CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200700145

On the Mechanism and Stereochemistry of Chiral Lithium-Carbenoid-Promoted Cyclopropanation Reactions

Zhuofeng Ke,[a] Yubing Zhou,[b] Hui Gao,[a] Cunyuan Zhao,*[a] and David Lee Phillips[c]

Abstract: An investigation into the mechanism and stereochemistry of chiral lithium-carbenoid-promoted cyclopropanation reactions by using density functional theory (DFT) methods is reported. Previous work suggested that this type of cyclopropanation reaction may proceed by competition between a methylene-transfer mechanism and a carbometalation mechanism. In this paper, it is demonstrated that the intramolecular cyclopropanation reactions promoted by chiral carbenoids **1** and **2** proceed by the methylene-transfer mechanism. The carbometalation mechanism was found to have a much higher reaction barrier and does not appear to compete with the methylene-transfer mechanism. The Lewis base group does not enhance the carbometalation pathway enough to compete with the methylene-transfer pathway. The present computational results are consistent with experimental observations for these cyclopropanation reactions. The factors governing the stereochemistry of the intramolecular cyclopropanation reaction by the methylene-transfer mechanism were examined to help elucidate the origin of the stereoselectivity observed in experiments. Both the directing group and the configuration at the C^1 centre were found to play a key role in the stereochemistry. Carbenoid **1** has a chiral C^1 centre of *R* configuration. The Lewis base group directs the cyclization of carbenoid **1** to form a single product. In contrast, the Lewis base group cannot direct the cyclization of carbenoid **2** to furnish a stereoselective product due to the *S* configuration of the chiral C^1 centre in carbenoid **2**. This relationship of the stereochemistry to the chiral character of the carbenoid has implications for the design of new efficient carbenoid reagents for stereoselective cyclopropanation.

Keywords: carbenoids · cyclopropanation · density functional calculations · reaction mechanisms · stereochemistry

Introduction

Cyclopropane-containing molecules can exhibit important biological activities.[1–7] They can also be used as inhibitors and versatile synthetic intermediates.[1–7] Cyclopropane-containing molecules can be produced from carbenoid-promoted cyclopropanation reactions. Therefore, much effort has been invested to develop carbenoid reagents which can make cyclopropanes from olefins with high efficiency and stereoselectivity.[8–11] There are four commonly used types of carbenoid reagents: zinc carbenoids (for example, Simmons–Smith reagents,[12,13] Furukawa reagents,[14] and Wittig–Denmark reagents[15,16]), lithium carbenoids ,[17] aluminum carbenoids,[18,19] and samarium carbenoids.[20,21] Among these various carbenoids, the lithium carbenoids are among the most efficient cyclopropanation reagents. For example, some lithium carbenoids can stereoselectively cyclopropanate olefins efficiently at −110 °C.[17,22,23]

Many experimental and theoretical efforts have been made to study the reaction mechanism(s) of carbenoid-promoted cyclopropanation reactions. Three types of mechanism have been suggested to be involved in the carbenoid-promoted cyclopropanation reactions: the free carbene mechanism, the methylene-transfer mechanism, and the carbometalation mechanism. It has been shown that the carbenoid-promoted cyclopropanation reactions do not involve the formation of a free carbene.[17,24] The methylene-transfer mechanism and the carbometalation mechanism have been

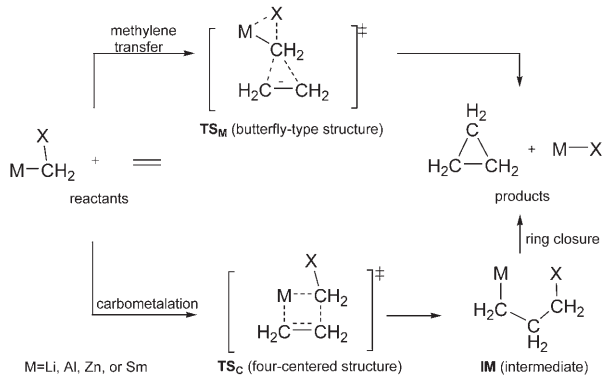
[a] Z. Ke, H. Gao, Prof. Dr. C. Zhao
MOE Laboratory of Bioinorganic and Synthetic Chemistry
School of Chemistry and Chemical Engineering
Sun Yat-sen University, Guangzhou 510275 (P. R. China)
Fax: (+86) 20-8411-0696
E-mail: ceszhcy@mail.sysu.edu.cn

[b] Y. Zhou
Department of Chemistry, Hexi University
Zhangye 734000 (P. R. China)

[c] Prof. Dr. D. L. Phillips
Department of Chemistry, The University of Hong Kong
Pokfulam Road, Hong Kong (P. R. China)

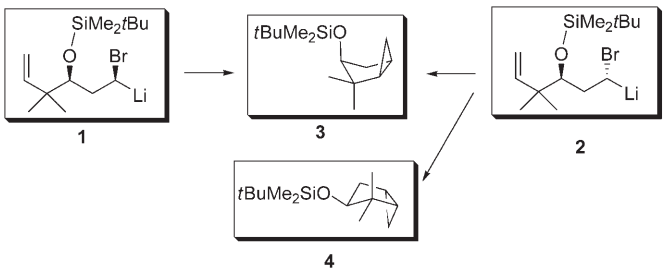
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

suggested to be the most reasonable reaction pathways (Scheme 1).[13,15,22,25–28] The methylene-transfer pathway is a concerted transformation which produces cyclopropanes through a "butterfly-type" transition state (TS_M). On the other hand, the carbometalation pathway is a two-step process involving a four-centered transition state (TS_C) to form an intermediate (IM) that subsequently undergoes a ring closure to furnish the products. Experimental and theoretical studies have demonstrated that the methylene-transfer mechanism should likely best represent the reaction reality for the cyclopropanation reactions of zinc carbenoids, aluminum carbenoids, and samarium carbenoids.[15,25–28] However, the debate concerning the mechanistic dichotomy for lithium-carbenoid-promoted cyclopropanation reactions has still not been resolved.



