Switching Diastereoselectivity in Catalytic Enantioselective (3 + 2) Cycloadditions of Azomethine Ylides Promoted by Metal Salts and Privileged Segphos Derived Ligands

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Dedicated to the memory of Prof. Teruaki Mukaiyama

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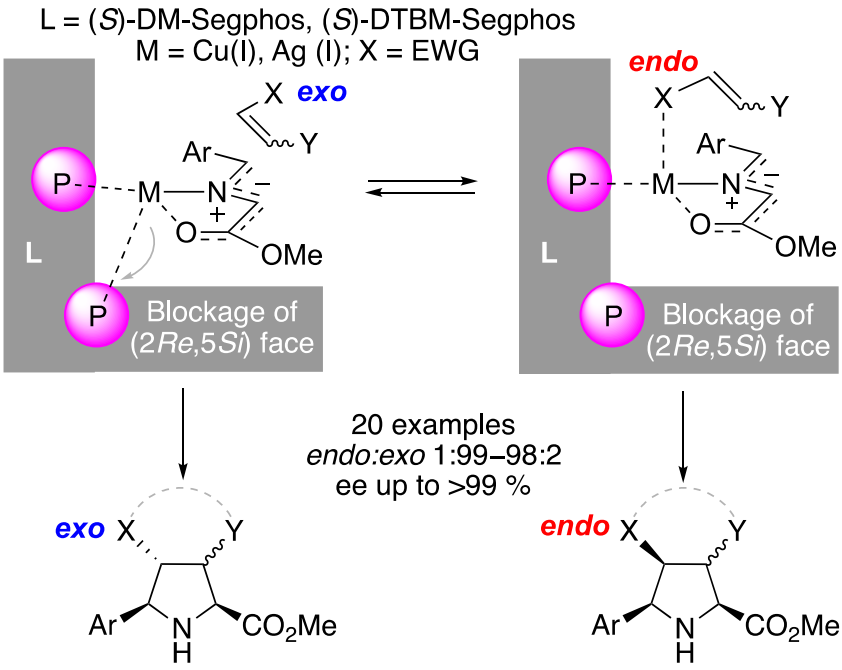
ABSTRACT: The catalytic enantioselective 1,3-dipolar cycloaddition between imino esters and electrophilic alkenes, employing chiral metal complexes derived from copper(I) and silver(I) salts and (*S*)-DM- or (*S*)-DTBM-Segphos as ligands resulted diasterodivergently giving either *exo*- or *endo*-cycloadducts, respectively. The effect of the functional group of the dipolarophile and the fine tuning of the catalyst play an important role promoting reverse diastereoselectivities. The origins of experimentally observed enantioselectivity and diastereoselectivity data, as well as the origin of the observed switched *endo:exo* ratios, are also explained by means of DFT calculations.



INTRODUCTION

The total control of the absolute configuration of the products in an asymmetric process is highly desirable. Much more attractive results the generation of different stereoisomers, starting from the same substrate, just modulating the structure of the catalyst. This last concept, considered as stereodivergence[1] is extremely efficient although not so frequent in asymmetric synthesis. However, the combination of different both homochiral ligands and metallic salts and the modification of the functional group in the substrate allows the design of catalytic reverse diastereoselective and or enantioselective processes.

Regarding catalytic enantioselective [3+2] 1,3-dipolar cycloadditions (1,3-DCs) [2] involving azomethine ylides and electrophilic alkenes, several enantiodivergent methodologies were based on switching primary/tertiary amine in a chiral ferrocenyl ligand·AgOAc,[3] or switching CuI/AgOAc in the presence of brucine diol as common ligand. [4] Besides, diastereodivergent processes (switching *endo*↔*exo* cycloadducts) were achieved by: a) modification of part of the structure of the same chiral ligand using a copper(II) salt,[5] or a copper(I) salt;[6,7] b) the employment of the same chiral ligand with different metal salts.[8,9,10]

During our search of optimal chiral catalysts for enantioselective 1,3-DC, employing privileged chiral ligands,[11] for the synthesis of key intermediates in the elaboration of natural or bioactive compounds, we found a weird behavior when the family of Segphos ligands was assessed. Not only changes in the ligand structure as well as the use of silver(I) or copper(I) salts but also the type of the dipolarophile resulted to be crucial.

It is known that chiral ligand Segphos **1** (Figure 1) has got a wide range of scope for catalytic enantioselective 1,3-DCs involving azomethine ylides.[2] Nevertheless, chiral ligands **2** and **3** (or their enantiomeric forms) have been extensively employed. Thus, (*S*)-DM-Segphos ligand **2**·$Cu(OTf)_2$ was employed into the *exo*-selective 1,3-DC of imino esters and benzoisothiazole-2,2-dioxide-3-ylidenes, [12] whereas **2**·AgOTf afforded *endo*-cycloadducts when α,β-unsaturated pyrazolamides were selected as dipolarophiles. [13] (*S*)-DTBM-Segphos ligand **3**·Cu^{I} complexes afforded *exo*-selectivity in the reactions of imino esters[14,15,16] with aryl alkenes,[17] acyclic activated 1,3-dienes,[18] (*E*)-*tert*-butyl 6-bromo-2-hexenoate, [19] 3-sulfonylpropenoates, [20] β-sulfonyl enones,[7] benzo[*b*]thiophene sulfones [21] and fullerenes.[8c,d] This analogous *exo*-diastereoselection [22] was found in 1,3-DC catalyzed by (*S*)-DTBM-Segphos ligand **3**·Ag^{I} complexes employing harsh reaction conditions,[23] when imino esters reacted with acrylic systems.[23b,c,24]

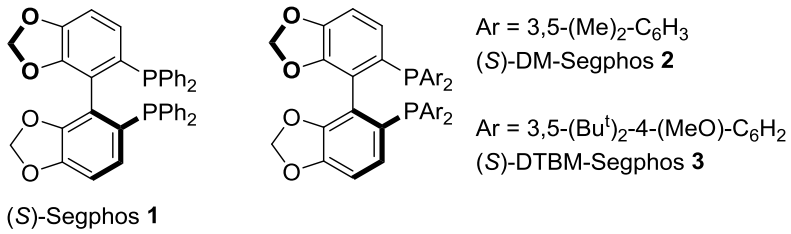


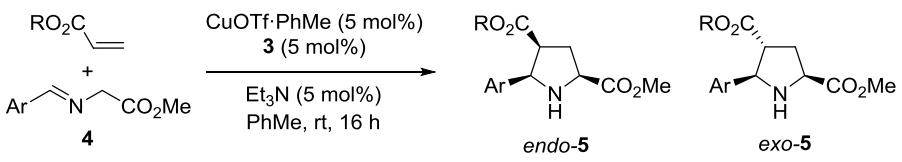
Figure 1. Privileged Segphos family ligands.

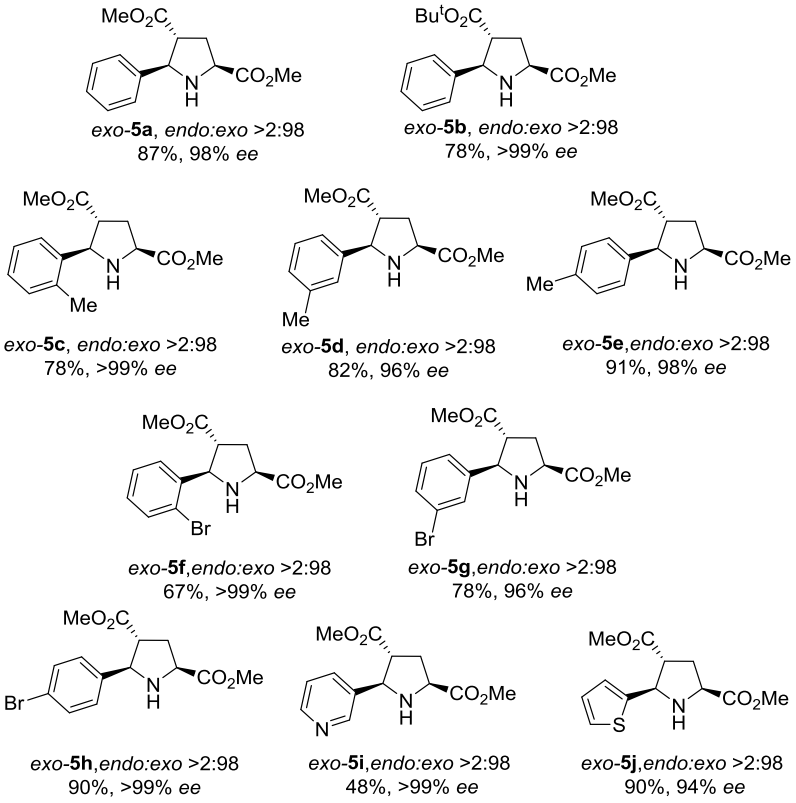
In this work, we describe the general scope of the 1,3-DC and study the origin of the complete reversal diastereoselectivity observed in the experimental results, involving chiral Segphos derived ligands **2** and **3** (Figure 1) with copper(I) or silver(I) salts.[25] We also try to rationalize these stereoselective outcomes by means of DFT computational analyses.

RESULTS AND DISCUSSION

Initially, a brief evaluation of the copper(I) and copper(II) salts with chiral ligands **2** and **3** was done choosing as benchmark reaction the 1,3-DC of imino ester **4a** (Ar = Ph) and methyl acrylate (see Table 1 in SI). Ligand **2** afforded better results in combination with CuOTf·PhMe complex achieving compound **5a** with very high *endo*:*exo* ratio (4:96) and high *ee* (88%). However, the combination of ligand **3**·copper(I) salt was much more suitable, in terms of the chemical yield achieved (87%), *dr* (2:98) and *ee* (98%) in the presence 5 mol% of triethylamine.[8c] On the other hand, this reaction without base did not proceeded at all. The absolute configuration of cycloadduct *exo*-**5a** was unambiguously assigned on the basis of the X-ray diffraction analysis of the corresponding *N*-phenylsulfonyl derivative NPS-*exo*-**5a** (see SI).[26]

The influence of the aryl moiety of the imino ester **4** was next evaluated. Such as shown in Scheme 1, methyl acrylate afforded excellent enantioselectivities in cycloadducts **5**, *o*-, *m*-, and *p*-substituted arenes and heteroarenes furnished very high enantiomeric excesses of the almost pure *exo*-diastereoisomer **5a**, **5c**-**5j**. In the same line, *tert*-butyl acrylate was an excellent dipolarophile for this enantioselective process giving enantiomerically pure cycloadduct *exo*-**5b**.

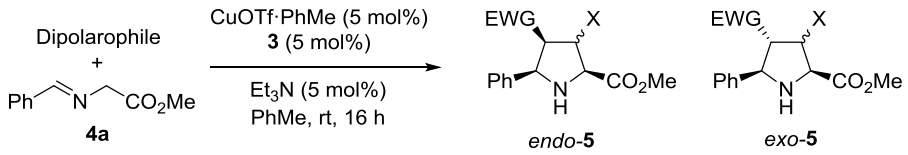


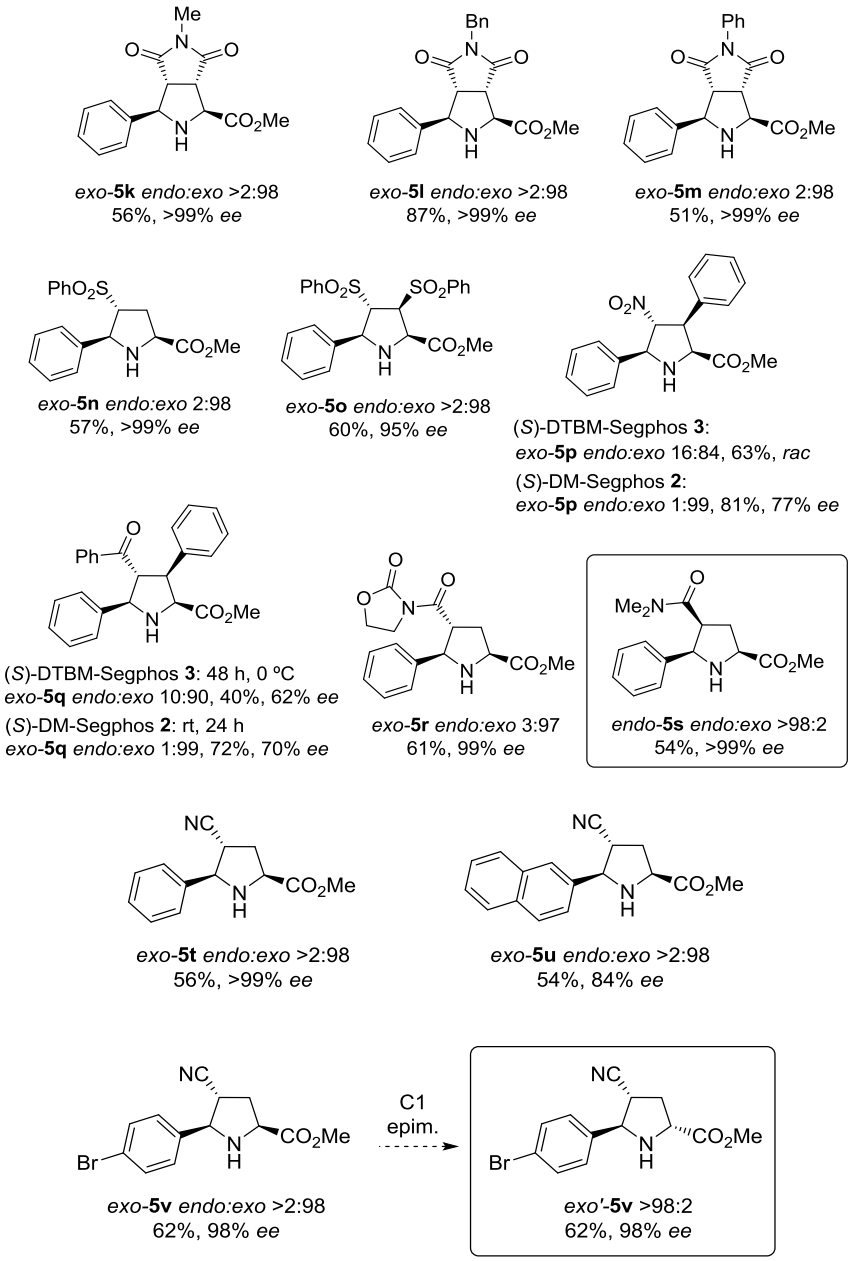


Scheme 1. Scope of the **3**·CuOTf·PhMe mediated 1,3-DC between acrylates and methyl arylideneglycinates **4**.

