Insights into the Competing Mechanisms and Origin of Enantioselectivity for N-Heterocyclic Carbene-Catalyzed Reaction of Aldehyde with Enamide

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Hydroacylation reactions and aza-benzoin reactions have attracted considerable attention from experimental chemists. Recently, Wang et al. reported an interesting reaction of N-heterocyclic carbene (NHC)-catalyzed addition of aldehyde to enamide, in which both hydroacylation and aza-benzoin reactions may be involved. Thus, understanding the competing relationship between them is of great interest. Now, density functional theory (DFT) investigation was performed to elucidate this issue. Our results reveal that enamide can tautomerize to its imine isomer with the assistance of HCO\(_3^-\). The addition of NHC to aldehydes formed Breslow intermediate, which can go through cross-coupling with enamide via hydroacylation reaction or its imine isomer via aza-benzoin reaction. The aza-benzoin reaction requires relatively lower free energy barrier than the hydroacylation reaction. The more polar characteristic of C=\(\text{N}\) group in the imine isomers, and the more advantageous stereoelectronic effect in the carbon-carbon bond forming transition states in aza-benzoin pathway were identified to determine that the imine isomer can react with the Breslow intermediate more easily. Furthermore, the origin of enantioselectivities for the reaction was explored and reasonably explained by structural analyses on key transition states. The work should provide valuable insights for rational design of switchable NHC-catalyzed hydroacylation and aza-benzoin reactions with high stereoselectivity.

As powerful organocatalysts, N-heterocyclic carbenes (NHCs) have been widely used in various carbon–carbon and carbon–heteroatom bonds forming reactions\(^1,2\). An attractive feature for NHCs is that they can catalyze the polarity reversal of various carbonyl compounds and generate acyl anion equivalents, which provide an elegant access to a wide range of organic transformations\(^3,4\). Among them, the NHC-catalyzed benzoin condensation and Stetter reactions are the two most exploited reactions as a result of the success of these reactions in various useful transformations\(^1\). Noteworthy, almost all the previously reported Stetter reactions catalyzed by NHC involve electron-withdrawing olefins, the use of electron-rich olefins in NHC-catalyzed cross-coupling reactions is still very challenging. Until recently, Wang et al. reported the first example of NHC-catalyzed highly enantioselective intermolecular addition of aldehydes to electron-rich olefins, i.e. enamides, to synthesize valuable N-acyl-protected amine derivatives (Fig. 1)\(^5\). As shown in Fig. 1, the reactions are proposed to be initiated by the nucleophilic attack of NHC to the aldehyde substrates yielding the well-known Breslow intermediate, which can then go through cross-coupling with substrate enamides and result into the final products. Interestingly, both hydroacylation and aza-benzoin reaction mechanisms may be involved in the special reaction, and some important mechanistic questions need to be answered. For example: (1) Substrate enamide 2 can tautomerize to its imine isomer 2'. However, how the tautomerization happen remains elusive. (2) The Breslow intermediate can react with 2 via hydroacylation pathway, while it can also react with 2' via aza-benzoin reaction pathway. Thus, it is very difficult to discern which one is the actual reactant and which competing reaction occurs preferentially.

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The reaction is highly enantioselective, and it is meaningful to explore the origin of the stereoselectivity and identify the factors that control the stereoselectivity. Due to the difficulty on the structural detection of the intermediates and transition states involved in the rate- and stereoselectivity-determining steps in the experiment, it is highly desirable to perform a theoretical study to obtain the general principle for this kind of organocatalytic reactions.

In recent years, NHC-catalyzed reactions have attracted much attention from theoretical chemists. Particularly, the NHC-catalyzed Stetter reactions and the NHC-catalyzed aldehyde-aldehyde and aldehyde-ketone cross-benzoin reactions have been theoretically investigated, respectively. However, the hydroacylation mechanism involved in the reaction shown in Fig. 1 has been demonstrated to be different from the Stetter reactions, and the aldehyde-imine aza-benzoin reactions catalyzed by NHC have never been studied in theory, not to mention the competing relationship between them. Besides, our interest in NHC-catalyzed reactions also prompts us to investigate the origin of selectivities for the competing reactions in detail.

