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An Amine-Catalyzed Enantioselective [3+2] Cycloaddition of Azomethine Ylides and α,β-Unsaturated Aldehydes: Applications and Mechanistic Implications

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Abstract: The catalytic enantioselective [3+2] cycloaddition between azomethine ylides and α,β-unsaturated aldehydes catalyzed by α,α-diphenylprolinol has been studied in detail. In particular, the reaction has been extended to the use of 2-alkenylidene aminomalonates generated in situ as azomethine ylide precursors. These reactions lead to the formation of pyrrolidines containing a 5-alkenyl side chain with potential for chemical manipulation. Moreover, a detailed and concise computational study has been carried out to understand the exact nature of the mechanism of this reaction and especially the consequences derived from the incorporation of the chiral secondary amine catalyst on the reaction pathway.

Keywords: asymmetric catalysis · cycloaddition · organocatalysis · pyrrolidines · reaction mechanisms

Introduction

1,3-Dipolar cycloaddition reactions constitute highly powerful methodologies for the fast assembly of five-membered heterocyclic structures from simple and readily available starting materials.[1] The rich reactivity profile of this transformation and the availability of many structurally different 1,3-dipoles and dipolarophiles amenable to participation in this reaction open the way for the application of this methodology to the preparation of a wide number of families of different heterocyclic architectures. Moreover, the stereospecificity associated with pericyclic processes makes 1,3-dipolar cycloaddition reactions to be very appropriate candidates for developing stereocontrolled variants that would eventually lead to the formation of the final heterocyclic compounds as single stereoisomers. In this context, enantioselective catalysis is a highly efficient approach to achieve the desired stereocontrol.

In particular, catalytic enantioselective [3+2] cycloaddition that uses azomethine ylides as 1,3-dipoles comprises an especially interesting transformation that has attracted the attention of many different research groups worldwide because it is an extremely easy and direct method for the stereoselective preparation of polysubstituted pyrrolidine compounds.[2] A great deal of the relevance gained by this reaction lies in the fact that the pyrrolidine skeleton constitutes an ubiquitous structural motif, with numerous applications seen throughout the pharmaceutical industry and among natural products. In this context, several catalytic enantioselective versions of this important reaction have been reported, most of them focused on the use of chiral transition-metal complexes as catalysts, which typically participate in the reaction by generating the azomethine ylide through metalation of the corresponding α-imino ester precursor.[2a] On the other hand, asymmetric organocatalysis has also contributed significantly to the field with several important contributions.[3] Related to this topic, a few years ago we developed the first amine-catalyzed enantioselective [3+2] cycloaddition reaction by using azomethine ylides as 1,3-dipoles, in which imines derived from diethyl aminomalonate were treated with α,β-unsaturated aldehydes and the cheap and commercially available α,α-diphenyl prolinol was used as the catalyst.[4a]

A commonly reported feature that was shared by all these methodologies, which either used metal catalysis or organocatalysis, is that the scope of the reaction, although very wide in regard to substitution at the dipolarophile, is rather limited with respect to the substituents that can be placed at the dipole. In particular, with the exception of a couple of recent examples,[3b,5] only α-imino esters derived from non-enolizable aldehydes can be normally used as suitable pre-

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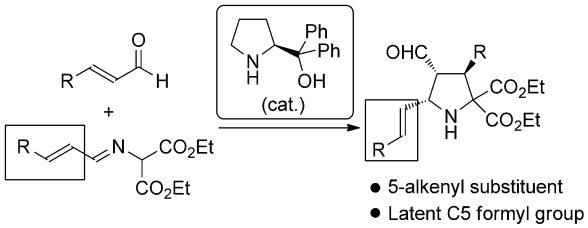
cursors of the azomethine ylide, which restricts the substituent at this position of the dipole to aryl or alkyl groups in which access to the α-hydrogen atom is sterically hindered (e.g., cyclohexyl or isopropyl groups). Among these previous reports, only a couple of examples in which a chemically modifiable substituent that has the potential for further manipulation has been introduced at this position, thus enabling a wider application of the methodology.[3b,5,6]

On the other hand, from a mechanistic point of view, [3+2] cycloaddition reactions in general, and especially those that involve azomethine ylides as 1,3-dipoles, have very often been the subject of controversy, in particular regarding the degree of concertedness of the process or the possibility that the reaction is more likely to proceed through a stepwise pathway rather than being strictly pericyclic in some cases.[7] In this context, previous computational studies that focused on the mechanism of [3+2] cycloaddition reactions under Lewis acid catalysis with *N*-unsubstituted azomethine ylides closely related to those employed in this study demonstrated that the stepwise or concerted nature of the reaction depends strongly on the structure and the nature of the substituents on the two reagents involved in the reaction.[8] However, with respect to the corresponding organocatalytic versions, the exact mechanistic nature of the reaction and the influence that the incorporation of the catalyst can exert on the mechanistic profile of the transformation have not yet been covered.

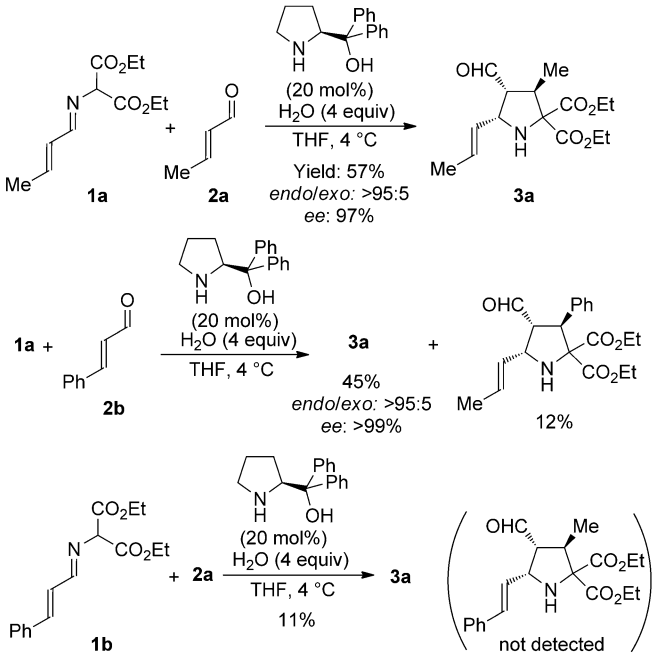
Herein, we present a detailed study directed on one hand toward the expansion of the scope of our previously reported amine-catalyzed [3+2] cycloaddition reaction between azomethine ylides and α,β-unsaturated aldehydes (Scheme 1). In particular, we have studied access to pyrrolidines that incorporate a 5-alkenyl substituent that can be easily converted into highly functionalized enantioenriched 5-formyl-substituted pyrrolidines susceptible to further modification. It is important to remark that this type of compound cannot be directly prepared by any of the catalytic enantioselective [3+2] cycloaddition reactions previously reported. In addition, we also present a concise mechanistic study based on DFT calculations that explains the reaction process and also clarifies the crucial role played by the organocatalyst.



