Cyclization–Carbonylation–Cyclization Coupling Reactions of *N*-Propargylanilines and *o*-Alkynylphenols with Palladium(II)–Bisoxazoline Catalysts

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Abstract: Cyclization–carbonylation–cyclization coupling reactions (CCC-coupling reactions) of *N*-propargylanilines and *o*-alkynylphenols catalyzed by (box)Pd(II) complexes afforded symmetrical bis(quinolin-3-yl) and bis(benzofuran-3-yl) ketones, respectively, in moderate to excellent yields.

Key words: palladium, tandem reaction, carbonylation, alkynes, dimerization

Quinolines and benzofurans occur in numerous natural products, many of which display important biological activity.[1] Diaryl ketones are also frequently found in natural products and pharmaceuticals[2] [e.g., suprofen (a nonsteroidal anti-inflammatory drug), raloxifene (a selective estrogen receptor modulator for the treatment of osteoporosis), benzbromarone (an antipodagric drug), and amiodarone (an antiarrhythmic drug)]. In addition, they are good precursors for nonsteroidal antiestrogen drugs (e.g., tamoxifen[3]) and diarylmethyl compounds[4a] [e.g., carbinoxamine (an antihistamic drug), antitubercular compounds,[4b] and tubulin polymerization inhibitors[4c]] (Figure 1).

A variety of heterocycles can be synthesized by transition-metal-catalyzed cyclization of unsaturated systems.[5] Among them, *N*-propargylanilines are good precursors for the synthesis of quinoline derivatives.[6] If these intramolecular cyclization reactions could be expanded to include carbonylative coupling reactions, the process would be a synthetically valuable method for the direct preparation of ketones bearing two heterocyclic groups. Recently, we reported a cyclization–carbonylation–cyclization-coupling reaction (CCC-coupling reaction) of propargylic acetates and amides catalyzed by palladium(II)–bisoxazoline (box) complexes (Scheme 1).

Symmetrical ketones possessing two cyclic orthoesters, furanones, oxazoles, and oxabicyclic derivatives were obtained in moderate to excellent yields.[7a,f] In this transformation, the triple bond of the substrate coordinates to palladium(II) and undergoes nucleophilic attack by the intramolecular nucleophile X followed by CO insertion to produce the acylpalladium intermediate **A**. Coordination of the triple bond of a second molecule induces the second cyclization. Reductive elimination then leads to the formation of a ketone bearing two heterocyclic groups. We believe that the box ligand enhances the π-electrophilicity of palladium(II),[7] and thus promotes coordination of the second triple bond to the acylpalladium intermediate **A**, leading to the dimerization reaction. To extend our concept of the CCC-coupling reaction, we investigated the [Pd(II)(tfa)$_2$(box)]-catalyzed carbonylation reaction of *N*-propargylanilines **1** and *o*-alkynylphenols **4** (Tables 1–3).

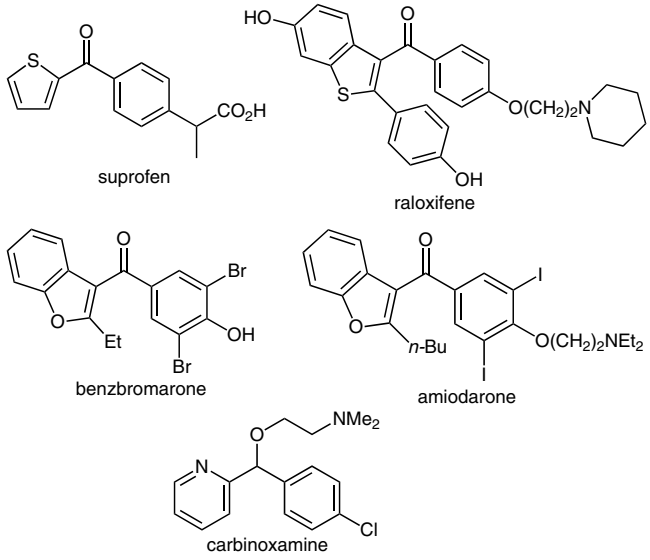

Figure 1 Some drugs with diaryl ketones and related structures

Initially, we selected **1a** as a standard substrate in a search for potential catalysts (Table 1). The reaction of **1a** with $PdCl_2(MeCN)_2$ (5 mol%) in the presence of *p*-benzoquinone (2 equiv) in methanol under a carbon monoxide atmosphere (balloon) generated the dimeric ketone **2a** in 14% yield along with a 12% yield of monomeric ester **3a** (entry 1).

The use of palladium(II) trifluoroacetate [Pd(tfa)$_2$], $PdCl_2(PPh_3)_2$, and (–)-sparteine/Pd(tfa)$_2$ generated **3a** as the sole product in 12–58% yields (entries 2–4). (2,2′-Bipyridine)dichloropalladium(II) did not show catalytic activity (entry 5). Next, we used the box ligands depicted in

