JOC Article

Regioselective Synthesis of *N*-Aminoisoindolones and Mono-*N*- and Di-*N,N′*-substituted Phthalazones Utilizing Hydrazine Nucleophiles in a Palladium-Catalyzed Three-Component Cascade Process

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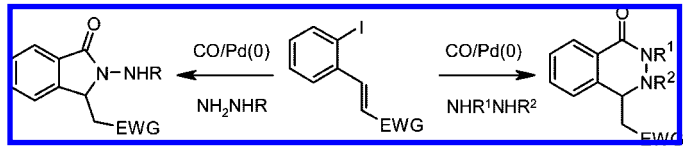

A palladium-catalyzed three-component cascade process for the synthesis of isoindolone and phthalazone derivatives is reported. The cascade process involves carbonylation of an aryl iodide/Michael acceptor to give an acylpalladium species which is intercepted by a hydrazine nucleophile. Intramolecular Michael addition follows to give either *N*-aminoisoindolones or mono-*N*- and di-*N,N′*-phthalazones depending on whether a monosubstituted or 1,2-disubstituted hydrazine nucleophile is used.

Introduction

Organic synthesis has classically involved the stepwise formation of individual bonds in the construction of a target molecule. However, it is substantially more efficient if several bonds are formed in a single synthetic operation without the need to isolate intermediates. Reactions that enable this are known as cascade processes and work through a sequence of discrete chemical transformations in which the preceding reaction creates the functionality to trigger the subsequent reaction, through a series of reactive intermediates, until the final product is formed. Cascade reactions have long attracted interest due to their many benefits including high atom economy, labor and waste saving attributes and ability to rapidly access structurally complex compounds from relatively simple starting materials.[1]

Our group has previously described two novel palladium-catalyzed cascade processes for the synthesis of *N*-substituted isoindolones from easily accessible starting materials.[2] Substituted isoindolones of general structure **1**, which are known to possess pharmacological activity,[3] were synthesized using a palladium-catalyzed three-component carbonylation/amination/Michael addition cascade sequence (Scheme 1) from the corresponding aryl iodide/Michael acceptor **2**, carbon monoxide **3**, and primary amine **4** in 43−99% yield.[2b]

In an effort to further diversify this cascade process, we evaluated the use of monosubstituted hydrazines **6** as cascade nucleophiles. These could lead to the formation of *N*-aminoisoindolones **8** or phthalazones of general structure **9** (Scheme 2). Both isoindolone and the dihydro-4-substituted phthalaz-1-one motifs **8** and **9** are of pharmacological interest with the former appearing as a subunit in potential sedatives[4] and the latter appearing as a subunit in the diuretic BTS3954.[5]

Prior literature on the synthesis and applications of phthalazones is almost entirely concerned with 4-substituted phthalaz-

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(1) (a) Nicolau, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (b) Dondas, H. A.; Fishwick, C. W. G.; Gai, X.; Grigg, R.; Kilner, C.; Dumronchai, N.; Kongkathip, B.; Kongkathip, N.; Ploysuk, C.; Sridharan, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 7570. (c) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65. (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (e) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195. (f) Grigg, R.; Inman, M.; Kilner, C.; Koppen, I.; Marchbank, J.; Selby, P. J.; Sridharan, V. *Tetrahedron* **2007**, *63*, 6152.

(2) (a) Grigg, R.; Zhang, L.; Collard, S.; Keep, A. *Tetrahedron Lett.* **2003**, *44*, 6979. (b) Gai, X.; Grigg, R.; Khamnaen, T.; Rajviroongit, S.; Sridharan, V.; Zhang, L.; Collard, S.; Keep, A. *Tetrahedron Lett.* **2003**, *44*, 7441.

(3) (a) Takahashi, I.; Kawakami, T.; Hirano, E.; Yokota, H.; Kitajima, H. *Synlett* **1996**, 353. (b) Sobera, L. A.; Leeson, P. A.; Silvestre, J.; Castaner, J. *Drugs Future* **2001**, *26*, 651. (c) Anzini, M.; Capelli, A.; Vomero, S.; Giorgi, G.; Langer, T.; Bruni, G.; Rome, M. K.; Baile, A. S. *J. Med. Chem.* **1996**, *39*, 4275. (d) Limeres, R.; Garcia, R.; Bayod, M.; Blieva, R. *Tetrahedron: Asymmetry* **1997**, *8*, 995.

