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Copper-Catalyzed Three-Component Reactions of α-Ketoaldehyde, 1,3-Dicarbonyl Compound, and Organic Boronic Acid in Water: A Route to 1,4-Diketones

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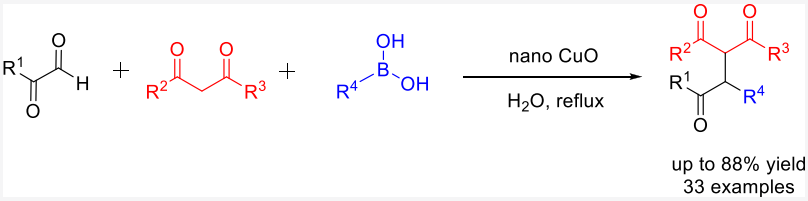
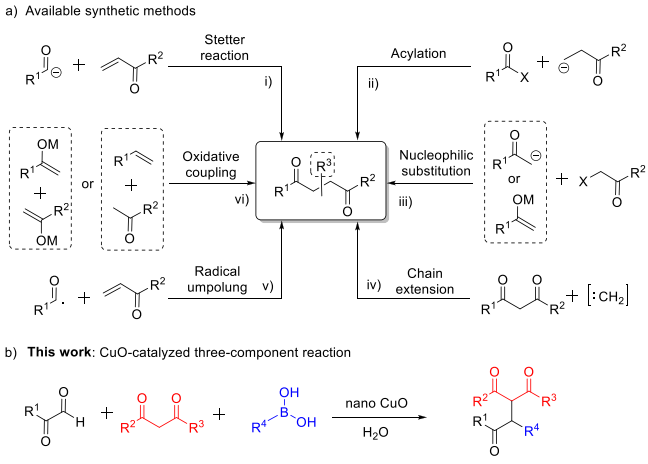


ABSTRACT: A novel three-component reaction of α-ketoaldehydes, 1,3-dicarbonyl compounds, and organic boronic acids catalyzed by CuO in water has been developed to give a wide range of products containing 1,3/1,4-diketones. The method has some advantages such as the use of readily available starting materials, wide substrate scopes, excellent yields, gram-scale synthesis, and mild reaction conditions.

Multicomponent reactions (MCRs) have emerged as an effective synthetic method for a diverse set of new molecules. Compared to traditional methods, MCRs processes have the advantages of high atomic economy, simplified operating steps, saving energy and resources, and affording highly functionalized molecules from simple starting materials, all of which are consistent with the concept of green organic synthesis.[1] With the prosperous development of high-throughput screening of drug candidates in pharmaceutical industries, the concept of MCRs has received great attention over the last two decades.[2] Additionally, as a nontoxic, cheap, readily available, and environmentally benign solvent, water has received special attention in green organic synthesis.[3] Besides being an environmentally friendly solvent, water often has a significant impact on the reaction process due to the network of hydrogen bonds, the large surface tension, the high specific heat capacity, the high cohesive energy, and the high polarity.[4]

1,4-Dicarbonyl compounds are prominent building blocks to prepare a broad range of carbocyclic and heteroaromatic compounds in organic synthesis. They have been regarded as highly versatile synthons for the synthesis of appealing valuable molecules, such as furan,[5] thiophene,[6] pyrrole,[7] and pyridazines[8] derivatives. Although 1,4-dicarbonyl compounds have been found in a wide range of applications in the chemical and pharmaceutical fields, the green and efficient synthesis of them remains a significant challenge.[9] The development of facile and environment-friendly methods for the construction of this highly valuable synthon is still highly desirable. Generally, 1,4-dicarbonyl compounds can be prepared with one of the following methods (Scheme 1a): (i) Michael additions of acyl anions onto enones;[10] (ii) the addition of homoenolate equivalents to acid derivatives;[11] (iii) nucleophilic substitution of α-haloketones equivalents;[12] (iv) chain-extension reactions of 1,3-dicarbonyls;[13] (v) radical umpolung

Scheme 1. Synthetic Approaches to 1,4-Dicarbonyl Compounds



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of acyl radicals with Michael acceptors;[14] (vi) oxidative coupling of enolates[15] or alkenes.[16] Although these methods are elegant, they often suffer from a number of limitations in terms of chemoselectivity problems, substrate scope, and functional group tolerance. Alternative and complementary multiple-component strategies toward 1,4-dicarbonyl compounds are still highly desirable. More recently, Gu has reported a straightforward approach for the formation of 1,4-dicarbonyls through a three-component reaction of α-ketoaldehydes, 1,3-diketones, and different nucleophiles.[17] Inspired by the advantages of multiple-component protocol, we envisioned that employing boronic acids as coupling partners would further enrich the diversity of 1,4-diketones synthesis.

Boronic acids are ideal partners in MCRs due to their diverse commercially available molecular structures, which is particularly noteworthy when designing reactions targeting high levels of molecular diversity.[18] In continuation of our previous researches toward the application of boronic acids in MCRs,[19] herein we report a CuO-catalyzed synthesis of 1,4-diketones through an unprecedented three-component reaction of α-ketoaldehydes, 1,3-dicarbonyl compounds, and organic boronic acids in water (Scheme 1b).

We initiated our investigation on the model reaction of ethyl glyoxalate (**1a**), acetylacetone (**2a**) and phenylboronic acid (**3a**) to screen various reaction parameters (Table 1). To our delight, the first experiment gave the corresponding product **4a** in a GC yield of 46% with CuCl (10 mol %) as the catalyst, water as the solvent, and refluxing for 45 min (Table 1, entry 1). Copper catalysts such as $CuCl_2·2H_2O$, CH_3COOCu, $Cu(CH_3COO)_2·H_2O$, $Cu(acac)_2$, nano Cu, nano CuO, ordinary CuO, and Cu_2O were also screened (Table 1, entries 2−9). The results demonstrated that nano CuO was the best catalyst, and the target product **4a** was isolated in 89% yield (92% GC yield). As expected, the reaction did not proceed in the absence of copper catalyst (Table 1, entry 10). Changing the reaction media to DMF, toluene, and EtOH did not improve the reaction yield (Table 1, entries 11−13). It was also found that decreasing the reaction temperature would erode the yield (Table 1, entries 14 and 15). Moreover, reducing or increasing the catalyst loading did not increase the yield further (Table 1, entries 16 and 17). Thus, the optimized reaction conditions were established as follow: **1a** (0.6 mmol), **2a** (0.5 mmol), **3a** (0.75 mmol), nano CuO (0.05 mmol) and water (1.5 mL) under reflux for 45 min (Table 1, entry 7).

Table 1. Optimization of Reaction Conditions[a]

entry	catalyst	solvent	temp (°C)	yield[b] (%)
1	CuCl	H_2O	100	46
2	$CuCl_2·2H_2O$	H_2O	100	10
3	CH_3COOCu	H_2O	100	50
4	$Cu(CH_3COO)_2·H_2O$	H_2O	100	63
5	$Cu(acac)_2$	H_2O	100	85
6	nano Cu	H_2O	100	70
7	nano CuO	H_2O	100	92 (89)[e]
8	CuO	H_2O	100	72
9	Cu_2O	H_2O	100	35
10		H_2O	100	
11	nano CuO	DMF	100	61
12	nano CuO	toluene	100	trace
13	nano CuO	EtOH	80	65
14	nano CuO	H_2O	90	82
15	nano CuO	H_2O	80	73
16[c]	nano CuO	H_2O	100	91
17[d]	nano CuO	H_2O	100	73

[a]Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), **3a** (0.75 mmol), catalyst (0.05 mmol), and solvent (1.5 mL) were reacted in an oil bath under air for 45 min. [b]Determined by GC and dodecane as an internal standard. [c]The amount of catalyst was 0.075 mmol. [d]The amount of catalyst was 0.025 mmol. [e]Isolated yield.

Having optimized reaction conditions in hand, we first explored the scope of the three-component reaction with various boronic acid substrates (Scheme 2). It was found that arylboronic acids bearing electron-neutral (**4a**), electron-donating (**4b**−**4d**, **4j**, **4k**, and **4n**), and electron-withdrawing groups (**4e**−**4h**, **4l**, **4m**, and **4o**) at different positions of the aryl ring were tolerated under the reaction conditions, and the corresponding 1,4-diketones were obtained in good yields (73%−89%). Compared with the excellent results of *para*- and *meta*-substituted arylboronic acids, *ortho*-substituted arylboronic acids led to slightly lower yields, possibly because of the electronic factors and steric hindrance of *ortho*-substituents. Di- and trisubstituted arylboronic acids were also explored with satisfactory yields (**4p**−**4r**). Moreover, the (4-Boc-aminophenyl)boronic acid (**3i**) gave the product **4i** in lower yield (23%) due to the poor solubility of **3i**. 2-Naphthylboronic acid remained unaffected, providing product **4s** in high yield (88%), while 2-furylboronic acid led to **4t** in relatively lower yield (68%). The catalytic system was well suited for the styryl and cyclohexylboronic acids too, and affording **4u** and **4v** in 79% and 43% yields, respectively. However, alkyl boronic acids like 1-hexylboronic acid and methylboronic acids do not react under optimized reaction conditions.