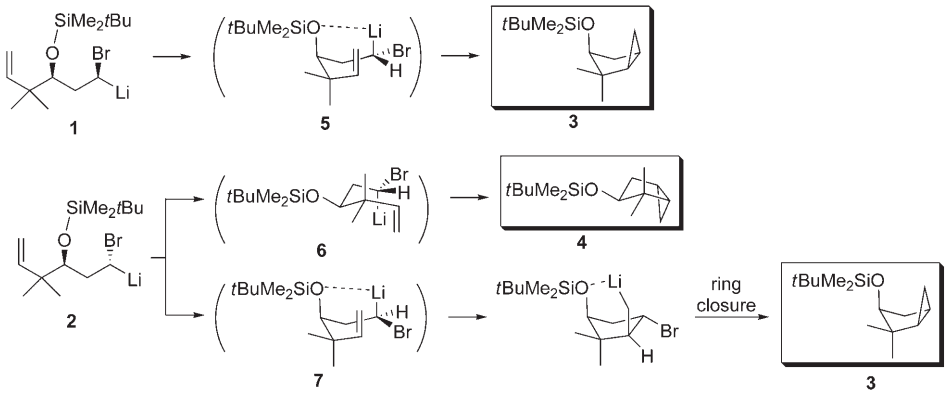
Scheme 1. The proposed methylene-transfer and carbometalation mechanisms for carbenoid-promoted cyclopropanation reactions.

Hoberg first suggested that the carbometalation mechanism might operate in lithium-carbenoid-promoted cyclopropanation reactions.[29] However, Burger thought carbometalation would be unreasonable for the addition of chloromethyllithium to alkenes.[30] A later study by Hoffmann and co-workers on the stereochemistry of lithium-carbenoid-promoted cyclopropanation reactions indicated that the formation of a mixed product from the lithium carbenoid **2** could result from competition between the methylene transfer and the carbometalation mechanisms.[22] Lithium carbenoids **1** and **2** are stereoisomers (Scheme 2). As shown in Scheme 3, carbenoid **1** forms a single product **3** by the Lewis base assisted methylene-transfer pathway (see conformer **5**) at −110 °C with a half-life of less than five minutes. However, the Lewis base assistance was suggested to help the carbometalation (see conformer **7**) pathway to compete with the methylene-transfer pathway (see conformer **6**



Scheme 2. The stereochemistry for the cyclopropanation reactions of carbenoids **1** and **2**.

which does not have Lewis base assistance) and this scenario then leads to the formation of a mixture of **3** and **4** (**3**/**4** 1.1:1) from carbenoid **2** at a higher temperature of −100 °C. A DFT study with a simple model in the gas phase by Nakamura and co-workers also suggested that there was competition between these two mechanisms.[27,28] However, our recent study with more complex models that include aggregation and solvation states which more accurately mimic the lithium-carbenoid-promoted cyclopropanation reactions demonstrated that these reactions proceed by the methylene-transfer mechanism in the real reaction systems (with the reaction barrier predicted to be in the 7.2–9.0 kcal mol^{-1} range), whereas the carbometalation pathway does not appear to make a significant contribution due to its higher reaction barrier in the aggregation and solvation states.[31] These results prompted us to investigate the important experimental work on chiral lithium-carbenoid-promoted intramolecular cyclopropanation reactions[22] which is thought to be an experimental support for the competition between the methylene-transfer and the carbometalation mechanisms. Our present study provides new insight into the mechanism(s) of this chiral lithium-carbenoid-promoted intramolecular cyclopropanation reaction. Our results show that the observed experimental facts can be well explained solely by the methylene-transfer mechanism. The carbometalation pathway does not appear to make a significant con-



Scheme 3. The reaction pathways proposed in reference [22].

tribution. The factors determining the stereoselectivity by the methylene-transfer mechanism have also been investigated to further understand the origin of the stereochemistry in these types of reactions.

Computational Methods

All of the molecules and transition states were fully optimized with the density functional theory (DFT) method by using the hybrid B3LYP density functional.[32,33] The B3LYP/6-311G** level of theory is a convenient method for these kinds of reactions for both computational cost and accuracy.[25,31] Analytical frequency calculations at the same level of theory were done in order to confirm that the optimized structures are at either a minimum or a first-order saddle point, as well as to obtain the zero-point energy (ZPE) correction. Intrinsic reaction coordinate (IRC) calculations[34,35] were performed to confirm the transition states connecting the relevant reactants and products. All of the geometry optimizations, frequency calculations, and IRC calculations were carried out with the standard split-valence polarized 6-311G** basis set for all the atoms of the reactions. All of the calculations were carried out by using the Gaussian 03 program.[36] To make the computations more tractable, the *tert*-butyldimethylsilyloxy groups were replaced with simple silyloxy groups in the carbenoids **1** and **2**. In order to consider solvent effects on the reactions, the polarized continuum model (PCM)[37] for tetrahydrofuran solvent ($\varepsilon = 7.58$) was applied for the calculations carried out at the temperature of $-100\,^{\circ}C$, by using Bondi's set of atomic radii.[38] Previous studies showed that the results with solvent effects included are more reliable than those calculated in the gas phase.[26,31] All of the relative free energies discussed in this paper are calculated at the B3LYP/6-311G**/PCM level of theory by using B3LYP/6-311G** gas-phase structures. According to previous studies of the mechanism dichotomy, the ring-closure process from IM to PC of the carbometalation pathway is not the rate-determining step, and will not be further discussed here.[26,28,31]