In the present study, the commonly used DFT theoretical investigation on the reaction between R1 (in which Ar1 = para chlorphenyl) and R2 (in which Ar2 = phenyl) catalyzed by NHC depicted in Fig. 1, was pursued in order to shed light on details of each elementary step at the molecular level and to reach more comprehensive understanding to the enantioselectivity of this interesting reaction.

Results

Our calculated results confirmed that NHC indeed initiate the reaction by nucleophilic attack to the aldehyde substrate yielding the well-known Breslow intermediate, which can then go through a cross-coupling with the other substrate via two competing pathways depicted in Fig. 1 to form the same final products. In the following sections, we will discuss the detailed reaction processes, including the formation of Breslow intermediate, the tautomerization between enamide and the corresponding imine isomer, hydroacylation reactions between Breslow intermediate and enamide, aza-benzoin reaction between Breslow intermediate and imine, the competition of hydroacylation reaction and aza-benzoin reaction, and origin of the enantioselectivity.
Formation of Breslow intermediate. As shown in Fig. 2, the reaction is initiated by the nucleophilic addition of NHC to 4-chlorobenzaldehyde R1. Noteworthy, R1 has a prechiral center, i.e. C2 atom. Attack from NHC on the Si or Re face of R1 can respectively lead to two stereoselective intermediate M1R or M1S, in which the R/S represents the chirality of C2 atom. The two kinds of stereocemically distinct attack modes have different free energy barriers. According to our calculations, the Si face attack requires the free energy barrier of 9.3 kcal/mol, which is 2.3 kcal/mol more stable than that of the Re face attack (ΔG = 11.5 kcal/mol). The produced intermediates M1R and M1S are zwitterions. In the following, zwitterionic intermediates M1R and M1S would go through 1,2-proton transfer to afford the Breslow intermediates M2/M2′, in which C2 has no chirality. Direct 1, 2-proton transfer is impossible because of the strong strain in the three-membered ring transition state. Protic solvents in the reaction system have been demonstrated many times to be able to mediate the proton transfer process in the formation of Breslow intermediates as well as in many other proton transfer processes. Herein, we proposed that the small amount of HCO3− in the reaction system can mediate the proton transfer process. The corresponding transition state TS2R was located 0.4 kcal/mol lower in free energy than TS2S. The newly formed Breslow intermediate M2 produced from TS2R is 7.0 kcal/mol more stable than M2′ generated via TS2S. Structural analyses (Supplementary Fig. S1) reveal that the advantageous π−π interaction, C−H•••π interaction, C−H•••Cl and C−H•••O hydrogen bond interactions determined that M2 is more stable than M2′. From the free energy profile shown in Fig. 2, it can be concluded that the reaction pathway affording Breslow intermediate M2 is more likely to occur. Therefore, in the following reaction steps, we only considered the reaction processes associated with M2.

The tautomerization between enamide and imine. The reactant enamide R2 can tautomerize to its imine isomer. In the imine configuration, we selected C3=C=N3 bond as a reference standard. As shown in Fig. 3, if the acyl group and phenyl group are in trans configuration, we denote it as t-R2-imine, while in cis configuration, we denote it as c-R2-imine. Correspondingly, t-R2-imine can tautomerize to t-R2, and c-R2-imine can tautomerize to c-R2. In total, there are four distinctive conformations for R2. In the following, we considered the tautomerization between t-R2 and t-R2-imine, and between c-R2 and c-R2-imine.

Firstly, we considered the bimolecular reaction mechanisms for the tautomerization between t-R2 and t-R2-imine. The bimolecular reaction consists of two reaction processes with the highest activation free energy barrier of 46.4 kcal/mol (Supplementary Fig. S2), which is so high that it is unlikely for the reaction to happen. In addition, we also considered HCO3−-mediated tautomerization mechanism between them. According to the calculated results, HCO3− would first abstract the hydrogen from –NH group via a transition state t-TS1-HCO3−. The free energy barrier for this step was calculated to be 2.8 kcal/mol. The formed intermediate t-M1-HCO3− is 0.3 kcal/mol lower in energy than t-TS1-HCO3−. However, by addition of the thermal correction, t-M1-HCO3− is 2.6 kcal/mol higher in free energy than t-TS1-HCO3−. Followed by the formation of t-M1-HCO3−, the hydrogen transfer from H2CO3 to the terminal alkene carbon C4 via a transition state t-TS2-HCO3− resulting into t-R2-imine. This reaction step requires a free energy barrier of 20.6 kcal/mol, which is significantly lower than that of the bimolecular fashion.