We then investigated the substrate scope of α-ketoaldehydes and 1,3-dicarbonyl compounds (Scheme 3), respectively. Various 1,3-dicarbonyl compounds containing a broad range of functional groups such as ether, ester, cyclopropyl, and allyl underwent the three-component reaction with **1a** and **3a** smoothly and gave the corresponding 1,4-diketones in moderate to good yields (**5a**−**5f**, 58%−80%). Aromatic 1,3-dicarbonyl compounds were also tested for the MCRs. However, 1-phenyl-1,3-butanedione was explored with moderate yields, while only a trace of the product was detected when ethyl benzoylacetate was used (**5g** and **5h**). Moreover, changing the electrophile to either methylglyoxal (**1b**) or arylglyoxal (**1c**) did not affect the reaction. Both **1b** and **1c** reacted well with **2a** and **3a** and give products **5i** and **5j** in the yields of 86% and 84%, respectively. Ethyl cyanoacetate was effectively employed as suitable substrates for this MCR and produced the corresponding products in moderate yields (**5k**). When methylglyoxal and ethyl 3-oxo-3-phenylpropanoate were employed, the three-component reaction product (**5l**) was afforded in 39% yield. For unsymmetrical malonate compounds, the diastereoselectivities of most reactions were 52:48 to 68:32. Notably, **5d** and **5e** were produced with a high diastereoselectivity (dr > 20:1), which could be due to the steric hindrance of cyclopropyl and ethyl.

In order to confirm the robustness and utility of this multicomponent process, a gram-scale reaction of methylglyoxal (**1b**, 30 mmol), acetylacetone (**2a**, 20 mmol), and phenylboronic acid (**3a**, 30 mmol) were performed under the standard conditions. A total of 3.8 g of compound **5i** was obtained in 83% yield (Scheme 4a), which was comparable with the small-scale reaction. It was worth mentioning that the

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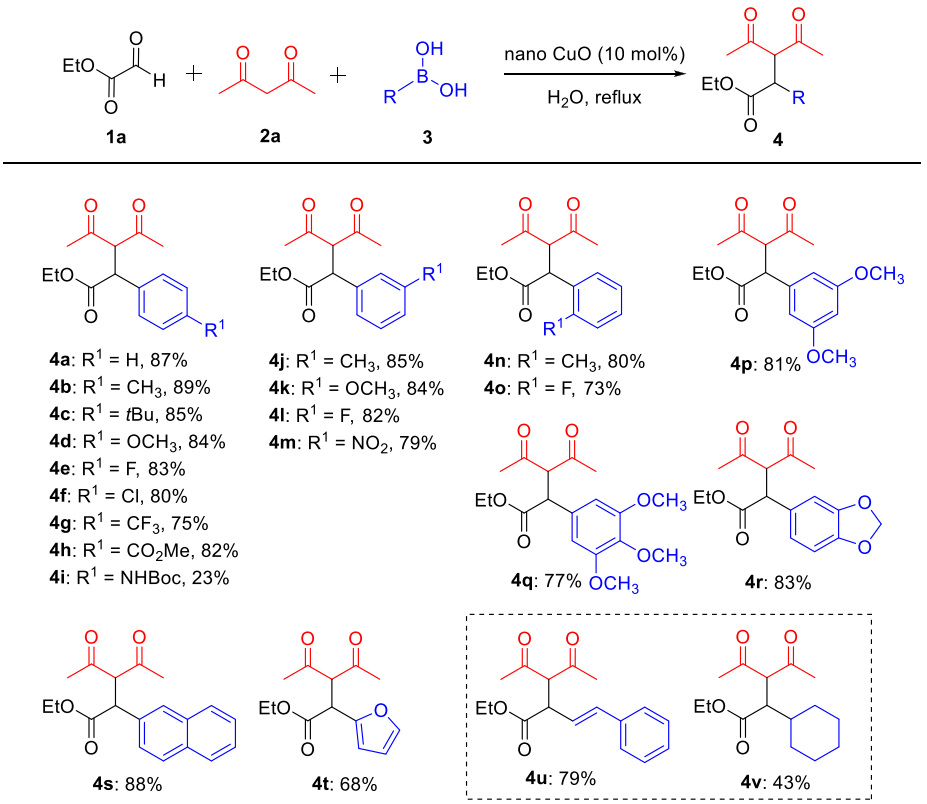
Scheme 2. Substrate Scope of Boronic Acids[a]



[a]Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), **3** (0.75 mmol), nano CuO (0.05 mmol), and H_2O (1.5 mL) were reacted in an oil bath under air. Yields of the isolated products are given.

three-component reaction products can be widely applied to the construction of various heterocyclic skeletons. For example, the 1,3-dicarbonyl compound of **4a** could be easily cyclized with hydrazine hydrate to afford pyrazole **6a** in 85% yield, and the corresponding isoxazole **6b** was readily obtained in 92% yield by condensation of **4a** with hydroxyamine hydrochloride in ethanol (Scheme 4b).[20] With the formed 1,4-diketone **5i**, a plethora of useful transformations were also easily conducted (Scheme 4c). Through the Paal–Knorr reaction,[5b] **5i** could directly react with phenylamine in water to produce a pyrrole **7a** in a yield of 75%, while treating **5i** in ethanol for 3 h in the presence of a catalytic amount of 4-toluene sulfonic acid (PTSA) gave a furan **7b** in 86% yield. In addition, in the presence of one equivalent of K_2CO_3, **5i** could be converted smoothly to **7c** in 62% yield using ethanol as a solvent.[21] Subsequently, we successfully performed Paal–Knorr reaction of the 1,4-diketones **7c** to deliver the corresponding pyrrole **8a** and furan **8b** in high yields.

To understand the mechanism of the reaction, some control experiments were carried out. Initially, we performed the reaction of **1a** with **2a** without the presence of phenylboronic acid **3a** under the standard conditions (Scheme 5a). We found that the intermediate **4a′** was isolated in a yield of 95%. Moreover, **4a′** was also isolated in the yields of about 93% in the absence of CuO. Next, the treatment of the intermediate **4a′** under the standard conditions could give the expected product **4a** in 92% yield (Scheme 5b). These results indicated that **4a′** is the key intermediate during this process, and the initial condensation reaction between **1a** and **2a** yielding **4a′** could be performed effectively in the absence of a catalyst.

The probable mechanism of this three-component reaction via a CuO-catalyzed tandem Aldol–Michael addition reaction was depicted in Scheme 6. Initially, the active methylene of **2a** is converted to enolate **2a′**, the formation of which is accelerated in water.[22] Undergoing an aldol-type addition, **2a′** reacts with α-ketoaldehyde **1a** to afford intermediate **A**, which is then dehydrated to give the intermediate **B**. At the same time, the reaction between boronic acid **3a** and the CuO NPs readily take place to deliver the intermediate **C**. Whereafter, coordination of copper catalyst with the carbonyl group of the intermediate **B** to produce an intermediate **D**. The aryl moiety of the boronic acid is migrated from the CuO NPs to give the intermediate **E** through a Michael-type reaction. The requirement of a coordinating atom on the aldehyde fragment would activate the CuO NPs and bringing it in close proximity to the electrophilic center. Subsequently, protonation followed by tautomerism affords the desired product **4a** and regenerates the active CuO NPs for the next catalytic cycle.

In summary, we reported a CuO-catalyzed three-component reaction of α-ketoaldehyde, 1,3-dicarbonyl compound, and organic boronic acid to give 1,4-diketones in good to excellent yields by using water as the solvent. The method has the advantages of a simple reaction setup, avoiding the use of organic solvents, wide substrate scope, and gram-scale synthesis. In addition, the generated products exhibited extensive application in the preparation of diverse heterocyclic compounds such as substituted furans, pyrroles, pyrazoles, and isoxazoles. Future efforts on the control of enantioselectivity in the process, as well as the extension of the range of aldehydes

