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Ring Opening of Donor–Acceptor Cyclopropanes with Acyclic 1,3-Diketones for the Synthesis of 1,6-Dicarbonyl Compounds

Dongxin Zhang,* Hu Cai, Yan Chen, Lei Yin, Junchao Zhong, Ying Zhang, and Qian-Feng Zhang*

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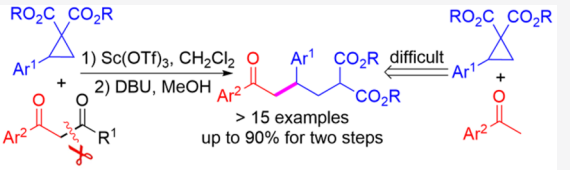
ABSTRACT: 1,6-Dicarbonyl compounds, representing the formal addition products of the α-position of acetophenone derivatives to donor–acceptor cyclopropanes, were synthesized in two steps via first ring opening of donor–acceptor cyclopropanes with acyclic 1,3-diketones followed by DBU catalyzed retro-Claisen-type C–C bond cleavage reactions. In the first step, acyclic 1,3-diketones selectively worked as C-nucleophiles to add to donor–acceptor cyclopropanes. In the second step, the alkyl ketone part of the ring-opening products resulting from unsymmetrical 1,3-diketones was selectively cleaved in the presence of DBU in methanol.

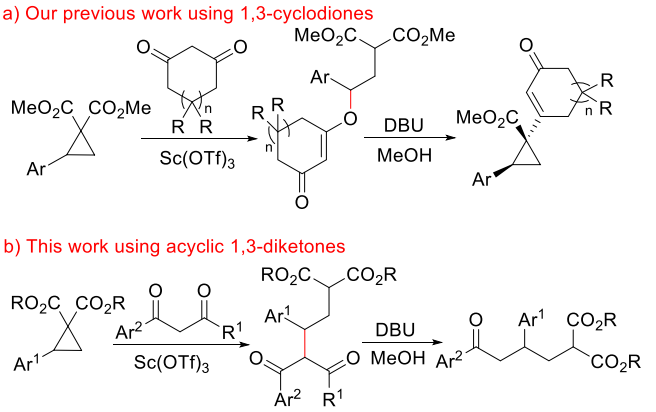


Donor–acceptor (D–A) cyclopropanes are one of the most useful building blocks in organic synthesis due to their special reactivities and have been widely applied for the synthesis of natural products and biologically active compounds.[1] Ring opening of D–A cyclopropanes with nucleophiles catalyzed by Lewis acids is the most straightforward way to obtain 1,3-bifunctionalized compounds. Both carbon[2,3] and heteroatom[4−6] nucleophile additions to D–A cyclopropanes have been well-developed.

Recently, our group has focused on the development of the reactions of D–A cyclopropanes with 1,3-diketone derivatives.[6] 1,3-Diketone derivatives can be used as both C- and O-nucleophiles due to their nature of easy keto–enol tautomerization. We have developed the use of 1,3-cyclodiones as nucleophilic partners to add to D–A cyclopropanes. 1,3-Cyclodiones selectively worked as O-nucleophiles in the reactions with D–A cyclopropanes catalyzed by scandium triflate to afford 1,3-cyclodione enol ether derivatives, which underwent an interesting intramolecular transformation catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methanol to furnish a new type of D–A cyclopropanes (Scheme 1a).[6a]

Our initial results indicated that acyclic 1,3-dicarbonyl compounds reacted in a different way, as C-nucleophiles, with D–A cyclopropanes catalyzed by Lewis acids. Here, we uncover the details of the reactions of acyclic 1,3-diketones with D–A cyclopropanes and that the resulting nucleophilic ring-opening products underwent retro-Claisen-type C–C bond cleavage under the catalytic conditions of DBU in methanol to accomplish a series of 1,6-dicarbonyl compounds,[7,8] which represent the formal addition products of the α-position of ketones to D–A cyclopropanes (Scheme 1b). The direct additions of ketones to D–A cyclopropanes are difficult, though the use of preformed enol silyl enthers to add to D–A cyclopropanes has been reported.[8]

Scheme 1. Different Reactivities of 1,3-Cyclodiones and Acyclic 1,3-Diketones with D–A Cyclopropanes



The reaction scope of dibenzoylmethane **1a** with various D–A cyclopropanes **2** was first investigated using $Sc(OTf)_3$ as the catalyst, and the results are shown in Scheme 2. Similar to our previously reported reactions of D–A cyclopropanes with 1,3-cyclodione derivatives, reactions of D–A cyclopropanes with strong electron-donating substituents on the phenyl ring were faster, and the corresponding products were obtained in higher yields under milder conditions (**3a–3e**).[6,9] Reactions of *para*-methylphenyl, phenyl, and *para*-chlorophenyl substituted D–A cyclopropanes with **1a** needed to be performed with higher

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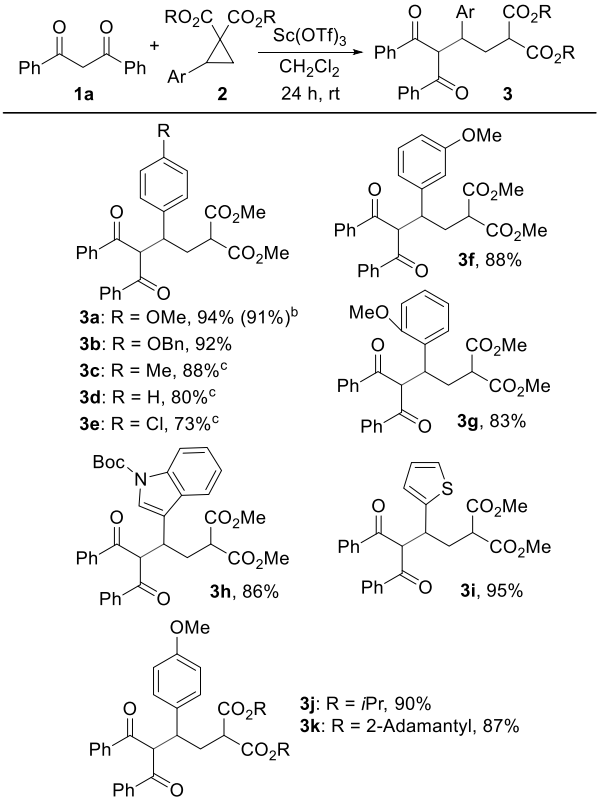
Scheme 2. Reaction Scope of Dibenzoylmethane 1a with Various D−A Cyclopropanes[a]



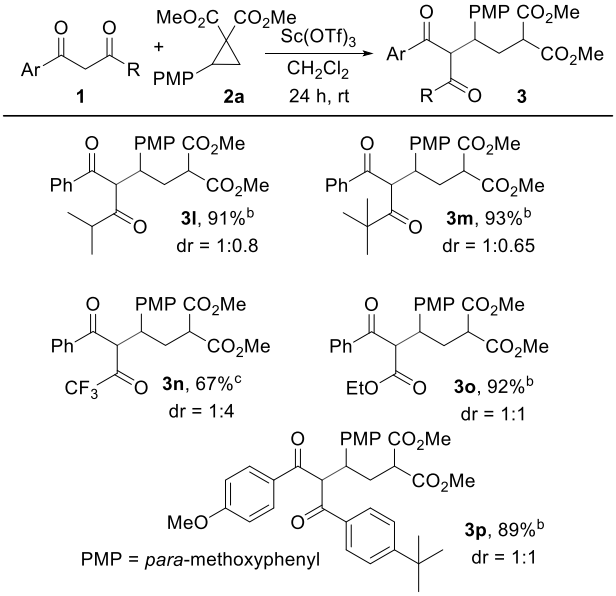
[a]Unless otherwise noted, reactions were carried out using dibenzoylmethane **1a** (0.18 mmol) and D−A cyclopropane (0.15 mmol) in the presence of $Sc(OTf)_3$ (0.0075 mmol) in CH_2Cl_2 (1.0 mL) at room temperature (25 °C) for 24 h. [b]Yield of a 5 mmol-scale reaction is shown in the parentheses. [c]$Sc(OTf)_3$ (0.015 mmol) was used, and the reaction was carried out at 45 °C in 1,2-dichloroethane.

catalyst loading and at higher temperature to furnish **3c**−**3e** with good yields. D−A cyclopropanes with *meta*-methoxyphenyl and *ortho*-methoxyphenyl substituents were successfully applied to give **3f** and **3g** in 88 and 83% yield, respectively. Heterocyclic substrates, such as 3-indolyl and 2-thienyl substituted D−A cyclopropanes, worked well in this reaction, and the corresponding products **3h** and **3i** were isolated in 86 and 95% yield, respectively. The substrate scope with respect to the ester group of the D−A cyclopropane was also investigated. D−A cyclopropanes with isopropyl and 2-adamantyl esters were well-tolerated to furnish products in high yields (**3j** and **3k**).

