Oxidative Annulation of Diphenylpropanamides via In Situ Hypervalent Iodine-Promoted Intramolecular C–N/C–O Bond Formation

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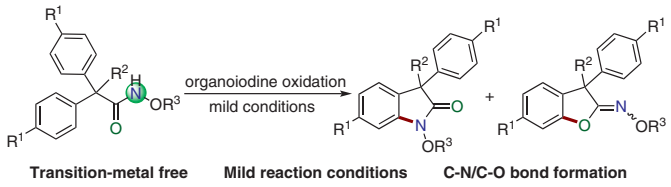

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Abstract An aryl iodide catalyzed intramolecular oxidative transformation of diphenylpropanamide derivatives is described that can readily afford the C–N/C–O coupling products in a single step. The speed of the 1,3-aryl iodide migration process determines the diversity of target compound generation in this reaction. This straightforward approach can be performed with the use of inexpensive and readily available catalyst, transition-metal-free, mild conditions and good functional group tolerance.

Key words catalytic, aryl iodide, C–N bond formation, C–O bond formation

Possessing properties of low toxicity, favourable safety profile and environmentally benign nature, hypervalent iodine reagents have been shown to be effective promoters of many organic transformations.[1] Since their catalytic utility was proposed in 2005,[2] chemists have focused on the use of catalytic systems in many reactions for the formation of C–C, C–N, C–O or C–X (X = halogen) bonds, such as dearomatization of phenol derivatives,[3] oxidation of alkenes[4] and α-functionalization of carbonyl compounds.[5] Among the various strategies developed to date, carbon–carbon double bonds, hydroxyl groups of phenol derivatives, and α-positions of ketone compounds have frequently emerged as activated positions in aryl iodide catalytic chemistry (Figure 1). However, the *N*-alkoxyl group of amides as a highly active group has rarely been studied in aryl iodide chemistry.[6]

Metal-catalyzed C–N/C–O bond-coupling reactions have been successfully utilized widely in organic synthesis as powerful synthetic tools.[7] Recently, Wang and co-workers reported the first example of a Pd(II)-catalyzed amination of aryl C–H bonds of diphenylpropanamide derivatives to afford various oxindole frameworks (Scheme 1).[8]

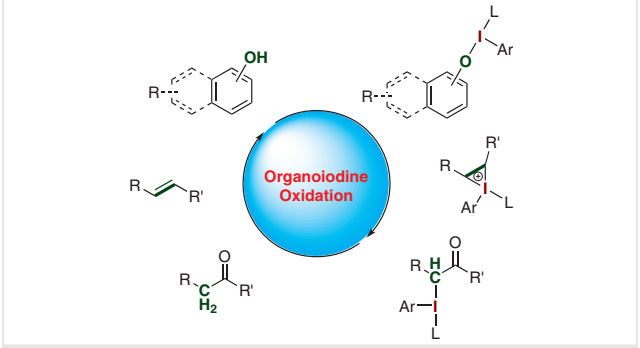
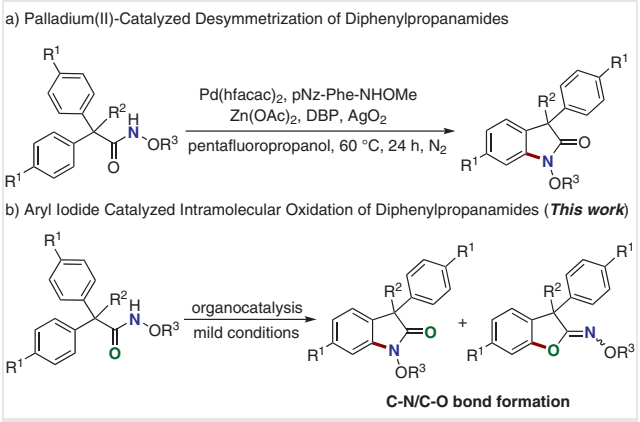


Figure 1 General activated groups in aryl iodide catalysis

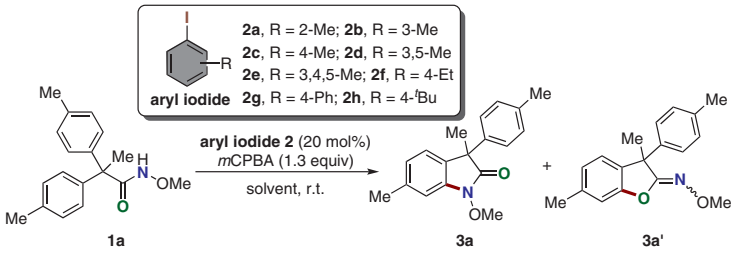


Scheme 1 Approaches to intramolecular annulation of diphenylpropanamides

An organocatalytic desymmetrization approach applied in C–H amination has many advantages. Based on previous work,[9] we have studied the construction of oxindole derivatives, mainly focused on those dialkyl-substituted at the α-position. We also found that a significant challenge in this reaction was when the starting materials had two aromatic rings that contained electron-donating or -withdrawing groups; in this case, in addition to C–N bond coupling products, C–O bond products also formed. In this work, we focussed on building C–O bond oxime molecules. Herein, we detail studies of the aryl iodide-catalyzed intramolecular oxidation of diphenylpropanamide derivatives.

