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Lewis Acid-Mediated Cycloaddition of Methylenecyclopropanes with Aldehydes and Imines: A Facile Access to Indene, THF, and Pyrrolidine Skeletons via Homoallylic Rearrangement Protocol

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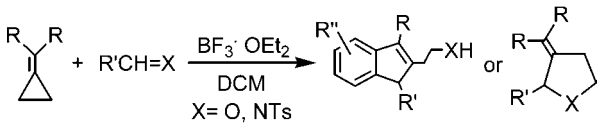
ABSTRACT



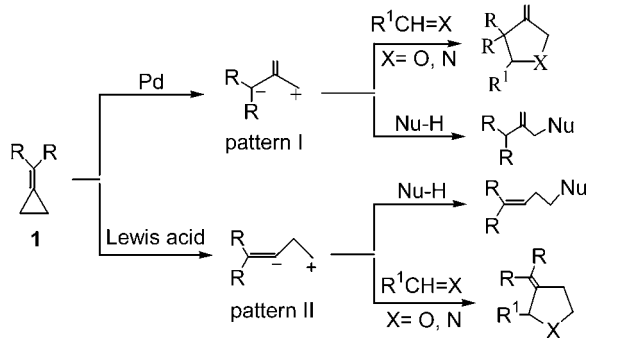
R could be various substituted aromatic groups or aliphatic groups, total yields based on the employed MCPs**1**: 40%-95%.

Methylenecyclopropanes (MCPs) 1 can react with aldehydes and aldimines to give the corresponding indene, THF, and pyrrolidine cycloaddition products in the presence of BF_3·OEt_2 under mild reaction conditions.

Methylenecyclopropanes (MCPs) **1** are highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis.[1,2] So far, it has been determined that in the presence of transition metals such as Pd catalysts, MCPs **1** can react with aldehydes[3] or imines[4] to produce the corresponding [3+2] cycloaddition products. In addition, they also can react with polar nucleophiles such as ROH[5] and R_2NH[6] to furnish ring-opened products (Scheme 1, pattern I).

Recently, we found that Lewis acid-mediated ring-opening reactions of MCPs **1** with nucleophiles, such as alcohols[7] and aromatic amines,[8] took place via a novel pathway (homoallylic rearrangement) to give the corresponding ring-opened products under mild conditions (Scheme 1, pattern II). In addition, we and others also reported Lewis acid-

Scheme 1. Pd-Catalyzed and Lewis Acid-Mediated Reaction Patterns of MCPs **1**



(1) For synthesis of MCPs: Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 598.

(2) For recent reviews, see: (a) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal*. **2002**, *344*, 111. (b) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev*. **2003**, *103*, 1213.

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(8) (a) Shi, M.; Chen, Y.; Xu, B.; Tang, J. *Tetrahedron Lett.* **2002**, *43*, 8019. (b) Xu, B.; Shi, M. *Org. Lett.* **2003**, *5*, 1415.

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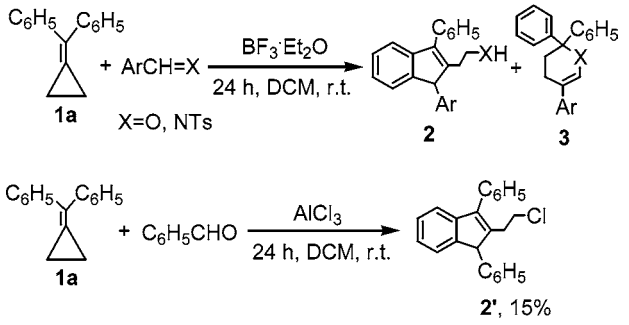
mediated or thermo-induced cycloadditions of MCPs **1** with aldehydes or ketones to give other types of cyclic products (Scheme 1, pattern II).[9] However, either activated aldehydes and ketones or activated MCPs **1** are required to render this type of cycloaddition possible. In fact, MCPs **1** are generally 13.6 kcal/mol more strained than cyclopropanes.[10] Strain in an organic molecule often correlates with its increased reactivity because the relief of ring strain provides a potent thermodynamic driving force. Therefore, MCPs **1** are also expected to react with the unactivated normal aldehydes in the presence of Lewis acid. In this paper, we wish to disclose this transformation in the presence of Lewis acid $BF_3{\cdot}Et_2O$ (Scheme 1, pattern II).

