

## Asymmetric Catalysis

## Application of 1,3-Dipolar Reactions between Azomethine Ylides and Alkenes to the Synthesis of Catalysts and Biologically Active Compounds

Iosune Arrastia,<sup>[a]</sup> Ana Arrieta,<sup>[b]</sup> and Fernando P. Cossío\*<sup>[a,b]</sup>

Dedicated to Professor Dr. Luis A. Oro.

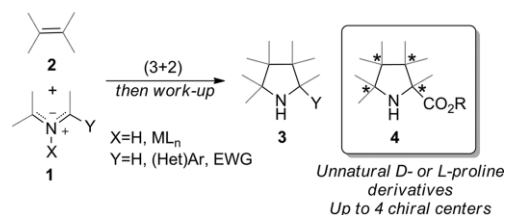
**Abstract:** The (3+2) cycloaddition between azomethine ylides and alkenes is an efficient, convergent and stereocontrolled method for the synthesis of unnatural pyrrolidine and proline scaffolds. In this review, the application of this reaction to the synthesis of enantiopure organometallic ligands for asymmetric catalysis is presented first. These new *EhuPhos* ligands can participate in a second generation of 1,3-dipolar reactions that generate an offspring of unnatural proline derivatives that be-

have as efficient organocatalysts. These densely substituted unnatural L-proline derivatives exhibit distinct features, different to those described for natural L-proline and its derivatives. Finally, several examples of biologically active proline derivatives obtained by means of (3+2) cycloadditions involving azomethine ylides are presented. These applications show the character of privileged structures of these polysubstituted pyrrolidine rings.

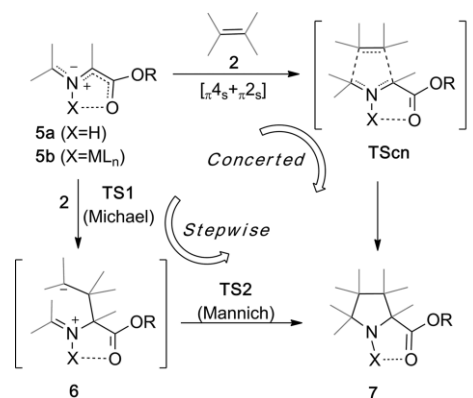
## 1. Introduction

1,3-Dipolar reactions are (3+2) cycloadditions that generate five-membered rings in a single preparative step.<sup>[1]</sup> In many cases, the reaction takes place with high or even complete regio-, diastereo- and enantiocontrol. Among the different dipole/dipolarophile combinations,<sup>[2]</sup> the 1,3-dipolar reaction between azomethine ylides **1** and alkenes **2** constitutes a very efficient and convergent method for the synthesis of pyrrolidines **3** (Scheme 1).<sup>[3]</sup> Given the fleeting nature of azomethine ylides, the rationalization of the different outcomes and the nature of the reaction mechanisms requires state-of-the-art computational tools, thus providing a very fruitful interplay between theory and experiment.<sup>[4]</sup> When the azomethine ylide is stabilized by an alkoxy carbonyl group the corresponding (3+2) cycloadduct is a proline scaffold **4** that can incorporate many different groups, thus permitting the synthesis of densely substituted and functionalized unnatural proline derivatives.

Although the 1,3-dipolar reaction depicted in Scheme 1 is formally a (3+2) cycloaddition, the actual mechanism can vary from a concerted (but not necessarily synchronous)  $[\pi_4s+\pi_2s]$  mechanism via supra-supra<sup>[5]</sup> transition structures **TS<sub>cn</sub>** to a stepwise process (Scheme 2).<sup>[6]</sup> This latter mechanism takes



Scheme 1. Synthesis of pyrrolidines **3** and, in particular, densely substituted prolines **4** by formal (3+2) cycloaddition between azomethine ylides **1** and alkenes **2**.



Scheme 2. Alternative concerted (not necessarily synchronous) and stepwise mechanisms in the 1,3-dipolar reaction between stabilized NH- or N-metalated azomethine ylides (**5a** and **5b**, respectively) and alkenes **2**.

[a] Donostia International Physics Center (DIPC),  
Manuel Lardizabal Ibilbidea 4, 20018 San Sebastian/Donostia, Spain  
E-mail: fp.cossio@ehu.es  
<https://www.ehu.es/eu/web/qbmm/hasiera>

[b] Department of Organic Chemistry I and Centro de Innovación en Química Avanzada (ORFEO-CINQA)  
Universidad del País Vasco/Euskal Herriko Unibertsitatea (UPV/EHU),  
Manuel Lardizabal Ibilbidea 3, 20018 San Sebastian/Donostia, Spain

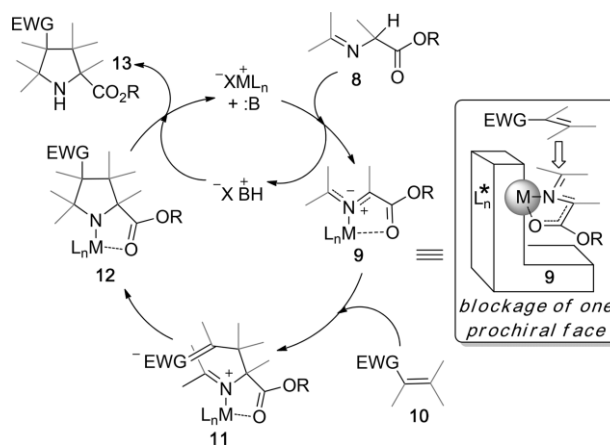
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under <https://doi.org/10.1002/ejoc.201800911>.

© 2018 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

place via a Michael/Mannich sequence and involves zwitterionic intermediates **6** that in some cases can be detected.<sup>[7]</sup> Therefore, this reaction does not follow a general mechanism and different reaction paths can be observed depending upon the substituents and the reaction conditions. In particular, *N*-metallated azomethine ylides **5b** (Scheme 2) in the presence of polarized  $\pi$ -deficient alkenes **2** follow stepwise reaction paths. However, as it will be discussed below, this non-concerted mechanism is compatible with an exquisite regio-, diastereo- an enantiocontrol.

Stabilized azomethine ylides **9** can be generated by thermal isomerization<sup>[8]</sup> or by metal-assisted deprotonation<sup>[9]</sup> of imines **8**. Other methods such as electrocyclic ring opening of aziridines are also available.<sup>[10]</sup> However, the metallic salt/base method possesses the advantage of allowing the development of a catalytic cycle that minimizes the introduction of additional reactants in the reaction medium. Although when doubly activated alkenes such as maleimides usually lead to concerted mechanisms, in the case of monoactivated dipolarophiles **10** the catalytic cycle leads to a *N*-metallated zwitterionic intermediate **11** via a Michael-like nucleophilic attack of 1,3-dipole **9**, which behaves as an enolate. Intramolecular Mannich-like cyclization of this intermediate gives rise to the corresponding *N*-metallated pyrrolidine **12**. This latter polycyclic intermediate has a considerable strain that promotes the release of the catalyst and the formation of the substituted proline ester **13** (Scheme 3).

Another advantage of the catalytic methodology depicted in Scheme 3 is that, in the presence of chiral ligands, the *N*-metallated azomethine ylide **9** only accepts the dipolarophile by the less hindered prochiral face, thus allowing the formation of Michael adducts **11** in which two chiral centers are generated



Scheme 3. Catalytic cycle of a stepwise 1,3-dipolar reaction between imines **8** mediated by *N*-metallated azomethine ylides **9**. EWG stands for an electron-withdrawing group. MX is a metallic salt where M usually is Cu<sup>I</sup>, Cu<sup>II</sup> or Ag<sup>I</sup> and the base B is a tertiary amine. The origin of the possible enantiocontrol by using chiral ligands in **9** is highlighted.

with high or even complete regio- and stereocontrol. From these intermediates the ring closure gives rise to the two remaining chiral centers, also with very high stereocontrol. Therefore, the highly restricted structure of intermediates **9** relies on the nature of the chiral ligands L\* (Scheme 3), which are ultimately responsible for the final enantiocontrol.

## 2. Synthesis of Catalysts by Means of 1,3-Dipolar Reactions

In this section the synthesis of L\* ligands shown in Scheme 2 by (3+2) cycloaddition reactions between azomethine ylides and



**Iosune Arrastia** studied Chemistry at the Universidad del País Vasco/Euskal Herriko Unibertsitatea (UPV/EHU) and received her PhD in 2001 (Prof. Fernando P. Cossío). She is an Associate Researcher at the Donostia International Physics Center (DIPC). Her current research interests focus on the computational study of the origins of stereocontrol in organocatalysis.



**Ana Arrieta** studied Chemistry at the Universidad del País Vasco/Euskal Herriko Unibertsitatea (UPV/EHU) and received her PhD in 1986 (Prof. Claudio Palomo). She joined the UPV/EHU as Profesor Titular in 1991. She has served as Dean of the Faculty of Chemistry and Vice Rector of the Campus of Gipuzkoa of the UPV/EHU. Her current research interests focus on the computational study of the reaction mechanisms and origins of stereocontrol in organocatalysis and (n+2) thermal cycloadditions, as well as on the mode of action and origins of selectivity of epigenetic enzymes.



**Fernando P. Cossío** (San Martín de Villafuere, Cantabria, Spain, 1960) studied Chemistry at the Universidad de Zaragoza (1977–1981) and in 1986 obtained his PhD in the Universidad del País Vasco/Euskal Herriko Unibertsitatea (UPV/EHU) under the supervision of Prof. Claudio Palomo. After a postdoctoral stage at the Université de Bordeaux I-CNRS (Dr. Jean-Paul Picard) he was promoted to associate professor in 1988. In 1993 he went to UCLA as visiting scholar (Prof. Kendall N. Houk). In 2002 he was promoted to full professor at the UPV/EHU. He has served as Dean of the Faculty of Chemistry and Vice Rector for Research and International Relations of the UPV/EHU. He is currently the scientific Director of Ikerbasque, the Basque foundation for science. His main research interests cover cycloaddition chemistry, asymmetric catalysis and medicinal chemistry. The methodology used in these studies is based on the synergistic interplay between computational and experimental chemistry.

alkenes will be discussed. Next, second-generation (3+2) cycloadditions catalyzed by these ligands will be presented and discussed. Finally, the organocatalytic activity of the (3+2) cycloadducts formed in the latter process will be shown.

## 2.1. Ferrocenyl Prolines as Enantiopure Ligands

The activated azomethine ylides **9** shown in Scheme 3 require a rigid environment around the 1,3-dipole to promote the preferential approach of the dipolarophile along the less hindered prochiral face. This conformationally restricted environment can be achieved by means of chiral ligands possessing donor atoms. Among the different possibilities, enantiopure ligands bearing phosphine and amine functional groups (P,N-ligands)<sup>[11]</sup> constitute the most efficient L\* groups that can promote asymmetric catalytic (3+2) cycloadditions between azomethine ylides and alkenes. Within this context, ferrocenylphosphine groups incorporating five-membered nitrogen-containing heterocycles are especially relevant because of the interplay between the planar chirality of the ferrocenyl moiety and the central chirality of the heterocycle. These ferrocenylphosphine ligands include triazoles **14**,<sup>[12]</sup> 1*H*-pyrazoles **15**,<sup>[13]</sup> 1*H*-imidazoles **16**,<sup>[14]</sup> oxazolines **17**<sup>[7b,7f,15]</sup> and pyrrolidines **18**<sup>[16]</sup> (Figure 1). Other families of P,N-ligands combining different kinds of chirality have been described, including spiro polycyclic systems and axially chiral aminophosphines.<sup>[11]</sup> However, ferrocenylphosphine ligands benefit from a unique combination of the bulky organometallic group, the already mentioned interplay between central and planar chiralities and, last but not least, a robust chemistry that permits the synthesis of different families of ligands.

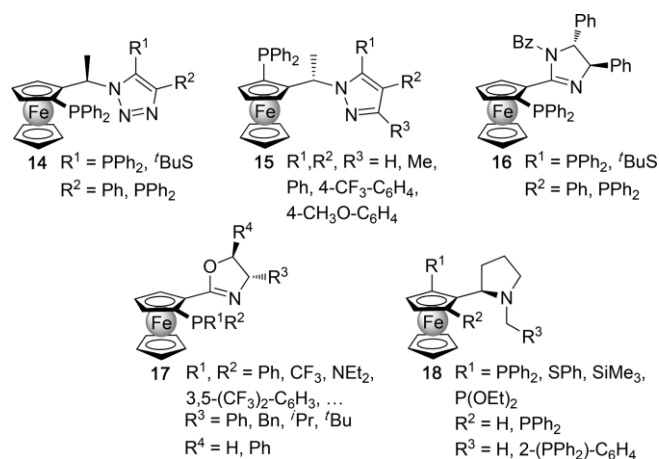
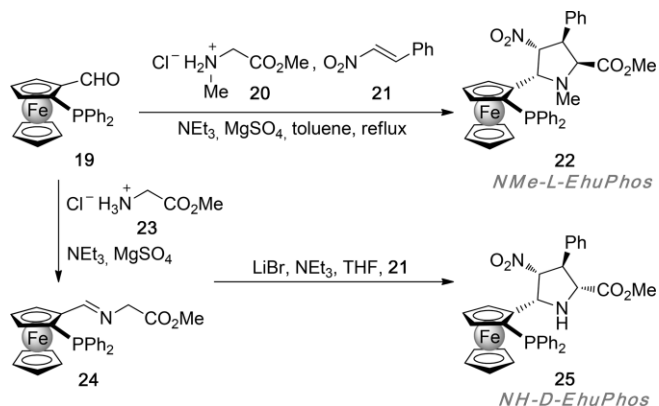


Figure 1. Different chiral ferrocenyl phosphines containing five-membered nitrogen heterocycles.