(4) Toyoka, K.; Kanamitsu, N.; Yoshimra, M. Patent WO2004048332, 2004.

(5) Cooling, M. J.; Sim, M. F. *Br. J. Pharmacol.* **1981**, *74*, 359.

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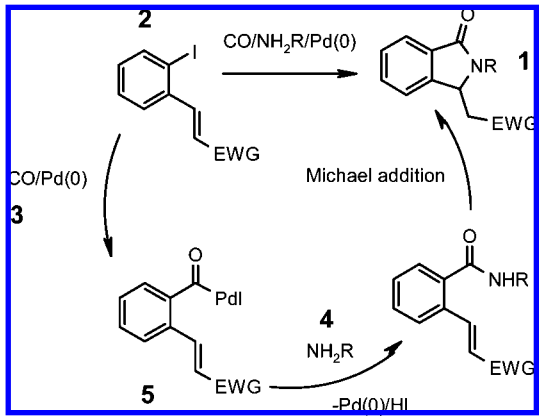
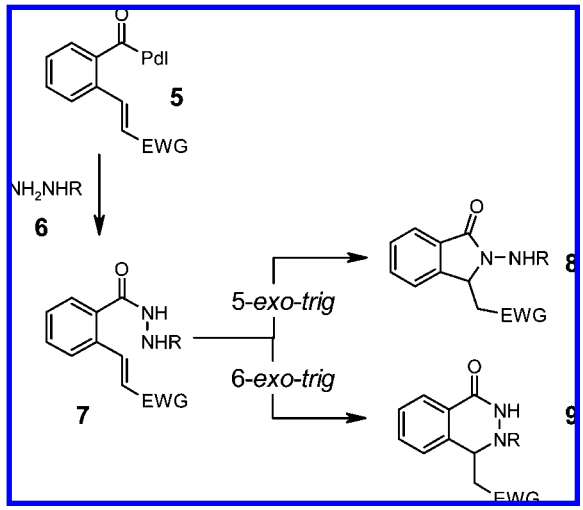
SCHEME 1



SCHEME 2



1-ones **10** (Figure 1). The majority of approaches involve phthaloyl derivatives as precursors and proceed via isoindolone intermediates.[6] Pyridyl versions **10b** and **10c** have also been reported.[6f] Katritzky has reported the 1,3-dipolar cycloaddition of 1-oxido-3-phenylphthalazinium **11** with the dipolarophiles diphenylacetylene and dimethyl acetylenedicarboxylate to afford bridged ring phthalaz-1-ones **12**.[7] These latter adducts are at the same oxidation level as the phthalaz-1-ones delivered by the palladium chemistry described herein.

It was anticipated that formation of general motifs **8** and **9** via our cascade methodology would involve nucleophilic attack on an intermediate acylpalladium species **5**, produced by the carbonylation of aryl iodide/Michael acceptor **2** in the presence of carbon monoxide and Pd(0), by the primary nitrogen of hydrazine **6** to give acylhydrazide **7** (Scheme 2). The terminating Michael addition step of the cascade could then involve the amidic *N*-atom to give isoindolone **8** via a 5-*exo-trig* ring closure or the nonamidic *N*-atom to give phthalazone **9** via a 6-*exo-trig* ring closure.

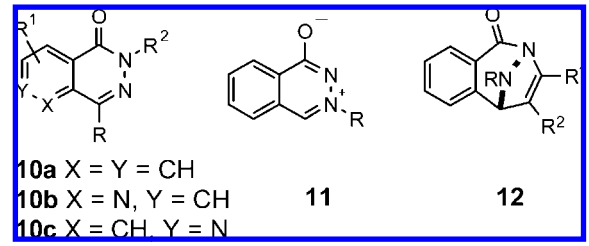


FIGURE 1. Products and intermediates of previously reported phthalazone syntheses.

