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PAPER

One pot synthesis of indene through copper(I)-catalyzed three-components coupling and cyclization reaction†

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A new and efficient synthesis of substituted indene has been achieved *via* copper(I)-catalyzed domino three-component coupling and cyclization reaction in moderate to good yield.

Introduction

The indene is an important class of compounds that exists widely in nature and has numerous applications in medicine.[1] Consequently, a number of approaches to the synthesis of the indene ring system have been developed, including classic methods such as the reduction/dehydration of indanones,[2] the cyclization of phenyl-substituted allylic alcohols,[3a–c] 2-substituted ethynylmalonates,[3d] acetylenic malonates[3e] and 1-alkyl-2-ethynylbenzenes[3f], and the ring expansion of substituted cyclopropenes.[4] Recently, Larock *et al.* reported synthesis of indenes by Pd-catalyzed or Cu-catalyzed carboannulation of alkynes.[5] Our group have described a convenient approach to the synthesis of 2-substituted indenes by palladium-catalyzed carboannulation of propargylic carbonates and nucleophiles.[6] To expand the method for the synthesis of indenes, we developed a copper(I)-catalyzed domino three-component coupling and cyclization reaction to construct the structure of indene.

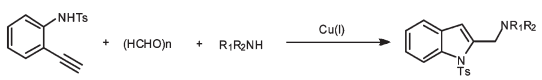
Multicomponent reactions (MCRs) involve a domino process with at least three different simple substrates. It has emerged as a powerful strategy.[7] This methodology allows molecular complexity and diversity to be created by the facile formation of several new covalent bonds in a one-pot transformation. Thus it is quite closely approaches the concept of an ideal synthesis.[8] A catalytic domino reaction including a MCR would be more attractive to achieve this goal.[9] Recently, Fujii *et al.* reported a convenient method for the preparation of functionalized indoles by the copper-catalyzed multicomponent reaction of *N*-(2-ethynylphenyl)-4-methybenzenesulfonamid with paraformaldehyde (Scheme 1).[10] A catalytic domino reaction including a MCR would be more attractive to achieve this goal.

In connection with our ongoing project on the carboannulation reaction,[11] we expected that secondary amine and paraformaldehyde could react with diethyl 2-(2-ethylphenyl)malonate under copper catalysis to give the 2-substituted indene (Scheme 2).

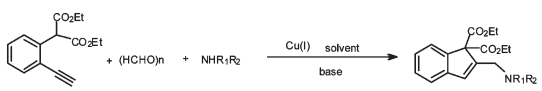
Results and discussion

Our initial study began with the 0.2 mmol diethyl 2-(2-ethylphenyl)malonate (**1a**), 2.0 equiv of disopropylamine, 2.0 equiv of paraformaldehyde, 1.2 equiv of *t*-BuOK, and 5 mol% equiv of CuI in THF at 60 °C for 20 min. However, the desired product diethyl 2-((diispropylamino)methyl)-1-*H*-indene-1,1-dicarboxylate (**5aa**) was not obtained. Only the Mannich reaction product diethyl 2-(2-(but-1-yl) phenyl)malonate (**4a**)[12] and the cyclization reaction product diethyl 1*H*-indene-1,1-dicarboxylate (**6a**) were observed (Scheme 3).

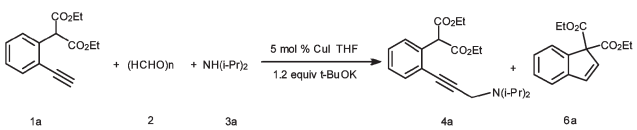
However, when the Mannich reaction finished, CuI (5 mol%) was added to the reaction mixture and stirred for 8 h, to our delight, the desired product was obtained. We suppose water was produced as a by-product, which had a disadvantageous effect



Scheme 1



Scheme 2



Scheme 3

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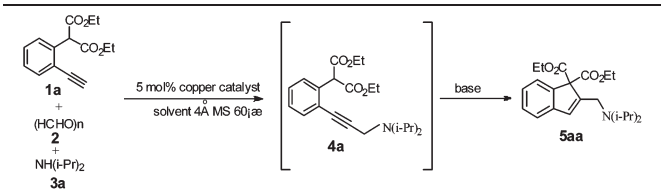
on the copper catalyst. Therefore, the molecular sieve was added to the reaction mixture to absorb the water generated by reaction.

Fortunately, the desired product was obtained, though **6a** was produced as a by-product simultaneously. In order to avoid the by-product **6a**, we first added **1a** (0.2 mmol), 2.0 equiv of diisopropylamine, 2.0 equiv of paraformaldehyde, 0.2 g 4 Å molecular sieve and 5 mol% of CuI in THF at 60 °C for 20 min. Then we added 1.2 equiv of *t*-BuOK. The product was isolated in 55% yield.

