

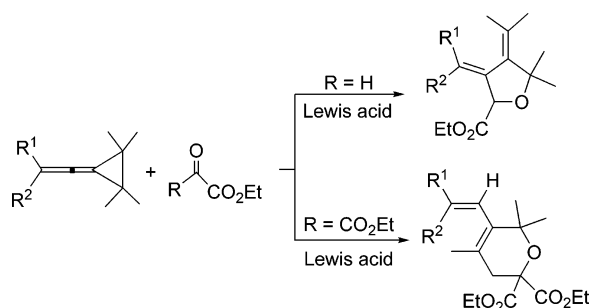
Lewis Acid Catalyzed Reactions of Vinylidenecyclopropanes with Activated Carbon–Oxygen Double Bond: A Facile Synthetic Protocol for Functionalized Tetrahydrofuran and 3,6-Dihydropyran Derivatives

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A number of functionalized tetrahydrofuran and 3,6-dihydropyran derivatives are prepared selectively in moderate to good yields by the reactions of vinylidenecyclopropanes with activated carbonyl compounds in the presence of Lewis acid.

Introduction

Vinylidenecyclopropanes **1**¹ are one of the most remarkable organic compounds known. They have an allene moiety connected by a cyclopropane ring, and yet they are thermally stable and reactive substances. Thermal and photochemical skeletal conversions of vinylidenecyclopropanes **1** have attracted much attention from mechanistic, theoretical, spectroscopic, and synthetic viewpoints.² Vinylidenecyclopropanes can also easily react with carbon–carbon or carbon–heteroatom multiple bonds to produce [3 + 2] or [2 + 2] cycloaddition products in good

yields upon heating or photoirradiation.³ Recently, we have been investigating the Lewis acid or Brønsted acid catalyzed/mediated ring-opening reactions of vinylidenecyclopropanes.⁴ Previously, we reported the Lewis acid catalyzed reaction of vinylidenecyclopropanes with acetals to produce indene derivatives in good yields (Scheme 1).⁵ Moreover, we recently also disclosed the Lewis acid catalyzed reaction of vinylidenecyclopropanes with activated imines [ethyl (arylimino)acetates] to afford pyrrolidine and 1,2,3,4-tetrahydroquinoline derivatives in moderate to good yields via [3 + 2] cycloaddition and aza-Diels–Alder reaction, respectively (Scheme 2).⁶

During our ongoing investigation, we found that functionalized tetrahydrofuran and 3,6-dihydropyran derivatives **9** and **10**

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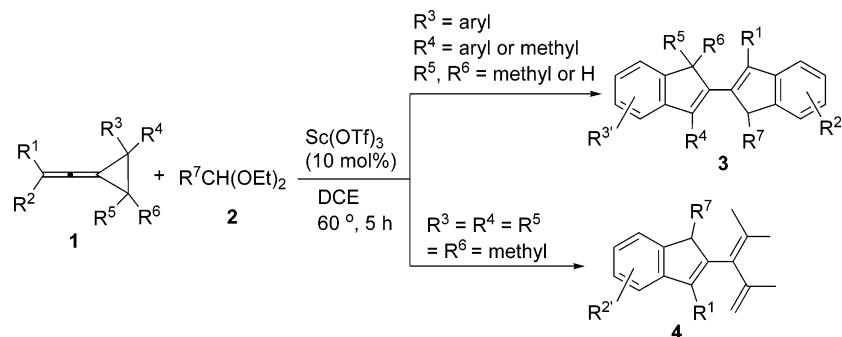
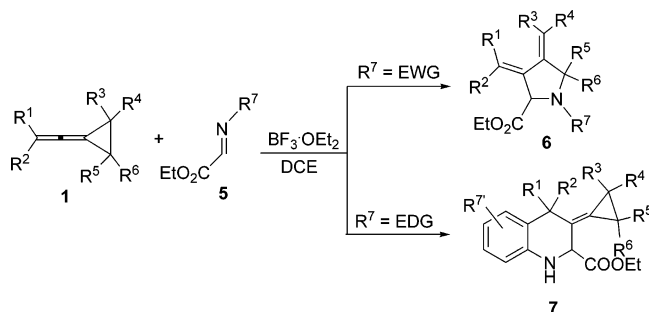
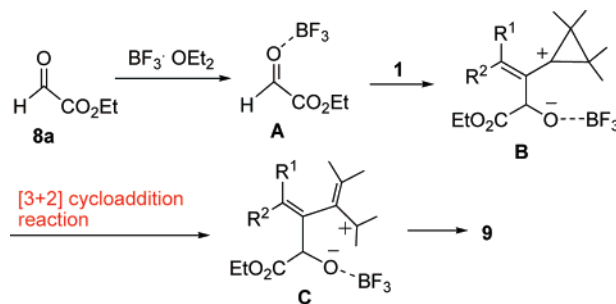
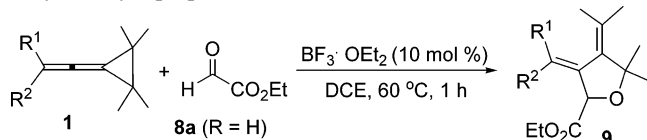
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SCHEME 1. Sc(OTf)₃-Catalyzed Reaction of Vinylidenecyclopropanes **1** with Acetals **2**SCHEME 2. BF₃·OEt₂-Catalyzed Reaction of Vinylidenecyclopropanes **1** with Imines **5**SCHEME 3. Proposed Mechanism for the Reaction of Vinylidenecyclopropanes **1** with **8a**TABLE 1. BF₃·OEt₂-Catalyzed Reaction of Vinylidenecyclopropanes **1** with **8a**