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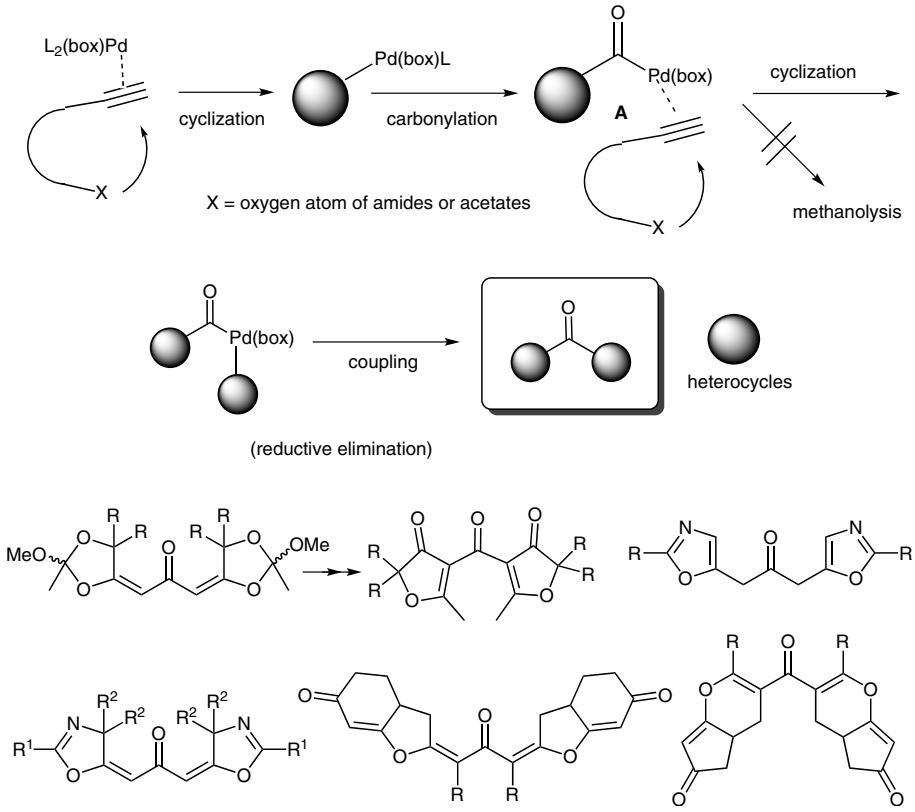
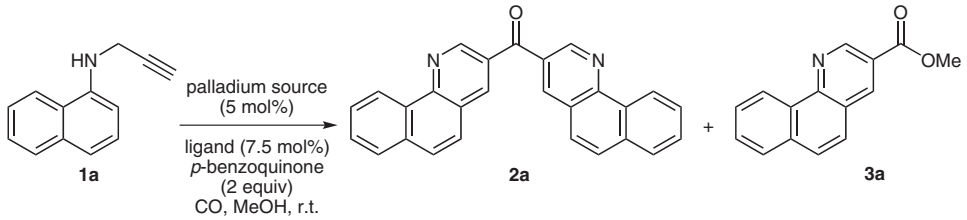


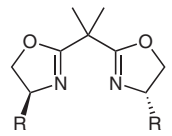
Scheme 1 Our concept of a cyclization–carbonylation–cyclization-coupling reaction (CCC-coupling reaction) of propargylic compounds, and previous synthesized bis(hetaryl) ketones

Table 1 The Effect of Different Palladium Sources and Ligands[a]



Entry	Pd source	Ligand	Time (h)	Yield (%)	
				2a	**3a**
1	$PdCl_2(MeCN)_2$	–	1	14	12
2	$Pd(tfa)_2$	–	2	–	12
3	$PdCl_2(PPh_3)_2$	–	21	–	30
4	$Pd(tfa)_2$	(–)-sparteine	21	–	58
5	$PdCl_2$(2,2′-bipy)[b]		18	–[c]	–[c]
6	$Pd(tfa)_2$	box **L1**	1	54	3
7	$Pd(tfa)_2$	box **L2**	19	34	3
8	$Pd(tfa)_2$	box **L3**	1	89	5

[a] Reaction conditions: Pd source (5 mol%), ligand (7.5 mol%), *p*-benzoquinone (2 equiv), CO, MeOH, r.t.
[b] 5 mol% of palladium complex was employed.
[c] **1a** was recovered (34%).



L1 R = *i*-Pr (*S*)-*i*-Prbox
L2 R = Bn (*S*)-Bnbox
L3 R = Ph (±)-Phbox

Figure 2 Box ligands

Figure 2 according to our previous report.[7a] Although the use of (*S*)-*i*-Prbox **L1** and (*S*)-Bnbox **L2** resulted in the formation of **2a** in 34–54% yield together with a small amount of **3a** (entries 6 and 7), (±)-Phbox accelerated the reaction, and the yield improved to 89% (entry 8). Dichloromethane, acetonitrile, and toluene were not suitable as solvents.

Having optimized the reaction conditions, we examined the reaction of various *N*-propargylanilines **1a–k** with the box ligand (±)-Phbox **L3** (Table 2). The substrates **1a–d** bearing alkyl groups at both *ortho*- and *meta*-positions ($R^1 + R^2$ or $R^1 + R^4$) were transformed in 70–89% yields (entries 1–4). In most cases, small amounts (3–5%) of monomeric ester **3** were obtained as a byproduct. Replacement of the methyl group **1e** (R^1 = Me) at the *ortho*-position with the bulkier isopropyl group **1f** (R^1 = *i*-Pr) resulted in an increased yield of **2** (entries 5 and 6); the structure of **2e** was determined by X-ray crystallographic analysis (Figure 3). However, steric hindrance in the acylpalladium intermediate also seemed to play an important role in the dimerization.[7a] The reaction of **1g** ($R^1 = SiEt_3$) afforded monomeric ester **3g** in 57% yield together with a small amount of dimeric ketone **2g** (entry 7). Unsubstituted substrate **1h** and *p*-methyl substrate **1i** (R^3 = Me) showed no reactivity (entries 8 and 9).