The base effect on the cyclization reaction was then evaluated. In all bases we examined, *t*-BuOLi was the best choice (entry 6). Other solvents, such as CH_3CN, dioxane and DMSO were also tested in the reaction, however, no superior results were obtained (entries 7–9). The efficiency with CuBr, CuCl, $CuCl{\cdot}Me_2S$ or $Cu(PPh_3)_2Br$ was much lower than that with CuI (entries 14–17). Thus, we chose the following reaction conditions as optimum for all subsequent cyclization: 1.0 equiv of **1**, 2.0 equiv of **2**, 2.0 equiv of **3** and 0.2 g 4 Å molecular sieve and 5 mol% equiv of CuI in THF at 60 °C under argon. When the first step finished, 1.2 equiv of *t*-BuOLi was added (Table 1).

To extend the general applicability of this three-component coupling and cyclization reaction, the reaction of diethyl malonate alkyne and paraformaldehyde with various amines under the optimized conditions was investigated. The results are summarized in Table 2. The volatile amine such as Et_2NH with **1a** and paraformaldehyde result in 70% yield (entry 2).[11b] $(n\text{-}Pr)_2NH$ and $(n\text{-}Bu)_2NH$ were also excellent amine components in this reaction (entries 3 and 4). Even when the long-chain aliphatic amine dioctylamine (entry 5) was used, the reaction proceeded very well (82% yield). The cycle secondary amine such as pyrrolidine, piperidine, 4-methylpipeidine and 1-methylpiperazine (entries 6–9)[11b] also afforded the desired products in good yields. The asymmetric secondary amines **3j** and **3k** (entries 10 and 11) also afforded the corresponding products in 64% and 62% yields, respectively. For **3l** (entry 12), a moderate yield (45%) was obtained which can be explained by the steric effects. In addition, piperazine (entry 13) was then employed in this reaction. The corresponding product **5am** was isolated in 56% yield (Scheme 4).

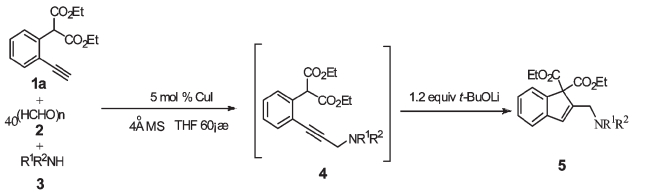
Table 1 Optimization of the copper-catalyzed three-components coupling and cyclization reaction of 2-(2-ethylphenyl)malonate, disopropylamine and paraformaldehyde[a]

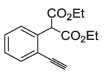
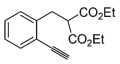
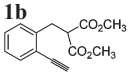


Entry	Base	Solvent	Copper	*t* (h)	Yield[c]
1	*t*-BuOK	THF	CuI	8	55
2	CH_3ONa	THF	CuI	2	42
3	NaH	THF	CuI	5	45
4	K_2CO_3	THF	CuI	5	n.r.[b]
5	*t*-BuOLi	THF	CuI	2	79
6	EtOLi	THF	CuI	2	55
7	*t*-BuOLi	CH_3CN	CuI	2	61
8	*t*-BuOLi	Dioxane	CuI	18	15
9	*t*-BuOLi	DMSO	CuI	7	26
10	*t*-BuOLi	THF	CuBr	6	57
11	*t*-BuOLi	THF	CuCl	18	10
12	*t*-BuOLi	THF	$CuCl{\cdot}Me_2S$	15	Trace
13	*t*-BuOLi	THF	$Cu(PPh_3)_2Br$	36	15

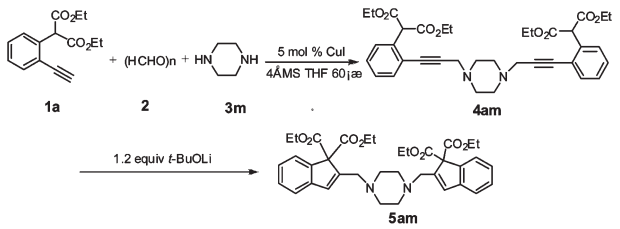
[a] Reactions conditions: 0.20 mmol of **1a**, 2.0 equiv of **2**, 2.0 equiv of **3** and 5 mol% of copper catalysts and 0.2 g 4 Å MS in 3 mL solvent at 60 °C under argon. When the first step finished, added 1.2 equiv of base for the specified period of time. [b] n.r. = no reaction. [c] Yield = isolated yield (%).

