

1,5-X Insertions of Free Alkylidene Carbenes: A Theoretical Study

Yi Zhou^[a] and Zhi-Xiang Yu^{*[a]}

1,5-X insertions of alkylidene carbenes are powerful methods to construct five-membered carbocycles and heterocycles, but the mechanisms of these 1,5-X insertions of alkylidene carbenes remain unclear (concerted or stepwise?). Here we disclose different mechanisms of 1,5-X insertions of free alkylidene carbenes based on DFT calculations. Except for the 1,5 S–H insertion, all 1,5-X insertions proceed through stepwise processes via forming ylide intermediates. However, subsequent 1,2 rearrangements of ylides occur through different mechanisms.

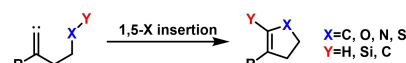
The formal 1,5 O–H/N–H insertion except S–H insertion happens through deprotonation rather than insertion reaction, while other pathways including nucleophilic substitution, 2,3-sigmatropic rearrangement, and homolysis of O–C bond are invoked in various 1,5 O–C insertions. The competition between 1,5-X insertions and other side reactions (such as 1,2 migration, dealkylation) has been discussed to answer why the target insertion products were not obtained in some cases.

Introduction

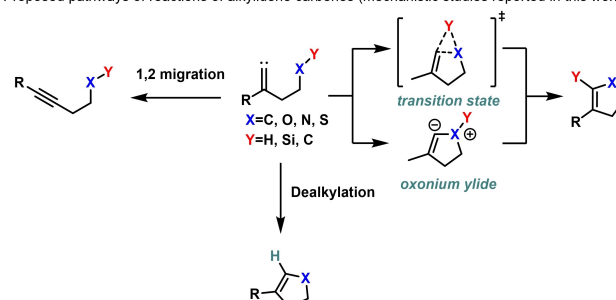
Insertions of alkylidene carbenes into C–H, N–H, and O–Si bonds can be applied to construct five-membered carbocycles and heterocycles (Scheme 1a).^[1] Among them, 1,5 C–H insertion of alkylidene carbenes with high regioselectivity and stereoselectivity is the most extensively utilized one.^[1d–f] Experimental and theoretic studies^[1e,2,3] indicated that the transition state of 1,5 C–H insertion adopts a chair or half chair-like conformation, in which the orbital interaction between the empty p orbital of carbene and σ orbital of C–H bond can be realized (Scheme 1b). Systematic investigations from Lee further revealed that electronic, steric, conformational, and stereoelectronic effects have profound impacts on the reactivity and regioselectivity of the C–H bond insertion reactions.^[4,5]

However, less attention has been paid to the mechanisms of 1,5-X insertions (X=O, N, S) of alkylidene carbenes, even though many experimental efforts have been made by the chemists, as exemplified by the reactions in Table 1. We noticed that both 1,5 O–Si and 1,5 O–H insertions could give the desired products,^[6] while 1,5 O–C insertions with different carbon groups might give side products (such as dealkylation and 1,2 migration). But the underlying reasons are elusive.^[7–9] 1,5 insertions of alkylidene carbenes into other bond types including S–H, N–H, and N–Bn have also been tested.^[10] Based on these experimental results, two possible pathways for the 1,5-X insertions of the alkylidene carbenes are proposed. One is the concerted pathway,^[11] similar to that in the 1,5-C–H insertion. The other is the stepwise pathway involving the

a) 1,5-X insertions are powerful tools to construct five-membered carbocycles and heterocycles



b) Proposed pathways of reactions of alkylidene carbenes (mechanistic studies reported in this work)



Scheme 1. (a) 1,5-X insertion reactions of free alkylidene carbenes (b) Proposed pathways of reactions of alkylidene carbenes (mechanistic studies reported in this work).

formation of ylides.^[1a] No theoretical studies of these mechanisms for 1,5-X insertions (X=O, N, S) of alkylidene carbenes have been reported. Therefore, understanding why there are these different reaction outcomes is consequently not available. To fill this gap, we report here our computational study, focusing on how the 1,5-X insertions for different X take place and how the side reactions, summarized in Scheme 1b, compete with the desired reactions. In addition, we present new pathways for some 1,5-X insertion reactions when our calculations did not agree with the experiments.

Results and Discussion

In order to study the mechanisms and elucidate effects of different heteroatoms and substituents in 1,5 insertions of alkylidene carbenes, we carried out DFT calculations on the general systems of MeC(C)CH₂CH₂XY (X=O, N, S; Y=Si, H, C). The

[a] Y. Zhou, Prof. Dr. Z.-X. Yu

Beijing National Laboratory for Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University Beijing 100871 (China)
E-mail: yuzx@pku.edu.cn

Supporting information for this article is available on the WWW under <https://doi.org/10.1002/ajoc.202300440>

Table 1. Selected 1,5-X insertions of free alkylidene carbenes.

reaction	carbene precursor	conditions	alkylidene carbene	product	yield
1a		TMSC(Li)N ₂ (1.2 eq.) THF, -78-0 °C			52%
1b		TMSC(Li)N ₂ (1.2 eq.) THF, -78-0 °C			21%
2a		ToISO ₂ Na (1.3 eq.) THF, reflux			35% : 25%
2b		ToISO ₂ Na (1.3 eq.) THF, reflux			41% : 27%
2c		ToISO ₂ Na (1.3 eq.) THF, reflux			36%
2d		ToISO ₂ Na (1.3 eq.) THF, reflux			<10%
3a		CH ₃ Li (1.1 eq.), Et ₂ O, r.t.			36%
3b		CH ₃ Li (2 eq.), Et ₂ O, r.t.			71%
3c		CH ₃ Li (1.1 eq.), Et ₂ O, r.t.			49%
4a		(1) TMSC(Li)N ₂ (1.2 eq.) THF, reflux; (2) MnO ₂			8%

singlet-triplet energy gaps for all free alkylidene carbenes in this study, computed by the SMD(THF)/ ω B97X-D/maug-cc-pVTZ//M06-2X/6-31+G(d,p) method, are more than 42 kcal/mol. This is consistent with the fact that alkylidene carbenes prefer to stay at their singlet ground states with a lone pair and an empty p orbital.^[11]

We found that different 1,5-X insertions have different pathways, which prompt us to present them one by one in the following parts:

a) Mechanism of O-Si insertion in reaction 1a. We first present the mechanism of 1,5 O-Si insertion. The competing 1,2 migration, which is also found in Corey-Fuchs reaction,^[12] Colvin,^[13] and Fritsch-Buttenberg-Wiechell (FBW) rearrangements,^[14] has also been considered in this work. The free energy surfaces of 1,5 O-Si insertion and 1,2 migration of **1** are shown in Figure 1. A stepwise mechanism for 1,5 O-Si insertions of the alkylidene carbene **1** was found. Calculations indicated that **1** could form oxonium ylide **2** after an σ -bond

