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Enantiodivergent Synthesis of Bis-Spiropyrrolidines via Sequential Interrupted and Completed (3 + 2) Cycloadditions

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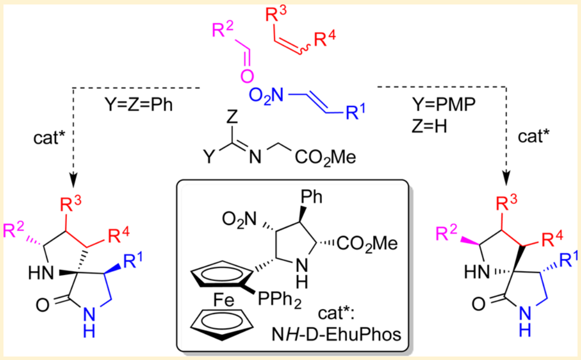
Ⓢ *Supporting Information*

ABSTRACT: Both (5*R*)- and (5*S*)-1,7-diazaspiro[4.4]nonan-6-ones are obtained via a sequence of interrupted and completed stepwise (3 + 2) cycloadditions between azomethine ylides and π-deficient alkenes. The only source of chirality along the whole process is an enantiopure ferrocenyl pyrrolidine catalytic ligand. When the starting imine incorporates two aryl groups or one aryl group with one electron-releasing substituent, the reaction between the azomethine ylide and the alkene stops at the first step, leading to the corresponding Michael adduct. When imines derived from *p*-methoxybenzaldehyde are used, the corresponding *syn*-α-amino-γ-nitro ester is obtained with almost complete enantiocontrol. In contrast, imines derived from benzophenone lead to the corresponding *anti* analogue. From this interrupted (3 + 2) cycloaddition, *cis*- and *trans*-α-amino-γ-lactams can be obtained via hydrogenation of the nitro group followed by in situ cyclization. Imines derived from these latter compounds are the precursors of *N*-metalated azomethine ylides from which up to four new chiral centers can be generated via completed (3 + 2) cycloaddition reactions with full regio- and diastereocontrol. *Cis*- and *trans*-γ-lactams lead to opposite bis-spiropyrrolidine enantiomers. Therefore, both enantiomeric series of spiro compounds can be obtained by means of the same catalytic system. The potential of these rigid, densely substituted homochiral compounds in medicinal chemistry is briefly described.



1. INTRODUCTION

Thermal cycloadditions can occur via concerted or stepwise mechanisms.[1] In the case of (3 + 2) cycloadditions between *N*-metalated azomethine ylides **INT1** (formed in situ from the corresponding imines **1**) and nitroalkenes **2**, the reaction usually occurs via zwitterionic intermediates **INT2**[2] (Scheme 1) that can evolve toward the corresponding pyrrolidine rings **3**, thus completing the formal (3 + 2) cycloaddition. The reaction mechanism of the whole stepwise process consists of a conjugate addition of in situ formed azomethine ylide **INT1** to Michael acceptor **2**, followed by an intramolecular Henry−Mannich-like cyclization. When **INT2** species are stable enough, it is possible to frustrate the (3 + 2) cycloaddition and to isolate the corresponding α-amino-γ-nitroesters **4** after appropriate hydrolytic workup (Scheme 1).[3] It is remarkable, however, that the synthetic potential provided by this stepwise mechanism has not been fully exploited for the asymmetric synthesis of polycyclic molecules, probably because of the difficulties associated with the control of completed and interrupted cycloadditions.

Spiro compounds obtained via formal or effective (3 + 2)[4] and (4 + 1)[5] cycloadditions are of great relevance in medicinal chemistry. Among the different systems obtained to date, the 1,7-diazaspiro[4.4]nonane scaffold **5**[6] has received little attention,[7] possibly because of the accumulation of chiral centers and functional groups in the bicyclic system, which poses a considerable synthetic challenge. We reasoned that bicyclic compounds **5** could be readily obtained by means of completed (3 + 2) cycloadditions between azomethine ylides of type **INT3** and π-deficient alkenes **2** or **7** (Scheme 2). In this cycloaddition, the whole stereocontrol relies only on one stereogenic center (Scheme 2). Azomethine ylides **INT3** can in turn be readily accessible from aldehydes **8** and γ-lactams **6**, which can be synthesized from the corresponding γ-nitro amino esters **4**. These latter adducts should be obtained by a conjugate addition that corresponds to the first step of an interrupted (3 + 2) reaction between *N*-metalated azomethine ylides **INT1** and nitroalkenes **2**. In this reaction, two issues must be addressed: (i) the stereocontrol in the generation of the two new chiral centers and (ii) the efficient interruption of the cyclization process to isolate the corresponding Michael adduct.

On the basis of our previous studies in stereocontrolled stepwise (3 + 2) cycloadditions, we speculated that, in the

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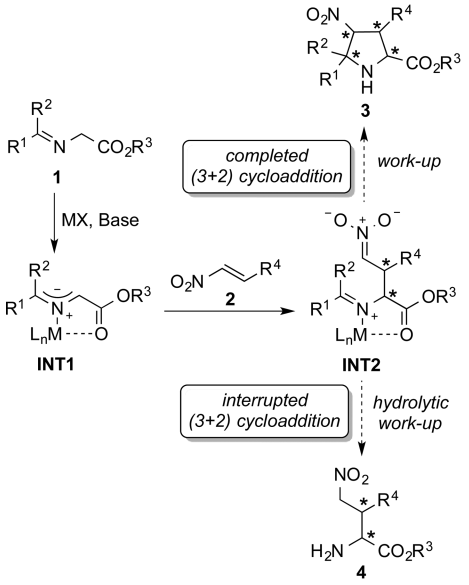
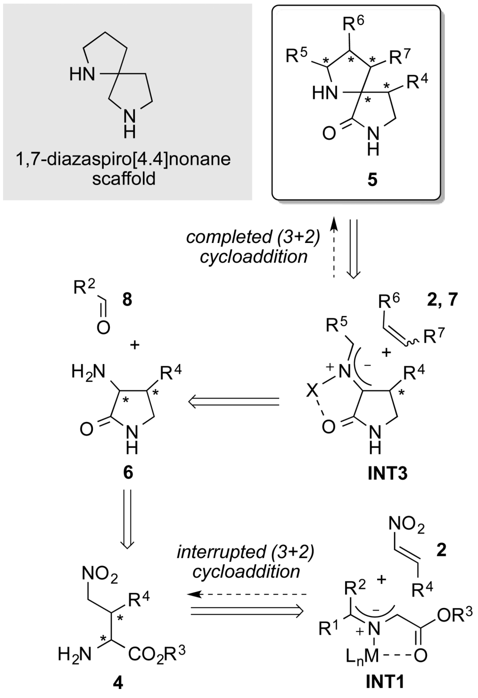
Scheme 1. Synthesis of Pyrrolidines 3 and α-Amino-γ-nitroesters 4 via Interrupted and Completed (3 + 2) Cycloadditions between Imines 1 and Nitroalkenes 2

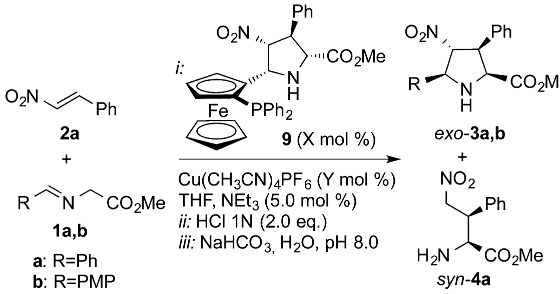


Scheme 2. Synthesis of 1,7-Diazaspiro[4.4]nonan-6-ones 5 via Sequential Interrupted and Completed (3 + 2) Cycloadditions



presence of a suitable catalyst of type EhuPhos previously described by our group and under carefully tuned reaction conditions, the reaction between azomethine ylides **INT1** and nitroalkenes **2** could be stopped at the conjugate addition step, thus yielding intermediates **4** as a result of this frustrated (3 + 2) cycloaddition (Scheme 2). In this case, the stereochemistry of the two new chiral centers should be determined by the *NH*-D-EhuPhos catalytic ligand **9** (Table 1). Once this first goal is successfully addressed, the subsequent completed (3 + 2) cycloaddition should take place with complete stereocontrol induced by the R^4 substituent.

Table 1. Interrupted and Completed (3 + 2) Cycloadditions between Imines 1a,b and Nitroalkene 2a



entry	R	*T* (°C)	*X*,*Y* (mol %)	time (h)	*exo*-**3**:*syn*-**4a**[a]	yield (%)[b]	ee (%)[c]
1	Ph	−20	3.3, 3.0	15	>99:01	85	97
2	Ph	−40	3.3, 3.0	15	69:31	n.d.[d]	n.d.[d]
3	Ph	−80	3.3, 3.0	5	30:70	53	96
4	Ph	−95	3.3, 3.0	60	30:70	n.d.[d]	n.d.[d]
5	PMP	−40	3.3, 3.0	0.5	<01:99	82	>99
6	PMP	−60	1.1, 1.0	0.5	<01:99	84	>99
7	PMP	−60	0.6, 0.5	0.5	<01:99	77	93

[a]Determined by ^1H NMR on the crude reaction mixture. [b]Isolated yield of the major adduct. [c]Determined by HPLC (see the Supporting Information). [d]Not determined (n.d.).

In this article, we present our results on the synthesis of homochiral bis-spiropyrrolodines by addressing the challenges posed by the required regio-, diastereo-, and enantiocontrol as well as the adequate interruption or completion of the (3 + 2) processes involved. Finally, to illustrate the potential of these conformationally restricted compounds, we report several preliminary results on their biological activity associated with relevant targets in medicinal chemistry.

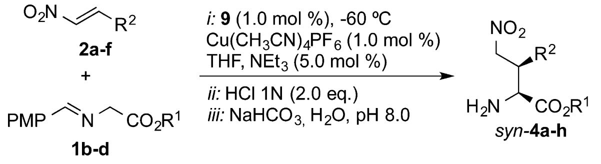
2. RESULTS AND DISCUSSION

2.1. Interrupted (3 + 2) Cycloadditions. Previous work carried out in our laboratory[8] and in collaboration with Martin et al.[9] showed that ferrocenyl compound **9** (*NH*-D-EhuPhos) is a very convenient catalytic ligand for (3 + 2) cycloadditions. With these results in mind, we tried to stop the reaction between imine **1a** and nitroalkene **2a** in the presence of ligand **9**. The results obtained are gathered in Table 1. Our experiments showed that at −20 °C the (3 + 2) cycloaddition was completed and that **4a** could not be observed. Instead, cycloadduct *exo*-**3a** was obtained (with a small amount of *endo*-**3a** in a *exo*:*endo* ratio of 95:05) in good agreement with our previously reported results[8a] (Table 1, entry 1). When the temperature was lowered to −80 °C, the amount of Michael adduct *syn*-**4a** grew to achieve an *exo*-**3a**:*syn*-**4a** ratio of 30:70, giving Michael adduct *syn*-**4a** in 53% yield and with an ee of 96% (Table 1, entry 3). Unfortunately, the *exo*-**3a**:*syn*-**4a** ratio could not be improved by lowering the reaction temperature at −95 °C for 60 h (Table 1, entry 4), thus showing that the results corresponding to entry 3 are the best that can be achieved with imine **1a** (R = Ph). Lower stereocontrol was observed when AgOAc was used as an alternative metallic source. Similarly, other bases (DBU, *t*-BuOK, Cs_2CO_3) and solvents (1,4-dioxane, toluene) resulted in lower stereocontrol and/or chemical yields.

We reasoned that an electron-releasing group such as *p*-methoxy (R = PMP, Table 1) in starting imine **1b** should stabilize the positive charge of the iminium moiety corresponding to zwitterionic intermediate **INT2**. This stabilization should in turn enhance the activation barrier associated with the intramolecular Mannich–Henry cyclization step leading to cycloadducts **3**. Under these conditions, the stepwise (3 + 2) cycloaddition could be interrupted, thus making feasible the isolation of Michael adduct *syn*-**4a**. In effect, we observed that with imine **1b**, even at −60 °C, only *syn*-**4a** was observed in the crude reaction mixture with excellent diastereo- and enantiocontrol (Table 1, entry 5). Moreover, we found that lowering the catalytic load to ∼1.0 mol % led to a similar result with no loss of chemical yield or stereocontrol (Table 1, entry 6). A lower catalytic ratio improved neither the chemical yield nor the enantiocontrol (Table 1, entry 7).

Once we determined these optimized reaction conditions to exclusively obtain adduct *syn*-**4a**, we extended these interrupted (3 + 2) cycloadditions to imines **1c**,**d** and nitroalkenes **2b**–**f** to obtain (2*S*,3*R*)-*α*-amino-*γ*-nitro esters *syn*-**4b**–**h**. The results are reported in Table 2 and indicate that in all cases both the diastereo- and enentiocontrol were excellent. Only in the case of nitroalkene **2f** (R^2 = 2-furyl) was the chemical yield and ee found to be slightly lower (Table 2, entry 6). In addition, the presence of a *tert*-butyl ester in imine **1d** resulted in a somewhat lower chemical yield.

Table 2. Interrupted (3 + 2) Cycloadditions between Imines 1b–d and Nitroalkenes 2a–f to Yield (2*S*,3*R*)-*α*-Amino-*γ*-nitro Esters *syn*-4a–h

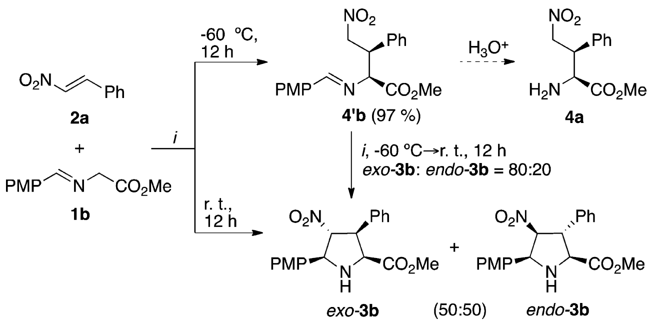


entry	1	2	4[a]	R^1	R^2	yield[b] (%)	ee[c] (%)
1	**1b**	**2a**	**4a**	Me	Ph	84	>99
2	**1b**	**2b**	**4b**	Me	4-F-C_6H_4	85	>99
3	**1b**	**2c**	**4c**	Me	4-MeO-C_6H_4	85	>99
4	**1b**	**2d**	**4d**	Me	4-Me-C_6H_4	86	>99
5	**1b**	**2e**	**4e**	Me	2-F-C_6H_4	80	>99
6	**1b**	**2f**	**4f**	Me	2-Furyl	75	95
7	**1c**	**2a**	**4g**	Et	Ph	85	>99
8	**1d**	**2a**	**4h**	*t*-Bu	Ph	58	>99

[a]In all cases, the measured *syn*-**4**:*anti*-**4** ratio was >99:01. [b]Isolated yield of the major adduct. [c]Determined by HPLC (see the Supporting Information).

