Supporting Information

*N,N*-Diisopropylformamidine (DIFA) protection of anilines in metalation reactions.

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EXPERIMENTAL SECTION

**General:** All protection and metalation reactions were carried out under a positive pressure of nitrogen in anhydrous solvents. Commercially available reagents and anhydrous solvents were used as supplied without further purification. $^1$H and $^{13}$C spectra were recorded on a Bruker AVANCE 300 or Bruker AVANCE 500 NMR spectrometer. All chemical shifts (δ) are reported in ppm, using TMS as a standard. High resolution mass spectra were obtained on a Waters Q-Tof micro mass spectrometer using ESI(+) ionization. Melting points were determined on an Electrothermal Mel-Temp apparatus and are uncorrected. Unless otherwise noted, all isolated compounds had purity greater than 95% (area percent) as judged by HPLC analysis.

$N'$(4-Bromophenyl)-$N,N$-dimethylformimidamide (2a)

![Chemical Structure of 2a]

A 500-mL three-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with DMF (1.6 mL, 1.50 g, 20.6 mmol) and CH$_2$Cl$_2$ (80 mL). The mixture was cooled to -5 °C and oxalyl chloride (1.8 mL, 2.66 g, 20.9 mmol) was added dropwise over 10 min. The reaction mixture was stirred at r.t. for 30 min. After that time, the resulting suspension of dimethylamino Vilsmeier reagent was cooled to 0 °C and 4-bromoaniline (3.44 g, 20.0 mmol) was added in portions under nitrogen atmosphere. The reaction mixture was stirred at r.t. for 1 h. After that time, the mixture was diluted with 10% aq K$_2$CO$_3$ (50 mL) and CH$_2$Cl$_2$ (100 mL). The aq layer was separated and extracted with CH$_2$Cl$_2$ (3 × 50 mL), and the combined organic layers were dried over sodium sulfate, concentrated and purified by column chromatography (silica, 0% to 10% MeOH/CH$_2$Cl$_2$) to afford a 79% yield (3.61 g) of 2a as a colorless oil: $^1$H NMR (300 MHz, CDCl$_3$) δ 7.48 (s, 1H), 7.33 (d, $J = 8.7$ Hz, 2H), 6.82 (d, $J = 8.7$ Hz, 2H), 3.01 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 153.3, 151.1, 131.7, 122.8, 114.8, 40.1, 34.4. HRMS calcd for C$_9$H$_{11}$BrN$_2$+H: 227.0184; found: 227.0189.

$N'$(4-Bromophenyl)-$N,N$-diisopropylformimidamide (2b)

![Chemical Structure of 2b]

Diisopropylamino Vilsmeier reagent was prepared by the dropwise addition of oxalyl chloride (1.8 mL, 2.66 g, 20.9 mmol) to a solution of $N,N$-diisopropylformamide (3.0 mL, 2.67 g, 20.7 mmol) in CH$_2$Cl$_2$ (20 mL), while keeping the reaction temperature at -5–0 °C. CAUTION. GAS EVOLUTION. The mixture was then stirred at r.t. for 30 min and again cooled to -5–0 °C.
4-Bromoaniline (3.44 g, 20.0 mmol) was added under a stream of nitrogen. After 30 min at r.t. the reaction was poured into 10% aq K$_2$CO$_3$ (100 mL). The organic layer was concentrated to afford a 95% yield (5.39 g) of 2b as a gray solid: mp 58–59 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.62 (s, 1H), 7.35 (d, $J = 8.7$ Hz, 2H), 6.81 (d, $J = 8.7$ Hz, 2H), 4.75 (br s, 1H), 3.60 (br s, 1H), 1.26 (d, $J = 6.9$ Hz, 12H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 152.2, 150.0, 131.3, 122.4, 114.6, 45.4, 24.2, 20.2. HRMS calcd for C$_{13}$H$_{19}$BrN$_2$: 283.0810; found: 283.0816.

$N'$-(3-Methoxyphenyl)-$N,N$-dimethylformimidamide (2c).

![2c](image)

2c was prepared from $m$-anisidine (4.84 g, 39.3 mmol) following the procedure described for 2a. After purification by column chromatography (silica, 0% to 10% MeOH/CH$_2$Cl$_2$) an 88% yield (6.11 g) of 2c was obtained as a brown oil: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.53 (s, 1H), 7.15 (t, $J = 8.4$ Hz, 1H), 6.59–6.53 (m, 3H), 3.79 (s, 3H), 3.01 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 160.3, 153.5, 153.4, 129.5, 113.4, 108.4, 106.9, 55.1, 40.1, 35.5. HRMS calcd for C$_{10}$H$_{14}$N$_2$O+: 179.1184; found: 179.1179.

$N,N$-Diisopropyl-$N'$-(3-methoxyphenyl)formimidamide (2d).

![2d](image)

To a solution of 20.7 mmol of diisopropylamino Vilsmeier reagent in CH$_2$Cl$_2$ (20 mL), $m$-anisidine (2.2 mL, 2.42 g, 19.7 mmol) was added dropwise, with cooling, while maintaining the internal temperature at 10–20 °C. After 30 min at r.t. the reaction was diluted with CH$_2$Cl$_2$ (20 mL) and poured into 10% aq K$_2$CO$_3$ (100 mL). The organic layer was separated and concentrated under reduced pressure. To remove residual $N,N$-diisopropylformimidamide the residue was dissolved in hexanes (30 mL), and the solution was washed with water (2 x 50 mL), dried over Na$_2$SO$_4$ and filtered. After evaporating the hexanes, an 86% yield (3.94 g) of 2d was obtained as a brown oil: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.69 (s, 1H), 7.16 (t, $J = 8.1$ Hz, 1H), 6.58–6.52 (m, 3H), 4.92 (br s, 1H), 3.80 (s, 3H), 3.68 (br s, 1H), 1.27 (m, 12H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 160.4, 154.6, 149.9, 129.5, 113.4, 107.9, 106.9, 55.1, 45.2, 24.1, 20.2. HRMS calcd for C$_{14}$H$_{22}$N$_2$O+: 235.1810; found: 235.1811.
**N,N-Diisopropyl-N'(2-methoxyphenyl)formimidamide (2e).**

![Image of 2e](image)

2e was prepared in 89% yield (4.16 g) from o-anisidine (2.25 mL, 2.46 g, 20.0 mmol), following the procedure for 2d, as a brown oil: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.69 (s, 1H), 6.95 (td, \(J = 7.6, 1.8\) Hz, 1H), 6.87 (td, \(J = 7.4, 1.5\) Hz, 1H), 6.86 (dd, \(J = 7.8, 1.4\) Hz, 1H), 6.79 (dd, \(J = 7.5, 2.0\) Hz, 1H), 4.88 (br s, 1H), 3.82 (s, 3H), 3.60 (br s, 1H), 1.26 (d, \(J = 6.0\) Hz, 12H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 152.4, 150.7, 143.0, 122.5, 121.5, 110.4, 55.9, 44.9, 24.1, 20.2. HRMS calcd for C\(_{14}\)H\(_{22}\)N\(_2\)O+H: 235.1810; found: 235.1811.

