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Theoretical Studies on the Mechanism of the C−H Amination of Silyl Cyclopropenes by Azodicarboxylates

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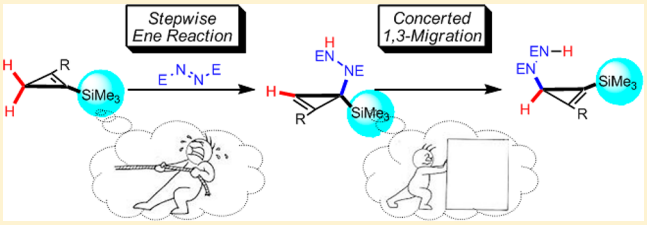
Supporting Information

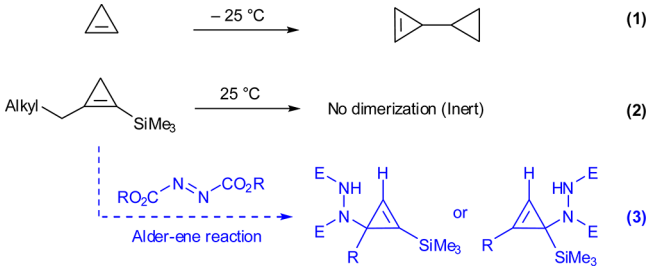
ABSTRACT: DFT/M06 calculations were carried out to better understand the mechanism and regio- and chemoselectivities of our previously discovered formal C−H amination of silyl cyclopropenes by azodicarboxylates (*Chem. Commun.* **2012**, *48*, 10990). The results revealed that the initial Alder-ene reaction between the two reactants follows a stepwise mechanism and the subsequent allylic transposition proceeds via a concerted [1,3]-migration of hydrazodicarboxylate. For the Alder-ene process of 1-silyl-2-methylcyclopropene, different electronic effects of the substituents make the C1 much more negatively charged and thus more reactive than C2 in the regiochemistry-determining electrophilic azodicarboxylate addition step. In addition, the poor regioselectivity caused by a C2 ether linkage and the lower reactivity of ene donors other than cyclopropenes with azodicarboxylate were well explained by the computational results. Furthermore, the divergent allylic transposition of the Alder-ene intermediates was rationalized, and the steric repulsion between the silyl group and the hydrazodicarboxylate moiety was suggested as the driving force in promoting the allylic transposition. The barrier for the rate-controlling [1,3]-migration of hydrazodicarboxylate from an intermediate containing the C1−N bond is 21.1 kcal/mol, whereas a higher barrier of 27.5 kcal/mol is required for the similar rearrangement of the thermodynamically more stable intermediate containing the C2−N bond.



1. INTRODUCTION

Over the past few decades, the introduction of nitrogen atoms into organic molecules has received a tremendous amount of attention, due to the fact that the nitrogen-containing molecules are of high biological interest and are prevalent in pharmaceuticals.[1] C−H amination represents a potentially attractive strategy for converting the abundant C−H into C−N bonds directly in an atom-economical way.[2] Catalytic C−H amination has been widely pursued over the years by using various transition metal-based catalysts.[3] To develop a greener process, C−H amination under transition metal-free conditions has emerged from the recent works of several groups,[4] including the selective and efficient amination of the sp^3-hybridized C−H bonds.[5] However, these reactions still suffer from the drawbacks of using organocatalyst/stoichiometric oxidant, thus generating significant quantities of byproducts, or requiring specialized conditions.

In comparison to the above approaches, ene reactions or related processes are considered to be more environmentally friendly and atom economical, not requiring any additional reagents other than the reacting enophile and ene-donor counterparts.[6] In this regard, we became interested in the unusual reactivity of cyclopropenes, for these molecules are one of the least stable hydrocarbon ring systems.[7] The unsubstituted parent cyclopropenes are known to undergo dimerization and polymerization even at −25 °C (eq 1).[8] It



was shown by Dowd and Houk that the dimerization of cyclopropenes via an Alder-ene reaction mechanism has a much lower activation barrier than the ene reactions of typical ene donors and enophiles, due mainly to the relief of their ring strain.[9] Despite the broad theoretical and mechanistic interests in the ene reaction of cyclopropenes, only sporadic studies on their reactions with other enophiles have been reported.[10] Substituted cyclopropenes are relatively more stable than unsubstituted ones, and thus a higher temperature is required for their dimerization.[11] In line with this trend, we observed that the 1-silyl-2-alkyl-substituted cyclopropenes remain intact even at room temperature (eq 2). On the basis of this observation, we envisaged that the heterodimerization between

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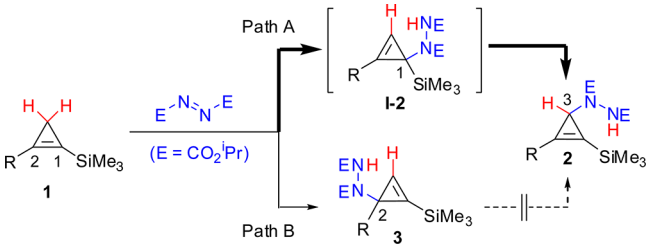
silyl-substituted cyclopropenes with reactive enophiles such as azodicarboxylate would undergo a selective Alder-ene reaction to generate formal amination products (eq 3).

