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Understanding the mechanism of stereoselective synthesis of cyclopentenes *via* N-heterocyclic carbene catalyzed reactions of enals with enones†

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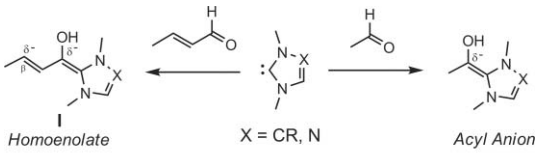
The N-heterocyclic carbene (NHC) catalyzed addition of enals to enones to yield *trans*-cyclopentenes has been investigated using DFT methods at B3LYP/6-31G** computational level. This NHC catalyzed reaction comprises several steps. The first one is the formation of a Breslow intermediate, which nucleophilically attacks to the conjugated position of the enone to yield an enol-enolate. 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, that by intramolecular nucleophilic attack on the carbonyl group yields a bicyclic ether. The extrusion of the NHC catalyst affords a bicyclic lactone, yielding by CO_2 elimination, the final *trans*-cyclopentene.

Introduction

In recent years, N-heterocyclic carbenes (NHCs) have been successfully utilized 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. Although the application of homoenolates in organic synthesis has been limited,[2] since no direct methods for their generation exists, it is noteworthy that a number of elegant protocols for the generation of homoenolate equivalents have been developed.[3] The renewed interest in these species can be attributed to the concept of "*conjugate umpolung*", introduced by Bode *et al.*[4] and Glorius *et al.*,[5] involving the reaction of NHCs and enals, allowing for the direct generation of homoenolates for the first time. These species 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.

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, which allows for the efficient synthesis of 3,4-*trans*-disubtituted-1-aryl cyclopentenes (see Scheme 2).[6] Thus, the reaction of 4-methoxy cinnamaldehyde **1** with chalcone **2** in presence of a catalytic amount of the *in situ* formed imidazolium NHC **3** afforded the *trans*-1,3,4-trisubstituted cyclopentene **4**.

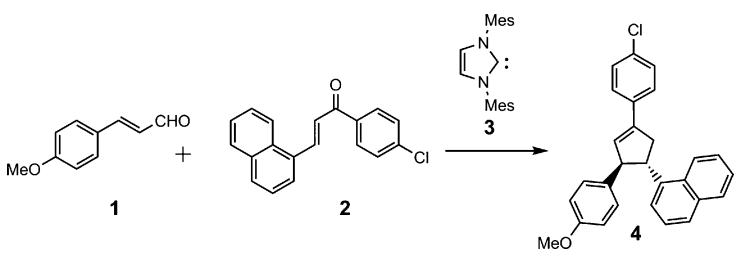


Umpolung reactivity catalyzed by NHCs

Scheme 1

Subsequently, Bode *et al.*[7] have reported the NHC-catalyzed annulation reaction of the cinnamaldehyde **5** with the γ-ketoenoate **6** mediated by the triazolium NHC catalyst **7a**. Interestingly, in contrast to the use of chalcone derivatives, which provided the *trans*-cyclopentene **4**, the γ-ketoenoate **6** selectively gave the *cis*-cyclopentene **8** (see Scheme 3).

For the reaction with chalcone **2**, Nair[6,8] proposed that the homoenolate **I** undergoes a conjugate addition to the chalcone, followed by proton transfer to generate the enolate **II**, participating in an intramolecular aldol reaction to yield the cyclopentene carbinolate **III** (see Scheme 4). This undergoes a β lactonization by extrusion of the NHC. The lactone **V** undergoes a further loss of CO_2 to yield the cyclopentene. In this mechanism, the conjugate addition is the stereoselective step allowing for the formation of the final *trans*-disubstituted cyclopentene.



Scheme 2

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† Electronic supplementary information (ESI) available: Supplementary tables. See DOI: 10.1039/c0ob00088d

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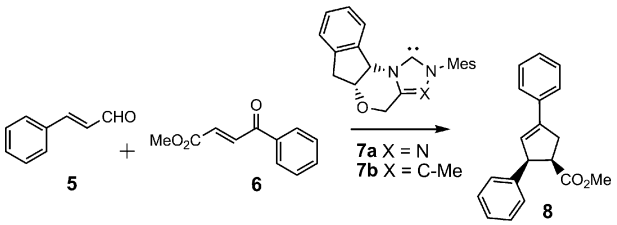
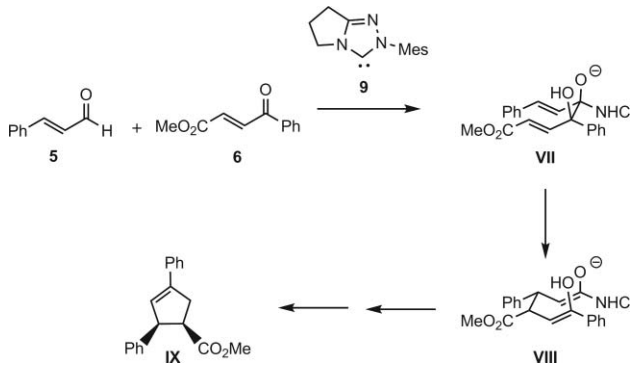


