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Consequent Construction of C−C and C−N Bonds via Palladium-Catalyzed Dual C−H Activation: Synthesis of Benzo[*c*]cinnoline Derivatives

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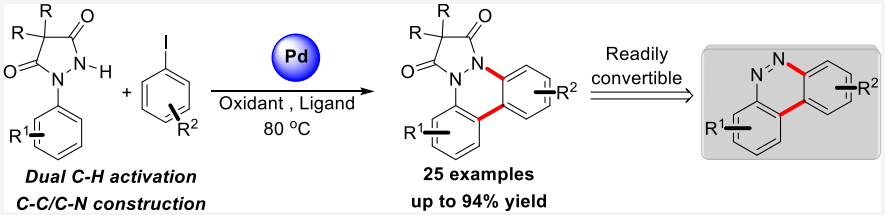

ABSTRACT: A highly efficient palladium-catalyzed cascade annulation of pyrazolones and aryl iodides to access various benzo[*c*]cinnoline derivatives has been achieved at 80 °C. A pyridine-type ligand could improve the reaction efficiency under current reaction conditions, giving a higher product yield up to 94%. This novel approach provided a one-pot dual C−H activation strategy with good functional group tolerance, such as halogen, methoxy, nitro, ester, phenol, and so forth. The product could readily convert into cinnoline derivatives.

INTRODUCTION

In view of the advantage in the directing-group (DG)-assisted palladium-catalyzed C−H activation,[1−6] great efforts have been made in C−C, C−N, and C−O construction, especially the achievements in the synthesis of many natural and biologically important nitrogen-containing molecular scaffolds.[7−9] Among the nitrogen-containing heterocycles, cinnolines are important structural motifs that are often found in various biologically active molecules.[10] They are known to display interesting pharmacological properties such as antibacterial, anticancer, antimicrobial, anti-inflammatory, antifungal, antihypertensive, and antiulcer activities.[11−14] In particular, benzo[*c*]cinnolines are considered privileged scaffolds in medicinal chemistry due to their promising anticancer properties. Subsequently, various cinnoline derivatives such as dibenzo[*c*,*h*]cinnoline,[15] indole-[3,2-*c*]cinnoline,[16] and substituted cinnoline carboxamide[17] have been identified as potent anticancer agents and kinase inhibitors (Figure 1). Due to the fact that none of the cinnoline derivatives existed in nature, these valuable skeletons are highly relied on organic synthesis.

Step-economy and atom-economy strategies via C−H functionalization offered a shortcut to synthesize cinnoline derivatives.[18−24] The developed methods usually involve expensive transition metals, such as iridium, rhodium catalysts, and prefunctionalization of aryl hydrazines, aryl hydrazones, aryl phthalazine, and so forth, which inevitably suffer from high cost performance, limited substrate scope, and multistep reaction sequences from the starting materials.[25−35] Several straightforward palladium-catalyzed strategies displayed good application in the synthesis of cinnoline derivatives. Zhang and co-workers found that the pyrazolone moiety as an internal DG could facilitate a palladium-catalyzed C−C/C−N bond formation reaction for a two-step one-pot synthesis of benzo[*c*]pyrazolo[1,2-*a*]cinnolin-ones.[36] Later, the carbamate group, deviated from arylhydrazines, was successfully applied as an efficient DG for ortho-arylation by Reddy and co-workers, the product of which could undergo oxidative *N*-arylation to give cinnoline derivatives (Figure 2a).[37] However, palladium-catalyzed C−C and C−N bond formation in a cascade way in one pot is challenging and limited strategies were achieved during these years, especially in the synthesis of cinnoline derivatives.[38,39] For example, Li and co-workers developed an elegant palladium-catalyzed dual C−H activation for utilization of CONHOMe as a DG to synthesize biologically important phenanthridinones in one pot (Figure 2b). Normally, electron-rich amide could be a better DG than electron neutron or electron-deficient ones. As our ongoing interest is in developing the C−X bond formation reaction,[40−42] we envision that pyrazolidine-3,5-dione, a relative electron-deficient amide, might serve as an internal DG for an intermolecular C−C bond formation, followed by a

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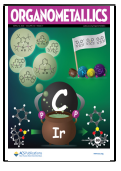

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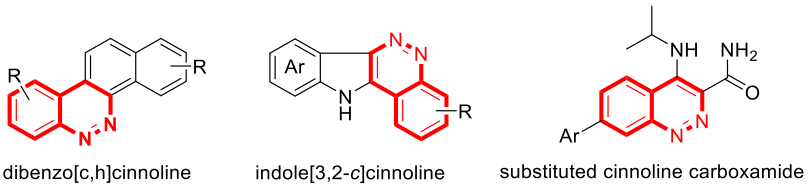

Figure 1. Bioactive cinnoline derivatives.

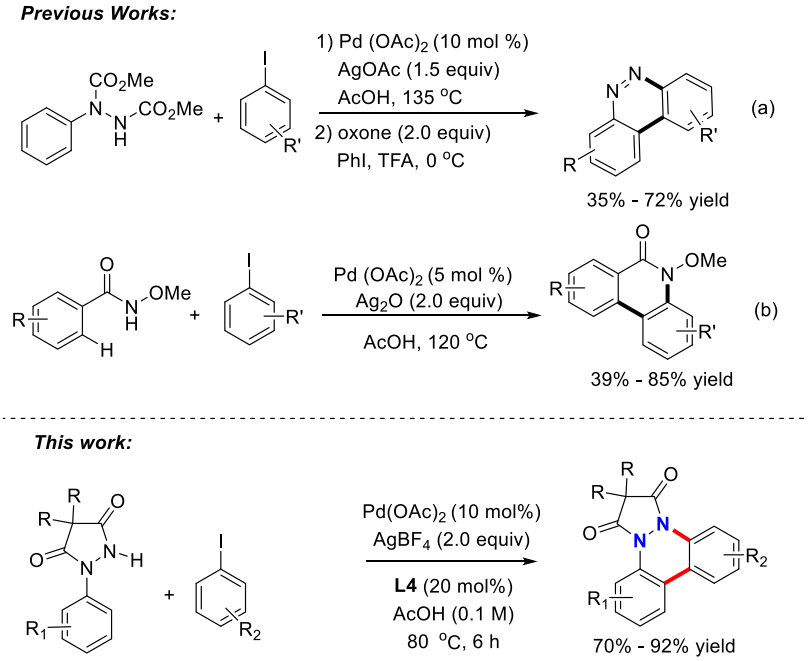

Figure 2. Selective examples for palladium-catalyzed C−H, N−H functionalization to establish polycyclic structures.

palladium-catalyzed intramolecular C−N bond formation to synthesize biologically important benzo[*c*]cinnoline derivatives (Figure 1). Herein, the preliminary study of the one-pot cascade synthesis of cinnoline derivatives via the palladium-catalyzed reaction between aryl pyrazolidine-3,5-diones and aryl iodides was present. It was found that a pyridine-type ligand could improve the reaction efficiency under optimal reaction conditions and the relative electron-deficient amide group could efficiently facilitate the one-pot C−C and C−N construction protocol.