Maleimides also gave both excellent diastereo- and enantioselectivities for cycloadducts **5k**-**5m** derived from methyl benzylideneglycinate **4a** (Scheme 2). Alkenyl sulfones provided high optical purities in compounds *exo*-**5n** and *exo*-**5o**. When both β-nitrostyrene and chalcone were independently tested, the results obtained for molecules **5p** and **5q** in the presence of ligand **2** were better than the obtained in the reaction performed with ligand **3**. At this point, the individual analysis of the absolute configuration of the cycloadducts **5** was confirmed on the basis of already mentioned X-ray diffraction pattern, nOe analysis, specific optical rotation and HPLC analysis using columns with chiral stationary phases, comparing the data with the supplied ones in the literature for the same molecules.[27]

Surprisingly, a non-expected stereodivergency was found when *N,N*-dimethylacrylamide was employed obtaining the corresponding *endo*-diastereoisomer **5s** with 99% *ee*. Cycloadditions involving acrylonitrile deserve a special comment. The initial *exo*-control in compounds **5t-v** (99% *ee*, Scheme 2) was determined by comparison of the retention times of the known published data of HPLC using chiral coated columns with the analogous isolated adducts (see SI). The cycloadduct *exo*-**5v** underwent a very fast epimerization at C1,[28] which was detected two days after the isolation of the original *exo*-compounds during the preparation of the sample for the X-ray diffraction analysis. Although this test did not give appropriate diffraction patterns, nOe experiments and vibrational circular dichroism (VCD) analysis confirmed the proposed structure of these new *exo'*-cycloadduct **5v** (see SI).[29]



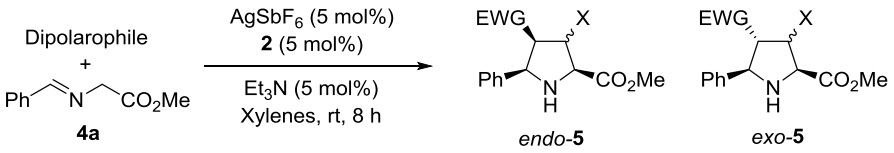


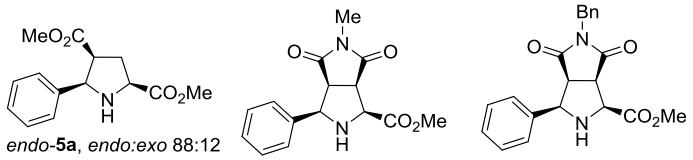
Scheme 2. Scope of the **3**·copper(I)-mediated 1,3-DC between several dipolarophiles and methyl benzylideneglycinate **4a**.

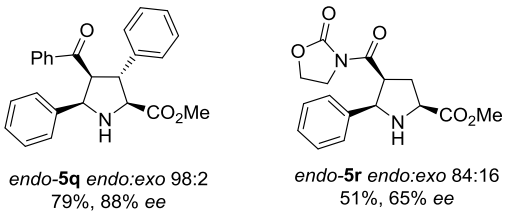
Looking for the diastereodivergent 1,3-DCs based on the change of copper by silver salts, the complex formed by **3** and different silver salts were tested for the benchmark reaction (see, Table 2 in SI). Surprisingly, again the *exo*-product **5a** was mainly obtained in 89% yield, 17:83 *endo:exo* ratio and 77% *ee* (in the

presence of $AgSbF_6$). However, the complex of ligand **2** with silver salts gave diastereodivergently mainly *endo*-**5a**, $AgSbF_6$ giving the best diastereoselectivities. Thus, the 1,3-DC of **4a** with methyl acrylate, mediated by **2**·$AgSbF_6$ afforded **5a** in 88:12 *endo:exo* ratio, 91% yield and 77% *ee* (Table 2 in SI). The reactions without base gave very poor results and no improvements were observed when chiral bases such as cinchonidine or cinchonine were added.[30]

With these optimal conditions in hands, the most representative dipolarophiles were assayed obtaining *endo*-cycloadducts **5** as major or unique diastereoisomer. In general, the enantioselectivities were good to excellent for maleimides, chalcone and *N*-acryloyloxazolidine-2-one (Scheme 3). Unfortunately, the enantioselective catalyzed reactions with phenyl vinyl sulfone, 1,2-bis(phenylsulfonyl)ethylene, *N,N*-dimethyl acrylamide and acrylonitrile afforded racemic *endo*-cycloadducts (>90:10 *endo:exo* ratio in all cases).







Scheme 3. Scope of the **2**·$AgSbF_6$–mediated 1,3-DCs between several dipolarophiles and methyl benzylideneglycinate **4a**.

At this point, we decided to perform DFT calculations [31] on selected reactions that capture the essentials of the factors that could be involved in the stereodivergent results found in our experimental studies. In particular, our aim was to unravel the *endo*:*exo* selectivities observed in the 1,3-DC of imino ester **4a** with methyl acrylate and acrylonitrile (*exo*-preference) or *N,N*-dimethylacrylamide (*endo*-preference) despite of using the same catalytic system [namely copper(I) salt in presence of chiral ligand **3**]. In addition, the reaction of imino ester **4a** with methyl acrylate in presence of Ag·**2** catalytic system was also analyzed. In previous reported theoretical studies[5b] we have demonstrated that the enantioselectivity observed in 1,3-DCs can be addressed to the effective blockage of one of the prochiral faces by the chiral ligand in the reactive complex. In addition, we have demonstrated that the *endo*:*exo* selectivities strongly depend on the metal coordination pattern and the counterion. [32] Remarkably, in the reaction presented here, the copper-induced diastereoselectivity is affected by the dipolarophile (*vide supra*). Recently, another unusual dipolarophile selectivity-biased (3 + 2) cycloaddition was reported. In this latter case the authors described dipolarophile–ligand π-π interactions as the driving force for the reaction outcome. [33]

Initial computational studies were performed analysing the possible initial copper(I) and silver(I) reactive complexes. Due to the chelating character of both **2** and **3** chiral ligands, at the beginning of the reaction, the metal atom is

coordinated to both phosphorus atoms of the ligand and to the nitrogen and the oxygen atoms of the 1,3-dipole precursor **4a**, thus fulfilling the preferred distorted tetrahedral environment of Cu and Ag central atoms. Once the dipolarophile approaches to the *in situ* formed metalated azomethine ylide, our initial hypothesis was twofold: (a) the coordination sphere of the metal is not affected by the interaction with the dipolarophile (**INT1** in Figure 2B); or (b) one of the M–P bonding interactions is replaced by a metal–oxygen interaction (**INT1'** in Figure 2B), thus incorporating the dipolarophile to the coordination sphere of the metallic centre. According to *hypothesis a*, since the coordination sphere of the metal is fulfilled and therefore the cyano or carboxamido group occupies a distal disposition with respect to the ester group of the azomethine ylide, *exo*–selectivity is expected in the corresponding (3+2) cycloadduct.[32] On the other hand, within *hypothesis b*, the previously mentioned M–O/M–N bonding interaction will act as the driving force towards preferential formation of *endo*-cycloadducts. Relative energies and main geometrical features of the computed *N*-metalated complexes are collected in Figure 2C.

Our results show that the binding affinity of the oxygen atom of methyl acrylate and the nitrogen atom of acrylonitrile are not strong enough to displace the phosphorus atom outside of the copper coordination sphere. Therefore, chelated species **INT1$_A$** and **INT1$_C$** are more stable than their open counterparts **INT1'$_A$** and **INT1'$_C$**. In the case of the interaction of **3**·Ag^I with methyl acrylate both reactive complexes are energetically closer to each other, with an energy difference for **INT1'$_D$** of 2 kcal·mol^{-1} with respect to **INT1$_D$**. On the other hand, the oxygen atom of *N,N*-dimethylacrylamide can displace one of the phosphorus atoms of **3**, being complexes **INT1'$_B$** the most stable ones in these cases. All

attempts to isolate species in which the nitrogen atom of *N,N*-dimethylacrylamide interacts with the metallic centre lead to uncoordinated species in few optimization steps (see Supporting Information for further details about other reactive complexes not included in Figure 2). This difference in the metal binding affinity can be addressed to a stronger metal–oxygen Coulombic interaction as a consequence of the higher charge of the oxygen atom in *N,N*-dimethylacrylamide[natural bond orbital (NBO) charge of -0.64 e *vs* -0.57 e in methyl acrylate. Remarkably, in all cases the chiral ligands **2** and **3** efficiently block the (2*Re*,5*Si*) prochiral face.

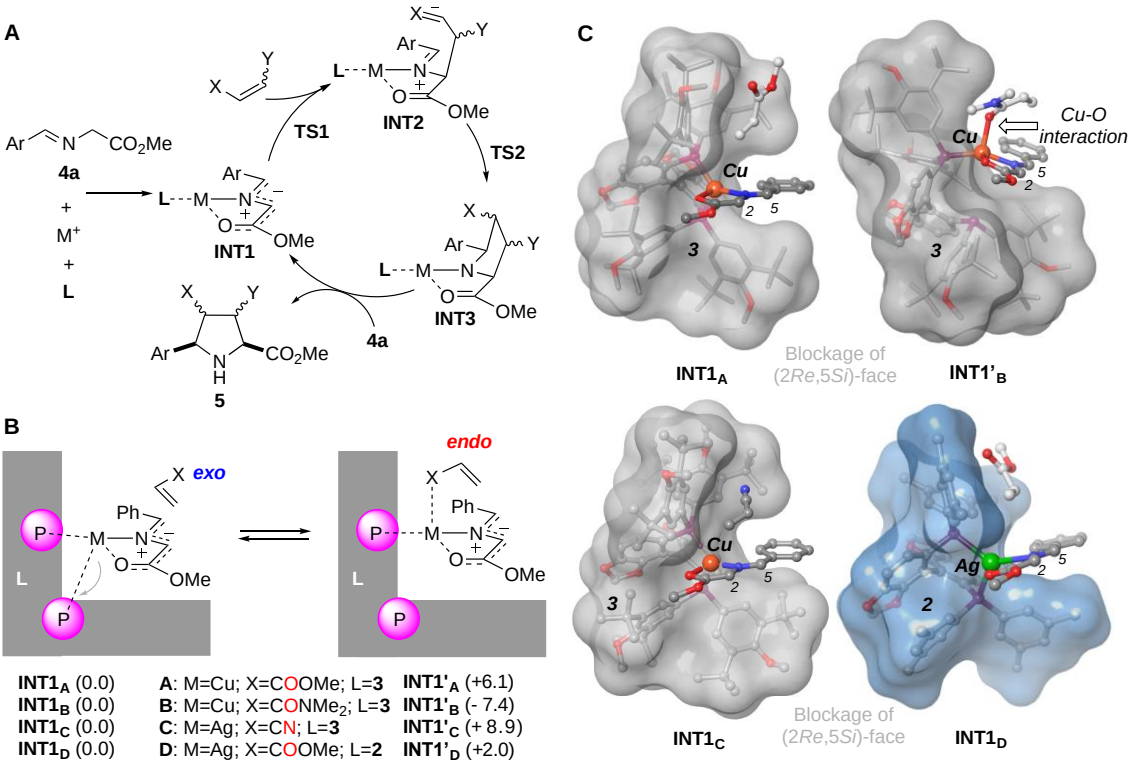


Figure 2. (A) Generally accepted stepwise mechanism of the metal catalyzed [3+2] cycloaddition. (B) Relative Gibbs free energies (in kcal·mol^{-1}) of reactive complexes associated with the 1,3-DC reaction of **4a** with methyl acrylate, *N,N*-dimethylacrylamide or acrylonitrile catalyzed by **3**·Cu(I) catalytic systems,

computed at B3LYP-D3/6-31G*&LANL2DZ/ONIOM(B3LYP/LANL2DZ:PM6) level of theory or **2**·Ag(I) catalytic system for the 1,3-DC of methyl acrylate and **4a** computed at B3LYP-D3/6-31G*&LANL2DZ level. Atoms capable to coordinate to the metal center are highlighted in red. (C) Main geometrical features of the most stable reactive complexes.

According to the widely accepted catalytic cycle associated with metal catalyzed 13-DCs, the reaction corresponds to a Michael addition–intramolecular Mannich stepwise mechanism, in which the stereochemical outcome of the whole reaction is determined in the first step (Figure 2A).[5b,17 ,30] The main geometrical features and the relative Gibbs free energies of the least energetic transition structures, corresponding to the first step of the reaction paths gathered in Figure 2, are collected in Figure 3 (see Supporting Information for the complete energetic profiles associated with the corresponding catalytic cycles).

Our calculations show that in the two least energetic transition structures associated with the 1,3-DC of imino ester **4a** with methyl acrylate catalyzed by **3**·Cu^{I} (**TS1$_A$**-*exo* and **TS1$_A$**-*exo*' in Figure 3) the dipolarophile approaches the azomethine ylide according to the *exo*-mode. This is a consequence of the absence of a copper vacant coordination site that would allow the stabilizing interaction between the oxygen atom and the metallic centre (*hypothesis a*). Indeed, the calculated enantioselectivity towards formation of *exo*-**5a** is ee_{calc} = 99, which is in excellent agreement with the experimental evidence (Scheme 2).

The opposite scenario is observed for *N,N*-dimethylacrylamide as dipolarophile. In this case, the existence of a strong Cu–O=C-NMe_2 interaction that displaces one of the P atoms of the ligand favours the *endo*-approach of the dipolarophile (*hypothesis b*). As in the previous case, the effective blockage of the (2*Re*,5*Si*) face, due to the chiral ligand, promotes an energetic difference of 3.4 kcal·mol^{-1} between **TS1$_B$**-*endo* and **TS1$_B$**-*endo*' due to the higher deformation energy required in the latter to reach the required TS geometry. In this case, the theoretical enantioselectivity towards *endo*-**5s** is ee_{calc} = 99, which also corresponds to a perfect match with experimental evidence (Scheme 1).

As far as acrylonitrile dipolarophile is concerned, our calculations show the preferential formation of *exo*-cycloaddutcs (**TS1**$_C$-*exo* in Figure 3). As in the imino ester **4a** case, the least energetic transition state shows a fulfilled metallic center coordination sphere, thus promoting the *exo*–conformation. However, the nitrogen atom of the CN group is also capable to displace a P catalytic atom (**TS1**$_C$-*endo* in Figure 3). Therefore, formation of *exo*-**5t** is computationally predicted, with high enantioselectivity (ee_{calc} = 99) and low diastereoselectivity (12:88 *exo*:*endo*), in nice agreement with the experimental evidences.