We reasoned that ferrocenylphosphino pyrrolidines bearing four chiral centers after (3+2) cycloadditions could constitute promising P,N-ligands<sup>[11]</sup> in which the high density of chiral centers would in turn catalyze with high stereocontrol other (3+2) cycloadditions between azomethine ylides and nitroalkenes. The synthesis of these P,N-ligands started with enantiomerically pure ferrocenyl carboxaldehyde **19** prepared according the method described by Kagan et al.<sup>[17]</sup> (Scheme 4). Direct three-component reaction between **19**, sarcosine methyl ester hydro-

chloride **20** and (*E*)- $\beta$ -nitrostyrene **21** yielded ligand *NMe-L-EhuPhos* **22** as the sole cycloadduct. Alternatively, imine **24** was formed from **19** and methyl glycinate hydrochloride **23**. Subsequent (3+2) cycloaddition of **24** with dipolarophile **21** yielded cycloadduct *NH-D-EhuPhos* **25** in the presence of LiBr and triethylamine (Scheme 4).<sup>[18]</sup>



Scheme 4. Synthesis of *EhuPhos* ligands **22** and **25**.

The structures of both ligands were confirmed by X-ray diffraction (Figure 2). It is noteworthy that both procedures yielded unnatural L- and D-proline scaffolds, being the configurations of the remaining chiral centers identical. It is noteworthy that both ligands are stable and can be prepared in just one or two preparative steps at multigram scale from readily available materials.

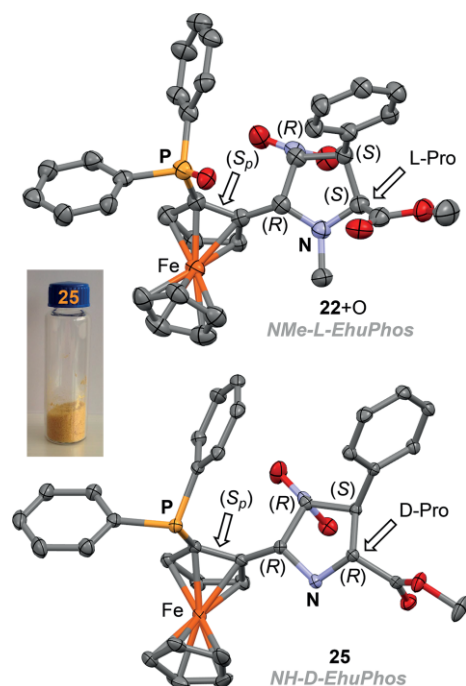
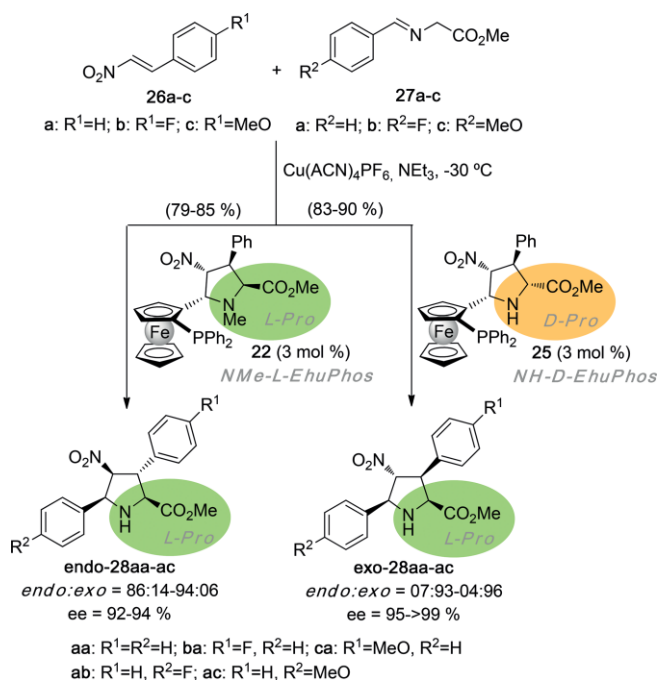


Figure 2. X ray diagrams (50 % probability) of ligands **22** (*NMe-L-EhuPhos*, CCDC 830011) and **25** (*NH-D-EhuPhos*, CCDC 830012). The different chirality descriptors are indicated. Crystal structure of **22** corresponds to the corresponding phosphine oxide. The L and D configurations of the respective proline moieties are highlighted. The macroscopic shape of a sample of **25** is also shown.

The behavior of these new ligands was tested in (3+2) cycloadditions between  $\pi$ -deficient alkenes and *N*-metallated azomethine ylides obtained in situ from the corresponding imines (Scheme 5).<sup>[18]</sup> Among other results, it was observed that Cu<sup>I</sup>-*N*-metallated azomethine ylides coordinated to *NMe-L-EhuPhos* ligand **22** produce *endo-L*-cycloadducts **28** with good yields and excellent ee's (Scheme 5), whereas the corresponding *exo-L*-pyrrolidines were obtained, also with excellent yields and enantiocontrol, in the presence of *NH-D-EhuPhos* ligand **25**. It is noteworthy that, considering the proline motif transmitted from *EhuPhos* ligands to cycloadducts **28**, the *D*-proline moiety of the ligand generates an offspring of *L*-proline derivatives *exo-L-28*, whereas the *L*-proline motif present in *NMe-L-EhuPhos* **22** is transmitted with retention of *L*-configuration to the *endo-L-28* offspring. In addition, neither ligand **22** nor **25** were able to catalyze the formation of *EhuPhos* ligands. Therefore, the (3+2) processes gathered in Scheme 4 cannot be made autocatalytic.



Scheme 5. (3+2) Cycloaddition reaction between nitroalkenes **26** and imines **27** catalysed by *EhuPhos* ligands **22** and **25**. The retention or inversion of configuration of the proline moieties in the ligands and cycloadducts are highlighted.

Computational studies<sup>[18]</sup> on the origins of the distinct behavior of both ligands revealed transition structures closely related to the shape of azomethine ylides **9** (see Figure 3 and Scheme 3). However, in the case of *NMe-L-EhuPhos* **22** the Cu<sup>I</sup> center cannot bind the nitrogen atom of the pyrrolidine moiety and therefore there is a vacant in the metallic center that can be filled by the nitro group of the alkene, thus giving rise to the corresponding *endo*-cycloadduct **28**. In contrast, *NH-D-EhuPhos* **25** behaves as a true *N,P*-ligand and the nitro group of nitroalkene **26** can occupy the *exo* position to yield the corresponding *exo*-cycloadduct. These calculations also provided a rationale for the enantioselectivity of the reaction. Thus, since both ligands **22** and **25** block the same prochiral (2*Re*, 5*Si*) face

of the azomethine ylide, only the *L*-configuration can be obtained in the corresponding cycloadduct **28**.

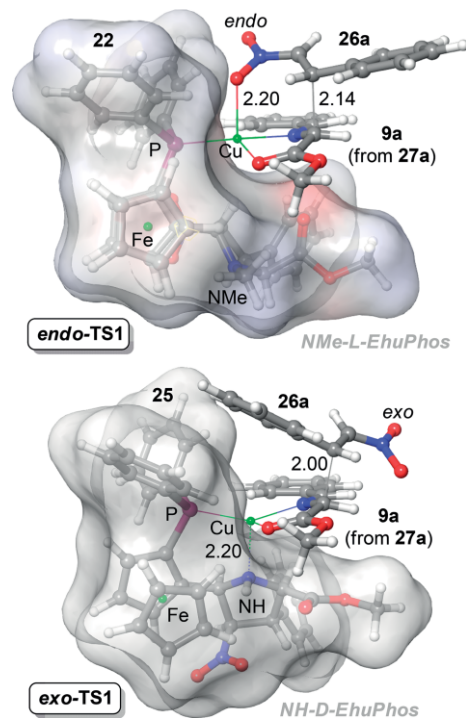


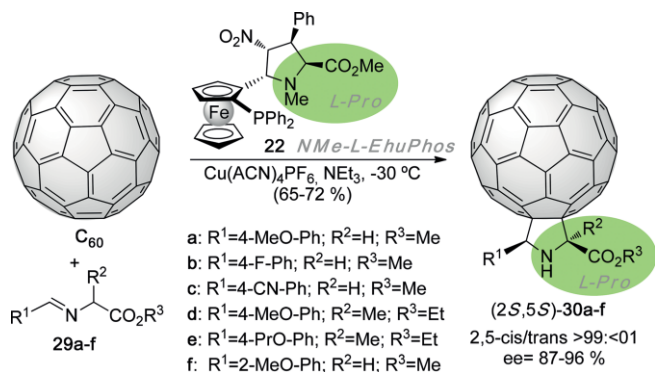
Figure 3. Transition structures *endo-TS1* and *exo-TS1* leading to (3+2) cycloadducts *endo-28aa* and *exo-28aa*, respectively, catalysed by *EhuPhos* ligands **22** and **25**. The *L*-shaped geometry of both ligands is highlighted (see Scheme 3). Both structures have been computed at the B3LYP/6-31G(d)&LANL2DZ:PM8 level of theory. Bond lengths are given in Å. This Figure was made using Cartesian coordinates reported in ref.<sup>[18]</sup>.

*NMe-L-EhuPhos* ligand **22** was also used by Martin et al.<sup>[19]</sup> in the diastereo- and enantioselective (3+2) cycloaddition between C<sub>60</sub> and *N*-metallated azomethine ylides derived from imines **29a-f**. Also in this case, the *L*-catalyst yields *L*-cycloadducts (Scheme 6) with good chemical yields and excellent stereocontrol. It is interesting to note that in this series of experiments chiral quaternary centers at the  $\alpha$ -position of the unnatural proline ring could be generated with excellent enantiocontrol.

DFT calculations<sup>[19]</sup> showed that the blockade of the (2*Re*, 5*Re*) prochiral side of the azomethine ylide is associated with the preferred conformation of ligand **22**, whose rigidity stems from the interaction of the phosphine moiety and the methoxycarbonyl group of the proline moiety with the Cu<sup>I</sup> metallic center. Therefore, in this case *NMe-L-EhuPhos* **22** behaves as a *P,O*-ligand, which interacts with the azomethine ylide but not with the dipolarophile C<sub>60</sub>. This interaction model is compatible with the high enantioselectivity observed, since transition structure (2*S*, 5*S*)-**TS2** (Figure 4) leading to the experimentally observed major cycloadducts (2*S*, 5*S*)-**30-af**, is predicted to be 3–8 kcal/mol less energetic than the alternative (2*R*, 5*R*) saddle point.

In the preceding examples, DFT calculations showed highly asynchronous and stepwise reaction paths. Actually, in the reaction between imines and nitroalkenes in the presence of Cu<sup>I</sup>





Scheme 6. (3+2) Cycloaddition between C<sub>60</sub> and imines **29** in the presence of *NMe-L-EhuPhos* ligand **22**. The retention of configuration of the L-proline scaffold in the ligand and cycloadduct is highlighted.

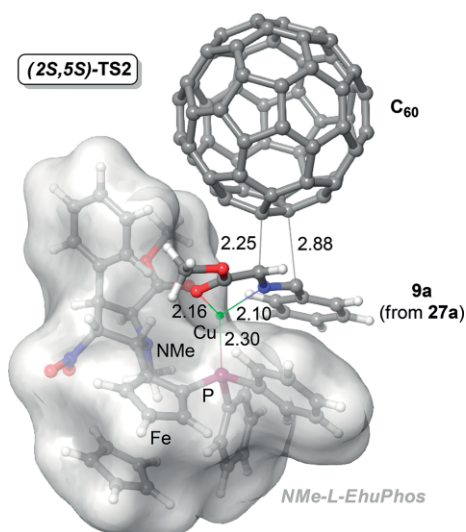
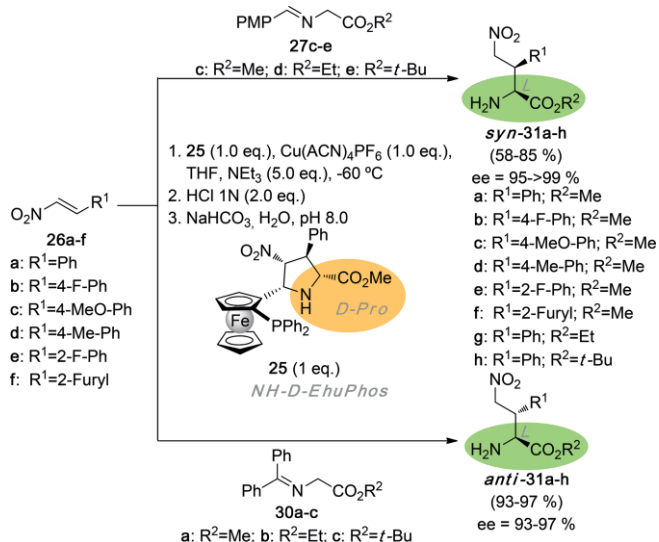


Figure 4. Transition structure **(2S,5S)-TS2**, calculated at the M06/LANL2DZ//B3LYP/LANL2DZ:PM6 level, associated with the formation of **(2S,5S)** cycloadducts **30** (see Scheme 6), in the presence of *NMe-L-EhuPhos* ligand **22**. Bond lengths are given in Å. This Figure was generated using Cartesian coordinates reported in ref.<sup>[19]</sup>.

salts (Scheme 5), the reaction takes place via zwitterionic intermediates of type **11** (Scheme 3). We reasoned that substituents that stabilize positive charges on the iminium moieties of these intermediates could frustrate the completion of the second step of the (3+2) cycloaddition, thus permitting the chemical synthesis of  $\gamma$ -nitro- $\alpha$ -amino esters and their derivatives. In effect, we found<sup>[20]</sup> that in the presence of 1 equiv. of *NH-D-EhuPhos* **25** and at -60 °C, reaction of nitroalkenes with imines **27** derived from 4-methoxybenzaldehyde permitted to isolate *syn*- $\gamma$ -nitro- $\alpha$ -amino esters **31** with excellent enantiocontrol (Scheme 7). Therefore, a simple electron donating group is enough to frustrate the (3+2) cycloaddition by stopping the stepwise process at the Michael-like addition step. Alternatively, an additional phenyl group present in imines **31** derived from acetophenone is able to frustrate the cycloaddition but, in this case, only *anti*- $\gamma$ -nitro- $\alpha$ -amino esters **32** were obtained in the presence of the same chiral ligand *NH-D-EhuPhos* **25** (Scheme 7). Also in this case, DFT calculations permitted to rationalize these different

stereochemical outcomes.<sup>[20]</sup> It is also noteworthy that, once again, *NH-D-EhuPhos*, an unnatural D-Proline ester, promoted the formation of L-amino esters via these frustrated (3+2) cycloadditions.