Scheme 3

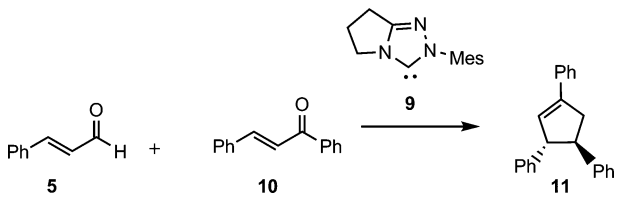
Alternatively, for *cis*-cyclopentene formation Bode[7] proposed that a NHC-catalyzed crossed benzoin reaction[9] between cinnamaldehyde **5** and the γ-ketoenoate **6** would lead to an intermediate **VII**, equilibrated by an oxy-Cope rearrangement with the *cis*-intermediate **VIII** (see Scheme 5). **VIII** is the enol of the product **II** in Nair's conjugate addition of the homoenolate **I** to the enone **II**, and it would undergo the sequence **II** to **VI** to afford cyclopentene **IX**.

Recent experimental studies on the direct annulation of cinnamaldehyde **5** with the γ-ketoenoate **6** using triazolium and imidazolium NHC catalysts (see **7a** and **7b** in Scheme 3) have shown that both catalysts promoted a similar *cis*-selectivity.[10] Consequently, the use of the triazolium and imidazolium NHC catalysts is not important in the control of the stereoselectivity observed. On the other hand, the presence of the carboxylate group in the enone was fundamental to obtain the *cis*-cyclopentane since the triazolium catalyzed reaction between cinnamaldehyde **5** and the chalcone **10** yielded exclusively the *trans*-cyclopentene **11** (see Scheme 6).[7]

Our interest in organocatalysis[11] has prompted us to carry out a series of theoretical investigations concerning the mechanisms of the NHC catalyzed reactions of aldehydes. Very recently, we have studied the NHC catalyzed ring-expansion of 4-formyl-β-lactams to succinimide derivatives.[12] Now, in this work, we would investigate the mechanisms of stereoselective formation of *trans* and *cis*-cyclopentenes *via* NHC catalyzed reactions of enals with enones using DFT methods at the well-established B3LYP/6-31G** level. For this purpose, the reaction of (*E*)-but-2-enal **12** with (*E*)-pent-3-en-2-one **13** to yield the *trans*-cyclopentenes



Scheme 5

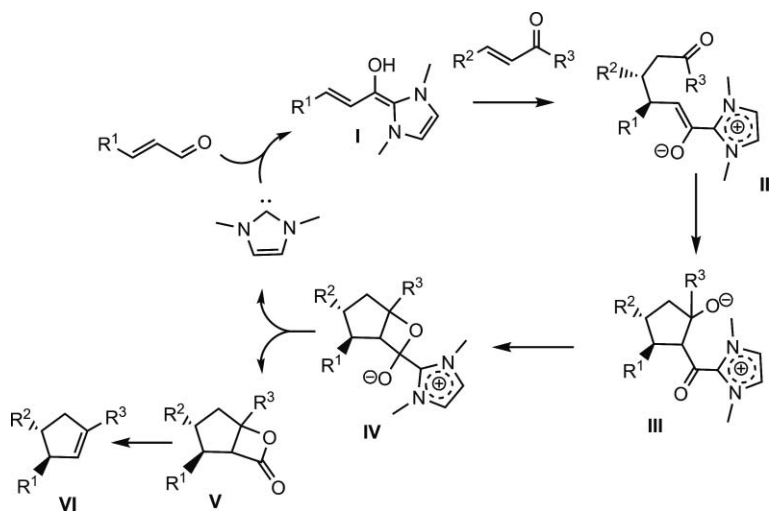


Scheme 6

15 in presence of the imidazolium NHC **14** was selected as a computational reaction model (see Scheme 7).

Computational methods

DFT calculations[13] were carried out using the B3LYP[14] exchange–correlation functional, together with the standard 6-31G** basis set.[15] Optimizations were carried out using the Berny analytical gradient optimization method.[16] The stationary points were characterized by frequency calculations in order to verify that the transition structures (TSs) have only one imaginary frequency. The intrinsic reaction coordinate (IRC)[17] 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.[18] The electronic structures of stationary points were analyzed by the NBO method.[19] Values



