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Rhodium(III)-Catalyzed C−H Functionalization of 1-(2*H*)-Phthalazinones at C8

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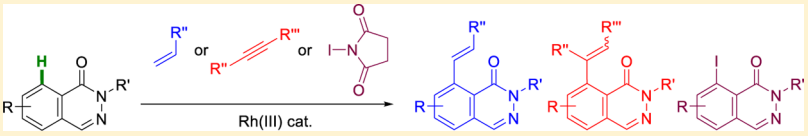
Supporting Information



ABSTRACT: The rhodium(III) catalyst tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate ($[Cp^*Rh(MeCN)_3](SbF_6)_2$) reacts with 1-(2*H*)-phthalazinones to promote a C−H functionalization event at C8. Preparation of a set of compounds arising from oxidative alkenylation with olefins, hydroarylation with alkynes, and iodination with *N*-iodosuccinimide is reported here. Oxidative alkenylation proceeds in very good yield, and the scope and limitations of the hydroarylation and halogenation reactions are discussed. Notably, this strategy enables rapid preparation of C8-substituted phthalazinones without requiring phthalazinone ring synthesis starting from a prefunctionalized arene.

1-(2*H*)-Phthalazinones are heteroaromatic scaffolds found embedded within the molecular structures of pharmaceuticals with sales in the last year of hundreds of millions of US dollars (Figure 1).[1,2] For example, azelastine, a histamine antagonist, is

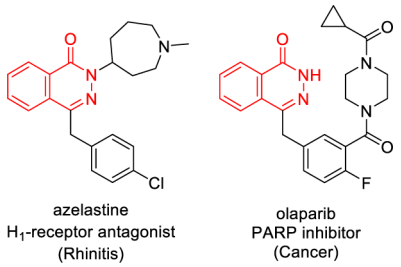
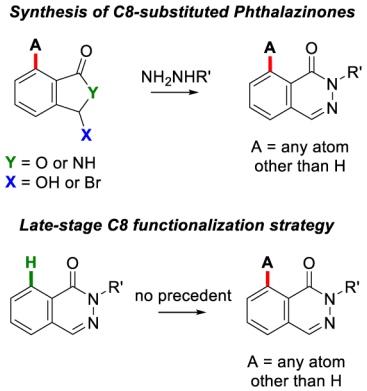


Figure 1. Examples of marketed drugs containing the 1-(2*H*)-phthalazinone substructure.

delivered as eye drops or nasal spray in rhinitis indications.[3] In addition, olaparib, an oral drug approved for ovarian cancer, is an inhibitor of poly(ADP-ribose) polymerase.[4] The successful application of these molecules in human disease validates 1-(2*H*)-phthalazinones as valuable heterocyclic units in discovery and lead optimization programs. Therefore, new methods to prepare or functionalize phthalazinones are of significant interest.

A recent medicinal chemistry campaign conducted in our laboratories called for the procurement of a set of 1-(2*H*)-phthalazinones possessing halogenation and a variable substitution at C8. Common methods for assembling the 1-(2*H*)-phthalazinone skeleton are depicted at the top of Scheme 1.[5] These approaches require the preparation of 3-hydroxy or 3-bromophthalides with the C8 functional group already in place and only furnish the desired phthalazinone ring system at the final stage. While conceivable that each of our targets of interest could ultimately be accessed in this linear fashion, a more efficient solution to their obtainment would be to construct the 1-(2*H*)-phthalazinone using standard methods and subsequently employ a transition-metal catalyzed C−H functionalization protocol to vary the C8 substituent.

Scheme 1. (Top) Typical Methods for the Preparation of 1-(2*H*)-Phthalazinones and (Bottom) No Examples for C−H Functionalization of 1-(2*H*)-Phthalazinones at C8 According to Elsevier Reaxys® or Chemical Abstracts Service Scifinder® Databases



To the best of our knowledge, no reactions have been described for functionalization of position C8 on 1-(2*H*)-phthalazinones (Scheme 1, bottom). Though expansive directing group literature suggested the possibility that the phthalazinone carbonyl group could facilitate a metalation event at C8,[6] use of carbonyl groups that are fused into adjacent aromatic rings to direct metal catalysts is uncommon.[7,8] An

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additional chemoselectivity requirement associated with our particular research program was that the chosen catalyst preserves aryl halide functionality. Therefore, exploration of functionalization methods beyond traditional palladium- and copper-based protocols was undertaken.

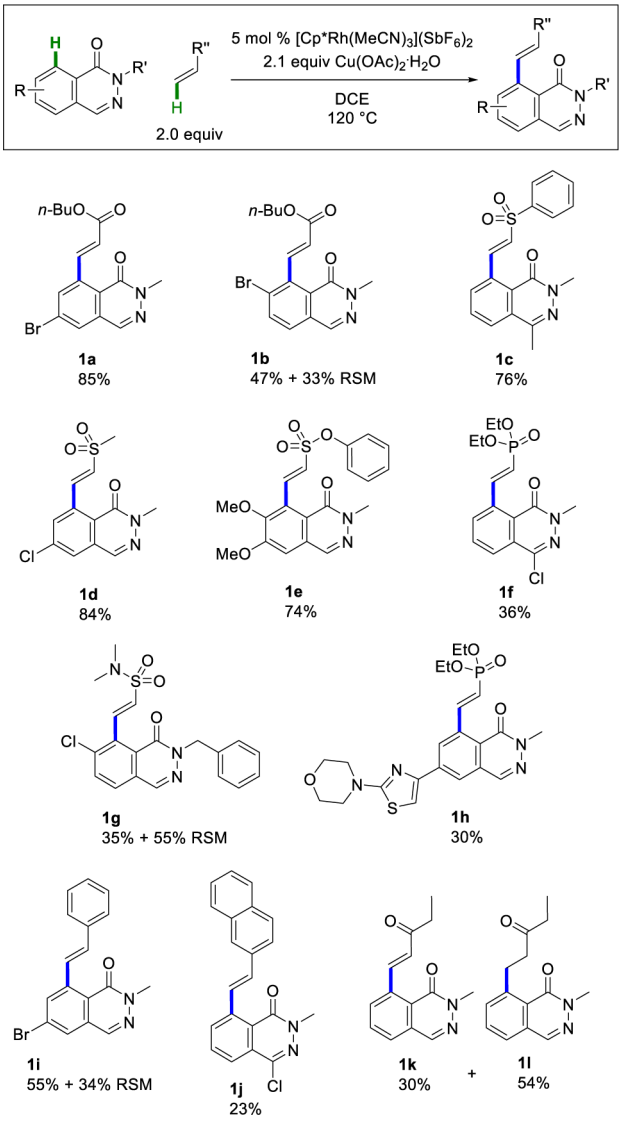
In principle, one class of catalysts that would satisfy the above requirements are the pentamethylcyclopentadienyl (Cp*) half-sandwich complexes of rhodium(III), iridium(III), and cobalt(III) (as well as η^6-*p*-cymene-ruthenium(II)).[9] Envisioning the possibility of achieving C−C bond formation via the Fujiwara−Moritani oxidative alkenylation,[10] we were successful in experiments using the bench stable, nonhygroscopic catalyst tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate, $[Cp^*Rh(MeCN)_3](SbF_6)_2$.[11] Reactions conducted with copper(II) acetate as oxidant afforded good yields of alkenylated phthalazinones and exclusively afforded the desired C8-substituted product (Table 1).[12]

