Sequential Knoevenagel Condensation/Cyclization for the Synthesis of Indene and Benzofulvene Derivatives

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ABSTRACT: Sequential Knoevenagel condensation/cyclization leading to indene and benzofulvene derivatives has been developed. The reaction of 2-(1-phenylvinyl)benzaldehyde with malonates gave benzylidene malonates, cyclized indenes, and dehydrogenated benzofulvenes. The product selectivity depends on the reaction conditions. The reaction with piperidine, AcOH in benzene at 80 °C for 1.5 h gave a benzylidene malonate in 75% yield as a major product. The reactions with piperidine, AcOH in benzene at 80 °C for 17 h and with TiCl$_4$-pyridine at room temperature gave an indene derivative in 56 and 79% yields, respectively, as a major product. The reaction with TiCl$_4$-Et$_3$N gave a benzofulvene in 40% yield selectively. Indene was transformed to a benzofulvene derivative using the reagents TiCl$_4$-Et$_3$N and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The reaction of variously substituted aryl derivatives with dimethyl malonate gave indene and benzofulvene derivatives. The reactions of 2-(1-phenylvinyl)benzaldehyde with Meldrum's acid or malononitrile also gave cyclized compounds in the suitable sequential or stepwise conditions. Furthermore, the reaction of 2-arylbenzaldehydes has been investigated. The limitation and scope have been described. The reaction mechanism of the cyclization steps has been examined by DFT calculations.
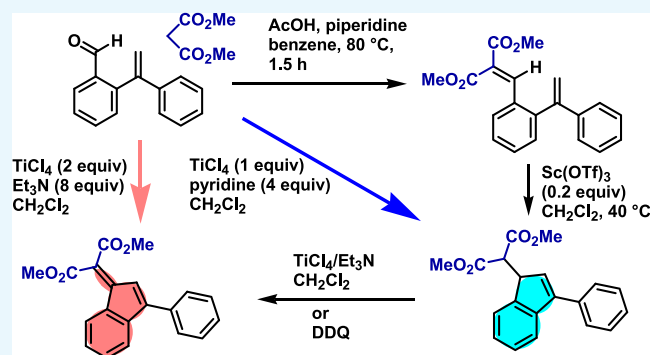
INTRODUCTION

Indenes and benzofulvenes are important core structures in organic chemistry due to their presence in many biologically active compounds[1] and functional materials.[2] Various methods to construct indene rings have been developed. For example, Lewis and Brønsted acid-catalyzed reactions such as Nazarov-type 4π-electrocyclization,[3] Friedel−Crafts cyclization, and reaction of styrylmalonates with aromatic aldehydes[4] have been reported recently. Among the methods developed, cyclization reactions of *ortho*-substitued arenes to provide functionalized indenes have been utilized efficiently. Transition-metal-catalyzed cyclization of *ortho*-substitued arenes has been investigated.[5] Iodine-promoted[6] and base-promoted[7] cyclization reactions have been reported. Lewis and Brønsted acid-catalyzed reactions of alkene conjugate addition have been studied.[8] It is desirable to find new efficient methods to construct variously functionalized indene derivatives.

Sequential reactions are considered to be efficient and favorable for the sustainable concepts.[9] The Knoevenagel condensation is the reactions of aldehydes and ketones with active methylene compounds to give alkylidene- or benzylidene-dicarbonyls or analogous compounds, for example, in the presence of amines, ammonium salts, and Lewis acids with amines.[10] Since Knoevenagel products are highly reactive

compounds, several sequential reactions involving Knoevenagel condensation have been reported.[11]

For example, originally, Knoevenagel reported formation of bis-adducts.[12] Various sequential reactions under the condensation conditions to give intermolecular Michael adducts including the reaction with two kinds of active methylene compounds and further transformation of the adducts and intermolecular hetero-Diels-Alder cycloadducts (Scheme 1A).[13] Sequential intramolecular hetero-Diels-Alder[14] and 1,5-hydride shift/cyclization[15] reactions were also reported as efficient methods (Scheme 1B). The initial alkylidene or benzylidene compounds are directly transformed by the subsequent step under the reaction conditions. It is of interest to find new sequential reactions involving Knoevenagel condensation.

In this work, a highly reactive diphenylethene moiety[16] in *ortho*-substitution of arenealdehydes has been used to cause

Previous work

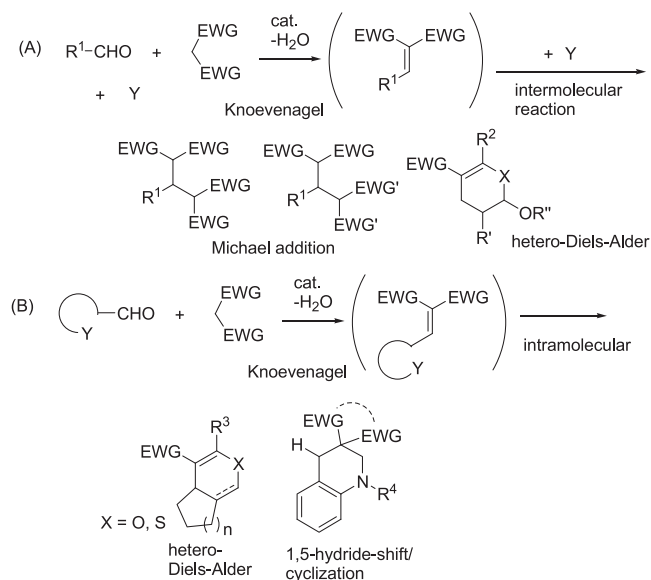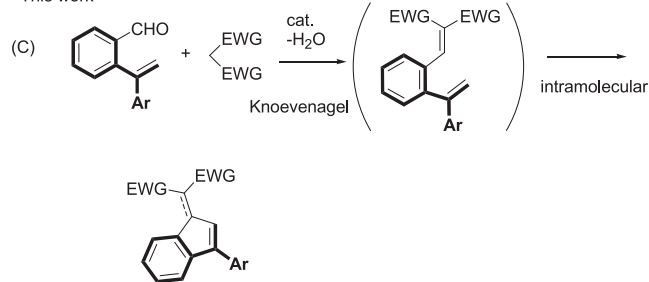sequential Knoevenagel condensation/cyclization reactions (Scheme 1C). The reaction mechanism has been examined by DFT calculations.

■ RESULTS AND DISCUSSION

The reaction of 2-(1-phenylvinyl)benzaldehyde **1a**[5b] with methyl malonate **2a** under the various Knoevenagel reaction conditions has been examined first.

The reaction of **1a** and **2a** with piperidine, AcOH in benzene at 80 °C for 1.5 h gave the benzylidene malonate **3a** in 75%

yield as a major product (Scheme 2). The same reaction conditions for 17 h gave an indene derivative **4a** in 56% yield. The reaction with TiCl$_4$-pyridine (1:4 equiv) in CH$_2$Cl$_2$ at room temperature gave an indene derivative **4a** in 79% yield (Scheme 3, Table 1, entry 1). The reaction of variously substituted aryl derivatives **1** with dimethyl malonate **2a** also gave indene derivatives **4** (Table 1).

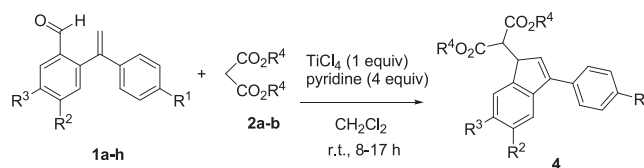**Scheme 3. Reaction of 1a−h and 2a,b with TiCl$_4$-Pyridine (1:4 equiv) in CH$_2$Cl$_2$**

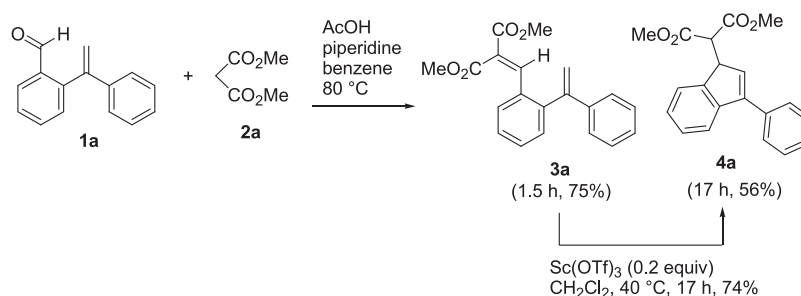**Table 1. Reaction of 1 and 2a,b with TiCl$_4$-Pyridine (1:4)**

entry	1	R^1	R^2	R^3	2	R^4	4	yield (%)
1	1a	H	H	H	2a	Me	4a	79
2	1b	Me	H	H	2a	Me	4b	46
3	1c	Cl	H	H	2a	Me	4c	54
4	1d	H	Me	H	2a	Me	4d	55
5	1e	H	Cl	H	2a	Me	4e	57
6	1f	H	H	Cl	2a	Me	4f	66
7	1g	H	F	H	2a	Me	4g	^{a}
8	1a	H	H	H	2b	Et	4h	50

^{a}An inseparable mixture of possible **4g** and **3g**.

Transformation of **3a** to **4a** was also achieved by the reaction with catalytic amounts of Sc(OTf)$_3$ in dichloromethane at 40 °C in 74% yield (Scheme 2).

Next, the reaction of **1a** and **2a** with TiCl$_4$-Et$_3$N (1:4 equiv ratio) was examined. The reaction gave a 1:1 mixture of **4a** and **5a** in 61% yield. After examining various ratios of TiCl$_4$-Et$_3$N, it was found that the reaction with TiCl$_4$-Et$_3$N (2:8 equiv) in CH$_2$Cl$_2$ at room temperature for 17 h gave a benzofulvene **5a** in 40% yield selectively (Scheme 4, Table 2, entry 1). The reaction of variously substituted aryl derivatives **1** and **2a** with TiCl$_4$-Et$_3$N also gave benzofulvene derivatives **5** as orange crystals (Table 2). The structure of **5e** was determined by X-ray analysis (Figure S1 in the Supporting Information, CCDC 2105106). The reaction of **1a** with diethyl malonate **2b** gave the corresponding indene **4h** and benzofulvene **5h**[17] (Tables 1 and 2). The reaction of naphtyl derivative **1i** and **2a** with TiCl$_4$-Et$_3$N (2:8) also gave **5i** as a major product in 41% yield.

Scheme 2. Reaction of 1a and 2a with Piperidine, AcOH in Benzene

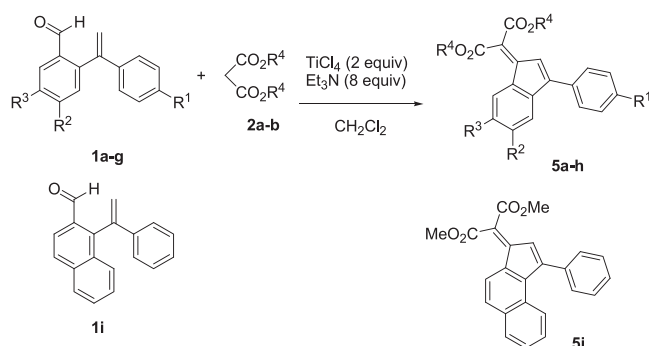**Scheme 4. Reaction of 1a−g,i and 2a,b with TiCl₄-Et₃N (2:8 equiv) in CH₂Cl₂**

Table 2. Reaction of 1 and 2a,b with TiCl₄-Et₃N (2:8)

entry	1	R^1	R^2	R^3	2	R^4	5	yield (%)
1	1a	H	H	H	2a	Me	5a	40
2	1b	Me	H	H	2a	Me	5b	45
3	1c	Cl	H	H	2a	Me	5c	57
4	1d	H	Me	H	2a	Me	5d	61
5	1e	H	Cl	H	2a	Me	5e	46
6	1f	H	H	Cl	2a	Me	5f	52
7	1g	H	F	H	2a	Me	5g	53
8	1a	H	H	H	2b	Et	5h	41
9	1i				2a	Me	5i	41

The indenes **4a,h** were transformed to benzofulvene derivatives **5a,h** using the reagents TiCl₄-Et₃N or DDQ in 67−98% yields (Scheme 5).