To evaluate the stepwise nature of these reactions and the role of Michael intermediates as precursors of (3 + 2) cycloadditions, we monitored by NMR the evolution of the reaction between imine **1b** and nitroalkene **2a** at different temperatures (Scheme 3). According to our results, after 12 h of reaction at −60 °C, only imine **4′b** (precursor of **4a**) was detected by ^{1}H and ^{13}C NMR (COSY and DEPT experiments, see the Supporting Information). When the temperature of the reaction mixture was allowed to reach room temperature, an 80:20 mixture of *exo*-**3b** and *endo*-**3b** was obtained. This result demonstrates not only the evolution of **4′b** toward the iminium-nitronate intermediate **INT2** and the corresponding (3 + 2) cycloadducts **3b** but also the reversibility of the Michael addition step, because a noticeable amount of *endo*-**3b** was observed. Interestingly, when the reaction between **1b** and **2a** was carried out at room temperature, a 50:50 mixture of both diastereomers **4b** was observed, thus confirming the importance of the temperature to stop the stepwise reaction at its first step, as well as to keep the stereoselectivity of the initial Michael addition under control.

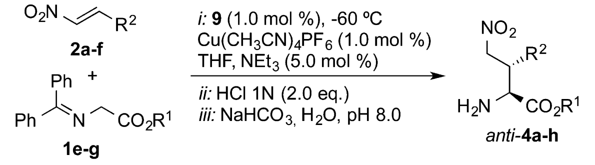
Scheme 3. Evolution of Michael Intermediates Obtained from Imine 1b towards (3 + 2) Cycloadducts[a]



[a]Reagents: (*i*) **9** (1.0 mol %), THF, NEt_3 (5.0 mol %), $Cu(CH_3CN)_4PF_6$ (1.0 mol %).

On the basis of the above results, we reasoned that an alternative way to stabilize the iminium moiety of zwitterionic intermediates **INT2** could consist of incorporating an additional phenyl group to the starting imines. Therefore, we studied the possibility of interrupting (3 + 2) cycloadditions between imines **1e**–**g** and nitroalkenes **2a**–**f**. The results of these experiments are collected in Table 3. Also in this case, under the previously optimized reaction conditions, we observed only the formation of *α*-amino-*γ*-nitro esters **4a**–**h**, but in this case, the *anti* diastereomers were obtained as major or exclusive (Table 3, entry 6) adducts. In general, both the enantiocontrol and the chemical yields were excellent with the exception of adducts **4d** and **4h** (Table 3, entries 4 and 8) for which the isolated yields were somewhat lower but still acceptable.

Table 3. Interrupted (3 + 2) Cycloadditions between Imines 1e–g and Nitroalkenes 2a–f to Yield (2*S*,3*R*)-*α*-Amino-*γ*-nitro Esters *anti*-4a–h



entry	1	2	4[a]	R^1	R^2	yield[b] (%)	ee[c] (%)
1	**1e**	**2a**	**4a**	Me	Ph	89	95
2	**1e**	**2b**	**4b**	Me	4-F-C_6H_4	82	90
3	**1e**	**2c**	**4c**	Me	4-MeO-C_6H_4	84	90
4	**1e**	**2d**	**4d**	Me	4-Me-C_6H_4	71	94
5	**1e**	**2e**	**4e**	Me	2-F-C_6H_4	94	93
6	**1e**	**2f**	**4f**	Me	2-Furyl	81	96
7	**1f**	**2a**	**4g**	Et	Ph	83	93
8	**1g**	**2a**	**4h**	*t*-Bu	Ph	68	97

[a]In all cases, the measured *anti*-**4**:*syn*-**4** ratio was >99:01, except for entry 6 with a ratio of 94:06. [b]Isolated yield of the major adduct. [c]Determined by HPLC (see the Supporting Information).

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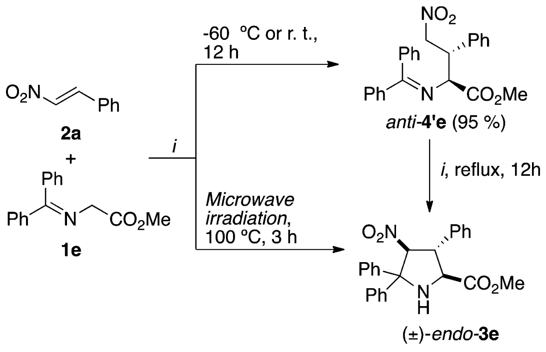
NMR experiments similar to those carried out for the reaction between imine **1b** and nitroalkene **2a** showed a more reluctant evolution of the Michael intermediates toward the corresponding cycloadducts. Thus, no cycloadduct **3e** was observed when the reaction was conducted at room temperature (Scheme 4), *anti*-**4′e** being the only reaction product observed by NMR after 12 h of reaction (see the Supporting Information). Under refluxing THF, complete conversion of *anti*-**4′e** to *endo*-**3e** was observed after 12 h. Microwave irradiation for 3 h was more efficient in this respect and promoted complete conversion of **1e** and **2a** to *endo*-**3e**. However, under both classical and dielectric heating, this latter cycloadduct was obtained as a racemic mixture.

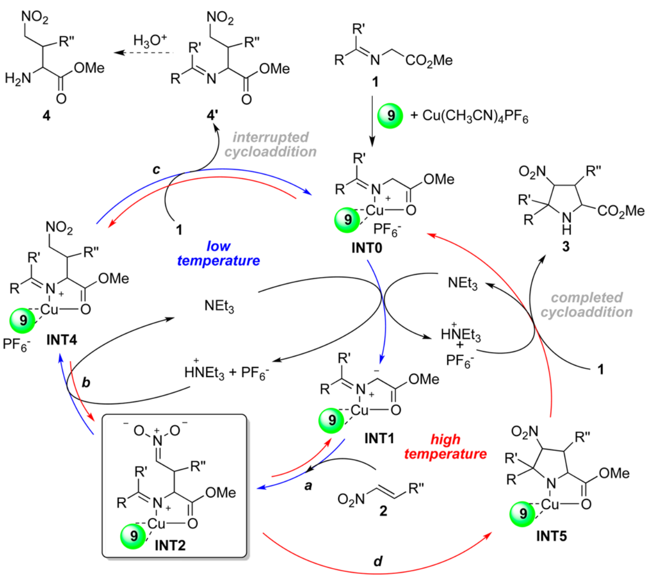
Scheme 4. Evolution of Michael Intermediate Obtained from Imine 1e towards (3 + 2) Cycloadduct 3e[a]



[a]Reagents: (*i*) **9** (1.0 mol %), THF, NEt_3 (5.0 mol %), $Cu(CH_3CN)_4PF_6$ (1.0 mol %).

From these data, we propose that the whole reaction mechanism involves two catalytic cycles (Scheme 5). Chiral ligand **9** and Cu(I) salt form complex **INT0** with imines **1** (immediate formation of this complex was observed by ^{31}P NMR, results not shown). Reaction with the amine results in the formation of azomethine ylide **INT1**, which can add one equivalent of dipolarophile (or Michael acceptor) **2** to form zwitterionic intermediate **INT2** (Scheme 5, step *a*). This latter intermediate can be reprotonated by the conjugate acid of the tertiary amine to form **INT4**, which in turn generates Michael adduct **4′** (observed by NMR in untreated reaction mixtures) and releases the catalyst-imine complex. At higher temperatures, reversible steps *c*, *b*, and even *a* can proceed toward the product of thermodynamic control. Therefore, **INT2** instead of being reprotonated (step *b*) can form another C−C bond by an intramolecular Mannich−Henry reaction between the nitronate and iminium moieties (step *d*), thus completing the catalytic cycle associated with (3 + 2) cycloaddition and yielding pyrrolidine **3**.

Scheme 5. Mechanistic Proposal for the Interrupted and Completed (3 + 2) Reaction between Nitroalkenes and Imines under Catalytic Conditions



We next examined the origins of the unexpected change in diastereoselectivity ongoing from aldimines **1a**−**d** to ketimines **1e**−**g**. DFT calculations[10] on the transition structures associated with the conjugate addition of azomethine ylides derived from aldimine **1b** and ketimine **1e** in the presence of Cu(I) and our previously developed chiral ligand **9** were carried out using the ONIOM methodology[11] at the M06/6-31+ +G**&LANL2DZ//ONIOM(B3LYP/LANL2DZ:PM6) level[12,13] of theory (see the Computational Methods section and the Supporting Information for additional details).

According to our results, in *syn*-**TS1**, the nitro group of nitroalkene **2a** occupies a distal position with respect to the Cu(I) center, thus minimizing the electrostatic repulsion between the nitro and methoxycarbonyl groups. In addition, in this saddle point, there is a stabilizing π-stacking interaction between the aryl group of Michael acceptor **2a** and one phenyl group of the diphenylphosphine moiety with a calculated Ph(**9**)-Ph(**2a**) distance of 3.3 Å. In contrast, saddle point *anti*-**TS1** involves a steric repulsion between the nitro group of **2a** and the Ph_2P-cyclopentadienyl moiety of **9**, which is not compensated by the attractive Coulombic interaction between the nitro group (with a charge of −0.42 a.u.) and the positively charged (+0.48 a.u.) Cu(I) center. These different interactions result in the preferential formation of *syn*-**4a** (Figure 1A) from the reaction between imine **1b** and nitroalkene **2a** in good agreement with the experimental results.

We also located and characterized transition structure *syn*-**TS2** associated with the reaction between imine **1e** and nitroalkene **2a**. In this saddle point, the previously mentioned Ph(**2a**)-Ph(**9**) π-stacking cannot overcome the steric clash between the nitro group of **2a** and one of the phenyl groups of the ketimine moiety of **1e**, which cannot be coplanar with respect to the other one (Figure 1B). As a consequence, transition structure *anti*-**TS2**, which is sterically less congested and incorporates the stabilizing Cu(I)-NO_2 interaction, is 5.9 kcal/mol lower in energy than *syn*-**TS2**. Therefore, in this latter case, the formation of Michael adduct *anti*-**4a** via *anti*-**TS2** is preferred (Figure 1B). It is noteworthy that because our chiral catalytic ligand **9** promotes in both cases the blockage of the same prochiral face of the intermediate azomethine ylide, the configuration of the carbon atom incorporating the α-amino group is the same in both cases (see the geometries and relative energies of the other four possible transition structures in Table S1 and Figure S4). Thus, D-ester **9** promotes the formation of L-esters *syn*- and *anti*-**4**. It is important to emphasize, however, that the stereochemical outcome of this reaction is the consequence of a complex trade off between stabilizing and repulsive nonbonding interactions.

2.2. Completed (3 + 2) Cycloadditions.

Once we prepared conjugate adducts *syn*- and *anti*-**4a**−**h**, we studied

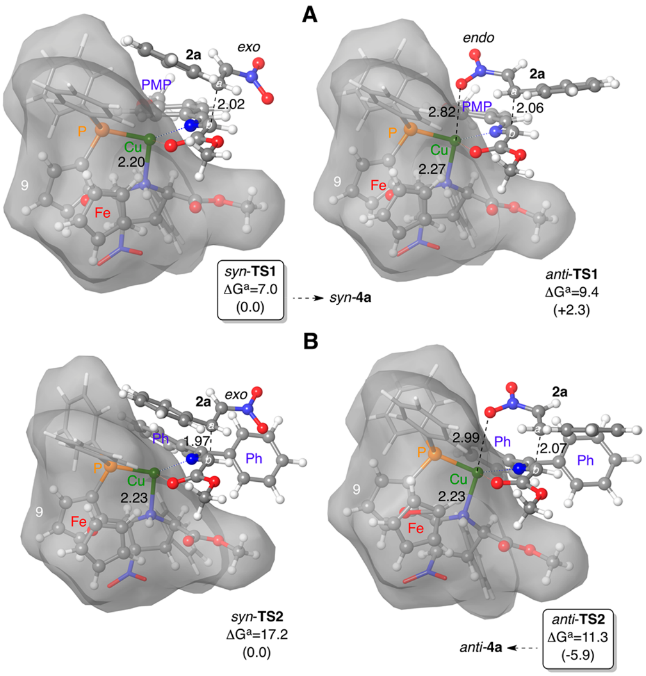


Figure 1. Fully optimized geometries (M06/6-31++G**&LANL2DZ//ONIOM(B3LYP/LANL2DZ:PM6) level of theory) of transition structures *syn*-**TS1** and *anti*-**TS1** (A) and *syn*-**TS2** and *anti*-**TS2** (B). These structures are formed from nitroalkenes **2a** and imines **1b** and **1e**, respectively, in the presence of chiral catalytic ligand **9**. Both saddle points lead preferentially to Michael adducts *syn*-**4a** and *anti*-**4a**, respectively. Bond distances are given in Å.

