Graphical Abstract

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Enantioselective synthesis of polysubstituted prolines by Binap-silver-catalyzed 1,3-dipolar cycloadditions.

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Carmen Nájera,[*a] M. de Gracia Retamosa[a] and José M. Sansano,[a]Abel de Cózar[b] and Fernando P. Cossío[c]

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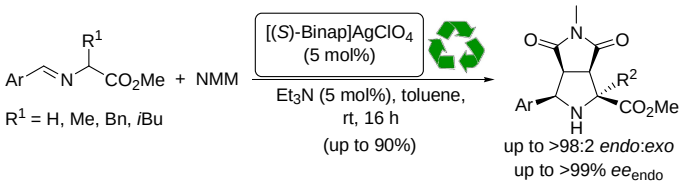
[c]*Departamento de Química Orgánica I, Facultad de Química, Universidad del País Vasco-Euskal Herriko Unibertsitatea, P. K. 1072, E-20018 San Sebastián-Donostia, Spain.*



Stereochemistry Abstract

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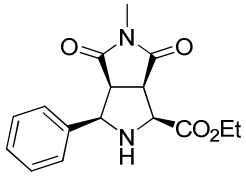
Carmen Nájera,* M. de Gracia Retamosa José M. Sansano, Abel de Cózar and Fernando P. Cossío



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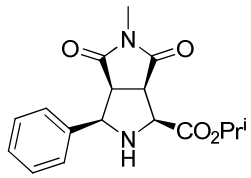
Source of chirality: (*S*)-Binap
Absolute configuration: (1*S*,3*R*,3a*S*,6a*R*)

$C_{16}H_{18}N_2O_4$
Ethyl (1*S*,3*R*,3a*S*,6a*R*)-5-methyl-3-phenyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate

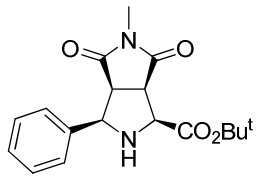
Carmen Nájera,* M. de Gracia Retamosa José M. Sansano, Abel de Cózar and Fernando P. Cossío



$[\alpha]_D$ = +63º (*c* 0.7, $CHCl_3$, 99% *ee* from HPLC)
Source of chirality: (*S*)-Binap
Absolute configuration: (1*S*,3*R*,3a*S*,6a*R*)

$C_{17}H_{20}N_2O_4$
Isopropyl (1*S*,3*R*,3a*S*,6a*R*)-5-methyl-3-phenyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate

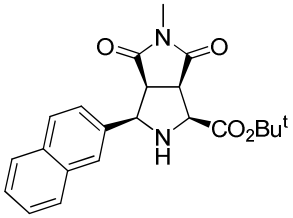
Carmen Nájera,* M. de Gracia Retamosa José M. Sansano, Abel de Cózar and Fernando P. Cossío



$[\alpha]_D$ = +33.9º (*c* 0.8, $CHCl_3$, 92% *ee* from HPLC)
Source of chirality: (S)-Binap
Absolute configuration: (1*S*,3*R*,3a*S*,6a*R*)

$C_{18}H_{22}N_2O_4$
tert-Butyl (1*S*,3*R*,3a*S*,6a*R*)-5-methyl-3-phenyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate

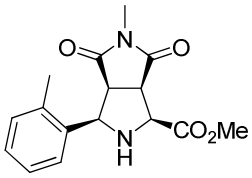
Carmen Nájera,* M. de Gracia Retamosa José M. Sansano, Abel de Cózar and Fernando P. Cossío



$[\alpha]_D$ = +39.8º (*c* 1, $CHCl_3$, 92% *ee* from HPLC, 75:25 *endo/exo*)
Source of chirality: (*S*)-Binap
Absolute configuration: (1*S*,3*R*,3a*S*,6a*R*)

$C_{22}H_{24}N_2O_4$
tert-Butyl (1*S*,3*R*,3a*S*,6a*R*)-5-methyl-3-(2-naphthyl)-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate

Carmen Nájera,* M. de Gracia Retamosa José M. Sansano, Abel de Cózar and Fernando P. Cossío



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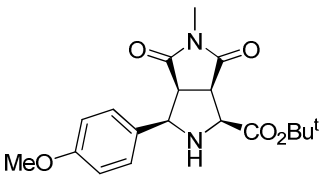
Absolute configuration: (1*S*,3*R*,3a*S*,6a*R*)

$C_{16}H_{18}N_2O_4$
(1*S*,3*R*,3a*S*,6a*R*)-Methyl 5-methyl-4,6-dioxo-3-(*o*-tolyl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate

Carmen Nájera,* M. de Gracia Retamosa José M. Sansano, Abel de Cózar and Fernando P. Cossío



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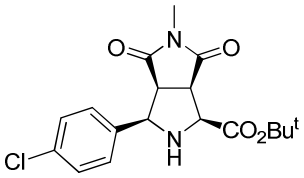
Source of chirality: (*S*)-Binap
Absolute configuration: (1*S*,3*R*,3a*S*,6a*R*)

$C_{19}H_{24}N_2O_5$
tert-Butyl (1*S*,3*R*,3a*S*,6a*R*)-3-(4-methoxyphenyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate

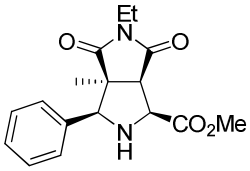
Carmen Nájera,* M. de Gracia Retamosa José M. Sansano, Abel de Cózar and Fernando P. Cossío



$[\alpha]_D$ = +16º (*c* 0.5, $CHCl_3$, 82% *ee* from HPLC)
Source of chirality: (*S*)-Binap
Absolute configuration: (1*S*,3*R*,3a*S*,6a*R*)

$C_{18}H_{21}ClN_2O_4$
tert-Butyl (1*S*,3*R*,3a*S*,6a*R*)-3-(4-chlorophenyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate

Carmen Nájera,* M. de Gracia Retamosa José M. Sansano, Abel de Cózar and Fernando P. Cossío



Source of chirality: (*S*)-Binap
Absolute configuration: (1*S*,3*R*,3a*S*,6a*R*)

$C_{17}H_{20}N_2O_4$
Methyl (1*S*,3*R*,3a*S*,6a*R*)-5-ethyl-3a-methyl-3-phenyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate

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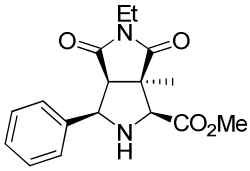
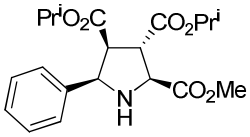


Source of chirality: (*S*)-Binap
Absolute configuration: (1*S*,3*R*,3a*S*,6a*R*)

$C_{17}H_{20}N_2O_4$
Methyl (1*S*,3*R*,3a*S*,6a*R*)-5-ethyl-6a-methyl-3-phenyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate

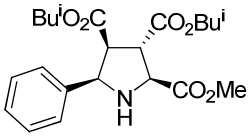
Carmen Nájera,* M. de Gracia Retamosa José M. Sansano, Abel de Cózar and Fernando P. Cossío



$[\alpha]_D$ = +32.1º (*c* 0.5, $CHCl_3$, 82% *ee* from HPLC)
Source of chirality: (*S*)-Binap
Absolute configuration: (2*S*,3*S*,4*S*,5*R*)

$C_{20}H_{27}NO_6$
(2*S*,3*S*,4*S*,5*R*)-3,4-Diisopropyl 2-methyl 5-phenylpyrrolidine-2,3,4-tricarboxylate

Carmen Nájera,* M. de Gracia Retamosa José M. Sansano, Abel de Cózar and Fernando P. Cossío



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Source of chirality: (*S*)-Binap
Absolute configuration: (2*S*,3*S*,4*S*,5*R*)

$C_{22}H_{31}NO_6$
(2*S*,3*S*,4*S*,5*R*)-3,4-Diisobutyl 2-methyl 5-phenylpyrrolidine-2,3,4-tricarboxylate

Pergamon

TETRAHEDRON:
ASYMMETRY

Enantioselective synthesis of polysubstituted prolines by Binap-silver-catalyzed 1.3-dipolar cycloadditions

Carmen Nájera,[*a] M. de Gracia Retamosa,[a] José M. Sansano,[a]
Abel de Cózar,[b] Fernando P. Cossío[#c]

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Dedicated to Prof. José M. Saá on the occasion of his 60th birthday

Abstract—. The enantioselective 1,3-dipolar cycloaddition reaction of stabilized azomethine ylides, generated from iminoesters, with maleimides was efficiently achieved by intermediacy of an equimolar mixture of chiral (*R*)- or (*S*)-Binap and $AgClO_4$. The high stability of the titled catalytic metal-complex to light exposure and its insolubility in toluene made possible its recovery and reutilization in other new process. In order to get a better understanding of the behaviour of these chiral catalysts, we have carried out DFT1 calculations demonstrating the experimentally observed *endo*-selectivity through a very asynchronous transition state.

Keywords: 1.3-Dipolar cycloaddition/azomethine ylides/iminoesters/Binap/silver/prolines

1. Introduction

Proline is singular among the genetically encoded α-amino acids (α-AA) due to the rigidity conferred by its pyrrolidine ring, which leads to a steric hindrance particularity useful in the design of biologically active peptides,[1] including the proline rich amphipathic cell-penetrating peptides.[2] The substitution on the pyrrolidine heterocycle opens new perspectives formed on these two mentioned areas, especially in structure-activity relationships studies of the newly generated peptides.[1] Restriction of the conformational space not only concerns proline or its derivative itself but also the preceding residue. The substituent attached in position 2 of the heterocycle (α-methylation) is widely used to stabilize helical conformation of peptides, as well as some type I β-*trans* arrangements. However, the substitution in position 3 has not been so studied and the results are not so predictable. Substituted prolines at the 4-position can be considered as a constrained analogues of homocysteine glutamate, homoarginine and homoserine depending on the nature of the functional group used as substituent. These 4-substituted surrogates, together with prolines incorporating a substituent in position 5 use to stabilize type VI β-turns conformations and favor the preference of the C^V-*exo*-puckering in the peptide.[1]

The proline derived structures themselves have been employed as organocatalyst[3] in many useful transformations and also as potent drugs. For example, antiviral agents **1**, active against hepatitis C virus,[4] kainoids **2** with neuro-excitatory activity or as insecticides,[5]

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For correspondence on computational studies.

neuroexcitotoxin (−)-dysibetaine **3**.[6] Hydroxyprolines **4** and **5** are crucial in collagen catabolism, and for stabilization of protocollagens and glycoproteins in plants and animals,[7] respectively, etc.