Scheme 1. Expanded scope of the amine-catalyzed enantioselective [3+2] cycloaddition with the azomethine ylides presented herein.

Results and Discussion

We started by evaluating the use of the imine derived from acrolein and diethyl aminomalonate as a suitable azomethine ylide precursor. The use of this imine would lead to the formation of a pyrrolidine cycloadduct incorporating a 5-vinyl substituent and would have the potential to be converted into a formyl moiety by means of an oxidative cleavage procedure, for example, through ozonolysis. Disappointingly, all our attempts to prepare this imine were unsuccessful, probably due to its high instability and tendency toward self-condensation. As an alternative, we subsequently evaluated imine **1a** (Scheme 2), which reacted in a satisfactory



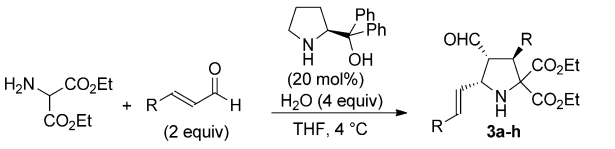
Scheme 2. Attempts to prepare 5-alkenyl-substituted pyrrolidines by a [3+2] cycloaddition reaction from imines **1a** and **1b**.

way with crotonaldehyde (**2a**) in the presence of α,α-diphenylprolinol as a catalyst under our previously reported conditions, furnishing the corresponding cycloadduct **3a** in moderate yield, albeit with excellent diastereo- and enantioselectivity. However, when we tried to extend this reaction to cinnamaldehyde (**2b**), a sluggish reaction took place, and the desired cycloaddition product was obtained in low yield accompanied by a significant amount of pyrrolidine **3a**. This outcome indicates that a dynamic process operates in which imine **1a** undergoes hydrolysis in the reaction medium, thus releasing crotonaldehyde and diethyl aminomalonate and the former participates as a more reactive dipolarophile in a competitive [3+2] cycloaddition reaction with remaining imine **1a**. In fact, the participation of the catalyst in this side process was also confirmed from the fact that the obtained pyrrolidine **3a** was isolated as a single *endo* diastereoisomer with very high enantiomeric excess. We also tested the reac-

tion between **2a** and cinnamaldehyde imine **1b**, with the latter expected to be more stable toward hydrolysis than **1a**, but a complex mixture of products was formed in which again minor amounts of pyrrolidine **3a** were detected in the reaction mixture, whereas the desired cycloaddition product that should arise from the participation of the azomethine ylide derived from **1b** was not observed.

With these results in hand and considering that the incorporation of the 5-alkylidene side chain in the final cycloadducts had been devised as an indirect strategy for the introduction of a formyl group by means of a subsequent oxidative cleavage process, we reasoned that general access to the 4,5-diformyl-substituted pyrrolidines incorporating different substituents at the 3-position could also be possible by carrying out the [3+2] cycloaddition reaction between the starting α,β-unsaturated aldehyde **2** and imine **1** derived from the same aldehyde **2**. In fact, when we mixed two equivalents of crotonaldehyde with one equivalent of diethyl aminomalonate in the presence of 20 mol% of α,α-diphenylprolinol under the optimized reaction conditions, pyrrolidine **3a** was isolated in good yield and as a single *endo* isomer with very high enantiomeric purity (Table 1). Under these conditions, one equivalent of the enal had to be involved in the formation of an imine by condensation with diethyl aminomalonate, which participated as the azomethine ylide precursor by undergoing a subsequent cycloaddition reaction with the remaining equivalent of the same α,β-unsaturated aldehyde reagent, with the latter activated by the catalyst through the formation of an iminium ion. We also tried to carry out the reaction with diethyl aminomalonate as the limiting reagent together with an excess (4 equiv) of α,β-unsaturated aldehyde **2a**, but the reaction proceeded more sluggishly and the isolated yield of **3a** remained essentially the same. After this experiment, we next proceeded to extend the optimized reaction conditions to a series of different α,β-unsaturated aldehydes (Table 1) and observed that the reaction behaved well in all cases, thus furnishing the target 2-alkenyl-substituted pyrrolidines as highly diastereoenriched *endo* isomers with very high *ee* values.

Table 1. Stereoselective synthesis of 5-alkenyl-substituted pyrrolidines.[a]

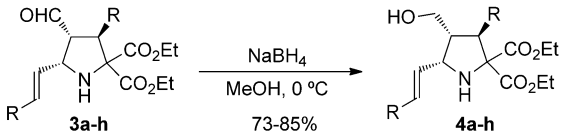


Entry	R	Product	Yield [%][b]	*endo*/*exo*[c]	*ee* [%][d]
1	Me	**3a**	66	>95:5	97
3	Ph	**3b**	90	90:10	90
2	Et	**3c**	59	>95:5	>99
4	*n*Bu	**3d**	63	96:4	92
5	*n*-C_5H_{11}	**3e**	59	92:8	98
6	*n*-C_6H_{13}	**3f**	72	92:8	97
7	*n*Pr	**3g**	56	94:6	93
8	(*E*)-$C_2H_3CH{=}CH_2CH_2$	**3h**	50	92:8	97

[a] All the reactions were performed on a scale of 1.00 mmol in THF (4 mL). [b] Yield of the isolated products after purification by column chromatography. [c] Determined by NMR spectroscopic analysis of the crude reaction mixture. [d] Determined by HPLC after reduction to the corresponding alcohol (see the Supporting Information for details).

Alternatively, we also surveyed the crossed reaction between diethyl aminomalonate and two different α,β-unsaturated aldehydes, but without success. In particular, when we mixed one equivalent of **2a**, another equivalent of **2b**, and diethyl aminomalonate with the catalyst under the typical reaction conditions, a complex mixture of products was formed in which the presence of homo-cycloaddition products **3a** and **3b** were observed by NMR spectroscopic analysis of the crude reaction mixture, but without any evidence of the presence of the desired crossed cycloadduct. Other reactions tested that used different combinations of enals also showed similar behavior.

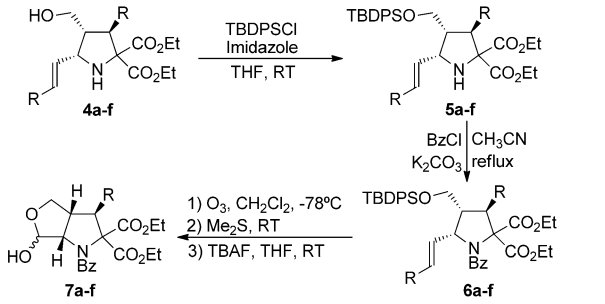
It should be mentioned at this point that cycloadducts **3a**–**h** were somewhat unstable, and therefore these compounds were subsequently reduced under standard conditions (Scheme 3), which would also allow better characterization. Thus, the corresponding alcohols **4a**–**h** were isolated, conveniently characterized, and could be stored for weeks without decomposition.



