

Copper(I)-Catalyzed A³-Coupling Based Reaction of Alkynes, Aldehydes, and Amines: An Efficient Approach to 2,5-Polysubstituted Dihydrofurans and 2,5-Disubstituted Furans

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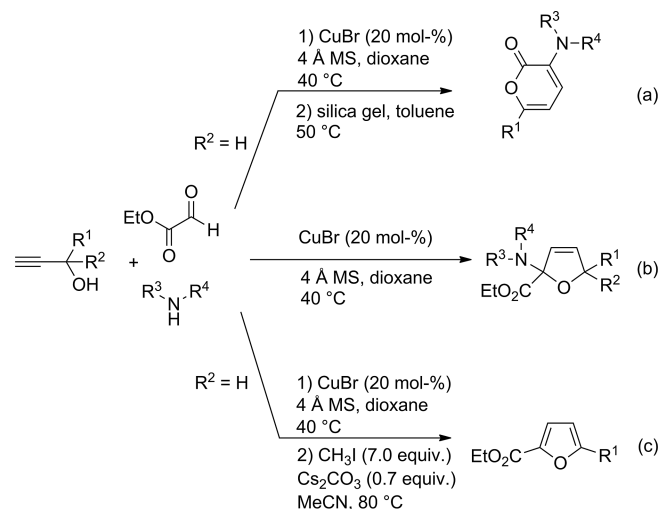
An efficient and practical A³-coupling based reaction that gives a variety of 2,5-polysubstituted dihydrofurans and 2,5-disubstituted furan derivatives has been developed. This domino copper-catalyzed three-component coupling reaction of propargylic alcohol, ethyl glyoxalate, and an amine affords a propargylic amine intermediate, which undergoes an alk-

yne–allene isomerization followed by a cyclization to yield the dihydrofuran. Upon treatment with CH₃I and base, the latter was smoothly converted into a 2,5-disubstituted furan. Alternatively, the furan derivatives can be directly prepared by a two-step reaction sequence.

Introduction

One goal of modern synthetic organic chemistry is the development of simple, convenient and efficient methods for the construction of target compounds from easily available starting materials. Multicomponent reactions, which allow the formation of several bonds including new C–C, C–O, and C–N bonds in one-pot, have emerged as an attractive and powerful strategy for this purpose. Of particular interest, copper-catalyzed A³-coupling reactions of terminal alkynes, aldehydes, and amines have been well-developed.^[1–3] Our group recently reported a unique copper-catalyzed three-component reaction for the synthesis of 3-amino-2-pyrones from secondary propargyl alcohols, ethyl glyoxalate, and amines (Scheme 1, a).^[3j] A mechanistic investigation of this reaction indicated that a 2,5-dihydrofuran intermediate, which is formed by an A³-coupling/alkyne–allene isomerization/cyclization process, was involved in the reaction pathway. We envision that by replacing the secondary propargyl alcohols with tertiary propargyl alcohols, the reaction would afford a five-membered 2,5-dihydrofuran as the only product. Herein, we report our investigation of copper(I)-catalyzed cascade three-component reactions for the formation of 2,5-dihydrofuran derivatives (Scheme 1, b). An efficient two-step sequence for the

construction of functionalized 2,5-disubstituted furans from secondary propargyl alcohols, ethyl glyoxalate, and piperidine is also presented (Scheme 1, c).



Scheme 1. Previous work and this work (MS = molecular sieves).

Results and Discussion

An initial study was performed by combining tertiary 2-methylbut-3-yn-2-ol (**1a**), piperidine (**2a**), and ethyl glyoxalate in 1,4-dioxane in the presence of a catalytic amount of CuBr at 40 °C, which produced the desired 2,5-dihydrofuran derivative **3aa** in 75% NMR yield (Table 1, Entry 1). A variety of copper salts were then studied, but no improvement to the yield was achieved (Table 1, Entries 2–6). Further solvent screening showed that ethereal solvents, such as tetrahydrofuran (THF) and 1,2-dimethox-

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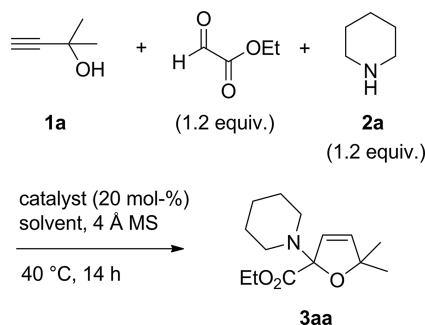
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yethane (DME), gave similar results as dioxane (Table 1, Entries 7 and 8). Finally, the reaction conditions that are reported in Entry 1 of Table 1 were defined as the standard for further studies.

Table 1. Optimization of reaction conditions for preparing **3aa**.^[a]

Entry	Catalyst	Solvent	% Yield 3aa ^[b]
1	CuBr	dioxane	75
2	CuI	dioxane	51
3	CuCl	dioxane	72
4	CuBr ₂	dioxane	65
5	CuCl ₂	dioxane	66
6	Cu(OTf) ₂ ^[c]	dioxane	5
7	CuBr	THF	74
8	CuBr	DME	73
9	CuBr	toluene	61
10	CuBr	DCM ^[c]	64
11	CuBr	CH ₃ CN	65

[a] Reagents and conditions: **1a** (1.0 mmol), ethyl glyoxalate (1.2 mmol), **2a** (1.2 mmol), MS (4 Å, 300 mg), and a copper salt (0.2 mmol) in solvent (3 mL) at 40 °C. [b] NMR yield. [c] Tf = trifluoromethylsulfonyl, DCM = dichloromethane.

With the optimized protocol in hand, we examined the scope of this three-component reaction (Table 2). A variety of different tertiary propargylic alcohols were compatible under the conditions and afforded the expected 2,5-dihydrofuran derivatives in good yields (Table 2, Entries 1–6). To our surprise, a five-membered 2,5-dihydrofuran ring could also be obtained by employing secondary propargylic alcohols (Table 2, Entries 7, 9, and 10). The employment of cyclic amines such as 1,2,3,6-tetrahydropyridine, pyrrolidine, and 3-pyrroline provided the desired products in decent yields (Table 2, Entries 11–13). Dibutyl and diallylamines were found to be similarly effective (Table 2, Entries 14 and 15). Isoindoline and 1,2,3,4-tetrahydroisoquinoline also formed the corresponding products (Table 2, Entries 16 and 17). Furthermore, when the reaction of **1g** with ethyl glyoxalate and **2a** was conducted on a gram-scale, the desired product **3ag** was produced in a similar yield to that afforded by the smaller scale reaction (Table 2, Entry 8).

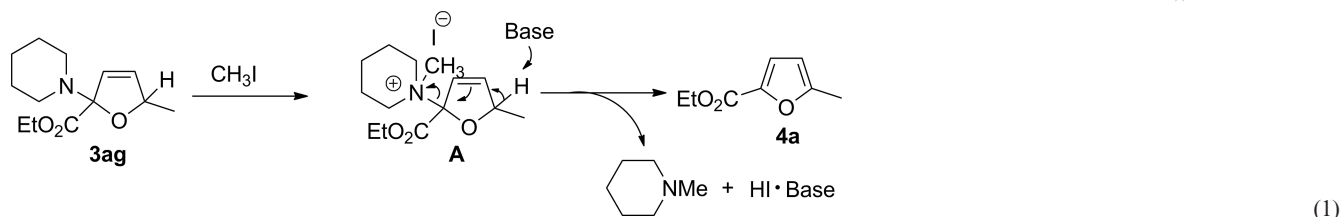
We reasoned that functionalized furans are important core frameworks that are widely present in numerous bioactive natural products and pharmaceuticals,^[4] and functionalized furans may also serve as versatile building blocks in organic synthesis because of their specific properties and latent functionality. Therefore, the development of a convenient and efficient method to prepare these frameworks is greatly desirable. We envisioned that the treatment of com-

Table 2. The scope of the three-component reaction to afford 2,5-dihydrofurans.^[a]

Entry	(R ¹ , R ²) (1)	2	Yield [%] (3) ^[b]
1	Me, Me (1a)	2a	64 (3aa)
2	Et, Et (1b)	2a	58 (3ab)
3	Me, Et (1c)	2a	59 (3ac)
4	–(CH ₂) ₃ – (1d)	2a	57 (3ad)
5	–(CH ₂) ₄ – (1e)	2a	63 (3ae)
6	–(CH ₂) ₅ – (1f)	2a	62 (3af)
7	Me, H (1g)	2a	56 (3ag)
8 ^[c]	Me, H (1g)	2a	55 (3ag)
9	<i>n</i> -C ₅ H ₁₁ , H (1h)	2a	65 (3ah)
10	Bn, H (1i)	2a	57 (3ai)
11	Me, Me (1a)	2b	62 (3ba)
12	Me, Me (1a)	2c	61 (3ca)
13	Me, Me (1a)	2d	64 (3da)
14	Me, Me (1a)	2e	68 (3ea)
15	Me, Me (1a)	2f	65 (3fa)
16	Me, Me (1a)	2g	61 (3ga)
17	Me, Me (1a)	2h	67 (3ha)

[a] Reagents and conditions: **1** (1.0 mmol), ethyl glyoxalate (1.2 mmol), **2** (1.2 mmol), MS (4 Å, 300 mg), and CuBr (0.2 mmol) in dioxane (3 mL) at 40 °C. [b] Isolated yield. [c] The reaction was carried on a 15 mmol scale of **1g** in THF (40 mL) with MS (4 Å, 1.5 g) and CuBr (10 mol-%).

