Supporting Information

Site-Selective Double and Tetra Cyclization Routes to Fused Polyheterocyclic Structures by Pd-Catalyzed Carbonylation Reactions

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1. General Methods

All reagents were used as received from commercial sources without further purification. All solvents were dried over activated molecular sieves. All reactions were carried out in stainless steel autoclaves and analyzed by TLC (Thin Layer Chromatography) on silica gel 60 F254. Flash column chromatography was performed on silica gel 60 (70–230 mesh). Melting points were measured with an Electrothermal apparatus and are uncorrected. GC analyses were performed with an Agilent Technologies 7820A equipped with a FID detector and a 30 m capillary column. GC-MS analyses (m/z, relative intensity %) were performed with an Agilent Technologies 7820A gas chromatograph coupled to a 5977B mass selective detector (Agilent Technologies) working at 70 eV ionizing voltage. Exact masses were recorded on a LTQ ORBITRAP XL Thermo Mass Spectrometer (ESI source). IR spectra were run on a Nicolet FT-IR 5700 spectrophotometer paired with a Diamond Smart Orbit accessory. Unless otherwise indicated NMR spectra were recorded on Bruker AVANCE 300 and 400 spectrometers in deuterated chloroform, using the solvent residual signals as internal reference (7.26 and 77.00 ppm, respectively for $^1$H and $^{13}$C). Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. The following abbreviations were used to explain the multiplicities: s=singlet, d= doublet, t=triplet, q=quartet, hept=heptet, m=multiplet, dd=double doublets, b=broad.
2. Optimization study for the oxidative carbonylation of amine/amide derivatives

2.1 Selected optimization experiments for the oxidative carbonylation of 1a (Table S1)

Table S1.[a]

| Entry | Solvent (dry) | KI (mol%) | CO/air (MPa) | T (°C) | Conv (%) 1a[b] | Yield (%) 2a[c–d] |
|-------|---------------|-----------|--------------|--------|----------------|------------------|
| 1     | MeCN          | 10        | 1.2/4.8      | 120    | 100            | 58               |
| 2     | MeCN          | 10        | 0.6/2.4      | 120    | 100            | 28               |
| 3     | MeCN          | 10        | 1.6/0.4      | 120    | 100            | 62               |
| 4     | MeCN          | 10        | 1.6/0.4      | 100    | 100            | 76               |
| 5     | MeCN          | 10        | 1.6/0.4      | 80     | 100            | 86(83)           |
| 6     | MeCN          | 10        | 0.8/0.2      | 80     | 100            | 55               |
| 7     | MeCN          | 10        | 1.6/0.4      | 60     | 100            | 65               |
| 8     | MeCN          | 5         | 1.6/0.4      | 80     | 100            | 42               |
| 9     | MeCN          | 20        | 1.6/0.4      | 80     | 73             | 56               |
| 10    | 1,4-Dioxane   | 10        | 1.6/0.4      | 80     | 100            | 15               |
| 11    | DME           | 10        | 1.6/0.4      | 80     | 100            | 27               |
| 12    | Toluene       | 10        | 1.6/0.4      | 80     | 89             | 6                |
| 13[e] | MeCN          | 10        | 1.6/0.4      | 80     | 100            | 63               |
| 14[f] | MeCN          | 10        | 1.6/0.4      | 80     | 100            | 32               |
| 15[g] | MeCN          | 10        | 1.6/0.4      | 80     | 100            | 75               |
| 16[h] | MeCN          | -         | 1.6/0.4      | 80     | 100            | 58               |

[a] Reaction conditions: 1a (0.5 mmol), PdI₂ (1 mol%), KI (Pd/KI molar ratio is 1/10), solvent (5 mL), CO/air (reported pressure measured at 25 °C), 45 ml autoclave, 24h. [b] Conversion of 1a was determined by ¹H NMR analysis with the internal standard method. [c] Yields were determined via ¹H NMR analysis with the internal standard method. [d] Isolated yield in brackets. [e] 10 mL of solvent. [f] 0.5 mol% of PdI₂. [g] 2.0 mol% of PdI₂. [h] 1 mol% of K₂PdI₄ in place of PdI₂/KI.
2.2 Selected optimization experiments for the oxidative carbonylation of 1t (Table S2)

Table S2.[4]

| Entry | Solvent (dry) | KI (mol%) | CO/air (MPa) | T (°C) | Conv (% 1t) | Yield (% 3a) |
|-------|---------------|-----------|--------------|--------|-------------|-------------|
| 1     | MeCN          | 10        | 1.6/0.4      | 120    | 100         | 57          |
| 2     | MeCN          | 10        | 1.6/0.4      | 100    | 100         | 73          |
| 3     | MeCN          | 10        | 1.6/0.4      | 80     | 100         | 83(81)      |
| 4     | MeCN          | 10        | 1.6/0.4      | 60     | 100         | 70          |
| 5     | MeCN          | 10        | 1.6/0.4      | 40     | 85          | 20          |
| 6     | MeCN          | 10        | 0.8/0.2      | 80     | 100         | 55          |
| 7     | MeCN          | 5         | 1.6/0.4      | 80     | 100         | 49          |
| 8     | MeCN          | 20        | 1.6/0.4      | 80     | 82          | 45          |
| 9     | 1,4-Dioxane   | 10        | 1.6/0.4      | 80     | 100         | 21          |
| 10    | DME           | 10        | 1.6/0.4      | 95     | 100         | 21          |
| 11    | Toluene       | 10        | 1.6/0.4      | 80     | 89          | 18          |

[a] Reaction conditions: 1t (0.5 mmol), PdI₂ (1 mol%), KI (Pd/KI molar ratio is 1/10), solvent (5 mL), CO/air (reported pressure measured at 25 °C), 45 ml autoclave, 24h. [b] Conversion of 1t was determined by ¹H NMR analysis with the internal standard method. [c] Yields were determined via ¹H NMR analysis with the internal standard method. [d] Isolated yield in brackets.

2.3 Oxidative carbonylation of N-benzyl-2-(3-(benzylamino)-3-methylbut-1-yn-1-yl)aniline

\[ \text{Scheme S1} \]

N-benzyl-2-(3-(benzylamino)-3-methylbut-1-yn-1-yl)aniline, bearing two NH₂ groups, was subjected to oxidative carbonylation reactions under a wide range of conditions showed in Table S1 and S2. In all cases, a complex organic mixture was recovered. On the contrary, with an OH group in place of NH₂ on the propargylic moiety, the reaction was selective towards the formation of indole-fused furanone derivatives [1].

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3. General Procedures

General Procedure A for the alkylation of 2-haloanilines\(^{[2]}\)

To a round-bottom flask the aniline derivative (1 equiv), the benzaldehyde derivative (1 equiv) and MeOH (2 mL/mmol of aniline) were added. The resulting mixture was stirred at rt overnight. After removal of solvent under vacuum, the residue was dissolved in AcOH (2 mL/mmol of aniline), then NaBH\(_4\) (1.2 equiv) was added in portions at 0 °C. After stirring at rt for 1 h, the solvent was evaporated and the residue was dissolved in EtOAc. A solution of NaOH (1N) was added to the mixture until pH 8−9. The two phases were stirred vigorously for 1 h then separated. The aqueous layer was extracted with EtOAc twice and the combined organic extracts were washed with brine, dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under vacuum to give the crude product, which was used for the next step without purification.

General Procedure B for the synthesis of substrates 1 (Sonogashira coupling)

To a solution of 2-iodoaniline (1 equiv) in triethylamine (4 mL/mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (2 mol%), CuI (6 mol%) and propargylic amine/amide (1.2 equiv) were added. A proper amount of CH\(_2\)Cl\(_2\) (1-2 mL/mmol) was added in order to obtain a homogeneous solution. The mixture was stirred at rt for 4-24 h. After filtration and evaporation of the solvent, the residue was diluted with EtOAc (40 mL) and washed with water (40 mL) and brine (30 mL). The organic layer was dried over anhydrous Na\(_2\)SO\(_4\), filtered and the solvent was removed under reduced pressure. Products 1 were isolated by flash column chromatography on silica gel using mixtures of hexane-EtOAc as eluent.
General Procedure C for the \(\text{PdI}_2/\text{KI}\)-catalyzed oxidative carbonylation of 1 to compounds 2 and 3 (Table S1, S2, and Chart 1 and 2 in the main article)

\[
\text{R}^1\text{NH} - \text{R}^2\text{C} = \text{N} - \text{R}^3\text{R}^4\text{CO} + \text{CO} \xrightarrow{\text{PdI}_2/\text{KI}} \text{R}^1\text{N} - \text{R}^2\text{C} = \text{N} - \text{R}^3\text{R}^4\text{O} + \text{R}^2\text{N} - \text{R}^3\text{R}^4\text{O}
\]

A 45 mL stainless steel autoclave was charged with substrate 1 (0.5 mmol), \(\text{PdI}_2\) (1.8 mg, 1 mol%), KI (8 mg, 10 mol%) and the solvent (5 mL). The autoclave was sealed and pressurized with CO (1.6 MPa) and air (up to 2.0 MPa), heated at 80–120 °C (oil bath) under stirring for 24 h. Then the autoclave was cooled, degassed and opened. After evaporation of the solvent, products were purified by column chromatography on silica gel using mixtures of hexane-EtOAc as eluent.

Catalytic synthesis of product 3a on a 2 mmol scale

\[
\text{R}^1\text{NH} - \text{R}^2\text{C} = \text{N} - \text{R}^3\text{R}^4\text{NH}_2 + 3\text{CO} \xrightarrow{\text{PdI}_2/\text{KI}} \text{R}^1\text{N} - \text{R}^2\text{C} = \text{N} - \text{R}^3\text{R}^4\text{O} + 3\text{R}^2\text{N} - \text{R}^3\text{R}^4\text{O}
\]

A 45 mL stainless steel autoclave was charged with substrate 1a (2.0 mmol), \(\text{PdI}_2\) (7.3 mg, 1 mol%), KI (32 mg, 10 mol%) and the solvent (20 mL). The autoclave was sealed and pressurized with CO (1.6 MPa) and air (up to 2.0 MPa), heated at 80 °C (oil bath) under stirring for 24 h. Then the autoclave was cooled, degassed and opened. After evaporation of the solvent, the crude product was purified by flash column chromatography using hexane/ethyl acetate (9/1) as eluent to give 2a (0.591 g, 75% yield).
4. Substrate characterizations

**N-(4-(2-(Benzylamino)phenyl)-2-methylbut-3-yn-2-yl)benzamide (1a)**

According to the general procedure B for Sonogashira coupling, \(N\)-benzyl-2-iodoaniline (1.085 g, 3.5 mmol), \(N\)-(2-methylbut-3-yn-2-yl)benzamide (0.749 g, 4.0 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (51 mg, 2 mol%) and CuI (41 mg, 6 mol%) were employed and the reaction mixture was stirred at rt for 6 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give 1a (0.837 g, 65% yield) as a pale yellow solid (m.p. 106.5–108.5 °C).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.74–7.66\) (m, 2H), 7.55–7.47 (m, 1H), 7.46–7.37 (m, 4H), 7.34–7.20 (m, 4H), 7.15–7.07 (m, 1H), 6.58 (td, \(J = 7.4, 0.9\) Hz, 1H), 6.53 (d, \(J = 8.3\) Hz, 1H), 6.34 (s, 1H), 6.31 (bs, 1H), 4.58 (s, 2H), 1.85 (s, 6H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 166.8, 149.9, 140.0, 134.8, 131.5, 131.2, 129.8, 128.6, 128.4, 127.1, 126.9, 126.7, 115.5, 109.6, 98.1, 78.8, 48.4, 47.3, 29.6; IR (ATR): \(\nu = 3407, 3365, 3021, 2982, 1636, 1601, 1575, 1518, 1484, 1287, 1182, 750, 737, 721\) cm\(^{-1}\). HRMS (ESI+) calcd for C\(_{25}\)H\(_{25}\)N\(_2\)O (M+1)\(^+\) m/z 369.1967, found m/z 369.1971.

**N-(4-(2-((4-Methoxybenzyl)amino)phenyl)-2-methylbut-3-yn-2-yl)benzamide (1b)**

According to the general procedure B for Sonogashira coupling, 2-iodo-\(N\)-(4-methoxybenzyl)aniline (1.036 g, 3.0 mmol), \(N\)-(2-methylbut-3-yn-2-yl)benzamide (0.669 g, 3.6 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (42 mg, 2 mol%) and CuI (36 mg, 6 mol%) were employed and the reaction mixture was stirred at rt for 6 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give 1b (0.871 g, 73% yield) as a brown solid (m.p. 128.5–130.0 °C). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.74–7.66\) (m, 2H), 7.51 (t, \(J = 7.4\) Hz, 1H), 7.41 (t, \(J = 7.5\) Hz, 2H), 7.34 (d, \(J = 8.5\) Hz, 2H), 7.26 (dd, \(J = 7.5, 1.5\) Hz, 1H), 7.14–7.08 (m, 1H), 6.83 (d, \(J = 8.6\) Hz, 2H), 6.60–6.50 (m, 2H), 6.33 (s, 1H), 6.18 (s, 1H), 4.49 (s, 2H), 3.79 (s, 3H), 1.84 (s, 6H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 166.7, 158.5, 149.8, 134.8, 132.0, 131.5, 131.2, 129.8, 128.6, 128.3, 126.9, 115.5, 113.8, 109.6, 106.9, 98.1, 78.8, 55.2, 48.4, 46.7, 29.6; IR (ATR): \(\nu = 3406, 3329, 2991, 2970, 1659, 1601, 1512, 1289, 1247, 1177, 1031, 755, 716\) cm\(^{-1}\). HRMS (ESI+) calcd for C\(_{26}\)H\(_{27}\)N\(_2\)O\(_2\) (M+1)** m/z 399.2073, found m/z 399.2072.
According to the general procedure B for Sonogashira coupling, N-benzyl-2-iodo-4-methylaniline (0.401 g, 1.25 mmol), N-(2-methylbut-3-yn-2-yl)benzamide (0.281 g, 1.5 mmol), PdCl$_2$(PPh$_3$)$_2$ (19 mg, 2 mol%) and CuI (14 mg, 6 mol%) were employed and the reaction mixture was stirred at rt for 6 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give 1c (0.224 g, 47% yield) as a brown solid (m.p. 129.5–131.0 °C).