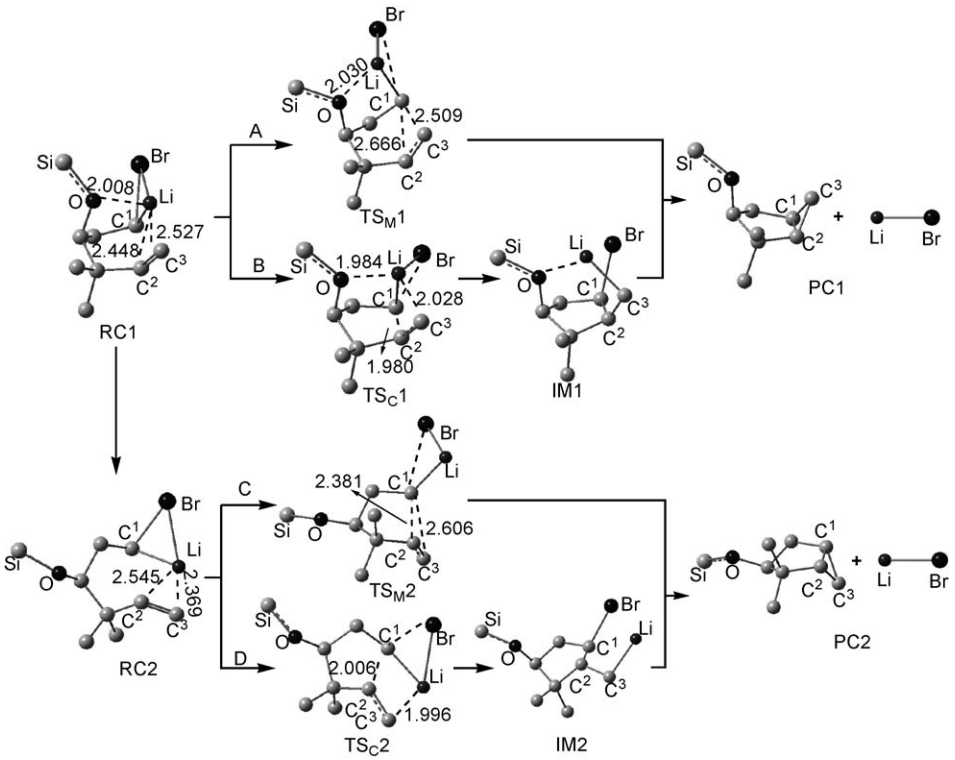


Figure 1. Optimized structures and key distances (Å) for the different reaction paths of the cyclopropanation reactions of carbenoid **1** calculated at the B3LYP/6-311G** level of theory. Hydrogen is omitted for conciseness.

Results and Discussion

Reaction mechanism(s): Based on the stereochemical pathways proposed in reference [22], we carried out a detailed computational examination of the methylene-transfer and the carbometalation pathways, for the cyclopropanation reaction of the chiral lithium carbenoids **1** and **2**. The optimized stationary structures (minima and saddle points) on the potential-energy surfaces are depicted schematically in Figures 1 and 2. Profiles of the free energies relative to the most stable reactant complex (RC) computed at the B3LYP/6-311G**/PCM level of theory are shown in Figures 3 and 4.

RC1 was found to be the most stable conformation of carbenoid **1**. In RC1, the silyloxy group coordinates to the lithium center with an O–Li distance of 2.008 Å and there is a π-type interaction between the C=C double bond and the lithium centre in RC1 (the distances between Li–C^2 and Li–C^3 are 2.448 and 2.527 Å respectively). Along the methylene-transfer pathway, RC1 goes through a "butterfly-type" transition state, TS_M1, to produce the product PC1 (bicyclohexane **3** and LiBr), as shown in path A of Figure 1. The transition state, TS_M1, corresponds to the reactive conformer **5** (Scheme 3), accompanied by Lewis base assistance (the O–Li distance is 2.030 Å) to the reaction. Figure 3 shows that path A has a reaction barrier of 7.5 kcal mol^{-1}. Along the stepwise carbometalation pathway, RC1 first forms an intermediate IM1 through a four-centered transition state, TS_C1, and then undergoes a ring closure of IM1 to produce bicyclohexane **3** and LiBr products (see path B in Figure 1). The relative free energy of TS_C1 was calculated to be 15.4 kcal mol^{-1} and this value is much higher than that for TS_M1. Reference [22] suggested that the cyclization could also occur through another type of reactive conformer without a Lewis base assisted interaction. As shown in Figure 1, the non-Lewis base assisted reaction paths require carbenoid **1** to overcome a conformational change from RC1 to RC2. RC2 also has a π-type interaction between the C=C double bond and the lithium center (the distances between Li–C^2 and Li–C^3 are 2.545 and 2.369 Å respectively). RC2