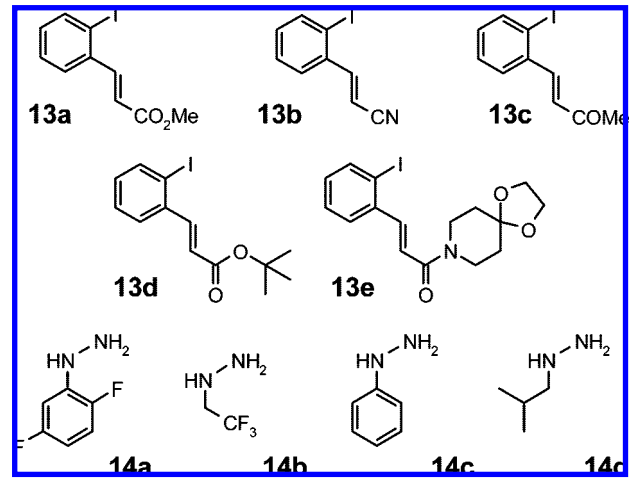


FIGURE 2. Michael acceptors and hydrazines used in the syntheses of *N*-aminoisoindolones **15a**−**j**.

Results and Discussion

The competing terminating pathways were initially examined by reacting dual aryl iodide/Michael acceptors **13a**−**c** (Figure 2)[8a] (1.0 molar equiv) with 2,5-difluorophenylhydrazine **14a** or 2,2,2-trifluoroethylhydrazine **14b** (1.2 molar equiv), carbon monoxide (1 atm), $Pd(OAc)_2$ (0.03−0.05 molar equiv), PPh_3 (0.06−0.10 molar equiv), and Cs_2CO_3 (2 molar equiv) in toluene at 90 °C for 18 h. Analysis of the crude reaction mixtures by NMR revealed that only a single ABX spin system had been created. This suggested that a single cyclized product had been formed. Subsequent NMR and X-ray analysis of the isolated cyclized products revealed that *N*-aminoisoindolones **15** (Table 1) (see the Supporting Information for X-ray data for **15c**, **15e**, and **15g**) had been formed in preference to the phthalazone ring system.

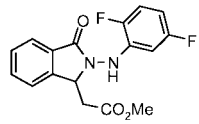
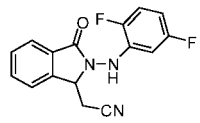
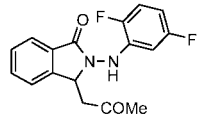
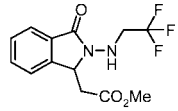
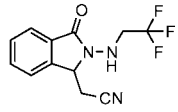
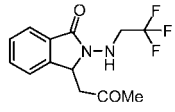
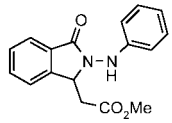
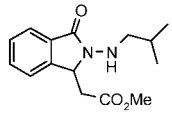
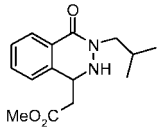
This exclusive formation was explained in terms of the 5-*exo-trig* process being kinetically favored over the competing 6-*exo-trig* process and occurred both with initial use of electron-deficient hydrazines (Table 1, entries 1−6) and on subsequent use of phenylhydrazine **14c** (Table 1, entry 7). However, when using hydrazine **14d**, analysis of the crude reaction mixture by NMR suggested that a 1:1 mixture of products **15h** and **15i** had been formed (Table 1, entry 8). This was indicated by the presence of two distinct ABX spin systems for each compound.