We first examined the Lewis acid $BF_3{\cdot}Et_2O$-mediated reaction of diphenylmethylenecyclopropane **1a** with aldehydes and aldimines (ArCH═NTs) at room temperature (20 °C) in dichloromethane (DCM) (Scheme 2). We found that

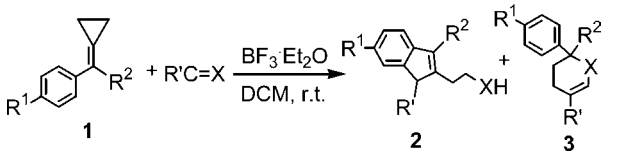
Scheme 2. The Cycloaddition of MCP **1a** with Aldehydes and Aldimines



the major reaction products were the indene derivatives **2** along with dihydro-2*H*-pyran derivatives **3** (in some cases) rather than the expected [3+2] cycloaddition products.[11] But no reaction occurred in the presence of weak Lewis acids such as $Yb(OTf)_3$, $Sn(OTf)_2$, $Cu(OTf)_2$, and AlF_3. By means of the stronger Lewis acid $AlCl_3$ in the reaction of **1a** with benzaldehyde, the corresponding chlorinated product **2′** was formed in 15% yield (Scheme 2). $BF_3{\cdot}Et_2O$ is the best Lewis acid for this transformation. This reaction proceeded smoothly in 1,2-dichloroethane (DCE) as well, but became sluggish in other solvents such as tetrahydrofuran (THF), ethylene glycol dimethyl ether (DMF), 1,4-dioxane, and acetonitrile (CH_3CN).

Table 1 summarizes of the results in the reaction of various MCPs **1** with aldehydes and aldimines under the optimized

Table 1. The Reaction of MCPs **1** with Aldehydes and Aldimines



				yield,[b] %	
entry[a]	MCP **1** (R^1/R^2)	R′	X	2	3
1	**1a** (H/C_6H_5)	4-ClC_6H_4	O	**2a**, 65	**3a**, 10
2	**1a**	4-BrC_6H_4	O	**2b**, 78	**3b**, 8
3	**1a**	4-MeC_6H_4	O	**2c**, 34	**3c**, 30
4	**1a**	4-$MeOC_6H_4$	O	**2d**, 5	**3d**, 45
5	**1a**	2,4-$Cl_2C_6H_3$	O	**2e**, 75	**3e**, trace
6	**1b** (MeO-/*p*-MeC_6H_4)	4-BrC_6H_4	O	**2f**, 91	
7	**1b**	4-ClC_6H_4	O	**2g**, 95	
8	**1a** (Me-/*p*-MeC_6H_4)	4-BrC_6H_4	O	**2h**, 68	
9	**1a**	^{i}Pr	O	**2i**, 66	
10	**1a**	C_6H_5	NTs	**2j**, 75	
11	**1a**	4-ClC_6H_4	NTs	**2k**, 71	
12	**1a**	4-$CF_3C_6H_4$	NTs	**2*l***, 73	
13	**1a**	2,4-$Cl_2C_6H_3$	NTs	**2m**, 71	
14	**1a**	3-FC_6H_4	NTs	**2n**, 75	

[a] All reactions were carried out with MCPs **1a**−**c** (0.5 mmol), aldehydes (1.0 mmol), or aldimines (0.75 mmol) in the presence of $BF_3{\cdot}Et_2O$ (20 mol %) at room temperature for 24 h. [b] Isolated yields.

conditions. The product **3** was only isolated in the reaction of **1a** with arylaldehydes (Table 1, entries 1−5). For MCP **1b** having a strongly electron-donating methoxy group on the benzene ring, the corresponding indene derivatives **2f** and **2g** were obtained in higher yields as a sole product in each reaction (Table 1, entries 6 and 7). In the reaction of **1a** with aliphatic aldehyde, the indene product **2i** was formed in moderate yield (Table 1, entry 9). By using aldimines as the substrates, similar results were obtained under the same conditions (Table 1, entries 10−14). However, with other imines such as ArCH═NR (R = alkyl or aryl group) as the substrate, no reaction occurred.

