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An efficient synthesis of polysubstituted tetrahydrofuran and indene derivatives via the Lewis acid-mediated cycloadditions of VCPs with aldehydes

Chenliang Su[a], QingYang Liu[a], Yong Ni[a], Xian Huang[a,b,*]

[a] Department of Chemistry, Zhejiang University (Xixi Campus), Hangzhou 310028, People's Republic of China
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, People's Republic of China

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ABSTRACT

A variety of polysubstituted tetrahydrofuran and indene derivatives were prepared in moderate to excellent yields via the cycloadditions of vinylidenecyclopropanes with common aldehydes in the presence of Lewis acid. The polysubstituted tetrahydrofuran **3** could undergo further transformations to the indene product **4** and furan derivatives **5**.

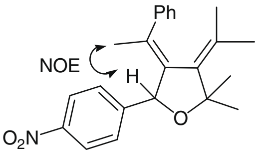
Vinylidenecyclopropanes (VCPs)[1] show unique reactivity in organic synthesis due to the presence of the cumulated C=C double bonds adjacent to the highly strained cyclopropyl ring, and yet they are thermally stable.[2] An attractive but often troublesome feature of VCPs is their multiform reactivities 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] Thus, controlling the regio- and stereoselective reactions of VCPs is a formidable challenge in organic synthesis.

Shi and co-workers reported the Lewis acid-catalyzed reactions of vinylidenecyclopropanes with activated aldehyde, providing an efficient access to polysubstituted tetrahydrofuran.[5c] However, the scope of the reaction is limited. For example, all the substituents of VCP on the cyclopropane moiety are methyl groups, and only the activated aldehyde is allowed. Recently, we have disclosed three kinds of Lewis acid-mediated reactions of vinylidenecyclopropanes and aromatic aldehydes, providing an efficient and selective synthesis of a variety of functionalized benzo[*c*]fluorene, furan, and furo[2,3-*b*]furan derivatives (Scheme 1).[6] As a continual research, we wish to report the selective synthesis of polysubstituted tetrahydrofuran or indene derivatives via $BF_3 \cdot EtO_2$-mediated cycloadditions of VCPs with normal aldehydes, which was controlled by the electronic nature of aldehydes and the temperature. In this Letter, we also disclosed that the substituents effects on the polysubstituted tetrahydrofuran **3** could result in its further transformation to the indene product **4** or furan derivatives **5**.

We initiated our study by performing the reaction of **1a** and **2a** in the presence of $BF_3 \cdot EtO_2$ (10%) in CH_2Cl_2 at −10 °C. After stirring for 48 h, polysubstituted tetrahydrofuran **3a** was obtained in 46% yield. Further investigations indicated that when the catalyst amount was enhanced to 30%, the yield of product was efficiently improved to 93%.

The results summarized in Table 1 prove that this method indeed provides a straightforward entry to a variety of polysubstituted tetrahydrofuran in moderate to excellent yields.[7] As can be seen from Table 1, the VCP **1a** smoothly reacted with normal aldehydes **2a–e** affording the corresponding tetrahydrofuran derivatives in moderate to excellent yields (Table 1, entries 1–5). We also found that VCPs 1b–c, in which $R^1 = R^2$ = Ar and Ar is electron-poor or electron-rich aromatic groups, the corresponding tetrahydrofurans **3g–h** were obtained in good yields. For substrate **1d**, in which R^1 = Ph, $R^2 = R^3 = R^4 = R^5 = R^6$ = Me, the reaction furnished **3h** in 78% yield with high selectivity (*E*-isomer). The configuration was established by the NOESY studies (Fig. 1). When bicyclic VCP **1e** was employed as substrate, tetrahydrofuran **3i** was obtained in 68% yield (1:1). Moreover, for substrate **1f**, where $R^1 = R^2 = R^3$ = Ph, $R^4 = R^5 = R^6$ = H, the polysubstituted tetrahydrofuran **3j** was obtained only in 31% yield along with 6-methyl-7-(4-nitrophenyl)-5-phenyl-7*H*-benzo[*c*]fluorene in a 22% yield.

Surprisingly, for aldehyde with an electron-donating methyloxyl group on the benzene ring, the tetrahydrofuran product was observed in a trace amount, and the indene product **4a** was ob-



3h

Figure 1. Configurations of *E*-**3h**.