Scheme 6. Synthesis of γ-Lactams 6a−c and 10a−e

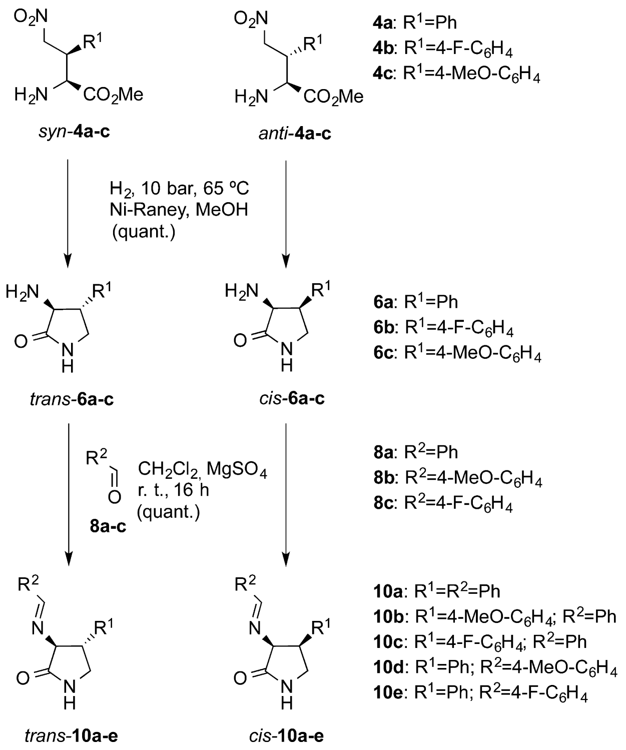
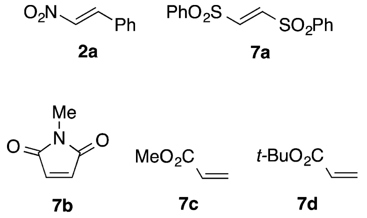


Chart 1. Dipolarophiles Used in (3 + 2) Cycloadditions Involving Azomethine Ylides Derived from γ-Lactams 10a−e



their conversion to γ-lactams **6** (Scheme 2). Catalytic hydrogenation of γ-nitro-α-amino esters **4a−c** resulted in the spontaneous and quantitative cyclization of the intermediate α,γ-diamino esters to form γ-lactams *cis*- and *trans*-**6a−c** (Scheme 6). Because the cyclization process takes place with double retention of configuration at the two chiral centers, *syn*-esters **4** give rise to the corresponding *trans*-lactams, whereas the analogue *anti*-esters yield lactams *cis*-**6a−c**. From α-amino-γ-lactams **6a−c**, the corresponding imines **10a−e** were also obtained in quantitative yield (Scheme 6). These imines are the precursors of the corresponding in situ formed azomethine ylides **INT3** that should lead to the corresponding bis-spiropyrrolidines **5** via completed (3 + 2) cycloadditions (Scheme 2).

We selected the π-deficient alkenes gathered in Chart 1 as suitable dipolarophiles for (3 + 2) cycloadditions involving azomethine ylides derived from γ-lactams *cis*- and *trans*-**10a−e**. These dipolarophiles include alkenes possessing one (**2a**, **7c**, and **7d**) or two (**7a**, **7b**) electron-withdrawing groups. From a stereochemical standpoint, *cis* (**7b**) and *trans*-alkenes (**2a**, **7a**) were selected to monitor the retention of the configuration of the dipolarophiles despite the stepwise nature of these completed (3 + 2) cycloadditions. Finally, these dipolarophiles permitted to assess the *endo* or *exo* diastereoselectivity of the corresponding 1,3-dipolar reactions depending upon the *cis* or *trans* disposition between the R^5 and R^6 groups of spiro cycloadducts **5**, respectively (Scheme 2).

Reaction between imines **10a−e** with either nitroalkene **2a** or dipolarophiles **7a−d** resulted in the fully regio- and diastereoselective formation of spiro cycloadducts **5a−i** (Schemes 7 and 8).[14] In these completed (3 + 2) cycloadditions, silver acetate in the presence of triethylamine efficiently promoted the formation of the corresponding *N*-metalated azomethine ylides. In all cases, retention of configuration of the dipolarophiles was observed, and the corresponding *endo* (3 + 2) cycloadducts were obtained. The only exception was observed when (*E*)-1,2-bis(phenylsulfonyl)ethene **7a** was used as the dipolarophile. In this case, *exo*-cycloadduct **5a** was obtained as the sole reaction product with complete enantiocontrol, as proven by HPLC and X-ray diffraction analysis[14] (Scheme 7).

It is interesting to note that in all of the cases studied only one enantiomer was obtained depending on the *cis* or *trans* configuration of the corresponding imino γ-lactam **10**. Therefore, both our catalyst **9** (*NH*-D-EhuPhos) and the starting aldimines **1b−d** and ketimine **1e** determine completely the configuration of bis-spiropyrrolidines **5**. In particular, aldimine **1b** gives rise to spiro compounds **5a−i** through the **1b** → *syn*-**4a−c** → *trans*-**10a−e** → **5a−i** sequence (Scheme 7). In contrast, ketimine **1e** results in the enantiomeric spiro compounds *ent*-**5** by means of the **1e** → *anti*-**4a−c** → *cis*-**10a−e** → *ent*-**5b−g**, **i** sequence (Scheme 8). In other words, our catalytic system based on enantiopure ligand **9** determines the enantiopurity of the final compounds, whereas the starting aldimine or ketimine azomethine precursors are responsible for

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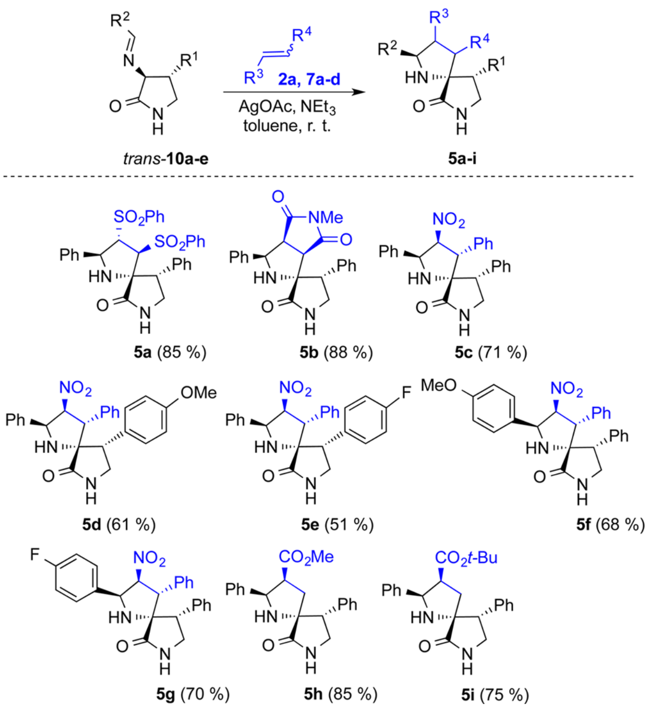
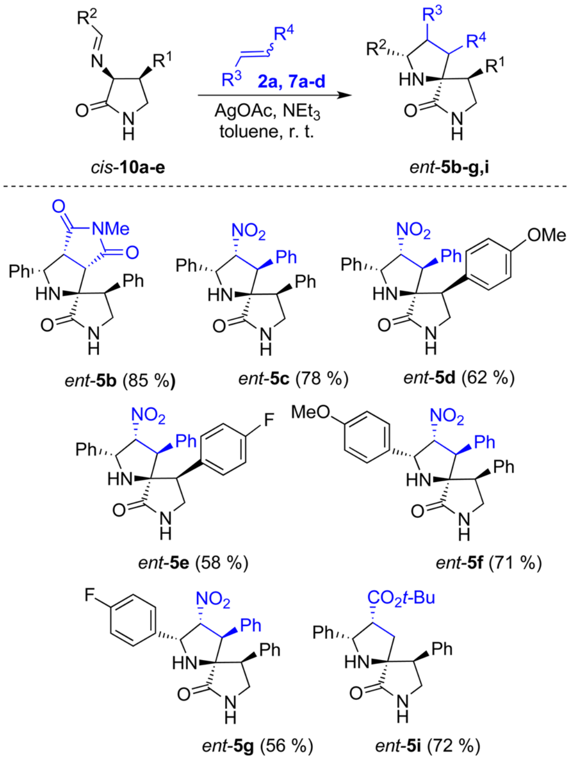
Scheme 7. Synthesis of Spiro Compounds 5a–i from *trans*-γ-Lactams 10a–e



Scheme 8. Synthesis of Spiro Compounds *ent*-5b-g,i from *cis*-γ-Lactams 10a–e



the enantiodivergence of the whole sequence. The origins of this enantiodivergent behavior are discussed below.

As a representative case study of these completed (3 + 2) cycloadditions, we performed additional DFT calculations (M06/6-31++G*&LanL2DZ//B3LYP/6-31+G*&LANL2DZ level of theory) associated with the stepwise transformation of azomethine ylide **INT3a** into cycloadduct **5c** by reaction with nitrostyrene **2a** in the presence of silver acetate. According to our calculations, interactions between 1,3-dipole **INT3a** and dipolarophile **2a** lead to a reactive complex **RC** from which zwitterionic intermediate **INT4a** is formed via a conjugated addition with no significant energy barrier. Therefore, these completed (3 + 2) cycloadditions are also stepwise. The chief geometric features of transition structures *endo*-**TS3a** and *endo*-**TS4a**, as well as the energy profile associated with this (3 + 2) stepwise cycloaddition, are gathered in Figure 2A. Our results indicate that the *endo* selectivity experimentally observed stems from the interaction between the nitro group and the metallic center along the entire reaction coordinate. The stepwise nature of the cycloaddition is demonstrated by the characterization of *endo*-**INT4a** as a true local minimum. The second activation energy associated with the formation of the C4–C5 bond of the pyrrolidine through *endo*-**TS4a** was computed to also be very low (Figure 2A) and can be interpreted as a metal-assisted intramolecular Mannich–Henry reaction.

It is interesting to note that formation of azomethine ylides **INT3** involves the temporary destruction of the chiral information borne by the α-carbon of the corresponding γ-lactam **10**. Therefore, during the completed (3 + 2) cycloaddition process, the β-carbon is the only source of chiral induction (Schemes 7 and 8). In principle, the dipolarophile should interact with the azomethine ylide along the opposite face that incorporates the R^1 substituent (the phenyl group highlighted in gray in Figure 2A). Our calculations indicate that the alternative transition structures are of significantly higher energy, thus resulting in complete enantiocontrol (see the Supporting Information for additional details). This means that *cis*- and *trans*-γ-lactams **10** should yield enantiomeric spiro (3 + 2) cycloadducts **5** (Figure 2B).

2.3. Preliminary Biological Studies.

To explore the potential of these spiranic scaffolds in medicinal chemistry, several bis-spiropyrrolodines **5** were tested[15] against different biological targets of relevance in oncology, neurosciences, and cardiovascular diseases. In several cases, moderate inhibitory activity was found. It was found that cycloadduct **5c** (Scheme 7) showed up to ~41% K-Ras Wnt synthetic lethal activity[16] against cell line Colo 320 Kras SL at 200 nM concentration. This activity has potential interest in the development of selective therapies against colon cancer. In addition, micromolar concentrations of *ent*-**5b** (10 μM) and *ent*-**5c** (100 μM) inhibited histone methyl transferases SetD8[17] (23.6%) and EZH2[18] (32%), respectively (Scheme 8). Inhibition of both epigenetic enzymes is of interest in the treatment of different types of cancer.[17,18] Aside from these inhibitory activities, **5c** was found to be a moderate Nav1.7 sodium channel antagonist with a potency of 28% at 3 μM. Because Nav1.7 is expressed in the peripheral nervous system and sympathetic ganglia, it has been suggested that inhibitors of this kind of voltage-gated sodium ion channels possess therapeutic potential in the treatment of chronic pain.[19] Finally, in vitro data indicate that **5b** (Scheme 7) inhibits proprotein convertase subtilisin kexin type 9 (PCSK9) with IC$_{50}$ = 5 μM. This result is interesting given the relevance of PCSK9 in the regulation of cholesterol homeostasis via low density lipoproteins (LDL).[20]

We also designed hydroxamic acid **14** as a potential histone deacetylases (HDAC) inhibitor (Scheme 9). Histone deacetylases are very relevant epigenetic enzymes whose therapeutic interest in cancer therapy is well recognized.[21] In previous work, we have demonstrated the potential of 1*H*-pyrrole

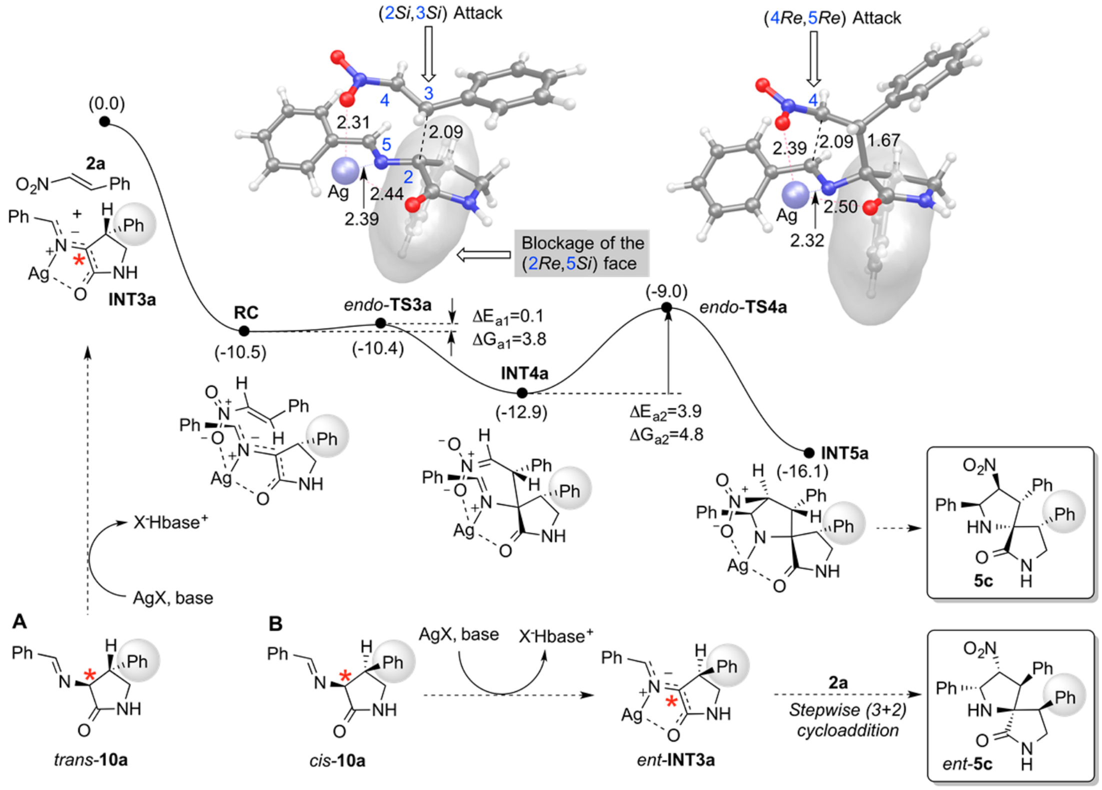
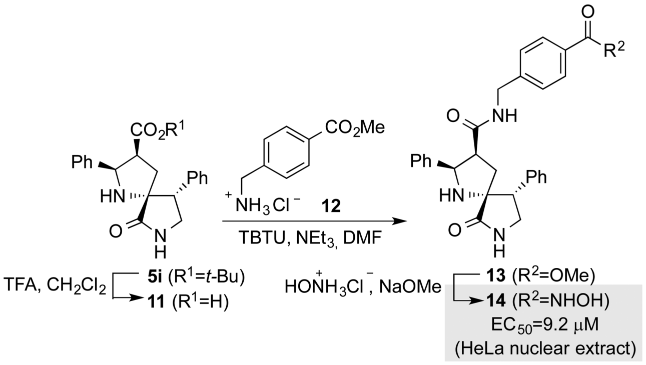


Figure 2. Enantiodivergent formation of spiro bispyrrolidines **5c** (A) and *ent*-**5c** (B) from *trans*-**10a** (A) and *cis*-**10a** (B), respectively. The reaction profile, computed at the M06(PCM)/6-31++G*&LANL2DZ//B3LYP(PCM)/6-31+G*&LANL2DZ level of theory is shown in (A). Internuclear distances and energies are given in Å and kcal/mol, respectively. Numbers in parentheses correspond to relative energies (in kcal/mol) with respect to separate reactants **2a** and **INT3a**. Red asterisks emphasize the temporary destruction of chiral information at C2.

