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# Multicomponent Synthesis of 4-Aminophthalazin-1(2*H*)-ones by Palladium-Catalyzed Isocyanide Insertion

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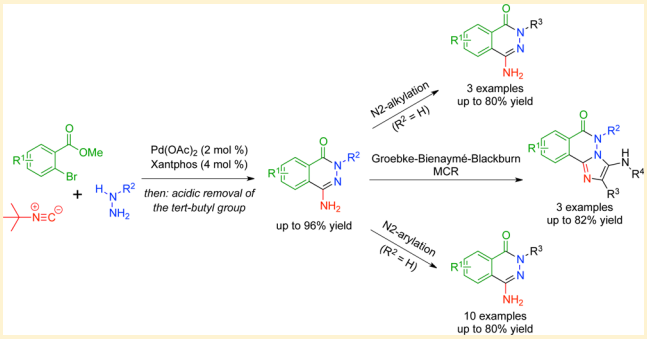
Supporting Information

**ABSTRACT:** 4-Aminophthalazin-1(2*H*)-ones (APOs) are underexplored heterocyclic compounds with promising and diverse biological activities. The classical synthesis of these compounds is tedious and does not allow the regioselective introduction of substituents. Here, we present our full studies on the Pd-catalyzed cross-coupling of substituted *o*-(pseudo)halobenzoates and hydrazines with isocyanide insertion allowing straightforward access to diversely substituted APOs. We illustrate the advantages of this method compared to other approaches and describe solutions for the limitations we encountered. In addition, we have developed efficient diversifications of this heterocyclic scaffold that allow access to more diverse APOs as well as novel heterocyclic scaffolds.




## INTRODUCTION

Novel and underexplored heterocyclic scaffolds exhibiting valuable biological activity are vital for the drug discovery and development process. Efficient synthetic approaches toward such scaffolds are instrumental to the rapid synthesis and evaluation of these compounds. Multicomponent reactions (MCRs)[1] and cascade reactions[2] are important tools to meet these goals, because several bond forming steps are combined in a single reaction vessel. As a result, fewer synthetic steps are required for the construction of a given target molecule. 4-Aminophthalazin-1(2*H*)-ones (APOs, **4**)[3] have recently shown promising activity as Aurora A kinase inhibitors and human A3 adenosine receptor antagonists (Scheme 1).[4] In addition, they have shown potential as PARP (poly(ADP-ribose) polymerase) inhibitors, which are associated with cancer treatment, and for the treatment of inflammatory and autoimmune diseases.[5] Despite this promising precedence, APOs have remained rather unexplored, most likely due to their tedious linear synthesis and the lack of new and regioselective approaches for synthesizing substituted APOs.[4a,6] The typical synthesis (Scheme 1, route A) starts from phthalic anhydride and is a multistep process that consists of condensation with hydrazine (I), dehydroxyhalogenation (II), and Buchwald–Hartwig amination (III).[4a] This sequence is highly inefficient for variation at the N2 position (**4**, $R^3$) due to the poor commercial availability of substituted hydrazines and the early incorporation of this group in the synthesis. To circumvent this, unsubstituted hydrazine (R = H) can be employed, and the resulting N2 position can be functionalized later on, thereby extending the sequence to five steps (Scheme 1, route B). In addition, selective introduction of substituents on the phenyl ring (**4**, $R^1$) is difficult in both routes A and B because condensation with substituted hydrazine and monodehydroxyhalogenation both proceed with very poor regioselectivity.

Palladium-catalyzed cross-coupling reactions have become essential tools for the mild and selective construction of C–C bonds.[7] Isocyanides (**2**, Scheme 1), which are isoelectronic with carbon monoxide, have emerged as powerful C1 building blocks in palladium catalysis during the last couple of years.[8] Isocyanides readily undergo transformations similar to carbon monoxide[9] but offer a distinct advantage for introducing diversity because they possess a variable group at nitrogen. As a result, palladium-catalyzed isocyanide insertion reactions offer a vast potential for the efficient and flexible synthesis of valuable nitrogen-containing heterocycles.[10] We have recently exploited this reactivity in a novel palladium-catalyzed coupling of *o*-(pseudo)halobenzoates (**1**), isocyanides (**2**) and hydrazines (**3**) that produces APOs in a more step- and atom-economic manner than the above-mentioned conventional methods

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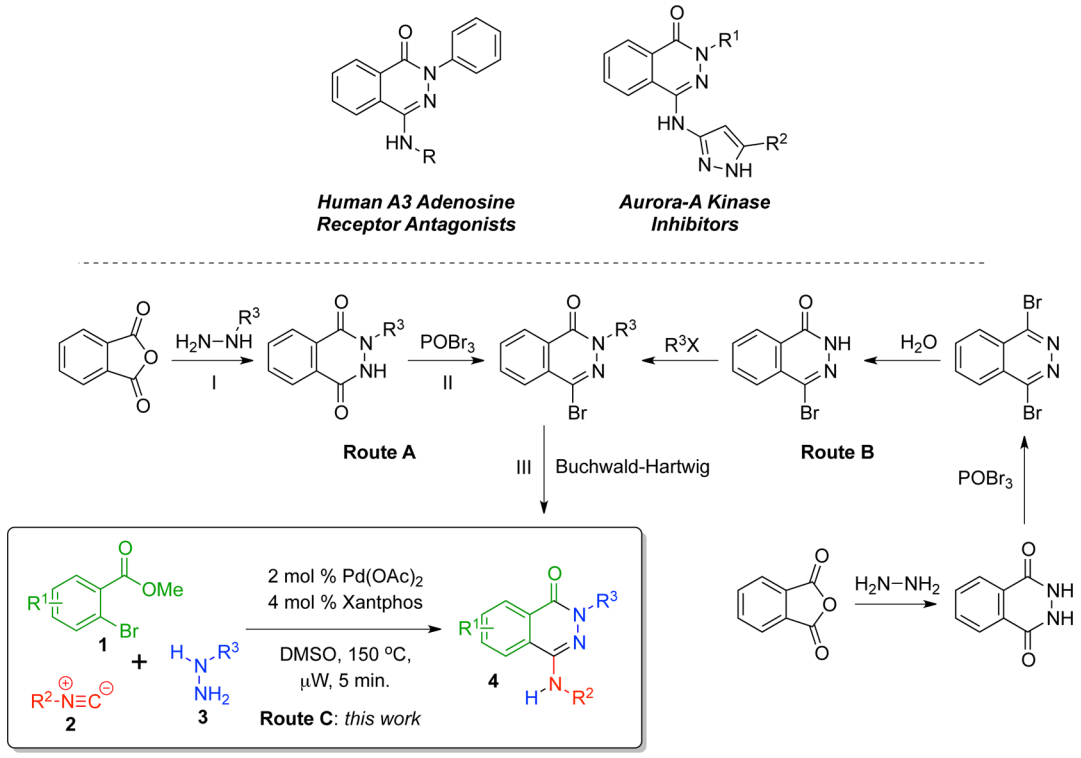
**Scheme 1. Biologically Active 4-Aminophthalazin-1(2*H*)-ones and Routes of Synthesis**




(Scheme 1, routes A and B) and allows, for the first time, regioselective introduction of substituents (Scheme 1, route C).[11,12] The reaction was unfortunately limited to tertiary aliphatic isocyanides and worked the best for unsubstituted hydrazines. Herein, we report the full details of this reaction and strategies to overcome the limitations of our approach, resulting in a two- or three-step sequence that selectively introduces substituents on *all* positions of the APO scaffold.

## RESULTS AND DISCUSSION

We previously established optimal conditions for the conversion of methyl 2-bromobenzoate to 4-(*tert*-butylamino)phthalazin-1(2*H*)-one (**4a**) using hydrazine monohydrate and *tert*-butyl isocyanide as reagents.[11] Hydrazine not only is used as a reactant but also acts as a base to neutralize the generated hydrobromic acid. Bidentate phosphine ligands proved essential for high yields, with Xantphos being most effective. Furthermore, dimethyl sulfoxide (DMSO) was the only solvent in which the reaction performed well, and microwave irradiation heating proved more effective than conventional heating.[13] With these optimized conditions, **4a** is readily obtained within 5 min in excellent yield (Table 1, 98%). The reaction can be extended to the corresponding aryl iodide and aryl triflate, but the aryl chloride provides a much lower yield of **4a**. Diverse substitution (e.g., Cl, $CF_3$, $NH_2$, F, and OMe) on the methyl *o*-halobenzoate (**1**) was well tolerated on various positions and led to the isolation of the corresponding products **4b**–**4k** in moderate to excellent yields. The structure of compound **4b** was unambiguously established by X-ray crystallography (see Figure S1 in the Supporting Information). Electron-poor methyl benzoates (**1**) are typically converted in moderate yield (**4b**–**4d**). This is probably due to compatibility issues as the aryl chloride (**1b**) might undergo competitive oxidative addition, and methyl 2-bromo-4-fluorobenzoate (**1c**) is an excellent substrate for nucleophilic aromatic substitution by hydrazine. Interestingly, the yield of **4b** increased significantly when the reaction time was reduced to just 2 min (from 62% to 80%), suggesting undesired Pd-catalyzed reactions of the aryl chloride occurred on the reaction product. It is important to note that the medicinally important fluoro- and trifluoromethyl substituents could be smoothly incorporated,[14] but the yields were modest (**4c** and **4d**). A naphthalene-fused derivative (**4e**) and a methyl-substituted APO (**4f**) were obtained in excellent yield (99% and 95%, respectively). Electron-rich methyl *o*-(pseudo)halobenzoates undergo the desired reaction extremely well, affording the corresponding APOs **4g**–**4k** in excellent yield, but reactions are sometimes slower, requiring 15 min reaction time (**4j** and **4k**). Substrate **1i**, containing a free amino group, was not fully consumed under the reaction conditions. The reaction tolerates heterocyclic substrates, as exemplified by the conversion of the pyridine analog **1l** to aza-APO **4l** in 84% yield. Azaphthalazinones lacking the 4-amino group very recently received attention as human histamine $H_1$ receptor antagonists.[15]

The main limitation in scope with respect to the benzoate (**1**) is the availability or straightforward access to this building block. We were therefore pleased to find that methyl 2-bromo-4-fluorobenzoate (**1c**), which can be obtained in one step from the commercially available corresponding carboxylic acid, is an excellent substrate for nucleophilic aromatic substitution reactions with amines. Benzoates **1j** and **1k** were readily obtained in the manner described in Scheme 2. Considering the fact that amines are prevalent in biologically active molecules, this is an important handle for introducing additional functionality.