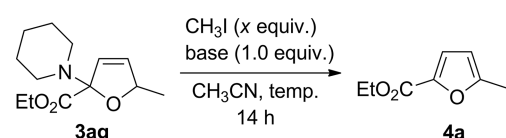
pound **3ag**, which was synthesized by the above-mentioned three-component reaction, with CH₃I should provide ammonium cationic intermediate **A**. Upon considering the strong leaving ability of the quaternary ammonium salt and the aromatization of the oxygen-containing heterocycle, we



then expect intermediate **A** to form furan derivative **4a** in the presence of a base, see Equation (1).

To test our hypothesis, 2,5-dihydrofuran derivative **3ag** was treated with CH₃I (5.0 equiv.) and K₂CO₃ (1.0 equiv.) in CH₃CN. After 14 h at 60 °C, the reaction yielded furan derivative **4a** in 77% yield along with the recovery of **3ag** in 14% yield (Table 3, Entry 1). When the loading of CH₃I

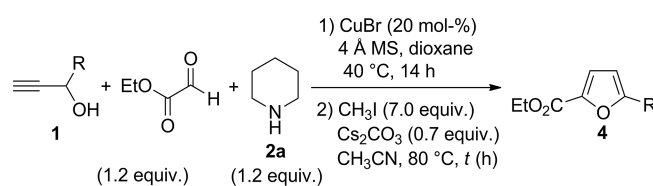
Table 3. Optimization of reaction conditions for preparing **4a**.^[a]



Entry	Base	X [equiv.]	T [°C]	% Yield 4a ^[b]	% Recovery 3ag ^[b]
1	K ₂ CO ₃	5	60	77	14
2	K ₂ CO ₃	7	60	88	5
3	K ₂ CO ₃	10	60	91	1
4	Cs ₂ CO ₃	10	60	94	2
5	Li ₂ CO ₃	10	60	74	0
6	K ₂ CO ₃	10	80	93	0
7	Cs ₂ CO ₃	10	80	96	0

[a] The reactions were carried with **3ag** (1.0 mmol) in CH₃CN (2 mL). [b] NMR yield.

Table 4. The scope of the three-component formation of 2,5-disubstituted furans.^[a]



Entry	R	t [h]	% Yield 4 ^[b]
1	H (1j)	19	50 (4b)
2	Me (1g)	17.5	56 (4a)
3	<i>n</i> -C ₅ H ₁₁ (1h)	19	65 (4c)
4 ^[c]	<i>n</i> -C ₅ H ₁₁ (1h)	19	56 (4c)
5	Bn (1i)	19	64 (4d)
6 ^[c]	Bn (1i)	19	60 (4d)
7	Ph (1k)	18.5	57 (4e)
8 ^[c]	Ph (1k)	18.5	61 (4e)
9	2-naphthyl (1l)	19	58 (4f)
10	2-furyl (1m)	18.5	58 (4g)
11	(<i>E</i>)-styryl (1n)	18.5	62 (4h)
12	(<i>E</i>)-hex-1-en-1-yl (1o)	18.5	64 (4i)
13 ^[c]	(<i>E</i>)-hex-1-en-1-yl (1o)	18.5	58 (4i)

[a] Reagents and conditions: (step 1) **1** (1.0 mmol), ethyl glyoxalate (1.2 mmol), **2** (1.2 mmol), and MS (4 Å, 300 mg) in dioxane (3 mL); (step 2) CH₃I (7.0 mmol), Cs₂CO₃ (0.7 mmol), and CH₃CN (5 mL). [b] Isolated yield. [c] K₂CO₃ was used as the base.

was increased to 10.0 equiv., a higher yield of **4a** was observed (Table 3, Entry 3). Further investigations of the base and reaction temperature suggest that the conditions reported in Entry 7 of Table 3 were most effective.

Subsequently, an efficient two-step sequence to prepare furan derivatives **4a** from propargylic alcohols **1g**, ethyl glyoxalate, and piperidine **2a** was developed. After a simple filtration to remove the copper catalyst, the crude 2,5-dihydrofuran derivative **3ag** was then treated with 0.7 equiv. of Cs₂CO₃ and 7.0 equiv. of CH₃I in CH₃CN at 80 °C for 17.5 h to afford the corresponding product **4a** in 56% overall yield (Table 4, Entry 2). To demonstrate the generality of this protocol, we extended the scope to various propargylic alcohols. As shown in Table 4, all products were obtained in good yields. In some cases, K₂CO₃ was found to be equally efficient in this transformation.

Conclusions

In summary, we have developed a simple, efficient, and mild synthesis of 2,5-dihydrofurans by employing a copper-catalyzed cascade three-component reaction with readily available propargylic alcohols, ethyl glyoxalate, and amines. The 2,5-disubstituted furans can also be prepared by a similar domino three-component reaction followed by a CH₃I-promoted aromatization. Further investigations including practical applications of this method are currently underway in our laboratory.

Experimental Section

General Methods: All reactions were carried out in oven-dried Schlenk tubes. CuBr (98%) was purchased from Acros and kept in a glove box, and ethyl glyoxalate (50% in toluene) was purchased from Alfa Aesar. Molecular sieves (4 Å) were purchased from Alfa Aesar and kept in glove box after activation. (To activate, the molecular sieves were heated at 450 °C for 10 h in a Muffle furnace, removed after cooling to 200 °C, and then kept in a glove box to cool to room temperature). Dioxane was dried by using sodium wire with benzophenone as the indicator and then distilled freshly before use. CH₃CN was dried with calcium hydride before distillation. Other reagents were used as received without further treatment. The reported temperatures refer to the temperature of the oil bath.

Typical Procedure for the Synthesis of 2-(Ethoxycarbonyl)-5,5-dimethyl-2-(piperidin-1-yl)-2,5-dihydrofuran (3aa**):** To a flame-dried Schlenk tube were added CuBr (98% purity, 29.2 mg, 0.2 mmol) and MS (4 Å, 300.0 mg) under Ar. Then, **1a** (84.1 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.1 mg,

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1.2 mmol) in dioxane (1.0 mL), and **2a** (102.5 mg, 1.2 mmol) in dioxane (1.0 mL) were added sequentially under Ar. The resulting mixture was then stirred at 40 °C until the reaction reached completion, as monitored by TLC (14 h). The crude reaction mixture was filtered through a short pad of silica gel [diethyl ether (30 mL)]. After evaporation of the filtrate, the residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate, 20:1) to afford **3aa** (161.5 mg, 64%) as a liquid. ¹H NMR (300 MHz, CDCl₃): δ = 5.96 (d, *J* = 5.7 Hz, 1 H, =CH), 5.64 (d, *J* = 5.7 Hz, 1 H, =CH), 4.37–4.16 (m, 2 H, OCH₂), 2.72–2.61 (m, 2 H, NCH₂), 2.50–2.40 (m, 2 H, NCH₂), 1.70–1.54 (m, 4 H, 2 CH₂), 1.50–1.35 (m, 8 H, CH₂ and 2 CH₃), 1.29 (t, *J* = 7.1 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 171.2, 139.6, 125.6, 106.4, 87.7, 61.2, 47.4, 27.5, 26.9, 25.8, 24.2, 14.0 ppm. MS (ESI): *m/z* = 254 [M + H]⁺, 276 [M + Na]⁺. IR (neat): ν̄ = 2975, 2934, 2854, 2820, 1747, 1467, 1454, 1444, 1361, 1336, 1311, 1248, 1216, 1172, 1120, 1093, 1081, 1032 cm⁻¹. HRMS (ESI): calcd. for C₁₄H₂₄NO₃ [M + H]⁺ 254.1751; found 254.1754.

2-(Ethoxycarbonyl)-5,5-diethyl-2-(piperidin-1-yl)-2,5-dihydrofuran (3ab): By following the same procedure as that described for **3aa**, the reaction of CuBr (98% purity, 29.2 mg, 0.2 mmol), MS (4 Å, 300.2 mg), **1b** (98% purity, 115.3 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.7 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (102.0 mg, 1.2 mmol) in dioxane (1.0 mL) gave the crude product, which was purified by column chromatography (petroleum ether/ethyl acetate, 20:1) to afford **3ab** (163.7 mg, 58%) as a liquid. ¹H NMR (300 MHz, CDCl₃): δ = 6.01 (d, *J* = 6.0 Hz, 1 H, =CH), 5.73 (d, *J* = 6.0 Hz, 1 H, =CH), 4.33–4.16 (m, 2 H, OCH₂), 2.73–2.61 (m, 2 H, NCH₂), 2.52–2.40 (m, 2 H, NCH₂), 1.80–1.50 (m, 8 H, 4 CH₂), 1.50–1.38 (m, 2 H, CH₂), 1.28 (t, *J* = 7.1 Hz, 3 H, CH₃), 0.96 (t, *J* = 7.5 Hz, 3 H, CH₃), 0.85 (t, *J* = 7.7 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 171.1, 137.7, 126.3, 105.7, 93.5, 61.1, 47.6, 29.9, 29.5, 26.0, 24.4, 14.1, 8.7, 8.4 ppm. MS (ESI): *m/z* = 304 [M + Na]⁺. IR (neat): ν̄ = 2964, 2935, 2879, 2853, 2819, 1748, 1456, 1445, 1383, 1311, 1274, 1256, 1226, 1206, 1164, 1119, 1085, 1061, 1034 cm⁻¹. HRMS (ESI): calcd. for C₁₆H₂₈NO₃ [M + H]⁺ 282.2064; found 282.2070.