Scheme 9. Synthesis and Biological Activity of Hydroxamic Acid 14



derivatives as potent HDAC paninhibitors and as chemotherapeutic reagents against different types of human cancer.[22] Acidic cleavage of the ester moiety in **5i** followed by amide coupling between the resulting carboxylic acid **11** and amino ester hydrochloride **12** yielded ester **13**. Hydroxamic acid **14** was readily obtained by reaction between **13** and hydroxymethyl amine hydrochloride. Interestingly, compound **14** showed low micromolar activity in HeLa nuclear extracts (Scheme 9). All these results show that, although certainly further development is required, spiro compounds **5** (in both enantiomeric forms) constitute promising scaffolds in oncology, neuroscience, and biomedicine.

3. CONCLUSIONS

In this paper, we show that enantiopure bis-spiropyrrolidines **5** can be prepared from readily available precursors by means of a highly efficient and enantiodivergent procedure based on a sequence of interrupted and completed (3 + 2) cycloadditions between metalated azomethine ylides and nitroalkenes or other dipolarophiles. A convenient choice of the substituents in the starting 1,3-dipole permits to stop the first (3 + 2) cycloadditions at the first step. Chiral catalytic ligand **9**, previously described by our group, is the only source of chiral induction. After acidic hydrolytic workup and catalytic reduction of the nitro group of the corresponding cycloadducts, enantiopure *α*-amino-*γ*-lactams are obtained with excellent yields. Bis-spiropyrrolidines **5** can be obtained in both enantiomerically pure forms via completed (3 + 2) cycloadditions involving suitable dipolarophiles and the imines derived from *cis*- or *trans*-*γ*-lactams **10**. Finally, the potential of these enantiopure rigid spiro compounds in medicinal chemistry has been explored. We think that this spiro scaffold as well as the concept of interrupted/completed stepwise cycloaddition can be extended to other enantiopure densely substituted compounds.

4. EXPERIMENTAL SECTION

General Experimental Procedures. All reactions were carried out under an atmosphere of argon unless otherwise stated. All melting points are uncorrected. Flash column chromatographies were carried out with silica gel 60 (0.040−0.063 mm) eluting with ethyl acetate/hexane. Infrared spectra were recorded on an FT-IR spectrometer. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded at 500 or 400 and 126 MHz or 101 and 375 MHz, respectively, in $CDCl_3$ and DMSO solvent with tetramethylsilane as internal reference TMS. Optical rotations were measured at the wavelength 589 nm (sodium D line). The absolute configurations of the known products were determined by comparing optical rotation values with the literature data. The HPLC chromatograms of the racemic and enantiomerically enriched products were performed using Daicel Chiralpak IA, IB, IC, and AS-H columns. HRMS analyses were carried out using the electron impact (EI) mode at 70 eV or by QTOF using electrospray ionization (ESI) mode. All solvents were of p.a. quality and were dried by standard procedures prior to use if necessary. The commercially available reagents (nitroalkenes **2a−f**, aldehydes **8a−b**, aminoesters **15a−c**, and imino esters **1f,g**) were used without further purification. Chiral ligand **9** was prepared according to previously published procedures.[8]

General Procedure for the Preparation of α-Iminoesters 1a−d. To a solution of the corresponding α-aminoester hydrochloride **15a−c** (3.0 mmol) in dry CH_2Cl_2 (5 mL) were added $MgSO_4$ and Et_3N (3.0 mmol) at room temperature. The resulting mixture was stirred at the same temperature for 1 h. Then, the aldehyde **8a** or **8b** (2.3 mmol) was added, and the resulting mixture was stirred for 18 h. Then, $MgSO_4$ was filtered off, and the organic layer was washed three times with water, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to afford the pure product, which was used in the next step without further purification.

*Methyl (E)-N-Benzylideneglycinate (**1a**).* The title compound[3a] was obtained as a colorless oil (342 mg, 1.93 mmol, 84%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (s, 1H), 7.80−7.75 (m, 2H), 7.47−7.38 (m, 3H), 4.42 (s, 2H), 3.78 (s, 3H).

*Methyl (E)-N-(4-Methoxybenzylidene)glycinate (**1b**).* The title compound[3a] was obtained as a yellow solid (329 mg, 1.59 mmol, 69%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 4.38 (s, 2H), 3.84 (s, 3H), 3.77 (s, 3H).

*Ethyl (E)-N-(4-Methoxybenzylidene)glycinate (**1c**).* The title compound[3a] was obtained as a yellow oil (372 mg, 1.68 mmol, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.69 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.32 (s, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H).

*tert-Butyl (E)-N-(4-Methoxybenzylidene)glycinate (**1d**).* The title compound[3a] was obtained as a yellow solid (298 mg, 1.20 mmol, 52%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.70 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.25 (d, *J* = 0.7 Hz, 2H), 3.82 (s, 3H), 1.47 (s, 9H).

*Methyl 2-[(Diphenylmethylene)amino]acetate (**1e**).* A mixture of diphelymethanimine (2.72 g, 15.0 mmol), glycine methyl ester hydrochloride (1.88 g,15.0 mmol), and $MgSO_4$ in dry CH_2Cl_2 (60 mL) was stirred at room temperature for 24 h. The solid was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in Et_2O and washed three times with water, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to afford the corresponding pure imine, which was used in the next step without further purification. The title compound[3a] was obtained as a pale yellow oil (3.08 g, 12.15 mmol, 81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60−7.56 (m, 2H), 7.45−7.35 (m, 4H), 7.26 (t, *J* = 7.5 Hz, 2H), 7.11 (dd, *J* = 7.4, 1.5 Hz, 2H), 4.15 (s, 2H), 3.67 (s, 3H).

General Procedure for the Enantioselective Conjugate Addition Reactions between α-Iminoesters 1b−g and nitroalkenes 2a−f. A solution of α-iminoester **1b−g** (0.45 mmol), chiral ligand **9** (4.95 μmol), and $Cu(CH_3CN)_4PF_6$ (4.50 μmol) in 2.0 mL of dry THF was stirred at room temperature for 15 min and for an additional 15 min at −60 °C. Then, a precooled (−60 °C) solution of the corresponding nitroalkene **2a−f** (0.50 mmol) in 1.0 mL of dry THF and triethylamine (3.2 μL, 0.023 mmol) were successively added (the reaction was monitored by TLC). Once the starting material was consumed, 1 N HCl (0.9 mL) was added at −60 °C, and the reaction was allowed to warm to room temperature. The mixture was stirred for 1 h, and after evaporation of THF under reduced pressure, the residue was washed three times with Et_2O. The aqueous solution was rendered alkaline by the addition of a saturated aqueous solution of $NaHCO_3$ (to pH 8.0), and the product was extracted several times with CH_2Cl_2. The organic layers were combined, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give the corresponding pure product *anti*- or *syn*-**4a−h**. The enantiomeric excesses were determined by comparison with the chromatogram recorded for the racemic mixture of the corresponding product.

*(2S,3R)-Methyl 2-Amino-4-nitro-3-phenylbutanoate (syn-**4a**).* The title compound was obtained as a white waxy solid (90 mg, 0.38 mmol, 84%). Mp 40−42 °C. IR (neat): 3387, 3326, 1735, 1546, 1378 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28−7.20 (m, 3H), 7.10 (dd, *J* = 7.4, 1.5 Hz, 2H), 5.00 (dd, *J* = 13.1, 8.2 Hz, 1H), 4.70 (dd, *J* = 13.1, 6.8 Hz, 1H), 3.96 (td, *J* = 7.5, 4.5 Hz, 1H), 3.73 (d, *J* = 4.1 Hz, 1H), 3.61 (s, 3H), 1.44 (bs, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.1, 135.1, 129.1, 128.6, 128.4, 76.9, 56.0, 52.4, 46.5. $[\alpha]^{24}_D$ +25.7 (*c* 1.00, $CHCl_3$), >99% ee. HPLC: Daicel Chiralpak IB, *iso*-propanol/hexane 10:90, flow rate = 1.0 mL/min, tr: 19.3 min (2*S*,3*R*) and 25.8 min (2*R*,3*S*), 210 nm. Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.5; H, 5.9; N, 11.8. Found: C, 55.7; H, 6.2; N, 11.8.

*(2S,3S)-Methyl 2-Amino-4-nitro-3-phenylbutanoate (anti-**4a**).* The title compound was obtained as a white solid (95 mg, 0.40 mmol, 89%). Mp 61−62 °C. IR (neat): 3365, 3276, 1728, 1537, 1379 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38−7.23 (m, 3H), 7.21 (d, *J* = 7.0 Hz, 2H), 5.05 (dd, *J* = 13.3, 5.7 Hz, 1H), 4.77 (dd, *J* = 13.3, 8.9 Hz, 1H), 3.81 (dd, *J* = 14.1, 8.0 Hz, 1H), 3.69 (d, *J* = 7.6 Hz, 1H), 3.54 (s, 3H), 1.62 (bs, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.9, 136.5, 128.9, 128.2, 127.9, 77.0, 57.8, 52.0, 47.7. $[\alpha]^{24}_D$ +9.9 (*c* 1.00, $CHCl_3$), 95% ee. HPLC: Daicel Chiralpak IC, *iso*-propanol/hexane 20:80, flow rate = 1.0 mL/min, tr: 25.3 min (2*S*,3*S*) and 27.7 min (2*R*,3*R*), 210 nm. Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.5; H, 5.9; N, 11.8. Found: C, 55.5; H, 6.2; N, 11.8.

*(2S,3R)-Methyl 2-Amino-3-(4-fluorophenyl)-4-nitrobutanoate (syn-**4b**).* The title compound was obtained as a yellow oil (98 mg, 0.38 mmol, 85%). IR (neat): 3391, 3329, 1735, 1547, 1377 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (dd, *J* = 8.5, 5.3 Hz, 2H), 6.94 (t, *J* = 8.6 Hz, 2H), 4.96 (dd, *J* = 13.0, 8.0 Hz, 1H), 4.68 (dd, *J* = 13.0, 7.1 Hz, 1H), 3.96 (td, *J* = 7.4, 4.2 Hz, 1H), 3.73 (bs, 1H), 3.61 (s, 3H), 1.47 (bs, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.8, 162.9 (d, *J* = 247.6), 130.8 (d, *J* = 2.9), 130.2 (d, *J* = 8.1), 116.1 (d, *J* = 21.4), 77.0, 55.8, 52.6, 45.7. $[\alpha]^{24}_D$ +22.1 (*c* 1.00, $CHCl_3$), >99% ee. HPLC: Daicel Chiralpak IA, *iso*-propanol/hexane 15:85, flow rate = 1.0 mL/min, tr: 12.0 min (2*S*,3*R*) and 15.1 min (2*R*,3*S*), 210 nm. Anal. Calcd for $C_{11}H_{13}FN_2O_4$: C, 51.6; H, 5.1; N, 10.9. Found: C, 51.2; H, 5.2; N, 10.9.

*(2S,3S)-Methyl 2-Amino-3-(4-fluorophenyl)-4-nitrobutanoate (anti-**4b**).* The title compound was obtained as a pale yellow oil (94 mg, 0.37 mmol, 82%). IR (neat): 3389, 3324, 1732, 1547, 1377 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (dd, *J* = 8.1, 5.3 Hz, 2H), 7.02 (t, *J* = 8.5 Hz, 2H), 5.05 (dd, *J* = 13.3, 5.4 Hz 1H), 4.73 (dd, *J* = 13.2, 9.3 Hz, 1H), 3.80 (dt, *J* = 8.6, 5.7 Hz, 1H), 3.65 (d, *J* = 7.9 Hz, 1H), 3.56 (s, 3H), 1.71 (bs, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.7, 162.3 (d, *J* = 247.3), 132.0 (d, *J* = 3.0), 129.5 (d, *J* = 8.2), 115.7 (d, *J* = 21.5), 77.0, 57.6, 52.0, 46.9. $[\alpha]^{24}_D$ +4.5 (*c* 1.00, $CHCl_3$), 90% ee. HPLC: Daicel Chiralpak IC, *iso*-propanol/hexane 20:80, flow rate = 1.0 mL/min, tr: 20.6 min (2*S*,3*S*) and 22.6 min (2*R*,3*R*), 210 nm. Anal. Calcd for $C_{11}H_{13}FN_2O_4$: C, 51.6; H, 5.1; N, 10.9. Found: C, 51.4; H, 5.1; N, 10.9.

