CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201103495

Highly Diastereoselective Construction of Fused Carbocycles from Cyclopropane-1,1-dicarboxylates and Cyclic Enol Silyl Ethers: Scope, Mechanism, and Origin of Diastereoselectivity

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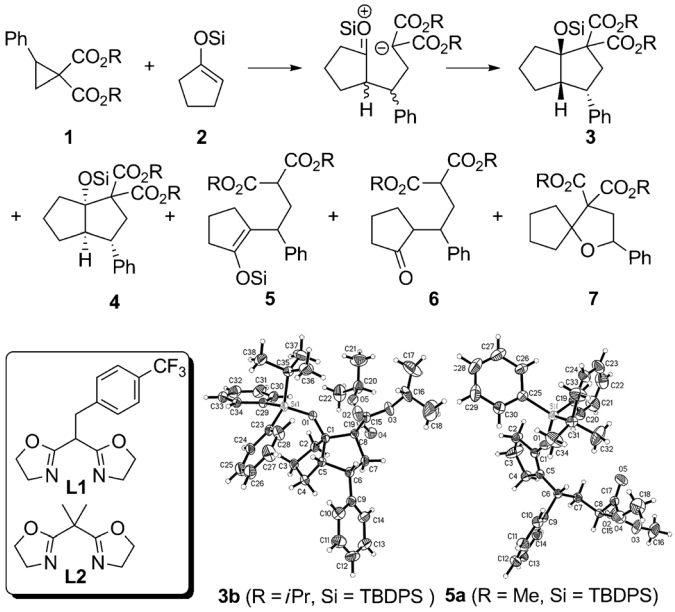
Five-membered carbocycles are present in a vast array of organic molecules, including pharmaceutical agents and natural products. Efficient and elegant syntheses, in particular, the stereoselective construction of fused five-membered carbocycles with multiple contiguous stereocenters, are of long-standing interest to organic chemists.[1] Although various methods for the construction of these carbocycles based on [3+2] cycloaddition reactions have proved successful,[2] a challenge inherent to this strategy resides in the control of the diastereoselectivities, especially in the [3+2] reactions of donor–acceptor cyclopropanes with carbon–carbon double bonds.[3] For example, the groups of Snider[3b] and Kuwajima[3f,g] have reported the annulation of alkenes with 2-substituted cyclopropanes induced by stoichiometric amounts of Lewis acids, which provided functionalized cyclopentanes in good yields but with poor diastereoselectivities. The catalytic version developed by the groups of Sugita[3h] and Takasu[3j] also provided mixtures of diastereomers.

As part of a program devoted to the development of new synthetic methods involving donor–acceptor cyclopropanes, which have been widely used in many synthetic transformations,[3–8] we recently reported the first ligand-switchable cycloaddition/ring-opening reaction of 2-substitued cyclopropane-1,1-dicarboxylates with enol silyl ethers, providing cyclopentane derivatives or 1,6-dicarbonyl compounds.[3l] However, the treatment of cyclic enol silyl ether **2** with cyclopropane **1** gives rise to two diastereomers of [3+2] cycloadducts and several byproducts (Scheme 1), which are difficult to separate, as reported in the literature.[3] With the intention of addressing this problem, our ongoing efforts were devoted to exploring the diastereoselective synthesis of bicyclic carbon skeletons with multiple contiguous stereocenters and investigating the reaction mechanism. Herein, we report the first successful realization of highly diastereoselective [3+2] cycloadditions of cyclopropane-1,1-dicarboxylates with cyclic enol silyl ethers and density functional theory (DFT) computations to understand the reaction mechanism and origin of the diastereoselectivity.