Scheme 4

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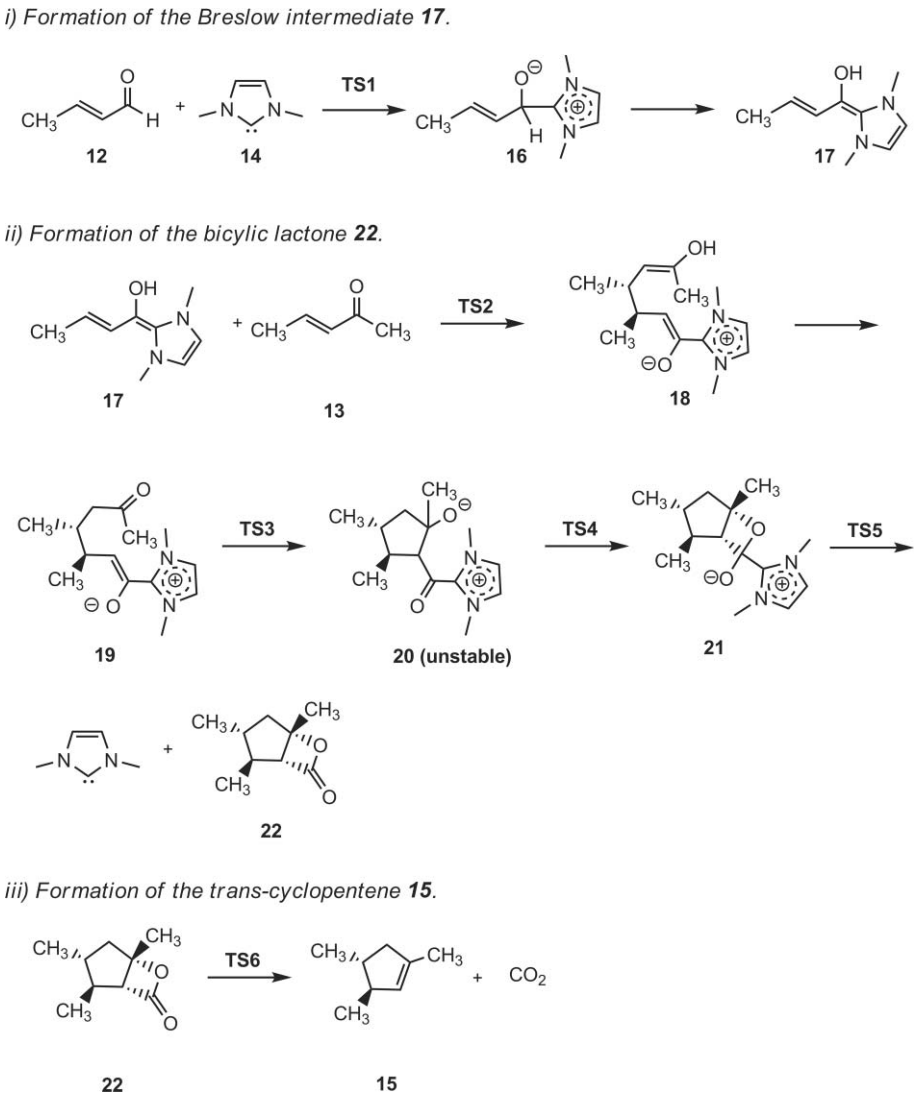

Scheme 7

of enthalpies and free energies in THF were obtained by frequency calculations over the B3LYP/6-31G** gas-phase geometries. Thermodynamic calculations were calculated with the standard statistical thermodynamics at 298.15 K and 1 atm.[15] and harmonic vibrational frequencies were scaled by a factor of 0.96.[20] Solvent effects of THF ($\varepsilon = 7.43$) on the thermodynamic calculations were considered using a self-consistent reaction field (SCRF)[21] based on the polarizable continuum model (PCM) of the Tomasi group.[22] All calculations were carried out with the Gaussian 03 suite of programs.[23]

Results and Discussion

a) Study of the NHC catalyzed addition of the *E*-but-2-enal 12 to *E*-pent-3-en-2-one 13 with formation of the *trans*-1,3,4-trimethylcyclopent-1-ene 15.

The NHC catalyzed addition of *E*-but-2-enal **12** to *E*-pent-3-en-2-one **13** to yield the *trans*-1,3,4-trimethylcyclopent-1-ene **15** comprises several elementary steps (see Scheme 7). The first one is the nucleophilic attack of the imidazol-2-ylidene **14** on the carbonyl carbon atom of *E*-but-2-enal **12** yielding the zwitterionic intermediate **16**, which by a proton transfer process affords the Breslow intermediate **17**. The subsequent conjugated addition of the intermediate **17** to enone **13** yields the enol-enolate **18**, becoming the keto-enolate **19** by means of a keto-enol type equilibrium. An intramolecular aldolic condensation on **19** allows for the formation of the alkoxy cyclopentane intermediate **20**, that by an intramolecular nucleophilic attack on the carbonyl group present in **20** affords the bicyclic ether **21**. Extrusion of the imidazolium NHC catalyst **14** from **21** provides the bicyclic lactone **22**, yielding by CO_2 elimination, the final *trans*-1,3,4-trimethylcyclopent-1-ene **15**. In order to simplify the discussion, this complex mechanism has been divided into three different parts: i) formation of the Breslow intermediate **17**; ii) formation of the bicyclic lactone **22**; and iii) formation of the *trans*-trimethylcyclopentene **15**. The relative enthalpies and free energies associated to this catalytic cycle are depicted in the Table 1, while a schematic representation of the free energy profile is shown in Fig. 1.