(6) (a) Peters, A. T.; Rowe, F. M.; Brodrick, C. I. *J. Chem. Soc.* **1948**, 1249. (b) Vaughan, W. R.; McCane, D. I.; Sloan, G. J. *J. Am. Chem. Soc.* **1951**, *73*, 2298. (c) Johnson, A. L. *J. Org. Chem.* **1976**, *41*, 836. (d) Ismail, M. F.; El-Bassiouny, F. A.; Younes, H. A. *Tetrahedron* **1984**, *40*, 2983. (e) Fahmy, A. F.; Sauer, J.; Youssef, M. S. K.; Halim, M. S. A.; Hasan, M. A. *Synth. Commun.* **1998**, *28*, 2871. (f) Saito, Y.; Sakamoto, T.; Kikugawa, Y. *Synthesis* **2001**, 221. (g) Chun, T. G.; Kim, K. S.; Lee, S.; Jeong, T. S.; Lee, H. Y.; Kim, Y. H.; Lee, W. S. *Synth. Commun.* **2004**, *34*, 1301. (h) Cheng, L.; Ying, L.; Feng, J.; Wang, C. Y.; Li, J. L.; Xu, Z. *J. Polymer Sci. Part A* **2007**, *45*, 1525. (i) Feldeak, S.; Puodzyunas, A. S.; Daugirdene, D. A.; Puodzhyunene, I. P.; Kost, A. *Khim. Farm. Zh.* **1969**, *3*, 5.

(7) Dennis, N.; Katritzky, A. R.; Ramaiah, M. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2281.

(8) (a) Grigg, R.; Gai, X.; Khamnaen, T.; Rajviroongit, S.; Sridharan, V.; Zhang, L.; Collard, S.; Keep, A. *Can. J. Chem.* **2005**, *83*, 990. (b) Bull, S. D.; Davies, S. G.; Smith, A. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, *22*, 2931.

TABLE 1. Cascade Synthesis of *N*-Aminoisoindolones from the Corresponding Aryl Iodide/Michael Acceptors and Primary Hydrazines[a]

Entry	Aryl Iodide	Hydra-zine	Product	Yield (%)
1	**13a**	**14a**	 **15a**	60[b]
2	**13b**	**14a**	 **15b**	52
3	**13c**	**14a**	 **15c**	50
4	**13a**	**14b**	 **15d**	68[c]
5	**13b**	**14b**	 **15e**	71[c]
6	**13c**	**14b**	 **15f**	59[c,d]
7	**13a**	**14c**	 **15g**	50
8	**13a**	**14d**	 **15h**	-
			 **15i**	-

[a] Reaction conditions: aryl iodide (1.0 mmol), hydrazine (1.2 mmol), CO (1 atm), $Pd(OAc)_2$ (0.03−0.05 mmol), PPh_3 (0.06−0.10 mmol), Cs_2CO_3 (2.0 mmol), toluene (20 mL), 90 °C, 18 h. [b] Reaction time: 3 h. [c] Cosolvent: acetonitrile (1 mL). [d] Reaction time: 6 h.

Unfortunately, neither of these products could be isolated cleanly by chromatography due to close-running impurities, although the suggested regiochemistry of **15i** was supported by mutual coupling of the NH proton to the corresponding ABX spin system. It was evident that formation of the isoindolone motif versus formation of the phthalazone motif was dependent on the nucleophilicity of the hydrazine used with more electron-rich nucleophiles permitting six-membered ring formation as well as five-membered ring formation.

Subsequent probing of the reaction mechanism also revealed that a small amount (~5% relative to unreacted Michael acceptor) of direct Michael adduct was formed when reacting Michael acceptor **13a** with phenylhydrazine **14c** in the absence of carbon monoxide under standard reaction conditions. This suggested that the cascade proceeded primarily through the amide intermediate **7** although direct Michael adduct formation was thought to be more likely as the nucleophile became more electron-rich.

Pursuing the 6-*exo-trig* mode of ring closure, it was anticipated that the phthalazone motif could be accessed by using 1,2-disubstituted hydrazines as cascade nucleophiles. Thus, 1-acetyl-2-phenylhydrazine **16a** (1.2 molar equiv) was reacted with aryl iodide/Michael acceptor **13a** (1.0 molar equiv), carbon monoxide (1 atm), $Pd(OAc)_2$ (0.05 molar equiv), PPh_3 (0.10 molar equiv), and Cs_2CO_3 (2.0 molar equiv) in acetonitrile (10 mL) at 85 °C for 20 h. Analysis of the crude reaction mixture by NMR indicated the formation of a single ABX spin system. This suggested that a single phthalazone product had been formed regioselectively. Subsequently, phthalazone **18a** (Table 2, entry 1) was isolated from the complex reaction mixture in 19% yield and the regiochemistry confirmed by X-ray crystallography (see the Supporting Information). Evidently, the more nucleophilic aniline hydrazine subunit had attacked the intermediate acylpalladium species leaving the less nucleophilic acetamide hydrazine subunit to take part in the Michael addition step of the cascade to give the [6,6]-heterocyclic system.

