Regioselective Functionalization of Chlorophthalazine Derivatives

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Abstract: Chlorophthalazines were efficiently metalated using tmpZnCl·LiCl under microwave irradiation. This provided novel substituted phthalazine derivatives after subsequent trapping of the resulting organometallic reagents with various electrophiles. Moreover, Negishi cross-coupling reactions have been performed affording new polyfunctionalized phthalazine scaffolds in very good yields.

Key words: chlorophthalazine derivatives, metalation, microwave irradiation, Negishi cross-coupling, zinc

Phthalazines and their derivatives are known to possess a wide range of biological activity. For example, Vatanalib (**I**) has been recently described as a tyrosine kinase inhibitor of angiogenesis.[1] Moreover, many triazolophthalazines of type **II** have been shown to bind to the benzodiazepane site of GABA-A receptors[2] and phthalazinone Zopolrestat (**III**) is a potent inhibitor of aldose reductase (Figure 1).[3] Recently, Carreira and co-workers developed an efficient ligand (PINAP) bearing a phthalazine moiety for catalytic and enantioselective alkyne addition.[4]

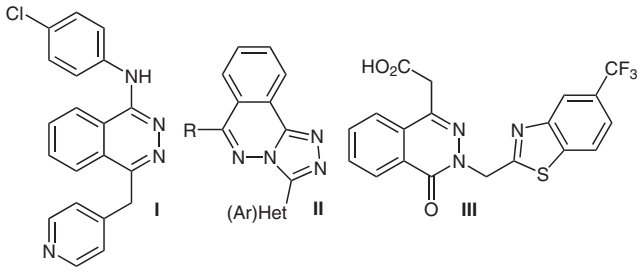
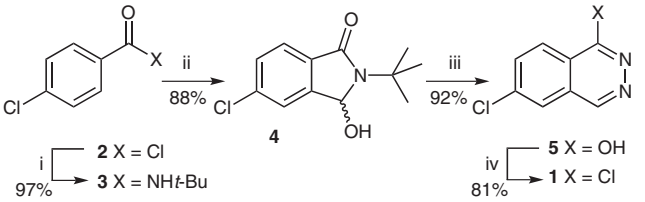


Figure 1 Examples of biologically active phthalazines

However, the construction of substituted and functionalized phthalazines reveals two major constraints. It requires the cyclization of substituted benzenes that are obtained after tedious multistep synthesis.[5] Moreover, a complex mixture is generally obtained due to the lack of regioselectivity and chemoselectivity.[6]

With this in mind, we have prepared an unsymmetrical dihalogenophthalazine **1** and have reacted it with recently developed Zn/Li bases[7] furnishing regioselective substituted phthalazines after subsequent trapping of the resulting zincated species with various electrophiles. Herein, we report an efficient metalation[8] protocol of chlorophthalazine derivatives providing a versatile, regioselective, and convenient procedure for the synthesis of new polyfunctionalized phthalazines.

Thus, the required 1,6-dichlorophthalazine (**1**) was readily prepared from commercially available 4-chlorobenzoyl chloride (**2**) in four steps in 65% overall yield on a multigram scale.[9] Hence *tert*-butylamide reacted with **2** providing the corresponding benzamide **3** in 97% yield. Subsequent addition of methyllithium and trapping of the resulting dianion with *N*,*N*-dimethylformamide furnished isoindolinone **4** in 88% yield. Finally, after reaction with hydrazine in glacial acetic acid (92 °C, 3 h, 92%), the ring-expanded phthalazinol **5** was converted into its chloro derivative **1** in 81% yield (Scheme 1).



Scheme 1 *Reagents and conditions:* (i) *t*-BuNH$_2$ (2.2 equiv), CH_2Cl_2, 0 °C to 25 °C, 1 h; (ii) (a) MeLi (2.05 equiv), anhyd THF, –45 °C to –10 °C, 3 h; (b) anhyd DMF (2 equiv), –30 °C to –10 °C, 30 min; (c) sat. aq NH_4Cl, –10 °C to 25 °C, 45 min; (iii) $NH_2NH_2·H_2O$ (1.05 equiv), glacial AcOH, 92 °C, 3 h; (iv) DIPEA (1 equiv), $POCl_3$ (10 equiv), 25 °C, 30 min then 100 °C for 4 h.

We first studied the metalation of dichlorophthalazine **1** by using the newly developed and mild complex base 2,2,6,6-tetramethylpiperidin-1-ylzinc chloride–lithium chloride complex (tmpZnCl·LiCl, **6**) prepared by treatment of 2,2,6,6-tetramethylpiperidine with butyllithium followed by the addition of zinc chloride (Scheme 2). Indeed, this active base allows chemoselective zincation of sensitive aromatic compounds as well as heterocyclic substrates.

Thus, 1,6-dichlorophthalazine (**1**) reacted at 25 °C with zinc base **6**, unfortunately to furnish instantly the ring fragmentation product 4-chlorophthalonitrile (**7**) in quantitative yield.[10] Alternatively, Negishi cross-coupling reaction[11] was performed using 4-MeC_6H_4ZnI·LiCl, obtained by the treatment of 4-iodotoluene with zinc dust in the presence of lithium chloride,[12] using PEPPSI-iPr as catalyst[13] to afford the single regioisomer C1-substituted phthalazine **8**, albeit in moderate yield (Scheme 2). Moreover, decomposition of the starting material **1** was mainly observed when benzylic zinc reagents as well as more re-

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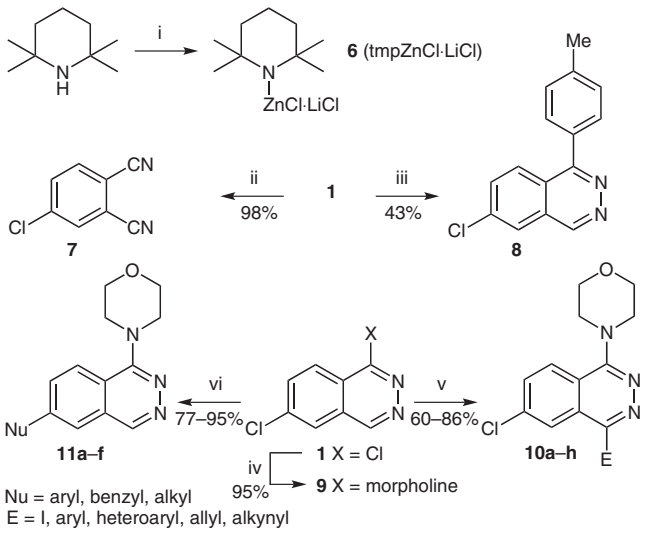


Scheme 2 *Reagents and conditions*: (i) (a) *n*-BuLi (1 equiv), anhyd THF, –50 °C to 0 °C; (b) $ZnCl_2$ (1 equiv), anhyd THF, 0 °C to 25 °C; (ii) **6** (1.1 equiv), anhyd THF, 1 min, 25 °C; (iii) 4-MeC_6H_4ZnI·LiCl (1.1 equiv), PEPPSI-iPr (1 mol%), 45 °C, 12 h; (iv) morpholine (4 equiv), toluene, 85 °C, 12 h; (v) (a) **6** (1.1 equiv), anhyd THF, 45 min, 60 °C, mw; (b) electrophile; (vi) NuZnCl·MgX_2·LiCl (1.4 equiv), PEPPSI-iPr (0.75 mol%), anhyd THF.

active zinc reagents of the type RZnCl·MgXCl·LiCl were used.[14]

1,6-Dichlorophthalazine (**1**) proved to be a highly sensitive heterocycle. A more stable 6-chlorophthalazine was prepared by introducing a morpholino group in position 1. Thus, treatment of **1** with morpholine at 85 °C for 12 hours in toluene gave the desired phthalazine **9** in 95% yield (Scheme 2). Direct zincation using tmpZnCl·LiCl (**6**)[7] required 48 hours at 25 °C and produced the zincated species in low yield. However, microwave irradiation[15] led to a complete zincation within 45 minutes (60 °C) furnishing the iodo derivative **10a** after iodolysis in 74% yield (Table 1, entry 1). Additionally, quenching of the metalated intermediate with 3-bromocyclohexene in the presence of CuCN·2LiCl[16] (5 mol%) provided the allylated phthalazine **10b** in 60% yield (entry 2). After palladium-catalyzed cross-coupling reactions, the functionalized phthalazines **10c–g** bearing an ester, a nitrile, a ketone, or a thiophene group were obtained in 72–86% yields (entries 3–7). Sonogashira reaction[17] of in situ generated 4-iodophthalazine **10a** with hex-1-yne afforded 4-alkynylphthalazine **10h** in 89% yield (entry 8).

