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Lewis Acid Catalyzed Ring-Opening Intramolecular Friedel−Crafts Alkylation of Methylenecyclopropane 1,1-Diesters

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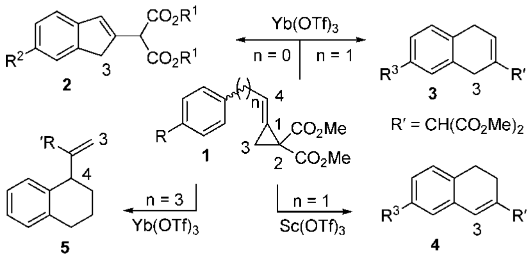
ABSTRACT



The first Friedel−Crafts reaction initiated by the direct generation of a carbocation at the C3 position of MCP 1,1-diesters through distal-bond cleavage was presented. The described method supplied a new synthetic strategy to prepare indene and hydronaphthalene derivatives in moderate to excellent yields under mild conditions.

The development of new and efficient reactions for the construction of carbocycles continues to be one of the most important themes in organic synthesis. Methylenecyclopropanes (MCPs), a kind of highly strained molecule, have been paid much attention due to their ready availability[1] and good reactivity.[2] Recently, Lewis acid catalyzed reactions involving ring opening of MCPs have been extensively investigated and demonstrated potentially high synthetic utility. Most of the Lewis acid-promoted ring opening processes were reported for unfunctionalized MCPs, each triggered by the initial generation of a carbocation at one of the two sp^2 carbons[3] followed by a tandem cyclization process.[4] For Lewis acid catalyzed ring opening of either EDG (electron-donating group)-[5] or EWG (electron-withdrawing group)-activated MCPs,[6,7] only a few examples have been reported in which the ring opening was initiated by the direct generation of a carbocation at one of the two sp^3 carbons on the cyclopropane ring.[8] Lautens[6] and Monti[7] studied the ring opening of mono-EWG-activated MCPs. These reactions were either promoted by the nucleophilic iodine anion or strong Lewis acids (e.g., $TiCl_4$). With the intention of probing functionalized MCPs, we envisioned that the geminal installation of two EWGs (e.g., diesters) at the C2 position of the

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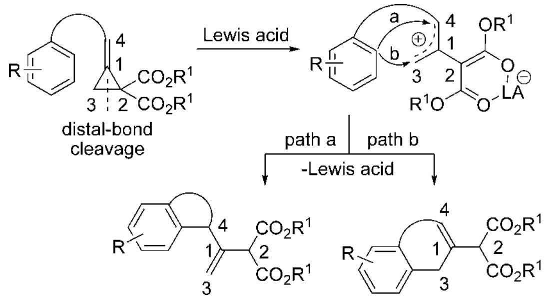
10.1021/ol802301e CCC: $40.75

cyclopropane ring (double-EWGs-activated MCPs) might make the C2−C3 bond be more activated under the promotion of mild Lewis acids. In this process, a discrete dipolar trimethylenemethane (TMM)[9] intermediate might be generated in which the allylic cation can be captured at the C3 or C4 position by a nucleophilic group connected with C4 to construct carbocycles (Scheme 1).

Scheme 1. Designed Tandem Ring Opening of MCP 1,1-Diester/Intramolecular Friedel−Crafts Reaction for Construction of Carbocycles



Herein, we report our recent results for implementing this strategy in which aryl was selected as the nucleophilic group and an intramolecular Friedel−Crafts reaction[10] would be expected. This method supplied an efficient synthesis of indene) and hydronaphthalene[12] skeletons (Figure 1). Indene derivatives are very useful compounds serving as building blocks for biologically active substances,[13] functional materials,[14] and metallocene complexes[15] utilized in the catalysis of olefin polymerization. The naphthalene derivatives are yet other important structural compounds present in a number of bioactive natural products and useful building blocks in organic synthesis.[16] Unlike most of the Friedel−Crafts alkylations which should be carried out under harsh conditions with either high concentrations of acids or large amounts of strong Lewis acids, the alkylations developed in this paper can be run under mild conditions. Additionally, to the best of our knowledge, this is the first Friedel−Crafts reaction initiated by the direct generation of a carbocation at the C3 position of MCPs through distal-bond cleavage.