As expected, our previous experiments showed that the silyl-substituted cyclopropenes **1** bearing various alkyl and alkoxy substituents smoothly underwent ene reactions with azodicarboxylates.[12] However, the major product **2** was found to be derived not from the expected Alder-ene reaction but from an unexpected C3−H animation. Only the minor compound **3** was consistent with being derived from the expected Alder-ene reaction (Scheme 1). Careful monitoring of the reaction

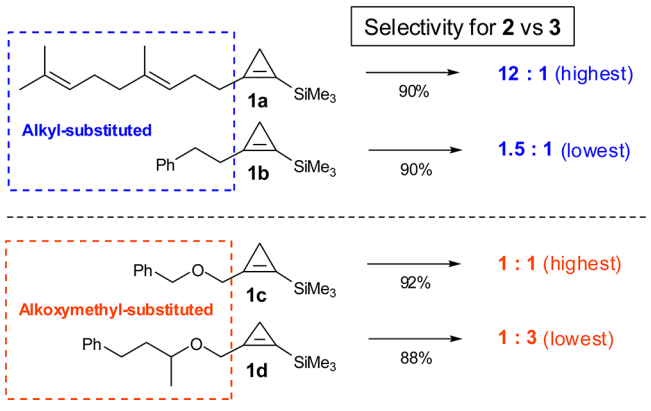
Scheme 1. Formal C−H Amination of Cyclopropene



provided solid evidence that this formal C−H amination reaction was initiated by a rapid Alder-ene reaction between cyclopropene **1** and diisopropyl azodicarboxylate (DIAD) to generate the hydrazodicarboxylate intermediate **I-2**, which then rearranged to the C3−H aminated product **2** via a slow allylic transposition (path A).[12]

Despite the facile C(sp^3)−H amination of cyclopropenes via an Alder-ene reaction with azodicarboxylate enophile, this process raises several interesting mechanistic questions. First, the origin of regioselectivity in the Alder-ene step is unclear. In most cases the reaction between **1** and DIAD formed predominantly the C−H aminated product **2** along with a small amount of Alder-ene product **3** (path B). However, the R substituent on C2 was found to exert a significant influence on the product distribution, thus giving a high selectivity for a substrate containing a large branched alkyl substituent (**1a**, 12:1) and much lower selectivity for a small unbranched substituent (**1b**, 1.5:1). In contrast, poor or reversed selectivity was observed for ether-substituted cyclopropenes, as shown by the product ratios of 1:1 and 1:3 from **1c**,**d**, respectively (Scheme 2).[12]

Scheme 2. Selectivity for 2 vs 3 in the Formal C−H Amination of Cyclopropenes of Different Substituents at C2



Therefore, a more detailed investigation is necessary to address the questions regarding the regioselectivity: why path A is more favorable over path B for alkyl-substituted cyclopropenes and how the ether substituent affects the selectivity. Second, the mechanism of the allylic transposition step is yet to be uncovered. Divergent reactivity of **I-2** and **3** was observed in this step, wherein the former regioisomer was found to rearrange to the final product **2** slowly while the latter remained unchanged even at elevated temperature.[12] Clearly, the silyl group plays an important role in the facile rearrangement of **I-2**, but how it facilitates this rearrangement must be clarified. Furthermore, predictions on the relative reactivity of other ene donors, for example a prenyl group in **1a**, toward azodicarboxylate will be highly desirable. This would shed light on the unique reactivity of the cyclopropene moiety and explain why other allylic systems incorporated in the substrates remain intact in the reaction. Once verified, this information will be further exploited for future development and design of new reactions.

In this report, we present a detailed mechanistic analysis of the C−H amination on the basis of DFT/M06 calculations,[13] and justifications for the experimentally observed regio- and chemoselectivity.

2. RESULTS AND DISCUSSION

In this section the reactions were first simulated computationally by using the 1-trimethylsilyl-2-methylcyclopropene (**1**) and dimethyl azodicarboxylate (DMAD) as model reactants to uncover the overall mechanisms for the formation of **2** and **3**; then the factors controlling the regio- and chemoselectivities of the Alder-ene and allylic transposition steps were analyzed in detail. The potential energy surface accounting for the transformations is depicted in Figure 1, and the geometric structures for key transition states and intermediates are given in Figure 2.

The computational results show that the Alder-ene reaction between **1** and DMAD follows a stepwise mechanism[14] and the subsequent allylic transposition is realized via a [1,3]-migration of the hydrazodicarboxylate moiety. In the stepwise Alder-ene processes, the electrophilic additions of DMAD to C1 and C2 of **1** proceed via **A-TS1** and **B-TS1**, respectively, with relative free energies of 17.1 and 18.5 kcal/mol. The geometric structures of **A-TS1** and **B-TS1** show that the forming C1−N1 (1.854 Å) and C2−N1 (1.884 Å) bonds are similar, and both species are stabilized by close interactions between the N2 of the DMAD moiety and the H on C3 (Figure 2).