As seen in Table 1, acrylates reacted readily with brominated phthalazinones to provide **1a** in 85% yield as well as a sterically encumbered 7-bromo substrate **1b** (47% yield plus 33% recovered starting phathalazinone). Vinyl sulfones afforded excellent yields of alkenylated products **1c** and **1d** (76 and 84% yields, respectively). A vinyl sulfonate performed equally well to provide **1e** in 74% yield, while a vinyl sulfonamide provided benzyl-protected **1g** with good mass balance (35% yield plus 55% recovered starting phthalazinone). Although vinyl phosphonates appeared less compatible (**1f**, 36%), the reaction conditions were nevertheless compatible with substructures typically encountered in medicinal chemistry programs (**1h**, 30% yield). Halogenated phthalazinones were also successfully coupled with aromatic alkenes such as styrene (**1i**, 55% yield plus 34% recovered phthalazinone) and 2-vinylnaphthalene (**1j**, 23% yield). Finally, in a reaction between 2-methyl-1(2*H*)-phthalazinone and ethyl vinyl ketone, the desired alkenylated product **1k** was isolated in 30% yield alongside the corresponding saturated C−H alkylation product **1l** (54% yield). This result, which is presumably driven by the relative rate of β-hydride elimination versus competitive protodemetalation of the migratory insertion intermediate,[13] opened the possibility of achieving an efficient hydroarylation reaction with alkynes.[14]

Accordingly, when 6-bromo-2-methyl-1(2*H*)-phthalazinone and diphenylacetylene were submitted to the action of the rhodium catalyst in the presence of acetic acid, trisubstituted alkene **2a** was isolated in 86% yield (Table 2).[15] For a more sterically congested 7-bromophthalazinone, the hydroarylation proceeded in 52% yield (**2c**). With regard to *N*-substitution, an acetate was compatible and afforded the desired coupling product in 40% yield (**2d**). An unprotected acetic acid moiety was similarly tolerated (**2b**, 57% yield). Although only trace conversion was seen in reactions with dialkylacetylenes (not shown), a reaction with 1-phenyl-1-propyne afforded a separable mixture of *E*/*Z* isomers in a combined yield of 73% (46% **2e** and 27% **2f**).

Recently, Glorius and others have described directed arene and alkene C−H halogenations using the Cp* half-sandwich metal complexes.[16] With respect to the current study, it was subsequently found that, while bromination results were not promising,[17] 1-(2*H*)-phthalazinones could be readily iodinated at C8 in good mass balance (Table 3). Iodination with 5.00 mmol of 2-methyl-1(2*H*)-phthalazinone provided 8-iodo-2-methyl-1(2*H*)-phthalazinone (**3a**) in 35% yield plus 40%

Table 1. Oxidative C−H Alkenylation of 1-(2*H*)-Phthalazinones at C8[a]



[a]Conditions: Under N_2, anhydrous 1,2-dichloroethane (5 mL) was added to a vial containing tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (0.05 equiv), copper(II) acetate monohydrate (2.1 equiv), the alkene (2.0 equiv), and the phthalazinone (0.250 mmol). The vial was sealed tightly, and the reaction mixture was stirred at 120 °C overnight. RSM = recovered starting material.

recovered starting material (RSM). The iodination reaction was compatible with 4-chloro and 4-methyl-phthalazinones, furnishing **3c** and **3d** (25 + 61% and 40 + 39% RSM, respectively). In addition, 6-bromo- and 6-chloro-phthalazinones were iodinated to produce compounds **3b** and **3e** (55 + 35% and 32 + 51% RSM, respectively). Finally, the hindered 7-bromo-8-iodo phthalazinone **3f** was prepared in 22% yield plus 28% RSM.

Despite considerable experimentation with various catalysts and reaction conditions, the yields for C−H iodination were not able to be improved beyond what is reported in Table 3. That no byproducts were ever detected led to the assumption that decomposition pathways are likely responsible for the modest yields. With rather little known about the exact reaction mechanism of this halogenation manifold,[8g] it remains to be

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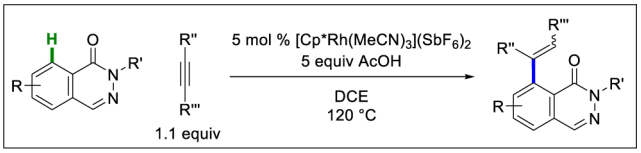
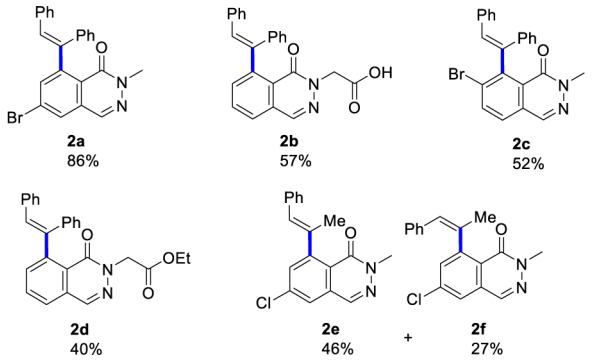
Table 2. Hydroarylation C−H Alkenylation of 1-(2*H*)-Phthalazinones at C8[a]

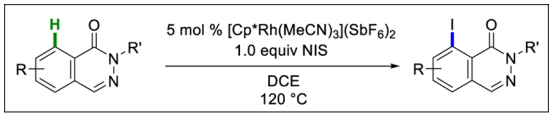


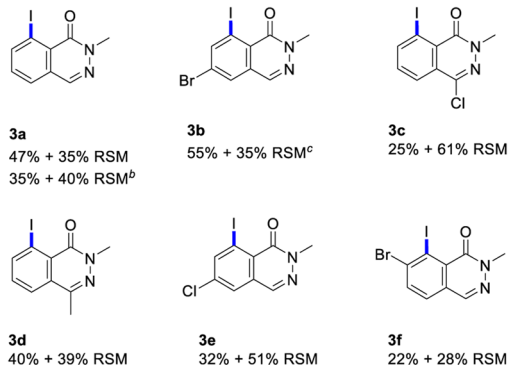


2a 86%
2b 57%
2c 52%
2d 40%
2e 46%
2f 27%

[a]Conditions: Under N_2, anhydrous 1,2-dichloroethane (5 mL) and acetic acid (5 equiv) were added to a vial containing tris(acetonitrile)-pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (0.05 equiv), the alkyne (1.1 equiv), and the phthalazinone (0.250 mmol). The vial was sealed tightly, and the reaction mixture was stirred at 120 °C overnight.

Table 3. C−H Iodination of 1-(2*H*)-Phthalazinones at C8[a]





3a 47% + 35% RSM; 35% + 40% RSM[b]
3b 55% + 35% RSM[c]
3c 25% + 61% RSM
3d 40% + 39% RSM
3e 32% + 51% RSM
3f 22% + 28% RSM

[a]Conditions: Under N_2, anhydrous 1,2-dichloroethane (5 mL) was added to a vial containing tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (0.05 equiv), *N*-iodosuccinimide (1.0 equiv), and the phthalazinone (0.250 mmol). The vial was sealed tightly, and the reaction mixture was stirred at 120 °C overnight. RSM = recovered starting material. [b]Reaction conducted at 5.00 mmol scale. [c]Reaction conducted at 0.125 mmol scale at 100 °C.

determined whether future experimentation can in general improve such transformations.

As described in this work, the employment of a rhodium(III) catalyst system led to a convenient C−H functionalization reaction of 1-(2*H*)-phthalazinones at C8. Specifically, these results provide a facile method for the installation of iodine on phthalazinones as well as several types of alkene functionality.

