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Silver-Catalyzed Decarboxylative Addition/Cyclization of Activated Alkenes with Aliphatic Carboxylic Acids

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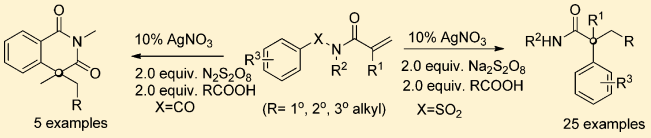
Supporting Information

ABSTRACT: A silver-catalyzed decarboxylative addition/aryl migration/desulfonylation of *N*-phenyl-*N*-(phenylsulfonyl)-methacrylamide with primary, secondary, and tertiary carboxylic acids was described. The protocol provides an efficient approach for the synthesis of α-all-carbon quaternary stereocenters amides and isoquinolinediones. It was proposed that the radical generated from the silver-catalyzed decarboxylation was involved in the sequence reaction.



Aliphatic carboxylic acids are readily available and inexpensive raw materials from fossil oil and biomass which can be easily transformed into a series of compounds with different functional groups. As early as the 1930s, decarboxylative halogenation of aliphatic carboxylic acids mediated by a silver salt (Hunsdiecker reaction) has been well developed.[1] After that, in 1968, Minisci found that carboxylic acids can undergo decarboxylative substitution of protonated heteroaromatic bases.[2] Recently, decarboxylative couplings catalyzed by transition metals or induced via photoredox catalysis have proven to be one of the most powerful and efficient processes for the formation of C−C,[3] C−N,[4] C−S,[5] C−Cl,[6] C−F,[7] and C−P[8] bonds under mild conditions. At the same time, the direct application of carboxylic acids as a traceless activation group for radical additions has also been studied by MacMillan and other researchers.[9] For instance, in 2014, MacMillan found that carboxylic acids can be used for radical Michael additions via visible-light-mediated photoredox catalysis.[9b] The Xiao group reported a silver-catalyzed radical tandem cyclization for the synthesis of 3,4-disubstituted dihydroquinolin-2(1*H*)-ones.[9c] However, these decarboxylative radical additions have not yet been well studied until now.

All-carbon quaternary stereocenters are important key structural components that are found ubiquitously in biologically and pharmaceutically active molecules, such as aldose reductase (ALR2) inhibitors and aminoglutethimide (Figure 1).[10] Therefore, the development of new synthetic pathway for their synthesis has become an intensive topic of synthetic organic chemistry.[11] Recently, Nevado and co-workers first reported an arene-migration incorporation strategy to construct acyclic all-carbon quaternary stereocenters by aryltrifluoromethylation, arylphosphonylation, and arylazidation of *N*-phenyl-*N*-(phenylsulfonyl)methacrylamide.[12] Subsequently, Li, Zhu, Xia, and other groups realized arylalkylation and aryltrifluoromethylation under the palladium-catalysis, metal-free, or

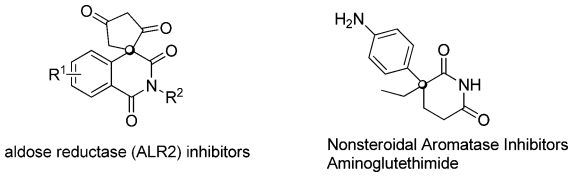
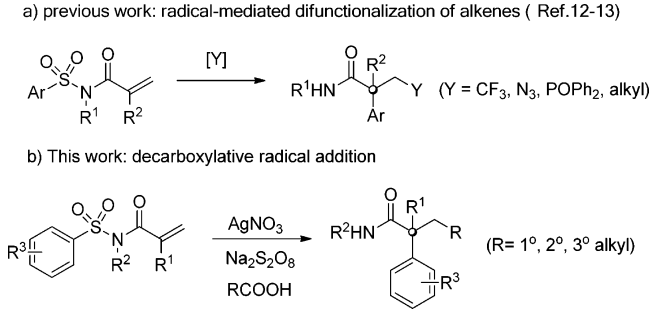


Figure 1. Some biologically and pharmaceutically active molecules.

visible-light-induced conditions using the same substrates, respectively (Scheme 1a).[13] However, in Zhu's work, only cyclic alkyl radical species can be involved. Herein, we develop a new type of arene incorporation strategy initiated by the decarboxylative radical addition, thus enabling the versatile assembly of acyclic all-carbon quaternary stereocenters from activated alkenes and a series of primary, secondary, and tertiary aliphatic carboxylic acids (Scheme 1b).

Scheme 1. Difunctionalization of Activated Alkenes



We started our model reaction by investigating *N*-phenyl-*N*-tosylmethacrylamide **1a** and 2,3-dihydrobenzo[*b*][1,4]dioxine-

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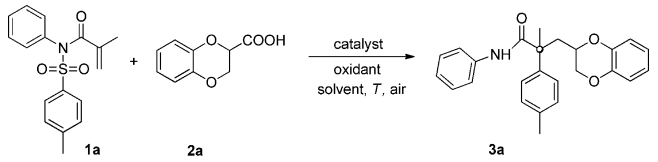
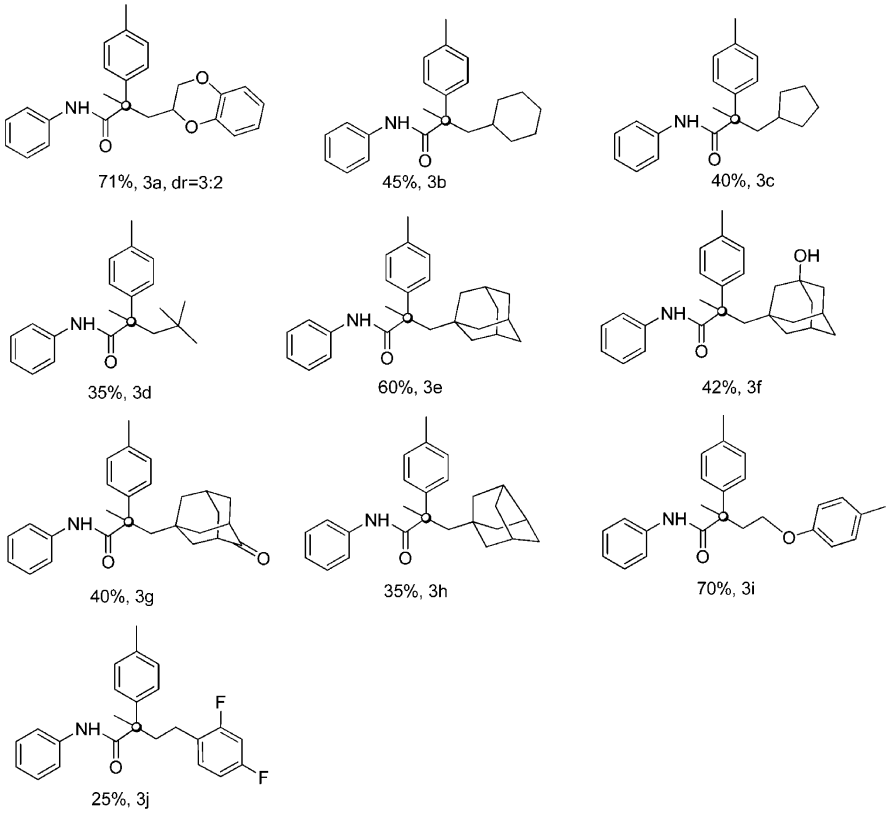
Table 1. Screening of Reaction Conditions[a]