entry ^a	1 (R ¹ /R ²)	yield ^b (%)
1	1a (C ₆ H ₅ /C ₆ H ₅)	9a , 99
2	1b (<i>p</i> -ClC ₆ H ₄ / <i>p</i> -ClC ₆ H ₄)	9b , 94
3	1c (<i>p</i> -FC ₆ H ₄ / <i>p</i> -FC ₆ H ₄)	9c , 97
4	1d (<i>p</i> -ClC ₆ H ₄ /C ₆ H ₅)	9d , 99 (1.5:1) ^c
5	1e (<i>p</i> -MeOC ₆ H ₄ /C ₆ H ₅)	9e , 90 (2.0:1) ^c
6	1f (<i>p</i> -MeOC ₆ H ₄ / <i>p</i> -MeC ₆ H ₄)	9f , 98
7	1g (<i>p</i> -MeOC ₆ H ₄ / <i>p</i> -MeOC ₆ H ₄)	9g , 77 ^d

^a All reactions were carried out using **1** (0.2 mmol), **8a** (0.3 mmol), and BF₃·OEt₂ (10 mol %) in DCE (2.0 mL) at 60 °C. ^b Isolated yields. ^c *E/Z*. ^d 7% of the rearrangement product was obtained.

could be obtained in good to high yields via the Lewis acid catalyzed reactions of vinylidenecyclopropanes **1** with activated carbonyl compounds **8** under mild conditions. Herein, we wish to report these results.

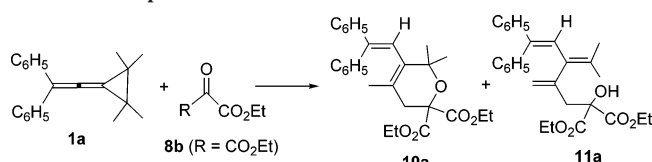
Results and Discussion

Initial examination revealed that the reaction of vinylidenecyclopropane **1a** with ethyl glyoxylate **8a** (R = H) proceeded smoothly in 1,2-dichloroethane (DCE) at 60 °C to give the corresponding tetrahydrofuran derivative **9a** in 99% yield in the presence of BF₃·OEt₂ (10 mol %) within 1 h (Table 1, entry 1). Therefore, we did not further optimize the reaction conditions and directly examined a variety of vinylidenecyclopropanes **1**

