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Synthesis of 2-Aryl-1,2-dihydrophthalazines via Reaction of 2-(Bromomethyl)benzaldehydes with Arylhydrazines

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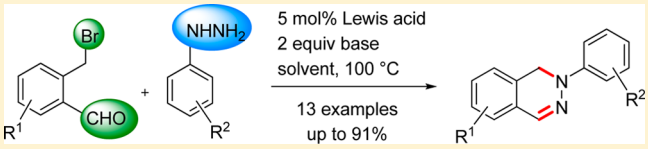
Supporting Information

ABSTRACT: The reaction of 2-(bromomethyl)benzaldehydes with arylhydrazines employing K_2CO_3 as a base and $FeCl_3$ as a catalyst in CH_3CN at 100 °C delivers 2-aryl-1,2-dihydrophthalazines with yields ranging from 60 to 91%. The transformation is considered to proceed as an intermolecular condensation/intramolecular nucleophilic substitution.



INTRODUCTION

Phthalazines and phthalazinones are N-heterocycles with a wide range of biological and pharmacological properties, such as anticonvulsant, antimicrobial, anti-inflammatory, antimycobacterial, antitumor, antihypertensive, antidiabetic, antifungal, and vasorelaxant activity, among others.[1] They also play an important role as intermediates in organic synthesis. This is why numerous methods have been developed for their preparation.[2] Besides fully aromatic phthalazines, partially unsaturated derivatives, such as the 1,2-dihydrophthalazines, are also of considerable interest in medicinal chemistry, as a number of them exhibit significant pharmacological properties. Among the most remarkable compounds are some 1,2-dihydrophthalazines that inhibit dihydrofolate reductase, an essential enzyme in most pathogenic bacteria. The 1,2-dihydrophthalazines have been demonstrated to have potent antibacterial activities against infections that are caused by multiresistant gram-positive pathogens, including staphylococci.[3] Of particular interest is the 1,2-dihydrophthalazine RAB1, which has been identified as a promising inhibitor of antibiotic-resistant *Staphylococcus aureus* and trimethoprim-resistant *Bacillus anthracis*.[4] In addition, it has been found that 1,2-dihydrophthalazines are potent, selective, and noncompetitive inhibitors of the AMPA subtype of glutamate receptors.[5]

In contrast to the synthesis of phthalazines and phthalazinones, the number of methods available for the preparation of 1,2-dihydrophthalazines is only modest. Most of them are based on the reduction of phthalazinium salts, phthalazines, or phthalazinones using reducing reagents, such as $[Fe_3(CO)_{12}]$[6] and $NaBH_4$,[7] or on the addition of organometallic reagents, such as organolithium,[5,8] or Grignard reagents[4b] to phthalazines. Another method is based on the cyclization of phthaldehyde monoarylhydrazones that can be obtained from the condensation of phthalaldehyde with arylhydrazines.[9] In addition, a few 1,2-dihydrophthalazines have been synthesized by reaction between 1,2-bis(halomethyl)benzenes and hydrazines under microwave conditions.[10] Recently, Xu et al. reported on the preparation of 1,2-dihydrophthalazines by the Rh-catalyzed oxidative annulation of sulphonylhydrazones with alkenes using $Cu(OAc)_2$ as the oxidant.[11] Altogether, the number of direct approaches to 1,2-dihydrophthalazines is rather limited. Therefore, the development of new methods for the synthesis of 1,2-dihydrophthalazines is highly desirable.

Recently, we have reported on new approaches to heterocycles that rely on reactions between *o*-disubstituted aromatics or heteroaromatics with disubstituted reagents.[12] As part of this work, we became interested in the reaction between 2-(halomethyl)benzaldehydes and arylhydrazines. In this contribution, we report on a practical synthesis of 2-substituted 1,2-dihydrophthalazines that is based on the reaction between 2-(bromomethyl)benzaldehydes and arylhydrazines under basic conditions and with $FeCl_3$ as the catalyst.

RESULTS AND DISCUSSION

It was envisaged that 1,2-dihydrophthalazines can be synthesized by a domino condensation/intramolecular substitution using a 2-(halomethyl)benzaldehyde **1** and a hydrazine **2** as the substrates. Therefore, in an initial experiment, 2-(bromomethyl)benzaldehyde (**1a**) and phenylhydrazine (**2a**) were reacted with 2 equiv of K_3PO_4 in DMF for 24 h at 110 °C in a sealed vial. After workup and purification, the desired 1,2-dihydrophthalazine **3a** could be isolated in 40% yield (Scheme 1). It is assumed that the reaction starts with the condensation between aldehyde **1a** and hydrazine **2a** to give the hydrazone **4a** as an intermediate. In the second step, **4a** undergoes an intramolecular nucleophilic substitution to yield the 2-substituted 1,2-dihydrophthalazine **3a**.

To facilitate the condensation between the aldehyde function of **1a** and the NH_2 group of the hydrazine **2a**, we decided to run the transformation in the presence of a Lewis acid. When the reaction between **1a** and **2a** with 2 equiv of K_3PO_4 was conducted in the presence of 10 mol % CuI in DMF, the yield of **3a** could be increased to 58% (Table 1, entry 1). The

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Scheme 1. Initial Experiment for the Synthesis of 2-Substituted 1,2-Dihydrophthalazines

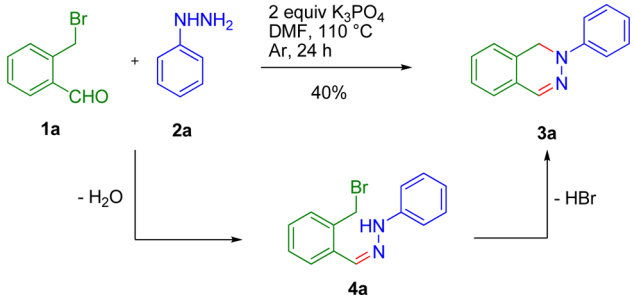
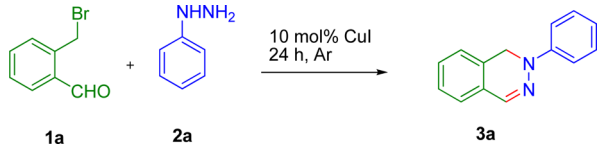


Table 1. Influence of Bases and Solvents on the Outcome of the Model Reaction[a]



entry	base (equiv)	solvent	T (°C)	yield of **3a** (%)
1	K_3PO_4 (2)	DMF	110	58
2	Cs_2CO_3 (2)	DMF	110	67
3	K_2CO_3 (2)	DMF	110	86
4	DABCO (2)	DMF	110	19
5	K_2CO_3 (3)	DMF	110	87
6	K_2CO_3 (1)	DMF	110	72
7	K_2CO_3 (2)	toluene	110	61
8	K_2CO_3 (2)	$C_2H_4Cl_2$	100	60
9	K_2CO_3 (2)	DMSO	110	84
10	K_2CO_3 (2)	DMA	110	80
11	K_2CO_3 (2)	NMP	100	37
12	K_2CO_3 (2)	CH_3CN	100	88
13	K_2CO_3 (2)	EtOH	100	66
14	K_2CO_3 (2)	H_2O	100	38
15	K_2CO_3 (2)		110	43

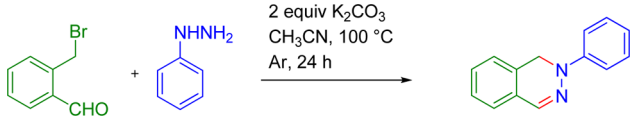
[a]All reactions were performed using 0.5 mmol of **1a** and 0.5 mmol of **2a** in a sealed vial. The temperatures given refer to oil bath temperatures.

reaction could be performed not only with K_3PO_4 as the base but also with Cs_2CO_3, K_2CO_3, and DABCO (Table 1, entries 2−4). With 2 equiv of K_2CO_3 in DMF, the yield of **3a** amounted to 86% (Table 1, entry 3). It is also remarkable that, with DABCO as the base, only 19% of the product could be isolated (Table 1, entry 4). An increase of the amount of K_2CO_3 to 3 equiv had a negligible impact on the yield (Table 1, entry 5). However, when the amount K_2CO_3 was reduced to 1 equiv, the yield of **3a** dropped to 72% (Table 1, entry 6).