For the cis configuration, we also considered the bimolecular and HCO3−-mediated mechanisms. The bimolecular fashion is also a two-step process with activation free energy barrier as high as 48.6 kcal/mol (Supplementary Fig. S3), while the HCO3−-mediated mechanism is a concerted process with activation free
energy barrier of only 2.5 kcal/mol. The produced isomer c-R2-imine is 2.0 kcal/mol unstable than c-R2, and
the free energy barrier for the reverse reaction is only 0.5 kcal/mol, indicating that this reaction process is highly
reversible. Given this reason, we did not take c-R2-imine into consideration in the following reaction processes.

As described on the above, the C= N group in enamides would undergo hydroacylation reactions with the
Breslow intermediate, while the C=N group in imines would undergo cross-aza-benzoin reactions with the
Breslow intermediate. Based on this, t-R2 and c-R2 would undergo hydroacylation reactions, while t-R2-imine
would go through cross-aza-benzoin reactions. In the following, we will discuss these competing reaction path-
ways in detail.

**Hydroacylation reactions between Breslow intermediate and enamide.** Firstly, we take t-R2 into
consideration for the hydroacylation reaction with M2. The negatively charged carbon atom C2 in Breslow inter-
mediate M2 would nucleophilic attack on the prechiral center C3 atom of t-R2. Attack to the Re-face of t-R2 via
transition state t-TS3S can lead to t-M3S, in which the “S” represents S configuration of C3 atom, while attack to
the Si-face of t-R2 via transition state t-TS3R can lead to t-M3R, in which C3 is in R configuration. As shown in
Fig. 4, the free energy barrier for t-TS3S with respect to M2 + t-R2 amounts to 23.9 kcal/mol, which is 1.3 kcal/
mol lower than that of t-TS3R (ΔG = 25.2 kcal/mol). Noteworthy, the nucleophilic attack is accompanied by
the proton transfer from O2 to C4 atom. In the newly formed intermediates t-M3S and t-M3R, C2-C3 bond is
formed and H2 atom is transferred to C4 atom. The bond distances for C2-C3, O2-H2, and H2-C4 in transition
states t-TS3S/t-TS3R are 2.73/2.75, 1.36/1.35 and 1.25/1.25 Å, respectively, indicating that proton migration
occurs prior to carbon-carbon bond formation. This observation is very different from the previous theoretical
study on Stetter reactions7. Subsequently, the elimination of NHC from

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**Figure 3.** Free energy profile for tautomerization between enamide and its imine isomer.