EXPERIMENTAL SECTION

General Methods. *Chemical.* All metal catalysts were stored in a desiccator (weighing to air). Dichloro(pentamethylcyclopentadienyl)-rhodium(III) dimer ($[RhCp^*Cl_2]_2$), silver hexafluoroantimonate(V), and copper(II) acetate were purchased from Strem Chemicals. $[Cp^*Rh(MeCN)_3](SbF_6)_2$ was synthesized (procedure below) but is also commercially available from several vendors. Copper(II) acetate was ground to a powder using a mortar and pestle. Thin-layer chromatograms were performed on Silica gel 60 F_{254} aluminum-backed plates and visualized with UV light. Flash chromatographic purifications were performed with Teledyne Isco RediSep Rf Gold silica cartridges on a Teledyne Isco Combiflash Rf.

Analytical. Nuclear magnetic resonance data is reported with chemical shift values relative to internal standards and operating frequencies shown in parentheses: ^1H (400.33 MHz) − trimethylsilane = 0.00 ppm, ^{13}C (100.67 MHz) − trimethylsilane = 0.0 ppm, ^{31}P (161.97 MHz) − internal calibration. In cases of uncertain assignments, structural confirmation was secured through 2D NMR experiments. High-resolution mass spectrometry was performed using electrospray ionization in positive mode to an Orbitrap mass analyzer. Reactions were monitored by HPLC-MS analysis with a C18 column, UV detection at 254 nm, and dual ESI/APCI to a single quadrupole mass analyzer. The method was conducted at a flow rate of 0.7 mL/min, whereby mobile phase A was 0.1% formic acid in water and mobile phase B was acetonitrile. The method began at 2% B, ramping linearly to 98% B over 2 min. The gradient was held at 98% B for 0.2 min and then ramped down to 2% B over 0.1 min and held at 2% B for 0.1 min.

Synthesis of Tris(acetonitrile)pentamethylcyclopentadienyl-rhodium(III) Hexafluoroantimonate. To a solution of dichloro-(pentamethylcyclopentadienyl)rhodium(III) dimer (6.00 g, 9.71 mmol) in anhydrous MeCN (80 mL) was added silver hexafluoroantimonate(V) (13.7 g, 39.9 mmol). The mixture was stirred for 30 min and then filtered over Celite and rinsed with acetonitrile. After concentrating to dryness, the residue was dissolved in 1:1 dichloromethane/acetonitrile, filtered through plug of silica gel, and eluted with 1:1 dichloromethane/acetonitrile. After the solution had been concentrated to a minimal volume, diethyl ether was added to precipitate the target organometallic compound as light yellow powder that was collected by filtration (13.0 g, 80%).

Synthesis of 1-(2*H*)-Phthalazinone Starting Materials. *General Procedure (A).* To a stirring solution of the 1-(2*H*)-phthalazinone in anhydrous DMF (0.3 M) was added sodium hydride (2.0 equiv, [60% in mineral oil]). After 1 h, iodomethane (1.5 equiv) was added, and the solution was stirred for the below-stated time period. The reaction mixture was then poured into water and extracted with isopropyl acetate. The organics were washed with water (1×) and brine (1×) and then dried over magnesium sulfate. Following concentration to dryness, the solids were dissolved in a minimal amount of dichloromethane. Heptane was added, and the dichloromethane was carefully evaporated, affording a suspension of the target product in heptane which was collected by filtration and rinsed with heptane.

2-Methylphthalazin-1(2H)-one (S1). Following general procedure A, reaction of phthalazin-1(2*H*)-one (2.00 g, 13.7 mmol) with sodium hydride (1.09 g, 27.4 mmol, [60% in mineral oil]) and iodomethane (1.3 mL, 21 mmol) for 20 h afforded the target compound as an orange solid (1.23 g, 56%); mp 109−111 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H), 8.26 (d, J = 8.2 Hz, 1H), 7.99−7.83 (m, 3H), 3.73 (s, 3H); $^{13}C\{^1H\}$NMR (101 MHz, DMSO-d_6) δ 159.1, 138.1, 133.8, 132.4, 130.0, 127.4, 127.2, 126.0, 39.4; HRMS m/z calcd for $C_9H_8N_2O$ $[M + H]^+$: 161.0709. Found 161.0707.

6-Chloro-2-methylphthalazin-1(2H)-one (S2). Following general procedure A, reaction of 6-chlorophthalazin-1(2*H*)-one (996 mg, 5.51 mmol) with sodium hydride (441 mg, 11.0 mmol, [60% in mineral oil]) and iodomethane (0.52 mL, 8.3 mmol) for 43 h afforded the target compound as a white solid (602 mg, 56%); mp 219−220 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 8.25 (d, J = 8.6 Hz, 1H), 8.10 (d, J = 2.0 Hz, 1H), 7.89 (dd, J = 8.6, 2.0 Hz, 1H), 3.72 (s, 3H); $^{13}C\{^1H\}$NMR (101 MHz, DMSO-d_6) δ 158.5, 138.6, 137.0, 132.6,

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131.4, 128.5, 126.6, 126.1, 39.5; HRMS m/z calcd for $C_9H_7ClN_2O$ [M + H]$^+$: 195.0320. Found 195.0317.

4-Chloro-2-methylphthalazin-1(2H)-one (S3). Following general procedure A, reaction of 4-chlorophthalazin-1(2*H*)-one (3.14 g, 17.4 mmol) with sodium hydride (1.39 g, 34.8 mmol, [60% in mineral oil]) and iodomethane (1.6 mL, 26 mmol) for 69.5 h afforded the target compound as a white solid (1.39 g, 41%); mp 128−129 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (d, J = 7.8 Hz, 1H), 8.07−7.95 (m, 3H), 3.70 (s, 3H); ^{13}C{^{1}H}NMR (101 MHz, DMSO-d_6) δ 158.6, 136.3, 134.7, 133.7, 128.5, 128.3, 127.2, 125.9, 39.4; HRMS m/z calcd for $C_9H_7ClN_2O$ [M + H]$^+$: 195.0320. Found 195.0316.

2,4-Dimethylphthalazin-1(2H)-one (S4). Following general procedure A, reaction of 4-methylphthalazin-1(2*H*)-one (946 mg, 5.90 mmol) with sodium hydride (472 mg, 11.8 mmol, [60% in mineral oil]) and iodomethane (0.55 mL, 8.9 mmol) for 69.5 h afforded the target compound as a white solid (571 mg, 55%); mp 111−112 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31−8.25 (m, 1H), 8.00−7.84 (m, 3H), 3.68 (s, 3H), 2.55 (s, 3H); ^{13}C{^{1}H}NMR (101 MHz, DMSO-d_6) δ 158.9, 143.6, 133.7, 132.2, 129.8, 127.4, 126.5, 126.1, 39.1, 18.9; HRMS m/z calcd for $C_{10}H_{10}N_2O$ [M + H]$^+$: 175.0866. Found 175.0862.

6,7-Dimethoxy-2-methylphthalazin-1(2H)-one (S5). Following general procedure A, reaction of 6,7-dimethoxyphthalazin-1(2*H*)-one (992 mg, 4.81 mmol) with sodium hydride (384 mg, 9.62 mmol, [60% in mineral oil]) and iodomethane (0.45 mL, 7.2 mmol) for 22 h afforded the target compound as a white solid (855 mg, 81%); mp 177−178 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 7.57 (s, 1H), 7.41 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.70 (s, 3H); ^{13}C{^{1}H}NMR (101 MHz, DMSO-d_6) δ 158.7, 153.8, 153.0, 137.2, 125.3, 122.2, 107.3, 105.8, 56.5, 56.4, 39.4; HRMS m/z calcd for $C_{11}H_{12}N_2O_3$ [M + H]$^+$: 221.0921. Found 221.0916.

