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Densely Substituted L-Proline Esters as Catalysts for Asymmetric Michael Additions of Ketones to Nitroalkenes

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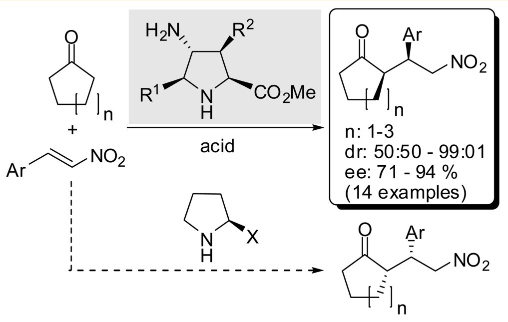
S *Supporting Information*

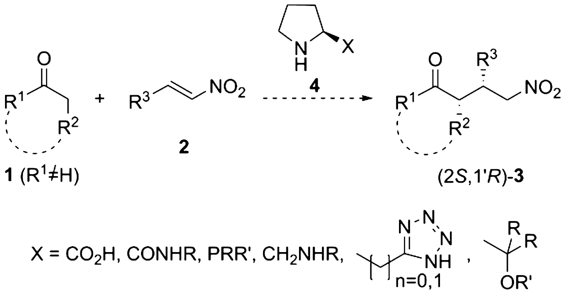
ABSTRACT: Homochiral methyl 4-aminopyrrolidine-2-carboxylates are readily obtained by means of asymmetric (3 + 2) cycloadditions between azomethine ylides and nitroalkenes, followed by catalytic hydrogenation of the intermediate 4-nitro cycloadducts. These 4-aminopyrrolidine-2-carboxylate esters belong to the L-series of natural amino acids and catalyze asymmetric Michael additions of ketones to nitroalkenes. However, the enantioselectivity observed with these novel unnatural organocatalysts is opposite to that obtained with L-proline. Since both 4-nitro and 4-amino L-proline esters are efficient organocatalysts of aldol reactions, these results permit to modulate asymmetric quimioselective aldol and conjugate addition reactions.



INTRODUCTION

Catalytic conjugate addition reactions constitute a very powerful method for the generation of C−C bonds in a stereocontrolled manner.[1] Among many different catalysts to perform this reaction, L-proline (L-Pro) derivatives have been described as suitable organocatalysts[2] that promote the reactions between ketones and nitroalkenes[3] (Scheme 1).

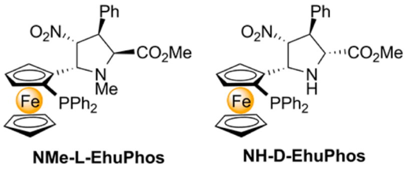
Scheme 1. Michael Addition of Ketones to Nitroalkenes Catalyzed by L-Pro Derivatives



Different authors[4] have described L-Pro-based organocatalysts incorporating functional groups at the α-position such as carboxylate, alcohol, amide, phosphino, tetrazole, etc. It is remarkable that in all these cases the (2*S*,1′*R*)-Michael adducts were reported as the major isomers.[3,4]

Recently, we have described[5] two novel enantiopure ligands (Chart 1) based on ferrocenylphosphino proline esters that are able to catalyze the (3 + 2) cycloaddition between nitroalkenes and azomethine ylides derived from imines. Recently, these ligands have been applied to (3 + 2) cycloadditions between azomethine ylides and C_{60}.[6] We have found that reaction between β-nitrostyrenes **2** and imines catalyzed by Cu(I) salts and **NH−D−EhuPhos** leads to the formation of *exo*-cycloadducts, whereas the same reaction leads to the formation of the corresponding *endo*-cycloadducts in the presence of **NMe−L−EhuPhos**. We also found that the *exo*-L-cycloadducts thus formed catalyze aldol reactions yielding the opposite enantiomers with respect to those found when L-Pro and its derivatives are used as organocatalysts.[5] In contrast, when *endo*-L-cycloadducts were used, the sense of chiral induction in aldol reactions was similar to that found with L-Pro. These results showed the subtle effects of distal substituents with respect to the active site of the organocatalysts.

Chart 1. Enantiopure Ligands Based on Ferrocenylphosphino Pyrrolidines



In this paper, we report our results on the ability of densely substituted proline esters as organocatalysts in conjugate additions. We shall show that the primary (3 + 2) 4-nitro cycloadducts are not well suited to catalyze these reactions, whereas their corresponding amino derivatives are efficient

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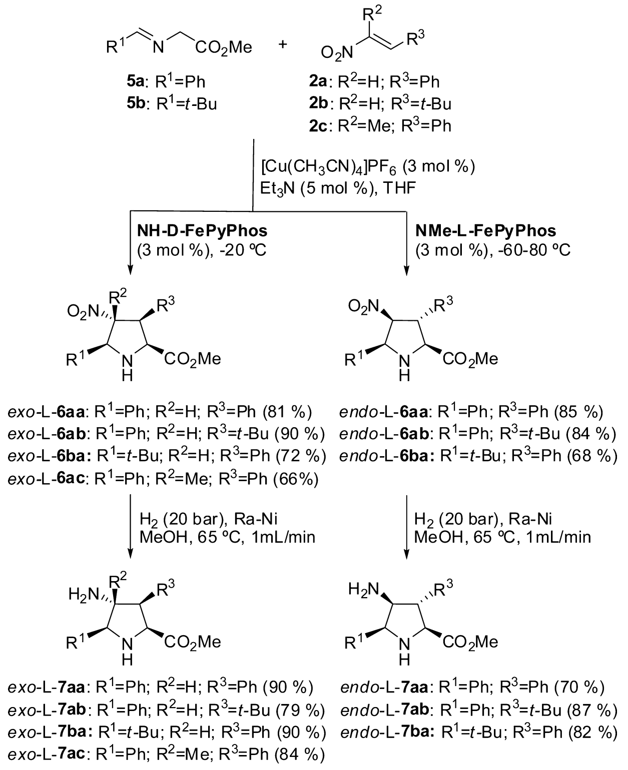
organocatalysts for the conjugate Michael reaction between cyclic ketones and *β*-nitrostyrenes. Therefore, a simple modification of one functional group in these densely substituted pyrrolidine derivatives results in the emergence of novel catalytic properties.

■ RESULTS AND DISCUSSION

We prepared 4-nitroproline methyl esters *endo*- and *exo*-L-**6aa**−**ba** following the procedure described in our previous work[5] (Scheme 2). Cycloadducts *exo*-L-**6aa**−**ac** were obtained in high yields and enantiomeric excesses in the presence of **NH-D-EhuPhos** and a suitable Cu(I) salt. It is remarkable that our enantiopure ligand belonging to the D-series promotes the formation of L-pyrrolidines via (3 + 2) cycloadditions at −20 °C between azomethine ylides derived from imines **5a,b** and nitroalkenes **2a**−**c** (Scheme 2). Cycloadducts *exo*-L-**6ab**−**ac** were obtained with excellent ee's ranging from 94% to >99% (see the Experimental Section). Similarly, (3 + 2) cycloadducts *endo*-L-**6aa**−**ba** were obtained in good yields and ee's at temperatures ranging from −60 to −80 °C via catalytic ligand **NMe-L-EhuPhos** (Scheme 2). Compound *endo*-L-**6ba** showed the lowest chemical yield and ee, with an L:D enantiomeric ratio of ca. 88.5:11.5; thus, it was purified by semipreparative HPLC resolution in a chiral column (see the Experimental Section). The ee's of cycloadducts **6aa** and **6ac** were ≥99% after recrystallization in ethyl acetate/hexane mixture, with the only exception of compound *endo*-L-**6ab**, for which an ee value of 95% was measured by HPLC.

Scheme 2. Enantioselective Synthesis of Unnatural L-Proline Methyl Esters 6aa−ac and 7aa−ac[a,b]

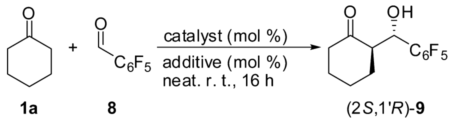


[a]Numbers in parentheses correspond to yields of isolated pure (3 + 2) cycloadducts. [b]Ra−Ni: Raney nickel.

In sharp contrast with the satisfactory results provided by 4-nitroproline methyl esters in organocatalytic aldol reactions,[5] our attempts to catalyze the conjugate addition between cyclohexanone **1a** and (*E*)-*β*-nitrostyrene **2a** with *exo*- and *endo*-L-**6aa** in the absence of any additive or in the presence of 30 mol % of benzoic acid met with no success (vide infra). We reasoned that a combination of steric and electrostatic adverse effects (repulsion between the nitro groups of the Michael acceptor and the organocatalysts) should be the responsible for this lack of reactivity. Since the ability of primary amines to catalyze conjugate additions is known,[7] we decided to transform (3 + 2) 4-nitro cycloadducts **6** into the corresponding 4-amino analogues **7** (Scheme 2). Catalytic hydrogenation of the nitro group in a flow reactor at 65 °C resulted in the formation of the corresponding 4-amino proline methyl esters with good to excellent yields.

We tested the ability of compounds *exo*-L-**7aa** and *endo*-L-**7aa** to catalyze the aldol reaction between cyclohexanone **1a** and 2,3,4,5,6-pentafluorobenzaldehyde **8** (Table 1). We observed a behavior similar to that reported for 4-nitro precursors *exo*-L-**6aa** and *endo*-L-**6aa** (Table 1, entries 1 and 2). Thus, our experiments indicate that *exo*-L-**7aa** promotes the preferential formation of *anti* aldol adduct (2*R*,1′*S*)-**9**, whereas *endo*-L-**7aa** catalyzes the aldol reaction between **1a** and **8** to yield the enantiomeric aldol adduct (2*S*,1′*R*)-**9** as the major product, although with a lower ee (Table 1, entries 7 and 8). A similar enantiodivergent outcome was observed for the nitro analogues *exo*-L-**6aa** and *endo*-L-**6aa**.[5,8] Our results also indicate that TFA is a convenient additive for this reaction, whereas the presence of benzoic acid and the absence of any acidic additive result in significantly lower ee's (Table 1, entries 3−6). It is also interesting to note that *exo*-L-**7aa** catalyzes this model aldol reaction even with a relatively low catalytic load of 5 mol % (Table 1, entries 10 and 11).