As expected, the dimerization of **1** via **D-TS** requires an activation barrier of 25.7 kcal/mol (Scheme 3),[9,15] being much more difficult than the heterodimerizations via **A-TS1** and **B-TS1**. Thus, no dimerization of substituted cyclopropenes was observed in experiments. The computational results in Scheme 3 show that the reactions between **1** and azodicarboxylate could also proceed via the concerted transition states **A-TS1′** and **B-TS1′**; however, these are higher in energy than the stepwise pathways shown in Figure 1. The geometric structures of **A-TS1′** and **B-TS1′** show that the C3−H bonds are substantially destroyed while the incipient C1−N1 bond in **A-TS1′** and C2−N1 bond in **B-TS1′** are very weak.

By passing the electrophilic addition transition states, zwitterionic intermediates **A-IN** and **B-IN** are formed endergonically by 11.0 and 10.3 kcal/mol, respectively. It is interesting to find that **B-IN** is about 0.7 kcal/mol lower in energy than **A-IN**, since the positive charges in the latter

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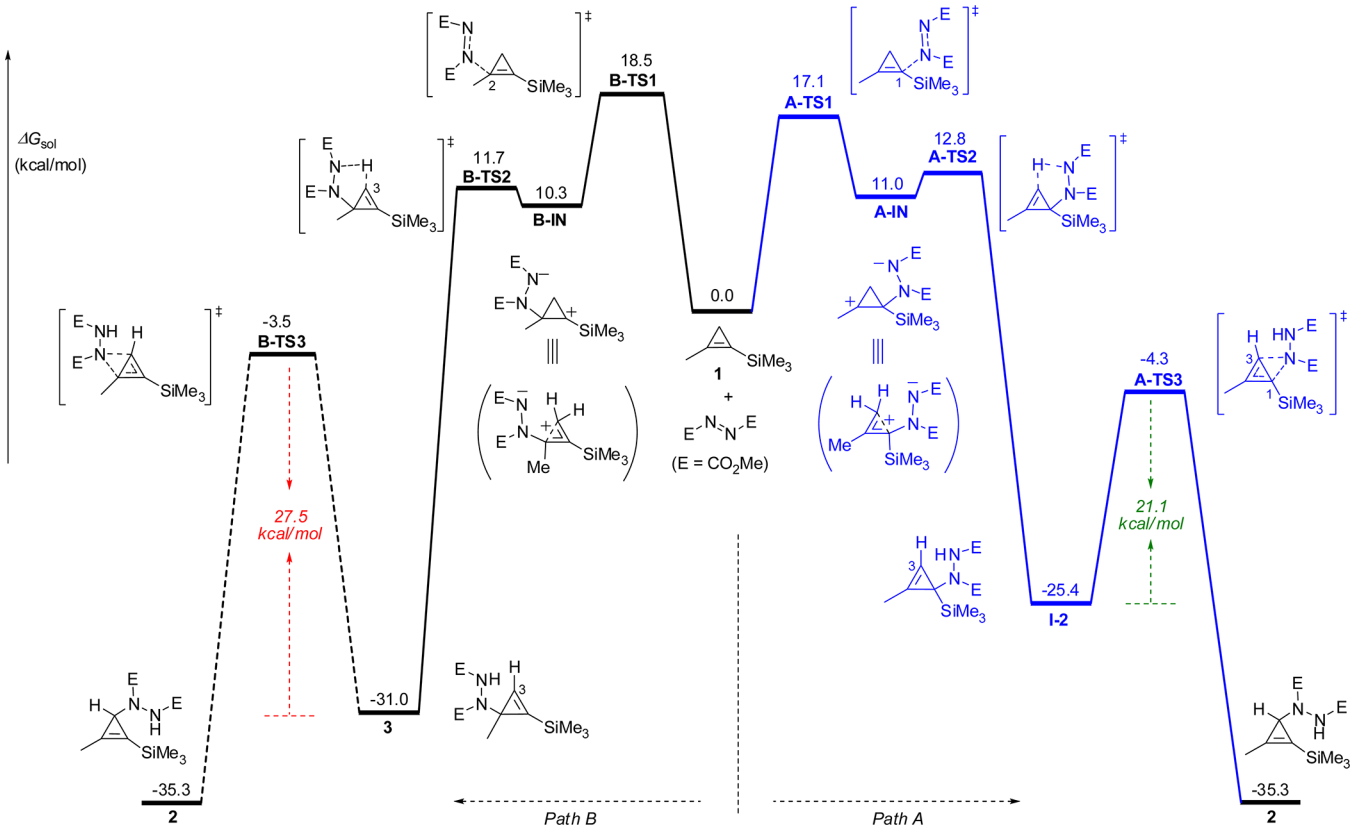

Figure 1. Potential energy diagram for the C−H amination of cyclopropene **1**.

