

## Late-stage functionalization of 4-arylphthalazin-1(2H)-ones by a regioselective iridium-catalyzed C-H bond amidation reaction

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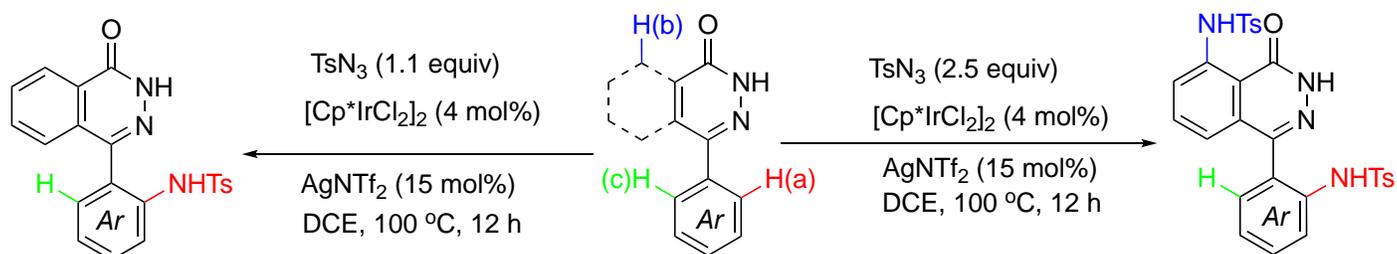
Received 07-11-2023

Accepted Manuscript 08-27-2023

Published on line 08-31-2023

### Abstract

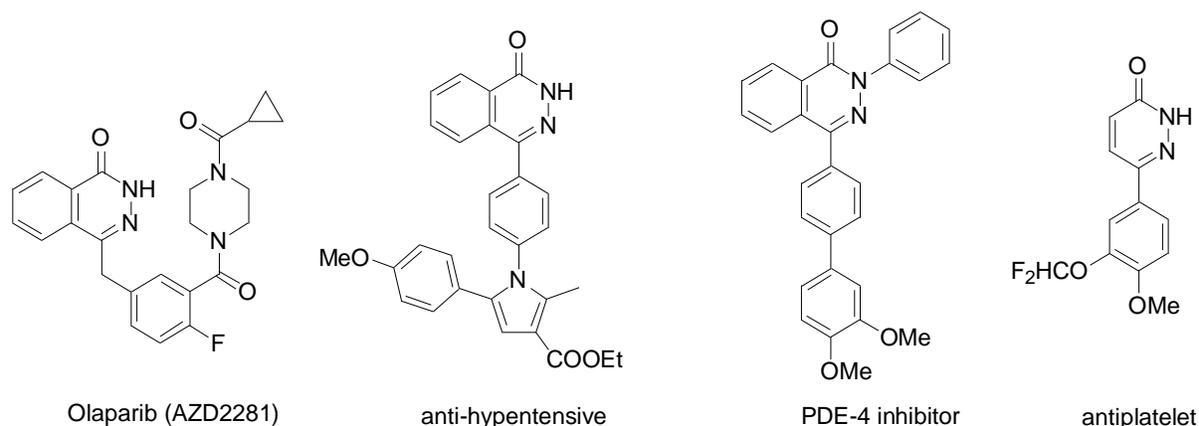
Herein, we demonstrate the viability of late-stage diversification of 4-arylphthalazin-1(2H)-one through iridium-catalyzed C-H bond amidation. These are an important class of heterocycles owing to their pharmacological potential. Notably, the amidation was conducted with excellent regioselectivity, and the mono-/diamidated products were obtained in good to high yields by simply controlling the ratio of substrates, respectively. This protocol features operational simplicity, a broad substrate scope, and good functional group tolerance.



