

# Lewis Acid Catalyzed Reaction of Arylvinylicyclopropanes with Acetals: A Facile Synthetic Protocol for the Preparation of Indene Derivatives

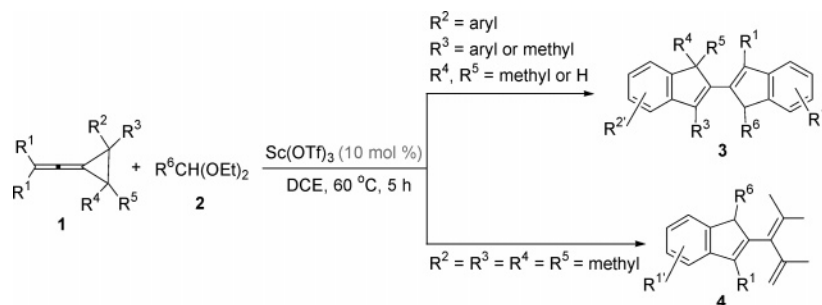
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## ABSTRACT



A number of highly substituted indene derivatives have been prepared in good yields by the reactions of arylvinylicyclopropanes **1** with acetals **2** in the presence of Lewis acid under mild conditions. The reaction is believed to proceed via regioselective addition of oxonium intermediate to arylvinylicyclopropane and the subsequent intramolecular Friedel–Crafts reaction.

Indene derivatives are remarkably useful compounds serving as building blocks for many functional materials,<sup>1</sup> nonsteroidal anti-inflammatory drugs,<sup>2</sup> and biologically active substances<sup>3</sup> as well as ligands for transition metals by deprotonation.<sup>4</sup> This has stimulated the development of a number of approaches for the synthesis of the indene ring system, including cycloalkylation procedures such as reduction/dehydration of indanones,<sup>5</sup> cyclization of phenyl-

substituted allylic alcohols in the presence of strong Brønsted acid,<sup>6</sup> thermal ring opening of substituted cyclopropenes,<sup>7</sup> and Friedel–Crafts reaction of *gem*-dihalocyclopropane derivatives with aromatic compounds mediated by aluminum chloride or ferric chloride.<sup>8</sup> Although these classic methods are quite efficient for the synthesis of simple indene derivatives, overall, these routes consist of several steps with low overall yields and only moderate flexibility for the preparation of substituted indene derivatives. These draw-

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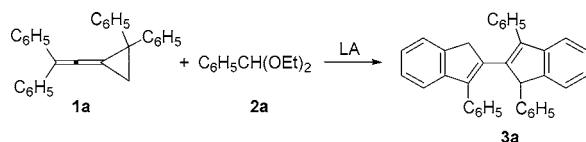
(8) Skattebol, L.; Boulette, B. *J. Org. Chem.* **1966**, *31*, 81–85.

backs have prompted us to develop a general synthetic protocol for the preparation of substituted indene derivatives.

Recently, we reported Lewis acid-catalyzed unimolecular rearrangements of arylvinylidenecyclopropanes **1** to produce naphthalene, 6*a*H-benzo[*c*]fluorine, and indene derivatives depending on the substitution pattern of the cyclopropyl rings and the electronic nature of aryl groups.<sup>9</sup> Herein, we present a new synthetic protocol for the preparation of substituted indene derivatives by Lewis acid (LA) catalyzed reaction of **1** with acetals under mild conditions.

Initial studies were aimed at finding the optimal reaction conditions for the Lewis acid catalyzed reaction. Using diphenylvinylidenecyclopropane **1a** as the substrate, we examined the reaction of **1a** with acetal **2a** in the presence of a variety of Lewis acids. The results are summarized in Table 1. Using Sc(OTf)<sub>3</sub> (10 mol %) as the catalyst in 1,2-