6-Bromo-2-methylphthalazin-1(2H)-one (S6). Following general procedure A, reaction of 6-bromophthalazin-1(2*H*)-one (5.02 g, 22.3 mmol) with sodium hydride (1.78 g, 44.6 mmol, [60% in mineral oil]) and iodomethane (2.1 mL, 33 mmol) was conducted for 92 h, but instead of the usual workup, the reaction mixture was cooled in an ice bath and then filtered and rinsed with heptane and then water. The title compound was collected as a white solid (4.63 g, 87%); mp 235−236 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 8.24 (d, J = 1.9 Hz, 1H), 8.16 (d, J = 8.5 Hz, 1H), 8.01 (dd, J = 8.5, 1.9 Hz, 1H), 3.71 (s, 3H); ^{13}C{^{1}H}NMR (101 MHz, DMSO-d_6) δ 158.6, 136.9, 135.4, 131.5, 129.7, 128.5, 127.5, 126.3, 39.5; HRMS m/z calcd for $C_9H_7BrN_2O$ [M + H]$^+$: 238.9815. Found 238.9812.

7-Bromo-2-methylphthalazin-1(2H)-one (S7). Following general procedure A, reaction of 7-bromophthalazin-1(2*H*)-one (946 mg, 4.20 mmol) with sodium hydride (336 mg, 8.40 mmol, [60% in mineral oil]) and iodomethane (0.39 mL, 6.3 mmol) was conducted for 22 h, but instead of the usual workup, the reaction mixture was cooled in an ice bath and then filtered and rinsed with heptane and then water. The title compound was collected as an orange solid (756 mg, 75%); mp 179−180 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.33 (d, J = 2.0 Hz, 1H), 8.11 (dd, J = 8.5, 2.0 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 3.72 (s, 3H); ^{13}C{^{1}H}NMR (101 MHz, DMSO-d_6) δ 157.8, 137.6, 136.8, 129.7, 128.9, 128.8, 128.3, 125.9, 39.5; HRMS m/z calcd for $C_9H_7BrN_2O$ [M + H]$^+$: 238.9815. Found 238.9811.

2-Benzyl-7-chlorophthalazin-1(2H)-one (S8). To a suspension of 5-chloro-2-formylbenzoic acid (2.00 g, 10.8 mmol) and benzylhydrazine hydrochloride (2.66 g, 16.3 mmol) in absolute ethanol (36 mL) was added sodium carbonate (3.45 g, 32.5 mmol). The reaction mixture was refluxed at 100 °C for 4 h, diluted with dichloromethane, washed with water (1×) and brine (1×), and organics were dried over magnesium sulfate. Following concentration to dryness, the crude solids were dissolved in a minimal amount of dichloromethane. Heptane was added, and the dichloromethane was carefully evaporated. The suspension was filtered and rinsed with heptane. Several minutes later, the mother liquor developed a precipitate which was filtered to collect the target compound as a white solid (787 mg, 27%); mp 125−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 1.5 Hz, 1H), 8.13 (s, 1H), 7.73 (dd, J = 8.5, 1.5 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.49−7.42 (m, 2H), 7.36−7.26 (m, 3H), 5.40 (s, 2H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 158.3, 138.2, 137.1, 136.7, 133.7, 129.3, 128.6, 128.6, 128.0, 127.8, 127.6, 126.6, 54.8; HRMS m/z calcd for $C_{15}H_{11}ClN_2O$ [M + H]$^+$: 271.0633. Found 271.0628.

2-Methyl-6-(2-morpholinothiazol-4-yl)phthalazin-1(2H)-one (S9). Into a vial was weighed 6-bromo-2-methylphthalazin-1(2*H*)-one (86.9 mg, 0.364 mmol), 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazol-2-yl)morpholine (108 mg, 0.364 mmol), chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) (15.3 mg, 0.0194 mmol), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (8.8 mg, 0.018 mmol), and potassium phosphate tribasic monohydrate (259 mg, 1.09 mmol). The vial was purged with nitrogen gas, charged with degassed tetrahydrofuran (1.8 mL) and distilled water (0.4 mL), then sealed, and the reaction mixture was stirred at 80 °C for 18 h. After cooling to rt, the mixture was concentrated to dryness. The reaction residue thus obtained was purified by flash column chromatography (CH_2Cl_2/MeOH, 100:0−95:5) to afford the title compound as a white solid (71 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 8.3 Hz, 1H), 8.26−8.08 (m, 3H), 7.04 (s, 1H), 3.90−3.84 (m, 4H), 3.86 (s, 3H), 3.65−3.53 (m, 4H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 171.4, 159.6, 150.0, 139.2, 137.9, 130.4, 129.1, 126.8, 126.7, 123.1, 104.8, 66.2, 48.6, 39.4; HRMS m/z calcd for $C_{16}H_{16}N_4O_2S$ [M + H]$^+$: 329.1067. Found 329.1058.

Rhodium(III)-Catalyzed C−H Alkenylation with Alkenes. *General Procedure (B).* Under nitrogen gas, anhydrous 1,2-dichloroethane (0.05 M) was added to a 4 dram vial containing tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (0.05 equiv), copper(II) acetate monohydrate (2.1 equiv), the phthalazin-1(2*H*)-one, and the alkene, if solid (2.0 equiv). If the alkene was a liquid, it was charged into the vial immediately before the solvent. The vial was sealed tightly, and the reaction mixture was stirred at 120 °C for the noted reaction time. Following concentration, the reaction residue was subjected to flash column chromatographic methods using the stated eluent system.

*Butyl (E)-3-(7-Bromo-3-methyl-4-oxo-3,4-dihydrophthalazin-5-yl)acrylate (**1a**).* Following general procedure B, reaction of 6-bromo-2-methylphthalazin-1(2*H*)-one (59.8 mg, 0.250 mmol), butyl acrylate (71.7 μL, 0.500 mmol), tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (10.4 mg, 0.0125 mmol), and copper(II) acetate monohydrate (108 mg, 0.525 mmol) for 23 h afforded after flash chromatography (heptane/iPrOAc, 100:0−75:25) the title compound as a white solid (77.7 mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, J = 16.0 Hz, 1H), 8.02 (s, 1H), 7.87 (d, J = 1.9 Hz, 1H), 7.83 (d, J = 1.9 Hz, 1H), 6.25 (d, J = 16.0 Hz, 1H), 4.24 (t, J = 6.7 Hz, 2H), 3.81 (s, 3H), 1.77−1.63 (m, 2H), 1.45 (sext, J = 7.3 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 165.9, 159.2, 143.1, 139.3, 135.9, 133.8, 132.3, 129.7, 127.3, 123.5, 123.0, 64.7, 39.9, 30.7, 19.2, 13.7; HRMS m/z calcd for $C_{16}H_{17}BrN_2O_3$ [M + H]$^+$: 365.0495. Found 365.0489.

*Butyl (E)-3-(6-Bromo-3-methyl-4-oxo-3,4-dihydrophthalazin-5-yl)acrylate (**1b**).* Following general procedure B, 7-bromo-2-methylphthalazin-1(2*H*)-one (59.8 mg, 0.250 mmol), butyl acrylate (71.7 μL, 0.500 mmol), tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (10.4 mg, 0.0125 mmol), and copper(II) acetate monohydrate (108 mg, 0.525 mmol) were reacted for 22 h. Flash chromatographic elution (heptane/iPrOAc, 100:0−65:35) afforded recovered starting material (20.0 mg, 33%) followed by the title compound as a white solid (43.1 mg, 47%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 16.4 Hz, 1H), 8.07 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 6.09 (d, J = 16.4 Hz, 1H), 4.25 (t, J = 6.8 Hz, 2H), 3.81 (s, 3H), 1.78−1.67 (m, 2H), 1.53−1.37 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 166.1, 158.5, 143.4, 138.0, 137.4, 136.7, 129.9, 127.1, 127.0, 127.0, 124.6, 64.7, 40.0, 30.7, 19.2, 13.8; HRMS m/z calcd for $C_{16}H_{17}BrN_2O_3$ [M + H]$^+$: 365.0495. Found 365.0490.