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Table 1 B3LYP/6-31G** Relative enthalpies (ΔH, in kcal mol^{-1}) and free energies (ΔG, in kcal mol^{-1}) computed at 298.15 K and 1 atm in THF of the stationary points involved in the NHC catalyzed addition of the *E*-but-2-enal **12** to *E*-pent-3-en-2-one **13**

	ΔH	ΔG
i) Formation of the Breslow intermediate **17**.		
12 + **14**	0.0	0.0
TS1	3.8	18.1
16	−1.1	11.6
17	−6.1	6.1
ii) Formation of the bicyclic lactone **22**.		
17 + **13**	0.0	0.0
TS2	3.4	19.5
TS7	5.9	22.9
18	−20.1	−4.0
23	−20.3	−3.0
19	−25.3	−9.5
TS3	−8.0	10.4
TS4	−11.0	8.6
21	−17.7	1.1
TS5	−10.5	7.9
22 + **14**	−19.7	−1.3
iii) formation of the *trans*–cyclopentene 15.		
22	0.0	0.0
TS6	28.1	26.3
15 + CO_2	−10.6	−16.4

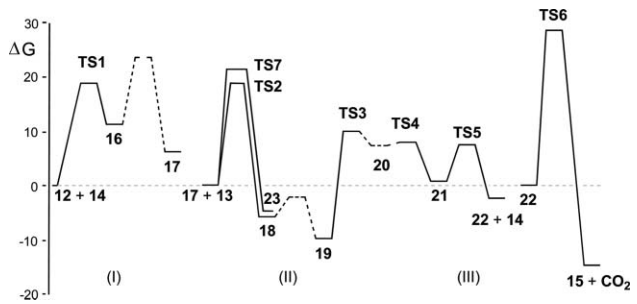


Fig. 1 Free energy profile (in kcal mol^{-1}) in THF for the NHC catalyzed reaction of the enal **12** with the enone **13**. (i) formation of the Breslow intermediate **17**; (II) Formation of the bicyclic lactone **22**; (iii) Formation of the *trans*-trimethylcyclopentene **15**.

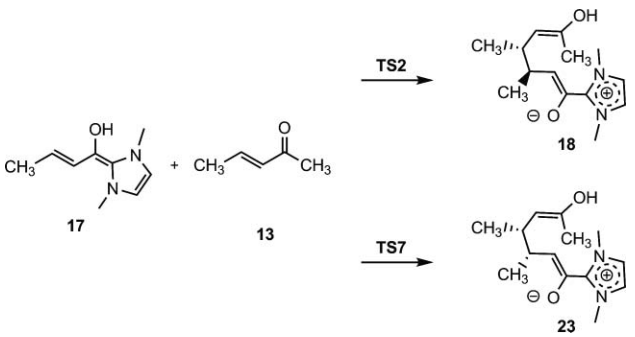
i) Formation of the Breslow intermediate 17

The **TS1** associated with the nucleophilic attack of the imidazolium NHC **14** on the enal **12** presents a free energy of activation of 18.1 (3.8) kcal mol^{-1}; formation of the zwitterionic intermediate **16** is endergonic by 11.6 (−1.1) kcal mol^{-1} (values in parentheses correspond with relative enthalpies).

The subsequent proton transfer process at the zwitterionic intermediate **16** affords the Breslow intermediate **17**. Recently, we have shown that the direct intramolecular proton transfer process with formation of the Breslow intermediates has a very high activation energy as a consequence of the strain associated with the three-membered ring TS.[12] Thus, this step must be acid/base catalyzed. These reactions are carried out in the presence 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) used in the generation of the imidazolium NHC catalyst, and thus, the $DBUH^+$/DBU pair can act as the acid/base catalyst. Although formation of the Breslow intermediate **17** is exothermic by −6.1 kcal mol^{-1}, the unfavorable entropy associated with the first bimolecular step makes endergonic the overall process; 6.1 kcal mol^{-1}.

ii) Formation of the bicyclic lactone 22.

The next step of this NHC catalyzed process is the nucleophilic addition of the Breslow intermediate **17** to α,β-unsaturated ketone **13** to yield the enol-enolate **18**. For this step, which is the stereoselective step responsible for the *cis* or *trans* stereochemistry of the final cyclopentenones, there are several stereoisomeric reactive channels. They are related with the nucleophilic attack of the γ position of the Breslow intermediate **17** by its *re-face* or *si-face* on the conjugated β position of enone **13** by the *re-face* or *si-face*. Along these stereoisomeric pathways several conformational TSs are possible. Among most of these, the hydroxylic hydrogen of **17** is hydrogen-bonded to the carbonyl oxygen atom of the enone **13**. This hydrogen-bond (HB) favors the subsequent C–C bond-formation by a stabilization of the negative charge that is developing at the oxygen atom of the ketone **13** along the nucleophilic attack.[11a] From these stereoisomeric TSs, we have selected the most favorable ones, **TS2** and **TS7**, allowing for the *trans* and *cis* relationship between the enolates **18** and **23** (see Scheme 8). They are related to the attack of the intermediate **17** by its *re-face* (**TS2**) or *si-face* (**TS7**) on the *re-face* of the β position of α,β-unsaturated ketone **13**. The free energy of activation associated with **TS2** and **TS7** from the separated reagents (**13** + **17**) is 19.5 (3.4) and 22.9 (5.9) kcal mol^{-1}, respectively. Formation of the corresponding enolates is exergonic by −4.0 (−20.1) (**18**) and −3.0 (−20.3) (**23**) kcal mol^{-1}. The free energy difference between **TS2** and **TS7**, 3.4 kcal mol^{-1}, accounts for the preferential formation of the *trans*-configuration of the cyclopentenone **15**.



