Synthesis G.-H. Pan et al. Paper

Synthesis of γ-Amino Esters by Copper-Catalyzed Intermolecular 1,2-Aminoalkylation of Alkenes with Amines and α-Bromoalkyl Esters

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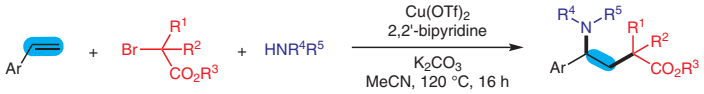

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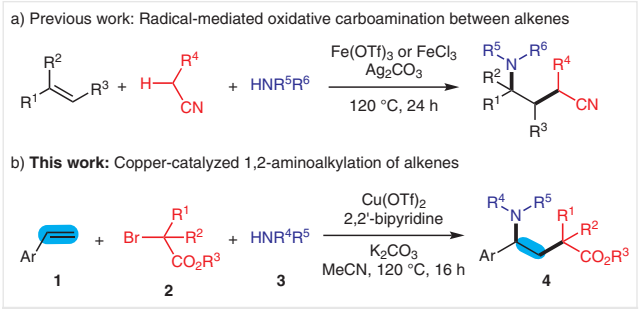
Abstract A new copper-catalyzed intermolecular 1,2-aminoalkylation of alkenes with α-bromoalkyl esters and amines for the synthesis of γ-amino esters is described. Employing the $Cu(OTf)_2$ and 2,2′-bipyridine catalytic system, the three-component reaction allows the formation of two new chemical bonds, including one C–C bond and one C–N bond, in a single reaction, and represents a new alkene difunctionalization using a radical strategy.

Key words copper, aminoalkylation, alkenes, γ-amino esters, α-bromoalkyl esters

γ-Amino esters have proven to be an important structural motif in bioactive natural products and pharmaceuticals, and they are as well synthetically versatile intermediates for chemical synthesis.[1,2] Most importantly, numerous γ-amino ester-based molecules display high bioactivity themselves in the treatment of epilepsy, HIV, neurodegenerative diseases, allergic disease, and depression. For these reasons, increased attention has been directed to develop efficient methods for accessing the γ-amino ester core.[2,3] Classical synthetic routes to γ-amino esters predominantly rely on the intermolecular 1,2-carboamination between a carboxylic group and an amine or an amine precursor, but available transformations still suffer from limited substrate scope, the requirement of expensive catalysts, and/or multistep processes.[4] Despite significant progress in the field, new methods for the synthesis of linear γ-amino esters remain a great challenge.

1,2-Carboamination reaction has attracted much attention due to the high step- and atom-economy.[4c,5] Recently, we reported an oxidative radical 1,2-carboamination of alkenes with alkyl nitriles and amines for the synthesis γ-amino alkyl nitriles (Scheme 1, a).[6] In continuation of our interest in the difunctionalization of alkenes, we herein report a new copper-catalyzed difunctionalization of alkenes with α-bromoalkyl esters and amines to synthesize γ-amino esters (Scheme 1, b). This three-component multicomponent reaction allows the formation of two new chemical bonds, including one C–C bond and one C–N bond, in a single reaction through intermolecular addition across alkene with α-bromoalkyl esters[7] followed by nucleophilic displacement by amines.[8]

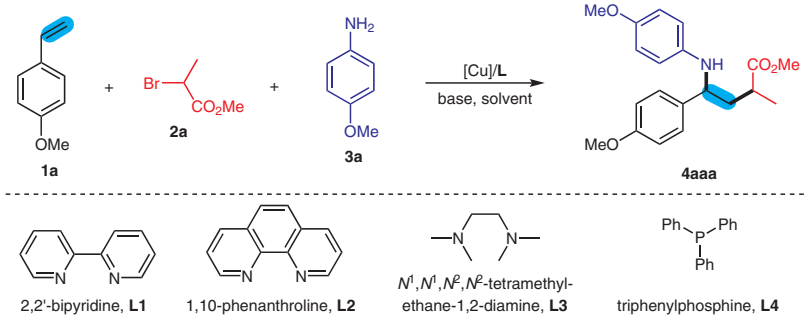


Scheme 1 1,2-Aminoalkylation of alkenes

We began our studies by treating 1-methoxy-4-vinylbenzene (**1a**) with methyl 2-bromopropanoate (**2a**) and 4-methoxyaniline (**3a**) (Table 1). Screening of various reaction parameters demonstrated that alkene **1a** reacted with bromide **2a**, amine **3a**, 10 mol% of $Cu(OTf)_2$, 20 mol% of 2,2′-bipyridine (**L1**), and 2 equivalents of K_2CO_3 in MeCN at 120 °C for 24 hours affording a satisfactory yield of the desired product **4aaa** (75% yield; Table 1, entry 1). The results showed that both $Cu(OTf)_2$ and K_2CO_3 are necessary, as the reaction could not occur in the absence of either $Cu(OTf)_2$ or K_2CO_3 (entries 2 and 3). It was noted that without ligands the reaction delivered **4aaa** in a lower yield (entry 4). Thus, the effect of ligands was examined, and control experiments revealed 2,2′-bipyridine (**L1**) as the preferred ligand

compared to 1,10-phenanthroline (Phen; **L2**), N^1,N^1,N^2,N^2-tetramethylethane-1,2-diamine (TMEDA; **L3**) and triphenylphosphine (PPh_3, **L4**) (entries 1 and 4–7). Although other Cu catalysts, including $CuBr_2$, CuOTf, CuI, CuBr, and CuCl, displayed high activity, they were all less efficient than $Cu(OTf)_2$ (entries 8–12). Two other bases, Na_2CO_3 and Cs_2CO_3, had lower reactivity (entries 13 and 14). Screening on the amount of the $Cu(OTf)_2$ and ligand **L1** system showed that a lower or a higher amount had a negative effect on the reaction (entries 15 and 16). We found that other polar solvents (e.g. 1,4-dioxane or DCE) were also highly reactive (entries 17 and 18), but a nonpolar solvent, toluene, resulted in trace yield of **4aaa** (entry 19). A lower temperature (100 °C) slightly decreased the yield of **4aaa** to 69% (entry 20). However, a higher temperature (130 °C) disfavored the formation of **4aaa** because of the generation of the side-product, 1,5-bis(4-methoxyphenyl)-3-methylpyrrolidin-2-one (**5aaa**) (entry 21).