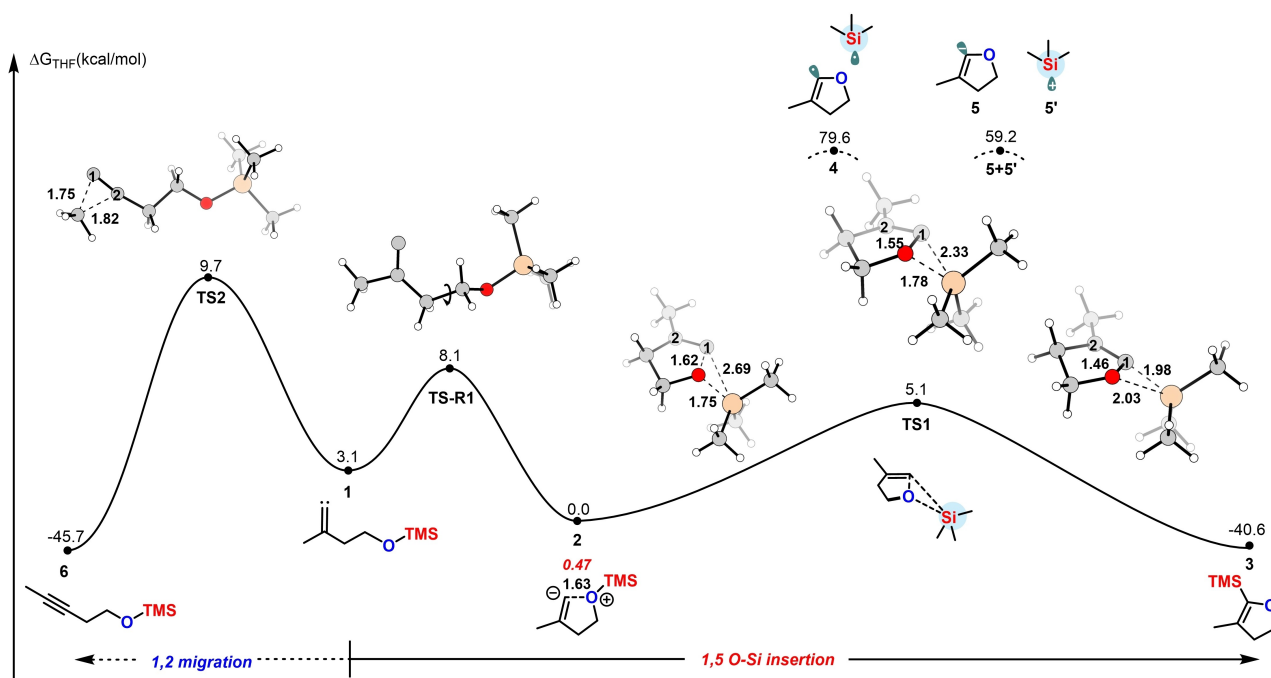


Figure 1. Computed reaction pathways for 1,5 O–Si insertion and 1,2-Me migration of **1** and selected structures from IRC calculations. The black numbers show corresponding bond lengths in angstrom, while the red numbers show the Mayer bond order. Color scheme: C, gray; Si, orange; H, white; O, red.

rotation (via transition state **TS-R1**) with an activation free energy of 5.0 kcal/mol, which is exergonic by 3.1 kcal/mol. This energy change originates from the interaction between *n* orbital of O and empty *p* orbital of C1. The Mayer bond order of C1–O in **2** is 0.47, indicating the oxonium ylide was partly formed (Figure 1).

Previously, oxonium ylide was suggested to undergo 1,2 Stevens rearrangement through either a homolytic or heterolytic pathway.^[8] DFT calculation showed that formation of the diradical species **4** (with a computed $\langle S^2 \rangle$ of 1.01) from O–Si homolysis in **2** was highly endergonic with a Gibbs free energy of 79.6 kcal/mol, and the heterolytic pathway via formation of ions **5** and **5'** was also endergonic by 59.2 kcal/mol. In contrast, a low-lying concerted transition state **TS1** for migration of the TMS group was localized, with an activation free energy of 5.1 kcal/mol. The computed Gibbs free energy of activation for 1,2-Me migration of alkylidene carbene **1** via **TS2** is 6.6 kcal/mol. This 1,2-Me migration reaction is highly exergonic by 45.7 kcal/mol, affording alkyne **6**. But this process is disfavored compared to the formation of oxonium ylide by 1.6 kcal/mol (**TS2** vs. **TS-R1**). Thus, the formal 1,5 O–Si insertion can happen, in accordance with the experimental observation in **reaction 1 a**.

It should be noted that the transition state corresponding to inversion of configuration of the migrating group could not be localized due to steric reasons (TMS group is big and does not have enough space for reaching the transition state). Instead, we found a three-membered ring transition state **TS1** for 1,2 rearrangement of oxonium ylide with retention of the configuration of the migrating group. IRC calculations showed that the silicon atom is approaching the plane of C1–C2–O gradually. This concerted 1,2 rearrangement of oxonium ylide **2**

is symmetry-forbidden according to Woodward-Hoffmann rules^[15] (Figure 3a). But it's not surprising here that **TS1** has relatively low free energy because silicon group could readily become pentacoordinate.^[16] The same phenomenon was observed in reverse Brook rearrangement^[17] and Wittig anionic rearrangement of silicon group.^[18] The 1,2 rearrangement of oxonium ylide can be regarded as a migration of a cationic group. The higher stability of **TS1** with a significant ionic character is attributed to the ability of its silicon atom to accommodate positive charge, considering that Si has a smaller electronegativity^[19] compared to H, C, O (the electronegativities for H, C, O, Si are 2.2, 2.5, 3.5 and 1.7, respectively, the natural population analysis (NPA) charge at Si is 1.961 e). This electrostatic interaction in pentacoordinate transition state overcomes the significant strain from the cyclic structure and lifts the restriction of the symmetry-forbidden process.^[16]

Moreover, the calculated Gibbs energies of activation for 1,5 O–Si insertion is as low as 5.1 kcal/mol, which is roughly faster than a diffusion-controlled reaction with a reaction rate constant of 10^9 s^{-1} .^[20] Therefore, we predict that neither the activation-controlled nor the diffusion-controlled bimolecular side reactions of alkylidene carbenes, such as addition reaction,^[1c] nucleophilic substitution,^[21] could compete with 1,5 O–Si insertions. This is the reason to answer why intramolecular 1,5 O–Si insertion of alkylidene carbenes can take place in high reaction yields and high compatibility.^[6]

b) Mechanism of 1,5 O–H insertion in reaction 1 b. 1,5 O–H insertions of alkylidene carbenes gave dihydrofurans in low yields. We wondered why 1,5 O–H insertions are more difficult than 1,5 O–Si insertions. The free energy surface of **reaction 1 b** is shown in Figure 2. DFT calculations showed that

