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Lewis Acid-Catalyzed Ring-Opening Reactions of Methylenecyclopropanes with Alcoholic or Acidic Nucleophiles

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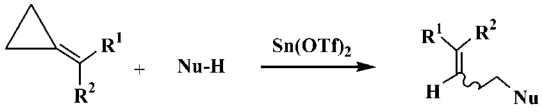
ABSTRACT

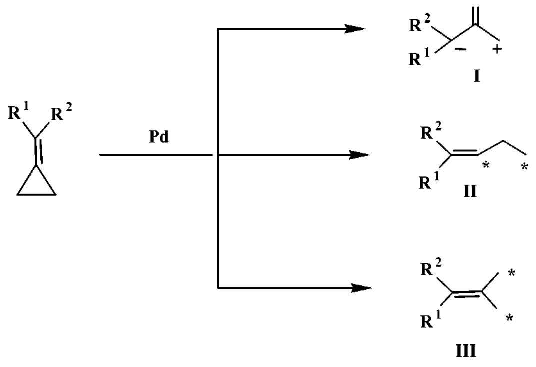


Nu-H can be alcohols, thiols, phenols, carboxylic acids
yield: 60%-100%.

Methylenecyclopropanes can react with various nucleophiles such as alcohols, phenols, carboxylic acids, and thiols to give the corresponding homoallylic esters or ethers in good yields with good stereoselectivities in the presence of Lewis acids.

Methylenecyclopropanes (MCPs) are highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis.[1] Strain in an organic molecule often correlates with increased reactivity. MCPs can undergo a variety of ring-opening reactions because the relief of ring strain provides a potent thermodynamic driving force for this process. Since numerous methodologies have been developed for the construction of MCPs,[1] MCPs have emerged as versatile tools in organic synthesis. Recently, much attention has been paid to reactions of MCPs with various reactants catalyzed by transition metals such as Pd, Rh, Ru, and Pt. Three kinds of reaction patterns of MCPs based on the concept of a synthon have been disclosed (Scheme 1). MCPs can react with polar reactants such as ROH,[2] R_2NH,[3] malonate derivatives,[4] carbon dioxide,[5] aldehydes,[6] and imines[7] in the presence of a Pd catalyst to give type I products. MCPs also can react with nonpolar reactants such as R_3SiH,[8] R_3SnH,[9] $R_2B{-}BR_2$,[10] $R_3Si{-}BR_2$,[11] $R_3Si{-}CN$,[12] and olefins[13] in the presence of a Pd, Ru, or Rh metal catalyst to afford type II and/or type III products depending on the reaction conditions (Scheme 1). But these reactions usually need severe reaction conditions such as very high temperatures (120 °C) and/or prolonged reaction time

Scheme 1. Three Reaction Patterns of MCPs



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* Fax: 86-21-64166128.

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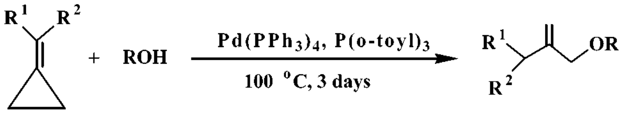
(3 days). These severe reaction conditions have certainly limited their practical utilization in organic synthesis.

For example, Yamamoto et al.[2] recently reported the Pd-catalyzed reactions of MCPs with alcohols, a powerful tool in the synthesis of allylic ethers (Scheme 2). This Pd-catalyzed addition of alcohols to MCPs was claimed to proceed via the activation of alcoholic pronucleophiles. However, the reaction was carried out at 100 °C for 3 days.

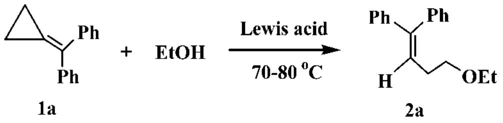
Scheme 2



On the other hand, Lewis acid-catalyzed ring-opening reactions of epoxides are very important transformations in organic synthesis.[14] However, to the best of our knowledge, no attention has been paid to the Lewis acid-catalyzed ring-opening reaction of MCPs. Herein, we report unprecedented Lewis acid-catalyzed ring-opening reactions of MCPs with alcoholic nucleophiles under mild conditions. Then, we extend the scope of this reaction to other nucleophiles such as phenols, carboxylic acids, water, and thiols.

