Stereocontrolled Synthesis of Highly Substituted Proline Esters via [3 + 2] Cycloaddition between N-Metalated Azomethine Ylides and Nitroalkenes. Origins of the Metal Effect on the Stereochemical Outcome

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The [3 + 2] cycloaddition reaction between several *N*-metalated azomethine ylides and nitroalkenes has been studied using AgOAc and $LiClO_4$ as metalating reagents in the presence of triethylamine. The reaction is found to be very versatile and can be extended to homochiral nitroalkenes. In general, lithium and silver salts promote preferential formation of the *endo* and *exo* cycloadducts, respectively. The presence of a phenol moiety induces a shift toward the *exo*-cycloadduct even when lithium is used. A model based upon the experimental results obtained and SCF-MO calculations is proposed to explain the variable stereochemical outcome of these reactions.

Introduction

The importance of substituted prolines[1] in the design of new catalysts[2] or in the chemical synthesis of pharmacologically[3] or biologically interesting[4] molecules is well recognized. The [3 + 2] reaction of azomethine ylides and alkenes is one of the most useful methods for the preparation of these molecules in a convergent manner.[5] Among the different versions of this reaction,[6] the interaction between N-metalated azomethine ylides and π-defficient alkenes is specially promising, since, in general, it allows the synthesis of proline nuclei under mild conditions and with good chemical yields.[7] In addition, the reaction is very versatile and consequently is well suited for combinatorial chemistry.[8] Another interesting feature of this reaction is that the stereocontrol observed is usually satisfactory. Thus, the reaction between α,β-unsaturated carbonyl compounds and N-metalated azomethine ylides derived from amino esters and aldehydes yields *endo*-cycloadducts[9] as the major stereoisomers.[10] However, Töke et al.[11] have observed a reversal of stereoselectivity in the 1,3-dipolar cycloaddition between several azomethine ylides and aryl nitro olefins. These authors reported that lithium metalation promotes the preferential formation of *endo* cycloadducts, whereas the use of silver salts favors the formation of *exo*-pyrrolidines as major stereoisomers.

Within this context and in connection to our ongoing research program on nitroalkene chemistry,[12] we present

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(4) See for example: (a) Fishwick, C. W. G.; Foster, R. J.; Carr, R. E. *Tetrahedron Lett.* **1996**, *37*, 3915. (b) Bianco, A.; Maggini, M.; Scorrano, G.; Toniolo, C.; Marconi, G.; Villani, C.; Prato, M. *J. Am. Chem. Soc.* **1996**, *118*, 4072. (c) Hirschmann, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1278. (d) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244.

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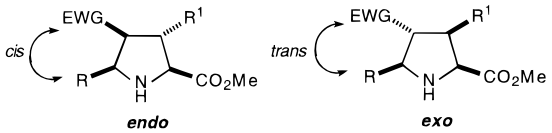
(7) Kanemasa, S.; Tsuge, O. In *Advances in Cycloaddition*; Curran, D. P., Ed.; Jai Press: Greenwich, 1993; Vol. 3, pp 99−159.

(8) (a) Murphy, M. M.; Schullek, J. R.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 7029. (b) Hamper, B. C.; Dukesherer, D. R.; South, M. S. *Tetrahedron Lett.* **1996**, *37*, 3671. (c) Marx, M. A.; Grillot, A.-L.; Louer, C. T.; Beaver, K. A.; Bartlett, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 6153.

(9) We denote the *endo* and *exo* stereoisomers as those in which the electron-withdrawing group at C4 and the substituent at the C5 position are in a cis and t*rans* relationship, respectively.



(10) See for example: (a) Tsuge, O.; Kanemasa, S.; Yoshioka, M. *J. Org. Chem.* **1988**, *53*, 1384. (b) Kanemasa, S.; Yoshiora, M.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2196. (c) Grigg, R.; Kemp, J. *J. Chem. Soc. Chem. Commun.* **1978**, 2885. (d) Tsuge, O.; Kanemasa, S.; Ohe, M.; Yorozu, K.; Takenaka, S.; Veno, K. *Chem. Lett.* **1986**, 1271. (e) Tsuge, O.; Kanemasa, S.; Ohe, M.; Yorozu, K.; Takenaka, S.; Veno, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4067.

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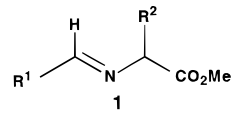
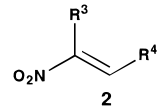
Chart 1



1

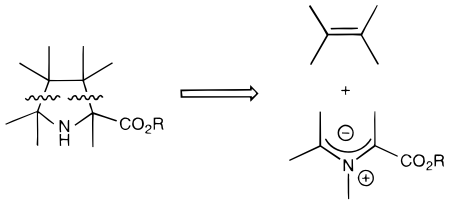
	R^1	R^2
a	C_6H_5	H
b	2-HO-C_6H_4	H
c	2-OH-C_6H_4	CH_3
d	2-$CH_3OC_6H_4$	H
e	2-$CH_3OC_6H_4$	CH_3
f	2-pyridyl	H
g	4-HO-3-$CH_3OC_6H_3$	H



2

	R^3	R^4
a	H	4-Cl-C_6H_4
b	H	4-$CH_3OC_6H_4$
c	CH_3	4-$CH_3OC_6H_4$
d	H	*(S)*-CH(OBn)CH_3

Scheme 1[a]



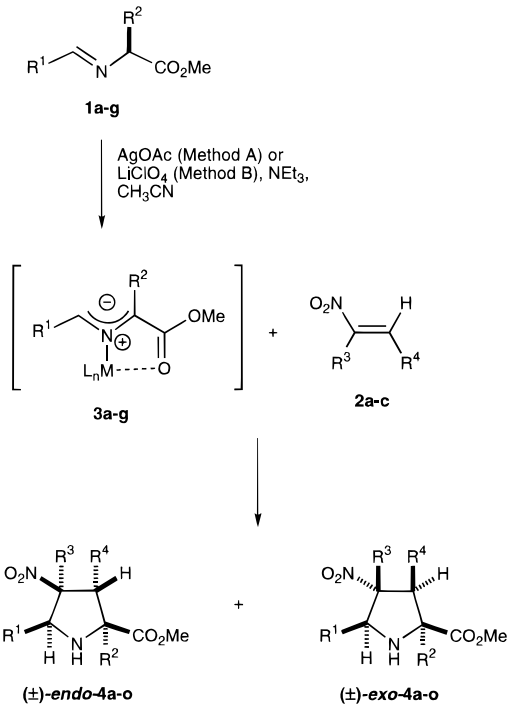
[a] The substituents at the different positions are not specified.

herein our results on the reaction between nitro olefins and azomethines. We have extended the reaction to highly substituted azomethine ylides and nitroalkenes, and we provide an explanation to the metal dependence of the stereochemical outcome of this important reaction.

Results and Discussion

To obtain structurally diverse cycloadducts, imines **1a**−**g** and nitroalkenes **2a**−**d** were selected (see Chart 1). In particular, compounds **1b**−**f** were studied because of the potential of the corresponding cycloadducts as tridentate ligands.[2] Nitroalkene **2d** was also selected in order to study the synthetic potential of the reaction when homochiral nitroalkenes are used as dipolarophiles. Lithium and silver azomethine ylides (see Scheme 2) derived from imines **1a**−**g** were generated from $LiClO_4$ and AgOAc, respectively, in the presence of triethylamine as base and acetonitrile as solvent. $LiClO_4$ has not been previously described as a source of N-lithiated azomethines. These reactive intermediates are usually generated by means of either the LiBr/NEt_3 or the LDA/NEt_3 systems.[7] We have observed that $LiClO_4$ usually leads to cleaner crude reaction mixtures with respect to the above-mentioned lithium salts. The results obtained are collected in Table 1. We have found that when AgAcO is used to promote the formation of azomethine ylides, the reaction takes place faster than when formation of the dipoles is assisted by $LiClO_4$. For example, reaction between **1a** and **2b** in the presence of 0.15 equiv of AgOAc yields a mixture of *endo*- and *exo*-**4b** after 3 h of reaction at room temperature in a 69% yield (see Table

Scheme 2[a]



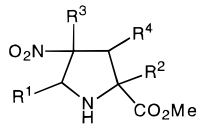
[a] Only one enantiomer of the cycloadducts **4** is drawn.

1, entry 2). In contrast, the same reaction in the presence of 0.15 equiv of $LiClO_4$ yields **4b** in a 30% yield with a *endo*:*exo* ratio of 63:37. When 5 equiv of $LiClO_4$ were used, the cycloadduct was obtained in a 47% yield and with higher stereocontrol (see Table 1, entry 2). This effect is more pronounced with more substituted substrates. Thus, when the **1c**+**2b** → **4e** transformation was performed in the presence of 0.15 equiv of $LiClO_4$, a reaction time of 20 h was required to obtain a 56:44 *endo*/*exo* mixture of cycloadducts **4e** in a 30% yield. When the same reaction was carried out with 5 equiv of $LiClO_4$, only 4 h were required to achieve a higher yield of **4e** (see Table 1, entry 5). Similar results were observed in other cases. Therefore, we decided to use 5 equiv of this salt in all cases, because of the lower reaction times required to achieve acceptable yields and/or the higher stereocontrol observed.

We have observed a preferential formation of the *exo*-cycloadduct when a silver azomethine ylide possessing a noncoordinating aromatic substituent reacts with an aromatic nitroalkene. In the case of the corresponding lithium azomethine, the *endo*-stereoisomer is formed preferentially under similar conditions. For instance, *exo*-**4a** is the major product in the reaction between **1a** and **2a** in the presence of AgOAc, whereas *endo*-**4a** is preferentially formed when $LiClO_4$ is used (see Table 1, entry 1). Similar results were obtained in the reaction between **1a** and **2b** (entry 2). When the same experiments were repeated using *N*,*N*-diisopropylethylamine as base instead of triethylamine, the same stereochemical outcome was observed. These results are in agreement with the observations of Töke et al.[11] for structurally related compounds.

