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Palladium-Catalyzed Dehydrogenation Coupling–Cyclization Reactions of Acetylenic Acids with Iodonium Ylides for the Synthesis of 2(5*H*)-Furanones

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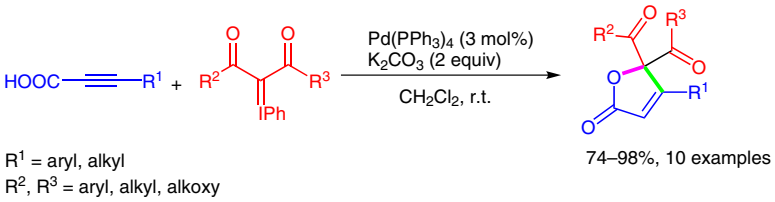

R^1 = aryl, alkyl
R^2, R^3 = aryl, alkyl, alkoxy

74–98%, 10 examples

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Abstract A new route for the synthesis of 2(5*H*)-furanones is presented via $Pd(PPh_3)_4$-catalyzed cascade reaction of acetlenic acids with iodonium ylides using K_2CO_3 as the base. The cascade proceeds through dehydrogenation coupling and cyclization under mild conditions.

Key words palladium, dehydrogenation, acetylenic acids, iodonium ylides, 2(5H)-furanones

2(5*H*)-Furanones (butenolides), important classes of oxygen-containing heterocyclic compounds, are ubiquitous in natural products, drugs, and materials, and important intermediates in organic synthesis (Figure 1).[1–4] 2(5*H*)-Furanone derivatives have been considered as potential insecticides, fungicides, antibiotics, bactericides, anticancer agents, allergy inhibitors, cyclooxygenase inhibitors, phospholipase A_2 inhibitors, etc.[5] For these reasons, considerable efforts have been devoted to the synthesis of 2(5*H*)-furanone and its derivatives.[6] The transition-metal-promoted or -catalyzed cyclization reaction of 2,3-allenoic acids/esters was one of useful methods for the construction of 2(5*H*)-furanones.[7] However, those methods were mostly limited by the structure of the starting materials. Thus, the development of new methods for the synthesis of 2(5*H*)-furanones is still attractive.

Transition-metal-catalyzed cascade reactions have proven to be a powerful shortcut for the assembly of complex ring systems in organic synthesis. Among these processes, the cyclization of alkynes is a particularly effective and atom-economical step for the construction of heterocycles. The Toste[8] and Yang[9] groups reported transition-metal-catalyzed Conia-ene reaction of 1,3-dicarbonyl compounds with alkynes. The Liang group[10] also demonstrated

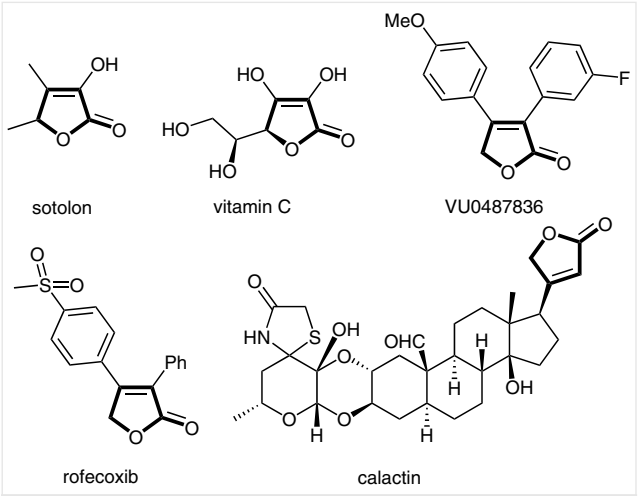
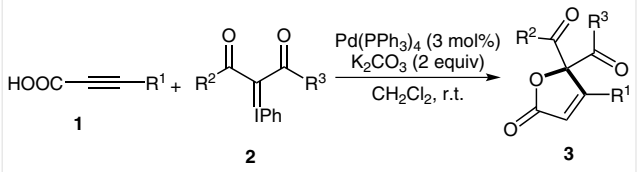


Figure 1 Examples of important 2(5*H*)-furanones

nickel(II)-catalyzed cyclization reactions of propargylic compounds for the indene formation. In connection with our ongoing projects on the synthesis of 2(5*H*)-furanones, we herein report a palladium-catalyzed cascade reaction of acetylenic acids with iodonium ylides at room temperature (Scheme 1) that proceeds through a cascade of dehydrogenation coupling and cyclization.