with **8a** under these reaction conditions. The results of these experiments are summarized in Table 1. As can be seen from Table 1, with respect to the electron-rich and electron-poor vinylidenecyclopropanes **1** (R¹ and R²), the corresponding tetrahydrofuran derivatives **9** were obtained in moderate to good yields (Table 1). For unsymmetrical vinylidenecyclopropanes **1d** and **1e** (R¹ ≠ R²), the corresponding tetrahydrofuran derivatives **9d** and **9e** were obtained as mixtures of *E/Z* isomers in 99% and 90% yields, respectively (Table 1, entries 4 and 5). For vinylidenecyclopropane **1g** (R¹ = R² = *p*-MeOC₆H₄), the product **9g** was obtained in 77% yield along with 7% of a naphthalene derivative as a byproduct (Table 1, entry 7).^{4e} Above reaction is believed to proceed via a Lewis acid catalyzed [3 + 2] cycloaddition pathway.^{6a} Intermediate **A**, generated from **8a** and BF₃·OEt₂, reacts with **1** to produce intermediate **B**, which undergoes ring-opening to afford intermediate **C**. Cyclization of intermediate **C** furnishes [3 + 2] cycloadduct **9** (Scheme 3).

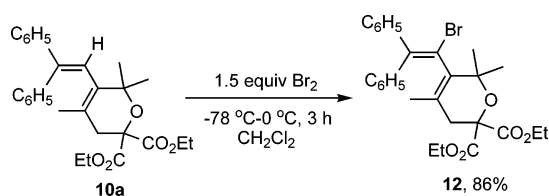
Interestingly, when diethyl ketomalonate **8b** (R = CO₂Et) was used as the activated carbonyl compound, 3,6-dihydropyran derivative **10a** was obtained in DCE at 60 °C in 40% yield in the presence of Nd(OTf)₃ (10 mol %) (Table 2, entry 1). Using diphenylvinylidenecyclopropane **1a** as the substrate, we examined its reaction with diethyl ketomalonate **8b** under a variety of reaction conditions to develop the best one. The results are summarized in Table 2. We found that the reaction proceeded smoothly in hexane to give the cyclic product **10a** in 67% yield in the presence of Nd(OTf)₃ (10 mol %) at 60 °C within 4 h (Table 2, entry 9). Using THF as the solvent, the cyclic and acyclic products **10a** and **11a** were obtained in 31% and 29% yields, respectively (Table 2, entry 10). When MeCN was used as the solvent, only acyclic product **11a** was obtained in 38% yield (Table 2, entry 11). Using other Lewis acids, such as Gd(OTf)₃, Sc(OTf)₃, Bi(OTf)₃·9H₂O, Cu(OTf)₂, In(OTf)₃, and Sn(OTf)₂, under identical conditions, **10a** was obtained in somewhat lower yields as a sole product (Table 2, entries 12–17). In the presence of Lewis acids such as La(OTf)₃, Yb(OTf)₃,

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TABLE 2. Optimization of the Reaction Conditions of **1a** with **8b**


entry ^a	solvent	catalyst	time (h)	yield ^b (%)	
				10a	11a
1	DCE	Nd(OTf) ₃	4	40	
2 ^c	toluene	Nd(OTf) ₃	4	54	
3 ^d	toluene	Nd(OTf) ₃	4	59	
4	chlorobenzene	Nd(OTf) ₃	4	57	
5	toluene	Nd(OTf) ₃	4	60	
6	hexane	Nd(OTf)₃	4	67	
7 ^e	CH ₂ Cl ₂	Nd(OTf) ₃	5	45	
8	benzene	Nd(OTf) ₃	4	60	
9	cyclohexane	Nd(OTf) ₃	4	64	
10	THF	Nd(OTf) ₃	23	31	29
11 ^f	MeCN	Nd(OTf) ₃	29		38
12	hexane	Gd(OTf) ₃	4	60	
13	hexane	Sc(OTf) ₃	4	57	
14	hexane	Bi(OTf) ₃ ·9H ₂ O	4	59	
15	hexane	Cu(OTf) ₂	4	45	
16	hexane	In(OTf) ₃	3	60	
17	hexane	Sn(OTf) ₂	5	66	
18	hexane	La(OTf) ₃	24	42	10
19	hexane	Yb(OTf) ₃	4	50	11
20	hexane	Eu(OTf) ₃	5	47	19
21 ^g	hexane	BF ₃ ·OEt ₂	24		16