Scheme 5. 4a,h Transformation to Benzofulvene Derivatives 5a,h
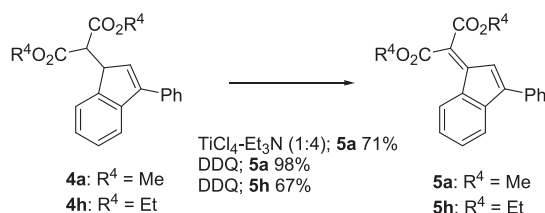
In order to examine the effect of phenyl on vinyl group of **1a**, the reaction of **6** with **2a** in the presence of TiCl₄-pyridine/Et₃N was carried out. The reaction under the examined conditions gave the Knoevenagel product **7** as an isolable product in 23−64% yield (Scheme 6).

The reactions of 2-(1-phenylvinyl)benzaldehydes **1** with other active methylene compounds were examined next. The

Scheme 6. Reaction of 6 and 2a under the Examined Conditions Giving the Knoevenagel product 7
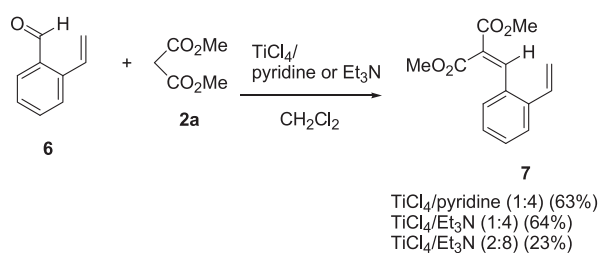
reaction of **1a** and Meldrum's acid **8** in the presence of TiCl₄-pyridine or TiCl₄-Et₃N gave a complex mixture. However, the reaction in the presence of piperidine (0.2 equiv) in benzene at room temperature gave cyclized product **9** in 80% yield (Scheme 7). The reaction with piperidine (0.2 equiv) and

Scheme 7. Reaction in the Presence of Piperidine in Benzene Giving Cyclized Product 9 and Its Dehydrogenation with DDQ Giving Benzofulvene 10
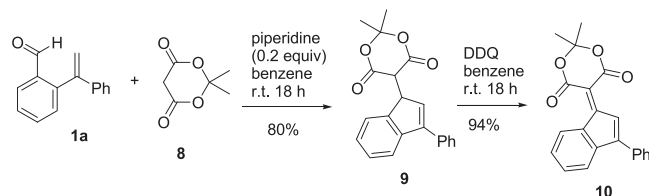

acetic acid (1 equiv) in benzene at room temperature gave **9** as an isolable product in lower yield (42%). The corresponding Knoevenagel adduct was not isolated under the examined conditions.

Since the properties of conjugated systems are of interest, dehydrogenation of indene products was examined.[18,6b,c] Dehydrogenation of **9** proceeded by the reaction with DDQ (1 equiv) in benzene at room temperature to give benzofulvene **10**[17] in 94% yield (Scheme 7).

The reaction of **1a** and malononitrile **11** with TiCl₄-pyridine or TiCl₄-Et₃N (1:4) gave Knoevenagel adduct **12a** in 50−39% yields. The reaction with TiCl₄-Et₃N (2:8 ratio) gave a mixture of **12a** and **13a** in 17 and 11% yields, respectively. The reaction in the presence of piperidine (0.2 equiv) in benzene at room temperature gave adduct **12a** in 82% yield (Scheme 8, Table

Scheme 8. Schematic of the Transformation of 1a−c to 14a−c
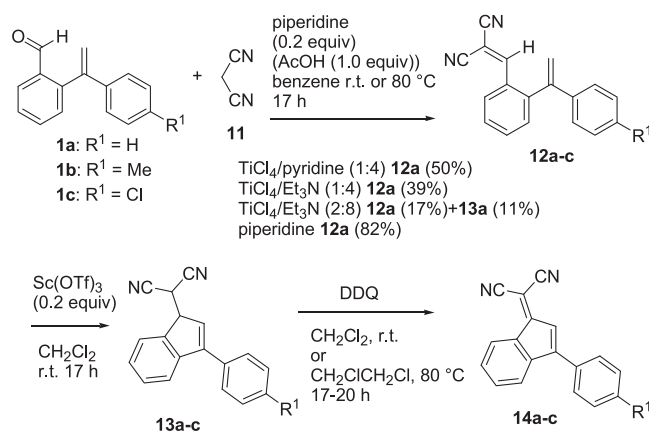
3). The reaction of **12a** with catalytic amounts of Sc(OTf)₃ in dichloromethane at room temperature gave **13a** in 99% yield. Dehydrogenation of **13a** with DDQ (1 equiv) in CH₂Cl₂ at room temperature provided **14a** in 61% yield. Thus, the effective reaction conditions to give cyclized product sequentially could not be found. The reaction of the Me and Cl substituted derivatives **1b,c** with malononitrile followed by cyclization and dehydration also proceeded stepwise to give **13b,c** and **14b,c**.

The electrophilicity parameters are reported as ethyl benzylidenemalonate (−20.55) < benzylidenemalononitrile

Table 3. Stepwise Reaction of 1a−c and 11 to 12a−c, 13a−c, and 14a−c

entry	1	R[1]	12	yield (%)	13	yield (%)	14	yield (%)
1	1a	H	12a	82[a]	13a	99	14a	61[c]
2	1b	Me	12b	73[a]	13b	91	14b	89[c]
3	1c	Cl	12c	70[b]	13c	95	14c	74[d]

[a]The reaction with piperidine (0.2 equiv) in benzene at r.t. [b]The reaction with piperidine (0.2 equiv) and acetic acid (1.0 equiv) in benzene at 80 °C. [c]The reaction with DDQ at r.t. in dichloromethane. [d]The reaction with DDQ at 80 °C in 1,2-dichloroethane.

(−9.42) < benzylidene Meldrum's acid (−9.15).[19] However, these cyclization reactions may not be easy to compare, partly because the cyclization may be accelerated by Lewis acid or H^{+} coordination to O or N. In addition, some intermediates seem to be unstable under the Lewis acid conditions.

Furthermore, to extend the scope of sequential Knoevenagel condensation/cyclization reaction, the reactions of 2-arylbenzaldehydes 15a−c with an active methylene compound have been investigated (Scheme 9, Table 4). However, the reaction

Scheme 9. Reactions of 2-Arylbenzaldehydes 15a−c to Form 18a−c
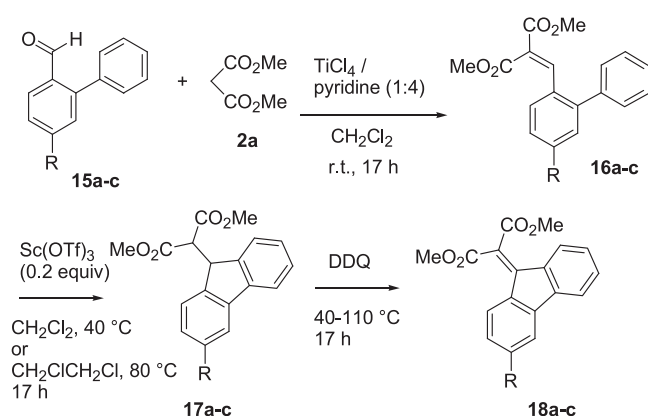
Table 4. Stepwise Reaction of 15a−c and 2a to 16a−c, 17a-c, and 18a−c

entry	15	R	16	yield (%)	17	yield (%)	18	yield (%)
1	15a	H	16a	78[a]	17a	94	18a	69[b]
2	15b	Me	16b	86	17b	88	18b	86[c]
3	15c	Cl	16c	82	17c	81	18c	40[d]

[a]The reaction of 15a and 2a with TiCl₄-Et₃N (2:8) gave 16a in 81% yield. [b]At 40 °C in CH₂Cl₂. [c]At 80 °C in 1,2-dichloroethane. [d]At 110 °C in toluene.

of 15a−c and methyl malonate 2a with TiCl₄/Et₃N or TiCl₄/pyridine gave the normal Knoevenagel adduct 16a-c as major products. The stepwise reaction of 16a−c to fluorenes 17a−c with Sc(OTf)₃ and subsequent treatment of 17a−c with DDQ gave 18a−c.

On the other hand, the reaction of 15d with electron-donating 3,5-dimethoxyphenyl group and 2a in the presence of TiCl₄/pyridine (1:4) gave cyclized product 17d in 63% yield in one pot (Scheme 10). However, the reaction with TiCl₄/Et₃N (2:8) gave a complex mixture including a small amount of 17d.

The reaction of 17d with DDQ at room temperature gave 18d in 92% yield.

Scheme 10. Reaction of 15d to form 18d
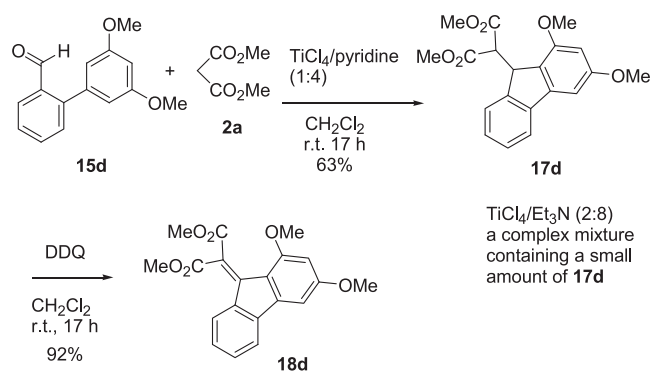
The reaction of 2-phenoxybenzaldehyde 19 and methyl malonate 2a with TiCl₄/Et₃N or TiCl₄/pyridine gave only Knoevenagel adduct 20. The stepwise reaction of 20 to the xanthene derivative 21 with Sc(OTf)₃ and subsequent treatment of 21 with DDQ gave 22 (Scheme 11).

Scheme 11. Reaction of 2-Phenoxybenzaldehyde 19 to Form 22
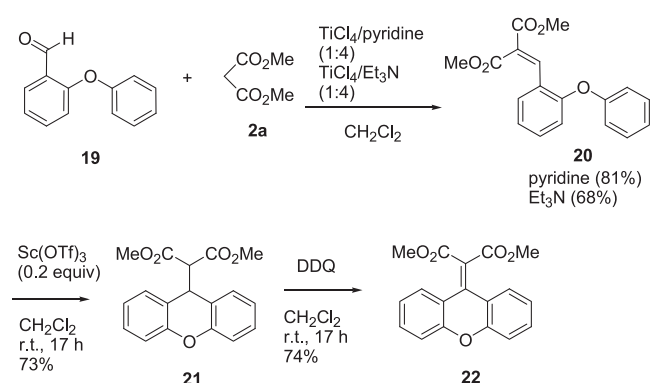
The probable reaction mechanism to give products sequentially is shown in Scheme 12. First, Knoevenagel condensation of the active methylene compound such as 2a gives Lewis acid coordinated or protonated intermediate A, according to the reported mechanism.[10,20] Intramolecular alkene addition affords the carbocation intermediate B, which is stabilized by two aryl groups. Intermediate B undergoes deprotonation to afford C. Protonation of the α-carbon of C may lead to indene 4a. Furthermore, dehydrogenation occurred to afford benzofulvene 5a in the presence of 2 equiv of TiCl₄ and 8 equiv of Et₃N in one pot.

The oxidative reactions using titanium tetrachloride and a tertiary amine have been reported previously.[21] Based on the reports, the intermediate C can be dehydrogenated to give Ti-complex D, which leads to 5a.

The reaction mechanism of the cyclization step in Scheme 12 has been examined by the DFT calculations in order to compare the observed reactivities of various substrates.