intermediate could be possibly stabilized by the well-known *β*-silicon effect.[16] The structural parameters of these zwitterionic intermediates provide an interpretation for this superficial contradiction, that the almost equidistant C1−C2 and C2−C3 bonds suggest the delocalization of the positive charge on the three-membered ring. These two distances are around 1.42 Å in **A-IN** and 1.44 Å in **B-IN**; both are apparently shorter than typical C−C single bonds in three-membered-ring systems (Figure 2).[17] Thus, the structures of **A-IN** and **B-IN** could be depicted as resonance hybrid forms shown in parentheses in Figure 1, reflecting the nature of a partially opened cyclopropyl cation as proposed by Schleyer, Schöllkopf, and People.[18] In addition, these zwitterionic intermediates are also stabilized by the strong N2- - -H interactions, although a slightly lesser extent of such interactions is found in intermediates **A-IN** and **B-IN** in comparison with those in **A-TS1** and **B-TS1**. These zwitterionic intermediates are relatively unstable and readily undergo an intramolecular proton transfer from C3 to the anionic nitrogen via **A-TS2** and **B-TS2**, which respectively lead irreversibly to the Alder-ene products **I-2** and **3** with barriers less than 2 kcal/mol.

Hence, the regioselectivity of the stepwise Alder-ene reaction is determined at the stage of the addition of azodicarboxylate to cyclopropene. The energy difference of 1.4 kcal/mol between **A-TS1** and **B-TS1** predicts the product ratio **2**-I:**3** to be about 9:1 at 45 °C,[19] in good agreement with the experimental observations.[12] Although **A-TS1** seems to be disfavored by the greater steric hindrance posed by the trimethylsilyl group on C1, the calculated energy values are in line with the NBO analysis of **1**, which shows the NPA charge populations on C1 (−0.50) and C2 (0.04), respectively. Thus, the more favorable C1 addition is a result of the different electronic effects of the silyl and alkyl substituents: the former group is known to be *π*-electron withdrawing,[20] while the latter is electron donating.

In experiments we found that the introduction of an ether linkage on C2 resulted in poor or reversed selectivity (Scheme 2).[12] To study this observation in detail, the computational results for the electrophilic addition step of the stepwise Alder-ene reaction of the ether-containing substrate **1_O** with DMAD is given in Scheme 4. The results are consistent with the experimental outcome that the addition of DMAD to C2 via **B-TS1_O** is slightly lower in energy than the C1 addition via **A-TS1_O** by 0.2 kcal/mol. To understand the origin of the slight preference of C2 addition in detail, the geometries of **B-TS1_O** and **A-TS1_O** are depicted in Scheme 4, which reveals different orientations of the C3′−O bonds in the lowest energy conformer of these two transition states. In **B-TS1_O** the C3′−O bond is nearly perpendicular to the cyclopropene ring, whereas in **B-TS1_O** this bond is in the same plane as the cyclopropene moiety. Notably, the C2−O distances in both transition states are around 2.34 Å, much shorter than the sum of the van der Waals radii of oxygen and carbon atoms.[21] This implies the possible interactions of the oxygen lone pairs with the *π* electrons between C1 and C2. The HOMO-1 Kohn−Sham orbital of **B-TS1_O** in Scheme 5 shows the interaction between the lone pair of oxygen and the C1═C2 moiety; however, no such interaction is noticeable in the frontier orbitals of **A-TS1_O**. Thus, the electrophilic addition of DMAD to C2 of **1_O** is stabilized by electron donation from the oxygen atom of the ether linkage. Such an orbital interaction could also be found in the generated intermediate **B-IN_O**, which is 1.6 kcal/mol more stable than **A-IN_O**. The charge population of **1_O** was also analyzed by NBO calculations, which turned out to be almost the same as the