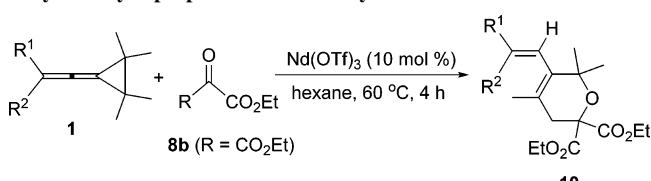
^a Unless otherwise specified, all reactions were carried out using **1a** (0.3 mmol), **8b** (0.9 mmol), catalyst (10 mol %), and solvent (3 mL) at 60 °C. ^b Isolated yields. ^c The ratio of **1a** and **8b** is 1:2. ^d The ratio of **1a** and **8b** is 1:3.5. ^e The reaction was carried out under reflux temperature. ^f 17% of **1a** was recovered. ^g 62% of **1a** was recovered.

SCHEME 4. Transformation of **10a** with Br₂

and Eu(OTf)₃, **10a** and **11a** were both obtained in good total yields with **10a** as the major product (Table 2, entries 18–20), and when BF₃·OEt₂ was used as the catalyst, only **11a** was obtained in 16% yield as a sole product (Table 2, entry 21). Different Lewis acidities between these metal triflates caused such difference on the catalytic abilities. When BF₃·OEt₂ was used as a Lewis acid, the coordination between the newly formed hydroxy group of **11a** with BF₃·OEt₂ might be able to take place, leading to the formation of **11a** as a sole product in 16% yield. However, when Nd(OTf)₃ was employed as a Lewis acid under identical conditions, such coordination could be weak and the formation of **10a** was facilitated in 67% yield exclusively.

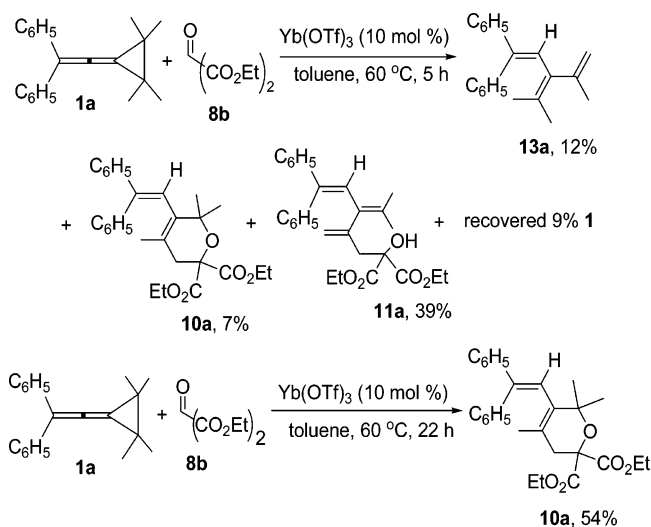
Transformation of **10a** using Br₂ (1.5 equiv) as the brominating agent afforded the product **12** in 86% yield (Scheme 4). The structure of **12** was determined unambiguously by an X-ray diffraction (see the Supporting Information), from which we can further confirm the structure of product **10a**. The structure of **11a** was determined by ¹H and ¹³C NMR spectroscopic data, HRMS, NOESY, HMBC, and HMQC analytic data (see the Supporting Information).

With the optimized reaction conditions in hand, we next examined an assortment of starting materials **1** and **8b** in order

TABLE 3. Nd(OTf)₃-Catalyzed Reaction of Vinylidenecyclopropanes **1** with Diethyl Ketomalonate **8b**