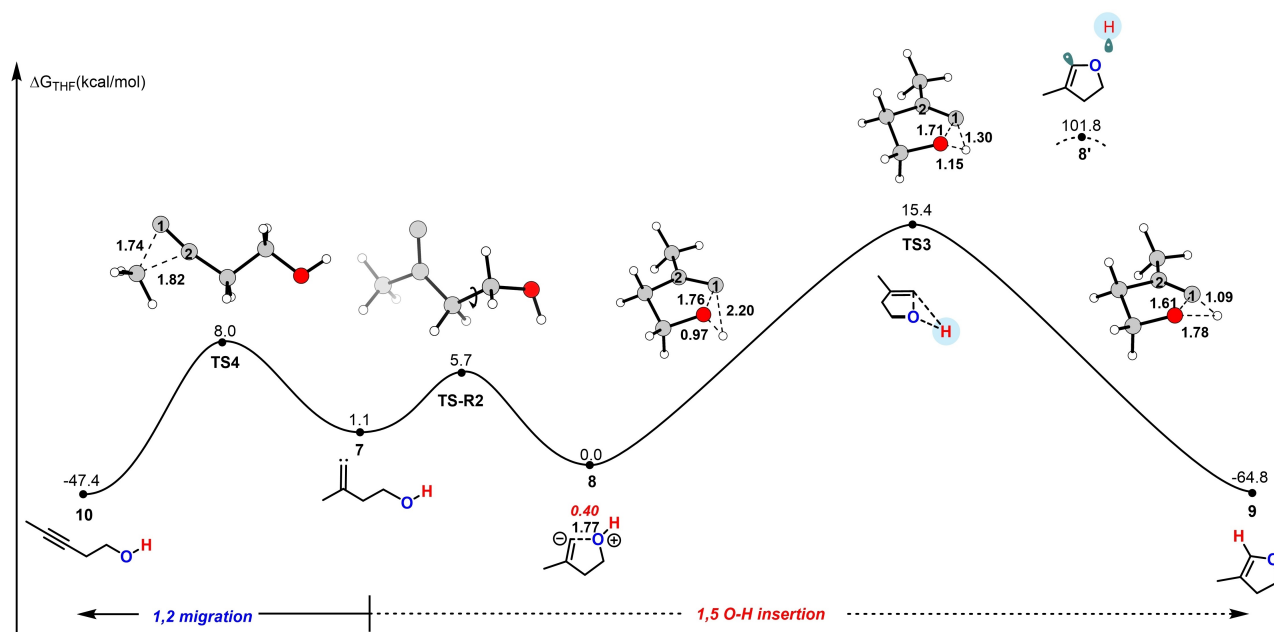


Figure 2. Computed reaction pathways for 1,5 O–H insertion and 1,2-Me migration of **7** and selected structures from IRC calculations. The black numbers show the corresponding bond lengths in bond angstrom, while the red numbers show the Mayer bond order. Color scheme: C, gray; H, white; O, red.

a conformational change from alkylidene carbene **7** to oxonium ylide **8** via **TS-R2** has an activation free energy of 4.6 kcal/mol, which is exergonic by 1.1 kcal/mol. The C–O bond in **8** is 1.77 Å (longer than that in **2**) and has a Mayer bond order of 0.40, indicating that this bond is weaker than the C–O bond in **2**. This can be understood by the fact that the hydrogen atom has a weaker electron-donating inductive effect compared to the TMS group.

Then a 1,2-proton shift generating the dihydrofuran product was proposed. But this should be a prohibited process because the 1,2-proton shift is symmetry-forbidden (Figure 3a): the activation barrier of the direct 1,2-proton shift in ethyl anion is 48.2 kcal/mol.^[22] However, the proposed 1,2-proton shift for oxonium ylide **8** via a half-chair-like transition state **TS3** only requires an activation free energy of 15.4 kcal/mol, indicating that the 1,2-proton shift can take place under room temperature. Why? The IRC calculation showed that C1-H bond forms ahead of the of C1-O bond (Figure 2). Therefore, transition state **TS3** is not proposed as a typical 1,2-proton shift, but has a character of insertion reaction of carbene into O–H bond, which lifts the restriction of symmetry-forbidden process for the 1,2-proton shift.

Unfortunately, the computed free energy surface shown in Figure 2 disagrees with experimental results. In Figure 2, the formation of dihydrofuran is disfavored kinetically because **TS3** is higher than **TS4** by 7.4 kcal/mol, in contrast to the experimental observation that a 21 % yield of the O–H insertion product was observed.^[6] Therefore, a new mechanism has to be proposed.

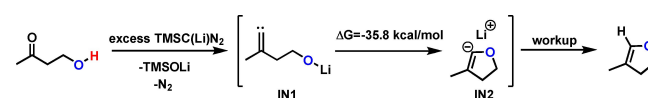
We proposed that **reaction 1b** is a formal O–H insertion.^[10] Experimentally, this alkylidene carbene was generated in situ, from excess TMSCHN₂ (1.2 eq.) and *n*-BuLi (1.2 eq.) reacting with

ketone. The used base would be partially consumed by the deprotonation reaction of the present OH group to form alkoxy lithium. We found the transformation from **IN1** to **IN2** is a barrierless process and very exergonic by 35.8 kcal/mol. Therefore, alkylidene carbene was first converted into **IN2**, which, after reaction workup, was then converted into the final protonated product (Scheme 2). Due to this process, neither 1,2 migration nor 1,5 O–H insertions occurred, but only the formal 1,5 O–H insertion through deprotonation took place, which can be used to explain Shiori's experiments.^[6]

c) Mechanism of 1,5 O–C insertion:

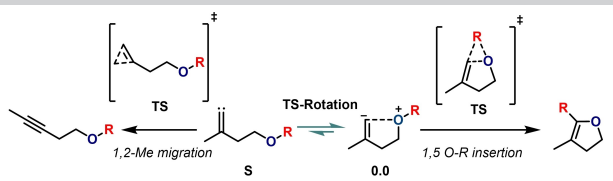
Intramolecular 1,5 O–C insertion. In this part, we want to know why some O–C insertions did not take place while other processes such as 1,2-Me migrations happened. We carried out DFT calculations of 1,5 O–Y insertions with different carbon groups in the same system shown in Table 2.






Here we found that, for most carbon groups except that in entry 7, the alkylidene carbenes could overcome the steric factors to form the oxonium ylides exothermically through single bond rotations (Table 2, entries 1–6). But the subsequent 1,2 rearrangements via concerted transition states **TS5–TS8** for these carbon groups (entries 1–4) are difficult, with the predicted Gibbs energies of activation of more than 30 kcal/mol. This could also be understood because the suprafacial 1,2-C shift is symmetry-forbidden according to Woodward-Hoff-



Scheme 2. The deprotonation pathway for formal 1,5 O–H insertion of alkylidene carbene.

Table 2. The competition between 1,2-Me migrations of alkylidene carbene and formal 1,5 O–C insertions via oxonium ylide.



entry	R	S	TS-Rotation	TS(1,5 O-R insertion)	TS(1,2-Me migration)	$\Delta\Delta G^\ddagger$
1	Me	4.0	8.4	40.3 (TS5)	10.9 (TS12)	29.4
2	^t Bu	3.1	7.8	34.6 (TS6)	9.9 (TS13)	24.7
3		2.3	6.9	33.1 (TS7)	9.2 (TS14)	23.9
4		1.3	7.2	35.4 (TS8)	8.0 (TS15)	27.4
5		0.9	5.6	21.4 (TS9)	7.7 (TS16)	13.7
6		0.0	4.7	22.5 (TS10)	9.0 (TS17)	13.5
7		-1.3	4.4	14.7 (TS11)	7.4 (TS18)	7.3

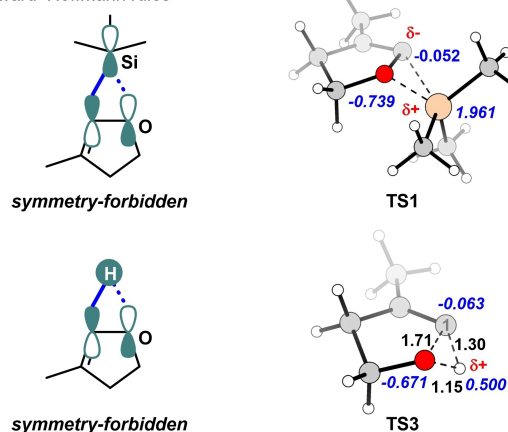
^aEnergies are reported in kcal/mol. $\Delta\Delta G^\ddagger = \text{TS}(1,5 \text{ O-R insertion}) - \text{TS}(1,2\text{-Me migration})$

mann rules. Due to these facts, we conclude that, for general carbon groups (Table 2, entries 1–4), the formal 1,5 O–C insertions of alkylidene carbenes through concerted 1,2 rearrangements of oxonium ylides could not occur under ambient temperature.