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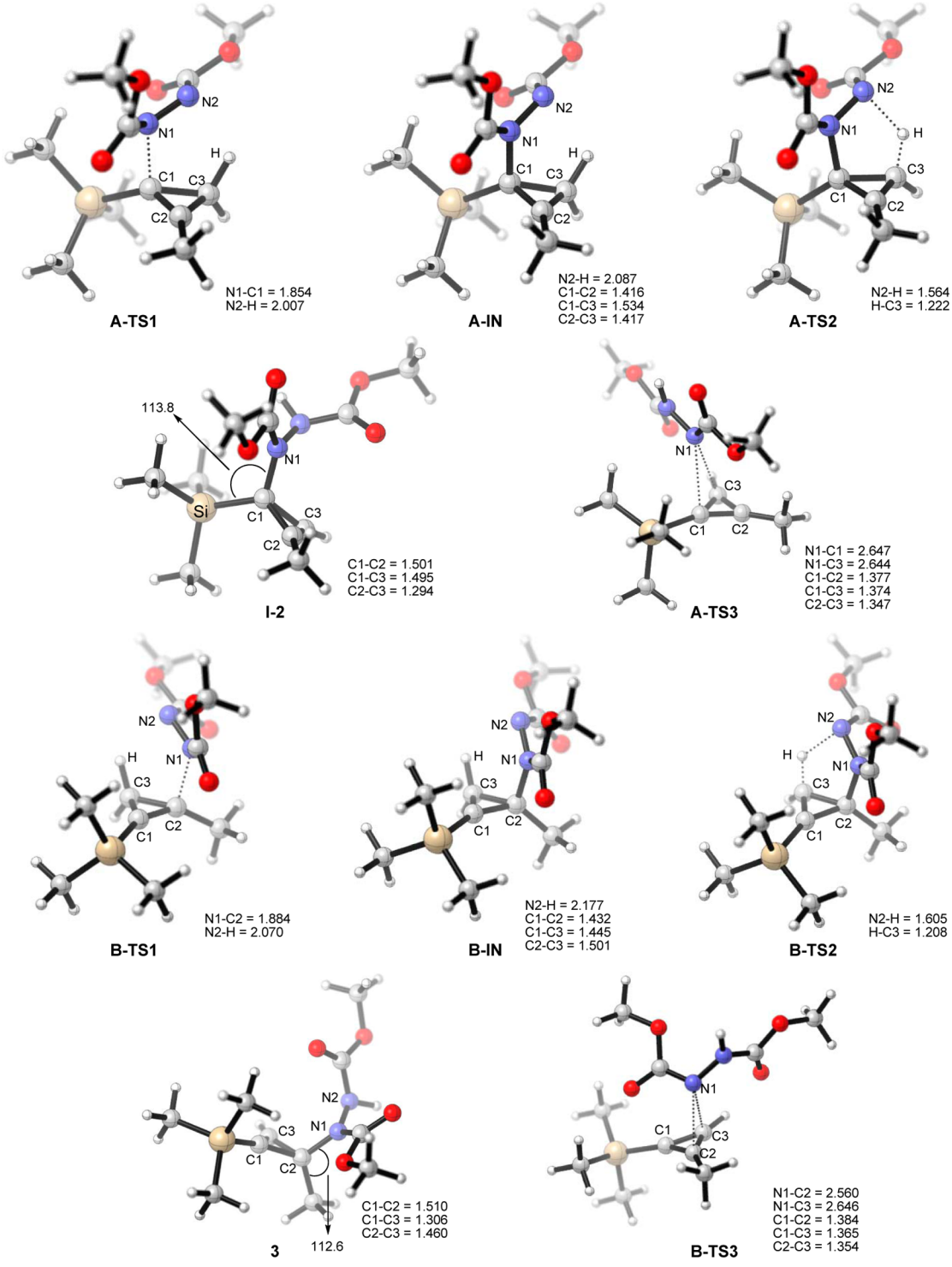

Figure 2. Geometric structures for selected transition states and intermediates. Distances and angles are given in Å and deg, respectively.

charge population in **1**, revealing that the inductive effect of the ether linkage on the electron distribution of the C1−C2 double bond is marginal. Hence, the slightly increased barriers (19.8 and 19.6 kcal/mol) for reactions of **1_O** as in comparison with those of **1** (17.1 and 18.5 kcal/mol) result from the repulsive interactions between the ether substituent and the cyclopropene moiety.

In addition to the electronic effects of the C1 trimethylsilyl substituent and the C2 ether linkage, experimental results indicate that the steric effect of the C2 alkyl substituent also influences the regioselectivity. These outcomes could be reproduced by DFT calculations. When the C2 methyl of **1** is replaced by an isopropyl and a *tert*-butyl group, respectively, the C1 addition would be more favorable than C2 addition by 2.2 and 5.3 kcal/mol (Scheme 6), predicting the more regioselective formation of the **I-2**-type intermediate with a bulkier C2 alkyl substituent. Furthermore, DFT calculations on the free energy of activation for other possible Alder-ene reactions of azodicarboxylate with ene donors other than cyclopropenes explain why only the cyclopropene moiety with