Initially, the reaction of *N*-methoxy-2,2-di-*p*-tolylpropanamide (**1a**) catalyzed by 20 mol% of 2-iodotoluene (**2a**) with *meta*-chloroperoxybenzoic acid as the stoichiometric oxidant in hexafluoro-2-propanol at room temperature was employed to optimize reaction conditions. The desired C–N/C–O annulation products **3a** and **3a′** were successfully obtained in a total of 64% yield in a 2:1 ratio, respectively (Table 1,

Table 1 Optimization of the Reaction Conditions[a]



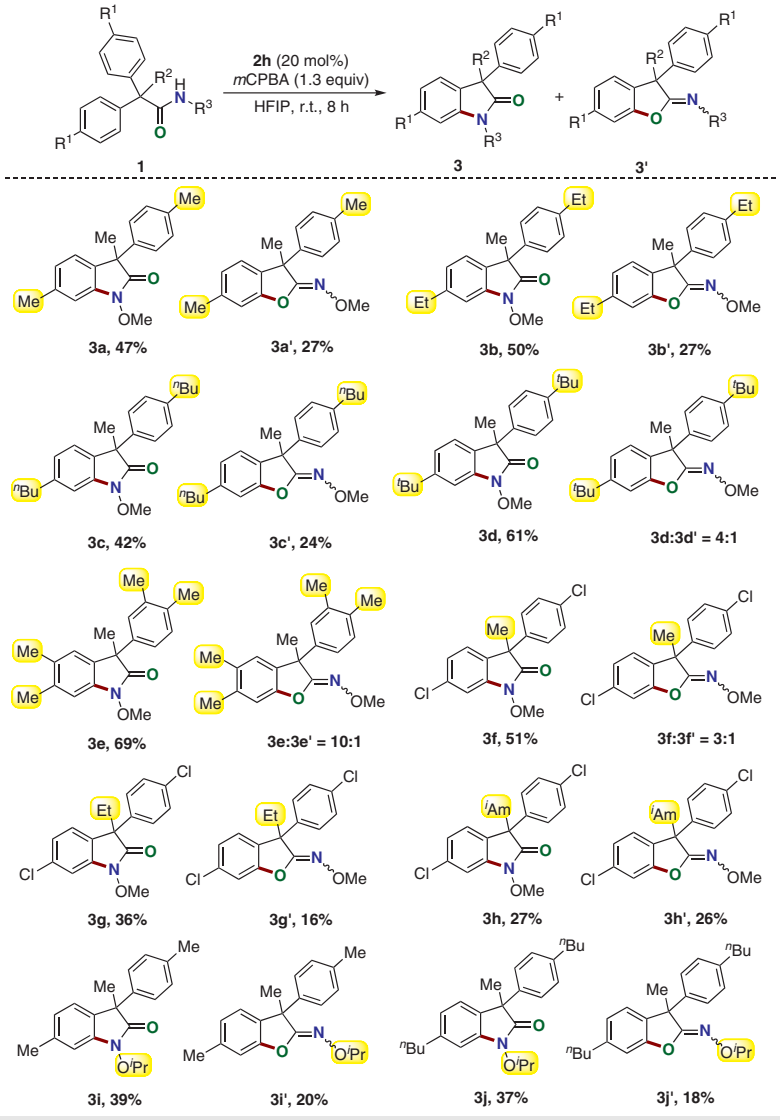
Entry	2	Oxidant	Solvent	Yield (%)[b] (**3a** + **3a′**)	Ratio (**3a**/**3a′**)[c]
1	**2a**	*m*CPBA	HFIP	64	2.0:1
2	**2b**	*m*CPBA	HFIP	57	3.0:1
3	**2c**	*m*CPBA	HFIP	82	2.0:1
4	**2d**	*m*CPBA	HFIP	72	1.7:1
5	**2e**	*m*CPBA	HFIP	41	1.5:1
6	**2f**	*m*CPBA	HFIP	54	2.1:1
7	**2g**	*m*CPBA	HFIP	47	2.0:1
8	**2h**	*m*CPBA	HFIP	77	1.6:1
9	**2h**	Selectfluor	HFIP	53	1.5:1
10	**2h**	H_2O_2	HFIP	trace	–
11	**2h**	$MeCO_3H$	HFIP	<10	–
12	**2h**	TBHP	HFIP	trace	–
13	**2h**	*m*CPBA	TFE	72	2.0:1
14	**2h**	*m*CPBA	TFIP	70	2.0:1
15	**2h**	*m*CPBA	DCM	52	3.0:1
16	**2h**	*m*CPBA	EtOAc	<10	–
17	**2h**	*m*CPBA	toluene	<10	–
18	**2h**	*m*CPBA	MeCN	81	2.0:1
19	**2h**	*m*CPBA	THF	trace	–
20	**2h**	*m*CPBA	MeOH	17	2.0:1
21[d]	**2h**	*m*CPBA	HFIP	71	1.6:1
22[e]	**2h**	*m*CPBA	HFIP	62	1.8:1