Scheme 1 Dehydrogenation coupling–cyclization reactions of acetylenic acids with iodonium ylides

Our initial investigations focused on the dehydrogenation coupling–cyclization of 3-phenylpropiolic acid (**1a**) with dimethyl 2-(phenyl-λ³-iodanylidene)malonate (**2a**, Table 1). Gratifyingly, treatment of the substrate 3-phenylpropiolic acid (**1a**) with **2a**, $Pd(PPh_3)_4$, and K_2CO_3 in CH_2Cl_2 at room temperature for six hours afforded the desired product dimethyl 5-oxo-3-phenylfuran-2,2(5*H*)-dicarboxylate (**3aa**, Figure 2) in 98% yield (Table 1, entry 1).[11] A serial of other palladium catalysts, including $Pd(dba)_2$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, and $PdCl_2$ were tested, and the results showed that they were less effective than $Pd(PPh_3)_4$ (Table 1, entries 2–5). For example, 90% yield of **3aa** was obtained when $Pd(dba)_2$ was used as catalyst, while 75% yield of **3aa** was afforded when $Pd(OAc)_2$ was used. However, no product **3aa** was detected by GC–MS in the absence of palladium catalyst (Table 1, entry 6). Screening revealed that the amount of catalyst affected the reaction: The identical yield of **3aa** was obtained at a loading of 5 mol% $Pd(PPh_3)_4$ (Table 1, entry 7), while only 73% yield of **3aa** was isolated in the presence of 1 mol% $Pd(PPh_3)_4$ (Table 1, entry 8). In light of these results, a series of other bases, namely Cs_2CO_3, KOH, and organic base Et_3N, were tested (Table 1, entries 9–11). The results showed that they were less effective than K_2CO_3 (Table 1, entry 1 vs. entries 9–11). The amount of K_2CO_3 was also examined, and the results demonstrated that two equivalents of K_2CO_3 were more efficient (Table 1, entry 1 vs. entries 12 and 13). Others solvents such as DCE, MeCN, toluene, and THF were less effective (Table 1, entries 14–17). Among the reaction temperatures tested, the yield of **3aa** decreased from 98% at room temperature to 90% at 40 °C and 95% at 10 °C. It turned out that the reaction at room temperature gave the best results (Table 1, entry 1 vs. entries 18 and 19).

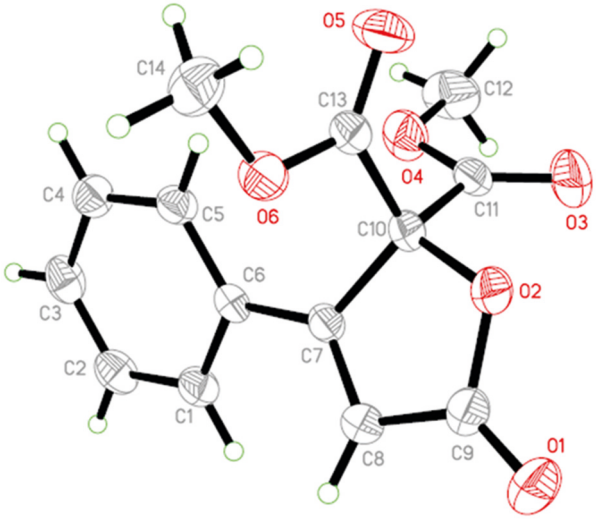
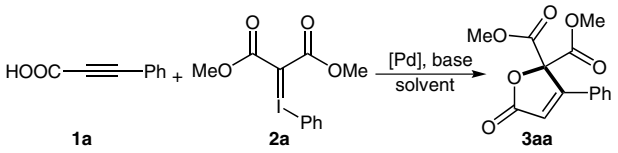


Figure 2 X-ray crystal structure of **3aa**

Table 1 Screening of the Optimal Conditions[a]