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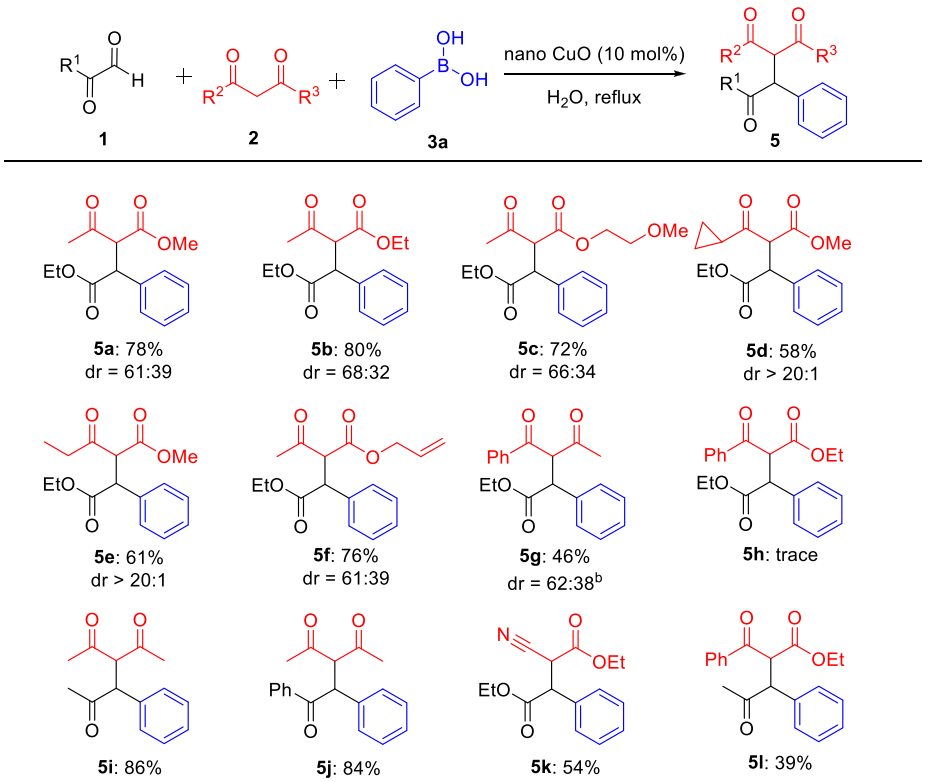
Scheme 3. Substrate Scope of α-Ketoaldehydes and 1,3-Dicarbonyl Compounds[a]



[a]Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol), **3a** (0.75 mmol), nano CuO (0.05 mmol), and H_2O (1.5 mL) were reacted in an oil bath under air. Yields of the isolated products are given, and diastereomeric ratios were determined by ^1H NMR. [b]Diastereomeric ratios were calculated from the yields of the separated diastereomeric products.

and organoboron reagents, are undergoing and will be reported in due course.

EXPERIMENTAL SECTION

General Information. All reactions involving water as a solvent were carried out in a moisture-free environment. Chemicals and solvents were procured from commercial sources, and solvents were dried by using standard methods. Nano CuO was purchased from Aladdin (99.5% metals basis, 40 nm) and used as received. Nano Cu was purchased from Aladdin (99.9% metals basis, 80−100 nm) and used as received. Melting points were recorded on an EZ-melt MPA120 (Stanford Research Systems, Inc., USA) and are uncorrected. The preparative thin-layer chromatography plates used were HSGF 254 plates (thickness of coating: 0.4−0.5 mm, 20 cm × 20 cm, Huanghai from Yantai, Shandong province, China). The ^1H NMR and $^{13}C\{^1H\}$ NMR spectra were recorded on a Bruker AM-400 spectrometer (400 and 100 MHz, respectively) using TMS as an internal standard. $CDCl_3$ was used as the NMR solvent for 1,4-dicarbonyl compounds in most cases. Chemical shifts were recorded in parts per million (d) relative to $CDCl_3$ at 7.26 for ^1H NMR and 77.23 for $^{13}C\{^1H\}$ NMR. Gas chromatography−mass spectrometry (GC−MS) was performed on an Agilent 7890A/5975C gas chromatograph. Gas chromatograms (GC) were recorded on an Agilent 7890A gas chromatograph.

General Procedure to Prepare 1,4-Dicarbonyl Compounds. A 10 mL sealed tube equipped with a stirring bar was charged with α-ketoaldehyde (0.6 mmol), 1,3-dicarbonyl compound (0.5 mmol), organic boronic acid (0.75 mmol), catalyst (0.05 mmol, 10 mol %), and H_2O (1.5 mL). The resulting solution was stirred at 100 °C for 45−210 min. Upon completion, the mixture was cooled to room temperature and then extracted with ethyl acetate (5 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified silica gel column chromatography using ethyl acetate and petroleum ether as the eluent to obtain the desired product. The products were further characterized by HRMS (EI), ^1H NMR, and $^{13}C\{^1H\}$ NMR.

Gram-Scale Preparation of 5i. A 150 mL flask equipped with a stirring bar was charged with methylglyoxal **1b** (1.585 g, 22 mmol, 1.1 equiv), acetylacetone **2a** (2.002 g, 20 mmol, 1.0 equiv), phenylboronic acid **3a** (2.926 g, 24 mmol, 1.2 equiv), nano CuO (159.09 mg, 2.0 mmol, 10 mol %), and H_2O (40 mL). The resulting solution was stirred at 100 °C for 60 min. Upon completion, the mixture was directly purified by flash column chromatography to provide **5i** as a yellow solid (3.855 g, 83% yield). The analytical data of the gram-scale reaction of **5i** were consistent with those of the 0.50 mmol scale experiment.

Ethyl 3-Acetyl-4-oxo-2-phenylpentanoate (4a): eluent = petroleum ether/ethyl acetate (3:1), white solid, 87% yield (114.1 mg); mp 101.4−102.6 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.25 (m, 5H), 4.63 (d, J = 11.8 Hz, 1H), 4.39 (d, J = 11.8 Hz, 1H), 4.14 (dq, J = 10.8, 7.1 Hz, 1H), 4.03 (dq, J = 10.8, 7.1 Hz, 1H), 2.29 (s, 3H), 1.90 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.8, 201.5, 172.1, 135.2, 129.1 (2C), 128.3 (2C), 128.1, 71.2, 61.5, 50.8, 30.3, 29.9, 13.9; HRMS (EI-TOF, m/z) calcd for $C_{15}H_{18}O_4$ $[M]^+$ 262.1205, found 262.1206.

Ethyl 3-Acetyl-4-oxo-2-(*p*-tolyl)pentanoate (4b): eluent = petroleum ether/ethyl acetate (3:1), white solid, 89% yield (123.0 mg); mp 94.9−95.7 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17−7.09 (m, 4H), 4.61 (d, J = 11.8 Hz, 1H), 4.35 (d, J = 11.8 Hz, 1H), 4.13 (dq, J = 10.8, 7.1 Hz, 1H), 4.01 (dq, J = 10.8, 7.1 Hz, 1H), 2.31 (s, 3H), 2.28 (s, 3H), 1.91 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.9, 201.7, 172.2, 137.9, 132.1, 129.8 (2C), 128.1 (2C), 71.3, 61.4, 50.4, 30.2, 29.9, 21.1, 13.9; HRMS (EI-TOF, m/z) calcd for $C_{16}H_{20}O_4$ $[M]^+$ 276.1362, found 276.1361.

Ethyl 3-Acetyl-2-(4-(*tert*-butyl)phenyl)-4-oxopentanoate (4c): eluent = petroleum ether/ethyl acetate (2:1), white solid, 85% yield (135.3 mg); mp 96.1−97.3 °C; ^1H NMR (400 MHz, $CDCl_3$) δ

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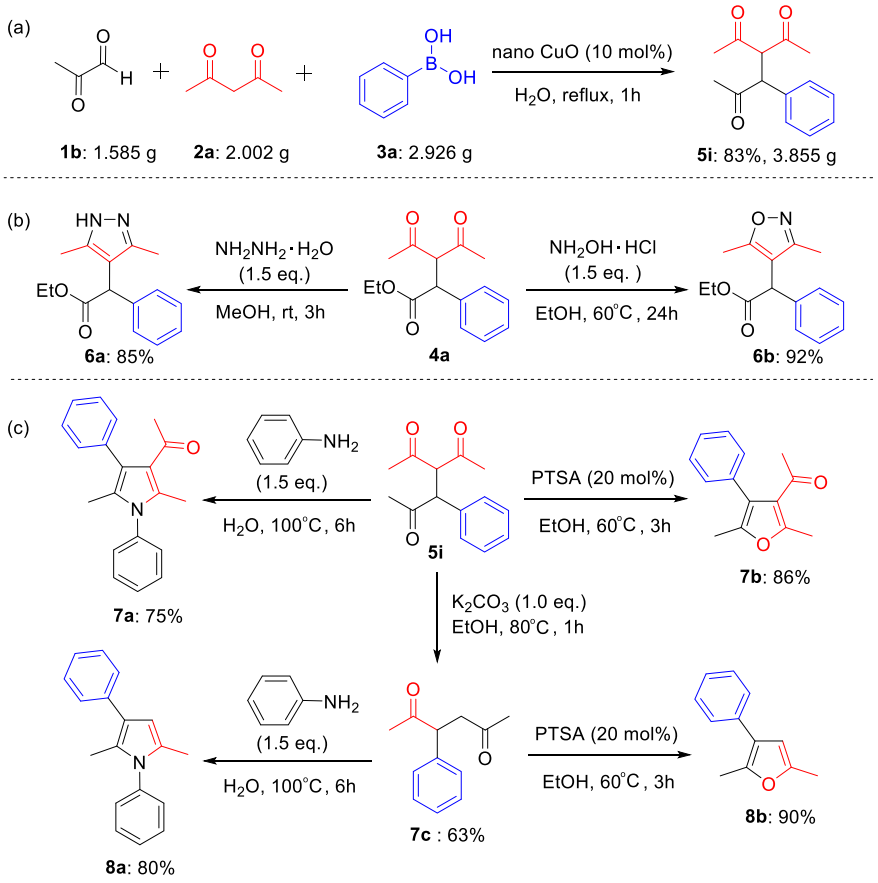
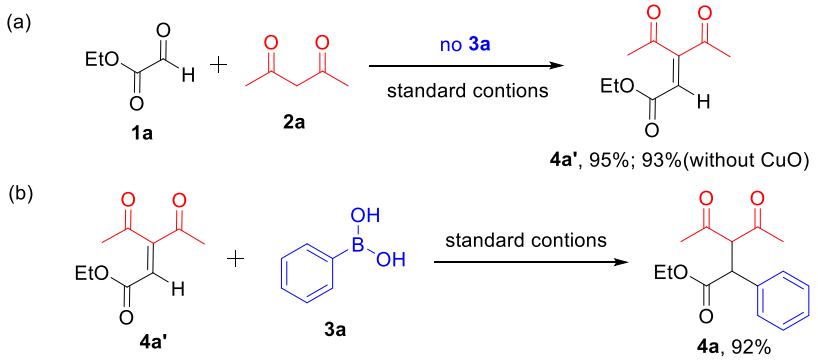
Scheme 4. Gram-Scale Reaction and Derivatization