The calculations were performed by the B3LYP/6-31G*[22,23] level including the PCM[24] solvent effect (solvent = CH₂Cl₂ or benzene). TS geometry was characterized by vibrational analysis, which checked whether the obtained geometry has

Scheme 12. Probable Reaction Mechanism from 1a to Give Products 4a and 5a Sequentially

Scheme 14. Cyclization Steps for Various TiOCl$_2$-Coordinate Substrate Models
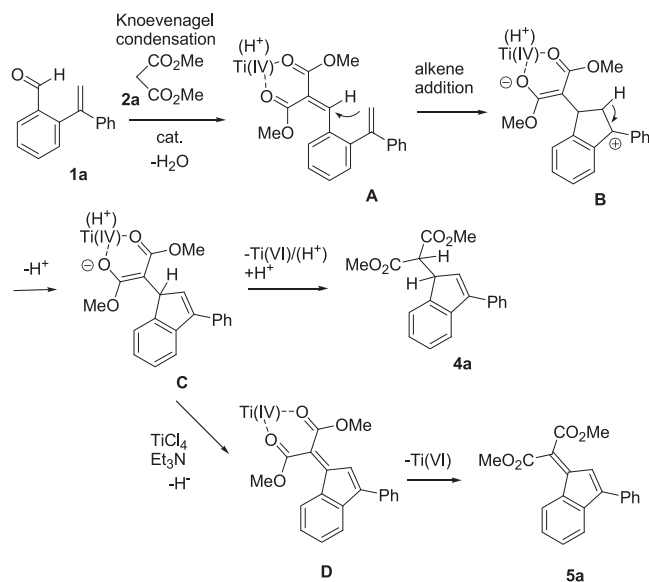
single imaginary frequencies ($\nu^{\ddagger}$). From TSs, reaction paths were traced by the intrinsic reaction coordina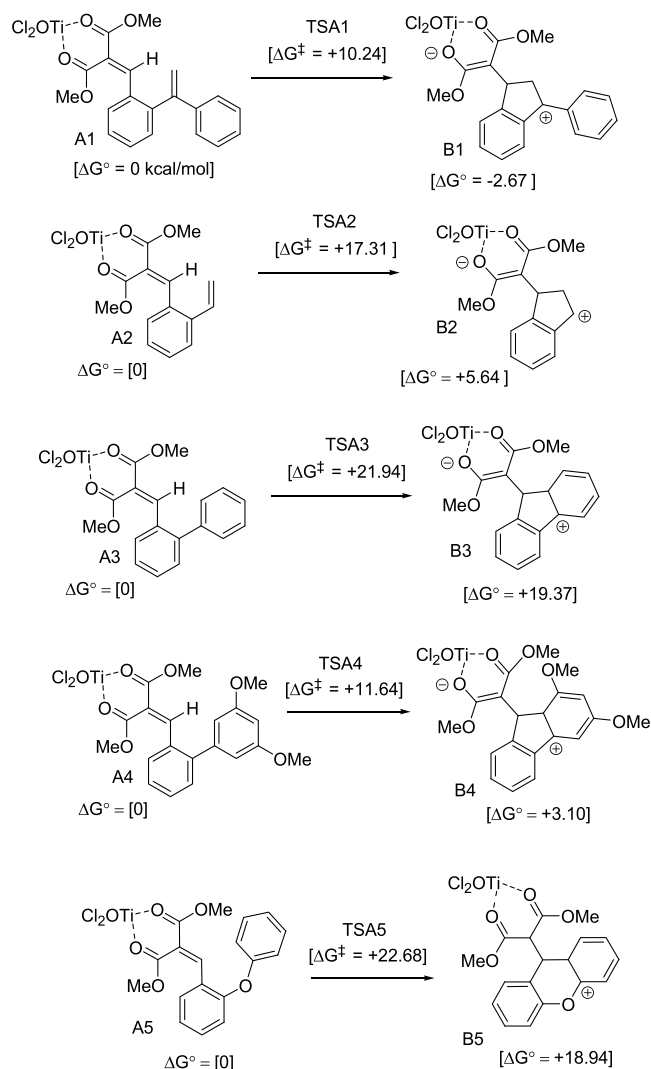te (IRC) method[25] to obtain the energy-minimum geometries. Relative Gibbs free energies in kcal/mol (T = 298.15 K, P = 1 atm) were refined by single-point calculations of RB3LYP/6-311+G(d,p) SCRF = (PCM, solvent = CH$_2$Cl$_2$ or benzene).

Based on the previous theoretical study by Marrone et al.,[20a,b] the TiCl$_4$-promoted Knoevenagel condensation of dimethyl malonate and aldehydes may give titanyl (TiOCl$_2$) complex in situ. In this study, the reaction mechanism starting from the Knoevenagel adduct **A** (in Scheme 12) in situ was calculated by the use of the titanyl (TiOCl$_2$) complex models.

Intramolecular addition of an alkene to the Knoevenagel adduct—TiOCl$_2$ complex AN with Me$_3$N, leading to the formation of intermediate BN, deprotonation of BN by Me$_3$N (as a model for an amine) to form an alkene, and generation of the intermediate CN.

The steps AN → BN → CN were calculated (Scheme 13). The energy of transition state of cyclization, TSAN ($\Delta G^{\ddagger}$ = +11.27 kcal/mol), is higher than that of deprotonation by Me$_3$N, TSBN ($\Delta G^{\ddagger}$ = +7.35 kcal/mol).

Since TSAN is higher than TSBN, cyclization steps for various TiOCl$_2$-coordinate substrate models without Me$_3$N have been calculated and compared (Scheme 14). The activation energy of TSA1 is similar to that of TSAN of the model with Me$_3$N. The transition state (TSA1) of cyclization for TiOCl$_2$-coordinate 2-(1-phenylvinyl) derivative **3a**, A1 to B1, is more stable than TSA2 for TiOCl$_2$-coordinate 2-vinyl

derivative 7, A2 to B2. The intermediate B1 is highly stabilized by two aryl groups. Furthermore, the reaction models A3 and A4 for Knowevenagel adducts **16a,d** from 2-arybenzaldehydes **15a,d** have been calculated. The activation energy of TS3A (+21.94 kcal/mol) is much higher than that of TSA1 due to destruction of the aromatic ring. However, the activation energy of TSA4 for the di-MeO derivative is +11.64 kcal/mol and comparable to the TSA1 because two electron-donating groups stabilize the cation intermediate. On the other hand, the activation energy of TSA5 for the oxygen-substituted derivative **20** is higher (+22.68 kcal/mol). This is probably

Scheme 13. Transition of AN to BN and then to CN
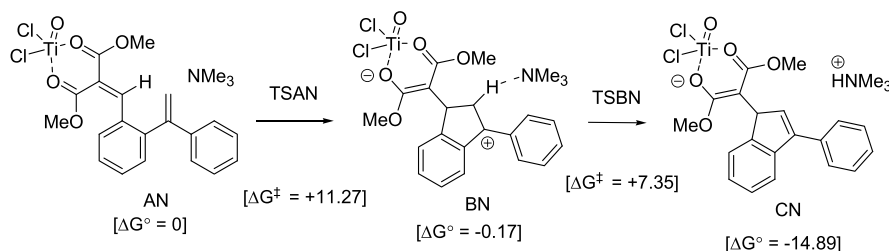
because of both the electronic effect and the steric reason by the six-membered ring formation. Those calculations are in agreement with the experimental results.

Next, the reactivity between dimethyl malonate and Meldrum's acid with dimethylammonium ion as a model of the piperidine-catalyzed reaction was compared (Scheme 15)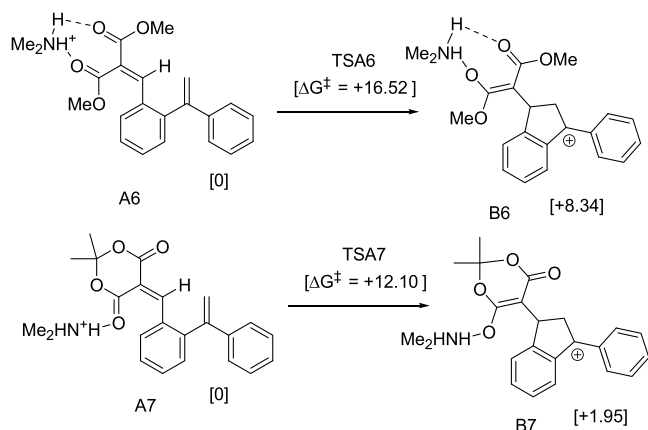. TSA7 is more stable than TSA6. This is in agreement with the electrophilicity of benzylidenemalonate and benzylidene Meldrum's acid, as described above.[19]

Scheme 15. Reactivity between Dimethyl Malonate and Meldrum's Acid with the Dimethylammonium Ion

Dehydrogenation step **C** to **D** in Scheme 16 was also examined. Hall et al. suggested formation of the iminium ion

Scheme 16. Dehydrogenation Step C to D
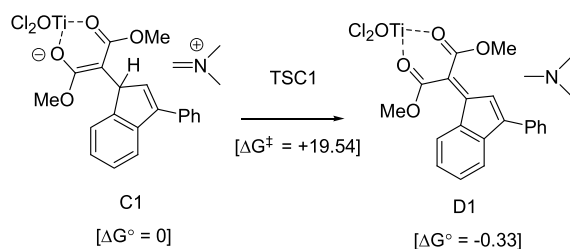
by the redox reaction between TiCl$_4$ and Et$_3$N.[21e] Therefore, hydride transfer of C1 with the iminium ion, formed in situ from TiCl$_4$ and Me$_3$N (as a model of Et$_3$N), is considered. The removal of a hydride from the indene ring gives intermediate D1. Although the full mechanism of dehydrogenation by TiCl$_4$-Et$_3$N is not clear, the hydride transfer path by the iminium ion may be possible as shown by the model calculations. Dehydrogenation by DDQ may also involve the hydride transfer step.[26]

In summary, sequential Knoevenagel condensation/cyclization leading to indene and benzofulvene derivatives has been developed. The reaction of 2-(1-phenylvinyl)benzaldehyde with malonates gave benzylidene malonates, cyclized indenes, and dehydrogenated benzofulvenes. The product selectivity depends on the reaction conditions. Reaction of variously substituted aryl derivatives with dimethyl malonate gave indene and benzofulvene derivatives. The reactions of 2-(1-phenylvinyl)benzaldehyde with Meldrum's acid or malononitrile also gave cyclized compounds in the suitable sequential or stepwise conditions. Furthermore, the reaction of 2-arylbenzaldehydes has been investigated. The limitation and scope

have been described. The reaction mechanism of the cyclization steps has been examined by the DFT calculations.

Further study on the transformation and the utility of the products is under investigation.

■ EXPERIMENTAL SECTION

General Methods. [1]H chemical shifts are reported in ppm relative to Me$_4$Si. [13]C chemical shifts are reported in ppm relative to CDCl$_3$ (77.1 ppm). [19]F chemical shifts are reported in ppm relative to CFCl$_3$. [13]C mutiplicities were determined by DEPT and HSQC. Mass spectra were recorded at an ionizing voltage of 70 eV by EI or CI. The mass analyzer type used for EI and CI is double-focusing. All reactions were carried out under a nitrogen atmosphere. Column chromatography was performed on silica gel (75−150 μm).

1a−i and **6** were prepared according to the literature.[5b] **15b,d** were prepared according to the literature.[27] **15c** was prepared according to the literature method.[27a]

15c: (5 mmol scale, 853 mg, 75%); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.36−7.39 (m, 2H), 7.45−7.51 (m, 5H), 7.98 (dd, J = 8.1, 0.6 Hz, 1H), 9.92 (d, J = 0.6 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 128.24 (CH), 128.70 (CH), 128.74 (CH), 129.24 (CH), 130.00 (CH), 130.78 (CH), 132.12 (C), 136.44 (C), 139.91 (C), 147.44 (C), 191.26 (CH); IR (KBr) 2875, 1684, 1588, 1392, 1253, 1094 cm^{-1}; MS (CI) m/z 219 ([M + H]$^+$, 30), 217 ([M + H]$^+$, 100%); HRMS (CI) m/z 217.0414, 219.0401 (calcd for C$_{13}$H$_{10}$ClO [M + H]$^+$ 217.0420, 219.0391).