Scheme 8

The enol-enolate **18** quickly equilibrates *via* a keto/enol tautomerization with the ketone-enolate **19**, which is located 5.5 (5.2) kcal mol^{-1} below **18**. As in the formation of the Breslow intermediate **17**, the intramolecular tautomerization of **18** is impeded as a consequence of the high energy associated with the corresponding four-membered TS.[24] Therefore, the tautomerization process must also be an acid–base catalyzed intermolecular process.[25] Although the formation of the Breslow intermediate **17** is endergonic by 6.1 kcal mol^{-1}, the strong exergonic character of the formation of the ketone-enolate **19**, −9.5 kcal mol^{-1}, causes the catalytic cycle to progress towards this point of the reaction (see Fig. 1).

The intermediate **19** experiences an intramolecular aldolic addition, *via* **TS3**, allowing for the formation of the alkoxy cyclopentane intermediate **20**. From **19**, the free energy of activation associated with the intramolecular aldolic addition *via* **TS3** is 19.9 (17.3) kcal mol^{-1}. The alkoxy cyclopentane intermediate **20** being

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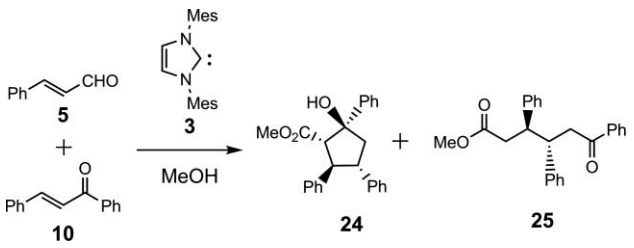
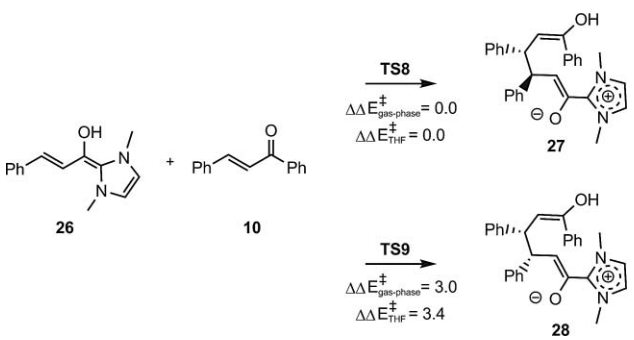
unstable, and with a low free energy of activation, is converted in the bicyclic ether **21**, *via* **TS4**. From the intermediate **19**, formation of the bicyclic ether **21** is endergonic by 10.6 (7.6) kcal mol^{-1}. However, with a low free energy of activation, 6.8 (7.2) kcal mol^{-1}, the intermediate **21** experiences an extrusion of the imidazolium NHC catalyst **14** to yield the bicyclic lactone **22**, *via* **TS5**. From **21**, formation of **22** is exergonic by –2.4 (–2.0) kcal mol^{-1}.

Very recently, Nair *et al.*[26] have reported that the imidazolium NHC catalyzed annulations of enals to chalcones in methanol afford the methyl β-hydroxycyclopentanecarboxylates **24** along with a small amount of the acyclic ε-ketoester **25** (ration 5 : 1) (see Scheme 9). These authors have suggested that the acyclic compounds **25**, which present the *trans* relationship of the cyclopentanes **24**, come from the protonation by methanol of ketone-enolates as **19** previous to the intramolecular cyclization to yield **24**. The major product **24** comes from the protonation by methanol of the unstable intermediates **20**, and the subsequent substitution of the NHC catalyst by methanol. Theses experimental results support the proposed mechanism.[8]



Scheme 9

At this point, a more complex model was further analized. We select the cinnamaldehyde **5** and the chalcone **10**, as they have been used in the experiments. As the nucleophilic addition of the Breslow intermediate **17** to enone **13** is the stereoselective step responsible for the *cis*/*trans* stereochemistry of the final cyclopentenes, only the TSs associated with the nucleophilic attacks of the Breslow intermediate **26** derived from cinnamaldehyde **5** on the chalcone **10** were studied (see Scheme 10). As for the computational models **TS2** and **TS7**, the **TS8** associated with nucleophilic attack of the Breslow intermediate **26** by its *re-face* on the *re-face* of the β position the chalcone **10** was 3.4 (3.0 in gas-phase) kcal mol^{-1} lower in energy than **TS9** associated with the attack of **26** by its *si-face*. These energy results, which are in reasonable agreement with the experimental results, allow for the explanation of the *trans* stereoselectivity found at the NHC catalyzed addition of enals to enones.



Scheme 10

iii) formation of the *trans*-trimethylcyclopentene 15

Finally, the CO_2 elimination from the lactone **22** yields the final *trans*-trimethylcyclopentene **15**. This step, which could be associated with a retro [2+2] cycloaddition *via* **TS6**, presents a free energy of activation of 26.3 (28.1) kcal mol^{-1}; this reaction is strongly exergonic, –16.4 (–10.6) kcal mol^{-1}, due to the favorable reaction entropy associated with the loss of CO_2. This fact makes the formation of the final *trans*-trimethylcyclopentene **15** irreversible.