Next, reactions of D−A cyclopropane **2a** with several different unsymmetrical 1,3-dicarbonyl compounds **1** were studied (Scheme 3). In all cases, the C-nucleophilic products were accomplished in good yields (89−93%), and there was almost no diastereoselectivity except for the reaction with 4,4,4-trifluoro-1-phenylbutane-1,3-dione, giving **3n** with moderate diastereoselectivity (dr = 1:4). It was worth noting that the NMR data of the inseparable mixtures **3q**, resulting from the reaction of 1-benzoylacetone and **2a**, showed complicated mixtures of diastereomers and keto−enol tautomers, which made it difficult to do the peak assignments.

It was initially assumed that **3** may undergo intramolecular aldol-type reactions under basic conditions to give five-membered carbocycles. Based on this assumption, we tried

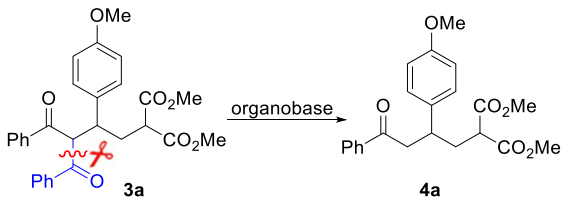
Scheme 3. Reactions of 2a with Unsymmetrical 1,3-Dicarbonyl Compounds[a]



[a]Unless otherwise noted, reactions were carried out using 1,3-dicarbonyl compounds (0.18 mmol) and **2a** (0.15 mmol) in the presence of $Sc(OTf)_3$ (0.0075 mmol) in CH_2Cl_2 (1.0 mL) at room temperature (25 °C) for 24 h. [b]Yield of diastereomer mixtures. [c]Yield of the major diastereomer.

to screen reaction conditions for compound **3a**. DBU was first used as the base catalyst[6a,10] because it has been reported as a good organobase catalyst for aldol reactions. However, no desired aldol cyclization product was obtained under the catalytic conditions of DBU in various common solvents (Table 1, entries 1−4). When methanol was used as the reaction solvent, the retro-Claisen-type C−C bond cleavage product **4a** was obtained in 43% yield in 48 h (Table 1, entry

Table 1. Reactions of 3a Catalyzed by Organobases[a]



entry	base[b] (40 mmol %)	solvent	time (h)	yield (%)
1	DBU	CH_2Cl_2	48	
2	DBU	THF	48	
3	DBU	$PhCH_3$	48	
4[c]	DBU	THF	48	
5	DBU	MeOH	48	43
6[c]	DBU	MeOH	12	98
7[c,d]	DBU	MeOH	24	69
8	DABCO	MeOH	48	
9	DMAP	MeOH	48	
10	Et_3N	MeOH	48	

[a]Unless otherwise noted, reactions were carried out using **3a** (0.10 mmol) in the presence of an organobase (0.04 mmol) in 1.0 mL of a solvent at room temperature (25 °C). [b]DABCO = 1,4-diazabicyclo[2.2.2]octane; DMAP = 4-(dimethylamino)pyridine. [c]The reaction was carried out at 50 °C. [d]The catalyst (0.02 mmol) was used.

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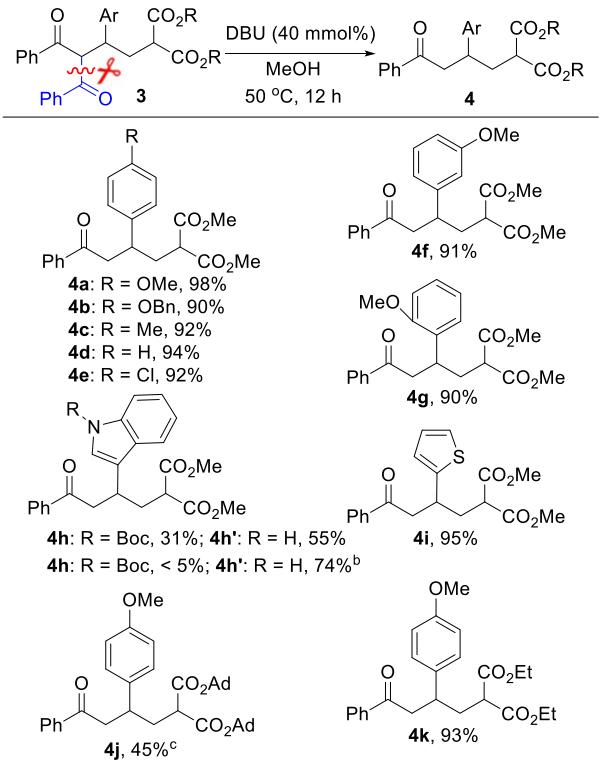
J. Org. Chem. XXXX, XXX, XXX−XXX

5).[11] **4a** was obtained in 98% yield within 12 h when the reaction was carried out at 50 °C (Table 1, entry 6). Reducing the loading of DBU, the reaction became slower (Table 1, entry 7). Other organobases, such as DACBO, DMAP, and Et_3N, were not able to catalyze this retro-Claisen-type reaction (Table 1, entries 8−10).

With the optimized conditions for the DBU-catalyzed retro-Claisen-type C−C bond cleavage reaction in hand, we further explored the scope of this reaction using **3**, which resulted from the reactions of **1a** and **2** (Scheme 4). New 1,6-

Scheme 4. DBU-Catalyzed retro-Claisen-type C−C Bond Cleavage Reactions of 3 Resulted from the Reactions of 1a and 2[a]

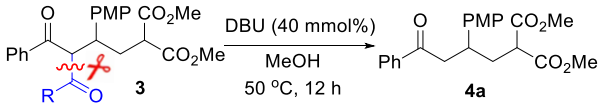


[a]Unless otherwise noted, reactions were carried out using **3** (0.10 mmol) in the presence of DBU (0.04 mmol) in MeOH (1.0 mL) at 50 °C for 12 h. [b]The reaction was carried out for 24 h. [c]**4a** was isolated separately in 32% yield.

dicarbonyl compounds **4a**−**4k** were all obtained in good yields, proving that DBU was an efficient catalyst for this type of reaction. For the reaction of **3h**, **4h** was obtained in 31% yield along with the N-Boc-deprotection product **4h′** in 55% yield. By extending the reaction time to 24 h, **4h′** was accomplished in 74% yield, which indicated that DBU might also be a good catalyst for the deprotection reaction of N-Boc compounds. For the reaction of **3k**, DBU catalyzed transesterification reaction took place, and **4j** (45%) and **4a** (32%) were both obtained. The transesterification reaction also took place when EtOH was used as the solvent for the reaction of **3a**, affording **4k** in 93% yield.

Compounds **3** shown in Scheme 3 were also applied in the DBU-catalyzed retro-Claisen-type C−C bond cleavage reactions (Table 2). For the reactions of **3l**, **3m**, **3n**, and **3q**, the C−C bond cleavage occurred selectively, with the alkyl ketone part cleaved, to afford only **4a** (Table 2, entries 1−3 and 5).

Table 2. DBU-Catalyzed Retro-Claisen-type C−C Bond Cleavage Reactions of 3 Resulted from the Reactions of Unsymmetrical 1,3-Dicarbonyl Compounds and 2a[a]

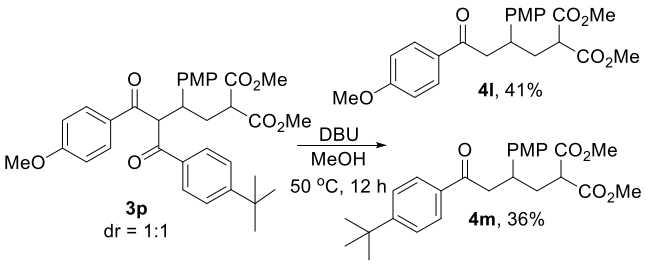


entry	3	product	yield (%)
1	**3l**	**4a**	71
2	**3m**	**4a**	63
3	**3n**	**4a**	68
4	**3o**		
5	**3q**	**4a**	92

[a]Unless otherwise noted, reactions were carried out using **3** (0.10 mmol) in the presence of DBU (0.04 mmol) in MeOH (1.0 mL) at 50 °C for 12 h.