**tert-Butyl 4-((Diisopropylamino)methyleneamino)phenylcarbamate (2f).**

![Image of 2f](image)

A solution of tert-butyl 4-aminophenylcarbamate (1.04 g, 5.00 mmol) and anhydrous pyridine (0.6 mL, 0.59 g, 7.44 mmol) in CH\(_2\)Cl\(_2\) (10 mL) was cooled to -35 °C. Diisopropylamino Vilsmeier reagent (5.01 mmol) in CH\(_2\)Cl\(_2\) (10 mL) was added dropwise at -35– -20 °C. The reaction was allowed to warm to 5 °C over 30 min, and then it was poured into 10% aq K\(_2\)CO\(_3\) (20 mL). The organic layer was separated and evaporated under reduced pressure on a rotary evaporator. To remove residual N,N-diisopropylformamide the residue was dissolved in hexanes/MTBE (30 mL:10 mL) (Note: if the residue does not completely dissolve, add minimal amount of CH\(_2\)Cl\(_2\)), and the solution was washed with water (3 × 50 mL). After the solvents were removed, an 88% yield (1.40 g) of 2f was obtained as a yellow solid: mp 110–112 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.63 (s, 1H), 7.23 (d, \(J = 7.5\) Hz, 2H), 6.86 (d, \(J = 8.5\) Hz, 2H), 6.41 (s, 1H), 4.74 (br s, 1H), 3.54 (br s, 1H), 1.50 (s, 9H), 1.24 (d, \(J = 6.0\) Hz, 12H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 153.4, 150.2, 149.2, 133.1, 121.6, 120.2, 80.4, 45.4, 28.7, 24.4, 20.4. HRMS calcd for C\(_{18}\)H\(_{29}\)N\(_3\)O\(_2\)+H: 320.2338; found: 320.2333.

**N-tert-Butyl-3-((diisopropylamino)methyleneamino)benzamide (4a).**

![Image of 4a](image)

Diisopropylamino Vilsmeier reagent (39.6 mmol) in CH\(_2\)Cl\(_2\) (60 mL) was cooled to -5 °C. 3-Aminobenzoic acid (2.74 g, 20.0 mmol) was added in one portion under a stream of nitrogen. After stirring at 0 °C for 0.5 h and at r.t. for 1 h, formation of the protected acid...
chloride was complete. The mixture was cooled to -30 °C, and r-butylamine (10.5 mL, 7.31 g, 100 mmol) was added dropwise at -30– -20 °C. The reaction was warmed to r.t. overnight and poured into a solution of K₂CO₃ (2.76 g, 20.0 mmol) in water (220 mL). The organic layer was separated and concentrated in vacuo. The residue was vigorously stirred in a mixture of hexanes (20 mL) and water (100 mL). The suspension was filtered, and the filter cake was washed with water (2 × 10 mL) and dried overnight in vacuo at 45 °C to afford an 87% yield (5.28 g) of 4a as a white solid: mp 106–107 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.71 (s, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.29–7.26 (m, 2H), 7.03 (d, J = 8.5 Hz, 1H), 6.00 (br s, 1H), 4.76 (br s, 1H), 3.60 (br s, 1H), 1.46 (s, 9H), 1.27 (d, J = 6.8 Hz, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 167.3, 153.2, 150.4, 136.8, 129.0, 123.8, 120.3, 119.3, 51.5, 45.5, 28.9, 24.2, 20.1; HRMS Calcd for C₁₈H₂₉N₃O⁺H: 304.2389; found: 304.2389.

N-tert-Butyl-2-((diisopropylamino)methyleneamino)benzamide (4b).

4b was prepared in 83% yield (5.00 g) from anthranilic acid (2.74 g, 20.0 mmol) following the procedure for 4a as a white solid: mp 139–140 °C; ¹H NMR (500 MHz, CDCl₃) δ 9.71 (s, 1H), 8.26 (dd, J = 7.9, 1.6 Hz, 1H), 7.70 (s, 1H), 7.31 (td, J = 7.8, 1.7 Hz, 1H), 7.09 (td, J = 8.0, 1.0 Hz, 1H), 6.72 (d, J = 7.7 Hz, 1H), 4.92 (heptet, J = 6.7 Hz, 1H), 3.64 (heptet, J = 6.8 Hz, 1H), 1.47 (s, 9H), 1.35 (d, J = 6.8 Hz, 6H), 1.24 (d, J = 6.8 Hz, 6H); ¹³C NMR (75 MHz, DMSO-d₆) δ 164.8, 150.7, 150.1, 131.5, 129.9, 125.6, 121.5, 119.6, 49.8, 45.3, 44.6, 28.7, 23.8, 19.8. HRMS calcd for C₁₈H₂₉N₃O⁺H: 304.2389; found: 304.2389.

N-tert-Butyl-4-((diisopropylamino)methyleneamino)benzamide (4c).

4c was prepared in 72% yield (4.75 g) from 4-aminobenzoic acid (3.00 g, 21.9 mmol), following the procedure for the preparation of 4a, as an off-white solid: mp 121–123 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.69 (s, 1H), 7.64 (d, J = 8.5 Hz, 2H), 6.94 (d, J = 8.0 Hz, 2H), 5.88 (s, 1H), 4.80 (br s, 1H), 3.60 (br s, 1H), 1.46 (s, 9H), 1.35–1.15 (br m, 12H); ¹³C NMR (125 MHz, CDCl₃) δ 167.2, 156.1, 150.6, 129.5, 128.1, 121.1, 51.7, 45.9, 29.3, 24.6, 20.4. HRMS calcd for C₁₈H₂₉N₃O⁺H: 304.2389; found: 304.2397.