Scheme 7. Synthesis of *syn*- and *anti*- $\gamma$ -nitro- $\alpha$ -amino esters **32** via frustrated 1,3-dipolar reaction between nitroalkenes **26** and amines **27**, **31** with stoichiometric amounts of *NH-D-EhuPhos* ligands **25**. The D and L configurations of ligand and products are highlighted.

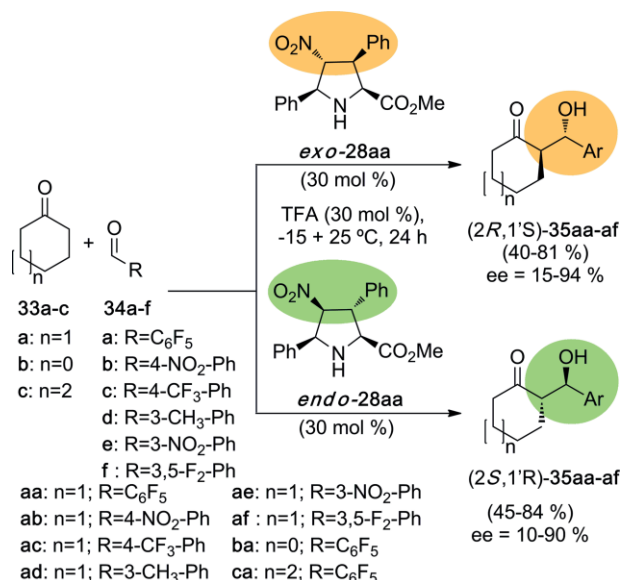
In summary, L- and D-proline-based *EhuPhos* catalysts **22** and **25** are able to promote a second generation of unnatural proline derivatives via (3+2) cycloadditions. This process is compatible with many dipolarophiles including fullerenes. In addition, the stepwise nature of the associated mechanism permits the synthesis of other  $\alpha$ -L-amino acid derivatives. It is expected that the catalytic scope of ligands **22** and **25** will be extended to other metal-assisted reactions.

## 2.2. Densely Substituted Prolines as Organocatalysts

Natural L-Proline and its derivatives constitute a privileged structure in the field of organocatalysis.<sup>[21]</sup> However, most of these organocatalysts are based on naturally occurring proline or its post-translational derivatives such as L-4-hydroxyproline or 4-L-aminoproline.<sup>[22]</sup> We reasoned that densely substituted proline derivatives such **(3+2)** cycloadducts **28** described in the preceding section could exhibit organocatalytic properties and, even more interestingly, could provide new outcomes not accessible to organocatalysts generated from the naturally occurring amino acid.

The aldol reaction was explored first.<sup>[23]</sup> Unnatural 4-nitro-L-prolines **28** in their *endo*- and *exo*-forms were tested in the aldol reaction between cyclic ketones **33** and aromatic aldehydes **34** (Scheme 8).<sup>[18,23]</sup> It was found that both L-derivatives yielded opposite enantiomers. Thus, *endo-28aa* yielded **(2S,1'R)-35** aldols, the same chiral induction generated by natural L-Pro and its derivatives. In contrast, *exo-28aa* gave rise to aldols possessing the **(2R,1'S)** stereochemistry. Therefore, since both unnatural organocatalysts **28** have L-configuration, the

stereochemistry of the distal positions with respect to the *NH* active site is responsible for the opposite enantioselectivities observed in these aldol reactions.



Scheme 8. Aldol reactions between cyclic ketones **33** and aldehydes **34** catalysed by unnatural proline esters **exo-L-28aa** and **endo-L-28aa**. The different stereochemical outcomes generated by the distal substituents of the L-cycloadducts **28** are highlighted.

DFT calculations showed that the stereochemical outcome of the aldol reactions gathered in Scheme 8 is determined by the equatorial/axial/isoclinal disposition of the four substituents of cycloadducts **28**. As it can be seen by inspection of Figure 5, both minimum energy transition structures (*2R,1'S*)-**exo-TS3** and (*2S,1'R*)-**endo-TS3** adopt conformations of the organocatalysts that maximize the number of equatorial groups. In the case of (*2R,1'S*)-**exo-TS3**, the aryl group of the aldehyde adopts a distal disposition with respect to the 5-phenyl group of the organocatalyst, whereas in the case of (*2S,1'R*)-**endo-TS3** this disposition is proximal. The relative energies emerged from these geometric features are in good agreement with the observed enantioselectivities (Figure 5).

When different substitution patterns were analyzed, it was observed that *cis*-substituents at C<sup>3</sup>,C<sup>4</sup> resulted in much less active organocatalysts than their C<sup>3</sup>,C<sup>4</sup>-*trans* congeners (Figure 6). In addition, quaternary centers at C<sup>2</sup> were found to be not convenient to generate good organocatalytic activity. These results can be rationalized in terms of the number of axial centers at the C<sup>2</sup>, C<sup>3</sup> and C<sup>4</sup> positions of the organocatalysts, since 3,4-*cis* pyrrolidine scaffolds and C<sup>2</sup> quaternized unnatural prolines must necessarily include axial substituents at the corresponding transition structures, thus raising the corresponding activation energies.

Despite their ability to catalyze aldol reactions, 4-nitroprolines **28** resulted to be unable to catalyze Michael additions of ketones and nitroalkenes. Instead of the expected conjugate addition, it was found that in the presence of equimolar amounts of acidic additives, a novel three-component reaction

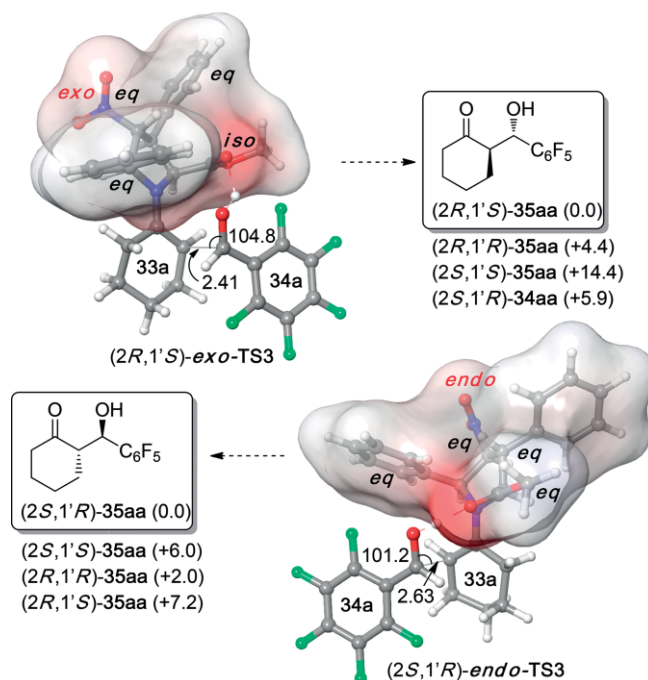


Figure 5. Optimized structures [M06-2X(PCM)/6-31G(d,p)//B3LYP(PCM)/6-31G(d) level of theory] of transition structures (*2R,1'S*)-**exo-TS3** and (*2S,1'R*)-**endo-TS3** leading to aldol adducts (*2R,1'S*)-**35aa** and (*2S,1'R*)-**35aa**, respectively. Numbers in parentheses correspond to the relative energies (in kcal/mol) of the transition structures leading to the respective stereoisomers. Bond lengths and angles are given in Å and deg, respectively. Cartesian coordinates were taken from ref.<sup>[23]</sup>.

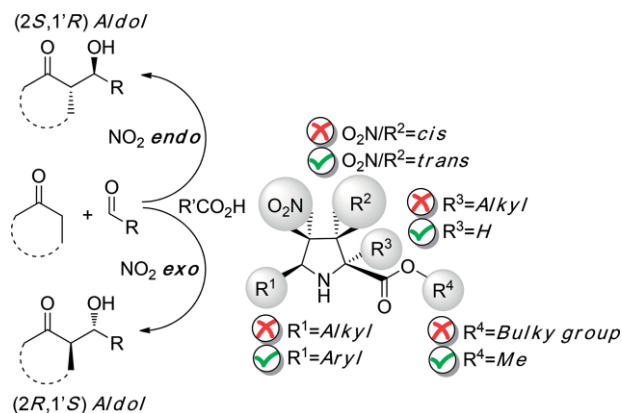
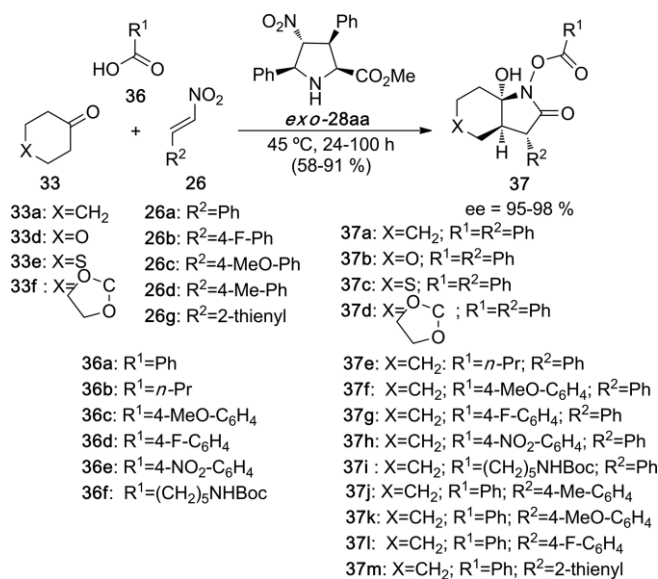


Figure 6. Effects of the substituents on the organocatalytic aldol activity of unnatural prolines **28**.

was produced.<sup>[24]</sup> This reaction, efficiently catalyzed by **exo-28aa**, consists of the synthesis of 7a-hydroxyoctahydro-2*H*-indol-2-ones **37** from ketones **33**, acids **36** and nitroalkenes **26** (Scheme 9). This unexpected addition-cyclization process involves the generation of three new chiral centers in one preparative step. In addition, it tolerates different heteroatoms at the starting ketone, as well as many substituents at the carboxylic acid and nitroalkene moieties.

Detailed experimental and computational work led to the catalytic cycle outlined in Figure 7A. After initial enamine formation and conjugate addition mediated by **TS4** (Figure 7B), the



Scheme 9. Three-component reaction between ketones **33**, acids **36** and nitroalkenes **26** to yield 7a-hydroxyoctahydro-2H-indol-2-ones **37**, catalyzed by unnatural proline ester **exo-28aa**.

key steps include an addition of the acid or the nitronate intermediate via saddle point **TS5** (Figure 7C) and a rearrangement to generate the carboxamide moiety before the cyclization step. As far as the origins of the chiral induction of **exo-L-28aa** are concerned, transition structure **TS4**, whose chief geometric features are gathered in Figure 7B, shows a very efficient blockage of one prochiral face of the nitroalkene, thus generating the final bicyclic compound with virtually complete stereocontrol.

The potential of this reaction was exemplified by its application to a concise synthesis of (+)-pancracine.<sup>[24,25]</sup> In this synthesis, adduct **37n** was obtained from readily available reactants **33f** and **26h** in satisfactory yield and virtually complete *ee*, despite working at a relatively high reaction temperature. It is interesting to note that nearly all the chiral information present in the alkaloid is generated in a single preparative step leading to adduct **37n** (Scheme 10).<sup>[24]</sup>

Although 4-nitroprolines **28** were unable to catalyze Michael reaction between ketones and nitroalkenes, we found that the corresponding amino analogs **46**, obtained by catalytic hydrogenation of their nitro precursors **28**, catalyzed very efficiently this reaction.<sup>[26]</sup> As it is shown in Scheme 11, organocatalyst **exo-46** generates Michael adducts (*2R,1'S*)-**47** with good to excellent *ee*'s. In contrast, diastereomer **endo-46** gives rise to (*2S,1'R*)-**47aa** enantiomer, similar to that produced by L-Pro, with somewhat lower *ee*. Therefore, we found that a single transformation of the nitro group to the corresponding amino derivative results in a transformation of the organocatalytic ability of the unnatural proline scaffold. Other transformations on adducts **28**<sup>[26]</sup> permitted to conclude that the exocyclic primary amino group in (3+2) cycloadducts **46** is essential for catalysis.