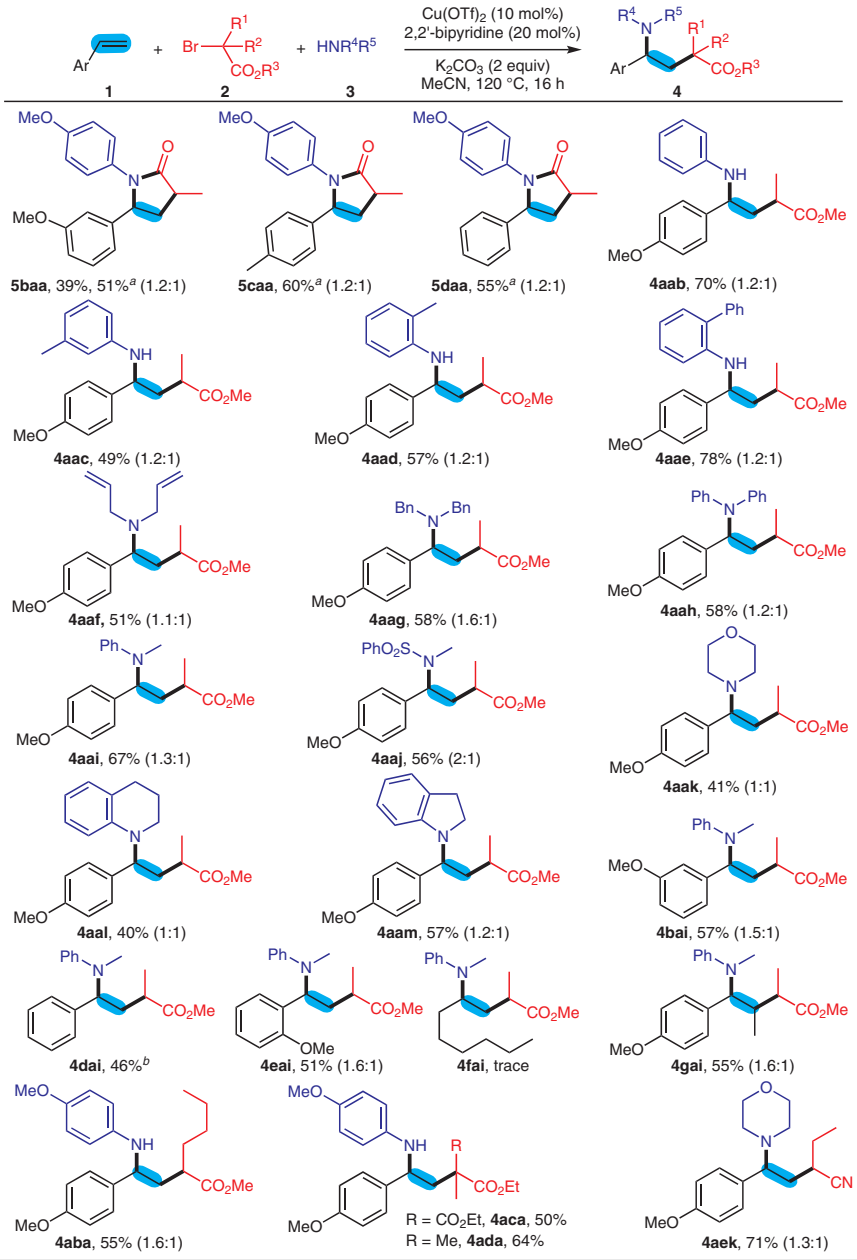
Table 1 Optimization of the Reaction Conditions[a]



Entry	[Cu] (mol%)	**L** (mol%)	Base (equiv)	Solvent	Yield (%)[b]
1	$Cu(OTf)_2$ (10)	**L1** (20)	K_2CO_3 (2)	MeCN	75
2	–	**L1** (20)	K_2CO_3 (2)	MeCN	0
3	$Cu(OTf)_2$ (10)	**L1** (20)	–	MeCN	0
4	$Cu(OAc)_2$ (10)	–	K_2CO_3 (2)	MeCN	5
5	$Cu(OTf)_2$ (10)	**L2** (20)	K_2CO_3 (2)	MeCN	65
6	$Cu(OTf)_2$ (10)	**L3** (20)	K_2CO_3 (2)	MeCN	30
7	$Cu(OTf)_2$ (10)	**L4** (20)	K_2CO_3 (2)	MeCN	0
8	$CuBr_2$ (10)	**L1** (20)	K_2CO_3 (2)	MeCN	44
9	CuOTf (10)	**L1** (20)	K_2CO_3 (2)	MeCN	45
10	CuI (10)	**L1** (20)	K_2CO_3 (2)	MeCN	73
11	CuBr (10)	**L1** (20)	K_2CO_3 (2)	MeCN	72
12	CuCl (10)	**L1** (20)	K_2CO_3 (2)	MeCN	20
13	$Cu(OTf)_2$ (10)	**L1** (20)	Na_2CO_3 (2)	MeCN	43
14	$Cu(OTf)_2$ (10)	**L1** (20)	Cs_2CO_3 (2)	MeCN	25
15	$Cu(OTf)_2$ (5)	**L1** (10)	K_2CO_3 (2)	MeCN	59
16	$Cu(OTf)_2$ (20)	**L1** (40)	K_2CO_3 (2)	MeCN	50
17	$Cu(OTf)_2$ (10)	**L1** (20)	K_2CO_3 (2)	1,4-dioxane	57
18	$Cu(OTf)_2$ (10)	**L1** (20)	K_2CO_3 (2)	DCE	71
19	$Cu(OTf)_2$ (10)	**L1** (20)	K_2CO_3 (2)	toluene	trace
20[c]	$Cu(OTf)_2$ (10)	**L1** (20)	K_2CO_3 (2)	MeCN	69
21[d]	$Cu(OTf)_2$ (10)	**L1** (20)	K_2CO_3 (2)	MeCN	49

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (2 equiv), **3a** (2 equiv), [Cu], ligand, and solvent (2 mL) at 120 °C under argon atmosphere for 16 h. The dr value of **4aaa** is 2:1 as determined by ^1H NMR analysis of the crude product.
[b] Isolated yield.
[c] At 100 °C.
[d] At 130 °C. A side-product, 1,5-bis(4-methoxyphenyl)-3-methylpyrrolidin-2-one (**5aaa**), was obtained in 23% yield.

With the optimal conditions in hand, the generality of this three-component reaction was next evaluated with respect to styrenes **1**, α-bromoalkyl esters **2**, and amines **3** (Scheme 2). Surprisingly, employing other styrenes, including 1-methoxy-3-vinylbenzene (**1b**), 1-methyl-4-vinylbenzene (**1c**), and styrene (**1d**), the reaction afforded pyrrolidin-2-ones **5baa–daa** as the major products, and not the expected γ-amino esters **4**. Notably, the reaction of 1-methoxy-4-vinylbenzene (**1a**) with a wide range of amines **3b–m** still succeeded in accessing the desired γ-amino esters **4aab–aam** in moderate to good yields. Primary arylamines **3b–e** were smoothly converted into **4aab–aae** in 49–78% yields. Likewise, a wide range of symmetrical and unsymmetrical secondary amines **3f–i** and *N*-methylbenzenesulfonamide (**3j**) were highly reactive to access **4aaf–aaj** in synthetically useful yields. Gratifyingly, the reaction