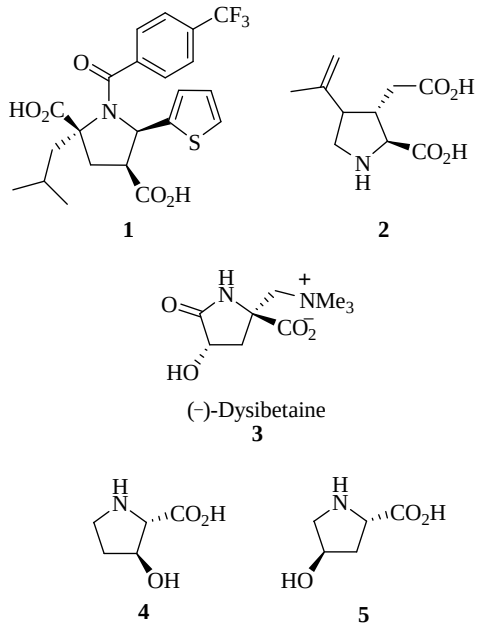


Figure 1. Some biologically active proline derivatives.

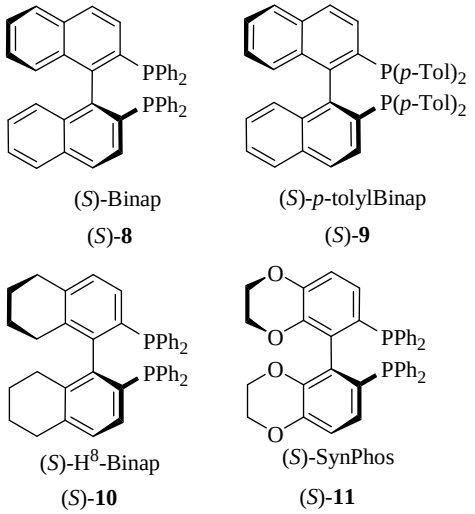
The synthesis of enantioenriched substituted prolines[8] can be achieved by several routes, as for example, starting from prolines or proline derivatives, and through C-N or C-C bond forming cyclizations. These routes operate under a diastereoselective key step included in a large synthetic sequence. Since 2002, several fascinating enantioselective syntheses of substituted prolines through 1.3-dipolar cycloaddition[9] (1,3-DC) of azomethine ylides and electron poor alkenes have been developed by several groups.[10] The simultaneous formation of the new three or four stereocentres of the resulting pyrrolidine can be achieved using chiral complexes of silver,[11] copper,[12] zinc,[13] nickel,[14] calcium,[15] or chiral organocatalysts,[16] the metal-catalyzed reaction being the most efficient and reliable route. Particularly, the most elevated *endo*:*exo* diastereoselectivities and enantioselectivities were obtained with mono- or bidentate chiral ligands Ag^I or Cu^I complexes.

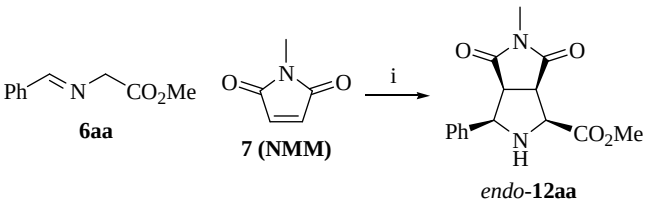
The combination of (*S*)-Binap-AgOAc showed low *ee* in 1,3-DC using dipoles derived from iminoesters and dimethyl maleate (up to 13% *ee*) in the first efficient silver-catalyzed enantioselective 1,3-DC,[11a] or phenyl vinyl sulfone (up to 26% *ee*),[12e,i] as dipolarophiles. In our group, we have used the Binap ligand[17] and $AgClO_4$ to generate active catalysts in the 1,3-DC using *N*-methylmaleimide (NMM) and iminoesters.[11h] In this work, we will describe the scope of this reaction as well as the study of another diphosphines as well as the origin of the elevated enantioselection and *endo*-diastereoselectivity.

2. Results and discussion

2.1. Optimization of the reaction conditions.

The selected model reaction between methyl benzylideneiminoglycinate **6aa** and NMM **7** was carried out in toluene at room temperature using 5 mol % of (*S*)-Binap **8** and 5 mol% of Ag^I salt as catalyst precursor (Scheme 1).





Scheme 1. Reagents and conditions: i) (*S*)-Diphosphine (5 mol%), Ag^I salt (5 mol%), Et_3N (5 mol%), toluene, rt, 16 h.

The reaction run with the equimolar amount of both Binap **8** and silver(I) salts such as $AgBF_4$, $AgNO_3$, Ag_2O, (5 mol%) gave poor results in terms of enantioselection and conversion (Table 1, entries 1-3). When AgOAc was used excellent results of the compound **6aa** were obtained (Table 1, entry 4), but the crude reaction product was not as clean as in the case of $AgClO_4$ does. AgOTf, and AgF were also tested obtaining in both cases, not reproducible results (Table 1, entries 5 and 6). However, reproducible results of a very clear crude **12aa** product with excellent enantioselectivities (>99% *ee*), high *endo*-diastereoselectivity (>98/2) and 90% yield were achieved with $AgClO_4$ (Table 1, entry 7). A 3 mol% of the catalytic complex also gave good enantioselections but the reaction time was too large (1.5 d, Table 1, entry 8). This $AgClO_4$ was used rather than the corresponding monohydrate because the last one was more difficult to weight (Table 1, entry 9). Next, different ratios of Binap:$AgClO_4$ were tested. Thus, when it was added a 2:1 mixture of Binap:$AgClO_4$ (Table 1, entry 10) the percentage of the *exo*-cycloadduct was increased. When a 1:2 mixture was prepared in situ the product **12aa** was obtained with a very

low enantioselectivity (Table 1, entry 11). In summary, the equimolar Binap:$AgClO_4$ was definitively the most efficient complex for this process (compare entries 7, 10, and 11).

The effect of the solvent was also important because almost racemic mixtures were obtained with diethyl ether, whilst dichloromethane and THF gave moderate enantioselections (<60% *ee*) of product **12aa**.

Three additional diphosphines (**9**-**11**) were evaluated in this particular model reaction (Scheme 1). It is very well known that the improvements of the enantioselection promoted by diphosphines was associated to changes in the corresponding both dihedral and bite angles of the resulting chiral metal complex.[18] Thus, equimolar mixtures of silver perchlorate and ligands **9**, **10**, and **11** (5 mol% each) afforded cycloadduct *endo*-**12aa** with very high conversions and excellent enatioselections (>99% *ee*) except in the example of the reaction product generated by intermediacy of the chiral complex **11**, which was isolated with a 98% *ee* (Table 1, entries 12-14).

According to these data, the Ag^I complex formed with (*R*)- and (*S*)-Binap **8** exhibited almost identical enantiodiscrimination than the other complexes generated from more expensive chiral ligands **9**-**11**. In addition, the resulting equimolar Binap-$AgClO_4$ can be recovered more easily than the analogous complexes generated from diphosphines **9**, **10**, and **11**.

The absolute configuration of the four stereocentres of known product *endo*-**14aa** (2*S*.3*R*.4*R*.5*R*) was confirmed by NOESY experiments and by comparison of the obtained data with the previous ones published in the literature.[19]

Table 1. Optimization of the reaction of iminoesters **6a** with NMM.

				Product **12**[a]			
Entry	Iminoester **6**	Ligand	Ag^I salt	No.	Yield (%)[b]	*endo*:*exo*[c]	*ee* (%)[d]
1	**6aa**	**8**	$AgBF_4$	**12aa**	77	89:11	72
2	**6aa**	**8**	$AgNO_3$	**12aa**	65	85:11	67
3	**6aa**	**8**	Ag_2O	**12aa**	65	90:10	18
4	**6aa**	**8**	AgOAc	**12aa**	89	>98:2	99
5	**6aa**	**8**	AgOTf	**12aa**	88	90:10	99
6	**6aa**	**8**	AgF	**12aa**	81	90:10	98
7	**6aa**	**8**	$AgClO_4$	**12aa**	90	>98:2	>99
8	**6aa**	**8**	$AgClO_4$[e]	**12aa**	90	>98:2	>99
9	**6aa**	**8**	$AgClO_4 \cdot H_2O$	**12aa**	89	>98:2	99
10	**6aa**	**8**	$AgClO_4$[f]	**12aa**	89	90:10	98
11	**6aa**	**8**	$AgClO_4$[g]	**12aa**	91	90:10	<50
12	**6aa**	**9**	$AgClO_4$	**12aa**	91	>98:2	>99
13	**6aa**	**10**	$AgClO_4$	**12aa**	90	>98:2	>99
14	**6aa**	**11**	$AgClO_4$	**12aa**	90	>98:2	98

[a] The conversions were higher than 95% (determined by ^{1}H NMR spectroscopy).

[b] Isolated yield after recrystallization.

[c] Determined by ^{1}H NMR spectroscopy of the crude product.

[d] Determined by chiral HPLC (Daicel Chiralpak AS) of the recrystallized product.

[e] Reaction performed with a 3 mol% of the catalyst taking more than 1.5 d to complete.

[f] Reaction performed with 2 equiv. of **8** and 1 equiv. of $AgClO_4$.

[g] Reaction performed with 1 equiv. of **8** and 2 equiv. of $AgClO_4$.

2.2. Characterization and properties of complexes formed by (*S*)-Binap 8 and $AgClO_4$.

Complexes formed from silver triflate and (*R*) or (*S*)-Binap **9**, were isolated at different temperatures and further characterized by X-ray diffraction analysis by Yamamoto's group.[20] These studies revealed that mixture of structures **13**-**15** are in equilibrium and at room temperature, being the 1:1 complex **14** the most abundant system (Figure 2).

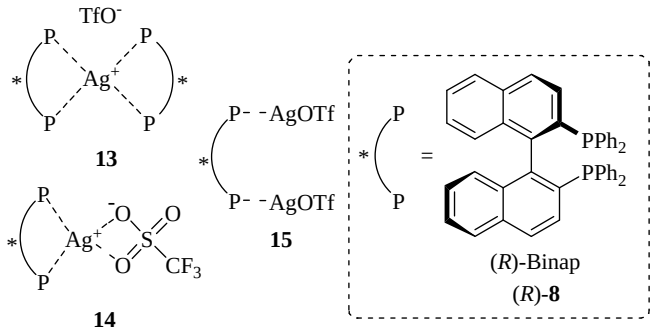
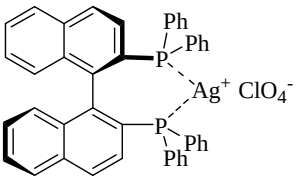


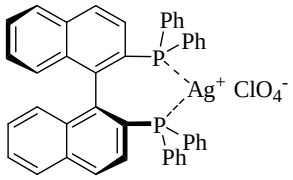
Figure 2. [(*R*)-Binap]AgOTf complexes.