*(2S,3R)-Methyl 2-Amino-3-(4-methoxyphenyl)-4-nitrobutanoate (syn-**4c**).* The title compound was obtained as a white solid (103 mg, 0.38 mmol, 85%). Mp 76−78 °C. IR (neat): 3383, 3324, 1729, 1551, 1375 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.03 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 4.96 (dd, *J* = 13.0, 8.1 Hz, 1H), 4.66 (dd, *J* = 13.0, 7.0 Hz, 1H), 3.92 (td, *J* = 7.5, 4.4 Hz, 1H), 3.72−3.67 (m, 4H), 3.62 (s, 3H), 1.46 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.0, 159.6, 129.3, 126.6, 114.4, 77.0, 55.9, 55.3, 52.3, 45.6. $[\alpha]^{24}_D$ +21.2 (*c* 1.00, $CHCl_3$), >99% ee. HPLC: Daicel Chiralpak IB, *iso*-propanol/hexane 15:85, flow rate = 1.0 mL/min, tr: 18.8 min (2*S*,3*R*) and 23.5 min (2*R*,3*S*), 210 nm. Anal. Calcd for $C_{12}H_{16}N_2O_5$: C, 53.7; H, 6.0; N, 10.4. Found: C, 53.9; H, 6.1; N, 10.5.

*(2S,3S)-Methyl 2-Amino-3-(4-methoxyphenyl)4-nitrobutanoate (anti-**4c**).* The title compound was obtained as a yellow solid (101 mg, 0.38 mmol, 84%). Mp 93−95 °C. IR (neat): 3383, 3323, 1731, 1546, 1378 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (d, *J* = 8.3 Hz,

2H), 6.85 (d, *J* = 8.3 Hz, 2H), 5.03 (dd, *J* = 12.8, 4.8 Hz, 1H), 4.73 (dd, *J* = 12.7, 9.0 Hz, 1H), 3.78 (s, 4H), 3.71−3.62 (m, 1H), 3.56 (s, 3H), 1.62 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.8, 159.1, 128.8, 127.8, 114.0, 77.1, 57.6, 54.9, 51.9, 46.8. $[\alpha]^{24}_{D}$ +5.0 (*c* 1.00, $CHCl_3$), 90% ee. HPLC: Daicel Chiralpak IC, *iso*-propanol/hexane 10:90, flow rate = 1.0 mL/min, tr: 74.1 min (2*S*,3*S*) and 80.8 min (2*R*,3*R*), 210 nm. Anal. Calcd for $C_{12}H_{16}N_2O_5$: C, 53.7; H, 6.0; N, 10.4. Found: C, 54.1; H, 6.1; N, 10.5.

*(2S,3R)-Methyl 2-Amino-3-(4-methylphenyl)-4-nitrobutanoate (syn-**4d**).* The title compound was obtained as a waxy solid (98 mg, 0.39 mmol, 86%). Mp 43−45 °C. IR (neat): 3409, 3342, 1737, 1541, 1380 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (d, *J* = 7.9 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 4.97 (dd, *J* = 13.0, 8.1 Hz, 1H), 4.68 (dd, *J* = 13.0, 6.9 Hz, 1H), 3.93 (dt, *J* = 11.6, 5.9 Hz, 1H), 3.70 (d, *J* = 2.7 Hz, 1H), 3.62 (s, 3H), 2.24 (s, 3H), 1.42 (bs, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.2, 138.3, 131.8, 129.8, 128.2, 77.0, 56.0, 52.4, 46.1, 21.2. $[\alpha]^{24}_{D}$ +22.9 (*c* 1.00, $CHCl_3$), >99% ee. HPLC: Daicel Chiralpak IB, *iso*-propanol/hexane 15:85, flow rate = 1.0 mL/min, tr: 12.8 min (2*S*,3*R*) and 16.6 min (2*R*,3*S*), 210 nm. Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.1; H, 6.4; N, 11.1. Found: C, 57.1; H, 6.5; N, 11.2.

*(2S,3S)-Methyl 2-Amino-3-(4-methylphenyl)-4-nitrobutanoate (anti-**4d**).* The title compound was obtained as a white solid (81 mg, 0.32 mmol, 71%). Mp 55−57 °C. IR (neat): 3386, 3323, 1732, 1547, 1377 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (d, *J* = 7.6 Hz, 2H), 7.09 (d, *J* = 7.7 Hz, 2H), 5.02 (dd, *J* = 13.2, 5.6 Hz, 1H), 4.75 (dd, *J* = 13.1, 8.9 Hz, 1H), 3.79 (dd, *J* = 13.7, 7.5 Hz, 1H), 3.69 (d, *J* = 6.4 Hz, 1H), 3.57 (s, 3H), 2.31 (s, 3H), 1.64 (bs, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.8, 137.8, 133.1, 129.5, 127.6, 77.0, 57.7, 52.0, 47.2, 20.9. $[\alpha]^{24}_{D}$ +4.6 (*c* 1.00, $CHCl_3$), 94% ee. HPLC: Daicel Chiralpak IC, *iso*-propanol/hexane 8:92, flow rate = 1.0 mL/min, tr: 51.8 min (2*S*,3*S*) and 57.2 min (2*R*,3*R*), 210 nm. Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.1; H, 6.4; N, 11.1. Found: C, 57.1; H, 6.4; N, 11.4.

*(2S,3R)-Methyl 2-Amino-3-(2-fluorophenyl)-4-nitrobutanoate (syn-**4e**).* The title compound was obtained as a pale yellow oil (92 mg, 0.36 mmol, 80%). IR (neat): 3390, 3330, 1735, 1548, 1377 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27−7.15 (m, 2H), 7.05 (t, *J* = 7.3 Hz, 1H), 7.01−6.96 (m, 1H), 4.99 (dd, *J* = 13.3, 7.8 Hz, 1H), 4.71 (dd, *J* = 13.3, 7.0 Hz, 1H), 4.25 (dd, *J* = 12.0, 7.2 Hz, 1H), 3.77 (d, *J* = 3.0 Hz, 1H), 3.63 (s, 3H), 1.46 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.9, 160.6 (d, *J* = 246.7), 129.9 (d, *J* = 8.6), 129.5 (d, *J* = 3.6), 124.4 (d, *J* = 3.4), 122.1 (d, *J* = 14.3), 115.9 (d, *J* = 22.7), 76.0, 55.0, 52.3, 39.9. $[\alpha]^{24}_{D}$ +44.0 (*c* 1.00, $CHCl_3$), >99% ee. HPLC: Daicel Chiralpak AS-H, *iso*-propanol/hexane 15:85, flow rate = 1.0 mL/min, tr: 27.4 min (2*R*,3*S*) and 40.3 min (2*S*,3*R*), 210 nm. Anal. Calcd for $C_{11}H_{13}FN_2O_4$: C, 51.6; H, 5.1; N, 10.9. Found: C, 51.7; H, 5.0; N, 10.7.

*(2S,3S)-Methyl 2-Amino-3-(2-fluorophenyl)-4-nitrobutanoate (anti-**4e**).* The title compound was obtained as a yellow oil (108 mg, 0.42 mmol, 94%). IR (neat): 3391, 3323, 1732, 1548, 1377 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (dd, *J* = 16.5, 11.5 Hz, 1H), 7.13 (t, *J* = 7.1 Hz, 1H), 7.09−6.94 (m, 2H), 5.05 (dd, *J* = 13.4, 5.3 Hz, 1H), 4.76 (dd, *J* = 13.4, 8.8 Hz, 1H), 3.89 (dd, *J* = 13.8, 8.3 Hz, 1H), 3.75 (d, *J* = 8.4 Hz, 1H), 3.43 (s, 3H), 1.60 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.0, 161.0 (d, *J* = 246.8), 130.4 (d, *J* = 4.3), 130.0 (d, *J* = 8.6), 124.5 (d, *J* = 3.0), 123.4 (d, *J* = 13.5), 116.0 (d, *J* = 22.2), 76.1, 56.3, 52.1, 43.6. $[\alpha]^{26}_{D}$ +15.8 (*c* 1.00, $CHCl_3$), 93% ee. HPLC: Daicel Chiralpak IC, *iso*-propanol/hexane 10:90, flow rate = 1.0 mL/min, tr: 33.1 min (2*S*,3*S*) and 35.9 min (2*R*,3*R*), 210 nm. Anal. Calcd for $C_{11}H_{13}FN_2O_4$: C, 51.6; H, 5.1; N, 10.9. Found: C, 51.3; H, 5.3; N, 10.9.

*(2S,3R)-Methyl 2-Amino-3-(2-furyl)-4-nitrobutanoate (syn-**4f**).* The title compound was obtained as a brown oil (77 mg, 0.34 mmol, 75%). IR (neat): 3385, 3339, 1736, 1549, 1376 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (dd, *J* = 1.8, 0.6 Hz, 1H), 6.24 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.10 (d, *J* = 3.2 Hz, 1H), 4.90 (dd, *J* = 13.4, 7.5 Hz, 1H), 4.73 (dd, *J* = 13.4, 7.2 Hz, 1H), 4.19 (dd, *J* = 10.8, 7.3 Hz, 1H), 3.67 (s, 4H), 1.55 (bs, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.9, 148.8, 143.0, 110.5, 108.6, 75.0, 55.2, 52.5, 40.7. $[\alpha]^{24}_{D}$ +37.2 (*c* 1.00, $CHCl_3$), 95% ee. HPLC: Daicel Chiralpak IC, *iso*-propanol/hexane 20:80, flow rate = 1.0 mL/min, tr: 21.8 min (2*S*,3*R*) and 25.9 min (2*R*,3*S*), 210 nm. Anal. Calcd for $C_9H_{12}N_2O_5$: C, 47.4; H, 5.3; N, 12.3. Found: C, 46.6; H, 5.5; N, 12.1.

*(2S,3S)-Methyl 2-Amino-3-(2-furyl)-4-nitrobutanoate (anti-**4f**).* The title compound was obtained as a yellow oil (83 mg, 0.36 mmol, 81%). IR (neat): 3390, 3323, 1732, 1549, 1376 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (dd, *J* = 1.9, 0.7 Hz, 1H), 6.31 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.21 (d, *J* = 3.1 Hz, 1H), 4.93 (dd, *J* = 13.5, 5.4 Hz, 1H), 4.81 (dd, *J* = 13.5, 8.6 Hz, 1H), 3.99 (dt, *J* = 8.4, 6.2 Hz, 1H), 3.81 (d, *J* = 6.7 Hz, 1H), 3.68 (s, 3H), 1.65 (bs, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.5, 149.8, 142.8, 110.5, 108.4, 75.0, 56.0, 52.4, 41.7. $[\alpha]^{24}_{D}$ +14.6 (*c* 1.00, $CHCl_3$), 96% ee. HPLC: Daicel Chiralpak IA, *iso*-propanol/hexane 5:95, flow rate = 1.0 mL/min, tr: 33.1 min (2*S*,3*S*) and 39.0 min (2*R*,3*R*), 210 nm. Anal. Calcd for $C_9H_{12}N_2O_5$: C, 47.4; H, 5.3; N, 12.3. Found: C, 47.3; H, 5.5; N, 12.2.

*(2S,3R)-Ethyl 2-Amino-4-nitro-3-phenylbutanoate (syn-**4g**).* The title compound was obtained as a colorless oil (96 mg, 0.38 mmol, 85%). IR (neat): 3390, 3328, 1730, 1547, 1377 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28−7.20 (m, 3H), 7.13 (dd, *J* = 7.5, 1.7 Hz, 2H), 4.99 (dd, *J* = 13.0, 8.1 Hz, 1H), 4.71 (dd, *J* = 13.0, 7.0 Hz, 1H), 4.05 (dd, *J* = 6.6, 3.6 Hz, 2H), 3.96 (td, *J* = 7.4, 4.4 Hz, 1H), 3.70 (d, *J* = 2.7 Hz, 1H), 1.45 (bs, 2H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.5, 135.0, 128.9, 128.44 (two signals in the HSQC spectra), 77.0, 61.6, 55.9, 46.4, 14.3. $[\alpha]^{24}_{D}$ +11.5 (*c* 1.00, $CHCl_3$), >99% ee. HPLC: Daicel Chiralpak IB, *iso*-propanol/hexane 10:90, flow rate = 1.0 mL/min, tr: 14.2 min (2*S*,3*R*) and 16.8 min (2*R*,3*S*), 210 nm. Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.1; H, 6.4; N, 11.1. Found: C, 56.9; H, 6.2; N, 10.8.

*(2S,3S)-Ethyl 2-Amino-4-nitro-3-phenylbutanoate (anti-**4g**).* The title compound was obtained as a white solid (94 mg, 0.37 mmol, 83%). Mp 46−47 °C. IR (neat): 3370, 3285, 1724, 1541, 1374 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27−7.14 (m, 5H), 5.01 (dd, *J* = 13.0, 4.7 Hz, 1H), 4.70 (dd, *J* = 12.8, 9.3 Hz, 1H), 3.92 (dd, *J* = 13.7, 6.8 Hz, 2H), 3.74 (dd, *J* = 13.8, 7.4 Hz, 1H), 3.62 (bs, 1H), 1.70 (bs, 2H), 0.97 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.3, 136.1, 128.6, 127.9, 127.8, 77.0, 60.9, 57.5, 47.6, 13.5. $[\alpha]^{26}_{D}$ +6.3 (*c* 1.00, $CHCl_3$), 93% ee. HPLC: Daicel Chiralpak IC, *iso*-propanol/hexane 10:90, flow rate = 1.0 mL/min, tr: 39.2 min (2*S*,3*S*) and 46.7 min (2*R*,3*R*), 210 nm. Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.1; H, 6.4; N, 11.1. Found: C, 57.1; H, 6.4; N, 11.1.