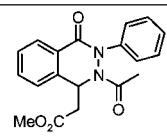
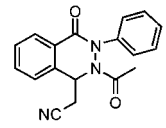
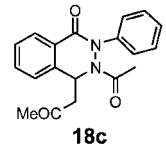
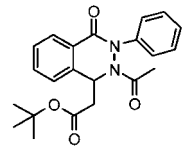
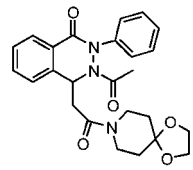
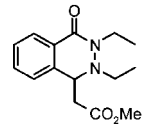
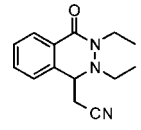
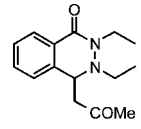
In an effort to improve the efficiency of the reaction and to simplify the synthetic procedure, reaction conditions employing palladacycle **17** were then explored. Our group has previously shown that palladacycle **17** is rapidly converted into catalytically active and ligand-less palladium(0) nanoparticles under an atmosphere of carbon monoxide.[9] Thus, 1-acetyl-2-phenylhydrazine **16a** (1.2 molar equiv) was reacted with aryl iodide/Michael acceptor **13a** (1.0 molar equiv), carbon monoxide (1 atm), palladacycle **17** (0.05 molar equiv), and Cs_2CO_3 (2.0 molar equiv) in DMF (5 mL) at 100 °C. The reaction was found to go to completion after 3 h and phthalazone **18a** was isolated as the sole cyclized product in 55% yield (Table 2, entry 1).

In subsequent exemplification, 1-acetyl-2-phenylhydrazine **13a** (1.4 molar equiv) or 1,2-diethylhydrazine dihydrochloride **13b** (1.3 molar equiv) was reacted with aryl iodide/Michael acceptors **13a**−**e**[8] (1.0 molar equiv), carbon monoxide (1 atm), palladacycle **17** (0.05 molar equiv), and Cs_2CO_3 (2.0 molar equiv) in DMF to give the corresponding phthalazones **18b**−**h** in 43−77% yield (Table 2). Reducing the reaction temperature from 100 to 60 °C avoided the formation of more complex reaction mixtures for the syntheses of phthalazones **18c** and **18e** (Table 2, entries 3 and 5). The regiochemistry of products **18b**−**e** was assumed on the basis of the X-ray structure for **18a**, and this was supported by NOE data.

The reasons for the generally moderate yields obtained in Tables 1 and 2 are unclear. Generally, no significant NMR signals, apart from those belonging to the subsequently isolated products, were observed in the crude reaction mixtures. The exception to this was the use of Michael acceptor **13a** with

(9) Grigg, R.; Zhang, L.; Collard, S.; Ellis, P.; Keep, A. *J. Organomet. Chem.* **2004**, *689*, 170.

TABLE 2. Cascade Synthesis of Di-*N,N′*-substituted Phthalazones from the Corresponding Aryl Iodide/Michael Acceptors and Disubstituted Hydrazines[a]

Entry	Aryl Iodide	Temp/ Time	Product	Yield (%)
1	**13a**	100 °C 3 h	 **18a**	19[b] 55
2	**13b**	100 °C 1.5 h	 **18b**	43
3	**13c**	60 °C 2.5 h	 **18c**	60
4	**13d**	100 °C 1.5 h	 **18d**	63
5	**13e**	60 °C 3 h	 **18e**	77
6	**13a**	70 °C 3 h	 **18f**	55[c]
7	**13b**	80 °C 2 h	 **18g**	50[c]
8	**13c**	70 °C 4.5 h	 **18h**	51[c]

