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REGULAR ARTICLE

Insights into the NHC-catalyzed formal [2 + 2 + 2] cycloaddition of ketenes with C=S double bond of isothiocyanate

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Abstract: The detailed mechanisms of cascade [2 + 2 + 2] cycloaddition reaction of bimolecular ketenes with isothiocyanate under the N-heterocyclic carbene (NHC) catalysis have been systematically investigated in depth with the density functional theory (DFT) calculations. The calculated results indicate that this reaction occurs through four steps: i.e., the complexation of ketene and NHC, regioselective addition of N-benzoyl isothiocyanate to enolate intermediate, addition of another molecule of ketene for the formation of six-membered heterocycle, and the regeneration of the catalyst. The computational results show that the second step is the rate-determining step. Moreover, the stereoselectivities associated with the chiral carbon center and the carbon double bond, are predicted to be determined in the second and third steps, respectively, and the E-type with R-configuration of the product is the predominant product, which is consistent with the experimental outcomes. The mechanistic insights obtained in the present study should be valuable for the synthesis of heterocycles under NHC catalysis.

AMS subject classifications: 92E99

Keywords: N-heterocyclic carbene, [2 + 2 + 2] cycloaddition, DFT, Stereoselectivity.

1. Introduction

Privileged heterocyclic systems are important objectives in chemical synthesis and

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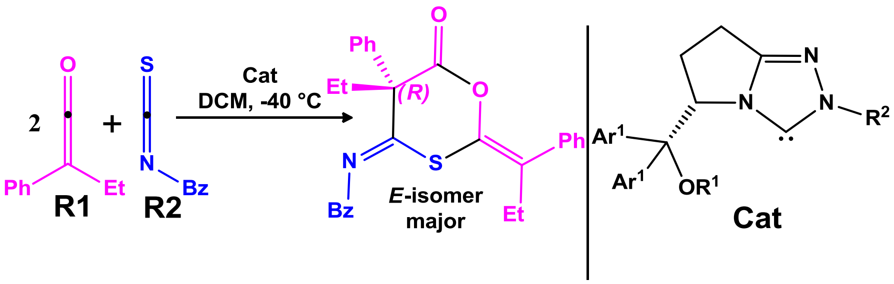
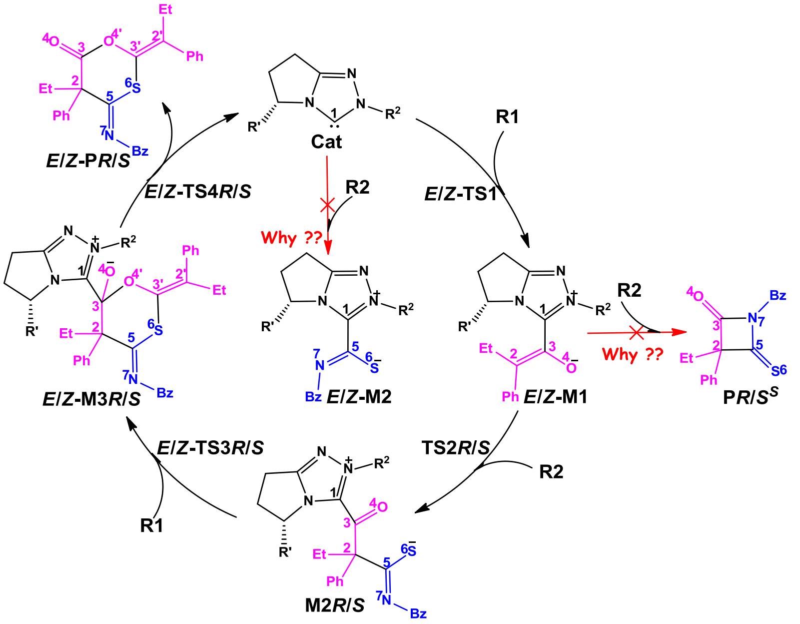
pharmaceutical sciences, due to their wide existence in numerous biologically active molecules. During the past decades, N-heterocyclic carbene (NHC) catalysis has emerged as a powerful tool for synthesis. Owing to the unique properties of NHC catalysts, huge advances have been made. As an important organocatalyst, NHC has been successfully used in carbon-carbon and carbon-heteroatom bond formation reactions including crossed-benzoin, Stetter, homoenolate, annulation, and cycloaddition reactions [1-5]. Among these advances in several different types of cycloaddition reactions, NHCs have been found to be powerful organocatalysts for ketene cycloaddition reactions (*i.e.*, [2 + 2] [6-8], [2 + 2 + 2] [9], and [4 + 2] [10, 11]) with high stereoselectivities, which can afford a facile and also effective route to obtain various heterocyclic skeletons.

A unique propensity in ketene chemistry is to give facile [2 + 2] or formal cascade [2 + 2 + 2] cycloaddition reactions with various reaction partners, such as alkenes, ketones, imines, isothiocyanates, and so on. It was first reported by Staudinger in 1905 [12], and then many modifications and improvements introduced during the last hundred years had extended the versatility of ketene cycloaddition reactions. However, these noncatalyzed ketene cycloaddition reactions between relatively unreactive reaction partners typically require forcing conditions. For example, Snider and co-workers explored a scope of intramolecular α,β-unsaturated ketene-alkene [2 + 2] cycloadditions with a yield of 75% in toluene at a high temperature [13]. Interestingly, many studies found that ketene cycloaddition reactions can proceed easily with the presence of Lewis acid. It should be noted that the recent reports show that the Lewis acid catalyst (especially for N-heterocyclic carbene) can also promote the cycloaddition reactions of ketene and significantly improve their stereoselectivities. An outstanding example of NHC-catalyzed cascade ketene [2 + 2 + 2] cycloaddition reaction with isothiocyanate (**Scheme 1**) is first reported by Ye's group [14], which deserves particular attention if we note the fact that the chemoselectivities of this reaction remain unsettled though cycloadditions of ketene have been widely reported.



