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Synthesis of Oxindoles and Benozfuranones via Oxidation of 2-Heterocyclic BMIDAs

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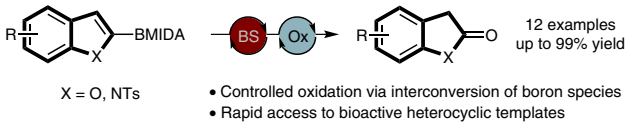

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Abstract The synthesis of functionalized oxindoles and benzofuranones via oxidation of 2-BMIDA indoles and benzofurans, respectively, is described. Interconversion of boron species (BMIDA→BF_3K) was necessary to enable oxidation and overcome boronic acid stability issues associated with a difficult BMIDA hydrolysis. Overall, a robust process was developed that allowed access to a small library of oxindole and benzofuranone products and facilitated the step-efficient synthesis of biologically active compounds containing the oxindole pharmacophore.

Key words boron, oxidation, heterocycles, lactams, lactones

The oxindole motif is present in the core of numerous biologically active natural products as well as pharmaceuticals such as tenidap, coreulescine, and semaxanib (Figure 1).[1] Consequently, numerous methods have been and continue to be developed to allow access to this privileged chemotype.

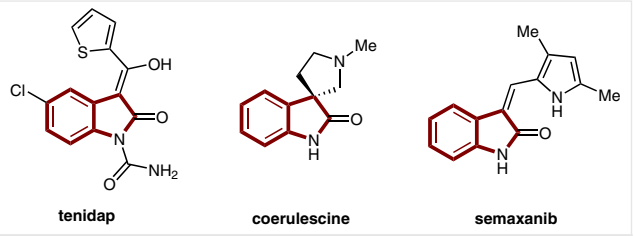
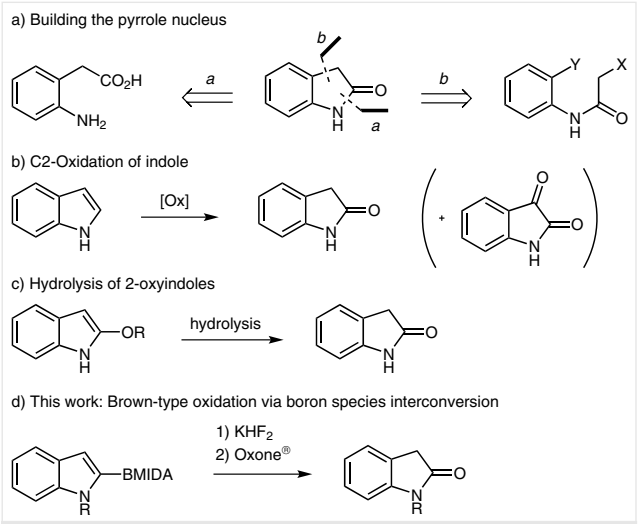


Figure 1 Pharmaceutically relevant oxindoles

The most common synthetic approaches towards the oxindole framework forge the pyrrole nucleus either via disconnection at the amide C–N bond to provide a phenylacetic acid precursor,[2] or at the C-3 position to afford an anilide precursor (Scheme 1a).[3] Despite significant research, preparation of oxindoles beginning from the corresponding indole starting materials are comparatively limited,[4] with oxidative methods often suffering from the problem of over-oxidation to deliver isatins (Scheme 1b).[5] Hydrolysis of 2-oxyindoles gives the corresponding oxindoles; however, this requires a pre-oxygenated indole as a starting material (Scheme 1c).[6] We recently disclosed a one-pot synthesis of 2-heterocyclic BMIDA derivatives,[7] which are bench-stable, free-flowing solids that can be stored indefinitely without degradation.[8] Here, we present the utility of 2-BMIDA indoles and benzofurans as readily accessible precursors to oxindoles and benzofuranones, respectively, and the scope and limitations of this process (Scheme 1d).

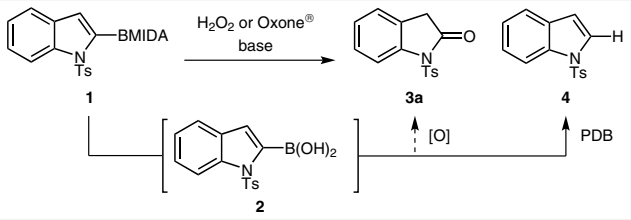


Scheme 1 Methods for the synthesis of oxindoles

Oxidation of 2-borylated indoles is limited to two single examples using two specific 2-BPin indole substrates.[9] This class of compounds is generally difficult to access and han-

dle due to issues with protodeboronation.[10] Consequently, a BMIDA-based process would offer significant synthetic advantages due to the accessibility and stability of these organoboron derivatives.[8]

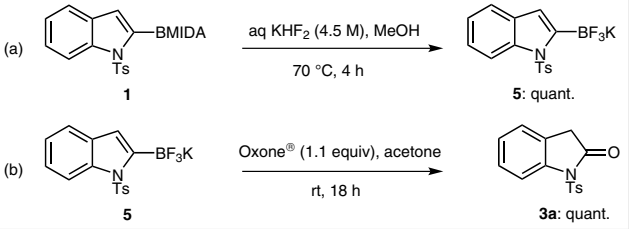
Our initial studies commenced with *N*-Ts-indole-2-BMIDA **1**, using well-established Brown-type reaction conditions: H_2O_2 in a range of solvent/water mixtures and in the presence of base (Scheme 2; see the Supporting Information for full details).[11]