Table 1 Synthesis and Yields of Phthalazine Derivatives **10** with tmpZnCl·LiCl (**6**) and Quenching with Electrophiles

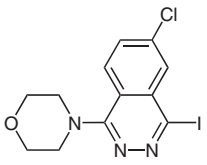
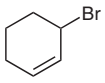
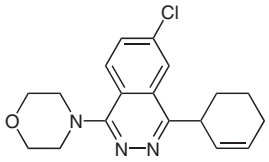
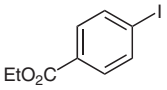
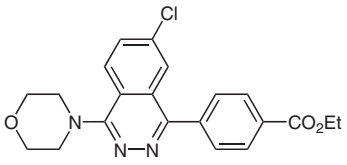
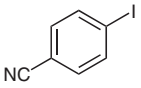
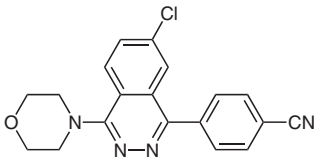
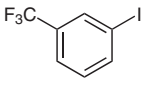
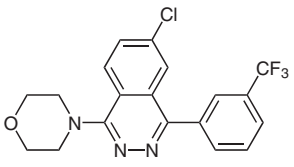
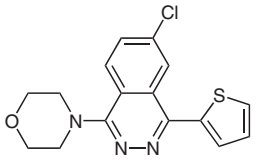
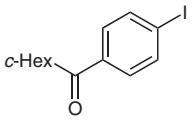
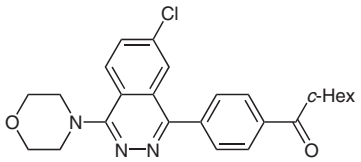
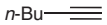
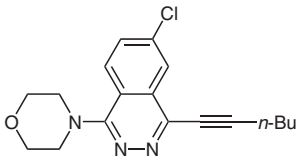
Entry	Electrophile	Product	Yield[a] (%)
1	I_2	 **10a**	71
2		 **10b**	60[b]
3		 **10c**	83[c]
4		 **10d**	74[c]
5		 **10e**	84[c]

Table 1 Synthesis and Yields of Phthalazine Derivatives **10** with tmpZnCl·LiCl (**6**) and Quenching with Electrophiles (continued)

Entry	Electrophile	Product	Yield[a] (%)
6		 **10f**	86[c]
7		 **10g**	72[c]
8		 **10h**	89[d]

[a] Yield (%) of isolated analytically pure product.
[b] Transmetalation performed with CuCN·2LiCl (5 mol%).
[c] Obtained by palladium-catalyzed cross-coupling reaction using $Pd(dba)_2$ (2 mol%) and $(o\text{-furyl})_3P$ (4 mol%).
[d] Obtained by Sonogashira reaction of in situ generated compound **10a**.

Table 2 Synthesis and Yields of Phthalazine Derivatives **11**

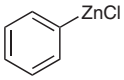
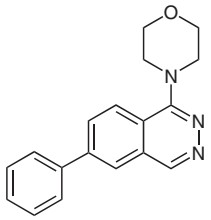
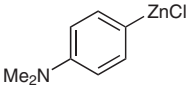
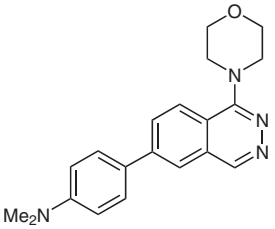
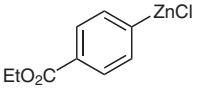
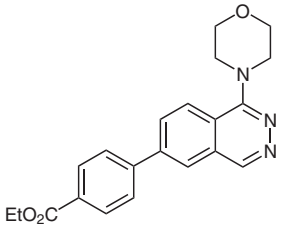
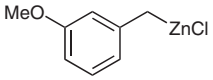
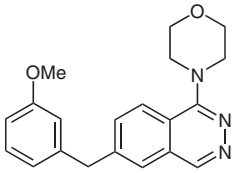
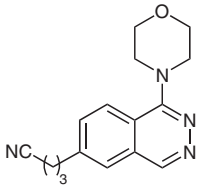
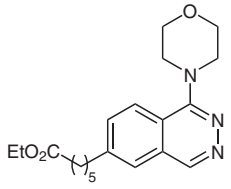
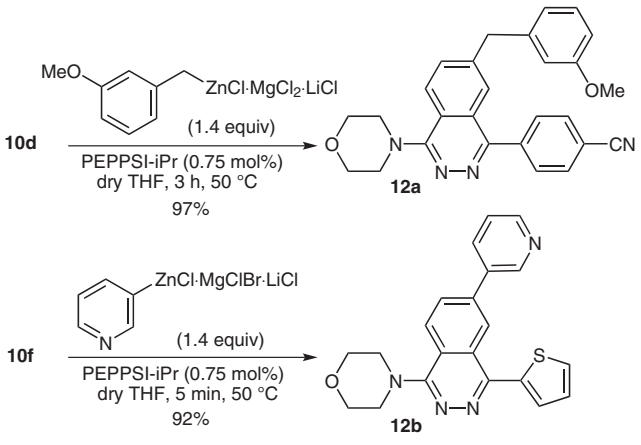
Entry	Nucleophile[a]	Temp, time[b]	Product	Yield[c] (%)
1		25 °C, 30 min	 **11a**	95, 87[d]
2		25 °C, 10 min	 **11b**	79
3		25 °C, 10 min	 **11c**	85

Table 2 Synthesis and Yields of Phthalazine Derivatives **11** (continued)

Entry	Nucleophile[a]	Temp, time[b]	Product	Yield[c] (%)
4		50 °C, 4 h	 **11d**	94
5	$NC(CH_2)_3ZnCl$	60 °C, 8 h	 **11e**	77
6	$EtO_2C(CH_2)_5ZnCl$	60 °C, 30 min	 **11f**	77

[a] $MgCl_2$·LiCl or MgClBr·LiCl salts are omitted for clarity.
[b] The reaction conditions for the cross coupling with **9**.
[c] Yield (%) of isolated analytically pure product.
[d] Using PhZnCl·$MgCl_2$ as zinc reagent at 45 °C for 12 h.

Furthermore, Negishi cross-coupling reactions were performed on the chlorophthalazine **9** (Scheme 2). Thus, using PEPPSI-iPr as catalyst PhZnCl·$MgCl_2$·LiCl[14] reacted with **9** at 25 °C within 30 minutes providing substituted phthalazine **11a** in 95% yield (Table 2, entry 1). Moreover, the treatment of arylzinc reagents bearing an ester or an amino group at 25 °C for 10 minutes furnished 6-arylphthalazides **11b**,**c** in 79–85% yields (entries 2 and 3). Heating at 50–60 °C and extending the reaction time allowed the synthesis of the expected benzyl and alkyl products **11d**–**f** in 77–94% yields (entries 4–6).



Scheme 3 Synthesis of polyfunctionalized phthalazines **12a**,**b**

Additionally, two examples for the synthesis of polyfunctionalized phthalazines are depicted in Scheme 3. Thus, phthalazine **10d** bearing a nitrile group underwent Negishi cross-coupling with a benzylic zinc reagent[18] providing the 1,4,6-trisubstituted heterocycle **12a** in 97% yield. Remarkably, pyridinylzinc reagent[18] reacted with thiophene **10f** within five minutes at 50 °C leading to the desired phthalazine **12b** in 92% yield.

