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Lewis Acid Catalyzed Cycloaddition of Methylenecyclopropanes with Salicylaldehydes

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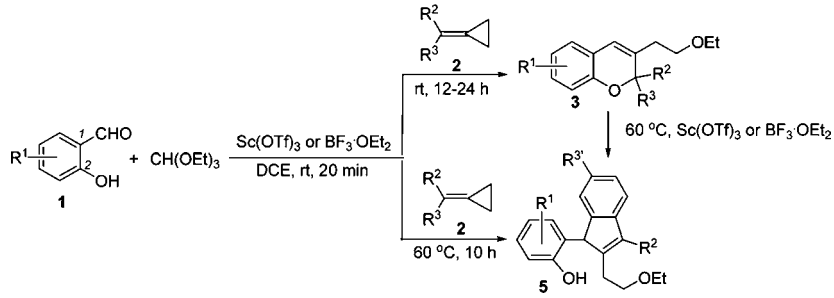
ABSTRACT



Lewis acid catalyzed cycloaddition of methylenecyclopropanes (MCPs) with *o*-quinonemethide analogues, derived from the corresponding salicylaldehydes and $CH(OEt)_3$, produces the corresponding cycloadducts 3 in moderate to high yields at room temperature (20 °C). Moreover, the compounds 3 can be transformed to the indene derivatives 5 at high temperature. Plausible mechanisms have been proposed on the basis of control experiments.

The 2*H*-1-benzopyran (chromene) skeleton has been found in many biologically active compounds.[1] Thus far, a variety of useful and efficient synthetic methods have been explored. Among these synthetic protocols, *o*-quinonemethides that can be generated from salicylaldehydes with $CH(OMe)_3$ act as particularly versatile intermediates for the synthesis of various oxygenated heterocycles[2] and have been widely used in the synthesis of many functional benzopyrans through intermolecular cycloaddition with various compounds containing C=C double bonds.[3] Methylenecyclopropanes (MCPs) are highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis[4] through a variety of ring-opening reactions in the presence of a transition metal or Lewis acid because the relief of ring strain can provide a potent thermodynamic driving force.[5] On the basis of above results, we envisaged that the Lewis acid catalyzed cycloaddition of *o*-quinonemethides with MCPs may produce novel benzopy-

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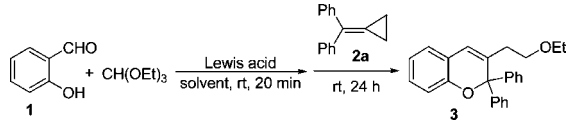
ran derivatives under mild conditions. Therefore, we attempted to examine the reaction of MCPs **1** with *o*-quinonemethide analogues, generated from salicylaldehydes and $CH(OEt)_3$ in the presence of a Lewis acid. In this Letter, we wish to present a novel $Sc(OTf)_3$- or BF_3•Et_2O-catalyzed cycloaddition of MCPs with *o*-quinonemethide analogues to produce the corresponding chromene derivatives in moderate to good yields under mild conditions along with the further transformation to indene derivatives at high temperature.

Initial examinations using diphenylmethylenecyclopropane **2a** (1.0 equiv) as the substrate to react with salicylaldehyde **1a** (2.5 equiv) and triethoxymethane ($CH(OEt)_3$, 3.0 equiv) in the presence of a Lewis acid (0.3 equiv) in various solvents were aimed at determining the optimal conditions, and the results of these experiments are summarized in Table 1. The reaction

Table 1. Optimization of the Reaction Conditions



entry[a]	Lewis acid	solvent	**3**, yield (%)[b]
1	$Yb(OTf)_3$	DCE	71
2	**$Sc(OTf)_3$**	**DCE**	**78**
3	$Yb(NTf_2)_3$	DCE	41
4	$Zr(OTf)_4$	DCE	47
5	$Bi(OTf)_2Cl$	DCE	38
6	$Fe(OTf)_2$•$2CH_3CN$	DCE	53
7	BF_3•Et_2O	DCE	75
8	$Yb(OTf)_3$	CH_2Cl_2	66
9	$Sc(OTf)_3$	THF	NR
10	$Sc(OTf)_3$	Et_2O	NR
11	$Sc(OTf)_3$	toluene	NR
12	$Sc(OTf)_3$	CH_3CN	28