2-(Ethoxycarbonyl)-5-ethyl-5-methyl-2-(piperidin-1-yl)-2,5-dihydrofuran (3ac): By following the same procedure as that described for **3aa**, the reaction of CuBr (98% purity, 29.2 mg, 0.2 mmol), MS (4 Å, 300.1 mg), **1c** (98% purity, 101.0 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.7 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (102.3 mg, 1.2 mmol) in dioxane (1.0 mL) gave the crude product, which was purified by column chromatography (petroleum ether/ethyl acetate, 10:1) to afford **3ac** (159.3 mg, 59%; mixture of two diastereomers, 1.26:1 *dr*) as a liquid. ¹H NMR (300 MHz, CDCl₃): δ = 6.03–5.93 (m, 1 H, =CH), 5.73–5.64 (m, 1 H, =CH), 4.39–4.15 (m, 2 H, OCH₂), 2.73–2.59 (m, 2 H, NCH₂), 2.52–2.38 (m, 2 H, NCH₂), 1.76–1.51 (m, 6 H, 3 CH₂), 1.50–1.38 (m, 2 H, CH₂), 1.37–1.23 (m, 6 H, 2 CH₃), [0.99 (t, *J* = 7.5 Hz, 1.33 H, minor isomer), 0.90 (t, *J* = 7.4 Hz, 1.67 H, major isomer), 3 H, CH₃] ppm. MS (ESI): *m/z* = 268 [M + H]⁺, 290 [M + Na]⁺. IR (neat): ν̄ = 2934, 2853, 2819, 1748, 1627, 1454, 1369, 1256, 1231, 1211, 1168, 1119, 1093, 1083, 1033, 1011 cm⁻¹. HRMS (ESI): calcd. for C₁₅H₂₆NO₃ [M + H]⁺ 268.1907; found 268.1911.

6-(Ethoxycarbonyl)-6-(piperidin-1-yl)-5-oxaspiro[3.4]oct-7-ene (3ad): By following the same procedure as that described for **3aa**, the reaction of CuBr (98% purity, 29.1 mg, 0.2 mmol), MS (4 Å, 300.1 mg), **1d** (95.7 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.4 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (102.1 mg, 1.2 mmol) in dioxane (1.0 mL) gave the crude product, which was purified by column chromatography (petro-

leum ether/ethyl acetate, from 15:1 to 10:1) to afford **3ad** (151.3 mg, 57%) as a liquid. ¹H NMR (300 MHz, CDCl₃): δ = 6.25 (d, *J* = 5.4 Hz, 1 H, =CH), 5.66 (d, *J* = 5.7 Hz, 1 H, =CH), 4.33–4.14 (m, 2 H, OCH₂), 2.70–2.32 (m, 6 H, 2 NCH₂ and CH₂), 2.25–2.08 (m, 2 H, CH₂), 1.81–1.38 (m, 8 H, 4 CH₂), 1.27 (t, *J* = 6.9 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 170.6, 136.6, 125.7, 106.6, 89.8, 61.3, 47.1, 35.3, 35.2, 25.6, 24.2, 14.0, 11.4 ppm. MS (ESI): *m/z* = 266 [M + H]⁺. IR (neat): ν̄ = 2981, 2934, 2852, 2820, 1748, 1620, 1468, 1453, 1344, 1312, 1249, 1221, 1186, 1153, 1118, 1092, 1075, 1031 cm⁻¹. HRMS (ESI): calcd. for C₁₅H₂₄NO₃ [M + H]⁺ 266.1751; found 266.1753.

2-(Ethoxycarbonyl)-2-(piperidin-1-yl)-1-oxaspiro[4.4]non-3-ene (3ae): By following the same procedure as that described for **3aa**, the reaction of CuBr (98% purity, 29.5 mg, 0.2 mmol), MS (4 Å, 300.0 mg), **1e** (98% purity, 112.9 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.7 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (102.5 mg, 1.2 mmol) in dioxane (1.0 mL) gave the crude product, which was purified by column chromatography (petroleum ether/ethyl acetate, 20:1) to afford **3ae** (176.6 mg, 63%) as a liquid. ¹H NMR (300 MHz, CDCl₃): δ = 5.94 (d, *J* = 5.7 Hz, 1 H, =CH), 5.64 (d, *J* = 5.7 Hz, 1 H, =CH), 4.37–4.11 (m, 2 H, OCH₂), 2.68–2.57 (m, 2 H, NCH₂), 2.47–2.36 (m, 2 H, NCH₂), 2.14–2.00 (m, 1 H), 1.96–1.80 (m, 3 H), 1.78–1.51 (m, 8 H, 4 CH₂), 1.49–1.37 (m, 2 H, CH₂), 1.28 (t, *J* = 7.1 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 171.2, 138.1, 125.6, 106.2, 97.8, 61.2, 47.4, 38.5, 38.1, 25.7, 24.7, 24.6, 24.3, 14.0 ppm. MS (ESI): *m/z* = 302 [M + Na]⁺. IR (neat): ν̄ = 2934, 2852, 2819, 1747, 1625, 1469, 1444, 1345, 1256, 1233, 1214, 1173, 1121, 1101, 1077, 1034, 1006 cm⁻¹. HRMS (ESI): calcd. for C₁₆H₂₆NO₃ [M + H]⁺ 280.1907; found 280.1912.

2-(Ethoxycarbonyl)-2-(piperidin-1-yl)-1-oxaspiro[4.5]dec-3-ene (3af): By following the same procedure as that described for **3aa**, the reaction of CuBr (98% purity, 29.3 mg, 0.2 mmol), MS (4 Å, 300.1 mg), **1f** (97% purity, 127.3 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 244.9 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (102.1 mg, 1.2 mmol) in dioxane (1.0 mL) gave the crude product, which was purified by column chromatography (petroleum ether/ethyl acetate, 20:1) to afford **3af** (182.5 mg, 62%) as a liquid. ¹H NMR (300 MHz, CDCl₃): δ = 6.13 (d, *J* = 6.0 Hz, 1 H, =CH), 5.68 (d, *J* = 6.0 Hz, 1 H, =CH), 4.34–4.13 (m, 2 H, OCH₂), 2.70–2.59 (m, 2 H, NCH₂), 2.49–2.39 (m, 2 H, NCH₂), 1.87–1.35 (m, 16 H, 8 CH₂), 1.28 (t, *J* = 7.2 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 171.5, 138.0, 126.1, 105.7, 89.7, 61.2, 47.5, 37.2, 36.4, 25.8, 25.3, 24.3, 23.3, 23.2, 14.0 ppm. MS (ESI): *m/z* = 294 [M + H]⁺. IR (neat): ν̄ = 2964, 2935, 2879, 2853, 2819, 1748, 1627, 1455, 1445, 1383, 1311, 1256, 1226, 1206, 1164, 1119, 1094, 1085, 1062, 1035 cm⁻¹. HRMS (ESI): calcd. for C₁₇H₂₈NO₃ [M + H]⁺ 294.2064; found 294.2069.

2-(Ethoxycarbonyl)-5-methyl-2-(piperidin-1-yl)-2,5-dihydrofuran (3ag): By following the same procedure as that described for **3aa**, the reaction of CuBr (98% purity, 29.2 mg, 0.2 mmol), MS (4 Å, 300.1 mg), **1g** (69.2 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.1 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (102.3 mg, 1.2 mmol) in dioxane (1.0 mL) gave the crude product, which was purified by column chromatography [petroleum ether (400 mL)/ethyl acetate (40 mL)/Et₃N (0.3 mL)] to afford **3ag** (133.0 mg, 56%; mixture of two diastereomers, 1.5:1 *dr*) as a liquid. ¹H NMR (300 MHz, CDCl₃): δ = [6.06 (dd, *J*₁ = 6.0 Hz, *J*₂ = 1.5 Hz, 0.40 H, minor isomer), 5.98 (dd, *J*₁ = 5.9 Hz, *J*₂ = 1.4 Hz, 0.60 H, major isomer), 1 H, =CH], 5.75–5.69 (m, 1 H, =CH), 5.07–4.95 (m, 1 H, CH), 4.36–4.15 (m, 2 H, OCH₂), 2.76–2.60 (m, 2 H, NCH₂), 2.51–2.39 (m, 2 H, NCH₂), 1.70–1.51 (m, 4 H, 2 CH₂),

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1.49–1.39 (m, 2 H, CH₂), 1.38–1.23 (m, 6 H, 2 CH₃) ppm. MS (ESI): *m/z* = 240 [M + H]⁺, 262 [M + Na]⁺. IR (neat): $\tilde{\nu}$ = 3060, 2982, 2970, 2933, 2882, 2850, 2822, 2759, 1730, 1466, 1444, 1386, 1363, 1346, 1325, 1309, 1273, 1255, 1230, 1184, 1158, 1136, 1116, 1079, 1060, 1030 cm⁻¹. C₁₃H₂₁NO₃ (239.31): calcd. C 65.25, H 8.84, N 5.85; found C 65.35, H 8.91, N 5.86.

