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Thermally-Induced Intramolecular [4+2] Cycloaddition of Allylamino- or Allyloxy-Tethered Alkylidenecyclopropanes

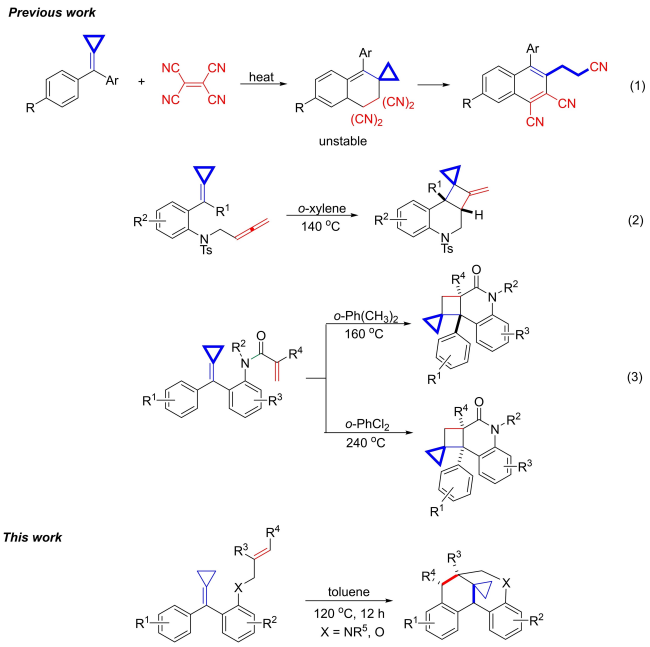
Leyi Tao, Yin Wei,* and Min Shi*[a]

Abstract: A thermally-induced intramolecular [4+2] cycloaddition reaction of allylamino- or allyloxy-tethered alkylidenecyclopropanes has been reported in this paper, giving a new protocol for the rapid construction of polycyclic skeleton molecules in moderate to excellent yields with a broad substrate scope. On the basis of control experiments and DFT calculations, we disclosed that the reaction proceeded through a [4+2] cycloaddition and trace of water assisted 1,3-H shift process to give the target product.

Alkylidenecyclopropanes (ACPs) are high-tension molecules with high activity and diverse reactivity. Nevertheless, they could be manipulated as stable compounds under ambient conditions. On the basis of these properties, transformation of ACPs has been a hot research topic in synthetic chemistry for a long time, and they have been extensively used in the rapid construction of various types of polycyclic skeleton molecules under mild conditions.[1] Due to the potent thermodynamic driving force of releasing the ring strain, a variety of cyclization reactions of ACPs were reported upon heating,[2] Lewis or Brønsted acid catalysis,[3] free radical initiated addition[4] and transition metal catalysis.[5] In particular, thermally-induced cyclization reactions of ACPs are mainly dominated by inter- or intramolecular cycloaddition reactions involving with their connected exocyclic double bond owing to that the electron cloud density of ACP's carbon-carbon double bond is higher than that of general olefin's one as a result of the conjugated electron-donating effect of cyclopropyl ring.[6] Therefore, ACPs can be used as a good carrier of the three-membered ring to use their connected exocyclic double bonds undergoing the cyclization reaction with dienes, dipoles and olefins via [4+2],[7] [3+2],[8] [2+2][9] and the other cycloaddition reactions. With regard to this aspect, in 1971–1972, Baldwin, Pasto and Noyori groups reported the intermolecular [4+2] cycloaddition reaction between diarylmethylenecyclopropanes and tetracyanoethylene (TCNE) successively.[7a,8a,9a] This cycloaddition reaction generated the relatively unstable cycloaddition product, affording the naphthalene derivatives through the process of losing one molecule of HCN and the ring-opening rearrangement of three-membered ring (Scheme 1, eq 1).