We have found that the above-mentioned trend can be modified when azomethines incorporating certain groups at the aromatic moiety are used. Thus, when imine **1b** derived from salicylaldehyde and glycine was allowed to

Table 1. [3 + 2] Cycloaddition between N-Metalated Azomethines Derived from Imines 1a−g and Nitroalkenes 2a−c Using Acetonitrile as Solvent and in the Presence of AgOAc and $LiClO_4$



						method A (AgOAc)			method B ($LiClO_4$)		
entry	product	R^1	R^2	R^3	R^4	time (h)	yield[a] (%)	*endo*:*exo*[b]	time (h)	yield[a] (%)	*endo*:*exo*[b]
1	**4a**	C_6H_5	H	H	4-Cl-C_6H_4	3	60	27:73	3	66	76:24
2	**4b**	C_6H_5	H	H	4-$CH_3OC_6H_4$	3	69	30:70	3	47	83:17
3	**4c**	2-HO-C_6H_4	H	H	4-Cl-C_6H_4	2.5	29[c]	2:98	2.5	24[c]	14:86
4	**4d**	2-HO-C_6H_4	H	H	4-$CH_3OC_6H_4$	2.5	41[c]	2:98	2.5	45[c]	2:98
5	**4e**	2-HO-C_6H_4	CH_3	H	4-$CH_3OC_6H_4$	48	49[c]	42:58	4	37[c]	58:42
6	**4f**	2-HO-C_6H_4	H	CH_3	4-$CH_3OC_6H_4$	17	24[c]	30:70	17	24[c]	55:45
7	**4g**	2-HO-C_6H_4	CH_3	CH_3	4-$CH_3OC_6H_4$	40	30[c]	30:70	7.5	27[c]	65:35
8	**4h**	2-$H_3COC_6H_4$	H	H	4-Cl-C_6H_4	2	62[d]	33:67	2	38[e]	43:57
9	**4i**	2-$CH_3OC_6H_4$	H	H	4-$CH_3OC_6H_4$	2	57	37:63	2	61	39:61
10	**4j**	2-$CH_3OC_6H_4$	CH_3	H	4-$CH_3OC_6H_4$	16	60	36:64	16	56	73:27
11	**4k**	2-$CH_3OC_6H_4$	CH_3	CH_3	4-$CH_3OC_6H_4$	24	60	33:67	16	60	34:66
12	**4l**	2-pyridyl	H	H	4-CL-C_6H_4	4	25[c]	33:67	2.5	54	65:35
13	**4m**	2-pyridyl	H	H	4-$CH_3OC_6H_4$	4	64	22:78	2.5	52	68:32
14	**4n**	4-HO-3-$CH_3OC_6H_3$	H	H	4-Cl-C_6H_4	2	36[c]	36:64	2	40[c]	23:77
15	**4o**	4-HO-3-$CH_3OC_6H_3$	H	H	4-$CH_3OC_6H_4$	2	42[c]	30:79	2	56	24:76

[a] Yield of the major stereoisomer purified by column chromatography. [b] Diastereomeric ratio measured by 300 MHz ^{1}H-NMR on crude reaction mixtures. [c] Yield of the major stereoisomer purified by crystallization. [d] Yield of the exo isomer estimated from the mixtures obtained from the column chromatography. This isomer couldn't be isolated. [e] Yield of the endo isomer estimated from the mixtures obtained from the column chromatography. This isomer could not be isolated.

react with nitroalkenes **2a** or **2b** in the presence of AgOAc and 2 equiv of triethylamine, the *exo* cycloadducts **4c** and **4d** were obtained with excellent stereocontrol (*endo*:*exo* = 2:98). When the same reaction was carried out in the presence of $LiClO_4$, the *exo* cycloadducts were also the major stereoisomers (see Table 1, entries 3 and 4). This effect is significantly lower when the imine **1d**, which incorporates a 2-methoxyphenyl group was used instead of **1b** (see Table 1, entries 8 and 9). When azomethines derived from imine **1f** which has a 2-pyridyl group were used, the "normal" sense of stereocontrol was observed, although the stereoselectivity was lower (see Table 1, entries 12 and 13). In all these systems, there is a Lewis basic center located at the *ortho* position, which is amenable to intramolecular coordination to the metallic center. To test if this effect can also operate intermolecularlly, imine **1g**, derived from vanillin and the methyl ester of glycine, was allowed to react with nitroalkenes **2a** and **2b**. The results are shown in entries 14 and 15 of Table 1. As can be seen, the ionized *para*-phenolic moiety also promotes preferential formation of the *exo* cycloadducts **4n** and **4o** in the presence of $LiClO_4$, although the effect is less pronounced than in the case of entries 3 and 4 (vide supra).

With these results in mind, we reasoned that the presence of additives incorporating highly coordinating moieties such as nitro or phenoxy groups might modify the stereochemical outcome of the reaction between aromatic nitroalkenes and *N*-lithium azomethines derived from **1a**. We performed the experiments reported in Table 2 to verify this hypothesis. In effect, the presence of phenol (entry 4), 2,6-di-*tert*-butyl phenol (entry 5) and nitrobenzene (entry 7) reverses the stereochemical outcome observed in the reaction between imine **1a** and nitroalkene **2a** to form the cycloadducts *endo*- and *exo*-**4a**. As expected, the effect induced by the hindered 2,6-di-*tert*-butylphenol is less pronounced than that promoted by phenol itself (see Table 2, entries 4 and 5). In the case of using AgOAc, these additives have negligible influence on the stereochemical outcome of the **1a**+**2a** → **4a** process (see Table 2, entries 1, 3, and 6).

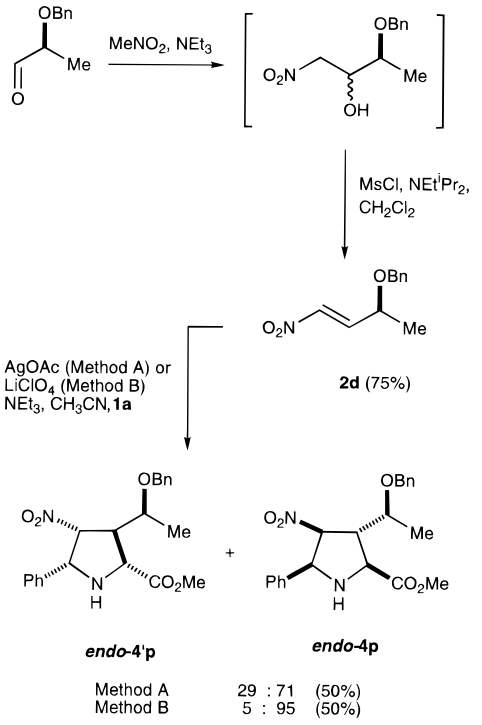
Table 2. Stereoselectivity in the [3 + 2] Cycloaddition between N-Metalated Azomethines Derived from Imine 1A and Alkene 2A in the Presence of Several Additives[a]

entry	MX	additive[b]	time (h)	*endo*-**4a**:*exo*-**4a**[c]
1	AgOAc	none	3	27:73
2	$LiClO_4$	none	3	76:24
3	AgOAc	C_6H_5OH[d]	5	30:70
4	$LiClO_4$	C_6H_5OH[d]	5	40:60
5	$LiClO_4$	2,6-di^{t}Bu-PhOH[d]	2	51:49
6	AgOAc	$C_6H_5NO_2$	5	27:73
7	$LiClO_4$	$C_6H_5NO_2$	5	36:64

[a] All experiments were conducted using acetonitrile as solvent and triethylamine as base. [b] One equivalent of the additive was used. [c] Diastereomeric ratio determined by 300 MHz ^{1}H-NMR on crude reaction mixtures. [d] Two equivalents of triethylamine were used.

According to our results azomethines derived from substituted amino esters such as alanine (see compounds **1c,e** in Chart 1) and (*E*)-1-methyl-2-(arylnitro)ethylenes (see compound **2c** in Chart 1) are much less reactive than the preceding reactants. For example, the reaction between **1c** (R^2 = Me) and **2b** to form **4e** requires 48 h at room temperature in the presence of AgOAc, whereas the reaction between **1b** (R^2 = H) and **2b** takes place in only 2.5 h under the same conditions (see Table 1, entry 4). In any case, the use of highly substituted reactants is of preparative value, since the cycloadducts are readily purified and obtained in acceptable yields. In addition, in these highly substituted substrates the effect of *ortho*-phenolic groups is very attenuated with respect to their less substituted analogues. Thus, in the reaction of imine **1c** with nitroalkene **2c** to yield cycloadducts *endo*- and *exo*-**4g** (Table 1, entry 7) a loss of stereocontrol is observed with respect to the nonmethylated substrates (see Table 1, entry 4). When $LiClO_4$ is used, the proportion of *exo*-**4g** is higher than that obtained in the case of the **1a**+**2b** → **4b** process, although the *endo* cycloadduct is the major one.

Scheme 3



We next extended our study to the chiral nitroalkene **2d** (see Chart 1). This compound was prepared via the Henry reaction between (*S*)-2-(benzyloxy)propanal and nitromethane in the presence of a catalytic amount of triethylamine. The diastereomeric nitro alcohols[13] thus formed were transformed in the corresponding mesylates[14] and treated in situ with *N*,*N*-diisopropylethylamine to yield the nitroalkene **2d** in good yield.[15] Reaction of this dipolarophile with azomethine ylides derived from **1a** lead to the diastereomeric pair *endo*-**4p** and *endo*-**4′p** (see Scheme 3). Interestingly, this aliphatic nitroalkene yields *endo* cycloadducts using both lithium and silver azomethines, thus suggesting that the aryl group in nitroalkenes **2a**−**c** also plays a role in the stereochemical outcome of the reaction (vide infra). When lithium perchlorate was used instead of silver acetate, the observed diastereomeric ratio was 95:5 in favor of *endo*-4p (see Scheme 3). The major cycloadduct was purified by crystallization in ethyl acetate−hexanes. Despite the higher stereocontrol observed when the lithium azomethine ylide of **1a** was used, the chemical yield of *endo*-**4p** was similar to that obtained using AgOAc as the metalating reagent (see Scheme 3). Therefore, the reaction was found to be of preparative value and provides a useful access to the asymmetric synthesis of compounds of this kind.