Scheme 1. The NHC-catalyzed [2 + 2 + 2] cycloaddition reaction of bimolecular ketenes with isothiocyanate.

In contrast to the great development of NHC-catalyzed cycloaddition reactions of ketene in experiment, the theoretical investigations on the mechanisms of NHC-catalyzed ketene cycloaddition reactions are rare. Our group has theoretically studied the mechanisms of NHC-catalyzed [2 + 2] [15, 16], [4 + 2] [17], and [2 + 2 + 2] [18] cycloaddition reactions of ketene using DFT methods. Actually, the reaction mechanisms might be diverse for different NHC catalytic cycloadditions of ketene, and these cycloaddition reactions are not always initiated by the coordination of NHC with ketene [17]. For example, in our previous theoretical study on ketene [2 + 2] cycloaddition reaction, we found that the "ketene-first" mechanism was exclusively more favorable to the "imine (or ketone)-first" catalytic mechanism. However, the computational investigations on NHC-catalyzed [4 + 2] cycloaddition reaction verified that the "diazene-first" mechanism was favorable in comparison with the "ketene-first" mechanism. To the best of our knowledge, the mechanisms and stereoselectivities of catalyst-controlled divergence in NHC-catalyzed [2 + 2] and [2 + 2 + 2] cycloaddition reactions of ketene with isothiocyanate remain to be hitherto unexplored. Thus, the theoretical investigation is still necessary for these special organocatalytic reactions. It should be noted that our previous work on NHC-catalyzed [2 + 2 + 2] cycloaddition reaction of ketene with carbon disulfide concentrated on the mechanism of this kind of cycloaddition reaction [18], while the origin of the stereoselectivity has still been unsettled to date.



Scheme 2. The proposed catalytic cycle for the NHC-catalyzed [2 + 2 + 2] cycloaddition reaction.

On the basis of the presumptive mechanism proposed by Ye [14], we suggested the possible mechanism of the reaction of ketenes with isothiocyanate catalyzed by NHC (Shown in **Scheme 2**). For the [2 + 2+ 2] cycloaddition reaction, there are generally four steps in the catalytic cycle, including (i) the nucleophilic addition of **Cat** to **R1** to form the zwitterionic intermediates ***E*/*Z*-M1** via transition states ***E*/*Z*-TS1**, (ii) the reaction between intermediates ***E*/*Z*-M1** and **R2** to generate the intermediates **M2*R*/*S*** via transition states **TS2*R*/*S***, (iii) the [4 + 2] cycloaddition of **M2*R*/*S*** with the second molecule of **R1** to form the six-membered adducts ***E*/*Z*-M3*R*/*S*** via transition states ***E*/*Z*-TS3*R*/*S***, and (iv) the dissociation of desired products ***E*/*Z*-P*R*/*S*** and regeneration of catalyst **Cat** via transition states ***E*/*Z*-TS4*R*/*S***.

Nevertheless, there are still some issues that need to be settled: As shown in **Scheme 2**, why the **Cat** cannot catalyze the [2 + 2] cycloaddition reaction of **R1** with **R2** and what is the main factor that controls the chemoselectivity in this divergent reaction? Why the NHC can not react with **R2** firstly? As the design of a new organocatalyst relies on a detailed understanding of the underlying factors that govern the stereoselectivity of these kinds of reactions, so what are the main factors governing the stereoselectivity of this reaction? With these questions as motivation, the present work will pursue a theoretical investigation on the title reaction to not only obtain a preliminary picture from the ketene [2 + 2 + 2] cycloaddition reaction, but also explore the factors that control the stereochemistry of this reaction. We believe that the mechanistic information should be important for understanding the NHC-catalyzed [2 + 2 + 2] cycloaddition reaction and providing novel insights into recognizing this kind of reaction in detail.

In this present study, we aim to disclose both the detailed mechanism and the stereoselectivity of this novel NHC-catalyzed [2 + 2 + 2] cycloaddition reaction of ketenes with isothiocyanate (**Scheme 1**) using density functional theory (DFT), which has been widely used in the study of organic [19-30], biological reaction mechanisms [31-34], and others [35, 36]. For the sake of convenience, the cycloaddition reaction between phenyl (ethyl) ketenes (**R1**, **Scheme 1**) and isothiocyanate (**R2**, **Scheme 1**) catalyzed by **Cat** (**Scheme 1,** Ar^1=Ph, R^1=TBS, R^2=2-^{i}PrC_6H_4) has been chosen as the object of investigation.

2. Computational details

Quantum mechanical calculations reported herein were carried out using the Gaussian 09 suite of programs [37], with density functional theory (DFT). All structures of the reactants, transition states, intermediates, and products were optimized using the M06-2X [38-40] density functional along with the 6-31G(d, p) basis set in the gas phase. The harmonic vibrational frequency calculations were performed at the same level of theory as that used for geometry optimizations to provide thermal corrections of Gibbs free energies. We confirmed that the local minima had no imaginary frequency, while the saddle points had only one imaginary frequency. The same level of intrinsic reaction coordinates (IRCs) [41, 42] were calculated to confirm that each transition state structure connected the correct reactant and product on the potential energy surface, and the natural bond orbital (NBO) [43-45] analysis was employed to assign the atomic charges.