entry	catalyst	oxidant	solvent	yield (%)[b]
1	10% $AgNO_3$	2 equiv $K_2S_2O_8$	CH_3CN/H_2O (1:1)	57
2[c]	10% $AgNO_3$	2 equiv $K_2S_2O_8$	CH_3CN/H_2O (1:1)	40
3	10% $AgNO_3$	2 equiv $(NH_4)_2S_2O_8$	CH_3CN/H_2O (1:1)	48
4	***10% $AgNO_3$***	***2 equiv $Na_2S_2O_8$***	***CH_3CN/H_2O (1:1)***	***71***
5	10% AgOAc	2 equiv $Na_2S_2O_8$	CH_3CN/H_2O (1:1)	65
6	10% Ag_2CO_3	2 equiv $Na_2S_2O_8$	CH_3CN/H_2O (1:1)	52
7[d]	10% $AgNO_3$	2 equiv $Na_2S_2O_8$	acetone/H_2O (1:1)	43
8[d]	10% $AgNO_3$	2 equiv $Na_2S_2O_8$	DCM/H_2O (1:1)	35
9	10% $AgNO_3$	2 equiv TBHP	CH_3CN/H_2O (1:1)	N.R.
10	10% $AgNO_3$	2 equiv DTBP	CH_3CN/H_2O (1:1)	N.R.
11	5% $AgNO_3$	2 equiv $Na_2S_2O_8$	CH_3CN/H_2O (1:1)	60
12		2 equiv $Na_2S_2O_8$	CH_3CN/H_2O (1:1)	0
13	10% $AgNO_3$		CH_3CN/H_2O (1:1)	0

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol, 2 equiv), 80 °C, solvent (2 mL), under air atmosphere, 12 h. [b]Isolated yield. N.R. = No reaction. [c]1.5 equiv of **2a**. [d]60 °C.

Scheme 2. Decarboxylative Alkylation of a Series of Aliphatic Carboxylic Acids



2-carboxylic acid **2a** for the optimization of reaction conditions (see Table 1). Using 10% $AgNO_3$ as catalyst and CH_3CN/H_2O (1:1) as solvent, several persulfates were first screened, and 2 equiv of $Na_2S_2O_8$ gave a better result (71% yield, entry 4). Other Ag(I) salts such as AgOAc and Ag_2CO_3 gave lower yields (entries 5 and 6). In order to further optimize the reaction condition, other mixed solvents such as acetone/H_2O (1:1) and DCM/H_2O (1:1) were screened, and no better results were obtained (entries 7 and 8). Investigation of other oxidants such as TBHP and DTBP for this transformation showed that no reaction occurred (entries 9 and 10). When the loading of the catalyst was decreased to 5%, a lower yield of 60% was observed (entry 11). Expectedly, omitting the catalyst or the oxidant, no reaction occurred, which indicated that both the catalyst and the oxidant were important in this transformation (entries 12 and 13).

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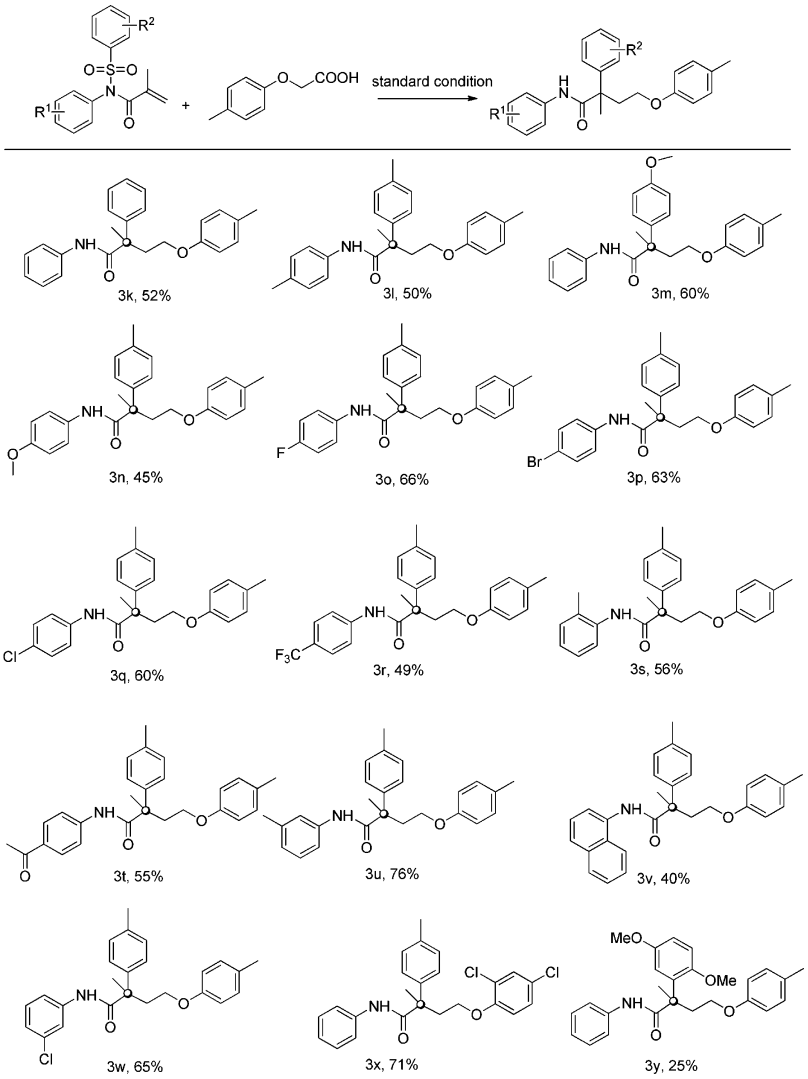
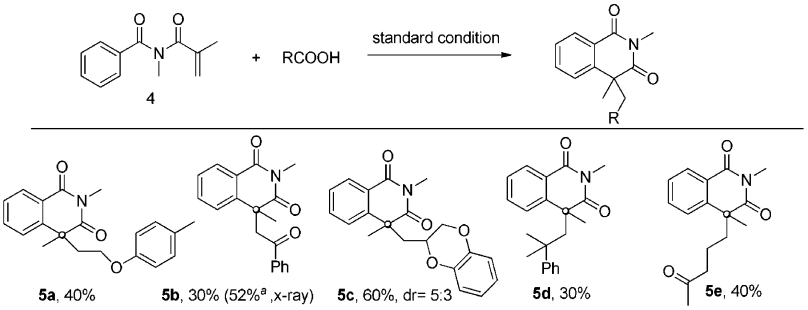
Scheme 3. Decarboxylative Alkylation of Substituted Benzsulfamides



Scheme 4. Decarboxylative Addition/Cyclization Reaction[a]



[a]Reaction conditions: **4** (0.3 mmol), 2-oxo-2-phenylacetic acid (0.6 mmol), 10% AgOAc, 2 equiv of $(NH_4)_2S_2O_8$, 2 equiv of CsOAc, CH_3CN/H_2O (V:V = 2:1), 60 °C, 6 h.