Scheme 5. Some Control Experiments



7.35−7.29 (m, 2H), 7.20−7.15 (m, 2H), 4.62 (d, J = 11.8 Hz, 1H), 4.36 (d, J = 11.8 Hz, 1H), 4.15 (dq, J = 10.8, 7.1 Hz, 1H), 4.01 (dq, J = 10.8, 7.1 Hz, 1H), 2.28 (s, 3H), 1.90 (s, 3H), 1.28 (s, 9H), 1.17 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 202.0, 201.7, 172.2, 151.0, 131.9, 127.9 (2C), 126.0 (2C), 71.3, 61.4, 50.3, 34.5, 31.2 (3C), 30.2, 29.9, 14.0; HRMS (EI-TOF, m/z) calcd for $C_{19}H_{26}O_4$ $[M]^+$ 318.1831, found 318.1832.

Ethyl 3-Acetyl-2-(4-methoxyphenyl)-4-oxopentanoate (4d): eluent = petroleum ether/ethyl acetate (2:1), white solid, 84% yield (122.8 mg); mp 78.3−80.7 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21−7.16 (m, 2H), 6.87−6.82 (m, 2H), 4.59 (d, J = 11.8 Hz, 1H), 4.33 (d, J = 11.8 Hz, 1H), 4.13 (dq, J = 10.8, 7.1 Hz, 1H), 4.02 (dq, J = 10.8, 7.1 Hz, 1H), 3.78 (s, 3H), 2.28 (s, 3H), 1.92 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 202.0, 201.6, 172.3, 159.3, 129.3 (2C), 127.0, 114.5 (2C), 71.3, 61.4, 55.2, 50.0, 30.3, 29.9, 13.9; HRMS (EI-TOF, m/z) calcd for $C_{16}H_{20}O_5$ $[M]^+$ 292.1311, found 292.1310.

Ethyl 3-Acetyl-2-(4-fluorophenyl)-4-oxopentanoate (4e): eluent = petroleum ether/ethyl acetate (3:1), white solid, 83% yield (116.3 mg); mp 97.5−99.1 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27−7.22 (m, 2H), 7.05−6.98 (m, 2H), 4.59 (d, J = 11.8 Hz, 1H), 4.38 (d, J = 11.8 Hz, 1H), 4.13 (dq, J = 10.8, 7.1 Hz, 1H), 4.03 (dq, J = 10.8, 7.1 Hz, 1H), 2.29 (s, 3H), 1.93 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.4, 201.2, 171.9 (d, J_{CF} = 0.6 Hz), 162.4 (d, J_{CF} = 247.5 Hz), 131.0 (d, J_{CF} = 3.3 Hz), 129.9 (d, J_{CF} = 8.2 Hz), 116.1 (d, J_{CF} = 21.6 Hz), 71.2, 61.6, 50.0, 30.4, 29.9, 13.9; HRMS (EI-TOF, m/z) calcd for $C_{15}H_{17}FO_4$ $[M]^+$ 280.1111, found 280.1110.

Ethyl 3-Acetyl-2-(4-chlorophenyl)-4-oxopentanoate (4f): eluent = petroleum ether/ethyl acetate (3:1), white solid, 80% yield (118.7 mg); mp 95.1−96.3 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.27 (m, 2H), 7.24−7.18 (m, 2H), 4.59 (d, J = 11.7 Hz, 1H), 4.38 (d, J = 11.7 Hz, 1H), 4.13 (dq, J = 10.8, 7.1 Hz, 1H), 4.03 (dq, J = 10.8, 7.1 Hz, 1H), 2.30 (s, 3H), 1.94 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H);

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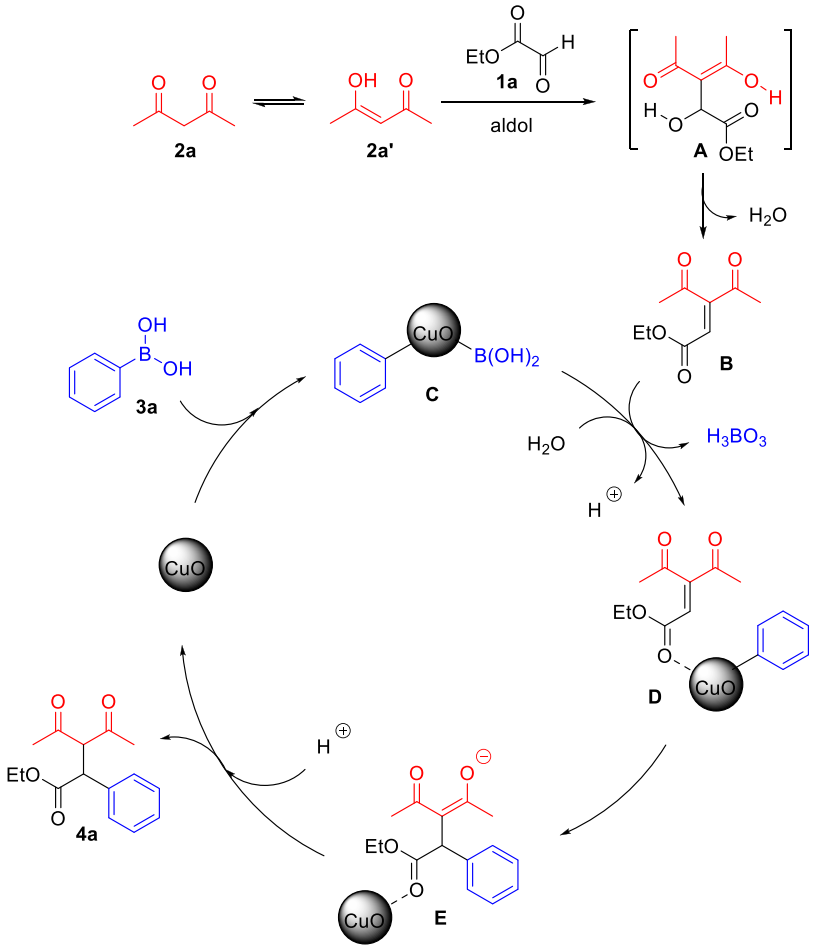
Scheme 6. Proposed Mechanism



$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.2, 201.1, 171.7, 134.1, 133.8, 129.6 (2C), 129.3 (2C), 71.1, 61.7, 50.2, 30.4, 29.9, 13.9; HRMS (EI-TOF, m/z) calcd for $C_{15}H_{17}{}^{35}ClO_4$ $[M]^+$ 296.0815, found 296.0818; HRMS (EI-TOF, m/z) calcd for $C_{15}H_{17}{}^{37}ClO_4$ $[M]^+$ 298.0786, found 298.0785.

Ethyl 3-Acetyl-4-oxo-2-(4-(trifluoromethyl)phenyl)-pentanoate (4g): eluent = petroleum ether/ethyl acetate (3:1), white solid, 75% yield (123.9 mg); mp 113.0−114.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.25 (m, 5H), 4.63 (d, J = 11.8 Hz, 1H), 4.39 (d, J = 11.8 Hz, 1H), 4.14 (dq, J = 10.8, 7.1 Hz, 1H), 4.03 (dq, J = 10.8, 7.1 Hz, 1H), 2.29 (s, 3H), 1.90 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 199.9, 199.8, 170.4, 138.3 (d, J_{CF} = 1.2 Hz, 2C), 129.4 (q, J_{CF} = 32.7 Hz), 127.8, 125.0 (q, J_{CF} = 3.8 Hz, 2C), 122.8 (q, J_{CF} = 272.2 Hz), 70.0, 60.8, 49.6, 29.4, 29.0, 12.9; HRMS (EI-TOF, m/z) calcd for $C_{16}H_{17}F_3O_4$ $[M]^+$ 330.1079, found 330.1083.

