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Copper(II)-Catalyzed Benzylic C(sp^3)-H Aerobic Oxidation of (Hetero)Aryl Acetimidates: Synthesis of Aryl α-Ketoesters

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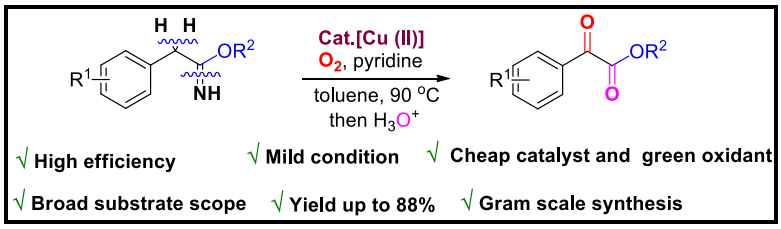


ABSTRACT

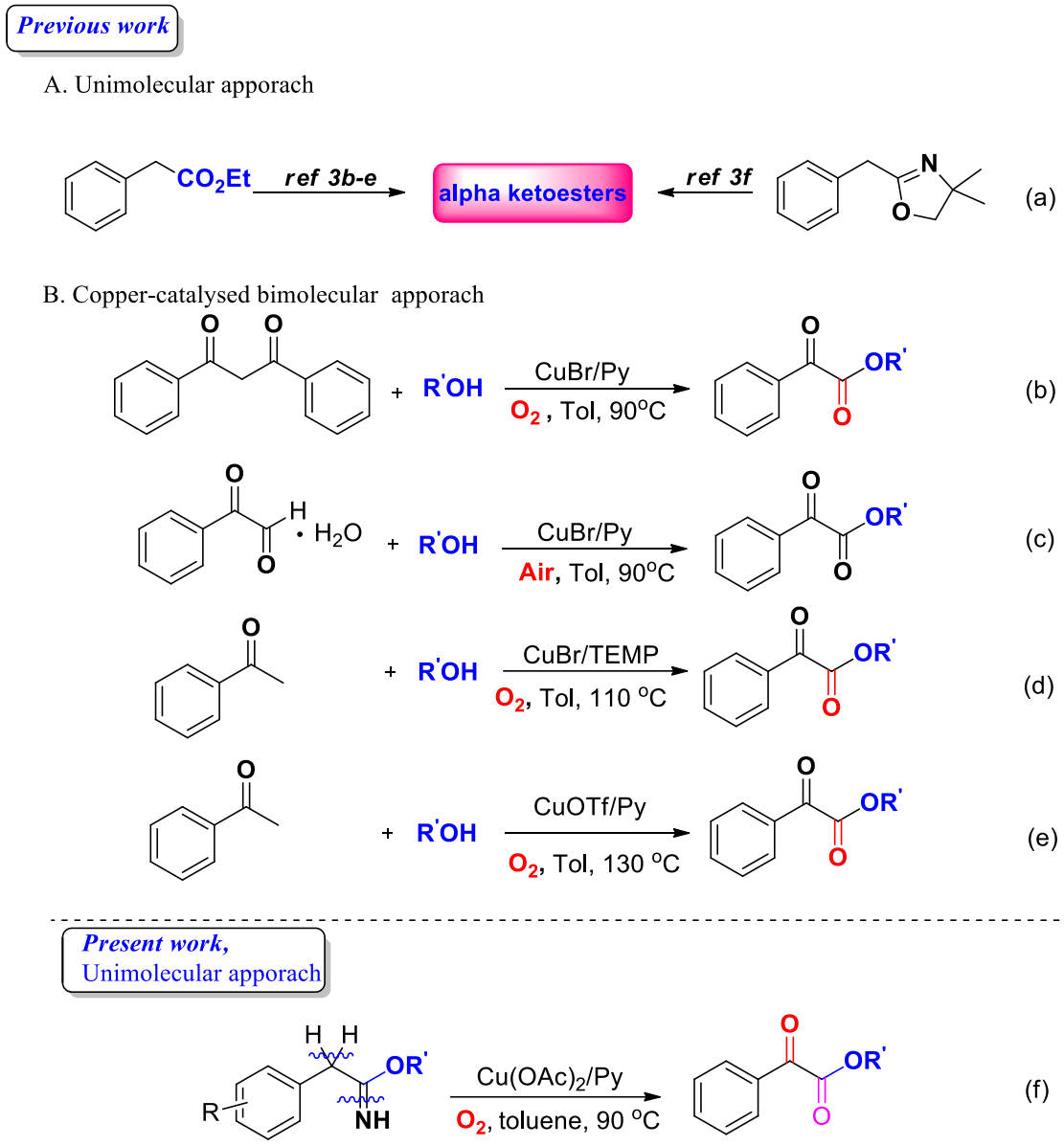
A straightforward method is developed in this paper for the synthesis of α-ketoesters through copper-catalyzed aerobic oxidation of (hetero)aryl acetimidates using molecular oxygen as a sustainable oxidant. The reaction represents the first example of the direct synthesis of aryl-α-ketoesters from arylacetimidates through the aerobic oxidation of a benzylic $C_{(sp3)}$–H (C=O) bond in moderate to good yield. This transformation occurs under mild reaction conditions with a wide range of substrates and utilizes a readily available oxidant and catalyst. The synthetic utility of this transformation is demonstrated through scaled-up synthesis. A plausible reaction mechanism is also proposed.

INTRODUCTION

Direct functionalization of the fairly reactive $C_{(sp3)}$−H bond at the benzylic position is an attractive, powerful and challenging task that has encouraged synthetic organic chemists to develop a cost effective, economical and environmentally friendly approach using unfunctionalized organic molecules.[1-3] Transition-metal–catalyzed aerobic oxidation is a versatile tool known for the generation of C-C and C-X bonds, resulting in the formation of complex molecules from small molecules.[4] In recent years, major effort has been devoted to oxidative transformation through transition metal catalysts.[5] Copper-catalyzed aerobic oxidation has emerged as a facile synthetic tool because it is less expensive and less toxic nature than other transition metals, such as palladium, rhodium and ruthenium.[6] Molecular oxygen is highly abundant, inexpensive and green in nature, making desirable for synthetic organic chemists.[5b,6] Stahl and co-workers demonstrated the practical application of copper/dioxygen for the functionalization of organic molecules on the gram scale.[4c,d,g] Nature uses molecular oxygen in combination with copper and other metals for the selective activation of unreactive C–H bonds, for instance, monooxygenase tyrosinase, galactose oxidase and β-monooxygenase.[7]

α-Ketoesters are key structural scaffolds in a great number of biologically active molecules, pharmaceuticals, anticancer agents, calpains, serine and cysteine protease inhibitors and thrombin inhibitors.[8] The presence of a keto group adjacent to an ester functionality creates an attractive synthon for asymmetric reduction, aminohydroxylation and aldol reaction.[9,10] They serve as versatile building blocks for the synthesis of biologically active natural compounds, such as (-) 9,10-dihydroecklonilactone B.[11]

Scheme 1. Different Synthetic Approaches towards Aryl-α-Ketoesters



Consequently, the synthesis of α-ketoesters has received much attention in recent years, and numerous methods have been developed for the construction of α-ketoesters and their analogues[3,12-14] using metal catalysts[12,13] or under metal-free conditions.[14] Bimolecular coupling

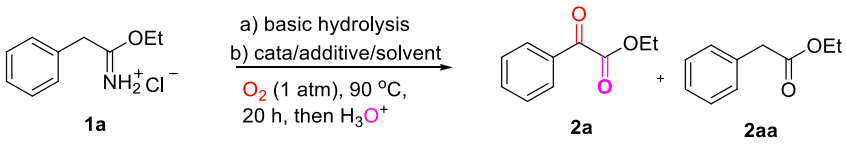
in the presence of a catalyst with precursors such as 1,3-diketones,[13d] 1,3-ketoaldehyde,[12c] acetophenone,[13b,c] and phenylacetylene derivatives[13a] has been used to generate aryl-α-ketoesters. Scheme 1 summarizes some of the established protocols for the synthesis of α-ketoesters. Despite this significant progress, a major limitation of these strategies is the choice of appropriate reagents (use of hazardous chemicals), substrates (proceeds through bimolecular coupling, which eventually requires a muti-step process), harsh reaction conditions and the use of expensive ligands. Thus, there is a need to develop an efficient strategy for the construction of aryl-α-ketoesters that satisfies the following criteria: (a) usage of a pre-functionalized single substrate, (b) usage of a benign oxidant and inexpensive catalyst, (c) liberation of gaseous byproducts to ease the purification process, (d) operationally mild and economically feasible method. This direct approach can be categorized as "green or sustainable" chemistry. Pursuing these limitations, we report for the first time a simple strategy for the synthesis of α-ketoesters *via* copper-catalyzed benzylic C-H aerobic oxidation of (hetero)aryl acetimidates. To the best of our knowledge, the use of arylacetimidates as a key starting material for the synthesis aryl α-ketoesters has not been reported (Scheme 1f).

We recently reported a copper-mediated aerobic oxidation of benzylimidate leading to the formation of primary α-ketoamides,[15a] which are important structural units in biologically active molecules.[15] We also obtained an α-ketoester as a side product in trace amounts during the course of the reaction, particularly when non-polar solvents, such as toluene, were used. This unexpected result encouraged us to optimize the reaction conditions to obtain aryl α-ketoesters in good yield from the readily available starting material 2-phenylacetimidate. It is interesting to evaluate the effect of a non-polar solvent, which likely changes the course of the reaction.[16]

RESULTS AND DISCUSSION

The present study was initiated from 2-phenylacetimidate **1a** as a designed substrate and toluene as the required solvent. Copper salt was selected as a catalyst since it has strong affinity to coordinate with nitrogen (NH),[15a] and molecular oxygen was selected as the ideal oxidant due to its high abundance, green and benign nature.[5b] First, **1a** was treated with 10 mol% of $Cu(OAc)_2$ in a non-polar solvent (toluene) under a molecular oxygen atmosphere (1.0 atm)[17] at 90 °C for 20 h (Table 1, entry 1). The targeted α-ketoester **2a** was isolated in an encouraging yield of 51% with the generation of ester **2aa** in trace amounts. A control experiment in the absence of copper salt yielded no product and the starting material remained intact (according to TLC analysis) (entry 2). Catalyst screening indicated that $Cu(OAc)_2$ was the best choice among $CuCl_2$, $Cu(OTf)_2$, CuBr, and CuCl (Table 1, entries 3-6).