Next, the influence of different solvents on the outcome of the model reaction was studied. It was established that it can be run in a number of solvents, including toluene, 1,2-dichloroethane, DMSO, DMA, NMP, CH_3CN, EtOH, and H_2O (Table 1, entries 7−14). The highest yield of **3a** was obtained in CH_3CN (Table 1, entry 12). It should be noted that, with DMSO or DMA as the solvents, the yield of **3a** was in the same range (Table 1, entries 9 and 10). In the absence of any solvent, the yield of **3a** dropped to 43% (Table 1, entry 15).

On the basis of the reaction conditions presented in Table 1, entry 12, the influence of different Lewis acids and different amounts of the catalysts was investigated (Table 2). It could be

Table 2. Influence of Lewis Acids on the Outcome of the Model Reaction[a]



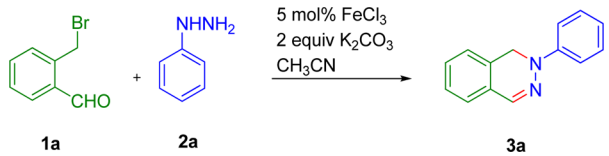
entry	Lewis acid	mol %	yield of **3a** (%)
1	$ZnCl_2$	10	77
2	Cu_2O	10	73
3	$InBr_3$	10	82
4	CuI	10	88
5	$FeCl_3$	10	89
6	CuI	5	70
7	$FeCl_3$	5	87
8	$FeCl_3$	2.5	73
9			49

[a]All reactions were performed using 0.5 mmol of **1a** and 0.5 mmol of **2a** in a sealed vial. The temperatures given refer to oil bath temperatures.

demonstrated that the reaction can be conducted with 10 mol % of a number of Lewis acids, including $ZnCl_2$, Cu_2O, $InBr_3$, CuI, and $FeCl_3$ (Table 2, entries 1−5). The best results were obtained with CuI and $FeCl_3$ (Table 2, entries 4 and 5). With 10 mol % CuI, 88% of **3a** was isolated (Table 2, entry 4). When the amount of CuI was decreased to 5 mol %, the yield of **3a** amounted to 70% (Table 2, entry 6). With 10 mol % $FeCl_3$ as the catalyst, the 1,2-dihydrophthalazine **3a** was obtained in 89% (Table 2, entry 5). Furthermore, it was found that the process tolerates a reduction of the amount of $FeCl_3$ from 10 to 5 mol % without a significant loss of yield (Table 2, entry 7). A further decrease of the $FeCl_3$ load to 2.5 mol % was also possible, but the yield dropped to 73% (Table 2, entry 8). A control experiment underlines the importance of the Lewis acid on the outcome of the reaction. In the absence of any Lewis acid, only 49% of the 1,2-dihydrophthalazine **3a** could be isolated (Table 2, entry 9).

Furthermore, it was demonstrated that the model reaction can also be conducted under reflux conditions and under microwave conditions in a sealed vial (Table 3). However, the yields were markedly lower than under our standard conditions. In summary, the best results were obtained when 1 equiv of 2-(bromomethyl)benzaldehyde (**1a**) and 1 equiv of arylhydrazine

Table 3. Reaction of 2a with 3a under Reflux and Microwave Conditions[a]



entry	conditions	yield of **3a** (%)
1	reflux	72
2[b]	microwave	64

[a]The reactions were performed using 0.5 mmol of **1a** and 0.5 mmol of **2a** under argon for 24 h. [b]The reaction was carried using a microwave apparatus (300 W, 20 bar, 100 °C) for 1 h.

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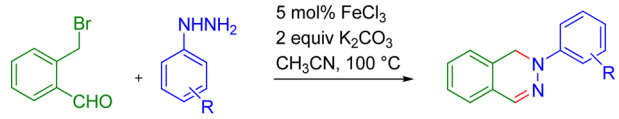
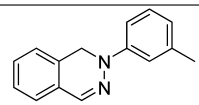
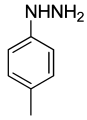
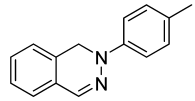
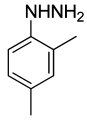
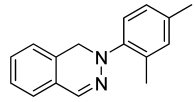
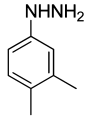
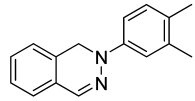
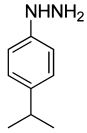
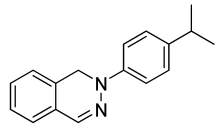
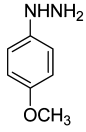
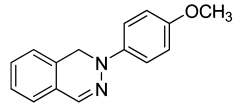
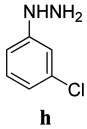
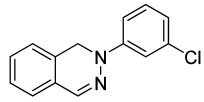
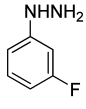
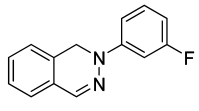
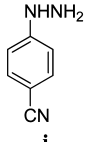
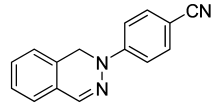
Table 4. Synthesis of 2-Aryl-1,2-dihydrophthalazines 3b−3j[a]



1a 2 3

entry	2	time (h)	3	Yield of 3 (%)
1	 **b**	24	 **b**	83
2	 **c**	22	 **c**	89
3	 **d**	23	 **d**	84
4	 **e**	23	 **e**	82
5	 **f**	22	 **f**	78
6	 **g**	22	 **g**	91
7	 **h**	22	 **h**	78
8	 **i**	24	 **i**	69
9	 **j**	27	 **j**	63

[a]All reactions were performed using 0.5 mmol of **1a** and 0.5 mmol of **2** in a sealed vial.

2a were reacted in the presence of 2 equiv of K_2CO_3 and 5 mol % $FeCl_3$ in CH_3CN in a sealed vial at 100 °C.

After optimizing the model reaction, we focused on the substrate scope of the new 1,2-dihydrophthalazine synthesis. For this purpose, arylhydrazines **2b−2j** carrying different substituents on the phenyl ring were studied. It was found that a number of substituents, such as methyl, isopropyl, methoxy, halo, and cyano substituents, were tolerated (Table 4, entries 1−9). The yields of the corresponding 2-substituted 1,2-dihydrophthalazines **3b−3j** were in the range between 63 and

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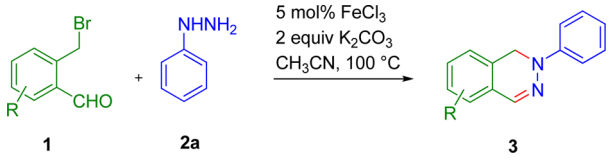
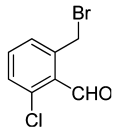
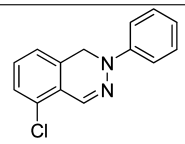
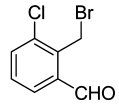
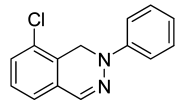
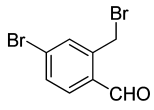
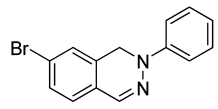
Table 5. Synthesis of 2-Phenyl-1,2-dihydrophthalazines 3k−3m[a]

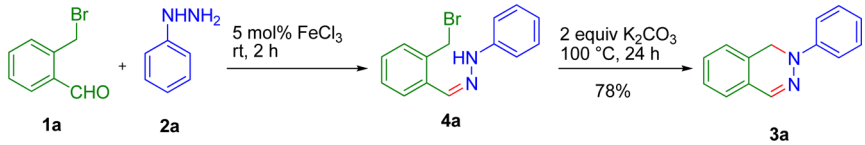


1 2a 3

entry	1	time (h)	3	Yield of 3 (%)
1	 b	22	 k	74
2	 c	22	 l	70
3	 d	20	 m	60

[a]All reactions were performed using 0.5 mmol of **1** and 0.5 mmol of **2a** in a sealed vial.