**Keywords:** late-stage functionalization, iridium-catalyzed, C-H bond amidation, 4-arylphthalazin-1(2H)-one

## Introduction

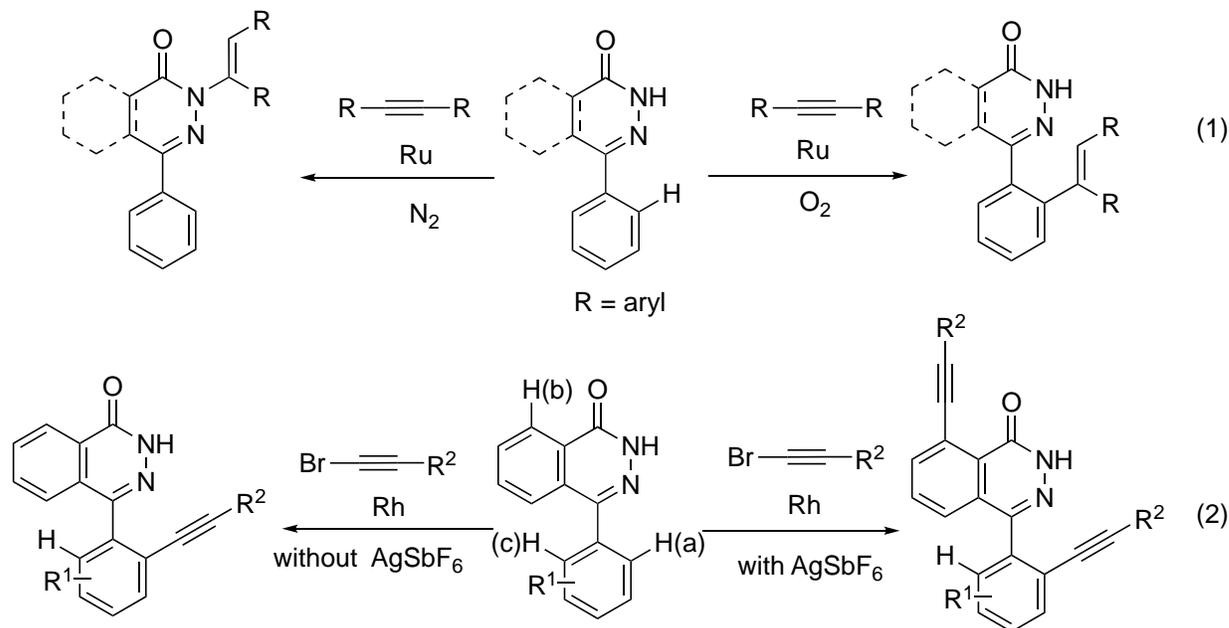
Late-stage functionalization of complex molecules and lead compounds *via* regioselective C–H bond functionalization currently represents a very hot topic in organic synthesis as it allows a fast tuning of the physical or biological properties in material and medical science.<sup>1–8</sup> Notably, the direct transformation of C–H bonds provides a short reaction sequence and previously unachievable synthetic disconnections compared with classical organic synthesis, thus rendering synthetic routes more straightforward and atom-economical. For example, Yu and co-workers disclosed the late-stage diversification of a sulfonamide drug candidate containing multiple potentially reactive C–H bonds, to directly synthesize six categorically distinct analogues as potential cyclooxygenase-II (COX-2)-specific inhibitors.<sup>9</sup> Lutz Ackermann and co-workers developed a novel manganese(I)-catalyzed C–H allylation strategy towards decorated peptides, nucleotides and drug molecules and a plethora of sensitive functional groups, were fully tolerated. The strategy is a viable tool for peptide assembly and diversification as well as the bioorthogonal assembly of hybrid and stapled peptides.<sup>10</sup> Recently, Dai and coworkers reported the convergent total synthesis of (±)-hamigeran M, enabled by five late-stage C–H functionalization reactions and proceeding in 11 steps in 3.9% overall yield.<sup>11</sup> In addition, Goto and co-workers successfully developed late-stage functionalization of the periphery of oligophenylene dendrimers with various arene units via fourfold C–H borylation.<sup>12</sup> Despite the large advances achieved, LSF strategies are still in their infancy and a number of challenges remain because of regio-(chemo)selectivity and functional group compatibility.<sup>13</sup>



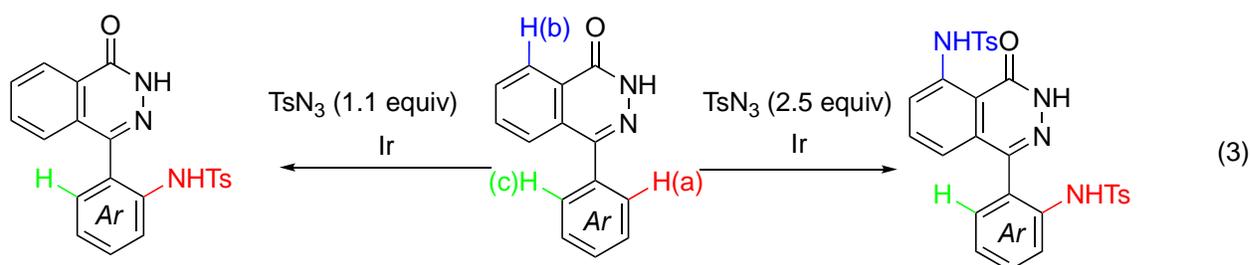
**Figure 1.** Selected examples of drugs and bioactive molecules containing a pyridazin-3(2H)-one motif.

Phthalazin-1(2H)-one and its analogues pyridazin-3(2H)-one are an important class of heterocycles and have gained more attention in the design and synthesis of novel drugs owing to their pharmacological potential,<sup>14–22</sup> as shown in Figure 1. Especially, Olaparib is a single digit nanomolar inhibitor of both PARP-1 and PARP-2 that shows stand-alone activity against BRCA1-deficient breast cancer cell lines and currently is a drug for the treatment of lung cancers.<sup>23</sup> In this regard, development of a late-stage C–H functionalization of 4-aryl phthalazin-1(2H)-one or its analogues would be valuable for their application in medicinal chemistry. Recently, Xu et al. developed a ruthenium-catalyzed switchable N–H/C–H alkenylation reaction of 6-aryl pyridazin-3(2H)-ones with alkynes under different reaction conditions (Scheme 1, eq 1).<sup>24</sup> More recently, our laboratory also realized Rh(III)-catalyzed alkynylation of 4-phenylphthalazin-1(2H)-ones, and the regioselective mono and dialkynylation was controlled by adding a catalytic amount of AgSbF<sub>6</sub> (Scheme 1, eq 2).<sup>25</sup>

