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Ring-Opening Reactions of Methylenecyclopropanes Promoted by Metal Halides

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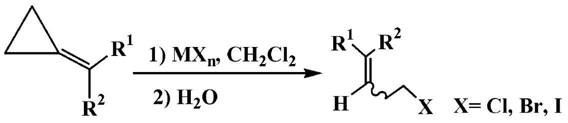
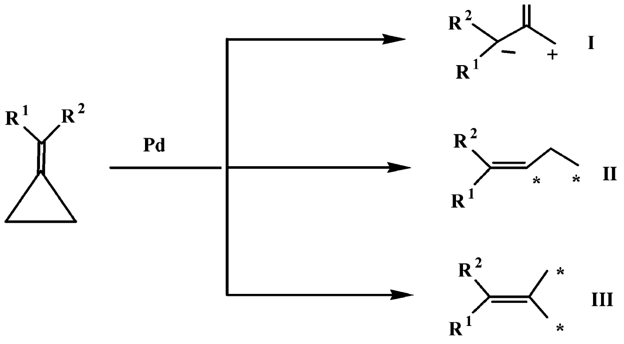
ABSTRACT



The methylenecyclopropanes (MCPs) react with various metal chlorides or bromides to give the corresponding homoallylic chlorides or bromides in good yields.

Methylenecyclopropanes (MCPs) are highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis.[1] MCPs undergo a variety of ring-opening reactions because the relief of ring strain provides a potent thermodynamic driving force. Three kinds of reaction patterns of MCPs have been disclosed (Scheme 1) for reactions with transition metals such as Pd, Rh, Ru, and Pt. MCPs can react with polar reactants such as ROH,[2] R$_2$NH,[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$_3$SiH,[8] R$_3$SnH,[9] R$_2$B−BR$_2$,[10] R$_3$Si−BR$_2$,[11] R$_3$Si−CN,[12] and olefins[13] in the presence of a Pd, Ru, Rh,

Scheme 1. Three Reaction Patterns of MCPs



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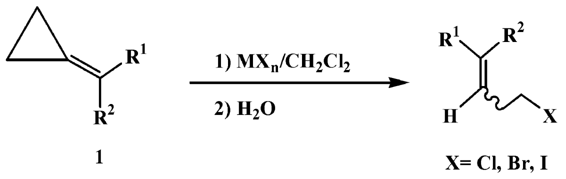
or Pt metal catalyst to afford the type II and/or type III products depending on the reaction conditions (Scheme 1).

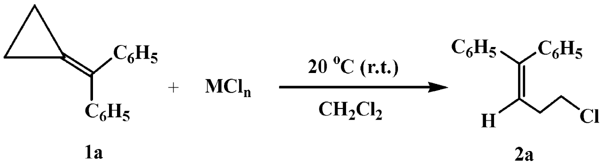
Recently, we found that the ring-opening reactions of MCPs **1** with alcohols and other nucleophiles catalyzed by Lewis acids [Ln(OTf)$_3$] took place via another novel manner to give the corresponding ring-opened products under mild conditions.[14] This interesting result stimulated us to further investigate the Lewis acid-catalyzed reactions of MCPs **1** with other reactants. Herein we wish to report the ring-opening reactions of MCPs **1** promoted by metal halides (Lewis acids) under mild conditions in which homoallylic halides can be obtained in high yields in dichloromethane (DCM) (Scheme 2).

Scheme 2. Reaction of MCPs **1** with Metal Halides



During our own investigations, we found that MCPs **1** could react with many metal halides (Lewis acids) to give the corresponding ring-opened homoallylic halides in good yields, and the Lewis acidities of metal halides played a critical role in this reaction. Using diphenylmethylenecyclopropane **1a** (0.5 mmol) as the substrate, various metal chlorides (0.75 mmol) have been tested for this ring-opening reaction in dichloromethane (DCM) at room temperature (20 °C). The results were summarized in Table 1. The reactions proceeded smoothly in the presence of $TiCl_4$, $BiCl_3$, $FeCl_3$, or $AlCl_3$ (strong Lewis acids) to give the corresponding homoallylic chloride **2a** in good yields (Table 1, entries 1−4), but using $ZnCl_2$ or $CoCl_2$ (weak Lewis acid) as the catalyst, no reaction occurred (Table 1, entries 6 and 7). In addition, only a trace of **2a** was formed in the presence of $CuCl_2$ (Table 1, entry 5).