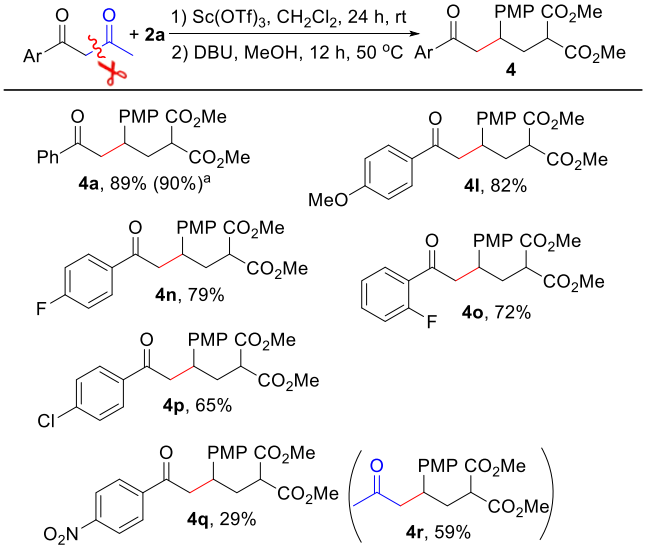
Particularly, in the case of complicated mixture **3q**, **4a** was obtained in excellent 92% yield (Table 2, entry 5). In the case of **3o**, no reaction occurred under the standard conditions (Table 2, entry 4). The reaction of **3p** afforded both **4l** and **4m** in 41 and 36% yield, respectively (Scheme 5).

Scheme 5. Retro-Claisen-type C−C Bond Cleavage Reaction of 3p



The synthesis of **4a** without the isolation of **3q** was tested, as shown in Scheme 6. After the reaction of 1-benzoylacetone and **2a** finished, simple workup was performed to remove

Scheme 6. Synthesis of 4 without the Isolation of 3



[a]Yield of a gram-scale reaction is shown in the parentheses.

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J. Org. Chem. XXXX, XXX, XXX−XXX

$Sc(OTf)_3$. Then, the crude product was directly applied under the standard conditions for the retro-Claisen-type C−C bond cleavage reaction. **4a** was obtained in 89% yield in two steps. In a gram-scale reaction, **4a** was accomplished in 90% yield. This two-step procedure was then applied for further expanding the scope for the synthesis of 1,6-dicarbonyl compounds **4** (Scheme 6). Reactions of **2a** with 1-benzoylacetone derivatives bearing electron-donating and halogen substituent on the phenyl ring worked well to afford corresponding product in 65−82% yield (**4l**, **4n**, **4o**, **4p**). The reaction of **2a** with 1-(4-nitrophenyl)butane-1,3-dione afforded **4q** and **4r** in a ratio of 1:2. The results indicated that the retro-Claisen-type C−C bond cleavage was less site-selective for strong electron-withdrawing group substituted substrates.

To conclude, we developed the ring-opening reactions of D−A cyclopropanes with acyclic 1,3-diketones, which selectively worked as C-nucleophiles, to furnish 1,6-dicarbonyl compounds **3**. The ring-opening products **3** underwent retro-Claisen-type C−C bond cleavage reaction in the presence of DBU in methanol to afford a series of new 1,6-dicarbonyl compounds **4**. We also developed the synthesis of 1,6-dicarbonyl compounds **4** without the isolation of intermediates **3**. 1,6-Dicarbonyl compounds **4** represent the formal addition products of the α-position of acetophenone derivatives to D−A cyclopropanes. The direct additions of acetophenone derivatives to D−A cyclopropanes are difficult. The method we developed here provides an alternative pathway for the additions of acetophenone derivatives to D−A cyclopropanes under mild conditions for the synthesis of 1,6-dicarbonyl compounds.

EXPERIMENTAL SECTION

^1H NMR and ^{13}C NMR were recorded on a Bruker-400 MHz spectrometer. Proton chemical shifts were reported in ppm downfield from tetramethylsilane or from the residual solvent as internal standard in $CDCl_3$ (δ 7.26 ppm). Carbon chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (δ 77.0 ppm). High-resolution mass spectra were recorded on a Thermo Scientific LTQ Orbitrap ESI ion trap mass spectrometer. Reagents obtained from commercial sources were used without further purification, and all solvents were purified and dried according to standard methods prior to use unless stated otherwise.

D−A cyclopropanes **2** used in this study were all prepared according to literature procedures from the corresponding aromatic aldehydes through a sequence of Knoevenagel condensation followed by a Corey−Chaykovsky cyclopropanation. Compounds **2** are all known compounds, and the characterization data all corresponded to the reported values.[6a]

General Procedure A for the Synthesis of 3. To a mixture of D−A cyclopropanes **2** (0.15 mmol, 1.0 equiv) and acyclic 1,3-dicarbonyl compounds **1** (0.18 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL), $Sc(OTf)_3$ (3.7 mg, 0.0075 mmol, 0.05 equiv) was added. The mixture was stirred at room temperature (25 °C) for 24 h. Then, the solvent was removed in vacuo, and the residue was purified by silica gel flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1) to provide product **3**.

General Procedure B for the Synthesis of 3. To a mixture of D−A cyclopropanes **2** (0.15 mmol, 1.0 equiv) and acyclic 1,3-dicarbonyl compounds **1** (0.18 mmol, 1.2 equiv) in 1,2-dichloroethane (1.0 mL), $Sc(OTf)_3$ (7.4 mg, 0.015 mmol, 0.1 equiv) was added. The mixture was stirred at 45 °C for 24 h. Then, the solvent was removed in vacuo and the residue was purified by silica gel flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1) to provide product **3**.

Procedure for a 5 mmol-Scale Reaction to Synthesize 3a. To a mixture of D−A cyclopropanes **2a** (1.32 g, 5.0 mmol) and dibenzoylmethane **1a** (1.35 g, 6.0 mmol) in CH_2Cl_2 (25.0 mL), $Sc(OTf)_3$ (123.0 mg, 0.25 mmol) was added. The mixture was stirred at room temperature (25 °C) for 36 h. Then, the mixture was diluted with CH_2Cl_2 (25.0 mL) and washed with saturated $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (25 mL × 3). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1) to provide product **3a** (2.22 g, 91%).

*Dimethyl 2-(3-Benzoyl-2-(4-methoxyphenyl)-4-oxo-4-phenylbutyl)malonate (**3a**).* Synthesized by the general procedure **A**, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 68.7 mg (94%). Colorless crystalline solid. mp 172−174 °C. Known compound.[6a] ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01−8.03 (m, 2H), 7.71−7.73 (m, 2H), 7.52−7.55 (m, 1H), 7.39−7.44 (m, 3H), 7.26−7.30 (m, 2H), 7.10−7.13 (m, 2H), 6.67−6.71 (m, 2H), 5.59 (d, J = 10.3 Hz, 1H), 3.90 (td, J = 10.8 Hz, 3.8 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 3.50 (s, 3H), 3.13 (dd, J = 5.0 Hz, 9.6 Hz, 1H), 2.24−2.37 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 194.1, 194.08, 169.4, 169.0, 158.4, 136.7, 133.6, 133.5, 133.0, 130.8, 129.8, 128.72, 128.71, 128.4, 128.3, 113.8, 64.5, 54.9, 52.4, 52.3, 49.7, 43.8, 32.9 ppm. IR (KBr, cm^{-1}): 2996, 2952, 2838, 1749, 1723, 1688, 1595, 1580, 1515, 1446, 1362, 1335, 840, 761, 687, 564.

*Dimethyl 2-(3-Benzoyl-2-(4-(benzyloxy)phenyl)-4-oxo-4-phenylbutyl)malonate (**3b**).* Synthesized by the general procedure **A**, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 77.9 mg (92%). Colorless amorphous solid. New compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01−8.04 (m, 2H), 7.71−7.73 (m, 2H), 7.53−7.57 (m, 1H), 7.40−7.45 (m, 3H), 7.27−7.37 (m, 7H), 7.12 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 5.59 (d, J = 10.3 Hz, 1H), 4.94 (s, 2H), 3.91 (td, J = 10.8 Hz, 3.8 Hz, 1H), 3.74 (s, 3H), 3.49 (s, 3H), 3.15 (dd, J = 5.2 Hz, 9.5 Hz, 1H), 2.24−2.38 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 194.2, 169.5, 169.1, 157.7, 136.81, 136.77, 136.7, 133.6, 133.1, 131.2, 129.9, 128.84, 128.80, 128.54, 128.50, 128.4, 127.9, 127.5, 114.8, 69.8, 64.7, 52.5, 52.4, 49.8, 43.8, 33.0 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{35}H_{33}O_7$ 565.2221; Found 565.2224.