Scheme 3. Reduction of cycloadducts **3a**–**h**.

We subsequently faced the oxidative cleavage of the alkenyl moiety by ozonolysis to reach to the target 5-formyl-substituted pyrrolidines. However, when we treated **4a** with ozone under standard conditions, a complex mixture of products was formed, which points toward the instability of the starting material under these conditions. For this reason, we protected the primary alcohol and the amine moieties of these derivatives by sequential *O*-silylation and *N*-benzoylation, thus cleanly forming pyrrolidines **6a**–**f** (Table 2). Next, we surveyed the ozonolysis reaction of protected derivative **6a** and isolated the corresponding 5-formyl pyrrolidine in good yield. However, this compound had a pronounced tendency to undergo epimerization at the C5 stereocenter, probably due to the configurational instability typically associated with α-amino aldehyde derivatives. As a result, we decided to deprotect the primary alcohol in situ after the oxidative cleavage process to stabilize the 5-formyl-substituted pyrrolidine as the corresponding hemiacetal derivative. Therefore, after ozonolysis of derivatives **6a**–**f** under the standard conditions, tetrabutylammonium fluoride was added to the reaction mixture, thus leading to the isolation of the corresponding hemiacetals **7a**–**f** in good yield in all the cases tested and without observing epimerization at the

Table 2. Stereoselective synthesis of 5-alkenyl-substituted pyrrolidines.[a]



Entry	R	Product	Yield [%][a]	Product	Yield [%][a]	Product	Yield [%][a]
1	Me	**5a**	83	**6a**	87	**7a**	68
3	Ph	**5b**	92	**6b**	79	**7b**	88
2	Et	**5c**	66	**6c**	87	**7c**	79
4	*n*Bu	**5d**	69	**6d**	97	**7d**	77
5	n-C_5H_{11}	**5e**	72	**6e**	96	**7e**	80
6	n-C_6H_{13}	**5f**	58	**6f**	91	**7f**	88

[a] Yield of the isolated products after purification by column chromatography. TBPDS = *tert*-butyldiphenylsilyl, TBAF = tetrabutylammonium fluoride.

C5 stereocenter (Table 2). These compounds were isolated as mixtures of α and β anomers.

We also surveyed the possibility of the selective chemical modification of the functionalities contained in compounds **7** (Scheme 4). For example, access to the tetrahydro-1*H*-furo[3,4-*b*]pyrrol-6(6a*H*)-one structure could be easily achieved by PCC-mediated oxidation of **7a–f**, thus leading to the formation of derivatives **8a–f** in good yields in all cases. Alternatively, a series of different bicyclic hexahydro-1*H*-furo-[3,4-*b*]pyrroles could also be cleanly obtained from the same type of precursor **7** by a $Et_3SiH/BF_3{\cdot}OEt_2$-promoted reduction of the hemiacetal moiety, which was tested on adducts **7b** and **7d** as representative substrates.

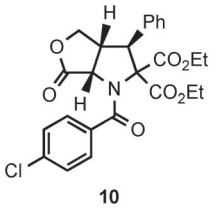
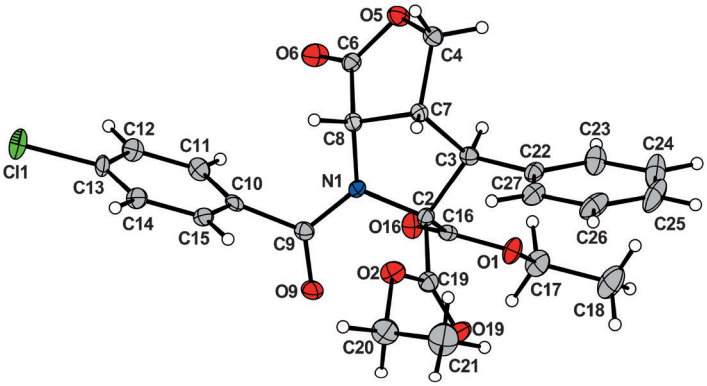
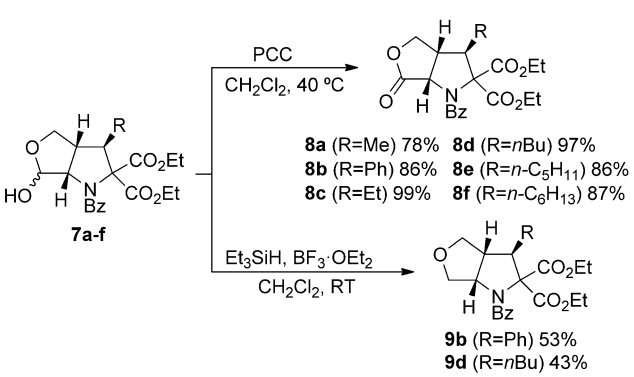


Figure 1. X-ray structure of **10**.



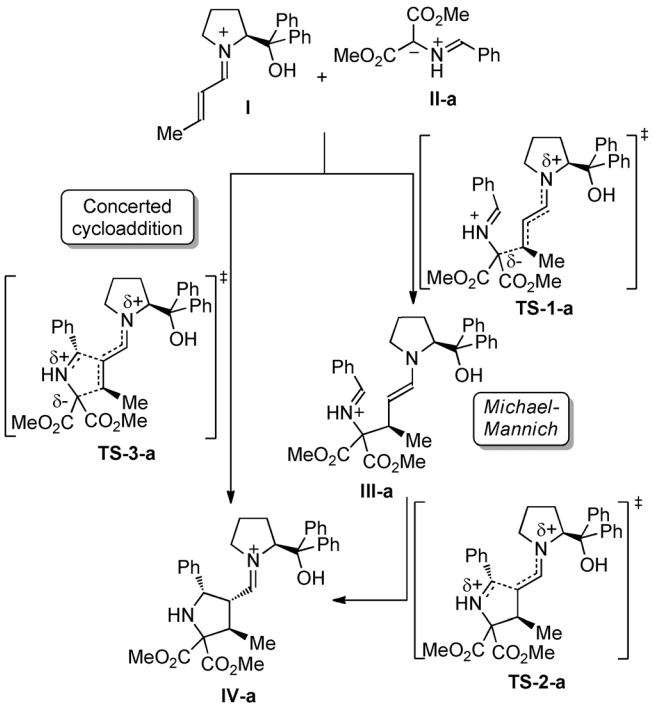
Finally, we also prepared tetrahydro-1*H*-furo[3,4-*b*]pyrrol-6(6a*H*)-one (**10**) by starting from cycloadduct **4b** and using a sequence analogous to that shown before (see Table 2 and Scheme 4), but changing the benzoyl protecting group to the related *para*-chlorobenzoyl group, which incorporates a heavy chlorine atom that should allow the determination of the absolute configuration by X-ray analysis based on the Flack parameters. With compound **10** in hand, we grew a crystal suitable for X-ray analysis, which showed a 3*S*,3a*R*,6a*S* absolute configuration for the three stereogenic centers present in the structure (Figure 1).[9] This configuration was extended to all cycloadducts **3** prepared in this study, the stereostructure of which had been previously assigned on the basis of our preliminary report, in which the absolute configuration of the products obtained in the [3+2] cycloaddition reaction between azomethine ylides and α,β-unsaturated aldehydes had been established by chemical correlation.[4a]



Scheme 4. Survey of chemical modifications carried out on adducts **7**. PCC = pyridinium chlorochromate.