Gram-Scale Preparation of 2-(Ethoxycarbonyl)-5-methyl-2-(piperidin-1-yl)-2,5-dihydrofuran (3ag): To a flame-dried Schlenk tube were added CuBr (98% purity, 218.9 mg, 1.5 mmol) and MS (4 Å, 1.5001 g) under Ar. Then, **1g** (1.0538 g, 15 mmol) in THF (15 mL), ethyl glyoxalate (50% in toluene, 3.6758 g, 18 mmol) in THF (15 mL), and **2a** (1.5300 g, 18 mmol) in THF (10 mL) were added sequentially under Ar. The resulting mixture was stirred at 40 °C until the reaction reached completion, as monitored by TLC (14 h). The crude reaction mixture was filtered through a short pad of silica gel [diethyl ether (50 mL)]. After evaporation of the filtrate, the residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate, 10:1) to afford **3ag** (1.9634 g, 55%; mixture of two diastereomers, 1.54:1 *dr*) as a liquid. ¹H NMR (400 MHz, CDCl₃): δ = [6.05 (d, *J* = 6.0 Hz, 0.39 H, minor isomer), 5.98 (d, *J* = 6.0 Hz, 0.60 H, major isomer), 1 H, =CH], 5.76–5.68 (m, 1 H, =CH), 5.07–4.94 (m, 1 H, CH), 4.35–4.16 (m, 2 H, OCH₂), 2.76–2.60 (m, 2 H, NCH₂), 2.52–2.40 (m, 2 H, NCH₂), 1.69–1.51 (m, 4 H, 2 CH₂), 1.49–1.39 (m, 2 H, CH₂), 1.38–1.23 (m, 6 H, 2 CH₃) ppm.

2-(Ethoxycarbonyl)-5-pentyl-2-(piperidin-1-yl)-2,5-dihydrofuran (3ah): By following the same procedure as that described for **3aa**, the reaction of CuBr (98% purity, 29.0 mg, 0.2 mmol), MS (4 Å, 300.1 mg), **1h** (126.0 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.3 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (102.1 mg, 1.2 mmol) in dioxane (1.0 mL) gave the crude product, which was purified by column chromatography (petroleum ether/ethyl acetate, 10:1) to afford **3ah** (193.3 mg, 65%; mixture of two diastereomers, 1.38:1 *dr*) as a liquid. ¹H NMR (400 MHz, CDCl₃): δ = [6.08 (dd, *J*₁ = 6.0 Hz, *J*₂ = 1.6 Hz, 0.42 H, minor isomer), 6.03 (dd, *J*₁ = 5.8 Hz, *J*₂ = 1.4 Hz, 0.58 H, major isomer), 1 H, =CH], [5.75 (dd, *J*₁ = 6.0 Hz, *J*₂ = 2.4 Hz, 0.42 H, minor isomer), 5.72 (dd, *J*₁ = 5.8 Hz, *J*₂ = 2.6 Hz, 0.58 H, major isomer), 1 H, =CH], 4.87–4.82 (m, 1 H, CH), 4.32–4.16 (m, 2 H, OCH₂), 2.74–2.61 (m, 2 H, NCH₂), 2.51–2.42 (m, 2 H, NCH₂), 1.75–1.48 (m, 6 H, 3 CH₂), 1.47–1.24 (m, 11 H, 4 CH₂ and CH₃), 0.94–0.84 (m, 3 H, CH₃) ppm. MS (ESI): *m/z* = 296 [M + H]⁺. IR (neat): $\tilde{\nu}$ = 2931, 2855, 1747, 1467, 1454, 1444, 1384, 1365, 1330, 1310, 1255, 1222, 1182, 1137, 1092, 1067, 1031 cm⁻¹. C₁₇H₂₉NO₃ (295.42): calcd. C 69.12, H 9.89, N 4.74; found C 68.96, H 10.06, N 4.96.

5-Benzyl-2-(ethoxycarbonyl)-2-(piperidin-1-yl)-2,5-dihydrofuran (3ai): By following the same procedure as that described for **3aa**, the reaction of CuBr (98% purity, 29.3 mg, 0.2 mmol), MS (4 Å, 300.1 mg), **1i** (146.4 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.1 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (103.0 mg, 1.2 mmol) in dioxane (1.0 mL) gave the crude product, which was purified by column chromatography (petroleum ether/ethyl acetate, 10:1) to afford **3ai** (179.4 mg, 57%; mixture of two diastereomers, 1.08:1 *dr*) as a liquid. ¹H NMR (400 MHz, CDCl₃): δ = 7.32–7.18 (m, 5 H, Ar-H), [6.01 (dd, *J*₁ = 6.0 Hz, *J*₂ = 1.2 Hz, 0.47 H, minor isomer), 5.97 (dd, *J*₁ = 5.8 Hz, *J*₂ = 1.8 Hz, 0.52 H, major isomer), 1 H, =CH], [5.78 (dd, *J*₁ = 5.8 Hz, *J*₂ = 2.2 Hz, minor isomer, 0.48 H), 5.75 (dd, *J*₁ = 5.8 Hz, *J*₂ = 2.6 Hz, 0.52 H, major isomer), 1 H, =CH], 5.09–4.98 (m, 1 H, CH), 4.36–4.15 (m, 2 H, OCH₂), 3.25–3.13 (m, 1 H, one proton from ArCH₂), 2.79–2.63 (m, 3 H, one proton of ArCH₂ and

NCH₂), 2.51–2.40 (m, 2 H, NCH₂), 1.68–1.51 (m, 4 H, 2 CH₂), 1.49–1.38 (m, 2 H, CH₂), [1.32 (t, *J* = 7.0 Hz, 1.49 H, minor isomer), 1.26 (t, *J* = 7.2 Hz, 1.75 H, major isomer), 3 H, CH₃] ppm. MS (ESI): *m/z* = 316 [M + H]⁺. IR (neat): $\tilde{\nu}$ = 3055, 2928, 1737, 1494, 1467, 1452, 1349, 1331, 1313, 1273, 1255, 1226, 1190, 1136, 1111, 1092, 1078, 1063, 1051, 1026 cm⁻¹. HRMS (ESI): calcd. for C₁₉H₂₆NO₃ [M + H]⁺ 316.1907; found 316.1907.

2-[5,6-Dihydropyridin-1(2H)-yl]-2-(ethoxycarbonyl)-5,5-dimethyl-2,5-dihydrofuran (3ba): By following the same procedure as that described for **3aa**, the reaction of CuBr (98% purity, 29.2 mg, 0.2 mmol), MS (4 Å, 300.0 mg), **1a** (83.9 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.9 mg, 1.2 mmol) in dioxane (1.0 mL), and **2b** (100.0 mg, 1.2 mmol) in dioxane (1.0 mL) gave the crude product, which was purified by column chromatography (petroleum ether/ethyl acetate, from 10:1 to 5:1) to afford **3ba** (156.0 mg, 62%) as a liquid. ¹H NMR (300 MHz, CDCl₃): δ = 5.99 (d, *J* = 5.4 Hz, 1 H, =CH), 5.79–5.62 (m, 3 H, 3 =CH), 4.37–4.17 (m, 2 H, OCH₂), 3.23 (br. d, *J* = 16.2 Hz, 1 H, one proton from NCH₂C=), 3.08 (br. d, *J* = 16.2 Hz, 1 H, one proton from NCH₂C=), 2.82–2.72 (m, 1 H, one proton from NCH₂), 2.70–2.59 (m, 1 H, one proton from NCH₂), 2.30–2.01 (m, 2 H, CH₂), 1.43 (s, 3 H, CH₃), 1.40 (s, 3 H, CH₃), 1.30 (t, *J* = 7.1 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 171.0, 140.0, 125.3, 125.1, 124.9, 105.8, 88.0, 61.4, 45.5, 43.8, 27.6, 27.0, 26.4, 14.1 ppm. MS (ESI): *m/z* = 274 [M + Na]⁺. IR (neat): $\tilde{\nu}$ = 3033, 2974, 2833, 1747, 1660, 1627, 1464, 1447, 1380, 1361, 1336, 1299, 1250, 1230, 1211, 1160, 1132, 1090, 1044, 1031 cm⁻¹. HRMS (ESI): calcd. for C₁₄H₂₂NO₃ [M + H]⁺ 252.1594; found 252.1602.

2-(Ethoxycarbonyl)-5,5-dimethyl-2-(pyrrolidin-1-yl)-2,5-dihydrofuran (3ca): By following the same procedure as that described for **3aa**, the reaction of CuBr (98% purity, 29.0 mg, 0.2 mmol), MS (4 Å, 300.0 mg), **1a** (84.1 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 244.2 mg, 1.2 mmol) in dioxane (1.0 mL), and **2c** (85.7 mg, 1.2 mmol) in dioxane (1.0 mL) gave the crude product, which was purified by column chromatography [petroleum ether (400 mL)/ethyl acetate (40 mL)/Et₃N (0.3 mL)] to afford **3ca** (145.1 mg, 61%) as a liquid. ¹H NMR (300 MHz, CDCl₃): δ = 5.94 (d, *J* = 5.7 Hz, 1 H, =CH), 5.74 (d, *J* = 5.7 Hz, 1 H, =CH), 4.36–4.19 (m, 2 H, OCH₂), 2.84–2.62 (m, 4 H, 2 NCH₂), 1.86–1.72 (m, 4 H, 2 CH₂), 1.41 (s, 3 H, CH₃), 1.40 (s, 3 H, CH₃), 1.31 (t, *J* = 7.2 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 170.8, 139.0, 126.2, 103.0, 87.4, 61.2, 46.0, 27.8, 26.9, 23.7, 14.0 ppm. MS (ESI): *m/z* = 240 [M + H]⁺. IR (neat): $\tilde{\nu}$ = 2970, 2932, 2873, 1748, 1628, 1462, 1361, 1338, 1242, 1148, 1086, 1040, 1029, 1003 cm⁻¹. HRMS (ESI): calcd. for C₁₃H₂₂NO₃ [M + H]⁺ 240.1594; found 240.1596.