[a] Unless otherwise indicated, the reaction was carried out at 0.1 mmol scale of **1a**, catalyzed by **2** (20 mol%) in solvent (1 mL) at room temperature for 8 h. The molar ratio of **1a**/*m*CPBA was 1:1.3.
[b] Isolated yield.
[c] The ratio of **3a**/**3a′** was determined by ^{1}H NMR analysis.
[d] Temperature of reaction was 0 °C.
[e] Temperature of reaction was 50 °C.

entry 1). Subsequently, various catalysts **2b–e** were screened in this transformation, which revealed that catalyst **2c**, with a methyl group at the *para*-position of the benzene ring, delivered the highest reactivity, resulting in 82% combined yield of **3a** and **3a′** (entries 2–5) with less C–O bond formation of oxime product (**3a**/**3a′** = 2:1). Inspired by these results, different substituents at the *para*-position of the catalyst were applied to this reaction (entries 6–8). When 1-ethyl-4-iodobenzene (**2f**) and 4-iodo-1,1′-biphenyl (**2g**) were utilized as the catalysts, the yields decreased significantly to 54% and 47%, respectively (entries 6 and 7). In contrast, 1-(*tert*-butyl)-4-iodobenzene (**2h**) promoted the reaction effectively, with a yield of 77% and 1.6:1.0 ratio of **3a**/**3a′** (entry 8). To increase the yield of C–O bond-formation product, various conditions including oxidants and solvents were tested in this oxidative reaction (entries 9–20). Unfortunately, the results revealed that this proved ineffective for optimization of C–O bond formation. However, when acetonitrile was employed as the solvent, the combined yield of **3a** and **3a′** increased to 81%, albeit with an unsatisfactory ratio of **3a**/**3a′** of 2:1 (entry 18).

Further attempts to improve the yield and the ratio of **3a**/**3a′** by changing temperature (entries 21 and 22), and additives also proved to be unfruitful.

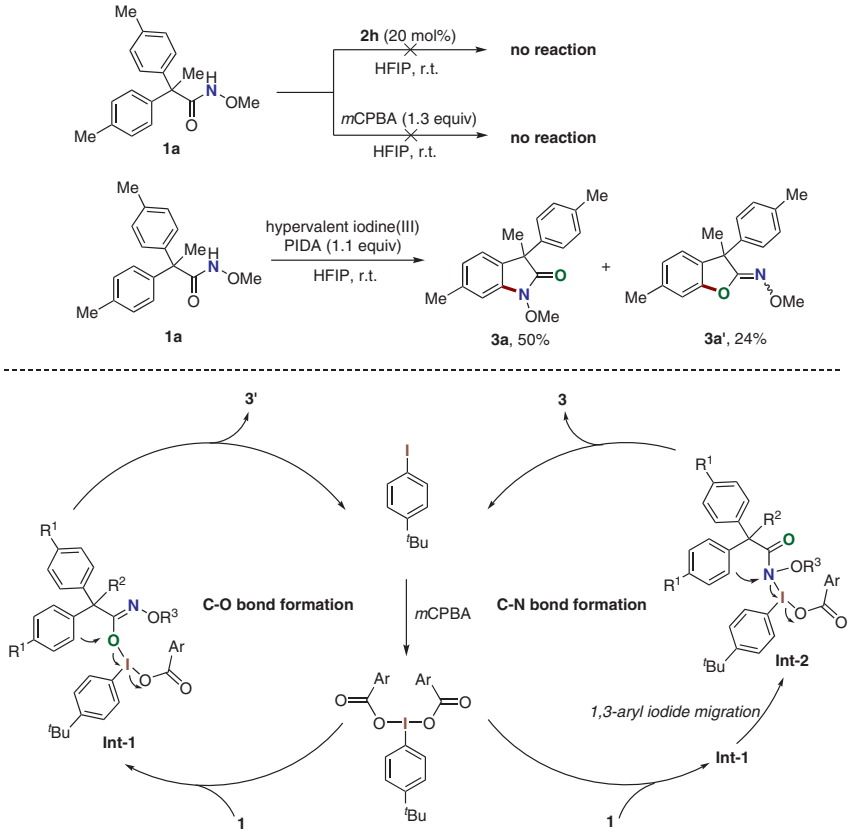
Under the optimized conditions, a series of diphenylpropanamides **1** was explored to demonstrate the scope and generality of this transformation. As shown in Scheme 2, a wide range of substrates was successfully employed, affording the corresponding C–N/C–O bond products in good combined yields. For example, 4-methyl substituted diphenylpropanamide **1a** gave the corresponding lactam **3a** in 47% yield accompanied by C–O bond oxime product **3a′**