The structure of cycloadducts **4a**−**p** was established by means of their ^{1}H NMR and ^{13}C NMR spectra. The most significant coupling constants are reported in Table 1 of the Supporting Information. In two cases, the relative stereochemistry was secured by X-ray diffraction analysis. The ORTEP diagrams of compounds *exo*-**4c** and *exo*-**4f** are shown in Figures 1 and 2 of the Supporting Information, respectively.[16]

In the case of compound *exo*-**4p**, its structure was assigned by NOE experiments, by analogy with structurally related compounds,[17] and applying the *endo*-alkoxy rule developed by Houk.[18] In several cases, oily cycloadducts were transformed in their solid *N*-acetylated derivatives[19] in order to facilitate their purification. Thus, cycloadducts *endo*-**4h** and *exo*-**4h,j** were heated with trifluoroacetic acid, and the corresponding salts were acylated with acetic anhydride for 48 h to yield the acetamides *endo*-**5h** and *exo*-**5h,j** respectively (see Supporting Information for additional details).

The next step in our study was to elucidate the origins of the observed changes in the sense of stereocontrol. Given that under kinetic conditions this stereocontrol is determined by the differences in energy between the corresponding diastereomeric transition structures,[20] the computational tools nowadays available to the organic chemist are particularly convenient to address this particular problem. Since it was presumed that solvent and substituent effects should play a significant role, the PM3 semiempirical Hamiltonian[21] was used, in view of its superior ability to model the particular features of the nitro group.[22]

We located first the saddle point **TS1** (Figure 1) associated with the [3 + 2] cycloaddition between ethylene and the lithium azomethine ylide of *N*-(formylmethyl)benzylideneamine. This transition structure corresponds to a concerted *supra-supra* topology as would be expected from the Woodward−Hoffmann rules for thermal six-electron cycloadditions. However, inclusion of a nitro group induces a drastic change in the potential energy hypersurface. Thus, nitroalkene is highly π-deficient and behaves as a Michael acceptor rather than a dipolarophile. Therefore, the [3 + 2] cycloaddition actually consists of a tandem Michael−Henry reaction, as it is shown in Scheme 4. The first step is a nucleophilic attack of the lithium azomethine ylide on the nitroalkene to form the zwitterionic species denoted in Scheme 4 as **INT**, in which the C2−C3 bond is formed.[23] The second step is a nitroaldol process[13] in which the nitronate moiety adds to the iminic part of **INT**. This is in agreement with the fact that several authors[7,24] have reported the formation of Michael adducts in the reaction

(13) (a) For a recent review see: Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 2, pp 321−340. (b) For an study on the mechanism of this reaction, see Lecea, B.; Arrieta, A.; Morao, I.; Cossío, F. P. *Eur. J. Chem.* **1997**, *3*, 20.

(14) Melton, J.; McMurry, J. E. *J. Org. Chem.* **1975**, *40*, 2185.

(15) Pätzel et al. have prepared structurally related chiral nitroalkenes using different reaction conditions and have observed a lower stereocontrol. See Galley, G.; Hübner, J.; Anklam, S.; Jones, P. G.; Pätzel, M. *Tetrahedron Lett.* **1996**, *37*, 6307.

(16) Crystallographic data (excluding structure factors) for the structures *exo*-**4c** and *exo*-**4f** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 IEZ, UK. (fax: +44-(0)1223-336033; email: deposit@chemcrys.cam.ac.uk).

(17) (a) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Pilati, T. *Tetrahedron: Asymmetry* **1991**, *2*, 1329. (b) Pätzel, M.; Galley, G.; Jones, P. G.; Chrapkowsky, A. *Tetrahedron Lett.* **1993**, *34*, 5707. (c) Galley, G.; Liebscher, J.; Pätzel, M. *J. Org. Chem.* **1995**, *60*, 5005.

(18) (a) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jager, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880. (b) Houk, K. N.; Wu, Y.-D.; Duh, H.-Y.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754.

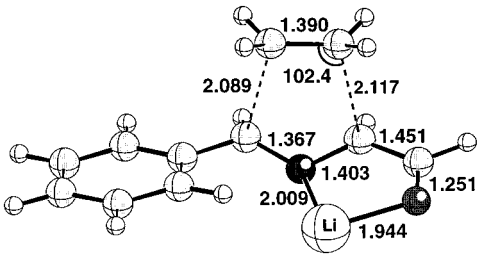
(19) Beausoleil, E.; Lubell, W. D. *J. Am. Chem. Soc.* **1996**, *118*, 12902.

(20) Seeman, J. I. *Chem. Rev. (Washington, D.C.)* **1983**, *83*, 83.

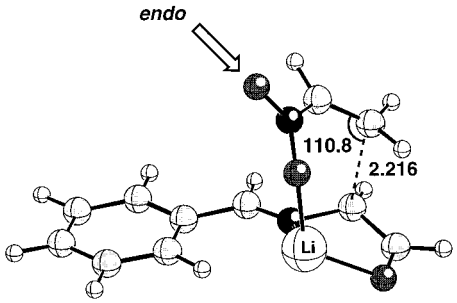
(21) (a) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209. (b) Anders, E.; Koch, R.; Freunscht, P. *J. Comput. Chem.* **1993**, *14*, 1301.

(22) Stewart, J. J. P. *J. Comput.-Aided Mol. Des.* **1990**, *4*, 1.

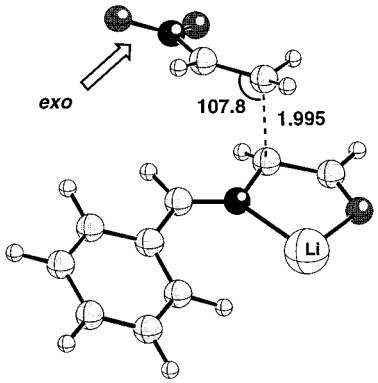
(23) For a related reaction mechanism involving azomethine ylides and α,β-unsaturated carbonyl compounds, see: Tatsukawa, A.; Kawatake, K.; Kanemasa, S.; Rudzinski, J. M. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2525.



TS1
ΔH_f = 47.38 kcal/mol
ν = 853.7 i cm^{-1}



***endo*-TS2**
ΔH_f = 7.34 kcal/mol
ΔG_{298} = -27.63 kcal/mol
ν = 403.5 i cm^{-1}



***exo*-TS2**
ΔH_f = 16.61 kcal/mol
ΔG_{298} = -28.87 kcal/mol
ν = 457.9 i cm^{-1}

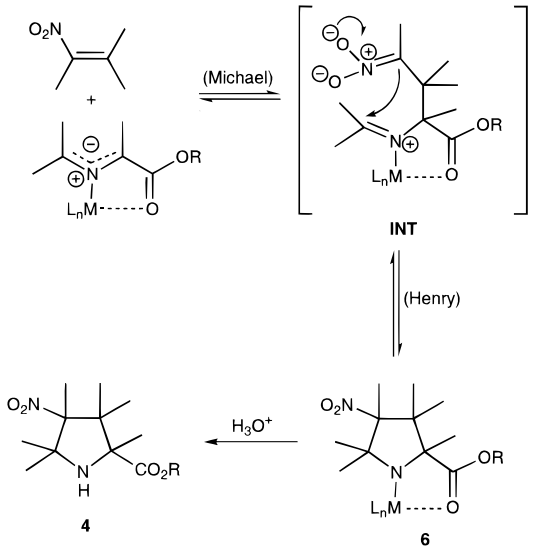
Figure 1. Computer plots of the transition structures **TS1**, *endo*-**TS2**, and *exo*-**TS2** computed at the RHF/PM3 level. Bond distances and angles are given in angstroms and deg, respectively. In this and the following figures, which incorporate ball-and-stick representations, unless otherwise noted, atoms are represented by increased order of shadowing as follows: H, C, O, N.

between π-deficient alkenes and azomethine ylides derived from alkyl aldehydes or ketones.

We tried to isolate and characterize several of these Michael intermediates in order to verify our computational results. However, in most cases the inherent instability of the intermediates precluded their isolation, although they were observed in the ^{1}H NMR spectra of several reaction mixtures. We reasoned that, since the more substituted the nitronate is the lower its reactivity,[13b] α-methyl nitroalkenes could be more convenient starting

(24) (a) Tsuge, O.; Kanemasa, S.; Ohe, M.; Yorozu, K.; Takenaka, S.; Ueno, K. *Chem. Lett.* **1986**, 1271. (b) Kanemasa, S.; Yoshioka, M.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 869.