When **2**·Ag^I was analyzed as catalyst in the 1,3-DC of imino ester **4a** with methyl acrylate, preferential formation of *endo*-cycloadducts was not expected since methyl acrylate is, in principle, not able to shift the stronger Ag–P bond[34] in the most stable intermediate reactive complex **INT1$_D$** (*vide supra*). However, in the first TS of the stepwise cycloaddition the silver(I) centre is able to adopt a distorted bipyramidal geometry that permits the interaction of the metallic centre with the 1,3-dipole, the oxygen atom of the dipolarophile and both P atoms of the

chiral ligand **2**. Within this geometry, one of the Ag–P bonds is elongated, but still kept, thus allowing the interaction with the incoming dipolarophile. In this case, the energy difference between **TS1$_D$**-*endo* and **TS1$_D$**-*endo*' is rather small (0.7 kcal·mol^{-1}), therefore a lower enantioselectivity towards *endo*-**5a** is theoretically computed (ee_{calc} = 55). In addition, since there is no complete cleavage of Ag–P bonding interactions in silver(I) systems, the ligand remains doubly coordinated to the metallic centre. As a consequence, the use of catalytic system **3**·Ag(I) would not favour e*ndo* adducts formation (Table 2 in the Supporting Information) because of the hindrance of dipolarophile-metal interaction hampered by the bulky Bu^t groups that hindered any dipolarophile–metal interaction (see Supporting Information for further details about DFT calculations of this reaction).

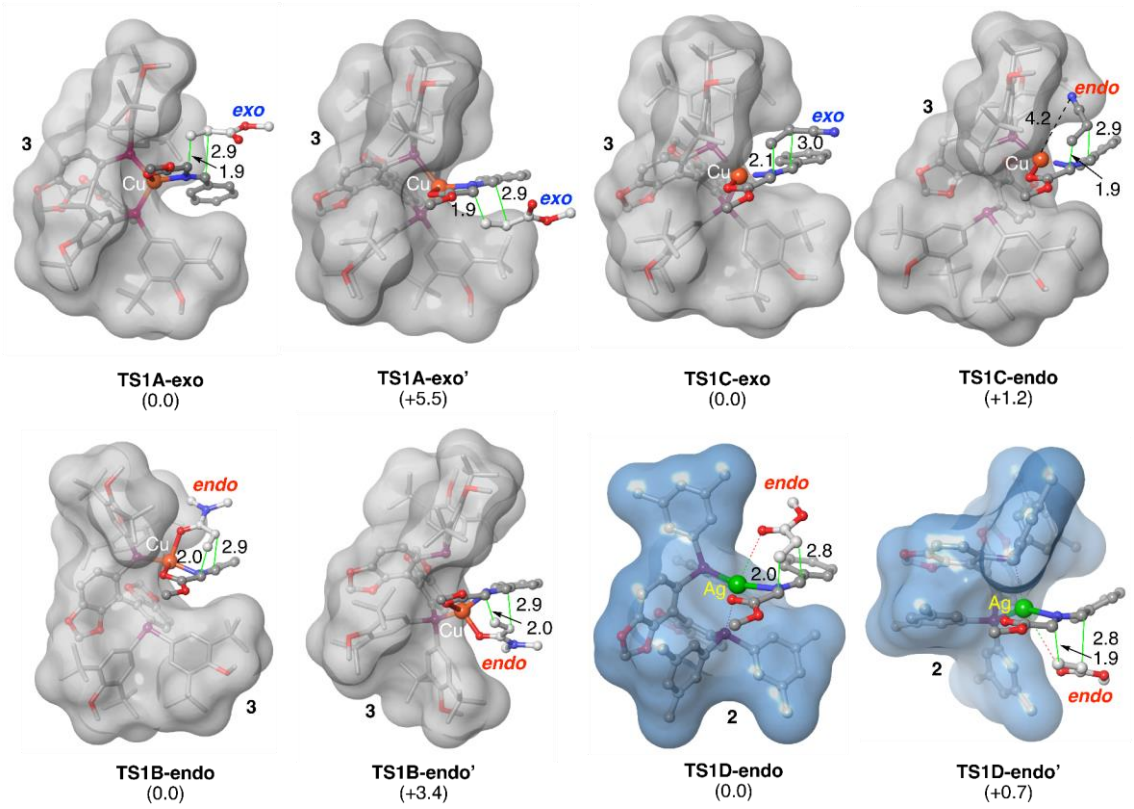


Figure 3. Relative Gibbs free energies (in kcal·mol^{-1}) of the least energetic transition structures associated with the reaction of **4a** with methyl acrylate, *N,N*-

dimethylacrylamide or acrylonitrile catalyzed by **3**·Cu(I) catalytic system computed at B3LYP-D3/6-31G*&LANL2DZ/ONIOM(B3LYP/LANL2DZ:PM6) or catalyzed by **2**·Ag(I) for the 1,3-DC of methyl acrylate and **4a** computed at B3LYP-D3/6-31G*&LANL2DZ level. In ONIOM calculations, Ball&stick and wire models correspond to the high and low level layers, respectively. Distances are in Å.

CONCLUSION

The (*S*)-DTBM-Segphos·CuOTf·PhMe complex promoted efficiently the *exo*-enantioselective 1,3-DC of stabilized azomethine ylides derived from imino esters and electrophilic alkenes different from *N,N*-dimethylacrylamide. However, with these last alkene a total enantioselective *endo*-approach was observed. In both approaches the final *ee*'s were excellent. In some cases, the employment of (*S*)-DM-Segphos·CuOTf·PhMe was crucial for the increment of the enantioselectivity. A switch of the diastereoselectivity was achieved when (*S*)-DM-Segphos·$AgSbF_6$ was used as catalyst. These results demonstrate the strong influence of the ligand structure in the diastereoselectivity in the (3 + 2) cycloadditions mediated by (*S*)-DM-Segphos·$AgSbF_6$ *versus* the observed one in the reaction run with (*S*)-DTBM-Segphos·$AgSbF_6$. In addition, an unexpected substrate-dependent reverse diastereoselectivity was demonstrated with the (*S*)-DTBM-Segphos·CuOTf·PhMe complex using *N,N*-dimethyl acrylamide. DFT analysis of the corresponding transition structures permitted to identify the origins of the *exo* to *endo* switching of diasteroselectivity in the case of these dipolarophiles with an amido group. The most important feature of this shift is the alteration of the coordination of the copper(I) sphere, which changes from a

bidentate to a monodentate mode of the bisphosphane-copper complex, thus allowing the coordination of the dipolarophile in an *endo*-mode . On the other hand, the change from *exo*- to *endo*-diasteroselectivity promoted by (*S*)-DM-Segphos·$AgSbF_6$ is due to a stronger bidentate coordination between the diphosphine ligand and the silver cation in a distorted bipyramidal geometry that permits the interaction of the metallic center with the 1,3-dipole. *Exo'*-cycloadducts bearing a nitrile group at 3-position, formed through epimerization in the C1 of the original *exo*-cycloadducts (stable around 1.5 days at rt), are more stable stereoisomers.

EXPERIMENTAL SECTION

1. General

All commercially available reagents and solvents were used without further purification, only aldehydes were also distilled prior to use. Analytical TLC was performed on Schleicher & Schuell F1400/LS 254 silica gel plates, and the spots were visualised under UV light (λ = 254 nm). Flash chromatography was carried out on hand packed columns of Merck silica gel 60 (0.040-0.063 mm). Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. Optical rotations were measured on a Perkin Elmer 341 polarimeter with a thermally jacketted 5 cm cell at approximately 25˚C and concentrations (*c*) are given in g/100 mL. The structurally most important peaks of the IR spectra (recorded using a Nicolet 510 P-FT) are listed and wavenumbers are given in cm^{-1}. NMR spectra were obtained using a Bruker AC-300 or AC-400 and were recorded at 300 or 400 MHz for ^{1}H NMR and 75 or 100 MHz for $^{13}C\{1H\}$ NMR,

using $CDCl_3$ as the solvent and TMS as internal standard (0.00 ppm) unless otherwise stated. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet q = quartet, m = multiplet or unresolved and br s = broad signal. All coupling constants (*J*) are given in Hz and chemical shifts in ppm. $^{13}C\{1H\}$ NMR spectra were referenced to $CDCl_3$ at 77.16 ppm. 2D-COSY experiments were performed for the NMR peak assignments for compounds *exo*-**5r** and *endo*-**5r** (in $CDCl_3$ and C_6D_6). 2D-NOESY experiments of *exo*-**5h**, *exo*-**5i**, *exo*-**5o**, and simple nOe of *exo*-**5t**, *exo*-**5r**, *endo*-**5r**, *endo*-**5s** and ***exo'*-5v** were crucial to control the relative configuration of all series of the reaction products. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV using a Shimadzu QP-5000 by injection or DIP; fragment ions in *m/z* are given with relative intensities (%) in parentheses. High-resolution mass spectra (HRMS) were measured on an instrument using a quadrupole time-of-flight mass spectrometer (QTOF) and also through the electron impact mode (EI) at 70 eV using a Finnigan VG Platform or a Finnigan MAT 95S. Enantiomeric excesses were determined by using a JASCO-2000 series equipped with a chiral column using mixtures of *n*-hexane/isopropyl alcohol as the mobile phase at 25 ˚C.

Computational methods: All the computational mechanistic studies were carried out with the Gaussian09[35] suite of programs. Density functional Theory (DFT) geometry optimizations and harmonic analysis were performed with the B3LYP[36] functional. Relative energies were computed by means of single-point calculations on the optimized geometries with the M06-2X[37] functional.

This latter functional was chosen because it is well suited for the treatment of nonbonding interactions and dispersion forces in densely substituted

interacting systems[38] and produce similar geometries to B3LYP, [39] although it tends to slightly overestimate the barriers of hetero Diels Alder reactions. [40]

The 6-31G* basis set was used. Solvent effects were computed with the PCM method using toluene as solvent. [41] All the stationary points were characterized by harmonic analysis. Reactants, intermediates and products showed positive definite Hessian values. Transition structures (TSs) showed one and only one imaginary frequency associated with nuclear motion along the chemical transformation. Activation and reaction (Gibbs) energies were calculated at 298.15 K. Figures including optimized structures were made with Maestro[42] and CYL-view[43] programs. Orbital diagrams were prepared by using the Gauss-view interface. [44]

2. Conventional Procedure for the Synthesis of known α-Imino Esters.

The amino ester (1.1 mmol) was dissolved in DCM (2 mL) and aldehyde (1 mmol) and Et_3N (1.1 mmol) were added. The mixture was then stirred for 16 h at room temperature. The reaction was quenched with (sat. aq.) NaCl, extracted with DCM (3x10 mL) and dried over $MgSO_4$.

Methyl (*E*)-2-(benzylideneamino)acetate (4a): (154 mg, 87%). All spectra were in agreement with reported data;[45] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.78 (s, 3H), 4.42 (s, 2H), 7.40-7.48 (m, 3H), 7.78 (d, *J* = 8.0 Hz, 2H), 8.29 (s, 1H).

Methyl (*E*)-2-[(2-methylbenzylidene)amino]acetate (4c): (172 mg, 90%). All spectra were in agreement with reported data;[46] ^{1}H NMR (300 MHz, $CDCl_3$): δ =

2.52 (s, 3H), 3.78 (s, 3H), 4.44 (s, 2H), 7.09-7.37 (m, 3H), 7.93 (dd, *J* = 7.7, 1.6 Hz, 1H), 8.60 (s, 1H).

Methyl (*E*)-2-[(3-methylbenzylidene)amino]acetate (4d): (174 mg, 91%). All spectra were in agreement with reported data;[45] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (s, 3H), 3.78 (s, 3H), 4.42 (s, 2H), 7.21-7.78 (m, 4H), 8.26 (s, 1H).

Methyl (*E*)-2-[(4-methylbenzylidene)amino]acetate (4e): (180 mg, 94%). All spectra were in agreement with reported data;[45] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (s, 3H), 3.77 (s, 3H), 4.40 (s, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.67 (d, *J* = 8.1 Hz, 2H), 8.25 (s, 1H).

Methyl (*E*)-2-[(2-bromobenzylidene)amino]acetate (4f): (210 mg, 82%). All spectra were in agreement with reported data;[46] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3H), 4.47 (s, 2H), 7.27-7.34 (m, 2H), 7.56-7.62 (m, 1H), 8.09 (d, *J* = 7.6 Hz, 1H), 8.67 (s, 1H).

Methyl (*E*)-2-[(3-bromobenzylidene)amino]acetate (4g): (223 mg, 87%). All spectra were in agreement with reported data;[47] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3H), 4.42 (s, 2H), 7.27-7.34 (m, 1H), 7.54-7.62 (m, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.98 (s, 1H), 8.23 (s, 1H).

Methyl (*E*)-2-[(4-bromobenzylidene)amino]acetate (4h): (228 mg, 89%). All spectra were in agreement with reported data;[47] ^{1}H NMR (300 MHz, $CDCl_3$): δ =

3.78 (s, 3H), 4.41 (s, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 8.24 (s, 1H).

Methyl (*E*)-2-[(thiophen-2-ylmethylene)amino]acetate (4j): (156 mg, 85%). All spectra were in agreement with reported data;[46] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77 (s, 3H), 4.38 (s, 2H), 7.07-7.11 (m, 1H), 7.36-7.40 (m, 1H), 7.45 (dd, *J* = 5.0, 1.1 Hz, 1H), 8.39 (s, 1H).

Methyl (*E*)-2-[(pyridin-2-ylmethylene)amino]acetate (4l): (142 mg, 80%). All spectra were in agreement with reported data;[48] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3H), 4.46 (s, 2H), 7.33-7.48 (m, 1H), 8.19 (d, *J* = 7.9 Hz, 1H), 8.35 (s, 1H), 8.65-8.75 (m, 1H), 8.90 (s, 1H).

Methyl (*E*)-2-[(naphthalen-2-ylmethylene)amino]acetate (4m): (204, 90%). All spectra were in agreement with reported data;[45] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3H), 4.46 (s, 2H), 7.45-8.12 (m, 7H), 8.42 (s, 1H).

3. General Experimental Procedure for the 1,3 Dipolar Cycloaddition of α-Imino Esters and Dipolarophiles.

Method A: In a flask was added CuOTf·PhMe (2.59 mg, 0.05 mmol), and (*S*)-DTBM-Segphos **3** (11.80 mg, 0.05 mmol) and toluene (1 mL), the resulting mixture was stirred for 1 h. Then, was added a solution of α-imino ester (0.2 mmol), dipolarophile (0.2 mmol) in toluene (1 mL). To the resulting suspension

trimethylamine (1.39 µL, 0.05 mmol) was added and the mixture stirred at room temperature (20 – 35 ˚C) for 16 – 24 h. The crude reaction mixture was filtered through a small Celite path and the residue was purified by flash chromatography yielding pure *exo*-cycloadducts or *endo*-cycloadducts, respectively.

Method B: In a covered flask by aluminium foil was added $AgSbF_6$ (3.34 mg, 0.05 mmol), and (*S*)-DM-Segphos **2** (7.22 mg, 0.05 mmol) and mixture of xylenes (1 mL), the resulting mixture was stirred for 1 h. Then, was added a solution of α-imino ester (0.2 mmol), dipolarophile (0.2 mmol) in mixture of xylenes (1 mL). To the resulting suspension trimethylamine (1.39 µL, 0.05 mmol) was added and the mixture stirred at room temperature (20 - 35 ˚ C) for 16 – 24 h. The crude reaction mixture was filtered through a small Celite path and the residue was purified by flash chromatography yielding pure endo-cycloadducts.