RESULTS AND DISCUSSION

Aryl iodide was widely used in palladium-catalyzed C−H arylation reactions and usually displays high efficiency in coupling sequences.[43,44] Thus, we chose the reaction of 4,4-dimethyl-1-phenylpyrazolidine-3,5-dione (**1a**) with phenyl iodide (**2a**) catalyzed by $Pd(OAc)_2$ in AcOH as the model reaction to verify our assumption and to screen the optimal conditions. At the beginning, no product formation was observed in the absence of any oxidant or ligand at 80 °C for 6 h (Table 1, entry 1). It is known that silver salts have been widely used as oxidants in palladium-catalyzed arylation and lactamization reactions.[45] Therefore, we first tested the common sliver salts, such as $AgNO_3$, AgOAc, Ag_2O, $AgBF_4$, and $AgSbF_4$ (Table 1, entries 2−6). To our delight, an annulated product **3a** was obtained in 66% yield when $AgBF_4$ (2.0 equiv) was used as the oxidant. Furthermore, other oxidants, such as $CuSO_4$ and $Cu(OAc)_2$, were subsequently investigated, which were found to be less effective than $AgBF_4$ for this reaction (Table 1, entries 7−8). Based on a previous report, a Pd(II)/Pd(IV) catalysis cycle should be involved in the reaction,[37] and the literature also shows that the Pd catalyst could be coordinated by a suitable ligand in such transformation to improve the reaction efficiency.[46,47] Thus, a variety of ligands were chosen to run the reaction (Table 1, entries 9−13). The result showed that most pyridine-type ligands could improve the yield of the reaction, especially $\mathbf{L}_4$ for giving the yield of **3a** in 94%. The bidentate ligand, phenanthroline ($\mathbf{L}_5$), significantly reduces the activity of the palladium catalyst (Table 1, entry 14). A further screening of reaction temperature revealed that a lower temperature of 60 °C could give a lower product yield **3a** (Table 1, entry 15) and a higher temperature of 100 °C could give a similar product yield **3a** (Table 1, entry 16). Other solvents, such as dichloroethane and tetrahydrofuran (THF), could not give any product, while the acidic solvents, such as CF_3CH_2OH and CF_3COOH, could deliver product 3a in relatively low yield (Table 1, entries 16−19). Finally, the optimized one-pot C−C/C−N bond formation reaction's reaction conditions were affirmed as follows: $Pd(OAc)_2$ as the catalyst, $AgBF_4$ as the oxidant, and $\mathbf{L}_4$ as the ligand in AcOH at 80 °C.

With the optimized conditions in hand, we first investigated the substrate scope of phenylpyrazolidine-3,5-dione derivatives for this one-pot Pd-catalyzed [4 + 2] annulation. As summarized in Table 2, diverse 4,4-dimethyl-1-aryl-pyrazolidine-3,5-dione with electronically differentiated groups (Me, F, Cl, Br, CF_3, and OCF_3) at different positions smoothly undergo [4 + 2] annulation with phenyl iodide to give the

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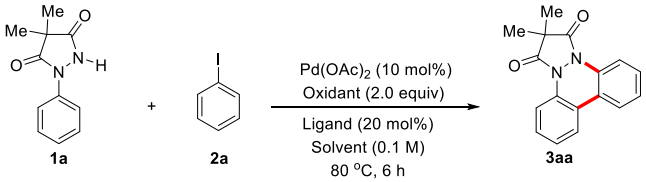
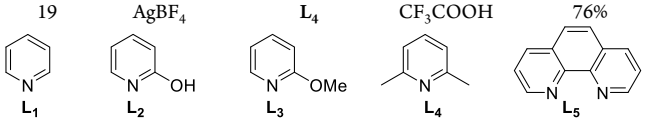
Table 1. Optimization of the One-Pot Procedure[a]



entry	oxidant	ligand	solvent	yield[b]
1			HOAc	NR[c]
2	$AgNO_3$		HOAc	36%
3	AgOAc		HOAc	46%
4	Ag_2O		HOAc	22%
5	$AgBF_4$		HOAc	66%
6	$AgSbF_4$		HOAc	20%
7	$CuSO_4$		HOAc	28%
8	$Cu(OAc)_2$		HOAc	32%
9	$AgBF_4$	L_1	HOAc	75%
10	$AgBF_4$	L_2	HOAc	79%
11	$AgBF_4$	L_3	HOAc	83%
12	$AgBF_4$	L_4	HOAc	94%
13	$AgBF_4$	L_5	HOAc	NR
14	$AgBF_4$	L_4	HOAc	65%[d]
15	$AgBF_4$	L_4	HOAc	93%[e]
16	$AgBF_4$	L_4	DCE	NR
17	$AgBF_4$	L_4	THF	NR
18	$AgBF_4$	L_4	CF_3CH_2OH	36%
19	$AgBF_4$	L_4	CF_3COOH	76%



[a]Conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), oxidant (0.4 mmol), ligand (20 mol %), under N_2, 6 h. [b]Isolated yield. [c]No reaction. [d]The reaction was conducted at 60 °C. [e]The reaction was conducted at 100 °C.

desired products (**3a**−**3n**) in good to excellent yields. In detail, the aryl pyrazolidine substrates with or without electron-donating groups on the benzene ring could give identical yield of the reaction (**3a**−**3d**); the methyl group at the para, meta, and ortho position of the phenyl ring had slight influence on the reaction efficiency by providing the corresponding products **3b**−**3d** in 86−90% yields; halogens (F, Cl, and Br) which were distributed at different positions of the benzene ring were tolerated under the current reaction system and offered the desired products **3e**−**3j** in 76−85% yields, thus allowing further manipulation of the initial products; and it was noted that there was apparent electronic effect of the reaction, resulting from different substituents on the phenyl ring, such as $-OCF_3$ and $-CF_3$, and the substrates with electron-withdrawing groups furnished lower yield of the product (**3ka**, 70%; **3la**, 72%). The four-membered ring embodied next to the dione of aryl pyrazolidine could be well-tolerated and products were obtained in good yields (**3m**, 81%, **3n**, 75%).

Encouraged by the satisfactory results using aryl pyrazolidine-3,5-dione, we attempted to extend the substrate scope to phenyl iodine derivatives (Table 3). Variations on the phenyl ring were examined, thus leading to the discovery that (1) aryl iodide could bear a large variety of functional groups, including methyl, methoxyl, fluoro, ester, free phenol, cyano, nitro, and so on; (2) the electron nature of the benzene ring had a slight impact on the efficiency of the cascade C−C/C−N formation reaction. Phenyl iodide with an electro-donating group gave the product a slightly higher yield (**3o**, 89%; **3p**, 88%) compared to those with the electron-withdrawing group (**3u**, 74%, **3v**, 72%, **3x**, 86%, **3y**, 86%); and (3) it was worth mentioning that the electro-donating free phenol group and the strongly electron-withdrawing nitro group show good reactivity in the current reaction system and gave good yields (**3t**, 76%; **3w**, 70%). The tertiary carbon between the two carbonyls of **1** was essential for this transformation thus far. Compounds A and B did not show any reactivity under the standard condition.

To study the reaction mechanism, control experiments were conducted to understand the reaction process (Scheme 1). Compound **4** was synthesized and applied in the standard condition. However, we did not observe any C−C coupling product **3a**. When compound **5** was reacted in the standard condition, product **3a** could be obtained in 97% yield. In addition, compound **6**, an analogue of **5**, was also treated with the palladium catalyst in the standard condition and no desired product **6a** was formed, indicating that the hydrazine unit in **5** was crucial for the success of the one-pot cascade reaction. The compound d_5-**1a** was synthesized and injected to the standard condition to deliver NMR pure d_4-**1a** and further intermolecular kinetic isotope effect (KIE) for the coupling reaction was confirmed around 3.0, indicating that the rate-determining step is prior to the C−H cleavage or C−H activation procedure. Based on the above results and previous literature, a possible reaction mechanism was proposed (Figure S1). Initially, a five-membered palladacycle was probably formed between phenylpyrazolidine-3,5-dione **1** and $Pd(OAc)_2$, which could readily react with aryl iodide to give the ortho-arylation product. The amide of **1a′** could further assist the palladium catalyst to activate vicinal C(sp^2)−H for the formation of a seven-membered palladacycle, which could proceed reductive elimination to deliver final product **3**. $AgBF_4$ served as an oxidant for the regeneration-active palladium species during the catalytic cycle.