Table 1. Aldol Reaction between Cyclohexanone 1a and Aldehyde 8 Catalyzed by Unnatural L-Proline Esters *exo*-L-6aa, *endo*-L-6aa, *exo*-L-7aa, and *endo*-L-7aa



entry[a]	catalyst	mol %	additive	*anti*:*syn*[b]	yield (%)[c]	ee (%)[d]
1	*exo*-L-**6aa**	30	TFA	95:05	73	89
2	*endo*-L-**6aa**	30	TFA	96:04	83	−81
3	*exo*-L-**7aa**	30	none	95:05	75	66
4	*endo*-L-**7aa**	30	none	95:05	60	−10
5	*exo*-L-**7aa**	30	$PhCO_2H$	92:08	61	45
6	*endo*-L-**7aa**	30	$PhCO_2H$	77:23	65	−12
7	*exo*-L-**7aa**	30	TFA	85:15	63	80
8	*endo*-L-**7aa**	30	TFA	81:19	62	−70
9	*exo*-L-**7aa**	10	TFA	91:09	67	82
10	*exo*-L-**7aa**	5	TFA	90:10	68	82
11[e]	*exo*-L-**7aa**	5	TFA	92:08	65	88

[a]Reactions were monitorized by TLC and stirred for 1 to 16 h at room temperature until consumption of the starting material (Conversion > 99%). [b]The *anti*:*syn* ratios were measured by ^{19}F-NMR of crude reaction mixtures. [c]Yields refer to isolated pure aldol adducts. [d]Enantiomeric excesses measured by HPLC correspond to the major *anti*-diastereomer **9** calculated as ee = 100([2*R*,1′*S*] − [2*S*,1′*R*])/([2*R*,1′*S*] + [2*S*,1′*R*]). [e]Reaction carried out at 0 °C for 48 h.

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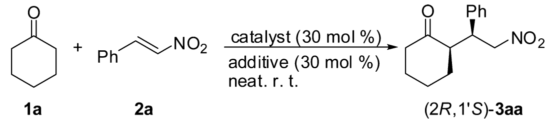
Once we verified that novel organocatalysts *endo*- and *exo*-L-**7aa** behave similarly to their 4-nitro analogues, we tested both novel compounds in the model conjugate addition between cyclohexanone **1a** and (*E*)-*β*-nitrostyrene **2a** to yield compound **3aa**. The results obtained are gathered in Table 2. As we have previously mentioned, (3 + 2) cycloadducts *endo*-L-**6aa** and *exo*-L-**6aa** did not yield detectable amounts of adducts **3aa** after up to 7 days of reaction at room temperature. In the presence of 30 mol % of TFA, *exo*-L-**6aa** promoted a conversion of only 35% as detected by ^{1}H NMR after 1 day of reaction. Even in this case, a very low diastereoselectivity was measured (Table 2, entries 1−3). In contrast, both 4-amino analogues *endo*-L-**7aa** and *exo*-L-**7aa** were found to be able to catalyze these Michael additions, yielding the corresponding *syn*-cycloadducts **3aa** after 16−48 h of reaction in the absence of any additive (Table 2, entries 5 and 6). When *exo*-L-**7aa** was used as catalyst, the (2*R*,1′*S*)-**3aa** adduct was obtained as the major enantiomer, which is the opposite stereoisomer obtained by using natural L-Pro derivatives. In contrast, *endo*-L-**7aa** promoted the preferential formation of (2*S*,1′*R*)-**3aa**, although with a significantly lower ee.

Table 2. Conjugate Addition Reaction between Cyclohexanone 1a and (*E*)-*β*-Nitrostyrene 2a Catalyzed by Unnatural L-Proline Esters *exo*-L-7aa and *endo*-L-7aa



entry	catalyst	additive	conv. (%)[a]	time (h)	*syn*:*anti*[b]	yield (%)[c]	ee (%)[d]
1	*exo*-L-6aa	none	<0.5	72	n. d.[e]	n. d.	n. d.
2	*exo*-L-6aa	benzoic acid	<0.5	168	n. d.	n. d.	n. d.
3	*exo*-L-6aa	TFA	35	24	67:33	n. d.	60
4	*endo*-L-6aa	TFA	20	24	n. d.	n. d.	n. d.
5	*exo*-L-7aa	none	>99	48	93:07	65	77
6	*endo*-L-7aa	none	>99	16	94:04	72	−44
7	*exo*-L-7aa	*p*-nitrophenol	>99	64	98:02	61	78
8	*exo*-L-7aa	TsOH·H$_2$O	21	168	n. d.	n. d.	66
9	*exo*-L-7aa	AcOH	>99	40	90:10	60	84
10	*exo*-L-7aa	butyric acid	>99	96	88:12	63	86
11	*exo*-L-7aa	TFA	>99	20	93:07	75	91
12[f]	*exo*-L-7aa	TFA	>99	36	87:13	85	91
13[g]	*exo*-L-7aa	TFA	44	96	n. d.	n. d.	n. d.
14	*endo*-L-7aa	TFA	>99	24	95:05	65	−78
15	*exo*-L-7aa	benzoic acid	>99	36	99:01	65	88
16	*endo*-L-7aa	benzoic acid	>99	24	90:10	58	−64
17	*exo*-L-7aa	salicylic acid	>99	16	94:06	70	90
18	*exo*-L-7aa	PNBA[h]	>99	16	93:07	81	92
19[f]	*exo*-L-7aa	PNBA	>99	36	95:05	70	87
20[g]	*exo*-L-7aa	PNBA	>99	60	86:14	83	89
21	*endo*-L-7aa	PNBA	>99	16	89:11	79	−42

[a] Conversions were measured by ^{1}H NMR on crude reaction mixtures. [b] The *syn*:*anti* ratios were measured by ^{1}H NMR on crude reaction mixtures. [c] Yields of isolated pure Michael adducts **3aa**. [d] Enantiomeric excesses of major *syn*-diastereomer **3aa** were measured by HPLC computed as ee = 100([2*R*,1′*S*] − [2*S*,1′*R*])/([2*R*,1′*S*] + [2*S*,1′*R*]). [e] n. d.: Not determined. [f] Reaction performed with 20 mol % catalyst load. [g] Reaction performed at 0 °C. [h] PNBA: 4-nitrobenzoic acid.

Addition of compounds with acidic groups resulted in faster and more selective reactions. Thus, *p*-nitrophenol promoted a relatively fast reaction (Table 2, entry 7), whereas *p*-toluensulfonic acid (Table 2, entry 8) was inefficient in this respect. Carboxylic acids proved to be more convenient additives for this reaction. Trifluoroacetic acid (TFA, Table 2, entry 14) was the most efficient additive for *endo*-L-**7aa** in terms of stereocontrol, although the conversion in this case was found to be less satisfactory. In the case of *exo*-L-**7aa**, TFA, benzoic acid, salicylic acid and, especially, 4-nitrobenzoic acid (Table 2, entries 11, 15, 17, and 18, respectively) proved to be convenient additives in terms of conversion, chemical yields, diastereoselectivity, and enantioselectivity. Lower catalytic loads and temperatures did not improve significantly the outcome obtained with a catalytic load of 30 mol % and at room temperature, respectively (Table 2, entries 12, 13, 19, and 20). It is noteworthy that, in all the cases studied, the behavior was found to be consistently enantiodivergent for *exo*-L-**7aa** and *endo*-L-**7aa**, and the enantiocontrol was lower in the latter case (Table 2, entries 14, 16, and 21).

Once reaction conditions of room temperature, 30 mol % catalytic load, and 4-nitrobenzoic acid as additive were selected, the scope of the reaction in the presence of *exo*-L-**7aa** was assessed. The results are collected in Table 3 (see also Scheme 3).

According to our results, cyclopentanone **1b** reacts easily with **2a**, but in the presence of *exo*-L-**7aa**, no diastereocontrol is observed (Table 3, entries 2 and 3). Cycloheptanone **1c** is more selective, and the *syn*:*anti* diastereomeric ratio and the ee are closer to the values obtained for cyclohexanone **1a** (Table 3, entries 1, 4, and 5). In this latter case, TFA is a more convenient acidic additive. When the reaction was carried out in the presence of acetone **1d**, a lower enantiocontrol was observed, although the chemical yield was acceptable (Table 3, entry 6). Nitroalkenes **2b**−**l** incorporating different aryl and heteroaryl substituents are suitable Michael acceptors for this reaction, and the (2*R*-1′*S*)-**3aa**-**am** adducts are always the major isomers with ee's in the range 74−92% (Table 3, entries 7−16). Electron-withdrawing substituents such as nitro (**2g**), trifluoromethyl (**2e**), and halogen (**2h,j**) lead to more electrophilic Michael acceptors but do not decrease significantly the ee's (Table 3, entries 8, 11, 12, and 13). Finally, 2-furyl (**2l**) and 2-naphthyl (**2m**) groups in the starting nitroalkenes result in low yields in the corresponding adducts **3al** and **3am**, respectively (Table 3, entries 15 and 16). Nitroalkenes **2b** and **2c** did not yield satisfactory results since the former led to complex reaction mixtures (maybe because of the instability of this compound) and the latter was inert under these reaction conditions.

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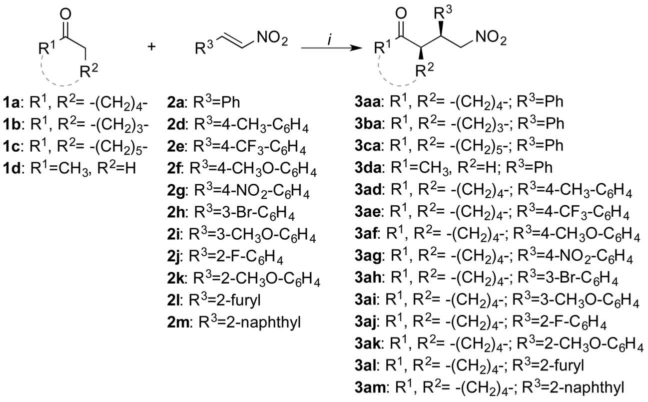
Table 3. Chemical Yields, Diastereoselectivities, and Enantiomeric Excesses Observed in Conjugate Addition Reactions between Ketones 1a–d and Nitroalkenes 2a–m To Yield Adducts (2*R*,1′*S*)-3aa–7da Catalyzed by Unnatural L-Proline Ester *exo*-L-7aa[a,b]

entry	R^1, R^2	R^3	1	2	(2*R*,1′*S*)-3	*syn*:*anti*[c]	yield (%)[d]	ee (%)[e]
1	$-(CH_2)_4-$	Ph	**1a**	**2a**	**3aa**	93:07	81	92
2	$-(CH_2)_3-$	Ph	**1b**	**2a**	**3ba**	47:53	88	64
3[f]	$-(CH_2)_3-$	Ph	**1b**	**2a**	**3ba**	50:50	75	72
4	$-(CH_2)_5-$	Ph	**1c**	**2a**	**3ca**	78:22	20	71
5[f]	$-(CH_2)_5-$	Ph	**1c**	**2a**	**3ca**	93:07	84	80
6[g]	CH_3, H	Ph	**1d**	**2a**	**3da**	-	79	−41
7	$-(CH_2)_4-$	$4\text{-}CH_3-C_6H_4$	**1a**	**2d**	**3ad**	93:07	58	87
8	$-(CH_2)_4-$	$4\text{-}CF_3-C_6H_4$	**1a**	**2e**	**3ae**	73:27	90	88
9	$-(CH_2)_4-$	$4\text{-}CH_3O-C_6H_4$	**1a**	**2f**	**3af**	89:11	75	88
10	$-(CH_2)_4-$	$4\text{-}NO_2-C_6H_4$	**1a**	**2g**	**3ag**	78:22	89	86
11	$-(CH_2)_4-$	$3-Br\text{-}C_6H_4$	**1a**	**2h**	**3ah**	95:05	93	88
12	$-(CH_2)_4-$	$3\text{-}CH_3O-C_6H_4$	**1a**	**2i**	**3ai**	99:01	72	88
13	$-(CH_2)_4-$	$2-F\text{-}C_6H_4$	**1a**	**2j**	**3aj**	84:16	90	92
14	$-(CH_2)_4-$	$2\text{-}CH_3O-C_6H_4$	**1a**	**2k**	**3ak**	97:03	83	74
15	$-(CH_2)_4-$	2-furyl	**1a**	**2l**	**3al**	90:10	59	84
16	$-(CH_2)_4-$	2-naphthyl	**1a**	**2m**	**3am**	77:23	23	82

[a] See Scheme 3 for the definition of reactants, products, and reaction conditions. [b] Reactions were monitorized by TLC or ^1H NMR and stirred at room temperature until conversion >99%. [c] The *syn*:*anti* ratios were measured by ^1H NMR or HPLC on crude reaction mixtures. [d] Yields refer to isolated pure Michael adducts **3**. [e] Enantiomeric excesses were measured by HPLC and were computed ee = 100([2*R*,1′*S*] − [2*S*,1′*R*])/([2*R*,1′*S*] + [2*S*,1′*R*]). [f] TFA was used as additive instead of 4-nitrobenzoic acid. [g] Reaction carried out with 16 equiv of acetone **1d** in the presence of *exo*-D-**7aa** as catalyst to provide (*R*)-**3da**.