2-(2,5-Dihydro-1H-pyrrol-1-yl)-2-(ethoxycarbonyl)-5,5-dimethyl-2,5-dihydrofuran (3da): By following the same procedure as that described for **3aa**, the reaction of CuBr (98% purity, 29.2 mg, 0.2 mmol), MS (4 Å, 300.0 mg), **1a** (84.7 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.0 mg, 1.2 mmol) in dioxane (1.0 mL), and **2d** (83.8 mg, 1.2 mmol) in dioxane (1.0 mL) gave the crude product, which was purified by column chromatography (petroleum ether/ethyl acetate, 10:1) to afford **3da** (152.5 mg, 64%) as a liquid. ¹H NMR (300 MHz, CDCl₃): δ = 5.97 (d, *J* = 6.0 Hz, 1 H, =CH), 5.77 (d, *J* = 6.0 Hz, 1 H, =CH), 5.73 (s, 2 H, 2 CH=), 4.35–4.20 (m, 2 H, OCH₂), 3.77–3.58 (m, 4 H, 2 NCH₂), 1.41 (s, 6 H, 2 CH₃), 1.31 (t, *J* = 7.1 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 170.7, 139.6, 126.6, 126.3, 102.9, 87.6, 61.4, 53.1, 27.9, 27.1, 14.1 ppm. MS (ESI): *m/z* = 260 [M + Na]⁺. IR (neat): $\tilde{\nu}$ = 3071, 2977, 2933, 2864, 2831, 1742, 1626, 1466, 1445, 1359, 1343, 1301, 1263, 1239, 1191, 1156, 1085, 1032, 1010 cm⁻¹.

HRMS (ESI): calcd. for $C_{13}H_{20}NO_3$ $[M + H]^+$ 238.1438; found 238.1439.

2-(Dibutylamino)-2-(ethoxycarbonyl)-5,5-dimethyl-2,5-dihydrofuran (3ea): By following the same procedure as that described for **3aa**, the reaction of CuBr (98% purity, 29.4 mg, 0.2 mmol), MS (4 Å, 300.1 mg), **1a** (83.1 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.0 mg, 1.2 mmol) in dioxane (1.0 mL), and **2e** (155.0 mg, 1.2 mmol) in dioxane (1.0 mL) gave the crude product, which was purified by column chromatography (petroleum ether/ethyl acetate, 40:1) to afford **3ea** (201.1 mg, 68%) as a liquid. 1H NMR (300 MHz, $CDCl_3$): δ = 5.92 (d, J = 5.7 Hz, 1 H, =CH), 5.67 (d, J = 5.7 Hz, 1 H, =CH), 4.28–4.15 (m, 2 H, OCH_2), 2.70–2.44 (m, 4 H, 2 NCH_2), 1.50–1.34 (m, 10 H, 2 CH_2 and 2 CH_3), 1.33–1.18 (m, 7 H, 2 CH_2 and CH_3), 0.88 (t, J = 7.4 Hz, 6 H, 2 CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6, 139.2, 126.9, 107.1, 87.1, 61.1, 49.4, 31.7, 27.6, 27.0, 20.4, 14.0, 13.9 ppm. MS (ESI): m/z = 298 $[M + H]^+$. IR (neat): $\tilde{\nu}$ = 2958, 2933, 2872, 1748, 1627, 1464, 1378, 1361, 1335, 1244, 1224, 1182, 1124, 1083, 1066, 1034 cm^{-1} . HRMS (ESI): calcd. for $C_{17}H_{32}NO_3$ $[M + H]^+$ 298.2377; found 298.2383.

2-(Diallylamino)-2-(ethoxycarbonyl)-5,5-dimethyl-2,5-dihydrofuran (3fa): By following the same procedure as that described for **3aa**, the reaction of CuBr (98% purity, 29.2 mg, 0.2 mmol), MS (4 Å, 300.1 mg), **1a** (84.5 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.1 mg, 1.2 mmol) in dioxane (1.0 mL), and **2f** (117.0 mg, 1.2 mmol) in dioxane (1.0 mL) gave the crude product, which was purified by column chromatography (petroleum ether/ethyl acetate, 40:1) to afford **3fa** (171.8 mg, 65%) as a liquid. 1H NMR (300 MHz, $CDCl_3$): δ = 5.95 (d, J = 5.7 Hz, 1 H, =CH), 5.93–5.78 (m, 2 H, 2 =CH), 5.69 (d, J = 5.7 Hz, 1 H, =CH), 5.13 (d, J = 17.1 Hz, 2 H, 2 =CH), 5.04 (d, J = 9.9 Hz, 2 H, 2 =CH), 4.28–4.12 (m, 2 H, OCH_2), 3.32 (dd, J_1 = 15.2 Hz, J_2 = 5.9 Hz, 2 H, 2 \times one proton of NCH_2), 3.21 (dd, J_1 = 15.3 Hz, J_2 = 6.6 Hz, 2 H, 2 \times one proton of NCH_2), 1.393 (s, 3 H, CH_3), 1.385 (s, 3 H, CH_3), 1.28 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 139.7, 136.9, 126.5, 116.2, 106.2, 87.5, 61.2, 51.3, 27.6, 27.1, 14.0 ppm. MS (ESI): m/z = 288 $[M + Na]^+$. IR (neat): $\tilde{\nu}$ = 3077, 2976, 2931, 2846, 1749, 1642, 1463, 1447, 1418, 1361, 1337, 1259, 1234, 1172, 1086, 1033 cm^{-1} . HRMS (ESI): calcd. for $C_{15}H_{24}NO_3$ $[M + H]^+$ 266.1751; found 266.1755.

2-(Ethoxycarbonyl)-2-(isoindolin-2-yl)-5,5-dimethyl-2,5-dihydrofuran (3ga): By following the same procedure as that described for **3aa**, the reaction of CuBr (98% purity, 29.8 mg, 0.2 mmol), MS (4 Å, 300.2 mg), **1a** (85.0 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.7 mg, 1.2 mmol) in dioxane (1.0 mL), and **2g** (143.1 mg, 1.2 mmol) in dioxane (1.0 mL) gave the crude product, which was purified by column chromatography (petroleum ether/ethyl acetate, 10:1) to afford **3ga** (176.0 mg, 61%) as a liquid. 1H NMR (300 MHz, $CDCl_3$): δ = 7.18 (s, 4 H, Ar-H), 6.03 (d, J = 5.7 Hz, 1 H, =CH), 5.85 (d, J = 5.7 Hz, 1 H, =CH), 4.30 (q, J = 7.1 Hz, 2 H, OCH_2), 4.25–4.17 (m, 2 H, $ArCH_2$), 4.13–4.04 (m, 2 H, $ArCH_2$), 1.43 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 1.33 (t, J = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 139.9, 139.0, 126.7, 126.2, 122.4, 102.9, 87.9, 61.6, 52.2, 28.0, 27.3, 14.2 ppm. MS (ESI): m/z = 310 $[M + Na]^+$. IR (neat): $\tilde{\nu}$ = 2972, 2834, 1747, 1463, 1442, 1378, 1362, 1338, 1327, 1296, 1277, 1239, 1197, 1181, 1171, 1141, 1085, 1064, 1032 cm^{-1} . HRMS (ESI): calcd. for $C_{17}H_{22}NO_3$ $[M + H]^+$ 288.1594; found 288.1601.

2-[3,4-Dihydroisoquinolin-2(1H)-yl]-2-(ethoxycarbonyl)-5,5-dimethyl-2,5-dihydrofuran (3ha): By following the same procedure as that described for **3aa**, the reaction of CuBr (98% purity, 29.4 mg, 0.2 mmol), MS (4 Å, 300.1 mg), **1a** (83.6 mg, 1.0 mmol) in dioxane

(1.0 mL), ethyl glyoxalate (50% in toluene, 245.0 mg, 1.2 mmol) in dioxane (1.0 mL), and **2h** (159.5 mg, 1.2 mmol) in dioxane (1.0 mL) gave the crude product, which was purified by column chromatography (petroleum ether/ethyl acetate, from 20:1 to 10:1) to afford **3ha** (201.7 mg, 67%) as a liquid. 1H NMR (300 MHz, $CDCl_3$): δ = 7.14–7.04 (m, 3 H, Ar-H), 7.03–6.95 (m, 1 H, Ar-H), 6.05 (d, J = 6.0 Hz, 1 H, =CH), 5.75 (d, J = 5.4 Hz, 1 H, =CH), 4.38–4.19 (m, 2 H, OCH_2), 3.92 (d, J = 14.7 Hz, 1 H, one proton of $ArCH_2$), 3.74 (d, J = 14.7 Hz, 1 H, one proton of $ArCH_2$), 3.02–2.79 (m, 4 H, 2 CH_2), 1.45 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 1.30 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9, 140.3, 134.6, 134.2, 128.5, 126.6, 125.8, 125.4, 125.3, 105.7, 88.2, 61.5, 48.7, 44.7, 29.5, 27.6, 27.1, 14.1 ppm. MS (ESI): m/z = 324 $[M + Na]^+$. IR (neat): $\tilde{\nu}$ = 2975, 2928, 2831, 1746, 1498, 1464, 1384, 1361, 1335, 1275, 1247, 1229, 1148, 1087, 1075, 1034, 1003 cm^{-1} . HRMS (ESI): calcd. for $C_{18}H_{24}NO_3$ $[M + H]^+$ 302.1751; found 302.1749.