Scheme 2. Proposed Reaction Mechanism for the Formation of 2-Phenyl-1,2-dihydrophthalazines



1a 2a 4a 3a

91%. It should be noted that the yields with arylhydrazines carrying electron-donating substituents were higher than the yields observed with arylhydrazines with electron-withdrawing substituents.

In addition, it was studied whether substituted 2-(bromomethyl)benzaldehydes can be employed as substrates for the 1,2-dihydrophthalazine synthesis (Table 5). To this end, the 2-(bromomethyl)benzaldehydes **1b−1d** were synthesized by reduction of the corresponding benzonitriles (see the Experimental Section) with DIBAL-H and reacted with phenylhydrazine (**2a**). It was found that the 1,2-dihydrophthalazines **3k−3m** could be obtained without any problem. The yields were in the range between 60 and 74% (Table 5, entries 1−3)

With respect to the reaction mechanism of the dihydrophthalazine formation, it is assumed that the first step is a condensation between the aldehyde group of **1** and the NH_2 group of hydrazine **2** to give the corresponding hydrazone **4** (Scheme 2). This was corroborated by the fact that, upon reaction between **1a** and **2a** in the presence of 5 mol % $FeCl_3$ for 2h, the CHO signal of **1a** at δ = 10.26 ppm had disappeared and was replaced by a signal at δ = 8.13 ppm, which corresponds to the signal of a CH═N group. The hydrazone **4a** could not be isolated, but when 2 equiv of K_2CO_3 were added to the above reaction mixture and the resulting mixture was reacted at 100 °C for 24 h, the dihydrophthalazine **3a** was formed in 78% yield.

The structures of the 2-substituted 1,2-dihydrophthalazines **3a−3m** were unambiguously elucidated by NMR spectroscopy and mass spectrometry. Full assignment of the ^1H and ^{13}C chemical shifts and structure elucidation of all compounds was achieved by evaluating their gCOSY, gHSQC, and gHMBC spectra. As an example, in the HMBC spectrum for compound **3c**, the quaternary carbon C-4a showed strong ^3J-HMBC correlations to protons 1-H, 6-H, and 8-H (Figure 1). The quaternary carbon C-8a displayed $^3J_{CH}$-correlations to the protons 4-H, 5-H, and 7-H as well as strong $^2J_{CH}$-correlations to the proton 1-H. Carbon C-1′ exhibited strong $^3J_{CH}$-correlations to the proton 3′-H. The quaternary carbon C-4′ correlated with the protons 2′-H and 1″-H.

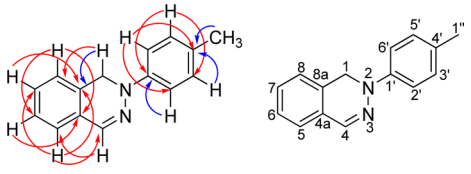


Figure 1. Important HMBC correlations of **3c** (red arrows, ^3J; blue arrows, ^2J).

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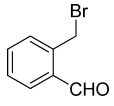
CONCLUSIONS

In conclusion, we have developed a simple to perform and efficient method for the synthesis of 2-substituted 1,2-dihydrophthalazines **3** employing simple starting materials. The 1,2-dihydrophthalazines **3** can be prepared in a single preparative step between 2-(bromomethyl)benzaldehydes **1** with arylhydrazines **2** via Lewis acid catalyzed domino condensation/intramolecular substitution. Best results were achieved when 1 equiv of 2-(bromomethyl)benzaldehyde **1** and 1 equiv of arylhydrazine **2** were reacted in the presence of 2 equiv of K_2CO_3 and 5 mol % $FeCl_3$ in CH_3CN. Using this protocol, the 2-substituted 1,2-dihydrophthalazines **3a**−**3m** were obtained selectively with yields ranging from 60 to 91%. The new method is one of the few examples for the synthesis of 1,2-dihydrophthalazines that does not start from a phthalazine or a phthalazine derivative.

EXPERIMENTAL SECTION

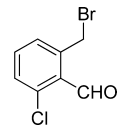
General Remarks. All commercially available reagents were used without further purification. Glassware was dried for 4 h at 140 °C. Solvents used in reactions were distilled over appropriate drying agents prior to use. Solvents used for extraction and purification were distilled prior to use. Reaction temperatures are reported as bath temperatures. Microwave-assisted reactions were performed using a Discover single-mode cavity microwave synthesizer (CEM Corp.) producing continuous microwave irradiation at 2450 MHz. The reaction temperatures were measured using an external IR probe. Thin-layer chromatography (TLC) was performed using TLC silica gel 60 F254. Compounds were visualized with UV light (λ = 254 nm) and/or by immersion in an ethanolic vanillin solution or by immersion in $KMnO_4$ solution, followed by heating. Products were purified by flash chromatography on silica gel, 0.04−0.063 mm. Melting points were obtained on a melting point apparatus with open capillary tubes and are uncorrected. IR spectra were measured on an FT-IR spectrometer. UV spectra were recorded with a spectrophotometer. ^{1}H (^{13}C) NMR spectra were recorded at 300 (75) and 500 (125) MHz using $CDCl_3$ or DMSO-d_6 as the solvent. The ^{1}H and ^{13}C chemical shifts were referenced to residual solvent signals at δ H/C 7.26/77.0 ($CDCl_3$) and 2.5/39.5 (DMSO-d_6) relative to TMS as internal standard. HSQC, HMBC, NOESY, ROESY, HSQMBC, and COSY spectra were recorded on an NMR spectrometer at 500 and 300 MHz. Coupling constants J [Hz] were directly taken from the spectra and are not averaged. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). 1D and 2D homonuclear NMR spectra were measured with standard pulse sequences. Low-resolution electron impact mass spectra (MS) and exact mass electron impact mass spectra (HRMS) were obtained at 70 eV using a double focusing sector field mass spectrometer. Intensities are reported as percentages relative to the base peak (I = 100%).

2-(Bromomethyl)benzaldehyde (1a).[13] A solution of 2-(bromomethyl)benzonitrile (2.5 g, 12.75 mmol) in dry dichloromethane (38 mL) was purged with argon for 20 min. The solution was cooled using an ice−water bath, and a 0.1 M solution of diisobutyl aluminum hydride (DIBAL-H) in hexane (13.0 mL, 13.0 mmol) was added dropwise during 25 min with stirring under argon. The reaction mixture was allowed to warm slowly to room temperature (4 h) by removing the ice−water bath. The reaction mixture was cooled again using an ice−water bath and poured into a 500 mL beaker filled with ice (50 g) and precooled aqueous 6 N HBr (50 mL). The mixture was vigorously stirred for 1.5 h and then extracted with dichloromethane (3 × 40 mL). The combined organic layers were washed with 1N $NaHCO_3$ (2 × 50 mL) and H_2O (2 × 50 mL) and dried over $MgSO_4$.

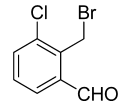


Evaporation of the solvents delivered **1a** as a brown liquid in 93% yield (2.37 g, 11.91 mmol): R_f = 0.50 (PE/EtOAc = 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.95 (s, 2H, CH_2Br), 7.49 (dd, ^4J = 1.8 Hz, ^3J = 7.2 Hz, 1H), 7.51 (td, ^4J = 1.8 Hz, ^3J = 7.2 Hz, 1H), 7.58 (td, ^4J = 1.8 Hz, ^3J = 7.2 Hz, 1H), 7.84 (dd, ^4J = 1.8 Hz, ^3J = 7.2 Hz, 1H), 10.25 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.5, 129.1, 131.7, 133.1, 133.8, 133.9, 139.2, 192.0.