Scheme 2 Attempted direct hydrolysis/oxidation of 2-BMIDA indole **1**. PDB = protodeboronation; MIDA = *N*-methyliminodiacetate

Based on the base lability of BMIDA and the well studied slow or fast release of the parent boronic acid,[10] we planned an in situ hydrolysis of **1** to deliver **2** that would then be oxidized to deliver **3a**. To our surprise, when using a base/oxidant system of $NaOH/H_2O_2$ at room temperature (fast hydrolysis conditions), the BMIDA group remained intact, i.e., no hydrolysis was observed, even in the presence of excess aqueous NaOH. In an attempt to drive the hydrolysis step, the reaction mixture was heated to 50 °C with increasing quantities of NaOH. However, although hydrolysis could be induced, these reactions returned the protodeboronated product **4** in quantitative yields in all cases, presumably due to the sensitivity of **2** under these reaction conditions. Attempting to temper the reaction conditions by using a slow hydrolysis protocol with either K_3PO_4 or K_2CO_3 in the presence of H_2O_2 returned starting material **1** only. Changing the oxidant to Oxone had a small positive effect; hydrolysis remained sluggish, requiring extended reaction times or elevated temperatures and, although trace quantities of **3a** were observed under these conditions, protodeboronation product **4** dominated along with degradation of **3a**.

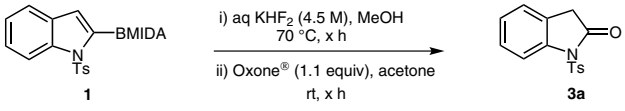
These initial investigations highlighted a compatibility issue between the conditions required to hydrolyze the BMIDA unit and the stability of the intermediate boronic acid (as well as the oxindole product). To overcome these issues, we postulated that a simple boron species interconversion process might be achieved under mild reaction conditions to deliver an organoboron derivative that could then be oxidized under conditions sufficiently mild to inhibit degradation of the organoboron intermediate or product. In particular, BMIDA species can be converted into the potassium organotrifluoroborate (BF_3K) derivative under relatively mild reaction conditions[12] and BF_3K species can also be oxidized under mild conditions.[13] However, BMIDA→BF_3K interconversion on this template was unknown. Accordingly, we evaluated conversion of BMIDA **1** into the BF_3K derivative **5**.



Scheme 3 Conversion of BMIDA **1** into BF_3K **5**

A short survey of reaction conditions revealed that **1** could be quantitatively converted into **5** upon treatment with aq KHF_2 in MeOH at 70 °C (Scheme 3a). In addition, **5** could be quantitatively converted into the desired oxindole product **3a** using Oxone. Combining these two events proved to be straightforward (Table 1). Oxidation of intermediate **5** was found to be sluggish in MeOH; however, a solvent switch to acetone before addition of the oxidant was more effective (entry 1 vs. entry 2). A short optimization of reaction time and KHF_2 stoichiometry (entries 2–5) revealed that the overall two-step process could be completed in 6 hours by using 5 equivalents of KHF_2 to facilitate conversion into **5**, ultimately delivering 99% conversion into **3a**. Interestingly, whereas oxidation of the intermediate BF_3K **5** was facile with Oxone, $NaBO_3$ and H_2O_2 were ineffective for oxidation of this intermediate (entries 6 and 7, respectively).

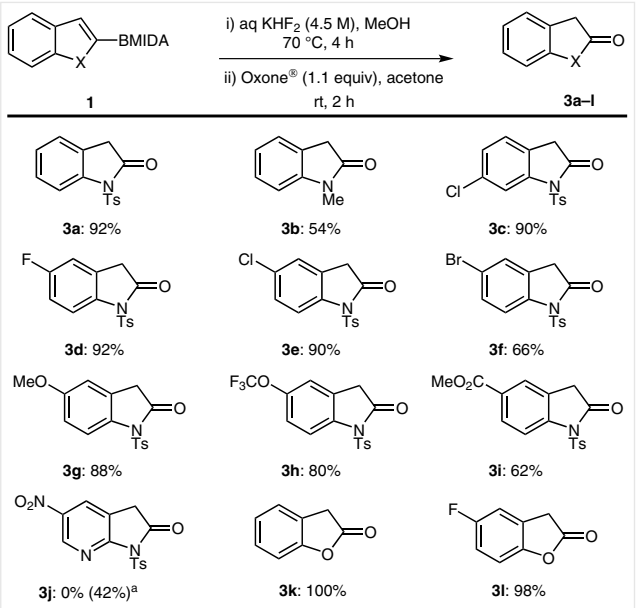
Table 1 Oxidation of Indole BMIDA via Speciation



Entry	Conditions	**3a** (%)[a]
1	aq KHF_2 (3 equiv), 2 h / Oxone, 18 h[b]	27
2	aq KHF_2 (3 equiv), 2 h / Oxone, 18 h[c]	44
3	aq KHF_2 (5 equiv), 2 h / Oxone, 18 h[c]	92
4	aq KHF_2 (5 equiv), 4 h / Oxone, 18 h[c]	99
5	aq KHF_2 (5 equiv), 4 h / Oxone, 2 h[c]	99
6	aq KHF_2 (5 equiv), 4 h / $NaBO_3$, 4 h[c]	0
7	aq KHF_2 (5 equiv), 4 h / H_2O_2, 4 h[c]	0

[a] Determined by HPLC analysis against an internal standard.
[b] Oxidant added directly.
[c] Solvent switch to acetone before addition of oxidant.