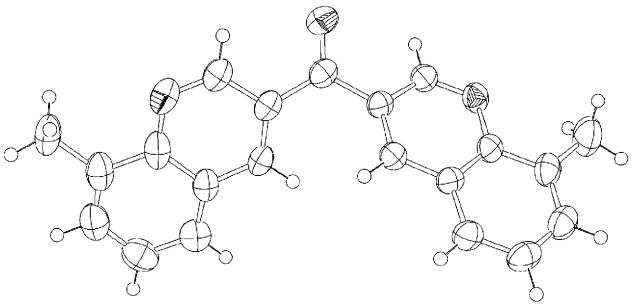
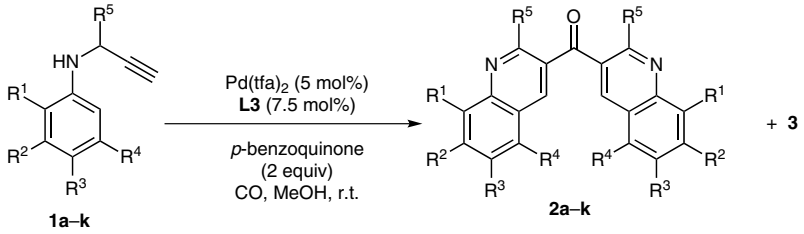


Figure 3 X-ray crystal structure of **2e**

However, introduction of a methyl group at the propargylic position (R^5) was found to be important for this reaction. The reaction of **1j** ($R^3 = R^5$ = Me) gave **2j** in 50% yield (entry 10). In addition, the substrate **1k** having two bulky substituents at the *meta*-positions ($R^2 = R^4$ = *t*-Bu)

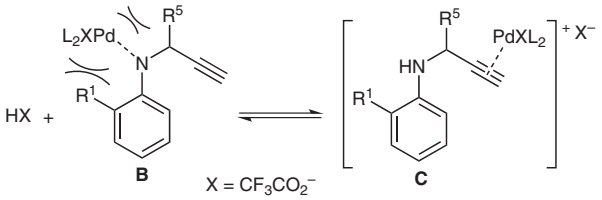
Table 2 CCC-Coupling Reaction of *N*-Propargylanilines **1**[a]



Entry	R^1	R^2	R^3	R^4	R^5	Time (h)	Product	Yield (%)
1	-(CH=CH)$_2$-		H	H	H	1	**2a**	89
2	-(CH$_2$)$_4$-		H	H	H	1	**2b**	77
3	Me	Me	H	H	H	2	**2c**	71
4	Me	H	H	Me	H	1	**2d**	70
5	Me	H	H	H	H	4	**2e**	55
6	*i*-Pr	H	H	H	H	1	**2f**	76
7	$SiEt_3$	H	H	H	H	3	**2g**	10[b]
8	H	H	H	H	H	12	**2h**	–
9	H	H	Me	H	H	24	**2i**	–
10	H	H	Me	H	Me	63	**2j**	50
11	H	*t*-Bu	H	*t*-Bu	H	48	**2k**	47

[a] Reaction conditions: Pd(tfa)$_2$ (5 mol%), **L3** (7.5 mol%), *p*-benzoquinone (2 equiv), CO, MeOH, r.t.
[b] The monomeric ester **3g** was obtained in 57% yield.

gave **2k** in 47% yield. Although we do not have a clear explanation for the observed substituent effects at this stage, we tentatively propose the following. An equilibrium mixture of **B** and **C** should be formed by coordination of the substrate **1** to palladium(II)[8] (Scheme 2). The steric repulsion present in **B** may allow the formation of the products **2** and **3** through intermediate **C**.



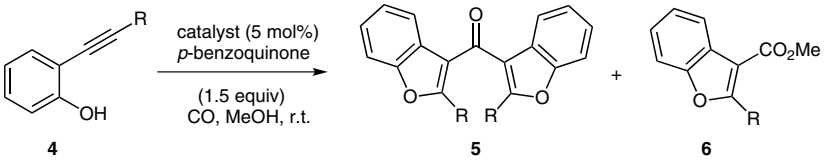
Scheme 2 Coordinated intermediates **B** and **C**

The palladium-catalyzed carbonylative cyclization of *o*-alkynylphenols has proven to be a useful method for the synthesis of benzofuran-3-carboxylates.[9a–d] Recently, many successful examples based on cascade cyclization coupling reactions of *o*-alkynylphenols have been reported.[9e–i] To investigate the generality of the CCC-coupling reaction, we next attempted the carbonylation of *o*-alkynylphenols **4** (Table 3). In the absence of the box ligand, carbonylative dimerization was not observed and the benzofuran-3-carboxylates **6** were obtained exclusively (entries 1, 3, 5, 7, and 9). The use of box ligands strikingly changed the course of the reaction,[7b,c] yielding the desired dimeric ketones **5** by the CCC-coupling reaction (entries 2, 4, 6, 8, and 10). For substrates **4a**–**e** with hydrocarbon substituents (R^1), the reaction proceeded well (85–93% yields) (entries 2, 4, 6, 8, and 10). Steric hindrance in the acylpalladium intermediate seemed to play an important role in the dimerization.[7a] The reaction of phenylacetylene **4f** afforded benzofuran-3-carboxylate **6f** exclusively (entry 11).

In conclusion, we have presented a CCC-coupling reaction of *N*-propargylanilines **1** and *o*-alkynylphenols **4** catalyzed by (box)Pd(II) complexes. Symmetrical bis(quinolin-3-yl) ketones **2** and bis(benzofuran-3-yl) ketones **5** were obtained in moderate to excellent yields. We believe that the box ligand enhances the π-electrophilicity of palladium(II),[7] and thus promotes coordination of the triple bond (second molecule) to the acylpalladium intermediate **A**, leading to the dimerization reaction. We are currently investigating other new cascade reactions based on the cyclization–carbonylation–cyclization strategy presented here for the synthesis of other types of ketones containing two heterocyclic groups.