On the other hand, we found that if the reaction was carried out at −25 °C, the corresponding [3+2] cycloaddition products **4**[11] (THF or pyrrolidine skeleton) were produced in moderate yields in the reaction of MCPs **1** (including aliphatic MCP **1e**) with aliphatic aldehydes and aldimines for 12 h. The results are summarized in Table 2. Meanwhile, with arylaldehydes as the substrates at −25 °C for 12 h, the reaction produces the same products as shown in Table 1.

(9) For the Lewis acid-mediated cycloaddition of MCPs with activated ketone or aldehyde, see: (a) Shi, M.; Xu, B. *Tetrahedron. Lett.* **2003**, *44*, 3839. For the MgI_2-mediated ring expansions of methylenecyclopropyl amides and imides, see: (b) Lautens, M.; Han, W. *J. Am. Chem. Soc.* **2002**, *124*, 6312. (c) Lautens, M.; Han, W.; Liu, J. H.-C. *J. Am. Chem. Soc.* **2003**, *125*, 4028. For the cycloaddition of silylated MCPs with aldehydes in the presence of $TiCl_4$, see: (d) Patient, L.; Berry, M. B.; Killburn, D. *Tetrahedron Lett.* **2003**, *44*, 1015. For the cycloaddition of MCPs activated by a carbonyl group with allyltrimethylsilane in the presence of $TiCl_4$ see: Monti, H.; Rizzotto, D.; Leandri, G. *Tetrahedron* **1998**, *54*, 6725. For the cycloaddition of *gem*-dialkoxy-substituted MCPs with aldehydes and imines upon heating, see: (e) Yamago, S.; Nakamura, E. *J. Org. Chem.* **1990**, *55*, 5553. (f) Yamago, S.; Yanagawa, M.; Nakamura, E. *Chem. Lett.* **1999**, 879. For Ni(0)-catalyzed reactions of MCPs that occur by the proximal bond cleavage (pattern II), see: (g) Binger, P.; Schafer, B. *Tetrahedron Lett.* **1988**, *29*, 4539. (h) Binger, P.; Wedemann, P. *Tetrahedron Lett.* **1985**, *26*, 1045. (i) Noyori, R.; Odagi, T. *J. Am. Chem. Soc.* **1970**, *92*, 5780. (j) Nakamura, E.; Yamago, S. *Acc. Chem. Res.* **2002**, *35*, 867.

(10) de Meijere, A.; Kozhushkov, S. I.; Khlebnikov, A. F. *Top. Curr. Chem.* **2000**, *207*, 89.

(11) The structures of **3d**, **4b**, and **5a** were further determined by X-ray diffraction (Supporting Information).

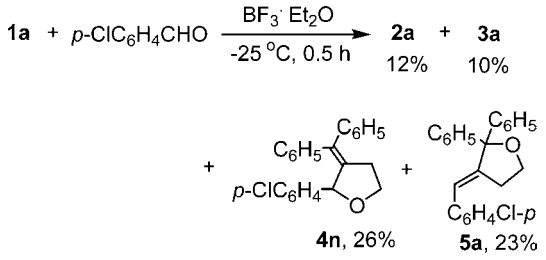
Table 2. The Reaction of MCPs **1** with Aldehydes and Aldimines at −25 °C