Table 1. Optimization of the reaction conditions[a]



Entry	Catalyst	Additive	Solvent	Yield (%)	
				2a	**2aa**
1	$Cu(OAc)_2$		toluene	51	trace
2	none		toluene	0	0
3	$CuCl_2$		toluene	32	8
4	$Cu(OTf)_2$		toluene	31	8
5	CuBr		toluene	40	trace

6	CuCl		toluene	28	10
7[b]	$Cu(OAc)_2$		toluene	31	10
8	$Cu(OAc)_2$	NEt_3	toluene	34	10
9	$Cu(OAc)_2$	DIPEA	toluene	24	12
10	**$Cu(OAc)_2$**	**pyridine**	**toluene**	**72**	**trace**
11[c]	$Cu(OAc)_2$	1,10-phen	toluene	15	8
12[d]	$Cu(OAc)_2$	pyridine	toluene	49	trace
13	$Cu(OAc)_2$	pyridine	xylene	53	trace
14[e]	$Cu(OAc)_2$	pyridine	PhCl	53	8
15[e]	$Cu(OAc)_2$	pyridine	dioxane	28	12
16[f]	$Cu(OAc)_2$	pyridine	DMF	10	trace
17[g]	$Cu(OAc)_2$	pyridine	toluene	none	trace
18[h]	$Cu(OAc)_2$	pyridine	toluene	46	12
19[i]	$Cu(OAc)_2$	pyridine	toluene	48	8
20[j]	$Cu(OAc)_2$	pyridine	toluene	10	trace
21[k]	$Cu(OAc)_2$	pyridine	toluene	10	trace
22	$Fe(NO_3)_3.9H_2O$	pyridine	toluene	none	trace

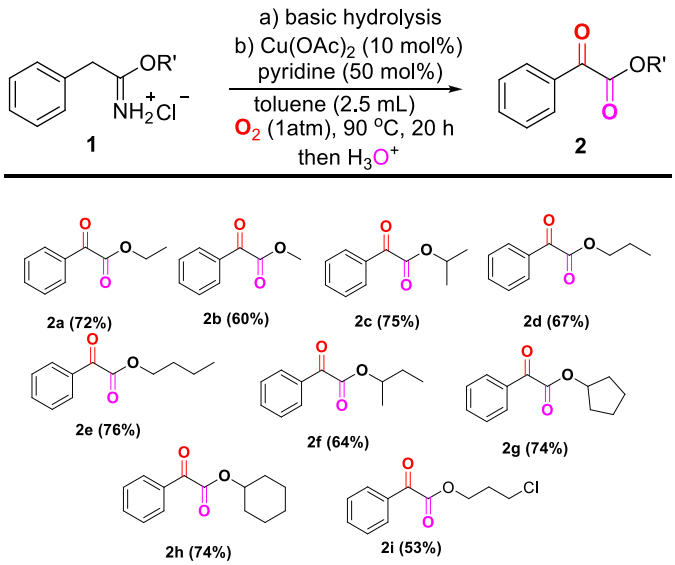
23	$Ni(OAc)_2.4H_2O$	pyridine	toluene	none	trace
24	$Pd(OAc)_2$	pyridine	toluene	none	trace

[a]Reaction conditions: a) Basic hydrolysis (see the experimental procedure). b) **1a** (0.5 mmol), catalyst (0.05 mmol), toluene (2.5 mL), additive (50 mol%), O_2 (1 atm), 90 °C, 20 h. [b]20 mol% of catalyst was used. [c]50 mol% of 1,10-phenanthroline was used. [d]100 mol% of pyridine was employed. [e]10% α-ketoamide product was isolated. [f]15% α-ketoamide was isolated. [g]In a N_2 (1 atm) atmosphere. [h]In an air (1 atm) atmosphere. [i]1.0 mmol TBHP was used as the oxidant in air (1 atm). [j]1.0 mmol TBHP was used as the oxidant in N_2 (1 atm). [k]1.0 mmol $K_2S_2O_8$ was used as the oxidant in N_2 (1 atm).

A further increase in the loading of the catalyst from 10 mol% to 20 mol% was reduced the yield to 31% (Table 1, entry 7). To increase the yield of the desired product, we focused on ligand screening; the addition of pyridine as the ligand improved the yield to 72% (Table 1, entry 10). In contrast to monodentate ligands, when a bidentate ligand such as 1,10-phenanthroline was used, the yield of the product decreased dramatically to 15% (Table 1, entry 11). Moreover, increasing the loading of pyridine did not enhance the efficiency of product formation (Table 1, entry 12). As the nature of solvent is a critical factor in this type of reaction, the effect of the solvent was surveyed, and toluene was found to be the prime solvent to achieve this transformation (Table 1, entry10). When the reaction was performed in a nitrogen atmosphere, no desired product was generated (Table 1, entry 17). However, when the reaction was performed in open air, **2a** was obtained, albeit in a moderate yield of 46% (Table 1, entry 18). The utilization of alternate oxidants, such as TBHP and $K_2S_2O_8$, failed to produce the desired product, and the starting material was recovered through flash column chromatography (entries

19-21). These preliminary results support the indispensable role of molecular oxygen in this particular reaction. Other transition metal catalysts, for instance, $Fe(NO_3)_3.9H_2O$, $Ni(OAc)_2.4H_2O$ and $Pd(OAc)_2$ were ineffective and led to inferior results (Table 1,entries 22-24).

Scheme 2. Substrate scope of 2-phenylacetimidates[a]

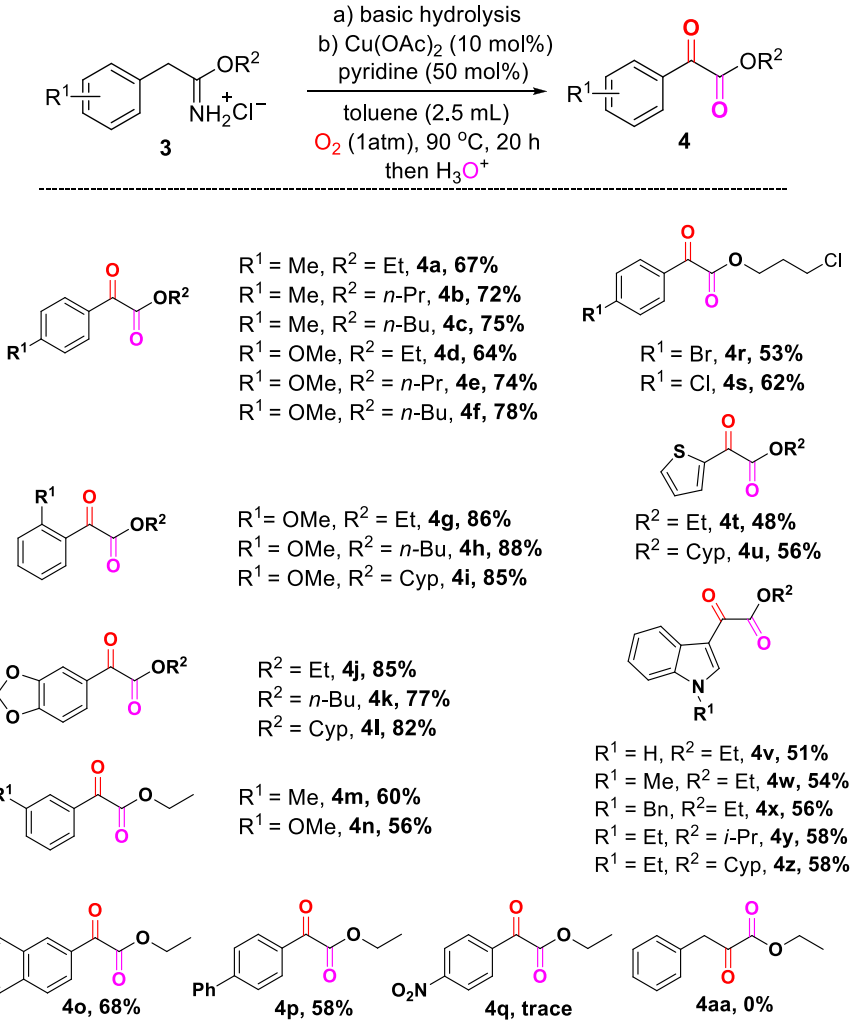


[a]For reaction conditions: a) Basic hydrolysis. b) See entry 10, Table 1.

With the optimized conditions, which satisfied the criteria set by us, we explored the scope and limitations of this protocol to synthesize a variety of substituted alcohols utilizing 2-phenylacetimidates **1** (Scheme 2) as key precursors. The results indicate that 2-phenylacetimidates **1** attached to acyclic primary and secondary alkyl alcohol, such as ethanol, methanol, *iso*-propanol, *n*-propanol, *n*-butanol, and *sec*-butanol afforded the corresponding phenyl-α-ketoesters (entries **2a-2f**), and the yields ranged from 60 to 76%. Cyclic secondary alkyl alcohols, such as cyclopentanol and cyclohexanol, which are susceptible to oxidative conditions, formed the corresponding α-ketoesters in good yields (74%, entries **2g** and **2h**).

Alcohols bearing a *chloro* group also tolerated the standard reaction conditions to obtain the products in 53% yield (entry **2i**), which could be used for further functionalization.

Scheme 3. Substrate scope for the synthesis of various aryl-ketoesters[a]

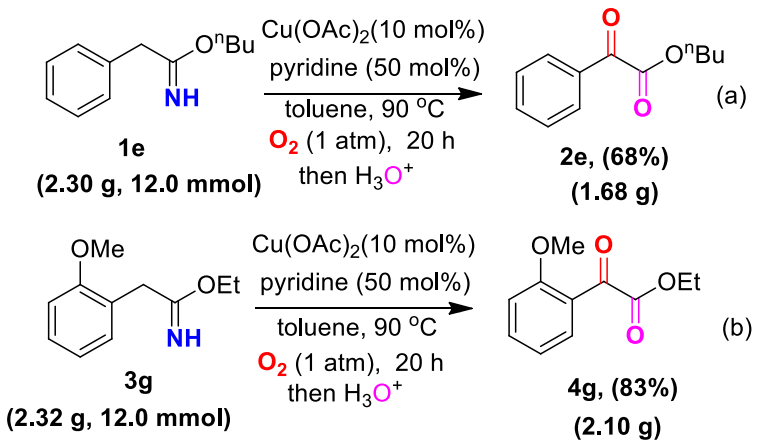


[a]For reaction conditions: a) Basic hydrolysis. b) See entry 10, Table 1.