Scheme 2 Aryl iodide catalyzed intramolecular oxidation of diphenylpropanamides: substrate scope.

in 27% yield. Initially, we examined potential substituent effects on the benzene ring of diphenylpropanamides **1a–f**. Ethyl-, *n*-butyl-, *tert*-butyl-, chloro- and multi-substituted reactants were employed in this transformation, and the results revealed that, whether the aryl ring possessed electron-donating or electron-withdrawing groups, the products of C–N bond formation **3a–f** were preferentially generated in moderate yields. Unfortunately, the yield of oxime (**3d′** and **3e′**) decreased in line with the increase in steric hindrance on the aryl ring in this transformation. For instance, the use of a multi-substituted benzene ring significantly favoured the oxindole over the oxime (**3e**/**3e′** = 10:1). Further exploration of the substrate scope focused on α-alkyl-substituted diphenylpropanamides **1g–h**. The results showed that bulky steric alkyl groups at the α-position could improve the ratio of C–O bond formation (**3h**/**3h′** = 1:1). Finally, we investigated the effect of substituents **1i–j** on the terminal N-atom in this reaction. The reaction proceeded well with an isopropyl group as functional substituent, although lactam products **3i** and **3j** were generated in 39% and 37% yield, respectively, along with reduced levels of C–O coupling products (**3i**/**3i′** = 2:1 and **3j**/**3j′** = 2:1).

We also monitored the progress of the reaction of **1a** without *m*CPBA or aryl iodide catalyst **2h**, but the reaction was highly inefficient under these conditions. Meanwhile, we utilized hypervalent iodine (PIDA) as a direct oxidant to mediate this transformation, which gave the corresponding products **3a** and **3a′** in 50% and 24% yield, respectively (**3a**/**3a′** = 2:1). Considering the various substrates in this oxidative transformation and a previous report,[10] a plausible mechanism is shown in Scheme 3. Aryl iodide **2h** is proposed to be oxidized to a hypervalent iodine(III) species by *m*CPBA. Subsequent coordination with the carbonyl group of **1** would enable a ligand exchange process to form an O-bonded hypervalent iodine intermediate **Int-1**. Subsequently, there are two possible pathways in this reaction: intramolecular 1,3-aryl iodide migration from oxygen to nitrogen atom would generate *N*-iodonium amide intermediate **Int-2**, and S_N2 type C–N bond formation between the carbon of the aryl ring and the amide nitrogen would yield the terminal lactam product **3**. Alternatively, direct C–O bond formation between the carbon of the benzene ring and the nitrogen atom of the amide without 1,3-aryl iodide migration would afford oxime product **3′**. Based on the experimental results, we found that the migration speed of aryl



Scheme 3 Proposed catalytic mechanism

iodide was relatively rapid, leading to simultaneous generation of the (major) C–N coupling lactam and C–O coupling oxime.

In summary, we have developed the aryl iodide-catalyzed intramolecular oxidation of diphenylpropanamide derivatives to afford C–N and C–O bond coupling products in a simple step. This protocol illustrates that the speed of 1,3-aryl iodide migration is fast in this reaction, leading to preferential formation of the C–N bond coupling lactams rather than the desired oxime products. This strategy not only takes advantage of organocatalytic oxidation, simultaneously to construct oxindole and oxime architectures with potential bioactivity in one step, but also greatly enriches the research area of aryl iodide chemistry. Further design of novel reactants containing *N*-alkoxyl functional groups and application of this methodology are underway in our laboratory.

All commercially available compounds were used as provided without further purification. Solvents used in reactions were technical grade and dried only if indicated. Solvents for chromatography were technical grade and were distilled prior to use. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel aluminium-backed plates (F-254 indicator). NMR spectra were recorded with a Bruker ARX 400 spectrometer and are reported in ppm (δ) downfield of TMS (δ = 0) in deuterated solvent as specified. Signal splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), or multiplet (m), with coupling constants (*J*) in hertz. Mass spectra were conducted with a Micromass Q-T instrument (ESI) and an Agilent Technologies 5973N (EI).