$\text{H NMR (400 MHz, CDCl}_3$: $\delta = 7.72–7.67$ (m, 2H), $7.53–7.47$ (m, 1H), $7.44–7.37$ (m, 4H), $7.32–7.26$ (m, 2H), $7.25–7.18$ (m, 1H), $7.09$ (d, $J = 2.0$ Hz, 1H), $6.91$ (dd, $J = 8.4$, 1.6 Hz, 1H), $6.43$ (d, $J = 8.4$ Hz, 1H), $6.29$ (bs, 1H), $6.02$ (bs, 1H), $4.53$ (s, 2H), $2.18$ (s, 3H), $1.84$ (s, 6H);

$\text{C NMR (101 MHz, CDCl}_3$: $\delta = 166.7$, $147.7$, $140.2$, $134.9$, $131.55$, $131.50$, $130.5$, $128.6$, $128.4$, $127.0$, $126.9$, $126.7$, $124.6$, $109.7$, $106.8$, $97.8$, $78.8$, $48.5$, $47.5$, $29.6$, $20.1$; IR (ATR): $\nu = 3402$, 3361, 3029, 2975, 1634, 1600, 1581, 1283, 1178, 751, 735 cm$^{-1}$. HRMS (ESI+) calcd for C$_{26}$H$_{27}$N$_2$O (M+1)$^+$ m/z 383.2123, found m/z 383.2120.

According to the general procedure B for Sonogashira coupling, N-benzyl-2-iodo-4-isopropylaniline (1.060 g, 3.0 mmol), N-(2-methylbut-3-yn-2-yl)benzamide (0.615 g, 3.3 mmol), PdCl$_2$(PPh$_3$)$_2$ (44 mg, 2 mol%) and CuI (37 mg, 6 mol%) were employed and the reaction mixture was stirred at rt for 6 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give 1d (0.762 g, 62% yield) as a yellow solid (m.p. 115.3–117.9 °C).

$\text{H NMR (400 MHz, CDCl}_3$: $\delta = 7.74–7.69$ (m, 2H), $7.54–7.48$ (m, 1H), $7.46–7.38$ (m, 4H), $7.34–7.28$ (m, 2H), $7.27–7.22$ (m, 1H), $7.17$ (d, $J = 2.1$ Hz, 1H), $7.00$ (dd, $J = 8.5$, 2.1 Hz, 1H), $6.49$ (d, $J = 8.5$ Hz, 1H), $6.35$ (bs, 1H), $6.08$ (bs, 1H), $4.55$ (s, 2H), $2.78$ (hept, $J = 6.9$ Hz, 1H), $1.86$ (s, 6H), $1.21$ (d, $J = 6.9$ Hz, 6H); $\text{C NMR (101 MHz, CDCl}_3$: $\delta = 166.8$, $148.1$, $140.3$, $136.0$, $134.9$, $131.5$, $128.9$, $128.6$, $128.4$, $128.1$, $127.1$, $126.9$, $126.7$, $109.7$, $106.7$, $97.8$, $79.0$, $48.5$, $47.6$, $33.0$, $29.6$, $24.2$; IR (ATR): $\nu = 3410$, 3347, 2987, 2973, 1664, 1597, 1513, 1288, 1178, 755 cm$^{-1}$. HRMS (ESI+) calcd for C$_{28}$H$_{31}$N$_2$O (M+1)$^+$ m/z 411.2436, found m/z 411.2431.
According to the general procedure B for Sonogashira coupling, \(N\)-benzyl-4-chloro-2-iodoaniline (0.429 g, 1.25 mmol), \(N\)-(2-methylbut-3-yn-2-yl)benzamide (0.289 g, 1.5 mmol), \(\text{PdCl}_2(\text{PPh}_3)_2\) (18 mg, 2 mol%) and CuI (15 mg, 6 mol%) were employed and the reaction mixture was stirred at rt for 6 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give \(1e\) (0.206 g, 41% yield) as a brown solid (m.p. 147.3–149.0 °C).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.72–7.67\) (m, 2H), \(7.51 \) (t, \(J = 7.4\) Hz, 1H), \(7.44–7.36\) (m, 4H), \(7.33–7.21\) (m, 4H), \(7.02 \) (dd, \(J = 8.8, 2.5\) Hz, 1H), 6.43 (bs, 1H), 6.41 (d, \(J = 8.9\) Hz, 1H), 6.31 (bs, 1H), 4.55 (s, 2H), 1.83 (s, 6H);

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 166.8, 148.6, 139.6, 134.6, 131.6, 130.4, 129.6, 128.6, 128.5, 127.0, 126.9, 126.8, 119.7, 110.6, 108.3, 98.9, 77.7, 48.2, 47.3, 29.6;\)

IR (ATR): \(\nu = 3421, 3342, 3053, 2969, 2918, 1646, 1602, 1579, 1513, 1486, 1323, 1290, 1172, 739, 709\) cm\(^{-1}\). HRMS (ESI+) calcd for \(C_{25}H_{24}ClN_2O\) (M+1)\(^+\) \(m/z 403.1577\), found \(m/z 403.1579\).

\(N\)-(4-(2-Benzylamino)-5-chlorophenyl)-2-methylbut-3-yn-2-yl)benzamide (1f)

According to the general procedure B for Sonogashira coupling, \(N\)-benzyl-4-bromo-2-iodoaniline (0.794 g, 2.0 mmol), \(N\)-(2-methylbut-3-yn-2-yl)benzamide (0.420 g, 2.2 mmol), \(\text{PdCl}_2(\text{PPh}_3)_2\) (29 mg, 2 mol%) and CuI (23 mg, 6 mol%) were employed and the reaction mixture was stirred at rt for 6 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give \(1f\) (0.633 g, 71% yield) as a brown solid (m.p. 136.8–138.5 °C).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.72–7.67\) (m, 2H), \(7.54–7.48\) (m, 1H), \(7.44–7.34\) (m, 5H), \(7.32–7.23\) (m, 3H), 7.15 (dd, \(J = 8.8, 2.4\) Hz, 1H), 6.46 (bs, 1H), 6.37 (d, \(J = 8.9\) Hz, 1H), 6.32 (bs, 1H), 4.54 (d, \(J = 2.7\) Hz, 2H), 1.83 (s, 6H);

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 166.8, 148.9, 139.5, 134.6, 133.2, 132.3, 131.6, 128.6, 128.5, 127.0, 126.89, 126.86, 111.1, 108.9, 106.4, 99.0, 77.6, 48.2, 47.2, 29.6;\)

IR (ATR): \(\nu = 3410, 3347, 2951, 2908, 1649, 1600, 1565, 1514, 1481, 1331, 1293, 1170, 802, 729\) cm\(^{-1}\). HRMS (ESI+) calcd for \(C_{25}H_{24}BrN_2O\) (M+1)\(^+\) \(m/z 447.1072\), found \(m/z 447.1078\).

\(N\)-(4-(2-Benzylamino)-5-bromophenyl)-2-methylbut-3-yn-2-yl)benzamide (1g)
According to the general procedure B for Sonogashira coupling, N-benzyl-4-fluoro-2-iodoaniline (0.665 g, 2.0 mmol), N-(2-methylbut-3-yn-2-yl)benzamide (0.446 g, 2.4 mmol), PdCl$_2$(PPh$_3$)$_2$ (29 mg, 2 mol%) and Cul (22 mg, 6 mol%) were employed and the reaction mixture was stirred at rt for 6 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give 1g (0.517 g, 67% yield) as a pale yellow solid (m.p. 150.2–150.5 °C). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.74–7.67 (m, 2H), 7.54–7.48 (m, 1H), 7.45–7.37 (m, 4H), 7.34–7.20 (m, 3H), 6.98 (dd, $J$ = 8.9, 3.0 Hz, 1H), 6.82 (td, $J$ = 8.7, 3.0 Hz, 1H), 6.41 (dd, $J$ = 9.1, 4.6 Hz, 1H), 6.32 (bs, 1H), 6.22 (bs, 1H), 4.53 (s, 2H), 1.84 (s, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 166.8, 153.9 (d, $J_{C,F}$ = 233.4 Hz), 146.6, 139.9, 134.7, 131.6, 128.6, 128.4, 127.0, 126.9, 116.5 (d, $J_{C,F}$ = 22.2 Hz), 110.2 (d, $J_{C,F}$ = 7.9 Hz), 107.4 (d, $J_{C,F}$ = 9.2 Hz), 98.7, 77.9, 48.2, 47.7, 29.5; IR (ATR): $\nu$ = 3403, 3332, 2954, 2917, 1644, 1602, 1511, 1489, 1324, 1297, 1172, 732, 710 cm$^{-1}$. HRMS (ESI+) calcd for C$_{25}$H$_{24}$FN$_2$O (M+1)$^+$ m/z 387.1873, found m/z 387.1874.

Methyl 3-(3-benzamido-3-methylbut-1-yn-1-yl)-4-(benzylamino)benzoate (1h)

According to the general procedure B for Sonogashira coupling, methyl 4-(benzylamino)-3-iodobenzoate (0.734 g, 2.0 mmol), N-(2-methylbut-3-yn-2-yl)benzamide (0.488 g, 2.6 mmol), PdCl$_2$(PPh$_3$)$_2$ (45 mg, 3 mol%) and Cul (25 mg, 6 mol%) were employed and the reaction mixture was stirred at rt for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give 1h (0.596 g, 70% yield) as a pale yellow solid (m.p. 161.2-163.0 °C). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.96 (d, $J$ = 1.9 Hz, 1H), 7.77 (dd, $J$ = 8.7, 1.8 Hz, 1H), 7.68 (d, $J$ = 7.6 Hz, 2H), 7.49 (t, $J$ = 7.1 Hz, 1H), 7.42–7.35 (m, 4H), 7.32–7.21 (m, 3H), 7.08 (b t, $J$ = 5.9 Hz, 1H), 6.49 (d, $J$ = 8.8 Hz, 1H), 6.42 (bs, 1H), 4.63 (d, $J$ = 5.9 Hz, 2H), 3.83 (s, 3H), 1.83 (s, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 167.0, 153.3, 139.1, 134.6, 133.1, 131.7, 131.6, 128.6, 128.5, 126.98, 126.96, 126.9, 116.7, 108.5, 106.6, 98.4, 77.9, 51.5, 48.1, 46.9, 29.6; IR (ATR): $\nu$ = 3400, 3323, 2955, 2915, 1709, 1641, 1554, 1504, 1484, 1328, 1298, 1172, 734 cm$^{-1}$. HRMS (ESI+) calcd for C$_{26}$H$_{26}$FN$_2$O$_3$ (M+1)$^+$ m/z 427.2022, found m/z 427.2026.
According to the general procedure B for Sonogashira coupling, N-benzyl-2-iodo-4-(trifluoromethyl)aniline (0.747 g, 2.0 mmol), N-(2-methylbut-3-yn-2-yl)benzamide (0.454 g, 2.4 mmol), PdCl₂(PPh₃)₂ (46 mg, 3 mol%) and CuI (28 mg, 7 mol%) were employed and the reaction mixture was stirred at rt for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give 1i (0.567 g, 65% yield) as a pale yellow solid (m.p. 133.5–134.5 °C).

1H NMR (400 MHz, CDCl₃): δ = 7.69 (d, J = 7.4 Hz, 2H), 7.55–7.47 (m, 2H), 7.45–7.37 (m, 4H), 7.33–7.21 (m, 4H), 6.93 (bs, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.31 (bs, 1H), 4.61 (d, J = 5.3 Hz, 2H), 1.84 (s, 6H);

13C NMR (101 MHz, CDCl₃): δ = 166.9, 152.1, 139.2, 134.5, 131.7, 128.6, 128.5, 128.2 (q, J₅,F = 3.4 Hz), 126.95, 126.87, 126.7 (q, J₅,F = 3.3 Hz), 124.7 (q, J₅,F = 270.3 Hz), 117.0 (q, J₅,F = 32.8 Hz), 108.8, 106.8, 98.9, 77.7, 48.1, 46.9, 29.6; IR (ATR): ν = 3397, 3325, 2965, 2910, 1634, 1604, 1508, 1488, 1322, 1300, 1169, 734 cm⁻¹.

HRMS (ESI+) calcd for C₂₆H₂₄F₃N₂O (M+1)⁺ m/z 437.1841, found m/z 437.1843.

According to the general procedure B for Sonogashira coupling, N-benzyl-2-iodo-4,6-dimethylaniline (0.687 g, 2.0 mmol), N-(2-methylbut-3-yn-2-yl)benzamide (0.450 g, 2.4 mmol), PdCl₂(PPh₃)₂ (42 mg, 3 mol%) and CuI (29 mg, 7 mol%) were employed and the reaction mixture was stirred at rt for 6 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give 1j (0.396 g, 50% yield) as a pale yellow solid (m.p. 79.0–80.0 °C).

1H NMR (400 MHz, CDCl₃): δ = 7.76–7.72 (m, 2H), 7.51–7.43 (m, 3H), 7.39 (t, J = 7.5 Hz, 2H), 7.34–7.27 (m, 2H), 7.26–7.22 (m, 1H), 7.11 (d, J = 1.6 Hz, 1H), 6.93 (d, J = 1.5 Hz, 1H), 6.55 (bs, 1H), 4.46 (two overlapping signals: bs and s, 3H), 2.35 (s, 3H), 2.26 (s, 3H), 1.83 (s, 6H); 13C NMR (101 MHz, CDCl₃): δ = 166.7, 146.9, 140.9, 135.1, 132.9, 131.4, 130.6, 129.6, 128.5, 128.4, 128.0, 127.9, 127.1, 127.0, 113.5, 96.8, 79.7, 52.3, 48.8, 29.2, 20.4, 19.2; IR (ATR): ν = 3406, 3356, 3023, 2979, 1637, 1601, 1579, 1511, 1481, 1281, 1182, 755, 734 cm⁻¹. HRMS (ESI+) calcd for C₂₇H₂₆F₂N₂O (M+1)⁺ m/z 397.2280, found m/z 397.2273.
According to the general procedure B for Sonogashira coupling, N-benzyl-2-bromo-4-ethyl-6-iodoaniline (0.325 g, 0.78 mmol), N-(2-methylbut-3-yn-2-yl)benzamide (0.195 g, 1.04 mmol), PdCl₂(PPh₃)₂ (17 mg, 3 mol%) and CuI (12 mg, 8 mol%) were employed and the reaction mixture was stirred at rt for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give 1k (0.295 g, 80% yield) as a pale yellow solid (m.p. 168.7–170.3 °C).

