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Studies on the ring-opening of bicyclic cyclopropanes activated by a carbonyl group

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ABSTRACT

Studies on the Friedel–Crafts reaction between carbonyl bicyclic cyclopropane and electronic-rich aromatic systems were conducted. Lewis acid and iminium cationic activation methods were examined. It was found that the cyclopropane ring-opening was highly dependent on the nature of the counter nucleophile as well as the activation method.

The cyclopropane is an important motif in organic synthesis. Among the cyclopropane-related reactions,[1,2] cyclopropane ring-opening processes are frequently reported. The unique three-membered ring structure of cyclopropanes (both strain[3] and electronic features[4]) allows them to demonstrate activity similar to alkenes. In order to enhance the reactivity of cyclopropanes, donor–acceptor or 1,3-dicarbonyl groups are commonly introduced.[5,6] Although good reactivity and selectivity can be achieved, these structural requirements somewhat limit the scope and applicability.

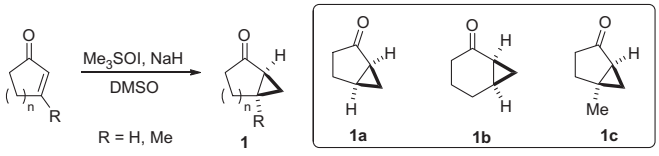
Compared to the above-mentioned cyclopropane activation methods, the use of mono-activated cyclopropane towards nucleophilic addition is rare. Herein, we report our recent progress on the study of the Friedel–Crafts reaction using carbonyl bicyclic cyclopropanes.

Our study was initiated by using cyclopropane **1** which could readily be synthesized by cyclopropanation of the corresponding unsaturated carbonyl-containing cycloalkenes (Scheme 1).

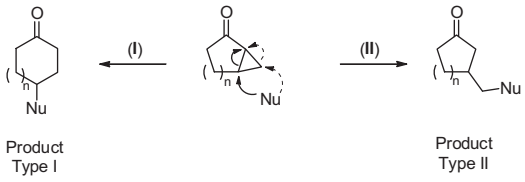
We reasoned that the ring strain due to the bicyclic system might facilitate ring-opening in the presence of a single carbonyl unit. It is noteworthy that for such bicyclic system, two bonds in the cyclopropane moiety are 'conjugated' to the carbonyl group; that is, both type I and type II products can potentially be obtained through this cyclopropane ring-opening activity (Scheme 2).

Thus, **1a** was subjected to the Friedel–Crafts reaction using 1,3,5-trimethoxybenzene as the nucleophile. Tin(IV) chloride was used as the Lewis acid to mediate the reaction. To our delight, compound **2a**, which corresponds to the type I product, was obtained in 52% yield (Table 1). The structure of **2a** was confirmed unambiguously by an X-ray crystallographic study[7] (Fig. 1).

Substrate **1b** was then subjected to the same conditions, but no reaction was observed. Nonetheless, product **2b**, which corre-



Scheme 1. Synthesis of carbonyl bicyclic cyclopropane.



Scheme 2. Synthesis of carbonyl bicyclic cyclopropane.

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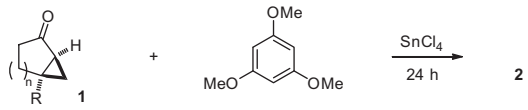
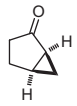
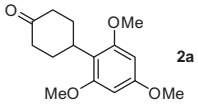
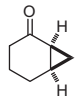
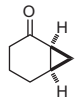
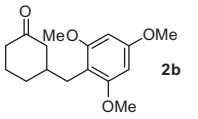
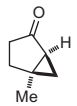
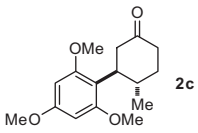
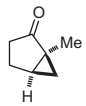
Table 1
Cyclopropane ring-opening reaction with 1,3,5-trimethoxybenzene promoted by $SnCl_4$



Entry[a]	Substrate	Solvent	Temp (°C)	Product	Isolated yield (%)
1	 **1a**	CH_2Cl_2	25	 **2a**	52
2	 **1b**	CH_2Cl_2	25	No reaction	
3	 **1b**	PhCl	60	 **2b**	45
4	 **1c**	CH_2Cl_2	25	 **2c**	63
4	 **1d**	PhCl	60	No reaction	

[a] Reactions were carried out with cyclopropane 1 (1.0 mmol), 1,3,5-trimethoxybenzene (1.1 mmol) and $SnCl_4$ (1.0 mmol) in solvent (2 mL).