Next, we explored the substrate scope of the other two components of this reaction and were disappointed to find low yields when monosubstituted hydrazines were employed (Table 1). We reasoned this might be due to the difference in basicity between different hydrazines and resolved this issue by the


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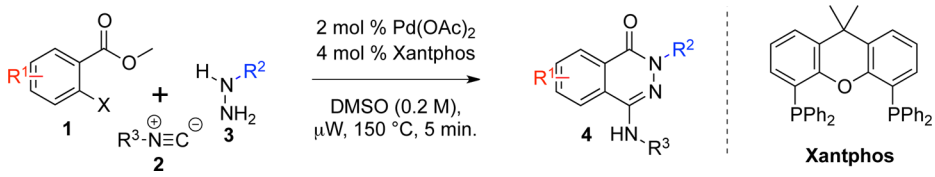
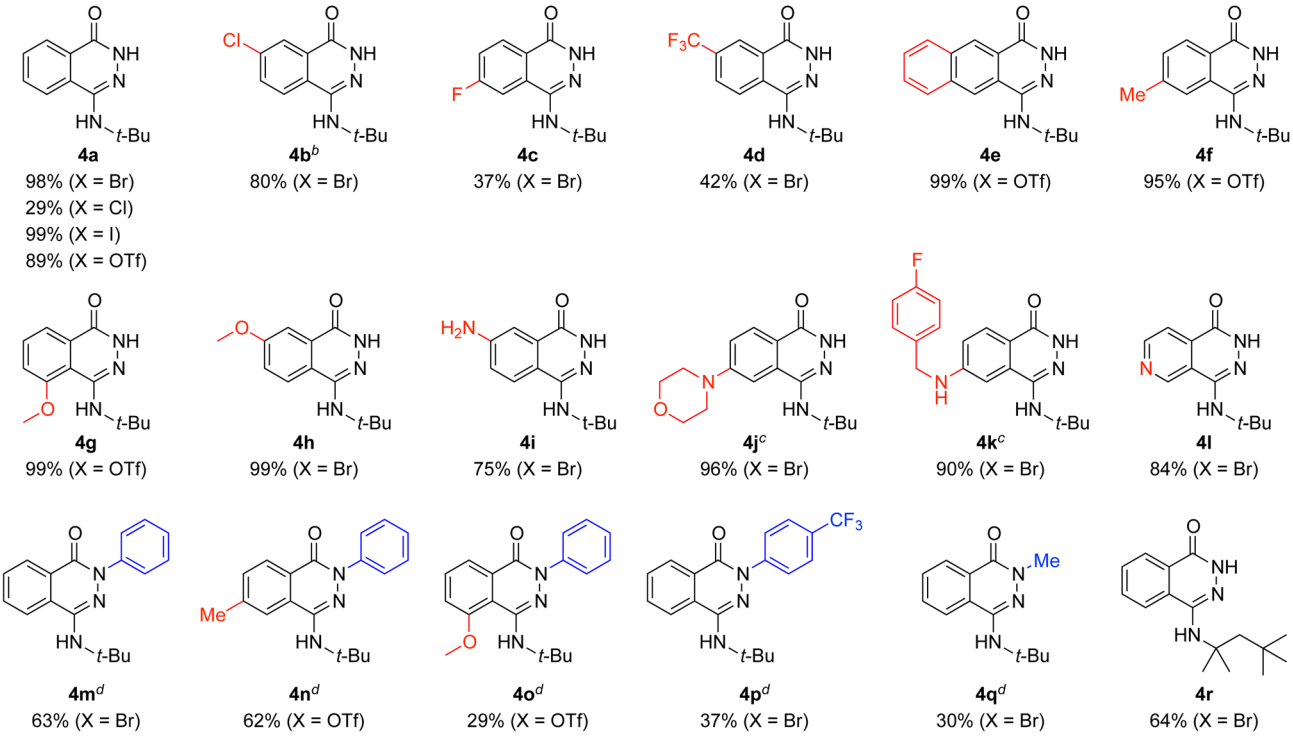
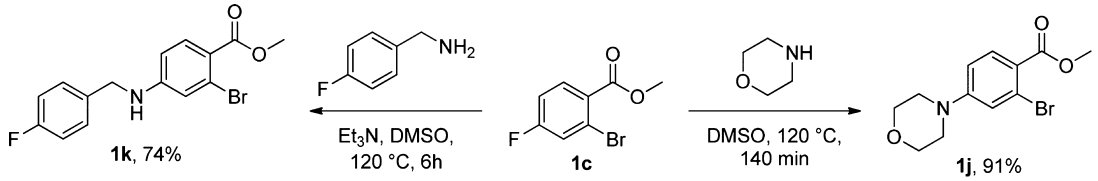
**Table 1. Substrate Scope of the Pd-Catalyzed MCR toward 4-Aminophthalazin-1(2*H*)-ones**[a]




[a]Conditions: ArX (0.50 mmol), isocyanide (0.75 mmol), hydrazine monohydrate (1.05 mmol), $Pd(OAc)_2$ (2 mol %), and Xantphos (4 mol %) in DMSO (2.5 mL) for 5 min at 150 °C (μW). Yields refer to isolated products. Compounds **4a**, **4b**, **4e−i**, and **4m−r** were reported by us previously.[11] [b]Reaction time: 2 min. [c]Reaction time: 15 min. [d]Conditions as under *a* but using a substituted hydrazine (1.25 mmol) and *i*-$Pr_2NH$ (1.50 mmol).

**Scheme 2. Synthesis of Substrates 1j and 1k**




addition of diisopropylamine as additional base. Aromatic hydrazines work reasonably well under these modified conditions (**4m−4p**), and methyl hydrazine provided 30% of reaction product **4q**. The isocyanide input is, unfortunately, limited to tertiary aliphatic isocyanides; only *tert*-butyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide provided the desired product.

To make further diversification possible, we envisioned a "deprotection" strategy. Removal of the *tert*-butyl group of the 4-(*tert*-butylamino)phthalazin-1(2*H*)-ones (**4**) should give APOs with a free amino group (**5**). Pleasingly, the acid-mediated removal of the *tert*-butyl group proceeds in excellent yields using conditions developed by Guchhait (Table 2).[16] The dealkylation can be performed without intermediate purification of the 4-(*tert*-butylamino)phthalazin-1(2*H*)-one (**4**), although a solvent switch to *n*-butanol was required. Also, scale-up of this one-pot, two-stage procedure was successful in demonstrating that practical quantities can be obtained via this approach. The reaction proceeds well on a 4 mmol scale, but the required reaction times for the multicomponent reaction are typically longer. For example, while 7-methoxy-substituted APO **4h** was obtained within 5 min on a 0.5 mmol scale (Table 1), 30 min were required for high yields on a 4 mmol scale (Step 1, **5e**, Table 2). In general, electron-rich methyl 2-(pseudo)-halobenzoates (**1**) need prolonged reaction times to allow full conversion and proceed in excellent yield (**5d−5f**). The chloro-substituted APO **5c** was obtained in optimal yield after just 2 min and required intermediate purification before dealkylation due to formation of side products (vide supra). Finally, N2-substituted APOs, as exemplified by the synthesis of **5g**, could also be obtained via this one-pot, two-stage procedure using phenylhydrazine as the reagent in the presence of *i*$Pr_2NH$ as the base.


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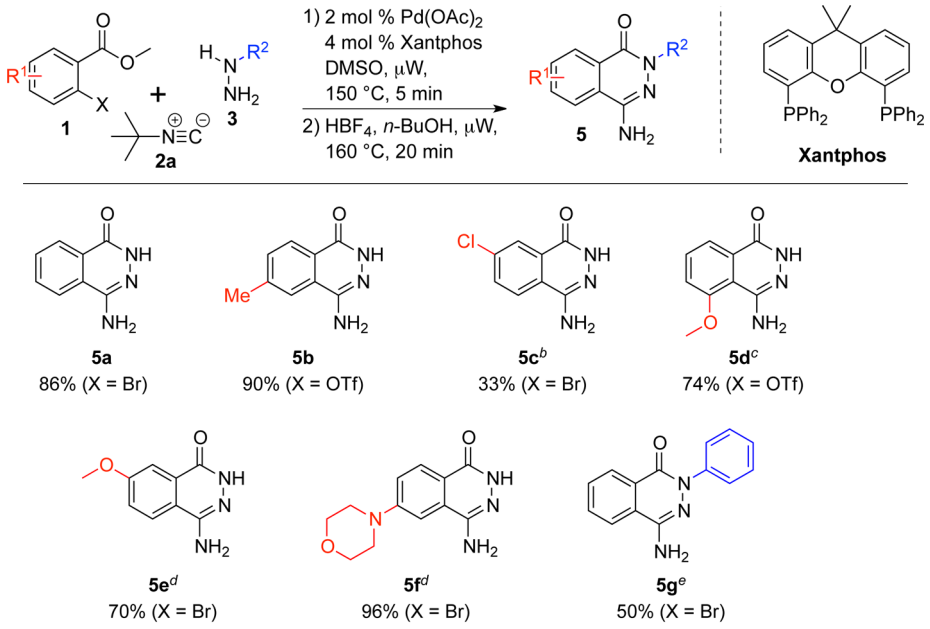
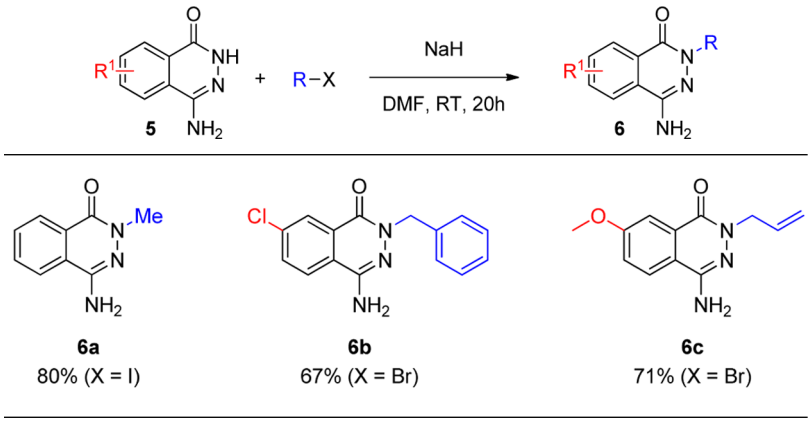
**Table 2. Substrate Scope of the One-Pot MCR and De-*tert*-Butylation Strategy**[a]




[a]Step 1 conditions: ArX (4.0 mmol), *t*-BuNC (6.0 mmol), $H_2NNH_2{\cdot}H_2O$ (8.4 mmol), $Pd(OAc)_2$ (2 mol %), and Xantphos (4 mol %) in DMSO (20 mL) for 5 min at 150 °C (μW). Step 2 conditions: $HBF_4$ (48 wt % in $H_2O$, 4.0 mmol), and *n*-BuOH (16 mL) for 20 min at 160 °C (μW). Yields refer to isolated products. Compound **5a** was reported by us previously.[11] [b]Reaction time for step 1: 2 min. Purification was necessary after step 1. [c]Reaction time for step 1: 15 min. [d]Reaction time for step 1: 30 min. [e]Conditions as under *a* but using phenylhydrazine (10 mmol) and *i*-$Pr_2NH$ (12 mmol).