Procedure for Preparation of 3a. To a solution of **1a** (491 mg, 2.3 mmol) in benzene (20 mL) were successively added dimethyl malonate **2a** (0.32 g, 0.27 mL, 2.5 mmol), piperidine (0.20 g, 0.23 mL, 2.3 mmol), and AcOH (0.15 g, 0.14 mL, 2.5 mmol) at 0 °C and then heated at reflux. After heating for 1.5 h, the crude products were concentrated in vacuo, and the residue was purified by column chromatography over silica gel eluting with hexane-EtOAc to give **3a** (586 mg, 75%).

3a: R$_f$ = 0.1 (hexane-EtOAc = 10:1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$). Compound **3a** decomposes partially to **4a** in CDCl$_3$. δ (ppm) 3.738 (s, 3H), 3.742 (s, 3H), 5.23 (d, J = 1.0 Hz, 1H), 5.86 (d, J = 1.0 Hz, 1H), 7.23−7.46 (m, 9H), 7.81 (s, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 52.46 (CH$_3$), 118.17 (CH$_2$), 126.13 (C), 127.30 (CH), 127.79 (CH), 127.99 (C), 128.01 (CH), 128.02 (CH), 128.40 (CH), 129.95 (CH), 130.24 (CH), 140.58 (C), 142.75 (C), 143.78 (CH), 147.33 (C), 164.25 (C), 166.91 (C); IR (neat) 2952, 1737, 1628, 1436, 1257, 1221, 1069 cm^{-1}; MS (EI) m/z 322 (M$^+$, 32), 290 (47), 262 (72), 202 (100%); HRMS (EI) m/z 322.1201 (calcd for C$_{20}$H$_{18}$O$_4$ 322.1205).

Procedure for Preparation of 4a. To a solution of **1a** (1.05 g, 5.0 mmol) in CH$_2$Cl$_2$ (20 mL) was added dimethyl malonate **2a** (660.6 mg, 0.55 mL, 5.0 mmol) and pyridine (1.57 g, 1.6 mL, 20 mmol). After cooling to 0 °C, TiCl$_4$ (948.4 mg, 5.0 mmol) in CH$_2$Cl$_2$ (2.5 mL) was slowly added to the reaction mixture. The reaction mixture was allowed to warm to room temperature and stirred for 8 h. The mixture was quenched with 1 M HCl solution and extracted with CH$_2$Cl$_2$. The organic layer was washed with saturated aqueous NaHCO$_3$, dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexane-EtOAc to give **4a** (1.27 g, 79%).

4a: R$_f$ = 0.4 (hexane-EtOAc = 10:1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 3.57 (d, J = 8.6 Hz, 1H),

3.69 (s, 3H), 3.83 (s, 3H), 4.28 (dd, J = 8.6, 2.1 Hz, 1H), 6.53 (d, J = 2.1 Hz, 1H), 7.24 (ddd, J = 7.4, 7.4, 1.0 Hz, 1H), 7.33 (ddd, J = 7.4, 7.4, 0.7 Hz, 1H), 7.36−7.40 (m, 2H), 7.42−7.47 (m, 2H), 7.54 (d, J = 7.6 Hz, 1H), 7.56−7.59 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 47.66 (CH), 52.71 (CH$_3$), 52.80 (CH$_3$), 53.59 (CH), 120.83 (CH), 123.80 (CH), 125.61 (CH), 127.46 (CH), 127.78 (CH), 128.03 (CH), 128.66 (CH), 132.65 (CH), 135.33 (C), 143.59 (C), 144.67 (C), 145.70 (C), 168.36 (C), 169.02 (C); IR (neat) 2952, 1736, 1599, 1492, 1435, 1234, 1155, 1030 cm^{-1}; MS (EI) m/z 322 (M$^+$, 20), 262 (47), 207 (71), 202 (100%); HRMS (EI) m/z 322.1195 (calcd for C$_{20}$H$_{18}$O$_4$ 322.1205).

4b: 1 mmol scale, 154 mg, 46%; R$_f$ = 0.2 (hexane-EtOAc = 10:1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 2.40 (s, 3H), 3.55 (d, J = 8.8 Hz, 1H), 3.68 (s, 3H), 3.82 (s, 3H), 4.27 (dd, J = 8.8, 2.1 Hz, 1H), 6.49 (d, J = 2.1 Hz, 1H), 7.21−7.26 (m, 3H), 7.30−7.34 (m, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.47 (d-like, J = 8.0 Hz, 2H), 7.53 (d, J = 7.4 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 21.34 (CH$_3$), 47.59 (CH), 52.66 (CH$_3$), 52.75 (CH$_3$), 53.61 (CH), 120.83 (CH), 123.74 (CH), 125.52 (CH), 127.40 (CH), 127.63 (CH), 129.33 (CH), 132.06 (CH), 132.39 (C), 137.82 (C), 143.71 (C), 144.69 (C), 145.53 (C), 168.36 (C), 169.01 (C); IR (neat) 2952, 1738, 1509, 1435, 1262, 1233, 1155 cm^{-1}; MS (EI) m/z 336 (M$^+$, 62), 276 (100%); HRMS (EI) m/z 336.1360 (calcd for C$_{21}$H$_{20}$O$_4$ 336.1362).

4c: 1 mmol scale, 174 mg, 46%; R$_f$ = 0.9 (hexane-EtOAc = 1:1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 3.59 (t, J = 8.6 Hz, 1H), 3.68 (s, 3H), 3.82 (s, 3H), 4.27 (dd, J = 8.6, 2.1 Hz, 1H), 6.54 (d, J = 2.1 Hz, 1H), 7.25 (ddd, J = 7.4, 7.4, 1.0 Hz, 1H), 7.33 (ddd, J = 7.5, 7.4, 0.7 Hz, 1H), 7.39−7.42 (m, 3H), 7.48 (d, J = 7.5 Hz, 1H), 7.50 (d-like, J = 8.6 Hz, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 47.65 (CH), 52.67 (CH$_3$), 52.78 (CH$_3$), 53.39 (CH), 120.57 (CH), 123.84 (CH), 125.76 (CH), 127.51 (CH), 128.83 (CH), 129.03 (CH), 133.09 (CH), 133.73 (C), 133.78 (C), 143.17 (C), 144.52 (C), 168.20 (C), 168.89 (C); IR (neat) 2953, 1735, 1488, 1434, 1234, 1155, 1089, 1014 cm^{-1}; MS (EI) m/z 358 (M$^+$, 11), 356 (M$^+$, 32), 296 (70), 83 (100%); HRMS (EI) m/z 356.0812, 358.0781 (calcd for C$_{20}$H$_{17}$ClO$_4$ 356.0815, 358.0786).

4d: 0.92 mmol scale, 171 mg, 55%; R$_f$ = 0.6 (hexane-ether = 1:1); yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 2.37 (s, 3H), 3.53 (d, J = 8.8 Hz, 1H), 3.69 (s, 3H), 3.81 (s, 3H), 4.24 (dd, J = 8.8, 2.1 Hz, 1H), 6.51 (d, J = 2.1 Hz, 1H), 7.05 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.33 (s, 3H), 7.33−7.39 (m, 1H), 7.42−7.46 (m, 2H), 7.55−7.57 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 21.58 (CH$_3$), 47.30 (CH), 52.60 (CH$_3$), 52.67 (CH$_3$), 53.68 (CH), 121.51 (CH), 123.45 (CH), 126.32 (CH), 127.75 (CH), 127.92 (CH), 128.59 (CH), 132.90 (CH), 135.40 (C), 137.15 (C), 141.69 (C), 143.75 (C), 145.60 (C), 168.34 (C), 168.98 (C); IR (neat) 2952, 1743, 1734, 1606, 1492, 1436, 1152, 1029 cm^{-1}; MS (EI) m/z 336 (M$^+$, 66), 276 (100%); HRMS (EI) m/z 336.1368 (calcd for C$_{21}$H$_{20}$O$_4$ 336.1362); anal. calcd for C$_{21}$H$_{20}$O$_4$: C, 75.43; H, 5.43. Found: C, 75.81; H, 5.07.

4e: 1 mmol scale, 207 mg, 57%; R$_f$ = 0.6 (hexane-Et$_2$O = 1:1); yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 3.60 (d, J = 8.2 Hz, 1H), 3.69 (s, 3H), 3.80 (s, 3H), 4.25 (dd, J = 8.2, 2.1 Hz, 1H), 6.58 (d, J = 2.1 Hz, 1H), 7.21 (dd, J = 8.0, 2.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.37−7.43 (m, 1H), 7.44−7.48 (m, 2H), 7.48 (d, J = 2.0 Hz, 1H), 7.51−7.54 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 47.34 (CH), 52.76

(CH$_3$), 52.84 (CH$_3$), 53.31 (CH), 121.14 (CH), 124.81 (CH), 125.53 (CH), 127.70 (CH), 128.31 (CH), 128.81 (CH), 133.64 (C), 134.25 (CH), 134.68 (C), 142.88 (C), 145.04 (C), 145.51 (C), 168.13 (C), 168.74 (C); IR (neat) 2953, 1754, 1730, 1598, 1565, 1491, 1435, 1156, 1072, 1029 cm^{-1}; MS (EI) m/z 356 (M$^+$, 47), 296 (100), 202 (64%); HRMS (EI) m/z 356.0810, 358.0793 (calcd for C$_{20}$H$_{17}$ClO$_4$ 356.0815, 358.0786).

4f: 1 mmol scale, 235 mg, 66%; R$_f$ = 0.5 (hexane-Et$_2$O = 1:1); yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 3.58 (d, J = 8.6 Hz, 1H), 3.71 (s, 3H), 3.83 (s, 3H), 4.26 (dd, J = 8.6, 2.0 Hz, 1H), 6.52 (d, J = 2.0 Hz, 1H), 7.30 (dd, J = 8.0, 2.0 Hz, 1H), 7.37−7.41 (m, 2H), 7.43−7.47 (m, 3H), 7.51−7.55 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 47.51 (CH), 52.82 (CH$_3$), 52.94 (CH$_3$), 53.28 (CH), 121.60 (CH), 124.48 (CH), 127.64 (CH), 127.69 (CH), 128.26 (CH), 128.76 (CH), 131.74 (C), 132.84 (CH), 134.86 (C), 142.16 (C), 145.10 (C), 146.46 (C), 168.13 (C), 168.75 (C); IR (KBr) 2958, 1754, 1436, 1154, 1007 cm^{-1}; MS (EI) m/z 356 (M$^+$, 47), 296 (100), 202 (56%); HRMS (EI) m/z 356.0814, 358.0791 (calcd for C$_{20}$H$_{17}$ClO$_4$ 356.0815, 358.0786).

4h: 1 mmol scale, 174 mg, 50%; R$_f$ = 0.5 (hexane-EtOAc = 10:1); yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.12 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 3.64 (d, J = 7.8 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 4.25−4.30 (m, 3H), 6.57 (d, J = 2.1 Hz, 1H), 7.24 (ddd, J = 7.4, 7.4, 1.0 Hz, 1H), 7.30−7.34 (m, 1H), 7.35−7.39 (m, 1H), 7.41−7.46 (m, 3H), 7.53 (d, J = 7.6 Hz, 1H), 7.56−7.59 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.02 (CH$_3$), 14.13 (CH$_3$), 47.65 (CH), 53.72 (CH), 61.51 (CH$_2$), 61.72 (CH$_2$), 120.69 (CH), 123.94 (CH), 125.49 (CH), 127.31 (CH), 127.76 (CH), 127.95 (CH), 128.63 (CH), 132.90 (CH), 135.46 (C), 143.66 (C), 144.87 (C), 145.51 (C), 167.90 (C), 168.58 (C); IR (neat) 2981, 1749, 1732, 1598, 1446, 1369, 1153, 1035 cm^{-1}; MS (EI) m/z 350 (M$^+$, 51), 276 (100%); HRMS (EI) m/z 350.1519 (calcd for C$_{22}$H$_{22}$O$_4$ 350.1518).