Scheme 4

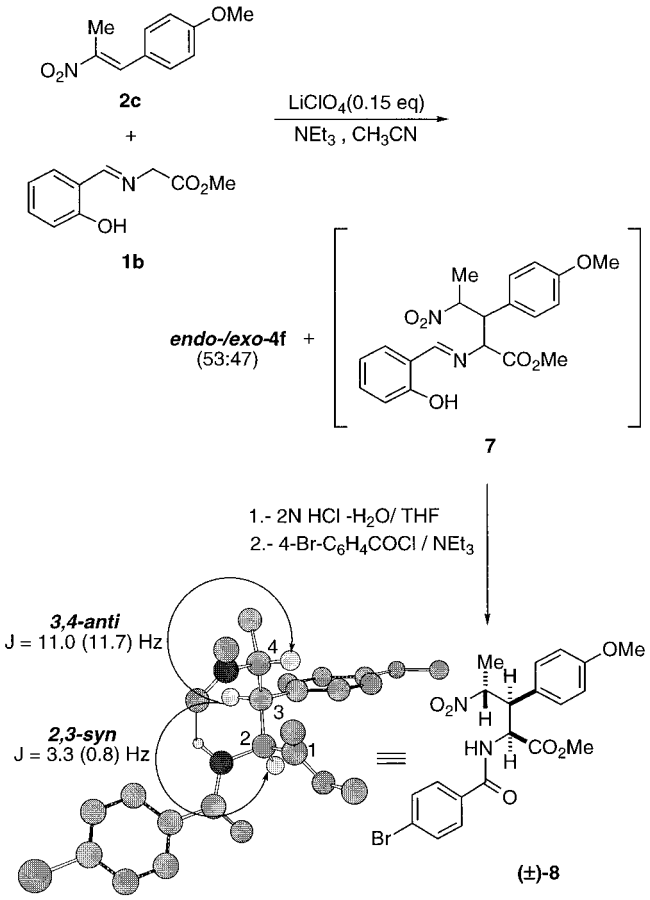


[a] The possible substituents at the different positions are not specified.

materials. On the other hand, we have found that the reaction takes place more slowly when it is carried out in the presence of only 0.15 equiv of $LiClO_4$ (vide supra). Therefore, we repeated the reaction between **1b** and **2c** in the presence of 0.15 equiv of $LiClO_4$ (Scheme 5). After 16 h reaction at room temperature, a 53:47 mixture of *endo*/*exo*-**4f** and a mixture of Michael intermediates **7** was observed. The cycloadducts **4f** and the intermediates were found to be in a ca. 2:1 ratio in the crude reaction mixture, while ca. 25% of **2c** remained un reacted. When this mixture was allowed to react for additional 10 h, the ^{1}H NMR signals of **7** disappeared and only a mixture of cycloadducts **4f** was observed. In this case a complex mixture of pyrrolidines was obtained because of the partial loss of the trans relationship between the nitro and the 4-methoxyphenyl groups. All our attempts to isolate and characterize these intermediates in a pure form failed. However, hydrolysis of the imine moiety in **7** followed by in situ acylation with 4-bromobenzoyl chloride allowed the complete characterization of amide **8**, which was the major diastereomer observed in the crude reaction mixture. The overall yield of **8** from **1b** was of 6%. Both the high δ value of the N−H signal and molecular mechanics optimizations (vide infra) indicate that in **8** there is a strong intramolecular hydrogen bond between the amidic hydrogen and the nitro group, thus yielding a pseudocyclic structure. Therefore, the relative stereochemistry of this product was established on the basis of the coupling constants between the contiguous methinic protons (see Scheme 5). In summary, the observation of intermediate **7**, its conversion to the corresponding cycloadducts and the complete characterization of its derivative **8** provide experimental support for the stepwise mechanism predicted by our calculations.

Since no isomerization is observed either in the azomethine ylide or in the nitroalkene during the course of the reaction, the stereochemistry of the cycloadducts is determined by the approaching mode between both partners. In Figure 1 we have included the two diastereomeric *endo*- and *exo*-**TS2** saddle points. In *endo*-**TS2**, the nitro group is coordinated to the lithium atom, with a Li···ONO bond distance of 1.955 Å. In the latter saddle

Scheme 5



[a] Numbers in parentheses correspond to computed coupling constants (see text). Nonrelevant hydrogen atoms have been omitted for clarity.

point, *exo*-**TS2** the lithium atom is dicoordinated and therefore the stabilizing Li···ONO interaction is not present. In contrast, this transition structure is much more flexible and the ΔG_{298} value for *exo*-**TS2** is calculated to be 1.24 kcal/mol lower than that obtained for *endo*-TS2 at the RHF/PM3 level (see Figure 1). These results are not in agreement with our experimental data, since we have observed that when azomethine ylides derived from benzaldehyde are used, the *endo* cycloadducts are obtained with a relatively low stereocontrol (vide supra). Therefore, we calculated additional transition structures taking into account as closely as possible the effects operating under the experimental conditions, namely the aryl substituent of the nitroalkene and the solvent. In Figure 2 we present the *endo*- and *exo*-**TS3** transition structures, which incorporate two acetonitrile molecules. In *endo*-**TS3**, the lithium atom is pentacoordinated, and its surrounding ligands adopt a bipyramidal disposition, in which the nitrogens of the azomethine moiety and of one solvent molecule occupy the axial positions. In contrast, *exo*-**TS3** shows a tetrahedrically coordinated lithium atom, with a close proximity between the methyl group of one acetonitrile molecule and the phenyl group of the nitroalkene. These combined effects result in a slightly higher stability of *endo*-**TS3**, whose ΔG_{298} calculated value is only 0.47 kcal/mol lower than that found for its *exo* congener. This result is in fair agreement with the diastereomeric excess experimentally found for dipoles of this type.

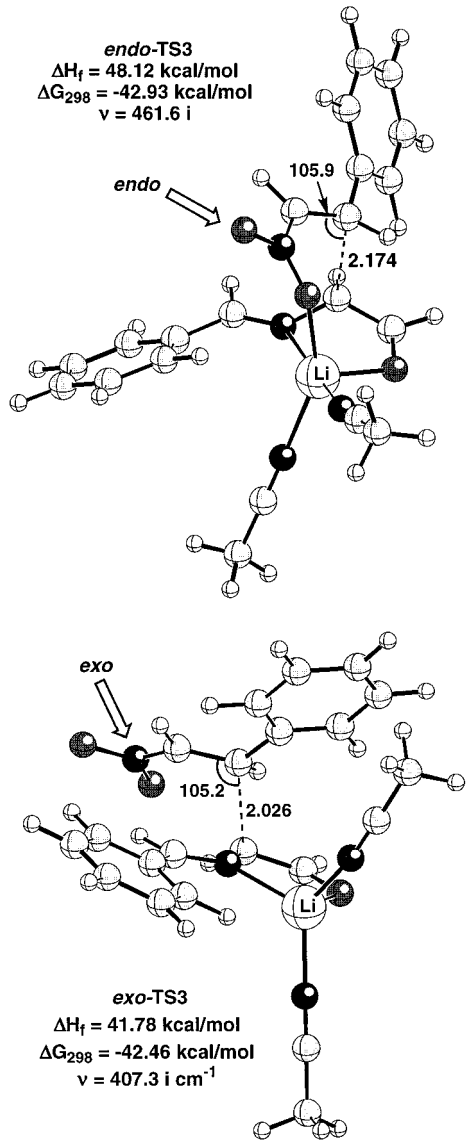


Figure 2. Computer plots of the transition structures *endo*-**TS3** and *exo*-**TS3** computed at the RHF/PM3 level. Bond distances and angles are given in angstroms and deg, respectively. See Figure 1 caption for additional details.

We next investigated computationally the effect of the *ortho*-phenoxy group on the stereochemical outcome. Figure 3 shows the three transition structures found for the *ortho*-phenoxy analogues of **TS2** saddle points in the RHF/PM3 energy hypersurface. Our calculations show that the phenoxy substituent has a remarkable effect.[25] The first saddle point is *endo′*-**TS4**, whose chief geometric features are similar to those of *endo*-**TS3**. However, in this case there is a remarkable repulsive Coulombic interaction between the nitro and the phenoxy groups coordinated to the lithium atom. Thus, partitioning of the total energy[26] reveals that the bicentric term between both groups is $\Delta E = +0.84$ kcal/mol, which corresponds to an almost purely Coulombic repulsion. We have also located another saddle point which is associated with the formation of the corresponding *endo* cycloadduct. This transition structure is denoted as *endo*-**TS4** in Figure 3.

(25) For a related metal-imine complexes involving *o*-alkoxy groups, see Gately, D. A.; Norton, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 3479.

(26) (a) Dewar, M. J. S.; Lo, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 7201. (b) Olivella, S.; Vilarrasa, J. *J. Heterocycl. Chem.* **1981**, *18*, 1189.

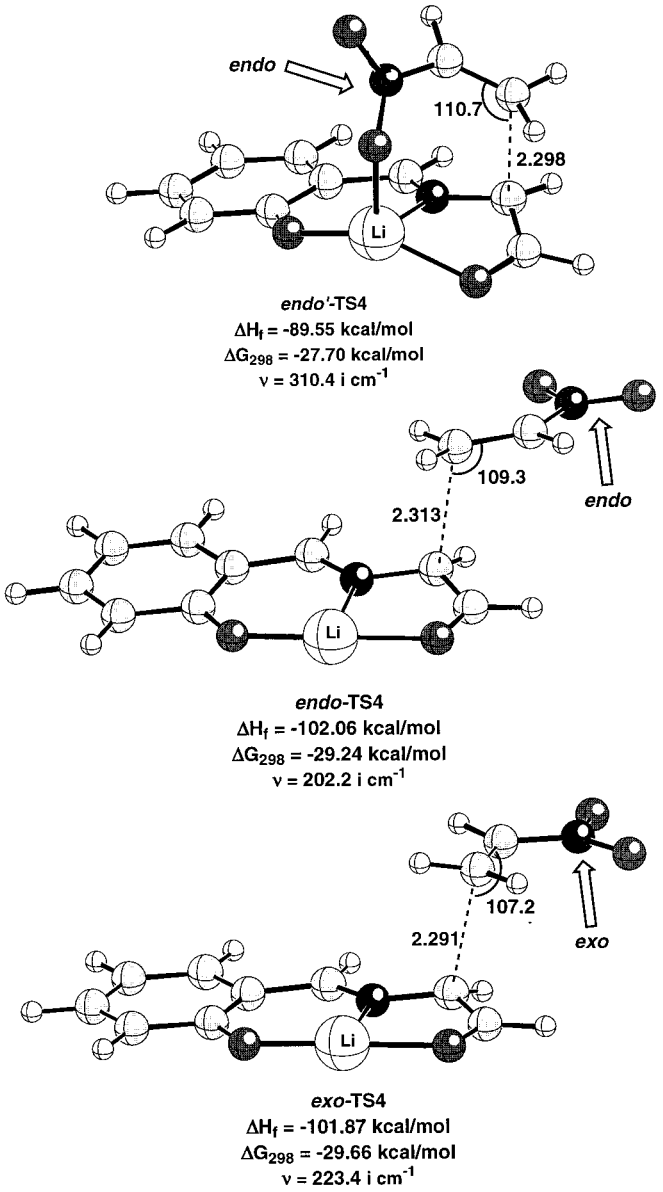


Figure 3. Computer plots of the transition structures *endo'*-**TS4** and *endo*-**TS4** and *exo*-**TS4** computed at the RHF/PM3 level. Bond distances and angles are given in angstroms and deg, respectively. See Figure 1 caption for additional details.

