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Lewis Acid Catalyzed Reactions of Chiral Imidazolidinones and Oxazolidinones: Insights on the Role of the Catalyst

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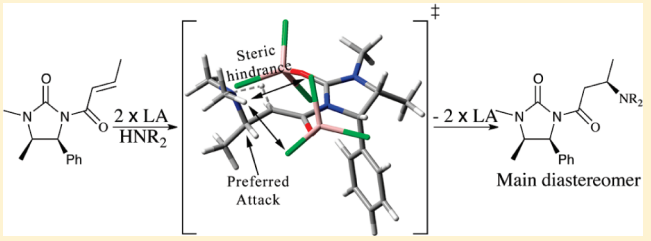
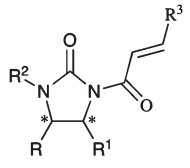
Supporting Information

ABSTRACT: The mechanism proposed by Evans to justify the selectivity obtained in Lewis acid catalyzed Diels−Alder reactions of cyclopentadiene with acyloxazolidinones has been generalized and used in the rationalization of selectivities obtained in many other systems. However, we recently proposed an alternative mechanism, on the basis of open-chain mono- and bicomplexes, that avoids the need for chelates and explains the selectivity obtained by Evans. In this manuscript we apply our proposal to the catalyzed conjugated addition of amines to acylimidazolidinones, reported by Cardillo, and we clearly show that aluminum chelates are not involved in the reaction, as they induce no selectivity, while Cardillo observed high experimental selectivities. Our data equally show that bicomplexes with carbonyl parallel orientation, proposed by Cardillo to justify the experimental selectivity with nonchelating Lewis acids, indeed induce the opposite selectivity and have also to be dismissed. On the other hand, our mechanistic proposal allows for the full rationalization of the data obtained by Cardillo with aluminum, boron, or zinc Lewis acids and supports our previous proposal on DA cycloadditions of dienes to Evans chiral auxiliary derivatives.



INTRODUCTION

Chiral α,β-unsaturated *N*-acylimidazolidinones (**1**) and *N*-acyloxazolidinones (**2**) undergo a variety of Lewis acid catalyzed addition reactions with moderate to excellent asymmetric induction.[1,2]



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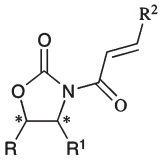

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While the enhanced electrophilicity of the β-carbon may be rationalized in a straightforward way as due to carbonyl complexation with the Lewis acid, the same is not true for the observed selectivities, considering the steric hindrance of the ring substituents (Scheme 1).

The unexpected results obtained by Evans in Diels−Alder (DA) additions of cyclopentadiene to oxazolidinones of type **2** (Scheme 1) were rationalized on the basis of a mechanism where the stereochemistry is attributed to a reacting conformer in which the two carbonyl groups are in coplanar orientation, as a result of their chelation with the LA (Scheme 1).[1g] Although the authors observed that LAs for which bidendate complexations are well established, e.g., $TiCl_4$,[3] were not effective catalysts, the concept of bidendate chelation, contributing as an important organizational constraint to the transition structures (TSs), has been widely accepted and used thereafter to explain the diastereoselectivities in DA and related reactions.[2a,4] However, the high energy needed for the amide-bond rotation[5] and the observation that some systems originate the Evans stereochemistry without any kind of chelation to account for the coplanarity of the carbonyl groups led to the proposal of alternative reaction mechanisms[6] that culminated in a recent proposal made by us for the rationalization of the stereoselectivity in dynamic kinetic resolution reactions (DKR).[5,7]

More recently, we also proposed an alternative mechanism for the LA promoted Diels−Alder reaction of Evans auxiliary derivatives[8] that explains the observed selectivities by the catalysis via low energetic open-chain mono- or bicomplexes, at the chain and the ring carbonyl groups, which are easily observed by NMR measurements (Scheme 2). As opposed to the Evans model, our proposal relies on a chirality transfer concept, in which an achiral Lewis acid works as a bridge for the transfer of chirality between the chiral auxiliary and the prochiral reactive center (Scheme 2). Thus, the preferential attack at the C_α-*si* face is a result of the bulkiness of the LA, which strongly hinders the

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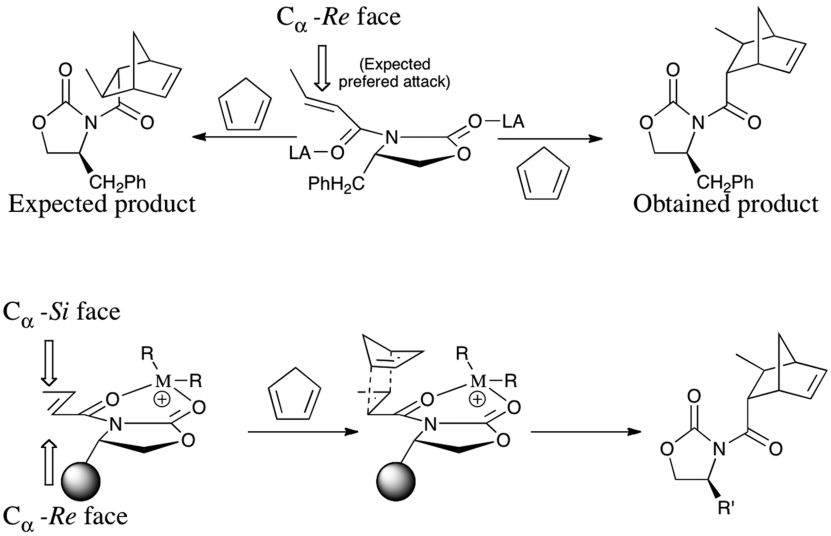
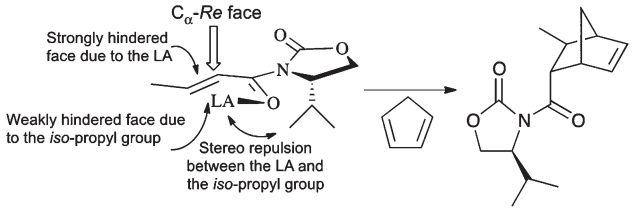
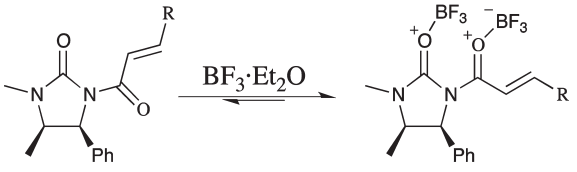
Scheme 1. Expected Stereoselectivity Due to Steric Hindrance by the Ring Substituent in a LA Complexed Oxazolidinone and Mechanism Proposed by Evans et al.[1g] To Explain Their Experimental Results in Diels–Alder Cycloadditions