Procedure for Preparation of 5a. To a solution of **1a** (209.9 mg, 1.0 mmol) in CH$_2$Cl$_2$ (6 mL) were added dimethyl malonate **2a** (132.1 mg, 0.11 mL, 1.0 mmol) and Et$_3$N (809.5 mg, 1.12 mL, 8.0 mmol). After cooling to 0 °C, TiCl$_4$ (379.4 mg, 2.0 mmol) in CH$_2$Cl$_2$ (1 mL) was slowly added to the reaction mixture. The reaction mixture was allowed to warm to room temperature and stirred for 17 h. The mixture was quenched with 1 M HCl solution and extracted with CH$_2$Cl$_2$. The organic layer was washed with saturated aqueous NaHCO$_3$, dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexane-EtOAc to give **5a** (135 mg, 40%).

5a: R$_f$ = 0.4 (hexane-EtOAc = 15: 1); orange crystals; mp 108−109 °C (hexane); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 3.88 (s, 3H), 4.00 (s, 3H), 7.18 (ddd, J = 7.6, 7.6, 1.0 Hz, 1H), 7.31 (ddd, J = 7.6, 7.4, 1.0 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.42−7.50 (m, 5H), 7.65−7.68 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 52.76 (CH$_3$), 53.18 (CH$_3$), 121.06 (C), 121.56 (CH), 124.11 (CH), 124.76 (CH), 127.08 (CH), 127.76 (CH), 128.82 (CH), 129.34 (CH), 130.33 (CH), 134.27 (C), 135.22 (C), 143.14 (C), 149.24 (C), 151.93 (C), 164.30 (C), 166.95 (C); IR (KBr) 2949, 1723, 1617, 1437, 1252, 1223, 1116, 1050 cm^{-1}; λ_{max} (CH$_3$CN) 250 (ε 22,700), 318 (10,000), 418 (2050) nm; MS (EI) m/z 320 (M$^+$, 14), 202 (85), 201 (100%); HRMS (EI) m/z 320.1056 (calcd for C$_{20}$H$_{16}$O$_4$ 320.1049); anal. calcd for C$_{20}$H$_{16}$O$_4$: C, 74.99; H, 5.03. Found: C, 75.08; H, 4.99.

5b: 1 mmol scale, 151 mg, 45%; R_f = 0.3 (hexane-EtOAc = 10:1); red-orange crystals; mp 108−110 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 2.42 (s, 3H), 3.87 (s, 3H), 3.99 (s, 3H), 7.18 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.30 (ddd, J = 7.6, 7.6, 1.0 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.45 (s, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.57 (d-like, J = 8.0 Hz, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 21.53 (CH$_3$), 52.70 (CH$_3$), 53.13 (CH$_3$), 120.64 (C), 121.57 (CH), 124.01 (CH), 124.17 (CH), 126.99 (CH), 127.67 (CH), 129.50 (CH), 130.25 (CH), 131.36 (C), 135.34 (C), 139.53 (C), 143.20 (C), 149.38 (C), 151.93 (C), 164.35 (C), 167.01 (C); IR (KBr) 2951, 1729, 1725, 1605, 1251, 1218 cm^{-1}; λ_{max} (CH$_3$CN) 251 (ε 19,400), 330 (10,000), 425 (2180) nm; MS (EI) m/z 334 (M$^+$, 100), 303 (24%); HRMS (EI) m/z 334.1201 (calcd for C$_{21}$H$_{18}$O$_4$ 334.1205).

5c: 1 mmol scale, 184 mg, 57%; R_f = 0.3 (hexane-EtOAc = 10:1); yellow crystals; mp 115−117 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 3.87 (s, 3H), 4.00 (s, 3H), 7.19 (ddd, J = 7.6, 7.5, 1.0 Hz, 1H), 7.30 (ddd, J = 7.5, 7.4, 0.8 Hz, 1H), 7.39 (d, J = 7.4 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.43 (d-like, J = 8.5 Hz, 2H), 7.47 (s, 1H), 7.58 (d-like, J = 8.5 Hz, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 52.78 (CH$_3$), 53.17 (CH$_3$), 121.30 (CH), 121.38 (C), 124.17 (CH), 125.00 (CH), 127.21 (CH), 129.00 (CH), 129.05 (CH), 130.38 (CH), 132.64 (C), 135.06 (C), 135.15 (C), 142.70 (C), 148.90 (C), 150.55 (C), 164.16 (C), 166.78 (C); IR (KBr) 2958, 1746, 1730, 1617, 1251, 1210 cm^{-1}; λ_{max} (CH$_3$CN) 252 (ε 32,700), 333 (11,200), 420 (3010) nm; MS (EI) m/z 356 (M$^+$, 43), 354 (M$^+$, 100%); HRMS (EI) m/z 354.0650, 356.0674 (calcd for C$_{20}$H$_{15}$ClO$_4$ 354.0659, 356.0629).

5d: 0.92 mmol scale, 188 mg, 61%; R_f = 0.5 (hexane-ether = 1:1); orange crystals; mp 112−113 °C (ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 2.36 (s, 3H), 3.87 (s, 3H), 3.98 (s, 3H), 6.98 (d, J = 7.8 Hz, 1H), 7.25 (s, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.41−7.50 (m, 3H), 7.44 (s, 1H), 7.63−7.66 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 21.88 (CH$_3$), 52.66 (CH$_3$), 53.08 (CH$_3$), 120.35 (C), 122.68 (CH), 124.02 (CH), 125.12 (CH), 127.41 (CH), 127.77 (CH), 128.79 (CH), 129.24 (CH), 132.43 (C), 134.37 (C), 140.87 (C), 143.46 (C), 149.32 (C), 151.86 (C), 164.40 (C), 167.03 (C); IR (KBr) 2949, 1735, 1728, 1604, 1430, 1250, 1218, 1048 cm^{-1}; λ_{max} (CH$_3$CN) 253 (ε 25,800), 325 (9960), 419 (1640) nm; MS (EI) m/z 334 (M$^+$, 100), 303 (23%); HRMS (EI) m/z 334.1201 (calcd for C$_{21}$H$_{18}$O$_4$ 334.1205).

5e: 1 mmol scale, 166 mg, 46%; R_f = 0.6 (hexane-ether = 1 1); orange crystals; mp 129−130 °C (ethanol); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 3.88 (s, 3H), 3.99 (s, 3H), 7.17 (dd, J = 8.2, 2.0 Hz, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.45−7.51 (m, 3H), 7.48 (s, 1H), 7.60−7.63 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 52.85 (CH$_3$), 53.21 (CH$_3$), 121.87 (C), 122.06 (CH), 125.00 (CH), 126.09 (CH), 126.67 (CH), 127.69 (CH), 128.98 (CH), 129.59 (CH), 133.36 (C), 133.68 (C), 136.52 (C), 145.01 (C), 147.96 (C), 150.81 (C), 164.16 (C), 166.55 (C); IR (KBr) 2951, 1735, 1723, 1617, 1444, 1249, 1216, 1046 cm^{-1}; MS (EI) m/z 356 (M$^+$, 59), 354 (M$^+$, 100), 296 (49%); λ_{max} (CH$_3$CN) 257 (ε 25,700), 334 (11,300), 413 (1930) nm; HRMS (EI) m/z 354.0659, 356.0648 (calcd for C$_{20}$H$_{15}$ClO$_4$ 354.0659, 356.0629); anal. calcd for C$_{20}$H$_{15}$ClO$_4$: C, 67.71; H, 4.26. Found: C, 67.54; H, 4.42.

5f: 1 mmol scale, 186 mg, 52%; R_f = 0.5 (hexane-ether = 1:1); orange crystals; mp 99−100 °C (hexane-EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 3.88 (s, 3H), 4.01 (s, 3H), 7.29 (dd, J = 8.0, 1.9 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 1.9 Hz, 1H), 7.42−7.50 (m, 3H), 7.44 (s, 1H), 7.61−7.64 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 52.90 (CH$_3$), 53.26 (CH$_3$), 122.12 (CH), 124.90 (CH), 124.94 (CH), 127.70 (CH), 128.92 (CH), 129.59 (CH), 129.84 (CH), 133.16 (C), 133.84 (C), 136.90 (C), 141.42 (C), 148.05 (C), 151.26 (C), 164.10 (C), 166.40 (C); IR (KBr) 2952, 1723, 1617, 1442, 1253, 1216, 1044 cm^{-1}; λ_{max} (CH$_3$CN) 256 (ε 12,700), 316 (7400), 430 (1100) nm; MS (EI) m/z 356 (M$^+$, 35), 354 (M$^+$, 100), 323 (20), 189 (29%); HRMS (EI) m/z 354.0652, 356.0632 (calcd for C$_{20}$H$_{15}$ClO$_4$ 354.0659, 356.0629); anal. calcd for C$_{20}$H$_{15}$ClO$_4$: C, 67.71; H, 4.26. Found: C, 67.70; H, 4.02.

5g: 1 mmol scale, 178 mg, 53%; R_f = 0.5 (hexane-ether = 1:1); orange crystals; mp 100−101 °C (hexane-EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 3.88 (s, 3H), 3.99 (s, 3H), 6.86 (ddd, J = 8.6, 8.4, 2.3 Hz, 1H), 7.16 (dd, J = 8.8, 2.3 Hz, 1H), 7.39 (dd, J = 8.4, 4.9 Hz, 1H), 7.41−7.51 (m, 3H), 7.51 (s, 1H), 7.60−7.63 (m, 2H); ^{19}F NMR (376 MHz, CDCl$_3$) δ (ppm) −109.17 (ddd, J_{FH} = 8.6, 8.6, 5.1 Hz); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 52.83 (CH$_3$), 53.21 (CH$_3$), 109.86 (d, J_{CF} = 25 Hz, CH), 112.94 (d, J_{CF} = 23 Hz, CH), 121.35 (C), 125.51 (d, J_{CF} = 9.2 Hz, CH), 126.38 (CH), 127.61 (CH), 128.95 (CH), 129.56 (CH), 130.75 (d, J_{CF} = 3.1 Hz, C), 133.71 (C), 145.91 (d, J_{CF} = 8.4 Hz, C), 147.96 (C), 150.43 (d, J_{CF} = 2.3 Hz, C), 164.21 (C), 164.33 (d, J_{CF} = 251 Hz, C), 166.68 (C); IR (KBr) 2949, 1738, 1723, 1614, 1593, 1458, 1257, 1195, 1046 cm^{-1}; λ_{max} (CH$_3$CN) 251 (ε 19,700), 321 (9370), 401 (1680) nm; MS (EI) m/z 338 (M$^+$, 100), 220 (69), 207 (60%); HRMS (EI) m/z 338.0950 (calcd for C$_{20}$H$_{15}$FO$_4$ 338.0954); anal. calcd for C$_{20}$H$_{15}$FO$_4$: C, 71.00; H, 4.47. Found: C, 71.13; H, 4.27.

5h:[17] 1.0 mmol scale, 143 mg, 41%; R_f = 0.4 (hexane-EtOAc = 10:1); orange crystals; mp 112.6−113.6 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.35 (t, J = 7.1 Hz, 3H), 1.41 (t, J = 7.1 Hz, 3H), 4.33 (q, J = 7.1 Hz, 2H), 4.47 (q, J = 7.1 Hz, 2H), 7.18 (ddd, J = 7.6, 7.6, 1.0 Hz, 1H), 7.30 (ddd, J = 7.6, 7.6, 1.0 Hz, 1H), 7.40−7.47 (m, 4H), 7.47 (s, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.64−7.67 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.03 (CH$_3$), 14.18 (CH$_3$), 61.71 (CH$_2$), 62.08 (CH$_2$), 121.42 (CH), 122.08 (C), 124.30 (CH), 124.90 (CH), 126.95 (CH), 127.75 (CH), 128.79 (CH), 129.23 (CH), 130.16 (CH), 134.40 (C), 135.33 (C), 143.14 (C), 148.54 (C), 151.56 (C), 163.97 (C), 166.40 (C); IR (KBr) 2981, 1724, 1708, 1451, 1250, 1217, 1047 cm^{-1}; λ_{max} (CH$_3$CN) 250 (ε 22,100), 313 (11,800), 419 (1950) nm; MS (EI) m/z 348 (M$^+$, 100), 303 (24), 202 (52%); HRMS (EI) m/z 348.1360 (calcd for C$_{22}$H$_{20}$O$_4$ 348.1362); anal. calcd for C$_{22}$H$_{20}$O$_4$: C, 75.84; H, 5.79. Found: C, 75.49; H, 5.93.