C–N/ C–O Bond Oxidative Coupling; General Procedure

To a reaction tube filled with reactant **1** (0.1 mmol) and aryl iodide **2** (20 mol%) was added *m*CPBA (1.3 equiv) and HFIP (1.0 mL). The resulting mixture was stirred at room temperature for 8 h, the reaction was quenched with aqueous saturated $NaHCO_3$, and the mixture was extracted with DCM (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. The residue was directly purified by preparative thin-layer chromatography to afford target products **3** and **3′**.

1-Methoxy-3,6-dimethyl-3-(*p*-tolyl)indolin-2-one (3a)

Purification by preparative thin-layer chromatography (petroleum ether/EtOAc = 30:1).

Yield: 13.2 mg (47%); colourless viscous oil.

IR (neat): 2916, 2848, 1726, 1444, 1292, 1029, 809, 734, 699, 511 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.16 (m, 2 H), 7.11 (d, *J* = 8.0 Hz, 2 H), 7.06 (d, *J* = 7.5 Hz, 1 H), 6.94–6.88 (m, 2 H), 4.01 (s, 3 H), 2.42 (s, 3 H), 2.30 (s, 3 H), 1.76 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 138.5, 137.5, 136.1, 136.1, 128.3, 127.4, 125.4, 123.1, 122.8, 107.3, 62.4, 49.3, 22.5, 20.7, 19.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}NO_2$: 282.1494; found: 282.1485.

3,6-Dimethyl-3-(*p*-tolyl)benzofuran-2(3*H*)-one O-Methyl Oxime (3a′)

Purification by preparative thin-layer chromatography (petroleum ether/EtOAc = 30:1).

Yield: 7.7 mg (27%); colourless oil.

IR (neat): 2917, 2849, 1722, 1473, 1264, 1028, 810, 733, 701, 510 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.16 (m, 2 H), 7.15–7.09 (m, 3 H), 6.98 (s, 1 H), 6.95 (d, *J* = 7.9 Hz, 1 H), 4.00 (s, 3 H), 2.33 (s, 3 H), 2.31 (s, 3 H), 1.77 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 137.2, 137.1, 137.1, 133.0, 131.7, 129.4, 129.3, 128.5, 126.4, 125.1, 107.3, 63.4, 50.6, 23.3, 21.2, 21.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}NO_2$: 282.1494; found: 282.1486.

6-Ethyl-3-(4-ethylphenyl)-1-methoxy-3-methylindolin-2-one (3b)

Purification by preparative thin-layer chromatography (petroleum ether/EtOAc = 30:1).

Yield: 15.5 mg (50%); colourless viscous oil.

IR (neat): 2928, 2857, 1728, 1445, 1219, 1028, 819, 734, 700, 534 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.3 Hz, 2 H), 7.11 (dd, *J* = 13.5, 7.8 Hz, 3 H), 6.99–6.89 (m, 2 H), 4.02 (s, 3 H), 2.71 (q, *J* = 7.6 Hz, 2 H), 2.61 (q, *J* = 7.6 Hz, 2 H), 1.77 (s, 3 H), 1.29 (t, *J* = 7.6 Hz, 3 H), 1.20 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.5, 144.9, 143.4, 139.5, 137.4, 128.7, 128.1, 126.5, 124.2, 122.7, 107.1, 63.5, 50.4, 29.1, 28.4, 23.6, 15.6, 15.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{24}NO_2$: 310.1807; found: 310.1798.

6-Ethyl-3-(4-ethylphenyl)-3-methylbenzofuran-2(3*H*)-one O-Methyl Oxime (3b′)

IR (neat): 2926, 2839, 1729, 1438, 1242, 1031, 821, 729, 696, 528 cm^{-1}.

Purification by preparative thin-layer chromatography (petroleum ether/EtOAc = 30:1).

Yield: 8.4 mg (27%); colourless viscous oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.19 (m, 2 H), 7.18–7.11 (m, 3 H), 7.02 (s, 1 H), 6.97 (d, *J* = 7.9 Hz, 1 H), 4.00 (s, 3 H), 2.62 (p, *J* = 7.6 Hz, 4 H), 1.78 (s, 3 H), 1.21 (td, *J* = 7.6, 6.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 143.4, 139.6, 137.3, 137.3, 131.6, 128.1, 128.1, 127.3, 126.5, 124.0, 107.3, 63.4, 50.7, 28.7, 28.4, 23.5, 15.9, 15.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{24}NO_2$: 310.1807; found: 310.1815.