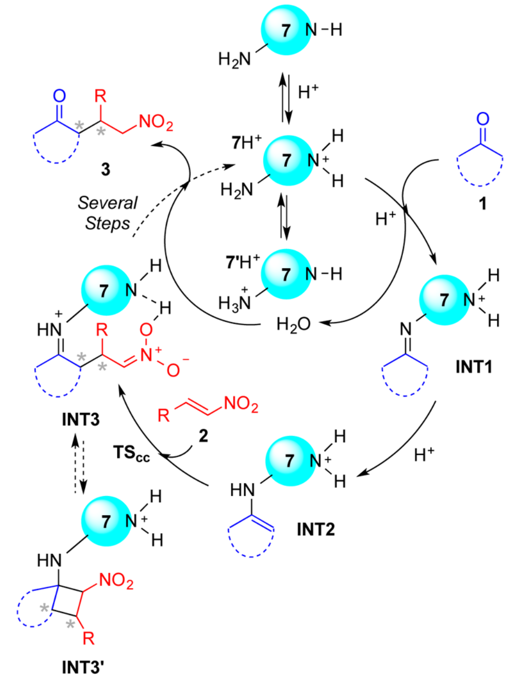
Scheme 3. Conjugate Addition between Ketones 1a–d and Nitroalkenes 2a–m To Yield Adducts (2*R*,1′*S*)-3aa–da Catalyzed by Unnatural L-Proline Ester *exo*-L-7aa[a]



[a] *i*: *exo*-L-**7aa** (30 mol %), 4-nitrobenzoic acid (30 mol %), rt, 16 h.

With this experimental information, we attempted to understand the origins of the observed behavior of catalysts **7** and, in particular, the enantiodivergent outcome obtained with the *endo* and *exo* series of 4-amino-L-proline methyl esters **7aa**. The accepted mechanism[9] for enamine organocatalysis possessing a primary amino group[10] in this kind of reactions consists of the formation of intermediate imines **INT1** (Scheme 4), which isomerize to the corresponding enamines **INT2**. These latter intermediates react with Michael acceptors **2** to form iminium−nitronate intermediates **INT3** via transition structures **TS$_{cc}$**. This step determines the stereochemical outcome of the reaction and can be hampered with an out-of-cycle intramolecular Henry−Mannich addition reaction[11] to generate the (2 + 2) cyclobutane intermediate **INT3′**, which have been detected when aldehydes were used as Michael nucleophiles. Hydrolysis of intermediates **INT3** leads to the release of Michael adducts **3** with concomitant regeneration of protonated diamine 7H+, which is the active species. This protonated state and the promotion of the imine−enamine stages is closely related to the nature of the acidic species present in the reaction mixture, but it is not essential. Actually, the catalytic reaction is feasible in the absence of acids (see Table 2, entries 5 and 6), although considerable acceleration is achieved with relatively strong acids such as TFA or PNBA.

Scheme 4. A Plausible Mechanism for the Michael Addition between Ketones 1 and Nitroalkenes 2 in the Presence of Unnatural 4-Amino-L-Proline Catalysts 7



The alternative mechanism involving formation of enamine intermediates via the amino group of the pyrrolidine ring and protonation of the primary amino group is less likely (see the Supporting Information). Thus, from the reported pK_a values for protonated pyrrolidine and benzylamine in acetonitrile[12] (19.58 and 16.76, respectively) or water[13] (11.27 and 9.3, respectively), we can estimate the $7H^+$:$7'H^+$ ratio (Scheme 4) as ca. 99:01. This result is consistent with the lower organocatalytic activity of (3 + 2) cycloadducts lacking the exocyclic primary amino group. Actually, when a mixture of *exo*-L-**7aa** (1 equiv), cyclohexanone **1a** (8 equiv), and 4-nitrobenzoic acid (1 equiv) was stirred at room temperature for 5 min, ^1H NMR analysis of the reaction mixture showed the formation of the imine **INT1** via reaction of the ketone with the primary amino group, with no detectable C═C−H bonding pattern associated with the enamine moiety, as proved by the corresponding COSY experiment. In contrast, a similar experiment using the nitro analogue *exo*-L-**6aa** (1 equiv) and cyclohexanone as solvent without any additive at 70 °C permitted the detection of the enamine formed between the NH group of this organocatalyst and cyclohexanone (see the Supporting Information). From these studies, we concluded that protonated $7H^+$ species is the most likely intermediate along the catalytic cycle.

Within this mechanism, the efficiency of the catalysts **7** is associated with the HOMO activation promoted by the enamine moiety as well as by the LUMO activation of the Michael acceptor **2** induced by the hydrogen bond formed between the nitro group and the protonated amino group of the pyrrolidine ring (Figure 1). According to this scheme, the origins of the stereocontrol should stem from the configuration of the chiral centers of the pyrrolidine ring and, in particular, from the *endo*/*exo* disposition of the primary amino group of the 4-amino-L-proline methyl esters **7aa**.

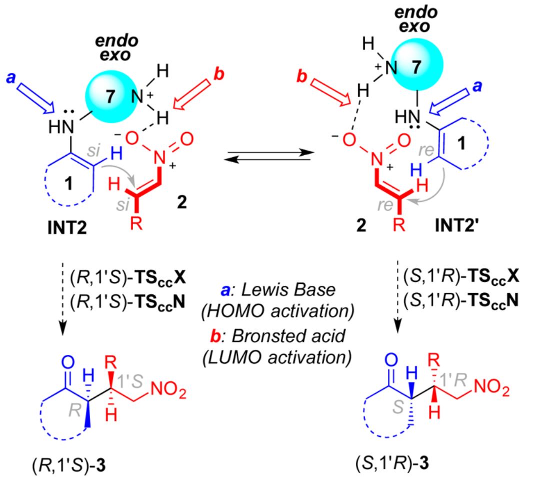


Figure 1. Activation of the substrates and origins of the enantiocontrol in the conjugate addition between ketones **1** and nitroalkenes **2** in the presence of *exo* and *endo* organocatalytic 4-amino-L-proline esters **7**.

Molecular mechanics studies involving Monte Carlo conformational searches and molecular dynamics simulations (MM and MD, respectively, see the Experimental Section for details) of intermediates *endo*-**INT2** and *exo*-**INT2** show mainly twist conformations for the pyrrolidine ring[14] (see Figure S5 of the Supporting Information). These simulations also show a considerable conformational flexibility of the enamine moiety. Both distal and proximal dispositions with respect to the protonated amine and carboxymethyl groups are energetically available (Figure 2), although in the case of *exo*-**INT2** there is a narrower disposition of the nucleophilic enamine moiety, as shown by the Ω values gathered in Figure 2B. It is also interesting to remark that, along both the Monte Carlo and MD simulations, the enamine moiety occupies equatorial positions with respect to the pyrrolidinium rings (Figure 2A), whereas the methoxycarbonyl group is isoclinal with respect to this ring.

The configuration of the transition structures (TSs) associated with the formation of the C−C bonds show appreciable differences with respect to reactive enamine intermediates **INT2**. As it is shown in Figure 3, LUMO activation of the Michael acceptor and its interaction with the nucleophilic enamine moiety result in axial and isoclinal dispositions of the enamine with respect to the pyrrolidinium ring, since the equatorial disposition cannot achieve the required critical C−C bond distance of ca. 2.1 Å. In these TSs, the nucleophilic attack angle θ is in the range 106−109°, which is close to the expected Bürgi−Dunitz angle[15] for saddle points associated with nucleophilic additions to sp^2-hybridized carbon atoms.

In the reaction catalyzed by *exo*-L-**7aa**, two transition structures leading to *syn*-**3aa** were found. Our calculations indicate that saddle point (*R*,1′*S*)-$\mathbf{TS_{cc}X}$ leading to (2*R*,1′*S*)-**3aa** lies 2.3 kcal/mol below the alternative TS leading to (2*S*,1′*R*)-**3aa** (Figure 3). In both saddle points, the dihedral angle ω is of ca. 170°, thus ensuring an antiperiplanar orientation between the phenyl group of β-nitrostyrene **2a** and the enamine moiety. In addition, the presence of two hydrogen bonds between the pyrrolidinium cation and the nitro and methoxycarbonyl groups of **2a** and the organocatalyst, respectively, contribute to the stabilization and loss of conformational freedom of these transition structures. The preference for (*R*,1′*S*)-$\mathbf{TS_{cc}X}$ with respect to (*S*,1′*R*)-$\mathbf{TS_{cc}X}$ stems from the presence in the latter saddle point of a considerable steric congestion between the cyclohexyl group and one phenyl group of *exo*-L-**7aa**, which is forced to adopt an isoclinal (instead of equatorial) disposition (Figure 3).

In the case of transition structures associated with *endo*-L-**7aa**, the chief features of saddle points (*R*,1′*S*)-$\mathbf{TS_{cc}N}$ and (*S*,1′*R*)-$\mathbf{TS_{cc}N}$ are quite similar to those found for the *exo* series (see Figure 3), although now the nucleophilic enamine moieties are isoclinal with respect to the pyrrolidine rings. Thus, the Bürgi−Dunitz angles are similar and the hydrogen bond arrays are also present. The main difference is that in (*R*,1′*S*)-$\mathbf{TS_{cc}N}$ there is a ω dihedral angle of ca. 120°, which leads to a steric clash between the cyclohexyl moiety and the phenyl group of **2a**, thus resulting in the preferential formation of Michael adduct (2*S*,1′*R*)-**3aa**. The relatively lower ee reported experimentally for *endo*-L-**7aa** (Table 2, entries 14, 16 and 21) should be related with the larger flexibility of the enamine moiety associated with this latter organocatalysts, as shown in the MD simulations (see the distribution of Ω dihedral angles in Figure 2B). As a consequence, the Boltzmann average for different conformations of the transition structures should result in an energetic preference for *endo*-L-**7aa**, which is somewhat lower than the 2.3 kcal/mol obtained for the "frozen" DFT conformations shown in Figure 3.