Scheme 2. Rationalization of the Stereoselectivity in DA[8] Reactions by Way of Lowest Energy Conformation (Antiparallel Carbonyl Groups) of the Amide Chain



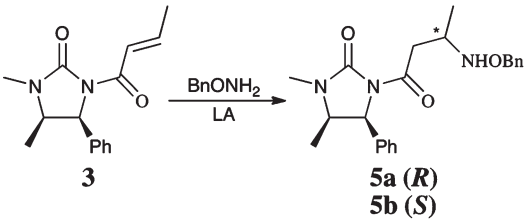
Scheme 3. Formation of Parallel Carbonyl Bicomplexes with $BF_3 \cdot Et_2O$ As Proposed by Cardillo[2a]



C_α-*re* face, while the isopropyl group in the auxiliary ring is too far away to directly interfere.

To verify the applicability of our proposal to other important reactions, we decided to test our model[8] on the system studied by Cardillo et al.[2a,9] in the conjugated addition of *O*-benzylhydroxylamine to chiral α,β-unsaturated *N*-acylimidazolidinones **3** and **4** (Scheme 3), catalyzed by BF_3, $AlMe_2Cl$, and $ZnCl_2$. This is a very interesting work that reports a broad range of complexing conditions, as BF_3 should be able to form only open neutral complexes,[10] whereas $ZnCl_2$ can form neutral open or chelated complexes and $AlMe_2Cl$ can form neutral open complexes or charged chelated complexes. In this manuscript we show that the

Table 1. Yield and Diastereomeric Ratios (dr) Reported by Cardillo for the Conjugated Addition of *O*-Benzylhydroxylamine to 3 in the Presence of Different LAs[2a,9]



entry	LA	equiv	yield (%)	dr (*R*:*S*)
1	$BF_3 \cdot Et_2O$	1.0	80	90:10
2	$BF_3 \cdot Et_2O$	2.0	>95	90:10
3	$AlMe_2Cl$	1.0	65	74:26
4	$AlMe_2Cl$	2.0	70	80:20
5	$ZnCl_2$	1.0	92	45:55

selectivities obtained by Cardillo[2a,9] can be fully rationalized by mechanisms based on open-chain antiparallel carbonyl complexes and that parallel carbonyl conformations, with or without chelate formation, induce no selectivity or inverted selectivity, respectively. These results can be extrapolated to other reactions based on similar auxiliaries and represent a good support to our previous study on DA reactions.[8]

RESULTS AND DISCUSSION

The conjugated addition of *O*-benzylhydroxylamine to chiral α,β-unsaturated *N*-acylimidazolidinones (**3** and **4**) in the presence of $BF_3 \cdot Et_2O$,[2a] $AlMe_2Cl$, or $ZnCl_2$[9] was reported by Cardillo et al. (selected results in Table 1).

The results in Table 1 are quite unexpected, as the chelating LAs (entries 3–5) should induce similar selectivities (excess of *R* isomer), whereas boron trifluoride (a nonchelating LA) is

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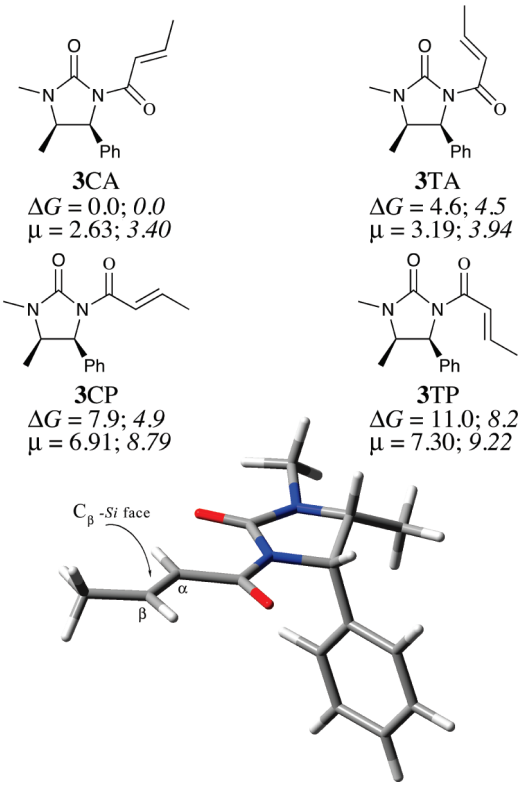

