Regioselective Palladium(II)-Catalyzed Desulfitative Heck-Type Reaction: Access to α-Benzyl-β-keto Esters from Baylis–Hillman Adducts and Sodium Sulfinates

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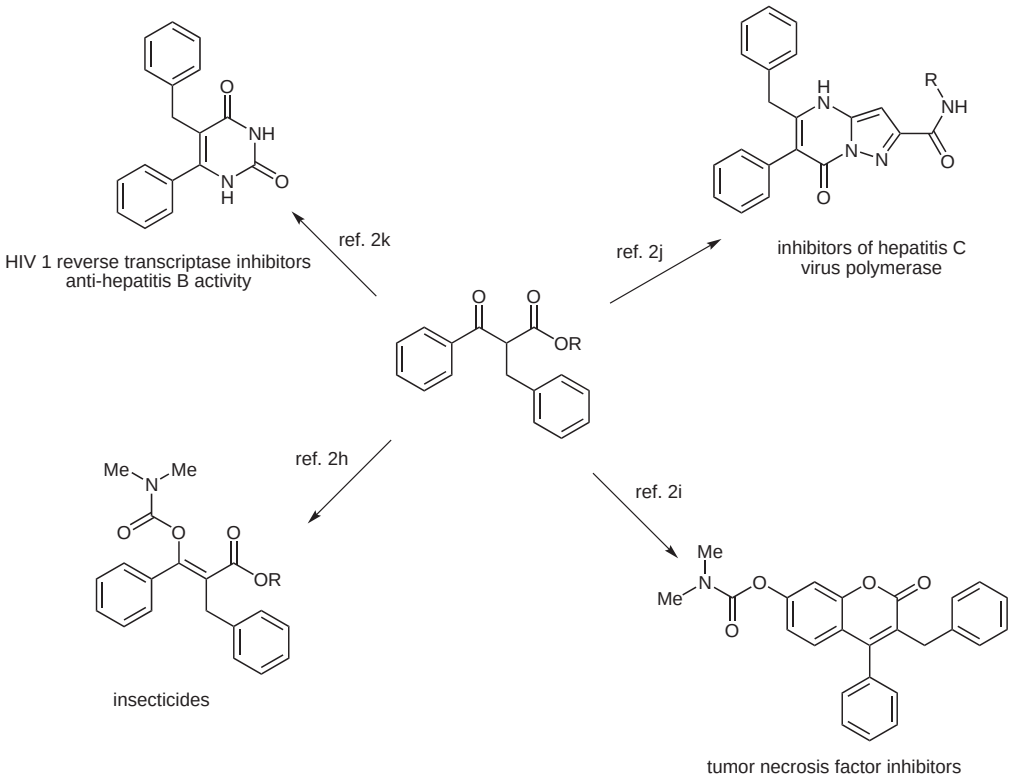
Abstract: A new palladium(II)-catalyzed desulfitative Heck-Type arylation from sodium arenesulfinates and Baylis–Hillman adducts for the synthesis of highly functionalized α-benzyl-β-keto ester derivatives in good to excellent yields has been developed. This methodology is simple and mild, it can utilize halogen bearing building blocks, and it has excellent regioselectivity.

Key words: Heck reaction, Baylis–Hillman adducts, palladium, desulfitative, α-benzyl-β-keto esters

The development of synthetic organic chemistry mostly depends on reactions involving the formation of new C–C bonds. The Heck reaction is one of the most important versatile C–C bond forming reactions catalyzed by a transition metal.[1] α-Benzyl-β-keto esters are a predominant structural motif with various important applications in organic synthesis, and they have been extensively used in the construction of natural products and other biologically active heterocyclic molecules (Scheme 1).[2] Many efforts have been made to achieve efficient preparation of these scaffolds through palladium-catalyzed Heck reaction between Baylis–Hillman adducts[3] and various aryl sources[4] [Scheme 2 (a)].

However, these methods suffer limited scope despite good yields, they require long reaction times at reflux, and they have a small methodological scope which lacks chemo- and regioselectivity. Recently, our group has reported a method for synthesis of α-benzyl-β-keto esters with good yields from arylboronic acids used as arylpalladium(II) precursors with Baylis–Hillman adducts.[5]



Scheme 1 Synthetic applications of α-benzyl β-keto esters

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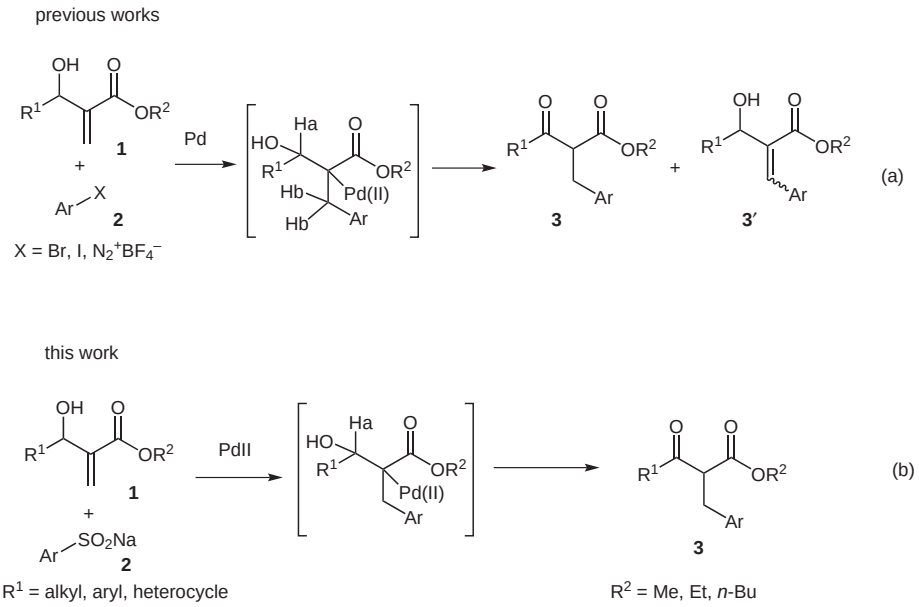