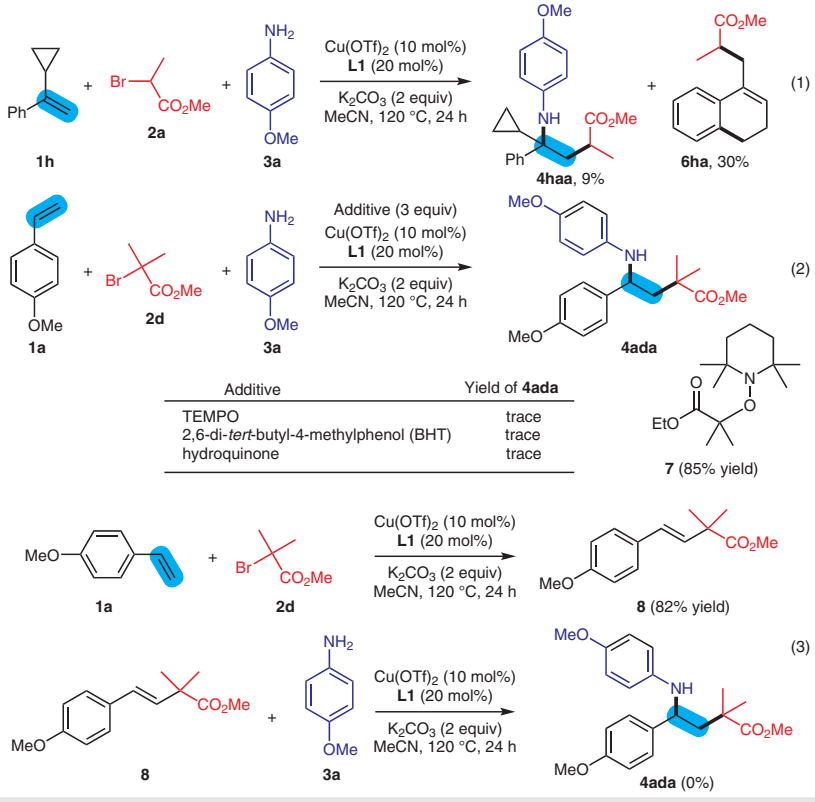
Scheme 2 The alkene aminoalkylation toward γ-amino esters. *Reagents and conditions*: **1** (0.2 mmol), **2** (2 equiv), amine **3** (2 equiv), $Cu(OTf)_2$ (10 mol%), **L1** (20 mol%), K_2CO_3 (2 equiv), MeCN (2 mL), 120 °C under argon atmosphere for 16 h. The dr value is given in the parenthesis as determined by ^1H NMR analysis of the crude product. [a] Reaction was conducted at 130 °C. [b] Some side-products, especially methyl *N*-methyl-*N*-phenylalaninate that was generated from the reaction between bromide **2a** and amine **3i**, were observed by GC-MS analysis.

was applicable to secondary cyclic amines **3k–m**, providing **4aak–aam** in 40–57% yields. Notably, employing secondary amine **3i**, 1-methoxy-3-vinylbenzene (**1b**) could be smoothly converted into the expected γ-amino ester **4bai**. Other arylalkenes, including styrene (**1d**), 1-methoxy-2-vinylbenzene (**1e**), and 1-methoxy-4-(prop-1-en-1-yl)benzene (**1g**) were suitable for producing γ-amino esters **4dai**, **4eai**, and **4gai**, but aliphatic alkene **1f** had no reactivity (**4fai**). The aminoalkylation reaction was applicable to secondary α-bromoalkyl ester **2b** and tertiary α-bromoalkyl esters **2c**,**d**, thus furnishing **4aba** and **4aca**,**ada** in moderate yields. With α-bromobutyronitrile (**1e**) the reaction was successful for preparing **4aek** in good yield.

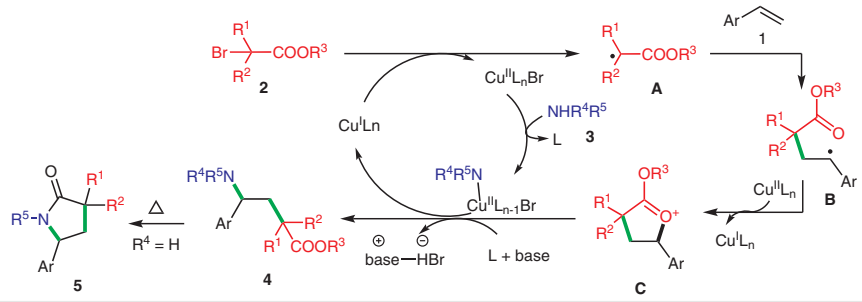
As shown in Scheme 3, (1-cyclopropylvinyl)benzene (**1h**) reacted with α-bromoalkyl ester **2a** and amines **3a** to afford **4haa** along with the monoalkylation/ring-opening/cyclization product **6ha** (Scheme 3, eq. 1).[8g] Notably, the reaction of alkene **1a** with ester **2a** and amine **3a** was completely suppressed when using a stoichiometric amount of radical inhibitors (3 equiv), including 2,2,6,6-tetramethylpiperidinooxy (TEMPO), 2,6-di-*tert*-butyl-4-methylphenol (BHT), and hydroquinone (Scheme 3, eq. 2). These results support the current reaction possessing a free-radical process. However, an 82% yield of ethyl (*E*)-4-(4-methoxyphenyl)-2,2-dimethylbut-3-enoate (**8**) was obtained in the absence of amine **3a**. The reaction between product **8** and amine **3a** was not successful under the optimal conditions (Scheme 3, eq. 3).

Therefore, a possible mechanism is outlined in Scheme 4 for this 1,2-aminoalkylation of alkenes with α-bromoalkyl esters and amines on the basis of the experimental and previous studies.[6–8] First, the α-C(sp^3)–Br bond of α-carbonyl alkyl bromide **2** was cleaved to generate the alkyl radical **A** in the presence of Cu^{II} species under heating condition via a single-electron transfer (SET) process. Oxidative addition of the alkyl radical **A** to the C=C bond of alkenes **1** leads to the new radical intermediate **B**. Subsequent oxidation of intermediate **B** by the active Cu^{II} species generates the oxocarbenium ion intermediate **C**. Finally, nucleophilic attack of intermediate **C** by amine **3** takes place to furnish the desired γ-amino esters **4**. In addition, the γ-amino esters **4** get converted into pyrrolidine-2-ones **5** when R^4 = H under heating conditions.

In summary, we have developed a new copper-catalyzed intermolecular 1,2-aminoalkylation of alkenes with α-bromoalkyl esters and amines for the synthesis of γ-amino esters. Employing $Cu(OTf)_2$ and 2,2′-bipyridine, the reaction allows the formation of two new chemical bonds, including one C–C bond and one C–N bond, in a single reaction, using a radical strategy, which features broad substrate scope and excellent selectivity.



Scheme 3 Control experiments



Scheme 4 Possible mechanism

NMR spectroscopy was performed on a Bruker Avance spectrometer operating at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR). Mass spectrometric analysis was performed by GC-MS analysis using a Shimadzu GCMS-QP2010 instrument and ESI-Q-TOF on a Bruker MicroQTOF-II spectrometer.

Copper-Catalyzed Synthesis of γ-Amino Esters 4; General Procedure

To a Schlenk tube were added alkene **1** (0.2 mmol), α-bromoalkyl ester **2** (0.4 mmol), amine **3** (0.4 mmol), $Cu(OTf)_2$ (10 mol%), 2,2′-bipyridine (**L1**; 20 mol%), K_2CO_3 (2 equiv), and MeCN (2 mL). Then the tube was charged with argon, and the contents were stirred at 120 °C for 16 h until complete consumption of the starting materials as monitored by TLC and/or GC-MS analysis. After completion of the reaction, the contents were concentrated under vacuum, and the resulting residue was purified by silica gel column chromatography (hexane/EtOAc) to afford the desired γ-amino ester **4**.

Methyl 4-(4-Methoxyphenyl)-4-[(4-methoxyphenyl)amino]-2-methylbutanoate (4aaa)

Yield: 51.5 mg (75%); yellow oil; dr = 2:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.20 (m, 2 H), 6.83 (d, *J* = 8.0 Hz, 2 H), 6.67 (d, *J* = 8.4 Hz, 2 H), 6.48–6.44 (m, 2 H), 4.30–4.22 (m, 1 H), 3.76 (s, 3 H), 3.67 (s, 3 H), 3.66 (s, 1 H), 3.61 (s, 2 H), 2.60–2.53 (m, 1 H), 2.24–2.14 (m, 1 H), 1.87–1.80 (m, 0.7 H), 1.75–1.70 (m, 0.3 H), 1.20 (d, *J* = 7.2 Hz, 2 H), 1.17 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 176.8, 158.6, 158.5, 151.9, 151.8, 141.4, 141.3, 135.7, 135.4, 127.4, 127.3, 114.7 (2 C), 114.4, 114.0, 113.9, 56.8, 56.4, 55.6, 55.1, 51.7, 51.6, 42.6, 42.1, 37.3, 36.4, 17.9, 17.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 343 (M^+, 28), 242 (62), 161 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{26}NO_4$: 344.1856; found: 344.1863.