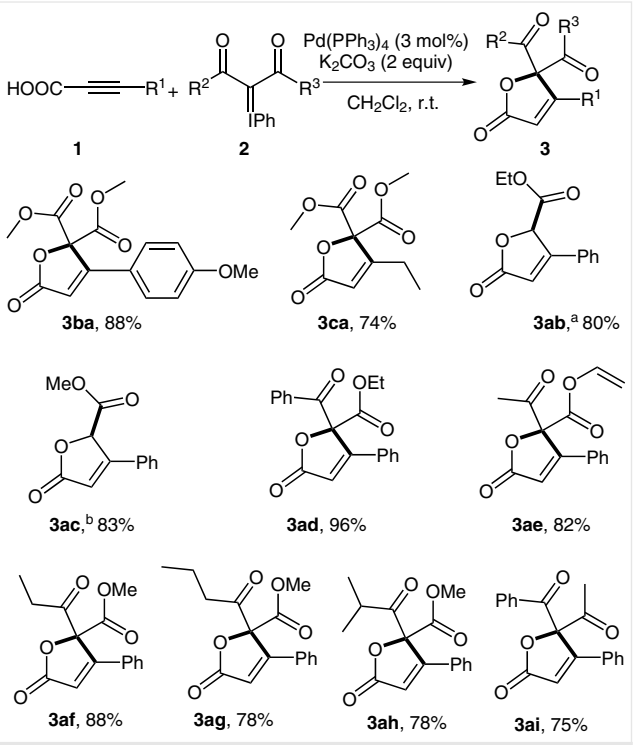


Entry	Pd (mol%)	Base (equiv)	Solvent	Isolated yield (%)
1	$Pd(PPh_3)_4$ (3)	K_2CO_3 (2)	CH_2Cl_2	98
2	$Pd(dba)_2$ (3)	K_2CO_3 (2)	CH_2Cl_2	90
3	$PdCl_2(PPh_3)_2$ (3)	K_2CO_3 (2)	CH_2Cl_2	76
4	$Pd(OAc)_2$ (3)	K_2CO_3 (2)	CH_2Cl_2	75
5	$PdCl_2$ (3)	K_2CO_3 (2)	CH_2Cl_2	82
6	–	K_2CO_3 (2)	CH_2Cl_2	0[b]
7	$Pd(PPh_3)_4$ (5)	K_2CO_3 (2)	CH_2Cl_2	97
8	$Pd(PPh_3)_4$ (1)	K_2CO_3 (2)	CH_2Cl_2	73
9	$Pd(PPh_3)_4$ (3)	Cs_2CO_3 (2)	CH_2Cl_2	93
10	$Pd(PPh_3)_4$ (3)	KOH (2)	CH_2Cl_2	73
11	$Pd(PPh_3)_4$ (3)	Et_3N (2)	CH_2Cl_2	68
12	$Pd(PPh_3)_4$ (3)	K_2CO_3 (3)	CH_2Cl_2	98
13	$Pd(PPh_3)_4$ (3)	K_2CO_3 (1)	CH_2Cl_2	90
14	$Pd(PPh_3)_4$ (3)	K_2CO_3 (2)	DCE	95
15	$Pd(PPh_3)_4$ (3)	K_2CO_3 (2)	MeCN	39
16	$Pd(PPh_3)_4$ (3)	K_2CO_3 (2)	toluene	46
17	$Pd(PPh_3)_4$ (3)	K_2CO_3 (2)	THF	41
18[c]	$Pd(PPh_3)_4$ (3)	K_2CO_3 (2)	CH_2Cl_2	90
19[d]	$Pd(PPh_3)_4$ (3)	K_2CO_3 (2)	CH_2Cl_2	95

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.2 equiv), [Pd], base, and solvent (2 mL) under Ar atmosphere at r.t.
[b] Dimethyl 2-[(3-phenylpropioloyl)oxy]malonate (**4**) was isolated in 85% yield.
[c] At 40 °C.
[d] At 10 °C.