The scope of the copper-catalyzed aerobic oxidative esterification of (hetero)aryl acetimidates with different *O*-alkyls in the alkoxy group **3** was further expanded, and the results are summarized in Scheme 3. α-Arylacetimidates bearing electron donating groups (EDGs), such as methyl, methoxy, and 3,4-dioxy, at the *ortho*, *para* and *meta* positions of the aryl ring, and a variety of alkoxy substituents (ethyl, propyl, butyl, cyclopentyl and cyclohexyl), generated the

products with good yields (56-88%, Scheme 3, entries **4a**-**4n**). The presence of different substituents at various positions of the aryl ring and the alkoxy group did not affect the overall efficiency of the product yield. Electronically neutral groups, such as *para*-phenyl and naphthyl, were tolerated well in this transformation (58-68%, entries **4o** and **4p**). However, the introduction of an electron-withdrawing (EWG) group, such as a nitro group, on the aryl ring of 2-arylacetimidate **3q** had a negative effect and completely inhibited the reaction. Arylacetimidates containing halo groups, such as *bromo* and *chloro*, at the *para* position afforded the desired product in moderate yields (53-62%, entries **4r** and **4s**), providing products for post-coupling transformation. The substrate scope was further extended for the synthesis of bioactive, medicinally important heteroaryl-α-ketoester derivatives[18] in 51-58% yields (entries **4t**-**4z**). However, when the reaction was performed with 3-phenylpropanimidate **3aa**, α-ketoester **4aa** was not obtained and the starting material remained intact (TLC analysis). These results confirm that the benzylic hydrogen adjacent to the imidate group is crucial for the success of this transformation.

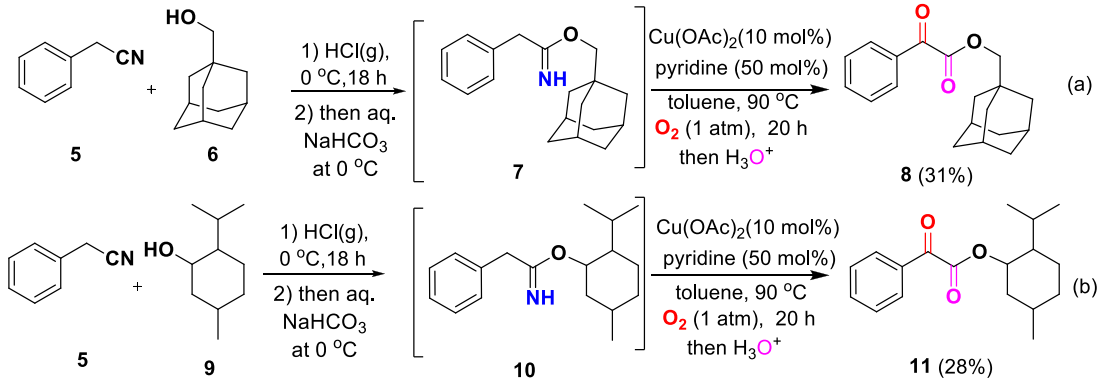
Scheme 4. Synthetic utility experiment



To demonstrate the synthetic applicability of this established protocol, gram-scale syntheses of butyl 2-oxo-2-phenylacetate **2e** and ethyl 2-(2-methoxyphenyl)-2-oxoacetate **4g** were conducted under the standard reaction conditions. This transformation proceeded smoothly to afford the desired products **2e** (68%, 1.68 g) and **4g** (83%, 2.1 g) (Scheme 4), and there was no substantial drop in the yield during the gram-scale synthesis.

Next, we evaluated the utility of the established methodologies to synthesize aryl α-ketoesters through two-step, one-pot synthesis. For this purpose, we selected 2-phenylacetonitrile **5** as the model substrate, along with 1-adamantanemethanol **6** and (±)-menthol **9** (Scheme 5) as the alcohols in the presence of dry HCl(g), followed by basic hydrolysis to afford the required benzylimidates. Without further purification, the crude reaction mixture was subjected to standard conditions to afford the aryl-α-ketoesters **8** and **11** in 31% and 28% yields, respectively (Scheme 5, yields were not optimized at this stage, but the examples are provided to showcase the utility of one-pot synthesis).

Scheme 5. One-pot synthesis of α-ketoesters from nitrile[a,b,c]



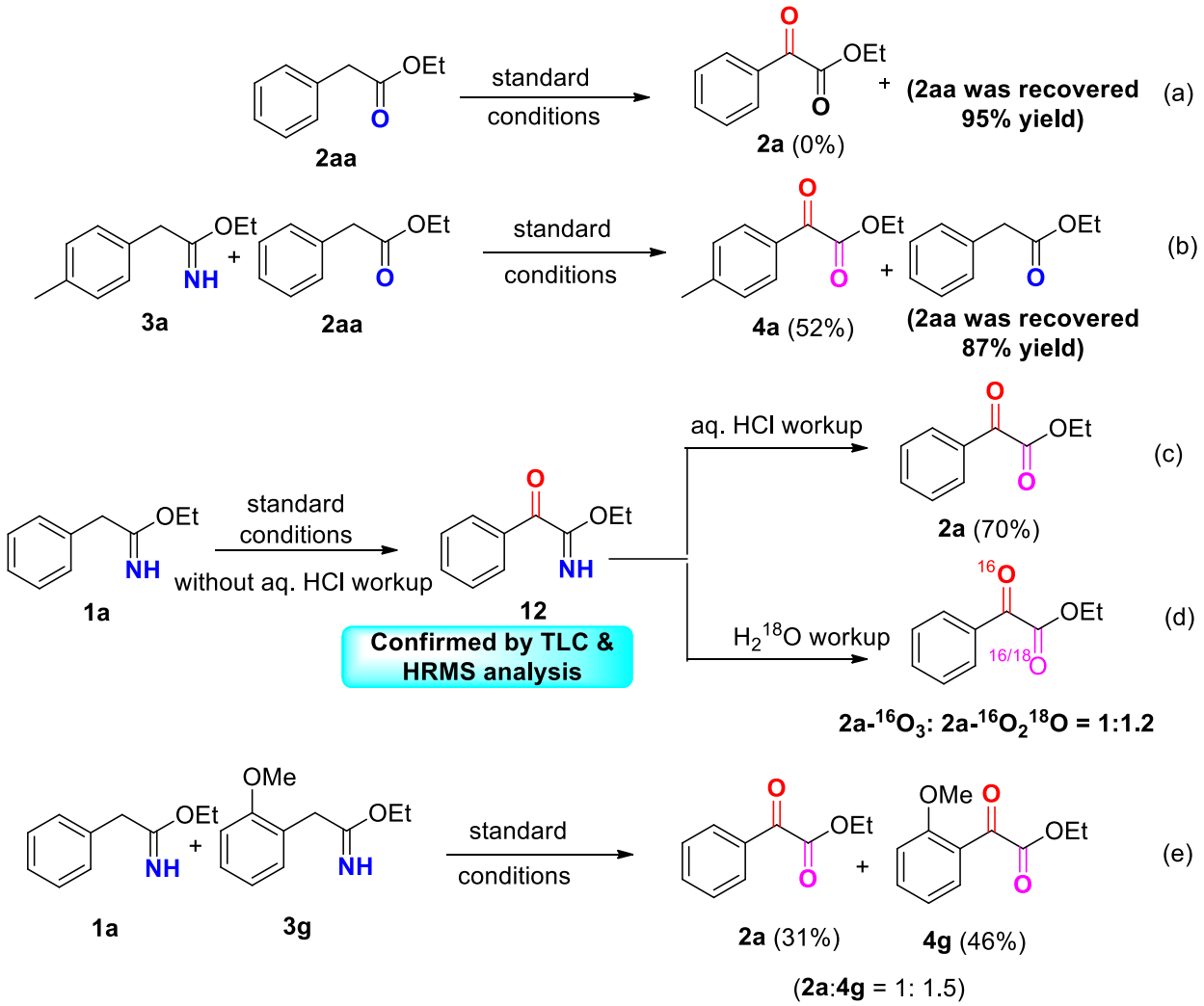
[a]Reactions were conducted with nitrile **5** (1.0 mmol) and alcohols **6** and **9** (1.1 mmol) in THF (5.0 mL) at 0 °C in a sealed round-bottom flask for 18 h under acidic conditions. The crude

reaction mixture was treated with $Cu(OAc)_2$ (10 mol%), pyridine (50 mol%) and toluene (5.0 mL) at 90 °C under an O_2 atmosphere (1atm) for 20 h. [b]Reactions were monitored by TLC. [c]Yield of the product after two steps.

To investigate the mechanistic aspects of this reaction, additional experiments were conducted. When 2-phenylacetate **2aa** was subjected to the optimized conditions, no desired product was obtained (Scheme 6a), and 95% of the starting material was recovered. Furthermore, when equimolar amounts of ethyl 2-*p*-tolylacetimidate **3a** was mixed with 2-phenylacetate **2aa** and subjected to the standard conditions, α-ketoester **4a** was isolated in 52% yield, and 2-phenylacetate **2aa** was recovered in 87% yield (Scheme 6b). These results indicate that **2aa** may not be an intermediate in this oxidative transformation and 2-phenylacetimidate, and an imidate group adjacent to the benzylic position is crucial in the starting material for this reaction. According to the outcome of the reaction, keto-imidate **12** could be the key intermediate in the reaction. Hence, we conducted an additional control experiment, in which imidate **1a** was subjected to the standard conditions without the subsequent aqueous HCl workup. The HRMS analysis of the reaction solution showed the presence of keto-imidate **12** as an intermediate, which upon aqueous HCl workup, afforded the desired product **2a** in 70% yield (Scheme 6c) (for details, see the Supporting Information).[19] To further elucidate the indispensable role of water for the reaction, ^{18}O isotopic labelling experiment was also investigated (Scheme 6d). When the reaction was performed under standard conditions, followed by aqueous workup in the presence of $H_2{}^{18}O$ (400 mol%), the ^{18}O labeling products were observed (**2a**-$^{16}O_3$:**2a**-$^{16}O_2{}^{18}O$ =1:1.2 by HMRS analysis). These experiments (Scheme 6c and 6d) clearly support that the one oxygen atom of ketoester originate from the water and conform the participation of water. Next,