Table 1. Effects of Metal Chlorides (Lewis Acids) on the Ring-Opening Reactions of MCP **1a**

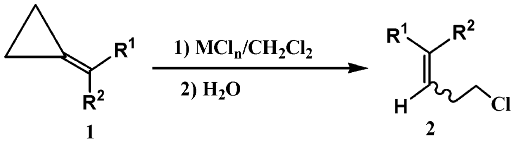


entry[a]	metal chloride	yield[b] (%)
1	$TiCl_4$	82
2	$BiCl_3$	80
3	$FeCl_3$	58
4	$AlCl_3$	68
5	$CuCl_2$	trace
6	$ZnCl_2$	no reaction
7	$CoCl_2$	no reaction

[a] All reactions were carried out with MCP (1a) (0.5 mmol) and metal chloride (0.75 mmol) using DCM as solvent at room temperature and then quenched with water. [b] Isolated yields.

Next, we utilized $TiCl_4$ and $BiCl_3$ as the Lewis acid promoters to examine the ring-opening reactions of various MCPs **1**. The results were shown in Table 2. For MCPs **1a**−**d** (both R^1 and R^2 are aromatic groups), the reactions proceeded very well to give **2a**−**g** in high yields within 2 h in the presence of $TiCl_4$ (Table 2, entries 1−4). For MCPs **1e**,**f** (both R^1 and R^2 are aliphatic groups), the corresponding homoallylic chlorides **2e** and **2f** were obtained in higher yields using $BiCl_3$ as the Lewis acid catalyst (reagent) for 24 h (Table 2, entries 5−8). However, it should be noted that for **1g**,**h** (R^1 is aromatic group and R^2 is hydrogen atom) and **1i** (R^1 is aromatic group and R^2 is methyl group) the reactions only gave a trace of products in the presence of $TiCl_4$ or $BiCl_3$ (Table 2, entries 9−12). It seems to us that this kind of MCP **1g**−**i** polymerizes easily in the presence of metal halides (Lewis acids).

Table 2. Reactions of MCPs **1** with $TiCl_4$ or $BiCl_3$



1a: $R^1 = C_6H_5$, $R^2 = C_6H_5$; **1b**: $R^1 = C_6H_5$, $R^2 = 4\text{-}ClC_6H_4$; **1c**: $R^1 = 4\text{-}ClC_6H_4$, $R^2 = 4\text{-}ClC_6H_4$; **1d**: $R^1 = 4\text{-}MeOC_6H_4$, $R^2 = 4\text{-}MeOC_6H_4$; **1e**: $R^1 = H$, $R^2 = n\text{-}C_{11}H_{23}$; **1f**: $R^1 = CH_3$, $R^2 = n\text{-}C_7H_{15}$; **1g**: $R^1 = C_6H_5$, $R^2 = H$; **1h**: $R^1 = 4\text{-}MeOC_6H_4$, $R^2 = H$; **1i**: $R^1 = 4\text{-}MeOC_6H_4$, $R^2 = CH_3$.

entry	MCPs	MCln	time (h)	yield[b] (%) (*E*/*Z*)
1	**1a**	$TiCl_4$	2	**2a**, 82
2	**1b**	$TiCl_4$	2	**2b**, 77 (1:1)
3	**1c**	$TiCl_4$	2	**2c**, 84
4	**1d**	$TiCl_4$	2	**2d**, 93
5	**1e**	$TiCl_4$	24	**2e**, 35 (3:4:1)
6	**1e**	$BiCl_3$	24	**2e**, 78 (3:4:1)
7	**1f**	$TiCl_4$	24	**2f**,30 (1:8:1)
8	**1f**	$BiCl_3$	24	**2f**, 75 (1:7:1)
9	**1g**	$TiCl_4$	2	trace
10	**1h**	$TiCl_4$	2	trace
11	**1h**	$BiCl_3$	2	trace
12	**1i**	$BiCl_3$	2	trace

[a] All reactions were carried out with MCPs (**1a**−**h**) (0.5 mmol) and metal chloride (0.75 mmol) using DCM solvent at room temperature and then quenched with water. [b] All yields were isolated yields.