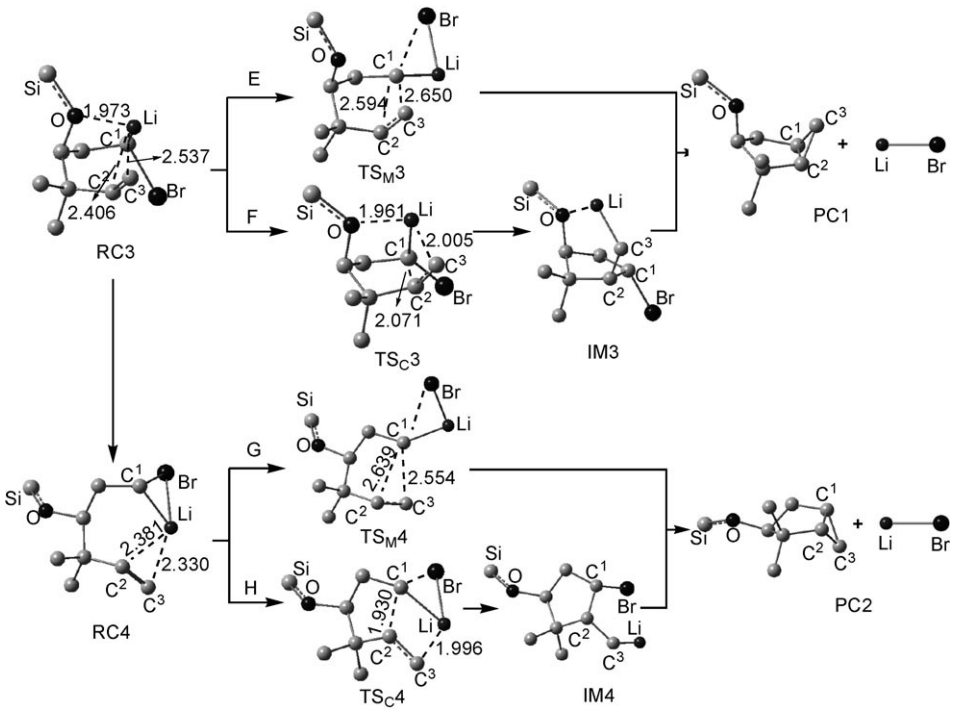


Figure 2. Optimized structures and key distances (Å) for the different reaction paths of the cyclopropanation reactions of carbenoid **2** calculated at the B3LYP/6-311G** level of theory. Hydrogen is omitted for conciseness.

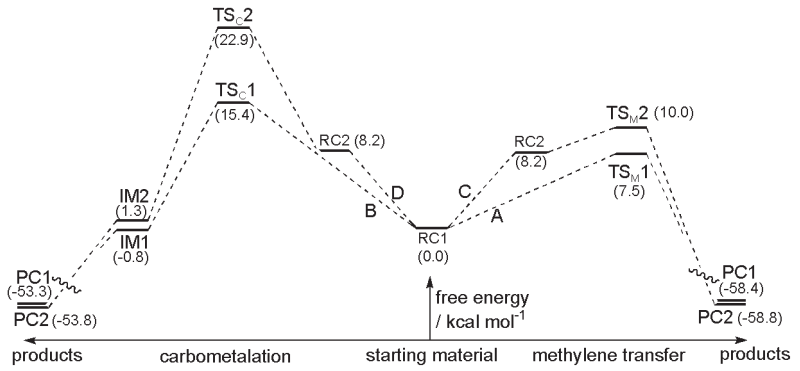


Figure 3. Free-energy profiles (computed at the B3LYP/6-311G**/PCM level of theory and by using a temperature of 173.15 K) for the different reaction paths of the cyclopropanation reactions of carbenoid **1.** Free energies relative to the starting materials are shown in parenthesis (in kcal mol^{-1}).

has 8.2 kcal mol^{-1} more free energy than RC1. This mainly arises from the absence of the interaction between the silyloxy group and the lithium centre. RC2 can proceed through the transition-state TS$_M$2 to form the bicyclohexane **4** and LiBr products (see path C for the methylene-transfer mechanism) or proceed through the four-centered transition-state TS$_C$2 to form the IM2 intermediate which then cyclizes to produce bicyclohexane **4** and LiBr products (see path D for the carbometalation mechanism). Unlike TS$_M$1 and TS$_C$1, both TS$_M$2 and TS$_C$2 have no interaction between the silyloxy group and the lithium centre. Figure 3 shows that the relative free energies of TS$_M$2 and TS$_C$2 are 10.0 and 22.9 kcal mol^{-1}, respectively.