However, when one adjacent oxygen atom is introduced, the Gibbs energies of activation for 1,5 O–C insertions via **TS9** and **TS10** are decreased to 21.4 kcal/mol (Table 2, entry 5) and 22.5 kcal/mol (Table 2, entry 6), respectively. Surprisingly, with two adjacent oxygen atoms (Table 2, entry 7), the overall Gibbs energy of activation for 1,5 O–C insertion via **TS11** is reduced to 16.0 kcal/mol, which makes it more possible to undergo 1,5 O–C insertion. We attribute this trend to the ionic character of the corresponding transition states, suggested by the proposed model mentioned above (see Figure 3): the oxygen atoms could stabilize the adjacent positive charge at the migrating group in the transition states through an n-p orbital interaction.

Other pathways for 1,5 O-allyl and 1,5 O-benzyl insertions through oxonium ylides have also been considered. As shown in Figure 4, the 2,3 sigmatropic rearrangement of oxonium ylide via **TS7'** requires 22.2 kcal/mol of Gibbs free energy of activation, which is favored over 1,2 rearrangement of oxonium ylide via **TS7** by 10.9 kcal/mol. This is consistent with the previous knowledge that allyl oxonium ylides from carbene precursors are good migration groups for 2,3-sigmatropic rearrangement.^[7] However, 1,2-Me migration via **TS14** is much favored over this formal 1,5 O-allyl insertions **TS7'** by 13 kcal/mol, indicating that only 1,2-Me migration product could be obtained. The homolysis of O–C bond via **TS8'** (with a computed $\langle S^2 \rangle$ of 0.26), requiring activation free energy of

a) Analysis of the suprafacial 1,2-Si/H shift of oxonium ylide according to the Woodward–Hoffmann rules



b) Optimized geometry and orbital interactions of the concerted 1,5 S–H insertion transition state **TS37**

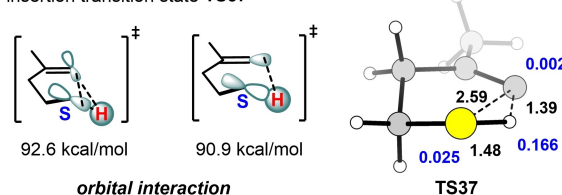


Figure 3. (a) Analysis of the suprafacial 1,2-Si/H shift of oxonium ylide **2/8** according to the Woodward–Hoffmann rules. (b) Orbital interaction describing $\sigma(\text{S-H}) \rightarrow \text{p}(\text{C})$ and $\text{n}(\text{C}) \rightarrow \sigma^*(\text{S-H})$ of the concerted 1,5 S–H insertion transition state **TS37**. The blue numbers showed the NPA charges. Color scheme: C, gray; Si, orange; H, white; O, red; S, yellow.

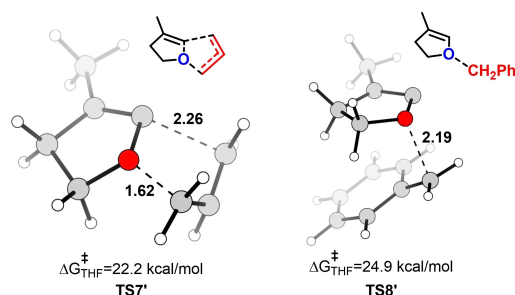


Figure 4. Optimized geometry for the 2,3 sigmatropic rearrangement of oxonium ylide **TS7'** and homolysis of O–C bond **TS8'**. The black numbers show corresponding bond lengths in angstrom. Color scheme: C, gray; O, red; H, white.

24.9 kcal/mol, was found as a competing process compared to the 1,5 O-benzyl insertion. This homolytic pathway is favored over heterolytic pathways (**TS8**) for 1,2 benzyl rearrangement of oxonium ylide by 10.5 kcal/mol. However, the 1,2-Me migration is also favored over homolysis of O–C bond by 16.9 kcal/mol, indicating 1,5 O-benzyl insertion could not happen in this case.

Our calculations predicted that the 1,2 migrations of the methyl group are all favored over formal 1,5 O–C insertions (Table 2, entry 1–7), which agrees with the experimental result for **reaction 3 a**. Thus, to achieve 1,5 O–C insertions, the 1,5 migrating groups should be strictly chosen to stabilize the positive charge in the corresponding transition states, while substituents with higher activation free energy of 1,2 migration

such as $p\text{-TolSO}_2^-$ are suggested to be used for inhibiting 1,2 migrations.^[9] Besides, another side reaction, a dealkylation process observed in **reaction 2a–2d** should also be considered. In other words, the right conditions of preparing alkylidene carbene are critical for these 1,5 O–C insertions.

Mechanism of 1,5 O-THF insertion in reaction 2a. The free energy surface for 1,5 O-THF insertion is shown in Figure 5. Firstly, there are three unimolecular pathways that could be taken by alkylidene carbene **11**. One is the 1,2-tosyl migration via **TS19**, requiring an activation free energy of 4.9 kcal/mol. Another is the formation of oxonium ylide **12** through a single bond rotation (**TS-R3**) which is favored over the former process by 0.6 kcal/mol. Subsequently, an intramolecular 1,2 rearrangement of THF group via **TS20** requires an activation free energy of 10.0 kcal/mol. In addition, we have also considered the pathway through heterolysis of C–O bond which gives an ionic pair species (**13** and **14**) and requires a Gibbs free energy of 14.9 kcal/mol. Therefore, this pathway is disfavored compared to **TS20** and can be excluded for further consideration.

Second, a bimolecular pathway between $p\text{-TolSO}_2\text{Na}$ and **12**, leading to the dealkylation product observed experimentally, was considered. Both oxygen atom and sulfur atom of the excess $p\text{-TolSO}_2\text{Na}$ can act as nucleophiles.^[23] Here we found using O atom in sulfinate anions to attack carbon atom of THF group via **TS21** requires an activation free energy of 9.7 kcal/mol, forming carbanions **14** and **15**. The S-attack reaction through **TS21'** requiring an activation free energy of 10.2 kcal/mol is slightly higher than that needed for O-attack reaction by 0.5 kcal/mol. It should be noted that the dealkylation process

(**TS21**) is slightly favored over formal 1,5 O–C insertion (**TS20**) by 0.3 kcal/mol, indicating both dealkylation and intramolecular 1,5 O-THF insertion could compete.