*(E)-2,4-Dimethyl-8-(2-(phenylsulfonyl)vinyl)phthalazin-1(2H)-one (**1c**).* Following general procedure B, reaction of 2,4-dimethylphthalazin-1(2*H*)-one (43.5 mg, 0.250 mmol), phenyl vinyl sulfone (84.1 mg, 0.500 mmol), tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (10.4 mg, 0.0125 mmol), and

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copper(II) acetate monohydrate (108 mg, 0.525 mmol) for 18 h afforded after flash chromatography (heptane/iPrOAc, 100:0−0:100) the title compound as a white solid (64.8 mg, 76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (d, J = 15.4 Hz, 1H), 8.13−8.05 (m, 2H), 7.85−7.73 (m, 2H), 7.73−7.67 (m, 1H), 7.66−7.52 (m, 3H), 6.65 (d, J = 15.5 Hz, 1H), 3.80 (s, 3H), 2.57 (s, 3H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 159.4, 144.3, 142.7, 140.7, 135.3, 133.3, 132.6, 131.3, 131.1, 129.7, 129.3, 128.0, 126.9, 125.3, 39.6, 19.1; HRMS m/z calcd for $C_{18}H_{16}N_2O_3S$ [M + H]$^+$: 341.0954. Found 341.0951.

*(E)-6-Chloro-2-methyl-8-(2-(methylsulfonyl)vinyl)phthalazin-1(2H)-one (**1d**).* Following general procedure B, reaction of 6-chloro-2-methylphthalazin-1(2*H*)-one (48.7 mg, 0.250 mmol), methyl vinyl sulfone (43.8 μL, 0.500 mmol), tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (10.4 mg, 0.0125 mmol), and copper(II) acetate monohydrate (108 mg, 0.525 mmol) for 18.5 h afforded after flash chromatography (heptane/EtOAc, 100:0−0:100) the title compound as a white solid (62.4 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, J = 15.5 Hz, 1H), 8.07 (s, 1H), 7.74 (d, J = 2.0 Hz, 1H), 7.70 (d, J = 2.0 Hz, 1H), 6.77 (d, J = 15.5 Hz, 1H), 3.82 (s, 3H), 3.12 (s, 3H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 158.9, 143.3, 139.2, 136.8, 136.0, 132.4, 131.3, 130.5, 127.4, 123.4, 43.0, 39.9; HRMS m/z calcd for $C_{12}H_{11}ClN_2O_3S$ [M + H]$^+$: 299.0252. Found 299.0246.

Phenyl (*E*)-2-(6,7-Dimethoxy-3-methyl-4-oxo-3,4-dihydrophthalazin-5-yl)ethene-1-sulfonate (1e). Following general procedure B, reaction of 6,7-dimethoxy-2-methylphthalazin-1(2*H*)-one (43.5 mg, 0.250 mmol), phenyl vinylsulfonate (92.1 mg, 0.500 mmol), tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (10.4 mg, 0.0125 mmol), and copper(II) acetate monohydrate (108 mg, 0.525 mmol) for 22 h afforded after flash chromatography (heptane/iPrOAc, 100:0−0:100) the title compound as a white solid (74.6 mg, 74%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, J = 15.7 Hz, 1H), 7.98 (s, 1H), 7.44−7.26 (m, 5H), 7.07 (s, 1H), 7.02 (d, J = 15.7 Hz, 1H), 4.03 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 159.0, 156.8, 151.3, 149.9, 140.3, 136.2, 129.7, 128.6, 126.9, 126.6, 126.5, 122.3, 120.1, 108.4, 61.0, 56.3, 39.9; HRMS m/z calcd for $C_{19}H_{18}N_2O_6S$ [M + H]$^+$: 403.0958. Found 403.0952.

*Diethyl (E)-(2-(1-Chloro-3-methyl-4-oxo-3,4-dihydrophthalazin-5-yl)vinyl)phosphonate (**1f**).* Following general procedure B, reaction of 4-chloro-2-methylphthalazin-1(2*H*)-one (59.8 mg, 0.250 mmol), diethyl vinylphosphonate (77.1 μL, 0.500 mmol), tris(acetonitrile)-pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (10.4 mg, 0.0125 mmol), and copper(II) acetate monohydrate (108 mg, 0.525 mmol) for 18.5 h afforded after flash chromatography (CH_2Cl_2/MeOH, 100:0−95:5) and preparative HPLC purification (Gemini-NX C18 50 × 30 mm, 5 μm packing, 110 Å particle size, 20:80−60:40 MeCN/0.1% aq NH_4OH) the title compound as a white solid (31.9 mg, 36%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (dd, J_{P-H} = 22.0 Hz, J_{H-H} = 17.5 Hz, 1H), 8.04 (dd, J = 7.0, 2.2 Hz, 1H), 7.95−7.78 (m, 2H), 6.12 (dd, J_{P-H} = 19.1 Hz, J_{H-H} = 17.5 Hz, 1H), 4.36−4.14 (m, 4H), 3.80 (s, 3H), 1.40 (t, J = 7.0 Hz, 6H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 159.0, 147.5 (d, J_{C-P} = 8.9 Hz), 138.8 (d, J_{C-P} = 25.2 Hz), 136.9, 133.4, 132.2 (d, J_{C-P} = 2.7 Hz), 129.9, 127.1, 125.3, 118.8 (d, J_{C-P} = 189.3 Hz), 62.2 (d, J_{C-P} = 6.2 Hz), 39.8, 16.5 (d, J_{C-P} = 7.0 Hz); ^{31}P{^{1}H}NMR (162 MHz, $CDCl_3$) δ 17.3; HRMS m/z calcd for $C_{15}H_{18}ClN_2O_4P$ [M + H]$^+$: 357.0765. Found 357.0759.

*(E)-2-(3-Benzyl-6-chloro-4-oxo-3,4-dihydrophthalazin-5-yl)-N,N-dimethylethene-1-sulfonamide (**1g**).* Following general procedure B, 2-benzyl-7-chlorophthalazin-1(2*H*)-one (67.7 mg, 0.250 mmol), ethenesulfonic acid dimethylamide (69.0 mg, 0.500 mmol), tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (10.4 mg, 0.0125 mmol), and copper(II) acetate monohydrate (108 mg, 0.525 mmol) were reacted for 18.5 h. Flash chromatographic elution (heptane/iPrOAc, 100:0−40:60) afforded recovered starting material (37.5 mg, 55%) followed by the title compound as a white solid (35.4 mg, 35%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 15.9 Hz, 1H), 8.09 (s, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 6.8 Hz, 2H), 7.36−7.27 (m, 3H), 6.43 (d, J = 15.9 Hz, 1H), 5.33 (s, 2H), 2.93 (s, 6H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 157.9, 139.8, 136.7, 136.6, 134.9, 133.5, 129.4, 128.8, 128.5, 127.9, 127.5, 127.4, 127.2, 127.2, 54.9, 37.7; HRMS m/z calcd for $C_{19}H_{18}ClN_3O_3S$ [M + H]$^+$: 404.0830. Found 404.0827.