With the optimized conditions in hand (Table 1, entry 4), we next set out to explore the substrate scope and the limitations of the decarboxylative alkylation reaction (Scheme 2). A series of aliphatic carboxylic acids including primary, secondary, and tertiary carboxylic acids were well tolerated under the optimized conditions to give the moderate yields. It is well-known that the adamantyl group frequently occurs in ligands and catalysts in organic synthesis.[14] It is notable that the adamantyl group was successfully incorporated into the substrates using this decarboxylative reaction (**3e**). In addition, adamantanecarboxylic acids containing hydroxyl or carbonyl groups can also participate in this reaction, and the substituents were well retained (**3f** and **3g**). Meanwhile, 3-noradamantane-carboxylic acid can also be tolerated in this reaction (**3h**). It is noteworthy that primary carboxylic acids containing heter-oatoms (O) at the adjacent position of the carboxyl group

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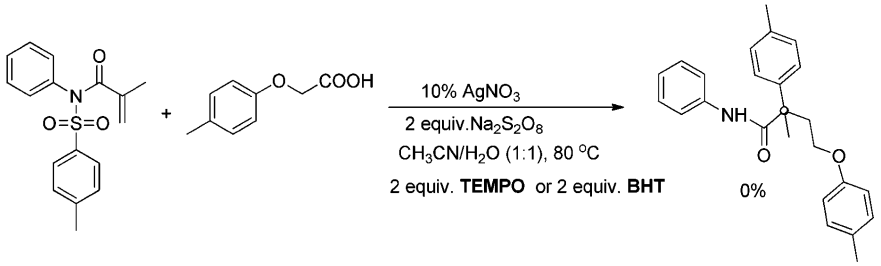
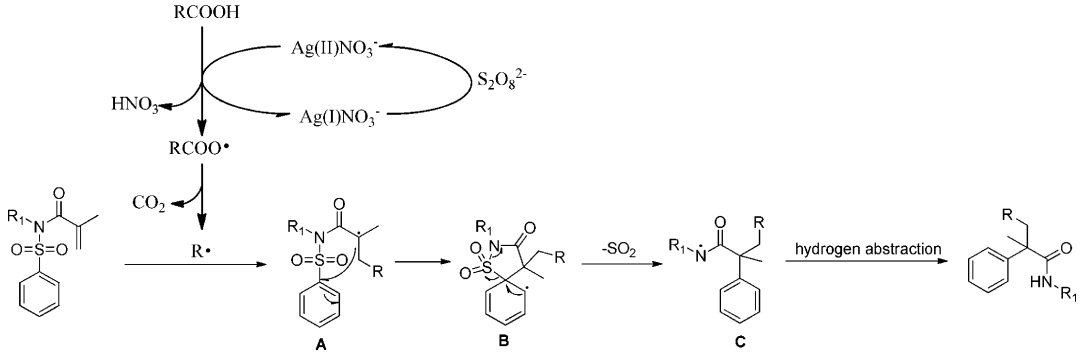
Scheme 5. Mechanistic Experiments



Scheme 6. Proposed Mechanism



displayed high reactivity in this transformation (**3i**). To our delight, primary carboxylic acid such as 2-(2,4-difluorophenyl)-acetic acid can undergo this decarboxylative addition using 20% $AgNO_3$ as the catalyst to give the product **3j** in a lower yield (25%).

Then, using 2-(*p*-tolyloxy)acetic acid as the template substrate, a series of electron-donating or electron-withdrawing sulfamide substituents were investigated under the standard conditions (Scheme 3). The effect of various substitution patterns at the *ortho*, *meta*, and *para* positions on the *N*-aryl moiety was first examined including fluoro, chloro, bromo, methoxyl, trifluoromethyl, acetyl, and methyl substituents, giving the corresponding products in moderate to good yields. However, the strong electron-withdrawing substituent (NO_2) cannot give any product, and the substrate **1** can be fully recovered. In addition, substituents such as Me and OMe on the benzenesulfonyl aromatic ring were also tolerated, but electron-withdrawing groups such as Cl or Br failed in this reaction. The naphthyl group can be also used in this reaction, and a 40% product **3v** was produced. 2-(2,4-Dichlorophenoxy)-acetic acid was also well tolerated to give a 71% yield of the product **3x**. When there were two OCH_3 groups on the phenyl (SO_2) moiety, the reaction occurred to give the product **3y**, which was in contrast to a previous report.[13c]

Encouraged by these results, we next extend this method to decarboxylative addition/cyclization reaction (Scheme 4). 2-(*p*-Tolyloxy)acetic acid can give the cyclization product **5a** in 40% yield. 2-Oxo-2-phenylacetic acid can be also tolerated in this cyclization reaction. When a base was added, a 52% yield (**5b**) was obtained under the slightly modified conditions. The structure of the product **5b** was further confirmed by X-ray crystallography (see the Supporting Information).[15] Secondary carboxylic acid 2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid gave mixed isomers **5c** (dr = 5:3) in 60% yield. When tertiary carboxylic acid 2-methyl-2-phenylpropanoic acid was subjected into the reaction, product **5d** was separated in 30% yield. Interestingly, the biomass derived levulinic acid can undergo decarboxylative addition to give the product **5e** in 40% yield.

To gain a further understanding about the reaction mechanism, inhibition experiments were conducted (Scheme 5). When 2.0 equiv of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or 2.0 equiv of BHT (2,6-di-*tert*-butyl-4-methylphenol) were added into the standard conditions, the desired transformation was found to be completely suppressed. These results suggested that the reaction proceeded through free-radical addition, which is consistent with the mechanisms proposed in previous reports.[9c]

On the basis of the above results and previous reports,[13] a possible mechanism is outlined in Scheme 6. First, Ag(I) is oxidized by the $S_2O_8^{2-}$ to generate the Ag(II) cation, which obtains a single electron from carboxylate to produce the carboxyl radical.[3h] The carboxyl radical quickly undergoes decarboxylation to provide the corresponding alkyl radical. Then, the alkyl radical adds to the double bond of the substrate **1**, which affords radical intermediate **A**. The 5-*ipso*-cyclization on the aromatic ring generates intermediate **B**, and a rapid desulfonylation affords the key amidyl radical **C**. Finally, radical intermediate **C** abstracts a hydrogen atom to give the desired product.

In conclusion, we have developed an efficient silver-catalyzed decarboxylative addition/aryl migration/desulfonylation for the synthesis of α-all-carbon quaternary stereocenters amides in moderate to good yields. In addition, the alkylated isoquinolinediones could also be easily obtained in this protocol. This transformation provides an operationally simple method for the functionalization of alkenes with simple aliphatic carboxylic acids.

EXPERIMENTAL SECTION

General Remarks. Column chromatography was carried out on silica gel. Unless noted, ^1H NMR spectra were recorded on 400 MHz in $CDCl_3$, and ^{13}C NMR spectra were recorded on 100 MHz in $CDCl_3$. IR spectra were recorded on an FT-IR spectrometer, and only

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major peaks are reported in cm^{-1}. Melting points were determined on a microscopic apparatus and were uncorrected. All new products were further characterized by HRMS (high-resolution mass spectrometry). HRMS spectra were obtained on a micrOTOF-Q instrument equipped with an ESI source. Copies of their ^1H NMR and ^{13}C NMR spectra are provided.

Procedure for the Synthesis of Products 3 and 5. To a solution of *N*-phenyl-*N*-tosylmethacrylamide (**1**, 0.3 mmol) in CH_3CN/H_2O (1:1, 2.0 mL) were added acid (**2**, 0.6 mmol), 10% $AgNO_3$ (0.03 mmol, 5.1 mg), and $Na_2S_2O_8$ (2.0 equiv, 0.6 mmol, 142.8 mg). The reaction mixture was then stirred for 12 h at 80 °C in air. After the reaction, the resulting mixture was extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Purification of the crude product by flash column chromatography afforded the product **3** (petroleum ether/ethyl acetate as eluent (6:1)).