6-Butyl-3-(4-butylphenyl)-1-methoxy-3-methylindolin-2-one (3c)

Purification by preparative thin-layer chromatography (petroleum ether/EtOAc = 30:1).

Yield: 15.4 mg (42%); colourless viscous oil.

IR (neat): 2933, 2857, 1731, 1448, 1299, 1024, 811, 742, 699, 519 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 7.9 Hz, 2 H), 7.14–7.05 (m, 3 H), 6.99–6.78 (m, 2 H), 4.02 (s, 3 H), 2.67 (t, *J* = 7.8 Hz, 2 H), 2.56 (t, *J* = 7.8 Hz, 2 H), 1.77 (s, 3 H), 1.68–1.61 (m, 2 H), 1.60–1.51 (m, 2 H), 1.43–1.30 (m, 4 H), 0.96 (t, *J* = 7.4 Hz, 3 H), 0.91 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.5, 143.6, 142.0, 139.5, 137.4, 128.6, 128.6, 126.4, 124.2, 123.3, 107.6, 63.4, 50.4, 36.0, 35.2, 33.7, 33.5, 23.7, 22.5, 22.4, 14.0, 13.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{31}NO_2$ + Na: 388.2253; found: 388.2246.

6-Butyl-3-(4-butylphenyl)-3-methylbenzofuran-2(3*H*)-one *O*-Methyl Oxime (3c')

Purification by preparative thin-layer chromatography (petroleum ether/EtOAc = 30:1).

Yield: 8.8 mg (24%); colourless oil.

IR (neat): 2931, 2852, 1727, 1446, 1294, 1022, 805, 744, 692, 515 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 8.3 Hz, 2 H), 7.16–7.08 (m, 3 H), 7.01 (s, 1 H), 6.96 (d, *J* = 7.9 Hz, 1 H), 4.00 (s, 3 H), 2.57 (q, *J* = 8.4 Hz, 4 H), 1.78 (s, 3 H), 1.61–1.53 (m, 4 H), 1.39–1.29 (m, 4 H), 0.91 (td, *J* = 7.3, 4.9 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 142.1, 138.3, 137.3, 137.3, 131.5, 128.7, 127.9, 126.4, 124.5, 107.3, 63.4, 50.7, 35.5, 35.2, 34.0, 33.5, 23.6, 22.4, 22.4, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{31}NO_2$ + Na: 388.2253; found: 388.2238.

6-(*tert*-Butyl)-3-(4-(*tert*-butyl)phenyl)-1-methoxy-3-methylindolin-2-one (3d)

Purification by preparative thin-layer chromatography (petroleum ether/EtOAc = 30:1).

Yield: 22.4 mg (61%); white solid; mp 156–157 °C.

IR (neat): 2931, 2854, 1728, 1440, 1288, 1030, 817, 739, 689, 510 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.30 (m, 2 H), 7.28–7.23 (m, 2 H), 7.15–7.11 (m, 2 H), 7.07 (s, 1 H), 4.04 (s, 3 H), 1.78 (s, 3 H), 1.37 (s, 9 H), 1.28 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 151.0, 149.1, 138.2, 136.1, 127.3, 125.2, 124.5, 122.9, 119.1, 103.7, 62.4, 49.3, 34.1, 33.4, 30.4, 30.2, 22.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{31}NO_2$ + Na: 388.2253; found: 388.2245.

3-(3,4-Dimethylphenyl)-1-methoxy-3,5,6-trimethylindolin-2-one (3e)

Purification by preparative thin-layer chromatography (petroleum ether/EtOAc = 30:1).

Yield: 21.3 mg (69%); colourless viscous oil.

IR (neat): 2929, 2849, 1741, 1453, 1283, 1031, 828, 751, 705, 527 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10–7.03 (m, 2 H), 7.02–6.96 (m, 1 H), 6.93 (s, 1 H), 6.86 (s, 1 H), 4.01 (s, 3 H), 2.32 (s, 3 H), 2.25–2.14 (m, 9 H), 1.75 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4, 137.7, 137.3, 136.8, 136.6, 135.8, 131.3, 129.8, 129.1, 127.7, 125.5, 123.9, 108.8, 63.3, 50.4, 23.4, 20.2, 20.0, 19.6, 19.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{23}NO_2$ + Na: 332.1627; found: 332.1620.

6-Chloro-3-(4-chlorophenyl)-1-methoxy-3-methylindolin-2-one (3f)

Purification by preparative thin-layer chromatography (petroleum ether/EtOAc = 30:1).

Yield: 16.3 mg (51%); colourless viscous oil.