*(2S,3R)-tert-Butyl 2-Amino-4-nitro-3-phenylbutanoate (syn-**4h**).* The title compound was obtained as a pale yellow oil (73 mg, 0.26 mmol, 58%). IR (neat): 3392, 3322, 1726, 1548, 1368 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29−7.12 (m, 5H), 4.96 (dd, *J* = 12.8, 8.0 Hz, 1H), 4.69 (dd, *J* = 12.8, 7.2 Hz, 1H), 3.91 (td, *J* = 7.5, 4.5 Hz, 1H), 3.60 (d, *J* = 4.2 Hz, 1H), 1.47 (bs, 2H), 1.31 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.4, 135.3, 128.8, 128.7, 128.3, 82.2, 77.4, 56.1, 46.4, 28.1. $[\alpha]^{26}_{D}$ +19.0 (*c* 1.00, $CHCl_3$), >99% ee. HPLC: Daicel Chiralpak IB, *iso*-propanol/hexane 10:90, flow rate = 1.0 mL/min, tr: 9.5 min (2*S*,3*R*) and 10.7 min (2*R*,3*S*), 210 nm. Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 60.0; H, 7.2; N, 10.0. Found: C, 60.2; H, 7.1; N, 10.1.

*(2S,3S)-tert-Butyl 2-Amino-4-nitro-3-phenylbutanoate (anti-**4h**).* The title compound was obtained as a white solid (86 mg, 0.31 mmol, 68%). Mp 84−86 °C. IR (neat): 3383, 3314, 1713, 1541, 1382 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30−7.10 (m, 5H), 5.00 (dd, *J* = 12.9, 4.9 Hz, 1H), 4.65 (dd, *J* = 12.6, 9.5 Hz, 1H), 3.60 (dd, *J* = 26.2, 17.9 Hz, 1H), 3.49 (d, *J* = 8.1 Hz, 1H), 1.57 (bs, 2H), 1.15 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.0, 136.6, 128.7, 128.4, 128.1, 81.8, 78.0, 58.1, 48.3, 27.6. $[\alpha]^{20}_{D}$ +8.6 (*c* 1.15, $CHCl_3$), 98% ee. HPLC: Daicel Chiralpak IC, *iso*-propanol/hexane 10:90, flow rate = 1.0 mL/min, tr: 22.8 min (2*S*,3*S*) and 25.9 min (2*R*,3*R*), 210 nm. Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 60.0; H, 7.2; N, 10.0. Found: C, 60.1; H, 7.2; N, 10.0.

General Method for the Synthesis of Iminoesters *syn*-4′b and *anti*-4′e. A solution of the corresponding α-iminoester **1b** (124 mg, 0.60 mmol) or **1e** (116 mg, 0.45 mmol), chiral ligand **9** (3.1 mg, 4.95 μmol), and $Cu(CH_3CN)_4PF_6$ (1.7 mg, 4.50 μmol) in 2.0 mL of dry THF was stirred at −60 °C for 1 h. Then, a precooled (−60 °C) solution of nitroalkene **2a** (89 mg, 0.60 mmol in the case of **1b**, and 68 mg, 0.46 mmol for **1e**) in 1.0 mL of dry THF and triethylamine (3.2 μL, 0.023 mmol) were added successively. The resulting mixture was stirred at −60 °C for 12 h, and then it was filtered through a pad of Celite. Rotary evaporation of the solvent gave an oily residue, which was purified by flash chromatography on silica gel (EtOAc/*n*-hexane 1:4).

*(2S,3R)-Methyl 2-(((E)-4-methoxybenzylidene)amino)-4-nitro-3-phenylbutanoate (syn-**4′b**).* The title compound was obtained as a yellow oil (207 mg, 0.58 mmol, 97%). IR (neat): 3022, 2953, 1735, 1547, 1208, 701 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.33 (s, 1H), 7.32−7.36 (d, J = 8.6 Hz, 2H), 7.19−7.21 (d, J = 7.0 Hz, 2H), 7.36 (d, J = 7.2 Hz, 1H), 7.30 (d, J = 7.3 Hz, 1H), 6.96 (d, J = 8.7 Hz, 2H), 5.10 (dd, J = 13.1, 8.2 Hz, 1H), 4.80 (dd, J = 13.1, 6.7 Hz, 1H), 4.05−4.08 (m, 1H), 3.82−3.84 (m, 1H), 3.71 (s, 6H).^{13}C NMR (126 MHz, CDCl$_3$) δ 173.9, 134.8, 129.2, 128.9, 128.8, 128.4, 128.2, 128.1, 128.0, 127.8, 127.3, 76.7, 55.8, 52.3, 46.2. Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.0; H, 5.7; N, 7.9. Found: C, 63.9; H, 5.7; N, 7.9. HRMS: [M + H]$^+$ calcd for $C_{19}H_{21}N_2O_5$, 357.1450; found, 357.1457. $[\alpha]^{21}{}_{D}$ −115 (*c* 0.4, CHCl$_3$).

*(2S,3R)-Methyl 2-((Diphenylmethylene)amino)-4-nitro-3-phenylbutanoate (anti-**4′e**).* The title compound was obtained as a yellow oil (169 mg, 0.42 mmol, 95%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.60 (d, J = 6.2 Hz, 2H), 7.30−7.45 (m, 4H), 7.14−7.22 (m, 10H), 6.61 (m, 2H), 5.14−5.23 (m, J = 9.4 Hz, 2H), 4.33−4.40 (m, J = 9.5, 4.6 Hz, 1H), 4.33 (d, J = 4.1 Hz, 1H), 3.71 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 171.8, 171.0, 139.0, 137.1, 135.8, 132.3, 129.0, 128.8, 128.8, 128.7, 128.6, 128.0, 127.5, 75.9, 68.5, 55.5, 51.9. $[\alpha]^{21}{}_{D}$ −137 (*c* 0.4, CHCl$_3$) (lit.[23] $[\alpha]^{23}{}_{D}$ −139 (*c* 0.4, CHCl$_3$)).

Synthesis of Pyrrolidines *exo*-3b and *endo*-3b. Method A: A solution of α-iminoester **1b** (124 mg, 0.60 mmol), chiral ligand **9** (3.1 mg, 4.95 μmol), and Cu(CH$_3$CN)$_4$PF$_6$ (1.7 mg, 4.50 μmol) in 2.0 mL of dry THF was stirred at −60 °C for 1 h. Then, a precooled (−60 °C) solution of nitroalkene **2a** (89 mg 0.60 mmol) in 1.0 mL of dry THF and triethylamine (3.2 μL, 0.023 mmol) were added successively. Then, the cooling bath was removed, and the reaction mixture was allowed to reach room temperature. Stirring was resumed at room temperature for an additional 12 h, and then it was filtered through a pad of Celite. Rotary evaporation of the solvent gave an oily residue, whose ^{1}H NMR analysis showed an *exo*-**3b**:*endo*-**3b** ratio of 80:20. Both diastereomers were separately purified by flash chromatography on silica gel (EtOAc/*n*-hexane 1:4). Method B: The procedure was similar to that indicated in Method A, but the addition of the reactants and catalysts as well as the whole reaction were conducted at room temperature for 12 h. ^{1}H NMR analysis of the reaction mixture showed an *exo*-**3b**:*endo*-**3b** ratio of 50:50.

*(2S,3S,4R,5S)-Methyl 5-(4-Methoxyphenyl)-4-nitro-3-phenylpyrrolidine-2-carboxylate (exo-**3b**).* The title compound was obtained as a pale yellow solid (Method B: 40%, (85 mg, 0.24 mmol, 40%). Mp 133−134 °C (lit.[24] 135−136 °C). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.48 (d, J = 8.5, 2H), 7.34−7.22 (m, 5H), 6.94 (d, J = 8.5, 2H), 5.19 (t, J = 8.2, 1H), 4.69 (d, J = 8.3, 1H), 4.47 (d, J = 9.1, 1H), 4.38 (t, J = 8.6, 1H), 3.82 (s, 3H), 3.28 (s, 3H), 2.69 (bs, 1H). $[\alpha]^{21}{}_{D}$ +81.7 (*c* 0.4, CHCl$_3$) (lit.[24] $[\alpha]^{20}{}_{D}$ +82.8 (*c* 1.68, CHCl$_3$)).

*(2S,3R,4S,5S)-Methyl 5-(4-Methoxyphenyl)-4-nitro-3-phenylpyrrolidine-2-carboxylate (endo-**3b**).* The title compound was obtained as a pale yellow solid (Method B: 78 mg, 0.22 mmol, 38%). Mp 118−120 °C (lit.[24] 116−118 °C). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.41 (t, J = 7.4, 2H), 7.37−7.27 (m, 5H), 6.89 (d, J = 8.6, 2H), 5.23 (dd, J = 6.4, 3.6, 1H), 4.88 (d, J = 6.5, 1H), 4.22 (dd, J = 7.2, 3.5, 1H), 4.13 (d, J = 7.4, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.28 (bs, 1H). $[\alpha]^{21}{}_{D}$ −47.3 (*c* 0.4, CHCl$_3$) (lit.[24] $[\alpha]^{21}{}_{D}$ −51.1 (*c* 0.4, CHCl$_3$)).

(2S,3R*,4S*)-Methyl 4-Nitro-3,5,5-triphenyl-pyrrolidine-2-carboxylate (endo-**3e**).* Method A: A solution of α-iminoester **1e** (116 mg, 0.45 mmol), chiral ligand **9** (3.1 mg, 4.95 μmol), and Cu(CH$_3$CN)$_4$PF$_6$ (1.7 mg, 4.50 μmol) in 2.0 mL of dry THF was stirred at −60 °C for 1 h. Then, a precooled (−60 °C) solution of nitroalkene **2a** (68 mg 0.46 mmol) in 1.0 mL of dry THF and triethylamine (3.2 μL, 0.023 mmol) were added successively. The resulting mixture was stirred at −60 °C or at room temperature for 12 h, and then it was refluxed for an additional 12 h. Then, it was filtered through a pad of Celite. Rotary evaporation of the solvent gave an oily residue, which was purified by by flash chromatography on silica gel (EtOAc/*n*-hexane 1:4). Method B: The reactants and catalysts were mixed in 3 mL of a 1:3 mixture of THF/toluene in a closed vessel and irradiated with microwaves at 100 °C for 3 h. After workup similar to that followed in Method A, an oily residue was obtained, which was purified by flash chromatography on silica gel (EtOAc/*n*-hexane 1:4). The title compound was obtained as a yellow oil (161 mg, 0.40 mmol, 90%). IR (neat): 3059, 2950, 1739, 1210, 1518, 653 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.85−7.73 (m, 2H), 7.52−7.45 (m, 2H), 7.41 (t, J = 7.7 Hz, 2H), 7.29 (dd, J = 5.3, 2.5 Hz, 2H), 7.22 (d, J = 7.2 Hz, 2H), 6.83−6.72 (m, 2H), 6.10 (d, J = 4.4 Hz, 1H), 4.16 (dd, J = 8.0, 4.4 Hz, 1H), 4.06 (d, J = 8.3 Hz, 2H), 3.77 (s, 3H).^{13}C NMR (126 MHz, CDCl$_3$): δ 171.8, 142.2, 141.8, 137.3, 129.2, 128.9, 128.8, 128.6, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.8, 127.3, 126.7, 125.4, 101.5, 77.4, 77.3, 77.1, 76.8, 65.4, 58.4, 52.6. Anal. Calcd for $C_{24}H_{22}N_2O_4$: C, 71.6; H, 5.5; N, 7.0. Found: C, 71.4; H, 5.6; N, 7.0. HRMS: [M + H]$^+$ calcd for $C_{24}H_{23}N_2O_4$, 403.1658; found, 403.1664.

General Procedure for the Synthesis of α-Aminolactams *trans*- and *cis*-6a−c. A solution of the corresponding adduct *syn*- or *anti*-**4a**−**c** (1.6 mmol) in MeOH (160 mL, 0.01 M) was filtered through a filter with a pore size of 0.20 μm. The resulting solution was passed through a H-Cube hydrogenator flow reactor provided with a Ni-Raney cartridge at 65 °C, 10 bar of hydrogen pressure, and a flow rate of 1.0 mL/min. The recovered solution was concentrated under reduced pressure to afford the corresponding pure α-aminolactam *trans*- or *cis*-**6a**−**c**.

*(3S,4R)-3-Amino-4-phenylpyrrolidin-2-one (trans-**6a**).* The title compound was obtained from *syn*-**4a** as a white solid (282 mg, 1.6 mmol, ∼100%). Mp 101−103 °C. IR (neat): 3361, 3327, 3267, 3159, 1712, 1667 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.45−7.25 (m, 5H), 6.06 (bs, 1H), 3.71−3.65 (m, 2H), 3.43 (t, J = 9.7 Hz, 1H), 3.33 (dd, J = 18.5, 9.9 Hz, 1H), 1.68 (bs, 2H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 178.1, 139.3, 129.1, 127.7, 127.6, 58.9, 51.2, 45.9. $[\alpha]^{26}{}_{D}$ −84.8 (*c* 1.00, CHCl$_3$). Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.2; H, 6.9; N, 15.9. Found: C, 68.6; H, 6.8; N, 15.9.

*(3S,4S)-3-Amino-4-phenylpyrrolidin-2-one (cis-**6a**).* The title compound was obtained from *anti*-**4** as a white solid. (282 mg, 1.6 mmol, ∼100%). Mp 140−141 °C. IR (neat): 3369, 3307, 3166, 3091, 1710, 1681 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.41−7.18 (m, 5H), 6.12 (bs, 1H), 3.84−3.74 (m, 3H), 3.62 (d, J = 9.0 Hz, 1H), 1.15 (bs, 2H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 178.5, 138.2, 129.0, 128.2, 127.7, 55.5, 45.6, 45.1. $[\alpha]^{26}{}_{D}$ −47.2 (*c* 1.00, CHCl$_3$). Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.2; H, 6.9; N, 15.9. Found: C, 68.2; H, 7.4; N, 16.0.