Methyl 4-(3-Acetyl-1-ethoxy-1,4-dioxopentan-2-yl)-benzoate (4h): eluent = petroleum ether/ethyl acetate (3:1), white solid, 82% yield (131.3 mg); mp 109.1−110.2 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03−7.95 (m, 2H), 7.39−7.33 (m, 2H), 4.64 (d, J = 11.7 Hz, 1H), 4.47 (d, J = 11.7 Hz, 1H), 4.13 (dq, J = 10.8, 7.1 Hz, 1H), 4.04 (dq, J = 10.8, 7.1 Hz, 1H), 3.91 (s, 3H), 2.31 (s, 3H), 1.93 (s, 3H), 1.15 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.1, 201.0, 171.5, 166.5, 140.3, 130.3 (2C), 130.0, 128.4 (2C), 70.9, 61.8, 52.2, 50.8, 30.5, 30.0, 13.9; HRMS (EI-TOF, m/z) calcd for $C_{17}H_{20}O_6$ $[M]^+$ 320.1260, found 320.1255.

Ethyl 3-Acetyl-2-(4-((*tert*-butoxycarbonyl)amino)phenyl)-4-oxopentanoate (4i): eluent = petroleum ether/ethyl acetate (2:1), white solid, 23% yield (43.4 mg); mp 158.3−159.7 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.5 Hz, 2H), 7.21−7.15 (m, 2H), 6.61 (s, 1H), 4.60 (d, J = 11.8 Hz, 1H), 4.33 (d, J = 11.8 Hz, 1H), 4.12 (dq, J = 10.8, 7.1 Hz, 1H), 4.01 (dq, J = 10.8, 7.1 Hz, 1H), 2.28 (s, 3H), 1.92 (s, 3H), 1.51 (s, 9H), 1.15 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.8, 201.6, 172.2, 152.6, 138.3, 129.4, 128.9 (2C), 118.9 (2C), 80.8, 71.2, 61.5, 50.2, 30.4, 29.9, 28.3 (3C), 13.9; HRMS (EI-TOF, m/z) calcd for $C_{20}H_{27}NO_6$ $[M]^+$ 377.1838, found 377.1837.

Ethyl 3-Acetyl-4-oxo-2-(*m*-tolyl)pentanoate (4j): eluent = petroleum ether/ethyl acetate (3:1), white solid, 85% yield (117.4 mg); mp 104.6−105.4 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23−7.16 (m, 1H), 7.07 (t, J = 8.1 Hz, 3H), 4.62 (d, J = 11.8 Hz, 1H), 4.34 (d, J = 11.8 Hz, 1H), 4.14 (dq, J = 10.8, 7.1 Hz, 1H), 4.02 (dq, J = 10.8, 7.1 Hz, 1H), 2.32 (s, 3H), 2.28 (s, 3H), 1.91 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.9, 201.6, 172.2, 138.8, 135.0, 128.9 (2C), 128.9, 125.3, 71.3, 61.5, 50.8, 30.3, 29.9, 21.4, 13.9; HRMS (EI-TOF, m/z) calcd for $C_{16}H_{20}O_4$ $[M]^+$ 276.1362, found 276.1363.

Ethyl 3-Acetyl-2-(3-methoxyphenyl)-4-oxopentanoate (4k): eluent = petroleum ether/ethyl acetate (2:1), white solid, 84% yield (122.8 mg); mp 79.5−80.9 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, J = 11.9, 4.0 Hz, 1H), 6.87−6.78 (m, 3H), 4.61 (d, J = 11.8 Hz, 1H), 4.35 (d, J = 11.8 Hz, 1H), 4.19−4.10 (m, 1H), 4.03 (dq, J = 10.8, 7.1 Hz, 1H), 3.79 (s, 3H), 2.29 (s, 3H), 1.93 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.7, 201.5, 172.0, 160.0, 136.6, 130.1, 120.5, 114.1, 113.5, 71.2, 61.5, 55.2, 50.8, 30.4, 29.9, 13.9; HRMS (EI-TOF, m/z) calcd for $C_{16}H_{20}O_5$ $[M]^+$ 292.1311, found 292.1315.

Ethyl 3-Acetyl-2-(3-fluorophenyl)-4-oxopentanoate (4l): eluent = petroleum ether/ethyl acetate (3:1), white solid, 82% yield (114.9 mg); mp 99.6−101.3 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.27 (m, 1H), 7.07−6.95 (m, 3H), 4.60 (d, J = 11.7 Hz, 1H), 4.40 (d, J = 11.7 Hz, 1H), 4.14 (dq, J = 10.8, 7.1 Hz, 1H), 4.04 (dq, J

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= 10.8, 7.1 Hz, 1H), 2.30 (s, 3H), 1.95 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.2, 201.1, 171.6, 162.9 (d, J_{CF} = 247.6 Hz), 137.6 (d, J_{CF} = 7.3 Hz), 130.6 (d, J_{CF} = 8.3 Hz), 124.1 (d, J_{CF} = 3.0 Hz), 115.3 (d, J_{CF} = 22.1 Hz), 115.2 (d, J_{CF} = 21.0 Hz), 71.1, 61.7, 50.5 (d, J_{CF} = 1.6 Hz), 30.4, 29.9, 13.9; HRMS (EI-TOF, m/z) calcd for $C_{15}H_{17}FO_4$ $[M]^+$ 280.1111, found 280.1112.

Ethyl 3-Acetyl-2-(3-nitrophenyl)-4-oxopentanoate (4m): eluent = petroleum ether/ethyl acetate (3:2), white solid, 79% yield (121.4 mg); mp 119.2−120.1 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26−8.10 (m, 2H), 7.64 (dd, J = 5.1, 3.9 Hz, 1H), 7.57−7.51 (m, 1H), 4.69 (d, J = 11.7 Hz, 1H), 4.56 (d, J = 11.7 Hz, 1H), 4.16 (dq, J = 10.8, 7.1 Hz, 1H), 4.05 (dq, J = 10.8, 7.1 Hz, 1H), 2.36 (s, 3H), 2.01 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 200.6, 200.4, 171.1, 148.6, 137.5, 134.8, 130.1, 123.2, 123.1, 70.9, 62.0, 50.6, 30.5, 30.2, 13.9; HRMS (EI-TOF, m/z) calcd for $C_{15}H_{17}NO_6$ $[M]^+$ 307.1056, found 307.1067.

Ethyl 3-Acetyl-4-oxo-2-(*o*-tolyl)pentanoate (4n): eluent = petroleum ether/ethyl acetate (3:1), white viscous liquid, 80% yield (110.5 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.25−7.21 (m, 1H), 7.20−7.12 (m, 3H), 4.77−4.68 (m, 2H), 4.11 (dq, J = 10.8, 7.1 Hz, 1H), 3.99 (dq, J = 10.8, 7.1 Hz, 1H), 2.45 (s, 3H), 2.31 (s, 3H), 1.88 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.7, 201.4, 172.5, 137.1, 133.7, 131.2, 127.9, 126.8, 126.5, 70.4, 61.4, 45.9, 30.6, 30.0, 19.9, 13.9; HRMS (EI-TOF, m/z) calcd for $C_{16}H_{20}O_4$ $[M]^+$ 276.1362, found 276.1364.

Ethyl 3-Acetyl-2-(2-fluorophenyl)-4-oxopentanoate (4o): eluent = petroleum ether/ethyl acetate (3:1), white solid, 73% yield (102.3 mg); mp 50.7−51.9 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30−7.23 (m, 2H), 7.14−7.03 (m, 2H), 4.77 (d, J = 11.7 Hz, 1H), 4.65 (d, J = 11.7 Hz, 1H), 4.15−4.03 (m, 2H), 2.33 (s, 3H), 1.97 (s, 3H), 1.15 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.4, 201.3, 171.3, 160.5 (d, J_{CF} = 247.5 Hz), 130.2 (d, J_{CF} = 3.6 Hz), 129.9 (d, J_{CF} = 8.3 Hz), 124.7 (d, J_{CF} = 3.6 Hz), 122.6 (d, J_{CF} = 14.8 Hz), 116.0 (d, J_{CF} = 22.1 Hz), 70.1 (d, J_{CF} = 1.1 Hz), 61.7, 44.4 (d, J_{CF} = 1.6 Hz), 30.1, 29.3, 13.9; HRMS (EI-TOF, m/z) calcd for $C_{15}H_{17}FO_4$ $[M]^+$ 280.1111, found 280.1110.

Ethyl 3-Acetyl-2-(3,5-dimethoxyphenyl)-4-oxopentanoate (4p): eluent = petroleum ether/ethyl acetate (2:1), white solid, 81% yield (130.6 mg); mp 100.6−102.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.40 (d, J = 2.2 Hz, 2H), 6.36 (t, J = 2.2 Hz, 1H), 4.60 (d, J = 11.8 Hz, 1H), 4.30 (d, J = 11.8 Hz, 1H), 4.15 (dq, J = 10.8, 7.1 Hz, 1H), 4.04 (dq, J = 10.8, 7.1 Hz, 1H), 3.77 (s, 6H), 2.28 (s, 3H), 1.96 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.7, 201.4, 171.9, 161.1 (2C), 137.3, 106.4 (2C), 99.9, 71.1, 61.5, 55.4 (2C), 51.0, 30.4, 29.9, 13.9; HRMS (EI-TOF, m/z) calcd for $C_{17}H_{22}O_6$ $[M]^+$ 322.1416, found 322.1417.