Scheme 2 Palladium-catalyzed synthesis of α-benzyl-β-keto esters from Baylis–Hillman adducts

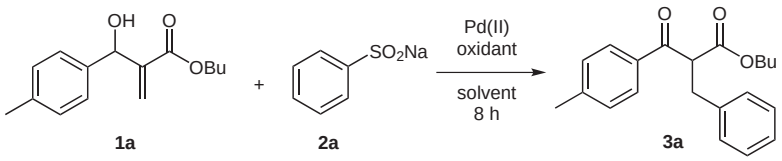
In recent years, desulfitative coupling for the construction of C–C bonds by using arenesulfinic acids,[6] sodium arenesulfinates,[7] and, less frequently, arenesulfonyl chlorides[8] as aryl sources via the extrusion of SO_2 has attracted increasing attention. Sulfinic acid salts are generally used as sulfonylation reagents in the preparation of compounds containing sulfonyl groups.[9] Most recently, the palladium-catalyzed desulfitative C–C bond forming reactions of sodium arenesulfinates with alkenes, nitriles, and aldehydes have been reported.[10] We have chosen sodium arenesulfinates as arylpalladium(II) precursors because they are stable in air and easy to handle; thus, sodium arenesulfinates are ideal aryl sources.[6,10a,11] Herein, we report the first regioselective desulfitative Heck-type coupling of Baylis–Hillman adducts with sodium sulfinates [Scheme 2 (b)].

At the outset of our study, the regioselective desulfitative Heck-type arylation was investigated with butyl 2-[hydroxy(4-tolyl)methyl]acrylate (**1a**) and sodium benzenesulfinate (**2a**) as the model substrates (Table 1). The use of palladium(II) acetate or chloride in presence of various ligands[12] and oxidants gave the product **3a** in low yields (entries 1–9). However, in the absence of a ligand, the reaction gave **3a** in a moderate 45% yield (entry 10). Next, we examined conditions without a ligand by replacing the oxidant copper(II) acetate monohydrate with other oxidants such as copper(II) acetate, copper(I) bromide, copper(II) bromide, silver carbonate, silver(I) acetate, and oxygen, this gave **3a** in unsatisfactory 18–34% yields (entries 11–16). The effect of solvent was also investigated by the replacement of 1,4-dioxane with other solvents like acetic acid, acetonitrile, dimethylformamide, 1,2-dichloroethane, and toluene; this furnished **3a** in poor <5–25% yields (entries 17–21). An improved yield was observed when palladium(II) chloride was used as the palladium(II) precursor (entry 22) instead of palladium(II) acetate (entry 10) and copper(II) chloride was used as the oxidant; this gave **3a** in a good 86% yield (entry 23); Increasing the amount of catalyst from 5 mol% to 10 mol% gave **3a** in excellent yield (entry 24). Under the optimized reaction conditions (entry 24) products of H_b-hydride elimination **3′** [Scheme 2 (a)] or decarboxylation were not observed[13] indicating total regioselectivity in the respective migratory aryl insertion and hydride elimination (H_a) steps in the catalytic cycle [Scheme 2 (b)].

With the optimized reaction conditions (Table 1, entry 24) in hand, the palladium-catalyzed desulfitative addition reaction was then extended to a wide array of sodium arenesulfinates **2** and Baylis–Hillman adducts **1** to explore the scope and limitation of the reaction (Table 2). The halogen-bearing Baylis–Hillman adducts and sodium arenesulfinates gave the desired products **3b–i** in good yields and excellent chemoselectivity without concomitant formation of competitive palladium(0)-catalyzed Heck and dehalogenation byproducts. 1-Heteroaryl Baylis–Hillman adducts gave the corresponding products **3i–l** in reasonable yields. Even the 1-alkyl-substituted substrates gave the corresponding coupling products **3m**,**n** in excellent yields. The 2-methylphenyl-substituted Baylis–Hillman adduct undergoes efficient coupling with sodium benzenesulfinate to give **3r** in 78% yield. Finally, electron-deficient or electron-rich Baylis–Hillman adducts and sodium arenesulfinates afforded **3o–w** in good to excellent yields.

An incomplete reaction was observed, when arenesulfonyl chlorides were used as the aryl source in the Heck reaction with a Baylis–Hillman adduct, and in the presence of strong base with high temperature (>160 °C) the corre-

Table 1 Optimization of the Reaction Conditions[a]