N-tert-Butyl-6-((diisopropylamino)methyleneamino)nicotinamide (4d).
Diisopropylamino Vilsmeier reagent (19.8 mmol) in CH$_2$Cl$_2$ (20 mL) was cooled to -3 °C. 6-Aminonicotinic acid (1.38 g, 10.0 mmol) was added in one portion under a stream of nitrogen. After stirring at r.t. for 1 h, formation of the protected acid chloride was incomplete. The mixture was cooled to -7 °C, and pyridine (1.7 mL, 1.67 g, 21.1 mmol) was added dropwise at -7–3 °C. Protection was complete after stirring at r.t. for 1 h. The reaction was cooled to -30 °C, and t-butylamine (12.0 mL, 8.35 g, 114 mmol) was added dropwise at -30– -20 °C. The reaction was warmed to r.t. overnight and treated with water (30 mL). The organic layer was separated and concentrated in vacuo. The residue was purified by flash chromatography on silica (gradient from 1:5 to 1:2 acetone/CH$_2$Cl$_2$) followed by trituration with MTBE (4 mL) to afford a 61% yield (1.85 g) of 4d as a light yellow solid: mp 127–128 ºC; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.68 (s, 1H), 8.60 (d, $J$ = 2.1 Hz, 1H), 7.86 (dd, $J$ = 8.5, 2.6 Hz, 1H), 6.88 (d, $J$ = 8.5 Hz, 1H), 5.84 (br s, 1H), 4.88 (heptet, $J$ = 6.8 Hz, 1H), 3.67 (heptet, $J$ = 6.8 Hz, 1H), 1.47 (s, 9H), 1.35 (d, $J$ = 6.8 Hz, 6H), 1.27 (d, $J$ = 6.8 Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 165.6, 164.7, 153.0, 147.2, 136.2, 124.6, 117.3, 51.6, 46.5, 46.2, 29.0, 24.2, 20.0. HRMS calcd for C$_{17}$H$_{28}$N$_4$O+H: 305.2341; found: 305.2343.

$N'$-(2-Bromo-3-methoxyphenyl)-N,N-diisopropylformimidamide (5a, Table 2, entry 8).

A solution of 2d (716 mg, 3.06 mmol) in Et$_2$O (6 mL) was cooled to -70 °C. 1.7 M t-BuLi in pentane (2.3 mL, 3.91 mmol) was added, keeping the reaction temperature under -50 °C. The mixture was stirred at -15– -7 °C for 1.5 h and then cooled to -75 °C. 1,2-Dibromotetrafluoroethane (480 µL, 1.05 g, 4.02 mmol) was added in one portion, and the reaction was allowed to warm to r.t. After this time, it was poured into water (25 mL) and extracted with hexanes (2 × 25 mL). The hexanes extracts were concentrated and purified by flash chromatography on silica (eluted with a gradient from 2% to 10% of EtOAc in hexanes) to afford a 59% yield (567 mg) of 5a as a light yellow solid: mp 65–66 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.53 (s, 1H), 7.13 (t, $J$ = 8.0 Hz, 1H), 6.56 (dd, $J$ = 8.0, 1.5 Hz, 1H), 6.50 (dd, $J$ = 8.0, 1.5 Hz, 1H), 4.67 (br s, 1H), 3.89 (s, 3H), 3.60 (br s, 1H), 1.30 (d, $J$ = 7.0 Hz, 12H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 156.8, 153.0, 150.3, 127.7, 113.7, 108.1, 105.4, 56.4, 46.0, 24.0, 20.0. HRMS calcd for C$_{14}$H$_{21}$BrN$_2$O+H: 313.0915; found: 313.0920.
N'-(2-Iodo-3-methoxyphenyl)-N,N-diisopropylformimidamide (5b, Table 2, entry 10).

2d (2.34 g, 10.0 mmol) was lithiated with t-BuLi as described above. The resulting solution was cannulated into a pre-cooled (-75 °C) solution of iodine (5.08 g, 20.0 mmol) in Et2O (100 mL). After warming to r.t. the reaction mixture was poured into a solution of Na2S2O3•5H2O (10 g) in water (100 mL). The organic layer was concentrated, and the resulting residue was purified by flash chromatography on silica (eluted with a gradient from 2% to 10% of EtOAc in hexanes) to afford a 52% yield (1.87 g) of 5b as a brown oil, which solidified to a brown solid after several days: mp 48–49 °C; 1H NMR (300 MHz, CDCl3) δ 7.51 (s, 1H), 7.16 (t, J = 8.1 Hz, 1H), 6.48 (dd, J = 8.2, 1.1 Hz, 1H), 6.46 (dd, J = 7.8, 1.1 Hz, 1H), 4.69 (br s, 1H), 3.88 (s, 3H), 3.61 (br s, 1H), 1.31 (d, J = 5.7 Hz, 12H); 13C NMR (75 MHz, CDCl3) δ 159.2, 155.5, 149.9, 129.2, 112.3, 104.7, 88.0, 56.5, 46.1, 24.0, 20.0. HRMS calcd for C14H21IN2O+H: 361.0777; found: 361.0761.

N'-(4-Formyl-3-methoxyphenyl)-N,N-diisopropylformimidamide (6d) and N'-(2-formyl-3-methoxyphenyl)-N,N-diisopropylformimidamide (5d) (Table 1, entry 12).

1.4 M s-BuLi in cyclohexane (3.0 mL, 4.2 mmol) was added at -75– -65 °C to a solution of 2d (702 mg, 3.00 mmol) and TMEDA (450 µL, 349 mg, 3.01 mmol) in Et2O (8.0 mL). After stirring the reaction at -54– -49 °C for 1 h, it was cooled to -75 °C and treated with DMF (460 µL, 433 mg, 5.93 mmol). Upon the addition of DMF, the mixture was allowed to warm to -12 °C and quenched with acetic acid (0.5 mL, 525 mg, 8.75 mmol) followed by 1 M aq K2CO3 (10 mL). The organic layer was separated and the aq layer was extracted with MTBE (10 mL). The combined organic extracts were evaporated and purified by flash chromatography on silica (eluted with 50% of EtOAc in hexanes) to afford a 27% yield (209 mg) of 6d (Rf = 0.5 in 50% of EtOAc in hexanes) and 30% yield (234 mg) of 5d (Rf = 0.1 in 50% of EtOAc in hexanes).