On the basis of the optimized structures in the gas phase at the M06-2X/6-31G(d, p) level, the energies were then refined by M06-2X/6-311+G(d, p) single-point calculations with solvent effects (dichloromethane, which was chosen from the available experiment) included and simulated by the integral equation formalism polarizable continuum model (IEF-PCM) [46, 47]. In the following parts of this paper, all discussions in this theoretical study are based on solution phase single point energy (M06-2X/6-311+G(d, p)) corrected by gas phase Gibbs free energy correction (M06-2X/6-31G(d, p)). We chose to make discussions based on Gibbs free energies rather than Born-Oppenheimer energies, which are the electronic (including nuclear-repulsion) energies plus ZPEs in this study. The computed structures were rendered using the CYLView software [48].

3. Results and discussion

It is a crucial but usually challenging issue to figure out how the catalyst will first exert its effect on reactants for a catalytic reaction. The answers might be different due to the various factors such as the specific structure of the catalyst, the reactant counterparts, and experimental conditions, which are important for the catalytic reactions. Based on the general study of the other NHC-catalyzed cycloaddition reactions, the NHCs do not always combine with ketene to initiate the cycloaddition. Meanwhile, in this reaction (**Scheme 1**), the two reaction patterns (**R1** and **R2**) can both react with NHC due to their electrophilic propensity of the carbonyl and/or thiocarbonyl carbon atom in **R1** and **R2**. In this present study, we only calculate the reaction between **R1** and **R2**, the dimerization reaction of ketene is left out from our computations, because (1) the dimerization reaction of ketene is a competitive side reaction of the title reaction and it is unnecessary to discuss its stereoselectivity in detail, (2) the selected computational method, including the density functional, basis set, and solvation model, is verified to be able to predict the right stereoselectivity for the title reaction system. Therefore, we believe it is reasonable to omit the dimerization reaction. Furthermore, the regioselective [2 + 2] cycloaddition reaction of **R1** with **R2** catalyzed by **Cat** is also studied.

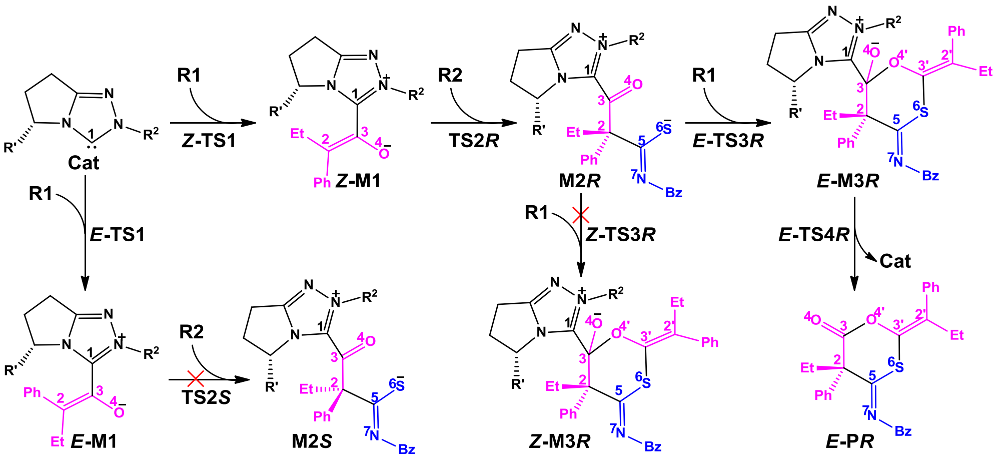
3.1. Reaction mechanism catalyzed by Cat

In this section, we firstly studied the **Cat** catalyzed [2 + 2 + 2] cycloaddition reaction of **R1** with **R2**, and then explored the **Cat** catalyzed [2 + 2] cycloaddition reaction of **R1** with **R2**.

The detailed discussion has been presented as follows.

3.1.1. [2 + 2 + 2] Cycloaddition mechanism

As shown in **Scheme 2**, we have first suggested the fundamental catalytic cycle for the [2 + 2 + 2] cycloaddition reaction. **Figure 1** presents the energy profile of the entire fundamental pathways.



Scheme 3. The E/Z-type and R/S chiral configurations involved in the NHC-catalyzed [2 + 2 + 2] cycloaddition reaction.