5i: 0.89 mmol scale, 136 mg, 41%; R_f = 0.5 (hexane-ether = 1:1); dark red crystals; mp 124−125 °C (hexane-EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 3.88 (s, 3H), 4.04 (s, 3H), 7.18 (ddd, J = 8.6, 6.7, 1.2 Hz, 1H), 7.26 (s, 1H), 7.63 (ddd, J = 8.1, 6.7, 1.2 Hz, 1H), 7.46−7.53 (m, 6H), 7.59 (d, J = 8.6 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 52.90 (CH$_3$), 53.29 (CH$_3$), 120.67 (CH), 123.08 (C), 125.15 (CH), 126.14 (CH), 126.54 (CH), 127.01 (CH), 127.57 (CH), 128.06 (C), 128.37 (CH), 128.45 (CH), 128.58 (CH), 128.69 (CH), 132.06 (C), 135.72 (C), 137.31 (C), 140.15 (C), 148.98 (C), 153.76 (C), 164.15 (C), 166.87 (C); IR (KBr) 2951, 1720, 1617, 1432, 1245, 1208, 1125, 1048 cm^{-1}; λ_{max} (CH$_3$CN) 221 (ε 21,300), 291 (17,100), 334 (5410) nm; MS (EI) m/z 370 (M$^+$, 100),

239 (27%); HRMS (EI) m/z 370.1198 (calcd for $C_{24}H_{18}O_4$ 370.1205).

5a was also obtained by treatment of **4a** (182 mg, 0.56 mmol) with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (127 mg, 0.56 mmol) in CH_2Cl_2 (2.0 mL) at room temperature for 17 h. Chromatography over silica gel eluting with hexane-EtOAc gave **5a** (175 mg, 98%).

7: TiCl$_4$/Et$_3$N = 1:4 equiv, 1 mmol scale, 160.8 mg, 64%; R_f = 0.2 (hexane-AcOEt = 10:1); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 3.72 (s, 3H), 3.87 (s, 3H), 5.44 (dd, J = 11.0, 1.1 Hz, 1H), 5.64 (dd, J = 17.3, 1.1 Hz, 1H), 6.90 (dd, J = 17.3, 11.0 Hz, 1H), 7.25 (ddd, J = 7.8, 7.8, 1.1 Hz, 1H), 7.31 (d-like, J = 7.8 Hz, 1H), 7.37 (ddd, J = 7.8, 7.8, 1.6 Hz, 1H), 7.50 (d-like, J = 7.8 Hz, 1H), 8.07 (s, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 52.61 (CH$_3$), 52.79 (CH$_3$), 118.75 (CH$_2$), 126.80 (CH), 127.43 (C), 127.80 (CH), 128.08 (CH), 130.23 (CH), 131.55 (C), 134.12 (CH), 137.89 (C), 143.04 (CH), 164.38 (C), 166.70 (C); IR (neat) 2952, 1735, 1625, 1437, 1260, 1215, 1070 cm^{-1}; MS (EI) m/z 246 (M$^+$, 1.4), 214 (100), 128 (59%); HRMS (EI) m/z 246.0884 (calcd for $C_{14}H_{14}O_4$ 246.0892).

Preparation of 9. To a solution of **1a** (833 mg, 4.0 mmol) in benzene (6 mL) were added Meldrum's acid **8** (576.5 mg, 4.0 mmol) and piperidine (68.1 mg, 0.08 mL, 0.8 mmol). The mixture was stirred at room temperature for 18 h. 1 M HCl was added to the mixture. The mixture was extracted with CH_2Cl_2. dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexane-CH_2Cl_2 to give **9** (1.04 g, 80%).

9: R_f = 0.1 (hexane-CH_2Cl_2 = 1:2); colorless crystals; mp 129−130 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.75 (s, 3H), 1.82 (s, 3H), 4.27 (d, J = 3.7 Hz, 1H), 4.56 (dd, J = 3.7, 2.1 Hz, 1H), 6.44 (d, J = 2.1 Hz, 1H), 7.27 (ddd, J = 7.4, 7.4, 1.0 Hz, 1H), 7.33−7.47 (m, 5H), 7.57 (d, J = 7.6 Hz, 1H), 7.59−7.61 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 27.49 (CH$_3$), 28.32 (CH$_3$), 46.84 (CH), 47.06 (CH), 105.15 (C), 121.16 (CH), 122.34 (CH), 125.70 (CH), 127.43 (CH), 127.88 (CH), 128.05 (CH), 128.64 (CH), 130.65 (CH), 135.34 (C), 144.16 (C), 144.46 (C), 146.68 (C), 163.52 (C), 163.87 (C); IR (KBr) 3001, 2871, 1781, 1748, 1457, 1383, 1328, 1303, 1205, 1063 cm^{-1}; MS (EI) m/z 334 (M$^+$, 1.2), 276 (18), 248 (100), 232 (95%); HRMS (EI) m/z 334.1204 (calcd for $C_{21}H_{18}O_4$ 334.1205).

Preparation of 10. Reaction of **9** (32.8 mg, 0.10 mmol) with DDQ (22.7 mg, 0.10 mmol) in benzene (0.5 mL) at room temperature for 18 h. Chromatography over silica gel eluting with hexane-CH_2Cl_2 gave **10** (30.1 mg, 94%).

10:[17] R_f = 0.2 (hexane-CH_2Cl_2 = 1: 1); red crystals; mp 130−131 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.81 (s, 6H), 7.23 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.32 (ddd, J = 7.6, 7.3, 1.0 Hz, 1H), 7.39 (d, J = 7.3 Hz, 1H), 7.47−7.51 (m, 4H), 7.66−7.69 (m, 2H), 8.44 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 27.39 (CH$_3$), 104.45 (C), 113.19 (C), 122.24 (CH), 126.26 (CH), 127.86 (CH), 128.76 (CH), 128.95 (CH), 129.33 (CH), 130.36 (CH), 132.13 (CH), 133.41 (C), 135.04 (C), 143.88 (C), 157.04 (C), 160.45 (C), 161.19 (C), 161.91 (C); IR (KBr) 2925, 1729, 1560, 1449, 1289, 1206 cm^{-1}; λ_{max} (CH$_3$CN) 254 (ε 19,300), 344 (13,000), 480 (2340) nm; MS (EI) m/z 332 (M$^+$, 9.9), 274 (100%); HRMS (EI) m/z 332.1048 (calcd for $C_{21}H_{16}O_4$ 332.1049).

12a: piperidine (0.2 equiv), 10.1 mmol scale, 2.14 g, 82%; R_f = 0.3 (hexane-CH_2Cl_2 = 2:1); yellow oil; ^{1}H NMR (400 MHz,

CDCl$_3$) δ (ppm) 5.20 (d, J = 0.7 Hz, 1H), 5.98 (d, J = 0.7 Hz, 1H), 7.19−7.22 (m, 2H), 7.32−7.36 (m, 3H), 7.39 (dd, J = 7.6, 1.2 Hz, 1H), 7.52 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 7.60 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 7.88 (s, 1H), 8.18 (d-like, J = 7.6 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 83.60 (C), 112.46 (C), 113.55 (C), 119.19 (CH$_2$), 127.04 (CH), 128.39 (CH), 128.63 (CH), 128.79 (CH), 128.90 (CH), 129.81 (C), 130.97 (CH), 133.70 (CH), 139.86 (C), 144.84 (C), 146.47 (C), 159.68 (CH); IR (KBr) 3047, 2227, 1581 cm^{-1}; MS (EI) m/z 256 (M$^+$, 100), 255 (66), 191 (78%); HRMS (EI) m/z 256.0999 (calcd for $C_{18}H_{12}N_2$ 256.1000).

12b: piperidine (0.2 equiv), 5.5 mmol scale, 1.08 g, 73%; R_f = 0.3 (hexane-CH_2Cl_2 = 2:1); yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 2.35 (s, 3H), 5.13 (s, 1H), 5.94 (s, 1H), 7.09 (d-like, J = 8.2 Hz, 2H), 7.14 (d-like, J = 8.2 Hz, 2H), 7.38 (dd, J = 7.6, 1.2 Hz, 1H), 7.51 (ddd, J = 7.6, 7.4, 1.2 Hz, 1H), 7.59 (ddd, J = 7.6, 7.6, 1.3 Hz, 1H), 7.88 (s, 1H), 8.18 (d, J = 7.4 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 21.21 (CH$_3$), 83.38 (C), 112.51 (C), 113.61 (C), 118.26 (CH$_2$), 126.91 (CH), 128.30 (CH), 128.51 (CH), 129.55 (CH), 129.78 (C), 130.92 (CH), 133.66 (CH), 137.03 (C), 138.82 (C), 145.08 (C), 146.23 (C), 159.72 (CH); IR (neat) 3029, 2229, 1581, 1510, 1214 cm^{-1}; MS (EI) m/z 270 (M$^+$, 100), 255 (62), 205 (88%); HRMS (EI) m/z 270.1159 (calcd for $C_{19}H_{14}N_2$ 270.1157).

12c: piperidine (0.2 equiv), acetic acid (1.0 equiv) at 80 °C, 1.0 mmol scale, 204 mg, 70%; R_f = 0.3 (hexane-CH_2Cl_2 = 1:1); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 5.21 (s, 1H), 5.98 (s, 1H), 7.14 (d-like, J = 8.6 Hz, 2H), 7.32 (d-like, J = 8.6 Hz, 2H), 7.36 (dd, J = 7.6, 1.4 Hz, 1H), 7.54 (ddd, J = 7.8, 7.6, 1.4 Hz, 1H), 7.61 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 7.86 (s, 1H), 8.20 (dd, J = 7.8, 0.7 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 83.93 (C), 112.41 (C), 113.54 (C), 119.76 (CH$_2$), 128.32 (CH), 128.54 (CH), 128.89 (CH), 129.11 (CH), 129.76 (C), 130.94 (CH), 133.84 (CH), 134.87 (C), 138.21 (C), 144.26 (C), 145.28 (C), 159.32 (CH); IR (KBr) 3037, 2236, 1588, 1487, 1089, 1010 cm^{-1}; MS (EI) m/z 292 (M$^+$, 22), 290 (M$^+$, 64), 255 (100), 225 (90%); HRMS (EI) m/z 290.0615, 292.0595 (calcd for $C_{18}H_{11}ClN_2$ 290.0611, 292.0581).

Procedure for Preparation of 13a. To a solution of **12a** (267 g, 1.0 mmol) in CH_2Cl_2 (3 mL) was added Sc(OTf)$_3$ (104 mg, 0.2 mmol). The reaction mixture was stirred for 17 h. Saturated aqueous NaHCO$_3$ was added to the mixture. The mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated in vacuo to give **13a** (265 mg, 99%).

13a: yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 4.01 (d, J = 6.8 Hz, 1H), 4.06 (dd, J = 6.8, 2.1 Hz, 1H), 6.47 (d, J = 2.1 Hz, 1H), 7.37 (ddd, J = 7.4, 7.4, 1.1 Hz, 1H), 7.41−7.50 (m, 4H), 7.58−7.61 (m, 3H), 7.74 (d, J = 7.4 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 25.83 (CH), 47.44 (CH), 111.59 (C), 111.82 (C), 121.88 (CH), 123.91 (CH), 126.93 (CH), 127.48 (CH), 127.80 (CH), 128.89 (CH), 128.90 (CH), 129.19 (CH), 133.94 (C), 141.23 (C), 143.50 (C), 149.59 (C); IR (KBr) 3049, 2922, 2258, 1489, 1443, 1351, 1071, 1009 cm^{-1}; MS (EI) m/z 256 (M$^+$, 20), 191 (100%); HRMS (EI) m/z 256.0997 (calcd for $C_{18}H_{12}N_2$ 256.1000).