With the optimized reaction conditions in hand, the scope of the cascade reaction was investigated with a variety of propiolic acids **1** and iodonium ylides **2** (Scheme 2). Initially, dimethyl 2-(phenyl-λ³-iodanylidene)malonate (**2a**) reacted with two different propiolic acids **1b** and **1c**, in the presence of $Pd(PPh_3)_4$ and K_2CO_3. The results demonstrated both aryl and alkyl propiolic acids were found to be suitable substrates for the reaction (products **3ba** and **3ca**). For example, substrate **1c**, an alkyl propiolic acid, was transformed into product **3ca** in 74% yield. Subsequently, a number of iodonium ylides **2b–i** were examined under the optimal conditions, and they were found to be suitable substrates for the reaction. To our surprise, the reaction preferably delivered the nonquaternary carbon products, dihydrofuranones **3ab** and **3ac**, in good yields via C–C bond cleavage from substrates ethyl propionate **2b** and methyl butyrate **2c**. We were happy to observe that substrates bearing a phenyl group (**2d**), an allyl group (**2e**), and an al-

kyl group (**2f**–**h**) could also react with 3-phenylpropiolic acid efficiently in moderate to good yields (products **3ad**–**ah**). Notably, **1a** and ketone iodonium ylide **2i** reacted smoothly in a 75% yield under the standard conditions (product **3ai**).

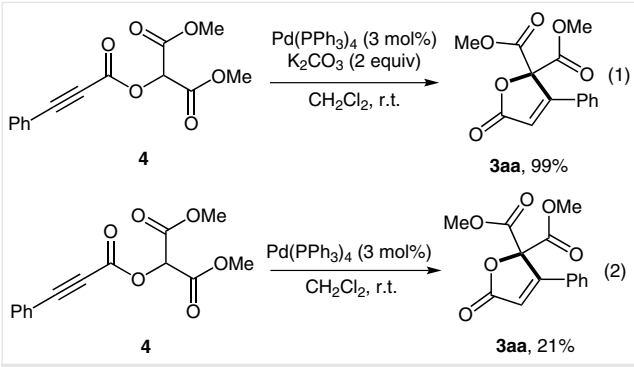


Scheme 2 Screening scope of propiolic acids **1** and iodonium ylides. *Reagents and conditions*: **1** (0.2 mmol), **2** (1.2 equiv), $Pd(PPh_3)_4$ (3 mol%), K_2CO_3 (0.4 mmol), and CH_2Cl_2 (2 mL) at r.t. under Ar atmosphere for 6 h. [a] R^1 = Me. [b] R^1 = Et.

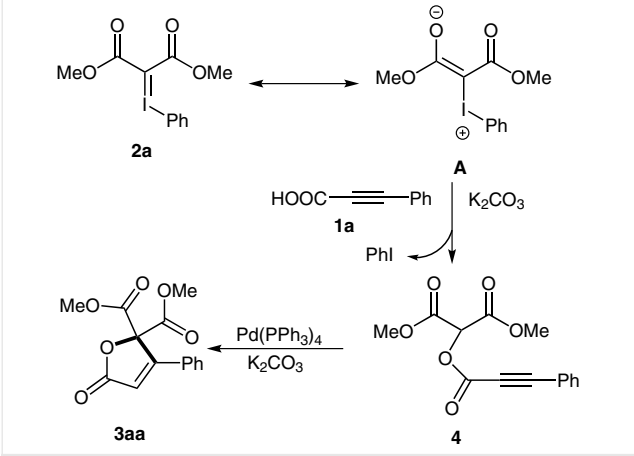
To understand the mechanism, two experiments were done. As shown in Table 1, entry 6, 85% yield of product **4** was isolated in the absence palladium catalyst. Compound **4** could transform to the desired product **3aa** in the presence of 3 mol% $P(PPh_3)_4$ and two equivalents K_2CO_3 (Scheme 3, eq. 1). However, product **3aa** was obtained with a lower yield under only palladium catalyst conditions (Scheme 3, eq. 2). This implies that the reaction proceeds via a dehydrogenation coupling and then cyclization of alkynes in a tandem pathway.

Proposed reaction mechanism based on the above results and previous reports[12] are shown in Scheme 4. Initially, dehydrogenation coupling of intermediate **A** with 3-phenylpropiolic acid (**1a**) to yield intermediate **4** and phenyl iodide, followed by intramolecular cyclization of intermediate **4** to afford the desired 2(5*H*)-furanones.