Dimethyl (2*S*,4*R*,5*R*)-5-phenylpyrrolidine-2,4-dicarboxylate (***exo*-5a**): All spectra were in agreement with reported data.[8c, 49] Purification by flash chromatography (*n*-Hexane-EtOAc 8:2). Pale yellow liquid (46 mg 87 % yield); Enantiomeric excess (98 % *ee*) was determined by HPLC. Chiralcel OD-H *n*-hexane/isopropyl alcohol = 90/10, 1.0 mL/min, t_{Rmaj}: 11.1 min, t_{Rmin}: 26.8 min, 220.5 nm. $[\alpha]_D^{28}$ = +45.6 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35-2.54 (m, 2H, C*H*$_2$), 2.74 (br s, 1H, N*H*), 2.94 (q, *J* = 8.6 Hz, 1H, PhCHC*H*), 3.64 (s, 3H, OC*H*$_3$), 3.78 (s, 3H, OC*H*$_3$), 4.06 (dd, *J* = 8.8, 5.5 Hz, 1H, NHC*H*CH$_2$), 4.44 (d, *J* = 8.6 Hz, 1H, PhC*H*), 7.25-7.37 (m, 3H, Ar*H*), 7.43-7.46 (m, 2H, Ar*H*). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ = 34.4 (*C*H$_2$), 51.0 (CH$_2$*C*HCO), 52.1, 52.6 (2xO*C*H$_3$), 59.3 (NH*C*HCO), 66.6 (Ph*C*HNH), 127.1, 128.1, 128.8, 140.4 (Ar*C*), 173.5, 174.2 (2x*C*=O).

4-(*tert*-Butyl) 2-methyl (2*S*,4*R*,5*R*)-5-phenylpyrrolidine-2,4-dicarboxylate (***exo*-5b**): All spectra were in agreement with reported data.[49,50] Purification by flash chromatography (*n*-Hexane-EtOAc 6:4). Pale yellow liquid (48 mg, 78 % yield); Enantiomeric excess (>99 % *ee*) was determined by HPLC. Chiralpak AS-H *n*-hexane/isopropyl alcohol = 95/5, 1.0 mL/min, t_{Rmaj}: 7.9 min, t_{Rmin}: 9.7 min, 220.5 nm. $[\alpha]_D^{28}$ = -38.7 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 [s, 9H, CH(C*H*$_3$)$_3$], 2.30-2.56 (m, 2H, C*H*$_2$), 2.82 (br s, 1H, N*H*), 2.80-2.90 (m, 1H, PhCHC*H*), 3.78 (s, 3H, OC*H*$_3$), 4.04 (dd, *J* = 9.0, 5.3 Hz, 1H, NHC*H*CH$_2$), 4.35 (d, *J* = 8.7 Hz, 1H, PhC*H*), 7.25-7.37 (m, 3H, Ar*H*), 7.42-7.47 (m, 2H, Ar*H*). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ = 28.0 [(CH_3)$_3$], 34.4 (*C*H$_2$), 51.1 (CH$_2$*C*HCOOCH$_3$), 52.5 (OCH$_3$), 59.3 (NH*C*HCO), 66.7 (Ph*C*HNH), 81.1 [O*C*H(CH$_3$)$_3$], 127.0, 128.0, 128.7, 140.8 (Ar*C*), 172.5, 173.7 (2x*C*=O).

Dimethyl (2*S*,4*R*,5*R*)-5-(2-methylphenyl)pyrrolidine-2,4-dicarboxylate (***exo*-5c**): Purification by flash chromatography (*n*-Hexane-EtOAc 6:4). Pale yellow liquid (43 mg, 78 % yield). Enantiomeric excess (>99 % *ee*) was determined by HPLC. Chiralpak AS-H *n*-hexane/isopropyl alcohol = 90/10, 1.0 mL/min, t_{Rmaj}: 8.9 min, t_{Rmin}: 12.2 min, 220.5 nm. IR (neat) υ_{max}: 2954, 2362, 2342, 1437, 1362, 1266, 1117, 1011, 703 cm^{-1}. $[\alpha]_D^{28}$ = + 55.3 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33-2.40 (m, 1H, C*H*$_2$), 2.38 (s, 3H, C*H*$_3$), 2.54 (ddd, *J* = 13.1, 8.7, 7.9 Hz, 1H, C*H*$_2$), 2.90 (br s, 1H, N*H*), 2.98 (q, *J* = 8.1 Hz, 1H, PhCHC*H*), 3.64 (s, 3H, OC*H*$_3$), 3.79 (s, 3H, OC*H*$_3$), 4.10 (dd, *J* = 8.7, 6.0 Hz, 1H, NHC*H*CH$_2$), 4.71 (d, *J* = 8.0 Hz, 1H, PhC*H*), 7.15-7.27 (m, 3H, Ar*H*), 7.58 (dd, *J* = 7.5, 1.4 Hz, 1H, Ar*H*). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ = 19.5 (*C*H$_3$), 34.4 (*C*H$_2$), 50.4

(CH_2CHCO), 52.2, 52.7 (2xOCH_3), 59.4 (NH*C*HCO), 62.3 (Ph*C*HNH), 126.0, 126.7, 127.9, 130.7, 136.8, 138.2 (Ar*C*), 173.5, 174.1 (2x*C*=O). MS (EI) *m/z*: 277 (M^+, 9%), 219 (14), 218 (100), 191 (47), 186 (27), 160 (17), 158 (53), 143 (17), 131 (54), 130 (24), 118 (16), 115 (20), 91 (16). HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{15}H_{19}NO_4$ 277.1314; Found 277.1317.

Dimethyl (2*S*,4*R*,*5*R)-5-(3-methylphenyl)pyrrolidine-2,4-dicarboxylate (***exo*-5d**): Purification by flash chromatography (*n*-Hexane-EtOAc 6:4). Pale yellow liquid (45 mg, 82 % yield). Enantiomeric excess (95 % *ee*) was determined by HPLC. Chiralcel OD-H *n*-hexane/isopropyl alcohol = 90/10, 1.0 mL/min, t_{Rmaj}: 12.4 min, t_{Rmin}: 42.2 min, 220.5 nm. IR (neat) υ_{max}: 2954, 1734, 1608, 1436, 1363, 1266, 1116, 1011, 940, 886, 734 cm^{-1}. $[\alpha]_D^{28}$ = + 47.1 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3H, C*H*$_3$), 2.36-2.44 (m, 1H, C*H*$_2$), 2.46-2.55 (m, 1H, C*H*$_2$), 2.96 (br s, 1H, N*H*), 2.88-2.99 (m, 1H, PhCHC*H*), 3.64 (s, 3H, OC*H*$_3$), 3.78 (s, 3H, OC*H*$_3$), 4.06 (dd, *J* = 8.8, 5.6 Hz, 1H, NHC*H*CH_2), 4.40 (d, *J* = 8.7 Hz, 1H, PhC*H*), 7.08-7.11 (m, 1H, Ar*H*), 7.22-7.27 (m, 3H, Ar*H*). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$): δ =21.6 (*C*H_3), 34.5 (*C*H_2), 50.9 (CH_2CHCO), 52.1, 52.6 (2xOCH_3), 59.3 (NH*C*HCO), 66.7 (Ph*C*HNH), 124.1, 127.8, 128.7, 128.9, 138.5, 140.0 (Ar*C*), 173.5, 174.1 (2x*C*=O). MS (EI) *m/z*: 277 (M^+, 11%), 219 (16), 218 (100), 191 (12), 191 (60), 186 (33), 160 (19), 158 (74), 143 (20), 131 (51), 130 (18), 115 (17), 91 (17). HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{15}H_{19}NO_4$ 277.1314; Found 277.1308.

Dimethyl (2*S*,4*R*,5*R*)-5-(4-methylphenyl)pyrrolidine-2,4-dicarboxylate (***exo*-5e**): Purification by flash chromatography (*n*-Hexane-EtOAc 6:4). Pale yellow liquid (50 mg, 91 % yield); Enantiomeric excess (98 % *ee*) was determined by

HPLC. Chiralcel OD-H *n*-hexane/isopropyl alcohol = 90/10, 1.0 mL/min, t_{Rmaj}: 9.7 min, t_{Rmin}: 30.4 min, 220.5 nm. IR (neat) υ_{max}: 2954, 2361, 2341, 1734, 1435, 1363, 1200, 1169, 1115, 1020, 1011, 702, 651 cm^{-1}. $[\alpha]_D^{28}$ = + 46.1 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3H, C*H*$_3$), 2.37-2.58 (m, 2H, C*H*$_2$), 2.93 (br s, 1H, N*H*), 2.86-2.95 (m, 1H, PhCHC*H*), 3.63 (s, 3H, OC*H*$_3$), 3.78 (s, 3H, OC*H*$_3$), 4.05 (dd, *J* = 8.9, 5.4 Hz, 1H, NHC*H*CH$_2$), 4.39 (d, *J* = 8.8 Hz, 1H, PhC*H*), 7.15 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.33 (d, *J* = 8.1 Hz, 2H, Ar*H*). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$): δ = 21.2 (*C*H$_3$), 34.5 (*C*H$_2$), 50.9 (CH$_2$*C*HCO), 52.1, 52.6 (2xO*C*H$_3$), 59.2 (NH*C*HCO), 66.5 (Ph*C*HNH), 127.0, 129.5, 137.2, 137.8 (Ar*C*), 173.5, 174.2 (2x*C*=O). MS (EI) *m/z*: 277 (M^+, 7%), 276 (10), 246 (12), 219 (14), 218 (100), 191 (93), 186 (43), 160 (20), 158 (86), 143 (25), 131 (69), 130 (18), 128 (13), 115 (19), 91 (18). HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{15}H_{19}NO_4$ 277.1314; Found 277.1310.

Dimethyl (2*S*,4*R*,5*R*)-5-(2-bromophenyl)pyrrolidine-2,4-dicarboxylate (***exo*-5f**): Purification by flash chromatography (*n*-Hexane-EtOAc 6:4). Brown liquid (46 mg, 67 % yield); Enantiomeric excess (>99 % *ee*) was determined by HPLC. Chiralpak AS-H *n*-hexane/isopropyl alcohol = 90/10, 1.0 mL/min, t_{Rmaj}: 12.4 min, t_{Rmin}: 14.6 min, 220.5 nm. IR (neat) υ_{max}: 2954, 1734, 1436, 1200, 1265, 1169, 1022, 757, 735, 702 cm^{-1}. $[\alpha]_D^{29}$ = - 44.8 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.31 (ddd, *J* = 13.1, 8.4, 7.3 Hz, 1H, C*H*$_2$), 2.51 (ddd, *J* = 13.1, 8.1, 6.1 Hz, 1H, C*H*$_2$), 2.96 (br s, 1H, N*H*), 2.94-3.01 (m, 1H, PhCHC*H*), 3.69 (s, 3H, OC*H*$_3$), 3.79 (s, 3H, OC*H*$_3$), 4.13-4.18 (m, 1H, NHC*H*CH$_2$), 4.93 (d, *J* = 6.4 Hz, 1H, PhC*H*), 7.13 (ddd, *J* = 8.0, 7.3, 1.7 Hz, 1H, Ar*H*), 7.34 (m, 1H, Ar*H*), 7.52 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.81 (dd, *J* = 7.8, 1.8 Hz, 1H, Ar*H*). $^{13}C\{1H\}$ NMR (101 MHz,

$CDCl_3$): δ = 33.1 (*C*H_2), 50.5 (CH_2*C*HCO), 52.4, 52.6 (2xO*C*H_3), 59.3 (NH*C*HCO), 64.3 (Ph*C*HNH), 123.7, 128.0, 128.9, 129.3, 132.9, 140.4 (Ar*C*), 173.4, 174.0 (2x*C*=O). MS (EI) *m/z*: 343 (M^+, 4%), 341 (4), 285 (13), 284 (96), 283 (15), 282 (100), 257 (19), 255 (20), 224 (37), 222 (36), 197 (18), 195 (18). HRMS (EI) *m/z*: $[M-Br]^+$ Calcd for $C_{14}H_{16}NO_4$ 262.1079; Found 262.1084.

Dimethyl (2*S*,4*R*,5*R*)-5-(3-bromophenyl)pyrrolidine-2,4-dicarboxylate (***exo*-5g**): Purification by flash chromatography (*n*-Hexane-EtOAc 6:4). Brown liquid (53 mg, 78 % yield); Enantiomeric excess (96 % *ee*) was determined by HPLC. Chiralcel OD-H *n*-hexane/isopropyl alcohol = 90/10, 1.0 mL/min, t_{Rmaj}: 11.3 min, t_{Rmin}: 20.9 min, 220.5 nm. IR (neat) υ_{max}: 2953, 1734, 1436, 1199, 1264, 1012, 786, 735, 697 cm^{-1}. $[\alpha]_D^{29}$ = -46.7 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.37-2.54 (m, 2H, C*H*$_2$), 2.92 (br s, 1H, N*H*), 2.87-2.96 (m, 1H, PhCHC*H*), 3.66 (s, 3H, OC*H*$_3$), 3.79 (s, 3H, OC*H*$_3$), 4.07 (dd, *J* = 8.6, 5.7 Hz, 1H, NHC*H*CH_2), 4.43 (d, *J* = 8.3 Hz, 1H, PhC*H*), 7.20 (t, *J* = 7.8 Hz,1H, Ar*H*), 7.40 (m, 2H, Ar*H*), 7.64 (t, *J* = 1.8 Hz, 1H, Ar*H*). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ = 33.8 (*C*H_2), 50.9 (CH_2*C*HCO), 52.3, 52.6 (2xO*C*H_3), 59.1 (NH*C*HCO), 65.6 (Ph*C*HNH), 122.8, 125.9, 130.3, 131.2, 143.0 (Ar*C*), 173.2, 173.9 (2x*C*=O). MS (EI) *m/z*: 343 (M^+, 6%), 341 (6), 285 (13), 284 (96), 283 (14), 282 (100), 257 (32), 255 (33), 252 (11), 250 (13), 225 (9), 224 (44), 223 (11), 222 (39), 197 (18), 195 (17). HRMS (EI) *m/z*: $[M-Br]^+$ Calcd for $C_{14}H_{16}NO_4$ 262.1079; Found 262.1079.

Dimethyl (2*S*,4*R*,5*R*)-5-(4-bromophenyl)pyrrolidine-2,4-dicarboxylate (***exo*-5h**): Purification by flash chromatography (*n*-Hexane-EtOAc 6:4). Brown liquid (61 mg, 90 % yield); Enantiomeric excess (>99 % *ee*) was determined by HPLC.