Ethyl 3-Acetyl-4-oxo-2-(3,4,5-trimethoxyphenyl)-pentanoate (4q): eluent = petroleum ether/ethyl acetate (2:1), white solid, 77% yield (135.7 mg); mp 121.2−122.3 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.46 (s, 2H), 4.61 (d, J = 11.7 Hz, 1H), 4.30 (d, J = 11.7 Hz, 1H), 4.17 (dq, J = 10.8, 7.1 Hz, 1H), 4.10−4.02 (m, 1H), 3.84 (s, 6H), 3.82 (s, 3H), 2.28 (s, 3H), 1.96 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.8, 201.3, 172.0, 153.5 (2C), 137.7, 130.5, 105.3 (2C), 71.1, 61.6, 60.8, 56.2 (2C), 50.9, 30.5, 29.9, 14.0; HRMS (EI-TOF, m/z) calcd for $C_{18}H_{24}O_7$ $[M]^+$ 352.1522, found 352.1523.

Ethyl 3-Acetyl-2-(benzo[*d*][1,3]dioxol-5-yl)-4-oxopentanoate (4r): eluent = petroleum ether/ethyl acetate (5:2), yellow solid, 83% yield (127.1 mg); mp 91.3−92.6 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.73 (ddd, J = 9.6, 8.4, 1.5 Hz, 3H), 5.95 (q, J = 1.5 Hz, 2H), 4.56 (d, J = 11.8 Hz, 1H), 4.29 (d, J = 11.8 Hz, 1H), 4.13 (ddd, J = 14.3, 9.0, 5.4 Hz, 1H), 4.03 (dq, J = 10.8, 7.1 Hz, 1H), 2.28 (s, 3H), 1.97 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.7, 201.5, 172.1, 148.2, 147.5, 128.6, 121.8, 108.7, 108.4, 101.3, 71.3, 61.5, 50.4, 30.3, 29.9, 14.0; HRMS (EI-TOF, m/z) calcd for $C_{16}H_{18}O_6$ $[M]^+$ 306.1103, found 306.1101.

Ethyl 3-Acetyl-2-(naphthalen-2-yl)-4-oxopentanoate (4s): eluent = petroleum ether/ethyl acetate (3:1), white solid, 88% yield (137.4 mg); mp 109.0−110.7 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, J = 8.7, 2.7 Hz, 3H), 7.73 (d, J = 1.2 Hz, 1H), 7.53−7.45 (m, 2H), 7.40 (dd, J = 8.5, 1.8 Hz, 1H), 4.76 (d, J = 11.8 Hz, 1H), 4.57 (d, J = 11.8 Hz, 1H), 4.15 (dq, J = 10.8, 7.1 Hz, 1H), 4.02 (dq, J = 10.8, 7.1 Hz, 1H), 2.33 (s, 3H), 1.90 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.7, 201.5, 172.1, 133.4, 132.9, 132.6, 129.0, 128.0, 127.7(0), 127.6(5), 126.6, 126.4, 125.7, 71.2, 61.6, 51.0, 30.4, 30.0, 13.9; HRMS (EI-TOF, m/z) calcd for $C_{19}H_{20}O_4$ $[M]^+$ 312.1362, found 312.1363.

Ethyl 3-Acetyl-2-(furan-2-yl)-4-oxopentanoate (4t): eluent = petroleum ether/ethyl acetate (3:1), white solid, 68% yield (85.8 mg); mp 49.1−50.2 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 1.2 Hz, 1H), 6.32 (dd, J = 3.2, 1.9 Hz, 1H), 6.22 (d, J = 3.2 Hz, 1H), 4.66 (d, J = 11.7 Hz, 1H), 4.58 (d, J = 11.7 Hz, 1H), 4.20−4.06 (m, 2H), 2.29 (s, 3H), 2.04 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.4, 201.2, 169.8, 148.3, 142.7, 110.9, 108.8, 68.6, 61.9, 44.7, 29.9, 29.5, 14.0; HRMS (EI-TOF, m/z) calcd for $C_{13}H_{16}O_5$ $[M]^+$ 252.0998, found 252.0999.

Ethyl (*E*)-3-Acetyl-4-oxo-2-styrylpentanoate (4u): eluent = petroleum ether/ethyl acetate (3:2), yellow solid, 79% yield (113.9 mg); mp 65.9−66.8 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.25 (m, 5H), 4.63 (d, J = 11.8 Hz, 1H), 4.39 (d, J = 11.8 Hz, 1H), 4.13 (dq, J = 10.8, 7.1 Hz, 1H), 4.07−3.98 (m, 1H), 2.29 (s, 3H), 1.90 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.8, 201.7, 171.8, 135.9, 135.2, 128.7 (2C), 128.2, 126.5 (2C), 122.6, 70.2, 61.6, 48.6, 30.0, 29.8, 14.1; HRMS (EI-TOF, m/z) calcd for $C_{17}H_{20}O_4$ $[M]^+$ 288.1362, found 288.1360.

Ethyl 3-Acetyl-2-cyclohexyl-4-oxopentanoate (4v): eluent = petroleum ether/ethyl acetate (1:1); yellow solid, 43% yield (57.7 mg); mp 48.3−50.7 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 4.26 (d, J = 11.5 Hz, 1H), 4.13 (pd, J = 7.6, 3.7 Hz, 2H), 3.24 (dd, J = 11.5, 2.4 Hz, 1H), 2.21 (s, 3H), 2.20 (s, 3H), 1.70 (dd, J = 28.2, 14.6 Hz, 4H), 1.35−1.23 (m, 6H), 1.23−1.04 (m, 3H), 0.90−0.80 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 202.7, 202.4, 172.5, 69.4, 60.6, 50.4, 38.8, 32.1, 29.9, 28.6(7), 28.6(5), 26.6, 26.3, 26.0, 14.2; HRMS (EI-TOF, m/z) calcd for $C_{15}H_{24}O_4$ $[M]^+$ 268.1675, found 268.1681.

4-Ethyl 1-Methyl 2-Acetyl-3-phenylsuccinate (5a): eluent = petroleum ether/ethyl acetate (3:1), white solid, 78% yield (108.5 mg); mp 69.3−71.7 °C; dr = 61:39; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.24 (m, 5H), 4.46−4.30 (m, 2H), 4.20−4.10 (m, 1H), 4.10−3.98 (m, 1H), 3.75 (s, 1.16H), 3.49 (s, 1.84H), 2.35 (s, 1.84H), 1.95 (s, 1.16H), 1.17 (dd, J = 13.3, 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.4, 200.9, 172.2, 172.1, 168.3, 167.2, 135.4, 135.1, 129.0, 128.8, 128.3, 128.2, 128.1, 127.9, 63.1, 61.7, 61.4, 52.8, 52.6, 50.4, 50.3, 31.6, 29.6, 14.0, 13.9; HRMS (EI-TOF, m/z) calcd for $C_{15}H_{18}O_5$ $[M]^+$ 278.1154, found 278.1155.

Diethyl 2-Acetyl-3-phenylsuccinate (5b): eluent = petroleum ether/ethyl acetate (3:1), white solid, 80% yield (116.9 mg); mp 71.5−72.8 °C; dr = 68:32; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.25 (m, 5H), 4.43−4.29 (m, 2H), 4.23−4.12 (m, 1.6H), 4.09−3.99 (m, 1H), 3.99−3.90 (m, 1.4H), 2.34 (s, 2.1H), 1.97 (s, 0.9H), 1.27 (t, J = 7.1 Hz, 0.9H), 1.17 (td, J = 7.1, 5.3 Hz, 3H), 0.99 (t, J = 7.1 Hz, 2.1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.4, 201.0, 172.3, 172.1, 167.8, 166.8, 135.4, 135.2, 129.0, 128.7, 128.4, 128.3, 128.1, 127.9, 63.2, 62.0, 61.9, 61.6, 61.4, 50.4, 50.2, 31.5, 29.4, 14.0(0), 13.9(6), 13.9, 13.8; HRMS (EI) calcd for $C_{16}H_{20}O_5$ $[M]^+$ 292.1311, found 292.1309.

4-Ethyl 1-(2-Methoxyethyl) 2-Acetyl-3-phenylsuccinate (5c): eluent = petroleum ether/ethyl acetate (2:1), white viscous liquid, 72% yield (116.0 mg); dr = 66:34; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.25 (m, 5H), 4.45 (dd, J = 11.6, 10.0 Hz, 1H), 4.38−4.27 (m, 1.7H), 4.19−4.11 (m, 1H), 4.11−3.97 (m, 2.4H), 3.65−3.53 (m, 0.8H), 3.37 (d, J = 3.4 Hz, 1.2H), 3.35−3.32 (m, 0.5H), 3.31−3.25 (m, 0.7H), 3.24 (s, 1.9H), 2.36 (s, 2H), 1.98 (s, 1H), 1.17 (td, J = 7.1, 3.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.2, 200.8, 172.2, 172.1, 167.9, 166.8, 135.4, 135.1, 129.0, 128.7, 128.4, 128.3, 128.1, 127.9, 70.1, 69.9, 64.6, 64.3, 63.1, 61.8, 61.4, 58.9, 58.8, 50.4, 50.2, 31.5, 29.5, 13.9; HRMS (EI-TOF, m/z) calcd for $C_{17}H_{22}O_6$ $[M]^+$ 322.1416, found 322.1412.