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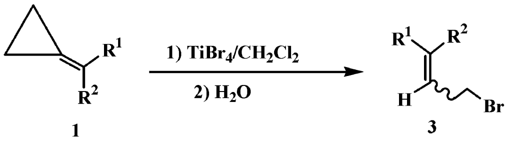
The MCPs **1** react with $TiBr_4$ to give the corresponding homoallylic bromides **3** in good yields. The results are elucidated in Table 3. For MCPs **1a**−**c** (both R^1 and R^2 are aromatic groups), the reaction proceeds very well to give **3a**−**c** in high yields within 2 h (Table 3, entries 1−3). For aliphatic MCP **1f**, the corresponding homoallylic bromide **3f** was obtained in the presence of $TiBr_4$ in good yield for 24 h as well (Table 3, entry 4).

Table 3. Reactions of MCPs **1** with $TiBr_4$ in CH_2Cl_2



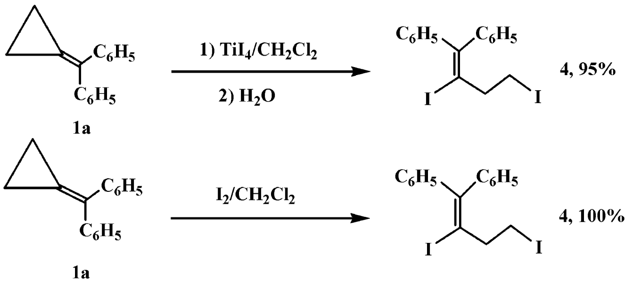
1a: $R^1 = C_6H_5$, $R^2 = C_6H_5$.
1b: $R^1 = C_6H_5$, $R^2 = 4\text{-}ClC_6H_4$.
1c: $R^1 = 4\text{-}ClC_6H_4$, $R^2 = 4\text{-}ClC_6H_4$.
1f: $R^1 = Me$, $R^2 = n\text{-}C_7H_{15}$.

entry[a]	MCPs	time (h)	yield[b] (%) (*E*/*Z*)
1	**1a**	2	**3a**, 80
2	**1b**	2	**3b**, 89 (1:1)
3	**1c**	2	**3c**, 84
4	**1f**	24	**3f**, 45 (1:7:1)

[a] All reactions were carried out with MCPs 1 (0.5 mmol) and titanium bromide (0.75 mol) using the DCM as solvents at room temperature and then quenched with water. [b] All yields were isolated yields.

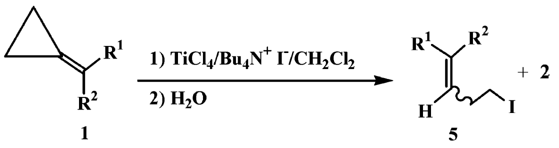
To complete this version of halogenation of MCPs **1**, we attempted to prepare the corresponding homoallylic iodides. We first conducted the reaction of MCP **1a** with TiI_4 under the same conditions as those described before. But, we found that this reaction only gave diiodide product **4** in high yield (95%) (Scheme 3). In fact, diiodide **4** can be obtained in the presence of iodine (I_2) quantitatively in DCM (Scheme 3). Because we can find the deep color of I_2 in the reaction mixture of MCPs with TiI_4, it can be concluded that part of TiI_4 was decomposed to I_2 during the reaction and MCP **1a** further react with I_2 to give diiodide product **4**.