**Aza-benzoin reaction between Breslow intermediate and imine.** As described above, t-R2 can
tautomerize to its imine isomer t-R2-imine, which then reacts with Breslow intermediate via aza-benzoin con-
densation. During this reaction process, C2 atom in Breslow intermediate M2 would nucleophilic attack on C3
atom of t-R2-imine. Attack to the Re-face of t-R2-imine via transition state t-TS3S-b can lead to t-M3S-b, in
which C3 is in S configuration. Attack to the Si-face of t-R2 via transition state t-TS3R-b can lead to t-M3R-b,
in which C3 is in R configuration. In contrast to the hydroacylation reaction for which the terminal alkene carbon
abstracts the proton from the hydroxyl group, it is the nitrogen atom in the C=N group that abstracts the proton
in the aza-benzoin reaction. As shown in Fig. 5, the free energy barriers for t-TS3S-b and t-TS3R-b with respect
to $M_2 + t\text{-}R_2$ amount to 14.1 and 15.3 kcal/mol, which are significantly lower than those of the hydroacylation reactions. Noteworthy, the nucleophilic attack is accompanied by proton transfer from O2 to N3 atom instead.
also analyzed the second-order perturbative donor-acceptor interactions for the two transition states. Listed proton migration occurs prior to carbon-carbon bond formation while the sequence is reversed in aza-benzoin reaction. However, the sequence of the two events is very different. In the hydroacylation reactions, proton transfer take place through a concerted but asynchronous mechanism in both hydroacylation reaction and hydroacylation reactions, we first performed NBO charge analyses on the reactants, we also compared the structures of two representative key transition states and 7t-SS3S-b. As indicated on the above, the carbon-carbon bond formation and proton migration occurs prior to carbon-carbon bond formation while the sequence is reversed in aza-benzoin reactions. By comparison, the forming C2–C3 bond in 7t-SS3S and 7t-SS3S-b is 2.73 and 2.21 Å (shown in Fig. 7b), respectively. The shorter C2–C3 bond distance in 7t-SS3S-b reveals that the interaction between the two fragments of 7M2 and 7t-R2-imine in 7t-SS3S-b should be stronger than that in t-SS3S. In order to verify this speculation, we also analyzed the second-order perturbative donor-acceptor interactions for the two transition states. Listed in Fig. 7c is the second-order perturbation energy $E(2)$ (kcal/mol) in transition states 7t-SS3S and 7t-SS3S-b. As shown, the main stabilization donor-acceptor interactions in transition state 7t-SS3S come from the charge transfer from the lone pair orbital of O2 atom to the $\sigma^*$ orbital of the forming C6–H2 bond ($E_{\text{C6-H2}} = 65.5$ kcal/mol and $E_{\text{O2}\rightarrow \sigma^*} = 26.0$ kcal/mol) and the charge transfer from the $\pi^*$ orbital of C1–C2 bond to the vacant lone pair orbital of C3 atom ($E_{\text{C1-C2}\rightarrow \pi^*} = 22.7$ kcal/mol). By comparison, the main stabilization interactions in 7t-SS3S-b come from the charge transfer from the lone pair orbital of O2 atom to the $\sigma^*$ orbital of the forming N2–H2 bond with $E_{\text{N2-H2}} = 316.3$ kcal/mol and $E_{\text{O2}\rightarrow \sigma^*} = 23.8$ kcal/mol. Besides, there are some other significant stabilization interactions in 7t-SS3-b, like the interaction between N2–H2 $\sigma$ orbital and the C2–C3 $\pi^*$ orbital with $E_{\text{N2-H2}\rightarrow \pi^*} = 47.8$ kcal/mol, and the interaction between N2–H2 $\sigma$ orbital and C9–O1 $\sigma^*$ orbital with $E_{\text{N2-H2}\rightarrow \sigma^*} = 45.0$ kcal/mol as well as the interaction between C1–N1 $\pi^*$ orbital and the C2–C3 $\pi^*$ orbital with $E_{\text{C1-N1}\rightarrow \pi^*} = 38.0$ kcal/mol. Taken together, the stereoelectronic effect in 7t-SS3-b is more favorable than that in 7t-SS3S.

To sum up, the high polar characteristic of C2–N2 group in 7t-R2-imine and the more advantageous stereoelectronic effect in 7t-SS3-b render the reaction of 7t-R2-imine with Breslow intermediate M2 more easily.

Pathway Comparison. By now, the reaction pathways for the three possible reactants 7t-R2, e-R2, and 7t-R2-imine leading to two enantioselective products have been discussed in detail. An overlay of each reaction pathway leading to the preferred product P1S is depicted in Fig. 6. Nucleophilic attack of NHC to the aldehyde R1 followed by a proton transfer forms Breslow intermediate M2, which can then go through cross-coupling with t-R2 and e-R2 via hydroacylation reactions. As described on the above, the trans configuration of enamide, i.e. t-R2, can cross transition state 7t-TS2-HCOO$^-$ with a potentially high barrier ($\Delta G = 20.6$ kcal/mol) to tautomerize to its imine isomer t-R2-imine, which can also react with the Breslow intermediate M2 via aza-benzoin reaction. As shown in Fig. 6, for the hydroacylation reactions involving t-R2 and e-R2, the carbon-carbon bond formation step has the highest free energy barrier and thus is rate-determining, while for the aza-benzoin reaction pathway involving t-R2-imine, the tautomerization step is rate-determining. Obviously, the aza-benzoin reaction pathways involving t-R2-imine have relative lower free energy barrier with respect to the hydroacylation reactions involving t-R2 and e-R2, indicating that aza-benzoin reaction pathway is very competitive.