With optimum conditions in hand, the scope of the reaction was investigated by application to a range of substituted 2-BMIDA indole architectures (Scheme 4).

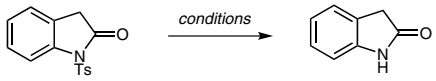


Scheme 4 Substrate scope of the oxidation process. Isolated yields. [a] Determined by ^{1}H NMR analysis.

The reaction was found to be tolerant of both electron-donating and electron-withdrawing groups (**3g**, **3h**, **3i**). Halogenated substrates were also effective, providing a synthetic handle for further functionalization (**3c–f**). In addition, azaindoline **3j** was delivered in moderate yield (42%) based on by NMR spectroscopic analysis, with the mass balance consisting of the product of protodeboronation; however, this product was found to be labile to hydrolysis on silica. The *N*-tosyl group could be replaced with a methyl unit but this resulted in a decrease in the yield of the corresponding oxindole **3b**. Other N-protecting groups were not assessed. Lastly, in addition to oxindoles, the oxidation process was applicable to 2-BMIDA benzofurans to allow access to benzofuranones **3k** and **3l** in excellent yields.

In keeping with our interests in medicinal chemistry,[14] we sought to utilize the oxindole products as building blocks in the synthesis of biologically active molecules. In particular, the ubiquity of the oxindole motif in kinase drug discovery[15] led us to target compounds of this class. First steps into derivatization of our oxindole products quickly identified an issue with deprotection of the *N*-tosyl group. Specifically, the lactam was found to be readily hydrolyzed under both acidic and basic conditions.[16] To our knowledge, no methods exist for the deprotection of *N*-Ts-oxindole, although sulfonamides have been removed from C3-substituted oxindoles by using several approaches.[17] Accordingly, we surveyed reaction conditions commonly used for sulfonamide cleavage; however, neither NaOH nor tetrabutylammonium fluoride (TBAF) afforded any of the desired product **6** (Table 2, entries 1–3);[17d] these conditions all resulted in hydrolysis of the lactam at room temperature.

Table 2 Deprotection of *N*-Ts Oxindole **3a**



Entry	Conditions	**6** (%)[a]
1	6 M NaOH, 1,4-dioxane, r.t.	0
2	1 M NaOH, 1,4-dioxane, r.t.	0
3	1 M TBAF, THF, r.t.	0
4	Mg, MeOH, r.t.	0
5	SmI_2, pyrrolidine, H_2O, r.t.	0
6	Na, naphthalene, –78 °C	90

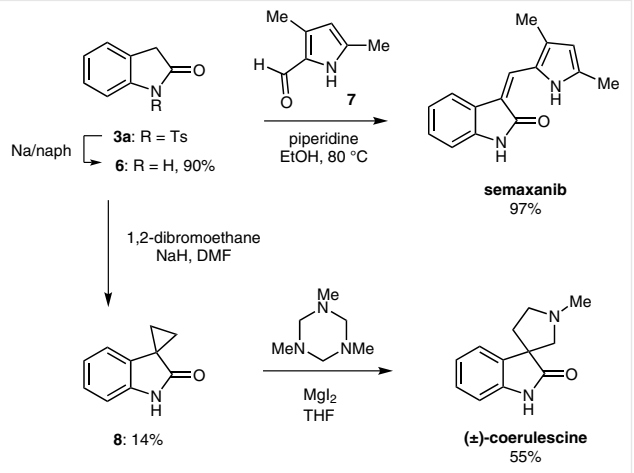
[a] Isolated yield.

To limit exposure to basic reaction conditions, we evaluated several single-electron methods. Mg powder in MeOH resulted in solvolysis of **3a**.[17b] SmI_2 conditions led to full consumption of the starting material within five minutes of addition; however, none of the desired oxindole was observed, delivering only an unidentifiable mixture of products.[18] Fortunately, application of sodium naphthalenide at –78 °C led to clean conversion into the desired oxindole product in 90% isolated yield.[19]

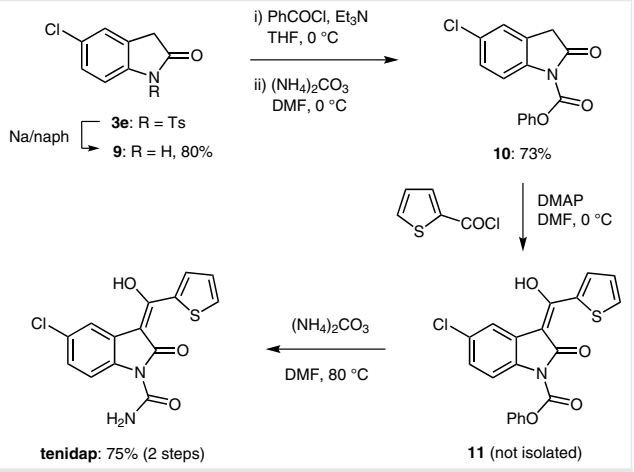
With effective conditions for the deprotection now available, we were able to prepare several biologically active products (Scheme 5 and Scheme 6). Both the natural product (±)-coerulescine[20] and kinase inhibitor semaxanib[21] could be quickly accessed via common oxindole **3a** following tosyl deprotection (Scheme 5). From this common intermediate, condensation with commercially available pyrrole **7** afforded semaxanib in excellent yield, while C3 alkylation followed by ring expansion[22] enabled access to (±)-coerulescine in moderate overall yield. Although the dialkylation to form the cyclopropane proceeded with good conversion (ca. 60%) based on NMR spectroscopic analysis, the desired spirocycle **8** was found to be highly unstable on silica, thereby limiting the yield of this process.

