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Lewis acid $BF_3{\cdot}OEt_2$-catalyzed Friedel–Crafts reaction of methylenecyclopropanes with arenes☆

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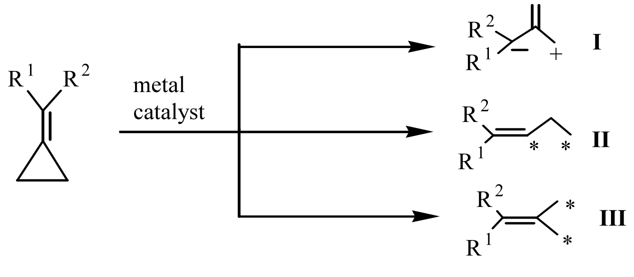
Abstract—Methylenecyclopropanes react with various arenes to give the Friedel–Crafts reaction products in good yields in the presence of Lewis acid $BF_3{\cdot}OEt_2$.

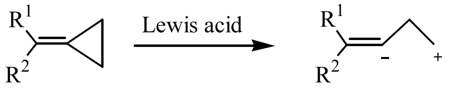
Methylenecyclopropanes (MCPs) are highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis. MCPs undergo a variety of ring-opening reactions because the relief of ring strain provides a potent thermodynamic driving force. Three general reaction pathways for MCPs have been disclosed for reactions promoted by transition metals such as Pd, Rh, Ru, and Pt (Scheme 1).[1] MCPs can react with polar reactants such as alcohols,[2] secondary amines,[3] malonates derivatives,[4] carbon dioxide,[5] aldehydes,[6] and imines[7] in the presence of Pd catalyst to give type I products. MCPs can also react with nonpolar reactants such as R_3SiH,[8] R_3SnH,[9] $R_2B\text{-}BR_2$,[10] $R_3Si\text{-}BR_2$,[11] $R_3Si\text{-}CN$[12] and olefins[13] in the presence of Pd, Ru or Rh metal catalyst to afford type II and/or type III products, depending on the reaction conditions (Scheme 1).



Scheme 1. Three reaction patterns of MCPs in the presence of transition metal catalysts.

Recently, we found that the ring-opening reactions of MCPs **1** with alcohols and other nucleophiles catalyzed by Lewis acids $[Ln(OTf)_n]$ (Ln = Sn, Yb, Sc) took place via a novel pathway to give the corresponding ring-opened products under mild conditions (Scheme 2).[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 an unprecedented Lewis acid-catalyzed Friedel–Crafts reaction of MCPs **1** with arenes under mild conditions.[15]

We found that **1a** could react with toluene (**2b**) to give the corresponding Friedel–Crafts reaction product **3b** as a mixture of *o*/*p*-isomers (*o*/*p* = 1.5:1) in moderate yield if the reaction was carried out in neat **2b** in the presence of the Lewis acid $BF_3{\cdot}OEt_2$ (0.1 equiv.) (Table 1). Other Lewis acids such as $Sn(OTf)_2$, $Sc(OTf)_3$, $Yb(OTf)_3$, $Zn(OTf)_2$, $BF_3{\cdot}OEt_2$, $Ti(OPr^i)_4$ (0.1 equiv.) and Brønsted acids such as CF_3SO_3H and TsOH were also tested in this reaction (Table 1). Clearly, $BF_3{\cdot}OEt_2$ is the best Lewis acid for this novel Friedel–Crafts reaction, and gives the corresponding ring-opened reaction product **3b** in 46% within 6 h in toluene at 60°C (Table 1, entry 8). The structure of **3b** (*o*/*p*-mixture) was established by the ^1H and ^{13}C NMR spectroscopic data and NOE analysis (see Supporting Information). Using $BF_3{\cdot}OEt_2$ as the Lewis acid, we subsequently optimized the reaction conditions. The results are sum-



Scheme 2. The reaction pattern of MCPs in the presence of Lewis acids.

Keywords: methylenecyclopropanes; Lewis acid; aromatic compounds; Friedel–Crafts reaction; ring-opening reaction.

