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PAPER

Understanding the cooperative NHC/LA catalysis for stereoselective annulation reactions with homoenolates. A DFT study†

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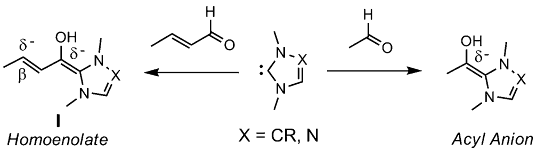
The role of Ti(O*i*-Pr)$_4$ Lewis acid (LA) in the cooperative N-heterocyclic carbene (NHC)/LA catalyzed addition of enals to enones to yield *cis*-cyclopentenes has been investigated using DFT methods at the B3LYP/6-31G** computational level. Ti(IV) effectively catalyzes the reaction by formation of a complex with cinnamaldehyde **1**, which favors the nucleophilic attack of NHC **5** on **1**, and the subsequent proton abstraction to yield the extended Ti(IV)–Breslow intermediate **21**. The nature of the metal involved in the LA catalyst plays a relevant role due to the more basic character of NHCs than aldehydes. Thus, strong LAs, such as Zn(OTf)$_2$, prevent the catalytic behavior of NHCs to form a very stable complex. The subsequent formation of a complex between chalcone **2** and the extended Ti(IV)–Breslow intermediate **21** favors the *cis* stereoselective C–C bond-formation. Analysis of the structures of Ti(IV)–complex precursors for the *cis* and *trans* C–C bond-formation steps allows for an explanation of the unexpected *cis* stereoselectivity.

Introduction

In recent years, N-heterocyclic carbenes (NHCs) have been utilized successfully as catalysts in organocatalytic reactions. One attractive feature of NHCs is their ability to assist in the *umpolung reactivity* of carbonyl compounds (Scheme 1). Homoenolates **I**,[1] species containing an anionic carbon β to a carbonyl group, have been used as a unique class of synthons for catalytic conjugate additions. The interest in these species can be attributed to the concept of "*conjugate umpolung*", introduced by Bode *et al.*[2] and Glorius *et al.*,[3] involving the reaction of NHCs and enals, which allowed for the direct generation of homoenolates for the first time. They can be efficiently trapped by aldehydes and other electrophilic species. Although it was known that annulation of enals occurred exclusively at the carbonyl, in the case of chalcones the C–C π system was expected to compete effectively with the carbonyl, thus leading to a cyclopentanone.



Umpolung reactivity catalyzed by NHCs

Scheme 1

In the course of their research on the reactions of homoenolates, Nair *et al.* have recently discovered a NHC-catalyzed homoenolate annulation of enals with chalcones, allowing for the efficient synthesis of 3,4-*trans*-disubstituted-1-aryl cyclopentenes (see Scheme 2).[4]

Very recently, Scheidt *et al.* have reported the cooperative NHC/Lewis acid (LA) catalysis for stereoselective annulation reactions with homoenolates (see Scheme 3).[5] Interestingly, the use of a 0.2 equiv of Ti(O*i*-Pr)$_4$ as LA catalyst afforded a 20 : 1 relationship of the *cis* : *trans* cyclopentenes **3**. The metal involved in the LA plays a relevant role in this cooperative NHC/LA catalysis since a LA and a Lewis base operate and activate starting materials simultaneously. Thus, strong LA as Zn(OTf)$_2$ or Mg(OTf)$_2$ can bind to Lewis base NHC yielding a strong NHC-LA interactions, avoiding the cooperative catalyst effect, while weak LA as Ti(O*i*-Pr)$_4$ can bind, yielding a weak association favoring the cooperative catalyst effect (see Scheme 3).

In the course of writing the present manuscript, Scheidt *et al.* reported further studies on the stereoselective cooperative NHC/LA catalyzed annulation of homoenolates to yield highly substituted cyclopentanes.[6] They suggest the significance of the concurrent coordination of the extended Ti(IV) Breslow intermediate **II** to the electrophilic carbonyl acceptor before the C–C bond formation step (see Scheme 4). The dual coordination present in the Ti(IV)-complex **III** does not only activate electrophilically the