Tenidap, a potent COX inhibitor,[23] was efficiently synthesized in five steps from oxindole **3e** (Scheme 6). Tosyl deprotection gave the free oxindole **9**, which, upon treatment with phenyl chloroformate followed by ammonium carbonate, gave oxindole **10** in 73% yield. Condensation with 2-thiophenecarbonyl chloride and subsequent exposure to ammonium carbonate afforded tenidap in excellent yield.

In conclusion, we have reported a novel method for the preparation of oxindoles from 2-BMIDA indoles. A boron species (BMIDA→BF_3K) interconversion was used to overcome the instability of the intermediate indole 2-boronic acid towards the conditions required for hydrolysis of an unusually robust BMIDA species. The BF_3K species was



Scheme 5 Synthesis of semaxanib and (±)-coerulescine (isolated yields)



Scheme 6 Synthesis of tenidap (isolated yields)

readily oxidized to the corresponding oxindole under mild conditions, allowing one-pot access to oxindole products. The scope of the reaction was evaluated by application to a series of substrates and further exemplified in the context of the synthesis of kinase inhibitors semaxanib and tenidap, and the natural product coerulescine.

All reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise stated. Where necessary, purification was carried out according to standard laboratory methods.[24] Reactions were carried out either using conventional glassware (preparation of intermediates) or in capped 5 mL microwave vials. Room temperature (rt) was generally ca. 18 °C. Reactions were carried out at elevated temperatures by using a temperature-regulated hotplate/stirrer. Thin-layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analyzed under 254 nm UV light or developed using potassium permanganate solution. Normal-phase flash chromatography was carried out using ZEOprep 60 HYD 40–63 µm silica gel. FTIR spectra were obtained with a Shimadzu IRAffinity-1 machine. ^{19}F NMR spectra were obtained with either a Bruker AV 400 at 376 MHz or a Bruker DRX 500 at 471 MHz. ^{11}B NMR spectra were obtained with a Bruker AV 400 spectrometer at 128 MHz. ^{1}H and ^{13}C NMR spectra were obtained with either a Bruker AV 400 at 400 MHz and 100 MHz, respectively, or Bruker DRX 500 at 500 MHz and 126 MHz, respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz with $CDCl_3$ referenced at δ = 7.26 (^{1}H) and 77.0 ppm (^{13}C) and DMSO-d_6 referenced at δ = 2.50 (^{1}H) and 39.5 ppm (^{13}C). ^{11}B NMR spectra are referenced to $BF_3{\cdot}Et_2O$. High-resolution mass spectra were obtained through analysis at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

Synthesis of Oxidation Products (Scheme 4); General Procedure

An oven-dried 10 mL microwave vial was charged with R-BMIDA (0.1 mmol, 1 equiv) before the addition MeOH (4 mL). The vial was capped before the addition of KHF_2 (100 µL, 4.5 M aq. solution, 0.5 mmol, 5 equiv). The solution was then heated to 70 °C for 4 h, then cooled, vented, decapped, and the MeOH solution was transferred to a clean flask and concentrated under reduced pressure to provide a white solid. The residue was diluted with hot acetone and the BF_3K solution was transferred to a 5 mL flask (2 × 2 mL acetone) and concentrated under reduced pressure. The resulting residue was diluted with acetone (0.5 mL) before the addition of Oxone (35 mg, 0.11 mmol, 1.1 equiv) in H_2O (0.5 mL). The reaction was stirred for 2 h before the addition of 1 M HCl (2 mL). The reaction mixture was then diluted with H_2O (2 mL) and extracted with CH_2Cl_2 (2 × 5 mL). The organic layers were filtered through 2 cm of silica gel and washed with CH_2Cl_2 (20 mL). The resulting solution was concentrated under vacuum to afford the desired product.

1-Tosylindolin-2-one (3a)

Prepared according to the general procedure from (1-tosyl-1*H*-indol-2-yl)boronic acid MIDA ester (43 mg).

Yield: 27 mg (92%); off-white amorphous solid.

IR (solid): 3092, 3058, 2962, 2947, 1768, 1595, 1478, 1465, 1377 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.3 Hz, 2 H), 7.83 (d, *J* = 8.3 Hz, 1 H), 7.29–7.20 (m, 3 H), 7.13 (d, *J* = 7.4 Hz, 1 H), 7.06 (t, *J* = 7.5 Hz, 1 H), 3.47 (s, 2 H), 2.34 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.3, 145.2, 139.9, 134.8, 129.3, 128.1, 127.5, 124.2, 124.1, 122.7, 113.2, 35.6, 21.2.

HRMS (NSI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}NO_3S$: 288.0689; found: 288.0690.

1-Methylindolin-2-one (3b)

Prepared according to the general procedure from (1-methyl-1*H*-indol-2-yl)boronic acid MIDA ester (29 mg).

Yield: 8 mg (54%); dark-green liquid.

