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Lewis Acid-Mediated Selective Cycloadditions of Vinylidenecyclopropanes with Aromatic Aldehydes: An Efficient Protocol for the Synthesis of Benzo[*c*]fluorene, Furan and Furo[2,3-*b*]furan Derivatives

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Abstract: Three kinds of Lewis acid-mediated reactions of vinylidenecyclopropanes and aromatic aldehydes are disclosed in this paper, providing an efficient and selective synthesis of a variety of functionalized benzo[*c*]fluorene, furan and furo[2,3-*b*]-furan derivatives.

Keywords: benzo[*c*]fluorenes; furans; furo[2,3-*b*]-furans; Lewis acids; vinylidenecyclopropanes

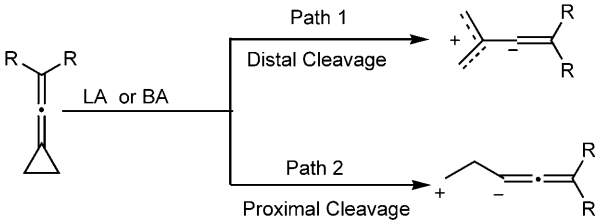
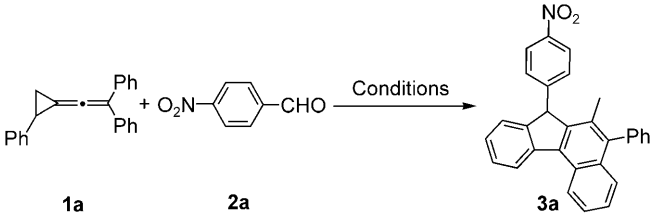


Figure 1. Lewis acid- or Brønsted acid-mediated ring opening reaction models for VCPs.

Vinylidenecyclopropanes (VCPs)[1] show unique reactivity in organic synthesis due to the presence of the cumulated C=C double bonds adjacent to the highly strained cyclopropyl ring, and yet they are thermal stable.[2] An attractive but often troublesome feature of VCPs is their multiform reactivities that may lead to formation of a variety of products through various reaction pathways: selective addition to a cumulated C=C double bond[3] or cleavage of proximal[4] and distal bonds[5,6]. Recently, we have investigated the transition metal-mediated, highly selective ring opening reactions of methylenecyclopropanes (MCPs) and VCPs.[7] Shi et al. reported the Lewis acid-catalyzed reactions of vinylidenecyclopropanes with acetals, activated imines and activated carbonyl compounds to produce many useful organic molecules.[6] The previous investigations have shown that Lewis acid- or Brønsted acid-mediated ring opening reactions of VCPs often took place *via* a cleavage of distal bonds of the three-membered ring (Figure 1, path 1).[5,6] Reports on Lewis acid- or Brønsted acid-mediated reactions of VCPs *via* a cleavage of proximal bonds of the three-membered ring (Figure 1, path 2) are rare.[4e] In this paper, we disclose three kinds of reaction patterns of VCPs and aromatic aldehydes mediated by a Lewis acid which include the above two kinds of ring opening models, providing an efficient and selective synthesis of a variety of functionalized benzo[*c*]fluorene, furan and furo[2,3-*b*]furan derivatives.

We initiated our study by attempting the reaction of VCP **1a** and aldehyde **2a** with 0.3 equiv. of $FeCl_3$ in CH_2Cl_2 under an N_2 atmosphere. After stirring for 24 h at 10 °C, the 6-methyl-7-(4-nitrophenyl)-5-phenyl-7*H*-benzo[*c*]fluorene **3a** was obtained in 21% yield. Recently, Shi et al. reported that the reaction of **1a** with 1-(diethoxymethyl)benzene could also produce 6-methyl-5,7-diphenyl-7*H*-benzo[*c*]fluorene but only in 16% yield.[6a] We then tried to optimize the reaction conditions to achieve a useful synthesis of these products. Various Lewis acids were carefully examined in this reaction; however, these Lewis acids had little effect in improving the yield of **3a** (Table 1, entries 1–5). Interestingly, when the reaction was carried in the presence of 1.2 equiv. of TMSCl, the yield of product **3a** was sharply improved to 67%, and the reaction was completed in 1 h (Table 1, entry 8). Fur-