## Previous work



## Present work



**Scheme 1.** Transition-metal-catalyzed late-stage functionalization of 4-aryl phthalazin-1(2H)-ones.

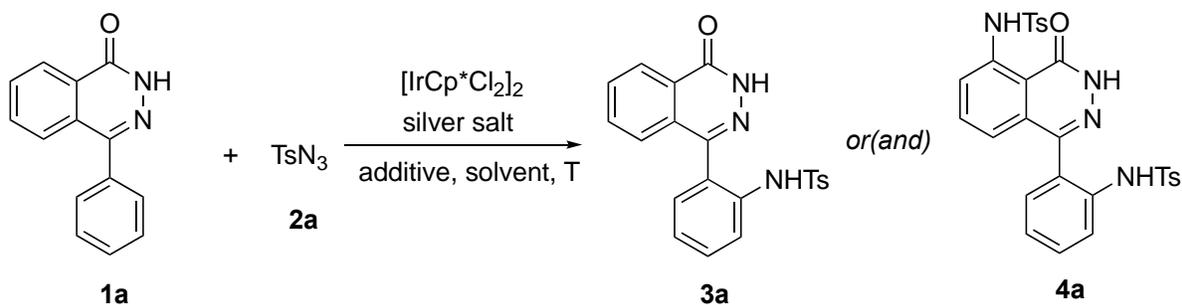
Given the practical importance of phthalazin-1(2H)-one and its analogues and derivatives in medicinal chemistry and polymeric materials discovery, the development of novel transformations to obtain various functionalized phthalazin-1(2H)-one derivatives is still highly desirable. Therefore, we were attracted to probing late-stage C–H bond functionalization of 4-arylphthalazin-1(2H)-one (Scheme 1, eq 3), notable features of our findings include efficient regioselective mono or diamidation in different arene cycles with  $\text{TsN}_3$ . This strategy could not only provide an additional example of DG-directed C–H activation, but also offer a late-stage structural diversification on the biologically interesting privileged scaffolds.

## Results and Discussion

Inspired by recently reported Ir(III)-catalyzed direct C–H amidation,<sup>26,27</sup> our study commenced with the reaction of 4-phenylphthalazin-1(2H)-one (**1a**) with  $\text{TsN}_3$  (**2a**) catalyzed by  $[\text{Cp}^*\text{IrCl}_2]_2$  (Table 1) in the presence of  $\text{AgNTf}_2$  (15 mol %) in 1,2-dichloroethane (DCE) at 100 °C for 12 h under air. The reaction proceeded smoothly and the monoamidation product **3a** was obtained in 54% yield, along with the diamidation product

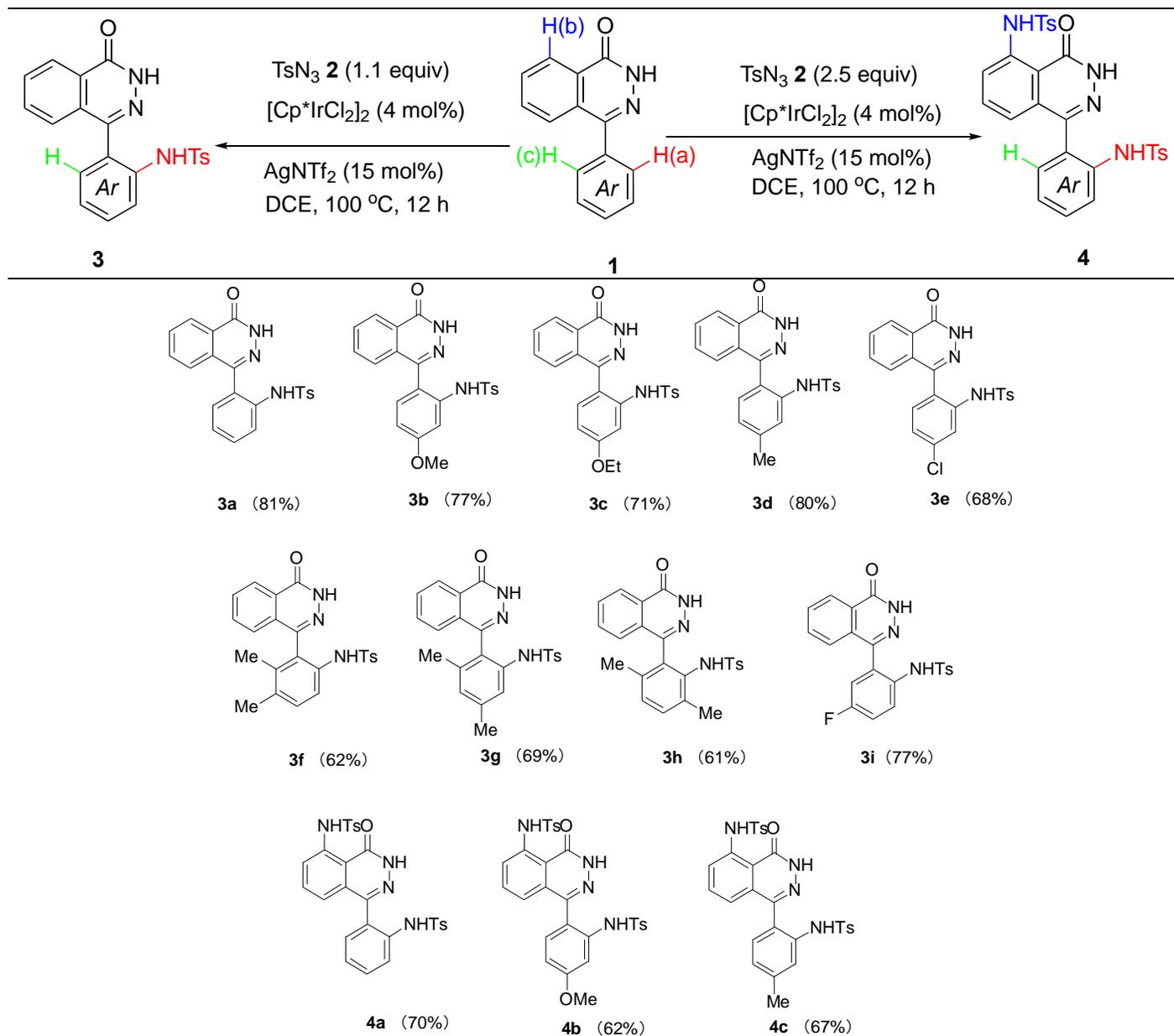
**4a** in 8% yield (Table 1, entry 1). To our delight, addition of HOAc (1 equiv) resulted in a higher yield of 81%, and only a trace amount of diamination product (entry 2). It is noteworthy that the corresponding diamidated product at C-H(c) position was not discovered, perhaps due to the distorted coplanar geometry arising from the steric repulsion which weakens the interaction between the Ir catalyst and proximate aromatic C-H bond. Next, we screened various silver salts under the similar conditions. Among various silver salts tested, AgNTf<sub>2</sub> gave the best yield (entries 3-9). Moderate yields were obtained when Li<sub>2</sub>CO<sub>3</sub> is used as additive (Table 1, entry 10). Subsequently, various solvents were tested, and DCE proved to be superior from a range of solvents (1,4-dioxane, toluene, and DMF) (Table 1, entries 11-13). Control experiments revealed that no reaction occurred without of silver salt, showing that the silver salt is essential for this transformation (Table 1, entry 14). Temperature also has a great impact on this reaction; the product **3a** was obtained in 63% yield at 80 °C (Table 1, entry 15). When the temperature was increased to 120 °C, a slightly decreased yield of **3a** was the result, and the corresponding diamination product **4a** was detected in 13% yield (Table 1, entry 16). Decreasing the catalyst loading to 2 mol % gave inferior results (Table 1, entry 17), while a similar yield was obtained with 6 mol % of [Cp\*IrCl<sub>2</sub>]<sub>2</sub> (Table 1, entry 18). Interestingly, the desired product **4a** was obtained in 68% yield, along with only 13% of the monoamidation product **3a**, when 2.2 equiv of TsN<sub>3</sub> (**2a**) was added (Table 1, entry 19). When we further increased the amount of TsN<sub>3</sub> (**2a**) to 2.5 equiv, the diamidation product **4a** was obtained as the major product, in 77% yield, and there was just a trace amount of monoamidation product (Table 1, entry 20).