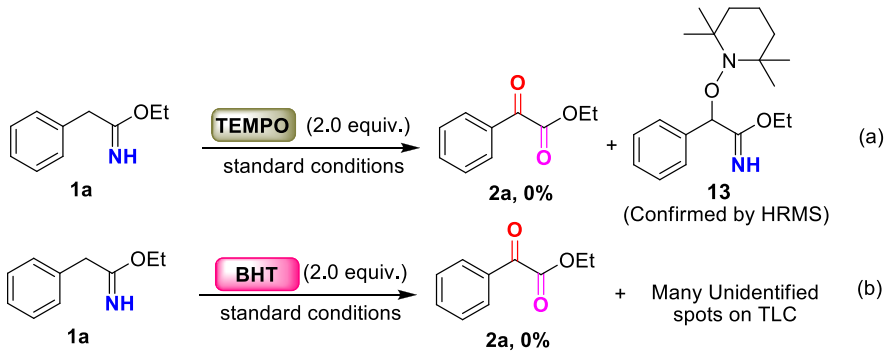
competition studies between substrates **1a** and **3g** were performed under the optimized conditions, and the desired products **2a** and **4g** were isolated through column chromatography in 31% and 46% yields, respectively (1:1.5) (Scheme 6e). The results indicate that EDGs are favored over electronically neutral groups (see the Supporting Information).[19]

Scheme 6. Identification of possible intermediates and competition experiment



To determine the possible radical pathways involved in the reaction, a radical scavenger (2,2,6,6-tetramethyl-1-piperidin-1-yl)oxyl (TEMPO)) was introduced to the reaction mixture (Scheme 7a). The reaction was inhibited completely, and a TEMPO-adduct was identified as the major product (TLC analysis), which was confirmed by HRMS analysis (Supporting Information).[19] Additionally, when a different radical scavenger, such as 2,6-di-*tert*-butyl-4-methylphenol (BHT), was used under similar conditions, no desired product was obtained (Scheme 7b). The results indicate that a radical pathway may be involved in the reaction mechanism. To further prove that a radical pathway is involved in this process, we performed electron paramagnetic resonance (EPR) experiments, in which 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) was used as a free radical spin trapping agent. In the EPR spectra, 4 classic peaks corresponding to DMPO-O(H) appeared, and the calculated values were g_o (2.0037) and α^H (15.0 G)[15a] (Figure 1B). Furthermore, the signal corresponding to DMPO-O(H) disappeared after the addition of superoxide dismutase (SOD) (Supporting Information).[19] These results confirm that the reaction proceeded *via* a radical pathway.

Scheme 7. Radical inhibition experiments



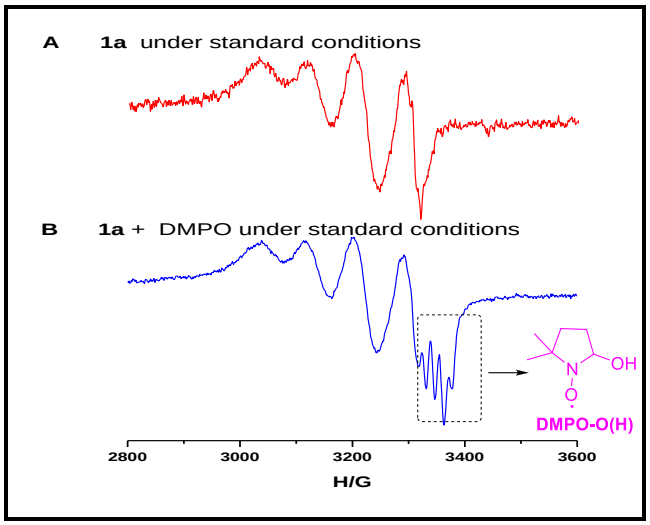
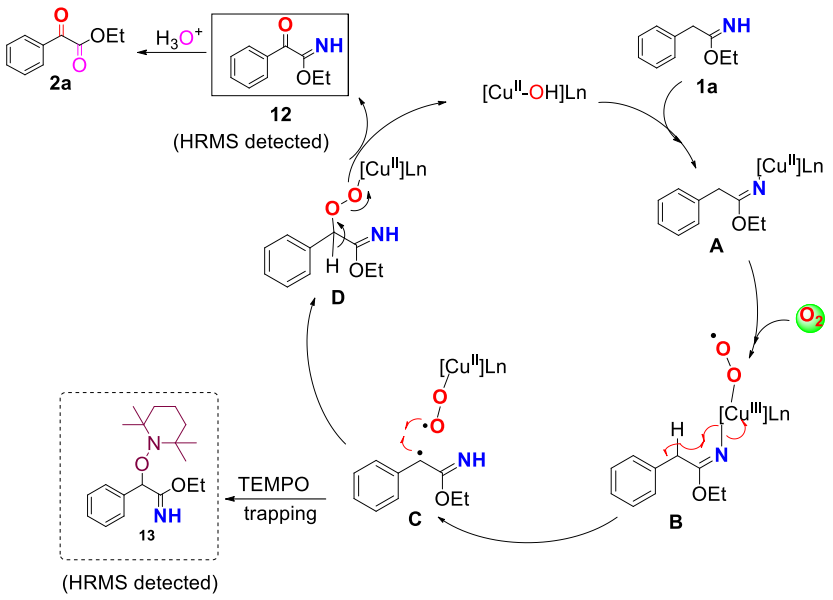


Figure 1. EPR spectra (X band, 9.4 GHz, room temperature) of the reaction under the standard conditions [**1a**, $Cu(OAc)_2$, O_2 balloon (1 atm), toluene, 90 °C]. (A) The reaction of **1a** under standard conditions. (B) The reaction of **1a** with the addition of DMPO under standard conditions. The calculated hyperfine splitting is $g_o = 2.0037$. All spectra were analyzed by EPR at 25 °C.

On the basis of these results and previous literature,[15a,20] plausible mechanistic details are proposed in Scheme 8. The coordination of imidate (NH) **1a** with the copper(II) catalyst leads to iminyl copper (II) species **A**.[20d] Subsequently, this species undergoes aerial oxidation in the presence of molecular oxygen to form the highly reactive peroxycopper(III) **B.**[15a,20] Then, the superoxide species **B** quickly rearranges *via* an intramolecular 1,3-hydrogen shift to from benzylic radical **C,** which is further transformed to peroxycopper species **D**. Subsequently, this peroxycopper species undergoes secondary hydrogen abstraction of the benzylic proton and elimination of [Cu(II)-OH] to produce the key intermediate keto-imidate **12**. The following hydrolysis of **12** produces the desired product aryl-α-ketoester **2a**.

Scheme 8. Possible reaction mechanism



CONCLUSION

In conclusion, we have developed the first example of the direct synthesis of aryl-α-ketoesters from (hetero)aryl acetimidates *via* copper (II)-catalyzed aerobic oxidation of a benzylic hydrogen. This strategy provides a simple, practical and straightforward method for the synthesis of α-ketoesters, which are important units in medicinally active compounds. The uniqueness of this strategy lies in the use of a) arylacetimidates as the single prefunctionalized key substrate, b) a simple catalytic system, c) gram-scale synthesis and d) broad substrate scope. Preliminary mechanistic studies show that the one oxygen atom of the ketoester originated from the water. Further synthetic applications of this methodology are currently under investigation in our laboratory.

EXPERIMENTAL SECTION

General Information

All reagents and solvents were purchased from commercial suppliers and were used without further purification. All reactions were monitored by TLC, followed by exposure of the mixtures to UV light and/or an iodine chamber to visualize the reaction spots. Column chromatography was performed using silica gel [ethyl acetate/hexane (in different ratios) solvent system]. FTIR spectra were recorded in ATR mode with the absorption in cm^{-1}. ^{1}H NMR (400 MHz) and $^{13}C\{^{1}H\}$ NMR (100 MHz) spectra were recorded in $CDCl_3$ or DMSO-d_6 as the solvent at 25 °C. Chemical shifts (in ppm) were reported using tetramethylsilane ($\delta = 0$) as an internal standard in $CDCl_3$ ($\delta = 7.26$) or DMSO-d_6 ($\delta = 2.50$) solvent. The following abbreviations were used to define the multiplicities: s = singlet; d = doublet; t = triplet; m = multiplet; dd (doublet of doublets); td (triplet of doublets); br s (broad singlet), coupling constants (J, in Hz). $^{13}C\{^{1}H\}$ NMR data were recorded in terms of the chemical shift (ppm, scale), using the central peak of $CDCl_3$ (77.0 ppm) or DMSO-*d6* ($\delta = 39.5$ ppm) as the internal standard. EPR data were recorded on 9.4 GHz spectrometers, with a modulation amplitude of 10 G and modulation frequency of 100 kHz. DMPO (5,5-dimethyl-1-pyrroline-*N*-oxide) was used as a selective superoxide free radical trapping reagent. HRMS was performed in ESI mode using Q-TOF (positive ion). Melting points were recorded with an automated melting point apparatus without correction.

General procedure for the preparation of imidate hydrochlorides.[15a,21a]

A 50 mL flask containing a solution of a nitrile (1.0 mmol) and an alcohol (12.0 mmol) was sealed with the rubber septum at 0 °C under N_2 and a solution of CH_3COCl (0.57 mL, 8.0 mmol) was added slowly to the solution using a glass syringe while stirring. The reaction was stirred at

room temperature for 12 h. Upon completion of the reaction (monitored by TLC), the volatile solvents were removed under reduced pressure. The crude product was dried under high vacuum to isolate the imidate hydrochloride salt.

The characterization data of compounds **1a**-**1d**, **3a**, **3d**, **3g**, **3j**, **3m**-**3p**, **3t**, **3v**-**3x** and **3aa** are consistent with those previously reported in the literature.[15a]

Butyl 2-phenylacetimidate hydrochloride (1e).White solid: yield 198 mg, 87%; mp 106-108 °C; IR (ATR) 2810, 1741, 1652, 1567, 1436, 1360, 1085, 897 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 12.47 (br s, 1H), 11.46 (br s, 1H), 7.28-7.17 (m, 5H), 4.34 (t, J = 6.4 Hz, 2H), 3.97 (s, 2H), 1.65-1.61 (m, 2H), 1.30-1.24 (m, 2H), 0.81 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 177.0, 134.0, 128.9, 128.0, 126.5, 73.0, 40.6, 30.1, 18.5, 13.3; HRMS (ESI) calcd for $C_{12}H_{18}NO$ $[M+H]^+$ 192.1383, found 192.1386.

sec-Butyl 2-phenylacetimidate hydrochloride (1f). White solid: yield 140 mg, 62%; mp 96-98 °C; IR (ATR) 3286, 3158, 2874, 1652, 1609, 1414, 1304, 1088, 900 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 12.34 (br s, 1H), 11.41 (br s, 1H), 7.32-7.22 (m, 5H), 5.06-4.99 (m, 1H), 3.38 (s, 2H), 1.62-1.55 (m, 2H), 1.22 (d, J = 6.0 Hz, 3H), 0.73 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 176.1, 132.0, 128.9, 128.6, 127.9, 82.1, 42.3, 27.7, 18.2, 8.5; HRMS (ESI) calcd for $C_{12}H_{18}NO$ $[M+H]^+$ 192.1383, found 192.1387.