Table 1. Optimization of the reaction conditions for the synthesis of **3a**.[a]



Entry	LA (equiv.)	Temp. [°C]	Time [h]	Yield of **3a** [%][b]
1	$BF_3{\cdot}Et_2O$ (0.1)	10	24	trace[c]
2	$BF_3{\cdot}Et_2O$ (0.3)	10	12	15
3	$FeCl_3$ (0.3)	10	24	21
4	$ZnCl_2$ (0.3)	10	48	trace[d]
5	$ZrCl_4$ (0.3)	10	20	trace[e]
6	$ZnCl_2$ (0.1)/TMSCl (1.2)	10	2	57
7	$BF_3{\cdot}Et_2O$ (0.1)/TMSCl (1.2)	10	48	trace[f]
8	$FeCl_3$ (0.1)/TMSCl (1.2)	10	1	67
9	$FeCl_3$ (0.1)/TMSCl (0.1)	10	12	27
10	$FeCl_3$ (0.1)/TMSCl (2.2)	10	1	72
11	**$FeCl_3$ (0.1)/TMSCl (1.2)**	**−10**	**2**	**76**
12	$FeCl_3$ (0.1)/TMSCl (1.2)	30	0.5	58

[a] Unless otherwise specified, the reaction was carried out using **1a** (0.2 mmol), **2a** (0.24 mmol) in 4 mL of CH_2Cl_2 at nitrogen atmosphere.
[b] Isolated yields.
[c] 61% of **1a** was recovered.
[d] 56% of **1a** was recovered.
[e] 28% of **1a** was recovered and 30% of 2-methyl-1,4-diphenylnaphthalene was obtained.
[f] 30% of **1a** was recovered and 35% of 2-methyl-1,4-diphenylnaphthalene was obtained.

ther investigations disclosed that when the reaction was conducted at a lower temperature (Table 1, entry 11), the yield was improved to 76%.

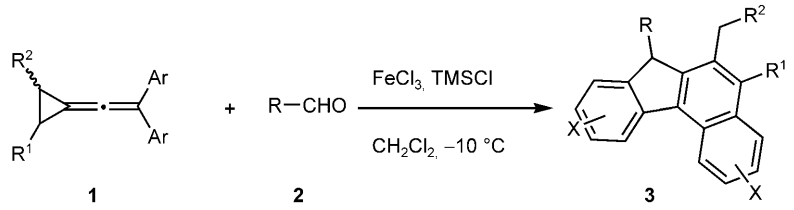
With the optimized conditions in hand, we next examined the reaction of various VCPs with different aromatic aldehydes under identical conditions. The results summarized in Table 2 prove that this reaction indeed provides a straightforward entry to a variety of benzo[*c*]fluorene derivatives in moderate to good yields. As can be seen from Table 2, the substrate **1a** smoothly reacted with various aromatic aldehydes affording the coresponding benzo[*c*]fluorene derivatives in moderate to good yields (Table 2, entries 1–7). we also found that VCPs **1b–d**, in which Ar is an electron-poor or an electron-rich aromatic group, where R^1 is an aryl group and R^2 is a hydrogen atom, the corresponding benzo[*c*]fluorenes **3h–k** were obtained in moderate yields. For substrate **1e**, in which R^1 is an *n*-C_4H_9 group, the corresponding benzo[*c*]fluorene was obtained in 61% (Table 2, entry 11). In addition, for substrate **1f**, in which R^1 = Ph, R^2 = Me (*trans* isomer), the corresponding benzo[*c*]fluorene was obtained in somewhat lower yield (Table 2, entry 12).