There are two possible pathways to quench carboanion **14**. One is the protonation process by THF solvent or intermediate **15**, giving the dealkylation product **18**. The protonation by THF is difficult, requiring activation free energy of 40.2 kcal/mol (**TS22**). While the E2 elimination of **15** via **TS23** requires an activation free energy of 26.2 kcal/mol, releasing the nucleophiles and the volatile 2,3-dihydrofuran **17**. Thus, the E2 elimination is a better way to abstract the proton, which agrees with the isotopic experiment from Feldman.^[9b]

The other reaction taken by anion **14** is a nucleophilic reaction, where **14** attacks **15**'s carbon atom via **TS24**, requiring an activation free energy of 26.0 kcal/mol. It's noted that these two continuous nucleophilic processes achieve the retention of configuration of the migrating group, which is consistent with the experiments by Feldman.^[9b] These two nucleophilic processes are also supposed to take place in the same solvent cage so that the crossover product was not observed experimentally.^[9b] Comparing the Gibbs free energies of **TS23** with **TS24**, and **TS20** with **TS21**, we conclude that the presence of nucleophiles in 1,5 O-THF insertion of alkylidene carbene could give both the formal 1,5 O–C insertion product and dealkylation product. This is consistent with the experiment that 35% insertion product **16** and 25% **18** were obtained in **reaction 2b**. Besides, similar energy surfaces for 1,5 O-allyl insertions and 1,5 O-benzyl insertions were also computed and are given in Supporting Information, which are consistent with

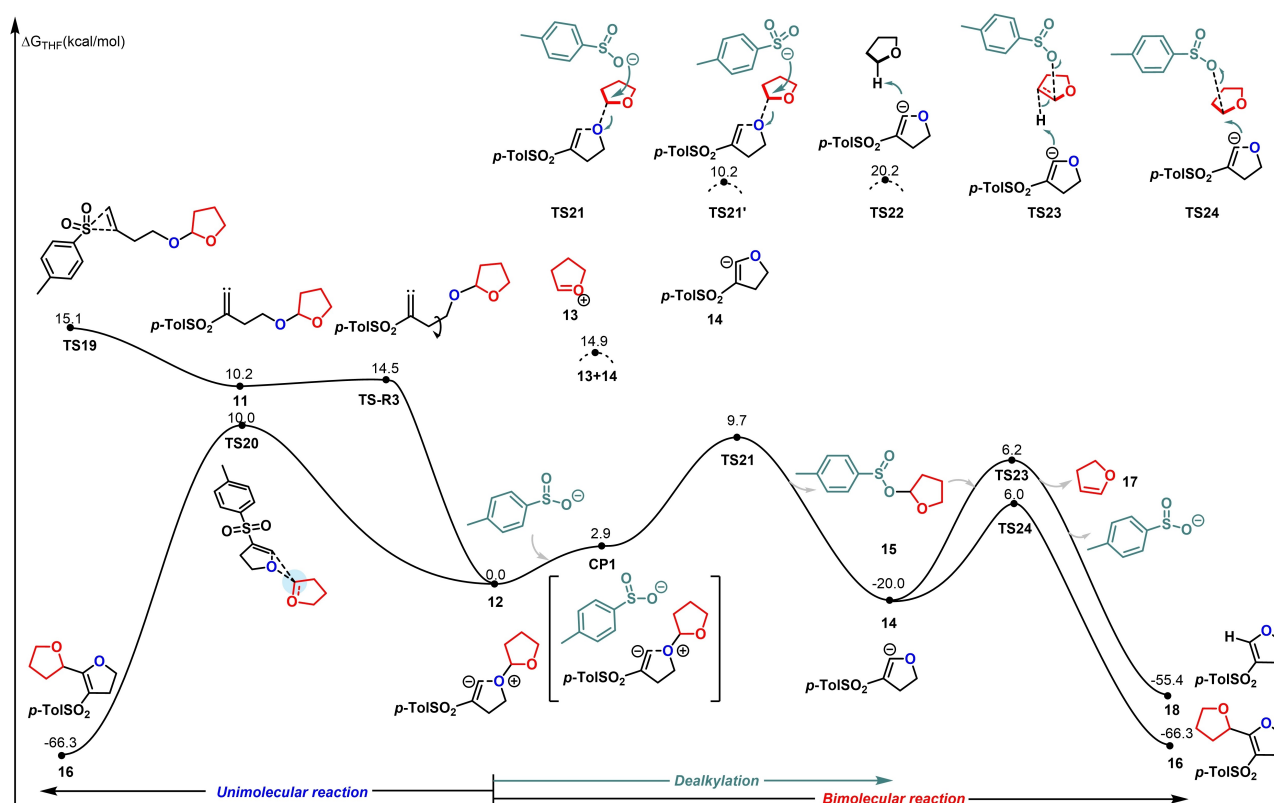


Figure 5. Computed reaction pathways for 1,5 O-THF insertion in **reaction 2a**.

experiments that reactions **2c** and **2d** gave majorly dealkylation products.

d) Mechanism of 1,5 S-H insertion in reaction 3b. In this part, we report our DFT study for understanding the role of heteroatoms in 1,5-X insertions. The free energy surface of 1,5 S-H insertion in **reaction 3b** is shown in Figure 6. The reaction starts from the generation of alkylidene carbene **30** from α -elimination in **reaction 3b**.^[10] Then **30** is easily converted into sulfonium ylide **31** via a bond rotation transition state **TS-R4** with an activation free energy of 4.8 kcal/mol. Calculations indicated that **31** is more stable than **30** by 11.2 kcal/mol. The Mayer bond order of C-S bond in **31** is 0.87, indicating a stronger n-p interaction for sulfonium ylide than that for oxonium ylide. This is due to the stronger electron-donating ability of sulfur atom.

To our surprise, the sulfonium ylide **31** could not be converted into **33** directly. A conformational change is needed firstly, converting **30** into **30'**, followed by a concerted 1,5 S-H insertion via transition state **TS37**. IRC calculation demonstrated the direct process of converting **30'** into **33** (instead of **31** into **33**). The overall Gibbs free energy of activation for this process is 13.3 kcal/mol.