*Dimethyl 2-(3-Benzoyl-4-oxo-4-phenyl-2-(p-tolyl)butyl)-malonate (**3c**).* Synthesized by the general procedure **B**, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 62.4 mg (88%). Colorless amorphous solid. New compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, J = 6.5 Hz, 2H), 7.76 (d, J = 6.5 Hz, 2H), 7.23−7.56 (m, 6H), 6.91−7.14 (m, 4H), 5.67 (d, J = 9.9 Hz, 1H), 3.95 (s, 1H), 3.76 (s, 3H), 3.52 (s, 3H), 3.16 (s, 1H), 2.36 (d, J = 4.3 Hz, 2H), 2.21 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 194.2, 194.0, 169.4, 169.1, 136.73, 136.70, 136.6, 136.0, 133.6, 133.0, 129.1, 128.8, 128.7, 128.6, 128.5, 128.3, 64.6, 52.5, 52.3, 49.7, 44.1, 32.9, 20.9 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{29}H_{29}O_6$ 473.1959; Found 473.1964.

*Dimethyl 2-(3-Benzoyl-4-oxo-2,4-diphenylbutyl)malonate (**3d**).* Synthesized by the general procedure **B**, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 55.0 mg (80%). Colorless amorphous solid. Known compound.[2i] ^1H NMR (400 MHz, $CDCl_3$): δ = 8.02−8.04 (m, 2H), 7.70−7.72 (m, 1H), 7.53−7.56 (m, 1H), 7.38−7.45 (m, 3H), 7.25−7.29 (m, 2H), 7.20−7.22 (m, 2H), 7.16 (t, J = 7.5 Hz, 2H), 7.06−7.09 (m, 1H), 5.64 (d, J = 10.3 Hz, 1H), 3.95 (td, J = 10.4 Hz, 4.7 Hz, 1H), 3.74 (s, 3H), 3.48 (s, 3H), 3.11−3.15 (m, 1H), 2.28−2.40 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 194.1, 194.0, 169.4, 169.1, 139.1, 136.7, 136.6, 133.1, 128.83, 128.80, 128.51, 128.49, 128.4, 127.2, 127.1, 64.5, 52.6, 52.4, 49.8, 44.6, 32.8 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{28}H_{27}O_6$ 459.1802; Found 459.1805.

*Dimethyl 2-(3-Benzoyl-2-(4-chlorophenyl)-4-oxo-4-phenylbutyl)-malonate (**3e**).* Synthesized by the general procedure **B**, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 54.0 mg (73%). Colorless amorphous solid. New compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, J = 7.5 Hz, 2H), 7.72 (d, J = 7.5 Hz, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.42−7.45 (m, 3H), 7.27−7.31 (m, 2H), 7.12−7.17 (m, 4H), 5.59 (d, J = 10.2 Hz, 1H), 3.94 (td, J = 10.8 Hz, 3.6 Hz, 1H), 3.73 (s, 3H), 3.50 (s, 3H), 3.09 (dd, J = 5.0 Hz, 9.6 Hz,

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J. Org. Chem. XXXX, XXX, XXX−XXX

1H), 2.24−2.38 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 193.9, 193.8, 169.2, 168.9, 137.8, 136.7, 136.5, 133.8, 133.0, 130.2, 128.9, 128.8, 128.6, 128.53, 128.50, 64.4, 52.6, 52.4, 49.7, 44.0, 32.9 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{28}H_{26}ClO_6$ 493.1412; Found 493.1414. IR (KBr, cm^{-1}): 2955, 1749, 1722, 1697, 1593, 1578, 1493, 1445, 1348, 1302, 1092, 845, 762, 686, 536.

*Dimethyl 2-(3-Benzoyl-2-(3-methoxyphenyl)-4-oxo-4-phenylbutyl)malonate (**3f**).* Synthesized by the general procedure **A**, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 64.5 mg (88%). Colorless amorphous solid. New compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, J = 7.6 Hz, 2H), 7.77 (d, J = 7.6 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.7 Hz, 3H), 7.31 (t, J = 7.7 Hz, 2H), 7.10 (t, J = 7.9 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.76 (s, 1H), 6.64 (dd, J = 1.8 Hz, 8.2 Hz, 1H), 5.68 (d, J = 10.2 Hz, 1H), 3.95 (td, J = 10.7 Hz, 3.6 Hz, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 3.54 (s, 3H), 3.18 (dd, J = 4.9 Hz, 9.7 Hz, 1H), 2.23−2.42 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 194.1, 193.9, 169.4, 169.0, 159.4, 140.8, 136.8, 136.7, 133.6, 133.0, 129.5, 128.78, 128.75, 128.5, 128.4, 121.0, 114.6, 112.7, 64.3, 55.0, 52.5, 52.3, 49.7, 44.6, 32.8 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{29}H_{29}O_7$ 489.1908; Found 489.1912.

*Dimethyl 2-(3-Benzoyl-2-(2-methoxyphenyl)-4-oxo-4-phenylbutyl)malonate (**3g**).* Synthesized by the general procedure **A**, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 64.5 mg (83%). Colorless amorphous solid. New compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, J = 7.4 Hz, 2H), 7.77 (d, J = 7.5 Hz, 2H), 7.51−7.54 (m, 1H), 7.39−7.44 (m, 3H), 7.27 (t, J = 7.7 Hz, 2H), 7.12 (d, J = 7.3 Hz, 1H), 7.05 (dt, J = 7.8 Hz, 1.6 Hz, 1H), 6.74−6.78 (m, 1H), 6.65 (d, J = 8.1 Hz, 1H), 6.07 (s, 1H), 4.10 (s, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 3.44 (s, 3H), 3.16 (dd, J = 5.3 Hz, 9.3 Hz, 1H), 2.61−2.69 (m, 1H), 2.23−2.30 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 194.7, 194.6, 169.6, 169.2, 157.6, 137.1, 136.6, 133.4, 132.9, 131.6, 128.70, 128.68, 128.4, 128.3, 128.2, 126.3, 120.6, 110.5, 60.9, 55.0, 52.4, 52.2, 50.3, 30.5 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{29}H_{29}O_7$ 489.1908; Found 489.1913.

*Dimethyl 2-(3-Benzoyl-2-(1-(tert-butoxycarbonyl)-1H-indol-3-yl)-4-oxo-4-phenylbutyl)malonate (**3h**).* Synthesized by the general procedure **A**, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 77.1 mg (86%). Pale yellow amorphous solid. New compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.96−7.99 (m, 3H), 7.65−7.68 (m, 2H), 7.61−7.63 (m, 1H), 7.52−7.56 (m, 1H), 7.35−7.44 (m, 3H), 7.31 (br, 1H), 7.19−7.27 (m, 4H), 5.78 (d, J = 9.5 Hz, 1H), 4.19−4.26 (m, 1H), 3.73 (s, 3H), 3.47 (s, 3H), 3.29 (dd, J = 7.2 Hz, 8.9 Hz, 1H), 2.44−2.52 (m, 2H), 1.62 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 194.4, 194.3, 169.4, 169.1, 149.2, 136.7, 136.4, 135.4, 133.6, 133.0, 129.3, 128.8, 128.7, 128.33, 128.27, 125.0, 124.5, 122.6, 119.4, 118.6, 115.2, 83.7, 62.5, 52.5, 52.3, 49.9, 35.5, 32.0, 28.1 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{35}H_{36}NO_8$ 598.2435; Found 598.2439. IR (KBr, cm^{-1}): 2979, 2953, 1734, 1697, 1667, 1596, 1580, 1450, 1373, 1257, 1094, 748, 689, 557.

*Dimethyl 2-(3-Benzoyl-4-oxo-4-phenyl-2-(thiophen-2-yl)butyl)-malonate (**3i**).* Synthesized by the general procedure **A**, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 66.2 mg (95%). Light red amorphous solid. New compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, J = 7.5 Hz, 2H), 7.80 (d, J = 7.6 Hz, 2H), 7.51 (t, J = 7.3 Hz, 1H), 7.37−7.46 (m, 3H), 7.30 (t, J = 7.7 Hz, 2H), 7.02 (d, J = 5.0 Hz, 1H), 6.81 (d, J = 3.0 Hz, 1H), 6.73 (dd, J = 3.6 Hz, 4.9 Hz, 1H), 5.67−5.69 (m, 1H), 4.26−4.32 (m, 1H), 3.73 (s, 3H), 3.55 (s, 3H), 3.30 (dd, J = 4.2 Hz, 10.4 Hz, 1H), 2.38−2.45 (m, 1H), 2.27−2.35 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 193.7, 193.5, 169.2, 168.8, 142.4, 136.4, 136.2, 133.6, 133.2, 128.7, 128.6, 128.44, 128.40, 127.3, 126.6, 124.4, 64.2, 52.5, 52.4, 49.6, 39.9, 34.1 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{26}H_{25}O_6S$ 465.1366; Found 465.1369.