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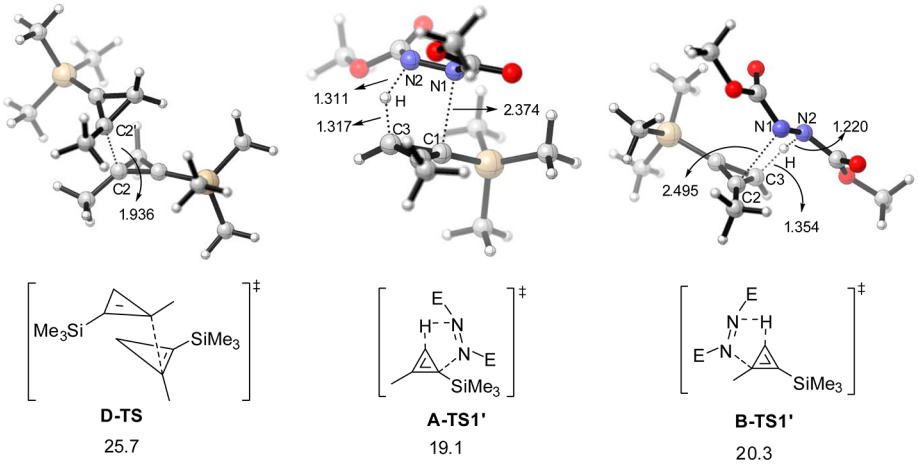
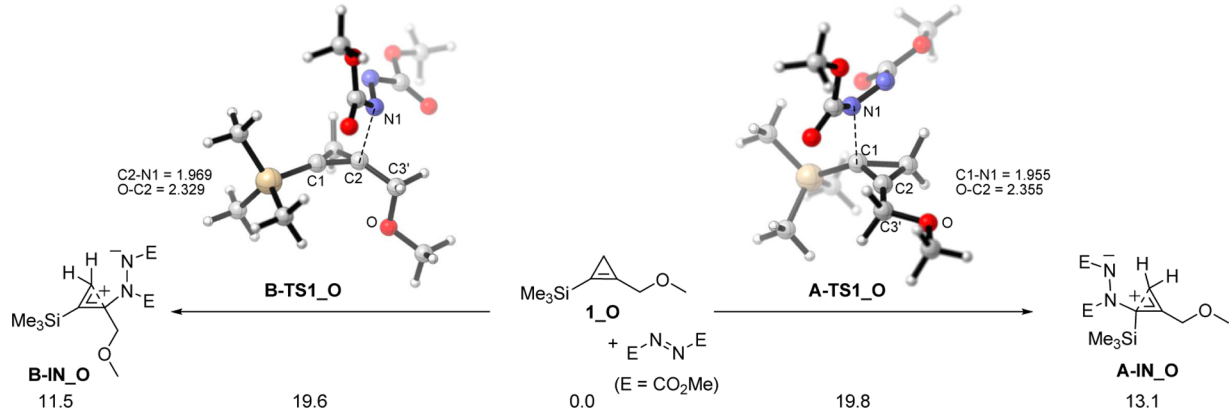
Scheme 3. Relative Energies (in kcal/mol) and Geometric Structures (Distances in Å) for the Transition States of the Dimerization and Concerted Alder-Ene Reactions

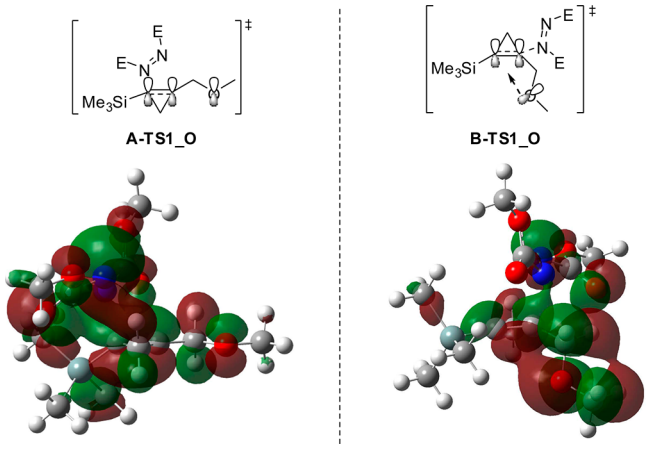


Scheme 4. Computational Results for Reactions of an Ether-Containing Substrate 1_O[a]

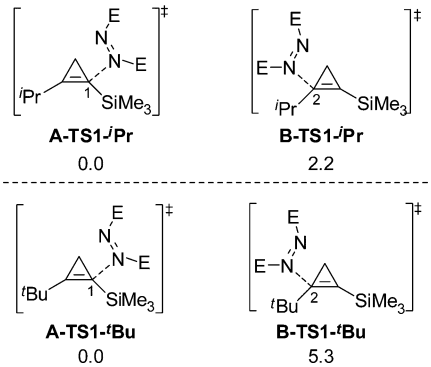


[a]Relative energies (ΔG_{sol}) are in kcal/mol, and distances are in Å.

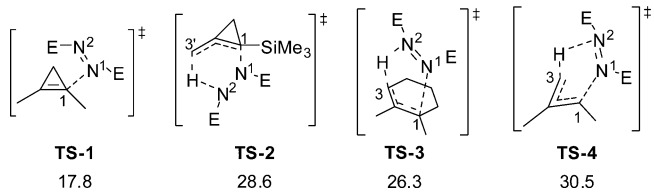
Scheme 5. HOMO-1 Kohn–Sham Orbital Analysis of A-TS1_O and B-TS1_O



Scheme 6. Steric Effect of the C2 Alkyl Substituent on the Regioselectivity



Scheme 7. Activation Free Energies (kcal/mol) for the Reactions of Different Ene Donors with Azodicarboxylate



C3–H participated in the reaction but not other ene donors including the cyclopropene with C3′–H and the remote alkene moieties,[12] which would cost at least 26.3 kcal/mol (Scheme 7). Replacement of the trimethylsilyl group with a methyl group did not change the activation barrier (17.1 kcal/mol in **A-TS1** to 17.8 kcal/mol in **TS-1**) noticeably, which is also

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consistent with the experimental observations. The preferred ene reaction of cyclopropenes over cyclohexenes and other trisubstituted alkenes can be justified by much higher free energies of activation for the last two cases (26.3 and 30.5 kcal/mol for **TS-3** and **TS-4**, respectively) in comparison to the cyclopropenes (17.1 and 17.8 kcal/mol for **A-TS1** and **TS-1**, respectively). It should be noted that the Alder-ene reactions via **TS-2**, **TS-3**, and **TS-4** turn out to be concerted, presumably because in these systems there is no charge delocalization and effective N2−H interaction such as those in **A-IN** and **B-IN**, so that no stable zwitterionic intermediates could be formed. These uncovered the unique reactivity of cyclopropenes in Alder-ene reactions with azodicarboxylate.