We also calculated the alternative transition structures (*R*,1′*S*)-$\mathbf{TS_{cc}X'}$ and (*S*,1′*R*)-$\mathbf{TS_{CC}N'}$ associated with C−C bond formation through enamines connected directly to the pyrrolidine ring via $7'H^+$ species (vide supra). In both cases, these saddle points were calculated to lie ca. 6 kcal/mol above

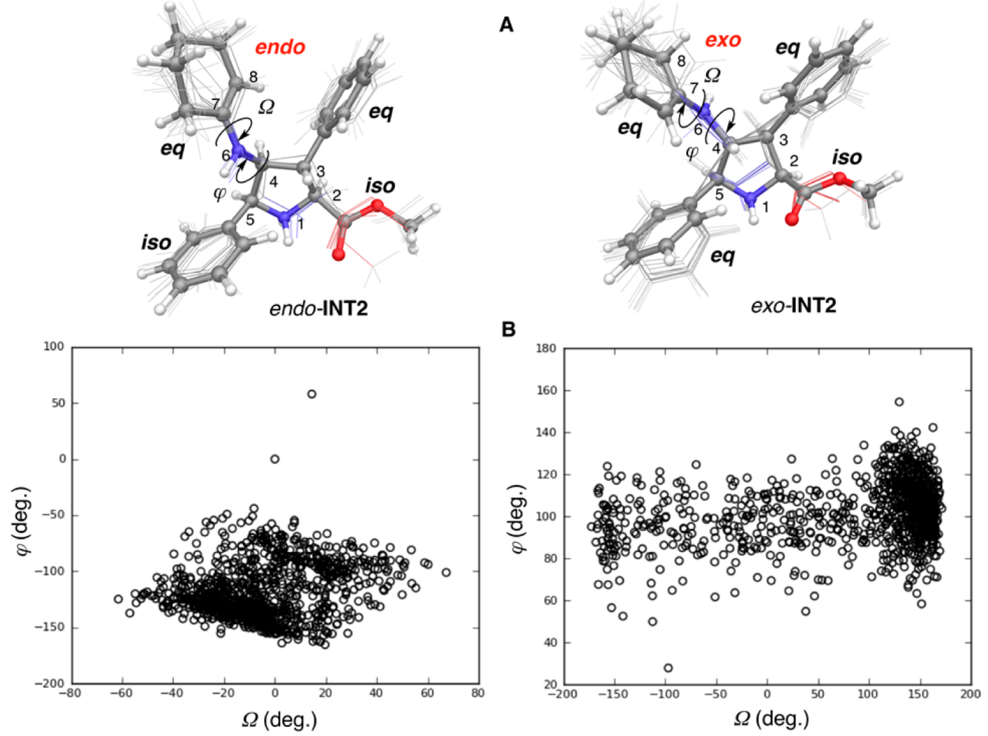


Figure 2. (A) Fully optimized (OPLS-2005 force field) structures of *endo*-**INT2** (left) and *exo*-**INT2** (right). The ball-and-stick structures correspond to the minimum energy conformations after Monte Carlo conformational searches, and the stick representations correspond to the 10 structures of lower energy (ca. 4 kcal/mol). Ω and *φ* dihedral angles are defined as Ω = C8−C7−N6−C4 and *φ* = C7−N6−C4−C5. Descriptors *ax*, *eq*, and *iso* denote axial, equatorial, and isoclinal positions, respectively. (B) Molecular dynamics simulations (OPLS-2005 force field, 1000 ps, see the Experimental Section) showing the distribution of Ω and *φ* dihedral angles of *endo*-**INT2** (left) and *exo*-**INT2** (right) along the production time.

the previously discussed congeners, thus confirming the catalytic cycle based on $7H^+$ as the most likely one (see the Supporting Information).

To check the stereochemical model emerged from the DFT and MM/MD calculations, we prepared compound **10** by *N*-acylation of *exo*-L-**7aa** (Scheme 5). All our attempts to catalyze the **1a** + **2a** → **3aa** reaction with amide **10** met with no success, a result compatible with our hypothesis that the primary amine moiety in *exo*-L-**7aa** is essential for catalysis. Similarly, we prepared *N*-methyl derivative **12** by reaction of *exo*-L-**6aa** with formaldehyde followed by hydrogenation of **11** with Raney nickel. Also in this case, compound **12** was unable to catalyze the **1a** + **2a** → **3aa** reaction, probably because of the disruption of the hydrogen bonding array required for the LUMO activation of Michael electrophile **2a**.

Our DFT model also predicted that the substitution pattern at the C3 position of *exo*-L-**7aa** should be relevant in the preferential formation of Michael adduct (2*R*,1′*S*)-**3aa**, whereas this effect should be irrelevant or lower in magnitude in reactions catalyzed by *endo*-L-**7aa**. To test the effect of bulky substituents at either C3 or C5, we prepared *tert*-butyl derivatives *exo*- and *endo*-L-**7ab**,**ba** (Scheme 2). The results are gathered in Table 4. These experimental results show that the presence of a *tert*-butyl group at C3 in *exo*-L-**7ab** results in a slightly higher ee with no apparent effect on the catalytic activity (Table 4, entry 1). In contrast, the presence of the *tert*-butyl group at C5 in *exo*-L-**7ba** erodes completely the catalytic activity of this compound (Table 4, entry 2). This substitution scheme is less important in the *endo* series, as expected from the lower dependence of the substituents on the corresponding transition structures (Table 4, entries 3 and 4).

Finally, we tested the effect of a quaternary center at C4 by studying the behavior of *exo*-L-**7ac** (Scheme 2, Table 4, entry 5). The presence of an equatorial methyl group in the corresponding transition structures resulted in a lower reactivity of this more substituted organocatalysts, since 7 days were required for a conversion of 85%. However, the effect of this additional substituent on stereocontrol of the reaction was quite low.

In summary, our DFT model shows that most of the activation energy and the stereoselection observed with these novel organocatalysts are related to the transition from equatorial enamine moieties of intermediates **INT2** to axial or at least isoclinal nucleophiles interacting with LUMO-activated nitroalkenes in the corresponding **TScc** saddle points, with a quite rigid polycyclic array of hydrogen bonds, most of the remaining substituents of the organocatalyst occupying equatorial (or al least isoclinal) positions. Almost any disruption of this delicate balance can result in lower catalytic activities and/or lower stereocontrol.

To complete our study, we explored the possibility of carrying out chemoselective aldol/conjugate additions using these organocatalysts. To this end, we prepared double electrophile **14** from of 4-vinylbenzaldehyde according to the procedure reported by Maiti et al.[16] (Scheme 6). As expected, reaction between **14** and **1a** resulted in the formation of *anti*-aldol **15** as the main stereoisomer, with no detectable formation of the Michael cycloadduct after 48 h of reaction at 0 °C. Conjugate addition between **15** and **1a** resulted in the formation of adduct *anti*-**16** as the major isomer, in which the expected stereochemistry was observed in the two new chiral centers (vide supra). However, the other isomer was

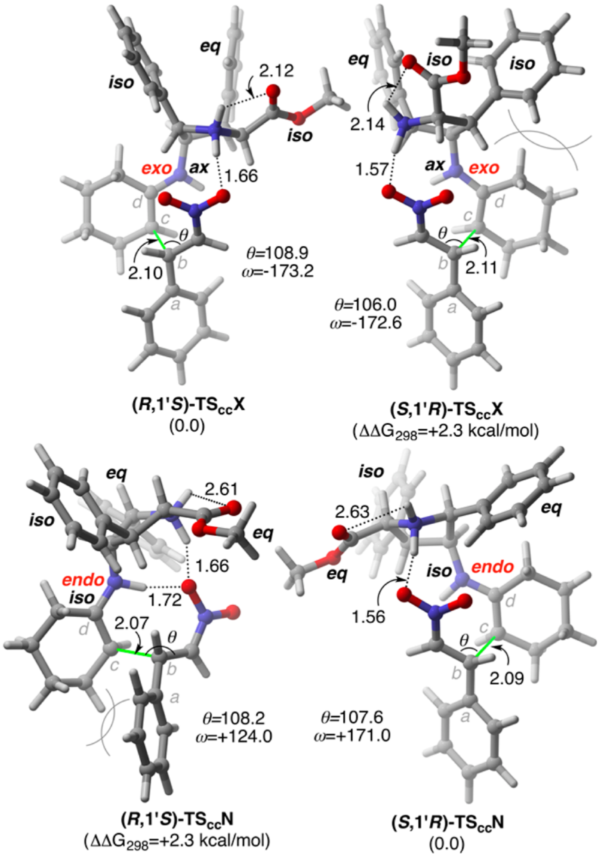
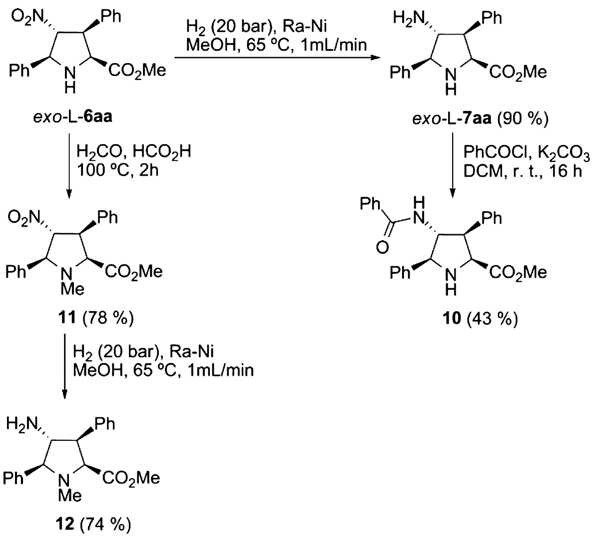


Figure 3. Fully optimized and relative Gibbs energies at 298 K (M06-2X/6-31+G**//B3LYP/6-31G*+TCGE level of theory, see the Experimental Section) of transition structures $\mathbf{TS_{cc}X}$ and $\mathbf{TS_{cc}N}$ corresponding to the C−C bond forming step (Scheme 4, Figure 1) associated with the Michael reaction between cyclohexanone **1a** and (*E*)-*β*-nitrostyrene **2a** in the presence of organocatalysts *exo*-L-**7aa** and *endo*-L-**7aa**, respectively. Distances and angles are given in angtroms (Å) and deg (°), respectively. Dihedral angles *ω* are defined as *ω* = C*a*−C*b*−C*c*−C*d*.

