Ru(II)/Ir(III)-Catalyzed C–H Bond Activation/Annulation of Cyclic Amides with 1,3-Diketone-2-diazo Compounds: Facile Access to 8H-Isoquinolino[1,2-b]quinazolin-8-ones and Phthalazino[2,3-a]cinnoline-8,13-diones

Panyuan Cai,† Enshen Zhang,† Yinsong Wu, Taibei Fang, Qianqian Li, Chen Yang, Jian Wang,* and Yongjia Shang†

Key Laboratory of Functional Molecular Solids, Ministry of Education, Anhui Key Laboratory of Molecule-Based Materials, College of Chemistry and Materials Science, Anhui Normal University, Wuhu 241000, P. R. China

Supporting Information

ABSTRACT: Efficient access to 8H-isouquinolino[1,2-b]quinazolin-8-ones and phthalazino[2,3-a]cinnoline-8,13-diones through cyclic amide-directed Ru(II)/Ir(III)-catalyzed C–H bond activation, has been developed. Consecutive C–H bond activation, carbene insertion, and condensation annulation processes were realized, affording 8H-isouquinolino[1,2-b]quinazolin-8-one and phthalazino[2,3-a]cinnoline-8,13-dione derivatives in good-to-excellent yields under mild conditions, with H2O and N2 being generated as the only byproducts.

INTRODUCTION

As poly cyclic nitrogen-containing heterocycles, 8H-isouquinolino[1,2-b]quinazolin-8-ones and phthalazino[2,3-a]cinnoline-8,13-diones are ubiquitous in many bioactive synthetic compounds as well as natural products (Scheme 1). For example, compounds A and B as shown in Scheme 1 were proved to have efficient antitumor activities. 1,2 Polycyclic nitrogen-containing heterocycles were also commonly applied in anticonvulsant,3 anti-inflammatory,4 anti-allergenic,5 anti-atherosclerotic,6 antimicrobial,7 cardiotonic,8 and cell imaging9 research. Scaffold of 11H-pyrido[2,1-b]quinazolin-11-one H was found in many natural products10 (Scheme 1). Traditional synthesis of such polycyclic compounds suffered from multiple steps and harsh reaction conditions. Thus, developing general and efficient approaches for the construction of 8H-isouquinolino[1,2-b]quinazolin-8-one and phthalazino[2,3-a]cinnoline-8,13-dione derivatives attracted a lot of efforts. For example, Peng and Cui developed ruthenium and palladium catalyzed directed C–H bond activation of 2-phenylquinazolin-4-(3H)-ones and alkyne insertion annulations for the synthesis of 8H-isouquinolino[1,2-b]quinazolin-8-ones, respectively (Scheme 2).11,12 Synthesis of phthalazino[2,3-a]cinnoline-8,13-diones was independently reported by Gandhi and Perumal via ruthenium and rhodium catalyzed alkyne insertion reactions with 2-phenyl-2,3-dihydropthalazine-1,4-diones.13,14 Transition-metal catalyzed C–H bond activation reactions have been a long-term research interest of organic chemists for the construction of new C–C and C–X (X = N, O, S et al.) bonds because of the environmental benignity and simple operation. As a C1 building block, carbene has attracted much attention based on its high and diverse reaction reactivities.15–18 1,3-Diketone-2-diazo compounds can not only react as a C1 synthon but also be used as an equivalent of alkynes, undergoing formal C2 insertion reaction with cyclic compounds being constructed.19 However, compared with alkynes, 1,3-diketone-2-diazo compounds have their unique characteristics. For instance, no additional oxidants, to which lots of substrates cannot tolerate, were needed. Additionally, cyclic 1,3-diketone-2-diazo compounds have their priorities because of the instability of cyclic alkynes.20 Herein, we report facile access to 8H-isouquinolino[1,2-b]quinazolin-8-ones and phthalazino[2,3-a]cinnoline-8,13-diones via ruthenium and iridium catalyzed C–H bond activation/annulation reaction of cyclic amide derivatives. In these reactions, both cyclic and acyclic 1,3-diketone-2-diazo compounds could be transformed to corresponding products smoothly in good to excellent yields with H2O and N2 as the only byproducts.
RESULTS AND DISCUSSION

The reaction was initiated with 2-(p-tolyl)quinazolin-4(3H)-one (1a) and 2-diazo-5-methylcyclohexane-1,3-dione (2a) as model substrates with the catalysis of (RhCp*Cl2)2/AgNTf2 at 90 °C (Table 1, entry 1). To our delight, the desired product 2,6-dimethyl-2,3-dihydro-4H-quinazolino[3,2-f]-phenanthridine-4,14(1H)-dione (3a) was obtained in 58% yield. Screening of catalysts revealed that 3 mol % of [(p-cymene)RuCl2]2 gave the best result (entries 2−5). Further investigation of additives and solvents showed lower efficacy (entries 6−11). In addition, no better results were found at lower or higher reaction temperatures (80 and 100 °C).