Figure 1. Relative free energies (ΔG) and dipole moments (μ), calculated in gas phase (roman) and solvent (italic), of four possible conformers of imidazolidinone **3**. The larger differences calculated in gas phase between the parallel and antiparallel conformers are due to the greater dipole moments calculated in the parallel structures.

expected to induce the inverse selectivity (excess of *S* isomer) due to the hindrance of the aromatic ring in the auxiliary. The selectivity obtained with catalysis by $AlMe_2Cl$ was explained according to the Evans proposal, but the other selectivities are not easy to justify. Thus, in order to rationalize the selectivity obtained with $BF_3 \cdot Et_2O$ and supported by NMR results that dismissed the formation of a pentacoordinated boron fluoride chelate, Cardillo suggested a parallel complex with coordination of each carbonyl group with a BF_3 molecule (Scheme 3). According to Cardillo,[2a] this complex would be formed due to electrostatic attractions between the LA at the chain carbonyl group and the partial positive ring carbonyl moiety, leading to the unexpected observed selectivity (excess of *R* isomer). The NMR data presented by the authors to support this proposal are compatible with the formation of the parallel complex, but there is no data that unequivocally support its formation. An interesting observation, reported by the authors but that was not relevant in the discussion, is the fact that the diastereoselectivity is independent of the LA concentration. Thus, if the bicomplex is mandatory for catalysis, it implies that the monocomplex at the chain carbonyl group would be totally inefficient, a conclusion that contradicts other results, namely, those originally obtained by Evans for DA additions to α,β-unsaturated *N*-acyloxazolidinones.[1g]

The possible conformers of compound **3** are shown in Figure 1. In the most stable conformation of compound **3**, the double bond is in *s-cis* orientation and the two carbonyl groups adopt the antiparallel conformation (**3CA**). The relative energy values in Figure 1 are in agreement with previous results[5] and indicate that the populations of the minor rotamers in the reactants have to be minimal.

Cardillo's results were obtained with $AlMe_2Cl$, BF_3, and $ZnCl_2$.[2a,9] As BF_3 is not a good LA for modeling purposes, as it establishes very strong electrostatic contacts that are overestimated too much in the calculations, we study computationally only aluminum and zinc complexes, while our NMR studies focus on boron trifluoride and aluminum complexes. To simplify the discussion of our data, we calculated the reaction pathway not only via $AlMe_2Cl$ complexes but also via $AlCl_3$ complexes. The advantage of using $AlCl_3$ is that it originates a low number of rotamers, while from the electrostatic point of view, $AlCl_3$ can be looked as a middle term between BF_3 and $AlMe_2Cl$, despite being a stronger LA. The results calculated with $AlCl_3$, $AlMe_2Cl$, or $ZnCl_2$ are always given in the tables and in the Supporting Information, but the discussion is based on $AlCl_3$ complexes.

Three types of complexes with antiparallel carbonyl orientation have to be studied, as well as a bicomplex with the imidazolidinone in its parallel conformation and, for $ZnCl_2$ and $AlMe_2Cl$, chelated complexes in which the LAs connect simultaneously to the two carbonyl groups (Figure 2). Complexes with the *s-trans* conformation of the crotonyl moiety are not discussed, as their energies are too high to be relevant (see Supporting Information).

According to Figure 2, in low concentrations of $AlCl_3$ there is preferential complexation at the chain carbonyl group (MAC), as the monocomplex at the ring carbonyl group is more energetic by ca. 1.7 kcal mol^{-1}, while the extra stabilization resulting from the bicomplexation (−19.0 kcal mol^{-1} for BMA and −12.5 kcal mol^{-1} for BMP) is lower than the first complexation at the chain carbonyl group (−26.2 kcal mol^{-1}). Figure 2 also indicates that the parallel complex (BMP) has no tendency to be formed, as it is 6.5 kcal mol^{-1} less stable than BMA. Thus, we can conclude that, according to our calculations, at low LA concentrations (<1 equiv of LA) MAC shall be the main species, while for high LA concentrations (>1 equiv of LA) BMA will be formed, in accordance with the NMR results discussed below. From the data in Figure 2, we can also conclude that although $AlMe_2Cl$ behaves as $AlCl_3$, $ZnCl_2$ preferentially forms chelated complexes, as it is usually accepted.

In most of the published reports, the characterization of the conformational behavior of free acylimidazolidinones or acyloxazolidinones and the modifications induced by the complexation with Lewis acids have been mainly addressed by the analysis of ^1H or ^{13}C chemical shift changes, upon the addition of Lewis acids.[2a,9,11] However, while ^1H and ^{13}C spectra indeed give useful information on complex formation, we have recently shown that, for related α,β-unsaturated *N*-acyloxazolidinones, the observed ^1H and ^{13}C chemical shifts do not allow differentiation between chelates and bicomplexes.[8] We have also demonstrated that, for the *N*-acyloxazolidinone system, substantial evidence for the formation of a chelate could be obtained in a nuclear Overhauser effect (NOE) based NMR experiment, since the rotation from the carbonyl antiparallel to the parallel conformation introduces dramatic changes in the interproton distances, which can be probed through the observation of NOE contacts. We have also shown that the complexation with $Mg(ClO_4)_2$ was a very efficient method of producing a chelate complex in solution and a straightforward way of recording NMR data of α,β-unsaturated *N*-acyloxazolidinone chelates with parallel carbonyl conformation. This information was then used as reference in studies with different Lewis acids.[8]