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* Corresponding author. Tel./fax: +86 571 88807077.
E-mail address: huangx@mail.hz.zj.cn (X. Huang).

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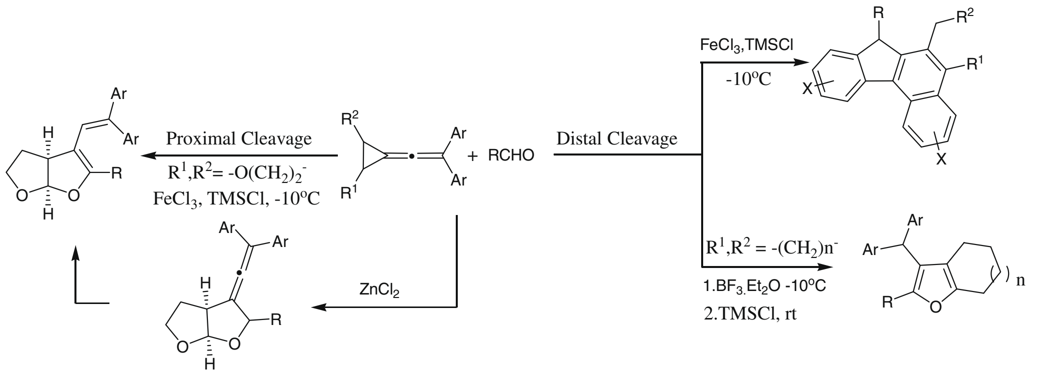
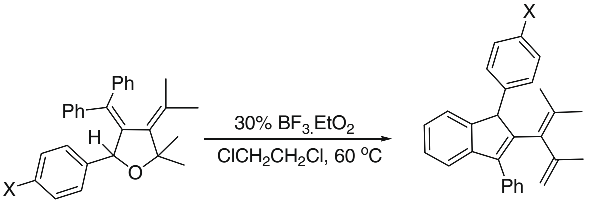


Scheme 1. Lewis acid-mediated selective cycloadditions of vinylidenecyclopropanes with aromatic aldehydes.

tained in 18% yield.[5a] When the reaction was performed in CH_2Cl_2 at rt for 24 h, **4a** could be improved to 61%.

With these observations, we next examined the reaction of various vinylidenecyclopropanes **1** and aldehyde under identical conditions.[8] As indicated in Table 2, it is noteworthy that substituents on the benzene ring of aldehydes significantly affected the reaction. When the aldehydes with an electron-donating group on the benzene ring were employed, the reaction proceeded to give the indene derivatives **4** in moderate yields (Table 2, entries 1–3, 6). For benzaldehyde **2d**, the indene derivative **4d** was obtained only in 29% yield along with the tetrahydrofuran product **3d** in 32% yield. When the aldehyde **2a** with an electron-withdrawing group on the benzene ring was employed, the indene product was obtained only in 5% yield and the polysubstituted tetrahydrofuran **3a** was observed as the main product.

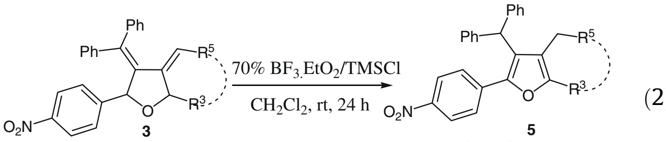
We also found that the substituents effects on the polysubstituted tetrahydrofuran **3** could result in its further transformation to the indene product **4** or furan derivatives **5**. When $R^3 = R^4 = R^5 = R^6 = Me$, **3** could smoothly change to the indene derivatives **4** in the presence of $BF_3.Et_2O$ in $ClCH_2CH_2Cl$ at 60 °C (Eq. 1); when $R^4 = R^6 = H$, tetrahydrofuran derivatives **3j** and **3k** could isomerize to furan derivatives **5** in high yield (Eq. 2).