Typical Procedure for the Synthesis of 2-(Ethoxycarbonyl)-5-methylfuran (4a): To a flame-dried Schlenk tube were added CuBr (98% purity, 29.3 mg, 0.2 mmol) and MS (4 Å, 300.2 mg) under Ar. Then, **1g** (70.2 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.3 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (102.4 mg, 1.2 mmol) in dioxane (1.0 mL) were added sequentially under Ar. The resulting mixture was stirred at 40 °C until the reaction reached completion, as monitored by TLC (14 h). The crude reaction mixture was filtered through a short pad of silica gel [diethyl ether (30 mL)]. After evaporation of the filtrate, the crude product was used in the next step without further treatment. To another flame-dried Schlenk tube were added CS_2CO_3 (228.7 mg, 0.7 mmol), the crude product in CH_3CN (4.0 mL), and CH_3I (d = 2.28 $g mL^{-1}$, 0.44 mL, 7.0 mmol) sequentially under Ar. The mixture was stirred at 80 °C until the reaction reached completion, as monitored by TLC (17.5 h). The crude reaction mixture was filtered through a short pad of silica gel [diethyl ether (30 mL)]. After evaporation of the filtrate, the residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate, 40:1) to afford **4a** (85.7 mg, 56%) as a liquid. 1H NMR (300 MHz, $CDCl_3$): δ = 7.08 (d, J = 3.3 Hz, 1 H, CH=), 6.12 (d, J = 3.3 Hz, 1 H, CH=), 4.35 (q, J = 7.1 Hz, 2 H, OCH_2), 2.38 (s, 3 H, CH_3), 1.37 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7, 156.9, 143.1, 119.1, 108.2, 60.5, 14.2, 13.8 ppm. MS (EI): m/z (%) = 154 (27.95) $[M]^+$, 109 (100). IR (neat): $\tilde{\nu}$ = 1716, 1599, 1533, 1447, 1371, 1299, 1259, 1209, 1135, 1019 cm^{-1} . HRMS (EI): calcd. for $C_8H_{10}O_3$ $[M]^+$ 154.0630; found 154.0632.

2-(Ethoxycarbonyl)furan (4b): By following the same procedure as that described for **4a**, the reaction of CuBr (98% purity, 29.2 mg, 0.2 mmol), MS (4 Å, 300.1 mg), **1j** (56.1 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.1 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (102.3 mg, 1.2 mmol) in dioxane (1.0 mL) afforded the 2,5-dihydrofuran intermediate, which was treated with CS_2CO_3 (228.3 mg, 0.7 mmol), CH_3I (d = 2.28 $g mL^{-1}$, 0.44 mL, 7.0 mmol), and CH_3CN (4.0 mL) to give the crude product. Purification by column chromatography (from petroleum ether to petroleum ether/ethyl acetate, 100:1) afforded **4b** (70.1 mg, 50%) as a liquid. 1H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, J = 0.6 Hz, 1 H, CH=), 7.18 (d, J = 3.3 Hz, 1 H, CH=), 6.51 (dd, J_1 = 3.3 Hz, J_2 = 1.8 Hz, 1 H, CH=), 4.37 (q, J = 7.1 Hz, 2 H, OCH_2), 1.38 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.6, 146.1, 144.8, 117.6, 111.7, 60.8, 14.2 ppm. MS (EI): m/z (%) = 140 (17.88) $[M]^+$, 44 (100). IR (neat): $\tilde{\nu}$ = 1718, 1581, 1571, 1475, 1400, 1390, 1367, 1295, 1260, 1231, 1182, 1114, 1076, 1009 cm^{-1} . HRMS (EI): calcd. for $C_7H_8O_3$ $[M]^+$ 140.0473; found 140.0474.

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2-(Ethoxycarbonyl)-5-pentylfuran (4c): By following the same procedure as that described for **4a**, the reaction of CuBr (98% purity, 29.4 mg, 0.2 mmol), MS (4 Å, 300.1 mg), **1h** (127.1 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 246.0 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (103.1 mg, 1.2 mmol) in dioxane (1.0 mL) afforded the 2,5-dihydrofuran intermediate, which was treated with Cs₂CO₃ (228.3 mg, 0.7 mmol), CH₃I (*d* = 2.28 g mL⁻¹, 0.44 mL, 7.0 mmol), and CH₃CN (4.0 mL) to give the crude product. Purification by column chromatography (petroleum ether/ethyl acetate, 200:1) afforded **4c** (136.6 mg, 65%) as a liquid. ¹H NMR (300 MHz, CDCl₃): δ = 7.09 (d, *J* = 3.3 Hz, 1 H, CH=), 6.11 (d, *J* = 3.3 Hz, 1 H, CH=), 4.34 (q, *J* = 7.1 Hz, 2 H, OCH₂), 2.68 (t, *J* = 7.8 Hz, 2 H, CH₂), 1.73–1.60 (m, 2 H, CH₂), 1.41–1.25 (m, 7 H, 2 CH₂ and CH₃), 0.90 (t, *J* = 6.8 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 161.4, 158.8, 143.0, 118.9, 107.3, 60.5, 31.2, 28.2, 27.3, 22.2, 14.3, 13.8 ppm. MS (EI): *m/z* (%) = 210 (32.33) [M]⁺, 153 (100). IR (neat): ν̄ = 1717, 1595, 1530, 1520, 1465, 1382, 1368, 1298, 1259, 1204, 1135, 1091, 1014 cm⁻¹. HRMS (EI): calcd. for C₁₂H₁₈O₃ [M]⁺ 210.1256, found 210.1254.

Preparation of 2-(Ethoxycarbonyl)-5-pentylfuran (4c) with K₂CO₃ as the Base: By following the same procedure as that described for **4a**, the reaction of CuBr (98% purity, 29.3 mg, 0.2 mmol), MS (4 Å, 300.1 mg), **1h** (126.1 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.2 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (102.4 mg, 1.2 mmol) in dioxane (1.0 mL) afforded the 2,5-dihydrofuran intermediate, which was treated with K₂CO₃ (97.0 mg, 0.7 mmol), CH₃I (*d* = 2.28 g mL⁻¹, 0.44 mL, 7.0 mmol), and CH₃CN (4.0 mL) to give the crude product. Purification by column chromatography (petroleum ether/ethyl acetate, 200:1) afforded **4c** (116.8 mg, 56%) as a liquid. ¹H NMR (400 MHz, CDCl₃): δ = 7.08 (d, *J* = 4.0 Hz, 1 H, CH=), 6.11 (d, *J* = 3.6 Hz, 1 H, CH=), 4.34 (q, *J* = 7.2 Hz, 2 H, OCH₂), 2.68 (t, *J* = 7.6 Hz, 2 H, CH₂), 1.73–1.63 (m, 2 H, CH₂), 1.40–1.27 (m, 7 H, 2 CH₂ and CH₃), 0.90 (t, *J* = 6.6 Hz, 3 H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 161.4, 158.8, 143.0, 118.9, 107.3, 60.5, 31.2, 28.2, 27.3, 22.2, 14.3, 13.8 ppm.

5-Benzyl-2-(ethoxycarbonyl)furan (4d): By following the same procedure as that described for **4a**, the reaction of CuBr (98% purity, 29.0 mg, 0.2 mmol), MS (4 Å, 300.2 mg), **1i** (146.9 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 246.0 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (102.9 mg, 1.2 mmol) in dioxane (1.0 mL) afforded the 2,5-dihydrofuran intermediate, which was treated with Cs₂CO₃ (228.7 mg, 0.7 mmol), CH₃I (*d* = 2.28 g mL⁻¹, 0.44 mL, 7.0 mmol), and CH₃CN (4.0 mL) to give the crude product. Purification by column chromatography (petroleum ether/ethyl acetate, from 200:1 to 100:1) afforded **4d** (148.4 mg, 64%) as a liquid. ¹H NMR (300 MHz, CDCl₃): δ = 7.36–7.19 (m, 5 H, Ar-H), 7.08 (d, *J* = 3.3 Hz, 1 H, CH=), 6.04 (d, *J* = 3.3 Hz, 1 H, CH=), 4.33 (q, *J* = 7.2 Hz, 2 H, OCH₂), 4.02 (s, 2 H, CH₂), 1.35 (t, *J* = 7.2 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 159.4, 158.8, 143.6, 136.6, 128.8, 128.6, 126.8, 118.9, 108.7, 60.6, 34.6, 14.3 ppm. MS (EI): *m/z* (%) = 230 (55.68) [M]⁺, 157 (100). IR (neat): ν̄ = 1713, 1595, 1518, 1496, 1454, 1383, 1367, 1297, 1205, 1127, 1015 cm⁻¹. HRMS (EI): calcd. for C₁₄H₁₄O₃ [M]⁺ 230.0943; found 230.0941.

Preparation of 5-Benzyl-2-(ethoxycarbonyl)furan (4d) with K₂CO₃ as the Base: By following the same procedure as that described for **4a**, the reaction of CuBr (98% purity, 29.5 mg, 0.2 mmol), MS (4 Å, 300.2 mg), **1i** (146.2 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.2 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (102.4 mg, 1.2 mmol) in dioxane (1.0 mL) afforded the 2,5-dihydrofuran intermediate, which was treated with

K₂CO₃ (97.0 mg, 0.7 mmol), CH₃I (*d* = 2.28 g/mL, 0.44 mL, 7.0 mmol), and CH₃CN (4.0 mL) to give the crude product. Purification by column chromatography (petroleum ether/ethyl acetate, from 200:1 to 100:1) afforded **4d** (138.2 mg, 60%) as a liquid. ¹H NMR (400 MHz, CDCl₃): δ = 7.34–7.27 (m, 2 H, Ar-H), 7.26–7.20 (m, 3 H, Ar-H), 7.07 (d, *J* = 3.2 Hz, 1 H, CH=), 6.05 (d, *J* = 3.2 Hz, 1 H, CH=), 4.33 (q, *J* = 7.2 Hz, 2 H, OCH₂), 4.02 (s, 2 H, CH₂), 1.35 (t, *J* = 7.0 Hz, 3 H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 159.5, 158.8, 143.6, 136.7, 128.8, 128.6, 126.8, 118.9, 108.7, 60.7, 34.7, 14.3 ppm.