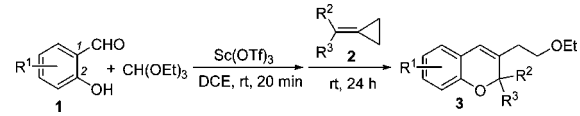
[a] Reaction conditions: **1a** (0.25 mmol), $CH(OEt)_3$ (0.3 mmol), $Sc(OTf)_3$ (0.03 mmol), and DCE (2.0 mL) were used, the reactions were carried out at rt for 20 min, and then MCP **2a** (0.1 mmol) was added. The reaction mixtures were stirred at rt for 24 h. [b] Isolated yields.

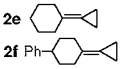
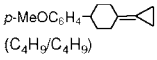
procedure is that after the reaction mixtures of salicylaldehyde **1a**, $CH(OEt)_3$, and Lewis acid were stirred in 1,2-dichloroethane (DCE) at room temperature (20 °C) for 20 min, then MCP **2a** was added, and the resulting mixtures were further stirred for 24 h. After the usual workup, the residue was subjected to the silica gel column chromatography to give the product. It was found that using $Yb(OTf)_3$ as the catalyst afforded the cycloaddition compound **3a** in 71% yield (Table 1, entry 1). Using $Sc(OTf)_3$ instead of $Yb(OTf)_3$ produced **3a** in 78% yield (Table 1, entry 2). Other Lewis acids such as $Yb(NTf_2)_3$, $Zr(OTf)_4$, $Bi(OTf)_2Cl$, $Fe(OTf)_2$•$2CH_3CN$, and BF_3•Et_2O were not as effective as $Sc(OTf)_3$, affording **3a** in 41−75% yields (Table 1, entries 3−7). The examination of solvent effects revealed that in tetrahydrofuran (THF), Et_2O, and toluene, no reaction occurred, and in dichloromethane or acetonitrile, **3a** was produced in 66% or 28% yield, respectively, under the standard conditions (Table 1, entries 9−11 and 8, 12). Therefore, the best conditions are to carry out the reaction in DCE at room temperature using **1a** (1.0 equiv), **2a** (2.5 equiv), and $CH(OEt)_3$ (3.0 equiv) in the presence of $Sc(OTf)_3$ (0.3 equiv).

The structure of **3a** was determined by NMR spectroscopic data and mass and HRMS analyses (see Supporting Information). Furthermore, the X-ray crystal structure of **3a** was determined and is presented with its CIF data in Supporting Information.[6]

With these optimal conditions in hand, we next carried out this reaction using a variety of starting materials **1** and methylenecyclopropanes **2** as shown in Table 2 to examine

Table 2. Scope and Limitations of This Cycloaddition Reaction



entry[a]	**1** (R^1)	**2** (R^2/R^3)	**3**, yield (%)[b]
1	**1b** (5-Me)	**2a** (C_6H_5/C_6H_5)	**3b**, 71
2	**1c** (5-NO_2)	**2a** (C_6H_5/C_6H_5)	**3c**, 73
3	**1d** (5-Br)	**2a** (C_6H_5/C_6H_5)	**3d**, 61
4	**1e** (5-Cl)	**2a** (C_6H_5/C_6H_5)	**3e**, 80
5	**1f** (3-Me)	**2a** (C_6H_5/C_6H_5)	**3f**, 75
6	**1a** (H)	**2b** (C_6H_5/Me)	**3g**, 80
7	**1a** (H)	**2c** (*p*-ClC_6H_4/H)	**3h**, 61
8	**1a** (H)	**2d** (C_4H_9/C_4H_9)	**3i**, 78
9	**1a** (H)	**2e** 	**3j**, 79
10	**1a** (H)	**2f** Ph- 	**3k**, 79 (2:1)[c]
11	**1a** (H)	**2g** *p*-$MeOC_6H_4$- 	**3l**, 78 (1.6:1.4)[c]
12	**1b** (5-Me)	**2d** (C_4H_9/C_4H_9)	**3m**, 82
13	**1b** (5-Me)	**2e**	**3n**, 78