To identify why the carbon-carbon bond formation transition state in aza-benzoin reaction has lower free energy barrier relative to the hydroacylation reactions, we first performed NBO charge analyses on t-R2 and t-R2-imine. As shown in Fig. 7a, the NBO charges on C2 of t-R2 and t-R2-imine are 0.14 e and 0.35 e, respectively, indicating that the electrophilicity of C2 in t-R2-imine is stronger than that in t-R2, which facilitates the nucleophilic attack of Breslow intermediate M2 on C2 atom of t-R2-imine. In addition, N2 atom of t-R2-imine is also more negative than C3 atom of t-R2, and the more negative charge on N2 relative to C3 atom should facilitate the proton transfer from the hydroxyl group of Breslow intermediate to N2 atom of t-R2-imine.

In addition to the NBO charge analysis on the reactants, we also compared the structures of two representative key transition states t-SS3S and t-SS3S-b. As indicated on the above, the carbon-carbon bond formation and proton transfer take place through a concerted but asynchronous mechanism in both hydroacylation reaction and aza-benzoin reaction. However, the sequence of the two events is very different. In the hydroacylation reactions, proton migration occurs prior to carbon-carbon bond formation while the sequence is reversed in aza-benzoin reactions. By comparison, the forming C2–C3 bond in t-SS3S and t-SS3S-b is 2.73 and 2.21 Å (shown in Fig. 7b), respectively. The shorter C2–C3 bond distance in t-SS3S-b reveals that the interaction between the two fragments of M2 and t-R2-imine in t-SS3S-b should be stronger than that in t-SS3S. In order to verify this speculation, we also analyzed the second-order perturbative donor-acceptor interactions for the two transition states. Listed in Fig. 7c is the second-order perturbation energy $E(2)$ (kcal/mol) in transition states t-SS3S and t-SS3S-b. As shown, the main stabilization donor-acceptor interactions in transition state t-SS3S come from the charge transfer from the lone pair orbital of O2 atom to the $\sigma^*$ orbital of the forming C6–H2 bond ($E_{\text{C6-H2}} = 65.5$ kcal/mol and $E_{\text{O2}\rightarrow \sigma^*} = 26.0$ kcal/mol) and the charge transfer from the $\pi^*$ orbital of C1–C2 bond to the vacant lone pair orbital of C3 atom ($E_{\text{C1-C2}\rightarrow \pi^*} = 22.7$ kcal/mol). By comparison, the main stabilization interactions in t-SS3S-b come from the charge transfer from the lone pair orbital of O2 atom to the $\sigma^*$ orbital of the forming N2–H2 bond with $E_{\text{N2-H2}} = 316.3$ kcal/mol and $E_{\text{O2}\rightarrow \sigma^*} = 23.8$ kcal/mol. Besides, there are some other significant stabilization interactions in t-SS3-b, like the interaction between N2–H2 $\sigma$ orbital and the C2–C3 $\pi^*$ orbital with $E_{\text{N2-H2}\rightarrow \pi^*} = 47.8$ kcal/mol, and the interaction between N2–H2 $\sigma$ orbital and C9–O1 $\sigma^*$ orbital with $E_{\text{N2-H2}\rightarrow \sigma^*} = 45.0$ kcal/mol as well as the interaction between C1–N1 $\pi^*$ orbital and the C2–C3 $\pi^*$ orbital with $E_{\text{C1-N1}\rightarrow \pi^*} = 38.0$ kcal/mol. Taken together, the stereoelectronic effect in t-SS3-b is more favorable than that in t-SS3S.

To sum up, the high polar characteristic of C2–N2 group in t-R2-imine and the more advantageous stereoelectronic effect in t-SS3-b render the reaction of t-R2-imine with Breslow intermediate M2 more easily.