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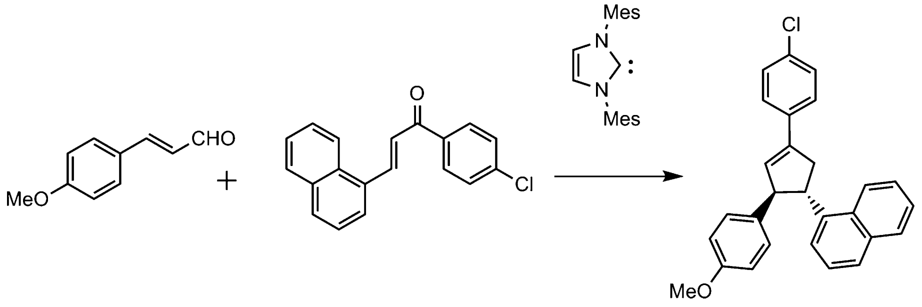
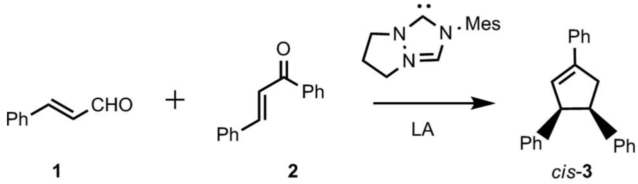
† Electronic supplementary information (ESI) available: B3LYP/6-31G** enthalpies and free energies for the stationary points involved in the NHC and the cooperative NHC/LA catalysis for stereoselective annulation reactions with homoenolates. Figure with top view of the sandwich **TS4** and **TS6**, associated with the *cis* reactive channels, and the twisted **TS5** and **TS7**, associated with the *trans* reactive channels. Complete citation for ref. 19 B3LYP/6-31G** computed total energies, unique frequency imaginary, and cartesian coordinates of the stationary points involved in the NHC and the cooperative NHC/LA catalysis for stereoselective annulation reactions with homoenolates. See DOI: 10.1039/c1ob05609c



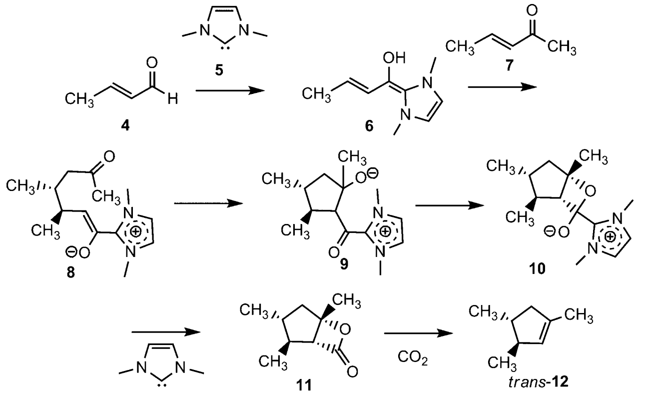
Scheme 2



LA (equiv)	% yield	*cis*:*trans*
-	73	1:3
$Zn(OTf)_2$ (1)	0	-
$Mg(OTf)_2$ (1)	0	-
$Ti(O\textit{i}\text{-}Pr)_4$ (0.2)	47 (71)[a]	20:1

a) in presence of 0.2 equiv of i-PrOH

Scheme 3

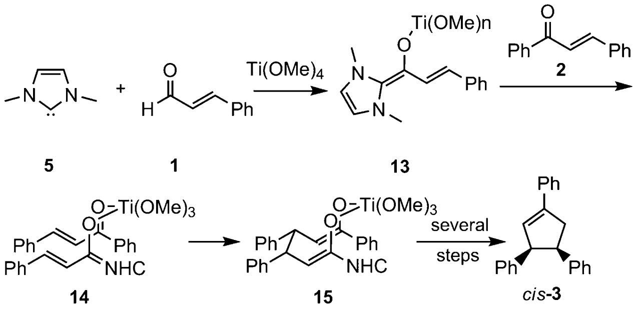


Scheme 5

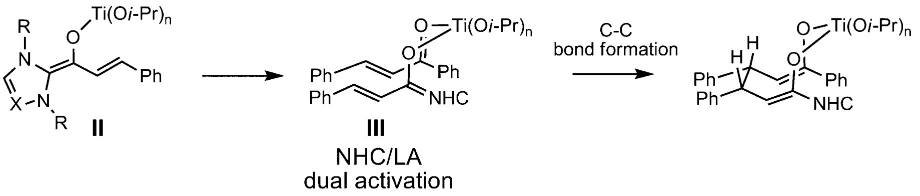
unsaturated ketones, but induces also a diastereo- and enantioselective addition.[5,6]

Our interest in organocatalysis[7] prompted us to carry out a theoretical investigation concerning the mechanisms of the NHC catalyzed reactions of enals with enones, experimentally studied by Nair, using DFT methods at the well-established B3LYP/6-31G** level.[8] The studied mechanism (see Scheme 5) showed that these NHC catalyzed reactions comprise several steps. The first one is the formation of a Breslow intermediate **6** that nucleophilically attacks the conjugated position of the enone **7** to yield an enol-enolate, which equilibrates with the keto-enolate **8**. This second step is responsible for the *trans* relationship at the final cyclopentene. An intramolecular aldolic condensation allows for the formation of the alkoxy cyclopentane intermediate **9**, that by intramolecular nucleophilic attack on the carbonyl group yields a bicyclic ether **10**. The extrusion of the NHC catalyst affords a bicyclic lactone **11**, yielding through CO_2 elimination, the final *trans*-cyclopentene *trans*-**12**.