6d: yellow solid, mp 85–87 °C; 1H NMR (500 MHz, CDCl3) δ 10.3 (s, 1H), 7.77 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 6.52 (s, 1H), 6.51 (d, J = 9.6 Hz, 1H) 4.78 (br s, 1H), 3.90 (s, 3H), 3.63 (br s, 1H), 1.33 (d, J = 5.5 Hz, 6H), 1.26 (d, J = 5.5 Hz, 6H); 13C NMR (125 MHz, CDCl3) δ 189.0, 163.5, 161.1, 150.8, 130.3, 120.1, 112.7, 105.3, 55.8, 46.23, 46.16, 24.5, 20.3. HRMS calcd for C15H22N2O2+H: 263.1759; found: 263.1762.
5d: yellow solid; mp 75–76 °C; \( {^1}H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 10.6 (d, \( J = 0.6 \) Hz, 1H), 7.58 (s, 1H), 7.35 (t, \( J = 8.1 \) Hz, 1H), 6.57 (d, \( J = 8.1 \) Hz, 1H), 6.43 (dd, \( J = 8.1, 0.9 \) Hz, 1H), 4.67 (br s, 1H), 3.89 (s, 3H), 3.61 (br s, 1H), 1.28 (br s, 12H); \( ^{13}C \) NMR (75 MHz, CDCl\(_3\)) \( \delta \) 192.6, 160.6, 158.1, 150.0, 135.2, 118.2, 113.0, 104.8, 55.9, 46.4, 46.0, 24.0, 20.0. HRMS calcd for C\(_{15}\)H\(_{22}\)N\(_2\)O\(_2\)+H: 263.1759; found: 263.1754.

\( \text{N'-(2-Formyl-3-methoxyphenyl)-N,N-diisopropylformimidamide (5d) (Table 2, entry 15).} \)

\[ \text{OMe} \quad \text{N} \quad \text{CHO} \quad \text{N} \quad \text{Ni-Pr}^2 \]

1.4 M s-BuLi in cyclohexane (6.4 mL, 9.0 mmol) was added at -75– -65 °C to a solution of 2d (702 mg, 3.00 mmol) and PMDTA (630 \( \mu \)L, 523 mg, 3.02 mmol) in Et\(_2\)O (8.0 mL). After stirring the reaction at -45– -40 °C for 2 h, it was cooled to -75 °C. DMF (850 \( \mu \)L, 801 mg, 11.0 mmol) was added dropwise while maintaining the temperature under -60 °C. Upon the addition of DMF, the mixture was allowed to warm to -15 °C and quenched with acetic acid (1.0 mL, 1.05 g, 17.5 mmol) followed by water (5 mL). The organic layer was separated, concentrated and purified by flash chromatography on silica (eluted with a gradient: hexanes/EtOAc 2:1 to 100% EtOAc) to afford a 49% yield (385 mg) of 5d as a yellow solid (characterized above).

\( \text{N'-(2-tert-Butyl-3-hydroxy-1-oxoisindolin-4-yl)-N,N-diisopropylformimidamide (7) (Table 2, entry 18).} \)

\[ \text{O} \quad \text{N} \quad \text{N} \quad \text{OH} \quad \text{Ni-Pr}^2 \]

1.7 M t-BuLi in pentane (5.6 mL, 9.5 mmol) was added at -50– -40 °C to a suspension of 4a (1.21 g, 4.00 mmol) in Et\(_2\)O (10 mL). After stirring the reaction at -15– -10 °C for 40 min, it was cooled to -70 °C and treated with DMF (0.93 mL, 12.0 mmol). Upon the addition of DMF, the mixture was allowed to warm to 0 °C and quenched with acetic acid (0.8 mL) followed by 1 M aq K\(_2\)CO\(_3\) (10 mL). EtOAc (10 mL) was added to dissolve the product. The organic layer was separated, washed with water (30 mL) and concentrated. The resulting residue was purified by flash chromatography on silica (eluted with a gradient: EtOAc in hexanes, from 0 to 50%). The fractions containing 7 were combined and evaporated, and the resulting residue was triturated with 2:1
hexanes/MTBE (3 mL) to afford a 43% yield (562 mg) of 7 as a white solid: mp 140–141 °C; \(^1\)H NMR (300 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 7.90 (s, 1H), 7.34 (t, \(J = 7.5\) Hz, 1H), 7.24 (d, \(J = 7.2\) Hz, 1H), 7.00 (d, \(J = 7.7\) Hz, 1H), 6.11 (s, 1H), 4.65 (heptet, \(J = 6.2\) Hz, 1H), 3.79 (br s, 1H), 3.67 (heptet, \(J = 6.8\) Hz, 1H), 1.59 (s, 9H), 1.30 (d, \(J = 4.5\) Hz, 12H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 169.0, 150.2, 146.7, 136.2, 133.5, 130.5, 120.0, 116.3, 81.1, 54.7, 46.7, 46.1, 28.5, 24.0, 20.0; HRMS calcd for C\(_{19}\)H\(_{29}\)N\(_3\)O\(_2\)+H: 332.2338; found: 332.2340.

\(N'-(2\text{-}\text{tert\text{-}Butyl\text{-}1-hydroxy\text{-}3-oxoisindolin\text{-}5\text{-}yl})\text{-}N,N\text{-}diisopropylformimidamide (8)\) (Table 2, entry 20).

\[\text{N} \& \text{N} \text{Pr}_2 \text{NO} \text{H} \text{Bu} \text{N} \text{N} \text{Pr}_2 \]

\(1.4 \text{ M s-BuLi in cyclohexane (5.0 mL, 7.0 mmol) was added at -75--65 °C to a suspension of 4a (909 mg, 3.00 mmol) and TMEDA (450 µL, 349 mg, 3.01 mmol) in Et}_2\text{O (8 mL). After stirring the reaction at -57--52 °C for 1 h, it was cooled to -75 °C and treated with DMF (460 µL, 433 mg, 5.93 mmol). Upon adding DMF, the mixture was allowed to warm to -20 °C and quenched with acetic acid (0.5 mL, 520 mg, 8.8 mmol) followed by 1 M aqueous K}_2\text{CO}_3 (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (20 mL). The organic extracts were combined and concentrated. The resulting residue was purified by flash chromatography on silica (eluted with a gradient: MeOH in CH\(_2\)Cl\(_2\) from 2.5 to 10%). Isomer 7 eluted first (R\(_f\)=0.4 in 7.5% MeOH in CH\(_2\)Cl\(_2\)) in 13% yield (125 mg) after evaporation and trituration with 1:4 MTBE/hexanes (1.5 mL). Isomer 8 eluted last (R\(_f\)=0.1 in 7.5% MeOH in CH\(_2\)Cl\(_2\)) in 69% yield (682 mg) as a white solid, after evaporating and drying in vacuo: mp 145–147 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.69 (s, 1H), 7.33 (d, \(J = 8.0\) Hz, 1H), 7.12 (d, \(J = 1.9\) Hz, 1H), 7.09 (dd, \(J = 8.0, 2.1\) Hz, 1H), 5.93 (s, 1H), 4.77 (br s, 1H), 3.60 (br s, 1H), 2.54 (br s, 1H), 1.61 (s, 9H), 1.27 (br s, 12H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 168.4, 154.1, 150.7, 137.2, 133.7, 126.6, 123.1, 113.4, 82.1, 54.5, 45.4, 28.6, 24.2, 20.0. HRMS calcd for C\(_{19}\)H\(_{29}\)N\(_3\)O\(_2\)+H: 332.2338; found: 332.2325.