Both RHF/PM3 calculated heats of formation and free energies predict that this latter saddle point, despite having a tricoordinated lithium cation, is significantly more stable than *endo'*-**TS4**. In addition, *endo*-**TS4** shows an almost perfect antiperiplanar arrangement between the N1−C2 and C3−C4 bonds, and the calculated C2···C3−C4 bond angle is found to be of 109.3°, a value in good agreement with the Bürgi−Dunitz trajectory[27] usually associated with nucleophilic attacks of organometallic compounds to electrophilic double bonds. Therefore, we can conclude that *endo*-**TS4** resembles the saddle point that one can expect for a Michael addition of an organometallic carbon nucleophile on a π-deficient olefin.

In addition, we have also located the transition structure *exo*-**TS4**, whose main geometric and energetic features are also reported in Figure 3. This latter saddle point does not exhibit an antiperiplanar arrangement between the N1−C2 and C3−C4 and therefore has a heat of formation ca. 0.2 kcal/mol higher than that calculated for *endo*-**TS4**. However, the total entropy of *exo*-**TS4** is higher than that of its *endo* congener. Therefore, according to our calculations the free energy at 298 K of *exo*-**TS4** is predicted to be 0.42 kcal/mol more stable than *endo*-**TS4** at the RHF/PM3 level (see Figure 3).

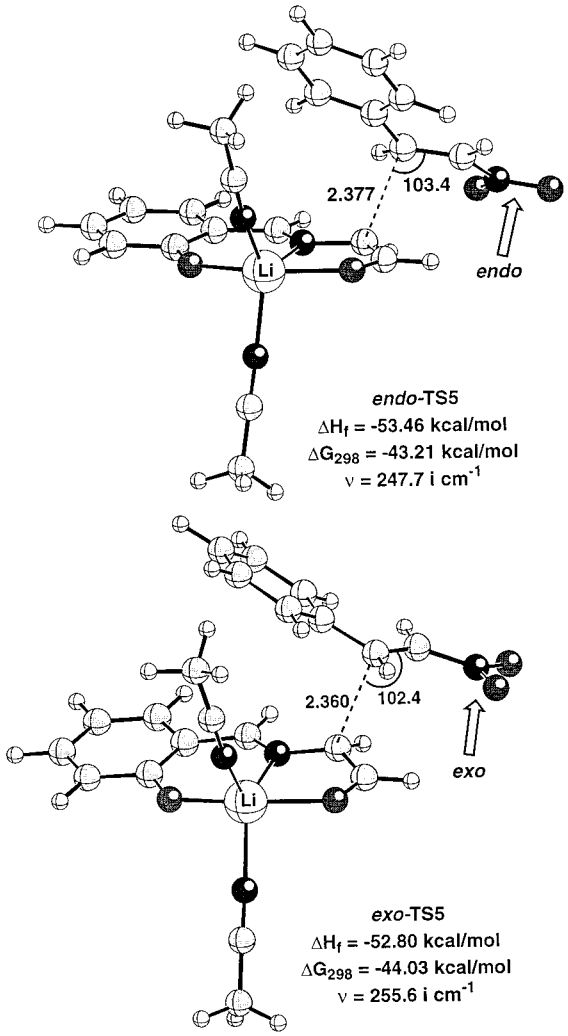


Figure 4. Computer plots of the transition structures *endo*-**TS5** and *exo*-**TS5** computed at the RHF/PM3 level. Bond distances and angles are given in angstroms and deg, respectively. See Figure 1 caption for additional details.

We have also calculated the transition structures including two molecules of the solvent and an additional phenyl ring for the nitroalkene moiety. The resulting diastereomeric *endo*- and *exo*-**TS5** saddle points are depicted in Figure 4. Both transition structures are quite similar to each other. Thus, in both stationary points the lithium atom is pentacoordinated, the oxygen and nitrogen atoms occupying the axial and equatorial positions, respectively. Once again, in *endo*-**TS5** the arrangement between the N1−C2 and C3−C4 bonds is almost perfectly antiperiplanar, thus resulting in a lower heat of formation for this transition structure. In contrast, the entropic term of *exo*-**TS5** is higher than in its *endo* congener. As a result, the free energy at 298 K of *exo*-**TS5** is calculated to be 0.82 kcal/mol lower than that of *endo*-**TS5** (see Figure 4). Therefore, the free energy

(27) (a) Bürgi, H. B.; Lehn, J.-M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 1956. (b) Bürgi, H. B.; Dunitz, J. D.; Lehn, J.-M. *Tetrahedron* **1974**, *30*, 1563.

balance favors formation of *exo*-**TS5** with a stereocontrol higher than that calculated for the non-*ortho*-substituted analogues, in good agreement with our experimental results.

In summary, our computational studies provide a useful information on the origins of the stereocontrol of these cycloadditions. When nonionizable substituents are present, entropic factors, the aryl group of the dipolarophile (or Michael acceptor), and the solvent favor the preferential formation of the *endo* cycloadduct by coordination of the nitro group with the lithium atom. In contrast, when groups other than the nitro group but with high affinity for the lithium cation are present, the same factors shift the sense of stereoselection toward the preferential formation of the *exo* cycloadduct.

At this stage of our study, there was another aspect which remained unexplored, namely the preferential formation of *exo* cycloadducts when silver azomethine ylides are used. Given that silver is not parametrized in PM3, we used an indirect approach to address this problem. As we have previously found, a possible source of stereocontrol can arise from the competition between the nitro and cyano groups. Therefore, the sign of the energy associated with eq 1 can serve as an indicator of the relative affinity of lithium and silver cations for the

$$HNO_2\cdots Ag^+ + HC{\equiv}N\cdots Li^+ \xrightarrow{\Delta E} HNO_2\cdots Li^+ + HC{\equiv}N\cdots Ag^+ \quad (1)$$

nitro and cyano groups. Given the number of electrons of silver cation, the relativistic compact effective potential developed by Stevens, Krauss, Basch and Jasien (SKBJ)[28] was used. At the MP2(FC)/SKBJ-6-31+G*+ΔZPVE level (vide infra) the silver cation is calculated to be softer than the lithium cation, the difference in hardness being of $\Delta\eta = 1.01$ au. In addition, the computed value for ΔE is −2.74 kcal/mol, thus indicating a higher affinity of silver for the cyano group. Therefore, in the presence of acetonitrile as solvent, the cyano group can compete more efficiently with the nitro group when silver azomethines are used, thus resulting in the preferential formation of *exo* cycloadducts.

Conclusions

From the combined experimental and computational studies reported in this paper, the following conclusions can be drawn:

(a) The reaction between substituted nitrostyrenes and lithium azomethines having *o*-phenoxy groups results in the preferential formation of the *exo* cycloadducts, both in the case of lithium or silver azomethine ylides.

(b) The reaction between chiral nitroalkenes and achiral lithium azomethines seems to be of preparative value, although the use of silver azomethines results in a lower stereocontrol.

(c) Computational studies suggest that the [3 + 2] cycloaddition is actually a tandem Michael−Henry process. In one case, a stable derivative of the reaction intermediate has been isolated and characterized.

(d) According to the computational studies, the stereochemical outcome of the reaction depends on the nature of the substituents and on the competition between the coordinating ability of the nitro group and that of the solvent or *ortho* ionizable groups, if present.

(e) The nature of the metal, in particular, its hardness, is closely related to the stereochemical outcome of the reaction. Aside from other effects, the nitro group shows more affinity for the hardest metal.

Experimental Section

General. Commercially available compounds were used as purchased without further purification. $LiClO_4$ (ACS reagent) was used as received (CAUTION: perchlorates are potentially explosive materials. Under the experimental conditions described below, this compound can be used safely). All solvents were dried and distilled according to standard protocols.[29] Nitroalkenes **2a**−**c** were prepared following reported procedures.[30](*S*)-2-(Benzyloxy)propanal was prepared as previously reported.[31] Melting points are uncorrected. Chemical shifts in the ^{1}H NMR and ^{13}C NMR spectra are reported as δ values (ppm) with respect to TMS and deuterated chloroform. Flash chromatography purifications were performed using silica gel 70−230 mesh and AcOEt/hexanes mixtures varying from 1:10 to 1:20. The organic layers were dried with Na_2SO_4 prior evaporation of the solvent under reduced pressure.

SCF-MO Calculations. All semiempirical calculations were performed by means of the PM3 Hamiltonian.[21a] The parameters for lithium developed by Anders et al.[21b] were used. All transition structures were located using the eigenvector-following algorithm[32] as implemented in MOPAC.[22] All saddle points were characterized by harmonic analysis[33] and showed only one imaginary frequency in their diagonalized Hessian matrixes, associated with nuclear motion along the reaction coordinate under study. Thermodynamic quantities were computed using the standard rigid rotor harmonic oscillator approximation.[34] The reported stationary points were refined until their gradient norm was below 0.25 kcal/mol/Å, deg, mol. In addition, the SCF convergence criteria were incremented 100 times, as suggested by Boyd et al.[35]

Ab initio computations were performed using the GAUSSIAN 94 series of programs.[36] For other elements than silver the 6-31+G* basis set[37] was used. Calculations involving silver cation were performed using the relativistic compact effective potential developed by Stevens, Krauss, Basch, and Jasien,[28] and denoted as SKBJ. Electron correlation was partially taken into account using the second-order Møller−Plesset approximation, keeping the core electrons frozen.[38] This level is denoted as MP2(FC). Zero point vibrational energy (ZPVE) corrections were scaled by 0.96.[39]

Molecular Mechanics Computations. The minimum energy conformation of compound **8** was computed using the

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(29) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1993.

(30) Bourguinon, J.; LeNard, G.; Gueguiner, G. *Can. J. Chem.* **1985**, *63*, 2354.