Use of diphenylmethylenecyclopropane (**1a**) as a substrate allowed the reaction of **1a** with ethanol to be carefully examined in the presence of Lewis acids (Table 1). Various Lewis acids have been tested in this reaction. We found that the reaction proceeded smoothly in the presence of $Sn(OTf)_2$, $Sc(OTf)_3$, $Yb(OTf)_3$, or $BF_3{\cdot}Et_2O$ (10 mol %) (Table 1, entries 1−4), but no reaction occurred in the presence of $Al(O^iPr)_3$, $Ti(O^iPr)_4$, $Zn(OTf)_2$, or $Cu(OTf)_2$ (Table 1, entries 6−9). This result suggests that the Lewis acid plays a critical role in this reaction. $Sn(OTf)_2$ is the best Lewis acid in this reaction and gives the corresponding ring-opening reaction product **2a** in 95% yield within 24 h in ethanol at 70−80 °C (Table 1, entry 3). It should be emphasized here that the protic acid TfOH (CF_3SO_3H) can also catalyze this reaction under the same conditions. But the yield is slightly lower than that obtained with $Sn(OTf)_2$ (Table 1, entry 5).

Table 1. Effects of Various Acids in the Reaction of MCPs (**1a**) with Alcohols

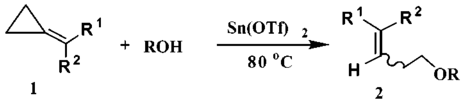


entry	Lewis acid	yield/%[a] (time/h)
1	$Yb(OTf)_3$	95% (72 h)
2	$Sc(OTf)_3$	94% (36 h)
3	$Sn(OTf)_2$	95% (24 h)
4	$BF_3{\cdot}Et_2O$	90% (50 h)
5	TfOH	85% (24 h)
6	$Cu(OTf)_2$	trace (72 h)
7	$Zn(OTf)_2$	trace (72 h)
8	$Ti(O^iPr)_4$	trace (72 h)
9	$Al(O^iPr)_3$	trace (72 h)

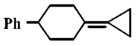
[a] Isolated yields.

Then, we carried out the reactions of various MCPs with alcohols or phenols in the presence of $Sn(OTf)_2$ (10 mol %) under the optimized conditions. The results are summarized in Table 2. In most cases, the ring-opening products **2** were obtained in excellent yields. To our surprise, the steric hindrance of alcohols do not affect this reaction rate (Table 2, entries 1−3). Especially, the reaction rate of diphenylmethylenecyclopropane (**1a**) with ^{i}PrOH is even faster than that of **1a** with EtOH (Table 2, entries 1 and 2). Water can

Table 2. Reactions of MCPs with ROH in the Presence of the Lewis Acid $Sn(OTf)_2$



a: $R^1 = C_6H_5$, $R^2 = C_6H_5$, **b**: $R^1 = C_6H_5$, $R^2 = 3\text{-}ClC_6H_4$,
c: $R^1 = p\text{-}MeOC_6H_4$, $R^2 = p\text{-}MeOC_6H_4$, **d**: $R^1 = H$, $R^2 = n\text{-}C_{11}H_{23}$,
e: $R^1 = Me$, $R^2 = n\text{-}C_7H_{15}$
f:



entry[a]	MCPs	ROH	time/h	yield[b] of **2** (*E*/*Z*)
1	**1a**	EtOH	24	**2a**, 95%
2	**1a**	^{i}PrOH	16	**2b**, 99%
3	**1a**	^{t}BuOH	48	**2c**, 93%
4	**1b**	EtOH	72	**2d**, 55% (5.6:1)
5	**1c**	EtOH	2	**2e**, 96%
6	**1d**	EtOH	48	**2f**, 59% (7.8:1)
7	**1e**	EtOH	2	**2g**, 96% (3.2:1)
8	**1f**	EtOH	48	**2h**, 98%
9	**1a**	H_2O	48	**2i**, 25%
10[c]	**1a**	$p\text{-}NO_2C_6H_4OH$	24	**2j**, 15%

[a] All reactions were carried out using 0.5 mmol of MCPs (**1a**−**d**) in alcohol in the presence of $Sn(OTf)_2$ (10 mol %) at 80 °C. [b] Isolated yields. [c] Using 1,2-dichloroethane (DCE) as a solvent.