☆ Suppplementary data associated with this article can be found at doi:10.1016/j.tetlet.2003.10.086

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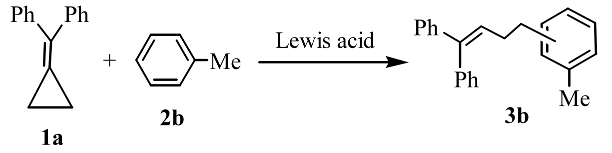
Table 1. The effects of various Lewis acids or Brønsted acid in the Friedel–Crafts reaction of MCP **1a** with toluene **2b** upon heating at 60°C



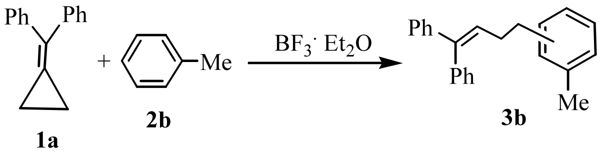
Entry	Lewis acid	Temp. (°C)	Time (h)	Yield (%)[a,b]
1	Yb(OTf)$_3$ (0.1 equiv.)	60	6	No reaction
2	Sn(OTf)$_2$ (0.1 equiv.)	60	8	No reaction
3	Zn(OTf)$_2$ (0.1 equiv.)	80	1	No reaction
4	Sc(OTf)$_3$ (0.1 equiv.)	80	1	No reaction
5	Ti(OPr^i)$_4$ (0.1 equiv.)	60	1	No reaction
6	CF$_3$SO$_3$H (0.1 equiv.)	60	12	<10
7	TsOH (0.1 equiv.)	60	12	<10
8	BF$_3$·OEt$_2$ (0.1 equiv.)	60	6	46[c]

[a] Isolated yields.

[b] The reaction was carried out in toluene.

[c] *o*:*p*=1.5:1.

Table 2. The Friedel–Crafts reactions of MCP **1a** with **2b** in the presence of Lewis acid BF$_3$·OEt$_2$



Entry	BF$_3$·OEt$_2$ (equiv.)	Temp. (°C)	Time (h)	Yield (%)[a,d]
1	1.0	rt	11	50
2	3.0	rt	8	44
3	5.0	rt	1	51
4	1.0	rt	3	8[b]
5	0.5	rt	3	9[c]
6	0.5	60	1	10[b]
7	0.5	80	1	60
8	0.2	120	1	56
9	1.0	120	1	53
10	1.0	60	1	64

[a] Isolated yields.

[b] The reaction was carried out in DCE and toluene (1:1).

[c] The reaction was carried out in hexane and toluene (1:1).

[d] *o*:*p*=1.5:1.

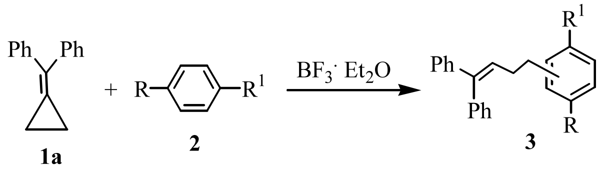
marized in Table 2. Increasing the amount of Lewis acid BF$_3$·OEt$_2$ accelerated the reaction rate, but **3b** was still only obtained in moderate yields at room temperature (44~51%) (Table 2, entries 1–3). In addition, this reaction needs to be carried out in neat toluene in order to get a good yield of **3b**. When the reaction was carried out in other solvents, such as 1,2-dichloroethane (DCE) or hexane, product **3b** was produced in lower yields (Table 2, entries 4–6). At higher temperature, the reaction proceeded quickly and the product **3b** was obtained in higher yields, even in the presence of catalytic amount of BF$_3$·OEt$_2$ (Table 2, entries 7 and 8). However, in the presence of 1.0 equiv. of BF$_3$·OEt$_2$ at 120°C, **3b** was still obtained in similar yield (53%) (Table 2, entry 9). The best results were found at 60°C in toluene, in the presence of 1.0 equiv. BF$_3$·OEt$_2$ (Table 2, entry 10).

Using benzene **2a**, 1,4-dimethylbenzene **2c**, and anisole **2d** as the substrates, we examined their Friedel–Crafts reactions with MCP **1a** under the optimized reaction conditions. The results are shown in Table 3. The Friedel–Crafts reaction of **1a** with **2a** gave the corresponding product **3a** only in low yield (12%) (Table 3, entry 1). However, the Friedel–Crafts reaction of **1a** with **2c** and **2d**, the corresponding products **3c** and **3d** were obtained in high yields (Table 3, entries 2, 3 and 4). Significantly, product **3d** was formed quantitatively as a mixture of *o*:*p*-isomers (*o*:*p*=1:1) under these conditions. This is due to the fact that electron rich aromatic compounds are usually more easily able to undergo Friedel–Crafts reactions.