13b: 1 mmol scale, 247 mg, 91%; yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 2.41 (s, 3H), 3.97 (d, J = 6.8 Hz, 1H), 4.01 (dd, J = 6.8, 2.1 Hz, 1H), 6.41 (d, J = 2.1 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.34 (ddd, J = 7.4, 7.4, 1.0 Hz, 1H), 7.42 (ddd, J = 7.6, 7.4, 0.9 Hz, 1H), 7.48 (d-like, J = 8.0 Hz, 2H),

7.58 (d, J = 7.6 Hz, 1H), 7.71 (d-like, J = 7.4 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 21.38 (CH$_3$), 25.80 (CH), 47.38 (CH), 111.65 (C), 111.88 (C), 121.86 (CH), 123.85 (CH), 126.80 (CH), 126.93 (CH), 127.66 (CH), 129.11 (CH), 129.54 (CH), 131.04 (C), 138.86 (C), 141.30 (C), 143.62 (C), 149.39 (C); IR (KBr) 2901, 2259, 1508, 1457, 1115 cm^{-1}; MS (EI) m/z 270 (M$^+$, 18), 205 (100%); HRMS (EI) m/z 270.1154 (calcd for C$_{19}$H$_{14}$N$_2$ 270.1157).

13c: 0.94 mmol scale, 259 mg, 95%; pale yellow crystals; mp 141−142 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 4.04 (d, J = 6.6 Hz, 1H), 4.09 (dd, J = 6.6, 2.0 Hz, 1H), 6.48 (d, J = 2.0 Hz, 1H), 7.40 (ddd, J = 7.4, 7.4, 1.2 Hz, 1H), 7.42−7.49 (m, 3H), 7.52−7.55 (m, 3H), 7.75 (d, J = 7.4 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 25.83 (CH), 47.56 (CH), 111.44 (C), 111.72 (C), 121.73 (CH), 124.02 (CH), 127.19 (CH), 127.85 (CH), 129.14 (CH), 129.18 (CH), 129.35 (CH), 132.39 (C), 134.89 (C), 141.15 (C), 143.20 (C), 148.64 (C); IR (KBr) 2219, 1568, 1541, 1089 cm^{-1}; MS (EI) m/z 292 (M$^+$, 5.3), 290 (M$^+$, 16), 227 (35), 225 (100%); HRMS (EI) m/z 290.0607, 292.0595 (calcd for C$_{18}$H$_{11}$ClN$_2$ 290.0611, 292.0581).

14a: r.t. in CH$_2$Cl$_2$, 17 h, 0.5 mmol scale, 77.1 mg, 61%; R$_f$ = 0.5 (hexane-CH$_2$Cl$_2$ = 1:1); orange crystals; mp 153−154 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 6.66 (s, 1H), 7.33 (dd, J = 7.6, 7.6 Hz, 1H), 7.41 (ddd, J = 7.6, 7.4, 0.9 Hz, 1H), 7.48 (d, J = 7.4 Hz, 1H), 7.50−7.55 (m, 3H), 7.65−7.67 (m, 2H), 8.15 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 77.51 (C), 112.88 (C), 122.79 (CH), 123.16 (CH), 125.79 (CH), 127.83 (CH), 129.12 (CH), 129.18 (CH), 131.13 (CH), 132.38 (C), 132.95 (CH), 133.30 (C), 142.90 (C), 157.31 (C), 165.31 (C); IR (KBr) 3062, 2222, 1570, 1540, 1446, 1373, 1100 cm^{-1}; MS (EI) m/z 254 (M$^+$, 100%); HRMS (EI) m/z 254.0835 (calcd for C$_{18}$H$_{10}$N$_2$ 254.0844).

14b: r.t. in CH$_2$Cl$_2$, 18 h, 0.59 mmol scale, 140.4 mg, 89%; R$_f$ = 0.5 (hexane-CH$_2$Cl$_2$ = 1:1); orange crystals; mp. 145 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 2.45 (s, 3H), 6.67 (s, 1H), 7.31−7.35 (m, 3H), 7.41 (ddd, J = 7.4, 7.4, 1.0, Hz, 1H), 7.50 (d, J = 7.4 Hz, 1H), 7.60 (d, J = 8.0 Hz, 2H), 8.17 (d, J = 7.4 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 21.74 (CH$_3$), 77.00 (C), 113.08 (C), 122.23 (CH), 123.21 (CH), 125.76 (CH), 127.90 (CH), 129.11 (CH), 129.69 (C), 129.96 (CH), 132.86 (CH), 133.58 (C), 141.91 (C), 143.05 (C), 157.48 (C), 165.54 (C); IR (KBr) 2920, 2225, 1577, 1559, 1367, 1105 cm^{-1}; MS (EI) m/z 268 (M$^+$, 100%); HRMS (EI) m/z 268.1000 (calcd for C$_{19}$H$_{12}$N$_2$ 268.1000).

14c: 80 °C, in CH$_2$ClCH$_2$Cl, 20 h, 0.5 mmol scale, 105.8 mg, 74%; R$_f$ = 0.5 (hexane-CH$_2$Cl$_2$ = 1:1); orange crystals; mp 208−210 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 6.70 (s, 1H), 7.36 (ddd, J = 7.4, 5.1, 3.7 Hz, 1H), 7.41−7.45 (m, 2H), 7.51 (d-like, J = 8.6 Hz, 2H), 7.63 (d-like, J = 8.6 Hz, 2H), 8.20 (ddd, J = 7.4, 0.9, 0.9 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 78.12 (C), 112.84 (C), 122.96 (CH), 123.14 (CH), 126.03 (CH), 129.15 (CH), 129.35 (CH), 129.59 (CH), 130.90 (C), 133.09 (CH), 133.27 (C), 137.25 (C), 142.71 (C), 156.01 (C), 165.12 (C); IR (KBr) 2921, 2259, 1490, 1401, 1096, 1012 cm^{-1}; MS (EI) m/z 290 (M$^+$, 34), 288 (M$^+$, 100%); HRMS (EI) m/z 288.0453, 290.0439 (calcd for C$_{18}$H$_9$ClN$_2$ 288.0454, 290.0425).

Procedure for Preparation of 16a. To a solution of **15a** (182.2 g, 1.0 mmol) in CH$_2$Cl$_2$ (5 mL) were added dimethyl malonate **2a** (132.1 mg, 0.11 mL, 1.0 mmol) and pyridine (316 mg, 0.32 mL, 4 mmol). After cooling to 0 °C, TiCl$_4$ (190 mg, 0.11 mL, 1.0 mmol) was slowly added to the reaction mixture.

The reaction mixture was allowed to warm to room temperature and stirred for 17 h. The mixture was quenched with water and extracted with CH$_2$Cl$_2$. The organic layer was washed with saturated aqueous NaHCO$_3$, dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexane-EtOAc to give **16a** (230 mg, 78%).

16a: R$_f$ = 0.4 (hexane-EtOAc = 10:1); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 3.777 (s, 3H), 3.781 (s, 3H), 7.32−7.47 (m, 9H), 7.70 (s, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 52.58 (CH$_3$), 126.57 (C), 127.49 (CH), 127.92 (CH), 128.31 (CH), 128.41 (CH), 129.78 (CH), 130.17 (CH), 130.20 (CH), 131.94 (C), 139.68 (C), 142.70 (C), 144.33 (CH), 164.32 (C), 167.04 (C); IR (neat) 2976, 2868, 1737, 1626, 1437, 1116, 1069 cm^{-1}; MS (EI) m/z 296 (M$^+$, 9.2), 264 (94), 204 (100%); HRMS (EI) m/z 296.1042 (calcd for C$_{18}$H$_{16}$O$_4$ 296.1049).

16b: 2.7 mmol scale, 726 mg, 86%; R$_f$ = 0.1 (hexane-EtOAc = 10:1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 2.40 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 7.15 (d-like, J = 8.0 Hz, 1H), 7.24 (s, 1H), 7.31−7.44 (m, 6H), 7.68 (s, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 21.47 (CH$_3$), 52.53 (CH$_3$), 52.60 (CH$_3$), 125.59 (C), 127.84 (CH), 128.26 (CH), 128.32 (CH), 128.35 (CH), 129.01 (C), 129.77 (CH), 130.97 (CH), 139.75 (C), 140.62 (C), 142.88 (C), 144.22 (CH), 164.48 (C), 167.34 (C); IR (neat) 2952, 1735, 1626, 1607, 1436, 1256, 1070 cm^{-1}; MS (EI) m/z 310 (M$^+$, 11), 278 (80), 250 (52), 219 (100%); HRMS (EI) m/z 310.1204 (calcd for C$_{19}$H$_{18}$O$_4$ 310.1205).

16c: 0.5 mmol scale, 137 mg, 82%; R$_f$ = 0.2 (hexane-EtOAc = 10:1); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 3.79 (s, 3H), 3.80 (s, 3H), 7.30−7.34 (m, 3H), 7.37−7.47 (m, 5H), 7.60 (s, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 52.71 (CH$_3$), 52.76 (CH$_3$), 127.02 (C), 127.64 (CH), 128.50 (CH), 128.60 (CH), 129.63 (CH), 130.18 (CH), 130.40 (C), 136.06 (C), 138.37 (C), 143.00 (CH), 144.28 (CH), 164.14 (C), 166.82 (C); IR (neat) 2953, 1740, 1721, 1629, 1590, 1435, 1260, 1071 cm^{-1}; MS (EI) m/z 332 (M$^+$, 3.5), 330 (M$^+$, 9.9), 298 (75), 263 (76), 239 (100%); HRMS (EI) m/z 330.0656, 332.0631 (calcd for C$_{18}$H$_{15}$ClO$_4$ 330.0659, 332.0629).

17d: 6.5 mmol scale, 1.46 g, 63%; R$_f$ = 0.1 (hexane-CH$_2$Cl$_2$ = 1:1); colorless crystals; mp 96−98 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 3.24 (s, 3H), 3.85 (s, 3H), 3.885 (s, 3H), 3.890 (s, 3H), 4.69 (d, J = 3.5 Hz, 1H), 4.70 (d, J = 3.5 Hz, 1H), 6.42 (d, J = 2.1 Hz, 1H), 6.88 (d, J = 2.1 Hz, 1H), 7.27 (ddd, J = 7.6, 7.5, 1.1 Hz, 1H), 7.35 (dd, J = 7.6, 7.5 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 44.62 (CH), 51.81 (CH), 51.84 (CH$_3$), 52.63 (CH$_3$), 55.49 (CH$_3$), 55.68 (CH$_3$), 96.47 (CH), 97.80 (CH), 119.80 (CH), 123.12 (C), 125.55 (CH), 127.19 (CH), 127.53 (CH), 141.51 (C), 143.46 (C), 144.45 (C), 156.91 (C), 161.66 (C), 167.88 (C), 169.93 (C); IR (KBr) 2952, 1733, 1595, 1428, 1053 cm^{-1}; MS (EI) m/z 356 (M$^+$, 30), 296 (37), 225 (100%); HRMS (EI) m/z 356.1260 (calcd for C$_{20}$H$_{20}$O$_6$ 356.1260); anal. calcd for C$_{20}$H$_{20}$O$_6$: C, 67.41; H, 5.66. Found: C, 67.39; H, 5.56.

Procedure for Preparation of 17a. To a solution of **16a** (702 mg, 2.37 mmol) in CH$_2$Cl$_2$ (7.1 mL) was added Sc(OTf)$_3$ (232 mg, 0.47 mmol). The reaction mixture was stirred at 40 °C for 17 h. After cooling to room temperature, saturated aqueous NaHCO$_3$ was added to the mixture. The

mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated in vacuo to give **17a** (658 mg, 94%).