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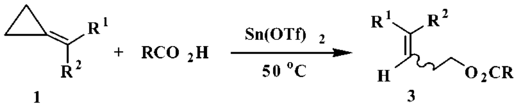
react with MCPs to give homoallylic alcohol as well, but the reaction is sluggish (Table 2, entry 9). The reaction of diphenylmethylenecyclopropane **1a** with phenols gives the corresponding product in very low yield along with many unidentified products. This may due to the Friedel−Crafts-type side reaction of MCPs with phenols in the presence of a Lewis acid. Only in the reaction of **1a** with *p*-nitrophenol in 1,2-dichloroethane (DCE) was **2e** obtained (15% yield; Table 2, entry 10). The substituents on the benzene ring of MCPs can significantly affect the reaction rate. For example, the reaction of **1b** with ethanol is much slower than that of **1a** with ethanol. However, the reaction of **1c** with ethanol is much faster than that of **1a** with ethanol (entries 1, 4, and 5). On the basis of these results, we can conclude that the electron-withdrawing groups on the benzene ring of MCPs such as Cl− slow the reaction, while electron-donating groups such as MeO− can significantly accelerate the reaction. For unsymmetric MCPs **1b**, **1d**, and **1e**, **2** was formed as an *E*/*Z* mixture in which *E*-**2** was a major isomer with fairly good stereoselectivity (Table 2, entries 4, 6, and 7).

To clarify the reaction rate in this novel ring-opening reaction, we recorded the yields of **2a** and **2e** from the reactions of **1a** and **1c** with EtOH under the same conditions over time (see Supporting Information). It is very clear that the reaction rate of **1c** is much faster than that of **1a**.

The reactions of carboxylic acids, very weak nucelophiles, with MCPs have also been examined. The reactions were carried out in DCE in the presence of a Lewis acid. We found that, in general, they can react more smoothly with MCPs than alcohols in the presence of $Sn(OTf)_2$ (10 mol %). The results are shown in Table 3. The corresponding ring-opening products **3** were obtained in very high yields at 50 °C for 24 h. For unsymmetric MCPs **1b**, **1d**, **1g**, and **1h**, **3** was formed as an *E*/*Z* mixture in which *E*-**3** was a major isomer with fairly good stereoselectivity (Table 3, entries 2−5).

Table 3. Reactions of MCPs with RCO_2H in the Presence of Lewis Acids



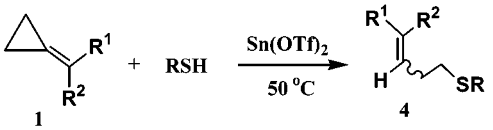
a: $R^1 = C_6H_5$, $R^2 = C_6H_5$
b: $R^1 = C_6H_5$, $R^2 = 3\text{-}ClC_6H_4$
d: $R^1 = H$, $R^2 = n\text{-}C_{11}H_{23}$
g: $R_1 = CH_3$, $R_2 = C_6H_5$
h: $R_1 = H$, $R_2 = C_6H_5CH_2CH_2CH_2$

entry[a]	substrate	RCO_2H	yield/%[b] (*E*/*Z*)
1	**1a**	CH_3CO_2H	**3a**, 97%
2	**1b**	CH_3CO_2H	**3b**, 100% (5.6:1)
3	**1d**	CH_3CO_2H	**3c**, 64% (7.2:1)
4	**1g**	CH_3CO_2H	**3d**, 97% (5.0:1)
5	**1h**	CH_3CO_2H	**3e**, 67% (9.2:1)
6	**1a**	$C_6H_5CO_2H$	**3f**, 83%

[a] All reactions were carried out using 0.5 mmol of MCPs (**1a**−**f**) and 1.0 mmol of acid in DCE or using the acid as a solvent at 50 °C for 24 h. [b] Isolated yields.

On the other hand, it was reported that thiols can add to the double bond of MCPs via a radical mechanism.[15] However, we found that, in the presence of $Sn(OTf)_2$, thiols also can react with MCPs to give a ring-opened product **4** similar to that obtained with alcohols, although the achieved yields are not as high as those of carboxylic acids or alcohols. The results are summarized in Table 4.