Mechanistic considerations: Two different mechanistic scenarios can be proposed for the transformation being studied (see the outline given in Scheme 5). The reaction might proceed through 1) a concerted mechanism or 2) a stepwise process that involves an initial Michael addition followed by an intramolecular Mannich reaction. In fact, previous reports on the [3+2] cycloaddition of the azomethine ylide generated from diethyl aminomalonate benzaldehyde imine with nitroalkenes under hydrogen-bonding catalysis indicate that this reaction can proceed in a stepwise manner,[10] thus detecting, in this case, the formation of intermediates that arise after the initial Michael addition step and that could be isolated and fully characterized. Other reports also propose a pericyclic mechanism that operates under similar conditions,[3b,e] which was supported by computational data.[3b]

In our case, we tried to gather some experimental data that would allow us to make a mechanistic proposal by identifying or isolating one of these possible intermediates, although with no success, which would eventually point



Scheme 5. Two possible mechanistic pathways for the catalytic formal [3+2] cycloaddition of azomethine ylides to α,β-unsaturated aldehydes.

toward the operation of concerted-type mechanism in our case.[11] However, this lack of evidence is not concluding proof that allows us to definitively exclude the participation of a stepwise mechanism because the inability to observe the formation of a Michael addition intermediate can be attributed to the fact that the subsequent intramolecular Mannich reaction could take place very quickly, thus leading to the instantaneous formation of the final cycloadducts after the initial Michael reaction had occurred. For this reason, we decided to carry out a detailed computational study directed to shed light on the exact nature of the mechanism of this reaction.

According to the two possible reaction mechanisms outlined in Scheme 5 and also in accord with previous proposals,[8] the 1,3-dipole generated in the reaction media was identified as the reactive species that participates in the cycloaddition reaction because it interacts with the α,β-unsaturated aldehyde, the latter being activated by the catalyst as the corresponding iminium ion.[12] We started by performing a conformational analysis of these two reagents (Figure 2), and our calculations indicated that azomethine ylide **II-a** remains in a preferred arrangement in which an internal hydrogen bond between the oxygen atom from one of the ethoxycarbonyl groups and the NH moiety would form. With respect to the preferred arrangement of iminium ion **I**, this intermediate would be formed preferentially as the more stable *E* isomer, thus adopting a preferred s-*trans* conformation in which the repulsion between the bulky hydroxydiphenymethyl substituent and the alkenyl side chain are minimized, which is also in agreement with previously presented calculations.[13]

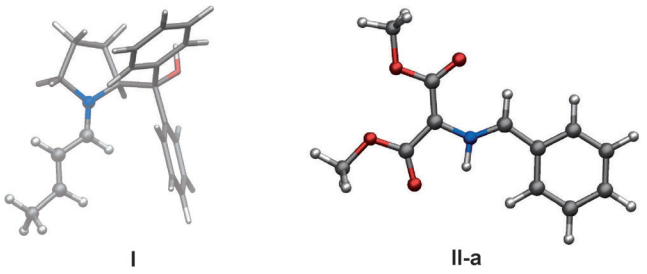


Figure 2. Main geometrical features of the iminium ion **I** and dipole **II-a** obtained at the B3LYP/6-31G* level of theory.

Next, we studied the [3+2] cycloaddition reaction between azomethine ylide **II-a** with iminium ion **I** that yields the corresponding cycloadducts **IV-a** (Figure 3). In all cases, we considered that the approach of the nucleophile to the Michael acceptor should occur from its less-hindered face, which is consistent with the absolute configuration of the stereogenic center generated at this position in the final cycloadducts obtained and is also in agreement with previous computational studies on other examples of conjugate addition reactions that involve the participation of iminium ions related to **I**.[12,13] It should also be pointed out that the participation of the free OH group of the α,α-diphenylprolinol

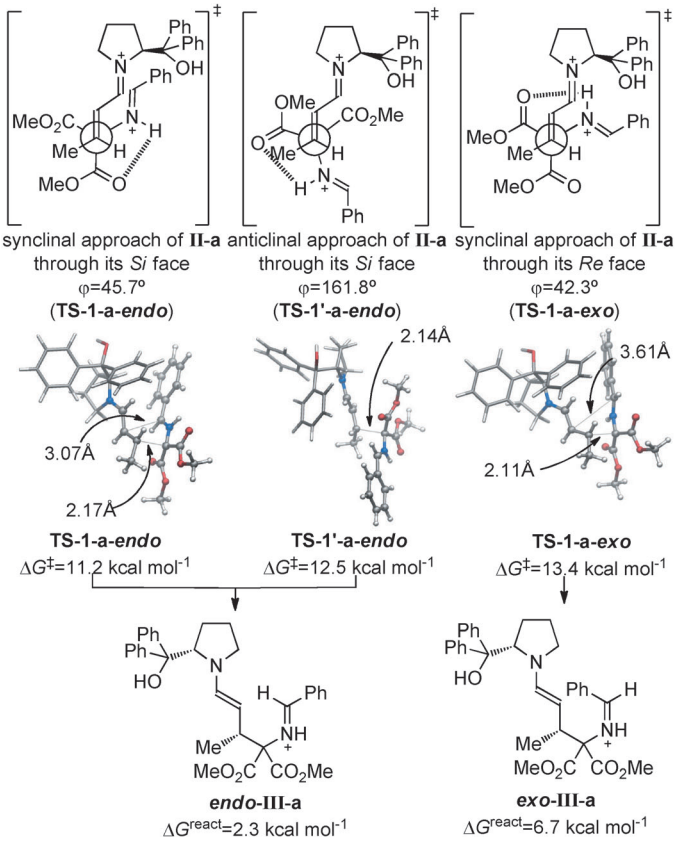


Figure 3. Optimized transition states for the Michael addition between **II-a** and **I** and ΔG^{react} values for optimized structures ***endo*-III-a** and ***exo*-III-a**.

catalyst on a possible stereodirecting effect through hydrogen-bonding interactions is ruled out by a previous related study[4b] that showed that *O*-trimethylsilyl-protected α,α-diphenylprolinol can catalyze the same reaction, thus giving rise to the corresponding cycloadducts with identical configurations.