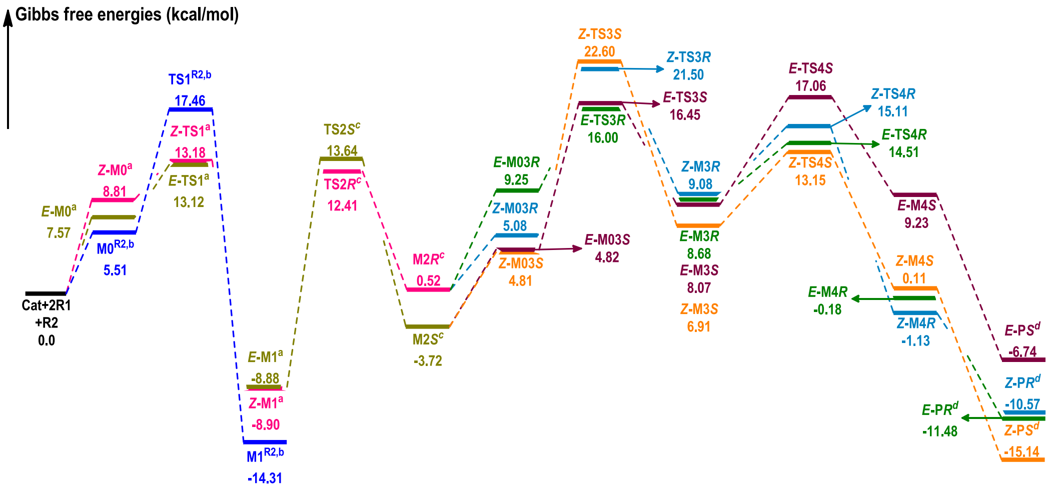
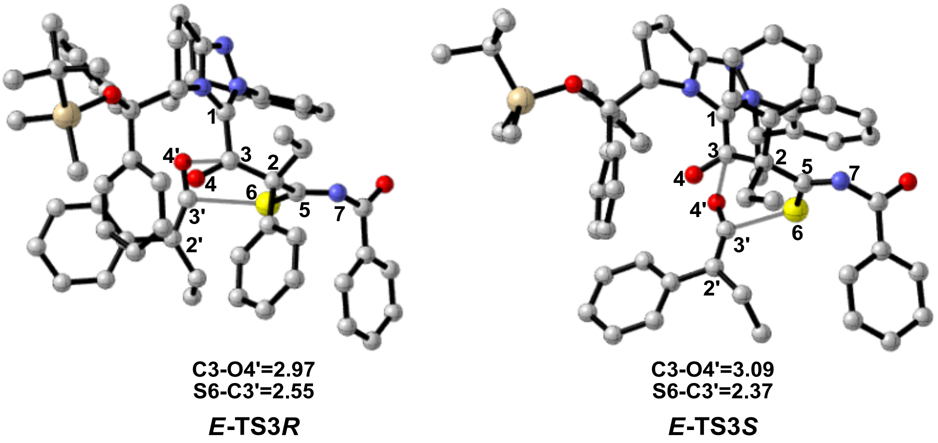


Figure 1: The Gibbs free energy profile of [2 + 2 + 2] cycloaddition reaction of ketenes with isothiocyanate catalyzed by **Cat** ([a] adding the free energy of **R2** and **R1**, [b] adding the free energy of 2**R1**, [c] adding the free energy of **R1**, [d] adding the free energy of **Cat**).

Initially, two reaction precursors ***E*/*Z*-M0** are formed with the approach of **Cat** to **R1**, this step is endergonic by 7.57/8.81 kcal/mol (**Figure 1**), respectively. From ***E*/*Z*-M0**, nucleophilic attack on the C3 atom of **R1** by C1 atom in **Cat** via the transition states ***E*/*Z*-TS1** produces the coordinated zwitterionic intermediates ***E*/*Z*-M1** with the energy barriers of 13.12/13.18 kcal/mol (**Figure 1**), respectively. Notably, the C5 atom of **R2** is also electron-deficient and can react with **Cat**, thus this possibility is also taken into consideration. The formation of zwitterionic intermediate **M1**^{R2} via the transition state **TS1**^{R2} requires an energy barrier of 17.46 kcal/mol (**Figure 1**). The Gibbs free energy barriers via transition states ***E*/*Z*-TS1** (13.12/13.18 kcal/mol) are found to be ~4.3 kcal/mol lower than that via **TS1**^{R2} (17.46 kcal/mol), which reveals that the reaction between **Cat** and **R1** occurs more favorably to initiate the reaction under the experimental condition. With regard to the stereoselectivity, as the free energy barrier difference via ***E*-TS1** (13.12 kcal/mol) in comparison to that via ***Z*-TS1** (13.18 kcal/mol) is predicted to be a value that lies within the error bar of the computational method, it is difficult to determine whether ***E*-M1** or ***Z*-M1** is preferred to be formed in this step.

The subsequent C–C bond formation reaction between ***E*/*Z*-M1** and **R2** occurs via transition states **TS2** (***E*-M1** associated with **TS2*S*** and ***Z*-M1** associated with **TS2*R***, respectively) to give the intermediates **M2*S*** and **M2*R***, separately. The chiral center C2 atom is introduced during the formation of C2–C5 in this step and marked as *R*/*S*. We have only considered the *Si* face addition of ***E*-M1** and *Re* face addition of ***Z*-M1** by **R2**, due to the large steric hindrance of *Re* face of ***E*-M1** and *Si* face of ***Z*-M1** for the subsequent [4 + 2] cycloaddition. As shown in **Figure 1**, the C–C bond formation via **TS2*R*/*S*** requires the energy barriers of 21.31/22.52 kcal/mol (***Z*-M1** → **TS2*R*** and ***E*-M1** → **TS2*S***), respectively.



E*-TS3*R ***E*-TS3*S***

Figure 2: Optimized 3-D structures involved in the third step of [2 + 2 + 2] cycloaddition reaction (distance in Å and all of the hydrogens are omitted for the sake of clarity).

