 2H, Ar*H*), 7.56–7.45 (m, 6H, Ar*H*), 7.72–7.60 (m, 7H, Ar*H*), 7.81–7.77 (m, 2H, Ar*H*); ^{13}C NMR δ_C: 38.5 (Me), 48.6 (CHCO$_2$Me), 49.1, 52.7 (2 × CHSO$_2$), 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 $C_{28}H_{25}NO_6S_2$: 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 (2*R*,3*R*,4*R*,5*S*)-2-methyl-5-(naphth-2-yl)-3,4-bis(phenyl sulfonyl)pyrrolidine-2-carboxylate *endo*-**12bba**: Colorless oil, $[\alpha]_D^{20} = +5.2$ (*c* 1, CH_2Cl_2) 24% *ee* from HPLC; IR (neat) ν_{max}: 1748 3341 cm^{-1}; ^1H NMR δ_H: 1.80 (s, 3H, CH_3), 3.79 (s, 3H, CO_2Me), 3.46–3.43 (m, 1H, NH), 4.48 (d, *J* = 3.9 Hz, 1H, ArCHC*H*SO_2Ph), 4.61 (dd, *J* = 3.9, 7.2 Hz, 1H, NCC*H*SO_2Ph), 4.83–4.77 (m, 1H, ArC*H*), 7.28–7.12 (m, 5H, Ar*H*), 7.51–7.43 (m, 5H, Ar*H*),7.73–7.57 (m, 6H, Ar*H*), 7.90–7.87 (m, 1H, Ar*H*); ^{13}C NMR δ_C: 25.2 (CH_3), 39.2 (CO_2Me), 49.0, 52.1 (2 × $CHSO_2$), 56.9 (ArCH), 73.5 (*C*Me), 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 (2*R*,3*R*,4*R*,5*S*)-3,4-bis(phenylsulfonyl)-5-(*o*-tolyl)pyrrolidine-2-carboxylate *endo*-**12caa**: Colorless 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 NMR δ_H: 2.42 (s, 3H, ArCH_3); 2.90 (br s, 1H, NH), 3.64 (s, 3H, CO_2Me), 4.32 (s, 1H, ArCHC*H*SO_2Ph), 4.48 (dd, *J* = 2.7, 6.2 Hz, 1H, NCC*H*SO_2Ph), 4.65 (dd, *J* = 2.7, 6.9 Hz, 1H, C*H*CO_2Me), 4.97 (s, 1H, ArC*H*), 7.25–7.16 (m, 2H, Ar*H*), 7.41 (t, *J* = 7.6 Hz, 8.0 Hz, 2H, Ar*H*), 7.58–7.54 (m, 5H, Ar*H*), 7.71–7.67 (m, 5H, Ar*H*), ^{13}C NMR δ_C: 37.4 (OMe), 44.3 (Ar*Me*), 50.0 (*C*HCO_2Me), 53.0, 55.5 (2 × *C*HSO_2), 57.8 (ArC*H*), 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 (2*R*,3*R*,4*R*,5*S*)-3,4-bis(phenylsulfonyl)-5-(*p*-tolyl)pyrrolidine-2-carboxylate **12daa**: Colorless 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 NMR δ_H: 2.30 (s, 3H, ArCH_3); 2.20 (br s, 1H, NH), 3.66 (s, 3H, CO_2Me), 4.31–4.27 (m, 1H, ArCHC*H*SO_2Ph), 4.35 (dd, *J* = 2.4, 6.4 Hz, 1H, NCC*H*SO_2Ph), 4.41 (dd, *J* = 2.4, 6.0 Hz, 1H, C*H*CO_2Me), 4.61–4.57 (m, 1H, ArC*H*), 7.06 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.20 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.54–7.40 (m, 6H, Ar*H*), 7.64–7.57 (m, 2H, Ar*H*), 7.70–7.66 (m, 4H, Ar*H*), ^{13}C NMR δ_C: 21.2 (*C*H_3Ar), 53.6 (OMe), 63.5, 64.2 (2 × $CHSO_2$), 67.9 (*C*HCO_2Me), 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 (2*R*,3*R*,4*R*,5*S*)-5-(4-methoxyphenyl)-3,4-bis(phenylsulfonyl) pyrrolidine-2-carboxylate *endo*-**12eaa**: Colorless 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 NMR δ_H: 2.70 (br s, 1H, NH), 3.68, 3.80 (2 × s, 6H, CO_2Me); 4.31 (s, 1H, ArCHC*H*SO_2Ph), 4.35 (dd, *J* = 2.4, 6.4 Hz, 1H, NCC*H*SO_2Ph), 4.44 (dd, *J* = 2.4, 6.0 Hz, 1H, C*H*CO_2Me), 4.61 (s, 1H, ArC*H*), 7.29–7.24 (m, 2H, Ar*H*), 7.47–7.43 (m, 2H, Ar*H*), 7.63–7.52 (m, 5H, Ar*H*), 7.72–7.66 (m, 