Table 2 Copper-catalyzed three-components coupling and cyclization reaction of 2-(2-ethylphenyl)malonate and paraformaldehyde with amine[a]



Entry	Alkyne	Amines	*t* (h)	Products	Yield[b]
1	 **1a**	$(i\text{-}Pr)_2NH$ **3a**	2	**5aa**	79
2	**1a**	Et_2NH **3b**	2.5	**5ab**	70
3	**1a**	$(n\text{-}Pr)_2NH$ **3c**	3	**5ac**	69
4	**1a**	$(n\text{-}Bu)_2NH$ **3d**	4.5	**5ad**	68
5	**1a**	Dioctylamine **3e**	2	**5ae**	82
6	**1a**		2	**5af**	80
7	**1a**		5	**5ag**	81
8	**1a**		3	**5ah**	71
9	**1a**		2	**5ai**	82
10	**1a**		4	**5aj**	62
11	**1a**		3	**5ak**	64
12	**1a**		3	**5al**	45
13	**1a**		5	**5am**	56
14	 **1b**	**3a**	5	**5ba**	68
15	**1b**	**3b**	6	**5bb**	51
16	**1b**	**3f**	8	**5bf**	55
17	**1b**	**3h**	7	**5bh**	57
18	 **1c**	**3a**	6	**5ca**	45

[a] Reaction conditions: 0.20 mmol of **1**, 2.0 equiv of **2**, 2.0 equiv of **3**, 5 mol% of CuI and 0.2 g 4 Å MS in 3 mL THF at 60 °C under argon. When the first step finished, added 1.2 equiv of *t*-BuOLi for the specified period of time. [b] Yield = isolated yield (%).



Scheme 4

Encouraged by the above results, we further investigated the reactivity of two other malonates. To our delight, various secondary amines such as $(i\text{-Pr})_2NH$, Et_2NH, pyrrolidine, 4-methylpipeidine could react with diethyl 2-(2-entynylbenzyl)malonate (**1b**) or dimethyl 2-(2-entynylbenzyl) malonate (**1c**) to give the desired products in moderate yields (entries 14–18). What's more, the symmetrical structure **5am** was obtained when we used amine **3m** react with **1a** and **2** (Scheme 4).

A plausible mechanism accounting for the formation of the indenes is depicted in Scheme 5.[6,10]

The reaction may undergo the following key steps: (1) The reaction of **1** and **2** with **3** though a Mannich-type mechanism to get the intermediate **4a**, (2) **4a** reacts with base, to afford a carbanion, (3) coordination of the alkynyl moiety of **4a** to CuI to generate the complex **A**, (4) the carbanion attacks the alkyne carbon activating the triple bond, leading to the indene **5a** and a regenerated copper catalyst, which then enters the next cycle.

Conclusions

In summary, we have developed a mild and efficient CuI catalytic method for the synthesis of indene. A variety of secondary amines undergo this process, giving the desired products in moderate to good yields.

Experimental

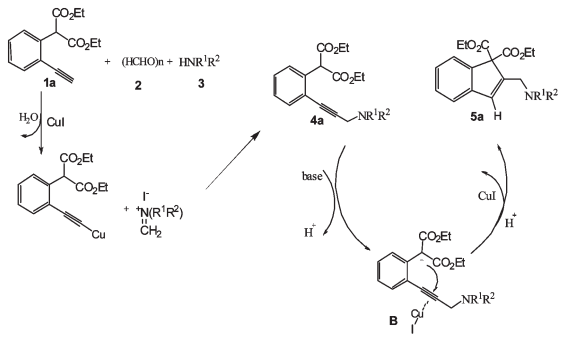
General remarks

Column chromatography was carried out on silica gel. ^1H NMR spectra were recorded on 400 MHz in $CDCl_3$ and ^{13}C NMR spectra were recorded on 100 MHz in $CDCl_3$ using TMS as internal standard. IR spectra were recorded on a FT-IR spectrometer and only major peaks are reported in cm^{-1}. Melting points were determined on a microscopic apparatus and were uncorrected. All new compounds were further characterized by elemental analysis; copies of their ^1H NMR and ^{13}C NMR spectra are provided in the ESI†. Unless otherwise stated, all amines were purchased from commercial suppliers and used without further purification.

Starting materials

Diethyl (2-iodophenyl)malonate was prepared according to the literature.[13]

Diethyl (2-iodobenzyl)malonate and dimethyl (2-iodobenzyl)-malonate were prepared according to the literature.[11]



Scheme 5

Typical procedure for the preparation of propargylic trimethylsilane

Diethyl 2-(2-(2-(trimethylsilyl)entynyl)phenyl)malonate. To a solution of diethyl (2-iodophenyl)malonate (1.81 g, 5.0 mmol) and ethynyltrimethylsiane (0.58 g, 6 mmol) in Et_2NH (20.0 mL) was added $Pd(PPh_3)_4$ (57.5 mg, 0.5 mol%). The mixture was stirred for 5 min and CuI (9.5 mg, 1 mol%) was added. The resulting mixture was then stirred under an argon atmosphere at room temperature for 3 h. The ammonium salt was removed by filtration. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica get to afford 1.53 g (92%) as an oil.

Diethyl 2-(2-(2-(trimethylsilyl)entynyl)benzyl)malonate. This was prepared by the same method, but employing diethyl-(2-iodobenzyl)malonate (1.88 g, 5.0 mmol) and (0.58 g, 6 mmol) for 3 h afforded 1.54 g (89%) as an oil.