When bicyclic VCP **1g** was employed, the reaction furnished the corresponding benzo[*c*]fluorene derivative **3m** in 17% yield along with the furan derivative **4a** in 26% under similar conditions (Scheme 1, *top*). Surprisingly, when we carried out the reaction in the presence of $BF_3{\cdot}Et_2O$ (0.7 equiv.) instead of $FeCl_3$ and TMSCl, THF, **5a** was obtained in 68% yield.[8] In the meantime, we also found that **5a** could smoothly progress to **4a** in the presence of $BF_3{\cdot}Et_2O$ and TMSCl (Scheme 1). With these observations, we next developed a one-pot synthesis of furan derivative **4**. After treatment of bicyclic VCPs **1** and aromatic aldehydes with 0.7 equiv. of $BF_3{\cdot}Et_2O$ at −10 °C for 24 h in CH_2Cl_2, 1.2 equiv. of TMSCl was subsequently added to the reaction mixture, which was then warmed to room temperature for another 24 h with stirring. With a general work-up, furan derivatives **4a–e** could be obtained in 54–72% yield (Scheme 1, *bottom*). Here it should be noted that the synthesis of multi-substituented furan derivatives is of high chemical and biochemical importance because these moieties are part of biologically important natural and unnatural compounds.[9]

A plausible mechanism for the formation of benzo[*c*]fluorene derivatives **3** and furan derivatives **4** is shown in Scheme 2.[6] Initially, the electrophilic addition of intermediate **A** with VCPs **1** produces cationic intermediate **B**,[6a] which then rearranges to give the cyclopropyl ring-opened intermediate **C** or the resonance-stabilized intermediates $\mathbf{C^1}$ and $\mathbf{C^2}$. When R^1 = Ar, R^2 = H or Me, the corresponding resonance-stabilized cationic intermediate $\mathbf{C^1}$ may be more stable than cationic intermediate $\mathbf{C^2}$, thus it undergoes an intramolecular Friedel–Crafts reaction to give intermediate **D**.[5d,6a] Aromatization of **D** produces the thermodynamically favoured naphthalene intermediate **E**, which could transform to the cation **F** in the presence of $FeCl_3$/TMSCl. Then, **F** undergoes another intramolecular Friedel–Crafts reaction to give the final product **3 (path a)**.[6a] For bicyclic VCPs, the cationic intermediate **C** undergoes intramolecular *O*-attacked cyclization instead of the intramolecular Friedel–Crafts reaction to produce **5**.[6b–c] The subsequent aromatization of **5** furnishes the thermodynamically favoured furan derivatives **4 (path b)**.

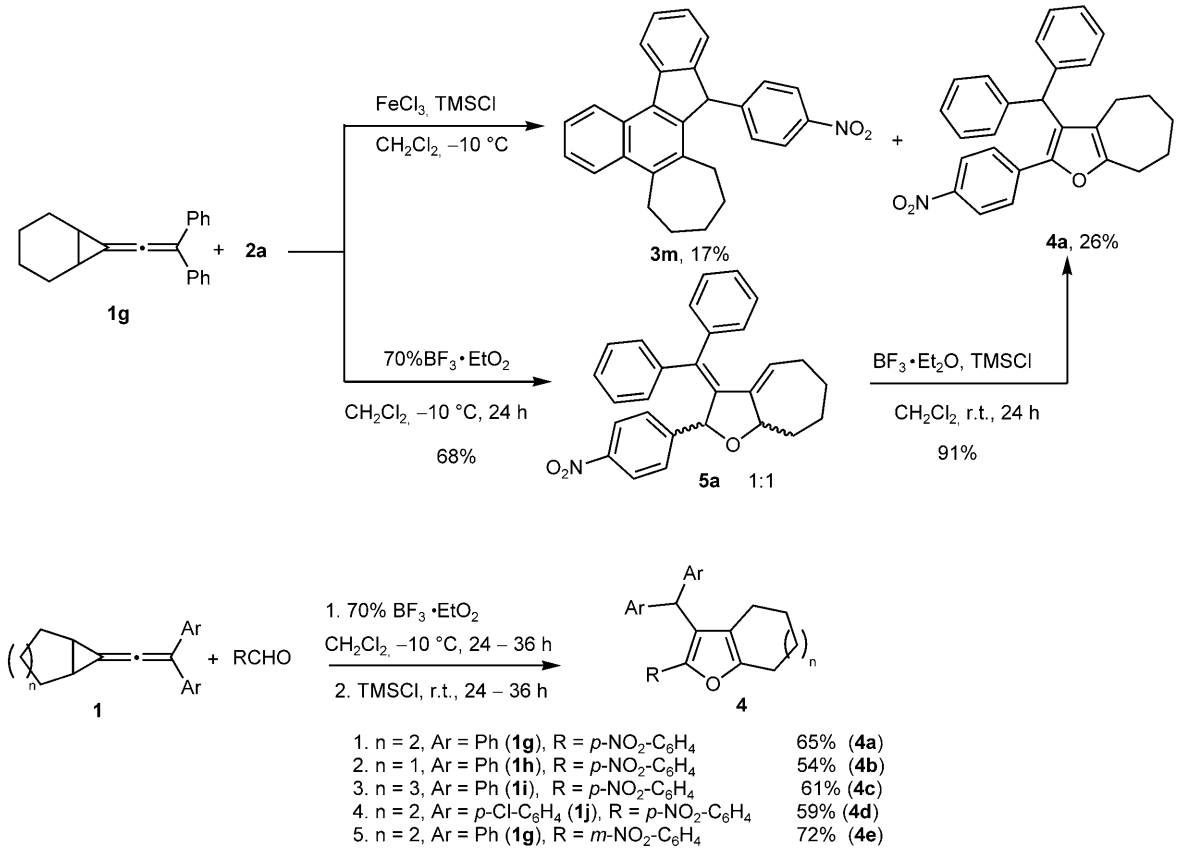
To the best of our knowledge, there are few reports on the reactions of VCPs with functional groups attaching to the cyclopropyl ring.[10,11] We thought that the presence of functional groups may facilitate the selective cleavage of C–C bonds of VCPs, thus delicately tunning the regio- and stereoselectivity of the reactions. As a matter of fact, we found the reaction gave another interesting product, **7a**, under similar conditions when the functionalized VCPs **6a** was employed as substrate [Eq. (1)].