As shown in **Scheme 2**, since **M2*R*/*S*** have been formed in the C–C bond formation step, the following step is to construct the six-membered heterocycle that is included in the final product, which obviously needs to add another molecule of **R1**, excluding the possibility of involving another molecule of **R2**. The NBO analysis shows that the negative charges are populated on the S6 atom (–0.282/–0.299 *e*) in **M2*R*/*S*** but positive charges on the C3′ atom (0.731 *e*) in **R1**, while in contrast the positive charges are assigned to the C3 atom (0.513/0.540 *e*) in **M2*R*/*S*** but negative charges to the O4′ atom (–0.442 *e*) in **R1** molecule, the electrostatic attraction between C3′ and S6 along with that between C3 and O4′ will lead to complexes in either *E* or *Z* configuration, depending on which face of **R1** that **M2** (**M2*R*/*S***) get close to. Subsequently, the six-membered ring is formed in ***E*/*Z*-M3** (***E*/*Z*-M3*R*** and ***E*/*Z*-M3*S***) via transition states ***E*/*Z*-TS3** (***E*/*Z*-TS3*R*** and ***E*/*Z*-TS3*S***), respectively. The IRC results demonstrate that the [4 + 2] cycloaddition process occurs via a concerted but highly asynchronous manner and the formation of C3′–S6 bond is more preferred over the formation of the C3–O4′ bond. The free energy profile mapped in **Figure 1** reveals that the energy barriers of the [4 + 2] cycloaddition step are 16.52 (***E*-TS3*R***) and 22.02 (***Z*-TS3*R***) kcal/mol with respect to **M2*R***, whereas those are 20.17 (***E*-TS3*S***) and 26.32 (***Z*-TS3*S***) kcal/mol with respect to **M2*S***, respectively. Obviously, the *Z*-type addition owns much higher energy barrier and the formation of ***Z*-M3*R*** and ***Z*-M3*S*** is unfavorable compared to *E*-type addition for the formation of ***E*-M3*R*** and ***E*-M3*S***, thus in the following parts, we think it is unnecessary to discuss these two possible reaction patterns. The formation of the ***E*-M3*R*** costs the lowest energy barrier and the energy barrier of ***E*-TS3*R*** is 3.65 kcal/mol lower than that of ***E*-TS3*S***, which indicates that the formation of ***E*-M3*R*** is more energy favorable and supports the reported preference to form the *E*-type with *R*-configuration of the product.

The last step is the dissociation of the catalyst with the product via transition state ***E*-TS4*R***, and this leads to the regeneration of the catalyst. The free energy barrier of this step is 5.83 kcal/mol, revealing that the dissociation process is a facilitated process and the catalyst is easy to regenerate.

3.1.2. Regioselective [2 + 2] cycloaddition mechanism

Having established the mechanism of the **Cat**-catalyzed [2 + 2 + 2] cycloaddition reaction of **R1** and **R2**, we alternatively considered the possibility of the regioselective [2 + 2] cycloaddition of one molecule of ketene and one molecule of isothiocyanate, in which the four-membered ring (C2–C3–N7–C5) intermediate is formed.

As shown in **Scheme 2**, these two cycloaddition reactions share the same nucleophilic addition of **Cat** to **R1**. Thus, we started studying the [2 + 2] cycloaddition reaction of ***E*/*Z*-M1** with **R2**. The IRC calculations show that the [2 + 2] cycloaddition reaction also occurs via a concerted but highly asynchronous manner and the formation of the C2–C5 bond (2.00/2.11 Å) is preferred over the formation of the C3–N7 bond (2.83/2.78 Å) in **TS2R^S/S^S**. The free energy barriers of **TS2R^S** (23.95 kcal/mol, **Figure 3**) and **TS2S^S** (28.23 kcal/mol, **Figure 3**) are higher than those of **TS2*R*** (21.31 kcal/mol, **Figure 1**) and **TS2*S*** (22.52 kcal/mol, **Figure 1**), which indicates that the [2 + 2] cycloaddition reaction of **R1** with **R2** catalyzed by **Cat** is unlikely to occur under the experimental condition. In other words, the [2 + 2 + 2] cycloaddition reaction in generation of six-membered ring product is preferred for **Cat** catalyzed system, which agrees with the experiment results.

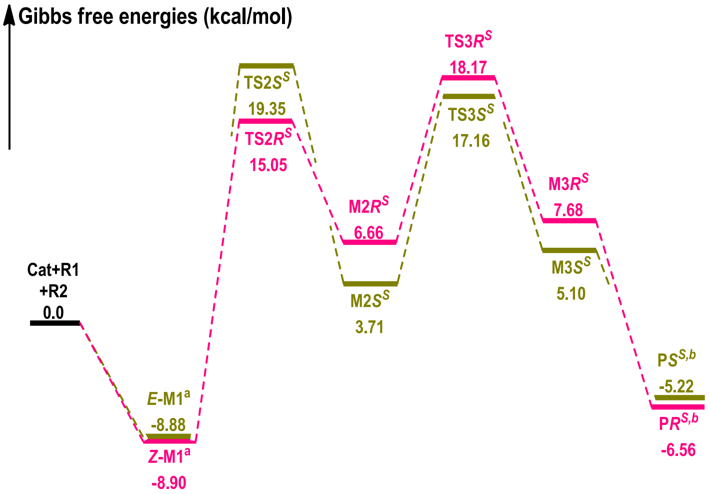
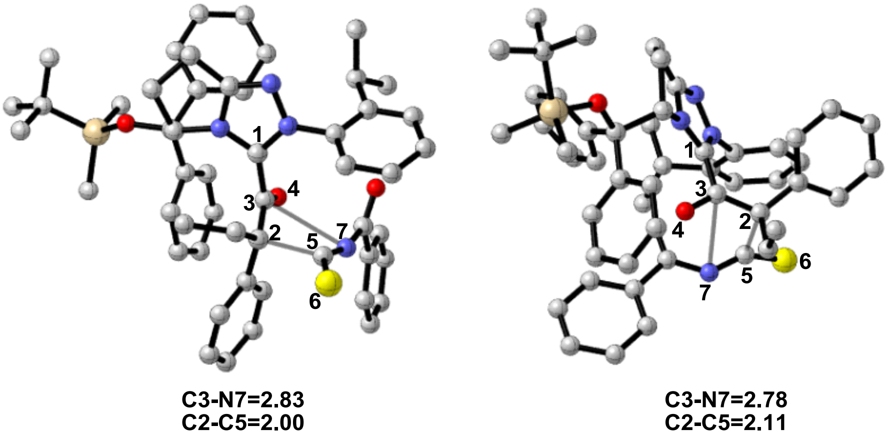