In recent years, we and others have found that functionalized alkylidenecyclopropanes (FACPs), which are produced by introducing functional groups into ACPs, can significantly expand the reaction modes of intra- or intermolecular cyclizations.[1m] For the thermally-induced cycloaddition reaction of ACPs, we found that ACPs tethered with functional groups such as allene and alkene, could be applied to synthesize complex polycyclic compounds effectively. In 2012, our group reported a thermally-induced intramolecular [2+2] cycloaddition of allene-tethered ACPs to synthesize a series of bicyclo [4.2.0] nitrogen atom containing heterocycles, bearing important spiro[2.3]hexane structural motifs in organic and medicinal chemistry (Scheme 1, eq 2).[10] In 2018, our group also reported the thermally-induced intramolecular [2+2] cycloaddition of acrylamide-tethered ACPs, affording the regio- and diastereoselective synthetic method of cyclobutane-containing spiro[2.3] hexane fused with six-membered heterocycles (Scheme 1, eq 3).[11]

Inspired by these interesting findings, we envisaged that allyl-tethered ACPs could also afford polycyclic compounds



Scheme 1. Previous work and this work.

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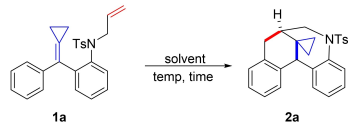
through an intramolecular cycloaddition pathway. Herein, we wish to report a thermally-induced intramolecular [4+2] cycloaddition of tosylated, mesylated and the other sulfonated allylamine- or allyloxy-tethered alkylidenecyclopropanes to furnish a series of polycyclic skeleton molecules. This interesting cyclization reaction features a [4+2] Diels-Alder cycloaddition and H_2O assisted 1,3-H shift process.

We first utilized substrate **1a** as a model substrate for the initial examination at 120 °C in toluene under argon atmosphere, and found that the desired polycyclic product **2a** was given in 84% NMR yield within 12 h along with 80% isolated yield (Table 1, entry 1). The structure of product **2a** has been unambiguously determined by X-ray diffraction (Figure 1), and its crystal data are presented in the Supporting Information (SI). Then, we further optimized the reaction conditions, and the results are summarized in Table 1. Firstly, we screened other organic solvents such as PhCl, 1,4-dioxane, DMF, DMSO, H_2O and DCE and identified that toluene was the best solvent for this cycloaddition reaction (entries 2–7). Then, we found that

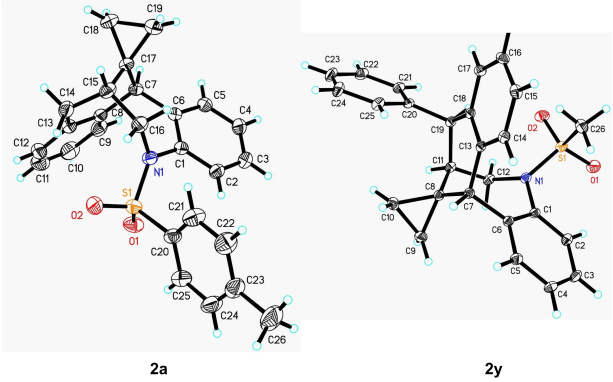
Table 1. Optimization of the reaction conditions.[a]



1a 2a

entry	solvent	temp [°C]	time [h]	yield [%][b]
1	***toluene (2 mL)***	***120***	***12***	***84 (80)***
2	PhCl (2 mL)	120	12	82
3	1,4-dioxane (2 mL)	120	12	32
4	DMF (2 mL)	120	12	34
5	DMSO (2 mL)	120	12	52
6	H_2O (2 mL)	120	12	56
7	DCE (2 mL)	80	12	-
8	toluene (2 mL)	110	12	52
9	toluene (2 mL)	130	12	84
10	toluene (2 mL)	120	8	73
11	toluene (2 mL)	120	16	84
12	***toluene (1 mL)***	***120***	***12***	***84***
13	toluene (4 mL)	120	12	81

[a] Unless otherwise specified, all reactions were carried out using **1a** (0.2 mmol) in solvent. [b] Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard and isolated yield in parentheses.