Table 2. Sequential intramolecular Friedel–Crafts reactions for the synthesis of benzo[*c*]fluorene derivatives **3**.[a]

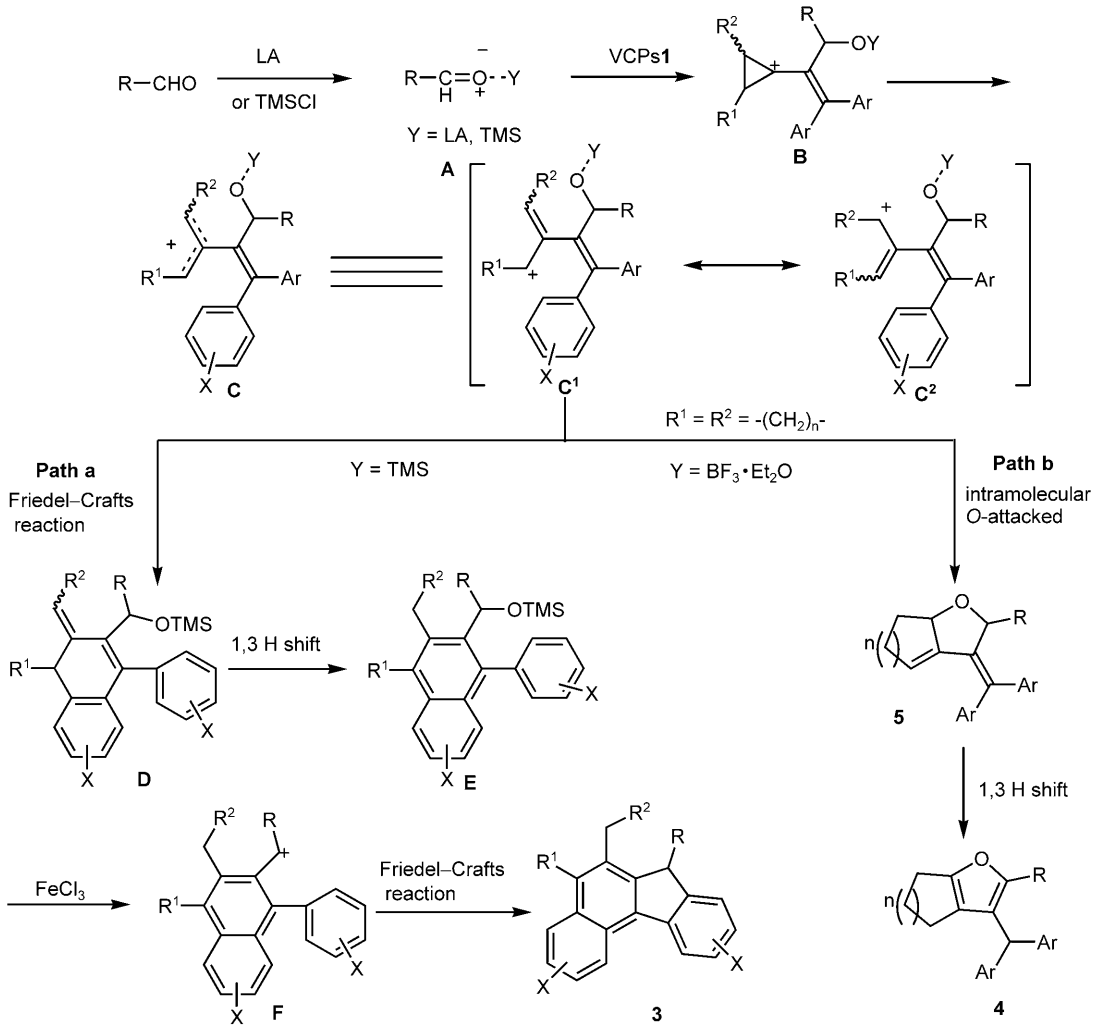


Entry	1			R (2)	Yield of **3** [%][b]
	Ar	R^1	R^2		
1	Ph	Ph	H (**1a**)	*p*-NO_2-C_6H_4 (**2a**)	76 (**3a**)
2	Ph	Ph	H (**1a**)	*p*-Br-C_6H_4 (**2b**)	65 (**3b**)
3	Ph	Ph	H (**1a**)	*o*-Br-C_6H_4 (**2c**)	61 (**3c**)
4	Ph	Ph	H (**1a**)	*p*-Cl-C_6H_4 (**2d**)	64 (**3d**)
5	Ph	Ph	H (**1a**)	Ph (**2e**)	69 (**3e**)
6	Ph	Ph	H (**1a**)	*p*-Me-C_6H_4 (**2f**)	65 (**3f**)
7	Ph	Ph	H (**1a**)	*p*-MeO-C_6H_4 (**2g**)	53 (**3g**)