In summary, we have developed an efficient and valuable microwave-assisted procedure for the regioselective metalation of the phthalazine scaffold using tmpZnCl·LiCl as an effective zinc base. This method allows easy access to new polyfunctionalized phthalazine libraries which should find wide applications for the synthesis of new biologically active and relevant molecules. Further studies concerning construction of new substituted derivatives are currently in progress.

All reactions were carried out under an argon atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. THF was continuously refluxed and freshly distilled from Na benzophenone ketyl under N_2. 2,2,6,6-Tetramethylpiperidine (tmpH) was distilled prior to use. Yields refer to isolated compounds estimated to be >95% pure as determined by ^{1}H NMR (25 °C) and capillary GC. NMR spectra were recorded on Bruker ARX-200, AC-300 or WH-400 using $CDCl_3$ or DMSO-d_6 as solvents. Gas chromatography (GC) were performed with machines of type Hewlett-Packard 6890 or 5890 series II using a column of type HP 5. Column chromatography was performed using silica gel (0.040–0.063 mm, 230–400

mesh ASTM) from Merck. Melting points were measured using a Büchi B-540 apparatus and are uncorrected. Mass spectra and HRMS were recorded on Finnigan MAT 95Q or Finnigan MAT 90 instrument using electron impact (EI); where otherwise noted electronspray ionization (ESI) was used. Microwave-assisted synthesis was carried out in a Biotage Initiator apparatus operating in single mode; the microwave cavity producing controlled irradiation at 2.45 GHz (Biotage AB, Uppsala, Sweden). The reactions were run in sealed vessels (2.0–5.0 mL). These experiments were performed by employing magnetic stirring and a fixed hold time using variable power to reach (over 1 min) and then maintain the desired temperature in the vessel for the programmed time period. The temperature was monitored by an IR sensor focused on a point on the reactor vial glass. The IR sensor was calibrated to internal soln reaction temperature by the manufacturer. PEPPSI-iPr catalyst {[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride} was obtained from Aldrich.

N-tert-Butyl-4-chlorobenzamide (3)[8]

t-$BuNH_2$ (132 mL, 1.26 mol, 2.2 equiv) was added dropwise over 45 min at 0 °C to a cooled soln of 4-chlorobenzoyl chloride (**2**, 100 g, 0.57 mol, 1 equiv) in anhyd CH_2Cl_2 (350 mL) under argon. The mixture was then allowed to warm to 25 °C over 1 h. Aq 5 M NaOH (200 mL) was slowly added and then the aqueous layer was removed. The organic layer was partially concentrated and heptane (200 mL) was added. CH_2Cl_2 was removed in vacuo and the white precipitated product was collected by filtration, washed with heptane (200 mL), and oven dried (40 °C overnight) affording **3** as a white solid; yield: 117.7 g (97%); R_f = 0.7 (EtOAc–pentane, 1:5).

^{1}H NMR (DMSO-d_6): δ = 7.78–7.83 (m, 3 H), 7.46 (d, *J* = 8.0 Hz, 2 H), 1.35 (s, 9 H).

^{13}C NMR (DMSO-d_6): δ = 165.6, 135.9, 135.0, 129.7 (2 C), 128.4 (2 C), 51.3, 29.0 (3 C).

MS (70 eV): *m*/*z* (%) = 211 (11) $[M]^+$, 141 (37), 139 (100), 127 (37), 114 (29), 111 (23), 97 (34), 83 (34).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{11}H_{14}ClNO$: 211.0764; found: 211.0759.

2-*tert*-Butyl-5-chloro-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one (4)[8]

A 3.0 M soln of MeLi in diethoxymethane (80.7 mL, 242 mmol, 2.05 equiv) was added dropwise over 45 min at –45 °C to a cooled soln of benzamide **3** (25 g, 118 mmol, 1 equiv) in anhyd THF (200 mL) under argon, keeping the temperature below –30 °C. The mixture was allowed to warm to –10 °C, stirred at this temperature for 3 h, and cooled down to –30 °C. Anhyd DMF (18.3 mL, 236 mmol, 2 equiv) was added dropwise over 15 min, keeping the temperature below –20 °C. The mixture was allowed to warm to –10 °C over 30 min and sat. aq NH_4Cl (100 mL) was slowly added, keeping internal temperature below –10 °C. The mixture was allowed to warm to 25 °C over 45 min; the aqueous layer was removed and the organic layer was concentrated to give an orange crude solid. Toluene (110 mL) was added and the mixture was heated to 110 °C for 1 h and cooled slowly to 25 °C over 3 h. The white precipitated product was collected by filtration, washed with toluene (200 mL), and oven dried at 60 °C overnight affording **4** as a white solid; yield: 25 g (88%); R_f = 0.6 (EtOAc–pentane, 1:4). The filtrate was concentrated and the starting material **3** (2.17 g, 9%) was recovered.

^{1}H NMR (DMSO-d_6): δ = 7.53–7.56 (m, 3 H), 6.40 (d, *J* = 10.0 Hz, 1 H), 6.00 (d, *J* = 10.0 Hz, 1 H), 1.50 (s, 9 H).

^{13}C NMR (DMSO-d_6): δ = 166.3, 147.3, 136.8, 131.7, 129.8, 124.1, 123.8, 81.3, 54.3, 28.4 (3 C).

MS (70 eV): *m*/*z* (%) = 239 (4), $[M]^+$, 224 (57), 169 (40), 167 (100), 139 (12).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{12}H_{14}ClNO_2$: 239.0713; found: 239.0678.

6-Chlorophthalazin-1-ol (5)[8]

Hydrazine hydrate soln (64 wt%, 5.49 g, 110 mmol, 1.05 equiv) was added dropwise over 1 h to a heated soln of isoindolinone **4** (25 g, 104 mmol, 1 equiv) in glacial AcOH (105 mL) under argon at 90 °C, keeping the temperature below 93 °C. The mixture was heated to 92 °C for 3 h, deionized H_2O (150 mL) preheated to 80 °C was added, and the mixture was allowed to cool to 25 °C over 3 h. The yellowish precipitated product was collected by filtration, washed with deionized H_2O (60 mL), and oven dried at 80 °C overnight affording **5** as a pale yellow solid; yield: 17.4 g (92%); R_f = 0.5 (EtOAc–pentane, 1:1).

^{1}H NMR (DMSO-d_6): δ = 12.74 (br s, 1 H), 8.30 (s, 1 H), 8.17 (d, *J* = 8.6 Hz, 1 H), 8.02 (d, *J* = 2.0 Hz, 1 H), 7.82 (dd, *J* = 8.5 Hz, *J* = 2.0 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 159.5, 138.8, 137.6, 132.3, 131.7, 128.3, 126.6, 126.5.

MS (70 eV): *m*/*z* (%) = 182 (27), 180 (100) $[M]^+$, 152 (14), 123 (21), 89 (10).

HRMS: *m*/*z* $[M]^+$ calcd for $C_8H_5ClN_2O$: 180.0090; found: 180.0087.

1,6-Dichlorophthalazine (1)[19]

DIPEA (7.44 mL, 45 mmol, 1 equiv) was added dropwise to a soln of phthalazinol **5** (8.13 g, 45 mmol, 1 equiv) in $POCl_3$ (42 mL, 450 mmol, 10 equiv) at 25 °C. The mixture was stirred for 30 min, heated at 100 °C for 4 h, and then cooled to 25 °C. $CHCl_3$ (175 mL) was added and the mixture was cooled to 0 °C. The yellowish precipitated product was collected by filtration, washed successively with cold $CHCl_3$ (40 mL), deionized H_2O (3 × 30 mL), and cold $CHCl_3$ (10 mL), and then oven dried at 80 °C overnight affording **1** as a pale yellow solid; yield: 7.30 g (81%); mp 147–148 °C; R_f = 0.65 (EtOAc–pentane, 1:1).