(31) Zemribo, R.; Romo, D. *Tetrahedron Lett.* **1995**, *36*, 4159.

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(34) Dewar, M. J. S.; Ford, G. P. *J. Am. Chem. Soc.* **1977**, *99*, 7822.

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(37) (a) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P.v. R. *J. Comput. Chem.* **1983**, *4*, 294. (b) Frisch, M. J.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys.* **1994**, *80*, 3265.

(38) (a) Binkley, J. S.; Pople, J. A. *Int. J. Quantum. Chem.* **1975**, *9*, 229. (b) Pople, J. A.; Binkley, J. S.; Seeger, R. *Int. J. Quantum Chem. Symp.* **1976**, *10*, 1.

MM2* force field[40] as implemented in the Macromodel 5.0 suite of programs.[41] The different possible diastereomers were optimized and then Monte Carlo[42] simulations were performed on 1000 structures. The theoretical coupling constants included in Scheme 5 were performed on the more stable conformations using the Altona method.[43]

General Procedure for the Preparation of the Imines 1a−g. To a solution of the corresponding amino acid methyl ester chlorhydrate (23 mmol) in CH_2Cl_2 (35 mL) were added $MgSO_4$ and of NEt_3 (3.5 mL, 25 mmol) at room temperature. The resulting mixture was stirred at the same temperature for 1 h. Then the aldehyde was added, and the resulting mixture was stirred for 16 h (except in the case of the imine **1f** which only needed 7 h). Then the $MgSO_4$ was filtered out and the organic layer washed with water (2 × 25 mL), dried, and evaporated. The imines showed satisfactory ^{1}H NMR spectra and were used in subsequent reactions immediately without further purification.

Synthesis of (*E*)−(3*S*)-3-(Benzyloxy)-1-nitro-1-butene (2d). A mixture of (*S*)-2-(benzyloxy)propanal (1.64 g, 10 mmol), nitromethane (2.7 mL, 50 mmol), and NEt_3 (0.2 mL) was stirred at room temperature for 3 h. The excess of nitromethane was removed by evaporation under reduced pressure. The nitroaldol thus obtained as a mixture of diastereomers was dissolved in CH_2Cl_2 (20 mL) and cooled to −70 °C. MsCl (0.9 mL, 12 mmol) was added dropwise followed by a solution of *N*,*N*-diisopropylethylamine (4.25 mL, 25 mmol) in CH_2Cl_2 (5 mL), keeping the reaction mixture below −60 °C. The mixture was stirred at −70 °C for 2.5 h and then allowed to reach room temperature. The solution was washed with water (5 mL), HCl 1 N (4 × 5 mL), and brine (5 mL), dried, and evaporated. The product was purified by flash column chromatography, yielding 75% of a pale yellow oil: bp 92−94 °C (0.04 mmHg); IR (film) 1523, 1351 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 7.19−7.17 (m, 2H), 4.61, (s, 2H), 4.32 (qd, 1H, J = 6.6 Hz, J' = 3.3 Hz), 1.39 (d, 3H, J = 6.6 Hz); ^{13}C NMR (δ ppm, $CDCl_3$) 142.8, 139.3, 137.3, 128.4, 127.8, 127.4, 70.9, 19.9; $[\alpha]^{25}_D$ = −39.11 (c = 1.23, CH_2Cl_2).

General Procedure for the Reaction of the Imines 1 and the Nitroalkenes 2. Method A. As a typical example the reaction between imine **1a** and nitroalkene **2a** is described below: The imine **1a** (0.89 g, 5 mmol) was solved in CH_3CN (50 mL), and then NEt_3 (0.7 mL, 5 mmol), the nitroalkene **2a** (0.92 g, 5 mmol), and AgOAc (0.13 g, 0.75 mmol) were added. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered through a Celite pad and washed with NH_4Cl saturated water solution (2 × 10 mL) and water (2 × 10 mL). After drying, the solution was evaporated, and the crude mixture separated by flash chromatography to give both *endo* and *exo* isomers which were crystallized separately in EtOH.

Method B. As a typical example the reaction between imine **1c** and nitroalkene **2b** is described below: The imine **1c** (0.97 g, 5 mmol) was solved in CH_3CN (25 mL), and then NEt_3 (1.4 mL, 10 mmol), the nitroalkene **2b** (0.90 g, 5 mmol), and $LiClO_4$ (2.66 g, 25 mmol) were added. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was washed with NH_4Cl-saturated water solution (2 × 10 mL) and water (4 × 5 mL). The residue was dried and evaporated. The crude mixture was triturated in Et_2O to give a white powder as a mixture of *endo* and *exo* isomers of **4d** which were separated by fractional crystallization in EtOH.

The other reactions were performed according to the procedures described above. The reaction conditions as well as the results are listed in Table 1.

(2*S,3*R**,4*S**,5*S**)-3-(4-Chlorophenyl)-2-(methoxycarbonyl)-4-nitro-5-phenylpyrrolidine (4a-*endo* isomer)**: mp 113−115 °C; IR 3360, 1733, 1547, 1362 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 7.38−7.18 (m, 9H), 5.23 (dd 1H, J = 6.6 Hz, J' = 3.9 Hz), 4.88 (t_b, 1H), 4.18 (dd, 1H, J = 7.6 Hz, J' = 3.9 Hz), 4.08 (t_b, 1H), 3.79 (s, 3H), 3.29 (t_b, 1H); ^{13}C NMR (δ ppm, $CDCl_3$) 171.4, 136.8, 134.3, 134.0, 129.4, 128.9, 128.8, 128.7, 126.4, 96.7, 67.5, 67.2, 54.4, 52.7. Anal. Calcd for $C_{18}H_{17}O_4N_2Cl$: C, 59.91; H, 4.76; N, 7.77. Found: C, 60.83; H, 4.86; N, 7.02.

(2*S,3*S**,4*R**, 5*S**)-3-(4-Chlorophenyl)-2-(methoxycarbonyl)-4-nitro-5-phenylpyrrolidine (4a-*exo* isomer)**: mp 115−117 °C; IR 3358, 1734, 1548, 1379 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 5.10 (t, 1H, J = 7.7 Hz), 4.74 (t, 1H, J = 7.7 Hz), 4.49 (dd, 1H, J = 8.8 Hz, J' = 5.4 Hz), 4.32 (dd, 1H, J = 8.8 Hz, J' = 7.7 Hz), 3.34 (s, 3H), 2.70 (t_b, 1H); ^{13}C NMR (δ ppm, $CDCl_3$) 171.5, 137.5, 134.7, 134.0, 129.2, 129.0, 128.9, 126.8, 95.1, 67.2, 64.0, 52.7, 51.9. Anal. Calcd for $C_{18}H_{17}O_4N_2Cl$: C, 59.91; H, 4.76; N, 7.77. Found: C, 56.79; H, 5.03; N, 7.12.

(2*S,3*R**,4*S**,5*S**)-2-(Methoxycarbonyl-3-(4-methoxyphenyl)-4-nitro-5-phenylpyrrolidine (4b-*endo* isomer)**: mp 99−100 °C; IR 3362, 1739, 1533, 1364 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 5.23 (dd 1H, J = 4.4 Hz, J' = 2.3 Hz), 4.89 (s_b, 1H), 4.17−4.08 (m 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.34 (s_b, 1H); ^{13}C NMR(δ ppm, $CDCl_3$) 171.8, 159.2, 134.4, 130.4, 128.6, 128.5, 126.4, 114.5, 97.1, 67.5, 67.4, 55.2, 54.7, 52.6. Anal. Calcd for $C_{19}H_{20}O_5N_2$: C, 64.02; H, 5.67; N, 7.86. Found: C, 63.91; H, 5.48; N, 7.92.

(2*S,3*S**,4*R**,5*S**)-3-(4-Methoxyphenyl)-2-(methoxycarbonyl)-4-nitro-5-phenylpyrrolidine (4b-*exo* isomer)**: mp 140−142 °C; IR 3328, 1730, 1542, 1359 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 5.16 (t, 1H J = 8.0 Hz), 4.74 (d_b 1H J = 7.9 Hz), 4.46 (d, 1H, J = 9.0 Hz), 4.32 t, 1H, J = 8.0 Hz), 3.77 (s, 3H), 3.34 (s, 3H), 2.72 (s_b, 1H); ^{13}C NMR (δ ppm, $CDCl_3$) 172.0, 159.3, 137.7, 129.1, 129.0, 128.7, 127.7, 126.8, 114.1, 95.3, 67.4, 64.2, 55.2, 53.2, 51.9. Anal. Calcd for $C_{19}H_{20}O_5N_2$: C, 64.02; H, 5.67; N, 7.86. Found: C, 64.96; H, 5.75; N, 7.98.

(2*S,3*S**,4*R**,5*S**)-3-(4-Chlorophenyl)-5-(2-hydroxyphenyl)-2-(methoxycarbonyl)-4-nitropyrrolidine (4c-*exo* isomer)**: mp 177−179 °C; IR 3270, 1737, 1545, 1355 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 10.07 (s_b, 1H), 5.45 (t, 1H, J = 9.3 Hz), 4.93 (d_b, 1H, J = 9.0 Hz), 4.56 (d_b, 1H, J = 10.4 Hz), 4.41 (t, 1H, J = 10.1 Hz, 3.29 (s, 3H), 3.00 (s_b, 1H); ^{13}C NMR (δ ppm, $CDCl_3$) 171.6, 156.8, 134.6, 132.3, 130.7, 129.4, 129.1, 129.0, 119.8, 119.7, 118.0, 90.6, 66.6, 61.9, 52.3, 51.6. Anal. Calcd for $C_{18}H_{17}N_2O_5Cl$: C,57.34; H, 4.56; N, 7.44. Found: C, 56.98; H, 4.67; N, 7.39.