[a] Reaction conditions: **1** (0.25 mmol), $CH(OEt)_3$ (0.3 mmol), $Sc(OTf)_3$ (0.03 mmol), and DCE (2.0 mL) were used, the reactions were carried out at rt for 20 min, then MCPs **2** (0.1 mmol) were added, and the reaction mixtures were stirred for 24 h. [b] Isolated yields. [c] The ratio of isomeric mixtures was determined by ^1H NMR spectroscopic data.

the scope and limitations of this cycloaddition. As for salicylaldehydes **1b**−**1f** having a variety of substituents on the benzene rings, the reactions with MCP **2a** proceeded smoothly to afford the corresponding cycloadducts **3b**−**3f** in 61−80% yields, indicating that the substituents on the aromatic ring of **1** did not have significant influence on the

(5) Selected recent contributions from our group: (a) Shi, M.; Liu, L. P.; Tang, J. *J. Am. Chem. Soc.* **2006**, *128*, 7430–7431. (b) Shao, L.-X.; Xu, B.; Huang, J.-W.; Shi, M. *Chem.—Eur. J.* **2006**, *12*, 510–517. (c) Shi, M.; Xu, B.; Huang, J.-W. *Org. Lett.* **2004**, *6*, 1175–1178. (d) Tian, G.-Q.; Shi, M. *Org. Lett.* **2007**, *9*, 4917–4920. (e) Shao, L.-X.; Li, Y.-X.; Shi, M. *Chem.—Eur. J.* **2007**, *13*, 862–869. (f) Yao, L. F.; Shi, M. *Org. Lett.* **2007**, *9*, 5187–5190. (g) Jiang, M.; Shi, M. *Organometallics* **2009**, *28*, 5600–5602. (h) Jiang, M.; Shi, M. *Tetrahedron* **2009**, *65*, 5222–5227. (i) Jiang, M.; Shi, M. *J. Org. Chem.* **2009**, *74*, 2516–2520.

(6) The crystal data of **3a** have been deposited in CCDC with number 760083. Empirical formula: $C_{25}H_{24}O_2$. Formula weight: 356.44. Crystal color, habit: colorless, prismatic. Crystal dimensions: 0.402 × 0.307 × 0.231 mm^3. Crystal system: monoclinic. Lattice type: primitive. Lattice parameters: a = 9.4459(9) Å, b = 11.0752(10) Å, c = 18.8988(18) Å, α = 90°, β = 100.572(2)°, γ = 90°, V = 19435(3)Å^3. Space group: $P2(1)/n$; Z = 4; D_{calc} = 1.218 g/cm^3; F_{000} = 760. Diffractometer: Rigaku AFC7R. Residuals: R, Rw 0.0479, 0.1174.

reaction outcomes (Table 2, entries 1−5). As for unsymmetrical MCPs **2b** where R^2 is an aromatic group and R^3 is a methyl and **2c** where R^2 is an aromatic group and R^3 is a proton, the corresponding products **3g** and **3h** were obtained in 80% and 61% yield, respectively (Table 2, entries 6 and 7). It should be noted that using aliphatic MCPs **2d**−**2g**, in which both R^1 and R^2 are alkyl groups, as the substrates, the expected products **3i**−**3l** were obtained in 78−79% yields (Table 2, entries 8−11). The products **3k** and **3l** were obtained as isomeric mixtures in which the ratios were determined by ^{1}H NMR spectroscopic data. At the same time, the corresponding cycloadducts **3m** and **3n** could be obtained in 82% and 78% yield, respectively, if using salicylaldehyde **1b** and aliphatic MCPs **2d** and **2e** as substrates under the standard condition (Table 2, entries 12 and 13).