2a 2y

Figure 1. X-ray crystal structures of **2a** and **2y**.

lowering the reaction temperature to 110 °C or raising the reaction temperature to 130 °C did not improve the yield of product **2a**, suggesting that the appropriate temperature for this reaction was 120 °C (entries 8 and 9). In addition, shortening or lengthening the reaction time did not give the desired product **2a** in better yields (entries 10 and 11). Finally, the reaction could give product **2a** with the same NMR yield (84% yield) using 1 mL of toluene, and increasing the volume of toluene to 4 mL did not improve the yield of **2a** (entries 12 and 13). To summarize, this cycloaddition reaction should be carried out in toluene (2.0 mL or 1.0 mL) at 120 °C within 12 h.

With the optimal conditions in hand, we next investigated the generality of this intramolecular cycloaddition reaction using various tosylated and mesylated allylamine- or allyloxy-tethered alkylidenecyclopropanes **1b**–**1aj** as substrates and the results are elucidated in Table 2. When R^1 group is a halogen atom at the *para*-position such as substrates **1b**–**1e**, the reaction proceeded smoothly, giving the desired products **2b**–**2e** in good to excellent yields ranging from 72%–92%. Substrates **1f**–**1j**, having an electron-rich aromatic ring, furnished the corresponding products in the yields depending on the position of substituent at the aromatic ring. When -CH_3, -OCH_3 and -^{t}Bu groups were present at the *para*-position of benzene ring, the corresponding products **2f**, **2g** and **2h** were obtained in 83%, 81% and 91% yields, respectively. However, when -CH_3 group was introduced at the *ortho*-position of benzene ring, none of the corresponding product **2i** was afforded presumably due to the steric hindrance. However, when -CH_3 group was present at the *meta*-position of benzene ring, products **2j** and **2j'** were obtained in 52% and 40% yields respectively as a regioisomeric mixture. These results indicate that the electronic effect of substituent did not have significant impact on product's yield, however the substituted position had an important influence on the reaction outcome due to the steric effect. Then, we examined the substituent effect at tosylated allylamine-tethered aryl moiety and found that the substituents could be halogen atoms, methyl or methoxy group and had little influence on the reaction outcomes of this cycloaddition reaction, affording the desired products **2k**–**2o** in 76%–92% yields. Next, substrates **1p** and **1q** having substituents on both aromatic rings were also examined, and the corresponding product **2p** was given in 76% yield, but the desired product **2q** could not be obtained due to the *ortho*-substituent of chlorine atom for the same reason of steric hindrance. In addition, substrate **1r** bearing a 2-naphthyl moiety and substrate **1s** having a thiophene group were also tolerated, furnishing products **2r** and **2s** in 93% and 70% yields, respectively. It is worth mentioning that 13% of [2+2] cycloadduct **2s'** was also obtained in the reaction of **1s**, perhaps due to that the electron-rich thiophene group affected electronic property of the connected olefinic unit as compared with phenyl group.

When R^1 group is a phenyl group, we also examined substituent effect of R^3 group and R^4 group in the allyl moiety and found that these substituents also had a significant effect on the reaction outcome. For substrate **1t**, in which R^4 is a methyl group, the desired product **2t** was formed in 73% yield.