Dimethyl 2-(2-(2-(trimethylsilyl)entynyl)benzyl)malonate. This was prepared by the same method, but employing dimethyl-(2-iodobenzyl)malonate (0.72 g, 2.0 mmol) and (0.17 g, 2.4 mmol) for 3 h afforded 0.54 g (90%) as an oil.

Typical procedure for the preparation of 1a–c. To a solution of diethyl 2-(2-(2-(trimethylsilyl)entynyl)phenyl)malonate (0.66 g, 2.0 mmol) in THF (10 mL) was added TBAF at −78 °C (0.76 g, 2.4 mmol). After stirring for 10 min the reaction mixture was diluted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by column chromatography on silica gel to afford the corresponding product **1a** 0.44 g (85%) as an oil.

1a: ^1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.55 (m, 2H), 7.37–7.39 (m, 1H), 7.27–7.32 (m, 1H), 5.33 (s, 1H), 4.23–4.26 (m, 4H), 3.25 (s, 1H), 1.26–1.27 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 135.2, 132.7, 129.1, 128.7, 127.9, 122.6, 82.2, 81.9, 61.9, 55.5, 13.9; IR (neat, cm^{-1}): 2956, 2252, 1631, 1309, 1248, 1146, 1045; Anal. Calcd for $C_{15}H_{16}O_4$: C 69.22; H 6.20 Found: C 69.08; H 6.33.

Diethyl 2-(2-entynylbenzyl)malonate. The **1b** was prepared by the above method, but employing diethyl 2-(2-(3-hydroxyprop-1-ynyl)benzyl)malonate (0.58 g, 2.0 mmol) and methyl chloroformate afforded **1b** 0.61 g (87%) as an oil.

1b: ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.48 (d, J = 7.2 Hz, 1H), 7.18–7.20 (m, 2H), 4.12–4.18 (m, 4H), 3.87–3.91 (t, J = 7.6 Hz, 1H), 3.37–3.39 (d, J = 7.6 Hz, 2H), 3.32 (s, 1H), 1.15–1.18 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

168.8, 140.2, 132.9, 129.7, 128.8, 126.7, 121.8, 81.8, 81.5, 61.3, 52.1, 33.4, 13.9; IR (neat, cm^{-1}): 2923, 2167, 1676, 1331, 1234, 1167, 1045; Anal. Calcd for $C_{22}H_{31}O_4$: C 70.06; H 6.61. Found: C 70.08; H 6.63.

Dimethyl 2-(2-entynylbenzyl) malonate. The **1c** was prepared by the above method, but employing dimethyl 2-(2-(2-(trimethylsilyl)entynyl)benzyl)malonate (0.58 g, 2.0 mmol) and methyl chloroformate afforded **1c** 0.61 g (87%) as an oil.

1c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.48 (m, 1H), 7.17–7.28 (m, 3H), 3.91–3.95 (t, J = 7.6 Hz, 1H), 3.69 (s, 6H), 3.38–3.40 (d, J = 7.6 Hz, 2H), 3.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 140.6, 133.1, 129.7, 128.9, 126.8, 121.8, 81.9, 81.4, 52.4, 51.8, 33.5; IR (neat, cm^{-1}): 2956, 2223, 1667, 1354, 1268, 1123; Anal. Calcd for $C_{14}H_{14}O_4$: C 68.28; H 5.73. Found: C 68.25; H 5.78.

4a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.52 (m, 1H), 7.23–7.33 (m, 3H), 5.35 (s, 1H), 4.15–4.28 (m, 4H), 3.70 (s, 2H), 3.23–3.29 (m, 2H), 1.24–1.28 (t, J = 7.2 Hz, 6H), 1.14–1.16 (d, J = 6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 134.4, 132.1, 128.0, 127.8, 124.2, 94.1, 81.2, 61.7, 55.4, 48.4, 34.7, 20.7, 14.0; IR (neat, cm^{-1}): 3437, 2982, 2232, 1671, 1301, 1228, 1154, 1032; Anal. Calcd for $C_{22}H_{31}NO_4$: C 70.75; H 8.37; N 3.75. Found: C 70.77; H 8.35; N 3.68. HRMS (ESI) Calcd for $C_{22}H_{31}NO_4$: M + H = 374.2326. Found: 374.2345.

6a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.62 (d, J = 7.2 Hz, 1H), 7.17–7.26 (m, 3H), 6.82–6.84 (d, J = 5.6 Hz, 1H), 6.49–6.50 (d, J = 5.6 Hz, 1H), 4.10–4.18 (m, 4H), 1.16–1.22 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 143.6, 139.8, 134.7, 133.4, 128.6, 126.3, 125.4, 121.5, 70.4, 62.12, 13.9; IR (neat, cm^{-1}): 2986, 1671, 1301, 1228, 1154, 1032; Anal. Calcd for $C_{15}H_{16}O_4$: C 69.22; H 6.20. Found: C 69.25; H 6.31. HRMS (ESI) Calcd for $C_{15}H_{16}O_4$: M + H = 261.1121. Found: 261.1144.