**Table 1.** Optimization of the Reaction Conditions of **1a** and **2a**



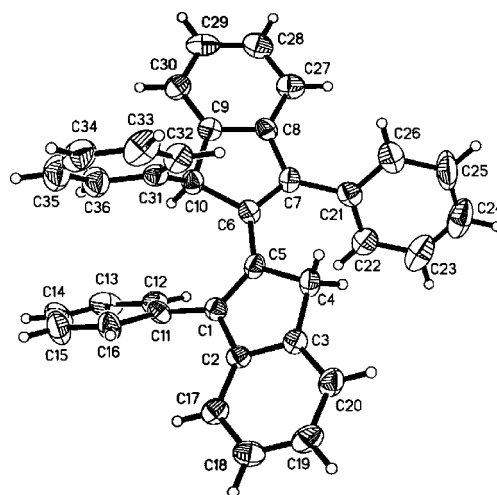
entry <sup>a</sup>	solvent	catalyst	<i>T</i> (°C)	time (h)	yield of <b>3a</b> <sup>b</sup> (%)
1	DCE	Yb(OTf) <sub>3</sub>	rt	24	12 <sup>c</sup>
2	DCE	Yb(OTf) <sub>3</sub>	60	6	76
3	DCE	Yb(OTf) <sub>3</sub>	80	6	72
4	DCE	Sc(OTf) <sub>3</sub>	60	5	90
5	DCE	Sn(OTf) <sub>2</sub>	60	5	78
6	DCE	Zr(OTf) <sub>4</sub>	60	5	69
7	DCE	BF <sub>3</sub> ·OEt <sub>2</sub>	60	5	86
8	DCE	In(OTf) <sub>3</sub>	60	5	88
9	DCE	La(OTf) <sub>3</sub>	60	24	11 <sup>d</sup>
10	THF	Sc(OTf) <sub>3</sub>	60	24	trace
11	CH <sub>3</sub> CN	Sc(OTf) <sub>3</sub>	60	4	78
12	toluene	Sc(OTf) <sub>3</sub>	60	4	69
13	dioxane	Sc(OTf) <sub>3</sub>	60	24	NR
14	CH <sub>2</sub> Cl <sub>2</sub>	Sc(OTf) <sub>3</sub>	40	5	44
15	Et <sub>2</sub> O	Sc(OTf) <sub>3</sub>	35	24	trace
16	hexane	Sc(OTf) <sub>3</sub>	60	7	57
17	EtOH	Sc(OTf) <sub>3</sub>	60	24	trace

<sup>a</sup> All reactions were carried out using **1a** (0.2 mmol), **2a** (0.4 mmol), and catalyst (10 mol %) in various solvents (2.0 mL). <sup>b</sup> Isolated yields. <sup>c</sup> 30% of **1a** was recovered. <sup>d</sup> 23% of **1a** was recovered.

dichloroethane (DCE) at 60 °C, 1,3-diphenyl-2-(3-phenyl-1*H*-inden-2-yl)-1*H*-indene **3a**, which was unambiguously determined by X-ray diffraction (Figure 1),<sup>10</sup> was formed in 90% yield (Table 1, entries 1–9). The examination of solvent effects revealed that DCE is the best one for the reaction (Table 1, entries 10–17).

(9) (a) Xu, G.-C.; Ma, M.; Liu, L.-P.; Shi, M. *Synlett* **2005**, 1869–1872. (b) Xu, G.-C.; Liu, L.-P.; Lu, J.-M.; Shi, M. *J. Am. Chem. Soc.* **2005**, *127*, 14552–14553. The lower stability of intermediate **H** under the standard reaction conditions might be the reason for the formation of complicated products in the case of arylvinylidenecyclopropane **1n**.

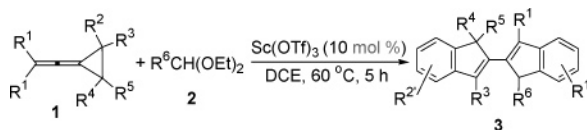
(10) The X-ray crystal data of **3a** has been deposited in CCDC with number 600539 and for **3i** with the number 604706. For the details, see the Supporting Information.