In spite of equimolar [(*S*)-Binap]-$AgClO_4$ and [(*S*)-Binap]-AgOAc complexes gave identical chemical yields of product *endo*-**12aa** and very high enantioselection (>99 and 99% *ee*, respectively, Table 1, 4 and 7) the presumed major complex **16** was much more insoluble in toluene than the analogous formed by AgOAc. This property allowed the separation of the complex **16** from the reaction mixture by simple filtration (see experimental part). Surprisingly, complexes (*R*)- and (*S*)-**16** exhibited a high stability and any apparent decomposition occurred upon the light exposure. Both complexes **16** and **17** were prepared and isolated by reaction with 1 and 2 equiv of (*R*)- or (*S*)-Binap together to 1 equiv. of $AgClO_4$, respectively. The mixture was stirred for 1h at room temperature and the complexes were obtained in quantitative yield. Complex (*S*)-**16** was further characterized by ESI-MS experiments showing an M^++1 signal at 731 and a tiny one at 1353 (Graphic 1). In the case of complex (*S*)-**17** (Graphic 2), the same experiment revealed a peak at 1353 and a very small one at 731. However, these two *in situ* formed Binap complexes **16** and **17** could not be differentiated by ^{31}P NMR spectroscopy. Unfortunately, we could not obtain appropriate crystals for their comprehensive and definitive characterization by X-ray diffraction analysis.



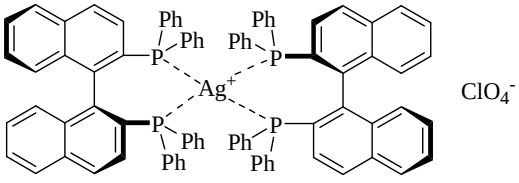
(*R*)-**16**

$[\alpha]_D$ = 174.5 (*c* 1, $CHCl_3$)



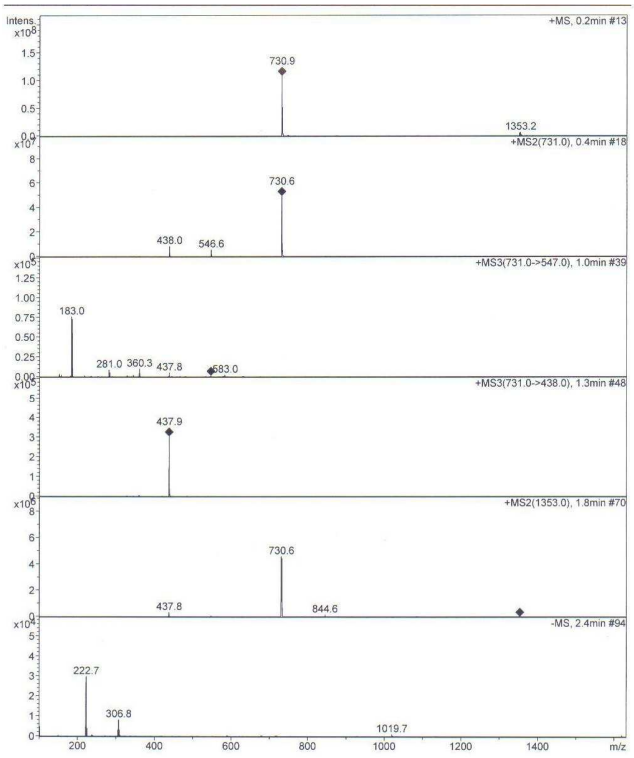
(*S*)-**16**

$[\alpha]_D$ = −174.5 (*c* 1, $CHCl_3$)

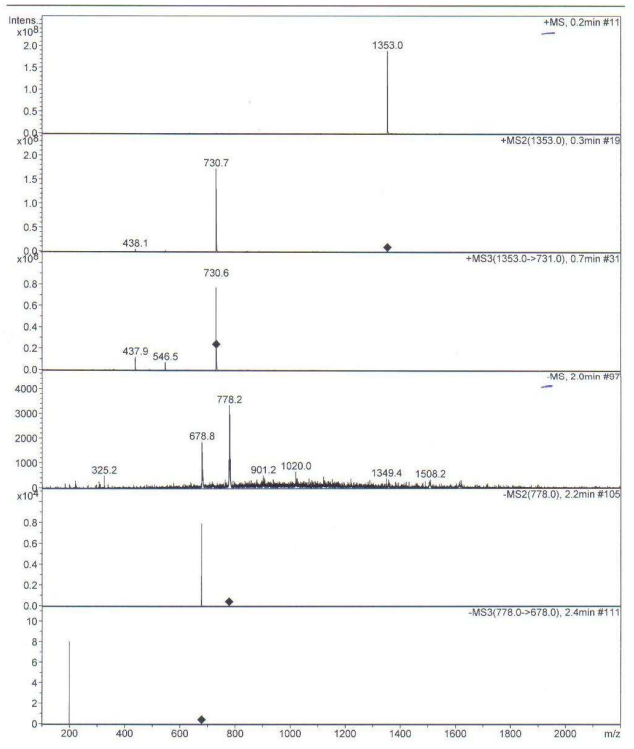


(*S*)-**17**

Figure 3. Structures of complexes (*R*)-**16**, (*S*)-**16**, and (*S*)-**17**.

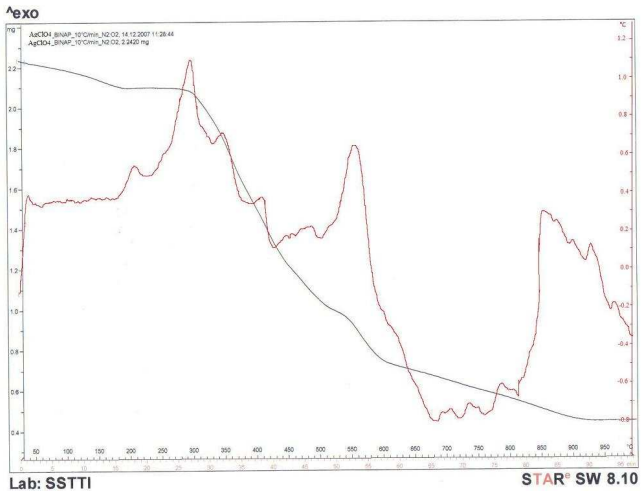


Graphic 1. ESI experiments of complex (*S*)-**16**.



Graphic 1. ESI experiments of complex (*S*)-**17**.

Due to the perchlorates are very hygroscopic materials and also classified as low order explosives and not excessively sensitive to rubbing the thermogravimetric (TG) and differential thermal analysis (DTA) of the stable species **16** were studied (Graphic 3). The integrated TG-DTA plot revealed that the loss of water of the sample occurred from 50 to 180 ºC without any variation of the heat of the system. The melting point of this complex **16** is placed in Graphic 3 in the range of 209-211 ºC. The three most important exothermic decomposition processes occurred approximately at 300, 550 and 860 ºC.



Graphic 3. TG-DTA plot of complex (*S*)-**16**

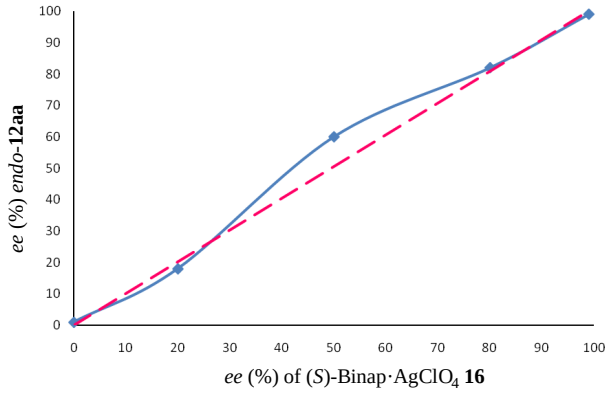
Such as it was described before, the easy separation of the most active major complex (*S*)-**16** was a very important feature to apply in a larger scale process. So, a series of cycles were run employing the same catalytic mixture (1:1 **8**-$AgClO_4$), which was recovered and reused without any additional purification (Scheme 1 and Table 2). The reaction shown in Scheme 1 was performed on a 1 mmol scale on **6aa** with a 10 mol% of catalyst to facilitate its manipulation and successive reutilization. In the cycles 1- 4 the enantioselectivity was higher than 99% *ee* keeping identical chemical yields (81-91%) (Table 2, entries 1-4). The fifth cycle also afforded the title product *endo*-**12aa** in high yield but with a slightly lower *ee* (98%) (Table 2, entry 5) due to the effect of the possible impurities contained in the catalyst. In all of the five cycles tested the *endo*:*exo* diastereoselectivity was higher than 98:2 according to ^{1H} NMR experiments.

Table 2. Recycling experiments of 1:1 [(*S*)-Binap **8**]:$AgClO_4$ complex.

Cycle	Reaction (mmol)	(*S*)-**6aa** (mmol) [a]	Recovered Catalyst (%)	Yield (%)[b]	ee_{endo} (%)[c]
1	1	0.100	95	91	>99
2	1	0.095[d]	93	89	>99
3	1	0.088[d]	92	91	>99
4	1	0.081[d]	90	90	99
5	1	0.073[d]	90	88	98

[a] Recovered after filtration of the crude reaction suspension and washed several times with toluene.
[b] Isolated yield of compound *endo*-**12aa** after recrystallization. The conversions were >99% and the *endo*:*exo* ratio were >98:2 in all of the essayed cycles.
[c] Determined by chiral HPLC (Daicel Chiralpak AS).
[d] Amount recovered from the previous cycle.

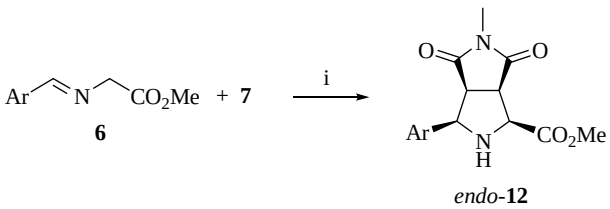
The existence of NLE was discarded when the reaction shown in the Scheme 1 was performed using different optical purities of the *in situ* generated major complex (*S*)-**16** (Graphic 4). In this case, an almost linear behavior was observed and, in consequence, it was reasonable to assume that monomeric complexes can be the catalytically active species.