8	*p*-Cl-C_6H_4	Ph	H (**1b**)	Ph (**2e**)	52 (**3h**)
9	*p*-MeO-C_6H_4	Ph	H (**1c**)	Ph (**2e**)	55 (**3i**)
10	Ph	*p*-Cl-C_6H_4	H (**1d**)	*p*-Br-C_6H_4 (**2b**)	57 (**3j**)
11	Ph	*n*-C_4H_9	H (**1e**)	*p*-$NO_2C_6H_4$ (**2a**)	61 (**3k**)
12	Ph	Ph	Me (**1f**)	*p*-NO_2-C_6H_4 (**2a**)	52 (**3l**)

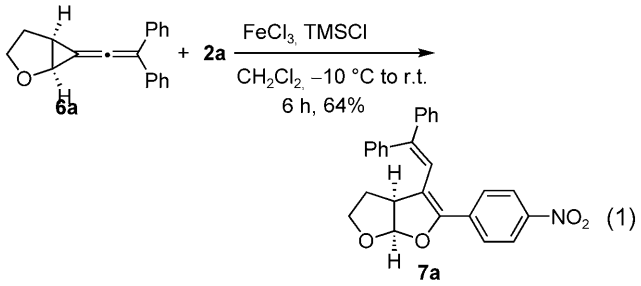
[a] Unless otherwise specified, the reaction was carried out using **1** (0.2 mmol) and **2** (0.24 mmol) in 4 mL CH_2Cl_2 at nitrogen atmosphere.
[b] Isolated yields.



Scheme 1.



Scheme 2. Proposed mechanism for the synthesis of benzo[*c*]fluorene derivatives **3** and furan derivatives **4**.