1H NMR (400 MHz, CDCl₃): δ = 7.82–7.76 (m, 1H), 7.72–7.67 (m, 2H), 7.52–7.47 (m, 1H), 7.46–7.37 (m, 4H), 7.32–7.25 (m, 2H), 7.24–7.19 (m, 1H), 7.17 (d, J = 1.6 Hz, 1H), 6.26 (bs, 1H), 4.73 (s, 2H), 2.52 (q, J = 7.6 Hz, 2H), 1.79 (s, 6H), 1.20 (t, J = 7.6 Hz, 3H);

13C NMR (101 MHz, CDCl₃): δ = 166.5, 145.6, 140.3, 136.8, 134.9, 133.1, 132.4, 131.4, 128.6, 128.5, 128.4, 127.9, 127.0, 126.9, 114.3, 133.6, 97.6, 79.2, 51.5, 48.8, 29.0, 27.5, 15.4; IR (ATR): ν = 3416, 3347, 3018, 2964, 1614, 1570, 1487, 1294, 1175, 729 cm⁻¹. HRMS (ESI+) calcd for C₂₇H₂₈BrN₂O (M+1)⁺ m/z 475.1385, found m/z 475.1388.

According to the general procedure B for Sonogashira coupling, N-benzyl-5-chloro-2-iodoaniline (0.678 g, 2.0 mmol), N-(2-methylbut-3-yn-2-yl)benzamide (0.443 g, 2.4 mmol), PdCl₂(PPh₃)₂ (30 mg, 2 mol%) and CuI (26 mg, 6 mol%) were employed and the reaction mixture was stirred at rt for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give 1l (0.525 g, 65% yield) as a pale yellow solid (m.p. 128.0–128.5 °C).

1H NMR (400 MHz, CDCl₃): δ = 7.68 (d, J = 8.0 Hz, 2H), 7.51 (t, J = 7.4 Hz, 1H), 7.43–7.37 (m, 4H), 7.34–7.22 (m, 3H), 7.15 (d, J = 8.0 Hz, 1H), 6.55–6.48 (m, 3H), 6.31 (bs, 1H), 4.54 (s, 2H), 1.82 (s, 6H); 13C NMR (101 MHz, CDCl₃): δ = 166.8, 150.8, 139.3, 135.6, 134.6, 131.9, 131.6, 128.6, 128.5, 127.0, 126.93, 126.88, 115.5, 109.4, 105.6, 98.7, 78.0, 48.2, 47.1, 29.6; IR (ATR): ν = 3409, 3329, 2981, 1654, 1595, 1292, 1171, 748 cm⁻¹. HRMS (ESI+) calcd for C₂₅H₂₅BrN₂O (M+1)⁺ m/z 403.1577, found m/z 403.1576.

N-(1-((2-(Benzylamino)phenyl)ethynyl)cyclohexyl)benzamide (1m)
According to the general procedure B for Sonogashira coupling, \textit{N}-benzyl-2-iodoaniline (0.247 g, 0.83 mmol), \textit{N}-\((1\text{-ethylencyclohexyl})\)benzamide (0.228 g, 1.0 mmol), \textit{PdCl}_2(\textit{PPh}_3)_2 (11 mg, 2 mol\%) and \textit{CuI} (10 mg, 6 mol\%) were employed and the reaction mixture was stirred at rt for 4 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give 1m (0.278 g, 82\% yield) as a pale yellow solid (m.p. 98.1–99.2 °C).  

\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\textsuperscript{)}: \(\delta = 7.73–7.68 \text{ (m, 2H)}, 7.50 \text{ (t, } J = 7.4 \text{ Hz, 1H)}, 7.44–7.37 \text{ (m, 4H)}, 7.33–7.21 \text{ (m, 4H)}, 7.13–7.08 \text{ (m, 1H)}, 6.58 \text{ (t, } J = 7.4 \text{ Hz, 1H)}, 6.53 \text{ (d, } J = 8.3 \text{ Hz, 1H)}, 6.34 \text{ (bs, 1H)}, 6.25 \text{ (bs, 1H)}, 4.56 \text{ (s, 2H)}, 2.47–2.35 \text{ (m, 2H)}, 2.97–1.77 \text{ (m, 4H)}, 1.76–162 \text{ (m, 3H)}, 1.45–1.34 \text{ (m, 1H)}; \text{\textsuperscript{13}C NMR (101 MHz, CDCl}_3\textsuperscript{)}: \(\delta = 166.6, 149.9, 140.0, 135.1, 131.5, 131.3, 129.7, 128.6, 128.4, 127.1, 126.9, 126.7, 115.4, 109.5, 107.2, 96.7, 80.9, 52.6, 47.3, 37.5, 25.4, 22.7; \text{IR (ATR): } \nu = 3347, 3060, 2938, 2853, 1635, 1601, 1571, 1515, 1487, 1448, 1322, 1289, 1160, 727 \text{ cm}^{-1} \text{. HRMS (ESI+) calcd for } \text{C}_{28}\text{H}_{29}\text{N}_2\text{O (M+1)}^+ \text{m/z 409.2280, found m/z 409.2284.}

\textit{N}-\((3\text{-}(2\text{-((Benzylamino)phenyl)prop-2-yn-1-yl)})\)benzamide (1n)

\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\textsuperscript{)}: \(\delta = 7.79 \text{ (d, } J = 7.3 \text{ Hz, 2H)}, 7.53 \text{ (t, } J = 7.4 \text{ Hz, 1H)}, 7.44 \text{ (t, } J = 7.5 \text{ Hz, 2H)}, 7.39–7.24 \text{ (m, 6H)}, 7.16 \text{ (t, } J = 7.4 \text{ Hz, 1H}), 6.64 \text{ (t, } J = 7.5 \text{ Hz, 1H}), 6.57 \text{ (d, } J = 8.3 \text{ Hz, 1H)}, 6.56 \text{ (bs, 1H)}, 4.53 \text{ (d, } J = 5.2 \text{ Hz, 2H)}, 4.45 \text{ (s, 2H)}; \text{\textsuperscript{13}C NMR (101 MHz, CDCl}_3\textsuperscript{)}: \(\delta = 167.2, 149.1, 139.1, 133.9, 132.4, 131.8, 130.2, 128.7, 128.6, 127.2, 127.08, 127.06, 116.5, 110.0, 106.7, 90.7, 80.6, 47.6, 31.0; \text{IR (ATR): } \nu = 3345, 3239, 3064, 3028, 2925, 1622, 1599, 1547, 1522, 1324, 1297, 724, 695 \text{ cm}^{-1} \text{. HRMS (ESI+) calcd for } \text{C}_{23}\text{H}_{21}\text{N}_2\text{O (M+1)}^+ \text{m/z 341.1654, found m/z 341.1651.}

\textit{N}-\((4\text{-}(2\text{-((Benzylamino)phenyl)2-methylbut-3-yn-2-yl)})\)4-chlorobenzamide (1o)

S14
According to the general procedure B for Sonogashira coupling, \(N\)-benzyl-2-iodoaniline (0.643 g, 2.0 mmol), 4-chloro-\(N\)-(2-methylbut-3-yn-2-yl)benzamide (0.552 g, 2.5 mmol), \(\text{PdCl}_2(\text{PPh}_3)_2\) (28 mg, 2 mol%) and \(\text{CuI}\) (22 mg, 6 mol%) were employed and the reaction mixture was stirred at rt for 4 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give \(10\) (0.482 g, 60% yield) as a pale yellow solid (m.p. 130.2–131.0 °C). 

\(1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.63–7.58\) (m, 2H), 7.46–7.42 (m, 2H), 7.38–7.25 (m, 6H), 7.15 (ddd, \(J = 8.4, 7.4, 1.6\) Hz, 1H), 6.62 (td, \(J = 7.5, 1.0\) Hz, 1H), 6.58 (d, \(J = 8.3\) Hz, 1H), 6.42 (bs, 1H), 6.25 (bs, 1H), 4.59 (s, 2H), 1.86 (s, 6H);

\(13C\) NMR (101 MHz, CDCl\(_3\)): \(\delta = 165.8, 149.9, 140.0, 137.7, 133.2, 131.3, 129.9, 128.8, 128.5, 128.4, 127.1, 126.9, 115.7, 109.7, 106.9, 98.1, 78.9, 48.6, 47.3, 29.6;

IR (ATR): \(\nu = 3348, 3283, 3031, 2987, 2918, 1635, 1602, 1572, 1525, 1451, 1313, 1281, 1184, 1083, 840, 741\) cm\(^{-1}\). HRMS (ESI+) calcd for \(C_{25}H_{24}ClN_2O\) (M+1)\(^+\) \(m/z\) 403.1577, found \(m/z\) 403.1578.

\(N\)-(4-(2-(Benzylamino)phenyl)-2-methylbut-3-yn-2-yl)-4-fluorobenzamide (1p)

According to the general procedure B for Sonogashira coupling, \(N\)-benzyl-2-iodoaniline (0.640 g, 2.0 mmol), 4-fluoro-\(N\)-(2-methylbut-3-yn-2-yl)benzamide (0.512 g, 2.5 mmol), \(\text{PdCl}_2(\text{PPh}_3)_2\) (29 mg, 2 mol%) and \(\text{CuI}\) (23 mg, 6 mol%) were employed and the reaction mixture was stirred at rt for 6 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give \(1p\) (0.463 g, 60% yield) as a brown solid (m.p. 100.1–101.0 °C). 

\(1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.73–7.67\) (m, 2H), 7.45 (d, \(J = 7.2\) Hz, 2H), 7.36–7.25 (m, 4H), 7.18–7.11 (m, 1H), 7.09–7.02 (m, 2H), 6.62 (td, \(J = 7.5, 0.9\) Hz, 1H), 6.58 (d, \(J = 8.3\) Hz, 1H), 6.48 (bs, 1H), 6.31 (bs, 1H), 4.60 (s, 2H), 1.86 (s, 6H); 

\(13C\) NMR (101 MHz, CDCl\(_3\)): \(\delta = 165.9, 164.7\) (d, \(J_{C,F} = 251.8\) Hz), 149.9, 140.0, 131.3, 131.0 (d, \(J_{C,F} = 3.1\) Hz), 129.9, 129.4 (d, \(J_{C,F} = 8.9\) Hz), 128.5, 127.1, 126.9, 115.6, 115.5 (d, \(J_{C,F} = 24.8\) Hz), 109.7, 107.0, 98.2, 78.8, 48.5, 47.3, 29.6; IR (ATR): \(\nu = 3343, 3027, 2979, 2917, 1654, 1602, 1574, 1491, 1288, 1226, 1157, 848, 731\) cm\(^{-1}\). HRMS (ESI+) calcd for \(C_{25}H_{24}FN_2O\) (M+1)\(^+\) \(m/z\) 387.1873, found \(m/z\) 387.1876.
According to the general procedure B for Sonogashira coupling, N-benzyl-2-iodoaniline (0.310 g, 1.0 mmol), N-(2-methylbut-3-yn-2-yl)-4-nitrobenzamide (0.276 g, 1.2 mmol), PdCl₂(PPh₃)₂ (21 mg, 3 mol%) and CuI (13 mg, 6 mol%) were employed and the reaction mixture was stirred at rt for 18 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give 1q (0.289 g, 70% yield) as a yellow solid (m.p. 125.1–126.5 °C).

1H NMR (400 MHz, CDCl₃): δ = 8.16 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 7.1 Hz, 2H), 7.37–7.11 (m, 1H), 6.65 (bs, 1H), 6.63–6.55 (m, 2H), 6.13 (bs, 1H), 4.56 (s, 2H), 1.87 (s, 6H); 13C NMR (101 MHz, CDCl₃): δ = 164.9, 149.8, 149.4, 140.3, 139.9, 131.4, 130.0, 128.5, 128.2, 127.1, 127.0, 123.7, 115.8, 109.7, 106.8, 97.7, 79.1, 48.9, 47.3, 29.5; IR (ATR): ν = 3339, 2961, 1642, 1514, 1476, 1287, 1175, 734 cm⁻¹. HRMS (ESI+) calcd for C₂₅H₂₄N₃O₃ (M+1⁺) m/z 414.1818, found m/z 414.1812.

According to the general procedure B for Sonogashira coupling, N-benzyl-2-iodoaniline (0.623 g, 2.0 mmol), N-(prop-2-yn-1-yl)acetamide (0.252 g, 2.6 mmol), PdCl₂(PPh₃)₂ (45 mg, 3 mol%) and CuI (25 mg, 6 mol%) were employed and the reaction mixture was stirred at rt for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give 1r (0.361 g, 65% yield) as a pale yellow solid (m.p. 139.5–141.0 °C). 1H NMR (400 MHz, CDCl₃): δ = 7.40–7.34 (m, 4H), 7.33–7.27 (m, 2H), 7.15 (ddd, J = 8.4, 7.4, 1.6 Hz, 1H), 6.63 (td, J = 7.5, 1.0 Hz, 1H), 6.56 (d, J = 8.2 Hz, 1H), 5.88 (bs, 1H), 5.13 (bs, 1H), 4.45 (s, 2H), 4.32 (d, J = 5.2 Hz, 2H), 2.01 (s, 3H); 13C NMR (101 MHz, CDCl₃): δ = 169.7, 149.0, 139.1, 132.3, 130.2, 128.7, 127.2, 127.1, 116.5, 110.0, 106.7, 90.7, 80.3, 47.6, 30.4, 23.1; IR (ATR): ν = 3351, 3269, 3061, 2927, 1630, 1602, 1554, 1514, 1459, 1329, 1290, 1275, 731 cm⁻¹. HRMS (ESI+) calcd for C₁₈H₁₉N₂O (M+1⁺) m/z 279.1497, found m/z 279.1499.