We initially considered a possible orientation for the approach of **II-a** to **I** in which the benzylidene substituent of the azomethine ylide remains close to the enamine moiety, which should be produced during the reaction and would also favor a subsequent intramolecular Mannich reaction in the following step. Assuming this conformational predisposition during the approach of these reagents, we calculated the transition states **TS-1-a-*endo*** and **TS-1-a-*exo*** that result from the approach of the azomethine ylide **II-a** through its *Si* or *Re* faces, respectively, which are named the *endo* and *exo* approaches and would lead to the formation of Michael addition intermediates ***endo*-III-a** and ***exo*-III-a** ($\Delta G^{react} = 2.3$ and 6.7 kcal mol^{-1}, respectively). The activation barrier associated with the formation of ***exo*-III-a** (**TS-1-a-*exo***) is 2.2 kcal mol^{-1} higher than the barrier associated with the formation of ***endo*-III-a** (**TS-1-a-*endo***), which indicates that the formation of ***endo*-III-a** is favored under kinetic control conditions. We evaluated an alternative possible approach of **II-a** to **I** (**TS-1′-a-*endo***) in which the orientation of the azomethine ylide is rotated with respect to the previously presented **TS-1-a-*endo*** species (dihedral angles for C=C···C–N are $\varphi = 42.3$ and 161.8°, respectively). In this case, this transition state would also lead to the formation of ***endo*-III-a**, but the benzylidene moiety would be placed far away from the enamine reactive center. Nevertheless, the computed energy for this transition state was higher than that obtained for **TS-1-a-*endo***, although lower than the computed energy for **TS-1-a-*exo***. These data confirmed that the preferential approach of the two reagents, that is, azomethine ylide **II-a** and iminium ion **I**, had to occur in a geometrical arrangement that closely resembles that of the concerted mechanism, although the calculated C4···C5 distance (i.e., 3.08 Å) in the lowest-energy transition state **TS-1-a-*endo*** indicates that no appreciable bonding interaction occurs between these two atoms.

We next evaluated the subsequent intramolecular Mannich reaction step, which should generate the pyrrolidine ring by the formation of the C4–C5 bond (Figure 4). As this bond formation had been carried out in the preceding step, we considered that the approach of the iminium electrophile should occur through the less-hindered *Si* face of the enamine moiety, which is formed as the *E* diastereoisomer and remains in the most-stable *anti* conformation in which the bulky hydroxydiphenylmethyl substituent is located as far as possible from the alkenyl moiety, as demonstrated in previously reported calculations that involved the reaction of enamines derived from diarylprolinol derivatives with different electrophiles.[12] At this point and as a consequence of the nature of the intermediate in which coulombic interactions are present, no rotation could possibly occur through the C–N bond in the enamine motif. For this reason, the following Mannich step should occur very quickly, and therefore the initial geometry adopted in the first Michael addition step would be maintained during the subsequent cyclization that results in the formation of the stereocenters at C4 and C5. This hypothesis is also consistent with the absolute configuration observed for the C5 stereocenter formed in the final pyrrolidine cycloadducts. Our calculations also indicate that transition state **TS-2-a-*endo*** for the reaction of enamine intermediate ***endo*-III-a**, which leads to the formation of the ***endo*-IV-a** product by means of a *Si–Si* interaction between the enamine unit and the iminium ion electrophile, respectively, is 3.0 kcal mol^{-1} more stable than the **TS-2-a-*exo*** species, which would produce the *exo* diastereoisomer from the intermediate enamine ***exo*-III-a** through a *Si–Re* interaction.

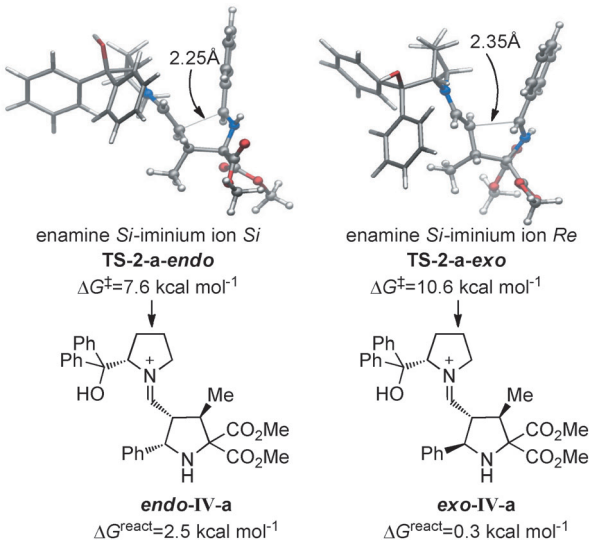
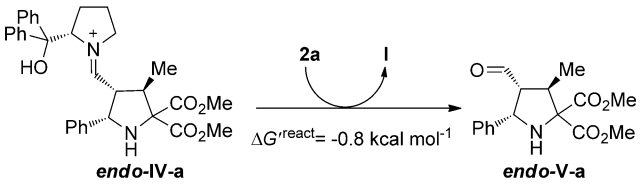


Figure 4. Optimized transition states for the intramolecular Mannich reaction step and ΔG^{react} values for optimized structures ***endo*-IV-a** and ***exo*-IV-a**.

We also computed the final step of the catalytic cycle, which involves the conversion of intermediate ***endo*-IV-a** into pyrrolidine cycloadduct ***endo*-V-a** after release of the catalyst, with concomitant generation of activated iminium ion **I** (Scheme 6), to complete the energy diagram. This final catalyst-turnover step involves a positive reaction energy (Scheme 6), and therefore the whole process continues with the formation of the final cycloaddition products and provides the required driving force for the reaction to proceed to completion. This finding also indicates that a possible equilibration between the iminium cation intermediates



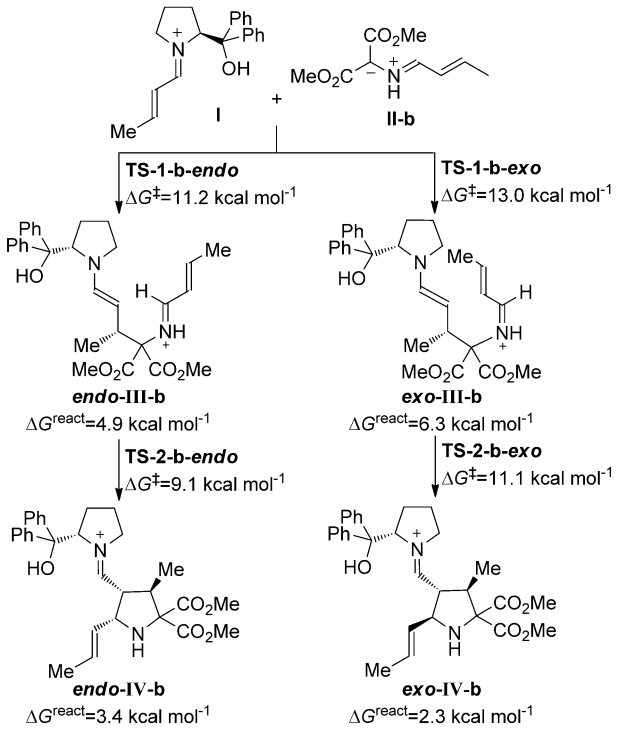
Scheme 6. Formation of ***endo*-V-a** from iminium intermediate ***endo*-IV-a**.