*Diisopropyl 2-(3-Benzoyl-2-(4-methoxyphenyl)-4-oxo-4-phenylbutyl)malonate (**3j**).* Synthesized by the general procedure **A**, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 73.5 mg (90%). Colorless amorphous solid. New compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.02−8.05 (m, 2H), 7.70−7.72 (m, 2H), 7.51−7.55 (m, 1H), 7.38−7.44 (m, 3H), 7.25−7.29 (m, 2H), 7.12 (d, J = 8.7 Hz, 2H), 6.67−6.70 (m, 2H), 5.59 (d, J = 10.4 Hz, 1H), 5.06−5.15 (m, 1H), 4.78−4.87 (m, 1H), 3.90−3.96 (m, 1H), 3.68 (s, 3H), 2.98 (dd, J = 4.4 Hz, 10.3 Hz, 1H), 2.18−2.34 (m, 2H), 1.28 (dd, J = 6.3 Hz, 10.2 Hz, 6H), 1.10 (dd, J = 5.1 Hz, 6.2 Hz, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 194.2, 194.1, 168.7, 168.2, 158.5, 137, 136.9, 133.5, 133.0, 131.2, 129.9, 128.82, 128.76, 128.5, 128.4, 113.9, 68.84, 68.80, 64.9, 55.1, 50.3, 43.7, 32.9, 21.6, 21.5, 21.43, 21.36 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{33}H_{37}O_7$ 545.2534; Found 545.2538. IR (KBr, cm^{-1}): 2978, 2934, 1748, 1718, 1693, 1611, 1596, 1514, 1448, 1374, 1264, 1206, 1179, 1097, 969, 763, 688, 553.

*Di(adamantan-2-yl) 2-(3-Benzoyl-2-(4-methoxyphenyl)-4-oxo-4-phenylbutyl)malonate (**3k**).* Synthesized by the general procedure **A**, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 95.1 mg (87%). Colorless amorphous solid. New compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.04−8.07 (m, 2H), 7.71−7.73 (m, 2H), 7.53−7.57 (m, 1H), 7.39−7.46 (m, 3H), 7.27 (t, J = 7.7 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 6.70 (d, J = 8.7 Hz, 2H), 5.62 (d, J = 10.3 Hz, 1H), 5.04 (s, 1H), 4.74 (s, 1H), 3.92−3.98 (m, 1H), 3.70 (s, 3H), 3.11 (dd, J = 4.4 Hz, 10.0 Hz, 1H), 2.24−2.39 (m, 2H), 1.41−1.97 (m, 28H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 194.11, 194.05, 168.7, 168.3, 158.5, 137.0, 136.9, 133.5, 133, 131.4, 129.9, 128.82, 128.81, 128.5, 128.4, 113.9, 64.6, 55.1, 50.6, 44.0, 37.4, 37.2, 36.3, 36.2, 36.1, 33.2, 31.9, 31.7, 31.5, 27.2, 27.04, 26.98, 26.8 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{47}H_{53}O_7$ 729.3786; Found 729.3792.

*Dimethyl 2-(3-Benzoyl-2-(4-methoxyphenyl)-5-methyl-4-oxohexyl)malonate (**3l**).* Synthesized by the general procedure **A**, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), dr = 1:0.8, 62.0 mg (91%). Colorless amorphous solid. New compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, J = 7.4 Hz, 2H × 0.8), 7.71 (d, J = 7.4 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H × 0.8), 7.43−7.49 (m, 2H × 0.8 + 1H), 7.31 (t, J = 7.7 Hz, 2H), 7.15 (d, J = 8.6 Hz, 2H × 0.8), 7.01 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H × 0.8), 6.64 (d, J = 8.6 Hz, 2H), 5.01 (d, J = 10.8 Hz, 1H × 0.8), 4.95 (d, J = 10.8 Hz, 1H), 3.752 (s, 3H), 3.747 (s, 3H × 0.8), 3.74 (s, 3H × 0.8), 3.64 (s, 3H), 3.52 (s, 3H), 3.47 (s, 3H × 0.8), 3.03−3.07 (m, 1H × 1.8), 2.84 (quintet, J = 6.8 Hz, 1H), 2.53 (quintet, J = 6.8 Hz, 1H × 0.8), 2.00−2.23 (m, 2H × 1.8), 1.03 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 7.0 Hz, 3H), 0.56 (d, J = 6.7 Hz, 3H × 0.8), 0.53 (d, J = 6.7 Hz, 3H × 0.8) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 208.5, 207.8, 194.4, 194.1, 169.4, 169.3, 169.1, 169.0, 158.7, 158.4, 137.00, 136.99, 133.7, 133.2, 130.9, 130.7, 129.8, 129.4, 128.8, 128.7, 128.5, 128.2, 114.0, 113.8, 68.7, 68.6, 55.1, 55.0, 52.54, 52.50, 52.4, 52.3, 49.5, 49.4, 43.2, 42.8, 39.3, 33.6, 33.1, 19.4, 18.9, 18.1, 17.6 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{26}H_{31}O_7$ 455.2064; Found 455.2070.

*Dimethyl 2-(3-Benzoyl-2-(4-methoxyphenyl)-5,5-dimethyl-4-oxohexyl)malonate (**3m**).* Synthesized by the general procedure **A**, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), dr = 1:0.65, 65.4 mg (93%). Colorless amorphous solid. New compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, J = 7.5 Hz, 2H × 0.65), 7.59−7.63 (m, 2H+1H × 0.65), 7.52 (d, J = 7.6 Hz, 2H × 0.65), 7.40 (t, J = 7.3 Hz, 1H), 7.27 (t, J = 7.7 Hz, 2H), 7.16 (d, J = 8.5 Hz, 2H × 0.65), 7.00 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.5 Hz, 2H × 0.65), 6.58 (d, J = 8.6 Hz, 2H), 5.29 (d, J = 10.7 Hz, 1H × 0.65), 5.21 (d, J = 10.0 Hz, 1H), 3.75 (s, 3H × 0.65), 3.71 (s, 3H), 3.66 (s, 3H × 0.65), 3.61 (s, 3H), 3.49 (s, 3H), 3.44 (s, 3H × 0.65), 3.07 (dd, J = 4.6 Hz, 9.8 Hz, 1H), 3.00 (dd, J = 4.4 Hz, 9.8 Hz, 1H × 0.65), 2.33 (td, J = 12.9 Hz, 4.7 Hz, 1H), 2.13−2.25 (m, 1H × 1.65), 2.02−2.09 (m, 1H × 0.65), 1.05 (s, 9H), 0.69 (s, 9H × 0.65) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 207.7, 206.6, 194.4, 194.0, 169.5, 169.4, 169.0, 168.9, 158.6, 158.5, 137.3, 136.7, 133.6, 132.8, 131.7, 129.9, 129.8, 128.9, 128.7, 128.4, 128.2, 113.8, 113.7, 62.2, 61.5, 55.1, 55.0, 52.5, 52.3, 49.83, 49.81, 45.32, 45.24, 45.16, 45.1, 32.4, 32.0, 26.2, 25.7 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{27}H_{33}O_7$ 469.2221; Found 469.2225.

*Dimethyl 2-(3-Benzoyl-5,5,5-trifluoro-2-(4-methoxyphenyl)-4-oxopentyl)malonate (**3n**).* Synthesized by the general procedure **A**, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1),

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J. Org. Chem. XXXX, XXX, XXX−XXX

major diastereomer, dr = 1:4, 48.4 mg (67%). Pale yellow amorphous solid. New compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 7.4 Hz, 2H), 7.47 (t, J = 7.3 Hz, 1H), 7.28−7.35 (m, 4H), 6.74 (d, J = 8.7 Hz, 2H), 6.48 (s, 1H), 4.66 (d, J = 11.6 Hz, 2H), 3.93 (dd, J = 10.2 Hz, 20.1 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.70 (s, 3H), 3.13 (dd, J = 10.4 Hz, 14.5 Hz, 1H), 2.80 (dd, J = 8.9 Hz, 14.5 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 201.9, 196.1 (C−F, $^2J_{C,F}$ = 29.7 Hz), 170.4, 168.9, 158.8, 136.9, 133.9, 131.9, 128.7, 128.5, 128.4, 124.2 (C−F, $^1J_{C,F}$ = 285.3 Hz), 114.2, 86.7, 65.4, 55.2, 53.5, 53.0, 46.6, 40.8 ppm. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{24}H_{24}F_3O_7$ 481.1469; Found 481.1474.