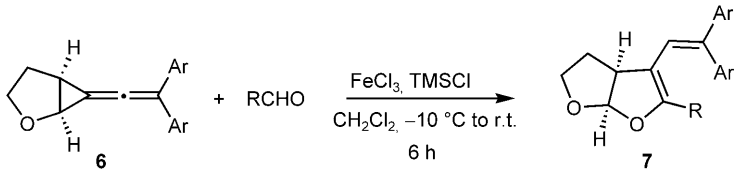


We next studied the scope of this methodology by examining the reaction of different VCPs **6** with various aldehydes under the identified reaction conditions (Table 3). As indicated in Table 3, it is noteworthy that substitutents on the benzene ring of the aldehydes significantly affected the reaction. For aldehydes **2a**, **2h–2k** having an electron-withdrawing group on the benzene ring, the corresponding products **7a–7d** were obtained in moderate yields (Table 3, entries 1–5). A slightly lower yield was obtained when benzaldehyde was employed (Table 3, entry 6). In addition, for aldehydes with an electron-donating methoxy group on the benzene ring, only a trace of product was obtained (Table 3, entry 7).

Mechanistically, this reaction may involve a novel proximal C–C bond cleavage of the cyclopropyl ring. A plausible mechanism is depicted in Scheme 3. Firstly an electrophilic addtion of the Lewis acid-activated aldehyde to VCP may occur to give the ring-opened cation **I**[4e] *via* an unusual proximal cleavage of C–C bonds. This process may be facilitated by the O atom attached to the cyclopropyl ring moiety. Then an intramolecular cyclization of cation **I** along with the release of the Lewis acid furnishes the [3+2]cycloaddition product **8**, which progresses to the corresponding product **7** *via* 1,3 H shift.

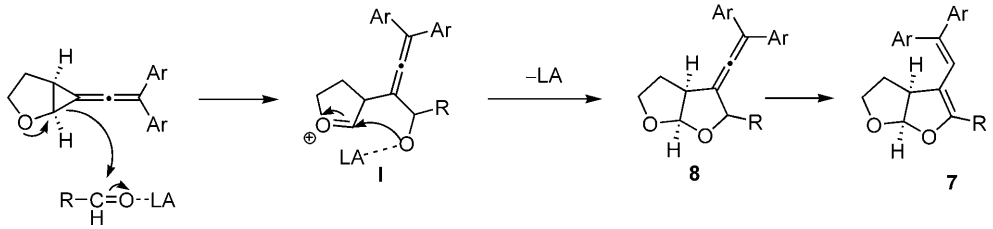
To clarify the proposed mechanism, a variety of reaction conditions were examined. When we carried out the reaction of **6a** with aldehyde **2a** with 0.1 equiv. of $ZnCl_2$, the intermediate product **8a** was obtained in 42% yield. Further investigations proved that **8a**

Table 3. The Lewis acid-mediated cycloadditions of VCPs **6** with aldehydes for the synthesis of **7**.



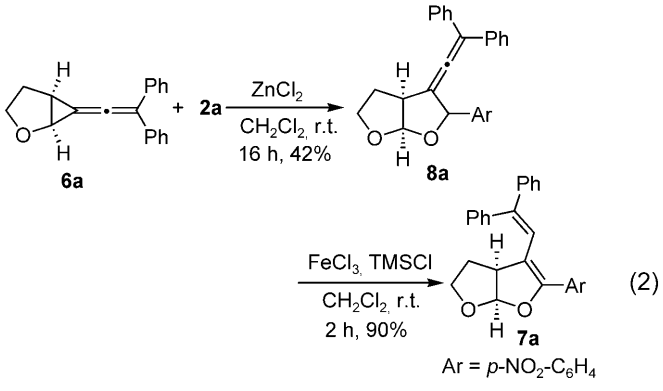
Entry	Ar (**6**)	R (**2**)	Yield of **7** [%][a]
1	Ph (**6a**)	*p*-NO_2-C_6H_4 (**2a**)	64[b] (**7a**)
2	Ph (**6a**)	*m*-NO_2-C_6H_4 (**2h**)	62 (**7b**)
3	Ph (**6a**)	*o*-NO_2-C_6H_4 (**2i**)	57 (**7c**)
4	Ph (**6a**)	*p*-CF_3-C_6H_4 (**2j**)	48 (**7d**)
5	Ph (**6a**)	3-NO_2,4-ClC_6H_3 (**2k**)	61 (**7e**)
6	Ph (**6a**)	Ph (**2e**)	37 (**7f**)
7	Ph (**6a**)	*p*-MeO-C_6H_4 (**2g**)	trace[c]
8	*p*-MeO-C_6H_4 (**6b**)	*p*-NO_2-C_6H_4 (**2a**)	45 (**7g**)

[a] Isolated yields.
[b] The configuration was established on the NOESY studies (see Supporting Information).
[c] Some other unidentified products were obtained.