General procedure for the preparation of indenes or dihydronaphthalene (5). A mixture of (**1**, 0.20 mmol), paraformaldehyde (**2**, 0.40 mmol), amine (**3**, 0.04 mol), CuI (1.9 mg, 5.0 mol %), 0.2 g 4 Å MS, THF (3.0 mL) was placed under argon atmosphere in a 10 mL flask. The resulting mixture was then heated at 60 °C. When it was considered that the first step of the reaction was complete (as determined by TLC analysis) *t*-BuOLi (19.2 mg, 0.24 mmol) was added, then when the reaction was considered complete as determined by TLC analysis, the reaction mixture was allowed to cool to room temperature. The reaction mixture was concentrated under reduced pressure and the residue was purified by chromatography on silica gel to afford the corresponding 2-substituted indenes **5a**.

5aa: The reaction mixture was chromatographed using 10 : 1 hexanes–EtOAc to afford 59 mg (79%) of the indicated compound as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.51 (d, J = 7.2 Hz, 1H), 7.14–7.20 (m, 2H), 7.05–7.18 (m, 1H), 6.19 (s, 1H), 4.09–4.19 (m, 4H), 3.441–3.448 (d, J = 2 Hz, 2H), 3.00–3.03 (t, J = 6.8 Hz, 2H), 1.15–1.18 (t, J = 7.2 Hz, 6H), 0.91–0.96 (d, J = 6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 140.1, 131.8, 130.0, 128.4, 126.8, 122.3, 96.7, 81.8, 61.6, 58.6, 52.5, 33.9, 24.2, 13.9; IR (neat, cm^{-1}): 3437, 2982, 1732, 1371, 1301, 1228, 1154, 1032; Anal. Calcd for $C_{22}H_{31}NO_4$: C 70.75; H 8.37; N 3.75. Found: C 70.78; H 8.33; N 3.69. HRMS (ESI) Calcd for $C_{22}H_{31}NO_4$: M + H = 374.2326. Found: 374.2351.

5ab: The reaction mixture was chromatographed using 10 : 1 hexanes–EtOAc to afford 48.3 mg (70%) of the indicated compound as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.51 (d, J = 7.2 Hz, 1H), 7.10–7.21 (m, 3H), 6.82 (s, 1H), 4.09–4.15 (m, 4H), 3.414–3.418 (d, J = 1.6 Hz, 2H), 2.48–2.53 (q, J = 7.2 Hz, 4H), 1.27–1.21 (t, J = 7.2 Hz, 6H), 1.06–1.01 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 146.2, 144.1, 141.4, 131.6, 128.5, 125.3, 124.8, 120.5, 70.7, 61.8, 52.3, 47.2, 13.9, 11.9; IR (neat, cm^{-1}): 3424, 2972, 1731, 1464, 1234, 1050; Anal. Calcd for $C_{20}H_{27}NO_4$: C 69.54; H 7.88; N 4.05. Found: C 69.48; H 7.84; N 3.96. HRMS (ESI) Calcd for $C_{20}H_{27}NO_{44}$: M + H = 346.2013. Found: 346.2019.

5ac: The reaction mixture was chromatographed using 10 : 1 hexanes–EtOAc to afford 52.3 mg (52%) of the indicated compound as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.58 (m, 1H), 7.14–7.29 (m, 3H), 6.90 (s, 1H), 4.15–4.23 (m, 4H), 3.45 (s, 2H), 2.41–2.45 (t, J = 7.6 Hz, 4H), 1.40–1.50 (m, 4H), 1.18–1.27 (m, 6H), 0.85–0.89 (t, J = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 144.2, 140.9, 139.6, 131.4, 128.5, 125.3, 124.8, 120.8, 70.7, 61.8, 56.5, 53.3, 13.9, 11.9; IR (neat, cm^{-1}): 3434, 2981, 1726, 1459, 1239, 1047; Anal. Calcd for $C_{22}H_{31}NO_4$: C 70.75; H 8.37; N 3.75. Found: C 70.79; H 8.35; N 3.70. HRMS (ESI) Calcd for $C_{22}H_{31}NO_4$: M + H = 374.2326. Found: 374.2350.