In the present paper, the role of the LA catalysts in the cooperative NHC/LA catalyzed addition of enals to enones to yield *cis*-cyclopentenes is being studied using DFT methods at the B3LYP/6-31G** level. For this purpose, the reaction between cinnamaldehyde **1** and chalcone **2** in the presence of NHC **5** and $Ti(OMe)_4$ LA, *via* the LA complex **14**, to yield the *cis* bis-enolate **15** has been studied as a theoretical model of the NHC/LA catalyzed addition of enals to enones, recently studied by Scheidt.[5] The simplified mechanism suggested is shown in Scheme 6.



Scheme 6



Scheme 4

Computational methods

DFT calculations were carried out using the B3LYP[9] exchange–correlation functional, together with the standard 6-31G** basis set.[10] Optimizations were carried out using the Berny analytical gradient optimization method.[11] Stationary points were characterized by frequency calculations in order to verify that transition state structures (TSs) have only one imaginary frequency. The intrinsic reaction coordinate (IRC)[12] path was followed to check the energy profiles connecting each TS to the two associated minima of the proposed mechanism by using the second order González-Schlegel integration method.[13] The electronic structures of stationary points were analyzed by the NBO method.[14] The suitability of the standard 6-31G** basis set to account for the Ti(VI) interactions on the Ti-complexes was validated against the LanL2DZ and the 6-311++G** basis sets.[10] While the LanL2DZ basis set underestimates Ti-O bond interactions, the results for the 6-31G** basis set were closer to those using the large 6-311++G** basis sets (see Table S1 in the ESI†). On the other hand, the B3LYP exchange–correlation functional was tested against the hybrid *meta* MPW1B95 functional.[15] Although similar results were obtained for the two functionals (see Table S1 in the ESI†) all attempts to locate some TSs with the MPW1B95 functional were unsuccessful.

Values of free energies in dichloromethane (DCM) were calculated with the standard statistical thermodynamics at 298.15 K and 1 atm over the optimized gas phase structures.[10] In the thermodynamic calculations, harmonic vibrational frequencies were scaled by a factor of 0.96.[16] Solvent effects of DCM were considered on the thermodynamic calculations using a self-consistent reaction field (SCRF)[17] based on the polarizable continuum model (PCM) of Tomasi's group.[18] The UFF radii model was used to generate the molecular cavity on the PCM calculations. All calculations were carried out with the Gaussian 03 suite of programs.[19]

Results and discussions

In order to understand the role of LA catalysts in the cooperative NHC/LA catalysis for stereoselective *cis* annulation reactions with homoenolates, this theoretical study has been divided into three different parts: i) study of the nature of the metal involved in the LA catalyst; ii) formation of the extended Ti(IV)–Breslow intermediate *versus* the Breslow intermediate, and iii) study of the *cis* stereoselectivity in the Ti(IV) LA assisted C–C bond-formation step.

1) Study of the nature of the metal involved in the LA catalyst

Scheidt found that the metal involved in the LA catalyst plays a relevant role in this cooperative NHC/LA catalysis.[5] Thus, while strong $Zn(OTf)_2$ or $Mg(OTf)_2$ LAs can bind to NHC yielding a strong NHC–LA interaction, avoiding the cooperative catalyst effect, a weak $Ti(Oi\text{-}Pr)_4$ LA can bind yielding a weak association, favoring the cooperative catalyst effect (see Scheme 3). In order to understand the role of the metal involved in the LA catalyst, the acid/base equilibrium between NHC–LA complexes **16** and **18** and the LA coordinated enone complexes **17** and **19** involving Ti- and Zn-based LAs were studied first (see Scheme 7).

Table 1 B3LYP/6-31G** Relative free energies (ΔG, in kcal mol^{-1}) in DCM of the stationary points involved in the formation of the extended Ti(IV) Breslow intermediate **21** and Breslow intermediate **23**

	ΔG	
MC1	−12.2[a]	(0.0)[d]
TS1	−4.7[a]	(7.6)[d]
20	−22.6[a]	(−10.4)[d]
TS2	−9.2[a]	(3.0)[d]
21	−17.3[a]	(−5.0)[d]
MC2	−3.7[b]	(0.0)[d]
TS3	6.5[b]	(10.2)[d]
22	−1.5[b]	(2.2)[d]
TS4	18.7[c]	(20.9)[d]
23	−6.8[b]	(−3.1)[d]

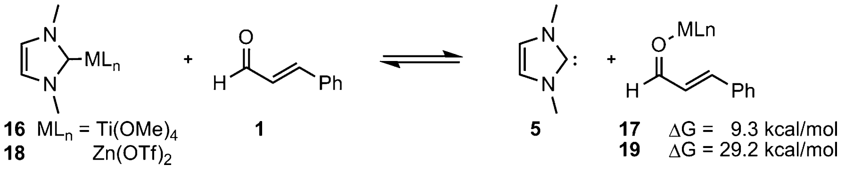
[a] Relative to **5** + **1** + $Ti(OMe)_4$. [b] Relative to **5** + **1**. [c] Relative to the **22** + MeOH molecular complex. [d] Relative to **MC1** or **MC2**.