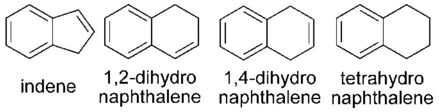


Figure 1.

Initial examinations using MCP 1,1-diester **1a** as the substrate in the presence of a catalytic amount of $Yb(OTf)_3$ in 1,2-dichloroethane (DCE) were aimed at determining the optimal conditions, and the results of these experiments are summarized in Table 1. While the reaction with $Yb(OTf)_3$ (10 mol %) as a Lewis acid in DCE at 50 °C was sluggish, the reaction proceeded smoothly at 80 °C to give an expected Friedel−Crafts alkylation product **2a** in 93% yield after 4.5 h (Table 1, entries 1 and 2). However, lowering catalyst loading in DCE resulted in decreased yield of **2a** even with prolonged reaction time (Table 1, entry 3). Using other Lewis acids such as $Sn(OTf)_2$, $Cu(OTf)_2$, and $Ni(ClO_4)_2{\cdot}6H_2O$ under identical conditions, **2a** was obtained in lower yields (Table 1, entries 5, 7, and 8). The Lewis acid $Sc(OTf)_3$ (10 mol %) is also fairly effective in this reaction giving **2a** in high yield (85%) at 80 °C, but $Zn(OTf)_2$ and $BF_3{\cdot}OEt_2$[17] did not promote the reaction at all (Table 1, entries 4, 6, and 9). In addition, several solvents were tested and showed that DCE is the best one for this transformation.

With suitable reaction conditions in hand, we next explored the scope of the Friedel−Crafts alkylation using a variety of C4-phenyl-substituted MCPs (Table 2). The reaction tolerated a wide range of aromatic substituents at the double bond (Table 2, entries 1−6) to afford **2** in moderate to excellent yields. Electron-donating as well as electron-withdrawing substituents are well accommodated. It was noteworthy that MCP **1j** bearing a naphthalene group rather

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(14) For examples, see: (a) Barberá, J.; Rakitin, O. A.; Ros, M. B.; Torroba, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 296. (b) Yang, J.; Lakshmikantham, M. V.; Cava, M. P. *J. Org. Chem.* **2000**, *65*, 6739.

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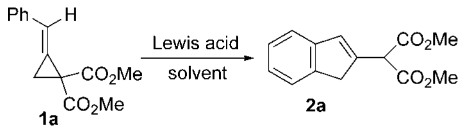
(18) Most of the similarly substituted indenes were reported as mixtures of two inseparable isomers: (a) Adamczyk, M.; Watt, D. S.; Netzel, D. A. *J. Org. Chem.* **1984**, *49*, 4226. (b) Boyd, D. R.; Sharma, N. D.; Bowers, N. I.; Boyle, R.; Harrison, J. S.; Lee, K.; Bugg, T. D. H.; Gibson, D. T. *Org. Biomol. Chem.* **2003**, *1*, 1298. (c) Capková, K.; Yoneda, Y.; Dickerson, T. J.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6463.

(19) The crystal data of **2j** and **4d** have been deposited in CCDC with nos. 701460 and 703792, respectively.

Table 1. Optimization of Conditions for the Intramolecular Friedel−Crafts Alkylation of MCP 1,1-Diester **1a** in the Presence of Lewis Acids[a]

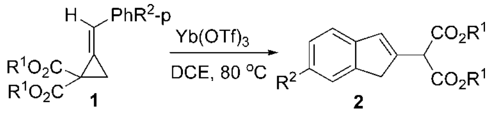


entry	Lewis acid	solvent	*T* (°C)	time (h)	yield[b] (%)
1	$Yb(OTf)_3$	DCE	50	4	trace
2	$Yb(OTf)_3$	DCE	80	4.5	93
3	$Yb(OTf)_3$	DCE	80	16.5	88[c]
4	$Sc(OTf)_3$	DCE	80	3	85
5	$Sn(OTf)_2$	DCE	80	4	77
6	$Zn(OTf)_2$	DCE	80	4	Nr[d]
7	$Cu(OTf)_2$	DCE	80	3.5	46
8	$Ni(ClO_4)_2{\cdot}6H_2O$	DCE	80	22.5	67
9	$BF_3{\cdot}OEt_2$	DCE	80	2	Nr[d]
10	$Yb(OTf)_3$	toluene	80−85	19.5	52
11	$Yb(OTf)_3$	1,4-dioxane	80−85	14	65