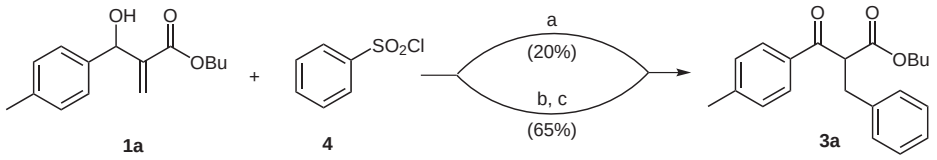
1a **2a** **3a**

Entry	Pd(II)	Oxidant	Solvent (°C)	Yield[b] (%)
1	$Pd(OAc)_2$	CuBr[c]	1,4-dioxane (90)	<5
2	$Pd(OAc)_2$	CuBr[d]	1,4-dioxane (90)	<5
3	$Pd(OAc)_2$	$Cu(OAc)_2$[c]	1,4-dioxane (90)	<5
4	$Pd(OAc)_2$	$Cu(OAc)_2·H_2O$[c]	1,4-dioxane (90)	<5
5	$Pd(OAc)_2$	$Cu(OAc)_2·H_2O$[d]	1,4-dioxane (90)	<5
6	$Pd(OAc)_2$	$Cu(OAc)_2·H_2O$[e]	1,4-dioxane (90)	8
7	$PdCl_2$	$Cu(OAc)_2·H_2O$[c]	1,4-dioxane (90)	10
8	$PdCl_2$	$Cu(OAc)_2·H_2O$[d]	1,4-dioxane (90)	12
9	$PdCl_2$	$Cu(OAc)_2·H_2O$[e]	1,4-dioxane (90)	11
10	$Pd(OAc)_2$	$Cu(OAc)_2·H_2O$	1,4-dioxane (90)	45
11	$Pd(OAc)_2$	$Cu(OAc)_2$	1,4-dioxane (90)	33
12	$Pd(OAc)_2$	CuBr	1,4-dioxane (90)	22
13	$Pd(OAc)_2$	$CuBr_2$	1,4-dioxane (90)	34
14	$PdCl_2$	Ag_2CO_3	1,4-dioxane (90)	25
15	$PdCl_2$	AgOAc	1,4-dioxane (90)	20
16	$PdCl_2$	O_2	1,4-dioxane (90)	18
17	$PdCl_2$	$Cu(OAc)_2·H_2O$	AcOH (100)	<5
18	$PdCl_2$	$Cu(OAc)_2·H_2O$	MeCN (90)	20
19	$PdCl_2$	$Cu(OAc)_2·H_2O$	DMF (100)	25
20	$PdCl_2$	$Cu(OAc)_2·H_2O$	DCE (80)	23
21	$PdCl_2$	$Cu(OAc)_2·H_2O$	toluene (90)	20
22	$PdCl_2$	$Cu(OAc)_2·H_2O$	1,4-dioxane (90)	65
23	$PdCl_2$	$CuCl_2$	1,4-dioxane (90)	86
24[f]	$PdCl_2$	$CuCl_2$	1,4-dioxane (90)	97
25[f]	$PdCl_2$		1,4-dioxane (90)	11

[a] Unless specified, the reaction was carried out with: **1a** (0.5 mmol), **2a** (0.6 mmol), Pd catalyst (0.05 equiv), solid oxidant (1.0 equiv) or O_2 balloon (1 atm); solvent (3.0 mL); 8 h.
[b] Isolated yield (average of 2 runs).
[c] 1,10-Phenanthroline (0.1 equiv).
[d] 2,9-Dimethyl-1,10-phenanthroline (0.1 equiv).
[e] 2,2′-Bipyridyl.
[f] Pd (0.1 equiv).

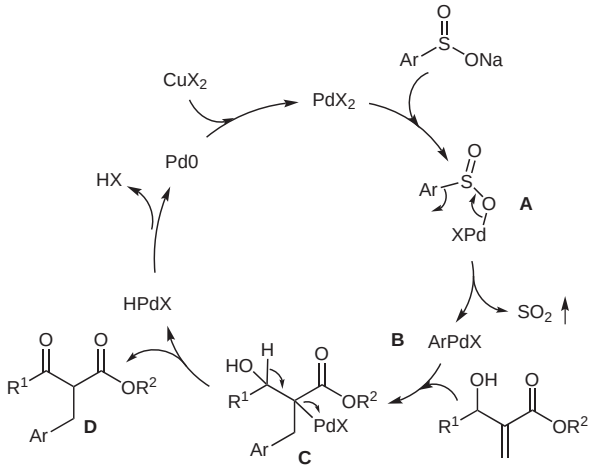
sponding α-benzyl-β-keto ester **3a** was formed in 65% isolated yield (Scheme 3). From this domino effect, it is apparent that sodium arenesulfinates are ideal aryl sources.

A plausible mechanism to rationalize this transformation is illustrated in Scheme 4. Although the mechanism is not well understood at this stage, on the basis of above observations, we proposed that a plausible catalytic route could consist the following steps: (a) coordination of sodium



Scheme 3 Palladium-catalyzed synthesis of α-benzyl-β-keto esters from Baylis–Hillman adducts with arenesulfonyl chlorides (a) standard condition: **1a** (0.5 mmol), **4** (0.6 mmol), $PdCl_2$ (0.1 equiv), $CuCl_2$ (1.0 equiv), 1,4-dioxane (3.0 mL), 90 °C, 8.0 h, 20% yield; (b) **1a** (0.5 mmol), **4** (0.6 mmol), $PdCl_2$ (0.1 equiv), $CuCl_2$ (1.0 equiv), Na_2CO_3 (1.0 equiv), 1,4-dioxane (3.0 mL), 160 °C, 16.0 h, 65% yield; (c) **1a** (0.5 mmol), **4** (0.6 mmol), $PdCl_2$ (0.1 equiv), without $CuCl_2$, Na_2CO_3 (1.0 equiv), 1,4-dioxane (3.0 mL), 160 °C, 8.0 h, 0% yield.

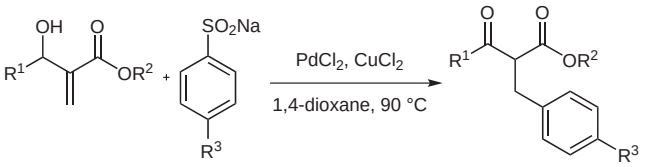
arenesulfinate to palladium(II) to give complex **A**; (b) desulfitative reaction of the sulfinic acid salt to generate the arylpalladium complex **B**; (c) oxidative addition of the olefinic group to form complex **C**; (d) reductive elimination followed by enol isomerization to produce the desired product **D**. When an oxidant was not used, incomplete reaction was observed and this supports the formation of palladium(0) and the necessity of the oxidant to regenerate the palladium(II) species in the catalytic cycle (Table 1, entry 25). A detailed experimental and theoretical investigation of mechanistic insight is in progress.



Scheme 4 Proposed reaction pathway

In summary, a new and efficient method for palladium(II)-catalyzed desulfitative Heck-Type arylation was demonstrated from sodium arenesulfinates and Baylis–Hillman adducts to access highly functionalized α-benzyl-β-keto ester derivatives in good to excellent yields. This reaction took place under mild conditions and it tolerates a wider range of functionalities than previously possible; methyl, bromo, and chloro on the sodium arenesulfinate were all well tolerated under these reaction conditions. Therefore this methodology offers an alternative to palladium-catalyzed aryl halide, arenediazonium tetrafluoroborate salts, and arylboronic acids addition to Baylis–Hillman adducts. Further investigation of the scope, mechanism, and synthetic applications of this reaction are in progress.