**Table 3. Substrate Scope of the N2 Alkylation of APOs**[a]




[a]Conditions: 4-aminophthalazin-1(2*H*)-one (0.5 mmol), alkyl halide (0.5 mmol), and NaH (60% in oil, 0.5 mmol) in dry DMF (3.5 mL) was stirred at RT for 20 h. Yields refer to isolated products. Compound **6a** was reported by us previously.[11]

With the dealkylated 4-aminophthalazin-1(2*H*)-ones (**5a**–**5g**) in hand, we set out to develop a strategy to access a broad range of decorated APOs by further functionalization. Two difficulties were apparent: (1) the APOs (**5a**–**5g**) are very polar and only dissolve in DMSO or DMF, and (2) differentiation between the N2 position and the 4-amino group is necessary. We have previously reported an N2 methylation of 4-aminophthalazin-1(2*H*)-one **5a** using methyl iodide and sodium hydride delivering **6a** in 80% yield (Table 3).[11] This selective alkylation was further applied by benzylation and allylation of **5c** and **5e**, yielding APOs **6b** and **6c**, respectively.

APOs with an aryl group at the N2 position are the most studied class of 4-aminophthalazin-1(2*H*)-ones in medicinal chemistry and typically show increased pharmaceutical potential compared to that of N2-alkylated APOs.[4] They are, however, difficult to access using traditional methods that rely on aryl hydrazines (Scheme 1) because of the poor commercial availability of substituted hydrazines. We therefore explored a selective N2 arylation with readily available aryl iodides under transition metal catalysis. Pleasingly, we found that a copper catalyst is able to differentiate between the N2 and 4-amino positions to furnish 2-arylated APOs under conditions derived from a procedure developed by Buchwald et al.[17] APO **5a** was arylated with *p*-iodotoluene to yield product **7a** in 72% yield, whereas only 7% of the double arylation product (**8**) was isolated (Table 4). Several electronically diverse aryl iodides coupled in good yield and with similar selectivities (**7b**–**7d**), and even 4-iodopyridine worked well (**7e**). We did not optimize the reaction for each substrate specifically but rather focused on one robust set of conditions that allows the smooth


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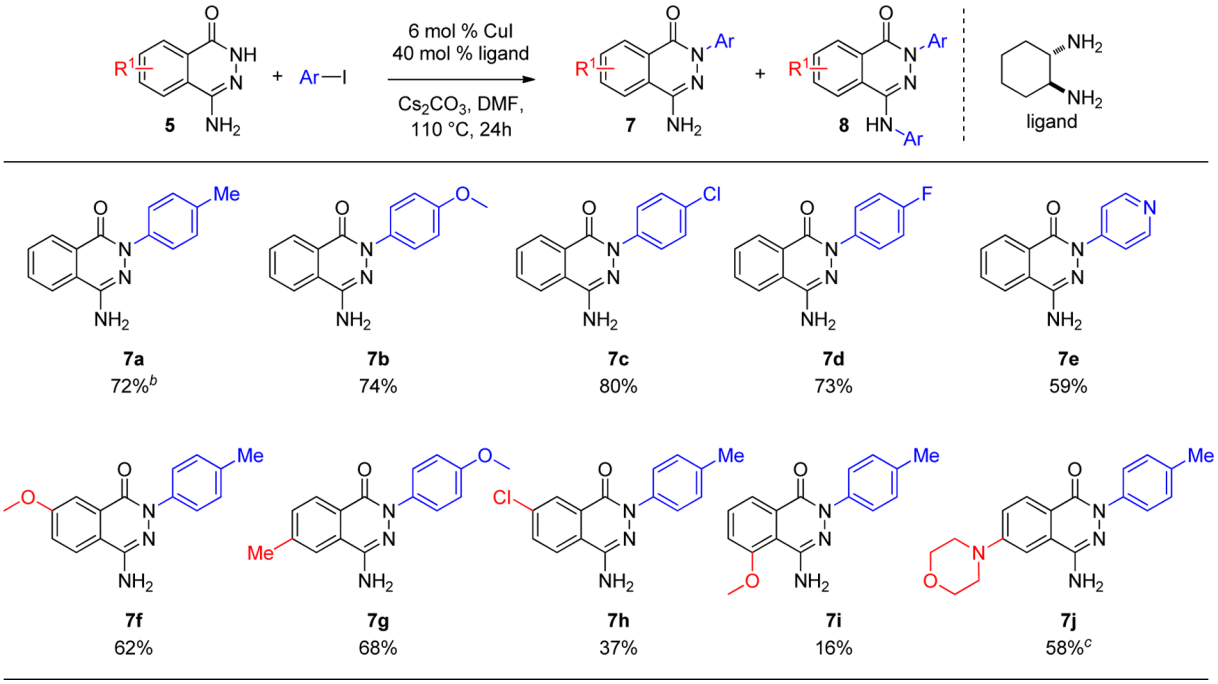
**Table 4. Substrate Scope of the N2 Arylation of APOs[a]**



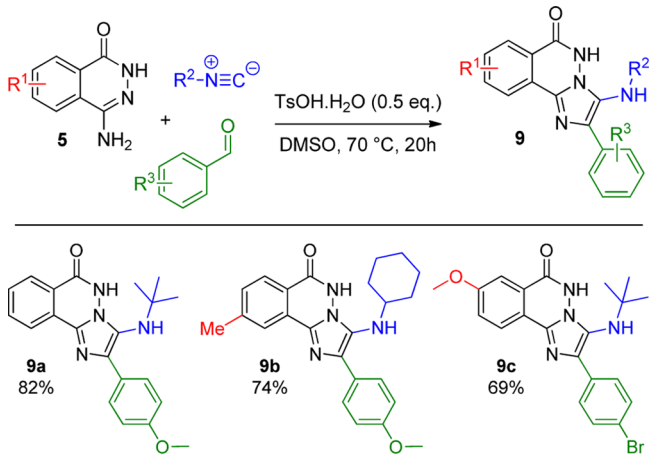

[a]Conditions: 4-aminophthalazin-1(2*H*)-one (0.50 mmol), aryl iodide (0.75 mmol), $Cs_2CO_3$ (1.25 mmol), CuI (6 mol %), and (±)-*trans*-1,2-diaminocyclohexane (40 mol %) in dry DMF (1 mL) at 110 °C for 20 h. Yields refer to isolated products. [b]7% of double arylation product was isolated. [c]27% of double arylation product was isolated.

conversion of a broad scope of APOs and aryl iodides. We then tested a range of substituted APOs and found good yields in most cases. For example, a 7-methoxy or 6-methyl group had no pronounced effect on the yield (**7f** and **7g**). In contrast, a chloro substituent decreased the yield significantly (**7h**), presumably due to the competing reaction of copper catalyst with the aryl chloride. A 5-methoxy group resulted in low conversion, and just 16% of product **7i** was isolated. We speculate that bidentate coordination of copper to the methoxy and amino groups inhibits catalysis. Finally, a 6-morpholino group was tolerated, and product **7j** was obtained in 58% yield. Surprisingly, in this specific case, a significant amount of double arylation product was found.

Considering the fact that the discovery of new molecular scaffolds is essential to meet the contemporary demand for improved materials and pharmaceuticals, we used the dealkylated APOs (**5**) as input in the complexity-generating Groebke–Bienaymé–Blackburn MCR (Table 5).[18] The resulting imidazo-[2,1-*a*]phthalazin-6-ones (**9**) are unexplored scaffolds and accessible in just 2 steps by this double MCR approach. The reaction proceeds in higher yields if *p*-toluenesulfonic acid is employed as mediator instead of ammonium chloride, which we reported previously.[11] The scope was evaluated and revealed that several APOs can be used as substrates, and both electron rich and electron poor aldehydes are tolerated.