DFT calculations<sup>[26]</sup> on the most relevant transition structures involved in these Michael additions reproduced correctly the trends in enantioselectivity found in the experimental studies. The shape of the transition structures associated with the be-

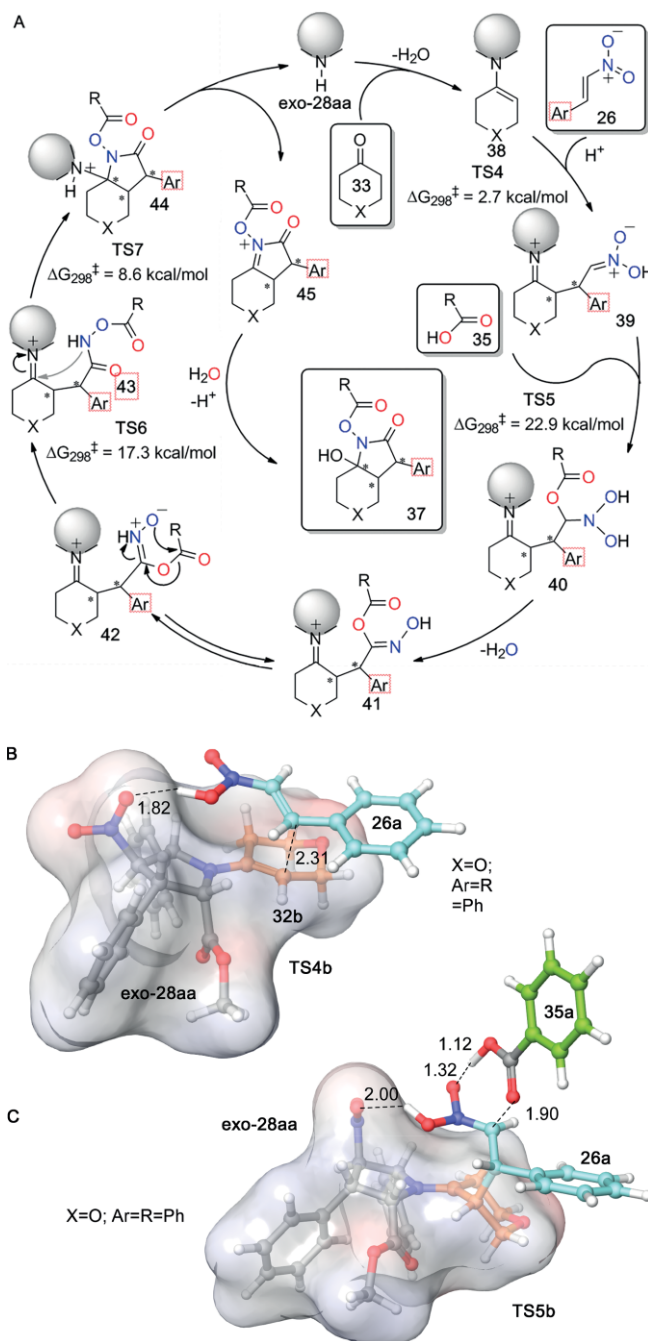
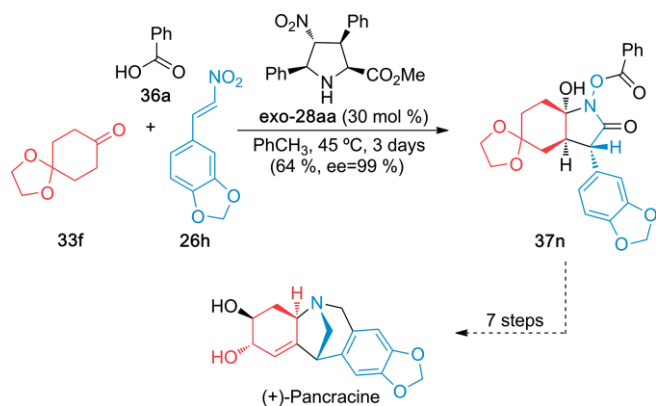


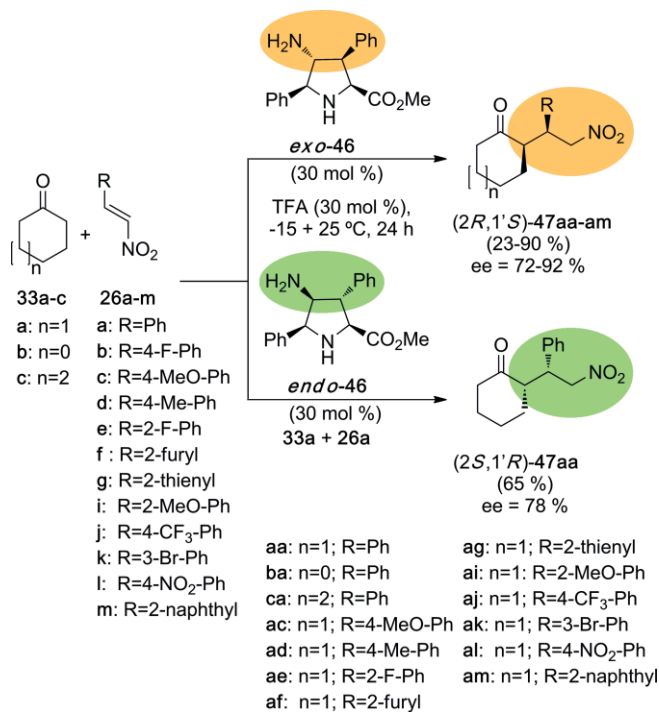
Figure 7. (A) Proposed catalytic cycle for the new reaction described in Scheme 9. Free activation energies calculated for the key steps of the **33b** + **26a** + **36a** → **37a** reaction, computed at the B3LYP-D3(PCM = cyclohexane)/6-311+G\*/B3LYP-D3/6-31G(d) level of theory, are also given. (B, C) Optimized structures for **TS4b** (B) and **TS5b** (C). Bond lengths are given in Å. This Figure was adapted from ref.<sup>[24]</sup>

havior of **exo-47** and **endo-47** showed that the enamine derived from the primary amino group must adopt axial and iso-clinal dispositions in (*R,1'S*)-**exo-TS6** and (*S,1'R*)-**endo-TS6**, respectively (Figure 8). We found that the stereocontrol is determined by the antiperiplanar conformation of the aryl substituent of the nitroalkene, by the optimal angle of attack associated with the formation of the new C–C bond and by the hydrogen bonding array between the organocatalyst and the nitro group





Scheme 10. Synthesis of (+)-pancracine initiated by the three-component reaction between ketone **33f** and nitroalkene **26h** promoted by organocatalyst **exo-28aa**. The origins of the scaffolds stemming from reactants **33f** and **26h** are highlighted in red and blue, respectively.



Scheme 11. Michael addition of cyclic ketones **33** on nitroalkenes **26** in the presence of organocatalysts **exo-46** and **endo-46**.

of the Michael acceptor. Actually, chemical transformations that eliminated these hydrogen bonds, for instance via *N*-acylation or *N*-methylation, resulted in inactive pyrrolidine derivatives, as predicted by the computational studies.

The distinct organocatalytic behavior of catalysts **28** and **46** permitted to perform selective aldol and Michael additions.<sup>[26]</sup> Thus, reaction of double electrophile **48** with cyclohexanone **33a** in the presence of **exo-28aa** yielded aldol **49** as the major isomer with good diastereo- and enantiocontrol. Subsequent reaction of this latter compound with cyclohexanone in the presence of **exo-46** gave rise to compound **anti-50** as the major diastereomer (Scheme 12). It is interesting to note that the Michael addition took place with total diastereo- and enantio-

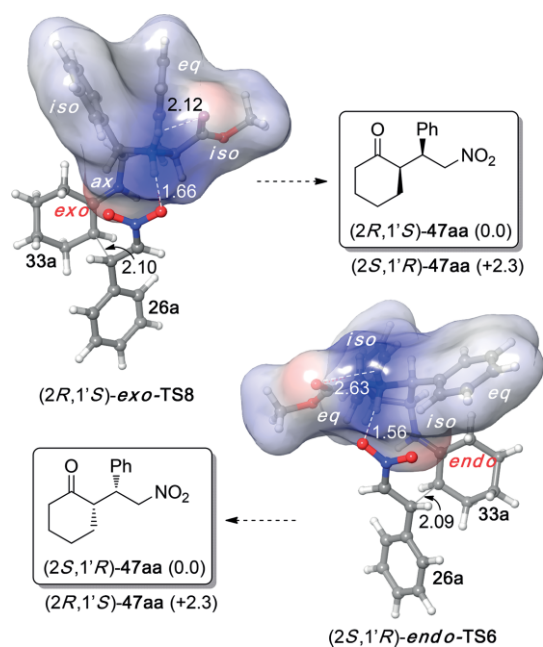
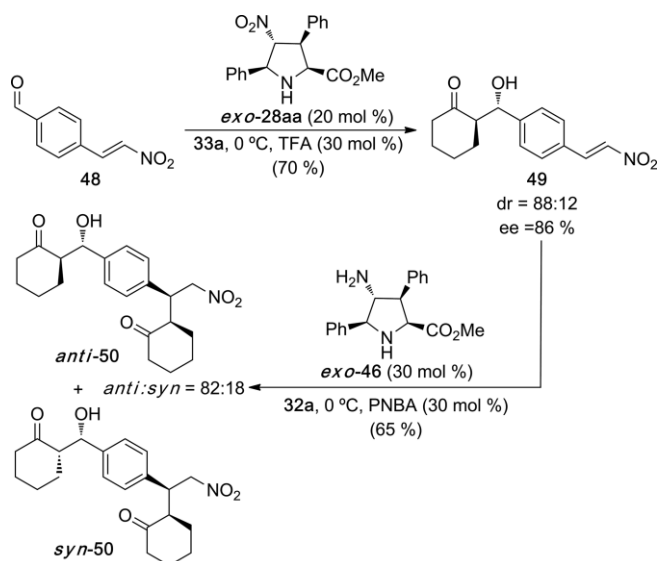


Figure 8. Optimized structures [M06-2X/6-31+G(d,p)//B3LYP/6-31G(d) level of theory] of transition structures (2*R*,1'*S*)-**exo-TS8** and (2*S*,1'*R*)-**endo-TS6** leading to Michael adducts (2*R*,1'*S*)-**47aa** and (2*S*,1'*R*)-**47aa**, respectively. Numbers in parentheses correspond to the relative energies (in kcal/mol) of the transition structures leading to the respective stereoisomers. Bond lengths are given in Å and deg, respectively. Cartesian coordinates were taken from ref.<sup>[23]</sup>.

control. However, a partial epimerization of the aldol moiety occurred and **syn-50** was obtained as a minor stereoisomer. In any case, this example indicates that unnatural organocatalysts can be used to achieve chemoselective transformations.

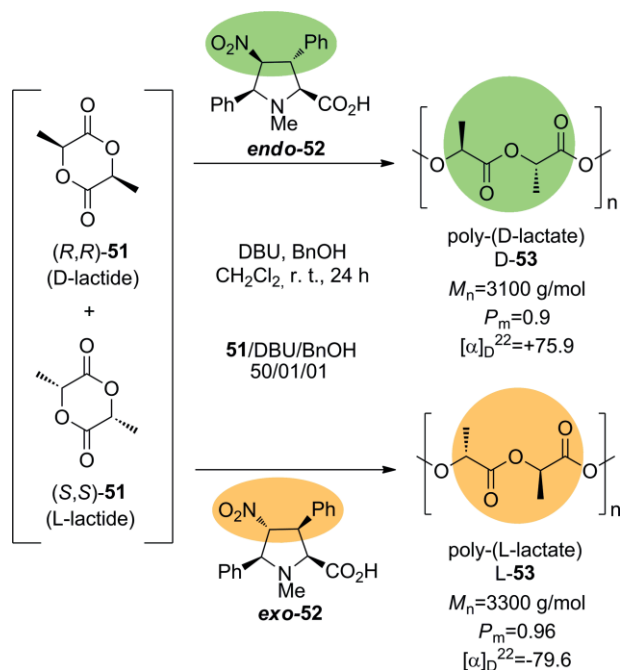


Scheme 12. Selective aldol and Michael additions on double electrophile **48** catalyzed by unnatural prolines **exo-28aa** and **exo-46**, respectively. PNBA: *para*-nitrobenzoic acid.

Highly substituted prolines formed from (3+2) cycloadditions can be used in selective polymerization reactions.<sup>[27]</sup> Using catalysts **endo**- and **exo-52**, it was found that *N*-methylated unnat-



ural proline *exo*-**52** is able to catalyze the selective polymerization of L-lactide **51** in a racemic mixture of **51**. In contrast, *endo*-**52** promoted the enantioselective polymerization of D-lactide **51**. In both cases, excellent stereoregularities (see the  $P_m$  and  $[\alpha]$  values in Scheme 13) were observed, as well as molecular weights that closely tracked the monomer-to-initiator ratio.



Scheme 13. Polymerization of racemic D- and L-lactide **51** in the presence of DBU and organocatalysts *endo*-**52** and *exo*-**52**. Benzyl alcohol was used as initiator.  $M_n$ : molecular weight.  $P_m$ : probability of *meso* linkage between monomeric units.

Also in this case, DFT calculations<sup>[27]</sup> permitted to explain the origins of this exceptional stereocontrol. The conformational flexibility of organocatalysts **52** allows different interaction patterns with the electrophilic and nucleophilic partners of the polymerization process (Figure 9). In this ring-opening polymerization (ROP) process, organocatalysis is not covalent and consists of LUMO activation of the lactide by means of its interaction with the carboxylic acid, together with HOMO activation of the nucleophilic alcohol, which is benzyl alcohol in the first catalytic cycle (methanol in our computational model), or terminal alkoxy groups of the growing chain during the polymerization process. This latter activation takes place by means of the interaction of the hydroxy group with the amino group of the organocatalyst. When *exo*-**52** catalyzes the ROP the double carboxy/methylamine interaction takes place via transition structure (*S,S*)-*exo*-**TS7**, in which the *N*-methyl group occupies an equatorial position and is *anti* with respect to the carboxy group. In contrast, in the case of *endo*-**52** these groups are *syn* to each other, which results in an axial disposition of the *N*-methyl group (Figure 9). These preferred interactions, aside the maximization of the equatorial groups of the catalysts, account for the selectivity of *exo*-**52** for L-**53** via preferred formation of first intermediate ester L-**54** and subsequent incorpo-

ration of additional equivalents of (*S,S*)-**51** (L-lactide). Similarly, these calculations resulted to be compatible with the selectivity of *endo*-**52** towards the ROP of (*R,R*)-**51** (D-lactide) to yield highly stereoregular polymer D-**53**, although with slightly lower stereocontrol.