(2*S,3*S**,4*R**,5*S**)-5-(2-Hydroxyphenyl)-2-(methoxycarbonyl)-3-(4-methoxyphenyl)-4-nitropyrrolidine (4d-*exo* isomer)**: mp 210 °C (dec); IR 2902, 1722, 1545, 1350 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 10.18 (s_b, 1H), 5.48 (t, 1H, J = 9.3 Hz), 4.93 (d, 1H, J = 9.2 Hz), 4.53 (d, 1H, J = 10.5 Hz), 4.40 (t, 1H, J = 10.2 Hz), 3.77 (s, 3H), 3.31 (s, 3H), 2.97 (s_b, 1H); ^{13}C NMR (δ ppm, $CDCl_3$) 171.9, 159.6, 156.9, 130.6, 129.2, 125.4, 128.9, 119.8, 119.7, 118.0, 90.9, 66.7, 62.1, 55.3, 52.2, 51.8. Anal. Calcd for $C_{19}H_2N_2O_6$: C, 61.27; H, 5.42; N, 7.52. Found: C, 61.96; H, 5.39; N, 7.57.

(2*S,3*R**,4*S**,5*S**)-5-(2-Hydroxyphenyl)-2-methyl-2-(methoxycarbonyl)-3-(4-methoxyphenyl)-4-nitropyrrolidine (4e-*endo* isomer)**: mp 161−163 °C; IR 3312, 1728, 1512, 1342 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 10.63 (s_b 1H), 5.36 (t, 1H, J = 8.8 Hz), 4.82 (d_b, 1H, J = 8.8 Hz), 4.32 (d, 1H, J = 8.8 Hz), 3.91 (s, 3H), 3.80 (s, 3H), 3.77 (s_b, 1H), 1.09 (s, 3H); ^{13}C NMR (δ ppm, $CDCl_3$) 176.0, 159.6, 157.1, 130.3, 130.1, 128.9, 126.6, 119.9, 117.6, 114.3, 93.9, 67.1, 65.7, 55.2, 54.4, 53.5, 24.3. Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.16; H, 5.75; N, 7.25. Found: C, 63.05; H, 5.82; N, 7.19.

(2*S,3*S**,4*R**, 5*S**)-5-(2-Hydroxyphenyl)-2-(methoxycarbonyl)-2-methyl-3-(4-methoxyphenyl)-4-nitropyrrolidine(4e-*exo* isomer)**: mp 164−166 °C; IR 3340, 1723, 1553, 1368 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 10.23 (s_b, 1H), 5.63 (dd, 1H, J = 11.2 Hz, J' = 9.4 Hz), 5.00 (dd, 1H, J = 9.4 Hz, J' = 5.3 Hz), 3.92 (d, 1H, J = 11.2 Hz), 3.76 (s, 3H), 3.35 (s,

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3H), 2.44 (d_b, 1H), 1.76 (s, 3H); ^{13}C NMR (δ ppm, $CDCl_3$) 173.6, 159.8, 157.0, 130.4, 128.9, 90.4, 67.9, 65.3, 59.9, 55.2, 52.5, 25.1. Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.16; H, 5.75; N, 7.25. Found: C, 62.45; H, 5.70; N, 7.30.

(2*S,3*S**,4*R**,5*S**)-5-(2-Hydroxyphenyl)-2-(methoxycarbonyl)-4-methyl-3-(4-methoxyphenyl)-4-nitropyrrolidine (4f-*endo* isomer)**: mp 178−180 °C; IR 3350, 1732, 1529, 1386 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 11.05 (s_b 1H), 5.41 (d, 1H, J = 6.2 Hz), 4.82 (dd, 1H, J = 10.8 Hz, J' = 3.8 Hz), 3.77 (s, 3H), 3.64 (s, 3H), 3.59 (s, 1H), 3.27 (s_b, 1H), 1.28 (s, 3H); ^{13}C NMR (δ ppm, $CDCl_3$) 171.7, 160.0, 157.9, 130.2, 129.6, 129.3, 123.2, 121.4, 119.7, 118.2, 114.3, 99.4, 70.0, 61.3, 59.7, 55.2, 52.7, 20.6. Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.16;H, 5.75; N, 7.25. Found: C, 61.85; H, 5.68; N, 7.31.

(2*S,3*S**,4*R**,5*S**)-5-(2-Hydroxyphenyl)-2-(methoxycarbonyl)-4-methyl-3-(4-methoxyphenyl)-4-nitropyrrolidine (4f-*exo* isomer)**: mp 181−183 °C; IR 3348, 1735, 1530, 1387 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 10.69 (s_b 1H), 5.21 (d, 1H, J = 4.4 Hz), 4.62 (dd, 1H, J = 9.9 Hz, J' = 4.4 Hz), 4.55 (d, 1H, J = 9.9 Hz), 3.78 (s, 3H), 3.49 (s, 3H), 3.10 (s_b 1H), 1.22 (s, 3H); ^{13}C NMR (δ ppm, $CDCl_3$) 171.4, 159.4, 158.0, 130.7, 130.2, 129.3, 125.9, 118.7, 117.6, 113.9, 98.2, 70.6, 61.9, 55.2, 55.0, 52.2, 18.0. Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.16;H, 5.75; N, 7.25. Found: C, 61.40; H, 5.82; N, 7.14.

(2*S,3*R**,4*S**,5*S**)-2,4-Dimethyl-5-(2-hydroxyphenyl)-2-(methoxycarbonyl)-3-(4-methoxyphenyl)-4-nitropyrrolidine (4g-*endo* isomer)**: mp 123−125 °C; IR 3278, 1726, 1588, 1377 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 11.08 (s_b, 1H), 5.22 (d_b, 1H, J = 5.9 Hz), 4.54 (s, 1H), 3.91 (d_b, 1H, J = 5.9 Hz), 3.82 (s, 3H), 3.80, (s, 3H), 1.36 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (δ ppm, $CDCl_3$) 176.4, 159.4, 158.1, 132.6, 129.9, 129.2, 125.6, 119.7, 118.7, 117.4, 113.8, 99.5, 69.5, 66.9, 58.7, 55.2, 53.4, 24.2, 18.8. Anal. Calcd for $C_{21}H_{24}N_2O_6$: C, 62.98; H, 6.05; N, 7.00. Found: C, 63.47; H, 6.02; N, 6.91.

(2*S,3*S**,4*R**,5*S**)-2,4-Dimethyl-5-(2-hydroxyphenyl)-2-(methoxycarbonyl)-3-(4-methoxyphenyl)-4-nitropyrrolidine (4g-*exo* isomer)**: mp 179−180 °C; IR 3316, 1716, 1534, 1375 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 11.10 (s_b, 1H), 5.38 (s_b, 1H), 4.27 (s, 1H), 3.78 (s, 3H), 3.54 (s, 3H), 2.53 (s_b, 1H), 1.75 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (δ ppm, $CDCl_3$) 174.2, 159.7, 158.4, 131.3, 130.2, 129.2, 124.5, 119.4, 117.7, 114.1, 113.8, 98.6, 69.0, 67.0, 63.7, 55.2, 52.5, 27.3, 16.2. Anal. Calcd for $C_{21}H_{24}N_2O_6$: C, 62.98; H, 6.05; N, 7.00. Found: C, 61.35; H, 6.13; N, 6.89.

(2*S,3*S**,4*R**,5*S**)-3-(4-Methoxyphenyl)-5-(2-methoxyphenyl)-4-nitropyrrolidine (4i-*exo* isomer)**: mp 94−97 °C; IR 3326, 1733, 1548, 1354 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 5.21 (dd, 1H, J = 7.6 Hz, J' = 6.2 Hz), 4.93 (d_b, 1H, J = 7.6 Hz), 4.53 (d_b, 1H, J = 8.7 Hz), 4.17 (dd, 1H, J = 8.7 Hz, J' = 6.2 Hz), 3.84 (s, 3H), 3.76 (s, 3H), 3.32 (s, 3H), 3.30 (s_b, 1H); ^{13}C NMR (δ ppm, $CDCl_3$) 171.2, 159.2, 157.2, 129.8, 129.2, 128.6, 128.4, 125.1, 121.0, 113.9, 110.7, 95.3, 64.5, 55.2, 54.3, 51.7. Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.16; H, 5.75; N, 7.25. Found: C, 61.89; H, 5.70; N, 7.36.

(2*S,3*R**,4*S**,5*S**)-2-(Methoxycarbonyl)-3-(4-methoxyphenyl)-5-(2-methoxyphenyl)-2-methyl-4-nitropyrrolidine (4j-*endo* isomer)**: mp 122−123 °C; IR 3342, 1724, 1541, 1372 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 5.25 (d_b, 1H, J = 6.8 Hz), 4.96 (dd, 1H, J = 6.8 Hz, J' = 4.5 Hz), 4.17 (d, 1H, J = 4.5 Hz), 3.86 (s, 3H), 3.77 (s, 3H), 3.70 (s, 3H), 2.94 (s_b, 1H), 1.01 (s, 3H); ^{13}C NMR (δ ppm, $CDCl_3$) 176.9, 159.0, 157.0, 130.0, 128.9, 127.8, 126.4, 120.6, 113.8, 110.2, 97.0, 68.6, 60.1, 56.8, 55.2, 54.7, 52.9, 23.2. Anal. Calcd for $C_{21}H_{24}N_2O_6$: C, 62.98; H, 6.05; N, 7.00. Found: C, 62.19; H, 5.89; N, 7.56.

(2*S,3*R**,4*S**,5*S**)-2,4-Dimethyl-2-(methoxycarbonyl)-3-(4-methoxyphenyl)-5-(2-methoxyphenyl)-4-nitropyrrolidine (4k-*endo* isomer)**: mp 132−133 °C; IR 3332, 1731, 1510, 1348 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 5.48 (s_b 1H), 4.17 (s, 1H), 3.85 (s, 3H), 3.63 (s, 3H), 2.89 (s_b, 1H), 1.18 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (δ ppm, $CDCl_3$) 177.7, 158.9, 156.9, 132.6, 128.6, 128.0, 127.1, 126.7, 120.4, 113.2, 109.6, 98.3, 67.7, 63.4, 61.5, 55.1, 54.7, 52.7, 23.7, 20.6. Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.74; H, 6.34; N, 6.76. Found: C, 63.93; H, 6.52; N, 6.98.