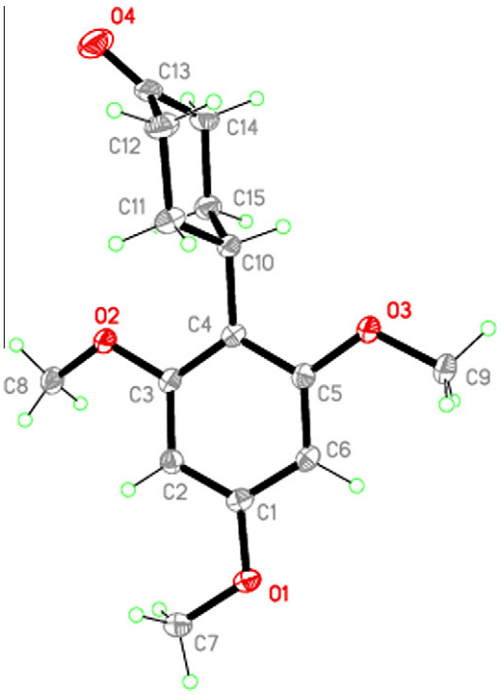


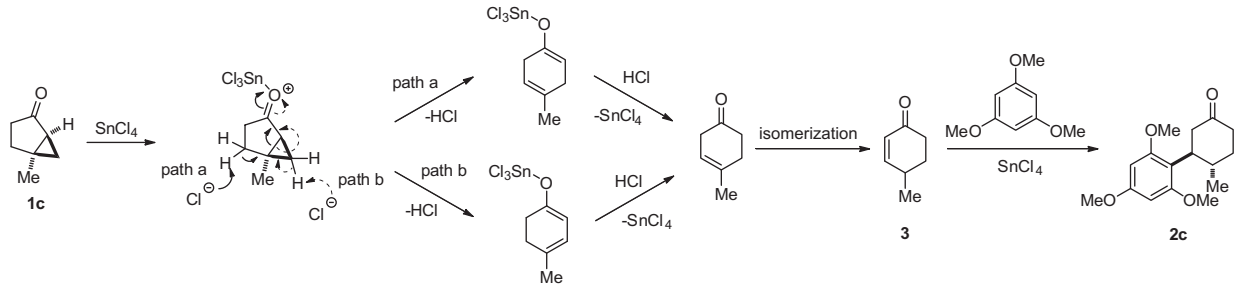
Figure 1. X-ray structure (ORTEP) of **2a**.

sponds to type II nucleophilic attack, was obtained in 45% yield when the reaction was conducted in chlorobenzene at 60 °C.[8] Compared to **1a**, there is no type I product in the ring-opening reaction of **1b**. A possible explanation is that type I ring-opening of **1b** involves the formation of a highly ring strain seven-membered ring system, which is energetically unfavourable (Table 1).

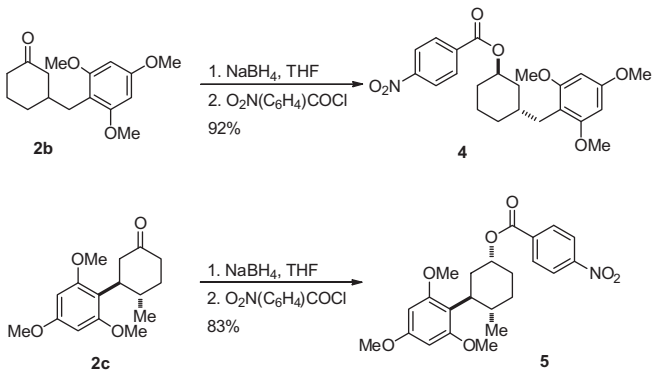
When using **1c** as the substrate, interestingly, **2c** was isolated in 63% yield and neither the type I nor the type II product was detected. We rationalize that this result can be explained by the pathway depicted in Scheme 3 which involves the formation of α,β-unsaturated ketone **3** from **1c** promoted by $SnCl_4$.[9] We have also examined cyclopropane **1d**, but no reaction was observed and the starting material was recovered quantitatively.

The structures and stereochemistry of products **2b** and **2c** were established by crystallographic analysis of the benzoate derivatives **4** and **5,** which could readily be synthesized from **2b** and **2c** through a reduction-esterification sequence (Scheme 4 and Fig. 2).[7] Interestingly, adducts **2** and their derivatives **4** and **5** resemble the structures of several biologically active compounds.[10]

We also examined an alternative activation mode, which involves an iminium cation derived from pyrrolidine (Table 2).[11] When using anthrone as the nucleophile, both **1a** and **1b** gave rise to the type II ring-opening products **6a** and **6b** which were isolated in 78% and 56% yields, respectively. However, there was no reaction when using 1,3,5-trimethoxybenzene as the nucleophile.[12]



Scheme 3. Plausible mechanisms for the synthesis of **2c**.



Scheme 4. Synthesis of derivatives **4** and **5**.

This suggests that the reaction is highly dependent on both the nature of the nucleophile as well as the mode of activation.

In summary, we have reported the use of carbonyl bicyclic cyclopropane in Friedel–Crafts reactions. The type of cyclopropane ring-opening appears to be highly dependent on various factors. Further investigations on the mechanism and applications are underway.

Acknowledgements

We thank the National University of Singapore for financial support (Grant No. 143-000-509-112) and the scholarship to X. Jiang (NUS Research Scholarship).