Figure 6. An overview of the reaction coordinates for the pathways leading to 1P1S.
Origin of the enantioselectivity. For both the hydroacylation reactions and the aza-benzoin reactions, the $S$-configured product is preferentially produced. To explain the observed enantioselectivity, we compared the structures of the enantioselective transition states (shown in Fig. 8). For $t$-TS3S and $t$-TS3R, the C–H•••O hydrogen bond interaction and \( \pi-\pi \) interaction present in $t$-TS3S (colored in red) are absent in $t$-TS3R, which
determined that t-TS3S has lower free energy relative to t-TS3R. For t-TS3S-b and t-TS3R-b, the N2•••H2 distance in t-TS3S-b is shorter than that in t-TS3R-b, demonstrating that N•••H-O hydrogen bond interaction in t-TS3S-b is stronger than that in t-TS3R-b. Therefore, it is the stronger N•••H-O hydrogen interaction in t-TS3S-b relative to t-TS3R-b that determines the lower energy of t-TS3S-b. On the whole, the more advantageous hydrogen bond interaction and π•••π interaction in the favorable carbon-carbon bond formation transition state determine the observed enantioselectivity.

Discussion

The detailed reaction mechanisms as well as the origin of enantioselectivity for the NHC-catalyzed cross-coupling reaction of aldehyde with enamide were investigated. Our calculated results indicate that the NHC catalyst initiate the nucleophilic attack on aldehyde to afford the Breslow intermediate, which can then react with enamide via hydroacylation reaction or its isomer imine via aza-benzoin reaction, preferentially leading to the experimentally observed S-configured product. According to the computational results, the tautomerization step is rate-limiting in aza-benzoin reaction pathway, while for the hydroacylation reactions, the carbon-carbon formation step is rate-determining. NBO analyses reveal that the more polar characteristic of C=N bond in t-R2-imine and advantageous stereoelectronic effect in t-TS3S-b determine that the reaction between M2 and t-R2-imine is more likely to occur. Further structural analyses on the key enantioselective transition states reveal that the hydrogen bond interaction and π•••π interaction determine the observed enantioselectivity. This present work can help people understand the details of the competing hydroacylation and aza-benzoin reaction pathways for NHC-catalyzed cross-coupling reactions of aldehydes with enamides, and thus provide valuable mechanistic insights for the rational design on the switchable and novel NHC-catalyzed cross-coupling reactions in future.

Methods

Computational details. The Gaussian 09\textsuperscript{44} software was used for all theoretical calculations in the present study. The M06-2X\textsuperscript{45–47} method with 6–31 G(d, p) basis set was used for all geometrical optimizations in gas phase. For transition states, the Berny algorithm was employed for both minimizations and optimizations\textsuperscript{48}. The corresponding vibrational frequencies were calculated at the same level to identify whether the structure is a transition state or a minimum. It was confirmed that all reagents and intermediates had no imaginary frequencies, and each transition state had only one imaginary frequency. Intrinsic reaction coordinate (IRC) calculations\textsuperscript{49,50}, at the same level of theory, were also performed to ensure that the transition states led to the expected reactants and products. Afterwards, the single-point energies in solvent methyl tert-butyl (MTBE) were refined at the M06-2X/6-311++G(d, p) level\textsuperscript{45–47} using IEFFPCM solvent model\textsuperscript{51,52}. Finally, the Gibbs free energies at the M06-2X/6-311++G(d, p) level in the solvent MTBE are used through the whole paper.

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Acknowledgements

We acknowledge financial support from the National Natural Science Foundation of China (nos. 21303167 and 21403199), the China Postdoctoral Science Foundation (nos. 2013M530340, 2014M552010, and 2015T80776), Outstanding Young Talent Research Fund of Zhengzhou University (no. 1521316001), and Zhengzhou University Scientific Research Foundation (no. 1411316003).

Author Contributions

Y.Q. and D.W. conceived and directed the project. Y.Q. performed theoretical calculations. Y.Q., X.C. and J.C. wrote the paper. All authors discussed the results and contributed to the preparation of the final manuscript.

Additional Information

Supplementary information accompanies this paper at http://www.nature.com/srep

Competing financial interests: The authors declare no competing financial interests.
How to cite this article: Qiao, Y. et al. Insights into the Competing Mechanisms and Origin of Enantioselectivity for N-Heterocyclic Carbene-Catalyzed Reaction of Aldehyde with Enamide. Sci. Rep. 6, 38200; doi: 10.1038/srep38200 (2016).

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