(2*S,3*S**,4*R**,5*S**)-2,4-Dimethyl-2-(methoxycarbonyl)-3-(4-methoxyphenyl)-5-(2-methoxyphenyl)-4-nitropyrrolidine (4k-*exo* isomer)**: mp 160−162 °C; IR 3344, 1725, 1536, 1334 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 5.51 (s, 1H), 4.50 (s, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.50 (s, 3H), 2.75 (s_b, 1H), 1.72 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (δ ppm, $CDCl_3$) 175.9, 159.1, 157.3, 131.7, 129.3, 127.4, 125.0, 120.6, 113.6, 110.2, 103.0, 69.6, 66.3, 63.6, 55.2, 51.9, 25.9, 21.6. Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.74; H, 6.34; N, 6.76. Found: C, 63.95; H, 6.16; N, 6.88.

(2*S,3*R**,4*S**,5*S**)-3-(4-Chlorophenyl)-2-(methoxycarbonyl)-4-nitro-5-(2-pyridyl)pyrrolidine (4l-*endo* isomer)**: mp 144−147 °C; IR 3277, 1742, 1548, 1362 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 5.38 (dd, 1H, J = 6.7 Hz, J' = 4.5 Hz), 4.96 (t_b, 1H), 4.23 (dd, 1H, J = 7.4 Hz, J' = 4.5 Hz), 4.10 (t_b, 1H), 3.92 (t_b, 1H), 3.79 (s, 3H); ^{13}C NMR (δ ppm, $CDCl_3$) 171.4, 154.2, 149.4, 136.8, 134.0, 129.4, 128.9, 123.4, 122.0, 95.9, 67.9, 67.6, 54.5, 52.6. Anal. Calcd for $C_{17}H_{16}N_3O_4Cl$: C, 56.43; H, 4.47; N, 11.62. Found: C, 57.25; H, 4.52; N, 11.41.

(2*S,3*R**,4*S**,5*S**)-3-(4-Chlorophenyl)-2-(methoxycarbonyl)-4-nitro-5-(2-pyridyl)pyrrolidine (4l-*exo* isomer)**: mp 154−156 °C; IR 3290, 1741, 1549, 1364 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 8.70 (d_b, 1H), 5.32 (dd, 1H, J = 7.2 Hz, J' = 6.1 Hz), 4.72 (s_b, 1H), 4.52 (s_b, 1H), 4.38 (dd, 1H, J = 8.7 Hz, J' = 6.1 Hz), 3.82 (s_b, 1H), 3.33 (s, 3H); ^{13}C NMR (δ ppm, $CDCl_3$) 170.2, 155.4, 150.0, 137.2, 135.4, 134.0, 129.6, 128.8, 124.0, 123.2, 95.8, 69.2, 65.6, 54.2, 52.0. Anal. Calcd for $C_{17}H_{16}N_3O_4$-Cl: C, 56.43; H, 4.47; N, 11.62. Found: C, 56.98; H, 4.39; N, 11.28.

(2*S,3*R**,4*S**,5*S**)-2-(Methoxycarbonyl)-3-(4-methoxyphenyl)-4-nitro-5-(2-pyridyl)pyrrolidine (4m-*exo*- isomer)**: mp 112−114 °C; IR 3290, 1742, 1550, 1368 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 5.32 (t, 1H, J = 6.5 Hz), 4.72 (d, 1H, J = 7.5 Hz), 4.50 (d, 1H, J = 8.7 Hz), 4.37 (dd, 1H, J = 8.7 Hz, J' = 6.5 Hz), 3.77 (s, 3H), 3.73 (s_b, 1H), 3.32 (s, 3H); ^{13}C NMR (δ ppm, $CDCl_3$) 170.6, 159.2, 155.6, 150.0, 137.1, 129.3, 128.6, 123.8, 123.1, 114.0, 96.0, 69.1, 65.6, 55.2, 54.4, 51.9. Anal. Calcd for $C_{18}H_{19}N_3O_5$: C, 60.49; H, 5.37; N, 11.76. Found: C, 60.05; H, 5.29; N, 11.95.

(2*S,3*R**,4*S**,5*S**)-3-(4-Chlorophenyl)-5-(4-hydroxy-3-methoxyphenyl)-2-(methoxycarbonyl)-4-nitropyrrolidine (4n-*exo* isomer)**: mp 167−169 °C; IR 3310, 1726, 1549, 1363 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 5.71 (s_b, 1H), 5.09 (t, 1H, J = 7.8 Hz), 4.67 (t, 1H, J = 7.3 Hz), 4.46 (dd, 1H, J = 5.2 Hz, J' = 9.1 Hz), 4.33 (t, 1H, J = 8.3 Hz), 3.91 (s, 3H), 3.34 (s, 3H), 2.64 (t_b, 1H); ^{13}C NMR (δ ppm, $CDCl_3$) 171.9, 147.0, 146.2, 134.3, 134.1, 129.4, 129.2, 129.0, 119.7, 114.8, 109.3, 94.8, 67.4, 63.8, 55.9, 52.7, 52.0. Anal. Calcd for $C_{19}H_{19}N_2O_6Cl$: C, 56.09; H, 4.72; N, 6.89. Found: C, 55.82; H, 4.57; N, 6.71.

(2*S,3*R**,4*S**,5*S**)-5-(4-Hydroxy-3-methoxyphenyl)-2-(methoxycarbonyl)-3-(4-methoxyphenyl)-4-nitropyrrolidine (4o-*exo* isomer)**: mp 163−164 °C; IR 3312, 1725, 1547, 1364 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 5.71 (s_b, 1H), 5.15 (t, 1H, J = 8.2 Hz), 4.67 (d_b, 1H), 4.43 (d, 1H, J = 9.0 Hz), 4.32 (t, 1H, J = 8.8 Hz), 3.92 (s, 3H), 3.77 (s, 3H), 3.33 (s, 3H), 2.63 (s_b, 1H); ^{13}C NMR (δ ppm, $CDCl_3$) 172.4, 159.4, 147.0, 146.1, 129.6, 128.9, 127.3, 119.7, 114.8, 114.1, 109.4, 95.0, 67.5, 64.0, 55.9, 55.2, 53.1, 51.9. Anal. Calcd for $C_{20}H_{22}N_2O_7$: C, 59.69; H, 5.52; N, 6.96. Found: C, 59.22; H, 5.39; N, 6.96.

(2*S*,3*R*,4*S*,5*S*)-3-(1(*S*)-Benzyloxyethyl)-2-(methoxycarbonyl)-4-nitro-5-phenylpyrrolidine (4p-*endo* isomer): mp 106−108 °C; IR 3309, 1736, 1545, 1378 cm^{-1}; ^{1}H NMR (δ ppm, $CDCl_3$) 5.39 (dd, 1H, J = 6.0 Hz, J' = 2.6 Hz), 4.72 (d, 1H, J = 11.6 Hz), 4.54 (t_b, 1H), 4.43, (d, 1H, J = 11.6 Hz), 3.96 (t_b, 1H), 3.88 (dd, 1H, J = 6.2 Hz, J' = 2.7 Hz), 3.81 (s, 3H), 3.32 (t_b, 1H), 2.92 (dt, 1H, J = 7.5 Hz, J'=2.7 Hz), 1.35 (d, 3H, J = 6.3 Hz); ^{13}C NMR (δ ppm, $CDCl_3$) 172.0, 137.7, 134.3, 128.6, 128.4, 128.3, 127.9, 126.2, 91.3, 73.2, 70.9, 67.9, 62.5, 57.7, 52.6, 18.2. Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.60; H, 6.30; N, 7.29. Found: C, 66.33; H, 6.52; N, 7.13.

Isolation and Characterization of Compound 8. Reaction between **1b** and **2c** was performed in the presence of 0.15 equiv of $LiClO_4$ and following the general procedure. After 16 h of reaction at room temperature, a mixture of cyloadducts **4f** and imines **7** was obtained. Purification of the crude reaction mixture by flash chromatography gave compounds **7**

as a syrup. To a solution of **7** (0.300 g, 0.8 mmol) in THF (2.4 mL) was added 2 N HCl (0.24 mL), and the resulting mixture was stirred for 2 h at rt. Usual basic workup and evaporation of the solvent gave a residue which was diluted with CH_2Cl_2 (2 mL). To the resulting solution triethylamine (0.06 mL, 0.43 mmol) and 4-bromobenzoyl chloride (0.114 g, 0.52 mmol) were added, and the resulting mixture was stirred at rt for 7 h. Usual workup gave a solid residue which was purified by flash chromatography and crystallization in AcOEt/hexane. Yield: 6%; mp = 161−163 °C; IR: 3380, 173, 1674, 1549 cm^{-1}. ^1H NMR (δ ppm, $CDCl_3$): 6.42 (db, J = 8.2 Hz); 5.21 (dd, J = 3 Hz, J' = 8.2 Hz, 1H); 5.02 (dq, 1H, J = 6.8 Hz, J' = 11 Hz); 4.07 (dd, 1H, J = 3 Hz, J' = 11 Hz); 3.80 (s, 3H); 3.77 (s, 3H); 1.38 (d, 3H, J = 6.8 Hz). ^{13}C NMR (δ ppm, $CDCl_3$): 170.7, 166.5, 159.6, 131.3, 129.7, 128.7, 125.5, 114.6, 113.9, 82.9, 55.2, 53.5, 52.9, 50.6, 19.4. Anal. Calcd for $C_{20}H_{21}N_2O_6Br$: C, 51.62; H, 4.56; N, 6.02. Found: C, 52.45; H, 4.54; N, 5.92.

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Supporting Information Available: Table reporting the main coupling constants in cycloadducts *endo*- and *exo*-**4**. ^1H NMR data of imines **1a**−**g**. Complete characterization data and experimental procedures for compounds **4h** and **5a,b**. *ORTEP* plots of the structures of compounds *exo*-**4c** and *exo*-**4f**. Cartesian coordinates of all the stationary points mentioned in this work (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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