Finally, when we treated **4a** with phosphoryl chloride in acetonitrile, we found conversion toward *N*-(*tert*-butyl)-4-chlorophthalazin-1-amine (**10**) in a modest 48% yield (Scheme 3). In this case, the *tert*-butyl group serves as a protecting group to prevent homocoupling of the reaction product. Such 4-chlorophthalazin-1-amines are classically obtained from 1,4-dichlorophthalazines and readily undergo nucleophilic aromatic substitution by amines to furnish 1,4-diaminophthalazines (**11**).[19] Our route allows regioselective amine introduction when

**Table 5. Substrate Scope of the Groebke–Bienaymé–Blackburn MCR with APOs[a]**




[a]Conditions: 4-aminophthalazin-1(2*H*)-one (0.50 mmol), *p*-toluenesulfonic acid monohydrate (0.25 mmol), aldehyde (0.60 mmol), and isocyanide (0.55 mmol) in dry DMSO (2.5 mL) at 70 °C for 20 h. Yields refer to isolated products. Compound **9a** was reported by us previously.[11]

substituents are present on the phenyl ring and therefore avoids the tedious separation of regioisomers. Furthermore, 4-chlorophthalazin-1-amines have also been used as substrates for Pd-catalyzed cross-coupling reactions, as exemplified by Suzuki reactions, furnishing medicinally interesting arylphthalazines (**12**).[20]

## CONCLUSION

We have developed a multicomponent reaction toward 4-aminophthalazin-1(2*H*)-ones that, unlike other methods, allows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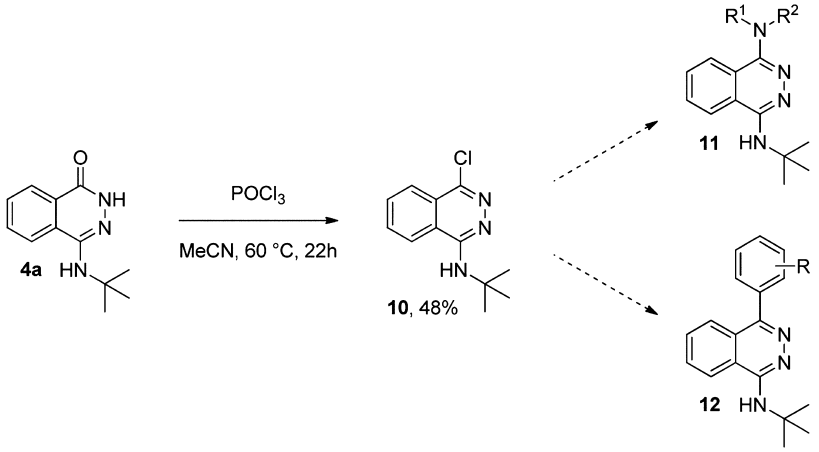
**Scheme 3. Dehydroxychlorination of 4a**




the regioselective introduction of functional groups on the C5−C8 positions. A one-pot MCR/dealkylation strategy overcomes the limited scope with respect to the isocyanide input and provides opportunities for scaffold postdiversification. The poor commercial availability of monosubstituted hydrazines prompted us to develop procedures for regioselective N2 functionalization that avoids the use of these reagents and allows straightforward access to both N-arylated and N-alkylated APOs. Additionally, we have used APOs as input in Groebke−Bienaymé−Blackburn MCRs to obtain new and highly functionalized scaffolds in just two synthetic steps. Finally, we have shown that 4-aminophthalazin-1(2*H*)-ones can be converted to 4-chlorophthalazin-1-amines, which are interesting intermediates toward medicinally relevant products.

## EXPERIMENTAL SECTION

**General Comments.** Unless stated otherwise, all solvents and commercially available reagents were used as received. Noncommercial starting materials were prepared as described below or according to literature procedures. The microwave reactions were performed in a sealed vessel using either a CEM Discover or a Biotage Initiator Plus, and the reaction temperatures were measured using IR. Reaction times refer to the hold time at the desired set temperature. $^1$H and $^{13}$C (attached proton test) nuclear magnetic resonance (NMR) spectra were recorded at ambient temperature using the residual solvent as an internal standard ($^1$H $\delta$ 2.50 ppm and $^{13}$C{$^1$H} $\delta$ 39.52 ppm for DMSO-$d_6$ and $^1$H $\delta$ 7.26 ppm and $^{13}$C{$^1$H} $\delta$ 77.16 ppm for $CDCl_3$). Chemical shifts ($\delta$) are given in parts per million, and coupling constants ($J$) are quoted in hertz. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad) or combinations thereof. Electrospray ionization (ESI) high-resolution mass spectrometry was carried out in positive ion mode (capillary potential of 4500 V) with TOF analysis. Flash chromatography was performed on $SiO_2$ (particle size 40−63 $\mu$m, pore diameter 60 Å) using the indicated eluent.

**Methyl 2-Bromo-4-fluorobenzoate (1c).** 2-Bromo-4-fluorobenzoic acid (4.38 g, 20 mmol, 1 equiv) and dry MeOH (60 mL) were added to a three-necked flask under an $N_2$ atmosphere. The solution was cooled to 0 °C, and $SOCl_2$ (2.9 mL, 40 mmol, 2 equiv) was added. The mixture was heated to reflux for 100 min and then concentrated in vacuo. The residue was dissolved in DCM, and the solution was washed twice with $NaHCO_3$ (aq, saturated). The organic layer was dried ($Na_2SO_4$), filtered, and concentrated in vacuo to give 4.30 g of a colorless oil (92%). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.88 (dd, $J$ = 8.8, 6.0 Hz, 1H), 7.41 (dd, $J$ = 8.3, 2.5 Hz, 1H), 7.08 (m, 1H), 3.92 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 165.7 (C), 164.0 (d, $J$ = 257 Hz, C), 133.5 (d, $J$ = 9.3 Hz, CH), 128.1 (d, $J$ = 3.5 Hz, C), 123.3 (d, $J$ = 10 Hz, C), 122.0 (d, $J$ = 24.6 Hz, CH), 114.7 (d, $J$ = 21.4 Hz, CH), 52.7 ($CH_3$).

**Methyl 2-Bromo-5-(trifluoromethyl)benzoate (1d).** A solution of 2-bromo-5-(trifluoromethyl)benzoic acid[21] (1.93 g, 7.1 mmol, 1 equiv) in dry MeOH (22.5 mL) under an $N_2$ atmosphere was cooled to 0 °C. $SOCl_2$ (1.09 mL, 15 mmol, 2.1 equiv) was slowly added, and then the mixture was refluxed for 5 h. The reaction mixture was concentrated in vacuo, dissolved in DCM, washed twice with $NaHCO_3$ (aq, saturated), and dried ($Na_2SO_4$). Purification by flash chromatography using cyclohexane/EtOAc (50:1 > 1:9) afforded 1.88 g of a yellow oil (93%). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.05 (d, $J$ = 2.1 Hz, 1H), 7.96 (d, $J$ = 8.4 Hz, 1H), 7.78 (dd, $J$ = 2.3, 8.4 Hz, 1H), 3.89 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 164.9 (C), 135.2 (CH), 133.3 (C), 129.3 (q, $J$ = 3.4 Hz, CH), 128.5 (q, $J$ = 32.9 Hz, C), 127.4 (q, $J$ = 3.7 Hz, CH), 124.9 (C), 123.3 (q, $J$ = 273 Hz, C), 52.9 ($CH_3$).

**Methyl 2-Bromo-4-morpholinobenzoate (1j).** Methyl 2-bromo-4-fluorobenzoate (**1c**, 2.32 g, 10 mmol, 1 equiv) and morpholine (4.37 mL, 50 mmol, 5 equiv) were dissolved in DMSO (10 mL), and the solution was stirred at 120 °C for 140 min. Subsequently, the reaction mixture was partitioned between EtOAc and $H_2O$. The aqueous layer was extracted with EtOAc (3 times). The combined organic extracts were dried ($Na_2SO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography using EtOAc/cyclohexane (1:3) afforded 2.73 g of an off-white solid (91%). Mp: 75.5−76.5 °C (decomposition). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.84 (d, $J$ = 8.5 Hz, 1H), 7.11 (d, $J$ = 2.5 Hz, 1H), 6.79 (dd, $J$ = 2.5, 9.0 Hz, 1H), 3.87 (s, 3H), 3.84 (t, $J$ = 5.0 Hz, 4H), 3.27 (t, $J$ = 5.0 Hz, 4H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 166.0 (CH), 153.7 (CH), 133.4 (C), 124.4 (CH), 120.5 (CH), 119.8 (C), 112.5 (C), 66.6 ($CH_2$), 52.1 ($CH_3$), 47.6 ($CH_2$). HRMS (ESI) $m/z$: calcd for $C_{12}H_{14}NO_3BrNa$ $[M + Na]^+$ 322.0049, found 322.0035.

**Methyl 2-Bromo-4-((4-fluorobenzyl)amino)benzoate (1k).** Methyl 2-bromo-4-fluorobenzoate (**1c**, 1.16 g, 5 mmol, 1 equiv), 4-fluorobenzylamine (0.86 mL, 7.5 mmol, 1.5 equiv), and triethylamine (1.4 mL, 10 mmol, 2 equiv) were dissolved in dry DMSO (10 mL). The reaction mixture was stirred at 120 °C for 5 h and then cooled and partitioned between EtOAc and $H_2O$. The aqueous layer was extracted with EtOAc (3 times), and the combined organic extracts were dried ($Na_2SO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography using EtOAc/cyclohexane (1:9 > 1:1) gave 1.15 g of an off-white solid (74%). Mp: 73.6−74.9 (decomposition). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 7.65 (d, $J$ = 8.8 Hz, 1H), 7.39−7.35 (m, 2H), 7.27 (t, $J$ = 6.0 Hz, 1H), 7.19−7.14 (m, 2H), 6.87 (d, $J$ = 2.2 Hz, 1H), 6.61 (dd, $J$ = 2.3, 8.8 Hz, 1H), 4.32 (d, $J$ = 5.9 Hz, 2H), 3.72 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 165.1 (C), 161.3 (d, $J$ = 243 Hz, C), 152.4 (C), 135.0 (d, $J$ = 2.7 Hz, C), 133.3 (CH), 129.2 (d, $J$ = 8.2 Hz, CH), 123.3 (C), 116.8 (CH), 116.1 (C), 115.2 (d, $J$ = 21.5 Hz, CH), 110.6 (CH), 51.6 ($CH_3$), 44.9 ($CH_2$). HRMS (ESI) $m/z$: calcd for $C_{15}H_{14}BrFNO_2$ $[M + H]^+$ 338.0186, found 338.0180.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**General Procedure for the MCR Toward 4-Aminophthalazin-1(2*H*)-ones (4).** A microwave tube was flame-dried under a flow of argon before addition of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 2 mol %) and Xantphos (11.6 mg, 0.02 mmol, 4 mol %). Dry DMSO (2.5 mL) was added to the catalyst, and the resulting mixture was stirred. Subsequently, isocyanide (0.75 mmol, 1.5 equiv), methyl benzoate (0.50 mmol, 1 equiv), and hydrazine monohydrate (51 μL, 1.05 mmol, 2.1 equiv) were added in this order. The tube was then placed in the microwave reactor and heated at 150 °C for 5 min unless indicated otherwise. The crude reaction mixture was filtered through a short plug of silica (EtOAc) and then concentrated in vacuo. Remaining DMSO was removed by freeze-drying. The crude product was purified by flash chromatography using the eluent specified below. Products **4a**, **4b**, **4e**, **4f**, **4g**, **4h**, **4i**, and **4r** and the synthesis of the corresponding starting materials have been reported by us previously.[11]

Modifications for monosubstituted hydrazines: 2.5 equiv of hydrazine derivative and $iPr_2NH$ (210 μL, 1.5 mmol, 3 equiv) was added. Products **4m**, **4n**, **4o**, **4p**, and **4q** have been reported by us previously.[11]

**4-(*tert*-Butylamino)-6-fluorophthalazin-1(2*H*)-one (4c).** Prepared from methyl 2-bromo-4-fluorobenzoate (**1c**). Flash chromatography using EtOAc/cyclohexane (1:2 > 1:1) gave 44 mg of a yellow solid (37%). Mp: 210.2−212.2 °C (decomposition). $^1$H NMR (500 MHz, DMSO-$d_6$): δ 11.63 (s, 1H), 8.26 (dd, *J* = 6.0, 9.0 Hz, 1H), 8.06 (dd, *J* = 2.0, 10.5 Hz, 1H), 7.64 (dt, *J* = 2.5, 9.0 Hz, 1H), 5.78 (s, 1H), 1.42 (s, 9H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 164.6 (d, *J* = 250 Hz, C), 156.8 (C), 143.3 (d, *J* = 2.5 Hz, C), 129.8 (d, *J* = 8.8 Hz, CH), 128.1 (d, *J* = 8.8 Hz, C), 125.3 (d, *J* = 1.3 Hz, C), 119.1 (d, *J* = 22.6 Hz, CH), 109.5 (d, *J* = 23.9 Hz, CH), 51.0 (C), 28.6 ($CH_3$). HRMS (ESI) *m*/*z*: calcd for $C_{12}H_{15}FN_3O$ $[M + H]^+$ 236.1194, found 236.1192.