2-(Bromomethyl)-6-chlorobenzaldehyde (1b).[15] A solution of 2-(bromomethyl)-6-chlorobenzonitrile (500 mg, 2.17 mmol) in dry dichloromethane (15 mL) was purged with argon for 20 min. The solution was cooled using an ice−water bath, and a 0.1 M solution of diisobutyl aluminum hydride (DIBAL-H) in hexane (2.5 mL, 2.5 mmol) was added dropwise during 25 min with stirring under argon. The reaction mixture was allowed to warm slowly to room temperature (4 h) by removing the ice−water bath. The reaction mixture was cooled again using an ice−water bath and poured into a 500 mL beaker filled with ice (35 g) and precooled aqueous 6 N HBr (15 mL). The mixture was vigorously stirred for 1.5 h and then extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with 1N $NaHCO_3$ (2 × 20 mL) and H_2O (2 × 20 mL) and dried over $MgSO_4$. Evaporation of the solvents delivered **1b** as a brown liquid in 60% yield (300 mg, 1.29 mmol): R_f = 0.46 (cyclohexane/EtOAc = 5:1); IR (ATR) ν 1691, 1583, 1425, 1246, 1148, 875, 833, 674 cm^{-1}; UV (MeCN) λ_{max} (log ε) 299 (3.18), 249 (3.72) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.90 (s, 2H, CH_2Br), 7.39−7.47 (m, 3H), 10.64 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.7, 129.9, 130.7, 131.0, 134.1, 139.5, 141.0, 191.7; MS (EI, 70 eV) m/z 233 (20) $[M]^+$, 153 (100); HRMS (EI, M^+) calcd for C_8H_6BrClO (231.9291), found 231.9268.



2-(Bromomethyl)-3-chlorobenzaldehyde (1c).[15] A solution of 2-(bromomethyl)-3-chlorobenzonitrile (2.472 g, 10.75 mmol) in dry dichloromethane (30 mL) was purged with argon for 20 min. The solution was cooled using an ice−water bath, and a 0.1 M solution of diisobutyl aluminum hydride (DIBAL-H) in hexane (11.0 mL, 11.0 mmol) was added dropwise during 25 min with stirring under argon. The reaction mixture was allowed to warm slowly to room temperature (4 h) by removing the ice−water bath. The reaction mixture was cooled again using an ice−water bath and poured into a 500 mL beaker filled with ice (40 g) and precooled aqueous 6 N HBr (40 mL). The mixture was vigorously stirred for 1.5 h and then extracted with dichloromethane (3 × 40 mL). The combined organic layers were washed with 1N $NaHCO_3$ (2 × 50 mL) and H_2O (2 × 50 mL) and dried over $MgSO_4$. Evaporation of the solvents delivered **1c** as a brown liquid in 78% yield (1.95 g, 8.35 mmol): R_f = 0.50 (cyclohexane/EtOAc = 5:1); IR (ATR) ν 1693, 1563, 1442, 1202, 1180, 878, 674 cm^{-1}; UV (MeCN) λ_{max} (log ε) 297 (3.54), 249 (4.06) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (s, 2H, CH_2Br), 7.47 (t, ^3J = 7.7 Hz, 1H), 7.65 (dd, ^4J = 1.3 Hz, ^3J = 7.7 Hz, 1H), 7.77 (td, ^4J = 1.4 Hz, ^3J = 7.7 Hz, 1H), 10.22 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 129.8, 132.3, 134.6, 134.7, 135.0, 136.7, 190.9; MS (EI, 70 eV) m/z 233 (16) $[M]^+$, 153 (8); HRMS (EI, M^+) calcd for C_8H_6BrClO (231.9291), found 231.9306.



4-Bromo-2-(bromomethyl)benzaldehyde (1d).[15] A solution of 4-bromo-2-(bromomethyl)-benzonitrile (2.0 g, 7.3 mmol) in dry dichloromethane (25 mL) was purged with argon for 20 min. The solution was cooled using an ice−water bath, and a 0.1 M solution of diisobutyl aluminum hydride (DIBAL-H) in hexane (7.5 mL, 7.5 mmol) was added dropwise during 25 min with stirring under argon.

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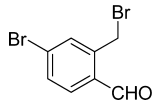
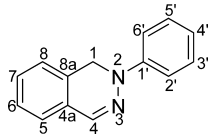


The reaction mixture was allowed to warm slowly to room temperature (4 h) by removing the ice−water bath. The reaction mixture was cooled again using an ice−water bath and poured into a 500 mL beaker filled with ice (35 g) and precooled aqueous 6 N HBr (35 mL). The mixture was vigorously stirred for 1.5 h and then extracted with dichloromethane (3 × 40 mL). The combined organic layers were washed with 1N $NaHCO_3$ (2 × 50 mL) and H_2O (2 × 50 mL) and dried over $MgSO_4$. Evaporation of the solvents delivered **1d** as a brown liquid in 99% yield (2.0 g, 7.2 mmol): R_f = 0.38 (cyclohexane/EtOAc = 5:1); IR (ATR) ν 1692, 1556, 1202, 1077, 896, 821, 761 cm^{-1}; UV (MeCN) λ_{max} (log ε) 265 (4.14), 221 (4.35) nm; ^1H NMR (300 MHz, $CDCl_3$) δ 4.88 (s, 2H, CH_2Br), 7.64−7.73 (m, 3H), 10.20 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 129.0, 131.9, 132.3, 134.7, 134.8, 140.8, 190.8; MS (EI, 70 eV) *m*/*z* 277 (8) $[M]^+$, 222 (8), 197 (24); HRMS (EI, M^+) calcd for $C_8H_6Br_2O$ (275.8785), found 275.8768.

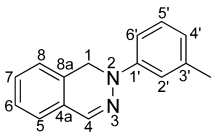
General Procedure for the Synthesis of 2-Aryl-1,2-dihydrophthalazines 3. An oven-dried vial was charged with K_2CO_3 (138 mg, 2 mmol), 2-(bromomethyl)benzaldehydes **1**, (99.5 mg, 0.5 mmol), arylhydrazine **2**[14] (0.5 mmol), and $FeCl_3$ (4 mg, 5 mol %) under argon. After sealing the vial, dry CH_3CN (2 mL) was added and the reaction mixture was stirred at 100 °C (oil bath temperature) until the aldehyde **1a** was consumed. After cooling to room temperature, the vial was opened and the reaction mixture was poured into water (40 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography over silica gel to afford the product.

*2-Phenyl-1,2-dihydrophthalazine (**3a**).*[9] According to the general procedure, a mixture of K_2CO_3 (138 mg, 0.5 mmol), 2-



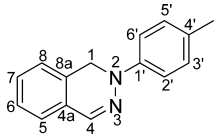
(bromomethyl)benzaldehyde (**1a**) (99.5 mg, 0.5 mmol), phenylhydrazine (**2a**) (54 mg, 0.5 mmol), and $FeCl_3$ (4 mg, 5 mol %) in dry CH_3CN (2 mL) was reacted for 24 h. Flash chromatography over silica gel (cyclohexane/Et_2O = 20:1) gave **3a** as a pale yellow solid in 87% yield (90 mg, 0.43 mmol): mp 137−138 °C (lit.[9] mp 136−137 °C); R_f = 0.56 (cyclohexane/Et_2O = 5:1); ^1H NMR (300 MHz, $CDCl_3$) δ 4.82 (s, 2H, 1-H), 7.02 (ddd, ^4J (2′-H, 4′-H) = 1.6 Hz, ^3J (3′-H, 4′-H) = 7.2 Hz, ^3J (4′-H, 5′-H) = 7.2 Hz, 1H, 4′-H), 7.15 (d, ^3J (7-H, 8-H) = 7.3 Hz, 1H, 8-H), 7.21 (brd, ^3J (5-H, 6-H) = 6.9 Hz, 1H, 5-H), 7.31−7.35 (m, 3H, 2′-H, 6′-H, 6-H), 7.36−7.40 (m, 3H, 3′-H, 5′-H, 7-H), 7.48 (s, 1H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.1 (C-1), 114.6 (C-2′), 121.2 (C-4′), 124.6 (C-5), 125.5 (C-4a), 125.7 (C-8), 128.1 (C-6), 129.0 (C-3′), 129.1 (C-8a), 130.2 (C-7), 136.1 (C-4), 147.0 (C-1′); MS (EI, 70 eV) *m*/*z* (%) 208 (40) $[M]^+$, 180 (3) $[M - N_2]^+$, 143 (5), 129 (6), 104 (40).