In summary, we have developed a mild and general cascade reaction of acetylenic acids with an iodonium ylide protocol for the synthesis of 2(5*H*)-furanones. In the presence of $Pd(PPh_3)_4$ and K_2CO_3, acetylenic acids successfully underwent the dehydrogenation coupling–cyclization tandem reaction with iodonium ylides at room temperature to afford the corresponding 2(5*H*)-furanones in moderate to good yields. Notably, 2(5*H*)-furanones are an important skeleton in natural products and exhibit a broad range of biological activities. Work to probe the detailed mechanism and apply the reaction in organic synthesis is currently in progress.



Scheme 3 Control experiments



Scheme 4 Proposed mechanism

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560554.

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(11) **Typical Experimental Procedure for the Palladium-Catalyzed Dehydrogenation Coupling–Cyclization Reactions of Acetylenic Acids with Iodonium Ylides**

To a Schlenk tube were added 3-phenylpropiolic acid (**1a**, 29.2 mg, 0.2 mmol), dimethyl 2-(phenyl-λ^3-iodanylidene)malonate (**2a**, 80.2 mg, 0.24 mmol), $Pd(PPh_3)_4$ (13.8 mg, 0.06 mmol), K_2CO_3 (60.8 mg, 0.4 mmol), and CH_2Cl_2 (2 mL). Then the tube was charged with argon and was stirred at r.t. for the indicated time until complete consumption of starting material as monitored by TLC and GC–MS analysis. After the reaction was finished, the reaction diluted in Et_2O and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (hexane–EtOAc) to afford the desired product **3aa** (54.1 mg, 98%).

Dimethyl 5-Oxo-3-phenylfuran-2,2(5*H*)-dicarboxylate (3aa)

Yield: 54.1 mg (98%); white solid; mp 104–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.56 (d, *J* = 8.0 Hz, 2 H), 7.42–7.37 (m, 3 H), 6.46 (s, 1 H), 3.76 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.13, 164.61, 162.24, 131.86, 128.86, 128.54, 116.20, 99.99, 88.06, 54.05. IR (neat): 2958, 2852, 1779, 1749, 1262, 797cm^{-1}. LRMS (EI, 70 eV): *m/z* (%) = 276 (5) [M], 232 (9), 188 (77), 161 (100), 115 (32), 102 (60). ESI-HRMS: *m/z* calcd for $C_{10}H_{13}O_6$ [M + H]$^+$: 227.0712; found: 277.0708.

Dimethyl 3-(4-Methoxyphenyl)-5-oxofuran-2,2(5*H*)-dicarboxylate (3ba)

Yield: 53.8 mg (88%); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.56 (d, *J* = 8.0 Hz, 2 H), 6.88 (d, *J* = 8.0 Hz, 2 H), 6.33 (s, 1 H), 3.86 (s, 6 H), 3.84 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 164.89, 162.80, 130.98, 120.91, 114.28, 113.19, 60.42, 55.50, 54.00, 53.87. IR (neat): 2924, 2855, 1761, 1376, 1265, 743 cm^{-1}. LRMS (EI, 70 eV): *m/z* (%): 307 (1) [M], 247 (10), 219 (27), 189 (3), 175 (3), 132 (37), 117 (15), 59 (100). ESI-HRMS: *m/z* calcd for $C_{10}H_{13}O_6$ [M + H]$^+$: 307.0818; found: 307.0812.

Dimethyl 3-Ethyl-5-oxofuran-2,2(5*H*)-dicarboxylate (3ca)

Yield: 33.8 mg (74%); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.92 (s, 1 H), 3.82 (d, *J* = 12.0 Hz, 6 H), 2.56–2.50 (m, 2 H), 1.19 (d, *J* = 8.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.36, 169.22, 164.31, 117.00, 88.7, 60.41, 53.90, 21.59, 11.20. IR (neat): 2954, 2924, 2854, 2361, 1784, 1755, 1458, 742, 684 cm^{-1}. LRMS (EI, 70 eV): *m/z* (%) = 226 (9) [M], 184 (20) [M], 168 (16), 141 (100), 126 (17). ESI-HRMS: *m/z* calcd for $C_{10}H_{13}O_6$ [M + H]$^+$: 229.0712; found: 229.0707.