5ad: The reaction mixture was chromatographed using 10 : 1 hexanes–EtOAc to afford 54.5 mg (68%) of the indicated compound as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.59 (d, J = 7.2 Hz, 1H), 7.19–7.31 (m, 3H), 6.93 (s, 1H), 4.19–4.23 (m, 4H), 3.47 (d, J = 1.6 Hz, 2H), 1.36–1.48 (m, 4H), 1.27–1.34 (m, 4H), 1.21–1.25 (m, 6H), 0.90–0.94 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 146.5, 144.2, 141.0, 131.2, 128.5, 125.32, 124.8, 120.8, 70.8, 61.8, 54.3, 53.3, 29.5, 20.6, 14.1, 13.9; IR (neat, cm^{-1}): 3434, 2972, 1731, 1464, 1234, 1050; Anal. Calcd for $C_{24}H_{35}NO_4$: C 71.79; H 8.79; N 3.49. Found: C 71.81; H 8.77; N 3.45. HRMS (ESI) Calcd for $C_{24}H_{35}NO_4$: M + H = 402.2639. Found: 402.2645.

5ae: The reaction mixture was chromatographed using 10 : 1 hexanes–EtOAc to afford 86.4 mg (82%) of the indicated compound as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.60 (d, J = 7.2 Hz, 1H), 7.23–7.30 (m, 2H), 7.14–7.18 (m, 1H), 6.91 (s, 1H), 4.12–4.22 (m, 4H), 3.45–3.46 (d, J = 1.6 Hz, 2H), 2.45–2.48 (t, J = 7.6 Hz, 4H), 1.46 (s, 4H), 1.19–1.28 (m, 26H), 0.85–0.89 (t, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 146.5, 144.2, 141.0, 131.2, 128.5, 125.32, 124.8, 120.7, 70.8, 61.8, 54.5, 53.3, 31.8, 29.6, 29.3, 27.5, 27.3, 22.6, 14.0, 13.9; IR (neat, cm^{-1}): 3451, 2980, 1736, 1468, 1254, 1038; Anal. Calcd for $C_{33}H_{55}NO_4$: C 75.10; H 10.12; N 2.65. Found: C 75.12; H 10.06; N 2.63. HRMS (ESI) Calcd for $C_{33}H_{55}NO_4$: M + H = 528.4073. Found: 528.4056.

5af: The reaction mixture was chromatographed using 10 : 1 hexanes–EtOAc to afford 54.8 mg (80%) of the indicated compound as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.61 (d, J = 8.0 Hz, 1H), 7.24–7.32 (m, 2H), 7.17–7.21 (m, 1H), 6.88 (s, 1H), 4.15–4.23 (m, 4H), 3.59 (s, 2H), 2.60–2.63 (t, J = 6.4 Hz, 4H), 1.78–1.81 (m, 4H), 1.22–1.30 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 145.2, 144.0, 140.9, 131.7, 128.5, 125.5, 124.9, 120.9, 71.0, 61.8, 54.5, 54.4, 23.7, 13.9; IR (neat,

cm^{-1}): 3402, 2964, 1731, 1463, 1234, 1050; Anal. Calcd for $C_{20}H_{25}NO_4$: C 69.95; H 7.34; N 4.08. Found: C 69.86; H 7.38; N 3.99. HRMS (ESI) Calcd for $C_{20}H_{25}NO_4$: M + H = 344.1856 Found: 344.1837.

5ag: The reaction mixture was chromatographed using 10 : 1 hexanes–EtOAc to afford 53.6 mg (81%) of the indicated compound as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.60 (d, J = 7.6 Hz, 1H), 7.25–7.31 (m, 2H), 7.16–7.20 (m, 1H), 6.85 (s, 1H), 4.16–4.23 (m, 4H), 3.39 (s, 2H), 2.46 (s, 4H), 1.56–1.60 (m, 4H), 1.44–1.45 (d, J = 4.4 Hz, 1H), 1.22–1.26 (t, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 144.5, 143.9, 141.1, 132.1, 128.5, 125.5, 124.8, 120.8, 70.8, 61.9, 57.6, 55.0, 26.1, 24.4, 13.9; IR (neat, cm^{-1}): 3431, 2934, 1731, 1465, 1236, 1049; Anal. Calcd for $C_{21}H_{27}NO_4$: C 70.56; H 7.61; N 3.92. Found: C 70.36; H 7.67; N 3.78. HRMS (ESI) Calcd for $C_{21}H_{27}NO_4$: M + H = 358.2013. Found: 358.2033.

5ah: The reaction mixture was chromatographed using 10 : 1 hexanes–EtOAc to afford 52.7 mg (71%) of the indicated compound as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.60 (d, J = 7.6 Hz, 1H), 7.23–7.30 (m, 2H), 7.16–7.20 (m, 1H), 6.85 (s, 1H), 4.15–4.23 (m, 4H), 3.996–3.999 (d, J = 1.2 Hz, 2H), 2.95–2.96 (d, J = 11.6 Hz, 2H), 1.94–2.00 (m, 2H), 1.59–1.62 (d, J = 12.8 Hz, 2H), 1.27–1.38 (m, 1H), 1.18–1.28 (m, 7H), 0.90–0.93 (t, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 144.6, 143.9, 141.1, 132.1, 128.5, 125.4, 124.8, 120.8, 70.8, 61.8, 57.3, 54.3, 34.6, 30.8, 21.9, 13.9; IR (neat, cm^{-1}): 3432, 2936, 1732, 1464, 1237, 1047; Anal. Calcd for $C_{22}H_{29}NO_4$: C 71.13; H 7.83; N 3.77. Found: C 71.16; H 7.87; N 3.79. HRMS (ESI) Calcd for $C_{22}H_{29}NO_4$: M + H = 372.2169. Found: 372.2154.