**4-(*tert*-Butylamino)-7-(trifluoromethyl)phthalazin-1(2*H*)-one (4d).** Prepared from methyl 2-bromo-5-(trifluoromethyl)benzoate (**1d**). Flash chromatography using EtOAc/cyclohexane/$NEt_3$ (10:90:2 > 33:66:2) gave 61 mg of a yellow solid (42%). Mp: 200.0−202.2 °C (decomposition). $^1$H NMR (500 MHz, DMSO-$d_6$): δ 11.88 (s, 1H), 8.44−8.40 (m, 2H), 8.22 (dd, *J* = 1.5, 8.5 Hz, 1H), 6.00 (s, 1H), 1.43 (s, 9H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 156.6 (C), 143.3 (C), 130.7 (q, *J* = 32.8 Hz, C), 128.8 (C), 128.7 (q, *J* = 3.5 Hz, CH), 128.5 (C), 125.6 (CH), 123.6 (q, *J* = 273 Hz, C), 123.1 (q, *J* = 4.0 Hz, CH), 51.1 (C), 28.5 ($CH_3$). HRMS (ESI) *m*/*z*: calcd for $C_{13}H_{14}F_3N_3NaO$ $[M + Na]^+$ 308.0981, found 308.0954.

**4-(*tert*-Butylamino)-6-morpholinophthalazin-1(2*H*)-one (4j).** Prepared from methyl 2-bromo-4-morpholinobenzoate (**1j**). Reaction time: 15 min. Flash chromatography using EtOAc/cyclohexane (1:2) gave 145 mg of an off-white solid (96%). Mp: >230 °C (decomposition). $^1$H NMR (500 MHz, DMSO-$d_6$): δ 11.24 (s, 1H), 8.01 (d, *J* = 9.0 Hz, 1H), 7.37 (dd, *J* = 2.5, 9.0 Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 5.62 (s, 1H), 3.78 (t, *J* = 4.5 Hz, 4H), 3.37 (t, *J* = 4.5 Hz, 4H), 1.43 (s, 9H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 157.6 (C), 153.7 (C), 143.6 (C), 127.6 (CH), 127.2 (C), 119.4 (C), 117.6 (CH), 105.6 (CH), 65.9 ($CH_2$), 50.8 (C), 47.2 ($CH_2$), 29.0 ($CH_3$). HRMS (ESI) *m*/*z*: calcd for $C_{16}H_{23}N_4O_2$ $[M + H]^+$ 303.1816, found 303.1801.

**4-(*tert*-Butylamino)-6-((4-fluorobenzyl)amino)phthalazin-1(2*H*)-one (4k).** Prepared from methyl 2-bromo-4-((4-fluorobenzyl)-amino)benzoate (**1k**). Reaction time: 15 min. Flash chromatography using EtOAc/cyclohexane/MeOH/$NEt_3$ (2:1:0:0 > 93:0:5:3) gave 153 mg of an off-white solid (90%). Mp: 181.2−185.2 °C (decomposition). $^1$H NMR (400 MHz, DMSO-$d_6$): δ 11.05 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 7.44 (dd, *J* = 5.6, 8.4 Hz, 2H), 7.16 (t, *J* = 8.8 Hz, 2H) 7.08 (t, *J* = 5.6 Hz, 1H), 7.00 (dd, *J* = 2.0, 8.8 Hz, 1H), 6.88 (d, *J* = 1.6 Hz, 1H), 5.23 (s, 1H), 4.43 (d, *J* = 6.0 Hz, 2H), 1.41 (s, 9H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 161.3 (d, *J* = 243 Hz, C), 157.8 (C), 152.0 (C), 143.4 (C), 135.4 (d, *J* = 2.5 Hz, C), 129.5 (d, *J* = 8.8 Hz, CH), 127.7 (C), 127.4 (CH), 117.4 (C), 117.2 (CH), 115.1 (d, *J* = 20.1 Hz, CH), 101.6 (CH), 50.7 (C), 45.3 ($CH_2$), 28.8 ($CH_3$). HRMS (ESI) *m*/*z*: calcd for $C_{19}H_{22}FN_4O$ $[M + H]^+$ 341.1772, found 341.1753.

**4-(*tert*-Butylamino)pyrido[4,3-*d*]pyridazin-1(2*H*)-one (4l).** Prepared from 3-bromopyridine-4-carboxylic acid methyl ester (**1l**). Flash chromatography using EtOAc/cyclohexane (2:1) gave 91 mg of an off-white solid (84%). Mp: 218.0−220.2 (decomposition). $^1$H NMR (400 MHz, DMSO-$d_6$): δ 11.86 (s, 1H), 9.50 (s, 1H), 8.94 (d, *J* = 4.8 Hz, 1H), 8.02 (t, *J* = 4.8 Hz, 2H), 6.07 (s, 1H), 1.44 (s, 9H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 156.2 (C), 150.5 (CH), 147.2 (CH), 143.0 (C), 133.6 (C), 120.1 (C), 118.4 (CH), 51.1 (C), 28.5 ($CH_3$). HRMS (ESI) *m*/*z*: calcd for $C_{11}H_{15}N_4O$ $[M + H]^+$ 219.1240, found 219.1254.

**General Procedure for the One-Pot MCR/Dealkylation Sequence toward 4-Aminophthalazin-1(2*H*)-ones (5).** A microwave tube was flame-dried under a flow of Ar before addition of $Pd(OAc)_2$ (18.0 mg, 0.08 mmol, 2 mol %) and Xantphos (92.6 mg, 0.16 mmol, 4 mol %). Dry DMSO (20 mL) was added to the catalyst, and the resulting mixture was stirred. Subsequently, *tert*-butyl isocyanide (0.68 mL, 6.0 mmol, 1.5 equiv), methyl benzoate (4.0 mmol, 1 equiv), and hydrazine monohydrate (0.41 mL, 8.4 mmol, 2.1 equiv) were added in this order. The tube was sealed, placed in the microwave reactor, and heated at 150 °C for 5 min unless indicated otherwise. The reaction mixture was then concentrated in vacuo, and the remaining DMSO was removed by freeze-drying. (*Note*: Traces of DMSO led to an unpleasant smell along with lower yields during dealkylation. We found cofreeze-drying with $H_2O$ helpful to remove all traces of DMSO.) The resulting solid was suspended in *n*-BuOH (16 mL), and $HBF_4$ (48 wt.% in $H_2O$, 0.52 mL, 4 mmol, 1 equiv) was added subsequently. The reaction mixture was heated in the microwave reactor at 160 °C for 20 min, resulting in a suspension of the product as $HBF_4$ salt and palladium black. This product was dissolved in DMSO, and the solution was applied to 30 g of activated DOWEX 50WX2 (50−100 mesh). $HBF_4$ was washed off with $H_2O$ (wash until pH = 7), and impurities were removed by eluting with MeOH. Then, the product was removed from the column by washing in succession with $NH_3$ (25% in $H_2O$) and MeOH. The solution was concentrated in vacuo, and the resulting solid was further purified by trituration to yield analytically pure product.

**4-Aminophthalazin-1(2*H*)-one (5a).** Prepared from methyl 2-bromobenzoate. Trituration with DCM gave 556 mg of an off-white solid (86%). Mp: 266.6−268.9 °C (decomposition). $^1$H NMR (500 MHz, DMSO-$d_6$): δ 11.50 (s, 1H), 8.21 (dd, *J* = 1.0, 8.0 Hz, 1H), 8.05 (d, *J* = 7.5 Hz, 1H), 7.88 (dt, *J* = 1.0, 7.5 Hz, 1H), 7.80 (t, *J* = 8.0 Hz, 1H), 5.98 (s, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 158.1 (C), 146.1 (C), 132.9 (CH), 131.6 (CH), 128.4 (C), 126.1 (CH), 125.0 (C), 123.9 (CH). HRMS (ESI) *m*/*z*: calcd for $C_8H_7N_3ONa$ $[M + Na]^+$ 184.0481, found 184.0484.

**4-Amino-6-methylphthalazin-1(2*H*)-one (5b).** Prepared from methyl 2-trifluoromethanesulfonyloxy-4-methylbenzoate. Trituration with $Et_2O$ gave 629 mg of a light yellow solid (90%). Mp: 285.8−289.5 °C (decomposition). $^1$H NMR (500 MHz, DMSO-$d_6$): δ 11.41 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.87 (s, 1H), 7.62 (dd, *J* = 1.0, 8.0 Hz, 1H), 5.89 (s, 2H), 2.49 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 158.1 (C), 146.0 (C), 143.0 (C), 132.1 (CH), 126.1 (C), 126.1 (CH), 125.0 (C), 123.7 (CH), 21.5 ($CH_3$). HRMS (ESI) *m*/*z*: calcd for $C_9H_9N_3ONa$ $[M + Na]^+$ 198.0638, found 198.0635.