5H, Ar*H*); ^{13}C NMR δ_C: 37.4, 40.1 (2 × OMe), 45.3 (*C*HCO_2Me), 49.0, 52.7 (2 × $CHSO_2$), 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 (2*R*,3*R*,4*R*,5*S*)-5-(4-chlorophenyl)-3,4-bis(phenylsulfonyl) pyrrolidine-2-carboxylate *endo*-**12faa**: Colorless 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 NMR δ_H: 2.40 (br s, 1H, NH), 3.67 (s, 3H, CO_2Me); 4.30 (dd, *J* = 2.3, 6.3 Hz, 1H, ArCHC*H*SO_2Ph), 4.34 (m, 1H, NCC*H*SO_2Ph), 4.38 (dd, *J* = 2.3, 5.9 Hz, 1H, C*H*CO_2Me), 4.66–4.61 (m, 1H, ArC*H*), 7.30–7.21 (m, 3H, Ar*H*), 7.53–7.43 (m, 4H, Ar*H*), 7.71–7.59 (m, 7H, Ar*H*); ^{13}C NMR δ_C: 37.5 (Me); 45.2 (*C*HCO_2Me), 48.9, 52.6 (2 × $CHSO_2$), 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 (2*R*,3*R*,4*R*,5*S*)-5-(4-chlorophenyl)-3,4-bis(phenylsulfonyl) pyrrolidine-2-carboxylate *endo*-**12fab**: Colorless 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 NMR δ_H: 1,33, 1.41 [2 × d, *J* = 6.2 Hz, 6H, $CO_2CH(CH_3)_2$], 2.42 (br s, 1H, NH), 4.30 (dd, *J* = 2.3, 6.3 Hz, 1H, ArCHC*H*SO_2Ph), 4.34 (m, 1H, NCC*H*SO_2Ph), 4.38 (dd, *J* = 2.3, 5.9 Hz, 1H, C*H*CO_2Me), 4.66–4.61 (m, 1H, ArC*H*), 5.20 (m, 1H, C*H*Me_2); 7.21–7.81 (m, 7 Hz, 14H, ArH); ^{13}C NMR δ_C: 21.6, 21.9 [$CH(CH_3)_2$], 45.2 (*C*HCO_2), 47.5, 48.9 (2 × $CHSO_2$), 55.9 (ArCH), 62.0 [$CH(CH_3)_2$], 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 $C_{26}H_{27}NO_6$ S_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 (2*R*,3*R*,4*R*,5*S*)-3,4-bis(phenylsulfonyl)-5-(pyrid-3-yl) pyrrolidine-2-carboxylate *endo*-**12gaa**: Colorless 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 NMR δ_H: 2.25 (br s, 1H, NH), 3.68 (s, 3H, Me); 4.33 (dd, *J* = 2.3, 6.4 Hz, 1H, ArCHC*H*SO_2Ph), 4.35 (s, 1H, NCCHSO_2Ph), 4.43 (dd, *J* = 2.3, 5.9 Hz, 1H, C*H*CO_2Me), 4.66 (d, *J* = 6.4 Hz, 1H, ArC*H*), 7.46 (t, *J* = 7.7 Hz, 8.0 Hz, 2H, Ar*H*), 7.53 (t, *J* = 7.4 Hz, 2H, Ar*H*), 7.61–7.65 (m, 3H, Ar*H*), 7.70 (t, *J* = 7.4 Hz, 5H, Ar*H*), 8.36 (s, 1H, Ar*H*), 8.52 (s, 1H, Ar*H*); ^{13}C NMR δ_C: 34.6, 37.5 (CHCO_2*Me*), 48.9, 52.4 (2 × $CHSO_2$), 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 (2*R*,3*R*,4*R*,5*S*)-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 NMR δ_H: 0.88 [d, *J* = 6.7 Hz, 3H, *C*H$(CH_3)_2$], 1.08 [d, *J* = 6.4 Hz, 3H, CH(*C*$H_3)_2$], 1.84–1.74 [m, 1H, *C*H$(CH_3)_2$], 1.98 [dd, *J* = 6.4, 14.6 Hz, 1H, *C*H_2CH$(CH_3)_2$], 2.22 [dd, *J* = 5.7 Hz, 14.6 Hz, 1H, *C*H_2CH$(CH_3)_2$], 3.10 (br s, 1H, NH), 3.82 (s, 3H, CO_2Me), 4.40 (d, *J* = 3.9 Hz, 1H, ArCHC*H*SO_2Ph), 4.46 (dd, *J* = 3.9 Hz, 7.2 Hz, 1H, NCC*H*SO_2Ph), 4.88 (m, 1H, ArC*H*), 7.21–7.13 (m, 2H, Ar*H*), 7.36–7.26 (m, 4H, Ar*H*), 7.54–7.45 (m, 4H, Ar*H*), 7.65–7.61 (m, 1H, Ar*H*), 7.76–7.23 (m, 1H, Ar*H*), 7.90 (d, *J* = 7.3 Hz, 1H, Ar*H*); ^{13}C NMR δ_C: 24.4, 24.6 [CH(*C*$H_3)_2$], 28.4 [*C*H$(CH_3)_2$], 37.7 (CH_2), 39.5,