Cyclopentyl 2-phenylacetimidate hydrochloride (1g). White solid: yield 210 mg, 88%; mp 124-126 °C; IR (ATR) 3357, 3158, 2838, 1638, 1411, 1127, 698 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 12.42 (br s, 1H), 11.40 (br s, 1H), 7.29-7.16 (m, 5H), 5.38-5.31 (m, 1H), 3.89 (s, 2H), 1.91-1.86 (m, 2H), 1.67-1.58 (m, 2H), 1.55-1.53 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz,

DMSO-d_6 with $CDCl_3$) δ 175.9, 131.6, 128.8, 128.5, 127.7, 86.7, 40.9, 31.8, 22.9; HRMS (ESI) calcd for $C_{13}H_{18}NO$ $[M+H]^+$ 204.1383, found 204.1382.

Cyclohexyl 2-phenylacetimidate hydrochloride (1h).White solid: yield 244 mg, 96%; mp 128-130 °C; IR (ATR) 2803, 1648, 1567, 1432, 1166, 875 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 12.36 (br s, 1H), 11.43 (br s, 1H), 7.27-7.18 (m, 5H), 5.03-4.98 (m, 1H), 3.90 (s, 2H), 1.79-1.72 (m, 2H), 1.60-1.52 (m, 2H), 1.48-1.34 (m, 4H), 1.30-1.24 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 175.5, 131.7, 128.8, 128.5, 127.7, 81.7, 41.0, 29.9, 24.1, 22.1; HRMS (ESI) calcd for $C_{14}H_{20}NO$ $[M+H]^+$ 218.1539, found 218.1539.

3-Chloropropyl 2-phenylacetimidate hydrochloride (1i). White solid: yield 228 mg, 92%; mp 122-124 °C; IR (ATR) 2810, 1741, 1652, 1563, 1436, 1368, 1092, 904 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 12.61 (br s, 1H), 11.58 (br s, 1H), 7.24-7.20 (m, 5H), 4.13 (t, J = 6.0 Hz, 2H), 3.59 (s, 2H), 3.55 (t, J = 6.4 Hz, 2H), 2.03-1.97 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 170.7, 133.9, 129.0, 128.1, 126.6, 60.9, 41.1, 40.4, 31.0; HRMS (ESI) calcd for $C_{11}H_{15}ClNO$ $[M+H]^+$ 212.0837, found 212.0850.

Propyl 2-p-tolylacetimidate hydrochloride (3b). White solid: yield 208 mg, 92%; mp 120-122 °C; IR (ATR) 2803, 1652, 1514, 1418, 1085, 893, 829 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 12.43 (br s, 1H), 11.46 (br s, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 4.29 (t, J = 6.4 Hz, 2H), 3.90 (s, 2H), 2.24 (s, 3H), 1.73-1.64 (m, 2H), 0.84 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 177.2, 137.2, 130.8, 129.2, 128.7, 74.5, 40.2, 21.4, 20.6, 10.0; HRMS (ESI) calcd for $C_{12}H_{18}NO$ $[M+H]^+$ 192.1383, found 192.1386.

Butyl 2-p-tolylacetimidate hydrochloride (3c). White solid: yield 228 mg, 95%; mp 125-127 °C; IR (ATR) 2810, 1656, 1517, 1436, 1092, 889 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 with $CDCl_3$)

δ 12.43 (br s, 1H), 11.42 (br s, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 4.32 (t, *J* = 6.4 Hz, 2H), 3.89 (s, 2H), 2.24 (s, 3H), 1.63-1.61 (m, 2H), 1.30-1.24 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 177.1, 137.2, 130.8, 129.2, 128.8, 73.0, 40.2, 30.1, 20.6, 18.5, 13.3; HRMS (ESI) calcd for $C_{13}H_{20}NO$ $[M+H]^+$ 206.1539, found 206.1546.

Propyl 2-(4-methoxyphenyl)acetimidate hydrochloride (3e). White solid: yield 201 mg, 83%; mp 102-104 °C; IR (ATR) 2824, 1737, 1652, 1507, 1436, 1379, 1241, 1099 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 12.37~~7~~8 (br s, 1H), 11.38 (br s, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.80 (d, *J* = 8.0 Hz, 2H), 4.28 (t, *J* = 6.4 Hz, 2H), 3.87 (s, 2H), 3.70 (s, 3H), 1.74-1.64 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 177.3, 158.1, 129.9, 125.9, 113.4, 74.5, 54.7, 39.7, 21.4, 10.0; HRMS (ESI) calcd for $C_{12}H_{18}NO_2$ $[M+H]^+$ 208.1332, found 208.1336.

Butyl 2-(4-methoxyphenyl)acetimidate hydrochloride (3f). White solid: yield 229 mg, 89%; mp 114-116 °C; IR (ATR) 2796, 1645, 1514, 1429, 1241, 1177, 1102, 900, 820 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 12.43 (br s, 1H), 11.40 (br s, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.79 (d, *J* = 8.0 Hz, 2H), 4.32 (t, *J* = 6.0 Hz, 2H), 3.86 (s, 2H), 3.70 (s, 3H), 1.66-1.62 (m, 2H), 1.30-1.24 (m, 2H), 0.82 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 177.2, 158.0, 129.8, 125.8, 113.4, 73.0, 54.7, 39.8, 30.1, 18.5, 13.3; HRMS (ESI) calcd for $C_{13}H_{20}NO_2$ $[M+H]^+$ 222.1489, found 222.1497.

Butyl 2-(2-methoxyphenyl)acetimidate hydrochloride (3h).White solid: yield 250 mg, 97%; mp 118-120 °C; IR (ATR) 2817, 1631, 1432, 1375, 1248, 1109, 1021 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 11.99 (br s, 1H), 11.50 (br s, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.06 (d, *J* =

8.0 Hz, 1H), 6.86 (t, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 4.35 (t, *J* = 6.0 Hz, 2H), 3.89 (s, 2H), 3.75 (s, 3H), 1.61-1.55 (m, 2H), 1.21-1.14 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 177.4, 156.8, 130.6, 129.3, 122.7, 120.3, 110.1, 73.0, 55.0, 35.4, 29.1, 17.9, 12.9; HRMS (ESI) calcd for $C_{13}H_{20}NO_2$ $[M+H]^+$ 222.1489, found 222.1498.

Cyclopentyl 2-(2-methoxyphenyl)acetimidate hydrochloride (3i). White solid: yield 240 mg, 89%; mp 114-116 °C; IR (ATR) 2824, 1726, 1638, 1570, 1407, 1361, 1113 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 11.95 (br s, 1H), 11.35 (br s, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.86-6.82 (m, 2H), 5.44-5.37 (m, 1H), 3.86 (s, 2H), 3.74 (s, 3H), 1.92-1.85 (m, 2H), 1.65-1.58 (m, 2H), 1.55-1.49 (m, 2H), 1.45-1.40 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 176.4, 156.7, 130.6, 129.3, 120.3, 119.8, 110.0, 86.5, 54.9, 34.5, 31.8, 22.8; HRMS (ESI) calcd for $C_{14}H_{20}NO_2$ $[M+H]^+$ 234.1489, found 234.1485.

Butyl 2-(benzo[d][1,3]dioxol-5-yl)acetimidate hydrochloride (3k). White solid: yield 250 mg, 92%; mp 124-126 °C; IR (ATR) 3350, 3172, 2824, 1641, 1425, 1361, 1127 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 12.45 (br s, 1H), 11.44 (br s, 1H), 6.86 (s, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 5.91 (s, 2H), 4.33 (t, *J* = 6.0 Hz, 2H), 3.86 (s, 2H), 1.67-1.63 (m, 2H), 1.31-1.26 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 177.1, 147.5, 147.0, 124.8, 122.5, 109.3, 108.1, 100.9, 73.0, 38.1, 29.2, 18.1, 13.1; HRMS (ESI) calcd for $C_{13}H_{18}NO_3$ $[M+H]^+$ 236.1281, found 236.1279.

Cyclopentyl 2-(benzo[d][1,3]dioxol-5-yl)acetimidate hydrochloride (3l). White solid: yield 260 mg, 92%; mp 144-146 °C; IR (ATR) 3115, 2973, 2796, 1748, 1641, 1397, 1372, 1099 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 12.23 (br s, 1H), 11.25 (br s, 1H), 6.87 (s, 1H), 6.77 (s, 1H), 6.72-6.68 (m, 1H), 5.95 (s, 2H), 5.32-5.29 (m, 1H), 3.81 (s, 2H), 1.95-1.86 (m, 2H),

1.72-1.64 (m, 2H), 1.59-1.55 (m, 4H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 176.2, 147.5, 147.0, 125.2, 122.4, 109.2, 108.2, 101.0, 86.4, 38.4, 31.8, 23.0; HRMS (ESI) calcd for $C_{14}H_{18}NO_3$ $[M+H]^+$ 248.1281, found 248.1282.

3-Chloropropyl 2-(4-bromophenyl)acetimidate hydrochloride (3r). White solid: yield 204 mg, 63%; mp 116-118 °C; IR (ATR) 2781, 1737, 1641, 1400, 1375, 1099, 911 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 7.43 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 4.13 (t, *J* = 6.0 Hz, 2H), 3.62 (s, 2H), 3.59 (t, *J* = 8.0 Hz, 2H), 2.04-1.98 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 170.4, 133.4, 131.3, 131.0, 120.1, 61.2, 41.3, 31.0; HRMS (ESI) calcd for $C_{11}H_{14}BrClNO$ $[M+H]^+$ 289.9942, found 289.9943.

3-Chloropropyl 2-(4-chlorophenyl)acetimidate hydrochloride (3s). White solid: yield 264 mg, 94%; mp 106-108 °C; IR (ATR) 3122, 2966, 2796, 1737, 1648, 1368, 1088, 904 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 7.28 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 4.14 (t, *J* = 6.0 Hz, 2H), 3.61 (s, 2H), 3.57 (t, *J* = 8.0 Hz, 2H), 2.04-1.99 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 170.4, 132.8, 131.9, 130.8, 128.1, 61.1, 41.1, 31.0, 20.5; HRMS (ESI) calcd for $C_{11}H_{14}Cl_2$ NO $[M+H]^+$ 246.0447, found 246.0447.