Under these optimal conditions, we further investigated the cycloaddition of a variety of MCPs **2h**−**2l** where either one or both of R^2 or R^3 are a substituted aromatic group and found that no reactions occurred at room temperature for these substrates. Raising the reaction temperature to 60 °C afforded the ring-opened products **4a**−**4e** in 70−80% yields within 3 h rather than the corresponding cycloadducts (Table 3, entries

Table 3. Scope and Limitations of This Cycloaddition Reaction

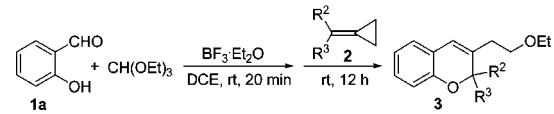
entry[a]	**2** (R^2/R^3)	**4**, yield (%)[b]
1	**2h** (o,p-$Me_2C_6H_3$/C_6H_5)	**4a**, 80 (*E*)
2	**2i** (*p*-MeC_6H_4/*p*-MeC_6H_4)	**4b**, 76
3	**2j** (*p*-$MeOC_6H_4$/*p*-$MeOC_6H_4$)	**4c**, 70
4	**2k** (*p*-ClC_6H_4/*p*-ClC_6H_4)	**4d**, 75
5	**2l** (*p*-ClC_6H_4/C_6H_5)	**4e**, 79 (E,Z)[c]

[a] Reaction conditions: **1** (0.25 mmol), $CH(OEt)_3$ (0.3 mmol), $Sc(OTf)_3$ (0.03 mmol), and DCE (2.0 mL) were used, the reactions were carried out at rt for 20 min, and then MCPs **2** were added. The reaction temperature was increased to 60 °C, and the reaction mixtures were stirred for 3 h. [b] Isolated yields. [c] Determined by NMR spectroscopic data.

1−5). For unsymmetrical aromatic groups substituted MCP **2l**, the corresponding product **4e** was obtained as mixtures of *E*- and *Z*-isomers in 79% yield (Table 3, entry 5). We assumed that the electronic and steric properties of MCPs **2h**−**2l** impaired the cycloaddition with the in situ generated *o*-quinonemethide analogues at room temperature. However, raising the temperature favored the ring-opening reaction of MCPs with EtOH generated from $CH(OEt)_3$ in the presence of $Sc(OTf)_3$, affording products **4** in good yields.[7]

Furthermore, using BF_3•OEt_2 instead of $Sc(OTf)_3$ as catalyst in the cycloaddition of **1a** with MCPs **2h**, **2i**, and **2k**−**2m**, we found that the corresponding cycloadducts **3o**−**3s** were formed in 72−83% yields within 12 h at room temperature whether electron-donating or electron-withdrawing substituents were introduced on the benzene rings of MCPs **2** (Table 4, entries 1−5).

Table 4. Scope and Limitations for this Cycloaddition Reaction with BF_3•OEt_2

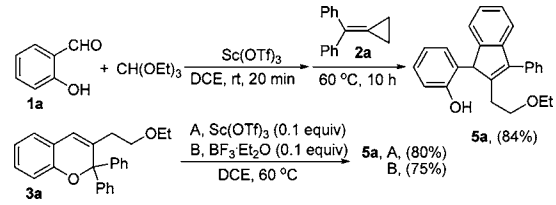


entry[a]	**2** (R^2/R^3)	**3**, yield (%)[b]
>1	**2h** (*o*,*p*-$Me_2C_6H_3$/C_6H_5)	**3o**, 72
2	**2i** (*p*-MeC_6H_4/*p*-MeC_6H_4)	**3p**, 78
3	**2k** (*p*-ClC_6H_4/*p*-ClC_6H_4)	**3q**, 73
4	**2l** (*p*-ClC_6H_4/C_6H_5)	**3r**, 80
5	**2m** (*p*-MeC_6H_4/*p*-BrC_6H_4)	**3s**, 83