\(N'-(3\text{-}(\text{Hydroxy}(\text{phenyl})\text{methyl})\text{-}2\text{-methoxyphenyl})\text{-}N,N\text{-}diisopropylformimidamide (9b)\) (Table 3, entry 2).

\[\text{N} \& \text{N} \text{Pr}_2 \text{OH} \text{OMe} \text{N} \text{Pr}_2 \]

\(N'-(3\text{-}(\text{Hydroxy}(\text{phenyl})\text{methyl})\text{-}2\text{-methoxyphenyl})\text{-}N,N\text{-}diisopropylformimidamide (9b)\) (Table 3, entry 2).
1.5 M t-BuLi in pentane (1.8 mL, 3.1 mmol) was added at -75– -65 °C to a solution of 2e (468 mg, 2.00 mmol) and TMEDA (450 µL, 349 mg, 3.01 mmol) in Et₂O (5 mL). After stirring the reaction at -42– -27 °C for 1 h, it was cooled to -75 °C and benzaldehyde (340 µL, 357 mg, 3.37 mmol) was added dropwise, keeping the temperature under -62 °C. Upon adding benzaldehyde, the mixture was allowed to warm to -50 °C and quenched with acetic acid (0.3 mL, 320 mg, 5.3 mmol) followed by 0.5 M aq K₂CO₃ (10 mL). The organic layer was separated, and the aq layer was extracted with Et₂O (5 mL). The organic extracts were combined and washed with water (10 mL). The product was then partially purified by extracting it with an acidic buffer (3 × 5 mL) (prepared by adding H₃PO₄ to 1 M aq KH₂PO₄ to pH 2.8). The acidic extracts were combined and basified with K₂CO₃ to pH 9. The mixture was extracted with MTBE (40 mL). After evaporating the MTBE extract, the residue was purified by column chromatography (basic alumina, 0% to 100% ethyl acetate/hexanes) to afford a 12% yield (80 mg) of 9b as a colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 7.65 (s, 1H), 7.41 (d, J = 7.3 Hz, 2H), 7.31 (t, J = 7.6 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 6.99 (t, J = 7.7, 1H), 6.90 (dd, J = 7.6, 1.6 Hz, 1H), 6.78 (dd, J = 7.7, 1.4 Hz, 1H), 5.96 (s, 1H), 4.77 (br s, 1H), 3.58 (br s, 1H), 3.51 (s, 3H), 3.30 (br s, 1H), 1.25 (d, J = 6.3 Hz, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 150.1, 146.3, 144.4, 137.1, 128.1, 126.9, 126.4, 124.0, 121.7, 121.2, 73.4, 59.6, 45.5, 24.1, 20.1. HRMS calcd for C₂₁H₂₈N₂O₂⁺H: 341.2229; found: 341.2232.

NOE:

\[ \text{9b} \]

\text{N'-(3-Formyl-2-methoxyphenyl)-N,N-diisopropylformimidamide (9c) (Table 3, entry 3).}

1 M t-BuOK in THF (4.0 mL, 4.0 mmol) was added at -60– -75 °C to a solution of 2e (710 mg, 3.03 mmol) in THF (8 mL), followed by addition of 2.5 M n-BuLi in hexanes (1.6 mL, 4.0 mmol) at -70– -75 °C. After stirring at -78– -75 °C for 1 h, the reaction was treated with DMF (460 µL, 433 mg, 8.00 mmol). Upon adding DMF, the mixture was allowed to warm to -40 °C and quenched with acetic acid (0.6 mL, 630 mg, 10.5 mmol)
followed by water (10 mL). The organic layer was separated, and the aqueous layer was extracted with Et₂O (10 mL). The organic layers were combined, washed with water (30 mL), dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica (eluting with a gradient: 10% to 20% ethyl acetate in hexanes, \( R_f = 0.15 \) in 20% EtOAc in hexanes) to afford a 19% yield (152 mg) of 9c as a yellow-brown solid: mp 37–38 °C; \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 10.45 (s, 1H), 7.69 (s, 1H), 7.44 (dd, \( J \) = 7.1, 2.3 Hz, 2H), 7.10–7.05 (m, 2H), 4.78 (br s, 1H), 3.93 (s, 3H), 3.62 (br s, 1H), 1.29 (d, \( J \) = 6.9 Hz, 12H); \(^{13}\)C NMR (125 MHz, CDCl₃) \( \delta \) 191.0, 156.2, 150.7, 147.1, 129.7, 128.0, 124.3, 120.9, 61.2, 45.9, 45.5, 24.1, 20.1. HRMS calcd for C₁₅H₂₂N₂O₂+H: 263.1760; found: 263.1764.

NOE:

\[ \text{N-tert-Butyl-2-((diisopropylamino)methyleneamino)-6-} \]
\[ \text{(hydroxy(phenyl)methyl)benzamide (9d) (Table 3, entry 4).} \]