Ethyl 5-Oxo-3-phenyl-2,5-dihydrofuran-2-carboxylate (3ab)

Yield: 37.2 mg (80%); white solid; mp 93–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.54 (t, *J* = 4.0 Hz, 2 H), 7.42–7.39 (m, 3 H), 6.37 (s, 1 H), 5.81 (s, 1 H), 4.11 (m, 2 H), 1.11 (m, 6 H). ^{13}CNMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.18, 166.16, 162.43, 132.02, 129.18, 128.71, 127.49, 114.50, 80.06, 62.71, 13.83. IR (neat): 3108, 2919, 2850, 1763, 1465, 1155, 763 cm^{-1}. LRMS (EI, 70 eV): *m/z* (%) = 233 (3) [M], 203 (25), 146 (100), 131 (29). ESI-HRMS: *m/z* calcd for $C_{13}H_{13}O_4$ [M + H]$^+$: 233.0814; found: 233.0808.

Methyl 5-Oxo-3-phenyl-2,5-dihydrofuran-2-carboxylate (3ac)
Yield: 36.2 mg (83%); white solid; mp 75–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.54 (t, *J* = 4.0 Hz, 2 H), 7.44–7.40 (m, 3 H), 6.38 (s, 1 H), 5.85 (s, 1 H), 3.65 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.15, 166.71, 162.32, 132.09, 129.29, 128.85, 128.82, 128.60, 171.44, 114.45, 53.38. IR (neat): 2957, 1766, 1621, 1437, 1158, 788, 688 cm^{-1}. LRMS (EI, 70 eV): *m/z* (%) = 218 (10) [M], 159 (100), 146 (20), 77 (56). ESI-HRMS: *m/z* calcd for $C_{12}H_{10}O_4$ [M + H]$^+$: 219.0657; found: 219.0650.

Ethyl 2-Benzoyl-5-oxo-3-phenyl-2,5-dihydrofuran-2-carboxylate (3ad)
Yield: 64.5 mg (96%); light yellow solid; mp 48–50 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.96 (d, *J* = 8.0 Hz, 2 H), 7.60 (d, *J* = 8.0 Hz, 3 H), 7.43–7.36 (m, 5 H), 6.50 (s, 1 H), 4.16–4.10 (m, 2 H), 1.02 (t, *J* = 6.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 189.13, 170.15, 165.88, 164.38, 134.15, 134.02, 131.64, 129.63, 129.29, 129.23, 128.73, 128.67, 116.49, 63.49, 13.67. IR (neat): 2925, 2854, 1767, 1712, 1450, 1262, 1028, 712 cm^{-1}. LRMS (EI, 70 eV): *m/z* (%) = 337 (1) [M], 207 (1), 105 (100), 103 (2), 77 (28). ESI-HRMS: *m/z* calcd for $C_{20}H_{17}O_5$ [M + H]$^+$: 337.1076; found: 337.1071.

Vinyl 2-Acetyl-5-oxo-3-phenyl-2,5-dihydrofuran-2-carboxylate (3ae)
Yield: 44.6 mg (82%); pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.47–7.45 (m, 2 H), 7.42–7.37 (m, 3 H), 6.49 (s, 1 H), 5.42–5.35 (m, 1 H), 5.00–4.90 (m, 2 H), 2.12 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 203.09, 117.82, 164.87, 131.71, 129.35, 129.06, 127.64, 121.02, 116.56, 93.90, 37.11, 29.71, 24.06. IR (neat): 2923, 2852, 1766, 1188, 769 cm^{-1}. LRMS (EI, 70 eV): *m/z* (%) = 272 (6) [M], 245 (14), 201 (37), 158 (100), 77 (30). ESI-HRMS: *m/z* calcd for $C_{15}H_{13}O_5$ [M + H]$^+$: 273.0763; found: 273.0758.