*4-Ethyl 1,1-Dimethyl 3-(4-methoxyphenyl)-5-oxo-5-phenylpentane-1,1,4-tricarboxylate (**3o**).* Synthesized by the general procedure **A**, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), dr 1:1, 63.0 mg (92%). Colorless gum. Known compound.[6a] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05−8.07 (m, 2H), 7.77−7.80 (m, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.43−7.47 (m, 3H), 7.33 (t, J = 7.3 Hz, 2H), 7.18 (d, J = 8.6 Hz, 2H), 7.06 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 4.70 (d, J = 10.7 Hz, 1H), 4.63 (d, J = 10.7 Hz, 1H), 4.12−4.22 (m, 2H), 3.751 (s, 3H), 3.746 (s, 3H), 3.65 (s, 3H), 3.53 (s, 3H), 3.47 (s, 3H), 3.10 (dt, J = 4.7 Hz, 10.3 Hz, 2H), 2.03−2.42 (m, 4H), 1.20 (t, J = 7.2 Hz, 3H), 0.83 (t, J = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 193.0, 192.6, 169.4, 169.3, 169.1, 168.0, 167.4, 158.7, 158.4, 137.7, 136.4, 136.3, 133.6, 131.2, 131.0, 129.7, 129.3, 128.6, 128.4, 128.3, 113.8, 113.7, 61.7, 61.2, 61.0, 60.6, 55.0, 54.9, 52.5, 52.4, 52.3, 52.2, 49.7, 49.4, 42.4, 42.3, 33.4, 32.9, 13.8, 13.5 ppm.

*Dimethyl 2-(3-(4-(tert-Butyl)benzoyl)-2,4-bis(4-methoxyphenyl)-4-oxobutyl)malonate (**3p**).* Synthesized by the general procedure **A**, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), dr = 1:1, 76.7 mg (89%). Colorless amorphous solid. New compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.6 Hz, 2H × 0.5), 7.77 (d, J = 9.0 Hz, 2H × 0.5), 7.69 (d, J = 8.6 Hz, 2H × 0.5), 7.42 (d, J = 8.5 Hz, 2H × 0.5), 7.28 (d, J = 8.6 Hz, 2H × 0.5), 7.11−7.14 (m, 4H × 0.5), 6.90 (d, J = 8.9 Hz, 2H × 0.5), 6.76 (d, J = 8.9 Hz, 2H × 0.5), 6.69 (d, J = 8.6 Hz, 4H × 0.5), 5.50 (s, 1H × 0.5), 5.47 (s, 1H × 0.5), 3.87−3.92 (m, 1H), 3.83 (s, 3H × 0.5), 3.77 (s, 3H × 0.5), 3.72 (s, 3H), 3.68 (s, 3H), 3.49 (s, 3H), 3.09−3.14 (m, 1H), 2.21−2.36 (m, 2H), 1.29 (s, 9H × 0.5), 1.24 (s, 9H × 0.5) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 194.0, 193.8, 192.7, 192.4, 169.5, 169.1, 163.8, 163.4, 158.4, 157.3, 156.8, 134.3, 134.2, 131.5, 131.3, 131.2, 131.1, 129.9, 129.8, 129.7, 128.8, 128.5, 125.7, 125.3, 113.9, 113.8, 113.6, 64.8, 55.4, 55.3, 55.0, 52.4, 52.3, 49.8, 43.8, 43.6, 35.0, 34.9, 33.1, 33.0, 30.91, 30.87 ppm. HRMS (ESI): calcd. for $C_{34}H_{39}O_8$ ([M + H]$^+$) 575.2639, found 575.2645.

General Procedure for the Synthesis of 4 from 3. To **3** (0.10 mmol, 1.0 equiv) in MeOH (1.0 mL), DBU (6.0 μL, 0.04 mmol, 0.4 equiv) was added. The mixture was stirred at 50 °C for 12 h. Then, the solvent was removed in vacuo, and the residue was purified by silica gel flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1) to provide product **4**.

*Dimethyl 2-(2-(4-Methoxyphenyl)-4-oxo-4-phenylbutyl)-malonate (**4a**).* Synthesized by the general procedure, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 37.7 mg (98%). Colorless gum. Known compound.[6a] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86−7.88 (m, 2H), 7.52 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.13 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 3.76 (s, 3H), 3.74 (s, 3H), 3.58 (s, 3H), 3.17−3.34 (m, 4H), 2.34−2.41 (m, 1H), 2.15−2.22 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 198.0, 169.6, 169.5, 158.3, 136.8, 134.4, 132.9, 128.6, 128.5, 127.9, 114.0, 55.1, 52.5, 52.4, 49.8, 45.8, 38.2, 35.2 ppm. IR (KBr, cm^{-1}): 2953, 2838, 1733, 1685, 1611, 1597, 1581, 1513, 1448, 1358, 1249, 1034, 832, 758, 692, 561.

*Dimethyl 2-(2-(4-(Benzyloxy)phenyl)-4-oxo-4-phenylbutyl)-malonate (**4b**).* Synthesized by the general procedure, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 41.4 mg (90%). Colorless gum. New compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87−7.89 (m, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.30−7.44 (m, 7H), 7.14 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 8.6 Hz, 2H), 3.75 (s, 3H), 3.57 (s, 3H), 3.19−3.35 (m, 4H), 2.35−2.42 (m, 1H), 2.17−2.24 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 198.0, 169.6, 169.5, 157.6, 136.9, 136.8, 134.6, 133.0, 128.7, 128.51, 128.50, 127.94, 127.90, 127.4, 114.9, 69.9, 52.5, 52.4, 49.8, 45.8, 38.2, 35.2 ppm. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{28}H_{29}O_6$ 461.1959; Found 461.1963. IR (KBr, cm^{-1}): 2957, 2923, 1730, 1683, 1609, 1581, 1510, 1449, 1360, 1083, 1018, 800, 737, 692, 557.

*Dimethyl 2-(4-Oxo-4-phenyl-2-(p-tolyl)butyl)malonate (**4c**).* Synthesized by the general procedure, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 33.9 mg (92%). Colorless gum. Known compound.[8b] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87−7.89 (m, 1H), 7.51−7.55 (m, 1H), 7.42 (t, J = 7.6 Hz, 2H), 7.08−7.13 (m, 4H), 3.74 (s, 3H), 3.58 (s, 3H), 3.22−3.36 (m, 3H), 3.19 (dd, J = 5.0 Hz, 9.9 Hz, 1H), 2.36−2.42 (m, 1H), 2.29 (s, 3H), 2.18−2.24 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 198.0, 169.6, 169.5, 139.4, 136.9, 136.4, 133.0, 129.3, 128.5, 128.0, 127.6, 52.5, 52.4, 49.8, 45.8, 38.5, 35.1, 21.0 ppm.

*Dimethyl 2-(4-Oxo-2,4-diphenylbutyl)malonate (**4d**).* Synthesized by the general procedure, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 33.3 mg (94%). Colorless gum. Known compound.[8b] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87−7.89 (m, 2H), 7.51−7.55 (m, 1H), 7.42 (t, J = 7.6 Hz, 2H), 7.27−7.31 (m, 2H), 7.18−7.26 (m, 3H), 3.75 (s, 3H), 3.57 (s, 3H), 3.24−3.41 (m, 3H), 3.20 (dd, J = 5.2 Hz, 9.7 Hz, 1H), 2.37−2.44 (m, 1H), 2.20−2.28 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 197.9, 169.6, 169.5, 142.5, 136.8, 133.0, 128.6, 128.5, 127.9, 127.7, 126.9, 52.5, 52.4, 49.8, 45.7, 38.9, 35.0 ppm. IR (KBr, cm^{-1}): 2951, 2932, 2851, 1756, 1733, 1687, 1597, 1580, 1495, 1450, 1437, 1371, 1358, 1049, 748, 706, 690.

*Dimethyl 2-(2-(4-Chlorophenyl)-4-oxo-4-phenylbutyl)malonate (**4e**).* Synthesized by the general procedure, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 35.8 mg (92%). Colorless gum. Known compound.[8b] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, J = 7.3 Hz, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 3.75 (s, 3H), 3.59 (s, 3H), 3.22−3.40 (m, 3H), 3.16 (dd, J = 5.2 Hz, 9.6 Hz, 1H), 2.36−2.42 (m, 1H), 2.18−2.24 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 197.5, 169.43, 169.36, 141.0, 136.7, 133.1, 132.6, 129.1, 128.8, 128.6, 127.9, 52.6, 52.5, 49.7, 45.5, 38.4, 35.1 ppm.