Scheme 3. Reaction of MCP **1a** with TiI_4 in CH_2Cl_2



To synthesize the corresponding homoallylic iodides **5**, the $TiCl_4/n\text{-}Bu_4N^{\bullet+}I^-$ (molar ratio 1/1.2) system developed by Oshima was employed.[15] The iodides **5** were indeed obtained in good yields, but along with small amounts of the corresponding homoallylic chlorides **3** (Table 4, entries 1−3). Moreover, the two halogenated products could not be separated by silica gel flash column chromatograph.

Table 4. Reactions of MCPs with$TiCl_4/n\text{-}Bu_4N^+I^-$



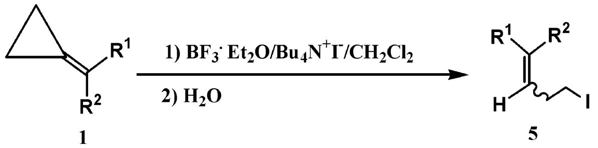
1a: $R^1 = C_6H_5$, $R^2 = C_6H_5$.
1c: $R^1 = 4\text{-}ClC_6H_4$, $R^2 = 4\text{-}ClC_6H_4$.
1d: $R^1 = 4\text{-}CH_3OC_6H_4$, $R^2 = 4\text{-}CH_3OC_6H_4$.

entry[a]	MCPs	time (h)	yield[b] (%)
1	**1a**	2	**5a**, 80 (**2a**, 19)
2	**1c**	2	**5c**, 75 (**2c**, 18)
3	**1d**	1	**5d**, 75 (**2d**, 17)

[a] All reactions were carried out with MCPs (**1a**, **1c**, and **1d**) (0.5 mmol), $TiCl_4$ (0.5 mmol), and $Bu_4N^+I^-$ (0.6 mmol) using DCM as solvent at room temperature and then quenched with water. [b] All yields were isolated yields.

To avoid the contamination of the corresponding homoallylic chlorides, we examined a $BF_3{\cdot}Et_2O/n\text{-}Bu_4N^{\bullet+}I^-$ (molar ratio: 1/1.5) system. We found that by means of this reaction system, the homoallylic iodides **5** could be isolated in excellent yields. The results were elucidated in Table 5. Only for MCP **1d**, the homoallyilc iodide **5d** was obtained in low yield (Table 5, entry 4). This is because the $BF_3{\cdot}Et_2O/n\text{-}Bu_4N^{\bullet+}I^-$ system can cleave the MeO− group from aromatic

Table 5. Reactions of MCPs **1** with $BF_3{\cdot}Et_2O/n\text{-}Bu_4N^+I^-$



1a: $R^1 = C_6H_5$, $R^2 = C_6H_5$. **1b**: $R^1 = C_6H_5$, $R^2 = 4\text{-}ClC_6H_4$.
1c: $R^1 = 4\text{-}ClC_6H_4$, $R^2 = 4\text{-}ClC_6H_4$.
1d: $R^1 = 4\text{-}MeOC_6H_4$, $R^2 = 4\text{-}MeOC_6H_4$.

entry[a]	MCPs	time (h)	yield[b] (%) (*E*/*Z*)
1	**1a**	2	**5a**, 95
2	**1b**	2	**5b**, 100 (1:1)
3	**1c**	2	**5c**, 98
4	**1d**	2	**5d**, 53 (36)[c]

[a] All reactions were carried out with MCPs (0.5 mmol) and $BF_3{\bullet}Et_2O$ (0.5 mmol) and $Bu_4N^+I^-$ (0.75 mmol) using DCM as solvent at room temperature and then quenched water. [b] All yields were isolated yields. [c] Yield of monodemethylation product.

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[15] Han, Z.; Uehira, S.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 7854.

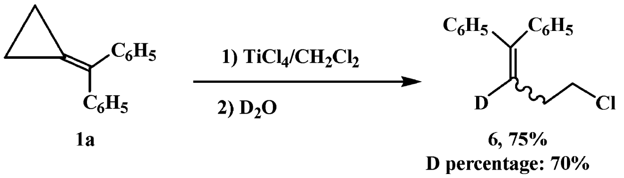
ring even at room temperature (the mono-demethyl product was isolated in 36% yield; see the Supporting Information).