*(3S,4R)-3-Amino-4-(4-fluorophenyl)pyrrolidin-2-one (trans-**6b**).* The title compound was obtained from *syn*-**4b** as a white solid (311 mg, 1.6 mmol, ∼100%). Mp 115−118 °C. IR (neat): 3217, 3081, 1686, 1602, 1589, 1160 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.35−7.29 (m, 2H), 7.08 (t, J = 8.3 Hz, 2H), 6.45 (bs, 1H), 3.68−3.62 (m, 2H), 3.40−3.31 (m, 2H), 1.97 (bs, 2H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 177.3, 163.1, 161.2, 134.7, 129.0, 115.8, 58.7, 50.1, 45.7. ^{19}F NMR (375 MHz, CDCl$_3$): δ −114.92. $[\alpha]\ ^{26}{}_{D}$ −27 (*c* 1.00, CHCl$_3$). Anal. Calcd for $C_{10}H_{11}FN_2O$: C, 61.8; H, 5.7; N, 14.4. Found: C, 61.8; H, 5.7 N, 14.3.

*(3S,4S)-3-Amino-4-(4-fluorophenyl)pyrrolidin-2-one (cis-**6b**).* The title compound was obtained from *anti*-**4b** as a white solid (311 mg, 1.6 mmol, ∼100%). Mp 137−141 °C. IR (neat): 3221, 3057, 1676, 1612, 1579, 1140 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.39−7.29 (m, 2H), 6.61 (bs, 1H), 3.83−376 (m, 2H), 3.64−3.61 (m, 1H), 1.65 (bs, 2H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 178.1, 163.3, 160.9, 133.8, 129.6, 129.6, 115.8, 115.6, 45.6, 44.3, 30.3, 29.6. ^{19}F NMR (375 MHz, CDCl$_3$): δ −114.75. $[\alpha]^{26}{}_{D}$ −10 (*c* 0.5, CHCl$_3$). Anal. Calcd for $C_{10}H_{11}FN_2O$: C, 61.8; H, 5.7; N, 14.4. Found: C, 61.9; H, 5.6 N, 14.3.

*(3S,4R)-3-Amino-4-(4-methoxyphenyl)pyrrolidin-2-one (trans-**6c**).* The title compound was obtained from *syn*-**4c** as a white solid (330 mg, 1.6 mmol, ∼100%). Mp 110−112 °C. IR (neat): 3207, 3151, 1701, 1610, 1513, 1248 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.22 (d, J = 8.3 Hz, 2H), 6.92 (dd, J = 15.5, 8.1 Hz, 2H), 5.93 (s, 1H), 3.83 (d, J = 4.6 Hz, 3H), 3.77 (d, J = 8.3 Hz, 1H), 3.60 (dd, J = 20.0, 10.8 Hz, 1H), 3.39 (t, J = 9.7 Hz, 1H), 3.27 (d, J = 9.3 Hz, 1H), 1.68 (bs, 2H).^{13}C NMR (126 MHz, CDCl$_3$): δ 177.3, 158.8, 130.7, 128.4(2C), 114.1(2C), 58.5, 55.1, 49.6, 45.98. $[\alpha]^{26}{}_{D}$ −80 (*c* 1.00, CHCl$_3$). Anal.

Calcd for $C_{11}H_{14}N_2O_2$: C, 64.1; H, 6.8; N, 13.6. Found: C, 63.9.; H, 6.7; N, 13.5.

*(3S,4S)-3-Amino-4-(4-methoxyphenyl)pyrrolidin-2-one (cis-**6c**).* The title compound was obtained from *anti*-**4c** as a white solid (330 mg, 1.6 mmol, ~100%). Mp 142−144 °C. IR (neat): 3242, 3186, 2285, 1704, 1720, 1586 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, J = 8.1 Hz, 2H), 6.89 (d, J = 8.3 Hz, 2H), 3.81 (s, 3H), 3.77 (d, J = 7.7 Hz, 1H), 3.57 (d, J = 9.8 Hz, 1H), 1.57 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 177.3, 158.9, 130.7, 128.4(2C), 114.2(2C), 58.6, 55.2, 49.7, 45.8. $[\alpha]^{26}_{D}$ +13.6 (c 1.00, $CHCl_3$). Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.1; H, 6.8; N, 13.6. Found: C, 63.9; H, 6.8; N, 13.3.

General Procedure for the Preparation of α-Iminolactams *cis*- and *trans*-10a−e. To a solution of α-amino-γ-lactam *trans*- or *cis*-**6a−c** (1.0 mmol) in dry CH_2Cl_2 (3 mL) were added the corresponding aldehyde **8a−c** (1.0 mmol) and $MgSO_4$ at room temperature. The resulting mixture was stirred at the same temperature for 18 h, and then the solid was filtered off. The solvent was evaporated under reduced pressure to afford the pure product, which was used in the next step without further purification.

General Procedure for the Synthesis of 1,7-Diazaspiro[4.4]-nonan-6-ones 5a−i and *ent*-5b−g, i via (3 + 2) Cycloadditions between α-Iminolactams *trans*- or *cis*-10a−e and π-Deficient Alkenes. A solution of α-imino-γ-lactam **10a−e** (0.6 mmol), the corresponding dipolarophile (0.6 mmol), AgOAc (0.9 mmol), and Et_3N (0.9 mmol) in 5 mL of toluene was stirred at room temperature in the absence of light. The reaction was monitored by TLC, and once the starting material was consumed, the mixture was filtered through a pad of Celite or silica gel. The filtrate was concentrated under reduced pressure, and the residue was purified by trituration with Et_2O or by flash chromatography on silica gel (EtOAc/*n*-hexane 1:3) to afford the corresponding pure product.

*(2S,3S,4S,5R,9R)-2,9-Diphenyl-3,4-bis(phenylsulfonyl)-1,7-diazaspiro[4.4]nonan-6-one (**5a**).* The title compound was obtained from *trans*-**10a** and **7a** as a white pale solid (292 mg, 0.51 mmol, 85%). Mp 231−233 °C. IR (neat): 3321, 3064, 1718, 1147 746 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, J = 7.7 Hz, 2H), 7.78 (t, J = 7.5 Hz, 2H), 7.68 (t, J = 7.6 Hz, 2H), 7.55 (d, J = 7.7 Hz, 2H), 7.49 (t, J = 7.5 Hz, 2H), 7.43 (d, J = 7.5 Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 7.31−7.26 (m, 2H), 7.06 (dt, J = 14.6, 6.6 Hz, 2H), 7.01 (d, J = 7.2 Hz, 2H), 6.36 (s, 1H), 4.49 (d, J = 3.2 Hz, 1H), 4.29 (d, J = 3.2 Hz, 1H), 4.11 (d, J = 5.8 Hz, 1H), 3.88 (dd, J = 10.8, 5.9 Hz, 1H), 3.50 (d, J = 10.6 Hz, 1H), 2.93 (d, J = 9.1 Hz, 1H), 1.63 (bs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.0, 138.7, 138.0, 137.5, 137.4, 134.6, 134.2, 129.6, 129.4, 129.2, 128.7, 128.5, 128.3, 128.2, 127.93, 127.8, 127.4, 73.6, 72.4, 71.7, 64.17 51.6, 45.4. $[\alpha]^{26}_{D}$ −63.8 (c 0.5, $CHCl_3$). Anal. Calcd for $C_{31}H_{28}N_2O_5S_2$: C, 65.0; H, 4.9; N, 4.9. Found: C, 64.9; H, 4.9; N, 5.1.

*(3S,3′R,3a′S,4R,6a′R)-5′-Methyl-3′,4-diphenyldihydro-2′H-spiro-[pyrrolidine-3,1′-pyrrolo[3,4-c]pyrrole]-2,4′,6′(5′H,6a′H)-trione (**5b**).* The title compound was obtained from *trans*-**10a** and **7b** as a white solid (198 mg, 0.53 mmol, 88%). Mp 237−238 °C. IR (neat): 3333 (broad signal), 1773, 1689 (broad signal), 1433 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36−7.20 (m, 10H), 6.93 (s, 1H), 4.33 (dd, J = 7.8, 5.3 Hz, 1H), 4.06 (dd, J = 10.7, 6.5 Hz, 1H), 3.64−3.57 (m, 2H), 3.53 (t, J = 7.9 Hz, 1H), 3.43 (d, J = 7.7 Hz, 1H), 2.91 (s, 3H), 2.12 (d, J = 5.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.2, 174.6, 174.5, 138.1, 136.8, 129.3, 128.2, 128.1, 128.1, 127.6, 127.1, 71.8, 62.7, 53.4, 51.5, 49.7, 45.3, 25.1. $[\alpha]^{26}_{D}$ +40.5 (c 1.00, $CHCl_3$). Anal. Calcd for $C_{22}H_{21}N_3O_3$: C, 70.4; H, 5.6; N, 11.2. Found: C, 70.3; H, 6.0; N, 11.5. *(3R,3′S,3a′R,4S,6a′S)-5′-Methyl-3′,4 diphenyltetrahydro-4′H-spiro-[pyrrolidine-3,1′-pyrrolo[3,4-c]pyrrole]-2,4′,6′(5′H)-trione (ent-**5b**)*: The title compound was obtained from *cis*-**10a** and **7b** as a white solid (192 mg, 0.51 mmol, 85%). $[\alpha]^{26}_{D}$ −36.3 (c 1.00, $CHCl_3$).

*(2S,3S,4S,5S,9R)-3-Nitro-2,4,9-triphenyl-1,7-diazaspiro[4.4]-nonan-6-one (**5c**).* The title compound was obtained from *trans*-**10a** and **2a** as a white solid (176 mg, 0.43 mmol, 71%). Mp 231−232 °C. IR (neat): 3381, 3355, 3197, 1726, 1699, 1549, 1366 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42−7.21 (m, 15H), 6.05 (s, 1H), 5.53 (dd, J = 11.3, 9.6 Hz, 1H), 4.87 (d, J = 11.4 Hz, 1H), 4.31 (dd, J = 9.1, 7.4 Hz, 1H), 3.32−3.24 (m, 2H), 2.83 (t, J = 7.7 Hz, 1H), 2.51 (d, J = 7.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.2, 138.2, 137.2, 133.6, 129.2, 129.0, 128.8, 128.5, 128.4, 128.1, 127.8, 127.6, 90.9, 72.5, 62.9, 53.9, 46.2, 45.5. $[\alpha]^{26}_{D}$ −85.2 (c 1.00, $CHCl_3$). Anal. Calcd for $C_{25}H_{23}N_3O_3$: C, 72.6; H, 5.6; N, 10.2. Found: C, 72.6; H, 5.9; N, 10.3. *(2R,3R,4R,5R,9S)-3-Nitro-2,4,9-triphenyl-1,7-diazaspiro[4.4]nonan-6-one (ent-**5c**)*: The title compound was obtained from *cis*-**10a** and **2a** as a white solid (186 mg, 0.45 mmol, 75%). $[\alpha]^{26}_{D}$ +84.3 (c 1.00, $CHCl_3$).

*(2S,3S,4S,5S,9R)-9-(4-Methoxyphenyl)-3-nitro-2,4-diphenyl-1,7-diazaspiro[4.4]nonan-6-one (**5d**).* The title compound was obtained from *trans*-**10b** and **2a** as a white solid (162 mg, 0.37 mmol, 61%). Mp 240−241 °C. IR (neat): 3259, 3407, 1703, 1547, 1509, 1228, 858, cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (dd, J = 7.4, 1.8 Hz, 2H), 7.39 (d, J = 1.5 Hz, 2H), 7.37−7.35 (m, 4H), 7.34−7.29 (m, 2H), 6.94 (d, J = 8.6 Hz, 2H), 5.93 (s, 1H), 5.54 (dd, J = 11.5, 9.4 Hz, 1H), 4.93 (d, J = 11.3 Hz, 1H), 4.43−4.34 (m, 1H), 3.87 (s, 3H), 3.80 (d, J = 8.4 Hz, 1H), 3.32 (dd, J = 9.5, 6.7 Hz, 1H), 3.29−3.21 (m, 1H), 3.00−2.88 (m, 1H), 2.56 (bs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.9, 137.3, 133.8, 130.1, 129.2, 128.9, 128.6, 128.3, 127.9, 127.6, 114.4, 91.2, 63.2, 55.3, 53.7, 46.3, 44.7. $[\alpha]^{26}_{D}$ −60.5 (c 1.00, $CHCl_3$). Anal. Calcd for $C_{26}H_{25}N_3O_4$: C, 70.4; H, 5.7; N, 9.5. Found: C, 70.3; H, 5.6; N, 9.6. *(2R,3R,4R,5R,9R)-9-(4-Methoxyphenyl)-3-nitro-2,4-diphenyl-1,7-diazaspiro[4.4]nonan-6-one (ent-**5d**)*: The title compound was obtained from *cis*-**10b** and **2a** as a white solid (165 mg, 0.37 mmol, 62%). $[\alpha]^{26}_{D}$ +61.2 (c 1.00, $CHCl_3$).

*(2R,3R,4R,5R,9S)-9-(4-Fluorophenyl)-3-nitro-2,4-diphenyl-1,7-diazaspiro[4.4]nonan-6-one (**5e**).* The title compound was obtained from *trans*-**10c** and **2a** as a white solid (132 mg, 0.31 mmol, 51%). Mp 219−223 °C. IR (neat): 3398, 1739, 1508, 1292, 1164, 749 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58−7.24 (m, 7H), 7.10 (t, J = 8.3 Hz, 1H), 6.22 (s, 1H), 5.53 (dd, J = 11.3, 9.1 Hz, 1H), 4.93 (d, J = 11.2 Hz, 1H), 4.35 (t, J = 8.1 Hz, 1H), 3.30 (dq, J = 13.8, 7.0 Hz, 1H), 2.95 (t, J = 8.0 Hz, 1H), 2.62 (d, J = 7.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.85, 162.4 (d, J^1_{C-F} = 245.7 Hz), 136.9, 133.6 (d, J^3_{C-F} = 3.23 Hz), 130.7, 130.7, 129.3, 129.1, 128.9, 128.6, 128.5, 128.4, 127.8, 127.6, 127.5, 116.0, 115.8, 91.1, 63.5, 54.0, 46.5, 44.8. ^{19}F NMR (375 MHz, $CDCl_3$): δ −110.95. $[\alpha]^{26}_{D}$ −40.2 (c 1.00, $CHCl_3$). Anal. Calcd for $C_{25}H_{22}FN_3O_3$: C, 69.5; H, 5.1; N, 9.7. Found: C, 69.5; H, 5.3; N, 9.8. *(2S,3S,4S,5S,9R)-9-(4-Fluorophenyl)-3-nitro-2,4-diphenyl-1,7-diazaspiro[4.4]nonan-6-one (ent-**5e**)*: The title compound was obtained from *cis*-**10c** and **2a** as a white solid (150 mg, 0.35 mmol, 58%). $[\alpha]^{26}_{D}$ +68.2 (c 1.00, $CHCl_3$).