Compound **3** could be further transformed into benzo[*c*]-cinnoline derivatives, important biologically active molecules. The double amide bond of compound **3a** can be cleaved by NaOH in ethanol under air at 70 °C. The desired product of benzo[*c*]cinnoline **7** was obtained in 90% yield (Scheme 2).[32,48]

CONCLUSIONS

In conclusion, we have successfully developed a novel one-pot cascade C−C/C−N formation reaction via the palladium catalytic protocol. The unique class of benzo[*c*]pyrazolo[1,2-*a*]cinnoline derivatives could be conveniently constructed in good yields. This strategy features the double C−H activation process: C−H activation/arylation and C−H activation/intramolecular C−N bond formation. The pyrazolone moiety was successfully used as an internal DG for C−H activation/functionalization and also served as a novel building block to multisubstituted benzo[*c*]cinnoline with a variety of functional groups. Further investigation of using electricity to replace the oxidant of $AgBF_4$ for this methodology is underway in our laboratory.

EXPERIMENTAL SECTION

General Considerations. All experimental reagents were purchased from commercial suppliers and used without further purification, such as Energy Chemical and Meryer Company. The

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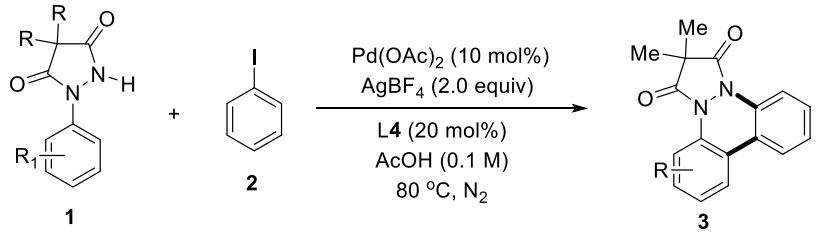
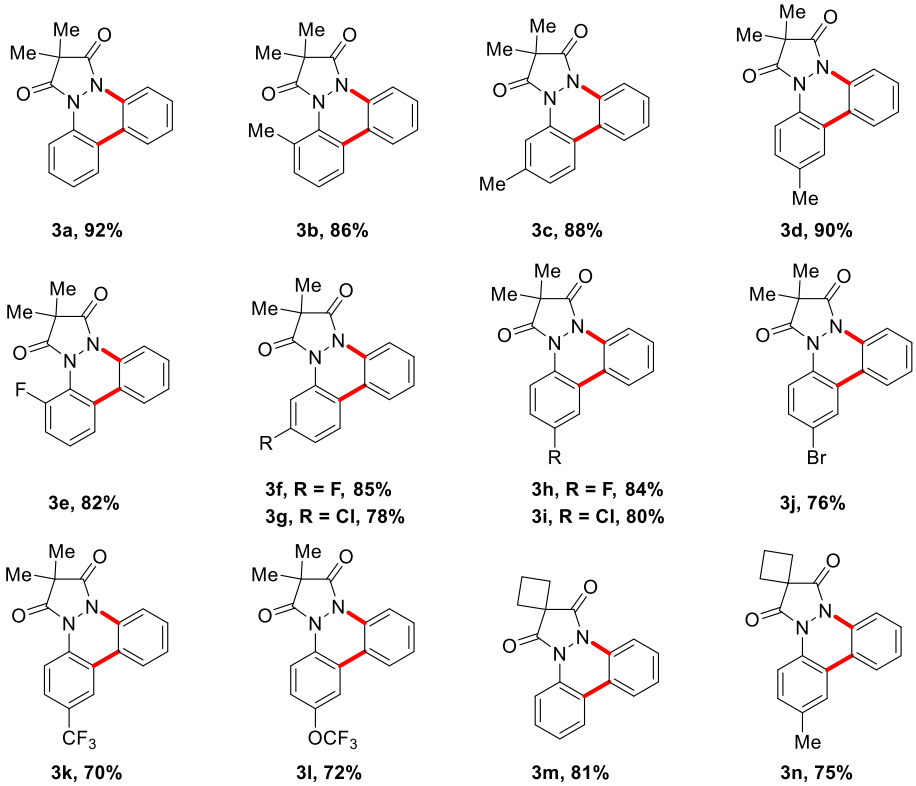
Table 2. Substrate Scope of Phenylpyrazolidine-3,5-dione[a]





[a]All reactions were performed with **1** (0.5 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (10 mol %), $AgBF_4$ (2.0 equiv), ligand (20 mol %), and AcOH (5.0 mL) at 80 °C until the diminish of **1**.

starting materials of phenyl pyrazolidine derivatives were prepared by following the previous reports.[49,50] For flash column chromatography, silica gel (200−300 mesh) was applied. Reactions were monitored using thin-layer chromatography (TLC) on commercial silica gel plates (GF 254). Visualization of the developed plates was performed under UV lights (GF 254 nm). ^1H and ^{13}C NMR spectra were recorded on a 300, 400 MHz spectrometer. Chemical shifts (δ) were reported in ppm referenced to an internal tetramethylsilane standard (δ 0.00) or the $CDCl_3$-d_1 residual peak (δ 7.26) for ^1H NMR. Chemical shifts of ^{13}C NMR were reported relative to $CDCl_3$ (δ 77.17). The following abbreviations were used to describe peak splitting patterns when appropriate: br s = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Coupling constant, *J*, was reported in Hz. High-resolution mass spectra were obtained on an ESI-LC−MS/MS spectrometer.

Detailed Procedure for the Synthesis of 5,6-Dihydrobenzo-[*c*]cinnoline Derivatives (3). Under an N_2 atmosphere, an oven-dried 10 mL tube was charged with phenyl pyrazolidine derivative **1** (0.5 mmol, 1.0 equiv), aryl iodide **2** (1.0 mmol 2.0 equiv), $Pd(OAc)_2$ (0.05 mmol, 10% equiv), $AgBF_4$ (1.0 mmol, 2.0 equiv), and 2,6-dimethylpyridine (0.1 mmol, 20% equiv) in AcOH (5.0 mL, 2.0 M). The reaction mixture was stirred at 80 °C until the reduction of compound **1**, which was monitored by TLC under the UV lamp. After the starting material completely disappeared, the reaction mixture was concentrated. The residue was purified on a silica gel column with petroleum ether/ethyl acetate (10/1, v/v to 1/1, v/v) to give the corresponding products **3**.

Characterization Data of Products. *2,2-Dimethyl-1H-benzo-[c]pyrazolo[1,2-a]cinnoline-1,3(2H)-dione (**3a**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.70) to provide **3a** (0.131 g, 0.47 mmol, 92% yield) as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 8.52 (d, *J* = 1.0, 1H), 8.49 (d, *J* = 1.0 Hz, 1H), 7.65 (s, 1H), 7.62 (s, 1H), 7.27 (dt, *J* = 7.6, 1.3 Hz, 2H), 7.19−7.14 (m, 2H), and 1.48 (s, 6H).·^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 134.7, 129.7, 126.1, 123.1, 121.1, 117.3, 44.8, and 21.8. Mass spectrometry high-resolution mass spectrometry (HRMS) (ESI-TOF) (*m*/*z*): calcd for $C_{17}H_{15}N_2O_2^+$ ($[M + H]^+$), 279.1128; found, 279.1124.