Scheme 1. Initial studies of the reaction of cyclopropanes **1** with enol silyl ethers **2**, structures of ligands **L1** and **L2**, and X-ray structures of cycloadduct **3b** and byproduct **5a**.[9]

Our previous experiments suggested that ligands can inhibit the formation of ring-opened products **6** by modulating the Lewis acidity of the catalyst, and that molecular sieves can suppress the formation of compounds **7**.[3l] For example, the reaction of cyclopropane **1a** (R = Me) with enol silyl ether **2a** (Si = TBDPS), catalyzed by $Cu(SbF_6)_2$ (10 mol%) in the presence of **L1**, carried out in 1,2-dichloroethane at 80 °C with 4 Å molecular sieves as an additive, gave the [3+2] cycloadducts **3a** and **4a** in a diastereoselectivity of

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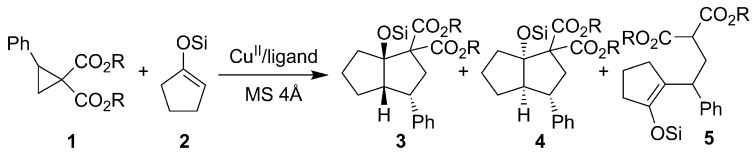
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201103495.

Table 1. Selected conditions for the optimization of [3+2] cycloaddition reactions of cyclopropanes with enol silyl ethers.[a]



1a R = Me, **1b** R = Ph, **1c** R = Et
1d R = Bn, **1e** R = *i*Pr, **1f** R = *i*Bu
1g R = CH_2*t*Bu, **1h** R = 2-adamantyl,
1i R = 2,4-dimethyl-3-pentyl
1j R = 1-adamantyl, **1k** R = *t*Bu

2a Si = TBDPS
2b Si = TIPS
2c Si = TBS
2d Si = TMS

Entry	R	Si	Conversion [%][e]	**3+4** [%][e]	d.r. (**3**/**4**)[e]	**5** [%][e]
1	**1a**	**2a**	100	68	79:21	32
2	**1b**	**2a**	100	65	78:22	35
3	**1c**	**2a**	99	68	94:6	32
4	**1d**	**2a**	100	79	91:9	21
5	**1e**	**2a**	100	70	>99:1	30
6	**1f**	**2a**	100	72	>99:1	28
7[b]	**1g**	**2a**	98	80 (70)[f]	>99:1	20
8	**1h**	**2a**	100	85	>99:1	15
9[c]	**1h**	**2a**	100	87 (80)[f]	>99:1	13
10[b]	**1i**	**2a**	42	82	>99:1	18
11[b]	**1j**	**2a**	0	–	–	–
12[b]	**1k**	**2a**	0	–	–	–
13[d]	**1h**	**2a**	100	82	>99:1	18
14[d]	**1h**	**2b**	87	82	>99:1	18
15[d]	**1h**	**2c**	100	93	65:35	7
16[d]	**1a**	**2d**	100	95	54:46	5
17[c]	**1a**	**2d**	100	95	54:46	5

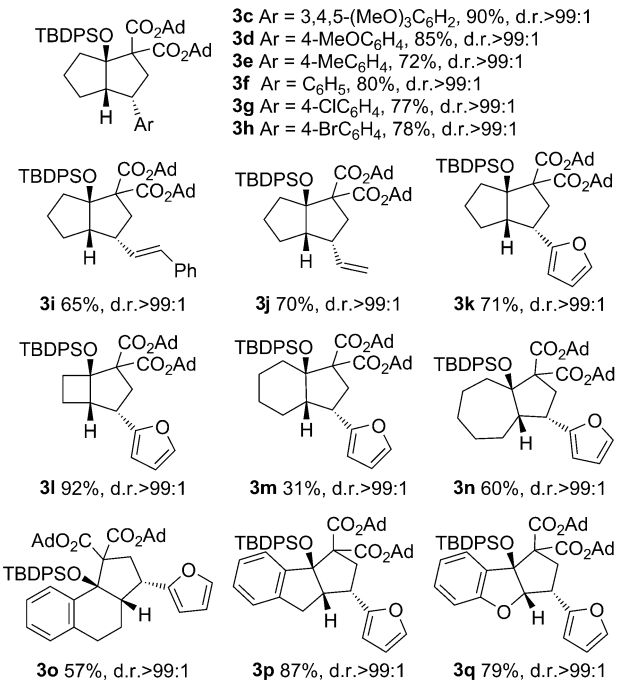
[a] Reaction conditions: $CuBr_2$ (0.01 mmol), $AgSbF_6$ (0.02 mmol), **L1** (0.01 mmol), **1** (0.10 mmol), and **2** (0.20 mmol) in 1,2-dichloroethane (0.5 mL) at 80 °C with 4 Å molecular sieves under a N_2 atmosphere. Bn = benzyl, TBDPS = *tert*-butyldiphenylsilyl, TIPS = triisopropylsilyl, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl. [b] $CuBr_2$ (0.02 mmol), $AgSbF_6$ (0.04 mmol), and **L1** (0.02 mmol) were used. [c] CH_2Cl_2 was used at RT. [d] **L2** was used instead of **L1**, and CH_2Cl_2 was used at RT. [e] Convertion of **1** and ratio of **3**, **4**, and **5** were determined by ^1H NMR spectroscopy. [f] Isolated yield.