1-Benzyl-3-(4-(2-(benzylamino)phenyl)-2-methylbut-3-yn-2-yl)urea (1s)
According to the general procedure B for Sonogashira coupling, $N$-benzyl-2-iodoaniline (0.623 g, 2.0 mmol), 1-benzyl-3-(2-methylbut-3-yn-2-yl)urea (0.562 g, 2.6 mmol), PdCl$_2$(PPh$_3$)$_2$ (45 mg, 3 mol%) and CuI (25 mg, 6 mol%) were employed and the reaction mixture was stirred at rt for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give 1s (0.667 g, 84% yield) as a pale yellow solid (m.p. 155.1–157.0 °C).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 7.38–7.18 (m, 10H), 7.16 (d, $J =$ 7.6 Hz, 1H), 7.10 (further split t, $J =$ 7.5 Hz, 1H), 6.55 (t, $J =$ 7.5 Hz, 1H), 6.48 (d, $J =$ 8.3 Hz, 1H), 5.93 (bs, 1H), 5.30 (bs, 1H), 4.90 (bs, 1H), 4.42 (d, $J =$ 4.2 Hz, 2H), 4.28 (d, $J =$ 5.4 Hz, 2H), 1.65 (s, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta =$ 157.4, 149.6, 139.8, 139.1, 131.3, 129.8, 128.6, 128.5, 127.4, 127.2, 126.9, 126.8, 115.7, 109.7, 106.8, 98.8, 79.1, 47.7, 47.2, 44.3, 30.4; IR (ATR): $\nu =$ 3401, 3347, 3285, 2959, 2905, 1641, 1601, 1563, 1480, 1295, 1153, 733 cm$^{-1}$. HRMS (ESI+) calcd for C$_{26}$H$_{28}$N$_3$O (M+1)$^+$ m/z 398.2232, found m/z 398.2230.

2-(3-Amino-3-methylbut-1-yn-1-yl)-N-benzylaniline (1t)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 7.43–7.35 (m, 4H), 7.34–7.27 (m, 2H), 7.16 (further split t, $J =$ 7.9 Hz, 1H), 6.66 (td, $J =$ 7.5, 1.0 Hz, 1H), 6.59 (d, $J =$ 8.2 Hz, 1H), 4.97 (bs, 1H), 4.44 (d, $J =$ 5.4 Hz, 2H), 1.84 (bs, 2H), 1.52 (s, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta =$ 148.6, 139.2, 131.8, 129.6, 128.7 (2C), 127.3, 127.1, 116.6, 109.8, 107.7, 76.7, 47.8, 46.0 32.1; IR (ATR): $\nu =$ 3410, 3343, 3059, 2966, 2920, 1602, 1514, 1450, 1264, 1187, 1141, 902, 864, 736 cm$^{-1}$. HRMS (ESI+) calcd for C$_{18}$H$_{20}$N$_2$O (M+1)$^+$ m/z 265.1705, found m/z 265.1701.

2-(3-Amino-3-methylbut-1-yn-1-yl)-N-(4-methoxybenzyl)aniline (1u)
According to the general procedure B for Sonogashira coupling, 2-iodo-N-(4-methoxybenzyl)aniline (0.679 g, 2.0 mmol), 2-methylbut-3-yn-2-amine (0.216 g, 2.6 mmol), PdCl₂(PPh₃)₂ (42 mg, 3 mol%) and CuI (24 mg, 6 mol%) were employed and the reaction mixture was stirred at rt for 6 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate/methanol (2/2/1) as eluent to give 1u (0.494 g, 84% yield) as a pale yellow oil. 

\[ \text{1H NMR (400 MHz, CDCl}_3\text{): } \delta = 7.31 \text{ (dd, } J = 7.6, 1.4 \text{ Hz, 1H}), 7.27 \text{ (d, } J = 8.4 \text{ Hz, 2H), 7.17} \text{–} 7.11 \text{ (m, 1H), 6.88 (d, } J = 8.6 \text{ Hz, 2H), 6.63 (t, } J = 7.3 \text{ Hz, 1H), 6.57 (d, } J = 8.2 \text{ Hz, 1H), 4.92 (bs, 1H), 4.28 (d, } J = 4.7 \text{ Hz, 2H), 3.73 (s, 3H), 1.79 (bs, 2H), 1.47 (s, 6H); }\]

\[ \text{13C NMR (101 MHz, CDCl}_3\text{): } \delta = 158.9, 148.7, 131.8, 131.2, 129.6, 128.5, 116.5, 114.1, 109.9, 107.8, 103.4, 76.8, 55.2, 47.3, 45.9, 32.1; \]

\[ \text{IR (ATR): } \nu = 3394, 3294, 3047, 2965, 2905, 1571, 1494, 1407, 1333, 1273, 1178, 874, 807, 727 \text{ cm}^{-1}. \]

HRMS (ESI+) calcd for C₁₉H₂₃N₂O (M+1)⁺ m/z 295.1810, found m/z 295.1814.

2-(3-Amino-3-methylbut-1-yn-1-yl)-N-benzyl-4-isopropylaniline (1v)

According to the general procedure B for Sonogashira coupling, N-benzyl-2-iodo-4-isopropylaniline (0.704 g, 2.0 mmol), 2-methylbut-3-yn-2-amine (0.217 g, 2.6 mmol), PdCl₂(PPh₃)₂ (45 mg, 3 mol%) and CuI (24 mg, 6 mol%) were employed and the reaction mixture was stirred at rt for 6 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate/methanol (2/2/1) as eluent to give 1v (0.453 g, 74% yield) as a pale yellow oil. 

\[ \text{1H NMR (400 MHz, CDCl}_3\text{): } \delta = 7.46 \text{–} 7.37 \text{ (m, 4H), 7.33 (t, } J = 7.0 \text{ Hz, 1H), 7.25 (d, } J = 2.1 \text{ Hz, 1H), 7.07} \text{ (dd, } J = 8.4, 2.1 \text{ Hz, 1H), 6.58 (d, } J = 8.4 \text{ Hz, 1H), 4.90 (bs, 1H), 4.45 (d, } J = 4.9 \text{ Hz, 2H), 2.84 (hept, } J = 6.9 \text{ Hz, 1H), 1.88 (bs, 2H), 1.55 (s, 6H), 1.27 (d, } J = 6.9 \text{ Hz, 6H); }\]

\[ \text{13C NMR (101 MHz, CDCl}_3\text{): } \delta = 146.9, 139.6, 137.0, 129.6, 128.7, 127.8, 127.3, 127.2, 110.1, 107.6, 77.1, 48.1, 46.0, 33.1, 32.2, 24.2; \]

\[ \text{IR (ATR): } \nu = 3394, 3283, 3037, 2959, 2913, 1583, 1491, 1410, 1341, 1279, 1172, 870, 801, 729 \text{ cm}^{-1}. \]

HRMS (ESI+) calcd for C₂₁H₂₇N₂O (M+1)⁺ m/z 307.2174, found m/z 307.2171.
According to the general procedure B for Sonogashira coupling, N-benzyl-4-bromo-2-iodoaniline (0.776 g, 2.0 mmol), 2-methylbut-3-yn-2-amine (0.218 g, 2.6 mmol), PdCl₂(PPh₃)₂ (29 mg, 2 mol%) and CuI (23 mg, 6 mol%) were employed and the reaction mixture was stirred at rt for 6 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate/methanol (2/2/1) as eluent to give 1w (0.610 g, 89% yield) as a pale yellow oil.

1H NMR (400 MHz, CDCl₃): δ = 7.41 (d, J = 2.3 Hz, 1H), 7.39–7.26 (m, 5H), 7.19 (d, d, J = 8.8, 2.3 Hz, 1H), 6.40 (d, J = 8.8 Hz, 1H), 5.01 (bs, 1H), 4.37 (d, J = 5.4 Hz, 2H), 1.82 (bs, 2H), 1.50 (s, 6H);

13C NMR (101 MHz, CDCl₃): δ = 147.6, 138.7, 134.0, 132.2, 128.8, 127.4, 127.1, 111.4, 109.7, 107.6, 75.6, 47.7, 46.0, 32.1; IR (ATR): ν = 3397, 3031, 2968, 2929, 1592, 1566, 1497, 1404, 1320, 1264, 1168, 878, 801, 731, 696 cm⁻¹. HRMS (ESI+) calcd for C₁₈H₂₀BrN₂ (M+1)⁺ m/z 343.0810, found m/z 343.0814.

According to the general procedure B for Sonogashira coupling, N-benzyl-4-fluoro-2-iodoaniline (0.655 g, 2.0 mmol), 2-methylbut-3-yn-2-amine (0.219 g, 2.6 mmol), PdCl₂(PPh₃)₂ (43 mg, 3 mol%) and CuI (23 mg, 6 mol%) were employed and the reaction mixture was stirred at rt for 6 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate/methanol (2/2/1) as eluent to give 1x (0.406 g, 72% yield) as a white solid (m.p. 139.5–141.0 °C).

1H NMR (400 MHz, CDCl₃): δ = 7.41–7.27 (m, 5H), 7.01 (dd, J = 8.9, 3.0 Hz, 1H), 6.87 (td, J = 8.7, 3.0 Hz, 1H), 6.48 (dd, J = 9.0, 4.6 Hz, 1H), 4.81 (bs, 1H), 4.40 (d, J = 5.3 Hz, 2H), 1.88 (bs, 2H), 1.50 (s, 6H); ¹³C NMR (101 MHz, CDCl₃): δ = 154.5 (d, J = 234.6 Hz), 145.3 (d, J = 1.6 Hz), 139.0, 128.7, 127.3, 127.1, 118.0 (d, J = 23.7 Hz), 116.3 (d, J = 22.2 Hz), 110.6 (d, J = 7.9 Hz), 108.4 (d, J = 9.1 Hz), 103.9, 75.9 (d, J = 3.0 Hz), 48.3, 46.0, 31.9; IR (ATR): ν = 3408, 3336, 3059, 2966, 2926, 2359, 1513, 1446, 1265, 1191, 1148, 904, 869, 801, 743, 697 cm⁻¹. HRMS (ESI+) calcd for C₁₈H₂₀FN₂ (M+1)⁺ m/z 283.1611, found m/z 283.1609.
According to the general procedure B for Sonogashira coupling, N-benzyl-2-iodoaniline (0.682 g, 2.2 mmol), 1,3-bis(2-methylbut-3-yn-2-yl)urea (0.193 g, 1.0 mmol), PdCl$_2$(PPh$_3$)$_2$ (31 mg, 2 mol%) and CuI (24 mg, 6 mol%) were employed and the reaction mixture was stirred at rt for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate/CH$_2$Cl$_2$ (8/2/1) as eluent to give 5a (0.227 g, 42% yield) as a white solid (m.p. 139.5–141.0 °C). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.43$–7.25 (m, 12H), 7.16 (further split t, $J = 7.5$ Hz, 2H), 6.63 (td, $J = 7.5$, 0.9 Hz, 2H), 6.52 (d, $J = 8.2$ Hz, 2H), 6.12 (b t, $J = 5.4$ Hz, 2H), 5.26 (s, 2H), 4.50 (d, $J = 5.6$ Hz, 4H), 1.66 (s, 12H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 156.7$, 149.8, 139.8, 131.3, 129.9, 128.5, 127.0, 126.8, 115.8, 109.9, 106.9, 98.9, 79.2, 47.7, 47.3, 30.4; IR (ATR): $\nu = 3387$, 3335, 3049, 2952, 2926, 1664, 1609, 1556, 1418, 1291, 1158, 732 cm$^{-1}$. HRMS (ESI+) calcd for C$_{37}$H$_{38}$N$_4$O (M+1)$^+$ $m/z$ 555.3124, found $m/z$ 555.3127.
5. Product characterizations

6-Benzyl-4,4-dimethyl-2-phenyl-4,6-dihydro-5H-[1,3]oxazino[5,6-c]quinolin-5-one (2a)

According to the general procedure C, substrate 1a (0.184 g, 0.5 mmol), PdI₂ (1.8 mg, 1 mol%) and KI (8.3 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (9/1) as eluent to give 2a (0.159 g, 83% yield) as a white solid (m.p. 211.2–212.0 °C). ¹H NMR (400 MHz, CDCl₃): δ = 8.22 (dd, J = 7.9, 1.7 Hz, 2H), 8.13 (dd, J = 8.2, 1.4 Hz, 1H), 7.58–7.47 (m, 4H), 7.38–7.24 (m, 7H), 5.60 (bs, 2H), 1.90 (s, 6H); ¹³C NMR (101 MHz, CDCl₃): δ = 161.0, 150.4, 146.1, 138.7, 136.6, 131.9, 131.2, 131.1, 128.9, 128.4, 127.5, 127.3, 126.5, 122.9, 122.1, 114.9, 114.0, 112.0, 52.9, 45.9, 30.1 IR (ATR): v = 3013, 2948, 1684, 1631, 1512, 1452, 1297, 1262, 1247, 1136, 1018, 743 cm⁻¹. HRMS (ESI+) calcd for C₂₆H₂₃N₂O₂ (M+1)⁺ m/z 395.1760, found m/z 395.1762.