*Diethyl (E)-(2-(3-Methyl-7-(2-morpholinothiazol-4-yl)-4-oxo-3,4-dihydrophthalazin-5-yl)vinyl)phosphonate (**1h**).* Following general procedure B, reaction of 2-methyl-6-(2-morpholinothiazol-4-yl)-phthalazin-1(2*H*)-one (70.3 mg, 0.214 mmol), diethyl vinylphosphonate (66.0 μL, 0.428 mmol), tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (8.9 mg, 0.0107 mmol), and copper(II) acetate monohydrate (92.5 mg, 0.450 mmol) for 17.5 h afforded after flash chromatography (CH_2Cl_2/MeOH, 100:0−95:5) and preparative HPLC purification (Gemini-NX C18 50 × 30 mm, 5 μm packing, 110 Å particle size, 20:80−60:40 MeCN/0.1% aq NH_4OH) the title compound as a yellow solid (31.8 mg, 30%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (dd, J_{P-H} = 22.0 Hz, J_{H-H} = 17.5 Hz, 1H), 8.20 (br s, 1H), 8.13 (br s, 1H), 8.12 (s, 1H), 7.07 (s, 1H), 6.22 (dd, J_{P-H} = 19.2 Hz, J_{H-H} = 17.5 Hz, 1H), 4.30−4.19 (m, 4H), 3.93−3.84 (m, 4H), 3.82 (s, 3H), 3.62−3.54 (m, 4H), 1.41 (t, J = 7.0 Hz, 6H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 171.5, 159.6, 149.3, 147.9 (d, J_{C-P} = 7.7 Hz), 139.0, 138.2 (d, J_{C-P} = 25.0 Hz), 137.6, 131.7, 128.3 (br), 124.3, 123.5, 118.0 (d, J_{C-P} = 189.6 Hz), 105.2, 66.2, 62.3 (d, J_{C-P} = 6.0 Hz), 48.6, 39.8, 16.5 (d, J_{C-P} = 6.0 Hz); ^{31}P{^{1}H}NMR (162 MHz, $CDCl_3$) δ 17.8; HRMS m/z calcd for $C_{22}H_{27}N_4O_5PS$ [M + H]$^+$: 491.1513. Found 491.1503.

*(E)-6-Bromo-2-methyl-8-styrylphthalazin-1(2H)-one (**1i**).* Following general procedure B, 6-bromo-2-methylphthalazin-1(2*H*)-one (59.8 mg, 0.250 mmol), styrene (57.5 μL, 0.500 mmol), tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (10.4 mg, 0.0125 mmol), and copper(II) acetate monohydrate (108 mg, 0.525 mmol) were reacted for 18.5 h. Flash chromatographic elution (heptane/iPrOAc, 100:0−80:20) afforded the title compound as a white solid (46.9 mg, 55%) followed by recovered starting material (20.4 mg, 34%). Data for target: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 16.2 Hz, 1H), 8.03 (d, J = 1.8 Hz, 1H), 7.97 (s, 1H), 7.69 (d, J = 1.8 Hz, 1H), 7.65−7.58 (m, 2H), 7.41−7.32 (m, 2H), 7.32−7.27 (m, 1H), 6.99 (d, J = 16.2 Hz, 1H), 3.81 (s, 3H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 159.9, 142.2, 136.9, 136.4, 133.5, 132.5, 132.5, 128.7, 128.4, 127.6, 127.2, 127.2, 127.0, 122.7, 40.0; HRMS m/z calcd for $C_{17}H_{13}BrN_2O$ [M + H]$^+$: 341.0284. Found 341.0280.

*(E)-4-Chloro-2-methyl-8-(2-(naphthalen-2-yl)vinyl)phthalazin-1(2H)-one (**1j**).* Following general procedure B, reaction of 4-chloro-2-methylphthalazin-1(2*H*)-one (48.7 mg, 0.250 mmol), 2-vinylnaphthalene (77.1 mg, 0.500 mmol), tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (10.4 mg, 0.0125 mmol), and copper(II) acetate monohydrate (108 mg, 0.525 mmol) for 22 h afforded after flash chromatography (heptane/iPrOAc, 100:0−85:15) the title compound as a yellow solid (20.3 mg, 23%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, J = 16.2 Hz, 1H), 8.07 (d, J = 7.7 Hz, 1H), 7.97−7.78 (m, 7H), 7.51−7.42 (m, 2H), 7.16 (d, J = 16.2 Hz, 1H), 3.83 (s, 3H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 159.9, 141.0, 137.5, 134.8, 133.6, 133.3, 133.3, 133.0, 131.3, 130.1, 128.4, 128.2, 128.1, 127.7, 127.3, 126.3, 126.1, 125.2, 124.6, 124.1, 39.9; HRMS m/z calcd for $C_{21}H_{15}ClN_2O$ [M + H]$^+$: 347.0946. Found 347.0940.

*2-Methyl-8-(3-oxopentyl)phthalazin-1(2H)-one (**1l**) and (E)-2-methyl-8-(3-oxopent-1-en-1-yl)phthalazin-1(2H)-one (**1k**).* Following general procedure B, 2-methylphthalazin-1(2*H*)-one (40.0 mg, 0.250 mmol), ethyl vinyl ketone (49.7 μL, 0.500 mmol), tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (10.4 mg, 0.0125 mmol), and copper(II) acetate monohydrate (108 mg, 0.525 mmol) were reacted for 17 h and purified by flash chromatography (heptane/iPrOAc, 100:0−50:50). The first to elute was 2-methyl-8-(3-oxopentyl)phthalazin-1(2*H*)-one as a colorless liquid (32.9 mg, 54%), followed by (*E*)-2-methyl-8-(3-oxopent-1-en-1-yl)phthalazin-1(2*H*)-one as a yellow solid (18.2 mg, 30%).

Data for first: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.66 (dd, J = 7.6, 7.6 Hz, 1H), 7.59 (dd, J = 7.6, 1.1 Hz, 1H), 7.54 (dd, J =

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7.6, 1.1 Hz, 1H), 3.82 (s, 3H), 3.60 (t, J = 7.3 Hz, 2H), 2.87 (t, J = 7.3 Hz, 2H), 2.44 (q, J = 7.4 Hz, 2H), 1.03 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$) δ 210.9, 159.9, 143.9, 137.9, 134.7, 132.6, 131.7, 125.4, 125.0, 44.0, 39.8, 35.9, 29.9, 7.7; HRMS m/z calcd for $C_{14}H_{16}N_2O_2$ $[M + H]^+$: 245.1285. Found 245.1280.

Data for second: ^1H NMR (400 MHz, $CDCl_3$) δ 9.12 (d, J = 16.5 Hz, 1H), 8.13 (s, 1H), 7.88−7.77 (m, 2H), 7.72 (dd, J = 7.5, 1.4 Hz, 1H), 6.48 (d, J = 16.5 Hz, 1H), 3.85 (s, 3H), 2.90 (q, J = 7.4 Hz, 2H), 1.20 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$) δ 201.8, 160.0, 142.8, 137.6, 137.5, 132.9, 131.3, 130.9, 130.7, 127.7, 124.9, 40.0, 32.2, 8.2; HRMS m/z calcd for $C_{14}H_{14}N_2O_2$ $[M + H]^+$: 243.1128. Found 243.1125.

Rhodium(III)-Catalyzed C−H Alkenylation with Alkynes. *General Procedure (C).* Under nitrogen gas, anhydrous 1,2-dichloroethane (0.05 M) and acetic acid (5 equiv) were added to a 4 dram vial containing tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (0.05 equiv), the phthalazin-1(2*H*)-one, and the alkyne, if solid (1.1 equiv). If the alkene was a liquid, it was charged into the vial immediately before the solvent and acetic acid. The vial was sealed tightly, and the reaction mixture was stirred at 120 °C for the noted reaction time. Following concentration, the reaction residue was subjected to flash column chromatographic methods using the stated eluent system.