The gas-phase geometries of the TSs involved in the NHC catalyzed addition of the enal **12** to the enone **13** are given in Fig. 2. At **TS1**, associated with the nucleophilic attack of the NHC catalyst **14** on the carbonyl carbon atom of the enal **12**, the length of the C–C forming bond is 1.930 Å. At the *trans* and *cis* TSs associated with the nucleophilic attack of the Breslow intermediate **17** to the β conjugated position of the enone **13**, the length of the C–C forming bond is 2.232 Å at **TS2** and 2.221 Å at **TS7**, while the distance of the hydroxyl hydrogen of **17** and the carbonyl oxygen atom of the enone **13** is 1.518 at **TS2** and 1.484 Å at **TS7**. These short distances point to a strong HB interactions

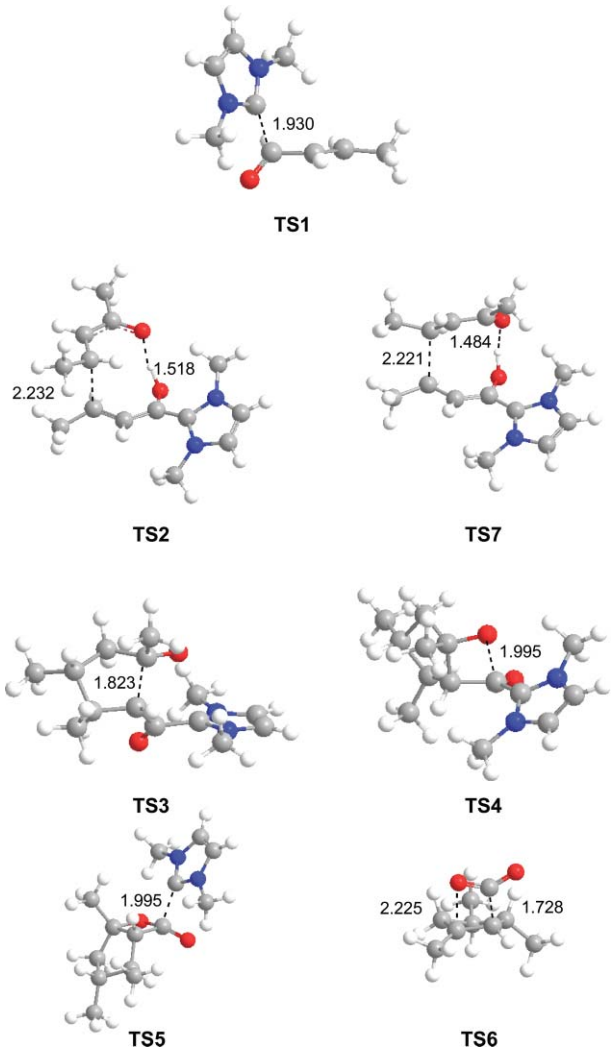


Fig. 2 Transition structures associated with the NHC catalyzed reaction of the enal **12** with the enone **13**. The distances are given in Å.

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at these TSs as a consequence of the negative charge that is developing at the carbonyl oxygen atom.[11a] At **TS3**, associated with the intramolecular aldolic addition at the intermediate **19**, the length of the C–C forming bond is 1.823 Å. This short distance, compared with that associated with **TS2**, can be related with the high activation enthalpy of **TS3**, $\Delta H^{\#}$ = 17.3 kcal mol^{-1}, as a consequence of the formation of an alkoxy anion. Note that **TS2** is HB stabilized, $\Delta H^{\#}$ = 3.4 kcal mol^{-1}. At **TS4** associated with the formation of the bicyclic ether **21** the length of the C–O forming bond is 1.995 Å. At **TS5** associated with the extrusion of the imidazolium NHC **14**, the length of the C–C breaking bond is 1.995 Å. Finally, at **TS6** associated with the loss of CO_2 from the lactone **21**, the lengths of the breaking bonds are 1.728 Å (C–C) and 2.225 Å (C–O). At this TS, the C–O breaking bond is more advanced than the C–C one.

The gas-phase geometries of the TSs involved in the nucleophilic attacks of the Breslow intermediate **26** on the chalcone **10** are given in Fig. 3. At these TSs, the length of the C–C forming bond is 2.091 Å at **TS8** and 2.122 Å at **TS9**, while the distance of the hydroxyl hydrogen of **26** and the carbonyl oxygen atom of the chalcone **10** is 1.371 at **TS8** and 1.369 Å at **TS9**. These lengths, which are slightly shorter than those at **TS2** and **TS7**, indicate that these TSs are slightly more advanced than those in the reduced computational models.