All melting points were measured on a Yanaco MP-3S micromelting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR and HMBC spectra were recorded on Jeol AL 400 and Jeol Lambda 500 spectrometers in $CDCl_3$ with TMS as internal reference. In the case of CD_3CN, solvent peaks were used as a reference (δ = 1.93 for ^{1}H,

Table 3 CCC-Coupling Reaction of *o*-Alkynylphenols **4**[a]



4 **5** **6**

Entry	R	Catalyst	Time (h)	Yield (%)	
				5	6
1	$(CH_2)_2$Ph	$Pd(tfa)_2$	29	**5a**: –	**6a**: 89
2	$(CH_2)_2$Ph	[$Pd(tfa)_2$(**L3**)]	6.5	**5a**: 90	**6a**: 10
3	$(CH_2)_3$Ph	$Pd(tfa)_2$	48	**5b**: –	**6b**: 88
4	$(CH_2)_3$Ph	[$Pd(tfa)_2$(**L3**)]		**5b**: 93	**6b**: 2
5	$(CH_2)_5$Me	$Pd(tfa)_2$	48	**5c**: –	**6c**: 91
6	$(CH_2)_5$Me	[$Pd(tfa)_2$(**L3**)]	6	**5c**: 86	**6c**: 6
7	$(CH_2)_7$Me	$Pd(tfa)_2$	48	**5d**: –	**6d**: 73
8	$(CH_2)_7$Me	[$Pd(tfa)_2$(**L3**)]		**5d**: 85	**6d**: 5
9	$(CH_2)_2$*i*-Pr	$Pd(tfa)_2$		**5e**: –	**6e**: 80
10	$(CH_2)_2$*i*-Pr	[$Pd(tfa)_2$(**L3**)]	6.5	**5e**: 85	**6e**: 10
11	Ph	[$Pd(tfa)_2$(**L3**)]	30	**5f**: –	**6f**: 82

[a] Reaction conditions: catalyst (5 mol%), *p*-benzoquinone (1.5 equiv), CO, MeOH, r.t.

and δ = 118.2 for ^{13}C). ^{13}C NMR spectra were recorded at 100 MHz. HRMS were obtained with Jeol GC Mate II, JMS-SX102 and Jeol JMS 600H spectrometer. IR spectra were recorded with Jasco FT/IR-300 spectrophotometer. All reagents were purchased from commercial sources and used without purification. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

Cyclization–Carbonylation–Cyclization Coupling Reaction of 1 or 4; General Procedure

A 30-mL 2-necked round-bottomed flask containing a magnetic stirring bar, $Pd(tfa)_2$ (0.025 mmol), ligand (0.038 mmol or 0.05 mmol), *p*-benzoquinone (0.75 mmol or 1 mmol), and MeOH (4 mL) was fitted with a rubber septum and a 3-way stopcock connected to a balloon filled with CO. The apparatus was purged with CO by pump-filling via the 3-way stopcock. A MeOH soln (1 mL) of substrate **1** or **4** (0.5 mmol) was added to the stirred soln via syringe at an appropriate temperature. The remaining substrate was washed with MeOH (2 × 1 mL). After stirring for a period of time (see Tables 2 and 3) at r.t., the mixture was diluted with CH_2Cl_2 (50 mL) and washed with 3% NaOH (40 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by column chromatography (silica gel). The fraction eluted with hexane–EtOAc afforded dimeric ketone **2** or **5** and monomeric ester **3** or **6**. In some cases, the dimeric ketones were then precipitated from the reaction mixture and the resulting precipitate was collected by filtration and washed with cold MeOH (2 × 1 mL). The filtrate was reprocessed via the above procedure to provide additional product after column chromatography.

Bis(benzo[*h*]quinolin-3-yl)methanone (2a)

Eluent: hexane–EtOAc, 50:1; pale yellow needles; yield: 85.5 mg (89%); mp 218–220 °C.

IR (KBr): 3047, 1639, 1591, 1326, 739 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.74–7.96 (m, 10 H), 8.67 (d, *J* = 2.4 Hz, 2 H), 9.34–9.36 (m, 2 H), 9.74 (d, *J* = 2.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 125.2 (2 C), 125.2 (2 C), 125.5 (2 C), 127.7 (2 C), 128.0 (2 C), 129.1 (2 C), 129.5 (2 C), 130.4 (2 C), 131.0 (2 C), 134.7 (2 C), 137.9 (2 C), 148.9 (2 C), 149.1 (2 C), 193.4.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{27}H_{16}N_2O$: 384.1263; found: 384.1269.

Methyl Benzo[*h*]quinoline-3-carboxylate (3a)

Eluent: hexane–EtOAc, 50:1; yield: 5.9 mg (5%). The spectroscopic data were identical to those reported in the literature.[6p]

Bis(7,8,9,10-tetrahydrobenzo[*h*]quinolin-3-yl)methanone (2b)

Eluent: hexane–EtOAc, 30:1; pale yellow needles; yield: 75.6 mg (77%); mp 224–225 °C (hexane).

IR (KBr): 2932, 2855, 1639, 1609, 782 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.91–2.02 (m, 8 H), 2.99 (t, *J* = 5.6 Hz, 4 H), 3.38 (t, *J* = 5.6 Hz, 4 H), 7.36 (d, *J* = 8.4 Hz, 2 H), 7.65 (d, *J* = 8.4 Hz, 2 H), 8.54 (d, *J* = 2.4 Hz, 2 H), 9.36 (d, *J* = 2.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 22.7 (4 C), 24.8 (2 C), 30.6 (2 C), 124.9 (2 C), 126.0 (2 C), 128.8 (2 C), 130.2 (2 C), 135.2 (2 C), 138.9 (2 C), 141.7 (2 C), 148.7 (2 C), 148.9 (2 C), 193.6.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{27}H_{24}N_2O$: 392.1889; found: 392.1883.

Methyl 7,8,9,10-Tetrahydrobenzo[*h*]quinoline-3-carboxylate (3b)

Eluent: hexane–EtOAc, 50:1; pale yellow needles; yield: 3.6 mg (3%); mp 93–94 °C (hexane).