**Figure 1.** ORTEP drawing of **3a**.

Next, we examined a variety of arylvinylidenecyclopropanes **1** with acetals **2** under these optimal reaction conditions. The results are summarized in Table 2. As can be seen

**Table 2.** Sc(OTf)<sub>3</sub>-Catalyzed Reaction of Arylvinylidenecyclopropanes **1** with Acetal **2**

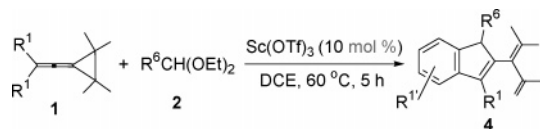


entry <sup>a</sup>	<b>1</b> (R <sup>1</sup> /R <sup>2</sup> /R <sup>3</sup> /R <sup>4</sup> /R <sup>5</sup> )	<b>2</b> (R <sup>6</sup> )	yield of <b>3</b> <sup>b</sup> (%)
1	<b>1b</b> ( <i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> /C <sub>6</sub> H <sub>5</sub> / C <sub>6</sub> H <sub>5</sub> /H/H)	<b>2a</b> (C <sub>6</sub> H <sub>5</sub> )	<b>3b</b> , 89
2	<b>1c</b> ( <i>p</i> -FC <sub>6</sub> H <sub>4</sub> /C <sub>6</sub> H <sub>5</sub> /C <sub>6</sub> H <sub>5</sub> /H/H)	<b>2a</b>	<b>3c</b> , 90
3	<b>1d</b> (C <sub>6</sub> H <sub>5</sub> / <i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> / <i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> /H/H)	<b>2a</b>	<b>3d</b> , 93
4	<b>1e</b> (C <sub>6</sub> H <sub>5</sub> / <i>p</i> -FC <sub>6</sub> H <sub>4</sub> / <i>p</i> -FC <sub>6</sub> H <sub>4</sub> /H/H)	<b>2a</b>	<b>3e</b> , 53
5	<b>1f</b> (C <sub>6</sub> H <sub>5</sub> / <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> / <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> /H/H)	<b>2a</b>	<b>3f</b> , 56
6	<b>1g</b> (C <sub>6</sub> H <sub>5</sub> /C <sub>6</sub> H <sub>5</sub> /C <sub>6</sub> H <sub>5</sub> /CH <sub>3</sub> /H)	<b>2a</b>	<b>3g</b> , 95
7	<b>1h</b> (C <sub>6</sub> H <sub>5</sub> /C <sub>6</sub> H <sub>5</sub> /CH <sub>3</sub> /CH <sub>3</sub> /H)	<b>2a</b>	<b>3h</b> , 87
8	<b>1i</b> (C <sub>6</sub> H <sub>5</sub> /C <sub>6</sub> H <sub>5</sub> /C <sub>6</sub> H <sub>5</sub> /CH <sub>3</sub> /CH <sub>3</sub> )	<b>2a</b>	<b>3i</b> , 86 <sup>c</sup>
9	<b>1j</b> (C <sub>6</sub> H <sub>5</sub> /C <sub>6</sub> H <sub>5</sub> /CH <sub>3</sub> /H/H)	<b>2a</b>	<b>3j</b> , 37
10	<b>1a</b> (C <sub>6</sub> H <sub>5</sub> /C <sub>6</sub> H <sub>5</sub> /C <sub>6</sub> H <sub>5</sub> /H/H)	<b>2b</b> ( <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> )	<b>3k</b> , 94
11	<b>1a</b>	<b>2c</b> ( <i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )	<b>3l</b> , 75
12	<b>1a</b>	<b>2d</b> ( <i>m</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )	<b>3m</b> , 49

<sup>a</sup> All reactions were carried out using **1** (0.2 mmol), **2** (0.4 mmol), and Sc(OTf)<sub>3</sub> (10 mol %) in DCE (2.0 mL). <sup>b</sup> Isolated yields. <sup>c</sup> The structure of **3i** was further unambiguously determined by X-ray diffraction.

from Table 2, the corresponding indene derivatives **3** were obtained in good to high yields within 5 h. For substrates **1e**, **1f**, and **1j**, in which R<sup>2</sup> and R<sup>3</sup> are electron-poor aromatic groups or R<sup>3</sup> is a methyl group and R<sup>4</sup> and R<sup>5</sup> are hydrogen