*2-(3-Methylphenyl)-1,2-dihydrophthalazine (**3b**).* According to the general procedure, a mixture of K_2CO_3 (138 mg, 1 mmol), 2-



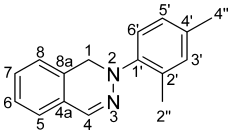
(bromomethyl)benzaldehyde (**1a**) (99.5 mg, 0.5 mmol), 3-methylphenylhydrazine (**2b**) (61 mg, 0.5 mmol), and $FeCl_3$ (4 mg, 5 mol %) in dry CH_3CN (2 mL) was reacted for 24 h. Flash chromatography over silica gel (cyclohexane/Et_2O = 20:1) gave **3b** as a pale yellow solid in 83% yield (92 mg, 0.41 mmol): mp 61−62 °C; R_f = 0.54 (cyclohexane/Et_2O = 5:1); IR (ATR) ν 1600 (C═N), 1561, 1486, 1451, 1395, 1322, 1143, 804, 752, 688 cm^{-1}; UV (MeCN) λ_{max} (log ε) 382 (4.08), 248 (4.21) nm; ^1H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H, CH_3), 4.79 (s, 2H, 1-H), 6.82 (d, ^3J (4′-H, 5′-H) = 7.2 Hz, 1H, 4′-H), 7.08 (dd, ^4J (4′-H, 6′-H) = 1.9 Hz, ^3J (5′-H, 6′-H) = 7.9 Hz, 1H, 6′-H), 7.13 (d, ^3J (7-H, 8-H) = 7.6 Hz, 1H, 8-H), 7.16−7.20 (m, 2H, 2′-H, 5-H), 7.24 (dd, ^3J (4′-H, 5′-H) = 7.8 Hz, ^3J (5′-H, 6′-H) = 7.8 Hz, 1H, 5′-H), 7.31 (ddd, ^4J (6-H, 8-H) = 0.9 Hz, ^3J (5-H, 6-H) = 7.1 Hz, ^3J (6-H, 7-H) = 7.1 Hz 1H, 6-H), 7.34 (ddd, ^4J (5-H, 7-H) = 1.4 Hz, ^3J (6-H, 7-H) = 7.3 Hz, ^3J (7-H, 8-H) = 7.3 Hz, 1H, 7-H), 7.45 (s, 1H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8 (CH_3), 46.2 (C-1), 111.7 (C-6′), 115.6 (C-2′), 122.1 (C-4′), 124.5 (C-5), 125.6 (C-4a), 125.7 (C-8), 128.1 (C-6), 128.8 (C-5′), 129.2 (C-8a), 130.2 (C-7), 136.0 (C-4), 138.8 (C-3′), 147.0 (C-1′); MS (EI, 70 eV) *m*/*z* 222 (100) $[M]^+$, 207 (38) $[M - CH_3]^+$; HRMS (EI, M^+) calcd for $C_{15}H_{14}N_2$ (222.1157), found 222.1140.

*2-(4-Methylphenyl)-1,2-dihydrophthalazine (**3c**).* According to the general procedure, a mixture of K_2CO_3 (138 mg, 1 mmol), 2-



(bromomethyl)benzaldehyde (**1a**) (99.5 mg, 0.5 mmol), 4-methylphenylhydrazine (**2c**) (61 mg, 0.5 mmol), and $FeCl_3$ (4 mg, 5 mol %) in dry CH_3CN (2 mL) was reacted for 22 h. Flash chromatography over silica gel (cyclohexane/Et_2O = 20:1) gave **3c** as a pale yellow solid in 89% yield (99 mg, 0.45 mmol): mp 102−103 °C; R_f = 0.52 (cyclohexane/Et_2O = 5:1); IR (ATR) ν 1600 (C═N), 1512, 1450, 1394, 1276, 1259, 1138, 903, 7987, 751, 715 cm^{-1}; UV (MeCN) λ_{max} (log ε) 363 (4.04), 249 (4.18) nm; ^1H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H, CH_3), 4.78 (s, 2H, 1-H), 7.14 (d, ^3J (7-H, 8-H) = 7.0 Hz, 1H, 8-H), 7.16−7.18 (m, 2H, 3′-H, 5′-H), 7.20−7.23 (m, 3H, 2′-H, 5-H, 6′-H), 7.31 (ddd, ^4J (6-H, 8-H) = 1.5 Hz, ^3J (5-H, 6-H) = 7.2 Hz, ^3J (6-H, 7-H) = 7.2 Hz 1H, 6-H), 7.35 (ddd, ^4J (5-H, 7-H) = 1.4 Hz, ^3J (6-H, 7-H) = 7.1 Hz, ^3J (7-H, 8-H) = 7.1 Hz, 1H, 7-H), 7.45 (s, 1H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (CH_3), 46.4 (C-1), 114.8 (C-2′, C-6′), 124.5 (C-5), 125.65 (C-4a), 125.70 (C-8), 128.1 (C-6), 129.2 (C-8a), 129.5 (C-3′, C-5′), 130.1 (C-7), 130.6 (C-4′), 135.8 (C-4), 144.9 (C-1′); MS (EI, 70 eV) *m*/*z* (%) 222 (44) $[M]^+$, 207 (3) $[M - CH_3]^+$ 193 (6), 165 (7); HRMS (EI, M^+) calcd for $C_{15}H_{14}N_2$ (222.1157), found 222.1144.

*2-(2,4-Dimethylphenyl)-1,2-dihydrophthalazine (**3d**).* According to the general procedure, a mixture of K_2CO_3 (138 mg, 1 mmol), 2-



(bromomethyl)benzaldehyde (**1a**) (99.5 mg, 0.5 mmol), 2,4-dimethylphenylhydrazine (**2d**) (68 mg, 0.5 mmol), and $FeCl_3$ (4 mg, 5 mol %) in dry CH_3CN (2 mL) was reacted for 23 h. Flash chromatography over silica gel (cyclohexane/Et_2O = 20:1) to give **3d** as a pale yellow oil in 84% yield (99 mg, 0.42 mmol): R_f = 0.52 (cyclohexane/Et_2O = 5:1); IR (ATR) ν 1610 (C═N), 1452, 1376, 1224, 1110, 904, 808, 757, 729 cm^{-1}; UV (MeCN) λ_{max} (log ε) = 321 (4.02), 238 nm (4.21); ^1H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 6H, CH_3), 4.38 (s, 2H, 1-H), 7.07 (brs, 1H, 3′-H), 7.10 (brd, ^3J (5′-H, 6′-H) = 8.0 Hz, 1H, 5′-H), 7.11−7.12 (m, 1H, 8-H), 7.20−7.22 (m, 1H, 5-H), 7.31 (d,^3J (5′-Ha, 6′-H) = 7.7 Hz, 1H, 6′-H), 7.34 (ddd, ^4J (6-H, 8-H) = 1.7 Hz, ^3J (5-H, 6-H) = 7.7 Hz, ^3J (6-H, 7-H) = 7.7 Hz, 1H, 6-H), 7.36 (ddd, ^4J (5-H, 7-H) = 1.7 Hz, ^3J (6-H, 7-H) = 7.6 Hz, ^3J (7-H, 8-H) = 7.6 Hz 1H, 7-H), 7.59 ppm (brs, 1H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0 (C-2″), 20.8 (C-4″), 50.8 (C-1), 122.7 (C-6′), 124.0 (C-5), 125.1 (C-8), 126.1 (C-4a), 127.3 (C-5′) 128.0 (C-6), 130.0 (C-7), 130.4 (C-8a), 131.8 (C-3′), 132.7 (C-2′ or C-4′), 134.8 (C-2′ or C-4′), 138.2 (C-4), 145.7 (C-1′); MS (EI, 70 eV) *m*/*z* (%)

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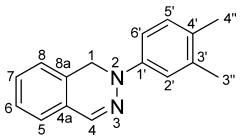
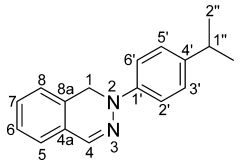
236 (100) $[M]^+$, 221 (100) $[M - CH_3]^+$, 206 (3) $[221 - CH_3]^+$; HRMS (EI, M^+) calcd for $C_{16}H_{16}N_2$ (236.1313), found 236.1340.