Scheme 5. Preparation of Compounds 10, 11, and 12 from *exo*-L-6aa[a]



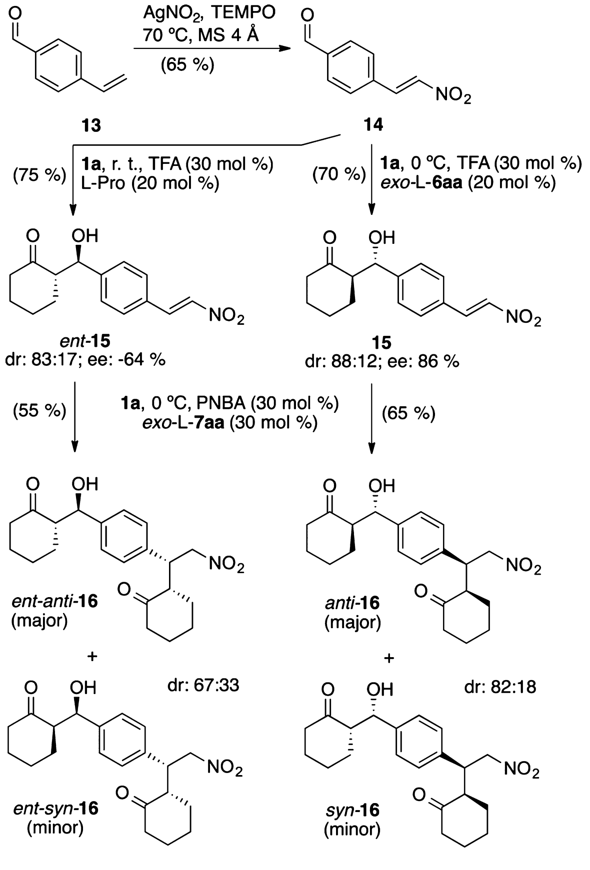
[a]Numbers in parentheses correspond to yields of isolated pure products.

Table 4. Conjugate Addition Reaction[a] 1a + 2a → 3aa Catalyzed by *exo*- and *endo*-L-7ab,ba, and *exo*-L-7ac

entry	catalyst	time (h)	conv. (%)[b]	*syn*:*anti*[c]	yield (%)[d]	ee (%)[e]
1	*exo*-L-**7ab**	16	>99	93:07	77	94
2	*exo*-L-**7ba**	48	<1	n. d.[f]	n. d.	n. d.
3	*endo*-L-**7ab**	16	>99	52:48	61	−16
4	*endo*-L-**7ba**[g]	144	87	44:56	45	−11
5	*exo*-L-**7ac**	168	85	89:11	69	73

[a]Reaction conditions: Catalyst (30 mol %), 4-nitrobenzoic acid (30 mol %), room temperature (see the Experimental Section of further details). [b]Determined by ^{1}H NMR on crude reaction mixtures. [c]The *syn*:*anti* ratios were measured by ^{1}H NMR or HPLC on crude reaction mixtures. [d]Yields refer to isolated pure Michael adducts **3**. [e]Enantiomeric excesses were measured by HPLC and were computed ee = 100([2*R*,1′*S*] − [2*S*,1′*R*])/([2*R*,1′*S*] + [2*S*,1′*R*]). [f]n. d.: not determined. [g]The optical purity of the catalyst was 97.5%.

Scheme 6. Synthesis of Compounds 15 and 16 by Sequential Aldol and Conjugate Additions Catalyzed by L-Pro, *exo*-L-6aa and *exo*-L-7aa[a]



[a]TEMPO, (2,2,6,6,-tetramethylpiperidin-1-yl)oxyl; PNBA, 4-nitrobenzoic acid.

found to be *syn*-**16**, in which the original *anti* stereochemistry of aldol **15** had been modified. This structure was established by X-ray diffraction analysis[17] (see the Supporting Information). Experiments with a mixture of *anti*-**16**, **1a**, *exo*-L-**7aa** and 4-nitrobenzoic acid resulted in the partial isomerization to *syn*-**16** of 30% as determined by ^{1}H NMR on the crude reaction mixture after 24 h of reaction at room temperature. This latter result demonstrates that the *syn*-**16** isomer stems from the in situ isomerization of the ketone moiety of the aldol adduct.

Natural L-Pro was also able to react with **14** to yield the *anti* aldol adduct *ent*-**15**, as expected from previous work reported by our group[5] and from the stereochemical outcomes reported for many L-Pro-based aldol reactions.[18] However, when *ent*-**15** reacted with **1a** in the presence of *exo*-L-**7aa**, a 63:37 mixture of diastereomers of *ent*−*anti*-**16** and *ent*−*syn*-**16** was observed. This unexpected result indicates that the stereochemistry of the final Michael cycloadducts is determined by the chiral centers of the aldol moiety and not by those of the organocatalyst. This conclusion was confirmed by repeating the reaction between *anti*-**15** and **1a** in the presence of *racemic* proline. Under these conditions, *anti*-**16** and *syn*-**16** were obtained with a diastereomeric ratio of 87:13, i.e., exactly the same stereocontrol observed in the presence of *exo*-L-**7aa**. Therefore, this final part of our study leads to the conclusion that when using these organocatalysts it is possible to control aldol and Michael addition reactions, but the stereocontrol of the conjugate addition is completely determined by the configuration of the previously formed aldol adduct.

■ CONCLUSIONS

From the experimental and computational results reported in this work the following conclusions can be drawn: (i) 3-Aminopyrrolidin carboxylate methyl esters are efficient enamine organocatalysts for the conjugate addition on nitroalkenes in the presence of carboxylic acids. (ii) *exo*-L-Cycloadducts lead to the stereochemistry that it would be expected from D-proline. (iii) *Endo* analogues produce the same sense of induction observed when L-proline is used as organocatalyst. However, *endo* amino cycloadducts are less stereoselective than their *exo* congeners. (iv) Substitution of either the exocyclic or pyrrolidine amino group destroys the catalytic activity. (v) The presence of bulky substituents at the C3 position of the *exo* organocatalyst can improve the chiral induction in these conjugate additions. (vi) All these results are compatible with computational models that suggest a larger conformational freedom in enamine intermediates involved in the catalytic cycle of *endo* cycloadducts as well as quite rigid transition structures associated with the C−C bond forming step, in which there is a hydrogen bond array involving pyrrolidinium cations. (vii) It is possible to control the aldol and Michael additions in double electrophiles. Both *exo*-L-aminopyrrolidin carboxylate methyl esters and natural L-proline can promote the enantiodivergent formation of aldol adducts. However, the stereochemical outcome of the subsequent conjugate addition is completely dictated by the configuration of the aldol moiety.

All these results indicate that both the organocatalytic efficiency and stereoselectivity of the (3 + 2) cycloadducts reported in this work are the result of a delicate balance among different phenomena. Therefore, unexpected effects can be found in other reactions involving enamine catalysis.

■ EXPERIMENTAL SECTION

Computational Methods. All the computational studies were carried out by means of either Gaussian 09[19] or Maestro[20] suites of programs. Density Functional Theory[21] (DFT) calculations were performed using the B3LYP[22] and M06-2X[23] functionals. This latter highly parametrized method is well suited for the treatment of nonbonding interactions and dispersion forces, which can be relevant in densely substituted interaction systems.[24] The 6-31G* and 6-31+G** basis sets were used. All the stationary points were characterized by harmonic analysis.[25] Reactants, intermediates and products showed positive definite Hessians. Transition structures (TSs) showed one and only one imaginary frequency associated with nuclear motion along the chemical transformation under study. Free energies at 298 K were calculated by including the corresponding thermal corrections to Gibbs free energies (TCGE). Molecular mechanics (MM) and molecular dynamics (MD) calculations of intermediates *exo*-**INT2** and *endo*-**INT2** were carried out using the OPLS-2005 force field[26] as implemented in MacroModel package.[27] MD simulations were performed with SHAKE[28] to constrain the C−H bonds. The temperature was set up to 298 K. The system was equilibrated for 500 ps with time steps of 1 fs. The production run was started from this point and lasted additional 1000 ps with time steps of 1 fs. In all cases, we observed that during the production period the energy and temperature of the whole system were equilibrated. During the production run, the coordinates of 1000 structures were saved.

General Remarks. Unless otherwise stated, reagents and substrates were purchased from commercial suppliers. Cyclohexanone **1a** was freshly distilled on thermally activated 4 Å molecular sieves before use. Catalysts **NMe-L-EhuPhos** and **NH-D-EhuPhos** were prepared following our previously described procedure.[5] Imines **5a**,**b** and nitroalkenes **2a**−**m** are known compounds and were synthesized following reported procedures.[29] Compounds *exo*-L-**6aa**, *endo*-L-**6aa**, and *exo*-L-**6ba** have been described in previous works from our group.[5,8] Adducts **9** and **3aa**−**am** are known compounds (see the Supporting Information for additional details). Compound **14** was prepared according to a previously reported procedure.[16] TLC was performed on silica gel 60 F254, using aluminum plates and visualized with UV lamps or potassium permanganate stain. Flash chromatography was carried out on columns of silica gel 60 (230−400 mesh). Hydrogenation reactions were performed with a flow reactor equipped with a Raney-Nickel cartridge. Hydrogen gas was generated electrochemically. Optical rotations were measured using a polarimeter with a thermally jacketed 5 cm cell at approximately 20 °C, and concentrations (*c*) are given in g/100 mL. FT-IR spectra were recorded with a spectrophotometer equipped with a single-reflection ATR module; wavenumbers are given in cm^{-1}. HRMS analyses were carried out using the electron impact (EI) mode at 70 eV or by Q-TOF using electrospray ionization (ESI) mode. ^{1}H NMR spectra were recorded at 400 or 500 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR, using CDCl$_3$ as the solvent and TMS as an internal standard (0.00 ppm). The data are reported as s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br s = broad signal, coupling constant(s) in Hz, integration. ^{13}C NMR spectra were recorded with ^{1}H- decoupling at 100 MHz and referenced to CDCl$_3$ at 77.00 ppm.

General Procedure for the Synthesis of *endo*-Cycloadducts 6. A solution of **NMe-L-EhuPhos** (0.015 mmol) and Cu(CH$_3$CN)$_4$PF$_6$ (5.2 mg, 0.014 mmol) in 1.0 mL of dry THF was stirred at −60 °C for 15 min. Then, a solution of imine **5** (0.45 mmol) in 1.0 mL of solvent, triethylamine (3.2 μL, 0.023 mmol), and the corresponding nitroalkenes **2** (0.50 mmol) in 1.0 mL of solvent were successively added. The reaction was monitored by TLC, and once the starting material was consumed, the mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexanes 1:2) to yield the corresponding *endo*-cycloadduct **6**. The enantiomeric excess was determined by comparison of the HPLC chromatogram recorded for the racemic mixture with that corresponding to the enantiomerically enriched cycloadduct.

*Methyl (2S,3R,4S,5S)-(3-tert-Butyl)-4-nitro-5-phenylpyrrolidine-2-carboxylate (endo-L-**6ab**).* The expected product was obtained from imine **5a** and nitroalkene **2b**. Yield: 116 mg, 84%, orange solid; mp = 113 °C; $[\alpha]^{25}_{D}$ = +14.4 (*c* 0.50, CHCl$_3$), ee, 95%. FTIR (neat, cm^{-1}): 1728, 1545, 1197, 1198, 733, 694. Carbon atoms in densely substituted pyrrolidine rings are numbered as in pyrrolidine, the nitrogen atom numbered 1, and proceeding toward the carboxyl ester group.[30] ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.32 (m, 5H, ArH), 5.12 (m, 1H, C^{4}H), 4.45 (dd, *J* = 11.6, 6.1 Hz, 1H, C^{5}H), 3.85 (s, 3H, CO$_2$Me), 3.27 (t, *J* = 10.8 Hz, 1H, C^{2}H), 2.97 (d, *J* = 5.3 Hz, 1H, C^{3}H), 1.05 (s, 9H, (CH$_3$)$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 172.6, 134.3, 128.4, 128.2, 126.0, 93.2, 67.9, 61.9, 61.1, 52.5, 32.4, 27.4; HRMS (ESI) for

$C_{16}H_{22}N_2O_4$: calculated [M + H]$^+$, 307.1658. Found [M + H]$^+$, 307.1673. HPLC (Chiralcel IB, hexane/^{i}PrOH = 90:10, flow rate 0.5 mL/min, λ = 210 nm), t_R (minor) = 29.05 min, t_R (major) = 30.53 min; ee = 95%.