The substituents on the aromatic rings of the MCPs significantly affect their reactivity. For MCPs **1** having an electron-withdrawing group, such as a chlorine atom, or a moderately electron-donating group, such as methyl group, the reaction proceeded smoothly to give the corresponding Friedel–Crafts reaction products **3e**–**p** in good to excellent yields (Table 4, entries 1–12). However, if the MCPs **1** have a strongly electron-donating group, such as a methoxy group, on the aromatic ring, i.e. **1e**, we found that the reaction solution immediately became dark in color and that although the starting material **1e** was consumed quickly, product **3** was only isolated in low yields (Table 4, entries 13–16). Even when the reactions were carried out at lower temperature (room temperature), the same results were obtained. We believe that since *p*-methoxyphenyl group is a more active moiety for the Friedel–Crafts reaction, a self Friedel–Crafts reaction takes place to give the complicated products if MCP **1e** is used as the substrate.[16] For unsymmetrical MCP **1b**, the corresponding Friedel–Crafts reaction product was obtained as a mixture of *trans*- and *cis*-isomers along with *o*:*p*-isomers (Table 4, entries 1–4).

We also examined the Friedel–Crafts reaction of alkyl group substituted MCPs with aromatic compounds. For MCP **1f** [R^1=R^2=-CH$_2$CH$_2$CH(C$_6$H$_5$)CH$_2$CH$_2$-], the Friedel–Crafts reaction with **2c** catalyzed by BF$_3$·OEt$_2$ produced the corresponding product **3u** in moderate yield (Table 4, entry 17). However, for aliphatic MCP **1g** (R^1=R^2=Bu), a novel double-Friedel–Crafts reaction takes place to give the corresponding 1,2,3,4-tetrahydronaphthalene derivative **3v** as

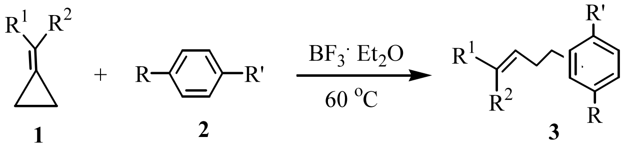
Table 3. The Friedel–Crafts reaction of MCP **1a** with **2a**, **2c** and **2d** in the presence of Lewis acid $BF_3{\cdot}OEt_2$

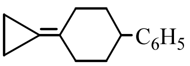


Entry[a]	R^1	R		Temp. (°C)	Time (h)	Yield (%)[b] (*o*:*p*)
1	H	H	**2a**	60	5	**3a**, 12
2	Me	Me	**2c**	rt	3	**3c**, 74
3	Me	Me	**2c**	60	3	**3c**, 77
4	H	OMe	**2d**	60	1	**3d**, 100 (1:1)

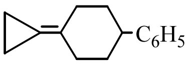
[a] All reactions were carried out using MCP **1a** (0.5 mmol) in neat **2**.
[b] Isolated yields.

Table 4. The Friedel–Crafts reactions of various MCPs **1** with **2a**–**d** in the presence of Lewis acid $BF_3{\cdot}OEt_2$



1b: $R^1 = C_6H_5$, $R^2 = p$-ClC_6H_4; **1c**: $R^1 = R^2 = p$-ClC_6H_4;
1d: $R^1 = R^2 = p$-MeC_6H_4; **1e**: $R^1 = R^2 = p$-$MeOC_6H_4$; **1f**: 

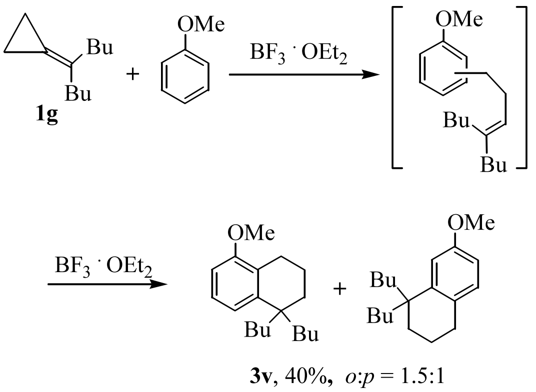
2a: R=R'= H; **2b**: R= H, R'= Me; **2c**: R=R'= Me; **2d**: R= H, R'= OMe.