(1)

4

X=H, **4d** 81%
X=NO$_2$, **4e** 76%

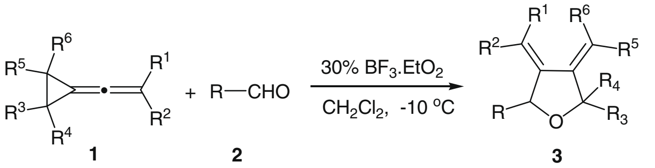


(2)

1. R^6=H,R^3,R^5= -$(CH_2)_4$- 90%
2. R^5=R^6=H,R^3= Ph 88%

A possible mechanism is proposed as depicted in Scheme 2.[5a,c,6] Initially, the electrophilic addition of intermediate **A** with VCPs **1** produces cationic intermediate **B**,[5c] which then rearranges to give the cyclopropyl ring-opened intermediate **C**. The intramolecular O-attacked cyclization of **C** produces the tetrahydrofuran product **3**.[5c,6] When $R^3 = R^4 = R^5 = R^6 = Me$, **3** can further furnish the intermediate **D** in the presence of Lewis acid at higher temperature (path a); when $R^4 = R^6 = H$, **3** may undergo an intramolecular isomerization to give furan derivatives **5**. The intermediate **D** might also come from **C** by the H^+ elimination (path b), which then transforms to **E**. The tandem intramolecular Friedel–Crafts reaction from **E** furnishes the indene derivatives **4**.[5a]

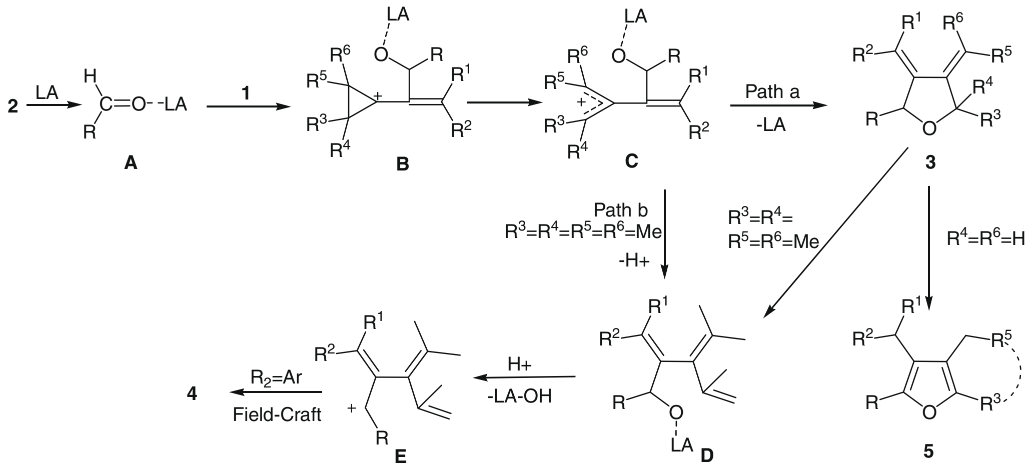
Table 1
The Lewis acid-mediated cycloadditions of VCPs **1** with aldehydes **2** to synthesis of polysubstituted tetrahydrofuran[a]



Entry	VCP **1**[b] (R^1/R^2)	R (**2**)	Time (h)	Yield of **3**[c] (%)
1	C_6H_5/C_6H_5(**1a**)	*p*-$NO_2C_6H_4$ (**2a**)	12	**3a**, 93
2	**1a**	*m*-$NO_2C_6H_4$ (**2b**)	12	**3b**, 90
3	**1a**	*o*-$NO_2C_6H_4$ (**2c**)	12	**3c**, 61
4	**1a**	Ph (**2d**)	24	**3d,** 53
5	**1a**	C_2H_5 (**2e**)	24	**3e**, 63
6	*p*-FC_6H_4/*p*-FC_6H_4(**1b**)	**2a**	12	**3f**, 87
7	*p*-$MeOC_6H_4$/*p*-$MeOC_6H_4$(**1c**)	**2a**	12	**3g**, 85
8	Ph/Me(**1d**)	**2a**	8	**3h**, 78 (E)
9[d]	Ph/Ph (**1e**)	**2a**	24	**3i**, 68 (1:1)
10[e]	Ph/Ph (**1f**)	**2a**	12	**3j**, 31

[a] The reaction was carried out using 1 (0.3 mmol), 2 (0.36 mmol), and $BF_3·EtO_2$ (0.09 mmol) in CH_2Cl_2 at −10 °C.
[b] Unless otherwise specified, $R^3 = R^4 = R^5 = R^6 = Me$.
[c] Isolated yields.
[d] R^3, R^5 = $-(CH_2)_4-$, $R^4 = R^6 = H$, and the catalyst amount was enhanced to 70%.
[e] R^3 = Ph, $R^4 = R^5 = R^6 = H$, and 6-methyl-7-(4-nitrophenyl)-5-phenyl-7*H*-benzo[*c*]fluorene was obtained in 22% yield.