IR (solid): 3060, 2924, 2855, 1698, 1614, 1496, 1470, 1370, 1349 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.26 (m, 1 H), 7.26–7.22 (m, 1 H), 7.05 (dd, *J* = 7.5, 0.9 Hz, 1 H), 6.82 (d, *J* = 7.8 Hz, 1 H), 3.52 (s, 2 H), 3.21 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.6, 144.7, 127.4, 123.8, 121.9, 107.6, 35.3, 25.7.

HRMS (NSI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{10}NO$: 148.0757; found: 148.0753.

6-Chloro-1-tosylindolin-2-one (3c)

Prepared according to the general procedure from (6-chloro-1-tosyl-1*H*-indol-2-yl)boronic acid MIDA ester (46 mg).

Yield: 29 mg (90%); white amorphous solid.

IR (solid): 2924, 2857, 1768, 1610, 1595, 1424, 1372, 1333, 1236 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.07–7.88 (m, 3 H), 7.35 (d, *J* = 8.1 Hz, 2 H), 7.14 (d, *J* = 1.1 Hz, 2 H), 3.52 (s, 2 H), 2.43 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.3, 146.0, 141.2, 135.0, 134.4, 129.9, 128.1, 125.5, 125.4, 124.7, 121.5, 114.4, 35.7, 21.7.

HRMS (TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}ClNO_3S$: 322.0305; found: 322.0304.

5-Fluoro-1-tosylindolin-2-one (3d)

Prepared according to the general procedure from (5-fluoro-1*H*-indol-2-yl)boronic acid MIDA ester (44 mg).

Yield: 28 mg (92%); off-white amorphous solid.

IR (solid): 3073, 2973, 2924, 1761, 1610, 1599, 1476, 1368 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.06–7.93 (m, 2 H), 7.88 (dd, *J* = 9.0, 4.5 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.04 (td, *J* = 9.0, 2.8 Hz, 1 H), 6.98–6.94 (m, 1 H), 3.55 (s, 2 H), 2.43 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.3, 159.9 (d, $^1J_{C-F}$ = 244.0 Hz), 145.8, 135.1, 129.8, 128.0, 124.9 (d, $^3J_{C-F}$ = 8.6 Hz), 115.1 (d, $^2J_{C-F}$ = 23.3 Hz), 114.9 (d, $^3J_{C-F}$ = 7.9 Hz), 112.4 (d, $^2J_{C-F}$ = 24.9 Hz), 36.2, 21.7.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –117.57.

HRMS (TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}FNO_3S$: 306.0600; found: 306.0602.

5-Chloro-1-tosylindolin-2-one (3e)

Prepared according to the general procedure from (5-chloro-1*H*-indol-2-yl)boronic acid MIDA ester (46 mg).

Yield: 29 mg (90%); white amorphous solid.

IR (solid): 2956, 2922, 1755, 1599, 1470, 1370, 1232 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.99–7.94 (m, 2 H), 7.86 (d, *J* = 8.8 Hz, 1 H), 7.36–7.29 (m, 3 H), 7.22–7.19 (m, 1 H), 3.55 (s, 2 H), 2.43 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 172.0, 145.9, 138.9, 135.0, 130.2, 129.8, 128.6, 128.0, 125.0, 124.9, 114.8, 35.9, 21.7.

HRMS (NSI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}ClNO_3S$: 322.0299; found: 322.0302.

5-Bromo-1-tosylindolin-2-one (3f)

Prepared according to the general procedure from (5-bromo-1-tosyl-1*H*-indol-2-yl)boronic acid MIDA ester (51 mg).

Yield: 24 mg (66%); light-brown amorphous solid.

IR (solid): 3088, 2958, 2924, 2854, 1757, 1599, 1469, 1455, 1375 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.96 (m, 2 H), 7.83 (d, *J* = 8.8 Hz, 1 H), 7.51–7.46 (m, 1 H), 7.39–7.33 (m, 3 H), 3.58 (s, 2 H), 2.45 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.4, 145.5, 138.9, 134.4, 131.0, 129.4, 127.5, 127.4, 124.7, 117.2, 114.7, 35.3, 21.3.

HRMS (NSI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}BrNO_3S$: 365.9794; found: 365.9798.

5-Methoxy-1-tosylindolin-2-one (3g)

Prepared according to the general procedure from (5-methoxy-1*H*-indol-2-yl)boronic acid MIDA ester (46 mg).

Yield: 28 mg (88%); light-brown amorphous solid.

IR (solid): 2950, 2924, 2855, 1757, 1601, 1483, 1470, 1372 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.3 Hz, 2 H), 7.82 (d, *J* = 9.0 Hz, 1 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 6.85 (dd, *J* = 9.0, 2.4 Hz, 1 H), 6.79 (s, 1 H), 3.79 (s, 3 H), 3.53 (s, 2 H), 2.42 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.7, 157.0, 145.6, 135.2, 133.8, 129.8, 127.9, 124.5, 114.5, 113.2, 111.2, 55.7, 36.5, 21.7.

HRMS (NSI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}NO_4S$: 318.0795; found: 318.0796.

1-Tosyl-5-(trifluoromethoxy)indolin-2-one (3h)

Prepared according to the general procedure from (1-tosyl-5-(trifluoromethoxy)-1*H*-indol-2-yl)boronic acid MIDA ester (51 mg).

Yield: 30 mg (80%); off-white amorphous solid.