***endo*-IV-a** and ***exo*-IV-a** through a hypothetic retro-Mannich/Mannich reaction sequence is very unlikely to occur.

The final energy profile of the reaction as it proceeds through a stepwise Michael/Mannich mechanism indicates that the first Michael addition step constitutes the rate-limiting step of the process; therefore, it is at this point that the kinetic control of this transformation takes place, with an overall activation barrier of 11.2 kcal mol^{-1}. Once this Michael addition occurs, the subsequent intramolecular Mannich reaction takes place very quickly, thus leading to the formation of the final cycloadducts after release of the catalyst. This process might also explain the difficulties encountered during our attempts to isolate or detect the formation of a Michael addition intermediate. It is important to note that even though only the stereocenter at C2 in the first transition states **TS-1-a-*endo*** and **TS-1-a-*exo*** (both have identical configurations) is generated the coulombic stabilizing interactions in this intermediate keep the geometry from being altered when going through the subsequent cyclization. Therefore, this initial Michael addition step determines all the stereochemical issues that will define the absolute configuration of the four stereocenters formed in the final cycloadducts. On the other hand, it should also be noted that there is a global kinetic preference for the formation of the *endo* intermediates and transition states during all the reaction coordinates. By taking into account that the difference in energy between transition states **TS-2-a-*endo*** and **TS-2-a-*exo***, which lead to the *endo* and *exo* adducts, respectively, was calculated to be $\Delta\Delta G^{\pm} = 2.2$ kcal mol^{-1}, an *endo*/*exo* relationship of 97:3 would be expected, which is in good agreement with the experimental results for the same reaction in which a diastereomeric ratio (d.r.) of 95:5 was observed. Finally, we tried to evaluate the energy profile associated with the concerted pathway, but all our attempts to find **TS-3-a** were unsuccessful.

In addition, we computed the energy profile that corresponds to the reaction between azomethine ylide **II-b** and iminium ion **I** (Scheme 7) in a reaction that leads to the formation of 5-alkenyl-substituted pyrrolidines of type **3** and proceeds in comparable yields and stereoselectivities both under the conditions employed in this study (which involve the formation of **1a** in situ) and our initially developed reaction conditions[4a] (which involve the previous preparation and isolation of **1a**).

In line with the data obtained up to this moment, the calculations indicate that the reaction also proceeds through a stepwise Michael/Mannich cascade process, with the initial conjugate addition reaction of the azomethine ylide **II-b**, with iminium ion **I** delivering the enamine intermediate ***endo*-III-b** in which the first stereocenter is generated, as the rate-determining step. Next, the subsequent intramolecular Mannich reaction takes place very quickly, thus delivering the iminium intermediate ***endo*-IV-b** concomitant with the formation of the other two stereocenters and finally releasing the catalysts to generate the final cycloadduct ***endo*-V-b** and complete the catalytic cycle. The calculations also show a clear preference for the formation of the *endo* diastereoisomer over the *exo* adduct, with a difference in energy between the transition states **TS-1-b-*endo*** and **TS-1-b-*exo*** of $\Delta\Delta G^{\pm} = 1.8$ kcal mol^{-1}, which is in good agreement with the experimental results.



Scheme 7. Calculated energy profile for the reaction of azomethine ylide **II-b** with iminium ion **I**.

Alternatively, and for comparative purposes, we evaluated the uncatalyzed direct background reaction between crotonaldehyde and azomethine ylide **II-a** to assess the influence of the catalyst in the mechanistic profile of the reaction and the ability of the catalyst to activate the α,β-unsaturated aldehyde through the cycloaddition process. In this case, and contrary our previous attempts, we could locate a transition state for the concerted pathway, thus leading to the formation of the *endo* cycloadduct (**TS-4** in Figure 5).

It is important to note that the calculated energy for the activation barrier associated with transition state **TS-4-a**, which participates in this uncatalyzed process, was higher than the calculated energy for the corresponding α,α-diphenylprolinol-catalyzed reaction that proceeded via the iminium ion **I** (**TS-1-a-*endo***; compare Figures 3 and 5). This finding is an indication of the ability of the catalyst to activate the α,β-unsaturated aldehyde toward the cycloaddition process through the reversible formation of an iminium ion intermediate and also shows that the participation of these iminium ion intermediates leads to a change in the mechanistic pathway of the reaction from being pericyclic in the uncatalyzed version to stepwise in the amine-catalyzed procedure.

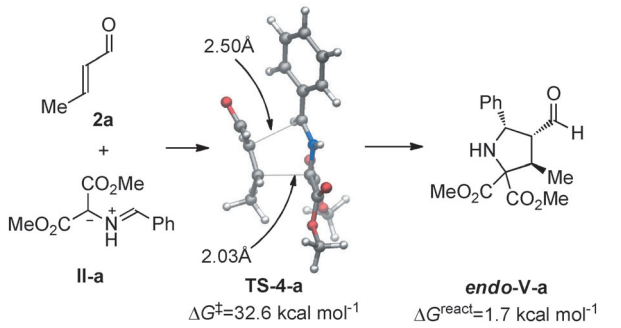


Figure 5. Optimized transition state structure **TS-4-a** for the reaction of crotonaldehyde with azomethine ylide **II-a**. Note that the ΔG^{react} value refers to the reaction of **II-a** with crotonaldehyde and not to the reaction with the iminium ion as in Figure 3.

We analyzed the behavior of the parent reaction of crotonaldehyde and azomethine ylide **II-a**, both in presence and absence of a catalyst, in greater detail to understand the reasons for this mechanistic change from a concerted to stepwise cycloaddition due to the use of α,α-diphenylprolinol as the catalyst. We considered $NHMe_2$ as a simpler analogue of the prolinol catalyst (see above). For the stepwise mechanism, the first step would involve nucleophilic attack of C3 on C4. In the case of the concerted [3+2] cycloaddition, there is a $[_{\pi}4_{s}+_{\pi}2_{s}]$ process, and an interaction between both C3/C4 and C1/C5 pairs is required that involves the corresponding molecular orbitals (MOs). These MOs in turn must have the appropriate symmetries to ensure a cyclic electronic delocalization associated with an aromatic transition structure.