*2,2,5-Trimethyl-1H-benzo[c]pyrazolo[1,2-a]cinnoline-1,3(2H)-dione (**3b**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.78) to provide **3b** (0.126 g, 0.43 mmol, 86% yield) as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 8.34 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.75 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.30−7.23 (m, 2H), 7.21−7.16 (m, 2H), 2.24 (s, 3H), and 1.50 (s, 6H).·^{13}C NMR (75 MHz, $CDCl_3$): δ 175.1, 168.6, 138.4, 132.2, 131.6, 130.1, 129.7, 127.8, 127.0, 125.6, 123.6, 121.6, 121.2, 115.4, 45.3, 21.8, and 20.5. Mass spectrometry HRMS (ESI-TOF)

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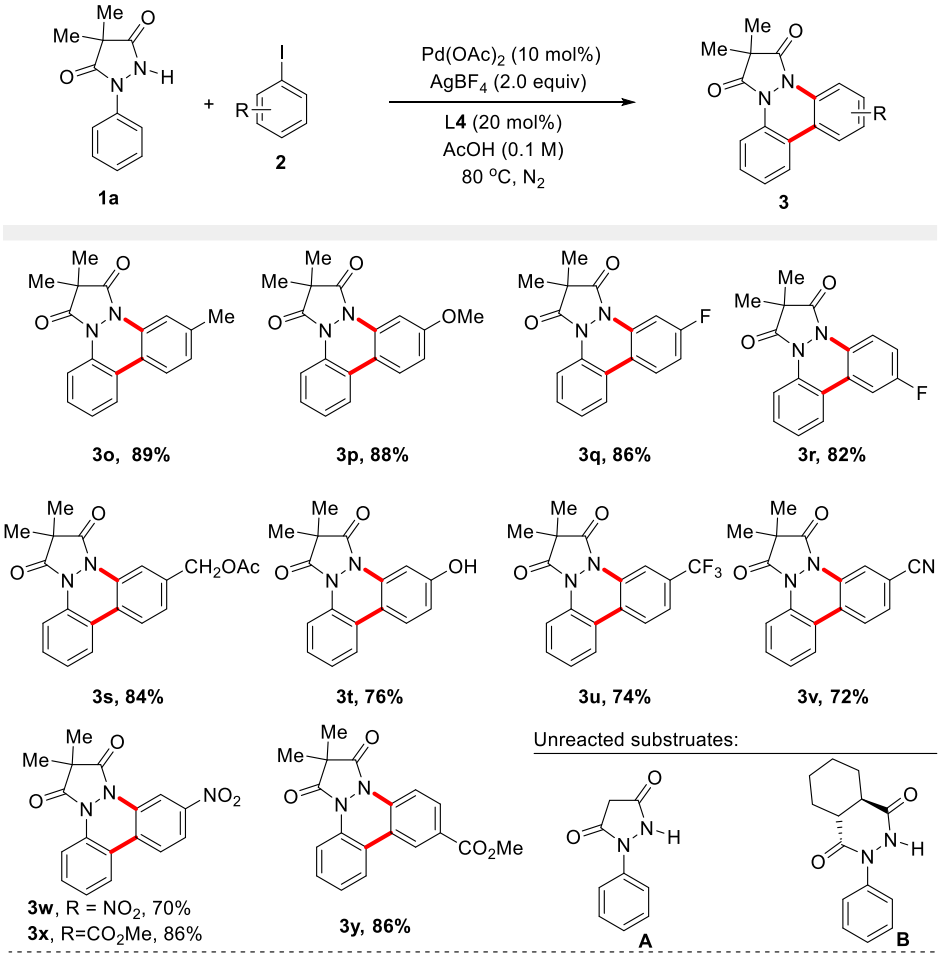
Table 3. Substrate Scope of Aryl Iodine[a]



[a]All reactions were performed with **1** (0.5 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (10 mol %), $AgBF_4$ (2.0 equiv), ligand (20 mol %), and AcOH (5.0 mL) at 80 °C until the diminish of **1**

(m/z): calcd for $C_{18}H_{17}N_2O_2^+$ ([M + H]$^+$), 293.1285; found, 293.1279.

*2,2,6-Trimethyl-1H-benzo[c]pyrazolo[1,2-a]cinnoline-1,3(2H)-dione (**3c**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.74) to provide **3c** (0.128 g, 0.44 mmol, 88% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.48 (dd, J = 8.3, 1.1 Hz, 1H), 8.35 (s, 1H), 7.58 (dd, J = 7.8, 1.4 Hz, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.23 (td, J = 7.7, 1.5 Hz, 1H), 7.13 (td, J = 7.7, 1.2, 1H), 6.96 (d, J = 8.0 Hz, 1H), 2.33 (s, 3H), and 1.47 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 140.2, 134.5, 134.3, 129.2, 126.9, 126.1, 122.9, 122.7, 121.3, 118.4, 117.7, 117.2, 44.7, 21.8, and 21.7. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{18}H_{17}N_2O_2^+$ ([M + H]$^+$), 293.1285; found, 293.1289.

*2,2,7-Trimethyl-1H-benzo[c]pyrazolo[1,2-a]cinnoline-1,3(2H)-dione (**3d**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.78) to provide **3d** (0.131 g, 0.45 mmol, 90% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.51 (dd, J = 8.3, 1.1 Hz, 1H), 8.39 (d, J = 8.5 Hz, 1H), 7.64 (dd, J = 7.8, 1.4 Hz, 1H), 7.44 (s, 1H), 7.29−7.22 (m, 3H), 7.16 (td, J = 7.7, 1.3 Hz, 1H), 7.07 (dd, J = 8.5, 1.2 Hz, 1H), 2.35 (s, 3H), and 1.47 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 169.4, 135.8, 134.8, 132.4, 130.3, 129.6, 126.0, 123.5, 123.0, 121.2, 120.9, 117.2, 117.2, 44.8, 21.8, and 21.3. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{18}H_{17}N_2O_2^+$ ([M + H]$^+$), 293.1285; found, 293.1285.

*5-Fluoro-2,2-dimethyl-1H-benzo[c]pyrazolo[1,2-a]cinnoline-1,3(2H)-dione (**3e**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.72) to provide **3e** (0.121 g, 0.41 mmol, 82% yield) as a light-brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (dd, J = 8.4, 1.0 Hz, 1H), 7.71 (dd, J = 7.8, 1.4 Hz, 1H), 7.39 (d, J = 7.7 Hz, 1H), 7.31 (td, J = 7.5, 1.4 Hz, 1H), 7.27−7.23 (m, 1H), 7.19 (td, J = 7.7, 1.2 Hz, 1H), 7.12−7.05 (m, 1H), and 1.50 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 168.1, 152.9 (d, J = 255.8 Hz), 137.9, 130.5, 128.3 (d, J = 7.9 Hz), 128.0 (d, J = 2.1, Hz), 125.8, 123.8, 120.8 (d, J = 2.7, Hz), 119.9 (d, J = 12.5 Hz), 119.1 (d, J = 3.2 Hz), 117.4 (d, J = 20.1 Hz), 116.0, 45.3, and 21.7. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{17}H_{14}FN_2O_2^+$ ([M + H]$^+$), 297.1034; found, 297.1028. ^{19}F NMR (282 MHz, $CDCl_3$): δ −110.14 (dd, J = 10.3, 4.8 Hz).