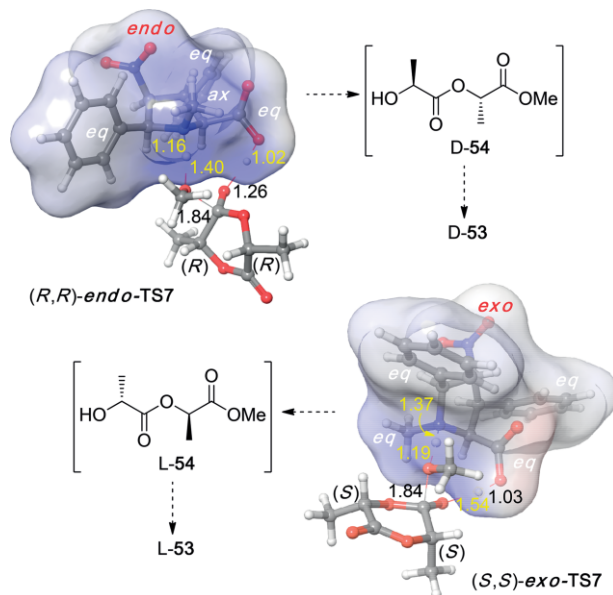
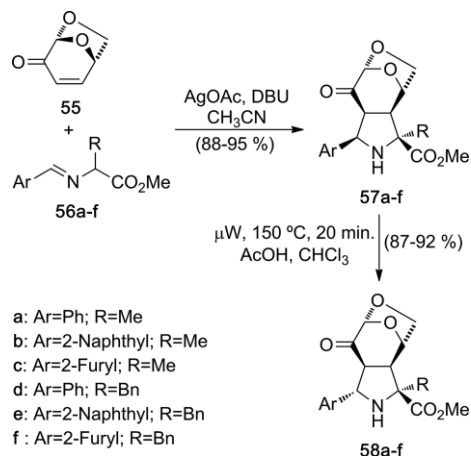


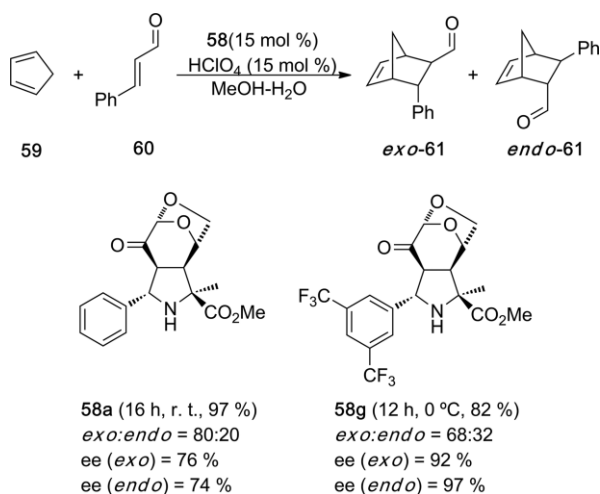
Figure 9. Optimized geometries [B3LYP/6-31G(d) level of theory] of preferred transition structures (*R,R*)-*endo*-**TS7** and (*S,S*)-*exo*-**TS7** associated with the interaction between methanol (as a model primary alcohol) and lactides (*R,R*)-**51** and (*S,S*)-**51** in the presence of *endo*-**52** and *exo*-**52** (*endo,syn*-**TS**). Distances are given in Å. Data taken from ref.<sup>[27]</sup>.

Chiral dipolarophiles can be used for the synthesis of enantiopure pyrrolidines than in turn are suitable organocatalysts. Sarotti, Suarez et al.<sup>[28]</sup> described the stereocontrolled synthesis of unnatural tricyclic proline derivatives by means of the (3+2) cycloaddition between imines **56** and levoglucosenone **55** to yield L-cycloadducts **57** via intermediate *N*-Ag azomethine ylides. These compounds isomerized under microwave irradiation to yield the thermodynamically more stable unnatural tricyclic L-proline esters **58** (Scheme 14).



Scheme 14. Synthesis of tricyclic unnatural L-proline esters **58** via (3+2) cycloaddition between levoglucosenone **55** and imines **56**.

Tricyclic unnatural L-proline esters **58** resulted to be efficient organocatalysts of Diels–Alder (DA) reactions between cyclopentadiene **59** and  $\alpha,\beta$ -unsaturated aldehydes such as cinnamaldehyde **60**. For instance, **58a** promoted the formation of norbornenes **61** with moderate *exo*-selectivity and ee's (Scheme 15). Intensive computational analysis of the DA reactions led to Sarotti et al.<sup>[29]</sup> to predict that organocatalyst **58g** should be more efficient in terms of enantiocontrol. This prediction was successfully corroborated by the experiment (Scheme 15).



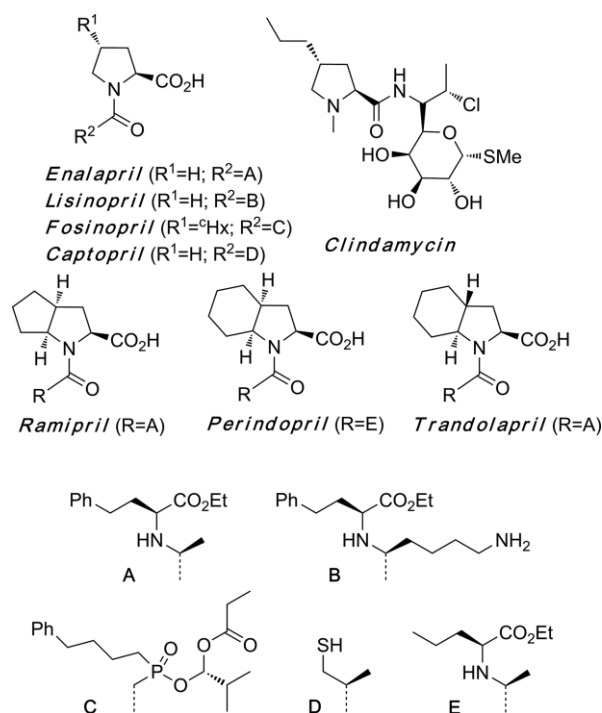
Scheme 15. Diels–Alder reaction between cyclopentadiene **59** and cinnamaldehyde **60** catalysed by (3+2) L-cycloadducts **58a** and **58g**.

In summary, the examples shown in this section demonstrate that densely substituted unnatural proline derivatives possess interesting covalent organocatalytic properties mediated by enamine intermediates. These unusual properties range from the reverse enantiocontrol induced from distal configurations with respect to the active sites, to different scopes by simple change of functional groups, including the ability to catalyze an unexpected complex three-component cyclization reaction. In addition, the above discussed example of enantioselective polymerization permits to expect further developments in non-covalent organocatalysis induced by this kind of synthetic organocatalysts.

### 3. Unnatural Synthetic Prolines as Biologically Active Compounds

Pyrrolidines are considered privileged structures in medicinal chemistry.<sup>[30]</sup> According to the definition proposed by Evans,<sup>[31]</sup> these saturated heterocycles are capable of providing useful ligands for more than one receptor. Therefore, “judicious modifications of such structures could be a viable alternative in the search for new receptor agonists and antagonists”.<sup>[31]</sup> More recently, an analysis of privileged structures based on Shannon entropy formalism<sup>[32]</sup> suggests that “heterocyclic, sp<sup>3</sup>-rich frameworks are particularly suited for target-focused library design.” Actually, an analysis of the structural diversity and substi-

tution patterns of nitrogen heterocycles among U.S. FDA approved pharmaceuticals<sup>[33]</sup> revealed that the pyrrolidine ring is the fifth heterocycle present in approved drugs. Among the 37 pyrrolidine-containing pharmaceuticals, eight of them incorporate the proline scaffold, with 1–3 additional substituents (Scheme 16). All these compounds are angiotensin converting enzyme (ACE) inhibitors,<sup>[34]</sup> with the exception of Clindamycin, an antibiotic for the treatment of several bacterial infections.<sup>[35]</sup>



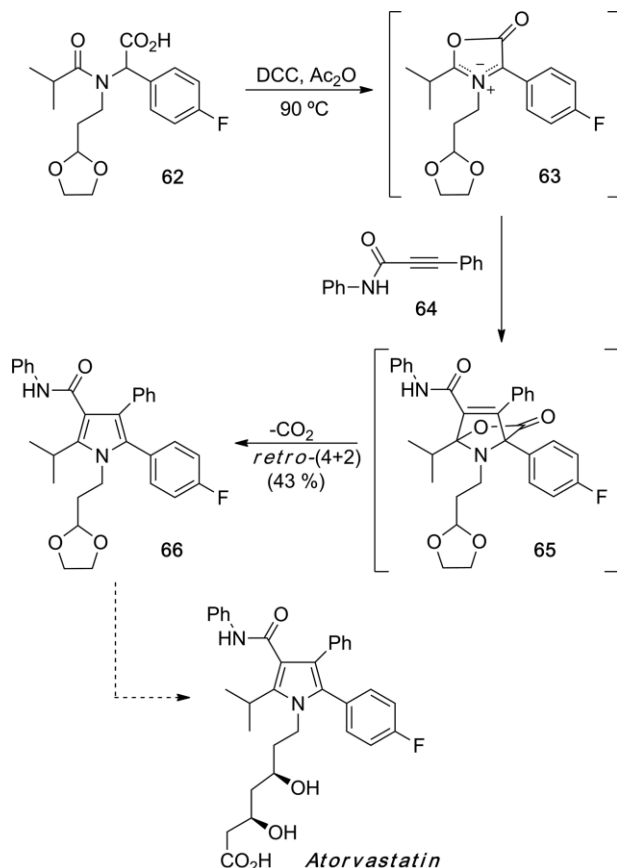
Scheme 16. U.S. FDA approved pharmaceuticals containing proline scaffolds.

The above indicated pharmaceuticals can be obtained by derivatization of L-proline or other post-translational proline derivatives. Therefore, as far as the chemical synthesis of highly prescribed drugs is concerned, to date (3+2) cycloadditions have been used for the synthesis of other aromatic five-membered nitrogen containing pharmaceuticals<sup>[36]</sup> such as celecoxib.<sup>[37]</sup> One patented synthesis of prescription drug atorvastatin<sup>[38]</sup> is an exception to this statement (vide infra). In the following sections the synthesis of biologically active substituted prolines or their aromatized 1*H*-pyrrole derivatives is presented. Although these compounds are not in clinical use so far, most likely the role of these compounds (or their analogs) in Medicinal chemistry will be more relevant in the years to come.

#### 3.1. Synthesis of Biologically Active Racemic Prolines via (3+2) Cycloadditions

Racemic proline derivatives are useful intermediates in the synthesis of pharmaceuticals when aromatization processes occur during or after the (3+2) cycloaddition to yield substituted 1*H*-

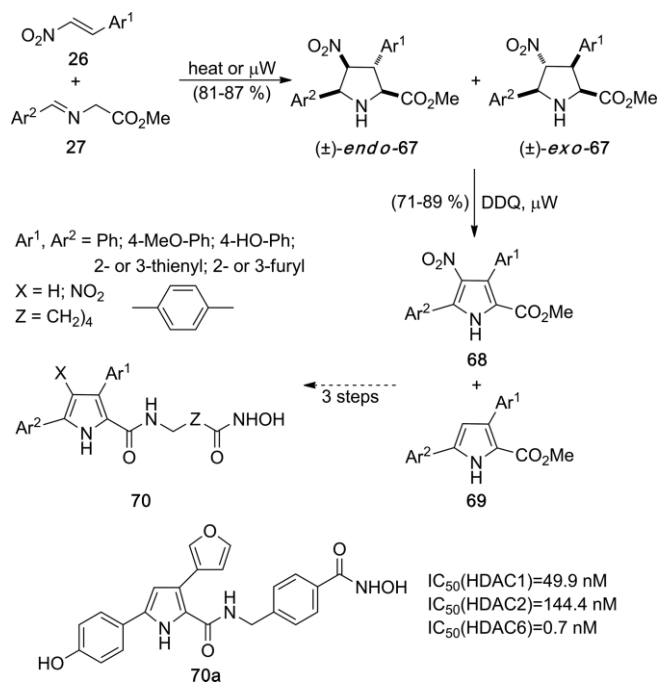
pyrroles. A relevant example consists of the (3+2) cycloaddition/(4+2) cycloreversion of azomethine ylide **63** (derived from amino acid **62**) with alkyne **64** to yield cycloadduct **65** that in situ decarboxylates to yield pentasubstituted 1*H*-pyrrole **66**,<sup>[38]</sup> a key precursor of atorvastatin (Scheme 17), a prescription drug used to lower blood cholesterol.



Scheme 17. Synthesis of atorvastatin by (3+2) cycloaddition between azomethine ylide **63** and alkyne **64**.

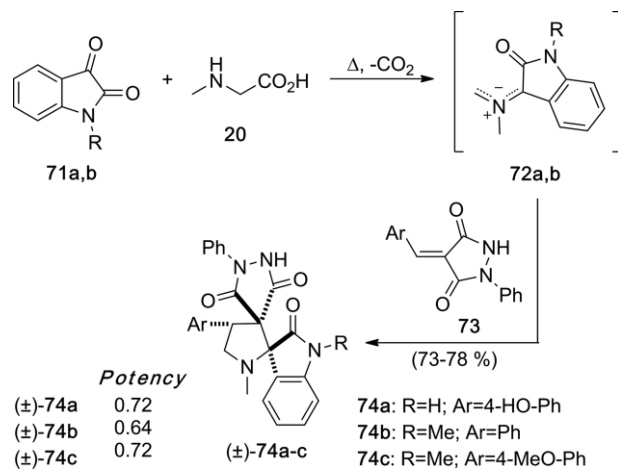
Another example of synthesis of biologically active 1*H*-pyrroles by aromatization of pyrrolidines is the synthesis of histone deacetylase (HDAC) inhibitors via (3+2) cycloaddition between imines **27** and nitroalkenes **26**.<sup>[39]</sup> Under thermal conditions, mixtures of *endo*- and *exo*-cycloadducts **67** were formed, whose aromatization under thermal heating or microwave irradiation<sup>[8a]</sup> gave mixtures of methyl 3,5-diaryl-1*H*-pyrrole-2-carboxylates **68** and **69**. Subsequent functionalization of these latter aromatic cycloadducts led to hydroxamic acids **70**, which in some cases such as of compound **70a**, resulted to be very potent HDAC inhibitors, with IC<sub>50</sub> values within the picomolar range<sup>[40]</sup> (Scheme 18). This latter molecule has shown strong growth-inhibitory effect in Burkitt's cell lymphoma, follicular lymphoma and, especially, mantle cell lymphoma (MCL).<sup>[40b]</sup>

Racemic dispiropyrrrolidines constitute potentially useful anti-inflammatory agents.<sup>[41]</sup> Reaction of isatins **71** with sarcosine **20** led to the formation of fleeting azomethine ylides **72**, whose



Scheme 18. Synthesis of HDAC inhibitors via consecutive (3+2) cycloaddition/aromatization reactions.