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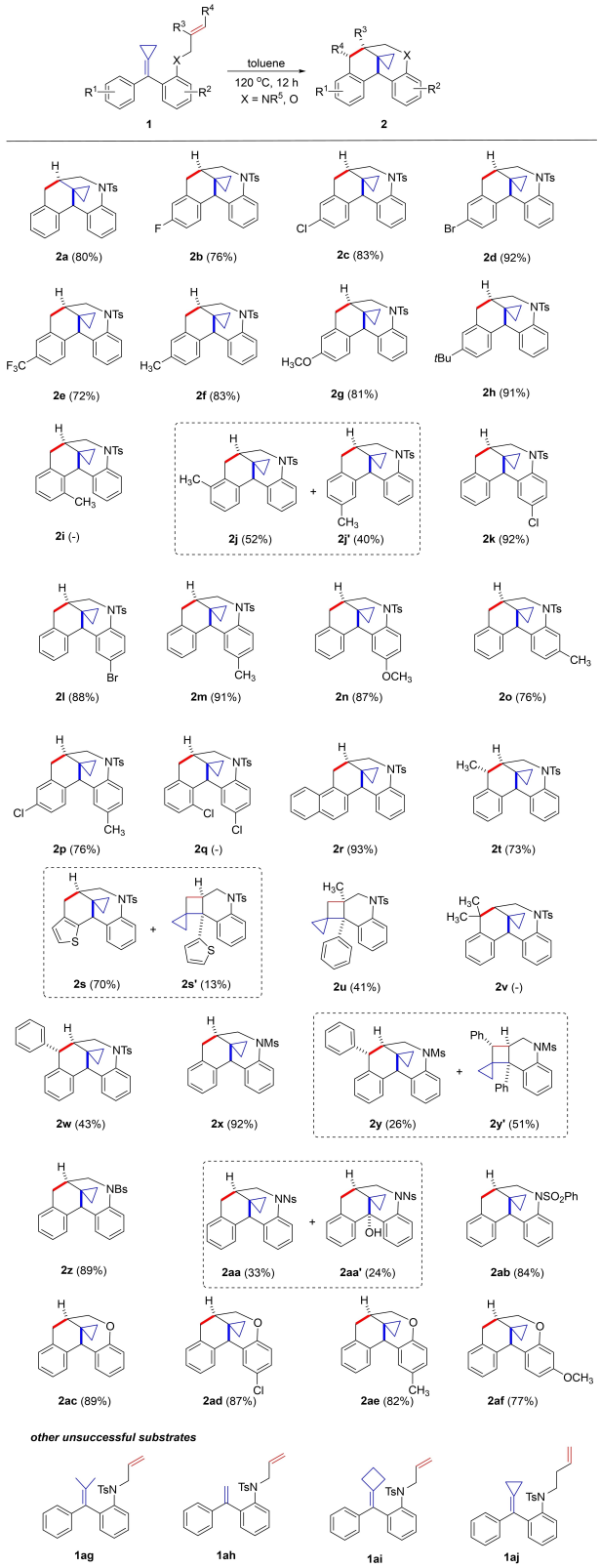
Table 2. Substrate scope of **1** for the cycloaddition reaction.[a,b]



[a] Unless otherwise specified, all reactions were carried out using **1** (0.2 mmol) in 2.0 mL toluene at 120 °C within 12 h under Ar atmosphere. [b] Isolated yield.

However, [2+2] cycloaddition took place to give cycloadduct **2u** in 41% yield and the recovered starting material (rsm) ratio was 37% when R^3 was a methyl group due to the steric effect as well as electron-donating effect, and its relative configuration was determined by ^{1}H-^{1}H NOESY spectra (for more detailed information, see pages S116–117 in the Supporting Information). When R^4 group was a *gem*-dimethyl group, none of the desired product **2v** was formed because of the serious steric effect. In the case of substrate **1w**, the corresponding product **2w** was furnished in 43% yield and trace amount of [2+2] cycloaddition byproduct was also observed. Furthermore, we also explored the tolerance of linker X in this cycloaddition and found that the reaction proceeded quite well when X is a NMs, NBs, and NSO_2Ph, giving the corresponding products **2x**, **2z**, and **2ab** in 92%, 89% and 84% yields, respectively. As for substrate **1y**, in which X is a NMs and R^4 is a phenyl group, the reaction furnished the [4+2] cycloadduct **2y** and the [2+2] cycloadduct **2y'** in 26% and 51% yields, respectively also due to the steric effect. Herein, we speculated that the reason for the different experimental results of substrates **1u**, **1w** and **1y** was mainly due to the steric hindrance of substituents R^3 and -Ts/-Ms because intramolecular reaction is quite sensitive to the steric effect. The structure of **2y** has been unequivocally determined by X-ray diffraction, and its ORTEP drawing is indicated in Figure 1 and the related structural data are shown in the SI. Moreover, the relative configuration of product **2y'** was also determined by ^{1}H-^{1}H NOESY spectra (see pages S117–120 in the Supporting Information for more details). More interestingly, when the linker X is a NNs group, the reaction produced the desired product **2aa** in 33% along with a benzylic oxidative product **2aa'** in 24% yield presumably due to the strong oxidizing property of -NO_2 group.