IR (KBr): 2934, 1715, 1435, 1254, 784 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.86–1.97 (m, 4 H), 2.93 (t, *J* = 6.0 Hz, 2 H), 3.32 (t, *J* = 6.0 Hz, 2 H), 3.99 (s, 3 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 7.61 (d, *J* = 8.4 Hz, 1 H), 8.70 (d, *J* = 2.4 Hz, 1 H), 9.39 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 22.7 (2 C), 24.8, 30.6, 52.3, 121.9, 125.0, 125.9, 129.8, 134.9, 138.6, 141.2, 148.7, 148.8, 166.2.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{15}H_{15}NO_2$: 241.1103; found: 241.1104.

Bis(7,8-dimethylquinolin-3-yl)methanone (2c)

Eluent: hexane–EtOAc, 40:1; pale yellow needles; yield: 60.4 mg (71%); mp 178–180 °C (hexane–EtOAc, 1:1).

IR (KBr): 2919, 1654, 1597, 1272, 855 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.56 (s, 6 H), 2.81 (s, 6 H), 7.46 (d, *J* = 8.4 Hz, 2 H), 7.67 (d, *J* = 8.4 Hz, 2 H), 8.55 (d, *J* = 2.4 Hz, 2 H), 9.37 (d, *J* = 2.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 13.4 (2 C), 21.0 (2 C), 124.9 (2 C), 126.2 (2 C), 128.6 (2 C), 130.7 (2 C), 134.9 (2 C), 139.1 (2 C), 140.6 (2 C), 148.7 (2 C), 148.9 (2 C), 193.6.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{23}H_{20}N_2O$: 340.1576; found: 340.1575.

Methyl 7,8-Dimethylquinoline-3-carboxylate (3c)

Eluent: hexane–EtOAc, 50:1; pale yellow needles; yield: 3.2 mg (3%); mp 91 °C (hexane).

IR (KBr): 2948, 1715, 1609, 1340, 1278, 1114 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.51 (s, 3 H), 2.75 (s, 3 H), 3.99 (s, 3 H), 7.39 (d, *J* = 8.2 Hz, 1 H), 7.62 (d, *J* = 8.2 Hz, 1 H), 8.70 (d, *J* = 2.4 Hz, 1 H), 9.39 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 13.4, 20.9, 52.3, 121.6, 125.1, 126.0, 130.3, 134.7, 138.8, 140.1, 148.7, 148.8, 166.2.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{13}H_{13}NO_2$: 215.0946; found: 215.0941.

Bis(5,8-dimethylquinolin-3-yl)methanone (2d)

Eluent: hexane–EtOAc, 30:1; pale yellow needles; yield: 59.6 mg (70%); mp 188–189 °C (hexane–EtOAc, 1:1).

IR (KBr): 2915, 1644, 1279, 824 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.68 (s, 6 H), 2.84 (s, 6 H), 7.39 (d, *J* = 7.5 Hz, 2 H), 7.62 (d, *J* = 7.5 Hz, 2 H), 8.82 (d, *J* = 2.0 Hz, 2 H), 9.40 (d, *J* = 2.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 18.2 (2 C), 18.7 (2 C), 126.3 (2 C), 128.1 (2 C), 129.0 (2 C), 132.2 (2 C), 134.1 (2 C), 135.5 (2 C), 135.8 (2 C), 148.6 (2 C), 149.2 (2 C), 194.1.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{23}H_{20}N_2O$: 340.1576; found: 340.1577.

Methyl 5,8-Dimethylquinoline-3-carboxylate (3d)

Eluent: hexane–EtOAc, 50:1; pale yellow needles; yield: 4.3 mg (4%); mp 108 °C (hexane).

IR (KBr): 2924, 1721, 1278, 823 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.66 (s, 3 H), 2.75 (s, 3 H), 4.01 (s, 3 H), 7.26 (d, *J* = 7.0 Hz, 1 H), 7.49 (d, *J* = 7.0 Hz, 1 H), 8.90 (d, *J* = 2.2 Hz, 1 H), 9.41 (d, *J* = 2.2 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 18.0, 18.5, 52.4, 122.0, 126.2, 127.5, 131.6, 133.8, 135.1, 135.2, 148.2, 149.2, 166.2.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{13}H_{13}NO_2$: 215.0946; found: 215.0947.

Bis(8-methylquinolin-3-yl)methanone (2e)

Eluent: hexane–EtOAc, 20:1; pale yellow needles; yield: 42.9 mg (55%); mp 138–139 °C (hexane).

IR (KBr): 2918, 1651, 1280, 782 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.87 (s, 6 H), 7.55 (dd, *J* = 7.0, 8.0 Hz, 2 H), 7.72 (d, *J* = 7.0 Hz, 2 H), 7.77 (d, *J* = 8.0 Hz, 2 H), 8.59 (d, *J* = 2.0 Hz, 2 H), 9.40 (d, *J* = 2.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 18.1 (2 C), 126.6 (2 C), 127.3 (2 C), 127.6 (2 C), 129.4 (2 C), 132.4 (2 C), 137.6 (2 C), 139.2 (2 C), 148.8 (2 C), 148.9 (2 C), 193.5.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{21}H_{16}N_2O$: 312.1263; found: 312.1260.

X-ray crystallographic analysis of **2e**: X-ray diffraction data were collected on a Bruker SMART APEX CCD diffractometer equipped with a graphite crystal and incident beam monochromator using MoKα radiation (λ = 0.71073 Å) at 223 K. The structure was solved by direct method. The non-hydrogen atoms were refined anisotropically. Crystallographic parameters: $C_{21}H_{26}N_2O$, M_W = 322.44, monoclinic, space group $P2_1/c$, with unit cell *a* = 11.8081(10) Å, *b* = 18.5799(16) Å, *c* = 7.3619(6) Å, β = 94.238(2)° and *V* = 1610.7(2) Å^3; *Z* = 4, D_{calcd} = 1.330 g cm^{-3}, $R1[I > 2\sigma(I)]$ = 0.0659, *wR*2 = 0.2010, 2407 independent reflections [*R*(int) = 0.0249], 219 parameters refined on F^2. Crystallographic data (excluding structure factors) for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. 847693.