Figure 3: The Gibbs free energy profile of [2 + 2] cycloaddition reaction of ketene with isothiocyanate catalyzed by **Cat** (^{a} adding the free energy of **R2**, ^{b} adding the free energy of **Cat**).



TS2R^S **TS2S^S**

Figure 4: Optimized 3-D structures involved in the second step of [2 + 2] cycloaddition reaction (distance in Å and all of the hydrogens are omitted for the sake of clarity).

Comparing the above two cycloaddition reactions, we find that the rate-determining steps are both the second step, namely, the C–C bond formation step. Obviously, the [2 + 2 + 2] cycloaddition reaction is preferred to the [2 + 2] one under the experimental condition. For the [2 + 2 + 2] cycloaddition reaction, the stereoselectivities associated with the chiral carbon center and the carbon double bond, are predicted to be determined in the second and third steps respectively, and the ***E*-P*R*** is the predominant product, which is consistent with the experimental outcomes.

4. Conclusions

In this paper, the mechanisms of the NHC-catalyzed enantioselective [2 + 2 + 2] cycloaddition of ketenes with isothiocyanate have been studied using the M06-2X density functional theory calculations. The computational results show that the most energy favorable reaction pathway contains four steps: *i.e.*, complexation of **R1** and **Cat** for the formation of enolate intermediate ***Z*-M1**, regioselective addition of **R2** to ***Z*-M1** to give intermediate **M2*R***, addition of another molecule of **R1** for the formation of six-membered heterocycle ***E*-M3*R***, and the regeneration of the catalyst. The stereoselectivities associated with the chiral carbon center and the carbon double bond, are predicted to be determined in the second and third steps respectively, and the ***E*-P*R*** is the predominant product, which is consistent with the experimental outcomes. This work can improve our understanding of the enantioselective N-heterocyclic carbene-catalyzed [2 + 2 + 2] cycloaddition of ketenes and isothiocyanate, and provide valuable insights for predicting the regio- and stereoselectivity for this kind of reaction.

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References

[1] T. Ema, Y. Oue, K. Akihara, Y. Miyazaki and T. Sakai, Stereoselective Synthesis of Bicyclic Tertiary Alcohols with Quaternary Stereocenters via Intramolecular Crossed Benzoin Reactions Catalyzed by N-Heterocyclic Carbenes, Org. Lett., 11 (2009), 4866-4869.

[2] T. Jousseaume, N. E. Wurz and F. Glorius, Highly Enantioselective Synthesis of alpha-Amino Acid Derivatives by an NHC-Catalyzed Intermolecular Stetter Reaction, Angew. Chem. Int. Ed., 50 (2011),

1410-1414.

[3] X. K. Chen, X. Q. Fang and Y. R. Chi, cis-Enals in N-heterocyclic carbene-catalyzed reactions: distinct stereoselectivity and reactivity, Chem. Sci., 4 (2013), 2613-2618.

[4] H. Lu, J. Y. Liu, C. G. Li, J. B. Lin, Y. M. Liang and P. F. Xu, A new chiral C1-symmetric NHC-catalyzed addition to α-aryl substituted α,β-disubstituted enals: enantioselective synthesis of fully functionalized dihydropyranones, Chem. Commun., 51 (2015), 4473-4476.

[5] J. Kaeobamrung, M. C. Kozlowski and J. W. Bode, Chiral N-heterocyclic carbene-catalyzed generation of ester enolate equivalents from α,β-unsaturated aldehydes for enantioselective Diels-Alder reactions, Proc. Natl. Acad. Sci. U. S. A., 107 (2010), 20661-20665.

[6] X. N. Wang, P. L. Shao, H. Lv and S. Ye, Enantioselective Synthesis of β-Trifluoromethyl-β-lactones via NHC-Catalyzed Ketene-Ketone Cycloaddition Reactions, Org. Lett., 11 (2009), 4029-4031.

[7] X. L. Huang, X. Y. Chen and S. Ye, Enantioselective Synthesis of Aza-β-lactams via NHC-Catalyzed [2 + 2] Cycloaddition of Ketenes with Diazenedicarboxylates, J. Org. Chem., 74 (2009), 7585-7587.