2-(Ethoxycarbonyl)-5-phenylfuran (4e): By following the same procedure as that described for **4a**, the reaction of CuBr (98% purity, 29.0 mg, 0.2 mmol), MS (4 Å, 300.2 mg), **1k** (134.7 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.7 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (102.7 mg, 1.2 mmol) in dioxane (1.0 mL) afforded the 2,5-dihydrofuran intermediate, which was treated with Cs₂CO₃ (228.0 mg, 0.7 mmol), CH₃I (*d* = 2.28 g/mL, 0.44 mL, 7.0 mmol), and CH₃CN (4.0 mL) to give the crude product. Purification by column chromatography (petroleum ether/ethyl acetate, 200:1) afforded **4e** (124.2 mg, 57%) as a liquid. ¹H NMR (300 MHz, CDCl₃): δ = 7.80–7.73 (m, 2 H, Ar-H), 7.43–7.28 (m, 3 H, Ar-H), 7.22 (d, *J* = 3.6 Hz, 1 H, CH=), 6.71 (d, *J* = 3.6 Hz, 1 H, CH=), 4.37 (q, *J* = 7.1 Hz, 2 H, OCH₂), 1.38 (t, *J* = 7.2 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 158.7, 157.3, 143.8, 129.4, 128.8, 128.7, 124.7, 119.7, 106.7, 60.7, 14.3 ppm. MS (EI): *m/z* (%) = 216 (100) [M]⁺. IR (neat): ν̄ = 1710, 1573, 1529, 1479, 1449, 1373, 1298, 1270, 1216, 1135, 1017 cm⁻¹. HRMS (EI): calcd. for C₁₃H₁₂O₃ [M]⁺ 216.0786; found 216.0784.

Preparation of 2-(Ethoxycarbonyl)-5-phenylfuran (4e) with K₂CO₃ as the Base: By following the same procedure as that described for **4a**, the reaction of CuBr (98% purity, 29.2 mg, 0.2 mmol), MS (4 Å, 300.1 mg), **1k** (134.0 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.1 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (102.3 mg, 1.2 mmol) in dioxane (1.0 mL) afforded the 2,5-dihydrofuran intermediate, which was treated with K₂CO₃ (97.2 mg, 0.7 mmol), CH₃I (*d* = 2.28 g/mL, 0.44 mL, 7.0 mmol), and CH₃CN (4.0 mL) to give the crude product. Purification by column chromatography (petroleum ether/ethyl acetate, 200:1) afforded **4e** (132.0 mg, 61%) as a liquid. ¹H NMR (400 MHz, CDCl₃): δ = 7.79–7.74 (m, 2 H, Ar-H), 7.43–7.37 (m, 2 H, Ar-H), 7.35–7.29 (m, 1 H, Ar-H), 7.22 (d, *J* = 3.6 Hz, 1 H, CH=), 6.71 (d, *J* = 3.2 Hz, 1 H, CH=), 4.37 (q, *J* = 7.1 Hz, 2 H, OCH₂), 1.38 (t, *J* = 6.8 Hz, 3 H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 158.8, 157.4, 143.8, 129.5, 128.8, 128.7, 124.7, 119.7, 106.7, 60.8, 14.3 ppm.

2-(Ethoxycarbonyl)-5-(naphthalen-2-yl)furan (4f): By following the same procedure as that described for **4a**, the reaction of CuBr (98% purity, 29.5 mg, 0.2 mmol), MS (4 Å, 300.0 mg), **1l** (183.0 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.9 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (103.0 mg, 1.2 mmol) in dioxane (1.0 mL) afforded the 2,5-dihydrofuran intermediate, which was treated with Cs₂CO₃ (228.0 mg, 0.7 mmol), CH₃I (*d* = 2.28 g/mL, 0.44 mL, 7.0 mmol), and CH₃CN (4.0 mL) to give the crude product. Purification by column chromatography (petroleum ether/ethyl acetate, 100:1) afforded **4f** (154.3 mg, 58%) as a liquid. ¹H NMR (300 MHz, CDCl₃): δ = 8.26 (s, 1 H, Ar-H), 7.89–7.74 (m, 4 H, Ar-H), 7.51–7.40 (m, 2 H, Ar-H), 7.24 (d, *J* = 3.6 Hz, 1 H, CH=), 6.79 (d, *J* = 3.6 Hz, 1 H, CH=), 4.39 (q, *J* = 7.1 Hz, 2 H, OCH₂), 1.40 (t, *J* = 7.2 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 158.8, 157.4, 143.9, 133.24, 133.18, 128.5, 128.3, 127.7, 126.7, 126.61, 126.57, 123.8, 123.3, 119.8, 107.2, 60.8, 14.3 ppm. MS (EI): *m/z* (%) = 266 (100) [M]⁺. IR (neat): ν̄ = 1719,

1582, 1526, 1496, 1476, 1459, 1439, 1379, 1365, 1338, 1301, 1277, 1268, 1232, 1215, 1160, 1145, 1060, 1023 cm⁻¹. HRMS (EI): calcd. for C₁₇H₁₄O₃ [M]⁺ 266.0943; found 266.0945.

5-(Ethoxycarbonyl)-2,2'-bifuran (4g): By following the same procedure as that described for **4a**, the reaction of CuBr (98% purity, 29.2 mg, 0.2 mmol), MS (4 Å, 300.1 mg), **1m** (122.6 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 246.0 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (102.5 mg, 1.2 mmol) in dioxane (1.0 mL) afforded the 2,5-dihydrofuran intermediate, which was treated with Cs₂CO₃ (228.0 mg, 0.7 mmol), CH₃I (*d* = 2.28 g/mL, 0.44 mL, 7.0 mmol), and CH₃CN (4.0 mL) to give the crude product. Purification by column chromatography (petroleum ether/ethyl acetate, 200:1) afforded **4g** (119.7 mg, 58%) as a liquid. ¹H NMR (300 MHz, CDCl₃): δ = 7.46 (d, *J* = 1.5 Hz, 1 H, CH=), 7.21 (d, *J* = 3.6 Hz, 1 H, CH=), 6.81 (d, *J* = 3.3 Hz, 1 H, CH=), 6.62 (d, *J* = 3.6 Hz, 1 H, CH=), 6.49 (dd, *J*₁ = 3.3 Hz, *J*₂ = 1.5 Hz, 1 H, CH=), 4.37 (q, *J* = 7.1 Hz, 2 H, OCH₂), 1.38 (t, *J* = 7.1 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 158.6, 149.6, 145.2, 143.4, 143.0, 119.5, 111.7, 108.0, 106.5, 60.8, 14.2 ppm. MS (EI): *m/z* (%) = 206 (100) [M]⁺. IR (neat): ν̄ = 1707, 1634, 1580, 1559, 1516, 1473, 1450, 1391, 1368, 1359, 1301, 1278, 1237, 1227, 1211, 1169, 1146, 1115, 1089, 1067, 1032, 1016, 1001 cm⁻¹. HRMS (EI): calcd. for C₁₁H₁₀O₃ [M]⁺ 206.0579; found 206.0580.

2-(Ethoxycarbonyl)-5-styrylfuran (4h): By following the same procedure as that described for **4a**, the reaction of CuBr (98% purity, 29.3 mg, 0.2 mmol), MS (4 Å, 300.0 mg), **1n** (158.0 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 246.0 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (103.0 mg, 1.2 mmol) in dioxane (1.0 mL) afforded the 2,5-dihydrofuran intermediate, which was treated with Cs₂CO₃ (229.0 mg, 0.7 mmol), CH₃I (*d* = 2.28 g/mL, 0.44 mL, 7.0 mmol), and CH₃CN (4.0 mL) to give the crude product. Purification by column chromatography (petroleum ether/ethyl acetate, 200:1) afforded **4h** (149.6 mg, 62%) as a liquid. ¹H NMR (300 MHz, CDCl₃): δ = 7.46 (d, *J* = 7.2 Hz, 2 H, Ar-H), 7.37–7.21 (m, 4 H, Ar-H and CH=), 7.16 (d, *J* = 3.6 Hz, 1 H, CH=), 6.88 (d, *J* = 16.5 Hz, 1 H, CH=), 6.41 (d, *J* = 3.6 Hz, 1 H, CH=), 4.36 (q, *J* = 7.1 Hz, 2 H, OCH₂), 1.37 (t, *J* = 7.2 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 158.6, 156.6, 143.4, 136.0, 131.1, 128.6, 128.3, 126.6, 119.6, 115.3, 109.6, 60.7, 14.2 ppm. MS (EI): *m/z* (%) = 242 (100) [M]⁺. IR (neat): ν̄ = 1708, 1570, 1506, 1446, 1383, 1367, 1294, 1257, 1225, 1196, 1131, 1016 cm⁻¹. HRMS (EI): calcd. for C₁₅H₁₄O₃ [M]⁺ 242.0943; found 242.0945.