Both equilibria are endergonic by 9.3 and 29.2 kcal mol^{-1} (see Scheme 7). Although these equilibria do not correspond with the experimental conditions, the high endergonic character of the reaction using the Zn-based LA catalyst makes it possible to assume that the equilibrium using $Zn(OTf)_2$ is completely shifted towards the NHC : $Zn(OTf)_2$ complex **18**, and consequently the nucleophilic attack of NHC on cinnamaldehyde **1** is impossible (see experimental results in Scheme 3). This analysis allows for an explanation of the absence of reaction in presence of $Zn(OTf)_2$ salt.[5]

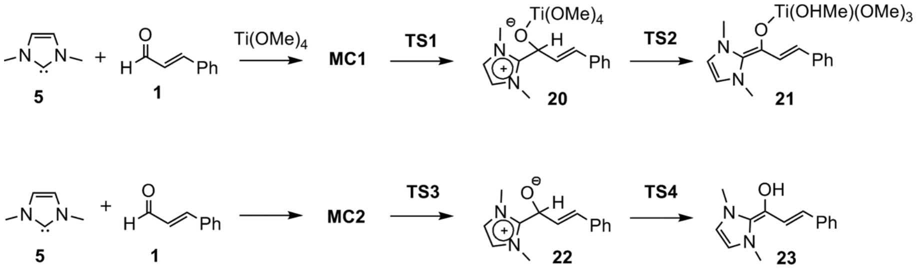
2) Formation of the extended Ti(IV)–Breslow intermediate 21 *versus* the Breslow intermediate 23

Formation of the extended Ti(IV)–Breslow intermediate **21** is a stepwise process that comprises two consecutive steps: i) nucleophilic attack of NHC **5** on cinnamaldehyde **1** activated by $Ti(OMe)_4$, yielding the zwitterionic intermediate **20**, and ii) a proton transfer process to a methoxy ligand to yield the extended Ti(IV) Breslow intermediate **21** (see Scheme 8). The relative enthalpies and free energies are given in Table 1.

Due to the basic character of NHC **5** and cinnamaldehyde **1**, both species can concurrently be coordinated to $Ti(OMe)_4$ to yield the molecular complex **MC1**. Formation of **MC1** from separated reagents, **1** + **5** + $Ti(OMe)_4$,[20] is exergonic by −12.2 kcal mol^{-1}; consequently, this species will be considered as the energy reference



Scheme 7



Scheme 8

for the cooperative NHC/LA catalyzed process. From **MC1**, the activation free energy associated with the nucleophilic attack of NHC **5** on the **1**-Ti(OMe)$_4$ complex, *via* **TS1**, is 7.6 kcal mol^{-1}; formation of the zwitterionic intermediate **20** is exergonic by –10.4 kcal/mol. The subsequent intramolecular proton transfer process to the oxygen atom of a methoxy ligand *via* **TS2** also presents a low activation free energy, 13.4 kcal/mol. Formation of the extended Ti(IV) Breslow intermediate **21** is exergonic by –5.0 kcal/mol. A schematic representation of the free energy profile for the cooperative NHC/LA catalyzed formation of the extended Ti(IV) Breslow intermediate **21** is given in Fig. 1.

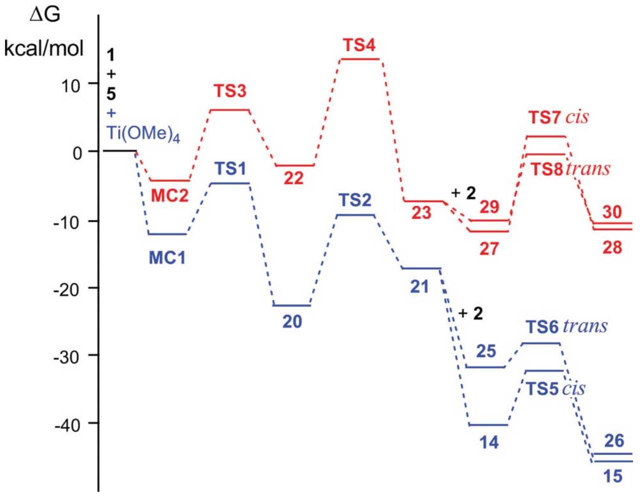


Fig. 1 Free energy profile (ΔG in kcal mol^{-1}) for the formation of the extended Ti(IV)–Breslow intermediate **21** (in blue) and the Breslow intermediate **23** (in red), and the corresponding stereoselective C–C bond formation steps.