When the linker X was an oxygen atom, we examined the substituent effect at allyloxy-tethered aryl moiety and found that the desired products **2ac**–**2af** could be furnished in 76%–89% yields when R^2 is a hydrogen atom, a chlorine atom, a methyl or a methoxy substituent. Finally, it should be also emphasized here that substrates **1ag**–**1aj** did not afford the corresponding products even at 140 °C, implying the importance of cyclopropane moiety and allyl unit in this thermally-induced [4+2] cycloaddition reaction.[6] The electron-donating effect of cyclopropyl group and the release of ring strain from 41 kcal/mol of methylenecyclopropane to 27.5 kcal/mol of cyclopropane both are beneficial for the smooth proceeding of this particular Diels-Alder reaction.

We attempted to change the temperature from 110 °C to 140 °C. However, the product distribution of substrates **1j**, **1s**, **1u**, **1y** and **1aa** remained basically unchanged. In addition, the substrates **1i** and **1ag**–**1aj** still did not react even at 140 °C. Meanwhile, it should be also mentioned here is that all the products shown in Table 2 were obtained as a single diastereomer.

Next, we focused on investigating the mechanism of this cycloaddition reaction. According to the previous reports,[7a,8a,9a,10,11] an initially proposed reaction mechanism for this cycloaddition reaction is shown in Scheme 2. Firstly, substrate **1** proceeds through a [4+2] Diels-Alder reaction

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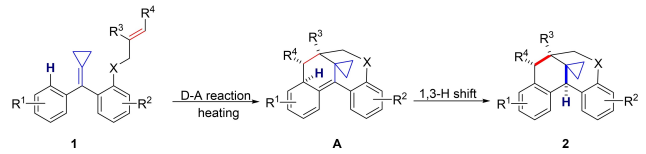
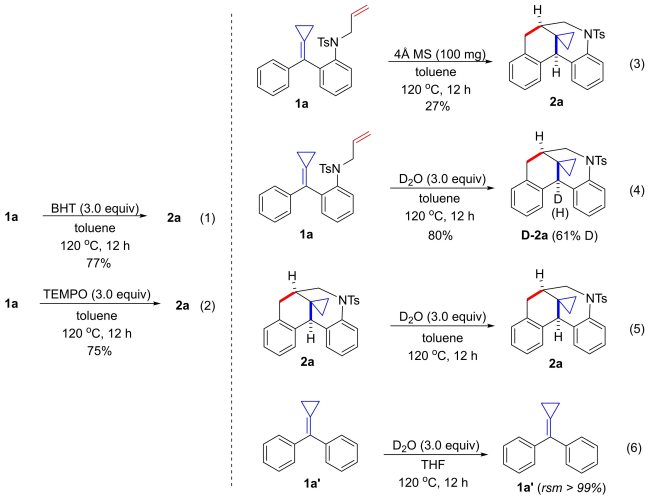


Scheme 2. The initially proposed reaction mechanism of this reaction.

process to afford intermediate **A** upon heating at high temperature. Then, intermediate **A** delivers the target product **2** via a 1,3-H shift process.

Then, we embarked DFT studies on the proposed reaction mechanism for this work. The mechanism was investigated by DFT calculations using the SMD/M06/6-311+G(d,p)//B3LYP/6-31G(d) level of theory with Gaussian 09 program. To simplify the calculation process, we investigated the reaction pathway starting from substrate **1a**. However, the suggested transition state from intermediate **A** to product **2a** could not be located after several attempts by the DFT calculations, prompting us to consider whether the proposed mechanism is reasonable.