**4-Amino-7-chlorophthalazin-1(2*H*)-one (5c).** Prepared from methyl 2-bromo-5-chlorobenzoate. Reaction time for MCR step: 2 min. The intermediate 4-(*tert*-butylamino)-7-chlorophthalazin-1(2*H*)-one (**4b**) was purified by flash chromatography using EtOAc/cyclohexane (1:2) to yield 468 mg of a solid, which was then subjected to the standard dealkylation conditions. Trituration with DCM afforded 257 mg of **5c** as a yellow solid (33%). Mp: 301.0−304.6 °C (decomposition). $^1$H NMR (400 MHz, DMSO-$d_6$): δ 11.66 (s, 1H), 8.14 (d, *J* = 2.0 Hz, 1H), 8.10 (d, *J* = 8.8 Hz, 1H), 7.97 (dd, *J* = 2.0, 8.8 Hz, 1H), 6.07 (s, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 157.0 (C), 145.8 (C), 136.2 (C), 133.0 (CH), 130.0 (C), 126.6 (CH), 125.4 (CH), 123.6 (C). HRMS (ESI) *m*/*z*: calcd for $C_8H_6ClN_3ONa$ $[M + Na]^+$ 218.0092, found 218.0090.

**4-Amino-5-methoxyphthalazin-1(2*H*)-one (5d).** Prepared from methyl 2-trifluoromethanesulfonyloxy-3-methoxybenzoate. Reaction time for the MCR step: 15 min. Trituration with DCM gave 563 mg of an off-white solid (74%). Mp: >240 °C (decomposition). $^1$H NMR (400 MHz, DMSO-$d_6$): δ 11.50 (s, 1H), 7.81 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.47 (dd, *J* = 1.2, 8.0 Hz, 1H), 6.07 (s, 2H), 3.99 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 157.2 (C), 156.1 (C),


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145.3 (C), 132.2 (CH), 130.4 (C), 118.3 (CH), 114.9 (CH), 114.3 (C), 56.5 ($CH_3$). HRMS (ESI) *m/z*: calcd for $C_9H_9N_3O_2Na$ $[M + Na]^+$ 214.0587, found 214.0583.

**4-Amino-7-methoxyphthalazin-1(2*H*)-one (5e).** Prepared from methyl 2-bromo-5-methoxybenzoate. Reaction time for the MCR step: 30 min. The product was obtained as an off-white solid (537 mg, 70%). Mp: >230 °C (decomposition). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.46 (s, 1H), 8.00 (d, $J$ = 9.0 Hz, 1H), 7.60 (d, $J$ = 3.0 Hz, 1H), 7.44 (dd, $J$ = 2.5, 9.0 Hz, 1H), 5.88 (s, 2H), 3.91 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 161.2 (C), 158.0 (C), 146.1 (C), 130.3 (C), 126.0 (CH), 121.5 (CH), 118.7 (C), 107.2 (CH), 55.7 ($CH_3$). HRMS (ESI) *m/z*: calcd for $C_9H_9N_3O_2Na$ $[M + Na]^+$ 214.0587, found 214.0583.

**4-Amino-6-morpholinophthalazin-1(2*H*)-one (5f).** Prepared from methyl 2-bromo-4-morpholinobenzoate (**1j**). Reaction time for the MCR step: 30 min. Trituration with $Et_2O$ gave 946 mg of an off-white solid (96%). Mp: >250 °C (decomposition). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.15 (s, 1H), 8.00 (d, $J$ = 9.0 Hz, 1H), 7.40 (dd, $J$ = 2.5, 9.0 Hz, 1H), 7.29 (d, $J$ = 2.0 Hz, 1H), 5.84 (s, 2H), 3.77 (t, $J$ = 4.5 Hz, 4H), 3.36 (m, 4H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 158.2 (C), 153.7 (C), 145.9 (C), 127.5 (CH), 126.4 (C), 119.3 (C), 118.0 (CH), 106.0 (CH), 65.9 ($CH_2$), 47.2 ($CH_2$). HRMS (ESI) *m/z*: calcd for $C_{12}H_{15}N_4O_2$ $[M + H]^+$ 247.1190, found 247.1192.

**4-Amino-2-phenylphthalazin-1(2*H*)-one (5g).** A microwave tube was flame-dried under a flow of Ar before addition of $Pd(OAc)_2$ (18.0 mg, 0.08 mmol, 2 mol %) and Xantphos (92.6 mg, 0.16 mmol, 4 mol %). Dry DMSO (20 mL) followed by $i$Pr$_2$NH (1.69 mL, 12 mmol, 3 equiv) was added to the catalyst, and the resulting mixture was stirred. Subsequently, *tert*-butyl isocyanide (0.68 mL, 6 mmol, 1.5 equiv), methyl 2-bromobenzoate (0.56 mL, 4 mmol, 1 equiv), and phenyl hydrazine (0.98 mL, 10 mmol, 2.5 equiv) were added in this order. The tube was sealed, placed in the microwave reactor, and heated at 150 °C for 5 min. The reaction mixture was concentrated in vacuo, and the remaining DMSO was removed by freeze-drying. The resulting solid was suspended in *n*-BuOH (16 mL), and $HBF_4$ (48 wt.% in $H_2O$, 0.52 mL, 4 mmol, 1 equiv) was added subsequently. The reaction mixture was heated in the microwave reactor at 160 °C for 20 min. The mixture was concentrated in vacuo, and the residue was dissolved in EtOAc and washed with 1 M NaOH. Subsequently, the water layer was extracted with EtOAc (3 times), and the combined organic extracts were dried ($Na_2SO_4$). Flash chromatography using EtOAc/cyclohexane/$NEt_3$ (33:66:2 > 50:50:2) afforded 470 mg of an off-white solid (50%). Mp: >160 °C (decomposition). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.32 (dd, $J$ = 1.2, 8.0 Hz, 1H), 8.14 (d, $J$ = 8.0 Hz, 1H), 7.95 (t, $J$ = 7.2 Hz, 1H), 7.88 (t, $J$ = 8.0 Hz, 1H), 7.64 (dd, $J$ = 1.2, 8.8 Hz, 2H), 7.46 (t, $J$ = 7.6 Hz, 2H), 7.32 (t, $J$ = 7.2 Hz, 1H), 6.30 (s, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 156.8 (C), 146.3 (C), 142.3 (C), 133.1 (CH), 131.8 (CH), 128.5 (C), 128.2 (CH), 127.0 (CH), 126.7 (CH), 125.8 (CH), 124.6 (C), 124.0 (CH). HRMS (ESI) *m/z*: calcd for $C_{14}H_{11}N_3ONa$ $[M + Na]^+$ 260.0794, found 260.0790.

**General Procedure for the N2 Alkylation of 4-Aminophthalazin-1(2*H*)-ones.** A flame-dried Schlenk tube under an $N_2$ atmosphere was charged with 4-aminophthalazin-1(2*H*)-one (0.5 mmol, 1 equiv) and dry DMF (3.5 mL). Subsequently, NaH (60% in mineral oil, 20 mg, 0.5 mmol, 1 equiv) was added, and the reaction mixture was stirred for 1 h at room temperature. Then the alkyl halide (0.5 mmol, 1 equiv) was added. After stirring for 20 h at room temperature, the reaction mixture was concentrated in vacuo. The residue was partitioned between EtOAc and $H_2O$, and the layers were separated. The water layer was extracted with EtOAc (3 times), and the combined organic layers were dried ($Na_2SO_4$). The product was purified using flash chromatography with the eluent specified below.

**2-Methyl-4-aminophthalazin-1(2*H*)-one (6a).** Prepared from methyl iodide. Flash chromatography using EtOAc/cyclohexane/$NEt_3$ (80:20:2) gave 70 mg of a white solid (80%). Mp: 161.1−163.2 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.23 (dd, $J$ = 1.0, 7.5 Hz, 1H), 8.07 (d, $J$ = 7.5 Hz, 1H), 7.85 (m, 1H), 7.81 (m, 1H), 6.17 (s, 2H), 3.53 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 156.8 (C), 145.9 (C), 132.5 (CH), 131.5 (CH), 128.1 (C), 126.4 (CH), 124.5 (C), 123.7 (CH), 38.0 ($CH_3$). HRMS (ESI) *m/z*: calcd for $C_9H_{10}N_3O$ $[M + H]^+$ 176.0818, found 176.0822.

**2-Benzyl-4-amino-7-chlorophthalazin-1(2*H*)-one (6b).** Prepared from benzyl bromide. Flash chromatography using EtOAc/DCM/$NEt_3$ (50:50:2 > 80:20:2) gave 96 mg of a white solid (67%). Mp: 207.0−207.6 °C (decomposition). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.21 (d, $J$ = 2.0 Hz, 1H), 8.13 (d, $J$ = 9.0 Hz, 1H), 7.98 (dd, $J$ = 2.5, 8.5 Hz, 1H), 7.33−7.24 (m, 5H), 6.31 (s, 2H), 5.14 (s, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 155.8 (C), 145.8 (C), 137.7 (C), 136.6 (C), 133.0 (CH), 129.6 (C), 128.4 (CH), 127.6 (CH), 127.2 (CH), 126.5 (CH), 125.9 (CH), 123.2 (C), 53.0 ($CH_2$). HRMS (ESI) *m/z*: calcd for $C_{15}H_{13}ClN_3O$ $[M + H]^+$ 286.0742, found 286.0740.

**2-Allyl-4-amino-7-methoxyphthalazin-1(2*H*)-one (6c).** Prepared from allyl bromide. Flash chromatography using EtOAc/DCM/$NEt_3$ (50:50:2 > 66:33:2) gave 82 mg of an off-white solid (71%). Mp: 138.5−141.3 °C (decomposition). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.02 (d, $J$ = 9.0 Hz, 1H), 7.63 (d, $J$ = 3.0 Hz, 1H), 7.45 (dd, $J$ = 2.5, 9.0 Hz, 1H), 6.09 (s, 2H), 5.93 (m, 1H), 5.11 (m, 2H), 4.55 (d, $J$ = 5.5 Hz, 2H), 3.92 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 161.5 (C), 156.3 (C), 146.0 (C), 133.6 (CH), 130.0 (C), 126.1 (CH), 121.4 (CH), 118.1 (C), 116.7 ($CH_2$), 107.6 (CH), 55.7 (CH), 52.0 ($CH_2$). HRMS (ESI) *m/z*: calcd for $C_{12}H_{14}N_3O_2$ $[M + H]^+$ 232.1081, found 232.1083.