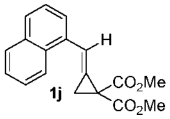
[a] Reaction conditions: 0.40 mmol scale, 10 mol % of Lewis acid, 7.0 mL of solvent, N_2. [b] Isolated yields by silica gel chromatography. [c] 5 mol % of $Yb(OTf)_3$ was used. [d] No reaction occurred.

than a phenyl group was also subjected to the reaction, and the desired product **2j** was obtained in good yield (Table 2, entry 9).

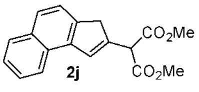
Table 2. $Yb(OTf)_3$-Catalyzed Intramolecular Friedel−Crafts Alkylation of a Variety of C4-Phenyl-Substituted MCP 1,1-Diesters **1**[a]



entry	MCP **1**	R¹	R²	product **2**	time (h)	yield (%)[b]
1	**1b**	Me	MeO	**2b**	3	88
2	**1c**	Me	Me	**2c**	3	97
3	**1d**	Me	F	**2d**	15	69
4	**1e**	Me	Cl	**2e**	10	72
5	**1f**	Me	Br	**2f**	10	80
6	**1g**	Me	I	**2g**	5	79
7	**1h**	Et	H	**2h**	5	99
8	**1i**	i-Pr	H	**2i**	6.5	76
9					3	85



1j



2j

[a] Reaction conditions: 0.40 mmol scale, 10 mol % of $Yb(OTf)_3$, 7.0 mL of DCE, 80 °C, N_2. [b] Isolated yields by silica gel chromatography.

It should be noted that the obtained products **2b−g** and **2j** were mixtures of two chromatographically inseparable isomers in which the carbon−carbon double bonds were at alternative positions of the cyclopentene rings.[18] The structure of the major isomer of **2j** was confirmed by single-crystal X-ray analysis[19] as a 3*H*-cyclopenta[*a*]naphthalene derivative (Figure 2).

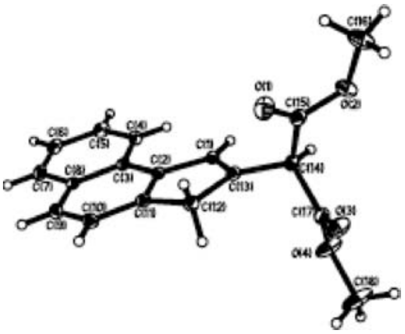
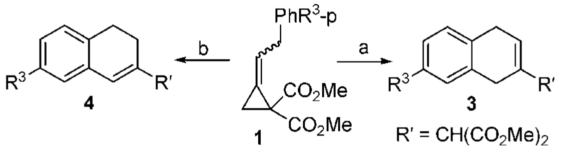


Figure 2. ORTEP drawing of the major isomer of **2j**.

Under the same conditions (10 mol % of $Yb(OTf)_3$), we further investigated the alkylation of several MCP 1,1-diesters **1k−n** where C4 is substituted with a benzyl group and found that these reactions also proceeded smoothly to give the corresponding 1,4-dihydronaphthalenes **3a−d** in moderate yields (Table 3, entries 1, 3, 5, and 7). However, in the presence of 20 mol % of $Sc(OTf)_3$, the products were 1,2-dihydronaphthalenes **4a−d** (Table 3, entries 2, 4, 6, and 8). The structure of **4d** was also confirmed by X-ray diffraction analysis[19] (Figure 3). When the reaction of **1n** (10 mol % of $Sc(OTf)_3$) was stopped midway (18 h), a mixture of **3d** and **4d** was obtained in a ratio of 2:1 (Table 3, entry 9), which implied that there was an isomerization of **3d** to **4d**.