*6-Fluoro-2,2-dimethyl-1H-benzo[c]pyrazolo[1,2-a]cinnoline-1,3(2H)-dione (**3f**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.70) to provide **3f** (0.124 g, 0.42 mmol, 85% yield) as a light-brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (d, J = 8.3 Hz, 1H), 8.33 (dd, J = 10.8, 2.6 Hz, 1H), 7.62−7.55 (m, 2H), 7.26 (dd, J = 15.6, 1.3 Hz, 1H), 7.19−7.14 (m, 1H), 6.87 (td, J = 8.0, 2.5 Hz, 1H), and 1.48 (s, 6H).·^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 169.3, 163.0 (d, J = 247.0 Hz), 135.5 (d, J = 11.5 Hz), 134.0, 129.6, 126.3, 124.6 (d, J = 9.4 Hz), 122.8, 120.6, 117.4, 117.2 (d, J = 3.4 Hz), 113.0 (d, J = 22.0 Hz), 105.3 (d, J = 29.6 Hz), 44.7, and 21.8. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{17}H_{14}FN_2O_2^+$ ([M + H]$^+$), 297.1034; found, 297.1032. ^{19}F NMR (282 MHz, $CDCl_3$): δ −109.06 (ddd, J = 10.8, 7.6, 6.0 Hz).

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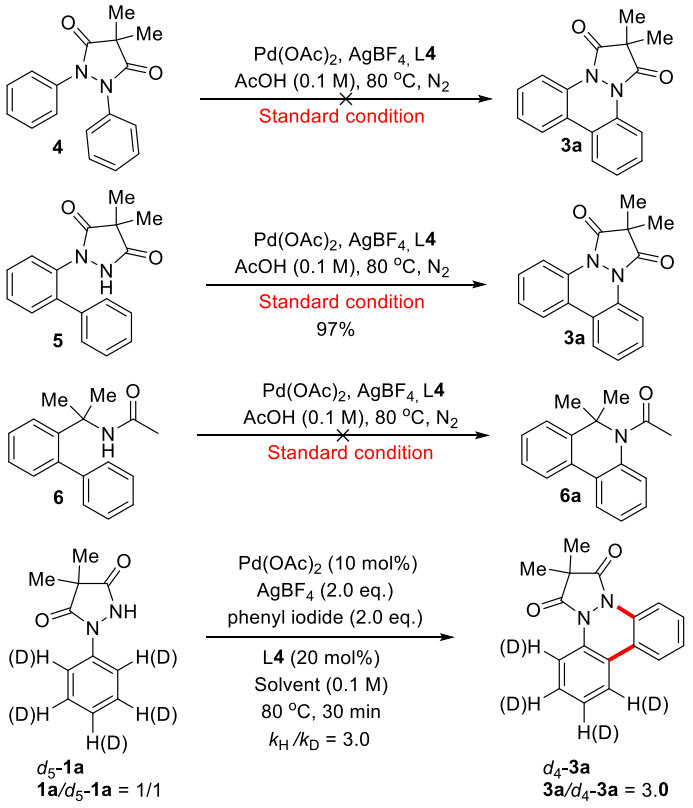
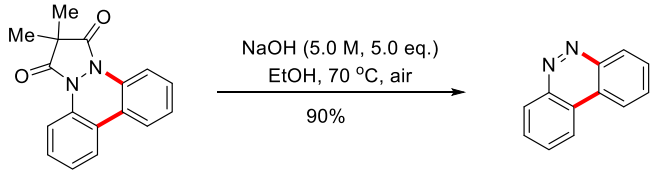
Scheme 1. Preliminary Mechanistic Studies



Scheme 2. Synthesis of Benzo[*c*]cinnoline



*6-Chloro-2,2-dimethyl-1H-benzo[c]pyrazolo[1,2-a]cinnoline-1,3(2H)-dione (**3g**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.8) to provide **3g** (0.122 g, 0.39 mmol, 78% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (d, J = 2.1 Hz, 1H), 8.47 (dd, J = 7.8, 0.5 Hz, 1H), 7.56−7.49 (m, 2H), 7.27 (dd, J = 15.8, 1.4 Hz, 1H), 7.15−7.11 (m, 2H), and 1.47 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 169.3, 135.4, 135.2, 134.3, 130.0, 126.2, 126.1, 124.0, 122.9, 120.2, 119.6, 117.3, 117.3, 44.7, and 21.7. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{17}H_{14}ClN_2O_2^+$ ([M + H]$^+$), 313.0738; found, 313.0731.

*7-Fluoro-2,2-dimethyl-1H-benzo[c]pyrazolo[1,2-a]cinnoline-1,3(2H)-dione (**3h**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.76) to provide **3h** (0.124 g, 0.42 mmol, 84% yield) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.54−8.50 (m, 2H), 7.55 (dd, J = 7.8, 1.2 Hz, 1H), 7.33−7.28 (m, 2H), 7.18 (td, J = 7.7, 1.1 Hz, 1H), 6.96 (ddd, J = 9.3, 7.8, 2.8 Hz, 1H), and 1.48 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 169.4, 160.6 (d, J = 244.0 Hz), 134.9, 130.8, 130.5, 126.2, 123.6 (d, J = 7.8 Hz), 123.3, 120.2, 119.3 (d, J = 8.1 Hz), 117.3, 116.6 (d, J = 22.5 Hz), 110.0 (d, J = 24.8 Hz), 44.7, and 21.8. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{17}H_{14}FN_2O_2^+$ ([M + H]$^+$), 297.1034; found, 297.1036. ^{19}F NMR (282 MHz, $CDCl_3$): δ −115.15 (ddd, J = 13.4, 8.3, 5.2 Hz).

*7-Chloro-2,2-dimethyl-1H-benzo[c]pyrazolo[1,2-a]cinnoline-1,3(2H)-dione (**3i**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.8) to provide **3i** (0.125 g, 0.40 mmol, 80% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (dd, J = 8.4, 1.0, 1H), 8.45 (d, J = 8.9 Hz, 1H), 7.57−7.54 (m, 2H), 7.32−7.26 (m, 1H), 7.21−7.13 (m, 2H), and 1.47 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 163.5, 134.8, 133.1, 131.5, 130.5, 129.3, 126.2, 123.1, 123.0, 122.96, 119.9, 118.6, 117.3, 44.7, and 21.8. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{17}H_{14}ClN_2O_2^+$ ([M + H]$^+$), 313.0738; found, 313.0734.

*7-Bromo-2,2-dimethyl-1H-benzo[c]pyrazolo[1,2-a]cinnoline-1,3(2H)-dione (**3j**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.66) to provide **3j** (0.136 g, 0.38 mmol, 76% yield) as a light-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.50 (dd, J = 8.4, 1.0, 1H), 8.40 (d, J = 8.9, 1H), 7.73 (d, J = 2.2, 1H), 7.57 (dd, J = 7.9, 1.2 Hz, 1H), 7.35 (dd, J = 8.9, 2.2 Hz, 1H), 7.30−7.27 (m, 1H), 7.20−7.17 (m, 1H), and 1.47 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 169.5, 134.8, 133.6, 132.3, 130.5, 129.7, 126.3, 126.0, 123.3, 123.2, 119.2, 118.9, 117.4, 44.7, and 21.8. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{17}H_{14}BrN_2O_2^+$ ([M + H]$^+$), 357.0233; found, 357.0230.