^{1}H NMR (DMSO-d_6): δ = 9.65 (d, *J* = 0.8 Hz, 1 H), 8.42 (d, *J* = 2.2 Hz, 1 H), 8.27 (d, *J* = 9.0 Hz, 1 H), 8.16 (dd, *J* = 9.0 Hz, *J* = 2.2 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 154.6, 151.6, 139.0, 135.4, 129.3, 127.4, 126.9, 124.1.

MS (70 eV): *m*/*z* (%) = 202 (10), 200 (66), 198 (100) $[M]^+$, 172 (23), 170 (37), 135 (15), 99 (15).

HRMS: *m*/*z* $[M]^+$ calcd for $C_8H_4Cl_2N_2$: 197.9752; found: 197.9741.

Preparation of tmpZnCl·LiCl (6)

A dry and argon-flushed 500-mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged successively with freshly distilled tmpH (8.45 mL, 50 mmol, 1 equiv) and anhyd THF (60 mL). The soln was cooled to –50 °C and 2.36 M *n*-BuLi in hexane (21.2 mL, 50 mmol, 1 equiv) was slowly added dropwise. The mixture was then allowed to warm to 0 °C over 1 h prior to addition dropwise of 1.0 M $ZnCl_2$ in THF (50 mL, 50 mmol, 1 equiv). The mixture was stirred at 25 °C for 1 h and the solvents were removed under vacuum affording a yellowish solid. Freshly distilled THF was slowly added under vigorous stirring until the salts were completely dissolved. The freshly prepared tmpZnCl·LiCl (**6**) was titrated prior to use at 25 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.72 M in THF was obtained.

4-Chlorophthalonitrile (7)[20]

To a soln of dichlorophthalazine **1** (199 mg, 1.0 mmol, 1 equiv) in anhyd THF (1 mL) was added dropwise 0.72 M tmpZnCl·LiCl (**6**) in THF (1.54 mL, 1.1 mmol, 1.1 equiv) at 25 °C over 1 min. The

mixture was stirred for 1 min then quenched with sat. aq NH_4Cl (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude material was purified by column chromatography (pentane–EtOAc, 1:1) to furnish **7** as a white solid; yield: 160 mg (98%).

^{1}H NMR ($CDCl_3$): δ = 7.72–7.65 (m, 3 H).

^{13}C NMR ($CDCl_3$): δ = 140.2, 134.6, 133.8, 133.6, 117.4, 114.7, 114.2 (2 C).

6-Chloro-1-(4-methylphenyl)phthalazine (8)

A 0.67 M soln of 4-methylphenylzinc iodide·LiCl in THF (1.79 mL, 1.2 mmol, 1.2 equiv) was added to a soln of dichlorophthalazine **1** (199 mg, 1.0 mmol, 1 equiv) in anhyd THF (0.6 mL) and PEPPSI-iPr (7 mg, 1 mol%) at 25 °C under argon. The mixture was stirred at this temperature for 1 h, then heated to 45 °C for 12 h and quenched with sat. aq NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude material was purified by chromatography (pentane–EtOAc, 1:1) to furnish **8** as a pale yellow solid; yield: 110 mg (43%); mp 112–113 °C (dec); R_f = 0.45 (EtOAc–pentane, 2:3).

^{1}H NMR ($CDCl_3$): δ = 9.42 (d, *J* = 0.2 Hz, 1 H), 8.03 (ddd, *J* = 10.0 Hz, *J* = 1.0 Hz, *J* = 0.6 Hz, 1 H), 7.96 (ddd, *J* = 2.2 Hz, *J* = 0.6 Hz, *J* = 0.2 Hz, 1 H), 7.75 (dd, *J* = 9.0 Hz, *J* = 2.2 Hz 1 H), 7.57–7.65 (m, 2 H), 7.32–7.38 (m, 2 H), 2.44 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 159.5, 149.3, 139.8, 138.2, 133.4, 132.7, 129.9 (2 C), 129.4 (2 C), 128.4, 127.9, 125.5, 123.7, 40.7.

MS (70 eV): *m/z* (%) = 254 (40) $[M]^+$, 253 (53), 241 (29), 240 (25), 239 (100), 207 (33), 189 (20).

HRMS: *m/z* $[M]^+$ calcd for $C_{15}H_{11}ClN_2$: 254.0611; found: 254.0535.

4-(6-Chlorophthalazin-1-yl)morpholine (9)[8]

Morpholine (3.14 g, 36 mmol, 4 equiv) was added to a soln of dichlorophthalazine **1** (1.79 g, 9 mmol, 1 equiv) in toluene (40 mL) at 25 °C. The mixture was heated to 85 °C for 12 h then cooled to 25 °C. Toluene was removed in vacuo and the crude material was taken up in EtOAc (50 mL) and washed successively with H_2O (50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (EtOAc) to give **9** as a pale yellow solid; yield: 2.13 g (95%); R_f = 0.25 (EtOAc).

^{1}H NMR ($CDCl_3$): δ = 9.08 (d, *J* = 0.8 Hz, 1 H), 8.01 (d, *J* = 8.8 Hz, 1 H), 7.93 (dd, *J* = 2.2 Hz, *J* = 0.8 Hz, 1 H), 7.80 (dd, *J* = 8.8 Hz, *J* = 2.2 Hz, 1 H), 3.88–4.01 (m, 4 H), 3.45–3.58 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 159.6, 147.0, 137.8, 132.4, 129.6, 126.1, 125.9, 119.6, 66.8 (2 C), 51.6 (2 C).

MS (70 eV): *m/z* (%) = 251 (11), 249 (33) $[M]^+$, 194 (28), 192 (100), 191 (47), 164 (24), 137 (48), 86 (47).

HRMS: *m/z* $[M]^+$ calcd for $C_{12}H_{12}ClN_3O$: 249.0669; found: 249.0649.

Zincation of Phthalazine Derivatives with 6; General Procedure 1

To a dry and argon-flushed 5-mL sealed vessel, equipped with a magnetic stirring bar and charged with the desired phthalazine (1 equiv), was successively added anhyd THF and the zinc reagent **6** (1.1 equiv) at 25 °C under argon. The mixture was heated at the given temperature under microwave irradiation. The completion of the metalation was checked by GC analysis of reaction aliquots quenched with a soln of I_2 in anhyd THF. The electrophile or its soln was added at the given temperature. When the reaction was complete (checked by GC-analysis of reaction aliquots quenched with sat. aq NH_4Cl soln), the mixture was quenched with sat. aq NH_4Cl. The aqueous layer was extracted with EtOAc (2 ×) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude material was purified by column chromatography.

4-(6-Chloro-4-iodophthalazin-1-yl)morpholine (10a)

To a soln of chlorophthalazine **9** (250 mg, 1.0 mmol, 1 equiv) in anhyd THF (1 mL) was added dropwise 0.72 M tmpZnCl·LiCl (**6**) in THF (1.54 mL, 1.1 mmol, 1.1 equiv) at 25 °C over 1 min. The mixture was heated under microwave irradiation for 45 min at 60 °C according to general procedure 1. A soln of I_2 (355 mg, 1.4 mmol, 1.4 equiv) in anhyd THF (0.5 mL) was then added dropwise at 55 °C and the resulting mixture was stirred at this temperature for 30 min. The mixture was quenched with sat. aq NH_4Cl (10 mL) and sat. aq $Na_2S_2O_3$ (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude material was purified by column chromatography (gradient elution, pentane–EtOAc, 1:1 to 1:2) to furnish **10a** as a pale orange solid; yield: 273 mg (71%); mp 183–184 °C (dec); R_f = 0.55 (pentane–EtOAc, 1:1).

^{1}H NMR ($CDCl_3$): δ = 8.02 (d, *J* = 2.2 Hz, 1 H), 7.91 (d, *J* = 8.6 Hz, 1 H), 7.78 (dd, *J* = 8.8 Hz, *J* = 2.0 Hz, 1 H), 3.90–4.00 (m, 4 H), 3.47–3.55 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 159.9, 139.3, 133.2, 132.7, 131.5, 126.7, 124.1, 120.2, 66.6 (2 C), 51.6 (2 C).