Graphic 4. NLE study of the model reaction catalyzed by the presumed major complex **16.**

2.3. Scope of the 1,3-DC catalyzed by complexes (*R*)- and (*S*)-16.

The scope of the reaction employing different aryl- and ester groups at the iminoester structure with assorted dipolarophiles, was surveyed. Several ester and aryl groups were appropriate substituents in iminoglycinates **6** to perform efficiently the 1,3-DC with NMM **11** (Scheme 2 and Table 3).



Scheme 2. Reagents and conditions: i) (*S*)-Binap **8** (5 mol%), $AgClO_4$ (5 mol%), base (5 mol%), toluene, rt, 16 h.

Table 3. 1.3-DC of iminoglycinates **6** and NMM **7**.

					Product *endo*-**12**			
Entry	Nº	Ar	R	Base	Nº	Yield. (%)[a]	*endo*:*exo*[b]	ee_{endo} (%)[c]
1	**6aa**	Ph	Me	Et_3N	**12aa**	90	>98:2	>99 (>99)[d]
2	**6aa**	Ph	Me	Et_3N	**12aa**[e]	90	>98:2	>99 (>99)[d]
3	**6ab**	Ph	Et	Et_3N	**12ab**	78	90:10	90 (91)
4	**6ac**	Ph	Pr^i	Et_3N	**12ac**	80	90:10	70 (72)
5	**6ad**	Ph	Bu^t	Et_3N	**12ad**	81	75:25	92 (92)
6	**6ba**	2-naphthyl	Me	Et_3N	**12ba**	89	>98:2	99 (>99)[d]
7	**6bd**	2-naphthyl	Bu^t	Et_3N	**12bd**	87	95:5	92 (94)
8	**6ca**	2-$CH_3C_6H_4$	Me	Et_3N	**12ca**	85[f]	>98:2	70 (75)
9	**6da**	2-ClC_6H_4	Me	Et_3N	**12da**	82[f]	>98:2	82 (85)
10	**6da**	2-ClC_6H_4	Me	Et_3N	**12da**	82[f,g]	>98:2	82 (85)
11	**6ea**	4-$CH_3C_6H_4$	Me	Et_3N	**12ea**	88	>98:2	86 (88)[d]
12	**6ea**	4-$CH_3C_6H_4$	Me	DBU	**12ea**	88	>98:2	99 (>99)[d]
13	**6fa**	4-$(CH_3O)C_6H_4$	Me	Et_3N	**12fa**	85	>98:2	80 (99)
14	**6fa**	4-$(CH_3O)C_6H_4$	Me	Et_3N	**12fa**	85[g]	>98:2	80 (99)
15	**6fd**	4-$(CH_3O)C_6H_4$	Bu^t	Et_3N	**12fd**	84	95:5	90 (91)
16	**6ga**	4-ClC_6H_4	Me	Et_3N	**12ga**	87	>98:2	64 (65)
17	**6ga**	4-ClC_6H_4	Me	DBU	**12ga**	87[g]	>98:2	98 (99)
18	**6gd**	4-ClC_6H_4	Bu^t	Et_3N	**12gd**	83	>98:2	80 (80)
19	**6ha**	2-thienyl	Me	Et_3N	**12ha**	87	>98:2	90 (92)[h]
20	**6ha**	2-thienyl	Me	Et_3N	**12ha**	87[g]	>98:2	90 (92)[h]

[a] Isolated yield after recrystallization.

[b] Determined by ^{1}H-MNR.

[c] Determined by chiral HPLC (Chiralcel OD-H), in parenthesis the results of the recrystallized product..

[d] Determined by chiral HPLC (Chiralpak AS).

[e] Molecule (2*R*.3*S*.4*S*.5*S*) *endo*-**12aa** obtained employing (*R*)-**16**.

[f] Purification by flash chromatography.

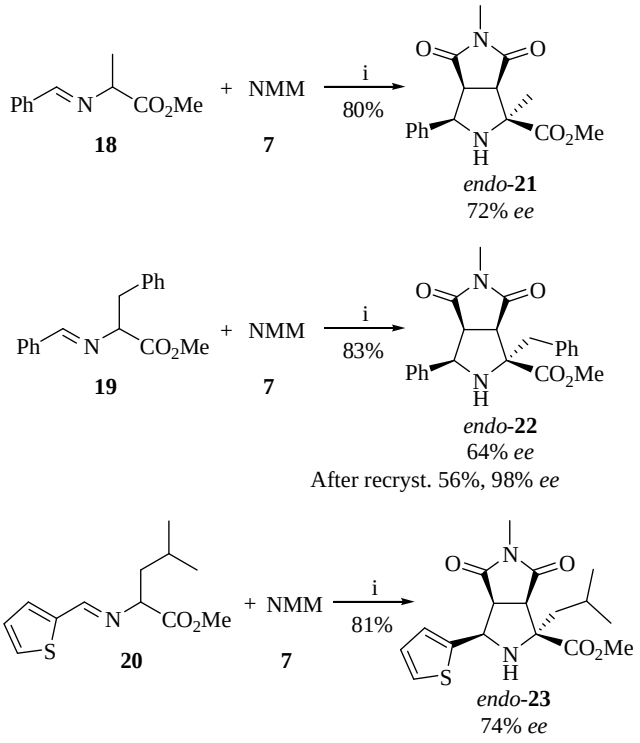
[g] Reaction performed with the recycled catalytic mixture.

[h] Determined by chiral HPLC (Chiralpak AD).

Non-substituted methyl aryliminoglycinates **6**, derived from benzaldehyde and 2-naphthalenecarbaldehyde, were the best substrates affording >99% *ee* (Table 3, entries 1, 2, and 6). In the example performed with catalytic complex (*R*)-**16**, the corresponding enantiomer (2*S*.3*R*.4*R*.5*R*)-*endo*-**12aa** was obtained (Table 3, entry 2). It was also demonstrated for these phenyl and 2-naphthyl derivatives that ethyl, isopropyl, and *tert*-butyl iminoglycinates were not suitable groups for obtaining the highest enantioselections (Table 3, entries 3, 4, 5, and 7). In these examples, it was also observed that larger amounts of the *exo*-diastereoisomer **12** were formed according to ^{1}H NMR spectroscopy and chiral HPLC. More sterically hindered iminoglycinates derived from *ortho*-substituted aromatic aldehydes gave lower enantioselections (Table 3, entries 8 and 9), even working at 0 or −20 ºC and with other bases different to Et_3N, such as DBU or DIEA. Using Et_3N as base, the imines derived from electron-donating or electron-withdrawing *para*-substituted aromatic aldehydes shown a very similar tendency (Table 3, compare entries

11, 13, 14 and 16). In a few compounds the *ee* was increased after recrystallization of the previously purified sample *endo*-**12fa** (Table 3, entry 13), but in other situations the employment of DBU as base at 0 ºC resulted to be crucial in order to achieve excellent enantioselections of *endo*-**12ea** and *endo*-**12ga** (Table 3, entries 12 and 17). Unlike the results described from phenyl and naphthyl derivatives the *terc*-butyl esters were more effective than the corresponding methyl esters in those examples containing a *para*-substituted aromatic residue imino group (compare entries 13 and 15, 16 and 18 of Table 3). Heteroaromatic iminoglycinate bearing a 2-thienyl group furnished *endo*-cycloadduct **12ha** with 92% *ee* after recrystallization (Table 3, entry 19). The recovery of the complex (*S*)-**16** was successfully attempted in the examples recorded in entries 10, 14 and 20 of the Table 3 in 88-93% yield by simple filtration.

Next, sterically hindered α-substituted benzaldimino esters were tested as substrate in this 1,3-DC with NMM. Methyl benzylidenealaninate **18**, methyl phenyliminophenylalaninate **19** and methyl 2-thienyliminoleucinate **20** reacted with NMM under the same reaction conditions at room temperature for 48 h (Scheme 3). Cycloadducts *endo*-**21**-**23** were diastereoselectivity obtained (>98:2 *endo*:*exo* ratio) and with good enantioselections (72-76% *ee*). However, compound *endo*-**22** was obtained after recrystallization in 98% *ee*, and 58% yield (Scheme 3). The absolute configuration of the heterocycle (2*R*.3*S*.4*S*.5*S*) *endo*-**21** was determined X-ray diffraction analysis (Figure 4). 2-Thienyl derivatives *endo*-**12ha** and *endo*-**23** can be considered as structurally related precursors of active inhibitors of the virus responsible of the hepatitis C **1** (Figure 1).[11i,21]



Scheme 3. Reagents and conditions: i) (*S*)-Binap **8** (5 mol%), $AgClO_4$ (5 mol%), Et_3N (5 mol%), toluene, rt, 48 h.

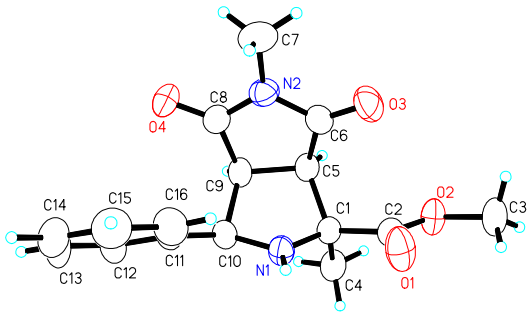


Figure 4. ORTEP of cycloadduct *endo*-**21**.

Several maleimides were essayed employing the model reaction described in Scheme 1, that means benzyliminoglycinate **6aa**, room temperature, (*S*)-**8** (5 mol%), $AgClO_4$(5 mol%) and Et_3N (5 mol%) in toluene. *N*-Ethylmaleimide afforded similar results of *endo*-**24** to the analogous obtained with NMM **7** after 8 h of reaction (Figure 5). Nevertheless, the bulkier *N*-phenylmaleimide (NPM) furnished lower *ee* (62%) of *endo*-**25** and lower diastereoselectivity (90:10 *endo*:*exo* ratio) (Figure 5).