Methyl 8-Methylquinoline-3-carboxylate (3e)
Eluent: hexane–EtOAc, 50:1; pale yellow needles; yield: 4.0 mg (4%); mp 98–99 °C (hexane).

IR (KBr): 2966, 1724, 1284, 785 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.83 (s, 3 H), 4.01 (s, 3 H), 7.49 (dd, *J* = 7.2, 8.0 Hz, 1 H), 7.66 (dt, *J* = 7.2, 1.2 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 1 H), 8.78 (d, *J* = 2.2 Hz, 1 H), 9.45 (d, *J* = 2.2 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 18.1, 52.4, 122.7, 126.8, 127.1, 127.2, 132.0, 137.4, 138.9, 148.8, 148.9, 166.0.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{12}H_{11}NO_2$: 201.0790; found: 201.0790.

Bis(8-isopropylquinolin-3-yl)methanone (2f)
Eluent: hexane–EtOAc, 100:1, colorless needles; yield: 70.0 mg (76%); mp 114–115 °C (hexane).

IR (KBr): 2936, 1646, 1574, 783 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.43 (d, *J* = 6.8 Hz, 12 H), 4.41 (septet, *J* = 6.8 Hz, 2 H), 7.63 (dd, *J* = 7.2, 8.0 Hz, 2 H), 7.76–7.80 (m, 4 H), 8.62 (d, *J* = 2.4 Hz, 2 H), 9.42 (d, *J* = 2.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 23.5 (4 C), 27.4 (2 C), 126.7 (2 C), 127.0 (2 C), 127.8 (2 C), 128.1 (2 C), 129.3 (2 C), 139.4 (2 C), 147.6 (2 C), 147.8 (2 C), 148.8 (2 C), 193.6.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{25}H_{24}N_2O$: 368.1889; found: 368.1883.

Methyl 8-Isopropylquinoline-3-carboxylate (3f)
Not isolated.

Bis[8-(triethylsilyl)quinolin-3-yl]methanone (2g)
Eluent: hexane–EtOAc, 150:1, colorless needles; yield: 12.8 mg (10%); mp 146–148 °C (hexane).

IR (KBr): 2951, 2873, 1650, 1604, 728 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.95–0.99 (m, 18 H), 1.04–1.10 (m, 12 H), 7.61 (dd, *J* = 8.0, 6.8 Hz, 2 H), 7.92 (dd, *J* = 8.0, 1.2 Hz, 2 H), 8.01 (dd, *J* = 6.8, 1.2 Hz, 2 H), 8.58 (d, *J* = 2.4 Hz, 2 H), 9.38 (d, *J* = 2.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 3.9 (6 C), 7.7 (6 C), 125.9 (2 C), 127.1 (2 C), 129.3 (2 C), 130.2 (2 C), 139.0 (2 C), 139.6 (2 C), 139.9 (2 C), 148.6 (2 C), 154.4 (2 C), 194.0.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{31}H_{40}N_2OSi_2$: 512.2679; found: 512.2678.

Methyl 8-(Triethylsilyl)quinoline-3-carboxylate (3g)
Eluent: hexane–EtOAc, 150:1, colorless needles; yield: 85.9 mg (57%); mp 58 °C.

IR (KBr): 2955, 2871, 1721, 1608, 1266, 789 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.92–0.96 (m, 9 H), 1.01–1.07 (m, 6 H), 3.99 (s, 3 H), 7.56 (dd, *J* = 8.0, 6.8 Hz, 1 H), 7.89 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.95 (ddd, *J* = 6.8, 1.2, 0.4 Hz, 1 H), 8.79 (d, *J* = 2.4 Hz, 1 H), 9.46 (dd, *J* = 2.4, 0.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 4.0 (3 C), 7.7 (3 C), 52.3, 122.4, 126.2, 126.8, 130.0, 138.8, 139.2, 139.7, 148.5, 154.6, 166.2.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{17}H_{23}NO_2Si$: 301.1498; found: 301.1497.

Bis(2,6-dimethylquinolin-3-yl)methanone (2j)
Eluent: hexane–EtOAc, 100:1; pale yellow needles; yield: 42.6 mg (50%); mp 147–149 °C.

IR (KBr): 2956, 2924, 1660, 1615, 1575, 1424, 1271, 1245, 1187, 845 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.84 (s, 6 H), 2.89 (s, 6 H), 7.38–7.42 (m, 2 H), 7.55 (d, *J* = 8.0 Hz, 2 H), 7.63 (d, *J* = 7.2 Hz, 2 H), 8.09 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 17.8 (2 C), 25.2 (2 C), 125.3 (2 C), 126.3 (2 C), 126.5 (2 C), 131.8 (2 C), 131.8 (2 C), 136.9 (2 C), 139.2 (2 C), 147.5 (2 C), 156.2 (2 C), 198.1.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{23}H_{20}N_2O$: 340.1576; found: 340.1576.

Methyl 2,6-Dimethylquinoline-3-carboxylate (3j)
Eluent: hexane–EtOAc, 100:1; pale yellow needles; yield: 18.3 mg (17%); mp 112–115 °C.

IR (KBr): 2956, 2920, 1720, 1272, 1251, 1100, 786 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.80 (s, 3 H), 3.00 (s, 3 H), 3.97 (s, 3 H), 7.39–7.43 (m, 1 H), 7.61 (d, *J* = 6.8 Hz, 1 H), 7.68 (d, *J* = 8.0 Hz, 1 H), 8.70 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 17.7, 26.0, 52.3, 123.1, 125.6, 126.2, 126.4, 131.7, 136.7, 140.2, 147.8, 157.3, 167.2.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{13}H_{13}NO_2$: 215.0946; found: 215.0945.