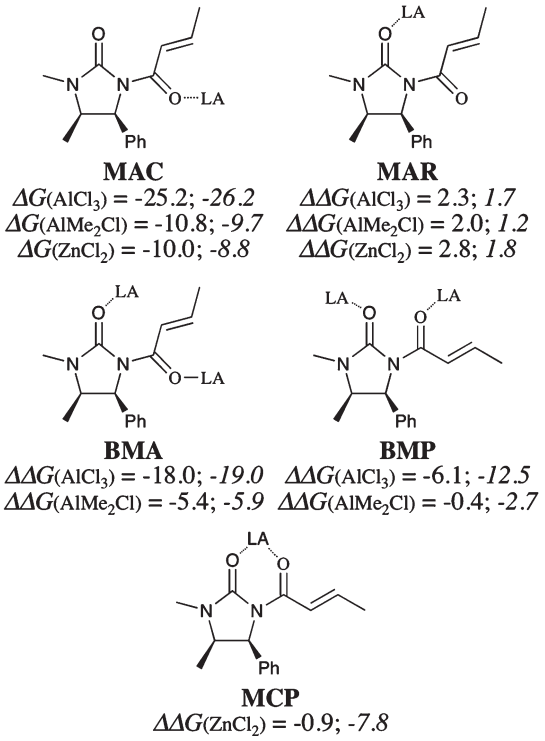

Figure 2. Relative free energies (ΔG), calculated in gas phase (roman) and solvent (italic), of five possible complexes (lowest energy conformers) between $AlCl_3$, $AlMe_2Cl$, or $ZnCl_2$ and imidazolidinone **3**. $ZnCl_2$ bicomplexes are not considered, as the chelated complex is already 7.8 kcal mol^{-1} more stable than the monocomplex MAC. Chelates with $AlMe_2Cl$ and $AlCl_3$ are not shown because of their charged nature. Complexes with the *s-trans* conformation of the crotonyl moiety are not discussed, as their energies are too high to be relevant (around 4 kcal mol^{-1} higher energy than the *s-cis* conformers; see Supporting Information).

For the present work, we have followed a similar approach in order to investigate the preference for the formation of chelates or open complexes with parallel or antiparallel carbonyl conformations, when BF_3 or $AlMe_2Cl$ is added to compound **3**.

According to the data in Figure 1, the 3D structures of the most stable conformations of compound **3** in the antiparallel (**3CA**) or parallel (**3CP**) carbonyl orientations are those depicted in Figure 3. As in the parallel carbonyl conformation the distance between protons H2′/H4 is much shorter (less than 2.5 Å) than in the antiparallel conformation, the first should lead to strong NOE contacts, while the antiparallel conformation should have very weak or even no visible contacts.

Following the above ideas, we have submitted compound **3** to a NOESY study, in the absence and in the presence of $Mg(ClO_4)_2$ (Figure 4), and the results are compared with the NOESY recorded in the presence of $BF_3 \cdot Et_2O$ or $AlMe_2Cl$, as discussed below.

The NOESY spectrum of **3** obtained in the absence of LA (Figure 4A) shows no contact between protons H2′ and H4, whereas in the presence of 1.0 equiv of $Mg(ClO_4)_2$ a strong contact can be observed between the same pair of protons (Figure 4B). Thus, in solution and in the absence of LA, compound **3** exists predominantly in conformation **3CA**, whereas in the presence of $Mg(ClO_4)_2$ the conformation changes from anti- to parallel carbonyl orientation, due to chelate formation with the LA. The possibility of a fast exchange equilibrium between **3CP** and

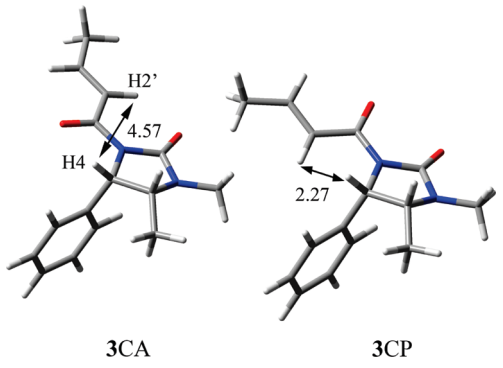

Figure 3. Comparison of the most stable conformations of compound **3**, with antiparallel (3CA) or parallel (3CP) carbonyl conformations, and indication of the H2′/H4 interproton distances.

3CA in the absence of the LA was ruled out by performing low temperature experiments (from 25 to −80 °C) as, with the exception of the aromatic protons, the signals showed minimal temperature dependence (see Supporting Information).

The downfield shift of H4 and the strong upfield shift of H2′, upon the addition of $Mg(ClO_4)_2$, are very similar to those previously observed with the related α,β-unsaturated *N*-acyloxazolidinone **2**, under similar conditions.[8] These shifts are indicative of complex formation and can be explained in terms of different carbonyl shielding environments due to rotation along the amide bond (see Supporting Information).