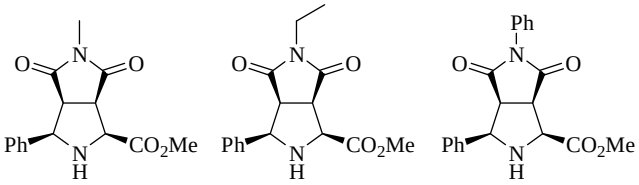
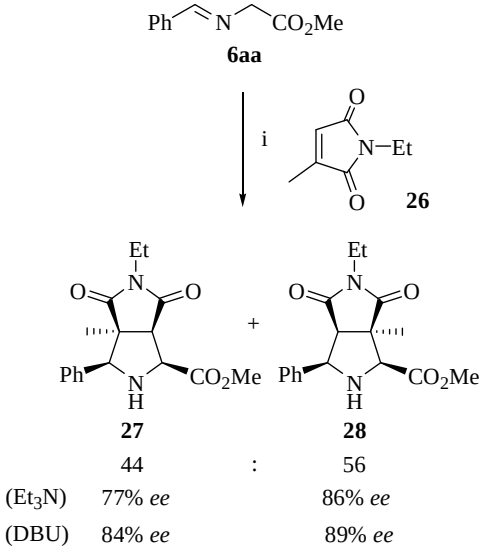


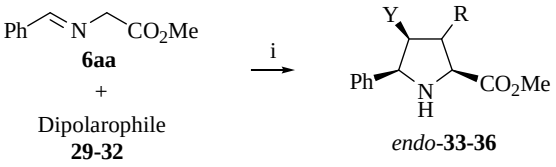
Figure 5. Products obtained from different *N*-substituted maleimides.

α–Monomethylated and α,β–dimethylated *N*-ethylmaleimides **26** and **29**, respectively, were prepared[22] and used as dipolarophiles. Non-symmetric maleimide **26** was an attractive reagent for studying how would be the regioselection of this process. When the reaction was completed cycloadducts **27** and **28** were obtained in a 44:56 ratio respectively. This ratio remained unaltered when the reaction was run at 0 or at –20 ºC, both in the presence of Et_3N or DBU. In general, better enantioselection was achieved with DBU (84 and 89% *ee*) (Scheme 4). However, no reaction was observed when 3,4-dimethyl-*N*-ethylmaleimide **29** was allowed to react with imino ester **6aa**.



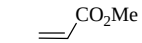
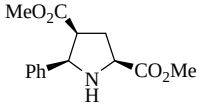
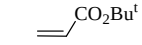
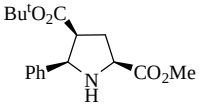
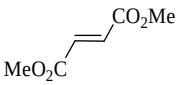
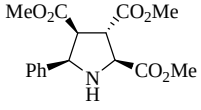
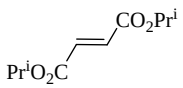
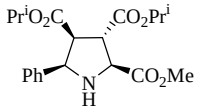
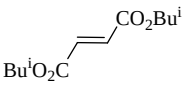
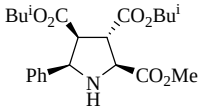
Scheme 4. Reagents and conditions: i) (*S*)-Binap **8** (5 mol%), $AgClO_4$ (5 mol%), Et_3N (5 mol%), toluene, rt, 16 h.

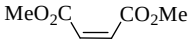
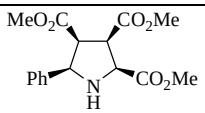
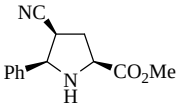
Dipolarophiles different to maleimides were not appropriate for the particular requirements of this enantioselective 1,3-DC catalyzed by the in situ generated complex (*S*)-**16** (Scheme 5 and Table 4). Acrylates **29**, fumarates **30**, maleate **31**, and acrylonitrile **32** gave very high reaction conversions but the enantioselections never exceeded of the 36% *ee* (Table 4) maintaining the high *endo*:*exo* diastereoselection. Maleic anhydride, nitrostyrene, acrylamide and *N*-isopropylacrylamide did not react at all in spite of using DBU (10 mol%) as base or even other chiral ligands **9**-**11**.



Scheme 5. (*S*)-Binap **8** (5 mol%), $AgClO_4$ (5 mol%), Et_3N (5 mol%), toluene, rt, 16 h.

Table 4. 1,3-DC of iminoester **6aa** with several dipolarophiles different to maleimides.

			Product				
Entry	Dipolarophile	No.	Structure	No.	Yield (%)[a]	*endo*:*exo*[b]	ee_{endo} (%)[c]
1		**29a**		**33a**	99	>98:2	30
2		**29d**		**33d**	99	>98:2	36
3		**30a**		**34a**	99	>98:2	28
4		**30c**		**34c**	99	>98:2	30
5		**30e**		**34e**	99	>98:2	36

Entry	Dipolarophile	No.	Product				
			Structure	No.	Yield (%)[a]	*endo*:*exo*[b]	ee_{endo} (%)[c]
6		**31a**		**35a**	99	>98:2	16
7		**32**		**36**	95	90:10	5

[a] Isolated crude yields.

[b] Determined by ^{1}H-MNR.

[c] Determined by chiral HPLC (see experimental part).

2.4. Computational studies.

In order to get a better understanding of the behaviour of these chiral catalysts, we have carried out DFT[23] calculations on the model reaction depicted in Scheme 1 and entry 7 of Table 1, using the DFT functional usually denoted as B3LYP.[24] Silver atoms were treated using the Hay and Wadt effective core potential and basis set[25] (denoted as LANL2DZ), whereas the remaining elements were described using the standard 6-31G* split-valence basis set.[26] All the calculations were carried out using the GAUSSIAN 03 suite of programs.[27] The graphics shown in Figures 6 and 7 were built up using the Maestro interface.[28] In the model systems **A**-**C** we have included the cationic part of the presumed active complex (*S*)-**16** as well as a model azomethine ylide and maleimide **B**.

The chief geometric features of complex (*S*)-**A** are gathered in Figure 6. The azomethine ylide part of (*S*)-**A** shows different distances for the two C-N bonds. These distances are compatible with an iminium-enolate structure as shown in Scheme 6, thus anticipating quite asynchronous transition structures in the reaction with the dipolarophile. It is also observed that the metallic centre is coordinated to the two phosphorus atoms of the catalysts and to the oxygen and nitrogen atoms of the azomethine ylide. This coordination pattern leads to the blockage of the *Re* face of (*S*)-**A** by one of the phenyl groups of the phosphine unit (Figure 6). This steric hindrance is also generated by the (*S*)-Binap moiety, in which the two α-naphthyl subunits form a dihedral angle of ca. 75 deg.

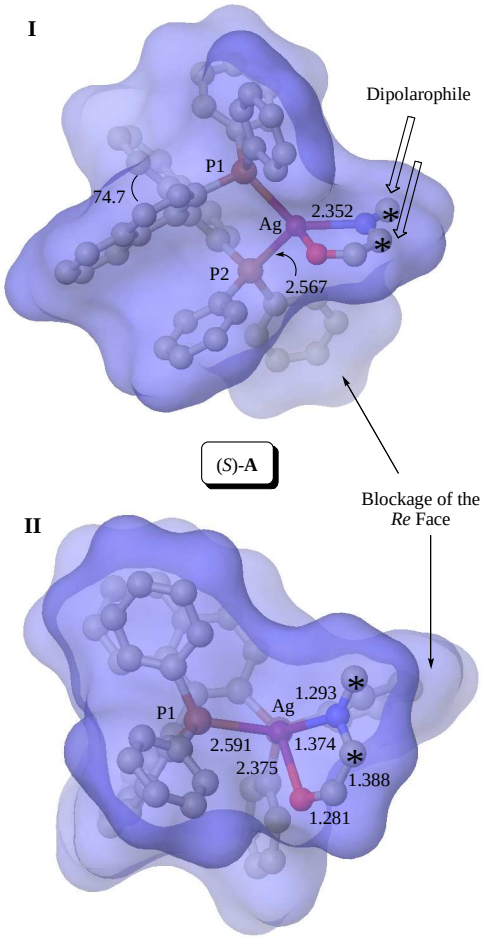
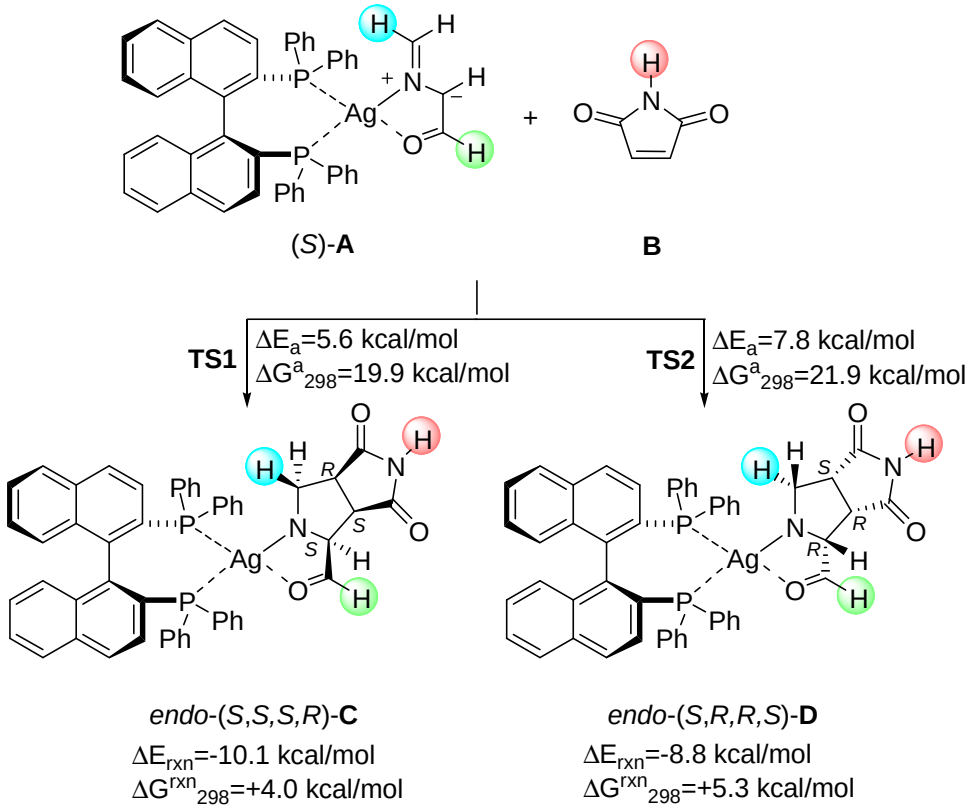


Figure 6. I: Fully optimized structure (B3LYP/LANL2DZ&6-31G* level) of (*S*)-**A**. The hydrogen atoms have been omitted for clarity. The carbon atoms of the azomethine ylide moiety have been highlighted with asterisks. Bond distances and dihedrals are given in Å and deg.,

respectively. The molecular surface (Probe radius: 1.4 Å) is also included. II: View over the *Si* face of (*S*)-**A** along the axis determined by the Ag and P2 atoms.



Scheme 6. Model reaction used in the computational studies. The hydrogen atoms highlighted in blue, green and red correspond to a phenyl, a methoxy and a methyl group in the reaction depicted in Scheme 1.