Cyclopentyl 2-(thiophen-2-yl)acetimidate hydrochloride (3u). White solid: yield 228 mg, 93%; mp 110-112 °C; IR (ATR) 2810, 1734, 1641, 1560, 1429, 1361, 1138, 843 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.59 (br s, 1H), 11.62 (br s, 1H), 7.26 (t, *J* = 4.4 Hz, 1H), 7.17 (t, *J* = 3.2 Hz, 1H), 6.99-6.97 (m, 1H), 5.68-5.59 (m, 1H), 4.25 (s, 2H), 2.20-2.10 (m, 2H), 1.86-1.76 (m, 2H), 1.74-1.64 (m, 4H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 175.0, 131.6, 128.9, 127.4, 126.3, 88.9, 33.9, 32.5, 23.6; HRMS (ESI) calcd for $C_{11}H_{16}NOS$ $[M+H]^+$ 210.0947, found 210.0947.

Isopropyl 2-(1-ethyl-1H-indol-3-yl)acetimidate hydrochloride (3y). White solid: yield 230 mg, 81%; mp 102-104 °C; IR (ATR) 2973, 1645, 1457, 1358, 1085, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.58 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 7.13-7.08 (m, 2H), 5.06-5.00 (m, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 2H), 1.44 (t, *J* = 7.2 Hz, 3H), 1.23 (d, *J* = 6.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177.1, 135.8, 127.8, 126.1, 125.9, 121.5, 119.2, 119.0, 109.3, 68.1, 40.9, 31.7, 21.9, 15.4; HRMS (ESI) calcd for $C_{15}H_{21}N_2O$ $[M+H]^+$ 245.1648, found 245.1658.

Cyclopentyl 2-(1-ethyl-1H-indol-3-yl)acetimidate hydrochloride (3z). White solid: yield 240 mg, 78%; mp 104-106 °C; IR (ATR) 2973, 1726, 1652, 1460, 1358, 1148, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 1H), 7.05-6.99 (m, 2H), 5.13-5.08 (m, 1H), 4.05 (q, *J* = 7.2 Hz, 2H), 3.64 (s, 2H), 1.81-1.71 (m, 2H), 1.66-1.55 (m, 4H), 1.53-1.44 (m, 2H), 1.37 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 175.4, 135.9, 127.9, 125.9, 121.5, 119.2, 119.0, 109.3, 107.2, 77.4, 40.8, 32.7, 31.7, 23.7, 15.5; HRMS (ESI) calcd for $C_{17}H_{23}N_2O$ $[M+H]^+$ 271.1805, found 271.1808.

General procedure for the synthesis of α-ketoesters.

Imidate hydrochloride salts (0.5 mmol) were dissolved in 20 mL of diethyl ether, and the reaction mixture was cooled to 0 °C. Saturated $NaHCO_3$ solution was added slowly until CO_2 gas evolution ceased. The product was extracted with Et_2O (2 x 10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the free imidates. Without further purification, the imidates were treated with anhydrous $Cu(OAc)_2$ (0.05 mmol, 9.18 mg), pyridine (0.25 mmol, 20 μL), and anhydrous toluene (2.5 mL) in a 25 mL round-bottom flask. The reaction flask was sealed with a rubber septum and degassed and refilled with O_2 (3 times). The

resulting reaction mixture was heated at 90 °C in a preheated oil bath for 20 h. Upon completion of the reaction (revealed by TLC), the reaction mixture was treated with 10% HCl solution (10 mL) and stirred at room temperature for 30 min. The resulting solution was extracted with ethyl acetate (15 mL × 3), and the combined organic layer was washed with brine solution (10 mL) and concentrated in *vacuo*. The crude residue was purified using silica gel column chromatography with hexanes and EtOAc (98:2) as the eluent to afford the corresponding products.

Ethyl 2-oxo-2-phenylacetate (2a).[13d] Yellow viscous liquid: yield 62 mg, 72%; R_f (9.8:0.2 hexanes/EtOAc) = 0.9; IR (ATR) 2997, 1736, 1683, 1605, 1292, 1203, 1175, 1015 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.0 Hz, 2H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 4.46 (q, *J* = 8.0 Hz, 2H), 1.43 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.4, 163.8, 134.9, 132.5, 130.1, 128.9, 62.4, 14.1.

Methyl 2-oxo-2-phenylacetate (2b).[14d] Yellow viscous liquid: yield 49.8 mg, 60%; R_f (9.8:0.2 hexanes/EtOAc) = 0.9; IR (ATR) 2956, 1735, 1687, 1595, 1581, 1450, 1325, 1203, 1172, 1002 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.0 Hz, 2H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 3.99 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.1, 164.0, 135.0, 132.5, 130.2, 128.9, 52.8.

Isopropyl 2-oxo-2-phenylacetate (2c).[14d] Yellow viscous liquid: yield 72.0 mg, 75%; R_f (9.8:0.2 hexanes/EtOAc) = 0.9; IR (ATR) 2983, 1728, 1687, 1597, 1450, 1375, 1296, 1201, 1176, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.0 Hz, 2H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 5.38-5.28 (m, 1H), 1.40 (d, *J* = 6.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 163.6, 134.8, 132.5, 130.0, 128.9, 70.7, 21.7.

Propyl 2-oxo-2-phenylacetate (2d).[22b] Yellow viscous liquid: yield 64.0 mg, 67%; R_f (9.8:0.2 hexanes/EtOAc) = 0.9; IR (ATR) 2970, 2881, 1732, 1685, 1597, 1450, 1323, 1195, 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.0 Hz, 2H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 4.36 (t, *J* = 8.0 Hz, 2H), 1.86-1.77 (m, 2H), 1.02 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.6, 164.0, 134.9, 132.5, 130.0, 128.9, 67.8, 21.9, 10.3.

Butyl 2-oxo-2-phenylacetate (2e).[13b] Yellow viscous liquid: yield 74 mg, 76%; R_f (9.8:0.2 hexanes/EtOAc) = 0.9; IR (ATR) 2960, 2873, 1732, 1689, 1597, 1450, 1323, 1197, 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.0 Hz, 2H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 4.40 (t, *J* = 8.0 Hz, 2H), 1.80-1.73 (m, 2H), 1.50-1.41 (m, 2H), 0.97 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.5, 164.0, 134.9, 132.5, 130.0, 128.9, 66.1, 30.5, 19.0, 13.7.

sec-Butyl 2-oxo-phenylacetate (2f).[22c] Yellow viscous liquid: yield 66.0 mg, 64%; R_f (9.8:0.2 hexanes/EtOAc) = 0.9; IR (ATR) 2974, 2937, 1730, 1689, 1597, 1450, 1203, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.0 Hz, 2H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 5.21-5.14 (m, 1H), 1.83-1.65 (m, 2H), 1.39 (d, *J* = 8.0 Hz, 3H), 0.98 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.8, 163.9, 135.0, 132.6, 130.1, 128.8, 75.2, 28.7, 19.4, 9.7.

Cyclopentyl 2-oxo-2-phenylacetate (2g).[22a] Yellow viscous liquid: yield 80 mg, 74%; R_f (9.8:0.2 hexanes/EtOAc) = 0.9; IR (ATR) 2963, 2878, 1727, 1672, 1689, 1593, 1448, 1325, 1201, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.0 Hz, 2H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 5.51-5.46 (m, 1H), 2.04-1.96 (m, 2H), 1.90-1.86 (m, 2H), 1.80-1.76 (m, 2H),

1.68-1.64 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.8, 164.0, 134.8, 132.5, 130.0, 128.9, 79.7, 32.7, 23.7.

Cyclohexyl 2-oxo-2-phenylacetate (2h).[12d] Yellow viscous liquid: yield 85 mg, 74%; R_f (9.8:0.2 hexanes/EtOAc) = 0.9; IR (ATR) 2941, 2860, 1728, 1687, 1452, 1199, 1174, 997 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.0 Hz, 2H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 5.13-5.07 (m, 1H), 2.03-1.99 (m, 2H), 1.82-1.77 (m, 2H), 1.63-1.56 (m, 4H), 1.49-1.38 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.8, 163.7, 134.8, 132.6, 130.0, 128.9, 75.5, 31.4, 25.2, 23.6.

3-Chloropropyl 2-oxo-2-phenylacetate (2i).[13d] Yellow viscous liquid: yield 60 mg, 53%; R*f* (9.8:0.2 hexanes/EtOAc) = 0.8; IR (ATR) 2941, 2860, 1728, 1687, 1452, 1199, 1174, 997 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.0 Hz, 2H), 7.68 (t, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 2H), 4.56 (t, *J* = 6.0 Hz, 2H), 3.67 (t, *J* = 6.0 Hz, 2H), 2.28-2.22 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.0, 163.6, 135.1, 132.4, 130.0, 129.0, 62.7, 40.8, 31.2.

Ethyl 2-oxo-2-p-tolylacetate (4a).[13a] Yellow viscous liquid: yield 64 mg, 67%; R_f (9.8:0.2 hexanes/EtOAc) = 0.9; IR (ATR) 2997, 1736, 1683, 1605, 1292, 1203, 1175, 1015 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.45 (q, *J* = 8.0 Hz, 2H), 2.44 (s, 3H), 1.42 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.2, 164.1, 146.3, 130.2, 130.0, 129.6, 62.3, 21.9, 14.1.

Propyl 2-oxo-2-p-tolylacetate (4b).[10e] Yellow viscous liquid: yield 73 mg, 72%; R_f (9.8:0.2 hexanes/EtOAc) = 0.9; IR (ATR) 2976, 1733, 1683, 1605, 1463, 1317, 1199, 1171, 1008 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.35 (t, *J* = 8.0 Hz, 2H), 2.44 (s, 3H), 1.85-1.76 (m, 2H), 1.01 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz,

$CDCl_3$) δ 186.2, 164.2, 146.3, 130.1, 130.0, 129.6, 67.7, 21.9, 10.3. HRMS (ESI) calcd for $C_{12}H_{14}O_3Na$ $[M+Na]^+$ 229.0835, found 229.0844.

Butyl 2-oxo-2-p-tolylacetate (4c). Yellow viscous liquid: yield 81 mg, 75%; R_f (9.8:0.2 hexanes/EtOAc) = 0.9; IR (ATR) 2961, 1735, 1682, 1604, 1460, 1305, 1199, 1172 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.39 (t, *J* = 8.0 Hz, 2H), 2.44 (s, 3H), 1.80-1.72 (m, 2H), 1.48-1.42 (m, 2H), 0.97 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.3, 164.2, 146.4, 130.2, 130.0, 129.7, 66.0, 30.5, 21.9, 19.1, 13.7; HRMS (ESI) calcd for $C_{13}H_{16}O_3Na$ $[M+Na]^+$ 243.0992, found 243.1010.