*Dimethyl 2-(2-(3-Methoxyphenyl)-4-oxo-4-phenylbutyl)-malonate (**4f**).* Synthesized by the general procedure, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 35.0 mg (91%). Colorless gum. New compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87−7.89 (m, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 7.21 (t, J = 7.8 Hz, 1H), 6.73−6.83 (m, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 3.59 (s, 3H), 3.19−3.37 (m, 4H), 2.36−2.42 (m, 1H), 2.17−2.24 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 197.9, 169.6, 169.5, 159.7, 144.2, 136.9, 133.0, 129.7, 128.5, 128.0, 120.0, 113.7, 112.1, 55.1, 52.5, 52.4, 49.8, 45.6, 39.0, 35.0 ppm. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{22}H_{25}O_6$ 385.1646; Found 385.1651.

*Dimethyl 2-(2-(2-Methoxyphenyl)-4-oxo-4-phenylbutyl)-malonate (**4g**).* Synthesized by the general procedure, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 34.5 mg (90%). Colorless gum. New compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89−7.91 (m, 2H), 7.50−7.54 (m, 1H), 7.41 (t, J = 15.2 Hz, 2H), 7.14−7.26 (m, 2H), 6.89 (td, J = 7.4 Hz, 0.8 Hz, 1H), 6.83 (d, J = 8.1 Hz, 1H), 3.78 (s, 3H), 3.71−3.75 (m, 1H), 3.70 (s, 3H), 3.54 (s, 3H), 3.41 (dd, J = 6.5 Hz, 16.7 Hz, 1H), 3.29 (dd, J = 7.4 Hz, 16.7 Hz, 1H), 3.20−3.24 (m, 1H), 2.35−2.39 (m, 2H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 198.6, 169.8, 169.5, 157.4, 136.9, 132.8, 130.0, 128.8, 128.4, 128.0, 127.8, 120.6, 110.7, 55.1, 52.4, 52.3, 50.0, 44.1, 34.0, 33.3 ppm. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{22}H_{25}O_6$ 385.1646; Found 385.1650.

*Dimethyl 2-(2-(1-(tert-Butoxycarbonyl)-1H-indol-3-yl)-4-oxo-4-phenylbutyl)malonate (**4h**).* Synthesized by the general procedure, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 15.3 mg (31%). Colorless gum. New compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (br, 1H) ppm, 7.88−7.91 (m, 2H), 7.60−7.62 (m, 1H), 7.51−7.56 (m, 1H), 7.40−7.44 (m, 3H), 7.28−7.32

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J. Org. Chem. XXXX, XXX, XXX−XXX

(m, 1H), 7.22−7.26 (m, 1H), 3.70−3.74 (m, 4H), 3.58 (s, 3H), 3.34−3.48 (m, 3H), 2.41−2.49 (m, 2H), 1.66 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 197.9, 169.6, 169.5, 136.9, 135.7, 133.1, 129.4, 128.6, 128.0, 124.5, 123.0, 122.5, 121.9, 119.4, 115.4, 83.7, 52.5, 52.4, 50.0, 44.4, 34.0, 30.0, 28.2 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{28}H_{32}NO_7$ 494.2173; Found 494.2174.

*Dimethyl 2-(2-(1H-Indol-3-yl)-4-oxo-4-phenylbutyl)malonate (**4h′**).* Synthesized by the general procedure, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 21.6 mg (55%). Colorless gum. New compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.08 (br, 1H), 7.86−7.89 (m, 2H), 7.67 (d, J = 7.9 Hz, 1H), 7.49−7.53 (m, 1H), 7.38−7.42 (m, 1H), 7.33−7.35 (m, 1H), 7.18 (td, J = 7.5 Hz, 1.1 Hz, 1H), 7.09−7.13 (m, 1H), 7.04 (d, J = 2.4 Hz, 1H), 3.67−3.76 (m, 4H), 3.48−3.54 (m, 4H), 3.34−3.43 (m, 2H), 2.44−2.55 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 198.6, 169.8, 169.7, 137.0, 136.6, 132.9, 128.5, 128.0, 126.2, 122.3, 122.0, 119.4, 119.3, 116.8, 111.4, 52.4, 52.3, 50.3, 44.9, 34.2, 31.0 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{24}NO_5$ 394.1649; Found 394.1670.

*Dimethyl 2-(4-Oxo-4-phenyl-2-(thiophen-2-yl)butyl)malonate (**4i**).* Synthesized by the general procedure, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 34.2 mg (95%). Colorless gum. New compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.89−7.91 (m, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.14 (dd, J = 0.8 Hz, 4.8 Hz, 1H), 6.87−6.91 (m, 2H), 3.71−3.78 (m, 4H), 3.63 (s, 3H), 3.25−3.43 (m, 3H), 2.41−2.48 (m, 1H), 2.17−2.25 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 197.4, 169.5, 169.4, 146.1, 136.7, 133.1, 128.5, 128.0, 126.7, 125.1, 123.8, 52.6, 52.5, 49.7, 46.5, 36.1, 34.3 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{21}O_5S$ 361.1104; Found 361.1102. IR (KBr, cm^{-1}): 2954, 2927, 2853, 1757, 1734, 1686, 1597, 1579, 1415, 1361, 1307, 1049, 1029, 760, 689, 520.

*Di(adamantan-2-yl) 2-(2-(4-Methoxyphenyl)-4-oxo-4-phenylbutyl)malonate (**4j**).* Synthesized by the general procedure, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 28.1 mg (45%). Colorless amorphous solid. New compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.84−7.87 (m, 2H), 7.49−7.53 (m, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.02 (s, 1H), 4.85 (s, 1H), 3.76 (s, 3H), 3.29−3.36 (m, 2H), 3.17−3.26 (m, 2H), 2.37−2.44 (m, 1H), 2.20−2.27 (m, 1H), 1.46−1.89 (m, 28H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 198.0, 168.8, 168.7, 158.3, 137.0, 134.6, 132.9, 128.7, 128.4, 128.0, 114.0, 78.1, 78.0, 55.1, 50.7, 46.0, 38.4, 37.5, 37.3, 37.2, 36.5, 36.27, 36.24, 36.17, 36.14, 35.0, 31.9, 31.74, 31.66, 31.64, 31.60, 31.0, 27.1, 27.0, 26.9, 26.8 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{40}H_{49}O_6$ 625.3524; Found 625.3528. IR (KBr, cm^{-1}): 2906, 2855, 2675, 1724, 1688, 1597, 1582, 1513, 1450, 1358, 1041, 831, 736, 691, 557.

*Diethyl 2-(2-(4-Methoxyphenyl)-4-oxo-4-phenylbutyl)malonate (**4k**).* Synthesized by the general procedure, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 38.4 mg (93%). Colorless gum. New compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.86−7.88 (m, 2H), 7.52 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 3.98−4.11 (m, 2H), 3.76 (s, 3H), 3.22−3.35 (m, 3H), 3.14 (dd, J = 4.9 Hz, 10.0 Hz, 1H), 2.33−2.40 (m, 1H), 2.14−2.21 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 198.1, 169.3, 169.2, 158.3, 137.0, 134.5, 132.9, 128.7, 128.5, 128.0, 114.0, 61.3, 55.2, 50.1, 45.9, 38.2, 35.2, 14.1, 13.9 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{29}O_6$ 413.1959; Found 413.1965.

*Dimethyl 2-(2,4-Bis(4-methoxyphenyl)-4-oxobutyl)malonate (**4l**).* Synthesized by the general procedure, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 34.0 mg (41%). Colorless gum. New compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, J = 8.9 Hz, 2H), 7.13 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 3.84 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.58 (s, 3H), 3.13−3.34 (m, 4H), 2.33−2.41 (m, 1H), 2.15−2.23 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 196.6, 169.7, 169.6, 163.4, 158.3, 134.6, 130.2, 130.1, 128.7, 114.0, 113.6, 55.4, 55.2, 52.5, 52.4, 49.9, 45.5, 38.4, 35.3 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{27}O_7$ 415.1751; Found 415.1750. IR (KBr, cm^{-1}): 2954, 2840, 1732, 1676, 1600, 1577, 1512, 1438, 1251, 1030, 833, 735, 701, 560.

*Dimethyl 2-(4-(4-(tert-Butyl)phenyl)-2-(4-methoxyphenyl)-4-oxobutyl)malonate (**4m**).* Synthesized by the general procedure, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 31.7 mg (36%). Colorless amorphous solid. New compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, J = 8.5 Hz, 2H), 7.43 (t, J = 8.5 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 3.76 (s, 3H), 3.74 (s, 3H), 3.58 (s, 3H), 3.17−3.31 (m, 4H), 2.34−2.41 (m, 1H), 2.15−2.22 (m, 1H), 1.32 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 197.7, 169.7, 169.6, 158.3, 156.7, 134.5, 134.4, 128.7, 127.9, 125.4, 114.0, 55.2, 52.5, 52.4, 49.9, 45.8, 38.2, 35.3, 35.0, 31.0 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{26}H_{33}O_6$ 441.2272; Found 441.2274.