Initially, we performed a relaxed potential energy surface (PES) scan of the possible reaction paths of both reactions (Figure 6). For the reaction of crotonaldehyde and azomethine ylide **II-a** in the absence of the catalyst, only the **TS-4-a** species was found as a saddle point that connects the reactants and products through a concerted mechanism (Figure 6A). In the case of the $NHMe_2$-catalyzed reaction, the potential-energy surface was qualitatively different because the reaction does not follow the concerted mechanism obtained for the uncatalyzed reaction (Figure 6B). Instead, a stepwise mechanism occurred in which the **TS-5-a** species connected the reactants with a zwiterionic intermediate, thus leading in turn to the final products through a second transition state **TS-6-a**.

We initially studied the MOs of the reactants to unveil the origins of these different profiles (Figure 7). Because the magnitude of the expansion coefficients in split-valence basis sets is difficult to assess, the respective orbital energies and expansion coefficients were recalculated using the AM1 semiempirical Hamiltonian.[14] The most relevant two-electron interactions arise from MOs φ_1 and φ_2 associated with the dipolarophile and ϕ_1 and ϕ_2 associated with the azomethine ylide. The main interaction patterns compatible with a concerted, symmetry-allowed [3+2] cycloaddition are $\phi_1 \rightarrow \varphi_2$ and $\varphi_1 \rightarrow \phi_2$, which correspond to the HOMO/LUMO and HOMO-1/LUMO two-electron interactions (the

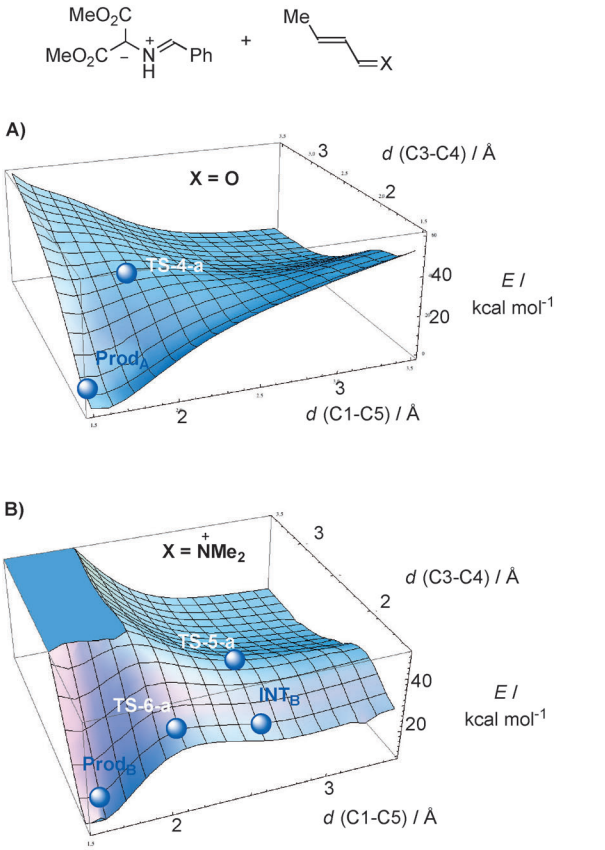


Figure 6. Potential energy surfaces (B3LYP/6-31G* level) projected on the C1/C5 and C3/C4 distances associated with the [3+2] cycloaddition of azomethine ylide **II-a** and crotonaldehyde without a catalyst (A) and with $NHMe_2$ as a catalyst (B). The stationary points of both reaction paths are shown as spheres.

HOMO orbital of the dipolarophile does not participate in the pericyclic process due to its σ symmetry).

Previously, we developed a simple model to understand the mechanistic change in [4+3] intermolecular cycloaddition reactions of different allyl cations[15] in terms of the second-order perturbation theory.[16] By applying this model to the present case, the contribution to the increase in energy on going from the reactants to the concerted [3+2] transition state can be reduced to two terms [Eq. (1)]: One associated with the four-electron repulsion $E^{(4)}_{CON}$ between the interacting carbon atoms and the other associated with the stabilizing two-electron interactions between these centers. This latter interaction can in turn be reduced to the contributions of electron transfer from the azomethine ylide (A) to the dipolarophile (B), which is denoted as $E^{(2)}_{A\rightarrow B}$, and the reverse electron transfer from B to A ($E^{(2)}_{B\rightarrow A}$), thus completing the cyclic electronic circulation required for a pericyclic mechanism:[15]

$$E_{CON} = E^{(4)}_{CON} + E^{(2)}_{A\rightarrow B} + E^{(2)}_{B\rightarrow A} \quad (1)$$

If the stepwise mechanism is considered, the first step associated with the nucleophilic attack of the azomethine

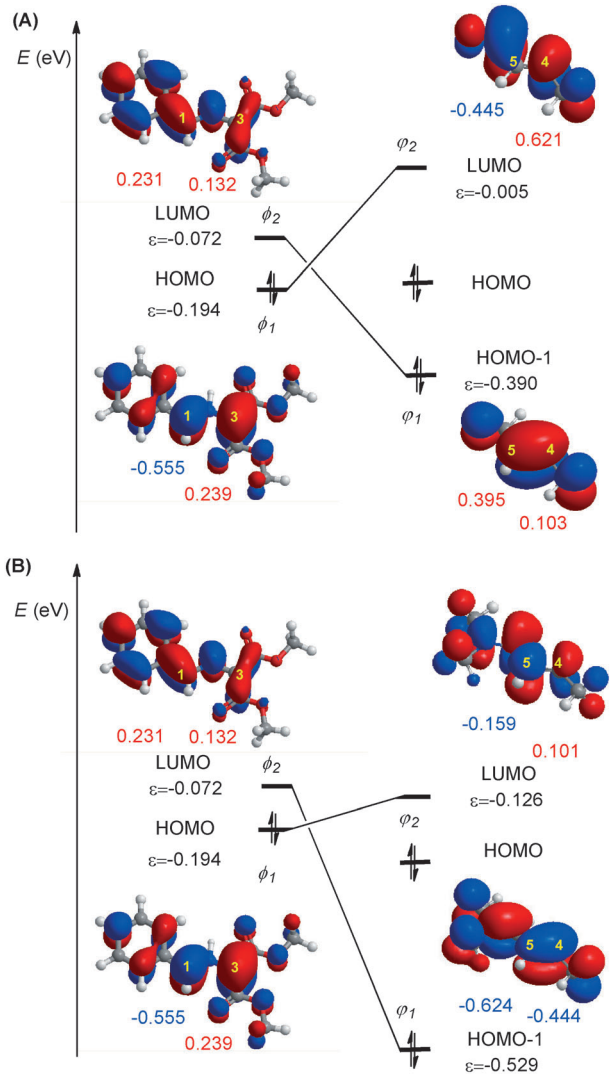


Figure 7. Significant MOs associated with the [3+2] cycloaddition of **II-a** and crotonaldehyde computed at the RHF/AM1 level of theory without a catalyst (A) and with $NHMe_2$ as a catalyst (B).