In the sequence of the validation study described above, the titration of compound **3** with BF_3 and $AlMe_2Cl$ was followed by ^1H NMR, leading to similar conclusions as previously obtained for the oxazolidinone system, when concerning the effect of complexation on chemical shifts (see Supporting Information).[8] Our BF_3 titration data in CD_2Cl_2 reproduces exactly the results previously reported by Cardillo.[2a] However, as we have demonstrated before,[8] an analysis of the chemical shifts do not allow the differentiation between a chelate and a 2:1 complex (parallel or antiparallel), because in both cases the two carbonyl groups are coordinated and the electronic effects due to complexation or chelation are expected to be very similar. The fundamental difference among the various LAs is the number of equivalents of acid that are needed for total complexation of the initial imidazolidinone **3**. Whereas full complexation is observed with 1.0 equiv of $Mg(ClO_4)_2$, 2.0 equiv of LA are needed when $AlMe_2Cl$ or BF_3 is used. These results are consistent with the formation of chelates between compound **3** and $Mg(ClO_4)_2$ and open-chain mono- or bicomplexes with $AlMe_2Cl$ or BF_3. The studies indicate also that for low LA concentrations, the first complexation takes place preferentially at the chain carbonyl group. The NMR results are in full accordance with the theoretical data. For a detailed analysis, see Supporting Information.

Once the stoichiometry of the BF_3 and $AlMe_2Cl$ complexes was established, the conformations were further investigated by NOESY experiments (Figure 5), and the conclusions are, in all aspects, identical to the results previously obtained for the complexation of compound **2** and $AlMe_2Cl$.[8] Despite the partial overlap of the H4/H2′ resonances, the analysis of the NOESY spectra and the comparison with the $Mg(ClO_4)_2$ experiment (Figure 4B) reveals that, for BF_3 and $AlMe_2Cl$ complexes, the carbonyl groups are in the antiparallel conformation, since no significant contact can be detected between H2′ and H4 (Figure 5A1 and 5B1).

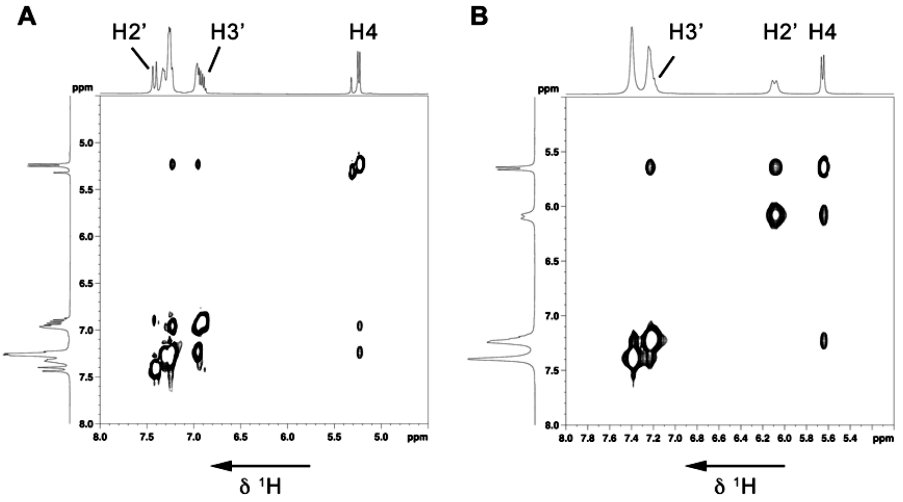

Figure 4. Expansion of the NOESY spectra of **3** obtained (A) in CD_2Cl_2 and (B) in the presence of 1.0 equiv of $Mg(ClO_4)_2$ in CD_3CN.

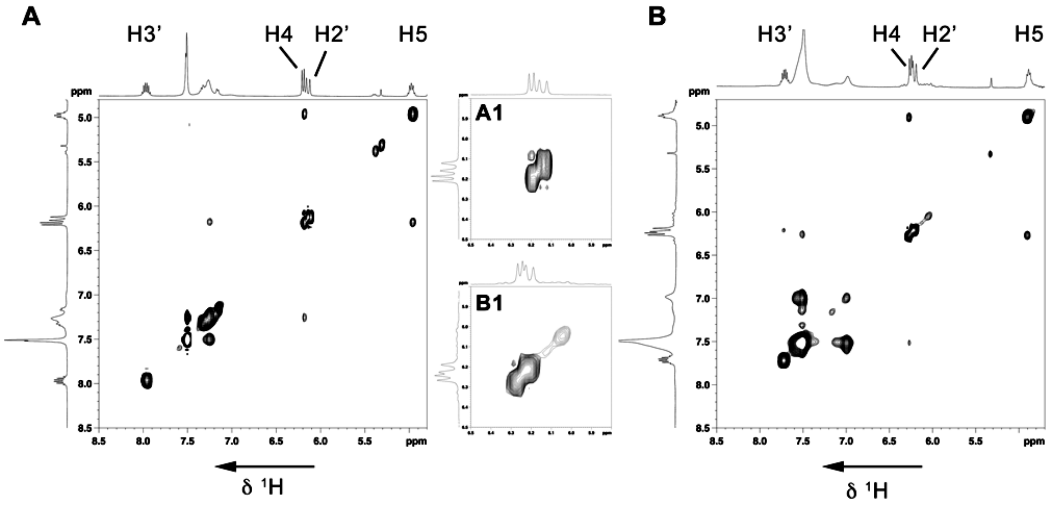

Figure 5. Expansion of the NOESY spectra of **3** obtained in the presence of (A) 2.0 equiv of $BF_3 \cdot Et_2O$, with a detailed view of the H4/H2′ region (A1), and (B) in the presence of 2.0 equiv of $AlMe_2Cl$, with detailed view of the H4/H2′ region (B1).