[a] Reaction conditions: 1 (0.25 mmol), $CH(OEt)_3$ (0.3 mmol), $Sc(OTf)_3$ (0.03 mmol), and DCE (2.0 mL) were used, the reactions were carried out at rt for 20 min, then MCPs **2** (0.10 mmol) were added, and the reaction mixtures were stirred for 12 h. [b] Isolated yields.

Using salicylaldehyde **1a** as substrate, we also attempted to raise the reaction temperature to 60 °C using $Sc(OTf)_3$ as the catalyst after adding the MCP **2a** into the reaction mixture. Interestingly, it was found that indene derivative **5a** was obtained in 84% rather than the cycloadduct **3a** (Scheme 1). The control experiment indicated that heating

Scheme 1. Reactions at Higher Temperature



cycloadduct **3a** in the presence of $Sc(OTf)_3$ or BF_3•OEt_2 in DCE at 60 °C produced **5a** in 80% and 75% yield, respectively, suggesting that **3a** could be transformed to **5a** upon heating in the presence of a Lewis acid (Scheme 1).

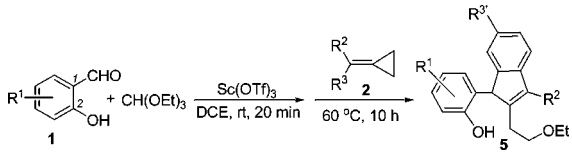
The structure of **5a** was also determined by spectroscopic data and mass and HRMS analyses (see Supporting Information). At the same time, the X-ray crystal structure of **5a** was determined and is presented with its CIF data in Supporting Information.[8]

Upon heating, we next investigated several substituted salicylaldehydes **1b**, **1d**, and **1e** with MCP **2a** (sterically less hindered MCP), and the results are summarized in Table 5. The corresponding indene products **5b**−**5d** were obtained in 64−72%

(7) Shi, M.; Xu, B. *Org. Lett.* **2002**, *4*, 2145–2148.

(8) The crystal data of **5a** have been deposited in CCDC with number 739822. Empirical formula: $C_{25}H_{24}O_2$. Formula weight: 356.44. Crystal color, habit: colorless, prismatic. Crystal dimensions: 0.401 × 0.311 × 0.269 mm^3. Crystal system: monoclinic. Lattice type: primitive. Lattice parameters: a = 15.829(2) Å, b = 7.5020(12) Å, c = 16.492(3) Å, α = 90°, β = 95.853(3)°, γ = 90°, V = 1948 2(5) Å^3. Space group: $P2(1)/n$; Z = 4; D_{calc} = 1.215 g/cm^3; F_{000} = 760. Diffractometer: Rigaku AFC7R. Residuals: *R*, *Rw* 0.0593, 0.1714.

Table 5. $Sc(OTf)_3$- and $BF_3{\cdot}OEt_2$-Catalyzed Cycloaddition of Salicylaldehydes **1b**, **1d**, and **1e** with MCPs **2a** and **2k** Upon Heating



1 2 5

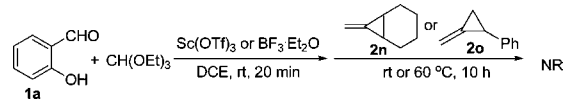
entry[a]	1 (R^1)	2 (R^2/R^3)	5, yield (%)[b] ($R^{3'}$)
1	**1b** (5-Me)	**2a** (C_6H_5/C_6H_5)	**5b**, 70 (H)
2	**1d** (5-Br)	**2a** (C_6H_5/C_6H_5)	**5c**, 64 (H)
3	**1e** (5-Cl)	**2a** (C_6H_5/C_6H_5)	**5d**, 72 (H)
4	**1a** (H)	**2k** (*p*-ClC_6H_4/*p*-ClC_6H_4)	**5e**, 62 (Cl)[c]