*2,2-Dimethyl-7-(trifluoromethyl)-1H-benzo[c]pyrazolo[1,2-a]-cinnoline-1,3(2H)-dione (**3k**).* Following the general procedure, the

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product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.64) to provide **3k** (0.121 g, 0.35 mmol, 70% yield) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60 (d, J = 8.7 Hz, 1H), 8.50 (dd, J = 8.3, 0.9 Hz, 1H), 7.81 (d, J = 1.1 Hz, 1H), 7.62 (dd, J = 7.9, 1.2, 1H), 7.47 (dd, J = 8.8, 1.3 Hz, 1H), 7.30 (td, J = 7.5, 1.4 Hz, 1H), 7.18 (td, J = 7.7, 1.1 Hz, 1H), and 1.48 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 169.2, 137.2, 134.7, 130.7, 128.0 (d, J = 8.2 Hz), 126.6 (q, J = 3.7 Hz), 126.4, 125.6, 123.2, 122.0, 121.7, 120.0 (q, J = 3.8 Hz), 119.8, 117.4 (d, J = 6.2 Hz), 44.7, and 21.2. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{18}H_{14}F_3N_2O_2^+$ ([M + H]$^+$), 347.1002; found, 347.0991.^{19}F NMR (282 MHz, $CDCl_3$): δ −62.88 (s).

*2,2-Dimethyl-7-(trifluoromethoxy)-1H-benzo[c]pyrazolo[1,2-a]-cinnoline-1,3(2H)-dione (**3l**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.68) to provide **3l** (0.130 g, 0.36 mmol, 72% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.54−8.50 (m, 2H), 7.55 (dd, J = 7.9, 1.2 Hz, 1H), 7.33−7.28 (m, 2H), 7.18 (td, J = 7.8, 1.1 Hz, 1H), 6.96 (ddd, J = 9.3, 7.8, 2.9 Hz, 1H), and 1.48 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 169.4, 160.6 (d, J = 243.8), 134.9, 130.9, 130.5, 126.6, 123.6 (d, J = 8.1 Hz), 123.3, 120.2, 119.2 (d, J = 8.0 Hz), 117.3, 116.1 (d, J = 22.5 Hz), 111.0 (d, J = 24.7 Hz), 44.7, and 21.8. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{18}H_{14}F_3N_2O_3^+$ ([M + H]$^+$), 363.0951; found, 363.0951. ^{19}F NMR (282 MHz, $CDCl_3$): δ −115.13 (d, J = 2.8 Hz).

*1H,3H-Spiro[benzo[c]pyrazolo[1,2-a]cinnoline-2,1′-cyclobutane]-1,3-dione (**3m**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.52) to provide **3m** (0.117 g, 0.41 mmol, 81% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.51 (dd, J = 0.7, 7.8 Hz, 2H), 7.57 (dd, J = 1.1, 7.8 Hz, 2H), 7.25 (td, J = 1.3, 8.5 Hz, 2H), 7.13 (td, J = 1.0, 7.8 Hz, 2H), 2.63 (t, J = 7.8 Hz, 4H), and 2.37−2.25 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 134.7, 129.6, 125.9, 122.9, 121.0, 117.1, 47.6, 28.7, and 16.4. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{18}H_{15}N_2O_2^+$ ([M + H]$^+$), 291.1128; found, 291.1125.

*7-Methyl-1H,3H-spiro[benzo[c]pyrazolo[1,2-a]cinnoline-2,1′-cyclobutane]-1,3-dione (**3n**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.58) to provide **3n** (0.114 g, 0.38 mmol, 75% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.53 (dd, J = 0.9, 8.3 Hz, 1H), 8.39 (s, 1H), 7.59 (dd, J = 1.3, 7.8 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.25 (td, J = 1.5, 8.5 Hz, 1H), 7.18 (td, J = 1.2, 7.5 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 2.64 (t, J = 7.8 Hz, 4H), and 2.37−2.25 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 168.5, 140.1, 134.6, 134.4, 129.2, 126.8, 125.9, 122.9, 122.7, 121.3, 118.4, 117.6, and 117.1. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{19}H_{17}N_2O_2^+$ ([M + H]$^+$), 305.1285; found, 305.1289.

*2,2,6-Trimethyl-1H-benzo[c]pyrazolo[1,2-a]cinnoline-1,3(2H)-dione (**3o**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.74) to provide **3o** (0.130 g, 0.45 mmol, 90% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.48 (dd, J = 8.4, 0.8 Hz, 1H), 8.34 (s, 1H), 7.57 (dd, J = 7.8, 1.2 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.22 (td, J = 7.7, 1.1 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 2.33 (s, 3H), and 1.47 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 140.1, 134.4, 134.3, 129.2, 126.9, 126.0, 122.9, 122.6, 121.2, 118.3, 117.6, 117.2, 44.7, 21.7, and 21.7. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{18}H_{17}N_2O_2^+$ ([M + H]$^+$), 293.1285; found, 293.1285.

*6-Methoxy-2,2-dimethyl-1H-benzo[c]pyrazolo[1,2-a]cinnoline-1,3(2H)-dione (**3p**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.76) to provide **3p** (0.136 g, 0.44 mmol, 88% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.50−8.47 (m, 1H), 8.21 (d, J = 2.5 Hz, 1H), 7.54 (d, J = 8.6 Hz, 2H), 7.23−7.18 (m, 1H), 7.16−7.11 (m, 1H), 6.72 (dd, J = 8.8, 2.5, 1H), 3.84 (s, 3H), and 1.48 (s, 6H).·^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 169.4, 160.7, 135.6, 133.6, 128.6, 126.2, 124.2, 122.2, 121.3, 117.3, 113.5, 112.6, 102.4, 55.7, 44.7, and 21.8. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{18}H_{17}N_2O_3^+$ ([M + H]$^+$), 309.1234; found, 309.1233.

*6-Fluoro-2,2-dimethyl-1H-benzo[c]pyrazolo[1,2-a]cinnoline-1,3(2H)-dione (**3q**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.70) to provide **3q** (0.127 g, 0.43 mmol, 86% yield) as a light-brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.48 (dd, J = 8.3, 1.1 Hz, 1H), 8.31 (dd, J = 10.8, 2.6 Hz, 1H), 7.60−7.53 (m, 2H), 7.28−7.22 (m, 1H), 7.15 (td, J = 7.7, 1.3, 1H), 6.86 (ddd, J = 8.8, 7.7, 2.6 Hz, 1H), and 1.47 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 169.3, 163.0 (d, J = 247.0 Hz), 135.5 (d, J = 11.5 Hz), 133.9, 129.6, 126.3, 124.5 (d, J = 9.3 Hz), 122.7, 120.5, 117.3, 117.2 (d, J = 3.6 Hz), 113.0 (d, J = 22.1 Hz), 105.2 (d, J = 29.7 Hz), 44.7, and 21.7. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{17}H_{14}FN_2O_2^+$ ([M + H]$^+$), 297.1034; found, 297.1038. ^{19}F NMR (282 MHz, $CDCl_3$): δ −109.04 (ddd, J = 10.8, 7.6, and 6.0 Hz).

*7-Fluoro-2,2-dimethyl-1H-benzo[c]pyrazolo[1,2-a]cinnoline-1,3(2H)-dione (**3r**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.76) to provide **3r** (0.121 g, 0.41 mmol, 82% yield) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.54−8.50 (m, 2H), 7.55 (dd, J = 7.8, 1.3 Hz, 1H), 7.34−7.28 (m, 2H), 7.18 (td, J = 7.7, 1.1 Hz, 1H), 6.96 (ddd, J = 9.2, 7.7, 2.8, 1H), and 1.48 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 169.4, 160.6 (d, J = 244.1 Hz), 134.9, 130.8 (d, J = 2.7 Hz), 130.5, 126.2, 123.6 (d, J = 7.7 Hz), 123.3, 120.1 (d, J = 2.1 Hz), 119.2 (d, J = 8.1 Hz), 117.2, 116.1 (d, J = 22.4 Hz), 110.0 (d, J = 24.8 Hz), 44.7, and 21.8. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{17}H_{14}FN_2O_2$ ([M + H]$^+$), 297.1034; found, 297.1031. ^{19}F NMR (282 MHz, $CDCl_3$): δ −115.13 (dd, J = 8.5 Hz).