Table 4. Reactions of MCPs with RSH in the Presence of $Sn(OTf)_2$



a: $R^1 = C_6H_5$, $R_2 = C_6H_5$
b: $R^1 = C_6H_5$, $R_2 = 3\text{-}ClC_6H_4$
c: $R^1 = p\text{-}MeOC_6H_4$, $R_2 = p\text{-}MeOC_6H_4$

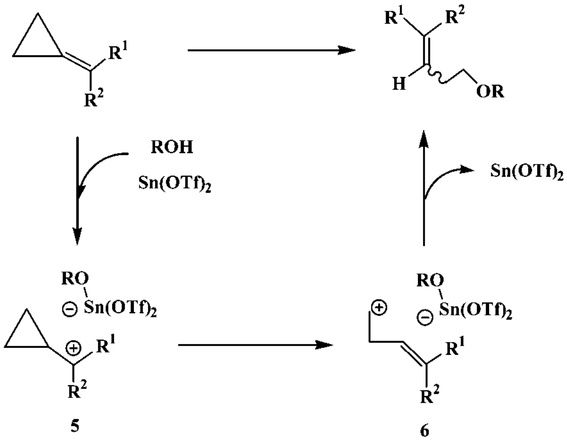
entry	substrate	RSH	yield/%[b] (*E*/*Z*)
1	**1a**	$n\text{-}C_6H_{13}SH$	**4a**, 50%
2	**1b**	$n\text{-}C_2H_5SH$	**4b**, 35% (10.8:1)
3	**1c**	$n\text{-}C_6H_{13}SH$	**4c**, 42%

[a] All reactions were carried out using 0.5 mmol of MCPs (**1a**−**c**) with 1.0 mmol of thiols in DCE at 50 °C for 24 h. [b] Isolated yields.

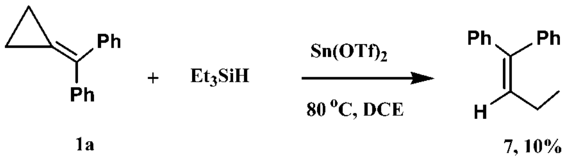
We also examined the reactions of MCPs with amines such as benzylamine in the presence of Lewis acids, but no reaction occurred at all. We believe this is because amine can strongly coordinate to the Lewis acid during the reaction and, therefore, deactivate the Lewis acid.

A plausible mechanism for the ring-opening reactions of MCPs with alcoholic or acidic nucleophiles was shown in Scheme 3. The alcohol first protonates the MCPs in the presence of the Lewis acid to give cation **5**, which immediately rearranges to another cation **6**. The subsequent nucleophilic attack affords the final product (Scheme 3). The

Scheme 3. Proposed Mechanism of Ring-Opening Reactions of MCPs Catalyzed by a Lewis Acid



Scheme 4. Trapping of a Carbocation by Et_3SiH



fast rearrangement of cation **5** to **6** was the key step in this reaction.[16] We also examined the reaction of **1b** with EtOH in the presence of the protic acid TfOH under the same conditions as those of $Sn(OTf)_2$. Product **2d** was obtained with the same regioselectivity, but in a low yield (20%). We confirmed that $Sn(OTf)_2$ does not decompose to give CF_3SO_3H upon heating at 80 °C.[17] Thus, as a result of using $Sn(OTf)_2$ as a Lewis acid, this novel ring-opening reaction does not involve CF_3SO_3H at all. We carried out a reaction of **1a** with Et_3SiH in the presence of $Sn(OTf)_2$ in which product **7**, derived from a trapping reaction of carboncation **6** with Et_3SiH,[16] was isolated in 10% yield (Scheme 4). This result suggests that carbocation **6** is indeed involved in this reaction.

Conclusion

We disclose an unknown transformation process of MCPs in the presence of a Lewis acid in this paper. The ring-opened products **2**−**4** can be obtained in good to excellent yields with fairly good stereoselectivities. A wide range of alcohols, carboxylic acids, and thiols act as nucleophiles in this reaction. This process will provide a novel and efficient route to the synthesis of homoallylic esters or ethers.

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Supporting Information Available: Spectroscopic data of the compounds shown in Tables 2−4 and a detailed description of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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