With the optimized reaction conditions in hand, we next explored the scope of 6-aryl pyridazin-3(2*H*)-one (**1**) with TsN<sub>3</sub> (1.1 equiv) under the optimized reaction conditions (Table 1, entry 2). To our delight, substrates (**1**) containing either an electron-donating group (OMe, OEt, and Me) or an electron-withdrawing group (Cl) at on the *para*-position provided the desired products in 68-80% yields (**3b-e**). Furthermore, substrates containing two methyl groups with different substituent pattern (**1f**, **1g**, **1h**) were well tolerated in this transformation, providing the corresponding products (**3f**, **3g**, **3h**) in good yields. Subsequently, we examined the scope of substituents on the aryl ring of 4-arylphthalazin-1(2*H*)-one (**1**) in the diamidation reactions under the optimized reaction conditions (Table 1, entry 20). To our delight, 4-arylphthalazin-1(2*H*)-one **1b** with *para*-substituted groups (OMe) gave the corresponding products **4b** in 62% yield, and the Me group-substituted 4-arylphthalazin-1(2*H*)-one **1d** afforded the corresponding product **4c** in 67% yield. It is also important to note that only trace amounts of monoamidation products were detected.

**Table 1.** Optimization Studies

Entry	Silver Salt	Additive	Solvent	<b>3a</b> Yield(%) <sup>b</sup>	<b>4a</b> Yield (%) <sup>b</sup>
1	AgNTf <sub>2</sub>	-	DCE	54	8
2	AgNTf <sub>2</sub>	AcOH	DCE	81	trace
3	AgSbF <sub>6</sub>	AcOH	DCE	57	14
4	AgOAc	AcOH	DCE	41	trace
5	Ag <sub>2</sub> O	AcOH	DCE	34	0
6	AgOTf	AcOH	DCE	53	trace
7	AgTFA	AcOH	DCE	43	0
8	Ag <sub>2</sub> CO <sub>3</sub>	AcOH	DCE	55	11
9	Cu(OAc) <sub>2</sub>	AcOH	DCE	24	0
10	AgNTf <sub>2</sub>	Li <sub>2</sub> CO <sub>3</sub>	DCE	47	trace
11	AgNTf <sub>2</sub>	AcOH	1,4-dioxane	18	0
12	AgNTf <sub>2</sub>	AcOH	toluene	15	0
13	AgNTf <sub>2</sub>	AcOH	DMF	28	trace
14	-	AcOH	DCE	trace	0
15 <sup>c</sup>	AgNTf <sub>2</sub>	AcOH	DCM	63	8
16 <sup>d</sup>	AgNTf <sub>2</sub>	AcOH	DCE	74	13
17 <sup>e</sup>	AgNTf <sub>2</sub>	AcOH	DCE	67	trace
18 <sup>f</sup>	AgNTf <sub>2</sub>	AcOH	DCE	82	trace
19 <sup>g</sup>	AgNTf <sub>2</sub>	AcOH	DCE	13	68
20 <sup>h</sup>	AgNTf <sub>2</sub>	AcOH	DCE	trace	77

<sup>a</sup> Unless otherwise stated, reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), silver salt (0.030 mmol), [Cp\**Rh*Cl<sub>2</sub>]<sub>2</sub> (0.008 mmol), additive (1.0 equiv) and DCE (1mL) heated at 100 °C for 12 h under air. <sup>b</sup> Isolated yields; <sup>c</sup> 80 °C; <sup>d</sup> 120 °C; <sup>e</sup> [Cp\**Rh*Cl<sub>2</sub>]<sub>2</sub> (0.006 mmol); <sup>f</sup> [Cp\**Rh*Cl<sub>2</sub>]<sub>2</sub> (0.012 mmol); <sup>g</sup> **2a** (0.44 mmol); <sup>h</sup> **2a** (0.50 mmol).