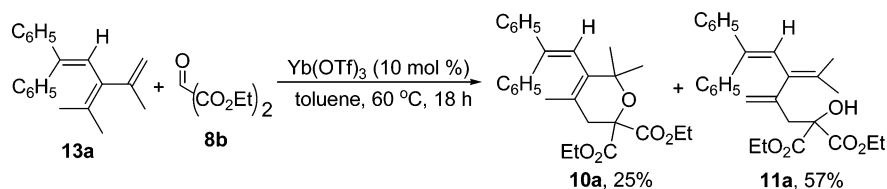
entry ^a	1 (R ¹ /R ²)	yield ^b (%)/ 10
1	1b (<i>p</i> -ClC ₆ H ₄ / <i>p</i> -ClC ₆ H ₄)	10b , 63
2	1c (<i>p</i> -FC ₆ H ₄ / <i>p</i> -FC ₆ H ₄)	10c , 66
3	1d (<i>p</i> -ClC ₆ H ₄ /C ₆ H ₅)	10d , 62 ^c
4	1e (<i>p</i> -MeOC ₆ H ₄ /C ₆ H ₅)	10e , 52 ^c
5	1f (<i>p</i> -MeC ₆ H ₄ / <i>p</i> -MeC ₆ H ₄)	10f , 62
6	1h (<i>p</i> -MeC ₆ H ₄ /C ₆ H ₅)	10g , 62 ^c
7	1i (<i>m</i> -Me, <i>p</i> -MeC ₆ H ₃ /C ₆ H ₅)	10h , 64 ^c
8	1j (<i>p</i> -MeC ₆ H ₄ /Me)	10i , 39 ^d
9	1k (<i>p</i> -BrC ₆ H ₄ /Me)	10j , 30 ^e

^a All reactions were carried out using **1** (0.3 mmol), **8b** (0.9 mmol), Nd(OTf)₃ (10 mol %) and hexane (3 mL) at 60 °C for 4 h. ^b Isolated yields. ^c E/Z = 1:1. ^d E/Z = 10:11. ^e E/Z = 5:4.

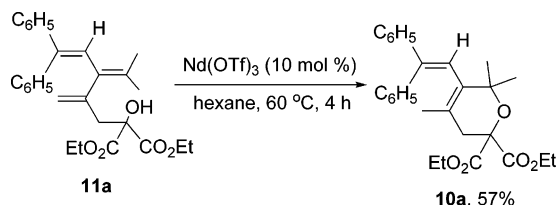
SCHEME 5. Yb(OTf)₃-Catalyzed Reaction of Vinylidenecyclopropane **1a** with Diethyl Ketomalonate **8b**

to evaluate the scope of this reaction. As can be seen from Table 3, for almost all cases in which R¹, R² = aryl group, the corresponding cyclic product 3,6-dihydropyran derivatives **10** can be obtained in moderate yields within 4 h as the sole products. For vinylidenecyclopropanes **1j** and **1k** in which R¹ = aryl, R² = methyl, the reaction can also proceed smoothly to give the corresponding 3,6-dihydropyran derivatives **10i** and **10j** in 39% and 30% yields, respectively (Table 3, entries 8 and 9). For the reactions with unsymmetrical vinylidenecyclopropanes **1** as the substrates (R¹ ≠ R²), products **10** were obtained as mixtures of *E*- and *Z*-isomers (Table 3, entries 3, 4, 6, and 7). When **8c** (R = Me) was used as the activated carbonyl compound, no product was detected. It should be noted here that only substrates **1** with four methyl groups on the cyclopropyl ring can undergo this transformation and this result will be further confirmed with the explanation of the reaction mechanism.

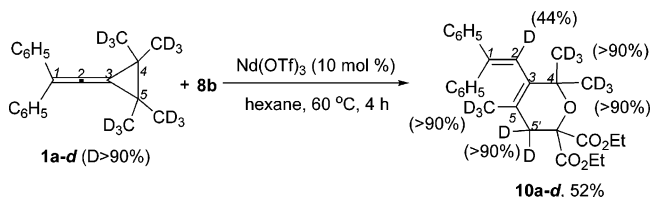
In order to clarify the mechanism of this reaction, the reaction of **1a** with **8b** was carried out in toluene at 60 °C using Yb(OTf)₃ (10 mol %) as the catalyst. The reaction was completed within 5 h; not only **10a** and **11a** were obtained in 7% and