1.4 M s-BuLi in cyclohexane (4.8 mL, 6.7 mmol) was added at -75–-65 °C to a suspension of 4b (909 mg, 3.00 mmol) and TMEDA (450 \( \mu \)L, 349 mg, 3.01 mmol) in Et₂O (8 mL). After stirring the reaction at -53–-48 °C for 1 h, it was cooled to -75 °C and treated with benzaldehyde (400 \( \mu \)L, 349 mg, 3.96 mmol). Upon adding benzaldehyde, the mixture was allowed to warm to -40 °C and quenched with acetic acid (0.5 mL, 520 mg, 8.8 mmol) followed by 1 M aq K₂CO₃ (10 mL). The organic layer was separated, and the aqueous layer was extracted with Et₂O (5 mL). The organic extracts were combined and washed with water (10 mL). The product was then partially purified by extracting it with an acidic buffer (3 × 10 mL) (prepared by adding H₃PO₄ to 1 M aq KH₂PO₄ to pH 2.8). The acidic extracts were combined and basified with K₂CO₃ to pH 9. The mixture was extracted with Et₂O (40 mL). After evaporating the Et₂O, the residue was purified by flash chromatography on silica (eluted with a gradient: acetone in CH₂Cl₂ from 5 to 30%) to afford a 65% yield (801 mg) of 9d as a white solid: mp 54–55 °C; \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 7.57 (s, 1H), 7.35 (d, \( J \) = 7.9 Hz, 2H), 7.27 (t, \( J \) = 7.5 Hz, 2H), 7.22 (t, \( J \) = 7.9 Hz, 1H), 7.19 (t, \( J \) = 7.6 Hz), 6.93 (d, \( J \) = 7.5 Hz, 1H), 6.76 (br s, 1H), 6.72 (d, \( J \) = 7.9 Hz,
1H), 5.87 (d, J = 7.9 Hz, 1H), 5.80 (d, J = 7.9 Hz, 1H), 4.79 (heptet, J = 6.5 Hz, 1H), 3.58 (heptet, J = 6.6 Hz, 1H), 1.30 (d, J = 6.8 Hz, 3H), 1.28 (d, J = 6.8 Hz, 3H), 1.21 (d, J = 6.4 Hz, 6H), 1.18 (s, 9H); 13C NMR (75 MHz, CDCl3) δ 169.4, 150.5, 149.7, 144.2, 143.7, 130.1, 129.9, 127.7, 126.5, 126.4, 124.5, 119.9, 75.7, 51.2, 45.3, 45.0, 28.5, 24.3, 20.2. HRMS calcd for C25H35N3O2+H: 410.2808; found: 410.2801.

N’-(2-tert-Butyl-1-hydroxy-3-oxoisodolin-4-yl)-N,N-diisopropylformimidamide (10) (Table 3, entry 5).

1.4 M s-BuLi in cyclohexane (5.0 mL, 7.0 mmol) was added at -75– -65 °C to a suspension of 4b (909 mg, 3.00 mmol) and TMEDA (450 µL, 349 mg, 3.01 mmol) in Et2O (8 mL). After stirring at -60– -50 °C for 1 h, the reaction was cooled to -75 °C and treated with DMF (460 µL, 433 mg, 5.93 mmol). Upon adding DMF, the mixture was allowed to warm to -20 °C and quenched with acetic acid (0.5 mL, 520 mg, 8.8 mmol) followed by 1 M aqueous K2CO3 (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (20 mL). The organic layers were combined, washed with water (40 mL) and concentrated. The residue was dissolved in EtOAc (20 mL), and the product was extracted with 1 M aq KH2PO4 (4 × 20 mL). The acidic aqueous extracts were combined and basified with K2CO3 to pH 9. The resulting mixture was extracted with EtOAc (20 mL). After evaporating the solvent, a 64% yield (632 mg) of pure 10 was obtained as a white solid: mp = 156–157 °C; 1H NMR (300 MHz, CDCl3) δ 7.71 (br s, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.05 (d, J = 7.3 Hz, 1H), 6.91 (br d, J = 4.8 Hz, 1H), 5.86 (d, J = 11.3 Hz, 1H), 4.88 (heptet, J = 6.6 Hz, 1H), 3.62 (br s, 1H), 2.58 (br d, J = 10.6 Hz, 1H), 1.59 (s, 9H), 1.33 (br d, J = 7.2 Hz, 6H), 1.28 (d, J = 6.8 Hz, 6H); 13C NMR (75 MHz, CDCl3) δ 167.6, 153.6, 151.3, 145.6, 132.0, 125.3, 121.1, 115.8, 80.9, 54.1, 45.5, 45.2, 28.7, 24.5, 24.2, 20.3, 20.1. HRMS calcd for C19H29N3O2+H: 332.2338; found: 332.2347.

N’-(2-tert-Butyl-3-hydroxy-1-oxoisodolin-5-yl)-N,N-diisopropylformimidamide (13a) (Table 4, entry 1).
1.4 M s-BuLi in cyclohexane (5.0 mL, 7.0 mmol) was added at -75–-65 °C to a suspension of 4c (909 mg, 3.00 mmol) and TMEDA (450 µL, 349 mg, 3.01 mmol) in Et₂O (8 mL). After vigorous stirring at -50–-40 °C for 1.5 h (Note: It is important to make sure that the starting material does not stick to the wall of the flask; the reaction is complete when a clear solution forms.), the reaction was cooled to -75 °C and treated with DMF (460 µL, 433 mg, 5.93 mmol). Upon adding DMF, the mixture was allowed to warm to -15 °C and quenched with acetic acid (0.6 mL) followed by water (10 mL). The organic layer was separated, dried over Na₂SO₄ and concentrated. The resulting residue was further kept under vacuum overnight to remove the side product, 2-methylbutanal. The residue was then dissolved in a minimal amount of 1:4 MTBE/hexanes (approx. 4–5 mL) and seeded. After stirring overnight at r.t., the precipitate was filtered to afford an 84% yield (835 mg) of 13a as a white solid: mp 134–136 ºC; ¹H NMR (300 MHz, CDCl₃) δ 7.67 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 6.99 (d, J = 1.8 Hz, 1H), 6.92 (dd, J = 8.0, 1.9 Hz, 1H), 5.90 (br d, J = 8.4 Hz, 1H), 4.77 (br s, 1H), 3.62 (br s, 1H), 2.67 (br d, J = 10.0 Hz, 1H), 1.60 (s, 9H), 1.28 (br s, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 168.6, 156.4, 150.5, 145.1, 127.8, 126.2, 123.8, 122.6, 120.8, 114.9, 82.1, 54.4, 45.4, 28.6, 24.2, 20.0. HRMS calcd for C₁₉H₂₉N₃O₂⁺H: 332.2338; found: 332.2345.