**Table 2.** Ir(III)-catalyzed C-H mono-/diamidation of 4-aryl phthalazin-1(2H)-ones<sup>a,b</sup>

<sup>a</sup>Reaction conditions: for monoamidation: **1** (0.2 mmol), **[Cp\*IrCl<sub>2</sub>]<sub>2</sub>** (0.008 mmol), **AgNTf<sub>2</sub>** (0.03 mmol), **2** (0.22 mmol), DCE (1 mL) at 100 °C, under air, 12 h. for diamidation: **1** (0.2 mmol), **[Cp\*IrCl<sub>2</sub>]<sub>2</sub>** (0.008 mmol), **AgNTf<sub>2</sub>** (0.03 mmol), **2** (0.5 mmol), DCE (1 mL) heated at 100 °C for 12 h under air. <sup>b</sup>Isolated yields.

## Conclusions

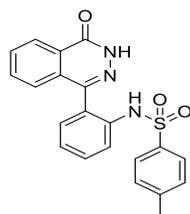
In summary, we have successfully realized direct late-stage diversification by iridium-catalyzed C-H bond amidation of 4-aryl phthalazin-1(2H)-ones. The monoamidation and diamidation were conducted with excellent regioselectivity, and a wide range of mono-/diamidated 4-aryl phthalazin-1(2H)-ones were synthesized in good to high yields. Future studies will be devoted to regiodivergent functionalization of other heteroarenes *via* transition metal-catalyzed C-H activation.

## Experimental Section

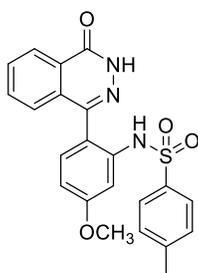
**General.** All reactions were carried out under atmosphere of air in oven-dried glassware with magnetic stirring, unless otherwise specified. All other reagents and solvents were purchased from Energy Chemical or J&K Chemical Company and used without any further purification. TLC information was recorded on GF-254 (Qingdao Haiyang Chemical Co., Ltd. P. R. China) plates. Purification of reaction products was carried out by flash chromatography using silica gel (200-300 mesh, Qingdao Haiyang Chemical Co. Ltd. P. R. China). All products were analysed using Bruker Avance-400 instruments, calibrated to TMS ( $^1\text{H}$  NMR spectra) and DMSO- $d_6$  ( $^{13}\text{C}$  NMR spectra) as the internal reference (0.00 ppm for  $^1\text{H}$  NMR spectra and 100.00 ppm for  $^{13}\text{C}$  NMR spectra). High-resolution mass spectra (HRMS) were recorded on a Bruker Apex IV FTMS mass spectrometer using ESI (electrospray ionization). Melting points are uncorrected. The substrates 4-aryl phthalazin-1(2H)-ones **1** were prepared according to well-known literature procedures.<sup>23</sup>

### General procedure for Ir(III)-catalyzed C-H amidation of 4-arylphthalazin-1(2H)-ones.

A mixture of 4-arylphthalazin-1(2H)-one **1** (0.20 mmol), TsN<sub>3</sub> **2a** (momoamidation for 0.22 mmol; diamidation for 0.5 mmol), [Cp\*IrCl<sub>2</sub>]<sub>2</sub> (0.008 mmol, 4 mol%), AgNTf<sub>2</sub> and DCE (1mL) were charged into a reaction tube. The reaction mixture was stirred at 100 °C for 12 h. After the mixture cooled to rt, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using petroleum ether/EtOAc to afford the desired products **3** or **4**.

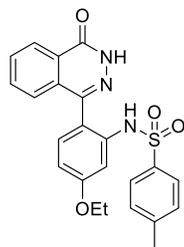


**N-[2-(4-Oxo-3,4-dihydrophthalazin-1-yl)phenyl]-4-methylbenzenesulfonamide (3a).** White solid, 63 mg, 81% yield, mp 244-245 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  12.71 (s, 1H), 9.55 (s, 1H), 8.22 (dd,  $J$  8.0, 1.3 Hz, 1H), 7.75 (t,  $J$  7.6 Hz, 1H), 7.65 (t,  $J$  7.0 Hz, 1H), 7.41 (d,  $J$  8.3 Hz, 2H), 7.35 (d,  $J$  2.5 Hz, 2H), 7.27 – 7.22 (m, 1H), 7.17 (ddd,  $J$  7.9, 5.3, 3.1 Hz, 1H), 7.11 (d,  $J$  8.0 Hz, 2H), 6.97 (d,  $J$  8.0 Hz, 1H), 2.21 (s, 3H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ ):  $\delta$  160.2, 144.4, 143.6, 137.5, 136.3, 133.5, 131.6, 130.2, 123.0, 128.6, 128.4, 127.0, 126.6, 126.0, 125.2, 123.0, 121.6, 118.4, 21.4; HRMS (ESI)  $m/z$  Calcd for C<sub>21</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>S [M+H]<sup>+</sup>392.1063, found 392.1062.