4-Ethyl 1-Methyl 2-(Cyclopropanecarbonyl)-3-phenylsuccinate (5d): eluent = petroleum ether/ethyl acetate (2:1), white viscous liquid, 58% yield (88.3 mg); dr > 20:1; ^1H NMR (400 MHz,

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$CDCl_3$) δ 7.32−7.26 (m, 5H), 4.56 (d, J = 11.6 Hz, 1H), 4.34 (d, J = 11.6 Hz, 1H), 4.13 (dq, J = 10.8, 7.1 Hz, 1H), 4.03 (dq, J = 10.8, 7.1 Hz, 1H), 3.50 (s, 3H), 2.18 (dq, J = 7.8, 4.5 Hz, 1H), 1.18−1.07 (m, 5H), 1.05−0.92 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 203.0, 172.1, 167.5, 135.4, 128.8 (2C), 128.3 (2C), 127.9, 63.4, 61.3, 52.5, 50.0, 20.3, 13.9, 12.1, 11.9; HRMS (EI-TOF, m/z) calcd for $C_{17}H_{20}O_5$ $[M]^+$ 304.1311, found 304.1310.

1-Ethyl 4-Methyl 2-Phenyl-3-propionylsuccinate (5e): eluent = petroleum ether/ethyl acetate (3:1), white viscous liquid, 61% yield (89.2 mg); dr >20:1; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.25 (m, 5H), 4.63 (d, J = 11.8 Hz, 1H), 4.39 (d, J = 11.8 Hz, 1H), 4.13 (dq, J = 10.8, 7.1 Hz, 1H), 4.07−3.98 (m, 1H), 2.29 (s, 3H), 1.90 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 203.7, 172.3, 167.4, 135.5, 128.8 (2C), 128.2 (2C), 127.9, 62.2, 61.4, 52.5, 50.3, 35.8, 13.9, 7.6; HRMS (EI-TOF, m/z) calcd for $C_{16}H_{20}O_5$ $[M]^+$ 292.1311, found 292.1310.

1-Allyl 4-Ethyl 2-Acetyl-3-phenylsuccinate (5f): eluent = petroleum ether/ethyl acetate (5:2), white solid, 76% yield (115.6 mg); mp 63.1−64.0 °C; dr = 61:39; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.26 (m, 5H), 5.89 (ddt, J = 16.2, 10.5, 5.7 Hz, 0.4H), 5.67−5.55 (m, 0.6H), 5.36−5.24 (m, 0.8H), 5.14−5.05 (m, 1.2H), 4.64 (d, J = 5.7 Hz, 0.7H), 4.49−4.31 (m, 3.3H), 4.19−4.10 (m, 1H), 4.04 (ddq, J = 14.2, 10.8, 7.1 Hz, 1H), 2.35 (s, 1.8H), 1.97 (s, 1.2H), 1.17 (td, J = 7.1, 3.5 Hz, 3H; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.3, 200.8, 172.2, 172.1, 167.5, 166.5, 135.4, 135.1, 131.3, 131.0, 129.0, 128.8, 128.4, 128.3, 128.1, 128.0, 119.0, 118.9, 66.3, 66.1, 63.2, 61.9, 61.4, 50.4, 50.2, 31.6, 29.5, 14.0, 13.9; HRMS (EI-TOF, m/z) calcd for $C_{17}H_{20}O_5$ $[M]^+$ 304.1311, found 304.1313.

Ethyl 3-Benzoyl-4-oxo-2-phenylpentanoate (5g): eluent = petroleum ether/ethyl acetate (3:1); total yield (46%, 74.6 mg). **5g**/**5g′** = 62:38. Compound **5g**: white solid; mp 94.3−95.7 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12−8.05 (m, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.7 Hz, 2H), 7.39−7.28 (m, 5H), 5.42 (d, J = 11.5 Hz, 1H), 4.66 (d, J = 11.5 Hz, 1H), 4.09 (dq, J = 10.8, 7.1 Hz, 1H), 4.00 (dq, J = 10.8, 7.1 Hz, 1H), 1.88 (s, 3H), 1.11 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.6, 194.3, 172.0, 136.3, 135.2, 133.9, 129.1 (2C), 128.9(2) (2C), 128.8(9) (2C), 128.5 (2C), 128.2, 66.5, 61.5, 51.4, 29.4, 13.9; HRMS (EI-TOF, m/z) calcd for $C_{20}H_{20}O_4$ $[M]^+$ 324.1362, found 324.1364. Compound **5g′**: white solid; mp 96.2−97.8 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82−7.74 (m, 2H), 7.51 (t, J = 7.4 Hz, 1H), 7.37 (t, J = 7.8 Hz, 2H), 7.25−7.19 (m, 2H), 7.18−7.05 (m, 3H), 5.48 (d, J = 11.4 Hz, 1H), 4.61 (d, J = 11.4 Hz, 1H), 4.20 (dq, J = 10.8, 7.1 Hz, 1H), 4.12−4.03 (m, 1H), 2.20 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 200.8, 194.2, 172.7, 136.8, 135.3, 133.7, 128.7(3) (2C), 128.7(2) (2C), 128.6 (2C), 128.4 (2C), 127.7, 65.2, 61.4, 51.4, 29.8, 14.0; HRMS (EI-TOF, m/z) calcd for $C_{20}H_{20}O_4$ $[M]^+$ 324.1362, found 324.1365.

3-Acetyl-4-phenylhexane-2,5-dione (5i): eluent = petroleum ether/ethyl acetate (3:1), yellow solid, 86% yield (99.9 mg); mp 99.6−101.3 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.28 (m, 3H), 7.24−7.17 (m, 2H), 4.63 (d, J = 11.4 Hz, 1H), 4.52 (d, J = 11.4 Hz, 1H), 2.28 (s, 3H), 2.08 (s, 3H), 1.88 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 205.9, 202.5, 201.7, 134.4, 129.4 (2C), 128.8 (2C), 128.3, 70.5, 58.7, 30.7, 30.2, 28.7; HRMS (EI-TOF, m/z) calcd for $C_{14}H_{16}O_3$ $[M - H_2O]^+$ 214.0994, found 214.0993.

3-Acetyl-1,2-diphenylpentane-1,4-dione (5j). eluent = petroleum ether/ethyl acetate (3:1), white solid, 84% yield (123.6 mg); mp 99.6−101.3 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99−7.88 (m, 2H), 7.46 (t, J = 7.4 Hz, 1H), 7.36 (t, J = 7.7 Hz, 2H), 7.31−7.26 (m, 4H), 7.24−7.17 (m, 1H), 5.37 (d, J = 11.1 Hz, 1H), 4.86 (d, J = 11.1 Hz, 1H), 2.28 (s, 3H), 1.92 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 203.2, 201.3, 197.7, 135.7, 135.2, 133.2, 129.4 (2C), 129.0 (2C), 128.8 (2C), 128.6 (2C), 128.0, 71.3, 53.8, 31.9, 30.2; HRMS (EI-TOF, m/z) calcd for $C_{19}H_{18}O_3$ $[M - H_2O]^+$ 276.1150, found 276.1149.

Diethyl 2-Cyano-3-phenylsuccinate (5k): eluent = petroleum ether/ethyl acetate (5:2), white viscous liquid, 54% yield (74.3 mg); dr = 59:41; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.29 (m, 5H), 4.37−4.10 (m, 5.6H), 3.94 (d, J = 7.6 Hz, 0.4H), 1.32 (t, J = 7.1 Hz, 1.8H), 1.21 (ddd, J = 12.1, 10.6, 6.0 Hz, 4.2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.6, 169.9, 164.8, 164.4, 133.7, 133.5, 129.3, 129.2, 129.0, 128.8, 128.4, 128.3, 115.1, 114.7, 63.4, 63.1, 62.2, 62.1, 51.1, 50.5, 41.5, 40.9, 14.0, 13.9(3), 13.9(0), 13.8; HRMS (EI-TOF, m/z) calcd for $C_{15}H_{17}NO_4$ $[M]^+$ 275.1158, found 275.1160.