79:21 and 68% yield and byproduct **5a** in 32% yield, as shown by NMR spectroscopy (Table 1, entry 1). Since further optimization shows that ligands have only a slight influence on the chemoselectivity and diastereoselectivity (for details, see the Supporting Information), we envisioned that the ester groups on the cyclopropane ring may have a significant influence on the selectivity. Therefore, a variety of cyclopropanes **1**, bearing different ester groups, were synthesized and investigated in the [3+2] cycloaddition reaction.

When the R group of the ester was switched from an aliphatic methyl group to an aromatic phenyl group, there was almost no change in selectivity (Table 1, entry 2), indicating that the electronic effect of the ester has little influence on this reaction. However, when an ethyl group was used instead of the methyl group, although the chemoselectivity did not change, the ratio of the two [3+2] cycloadducts increased to 94:6 (Table 1, entry 3). This suggests that the steric bulk of the R group is important in controlling the diastereoselectivity of this reaction. To our delight, the reaction of cyclopropane **1e**, bearing a larger R group (R = *i*Pr), gave only one [3+2] product, **3b**, along with a 30% yield of byproduct **5b** (Table 1, entry 5). The best result, however, was obtained by using rigidly bulky 2-adamantyl as the R group of the diester (Table 1, entry 8). When the reaction was carried out at room temperature in dichloromethane, the NMR yield of the desired [3+2] cycloadduct further increased to 87% (Table 1, entry 9). No further improvement was observed by reducing the catalyst loading or lowering the temperature to 0 °C. Noticeably, sterically much bulkier 1-adamantyl and *tert*-butyl ester substituted cyclopropanes did not undergo the [3+2] reactions, probably due to too strong steric repulsion in the cycloaddition transition states (Table 1, entries 11 and 12).

We found that the size of the silyl group also played an important role in the diastereoselectivity of the [3+2] cycloaddition. For instance, in the reactions of cyclopropane **1h** with enol silyl ethers **2a–c** (Table 1, entries 13–15), ether **2c**, bearing a relatively small silyl group (TBS) gave two diastereomers of [3+2] cycloadducts in quite a low ratio of 65:35. Furthermore, when both the silyl and ester groups were small (Si = TMS, R = Me), the [3+2] reactions afforded mixtures of diastereomers with almost no selectivity (Table 1, entries 16 and 17).

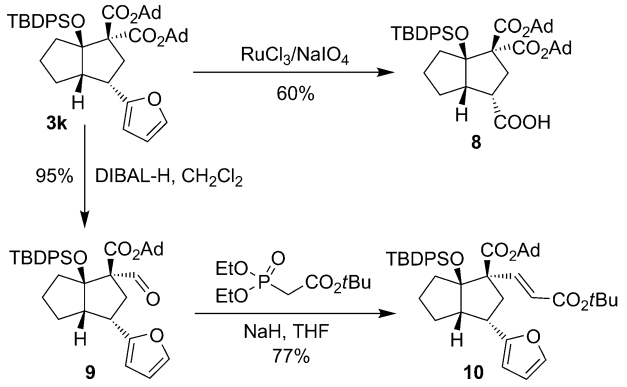
Under the optimal conditions, we next evaluated the scope and generality of the [3+2] cycloaddition of cyclopropane-1,1-dicarboxylates and cyclic enol silyl ethers. As shown in Scheme 2, a variety of cyclopropanes reacted smoothly with enol silyl ether **2a** to afford [3+2] cycloadducts **3c–k** in excellent diastereoselectivities (d.r. > 99:1). Cyclopropanes with both electron-rich and electron-deficient phenyl groups could be efficiently converted into the