Alternatively, **30'** may also undergo 1,2-Me migration via **TS36** with an overall activation free energy of 17.8 kcal/mol (a conformational search for **TS36** has also been carried out and the most stable one was reported here). Different from **reaction 1b**, 1,5 S-H insertion is favored over 1,2 migrations of alkylidene carbene by 4.5 kcal/mol, suggesting that the product in **reaction 3b** could be obtained from intramolecular 1,5 S-H insertion via a concerted mechanism. Besides, intermolecular

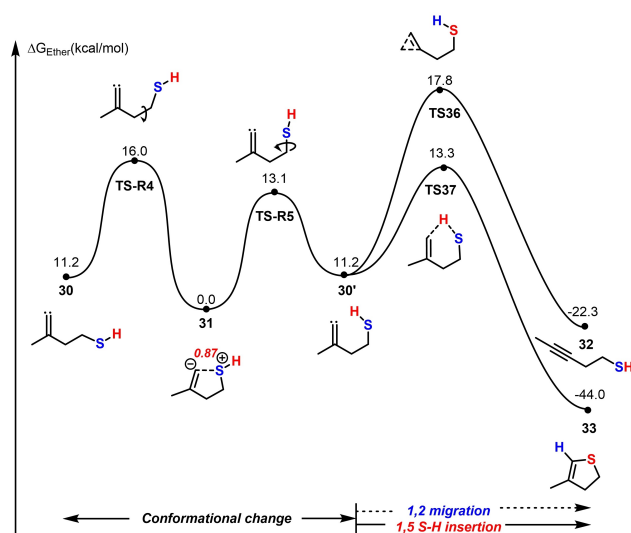
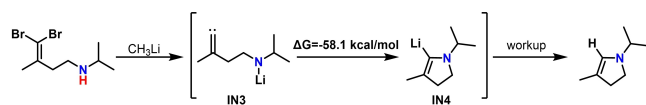


Figure 6. Computed reaction pathways for 1,5 S-H insertions in **reaction 3b**.



Scheme 3. The deprotonation pathway for formal 1,5 N-H insertion of alkylidene carbene.

deprotonation with excess base, which works on 1,5 O-H insertions in Scheme 3, could not be excluded if the intermolecular deprotonation is comparable with the complex lithium-halogen exchange. Therefore, we predicted that 1,5 S-H insertions could undergo both the concerted pathway and deprotonation pathway easily. That could be the reason why 1,5 S-H insertions gave a high yield of 71% experimentally.

Rationalization of the Concerted Mechanism of 1,5 S-H insertion of the free alkylidene carbene. It's surprising that both stepwise and concerted mechanisms can be found in 1,5-X insertions of free alkylidene carbenes. We wondered why S-H insertions favor the concerted pathway while all O-Y insertions prefer stepwise pathways.

The chair-like geometry for the concerted 1,5 S-H insertion transition state is shown in Figure 3b. The C-S bond in **TS37** is far from formation, different from the forming bond in **TS3**, and **TS(1,5 migration)** in Table 2. We attribute the different reaction mechanisms to the unique properties of σ (S-H) bonds. It is known that the sulfur atom has smaller electronegativity than oxygen atom (2.6 for S vs. 3.4 for O, 2.1 for H).^[19] Therefore, the polarity of S-H bond is much weaker than O-H bond. This is consistent with NBO calculations,^[24] which showed the contribution of hydrogen atom to the natural bond orbitals of S-H bond in **30'** is 42% while only 24% of natural bond orbital of O-H bond in **7** is contributed by hydrogen atom. Thus, the initial stage of S-H insertion should be the interaction between the empty p orbital and σ (S-H) bond, leading to the partly formation of C-H bond in **TS37**. Then, the lone pair of carbene could interact with σ^* (S-H) bond as a secondary orbital interaction to assist S-H insertion (the process was also illustrated by IBO analysis,^[25] see SI). NBO calculations revealed that the stabilization energy in **TS37** generated from the interaction between σ (S-H) and p orbital of carbene is 92.6 kcal/mol, and the secondary stabilization energy from the interaction between σ^* (S-H) and lone pair of carbene is 90.9 kcal/mol (Figure 3b).

In contrast, for the 1,5 O-H insertion in **8**, the empty p orbital of carbene strongly favors interacting with electrons at the oxygen atom due to the high polarity of O-H bond. Consequently, the oxonium ylide **8** was located rather than a transition state of concerted 1,5 O-H insertion. That's why 1,5 S-H insertions undergo the concerted mechanism while O-H insertions prefer the stepwise mechanism.

e) Mechanism of 1,5 N-H insertion in reaction 3c. When replacing the sulfur atom with a nitrogen atom, the alkylidene carbene **34** forms the ammonium ylide **35** through a single bond rotation (via **TS-R6**) with an activation free energy of 5.0 kcal/mol, which is favored over 1,2 migrations via **TS38** by 1.7 kcal/mol (Figure 7). This process is highly exergonic by 27.0 kcal/mol. The Mayer bond order of N-C in **35** is 0.69, which is smaller than that in **31** due to the weaker electron-donating ability of nitrogen atom compared to sulfur atom. Subsequently, a concerted 1,2 proton shift from **35** was found, requiring activation free energy of 30.7 kcal/mol. This process is favored over 1,2 migrations by 2.9 kcal/mol. In addition, the diradical mechanism^[8] of 1,2 proton shift of ammonium ylide via **TS39'** ($\langle S^2 \rangle = 0.87$) was also considered, but this process

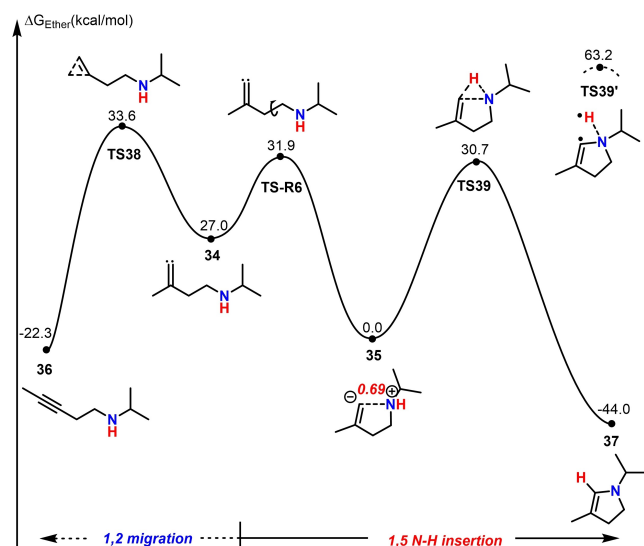


Figure 7. Computed reaction pathways for 1,5 N-H insertions in reaction 3c.

requires a higher activation free energy (63.2 kcal/mol) and can be excluded.

However, the overall activation free energy for 1,5 N-H insertion is too high to take place under room temperature. This can be understood because this is a symmetry-forbidden 1,2-proton shift. How to reconcile these calculation results with the fact that N-H insertion into alkylidene carbenes was observed experimentally? We hypothesized that the intermolecular deprotonation by the base is comparable with the lithium-halogen exchange in reaction 3c (Scheme 3).^[10] Thus, the deprotonated alkylidene carbene IN3 may exist and it can then be easily transformed into IN4, with a free energy decrease of 58.1 kcal/mol. Reaction workup then converted IN4 into the final product.

f) Mechanism of 1,5 N-Bn insertion in reaction 4a. It's surprising to find that 1,5 N-Bn insertions could take place though the reaction yields were low. This is different from 1,5 O-Bn insertions. We hypothesized that nitrogen atom could accelerate this process. The free energy surface of reaction 4a is shown in Figure 8. The 1,2-Me migration of 38 via TS40 requires an activation free energy of 12.5 kcal/mol, while the formation of ammonium ylide 39 requires an activation free energy of 3.7 kcal/mol via TS-R7, which is highly exergonic by 23.7 kcal/mol. Thus, 1,2 migration of methyl group could not happen due to the easy formation of ammonium ylide 39.