IR (solid): 2958, 2928, 2857, 1761, 1601, 1480, 1374 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.3 Hz, 2 H), 7.87 (d, *J* = 8.9 Hz, 1 H), 7.27 (d, *J* = 8.1 Hz, 2 H), 7.14 (d, *J* = 8.9 Hz, 1 H), 7.04 (s, 1 H), 3.51 (s, 2 H), 2.36 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.0, 146.0, 138.9, 135.0, 129.9, 128.1, 124.8, 121.6, 119.4, 118.2, 114.7, 36.1, 21.7. Trifluoromethyl carbon not observed.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –58.21.

HRMS (TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{12}F_3NO_4S$: 372.0517; found: 372.0527.

Methyl 2-Oxo-1-tosylindoline-5-carboxylate (3i)

Prepared according to the general procedure from (5-(methoxycarbonyl)-1-tosyl-1*H*-indol-2-yl)boronic acid MIDA ester (48 mg).

Yield: 22 mg (62%); white amorphous solid.

IR (solid): 2956, 2924, 2855, 1766, 1711, 1623, 1601, 1483, 1450, 1374 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.6 Hz, 1 H), 7.92 (d, *J* = 7.0 Hz, 3 H), 7.83 (s, 1 H), 7.27 (d, *J* = 8.2 Hz, 2 H), 3.84 (s, 3 H), 3.53 (s, 2 H), 2.36 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.9, 165.8, 145.6, 143.6, 134.4, 130.2, 129.4, 127.6, 126.1, 125.5, 122.8, 112.8, 51.8, 35.3, 21.3.

HRMS (NSI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}NO_5S$: 346.0744; found: 346.0746.

Benzofuran-2(3*H*)-one (3k)[25a]

Prepared according to the general procedure from benzofuran-2-ylboronic acid MIDA ester (27 mg).

Yield: 14 mg (100%); white amorphous solid.

IR (solid): 2956, 2926, 1798, 1779, 1616, 1601, 1480, 1465, 1299 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.19 (m, 2 H), 7.06 (t, *J* = 7.5 Hz, 1 H), 7.03 (d, *J* = 8.0 Hz, 1 H), 3.66 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.6, 154.2, 128.4, 124.1, 123.6, 122.6, 110.3, 32.5.

5-Fluorobenzofuran-2(3*H*)-one (3l)

Prepared according to the general procedure from (5-fluorobenzofuran-2-yl)boronic acid MIDA ester (29 mg).

Yield: 15 mg (98%); white amorphous solid.

IR (solid): 3081, 2958, 2926, 2855, 1796, 1634, 1610, 1483, 1400, 1388 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.07–6.82 (m, 3 H), 3.69 (s, 2 H).

^{13}C NMR (500 MHz, $CDCl_3$): δ = 173.6, 159.4 (d, $^1J_{C-F}$ = 242.5 Hz), 150.6, 124.4 (d, $^3J_{C-F}$ = 9.5 Hz), 115.5 (d, $^2J_{C-F}$ = 24.3 Hz), 112.2 (d, $^2J_{C-F}$ = 25.6 Hz), 111.7 (d, $^3J_{C-F}$ = 8.4 Hz), 33.5.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –118.2.

HRMS (TOF): *m*/*z* [M + H]$^+$ calcd for $C_8H_5FO_2$: 153.0352; found: 153.0354.

Oxindole (6)[25b]

A 10 mL flask was charged with sodium metal (138 mg, 6 mmol, 60 equiv) and naphthalene (385 mg, 3 mmol, 30 equiv) before the addition of DME (5 mL) and the reaction mixture was stirred at r.t. for 30 min to form a blue/green solution. A solution of 1-tosylindolin-2-one (28 mg, 0.1 mmol, 1 equiv) in DME (0.5 mL, 0.2 M) was cooled to –78 °C and the Na-naphthalenide solution was then added dropwise until an orange/red color persisted (1.5 mL). The solution was then warmed to r.t. and further naphthalenide solution (0.5 mL) was added. The reaction was quenched with H_2O (2 mL), and the mixture was extracted with EtOAc (5 mL), and washed with brine (5 mL). The organic layers were then passed through a hydrophobic frit and concentrated under vacuum before being purified (silica gel; EtOAc–petroleum ether, 10–40%) to afford the desired product.

Yield: 12 mg (90%); beige amorphous solid.

IR (solid): 3161, 1692, 1618, 1469, 1332 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.20 (s, 1 H), 7.24 (t, *J* = 7.4 Hz, 2 H), 7.05 (d, *J* = 7.5 Hz, 1 H), 6.93 (d, *J* = 7.8 Hz, 1 H), 3.57 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.7, 142.1, 127.4, 124.8, 124.1, 121.8, 109.3, 35.8.

Semaxanib

A 25 mL flask was charged with oxindole (133 mg, 1 mmol, 1 equiv) and 3,5-dimethyl-1*H*-pyrrole-2-carbaldehyde (148 mg, 1.2 mmol, 1.2 equiv) before the addition of EtOH (0.5 M, 10 mL). Piperidine (12 µL, 0.01 mmol, 0.01 equiv) was then added and the flask was equipped with a condenser before heating to reflux for 4 h. The reaction mixture was then cooled to r.t. and concentrated under vacuum to afford a red/orange solid. The precipitate was collected by filtration and washed with chloroform to afford the desired product.

Yield: 230 mg (97%); red/orange amorphous solid.