As the NMR confirms the theoretical data, indicating that BF_3 and $AlMe_2Cl$ form open-chain carbonyl antiparallel complexes with **3** (monocomplexes preferentially at the chain carbonyl group and bicomplexes for concentrations of LA over 1 equiv) and Cardillo's results[2a,9] show that different concentrations of these LAs induce similar selectivities, an alternative mechanism to that proposed by Cardillo[2a] has to be established, based on carbonyl antiparallel complexes and able to account for the similar induction of selectivity in reactions via mono- or bicomplexes. Thus, we studied the applicability and performance of the mechanism recently proposed by us for DA reactions of derivatives of the Evans auxiliary catalyzed by aluminum-based LAs (Scheme 2),[8] and the results are discussed below (Figure 6 and Table 2).

In the reaction studied by Cardillo[2a,9] *O*-benzylhydroxylamine was used as reagent. However, this amine offers special difficulties in modeling studies, as it allows for several possible conformers that strongly complicate the calculations and analysis of the results. Thus, we use dimethylamine (DMA) in the following discussion, as it is not much bulkier than *O*-benzylhydroxylamine and originates TSs with a single conformer. Due to the slightly larger bulkiness of DMA and reduced electrostatic contacts, slightly overestimated calculated selectivities are obtained. As a result and aiming at an easy comparison between calculated and experimental values, we discuss the results using a scaling factor when the amine is DMA. However, Table 2 also shows the selectivities calculated without any scaling. Results obtained with methoxyamine (MA), an amine similar to *O*-benzylhydroxylamine via MAC- and BMA-$AlCl_3$ complexes, are also shown in Table 2. These results are similar to those obtained with DMA, after application of the scaling factor (see Computational Methods).[12]

The results in Table 2 and Figure 6 indicate that our model can indeed explain the experimental selectivity, when the reaction occurs via the monocomplex at the chain carbonyl group or via the bicomplex in antiparallel carbonyl orientation. The analysis of the 3D models in Figure 6 indicate that, in order to minimize the steric interactions, the LA bound to the chain carbonyl group has to orientate itself away from the aromatic ring in the auxiliary, thus hindering the C_β *si*-face more efficiently than the aromatic ring in the auxiliary hinders the C_β *re*-face. The net result is the preferred attack at the C_β *re*-face.

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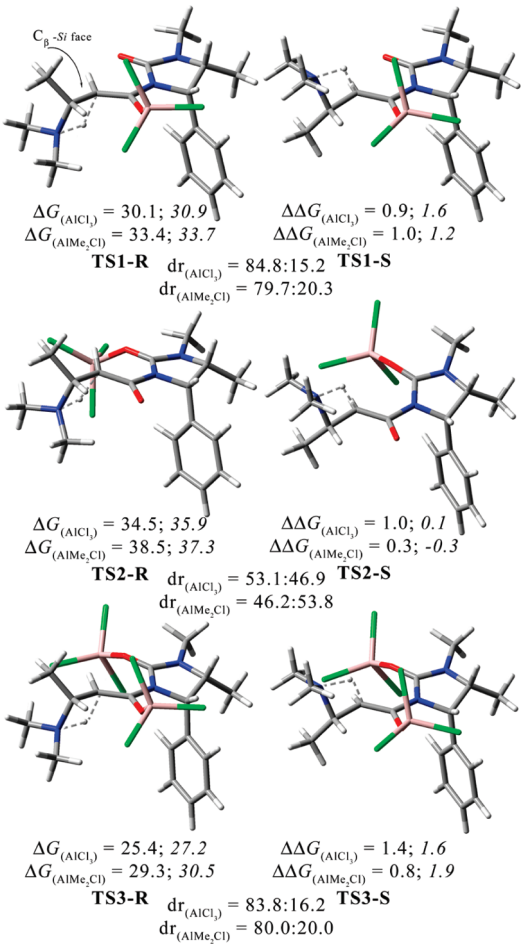

Figure 6. Unscaled relative free energies (ΔG) and scaled diastereomeric ratios (dr, in solvent) for the addition of DMA to imidazolidinone **3** in antiparallel carbonyl orientation, complexed with one or two molecules of $AlCl_3$ or $AlMe_2Cl$, calculated in gas phase (roman) and solvent (italic). Only the most stable structures are shown.

As Cardillo[2a] proposed a mechanism based on open-chain parallel carbonyl complexes, we decided to study also this possibility, even knowing that such complexes should not be formed, according to our theoretical data (Figure 2). We discuss this possibility using $AlCl_3$, but the results for $AlMe_2Cl$ are also given in Table 3 and Figure 7.

The results in Table 3 (entries 1−4) and Figure 7 indicate that bimetal parallel carbonyl complexes indeed catalyze the addition reaction, but they also clearly show that inverted selectivity would be obtained. This is well explained by our model, as the LA at the ring carbonyl group hinders the C_β *si*-face and forces the LA at the chain carbonyl group to orientate into the opposite direction, laying at the C_β *re*-face. Thus, the C_β *si*-face becomes less hindered, which leads to the final product with (*S*) configuration. This result shows that not only does our proposed model totally explain the experimental selectivity obtained by Cardillo, but it also clearly shows that the model based on a carbonyl parallel bicomplex induces the opposite selectivity, which is a strong indication of its low probability.