[a] Reaction conditions: **1** (0.25 mmol), $CH(OEt)_3$ (0.3 mmol), $Sc(OTf)_3$ (0.03 mmol), and DCE (2.0 mL) were used, the reactions were carried out at rt for 20 min, and then MCPs **2** (0.10 mmol) were added. The reaction mixtures were stirred at 60 °C for 10 h. [b] Isolated yields. [c] $BF_3{\cdot}Et_2O$ was used instead of $Sc(OTf)_3$.

yields (Table 5, entries 1−3). In the case of MCP **2k** with Cl substituents on the benzene rings (sterically hindered MCP), the expected product **5e** was formed in 62% yield when $BF_3{\cdot}OEt_2$ was used as the catalyst (Table 5, entry 4).

Using MCPs **2n** and **2o** in which both R^2 and R^3 are hydrogen atoms as substrates did not give the cycloadducts under the standard conditions (Scheme 2).

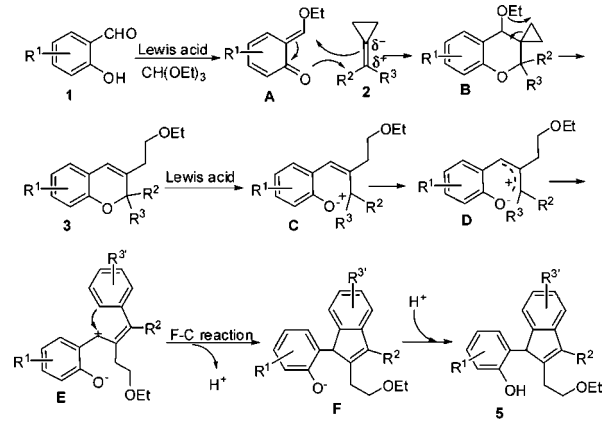
Scheme 2. Reactions with MCPs **2n** and **2o**



1a

A plausible mechanism for the formation of cycloaddition products **3** and the further transformation to products **5** is outlined in Scheme 3 based on the control experiments. The reaction of salicylaldehyde and triethoxymethane generates in situ the corresponding intermediate **A** of the *o*-quinonemethide analogue in the presence of the Lewis acid. Then the cycloaddition of MCP **2** with intermediate **A** takes place to give intermediate **B**, which undergoes ethoxyl (EtO) group elimination along with addition to the cyclopropane ring in the presence of the Lewis acid to give the corresponding product **3**.[9] The electronic distribution of MCPs has been shown in Scheme 3. This is why this cycloaddition can take place regioselectively. At high temperature, the C−O bond

Scheme 3. Proposed Reaction Mechanism



of compound **3** is cleaved in the presence of the Lewis acid to produce intermediate **C**,[10] which undergoes allylic rearrangement to give intermediate **E** via intermediate **D**. Intramolecular Friedel−Crafts reaction of intermediate **E** gives intermediate **F**, which undergoes protonation to afford indene product **5**.

In summary, we have developed an efficient Lewis acid catalyzed cycloaddition of methylenecyclopropanes with *o*-quinonemethide analogues, generated in situ from salicylaldehydes and $CH(OEt)_3$, to produce cycloadducts **3** in moderate to good yields under mild conditions. Furthermore, compounds **3** can be transformed to products **5** in good yields at high temperature in the presence of a Lewis acid. A plausible mechanism has been proposed on the basis of control experiments and previous literature. These functionalized 2*H*-chromenes and 3-phenyl-1*H*-indenes are common structural motifs found in many natural products and biologically active compounds. Clarification of the reaction mechanism and further application of this interesting cycloaddition reaction are in progress.

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Supporting Information Available: Detailed description of experimental procedures, full characterization of new compounds shown in Tables 1−5, and X-ray crystal analysis data for **3a** and **5a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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