Characterization Data of Compounds 3 and 5. *3-(2,3-Dihydrobenzo[b][1,4]dioxin-2-yl)-2-methyl-N-phenyl-2-(p-tolyl)-propanamide,* ***3a.*** dr = 3:2, 71%, 82.5 mg, m.p. = 107−108 °C, ^1H NMR (400 MHz): 7.34−7.36 (m, 2 H), 7.21−7.34 (m, 5 H), 7.20−7.22 (m, 2 H), 7.06−7.08 (m, 1 H), 6.75−6.78 (m, 3 H), 4.10−4.24 (m, 1 H), 3.81−3.93 (m, 2 H), 2.40−2.50 (m, 1 H), 2.36 (s, 3.6 H), 2.18−2.30 (m, 1 H), 1.86 (s, 1.8 H), 1.83 (s, 1.2 H); ^{13}C NMR (100 MHz): 174.9, 174.6, 142.9, 142.8, 140.2, 138.8, 137.8, 137.7, 137.6, 137.3, 129.8, 128.8, 126.9, 124.5, 124.2, 121.3, 121.1, 119.7, 117.3, 116.8, 70.9, 70.5, 68.4, 50.4, 50.2, 41.2, 39.9, 24.1, 23.6, 20.9; IR (cm^{-1}): 3379, 3101, 3066, 2987, 2929, 1712, 1594, 1493, 1171, 1088, 1017, 814, 737, 706, 664; HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{26}NO_3$: M + H = 388.1913; found: 388.1907.

3-Cyclohexyl-2-methyl-N-phenyl-2-(p-tolyl)propanamide, ***3b.*** 45%, 45 mg, m.p. = 94−95 °C, ^1H NMR (400 MHz): 7.23−7.35 (m, 6 H), 7.17−7.19 (m, 2 H), 7.02−7.06 (m, 1 H), 6.82 (s, 1 H, NH), 2.35 (s, 3 H), 1.92−2.01 (m, 2 H), 1.66−1.70 (m, 1 H), 1.62 (s, 3 H), 1.53−1.60 (m, 3 H), 1.37−1.42 (m, 1 H), 1.26−1.29 (m, 2 H), 1.00−1.17 (m, 3 H), 0.83−0.92 (m, 1 H); ^{13}C NMR (100 MHz): 175.6, 141.2, 136.8, 129.5, 128.8, 126.8, 123.9, 119.7, 51.2, 45.9, 35.3, 35.2, 34.0, 26.4, 26.2, 24.3, 20.9; IR (cm^{-1}): 3336, 2923, 2851, 1667, 1598, 1519, 1439, 1310, 1242, 817, 751, 691; HRMS (ESI) *m*/*z*: calcd for $C_{23}H_{28}NO^-$: M − H = 334.2171; found: 334.2170.

3-Cyclopentyl-2-methyl-N-phenyl-2-(p-toly)propanamide, ***3c.*** 40%, 38.5 mg, m.p. = 107−109 °C, ^1H NMR (400 MHz): 7.33−7.36 (m, 2 H), 7.29−7.31 (m, 2 H), 7.23−7.27 (m, 2 H), 7.17−7.19 (m, 2 H), 7.02−7.06 (m, 1 H), 6.82 (s, 1 H, NH), 2.36 (s, 3 H), 2.14−2.25 (m, 2 H), 1.68−1.80 (m, 2 H), 1.63 (s, 3 H), 1.58−1.59 (m, 1 H), 1.49−1.56 (m, 2 H), 1.37−1.42 (m, 2 H), 1.09−1.18 (m, 1 H), 0.95−1.01 (m, 1 H); ^{13}C NMR (100 MHz): 175.7, 141.1, 136.9, 129.5, 128.8, 126.9, 123.9, 119.6, 51.5, 44.9, 36.6, 34.6, 34.5, 24.9, 24.5, 20.9; IR (cm^{-1}): 3410, 3340, 2948, 2866, 1668, 1598, 1518, 1437, 1310, 1241, 817, 751, 691; HRMS (ESI) *m*/*z*: calcd for $C_{22}H_{26}NO^-$: M − H = 320.2014; found: 320.2032.

2,4,4-Trimethyl-N-phenyl-2-(p-tolyl)pentanamide, ***3d.*** 35%, 32.5 mg, m.p. = 127−128 °C, ^1H NMR (400 MHz): 7.32−7.35 (m, 4 H), 7.23−7.26 (m, 2 H), 7.16−7.18 (m, 2 H), 7.02−7.06 (m, 1 H), 6.83 (s, 1 H, NH), 2.35 (s, 3 H), 2.30−2.34 (m, 1 H), 2.10−2.14 (m, 1 H), 1.75 (s, 3 H), 0.88 (s, 9 H); ^{13}C NMR (100 MHz): 175.8, 141.8, 136.8, 129.4, 128.8, 126.9, 123.9, 119.6, 51.5, 50.3, 31.9, 31.7, 25.1, 20.9; IR (cm^{-1}): 3348, 2951, 1667, 1598, 1518, 1437, 1308, 1242, 817, 751, 691; HRMS (ESI) *m*/*z*: calcd for $C_{21}H_{26}NO^-$: M − H = 308.2014; found: 308.1992.

3-Adamantan-2-methyl-N-phenyl-2-(p-tolyl)propanamide, ***3e.*** 60%, 69 mg, m.p. = 139.8−140.8 °C, ^1H NMR (400 MHz): 7.32−7.33 (m, 4 H), 7.22−7.26 (m, 2 H), 7.15−7.17 (m, 2 H), 7.01−7.05 (m, 1 H), 6.81 (s, 1 H, NH), 2.34 (s, 3 H), 2.12−2.14 (m, 1 H), 1.94−1.98 (m, 1 H), 1.83 (s, 3 H), 1.76 (s, 3 H), 1.50−1.61 (m, 12 H); ^{13}C NMR (100 MHz): 175.8, 142.2, 138.1, 136.7, 128.8, 126.7, 123.9, 119.6, 52.0, 51.1, 43.9, 36.9, 34.2, 25.8, 20.9; IR (cm^{-1}): 3348, 2905, 2854, 1669, 1598, 1516, 1442, 1309, 1242, 1183, 972, 819, 745, 694; HRMS (ESI) *m*/*z*: calcd for $C_{27}H_{32}NO^-$: M − H = 386.2484; found: 386.2458.

3-Hydroxyadamantan-2-methyl-N-phenyl-2-(p-tolyl)-propanamide, ***3f.*** 42%, 51 mg, oil, ^1H NMR (400 MHz): 7.31−7.33 (m, 4 H), 7.23−7.25 (m, 2 H), 7.16−7.18 (m, 2 H), 7.03−7.07 (m, 1 H), 6.83 (s, 1 H, NH), 2.36 (s, 3 H), 2.22−2.26 (m, 1 H), 2.07 (s, 2 H), 2.03−2.04 (m, 1 H), 1.77 (s, 3 H), 1.51−1.60 (m, 5 H), 1.40−1.46 (m, 7 H); ^{13}C NMR (100 MHz): 175.7, 141.6, 136.9, 129.4, 128.8, 126.8, 124.0, 119.7, 68.7, 51.7, 51.1, 50.9, 44.4, 42.3, 35.2, 30.7, 25.6, 20.9; IR (cm^{-1}): 3402, 2915, 2851, 1668, 1597, 1518, 1437, 1310, 1242, 1131, 1039, 817, 751, 692; HRMS (ESI) *m*/*z*: calcd for $C_{27}H_{32}NO_2^-$: M − H = 402.2433; found: 402.2444.