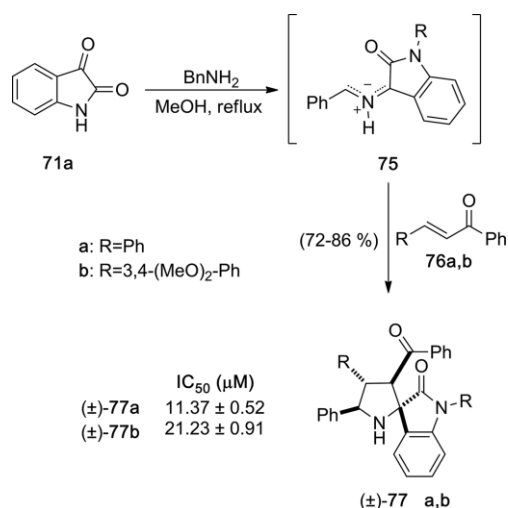
reaction with dipolarophile **73** yielded racemic tricyclic dispiropyrrrolidines **74** in good yields (Scheme 19). These racemic compounds showed interesting in vivo anti-inflammatory activity, measured as aedema inhibition.



Scheme 19. Synthesis of anti-inflammatory racemic dispiropyrrrolidines (±)-**74** by reaction of isatins **71a,b** with sarcosine **20**. Potencies were measured with respect to reference standard indometracin.

A similar approach was followed to synthesize inhibitors of advanced glycation end product, which is a relevant target in the treatment of diabetes mellitus.<sup>[42]</sup> Reaction of isatin **71a** with benzylamine led to highly substituted racemic spiroprolines **77** with excellent diastereocontrol and chemical yields via reaction of azomethine ylide **75** with  $\alpha,\beta$ -unsaturated ketones **76**. (Scheme 20).





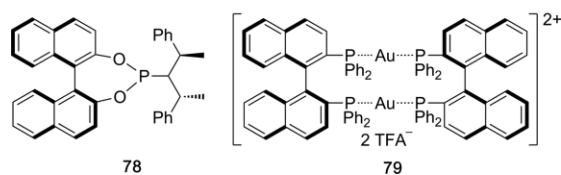
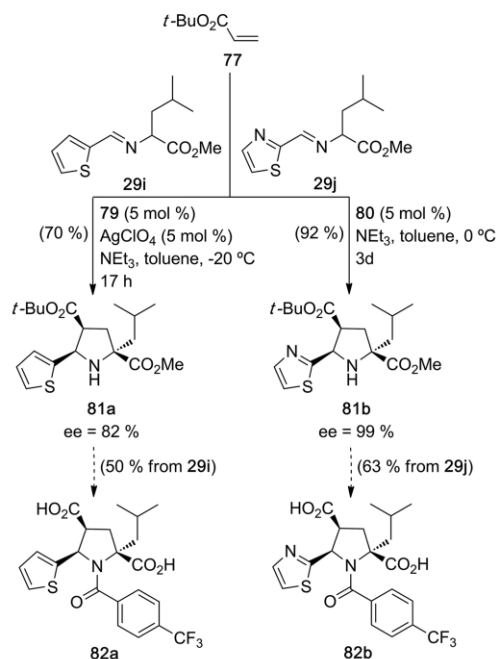
Scheme 20. Synthesis of inhibitors of advanced glycation end products by (3+2) cycloaddition between azomethine ylide **75** and  $\alpha,\beta$ -unsaturated ketones **76**.

### 3.2. Synthesis of Biologically Active Prolines via Asymmetric Catalysis on (3+2) Cycloadditions

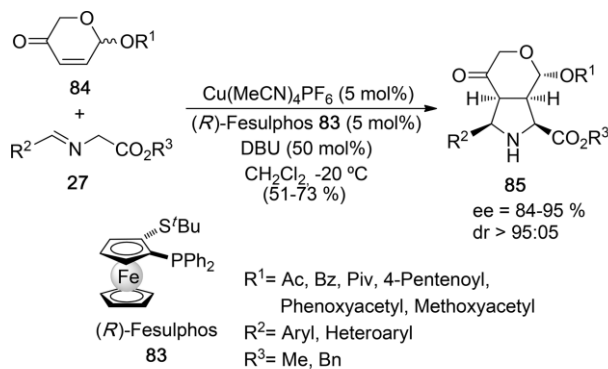
Nájera and Sansano<sup>[43]</sup> have demonstrated the usefulness of 1,3-dipolar reactions with *N*-metallated azomethine ylides for the synthesis of drug candidates for hepatitis C treatment. Reaction of *tert*-butyl acrylate **78** with imines **29i,j** led to substituted *L*-prolines **81a,b** with high chemical yield and diastereo- and enantiocontrol in the presence of chiral ligands **79**<sup>[44]</sup> and **80**<sup>[45]</sup> and using Ag<sup>I</sup> and Au<sup>I</sup> metallic salts, respectively (Scheme 21). *N*-Acylation and deprotection of both ester groups led to the inhibitors of hepatitis C virus **82a,b** in good overall yields and excellent enantioselectivities.

Using (*R*)-Fesulphos **83** as chiral ligand, Antonchick and Waldmann<sup>[46]</sup> described the enantioselective synthesis of iridoid-inspired bicyclic proline derivatives (Scheme 22) by means of a (3+2) cycloaddition between imines **27** and racemic 2*H*-pyran-3(6*H*)-one derivatives **84**. Under the reaction conditions gathered in Scheme 22, the authors obtained bicyclic (3+2) cycloadducts with good yields and stereoselectivities. In all the reported examples, *endo* diastereomers were obtained with diastereomeric excesses of ca. 90 % and ee's up to 96 %, *L*-proline configuration being the major one. Since only the (*S*)-enantiomer of dipolarophiles **84** was able to react with the corresponding imine **27**, the method provides a kinetic resolution of racemic 2*H*-pyran 3(6*H*)-ones **84**. Among the 28 cycloadducts thus synthesized, five of them showed promising inhibitory activity of the Hedgehog (Hh) and Wingless/integration (Wnt) signaling pathways (Scheme 22).<sup>[46]</sup>

The same research group<sup>[47]</sup> reported the synthesis of functionalized tropanes by means of (3+2) cycloaddition between nitroalkenes **86** and azomethine ylides derived from tryptophan derivatives **87** (Scheme 23). Using Cu<sup>I</sup> as source of the *N*-metallated azomethine ylide and (*R*)-Fesulphos **83** as chiral ligand, the authors obtained tetracyclic proline esters **88** in good yields and excellent ee's. In this case, *exo* cycloadducts were obtained. The structure of amino esters **88** is closely related to that of tropanes, whose biological activity in naturally occurring com-



Scheme 21. Asymmetric synthesis of hepatitis C virus polymerase inhibitors **82a,b** from imines **29i,j**.

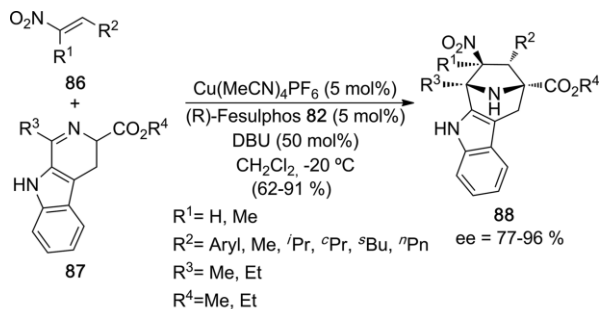


	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	IC <sub>50</sub> (μM)
<b>85a</b>	Ac	4-Br-Ph	Me	4.4±0.5 (Wnt)
<b>85b</b>	Ac	2-F-Ph	Me	7.5±0.9 (Wnt)
<b>85c</b>	Phenoxyacetyl	β-Naphthyl	Me	3.1±0.6 (Wnt)
<b>85d</b>	4-Pentenyl	α-Naphthyl	Me	4.3±1.8 (Hh)
<b>85e</b>	Methoxyacetyl	β-Naphthyl	Me	5.0±1.3 (Hh)
<b>85f</b>	Methoxyacetyl	β-Naphthyl	Bn	5.9±1.0 (Hh)

Scheme 22. Synthesis of Hedgehog (Hh) and Wingless/integration (Wnt) signaling pathways inhibitors **85** from 2*H*-pyran-3(6*H*)-one dipolarophiles **84** and imines **27**.

pounds is well known. The authors prepared 22 (3+2) cycloadducts **88**. In three cases, significant Hh activity was observed (Scheme 23). Interestingly, the chiral configuration of these

(3+2) cycloadducts was found to be relevant for biological activity, since in the case of racemic **88a** no Hh inhibitory activity was observed.<sup>[47]</sup>

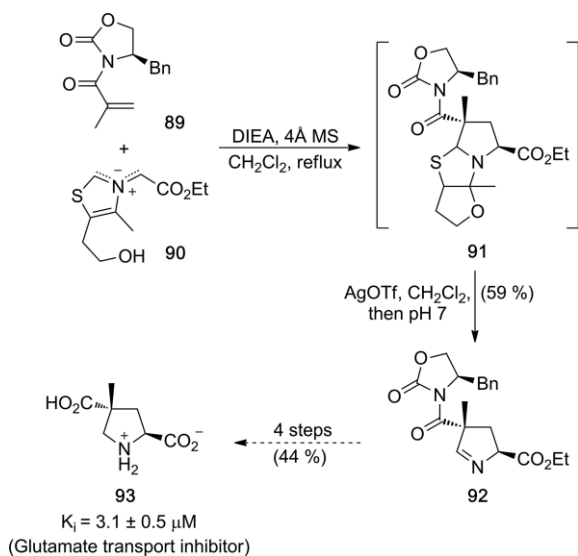


	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	IC <sub>50</sub> (μM)
<b>88a</b>	Me	Me	Me	Me	3.83±0.89
<b>88b</b>	H	( <i>NH</i> )-Indol-3-yl	Me	Et	2.21±0.34
<b>88c</b>	H	2,4-(MeO) <sub>2</sub> -Ph	Me	Et	3.68±0.69

Scheme 23. Synthesis of Hedgehog (*Hh*) signaling pathway inhibitors **88** from nitroalkenes **86** and tryptophan-derived imines **87**.

### 3.3. Synthesis of Biologically Active Prolines via (3+2) Cycloadditions Involving Enantiopure Dipolarophiles

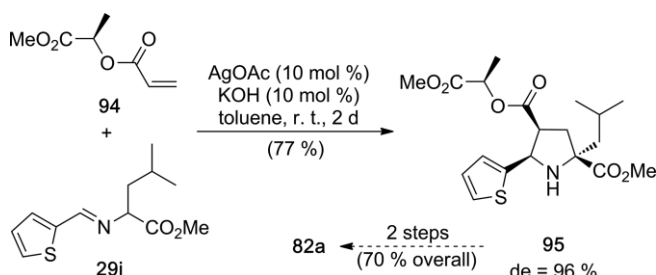
1,3-Dipolar reactions between azomethine ylides usually require  $\pi$ -deficient alkenes incorporating electron-withdrawing groups such as carboxamido, ester or nitro groups. A relevant example of dipolarophiles incorporating chiral esters consists of the reaction between azomethine ylide **90** and enantiopure alkene **89** to yield tricyclic (3+2) adduct **91**. Treatment of this latter compound with AgOTf led to 3,4-dihydro-2*H*-pyrrole **92** together with two additional diastereomers in a diastereomeric excess of 66%. Compound **92** was converted to (2*S*,4*R*)-**93** (Scheme 24). This proline derivative proved to be a potent in-



Scheme 24. Synthesis of glutamate transport inhibitors **93** by reaction between azomethine ylide **90** and chiral alkene **89**.

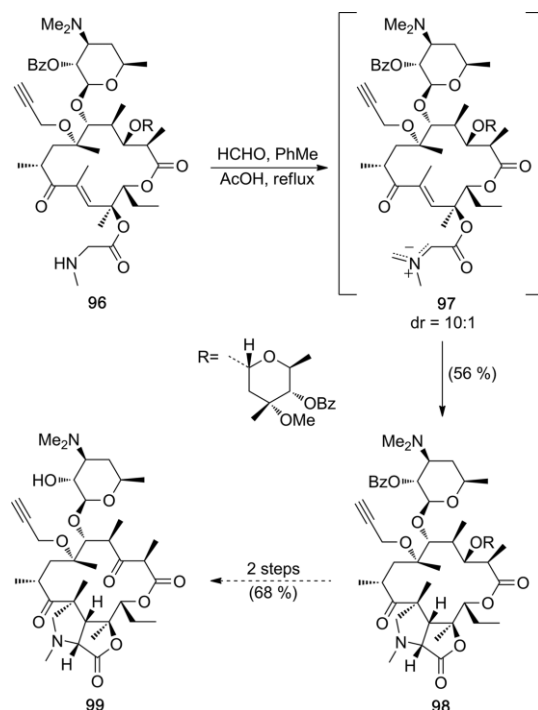
hibitor of CNS L-glutamate neurotransmitter transporters. Interestingly, (2*S*,4*R*)-**93** showed non-substrate inhibitory activity, in contrast with the biological behavior observed for its non-methylated analogue.<sup>[48]</sup>

Nájera, Sansano et al.<sup>[49]</sup> used acrylates derived from (*R*) and (*S*)-lactate to synthesize hepatitis C inhibitors **82** (Scheme 25). Reaction between imine **29i** and (*R*)-acrylate **94** [prepared from acrylic acid and methyl (*R*)-lactate] in the presence of silver acetate yielded unnatural L-proline **95** with excellent diastereomeric excess. Subsequent derivatization of this latter cycloadduct permitted to obtain compound **82a** with high yield and enantiocontrol. A similar route starting from (*S*)-lactic acid led to *ent*-**82b**.