MS (70 eV): *m/z* (%) = 376 (17), 375 (24) $[M]^+$, 374 (41), 318 (51), 317 (32), 248 (26), 192 (20), 165 (27), 164 (20), 163 (81), 162 (26), 86 (100).

HRMS: *m/z* $[M]^+$ calcd for $C_{12}H_{11}ClIN_3O$: 374.9635; found: 374.9614.

4-[6-Chloro-4-(cyclohex-2-enyl)phthalazin-1-yl]morpholine (10b)

To a soln of chlorophthalazine **9** (250 mg, 1.00 mmol, 1 equiv) in anhyd THF (1.00 mL) was added dropwise 0.72 M tmpZnCl·LiCl (**6**) in THF (1.54 mL, 1.1 mmol, 1.1 equiv) at 25 °C over 1 min. The mixture was heated under microwave irradiation for 45 min at 60 °C according to general procedure 1. The mixture was cooled to –55 °C and 1 M CuCN·2 LiCl in THF (5 mol%, 5 drops) was added. The resulting mixture was stirred at this temperature for 10 min and then 3-bromocyclohexene (225 mg, 1.40 mmol, 1.4 equiv) was added dropwise. The mixture was allowed to warm to 25 °C over 12 h then quenched with sat. aq NH_4Cl (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude material was purified by column chromatography (pentane–EtOAc, 1:2) to furnish **10b** as a yellow oil; yield: 196 mg (60%); R_f = 0.5 (pentane–EtOAc, 1:2).

^{1}H NMR ($CDCl_3$): δ = 8.07 (d, *J* = 2.0 Hz, 1 H), 7.91 (d, *J* = 8.8 Hz, 1 H), 7.69 (dd, *J* = 8.8 Hz, *J* = 2.0 Hz, 1 H), 5.79–5.97 (m, 2 H), 4.10–4.24 (m, 1 H), 3.86–3.96 (m, 4 H), 3.39–3.46 (m, 4 H), 1.62–2.21 (m, 6 H).

^{13}C NMR ($CDCl_3$): δ = 159.0, 158.1, 137.4, 131.6, 128.7, 128.1, 127.9, 126.8, 124.0, 120.0, 66.8 (2 C), 51.7 (2 C), 39.3, 29.2, 24.9, 21.7.

MS (70 eV): *m/z* (%) = 330 (25), 329 (92) $[M]^+$, 328 (29), 302 (36), 301 (28), 300 (100), 288 (22), 272 (39), 263 (36), 163 (22), 86 (40).

HRMS: *m/z* $[M]^+$ calcd for $C_{18}H_{20}ClN_3O$: 329.1295; found: 329.1280.

Ethyl 4-(7-Chloro-4-morpholinophthalazin-1-yl)benzoate (10c)

To a soln of chlorophthalazine **9** (250 mg, 1.0 mmol, 1 equiv) in anhyd THF (1 mL) was added dropwise 0.72 M tmpZnCl·LiCl (**6**) in

THF (1.54 mL, 1.1 mmol, 1.1 equiv) at 25 °C over 1 min. The mixture was heated under microwave irradiation for 45 min at 60 °C according to general procedure 1. A pre-mixed soln of ethyl 4-iodobenzoate (331 mg, 1.2 mmol, 1.2 equiv), (*o*-furyl)$_3$P (9 mg, 4 mol%), and Pd(dba)$_2$ (12 mg, 2 mol%) in anhyd THF (0.5 mL) under argon was then added dropwise at 55 °C and the resulting mixture was stirred at this temperature for 12 h. The mixture was quenched with sat. aq NH_4Cl (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude material was purified by column chromatography (pentane–EtOAc, 1:2) to furnish **10c** as a pale green solid; yield: 330 mg (83%); mp 221–223 °C; R_f = 0.5 (pentane–EtOAc, 1:2).

^{1}H NMR ($CDCl_3$): δ = 8.24 (d, *J* = 10.0 Hz, 2 H), 8.07 (d, *J* = 10.0 Hz, 2 H), 7.92 (d, *J* = 2.0 Hz, 1 H), 7.75–7.83 (m, 2 H), 4.44 (d, *J* = 8.0 Hz, 2 H), 3.95–4.05 (m, 4 H), 3.56–3.65 (m, 4 H), 1.44 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 166.2, 158.9, 154.6, 139.6, 138.4, 132.4, 131.3, 129.90 (2 C), 129.86 (2 C), 128.5, 126.7, 125.8, 119.9, 66.8 (2 C), 61.3, 51.6 (2 C), 14.4.

MS (70 eV): *m*/*z* (%) = 398 (35), 397 (63) [M]$^+$, 396 (63), 342 (36), 341 (44), 340 (100), 339 (71), 283 (20), 137 (10).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{21}H_{20}ClN_3O_3$: 397.1193; found: 397.1177.

4-(7-Chloro-4-morpholinophthalazin-1-yl)benzonitrile (10d)

Following the procedure for **10c** using 4-iodobenzonitrile (275 mg, 1.2 mmol, 1.2 equiv) as electrophile with chromatographic purification (pentane–EtOAc, 1:4) gave **10d** as a pale yellow solid; yield: 258 mg (74%); mp 229–230 °C; R_f = 0.55 (pentane–EtOAc, 1:4).

^{1}H NMR ($CDCl_3$): δ = 8.08 (d, *J* = 8.6 Hz, 1 H), 7.76–7.88 (m, 6 H), 3.94–4.03 (m, 4 H), 3.56–3.65 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 159.2, 153.6, 140.4, 138.3, 132.5 (2 C), 132.3, 130.5 (2 C), 128.0, 126.8, 125.1, 119.7, 118.4, 113.1, 66.8 (2 C), 51.6 (2 C).

MS (70 eV): *m*/*z* (%) = 351 (27), 350 (44) [M]$^+$, 349 (59), 319 (28), 305 (22), 294 (46), 293 (100), 292 (71), 264 (28), 137 (26), 102 (26), 86 (56).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{19}H_{15}ClN_4O$: 350.0934; found: 350.0899.

4-{6-Chloro-4-[3-(trifluoromethyl)phenyl]phthalazin-1-yl}morpholine (10e)

Following the procedure for **10c** using 1-iodo-3-(trifluoromethyl)benzene (326 mg, 1.2 mmol, 1.2 equiv) as electrophile with chromatographic purification (pentane–EtOAc, 1:1) gave **10e** as a pale greenish solid; yield: 330 mg (84%); mp 142–144 °C; R_f = 0.5 (pentane–EtOAc, 1:1).

^{1}H NMR ($CDCl_3$): δ = 8.08 (d, *J* = 8.8 Hz, 1 H), 8.01–8.05 (br s, 1 H), 7.64–7.93 (m, 5 H), 3.95–4.04 (m, 4 H), 3.56–3.65 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 159.0, 151.4, 138.3, 136.6, 133.0, 132.3, 131.3 (q, *J* = 33.2 Hz), 129.1, 128.3, 126.74 (q, *J* = 3.0 Hz), 126.69, 126.0 (q, *J* = 3.0 Hz), 125.4, 123.9 (q, *J* = 271.3 Hz), 119.2, 66.7 (2 C), 51.6 (2 C).

MS (70 eV): *m*/*z* (%) = 394 (27), 393 (48) [M]$^+$, 392 (62), 362 (29), 338 (34), 337 (44), 336 (100), 335 (67), 309 (19), 307 (24), 172 (14), 145 (23), 137 (30), 86 (62).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{19}H_{15}ClF_3N_3O$: 393.0856; found: 393.0844.