Methyl 4-(4-Methoxyphenyl)-2-methyl-4-(phenylamino)butanoate (4aab)

Yield: 43.8 mg (70%); yellow oil; dr = 1.2:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (t, *J* = 7.0 Hz, 2 H), 7.07 (t, *J* = 7.6 Hz, 2 H), 6.84 (d, *J* = 8.0 Hz, 2 H), 6.62 (t, *J* = 7.4 Hz, 1 H), 6.52–6.49 (m, 2 H), 4.36 (t, *J* = 7.0 Hz, 0.6 H), 4.31 (t, *J* = 7.4 Hz, 0.5 H), 4.10 (s, 0.8 H), 3.76 (s, 3 H), 3.67 (s, 1.4 H), 3.62 (s, 1.6 H), 2.60–2.52 (m, 1 H), 2.27–2.16 (m, 1 H), 1.89–1.82 (m, 0.6 H), 1.77–1.70 (m, 0.5 H), 1.21 (d, *J* = 6.8 Hz, 1.7 H), 1.18 (d, *J* = 6.8 Hz, 1.3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 176.8, 158.6, 158.6, 147.2, 147.1, 135.5, 135.1, 129.0 (2 C), 127.3 (2 C), 117.2 (2 C), 114.0 (2 C), 113.3, 113.2, 56.0, 55.5, 55.2, 51.7 (2 C), 42.6, 42.1, 37.4, 36.4, 17.9, 17.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 313 (M^+, 19), 212 (100), 161 (72).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{24}NO_3$: 314.1751; found: 314.1753.

Methyl 4-(4-Methoxyphenyl)-2-methyl-4-(*m*-tolylamino)butanoate (4aac)

Yield: 32.0 mg (49%); yellow oil; dr = 1.2:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.21 (m, 2 H), 6.96 (t, *J* = 7.8 Hz, 1 H), 6.84 (d, *J* = 8.0 Hz, 2 H), 6.45 (d, *J* = 7.6 Hz, 1 H), 6.34 (s, 1 H), 6.30 (t, *J* = 7.4 Hz, 1 H), 4.36 (t, *J* = 7.0 Hz, 0.6 H), 4.31 (t, *J* = 7.2 Hz, 0.4 H), 4.04 (s, 0.8 H), 3.76 (s, 3 H), 3.67 (s, 1.3 H), 3.62 (s, 1.6 H), 2.60–2.51 (m, 1 H), 2.27–2.16 (m, 4 H), 1.87–1.81 (m, 0.6 H), 1.76–1.70 (m, 0.5 H), 1.21 (d, *J* = 7.2 Hz, 1.7 H), 1.18 (d, *J* = 6.8 Hz, 1.4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 176.8, 158.6 (2 C), 147.2, 147.1, 138.7, 135.7, 135.3, 128.9, 127.3 (2 C), 118.2 (2 C), 114.2, 114.0 (3 C), 110.3, 110.2, 56.0, 55.4, 55.2, 51.7 (2 C), 42.6, 42.1, 37.4, 36.4, 21.6, 17.9, 17.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 327 (M^+, 8), 226 (100), 161 (66).

HRMS: (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{26}NO_3$: 328.1907; found: 328.1915.

Methyl 4-(4-Methoxyphenyl)-2-methyl-4-(*o*-tolylamino)butanoate (4aad)

Yield: 37.3 mg (57%); yellow oil; dr = 1.2:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.21 (m, 2 H), 7.03–7.00 (m, 1 H), 6.96–6.91 (m, 1 H), 6.84 (d, *J* = 8.4 Hz, 2 H), 6.59–6.55 (m, 1 H), 6.39 (d, *J* = 8.0 Hz, 0.5 H), 6.34 (d, *J* = 8.0 Hz, 0.6 H), 4.43 (t, *J* = 6.8 Hz, 0.6 H), 4.39–4.36 (m, 0.5 H), 4.01 (s, 0.8 H), 3.76 (s, 3 H), 3.67 (s, 1.4 H), 3.62 (s, 1.7 H), 2.62–2.53 (m, 1 H), 2.32–2.24 (m, 1 H), 2.19 (m, 1.7 H), 2.18 (m, 1.3 H), 1.95–1.88 (m, 0.6 H), 1.80–1.74 (m, 0.5 H), 1.22 (d, *J* = 7.2 Hz, 1.7 H), 1.19 (d, *J* = 6.8 Hz, 1.4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 177.0, 158.6 (2 C), 145.1, 144.9, 135.7, 135.1, 129.9 (2 C), 127.3, 127.2, 126.9 (2 C), 121.8, 121.7, 116.8, 116.7, 114.0 (2 C), 110.9, 110.8, 56.1, 55.4, 55.2, 51.7 (2 C), 42.7, 42.0, 37.6, 36.3, 18.2, 17.7, 17.6 (2 C).

LRMS (EI, 70 eV): *m*/*z* (%) = 327 (M^+, 24), 226 (83), 161 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{26}NO_3$: 328.1907; found: 328.1921.

Methyl 4-([1,1′-Biphenyl]-2-ylamino)-4-(4-methoxyphenyl)-2-methylbutanoate (4aae)

Yield: 60.7 mg (78%); yellow oil; dr = 1.2:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.43 (m, 4 H), 7.37 (t, *J* = 7.0 Hz, 1 H), 7.19–7.15 (m, 2 H), 7.08–7.03 (m, 2 H), 6.83 (d, *J* = 8.4 Hz, 2 H), 6.69 (t, *J* = 7.4 Hz, 1 H), 6.52 (d, *J* = 8.0 Hz, 0.5 H), 6.47 (d, *J* = 8.4 Hz, 0.6 H), 4.37–4.29 (m, 2 H), 3.75 (s, 3 H), 3.57 (s, 1.4 H), 3.54 (s, 1.7 H), 2.46–2.39 (m, 1 H), 2.12–2.06 (m, 1 H), 1.70–1.60 (m, 1 H), 1.12 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.6, 176.5, 158.6 (2 C), 143.9, 143.8, 139.5 (2 C), 135.3, 135.1, 130.1, 130.0, 129.3 (2 C), 128.9, 128.4, 127.8, 127.7, 127.3, 127.2, 116.9, 114.0 (2 C), 111.7, 111.6, 55.9, 55.7, 55.1, 51.6 (2 C), 42.4, 42.3, 36.9, 36.4, 17.7, 17.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 389 (M^+, 18), 288 (100), 161 (67).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{28}NO_3$: 390.2064; found: 390.2071.