Scheme 3. Proposed mchanism.

could isomerize to **7a** in the presence of $FeCl_3$/TMSCl [Eq. (2)]. These results may partially support the proposed mechanism.



In conclusion, we have disclosed two kinds of reaction patterns of VCPs **1** and aromatic aldehydes **2** mediated by Lewis acids *via* a classic distal cleavage of C–C bonds, providing an efficient and selective synthesis of a variety of functionalized benzo[*c*]fluorene and furan derivatives. Attractively, when the functionalized VCPs **6** were employed as substrates, the useful furo[2,3-*b*]furan skeleton was formed *via* a very different and selective proximal cleavage of C–C bonds. Moreover, plausible reaction mechanisms were also discussed based on the obtained intermediates. Hence, the reaction may be of interest both from the mechanistic and synthetic standpoints. Further studies to expand the scope and synthetic utility of these reactions are underway.

Experimental Section

Typical Experimental Procedure for the Synthesis of Benzo[*c*]fluorene Derivatives

Under an atmosphere of dry nitrogen, $FeCl_3$ (3 mg, 10 mmol%) was added to a solution of aldehyde **2a** (36 mg, 0.24 mmol) in 2 mL of dry CH_2Cl_2 at −10 °C. Then TMSCl (26 mg, 0.24 mmol) was injected. The mixture was stirred for 10 min, then a solution of VCP **1a** (59 mg, 0.2 mmol) in 2 mL CH_2Cl_2 was added slowly. After stirring for 2 h (monitored by TLC), the reaction mixture was quenched with 5 mL of water and extracted with EtOAc (3×5 mL). The combined organic layers were dried over anhydrous $MgSO_4$. After filtration and removal of the solvent under vacuum,

the residues were purified with flash chromatography (silica/petroleum ether-ethyl acetate, 100:1 to 10:1 v/v) to afford **3a**; yield: 65 mg (76%).

Typical Experimental Procedure for the One-Pot Reaction Synthesis of Furan Derivatives

Under an atmosphere of dry nitrogen, bicyclic VCP **1g** (81 mg, 0.3 mmol) was added to a solution of aldehyde **2a** (54 mg, 0.36 mmol) in 5 mL of dry CH_2Cl_2 at −10 °C. Then $BF_3{\cdot}Et_2O$ (30 mg, 70 mmol%) was injected. After stirring for 24 h (monitored by TLC), TMSCl (39 mg, 0.36 mmol) was injected and the reaction mixture was allowed warmed to room temperature. After stirring for another 24 h, the reaction mixture was quenched with 5 mL of water and extracted with EtOAc (3×5 mL). The combined organic layers were dried over anhydrous $MgSO_4$. After filtration and removal of the solvent under vacuum, the residues were purified with flash chromatography (silica/petroleum ether-ethyl acetate 15:1 to 10:1 v/v) to afford **4a**; yield: 99 mg (65%).

Typical Experimental Procedure for the Synthesis of Furo[2,3-*b*]furan Derivatives

Under an atmosphere of dry nitrogen, $FeCl_3$ (3 mg, 10 mmol%) was added to a solution of aldehyde **2a** (36 mg, 0.24 mmol) in 2 mL of dry CH_2Cl_2 at −10 °C. Then TMSCl (26 mg, 0.24 mmol) was injected. The mixture was stirred for 10 min, then a solution of VCP **6a** (52 mg, 0.2 mmol) in 2 mL CH_2Cl_2 was added slowly. The mixture was very slowly warmed to room temperature. After the reaction was complete (monitored by TLC), the reaction mixture was quenched with 5 mL of water and extracted with EtOAc (3×5 mL). The combined organic layers were dried over anhydrous $MgSO_4$. After filtration and removal of the solvent under vacuum, the residues were purified with flash chromatography (silica/petroleum ether-ethyl acetate, 15:1 to 10:1 v/v) to afford **7a**; yield: 53 mg (64%).

Acknowledgements

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