In previous work on chiral Ag-based catalysts we have observed a clear preference for the *endo*-cycloadducts because of the electrostatic interaction between the nitrogen atom of maleimide and the silver atom.[12e] Therefore, we considered the formation of the diastereomeric *endo*-cycloadducts **C** and **D** via transition structures **TS1** and **TS2**, respectively. The main geometric features and the relative energies of these transition structures are reported in Figure 7. It is found that the Gibbs activation energies are larger than the total activation energies because of the unfavourable entropic balance on going from the reactants to the saddle points, thus resulting in larger reaction times. As expected both **TS1** and **TS2** are quite asynchronous, **TS1** being ca. 2 kcal/mol more stable than **TS2**. In this latter transition structure there is an appreciable steric clash between one of the phenyl groups of the phosphine moiety of (*S*)-**16** and the dipolarophile **B**. This results in a larger distortion of the (S)-**16** moiety in **TS2** with respect to (*S*)-**A**. As a result, exclusive formation of *endo*-(*S*,*S*,*S*,*R*)-**C** is predicted, in full agreement with the experimentally observed formation of cycloadducts *endo* described across the text. The same trend is found for the cycloadducts *endo*-(*S*,*S*,*S*,*R*)-**C** and *endo*-(*S*,*R*,*R*,*S*)-**D**, the latter being ca. 1.3 kcal/mol less stable than the former. Moreover, the slightly positive values of the Gibbs reaction energies associated with the formation of these catalyst-bound cycloadducts are compatible with the catalyst turnover since there is no inhibition of the catalyst by the product of the cycloaddition step. These calculations support that NMM is the best dipolarophile due to the coordination of the nitrogen atom to the metal centre. On the other hand, the presence of a bulkier substituent in this nitrogen atom blocks the *endo*-approach reducing the enantioselection, such as occurred with NPM. In summary, our calculations are in full agreement with the experimental findings and provide a rationale for the excellent asymmetric induction and catalytic efficiency of species similar to (*S*)-**16**.

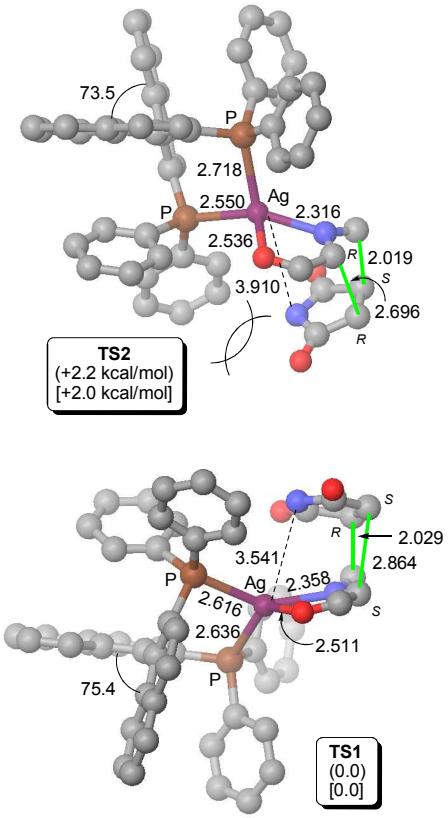


Figure 7. Fully optimized structure (B3LYP/LANL2DZ&6-31G* level) of **TS1** and **TS2**, leading to *endo*-(*S*,*S*,*R*)-**C** and *endo*-(*S*,*R*,*R*,*S*)-**D**, respectively. The hydrogen atoms have been omitted for clarity. Bond distances and dihedrals are given in Å and deg., respectively. Numbers in parentheses and in square brackets are the relative total and Gibbs free energies respectively, computed at the B3LYP/LANL2DZ&6-31G*+ΔZPVE level.

3. Conclusions

Evaluating all the data described in the main text, the employment of the complex generated by the 1:1 mixture of chiral Binap and $AgClO_4$ is very stable and can be manipulate without any special care. It was efficient in the catalyzed 1,3-DC using maleimides and aryliminoesters, however other dipolarophiles did not work satisfactorily. The whole catalytic mixture can be recovered from the reaction mixture and reused without any loss of efficiency. The TS responsible of the enantiodiscrimination is, as expected, quite asynchronous, an appreciable steric clash between one of the phenyl groups of the phosphine moiety of (*S*)-**16** and the dipolarophile being the crucial interaction.

4. Experimental section

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 iminoesters. 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. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained on a Bruker AC-300 using $CDCl_3$ 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 ºC. 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).

4.2. 1,3-Dipolara cycloaddition of iminoesters 6 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 $AgClO_4$ (0.05 mmol, 10 mg) 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.

The solid was washed with warm toluene twice and then dissolved in DCM in order to transfer the catalytic complex into the flask. After evaporation of DCM the resulting solid was ready to catalyze a new batch.

4.2.1. Methyl (1S,3R,3aS,6aR)-5-methyl-3-phenyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate ***12aa***.[12a,19]

4.2.2. Ethyl (1S,3R,3aS,6aR)-5-methyl-3-phenyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate ***12ab***. Colorless prisms, mp, 195-197 ºC (CH_2Cl_2/hex); $[\alpha]_D^{20}$ = +74º (*c* 1, $CHCl_3$, 90% *ee* from HPLC); R_f: 0.36 (*n*-hexane/ethyl acetate: 1/5); IR (KBr) *ν*: 1752, 1702, 3325 cm^{-1}; ^{1}H NMR δ_H: 1.38 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.41 (br s, 1H, NH), 2.85 (s, 3H, NCH_3), 3.41 (dd, *J* = 8.2, 8.0 Hz, 1H, C*H*CHAr), 3.55 (dd, *J* = 7.3, 7.1 Hz, 1H,

C*H*CHCO$_2$Et), 4.01 (d, *J* = 5.7 Hz, 1H, C*H*CO$_2$CH$_3$), 4.32 (m, 2H, CO$_2$C*H*$_2$CH$_3$), 4.47 (d, *J* = 8.1 Hz, 1H, CHPh), 7.28-7.36 (m, 5H, ArH); ^{13}C NMR δ_C: 14.1 (CO$_2$CH$_2$*C*H$_3$), 24.9 (NCH$_3$), 48.1, 49.5 (2*C*HCON), 61.3 (CO$_2$*C*H$_2$CH$_3$), 61.7 (*C*HCO$_2$Et), 63.9 (Ph-CH), 126.9, 128.2, 128.3 (ArCH), 136.7 (ArC), 169.6, 174.7, 175.8 (CO$_2$Me and CON); MS (EI) *m/z* (%): 302 (M$^+$, 3.90%), 230 (16), 229 (100), 191 (37), 144 (37), 117 (43); HRMS calcd. for $C_{16}H_{18}N_2O_4$: 302.1267, found: 302.1292; Microanalysis calcd. for $C_{16}H_{18}N_2O_4$: C, 63.5; H, 6.0; N, 9.2, found: C, 63.5; H, 5.7; N, 9.1; HPLC (Chiralcel ODH, 1 mL/min, *n*-hexane/*i*-PrOH: 80/20, λ 215 nm), t_{Rmaj} = 24.1 min, t_{Rmin} = 25.8 min.

4.2.3. Isopropyl (1S,3R,3aS,6aR)-5-methyl-3-phenyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate ***12ac***. Colorless prisms, mp, 202 ºC (CH_2Cl_2/hex); $[\alpha]_D^{20}$ = +63º (*c* 0.7, $CHCl_3$, 99% *ee* from HPLC); R_f: 0.50 (*n*-hexane/ethyl acetate: 1/5); IR (KBr) ν: 1735, 1703, 3328 cm^{-1}; ^{1}H NMR δ_H: 1.33 [d, *J* = 6.2 Hz, 3H, CO$_2$CH(C*H*$_3$)$_2$], 1.41 [d, *J* = 6.3 Hz, 3H, CO$_2$CH(C*H*$_3$)$_2$], 2.42 (br s, 1H, NH), 2.87 (s, 3H, NCH$_3$), 3.43 (dd, *J* = 8.3, 8.0 Hz, 1H, C*H*CHPh), 3.56 (dd, *J* = 7.2, 7.1 Hz, 1H, C*H*CHCO$_2$Pr^i), 4.00 (dd, *J* = 6.7, 5.7 Hz, 1H, C*H*CO$_2$Pr^i), 4.49 (dd, *J* = 8.4, 5.8 Hz, 1H, CHPh), 5.22 [m, 1H, CO$_2$C*H*(CH$_3$)$_2$], 7.29-7.40 (m, 5H, ArH); ^{13}C NMR δ_C: 21.6, 21.9 [CO$_2$CH(*C*H$_3$)$_2$], 24.9 (NCH$_3$), 48.2, 49.7 (2*C*HCON), 62.0 [CO$_2$*C*H(CH$_3$)$_2$], 64.0 (*C*HCO$_2$ Pr^i), 69.3 (Ph-CH), 126.6, 128.3, 128.4 (ArCH), 136.6 (ArC), 169.1, 174.8, 175.8 (CO$_2$Me and CON); MS (EI) *m/z* (%):316 (M$^+$, 2.23%), 230 (15), 229 (100), 205 (14), 144 (29), 117 (19); HRMS calcd. for $C_{17}H_{20}N_2O_4$: 316.1423, found: 316.1426; Microanalysis calcd. for $C_{17}H_{20}N_2O_4$: C, 64.5; H, 6.3; N, 8.8, found: C, 64.5; H, 6.3; N, 8.5; HPLC (Chiralcel OD-H, 1 mL/min, *n*-hexane/*i*-PrOH: 80/20, λ 215 nm), t_{Rmaj} = 21.5 min, t_{Rmin} = 33.4 min.