IR (neat): 2955, 2879, 1736, 1491, 1231, 1077, 959, 815, 744, 511 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.22 (m, 2 H), 7.18 (d, *J* = 8.3 Hz, 2 H), 7.12–7.01 (m, 3 H), 3.98 (s, 3 H), 1.73 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 139.6, 136.8, 133.5, 132.8, 127.9, 127.9, 126.9, 124.4, 122.4, 107.4, 62.7, 49.2, 22.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{13}Cl_2NO_2$ + Na: 344.0221; found: 344.0211.

6-Chloro-3-(4-chlorophenyl)-3-ethyl-1-methoxyindolin-2-one (3g)

Purification by preparative thin-layer chromatography (petroleum ether/EtOAc = 30:1).

Yield: 12.1 mg (36%); colourless viscous oil.

IR (neat): 2957, 2870, 1731, 1478, 1230, 1081, 961, 810, 743, 508 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.25 (m, 4 H), 7.17–7.11 (m, 2 H), 7.09–7.06 (m, 1 H), 4.00 (s, 3 H), 2.47–2.35 (m, 1 H), 2.22–2.12 (m, 1 H), 0.72 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 141.6, 137.4, 134.7, 133.9, 129.0, 128.4, 126.3, 126.1, 123.4, 108.5, 63.9, 55.4, 31.0, 9.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{15}Cl_2NO_2$ + Na: 358.0378; found: 358.0372.

6-Chloro-3-(4-chlorophenyl)-3-ethylbenzofuran-2(3*H*)-one *O*-Methyl Oxime (3g')

Purification by preparative thin-layer chromatography (petroleum ether/EtOAc = 30:1).

Yield: 5.4 mg (16%); colourless viscous oil.

IR (neat): 2961, 2848, 1730, 1471, 1259, 1013, 947, 793, 738, 509 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (dd, *J* = 8.3, 2.0 Hz, 1 H), 7.31–7.26 (m, 4 H), 7.20–7.16 (m, 1 H), 7.00 (d, *J* = 8.3 Hz, 1 H), 4.00 (s, 3 H), 2.49–2.33 (m, 1 H), 2.27–2.10 (m, 1 H), 0.73 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 139.0, 137.3, 134.0, 129.9, 129.1, 129.0, 128.8, 128.3, 125.4, 108.8, 63.8, 55.8, 30.9, 9.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{15}Cl_2NO_2$ + Na: 358.0378; found: 358.0386.

6-Chloro-3-(4-chlorophenyl)-3-isopentyl-1-methoxyindolin-2-one (3h)

Purification by preparative thin-layer chromatography (petroleum ether/EtOAc = 30:1).

Yield: 10.2 mg (27%); colourless viscous oil.

IR (neat): 2965, 2849, 1728, 1492, 1261, 1093, 1013, 811, 737, 506 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.24 (m, 4 H), 7.16–7.12 (m, 2 H), 7.10–7.06 (m, 1 H), 3.98 (s, 3 H), 2.38 (dd, *J* = 13.9, 7.8 Hz, 1 H), 2.09 (dd, *J* = 13.9, 5.1 Hz, 1 H), 1.45–1.36 (m, 1 H), 0.77 (d, *J* = 6.6 Hz, 3 H), 0.71 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 141.6, 138.8, 134.7, 133.8, 128.9, 128.1, 126.7, 126.1, 123.2, 108.6, 63.8, 54.4, 46.5, 25.8, 24.4, 23.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{21}Cl_2NO_2$ + Na: 400.0847; found: 400.0851.

6-Chloro-3-(4-chlorophenyl)-3-isopentylbenzofuran-2(3*H*)-one *O*-Methyl Oxime (3h′)

Purification by preparative thin-layer chromatography (petroleum ether/EtOAc = 30:1).

Yield: 9.8 mg (26%); colourless viscous oil.

IR (neat): 2970, 2936, 1730, 1491, 1267, 1209, 1013, 812, 736, 505 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36 (dd, *J* = 8.3, 2.0 Hz, 1 H), 7.30–7.26 (m, 4 H), 7.23–7.19 (m, 1 H), 7.00 (d, *J* = 8.3 Hz, 1 H), 3.98 (s, 3 H), 2.39 (dd, *J* = 14.0, 7.9 Hz, 1 H), 2.09 (dd, *J* = 13.9, 5.2 Hz, 1 H), 1.49–1.38 (m, 1 H), 0.77 (d, *J* = 6.6 Hz, 3 H), 0.72 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 139.0, 138.7, 133.9, 129.7, 129.0, 128.9, 128.8, 128.0, 126.0, 109.0, 63.7, 54.8, 46.4, 25.8, 24.4, 23.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{21}Cl_2NO_2$ + Na: 400.0847; found: 400.0839.