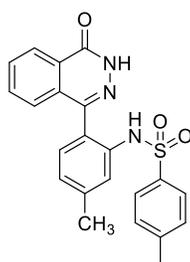


**N-[5-Methoxy-2-(4-oxo-3,4-dihydrophthalazin-1-yl)-phenyl]-4-methylbenzenesulfonamide (3b).** White solid, 65 mg, 77% yield, mp 251-252 °C;  $^1\text{H}$  NMR: (400 MHz, DMSO- $d_6$ )  $\delta$  12.67 (s, 1H), 9.55 (s, 1H), 8.22 (d,  $J$  7.9 Hz, 1H), 7.73 (t,  $J$  7.6 Hz, 1H), 7.68 – 7.61 (m, 1H), 7.44 (d,  $J$  8.1 Hz, 2H), 7.13 (t,  $J$  7.9 Hz, 3H), 6.99 (d,  $J$  8.0 Hz,

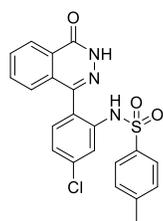
1H), 6.91 (d, *J* 2.6 Hz, 1H), 6.73 (dd, *J* 8.6, 2.5 Hz, 1H), 3.67 (s, 3H), 2.19 (s, 3H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 160.3, 160.2, 144.2, 143.7, 137.5, 137.3, 133.4, 132.8, 131.5, 130.6, 123.0, 128.6, 127.1, 126.7, 126.0, 110.1, 108.1, 55.7, 21.4. HRMS (ESI) *m/z* Calcd for C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>S [M+H]<sup>+</sup>422.1169, found 422.1167.



**N-(5-Ethoxy-2-(4-oxo-3,4-dihydrophthalazin-1-yl)phenyl)-4-methylbenzenesulfonamide (3c).** White solid, 71 mg, 72% yield, mp 205-206 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.74 (s, 1H), 9.61 (s, 1H), 8.29 (d, *J* 7.9 Hz, 1H), 7.82 (t, *J* 7.6 Hz, 1H), 7.72 (t, *J* 7.6 Hz, 1H), 7.52 (d, *J* 7.9 Hz, 2H), 7.21 (d, *J* 8.2 Hz, 3H), 7.07 (d, *J* 8.0 Hz, 1H), 6.97 (d, *J* 2.5 Hz, 1H), 6.79 (d, *J* 8.5 Hz, 1H), 4.01 (q, *J* 6.9 Hz, 2H), 2.28 (s, 3H), 1.33 (t, *J* 6.9 Hz, 3H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 160.2, 159.6, 144.2, 143.7, 137.5, 137.4, 133.4, 132.8, 131.5, 130.6, 130.0, 128.7, 127.0, 126.7, 126.0, 120.1, 110.8, 108.4, 63.8, 21.4, 15.0 ; HRMS (ESI) *m/z* Calcd for C<sub>23</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub>S [M+H]<sup>+</sup>436.1523, found 436.1328.

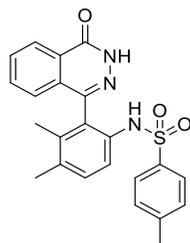


**4-Methyl-N-(5-methyl-2-(4-oxo-3,4-dihydrophthalazin-1-yl)phenyl)-4-methylbenzenesulfonamide (3d).** White solid, 65 mg, 80% yield, mp 225-226 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 14.25 (s, 1H), 13.02 (d, *J* 7.9 Hz, 1H), 12.57 (t, *J* 7.6 Hz, 1H), 12.45 (t, *J* 7.7 Hz, 1H), 12.19 (d, *J* 8.0 Hz, 2H), 12.01 (s, 1H), 11.92 (dd, *J* 16.4, 7.9 Hz, 3H), 11.80 (dd, *J* 14.4, 7.9 Hz, 2H), 7.07 (s, 3H), 7.01 (s, 3H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 164.8, 149.1, 148.3, 144.5, 142.2, 140.8, 138.1, 136.4, 136.3, 135.0, 134.6, 133.3, 131.7, 131.4, 130.7, 130.5, 128.6, 26.2, 26.2 ; HRMS (ESI) *m/z* Calcd for C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>S [M+H]<sup>+</sup>406.1220, found 406.1220.

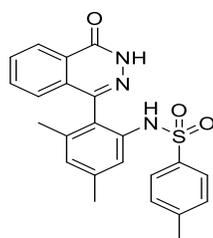


**N-[5-Chloro-2-(4-oxo-3,4-dihydro-phthalazin-1-yl)-phenyl]-4-methylbenzenesulfonamide (3e).** White solid, 58 mg, 68% yield, mp 219-220°C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 12.74 (d, *J* 2.3 Hz, 1H), 9.85 (s, 1H), 8.22 (d, *J* 7.9 Hz, 1H), 7.73 (t, *J* 7.6 Hz, 1H), 7.61 (t, *J* 7.7 Hz, 1H), 7.49 – 7.40 (m, 3H), 7.25 (d, *J* 8.2 Hz, 1H), 7.19 (dd, *J* 8.2, 2.0 Hz, 1H), 7.16 – 7.10 (m, 2H), 6.93 (d, *J* 8.0 Hz, 1H), 2.20 (s, 3H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 160.3,

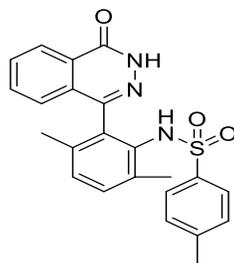
144.0, 143.3, 138.0, 137.1, 134.5, 133.5, 133.5, 131.7, 130.2, 130.1, 128.7, 127.0, 126.6, 126.3, 126.1, 124.7, 121.5, 21.4; HRMS (ESI)  $m/z$  Calcd for  $C_{21}H_{16}ClN_3O_3S$   $[M+H]^+$  426.0674, found 426.0682.