6-(4-Methoxybenzyl)-4,4-dimethyl-2-phenyl-4,6-dihydro-5H-[1,3]oxazino[5,6-c]quinolin-5-one (2b)

According to the general procedure C, substrate 1b (0.199 g, 0.5 mmol), PdI₂ (1.8 mg, 1 mol%) and KI (8.0 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (9/1) as eluent to give 2b (0.170 g, 80% yield) as a white solid (m.p. 159.4–160.0 °C). ¹H NMR (400 MHz, CDCl₃): δ = 8.22 (dd, J = 7.8, 1.8 Hz, 2H), 8.11 (dd, J = 8.0, 1.3 Hz, 1H), 7.57–7.47 (m, 4H), 7.34 (d, J = 8.5 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.52 (bs, 2H), 3.77 (s, 3H), 1.92 (s, 6H); ¹³C NMR (101 MHz, CDCl₃): δ = 161.0, 158.8, 150.4, 146.1, 138.6, 131.8, 131.2, 131.1, 128.7, 128.4, 128.0, 127.5, 122.8, 122.1, 114.9, 114.3, 113.9, 111.9, 55.3, 53.0, 45.3, 30.2; IR (ATR): v = 3001, 2959, 1691, 1634, 1510, 1458, 1295, 1274, 1244, 1177, 1124, 1021, 746 cm⁻¹. HRMS (ESI+) calcd for C₂₇H₂₅N₂O₃ (M+1)⁺ m/z 425.1865, found m/z 425.1861.
According to the general procedure C, substrate 1c (0.191 g, 0.5 mmol), Pd(II) (1.8 mg, 1 mol%) and KI (8.0 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (9/1) as eluent to give 2c (0.180 g, 88% yield) as a white solid (m.p. 192.0–193.0 °C).

\[ \text{1H NMR (400 MHz, CDCl}_3\text{): } \delta = 8.25–8.20 (m, 2H), 7.89 (d, } J = 0.7 \text{ Hz, 1H), 7.60–7.51 (m, 3H), 7.37–7.17 (m, 7H), 5.58 (bs, 2H), 2.50 (s, 3H), 1.89 (s, 6H); } \]
\[ \text{13C NMR (101 MHz, CDCl}_3\text{): } \delta = 160.9, 150.3, 146.2, 136.75, 136.69, 132.5, 131.9, 131.7, 131.2, 128.8, 128.5, 127.5, 127.2, 126.5, 122.4, 114.8, 113.8, 111.9, 53.0, 45.8, 30.1, 21.0; } \]
\[ \text{IR (ATR): } \nu = 2969, 1693, 1642, 1578, 1503, 1435, 1318, 1272, 1135, 1015, 803, 725 \text{ cm}^{-1}. \]
\[ \text{HRMS (ESI+) calcd for C}_{27}\text{H}_{25}\text{N}_{2}\text{O}_{2}(M+1)^{+} m/z 409.1916, \text{ found } m/z 409.1916. \]

6-Benzyl-9-isopropyl-4,4-dimethyl-2-phenyl-4,6-dihydro-5H-[1,3]oxazino[5,6-c]quinolin-5-one (2d)

According to the general procedure C, substrate 1d (0.205 g, 0.5 mmol), Pd(II) (1.8 mg, 1 mol%) and KI (8.0 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (9/1) as eluent to give 2d (0.203 g, 93% yield) as a white solid (m.p. 183.5–183.9 °C).

\[ \text{1H NMR (400 MHz, CDCl}_3\text{): } \delta = 8.25–8.18 (m, 2H), 7.94 (d, } J = 2.0 \text{ Hz, 1H), 7.61–7.52 (m, 3H), 7.40 (dd, } J = 8.8, 2.1 \text{ Hz, 1H), 7.35 (t, } J = 7.3 \text{ Hz, 2H), 7.31–7.24 (m, 4H), 5.59 (bs, 2H), 3.08 (hept, } J = 6.9 \text{ Hz, 1H), 1.87 (s, 6H), 1.35 (d, } J = 6.9 \text{ Hz, 6H); } \]
\[ \text{13C NMR (101 MHz, CDCl}_3\text{): } \delta = 160.9, 150.4, 146.1, 142.7, 137.0, 136.8, 132.0, 131.2, 129.9, 128.8, 128.5, 127.4, 127.2, 126.6, 119.9, 115.0, 113.8, 111.8, 53.0, 45.9, 33.7, 30.1, 24.1; } \]
\[ \text{IR (ATR): } \nu = 3024, 2948, 1691, 1645, 1568, 1500, 1435, 1322, 1269, 1129, 1013, 808, 728 \text{ cm}^{-1}. \]
\[ \text{HRMS (ESI+) calcd for C}_{29}\text{H}_{32}\text{N}_{2}\text{O}_{2}(M+H)^{+} m/z 437.2229, \text{ found } m/z 437.2233. \]
6-Benzyl-9-chloro-4,4-dimethyl-2-phenyl-4,6-dihydro-5H-[1,3]oxazino[5,6-c]quinolin-5-one (2e)

According to the general procedure C, substrate 1e (0.200 g, 0.5 mmol), PdI₂ (1.8 mg, 1 mol%), and KI (8.3 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (9/1) as eluent to give 2e (0.154 g, 72% yield) as a white solid (m.p. 224.8–226.1 °C).

1H NMR (400 MHz, CDCl₃): δ = 8.17 (dd, J = 8.0, 1.7 Hz, 2H), 8.02 (d, J = 2.4 Hz, 1H), 7.61–7.51 (m, 3H), 7.43 (dd, J = 9.0, 2.5 Hz, 1H), 7.37–7.31 (m, 2H), 7.30–7.18 (m, 4H), 5.56 (bs, 2H), 1.84 (s, 6H);

13C NMR (101 MHz, CDCl₃): δ = 160.6, 149.5, 145.9, 137.1, 136.1, 131.5, 131.4, 129.0, 128.5, 127.8, 127.5, 126.4, 122.3, 116.4, 115.1, 113.0, 53.0, 46.0, 30.0; IR (ATR): ν = 3044, 2958, 2907, 1647, 1604, 1561, 1496, 1339, 1291, 1171, 809, 726 cm⁻¹. HRMS (ESI+) calcd for C₂₆H₂₂ClN₂O₂ (M+1)+ m/z 429.1370, found m/z 429.1376.

6-Benzyl-9-bromo-4,4-dimethyl-2-phenyl-4,6-dihydro-5H-[1,3]oxazino[5,6-c]quinolin-5-one (2f)

According to the general procedure C, substrate 1f (0.223 g, 0.5 mmol), PdI₂ (1.8 mg, 1 mol%), and KI (8.0 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (9/1) as eluent to give 2f (0.191 g, 81% yield) as a white solid (m.p. 209.1–211.5 °C).

1H NMR (400 MHz, CDCl₃): δ = 8.21–8.14 (m, 3H), 7.60–7.51 (m, 4H), 7.35 (t, J = 7.3 Hz, 2H), 7.28 (t, J = 7.2 Hz, 1H), 7.24–7.19 (m, 2H), 7.16 (d, J = 9.0 Hz, 1H), 5.55 (bs, 2H), 1.86 (s, 6H);

13C NMR (101 MHz, CDCl₃): δ = 160.6, 149.4, 145.8, 137.5, 136.1, 133.9, 131.5, 131.4, 129.0, 128.5, 127.49, 127.47, 126.4, 125.3, 116.6, 115.5, 115.2, 113.0, 53.0, 46.0, 30.0; IR (ATR): ν = 3041, 2955, 2915, 1643, 1599, 1547, 1485, 1327, 1283, 1179, 801, 724 cm⁻¹. HRMS (ESI+) calcd for C₂₆H₂₂BrN₂O₂ (M+1)+ m/z 473.0865, found m/z 473.0868.
6-Benzyl-9-fluoro-4,4-dimethyl-2-phenyl-4,6-dihydro-5H-[1,3]oxazino[5,6-c]quinolin-5-one (2g)

\[
\begin{align*}
\text{Bn} & & \text{Ph} \\
\text{F} & & \text{N} \\
\text{O} & & \text{N} \\
\end{align*}
\]

According to the general procedure C, substrate 1g (0.193 g, 0.5 mmol), PdI\(_2\) (1.8 mg, 1 mol%) and KI (8.1 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/1) as eluent to give 2g (0.183 g, 89% yield) as a white solid (m.p. 219.7–220.1 °C). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 8.20–8.15 (m, 2H), 7.75 (dd, J = 8.6, 2.6 Hz, 1H), 7.60–7.50 (m, 3H), 7.37–7.32 (m, 2H), 7.31–7.19 (m, 5H), 5.58 (bs, 2H), 1.86 (s, 6H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 160.6, 157.9 (d, J_{C,F} = 242.7 Hz), 149.7 (d, J_{C,F} = 3.1 Hz), 145.8, 136.3, 135.1, 131.5, 128.9, 128.5, 127.4, 126.4, 119.0 (d, J_{C,F} = 24.0 Hz), 116.6 (d, J_{C,F} = 8.0 Hz), 114.9 (d, J_{C,F} = 8.5 Hz), 113.1, 108.4 (d, J_{C,F} = 24.3 Hz), 53.0, 46.1, 30.0; IR (ATR): \(\nu = 3038, 2949, 2902, 1642, 1605, 1573, 1512, 1485, 1324, 1281, 1174, 809, 729 \text{ cm}^{-1}. \) HRMS (ESI+) calcd for C\(_{26}\)H\(_{22}\)FN\(_2\)O\(_2\) (M+1)\(^+\) m/z 413.1665, found m/z 413.1661.

Methyl 6-benzyl-4,4-dimethyl-5-oxo-2-phenyl-5,6-dihydro-4H-[1,3]oxazino[5,6-c]quinoline-9-carboxylate (2h)

\[
\begin{align*}
\text{MeO}_2\text{C} & & \text{Bn} \\
\text{N} & & \text{O} \\
\text{O} & & \text{N} \\
\end{align*}
\]

According to the general procedure C, substrate 1h (0.213 g, 0.5 mmol), PdI\(_2\) (1.8 mg, 1 mol%) and KI (8.0 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (9/1) as eluent to give 2h (0.108 g, 48% yield) as a white solid (m.p. 258.1–259.9 °C). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 8.78 (d, J = 2.0 Hz, 1H), 8.23–8.18 (m, 2H), 8.12 (dd, J = 8.9, 2.0 Hz, 1H), 7.61–7.51 (m, 3H), 7.37–7.25 (m, 4H), 7.23 (d, J = 7.1 Hz, 2H), 5.60 (bs, 2H), 3.99 (s, 3H), 1.84 (s, 6H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 166.2, 161.0, 150.5, 145.9, 141.4, 136.0, 131.8, 131.5, 131.3, 129.0, 128.5, 127.5 (2C), 126.5, 125.2, 123.9, 114.9, 113.7, 112.6, 52.9, 52.4, 46.1, 30.0; IR (ATR): \(\nu = 3053, 2956, 2923, 1639, 1601, 1562, 1503, 1486, 1330, 1291, 1165, 789, 727 \text{ cm}^{-1}. \) HRMS (ESI+) calcd for C\(_{28}\)H\(_{25}\)N\(_2\)O\(_4\) (M+1)\(^+\) m/z 453.1814, found m/z 453.1812.
According to the general procedure C, substrate 1i (0.218 g, 0.5 mmol), PdI₂ (1.8 mg, 1 mol%) and KI (8.2 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (9/1) as eluent to give 2i (0.150 g, 75% yield) as a white solid (m.p. 222.1–224.2 °C).

\[ \text{^1H NMR (400 MHz, CDCl}_3\text{): } \delta = 8.35 (d, J = 1.2 Hz, 1H), 8.19 (dd, J = 7.8, 1.8 Hz, 2H), 7.72 (dd, J = 8.9, 1.9 Hz, 1H), 7.62–7.52 (m, 3H), 7.43–7.34 (m, 3H), 7.33–7.27 (m, 1H), 7.24 (d, J = 7.2 Hz, 2H), 5.61 (bs, 2H), 1.87 (s, 6H); \]

\[ \text{^13C NMR (101 MHz, CDCl}_3\text{): } \delta = 160.9, 150.1, 145.7, 140.5, 135.9, 131.43, 131.41, 129.0, 128.6, 127.6, 127.48 (q, J_{C,F} = 3.5 Hz), 127.43, 126.4, 124.3 (q, J_{C,F} = 33.4 Hz), 124.0 (q, J_{C,F} = 271.7 Hz), 120.5 (q, J_{C,F} = 4.1 Hz), 115.4, 113.8, 113.3, 52.9, 46.1, 30.0; IR (ATR): v = 3049, 2966, 2942, 2912, 1644, 1601, 1559, 1519, 1488, 1328, 1295, 1177, 803, 730 cm\textsuperscript{-1}. \]

HRMS (ESI+) calcd for C\textsubscript{27}H\textsubscript{22}F\textsubscript{3}N\textsubscript{2}O\textsubscript{2} (M+1)\textsuperscript{+} m/z 463.1633, found m/z 463.1634.

According to the general procedure C, substrate 1j (0.198 g, 0.5 mmol), PdI₂ (1.8 mg, 1 mol%) and KI (8.1 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (9/1) as eluent to give 2j (0.137 g, 62% yield) as a white solid (m.p. 188.2–189.5 °C).

\[ \text{^1H NMR (400 MHz, CDCl}_3\text{): } \delta = 8.24–8.19 (m, 2H), 7.84 (s, 1H), 7.60–7.50 (m, 3H), 7.34 (t, J = 7.3 Hz, 2H), 7.25 (t, J = 7.3 Hz, 1H), 7.20 (s, 1H), 7.11 (d, J = 7.6 Hz, 2H), 5.70 (bs, 2H), 2.56 (s, 3H), 2.48 (s, 3H), 1.83 (s, 6H); \]

\[ \text{^13C NMR (101 MHz, CDCl}_3\text{): } \delta = 162.5, 150.6, 146.4, 138.8, 138.0, 137.7, 132.0, 131.8, 131.2, 128.7, 128.5, 127.5, 126.7, 125.4, 124.4, 121.0, 115.7, 111.4, 52.9, 49.9, 30.0, 24.1, 20.8; IR (ATR): v = 3058, 3035, 2950, 2927, 1643, 1605, 1561, 1513, 1481, 1324, 1298, 1172, 818, 732 cm\textsuperscript{-1}. \]

HRMS (ESI+) calcd for C\textsubscript{27}H\textsubscript{22}N\textsubscript{2}O\textsubscript{2} (M+1)\textsuperscript{+} m/z 432.2073, found m/z 423.2077.
6-Benzyl-7-bromo-9-ethyl-4,4-dimethyl-2-phenyl-4,6-dihydro-5H-[1,3]oxazino[5,6-c]quinolin-5-one (2k)

According to the general procedure C, substrate 1k (0.237 g, 0.5 mmol), PdI$_2$ (1.8 mg, 1 mol%) and KI (8.2 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (15/1) as eluent to give 2k (0.030 g, 12% yield) as a pale yellow solid (m.p. 185.6–186.1 °C).