An interesting result from Cardillo[9] was obtained with $ZnCl_2$ as LA, a compound that is supposed to easily form neutral chelates.[13] While our theoretical values indeed indicate that this LA should form chelated complexes with compound **3** (Figure 2),

Table 2. Lowest Activation Free Energies (ΔG) and Diastereomeric Ratios (dr) for the Addition of DMA to Imidazolidinone 3 Complexed with $AlCl_3$, $AlMe_3$, and $AlMe_2Cl$[a]

					dr (*R*:*S*)	
entry	LA	complex	epimer	ΔG	unscaled	scaled
1			*R*	40.8; *40.9*	71.1:28.9	63.4:36.6
2			*S*	41.6; *41.4*		
3	$AlCl_3$	MAC	*R*	30.1; *30.9*	94.2:5.8	84.8:15.2
4			*S*	31.0; *32.5*		
5		MAR	*R*	34.5; *35.9*	55.0:45.0	53.1:46.9
6			*S*	35.5; *36.0*		
7		BMA	*R*	25.4; *27.2*	93.5:6.5	80.9:19.1
8			*S*	26.8; *28.8*		
9		MAC MA	*R*	31.8; *34.8*	88.0:12.0	
10			*S*	31.9; *35.0*		
11		BMA MA	*R*	27.8; *30.6*	72.5:27.5	
12			*S*	27.2; *31.1*		
13	$Al(CH_3)_3$	MAC	*R*	36.4; *35.6*	98.7:1.3	93.4:6.6
14			*S*	38.3; *38.1*		
15		MAR	*R*	36.8; *37.8*	56.2:43.8	53.8:46.2
16			*S*	37.7; *38.0*		
17		BMA	*R*	33.1; *34.6*	41.7:58.3	44.9:55.1
18			*S*	32.7; *34.4*		
19	$AlMe_2Cl$	MAC	*R*	33.4; *33.7*	90.3:9.7	79.7:20.3
20			*S*	34.4; *34.9*		
21		MAR	*R*	36.5; *37.3*	41.7:58.3	46.2:53.8
22			*S*	36.8; *37.0*		
23		BMA	*R*	29.3; *30.5*	92.4:7.6	80.0:20.0
24			*S*	30.1; *32.4*		

[a] Calculated in gas phase (roman) and solvent (italic). The diastereomeric ratios were calculated from the unscaled and scaled PCM energy values. When the LA is $AlMe_2Cl$, the selectivity via MAC or MAR was calculated by Boltzmann averaging over 6 possible TSs and 18 possible TSs for BMA. When the amine is methoxyamine (MA) 4 possible TSs were used for $AlCl_3$. When more than two TSs are considered, the table lists the relative energies of the lowest *R* and *S* structures.

Cardillo's results indicate that $ZnCl_2$ induces no selectivity (Table 1). This observation strongly conflicts with Cardillo's mechanistic proposal and needs to be tested against our own model. A positive result will be a very good confirmation of the validity of our model, as it will be able to justify all of the experimental results obtained by Cardillo and can also be easily extrapolated to other systems. We studied the catalysis using this LA, and the results are in Table 3 (entries 7 and 8) and Figure 8.[14]

The theoretical data in Table 3 and Figure 8 indicate that the chelated complex with $ZnCl_2$ induces no stereoselectivity, in full accordance with the experimental results. This is not unexpected and agrees with recent results published by us[15] on the induction of selectivity in radical additions. As the β carbon atom is too far away from the auxiliary substituent, the attacking amine does not suffer a relevant steric contact, even when the amide bond conformation is inverted to form the chelate. According to the data in Table 3 (entries 5 and 6), a similar result is obtained when the chelating LA is $AlMe_2Cl$.[16]

The above-discussed results clearly indicate that the conjugated addition of amines to chiral α,β-unsaturated *N*-acylimidazolidinones catalyzed by $AlMe_2Cl$ or BF_3 does not proceed

Table 3. Lowest Activation Free Energies (ΔG) and Scaled and Unscaled Diastereomeric Ratios (dr, in Solvent) for the Addition of DMA to Imidazolidinone 3 in Carbonyl Parallel Conformation, Complexed with $AlCl_3$, $AlMe_2Cl$, and $ZnCl_2$[a]

					dr (*R*:*S*)	
entry	LA	complex	epimer	ΔG	unscaled	scaled
1	$AlCl_3$	BMP	*R*	20.5; *26.1*	4.4:95.6	13.1:86.9
2			*S*	19.7; *24.3*		
3	$AlMe_2Cl$	BMP	*R*	30.0; *30.8*	26.6:73.4	34.3:65.7
4			*S*	29.0; *30.4*		
5		MCP	*R*	24.7; *28.1*	52.8:47.2	51.7:48.3
6			*S*	25.1; *28.2*		
7	$ZnCl_2$	MCP	*R*	32.7; *33.6*	60.1:39.9	56.2:43.8
8			*S*	31.9; *33.8*		

[a] Calculated in gas phase (roman) and solvent (italic). When the LA is $AlMe_2Cl$, the selectivity via BMP was calculated by Boltzmann averaging over 9 possible TSs.