Scheme 2. The [3+2] cycloaddition reactions of cyclopropane-1,1-dicarboxylates with cyclic enol silyl ethers (Ad = 2-adamantyl).

desired products in good yields. The reactions of cyclopropanes bearing styryl, vinyl, and 2-furyl groups also worked well, affording [3+2] products **3i–k** exclusively, which could easily be further functionalized and transformed. Next, a series of enol silyl ethers with a different type or size of ring system were evaluated with the 2-furyl-substituted cyclopropane by using $Cu(SbF_6)_2$/**L1** (5 mol%) as the catalyst system. It was found that all of these reactions diastereoselectively gave the desired [3+2] cycloadducts as various fused-ring systems in moderate to good yields.

Highly functionalized ring-fused five-membered carbocycles are potentially useful in organic synthesis and pharmaceutical science. For example, the furyl group in **3k** can be easily oxidized to form a carboxyl group by treatment with $RuCl_3/NaIO_4$ (Scheme 3). The DIBAL-H reduction of **3k**, followed by a Horner–Wadsworth–Emmons reaction gave product **10** with four contiguous stereocenters as a single diastereomer (Scheme 3). The relative configuration of aldehyde intermediate **9** was confirmed by X-ray diffraction



Scheme 3. Transformations of product **3k**.

analysis.[9]

We applied DFT calculations by using the (U)B3LYP method[10] to study the reaction mechanisms of two representative reactions **A** and **B** (Figure 1) and rationalize the method by which the substituents on the ester and silyl groups influence the diastereoselectivity of the [3+2] cycloaddition reaction.[11] Our mechanistic studies started from the commonly accepted complex **C** because the formation of **C** from cyclopropane-1,1-dicarboxylate **1** and the copper catalyst Cu^{2+}**L2** is highly exergonic.[12] It is interesting to note that the C1−C2 bond in the cyclopropane in complex **C** is about 0.15 Å longer than the C1−C3 bond (Figure 1, and for DFT-calculated structures, see Figure S3 in the Supporting Information). This indicates that the C1−C2 bond will be broken much more easily. DFT calculations further revealed that complex **C** can react at the C2 position with enol silyl ether **2** to generate two different zwitterionic intermediates **I-*cis*** and **I-*trans*** through transition states **TS1-*cis*** and **TS1-*trans***, respectively (Figure 1). In the zwitterionic intermediate **I-*cis***, the carbanion functions as either a nucleophile to attack the silylcarboxonium (via transition state **TS2-*cis***) to form one [3+2] cycloadduct **3** with two methine hydrogen atoms in a *cis* configuration, or as a base to abstract the methine proton at the α-position of the silylated carbonyl group (via transition state **TS3-*cis***) to generate byproduct **5**. Similarly, from **I-*trans***, the other [3+2] cycloadduct **4** with two methine hydrogen atoms in a *trans* configuration and byproduct **5** can be generated. Therefore, the selectivity of this reaction depends on the relative energies in these transformations. Our DFT calculations indicate that the steric effect of substituents on the ester and silyl groups is responsible for obtaining high diastereoselectivities in the [3+2] cycloaddition reaction.[13]