Table 2 Preparative Scope of α-Benzyl-β-keto Esters from Baylis–Hillman Adducts



R^1	R^2	R^3	Product	Yield (%)
4-NCC_6H_4	Bu	Cl	**3b**	83
4-$O_2NC_6H_4$	Bu	Br	**3c**	81
4-$MeOC_6H_4$	Bu	Br	**3d**	93
4-BrC_6H_4	Bu	Me	**3e**	87
Ph	Et	Br	**3f**	92
4-BrC_6H_4	Bu	H	**3g**	87
Ph	Et	Cl	**3h**	91
2-thienyl	Bu	Br	**3i**	79
2-furyl	Bu	H	**3j**	86
2-furyl	Bu	Me	**3k**	80
2-thienyl	Bu	H	**3l**	92
$(CH_2)_4Me$	Bu	H	**3m**	96
$(CH_2)_6Me$	Bu	H	**3n**	94
4-NCC_6H_4	Bu	Me	**3o**	87
4-$MeOC_6H_4$	Bu	H	**3p**	92
4-$O_2NC_6H_4$	Bu	H	**3q**	80
2-MeC_6H_4	Bu	H	**3r**	78
Ph	Et	Me	**3s**	95
Ph	Me	Me	**3t**	89
4-*i*-PrC_6H_4	Bu	H	**3u**	92
Ph	Bu	H	**3v**	92
Ph	Bu	Me	**3w**	95

All solvents and reagents were used, as received. TLC was performed on Merck Kiesel gel 60, F_{254} plates; 0.25-mm thickness. Column chromatography was performed on silica gel (100–200 mesh) with a EtOAc–hexane gradient. Melting points were determined on a Fisher Johns melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer RX-1 FT-IR system. ^{1}H NMR spectral data were collected at 300, 400, and 500 MHz, while ^{13}C NMR were recorded at 75, 100 and 150 MHz. HRMS (ESI) spectral data were collected using an ORBITRAP high resolution mass spectrometer.

α-Benzyl-β-keto Esters 3 from Baylis–Hillman Adducts; General Procedure

A mixture of sulfinic acid sodium salt **2** (0.60 mmol), $PdCl_2$ (0.10 equiv), Baylis–Hillman adduct **1** (0.50 mmol), and $CuCl_2$ (1.0 equiv) was dissolved in 1,4-dioxane (3.0 mL) in a 10-mL round-bottomed flask. The mixture was vigorously stirred at 90 °C for 8 h. After cooling to r.t., the mixture was partitioned between EtOAc (25.0 mL) and H_2O (25.0 mL) and filtered through a celite pad. The filtrate was transferred to a separatory funnel, and the organic layer was washed with H_2O and brine, dried (anhyd Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by column chromatography (gradient, hexane–EtOAc) to afford the pure product.

Butyl 2-Benzyl-3-oxo-3-(4-tolyl)propanoate (3a)

Colorless liquid; yield: 0.158 g (97%).

IR (neat): 3026, 2960, 2930, 1733, 1681, 1606, 1454, 1273, 1215, 1181, 909, 748, 698, 666, 595 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.3 Hz, 1 H), 7.36–7.13 (m, 8 H), 4.62 (t, *J* = 7.3 Hz, 1 H), 4.05 (t, *J* = 6.5 Hz, 2 H), 3.34 (d, *J* = 7.3 Hz, 2 H), 2.42 (s, 3 H), 1.56–1.40 (m, 2 H), 1.18 (m, 2 H), 0.83 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.1, 169.5, 144.4, 138.5, 133.7, 129.4, 128.9, 128.8, 128.5, 126.6, 65.3, 56.1, 34.7, 30.4, 21.6, 18.8, 13.5.

MS (ESI): *m*/*z* = 325 $[M + H]^+$, 347 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{25}O_3$: 325.17976; found: 325.17982.

Butyl 2-(4-Chlorobenzyl)-3-(4-cyanophenyl)-3-oxopropanoate (3b)

Colorless solid; yield: 0.154 g (83%); mp 76–80 °C.

IR (neat): 3020, 2961, 2232, 1734, 1692, 1492, 1216, 1093, 1015, 931, 848, 817, 771, 667 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06–7.99 (m, 2 H), 7.80–7.73 (m, 2 H), 7.30–7.22 (m, 2 H), 7.20–7.12 (m, 2 H), 4.56 (t, *J* = 7.4 Hz, 1 H), 4.05 (t, *J* = 6.6 Hz, 2 H), 3.32 (d, *J* = 7.4 Hz, 2 H), 1.48 (m, 2 H), 1.28–1.10 (m, 2 H), 0.84 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.1, 168.4, 139.1, 136.3, 132.6, 130.3, 128.9, 128.8, 117.7, 116.8, 65.8, 56.3, 33.7, 30.3, 18.8, 13.5.

MS (ESI): *m*/*z* = 370 $[M + H]^+$, 392 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{20}ClNO_3$: 392.10239; found: 392.10268.

Butyl 2-(4-Bromobenzyl)-3-(4-nitrophenyl)-3-oxopropanoate (3c)

Colorless solid; yield: 0.175 g (81%); mp 89–92 °C.

IR (neat): 3020, 1735, 1695, 1528, 1346, 1215, 1071, 1012, 931, 852, 743, 667, 624 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.8 Hz, 2 H), 8.08 (d, *J* = 8.8 Hz, 2 H), 7.39 (d, *J* = 8.3 Hz, 2 H), 7.10 (d, *J* = 8.3 Hz, 2 H), 4.57 (t, *J* = 7.4 Hz, 1 H), 4.04 (t, *J* = 6.6 Hz, 2 H), 3.30 (t, *J* = 7.2 Hz, 2 H), 1.52–1.40 (m, 2 H), 1.26–1.10 (m, 2 H), 0.82 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.9, 168.4, 150.5, 140.6, 136.8, 131.7, 130.6, 129.5, 123.9, 120.9, 65.8, 56.5, 33.8, 30.3, 18.9, 13.5.