*2-(3,4-Dimethylphenyl)-1,2-dihydrophthalazine (**3e**).* According to the general procedure, a mixture of K_2CO_3 (138 mg, 1 mmol), 2-



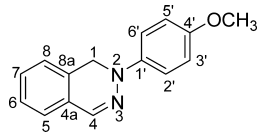
(bromomethyl)benzaldehyde (**1a**) (99.5 mg, 0.5 mmol), 3,4-dimethylphenylhydrazine (**2e**) (68 mg, 0.5 mmol), and $FeCl_3$ (4 mg, 5 mol %) in dry CH_3CN (2 mL) was reacted for 23 h. Flash chromatography over silica gel (cyclohexane/Et_2O = 20:1) gave **3e** as a pale yellow solid in 82% yield (97 mg, 0.41 mmol): mp 84−85 °C ; R_f = 0.36 (cyclohexane/Et_2O = 5:1); IR (ATR) ν 1588 (C═N), 1499, 1451, 1395, 1380, 1323, 1226, 1142, 1104, 910, 862, 795, 752, 715 cm^{-1}; UV (MeCN) λ_{max} (log ε) = 364 (4.08), 248 (4.23) nm; ^1H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 3H, 4″-H), 2.35 (s, 3H, 3″-H), 4.86 (s, 2H, 1-H), 7.05 (dd, ^4J (2′-H, 6′-H) = 2.7 Hz, ^3J (5′-H, 6′-H) = 8.3 Hz, 1H, 6′-H), 7.15 (brd, ^3J (7-H, 8-H) = 8.3 Hz, 1H, 8-H), 7.16 (d, ^3J (5′-Ha, 6′-H) = 8.3 Hz, 1H 5′-H), 7.20 (dd, ^4J (5-H, 7-H) = 1.3 Hz, ^3J (5-Ha, 6-H) = 10.0 Hz, 1H, 5-H), 7.21 (brs, 1H, 2′-H), 7.32 (ddd, ^4J (6-H, 8-H) = 1.7 Hz, ^3J (5-H, 6-H) = 7.3 Hz, ^3J (6-H, 7-H) = 7.3 Hz, 1H, 6-H), 7.36 (ddd, ^4J (5-H, 7-H) = 1.8 Hz, ^3J (6-H, 7-H) = 7.3 Hz, ^3J (7-H, 8-H) = 7.3 Hz, 1H, 7-H), 7.48 (s, 1H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9 (C-4″), 20.2 (C-3″), 46.3 (C-1), 112.0 (C-6′), 116.4 (C-2′), 124.3 (C-5), 125.60 (C-4a), 125.62 (C-8) 128.0 (C-6), 129.15 (C-8a), 129.30 (C-4′), 129.92 (C-5′), 129.94 (C-7), 135.5 (C-4), 137.1 (C-3′), 145.2 (C-1′); MS (EI, 70 eV) *m*/*z* (%) 236 (92) $[M]^+$, 221 (5) $[M - CH_3]^+$, 206 (3) $[221 - CH_3]^+$ 192 (4); HRMS (EI, M^+) calcd for $C_{16}H_{16}N_2$ (236.1313), found 236.1304.

*2-(4-Isopropylphenyl)-1,2-dihydrophthalazine (**3f**).* According to the general procedure, a mixture of K_2CO_3 (138 mg, 1 mmol), 2-



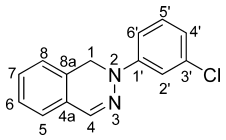
(bromomethyl)benzaldehyde (**1a**) (99.5 mg, 0.5 mmol), 3-isopropylphenylhydrazine (**2f**) (75 mg, 0.5 mmol), and $FeCl_3$ (4 mg, 5 mol %) in dry CH_3CN (2 mL) was reacted for 22 h. Flash chromatography over silica gel (cyclohexane/Et_2O = 20:1) gave **3f** as a pale yellow solid in 78% yield (98 mg, 0.39 mmol): mp 108−109 °C; R_f = 0.53 (cyclohexane/Et_2O = 3:1); IR (ATR) ν 1606 (C═N), 1560, 1510, 1451, 1392, 1135, 1110, 829, 805, 755, 718 cm^{-1}; UV (MeCN) λ_{max} (log ε) = 351 (4.08), 249 (4.25) nm; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, ^3J (1″-H, 2″-H) = 7.0 Hz, 6H, 2″-H), 2.89 (m, 1H, 1″-H), 4.77 (s, 2H, 1-H), 7.12 (d, ^3J (7-H, 8-H) = 7.1 Hz, 1H, 8-H), 7.17 (dd, ^4J (5-H, 7-H) = 1.4 Hz, ^3J (5-H, 6-H) = 7.3 Hz, 1H, 5-H), 7.21−7.25 (m, 4H, 2′-H, 3′-H, 5′-H and 6′-H,), 7.29 (ddd, ^4J (6-H, 8-H) = 1.4 Hz, ^3J (5-H, 6-H) = 7.4 Hz, ^3J (6-H, 7-H) = 7.4 Hz, 1H, 6-H), 7.33 (ddd, ^4J (5-H, 7-H) = 1.5 Hz, ^3J (6-H, 7-H) = 7.3 Hz, ^3J (7-H, 8-H) = 7.3 Hz, 1H, 7-H), 7.44 (s, 1H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1 (C-2″), 33.3 (C-1″), 46.3 (C-1), 114.8 (C-2′, C-6′), 124.4 (C-5), 125.6 (C-4a), 125.7 (C-8), 126.9 (C-3′, C-5′), 128.1 (C-6), 129.2 (C-8a), 130.0 (C-7), 135.7 (C-4), 141.8 (C-4′), 145.1 (C-1′); MS (EI, 70 eV) *m*/*z* 250 (88) $[M]^+$, 249 (100) $[M - 1]^+$, 235 (6) $[M - CH_3]^+$ 205 (6); HRMS (EI, M^+) calcd for $C_{17}H_{18}N_2$ (250.1470), found 250.1456.

*2-(4-Methoxyphenyl)-1,2-dihydrophthalazine (**3g**).*[9] According to the general procedure, a mixture of K_2CO_3 (138 mg, 1 mmol), 2-(bromomethyl)benzaldehyde (**1a**) (99.5 mg, 0.5 mmol), 4-methoxyphenylhydrazine (**2g**) (69 mg, 0.5 mmol), and $FeCl_3$ (4 mg, 5 mol %) in dry CH_3CN (2 mL) was reacted in a sealed vial at 100 °C for 22 h. Flash chromatography over silica gel (cyclohexane/Et_2O = 15:1) gave **3g** as a pale yellow solid in 91% yield (108 mg, 0.45 mmol): mp 131−



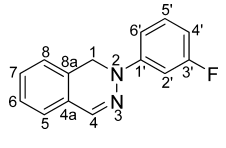
132 °C (lit.[9] mp 132−133 °C); R_f = 0.31 (cyclohexane/Et_2O = 5:1); IR (ATR) ν 1603 (C═N), 1506, 1448, 1277, 1225, 1184, 1134, 1034, 816, 754, 717 cm^{-1}; UV (MeCN) λ_{max} (log ε) 366 (4.12), 248 (4.31) nm; ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 3H, OCH_3), 4.74 (s, 2H, 1-H), 6.90−6.94 (m, 2H, 3′-H, 5′-H), 7.13 (d, ^3J (7-H, 8-H) = 7.9 Hz, 1H, 8-H), 7.18 (dd, ^4J (5-H, 7-H) = 1.5 Hz, ^3J (5-H, 6-H) = 7.4 Hz, 1H, 5-H), 7.23−7.26 (m, 2H, 2′-H, 6′-H), 7.31 (ddd, ^4J (6-H, 8-H) = 1.4 Hz, ^3J (5-H, 6-H) = 7.4 Hz, ^3J (6-H, 7-H) = 7.4 Hz 1H, 6-H), 7.34 (ddd, ^4J (5-H, 7-H) = 1.4 Hz, ^3J (6-H, 7-H) = 7.4 Hz, ^3J (7-H, 8-H) = 7.3 Hz, 1H, 7-H), 7.45 (s, 1H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.9 (C-1), 55.6 (OCH_3), 114.3 (C-3′, C-5′), 116.4 (C-2′, C-6′), 124.3 (C-5), 125.64 (C-8), 125.67 (C-4a), 128.1 (C-6), 129.1 (C-8a), 130.0 (C-7), 135.9 (C-4), 141.4 (C-1′), 154.7 (C-4′); MS (EI, 70 eV) *m*/*z* (%) 238 (96) $[M]^+$, 223 (12) $[M - CH_3]^+$, 205 (6), 193 (4), 167 (5); HRMS (EI, M^+) calcd for $C_{15}H_{14}N_2O$ (238.1106), found 238.1117.