17a: colorless crystals; mp 129−131 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.66 (s, 6H), 3.88 (d, J = 6.4 Hz, 1H), 4.70 (d, J = 6.4 Hz, 1H), 7.28 (ddd, J = 7.6, 7.4, 1.2 Hz, 2H), 7.38 (dd, J = 7.6, 7.4 Hz, 2H), 7.46 (dd, J = 7.6, 0.8 Hz, 2H), 7.74 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 46.24 (CH), 52.56 (CH_3), 55.34 (CH), 120.02 (CH), 124.76 (CH), 127.22 (CH), 127.93 (CH), 141.26 (C), 143.65 (C), 168.56 (C); IR (KBr) 2948, 1740, 1718, 1437, 1267, 1019 cm^{-1}; MS (EI) m/z 296 (M^+, 42), 236 (100%); HRMS (EI) m/z 296.1050 (calcd for $C_{18}H_{16}O_4$ 296.1049); anal. calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.97; H, 5.53.

17b: 0.39 mmol scale, 106.5 mg, 88%; R_f = 0.5 (hexane-EtOAc = 5: 1); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.41 (s, 3H), 3.647 (s, 3H), 3.650 (s, 3H), 3.82 (d, J = 6.6 Hz, 1H), 4.65 (d, J = 6.6 Hz, 1H), 7.08 (dd, J = 7.8, 0.8 Hz, 1H), 7.25 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 7.31−7.37 (m, 2H), 7.43 (dd, J = 7.5, 0.9 Hz, 1H), 7.54 (s, 1H), 7.69 (d, J = 7.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 21.53 (CH_3), 45.86 (CH), 52.45 (CH_3), 55.38 (CH), 119.82 (CH), 120.59 (CH), 124.36 (CH), 124.66 (CH), 126.99 (CH), 127.80 (CH), 128.10 (CH), 137.59 (C), 140.70 (C), 141.23 (C), 141.29 (C), 143.99 (C), 168.52 (C), 168.54 (C); IR (neat) 2952, 1740, 1435, 1256, 1157 cm^{-1}; MS (EI) m/z 310 (M^+, 43), 250 (100%); HRMS (EI) m/z 310.1202 (calcd for $C_{19}H_{18}O_4$ 310.1205).

17c: 2.0 mmol scale, 535 mg, 81%; colorless crystals; mp 117 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.63 (s, 3H), 3.68 (s, 3H), 3.90 (d, J = 6.1 Hz, 1H), 4.66 (d, J = 6.1 Hz, 1H), 7.25 (dd, J = 8.2, 2.1 Hz, 1H), 7.32 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 7.38−7.42 (m, 2H), 7.47 (dd, J = 7.5, 0.8 Hz, 1H), 7.70−7.71 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 45.86 (CH), 52.64 (CH_3), 52.70 (CH_3), 55.02 (CH), 120.29 (CH), 124.81 (CH), 125.96 (CH), 127.14 (CH), 127.96 (CH), 128.15 (CH), 134.04 (C), 140.07 (C), 141.88 (C), 143.12 (C), 144.10 (C), 168.29 (C), 168.46 (C); IR (KBr) 2948, 1748, 1729, 1435, 1368, 1154 cm^{-1}; MS (EI) m/z 332 (M^+, 12), 330 (M^+, 35), 270 (100%); HRMS (EI) m/z 330.0660, 332.0628 (calcd for $C_{18}H_{15}ClO_4$ 330.0659, 332.0629).

Preparation of 18a. To a solution of **17a** (241 mg, 0.8 mmol) in CH_2Cl_2 (6.6 mL) was added DDQ (183 mg, 0.8 mmol). The reaction mixture was stirred at 40 °C for 17 h. After cooling to room temperature, the mixture was purified by chromatography over silica gel eluting with hexane-CH_2Cl_2 to give **18a** (168 mg, 69%).

18a: R_f = 0.1 (hexane-CH_2Cl_2 = 1:1); yellow crystals; mp 79.2−80.0 °C (hexane-CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.94 (s, 6H), 7.18 (ddd, J = 8.0, 7.6, 1.1 Hz, 2H), 7.34 (ddd, J = 7.6, 7.4, 0.9 Hz, 2H), 7.55 (d, J = 7.4 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 53.07 (CH_3), 119.75 (CH), 122.02 (C), 125.96 (CH), 127.76 (CH), 131.14 (C), 135.47 (C), 141.73 (C), 144.74 (C), 165.83 (C); IR (KBr) 2950, 1722, 1595, 1449, 1250, 1077 cm^{-1}; MS (EI) m/z 294 (M^+, 100), 263 (27), 195 (56%); HRMS (EI) m/z 294.0894 (calcd for $C_{18}H_{14}O_4$ 294.0892).

18b: 80 °C in 1,2-dichloroethane, 0.54 mmol scale, 144 mg, 86%; R_f = 0.4 (hexane-CH_2Cl_2 = 1:1); pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.39 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 7.00 (dd, J = 8.0, 0.9 Hz, 1H), 7.18 (ddd, J = 7.8, 7.5, 1.2 Hz, 1H), 7.35 (ddd, J = 7.6, 7.5, 0.9 Hz, 1H), 7.38 (s, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.75

(d, J = 7.8 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 21.78 (CH_3), 53.05 (CH_3), 119.63 (CH), 120.53 (CH), 121.18 (C), 126.02 (CH), 126.08 (CH), 127.73 (CH), 128.66 (CH), 131.07 (CH), 132.99 (C), 136.04 (C), 141.82 (C), 141.85 (C), 142.08 (C), 145.13 (C), 166.01 (C), 166.04 (C); IR (neat) 2950, 1732, 1716, 1615, 1456, 1244, 1076 cm^{-1}; MS (EI) m/z 308 (M^+, 100), 209 (67), 189 (64%); HRMS (EI) m/z 308.1044 (calcd for $C_{19}H_{16}O_4$ 308.1049).

18c: 110 °C in toluene, 0.53 mmol scale, 70 mg, 40%; R_f = 0.1 (hexane-CH_2Cl_2 = 2:1); mp 138.5−139.3 °C (hexane-$CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.95 (s, 3H), 3.97 (s, 3H), 7.17 (dd, J = 8.4, 2.0 Hz, 1H), 7.25 (ddd, J = 7.8, 7.7, 1.2 Hz, 1H), 7.39 (ddd, J = 7.7, 7.5, 0.9 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 7.56 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 53.21 (CH_3), 120.09 (CH), 120.16 (CH), 122.56 (C), 126.05 (CH), 127.48 (CH), 127.72 (CH), 128.56 (CH), 131.36 (CH), 133.84 (C), 136.02 (C), 137.40 (C), 140.54 (C), 143.59 (C), 143.94 (C), 165.51 (C), 165.88 (C); IR (KBr) 2955, 1719, 1588, 1444, 1244, 1073 cm^{-1}; MS (EI) m/z 330 (M^+, 35), 328 (M^+, 100), 297 (32), 229 (54%); HRMS (EI) m/z 328.0502, 330.0472 (calcd for $C_{18}H_{13}ClO_4$ 328.0502, 330.0473).

18d: r.t. in CH_2Cl_2, 0.5 mmol scale, 163 mg, 92%; R_f = 0.5 (hexane-CH_2Cl_2 = 1:2); yellow crystals; mp 159.5−161.0 °C (Et_2O); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.837 (s, 3H), 3.842 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 6.29 (d, J = 2.1 Hz, 1H), 6.78 (d, J = 2.1 Hz, 1H), 7.19 (ddd, J = 8.2, 7.4, 1.1 Hz, 1H), 7.32 (ddd, J = 7.4, 7.4, 1.2 Hz, 1H), 7.54−7.56 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 52.45 (CH_3), 53.02 (CH_3), 55.66 (CH_3), 55.77 (CH_3), 97.88 (CH), 98.08 (CH), 116.70 (C), 119.93 (CH), 121.58 (C), 124.42 (CH), 128.06 (CH), 130.08 (CH), 138.09 (C), 140.82 (C), 142.69 (C), 144.81 (C), 158.57 (C), 164.41 (C), 166.86 (C), 168.97 (C); IR (KBr) 2954, 1734, 1715, 1591, 1430, 1249, 1146 cm^{-1}; MS (EI) m/z 354 (M^+, 100), 323 (52), 265 (58), 235 (79%); HRMS (EI) m/z 354.1096 (calcd for $C_{20}H_{18}O_6$ 354.1103).

20: $TiCl_4$/pyridine = 1: 4 equiv, 1.0 mmol scale, 252 mg, 81%; R_f = 0.4 (hexane-AcOEt = 10:1); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.80 (s, 3H), 3.82 (s, 3H), 6.85 (dd, J = 8.4, 0.8 Hz, 1H), 7.01 (d-like, J = 7.6 Hz, 2H), 7.07 (dd, J = 7.8, 7.8 Hz, 1H), 7.15 (t-like, J = 7.3 Hz, 1H), 7.32 (dd, J = 8.4, 7.8 Hz, 1H), 7.33−7.38 (m, 2H), 7.44 (dd, J = 7.8, 1.6 Hz, 1H), 8.14 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 52.66 (CH_3), 52.72 (CH_3), 118.19 (CH), 119.43 (CH), 123.27 (CH), 124.04 (CH), 124.53 (C), 126.42 (C), 129.24 (CH), 129.97 (CH), 132.06 (CH), 138.44 (CH), 156.29 (C), 156.46 (C), 164.60 (C), 167.10 (C); IR (KBr) 2952, 1740, 1700, 1600, 1482, 1433, 1232, 1065 cm^{-1}; MS (EI) m/z 312 (M^+, 3.2). 280 (7.0), 248 (20), 219 (100%); HRMS (EI) m/z 312.1000 (calcd for $C_{18}H_{16}O_5$ 312.0998).

21: 1.0 mmol scale, 227 mg, 73%; R_f = 0.2 (hexane-AcOEt = 10:1); colorless crystals; mp 61.6−62.4 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.56 (s, 6H), 3.60 (d, J = 9.2 Hz, 1H), 4.82 (d, J = 9.2 Hz, 1H), 7.06 (ddd, J = 7.4, 7.4, 1.2 Hz, 2H), 7.15 (d-like, J = 8.1 Hz, 2H), 7.26 (dd-like, J = 8.1, 7.4 Hz, 2H), 7.30 (d-like, J = 7.4 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 39.89 (CH), 52.58 (CH_3), 59.94 (CH), 116.83 (CH), 122.68 (C), 123.45 (CH), 128.66 (CH), 128.88 (CH), 153.25 (C), 167.79 (C); IR (KBr) 2953, 1752, 1726, 1476, 1255, 1145 cm^{-1}; MS (EI) m/z 312 (M^+, 2.8), 181 (100%); HRMS (EI) m/z 312.1000 (calcd for $C_{18}H_{16}O_5$ 312.0998).

22: 0.5 mmol scale, 116.7 mg, 74%; R_f = 0.1 (hexane-AcOEt = 10:1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 3.75 (s, 6H), 7.16 (ddd, J = 8.0, 7.2, 1.2 Hz, 2H), 7.31 (dd, J = 8.0, 1.0 Hz, 2H), 7.43 (ddd, J = 8.0, 7.2, 1.6 Hz, 2H), 7.65 (dd, J = 8.0, 1.6 Hz, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 52.70 (CH$_3$), 117.01 (CH), 119.97 (C), 120.89 (C), 123.25 (CH), 127.06 (CH), 131.01 (CH), 137.94 (C), 152.59 (C), 166.28 (C); IR (KBr) 2955, 1740, 1712, 1600, 1449, 1250, 1071 cm^{-1}; MS (EI) m/z 310 (M$^+$, 100), 279 (66%); HRMS (EI) m/z 310.0844 (calcd for C$_{18}$H$_{14}$O$_5$ 310.0841).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c05283.

> Optimized structures of Schemes 13−16, Cartesian coordinates of the optimized geometries, crystallographic data, copies of the ^{1}H and ^{13}C NMR spectra (PDF)
>
> Crystallographic data of **5e** (CIF)

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Notes

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