Entry[a]	R^1	R^2	R′	R	Time (h)	Yield (%)[b] (*o*:*p*)
1	C_6H_5	*p*-ClC_6H_4	H	H	5	**3e**, 40 (*trans*:*cis* = 1:1)
2	C_6H_5	*p*-ClC_6H_4	H	Me	3	**3f**, 67 (2:1) (*trans*:*cis* = 1:1)
3	C_6H_5	*p*-ClC_6H_4	Me	Me	1	**3g**, 73 (*trans*:*cis* = 1:1)
4	C_6H_5	*p*-ClC_6H_4	H	OMe	1	**3h**, 93 (1.3:1) (*trans*:*cis* = 1:1)
5	*p*-ClC_6H_4	*p*-ClC_6H_4	H	H	5	**3i**, 55
6	*p*-ClC_6H_4	*p*-ClC_6H_4	H	Me	5	**3j**, 85 (1.3:1)
7	*p*-ClC_6H_4	*p*-ClC_6H_4	Me	Me	2	**3k**, 88
8	*p*-ClC_6H_4	*p*-ClC_6H_4	H	OMe	2	**3l**, 90 (1:1)
9	*p*-MeC_6H_4	*p*-MeC_6H_4	H	H	1	**3m**, 16
10	*p*-MeC_6H_4	*p*-MeC_6H_4	H	Me	1	**3n**, 66 (1.8:1)
11	*p*-MeC_6H_4	*p*-MeC_6H_4	Me	Me	1	**3o**, 58
12	*p*-MeC_6H_4	*p*-MeC_6H_4	H	OMe	1	**3p**, 91 (1:0.9)
13	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	H	H	1	**3q**, trace
14	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	H	Me	1	**3r**, trace
15	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	Me	Me	1	**3s**, trace
16	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	H	OMe	1	**3t**, <10
17	 C_6H_5		Me	Me	5	**3u**, 64

[a] All reactions were carried out using MCP **1** (0.5 mmol) and $BF_3{\cdot}OEt_2$ (0.5 mmol) in 1.0 mL of **2**.
[b] Isolated yields.

a mixture of *o*:*p*-isomers (*o*:*p* = 1.5:1) in moderate yield in the reaction with **2d** (Scheme 3). The structure of **3v** was established spectroscopically (see Supporting Information).

A plausible mechanism for this novel Friedel–Crafts reaction of MCPs **1** with aromatic compounds is shown in Scheme 4. The MCPs **1** are first cationically charged by the Lewis acid $BF_3{\cdot}OEt_2$ and trace ambient water to give the cation **4**, which immediately rearranges to cation **5** (initiation).[17] Subsequent nucleophilic attack affords the final product and reproduces the proton which protonate the next MCPs **1** to accomplish the catalytic cycle (Scheme 4). The fast rearrangement of



3v, 40%, *o*:*p* = 1.5:1

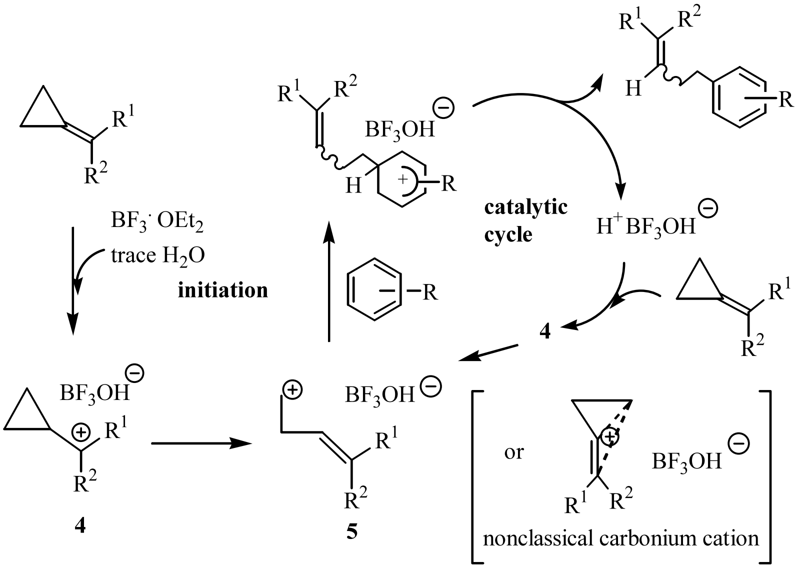
Scheme 3. The formation of 1,2,3,4-tetrahydronaphthalene derivative **3v** from the reaction of MCP **1g** with **2d** catalyzed by $BF_3 \cdot OEt_2$.

cation **4** to **5** is the key step in this reaction.[18] Another possible mechanistic explanation is that a non-classical cyclopropyl carbocation may be involved.[19] However, in either case the same Friedel–Crafts reaction product is formed (Scheme 4).