[a] Reaction conditions: aryl iodide (0.5 mmol), 1-acetyl-2-phenylhydrazine **16a** (0.7 mmol), CO (1 atm), palladacycle **17** (0.025 mmol), Cs_2CO_3 (1.0 mmol), DMF (5 mL). [b] Aryl iodide (0.5 mmol), 1-acetyl-2-phenylhydrazine **16a** (0.6 mmol), CO (1 atm), $Pd(OAc)_2$ (0.025 mmol), PPh_3 (0.05 mmol), Cs_2CO_3 (1.0 mmol), MeCN (10 mL), 85 °C, 20 h. [c] Aryl iodide (0.5 mmol), $Et_2NH.2HCl$ **16b** (0.65 mmol), CO (1 atm), palladacycle **17** (0.025 mmol), Cs_2CO_3 (1.5 mmol), water (0.2 mL), DMF (5 mL).

hydrazine **14d** to give products **15h** and **15i**. It is possible that some products may have undergone retro-Michael addition during column chromatography, contributing toward poorer yields.

SCHEME 3

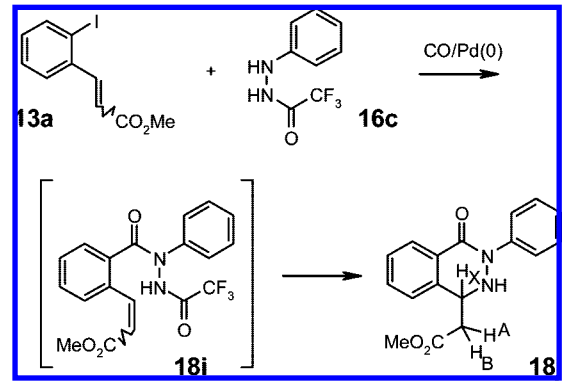


FIGURE 3. Hydrazines and precatalyst used in the syntheses of phthalazones **18a**−**h**.

In seeking access to regioselective mono-*N*-substituted phthalazones, we took advantage of a prior observation arising from our synthesis of isoindolones where trifluoroacetamide was shown to be an excellent cascade nucleophile with hydrolytic cleavage of the trifluoroacyl moiety being achieved in situ.[2b] Hence, hydrazine **16c** (1.2 molar equiv) was reacted with Michael acceptor **13a** (1.0 molar equiv), carbon monoxide (1 atm), palladacycle **17** (0.025 molar equiv), and Cs_2CO_3 (2.0 molar equiv) in nondistilled dioxane at 100 °C for 16 h (Scheme 3). Analysis of the product by ^1H NMR spectroscopy confirmed ring formation had taken place as characterized by the formation of a single ABX spin system while mass spectrometry and ^{13}C NMR spectroscopy suggested that hydrolysis of the exocyclic N−CO bond had occurred to give phthalazone **18j** regioselectively in 54% yield. On the basis of previous observations, it was suggested that the reaction proceeded through amide intermediate **18i** although it is unclear whether hydrolysis of the exocyclic N−CO bonds occurs before or after the Michael addition ring-closing step.

Conclusion

Both *N*-aminoisoindolone and phthalazone derivatives have been synthesized in a three-component carbonylation/amination/Michael addition cascade sequence using substituted hydrazines as cascade nucleophiles. In general using monosubstituted hydrazines, 5-*exo-trig* ring closure was found to be kinetically favored over the competing 6-*exo-trig* process and resulted in [6,5]-heterocyclic products (isoindolones). However use of isobutylhydrazine showed evidence of competitive 5-and 6-*exo-trig* processes suggesting a link to the nucleophilicty of the hydrazine. Use of 1,2-disubstituted hydrazines facilitated regioselective 6-*exo-trig* ring closure and gave *N,N′*-disubstituted phthalazones. Use of trifluoroacyl-substituted phenylhydrazine provides access to mono-*N*-substituted phthalazones regioselectively. These heterocyclic motifs occur as subunits in molecules of pharmacological interest, and work continues to further exploit the cascade methodology described.

Experimental Section

General Procedure (A) for the Synthesis of Isoindolones. The reagents were stirred in toluene (presaturated with carbon monoxide) in a round-bottomed flask with palladium acetate added last. A balloon containing carbon monoxide (CO) was used to flush the system of air and maintain an atmosphere of CO while the stirred reaction mixture was heated.