ylide subunit on the conjugate iminium ion moiety is given by Equation (2):

$$E_{STP} = E^{(4)}_{STP} + E^{(2)}_{Nu} + E^{Coul}_{AB} \quad (2)$$

In this equation, $E^{(4)}_{STP}$ corresponds to the four-electron interaction between the enolate-type part of A and the Michael acceptor moiety of dipolarophile B, $E^{(2)}_{Nu}$ represents the stabilizing two-electron interaction between these centers and E^{Coul}_{AB} is the electrostatic (coulombic) interaction between A and B. We evaluated E_{CON} and E_{STP} for the different values of R_{ij}, which correspond to the early stages of the concerted and stepwise processes, respectively. The values of the expansion coefficients and orbital energies are gathered in Figure 7. The point charges were determined from the natural-bonding analysis of each structure, including the attached hydrogen atoms when necessary. The obtained results for the early stages of the corresponding Born–Oppenheimer surfaces are shown in Figure 8.

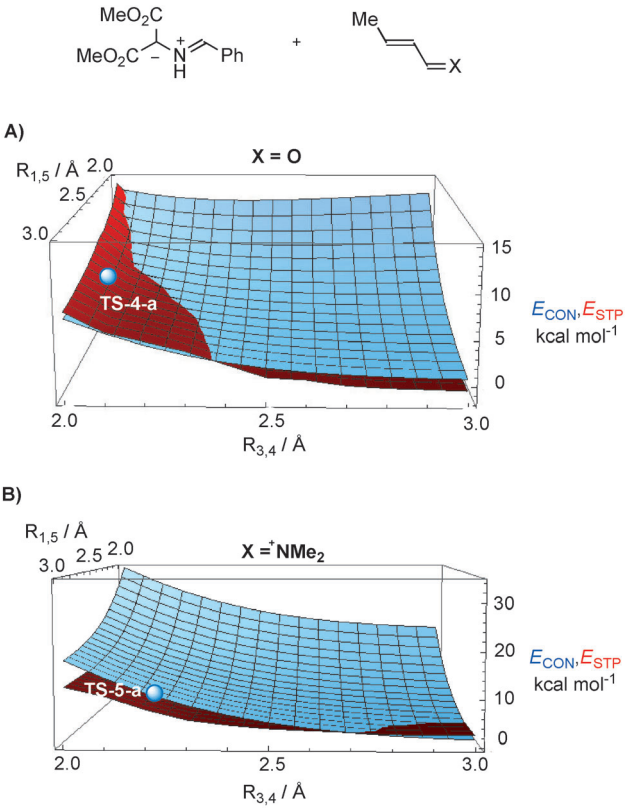


Figure 8. Plots of the interaction energies associated with the initial stages of the concerted E_{CON} and stepwise mechanism E_{STP} of the cycloaddition of **II-a** and crotonaldehyde without a catalyst (A) and with $NHMe_2$ as a catalyst (B). In both diagrams, spheres represent the C1/C5 and C3/C4 critical distances of the calculated transition state structures.

In the case of the noncatalyzed reaction (X=O; Figure 8A), the concerted mechanism is the less energetic one according to our model for low values of C1/C5 and C3/C4 distances. This behavior could be assigned to an important contribution of the $E^{(2)}_{B\rightarrow A}$ term (associated with the $\varphi_1\rightarrow\phi_2$ process), which ensures the cyclic electronic circulation required to complete the concerted mechanism. Activation of the electrophile by the $NHMe_2$ catalyst promotes an important decrease in the energy of φ_2 (Figure 8B). Therefore, in this case the $\phi_1\rightarrow\varphi_2$ gap is decreased relative to the noncatalyzed reaction, and now $E^{(2)}_{Nu}$ is the most important stabilizing contribution. In addition, the low contribution of the $E^{(2)}_{B\rightarrow A}$ term results in a disruption of the cyclic electronic circulation; therefore, the stepwise mechanism is preferred.

Conclusion

We have demonstrated that our initially developed procedure to carry out the enantioselective [3+2] cycloaddition of azomethine ylides with α,β-unsaturated aldehydes is a process with a very wide scope that allows the preparation of a variety of different pyrrolidine cycloadducts containing

several substituents and several stereocenters, with exceptional levels of chemical efficiency and stereoselectivity in all cases. In particular, 2-alkenylideneaminomalonates generated in situ can be used as suitable azomethine ylide precursors that lead to the formation of a new family of pyrrolidine cycloadducts containing an alkenyl side chain at C5, which has the potential for being chemically manipulated to increase the synthetic potential of this methodology. On the other hand, computational studies carried out on this reaction demonstrate that the reaction proceeds through a stepwise Michael/Mannich mechanism, with the initial Michael addition as the rate-determining step of the process and also the point at which all the stereochemical information is placed. Moreover, our calculations have also shown that the formation of the iminium ion leads to the activation of the enal toward the formal cycloaddition process, which also leads to a change in the mechanistic profile of the reaction from being pericyclic in the uncatalyzed version to stepwise in the reaction proceeding through iminium activation. A simple model has also been developed to understand these processes, which can also be extended to other similar and related transformations.

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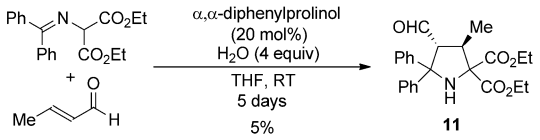

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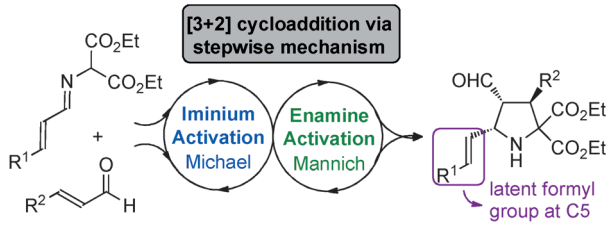

Wide ranging potential: The organocatalytic enantioselective [3+2] cycloaddition between azomethine ylides and enals has been extended to include 2-alkenylideneaminomalonates as azomethine ylide precursors. The resulting pyrrolidines contain a 5-alkenyl side chain with potential for further chemical manipulation (see scheme). Moreover, a detailed computational study reveals the nature of the reaction mechanism and the consequences derived from the incorporation of the catalyst on the reaction.

Organocatalysis