Scheme 25. Synthesis of hepatitis C virus inhibitor **82a** from chiral acrylate **94**.

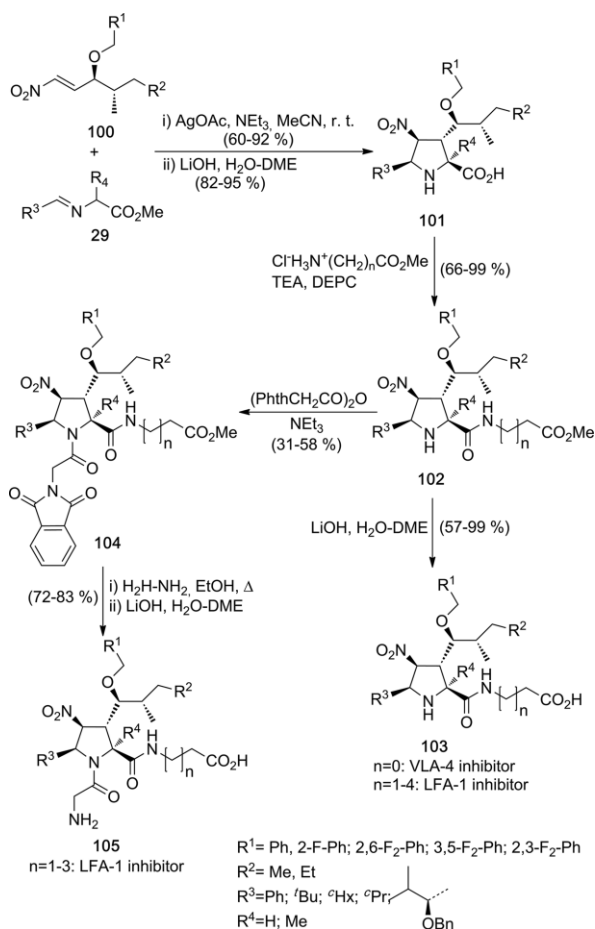
The 1,3-dipolar reaction between azomethine ylides and  $\alpha,\beta$ -unsaturated carbonyl compounds can be extended to intramolecular processes that actually involve a common chiral precursor. For instance, in situ formation of azomethine ylides **97** (Scheme 26) from amine **96** led to a tricyclic cycloadduct **98**.<sup>[50]</sup>



Scheme 26. Synthesis of an analogue of antibacterial agent cethromycin **99** by intramolecular (3+2) cycloaddition of azomethine ylide **97**.

Compound **99**, which incorporates a highly substituted polycyclic L-proline scaffold, is a cyclic analogue of antibacterial agent cethromycin and was obtained from **98** after a deprotection/oxidation sequence.

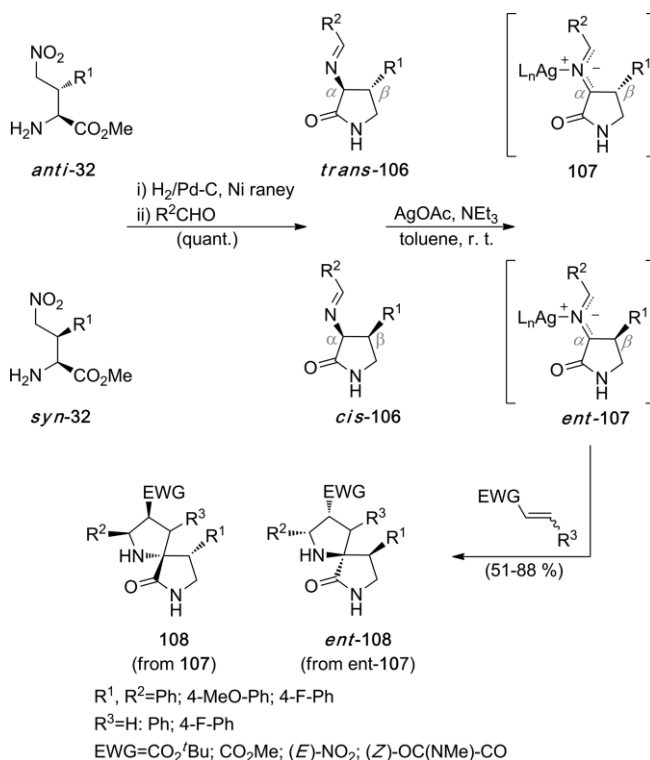
Enantiopure nitroalkenes can also be used for the synthesis of biologically active compounds. We prepared chiral nitroalkenes **100** from L-Leu and L-Ile (Scheme 27). These latter dipolarophiles reacted with *N*-Ag azomethine ylides derived from imines **29** to yield, after a (3+2) cycloaddition/ester hydrolysis sequence, L-prolines **101** with excellent *endo* diastereocontrol.<sup>[51]</sup> Subsequent amide coupling with linear amino esters and hydrolysis led to compounds **103**. When the coupling reactions were carried out with glycine methyl ester ( $n = 0$ ), the corresponding adducts showed excellent inhibitory activity of Very Late Antigen-4 (VLA-4), an  $\alpha_4\beta_1$  integrin involved in murine models of hepatic melanoma metastasis.<sup>[51]</sup> On the other hand, when  $n = 1,4$  adducts **103** showed excellent antagonists ability of Leucocyte Function Associated Antigen-1 (LFA-1)  $\alpha_L\beta_2$  integrin,<sup>[52]</sup> which is involved in early and late stages of cancer development. Alternatively, *N*-acylation of compounds **102** followed by deprotection of the phthalimido group yielded compounds **105**, which also showed LFA-1 antagonist activity in a murine model of colon cancer<sup>[52]</sup> (Scheme 27).



Scheme 27. Synthesis of VLA-4 and LFA-1 integrin inhibitors **103** and **105** via (3+2) cycloadditions involving enantiopure nitroalkenes **100**.

### 3.4. Synthesis of Biologically Active Prolines via (3+2) Cycloadditions Involving Enantiopure Azomethine Ylides

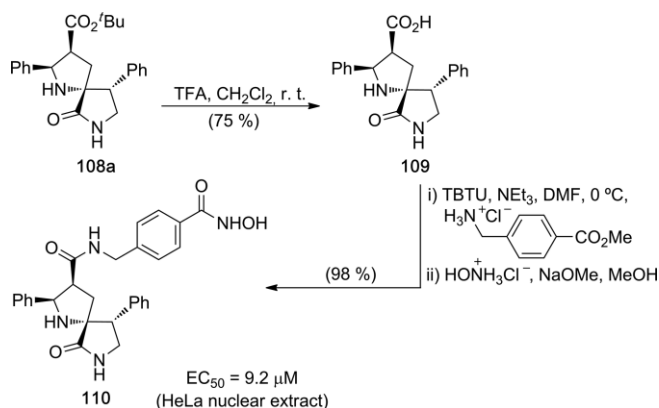
In Section 2.1, we have shown that *NH*-D-*EhuPhos* **25** can react with imines **27c-e** and **31a-c** to yield *syn*- and *anti*- $\gamma$ -nitro- $\alpha$ -amino esters **32** by an interrupted stepwise 1,3-dipolar reaction that stops at the Michael addition step.<sup>[20]</sup> From these amino esters we generated *cis*- and *trans*- $\gamma$ -lactams **106** after a catalytic hydrogenation/imine formation sequence (Scheme 28). In situ formation of the *N*-Ag azomethine ylides **107** and reaction with suitable dipolarophiles yielded spiro-L-proline derivatives **108** with excellent *endo* stereocontrol. It is noteworthy that the chiral information of  $\alpha$ -carbon atoms of  $\gamma$ -lactams **106** is lost after formation of the corresponding azomethine ylides. Therefore, the chirality of the C <sub>$\beta$</sub>  atom of the 1,3-dipoles is the only responsible for the formation of one given enantiomer of (3+2) cycloadducts **108**, which incorporate up to four additional chiral centers.



Scheme 28. Formation of spiro-L-prolines **108** from  $\gamma$ -nitro- $\alpha$ -amino esters **32**.

Some of these spiro-L-proline lactams showed interesting biological activity.<sup>[20]</sup> For example, spiro compound **108** with R<sup>1</sup> = R<sup>2</sup> = Ph and EWG-R<sup>3</sup> = *N*-methyl phthalimido is an inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme with IC<sub>50</sub> = 5  $\mu\text{M}$ . In addition, conversion of *tert*-butyl ester **108a** into acid **109**, followed by *N*-acylation, deprotection of the methyl ester and *N*-hydroxyamidation led to hydroxamic acid **110** with good yield (Scheme 29). This latter compound showed antiproliferative activity in HeLa nuclear extracts via HDAC inhibition.<sup>[20]</sup>





Scheme 29. Synthesis of HDAC inhibitor **110** from spiro-L-proline derivative **108a**.

## 4. Conclusions and Outlook

The pyrrolidine ring present in L-Pro represents a good compromise between preorganization and a certain conformational flexibility. Highly substituted unnatural proline derivatives allow for the incorporation of chirality sources and additional functional groups. These features confer convenient properties upon densely substituted unnatural proline scaffolds. Fortunately, (3+2) cycloaddition between azomethine ylides and  $\pi$ -deficient alkenes is a powerful chemical tool to generate the pyrrolidine ring in a highly regio-, diastereo- and enantiocontrolled manner. This stereochemical control can be achieved by using enantiopure reactants and by means of asymmetric catalysis.

The (3+2) cycloaddition between enantiopure ferrocenyl imines and nitroalkenes leads to the synthesis of chiral *EhuPhos* ligands, in which the interplay between planar and central chiralities results in highly efficient and selective P-, P,O- and P,N-ligands. These ligands can be used as chiral catalysts in other chemical transformations, including asymmetric (3+2) cycloaddition between similar reactants, to generate an off-spring of unnatural L-proline derivatives.

These latter cycloadducts are excellent organocatalysts (off-spring catalysts) in different reactions that include aldol and Michael additions, as well as enantioselective ring opening polymerizations. In one case, an unexpected three-component reaction has been observed. The behavior of these unnatural L-prolines is different to that observed for organocatalysts derived from the natural amino acid. In particular, the origins of the stereocontrol are related to the chirality of the distal substituents with respect to the active site. Thus, *endo* and *exo* cycloadducts show different stereochemical outcomes. The possibilities of this kind of organocatalysts in both enamine (HOMO raising) and non-covalent (LUMO lowering) catalysis remain largely unexplored.

The above-mentioned tradeoff between preorganization and flexibility present in the  $\text{sp}^3$ -rich pyrrolidine ring can be useful in the chemical synthesis of novel biologically active unnatural proline derivatives. A relatively reduced number of molecules of this kind of compounds has been reported so far. However, we are convinced that the favorable features of the (3+2) cyclo-

addition between azomethine ylides and alkenes will be increasingly used in the synthesis of proline derivatives as privileged structures for drug discovery.

## Acknowledgments

Financial support was provided by the Ministerio de Economía y Competitividad (MINECO) of Spain and FEDER (projects CTQ2016-80375-P and Red de Excelencia Consolider CTQ2014-51912-REDC) and the Basque Government (GV/EJ, grant IT-324-07). The authors thank the SGI/IZO-SGIker UPV/EHU and the DIPC for generous allocation of computational and analytical resources.

**Keywords:** 1,3-Dipolar reactions · Cycloaddition · Asymmetric catalysis · Organocatalysis · Medicinal chemistry

- [1] L. M. Harwood, R. J. Vickers in *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Eds.: A. Padwa, W. H. Pearson), J. Wiley & Sons, Hoboken, NJ, **2002**, pp. 169–252.
- [2] a) S. Sankararaman in *Pericyclic Reactions - A Textbook*, Wiley-VCH, **2005**, pp. 169–191; b) F. E. Held, S. B. Tsogoeva, *Catal. Sci. Technol.* **2016**, *6*, 645.
- [3] a) G. Pandey, P. Banerjee, S. R. Gadre, *Chem. Rev.* **2006**, *106*, 4484–4517; b) L. M. Stanley, M. P. Sibi, *Chem. Rev.* **2008**, *108*, 2887–2902; c) J. Adrio, J. C. Carretero, *Chem. Commun.* **2011**, *47*, 6784–6794; d) C. Najera, J. M. Sansano, M. Yus, *J. Braz. Chem. Soc.* **2010**, *21*, 377–412; e) R. Narayan, M. Potowski, Z.-J. Jia, A. P. Antonchick, H. Waldmann, *Acc. Chem. Res.* **2014**, *47*, 1296–1310.
- [4] a) A. de Cozar, F. P. Cossio, *Phys. Chem. Chem. Phys.* **2011**, *13*, 10858–10868; b) A. Arrieta, M. C. de la Torre, A. de Cozar, M. A. Sierra, F. P. Cossio, *Synlett* **2013**, *24*, 535–549.
- [5] a) I. Fleming in *Molecular Orbitals and Organic Chemical Reactions*, J. Wiley & Sons, Chichester, U. K. **2010**, pp. 258–260; b) R. B. Woodward, R. Hoffmann in *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim, **1970**.
- [6] a) C. Di Valentin, M. Freccero, R. Gandolfi, A. Rastelli, *J. Org. Chem.* **2000**, *65*, 6112–6120; b) Y. Lan, K. N. Houk, *J. Am. Chem. Soc.* **2010**, *132*, 17921–17927; c) G. Jin, J. Sun, R.-Y. Yang, C.-G. Yan, *Sci. Rep.* **2017**, *7*, 46470; d) S. Emamian, *RSC Adv.* **2016**, *6*, 75299–75314.
- [7] a) S. Vivanco, B. Lecea, A. Arrieta, P. Prieto, I. Morao, A. Linden, F. P. Cossio, *J. Am. Chem. Soc.* **2000**, *122*, 6078–6092; b) Q. Li, C.-H. Ding, X.-L. Hou, L.-X. Dai, *Org. Lett.* **2010**, *12*, 1080–1083; c) H. Y. Kim, J.-Y. Li, S. Kim, K. Oh, *J. Am. Chem. Soc.* **2011**, *133*, 20750–20753; d) K. Imae, T. Konno, K. Ogata, S. Fukuzawa, *Org. Lett.* **2012**, *14*, 4410–4413; e) L. M. Castello, C. Najera, J. M. Sansano, O. Larranaga, A. de Cozar, F. P. Cossio, *Org. Lett.* **2013**, *15*, 2902–2905; f) X.-X. Yan, Q. Peng, Q. Li, K. Zhang, J. Yao, X.-L. Hou, Y.-D. Wu, *J. Am. Chem. Soc.* **2008**, *130*, 14362–14363.
- [8] a) A. Arrieta, D. Otaegui, A. Zubia, F. P. Cossio, A. Diaz-Ortiz, A. de la Hoz, M. A. Herrero, P. Prieto, C. Foces-Foces, J. L. Pizarro, M. I. Arriortua, *J. Org. Chem.* **2007**, *72*, 4313–4322; b) R. Grigg, *Chem. Soc. Rev.* **1987**, *16*, 89–121.
- [9] a) M. Ayerbe, A. Arrieta, F. P. Cossio, A. Linden, *J. Org. Chem.* **1998**, *63*, 1795–1805; b) S. Kanemasa, O. Tsuge in *Advances in Cycloadditions*, Vol. 3 (Ed. D. P. Curran), Jai Press, Greenwich, **1993**, pp. 99–159.
- [10] H. D. Banks, *J. Org. Chem.* **2010**, *75*, 2510–2517.
- [11] a) M. P. Carroll, P. J. Guiry, *Chem. Soc. Rev.* **2014**, *43*, 819–833; b) P. J. Guiry, C. P. Saunders, *Adv. Synth. Catal.* **2004**, *346*, 497–537.
- [12] a) I. Oura, K. Shimizu, K. Ogata, S. Fukuzawa, *Org. Lett.* **2010**, *12*, 1752–1755; b) K. Shimizu, K. Ogata, S. Fukuzawa, *Tetrahedron Lett.* **2010**, *51*, 5068–5070; c) S. Fukuzawa, H. Oki, *Org. Lett.* **2008**, *10*, 1747–1750.
- [13] a) H. C. L. Abbenhuis, U. Burckhardt, V. Gramlich, A. Togni, A. Albinati, B. Mueller, *Organometallics* **1994**, *13*, 4481–4493; b) U. Burckhardt, L. Hintermann, A. Schnyder, A. Togni, *Organometallics* **1995**, *14*, 5415–5425.