General Procedure for the Synthesis of 4 without the Isolation of 3. To a mixture of D−A cyclopropanes **2a** (52.8 mg, 0.2 mmol, 1.0 equiv) and 1-benzoylacetone derivative **1** (0.24 mmol, 1.2 equiv) in CH_2Cl_2 (1.5 mL), $Sc(OTf)_3$ (4.9 mg, 0.01 mmol, 0.05 equiv) was added. The mixture was stirred at room temperature (25 °C) for 24 h. Then, the mixture was diluted with CH_2Cl_2 (3.0 mL) and washed with saturated $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (5 mL × 3). The organic layers were combined, washed with brine, dried over Na_2SO_4, and the solvent was removed in vacuo. The residue was dissolved in MeOH (2.0 mL), and DBU (12.0 μL, 0.08 mmol, 0.4 equiv) was added. The mixture was stirred at 50 °C for 12 h. Then, the solvent was removed in vacuo, and the residue was purified by silica gel flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1) to provide product **4**.

Procedure for a 5 mmol-Scale Reaction to Synthesize 4a. To a mixture of D−A cyclopropanes **2a** (1.32 g, 5.0 mmol) and 1-benzoylacetone (973.1 mg, 6.0 mmol) in CH_2Cl_2 (25.0 mL), $Sc(OTf)_3$ (123.0 mg, 0.25 mmol) was added. The mixture was stirred at room temperature (25 °C) for 40 h. Then, the mixture was diluted with CH_2Cl_2 (25.0 mL) and washed with saturated $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (25 mL × 3). The organic layers were combined, washed with brine, dried over Na_2SO_4, and the solvent was removed in vacuo. The residue was dissolved in MeOH (50.0 mL), and DBU (0.3 mL, 2.0 mmol) was added. The mixture was stirred at 50 °C for 16 h. Then, the solvent was removed in vacuo, and the residue was purified by silica gel flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1) to provide product **4a** (1.73 g, 90%).

*Dimethyl 2-(4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-4-oxobutyl)malonate (**4n**).* Synthesized by the general procedure, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 63.6 mg (79%). Colorless gum. New compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.71 (td, J = 7.6 Hz, 1.8 Hz, 1H), 7.45−7.50 (m, 1H), 7.15−7.19 (m, 1H), 7.07−7.12 (m, 3H), 6.78−6.83 (m, 2H), 3.76 (s, 3H), 3.74 (s, 3H), 3.59 (s, 3H), 3.24−3.34 (m, 3H), 3.17 (dd, J = 5.0 Hz, 9.8 Hz, 1H), 2.32−2.38 (m, 1H), 2.12−2.21 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 196.5, 169.7, 169.6, 161.7 (C−F, $^1J_{C,F}$ = 252.6 Hz), 158.3, 134.3, 130.6, 128.7, 125.7 (C−F, $^3J_{C,F}$ = 13.0 Hz), 116.5 (C−F, $^2J_{C,F}$ = 23.7 Hz), 114.0, 55.2, 52,5, 52.4, 50.8, 49.8, 38.0, 35.3 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{24}FO_6$ 403.1551; Found 403.1555.

*Dimethyl 2-(4-(2-Fluorophenyl)-2-(4-methoxyphenyl)-4-oxobutyl)malonate (**4o**).* Synthesized by the general procedure, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 57.9 mg (72%). Colorless gum. New compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.85−7.91 (m, 2H), 7.04−7.13 (m, 4H), 6.80−6.83 (m, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 3.58 (s, 3H), 2.34−2.41 (m, 16H), 2.14−2.23 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 196.5, 169.6, 169.5, 165.6 (C−F, $^1J_{C,F}$ = 253.1 Hz), 158.4, 134.2, 133.4 (C−F, $^4J_{C,F}$ = 2.9 Hz), 131.3 (C−F, $^3J_{C,F}$ = 9.4 Hz), 130.6 (C−F, $^3J_{C,F}$ = 9.4 Hz), 128.6, 115.6 (C−F, $^2J_{C,F}$ = 21.7 Hz), 115.5 (C−F, $^2J_{C,F}$ = 21.9 Hz), 114.0, 55.1, 52.5, 52.4, 49.8, 45.8, 38.3, 35.2 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{24}FO_6$ 403.1551; Found 403.1557.

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J. Org. Chem. XXXX, XXX, XXX−XXX

*Dimethyl 2-(4-(4-Chlorophenyl)-2-(4-methoxyphenyl)-4-oxobutyl)malonate (**4p**).* Synthesized by the general procedure, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 54.5 mg (65%). **4p** was mixed with small amount of inseparable ring-opening product. Colorless gum. New compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 3.58 (s, 3H), 3.16−3.31 (m, 4H), 2.33−2.40 (m, 1H), 2.12−2.22 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 196.9, 169.6, 169.5, 158.4, 139.4, 135.2, 134.1, 129.4, 128.8, 128.6, 114.1, 55.2, 52.53, 52.46, 49.8, 45.8, 38.3, 35.2 ppm. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{22}H_{24}ClO_6$ 419.1256; Found 419.1253.

*Dimethyl 2-(2-(4-Methoxyphenyl)-4-(4-nitrophenyl)-4-oxobutyl)-malonate (**4q**); Dimethyl 2-(2-(4-Methoxyphenyl)-4-oxopentyl)-malonate (**4r**).* Synthesized by the general procedure, flash chromatography (petroleum ether:ethyl acetate = 4:1 to 2:1), 63.0 mg, **4q** (29.3%):**4r** (58.5%) = 0.5:1. **4q** and **4r** were not able to be separated by silica gel flash chromatography and thus were characterized as a mixture. **4q** and **4r** are both new compounds. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, J = 9.0 Hz, 2H × 0.5, **4q**), 7.99 (d, J = 9.0 Hz, 2H × 0.5, **4q**), 7.05−7.11 (m, 2H+2H × 0.5, **4r** +**4q**), 6.80−6.84 (m, 2H+2H × 0.5, **4r**+**4q**), 3.76 (s, 3H, **4r**), 3.752 (s, 3H × 0.5, **4q**), 3.750 (s, 3H × 0.5, **4q**), 3.74 (s, 3H, **4r**), 3.59 (s, 3H × 0.5, **4q**), 3.57 (s, 3H, **4r**), 3.26−3.34 (m, 3H × 0.5, **4q**), 3.05−3.22 (m, 3H, **4r**), 2.65−2.77 (m, 2H, **4r**), 2.35−2.42 (m, 1H × 0.5, **4q**), 2.21−2.28 (m, 2H × 0.5, **4q**), 2.04−2.11 (m, 1H, **4r**), 2.00 (s, 3H, **4r**) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 206.9, 196.7, 169.6, 169.53, 169.50, 169.4, 158.6, 158.4, 150.2, 141.3, 133.9, 133.7, 128.9, 128.60, 128.56, 123.7, 114.1, 114.0, 55.1, 52.6, 52.5, 52.4, 50.8, 49.6, 46.4, 38.2, 35.2, 30.4 ppm. HRMS (ESI) m/z: [M + H]$^+$ Calcd for (**4q**) $C_{22}H_{24}NO_8$ 430.1496; Found 430.1499. HRMS (ESI) m/z: [M + H]$^+$ Calcd for (**4r**) $C_{17}H_{23}O_6$ 323.1489; Found 323.1495.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02290.

Copies of NMR spectra (^{1}H, ^{13}C, 2D-NMR) (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Dongxin Zhang − *Institute of Molecular Engineering and Applied Chemistry, Anhui University of Technology, Ma'anshan, Anhui 243002, China;* orcid.org/0000-0002-2185-4692; Email: dxzhang@ahut.edu.cn

Qian-Feng Zhang − *Institute of Molecular Engineering and Applied Chemistry, Anhui University of Technology, Ma'anshan, Anhui 243002, China*; Email: zhangqf@ahut.edu.cn

Authors

Hu Cai − *Institute of Molecular Engineering and Applied Chemistry, Anhui University of Technology, Ma'anshan, Anhui 243002, China*

Yan Chen − *Institute of Molecular Engineering and Applied Chemistry, Anhui University of Technology, Ma'anshan, Anhui 243002, China*

Lei Yin − *Institute of Molecular Engineering and Applied Chemistry, Anhui University of Technology, Ma'anshan, Anhui 243002, China*

Junchao Zhong − *Institute of Molecular Engineering and Applied Chemistry, Anhui University of Technology, Ma'anshan, Anhui 243002, China*

Ying Zhang − *Institute of Molecular Engineering and Applied Chemistry, Anhui University of Technology, Ma'anshan, Anhui 243002, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02290

Notes

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