MS (ESI): *m*/*z* = 434 $[M + H]^+$, 456 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{20}BrNNaO_5$: 456.0462; found: 456.04010.

Butyl 2-(4-Bromobenzyl)-3-(4-methoxyphenyl)-3-oxopropanoate (3d)

Colorless liquid; yield: 0.194 g (93%).

IR (neat): 2959, 2928, 1732, 1677, 1599, 1511, 1216, 1171, 1070, 1029, 841, 771, 667 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01–7.91 (m, 2 H), 7.41–7.36 (m, 2 H), 7.12 (d, *J* = 8.4 Hz, 2 H), 6.96–6.91 (m, 2 H), 4.55 (t, *J* = 7.4 Hz, 1 H), 4.05 (t, *J* = 6.6 Hz, 2 H), 3.88 (s, 3 H), 3.28 (d, *J* = 7.4 Hz, 2 H), 1.54–1.41 (m, 2 H), 1.18 (d, *J* = 14.8 Hz, 2 H), 0.84 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.3, 169.3, 163.9, 137.6, 131.5, 131.1, 130.7, 129.1, 120.5, 113.9, 65.4, 55.6, 34.1, 30.4, 29.7, 18.9, 13.5.

MS (ESI): *m*/*z* = 419 $[M + H]^+$, 441 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{23}BrNaO_4$: 441.08269; found: 441.08368.

Butyl 3-(4-Bromophenyl)-2-(4-methylbenzyl)-3-oxopropanoate (3e)

Colorless liquid; yield: 0.175 g (87%).

IR (neat): 2959, 2926, 1735, 1688, 1584, 1515, 1455, 1378, 1271, 1220, 1172, 1070, 1008, 931, 841, 810, 772, 653, 571 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.5 Hz, 1 H), 7.85–7.78 (m, 2 H), 7.63–7.56 (m, 2 H), 7.43 (d, *J* = 8.3 Hz, 1 H), 7.09 (q, *J* = 8.2 Hz, 2 H), 4.55 (t, *J* = 7.4 Hz, 1 H), 4.05 (t, *J* = 6.6 Hz, 2 H), 3.30 (d, *J* = 7.3 Hz, 2 H), 2.30 (s, 3 H), 1.54–1.41 (m, 2 H), 1.18 (dt, *J* = 14.8, 7.3 Hz, 2 H), 0.84 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.6, 169.1, 136.2, 135.1, 132.1, 130.2, 130.1, 129.2, 128.7, 127.1, 65.5, 56.3, 34.2, 30.3, 21.1, 18.9, 13.5.

MS (ESI): *m*/*z* = 403 $[M + H]^+$, 425 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{23}BrNaO_3$: 425.07228; found: 425.07176.

Ethyl 2-(4-Bromobenzyl)-3-oxo-3-phenylpropanoate (3f)

Colorless liquid; yield: 0.167 g (92%).

IR (neat): 3021, 2982, 2929, 2871, 1733, 1686, 1596, 1488, 1446, 1403, 1368, 1302, 1268, 1215, 1181, 1153, 1100, 966, 931, 852, 813, 746, 688, 665, 620 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.8 Hz, 2 H), 7.57 (t, *J* = 7.3 Hz, 1 H), 7.45 (t, *J* = 7.7 Hz, 2 H), 7.37 (d, *J* = 8.3 Hz, 2 H), 7.11 (d, *J* = 8.3 Hz, 2 H), 4.58 (t, *J* = 7.3 Hz, 1 H), 4.12–4.07 (t, *J* = 6.9 Hz, 2 H), 3.28 (d, *J* = 7.3 Hz, 2 H), 1.11 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.1, 169.1, 137.4, 136.1, 133.7, 131.6, 130.7, 128.8, 128.6, 120.5, 61.6, 55.9, 34.1, 13.9.

MS (ESI): *m*/*z* = 363 $[M + H]^+$, 385 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{17}BrNaO_3$: 385.02976; found: 385.02978.

Butyl 2-Benzyl-3-(4-bromophenyl)-3-oxopropanoate (3g)

Colorless liquid; yield: 0.168 g (87%).

IR (neat): 2958, 2927, 1736, 1689, 1584, 1488, 1454, 1396, 1273, 1219, 1180, 1071, 1008, 940, 840, 771, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86–7.75 (m, 2 H), 7.58 (d, *J* = 8.4 Hz, 2 H), 7.31–7.15 (m, 5 H), 4.56 (t, *J* = 7.3 Hz, 1 H), 4.02 (t, *J* = 15.1, 8.5 Hz, 2 H), 3.32 (d, *J* = 7.4 Hz, 2 H), 1.54–1.39 (m, 2 H), 1.21 (m, 2 H), 0.82 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.5, 169.1, 138.2, 135.1, 132.1, 130.1, 128.8, 128.6, 126.7, 65.5, 56.2, 34.6, 30.4, 18.9, 13.5.

MS (ESI): *m*/*z* = 389 $[M + H]^+$, 411 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{22}O_3Br$: 389.07528; found: 389.07468.

Ethyl 2-(4-Chlorobenzyl)-3-oxo-3-phenylpropanoate (3h)
Colorless liquid; yield: 0.144 g (91%).

IR (neat): 3063, 3024, 2981, 2927, 2852, 1732, 1684, 1596, 1492, 1446, 1408, 1368, 1324, 1267, 1227, 1180, 1151, 1092, 1058, 1015, 966, 931, 896, 851, 815, 739, 688, 639, 600 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.8 Hz, 2 H), 7.57 (t, *J* = 7.2 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 2 H), 7.27–7.13 (m, 4 H), 4.59 (t, *J* = 7.3 Hz, 1 H), 4.10 (t, *J* = 6.7 Hz, 2 H), 3.29 (d, *J* = 7.3 Hz, 2 H), 1.11 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.2, 169.1, 136.9, 136.1, 133.7, 132.5, 130.4, 128.7, 128.6, 61.7, 55.9, 34.1, 13.9.

MS (ESI): *m*/*z* = 317 $[M + H]^+$, 339 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{17}ClNaO_3$: 339.34190; found: 339.34186.