In reaction **A** (R = Me, Si = TMS, Figure 1), the generation of zwitterionic intermediates **I-*cis*** and **I-*trans*** through nucleophilic attack of enol silyl ether **2** on the copper(II) activated cyclopropane in complex **C** is rate determining and irreversible,[14] requiring activation free energies of 15.7 and 15.4 kcal mol^{-1} in CH_2Cl_2, respectively (Figure 1, blue line). The very close energies suggest that these two intermediates will be formed in nearly equal amounts. From **I-*cis***, the [3+2] cycloadduct **3** will be generated exclusively through **TS2-*cis*** because the transition state **TS3-*cis***, which gives byproduct **5**, is higher in energy than **TS2-*cis*** by 7.0 kcal mol^{-1} (Figure 1). However, cycloadduct **4** along with a minor amount of byproduct **5** will be generated from **I-*trans***. This is because the activation free energy of the transformation of **I-*trans*** into **5** is just 1.3 kcal mol^{-1} higher than that of the intramolecular cyclization through **TS2-*trans*** (14.2 versus 12.9 kcal mol^{-1}, Figure 1). Therefore, the computational results show that the major products of reaction **A** are the [3+2] cycloadducts **3** and **4**, but the ratio of **3** to **4** is poor (about 1:1). This computational result is in good agreement with the experimental results (Table 1, entry 16).

In reaction **B** (R = *i*Pr, Si = TBDPS, Figure 1), there is still no clear preference for the generation of zwitterionic intermediate **I-*cis*** or **I-*trans***. This is because the free energy difference between the two nucleophilic attack transition states **TS1-*cis*** and **TS1-*trans*** is only 0.8 kcal mol^{-1} (20.9 versus 21.7 kcal mol^{-1}, Figure 1, red line). In contrast to reaction **A**, for which the rate-determining step is the first step (nucleophilic attack), reaction **B** has the intramolecular cyclization as the rate-limiting step. As a result, the diastereoselectivity of this reaction will be determined by the free-energy difference between the two cyclization transition states **TS2-*cis*** and **TS2-*trans***. According to the DFT calculations, transition state **TS2-*cis***, leading to product **3**, is 2.8 kcal mol^{-1} lower in energy than transition state **TS2-*trans***, giving product **4** (24.4 versus 27.2 kcal mol^{-1}, Figure 1), which predicts a **3/4** ratio of 110:1 at 298 K. This is consistent with the experimentally observed excellent diastereoselectivity (d.r. > 99:1, Table 1, entry 5). Furthermore, the DFT calculations indicate that a 21% yield of byproduct **5** will also be generated from **I-*trans*** (via **TS3-*trans***, 25.2 kcal mol^{-1}, 0.8 kcal mol^{-1} higher than **TS2-*cis***, Figure 1), which is also close to the experimental result.

In both reactions **A** and **B**, the selectivity of the first step (nucleophilic attack) is poor, but the selectivity of the second step (intramolecular cyclization) is high. However, in