Chiralcel OD-H *n*-hexane/isopropyl alcohol = 90/10, 1.0 mL/min, t_{Rmaj}: 10.4 min, t_{Rmin}: 17.7 min, 220.5 nm. IR (neat) υ_{max}: 2953, 1734, 1436, 1201,1170, 1011, 822, 734, 703 cm^{-1}. $[\alpha]_D^{29}$ = - 45.3 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CHCl_3$): δ = 2.34-2.55 (m, 2H, C*H*$_2$), 2.88 (q, *J* = 8.6 Hz, 1H, PhCHC*H*), 2.92 (br s, 1H, N*H*), 3.64 (s, 3H, OC*H*$_3$), 3.77 (s, 3H, OC*H*$_3$), 4.06 (dd, *J* = 8.8, 5.4 Hz, 1H, NHC*H*CH$_2$), 4.41 (d, *J* = 8.6 Hz, 1H, PhC*H*), 7.35 (d, *J* = 8.3 Hz, 2H, Ar*H*), 7.46 (d, *J* = 8.5 Hz, 2H, Ar*H*). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ = 34.1 (*C*H$_2$), 51.0 (CH$_2$*C*HCO), 52.2, 52.6 (2xO*C*H$_3$), 59.1 (NH*C*HCO), 65.8 (Ph*C*HNH), 122.0, 129.0, 131.8, 139.6 (Ar*C*), 173.2, 174.0 (2x*C*=O). MS (EI) *m/z*: 343 (M^+, 4%), 341 (5), 312 (7), 310 (8), 285 (12), 284 (97), 283 (16), 282 (100), 257 (63), 255 (64), 252 (18), 250 (21), 224 (49), 223 (17), 222 (41), 197 (30), 195 (26). HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{14}H_{16}NO_4$ 262.1079; Found 262.1072.

Dimethyl (2*S*,4*R*,5*R*)-5-(pyridin-3-yl)pyrrolidine-2,4-dicarboxylate (***exo*-5i**): Purification by flash chromatography (*n*-Hexane-EtOAc 5:5). Pale yellow solid (26 mg, 48 % yield); Enantiomeric excess (>99 % *ee*) was determined by HPLC. Chiralpak AS-H *n*-hexane/isopropyl alcohol = 90/10, 1.0 mL/min, t_{Rmaj}: 26.0 min, t_{Rmin}: 29.7 min, 210.0 nm. IR (neat) υ_{max}: 2953, 1733, 1435, 1200, 1171, 1026, 809, 714 cm^{-1}. $[\alpha]_D^{25}$ = -23.9 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 2.38-2.58 (m, 2H, C*H*$_2$), 2.92-3.00 (m, 1H, PhCHC*H*), 2.93 (br s, 1H, N*H*), 3.67 (s, 3H, OC*H*$_3$), 3.79 (s, 3H, OC*H*$_3$), 4.10 (dd, *J* = 8.7, 5.4 Hz, 1H, NHC*H*CH$_2$), 4.50 (d, *J* = 8.5 Hz, 1H, PhC*H*), 7.32 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 1H, Ar*H*), 7.93 (td, *J* = 7.9, 1.9 Hz, 1H, Ar*H*), 8.54 (dd, *J* = 4.9, 1.6 Hz, 1H, Ar*H*), 8.65 (d, *J* = 2.3 Hz, 1H, Ar*H*). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ = 34.0 (*C*H$_2$), 51.0 (CH$_2$*C*HCO), 52.3, 52.6 (2xO*C*H$_3$), 59.1 (NH*C*HCO), 63.6 (Ph*C*HNH), 124.12, 136.1, 137.6, 148.0,

148.2 (Ar*C*), 173.0, 174.1 (2x*C*=O). MS (EI) *m/z*: 264 (M^+, 3%), 233 (5), 206 (12), 205 (100), 178 (33), 173 (15), 146 (10), 145 (56), 118 (28). HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{13}H_{16}N_2O_4$ 264.1110; Found 264.1105.

Dimethyl (2*S*,4*R*,5*R*)-5-(thiophen-2-yl)pyrrolidine-2,4-dicarboxylate (***exo*-5j**): Purification by flash chromatography (*n*-Hexane-EtOAc 6:4). Pale red liquid (48 mg, 90 % yield); Enantiomeric excess (94 % *ee*) was determined by HPLC. Chiralpak AS-H *n*-hexane/isopropyl alcohol = 90/10, 1.0 mL/min, t_{Rmin}: 14.0 min, t_{Rmaj}: 15.4 min, 220.5 nm. IR (neat) υ_{max}: 2953, 1734, 1437, 1266, 1200, 1171, 1030, 936, 734, 701 cm^{-1}. $[\alpha]_D^{27}$ = +46.2 (*c* 0.96, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37-2.56 (m, 2H, C*H*$_2$), 2.98-3.03 (m, 1H, PhCHC*H*), 2.98 (br s, 1H, N*H*), 3.69 (s, 3H, OC*H*$_3$), 3.77 (s, 3H, OC*H*$_3$), 4.05 (dd, *J* = 8.6, 5.9 Hz, 1H, NHC*H*CH$_2$), 4.73 (dd, *J* = 8.3, 0.8 Hz, 1H, PhC*H*), 6.95 (dd, *J* = 5.1, 3.5 Hz, 1H, Ar*H*), 7.06 (ddd, *J* = 3.5, 1.2, 0.8 Hz, 1H, Ar*H*), 7.23 (dd, *J* = 5.1, 1.2Hz, 1H, Ar*H*). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ = 34.2 (*C*H$_2$), 51.5 (CH$_2$*C*HCO), 52.3, 52.6 (2xO*C*H$_3$), 59.2 (NH*C*HCO), 61.9 (Ph*C*HNH), 125.1, 125.2, 127.0, 144.0 (Ar*C*), 173.1, 173.6 (2x*C*=O). MS (EI) *m/z*: 270 (M^+, 6%), 269 (25), 238 (21), 210 (77), 184 (11), 183 (100), 178 (84), 152 (18), 151 (50), 150 (97), 149 (18), 123 (75), 117 (21), 96 (25). HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{12}H_{15}NO_4S$ 269.0722; Found 269.0723.

Methyl (1*S*,3*R*,3a*R*,6a*S*)-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (***exo*-5k**): All spectra were in agreement with reported data;[25a] Purification by column chromatography (*n*-Hexane-EtOAc 6:4). White solid (32 mg, 56 % yield); Enantiomeric excess (>99 % *ee*) was determined by

HPLC. Chiralpak AS-H *n*-hexane/isopropyl alcohol = 65/35, 0.5 mL/min, t_{Rmin}: 32.5 min, t_{Rmaj}: 44.4 min, 210.0 nm; $[\alpha]_D^{27}$ = -9.9 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.03 (s, 3H, OC*H*$_3$), 3.50 (dd, *J* = 8.9, 5.3 Hz, 1H, PhCHC*H*), 3.62 (s, 3H, OC*H*$_3$), 3.90 (dd, *J* = 8.9, 4.5 Hz, 1H, C*H*CHCOOMe), 4.09 (d, *J* = 4.6 Hz, 1H, C*H*COOMe), 4.52 (d, *J* = 5.3 Hz, 1H, PhC*H*), 7.27-7.43 (m, 5H, Ar*H*). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ = 25.4 (N*C*H$_3$), 49.2, 52.0 (2x*C*HCO), 52.8 (*C*H$_3$), 62.3 (*C*HCOO), 65.3 (Ph*C*HNH), 126.7, 128.1, 128.8, 140.4, (Ar*C*), 171.9, 177.0, 177.1 (3x*C*=O).

Methyl (1*S*,3*R*,3a*R*,6a*S*)-5-benzyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (***exo*-5l**): Purification by column chromatography (*n*-Hexane-EtOAc 6:4). White solid (64 mg, 87 % yield); Enantiomeric excess (>99 % *ee*) was determined by HPLC. Chiralpak AS-H *n*-hexane/isopropyl alcohol = 65/35, 0.5 mL/min, t_{Rmin}: 37.5 min, t_{Rmaj}: 47.1 min, 210.0 nm. IR (neat) υ_{max}: 2953, 1736, 1432, 1394, 1343, 1266, 1223, 1168, 1029, 920, 730 cm^{-1}. mp: 145-150 ºC; $[\alpha]_D^{27}$ = - 43.6 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.76 (br s, 1H, N*H*), 3.44 (dd, *J* = 8.9, 5.6 Hz, 1H, PhCHC*H*), 3.62 (s, 3H, OC*H*$_3$), 3.84 (dd, *J* = 8.9, 4.8 Hz, 1H, C*H*CHCOOMe), 4.04 (d, *J* = 4.8 Hz, 1H, C*H*COOMe), 4.42 (d, *J* = 5.6 Hz, 1H, PhC*H*), 4.67 (s, 2H, NC*H*$_2$Ph), 7.24-7.40 (m, 10H, Ar*H*). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ = 42.9 (CH2), 48.8, 51.5 (2x*C*HCO), 53.0 (*C*H$_3$), 62.0 (*C*HCOO), 65.2 (Ph*C*HNH), 127.1, 128.2, 128.4, 128.7, 128.8, 128.6, 135.6 (Ar*C*), 171.0, 176.1, 176.0 (3x*C*=O). MS (EI) *m/z*: 364 (M^+, 6%), 306 (21), 305 (100), 177 (13), 144 (45), 117 (20), 91 (23). HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{21}H_{20}N_2O_4$ 364.1423; Found 364.1423.

Methyl (1*S*,3*R*,3a*R*,6a*S*)-4,6-dioxo-3,5-diphenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (***exo*-5m**): All spectra were in agreement with reported data;[25a] Purification by flash chromatography (*n*-Hexane-EtOAc 6:4), White solid (36 mg, 51 % yield); Enantiomeric excess (>99 % *ee*) was determined by HPLC. Chiralpak AS-H *n*-hexane/isopropyl alcohol = 65/35, 0.5 mL/min, t_{Rmaj}: 43.5 min, t_{Rmin}: 51.3 min, 210.0 nm; $[\alpha]_D^{27}$ = - 31.8 (*c* 0.97, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.55 (br s, 1H, N*H*), 3.58-3.63 (m, 1H, PhCHC*H*), 3.64 (s, 3H, OCH_3), 4.05 (dd, *J* = 9.0, 4.3 Hz, 1H, C*H*CHCOOMe), 4.21 (d, *J* = 4.3 Hz, 1H, C*H*COOMe), 4.64 (d, *J* = 5.2 Hz, 1H, PhC*H*), 7.28-7.51 (m, 10H, Ar*H*). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ = 49.0, 51.6 (2x*C*HCO), 53 (*C*H_3), 62.4 (*C*HCOO), 65.7 (Ph*C*HNH), 126.5, 127.0, 128.4, 128.9, 129.3, 131.7, 139.5, (Ar*C*), 171.5, 175.7, 175.7 (3x*C*=O).

Methyl (2*S*,4*R*,5*S*)-5-phenyl-4-(phenylsulfonyl)pyrrolidine-2-carboxylate (***exo*-5n**): All spectra were in agreement with reported data.[6a,15] Purification by flash chromatography (*n*-Hexane-EtOAc 6:4). White solid (39 mg, 57 % yield); Enantiomeric excess (>99 % *ee*) was determined by HPLC. Chiralpak AS-H *n*-hexane/isopropyl alcohol = 65/35, 0.5 mL/min, t_{Rmaj}: 56.4 min, t_{Rmin}: 61.0 min, 210.0 nm. $[\alpha]_D^{27}$ = +19.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38 (ddd, *J* = 14.1, 9.0, 8.3 Hz, 1H, CH_2), 2.57 (br s, 1H, N*H*), 2.72 (ddd, *J* = 14.0, 7.5, 4.5 Hz, 1H, CH_2), 3.62-3.73 (m, 1H, PhCHC*H*), 3.76 (s, 3H, OCH_3), 4.16-4.21 (m, 1H, NHC*H*CH_2), 4.73 (d, *J* = 5.9 Hz, 1H, PhC*H*), 7.22 (s, 5H, Ar*H*), 7.42-7.67 (m, 3H, Ar*H*), 7.77-7.87 (m, 2H, Ar*H*). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ = 31.0 (*C*H_2), 52.5 (O*C*H_3), 59.4 (NH*C*HCO), 63.0 (CH_2*C*HSO_2Ph), 69.8 (Ph*C*HNH), 127.2, 128.1, 128.6, 128.7, 129.4, 134.0, 138.0, 140.3 (Ar*C*), 172.9 (*C*=O).

Methyl (2*R*,3*S*,4*S*,5*S*)-5-phenyl-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate (***exo*-5o**): All spectra were in agreement with reported data.[¡Error! Marcador no definido.6a] Purification by recrystallization, white solid (59 mg, 60 % yield); Enantiomeric excess (95 % *ee*) was determined by HPLC. Chiralpak AD-H *n*-hexane/isopropyl alcohol = 50/50, 1 mL/min, t_{Rmaj}: 15.8 min, t_{Rmin}: 19.3 min, 220.0 nm; $[\alpha]_D^{29}$ = -4.6 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.80 (br s, 1H, N*H*), 3.65 (s, 3H, OC*H*$_3$), 4.32 (d, *J* = 6.0, 1H, NHC*H*COOMe), 4.38 (dd, *J* = 6.4, 2.4, 1H, C*H*SO_2Ph), 4.44 (dd, *J* = 6.0, 2.4, 1H, C*H*SO_2Ph), 4.63 (d, *J* = 6.4, 1H, PhC*H*), 7.20-7.70 (m, 15 H, Ar*H*). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ = 52.9 (O*C*H_3), 63.7 (NHC*H*COOMe), 64.0, 67.5 (2x*CH*SO_2Ph), 70.8 (Ph*C*HNH), 126.2, 127.6, 128.6, 128.7, 128.8, 129.1, 129.6, 129.7, 134.6, 134.7, 137.0, 137.2 (Ar*C*), 167.1 (*C*=O).

Methyl (2*S*,3*S*,4*R*,5*S*)-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (***exo*-5p**): All spectra were in agreement with reported data;[51] Purification by recrystallization (*n*-Hexane-Ether 4:1). White solid (53 mg, 81% yield); Enantiomeric excess (77 % *ee*) was determined by HPLC. Chiralpak IA *n*-hexane/isopropyl alcohol = 98/2, 1.0 mL/min, t_{Rmaj}: 33.6 min, t_{Rmin}: 36.5 min, 220.5 nm; $[\alpha]_D^{27}$ = + 74.5 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.22 (s, 3H, OC*H*$_3$), 4.30-4.36 (m, 1H, C*H*CO), 4.45 (d, *J* = 9.1 Hz, 1H, C*H*Ph), 4.73 (d, *J* = 8.4 Hz, 1H, PhC*H*NH), 5.19 (t, *J* = 8.3 Hz, 1H, C*H*NO) 7.15-7.40 (m, 8H, Ar*H*), 7.48-7.52 (m, 2H, Ar*H*). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ = 52.2 (*C*H_3), 53.6 (*C*HPh), 64.1 (*C*HCO), 67.3 (Ph*C*HNH), 94.4 (*C*HNO_2), 127.2, 127.9, 128.5, 129.0, 129.3, 129.4, 129.5, 135.2, 136.7 (Ar*C*), 171.5 (*C*=O).