Butyl 2-(4-Bromobenzyl)-3-oxo-3-(thiophen-2-yl)propanoate (3i)
Colorless liquid; yield: 0.155 g (79%).

IR (neat): 3019, 1733, 1664, 1413, 1215, 1070, 1012, 744, 667 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (dd, *J* = 3.9, 1.0 Hz, 1 H), 7.68 (dd, *J* = 5.0, 1.0 Hz, 1 H), 7.41–7.34 (m, 2 H), 7.14–7.07 (m, 3 H), 4.45–4.35 (t, *J* = 7.3 Hz, 1 H), 4.06 (t, *J* = 6.6 Hz, 2 H), 3.28 (d, *J* = 7.4 Hz, 2 H), 1.49 (ddd, *J* = 14.0, 8.8, 6.6 Hz, 2 H), 1.29–1.12 (m, 2 H), 0.84 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.5, 168.7, 143.3, 137.3, 135.1, 133.1, 131.6, 130.7, 128.3, 120.6, 65.6, 57.2, 34.1, 30.4, 18.9, 13.5.

MS (ESI): *m*/*z* = 395 $[M + H]^+$, 417 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{19}BrNaO_3S$: 417.01053; found: 417.01019.

Butyl 2-Benzyl-3-(furan-2-yl)-3-oxopropanoate (3j)
Colorless liquid; yield: 0.130 g (86%).

IR (neat): 3322, 2943, 2831, 1669, 1450, 1414, 1219, 1020, 915, 772, 731, 645 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (dd, *J* = 1.6, 0.7 Hz, 1 H), 7.34–7.09 (m, 6 H), 6.54 (dd, *J* = 3.6, 1.7 Hz, 1 H), 4.43 (t, *J* = 7.5 Hz, 1 H), 4.08 (t, *J* = 6.6 Hz, 2 H), 3.33 (d, *J* = 7.5 Hz, 2 H), 1.52 (m, 2 H), 1.23 (m, 2 H), 0.86 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.1, 169.1, 151.9, 146.9, 138.2, 128.9, 128.5, 126.6, 118.5, 112.5, 65.4, 56.3, 34.2, 30.4, 18.9, 13.6.

MS (ESI): *m*/*z* = 301 $[M + H]^+$, 323 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{21}O_4$: 301.14344; found: 325.14323.

Butyl 3-(Furan-2-yl)-2-(4-methylbenzyl)-3-oxopropanoate (3k)
Colorless liquid; yield: 0.127 g (80%).

IR (neat): 2960, 2928, 1733, 1676, 1566, 1515, 1464, 1391, 1216, 1155, 1015, 880, 771, 667, 592 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (dd, *J* = 1.6, 0.7 Hz, 1 H), 7.29–7.23 (m, 2 H), 7.10 (dd, *J* = 17.7, 8.1 Hz, 3 H), 6.54 (dd, *J* = 3.6, 1.7 Hz, 1 H), 4.40 (t, *J* = 7.5 Hz, 1 H), 4.08 (t, *J* = 6.6 Hz, 2 H), 3.29 (d, *J* = 7.4 Hz, 2 H), 2.30 (s, 3 H), 1.51 (dt, *J* = 14.6, 6.7 Hz, 2 H), 1.31–1.16 (m, 2 H), 0.85 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.2, 169.1, 152.1, 146.9, 136.1, 135.2, 129.2, 128.8, 118.5, 112.5, 65.3, 56.4, 33.7, 30.4, 21.1, 18.9, 13.6.

MS (ESI): *m*/*z* = 315 $[M + H]^+$, 337 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{22}NaO_4$: 337.14103; found: 337.14072.

Butyl 2-Benzyl-3-oxo-3-(thiophen-2-yl)propanoate (3l)
Pale yellow oil; yield: 0.145 g (92%).

IR (neat): 2959, 2928, 1732, 1661, 1516, 1454, 1412, 1356, 1274, 1221, 1148, 1063, 847, 772, 726, 699, 595 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79–7.66 (d, *J* = 7.1 Hz, 1 H), 7.68 (d, *J* = 4.9 Hz, 1 H), 7.31–7.18 (m, 5 H), 7.13 (dd, *J* = 8.6, 4.6 Hz, 1 H), 4.47 (t, *J* = 7.4 Hz, 1 H), 4.08 (t, *J* = 6.6 Hz, 2 H), 3.35 (d, *J* = 7.4 Hz, 2 H), 1.58–1.45 (m, 2 H), 1.30–1.14 (m, 2 H), 0.85 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.8, 169.1, 143.2, 138.5, 134.9, 133.1, 128.9, 128.5, 128.3, 126.7, 65.5, 57.4, 34.7, 30.4, 18.9, 13.6.

MS (ESI): *m*/*z* = 317 $[M + H]^+$, 339 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{20}NaO_3S$: 339.10254; found: 325.10177.

Butyl 2-Benzyl-3-oxooctanoate (3m)
Colorless liquid; yield: 0.145 g (96%).

IR (neat): 3029, 2958, 2929, 2871, 2255, 1738, 1713, 1604, 1495, 1456, 1360, 1312, 1243, 1164, 1064, 1029, 963, 908, 729, 699, 648, 594 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (t, *J* = 7.3 Hz, 2 H), 7.21–7.13 (m, 3 H), 4.08 (t, *J* = 6.6 Hz, 2 H), 3.78 (t, *J* = 7.6 Hz, 1 H), 3.15 (t, *J* = 7.2 Hz, 2 H), 2.51 (dt, *J* = 17.1, 7.4 Hz, 1 H), 2.32 (dd, *J* = 17.4, 7.3 Hz, 1 H), 1.58–1.45 (m, 4 H), 1.34–1.13 (m, 6 H), 0.86 (dt, *J* = 19.1, 7.3 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.8, 169.3, 138.3, 128.8, 128.5, 126.6, 65.3, 60.5, 42.8, 34.1, 31.1, 30.5, 29.7, 23.1, 22.4, 19.1, 13.8, 13.6.