2-Methyl-4-oxoadamantan-N-phenyl-2-(p-tolyl)propanamide, ***3g.*** 40%, 48 mg, oil, ^1H NMR (400 MHz): 7.29−7.32 (m, 4 H), 7.25−7.26 (m, 2 H), 7.17−7.19 (m, 2 H), 7.03−7.07 (m, 1 H), 6.80 (s, 1 H, NH), 2.39 (s, 2 H), 2.36 (s, 3 H), 2.26−2.29 (m, 1 H), 2.03−2.08 (m, 1 H), 2.00 (s, 1 H), 1.83−1.90 (m, 4 H), 1.74−1.77 (m, 3 H), 1.70−1.71 (m, 5 H), 1.61 (s, 1 H); ^{13}C NMR (100 MHz): 175.5, 140.9, 137.3, 129.6, 128.9, 126.9, 124.2, 119.7, 51.1, 49.9, 46.7, 42.7, 38.5, 34.1, 27.9, 25.4, 20.9; IR (cm^{-1}): 3348, 2923, 2856, 1720, 1682, 1597, 1520, 1437, 1310, 1242, 1176, 1062, 819, 753, 693; HRMS (ESI) *m*/*z*: calcd for $C_{27}H_{30}NO_2^-$: M − H = 400.2277; found: 400.2305.

2-Methyl-3-octahydro-2,5-methanopentalen-N-phenyl-2-(p-tolyl)propanamide, ***3h.*** 35%, 39 mg, m.p. = 126−127 °C, ^1H NMR (400 MHz): 7.33−7.36 (m, 4 H), 7.23−7.25 (m, 2 H), 7.16−7.18 (m, 2 H), 7.02−7.06 (m, 1 H), 6.86 (s, 1 H, NH), 2.59−2.63 (m, 1 H), 2.40−2.44 (m, 1 H), 2.35 (s, 3 H), 2.05−2.13 (m, 3 H), 1.74 (s, 3 H), 1.64−1.70 (m, 4 H), 1.44−1.49 (m, 3 H), 1.33−1.34 (m, 1 H), 1.26−1.29 (m, 2 H); ^{13}C NMR (100 MHz): 175.9, 141.8, 136.8, 129.4, 128.8, 126.9, 123.9, 119.6, 51.6, 49.8, 49.4, 48.3, 48.0, 47.5, 43.3, 37.9, 34.9, 24.6, 20.9; IR (cm^{-1}): 3340, 2924, 2862, 1667, 1598, 1437, 1308, 1242, 751, 690; HRMS (ESI) *m*/*z*: calcd for $C_{26}H_{30}NO^-$: M − H = 372.2327; found: 372.2321.

2-Methyl-N-phenyl-2-(p-tolyl)-4-(p-tolyloxy)butanamide, ***3i.*** 70%, 78 mg, oil, ^1H NMR (400 MHz): 7.34−7.36 (m, 2 H), 7.30−7.32 (m, 2 H), 7.23−7.25 (m, 2 H), 7.18−7.20 (m, 2 H), 7.00−7.07 (m, 3 H), 6.93 (s, 1 H, NH), 6.67−6.70 (m, 2 H), 3.91−3.94 (m, 2 H), 2.45−2.59 (m, 2 H), 2.35 (s, 3 H), 2.24 (s, 3 H), 1.73 (s, 3 H); ^{13}C NMR (100 MHz): 174.8, 156.5, 139.8, 137.8, 137.2, 129.7, 126.7, 124.2, 119.8, 114.3, 64.8, 50.1, 38.1, 24.2, 20.9, 20.4; IR (cm^{-1}): 3403, 3336, 2923, 2877, 1676, 1598, 1512, 1437, 1311, 1241, 1175, 1019, 817, 752, 691; HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{26}NO_2^-$: M − H = 372.1964; found: 372.1962.

4-(2,4-Difluorophenyl)-2-methyl-N-phenyl-2-(p-tolyl)-butanamide, ***3j.*** 25%, 28.5 mg, m.p. = 116−118 °C, ^1H NMR (400 MHz): 7.32−7.37 (m, 4 H), 7.21−7.26 (m, 4 H), 7.04−7.11 (m, 2 H), 6.88 (s, NH, 1 H), 6.70−6.78 (m, 2 H), 2.54−2.60 (m, 1 H), 2.40−2.44 (m, 1 H), 2.37 (s, 3 H), 2.25−2.34 (m, 2 H), 1.72 (s, 3 H); ^{13}C NMR (100 MHz): 174.9, 162.6, 162.1, 160.2, 159.6, 159.5, 139.7, 137.9, 137.2, 131.0, 128.8, 124.1, 119.7, 110.9, 110.8, 103.8, 103.5, 103.3, 51.1, 39.5, 23.9, 23.6, 20.9; IR (cm^{-1}): 3410, 3336, 2926, 2869, 1682, 1599, 1503, 1437, 1274, 1137, 961, 849, 753, 691; HRMS (ESI) *m*/*z*: calcd for $C_{24}H_{22}NF_2O^-$: M − H = 378.1669; found: 378.1665.

2-Methyl-N,2-diphenyl-4-(p-tolyloxy)butanamide, ***3k.*** 52%, 56 mg, oil, ^1H NMR (400 MHz): 7.21−7.43 (m, 9 H), 7.03−7.07 (m, 3 H), 6.94 (s, 1 H, NH), 6.66−6.68 (m, 2 H), 3.91−3.95 (m, 2 H), 2.53−2.62 (m, 1 H), 2.46−2.51 (m, 1 H), 2.24 (s, 3 H), 1.74 (s, 3 H); ^{13}C NMR (100 MHz): 174.5, 156.4, 143.0, 137.7, 128.8, 127.5, 126.7, 124.2, 119.8, 114.3, 64.7, 50.5, 38.1, 24.1, 20.4; IR (cm^{-1}): 3406, 3340, 3056, 3028, 2929, 1676, 1600, 1514, 1310, 1238, 1077, 816, 749, 697; HRMS (ESI) *m*/*z*: calcd for $C_{24}H_{24}NO_2^-$: M − H = 358.1807; found: 358.1823.

2-Methyl-N,2-di-p-tolyl-4-(p-tolyloxy)butanamide, ***3l.*** 50%, 58 mg, oil, ^1H NMR (400 MHz): 7.29−7.31 (m, 2 H), 7.18−7.24 (m, 4 H), 7.00−7.06 (m, 4 H), 6.88 (s, 1 H, NH), 6.68−6.70 (m, 2 H), 3.91−3.94 (m, 2 H), 2.56−2.65 (m, 1 H), 2.44−2.51 (m, 1 H), 2.35 (s, 3 H), 2.27 (s, 3 H), 2.24 (s, 3 H), 1.72 (s, 3 H); ^{13}C NMR (100 MHz): 174.7, 156.5, 140.0, 137.1, 133.8, 129.3, 126.7, 119.9, 114.3, 64.8, 50.0, 38.1, 24.2, 20.9, 20.7, 20.4; IR (cm^{-1}): 3410, 3340, 2923, 1673, 1596, 1513, 1402, 1311, 1240, 1025, 814; HRMS (ESI) *m*/*z*: calcd for $C_{26}H_{28}NO_2^-$: M − H = 386.2120; found: 386.2139.

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2-(4-Methoxyphenyl)-2-methyl-N-phenyl-4-(p-tolyloxy)-butanamide, ***3m.*** 60%, 70 mg, oil, ^{1}H NMR (400 MHz): 7.32−7.37 (m, 4 H), 7.23−7.27 (m, 2 H), 7.04−7.06 (m, 1 H), 6.99−7.02 (m, 2 H), 6.96 (s, 1 H, NH), 6.90−6.92 (m, 2 H), 6.68−6.70 (m, 2 H), 3.90−3.94 (m, 2 H), 3.81 (s, 3 H), 2.57−2.62 (m, 1 H), 2.45−2.51 (m, 1 H), 2.25 (s, 3 H), 1.72 (s, 3 H); ^{13}C NMR (100 MHz): 174.9, 158.8, 156.4, 137.8, 134.7, 127.9, 124.1, 119.7, 114.3, 64.8, 55.2, 49.8, 38.1, 24.3, 20.4; IR (cm^{-1}): 3328, 2925, 1664, 1611, 1511, 1403, 1295, 1230, 1023, 818; HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{26}NO_3^-$: M − H = 388.1913; found: 388.1937.