43.7, 57.8 (OMe and 2 × $CHSO_2$), 58.4, 58.9 (*C*CO, 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, (Ar*C*), 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 (2*R*,3*R*,4*R*,5*S*)-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) υ_{max}: 1735, 3328 cm^{-1}. ^1H NMR δ_H: 0.87, 1.07 [2 × d, *J* = 6.7 Hz, 6H, CH(CH_3)$_2$], 1.86–1.73 [m, 1H, C*H*(CH$_3$)$_2$], 1.98 (dd, *J* = 6.4 Hz, 14.6 Hz, 1H, CH_2), 2.22 (dd, *J* = 5.7 Hz, 14.6 Hz, 1H, CH_2), 3.79 (s, 3H, OMe), 4.40 (d, *J* = 4.1 Hz, 1H, ArCHC*H*SO_2Ph), 4.97 (dd, *J* = 7.1 Hz, 12.2 Hz, 1H, NCC*H*SO_2Ph), 5.11 (dd, *J* = 4.1 Hz, 7.1 Hz, 1H, ArC*H*), 7.26–7.19 (m, 3H, Ar*H*), 7.38–7.33 (m, 2H, Ar*H*), 7.62–7.50 (m, 5H, Ar*H*), 7.74–7.68 (m, 1H, Ar*H*), 7.88–7.85 (m, 2H, Ar*H*); ^{13}C NMR δ_C: 24.5, 24.7 [CH(*C*H$_3$)$_2$], 28.0 [*C*H(CH$_3$)$_2$], 37.9 (CH_2), 39.9, 43.9, 57.2 (OMe and 2 × $CHSO_2$), 58.4, 58.4 (*C*CO, NCH), 110.2, 110.5, 111.7, 113.4, 114.4, 114.2, 118.4, 119.2, 123.1, 123.3, 125.9, (Ar*C*), 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.