Competitively, NHC **5** can cause a nucleophilic attack on cinnamaldehyde **1** to yield the zwitterionic intermediate **22**, which by a proton shift will yield the Breslow intermediate **23** (see Scheme 8). NHC **5** and cinnamaldehyde **1** form a molecular complex, **MC2**, in an earlier step of the addition, in which the two reagents are hydrogen-bonded (HB). Formation of **MC2** from the separated reagents is exergonic by –3.7 kcal/mol. The activation free energy associated with the nucleophilic attack of NHC **5** on cinnamaldehyde **1** from **MC2**, *via* **TS3**, is 10.2 kcal mol^{-1}; formation of the zwitterionic intermediate **22** is endergonic by 2.2 kcal/mol. The free activation energy associated with **TS3** is 2.6 kcal mol^{-1} higher than that associated with **TS1**; in addition, while formation of the zwitterionic intermediate **20** is strongly exergonic, formation **22** is slightly endergonic. These results are a consequence of the unfavorable negative charge location in the oxygen atom of the zwitterionic intermediate **22**; note that in intermediate **20** the negatively charged oxygen atom participates in the formation of a dative bond to Ti(IV).

The subsequent step is a 1,2-shift at the zwitterionic intermediate **22** to yield Breslow intermediate **23**. The intramolecular 1,2-shift is very unfavorable, about 40 kcal mol^{-1}, due to the formation of a three-membered cyclic TS.[21] The necessity to include one acid/base molecule in order to favor the 1,2-shift through a more extended TS has been demonstrated.[21] Thus, the inclusion of a methanol molecule to favor this hydrogen shift decreases this unfavorable energy to 18.7 kcal mol^{-1} (20.9 kcal mol^{-1} from **MC2**) (see **TS4** in Fig. 1).[21] Therefore, this step is the rate-determining step for the formation of Breslow intermediates. From **MC2**, formation of Breslow intermediate **23** is exergonic by –3.1 kcal/mol. Consequently, in presence of Ti(OMe)$_4$, formation of Breslow intermediate **23** is not competitive with the formation of the extended Ti(IV) Breslow intermediate **21** (see Fig. 1).

The geometries of the TSs involved in the formation of the intermediates **21** and **23** are given in Fig. 2. At **TS1** and **TS3** associated with the nucleophilic attack of NHC **5** on the **1**-Ti(OMe)$_4$ complex and cinnamaldehyde **1**, the length of the C–C forming-bond is 2.308 and 1.935 Å, respectively. At **TS2**, associated with the proton transfer process to the oxygen atom of a methoxy ligand, the lengths of C–H breaking-bond and the O–H forming-bonds are 1.363 and 1.245 Å, respectively. At the extended Ti(IV)–Breslow intermediate **21**, the methanol molecule formed

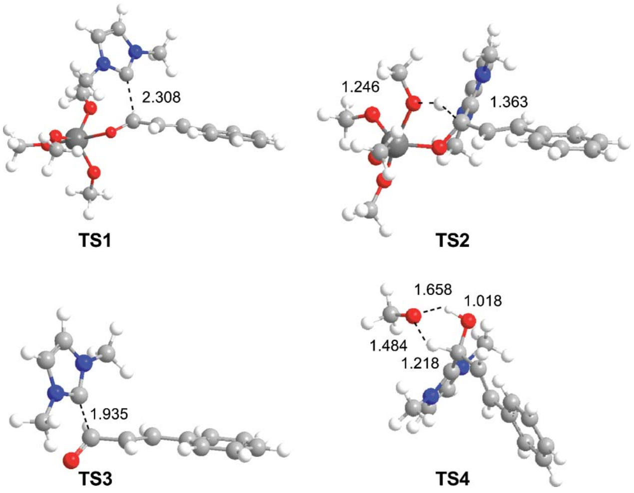
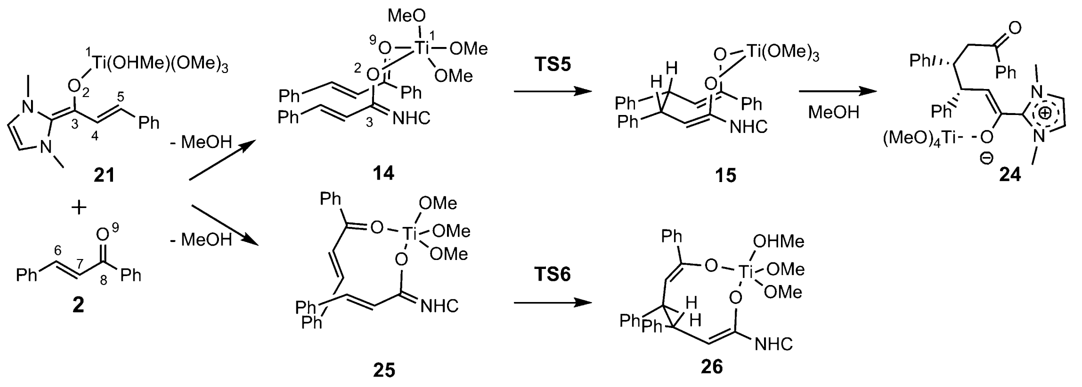