$^1$H NMR (400 MHz, CDCl$_3$): δ = 8.16 (dd, $J = 7.9$, 1.6 Hz, 2H), 7.91 (d, $J = 2.0$ Hz, 1H), 7.70 (d, $J = 2.1$ Hz, 1H), 7.61–7.51 (m, 3H), 7.33–7.27 (m, 2H), 7.22 (t, $J = 7.3$ Hz, 1H), 7.11 (d, $J = 7.3$ Hz, 2H), 6.00 (s, 2H), 2.77 (q, $J = 7.6$ Hz, 2H), 1.77 (s, 6H), 1.34 (t, $J = 7.6$ Hz, 3H);

$^{13}$C NMR (101 MHz, CDCl$_3$): δ = 162.3, 149.7, 146.1, 139.5, 138.7, 138.6, 136.4, 131.7, 131.3, 128.5, 128.3, 127.4, 126.5, 126.0, 121.3, 117.5, 112.5, 107.6, 52.9, 49.6, 29.9, 27.7, 15.3; IR (ATR): ν = 3036, 2948, 1642, 1604, 1560, 1513, 1486, 1332, 1298, 1172, 724 cm$^{-1}$. HRMS (ESI+) calcd for C$_{28}$H$_{26}$BrN$_2$O$_2$ (M+1)$^+$ m/z 501.1178, found m/z 501.1171.

6-Benzyl-8-chloro-4,4-dimethyl-2-phenyl-4,6-dihydro-5H-[1,3]oxazino[5,6-c]quinolin-5-one (2l)

According to the general procedure C, substrate 1l (0.201 g, 0.5 mmol), PdI$_2$ (1.8 mg, 1 mol%) and KI (8.3 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (9/1) as eluent to give 2l (0.180 g, 84% yield) as a pale yellow solid (m.p. 245.1-247.0 °C).

$^1$H NMR (400 MHz, CDCl$_3$): δ = 8.18–8.13 (m, 2H), 8.01 (d, $J = 8.5$ Hz, 1H), 7.59–7.49 (m, 3H), 7.40–7.22 (m, 7H), 5.53 (bs, 2H), 1.83 (s, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ = 160.9, 150.1, 145.8, 139.4, 137.3, 136.0, 131.6, 131.3, 129.0, 128.4, 127.5, 127.4, 126.5, 124.1, 122.6, 114.7, 112.5, 112.1, 52.9, 46.0, 30.0; IR (ATR): ν = 3042, 2962, 2938, 1641, 1603, 1581, 1510, 1457, 1328, 1269, 1173, 801, 721 cm$^{-1}$. HRMS (ESI+) calcd for C$_{26}$H$_{22}$ClN$_2$O$_2$ (M+1)$^+$ m/z 429.1370, found m/z 429.1367.
6'-Benzyl-2'-phenylspiro[cyclohexane-1,4'-[1,3]oxazino[5,6-c]quinolin]-5'(6'H)-one (2m)

![Chemical Structure of 2m]

According to the general procedure C, substrate 1m (0.204 g, 0.5 mmol), PdI$_2$ (1.8 mg, 1 mol%) and KI (8.3 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (9/1) as eluent to give 2m (0.158 g, 73% yield) as a pale yellow solid (m.p. 198.1–200.0 °C). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 8.24 (d, $J$ = 7.9 Hz, 2H), 8.13 (d, $J$ = 8.1 Hz, 1H), 7.56–7.47 (m, 4H), 7.35–7.22 (m, 7H), 5.58 (bs, 2H), 2.94 (td, $J$ = 13.2, 3.8 Hz, 2H), 2.25–2.13 (m, 2H), 1.85 (d, $J$ = 13.1 Hz, 1H), 1.73 (d, $J$ = 12.9 Hz, 2H), 1.65–1.56 (m, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 161.1, 152.0, 150.1, 138.7, 136.4, 131.6, 131.3, 128.9, 128.5, 127.5, 127.4, 126.7, 126.2, 122.4, 122.2, 115.3, 114.1, 104.2, 45.9, 42.0; IR (ATR): $\nu$ = 3032, 2973, 2919, 1636, 1604, 1549, 1511, 1469, 1347, 1290, 1178, 812, 737 cm$^{-1}$. HRMS (ESI+) calcd for C$_{29}$H$_{27}$N$_2$O$_2$ (M+1)$^+$ m/z 435.2073, found m/z 435.2074.

6-Benzyl-2-phenyl-4,6-dihydro-5H-[1,3]oxazino[5,6-c]quinolin-5-one (2n)

![Chemical Structure of 2n]

According to the general procedure C, substrate 1n (0.170 g, 0.5 mmol), PdI$_2$ (1.8 mg, 1 mol%) and KI (8.3 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give 2n (0.106 g, 58% yield) as a pale yellow solid (m.p. 209.0–210.5 °C). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 8.18–8.12 (m, 2H), 8.05 (dd, $J$ = 7.9, 1.4 Hz, 1H), 7.59–7.48 (m, 4H), 7.35–7.22 (m, 7H), 5.56 (bs, 2H), 4.76 (s, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 161.2, 152.0, 150.1, 138.7, 136.4, 131.6, 131.3, 129.0, 128.9, 128.5, 127.5, 127.4, 126.7, 122.4, 122.2, 115.3, 114.1, 104.2, 45.9, 42.0; IR (ATR): $\nu$ = 3032, 2973, 2919, 1636, 1604, 1549, 1511, 1469, 1347, 1290, 1178, 812, 737 cm$^{-1}$. HRMS (ESI+) calcd for C$_{24}$H$_{19}$N$_2$O$_2$ (M+1)$^+$ m/z 367.1447, found m/z 367.1452.
6-Benzyl-2-(4-chlorophenyl)-4,4-dimethyl-4,6-dihydro-5H-[1,3]oxazino[5,6-c]quinolin-5-one (2o)

According to the general procedure C, substrate 1o (0.201 g, 0.5 mmol), PdI₂ (1.8 mg, 1 mol%) and KI (8.0 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (9/1) as eluent to give 2o (0.145 g, 68% yield) as a white solid (m.p. 195.6–197.3 °C). 

1H NMR (400 MHz, CDCl₃): δ = 8.15–8.10 (m, 2H), 8.07 (dd, J = 8.1, 1.4 Hz, 1H), 7.54–7.47 (m, 3H), 7.37–7.20 (m, 7H), 5.59 (bs, 2H), 1.84 (s, 6H); 13C NMR (101 MHz, CDCl₃): δ = 160.9, 150.2, 145.3, 138.6, 137.4, 136.5, 131.2, 130.3, 128.9, 128.8, 128.7, 127.3, 126.5, 122.7, 122.2, 114.9, 113.8, 111.9, 53.0, 45.9, 30.0; IR (ATR): ν = 3021, 2961, 2929, 1643, 1602, 1561, 1509, 1487, 1278, 1175, 817, 741 cm⁻¹. HRMS (ESI⁺) calcd for C₂₆H₂₂ClN₂O₂ (M+1)⁺ m/z 429.9240, found m/z 429.9243.

6-Benzyl-2-(4-fluorophenyl)-4,4-dimethyl-4,6-dihydro-5H-[1,3]oxazino[5,6-c]quinolin-5-one (2p)

According to the general procedure C, substrate 1p (0.193 g, 0.5 mmol), PdI₂ (1.8 mg, 1 mol%) and KI (8.2 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (9/1) as eluent to give 2p (0.130 g, 63% yield) as a pale yellow solid (m.p. 225.7–226.8 °C). 

1H NMR (400 MHz, CDCl₃): δ = 8.24–8.15 (m, 2H), 8.08 (dd, J = 8.2, 1.4 Hz, 1H), 7.55–7.47 (m, 1H), 7.38–7.16 (m, 9H), 5.59 (bs, 2H), 1.84 (s, 6H); 13C NMR (101 MHz, CDCl₃): δ = 164.7 (d, J_{C,F} = 251.4 Hz), 160.9, 150.3, 145.2, 138.6, 136.5, 131.2, 129.7 (d, J_{C,F} = 8.8 Hz), 128.9, 128.0 (d, J_{C,F} = 3.0 Hz), 127.3, 126.5, 122.7, 122.1, 115.5 (d, J_{C,F} = 21.9 Hz), 114.9, 113.8, 111.9, 52.9, 45.9, 30.0; IR (ATR): ν = 3027, 2963, 2912, 1639, 1598, 1546, 1510, 1491, 1323, 1168, 805, 728 cm⁻¹. HRMS (ESI⁺) calcd for C₂₆H₂₂FN₂O₂ (M+1)⁺ m/z 413.1665, found m/z 413.1665.
6-Benzyl-4,4-dimethyl-2-(4-nitrophenyl)-4,6-dihydro-5H-[1,3]oxazino[5,6-c]quinolin-5-one (2q)

According to the general procedure C, substrate 1q (0.206 g, 0.5 mmol), PdI₂ (1.8 mg, 1 mol%) and KI (8.1 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (6/1) as eluent to give 2q (0.180 g, 82% yield) as a yellow solid (m.p. 204.2–206.4 °C). ¹H NMR (400 MHz, CDCl₃): δ = 8.44–8.31 (m, 4H), 8.08 (dd, J = 8.2, 1.4 Hz, 1H), 7.56–7.50 (m, 1H), 7.37–7.30 (m, 4H), 7.29–7.22 (m, 3H), 5.59 (bs, 2H), 1.87 (s, 6H); ¹³C NMR (101 MHz, CDCl₃): δ = 160.7, 150.0, 149.5, 144.7, 138.7, 137.5, 136.4, 131.5, 128.9, 128.5, 127.3, 126.5, 123.6, 122.6, 122.3, 115.0, 113.5, 111.8, 53.5, 46.0, 30.0; IR (ATR): ν = 3046, 2948, 2908, 1647, 1601, 1555, 1525, 1484, 1338, 1296, 1173, 803, 730 cm⁻¹. HRMS (ESI+) calcd for C₂₆H₂₂N₃O₄ (M+1)⁺ m/z 440.1610, found m/z 440.1612.

6-Benzyl-2-methyl-4,6-dihydro-5H-[1,3]oxazino[5,6-c]quinolin-5-one (2r)

According to the general procedure C, substrate 1r (0.139 g, 0.5 mmol), PdI₂ (1.8 mg, 1 mol%) and KI (8.1 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give 2r (0.058 g, 38% yield) as a white solid (m.p. 255.2–257.0 °C). ¹H NMR (400 MHz, CDCl₃): δ = 7.98–7.94 (m, 1H), 7.48–7.42 (m, 1H), 7.41–7.31 (m, 5H), 7.22–7.17 (m, 2H), 5.34 (s, 2H), 4.57 (s, 2H), 2.65 (s, 3H); ¹³C NMR (101 MHz, CDCl₃): δ = 171.1, 163.8, 153.0, 142.0, 134.6, 129.3, 128.7, 127.3, 123.9, 122.6, 122.2, 120.7, 111.4, 110.8, 49.0, 43.6, 24.3; IR (ATR): ν = 2924, 2876, 1687, 1625, 1546, 1437, 1359, 1272, 1135, 747 cm⁻¹. HRMS (ESI+) calcd for C₁₉H₁₇N₆O₂ (M+1)⁺ m/z 305.1290, found m/z 305.1286.
6-Benzyl-2-(benzylamino)-4,4-dimethyl-4,6-dihydro-5H-[1,3]oxazino[5,6-c]quinolin-5-one (2s)

According to the general procedure C, substrate 1s (0.198 g, 0.5 mmol), PdI$_2$ (1.8 mg, 1 mol%) and KI (8.1 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (7/3) as eluent to give 2s (0.169 g, 80% yield) as a pale yellow solid (m.p. 144.2 - 146.0 °C).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.84 (dd, $J$ = 8.0, 1.3 Hz, 1H), 7.49 - 7.36 (m, 5H), 7.36 - 7.15 (m, 8H), 5.56 (bs, 2H), 4.54 (s, 2H), 4.26 (s, 1H), 1.78 (s, 6H);

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 161.0, 150.5, 143.2, 139.1, 138.5, 136.7, 130.9, 128.8, 128.6, 127.9, 127.4, 127.2, 126.5, 122.6, 121.9, 114.7, 113.8, 113.5, 52.5, 45.9, 45.8, 30.7; IR (ATR): $\nu$ = 3013, 2934, 2883, 1636, 1612, 1536, 1473, 1345, 1292, 1078, 748 cm$^{-1}$. HRMS (ESI+) calcd for C$_{27}$H$_{26}$N$_3$O$_2$ (M+1)$^+$ m/z 424.2025, found m/z 424.2028.