*2,2-Dimethyl-1,3-dioxo-2,3-dihydro-1H-benzo[c]pyrazolo[1,2-a]-(cinnolin-6-yl)methyl Acetate (**3s**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.84) to provide **3s** (0.147 g, 0.42 mmol, 84% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.54 (d, J = 1.4 Hz, 1H), 8.51 (dd, J = 8.3, 1.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.31−7.25 (m, 1H), 7.20−7.14 (m, 2H), 5.07 (s, 2H), 2.14 (s, 3H), and 1.48 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 169.8, 169.6, 137.9, 134.8, 134.6, 130.0, 126.2, 125.6, 123.3, 123.1, 121.0, 120.7, 117.3, 116.7, 65.7, 44.8, 21.8, and 21.1. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{20}H_{19}N_2O_4^+$ ([M + H]$^+$), 351.1339; found, 351.1337.

*6-Hydroxy-2,2-dimethyl-1H-benzo[c]pyrazolo[1,2-a]cinnoline-1,3(2H)-dione (**3t**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.64) to provide **3t** (0.112 g, 0.38 mmol, 76% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO): δ 10.03 (s, 1H), 8.35 (dd, J = 8.2, 1.3 Hz, 1H), 7.96 (d, J = 2.4 Hz, 1H), 7.74−7.67 (m, 2H), 7.25−7.12 (m, 2H), 6.60 (dd, J = 8.6, 2.5 Hz, 1H), and 1.35 (s, 6H).·^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 169.2, 158.6, 135.3, 133.2, 128.0, 125.8, 124.8, 122.3, 121.1, 116.4, 112.9, 111.4, 103.6, and 21.4. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{17}H_{13}N_2O_3^-$ ([M − H]$^-$), 293.0932; found, 293.0938.

*2,2-Dimethyl-6-(trifluoromethyl)-1H-benzo[c]pyrazolo[1,2-a]-cinnoline-1,3(2H)-dione (**3u**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.38) to provide **3u** (0.128 g, 0.37 mmol, 74% yield) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.81 (s, 1H), 8.51 (dd, J = 8.4, 0.8 Hz, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.63 (dd, J = 7.9, 1.2 Hz, 1H), 7.40 (d, J = 0.9 Hz, 1H), 7.32 (td, J = 7.6, 1.4 Hz, 1H), 7.19 (td, J = 7.8, 1.1 Hz, 1H), and 1.49 (s, 6H).·^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 169.4, 135.0 (d, J = 6.1 Hz), 131.7, 131.3, 131.0, 126.4, 125.3, 124.4, 123.5 (d, J = 13.1 Hz), 122.7 (q, J = 3.8 Hz) 121.7, 119.7, 117.4, 114.4 (q, J = 4.1 Hz), 44.71, and 21.8. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{18}H_{14}F_3N_2O_2^+$ ([M + H]$^+$), 347.1002; found, 347.1001. ^{19}F NMR (282 MHz, $CDCl_3$): δ −63.26 (s).

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*2,2-Dimethyl-1,3-dioxo-2,3-dihydro-1H-benzo[c]pyrazolo[1,2-a]-cinnoline-6-carbonitrile (**3v**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.40) to provide **3v** (0.109 g, 0.36 mmol, 72% yield) as a yellow solid. ^{1}H NMR (300 MHz, DMSO): δ 8.95 (d, J = 1.6 Hz, 1H), 8.41−8.38 (m, 1H), 8.00−7.92 (m, 2H), 7.71 (dd, J = 8.2, 1.7 Hz, 1H), 7.42−7.39 (m, 1H), 7.26−7.21 (m, 1H), and 1.37 (s, 6H).·^{13}C NMR (75 MHz, DMSO): δ 169.6, 169.3, 166.4, 134.9, 134.6, 131.4, 130.8, 126.5, 126.0, 124.5, 124.2, 123.6, 119.5, 117.3, 116.5, 44.2, and 21.4. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{18}H_{14}N_3O_2^+$ ([M + H]$^+$), 304.1081; found, 304.1078.

*2,2-Dimethyl-6-nitro-1H-benzo[c]pyrazolo[1,2-a]cinnoline-1,3(2H)-dione (**3w**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.46) to provide **3w** (0.113 g, 0.35 mmol, 70% yield) as a red solid. ^{1}H NMR (300 MHz, DMSO): δ 9.18 (d, J = 2.3 Hz, 1H), 8.40 (d, J = 7.6 Hz, 1H), 8.13 (d, J = 8.8, 1H), 8.01−7.91 (m, 2H), 7.48−7.42 (m, 1H), 7.28−7.23 (m, 1H), and 1.39 (s, 6H).·^{13}C NMR (75 MHz, DMSO): δ 170.0, 168.9, 147.2, 134.9, 134.9, 131.8, 126.8, 126.1, 124.8, 124.4, 120.4, 118.4, 116.6, 111.0, 44.2, and 21.4. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{17}H_{14}N_3O_4^+$ ([M + H]$^+$), 324.0979; found, 324.0978.

*Methyl 2,2-Dimethyl-1,3-dioxo-2,3-dihydro-1H-benzo[c]-pyrazolo[1,2-a]cinnoline-6-carboxylate (**3x**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.60) to provide **3y** (0.144 g, 0.43 mmol, 86% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.11 (d, J = 1.5 Hz, 1H), 8.51 (d, J = 8.4 Hz, 1H), 7.83 (dd, J = 8.3, 1.6 Hz, 1H), 7.70−7.65 (m, 2H), 7.35−7.29 (m, 1H), 7.21−7.16 (m, 1H), 3.92 (s, 3H), and 1.49 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 169.6, 166.1, 135.2, 134.6, 131.1, 131.0, 127.4, 126.3, 125.4, 123.8, 123.0, 120.1, 118.1, 117.4, 52.6, 44.8, and 21.8. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{19}H_{17}N_2O_4^+$ ([M + H]$^+$), 337.1183; found, 337.1184.

*Methyl 2,2-Dimethyl-1,3-dioxo-2,3-dihydro-1H-benzo[c]-pyrazolo[1,2-a]cinnoline-7-carboxylate (**3y**).* Following the general procedure, the product was obtained by silica gel chromatography purification (petroleum ether/ethyl acetate = 10:1, R_f = 0.60) to provide **3x** (0.137 g, 0.43 mmol, 86% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (dd, J = 8.3, 1.4 Hz, 1H), 8.37 (dd, J = 8.0, 1.5 Hz, 1H), 8.13 (dd, J = 8.4, 0.8 Hz, 1H), 7.27−7.15 (m, 3H), 6.81 (d, J = 8.3 Hz, 1H), 3.93 (s, 3H), and 1.47 (s, 6H).·^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 170.2, 157.1, 137.4, 135.5, 129.9, 128.7, 128.6, 125.8, 121.5, 116.3, 111.7, 109.7, 109.6, 56.0, 45.3, and 21.8. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{19}H_{17}N_2O_4^+$ ([M + H]$^+$), 337.1183; found, 337.1179.