Methyl 4-(Diallylamino)-4-(4-methoxyphenyl)-2-methylbutanoate (4aaf)

Yield: 32.3 mg (51%); yellow oil; dr = 1.1:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13–7.10 (m, 2 H), 6.86 (d, *J* = 8.0 Hz, 2 H), 5.84–5.73 (m, 2 H), 5.17–5.09 (m, 4 H), 3.81 (s, 3 H), 3.78–3.72 (m, 1 H), 3.67 (s, 1.6 H), 3.60 (s, 1.4 H), 3.29–3.22 (m, 2 H), 2.69–2.45 (m, 4 H), 2.14–2.07 (m, 0.6 H), 2.00–1.93 (m, 0.5 H), 1.16–1.14 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.5, 177.1, 158.6 (2 C), 137.2, 130.8, 130.4, 129.8, 129.7, 116.9, 116.7, 113.3 (2 C), 60.1, 59.7, 55.2, 52.6, 52.5, 51.4, 37.4, 36.8, 36.3, 35.8, 17.7, 17.4.

LRMS (EI, 70 eV): *m*/*z* (%) = 317 (M^+, 1), 216 (100), 161 (26).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{28}NO_3$: 318.2064; found: 318.2073.

Methyl 4-(Dibenzylamino)-4-(4-methoxyphenyl)-2-methylbutanoate (4aag)

Yield: 48.4 mg (58%); yellow oil; dr = 1.6:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.35 (m, 4 H), 7.32–7.28 (m, 4 H), 7.24–7.19 (m, 2 H), 7.15–7.13 (m, 2 H), 6.93–6.90 (m, 2 H), 3.83 (s, 3 H), 3.79–3.74 (m, 2 H), 3.72–3.70 (m, 0.6 H), 3.64 (t, *J* = 7.6 Hz, 0.4 H), 3.55 (s, 1.2 H), 3.50 (s, 1.9 H), 3.13 (d, *J* = 13.6 Hz, 1.3 H), 3.07 (d, *J* = 13.2 Hz, 0.8 H), 2.71–2.63 (m, 1 H), 2.56–2.49 (m, 0.4 H), 2.28–2.21 (m, 0.6 H), 2.05–1.98 (m, 0.6 H), 1.73–1.66 (m, 0.4 H), 1.07 (d, *J* = 6.8 Hz, 1.9 H), 0.95 (d, *J* = 6.8 Hz, 1.2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 176.9, 158.7, 158.6, 140.1, 130.1 (2 C), 130.0, 129.8, 128.9, 128.7, 128.2 (2 C), 126.8, 126.7, 113.3 (2 C), 58.8, 58.4, 55.2, 53.7, 53.5, 51.5, 51.4, 36.5 (2 C), 35.8, 35.1, 17.6, 16.9.

LRMS (EI, 70 eV): *m*/*z* (%) = 417 (M^+, 1), 316 (100), 91 (80).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{32}NO_3$: 418.2377; found: 418.2386.

Methyl 4-(Diphenylamino)-4-(4-methoxyphenyl)-2-methylbutanoate (4aah)

Yield: 45.1 mg (58%); yellow oil; dr = 1.2:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.16 (m, 4 H), 7.11 (d, *J* = 8.4 Hz, 1 H), 7.01 (d, *J* = 8.4 Hz, 1 H), 6.95–6.91 (m, 2 H), 6.82–6.73 (m, 6 H), 5.37 (t, *J* = 7.8 Hz, 0.6 H), 5.29–5.26 (m, 0.5 H), 3.76 (s, 3 H), 3.67 (s, 1.4 H), 3.62 (s, 1.6 H), 2.58–2.55 (m, 0.6 H), 2.49–2.39 (m, 1.5 H), 2.10–2.03 (m, 0.6 H), 1.97–1.91 (m, 0.4 H), 1.19 (d, *J* = 6.4 Hz, 1.4 H), 1.15 (d, *J* = 6.8 Hz, 1.7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 176.7, 158.7, 158.6, 146.6, 146.5, 132.9, 132.4, 129.5, 129.0 (2 C), 123.1, 122.8, 121.7, 121.6, 113.4 (2 C), 59.1, 58.8, 55.1 (2 C), 51.6 (2 C), 36.5 (2 C), 35.7, 35.6, 18.0, 17.5.

(EI, 70 eV): *m*/*z* (%) = 389 (M^+, 8), 221 (65), 161 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{28}NO_3$: 390.2064; found: 390.2072.

Methyl 4-(4-Methoxyphenyl)-2-methyl-4-[methyl(phenyl)amino]butanoate (4aai)

Yield: 43.8 mg (67%); yellow oil; dr = 1.3:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.20 (m, 2 H), 7.15 (d, *J* = 8.4 Hz, 1 H), 7.12 (d, *J* = 8.4 Hz, 1 H), 6.85–6.78 (m, 4 H), 6.74–6.69 (m, 1 H), 5.08–5.00 (m, 1 H), 3.77 (s, 3 H), 3.56 (s, 1.3 H), 3.54 (s, 1.7 H), 2.61 (s, 1.7 H), 2.57 (s, 1.3 H), 2.54–2.51 (m, 1 H), 2.49–2.42 (m, 1 H), 2.03–1.96 (m, 1 H), 1.23 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8 (2 C), 158.6, 158.5, 150.6, 150.5, 132.6, 132.4, 129.1 (2 C), 128.2, 116.9, 116.8, 113.6 (2 C), 113.4, 113.2, 58.8, 58.7, 55.2, 51.5 (2 C), 37.1, 36.4, 35.5 (2 C), 31.5, 31.4, 18.2, 17.4.

LRMS (EI, 70 eV): *m*/*z* (%) = 327 (M^+, 14), 221 (47), 161 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{26}NO_3$: 328.1907; found: 328.1913.

Methyl 4-(4-Methoxyphenyl)-2-methyl-4-(*N*-methylphenylsulfonamido)butanoate (4aaj)

Yield: 43.8 mg (56%); yellow oil; dr = 2:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.2 Hz, 2 H), 7.56–7.51 (m, 1 H), 7.48 (m, 2 H), 7.05 (t, *J* = 7.6 Hz, 2 H), 6.75 (t, *J* = 7.8 Hz, 2 H), 5.17–5.10 (m, 1 H), 3.76 (s, 3 H), 3.69 (s, 1 H), 3.64 (s, 2 H), 2.61 (s, 1.9 H), 2.60 (s, 1.0 H), 2.51–2.42 (m, 1 H), 2.39–2.30 (m, 1 H), 1.81–1.74 (m, 0.4 H), 1.70–1.63 (m, 0.7 H), 1.23 (d, *J* = 6.8 Hz, 1 H), 1.17 (d, *J* = 7.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5, 176.2, 159.1 (2 C), 140.1 (2 C), 132.3 (2 C), 129.5, 129.3, 129.1, 129.0, 128.9, 128.8, 127.1 (2 C), 113.7, 113.6, 57.6, 55.2, 51.7 (2 C), 36.5, 36.2, 34.6, 34.2, 28.8, 28.7, 17.2, 17.1.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{26}NO_5S$ [M + H]$^+$: 392.1526; found: 392.1533.

Methyl 4-(4-Methoxyphenyl)-2-methyl-4-morpholinobutanoate (4aak)

Yield: 25.2 mg (41%); yellow oil; dr = 1:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (t, *J* = 9.2 Hz, 2 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 3.80 (s, 3 H), 3.68 (s, 1.5 H), 3.65–3.62 (m, 4 H), 3.56 (s, 1.5 H), 3.34–3.31 (m, 0.5 H), 3.26 (t, *J* = 7.4 Hz, 0.5 H), 2.49–2.43 (m, 0.5 H), 2.38–2.29 (m, 5 H), 2.15–2.08 (m, 0.5 H), 2.04–1.97 (m, 0.5 H), 1.60–1.54 (m, 0.6 H), 1.13 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 176.9, 158.9, 158.8, 130.9, 130.3, 129.8, 129.6, 113.5, 113.4, 67.9, 67.2 (2 C), 55.2, 51.5 (2 C), 50.6, 50.5, 37.4, 36.6, 36.2, 35.6, 18.4, 16.8.