Similar to carbenoid **1**, carbenoid **2** also has four different reaction paths for the cyclopropanation reactions (paths E–H, shown in Figure 2). Reaction path E (RC3→TS$_M$3→PC1) represents the Lewis base assisted methylene-transfer pathway. RC3 is the most stable conformation of carbenoid **2** and this appears to be due to a strong interaction between the silyloxy group and the lithium centre (the O–Li distance is 1.973 Å). However, the interaction between O and Li vanishes in the transition-state TS$_M$3, in which the lithium atom is at a position opposite to the silyloxy group. Figure 4 shows that the activation free energy for path E was calculated to be 8.9 kcal mol^{-1}. Path F (RC3→TS$_C$3→IM3→PC1) depicts the Lewis base assisted methylene-transfer pathway for carbenoid **2**. As RC3 proceeds to the transition-state TS$_C$3, there still exists a strong interaction between the silyloxy group and the lithium centre in TS$_C$3 (the O–Li distance is 1.961 Å). The activation free energy for path F was calculated to be 20.6 kcal mol^{-1} and this value is much higher than that for path E. Path G (RC3→RC4→TS$_M$4→PC2) represents a non-Lewis base assisted methylene-transfer pathway for carbenoid **2**. Firstly, carbenoid **2** needs to conformationally change from RC3 to RC4 for this reaction to occur. RC4 is higher in free energy by 2.9 kcal mol^{-1} than RC3 and this can be attributed to the absence of the interaction between the silyloxy group and the lithium centre. The silyloxy group lies on the equatorial bond of the six-membered ring in transition-state TS$_M$4 and there is no Lewis base assistance in this transition state. Figure 4 shows that the activation free energy for path G is 9.6 kcal mol^{-1} and this is very similar to the 8.9 kcal mol^{-1} for path E. Path H (RC3→RC4→TS$_C$4→IM4→PC2) depicts the non-Lewis base assisted carbometalation pathway for carbenoid **2**. There is no interaction between the silyloxy group and the lithium atom in TS$_C$4 and the activation free energy for path H was calculated to be 20.0 kcal mol^{-1}. This is higher

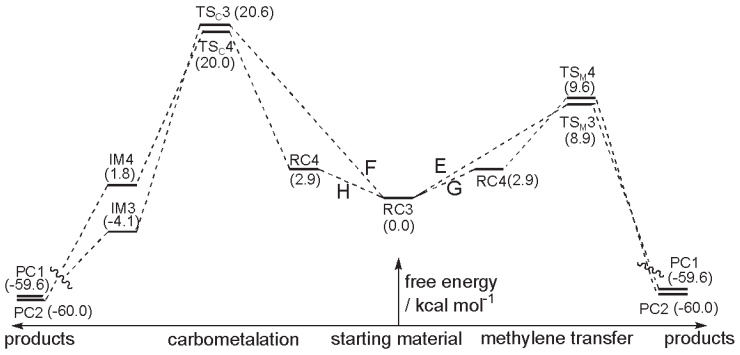


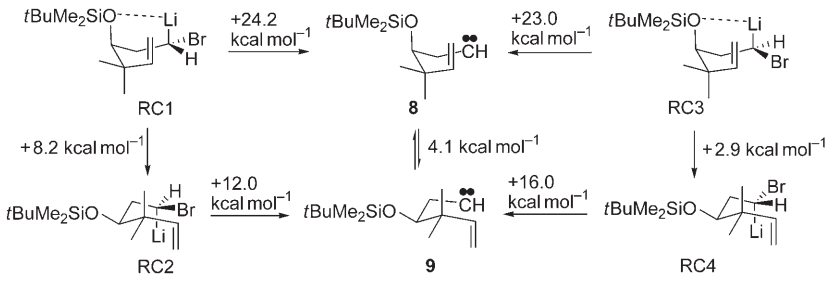
Figure 4. Free-energy profiles (computed at the B3LYP/6-311G**/PCM level of theory and by using a temperature of 173.15 K) for the different reaction paths of the cyclopropanation reactions of carbenoid **2**. Free energies relative to the starting materials are shown in parenthesis (in kcal mol^{-1}).

than that for path G (9.6 kcal mol^{-1}), but similar to that for path F (20.6 kcal mol^{-1}).

Analysis of the free energies shown in Figures 3 and 4 reveals that our theoretical results are consistent with the experimental observations of reference [22]. For carbenoid **1**, path A has the lowest activation free energy (7.5 kcal mol^{-1}) among the four reaction paths A–D. The relative free energy for transition state TS$_M$2 (10.0 kcal mol^{-1}, path C) is higher than that of TS$_M$1. The relative free energies for transition states TS$_C$1 (15.4 kcal mol^{-1}, path B) and TS$_C$2 (22.9 kcal mol^{-1}, path D) are much higher than that of TS$_M$1. This indicates that path A is predominantly favored for carbenoid **1** to produce a single bicyclohexane **3** product. With respect to carbenoid **2**, the reaction paths E and G are closely favored during cyclization. The relative free energies for transition states TS$_M$3 (path E) and TS$_M$4 (path G) are 8.9 and 9.6 kcal mol^{-1}, respectively. Inspection of Figure 4 shows that the other two path F and H have much higher activation free energies (20.6 kcal mol^{-1} for TS$_C$3 and 20.0 kcal mol^{-1} for TS$_C$4). Paths E and G compete with each other to produce a mixture of two bicyclohexanes **3** and **4** and this is in good agreement with the experimental observation that the stereomeric carbenoid **2** cyclizes to produce a mixture of two bicyclohexanes **3** and **4** (**3**/**4** 1.1:1). Furthermore, the experiments showed that carbenoid **1** can cyclopropanate at temperatures as low as −110 °C with a half-life of less than five minutes, while carbenoid **2** cyclizes at a higher temperature of −100 °C. Our results show that the lowest activation free energy for the cyclopropanation of carbenoid **1** is about 7.5 kcal mol^{-1} and this is lower than that of carbenoid **2** (8.9 kcal mol^{-1}). Thus, our calculations predict a faster reaction rate and a lower reaction temperature for the carbenoid **1** cyclopropanation reaction and this is consistent with experimental observations.