4.3. 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 $AgSbF_6$ (17 mg, 0.05 mmol) in toluene (3 mL), triethylamine (6.6 μL, 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 for 16 or 48 h (see Scheme 6). The solvent was evaporated in vacuo and the residue was purified by flash chromatography yielding products *endo*-**5aa** or *endo*-**12gaa**.

4.4. 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 (3 ml), 10% Na(Hg) (69.3 mg) and Na_2HPO_4 (22.4 mg, 0.16 mmol) were sequentially added at 0 °C. After stirring for 1 h at room temperature, ethyl acetate (10 ml) was added, and the resulting suspension was filtered and washed with water (2 × 5 ml). The aqueous phase was extracted with ethyl acetate (2 × 5 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 then dissolved in methanol (3 ml) and Pt/C (10%) (30 mg) was added. The reaction was stirred for 48 h under a hydrogen atmosphere (1 atm) at 25 °C and the final mixture was filtered over a Celite pad. The remaining solution was evaporated in vacuo and the residue was purified by flash chromatography to give product **16a** in 47% overall yield.

Methyl 5-phenylpyrrolidine-2-carboxylate **16a**.[16]

4.5. Synthesis of imine 21

To a solution of 3,4-dimethoxyphenethyl alcohol (3.0 g, 16.6 mmol) in pyridine (4 ml), Ac_2O (1.6 ml, 16.6 mmol), DMAP (0.040 g, 0.33 mmol), and Et_3N (2.35 ml, 16.6 mmol) were added in this order. The mixture was then stirred for 4 h. Next, water (5 mL) and ethyl acetate (3 × 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][20] (252 mg, 1 mmol), glycine methyl ester hydrochloride (126 mg, 1 mmol), Et_3N (1.1 mmol), and $MgSO_4$ (100 mg) were suspended in chloroform and the mixture was refluxed for 16 h. The mixture was then filtered and the resulting organic phase was washed with water (2 × 5 mL). The organic layer was dried ($MgSO_4$) and evaporated in vacuo to obtain imine **21** in 96% yield.

Methyl (*E*)-2-{[(2-(2-acetoxyethyl)-4,5-dimethoxybenzylidene] amino}acetate **21**: Pale yellow oil; IR (neat) υ_{max}: 1741, 1731, 1634 cm^{-1}; ^1H NMR δ_H: 1.96 (s, 3H, CH_3CO_2), 3.05 (t, *J* = 7.3 Hz, 2H, AcOCH_2), 3.61 (s, 3H, CO_2CH_3), 3.84, 3.85 (2 × s, 6H, 2 × OCH_3), 4.16 (t, *J* = 7.3 Hz, 2H, PhCH_2), 4.36 (s, 2H, NCH_2), 6.61 (s, 1H, Ar*H*), 7.46 (s, 1H, Ar*H*), 8.48 (s, 1H, NC*H*); ^{13}C NMR δ_C: 20.9 (*C*H$_3$CO), 31.3 (*C*H$_2$Ar), 52.0, 55.8, 56.0 (3 × OMe), 62.1, 65.0 (*C*H$_2$CO, *C*H$_2$O), 109.7, 112.8, 126.5, 131.3, 148.1, 151.4 (Ar*C*), 162.9 (CN), 170.7, 170.9 (2 × CO); MS (EI) *m*/*z* (%): 323.2 (M^+, 5%), 264 (21), 263 (26), 262 (100), 190 (13), 176 (14), 175 (59); HRMS calculated for $C_{16}H_{21}NO_6$: 323.1369; found: 323.1361.

4.6. 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 exposure to light. Next, 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 for 48 h at 25 °C after which water (5 ml) and the aqueous phase extracted with ethyl acetate (2 × 5 ml). The organic layer was dried ($MgSO_4$) and evaporated in vacuo to obtain 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**: Colorless needles, mp 92–94 °C (*n*-hexane/ethyl acetate); $[\alpha]_D^{20} = -25.3$ (*c* 1, $CHCl_3$) 50% *ee* from HPLC; IR (KBr) υ_{max}: 1148, 1309, 1738, 3306 cm^{-1}; ^1H NMR δ_H: 2.05 (s, 3H, CH_3CO_2), 2.30 (br s, 1H, NH), 2.85, 3.18 (2 m, 2H, PhCH_2), 3.60 (s, 3H, CO_2CH_3), 3.88, 3.91 (2s, 6H, 2 × OCH_3), 4.25–4.28 (m, 4H, AcOCH_2, C*H*S, C*H*CO_2Me), 4.60 (dd, *J* = 6.3, 1.9 Hz, 1H, C*H*S), 5.04 (d, *J* = 6.3 Hz, 1H, PhC*H*), 6.63 (s, 1H, Ar*H*), 7.31 (s, 1H, Ar*H*), 7.43–7.74 (m, 10H, Ar*H*); ^{13}C NMR δ_C: 21.0 (*C*H$_3$CO), 31.9 (*C*H$_2$Ar), 45.6, 49.9, 52.4, 55.9, 56.1, 58.6 (*C*HCO$_2$Me 3xOMe and 2 CHS), 64.4, 64.8 (*C*H$_2$CO, *C*H$_2$O), 68.5 (Ar*C*H), 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 (Ar*C*), 167.4, 171.0 (2 × CO); 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 $C_{30}H_{33}NO_{10}S_2$: C, 57.0; H, 5.3; N, 2.2%, found: C, 57.3; H, 5.3; N, 2.5; HPLC (Chiralpak AD, 1 mL/min, *n*-hexane/*i*-PrOH: 70/30, λ 217 nm), t_{Rmaj} = 28.20 - min, t_{Rmin} = 21.53.