**Table 3.** Sc(OTf)<sub>3</sub>-Catalyzed Reaction of Arylvinylicyclopropanes **1k–m** with Acetal **2**

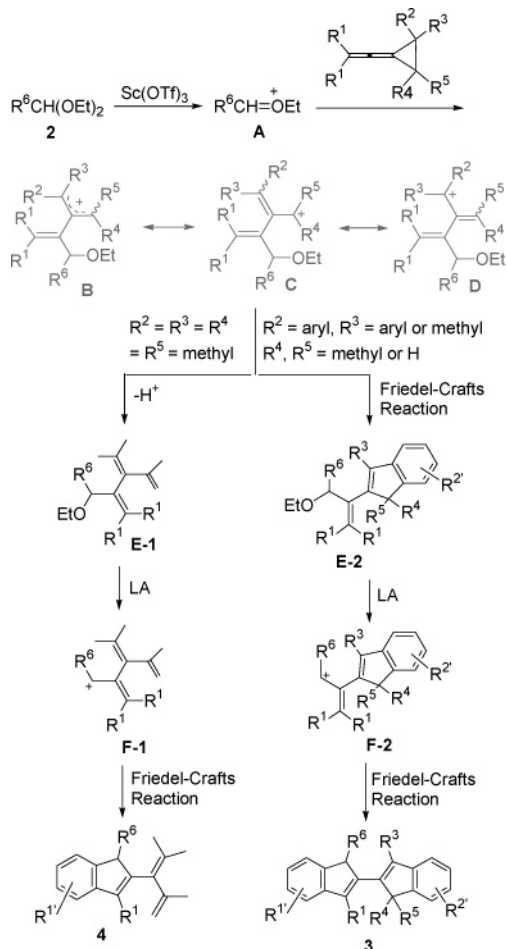


entry <sup>a</sup>	R <sup>1</sup>	<b>2</b> (R <sup>6</sup> )	yield of <b>4</b> <sup>b</sup> (%)
1	<b>1k</b> (C <sub>6</sub> H <sub>5</sub> )	<b>2a</b> (C <sub>6</sub> H <sub>5</sub> )	<b>4a</b> , 54
2	<b>1l</b> ( <i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )	<b>2a</b>	<b>4b</b> , 74
3	<b>1m</b> ( <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> )	<b>2a</b>	<b>4c</b> , 93
4	<b>1k</b>	<b>2b</b> ( <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> )	<b>4d</b> , 99
5	<b>1k</b>	<b>2c</b> ( <i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )	<b>4e</b> , 84
6	<b>1k</b>	<b>2d</b> ( <i>m</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )	<b>4f</b> , 60

<sup>a</sup> All reactions were carried out using **1** (0.2 mmol), **2** (0.4 mmol), and Sc(OTf)<sub>3</sub> (10 mol %) in DCE (2.0 mL). <sup>b</sup> Isolated yields.

atoms, the corresponding indenenes **3e**, **3f**, and **3j** were obtained in somewhat lower yields (Table 2, entries 4, 5, and 9). In addition, similar results were obtained for other acetals **2b–d** under identical conditions (Table 2, entries 10–12).

**Scheme 1.** Proposed Mechanism for the Formation of Indene Derivatives

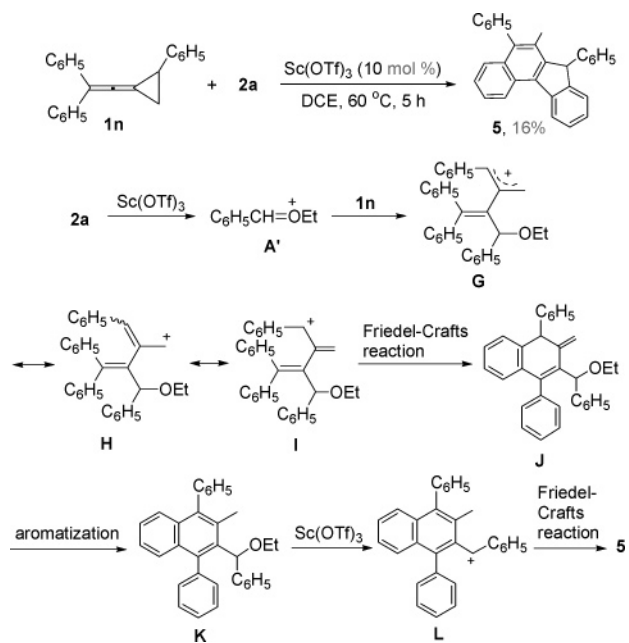


Furthermore, we also found that arylvinylicyclopropanes **1k–m**, in which R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and R<sup>5</sup> are methyl groups, reacted with acetals **2** to give the corresponding 2-(2,4-dimethylpenta-1,3-dien-3-yl)-*1H*-indene derivatives **4** in moderate to good yields under the standard conditions (Table 3).