entry[a]	R(MCPs)	R′	X	yield,[b] % **4**
1	C_6H_5 **1a**	^{n}Bu	O	**4a**, 45
2	**1a**	^{i}Pr	O	**4b**, 58
3	4-MeC_6H_4 **1c**	^{i}Pr	O	**4c**, 54
4	4-ClC_6H_4 **1d**	^{i}Pr	O	**4d**, 50
5	Bu **1e**	^{i}Pr	O	**4e**, 41
6	**1e**	^{i}Bu	O	**4f**, 45
7	**1a**	C_6H_5	NTs	**4g**, 41
8	**1a**	4-ClC_6H_4	NTs	**4h**, 40
9	**1a**	4-BrC_6H_4	NTs	**4i**, 43
10	**1a**	4-$CF_3C_6H_4$	NTs	**4j**, 45
11	**1a**	2,4-$Cl_2C_6H_3$	NTs	**4k**, 48
12	**1a**	4-BrC_6H_4	NTs	**4*l***, 54
13	**1a**	^{i}Pr	NTs	**4m**, 55

[a] All reactions were carried out with MCPs **1** (0.5 mmol), aldehydes (1.0 mmol), or aldimines (0.75 mmol) in the presence of BF_3·Et_2O (20 mol %) at −25 °C, using DCM as a solvent. [b] Isolated yields.

To probe the reaction pathway for the formation of **2** and/or **3**, we investigated the reaction of MCP **1a** with *p*-chlorobenzaldehyde at −25 °C within shorter reaction time (0.5 h). The desired [3+2] cycloaddition products **4n** and **5a**[11] were isolated besides **2a** and **3a** by careful isolation (Scheme 3). We further confirmed that **4n** and **5a** can be

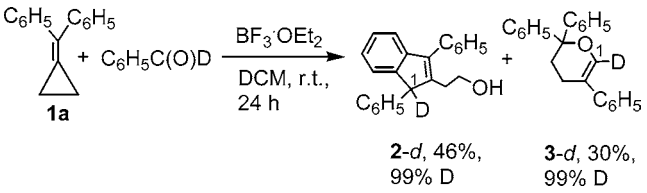
Scheme 3. The Reaction of MCP **1a** with *p*-Chlorobenzylaldehyde at −25 °C within 0.5 h



completely transformed to **2a** in the presence of BF_3·Et_2O at room temperature within 0.5 h (intramolecular Friedel−Crafts reaction). Thus, we believe that indene **2** is derived from the further reaction of the [3+2] annulation product catalyzed by BF_3·Et_2O.

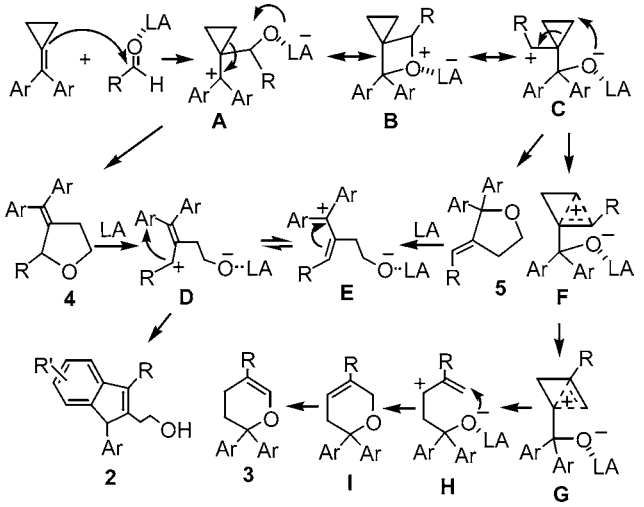
To clarify the mechanism of this reaction, the deuterium-labeling experiment was carried out by conducting the reaction of **1a** with $C_6H_5C(O)D$ under the same conditions (Scheme 4). **2**-*d* and **3**-*d* are obtained in 46% and 30% with 99% D content at the C-1 position, respectively (^{1}H NMR and ^{13}C NMR charts in the Supporting Information). Deuterium incorporation did not occur at other carbons of **2** and **3**.