1-Isopropoxy-3,6-dimethyl-3-(*p*-tolyl)indolin-2-one (3i)

Purification by preparative thin-layer chromatography (petroleum ether/EtOAc = 50:1).

Yield: 12.1 mg (39%); colourless viscous oil.

IR (neat): 2931, 2810, 1724, 1457, 1281, 1011, 817, 752, 703, 522 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.16 (m, 2 H), 7.14–7.08 (m, 3 H), 6.96 (s, 1 H), 6.92 (d, *J* = 7.9 Hz, 1 H), 4.66–4.56 (m, 1 H), 2.32 (s, 1 H), 2.30 (s, 3 H), 1.76 (s, 3 H), 1.35–1.31 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3, 139.2, 137.6, 137.2, 132.8, 131.8, 129.5, 128.5, 126.6, 124.9, 108.0, 78.8, 50.7, 23.6, 21.3, 21.2, 21.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{23}NO_2$ + Na: 332.1627; found: 332.1633.

3,6-Dimethyl-3-(*p*-tolyl)benzofuran-2(3*H*)-one *O*-Isopropyl Oxime (3i′)

Purification by preparative thin-layer chromatography (petroleum ether/EtOAc = 50:1).

Yield: 6.2 mg (20%); colourless oil.

IR (neat): 2936, 2825, 1733, 1451, 1270, 1022, 822, 749, 700, 517 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.16 (m, 2 H), 7.12–7.08 (m, 2 H), 7.04 (d, *J* = 7.5 Hz, 1 H), 6.92–6.88 (m, 1 H), 6.85 (s, 1 H), 4.65–4.58 (m, 1 H), 2.41 (s, 3 H), 2.30 (s, 3 H), 1.76 (s, 3 H), 1.34 (s, 3 H), 1.33 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.7, 141.6, 138.5, 137.6, 137.1, 129.5, 129.4, 128.6, 126.5, 124.0, 123.8, 109.0, 78.8, 50.4, 23.8, 21.9, 21.2, 21.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{23}NO_2$ + Na: 332.1627; found: 332.1622.

6-Butyl-3-(4-butylphenyl)-1-isopropoxy-3-methylindolin-2-one (3j)

Purification by preparative thin-layer chromatography (petroleum ether/EtOAc = 50:1).

Yield: 14.5 mg (37%); colourless oil.

IR (neat): 2939, 2866, 1727, 1451, 1221, 1033, 822, 747, 693, 522 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 8.1 Hz, 2 H), 7.15–7.06 (m, 3 H), 7.01–6.97 (m, 1 H), 6.93 (d, *J* = 7.9 Hz, 1 H), 4.66–4.55 (m, 1 H), 2.63–2.51 (m, 4 H), 1.77 (s, 3 H), 1.61–1.52 (m, 4 H), 1.39–1.30 (m, 10 H), 0.95–0.87 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.4, 142.1, 139.4, 138.1, 137.8, 131.6, 128.8, 127.9, 126.6, 126.5, 124.3, 108.0, 78.8, 50.8, 35.6, 35.3, 34.1, 33.6, 23.7, 22.5, 21.2, 21.2, 14.1, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{35}NO_2$ + Na: 416.2566; found: 416.2571.

6-Butyl-3-(4-butylphenyl)-3-methylbenzofuran-2(3*H*)-one *O*-Isopropyl Oxime (3j′)

Purification by preparative thin-layer chromatography (petroleum ether/EtOAc = 50:1).

Yield: 7.1 mg (18%); colourless oil.

IR (neat): 2936, 2849, 1721, 1452, 1218, 1036, 824, 749, 698, 518 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.2 Hz, 2 H), 7.12–7.04 (m, 3 H), 6.93–6.87 (m, 1 H), 6.86–6.82 (m, 1 H), 4.67–4.57 (m, 1 H), 2.65 (t, *J* = 7.8 Hz, 2 H), 2.55 (t, *J* = 7.8 Hz, 2 H), 1.76 (s, 3 H), 1.70–1.61 (m, 3 H), 1.60–1.50 (m, 3 H), 1.45–1.37 (m, 2 H), 1.36–1.34 (m, 3 H), 1.34–1.33 (m, 3 H), 0.95 (t, *J* = 7.3 Hz, 3 H), 0.90 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.7, 143.6, 142.1, 141.5, 137.8, 128.8, 128.8, 126.5, 124.0, 123.2, 108.3, 78.8, 50.5, 36.1, 35.3, 33.8, 33.6, 23.8, 22.6, 22.5, 21.2, 21.1, 14.1, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{35}NO_2$ + Na: 416.2566; found: 416.2562.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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