*Methyl (2S,3R,4S,5S)-(5-tert-Butyl)-4-nitro-3-phenylpyrrolidine-2-carboxylate (endo-L-**6ba**).* The expected product was obtained from imine **5b** and nitroalkene **2a**. Yield: 94 mg, 68%; ee, 77% (91% yield was obtained as an 82:18 diastereomeric ratio *exo*:*endo*), orange syrup; $[\alpha]^{25}_D$ = −113.6 (*c* 1.08, $CHCl_3$); ee, 99% after semipreparative HPLC purification (Chiralcel IA, hexane/^{i}PrOH = 99:1, flow rate 3 mL/min, λ = 210 nm). FTIR (neat, cm^{-1}): 1740, 1543, 908, 729, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (t, *J* = 7.4 Hz, 2H, ArH), 7.33 (d, *J* = 7.1 Hz, 1H, ArH), 7.22 (d, *J* = 7.4 Hz, 2H, ArH), 4.98 (d, *J* = 4.2 Hz, 1H, C^4H), 4.04 (d, *J* = 5.7 Hz, 1H, C^2H), 3.97 (d, *J* = 5.7 Hz, 1H, C^3H), 3.82 (s, 3H, CO_2Me), 3.23 (s, 1H, C^5H), 3.11 (s, 1H, NH), 1.08 (s, 9H, $(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 139.5, 129.0, 127.7, 127.1, 92.6, 74.8, 67.4, 56.7, 52.3, 32.5, 26.7; HRMS (ESI) for $C_{16}H_{22}N_2O_4$: calculated [M + H]$^+$, 307.1658. Found [M + H]$^+$, 307.1673. HPLC (Chiralcel IA, hexane/^{i}PrOH = 99:1, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 21.57 min; ee = >99%.

General Procedure for the Synthesis of *exo*-Cycloadducts 6. A solution of **NH-D-EhuPhos** (0.015 mmol) and $Cu(CH_3CN)_4PF_6$ (5.2 mg, 0.014 mmol) in 1.0 mL of dry THF was stirred at −20 °C for 15 min. Then, a solution of imine **5** (0.45 mmol) in 1.0 mL of solvent, triethylamine (3.2 μL, 0.023 mmol), and the corresponding nitroalkenes **2** (0.50 mmol) in 1.0 mL of solvent were successively added. The course of the reaction was monitored by TLC, and once the starting material was consumed, the mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate.hexanes 1:2) to yield the corresponding *exo*-cycloadduct **6**. The enantiomeric excess was determined by comparison of the HPLC chromatogram recorded for the racemic mixture with that corresponding to the enantiomerically enriched cycloadduct.

*Methyl (2S,3S,4R,5S)-(3-tert-Butyl)-4-nitro-5-phenylpyrrolidine-2-carboxylate (exo-L-**6ab**).* The expected product was obtained from imine **5a** and nitroalkene **2b**. Yield: 99 mg, 72% (83% yield was obtained as an 87:13 diastereomeric ratio *exo*:*endo*), white syrup; $[\alpha]^{25}_D$ = +11.4 (*c* 1.28, $CHCl_3$), ee 98%. FTIR (neat, cm^{-1}): 1735, 1549, 1200, 1174, 730, 699; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.0 Hz, 2H, ArH), 7.41−7.32 (m, 3H, ArH), 5.07 (t, J = 8.2 Hz, 1H, C^4H), 4.67 (d, J = 7.9 Hz, 1H, C^5H), 4.23 (d, J = 7.9 Hz, 1H, C^2H), 3.77 (s, 3H, CO_2Me), 3.11 (t, J = 8.2 Hz, 1H, C^3H), 2.42 (bs, 1H, NH), 0.98 (s, 9H, $(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 138.8, 128.9, 128.6, 126.7, 92.7, 68.1, 61.7, 59.6, 52.0, 32.8, 27.8. HRMS (ESI) for $C_{16}H_{22}N_2O_4$: calculated [M + H]$^+$, 307.1658. Found [M + H]$^+$, 307.1676; HPLC (Chiralcel IB, hexane/^{i}PrOH = 80:20, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 18.76 min, t_R (minor) = 44.74 min; ee = 98%.

*Methyl (2S,3S,4R,5S)-4-Methyl-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (exo-L-**6ac**).* The expected product was obtained from imine **5a** and nitroalkene **2c**. Yield: 101 mg, 66%, white solid; mp = 114−115 °C; $[\alpha]^{25}_D$ = +84.2 (*c* 1.00, $CHCl_3$), ee 94%. FTIR (neat, cm^{-1}): 3339, 1742, 1536, 1381; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61−7.18 (m, 10H, ArH), 5.04 (s, 1H, C^5H), 4.67 (d, *J* = 8.2 Hz, 1H, C^3H), 4.47 (d, *J* = 8.2 Hz, 1H, C^2H), 3.44 (s, 3H, CO_2Me), 2.84 (bs, 1H, NH), 0.88 (s, 3H. CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.3, 136.7, 136.5, 129.7, 128.5 (two signals), 128.3, 127.8, 127.8, 98.3, 69.8, 63.0, 56.0, 51.8, 20.8. HRMS (ESI) for $C_{19}H_{20}N_2O_4$: calculated [M + H]$^+$, 341.1501. Found [M + H]$^+$, 341.1503; HPLC (Chiralcel IA, hexane/^{i}PrOH = 85:15, flow rate 1 mL/min, λ = 254 nm), t_R (minor) = 10.9 min, t_R (major) = 13.4 min; ee = 94%.

General Procedure for the Methylation of *exo*-L-6aa.[31] Pyrrolidine *exo*-L-**6aa** (500 mg, 1,53 mmol) was dissolved in 10 mL of 88% aqueous formic acid. Ten milliliters of 35% aqueous formaldehyde was added and the reaction mixture was heated at 100 °C for 2 h. After cooling to room temperature, the acidic solution was basified with saturated K_2CO_3 solution from which a precipitated appeared. Then, this solution was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was filtered through a plug of silica eluting with ethyl acetate affording the pure product.

*Methyl (2S,3S,4R,5S)-1-Methyl-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (**11**).* Yield: 406 mg, 78%, dark yellow solid; mp = 63−64 °C; $[\alpha]^{25}_D$ = +31.9 (*c* 0.75, $CHCl_3$). FTIR (neat, cm^{-1}): 3061, 3030, 2951, 1739, 1702, 1551, 1448, 1365, 1203, 1175, 751, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.3 Hz, 2H, ArH), 7.45−7.21 (m, 8H, ArH), 5.00 (m, 1H, C^4H), 4.24 (dd, *J* = 9.3, 5.9 Hz, 1H, C^3H), 3.97 (d, *J* = 8.0 Hz, 1H, C^5H), 3.92 (d, *J* = 9.3 Hz, 1H, C^2H), 3.27 (s, 3H, CO_2Me), 2.33 (s, 3H, NCH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.7, 137.8, 137.2, 129.1, 129.0, 128.6, 128.4, 128.0, 127.6, 97.1, 75.1, 71.8, 51.4, 51.1, 39.3. HRMS (ESI) for $C_{19}H_{20}N_2O_4$: calculated [M + H]$^+$, 341.1501. Found [M + H]$^+$, 341.1501.

General Procedure for the Synthesis of Amino Derivatives 7 and 12. A solution of the corresponding 4-nitro cycloadducts **6** (1 mmol) in 100 mL of methanol was pumped at 1 mL/min through the H-Cube Hydrogenation Reactor using a Raney/Nickel CatCart as catalyst. The pressure of the system was set to 20 bar and the temperature to 65 °C. After all the reaction mixture had passed through the reactor, the solvent was reduced to dryness. The crude mixture was filtered through a plug of silica eluting with ethyl acetate affording the pure product.

*Methyl (2S,3S,4S,5S)-4-Amino-3,5-diphenylpyrrolidine-2-carboxylate (endo-L-**7aa**).* The expected product was obtained from *endo*-L-**6aa**. Yield: 207 mg, 70%, yellow syrup; $[\alpha]^{25}_D$ = +24.2 (*c* 0.60, $CHCl_3$). FTIR (neat, cm^{-1}): 3382, 1727, 1219, 700; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 7.3 Hz, 2H, ArH), 7.44−7.31 (m, 8H, ArH), 4.63 (d, J = 6.1 Hz, 1H, C^5H), 4.12 (d, J = 7.8 Hz, 1H, C^2H), 3.74 (s, 3H, CO_2Me), 3.64 (t, J = 6.2 Hz, 1H, C^3H), 3.24 (t, J = 6.2 Hz, 1H, C^4H), 1.70 (bs, 2H, NH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 140.2, 139.8, 128.6, 128.2, 127.6, 127.5, 127.2, 126.9, 65.4, 64.9, 62.9, 57.0, 52.0. HRMS (ESI) for $C_{18}H_{20}N_2O_2$: calculated [M + H]$^+$, 297.1603. Found [M + H]$^+$, 297.1610.

*Methyl (2S,3S,4S,5S)-4-Amino-3-(tert-butyl)-5-phenylpyrrolidine-2-carboxylate (endo-L-**7ab**).* The expected product was obtained from *endo*-L-**6ab**. Yield: 226 mg, 82%, orange syrup; $[\alpha]^{25}_D$ = +37.4 (*c* 0.34, $CHCl_3$) (ee 95%). FTIR (neat, cm^{-1}): 2952, 1735, 1199, 1170, 755, 701; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 5H, ArH), 4.19 (d, *J* = 3.5 Hz, 1H, C^5H), 3.78 (s, 3H, CO_2Me), 3.73 (d, *J* = 6.2 Hz, 1H, C^2H), 3.30 (d, *J* = 3.3 Hz 1H, C^4H), 2.05 (d, *J* = 5.6 Hz, 1H, C^3H), 1.02 (s, 9H, $(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 138.5, 128.2, 127.0 (two signals ArC), 67.2, 62.5, 60.4, 57.5, 52.1, 32.3, 27.8. HRMS (ESI) for $C_{16}H_{24}N_2O_2$: calculated [M + H]$^+$, 277.1916. Found [M + H]$^+$, 277.1926.