*(E)-6-Bromo-8-(1,2-diphenylvinyl)-2-methylphthalazin-1(2H)-one (**2a**).* Following general procedure C, reaction of 6-bromo-2-methylphthalazin-1(2*H*)-one (59.8 mg, 0.250 mmol), diphenylacetylene (44.6 mg, 0.250 mmol), tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (10.4 mg, 0.0125 mmol), and acetic acid (71.6 μL, 1.25 mmol) for 18 h afforded after flash chromatography (heptane/iPrOAc, 100:0−80:20) the title compound as a white solid (89.8 mg, 86%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.83 (d, J = 1.8 Hz, 1H), 7.58 (d, J = 1.8 Hz, 1H), 7.35−7.20 (m, 5H), 7.14−7.03 (m, 4H), 6.93−6.80 (m, 2H), 3.66 (s, 3H); $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$) δ 157.7, 143.3, 141.9, 141.0, 137.6, 136.8, 135.6, 132.8, 129.4, 128.4, 128.3, 128.1, 127.7, 127.4, 127.3, 126.8, 126.5, 125.7, 39.7; HRMS m/z calcd for $C_{23}H_{17}BrN_2O$ $[M + H]^+$: 417.0597. Found 417.0591.

*(E)-2-(8-(1,2-Diphenylvinyl)-1-oxophthalazin-2(1H)-yl)acetic Acid (**2b**).* Following general procedure C, reaction of 2-(1-oxophthalazin-2(1*H*)-yl)acetic acid (51.0 mg, 0.250 mmol), diphenylacetylene (49.0 mg, 0.275 mmol), tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (10.4 mg, 0.0125 mmol), and acetic acid (71.6 μL, 1.25 mmol) for 17 h afforded after preparative HPLC purification (Gemini-NX C18 50 × 30 mm, 5 μm packing, 110 Å particle size, 30:70−70:30 MeCN/0.1% aq HCOOH) the title compound as a white solid (54.1 mg, 57%); ^1H NMR (400 MHz, DMSO-d_6) δ 12.91 (br s, 1H), 8.47 (s, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.92 (t, J = 7.6 Hz, 1H), 7.45 (d, J = 7.4 Hz, 1H), 7.32−7.17 (m, 5H), 7.13 (s, 1H), 7.10−7.00 (m, 3H), 6.84 (d, J = 7.3 Hz, 2H), 4.75−4.57 (m, 2H); $^{13}C\{^1H\}$NMR (101 MHz, DMSO-d_6) δ 169.2, 157.3, 141.7, 141.7, 139.9, 137.9, 136.9, 134.7, 133.9, 131.3, 128.9, 128.0, 127.9, 127.0, 126.9, 126.5, 126.0, 125.9, 125.9, 52.4; HRMS m/z calcd for $C_{24}H_{18}N_2O_3$ $[M + H]^+$: 383.1390. Found 383.1384.

*(E)-7-Bromo-8-(1,2-diphenylvinyl)-2-methylphthalazin-1(2H)-one (**2c**).* Following general procedure C, reaction of 7-bromo-2-methylphthalazin-1(2*H*)-one (59.8 mg, 0.250 mmol), diphenylacetylene (49.0 mg, 0.275 mmol), tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (10.4 mg, 0.0125 mmol), and acetic acid (71.6 μL, 1.25 mmol) for 18 h afforded after flash chromatography (heptane/iPrOAc, 100:0−75:25) and preparative HPLC purification (Gemini-NX C18 50 × 30 mm, 5 μm packing, 110 Å particle size, 40:60−80:20 MeCN/0.1% aq NH_4OH), the title compound as a white solid (54.7 mg, 52%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 8.03 (d, J = 8.3 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.33−7.19 (m, 6H), 7.09−7.02 (m, 3H), 6.89−6.81 (m, 2H), 3.68 (s, 3H); $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$) δ 157.2, 141.1, 140.4, 139.8, 137.8, 137.2, 136.4, 130.5, 129.7, 128.5, 128.4, 128.3, 128.1, 127.3, 126.9, 126.9, 126.4, 40.0 (one carbon is not observed); HRMS m/z calcd for $C_{23}H_{17}BrN_2O$ $[M + H]^+$: 417.0597. Found 417.0589.

*Ethyl (E)-2-(8-(1,2-Diphenylvinyl)-1-oxophthalazin-2(1H)-yl)-acetate (**2d**).* Following general procedure C, reaction of ethyl 2-(1-oxophthalazin-2(1*H*)-yl)acetate (58.1 mg, 0.250 mmol), diphenylacetylene (49.0 mg, 0.275 mmol), tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (10.4 mg, 0.0125 mmol), and acetic acid (71.6 μL, 1.25 mmol) for 18 h afforded after flash chromatography (heptane/iPrOAc, 100:0−70:30) and preparative HPLC purification (Gemini-NX C18 50 × 30 mm, 5 μm packing, 110 Å particle size, 40:60−80:20 MeCN/0.1% aq NH_4OH) the title compound as a white solid (40.5 mg, 40%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.79−7.65 (m, 2H), 7.47 (dd, J = 7.1, 1.5 Hz, 1H), 7.26−7.18 (m, 5H), 7.11 (s, 1H), 7.09−7.00 (m, 3H), 6.92−6.83 (m, 2H), 4.90 (d, J = 16.8 Hz, 1H), 4.71 (d, J = 16.7 Hz, 1H), 4.15−4.02 (m, 2H), 1.13 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$) δ 168.0, 158.1, 142.3, 142.2, 141.4, 138.0, 137.3, 135.4, 133.4, 131.8, 129.4, 128.2, 128.0, 127.2, 127.1, 127.0, 126.5, 126.4, 126.2, 61.4, 52.6, 14.0; HRMS m/z calcd for $C_{26}H_{22}N_2O_3$ $[M + H]^+$: 411.1703. Found 411.1696.

*(E)-6-Chloro-2-methyl-8-(1-phenylprop-1-en-2-yl)phthalazin-1(2H)-one (**2e**) and (Z)-6-Chloro-2-methyl-8-(1-phenylprop-1-en-2-yl)phthalazin-1(2H)-one (**2f**).* Following general procedure C, 6-chloro-2-methylphthalazin-1(2*H*)-one (48.7 mg, 0.250 mmol), 1-phenyl-1-propyne (31 μL, 0.250 mmol), tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (10.4 mg, 0.0125 mmol), and acetic acid (71.6 μL, 1.25 mmol) were reacted for 19.5 h and purified by flash chromatography (heptane/iPrOAc, 100:0−80:20). The first to elute was (*E*)-6-chloro-2-methyl-8-(1-phenylprop-1-en-2-yl)phthalazin-1(2*H*)-one as a colorless liquid (36.0 mg, 46%), followed by (*Z*)-6-chloro-2-methyl-8-(1-phenylprop-1-en-2-yl)-phthalazin-1(2*H*)-one as a white solid (21.0 mg, 27%);

Data for first: ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.46 (d, J = 7.6 Hz, 2H), 7.41−7.33 (m, 2H), 7.26−7.23 (m, 1H), 6.36 (s, 1H), 3.81 (s, 3H), 2.28 (s, 3H); $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$) δ 158.3, 149.4, 139.8, 138.7, 137.5, 136.1, 132.9, 132.4, 129.1, 128.2, 127.6, 126.7, 124.6, 123.5, 39.8, 20.5; HRMS m/z calcd for $C_{18}H_{15}ClN_2O$ $[M + H]^+$: 311.0946. Found 311.0942.