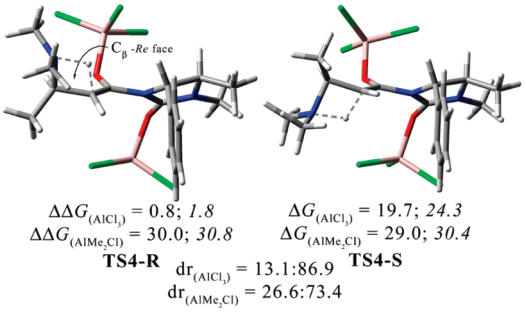

Figure 7. Unscaled relative free energies (ΔG) and scaled diastereomeric ratios (dr, in solvent) for the addition of DMA to imidazolidinone **3** in parallel carbonyl orientation, complexed with two molecules of $AlCl_3$ or $AlMe_2Cl$, calculated in gas phase (roman) and solvent (italic). Only the most stable structures are shown.

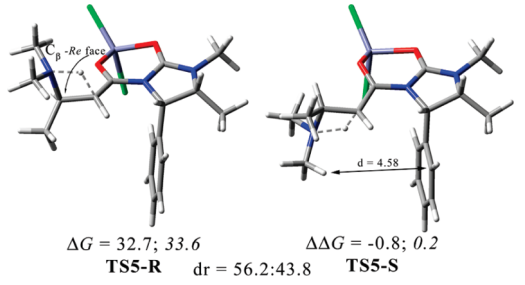

Figure 8. Unscaled relative free energies (ΔG) and diastereomeric ratios (dr, in solvent) for the addition of DMA to imidazolidinone **3** as a chelated complex with $ZnCl_2$ (top) or $AlMe_2Cl$ (bottom), calculated in gas phase (roman) and solvent (italic). The diastereomeric ratio was calculated from the scaled PCM energy values.

via chelated complexes, as the selectivity would be very low, or via open-chain carbonyl parallel complexes, as the selectivity would be inverted. These conclusions can be also applied to other systems, under similar reaction conditions. In particular, the results here obtained are a very strong support for the alternative mechanism proposed by us[8] to justify the selectivity obtained by Evans[1g] in DA additions of dienes to chiral α,β-unsaturated *N*-acyloxazolidinones catalyzed by $AlMe_2Cl$.

The conclusion that the traditional concept of direct steric hindrance by the substituents in oxazolidinone or imidazolidinone auxiliaries does not have to be always correct gets support on a recent paper by Hsung,[17] where the unexpected selectivity obtained in (4 + 3) cycloaddition reactions of oxyallyls was explained not as a result of steric contacts but of CH-π interactions between the attacking cyclopentadiene and the aromatic ring in the auxiliary.

CONCLUSIONS

In this paper we studied, by NMR and theoretical methods, the catalyzed conjugated addition of amines to acylimidazolidinones that was reported by Cardillo. Our results clearly show that aluminum chelates are not involved in the reaction, as they induce no selectivity, while Cardillo observed high experimental selectivities. Our data equally show that bicomplexes with carbonyl parallel orientation, proposed by Cardillo to justify the experimental selectivity with nonchelating Lewis acids, indeed induce the opposite selectivity and have also to be dismissed. On the other hand, our mechanistic proposal, based on open-chain carbonyl antiparallel complexes, allows for the full rationalization of the data obtained by Cardillo with aluminum, boron, or zinc Lewis acids and supports our previous proposal on DA cycloadditions of dienes to Evans chiral auxiliary derivatives. Extrapolation to other systems is possible, which makes this proposal a very powerful tool to help in the rationalization of known and new obtained data.

COMPUTATIONAL METHODS

Full geometry optimizations have been performed with the Gaussian 03, Revision E.01, software package[18] suite of programs employing density functional theory (DFT)[19] with the hybrid functional PBE1PBE[20] and the 6-31G(d) basis set. Harmonic vibrational frequencies have been calculated for all located stationary structures to verify whether they are minima or transition states. Zero-point energies and thermal corrections have been taken from unscaled vibrational frequencies. Free energies of activation, unless otherwise stated, are given at 25 °C. The energy values have been refined by single point DFT calculations at the PBE1PBE/6-311+G(2d,p) level of theory, over the optimized gas phase geometries. Solvent effects in dichloromethane (DCM) have been taken into account by single point calculations with the polarizable continuum model (PCM)[21] over the respective gas-phase geometries. Complexation and activation energies are calculated relative to the reagents. As the selectivities obtained when the reacting amine is dimethylamine are, as expected, slightly overestimated, scaled values are also shown in the tables. A scaling factor of 0.615 was used over the obtained PCM computed activation free energy differences. This value was obtained by fitting the theoretical and experimental diastereomeric ratios obtained for the reaction catalyzed by 2.0 equiv of $AlMe_2Cl$. All bond lengths are in angstroms (Å), energies are in kcal mol^{-1}, and dipole moments are in debye (D).

EXPERIMENTAL SECTION

NMR Methods. **4*S*,5*R*-3** was prepared according to reported procedures.[9] All NMR spectra were recorded on a NMR spectrometer, operating at 400.13 MHz for hydrogen. Chemical shifts were referenced to the chemical shift of the residual proton of the solvent peak. Standard 2D homonuclear (COSY) and heterenuclear correlations (HMQC) were performed whenever necessary for spectral assignment. The two-dimensional gs-NOESY experiments were acquired in phase-sensitive mode, using standard pulse sequences[22] with mixing times ranging from

500 ms up to 1.5 s. Generally, 8 or 16 scans and 256 F1 increments were obtained, and the spectral width in both dimensions was 5000 Hz.

■ ASSOCIATED CONTENT

Supporting Information. Extra structures for the uncatalyzed conjugated addition with respective energies. Cartesian coordinate matrixes and electronic energies of all calculated structures. Extra NMR spectral information. This material is available free of charge via the Internet at http://pubs.acs.org.

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