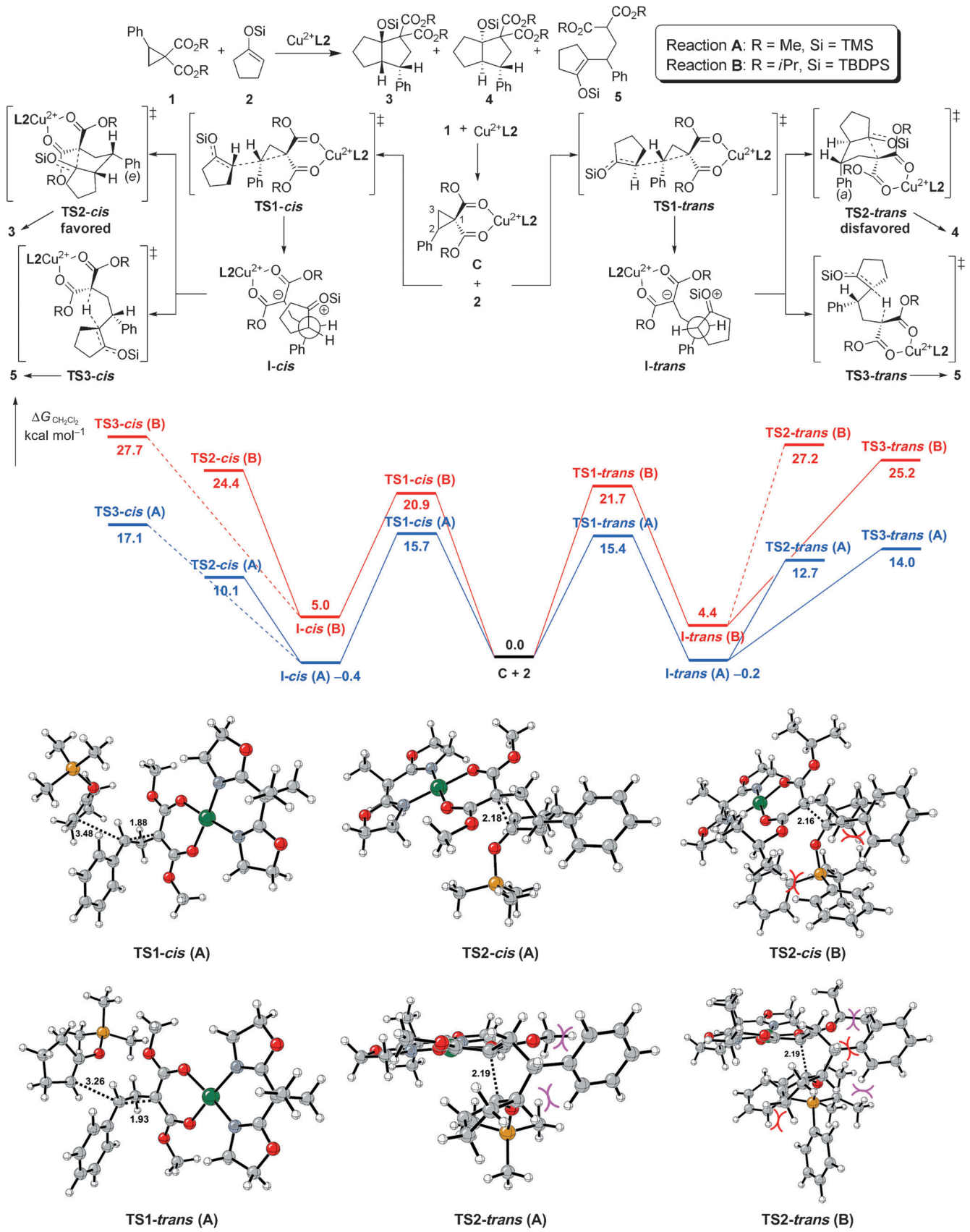


Figure 1. DFT studies on the [3+2] cycloaddition reactions of cyclopropanes with enol silyl ethers, involving different substituents on the ester and silyl groups, DFT-calculated free-energy surfaces (Reaction **A**: blue line; Reaction **B**: red line), and the structures of several representative transition states (C gray; H white; O red; N blue; Si yellow; Cu green; distances are given in Å).

the case of reaction **A**, the first step is rate determining and irreversible, thus leading to the whole reaction being performed without clear diastereoselectivity. In contrast, the second step is rate limiting in reaction **B**, which makes the [3+2] cycloaddition reaction highly diastereoselective. By analyzing the structures of transition states **TS1-*cis*** and **TS1-*trans*** (Figure 1),[15] we found that the C–C bonds forming between the C=C double bond in **2** and the cyclopropane ring in **C** are quite long (around 3.3 Å), which was further supported by intrinsic reaction coordinate (IRC) calculations.[16] Therefore, different orientations of the silyl group in nucleophilic attack transition states **TS1-*cis*** and **TS1-*trans*** could not result in a significant energy difference. In the cyclization transition state **TS2-*cis*** (Figure 1), the phenyl group is in a pseudoequatorial position with respect to the forming five-membered ring, suggesting less (or no) steric repulsion between the phenyl group and other substituents on the five-membered ring. However, in **TS2-*trans***, the phenyl group is in a pseudoaxial position and has clear 1,3-eclipsing interactions with both the ester and silyl groups. As a result, transition state **TS2-*trans*** is higher in energy than **TS2-*cis*** by 2.6 and 2.8 kcal mol^{-1} in reactions **A** and **B**, respectively. More importantly, in both **TS2-*cis* (B)** and **TS2-*trans* (B)**, the larger silyl group suffers from very severe steric repulsions from both the ester group and the original five-membered ring in substrate **2** that are absent in **TS2-*cis* (A)** and **TS2-*trans* (A)** (Figure 1). Therefore, the free-energy barriers to form **TS2-*cis*** and **TS2-*trans*** in reaction **B** dramatically increase by about 14 kcal mol^{-1} as compared with those in reaction **A**, that is, when the size of the substituents on the ester and silyl groups is increased from reaction **A** to **B**. This significant change makes the highly selective intramolecular cyclization step become rate determining in reaction **B**, and thus an excellent diastereoselectivity is obtained.