It was proposed that 1,2 rearrangements of ammonium ylides could take place through a homolytic process.^[8] Our calculation found that the computed Gibbs free energy of activation for homolysis of C-N bond via TS41 ($\langle S^2 \rangle = 0.56$) is 29.5 kcal/mol, giving diradical intermediate 41 ($\langle S^2 \rangle = 1.02$). Then a barrierless recombination of radical pair affords the product. The whole process is exergonic by 56.6 kcal/mol. On the other hand, the activation free energy for a concerted 1,2 rearrangement of ammonium ylide via TS42 is 48.1 kcal/mol, which can be ruled out for further consideration. Therefore, we conclude that the 1,5 N-Bn insertion via ammonium ylide could

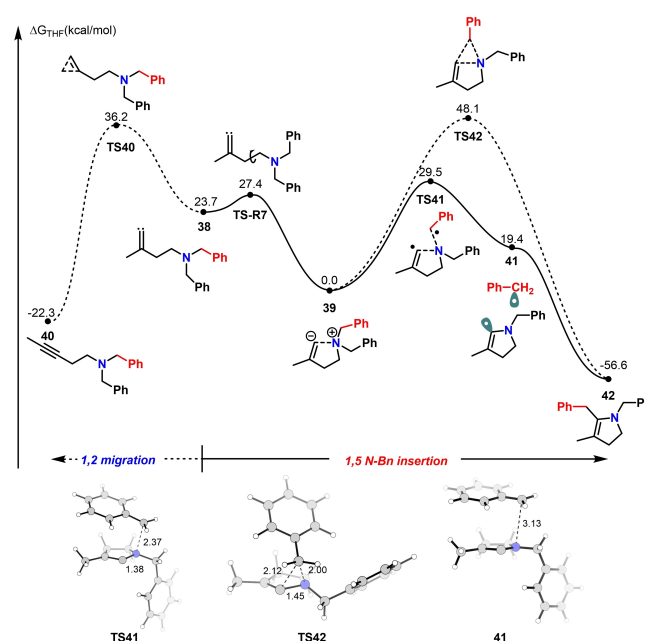


Figure 8. Computed reaction pathways for 1,5 N-Bn insertions in reaction 4a.

take place slowly through homolytic pathway under the reflux reaction conditions, which is consistent with experimental observation (reaction 4a, 8% yield after 2 steps).

Conclusions

The mechanisms of 1,5-X insertions of free alkylidene carbenes have been rationalized based on DFT calculations. The 1,5-X insertions except S-H proceed through a stepwise mechanism with formed ylides as intermediates. In most cases, the activation free energies for the subsequent 1,2 rearrangements of ylides depend on the stability of the positive charge on the migrating group in cyclic transition states. Thus, 1,5 O-Si insertion with a five-coordinated transition state is favored over 1,2-Me migration and even faster than diffusion-controlled process. While 1,5 O-H, O-C insertions including O-THF, and O-THP insertions are disfavored over 1,2-Me migration. The formal 1,5 O-H insertion could only proceed through intermolecular deprotonation. We suggest that nucleophiles could react with ylides in 1,5 O-C insertions, giving the formal insertion/dealkylation products. We have also studied the effect of different heteroatoms: the 1,5 S-H insertion occurs through a concerted mechanism and is favored over 1,2-Me migration, while 1,5 N-H insertion takes place though deprotonation; for 1,5 N-Bn insertion, 1,2 rearrangement of ammonium ylide was suggested to proceed through homolytic pathway. These computational results reported here further deepen our understanding of 1,5-X insertions of free alkylidene carbenes.

Computational Methods

All calculations were performed with Gaussian 09 software package.^[26] Pruned integration grids with 99 radial shells and 590 angular points per shell were used. Geometry optimizations of all the stationary points were carried out using M06-2X^[27] functional and 6-31 + G(d,p). The M06-2X functional was chosen because it could provide relative accurate structure of alkylidene carbene compared with several popular functionals (see SI). Diradical intermediates and transition states were located with UM06-2X/6-31 + G(d,p)^[27c] using the keywords: guess = (mix always). The value of the spin operator S^2 applied to the contaminated singlet indicates the diradical character. Spin contamination was not considered in these DFT calculations.^[28] Unscaled harmonic frequency calculations at the same level were performed to validate each structure as either a minimum or a transition state and to evaluate its zero-point energy and thermal corrections at 298 K. Based on these optimized structures, single-point energy refinements were performed at the ω B97X-D/maug-cc-pVTZ level with SMD(THF/Et₂O) solvation model.^[29] The ω B97X-D functional was chosen because it has excellent performance on both 1,5 insertion and 1,2 migration of alkylidene carbenes (see SI). Using the optimized structures, NBO calculations (NPA charges) were performed at M062X-2X/6-31 + G(d,p) with NBO 3.1^[30] in Gaussian, while the Mayer bond orders were calculated at M06-2X/6-31G(d,p) level. All discussed energy differences were based on Gibbs free energies at 298 K (standard states are the hypothetical states at 1 mol/L). 3D structures were prepared with CYLview.^[31]

Acknowledgements

We thank National Natural Science Foundation of China for financial support (21933003) and the High-Performance Computing Platform of Peking University.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: carbene · insertion · cyclization · DFT calculations

- [1] For reviews in alkylidene carbene chemistry, see: a) R. S. Grainger, K. R. Munro, *Tetrahedron* **2015**, *71*, 7795; b) D. Habrant, V. Rauhala, A. M. P. Koskinen, *Chem. Soc. Rev.* **2010**, *39*, 2007–2017; c) K. Rudolf, *Chem. Rev.* **2004**, *104*, 3795–3849. For C–H bond, see: d) J. C. Gilbert, D. H. Giamalva, U. Weerasooriya, *J. Org. Chem.* **1983**, *48*, 5251–5256; e) A. Nguyen Van Nhien, E. Soriano, J. Marco-Contelles, D. Postel, *Carbohydr. Res.* **2009**, *344* (13), 1605–1611; f) S. R. Buxton, K. H. Holm, L. Skattebøl, *Tetrahedron Lett.* **1987**, *28*, 2167–2168. For N–H insertion, see: g) T. Yagi,