**General Procedure for the N2 Arylation of 4-Aminophthalazin-1(2*H*)-ones.** A Schlenk tube was charged with 4-aminophthalazin-1(2*H*)-one (0.5 mmol, 1 equiv), CuI (5.7 mg, 6 mol %), $Cs_2CO_3$ (411 mg, 1.25 mmol, 2.5 equiv), and aryl iodide (0.75 mmol, 1.5 equiv). The Schlenk tube was put under vacuum and backfilled with Ar (3 times). Subsequently, a stock solution of (±)-*trans*-1,2-cyclohexanediamine in DMF (0.2 mM, 1 mL, 0.20 mmol, 40 mol %) was added. The tube was sealed and placed in an oil bath for 24 h at 110 °C. The crude reaction mixture was filtered through a short plug of silica (EtOAc) and then concentrated in vacuo. The crude product was purified by flash chromatography using the eluent specified below.

**2-(*p*-Tolyl)-4-aminophthalazin-1(2*H*)-one (7a).** Flash chromatography using EtOAc/cyclohexane (1:2 > 2:1) gave 91 mg of product as an off-white solid (72%) along with 13 mg (7%) of double arylation product **8a**. Product **7a**. Mp: 209.8−210.4 °C (decomposition). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.31 (dd, $J$ = 0.5, 8.0 Hz, 1H), 8.13 (d, $J$ = 8.0 Hz, 1H), 7.93 (dt, $J$ = 1.5, 8.0 Hz, 1H), 7.87 (dt, $J$ = 1.5, 8.0 Hz, 1H), 7.51 (d, $J$ = 8.0 Hz, 2H), 7.25 (d, $J$ = 8.5 Hz, 2H), 6.28 (s, 2H), 2.35 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 156.7 (C), 146.2 (C), 139.9 (C), 135.9 (C), 133.1 (CH), 131.7 (CH), 129.0 (CH), 128.6 (C), 127.0 (CH), 125.6 (CH), 124.5 (C), 124.0 (CH), 20.7 ($CH_3$). HRMS (ESI) *m/z*: calcd for $C_{15}H_{13}N_3ONa$ $[M + Na]^+$ 274.0951, found 274.0945. Product **8a**. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.70−8.68 (m, 1H), 7.91−7.87 (m, 3H), 7.74 (d, $J$ = 8.4 Hz, 2H), 7.42 (d, $J$ = 8.4 Hz, 2H), 7.36 (t, $J$ = 4.0 Hz, 3H), 7.20 (d, $J$ = 8.4 Hz, 2H), 6.52 (s, 1H), 2.49 (s, 3H), 2.40 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 158.1 (C), 141.8 (C), 139.9 (C), 138.4 (C), 137.0 (C), 133.1 (CH), 132.0 (C), 131.8 (CH), 129.8 (C), 129.7 (CH), 129.3 (CH), 128.7 (CH), 125.4 (C), 125.3 (CH), 122.1 (CH), 119.4 (CH), 21.3 ($CH_3$), 20.9 ($CH_3$). HRMS (ESI) *m/z*: calcd for $C_{22}H_{20}N_3O$ $[M + H]^+$ 342.1601, found 342.1599.

**2-(4-Methoxyphenyl)-4-aminophthalazin-1(2*H*)-one (7b).** Flash chromatography using EtOAc/cyclohexane (1:2 > 2:1) gave 99 mg of product as an off-white solid (74%). Mp: 208.6−209.6 °C (decomposition). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.30 (dd, $J$ = 1.0, 8.0 Hz, 1H), 8.12 (d, $J$ = 8.0 Hz, 1H), 7.93 (dt, $J$ = 1.0, 8.0 Hz, 1H), 7.86 (dt, $J$ = 1.0, 8.0 Hz, 1H), 7.53 (dd, $J$ = 2.0, 7.0 Hz, 2H), 7.00 (dd, $J$ = 2.0, 7.0 Hz, 2H), 6.27 (s, 2H), 3.80 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 157.7 (C), 156.7 (C), 146.1 (C), 135.4 (C), 133.0 (CH), 131.7 (CH), 128.6 (C), 127.0 (CH), 126.9 (CH), 124.5 (C), 124.0 (CH), 113.7 (CH), 55.3 ($CH_3$). HRMS (ESI) *m/z*: calcd for $C_{15}H_{13}N_3O_2Na$ $[M + H]^+$ 290.0900, found 290.0900.

**2-(4-Chlorophenyl)-4-aminophthalazin-1(2*H*)-one (7c).** Flash chromatography using EtOAc/cyclohexane/$NEt_3$ (25:75:2 > 50:50:2) gave 109 mg of product as an off-white solid (80%). Mp: 216.3-217.3 °C (decomposition). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.32 (d, $J$ = 7.5 Hz, 1H), 8.15 (d, $J$ = 8.0 Hz, 1H), 7.95 (t, $J$ = 8.0 Hz, 1H), 7.88


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(t, $J$ = 7.5 Hz, 1H), 7.73 (d, $J$ = 9.0 Hz, 2H), 7.52 (d, $J$ = 9.0 Hz, 2H), 6.38 (s, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 156.8 (C), 146.5 (C), 141.0 (C), 133.3 (CH), 131.9 (CH), 130.7 (C), 128.4 (C), 128.2 (CH), 127.2 (CH), 127.1 (CH), 124.6 (C), 124.0 (CH). HRMS (ESI) $m/z$: calcd for $C_{14}H_{11}ClN_3O$ $[M + H]^+$ 272.0585, found 272.0584.

**2-(4-Fluorophenyl)-4-aminophthalazin-1(2*H*)-one (7d).** Flash chromatography using EtOAc/cyclohexane/$NEt_3$ (50:50:2 > 66:33:2) gave 93 mg of product as an off-white solid (73%). Mp: >225 °C (decomposition). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.31 (d, $J$ = 8.0 Hz, 1H), 8.14 (d, $J$ = 8.0 Hz, 1H), 7.95 (t, $J$ = 7.0 Hz, 1H), 7.87 (t, $J$ = 7.5 Hz, 1H), 7.69−7.66 (m, 2H), 7.29−7.27 (m, 2H), 6.34 (s, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 160.3 (d, $J$ = 244 Hz, C), 156.8 (C), 146.4 (C), 138.6 (d, $J$ = 2.5 Hz, C), 133.2 (CH), 131.8 (CH), 128.4 (C), 127.8 (d, $J$ = 8.8 Hz, CH), 127.0 (CH), 124.6 (C), 124.0 (CH), 115.0 (d, $J$ = 22.6 Hz, CH). HRMS (ESI) $m/z$: calcd for $C_{14}H_{11}FN_3O$ $[M + H]^+$ 256.0881, found 256.0880.

**2-(4-Pyridinyl)-4-aminophthalazin-1(2*H*)-one (7e).** Flash chromatography using EtOAc/MeOH (9:1) gave 70 mg of product as an off-white solid (59%). Mp: >240 °C (decomposition). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.63 (dd, $J$ = 1.5, 5.0 Hz, 2H), 8.36 (dd, $J$ = 1.0, 8.0 Hz, 1H), 8.17 (d, $J$ = 8.0 Hz, 1H), 7.99−7.88 (m, 4H), 6.52 (s, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 157.5 (C), 150.0 (CH), 148.6 (C), 146.9 (C), 133.8 (CH), 132.1 (CH), 128.4 (C), 127.3 (CH), 124.5 (C), 124.1 (CH), 118.2 (CH). HRMS (ESI) $m/z$: calcd for $C_{13}H_{11}N_4O$ $[M + H]^+$ 239.0927, found 239.0912.

**2-(*p*-Tolyl)-4-amino-7-methoxyphthalazin-1(2*H*)-one (7f).** Flash chromatography using EtOAc/cyclohexane (1:2 > 2:1) gave 86 mg of product as an off-white solid (62%). Mp: >210 °C (decomposition). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.08 (d, $J$ = 8.8 Hz, 1H), 7.70 (d, $J$ = 2.8 Hz, 1H), 7.51−7.48 (m, 3H), 7.25 (d, $J$ = 8.0 Hz, 2H), 6.16 (s, 2H), 3.94 (s, 3H), 2.35 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 162.1 (C), 157.0 (C), 146.6 (C), 140.4 (C), 136.3 (C), 131.0 (C), 129.1 (CH), 126.7 (CH), 126.0 (CH), 122.2 (CH), 118.6 (C), 108.6 (CH), 56.2 ($CH_3$), 21.1 ($CH_3$). HRMS (ESI) $m/z$: calcd for $C_{16}H_{15}N_3O_2Na$ $[M + Na]^+$ 304.1056, found 304.1046.

**2-(4-Methoxyphenyl)-4-amino-6-methylphthalazin-1(2*H*)-one (7g).** Flash chromatography using EtOAc/cyclohexane (1:1 > 2:1) gave 96 mg of product as an off-white solid (68%). Mp: 239.4−241.2 °C (decomposition). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.19 (d, $J$ = 8.0 Hz, 1H), 7.95 (s, 1H), 7.68 (d, $J$ = 8.5 Hz, 1H), 7.52 (d, $J$ = 9.0 Hz, 2H), 6.98 (d, $J$ = 9.0 Hz, 2H), 6.19 (s, 2H), 3.79 (s, 3H), 2.52 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 157.6 (C), 156.8 (C), 146.0 (C), 143.3 (C), 135.4 (C), 132.8 (CH), 126.7 (CH), 126.3 (C), 124.6 (C), 123.7 (CH), 113.4 (CH), 56.3 ($CH_3$), 21.5 ($CH_3$). HRMS (ESI) $m/z$: calcd for $C_{16}H_{16}N_3O_2$ $[M + H]^+$ 282.1237, found 282.1219.

**2-(*p*-Tolyl)-4-amino-7-chlorophthalazin-1(2*H*)-one (7h).** Flash chromatography using EtOAc/cyclohexane (1:2) gave 53 mg of product as an off-white solid (37%). Mp: >230 °C (decomposition). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.23 (d, $J$ = 2.0 Hz, 1H), 8.17 (d, $J$ = 9.0 Hz, 1H), 8.02 (dd, $J$ = 2.5, 8.5 Hz, 1H), 7.50 (d, $J$ = 8.5 Hz, 2H), 7.26 (d, $J$ = 8.5 Hz, 2H), 6.37 (s, 2H), 3.94 (s, 3H), 2.35 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 155.6 (C), 145.8 (C), 139.6 (C), 136.7 (C), 136.2 (C), 133.2 (CH), 130.2 (C), 128.7 (CH), 126.5 (CH), 126.2 (CH), 125.5 (CH), 123.2 (C), 20.7 ($CH_3$). HRMS (ESI) $m/z$: calcd for $C_{15}H_{12}ClN_3ONa$ $[M + Na]^+$ 308.0561, found 308.0557.