N-(4-Methoxyphenyl)-2-methyl-2-(p-tolyl)-4-(p-tolyloxy)-butanamide, ***3n.*** 45%, 54.5 mg, oil, ^{1}H NMR (400 MHz): 7.29−7.31 (m, 2 H), 7.23−7.26 (m, 2 H), 7.18−7.20 (m, 2 H), 7.00−7.02 (m, 2 H), 6.86 (s, 1 H, NH), 6.78−6.80 (m, 2 H), 6.68−6.70 (m, 2 H), 3.91−3.94 (m, 2 H), 3.74 (s, 3 H), 2.56−2.64 (m, 1 H), 2.45−2.51 (m, 1 H), 2.35 (s, 3 H), 2.24 (s, 3 H), 1.72 (s, 3 H); ^{13}C NMR (100 MHz): 174.6, 156.5, 156.4, 140.1, 137.1, 129.7, 126.6, 121.7, 114.3, 113.9, 64.8, 55.4, 49.9, 38.1, 24.2, 20.9, 20.4; IR (cm^{-1}): 3340, 2928, 1668, 1607, 1513, 1296, 1238, 1177, 1115, 1033, 821; HRMS (ESI) *m*/*z*: calcd for $C_{26}H_{28}NO_3^-$: M − H = 402.2069; found: 402.2070.

N-(4-Fluorophenyl)-2-methyl-2-(p-tolyl)-4-(p-tolyloxy)-butanamide, ***3o.*** 66%, 77.5 mg, oil, ^{1}H NMR (400 MHz): 7.28−7.31 (m, 4 H), 7.19−7.21 (m, 2 H), 7.00−7.02 (m, 2 H), 6.91−6.95 (m, 3 H), 6.67−6.69 (m, 2 H), 3.90−3.93 (m, 2 H), 2.57−2.64 (m, 1 H), 2.43−2.51 (m, 1 H), 2.35 (s, 3 H), 2.24 (s, 3 H), 1.72 (s, 3 H); ^{13}C NMR (100 MHz): 174.8, 160.5, 158.1, 156.4, 139.8, 137.3, 133.8, 129.7, 126.6, 121.7, 115.5, 115.3, 114.3, 64.7, 50.0, 38.0, 24.2, 20.9, 20.4; IR (cm^{-1}): 3404, 3028, 2973, 2924, 1667, 1611, 1511, 1403, 1238, 1022, 817, 740; HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{25}NFO_2^-$: M − H = 390.1869; found: 390.1888.

N-(4-Bromophenyl)-2-methyl-2-(p-tolyl)-4-(p-tolyloxy)-butanamide, ***3p.*** 63%, 85 mg, m.p. = 139−140 °C, ^{1}H NMR (400 MHz): 7.34−7.35 (m, 2 H), 7.25−7.32 (m, 4 H), 7.18−7.20 (m, 2 H), 6.99−7.01 (d, *J* = 8.0 Hz, 2 H), 6.66−6.68 (d, *J* = 8.0 Hz, 2 H), 3.89−3.92 (m, 2 H), 2.50−2.59 (m, 1 H), 2.43−2.48 (m, 1 H), 2.35 (s, 3 H), 2.24 (s, 3 H), 1.71 (s, 3 H); ^{13}C NMR (100 MHz): 174.8, 156.4, 139.6, 137.3, 136.9, 131.7, 129.8, 126.6, 121.3, 116.7, 114.3, 64.7, 50.2, 38.0, 24.1, 20.9, 20.4; IR (cm^{-1}): 3336, 2921, 1676, 1588, 1510, 1391, 1239, 1072, 1007, 817; HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{25}NBrO_2^-$: M − H = 450.1069; found: 450.1078.

N-(4-Chlorophenyl)-2-methyl-2-(p-tolyl)-4-(p-tolyloxy)-butanamide, ***3q.*** 60%, 73 mg, m.p. = 135−136 °C, ^{1}H NMR (400 MHz): 7.28−7.31 (m, 4 H), 7.18−7.23 (m, 4 H), 6.98−7.00 (m, 3 H), 6.66−6.68 (d, *J* = 8.0 Hz, 2 H), 3.89−3.93 (m, 2 H), 2.56−2.60 (m, 1 H), 2.43−2.50 (m, 1 H), 2.35 (s, 3 H), 2.24 (s, 3 H), 1.71 (s, 3 H); ^{13}C NMR (100 MHz): 174.8, 156.4, 139.6, 136.4, 129.8, 129.7, 129.1, 128.8, 126.6, 121.0, 114.3, 64.7, 50.1, 38.0, 24.1, 20.9, 20.4; IR (cm^{-1}): 3336, 3028, 2970, 2923, 1671, 1592, 1511, 1395, 1301, 1239, 1091, 1015, 817; HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{25}NClO_2^-$: M − H = 406.1574; found: 406.1598.

2-Methyl-2-(p-tolyl)-4-(p-tolyloxy)-N-(4-(trifluoromethyl)phenyl)-butanamide, ***3r.*** 49%, 65 mg, m.p. = 105−106 °C, ^{1}H NMR (400 MHz): 7.44−7.49 (m, 4 H), 7.26−7.28 (m, 2 H), 7.17−7.20 (m, 2 H), 7.10 (s, 1 H), 7.00−7.02 (d, *J* = 8.0 Hz, 2 H), 6.66−6.68 (d, *J* = 8.0 Hz, 2 H), 3.90−3.94 (m, 2 H), 2.58−2.63 (m, 1 H), 2.45−2.52 (m, 1 H), 2.36 (s, 3 H), 2.25 (s, 3 H), 1.73 (s, 3 H); ^{13}C NMR (100 MHz): 175.1, 156.4, 140.9, 139.5, 137.5, 129.8, 126.6, 126.0, 119.3, 114.3, 64.7, 50.3, 38.0, 24.1, 20.9, 20.4; IR (cm^{-1}): 3402, 3335, 2925, 2877, 1675, 1613, 1601, 1512, 1406, 1324, 1242, 1165, 1118, 1067, 840, 817, 741; HRMS (ESI) *m*/*z*: calcd for $C_{26}H_{25}NF_3O_2^-$: M − H = 440.1837; found: 440.1864.

2-Methyl-N-(o-tolyl)-2-(p-tolyl)-4-(p-tolyloxy)butanamide, ***3s.*** 56%, 65 mg, m.p. = 62−63 °C, ^{1}H NMR (400 MHz): 7.80−7.82 (d, *J* = 8.0 Hz, 1 H), 7.35−7.37 (d, *J* = 8.0 Hz, 2 H), 7.22−7.23 (m, 2 H), 7.14−7.18 (m, 1 H), 6.99−7.06 (m, 4 H), 6.77 (s, 1 H, NH), 6.68−6.70 (d, *J* = 8.0 Hz, 2 H), 3.93−3.96 (m, 2 H), 2.56−2.66 (m, 1 H), 2.49−2.54 (m, 1 H), 2.36 (s, 3 H), 2.24 (s, 3 H), 1.83 (s, 3 H), 1.76 (s, 3 H); ^{13}C NMR (100 MHz): 174.8, 156.5, 139.9, 137.3, 135.7, 129.7, 128.3, 126.8, 124.7, 122.1, 114.3, 64.8, 50.0, 37.8, 23.9, 20.4, 17.0; IR (cm^{-1}): 3415, 3324, 3026, 2924, 1680, 1587, 1513, 1452, 1292, 1241, 1029, 816, 751; HRMS (ESI) *m*/*z*: calcd for $C_{26}H_{28}NO_2^-$: M − H = 386.2120; found: 386.2124.