4-[6-Chloro-4-(thiophen-2-yl)phthalazin-1-yl]morpholine (10f)

Following the procedure for **10c** using 2-iodothiophene (252 mg, 1.2 mmol, 1.2 equiv) as electrophile with chromatographic purification (pentane–EtOAc, 1:1) gave **10f** as a pale greenish solid; yield: 285 mg (86%); mp 157–158 °C; R_f = 0.55 (pentane–EtOAc, 1:1).

^{1}H NMR ($CDCl_3$): δ = 8.36 (d, *J* = 1.8 Hz, 1 H), 8.03 (d, *J* = 8.8 Hz, 1 H), 7.76 (dd, *J* = 8.8 Hz, *J* = 2.0 Hz, 1 H), 7.50–7.59 (m, 2 H), 7.18–7.28 (m, 1 H), 3.95–4.05 (m, 4 H), 3.56–3.65 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 158.6, 149.6, 138.7, 138.2, 132.0, 128.7, 128.5, 127.8, 127.6, 126.6, 125.4, 119.8, 66.8 (2 C), 51.6 (2 C).

MS (70 eV): *m*/*z* (%) = 332 (36), 331 (62) [M]$^+$, 330 (59), 300 (19), 275 (40), 274 (100), 273 (76), 247 (25), 246 (24), 245 (26), 110 (27), 86 (58).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{16}H_{14}ClN_3OS$: 331.0546; found: 331.0532.

[4-(7-Chloro-4-morpholinophthalazin-1-yl)phenyl](cyclohexyl)methanone (10g)

Following the procedure for **10c** using cyclohexyl(4-iodophenyl)methanone (377 mg, 1.2 mmol, 1.2 equiv) as electrophile with chromatographic purification (pentane–EtOAc, 1:2) gave **10g** as a yellow oil; yield: 310 mg (72%); R_f = 0.5 (pentane–EtOAc, 1:2).

^{1}H NMR ($CDCl_3$): δ = 8.07 (d, *J* = 8.4 Hz, 2 H), 8.03 (dd, *J* = 8.9 Hz, *J* = 0.4 Hz, 1 H), 7.88 (dd, *J* = 2.1 Hz, *J* = 0.4 Hz, 1 H), 7.76 (d, *J* = 8.4 Hz, 2 H), 7.72 (dd, *J* = 8.9 Hz, *J* = 2.1 Hz, 1 H), 3.91–3.96 (m, 4 H), 3.53–3.57 (m, 4 H), 3.25–3.32 (m, 1 H), 1.87–1.93 (m, 2 H), 1.78–1.84 (m, 2 H), 1.67–1.73 (m, 1 H), 1.44–1.52 (m, 2 H), 1.33–1.42 (m, 2 H), 1.18–1.27 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 203.3, 159.0, 154.6, 140.0, 137.9, 136.7, 132.1, 130.0 (2 C), 128.5 (2 C), 128.2, 126.6, 125.5, 119.7, 66.7 (2 C), 51.5 (2 C), 45.8, 29.4 (2 C), 25.9, 25.8 (2 C).

MS (70 eV): *m*/*z* (%) = 436 (39), 435 (67) [M]$^+$, 434 (76), 404 (30), 380 (36), 379 (52), 378 (100), 377 (75), 267 (40), 86 (68).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{25}H_{26}ClN_3O_2$: 435.1714; found: 435.1698.

4-[6-Chloro-4-(hex-1-ynyl)phthalazin-1-yl]morpholine (10h)

To a soln of generated in situ iodophthalazine **10a** [starting from phthalazine **9** (250 mg, 1.0 mmol, 1 equiv) and according to general procedure 1] was successively added anhyd Et_3N (5 mL), CuI (4 mol%, 8 mg), (*o*-furyl)$_3$P (4 mol%, 9 mg), Pd(dba)$_2$ (2 mol%, 12 mg), and hex-1-yne (119 mg, 1.4 mmol, 1.5 equiv) under argon. The mixture was heated at 60 °C for 1 h, quenched with deionized H_2O (20 mL), and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude material was purified by column chromatography (pentane–EtOAc, 1:1) to furnish **10h** as a pale yellow solid; yield: 293 mg (89%); mp 130–132 °C; R_f = 0.4 (pentane–EtOAc, 1:1).

^{1}H NMR ($CDCl_3$): δ = 8.19 (d, *J* = 2.2 Hz, 1 H), 7.93 (d, *J* = 8.2 Hz, 1 H), 7.72 (dd, *J* = 8.2 Hz, *J* = 2.2 Hz, 1 H), 3.90–3.97 (m, 4 H), 3.50–3.56 (m, 4 H), 2.59 (t, *J* = 7.5 Hz, 2 H), 1.71 (quint, *J* = 7.5 Hz, 2 H), 1.55 (sext, *J* = 7.5 Hz, 2 H), 0.97 (d, *J* = 7.5 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 158.0, 142.3, 137.9, 132.2, 130.3, 126.1, 125.7, 118.6, 98.6, 75.5, 66.7 (2 C), 51.6 (2 C), 30.4, 22.1, 19.4, 13.6.

MS (70 eV): *m*/*z* (%) = 330 (32), 329 (60) [M]$^+$, 328 (67), 300 (29), 298 (32), 273 (42), 272 (100), 271 (76), 86 (56).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{18}H_{20}ClN_3O$: 329.1295; found: 329.1284.

Preparation of Functionalized Aryl, Alkyl, Benzylic, and Heteroarylzinc Reagents Using Mg/LiCl/$ZnCl_2$; General Procedure 2

A dry and argon-flushed 10-mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with LiCl (2.5 equiv)

and heated with a heat gun for 3 min under high vacuum. After cooling to 25 °C, $ZnCl_2$ (1 equiv) in anhyd THF and Mg turnings (2.5 equiv) were successively added and the mixture was stirred for 5 min. The desired halide reagent (1 equiv) was added at the given temperature and the mixture was stirred at this temperature. The completion of the insertion was checked by GC analysis of reaction aliquots quenched with a soln of I_2 in anhyd THF. Then the supernatant soln was cannulated to a new dry Schlenk flask and titrated prior to use at 25 °C with a soln of I_2 in anhyd THF.[21]

Negishi Cross-Coupling Reactions; General Procedure 3

In a Schlenk flask zinc reagent (1.4 equiv) obtained according to general procedure 2 was slowly added to a soln of desired phthalazine derivative (1 equiv) in anhyd THF at 25 °C under argon. The mixture was stirred for 5 min prior to addition of PEPPSI-iPr (0.75 mol%) and stirred at the given temperature (Table 2). When the reaction was complete (GC analysis of reaction aliquots quenched with sat. aq NH_4Cl), the mixture was quenched with sat. aq NH_4Cl. The aqueous layer was extracted with EtOAc (2 ×) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude material was purified by column chromatography.

4-(6-Phenylphthalazin-1-yl)morpholine (11a)

A dry and argon-flushed 5-mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with LiCl (36 mg, 0.84 mmol, 1.4 equiv) and heated with a heat gun for 3 min under high vacuum. The mixture was cooled to 25 °C, 1.0 M $ZnCl_2$ in THF (0.84 mL, 0.84 mmol, 1.4 equiv) and 1.73 M PhMgCl in THF (0.49 mL, 0.84 mmol, 1.4 equiv) were successively added, and the mixture was stirred for 10 min and then slowly added to a soln of chlorophthalazine **9** (150 mg, 0.60 mmol, 1 equiv) in anhyd THF (0.6 mL) at 25 °C under argon. The mixture was stirred at 25 °C for 5 min, PEPPSI-iPr (4 mg, 0.75 mol%) was added, stirring was continued at this temperature for 30 min, and the reaction was quenched with sat. aq NH_4Cl (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude material was purified by column chromatography (EtOAc) to furnish **11a** as a white solid; yield: 166 mg (95%); mp 165–166 °C; R_f = 0.45 (EtOAc).