*2-(3-Chlorophenyl)-1,2-dihydrophthalazine (**3h**).* According to the general procedure, a mixture of K_2CO_3 (138 mg, 1 mmol), 2-



(bromomethyl)benzaldehyde (**1a**) (99.5 mg, 0.5 mmol), 3-chlorophenylhydrazine (**2h**) (71 mg, 0.5 mmol), and $FeCl_3$ (4 mg, 5 mol %) in dry CH_3CN (2 mL) was reacted for 22 h. Flash chromatography over silica gel (cyclohexane/Et_2O = 15:1) gave **3h** as a pale yellow solid in 78% yield (95 mg, 0.39 mmol): mp 106−107 °C; R_f = 0.49 (cyclohexane/Et_2O = 5:1); IR (ATR) ν 1600 (C═N), 1560, 1452, 1390, 1392, 1323, 1275, 1137, 1003, 906, 850, 716 cm^{-1}; UV (MeCN) λ_{max} (log ε) 356 (4.07), 250 (4.16) nm; ^1H NMR (300 MHz, $CDCl_3$) δ 4.79 (s, 2H, 1-H), 6.94−6.96 (m, 1H, 4′-H), 7.14−7.18 (m, 2H, 6′-H, 8-H), 7.21 (brd, ^3J (5-H, 6-H) = 7.3 Hz 1H, 5-H,), 7.26 (dd, ^3J (4′-H, 5′-H) = 7.3 Hz, ^3J (5′-H, 6′-H) = 7.3 Hz, 1H, 5′-H), 7.30−7.34 (m, 2H, 2′-H, 6-H), 7.37 (ddd, ^4J (5-H, 7-H) = 1.4 Hz, ^3J (6-H, 7-H) = 7.4 Hz, ^3J (7-H, 8-H) = 7.4 Hz, 1H, 7-H), 7.46 (s, 1H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.0 (C-1), 112.4 (C-6′), 114.6 (C-2′), 120.8 (C-4′), 124.9 (C-5), 125.2 (C-4a), 125.8 (C-8), 128.3 (C-6), 129.0 (C-8a), 129.9 (C-5′), 130.5 (C-7), 134.9 (C-3′), 136.7 (C-4), 148.0 (C-1′); MS (EI, 70 eV) *m*/*z* 242 (46) $[M]^+$, 241 (100) $[M - 1]^+$, 206 (4); HRMS (EI, M^+) calcd for $C_{14}H_{11}ClN_2$ (242.0611), found 242.0586.

*2-(3-Fluorophenyl)-1,2-dihydrophthalazine (**3i**).* According to the general procedure, a mixture of K_2CO_3 (138 mg, 1 mmol), 2-



(bromomethyl)benzaldehyde (**1a**) (99.5 mg, 0.5 mmol), 3-fluorophenylhydrazine (**2i**) (63 mg, 0.5 mmol), and $FeCl_3$ (4 mg, 5 mol %) in dry CH_3CN (2 mL) was reacted for 24 h. Flash chromatography over silica gel (cyclohexane/Et_2O = 15:1) gave **3i** as a pale yellow solid in 69% yield (78 mg, 0.35 mmol): mp 116−117 °C; R_f = 0.46 (cyclohexane/Et_2O = 5:1); IR (ATR) ν 1587 (C═N), 1563, 1454, 1330, 1224, 1162, 1103, 911, 861, 756, 718 cm^{-1}; UV (MeCN) λ_{max} (log ε) 356 (3.97), 248 (4.11) nm; ^1H NMR (300 MHz, $CDCl_3$) δ 4.79 (s, 2H, 1-H), 6.65−6.70 (m, 1H, 4′-H), 7.01−7.04 (m, 1H, 6′-H), 7.05−7.07 (m, 1H, 2′-H), 7.14 (d, ^3J (7-H, 8-H) = 7.4 Hz, 1H, 8-H), 7.20 (dd, ^4J (5-H, 7-H) = 1.3 Hz, ^3J (5-H, 6-H) = 7.4 Hz 1H, 5-H,), 7.27−7.30 (m, 1H, 5′-H), 7.32 (ddd, ^4J (6-H, 8-H) = 1.1 Hz, ^3J (5-H,

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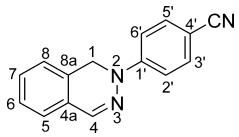
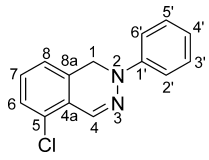
6-H) = 7.4 Hz, ^3J (6-H, 7-H) = 7.4 Hz, 1H, 6-H), 7.37 (ddd, ^4J (5-H, 7-H) = 1.3 Hz, ^3J (6-H, 7-H) = 7.4 Hz, ^3J (7-H, 8-H) = 7.4 Hz, 1H, 7-H), 7.46 (s, 1H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.0 (C-1), 101.9 (d, $^2J_{CF}$ = 26.9 Hz, C-2′), 107.5 (d, $^2J_{CF}$ = 21.9 Hz, C-4′), 109.5 (d, $^4J_{CF}$ = 2.9 Hz, C-6′), 124.9 (C-5), 125.2 (C-4a), 125.8 (C-8), 128.3 (C-6), 129.0 (C-8a), 130.0 (d, $^3J_{CF}$ = 9.8 Hz, C-5′), 130.5 (C-7), 136.5 (C-4), 148.6 (d, $^3J_{CF}$ = 10.8 Hz, C-1′), 163 (d, $^1J_{CF}$ = 163.7 Hz, C-3′); MS (EI, 70 eV) m/z (%) 226 (26) $[M]^+$, 197 (4), 170 (5), 151 (5); HRMS (EI, M^+) calcd for $C_{14}H_{11}FN_2$ (226.0906), found 226.0891.

*2-(4-Cyanophenyl)-1,2-dihydrophthalazine (**3j**).* According to the general procedure, a mixture of K_2CO_3 (138 mg, 1 mmol), 2-



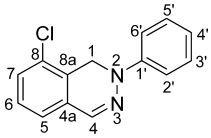
(bromomethyl)benzaldehyde (**1a**) (99.5 mg, 0.5 mmol), 4-cyanophenylhydrazine (**2j**) (67 mg, 0.5 mmol), and $FeCl_3$ (4 mg, 5 mol %) in dry CH_3CN (2 mL) was reacted for 27 h. Flash chromatography over silica gel (cyclohexane/Et_2O = 5:1) gave **3j** as a white solid in 63% yield (73 mg, 0.31 mmol): mp 166−167 °C; R_f = 0.14 (cyclohexane/Et_2O = 3:1); IR (ATR) ν 2220 (C≡N), 1600 (C═N), 1507, 1451, 1390, 1317, 1224, 1179, 1137, 1107, 900, 865, 831, 805, 762 cm^{-1}; UV/vis (MeCN) λ_{max} (log ε) 363 (4.53), 280 (4.11), 244 (1.39) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.95 (s, 2H, 1-H), 7.30 (d, ^3J (7-H, 8-H) = 7.8 Hz, 1H, 8-H), 7.30−7.38 (m, 2H, 5-H, 6-H), 7.43 (d, ^3J (2′-H, 3′-H) = 8.6 Hz, 2H, 2′-H, 6′-H), 7.45 (d, ^3J (2′-H, 3′-H) = 8.2 Hz, 2H, 3′-H, 5′-H), 7.45−7.48 (m, 1H, 7-H), 7.70 (s, 1H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.7 (C-1), 101.3 (C-4′), 114.0 (C-2′, 6′-C), 119.7 (CN), 124.2 (C-4a), 125.4 (C-5), 126.1 (C-8), 128.3 (C-6), 129.2 (C-8a), 131.1 (C-7), 133.2 (C-3′, 5′-H), 138.6 (C-4), 149.5 (C-1′); MS (EI, 70 eV) m/z (%) 233 (42) $[M]^+$, 205 (6), 177 (5), 151 (5); HRMS (EI, M^+) calcd for $C_{15}H_{11}N_3$ (233.0953), found 233.0936.