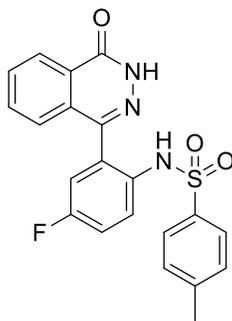
***N*-(3,4-Dimethyl-2-(4-oxo-3,4-dihydrophthalazin-1-yl)phenyl)-4-methylbenzenesulfonamide (3f)**. White solid, 52 mg, 62% yield, mp 226-227 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  12.62 (s, 1H), 9.30 (s, 1H), 8.19 (dd,  $J$  8.0, 1.3 Hz, 1H), 7.77 – 7.70 (m, 1H), 7.62 (td,  $J$  7.7, 1.4 Hz, 1H), 7.32 (d,  $J$  8.1 Hz, 2H), 7.12 (s, 1H), 7.04 – 6.95 (m, 4H), 2.16 (s, 3H), 2.15 (s, 3H), 2.11 (s, 3H).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  160.0, 144.4, 143.3, 138.4, 137.5, 133.8, 133.5, 133.4, 132.4, 131.5, 130.2, 129.8, 128.5, 126.9, 126.8, 126.6, 125.9, 125.4, 21.4, 19.9, 19.1; HRMS (ESI)  $m/z$  Calcd for  $C_{23}H_{21}N_3O_3S_2$   $[M+H]^+$  419.1574, found 419.1567.



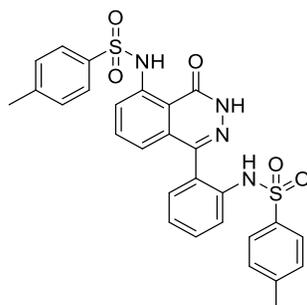
***N*-(3,5-Dimethyl-2-(4-oxo-3,4-dihydrophthalazin-1-yl)phenyl)-4-methylbenzenesulfonamide (3g)**. White solid, 68 mg, 69% yield, mp 206-207 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  13.14 (s, 1H), 12.74 (s, 1H), 7.76 (d,  $J$  8.4 Hz, 2H), 7.68 – 7.61 (m, 2H), 7.29 (d,  $J$  8.0 Hz, 2H), 7.07 (s, 1H), 7.03 (s, 2H), 6.69 (d,  $J$  7.6 Hz, 1H), 2.25 (s, 3H), 2.23 (s, 3H), 1.88 (s, 3H).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  162.7, 148.5, 144.7, 140.1, 139.0, 136.7, 136.1, 135.6, 131.7, 131.5, 131.3, 130.5, 130.1, 127.5, 126.9, 120.8, 118.2, 114.1, 21.4, 21.3, 19.5; HRMS (ESI)  $m/z$  Calcd for  $C_{23}H_{21}N_3O_3S_2$   $[M+H]^+$  419.1574, found 419.1567.



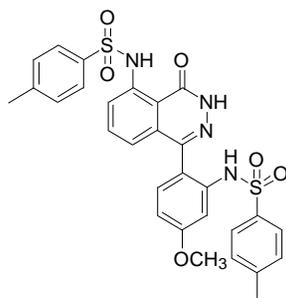
***N*-(3,6-Dimethyl-2-(4-oxo-3,4-dihydrophthalazin-1-yl)phenyl)-4-methylbenzenesulfonamide (3h)**. White solid, 51 mg, 61% yield, mp 211-212 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  13.15 (s, 1H), 12.73 (s, 1H), 7.75 (d,  $J$  8.1 Hz, 2H), 7.69 – 7.60 (m, 2H), 7.27 (d,  $J$  8.1 Hz, 2H), 7.12 (s, 2H), 6.95 (s, 1H), 6.70 – 6.64 (m, 1H), 2.21 (s, 3H), 2.18 (s, 3H), 1.85 (s, 3H).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  162.7, 148.6, 144.7, 140.1, 136.1, 135.6, 135.4, 134.4, 133.7, 131.3, 130.6, 130.6, 130.5, 130.2, 127.5, 120.8, 118.2, 114.1, 21.4, 20.8, 19.1. ; HRMS (ESI)  $m/z$  Calcd for  $C_{23}H_{21}N_3O_3S_2$   $[M+H]^+$  419.1574, found 419.1586.



**N-(4-Fluoro-2-(4-oxo-3,4-dihydrophthalazin-1-yl)phenyl)-4-methylbenzenesulfonamide (3i)**. White solid, 63 mg, 77% yield, mp 237-238 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  12.68 (s, 1H), 9.74 (s, 1H), 8.23-8.16 (m, 1H), 7.79 (dtt,  $J$  10.1, 7.3, 3.7 Hz, 2H), 7.51 – 7.41 (m, 2H), 7.27-7.21 (m, 2H), 7.20-7.16 (m, 2H), 6.97 (d,  $J$  7.9 Hz, 2H), 2.24 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  159.7, 142.8, 138.4, 136.8, 133.5, 131.6, 129.6, 129.4, 128.0, 127.6, 127.0, 126.0, 125.8, 121.6, 118.4, 117.4, 117.2, 21.4. HRMS (ESI)  $m/z$  Calcd for  $\text{C}_{21}\text{H}_{16}\text{FN}_3\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$  409.0896, found 409.0897.