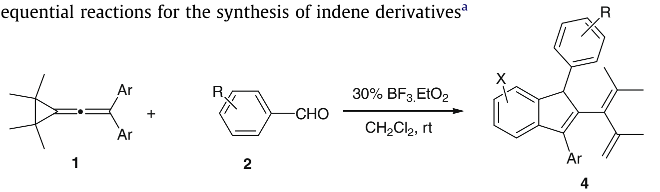
In conclusion, we have developed a cycloaddition of VCPs with normal aldehydes in the presence of Lewis acid, providing a convenient access to a variety of polysubstituted tetrahydrofuran and indene derivatives. The electronic nature of aldehydes and the temperature effect play a crucial role in controlling the selectivity of the reactions of vinylcyclopropenes and aldehyde. Attractively, the polysubstituted tetrahydrofuran **3** could transform further to the indene product **4** and furan derivatives **5** due to the substituent effects. A plausible mechanism for the reactions has also been proposed. Further studies to expand the scope and synthetic utility of the method are underway.



Scheme 2. A plausible mechanism for the cycloadditions of VCPs with common aldehydes.

Table 2

Sequential reactions for the synthesis of indene derivatives[a]



Entry	VCP **1** (R^1/R^2)	R (**2**)	Time (h)	Yield of **4**[b] (%)
1	**1a**	*p*-OMeC_6H_4 (**2g**)	24	**4a**, 61
2	**1a**	*p*-$CH_3C_6H_4$ (**2h**)	36	**4b**, 57
3	**1a**	*o*-OMeC_6H_4 (**2i**)	36	**4c**, 36
4	**1a**	**2d**	48	**4d**, 29[c]
5	**1a**	**2a**	24	**4e**, 5[d]
6	**1c**	**2g**	60	**4f**, 53

[a] Unless otherwise specified, the reaction was carried out using **1** (0.3 mmol), **2** (0.36 mmol), and $BF_3{\cdot}EtO_2$ (0.09 mmol) in CH_2Cl_2.

[b] Isolated yields.

[c] Compound **3d** was obtained in 32% yield.

[d] Compound **3a** was obtained in 71% yield.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.038.