Fig. 2 Transition structures associated with the formation of the extended Ti(IV)–Breslow intermediate **21** and Breslow intermediate **23**.



Scheme 9

Table 2 B3LYP/6-31G** Relative free energies (ΔG, in kcal mol^{-1}) in DCM of the stationary points involved in the stereoselective C–C bond-formation steps

	ΔG	
14 + MeOH	−22.7[a]	
TS5	7.9[b]	
15	−5.6[b]	
24	−5.8[b]	
25	8.4[b]	
TS6	11.4[b]	
26	−4.2[b]	
27	−8.8[c]	(0.0)[d]
TS7	5.3[c]	(14.0)[d]
28	−10.9[c]	(−2.2)[d]
29	−6.4[c]	(2.3)[d]
TS8	2.8[c]	(11.6)[d]
30	−10.4[c]	(−1.6)[d]

[a] Relatives to **21** + **2**. [b] Relatives to **14**. [c] Relatives to **23** + **2**. [d] Relative to **27**.

by the proton transfer remains coordinated to Ti(IV). At **TS4**, associated with the methanol promoted proton transfer process on the intermediate **22**, the lengths of C–H breaking-bond, 1.218 Å, and the O–H forming-bond, 1.108 Å, indicate that formation of the alcohol H–O bond is more advanced than the C–H breaking-bond.

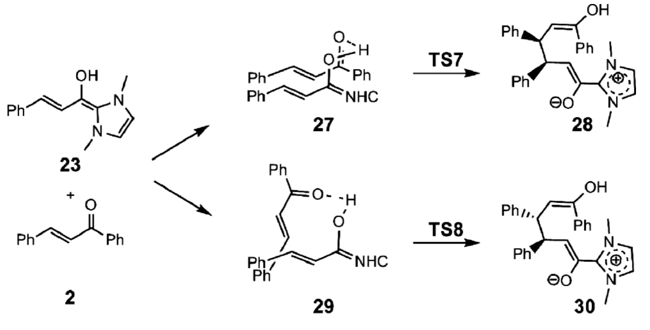
3) Study of the *cis*/*trans* stereoselectivity at the C–C bond-formation step in presence and absence of the Ti(IV) LA catalyst

The subsequent nucleophilic attack of the extended Ti(IV)–Breslow intermediate **21** on chalcone **2** (see Scheme 9) is the decisive step for the *cis* or *trans* stereochemistry of the final cyclopentenones. For this step there are several stereoisomeric reactive channels, which are related with the nucleophilic attack of the β position of intermediate **21** through its *re*-face or *si*-face on the conjugated β position of chalcone **2** through the *re*-face or *si*-face. We performed a structural search for the two most favorable reactive channels associated with the formation of *cis* and *trans* enolates **15** and **26**. This study shows that there is a previous coordination of **21** and **2** to yield Ti-complexes **14** and **25**, with trigonal bipyramidal geometries around the Ti atom. In these complexes, the extended Ti(IV)–Breslow intermediate **21** is coordinated in an axial disposition, while chalcone **2** is coordinated in an equatorial disposition. These complexes open the channels associated with the formation of *cis* dienolate **15** and *trans* dienolate **26**, through **TS5** and **TS6**, respectively.

From the extended Ti(IV)–Breslow intermediate **21** plus chalcone **2**, formation of Ti-complex **14** plus MeOH is exergonic by −22.7 kcal mol^{-1} (see Table 2 and Fig. 1). Ti-complex **25** is 8.4 kcal mol^{-1} higher in free energy than Ti-complex **14**. From the most favorable Ti–complex **14**, the activation free energies associated with the C–C bond-formations are: 7.9 (**TS5**) and 11.4 (**TS6**) kcal/mol. Therefore, formation of *trans* intermediate **26** *via* **TS6** is 3.5 kcal mol^{-1} higher in free energy than formation of *cis* intermediate **15** *via* **TS5**. This relative free energy is in agreement with the *cis* stereoselectivity experimentally found for the cooperative NHC/LA catalysis for stereoselective annulation reactions with homoenolates.[5] Formation of dienolate intermediates **15** and **26** are exergonic by −5.6 and −4.2 kcal mol^{-1}, respectively.