Scheme 4. The Reaction of MCP **1a** with $C_6H_5C(O)D$ Promoted by Lewis Acid



The mechanism of this novel annulation is proposed in Scheme 5 on the basis of the obtained results. The addition

Scheme 5. The Proposed Mechanism of Cycloaddition of MCPs with Aldehyde Promoted by Lewis Acid



of MCP **1** to the Lewis acid-activated aldehyde gives the cyclopropylcarbinyl cation **A** and its resonance-stabilized zwitterionic intermediate **B** and **C**, respectively. The homoallylic rearrangement of cations **A** and **C** produces **4** and **5**[12] which can further produce the exchangeable intermediates **D** and **E**, respectively, in the presence of Lewis acid.[13] The tandem intramolecular Friedel−Crafts reaction from **D** produces the indene derivative **2** (for arylaldehydes). The intramolecular cyclization of cation **C** furnishes cation **F**, which can be viewed as a nonclassical carbenium cation.[14] The aryl migration in cation **F** (for arylaldehydes), which has been clearly indicated by the deuterium-labeling experiment, takes place in the presence of Lewis acid to produce another cation **G**, which gives intermediates **H** and **I**. The proton migration of **I** finally affords product **3**.[15] On the basis of this proposed mechanism, the results shown in Tables 1

(12) Carey, F. A.; Tremper, H. S. *J. Am. Chem. Soc.* **1969**, *91*, 2967.
(13) Kulkarni, S. U.; Patil, V. D. *Heterocycles* **1982**, *18*, 163.
(14) Olah, G. A.; Schleyer, P. v. R. *Carbonium Ions*; Wiley: New York, 1968; Vol. 1, pp 45−47.

and 2 can be rationalized as follows. For MCPs **1** having a strongly electron-donating group on the benzene ring (electron-rich aromatic ring), the intramolecular Friedel−Crafts reaction preferably takes place to give indene **2** as a sole product (Table 1, entries 6−8). For aliphatic aldehydes, the formation of intermediates **C** and **D** is a disfavored process because the alkyl group cannot stabilize these cationic intermediates and the formal [3+2] cycloaddition product **4** is exclusively formed at low temperature (Table 2, entries 1−6). On the other hand, for aldimine, it is impossible to produce the intermediate **B** due to the steric hindrance of NTs group. Therefore, the formation of **4** or **2** is a favorable process. At any rate, in this novel transformation of MCPs **1** mediated by $BF_3{\cdot}Et_2O$, the thermodynamically stable cyclized product is exclusively formed in each case during a long reaction time.

In this letter, we described a Lewis acid $BF_3{\cdot}Et_2O$-mediated novel cycloaddition reaction of MCPs **1** with normal aldehydes and aldimines. The indene, THF, and pyrrolidine skeletons generated in this novel [3+2] annulation or tandem intramolecular Friedel−Crafts reaction may be potentially useful for the construction of several biologically important products such as pyrrolizidine alkaloids.[16] Efforts are underway to elucidate the mechanistic details of this reaction and to disclose the scope and limitations of this reaction.[17]

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Supporting Information Available: ^{13}C and ^{1}H NMR spectral and analytic data and X-ray diffraction data for compounds in Tables 1 and 2 and Schemes 1−4. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) This type of phenyl migration has been reported. See: (a) Kirmse, W.; Gunther, B. R. *J. Am. Chem. Soc.* **1978**, *100*, 3619. (b) Wiberg, K. B.; Ashe, A. J. *J. Am. Chem. Soc.* **1968**, *90*, 63. (c) Schleyer, P. R.; Majerski, Z. *J. Am. Chem. Soc*. **1970**, *93*, 665. (d) Majerski, Z.; Schleyer, P. R. *J. Am. Chem. Soc*. **1971**, *93*, 665.

(16) For example, **4m**, which shows strong *anti*-acetylcholine, *anti*-histamine, and *anti*-barium activities, has been synthesized by a much longer procedure. Ohki, S.; Hamaguchi, F.; Yanagi, T.; Yoshino, M. *Chem. Pharm. Bull*. **1966**, *14*, 187.

(17) For other special transformations of MCPs **1** with aldehydes, see the Supporting Information.