*(2S,3S,4S,5S,9R)-2-(4-Methoxyphenyl)-3-nitro-4,9-diphenyl-1,7-diazaspiro[4.4]nonan-6-one (**5f**).* The title compound was obtained from *trans*-**10d** and **2a** as a white solid (181 mg, 0.41 mmol, 68%). Mp 246−247 °C. IR (neat): 3273, 3012, 1703, 1549, 1512, 1246, 1030 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, J = 7.8 Hz, 2H), 7.42−7.37 (m, 6H), 7.35 (s, 2H), 7.29 (d, J = 2.2 Hz, 2H), 6.94−6.72 (m, 2H), 6.30 (bs, 1H), 5.61−5.45 (m, 1H), 4.91 (d, J = 11.6 Hz, 1H), 4.41−4.28 (m, 1H), 3.78 (d, J = 2.1 Hz, 3H), 3.33 (dd, J = 15.7, 8.0 Hz, 1H), 2.89 (t, J = 8.5 Hz, 1H), 2.49 (d, J = 9.1 Hz, 1H), 1.61 (bs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.1, 159.9, 138.1, 133.7, 129.2, 129.0, 129.0, 128.8, 128.1, 127.9, 113.95, 90.9, 72.4, 62.6, 55.2, 53.7, 46.2, 45.5. $[\alpha]^{26}_{D}$ −65.1 (c 1.00, $CHCl_3$). Anal. Calcd for $C_{26}H_{25}N_3O_4$: C, 70.4; H, 5.7; N, 9.5. Found: C, 70.2; H, 5.9; N, 9.9. *(2R,3R,4R,5R,9S)-2-(4-Methoxyphenyl)-3-nitro-4,9-diphenyl-1,7-diazaspiro[4.4]nonan-6-one (ent-**5f**)*: The title compound was obtained from *cis*-**10d** and **2a** as a white solid (189 mg, 0.43 mmol, 71%). $[\alpha]^{26}_{D}$ +60.5 (c 1.00, $CHCl_3$).

*(2S,3S,4S,5S,9R)-2-(4-Fluorophenyl)-3-nitro-4,9-diphenyl-1,7-diazaspiro[4.4]nonan-6-one (**5g**).* The title compound was obtained from *trans*-**10e** and **2a** as a pale brown solid (181 mg, 0.42 mmol). Mp 246−247 °C. IR (neat): 3390, 1751, 1510, 1275, 1174, 751 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50−7.46 (m, 4H), 7.37−7.40 (m, J = 7.6 Hz, 6H), 7.35−7.33 (m, 2H), 7.00−6.97 (m, 2H), 6.52 (bs, 1H), 5.61 (t, J = 10.5 Hz, 1H), 4.87 (d, J = 11.6 Hz, 1H), 4.41 (d, J = 9.4 Hz, 1H), 3.33 (d, J = 6.3 Hz, 2H), 2.92−2.75 (m, 1H), 2.46 (s, 1H), 1.71−1.50 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.0, 162.9 (d, J^1_{C-F} = 247.8 Hz), 138.1, 133.1(d, J^3_{C-F} = 3.23 Hz), 129.4, 129.3, 129.1, 128.6, 128.4, 128.1, 127.7, 115.4 (d, J^2_{C-F} = 21.63 Hz), 90.3, 72.1, 61.8, 53.3, 45.9, 45.5, 41.3, 31.5, 22.6, 14.1. ^{19}F NMR (376 MHz,

$CDCl_3$): δ −112.93. $[\alpha]^{26}_D$ −21.0 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{25}H_{22}FN_3O_3$: C, 69.5; H, 5.1; N, 9.7. Found: C, 69.7; H, 5.0; N, 9.5. *(2R,3R,4R,5R,9S)-2-(4-Fluorophenyl)-3-nitro-4,9-diphenyl-1,7-diazaspiro[4.4]nonan-6-one (ent-**5g**)*: The title compound was obtained from *cis*-**10e** and **2a** as a pale brown solid (145 mg, 0.34 mmol, 56%). $[\alpha]^{26}_D$ +20.6 (*c* 1.00, $CHCl_3$).

*(2R,3S,5R,9R)-3-Methoxycarbonyl-2,9-diphenyl-1,7-diazaspiro-[4.4]nonan-6-one (**5h**).* The title compound was obtained from *trans*-**10a** and **7c** as a white solid (179 mg, 0.51 mmol, 85%). Mp 210−211 °C. IR (neat): 3465 (broad signal), 1725, 1697 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32−7.06 (m, 11H), 4.09 (d, *J* = 9.4 Hz, 1H), 3.66 (dd, *J* = 9.8, 7.4 Hz, 1H), 3.54 (dd, *J* = 10.0, 4.1 Hz, 1H), 3.27 (dd, *J* = 6.6, 4.5 Hz, 1H), 3.22 (ddd, *J* = 10.7, 9.6, 7.5 Hz, 1H), 3.10 (s, 3H), 2.75 (t, *J* = 12.0 Hz, 1H), 2.14 (bs, 1H), 2.05 (dd, *J* = 12.6, 7.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 178.5, 171.8, 141.1, 139.1, 128.8, 128.2, 127.9, 127.6, 127.4, 127.4, 70.2, 63.8, 51.8, 51.2, 49.8, 45.5, 36.8. $[\alpha]^{26}_D$ −10.5 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 72.0; H, 6.3; N, 8.0. Found: C, 72.1; H, 5.9; N, 8.2.

*(2R,3S,5R,9R)-tert-Butyl-6-oxo-2,9-diphenyl-1,7-diazaspiro[4.4]-nonane-3-carboxylate (**5i**).* The title compound was obtained from *trans*-**10a** and **7d** as a white solid (177 mg, 0.45 mmol, 75%). Mp 223−225 °C. IR (neat): 3222 (broad signal), 2975, 2919, 1701, 1151, 698 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47−7.14 (m, 10H), 6.42 (s, 1H), 4.13 (d, *J* = 9.4 Hz, 1H), 3.75 (dd, *J* = 10.0, 7.0 Hz, 1H), 3.62 (t, *J* = 5.1 Hz, 1H), 3.36 (dd, *J* = 7.1, 4.3 Hz, 1H), 3.24 (td, *J* = 10.2, 9.7, 7.3 Hz, 1H), 2.81 (t, *J* = 12.1 Hz, 1H), 2.16 (dd, *J* = 12.8, 7.2 Hz, 1H), 1.03 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 178.2, 170.5, 141.7, 139.3, 129.0, 128.8, 128.2, 128.1, 128.0, 127.6, 127.4, 127.36, 80.5, 69.9, 63.9, 52.0, 50.7, 45.6, 45.5, 37.6, 27.5. $[\alpha]^{26}_D$ −8.5 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{24}H_{28}N_2O_3$: C, 73.4; H, 7.2; N, 7.1. Found: C, 73.0; H, 7.4; N, 7.5. *(2S,3R,5S,9S)-tert-Butyl-6-oxo-2,9-diphenyl-1,7-diazaspiro[4.4]nonane-3-carboxylate (ent-**5i**)*: The title compound was obtained from *cis*-**10a** and **7d** as a white solid (170 mg, 0.43 mmol, 72%). $[\alpha]^{26}_D$ +10.7 (*c* 1.00, $CHCl_3$).

General Procedure for the Synthesis of Spiro Acids 11 and *ent*-11. Spiro *tert*-butyl ester **5i** or *ent*-**5i** (392 mg, 1.0 mmol) was allowed to react with TFA (8 mL) in CH_2Cl_2 (15 mL) overnight at room temperature. Rotary evaporation of the reaction mixture under reduced pressure yielded a residue that was purified by precipitation in EtOAc/*n*-hexane to afford the desired acid.

*(2R,3S,5R,9R)-6-Oxo-2,9-diphenyl-1,7-diazaspiro[4.4]nonane-3-carboxylic Acid. (**11**).* The title compound was obtained from **11** as a white solid (242 mg, 0.72 mmol, 72%). Mp 245−247 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.88 (bs, 1H), 8.18 (s, 1H), 7.42 (d, *J* = 7.3 Hz, 2H), 7.38−7.25 (m, 5H), 7.24−7.12 (m, 3H), 3.94 (d, *J* = 9.1 Hz, 1H), 3.54−3.47 (m, 1H), 3.47−3.29 (m, 3H), 3.04 (q, *J* = 9.2 Hz, 1H), 2.45 (d, *J* = 11.9 Hz, 1H), 2.07 (dd, *J* = 12.6, 7.2, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 177.7, 173.0, 142.7, 140.1, 129.1, 128.7, 128.0, 127.3, 69.9, 63.5, 51.4, 49.8, 44.8, 36.5. $[\alpha]^{26}_D$ +40.5 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{22}H_{21}N_3O_3$: C, 70.4; H, 5.6; N, 11.2. Found: C, 70.3; H, 6.0; N, 11.5. *(2S,3R,5S,9S)-6-Oxo-2,9-diphenyl-1,7-diazaspiro[4.4]nonane-3-carboxylic acid (ent-**11**)*: 229 mg, 0.68 mmol, 68%. White solid. $[\alpha]^{26}_D$ −37.1 (*c* 1.00, $CHCl_3$).

General Procedure for the Synthesis of Hydroxamic Acids 14 and *ent*-14. A mixture of spiro acid **11** or *ent*-**11** (336 mg, 1.0 mmol), methyl-4-(aminomethyl)benzoate hydrochloride **12** (202 mg, 1.0 mmol), and *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (353 mg, 1.1 mmol) in dry DMF (1.8 mL) was cooled to 0 °C under argon atmosphere. Then, a mixture of Et_3N (0.42 mL, 3.0 mmol) and dry DMF (1 mL) was added dropwise, and the resulting mixture was stirred for 1.5 h at 0 °C. Then, EtOAc was added, and the organic layer washed five times with water, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure to afford the corresponding methyl ester **13** or *ent*-**13**, which was used in the next step without further purification.

To a solution of hydroxylamine hydrochloride (261 mg, 3.75 mmol) and phenolphthalein (1 mg) in methanol (1.25 mL) at 0 °C and under argon atmosphere was dropwise added a precooled 4 M solution of NaOMe in methanol until a permanent pink color was observed. Then, the corresponding methyl ester **13** or *ent*-**13** (604 mg, 1.25 mmol) was added, followed by 1.4 mL of the same precooled 4 M solution of NaOMe in methanol. The resulting mixture was stirred for 26 h at room temperature. During the course of the reaction, a precipitate was observed. Then, water was added (3 mL), and the solution was acidified with glacial acetic acid to pH 2. The organic layer was separated and extracted three times with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure to afford the pure product **14** or *ent*-**14**, which was purified by trituration in EtOAc/*n*-hexane.

*(2R,3S,5R,9R)-N-(4-(Hydroxycarbamoyl)benzyl)-6-oxo-2,9-diphenyl-1,7-diazaspiro[4.4]nonane-3-carboxamide (**14**).* The title compound was obtained from **13** as a pale red solid (594 mg, 1.23 mmol, 98%). Mp 50−51 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.51 (t, *J* = 5.6 Hz, 1H), 8.25 (bs, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.28−7.25 (m, 1H), 7.19−7.12 (m, 5H) 7.03 (t, *J* = 7.0 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 2H), 6.84 (d, *J* = 7.7 Hz, 1H), 4.00−3.91 (m, 1H), 3.80−3.66 (m, 1H), 3.52 (m, 2H), 3.44 (d, *J* = 6.4 Hz, 1H), 3.01 (m, 1H), 2.70 (s, 1H), 2.19 (dd, *J* = 13.3, 7.4 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 178.4, 174.3, 171.5, 163.8, 142.8, 141.4, 139.6, 131.8, 129.4, 129.0, 128.8, 128.0, 127.9, 127.5, 127.0, 126.7, 122.4, 121.5, 118.3, 112.5, 69.2, 64.2, 51.8, 50.7, 44.8, 42.3, 37.3, 24.0. $[\alpha]^{26}_D$ −30.1 (*c* 0.50, CH_3OH). HRMS: $[M + H]^+$ calcd for $C_{28}H_{29}N_4O_4$, 485.2193; found, 485.2189. *(2S,3R,5S,9S)-N-(4-(Hydroxycarbamoyl)benzyl)-6-oxo-2,9-diphenyl-1,7-diazaspiro[4.4]nonane-3-carboxamide (ent-**14**)*: The title compound was obtained from *ent*-**13** as a pale red solid (594 mg, 1.23 mmol, 98%). $[\alpha]^{26}_D$ +30.7 (*c* 0.78, CH_3OH).

5. COMPUTATIONAL METHODS

DFT calculations were performed with the Gaussian 09 package.[10] The ONIOM(B3LYP/LANL2DZ):PM6 method[11−13] was employed for the optimization of the stationary points along the frustrated (3 + 2) cycloadditions between imines and nitrostyrene (**2a**). B3LYP/6-31+G* level of theory was used for the optimization of the stationary points along the reaction of azomethine ylides **INT3a,e** and nitrostyrene (**2a**). Single-point calculations of the optimized geometries were performed using the M06 functional[12f] and the 6-31++G(d,p) basis set for the C, N, P, H and O atoms and LANL2DZ effective core potential for Cu, Ag, and Fe atoms. The geometries for all species described were optimized in the gas phase without symmetry restrictions. Frequency calculations were performed on the optimized structures at the same level of theory used to characterize the stationary points (see the Supporting Information for additional details).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01418.

Full characterization of all novel compounds, cartesian coordinates, harmonic analyses, and energies of all of the stationary points discussed in this work (PDF)
CIF file for compound **5e** (CIF)
CIF file for compound *cis*-**6b** (CIF)
CIF file for compound **5a** (CIF)

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Notes

The authors declare no competing financial interest.

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