Finally, addition of a methanol molecule to the dienolate **15** may yield the ketoenolate **24** (see Scheme 9). From this point, the stereochemistry cannot change and the mechanism may follow a process similar to the one studied in Scheme 5 (see **8** to **12**), to give the corresponding *cis* cyclopentenone (see *cis*-**3** in Scheme 6).

In order to assert the role of the Ti(IV) LA catalyst in the *cis* stereoselectivity, the nucleophilic attack of Breslow intermediate **23** on chalcone **2** was also analyzed. This step is assisted by the formation of a hydrogen-bond between the acidic hydrogen atom of Breslow intermediate **23** and the oxygen atom of chalcone **2**, favoring the subsequent conjugated nucleophilic attack.[8] There are several stereoisomeric pathways for this step. Herein we present only the most favorable reaction pathways associated with the formation of *cis* and *trans* relationship of the two phenyl substituents (see Scheme 10).



Scheme 10

The IRCs from the TSs associated with the nucleophilic attacks of Breslow intermediate **23** on chalcone **2**, **TS7** and **TS8**, to reagents allow for the characterization of two molecular complexes, **27** and **29**, in which both reagents are HB (see Scheme 10). Formation of these molecular complexes is exergonic by −8.8 (**27**) and −6.4 (**29**) kcal mol^{-1} (see Table 2 and Fig. 1).

From the most favorable molecular complex **27**, the relative free energies associated with **TS7** and **TS8** are 14.0 and 11.6 kcal mol^{-1}, respectively. In absence of the Ti(IV) LA catalyst, *cis* **TS7** is 2.4 kcal mol^{-1} higher in free energy than *trans* **TS8**, in agreement with the experimental results reported by Scheidt for lonely NHC catalyzed reactions (see Scheme 3).[5] On the other hand, free activation energy for *cis* **TS5**, associated with the Ti(IV) LA catalyzed C–C bond formation, is 3.7 kcal mol^{-1} lower in free energy than that for *trans* **TS8**, associated with the HB catalyzed C–C bond formation. This behavior evidences the catalytic effect of TI(IV) in the C–C bond formation step of cooperative NHC/LA catalyzed reactions. Consequently, the presence of the TI(IV) LA catalyst not only changes the stereoselectivity, but also accelerates the C–C bond-formation step.

The geometries of the TSs involved in the intramolecular nucleophilic attacks of the intermediates **21** and **23** on the chalcone **2** are given in Fig. 3. At **TS5** and **TS6** the lengths of the C5–C6 forming bond are 2.229 and 2.459 Å, respectively. At **TS5**, the two-reactant molecules present a sandwich rearrangement, in which the axial extended Ti(IV)–Breslow intermediate **21** is positioned parallel above the equatorial chalcone **2**. At the more energetic **TS6** the two molecules are twisted (see Figure S1 in the ESI†). The C4–C5–C6–C7 dihedral angles at these TSs are −14.6 degrees at **TS5** and 146.8 degrees at **TS6**.

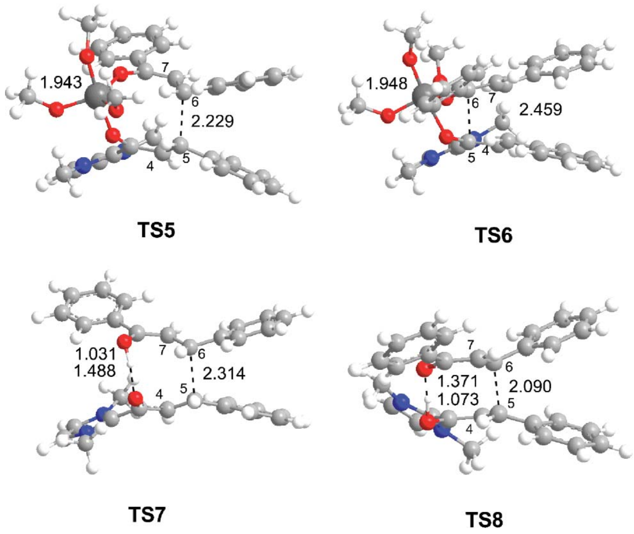


Fig. 3 Transition structures involved in the stereoselective C–C bond formation steps. The distances are given in Å.