4.2.4. tert-Butyl (1S,3R,3aS,6aR)-5-methyl-3-phenyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate ***12ad***. Colorless prisms, mp, 210 ºC (subl.) (CH_2Cl_2/hex); $[\alpha]_D^{20}$ = +33.9º (*c* 0.8, $CHCl_3$, 92% *ee* from HPLC); R_f: 0.39 (*n*-hexane/ethyl acetate: 1/5); IR (KBr) ν: 1734, 1705, 3328 cm^{-1}; ^{1}H NMR δ_H: 1.58 [s, 9H, CO$_2$C(C*H*$_3$)$_3$], 2.40 (br s, 1H, NH), 2.86 (s, 3H, NCH$_3$), 3.42 (dd, *J* = 8.2, 8.1 Hz, 1H, C*H*CHPh), 3.54 (dd, *J* = 7.2, 7.1 Hz, 1H, C*H*CHCO$_2$Bu^t), 3.94 (m, 1H, C*H*CO$_2$Bu^t), 4.49 (dd, *J* = 8.5, 6.1 Hz, 1H, CHPh), 7.26-7.36 (m, 5H, ArH); ^{13}C NMR δ_C: 24.9 (NCH$_3$), 28.1 [CO$_2$C(*C*H$_3$)$_3$].48.2, 49.8 (2*C*HCON), 62.4 (*C*HCO$_2$Bu^t), 63.8 (Ph-CH), 82.5 [CO$_2$*C*(CH$_3$)$_3$], 126.6, 128.2, 128.4 (ArCH), 136.7 (ArC), 174.8, 175.8 (CON); MS (EI) *m/z* (%):330 (M$^+$, 0.01%), 230 (18), 229 (100), 144 (25)117 (18); HRMS calcd. for$C_{18}H_{22}N_2O_4$: 330.1580, found: 229.0986; Microanalysis calcd. for $C_{18}H_{22}N_2O_4$: C, 65.4; H, 6.7; N, 8.5, found: C, 65.4; H, 6.6; N, 8.3; HPLC (Chiralcel ODH, 1 mL/min, *n*-hexane/*i*-PrOH: 70/30, λ 215 nm), t_{Rmaj} = 12.1 min, t_{Rmin} = 17.3 min.

4.2.5. Methyl (1S,3R,3aS,6aR)-5-methyl-3-(2-naphthyl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate ***12ba***[11h]

4.2.6. tert-Butyl (1S,3R,3aS,6aR)-5-methyl-3-(2-naphthyl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate ***12bd***. Colorless prisms, mp, 150-152 ºC (CH_2Cl_2/hex); $[\alpha]_D^{20}$ = +39.8º (*c* 1, $CHCl_3$, 92% *ee* from HPLC, 75:25 *endo/exo*); R_f: 0.46 (*n*-hexane/ethyl acetate: 1/5); IR (KBr) ν: 1715, 1689, 1678, 3341 cm^{-1}; ^{1}H NMR δ_H: 1.32 [s, 9H, CO$_2$C(C*H*$_3$)$_3$], 2.29 (br s, 1H, NH), 3.05 (s, 3H, NCH$_3$), 3.56 (m, 1H, C*H*CHAr), 3.86 (m, 1H, C*H*CHCO$_2$CH$_3$), 4.00 (d, *J* = 4.2 Hz, 1H, C*H*CO$_2$CH$_3$), 4.65 (d, *J* = 4.9 Hz, 1H, CHAr), 7.40-7.49 (m, 3H, ArH), 7.80-7.86 (m, 4H, ArH); ^{13}C NMR δ_C: 25.2 (NCH$_3$), 27.7 [CO$_2$C(*C*H$_3$)$_3$].48.2, 49.1, 52.0 (2*C*HCON and CO$_2$*C*H$_3$), 63.3 (*C*HCO$_2$Bu^t), 65.3 (2-Napht-CH), 82.6 [CO$_2$*C*(CH$_3$)$_3$], 124.8, 125.2, 126.2, 126.4, 127.6, 128.0, 128.7 (ArCH), 133.0, 133.3 137.9 (ArC), 170.4, 176.9, 177.1 (CO$_2$ Bu^t and CON); MS (EI) *m/z* (%): 380 (M$^+$, 1.78%), 280 (18), 279 (100), 194 (22), 167 (13); HRMS calcd. for $C_{22}H_{24}N_2O_4$: 380.1736, found: 380.1725; Microanalysis calcd. for $C_{22}H_{24}N_2O_4$: C, 69.5; H, 6.4; N, 7.4, found: C, 69.5; H, 6.3; N, 7.1; HPLC (Chiralcel OD-H, 1 mL/min, *n*-hexane/*i*-PrOH: 70/30, λ 225 nm), t_{Rmaj} = 13.5 min, t_{Rmin} = 22.0 min.

4.2.7. Methyl (1S,3R,3aS,6aR)-5-methyl-4,6-dioxo-3-o-tolyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate ***12ca***. Colorless prisms, mp, 151 ºC (CH_2Cl_2/hex); $[\alpha]_D^{20}$ = 50,8º (*c* 0.6, $CHCl_3$, 75% *ee* from HPLC); R_f: 0.25 (*n*-hexane/ethyl acetate*:* 1/5); IR (KBr) ν: 1768, 1734, 1698, 2954 cm^{-1}; ^{1}H NMR δ_H: 2.35 (s, 3H, ArCH$_3$), 2.75 (s, 3H, NCH$_3$), 3.46 (m, 1H, C*H*CHAr), 3.67 (m, 1H, C*H*CHCO$_2$CH$_3$), 3.82 (s, 3H, CO$_2$CH$_3$), 3.99 (d, *J* = 6.2 Hz, 1H, C*H*CO$_2$CH$_3$), 4.54 (d, *J* = 8.1 Hz, 1H, CHAr), 7.08-7.15 (m, 3H, ArH), 7.36-7.39 (m, 1H, ArH); ^{13}C NMR δ_C: 19.4 (ArCH$_3$), 24.9 (NCH$_3$), 46.9, 48.0, 52.3 (2*C*HCON and CO$_2$*C*H$_3$), 61.2 (*C*HCO$_2$Me), 67.9 (2-MePh-CH), 125.1, 126.1, 127.8, 130.1 (ArCH), 135.2, 135.5 (ArC), 170.2, 174.4, 176.1 (CO$_2$Me and CON); MS (EI) *m/z* (%): 302 (M$^+$, 15.36%), 243 (67), 244 (10), 193 (10), 192 (85), 191 (78), 160 (28), 159 (11), 158 (38), 132 (38), 131 (100), 130 (36), 118 (15), 115 (14), 105 (20), 104 (11), 103 (13), 91 (15), 77 (11); HRMS calcd. for $C_{16}H_{18}N_2O_4$: 302.1267, found: 302.1247; Microanalysis calcd. for $C_{16}H_{18}N_2O_4$: C, 63.6; H, 6.0; N, 9.3, found: C, 63.6; H, 6.3; N, 9.0; HPLC (Chiralcel OD-H, 1 mL/min, *n*-hexane/*i*-PrOH: 70/30, λ 225 nm), t_{Rmin} = 24.7 min, t_{Rmaj} = 28.1 min.

4.2.8. Methyl (1S,3R,3aS,6aR)-3-(2-chlorophenyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate ***12da***.[11h]

4.2.9. Methyl (1S,3R,3aS,6aR)-5-methyl-3-(4-methylphenyl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate ***12ea***.[11h]

4.2.10. Methyl (1S,3R,3aS,6aR)-3-(4-methoxyphenyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate ***12fa***.[11h]

*4.2.11. tert-Butyl (1S,3R,3aS,6aR)-3-(4-methoxyphenyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**12fd**).* Colorless prisms, mp, 179 ºC (CH_2Cl_2/hex); $[\alpha]_D^{20}$ = 93º (*c* 0.5, $CHCl_3$, 84% *ee* from HPLC); R_f: 0.29 (*n*-hexane/ethyl acetate: 1/5); IR (KBr) ν: 1702, 1733, 2977 cm^{-1}; ^1H NMR δ_H: 1.58 [s, 9H, $CO_2C(CH_3)_3$], 1.86 (br s, 1H, NH), 2.88 (s, 3H, NCH_3), 3.38 (dd, *J* = 8.2, 8.0 Hz, 1H, C*H*CHAr), 3.53 (dd, *J* = 7.1, 7.0 Hz, 1H, C*H*CHCO$_2$Bu^t), 3.80 (s, 3H, OCH_3), 3.92 (d, *J* = 6.7 Hz, 1H, C*H*CO$_2$Bu^t), 4.43 (d, *J* = 8.6 Hz, 1H, CHAr), 6.87 (d, *J* = 8.7 Hz, 2H, ArH), 7.24 (d, *J* = 8.7 Hz, 2H, ArH); ^{13}C NMR δ_C: 24.9 (NCH_3), 28.1 [$CO_2C(CH_3)_3$], 48.2, 49.7 (2*C*HCON), 55.1 (OCH_3), 62.3 (*C*HCO$_2$Bu^t), 63.4 (4-MeOPh-CH), 82.5 [$CO_2C(CH_3)_3$], 113.7, 128.1 (ArCH), 159.3, 168.6 (ArC), 175.1, 175.9 (CON); MS (EI) *m/z* (%):360 (M^+, 4.15%), 260 (15), 259 (100), 249 (12), 193 (45), 174 (24), 147 (29); HRMS calcd. for $C_{19}H_{24}N_2O_5$: 360.1685, found: 360.1674; Microanalysis calcd. for $C_{19}H_{24}N_2O_5$: C, 63.3; H, 6.7; N, 7.7, found: C, 63.5; H, 6.6; N, 7.4; HPLC (Chiralpak AS, 1 mL/min, *n*-hexane/*i*-PrOH: 90/10, λ 205 nm), t_{Rmin} = 25.2 min, t_{Rmaj} = 43.7 min.

*4.2.12. Methyl (1S,3R,3aS,6aR)-3-(4-chlorophenyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate **12ga**.*[11h]

*4.2.13. tert-Butyl (1S,3R,3aS,6aR)-3-(4-chlorophenyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate **12gd**.* Colorless prisms, mp, 129-131 ºC (CH_2Cl_2/hex); $[\alpha]_D^{20}$ = +16º (*c* 0.5, $CHCl_3$, 82% *ee* from HPLC); R_f: 0.36 (*n*-hexane/ethyl acetate: 1/5); IR (KBr) ν: 1729, 1708, 3328 cm^{-1}; ^1H NMR δ_H: 1.57 [s, 9H, $CO_2C(CH_3)_3$], 2.39 (br s, 1H, NH), 2.84 (s, 3H, NCH_3), 3.41 (dd, *J* = 8.2, 8.1 Hz, 1H, C*H*CHAr), 3.54 (dd, *J* = 7.6, 6.9 Hz, 1H, C*H*CHCO$_2$Bu^t), 3.95 (dd, *J* = 6.4, 5.7 Hz, 1H, C*H*CO$_2$Bu^t), 4.45 (dd, *J* = 8.6, 5.8 Hz, 1H, CHAr), 7.24-7.31 (m, 5H, ArH); ^{13}C NMR δ_C: 24.9 (NCH_3), 28.0 [$CO_2C(CH_3)_3$], 47.8, 49.4 (2*C*HCON), 62.2 (*C*HCO$_2$Bu^t), 63.0 (*p*-Cl-CH), 82.6 [$CO_2C(CH_3)_3$], 128.3, 128.6 (ArCH), 133.9, 135.3 (ArC), 174.6, 175.6 (CON); MS (EI) *m/z* (%):364 (M^+, 0.21%), 265 (32), 264 (15), 263 (100), 178 (21), 151 (10), 143 (11), 57 (12); HRMS calcd. for $C_{18}H_{21}ClN_2O_4$: 364.1190, found: 364.1207 ; Microanalysis calcd. for $C_{18}H_{21}ClN_2O_4$: C, 59.3; H, 5.8; N, 7.7, found: C, 59.1; H, 5.8; N, 7.4; HPLC (Chiralcel ODH, 1 mL/min, *n*-hexane/*i*-PrOH: 80/20, λ 215 nm), t_{Rmaj} = 14.5 min, t_{Rmin} = 26.5 min.