IR (solid): 3166, 3122, 2917, 2842, 1668, 1617, 1565, 1554, 1539, 1463, 1455, 1340, 1316, 1204 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.12 (s, 1 H), 8.00 (s, 1 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.40 (s, 1 H), 7.13 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.05 (td, *J* = 7.6, 1.1 Hz, 1 H), 6.90 (d, *J* = 7.6 Hz, 1 H), 5.98 (d, *J* = 2.5 Hz, 1 H), 2.39 (s, 3 H), 2.34 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.8, 137.0, 136.9, 132.6, 127.1, 126.6, 125.6, 123.6, 121.5, 117.4, 112.7, 111.8, 109.2, 13.9, 11.6.

HRMS (NSI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}N_2O$: 239.1179; found: 239.1177.

Spiro[cyclopropane-1,3′-indolin]-2′-one (8)

An oven-dried flask was charged with oxindole (133 mg, 1 mmol, 1 equiv) before the addition of anhydrous DMF (0.8 M, 1.25 mL) and dibromoethane (94 µL, 1.1 mmol, 1.1 equiv). The solution was then cooled to 0 °C before the addition of NaH (60% dispersion in mineral oil, 180 mg, 4.5 mmol, 4.5 equiv) portionwise over 20 min. The mixture was then warmed to r.t. and stirred overnight, then the reaction was quenched with H_2O (3 mL) and the mixture was extracted with EtOAc (5 mL). The organic layers were then washed with H_2O (2 × 5 mL) and brine (2 × 5 mL) and passed through a hydrophobic frit and concentrated under vacuum before being purified (silica gel; EtOAc/petroleum ether, 20–40%) to afford the desired product.

Yield: 23 mg (14%); red/brown amorphous solid.

IR (solid): 3200, 1701, 1684, 1671, 1627, 1474, 1357 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (s, 1 H), 7.19 (t, *J* = 7.7 Hz, 1 H), 7.01 (t, *J* = 7.5 Hz, 1 H), 6.96 (d, *J* = 7.7 Hz, 1 H), 6.83 (d, *J* = 7.4 Hz, 1 H), 1.76 (d, *J* = 3.0 Hz, 2 H), 1.54 (d, *J* = 2.9 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.1, 140.6, 131.3, 126.7, 122.0, 118.6, 109.7, 27.4, 19.5.

HRMS (NSI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{10}NO$: 160.0757; found: 160.0753.

Coerulescine

A 5 mL microwave vial equipped with a stirrer bar was charged with spiro[cyclopropane-1,3′-indolin]-2′-one (20 mg, 0.125 mmol, 1 equiv) and MgI_2 (1.74 mg, 6.25 µmol, 5 mol%) before being capped and purged with N_2. THF (0.6 M, 0.2 mL) and trimethyl triazinane (18 µL, 0.125 mmol, 1 equiv) were then added and the reaction mixture was heated to 125 °C in a sand-bath for 60 h. The reaction mixture was then cooled to r.t. before being diluted with EtOAc (5 mL) and washed with H_2O (5 mL) and brine (5 mL). The organic layers were then passed through a hydrophobic frit and concentrated under vacuum before being purified (silica gel; EtOAc–petroleum ether, 50% then MeOH–CH_2Cl_2, 20%) to afford the desired product.

Yield: 14 mg (55%); pale-yellow oil.

IR (solid): 3192, 3060, 2943, 2787, 1707, 1619, 1472, 1336, 1195 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (s, 1 H), 7.41 (d, *J* = 7.3 Hz, 1 H), 7.19 (td, *J* = 7.7, 1.2 Hz, 1 H), 7.04 (td, *J* = 7.6, 1.0 Hz, 1 H), 6.89 (d, *J* = 7.7 Hz, 1 H), 3.11–3.00 (m, 1 H), 2.91 (s, 2 H), 2.88–2.74 (m, 1 H), 2.49 (s, 3 H), 2.41 (ddd, *J* = 12.5, 7.7, 4.7 Hz, 1 H), 2.12 (dt, *J* = 12.9, 7.5 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 182.7, 140.1, 136.0, 127.8, 123.4, 122.9, 109.5, 66.2, 56.7, 53.6, 41.8, 38.0.

HRMS (NSI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}N_2O$: 203.1179; found: 203.1177.

5-Chloroindolin-2-one (9)

To a 10 mL flask charged with sodium metal (83 mg, 3.6 mmol, 60 equiv) and naphthalene (231 mg, 1.8 mmol, 30 equiv) was added DME (5 mL) and the reaction mixture was stirred at r.t. for 30 min to form a blue/green solution. A solution of 5-chloro-1-tosylindolin-2-one (20 mg, 0.06 mmol, 1 equiv) in DME (0.3 mL, 0.2 M) was cooled to –78 °C and the Na-naphthalenide solution was then added dropwise until an orange/red color persisted (1.5 mL). The solution was then warmed to r.t. and further Na-naphthalenide solution (0.5 mL) was added. The reaction was then quenched with H_2O (2 mL), and the mixture was extracted with EtOAc (5 mL), and washed with brine (5 mL). The organic layers were then passed through a hydrophobic frit and concentrated under vacuum before being purified (silica gel; EtOAc–petroleum ether, 10–40%) to afford the desired product.

Yield: 8 mg (80%); off-white amorphous solid.

IR (solid): 3159, 3047, 2960, 2926, 2855, 1699, 1621, 1478, 1379, 1316 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 7.20 (d, *J* = 11.5 Hz, 2 H), 6.80 (d, *J* = 8.1 Hz, 1 H), 3.54 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.5, 139.8, 127.0, 126.7, 125.9, 124.1, 109.4, 35.0.