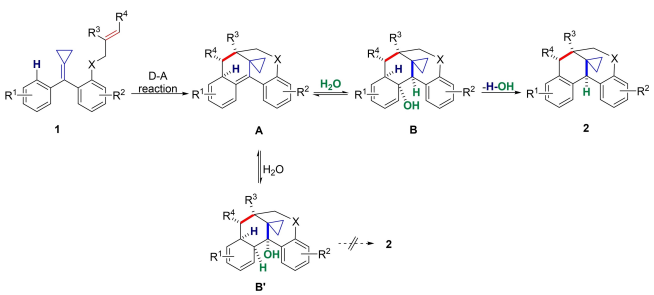
On the basis of Yu's work,[12] a trace amount of water can play a critical role in assisting the process of 1,2- or 1,4-H shift. Therefore, to verify the reaction mechanism, several control experiments were conducted, and the results are shown in Scheme 3. Firstly, using butylated hydroxytoluene (BHT) and 2,2,6,6-tetramethylpiperidinooxy (TEMPO) as radical inhibitors, the yields of the desired product **2a** were obtained in 77% and 75% respectively under the standard conditions, suggesting a non-radical reaction pathway (Scheme 3, eqs 1 and 2). Then, it is surprising that adding 4 Å molecular sieves (100 mg) to get rid of trace amount of water in the reaction system could decrease the yield of **2a** to 27% (Scheme 3, eq 3). Next, two deuterium labeling experiments were performed by adding D_2O as deuterium source under the standard conditions. We found that the corresponding product **2a** was formed in 80% yield along with 61% D content incorporation at the benzylic carbon atom. Furthermore, no deuterium incorporation was observed upon treating product **2a** under the same conditions (Scheme 3, eqs 4 and 5). Finally, when the substrate **1a'** without the tethered allyl group was employed to undergo the same reaction in the presence of D_2O in a sealed tube, no reaction occurred and the recovered starting material (rsm) ratio of **1a'** was more than 99% (Scheme 3, eq 6). These results indicated that ambient H_2O in the reaction system is likely to participate in this particular cycloaddition reaction process.



Scheme 3. Control experiments of this reaction.

On the basis of these mechanistic studies and the previous DFT calculations, another plausible mechanism is outlined in Scheme 4. The reaction firstly proceeds through a [4+2] Diels-Alder reaction pathway to afford cyclohexadiene intermediate **A** with an exocyclic carbon-carbon double bond. Then, the exogenous water in the reaction system adds to the exocyclic carbon-carbon double bond of intermediate **A** at high temperature to furnish intermediate **B**, which undergoes a dehydration process with another adjacent hydrogen atom to deliver the target polycyclic skeleton product **2** along with the regeneration of water molecule. Thus, the formal 1,3-H shift process is assisted by the trace of water existed in the reaction system. It is worth noting that another addition intermediate **B'** may also be formed, however, it could be reconverted to intermediate **A** through releasing of water molecule (Scheme 4). We also tried to capture intermediate **A** or **B** upon adding external electron deficient olefin such as methyl cinnamate into the reaction system of substrate **1a**. However, this trapping experiment was not successful, and the corresponding product **2a** was still obtained along with the recovery of methyl cinnamate (for the detailed information, see Scheme S8 and Figure S2 at page S11 in the Supporting Information).

The proposed reaction mechanism shown in Scheme 4 was also investigated by DFT calculations using the same program mentioned above. The solvation Gibbs free energy profile in toluene for the suggested reaction pathway is shown in Figure 2 (the ΔG_{298} (kcal/mol), see Supporting Information for the details). In order to directly reflect the change of solvation Gibbs free energy in the reaction process, the calculated solvation Gibbs free energy values of **1a**, **TS1**, **A** and **2a** were added the value of H_2O's calculated solvation Gibbs free energy. We investigated the reaction pathway starting from intermediate **1a**+$\mathbf{H_2O}$ shown in Figure 1. Firstly, substrate **1a** proceeds through the Diels-Alder process to form intermediate **A** via **TS1** with an energy barrier of 34.5 kcal/mol. Subsequently, the addition of water molecule to the exocyclic carbon-carbon



Scheme 4. The proposed reaction mechanism of this reaction.