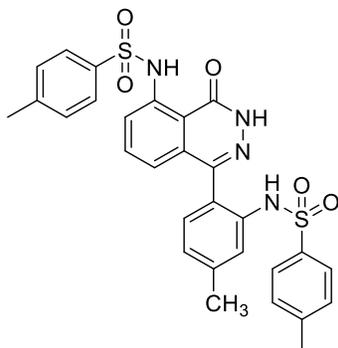


**4-Methyl-N-[2-(5-benzenesulfonylamino-4-oxo-3,4-dihydro-phthalazin-1-yl)-phenyl]-4-methylbenzenesulfonamide (4a)**. White solid, 79 mg, 70% yield, mp 171-172 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  13.10 (s, 1H), 12.78 (s, 1H), 9.51 (s, 1H), 7.79 (d,  $J$  8.3 Hz, 2H), 7.64 (d,  $J$  8.2 Hz, 1H), 7.49 (t,  $J$  8.1 Hz, 1H), 7.40 – 7.29 (m, 6H), 7.17 – 7.08 (m, 2H), 7.05 (d,  $J$  8.0 Hz, 2H), 6.45 (dd,  $J$  8.0, 0.9 Hz, 1H), 2.26 (s, 3H), 2.20 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  170.8, 163.1, 160.5, 145.7, 144.8, 143.8, 139.7, 137.6, 136.3, 134.9, 132.7, 132.0, 130.6, 130.0, 127.6, 127.1, 120.4, 119.5, 117.5, 114.4, 109.9, 107.5, 55.7, 21.4, 21.20.; HRMS (ESI)  $m/z$  Calcd for  $\text{C}_{21}\text{H}_{17}\text{N}_3\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$  561.1261, found 561.1249.



**N-[2-(5-benzenesulfonylamino-4-oxo-3,4-dihydro-phthalazin-1-yl)-5-methoxyphenyl]-4-methylbenzenesulfonamide (4b)**. White solid, 73 mg, 62% yield, mp 192-193 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  13.07 (s, 1H), 12.82 (s, 1H), 9.50 (s, 1H), 7.83 – 7.75 (m, 2H), 7.65 (d,  $J$  8.2 Hz, 1H), 7.49 (t,  $J$  8.1 Hz, 1H), 7.40 (d,  $J$  8.1 Hz, 2H), 7.32 (d,  $J$  8.0 Hz, 2H), 7.06 (dd,  $J$  12.7, 8.4 Hz, 3H), 6.92 (d,  $J$  2.4 Hz, 1H), 6.67 (dt,  $J$  8.6, 1.9

Hz, 1H), 6.48 (d, *J* 8.0 Hz, 1H), 3.65 (s, 3H), 2.24 (s, 3H), 2.19 (s, 3H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 170.8, 163.1, 160.5, 145.7, 144.8, 143.8, 139.7, 137.6, 136.3, 134.9, 132.7, 132.0, 130.6, 130.0, 127.6, 127.1, 120.4, 119.5, 117.5, 114.4, 109.9, 107.5, 55.7, 21.4, 21.2.; HRMS (ESI) *m/z* Calcd for C<sub>29</sub>H<sub>26</sub>N<sub>4</sub>O<sub>6</sub>S<sub>2</sub> [M+H]<sup>+</sup>591.1367, found 591.1359.



**N-[2-(5-Benzenesulfonylamino-4-oxo-3,4-dihydro-phthalazin-1-yl)-5-methyl-phenyl]-4-methylbenzenesulfonamide (4c).** White solid, 77 mg, 67% yield, mp 257-258 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 13.06 (s, 1H), 12.78 (s, 1H), 9.40 (s, 1H), 7.81-7.77 (m, 2H), 7.63 (dd, *J* 7.6, 1.6 Hz, 1H), 7.48 (t, *J* 8.2 Hz, 1H), 7.34 (dd, *J* 8.3, 3.3 Hz, 4H), 7.21 (d, *J* 1.7 Hz, 1H), 7.05 – 6.99 (m, 3H), 6.94 (dd, *J* 8.0, 1.6 Hz, 1H), 6.45 (dd, *J* 8.1, 0.9 Hz, 1H), 2.26 (s, 3H), 2.22 (s, 3H), 2.18 (s, 3H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 1664.0, 145.8, 144.8, 143.6, 140.1, 139.7, 137.4, 136.2, 136.1, 135.0, 131.7, 130.6, 129.8, 127.6, 126.9, 126.1, 125.8, 123.2, 120.4, 117.5, 114.3, 21.5, 21.4, 21.4. HRMS (ESI) *m/z* Calcd for C<sub>29</sub>H<sub>26</sub>N<sub>4</sub>O<sub>5</sub>S<sub>2</sub> [M+H]<sup>+</sup>575.1417, found 575.1421.

## Acknowledgements

This work is supported by the National Natural Science Foundation of China (21762022) and the Foundation of Jiangxi Educational Committee (Grant No. GJJ160287).

## Supplementary Material

Copies of NMR spectra of compounds **3,4** are given in the supplementary material file associated with this paper.

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