SCHEME 6. Yb(OTf)₃-Catalyzed Reaction of 13a with Diethyl Ketomalonate 8b

SCHEME 7. Transformation of 11a to 10a



SCHEME 9. Deuterium-Labeling Experiment of Reaction of 1a-d with 8b



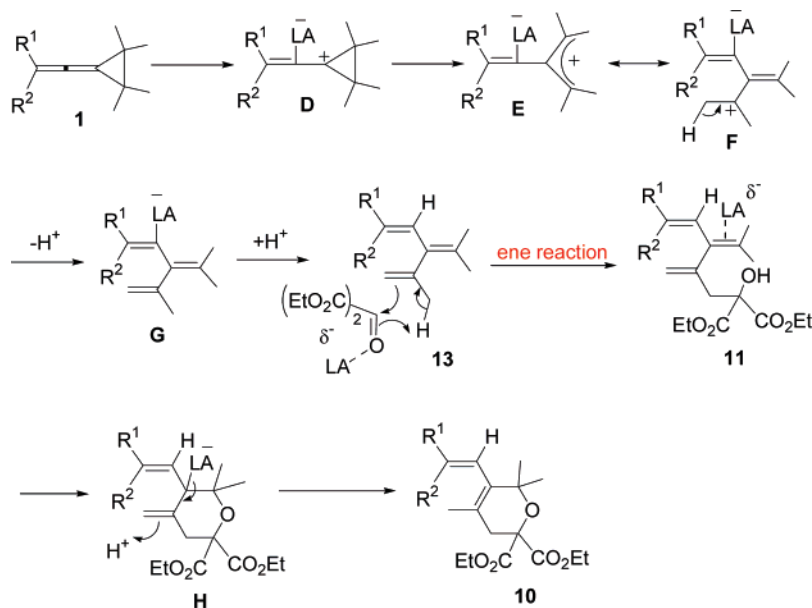
39% yields, respectively, but also triene **13a** was obtained in 12% yield. When the reaction time was prolonged to 22 h, only **10a** was obtained in 54% yield as the sole product (Scheme 5). The control experiment indicated that triene **13a** could also be obtained in the presence of Lewis acid without **8b**. When trienes **13a** and **8b** were used as the substrates under identical reaction conditions, products **10a** and **11a** were obtained in 25% and 57% yields within 18 h, respectively, suggesting that a carbonyl–ene reaction⁷ is involved in this transformation (Scheme 6). Further studies revealed that acyclic product **11a** could be easily transformed to cyclic products **10a** under identical conditions, indicating that **10a** is derived from the ene reaction product **11a** (Scheme 7). The product **11a** could also be detected by GLC when the reaction was carried out using Nd(OTf)₃ as the catalyst (Supporting Information).

A plausible mechanism for the formation of 3,6-dihydropyran derivatives **10** is outlined in Scheme 8 based on the above control experiments. The coordination of **1** to the Lewis acid initially gives the vinyl group stabilized cyclopropyl cationic intermediate **D**, which results in the formation of cyclopropane ring-opened zwitterionic intermediate **E** or the resonance-stabilized zwitterionic intermediate **F**. Deprotonation of intermediate **F** and reprotonation of intermediate **G** will give triene

13. The carbonyl–ene reaction⁷ of triene **13** with diethyl ketomalonate **8b**, which is activated by Lewis acid, generates homoallylic alcohol **11**. The subsequent ring closure of homoallylic alcohol **11** and protonation of intermediate **H** produces the product **10**. The deuterium-labeling experiment was also examined under the standard conditions (Scheme 9). It was found that deuterium incorporation occurred at the olefinic proton of C₂ (D content 44%) based on the corresponding ¹H NMR spectroscopic data. The observation of 44% D content at C₂ supports the mechanism shown in Scheme 9 because it is derived from the deprotonation of intermediate **F** and reprotonation of intermediate **G**. In addition, a total primary isotope effect of $k_H/k_D = 5.8$ was observed for this deuterium labeling experiment, further suggesting the ene reaction pathway (see the Supporting Information for details). Since this reaction includes three steps, products **10** are produced in moderate yields.