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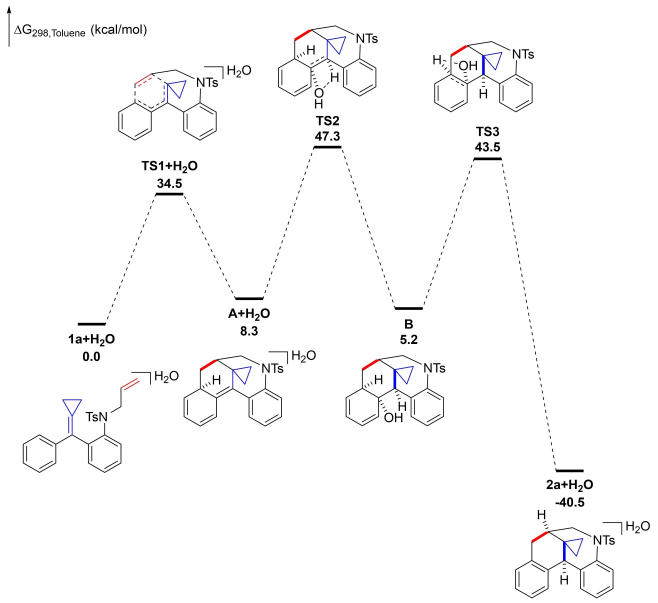

Figure 2. DFT calculation on reaction pathway of this work (relative Gibbs energy values in toluene solution are given in kcal/mol).

double bond of intermediate **A** generates intermediate **B** through **TS2** with an energy barrier of 39.0 kcal-mol, which is the rate-determining step in the reaction. Finally, the hydroxyl group of intermediate **B** is dehydrated away with another adjacent hydrogen atom, delivering the target product **2a** through the transition state **TS3** peaked at 38.3 kcal/mol. This calculation result is in line with the experimental conditions in which the high temperature is required for this reaction. Moreover, the total $\triangle G_{298,rxn}$ in toluene of this reaction is –40.5 kcal/mol overall, accounting for a thermodynamically favourable process.

In conclusion, we have discovered a novel thermally-induced intramolecular [4+2] cycloaddition reaction of sulfonated allylamine- or allyloxy-tethered alkylidenecyclopropanes, giving a series of polycyclic skeleton molecules in moderate to excellent yields with a broad substrate scope. On the basis of control experiments and DFT calculations, a plausible reaction mechanism has been proposed. In general, the reaction proceeded through an intramolecular [4+2] cycloaddition and trace of water assisted 1,3-H shift processes to afford the desired polycyclic skeleton product. Further investigations on expanding the applications of this synthetic method are ongoing in our laboratory.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Alkylidenecyclopropanes · [4+2] cycloaddition · DFT calculations · Water assistance · 1,3-H shift

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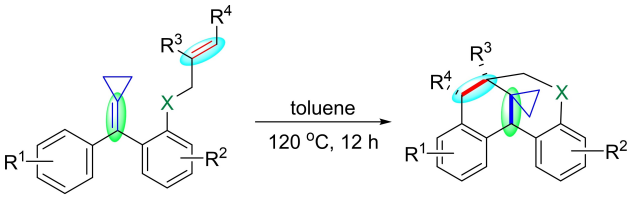

R^1 = halogen, alkyl, (het)aryl
R^2 = Cl, Br, CH_3, OCH_3
R^3 = CH_3
R^4 = CH_3, Ph
X = Ts, Ns, Bs, Ms, SO_2Ph, O

32 examples
up to 93% yield

L. Tao, Dr. Y. Wei, Prof. Dr. M. Shi**

Thermally-Induced Intramolecular [4+2] Cycloaddition of Allylamino- or Allyloxy-Tethered Alkylidenecyclopropanes

A novel thermally-induced intramolecular [4+2] cycloaddition of allylamino- or allyloxy-tethered alkylidenecyclopropanes for the rapid construction of polycyclic skeleton molecules.