MS (ESI): *m*/*z* = 305 $[M + H]^+$, 327 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{28}NaO_3$: 327.19307; found: 327.19208.

Butyl 2-Benzyl-3-oxodecanoate (3n)
Colorless liquid; yield: 0.156 g (94%).

IR (neat): 2957, 2927, 2856, 2255, 1740, 1713, 1604, 1495, 1456, 1376, 1310, 1262, 1202, 1163, 1065, 1028, 907, 729, 699, 648 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (t, *J* = 7.3 Hz, 2 H), 7.18 (dd, *J* = 16.5, 7.6 Hz, 3 H), 4.08 (t, *J* = 6.6 Hz, 1 H), 3.78 (t, *J* = 7.6 Hz, 2 H), 3.15 (dd, *J* = 7.5, 4.2 Hz, 2 H), 2.51 (dt, *J* = 17.1, 7.3 Hz, 1 H), 2.32 (dt, *J* = 17.2, 7.2 Hz, 1 H), 1.59–1.46 (m, 4 H), 1.33–1.17 (m, 10 H), 0.88 (dt, *J* = 11.5, 7.3 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.8, 169.2, 138.3, 128.8, 128.5, 126.6, 65.3, 60.5, 42.9, 34.1, 31.6, 30.5, 28.8, 28.9, 23.3, 22.6, 19.1, 14.1, 13.6.

MS (ESI): *m*/*z* = 333 $[M + H]^+$, 355 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{32}NaO_3$: 355.22437; found: 355.22340.

Butyl 3-(4-Cyanophenyl)-2-(4-methylbenzyl)-3-oxopropanoate (3o)
Colorless liquid; yield: 0.152 g (87%).

IR (neat): 3021, 2960, 2930, 2232, 1734, 1692, 1515, 1460, 1404, 1269, 1218, 1113, 1063, 1018, 931, 850, 808, 770, 667 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.3 Hz, 2 H), 7.72 (d, *J* = 8.3 Hz, 2 H), 7.06 (q, *J* = 8.1 Hz, 4 H), 4.55 (t, *J* = 7.3 Hz, 1 H), 4.04 (t, *J* = 6.6 Hz, 2 H), 3.29 (d, *J* = 7.3 Hz, 2 H), 2.27 (s, 3 H), 1.45 (dt, *J* = 13.3, 6.6 Hz, 2 H), 1.21–1.11 (m, 2 H), 0.82 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.6, 168.7, 139.4, 136.4, 134.7, 132.5, 129.3, 128.9, 128.7, 117.7, 116.6, 65.6, 56.6, 34.2, 30.3, 21.1, 18.8, 13.5.

MS (ESI): *m*/*z* = 350 $[M + H]^+$, 372 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{23}NNaO_3$: 372.15701; found: 372.15659.

Butyl 2-Benzyl-3-(4-methoxyphenyl)-3-oxopropanoate (3p)
Colorless liquid; yield: 0.156 g (92%).

IR (neat): 2959, 2927, 2871, 1732, 1676, 1575, 1510, 1456, 1420, 1310, 1258, 1222, 1116, 1062, 1026, 968, 940, 840, 698, 635, 600, 563 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.8 Hz, 2 H), 7.27–7.11 (m, 5 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 4.50 (t, *J* = 7.7 Hz, 1 H), 4.06–3.98 (t, *J* = 6.8 Hz, 2 H), 3.85 (s, 3 H), 3.30–3.26, (d, *J* = 3.4 Hz, 2 H), 1.51–1.43 (m, 2 H), 1.24–1.17 (m, 2 H), 0.84 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.9, 169.1, 163.6, 138.6, 130.9, 129.3, 128.8, 128.4, 126.4, 113.7, 96.2, 64.9, 55.8, 55.2, 34.7, 30.4, 29.7, 18.9, 13.6.

MS (ESI): *m*/*z* = 353 $[M + H]^+$, 375 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{25}O_4$: 353.21112; found: 325.21115.

Butyl 2-Benzyl-3-(4-nitrophenyl)-3-oxopropanoate (3q)
Colorless solid; yield: 0.143 g (80%); mp 86–88 °C.

IR (neat): 3020, 1736, 1696, 1529, 1346, 1214, 742, 667 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 8.8 Hz, 2 H), 8.06 (d, *J* = 8.8 Hz, 2 H), 7.33–7.12 (m, 5 H), 4.62 (t, *J* = 7.4 Hz, 1 H), 4.05 (t, *J* = 6.6 Hz, 2 H), 3.36 (d, *J* = 7.4 Hz, 2 H), 1.56–1.37 (m, 2 H), 1.28–1.09 (m, 2 H), 0.82 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.4, 168.6, 150.5, 140.8, 137.8, 129.5, 128.9, 128.7, 126.6, 123.8, 65.7, 56.6, 34.5, 30.3, 18.8, 13.5.

MS (ESI): *m*/*z* = 356 $[M + H]^+$, 378 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{22}NO_5$: 356.14925; found: 356.14947.

Butyl 2-Benzyl-3-oxo-3-(2-tolyl)propanoate (3r)
Colorless liquid; yield: 0.127 g (78%).

IR (neat): 3023, 2960, 2929, 1733, 1690, 1606, 1454, 1258, 1216, 1160, 1061, 934, 909, 748, 666, cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 7.7 Hz, 1 H), 7.37 (dd, *J* = 10.9, 4.1 Hz, 2 H), 7.27–7.17 (m, 5 H), 7.01 (d, *J* = 6.9 Hz, 1 H), 4.54 (t, *J* = 7.5 Hz, 1 H), 4.17 (t, *J* = 6.5 Hz, 2 H), 3.33 (d, *J* = 6.4 Hz, 2 H), 2.44 (s, 3 H), 1.55–1.41 (m, 2 H), 1.28–1.12 (m, 2 H), 0.87–0.83 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.1, 169.4, 138.4, 131.9, 131.6, 128.9, 128.5, 128.3, 126.6, 125.6, 65.2, 58.6, 34.7, 30.4, 20.9, 18.8, 13.6.