Table 3. $Yb(OTf)_3$- and $Sc(OTf)_3$-Catalyzed Intramolecular Friedel−Crafts Alkylation of Several C4-Benzyl-Substituted MCP 1,1-Diesters **1**[a]



entry	MCP **1**	R³	*E*/*Z*	product (**3**/**4**)	time (h)	yield[b] (%)
1	**1k**	H	2.0:1	**3a**	11	65
2				**4a**	62	87
3	**1l**	Me	2.6:1	**3b**	14	70
4				**4b**	51	70
5	**1m**	Br	2.0:1	**3c**	15	26
6				**4c**	51	56
7	**1n**	Cl	3.6:1	**3d**	14	38
8				**4d**	50.5	58
9				**3d/4d**	18[c]	67[d]

[a] Conditions: (a) the same as those in Table 2; (b) 0.40 mmol scale, 20 mol % of $Sc(OTf)_3$, 7.0 mL of DCE, 80 °C, N_2. For details of operation and analysis, see the Supporting Information. [b] Isolated yields by silica gel chromatography. [c] 10 mol % of $Sc(OTf)_3$ was used. [d] Isolated yield of a mixture of two isomers (**3d**/**4d** = 2:1, determined by ^1H NMR on the isolated product.

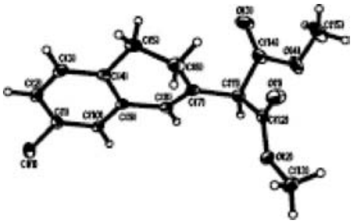
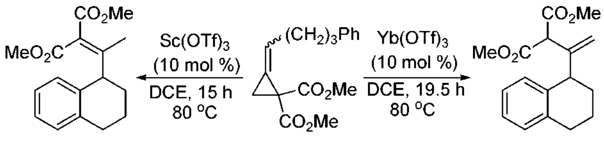


Figure 3. ORTEP drawing of compound **4d**.

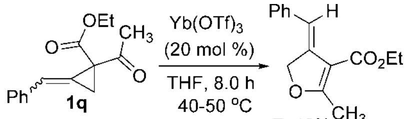
Afterward, using C4-phenylethyl-substituted MCP 1,1-diester **1o** as the substrate under the standard conditions, the reaction was complex.[20] For C4-phenylpropyl-substituted MCP 1,1-diester **1p**, the corresponding alkylation products tetrahydronaphthalenes **5** and **6** were obtained, respectively (Scheme 2).

Scheme 2. Yb(OTf)$_3$- and Sc(OTf)$_3$-Catalyzed Intramolecular Friedel−Crafts Alkylation of C4-Phenylpropyl-Substituted MCP 1,1-Diester **1p**



6, 78% **1p** (E:Z = 2.7:1) **5**, 31%

Scheme 3. Yb(OTf)$_3$-Promoted Cycloisomerization of MCP 1,1-Ketoester **1q**



1q (E:Z = 7.0:1) **7**, 40%

Different from the MCP 1,1-diesters, when MCP 1,1-ketoester **1q** was run in Yb(OTf)$_3$/THF, instead of the ring opening/Friedel−Crafts process, a cycloisomerization happened[21] in which dihydrofuran **7** was obtained as a sole isomer (Scheme 3).

In summary, we present the first Friedel−Crafts reaction initiated by the direct generation of a carbocation at the C3 position of MCPs through distal-bond cleavage. The described method supplied a new synthetic strategy to prepare indene and hydronaphthalene skeletons under mild conditions. The scope and synthetic applications of this new reaction are under investigation.

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Supporting Information Available: Detailed description of experimental procedures, ^{1}H and ^{13}C NMR spectra of the compounds, and NOESY of compound **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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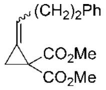
[20] When treated with either 10 mol % of Yb(OTf)$_3$ or Sc(OTf)$_3$ in DCE at 80 °C for 13 h, MCP 1,1-diester **1o** decomposed.



1o (E:Z = 2.4:1)

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