We highlight several points of insight gained from our current investigation and briefly discuss some mechanistic assumptions reported in previous studies.

The lithium-carbenoid-promoted cyclopropanation reaction proceeds solely through the methylene-transfer mechanism; the carbometalation mechanism, however, does not appear to make a significant contribution: The Lewis base assisted methylene-transfer pathway is the most-favored path for carbenoid **1** and is predicted to have the lowest activation free energy (7.5 kcal mol^{-1}). Both the Lewis base and non-Lewis base assisted carbometalation pathways for carbenoid **1** have much higher activation free energies of 15.4 kcal mol^{-1} for path B and 22.9 kcal mol^{-1} for path D. On the other hand, the activation free energies for the methylene-transfer pathways of carbenoid **2** are about 9 kcal mol^{-1} and these are also much lower than those of the carbometalation pathways for carbenoid **2** which are about 20 kcal mol^{-1}. These results indicate that the carbometalation mechanism cannot compete effectively with the methylene-transfer mechanism due to its much higher activation free energies. Further work was done to estimate the probability that the free carbene mechanism for carbenoids **1** and **2** could take place. As shown in Scheme 4, **8** and **9** are two stable conformers of the free carbene which can be formed from carbenoids **1** and **2**. However, the formation of the free carbenes **8** and **9** both need to overcome free energies higher than about 20 kcal mol^{-1} as computed at the B3LYP/6-311G**/PCM level of theory. The formation of carbene **8** from RC1 and RC3 are endothermic by 24.2 and 23.0 kcal mol^{-1}, respectively. Similarly, the formation of carbene **9** from RC1 and RC3 are endothermic by +20.2 and 18.9 kcal mol^{-1}, respectively. Considering that the activation free energies of the methylene-transfer pathways for carbenoids **1** and **2** are in the 7.5–9.6 kcal mol^{-1} range, the free carbene mechanism is not probable. This is in good agreement with the experimental observations that α-bromoalkyllithium compounds are



Scheme 4. Formation of free carbenes from carbenoids **1** and **2**.

both chemically and configurationally stable over the reaction temperature range of the cyclopropanation reactions.[39] It is interesting that the reaction barriers for the carbometalation mechanism are as high as those relative free energies computed for the formation of free carbenes. This provides further evidence that the carbometalation mechanism is not reasonable for the cyclopropanation reactions of carbenoids **1** and **2**. This conclusion is also indirectly supported by a recent theoretical study which found some other lithium-carbenoid-promoted cyclopropanation reactions proceed solely by the concerted methylene-transfer mechanism in aggregation and solvation states.[31] Our results here are also consistent with early reports that carbometalation is not involved in the cyclopropanation of alkenes by α-chloromethyllithim[30] and carbometalation of simple alkenes occurs with difficulty at a low temperature, such as −100 °C.[40]

Lewis base assistance cannot significantly help the carbometalation pathway to compete with the concerted methylene transfer pathway: Reference [22] suggested that Lewis-base assistance could help the carbometalation pathway to compete with the concerted methylene transfer pathway for carbenoid **2** and therefore lead to the mixed products of **3** and **4** seen in experiments (Scheme 3). Our results show that the Lewis base assisted carbometalation pathway (20.6 kcal mol^{-1}, path F) of carbenoid **2** has a similar activation free energy as the non-Lewis base assisted one (20.0 kcal mol^{-1}, path H). Analysis of the transition-state structures show that although TS_C3 has a strong interaction between the silyloxy group and the lithium center, the elongation of the Br–Li distance destabilizes the transition state. The Br–Li distance is 3.914 Å in TS_C3 and is much longer than that of TS_C4 (2.148 Å). Although TS_C4 has no interaction between the silyloxy group and the lithium center (the O–Li distance is 5.163 Å), the interaction between the bromine atom and the lithium center can compensate for the stability of TS_C4. Actually, the Lewis base assistance can decrease the activation free energy of the carbometalation for carbenoid **1** from 22.9 to 15.4 kcal mol^{-1}. But it still cannot compete with the Lewis base assisted methylene-transfer pathway which has an activation free energy of only 7.5 kcal mol^{-1}.

The methylene-transfer mechanism by itself can result in the experimentally observed stereochemical outcome: Competition between the methylene-transfer mechanism and the carbometalation mechanism was found to be unnecessary to explain the formation of mixed products from carbenoid **2**. Carbenoid **1** can cyclopropanate by the methylene-transfer mechanism through paths A and C. The Lewis base assisted path A (7.5 kcal mol^{-1}, activation free energy) is much more preferred than the non-Lewis base assisted path C (10.0 kcal mol^{-1}, activation free energy) and this results in the formation of a single bicyclohexane **3** product from carbenoid **1**. On the other hand, the cyclization of carbenoid **2** by the methylene-transfer mechanism also includes two paths, namely paths E and G. However, in this case, the Lewis base assisted path E (activation free energy of 8.9 kcal mol^{-1}) competes effectively with the non-Lewis base assisted path G (activation free energy of 9.6 kcal mol^{-1}), leading to a mixture of products **3** and **4**. This scenario can explain the experimental observations very well. To better understand the origin of the stereochemistry of this type of chiral lithium-carbenoid-promoted cyclopropanation reaction, we also investigated the role of selected factors which help determine the stereochemistry by the methylene-transfer mechanism.