MS (ESI): *m*/*z* = 325 $[M + H]^+$, 347 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{25}O_3$: 325.17982; found: 325.17970.

Ethyl 2-(4-Methylbenzyl)-3-oxo-3-phenylpropanoate (3s)
Colorless liquid; yield: 0.140 g (95%).

IR (neat): 2981, 2924, 2854, 2254, 1733, 1685, 1597, 1515, 1447, 1369, 1268, 1217, 1182, 1152, 1111, 1023, 906, 852, 808, 728, 689, 667, 649, 604 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02–7.90 (d, *J* = 7.5 Hz, 2 H), 7.56 (t, *J* = 7.4 Hz, 1 H), 7.44 (t, *J* = 7.7 Hz, 2 H), 7.12 (d, *J* = 7.9 Hz, 2 H), 7.06 (d, *J* = 7.8 Hz, 2 H), 4.60 (t, *J* = 7.3 Hz, 1 H), 4.10 (t, *J* = 7.1 Hz, 2 H), 3.32–3.26 (d, *J* = 6.2 Hz, 2 H), 2.29 (s, 3 H), 1.12 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.6, 169.3, 136.2, 136.2, 135.3, 133.5, 129.2, 128.8, 128.67, 61.5, 56.3, 34.3, 21.1, 13.9.

MS (ESI): *m*/*z* = 297 $[M + H]^+$, 319 $[M + Na]^+$

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{20}NaO_3$: 319.13047; found: 319.12958.

Methyl 2-(4-Methylbenzyl)-3-oxo-3-phenylpropanoate (3t)
Colorless liquid; yield: 0.125 g (89%).

IR (neat): 2924, 2254, 1737, 1686, 1596, 1581, 1515, 1446, 1329, 1273, 1231, 1148, 904, 809, 723, 648, 584 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.3 Hz, 2 H), 7.55 (d, *J* = 7.3 Hz, 1 H), 7.44 (t, *J* = 7.5 Hz, 2 H), 7.15–7.01 (m, 4 H), 4.63 (t, *J* = 7.3 Hz, 1 H), 3.63 (s, 3 H), 3.29 (dd, *J* = 7.0, 3.3 Hz, 2 H), 2.28 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.5, 169.8, 136.2, 136.1, 135.3, 133.6, 129.3, 128.7, 128.7, 128.4, 56.1, 52.5, 34.4, 21.1.

MS (ESI): *m*/*z* = 283 $[M + H]^+$, 305 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{18}NaO_3$: 305.11482; found: 305.11386.

Butyl 2-Benzyl-3-(4-isopropylphenyl)-3-oxopropanoate (3u)
Colorless liquid; yield: 0.161 g (92%).

IR (neat): 2962, 1733, 1681, 1604, 1457, 1273, 1217, 1057, 907, 847, 728, 698, 667 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.3 Hz, 2 H), 7.23 (ddd, *J* = 10.6, 8.3, 5.3 Hz, 7 H), 4.61 (t, *J* = 7.3 Hz, 1 H), 4.03 (t, *J* = 6.5 Hz, 2 H), 3.32 (d, *J* = 7.3 Hz, 2 H), 2.94 (m, 1 H), 1.52–1.38 (m, 2 H), 1.25 (d, *J* = 6.9 Hz, 6 H), 1.14 (d, *J* = 7.4 Hz, 2 H), 0.80 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.9, 169.5, 155.2, 138.5, 134.1, 128.9, 128.5, 126.8, 126.6, 65.3, 56.1, 34.7, 34.3, 30.4, 29.7, 23.6, 18.9, 13.6.

MS (ESI): *m*/*z* = 353 $[M + H]^+$, 375 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{29}O_3$: 353.21112; found: 325.21115.

Butyl 2-Benzyl-3-oxo-3-phenylpropanoate (3v)
Colorless liquid; yield: 0.143 g (92%).

IR (neat): 2959, 2929, 1733, 1684, 1450, 1220, 1181, 1148, 1078, 940, 772, 688, 576 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.3 Hz, 2 H), 7.57 (dd, *J* = 13.7, 6.5 Hz, 1 H), 7.44 (t, *J* = 7.5 Hz, 2 H), 7.30–7.16 (m, 5 H), 4.63 (t, *J* = 7.3 Hz, 1 H), 4.03 (t, *J* = 6.6 Hz, 2 H), 3.33 (d, *J* = 7.3 Hz, 2 H), 1.53–1.38 (m, 2 H), 1.32–1.09 (m, 2 H), 0.80 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.4, 169.3, 138.5, 136.3, 133.5, 128.9, 128.6, 128.7, 128.5, 126.6, 65.6, 56.2, 34.7, 30.4, 18.8, 13.5.

MS (ESI): *m*/*z* = 311 $[M + H]^+$, 333 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{23}O_3$: 311.16417; found: 325.16400.

Butyl 2-(4-Methylbenzyl)-3-oxo-3-phenylpropanoate (3w)
Colorless liquid; yield: 0.154 g (95%).

IR (neat): 3021, 1733, 1687, 1515, 1448, 1217, 907, 728 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.4 Hz, 2 H), 7.56 (t, *J* = 7.3 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 2 H), 7.09 (dd, *J* = 18.0, 8.0 Hz, 4 H), 4.60 (t, *J* = 7.3 Hz, 1 H), 4.03 (t, *J* = 6.6 Hz, 2 H), 3.29 (d, *J* = 7.3 Hz, 2 H), 2.28 (s, 3 H), 1.52–1.40 (m, 2 H), 1.16 (dt, *J* = 14.7, 7.3 Hz, 2 H), 0.80 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.45, 169.38, 136.18, 136.08, 135.30, 133.44, 129.16, 128.73, 128.62, 65.27, 56.29, 34.23, 30.33, 20.97, 18.83, 13.51.

MS (ESI): m/z = 325 $[M + H]^+$, 347 $[M + Na]^+$.

HRMS (ESI) : m/z $[M + Na]^+$ calcd for $C_{21}H_{24}NaO_3$: 347.1617; found: 347.1609.

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