Data for second: ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.28 (d, J = 2.0 Hz, 1H), 7.08−6.97 (m, 3H), 6.80−6.70 (m, 2H), 6.55 (s, 1H), 3.81 (s, 3H), 2.25 (s, 3H); $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$) δ 158.1, 146.3, 139.2, 138.6, 137.0, 136.1, 133.0, 132.6, 128.6, 128.0, 126.2, 126.1, 124.6, 124.2, 39.6, 27.1; HRMS m/z calcd for $C_{18}H_{15}ClN_2O$ $[M + H]^+$: 311.0946. Found 311.0938.

Rhodium(III)-Catalyzed C−H Iodination with *N*-Iodosuccinimide. *General Procedure (D).* Under nitrogen gas, anhydrous 1,2-dichloroethane (0.05 M) was added to a 4 dram vial containing tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (0.05 equiv), *N*-iodosuccinimide (1.0 equiv), and the phthalazin-1(2*H*)-one. The vial was sealed tightly, and the reaction mixture was stirred at 120 °C for the noted reaction time. The mixture was diluted with dichloromethane, washed with 1 M aqueous sodium thiosulfate, and organics dried over magnesium sulfate. Following concentration, the reaction residue was subjected to flash column chromatographic methods using the stated eluent system.

*8-Iodo-2-methylphthalazin-1(2H)-one (**3a**).* Following general procedure D, 2-methylphthalazin-1(2*H*)-one (801 mg, 5.00 mmol), *N*-iodosuccinimide (1.15 g, 5.00 mmol), and tris(acetonitrile)-pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (208 mg, 0.250 mmol) were reacted for 18 h. Flash chromatographic elution (heptane/iPrOAc, 100:0−70:30) afforded the title compound as a white solid (501 mg, 35%) followed by recovered starting material (320 mg, 40%). Data for target: ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (dd, J = 8.0, 0.7 Hz, 1H), 8.11 (s, 1H), 7.65 (dd, J = 8.0, 0.7 Hz, 1H), 7.36 (dd, J = 7.8, 7.8 Hz, 1H), 3.82 (s, 3H); $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$) δ 157.6, 145.8, 137.0, 133.2, 130.9, 126.9, 126.4, 92.0, 40.2; HRMS m/z calcd for $C_9H_7IN_2O$ $[M + H]^+$: 286.9676. Found 286.9671.

*6-Bromo-8-iodo-2-methylphthalazin-1(2H)-one (**3b**).* Following general procedure D, 6-bromo-2-methylphthalazin-1(2*H*)-one (30.0

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mg, 0.125 mmol), *N*-iodosuccinimide (28.8 mg, 0.125 mmol), and tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (5.2 mg, 0.0063 mmol) were reacted at 100 °C for 18 h. Flash chromatographic elution (heptane/iPrOAc, 100:0−80:20) afforded the title compound as a white solid (25.1 mg, 55%), followed by recovered starting material (10.4 mg, 35%). Data for target: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 2.0 Hz, 1H), 8.04 (s, 1H), 7.79 (d, J = 2.0 Hz, 1H), 3.80 (s, 3H); $^{13}C\{^{1}H\}$NMR (101 MHz, $CDCl_3$) δ 157.2, 147.7, 135.6, 131.3, 129.2, 127.3, 125.1, 93.2, 40.2; HRMS m/z calcd for $C_9H_6BrIN_2O$ $[M + H]^+$: 364.8781. Found 364.8774.

4-Chloro-8-iodo-2-methylphthalazin-1(2H)-one (**3c**). Following general procedure D, 4-chloro-2-methylphthalazin-1(2*H*)-one (48.7 mg, 0.250 mmol), *N*-iodosuccinimide (57.4 mg, 0.250 mmol), and tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (10.4 mg, 0.0125 mmol) were reacted for 16.5 h. Flash chromatographic elution (heptane/iPrOAc, 100:0−70:30) afforded the title compound as a white solid (20.2 mg, 25%), followed by recovered starting material (29.9 mg, 61%). Data for target: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (dd, J = 7.9, 0.7 Hz, 1H), 8.03 (dd, J = 8.1, 0.7 Hz, 1H), 7.45 (dd, J = 8.0, 8.0 Hz, 1H), 3.81 (s, 3H); $^{13}C\{^{1}H\}$NMR (101 MHz, $CDCl_3$) δ 157.0, 147.0, 136.3, 133.7, 129.9, 126.8, 126.7, 93.2, 40.1; HRMS m/z calcd for $C_9H_6ClIN_2O$ $[M + H]^+$: 320.9286. Found 320.9279.

8-Iodo-2,4-dimethylphthalazin-1(2H)-one (**3d**). Following general procedure D, 2,4-dimethylphthalazin-1(2*H*)-one (43.5 mg, 0.250 mmol), *N*-iodosuccinimide (57.4 mg, 0.250 mmol), and tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (10.4 mg, 0.0125 mmol) were reacted for 18 h. Flash chromatographic elution (heptane/iPrOAc, 100:0−60:40) afforded the title compound as a white solid (29.6 mg, 40%), followed by recovered starting material (16.8 mg, 39%). Data for target: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dd, J = 8.0, 0.8 Hz, 1H), 7.74 (dd, J = 8.0, 0.8 Hz, 1H), 7.36 (dd, J = 7.9, 7.9 Hz, 1H), 3.79 (s, 3H), 2.53 (s, 3H); $^{13}C\{^{1}H\}$NMR (101 MHz, $CDCl_3$) δ 157.4, 145.6, 142.4, 132.9, 131.0, 126.2, 125.5, 92.7, 39.9, 19.5; HRMS m/z calcd for $C_{10}H_9IN_2O$ $[M + H]^+$: 300.9832. Found 300.9827.

6-Chloro-8-iodo-2-methylphthalazin-1(2H)-one (**3e**). Following general procedure D, 6-chloro-2-methylphthalazin-1(2*H*)-one (48.7 mg, 0.250 mmol), *N*-iodosuccinimide (57.4 mg, 0.250 mmol), and tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (10.4 mg, 0.0125 mmol) were reacted for 17 h. Flash chromatographic elution (heptane/iPrOAc, 100:0−70:30) afforded the title compound as a white solid (25.9 mg, 32%), followed by recovered starting material (24.7 mg, 51%). Data for target: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 2.0 Hz, 1H), 8.05 (s, 1H), 7.63 (d, J = 2.0 Hz, 1H), 3.81 (s, 3H); $^{13}C\{^{1}H\}$NMR (101 MHz, $CDCl_3$) δ 157.1, 145.2, 138.9, 135.7, 131.1, 126.0, 124.8, 93.0, 40.2; HRMS m/z calcd for $C_9H_6ClIN_2O$ $[M + H]^+$: 320.9286. Found 320.9281.

7-Bromo-8-iodo-2-methylphthalazin-1(2H)-one (**3f**). Following general procedure D, reaction of 7-bromo-2-methylphthalazin-1(2*H*)-one (59.8 mg, 0.250 mmol), *N*-iodosuccinimide (57.4 mg, 0.250 mmol), and tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (10.4 mg, 0.0125 mmol) for 18 h afforded after flash chromatography (heptane/iPrOAc, 100:0−70:30) and preparative HPLC purification (Gemini-NX C18 50 × 30 mm, 5 μm packing, 110 Å particle size, 20:80−60:40 MeCN/0.1% aq NH_4OH) recovered starting material (16.6 mg, 28%) and the title compound as a white solid (19.8 mg, 22%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 3.84 (s, 3H); $^{13}C\{^{1}H\}$NMR (101 MHz, $CDCl_3$) δ 156.5, 138.7, 136.4, 136.1, 129.4, 128.9, 127.4, 100.3, 40.7; HRMS m/z calcd for $C_9H_6BrIN_2O$ $[M + H]^+$: 364.8781. Found 364.8774.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02522.

^{1}H, ^{13}C, and ^{31}P NMR spectra (PDF)

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Notes

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