Bis(5,7-di-*tert*-butylquinolin-3-yl)methanone (2k)
Eluent: hexane–EtOAc, 10:1, colorless needles; yield: 59.8 mg (47%); mp 256–258 °C (hexane–EtOAc, 10:1).

IR (KBr): 2964, 1657, 1594, 1288, 763 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.48 (s, 18 H), 1.64 (s, 18 H), 7.77 (d, *J* = 2.2 Hz, 2 H), 8.07 (dd, *J* = 0.7, 1.9 Hz, 2 H), 9.29 (d, *J* = 2.2 Hz, 2 H), 9.35 (dd, *J* = 0.7, 1.9 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 31.0 (6 C), 32.3 (6 C), 35.6 (2 C), 36.5 (2 C), 123.3 (2 C), 123.8 (2 C), 124.0 (2 C), 127.8 (2 C), 137.4 (2 C), 147.8 (2 C), 148.7 (2 C), 151.9 (2 C), 154.8 (2 C), 193.7.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{35}H_{44}N_2O$: 508.3454; found: 508.3454.

Methyl 5,7-Di-*tert*-butylquinoline-3-carboxylate (3k)
Eluent: hexane–EtOAc, 25:1; brown oil; yield: 6.0 mg (4%).

IR (neat): 2956, 1724, 1283, 1249, 768 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.44 (s, 9 H), 1.65 (s, 9 H), 4.01 (s, 3 H), 4.03 (s, 3 H), 7.70 (d, *J* = 1.6 Hz, 1 H), 7.99 (d, *J* = 0.8 Hz, 1 H), 9.37 (d, *J* = 1.6 Hz, 1 H), 9.45 (t, *J* = 0.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 31.0 (3 C), 32.2 (3 C), 35.5, 36.5, 52.5, 120.6, 123.3, 123.5, 123.8, 137.2, 147.5, 148.5, 154.4, 155.3, 166.3.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{19}H_{25}NO_2$: 299.1885; found: 299.1886.

Bis(2-phenethylbenzofuran-3-yl)methanone (5a)
Eluent: hexane–EtOAc, 400:1; yellow oil; yield: 105.9 mg (90%).

IR (KBr): 3028, 2927, 2857, 1720, 1637, 1574, 1453, 749 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.01–3.17 (m, 8 H), 6.99–7.01 (m, 2 H), 7.08–7.15 (m, 7 H), 7.20–7.29 (m, 7 H), 7.48–7.51 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 30.0 (2 C), 34.0 (2 C), 110.0 (2 C), 118.9 (2 C), 121.2 (2 C), 123.6 (2 C), 124.6 (2 C), 125.9 (2 C), 126.2 (2 C), 128.3 (4 C), 128.4 (4 C), 140.3 (2 C), 153.7 (2 C), 163.4 (2 C), 185.9.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{33}H_{26}O_3$: 470.1882; found: 470.1881.

Methyl 2-Phenethylbenzofuran-3-carboxylate (6a)
Eluent: hexane–EtOAc, 400:1, yellow solid; yield: 124.7 mg (89%); mp 40–42 °C.

IR (KBr): 3028, 2951, 2884, 1708, 1590, 1061, 747 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.09 (t, *J* = 8.0 Hz, 2 H), 3.49 (t, *J* = 8.0 Hz, 2 H), 3.92 (s, 3 H), 7.18–7.32 (m, 7 H), 7.43–7.46 (m, 1 H), 7.96–7.98 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 30.2, 34.1, 51.4, 108.9, 110.9, 121.9, 123.8, 124.5, 126.1, 126.3, 128.4 (2 C), 128.5 (2 C), 140.6, 153.7, 164.7, 166.2.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{18}H_{16}O_3$: 280.1099; found: 280.1101.

Bis[2-(3-phenylpropyl)benzofuran-3-yl]methanone (5b)
Eluent: hexane–EtOAc, 300:1; colorless oil; yield: 115.9 mg (93%).

IR (KBr): 3026, 2933, 2859, 1635, 1572, 1453, 749 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.06 (quint, *J* = 7.6 Hz, 4 H), 2.60 (t, *J* = 7.6 Hz, 4 H), 2.92 (t, *J* = 7.6 Hz, 4 H), 7.07–7.28 (m, 14 H), 7.37 (d, *J* = 7.6 Hz, 2 H), 7.49 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 27.7 (2 C), 29.6 (2 C),35.4 (2 C), 110.1 (2 C), 118.8 (2 C), 121.1 (2 C), 123.7 (2 C), 124.5 (2 C), 125.9 (2 C), 126.1 (2 C), 128.3 (4 C), 128.4 (4 C), 141.3 (2 C), 153.7 (2 C), 164.2 (2 C), 186.1.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{35}H_{30}O_3$: 498.1295; found: 498.1296.

Methyl 2-(3-Phenylpropyl)benzofuran-2-carboxylate (6b)
Eluent: hexane–EtOAc, 300:1; white oil; yield: 129.5 mg (88%).

IR (KBr): 3028, 2949, 1714, 1590, 1237, 751 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.12 (quint, *J* = 7.6 Hz, 2 H), 2.72 (t, *J* = 7.6 Hz, 2 H), 3.22 (t, *J* = 7.6 Hz, 2 H), 3.90 (s, 3 H), 7.19–7.43 (m, 8 H), 7.96–7.97 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 27.7, 29.4, 35.4, 51.3, 108.7, 110.8, 121.8, 123.7, 124.4,125.9, 126.1, 128.3 (2 C), 128.4 (2 C), 141.5, 153.6, 164.7, 166.9.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{19}H_{18}O_3$: 294.1256; found: 294.1257.

Bis(2-hexylbenzofuran-3-yl)methanone (5c)
Eluent: hexane–EtOAc, 500:1; yellow liquid; yield: 92.6 mg (86%).