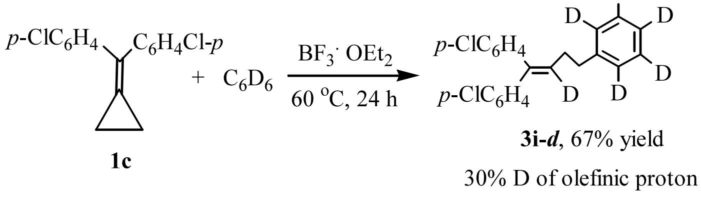
To identify the proton source in this reaction, we used deuterated [D_6]benzene as a substrate to examine its reaction with MCP **1c**. We found that the corresponding Friedel–Crafts reaction product was obtained in 67% yield (D content 30% of olefinic proton, see Supporting Information) (Scheme 5).[17,20] Deuterium incorporation did not occur at the other carbons of **3i**, which is in agreement with the proposed mechanism.

In conclusion, we disclose a previously unknown transformation involving MCPs **1** and aromatic compounds in the presence of Lewis acid $BF_3 \cdot OEt_2$ in this paper. In this transformation, the Friedel–Crafts products **3** can be obtained in good to excellent yields, depending on the substituents of MCPs **1** and aromatic compounds **2**. A wide range of aromatic compounds **2** and MCPs **1** have been examined in this reaction. For the reaction of aliphatic MCP **1g** with anisole in the presence of $BF_3 \cdot OEt_2$, an interesting double-Friedel–Craft reaction takes place to afford the tetrahydronaphthalene derivative. This process provides a novel and efficient route to the synthesis of homoallylic aromatic compounds. Efforts are in progress to further elucidate the mechanistic details of this reaction and to disclose its scope and limitations.

General procedure for the Lewis acid $BF_3 \cdot OEt_2$-catalyzed Friedel–Crafts reaction of methylenecyclopropanes with arenes: To a solution of diphenylmethylenecyclopropane **1a** (103 mg, 0.5 mmol) in toluene **2b** (2.0 mL) was added $BF_3 \cdot OEt_2$ (100 μl, 0.5 mmol) and the reaction mixture was then heated to 60°C. After the reaction solution was stirred for 1 h under an argon



Scheme 4. The proposed mechanism of ring-opening reactions of MCPs **1** catalyzed by Lewis acid $BF_3 \cdot OEt_2$.



Scheme 5. The reaction of benzene-d_6 with MCP **1c** catalyzed by $BF_3 \cdot OEt_2$.

atmosphere (monitored by TLC), it was quenched by the addition of 3.0 mL of water. The reaction mixture was extracted with CH_2Cl_2 (3×5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica flash column chromatography (SiO_2, eluent: petroleum ether) to give the desired product **3b** as a colorless oil (96 mg, 64%).

1-(4,4-Diphenylbut-3-enyl)-4-methylbenzene and 1-(4,4-diphenylbut-3-enyl)-2-methylbenzene 3b (a mixture of *o*- and *p*-isomers, *o*:*p*=1.5:1): **3b** was obtained as a colorless oil. Yield: 64%. IR (thin film) ν 3078, 3055, 3020, 2925, 2860, 1598, 1514, 1494, 1443, 1363, 1073, 1031 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, TMS) for *o*-isomer: δ 2.17 (s, 3H, CH_3), 2.32–2.44 (m, 2H, CH_2), 2.66–2.73 (m, 2H, CH_2), 6.17 (t, $J=7.8$ Hz, 1H, C=CH), 7.02–7.33 (m, 14H, ArH); for *p*-isomer: δ 2.29 (s, 3H, CH_3), 2.32–2.44 (m, 2H, CH_2), 2.66–2.73 (m, 2H, CH_2), 6.11 (t, $J=7.5$ Hz, 1H, C=CH), 7.02–7.33 (m, 14H, ArH). EI-MS (*m*/*z*) 298 (M^+) (3), 193 (100), 178 (21), 165 (8), 115 (49), 105 (10), 91 (15). HRMS (EI): calcd for $C_{23}H_{22}$ (M^+), 298.1722, found: 298.1740.

Acknowledgements

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20. We believe that the low D content is due to the partially quenching by ambient water during the reaction.