General Procedure (B) for the Synthesis of Phthalazones. A carousel tube was loaded with the reagents and the solvent added last. A balloon containing carbon monoxide (CO) was used to flush the system of air via a PTFE cap fitted with septum and to maintain an atmosphere of CO while the stirred reaction mixture was heated.

General Procedure (C) for the Synthesis of Phthalazones. A carousel tube was loaded with the hydrazine salt, cesium carbonate, water, and DMF and allowed to stir at 25 °C for 5 min before the remainder of the reagents were added. A balloon containing carbon monoxide (CO) was used to flush the system of air via a PTFE cap fitted with septum and to maintain an atmosphere of CO while the reaction was heated.

Methyl {2-[(2,5-difluorophenyl)amino]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}acetate (15a). Prepared by general procedure A from methyl 3-(2-iodophenyl)acrylate **13a** (144 mg, 0.5 mmol), 2,5-difluorophenylhydrazine **14a** (86 mg, 0.6 mmol), palladium acetate (6 mg, 0.025 mmol), triphenylphosphine (13 mg, 0.05 mmol), and cesium carbonate (324 mg, 1.0 mmol) in toluene (10 mL) at 90 °C over 3 h. The crude product was purified by flash chromatography (eluting with 3:7 v/v EtOAc−hexane) to give **15a** (100 mg, 60%) as a pale brown gum: R_f 0.25 (3:7 v/v EtOAc−hexane); δ_H (300 MHz, $CDCl_3$) 7.91 (1H, d, *J* 7.7), 7.66 (1H, t, *J* 7.7), 7.65 (1H, d, *J* 7.7), 7.54 (1H, t, *J* 7.7), 7.00 (1H, ddd, $^3J_{HF}$ 10.7, $^3J_{HH}$ 8.7, and $^4J_{HF}$ 5.1), 6.56−6.48 (1H, m), 6.46 (1H, br s), 6.44−6.38 (1H, m), 5.19 (1H, t, *J* 6.2), 3.65 (3H, s), 3.02 (1H, dd, *J* 15.9 and 6.2), 2.82 (1H, dd, *J* 15.9 and 6.2); δ_C (75 MHz, $CDCl_3$) 171.0 (C), 167.4 (C), 162.9 (CF, d, *J* 235), 147.6 (CF, d, *J* 235), 143.4 (C), 136.5 (C, d, *J* 23), 133.3 (CH), 130.1 (C), 129.5 (CH), 124.8 (CH), 123.4 (CH), 116.4 (CH, dd, *J* 21 and 10), 107.3 (CH, dd, *J* 24 and 8), 101.9 (CH, d, *J* 28), 58.4 (CH), 52.5 (CH_3), 37.3 (CH_2); ν_{max}/cm^{-1} (film) 3278, 2955, 1716 (C═O), 1633 (C═O), 1515, 1471; *m*/*z* (ES+) 333 (100, MH^+); HRMS (ES+) found MH^+ 333.1046, $C_{17}H_{14}F_2N_2O_3$ requires MH^+ 333.1045.