Ethyl 2-(4-methoxyphenyl)-2-oxoacetate (4d).[10e] Yellow viscous liquid: yield 66.5 mg, 64%; R_f (9.8:0.2 hexanes/EtOAc) = 0.9; IR (ATR) 2980, 2938, 2842, 1732, 1672, 1605, 1597, 1571, 1265, 1205, 1175, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 4.44 (q, *J* = 8.0 Hz, 2H), 3.90 (s, 3H), 1.42 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 184.9, 165.0, 164.2, 132.6, 125.5, 114.2, 62.2, 55.7, 14.1.

Propyl 2-(4-methoxyphenyl)-2-oxoacetate (4e). Yellow viscous liquid: yield 82 mg, 74%; R_f (9.8:0.2 hexanes/EtOAc) = 0.9; IR (ATR) 2960, 2938, 2872, 1729, 1672, 1594, 1512, 1262, 1204, 1160, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 4.34 (t, *J* = 6.8 Hz, 2H), 3.89 (s, 3H), 1.85-1.76 (m, 2H), 1.01 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.0, 165.0, 164.4, 132.5, 125.6, 114.3, 67.6, 55.6, 21.9, 10.3. HRMS (ESI) calcd for $C_{12}H_{14}O_4Na$ $[M+Na]^+$ 245.0784, found 245.0798.

Butyl 2-(4-methoxyphenyl)-oxoacetate (4f).[13c] Yellow viscous liquid: yield 92 mg, 78%; R_f (9.8:0.2 hexanes/EtOAc) = 0.9; IR (ATR) 2959, 2936, 2874, 1730, 1674, 1595, 1511, 1263, 1202, 1159, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8

Hz, 2H), 4.38 (t, J = 6.8 Hz, 2H), 3.90 (s, 3H), 1.80-1.73 (m, 2H), 1.50-1.40 (m, 2H), 0.97 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 185.0, 165.0, 164.4, 132.6, 125.6, 114.3, 65.9, 55.7, 30.5, 19.1, 13.7.

Ethyl 2-(2-methoxyphenyl)-2-oxoacetate (4g).[10e] Yellow viscous liquid: yield 89 mg, 86%; R_f (9.5:0.5 hexanes/EtOAc) = 0.6; IR (ATR) 2987, 2938, 1734, 1674, 1600, 1487, 1272, 1190, 1017 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 4.39 (q, *J* = 8.0 Hz, 2H), 3.87 (s, 3H), 1.39 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.6, 165.3, 160.3, 136.4, 130.8, 122.8, 121.3, 112.0, 61.8, 56.0, 14.2.

Butyl 2-(2-methoxyphenyl)-2-oxoacetate (4h). Yellow viscous liquid: yield 102 mg, 88%; R_f (9.5:0.5 hexanes/EtOAc) = 0.6; IR (ATR) 2960, 1734, 1669, 1599, 1482, 1458, 1272, 1187, 1019 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.6 Hz, 2.0 Hz, 1H), 7.58 (td, *J* = 7.2 Hz, 2.0 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 4.32 (t, *J* = 6.8 Hz, 2H), 3.87 (s, 3H), 1.77-1.70 (m, 2H), 1.49-1. 40 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.6, 165.5, 160.3, 136.3, 130.8, 122.9, 121.3, 112.0, 65.6, 56.1, 30.5, 19.0, 13.7; HRMS (ESI) calcd for $C_{13}H_{16}O_4Na$ $[M+Na]^+$ 259.0941, found 259.0964.

Cyclopentyl 2-(2-methoxyphenyl)-2-oxoacetate (4i).Yellow viscous liquid: yield 105 mg, 85%; R_f (9.5:0.5 hexanes/EtOAc) = 0.6; IR (ATR) 2965, 2948, 1730, 1669, 1599, 1465, 1272, 1194, 1060, 1020 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.58 (td, *J* = 8.2 Hz, 2.0 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 5.43-5.38 (m, 1H), 3.87 (s, 3H), 2.00-1.93 (m, 2H), 1.91-1.83 (m, 2H), 1.79-1.70 (m, 2H), 1.67-1.61 (m, 2H); $^{13}C\{^{1}H\}$

NMR (100 MHz, $CDCl_3$) δ 186.9, 165.2, 160.2, 136.2, 130.9, 122.9, 121.3, 111.9, 79.0, 55.8, 32.4, 23.7; HRMS (ESI) calcd for $C_{14}H_{16}O_4Na$ $[M+Na]^+$ 271.0941, found 271.0972.

Ethyl 2-(benzo[d][1,3]dioxol-5-yl)-2-oxoacetate (4j).[23b] Yellow viscous liquid: yield 94 mg, 85%; R_f (9.8:0.2 hexanes/EtOAc) = 0.8; IR (ATR) 2924, 1731, 1671, 1605, 1508, 1448, 1240, 1194, 1098, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 8.0 Hz,4.0 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.09 (s, 2H), 4.43 (q, *J* = 8.0 Hz, 2H), 1.42 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 184.6, 164.0, 153.5, 148.5, 127.9, 127.3, 108.7, 108.3, 102.3, 62.3, 14.1.

Butyl 2-(benzo[d][1,3]dioxol-5-yl)-2-oxoacetate (4k).[13b] Yellow viscous liquid: yield 97 mg, 77%; R_f (9.8:0.2 hexanes/EtOAc) = 0.8; IR (ATR) 2962, 2915, 1730, 1669, 1506, 1490, 1447, 1241, 1187, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 8.4 Hz,1.6 Hz, 1H), 7.47 (d, *J* = 1.6 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.09 (s, 2H), 4.37 (t, *J* = 6.8 Hz, 2H), 1.79-1.72 (m, 2H), 1.49-1.40 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 184.7, 164.2, 153.5, 148.5, 127.8, 127.3, 108.7, 108.3, 102.3, 66.1, 30.5, 19.0, 13.6.

Cyclopentyl 2-(benzo[d][1,3]dioxol-5-yl)-2-oxoacetate (4l). Yellow viscous liquid: yield 108 mg, 82%; R_f (9.8:0.2 hexanes/EtOAc) = 0.8; IR (ATR) 2962, 2909, 1723, 1669, 1601, 1490, 1427, 1239, 1191, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.0 Hz,1.6 Hz, 1H), 7.46 (d, *J* = 1.6 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.09 (s, 2H), 5.48-5.43 (m, 1H), 2.03-1.95 (m, 2H), 1.89-1.83 (m, 2H), 1.81-1.74 (m, 2H), 1.69-1.61 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.0, 164.1, 153.4, 148.5, 127.7, 127.3, 108.7, 108.3, 102.2, 79.6, 32.7, 23.7; HRMS (ESI) calcd for $C_{14}H_{14}O_5Na$ $[M+Na]^+$ 285.0733, found 285.0752.

Ethyl 2-oxo-2-m-tolylacetate (4m).[23a] Yellow viscous liquid: yield 58 mg, 60%; R_f (9.8:0.2 hexanes/EtOAc) = 0.9; IR (ATR) 2987, 2924, 1732, 1683, 1307, 1230, 1151, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81-7.79 (m, 2H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 4.45 (q, *J* = 8.0 Hz, 2H), 2.43 (s, 3H), 1.43 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 164.0, 138.9, 135.8, 132.4, 130.3, 128.8, 127.4, 62.3, 21.3, 14.1.

Ethyl 2-(3-methoxyphenyl)-2-oxoacetate (4n).[23a] Yellow viscous liquid: yield 58 mg, 56%; R_f (9.8:0.2 hexanes/EtOAc) = 0.9; IR (ATR) 2984, 2941, 1734, 1689, 1600, 1487, 1250, 1155, 1021 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 1H), 7.53 (s 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 4.45 (q, *J* = 8.0 Hz, 2H), 3.87 (s, 3H), 1.43 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.3, 163.9, 159.9, 133.7, 129.9, 123.2, 121.9, 113.2, 62.4, 55.5, 14.1.

Ethyl 2-(naphthalen-2-yl)-2-oxoacetate (4o).[10e] Yellow viscous liquid: yield 78 mg, 68%; R_f (9.8:0.2 hexanes/EtOAc) = 0.9; IR (ATR) 3058, 2984, 1734, 1681, 1626, 1310, 1176, 1123 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 4.52 (q, *J* = 8.0 Hz, 2H), 1.47 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.3, 163.9, 136.4, 133.5, 132.3, 130.0, 129.8, 129.6, 129.0, 127.9, 127.1, 124.0, 62.4, 14.2.

Ethyl 2-(biphenyl-4-yl)-2-oxoacetate (4p).[13a] Yellow viscous liquid: yield 73.6 mg, 58%; R_f (9.8:0.2 hexanes/EtOAc) = 0.9; IR (ATR) 2984, 2927, 1734, 1681, 1604, 1204, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.44 (t, *J* = 8.0 Hz, 1H), 4.49 (q, *J* = 8.0 Hz, 2H), 1.46 (t, *J* =

8.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 185.9, 163.8, 147.6, 139.5, 131.2, 130.7, 129.1, 128.7, 127.5, 127.4, 62.4, 14.2.

3-Chloropropyl 2-(4-bromophenyl)-2-oxoacetate (4r). Orange viscous liquid: yield 80 mg, 53%; R*f* (9.8:0.2 hexanes/EtOAc) = 0.9; IR (ATR) 2959, 1737, 1690, 1577, 1163, 1010 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3) δ 7.90 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 4.55 (t, *J* = 6.0 Hz, 2H), 3.67 (t, *J* = 6.0 Hz, 2H), 2.27-2.21 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 184.7, 163.0, 132.4, 131.4, 131.2, 62.9, 40.7, 31.1. HRMS (ESI) calcd for $C_{11}H_{10}BrClO_3Na$ $[M+Na]^+$ 326.9394, found 326.9386.

3-Chloropropyl 2-(4-chlorophenyl)-2-oxoacetate (4s). Orange viscous liquid: yield 71 mg, 62%; R_f (9.8:0.2 hexanes/EtOAc) = 0.9; IR (ATR) 2973, 1734, 1691, 1585, 1230, 1194, 1085, 1003 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.8 Hz, 2H), 7. 50 (d, *J* = 8.4 Hz, 2H), 4.55 (t, *J* = 6.0 Hz, 2H), 3.67 (t, *J* = 6.0 Hz, 2H), 2.28-2.22 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 184.5, 163.0, 141.8, 132.3, 131.4, 129.4, 62.9, 41.2, 31.6. HRMS (ESI) calcd for $C_{11}H_{10}Cl_2O_3Na$ $[M+Na]^+$ 282.9899, found 282.9896.