5,14-Dibenzyl-7,7,16,16-tetramethyl-5H,14H-benzopyrido[3'',4'':5,6]pyrimido[2',1':2,3][1,3]oxazino[5,6-c]quinoline-6,15-dione (3a)

According to the general procedure C, substrate 1v (0.133 g, 0.5 mmol), PdI$_2$ (1.8 mg, 1 mol%) and KI (8.3 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (7/3) as eluent to give 3a (0.123 g, 81% yield) as a pink solid (m.p. 213.8 - 213.5 °C).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 8.24 (dd, $J$ = 8.0, 1.2 Hz, 1H), 7.85 (dd, $J$ = 8.0, 1.0 Hz, 1H), 7.51 (further split t, $J$ = 7.6 Hz, 1H), 7.41 - 7.16 (m, 14H), 7.07 (t, $J$ = 7.4 Hz, 1H), 5.75 (d, $J$ = 16.1 Hz, 1H), 5.67 - 5.47 (m, 2H), 5.40 (d, $J$ = 16.1 Hz, 1H), 1.98 (s, 3H), 1.85 (s, 3H), 1.83 (s, 3H), 1.76 (s, 2H);

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 160.5, 160.0, 153.4, 148.7, 141.6, 138.9, 138.0, 136.4 (2C), 131.9, 130.3, 129.6, 128.9 (2C), 127.4, 127.3, 126.8, 126.5, 126.4, 123.8, 122.4, 120.8, 119.4, 114.8, 114.7, 114.2, 114.0, 64.6, 57.5, 46.3, 46.1, 31.6, 28.8, 28.1, 27.0; IR (ATR): $\nu$ = 2983, 2933, 1743, 1496, 1440, 1400, 1268, 1193, 983, 851, 754, 725 cm$^{-1}$. HRMS (ESI+) calcd for C$_{39}$H$_{35}$N$_4$O$_3$ (M+1)$^+$ m/z 607.2709, found m/z 607.2711.
According to the general procedure C, substrate 1w (0.149 g, 0.5 mmol), PdI₂ (1.8 mg, 1 mol%) and KI (8.3 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (6/4) as eluent to give 3b (0.100 g, 60% yield) as a white solid (m.p. 158.9–160.5 °C).

$^1$H NMR (400 MHz, CDCl₃): $\delta$ = 8.20 (dd, $J$ = 8.1, 1.4 Hz, 1H), 7.79 (dd, $J$ = 8.1, 1.3 Hz, 1H), 7.52 (ddd, $J$ = 8.6, 7.2, 1.5 Hz, 1H), 7.34 (d, $J$ = 8.5 Hz, 2H), 7.26 (d, $J$ = 8.2 Hz, 2H), 7.21–7.13 (m, 4H), 7.05 (further split t, $J$ = 8.3 Hz, 1H), 6.89–6.83 (m, 4H), 5.74–5.22 (m, 4H), 3.77 (s, 3H), 3.76 (s, 3H), 1.93 (s, 3H), 1.80 (s, 3H), 1.77 (s, 3H), 1.71 (s, 3H); $^{13}$C NMR (101 MHz, CDCl₃): $\delta$ = 160.5, 160.0, 158.9, 158.8, 153.3, 148.7, 141.5, 138.9, 138.0, 131.8, 130.2, 129.6, 128.4, 127.9, 127.8, 126.8, 123.7, 122.3, 120.7, 119.4, 114.8, 114.7, 114.3 (2C), 114.2, 114.1, 114.0, 64.5, 57.5, 55.3 (2C), 45.7, 45.6, 31.5, 28.7, 28.1, 26.9; IR (ATR): $\nu$ = 2931, 2835, 1701, 1636, 1512, 1305, 1275, 1197, 1137, 1032, 741 cm⁻¹. HRMS (ESI⁺) calcd for C₄₁H₃₉N₄O₅ (M+1)⁺ m/z 667.2920, found m/z 667.2922.

According to the general procedure C, substrate 1x (0.153 g, 0.5 mmol), PdI₂ (1.8 mg, 1 mol%) and KI (8.3 mg, 10 mol%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give 3c (0.100 g, 58% yield) as a white solid (m.p. 178.5–180.0 °C).

$^1$H NMR (400 MHz, CDCl₃): $\delta$ = 8.10 (s, 1H), 7.62 (s, 1H), 7.43 (d, $J$ = 8.7 Hz, 1H), 7.38–7.32 (m, 4H), 7.31–7.22 (m, 8H), 7.19 (d, $J$ = 8.7 Hz, 1H), 5.76–5.65 (m, 2H), 5.48–5.35 (m, 2H), 3.02 (hept, $J$ = 6.9 Hz, 1H), 2.88 (hept, $J$ = 6.8 Hz, 1H), 1.98 (s, 3H), 1.85 (s, 3H), 1.82 (s, 3H), 1.76 (s, 3H), 1.30 (d, $J$ = 6.9 Hz, 6H), 1.20 (t, $J$ = 7.9 Hz, 6H); $^{13}$C NMR (101 MHz, CDCl₃): $\delta$ = 160.5, 159.8, 153.5, 148.9,
143.2, 141.6, 140.9, 137.2, 136.0, 129.4, 129.1, 128.9, 127.34, 127.28, 126.53, 126.47, 124.0, 121.0, 119.2, 114.9, 114.7, 114.2, 114.0, 64.4, 57.5, 46.3, 45.9, 33.8, 33.4, 31.6, 28.8, 28.2, 27.0, 24.1, 23.5;
IR (ATR): \( \nu = 3021, 2943, 2852, 1694, 1631, 1523, 1300, 1261, 1240, 1182, 1132, 1039, 737 \text{ cm}^{-1} \).
HRMS (ESI+) calcd for C_{45}H_{47}N_{4}O_{3} (M+1)^{+} m/z 691.3648, found m/z 691.3651.

5,14-Dibenzyl-2,11-dibromo-7,7,16,16-tetramethyl-5H,14H-benzopyrido[3'',4'':5,6']pyrimido[2',1':2,3][1,3]oxazino[5,6-c]quinoline-6,15-dione (3d)

According to the general procedure C, substrate 1y (0.171 g, 0.5 mmol), PdI\(_2\) (1.8 mg, 1 mol\%) and KI (8.3 mg, 10 mol\%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by flash column chromatography using hexane/ethyl acetate (8/2) as eluent to give 3d (0.070 g, 37% yield) as a white solid (m.p. 96.8–98.2 °C). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 8.38 \) (d, \( J = 2.3 \) Hz, 1H), 7.91 (d, \( J = 2.3 \) Hz, 1H), 7.60 (dd, \( J = 9.0, 2.3 \) Hz, 1H), 7.44 (dd, \( J = 9.0, 2.3 \) Hz, 1H), 7.39–7.33 (m, 4H), 7.32–7.25 (m, 2H), 7.25–7.17 (m, 5H), 7.12 (d, \( J = 9.0 \) Hz, 1H), 5.73 (d, \( J = 16.2 \) Hz, 1H), 5.64–5.50 (m, 2H), 5.34 (d, \( J = 16.0 \) Hz, 1H), 1.94 (s, 3H), 1.81 (s, 3H), 1.80 (s, 3H), 1.74 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \( \delta = 160.1, 159.6, 152.2, 148.0, 140.4, 137.8, 136.9, 135.9, 135.8, 134.7, 133.0, 131.0, 129.0 (2C), 128.9, 127.6, 127.5, 126.39, 126.36, 126.19, 120.9, 116.55, 116.51, 115.6, 115.4, 114.8, 114.0, 65.1, 57.7, 46.4, 46.1, 31.5, 28.5, 27.8, 26.9; IR (ATR): \( \nu = 3033, 2947, 2861, 1699, 1641, 1502, 1313, 1268, 1192, 1125, 1015, 746 \text{ cm}^{-1} \). HRMS (ESI+) calcd for C_{39}H_{33}Br_{2}N_{4}O_{3} (M+1)^{+} m/z 763.0919, found m/z 763.0917.

5,14-Dibenzyl-2,11-difluoro-7,7,16,16-tetramethyl-5H,14H-benzopyrido[3'',4'':5,6']pyrimido[2',1':2,3][1,3]oxazino[5,6-c]quinoline-6,15-dione (3e)

According to the general procedure C, substrate 1z (0.142 g, 0.5 mmol), PdI\(_2\) (1.8 mg, 1 mol\%) and KI (8.3 mg, 10 mol\%) were employed and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified...
by flash column chromatography using hexane/ethyl acetate (7/3) as eluent to give 3e (0.112 g, 70% yield) as a white solid (m.p. 230.5-232.0 °C). 1H NMR (400 MHz, CDCl3): δ = 7.90 (dd, J = 8.7, 2.5 Hz, 1H), 7.51 (dd, J = 9.3, 2.9 Hz, 1H), 7.40–7.32 (m, 4H), 7.31–7.18 (m, 9H), 7.13–7.06 (m, 1H), 5.75 (d, J = 16.1 Hz, 1H), 5.61 (d, J = 16.3 Hz, 1H), 5.52 (d, J = 15.8 Hz, 1H), 5.36 (d, J = 16.1 Hz, 1H), 1.96 (s, 3H), 1.83 (s, 2H), 1.82 (s, 3H), 1.75 (s, 3H); 13C NMR (101 MHz, CDCl3): δ = 160.1, 159.6, 158.0 (d, JCF = 243.5 Hz), 156.9 (d, JCF = 241.8 Hz), 152.5 (d, JCF = 3.1 Hz), 148.2, 140.7 (d, JCF = 2.8 Hz), 136.0, 135.5, 134.5, 131.2, 129.0, 127.5 (d, JCF = 4.2 Hz), 126.4 (d, JCF = 5.0 Hz), 120.7 (d, JCF = 8.2 Hz), 119.9 (d, JCF = 24.0 Hz), 118.1 (d, JCF = 23.8 Hz), 116.7 (d, JCF = 7.9 Hz), 116.5 (d, JCF = 7.9 Hz), 115.0, 114.96 (d, JCF = 9.3 Hz), 112.2 (d, JCF = 24.9 Hz), 109.2 (d, JCF = 24.8 Hz), 65.0, 57.7, 46.5, 46.4, 31.5, 28.6, 27.8, 26.7; IR (ATR): ν = 3012, 2958, 2839, 1700, 1632, 1523, 1342, 1272, 1242, 1193, 1139, 1024, 736 cm⁻¹. HRMS (ESI+) calcd for C39H33F2N4O3 (M+1)⁺ m/z 643.2521, found m/z 643.2524.
6. NMR Spectra

$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1a

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 1a
$^1\text{H}$ NMR spectrum (400 MHz, CDCl$_3$) of 1b

$^{13}\text{C}(^1\text{H})$ NMR spectrum (101 MHz, CDCl$_3$) of 1b
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1c

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 1c
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1d

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 1d
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1e

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 1e
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1f

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 1f
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1g

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 1g
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1h

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 1h
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1i

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 1i
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1j

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 1j
\(^1\)H NMR spectrum (400 MHz, CDCl\(_3\)) of 1k

\(^{13}\)C\(^1\)H NMR spectrum (101 MHz, CDCl\(_3\)) of 1k
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 1
\(^1\)H NMR spectrum (400 MHz, CDCl\(_3\)) of 1m

\(^{13}\)C\(^{(1)}\)H\) NMR spectrum (101 MHz, CDCl\(_3\)) of 1m
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1n

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 1n
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1o

$^{13}$C$^1$H NMR spectrum (101 MHz, CDCl$_3$) of 1o
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1p

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 1p
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1q

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 1q
$\textbf{H NMR spectrum (400 MHz, CDCl}_3$) of 1r



$\textbf{^{13}C(1H) NMR spectrum (101 MHz, CDCl}_3$) of 1r



S51
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1s

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 1s
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1t

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 1t
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1u

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 1u
'H NMR spectrum (400 MHz, CDCl₃) of 1v

\[
\begin{array}{c}
\text{7.5} & \text{7.4} & \text{7.3} & \text{7.2} & \text{7.1} & \text{7.0} & \text{6.9} & \text{6.8} & \text{6.7} & \text{6.6} & \text{6.5} \\
\end{array}
\]

\[
\begin{array}{c}
\text{13}C('H) NMR spectrum (101 MHz, CDCl₃) of 1v
\end{array}
\]
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1w

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 1w
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1x

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 1x
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 5a

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 5a
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2a

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 2a
^1H NMR spectrum (400 MHz, CDCl$_3$) of 2b

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 2b
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2c

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 2c
$^{1}H$ NMR spectrum (400 MHz, CDCl$_3$) of 2d

$^{13}C(1H)$ NMR spectrum (101 MHz, CDCl$_3$) of 2d
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2e

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 2e
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2f

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 2f
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2g

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 2g
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2h

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 2h
\(^1\text{H NMR spectrum (400 MHz, CDCl}_3\text{) of 2i}\)

\[^{13}\text{C}\{^1\text{H}\} \text{NMR spectrum (101 MHz, CDCl}_3\text{) of 2i}\]
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2j

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 2j
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2k

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 2k
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2I

$^{13}$C$^1$H NMR spectrum (101 MHz, CDCl$_3$) of 2I
$^{1}$H NMR spectrum (400 MHz, CDCl$_3$) of 2m

$^{13}$C($^{1}$H) NMR spectrum (101 MHz, CDCl$_3$) of 2m
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2n

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 2n
$^1\text{H} \text{NMR spectrum (400 MHz, CDCl}_3\text{)}$ of 2o

$^{13}\text{C}(^1\text{H}) \text{NMR spectrum (101 MHz, CDCl}_3\text{)}$ of 2o
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2p

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 2p
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2q

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 2q
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2r

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 2r
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2s

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 2s

2s

H NMR spectrum (101 MHz, CDCl$_3$) of 2s
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 3a

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 3a
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 3b

$^{13}$C(1H) NMR spectrum (101 MHz, CDCl$_3$) of 3b
$^{1}$H NMR spectrum (400 MHz, CDCl$_3$) of 3c

$^{13}$C($^{1}$H) NMR spectrum (101 MHz, CDCl$_3$) of 3c
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 3d

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 3d
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 3e

$^{13}$C($^1$H) NMR spectrum (101 MHz, CDCl$_3$) of 3e
7. Computational Study

Computational details

The calculations have been performed using the Gaussian09 program package.\textsuperscript{[3]} We have applied the global hybrid, M06 functional containing exact exchange which has been shown to have good performance for Pd-catalyzed reactions.\textsuperscript{[4]} A smaller basis set (B\textsubscript{1}) has been used for the geometry optimizations, frequency calculations and the calculations of the Gibbs free energy contributions at the experimental 353 K temperature and for the standard 1 M concentration. For the routes leading to formation of 2 the 6-31+G* basis set was used. For the exploration of the routes leading to 3 the 6-31G* basis set was employed. For CO we have taken into account the experimental 1.2 MPa. The larger 6-311++G(3df,3pd) basis set (B\textsubscript{2}) and the SMD implicit solvation model\textsuperscript{[5]} has been applied to recalculate the optimized structures to obtain the solvent corrected energies for acetonitrile as solvent. The final Gibbs free energy values for constructing the energy profiles have been calculated in the following way:

\[ \Delta G_{\text{solv}} = \Delta G_{\text{virt}}^{B_1} + E_{\text{SMD}}^{B_2}, \]

where \( \Delta G_{\text{virt}}^{B_1} \) is the sum of the vibrational, rotational, and translational thermal corrections to Gibbs free energy (harmonic oscillator, rigid rotor, ideal gas approximation, calculated on the smaller basis set B\textsubscript{1}) while \( E_{\text{SMD}}^{B_2} \) is the electronic energy calculated with SMD model (employing B\textsubscript{2}). The "Ultrafine" grid point density has been used for the integrations. The nature of the optimized states has been verified by analyzing the vibrational spectrum of the structures (zero imaginary frequency for reactants, products and intermediates whereas 1 imaginary frequency for transition states). IRC and subsequent optimizations have been performed to see that the TS-s connect the corresponding intermediate states.