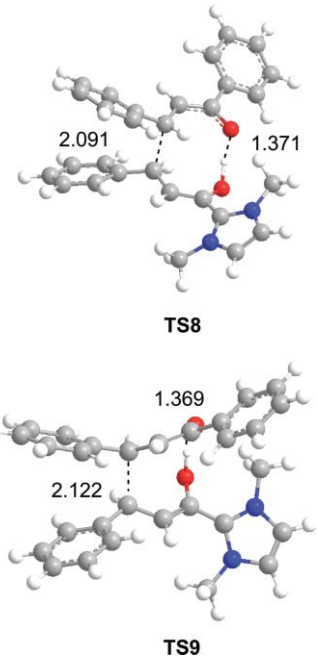
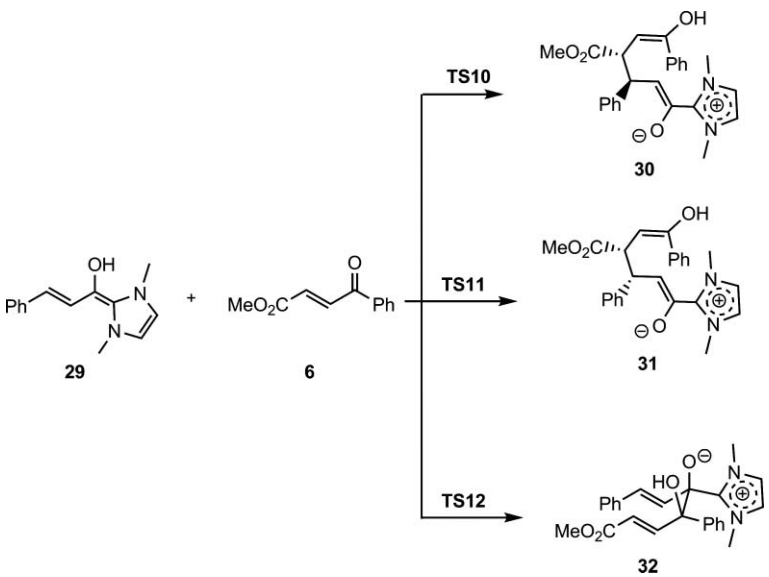


Fig. 3 Transition structures associated with the nucleophilic attacks of the Breslow intermediate **26** on the chalcone **10**. The distances are given in Å.

b) Study of the nucleophilic addition of the Breslow intermediate 29 to (*E*)-methyl 4-oxo-4-phenylbut-2-enoate 6

In order to explain the mechanism for the formation of the *cis*-cyclopentene **8** (see Scheme 3), we also investigated the conjugated and the direct nucleophilic additions of the imidazolium Breslow intermediate **29** to the γ-ketoenoate **6** to yield the intermediates **30**, **31** and **32** (see Scheme 11). Note that in these NHC catalyzed reactions formation of the *cis*-cyclopentene are not experimentally dependent of imidazolium or triazolium NHC catalyst.[10] While the attack of the γ position of the Breslow intermediate **29** by its *re-face* on the β conjugated position of the enone **6** by its *si-face via* **TS11** directly affords the *cis* relationship of the final cyclopentene, the direct attack *via* **TS12** demands a further oxy-Cope rearrangement on the intermediate **23**, as is proposed in Scheme 5.[7]

The TSs associated with the nucleophilic attacks of the Breslow intermediate **29** on the γ-ketoenoate **6** are located 15.2 (0.9) (**TS10**), 17.6 (1.6) (**TS11**) and 27.4 (14.1) (**TS12**) kcal mol^{-1} above the separated reagents (**29** + **6**) (see Table 2). As for the addition to enones, the earlier formation of an HB between the hydroxyl hydrogen atom of **29** and the carbonyl oxygen atom of **6** favors the subsequent nucleophilic attack by a stabilization of the negative charge that is developing at the carbonyl oxygen atom of **6**.[11a]



Scheme 11

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Table 2 B3LYP/6-31G** Relative enthalpies (ΔH, in kcal mol^{-1}) and free energies (ΔG, in kcal mol^{-1}) computed at 298.15 K and 1 atm in THF of the stationary points associated with the addition of the Breslow intermediate **29** to the γ-ketoenoate **6**

	ΔH	ΔG
6 + **29**	0.0	0.0
TS10	0.9	15.2
TS11	1.6	17.6
TS12	14.1	27.4
30	–12.3	1.3
31	–14.2	2.4
32	14.4	26.5

The **TS11** and **TS12** associated with the formation of the *cis*-cyclopentene **8** are located 2.4 and 12.2 kcal mol^{-1} above the **TS10** associated with the formation of *trans*-cyclopentene.

The high free energy of **TS12** relative to **TS10** and **TS11** prevents the crossed benzoin reaction of the Breslow intermediate **29** with the γ-ketoenoate **6** to form the intermediate **32**, as proposed in Scheme 5. These energy results make it possible to discard the formation of the *cis*-cyclopentenes by a NHC crossed benzoin reaction followed by an oxy-Cope rearrangement.[7] In addition, all attempts to locate the TS associated with the oxy-Cope rearrangement to convert the alkoxy intermediate **32** into the *cis* intermediate **31** were unsuccessful, yielding the separated reagents, **29** + **6**.

Formation of the intermediates **30**, **31** and **32** is endergonic by 1.3 (–12.3) 2.4 (–14.2) and 26.5 (14.4) kcal mol^{-1}, respectively. While formation of the intermediates **30** and **31** are exothermic processes, formation of **32** is strongly endothermic. These energy results can be related with the electronic structures of these zwitterionic intermediates; while at the intermediates **30** and **31** the negative charge is delocated in an enolate, at the intermediate **32** the negative charge is located in an alkoxydic oxygen atom. Thus, the high endothermic character of the formation of the alkoxyde **32** is responsible of the high activation energy associated with **TS12**,[27] and consequently the reaction path associated with the NHC-catalyzed crossed benzoin reaction will not be competitive with the conjugated addition.