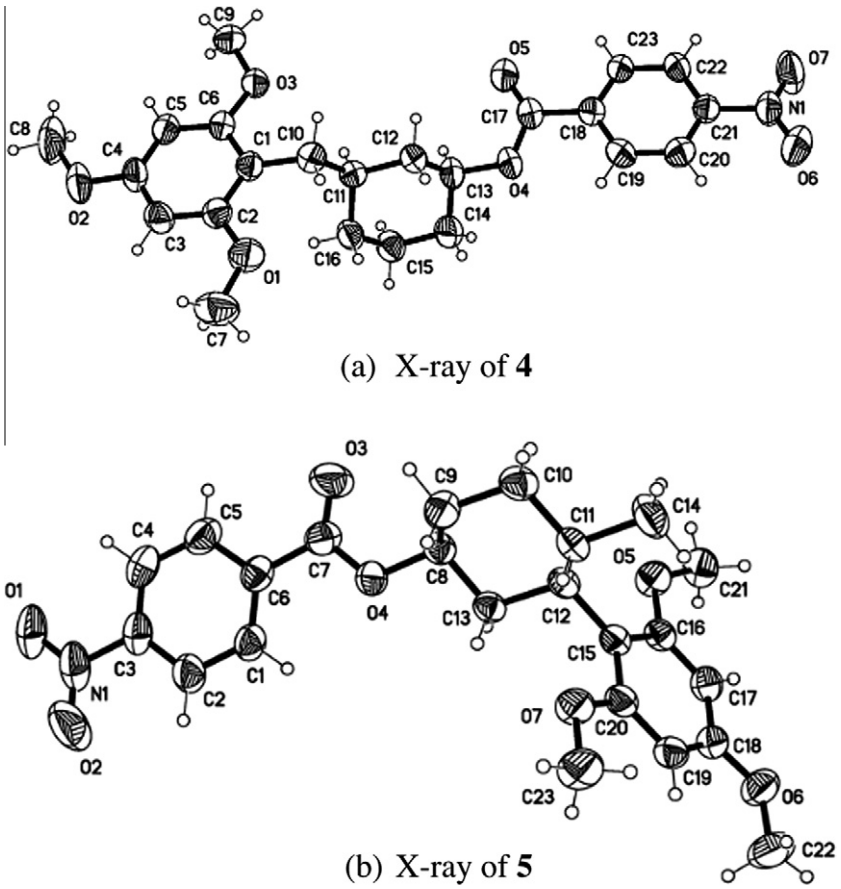
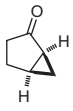
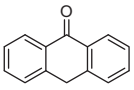
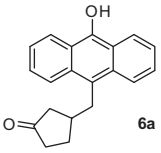
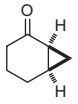
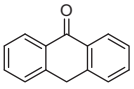
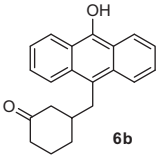
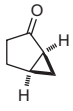
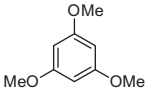


Figure 2. X-ray structures (ORTEP) of **4** and **5**.

Table 2
Cyclopropane ring-opening reaction promoted by an iminium cation[a]

Substrate	Nucleophile	Product	Isolated yield (%)
 1a		 6a	78
 1b		 6b	56
 1a		No reaction	

[a] Reactions were carried out with cyclopropane 1 (1.0 mmol), pyrrolidine (2.5 mmol) and 4 Å molecular sieves (200 mg) in toluene (2.0 mL) at reflux.

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7. CCDC-912261, CCDC-912262 and CCDC-912260 contain the supplementary crystallographic data for compounds **2a**, **4** and **5**, respectively, which are available free of charge via www.ccdc.cam.ac.uk.
8. *Representative procedure:* To a solution of **1b** (110 mg, 1.0 mmol) and 1,3,5-trimethoxybenzene (185 mg, 1.1 mmol) in PhCl (2 mL) was added $SnCl_4$ (0.1 mL, 1.0 mmol, 1 M in CH_2Cl_2) at 25 °C under nitrogen atmosphere. The reaction mixture was heated to 60 °C and stirred for 24 h. The resultant mixture was diluted with water (4 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel (EtOAc/Hexanes, 1:5) to yield **2b** as a colourless oil (45% yield). ^1H NMR ($CDCl_3$, 500 MHz): 6.11 (s, 2H), 3.76 (s, 9H), 2.64–2.52 (m, 2H), 2.33–2.24 (m, 3H), 2.12–1.93 (m, 3H), 1.83–1.80 (m, 1H), 1.43–1.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 212.9, 159.5, 159.0, 108.8, 90.4, 55.4, 48.1, 41.5, 39.4, 31.3, 29.3, 25.5; MS(ESI) for $C_{16}H_{22}O_4$ $[M+H]^+$: 279.1.
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12. We also performed the reaction using anthrone as the nucleophile and $SnCl_4$ as the Lewis acid promoter. However, no reaction was observed for both **1a** and **1b**.