5ai: The reaction mixture was chromatographed using 1 : 1 CH_3OH–EtOAc to afford 53.6 mg (82%) of the indicated compound as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.53 (d, J = 7.6 Hz, 1H), 7.12–7.22 (m, 3H), 6.78 (s, 1H), 4.11–4.13 (m, 4H), 3.385–3.389 (d, J = 1.6 Hz, 2H), 2.52 (s, 8H), 1.19–1.15 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 143.7, 143.6, 141.0, 132.4, 128.5, 125.6, 124.8, 120.9, 70.8, 61.9, 56.6, 55.2, 53.0, 45.9, 13.9; IR (neat, cm^{-1}): 3435, 2939, 1738, 1465, 1238, 1056; Anal. Calcd for $C_{21}H_{28}N_2O_4$: C 69.72; H 7.58; N 7.52. Found: C 69.75; H 7.62; N 7.49. HRMS (ESI) Calcd for $C_{21}H_{28}N_2O_4$: M + H = 373.2122. Found: 373.2123.

5aj: The reaction mixture was chromatographed using 10 : 1 hexanes–EtOAc to afford 48.7 mg (62%) of the indicated compound as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.53 (d, J = 7.6 Hz, 1H), 7.19–7.38 (m, 8H), 7.00 (s, 1H), 4.10–4.20 (m, 4H), 3.60–3.62 (d, J = 10.4 Hz, 2H), 3.48–3.52 (m, 2H), 2.24 (s, 3H), 1.18–1.21 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 145.1, 143.9, 141.0, 139.5, 132.0, 128.7, 128.6, 125.5, 124.8, 120.9, 70.8, 62.3, 61.9, 56.3, 42.5, 13.9; IR (neat, cm^{-1}): 3435, 2939, 1738, 1465, 1238, 1042; Anal. Calcd for $C_{24}H_{27}NO_4$: C 72.36; H 6.92; N 3.56. Found: C 72.38; H 7.01; N 3.58. HRMS (ESI) Calcd for $C_{24}H_{27}NO_4$: M + H = 394.2013. Found: 394.2041.

5ak: The reaction mixture was chromatographed using 10 : 1 hexanes–EtOAc to afford 52.1 mg (64%) of the indicated compound as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.53 (d, J = 7.6 Hz, 1H), 7.19–7.38 (m, 8H), 7.00 (s, 1H), 4.08–4.18 (m, 4H), 3.67–3.62 (s, 2H), 3.51–3.50 (d, J = 1.6 Hz, 2H), 2.55–2.60 (q, J = 7.2 Hz, 4H), 1.16–1.20 (t, J = 7.2 Hz, 6H), 1.06–1.10 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 145.1, 143.9, 141.0, 139.5, 132.0, 128.7, 128.6, 125.5, 124.8, 120.9, 70.8, 62.3, 61.9, 56.3, 42.5, 13.9; IR (neat, cm^{-1}): 3435, 2939, 1738, 1465, 1238, 1047; Anal. Calcd for $C_{25}H_{29}NO_4$: C 73.68; H 7.17; N 3.44. Found: C 73.36; H 7.18; N 3.45. HRMS (ESI) Calcd for $C_{25}H_{29}NO_4$: M + H = 408.2169. Found: 408.2187.

5al: The reaction mixture was chromatographed using 10 : 1 hexanes–EtOAc to afford 34.1 mg (45%) of the indicated compound as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.64 (d, J = 7.6 Hz, 1H), 7.15–7.28 (m, 8H), 7.76–7.78 (m, 2H), 6.58 (s, 1H), 3.44–3.45 (d, J = 1.6 Hz, 2H), 4.13–4.11 (m, 4H), 3.07 (s, 3H), 1.27–1.30 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 143.4, 143.1, 140.9, 131.3, 129.1, 128.7, 125.6, 125.0, 121.0, 116.2, 111.7, 70.4, 62.34, 52.2, 38.5, 13.9; IR (neat, cm^{-1}): 3453, 2949, 1756, 1467, 1055; Anal. Calcd for $C_{23}H_{25}NO_4$: C 72.80; H 6.64; N 3.69. Found: C 72.86; H 6.67; N 3.68. HRMS (ESI) Calcd for $C_{23}H_{25}NO_{44}$: M + H = 380.1856. Found: 380.1863.