The reactive channel associated with the formation of final *trans*-cyclopentane *via* **TS10** is favored over the reactive channel associated with the formation of the *cis* one *via* **TS11**. These energy results indicate that as for the conjugated addition of the Breslow intermediate **26** to the chalcone **10** (see Scheme 10), the more favorable reactive channels are those associated with the nucleophilic attack of the γ position of the Breslow intermediates by its *si-face* on the β conjugated position of the enones by its *si-face* to afford the *trans*-cyclopentenes. Consequently, for the NHC-catalyzed annulation reactions of cinnamaldehydes with γ-ketoenoates, the step associated with the nucleophilic attack of the Breslow intermediates on the γ-ketoenoates appears not to be responsible for the final *cis* relationship. We suggest that the *cis*-cyclopentenes may come from of the *trans* ones by an epimerization at the acidic α position with respect to the carboxyl group. Note that these reactions are carried out in the presence of an excess of DBU relative to the precursor of the NHC catalyst,[6] which can promote the epimerization in a further step of the reaction.

The geometries of the TSs involved in the nucleophilic attacks of the Breslow intermediate **29** on the γ-ketoenoate **6** are depicted in Fig. 4. At the TSs, the length of C–C forming bond is 2.130 Å at **TS10**, 2.130 Å at **TS11** and 1.903 Å at **TS12**. The most unfavorable **TS12** associated with the direct addition is more advanced than the TSs associated with the conjugated additions.[27] The distance between the hydroxylic hydrogen atom of **29** and the carbonyl oxygen atom of **6** at these TSs is 1.401 Å at **TS10**, 1.353 Å at **TS11** and 1.004 Å at **TS12**. These lengths indicate that at **TS12** the hydroxylic hydrogen atom of the Breslow intermediate **29** has already been transferred to the carbonyl oxygen atom of the γ-ketoenoate **6** (see Fig. 4).

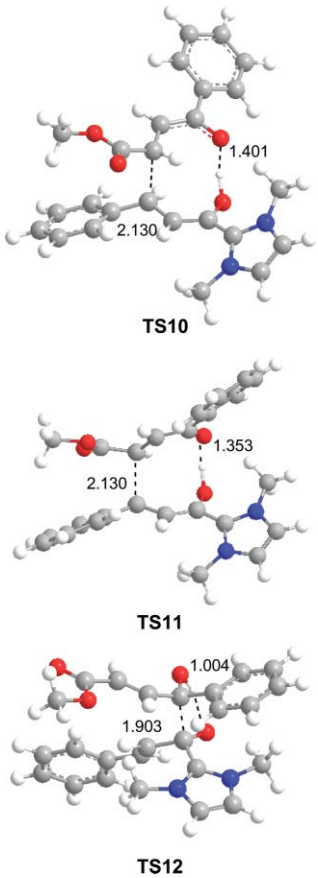

Fig. 4 Transition structures associated with the nucleophilic attacks of the Breslow intermediate **29** on the γ-ketoenoates **6**. The distances are given in Å.

Conclusions

The NHC catalyzed addition of *E*-but-2-enal **12** to *E*-pent-3-en-2-one **13** to yield the *trans*-1,3,4-trimethylcyclopent-1-ene **15** has been investigated using DFT methods at the B3LYP/6-31G** computational level. Formation of the final *trans*-cyclopentene **15** comprises several consecutive steps. The first one is the formation of the Breslow intermediate **17** that nucleophilically attacks the conjugated position of the enone **13** to yield the enol-enolate **18**. This step is responsible for the *trans* relationship at the final cyclopentene **15**. A quick keto-enol type equilibrium at the intermediate **18** provides the keto-enolate **19**. In spite of the

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endergonic character of the formation of the Breslow intermediate **17**, the high exergonic character of the formation of the keto-enolate **19** displaces the reaction towards its formation.

An intramolecular aldolic condensation at **19** allows for the formation of the alkoxy cyclopentane intermediate **20**, that by an intramolecular nucleophilic attack on the carbonyl group present in **20** provides the bicyclic ether **21**. The extrusion of the NHC catalyst **14** from **21** affords the bicyclic lactone **22**, yielding by CO_2 elimination, the final *trans*-1,3,4-trimethylcyclopent-1-ene **15**. In spite of the high free energy associated with the loss of CO_2, the strong exergonic character of this step makes the process as irreversible, and thus, the reaction is completely displaced towards the formation of the final *trans* cyclopentene **15**.

An analysis of nucleophilic additions of the Breslow intermediate **29** to the γ-ketoenoate **6** indicates that the conjugated addition allowing for the *trans* relationship on the final cyclopentene is kinetically favored over the *cis* one. In addition, the high energy associated with the NHC-catalyzed crossed benzoin reaction[7] allows for the rejection of the mechanism trough an oxy-Cope rearrangement.

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