^{1}H NMR ($CDCl_3$): δ = 9.24 (s, 1 H), 8.03–8.14 (m, 3 H), 7.66–7.73 (m, 2 H), 7.41–7.58 (m, 3 H), 3.97–4.03 (m, 4 H), 3.56–3.62 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 159.8, 148.3, 144.6, 139.2, 131.0, 129.24 (2 C), 129.20, 128.7, 127.4 (2 C), 124.7, 124.5, 120.3, 66.9 (2 C), 51.6 (2 C).

MS (70 eV): *m*/*z* (%) = 291 (59) $[M]^+$, 290 (59), 260 (35), 246 (25), 234 (100), 233 (58), 206 (26), 205 (22), 179 (49), 86 (20).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{18}H_{17}N_3O$: 291.1372; found: 291.1366.

***N*,*N*-Dimethyl-4-(1-morpholinophthalazin-6-yl)aniline (11b)**

A dry and argon-flushed 5-mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged successively with 1.0 M $ZnCl_2$ in THF (0.84 mL, 0.84 mmol, 1.4 equiv) and 0.98 M 4-(dimethylamino)phenylmagnesium bromide·LiCl in THF (0.86 mL, 0.84 mmol, 1.4 equiv); the mixture was stirred for 10 min then slowly added to a soln of chlorophthalazine **9** (150 mg, 0.60 mmol, 1 equiv) in anhyd THF (0.6 mL) at 25 °C under argon. The mixture was stirred at 25 °C for 5 min, PEPPSI-iPr (4 mg, 0.75 mol%) was added, stirring was continued at this temperature for 10 min, and the reaction was quenched with sat. aq NH_4Cl (5 mL). The pH value was adjusted to pH 10 by addition of aq 1 M NaOH and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude material was purified by column chromatography (CH_2Cl_2–MeOH, 30:1) to furnish **11b** as a yellow solid; yield: 158 mg (79%); mp 188–190 °C; R_f = 0.2 (EtOAc).

^{1}H NMR ($CDCl_3$): δ = 9.13 (s, 1 H), 7.90–8.00 (m, 3 H), 7.58 (d, *J* = 8.8 Hz, 2 H), 6.78 (d, *J* = 8.8 Hz, 2 H), 3.92–3.99 (m, 4 H), 3.49–3.56 (m, 4 H), 2.99 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 159.8, 150.8, 148.5, 144.4, 130.2, 129.4, 128.0 (2 C), 126.2, 124.4, 122.3, 119.3, 112.6 (2 C), 66.9 (2 C), 51.6 (2 C), 40.3 (2 C).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{23}N_4O$: 335.1872; found: 335.1865.

Ethyl 4-(1-Morpholinophthalazin-6-yl)benzoate (11c)

Following general procedure 2, LiCl (212 mg, 5 mmol), 1.0 M $ZnCl_2$ in THF (2 mL, 2 mmol), Mg turnings (122 mg, 5 mmol), and ethyl 4-bromobenzoate (458 mg, 2 mmol) were successively added to a Schlenk flask under argon at 0 °C and the mixture was allowed to warm to 25 °C and stir for 2 h at this temperature. Then following general procedure 3, the freshly obtained zinc reagent (0.99 M in THF, 0.85 mL, 0.84 mmol, 1.4 equiv) was added to a soln of chlorophthalazine **9** (150 mg, 0.60 mmol, 1 equiv) in anhyd THF (0.6 mL) at 25 °C under argon. The mixture was stirred for 5 min, PEPPSI-iPr (4 mg, 0.75 mol%) was added, stirring was continued at this temperature for 10 min, and the reaction was quenched with sat. aq NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude material was purified by column chromatography (CH_2Cl_2–MeOH, 30:1) to furnish **11c** as a pale yellow solid; yield: 185 mg (85%); mp 169–171 °C; R_f = 0.2 (EtOAc).

^{1}H NMR ($CDCl_3$): δ = 9.20 (s, 1 H), 8.05–8.16 (m, 3 H), 7.71 (d, *J* = 8.6 Hz, 2 H), 6.78 (d, *J* = 8.8 Hz, 2 H), 4.36 (q, *J* = 7.0 Hz, 2 H), 3.90–3.97 (m, 4 H), 3.49–3.56 (m, 4 H), 1.37 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 166.0, 159.7, 148.2, 143.21, 143.17, 130.8, 130.5, 130.3 (2 C), 129.0, 127.3 (2 C), 125.0, 124.9, 120.5, 66.8 (2 C), 61.2, 51.5 (2 C), 14.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{22}N_3O_3$: 364.1661; found: 364.1654.

4-[6-(3-Methoxybenzyl)phthalazin-1-yl]morpholine (11d)

Following general procedure 2, LiCl (212 mg, 5 mmol), 1.0 M $ZnCl_2$ in THF (2 mL, 2 mmol), Mg turnings (122 mg, 5 mmol), and 3-methoxybenzyl chloride (313 mg, 2.0 mmol) were successively added to a Schlenk flask under argon at 25 °C and the mixture was stirred for 2 h at 25 °C. Then following general procedure 3, the freshly obtained zinc reagent (0.78 M in THF, 1.08 mL, 0.84 mmol, 1.4 equiv) was added to a soln of chlorophthalazine **9** (150 mg, 0.60 mmol, 1 equiv) in anhyd THF (0.6 mL) at 25 °C under argon. The mixture was stirred for 5 min, PEPPSI-iPr (4 mg, 0.75 mol%) was added, stirring was continued at 50 °C for 4 h, and the reaction was quenched with sat. aq NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude material was purified by column chromatography (EtOAc) to furnish **11d** as a yellow solid; yield: 190 mg (94%); mp 102–103 °C; R_f = 0.45 (EtOAc).

^{1}H NMR ($CDCl_3$): δ = 9.11 (d, *J* = 0.6 Hz, 1 H), 7.95 (dd, *J* = 9.0 Hz, *J* = 0.6 Hz, 1 H), 7.62–7.69 (m, 2 H), 7.20–7.29 (m, 1 H), 6.72–6.82 (m, 3 H), 4.16 (s, 2 H), 3.93–3.99 (m, 4 H), 3.77 (s, 3 H), 3.50–3.56 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 160.0, 159.8, 148.1, 145.3, 140.9, 133.0, 129.8, 129.0, 126.0, 124.3, 121.4, 120.0, 115.1, 111.7, 66.9 (2 C), 55.2, 51.6 (2 C), 42.0.

MS (70 eV): *m*/*z* (%) = 335 (75) $[M]^+$, 334 (61), 304 (32), 290 (20), 279 (21), 278 (100), 277 (57), 250 (13), 249 (25), 86 (33).

HRMS: *m/z* $[M]^+$ calcd for $C_{20}H_{21}N_3O_2$: 335.1634; found: 335.1624.

4-(1-Morpholinophthalazin-6-yl)butanenitrile (11e)

Following general procedure 2, LiCl (424 mg, 10 mmol), 1.0 M $ZnCl_2$ in THF (4 mL, 4 mmol), Mg turnings (244 mg, 10 mmol), and 4-bromobutyronitrile (592 mg, 4 mmol) were successively added to a Schlenk flask under argon at 25 °C and the mixture was stirred for 4 h at this temperature. Then following general procedure 3, the freshly obtained zinc reagent (0.49 M in THF, 1.71 mL, 0.84 mmol, 1.4 equiv) was added to a soln of chlorophthalazine **9** (150 mg, 0.60 mmol, 1 equiv) in anhyd THF (0.6 mL) at 25 °C under argon. The mixture was stirred for 5 min, PEPPSI-iPr (4 mg, 0.75 mol%) was added, stirring was continued at 60 °C for 8 h, and the reaction was quenched with sat. aq NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude material was purified by column chromatography (gradient elution, CH_2Cl_2–MeOH, 30:1 to 20:1) to furnish **11e** as a pale yellow solid; yield: 130 mg (77%); mp 124–126 °C; R_f = 0.45 (CH_2Cl_2–MeOH, 20:1).