5am: The reaction mixture was chromatographed using EtOAc to afford 53.6 mg (56%) of the indicated compound as a solid: mp 146–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.61 (d, J = 7.6 Hz, 2H), 7.17–7.31 (m, 6H), 6.85 (s, 2H), 4.16–4.23 (m, 8H), 3.45 (s, 4H), 2.56 (s, 8H), 1.19–1.15 (t, J = 7.2 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) 168.0, 144.0, 143.8, 141.0, 132.4, 128.5, 125.6, 124.9, 120.9, 70.8, 61.9, 56.8, 13.9; IR (neat, cm^{-1}): 3435, 2939, 1738, 1465, 1238, 1047; Anal. Calcd for $C_{36}H_{42}N_2O_8$: C 68.55; H 6.71; N 4.44. Found: C 68.48; H 6.67; N 4.47. HRMS (ESI) Calcd for $C_{36}H_{42}N_2O_8$: M + H = 631.3014. Found: 631.3061.

5ba: The reaction mixture was chromatographed using 10 : 1 hexanes–EtOAc to afford 53.4 mg (69%) of the indicated compound as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.53 (d, J = 7.6 Hz, 1H), 7.12–7.22 (m, 3H), 6.78 (s, 1H), 4.13–4.11 (m, 4H), 3.385–3.389 (d, J = 1.6 Hz, 2H), 2.52 (s, 8H), 1.19–1.15 (t, J = 7.2 Hz, 6H), 1.02–1.03 (d, J = 6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.8, 137.9, 133.1, 132.1, 127.1, 126.9, 126.8, 126.0, 125.0, 61.5, 58.7, 48.0, 47.5, 20.7, 14.0; IR (neat, cm^{-1}): 3432, 2923, 1743, 1463, 1248, 1056; Anal. Calcd for $C_{23}H_{33}NO_4$: C 71.29; H 8.58; N 3.61. Found: C 71.36; H 8.57; N 3.68. HRMS (ESI) Calcd for $C_{23}H_{33}NO_4$: M + H = 388.2482. Found: 388.2514.

5bb: The reaction mixture was chromatographed using 10 : 1 hexanes–EtOAc to afford 36.6 mg (51%) of the indicated compound as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07–7.26 (m, 4H), 6.71 (s, 1H), 4.06–4.22 (m, 4H), 3.45 (s, 2H), 3.30–3.33 (d, J = 1.6 Hz, 2H), 2.53–2.60 (m, 4H), 1.19–1.23 (t, J = 7.2 Hz, 6H), 0.99 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 139.6, 132.4, 130.6, 128.5, 128.2, 127.2, 126.8, 126.1, 61.4, 57.9, 46.03, 36.2, 14.0, 13.9, 10.9; IR (neat, cm^{-1}): 3436, 2949, 1768, 1467, 1238, 1087; Anal. Calcd for $C_{21}H_{29}NO_4$: C 70.17; H 8.13; N 3.90. Found: C 70.16; H 8.17; N 3.98. HRMS (ESI) Calcd for $C_{21}H_{29}NO_4$: M + H = 360.2169. Found: 360.2197.

5be: The reaction mixture was chromatographed using 10 : 1 hexanes–EtOAc to afford 41.4 mg (56%) of the indicated compound as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07–7.16 (m, 4H), 6.04 (s, 1H), 4.06–4.20 (m, 4H), 3.46 (s, 2H), 3.39 (s, 2H), 2.49 (s, 4H), 1.75 (s, 4H), 1.20–1.24 (m, 6H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 170.8, 132.7, 132.5, 127.3, 127.2, 126.9, 126.8, 61.51, 59.6, 57.7, 53.8, 36.1, 23.9, 23.7, 13.9; IR (neat, cm^{-1}): 3454, 2980, 1743, 1455, 1239, 1043; Anal. Calcd for $C_{21}H_{27}NO_4$: C 70.56; H 7.61; N 3.92. Found: C 70.36; H 7.67; N 3.78. HRMS (ESI) Calcd for $C_{21}H_{27}NO_4$: M + H = 358.2013. Found: 358.2037.

5ca: The reaction mixture was chromatographed using 10 : 1 hexanes–EtOAc to afford 53.4 mg (69%) of the indicated compound as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06–7.16 (m, 4H), 6.97 (s, 1H), 3.74 (s, 6H), 3.45 (s, 2H), 3.27–3.28 (d, J = 1.6 Hz, 2H), 3.05–3.12 (m, 2H), 1.01–1.03 (d, J = 6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.4, 137.6, 132.9, 131.9, 127.1, 127.0, 126.1, 125.5, 58.6, 48.5, 47.6, 36.5, 20.7; IR (neat, cm^{-1}): 3435, 2939, 1738, 1465, 1238, 1047; Anal. Calcd for $C_{21}H_{29}NO_4$: C 70.17; H 8.13; N 3.90. Found: C 70.26; H 8.17; N 3.98. HRMS (ESI) Calcd for $C_{21}H_{29}NO_4$: M+H = 360.2169. Found: 360.2190.

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