Origin of stereochemistry:

Directing group/Lewis base assistance: Simmons and Winstein suggested early in the 1950s that a proximal Lewis base group could "direct" the delivery of the methylene moiety of the carbenoid.[12,13,41] The directing group/Lewis base assistance can enhance the rate of the reaction path to control the stereochemical outcome of the cyclopropanation reactions.[7] In this investigation, a Lewis base group at a position *meta* to the double bond can also direct the intramolecular cyclopropanation reaction. This interaction between the silyloxy group and the lithium centre (O–Li distance is 2.030 Å) can strongly stabilize the transition-state TS_M1 and lead to an enhancement of the rate of the path A reaction. In contrast, TS_M2 has a higher transition-state energy than TS_M1 due to the absence of the coordination interaction of the silyloxy group and the lithium centre. The Lewis base assistance thus directs the cyclization of carbenoid **1** to form a single bicyclohexane **3** product. However, it is surprising that the Lewis base group cannot direct the cyclization of carbenoid **2** to produce a similar stereoselective product. Both the transition states of paths E and G have no silyloxy–lithium interaction and this leads to competition between these two reaction paths to produce a mixture of bicyclohexane **3** and **4** products. This should be attributed to some other meaningful factor(s) than Lewis base assistance.

Configuration: Configuration is another key factor influencing the stereochemistry of this cyclization. Previous studies showed that the most stable isomer of the $LiCH_2X$ carbenoid is the one that has a X-bridged carbon–lithium bond.[42–44] As for carbenoid **1**, which has a chiral C^1 centre of *R* configuration, there exists a Br-bridged Li–C^1 bond in RC1. The C^1–Br distance is calculated to be 2.146 Å and the Li–Br distance is 2.550 Å. The Li-C^1-Br angle is 76.0°. The situation for carbenoid **2** is very different. With a chiral C^1 centre of *S* configuration, the most stable conformer of carbenoid **2** (RC3) has no Br-bridged Li–C^1 bond due to the steric repulsion between the bromine atom and the vinyl group. The C^1–Br distance is calculated to be 2.071 Å and the distance between the lithium centre and the bromine atom is 3.450 Å which is much longer than that in RC1. The Li-C^1-Br angle is 114.6° and is much greater than that in RC1 and even greater than the normal angle of a regular tetrahedron (109.5°). When RC proceeds to the "butterfly-type" transition state, the π electrons of the C^2=C^3 double bond nucleophilically attack the C^1–Br σ* bond and this is

accompanied by the bromine atom leaving the C^1 atom to go to the lithium center.[31] The leaving bromine atom is required to take the position opposite to the vinyl group in the transition state. As for carbenoid **1** (*R* configuration), there still exists an interaction between the silyloxy group and the lithium centre in the transition state TS_M1 of path A (here the O–Li distance is 2.030 Å) when the bromine takes the position opposite to the vinyl group. This directing-group assistance makes TS_M1 lower in free energy than the nondirecting-group-assisted TS_M2 by 2.5 kcal mol^{-1} and therefore leads to a single bicyclohexane **3** product for the cyclopropanation of carbenoid **1**. Because of the *S* configuration of the chiral C^1 centre for carbenoid **2**, the transition state TS_M3 of path E has no interaction between the silyloxy group and the lithium centre. When the bromine atom takes the position opposite to the vinyl group, the lithium center must take the position opposite to the silyloxy group, as shown in Figure 2. Thus, TS_M3 and the non-Lewis base assisted TS_M4 are similar in free energy and this results in effective competition between paths E and G. This is the origin for why carbenoid **2** cyclizes to furnish a mixture of bicyclohexanes **3** and **4** by means of the methylene-transfer mechanism.

Conclusion

A DFT computational study was reported for the different reaction paths of the intramolecular cyclopropanation reactions promoted by chiral carbenoids **1** and **2**. This investigation provides new insight into the reaction mechanisms. Previous literature reports have suggested that the formation of a mixture of products from the intramolecular cyclopropanation reaction promoted by the chiral carbenoid **2** should result from the competition between the methylene-transfer and the carbometalation pathways. Our results have demonstrated that this cyclopropanation reaction proceeds by the methylene-transfer mechanism and that the carbometalation mechanism does not appear to make a significant contribution because it has much higher activation free energy than the methylene-transfer mechanism. Our results also suggest that the Lewis base cannot enhance the carbometalation pathway enough to compete with the methylene-transfer pathway. Our results are in good agreement with experimental observations in the literature.

The factors influencing the stereoselectivity by the methylene-transfer mechanism were investigated to better understand the origin of the stereochemistry of the intramolecular cyclopropanation reactions examined. The directing group and the configuration of the C^1 centre were found to be the key factors determining the stereochemistry. Carbenoid **1** has a chiral C^1 centre of *R* configuration. The Lewis base group directs the cyclization of carbenoid **1** to form a single product. In contrast, the Lewis base group cannot direct the cyclization of carbenoid **2** to produce a similar stereoselective product due to the *S* configuration of the chiral C^1 centre in carbenoid **2**. The stereochemistry is revealed to be sensitive to the chiral character of the electrophilic carbon center of the lithium carbenoid. Our analysis here should assist in the design of carbenoid reagents for stereoselective cyclopropanation reactions.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (grant no. 20673149), the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry and grants from the Sun Yat-sen University to C.Y.Z. and the Research Grants Council of Hong Kong (HKU-7021/03P) to D.L.P.