LRMS (EI, 70 eV): *m*/*z* (%) = 307 (M^+, 1), 206 (100), 161 (16).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{26}NO_4$: 308.1856, found 308.1865.

Methyl 4-[3,4-Dihydroquinolin-1(2*H*)-yl]-4-(4-methoxyphenyl)-2-methylbutanoate (4aal)

Yield: 28.2 mg (40%); yellow oil; dr = 1:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (t, *J* = 8.4 Hz, 2 H), 7.07–7.00 (m, 1 H), 6.94 (d, *J* = 7.2 Hz, 1 H), 6.84 (t, *J* = 9.4 Hz, 2.5 H), 6.72 (d, *J* = 8.4 Hz, 0.5 H), 6.58–6.53 (m, 1 H), 5.10–5.06 (m, 1 H), 3.78 (s, 3 H), 3.60 (s, 1.5 H), 3.58 (s, 1.5 H), 3.15–3.05 (m, 1 H), 2.99–2.89 (m, 1 H), 2.73–2.68 (m, 2 H), 2.62–2.55 (m, 1 H), 2.51 (m, 1 H), 2.04–1.97 (m, 1 H), 1.88–1.81 (m, 1 H), 1.77–1.68 (m, 1 H), 1.59 (s, 1 H), 1.24 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9 (2 C), 158.6, 158.5, 145.8, 145.7, 132.6 (2 C), 129.3, 128.4 (2 C), 127.1, 127.0, 122.9, 122.6, 115.5, 115.4, 113.7 (2 C), 110.9 (2 C), 56.6, 56.3, 55.2, 51.6 (2 C), 42.5, 42.0, 36.7, 36.3, 34.6 (2 C), 28.6, 28.5, 22.0, 21.9, 18.1, 17.3.

LRMS (EI, 70 eV): *m*/*z* (%) = 353 (M^+, 19), 271 (49), 161 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{28}NO_3$: 354.2064; found: 354.2074.

Methyl 4-(Indolin-1-yl)-4-(4-methoxyphenyl)-2-methylbutanoate (4aam)

Yield: 38.6 mg (57%); yellow oil; dr = 1.2:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.08 (m, 2 H), 7.06–6.97 (m, 2 H), 6.82 (d, *J* = 7.6 Hz, 2 H), 6.59–6.54 (m, 1.5 H), 6.49 (d, *J* = 8.0 Hz, 0.6 H), 4.74–4.67 (m, 1 H), 3.76 (s, 3 H), 3.59 (s, 1.7 H), 3.55 (s, 1.4 H), 3.41–3.35 (m, 1 H), 3.17–3.10 (m, 0.6 H), 3.06–3.01 (m, 0.5 H), 2.93–2.82 (m, 2 H), 2.63–2.53 (m, 1 H), 2.51–2.48 (m, 0.5 H), 2.39–2.32 (m, 0.6 H), 2.09–2.03 (m, 0.6 H), 1.91–1.88 (m, 0.4 H), 1.25–1.21 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 176.7, 158.7 (2 C), 151.3, 151.2, 131.6, 131.4, 129.6, 129.5, 128.9 (2 C), 127.2, 124.5, 124.4, 116.7, 116.6, 113.6, 106.5, 106.4, 56.0, 55.7, 55.1, 51.5, 51.4, 46.5, 46.1, 37.2, 36.5, 35.3, 34.9, 28.0 (2 C), 17.5, 17.4.

LRMS (EI, 70 eV): *m*/*z* (%) = 339 (M^+, 22), 221 (46), 161 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{26}NO_3$: 340.1907; found: 340.1916.

Methyl 4-(3-Methoxyphenyl)-2-methyl-4-[methyl(phenyl)amino]butanoate (4bai)

Yield: 40.7 mg (57%); yellow oil; dr = 1.5:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.19 (m, 3 H), 6.85 (s, 0.7 H), 6.83 (s, 0.5 H), 6.79–6.75 (m, 3 H), 6.74–6.69 (m, 1 H), 5.09–5.05 (m, 0.6 H), 5.03–5.01 (m, 0.4 H), 3.74 (s, 1.8 H), 3.73 (s, 1.2 H), 3.56 (s, 1.2 H), 3.53 (s, 1.7 H), 2.66 (s, 1.8 H), 2.62 (s, 1.2 H), 2.59–2.54 (m, 1 H), 2.50–2.41 (m, 1 H), 2.04–1.98 (m, 1 H), 1.25–1.21 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8, 176.7, 159.6, 150.5 (2 C), 142.5, 142.2, 129.3 (2 C), 129.1 (2 C), 119.4 (2 C), 117.0, 116.8, 113.4, 113.1 (2 C), 113.0, 112.0 (2 C), 59.3, 59.2, 55.1, 51.5 (2 C), 37.0, 36.3, 35.6, 35.5, 31.7, 31.6, 18.3, 17.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{28}NO_4$: 358.2014; found: 358.2019.

Methyl 4-(2-Methoxyphenyl)-2-methyl-4-[methyl(phenyl)amino]butanoate (4eai)

Yield: 33.4 mg (51%); yellow oil; dr = 1.6:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.0 Hz, 1 H), 7.21–7.18 (m, 3 H), 6.91 (t, *J* = 8.0 Hz, 1 H), 6.85–6.80 (m, 3 H), 6.67 (t, *J* = 7.2 Hz, 1 H), 5.40–5.37 (m, 0.6 H), 5.34–5.32 (m, 0.4 H), 3.68 (s, 1.9 H), 3.67 (s, 1.2 H), 3.55 (s, 3 H), 2.79 (s, 1.2 H), 2.72 (s, 1.9 H), 2.53–2.45 (m, 1 H), 2.43–2.34 (m, 1 H), 2.02–1.89 (m, 1 H), 1.20 (t, *J* = 6.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 176.8, 157.6, 157.2, 150.4, 150.3, 129.4, 128.8, 128.7, 128.2, 128.1, 127.3, 127.1, 120.2, 120.0, 116.5, 116.4, 113.4, 113.1, 110.7, 110.6, 55.3, 55.2, 54.0, 53.9, 51.4, 51.4, 37.0, 36.6, 35.6, 34.8, 31.9, 31.7, 17.6, 17.0.

LRMS (EI, 70 eV): *m*/*z* (%) = 327 (M^+, 19), 221 (45), 161 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{25}NO_3$: 328.1907; found: 328.1913.

Methyl 4-(4-Methoxyphenyl)-2,3-dimethyl-4-[methyl(phenyl)amino]butanoate (4gai)

Yield: 37.5 mg (55%); yellow oil; d.r. = 1.6:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.19 (m, 2 H), 7.13 (d, *J* = 8.0 Hz, 1.2 H), 7.05 (d, *J* = 7.8 Hz, 0.8 H), 6.92 (d, *J* = 8.0 Hz, 0.8 H), 6.85–6.80 (m, 2.4 H), 6.76 (d, *J* = 8.2 Hz, 1 H), 6.71–6.67 (m, 1 H), 5.23 (d, *J* = 11.2 Hz, 0.6 H), 4.96 (d, *J* = 11.2 Hz, 0.4 H), 3.76 (s, 1.8 H), 3.74 (s, 1.2 H), 3.68 (s, 1.9 H), 3.62 (s, 1.1 H), 3.10–3.04 (m, 0.4 H), 2.55–2.53 (m, 3 H), 2.50–2.41 (m, 1.6 H), 1.28 (d, *J* = 7.2 Hz, 1.2 H), 1.18 (d, *J* = 7.2 Hz, 1.8 H), 1.00 (d, *J* = 6.8 Hz, 1.8 H), 0.86 (d, *J* = 6.8 Hz, 1.2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5, 175.0, 158.6, 158.5, 150.8, 150.6, 130.6, 130.0, 129.1, 129.0, 128.9, 128.8, 117.6, 116.6, 115.3, 113.6, 113.5, 113.3, 66.0, 64.3, 55.1, 55.1, 51.3, 51.2, 40.1, 39.1, 38.2, 37.5, 31.3, 30.8, 16.0, 15.8, 13.3, 12.3.