Methyl (2*S*,3*S*,4*R*,5*R*)-4-benzoyl-3,5-diphenylpyrrolidine-2-carboxylate (***exo*-5q**): All spectra were in agreement with reported data;[52] Purification by flash chromatography (*n*-Hexane-EtOAc 7:3). White solid (55 mg, 72% yield); Enantiomeric excess (70% *ee*) was determined by HPLC. Chiralpak IA *n*-hexane/isopropyl alcohol = 90/10, 1.0 mL/min, t_{Rmin}: 17.1 min, t_{Rmaj}: 22.2 min, 220.5 nm; $[\alpha]_D^{27}$ = +59.4 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.27 (s, 3H, OC*H*$_3$), 4.14 (t, *J* = 8.9 Hz, 1H, C*H*Ph), 4.35 (t, *J* = 9.0 Hz, 1H, PhCOC*H*), 4.46 (d, *J* = 9.0 Hz, 1H, C*H*COO), 4.73 (d, *J* = 9.3 Hz, 1H, PhC*H*NH), 7.16-7.30 (m, 10H, Ar*H*), 7.30-7.56 (m, 5H, Ar*H*). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ = 52.0 (*C*H_3), 53.7 (*C*HPhCHNH), 59.3 (*C*HCO), 65.0 (*C*HCOO), 67.1 (Ph*C*HNH), 127.2, 127.7, 127.9, 128.0, 128.2, 128.3, 128.4, 128.5, 128.6, 128.9, 129.0, 133.4, 136.9, 137.1, 140.3 (Ar*C*), 172.4, 199.4 (2x*C*=O).

Methyl (2*S*,4*R*,5*R*)-4-(2-oxooxazolidine-3-carbonyl)-5-phenylpyrrolidine-2-carboxylate (***exo*-5r**): Purification by flash chromatography (*n*-Hexane-EtOAc 6:4). Pale yellow liquid (39 mg, 61% yield); Enantiomeric excess (>99% *ee*) was determined by HPLC. Chiralpak IC *n*-hexane/isopropyl alcohol = 80/20, 1 mL/min, t_{Rmaj}: 25.5 min, t_{Rmin}: 36.3 min, 220.0 nm.IR (neat) u_{max}: 2923, 1779, 1736, 1687, 1384, 1363, 1216, 1040,732 cm^{-1}. $[\alpha]_D^{25}$ = -16. 6 (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32-2.42 (m, 1H, C*H*$_2$), 2.62-2.71 (m, 1H, C*H*$_2$), 2.89 (br s, 1H, N*H*), 3.81 (s, 3H, OC*H*$_3$), 3.90-3.98 (m, 2H, NC*H*$_2$), 4.10-4.17 (m, 2H, C*H*COOMe, CH_2C*H*CPh), 4.26-4.42 (m, 2H, COOC*H*$_2$) 4.70 (d, *J* = 9.1 Hz, 1H, PhC*H*), 7.24-7.37 (m, 3H, Ar*H*), 7.46-7.50 (m, 2H, Ar*H*). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ = 35.3 (*C*H_2), 42.8 (N*C*H_2), 49.9 (CH_2*C*HCO), 52.7 (O*C*H_3), 59.4 (NH*C*HCO), 62.1

(O*C*H_2), 66.1 (Ph*C*HNH), 127.5, 128.2, 128.3, 128.8, 140.1 (Ar*C*), 153.1 (N*C*=OCO), 172.9, 174.1 (2xC=O). MS (EI) *m/z*: 318 (M^+, 5%), 286 (5), 260 (17), 259 (79), 234 (12), 232 (84), 204 (23), 177 (23), 172 (51), 170 (21), 146 (46), 145 (25), 144 (46), 117 (59), 115 (26), 91 (13). HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{16}H_{18}N_2O_5$ 318.1216; Found 318.1206.

Methyl (2*S*,4*S*,5*R*)-4-(dimethylcarbamoyl)-5-phenylpyrrolidine-2-carboxylate (***endo*-5s**): Purification by flash chromatography (*n*-Hexane-EtOAc 3:7). Pale yellow liquid (30 mg, 54 % yield); Enantiomeric excess (>99 % *ee*) was determined by HPLC. Chiralpak AS-H *n*-hexane/isopropyl alcohol = 80/20, 1 mL/min, t_{Rmin}: 12 min, t_{Rmaj}: 16.0 min, 210.0 nm. IR (neat) υ_{max}: 2953, 1745, 1636, 1454, 1400, 1248, 1145, 1030, 701 cm^{-1}. $[\alpha]_D^{27}$ = - 33.2 (*c* 1, $CHCl_3$);^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (ddd, *J* = 13.1, 8.4, 5.0 Hz, 1H, C*H*$_2$), 2.52 (br s, 1H, N*H*), 2.48-2.56 (m, 1H, C*H*$_2$), 2.62 (s, 3H, NC*H*$_3$), 2.88 (s, 3H, NC*H*$_3$), 3.14 (q, *J* = 8.8 Hz, 1H, C*H*CON(CH_3)$_2$), 3.79 (s, 3H, OC*H*$_3$), 4.12 (dd, *J* = 9.3, 5.0 Hz, 1H, C*H*COOMe), 4.48 (d, *J* = 8.8 Hz, 1H, PhC*H*),7.28-7.48 (m, 5H, Ar*H*). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ = 33.1 (*C*H_2), 35.9, 37.1 (2xN*C*H_3), 47.3 [CH_2*C*HCON(CH_3)$_2$], 52.8 (O*C*H_3), 59.1 (NH*C*HCO), 66.8 (Ph*C*HNH), 127.8, 128.6, 128.9, 138.0 (Ar*C*), 171.3, 172.6 (2x*C*=O). MS (EI) *m/z*: 276 (M^+, 4%), 275 (7), 217 (24), 204 (14), 203 (13), 190 (68), 180 (49), 177 (20), 176 (58), 165 (15), 146 (100), 144 (87), 117 (36), 91 (16). HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{15}H_{20}N_2O_3$ 276.1474; Found 276.1474.

Methyl (2*S*,4*S*,5*R*)-4-cyano-5-phenylpyrrolidine-2-carboxylate (***exo*-5t**): All spectra were in agreement with reported data;[8c] Purification by flash

chromatography (*n*-Hexane-EtOAc 6:4). Pale yellow liquid (26 mg, 56 % yield); Enantiomeric excess (>99 % *ee*) was determined by HPLC. Chiralpak AD-H *n*-hexane/isopropyl alcohol = 95/5, 0.5 mL/min, t_{Rmin}: 44.7 min, t_{Rmaj}: 53.8 min, 210.0 nm; $[\alpha]_D^{27}$ = - 32.9 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.46-2.62 (m, 2H, C*H*$_2$), 2.47 (br s, 1H, N*H*), 2.79-2.88 (m, 1H, C*H*CN), 3.80 (s, 3H, CH_3), 4.08 (dd, *J* = 8.6, 5.3 Hz, 1H, C*H*COOMe), 4.37 (d, *J* = 9.1 Hz, 1H, PhC*H*), 7.34-7.51 (m, 5H, Ar*H*). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ = 34.0 (*C*H_2), 36.0 (*C*CN), 52.9 (O*C*H_3), 58.6 (NH*C*HCO), 67.1 (Ph*C*HNH), 119.3 (*C*N), 127.1, 129.1, 129.2, 137.4 (Ar*C*), 172.9 (*C*=O).

Methyl (2*R*,4*R*,5*S*)-4-cyano-5-(naphtalen-2-yl)pyrrolidine-2-carboxylate (***exo*-5u**): All spectra were in agreement with reported data.[8c] Purification by column chromatography (*n*-Hexane-EtOAc 6:4). White solid (33 mg, 59% yield); Enantiomeric excess (84% *ee*) was determined by HPLC. Chiralpak AD-H *n*-hexane/isopropyl alcohol = 90/10, 1 mL/min, t_{Rmin}: 25.2 min, t_{Rmaj}: 28.2 min, 220.0 nm. IR (neat) υ_{max}: 2360, 2348, 1869, 1734, 1558, 1050, 840 cm^{-1}.$[\alpha]_D^{27}$ = -47.88 (*c* 1.0, $CHCl_3$); mp: 137-141 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.53-2.69 (m, 2H, C*H*$_2$), 2.91-3.05 (m, 1H, CNC*H*), 3.12 (br s, 1H, N*H*), 3.77 (s, 3H, OC*H*$_3$), 4.18-4.09 (m, 1H, C*H*COOMe), 4.57 (d, *J* = 9.3 Hz, 1H, NC*H*Ph), 7.46-7.64 (m, 3H, Ar*H*), 7.83-8.06 (m, 4H, Ar*H*). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ = 34.4 (*C*H_2), 36.5 (*C*HCN), 52.8 (O*C*H_3), 58.7 (NH*C*HCO), 67.5 (Ph*C*HNH), 119.8, 124.1, 126.2, 126.5, 126.6, 1247.8, 128.2, 129.1, 133.4, 133.6, 136.0 (Ar*C*), 173.8 (C=O). MS (EI) *m/z*: 280 (M^+, 21%), 227 (37), 221 (39), 204 (40), 196 (34), 168 (31), 167(100), 166 (12), 165 (11), 140 (18), 139 (19), 128 (11). HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{17}H_{16}N_2O_2$ 280.1212; Found 280.1218.

Methyl (2*R*,4*R*,5*S*)-5-(4-bromophenyl)-4-cyanopyrrolidine-2-carboxylate (***exo*-5v**):[8c] Purification by column chromatography (*n*-Hexane-EtOAc 6:4). White solid (38 mg, 62% yield); Enantiomeric excess (98% *ee*) was determined by HPLC. Chiralpak AD *n*-hexane/isopropyl alcohol = 95/5, 1 mL/min, t_{Rmin}: 36.2 min, t_{Rmaj}: 39.0 min, 220.0 nm. IR (neat) υ_{max}: 2360, 2159, 1869, 1734, 1558, 1011, 844 cm^{-1}. $[\alpha]_D^{26}$ = -58.82 (*c* 1.0, $CHCl_3$); mp: 140-144 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.43-2.69 (m, 2H, C*H*$_2$), 2.89-2.98 (m, 1H, CNC*H*), 3.39 (br s, 1H, N*H*), 3.76 (s, 3H, OC*H*$_3$), 4.10-4.18 (m, 1H, C*H*COOMe), 4.40 (d, *J*= 9.4 Hz, 1H, NC*H*Ph), 7.42 (d, *J* = 8.5, 2H, Ar*H*), 7.52 (d, *J* = 8.7, 2H, Ar*H*). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ = 34.0 (*C*H_2), 36.4 (*C*HCN), 52.7 (O*C*H_3), 58.3 (NH*C*HCO), 66.5 (Ph*C*HNH), 119.4, 122.6, 128.5, 132.1, 137.8 (Ar*C*), 173.5 (C=O). MS (EI) *m/z*: 308 (M^+, 8%), 257 (36), 255 (37), 252 (13), 251 (94), 250 (14), 244 (100), 223 (12), 197 (36), 170 (19), 169 (33), 153 (39), 116 (27), 89 (24), 43 (18). HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{13}H_{13}BrN_2O_2$ 308.0160; Found 308.0026.

Methyl (2*R*,4*R*,5*S*)-5-(4-bromophenyl)-4-cyanopyrrolidine-2-carboxylate (***exo'*-5v**): White solid, (38 mg, 62%), mp: 139-141°C; Enantiomeric excess (99% *ee*) was determined by HPLC. Chiralpak AD *n*-hexane/isopropyl alcohol = 95/5, 1 mL/min, t_{Rmaj}: 61.1 min, 220.0 nm. IR (neat) υ_{max}: 2356, 2157, 1873, 1740, 1560, 998, 870 cm^{-1}.$[\alpha]_D^{26}$ = -60.09 (*c* 0.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.50-2.70 (m, 2H, C*H*$_2$), 3.02-3.10 (m, 1H, CNC*H*), 3.71 (s, 3H, OC*H*$_3$), 4.18-4.26 (m, 1H, C*H*COOMe), 4.48 (d, *J*= 9.8 Hz, 1H, NC*H*Ph), 7.85 (d, *J* = 8.5, 2H, Ar*H*), 7.53 (d, *J* = 8.5, 2H, Ar*H*). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$): δ = 33.3 (*C*H_2), 35.5 (*C*HCN), 53.0 (O*C*H_3), 58.5 (NH*C*HCO), 66.2 (Ph*C*HNH), 118.6, 123.5, 129.0,

132.4, 135.3 (Ar*C*), 172.0 (C=O). MS (EI) *m/z*: 308 (M^+, 8%), 257 (39), 255 (39), 251 (91), 250 (14), 244 (100), 225 (11), 223 (12), 195 (38), 170 (19), 169 (34), 153 (39), 115 (14), 89 (27). HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{13}H_{13}BrN_2O_2$ 308.0160; Found 308.0026.

Dimethyl (2*S*,4*S*,5*R*)-5-phenylpyrrolidine-2,4-dicarboxylate (***endo*-5a**): All spectra were in agreement with reported data;[10c] Purification by column chromatography (*n*-Hexane-EtOAc 7:3), Colourless liquid (44 mg, 84% yield); Enantiomeric excess (41 mg, 77 % *ee*) was determined by HPLC. Chiralcel OD-H *n*-hexane/isopropyl alcohol = 80/20, 1.0 mL/min, t_{Rmaj}: 14.4 min, t_{Rmin}: 28.9 min, 220.5 nm; $[\alpha]_D^{27}$ = + 44 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41-2.45 (m, 2H, CH_2), 2.66 (br s, 1H, N*H*), 3.22 (s, 3H, OCH_3), 3.29-3.36 (m, 1H, CH_2C*H*COOMe), 3.83 (s, 3H, OCH_3), 4.01 (t, *J* = 8.1 Hz, 1H, NHC*H*COOMe), 4.56 (d, *J* = 7.8 Hz, 1H, PhC*H*NH), 6.91-7.32 (m, 5H, Ar*H*). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ = 33.42 (*C*H_2), 49.8, 51.4 (*C*HC=O), 52.5 (O*C*H_3), 60.0 (NH*C*HCO), 66.0 (Ph*C*HNH), 126.9, 127.8, 128.4, 139.0 (Ar*C*), 173.1, 173.78 (2x*C*=O).