N-(4-Acetylphenyl)-2-methyl-2-(p-tolyl)-4-(p-tolyloxy)-butanamide, ***3t.*** 55%, 68.5 mg, oil, ^{1}H NMR (400 MHz): 7.83−7.85 (m, 2 H), 7.46−7.48 (m, 2 H), 7.27−7.29 (m, 2 H), 7.18−7.20 (m, 2 H), 6.99−7.01 (m, 2 H), 6.65−6.67 (m, 2 H), 3.89−3.93 (m, 2 H), 2.57−2.64 (m, 1 H), 2.51 (s, 3 H), 2.44−2.49 (m, 1 H), 2.34 (s, 3 H), 2.24 (s, 3 H), 1.73 (s, 3 H); ^{13}C NMR (100 MHz): 196.8, 175.1, 156.3, 142.2, 137.4, 132.7, 129.5, 126.6, 118.8, 114.2, 64.6, 50.3, 37.9, 26.3, 24.1, 20.9, 20.3; IR: 3336, 3028, 2923, 2878, 1681, 1588, 1506, 1404, 1359, 1271, 1243, 1178, 817, 736; HRMS (ESI) *m*/*z*: calcd for $C_{27}H_{28}NO_3^-$: M − H = 414.2069; found: 414.2091.

2-Methyl-N-(m-tolyl)-2-(p-tolyl)-4-(p-tolyloxy)butanamide, ***3u.*** 76%, 88 mg, oil, ^{1}H NMR (400 MHz): 7.29−7.31 (d, *J* = 8.0 Hz, 2 H), 7.18−7.23 (m, 3 H), 7.12−7.13 (m, 2 H), 7.00−7.02 (d, *J* = 8.0 Hz, 2 H), 6.91 (s, 1 H, NH), 6.86−6.88 (m, 1 H), 6.68−6.70 (m, 2 H), 3.91−3.94 (m, 2 H), 2.57−2.64 (m, 1 H), 2.46−2.51 (m, 1 H), 2.35 (s, 3 H), 2.28 (s, 3 H), 2.24 (s, 3 H), 1.72 (s, 3 H); ^{13}C NMR (100 MHz): 174.7, 156.5, 139.9, 138.7, 137.7, 137.2, 129.7, 128.6, 126.6, 124.9, 120.4, 116.8, 114.3, 64.8, 50.1, 38.1, 24.2, 21.3, 20.9, 20.4; IR (cm^{-1}): 3406, 3340, 2923, 1672, 1609, 1514, 1295, 1238, 1026, 779; HRMS (ESI) *m*/*z*: calcd for $C_{26}H_{28}NO_2^-$: M − H = 386.2120; found: 386.2135.

2-Methyl-N-(naphthalene-1-yl)-2-(p-tolyl)-4-(p-tolyloxy)-butanamide, ***3v.*** 40%, 51 mg, m.p. = 107−108 °C, ^{1}H NMR (400 MHz): 7.89−7.91 (d, *J* = 8.0 Hz, 1 H), 7.78−7.80 (d, *J* = 8.0 Hz, 1 H), 7.61−7.64 (m, 1 H), 7.39−7.46 (m, 4 H), 7.31−7.33 (m, 1 H), 7.23−7.27 (m, 2 H), 7.16−7.19 (m, 1 H), 7.01−7.03 (d, *J* = 8.0 Hz, 2 H), 6.70−6.72 (d, *J* = 8.0 Hz, 2 H), 3.98−4.01 (m, 2 H), 2.70−2.77 (m, 1 H), 2.56−2.63 (m, 1 H), 2.40 (s, 3 H), 2.25 (s, 3 H), 1.85 (s, 3 H); ^{13}C NMR (100 MHz): 175.4, 156.5, 140.0, 137.5, 129.9, 126.9, 125.7, 125.4, 120.2, 120.0, 114.4, 64.9, 50.3, 37.9, 24.1, 20.9, 20.4; IR (cm^{-1}): 3414, 3316, 3052, 3028, 2923, 1679, 1623, 1512, 1493, 1241, 816, 793, 771; HRMS (ESI) *m*/*z*: calcd for $C_{29}H_{28}NO_2^-$: M − H = 422.2120; found: 422.2148.

N-(3-Chlorophenyl)-2-methyl-2-(p-tolyl)-4-(p-tolyloxy)-butanamide, ***3w.*** 65%, 79.5 mg, oil, ^{1}H NMR (400 MHz): 7.47−7.48 (m, 1 H), 7.27−7.29 (d, *J* = 8.0 Hz, 2 H), 7.12−7.20 (m, 4 H), 7.00−7.02 (m, 3 H), 6.97 (s, 1 H, NH), 6.66−6.68 (d, *J* = 8.0 Hz, 2 H), 3.89−3.93 (m, 2 H), 2.56−2.63 (m, 1 H), 2.43−2.50 (m, 1 H), 2.35 (s, 3 H), 2.24 (s, 3 H), 1.71 (s, 3 H); ^{13}C NMR (100 MHz): 174.9, 156.4, 139.5, 138.9, 137.4, 134.5, 129.8, 129.7, 126.6, 124.1, 117.7, 114.3, 64.7, 50.2, 38.0, 24.1, 20.9, 20.4; IR (cm^{-1}): 3402, 3336, 3027, 2973, 2923, 1671, 1592, 1513, 1480, 1417, 1239, 816, 778, 682; HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{25}NClO_2^-$: M − H = 406.1574; found: 406.1578.

4-(2,4-Dichlorophenoxy)-2-methyl-N-phenyl-2-(p-tolyl)-butanamide, ***3x.*** 71%, 91 mg, oil, ^{1}H NMR (400 MHz): 7.32−7.34 (d, *J* = 8.0 Hz, 2 H), 7.28−7.29 (m, 3 H), 7.22−7.26 (m, 2 H), 7.18−7.20 (d, *J* = 8.0 Hz, 2 H), 6.90 (s, 1 H, NH), 6.72−6.74 (d, *J* = 8.0 Hz, 2 H), 4.00−4.06 (m, 1 H), 3.88−3.94 (m, 1 H), 2.59−2.66 (m, 1 H), 2.46−2.53 (m, 1 H), 2.34 (s, 3 H), 1.77 (s, 3 H); ^{13}C NMR (100 MHz): 174.8, 153.0, 139.4, 137.7, 137.4, 129.8, 125.4, 124.3, 123.4, 119.8, 113.8, 66.3, 50.1, 37.9, 24.2, 20.9; IR (cm^{-1}): 3402, 3336, 2929, 1675, 1597, 1518, 1485, 1289, 1246, 813; HRMS (ESI) *m*/*z*: calcd for $C_{24}H_{22}NCl_2O_2^-$: M − H = 426.1028; found: 426.1051.

2-(2,5-Dimethoxyphenyl)-2-methyl-N-phenyl-4-(p-tolyloxy)-butanamide, ***3y.*** Oil, 25%, 31 mg, ^{1}H NMR (400 MHz): 7.33−7.35 (m, 2 H), 7.23−7.27 (m, 2 H), 6.98−7.06 (m, 4 H), 6.93 (s, 1 H, NH), 6.83 (m, 2 H), 6.64−6.66 (m, 2 H), 3.83−3.87 (m, 2 H), 3.78 (s, 3 H), 3.66 (s, 3 H), 2.65−2.72 (m, 1 H), 2.48−2.55 (m, 1 H), 2.24 (s, 3 H), 1.71 (s, 3 H); ^{13}C NMR (100 MHz): 175.3, 156.5, 153.6, 151.5, 138.2, 129.7, 128.8, 123.8, 119.9, 115.1, 114.3, 112.3, 64.9, 55.9, 55.7, 48.4, 35.2, 23.9, 20.4; IR (cm^{-1}): 3403, 3339, 2940, 2834, 1686, 1597, 1511, 1437, 1229, 1177, 1046, 1026, 813, 752, 693; HRMS (ESI) *m*/*z*: calcd for $C_{26}H_{28}NO_4^-$: M − H = 418.2018; found: 418.2019.