^{1}H NMR ($CDCl_3$): δ = 9.14 (s, 1 H), 8.00 (d, *J* = 8.4 Hz, 1 H), 7.70 (d, *J* = 1.8 Hz, 1 H), 7.67 (dd, *J* = 8.6 Hz, *J* = 1.8 Hz, 1 H), 3.93–3.99 (m, 4 H), 3.50–3.57 (m, 4 H), 3.01 (t, *J* = 7.8 Hz, 2 H), 2.39 (t, *J* = 7.8 Hz, 2 H), 2.08 (quint, *J* = 7.8 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 159.7, 147.8, 144.1, 132.5, 129.0, 125.9, 124.7, 120.2, 119.0, 66.9 (2 C), 51.6 (2 C), 34.5, 26.4, 16.6.

MS (70 eV): *m/z* (%) = 282 (37) $[M]^+$, 281 (48), 251 (34), 225 (100), 224 (49), 169 (24), 116 (26), 86 (68).

HRMS: *m/z* $[M]^+$ calcd for $C_{16}H_{18}N_4O$: 282.1481; found: 282.1470.

Ethyl 6-(1-Morpholinophthalazin-6-yl)hexanoate (11f)

Following general procedure 2, LiCl (424 mg, 10 mmol), 1.0 M $ZnCl_2$ in THF (4 mL, 4 mmol), Mg turnings (244 mg, 10 mmol), and ethyl 6-bromohexanoate (892 mg, 4 mmol) were successively added to a Schlenk flask under argon at 25 °C and the mixture was stirred for 4 h at this temperature. Then following general procedure 3, the freshly obtained zinc reagent (0.39 M in THF, 2.15 mL, 0.84 mmol, 1.4 equiv) was added to a soln of chlorophthalazine **9** (150 mg, 0.60 mmol, 1 equiv) in anhyd THF (0.6 mL) at 25 °C under argon. The mixture was stirred for 5 min, PEPPSI-iPr (4 mg, 0.75 mol%) as added, stirring was continued at 60 °C for 30 min, and the reaction was quenched with sat. aq NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude material was purified by column chromatography (gradient elution, CH_2Cl_2–MeOH, 30:1 to 20:1) to furnish **11f** as a pale yellow oil; yield: 165 mg (77%); R_f = 0.5 (CH_2Cl_2–MeOH, 20:1).

^{1}H NMR ($CDCl_3$): δ = 9.09 (s, 1 H), 7.92 (d, *J* = 9.0 Hz, 1 H), 7.61–7.64 (m, 2 H), 4.07 (q, *J* = 7.2 Hz, 2 H), 3.90–3.96 (m, 4 H), 3.47–3.53 (m, 4 H), 2.80 (t, *J* = 7.5 Hz, 2 H), 2.26 (t, *J* = 7.5 Hz, 2 H), 1.70 (quint, *J* = 7.5 Hz, 2 H), 1.64 (quint, *J* = 7.5 Hz, 2 H), 1.37 (quint, *J* = 7.5 Hz, 2 H), 1.19 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 173.5, 159.8, 148.0, 146.8, 132.8, 128.9, 125.4, 124.0, 119.8, 66.9 (2 C), 60.2, 51.5 (2 C), 35.8, 34.1, 30.6, 28.6, 24.6, 14.2.

MS (70 eV): *m/z* (%) = 358 (19), 357 (62) $[M]^+$, 356 (76), 326 (44), 312 (58), 300 (100), 299 (64), 272 (15), 171 (20), 157 (36), 86 (48).

HRMS: *m/z* $[M]^+$ calcd for $C_{20}H_{27}N_3O_3$: 357.2052; found: 357.2036.

4-[7-(3-Methoxybenzyl)-4-morpholinophthalazin-1-yl]benzonitrile (12a)

Following general procedure 2, LiCl (212 mg, 5 mmol), 1.0 M $ZnCl_2$ in THF (2 mL, 2.0 mmol), Mg turnings (122 mg, 5 mmol, 2.5 equiv), and 3-methoxybenzyl chloride (313 mg, 2 mmol) were successively added to a Schlenk flask under argon at 25 °C and the mixture was stirred for 2 h at 25 °C. Then following general procedure 3, the freshly obtained zinc reagent (0.78 M in THF, 1.08 mL, 0.84 mmol, 1.4 equiv) was added to a soln of chlorophthalazine **10d** (210 mg, 0.60 mmol, 1 equiv) in anhyd THF (1.2 mL) at 25 °C under argon. The mixture was stirred for 5 min, PEPPSI-iPr (4 mg, 0.75 mol%) was added, stirring was continued at 50 °C for 3 h, and the reaction was quenched with sat. aq NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude material was purified by column chromatography (EtOAc) to furnish **12a** as a white solid; yield: 254 mg (97%); mp 168–170 °C; R_f = 0.55 (EtOAc).

^{1}H NMR ($CDCl_3$): δ = 8.04 (d, *J* = 9.0 Hz, 1 H), 7.77–7.84 (m, 4 H), 7.67–7.70 (m, 2 H), 7.21 (t, *J* = 8.4 Hz, 1 H), 6.77 (dd, *J* = 8.4 Hz, *J* = 2.3 Hz, 1 H), 6.73 (d, *J* = 7.8 Hz, 1 H), 6.66–6.68 (m, 1 H), 4.10 (s, 2 H), 3.93–3.98 (m, 4 H), 3.75 (s, 3 H), 3.56–3.62 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 159.9, 159.4, 154.4, 145.6, 141.1, 140.8, 132.8, 132.2 (2 C), 130.6 (2 C), 129.8, 127.2, 125.13, 125.05, 121.3, 120.0, 118.6, 115.2, 112.6, 111.5, 66.8 (2 C), 55.2, 51.5 (2 C), 42.1.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{25}N_4O_2$: 437.1978; found: 437.1969.

4-[6-(Pyridin-3-yl)-4-(thiophen-2-yl)phthalazin-1-yl]morpholine (12b)

Following general procedure 2, LiCl (212 mg, 5 mmol), 1.0 M $ZnCl_2$ in THF (2 mL, 2 mmol), Mg turnings (122 mg, 5 mmol, 2.5 equiv), and 3-bromopyridine (313 mg, 2 mmol) were successively added to a Schlenk flask under argon at 25 °C and the mixture was stirred for 1 h at 0 °C. Then following general procedure 3, the freshly obtained zinc reagent (0.89 M in THF, 0.95 mL, 0.84 mmol, 1.4 equiv) was added to a soln of chlorophthalazine **10f** (199 mg, 0.60 mmol, 1 equiv) in anhyd THF (1.2 mL) at 25 °C under argon. The mixture was stirred for 5 min, PEPPSI-iPr (4 mg, 0.75 mol%) was added, stirring was continued at 50 °C for 5 min, and the reaction was quenched with sat. aq NH_4Cl (5 mL). The pH value was adjusted to pH 2 by the addition of 1 M HCl and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were discarded then the pH value was adjusted to pH 10 by the addition of aq 1 M NaOH and the aqueous layer was extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude material was purified by column chromatography (CH_2Cl_2) to furnish **12b** as a pale yellow solid; yield: 254 mg (97%); mp 218–219 °C; R_f = 0.35 (CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ = 8.99 (d, *J* = 1.2 Hz, 1 H), 8.74 (dd, *J* = 3.2 Hz, *J* = 1.0 Hz, 1 H), 8.65 (d, *J* = 1.2 Hz, 1 H), 8.26 (d, *J* = 7.0 Hz, 1 H), 8.05–8.14 (m, 2 H), 7.68 (dd, *J* = 2.6 Hz, *J* = 0.8 Hz, 1 H), 7.52–7.61 (m, 2 H), 7.25–7.29 (m, 1 H), 4.01–4.07 (m, 4 H), 3.64–3.69 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 158.7, 150.4, 148.8, 147.6, 141.0, 138.7, 135.7, 135.5, 130.2, 128.9, 128.6, 127.8, 127.4, 126.0, 124.7, 124.3, 121.0, 66.8 (2 C), 51.6 (2 C).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{19}N_4OS$: 375.1280; found: 375.1272.

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