In conclusion, we successfully developed a method for the diastereoselective construction of highly functionalized fused cyclopentane derivatives with multiple contiguous stereocenters through Cu^{II}/bisoxazoline-catalyzed intermolecular [3+2] cycloaddition reactions of cyclopropane-1,1-dicarboxylates and cyclic enol silyl ethers. High efficiency, high selectivity, easy transformation of the multifunctional groups, and the use of an inexpensive copper catalyst potentially make this new method useful. The mechanism and origin of the diastereoselectivity were studied by DFT calculations. From the calculations, we discovered that this [3+2] reaction is stepwise, and that the selectivity of its first step (nucleophilic attack) is poor, but its second step (intramolecular cyclization) is highly selective. Increasing the size of substituents on the ester and silyl groups can greatly increase the energies of the cyclization transition states. This makes the second step rate determining, and thus allows excellent diastereoselectivity to be obtained. These mechanistic insights will be helpful in understanding the selectivity of other cycloaddition reactions. Further studies on the asymmetric version of this reaction and its application in synthesis are ongoing.

Acknowledgements

We are grateful for financial support from the Natural Sciences Foundation of China (No. 20821002, 20932008, and 20825205), the Major State Basic Research Development Program (No. 2009CB825300), and the Chinese Academy of Sciences.

Keywords: cycloaddition · cyclopropane · density functional calculations · diastereoselectivity · reaction mechanisms

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[11] All of the geometry optimizations and frequency calculations were performed with the (U)B3LYP functional implemented in Gaussian 03. For all monoradical species, the UB3LYP method was used, whereas for even-electron species, the B3LYP method was used. The LANL2DZ basis set and pseudopotential were used for copper and the 6-31G(d) basis set was used for all other atoms. Solvent effects were computed at the (U)B3LYP/6–311G(d,p)-LANL2DZ level by using the CPCM model in CH_2Cl_2. All energies discussed in the paper are Gibbs free energies in CH_2Cl_2. Computational details and references are given in the Supporting Information. We must point out that the computed activation enthalpies of the nucleophilic attack steps are negative in the gas phase. This phenomenon is often observed in modeling gas-phase ion/molecule reactions, see: Y.-h. Lam, P. H.-Y. Cheong, J. M. B. Mata, S. J. Stanway, V. Gouverneur, K. N. Houk, *J. Am. Chem. Soc.* **2009**, *131*, 1947, and references therein.

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[14] Considering the overestimation of entropic contributions in solution for a bimolecular process, the free-energy barriers in CH_2Cl_2 to form **TS1-*cis*** and **TS1-*trans*** from **2** and **C** in reaction **A** (15.7 and 15.4 kcal mol^{-1}, Figure 1) may be overestimated, making this step not rate determining. However, this step is irreversible. The path from the generated **I-*cis* (A)** to the [3+2] product is easier by 5.6 kcal mol^{-1} than the return to reactants **C** and **2**. The same is true for the generated **I-*trans* (A)**, which favors giving **4** and **5** instead of the reactants. There are no (or negligible) entropy overestimations for the processes starting from intermediates **I-*cis* (A)** and **I-*trans* (A)**. Therefore, the diastereoselectivity of the reaction is still mainly controlled by the free-energy difference between transition states **TS1-*cis* (A)** and **TS1-*trans* (A)**.

[15] The DFT-calculated structures of transition states **TS1-*cis* (B)** and **TS1-*trans* (B)** are provided in the Supporting Information.

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Received: November 7, 2011
Revised: December 16, 2011
Published online: January 20, 2012