Ethyl 2-oxo-2-(thiophen-2-yl) acetate (4t).[10e] Orange viscous oil: yield 46 mg, 48%; R_f (9.5:0.5 hexanes/EtOAc) = 0.7; IR (ATR) 3104, 2984, 1730, 1657, 1508, 1408, 1301, 1194, 1053 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 8.0 Hz, 4.0 Hz, 1H), 7.82 (dd, *J* = 8.0 Hz, 4.0 Hz,1H), 7.20 (td, *J* = 8.0 Hz, 4.0 Hz, 1H), 4.44 (q, *J* = 8.0 Hz, 2H), 1.43 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 176.4, 161.7, 139.1, 137.5, 137.2, 128.7, 62.8, 14.1.

Cyclopentyl 2-oxo-2-(thiophen-2-yl) acetate (4u). Orange viscous oil: yield 63 mg, 56%; R_f (9.5:0.5 hexanes/EtOAc) = 0.7; IR (ATR) 2985, 2873, 1723, 1634, 1408, 1200, 1161, 1054 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 4.0 Hz, 1.2 Hz, 1H), 7.81 (dd, *J* = 4.8 Hz, 1.2 Hz,

1H), 7.19 (td, *J* = 4.6 Hz, 4.2 Hz, 1H), 5.45-5.41 (m, 1H), 2.04-1.95 (m, 2H), 1.92-1.86 (m, 2H), 1.85-1.78 (m, 2H), 1.69-1.64 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 176.9, 161.7, 139.2, 137.2, 137.0, 128.6, 80.1, 32.6, 23.8; HRMS (ESI) calcd for $C_{11}H_{12}O_3SNa$ $[M+Na]^+$ 247.0399, found 247.0413.

Ethyl 2-(1H-indol-3-yl)-2-oxoacetate (4v).[23c] Brownish solid: yield 60 mg, 51%; R_f (7.5:2.5 hexanes/EtOAc) = 0.6; IR (ATR) 3228, 2924, 2853, 1720, 1632, 1614, 1505, 1431, 1265, 1243, 1130 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81(s, 1H), 8.42 (s, 1H), 8.39-8.37 (m, 1H), 7.39-7.37 (m, 1H), 7.29-7.26 (m, 2H), 4.35 (q, *J* = 8.0 Hz, 2H), 1.37 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 178.4, 162.9, 136.4, 136.0, 126.2, 124.5, 123.6, 122.6, 114.5, 111.6, 62.2, 14.1.

Ethyl 2-(1-methyl-1H-indol-3-yl)-2-oxoacetate (4w). Brownish viscous liquid: yield 63 mg, 54%; R_f (8.0:2.0 hexanes/EtOAc) = 0.8; IR (ATR) 2931, 1726, 1643, 1195, 1082 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45-8.42 (m, 1H), 8.33 (s, 1H), 7.37-7.35 (m, 3H), 4.41 (q, *J* = 8.0 Hz, 2H), 3.87 (s, 3H), 1.43 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 177.5, 163.1, 140.4, 137.4, 127.2, 124.2, 123.6, 122.9, 112.9, 110.0, 62.1, 33.9, 14.2; HRMS (ESI) calcd for $C_{13}H_{13}NO_3Na$ $[M+Na]^+$ 254.0788, found 254.0807.

Ethyl 2-(1-benzyl-1H-indol-3-yl)-2-oxoacetate (4x). Brownish viscous liquid: yield 86.5 mg, 56%; R_f (8.0:2.0 hexanes/EtOAc) = 0.8; IR (ATR) 3228, 2924, 853, 1720, 1632, 1614, 1505, 1431, 1265, 1243, 1130 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 4.0 Hz, 1H), 8.42 (s, 1H), 7.37-7.29 (m, 6H), 7.19-7.18 (m, 2H), 5.38 (s, 2H), 4.39 (q, *J* = 8.0 Hz, 2H), 1.42 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 177.6, 162.9, 139.7, 136.9, 135.2, 129.1, 128.4,

127.3, 127.1, 124.3, 123.7, 122.9, 113.4, 110.5, 62.1, 51.2, 14.1. HRMS (ESI) calcd for $C_{19}H_{17}NO_3Na$ $[M+Na]^+$ 330.1101, found 330.1085.

Isopropyl 2-(1-ethyl-1H-indol-3-yl)-2-oxoacetate (4y). Brownish viscous liquid: yield 76 mg, 58%; R_f (8.0:2.0 hexanes/EtOAc) = 0.6; IR (ATR) 2984, 2938, 1720, 1645, 1519, 1394, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45-8.43 (m, 1H), 8.37 (s, 1H), 7.40-7.37 (m, 1H), 7.35-7.33 (m, 2H), 5.29-5.20 (m, 1H), 4.23 (q, *J* = 8.0 Hz, 2H), 1.56 (t, *J* = 8.0 Hz, 3H), 1.42 (d, *J* = 8.0 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177.9, 162.8, 138.5, 136.5, 127.4, 124.0, 123.5, 123.0, 113.0, 110.0, 70.0, 42.1, 21.7, 15.1. HRMS (ESI) calcd for $C_{15}H_{17}NO_3Na$ $[M+Na]^+$ 282.1101, found 282.1082.

Cyclopentyl 2-(1-ethyl-1H-indol-3-yl)-2-oxoacetate (4z). Brownish viscous liquid: yield 82 mg, 58%; R_f (8.0:2.0 hexanes/EtOAc) = 0.6; IR (ATR) 2964, 2933, 1718, 1638, 1517, 1392, 1188, 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.46-8.43 (m,1H), 8.35 (s, 1H), 7.41-7.37 (m, 1H), 7.36-7.33 (m, 2H), 5.42-5.37 (m, 1H), 4.24 (q, *J* = 8.0 Hz, 2H), 2.04-1.96 (m, 2H), 1.93-1.86 (m, 2H), 1.84-1.80 (m, 2H), 1.67-1.63 (m, 2H), 1.56 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177.9, 163.2, 138.5, 136.5, 127.3, 124.0, 123.5, 122.9, 113.0, 110.0, 79.1, 42.1, 32.7, 23.9, 15.0. HRMS (ESI) calcd for $C_{17}H_{19}NO_3Na$ $[M+Na]^+$ 308.1257, found 308.1232.

Experimental procedure for the gram-scale synthesis of α-ketoesters.

Imidates **1e** (2.30 g) and **3g** (2.32 g) (12.0 mmol), anhydrous $Cu(OAc)_2$ (1.2 mmol, 220.0 mg), anhydrous pyridine (6.0 mmol, 480 μL) and anhydrous toluene (60 mL) were placed in a 250 mL round-bottom flask. The flask was sealed with a rubber septum and degassed and refilled with O_2 (3 times). Then, the reaction flask was heated at 90 °C in a preheated oil bath for 20 h. Upon completion of the reaction (monitored by TLC), the reaction mixture was treated with 10% HCl

solution (100 mL) and stirred at room temperature for 30 min. The resulting solution was extracted with ethyl acetate (50 mL × 3), and the combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography with hexanes and EtOAc as the eluent to afford the corresponding products **2e** (68%, 1.68 gm) and **4g** (83%, 2.10 gm), respectively.

Experimental procedure for the one-pot synthesis of α-ketoesters.

A 50 mL flask containing a solution of a nitrile **5** (1.0 mmol, 117.5 mg) and alcohols**6** and **9** (1.1 mmol) was sealed with a rubber septum. The reaction mixture was cooled to 0 °C, and dry HCl(g) was passed through the solution while stirring for 1.0 h. The reaction mixture was stirred at room temperature for an additional 12 h.[21b] Upon completion of the reaction (monitored by TLC), the solvent was concentrated under reduced pressure to produce the crude imidate hydrochloride salts. The residue was further cooled to 0 °C, and a saturated $NaHCO_3$ solution was added slowly until CO_2 gas evolution ceased. The product was extracted with Et_2O (2 x 10 mL), and dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain the imidates. The resulting imidates, without further purification, were treated with anhydrous $Cu(OAc)_2$ (0.05 mmol, 18.2 mg), pyridine (0.25 mmol, 40 μL) and toluene (5.0 mL) in a 25 mL round-bottom flask. The reaction flask was sealed with a rubber septum and degassed and refilled with O_2 (3 times). The reaction flask was then heated at 90 °C in a preheated oil bath for 20 h. After completion of the reaction, 10% HCl solution (10 mL) was added to the reaction mixture and stirred at room temperature for 30 min. The resulting solution was extracted with ethyl acetate (15 mL × 3), and the combined organic layer was washed with brine (10 mL),dried over anhydrous Na_2SO_4,and evaporated under reduced pressure. The crude product was purified

by silica gel column chromatography (98:2 hexanes/EtOAc as the eluent) and dried under *vacuo* to afford the corresponding products **8** and **11**.

1-Adamantanylmethyl 2-oxo-2-phenylacetate (8).[23d] Yellow viscous liquid: yield 36.0 mg, 31%; R_f (9.8:0.2 hexanes/EtOAc) = 0.8; IR (ATR) 2958, 1734, 1688, 1596, 1582, 1451, 1326, 1204, 1172, 1002 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.0 Hz, 2H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 3.99 (s, 2H), 2.00 (s, 3H), 1.75-1.72 (m, 3H), 1.67-1.64 (m, 3H), 1.61-1.60 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 164.3, 134.9, 132.5, 130.0, 128.9, 75.5, 39.1, 36.8, 33.4, 27.9. HRMS (ESI) calcd for $C_{19}H_{22}O_3Na$ $[M+Na]^+$ 321.1461, found 321.1478.

2-Isopropyl-5-methylcyclohexyl 2-oxo-2-phenylacetate (11).[13c] Yellow viscous liquid: yield 32.0 mg, 28%; R_f (9.8:0.2 hexanes/EtOAc) = 0.8; IR (ATR) 2942, 2862, 1730, 1686, 1454, 1200, 1174, 997 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.0 Hz, 2H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 5.13-5.07 (m, 1H), 2.03-1.95 (m, 2H), 1.83-1.77 (m, 2H), 1.65-1.56 (m, 2H), 1.47-1.39 (m, 3H), 0.94-0.90 (m, 6H), 0.82-0.80 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.8, 163.7, 134.8, 132.6, 130.0, 128.9, 71.6, 50.2, 45.1, 34.6, 31.4, 25.9, 23.1, 22.2, 21.0, 16.1.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR spectra of the starting materials and products, EPR analysis, and control experiment results (PDF).

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The authors declare no competing financial interest.

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