2,4-Dimethyl-4-(2-(p-tolyloxy)ethyl)isoquinoline-1,3-(2H,4H)-dione, ***5a.*** 40%, 39 mg, m.p. = 82−83 °C, ^{1}H NMR (400 MHz): 8.21−8.23 (m, 1 H), 7.61−7.65 (m, 1 H), 7.40−7.45 (m, 2 H), 6.93−

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6.95 (d, J = 8.0 Hz, 2 H), 6.43−6.45 (d, J = 8.0 Hz, 2 H), 3.66−3.71 (m, 1 H), 3.42−3.46 (m, 1 H), 3.40 (s, 3 H), 2.92−3.00 (m, 1 H), 2.26−2.32 (m, 1 H), 2.20 (s, 3 H), 1.68 (s, 3 H); ^{13}C NMR (100 MHz): 176.3, 164.2, 155.9, 142.6, 133.7, 129.7, 128.9, 127.4, 126.4, 124.9, 113.9, 64.1, 45.4, 41.5, 30.0, 27.2, 20.3; IR (cm^{-1}): 2929, 1711, 1667, 1511, 1466, 1309, 1238, 1060, 817, 701; HRMS (ESI) m/z: calcd for $C_{20}H_{21}NNaO_3^+$: M + Na = 346.1419; found: 346.1387.

2,4-Dimethyl-4-(2-oxo-2-phenylethyl)isoquinoline-1,3-(2H,4H)-dione, ***5b***. 52%, 48 mg, m.p. = 127−129 °C, ^{1}H NMR (400 MHz): 8.30−8.32 (m, 1 H), 7.84−7.86 (m, 2 H), 7.51−7.56 (m, 2 H), 7.36−7.49 (m, 3 H), 7.26−7.28 (m, 1 H), 4.20−4.24 (m, 1 H), 3.95−4.00 (m, 1 H), 3.45 (s, 3 H), 1.62 (s, 3 H); ^{13}C NMR (100 MHz): 196.2, 176.7, 164.6, 143.7, 135.9, 133.7, 133.5, 129.3, 128.6, 127.9, 127.1, 125.0, 123.5, 49.1, 44.5, 30.8, 27.3; IR (cm^{-1}): 2925, 1710, 1664, 1467, 1417, 1314, 1211, 1099, 1056, 760, 701; HRMS (ESI) m/z: calcd for $C_{19}H_{17}NNaO_3^+$: M + Na = 330.1106; found: 330.1105.

4-((2,3-Dihydrobenzo[b][1,4]dioxin-2-yl)methyl)-2,4-dimethylisoquinoline-1,3-(2H,4H)-dione, ***5c***. 60%, 61 mg, dr = 5:3, Major isomer: oil, ^{1}H NMR (400 MHz): 8.25−8.27 (m, 1 H), 7.47−7.51 (m, 1 H), 7.38−7.42 (m, 1 H), 7.30−7.32 (m, 1 H), 6.68−6.72 (m, 2 H), 6.59−6.63 (m, 1 H), 6.06−6.08 (m, 1 H), 3.95−4.01 (m, 2 H), 3.77−3.80 (m, 1 H), 3.42 (s, 3 H), 2.44−2.58 (m, 2 H), 1.65 (s, 3 H); ^{13}C NMR (100 MHz): 176.2, 164.3, 143.4, 142.6, 141.9, 132.6, 128.8, 127.2, 125.5, 124.3, 121.2, 117.0, 116.7, 70.6, 67.3, 45.9, 42.4, 31.0, 27.2; IR (cm^{-1}): 1710, 1665, 1493, 1362, 1310, 1264, 1101, 1058, 749, 698.

Minor isomer: m.p. = 156−158 °C, ^{1}H NMR (400 MHz): 8.27−8.29 (m, 1 H), 7.62−7.66 (m, 1 H), 7.41−7.46 (m, 2 H), 6.73−6.77 (m, 3 H), 6.47−6.50 (m, 1 H), 3.98−4.01 (m, 1 H), 3.78−3.82 (m, 1 H), 3.51−3.54 (m, 1 H), 3.47 (s, 3 H), 2.81−2.87 (m, 1 H), 2.04−2.14 (m, 1 H), 1.68 (s, 3 H); ^{13}C NMR (100 MHz): 176.1, 164.3, 142.7, 142.3, 142.0, 133.8, 129.3, 127.7, 125.1, 121.5, 117.1, 116.9, 70.1, 67.5, 44.6, 42.9, 30.3, 27.3; IR (cm^{-1}): 2929, 1711, 1666, 1493, 1315, 1264, 1105, 1062, 751, 702; HRMS (ESI) m/z: calcd for $C_{20}H_{19}NNaO_4^+$: M + Na = 360.1212; found: 360.1196.

2,4-Dimethyl-4-(2-methyl-2-phenylpropyl)isoquinoline-1,3-(2H,4H)-dione, ***5d***. 30%, 29 mg, oil, ^{1}H NMR (400 MHz): 8.13−8.15 (m, 1 H), 7.31−7.36 (m, 2 H), 7.19−7.21 (m, 1 H), 7.09−7.12 (m, 2 H), 7.04−7.06 (m, 1 H), 6.94−6.96 (m, 2 H), 2.98 (s, 3 H), 2.92−2.95 (m, 1 H), 2.35−2.39 (m, 1 H), 1.54 (s, 3 H), 1.09 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR (100 MHz): 175.9, 164.1, 146.7, 142.8, 132.8, 128.5, 127.8, 127.0, 126.8, 126.1, 125.7, 124.4, 55.9, 46.0, 38.0, 33.1, 30.4, 29.7, 26.9; IR (cm^{-1}): 2962, 2929, 1710, 1667, 1462, 1419, 1364, 1324, 1300, 1091, 1056, 763, 699; HRMS (ESI) m/z: calcd for $C_{21}H_{23}NNaO_2^+$: M + Na = 344.1626; found: 344.1600.

2,4-Dimethyl-4-(4-oxopentyl)isoquinoline-1,3-(2H,4H)-dione, ***5e***. 40%, 33 mg, oil, ^{1}H NMR (400 MHz): 8.24−8.26 (m, 1 H), 7.64−7.68 (m, 1 H), 7.43−7.46 (m, 2 H), 3.39 (s, 3 H), 2.25−2.35 (m, 2 H), 2.03 (s, 3 H), 1.89−1.97 (m, 1 H), 1.65−1.71 (m, 1 H), 1.59 (s, 3 H), 1.08−1.15 (m, 2 H); ^{13}C NMR (100 MHz): 207.9, 176.5, 164.3, 143.1, 134.0, 128.8, 127.4, 125.2, 124.8, 47.7, 43.1, 41.6, 29.8, 29.7, 27.1, 19.2; IR (cm^{-1}): 2925, 2850, 1714, 1668, 1606, 1468, 1417, 1363, 1323, 1297, 769, 702; HRMS (ESI) m/z: calcd for $C_{16}H_{19}NNaO_3^+$: M + Na = 296.1263; found: 296.1263.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02594.

X-ray crystallographic data of **5b**, and ^{1}H NMR and ^{13}C NMR spectra of all compounds (PDF)

X-ray crystallographic data of **5b** (CIF)

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Notes

The authors declare no competing financial interest.

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(15) CCDC 1431817 (**5b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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