*4.2.14. Methyl (1S,3R,3aS,6aR)-5-methyl-4,6-dioxo-3-(2-thienyl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate **12ha**.*[11h]

*4.2.15. Methyl (1S,3R,3aS,6aR)-1,5-dimethyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate **21**.*[11h]

*4.2.16. Methyl (1S,3R,3aS,6aR)-1-benzyl-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate **22**.*[11h]

*4.2.17. Methyl (1S,3R,3aS,6aR)-1-isobutyl-5-methyl-4,6-dioxo-3-(2-thienyl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate **23**.*[11h]

*4.2.18. Methyl (1S,3R,3aS,6aR)-5-ethyl-3-phenyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate **24**.*[12a,19]

*4.2.19. Methyl (1S,3R,3aS,6aR)-3,5-diphenyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate **25**.*[12a,19]

*4.2.20. Methyl (1S,3R,3aS,6aR)-5-ethyl-3a-methyl-3-phenyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate **27**.* (Isolated together isomer **28**): ^1H NMR δ_H:1.09 (t, *J* = 7.2 Hz, 3H, NCH_2CH_3), 1.49 (s, 3H, CCH_3), 2.39 (br s, 1H, NH), 3.12 (d, *J* = 6.4 Hz, 1H, C*H*CHCO$_2$CH$_3$), 3.43 (m, 2H, NC*H*$_2$CH$_3$), 3.87 (s, 3H, CO_2CH_3), 4.00 (br s, 1H, CHPh), 4.07 (d, *J* = 4.4, Hz, 1H, C*H*CO$_2$CH$_3$), 7.32-7.34 (m, 4H, ArH); ^{13}C NMR δ_C: 13.1 (CH_2CH_3), 20.0 (CCH_3), 33.9 (CH_2CH), 52.2 (CO_2CH_3), 54.5 (*C*HCON), 54.6 (*C*CH$_3$), 60.4 (*C*HCO$_2$Me), 71.9 (Ph-CH), 126.9, 128.2, 128.5 (ArCH), 136.6, 136.9 (ArC), 170.2, 173.9, 175.1 (CO_2Me and CON).

*4.2.21. Methyl (1S,3R,3aS,6aR)-5-ethyl-6a-methyl-3-phenyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate **28**.* (Isolated together isomer **27**). ^1H NMR δ_H:1.09 (t, *J* = 7.2 Hz, 3H, NCH_2CH_3), 1.60 (s, 3H, CCH_3), 2.39 (br s, 1H, NH), 2.98 (d, *J* = 8.4 Hz, 1H, C*H*CHPh), 3.43 (m, 2H, NC*H*$_2$CH$_3$), 3.71 (d, *J* = 3.4 Hz, 1H, C*H*CO$_2$CH$_3$), 3.87 (s, 3H, CO_2CH_3), 4.53 (dd, *J* = 8.2, 4.1, Hz, 1H, CHAr), 7.32-7.34 (m, 4H, ArH); ^{13}C NMR δ_C: 13.1 (CH_2CH_3), 20.0 (CCH_3), 33.9 (CH_2CH), 52.2 (CO_2CH_3), 54.6 (*C*CH$_3$), 56.9 (*C*HCON), 63.0 (Ph-CH), 68.2 (*C*HCO$_2$Me), 126.9, 128.2, 128.5 (ArCH), 136.6, 136.9 (ArC), 170.2, 177.3, 178.7(CO_2Me and CON)

*4.2.22. Dimethyl (2S,4S,5R)-5-phenylpyrrolidine-2,4-dicarboxylate **33a**.*[11b]

*4.2.23. 4-tert-Butyl 2-methyl (2S,4S,5R)-5-phenylpyrrolidine-2,4-dicarboxylate **33b**.*[11b]

*4.2.24. Trimethyl (2S,3S,4S,5R)-5-phenylpyrrolidine-2,3,4-tricarboxylate **34a**.*[12a,19]

*4.2.25. 3,4-Diisopropyl (2S,3S,4S,5R)-2-methyl-5-phenylpyrrolidine-2,3,4-tricarboxylate **34c**.* Sticky oil; $[\alpha]_D^{20}$ = 32,1º (*c* 0.5, $CHCl_3$.82% *ee* from HPLC); R_f: 0.37 (*n*-hexane/ethyl acetate: 3/2); IR (liq.) ν: 1741, 1731, 2982 cm^{-1}; ^1H NMR δ_H: 0.65 [d, *J* = 6.2 Hz, 3H, $CH(CH_3)_2$], 0.94 [d, *J* = 6.2 Hz, 3H, $CH(CH_3)_2$], 1.27 [d, *J* = 6.2 Hz,

3H, $CH(CH_3)_2$], 1, 28 [d, J = 6.2 Hz, 3H, $CH(CH_3)_2$], 2.86 (br s, 1H, NH), 3.55 (m, 2H, 2×C*H*CO_2Pr^i), 3.83 (s, 3H, CO_2CH_3), 4.14 (d, J = 7.3 Hz, 1H, $CHCO_2Me$), 4.56 [sept, J = 6.2 Hz, 1H, C*H*$(CH_3)_2$], 4.65 (d, J = 7.3 Hz, 1H, CH-Ph), 5.08 [sept, J = 6.2 Hz, 1H, C*H*$(CH_3)_2$], 7.22-7.34 (m, 5H, ArH); ^{13}C NMR δ_C: 20.8, 21.4, 21.6 [$CH(CH_3)_2$], 51.4, 52.4 ($CHCO_2Pr^i$), 53.8 (CO_2CH_3), 63.4 [$CHCO_2Me$], 65.2 (Ph-CH), 68.2, 68.8 [$CH(CH_3)_2$], 127.0, 127.7, 128.2 (ArCH), 138.4 (ArC), 170.5, 171.5, 171.6 (CO_2Me, CO_2Pr^i); MS (EI) *m/z* (%): 377 (M^+, 13.84%), 318 (33), 317 (23), 316 (23), 290 (20), 276 (17), 274 (12), 258 (38), 248 (15), 230 (43), 228 (17), 216 (10), 205 (25), 202 (50), 188 (47), 187 (23), 177 (67), 170 (34), 149 (12), 146 (29), 145 (46), 144 (100), 143 (29), 119 (22), 118 (19), 117 (96), 116 (14), 115 (28), 106 (11), 104 (10), 91 (12), 90 (10); HRMS calcd. for $C_{20}H_{27}NO_6$: 377.1838, found: 377.1863; HPLC (Chiralcel OD-H, 1 mL/min, *n*-hexane/*i*-PrOH: 80:20, λ 220 nm), t_{Rmaj} = 6.6 min, t_{Rmin} = 13.5 min.

4.2.26. 3,4-Diisobutyl 2-methyl (2S,3S,4S,5R)-5-phenylpyrrolidine-2,3,4-tricarboxylate ***35e***. Sticky oil; $[\alpha]_D^{20}$ = 47,1º (*c* 0.5, $CHCl_3$.82% *ee* from HPLC); R_f: (*n*-hexane/ethyl acetate: 1/5); IR (liq.) ν: 1737, 1730, 2958 cm^{-1}; ^{1}H NMR δ_H: 0.66 [d, J = 6.7 Hz, 3H, $CH(CH_3)_2$], 0.68 [d, J = 6.6 Hz, 3H, $CH(CH_3)_2$], 0.95 [d, J = 6.7 Hz, 6H, $CH(CH_3)_2$], 1.51 [d, J = 6.7 Hz, 1H, C*H*$(CH_3)_2$], 1.63 (br s, 1H, NH), 1.97 [d, J = 6.7 Hz, 1H, C*H*$(CH_3)_2$], 3.25 [dd, J = 10.5, 6.6 Hz, 1H, $CH_2CH(CH_3)_2$], 3.50 [dd, J = 10.6, 6.6 Hz, 1H, $CH_2CH(CH_3)_2$], 3.63 (m, 2H, 2×C*H*CO_2Bu^i), 3.83 (s, 3H, CO_2CH_3), 3.96 [m, 2H, $CH_2CH(CH_3)_2$], 4.19 (d, J = 7.3 Hz, 1H, $CHCO_2Me$), 4.66 (d, J = 7.5 Hz, 1H, CH-Ph), 7.25-7.32 (m, 5H, ArH); ^{13}C NMR δ_C: 18.8, 18.9, 19.0 [$CH(CH_3)_2$], 27.2, 27.7 [$CH(CH_3)_2$], 51.3 ($CHCO_2Bu^i$), 52.5 (CO_2CH_3), 54.0 ($CHCO_2Bu^i$), 63.4 [$CHCO_2Me$], 65.5 (Ph-CH), 71.1, 71.5 (CH_2), 126.9, 127.8, 128.3 (ArCH), 138.1 (ArC), 171.4, 172.1, 172.2 (CO_2Me, CO_2Bu^i); MS (EI) *m/z* (%): 405 (M^+, 10.61%), 346 (11), 345 (22), 332 (20), 304 (20), 272 (36), 245 (11), 244 (54), 219 (11), 202 (38), 188 (38), 178 (11), 177 (90), 170 (26), 164 (46), 155 (12).149 (14), 146 (54), 145 (46), 144 (82), 143 (24), 119 (12), 118 (19), 117 (100), 116 (13), 115 (21), 106 (11), 105 (11), 90 (11), 57 (46), 56 (21), 55 (12); HRMS calcd. for $C_{22}H_{31}NO_6$: 405.2151, found: 405.2171; HPLC (Chiralcel OD-H, 1 mL/min, *n*-hexane/*i*-PrOH: 80:20, λ 220 nm), t_{Rmaj} = 8.5 min, t_{Rmin} = 16.7 min.

4.2.27. Trimethyl (2S,3R,4S,5R)-5-phenylpyrrolidine-2,3,4-tricarboxylate ***35a***.[12a,19]

4.2.28. Methyl (2S,4S,5R)-4-cyano-5-phenylpyrrolidine-2-carboxylate ***36***.[29]

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