- [14] I. G. Smilovic, E. Casas-Arce, S. J. Roseblade, U. Nettekoven, A. Zanotti-Gerosa, M. Kovacevic, Z. Casar, *Angew. Chem. Int. Ed.* **2012**, *51*, 1014–1018; *Angew. Chem.* **2012**, *124*, 1038.
- [15] a) R. Schuecker, A. Zirakzadeh, K. Mereiter, F. Spindler, W. Weissensteiner, *Organometallics* **2011**, *30*, 4711–4719; b) Z. Hu, Y. Li, K. Liu, Q. Shen, *J. Org. Chem.* **2012**, *77*, 7957–7967; c) X.-X. Yan, Q. Peng, Y. Zhang, K. Zhang, W. Hong, X.-L. Hou, Y.-D. Wu, *Angew. Chem. Int. Ed.* **2006**, *45*, 1979–1983; *Angew. Chem.* **2006**, *118*, 2010; d) W. Liu, D. Chen, X.-Z. Zhu, X.-L. Wan, X.-L. Hou, *J. Am. Chem. Soc.* **2009**, *131*, 8734–8735; e) W. Zeng, Y.-G. Zhou, *Org. Lett.* **2005**, *7*, 5055–5058; f) W. Gao, X. Zhang, M. Raghunath, *Org. Lett.* **2005**, *7*, 4241–4244; g) W. Zhang, Y.-I. Yoneda, T. Kida, Y. Nakatsuiji, I. Ikeda, *Tetrahedron: Asymmetry* **1998**, *9*, 3371–3380; h) J. Park, Z. Quan, S. Lee, K. Han Ahn, C.-W. Cho, *J. Organomet. Chem.* **1999**, *584*, 140–146; i) W.-P. Deng, X.-L. Hou, L.-X. Dai, Y.-H. Yu, W. Xia, *Chem. Commun.* **2000**, 285–286; j) W.-P. Deng, S.-L. You, X.-L. Hou, L.-X. Dai, Y.-H. Yu, W. Xia, J. Sun, *J. Am. Chem. Soc.* **2001**, *123*, 6508–6519; k) S.-L. You, X.-L. Hou, L.-X. Dai, Y.-H. Yu, W. Xia, *J. Org. Chem.* **2002**, *67*, 4684–4695; l) E. Manoury, J. S. Fossey, H. Aiet-Haddou, J.-C. Daran, G. G. A. Balavoine, *Organometallics* **2000**, *19*, 3736–3739; m) T. Sammakia, H. A. Latham, *J. Org. Chem.* **1995**, *60*, 6002–6003; n) C. J. Richards, A. J. Locke, *Tetrahedron: Asymmetry* **1998**, *9*, 2377–2407; o) G. Jones, C. J. Richards, *Tetrahedron Lett.* **2001**, *42*, 5553–5555; p) S.-L. You, X.-Z. Zhu, Y.-M. Luo, X.-L. Hou, L.-X. Dai, *J. Am. Chem. Soc.* **2001**, *123*, 7471–7472; q) L. Dai, D. Xu, L.-W. Tang, Z.-M. Zhou, *ChemCatChem* **2015**, *7*, 1078–1082; r) H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *104*, 4151–4202.
- [16] P.-O. Delaye, M. Ahari, J.-L. Vasse, J. Szymoniak, *Tetrahedron: Asymmetry* **2010**, *21*, 2505–2511.
- [17] O. Riant, O. Samuel, T. Flessner, S. Taudien, H. B. Kagan, *J. Org. Chem.* **1997**, *62*, 6733–6745.
- [18] E. Conde, D. Bello, A. de Cozar, M. Sanchez, M. A. Vazquez, F. P. Cossio, *Chem. Sci.* **2012**, *3*, 1486–1491.
- [19] E. E. Maroto, S. Filippone, M. Suarez, R. Martinez-Alvarez, A. de Cozar, F. P. Cossio, N. Martin, *J. Am. Chem. Soc.* **2014**, *136*, 705–712.
- [20] E. Conde, I. Rivilla, A. Larumbe, F. P. Cossio, *J. Org. Chem.* **2015**, *80*, 11755–11767.
- [21] a) A. Dondoni, A. Massi, *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660; *Angew. Chem.* **2008**, *120*, 4716; b) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; *Angew. Chem.* **2004**, *116*, 5248; c) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; d) U. Scheffler, R. Mahrwald, *Synlett* **2011**, 1660–1667; e) L. Albrecht, H. Jiang, K. A. Jorgensen, *Angew. Chem. Int. Ed.* **2011**, *50*, 8492–8509; *Angew. Chem.* **2011**, *123*, 8642.
- [22] a) B. M. Trost, C. S. Brindle, *Chem. Soc. Rev.* **2010**, *39*, 1600–1632; b) S. Bertelsen, K. A. Jorgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178–2189; c) D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308.
- [23] M. d. G. Retamosa, A. de Cozar, M. Sanchez, J. I. Miranda, J. M. Sansano, L. M. Castello, C. Najera, A. I. Jimenez, F. J. Sayago, C. Cativiela, F. P. Cossio, *Eur. J. Org. Chem.* **2015**, 2503–2516.
- [24] M. de Gracia Retamosa, A. Ruiz-Olalla, T. Bello, A. de Cozar, F. P. Cossio, *Angew. Chem. Int. Ed.* **2018**, *57*, 668–672; *Angew. Chem.* **2018**, *130*.
- [25] a) L. E. Overman, J. Shim, *J. Org. Chem.* **1993**, *58*, 4662–4672; b) X.-Y. Chen, D. Enders, *Chem* **2018**, *4*, 21–23.
- [26] A. Ruiz-Olalla, M. d. G. Retamosa, F. P. Cossio, *J. Org. Chem.* **2015**, *80*, 5588–5599.
- [27] A. Sanchez-Sanchez, I. Rivilla, M. Agirre, A. Basterretxea, A. Etxeberria, A. Veloso, H. Sardon, D. Mecerreyes, F. P. Cossio, *J. Am. Chem. Soc.* **2017**, *139*, 4805–4814.
- [28] A. M. Sarotti, R. A. Spanevello, A. G. Suarez, G. A. Echeverria, O. E. Piro, *Org. Lett.* **2012**, *14*, 2556–2559.
- [29] G. G. Gerosa, R. A. Spanevello, A. G. Suarez, A. M. Sarotti, *J. Org. Chem.* **2015**, *80*, 7626–7634.
- [30] G. Müller in *Chemogenomics in Drug Discovery*. (Eds.: H. Kubinyi, G. Müller), Wiley-VCH, Weinheim, **2004**, pp. 18–21.
- [31] B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, et al., *J. Med. Chem.* **1988**, *31*, 2235–2246.
- [32] P. Schneider, G. Schneider, *Angew. Chem. Int. Ed.* **2017**, *56*, 7971–7974; *Angew. Chem.* **2017**, *129*, 8079.
- [33] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274.
- [34] K. R. Acharya, E. D. Sturrock, J. F. Riordan, M. R. W. Ehlers, *Nat. Rev. Drug Discovery* **2003**, *2*, 891–902.
- [35] C. Thomas, M. Stevenson, T. V. Riley, *J. Antimicrob. Chemother.* **2003**, *51*, 1339–1350.
- [36] M. Baumann, I. R. Baxendale, S. V. Ley, N. Nikbin, *Beilstein J. Org. Chem.* **2011**, *7*, 442–495.
- [37] L. M. Oh, *Tetrahedron Lett.* **2006**, *47*, 7943–7946.
- [38] B. D. Roth Trans-6-[2-(3- or 4- carboxamido-substituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-one Inhibitors of Cholesterol Synthesis US Patent 4, 681, 893 July 21 1987.
- [39] A. Zubia, S. Roperio, D. Otaegui, E. Ballestar, M. F. Fraga, M. Boix-Chornet, M. Berdasco, A. Martinez, L. Coll-Mulet, J. Gil, F. P. Cossio, M. Esteller, *Oncogene* **2009**, *28*, 1477–1484.
- [40] a) F. P. Cossio, A. Zubia, Y. I. Vara, E. San Sebastián, D. Otaegui, M. d. C. Masdeu, E. Aldaba *New Histone Deacetylase Inhibitors Based Simultaneously on Trisubstituted 1H-Pyrroles and Aromatic and Heteroaromatic Spacers* PCT/EP2010/064653 7 April 2011; b) M. Perez-Salvia, E. Aldaba, Y. Vara, M. Fabre, C. Ferrer, C. Masdeu, A. Zubia, E. San Sebastian, D. Otaegui, P. Llinàs-Arias, A. Rosselló-Tortella, M. Berdasco, C. Moutinho, F. Setien, A. Villanueva, E. González-Barca, J. Muncunill, J.-T. Navarro, M. A. Piris, F. P. Cossio, M. Esteller, *Haematologica* **2018**, (<https://doi.org/10.3324/haematol.2018.189241>).
- [41] E. M. Hussein, M. I. Abdel-Monem, *ARKIVOC* **2011**, 85–98.
- [42] A. Kaur, B. Singh, B. Vyas, O. Silakari, *Eur. J. Med. Chem.* **2014**, *79*, 282–289.
- [43] C. Najera, J. M. Sansano, *Actual. Chim.* **2013**, *370*, 28–30.
- [44] C. Najera, M. d. G. Retamosa, M. Martin-Rodriguez, J. M. Sansano, A. de Cozar, F. P. Cossio, *Eur. J. Org. Chem.* **2009**, 5622–5634.
- [45] M. Martin-Rodriguez, C. Najera, J. M. Sansano, A. de Cozar, F. P. Cossio, *Beilstein J. Org. Chem.* **2011**, *7*, 988–996.
- [46] H. Takayama, Z.-J. Jia, L. Kremer, J. O. Bauer, C. Strohmann, S. Ziegler, A. P. Antonchick, H. Waldmann, *Angew. Chem. Int. Ed.* **2013**, *52*, 12404–12408; *Angew. Chem.* **2013**, *125*, 12630.
- [47] R. Narayan, J. O. Bauer, C. Strohmann, A. P. Antonchick, H. Waldmann, *Angew. Chem. Int. Ed.* **2013**, *52*, 12892–12896; *Angew. Chem.* **2013**, *125*, 13130.
- [48] C. S. Esslinger, J. Titus, H. P. Koch, R. J. Bridges, A. R. Chamberlin, *Bioorg. Med. Chem.* **2002**, *10*, 3509–3515.
- [49] C. Najera, M. d. G. Retamosa, J. M. Sansano, A. de Cozar, F. P. Cossio, *Eur. J. Org. Chem.* **2007**, 5038–5049.
- [50] Y. G. Gu, X. Zhang, R. F. Clark, S. W. Djuric, Z. Ma, *Tetrahedron Lett.* **2004**, *45*, 3051–3053.
- [51] A. Zubia, L. Mendoza, S. Vivanco, E. Aldaba, T. Carrascal, B. Lecea, A. Arrieta, T. Zimmerman, F. Vidal-Vana-clocha, F. P. Cossio, *Angew. Chem. Int. Ed.* **2005**, *44*, 2903–2907; *Angew. Chem.* **2005**, *117*, 2963.
- [52] E. San Sebastian, T. Zimmerman, A. Zubia, Y. Vara, E. Martin, F. Sirockin, A. Dejaegere, R. H. Stote, X. Lopez, D. Pantoja-Uceda, M. Valcarcel, L. Mendoza, F. Vidal-Vanaclocha, F. P. Cossio, F. J. Blanco, *J. Med. Chem.* **2013**, *56*, 735–747.

Received: June 11, 2018