IR (KBr): 2957, 2929, 2857, 1638, 1574, 1454, 749 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.83 (t, *J* = 6.8 Hz, 6 H), 1.22–1.28 (m, 12 H), 1.71–1.78 (m, 4 H), 2.91 (t, *J* = 7.6 Hz, 4 H), 7.11–7.15 (m, 2 H), 7.23–7.28 (m, 2 H), 7.36–7.38 (m, 2 H), 7.47–7.49 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 14.0 (2 C), 22.5 (2 C), 28.0 (4 C), 28.9 (2 C), 31.4 (2 C), 111.0 (2 C), 118.6 (2 C), 121.1 (2 C), 123.6 (2 C), 124.4 (2 C), 126.2 (2 C), 153.7 (2 C), 164.8 (2 C), 186.3.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{29}H_{34}O_3$: 430.2508; found: 430.2509.

Methyl 2-Hexylbenzofuran-3-carboxylate (6c)
Eluent: hexane–EtOAc, 500:1; yellow liquid; yield: 118.5 mg (91%).

IR (KBr): 2954, 2931, 2859, 1716, 1591, 1062, 751 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H), 1.25–1.40 (m, 6 H), 1.73–1.81 (m, 2 H), 3.18 (t, *J* = 7.6 Hz, 2 H), 3.94 (s, 3 H), 7.24–7.30 (m, 2 H), 7.41–7.45 (m, 1 H), 7.93–7.97 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 14.1, 22.5, 27.9, 28.1, 29.0, 31.5, 51.3, 108.4, 110.9, 121.9, 123.7, 124.3, 126.2, 153.6, 164.9, 167.8.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{16}H_{20}O_3$: 260.1413; found: 260.1414.

Bis(2-octylbenzofuran-3-yl)methanone (5d)
Eluent: hexane–EtOAc, 500:1; yellow liquid; yield: 103.4 mg (85%).

IR (KBr): 2926, 2855, 1638, 1573, 1454, 749 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.85 (t, *J* = 6.8 Hz, 6 H), 1.21–1.27 (m, 20 H), 1.74 (quint, *J* = 7.2 Hz, 4 H), 2.91 (t, *J* = 7.6 Hz, 4 H), 7.11–7.15 (m, 2 H), 7.23–7.28 (m, 2 H), 7.35–7.38 (m, 2 H), 7.46–7.48 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 14.1 (2 C), 22.6 (2 C), 28.0 (2 C), 28.1 (2 C), 29.1 (2 C), 29.2 (2 C), 29.3 (2 C), 31.8 (2 C), 111.1 (2 C), 118.6 (2 C), 121.1 (2 C), 123.6 (2 C), 124.4 (2 C), 126.2 (2 C), 153.7 (2 C), 164.8 (2 C), 186.3.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{33}H_{42}O_3$: 486.3134; found: 486.3136.

Methyl 2-Octylbenzofuran-3-carboxylate (6d)
Eluent: hexane–EtOAc, 500:1; yellow liquid; yield: 144.2 mg (73%).

IR (KBr): 2953, 2928, 2885, 1717, 1591, 1067, 751 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.87 (t, *J* = 7.0 Hz, 3 H), 1.26–1.41 (m, 10 H), 1.77 (quint, *J* = 7.6 Hz, 2 H), 3.17 (t, *J* = 7.6 Hz, 2 H), 3.94 (s, 3 H), 7.27–7.29 (m, 2 H), 7.42–7.44 (m, 1 H), 7.95–7.97 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 14.1, 22.7, 27.9, 28.1, 29.2, 29.3, 29.4, 31.9, 51.3, 108.4, 110.9, 121.9, 123.7, 124.3, 126.2, 153.6, 164.9, 167.8.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{18}H_{24}O_3$: 288.1726; found: 288.1729.

Bis[2-(3-methylbutyl)benzofuran-3-yl]methanone (5e)
Eluent: hexane–EtOAc, 1000:1; yellow oil; yield: 85.5 mg (85%).

IR (KBr): 2956, 2927, 2870, 1637, 1573, 1456, 748 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.84 (d, *J* = 6.4 Hz, 12 H), 1.48–1.67 (m, 6 H), 2.91 (t, *J* = 7.8 Hz, 4 H), 7.11–7.15 (m, 2 H), 7.23–7.28 (m, 2 H), 7.36–7.38 (m, 2 H), 7.45–7.48 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 22.1 (4 C), 26.1 (2 C), 27.8 (2 C), 36.9 (2 C), 111.0 (2 C), 118.5 (2 C), 121.0 (2 C), 123.6 (2 C), 124.4 (2 C), 126.2 (2 C), 153.7 (2 C), 164.9 (2 C), 186.3.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{27}H_{30}O_3$: 402.2195; found: 402.2196.

Methyl 2-(3-Methylbutyl)benzofuran-3-carboxylate (6e)
Eluent: hexane–EtOAc, 1000:1; yellow liquid: yield: 98.5 mg (80%).

IR (KBr): 2955, 2929, 2871, 1716, 1591, 1062, 751 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.97 (d, *J* = 6.0 Hz, 6 H), 1.62–1.68 (m, 3 H), 3.19 (t, *J* = 7.6 Hz, 2 H), 3.95 (s, 3 H), 7.24–7.30 (m, 2 H), 7.41–7.44 (m, 1 H), 7.93–7.97 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 22.3 (2 C), 26.2, 27.9, 36.8, 51.3, 108.3, 110.8, 121.8, 123.7, 124.3, 126.2, 153.6, 164.9, 167.9.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{15}H_{18}O_3$: 246.1256; found: 246.1254.

Methyl 2-Phenylbenzofuran-3-carboxylate (6f)
Yield: 103.4 mg (82%).

The spectroscopic data were identical to those reported in the literature.[91]

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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