Methyl (1*S*,3*R*,3a*S*,6a*R*)-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (***endo*-5k**):

All spectra were in agreement with reported data;[30] Purification by column chromatography (*n*-Hexane-EtOAc 6:4), White solid (40 mg, 85 % yield); Enantiomeric excess (99 % *ee*) was determined by HPLC. Chiralpak IA *n*-hexane/isopropyl alcohol = 60/40, 1.0 mL/min, t_{Rmaj}: 24.7 min, t_{Rmin}: 28.2 min,

220.5 nm; $[\alpha]_D^{25}$ = + 46.7 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.85 (s, 3H, NC*H*$_3$), 3.39-3.44 (m, 1H, CHC*H*CO), 3.52-3.57 (m, 1H, PhCC*H*), 3.87 (s, 3H, C*H*$_3$), 4.04 (d, *J* = 6.8 Hz, 1H, C*H*COO), 4.48 (d, *J* = 8.6 Hz, 1H, PhC*H*NH), 7.28-7.39 (m, 5H, Ar*H*). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ = 25.1 (N*C*H$_3$), 48.2 (O*C*H$_3$) 49.5, 52.5 (2x*C*HC=O), 61.7 (NH*C*HCO), 64.1 (Ph*C*HNH), 127.2, 128.5, 136.4 (Ar*C*), 170.1, 174.7, 175.9 (3x*C*=O).

Methyl (1*S*,3*R*,3a*S*,6a*R*)-5-benzyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (***endo*-5l**): All spectra were in agreement with reported data;[30] Purification by flash chromatography (*n*-Hexane-EtOAc 6:4). White solid (42 mg, 79 % yield); Enantiomeric excess (53 mg, 93 % *ee*) was determined by HPLC. Chiralpak AS-H *n*-hexane/isopropyl alcohol = 80/20, 1.0 mL/min, t_{Rmaj}: 16.4 min, t_{Rmin}: 23.4 min, 220.5 nm; $[\alpha]_D^{25}$ = +39.3 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (br s, 1H, N*H*), 3.39 (dd, *J* = 8.6, 7.7 Hz, 1H, PhCHC*H*), 3.56 (dd, *J* = 7.7, 6.9 Hz, 1H, C*H*CHCOOMe), 3.88 (s, 3H, OC*H*$_3$), 4.07(d, *J* = 7.0 Hz, 1H, C*H*COOMe), 4.45-4.60 (m, 3H, PhC*H; CH*$_2$), 7.12-7.33 (m, 10H, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 42.7 (CH2), 48.4, 49.5 (2x*C*HCO), 52.5 (*C*H$_3$), 62.0 (*C*HCOO), 64.4 (Ph*C*HNH), 127.2, 128.0, 128.3, 128.5, 128.7, 129.1, 135.7, 136.3 (Ar*C*), 170.1, 174.3, 175.6 (3x*C*=O).

Methyl (2*S*,3*R*,4*S*,5*R*)-4-benzoyl-3,5-diphenylpyrrolidine-2-carboxylate (***endo*-5q**): All spectra were in agreement with reported data;[30] Purification by flash chromatography (*n*-Hexane-EtOAc 7:3), Colourless liquid (61 mg, 79 % yield); Enantiomeric excess (88 % *ee*) was determined by HPLC. Chiralcel OD-H *n*-hexane/isopropyl alcohol = 90/10, 0.8 mL/min, t_{Rmaj}: 22.4 min, t_{Rmin}: 25.8 min,

220.5 nm. $[\alpha]_D^{23}$ = -15.3 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.89 (br s, 1H, N*H*), 3.75 (s, 3H, OCH_3), 4.10-4.17 (m, 1H, NHC*H*COOMe), 4.22 (d, *J* = 8.9 Hz, 1H, NHCHC*H*Ph), 4.54 (dd, *J* = 7.6, 8.7 Hz, 1H, NHCHC*H*COPh), 5.05 (d, *J* = 8.4 Hz, 1H, NHC*H*Ph), 7.02-7.56 (m, 15H, Ar*H*).^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ = = 52.6 (*C*H_3), 52.7 (*C*HPhCHNH), 60.6 (*C*HCO), 66.7 (*C*HCOO), 67.6 (Ph*C*HNH), 127.4, 127.5, 127.9, 128.2, 128.3, 128.4, 129.0, 133.0, 137.4, 140.6 (Ar*C*), 173.2, 198.6 (2x*C*=O).

Methyl (2*S*,4*S*,5*R*)-4-(2-oxooxazolidine-3-carbonyl)-5-phenylpyrrolidine-2-carboxylate (***endo*-5r**): Purification by flash chromatography (*n*-Hexane-EtOAc 6:4). Pale yellow liquid (32 mg, 51% yield); Enantiomeric excess (65% *ee*) was determined by HPLC. Chiralpak IC *n*-hexane/isopropyl alcohol = 80/20, 1 mL/min, t_{Rmin}: 18.8 min, t_{Rmaj}: 42.1 min, 220.0 nm. IR (neat) υ_{max}: 2924, 1780, 1736, 1687, 1385, 1363, 1265, 1215, 1041,732, 700 cm^{-1}.$[\alpha]_D^{25}$ = -20.15 (*c* 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39-2.49 (m, 1H, CH_2), 2.56-2.65 (m, 1H, CH_2), 3.00 (br s, 1H, N*H*), 3.10-3.18 (m, 1H, NCH_2), 3.63-3.74 (m, 2H, NCH_2, COOCH_2), 3.85 (s, 3H, OCH_3), 4.02-4.17 (m, 2H, COOCH_2, CH_2C*H*CPh), 4.73-4.80 (m, 2H, C*H*COOMe, NC*H*Ph), 7.24-7.36 (m, 5H, Ar*H*). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ = 32.9 (*C*H_2), 42.6 (N*C*H_2), 47.79 (CH_2*C*HCO), 52.7 (O*C*H_3), 60.0 (NH*C*HCO), 62.0 (O*C*H_2), 66.1 (Ph*C*HNH), 127.2, 128.3, 128.4, 137.8 (Ar*C*), 153.0 (N*C*=OCO), 172.7, 173.2 (2xC=O). MS (EI) *m/z*: 318 (M^+, 5%), 260 (19), 259 (93), 232 (31), 177 (73), 172 (44), 170 (17), 146 (29), 145 (31), 144 (67), 142 (15), 118 (19), 117 (100), 115 (21), 91 (13). HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{16}H_{18}N_2O_5$ 318.1216; Found 318.1219.

General Procedure for the Synthesis of *N*-phenylsulfonyl derivative of Cycloadduct *exo*-5a (NPS-*exo*-5a)

In a round bottom flask cycloadduct *exo*-**5a** (263.3 mg, 1 mmol) and *p*-toluenesulfonic acid (285.97 mg, 1.5 mmol) with 3.5 mL of DCM was added and the resulting mixture was stirred for 10 minutes at 0˚C. Then, pyridine (0.16 mL, 2.5 mmol) was added. The mixture was stirred 48 h. Later the crude mixture was concentrated under reduced pressure and the residue was purified by flash chromatography to afford the corresponding final product.

Dimethyl (2*R*,4*S*,5*S*)-5-phenyl-1-tosylpyrrolidine-2,4-dicarboxylate (NPS-*exo*-5a). Purification by flash chromatography (*n*-Hexane-EtOAc 5:5). White solid liquid (263 mg, 63% yield); Recrystallization from ethanol. mp 102-104 ºC; IR (neat) υ_{max}: 2953, 1763, 1737, 1687, 1434, 1346, 1200, 1160, 1025, 751, 704, 671 cm^{-1}.$[\alpha]_D^{25}$ = -11.7 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.23-2.37 (m, 2H, C*H*$_2$), 2.39 (s, 3H, C*H*$_3$), 3.03-3.13 (m, 1H, PhCHC*H*), 3.51 (s, 3H,OC*H*$_3$), 3.83 (s, 3H, OC*H*$_3$), 4.67 (dd, *J* = 8.1, 5.5 Hz, 1H, NHC*H*CH$_2$), 5.04 (d, *J* = 6.1 Hz, 1H, PhC*H*), 7.28-7.48 (m, 5H, Ar*H*), 7.48-7.52 (m, 2H, Ar*H*), 7.55 (d, *J* = 8.3 Hz, 2H, Ar*H*). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ = 21.7 (C*H*$_3$) 32.2 (*C*H$_2$), 52.4 (CH$_2$*C*HCO), 52.7, 52.8 (2xO*C*H$_3$), 61.2 (NH*C*HCO), 67.2 (Ph*C*HNH), 127.2, 127.8, 128.0, 128.5, 129.5, 135.0, 140.0, 143.8 (Ar*C*), 171.5, 172.4 (2x*C*=O).MS (EI) *m/z*: 359 (M^+-$C_2H_3O_2$, 21%), 358 (100), 263 (14), 262 (89), 203 (17), 155 (30), 144 (25), 143 (12), 117 (14), 91 (73), 65 (10). HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{21}H_{23}NO_6S$ 417.1242; Found 417.1236.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxx

Detailed information about the NMR spectra, VCD, X-ray diffraction analysis (characterization-SI).

Cartesian coordinates, energies and number of imaginary frequencies of all local minima and transition structures discussed in this work. (calculations-SI)

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REFERENCES AND NOTES

(1) Beletskaya, I. P.; Nájera, C.; Yus, M. Stereodivergent Catalysis. *Chem. Rev.* **2018**, *118*, 5080-5200.

(2) For recent reviews concerning catalytic enantioselective 1,3-DCs, see: (a) Hashimoto, T.; Maruoka, K. Recent Advances of Catalytic Asymmetric 1,3-Dipolar Cycloadditions. *Chem. Rev*. **2015**, *115*, 5366-5412. (b) Bdiri, B.; Zhao, B.-J.; Zhou, Z.-M. Recent advances in the enantioselective 1, 3-dipolar cycloaddition of azomethine ylides and dipolarophiles. *Tetrahedron: Asymmetry* **2017**, *28*, 876-899.

(3) Zeng, W.; Chen, G.-Y.; Zhou, Y.-G.; Li, Y.-X. Hydrogen-Bonding Directed Reversal of Enantioselectivity. *J. Am. Chem. Soc*. **2007**, *129*, 750−751.

(4) (a) Kim, H. Y.; Li, J.-Y.; Kim, S.; Oh, K. Stereodivergency in Catalytic Asymmetric Conjugate Addition Reactions of Glycine (Ket)imines. *J. Am. Chem. Soc*. **2011**, *133*, 20750−20753. (b) Li, J.-Y.; Kim, H. Y.; Oh, K. Brucine Diol–Copper-Catalyzed Asymmetric Synthesis of endo-Pyrrolidines: The Mechanistic Dichotomy of Imino Esters. *Org. Lett.* **2015**, *17*, 1288−1291. (c) Li, J.-Y.; Kim, H. Y.; Oh, K. Enantiodivergent Brucine Diol-Catalyzed 1,3-Dipolar Cycloaddition of Azomethine Ylides with α,β-Unsaturated Ketones. *Adv. Synth. Catal*. **2016**, *358*, 984−993.

(5) (a) Yan, Y.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. A highly enantio- and diastereoselective Cu-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with nitroalkenes. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979−1983. (b) de Cózar, A.; Cossío, F. P. Stereocontrolled (3+2) cycloadditions between azomethine ylides and dipolarophiles: a fruitful interplay between theory and experiment. *Phys. Chem. Chem*. *Phys*. **2011**, *13*, 10858−10868.

(6) (a) Conde, E.; Bello, D.; de Cózar, A.; Sánchez, M.; Vázquez, M. A.; Cossío, F. P. Densely substituted unnatural L- and D-prolines as catalysts for highly enantioselective stereodivergent (3 + 2) cycloadditions and aldol reactions. *Chem. Sci.* **2012**, *3*, 1486−1491. (b) Arrastia, I.; Arrieta, A.; Cossío, F. P. Application of 1,3-Dipolar Reactions between Azomethine Ylides and Alkenes to the Synthesis of Catalysts and Biologically Active Compounds. *Eur. J. Org. Chem.* **2018**, 5889−5904.

(7) Robles-Machín, R.; González-Esguevillas, M.; Adrio, J.; Carretero, J. C. Cu-Catalyzed Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides with β-Phenylsulfonyl Enones. Ligand Controlled Diastereoselectivity Reversal. *J. Org. Chem*. **2010**, *75*, 233−236.

(8) (a) Filippone, S.; Maroto, E. E.; Martín-Domenech, A.; Suárez, M.; Martín, N. An efficient approach to chiral fullerene derivatives by catalytic enantioselective 1,3-dipolar cycloadditions. *Nat. Chem*. **2009**, *1*, 578−582. (b) Maroto, E. E.; de Cózar, A.; Filippone, S.; Martín-Domenech, A.; Suárez, M.; Cossío, F. P.; Martín, N. Hierarchical Selectivity in Fullerenes: Site-, Regio-, Diastereo-, and Enantiocontrol of the 1,3-Dipolar Cycloaddition to C_{70}. *Angew. Chem., Int. Ed.* **2011**, *50*, 6060−6064. (c) Maroto, E. E.; Filippone, S.; Martín-Domenech, A.; Suárez, M.; Martín, N. Switching the Stereoselectivity: (Fullero)Pyrrolidines "a la Carte". *J. Am. Chem. Soc*. **2012**, *134*, 12936−12938. (d) Maroto, E. E.; Izquierdo, M.; Murata, M.; Filippone, S.; Komatsu, K.; Murata, Y.; Martín, N. Catalytic stereodivergent functionalization of H_2@C_{60}. *Chem. Commun*. **2014**, *50*, 740−742.

(9) (a) Arai, T.; Mishiro, A.; Yokoyama, N.; Suzuki, K.; Sato, H. Chiral Bis(imidazolidine)pyridine−Cu(OTf)$_2$: Catalytic Asymmetric Endo-Selective [3 + 2] Cycloaddition of Imino Esters with Nitroalkenes. *J. Am. Chem. Soc.* **2010**, *132*, 5338−5339. (b) Arai, T.; Yokoyama, N.; Mishiro, A.; Sato, H. Catalytic asymmetric *exo*'-selective [3+2] cycloaddition of iminoesters with nitroalkenes. *Angew. Chem., Int. Ed*. **2010**, *49*, 7895−7898. (c) Arai, T.; Tokumitsu, C.; Miyazaki, T.; Kuwano, S.; Awata, A.

Catalytic asymmetric [3 + 2]-cycloaddition for stereodivergent synthesis of chiral indolyl-pyrrolidines. *Org. Biomol. Chem*. **2016**, *14*, 1831−1839.