The reactants and intermediates in several cases have large conformational freedom. To find the most stable conformers which are necessary to set the initial free energy levels of the profiles we have performed molecular mechanics simulations with the OPLS force field using the Macromodel software.\textsuperscript{[6]} The conformational searches were performed with a mixed Monte Carlo torsional sampling and a low-mode sampling which together can efficiently explore the conformational space of the molecule in question. We obtained a few hundreds of conformers within a 10 kcal/mol window which then were the subject of clustering. From the located clusters the most stable structures were selected and DFT calculations were performed to find the lowest conformers.

Effect of increased pressure

It follows from the ideal gas model employed in our calculations that the effect of a pressure change can be calculated by the following equation:

\[ \Delta G = RT \ln \left( \frac{p_2}{p_1} \right) \]

where \( p_2 \) and \( p_1 \) are the new and the original pressures, respectively, \( T \) is the actual absolute temperature, \( R \) is the universal gas constant, whereas \( \Delta G \) is the change in the free energy. It can be seen that a 10-fold increase in the pressure yields a +1.6 kcal/mol destabilization in the reactant state (the TS is not affected because its concentration (pressure) is set by the reactant present in smaller amount), ie. the barrier becomes smaller implying a faster reaction.
Free energy profiles

Figure S1. Free energy profile of reaction 1a to 2a. The final dashed line indicates further stabilization by the highly exergonic process of regenerating the active Pd(II) state by oxidation. The rate determining step is the CO insertion with a 26.5 kcal/mol which suggests a rapid reaction at the experimental 80 °C.

Figure S2. Free energy profile of dimerization reaction 1t to urea 5a. The level of NCO (isocyanate intermediate) is set arbitrarily because of the highly exergonic oxidation of Pd(0) to Pd(II) and the subsequent levels are referenced to the level of NCO. The rate determining step is the non-catalyzed C-N urea bond formation with a 23.3 kcal/mol activation barrier which is compatible with the experimental 80 °C.
**Figure S3.** Free energy profile of reaction urea 5a toward 6a. The final dashed line indicates further stabilization and formation of 6a by HI and PdICO\(^-\) elimination and by the highly exergonic process of regenerating the active Pd(II) state by oxidation. The rate determining step is the CC coupling of CO with a 31.7 kcal/mol which is compatible with the experimental 80 °C.

**Figure S4.** Free energy profile of reaction urea 6a to 3a. The final dashed line indicates further stabilization by the highly exergonic process of regenerating the active Pd(II) state by oxidation. The rate determining step is the insertion of CO with a 22.5 kcal/mol which suggests a rapid process at the experimental 80 °C.
Less favourable routes

As it is noted in the article we have explored different routes and selected the most favorable ones on the basis of the computed Gibbs free energy profiles. We found that reaction paths leading to indolization or quinoline framework require high activation free energies. In particular, we obtained 53.3 kcal/mol.
barrier for the formation of indoline-2-one frame (from 1a'-2 toward 1a'-3') and 61.1 kcal/mol for the formation of quinoline-2-one scaffold (from 1a'-2 toward 1a'-3''). Therefore, we have excluded these paths. When exploring the initial amid-attack we found that an initial 5-exo-dig attack by the carbonyl group requires 29.8 kcal/mol activation free energy, much higher than that of the 6-endo-dig attack (16.7 kcal/mol). Finally, we have obtained that initial enolization is not necessary as the enol attacks on the activated triple bond leading to either 6-endo-dig or 5-exo-dig cyclization feature very high activation barriers (39.3 and 47.2 kcal/mol, respectively).

**Resting state of the reactions under experimental conditions**

![Diagrams showing the different states and their Gibbs free energies relative to the resting state.](image)

**Figure S6.** Selected initial states and their Gibbs free energies referenced to the resting state.

An important task is to set the zero level for the free energy profile and this is defined by the resting state. In this regard the composition of the Pd(II) catalyst is an important issue, because the excess iodine anion and CO concentrations can yield the formation of various species which can subsequently interact with the substrates. Comparison of the free energies of the possible situations showed that the initial resting state of the reaction is when the catalyst is in the form of PdI₃CO and does not yet form any complex with the substrate. In Figure S6 we show several possible intermediates with the corresponding free energy values relative to the resting state. These situations are chemically plausible, however the calculations have showed that they are higher in free energy than the resting state.
Coordinates (Å) and energies (Ha) of the optimized structures

(All molecules and ions are in singlet state except O₂ which has a triplet ground state.)
\[
\begin{align*}
E &= -2213.92154486; \quad E_{\text{B3LYP}} &= -2214.69740316 \\
S_{\text{B3LYP}} &= 2.71237415; \quad S_{\text{MP2}} &= 2.72137415; \quad S_{\text{B3LYP}} &= 2.71237415 \\
\end{align*}
\]
8. Single Crystal X-ray Diffraction for 2g, 2o, 2s and 3d

SC-XRD analyses were performed on single crystal samples of 2o, 2g, 2s and 3d on a Bruker D8 Venture diffractometer equipped with a kappa goniometer. Data collection were performed using microfocused MoKα radiation (λ = 0.71073 Å) under nitrogen flux with Oxford Cryosteam. Lorentz polarization and absorption correction were applied. Data were reprocessed using APEX v3 software. Structures were solved by direct methods using SHELXT[7] and refined by full-matrix least-squares on all F² using SHELXL[8] implemented in Olex2.21[9]. For all samples anisotropic displacement parameters were refined except for hydrogen atoms. Samples 2o, 2g and 2s crystallizes in monoclinic system as anhydrous compound while 3d crystallizes as CHCl₃ solvate in triclinic systems. The X-ray crystallographic coordinates for structures reported in this paper have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 1943405-1943408. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre (http://www.ccdc.cam.ac.uk/data_request/cif).

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Table S3. Crystal data and structure refinement for 2o, 2g, 2s and 3d

| Identification code | 2o | 2g | 2s | 3d |
|---------------------|----|----|----|----|
| **Empirical formula** | C₂₀H₂₁Cl₂N₂O₂ | C₂₀H₂₂FN₂O₂ | C₂₁H₂₅N₂O₂ | C₂₀H₂₃Br₂Cl₃N₂O₃ |
| **Formula weight** | 428.90 | 413.45 | 423.50 | 883.87 |
| **Temperature/K** | 240 | 250 | 200 | 105 |
| **Crystal system** | monoclinic | monoclinic | monoclinic | triclinic |
| **Space group** | P₂₁/c | P₂₁/c | P₂₁/c | P-1 |
| **a/Å** | 12.507(5) | 12.38(3) | 10.1911(2) | 9.3169(10) |
| **b/Å** | 21.942(7) | 20.26(4) | 11.9810(2) | 13.6206(15) |
| **c/Å** | 7.728(3) | 8.237(16) | 18.1659(4) | 15.9984(14) |
| **α°** | 90 | 90 | 90 | 76.430(3) |
| **β°** | 96.620(11) | 95.49(2) | 102.0120(10) | 73.750(3) |
| **γ°** | 90 | 90 | 90 | 71.504(3) |
| **Volume/Å³** | 2106.6(13) | 2057(7) | 2169.48(7) | 1824.6(3) |
| **Z** | 4 | 4 | 4 | 2 |
| **ρ calc/g/cm³** | 1.352 | 1.335 | 1.297 | 1.609 |
| **µ/mm⁻¹** | 0.208 | 0.091 | 0.083 | 2.487 |
| **F(000)** | 896.0 | 868.0 | 896.0 | 892.0 |
| **Crystal size/mm³** | 0.1 x 0.1 x 0.05 | 0.15 x 0.1 x 0.4 x 0.2 x 0.2 | 0.2 x 0.16 x 0.12 | 0.08 |
| **Radiation** | MoKα | MoKα | MoKα | MoKα |
| **λ = 0.71073** | (λ = 0.71073) | (λ = 0.71073) | (λ = 0.71073) | (λ = 0.71073) |
| **2θ range for data collection/°** | 6.812 to 59.05 | 6.392 to 53.158 | 6.392 to 53.158 | 6.392 to 53.158 |
| **Index ranges** | -17 ≤ h ≤ 17, -15 ≤ s ≤ 15, -14 ≤ s ≤ 14, -12 ≤ s ≤ 12, -16 ≤ s ≤ 16, -13 ≤ s ≤ 13, -18 ≤ s ≤ 18, -19 ≤ s ≤ 19, -20 ≤ s ≤ 20, -21 ≤ s ≤ 21, -22 ≤ s ≤ 22 | -16 ≤ h ≤ 16, -15 ≤ s ≤ 15, -14 ≤ s ≤ 14, -12 ≤ s ≤ 12, -16 ≤ s ≤ 16, -13 ≤ s ≤ 13, -18 ≤ s ≤ 18, -19 ≤ s ≤ 19, -20 ≤ s ≤ 20, -21 ≤ s ≤ 21, -22 ≤ s ≤ 22 | -17 ≤ h ≤ 17, -15 ≤ s ≤ 15, -14 ≤ s ≤ 14, -12 ≤ s ≤ 12, -16 ≤ s ≤ 16, -13 ≤ s ≤ 13, -18 ≤ s ≤ 18, -19 ≤ s ≤ 19, -20 ≤ s ≤ 20, -21 ≤ s ≤ 21, -22 ≤ s ≤ 22 | -16 ≤ h ≤ 16, -15 ≤ s ≤ 15, -14 ≤ s ≤ 14, -12 ≤ s ≤ 12, -16 ≤ s ≤ 16, -13 ≤ s ≤ 13, -18 ≤ s ≤ 18, -19 ≤ s ≤ 19, -20 ≤ s ≤ 20, -21 ≤ s ≤ 21, -22 ≤ s ≤ 22 |
| **Reflections collected** | 35404 | 31891 | 38001 | 62550 |
| **Independent reflections** | 5830 | 4160 | 6092 | 10220 |
| **Data/restraints/parameters** | [Rint = 0.0451, Rsigma = 0.01986] | [Rint = 0.0411, Rsigma = 0.0305] | [Rint = 0.1684, Rsigma = 0.1167] | [Rint = 0.1302] |
| **Goodness-of-fit on F²** | 1.016 | 0.962 | 1.065 | 1.012 |
| **Final R indexes [l>=2o (l)]** | R1 = 0.0407, wR2 = 0.0524, R1 = 0.0503, wR2 = 0.0538, | R1 = 0.0407, wR2 = 0.0524, R1 = 0.0503, wR2 = 0.0538, | R1 = 0.0561, wR2 = 0.1526, R1 = 0.0830, wR2 = 0.1332, | R1 = 0.0651, wR2 = 0.1526, R1 = 0.0830, wR2 = 0.1332, |
| **Final R indexes [all data]** | R1 = 0.1048, wR2 = 0.1516, R1 = 0.1586, wR2 = 0.1259, | R1 = 0.1048, wR2 = 0.1516, R1 = 0.1586, wR2 = 0.1259, | R1 = 0.1048, wR2 = 0.1516, R1 = 0.1586, wR2 = 0.1259, | R1 = 0.1048, wR2 = 0.1516, R1 = 0.1586, wR2 = 0.1259, |
| **Largest diff. peak/hole / e Å⁻³** | 0.21/-0.25 | 0.16/-0.33 | 0.41/-0.41 | 0.69/-0.66 |
**Figure S7.** Ellipsoid plot of 2g. All non-hydrogen atoms shown as ellipsoids at the 50% probability level. H atoms (isotropically refined) are reported in ball-and-stick style for the sake of clarity.

**Figure S8.** Ellipsoid plot of 2a. All non-hydrogen atoms shown as ellipsoids at the 50% probability level. H atoms (isotropically refined) are reported in ball-and-stick style for the sake of clarity.
Figure S9. Ellipsoid plot of 2s. All non-hydrogen atoms shown as ellipsoids at the 50% probability level. H atoms (isotropically refined) are reported in ball-and-stick style for the sake of clarity.

Figure S10. Ellipsoid plot of 3d. All non-hydrogen atoms shown as ellipsoids at the 50% probability level. H atoms (isotropically refined) are reported in ball-and-stick style for the sake of clarity.
9. References

[1] A. Acerbi, C. Carfagna, M. Costa, R. Mancuso, B. Gabriele, N. Della Ca’, Chem. Eur. J. 2018, 24, 4835–4840.

[2] M. Jiang, J. Li, F. Wang, Y. Zhao, F. Zhao, X. Dong, W. Zhao, Org. Lett. 2012, 14, 1420–1423.

[3] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Mont-gomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Dan-iiels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, Revision A.02; Gaussian, Inc.: Wallingford, CT, 2009.

[4] Y. Zhao, D. Truhlar, Theor. Chem. Acc. 2006, 120, 215-241., T. Sperger, I. A. Sanhueza, I. Kalvet, F. Schoenebeck, Chemical Reviews 2015, 115, 9532–9586.

[5] Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. J. Phys. Chem. B 2009, 113, 6378-6396.

[6] MacroModel, Schrödinger, LLC, New York, NY, 2016.

[7] Sheldrick, G.M. Acta Cryst. 2015, A71, 3-8.

[8] Sheldrick, G.M. Acta Cryst. 2008, A64, 112-122.

[9] Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. J. Appl. Cryst. 2009, 42, 339-341.