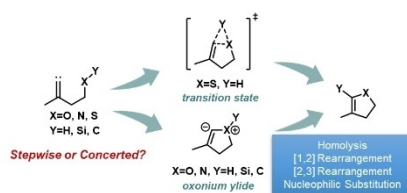
- T. Aoyama, T. Shioiri, *Synlett* **1997**, *1997(09)*, 1063–1064. For O–Si insertion, see: h) G. Hobley, K. Stuttle, M. Wills, *Tetrahedron* **2003**, *59(26)*, 4739–4748; i) S. Kim, C. M. Cho, *Tetrahedron Lett.* **1995**, *36*, 4845–4848.
- [2] J. C. Gilbert, D. H. Giamalva, M. E. Baze, *J. Org. Chem.* **1985**, *50*, 2557–2563.
- [3] a) D. F. Taber, R. P. Meagley, D. J. Doren, *J. Org. Chem.* **1996**, *61*, 5723–5728; b) D. F. Taber, H. Yu, *J. Org. Chem.* **1997**, *62*, 1687–1690.
- [4] S. Y. Yun, J.-C. Zheng, D. Lee, *J. Am. Chem. Soc.* **2009**, *131*, 8413–8415.
- [5] J.-C. Zheng, S. Y. Yun, C. Sun, N.-K. Lee, D. Lee, *J. Org. Chem.* **2011**, *76*, 1086–1099.
- [6] K. Miwa, T. Aoyama, T. Shioiri, *Synlett* **1994**, *6*, 461–462.
- [7] a) J. S. Clark, S. A. Krowiak, L. J. Street, *Tetrahedron Lett.* **1993**, *34*, 4385–4388; b) A. Padwa, S. F. Hornbuckle, *Chem. Rev.* **1991**, *91*, 263–309; c) E. J. Roskamp, C. R. Johnson, *J. Am. Chem. Soc.* **1986**, *108*, 6062–6063; d) D. M. Jaber, R. N. Burgin, M. Helper, P. Y. Zavalij, M. P. Doyle, *Org. Lett.* **2012**, *14(7)*, 1676–1679.
- [8] For the mechanism of 1,2 rearrangement of ylides, see: a) F. G. West, B. N. Naidu, *J. Am. Chem. Soc.* **1993**, *115*, 1177–1178; b) K. Friedrich, U. Jansen, W. Kirmse, *Tetrahedron Lett.* **1985**, *26*, 193–196; c) G. Ghigo, S. Cagnina, A. Maranzana, G. Tonachini, *J. Org. Chem.* **2010**, *75*, 3608–3617.
- [9] a) K. S. Feldman, M. L. Wroblewski, *Org. Lett.* **2000**, *2*, 2603–2605; b) K. S. Feldman, M. L. Wroblewski, *J. Org. Chem.* **2000**, *65(25)*, 8659–8668.
- [10] M. S. Baird, A. G. W. Baxter, A. Hoorfar, I. Jefferies, *J. Chem. Soc., Perkin Trans. I* **1991**, 2575–2581.
- [11] For structure of alkylidene carbene, see: a) S. C. Reed, G. J. Capitosti, Z. Zhu, D. A. Modarelli, *J. Org. Chem.* **2001**, *66(1)*, 287–299; b) H. Lee, J. H. Baraban, R. W. Field, J. F. Stanton, *J. Phys. Chem. A* **2013**, *117(46)*, 11679–11683.
- [12] E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, *13*, 3769–3772.
- [13] E. W. Colvin, B. J. Hamill, *J. Chem. Soc., Perkin Trans. I* **1977**, 869–874.
- [14] a) P. Fritsch, *Justus Liebigs Ann. Chem.* **1894**, *279*, 319–323; b) W. P. Buttenberg, *Justus Liebigs Ann. Chem.* **1894**, *279*, 324–337; c) H. Wiechell, *Ann. Chem.* **1894**, *279*, 337–344.
- [15] a) R. B. Woodward, R. J. Hoffmann, *Am. Chem. Soc.* **1965**, *87*, 2511; b) R. Hoffmann, R. B. Woodward, *Acc. Chem. Res.* **1968**, *1*, 17; c) R. B. Woodward, R. Hoffmann, *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 781.
- [16] A. E. Reed, P. v. R. Schleyer, *J. Am. Chem. Soc.* **1990**, *112*, 1434–1445.
- [17] a) A. G. Brook, *Acc. Chem. Res.* **1974**, *7*, 77–84; b) Y. Wang, M. Dolg, *Tetrahedron* **1999**, *55*, 12751–12756; c) E. L. Werkema, A. Yahia, L. Maron, O. Eisenstein, R. A. Andersen, *Organometallics*. **2010**, *29*, 5103–5110.
- [18] P. Antoniotti, G. Tonachini, *J. Org. Chem.* **1993**, *58*, 3622–3632.
- [19] L. Pauling, *J. Am. Chem. Soc.* **1932**, *54*, 3570–3582.
- [20] For a diffusion-controlled bimolecular reaction $A + B = P$ (reaction rate constant $k_d = 10^{-9}$ L/mol*s and concentration of B $[B] = 0.01$ M), the activation free energy was estimated to $\Delta G^\ddagger = 8.0$ kcal/mol based on the equation ($k_d[B][A] = k_bT[A]/h \cdot \exp(-\Delta G^\ddagger/RT)$, $k_b = 1.38 \cdot 10^{-23}$ J/K, $h = 6.63 \cdot 10^{-34}$ Js, $T = 300$ K).
- [21] T. Sueda, T. Nagaoka, S. Goto, M. Ochiai, *J. Am. Chem. Soc.* **1996**, *118*, 10141–10149.
- [22] a) Y. Wang, P.-J. Cai, Z.-X. Yu, *J. Org. Chem.* **2017**, *82*, 4604–4612; b) In ref. 22a, the authors did not compute the 1,2-proton shift of ethyl anion via a diradical mechanism, which was found in Stevens rearrangement, see ref. 8a and also part e in the main text. We found that the dissociation of ethyl anion into ethylene anion radical and hydrogen atom is highly endergonic by 59.7 kcal/mol in terms of Gibbs free energy, calculated at the same ω B97X-D/6-311 + G(d,p) level as in ref. 22a, see the Supporting Information.
- [23] a) M. Baidya, S. Kobayashi, H. Mayr, *J. Am. Chem. Soc.* **2010**, *132*, 4796–4805; b) Y.-Z. Ji, H.-J. Li, J.-Y. Zhang, Y.-C. Wu, *Eur. J. Org. Chem.* **2019**, *2019*, 1846–1855.
- [24] A. E. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev.* **1988**, *88*, 899–926.
- [25] a) G. Knizia, *J. Chem. Theory Comput.* **2013**, *9*, 4834–4843; b) G. Knizia, J. E. M. N. Klein, *Angew. Chem. Int. Ed.* **2015**, *54*, 5518–5522.
- [26] 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. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, 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, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09*, Revision E.01, Gaussian, Inc., Wallingford CT, 2013.
- [27] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B.* **1988**, *37*, 785–789; c) D. H. Ess, T. C. Cook, *J. Phys. Chem. A* **2012**, *116*, 4922–4929.
- [28] a) J. A. Pople, P. M. W. Gill, N. C. Handy, *Int. J. Quantum Chem.* **1995**, *56*, 303–305; b) K. Yamaguchi, F. Jensen, A. Dorigo, K. N. Houk, *Chem. Phys. Lett.* **1988**, *149*, 537–542.
- [29] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378–6396.
- [30] E. D. Glendening, A. E. Reed, J. E. Carpenter, F. Weinhold, *NBO*, Version 3.1.
- [31] C. Y. Legault, *CYView*, 1.0b, Université de Sherbrooke, **2009**. <http://www.cylview.org>.

Manuscript received: August 21, 2023
 Revised manuscript received: October 7, 2023
 Accepted manuscript online: October 11, 2023
 Version of record online: ■■, ■■

RESEARCH ARTICLE

Different mechanisms of 1,5-X insertions of free alkylidene carbenes were studied by DFT calculations. Except for the 1,5 S–H insertion, all 1,5-X insertions proceed through stepwise processes via forming ylide intermediates. However, subsequent 1,2 rearrangements of ylides occur through different mechanisms. The detailed analysis of the mechanistic differences is present.



Y. Zhou, Prof. Dr. Z.-X. Yu*

1 – 11

1,5-X Insertions of Free Alkylidene
Carbenes: A Theoretical Study