References and notes

1. For synthesis of vinylidenecyclopropanes, see: (a) Isagawa, K.; Mizuno, K.; Sugita, H.; Otsuji, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2283. and references therein; (b) Al-Dulayymi, J. R.; Baird, M. S. *J. Chem. Soc., Perkin Trans.* **1994**, *1*, 1547; (c) Maeda, H.; Hirai, T.; Sugimoto, A.; Mizuno, K. *J. Org. Chem.* **2003**, *68*, 7700.
2. For some reviews related to VCPs, see: (a) Poutsma, M. L.; Ibarbia, P. A. *J. Am. Chem. Soc.* **1971**, *93*, 440; (b) Smadja, W. *Chem. Rev.* **1983**, *83*, 263; (c) Sydnes, L. K. *Chem. Rev.* **2003**, *103*, 1133; (d) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213.
3. (a) Li, W.; Shi, M. *Tetrahedron* **2007**, *63*, 6654; (b) Liu, L. P.; Lu, J. M.; Shi, M. *Org. Lett.* **2007**, *9*, 1303.
4. (a) Mizuno, K.; Maeda, H.; Sugita, H.; Nishioka, S.; Hirai, T.; Sugimoto, A. *Org. Lett.* **2001**, *3*, 581; (b) Mizuno, K.; Sugita, H.; Hirai, T.; Maeda, H.; Otsuji, Y.; Yasuda, M.; Hashiguchi, M.; Shima, K. *Tetrahedron Lett.* **2001**, *42*, 3363; (c) Shi, M.; Lu, J. M.; Xu, G. C. *Tetrahedron Lett.* **2005**, *46*, 4745; (d) Su, C. L.; Huang, X.; Liu, Q. Y. *J. Org. Chem.* **2008**, *73*, 6421; (e) Li, W.; Shi, M. *J. Org. Chem.* **2008**, *73*, 4151.
5. (a) Lu, J. M.; Shi, M. *Org. Lett.* **2006**, *8*, 5317; (b) Lu, J. M.; Shi, M. *Org. Lett.* **2007**, *9*, 1805; (c) Lu, J. M.; Shi, M. *J. Org. Chem.* **2008**, *73*, 2206; (d) Huang, X.; Su, C. L.; Liu, Q. Y.; Song, Y. T. *Synlett* **2008**, 229; (e) Shi, M.; Yao, L. F. *Chem. Eur. J.* **2008**, *14*, 8725; (f) Lu, J. M.; Zhu, Z. B.; Shi, M. *Chem. Eur. J.* **2009**, *15*, 963; (g) Li, W.; Shi, M. *J. Org. Chem.* **2009**, *74*, 856; (h) Li, W.; Shi, M. *Org. Biomol. Chem.* **2009**, *7*, 1775.
6. Su, C. L.; Huang, X. *Adv. Synth. Catal.* **2009**, *351*, 135.
7. *Typical procedure for synthesis of polysubstituted tetrahydrofuran* **3**: Under an atmosphere of dry nitrogen, $BF_3{\cdot}Et_2O$ (0.09 mmol) was added to a solution of aldehyde **2** (0.36 mmol) in 2 mL of dry CH_2Cl_2 at −10 °C. Then a solution of VCP **1** (0.3 mmol) in 2 mL CH_2Cl_2 was added slowly. The progress of the reaction was monitored by TLC, and the mixture was stirred until the starting material disappeared. 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 $MgSO_4$. Evaporation and column chromatography on silica gel afforded **3**. Spectral data for **3a**: ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 9.2 Hz, 2H), 7.17–7.32 (m, 6H), 7.12 (t, J = 7.2 Hz, 2H), 6.88 (d, J = 7.2 Hz, 2H), 5.15 (s, 1H), 1.67 (s, 3H), 1.62 (s, 3H), 1.35 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 25.0, 28.5, 29.1, 79.4, 81.6, 123.6, 126.9, 127.6, 127.8, 128.3, 128.7, 128.7, 129.7, 137.2, 140.4, 142.3, 142.9, 147.1, 151.8; IR (neat): 2967, 1598, 1517, 1343, 1266, 1010, 762, 734, 699 cm^{-1}. MS (70 eV, EI) *m/z*: 425 (M^+). HRMS (EI): *m/z* calcd for $C_{28}H_{27}NO_3$ (M^+): 425.1991. Found, 425.1986.
8. *Typical procedure for synthesis of indene derivatives* **4**: Under an atmosphere of dry nitrogen, $BF_3{\cdot}Et_2O$ (0.09 mmol) was added to a solution of aldehyde **2** (0.36 mmol) in 2 mL of dry CH_2Cl_2 at rt. Then a solution of VCP **1** (0.3 mmol) in 2 mL CH_2Cl_2 was added slowly. The progress of the reaction was monitored by TLC, and the mixture was stirred until the starting material disappeared. 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 $MgSO_4$. Evaporation and column chromatography on silica gel afforded **4**. Spectral data for **4a**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 7.6 Hz, 2H), 7.10–7.43 (m, 7H), 6.95 (d, J = 8.4 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 4.98 (s, 1H), 4.63 (s, 1H), 4.45 (s, 1H), 3.76 (s, 3H), 1.76 (s, 3H), 1.51 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 22.2, 23.2, 55.1, 57.3, 113.4, 115.5, 119.8, 123.9, 125.1, 126.5, 126.9, 128.2, 128.5, 129.6, 131.5, 131.6, 131.6, 136.1, 140.2, 144.5, 145.7, 147.5, 148.6, 158.1; IR (neat): 2956, 2922, 2852, 1606, 1510, 1460, 1248, 1034, 756, 700 cm^{-1}. MS (70 eV, EI) *m/z*: 392 (M^+). HRMS (EI): *m/z* calcd for $C_{29}H_{28}O$ (M^+): 392.2140. Found, 392.2138.