In general, for unsymmetric MCPs **1** such as **1b**, **1e**, and **1f**, the corresponding homoallylic halides are obtained as the *E*/*Z* mixture with low stereoselectivities.

With the success of the $BF_3 \cdot Et_2O$/*n*-$Bu_4N^{\bullet +}I^-$ system, we then turned to the $BF_3 \cdot Et_2O$/*n*-$Bu_4N^{\bullet +}F^-$ system in order to synthesize the corresponding homoallylic fluorides. But only a trace of homoallylic fluoride product was obtained under the same conditions. The major product was the homoallic alcohol derived from the reaction of MCPs with water in the presence of Lewis acid $BF_3 \cdot Et_2O$.[14a] This may be due to the weak nucleophilicity of fluoride ion and the large amount of water present in commercially available *n*-$Bu_4N^{\bullet +}F^-$.

To probe the mechanism of this reaction and clarify the proton source of this reaction, we quenched the reaction by D_2O instead of H_2O. As a result, the deuterated product **6** was isolated in 75% yield with 70% D (Scheme 4).[16] This result suggest that the hydrogen atoms of homoallylic halides were derived from the quenching proton source.

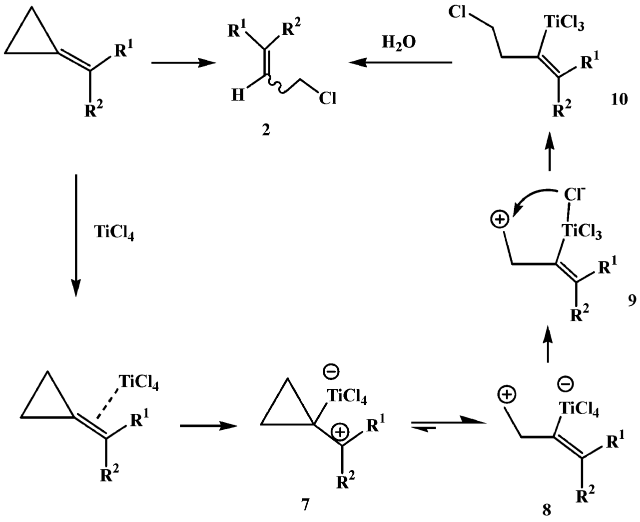
Scheme 4. Quenching Experiment Using D_2O in the Reaction of MCP **1a** with $TiCl_4$



A plausible mechanism for the ring-opening reaction of MCPs **1** promoted by $TiCl_4$ was shown in Scheme 5. The rearrangement of carbon cation **7** to **8** induced by Lewis acid $TiCl_4$ was the key step of this reaction.[17] The intramolecular chlorination of **9** gave intermediate **10,** which produced the final homoallylic chloride **2** by quenching with water.

After this work was submitted, Yamamoto reported that the reaction of alkylidenecyclopropanes with HCl or with HBr proceeds very smoothly at 120 °C to produce the corresponding homoallylic halides stereoselectively in good to excellent yields.[18]

Scheme 5. Proposed Mechanism of the Ring-Opening Reaction of MCPs **1** Promoted by $TiCl_4$



In conclusion, we disclosed a transformation process of MCPs **1** from the reaction with metal halides (Lewis acids) to give the corresponding homoallylic halides in high yields under mild reaction conditions. Efforts are in progress to elucidate the mechanistic details of this reaction and to determine its scope and limitations.

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Supporting Information Available: Spectroscopic data of the compounds shown in Tables 1−5 and Scheme 3 and detailed descriptions of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] The percentage of D was determined by the integration of ^1H NMR spectroscopic data of **6**. We believe that part of reaction product was quenched by ambient moisture (H_2O) during reaction.

[17] Carey, F. A.; Tremper, H. S. *J. Am. Chem. Soc*. **1969**, *91*, 2967.

[18] Siriwardana, A. I.; Nakamura, I.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 985.