[8] T. Wang, X. L. Huang and S. Ye, Enantioselective formal [2+2] cycloaddition of ketenes with nitroso compounds catalyzed by N-heterocyclic carbenes, Org. Biomol. Chem., 8 (2010), 5007-5011.

[9] X. N. Wang, L. T. Shen and S. Ye, Enantioselective [2+2+2] cycloaddition of ketenes and carbon disulfide catalyzed by N-heterocyclic carbenes, Chem. Commun., 47 (2011), 8388-8390.

[10] T. Y. Jian, X. Y. Chen, L. H. Sun and S. Ye, N-heterocyclic carbene-catalyzed [4 + 2] cycloaddition of ketenes and 3-aroylcoumarins: highly enantioselective synthesis of dihydrocoumarin-fused dihydropyranones, Org. Biomol. Chem., 11 (2013), 158-163.

[11] T. Y. Jian, P. L. Shao and S. Ye, Enantioselective [4+2] cycloaddition of ketenes and 1-azadienes catalyzed by N-heterocyclic carbenes, Chem. Commun., 47 (2011), 2381-2383.

[12] H. Staudinger, Ketene, eine neue Körperklasse, Chem. Ber., 38 (1905), 1735-1739.

[13] S. Y. Lee, Y. S. Kulkarni, B. W. Burbaum, M. I. Johnston and B. B. Sinder, Type I intramolecular cycloadditions of vinylketenes, J. Org. Chem., 53 (1988), 1848-1855.

[14] X. N. Wang, L. T. Shen and S. Ye, NHC-Catalyzed Enantioselective [2+2] and [2+2+2] Cycloadditions of Ketenes with Isothiocyanates, Org. Lett., 13 (2011), 6382-6385.

[15] D. H. Wei, Y. Y. Zhu, C. Zhang, D. Z. Sun, W. J. Zhang and M. S. Tang, A DFT study on enantioselective synthesis of aza-β-lactams via NHC-catalyzed [2+2] cycloaddition of ketenes with diazenedicarboxylates, J. Mol. Catal. A: Chem., 334 (2011), 108-115.

[16] M. M. Zhang, D. H. Wei, Y. Wang, S. J. Li, J. F. Liu, Y. Y. Zhu and M. S. Tang, DFT study on the reaction mechanisms and stereoselectivities of NHC-catalyzed [2 + 2] cycloaddition between arylalkylketenes and electron-deficient benzaldehydes†, Org. Biomol. Chem., 12 (2014), 6374-6383.

[17] W. J. Zhang, Y. Y. Zhu, D. H. Wei, Y. X. Li and M. S. Tang, Theoretical Investigations toward the [4 + 2] Cycloaddition of Ketenes with N-Benzoyldiazenes Catalyzed by N-Heterocyclic Carbenes: Mechanism and Enantioselectivity, J. Org. Chem., 77 (2012), 10729-10737.

[18] W. J. Zhang, D. H. Wei and M. S. Tang, DFT Investigation on Mechanisms and Stereoselectivities of [2

+ 2 + 2] Multimolecular Cycloaddition of Ketenes and Carbon Disulfide Catalyzed by N-Heterocyclic Carbenes, J. Org. Chem., 78 (2013), 11849-11859.

[19] Y. Qiao and K. L. Han, Elucidation of the reaction mechanisms and diastereoselectivities of phosphine-catalyzed [4+2] annulations between allenoates and ketones or aldimines, Org. Biomol. Chem., 10 (2012), 7689-7706.

[20] Y. Wang, D. H. Wei, Z. Y. Li, Y. Y. Zhu and M. S. Tang, DFT Study on the Mechanisms and Diastereoselectivities of Lewis Acid-Promoted Ketene−Alkene [2 + 2] Cycloadditions: What is the Role of Lewis Acid in the Ketene and C = X (X = O, CH2, and NH) [2 + 2] Cycloaddition Reactions?, J. Phys. Chem. A, 118 (2014), 4288-4300.

[21] Y. Wang, D. H. Wei, W. J. Zhang, Y. Y. Wang, Y. Y. Zhu, Y. Jia and M. S. Tang, A theoretical study on the mechanisms of the reactions between 1,3-dialkynes and ammonia derivatives for the formation of five-membered N-heterocycles, Org. Biomol. Chem., 12 (2014), 7503-7514.

[22] Y. Wang, B. H. Wu, H. Y. Zhang, D. H. Wei and M. S. Tang, A computational study on the N-heterocyclic carbene-catalyzed Csp2–Csp3 bond activation/[4+2] cycloaddition cascade reaction of cyclobutenones with imines: a new application of the conservation principle of molecular orbital symmetry†, Phys. Chem. Chem. Phys., 18 (2016), 19933-19943.

[23] Y. Wang, M. S. Tang, Y. Y. Wang and D. H. Wei, Insights into Stereoselective Aminomethylation Reaction of α,β-Unsaturated Aldehyde with N,O-Acetal via N-Heterocyclic Carbene and Brønsted Acid/Base Cooperative Organocatalysis, J. Org. Chem., 81 (2016), 5370-5380.

[24] Y. Y. Wang, D. H. Wei, Y. Wang, W. J. Zhang and M. S. Tang, N-Heterocyclic Carbene (NHC)-Catalyzed sp3 β-C–H Activation of Saturated Carbonyl Compounds: Mechanism, Role of NHC, and Origin of Stereoselectivity, ACS Catal., 6 (2016), 279-289.