**2-(*p*-Tolyl)-4-amino-5-methoxyphthalazin-1(2*H*)-one (7i).** Flash chromatography using EtOAc/cyclohexane (1:2 > 2:1) gave 23 mg of product as an off-white solid (16%). Mp: >200 °C (decomposition). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 7.92 (d, $J$ = 8.0 Hz, 1H), 7.80 (t, $J$ = 8.0 Hz, 1H), 7.54−7.52 (m, 3H), 7.25 (d, $J$ = 8.0 Hz, 2H), 6.35 (s, 2H), 4.02 (s, 3H), 2.35 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 156.2 (C), 155.9 (C), 145.3 (C), 139.7 (C), 135.9 (C), 132.8 (CH), 130.7 (C), 128.7 (CH), 125.3 (CH), 119.1 (CH), 115.3 (CH), 113.7 (C), 56.7 ($CH_3$), 20.7 ($CH_3$). HRMS (ESI) $m/z$: calcd for $C_{16}H_{16}N_3O_2$ $[M + H]^+$ 282.1237, found 282.1233.

**2-(p-Tolyl)-4-amino-6-morpholinophthalazin-1(2*H*)-one (7j).** Flash chromatography using EtOAc/cyclohexane/$NEt_3$ (80:20:2) gave 97 mg of product as an off-white solid (58%) along with 58 mg (27%) of double arylation product **8j**. Product **7j**. Mp: >220 °C (decomposition). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.10 (d, $J$ = 9.0 Hz, 1H), 7.50 (d, $J$ = 8.0 Hz, 2H), 7.44 (dd, $J$ = 2.0, 9.0 Hz, 1H), 7.37 (d, $J$ = 2.0 Hz, 1H), 7.22 (d, $J$ = 8.0 Hz, 2H), 6.15 (s, 2H), 3.78 (t, $J$ = 4.5 Hz, 4H), 3.40 (t, $J$ = 4.5 Hz, 4H), 2.34 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 156.8 (C), 153.9 (C), 146.0 (C), 140.0 (C), 135.3 (C), 128.7 (CH), 128.4 (CH) 126.0 (C), 125.3 (CH), 119.1 (C), 118.2 (CH), 105.9 (CH), 65.8 ($CH_2$), 47.1 ($CH_2$), 20.7 ($CH_3$). HRMS (ESI) $m/z$: calcd for $C_{19}H_{21}N_4O_2$ $[M + H]^+$ 337.1659, found 337.1672. Product **8j**. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 8.40 (d, $J$ = 9.0 Hz, 1H), 7.61 (d, $J$ = 8.5 Hz, 2H), 7.31−7.29 (m, 3H), 7.22 (d, $J$ = 8.0 Hz, 2H), 7.08 (d, $J$ = 8.0 Hz, 2H), 6.99 (d, $J$ = 2.0 Hz,1H), 6.40 (br, 1H), 3.86 (t, $J$ = 4.5 Hz, 4H), 3.33 (t, $J$ = 4.5 Hz, 4H), 2.37 (s, 3H), 2.29 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 158.2 (C), 154.2 (C), 141.7 (C), 139.9 (C), 138.8 (C), 136.6 (C), 131.7 (C), 129.9 (CH), 129.6 (CH), 129.2 (CH), 127.2 (C), 125.2 (CH), 121.2 (C), 119.5 (CH), 119.1 (CH), 104.9 (CH), 67.1 ($CH_2$), 47.9 ($CH_2$), 21.2 ($CH_3$), 20.9 ($CH_3$). HRMS (ESI) $m/z$: calcd for $C_{26}H_{27}N_4O_2$ $[M + H]^+$ 427.2129, found 427.2133.

**General Procedure for the Groebke-Bienaymé-Blackburn MCR with 4-Aminophthalazin-1(2*H*)-ones.** A flame-dried Schlenk tube was charged with 4-aminophthalazin-1(2*H*)-one (0.5 mmol, 1 equiv) and *p*-toluenesulfonic acid monohydrate (48 mg, 0.25 mmol, 0.5 equiv) and then purged with $N_2$ (3 times). Dry DMSO (2.5 mL) was added followed by aldehyde (0.6 mmol, 1.2 equiv) and isocyanide (0.55 mmol, 1.1 equiv). The reaction mixture was stirred at 70 °C for 20 h. Subsequently, the reaction mixture was concentrated and partitioned between EtOAc and $H_2O$. The aqueous layer was extracted with EtOAc (3 times), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The product was purified using flash chromatography with the eluent specified below.

**3-(*tert*-Butylamino)-2-(4-methoxyphenyl)imidazo[2,1-*a*]-phthalazin-6(5*H*)-one (9a).** Flash chromatography using EtOAc/heptane (1:2 > 2:1) gave 149 mg of product as an off-white solid (82%). Mp: > 210 °C (decomposition). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 12.17 (br, 1H), 8.33 (d, $J$ = 7.9 Hz, 1H), 8.15 (d, $J$ = 8.8 Hz, 2H), 8.10 (d, $J$ = 7.9 Hz, 1H), 7.89 (td, $J$ = 1.0, 8.1 Hz, 1H), 7.67 (td, $J$ = 1.0, 8.1 Hz, 1H), 6.97 (d, $J$ = 8.8 Hz, 2H), 3.94 (s, 1H), 3.79 (s, 3H), 1.09 (s, 9H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 157.9 (C), 156.1 (C), 133.3 (C), 132.9 (CH), 130.9 (C), 128.1 (C), 128.0 (CH), 128.0 (CH), 127.1 (C), 126.6 (C), 125.1 (CH), 121.1 (CH), 117.5 (C), 113.3 (CH), 55.7 (C), 54.9 ($CH_3$), 30.1 ($CH_3$). HRMS (ESI) $m/z$: calcd for $C_{21}H_{23}N_4O_2$ $[M + H]^+$ 363.1816, found 363.1795.

**3-(Cyclohexylamino)-2-(4-methoxyphenyl)-9-methylimidazo-[2,1-*a*]phthalazin-6(5*H*)-one (9b).** Flash chromatography using EtOAc/heptane (1:2 > 2:1) gave 149 mg of product as a white solid (74%). Mp: >170 °C (decomposition). $^1$H NMR (400 MHz, DMSO-$d_6$): 12.15 (br, 1H), 8.12−8.09 (m, 3H), 7.98 (d, $J$ = 8.4 Hz, 1H), 7.48 (dd, $J$ = 1.2, 8.4 Hz, 1H), 7.00 (d, $J$ = 8.8 Hz, 1H), 4.13 (d, $J$ = 6.8 Hz, 1H), 3.80 (s, 3H), 3.17−3.13 (m, 1H), 2.55 (s, 3H), 1.80−1.14 (m, 11H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 157.8 (C), 156.5 (C), 143.5 (C), 130.2 (C), 129.3 (CH), 128.8 (C), 128.6 (C), 127.4 (C), 127.0 (CH), 126.5 (C), 125.2 (CH), 120.6 (CH), 115.1 (C), 113.6, (CH), 55.1 (CH), 55.0 ($CH_3$), 33.3 ($CH_2$), 25.4 ($CH_2$), 24.3 ($CH_2$), 21.5 ($CH_3$). HRMS (ESI) $m/z$: calcd for $C_{24}H_{27}N_4O_2$ $[M + H]^+$ 403.2129, found 403.2106.

**2-(4-Bromophenyl)-3-(*tert*-butylamino)-8-methoxyimidazo-[2,1-*a*]phthalazin-6(5*H*)-one (9c).** Flash chromatography using EtOAc/heptane (1:2 > 2:1) gave 152 mg of product as a white solid (69%). Mp: 231.1−233.6 °C (decomposition). $^1$H NMR (400 MHz, DMSO-$d_6$): 12.26 (br, 1H), 8.28 (d, $J$ = 8.7 Hz, 1H), 8.20 (d, $J$ = 8.5 Hz, 2H), 7.57−7.50 (m, 4H), 4.00 (s, 1H), 3.92 (s, 3H), 1.10 (s, 9H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 159.3 (C), 155.8 (C), 134.9 (C), 131.8 (C), 131.5 (C), 130.7 (CH), 128.5 (CH), 127.6 (C), 123.2 (CH), 122.4 (CH), 120.6 (C), 119.3 (C), 119.0 (C), 106.3 (CH), 55.9 (C), 55.6 ($CH_3$), 30.4 ($CH_3$). HRMS (ESI) $m/z$: calcd for $C_{21}H_{22}BrN_4O_2$ $[M + H]^+$ 441.0921, found 441.0902.

***N*-(*tert*-Butyl)-4-chlorophthalazin-1-amine (10).** 4-(*tert*-Butylamino)phthalazin-1(2*H*)one (**4a**, 108.6 mg, 0.5 mmol, 1 equiv) was suspended in dry MeCN (1 mL) under an $N_2$ atmosphere. $POCl_3$ (140 $\mu$L, 1.5 mmol, 3 equiv) was added, and the mixture was stirred at


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60 °C for 22 h. Then, the reaction mixture was cooled, diluted with EtOAc, washed with $NaHCO_3$ (aq, saturated), $H_2O$, and brine, and dried ($Na_2SO_4$). Flash chromatography using cyclohexane/EtOAc (3:1) gave 57 mg of product as a white solid (48%). Mp: 176.2–177.0 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): 8.48–8.44 (m, 1H), 8.06–7.92 (m, 3H), 6.75 (s, 1H), 1.54 (s, 9H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 153.8 (C), 144.0 (C), 132.7 (CH), 132.2 (CH), 125.3 (C), 124.4 (CH), 123.5 (CH), 120.5 (C), 52.9 (C), 28.4 ($CH_3$). HRMS (ESI) $m/z$: calcd for $C_{12}H_{15}N_3Cl$ $[M + H]^+$ 236.0949, found 236.0940.

## ■ ASSOCIATED CONTENT

### Supporting Information

Copies of $^1$H and $^{13}$C NMR spectra for all new compounds and a CIF file for **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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