N-tert-Butyl-6-((diisopropylamino)methyleneamino)-4-iodonicotinamide (12b) (Table 4, entry 3)

“LiMgt-BuTMP₂” was prepared as follows. 1.6 M n-BuLi in hexanes (5.6 mL, 9.0 mmol) was added to a solution of 2,2,6,6-tetramethylpiperidine (1.50 mL, 1.28 g, 9.07 mmol) in THF (5 mL) at -15–-10 °C, and the mixture was stirred at that temperature for 15 min. 1 M t-BuMgCl in THF (4.5 mL, 4.5 mmol) was added at -15–-10 °C, and the mixture was stirred at 0 °C for 30 min.
A solution of 4d (912 mg, 3.00 mmol) in THF (3.5 mL) was added dropwise to the base at -15–-10 °C and the reaction was stirred at 0 °C for 30 min. The resulting solution was cooled to -75 °C and cannulated into a solution of iodine (4.45 g, 17.5 mmol) in Et₂O (50 mL) pre-cooled to -75 °C, maintaining the reaction temperature below -60 °C. After the cannulation was finished, the reaction mixture was allowed to warm to -8 °C, and a concentrated aqueous solution of Na₂S₂O₃ was added portionwise until the organic layer became light yellow. The organic layer was separated, and the aqueous layer was extracted with EtOAc (20 mL). The organic layers were combined and concentrated. The resulting residue was purified by flash chromatography on silica (eluted with a gradient from 1:1 to 2:1 EtOAc/hexanes) to afford a 73% yield (621 mg) of 12b as a brown solid: mp 53–55 ºC; ¹H NMR (300 MHz, CDCl₃) δ 8.62 (s, 1H), 8.22 (s, 1H), 7.41 (s, 1H), 5.67 (br s, 1H), 4.81 (heptet, J = 6.8 Hz, 1H), 3.67 (heptet, J = 6.8 Hz, 1H), 1.48 (s, 9H), 1.34 (d, J = 6.8 Hz, 6H), 1.26 (d, J = 6.8 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 166.7, 163.5,
153.2, 147.0, 131.2, 128.6, 104.7, 52.3, 46.8, 46.3, 28.8, 24.1, 20.0. HRMS calcd for C\textsubscript{17}H\textsubscript{27}IN\textsubscript{4}O\textsubscript{4}H: 431.1308; found: 431.1320.

tert-Butyl 4-((diisopropylamino)methyleneamino)-2-formylphenylcarbamate (12d) and tert-butyl 4-((diisopropylamino)methyleneamino)-3-formylphenylcarbamate (11d) (Table 4, entry 7).

\[
\text{CHO} \\ \text{NHBoc} \\ \text{i-Pr}_2\text{N} \\ 12d \\
\text{OHC} \\ \text{NH使命} \\ \text{i-Pr}_2\text{N} \\ 11d
\]

1.4 M s-BuLi in cyclohexane (6.5 mL, 9.1 mmol) was added at -75—65 °C to a solution of 2f (957 mg, 3.00 mmol) and TMEDA (450 µL, 349 mg, 3.01 mmol) in Et\textsubscript{2}O (8 mL). After vigorous stirring at -37 – -32 °C for 3 h, the reaction was cooled to -75 °C and DMF (620 µL, 584 mg, 8.00 mmol) was added dropwise at -75—60 °C. Upon adding DMF, the mixture was allowed to warm to -15 °C and quenched with acetic acid (0.72 mL, 756 mg, 12.6 mmol) followed by water (10 mL). The organic layer was separated and extracted with Et\textsubscript{2}O (10 mL). The organic layers were combined, washed with water (30 mL), dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated. The resulting residue was further kept under vacuum overnight to remove the side product 2-methylbutanal. The residue was then purified by flash chromatography on silica (eluted with a gradient from 2.5% to 10% acetone in CH\textsubscript{2}Cl\textsubscript{2}) to afford a 46% yield (477 mg) of 12d (R\text{f} = 0.43 in 10% acetone in CH\textsubscript{2}Cl\textsubscript{2}) and 8% yield (88 mg) of 11d (R\text{f} = 0.37 in 10% acetone in CH\textsubscript{2}Cl\textsubscript{2}).

12d: yellow solid; mp 84 –86 °C; \(^1\)H NMR (500 MHz, DMSO-\textit{d}_6) \(\delta\) 10.0 (s, 1H), 9.92 (s, 1H), 7.98 (d, \(J = 8.8\) Hz, 1H), 7.88 (s, 1H), 7.38 (d, \(J = 2.7\) Hz, 1H), 7.23 (dd, \(J = 8.8, 2.7\) Hz, 1H), 4.59 (br s, 1H), 3.67 (br s, 1H), 1.48 (s, 9H), 1.23 (br d, \(J = 9.0\) Hz, 12H); \(^13\)C NMR (75 MHz, DMSO-\textit{d}_6) \(\delta\) 195.5, 152.4, 150.2, 147.4, 134.5, 128.1, 125.7, 123.2, 119.5, 79.9, 45.8, 44.8, 27.9, 23.4, 19.6; HRMS Calcd for C\textsubscript{19}H\textsubscript{29}N\textsubscript{3}O\textsubscript{3}+H: 348.2287; found: 348.2276.

NOE:

11d: yellow solid; purity 83% (HPLC, area method); \(^1\)H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 10.6 (s, 1H), 7.74 (br s, 1H), 7.62 (s, 1H), 7.51 (d, \(J = 2.7\) Hz, 1H), 6.84 (d, \(J = 8.7\) Hz, 1H), 6.39 (br s, 1H), 4.66 (br s, 1H), 3.63 (br s, 1H), 1.51 (s, 9H), 1.28 (br s, 12H).
**tert-Butyl 4-((diisopropylamino)methyleneamino)-2-formylphenylcarbamate (12d)** (Table 4, entry 8).

![Structure of 12d](image)

2f (565 mg, 1.77 mmol) was metalated and quenched with DMF as described above, except metalation was conducted at -38--28 °C for 3 h and more TMEDA (735 µL, 570 mg, 4.91 mmol) was used. After the work-up and purification, a 47% yield (290 mg) of 12d was obtained.

**N’-(2-tert-Butyl-1-hydroxy-3-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)-N,N-diisopropylformimidamide (13b)** (Table 4, entry 4).

![Structure of 13b](image)

4d (912 mg, 3.00 mmol) was metalated as described above. DMF (460 µL, 433 mg, 5.93 mmol) was added dropwise to the resulting solution at -75–-65 °C. Upon adding DMF, the mixture was allowed to warm to 13 °C and quenched with acetic acid (1.0 mL) followed by water (5 mL). The organic layer was separated, dried over Na₂SO₄ and concentrated. The resulting residue was purified by flash chromatography on silica (eluted with CH₂Cl₂/acetone/triethylamine 27:6:0.2) to afford a 73% yield (728 mg) of 13b as light yellow solid: mp 168–169 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.71 (s, 1H), 8.49 (d, J = 0.7 Hz, 1H), 6.89 (s, 1H), 5.89 (d, J = 10.0 Hz, 1H), 4.86 (heptet, J = 6.8 Hz, 1H), 3.68 (heptet, J = 6.8 Hz, 1H), 2.99 (d, J = 10.2 Hz, 1H), 1.60 (s, 9H), 1.39–1.35 (m, 6H), 1.37 (d, J = 6.8 Hz, 3H), 1.36 (d, J = 6.7 Hz, 3H), 1.28 (d, J = 6.8 Hz, 3H), 1.27 (d, J = 6.8 Hz, 3H), 13C NMR (75 MHz, CDCl₃) δ 167.3, 165.1, 153.6, 153.0, 144.0, 121.9, 111.0, 81.6, 54.8, 46.5, 46.3, 28.7, 24.3, 24.1, 20.0. HRMS calcd for C₁₈H₂₈N₄O₂:H: 333.2291; found: 333.2298.