At **TS7** and **TS8**, the lengths of the C5–C6 forming bond are 2.314 and 2.090 Å, respectively. The lengths of the O–H breaking and forming bonds at these TSs are 1.488 and 1.031 Å at **TS7** and 1.073 and 1.371 at **TS8**. Consequently, at the most favorable **TS8**, the proton transfer process is more delayed. The C4–C5–C6–C7 dihedral angles at these TSs are −22.7 degrees at **TS7** and 127.1 degrees at **TS8**. Just as **TS5** and **TS6**, at **TS7** the two molecules present a sandwich rearrangement, while at the more favorable **TS8** they are twisted (see Figure S1 in the ESI†).

Table 3 Charge transfer (in e) to the chalcone framework along the nucleophilic attacks of the extended Ti(IV)–Breslow intermediate **21** and Breslow intermediate **23** on chalcone **2**

	cis channels		*trans* channels	
i) cooperative NHC/LA catalyzed process.				
	14	**TS5**	**25**	**TS6**
	−0.41	−0.57	−0.38	−0.50
ii) NHC catalyzed process.				
	27	**TS7**	**29**	**TS8**
	−0.10	−0.05	−0.07	−0.51

Where is the origin of the change in the cis/trans stereoselectivity in the cooperative NHC/LA catalyst process?. cis Ti–complex **14** and **TS5** are 8.4 and 3.5 kcal mol^{-1} more stable than *trans* Ti–complex **25** and **TS6**, respectively (see Scheme 9, Table 2 and Fig. 1). At *cis* Ti–complex **14** and **TS5**, the extended Ti(IV)–Breslow intermediate **21** and chalcone **2** frameworks adopt a sandwich parallel rearrangement, while at *trans* Ti–complex **25** and **TS6**, they are twisted. These rearrangements are similar to those present in HB complexes **27** and **29** and **TS7** and **TS8** associated with the nucleophilic attack of Breslow intermediate **23** on chalcone **2** (see Figure S1 in the ESI†). An NBO analysis at complexes **14** and **25** and the corresponding **TS5** and **TS6** shows that along the sandwich parallel *cis* channel there is a larger charge transfer from the nucleophilic extended Ti(IV)–Breslow intermediate **21** to the electrophilic chalcone **2** than along the twisted *trans* channel. The charges in the chalcone framework at the corresponding complexes and TSs are given in Table 3. An unlike charge transfer process is found at *cis* and *trans* HB molecular complexes **27** and **29** and the corresponding **TS7** and **TS8** associated with the attacks of Breslow intermediate **23** on chalcone **2** (see Table 3). The low charge transfer found at **TS7** is due to the fact that at this TS, the acidic hydrogen of Breslow intermediate **23** has been already transferred to chalcone **2**. Note the larger charge transfer found in the chalcone framework at Ti-complexes **14** and **25**, *ca.* −0.4e, than at HB molecular complexes **27** and **29**, *ca.* −0.1e. Therefore, the more favorable nucleophilic/electrophilic interactions that appear along the *cis* channel of the cooperative NHC/LA catalyzed process overcome the unfavorable steric interactions (sandwich parallel rearrangement) allowing for an explanation of the change of *cis* stereoselectivity in the NHC/LA catalyst process.

Conclusions

The role of Ti(O*i*-Pr)$_4$ LA in the cooperative NHC/LA catalysis for *cis* stereoselective annulation reactions with homoenolates has been investigated using DFT methods at the B3LYP/6-31G** computational level. Ti(IV) effectively catalyzes the reaction by formation of a Ti–complex with cinnamaldehyde **1**, which favors the nucleophilic attack of NHC **5** on **1**, and the subsequent proton abstraction to yield the extended Ti(IV)–Breslow intermediate **21**. The nature of the metal involved in the LA catalyst plays a relevant role due to the more basic character of NHCs than aldehydes. Thus, strong LAs, such as Zn(OTf)$_2$, prevent the catalytic behavior of NHCs from forming a very stable complex. Finally, formation of a complex between chalcone **2** and the extended Ti(IV)–Breslow intermediate **21** favors the subsequent *cis* stereoselective C–C bond-formation, present in the final cyclopentene.

A comparative analysis of the studied reactive channels for cooperative NHC/LA catalyzed reactions with those associated with the common NHC catalyzed processes asserts the catalytic effect of Ti(IV), and consequently the last pathways turn out to be non-competitive.

Analysis of the structures of Ti(IV)–complex precursors for the *cis* and *trans* C–C bond-formation steps allows for an explanation of the *cis* stereoselectivity. Along the *cis* reactive channel, the favorable charge transfer between the nucleophilic extended Ti(IV)–Breslow intermediate **21** and the electrophilic coordinated chalcone **2** overcomes the unfavorable interactions that appear at the sandwich parallel rearrangement in the *cis* channel associated with common NHC catalyzed stereoselective annulation reactions with homoenolates.

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