A plausible mechanism for the formation of indene derivatives is outlined in Scheme 1. Initially, the reaction of acetals **2** with Sc(OTf)<sub>3</sub> generates oxonium intermediate **A**.<sup>11</sup> The reaction of intermediate **A** with arylvinylicyclopropanes **1** produces the cyclopropyl ring-opened π-allylic cationic intermediate **B** or the resonance-stabilized cationic intermediate **C** and **D**. Intermediate **C** undergoes intramolecular Friedel–Crafts reaction to give intermediate **E-2** when R<sup>2</sup> is aryl group, R<sup>3</sup> is aryl or methyl group, R<sup>4</sup> and R<sup>5</sup> are methyl group or hydrogen atoms. When R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and R<sup>5</sup> are methyl groups, deprotonation of intermediate **C** takes place to afford the corresponding intermediate **E-1**. In the presence of Sc(OTf)<sub>3</sub> (LA), intermediate **E-1** or **E-2** loses an ethoxy group to give the corresponding cationic intermediate **F-1** or **F-2**.<sup>12</sup> The subsequent intramolecular Friedel–Crafts reaction of **F-1** and **F-2** produces the indene derivatives **4** and **3**, respectively.

Interestingly, using arylvinylicyclopropane **1n**, which has only one phenyl group at the cyclopropyl ring, as the substrate under identical conditions, we found that 6-methyl-5,7-diphenyl-*7H*-benzo[*c*]fluorene **5** was formed in 16% yield

**Scheme 2.** Reaction of Arylvinylicyclopropane **1n** with Acetal **2a** in the Presence of Sc(OTf)<sub>3</sub> and a Plausible Mechanism



along with other unidentified byproducts (Scheme 2). The structure of **5** was determined on the basis of IR and <sup>1</sup>H and

(11) Meerwein, H.; Florian, W.; Schon, N.; Stopp, G. *Ann. Chem.* **1961**, *641*, 1–39.

$^{13}\text{C}$  NMR spectroscopic data and HRMS analysis. A plausible mechanism for the formation of **5** is shown in Scheme 2. Similar to the previous example, the cyclopropyl ring-opened  $\pi$ -allylic cationic intermediate **G** is formed from the reaction of the corresponding cationic intermediate **F** with **1n**. Because the corresponding resonance-stabilized cationic intermediate **H** is less stable than cationic intermediate **C**, the resonance-stabilized cationic intermediate **I** should be the major intermediate, which undergoes intramolecular Friedel–Crafts reaction to give intermediate **J**.<sup>9</sup> Aromatization of **J** produces the thermodynamically favored naphthalene intermediate **K**, which, also similar to the previous example, produces intermediate **L** in the presence of  $\text{Sc}(\text{OTf})_3$ . Then, the final product **5** was formed similarly via intramolecular Friedel–Crafts reaction.

In conclusion, we have succeeded in an effective Lewis acid-catalyzed synthesis of substituted indene derivatives by

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(12) (a) Wilcox, C. F.; Hellwinkel, D.; Stahl, H.; Gaa, H. G.; Doerner, M. *Tetrahedron Lett.* **1988**, *29*, 5501–5504. (b) Santry, L. J.; McClelland, R. A. *J. Am. Chem. Soc.* **1983**, *105*, 3167–3172.

the reactions of arylvinylidenecyclopropanes **1** with acetals **2** under mild conditions. The reaction is believed to proceed via regioselective addition of oxonium intermediate to arylvinylidenecyclopropane and the subsequent intramolecular Friedel–Crafts reaction. Efforts are in progress to elucidate further mechanistic details of these reactions and to understand their scope and limitations.

**Acknowledgment.** We thank the State Key Project of Basic Research (Project 973) (No. G2000048007), Shanghai Municipal Committee of Science and Technology (04JC14083, 06XD14005), Chinese Academy of Sciences (KGCX2-210-01), and the National Natural Science Foundation of China for financial support (20472096, 203900502, and 20272069).

**Supporting Information Available:** Spectroscopic data of all the new compounds, the detailed descriptions of experimental procedures, and X-ray data for compounds **3a** and **3i**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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