*5-Chloro 2-phenyl-1,2-dihydrophthalazine (**3k**).* According to the general procedure, a mixture of K_2CO_3 (138 mg, 0.5 mmol), 2-



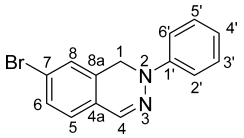
(bromomethyl)-6-chlorobenzaldehyde (**1b**) (117 mg, 0.5 mmol), phenylhydrazine (**2a**) (54 mg, 0.5 mmol), and $FeCl_3$ (4 mg, 5 mol %) in dry CH_3CN (2 mL) was reacted for 22 h. Flash chromatography over silica gel (cyclohexane/Et_2O = 5:1) gave **3k** as a pale yellow solid in 74% yield (90 mg, 0.37 mmol): mp 86−87 °C; R_f = 0.24 (cyclohexane/Et_2O = 5:1); IR (ATR) ν 1592 (C═N), 1497, 1445, 1397, 1313, 1133, 946, 808, 782, 687 cm^{-1}; UV/vis (MeCN) λ_{max} (log ε) 370 (4.01), 252 (4.16) nm; ^{1}H NMR[16] (300 MHz, $CDCl_3$) δ 4.75 (s, 2H, 1-H), 6.98 (d, ^3J (7-H, 8-H) = 7.5 Hz, 1H, 8-H), 7.01 (t-like, ^3J (3′-H, 4′-H) = 7.1 Hz, 1H, 4′-H), 7.21 (dd, ^3J (6-H, 7-H) = 8.1 Hz, ^3J (7-H, 8-H) = 8.1 Hz 1H, 7-H), 7.28 (d, ^3J (6-H, 7-H) = 8.5 Hz, 1H, 6-H), 7.29 (d-like, ^3J (2′-H, 3′-H) = 8.7 Hz, 2H, 2′-H, 6′-H), 7.33 (brt-like, ^3J (2′-H, 3′-H) = 8.3 Hz, 2H, 3′-H, 5′-H), 7.81 (s, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.8 (C-1), 114.9 (C-2′, C-6′), 121.7 (C-4′), 123.0 (C-4a), 124.3 (C-8), 129.0 (C-3′, C-5′), 129.1 (C-6), 130.4 (C-5 or C-8a), 130.7 (C-7),, 130.8 (C-5 or C-8a), 132.3 (C-4), 146.5 (C-1′); MS (EI, 70 eV) m/z (%) 242 (100) $[M]^+$, 202 (4), 179 (8); HRMS (EI, M^+) calcd for $C_{14}H_{11}ClN_2$ (242.0611), found 242.0594.

*8-Chloro-2-phenyl-1,2-dihydrophthalazine (**3l**).* According to the general procedure, a mixture of K_2CO_3 (138 mg, 0.5 mmol), 2-



(bromomethyl)-3-chlorobenzaldehyde[15] (**1c**) (117 mg, 0.5 mmol), phenylhydrazine (**2a**) (54 mg, 0.5 mmol), and $FeCl_3$ (4 mg, 5 mol %) in dry CH_3CN (2 mL) was reacted for 22 h. Flash chromatography over silica gel (cyclohexane/Et_2O = 5:1) gave **3l** as a pale yellow solid in 70% yield (82 mg, 0.35 mmol): mp 91−92 °C; R_f = 0.26 (cyclohexane/Et_2O = 5:1); IR (ATR) ν 1597 (C═N), 1545, 1445, 1132, 919, 848, 775, 751 cm^{-1}; UV/vis (MeCN) λ_{max} (log ε) 371 (3.94), 252 (4.13) nm; ^{1}H NMR[16] (300 MHz, $CDCl_3$) δ 4.87 (s, 2H, 1-H), 7.02 (d-like, ^3J (3′-H, 4′-H) = 7.4 Hz, 1H, 4′-H), 7.03 (d, ^3J (5-H, 6-H) = 8.1 Hz, 1H, 5-H), 7.21 (dd, ^3J (5-H, 6-H) = 8.4 Hz, ^3J (6-H, 7-H) = 8.3 Hz 1H, 6-H), 7.32 (d, ^3J (6-H, 7-H) = 8.2 Hz, 1H, 7-H), 7.33 (brd-like, ^3J (2′-H, 3′-H) = 8.3 Hz, 2H, 2′-H, 6′-H), 7.34 (s, 1H, 4-H), 7.36 (brd-like, ^3J (2′-H, 3′-H) = 8.1 Hz, 2H, 3′-H, 5′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.6 (C-1), 114.4 (C-2′, C-6′), 121.4 (C-4′), 122.8 (C-5), 127.07 (C-8a), 127.14 (C-4a or C-8), 128.97 (C-6), 129.0 (C-3′, C-5′), 130.2 (C-7), 131.6 (C-4a or C-8), 134.1 (C-4), 146.5 (C-1′); MS (EI, 70 eV) m/z (%) 242 (76) $[M]^+$, 179 (8); HRMS (EI, M^+) calcd for $C_{14}H_{11}ClN_2$ (242.0611), found 242.0590.

*7-Bromo-2-phenyl-1,2-dihydrophthalazine (**3m**).* According to the general procedure, a mixture of K_2CO_3 (138 mg, 0.5 mmol), 4-



bromo-2-(bromomethyl)benzaldehyde[15] (**1d**) (139 mg, 0.5 mmol), phenylhydrazine (**2a**) (54 mg, 0.5 mmol), and $FeCl_3$ (4 mg, 5 mol %) in dry CH_3CN (2 mL) was reacted for 20 h. Flash chromatography over silica gel (cyclohexane/Et_2O = 5:1) gave **3m** as a pale yellow solid in 60% yield (86 mg, 0.30 mmol): mp 116−117 °C; R_f = 0.32 (cyclohexane/Et_2O = 5:1); IR (ATR) ν 1597 (C═N), 1562, 1387, 1308, 1136, 904, 868, 818, 747, 688 cm^{-1}; UV/vis (MeCN) λ_{max} (log ε) 370 (4.02), 250 (4.20) nm; ^{1}H NMR[16] (300 MHz, $CDCl_3$) δ 4.77 (s, 2H, 1-H), 7.04 (t-like, ^3J (3′-H, 4′-H) = 8.7 Hz, 1H, 4′-H), 7.06 (d, ^3J (5-H, 6-H) = 8.4 Hz, 1H, 5-H), 7.28 (brd-like, ^3J (2′-H, 3′-H) = 8.5 Hz, 2H, 2′-H, 6′-H), 7.30 (brs, 1H, 8-H), 7.36 (t-like, ^3J (2′-H, 3′-H) = 8.5 Hz, 2H, 3′-H, 5′-H), 7.41 (s, 1H, 4-H), 7.42 (dd, ^4J (6-H, 8-H) = 1.8 Hz, ^3J (5-H, 6-H) = 8.1 Hz, 1H, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.6 (C-1), 114.7 (C-2′, C-6′), 121.5 (C-4′), 123.8 (C-7), 124.3 (C-4a), 125.9 (C-5), 128.9 (C-8), 129.0 (C-3′, C-5′), 130.8 (C-8a), 131.3 (C-6), 135.0 (C-4), 146.7 (C-1′); MS (EI, 70 eV) m/z (%) 287 (12) $[M]^+$, 207 (4), 179 (6); HRMS (EI, M^+) calcd for $C_{14}H_{11}BrN_2$ (286.0106), found 286.0090.

■ ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectra for all compounds. 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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