[1] S. Patai, Z. Rappoport, *The Chemistry of the Cyclopropyl Group*, Wiley & Sons, New York, **1987**.
[2] A. J. DelMonte, E. D. Dowdy, D. J. Watson, *Top. Organomet. Chem.* **2004**, *6*, 97–122.
[3] H. Fritschi, U. Leutenegger, A. Pfaltz, *Angew. Chem.* **1986**, *98*, 1028–1029; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1005–1006.
[4] C. J. Suckling, *Angew. Chem.* **1988**, *100*, 555–570; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 537–552.
[5] M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49–92.
[6] A. de Meijere, *Small Ring Compounds in Organic Synthesis VI, Vol. 207*, Springer, Berlin, **2000**.
[7] H. Lebel, J. F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977–1050.
[8] J. Long, H. Du, K. Li, Y. Shi, *Tetrahedron Lett.* **2005**, *46*, 2737–2740.
[9] M. C. Lacasse, C. Poulard, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 12440–12441.
[10] J. F. Fournier, S. Mathieu, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 13140–13141.
[11] H. Du, J. Long, Y. Shi, *Org. Lett.* **2006**, *8*, 2827–2829.
[12] H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1958**, *80*, 5323–5324.
[13] H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1959**, *81*, 4256–4265.
[14] J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron Lett.* **1966**, *7*, 3353–3355.
[15] G. Wittig, F. Wingler, *Chem. Ber.* **1964**, *97*, 2146–2164.
[16] S. E. Denmark, J. P. Edwards, *J. Org. Chem.* **1991**, *56*, 6974–6981.
[17] G. L. Closs, R. A. Moss, *J. Am. Chem. Soc.* **1964**, *86*, 4042–4053.
[18] K. Maruoka, Y. Fukutani, H. Yamamoto, *J. Org. Chem.* **1985**, *50*, 4412–4414.
[19] K. Maruoka, S. Sakane, H. Yamamoto, *Org. Synth.* **1989**, *67*, 176–179.
[20] G. A. Molander, J. B. Etter, P. W. Zinke, *J. Am. Chem. Soc.* **1987**, *109*, 453–463.
[21] G. A. Molander, L. S. Harring, *J. Org. Chem.* **1989**, *54*, 3525–3532.
[22] H. C. Stiasny, R. W. Hoffmann, *Chem. Eur. J.* **1995**, *1*, 619–624.
[23] M. G. B. Drew, L. M. Harwood, A. J. Macias-Sanchez, R. Scott, R. M. Thomas, D. Uguen, *Angew. Chem.* **2001**, *113*, 2373–2375; *Angew. Chem. Int. Ed.* **2001**, *40*, 2311–2313.
[24] W. T. Miller, D. M. Whalen, *J. Am. Chem. Soc.* **1964**, *86*, 2089–2090.
[25] Z.-H. Li, Z. F. Ke, C. Y. Zhao, Z.-Y. Geng, Y.-C. Wang, D. L. Phillips, *Organometallics* **2006**, *25*, 3735–3742.
[26] C. Y. Zhao, D. Q. Wang, D. L. Phillips, *J. Am. Chem. Soc.* **2003**, *125*, 15200–15209.
[27] A. Hirai, M. Nakamura, E. Nakamura, *Chem. Lett.* **1998**, 927–928.
[28] M. Nakamura, A. Hirai, E. Nakamura, *J. Am. Chem. Soc.* **2003**, *125*, 2341–2350.
[29] H. Hoberg, *Liebigs Ann. Chem.* **1962**, *656*, 1–14.
[30] U. Burger, R. Huisgen, *Tetrahedron Lett.* **1970**, *11*, 3049–3051.
[31] Z. F. Ke, C. Y. Zhao, D. L. Phillips, *J. Org. Chem.* **2007**, *72*, 848–860.
[32] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789.

[33] E. Niecke, P. Becker, M. Nieger, D. Stalke, W. W. Schoeller, *Angew. Chem.* **1995**, *107*, 2012–2015; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1849–1852.
[34] C. Gonzalez, H. B. Schlegel, *J. Chem. Phys.* **1989**, *90*, 2154–2161.
[35] C. Gonzalez, H. B. Schlegel, *J. Phys. Chem.* **1990**, *94*, 5523–5527.
[36] Gaussian 03, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, 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, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**.
[37] M. Cossi, G. Scalmani, N. Rega, V. Barone, *J. Chem. Phys.* **2002**, *117*, 43–54.
[38] A. Bondi, *J. Phys. Chem.* **1964**, *68*, 441–451.
[39] R. W. Hoffmann, M. Bewersdorf, *Chem. Ber.* **1991**, *124*, 1259–1264.
[40] W. F. Bailey, A. D. Khanolkar, T. V. Ovaska, K. Rossi, Y. Thiel, K. B. Wiberg, *J. Am. Chem. Soc.* **1991**, *113*, 5720–5727.
[41] S. Winstein, J. Sonnenberg, L. De Vries, *J. Am. Chem. Soc.* **1959**, *81*, 6523–6524.
[42] G. Boche, J. C. W. Lohrenz, *Chem. Rev.* **2001**, *101*, 697–756.
[43] J. Mareda, N. G. Rondan, K. N. Houk, T. Clark, P. v. R. Schleyer, *J. Am. Chem. Soc.* **1983**, *105*, 6997–6999.
[44] L. M. Pratt, B. Ramachandran, J. D. Xidos, C. J. Cramer, D. G. Truhlar, *J. Org. Chem.* **2002**, *67*, 7607–7612.

Received: January 29, 2007
Published online: May 16, 2007