*Procedure for the Synthesis of (S,S)-2-Phenyloctahydrophthalazine-1,4-dione (**B**).* To a stirred solution of DMF (0.15 mL) and (*S*,*S*)-cyclohexanedicarboxylic acid (1.72 g, 10 mmol) in dry dichloromethane (DCM) (30 mL) was dropwise added oxalyl dichloride (30 mmol) under an ice bath condition. Upon stirring for 3 h, phenyl hydrazine hydrochloride (1.45 g, 10 mmol) was added portionwise. The mixture was further stirred under N_2 for 30 min. Et_3N was added. The reaction was allowed to warm to room temperature (rt) and react for 4 h, which was diluted with DCM (20 mL). The reaction mixture was washed with distilled water (30 mL), dried by anhydrous $MgSO_4$, and concentrated and purified by flash column chromatography on silica gel with EtOAc/petroleum ether (1/2) to give compound **4** as a light yellow solid (1.83 g, 7.5 mmol, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (t, J = 8.2 Hz, 2H), 7.01 (t, J = 8.2 Hz, 1H), 6.81 (d, J = 8.2 Hz, 2H), 6.14 (br s, 1H), 3.02−2.99 (m, 2H), 1.95−1.85 (m, 4H), and 1.54−1.52 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.5, 145.6, 129.5, 122.7, 114.8, 38.5, 24.0, and 21.9. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{14}H_{15}N_2O_2^-$ ([M − H]$^-$), 243.1139; found, 243.1132.

*Procedure for the Synthesis of 4,4-Dimethyl-1,2-diphenylpyrazolidine-3,5-dione (**4**).* To a stirred solution of DMF (0.10 mL) and 2,2-dimethylmalonic acid (291 mg, 2.2 mmol) in water-free CH_2Cl_2 (10 mL) was dropwise added oxalyl dichloride (634 mg, 5.0 mmol). The reaction was cooled by an ice bath. Upon stirring at 0 °C for 3 h, the reaction mixture was concentrated under reduced pressure and the residue was dissolved in anhydrous THF (10 mL) at rt. A solution of 1,2-diphenylhydrazine (368 mg, 2.0 mmol) in THF (5 mL) was added to the above mixture, followed by Et_3N (4.0 mmol). The reaction was stirred at rt for 6 h. The reaction was quenched by water, and the mixture was extracted with EtOAc (15 mL × 3), dried by anhydrous $MgSO_4$, and concentrated and purified by flash column chromatography on silica gel with EtOAc/petroleum ether (from 1/5 to 1/2) to give compound **4** as a light-yellow solid (230 mg, 0.82 mmol, 41%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−7.26 (m, 8H), 7.21−7.14 (m, 2H), and 1.50 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.3, 136.1, 129.1, 126.8, 122.5, 44.4, and 21.8. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{17}H_{17}N_2O_2^+$ ([M + H]$^+$), 281.1285; found, 281.1281.

*Procedure for the Synthesis of 1-([1,1′-Biphenyl]-2-yl)-4,4-dimethylpyrazolidine-3,5-dione (**5**).* Compound **5** was synthesized following the same procedure as that of 4. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54−7.46 (m, 4H), 7.41 (t, J = 7.2 Hz, 2H), 7.37−7.31 (m, 1H), 6.86 (d, J = 8.6 Hz, 2H), 6.16 (s, 1H), and 1.50 (6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.9, 143.6, 140.6, 136.0, 128.9, 128.4, 127.1, 126.9, 114.3, 56.8, and 17.7. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{17}H_{17}N_2O_2^+$ ([M + H]$^+$), 281.1285; found, 281.1285.

*Procedure for the Synthesis of 4,4-Dimethyl-1-(phenyl-d_5)-pyrazolidine-3,5-dione (d_5-**1a**).* (Phenyl-d_5)hydrazine hydrochloride (339 mg, 3.0 mmol) and K_2CO_3 (828 mg, 6.0 mmol) were suspended in THF (20 mL) at 0 °C under N_2. A solution of 2,2-dimethylmalonyl dichloride (3.0 mmol) in THF (10 mL) was added to the above mixture. The reaction was stirred at rt for 4 h, which was quenched with H_2O (15 mL) and extracted with EtOAc (15 mL X 3). The extraction was dried over with anhydrous $MgSO_4$, concentrated, and purified by flash column chromatography on silica gel with EtOAc/petroleum ether (1/1) to give compound d_5-**1a** as a white solid (470 mg, 2.25 mmol, 75%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.6 (s, 1H), 1.27 (2, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.2, 48.9, and 22.7. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{11}H_6D_5N_2O_2^-$ ([M − H]$^-$), 208.1140; found, 208.1146.

*Procedure for the Synthesis of 2,2-Dimethyl-1H-benzo[c]-pyrazolo[1,2-a]cinnoline-1,3(2H)-dione-5,6,7,8-d_4 (d_4-**3a**).* Under an N_2 atmosphere, an oven-dried 10 mL tube was charged with 4,4-dimethyl-1-(phenyl-d_5)pyrazolidine-3,5-dione (**d_5-1a**) (0.5 mmol, 1.0 equiv), phenyl iodide **2** (1.0 mmol 2.0 equiv), $Pd(OAc)_2$ (0.05 mmol, 10% equiv), $AgBF_4$ (1.0 mmol, 2.0 equiv), and 2,6-dimethylpyridine (0.1 mmol, 20% equiv) in AcOH (5.0 mL, 2.0 M). The reaction mixture was stirred at 80 °C for 30 min. The reaction mixture was concentrated. The residue was purified on a silica gel column with petroleum ether/ethyl acetate (10/1, v/v to 1/1, v/v) to give products d_4-**3a** (25 mg) which were further characterized. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.51 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 6.8 Hz, 1H), 7.26 (t, J = 8.9 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), and 1.48 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 134.7, 129.7, 126.1, 123.0, 121.1, 117.3, 44.8, and 21.8. Mass spectrometry HRMS (ESI-TOF) (m/z): calcd for $C_{17}H_{11}D_4N_2O_2^+$ ([M + H]$^+$), 283.1379; found, 283.1381.

KIE Studies. Under an N_2 atmosphere, an oven-dried 10 mL tube was charged with the 4,4-dimethyl-1-(phenyl-d_5)pyrazolidine-3,5-dione (d_5-**1a**) (0.25 mmol, 0.5 equiv), **1a** (0.25 mmol, 0.5 equiv), phenyl iodide **2** (1.0 mmol 2.0 equiv), $Pd(OAc)_2$ (0.05 mmol, 10% equiv), $AgBF_4$ (1.0 mmol, 2.0 equiv), and 2,6-dimethylpyridine (0.1 mmol, 20% equiv) in AcOH (5.0 mL, 2.0 M). The reaction mixture was stirred at 80 °C for 30 min. The reaction mixture was concentrated. The residue was purified on a silica gel column with petroleum ether/ethyl acetate (10/1, v/v to 1/1, v/v) to give a mixture of **3a** and d_4-**3a** (36 mg), which was further characterized. The intermolecular KIE for cross coupling is around 3.0 according to the NMR spectrum of the mixture of **3a** and d_4-**3a**.

*Procedure for the Synthesis of Benzo[c]cinnoline (**7**).*[48] Compound **3a** (139 mg, 0.5 mmol) was dissolved in ethanol (2.5 mL, 0.2 M) with a stir bar in a test tube, followed by the dropwise

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addition of sodium hydroxide aqueous solution (5.0 M, 0.5 mL, 2.5 mmol). The resulting solution was heated at 70 °C for 10 h under an oxygen atmosphere. After cooling to rt, the reaction mixture was partitioned between water (20 mL) and DCM (20 mL). The mixture was separated, and the resulting aqueous solution was further extracted with DCM (2 × 20 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo to give the crude product which was purified by silica gel column with petroleum ether/ethyl acetate (10/1, v/v to 5/1, v/v) to give the light-yellow solid (0.081 g, 0.45 mmol, 90%) as product **7**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.76−8.68 (m, 2H), 8.57−8.48 (m, 2H), and 7.92−7.84 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.4, 131.7, 131.4, 129.3, 121.5, and 121.0.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.0c00800.

Proposed reaction mechanism and NMR spectra and chemical structures of the new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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