4.7. 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 was stirred for 16 h at 26 °C. Ethyl acetate was then added (10 mL) and the organic phase was washed with brine (3 × 4 ml). The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash chromatography to obtain the silyl-protected derivative (0.84 g, 99%). A solution of this derivative (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 was continued at 25 °C for 30 min. Next, $PhSO_2Cl$ (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 (3 × 15 ml). The combined organic phases were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash chromatography to obtain 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 25 °C and then immediately cooled to −78 °C. Next, DMF (0.77 ml, 1 mmol) 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 (3 × 15 mL). The combined organic phases were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash chromatography to obtain the desired aldehyde (0.63 g, 75%).[24b]

Imine **22** was prepared in 95% pure crude yield as described for **21** (see above).

(*E*)-Methyl 2-{[3-(2-[(*tert*-butyldimethylsilyloxy)ethyl]-1-(phenyl sulfonyl)-1*H*-indol-2-yl]methylene}aminoacetate **22**: Orange sticky oil; IR (neat) υ_{max}: 1747, 1631, 1371, 1170 cm^{-1}; ^1H NMR δ_H: −0.17, 0.02 (2 × s, 6H, 2 × $SiCH_3$), 0.87 [s, 9H, $SiC(CH_3)_3$], 2.88 (t, *J* = 6.7 Hz, 2H, CCH_2), 3.31 (t, *J* = 6.7 Hz, 2H, OCH_2), 3.81 (s, 3H, CO_2CH_3), 4.53 (s, 2H, NCH_2), 7.41–8.00 (m, 9H, ArC*H*), 8.84 (s, 1H, NC*H*); ^{13}C NMR 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 $C_{26}H_{34}N_2O_5SSi$: 514.1958; found: 514.1967.

4.8. 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 while avoiding exposure to light. Next, imine **22** (51 mg, 0.1 mmol), 1,2-bis(phenylsulfonyl)ethylene (31 mg, 0.1 mmol), and DABCO (2 mg, 0.01 mmol) were added in this order. The reaction was stirred for 48 h at 25 °C and water (5 mL) and the aqueous phase extracted with ethyl acetate (2 × 5 mL). The organic layer was dried ($MgSO_4$) and evaporated in vacuo to obtain cycloadduct **20**.

Methyl (2*R*,3*R*,4*R*,5*S*)-5-{3-[2-((tert-butyldimethylsilyl)oxy)ethyl]-1-(phenylsulfonyl)-1*H*-indol-2-yl}-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate **20**: Colorless needles, mp 155 °C (*n*-hexane/ethyl acetate); $[\alpha]_D^{20} = -4.5$ (*c* 1, $CHCl_3$) 12% *ee* from HPLC; IR (KBr) υ_{max}: 1142, 1309, 1765, 3286 cm^{-1}; ^1H NMR δ_H: −0.137, −0.04 (2 × s, 6H, 2 × $SiCH_3$), 0.79 [s, 9H, $SiC(CH_3)_3$], 2.81 (t, *J* = 6.6 Hz, 2H, $OTBDMSCH_2$), 3.02 (td, *J* = 6.6, 1.9 Hz, 2H, CCH_2), 3.76–3.79 (m, 5H, CO_2CH_3, S*CH*, *CH*CO_2CH_3), 4.26 (d, *J* = 7.1 Hz, 1H, NCH_2), 4.87 (dd, *J* = 7.1, 4.7 Hz, 1H, C*H*N), 5.40 (s, 1H, N*H*), 7.07–8.01 (m, 19H, ArC*H*); ^{13}C-NMR 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 $C_{40}H_{46}N_2O_9S_3Si$: 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 222 nm), t_{Rmaj} = 24.5 min, t_{Rmin} = 27.8 min.

4.9. Synthesis of the antiviral precursor 24[25]

Compound **24** was prepared according to the procedure described earlier (see Section 4.2).

tert-Butyl methyl (2*S*,4*S*,5*R*)-2-isobutyl-5-(thiazol-2-yl)pyrrolidine-2,4-dicarboxylate **24**: $[\alpha]_D^{20} = +38$ (*c* 1, CH_2Cl_2) 99% *ee* by HPLC Lit.[25] $[\alpha]_D^{20} = +43$ (*c* 1, CH_2Cl_2) 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 Sanduíche stay.

References

1. *Privileged Chiral Ligands and Catalysts*; Qi-Lin Zhou, Ed.; Wiley-VCH: New York, 2011.
2. For the pioneering catalytic enantioselective 1,3-DC work carried out by Grigg et al., see (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 is frequently 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*; Hassner, A., Ed.; Springer: 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$(MeCN)_4ClO_4$ 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. $[(S_a)$-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 corringendum, **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 $[(S_a)$-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 for 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 enantioselective gold(I)-catalyzed cycloadditions 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.