LRMS (EI, 70 eV): *m*/*z* (%) = 341 (M^+, 3.2), 226 (100), 175 (11).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{28}NO_3$: 342.2064; found: 342.2080.

Methyl 2-{2-(4-Methoxyphenyl)-2-[(4-methoxyphenyl)amino]ethyl}hexanoate (4aba)

Yield: 42.4 mg (55%); yellow oil; dr = 1.6:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.0 Hz, 2 H), 6.83 (d, *J* = 8.4 Hz, 2 H), 6.67 (d, *J* = 8.0 Hz, 2 H), 6.47–6.44 (m, 2 H), 4.25–4.22 (m, 0.6 H), 4.20–4.16 (m, 0.4 H), 3.75 (s, 3 H), 3.67 (s, 4.2 H), 3.59 (s, 1.9 H), 2.60–2.52 (m, 0.6 H), 2.43–2.36 (m, 0.4 H), 2.20–2.11 (m, 1 H), 1.87–1.74 (m, 1 H), 1.66–1.57 (m, 1 H), 1.54–1.42 (m, 1 H), 1.28–1.22 (m, 4 H), 0.89–0.83 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 176.5, 158.5 (2 C), 151.8 (2 C), 141.5, 141.3, 135.6, 135.5, 127.3, 114.7, 114.6 (2 C), 114.4, 113.9 (2 C), 57.2, 56.6, 55.6, 55.1, 51.5, 51.4, 43.3, 42.3, 41.1, 40.9, 32.8, 32.5, 29.2 (2 C), 22.5 (2 C), 13.8 (2 C).

LRMS (EI, 70 eV): *m*/*z* (%) = 385 (M^+, 36), 203 (100), 121 (67).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{32}NO_4$: 386.2326; found: 386.2332.

Methyl 2-{2-(4-Methoxyphenyl)-2-[(4-methoxyphenyl)amino]ethyl}hexanoate (4aca)

Yield: 42.9 mg (50%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.8 Hz, 2 H), 6.83 (d, *J* = 8.4 Hz, 2 H), 6.65 (d, *J* = 8.8 Hz, 2 H), 6.40 (d, *J* = 8.8 Hz, 2 H), 4.43–4.41 (m, 1 H), 4.21–4.16 (m, 2 H), 4.11–4.07 (m, 1 H), 4.01–3.97 (m, 1 H), 3.76 (s, 3 H), 3.67 (s, 3 H), 2.43–2.37 (m, 1 H), 2.21–2.16 (m, 1 H), 1.52 (s, 3 H), 1.22 (t, *J* = 7.0 Hz, 3 H), 1.15 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6 (2 C), 158.5, 151.7, 141.0, 136.1, 127.2, 114.7, 114.3, 113.9, 61.6, 61.5, 55.7, 55.2, 54.4, 52.8, 44.4, 20.4, 14.0, 13.9.

LRMS (EI, 70 eV): *m*/*z* (%) = 429 (M^+, 33), 233 (70), 159 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{32}NO_6$: 430.2224; found: 430.2237.

Ethyl 4-(4-Methoxyphenyl)-4-[(4-methoxyphenyl)amino]-2,2-dimethylbutanoate (4ada)

Yield: 45.7 mg (64%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 8.8 Hz, 2 H), 6.82 (d, *J* = 8.4 Hz, 2 H), 6.65 (d, *J* = 8.8 Hz, 2 H), 6.39 (d, *J* = 9.6 Hz, 2 H), 4.36–4.32 (m, 1 H), 4.15–4.00 (m, 2 H), 3.76 (s, 3 H), 3.67 (s, 6 H), 2.29–2.23 (m, 1 H), 1.76–1.72 (m, 1 H), 1.25 (d, *J* = 18.4 Hz, 6 H), 1.20 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4, 158.4, 151.7, 141.2, 136.7, 127.2, 114.7, 114.2, 113.9, 69.8, 60.7, 55.7, 55.2, 55.1, 49.3, 41.3, 28.1, 23.6, 14.1.

LRMS (EI, 70 eV): *m*/*z* (%) = 357 (M^+, 13), 233 (49), 159 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{28}NO_4$: 358.2013; found: 358.2018.

2-Ethyl-4-(4-methoxyphenyl)-4-morpholinobutanenitrile (4aek)

Yield: 40.9 mg (71%); colorless oil; dr = 1.3:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 7.6 Hz, 2 H), 7.09 (d, *J* = 7.6 Hz, 2 H), 6.90–6.87 (m, 4 H), 3.81 (s, 6 H), 3.67–3.61 (m, 9 H), 3.48–3.42 (m, 1 H), 2.81–2.73 (m, 1 H), 2.42–2.06 (m, 11 H), 1.90–1.74 (m, 2 H), 1.71–1.55 (m, 4 H), 1.09 (t, *J* = 7.2 Hz, 3 H), 1.01 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 159.1, 130.2, 129.6, 129.4, 128.7, 122.2, 121.9, 113.9, 113.5, 67.6, 67.2, 67.0, 66.1, 55.2, 51.0, 49.7, 35.0, 33.7, 30.7, 30.4, 25.9, 25.3, 11.5, 11.4.

LRMS (EI, 70 eV): *m*/*z* (%) = 288 (M^+, 2), 206 (100), 134 (26), 121 (12).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{25}N_2O_2$: 289.1911; found: 289.1925.

1,5-Bis(4-Methoxyphenyl)-3-methylpyrrolidin-2-one (5aaa)

The isomers of compounds **5aaa**-**5daa** were separated by silica gel column chromatography (hexane/ethyl acetate) and their correspondent characterization is reported below.

Yield: 14.3 mg (23%); dr = 1.2:1.

Isomer A

Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 8.4 Hz, 2 H), 7.11 (d, *J* = 8.0 Hz, 2 H), 6.82 (d, *J* = 8.4 Hz, 2 H), 6.77 (d, *J* = 8.8 Hz, 2 H), 5.09–5.06 (m, 1 H), 3.74 (s, 3 H), 3.71 (s, 3 H), 2.87–2.77 (m, 1 H), 2.23–2.18 (m, 2 H), 1.29 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 158.8, 156.4, 133.1, 131.7, 126.9, 123.1, 114.1, 113.8, 61.4, 55.2, 55.1, 37.8, 35.7, 15.9.

LRMS (EI, 70 eV): *m*/*z* (%) = 311 (M^+, 77), 161 (100), 147 (25).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}NO_3$: 312.1594; found: 312.1603.