In conclusion, we have developed a Lewis acid-catalyzed synthesis of functionalized tetrahydrofuran and 3,6-dihydropyran derivatives by the reaction of vinylidenecyclopropanes **1** with activated carbonyl compounds **8** under mild conditions. The different products **9** and **10** may be caused by the electronic

SCHEME 8. Proposed Mechanism for the Formation of 10 and 11



nature and steric effect of **8**. Efforts are in progress to elucidate further mechanistic details of these reactions and to understand their scope and limitations.

Experimental Section

General Procedure for Lewis Acid Catalyzed Reaction of Vinylidenecyclopropanes **1 with Ethyl Glyoxylate **8a**.** Under an argon atmosphere, vinylidenecyclopropane **1** (0.2 mmol), ethyl glyoxylate **8a** (0.3 mmol), and DCE (2.0 mL) were added into a Schlenk tube, and then $\text{BF}_3 \cdot \text{OEt}_2$ (10 mol %) was added. The reaction mixture was stirred at 60 °C for 1.0 h, and then the solvent was removed under reduced pressure and the residue was purified by a flash column chromatography.

General Procedure for Lewis Acid Catalyzed Reaction of Vinylidenecyclopropanes **1 with Diethyl Ketomalonate **8b**.** Under an argon atmosphere, vinylidenecyclopropane **1** (0.3 mmol), diethyl ketomalonate **8b** (0.9 mmol), $\text{Nd}(\text{OTf})_3$ (10 mol %), and hexane (3.0 mL) were added into a Schlenk tube. The reaction mixture was stirred at 60 °C for 4.0 h, and then the solvent was removed under reduced pressure and the residue was purified by flash column chromatography.

Compound 9a: colorless oil; ^1H NMR (CDCl_3 , 300 MHz, TMS) δ 1.10 (s, 3H, CH_3), 1.28 (t, $J = 7.2$ Hz, 3H), 1.58 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 4.18 (q, $J = 7.2$ Hz, 2H), 4.50 (s, 1H), 7.15–7.28 (m, 10H, Ar); ^{13}C NMR (CDCl_3 , 75 MHz,

TMS) δ 14.1, 21.0, 24.8, 28.2, 28.6, 60.8, 78.3, 82.3, 126.7, 127.6, 127.8, 128.1, 128.9, 129.8, 129.9, 135.1, 135.8, 1402, 142.6, 143.0, 172.4; IR (CH_2Cl_2) ν 3056, 2979, 2906, 1738, 1492, 1444, 1362, 1277, 1189, 1170, 1132, 1032, 771, 748, 701 cm^{-1} ; MS m/z 376 (12), 303 (100), 105 (50), 275 (37), 229 (22.3), 77 (21.6), 215 (19.6), 167 (19.5), 233 (18); HRMS (EI) calcd for $\text{C}_{25}\text{H}_{28}\text{O}_3$ 376.2038, found 376.2072.

Compound 10a: colorless liquid; ^1H NMR (CDCl_3 , 300 MHz, TMS) δ 1.25 (t, $J = 6.9$ Hz, 6H, 2CH_3), 1.31 (s, 3H, CH_3), 1.46 (s, 6H, 2CH_3), 2.43 (s, 2H), 4.21 (q, $J = 6.9$ Hz, 4H), 6.20 (d, $J = 1.2$ Hz, 1H), 7.15–7.17 (m, 2H, Ar), 7.23–7.31 (m, 8H, Ar); ^{13}C NMR (CDCl_3 , 75 MHz, TMS) δ 13.9, 21.5, 29.0, 33.9, 61.7, 77.6, 78.2, 124.9, 125.0, 127.0, 127.4, 127.97, 128.02, 128.2, 129.7, 133.2, 140.5, 143.9, 145.1, 169.5; IR (CH_2Cl_2) ν 2980, 2933, 1767, 1743, 1493, 1465, 1444, 1367, 1277, 1216, 1180, 1158, 1113, 1078, 1061, 1024, 774, 699 cm^{-1} ; MS (MALDI) m/z 449 ($\text{M}^+ + 1$); HRMS (MALDI) calcd for $\text{C}_{28}\text{H}_{32}\text{O}_5\text{Na}$ 471.2142, found 471.2150.

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Supporting Information Available: Spectroscopic data of all new compounds, detailed descriptions of experimental procedures, and X-ray data for compound **12**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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