3-Acetyl-4-[2-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2-oxoethyl]-2-phenyl-3,4-dihydro-2*H*-phthalazin-1-one (18e). Prepared by general procedure B from a stirred mixture of 8-[(2*E*)-3-(2-iodophenyl)prop-2-enoyl]-1,4-dioxa-8-azaspiro[4.5]decane **13e** (200 mg, 0.5 mmol), 1-acetyl-2-phenylhydrazine **16a** (105 mg, 0.7 mmol), palladacycle **17** (19 mg, 0.025 mmol), and cesium carbonate (326 mg, 1.0 mmol) in DMF (5 mL) at 60 °C for 3 h. The crude product was purified by flash chromatography (eluting with EtOAc) to give **18e** (172 mg, 77%) as colorless prisms: mp 215−217 °C (from DCM−hexane); R_f 0.42 (EtOAc); δ_H (500 MHz, $CDCl_3$, 60 °C) 8.15 (1H, d, *J* 7.6), 7.83 (2H, br m), 7.50 (1H, td, *J* 7.6 and 1.2), 7.43 (1H, td, *J* 7.6 and 1.2), 7.38 (3H, m), 7.17 (1H, t, *J* 7.3), 6.40 (1H, br s), 3.89 (4H, br m), 3.79 (1H, br m), 3.61 (1H, br m), 3.18 (2H, br m), 2.99 (1H, br m), 2.59 (1H, dd, *J* 16.3 and 4.6), 2.02 (3H, br s), 1.48 (2H, br m), 1.31 (2H, br m); δ_C (75 MHz, $CDCl_3$) 174.8 (C),167.0 (C), 163.0 (C), 142.9 (C), 142.0 (C), 133.7 (CH), 129.8 (CH), 129.6 (CH), 128.9 (CH), 127.5 (C), 125.9 (CH), 120.8 (CH), 119.5 (CH), 106.9 (C), 64.8 (CH_2), 51.8 (CH), 43.6 (CH_2), 40.4 (CH_2), 36.2 (CH_2), 35.4 (CH_2), 35.1 (CH_2), 22.3 (CH_3); ν_{max}/cm^{-1} (film) 3062, 2961, 2930, 2884, 1696 (C═O), 1674 (C═O), 1642 (C═O), 1596, 1489, 1456; *m*/*z* (ES+) 921 (100, M_2Na^+), 472 (36, MNa^+), 450 (14, MH^+); HRMS (ES+) found MH^+ 450.2016, $C_{25}H_{27}N_3O_5$ requires MH^+ 450.2023.

Methyl (2,3-Diethyl-4-oxo-1,2,3,4-tetrahydrophthalazin-1-yl)acetate (18f). Prepared by general procedure C from methyl 3-(2-iodophenyl)acrylate **13a** (144 mg, 0.5 mmol), 1,2-diethylhydrazine dihydrochloride **16b** (104 mg, 0.65 mmol) in water (0.5 mL), palladacycle **17** (19 mg, 0.025 mmol), and cesium carbonate (326 mg, 1.0 mmol) in DMF (5 mL) at 70 °C over 3 h. The crude product was purified by flash chromatography (eluting with 1:9 v/v EtOAc−DCM) to give **18f** (76 mg, 55%) as a colorless gum: R_f 0.56 (1:9 v/v EtOAc−DCM); δ_H (500 MHz, $CDCl_3$) 8.03 (1H, dd, *J* 7.7 and 1.1), 7.48 (1H, td, *J* 7.7 and 1.1), 7.39 (1H, td, *J* 7.7 and 1.1), 7.20 (1H, d, *J* 7.7), 4.52 (1H, dd, *J* 9.0 and 5.6), 4.15 (1H, dq, *J* 13.7 and 7.3), 3.71 (3H, s), 3.13 (1H, dq, *J* 13.7 and 7.3), 2.90−2.80 (2H, m), 2.70 (1H, dq, *J* 12.4 and 7.3), 2.53 (1H, dd, *J* 15.8 and 5.6), 1.26 (3H, t, *J* 7.3), 1.05 (3H, t, *J* 7.3); δ_C (75 MHz, $CDCl_3$) 171.6 (C), 162.6 (C), 137.8 (C), 132.8 (CH), 128.5 (CH), 127.9 (CH), 127.3 (C), 126.6 (CH), 56.1 (CH), 52.2 (CH_3), 49.5 (CH_2), 42.3 (CH_2), 40.2 (CH_2), 13.3 (CH_3), 12.8 (CH_3); ν_{max}/cm^{-1} (film) 2975, 2951, 2853, 1741 (C═O), 1650 (C═O), 1605; *m*/*z* (ES+) 277 (51, MH^+), 299 (100, MNa^+), 575 (70, M_2Na^+); HRMS (ES+) found MNa^+ 299.1375, $C_{15}H_{20}N_2O_3$ requires MNa^+ 299.1366.

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Supporting Information Available: ^1H and ^{13}C NMR spectra and CIF files of the X-ray structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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