HRMS (NSI): *m*/*z* [M + H]$^+$ calcd for C_8H_7ClNO: 168.0211; found: 168.0207.

Phenyl 5-Chloro-2-oxoindoline-1-carboxylate (10)

Step 1: Synthesis of Phenyl 5-Chloro-2-[(phenoxycarbonyl)oxy]-1*H*-indole-1-carboxylate

To a flask charged with 5-chloro-2-oxindole (1 g, 6 mmol, 1 equiv) was added anhydrous THF (20 mL) followed by triethylamine (1.75 mL, 12.6 mmol, 2.1 equiv). The reaction mixture was cooled to 0 °C before the dropwise addition of phenyl chloroformate (1.6 mL, 13.2 mmol, 2.2 equiv). The mixture was stirred at 0 °C for 1 h, the resulting precipitate was then removed by filtration and the filter cake was washed with THF (2 × 20 mL). The filtrate was concentrated under vacuum to obtain a pink solid which was stirred in H_2O (20 mL) to form an emulsion, which was then filtered, washed with H_2O (2 × 20 mL), and dried by drawing air through the filter cake to afford the desired product phenyl 5-chloro-2-((phenoxycarbonyl)oxy)-1*H*-indole-1-carboxylate (2.4 g crude weight) as a white solid. The product was used directly in the next step without further purification.

Step 2

A solution of phenyl 5-chloro-2-[(phenoxycarbonyl)oxy]-1*H*-indole-1-carboxylate (1.11 g, 2.75 mmol, 1 equiv) in anhydrous DMF (10 mL) was cooled to 0 °C, followed by the portionwise addition of ammonium carbonate powder (300 mg, 3.16 mmol, 1.15 equiv). The resulting solution was stirred for 1 h at 0 °C. Upon consumption of the starting material, the pale-yellow solution was then poured into ice water (30 mL) to provide a white precipitate. The suspension was then stirred for 30 min before being filtered, washed with H_2O (2 × 10 mL) and dried by pulling air through the filter cake to afford the desired product **10**.

Yield: 585 mg (73% over two steps); white amorphous solid.

IR (solid): 3137, 3060, 2956, 2932, 1770, 1737, 1595, 1478 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.7 Hz, 1 H), 7.47 (t, *J* = 7.9 Hz, 2 H), 7.37–7.29 (m, 5 H), 3.80 (s, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.5, 150.0, 149.4, 138.9, 130.5, 129.7, 128.5, 126.6, 125.0, 124.6, 121.5, 116.7, 36.3.

HRMS (NSI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}ClNO_3$: 288.0422; found: 288.0423.

Tenidap

Step 1: Synthesis of Phenyl (*E*)-5-Chloro-3-[hydroxy(thiophen-2-yl)methylene]-2-oxoindoline-1-carboxylate (**11**)

To a 50 mL flask charged with phenyl 5-chloro-2-oxoindoline-1-carboxylate (100 mg, 0.35 mmol, 1 equiv) and 4-dimethylaminopyridine (10.7 g, 74 mg, 0.735 mmol, 2.1 equiv) was added anhydrous DMF (0.25 M, 1.4 mL), and the solution was cooled to 0 °C. A solution of thiophene-2-carbonyl chloride (56 mg, 0.385 mmol, 1.1 equiv) in anhydrous DMF (0.6 mL) was then added dropwise and the resulting suspension was stirred at 0 °C until consumption of the starting material (ca. 1 h). The solution was then poured into ice water (3 mL), acidified to pH 2–3 with concentrated hydrochloric acid and stirred for 3 h. The resulting precipitate was then filtrated, washed with H_2O (2 × 5 mL), and dried by drawing air through the filter cake to afford the desired product **11** (111 mg crude weight) as a pale-yellow solid. The product was used directly in the next step without further purification.

Step 2

To a solution of phenyl (*E*)-5-chloro-3-[hydroxy(thiophen-2-yl)methylene]-2-oxoindoline-1-carboxylate (12 mg, 0.03 mmol, 1 equiv) in anhydrous DMF (0.15 M, 0.2 mL) was added ammonium carbonate powder (3 mg, 0.03 mmol, 1 equiv). The resulting solution was then stirred at 80 °C for 4 h, then the reaction mixture was cooled to r.t. before being diluted with EtOAc (5 mL) and washed with H_2O (5 mL). The organic layers were then passed through a hydrophobic frit and concentrated under vacuum before being purified (silica gel; MeOH–CH_2Cl_2, 0–100%) to afford the desired product.

Yield: 9 mg (75% over two steps); yellow amorphous solid.

IR (solid): 3330, 2254, 1694, 1627, 1595, 1571, 1457, 1424 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.35 (s, 1 H), 8.59 (d, *J* = 3.3 Hz, 1 H), 8.16 (d, *J* = 1.8 Hz, 1 H), 8.01 (d, *J* = 8.5 Hz, 1 H), 7.59 (d, *J* = 4.9 Hz, 1 H), 7.11–7.04 (m, 2 H), 6.79 (dd, *J* = 8.5, 2.3 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 176.8, 165.7, 154.7, 149.1, 132.0, 130.1, 129.5, 129.1, 126.9, 126.0, 118.3, 117.3, 113.9, 94.3.

HRMS (NSI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{10}ClN_2O_3S$: 321.0095; found: 321.0099.

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Supporting Information

Optimization data, and ^{1}H and ^{13}C NMR spectra for all new compounds. Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562619.

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