*Methyl (2S,3S,4S,5S)-4-Amino-5-(tert-butyl)-3-phenylpyrrolidine-2-carboxylate (endo-L-**7ba**).* The expected product was obtained from *endo*-L-**6ba**. Yield: 240 mg, 87%, yellow syrup; $[\alpha]^{25}_D$ = +51.3 (*c* 0.87, $CHCl_3$). FTIR (neat, cm^{-1}): 3342, 2951, 1735, 1217, 757, 701; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.16 (m, 5H, ArH), 3.90 (d, *J* = 4.9 Hz, 1H, C^2H), 3.73 (s, 3H, CO_2Me), 3.46 (s, 1H, NH), 3.44−3.40 (m, 1H, C^4H), 3.20−3.19 (m, 1H, C^3H), 2.90 (d, *J* = 4.4 Hz, 1H, C^5H), 2.26 (bs, 2H, NH_2), 1.11 (s, 9H, $(CH_3)_3$)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 142.1, 128.6, 127.3, 126.8, 70.4, 65.0, 62.2, 60.3, 52.3, 32.6, 28.3. HRMS (ESI) for $C_{16}H_{24}N_2O_2$: calculated [M + H]$^+$, 277.1916. Found [M + H]$^+$, 277.1923.

*Methyl (2S,3R,4R,5S)-4-Amino-3,5-diphenylpyrrolidine-2-carboxylate (exo-L-**7aa**).* The expected product was obtained from *exo*-L-**6aa**. Yield: 266 mg, 90%, white solid; mp = 75−77 °C; $[\alpha]^{25}_D$ = +100.1 (*c* 0.50, $CHCl_3$). FTIR (neat, cm^{-1}): 1731, 1173, 1107, 696; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70−7.64 (m, 2H, ArH), 7.42 (dd, *J* = 10.3, 4.7 Hz, 2H, ArH), 7.38−7.30 (m, 3H, ArH), 7.28−7.24 (m, 3H, ArH), 4.29 (d, *J* = 9.8 Hz, 1H, C^5H), 3.93 (d, *J* = 8.9 Hz, 1H, C^2H), 3.66 (dd, *J* = 10.3, 9.0 Hz, 1H, C^3H), 3.49 (t, *J* = 10.1 Hz, 1H, C^4H), 3.24 (s, 3H, CO_2Me), 1.65 (bs, 2H, NH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 140.8, 137.5, 128.7, 128.4, 128.2, 127.9, 127.3, 127.3, 70.3, 63.8, 62.9, 57.1, 51.3. HRMS (ESI) for $C_{18}H_{20}N_2O_2$: calculated [M + H]$^+$, 297.1603. Found [M + H]$^+$, 297.1604.

*Methyl (2S,3R,4R,5S)-4-Amino-3-(tert-butyl)-5-phenylpyrrolidine-2-carboxylate (exo-L-**7ab**).* The expected product was obtained from *exo*-L-**6ab**. Yield: 248 mg, 90%, white syrup; $[\alpha]^{25}_{D}$ = +62.7 (*c* 1.85, $CHCl_3$). FTIR (neat, cm^{-1}): 2948, 1729, 1196, 1175, 701; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.3 Hz, 2H, ArH), 7.37 (t, *J* = 7.3 Hz, 2H, ArH), 7.31 (d, *J* = 7.1 Hz, 1H, ArH), 4.05 (d, *J* = 7.9 Hz, 1H, C^5H), 3.76 (s, 3H, CO_2Me), 3.71 (d, *J* = 8.1 Hz, 1H, C^2H), 3.43 (t, *J* = 8.4 Hz, 1H, C^4H), 2.10 (t, *J* = 8.3 Hz, 1H, C^3H), 1.49, (bs, 2H, NH_2), 1.05 (s, 9H, $(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 142.0, 128.5, 127.6, 127.4, 71.5, 61.4, 61.1, 60.5, 51.6, 32.2, 28.6. HRMS (ESI) for $C_{16}H_{24}N_2O_2$: calculated $[M + H]^+$, 277.1916. Found $[M + H]^+$, 277.1921.

*Methyl (2S,3R,4R,5S)-4-Amino-5-(tert-butyl)-3-phenylpyrrolidine-2-carboxylate (exo-*L*-**7ba**).* The expected product was obtained from *exo*-L-**6ba**. Yield: 218 mg, 79%, yellow oil; $[\alpha]^{25}_{D}$ = +81.7 (*c* 0.52, $CHCl_3$). FTIR (neat, cm^{-1}): 2950, 1734, 1204, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 6.7 Hz, 2H), 7.25 (d, *J* = 7.2 Hz, 3H), 4.20 (d, *J* = 9.4 Hz, 1H), 3.43 (t, *J* = 7.8 Hz, 1H), 3.30 (t, *J* = 8.5 Hz, 1H), 3.23 (s, 3H, CO_2Me), 2.72 (d, *J* = 8.1 Hz, 1H), 1.14 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 139.6, 128.3, 128.3, 127.0, 74.7, 63.1, 59.2, 58.9, 51.2, 33.1, 27.3. HRMS (ESI) for $C_{16}H_{24}N_2O_2$: calculated $[M + H]^+$, 277.1916. Found $[M + H]^+$, 277.1923.

*Methyl (2S,3S,4R,5S)-4-Amino-4-methyl-3,5-diphenylpyrrolidine-2-carboxylate (exo-*L*-**7ac**).* The expected product was obtained from *exo*-L-**6ac**. Yield: 260 mg, 84%, white solid; mp = 102−103 °C; $[\alpha]^{25}_{D}$ = +61.7 (*c* 0.40, $CHCl_3$). FTIR (neat, cm^{-1}): 3347, 1735, 1205, 728, 702; ^1H NMR (400 MHz, $CHCl_3$) δ 7.53 (d, *J* = 7.3 Hz, 2H, ArH), 7.37 (d, *J* = 7.5 Hz, 2H, ArH), 7.29 (m, 6H, ArH), 4.41 (d, *J* = 10.2 Hz, 1H, C^2H), 4.11 (s, 1H, C^5H), 3.51 (d, *J* = 10.3 Hz, 1H, C^3H), 3.45 (s, 3H, CO_2Me), 1.51, (bs, 2H, NH_2), 0.62 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 138.6, 137.3, 129.7, 128.0, 127.8, 127.4, 127.2, 126.9, 72.9, 62.3, 61.7, 61.3, 51.4, 22.3. HRMS (ESI) for $C_{19}H_{22}N_2O_2$: calculated $[M + H]^+$, 311.1760. Found $[M + H]^+$, 311.1770.

*Methyl (2S,3R,4R,5S)-4-Amino-1-methyl-3,5-diphenylpyrrolidine-2-carboxylate (**12**).* The expected product was obtained from **11**. Yield: 242 mg, 78%, bright yellow solid; mp = 108−110 °C; $[\alpha]^{25}_{D}$ = +93.5 (*c* 0.51, $CHCl_3$). FTIR (neat, cm^{-1}): 3389, 3027, 2950, 2796, 1741, 1453, 1435, 1197, 1177, 1056, 746, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.5 Hz, 2H, ArH), 7.40 (t, *J* = 7.5 Hz, 2H, ArH), 7.37−7.19 (m, 6H, ArH), 3.72 (d, *J* = 10.4 Hz, 1H, C^5H), 3.52 (t, *J* = 8.4 Hz, 1H, C^3H), 3.40−3.32 (m, 1H, C^4H), 3.21 (s, 3H, CO_2Me), 3.18 (d, *J* = 8.3 Hz, 1H, C^2H), 2.25 (s, 3H, NCH_3), 1.35 (bs, 2H, NH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 140.3, 139.5, 128.7, 128.6, 128.3, 127.9, 127.9, 127.1, 78.9, 72.1, 66.0, 55.4, 51.1, 39.9. HRMS (ESI) for $C_{19}H_{22}N_2O_2$: calculated $[M + H]^+$, 311.1760. Found $[M + H]^+$, 311.1773.

General Procedure for the Synthesis of Amide Derivative 10. Amine *exo*-L-**7aa** (0.67 mmol, 200 mg) and K_2CO_3 (0.80 mmol, 111 mg) were dissolved in 2.5 mL of DCM. Benzoyl chloride (0.67 mmol, 78 μL) was added to the reaction mixture and it was let stir until consumption of the starting material, followed by TLC. Then, the reaction mixture was washed with H_2O three times, brine and dried onto Na_2SO_4, and the solvent was evaporated under reduced pressure to afford **10**.

*Methyl (2S,3R,4R,5S)-4-Benzamido-3,5-diphenylpyrrolidine-2-carboxylate (**10**).* Yield: 115 mg, 43%, white solid; mp = 258−260 °C; $[\alpha]^{25}_{D}$ = −54.9 (*c* 0.49, DMF). FTIR (neat, cm^{-1}): 1734, 1654, 1383, 1174, 1153, 726. ^1H NMR (500 MHz, DMSO-d_6) δ 7.50 (s, 2H), 7.43−7.06 (m, 13H), 4.67 (d, *J* = 8.5 Hz, 1H), 3.81 (dd, *J* = 11.8, 8.5 Hz, 1H), 3.70 (dd, *J* = 11.7, 9.0 Hz, 1H), 3.26 (s, 1H, signal under water peak), 3.04 (s, 3H), 1.48 (bs, 1H); ^{13}C NMR (126 MHz, DMSO-d_6, 70 °C) δ 171.1, 169.4, 141.2, 136.1, 134.9, 128.9, 128.2, 127.8, 127.4, 127.3, 126.9, 126.8, 126.2, 126.1, 70.1, 64.9, 61.7, 52.3, 50.6. HRMS (ESI) for $C_{25}H_{24}N_2O_3$: calculated $[M + H]^+$, 401.1865. Found $[M + H]^+$, 401.1869.

General Procedure for the Synthesis of 14. To a flask was added $AgNO_2$ (23.4 mmol, 3.6 g), TEMPO (3.12 mmol, 487 mg), and oven-dried molecular sieves 4 Å (2.34 g). Then, the olefin **13**[32] (7.8 mmol, 1.012 g) previously dissolved in 32 mL of 1,2-dichloroethane was added. The reaction mixture was placed in a preheated oil bath at 70 °C and stirred vigorously for 12 h. Then, the mixture was cooled to room temperature and filtered through a plug of Celite and diluted with ethyl acetate. After removal of all the solvent, the residue was purified by silica gel chromatography (hexane/EtOAc 80:20) to afford **14**.

*(E)-4-(2-Nitrovinyl)benzaldehyde (**14**).* Yield: 898 mg, 65%, yellow solid; mp = 113−114 °C. FTIR (neat, cm^{-1}): 3112, 2837, 1639, 1538, 966, 810, 730; ^1H NMR (500 MHz, $CDCl_3$) δ 10.07 (s, 1H, CHO), 8.03 (d, *J* = 13.7 Hz, 1H, $CHNO_2$), 7.97 (d, *J* = 8.1 Hz, 2H, ArH), 7.72 (d, *J* = 8 Hz, 2H, ArH), 7.64 (d, *J* = 13.7 Hz, 1H, CHAr); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.2, 139.1, 138.5, 137.4, 135.7, 130.5, 129.7, 77.4, 77.2, 76.9. HRMS (ESI) for $C_9H_8NO_3$: calculated $[M + H]^+$, 178.0504. Found $[M + H]^+$, 178.0504.