Ethyl 2-Benzoyl-4-oxo-3-phenylpentanoate (5l): eluent = petroleum ether/ethyl acetate (3:1); total yield (39%, 63.3 mg). **5l**/**5l′** = 52:48. Compound **5l**: white solid; mp 89.6−90.8 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 7.4 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.7 Hz, 2H), 7.40−7.32 (m, 5H), 5.14 (d, J = 11.1 Hz, 1H), 4.79 (d, J = 11.1 Hz, 1H), 3.84 (dtt, J = 10.8, 7.4, 3.7 Hz, 2H), 2.18 (s, 3H), 0.88 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 205.8, 193.2, 167.9, 135.8, 134.5, 133.7, 129.1(2), 129.0(6), 128.9, 128.7, 128.2, 61.4, 58.5, 58.1, 28.9, 13.7; HRMS (EI-TOF, m/z) calcd for $C_{20}H_{20}O_4$ $[M]^+$ 324.1362, found 324.1360. Compound **5l′**: white solid; mp 90.4−91.8 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.4 Hz, 2H), 7.49 (t, J = 7.4 Hz, 1H), 7.35 (t, J = 7.7 Hz, 2H), 7.24−7.10 (m, 5H), 5.33 (d, J = 11.3 Hz, 1H), 4.77 (d, J = 11.3 Hz, 1H), 4.16 (dtt, J = 10.8, 7.1, 3.6 Hz, 2H), 2.20 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 206.6, 194.7, 168.4, 136.7, 134.1, 133.4, 128.9(9), 128.9(7), 128.8, 128.4, 128.0, 61.9, 58.4, 55.8, 29.1, 13.9; HRMS (EI-TOF, m/z) calcd for $C_{20}H_{20}O_4$ $[M]^+$ 324.1362, found 324.1363.

Derivatization of the Product 4a.[21] The analytical data of the gram-scale reaction of **5i** were consistent with those of the 0.50 mmol scale experiment. To a solution of **4a** (131.06 mg, 0.5 mmol, 1.0 equiv) in MeOH (1.5 mL) was added hydrazine hydrate (37.55 mg, 0.75 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 3 h. Upon completion, the mixture was purified by silica gel column chromatography to afford pure **6a** as a white oil (109.7 mg, 85% yield).

Ethyl 2-(3,5-Dimethyl-1*H*-pyrazol-4-yl)-2-phenylacetate (6a): eluent = petroleum ether/ethyl acetate (5:1), white viscous liquid, 85% yield (109.9 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.25 (m, 5H), 4.63 (d, J = 11.8 Hz, 1H), 4.39 (d, J = 11.8 Hz, 1H), 4.13 (dq, J = 10.8, 7.1 Hz, 1H), 4.07−3.98 (m, 1H), 2.29 (s, 3H), 1.90 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.6, 143.1, 138.0, 128.4, 128.0, 126.9, 112.7, 61.1, 46.9, 14.2, 11.5; HRMS (EI-TOF, m/z) calcd for $C_{15}H_{18}N_2O_2$ $[M]^+$ 258.1368, found 258.1367.

To a solution of **4a** (131.06 mg, 0.5 mmol, 1.0 equiv) in EtOH (1.5 mL) was added hydroxylamine hydrochloride (52.12 mg, 0.75 mmol, 1.5 equiv). The reaction mixture was stirred at 60 °C for 24 h. Upon completion, the mixture was purified by silica gel column chromatography to afford pure **6b** as a white oil (119.2 mg, 92% yield).

Ethyl 2-(3,5-Dimethylisoxazol-4-yl)-2-phenylacetate (6b): eluent = petroleum ether/ethyl acetate (5:1), white viscous liquid, 92% yield (119.3 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (dt, J = 13.9, 6.9 Hz, 3H), 7.17 (d, J = 7.3 Hz, 2H), 4.84 (s, 1H), 4.24 (q, J = 7.1 Hz, 2H), 2.25 (s, 3H), 2.10 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.3, 166.5, 159.7, 136.4, 128.7, 127.9, 127.5, 111.5, 61.6, 46.1, 14.2, 11.6, 10.7; HRMS (EI-TOF, m/z) calcd for $C_{15}H_{17}NO_3$ $[M]^+$ 259.1208, found 259.1207.

Derivatization of the Product 5i..[5b,22] To a 10 mL sealed tube were added **5i** (116.06 mg, 0.5 mmol), phenylamine (69.86 mg, 0.75 mmol) and H_2O (1.5 mL). The mixture was kept stirring at 100 °C for 6 h. Upon completion, the solvent was evaporated under reduced pressure. The mixture was purified by silica gel column chromatography to afford pure **7a** as a brownish oil (108.4 mg, 75% yield). Compound **7c** (95.05 mg, 0.5 mmol) synthesized **8a** (brownish oil, 98.85 mg, 80% yield) by the same process as above.

1-(2,5-Dimethyl-1,4-diphenyl-1*H*-pyrrol-3-yl)ethan-1-one (7a): eluent = petroleum ether/ethyl acetate (6:1), brownish viscous liquid, 75% yield (108.5 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.25 (m, 5H), 4.63 (d, J = 11.8 Hz, 1H), 4.39 (d, J = 11.8 Hz, 1H), 4.13 (dq, J = 10.8, 7.1 Hz, 1H), 4.07−3.98 (m, 1H), 2.29 (s, 3H), 1.90 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 197.4, 137.6, 136.9, 135.0, 130.5, 129.5, 128.6, 128.2(3),

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128.2(0), 126.7, 126.6, 122.1, 121.9, 31.0, 13.1, 11.2; HRMS (EI-TOF, m/z) calcd for $C_{20}H_{19}NO$ $[M]^+$ 289.1467, found 289.1466.

2,5-Dimethyl-1,3-diphenyl-1*H*-pyrrole (8a): eluent = petroleum ether/ethyl acetate (6:1), white viscous liquid, 80% yield (98.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.40 (m, 5H), 7.37 (dd, J = 9.7, 4.2 Hz, 2H), 7.26 (dt, J = 3.6, 2.1 Hz, 2H), 7.21−7.16 (m, 1H), 6.15 (s, 1H), 2.15 (s, 3H), 2.07 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 138.9, 137.4, 129.2, 128.7, 128.5, 128.3, 127.8(7), 127.8(5), 125.2, 125.1, 121.1, 106.6, 12.9, 12.3; HRMS (EI-TOF, m/z) calcd for $C_{18}H_{17}N$ $[M]^+$ 247.1361, found 247.1362.

To a 10 mL sealed tube were added **5i** (116.06 mg, 0.5 mmol), PTSA (17.22 mg, 0.1 mmol), and EtOH (1.5 mL). The mixture was kept stirring at 60 °C for 3 h. Upon completion, the solvent was evaporated under reduced pressure. The mixture was purified by silica gel column chromatography to afford pure **7b** as a white oil (92.06 mg, 86% yield). Compound **7c** (95.05 mg, 0.5 mmol) synthesized **8b** (white oil, 77.44 mg, 90% yield) by the same process as above.

1-(2,5-Dimethyl-4-phenylfuran-3-yl)ethan-1-one (7b): eluent = petroleum ether/ethyl acetate (6:1), white viscous liquid, 86% yield (92.1 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 11.3, 4.3 Hz, 2H), 7.36−7.31 (m, 1H), 7.25 (dd, J = 6.8, 5.3 Hz, 2H), 2.53 (s, 3H), 2.16 (s, 3H), 1.93 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 196.1, 156.2, 145.0, 133.8, 129.9, 128.5, 127.4, 123.0, 120.8, 30.7, 14.2, 11.6; HRMS (EI-TOF, m/z) calcd for $C_{14}H_{14}O_2$ $[M]^+$ 214.0994, found 214.0992.

2,5-Dimethyl-3-phenylfuran (8b): eluent = petroleum ether/ethyl acetate (6:1), white viscous liquid, 90% yield (77 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.33 (m, 4H), 7.26−7.20 (m, 1H), 6.10 (s, 1H), 2.40 (s, 3H), 2.28 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.8, 145.8, 134.6, 128.5, 127.4, 126.1, 121.5, 107.0, 13.4, 13.0; HRMS (EI-TOF, m/z) calcd for $C_{12}H_{12}O$ $[M]^+$ 172.0888, found 172.0887.

To a 10 mL sealed tube were added **5i** (116.06 mg, 0.5 mmol), K_2CO_3 (69.11 mg, 0.5 mmol), and EtOH (1.5 mL). The mixture was kept stirring at 80 °C for 1 h. Upon completion, the solvent was evaporated under reduced pressure. The mixture was purified by silica gel column chromatography to afford pure **7c** as a white oil (59.88 mg, 63% yield).

3-Phenylhexane-2,5-dione (7c): eluent = petroleum ether/ethyl acetate (3:1), white viscous liquid, 63% yield (59.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dq, J = 14.5, 7.1 Hz, 3H), 7.24−7.16 (m, 2H), 4.22 (dd, J = 10.2, 3.8 Hz, 1H), 3.44 (dd, J = 18.0, 10.2 Hz, 1H), 2.57 (dd, J = 18.0, 3.8 Hz, 1H), 2.16 (s, 3H), 2.12 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 207.1, 206.8, 137.8, 129.1, 128.2, 127.6, 54.0, 46.4, 30.0, 29.0; HRMS (EI-TOF, m/z) calcd for $C_{12}H_{14}O_2$ $[M]^+$ 190.0994, found 190.0995.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01100.

^{1}H and $^{13}C\{^1H\}$ NMR spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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