

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.

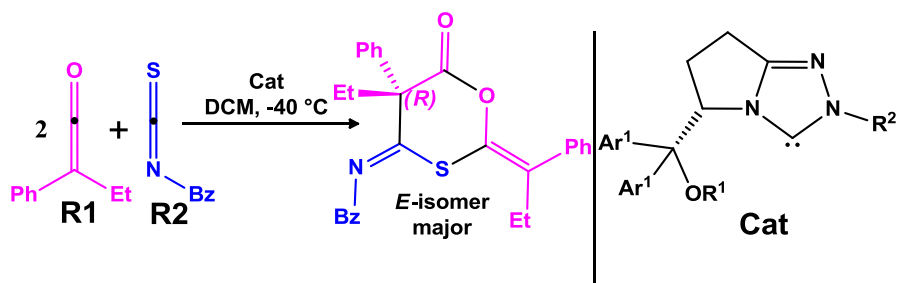
1. Introduction

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