(10) (a) Antonchick, A. P.; Gerding-Reimers, C.; Catarinella, M.; Schurmann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. Highly enantioselective synthesis and cellular evaluation of spirooxindoles inspired by natural products. *Nat. Chem*. **2010**, *2*, 735−740. (b) Antonchick, A. P.; Schuster, H.; Bruss, H.; Schürmann, M.; Preut, H.; Rauh, D.; Waldmann, H. Enantioselective synthesis of the spirotryprostatin A scaffold. *Tetrahedron* **2011**, *67*, 10195−10202. (c) Cabrera, S.; Arrayás, R. G.; Carretero, J. C. Highly Enantioselective Copper(I)−Fesulphos-Catalyzed 1,3-Dipolar Cycloaddition of Azomethine Ylides. *J. Am. Chem. Soc*. **2005**, *127*, 16394−16395. (d) Awata, A.; Arai, T. Catalytic Asymmetric exo'-Selective [3+2] Cycloaddition for Constructing Stereochemically Diversified Spiro[pyrrolidin-3,3'-oxindole]s. *Chem. Eur. J.* **2012**, *18*, 8278−8282. (e) Arai, T.; Ogawa, H.; Awata, A.; Sato, M.; Watanabe, M.; Yamanaka, M. PyBidine-Cu(OTf)2 -catalyzed asymmetric [3+2] cycloaddition with imino esters: harmony of Cu-Lewis acid and imidazolidine-NH hydrogen bonding in concerto catalysis. *Angew. Chem., Int. Ed.* **2015**, *54*, 1595−1599.

(11) Nájera, C.; Sansano, J. M. Binap and Phosphoramidites as Privileged Chiral Ligands for the Metal-Catalyzed Enantioselective 1,3-Dipolar Cycloaddition of Azomethine Ylides. *Chem. Rec.* **2016**, *16*, 2430-2448.

(12) Li, F.; Cao, G.; Gao, Y.; Teng, D. Cu(II)/DM-Segphos catalyzed asymmetric 1,3-dipolar cycloaddition of benzoisothiazole-2,2-dioxide-3-ylidenes and azomethine ylides. *RSC Adv.* **2017**, *7*, 10816-10820.

(13) A enantioselective double 1,3-DC was also successfully accomplished. Ray, S. K.; Biswas, R. G.; Suneja, A.; Sadhu, M. M.; Singh, V. K. (*R*)-DM-SEGPHOS–Ag(I)-Catalyzed Enantioselective Synthesis of Pyrrolidines and Pyrrolizidines via (1,3)- and Double (1,3)-Dipolar Cycloaddition Reactions. *J. Org. Chem.* **2018**, *83*, 2293-2308.

(14) Multicomponent 1,3-DC employing achiral glycine sultam with (*S*)-DTBM-Segphos ligand **3**·CuI complex, was reported. Joseph, R.; Murray, C.; Garner, P. Catalytic Asymmetric Exo-Selective [C+NC+CC] Reaction. *Org. Lett.* **2014**, *16*, 1550-1553.

(15) α-Imino amides were succesfully employed in 1,3-DCs with different dipolarophiles in the presence of a (*S*)-DTBM-Segphos ligand **3**·CuI complex. González-Esguevillas, M.; Adrio, J.; Carretero, J. C. Cu-catalyzed asymmetric [3+2] cycloaddition of α-iminoamides with activated olefins. *Chem. Commun.* **2012**, *48*, 2149-2151.

(16) For 1,3-DC of α-silylimines catalyzed by (*S*)-DTBM-Segphos ligand **3**·CuI complex, see: Hernández-Toribio, J.; Padilla, S.; Adrio, J.; Carretero, J. C. Catalytic asymmetric synthesis of α-quaternary proline derivatives by 1,3-dipolar cycloaddition of α-silylimines. *Angew. Chem. Int. Ed.* **2012**, *51*, 8854-8858.

(17) Escudero, A. P.; de Cózar, A.; Cossío, F. P.; Adrio, J.; Carretero, J. C. Alkenyl Arenes as Dipolarophiles in Catalytic Asymmetric 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides. *Angew. Chem. Int. Ed.* **2016**, *55*, 15334-15338.

(18) González-Esguevillas, M.; Escudero, A. P.; Adrio, J.; Carretero, J. C. Highly Selective Copper-Catalyzed Asymmetric [3+2] Cycloaddition of Azomethine Ylides with Acyclic 1,3-Dienes. *Chem. Eur. J.* **2015**, *21*, 4561-4565.

(19) Arpa, E. M.; González-Esguevillas, M.; Escudero, A. P.; Adrio, J.; Carretero, J. C. Catalytic Asymmetric Synthesis of Bicycloprolines by a 1,3-Dipolar Cycloaddition/Intramolecular Alkylation Strategy. *J. Org. Chem.* **2016**, *81*, 6128-6135.

(20) López-Pérez, A.; Adrio, J.; Carretero, J. C. The phenylsulfonyl group as a temporal regiochemical controller in the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides. *Angew. Chem. Int. Ed.* **2009**, *48*, 340-343.

(21) Harada, M.; Kato, S.; Haraguchi, R.; Fukuzawa, S.-I. Metal Complex-Controlled Regio-, Diastero- and Enantioselective 1,3-Dipolar Cycloaddition of Azomethine Ylides with Benzo[*b*]thiophene Sulfones. *Chem. Eur. J.* **2018**, *24*, 2580-2583.

(22) These type of silver(I) complex promoted *endo*-diastereoselectivities in the 1,3-DC between benzylideneamino glycinate and a β-boryl acrylate or alkylidene azlactones. (a) López-Pérez, A.; Segler, M.; Adrio, J.; Carretero, J. C. Silver-Catalyzed 1,3-Dipolar Cycloaddition of Azomethine Ylides with β-Boryl Acrylates. *J. Org. Chem.* **2011**, *76*, 1945-1948. (b) González-Esguevillas, M.; Adrio, J.; Carretero, J. C. Enantioselective synthesis of 4-aminopyrrolidine-2,4-dicarboxylate derivatives via Ag-catalyzed cycloaddition of azomethine ylides with alkylidene azlactones. *Chem. Commun.* **2013**, *49*, 4649-4651.

(23) For 1,3-DC with α-amino phosphonates, see: (a) Yamashita, Y.; Guo, X.-X.; Takashita, R.; Kobayashi, S. Chiral Silver Amide-Catalyzed Enantioselective [3 + 2] Cycloaddition of α-Aminophosphonates with Olefins. *J. Am. Chem. Soc.* **2010**, *132*, 3262-3263. (b) Yamashita, Y.; Imaizumi, T.; Guo, X.-X.; Kobayashi, S. Chiral Silver Amides as Effective Catalysts for Enantioselective [3+2] Cycloaddition Reactions. *Chem. Asian J.* **2011**, *6*, 2550-2559. (c) Yamashita, Y.; Kobayashi, S. Metal Amides as the Simplest Acid/Base Catalysts for Stereoselective Carbon–Carbon Bond-Forming Reactions. *Chem. Eur. J.* **2013**, *19*, 9420-9427.

(24) Yamashita, Y.; Imaizumi, T.; Kobayashi, S. Chiral silver amide catalyst for the [3+2] cycloaddition of α-amino esters to olefins. *Angew. Chem. Int. Ed.* **2011**, *50*, 4893-4896.

(25) For seminal works of the catalytic enantioselective 1,3-DC using copper(I) and silver(I), see respectively: (a) Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu M. *exo*- and Enantioselective Cycloaddition of Azomethine Ylides Generated from N-Alkylidene Glycine Esters Using Chiral Phosphine−Copper Complexes. *Org. Lett.*, **2003**, *5*, 5043-5046. (b) Longmire, J. M.; Wang, B.; Zhang, X. Highly Enantioselective Ag(I)-Catalyzed [3 + 2] Cycloaddition of Azomethine Ylides. *J. Am. Chem. Soc*. **2002**, *124*, 13400-13401.

(26) The data of this analysis was assigned to the following deposition number: CCDC 1882300.

(27) The careful individual analysis of the absolute configuration for each compound corresponded unambiguously with its enantiomeric form drawn. The data of the *exo*-cycloadducts obtained in this work does not match with some of the analogous structures drawn and characterized in ref. 23. However, the data obtained of the *endo*-cycloadducts is identical to those reported in the literature (see also SI).

(28) The *exo'*-cycloadduct **5v** are much more stable (around 2.9 kcal·mol^{-1}) than stereoisomers *exo*-**5v**. A strong hydrogen bonding of NH···O=C (ester group) favoured this stability.

(29) During the revision of this article the synthesis and fully characterization of the corresponding *endo*-cycloadducts from acrylonitrile was published. The characterization data did not match at all with the isolated *exo'*-adduct **5v**: Xiong, Y.; Du, Z.; Chen, H.; Yang, Z.; Tan, Q.; Zhang, C.; Zhu, L.; Lan, Y.; Zhang, M. Well-Designed Phospnine-Urea Ligand for Highly Diastereo- and Enantioselective 1,3-Dipolar Cycloaddition of Methacrylonitrile: A Combined Experimental and Theoretical Study. *J. Am. Chem. Soc.* **2019**, *141*, 961-971.

(30) Cayuelas, A.; Larrañaga, O.; Selva, V.; Nájera, C.; Akiyama, T.; Sansano, J. M.; de Cózar, A.; Miranda, J. I.; Cossío, F. P. Cooperative Catalysis with Coupled Chiral Induction in 1,3-Dipolar Cycloadditions of Azomethine Ylides. *Chem. Eur. J.* **2018**, *24*, 8092-8097.

(31) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: Oxford, New York, **1989**.

(32) Castelló, L. M.; Nájera, C.; Sansano, J. M.; Larrañaga, O.; de Cózar, A.; Cossío, F. P. Efficient Diastereo- and Enantioselective Synthesis of exo-Nitroprolinates by 1,3-Dipolar Cycloadditions Catalyzed by Chiral Phosphoramidite·Silver(I) Complexes. *Adv. Synth. Catal.* **2014**, *356*, 3861–3870.

(33) S. Xu, Z.–M. Zhang, B. Xu, B. Liu, Y. Liu, J. Zhang. Enantioselective Regiodivergent Synthesis of Chiral Pyrrolidines with Two Quaternary Stereocenters via Ligand-Controlled Copper(I)-Catalyzed Asymmetric 1,3-Dipolar Cycloadditions. *J. Am. Chem. Soc.* **2018**, *140*, 2272–2283.

(34) Nájera, C.; Retamosa, M. G.; Sansano, J. M.; de Cózar, A.; Cossío, F. P. Enantioselective synthesis of polysubstituted prolines by Binap-silver-catalyzed 1,3-dipolar cycloadditions. *Tetrahedron: Asymmetry* **2008**, *19*, 2913–2923.

(35) Gaussian 09, Revision D.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortíz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2009.

(36) Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys*. **1993**, *98*, 5648-5650.

(37) Zhao, Y.; Truhlar, D. G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: Two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc*. **2008**, *120*, 215-241.

(38) (a) Zhao, Y.; Truhlar, D. G. Density Functionals with Broad Applicability in Chemistry. *Acc. Chem. Res.* **2008**, *41*, 157-167. (b) Chen, J. L.; Hong, J. T.; Wu, K. J.; Hu, W. P. The MC-DFT approach to the M06-2X, B2K-PLYP, and B2T-PLYP functionals. *Chem. Phys. Lett*. **2009**, *468*, 307-312.

(39) (a) Ess, D. H:; Houk, K. N. Activation Energies of Pericyclic Reactions: Performance of DFT, MP2, and CBS-QB3 Methods for the Prediction of Activation Barriers and Reaction Energetics of 1,3-Dipolar Cycloadditions, and Revised Activation Enthalpies for a Standard Set of Hydrocarbon Pericyclic Reactions. *J. Phys. Chem. A* **2005**, *109*, 9542-9553. (b) Pieniazek, S. N.; Clemente, F. R.; Houk, K. N. Sources of error in DFT computations of C-C bond formation thermochemistries: pi-->sigma transformations and error cancellation by DFT methods. *Angew. Chem., Int. Ed.* **2008**, *47*, 7746-7749.

(40) Jasinski, R. Searching for zwitterionic intermediates in Hetero Diels–Alder reactions between methyl α,p-dinitrocinnamate and vinyl-alkyl ethers. *Comput. Theor. Chem*. **2014**, *1046*, 93-98.

(41) Cammi, R.; Mennucci, B.; Tomasi, J. Fast Evaluation of Geometries and Properties of Excited Molecules in Solution: A Tamm-Dancoff Model with Application to 4-Dimethylaminobenzonitrile. *J. Phys. Chem*. *A* **2000**, *104*, 5631-5637.

(42) Maestro, v. 9.2, Schrödinger LLC, New York, 2013.

(43) Legaut, C. Y. CYL view v.1.0.374 BETA 2007-2010.

(44) Dennington, R.; Keith, T.; Millam, J. Gauss View version 5.0, Semichem Inc., Shawnee Mission, KS, USA, 2009.

(45) López-Pérez, A.; Adrio, J.; Carretero, J. C. Bis-Sulfonyl Ethylene as Masked Acetylene Equivalent in Catalytic Asymmetric [3 + 2] Cycloaddition of Azomethine Ylides. *J. Am. Chem. Soc*. **2008**, *130*, 10084–10085

(46) Corpas, J.; Ponce, A.; Adrio, J.;Carretero, J. C. CuI-Catalyzed Asymmetric [3 + 2] Cycloaddition of Azomethine Ylides with Cyclobutenones. *Org. Lett.* **2018**, *20*, 3179-3182.

(47) Tian, F.; He, F.; Deng, H.; Yang, W.; Deng, W. Asymmetric Construction of 3-Azabicyclo[3.1.0]hexane Skeleton with Five Contiguous Stereogenic Centers by Cu-Catalyzed 1,3-Dipolar Cycloaddition of Trisubstituted Cyclopropenes. *Org. Lett.*, **2018**, *20*, 3838-3842.

(48) Liu, Y.; Hu, H.; Wang, X.; Zhi, S.; Kan, Y.; Wang, C. Synthesis of Pyrrole via a Silver-Catalyzed 1,3-Dipolar Cycloaddition/Oxidative Dehydrogenative Aromatization Tandem Reaction. *J. Org. Chem.* **2017**, *82*, 4194-4202

(49) Fukuzawa, S.; Oki, H. Highly Enantioselective Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylide Catalyzed by a Copper(I)/ClickFerrophos Complex. *Org. Lett.* **2008**, *10*, 1747-1750.

(50) Gao, W.; Zhang, X., Raghunath, M. Cu(I)-Catalyzed Highly Exo-selective and Enantioselective [3 + 2] Cycloaddition of Azomethine Ylides with Acrylates. *Org. Lett.* **2005**, *7*, 4241-4244.

(51) Castelló, L. M.; Nájera, C.; Sansano, J. M.; Larrañaga, O.; de Cózar, A.; Cossío, F. P. Phosphoramidite–$Cu(OTf)_2$ Complexes as Chiral Catalysts for 1,3-Dipolar Cycloaddition of Iminoesters and Nitroalkenes. *Org. Lett.* **2013**, *15*, 2902–2905.

(52) Hernández-Toribio, J.; Gómez Arrayás, R.; Martín-Matute, B.; Carretero, J.C. Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides with α,β-Unsaturated Ketones. *Org. Lett.* **2009**, *11*, 393–396.