For the rearrangement of the initially formed intermediate **I-2** to the final product **2** via the allylic transposition of the C−N bond[22] from C1 to C3, we hypothesized three possible mechanisms (Figure 3). In a concerted pathway, an unconventional [2,3]-type rearrangement[23] with concomitant [1,2]-proton shift or a symmetry-forbidden [1,3]-rearrangement is proposed. Alternatively, a stepwise process can be formulated that involves heterolytic C−N bond cleavage to form an ion pair followed by its recombination. To differentiate the concerted and stepwise pathways, we carried out a crossover experiment,[24] but no crossover products were detected. Computational results are consistent with the experiment that the energy required for dissociation of **I-2** into charged species is 32.9 kcal/mol, much higher than that of the concerted [1,3]-rearrangement (vide infra). The possible formation of a tight ion pair from **I-2** could also be ruled out by calculations (see the Supporting Information for details). Although the stepwise pathway is excluded, allylic transposition via the hypothetical concerted [2,3]-type rearrangement with a concomitant [1,2]-proton transfer or [1,3]-rearrangement cannot be differentiated.

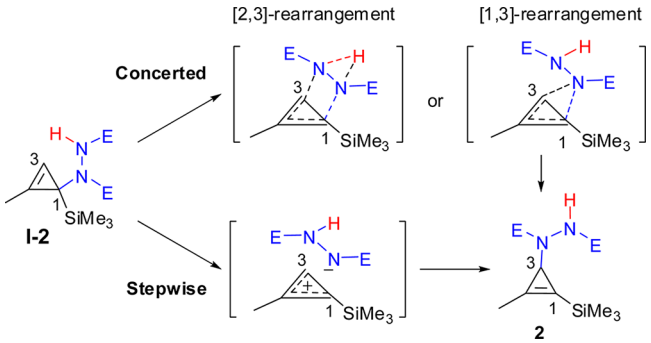


Figure 3. Concerted vs stepwise mechanism for a C−N bond allylic transposition.

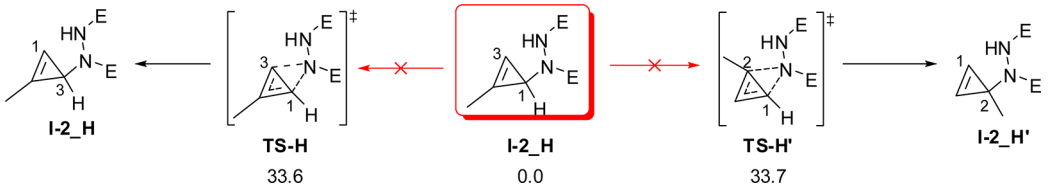
In the calculations, a transition state for the concerted [2,3]-rearrangement on the energy surface was not found. Instead, the results suggest that a formal [1,3]-migration of the hydrazodicarboxylate moiety via **A-TS3** from intermediate **I-2** delivers the thermodynamically more favorable cyclopropene **2** with an activation barrier of 21.1 kcal/mol (Figure 1). This is the highest barrier in the whole reaction, being in good agreement with the relatively slow rearrangement of **I-2**. The geometry of **A-TS3** shows that the migrating nitrogen atom (N1) is far from both C1 and C3 (C1−N1= 2.647 Å, C3−N1 = 2.644 Å), and the three-membered ring moiety exhibits aromatic character with short and almost equidistant C1−C2, C2−C3, and C1−C3 bonds, as shown in Figure 2. We wonder if the rearrangement of **I-2** to **3** is possible, however, the transition state of this case would be 3.2 kcal/mol higher in energy than **A-TS3**, indicating that the equilibration of **I-2** and **3** is more difficult than the formation of **2**.

When the more stable intermediate **3** is involved, although **B-TS3** is only 0.8 kcal/mol higher in energy than **A-TS3**, a much larger energy gap of 27.5 kcal/mol between **3** and **B-TS3** was calculated, implying the difficult rearrangement of **3** to **2** under the mild experimental conditions. Thus, the energetic scenario in Figure 1 suggests the [1,3]-migration of the hydrazodicarboxylate moiety in the cyclopropene derivative is determined predominantly by the stability of the Alder-ene intermediate. The geometric structures in Figure 2 show that the N1−C1−Si angle (113.8°) in **I-2** is larger than the N1−C2−C3′ angle (112.6°) in **3**, implying the greater steric effect of the trimethylsilyl group in the former intermediate. Experiments showed when the silyl group of **2** was replaced by a deuterium or proton, the expected rearrangement was not observed.[12] This observed reactivity corroborates the calculations that the rearrangement of this nonsilylated intermediate **I-2_H** requires a much higher activation energy of 33.6 kcal/mol (Scheme 8).