[25] Y. Wang, B. H. Wu, L. J. Zheng, D. H. Wei and M. S. Tang, DFT perspective toward [3+2] annulation reaction of enals with α-ketoamides through NHC and Bronsted acid cooperative catalysis: mechanism, stereoselectivity, and role of NHC, Org. Chem. Front., 3 (2016), 190-203.

[26] Y. Wang, L. J. Zheng, D. H. Wei and M. S. Tang, A quantum mechanical study of the mechanism and stereoselectivity of the N-heterocyclic carbene catalyzed [4+2] annulation reaction of enals with azodicarboxylates, Org. Chem. Front., 2 (2015), 874-884.

[27] L. J. Zheng, M. S. Tang, Y. Wang, X. K. Guo, D. H. Wei and Y. Qiao, A DFT study on PBu3-catalyzed intramolecular cyclizations of N-allylic substituted α-amino nitriles for the formation of functionalized pyrrolidines: mechanisms, selectivities, and the role of catalysts, Org. Biomol. Chem., 14 (2016), 3130-3141.

[28] W. Zhang, Y. Wang, D. H. Wei, M. S. Tang and X. J. Zhu, A DFT study on NHC-catalyzed intramolecular aldehyde–ketone crossed-benzoin reaction: mechanism, regioselectivity, stereoselectivity, and role of NHC†, Org. Biomol. Chem., 14 (2016), 6577-6590.

[29] X. K. Guo, L. B. Zhang, D. H. Wei and J. L. Niu, Mechanistic insights into cobalt(II/III)-catalyzed C–H oxidation: a combined theoretical and experimental study, Chem. Sci., 6 (2015), 7059-7071.

[30] Y. Wang, X. K. Guo, B. H. Wu, D. H. Wei and M. S. Tang, Mechanistic and stereoselectivity study for the reaction of trifluoropyruvates with arylpropenes catalyzed by a cationic Lewis acid rhodium complex, RSC Adv., 5 (2015), 100147-100158.

[31] Y. Qiao, K. L. Han and C. G. Zhan, Reaction pathways and free energy profiles for cholinesterase-catalyzed hydrolysis of 6-monoacetylmorphine, Org. Biomol. Chem., 12 (2014), 2214-2227.

[32] D. H. Wei, B. L. Lei, M. S. Tang and C. G. Zhan, Fundamental Reaction Pathway and Free Energy Profile for Inhibition of Proteasome by Epoxomicin, J. Am. Chem. Soc., 134 (2012), 10436-10450.

[33] D. M. Li, Y. Wang and K. L. Han, Recent density functional theory model calculations of drug metabolism by cytochrome P450, Coord. Chem. Rev., 256 (2012), 1137-1150.

[34] D. M. Li, X. Q. Huang, K. L. Han and C. G. Zhan, Catalytic Mechanism of Cytochrome P450 for 5 '-Hydroxylation of Nicotine: Fundamental Reaction Pathways and Stereoselectivity, J. Am. Chem. Soc., 133 (2011), 7416-7427.

[35] L. Zhang and D. C. Fang, Catalytic C–H Activation/C–C Coupling Reaction: DFT Studies on the Mechanism, Solvent Effect, and Role of Additive, J. Org. Chem., 78 (2013), 2405-2412.

[36] J. Y. Tao, D. C. Fang and G. A. Chass, Simplification through complexity: the role of Ni-complexes in catalysed diyne-cyclobutanone [4+2+2] cycloadditions, a comparative DFT study, Phys. Chem. Chem. Phys., 14 (2012), 6937-6945.

[37] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

[38] Y. Zhao and D. G. Truhlar, The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals, Theor. Chem. Acc., 120 (2008), 215-241.

[39] Y. Zhao and D. G. Truhlar, Density Functionals with Broad Applicability in Chemistry, Acc. Chem. Res., 41 (2008), 157-167.

[40] W. J. Zhang, D. G. Truhlar and M. S. Tang, Tests of Exchange-Correlation Functional Approximations Against Reliable Experimental Data for Average Bond Energies of 3d Transition Metal Compounds, J. Chem. Theory Comput., 9 (2013), 3965-3977.

[41] C. Gonzalez and H. B. Schlegel, An improved algorithm for reaction path following, J. Chem. Phys., 90 (1989), 2154-2161.

[42] C. Gonzalez and H. B. Schlegel, Reaction path following in mass-weighted internal coordinates, J. Phys. Chem., 94 (1990), 5523-5527.

[43] A. E. Reed and F. J. Weinhold, Natural bond orbital analysis of near-Hartree-Fock water dimer, J. Chem. Phys., 78 (1983), 4066-4073.

[44] J. P. Foster and F. J. Weinhold, Natural hybrid orbitals, J. Am. Chem. Soc., 102 (1980), 7211-7218.

[45] E. D. Glendening, A. E. Reed, J. E. Carpenter and F. J. Weinhold, NBO Version 3.1, 1998.

[46] B. Mennucci and J. Tomasi, Continuum solvation models: A new approach to the problem of solute's charge distribution and cavity boundaries, J. Chem. Phys., 106 (1997), 5151-5158.

[47] V. Barone and M. Cossi, Quantum Calculation of Molecular Energies and Energy Gradients in Solution by a Conductor Solvent Model, J. Phys. Chem. A, 102 (1998), 1995-2001.

[48] C. Y. Legault, CYLView, 1.0b, Université de Sherbrooke, 2009, and http://www.cylview.org.