Methyl 5-Oxo-3-phenyl-2-propionyl-2,5-dihydrofuran-2-carboxylate (3af)
Yield: 48.2 mg (88%); white solid; mp 101–103. ^{1}H NMR (400 MHz,$CDCl_3$, 25 °C): δ = 7.61–7.59 (d, *J* = 8.0 Hz, 2 H), 7.49–7.27 (m, 3 H), 6.54 (s, 1 H), 3.83 (s, 3 H), 2.87–2.77 (m, 1 H), 2.65–2.55 (m, 1 H), 1.09–1.05 (t, *J* = 8.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 201.0, 170.4, 165.4, 162.8, 131.9, 120.3, 128.8, 128.8, 128.7, 127.4, 115.7, 92.5, 92.5, 79.0 , 77.4, 53.9, 31.4. IR (neat): 2957, 2851, 2359, 1776, 1255, 739 cm^{-1}. LRMS (EI, 70 eV): *m/z* (%) = 274 (6) [M], 259 (14), 200 (37), 146 (100), 77 (30). ESI-HRMS: *m/z* calcd for $C_{15}H_{14}O_5$ [M + H]$^+$: 274.0841; found: 275.0837.

Methyl 2-Butyryl-5-oxo-3-phenyl-2,5-dihydrofuran-2-carboxylate (3ag)
Yield: 44.9 mg (78%); white solid; mp 113–117. ^{1}H NMR (400 MHz,$CDCl_3$, 25 °C): δ = 7.61–7.59 (d, *J* = 8.0 Hz, 2 H), 7.49–7.41 (m, 3 H), 6.54 (s, 1 H), 3.83 (s, 3 H), 2.77–2.71 (m, 1 H), 2.58–2.40 (m, 1 H), 1.66–1.55 (m, 2 H), 0.89–0.86 (t, *J* = 4.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 198.0, 170.4, 165.6, 164.2, 162.8, 162.6, 131.8, 129.1, 128.9, 128.7, 127.5, 115.9, 114.5, 92.7, 80.2, 71.8, 26.0, 21.5, 21.3. IR (neat): 2937, 2811, 2359, 1789, 1345, 741 cm^{-1}. LRMS (EI, 70 eV): *m/z* (%) = 288 (1) [M], 240 (12), 210 (13) 160 (6), 77 (100). ESI-HRMS: *m/z* calcd for $C_{16}H_{16}O_5$ [M + H]$^+$: 288.0997; found: 288.0992.

Methyl 2-Isobutyryl-5-oxo-3-phenyl-2,5-dihydrofuran-2-carboxylate (3ah)
Yield: 44.9 mg (78%); white solid; mp 110.3–112.0 ^{1}H NMR (400 MHz,$CDCl_3$, 25 °C): δ = 7.60–7.40 (m, 2 H), 7.45–7.41 (m, 3 H), 6.55 (s, 1 H), 3.84 (s, 3 H), 3.09 (t, *J* = 6.0 Hz, 1 H), 1.23–1.21 (d, *J* = 8.0 Hz, 3 H), 1.01–0.99 (d, *J* = 8.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 204.68, 170.51, 165.49, 162.99, 131.86, 128.90, 128.71, 115.96, 92.92, 53.89, 36.56, 19.21, 19.17. IR (neat): 2957, 2851, 2359, 1776, 1255, 739 cm^{-1}. LRMS (EI, 70 eV): *m/z* (%) = 274 (6) [M], 259 (14), 200 (37) 146 (100), 77 (30). ESI-HRMS: *m/z* calcd for $C_{16}H_{16}O_5$ [M + H]$^+$: 288.2951; found: 288.2946.

4-Acetyl-4-benzoyl-3-phenylcyclopent-2-enone (3ai)
Yield 47.4 mg (75%); yellow solid; mp 52–55 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.89 (d, *J* = 8.0 Hz, 2 H), 7.62 (t, *J* = 10.0 Hz, 3 H),7.49–7.43 (m, 5 H), 6.67 (s, 1 H), 2.39 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.51, 164.29, 134.08, 132.01, 129.70, 129.26, 128.87, 115.84, 24.78. IR (neat): 2925, 2854, 1770, 1693, 1450, 1266, 713, 685 cm^{-1}. LRMS (EI, 70 eV): *m/z* (%) = 306 (0.02) [M], 218 (4), 189 (6), 173 (27), 158 (65), 105 (100). ESI-HRMS: *m/z* calcd for $C_{20}H_{17}O_3$ [M + H]$^+$: 306.3121; found: 306.0892.

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