General Procedure for the Synthesis of Aldol Adduct 9 under Different Conditions. The corresponding aldehyde **8** (0.25 mmol) was dissolved in neat ketone **1a** (1.5 mL, 15.3 mmol, 61.2 equiv), the resulting mixtures in one case was cooled to 0 °C, and the organocatalyst (0.0125−0.075 mmol, 0.05−0.3 equiv) was added, followed by additive acid (75.0 μmol, 0.3 equiv). The resulting mixtures were stirred at room temperature or at 0 °C, then warmed to room temperature, diluted with ethyl acetate, washed with 0.1 M (pH 7) phosphate buffer solution, dried onto sodium sulfate, filtered and concentrated under reduced pressure. The afforded crude product was purified by flash chromatography over silica gel using ethyl acetate/hexane system as eluent.

*(R)-2-[(S)-Hydroxy(4-((E)-2-nitrovinyl)phenyl)methyl]cyclohexan-1-one (**15**).* Yield: 48 mg, 70%, yellow solid; mp = 137−138 °C; $[\alpha]^{25}_{D}$ = −12.8 (*c* 0.60, $CHCl_3$); ee 86%. FTIR (neat, cm^{-1}): 3498, 2944, 2858, 1678, 1337, 827; ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 13.7 Hz, 1H, $CHNO_2$), 7.58 (d, *J* = 13.6 Hz, 1H, CHAr), 7.54 (d, *J* = 8.4 Hz, 2H, ArH), 7.42 (d, *J* = 7.9 Hz, 2H, ArH), 4.83 (dd, *J* = 8.6, 3.1 Hz, 1H, C*H*OH), 4.02 (d, *J* = 2.8 Hz, 1H, OH), 2.60 (m, 1H, COC*H*COH), 2.49 (m, 1H, $-CH_2-$), 2.36 (m, 1H, $-CH_2-$), 2.15−2.07 (m, 1H, $-CH_2-$), 1.82 (d, *J* = 13.1 Hz, 1H, $-CH_2-$), 1.68 (m, 1H, $-CH_2-$), 1.62−1.56 (m, 2H, $-CH_2-$), 1.36 (m, 1H, $-CH_2-$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.0, 145.5, 138.6, 137.0, 129.1, 129.0, 128.0, 74.3, 57.2, 42.6, 30.7, 27.6, 24.7. HRMS (ESI) for $C_{15}H_{17}NO_4Na$: calculated $[M + Na]^+$, 298.1055. Found $[M + Na]^+$, 298.1056. HPLC (Chiralcel AD-H, hexane/^{i}PrOH = 80:20, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 26.43 min, t_R (minor) = 29.17 min; ee = 86%.

*(S)-2-[(R)-Hydroxy(4-((E)-2-nitrovinyl)phenyl)methyl]cyclohexan-1-one (ent-**15**).* Yield: 51 mg, 75%, yellow solid; $[\alpha]^{25}_{D}$ = 8.0 (*c* 0.90, $CHCl_3$), ee, −64%. ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 13.6 Hz, 1H, $CHNO_2$), 7.58 (d, *J* = 13.6 Hz, 1H, CHAr), 7.54 (d, *J* = 7.9 Hz, 2H, ArH), 7.42 (d, *J* = 7.9 Hz, 2H, ArH), 4.83 (dd, *J* = 8.1, 2.9 Hz, 1H, C*H*OH), 4.02 (d, *J* = 3.0 Hz, 1H, OH), 2.61 (m, 1H, COC*H*COH), 2.49 (m, 1H, $-CH_2-$), 2.36 (td, *J* = 13.4, 6.2 Hz, 1H, $-CH_2-$), 2.11 (m, 1H, $-CH_2-$), 1.82 (d, *J* = 12.7 Hz, 1H, $-CH_2-$), 1.74−1.49 (m, 3H, $-CH_2-$), 1.37 (m, 1H, $-CH_2-$). HPLC (Chiralcel AD-H, hexane/^{i}PrOH = 80:20, flow rate 1 mL/min, λ = 210 nm), t_R (minor) = 26.51 min, t_R (major) = 28.82 min; ee = −64%.

General Procedure for the Synthesis of Michael Adducts 3 under Different Conditions. A reaction mixture of amine catalyst **7** (0.03 mmol), additive acid (0.03 mmol), ketone **1** (0.8 mmol) and nitroalkene **2** (0.1 mmol) was allowed to stir at room temperature. The progress of the reaction was monitored by TLC (1:3 of EtOAc/Hex). After consumption of the nitroalkene, ketone was evaporated under reduced pressure. The afforded crude product was purified by flash chromatography over silica gel using ethyl acetate/hexane system as eluent.

Synthesis of Adducts 16. Adduct **16** was synthesized according to the procedure above-described using alkene **15** and amine *exo*-L-**7aa** as catalyst. The reaction was let stir at 0 °C until consumption of the starting material.

*(R)-2-[(S)-1-(4-((S)-Hydroxy((R)-2-oxocyclohexyl)methyl)phenyl)-2-nitroethyl]cyclohexan-1-one (anti-**16**).* Yield: 20 mg, 53%, white solid; mp = 82−83 °C; $[\alpha]^{25}_{D}$ = 6.8 (*c* 0.31, $CHCl_3$). FTIR (neat, cm^{-1}): 3517, 2925, 2856, 1700, 1550; ^1H NMR (500 MHz $CDCl_3$) δ 7.27 (d, *J* = 8.9 Hz, 2H, ArH), 7.15 (d, *J* = 7.6 Hz, 2H, ArH), 4.94 (dd, *J* = 12.8, 4.4 Hz, 1H, $CHNO_2$), 4.75 (d, *J* = 8.9 Hz, 1H, C*H*OH), 4.63

(dd, J = 12.6, 9.8 Hz, 1H, CHNO$_2$), 4.02 (s, 1H, OH), 3.76 (q, J = 5.3 Hz, 1H, CHAr), 2.66 (d, J = 3.2 Hz, 1H, CH), 2.57 (t, J = 13.7 Hz, 1H, CH), 2.47 (d, J = 9.6 Hz, 2H, −CH$_2$−), 2.36 (d, J = 11.8 Hz, 2H, −CH$_2$−), 2.07 (m, 2H, −CH$_2$−), 1.87−1.45 (m, 8H, −CH$_2$−), 1.24 (m, 2H, −CH$_2$−); ^{13}C NMR (101 MHz, CDCl$_3$) δ 215.6, 211.9, 140.5, 137.4, 128.2, 127.6, 78.8, 74.5, 57.2, 52.6, 43.6, 42.8, 42.7, 33.2, 30.8, 28.5, 27.8, 25.0, 24.7. HRMS (ESI) for C$_{21}$H$_{27}$NO$_5$Na: calculated [M + Na]$^+$, 396.1787. Found [M + Na]$^+$, 396.1793.

*(R)-2-[(S)-1-(4-((S)-Hydroxy((S)-2-oxocyclohexyl)methyl)phenyl)-2-nitroethyl]cyclohexan-1-one (syn-**16**).* Yield: 4 mg, 11%, pale yellow solid; mp = 110−112 °C $[\alpha]^{25}_{\mathrm{D}}$ = 7.9 (c 0.31 CHCl$_3$). FTIR (neat, cm^{-1}): 3498, 2935, 2860, 1700, 1549; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.28 (d, J = 8.4 Hz, 2H, ArH), 7.16 (d, J = 7.9 Hz, 2H, ArH), 5.37 (s, 1H, C*H*OH), 4.97 (dd, J = 12.5, 4.5 Hz, 1H, CHNO$_2$), 4.65 (dd, J = 12.7, 9.9 Hz, 1H, CHNO$_2$), 3.78 (m, 1H, CHAr), 3.07 (bs, 1H, OH), 2.69 (m, 1H, CH), 2.58 (d, J = 8.5 Hz, 1H, CH), 2.48 (m, 2H, −CH$_2$−), 2.40 (m, 2H, −CH$_2$−), 2.11 (m, 2H, −CH$_2$−), 1.89−1.54 ((m, 8H, −CH$_2$−), 1.26 (m, 2H, −CH$_2$−); ^{13}C NMR (101 MHz, CDCl$_3$) δ 214.9, 211.9, 141.0, 136.4, 128.0, 126.4, 78.8, 70.4, 56.9, 52.6, 43.6, 42.7, 42.7, 33.2, 28.5, 28.0, 26.0, 25.0, 24.8. HRMS (ESI) for C$_{21}$H$_{27}$NO$_5$Na: calculated [M + Na]$^+$, 396.1787. Found [M + Na]$^+$, 396.1789.

*(S)-2-[(R)-1-(4-((R)-Hydroxy((S)-2-oxocyclohexyl)methyl)phenyl)-2-nitroethyl]cyclohexan-1-one (ent−anti-**16**).* Yield: 14 mg, 37%, white solid; $[\alpha]^{25}_{\mathrm{D}}$ = −4.7 (c 0.41, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.27 (d, J = 8.9 Hz, 2H, ArH), 7.15 (d, J = 7.5 Hz, 2H, ArH), 4.94 (d, J = 12.7 Hz, 1H, CHNO$_2$), 4.75 (d, J = 8.7 Hz, 1H, C*H*OH), 4.63 (t, J = 11.4 Hz, 1H, CHNO$_2$), 4.02 (s, 1H, OH), 3.75 (d, J = 11.1 Hz, 1H, CHAr), 2.65 (s, 1H, CH), 2.56 (s, 1H, CH), 2.52−2.32 (m, 4H, −CH$_2$−), 2.07 (m, 2H, −CH$_2$−), 1.84−1.48 (m, 8H, −CH$_2$−), 1.23 (m, 2H, −CH$_2$−).

*(S)-2-[(R)-1-(4-((R)-Hydroxy((R)-2-oxocyclohexyl)methyl)phenyl)-2-nitroethyl]cyclohexan-1-one (ent−syn-**16**).* Yield: 7 mg, 19%, pale yellow solid; $[\alpha]^{25}_{\mathrm{D}}$ = −5.4 (c 0.34, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.25 (d, J = 8.4 Hz, 2H, ArH), 7.13 (d, J = 7.9 Hz, 2H, ArH), 5.35 (s, 1H, C*H*OH), 4.94 (dd, J = 12.3, 4.9 Hz, 1H, CHNO$_2$), 4.62 (t, J = 11.2 Hz, 1H, CHNO$_2$), 3.76 (m, 1H, CHAr), 3.04 (bs, 1H, OH), 2.66 (td, J = 11.2, 5.0 Hz, 1H, CH), 2.56 (t, J = 9.2 Hz, 1H, CH), 2.50−2.33 (m, 4H, −CH$_2$−), 2.07 (s, 2H, −CH$_2$−), 1.89−1.49 (m, 8H, −CH$_2$−), 1.23 (m, 2H, −CH$_2$−).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra for all novel compounds described in this work. HPLC chromatograms of aldol and Michael adducts reported in Tables 1−4. Energies, harmonic analyses and Cartesian coordinates of transition structures shown in Figure 3 and of those associated with the formation of enamines through the *NH*-pyrrolidine moiety of *exo*-L-**7aa**. Crystallographic data (CIF) for compound *syn*-**16**. Complete ref 18. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00495.

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Notes

The authors declare no competing financial interest.

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