2-(Ethoxycarbonyl)-5-(hex-1-en-1-yl)furan (4i): By following the same procedure as that described for **4a**, the reaction of CuBr (98% purity, 29.4 mg, 0.2 mmol), MS (4 Å, 300.1 mg), **1o** (139.0 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.6 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (103.0 mg, 1.2 mmol) in dioxane (1.0 mL) afforded the 2,5-dihydrofuran intermediate, which was treated with Cs₂CO₃ (228.7 mg, 0.7 mmol), CH₃I (*d* = 2.28 g/mL, 0.44 mL, 7.0 mmol), and CH₃CN (4.0 mL) to give the crude product. Purification by column chromatography (petroleum ether/ethyl acetate, 200:1) afforded **4i** (143.0 mg, 64%) as a liquid. ¹H NMR (300 MHz, CDCl₃): δ = 7.12 (d, *J* = 3.3 Hz, 1 H, CH=), 6.45 (dt, *J*₁ = 15.8 Hz, *J*₂ = 7.0 Hz, 1 H, CH=), 6.27–6.18 (m, 2 H, 2 CH=), 4.34 (q, *J* = 7.1 Hz, 2 H, OCH₂), 2.20 (q, *J* = 6.9 Hz, 2 H, CH₂), 1.51–1.24 (m, 7 H, 2 CH₂ and CH₃), 0.91 (t, *J* = 7.2 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 158.7, 156.9, 142.8, 135.0, 119.4, 117.8, 107.4, 60.6, 32.4, 30.8, 22.1, 14.2, 13.7 ppm. MS (EI): *m/z* (%) = 222 (45.65) [M]⁺, 166 (100). IR (neat): ν̄ = 1714, 1655, 1577, 1504, 1465, 1382, 1298, 1207, 1138, 1115, 1016 cm⁻¹. HRMS (EI): calcd. for C₁₃H₁₈O₃ [M]⁺ 222.1256; found 222.1258.

Preparation of 2-(Ethoxycarbonyl)-5-(hex-1-en-1-yl)furan (4i) with K₂CO₃ as the Base: By following the same procedure as that described for **4a**, the reaction of CuBr (98% purity, 29.5 mg, 0.2 mmol), MS (4 Å, 300.1 mg), **1o** (137.3 mg, 1.0 mmol) in dioxane (1.0 mL), ethyl glyoxalate (50% in toluene, 245.1 mg, 1.2 mmol) in dioxane (1.0 mL), and **2a** (102.7 mg, 1.2 mmol) in dioxane (1.0 mL) afforded the 2,5-dihydrofuran intermediate, which was treated with K₂CO₃ (97.0 mg, 0.7 mmol), CH₃I (*d* = 2.28 g/mL, 0.44 mL, 7.0 mmol), and CH₃CN (4.0 mL) to give the crude product. Purification by column chromatography (petroleum ether/ethyl acetate, 200:1) afforded **4i** (128.4 mg, 58%) as a liquid. ¹H NMR (400 MHz, CDCl₃): δ = 7.11 (d, *J* = 3.6 Hz, 1 H, CH=), 6.45 (dt, *J*₁ = 15.7 Hz, *J*₂ = 7.0 Hz, 1 H, CH=), 6.27–6.18 (m, 2 H, 2 CH=), 4.35 (q, *J* = 7.1 Hz, 2 H, OCH₂), 2.20 (q, *J* = 7.2 Hz, 2 H, CH₂), 1.50–1.30 (m, 7 H, 2 CH₂ and CH₃), 0.91 (t, *J* = 7.2 Hz, 3 H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 158.8, 156.9, 142.9, 135.0, 119.5, 117.8, 107.4, 60.6, 32.5, 30.9, 22.1, 14.3, 13.8 ppm.

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- [1] For selected reviews, see: a) C. Wei, Z. Li, C.-J. Li, *Synlett* **2004**, 1472–1483; b) L. Zani, C. Bolm, *Chem. Commun.* **2006**, 4263–4275; c) V. V. Kouznetsov, L. Y. Vargas Méndez, *Synthesis* **2008**, 491–506; d) C.-J. Li, *Acc. Chem. Res.* **2010**, *43*, 581–590; e) W.-J. Yoo, L. Zhao, C.-J. Li, *Aldrichimica Acta* **2011**, *44*, 43–51; f) V. A. Peshkov, O. P. Pereshivko, E. V. Van der Eycken, *Chem. Soc. Rev.* **2012**, *41*, 3790–3807.
- [2] For selected examples of the copper-catalyzed synthesis of propargylamines by A³-coupling reactions, see: a) M. K. Patil, M. Keller, B. M. Reddy, P. Pale, J. Sommer, *Eur. J. Org. Chem.* **2008**, 4440–4445; b) M. Lakshmi Kantam, S. Laha, J. Yadav, S. Bhargava, *Tetrahedron Lett.* **2008**, *49*, 3083–3086; for the enantioselective version, see: c) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638–5639; d) N. Gommermann, C. Koradin, K. Polborn, P. Knochel, *Angew. Chem. Int. Ed.* **2003**, *42*, 5763–5766; *Angew. Chem.* **2003**, *115*, 5941–5944; e) T. F. Knopf, P. Aschwanden, T. Ichikawa, T. Watanabe, E. M. Carreira, *Angew. Chem. Int. Ed.* **2004**, *43*, 5971–5973; *Angew. Chem.* **2004**, *116*, 6097–6099; f) A. Bisai, V. K. Singh, *Org. Lett.* **2006**, *8*, 2405–2408; g) Z. Shao, X. Pu, X. Li, B. Fan, A. S. C. Chan, *Tetrahedron: Asymmetry* **2009**, *20*, 225–229; h) S. Nakamura, M. Ohara, Y. Nakamura, N. Shibata, T. Toru, *Chem. Eur. J.* **2010**, *16*, 2360–2362; i) W. Fan, S. Ma, *Chem. Commun.* **2013**, *49*, 10175–10177.
- [3] For selected examples of copper-catalyzed cascade A³-coupling reactions, see: a) Y. Yamamoto, H. Hayashi, T. Saigoku, H. Nishiyama, *J. Am. Chem. Soc.* **2005**, *127*, 10804–10805; b) H. Ohno, Y. Ohta, S. Oishi, N. Fujii, *Angew. Chem. Int. Ed.* **2007**, *46*, 2295–2298; *Angew. Chem.* **2007**, *119*, 2345–2348; c) E. R. Bonfield, C.-J. Li, *Adv. Synth. Catal.* **2008**, *350*, 370–374; d) W.-J. Yoo, C.-J. Li, *Adv. Synth. Catal.* **2008**, *350*, 1503–1506; e) N. Chernyak, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2010**, *49*, 2743–2746; *Angew. Chem.* **2010**, *122*, 2803–2806; f) D. Chernyak, N. Chernyak, V. Gevorgyan, *Adv. Synth. Catal.* **2010**, *352*, 961–966; g) W. Fan, W. Yuan, S. Ma, *Nat. Commun.* **2014**, *5*, 3884; h) A. Kumar, M. Kumar, S. Maurya, R. S. Khanna, *J. Org. Chem.* **2014**, *79*, 6905–6912; i) C. E. Meyet, C. H. Larsen, *J. Org. Chem.* **2014**, *79*, 9835–9841; j) W. Fan, S. Ma, *Angew. Chem. Int. Ed.* **2014**, *53*, 14542–14545; *Angew. Chem.* **2014**, *126*, 14770–14773.

A³-Coupling Based Reaction of Alkynes, Aldehydes, and Amines

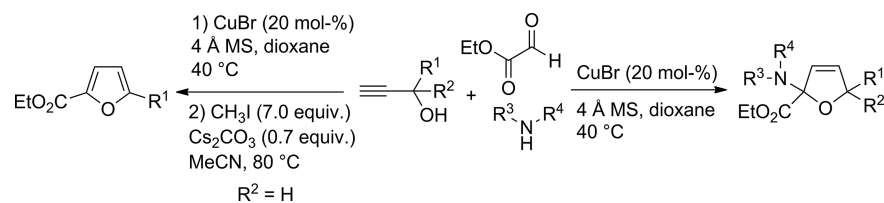
- [4] a) B. H. Lipshutz, *Chem. Rev.* **1986**, *86*, 795–819; b) S. F. Martin, P. W. Zinke, *J. Org. Chem.* **1991**, *56*, 6600–6606; c) L. A. Paquette, A. M. Doherty, C. M. Rayner, *J. Am. Chem. Soc.* **1992**, *114*, 3910–3926; d) P. A. Jacobi, K. M. Touchette, H. G. Selnick, *J. Org. Chem.* **1992**, *57*, 6305–6313; e) S. P. Tanis, E. D. Robinson, M. C. McMills, W. Watt, *J. Am. Chem. Soc.* **1992**, *114*, 8349–8362; f) L. A. Paquette, P. C. Astles, *J. Org. Chem.* **1993**, *58*, 165–169; g) I. Francesconi, W. D. Wilson, F. A. Tani-ous, J. E. Hall, B. C. Bender, R. R. Tidwell, D. McCurdy, D. W. Boykin, *J. Med. Chem.* **1999**, *42*, 2260–2265; h) S. M. Rahmathullah, J. E. Hall, B. C. Bender, D. R. McCurdy, R. R. Tidwell, D. W. Boykin, *J. Med. Chem.* **1999**, *42*, 3994–4000; i) D. J. Mortensen, A. L. Rodriguez, K. E. Carlson, J. H. Sun, B. S. Katzenellenbogen, J. A. Katzenellenbogen, *J. Med. Chem.* **2001**, *44*, 3838–3848.

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Multicomponent Reactions

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An efficient and practical A³-coupling based reaction that gives a variety of 2,5-polysubstituted dihydrofurans has been developed. The starting materials are commercially available, and the reaction con-

ditions are mild. In addition, 2,5-disubstituted furans can be prepared by treating the dihydrofuran derivatives with CH₃I and base in a two-step reaction sequence.

Copper(I)-Catalyzed A³-Coupling Based Reaction of Alkynes, Aldehydes, and Amines: An Efficient Approach to 2,5-Polysubstituted Dihydrofurans and 2,5-Disubstituted Furans

Keywords: Domino reactions / Multicomponent reactions / Oxygen heterocycles / Copper / Alkynes / Amines