Isomer B

Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (d, *J* = 8.4 Hz, 2 H), 7.09 (d, *J* = 8.4 Hz, 2 H), 6.76 (d, *J* = 8.0 Hz, 2 H), 6.73 (d, *J* = 8.8 Hz, 2 H), 5.03–5.00 (m, 1 H), 3.70 (s, 3 H), 3.67 (s, 3 H), 2.78–2.66 (m, 2 H), 1.66–1.58 (m, 1 H), 1.35 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 158.8, 156.6, 132.9, 130.8, 127.8, 124.8, 113.9, 113.6, 61.7, 55.1 (2 C), 38.9, 37.3, 16.4.

LRMS (EI, 70 eV): *m*/*z* (%) = 311 (M^+, 77), 161 (100), 147 (26).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}NO_3$: 312.1594; found: 312.1601.

5-(3-Methoxyphenyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (5baa)

Yield: 31.7 mg (51%); dr = 1.2:1.

Isomer A

Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.8 Hz, 2 H), 7.22 (t, *J* = 8.0 Hz, 1 H), 6.80–6.74 (m, 4 H), 6.74 (s, 1 H), 5.10–5.07 (m, 1 H), 3.75 (s, 3 H), 3.73 (s, 3 H), 2.86–2.80 (m, 1 H), 2.25–2.21 (m, 2 H), 1.29 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 160.1, 156.5, 143.1, 131.8, 130.0, 123.0, 118.0, 113.9, 112.7, 111.6, 61.9, 55.3, 55.2, 37.7, 35.7, 16.0.

LRMS (EI, 70 eV): *m*/*z* (%) = 311 (M^+, 100), 242 (18), 204 (20).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}NO_3$: 312.1594; found: 312.1602.

Isomer B

Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.4 Hz, 2 H), 7.16 (t, *J* = 8.0 Hz, 1 H), 6.79–6.70 (m, 5 H), 5.07–5.03 (m, 1 H), 3.72 (s, 3 H), 3.71 (s, 3 H), 2.82–2.68 (m, 2 H), 1.65–1.60 (m, 1 H), 1.36 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 159.8, 156.7, 143.0, 131.0, 129.7, 124.6, 118.9, 113.8, 112.7, 112.3, 62.1, 55.2, 55.1, 38.7, 37.4, 16.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 311 (M^+, 100), 242 (13), 204 (25).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}NO_3$: 312.1594; found: 312.1599.

1-(4-Methoxyphenyl)-3-methyl-5-(*p*-tolyl)pyrrolidin-2-one (5caa)

Yield: 35.4 mg (60%); dr = 1.2:1.

Isomer A

Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.8 Hz, 2 H), 7.13–7.07 (m, 4 H), 6.78 (d, *J* = 8.8 Hz, 2 H), 5.10–5.07 (m, 1 H), 3.72 (s, 3 H), 2.87–2.77 (m, 1 H), 2.30 (s, 3 H), 2.24–2.19 (m, 2 H), 1.29 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 156.4, 138.3, 137.7, 131.9, 129.6, 125.7, 123.1, 113.9, 61.7, 55.3, 37.9, 35.7, 21.0, 16.0.

LRMS (EI, 70 eV): *m*/*z* (%) = 295 (M^+, 100), 226 (10), 145 (71).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}NO_2$: 296.1645; found: 296.1653.

Isomer B

Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.8 Hz, 2 H), 7.08–7.03 (m, 4 H), 6.74 (d, *J* = 8.8 Hz, 2 H), 5.06–5.02 (m, 1 H), 3.70 (s, 3 H), 2.80–2.67 (m, 2 H), 2.26 (s, 3 H), 1.64–1.59 (m, 1 H), 1.36 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 156.7, 138.2, 137.3, 131.0, 129.4, 126.5, 124.7, 113.7, 62.0, 55.2, 39.0, 37.5, 21.0, 16.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 295 (M^+, 100), 226 (13), 145 (74).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}NO_2$: 296.1645; found: 296.1657.

1-(4-Methoxyphenyl)-3-methyl-5-phenylpyrrolidin-2-one (5daa)

Yield: 30.9 mg (55%); dr = 1.2:1.

Isomer A

Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.4 Hz, 2 H), 7.31 (t, *J* = 7.6 Hz, 2 H), 7.25 (d, *J* = 7.2 Hz, 1 H), 7.20 (d, *J* = 7.6 Hz, 2 H), 6.77 (d, *J* = 8.4 Hz, 2 H), 5.13–5.10 (m, 1 H), 3.72 (s, 3 H), 2.88–2.78 (m, 1 H), 2.26–2.21 (m, 2 H), 1.30 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 156.5, 141.3, 131.8, 128.9, 127.5, 125.8, 123.0, 113.9, 61.9, 55.3, 37.8, 35.6, 15.9.

LRMS (EI, 70 eV): *m*/*z* (%) = 281 (M^+, 100), 204 (25), 149 (25).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}NO_2$: 282.1489; found: 282.1496.

Isomer B

Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.17 (m, 7 H), 6.74 (d, *J* = 8.4 Hz, 2 H), 5.10–5.06 (m, 1 H), 3.69 (s, 3 H), 2.82–2.68 (m, 2 H), 1.68–1.60 (m, 1 H), 1.36 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1, 156.7, 141.2, 130.9, 128.7, 127.6, 126.6, 124.7, 113.7, 62.2, 55.2, 38.9, 37.4, 16.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 281 (M^+, 100), 204 (29), 149 (21).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}NO_2$: 282.1489; found: 282.1493.

Methyl 3-(3,4-Dihydronaphthalen-1-yl)-2-methylpropanoate (6ha)

Yield: 13.8 mg (30%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.18 (m, 2 H), 7.13 (d, *J* = 4.0 Hz, 2 H), 5.87 (t, *J* = 4.4 Hz, 1 H), 3.64 (s, 3 H), 2.97–2.91 (m, 1 H), 2.73–2.69 (m, 3 H), 2.44–2.39 (m, 1 H), 2.25–2.20 (m, 2 H), 1.15 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 136.8, 134.1, 133.8, 127.6, 127.1, 126.7, 126.3, 122.5, 51.5, 38.1, 37.0, 28.3, 23.1, 16.7.

LRMS (EI, 70 eV): *m*/*z* (%) = 230 (M^+, 28), 171 (23), 143 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}O_2$: 231.1380; found: 231.1385.

Ethyl 2-Methyl-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]propanoate (7)

Yield: 92.1 mg (85%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.20–4.14 (m, 2 H), 1.56 (t, *J* = 6 Hz, 2 H), 1.47 (s, 6 H), 1.33–1.25 (m, 7 H), 1.15 (s, 6 H), 1.00 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.5, 80.8, 60.3, 59.3, 40.4, 33.2, 24.2, 20.2, 16.8, 13.9.

LRMS (EI, 70 eV): *m*/*z* (%) = 271 (M^+, 43), 156 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{30}NO_3$: 272.2220; found: 272.2225.

Ethyl 4-(4-Methoxyphenyl)-2,2-dimethylbut-3-enoate (8)

Yield: 38.4 mg (82%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.8 Hz, 2 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 6.37 (d, *J* = 16.4 Hz, 1 H), 6.25 (d, *J* = 16 Hz, 1 H), 4.17–4.11 (m, 2 H), 3.80 (s, 3 H), 1.39 (s, 6 H), 1.25 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5, 159.1, 132.4, 130.0, 127.4, 127.3, 114.0, 60.7, 60.1, 55.3, 44.3, 25.1, 14.2.

LRMS (EI, 70 eV): *m*/*z* (%) = 234 (M^+, 23), 133 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{19}O_3$: 235.1329; found: 235.1334.

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Supporting Information

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