3. CONCLUSIONS

In summary, the mechanistic questions regarding the regio- and chemoselectivities of the formal C−H amination of silylcyclopropene by azodicarboxylate were explored by DFT calculations. In the regiochemistry-determining electrophilic azodicarboxylate addition step of the stepwise Alder-ene process, the different electronic effects of silyl and alkyl substituents on cyclopropene make the C1 much more negatively charged, and thus the C1 addition is more favorable by 1.4 kcal/mol. However, when an ether linkage is attached to C2 of the cyclopropene, the reaction at this site becomes 0.2 kcal/mol lower in activation energy than the C1 reaction, due to the favorable orbital interaction between the ether oxygen and the C1═C2 bond in the transition state, resulting in diminished selectivity. The unique reactivity of cyclopropene was shown by a comparison of the activation energies for reactions of different ene donors, and the high barriers for other cyclic and acyclic allylic systems demonstrate the importance of charge delocalization and strong N2−H interactions in the electrophilic addition step of the Alder-ene reaction of cyclopropenes. From the quaternary hydrazodicarboxylate

Scheme 8. Relative Free Energies (in kcal/mol) for the Rearrangements of the Nonsilylated Intermediate I-2_H



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intermediate of the Alder-ene reaction forming a C1−N bond, the steric effect of the silyl group facilitates the allylic transposition via a concerted [1,3]-migration of the hydrazodicarboxylate moiety, which generates the formal C−H amination product with an activation energy of 21.1 kcal/mol. On the other hand, the intermediate of the Alder-ene reaction forming a C2−N bond is more stable and the barrier of a similar rearrangement will be increased to 27.5 kcal/mol, accounting for the divergent reactivities of the two regioisomers. This study provided an in-depth understanding of the experimental results of the formal C−H amination of silylcyclopropene by azodicarboxylate and should be useful for future design.

4. COMPUTATIONAL DETAILS

All DFT calculations were carried out with the Gaussian 09 suite of computational programs.[25] The geometries of all stationary points were optimized using the M06 hybrid functional[13] at the basis set level of 6-31+G(d). Frequencies were analytically computed at the same level of theory to obtain the gas phase free energies and to confirm whether the structures are minima (no imaginary frequency) or transition states (only one imaginary frequency). All transition state structures were confirmed to connect the proposed reactants and products by intrinsic reaction coordinate (IRC)[26] calculations. For each final geometry, the stability of the wave function was tested by using the "stable" keyword. The effect of solvent was examined by performing single-point self-consistent reaction field (SCRF) calculations based on the polarizable continuum model (PCM)[27] for gas-phase optimized structures. Chloroform (ε = 4.711) was used as the solvent, for simulation of the experimentally used $CDCl_3$ solvent, and the default UFF atomic radii was used in all PCM calculations. All the energies discussed in the main text are relative solvation free energies (ΔG_{sol}), which were obtained by adding the solvation corrections to the computed gas-phase relative free energies (ΔG_{298}).

The M06 method developed by Zhao and Truhlar[13] is considered to include "medium-range" electron correlation and has been shown to be very promising in describing the dispersion interactions within many systems.[28] To verify the computed energy values, optimization and frequency calculations were carried out at the B3LYP level with a larger basis set of 6-311+G(2d,p). The ΔG_{sol} values from B3LYP calculations showed that the barriers for the stepwise Alder-ene reactions via **A-TS1** and **B-TS1** would be 32.7 and 32.5 kcal/mol, respectively, which are much higher than the barrier of the allylic transposition from **I-2**. These are inconsistent with the experiments, which showed that the Alder-ene step is very facile while the allylic transposition determines the rate of the whole transformation. We explained this discrepancy as a result of a failure in description of dispersion interactions in noncovalently bound species by the B3LYP functional. To prove this, dispersion correction on the B3LYP energy was calculated by using the B3LYP-D method of Grimme.[29] The inclusion of dispersion correction in B3LYP calculations reproduced the experimental results faithfully and led to the same conclusions as the reported results from M06 calculations. The B3LYP results are given in the Supporting Information for reference.

■ ASSOCIATED CONTENT

Supporting Information

Text giving the full ref 25, additional calculation results, energies, and Cartesian coordinates of all stationary points. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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$$\frac{\textbf{2-I}}{\textbf{3}} = e^{\Delta G_{sol}(\textbf{B-TS1}) - \Delta G_{sol}(\textbf{A-TS1})/RT}$$

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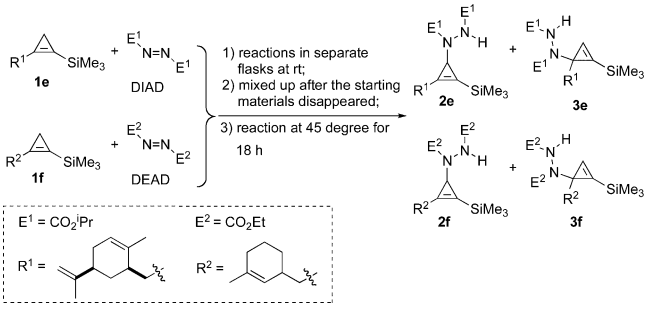

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