N’-(4’-Chloro-6-methoxybiphenyl-2-yl)-N,N-diisopropylformimidamide (14).
A mixture of 5a (313 mg, 1.00 mmol), 4-chlorophenylboronic acid (3 13 mg, 2.00 mmol), Na₂CO₃ (318 mg, 3.00 mmol), water (2 mL) and 1,4-dioxane (8 mL) was degassed by bubbling nitrogen through for 30 min. Tetrakis(triphenylphosphine)palladium(0) (116 mg, 0.10 mmol) was added, and the reaction mixture was heated at reflux for 14 h. After that time, the mixture was cooled to r.t. and diluted with EtOAc (100 mL) and water (20 mL). The organic layer was separated, and the aq layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0% to 100% EtOAc/hexanes) to afford a 62% yield (213 mg) of 14 as a white solid: mp 78–79 ºC; ¹H NMR (300 MHz, CDCl₃) δ 7.32 (s, 1H), 7.30–7.24 (m, 4H), 7.20 (t, J = 8.1 Hz, 1H), 6.65 (dd, J = 8.3, 0.8 Hz, 1H), 6.58 (dd, J = 8.0, 0.9 Hz, 1H), 4.39 (br s, 1H), 3.73 (s, 3H), 3.42 (br s, 1H), 1.05 (d, J = 6.8 Hz, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 157.3, 152.6, 150.4, 135.1, 133.2, 131.6, 128.5, 127.4, 122.5, 114.4, 105.0, 55.8, 45.4, 23.7, 20.1. HRMS calcd for C₂₀H₂₅ClN₂O+H: 345.1734; found: 345.1731.


A 15-mL pressure tube equipped with a magnetic stirrer and screw cap with a septum was charged with 14 (259 mg, 0.75 mmol), N,N'-dimethylethlyenediamine (198 mg, 2.25 mmol), a 4 M HCl in 1,4-dioxane (0.19 mL, 0.76 mmol) and EtOH (0.2 mL). (Note: catalytic acid accelerates the deprotection.) The mixture was heated at 110 ºC for 3 h. After that time, the mixture was cooled to r.t. and diluted with EtOAc (25 mL) and water (10 mL). The organic layer was separated, and the aq layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0% to 100% EtOAc/hexanes) to afford a 71% yield (126 mg) of 15 as a white solid: mp 45–46 ºC; ¹H NMR (300 MHz, CDCl₃) δ 7.41 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 7.10 (t, J = 8.1 Hz, 1H), 6.40 (d, J = 7.9 Hz, 1H), 6.39 (d, J = 8.2 Hz, 1H), 3.67 (s, 3H), 3.52 (br s, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 157.5, 145.1, 133.5, 133.1, 132.1, 129.08, 128.97, 115.0, 108.6, 101.0, 55.6. HRMS calcd for C₁₃H₁₂ClN₂O+H: 234.0686; found: 234.0684.
**N’-(3-Hydroxy-1-oxo-1,3-dihydroisobenzofuran-4-yl)-N,N-diisopropylformimidamide hydrochloride (16).**

7 (524 mg, 1.58 mmol) was heated at 90 °C for 18 h with 6 M aq. HCl (20 mL). Carefully, with cooling, keeping the reaction temperature below 30 °C, a 50% aq solution of NaOH (approx. 5.5 mL) was added until pH reached 5.2. The mixture was extracted with EtOAc (3 × 50 mL), and the combined extracts were briefly dried over Na₂SO₄. As the product is somewhat unstable as a free base, it was converted to its hydrochloride salt by adding 4 M HCl in 1,4-dioxane (0.4 mL). The resulting mixture was concentrated and dried under vacuum overnight. The residue was triturated with CH₂Cl₂ (5 mL) to afford a 50% yield (248 mg) of 16 as a yellow solid: mp 203–204 ºC; ¹H NMR (300 MHz, DMSO-d₆) δ 11.81 (br s, 1H), 8.51 (br m, 2H), 7.80 (br s, 3H), 7.00 (br d, 1H), 4.73 (heptet, J = 6.4 Hz, 1H), 4.10 (heptet, J = 6.2 Hz, 1H), 1.40–1.32 (m, 12H); ¹³C NMR (75 MHz, DMSO-d₆) δ 167.6, 152.8, 139.4, 134.1, 131.9, 129.5, 128.3, 123.0, 97.3, 50.5, 49.1, 23.1, 19.0, HRMS calcd for C₁₅H₂₁N₂O₃⁺H: 277.1552; found: 277.1554.

**4-Amino-2-tert-butyl-3-hydroxyisoindolin-1-one (17).**

A 15-mL pressure tube equipped with a magnetic stirrer and screw cap with a septum was charged with 7 (200 mg, 0.60 mmol), N,N’-dimethylethylenediamine (160 mg, 1.80 mmol), 2 M HCl in 1,4-dioxane (0.30 mL, 0.60 mmol) and ethanol (0.2 mL). (Note: catalytic acid accelerates the deprotection.) The mixture was heated in an oil bath at 110 °C for 16 h. After cooling to r.t. it was diluted with EtOAc (25 mL) and water (10 mL). The organic layer was separated, and the aq layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography (basic alumina, 0% to 100% hexanes/EtOAc) to afford a 62% yield (82 mg) of 17 as a white solid: mp 43–44 ºC; ¹H NMR (500 MHz, CD₂Cl₂) δ 7.26 (t, J = 7.5 Hz, 1H), 7.17 (dd, J = 7.3, 0.8 Hz, 1H), 6.81 (dd, J = 7.9, 0.9 Hz, 1H), 6.32 (br s, 1H), 4.05 (d, J = 6.4 Hz, 1H), 1.63 (s, 9H), 1.59 (br s, 2H); ¹³C NMR (75 MHz, CD₂Cl₂) δ 168.8, 140.0, 134.7, 130.4, 130.2, 121.2, 114.5, 70.9, 55.7, 28.8. HRMS calcd for C₂₄H₂₈N₂O₃⁺H: 405.2291; found: 405.2291.