With the optimized conditions in hand, the substrate scope of 2-phenylquinazolin-4(3H)-one derivatives were investigated first (Scheme 3). Substituents such as OMe, OBn, Br, iBu, Cl, and OH on the aromatic rings were well tolerated under the optimal conditions, generating the corresponding products in moderate-to-good yields (3a−3i). It is worthy to note that the substrate with the hydroxyl group which is intolerable under many reaction conditions could be transformed to product 3i in an acceptable 50% yield. When phenyl, dimethyl, or nonsubstituted cyclic diazo compounds worked as the reactants, products 3j−3l were obtained in moderate yields. Meanwhile, heterocyclic C−H bond activation was realized to generate 3m in 68% yield. However, acyclic 1,3-diketone-2-diazo compounds failed to suffer the reaction conditions.

Other types of cyclic amide-directed C−H bond activations were further investigated with easily accessible 2-phenyl-2,3-dihydrophthalazine-1,4-diones (4a) and 2-diazo-5,5-dimethylcyclohexane-1,3-dione (2b) as model substrates. With the above optimized catalytic system at a higher temperature of 100 °C, 2,2-dimethyl-2,3-dihydrobenzo[c]phthalazino[2,3-a]-cinnoline-4,10,15(1H)-trione (5a) was generated in 60% yield (Table 2, entry 1). After optimization of the reaction
conditions, the yield of 5a was increased to 93% under the condition of (IrCp*Cl₂)$_2$/AgSbF₆ as catalyst in DCE at 100 °C (entry 3).

Next, the scope of the reaction was investigated under the optimized conditions (Scheme 4). Substrates with Me, tBu, F, Cl, and Br underwent the reaction efficiently with 2-diazo-5,5-dimethylcyclohexane-1,3-dione (2b), generating the corresponding products in good to excellent yields (5a−5i). Steric hindered ortho-substituted substrates could tolerate the reaction conditions, generating 5g and 5h in 81 and 82% yields, respectively. Diverse poly cyclic heterocycles were obtained in good yields when using monomethyl, phenyl, and nonsubstituted cyclic diazo compounds as the reaction partners (5j−5r). It is worthy to note that five-membered-cyclic and acyclic 1,3-carbonyl-2-diazo compounds tolerated the reaction conditions, generating the corresponding products 5s−5x in excellent yields.

On the basis of the reported transition-metal-catalyzed C−H bond activation/carbene insertion reactions$^{22,23,24}$ and the experiment results, a possible mechanism was proposed in
Scheme 5. An active catalytic species I was generated by ligand exchange, which catalyzed C–H bond activation to form intermediate II. Carbene coordination and migratory insertion to intermediate II generated alkyl-ruthenium intermediate IV, which was then protonated to intermediate V. The catalyst I was released to complete the catalytic cycle. An isomerization/intramolecular condensation process of V took place spontaneously, affording the compound 3.

**CONCLUSION**

In conclusion, we have developed an efficient and practical method for the synthesis of 8H-isoquinolinol[1,2-b]quinazolin-8-one and phthalazino[2,3-a]cinnoline-8,13-dione derivatives.
via ruthenium and iridium catalyzed C–H bond activation reactions. Diverse nitrogen-containing poly cyclic compounds were synthesized effectively under mild conditions. The reaction proceeds through consecutive C–H bond activation, carbene insertion, and annulation reaction with water and N₂ as the only byproducts, revealing the environmental benignity of this reaction.

**EXPERIMENTAL SECTION**

**General Comments.** Unless otherwise specified, all reagents and starting materials were purchased from commercial sources and used as received and the solvents were purified and dried using standard procedures. The chromatography solvents were of technical grade and distilled to standard techniques. The ¹H and ¹³C NMR data were recorded on 300/500 and 75/125 MHz NMR spectrometers, and indicated as ¹³C{¹H} NMR. Multiplicities are described as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet), and the coupling constants (J) are reported in hertz. HRMS analysis with a quadrupole time-of-flight mass spectrometer yielded ion mass/charge (m/z) ratios in atomic mass units. IR spectra were measured as dry films (KBr), and the peaks are reported in terms of wave number (cm⁻¹).

**Procedure A: The Synthesis of 8H-Isouquinolino[1,2-b]quinazolin-8-one Derivatives 3.** To a solution of 2-p-tolylquinazolin-4(3H)-one (0.5 mmol) and [(p-cymene)RuCl₃]₂ (3 mol %)/AgNTf₂ (30 mol %) in t-BuOH (2 mL) at 90 °C was added portion wise a solution of 2-diazo-5-methylcyclohexane-1,3-dione (0.5 mmol). After being stirred for another 40 min, the mixture was cooled to room temperature. The reaction was quenched with water, and the mixture was extracted with DCM three times. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to afford 2,6-dimethyl-2,3-dihydro-4'H-quinazolino[3,2-f] phenanthidine-4,14(1H)-dione 3.

**Procedure B: The Synthesis of Phthalazino[2,3-a]cinnolino-8,13-dione Derivatives 5.** A mixture of cyclic 2-diazo-1,3-diketones 2 (0.5 mmol), 2-phenyl-2,3-dihydrophthalazine-1,4-dione 4 (0.5 mmol), [Cp*IrCl₃]₂ (2 mol %), and AgSbF₆ (20 mol %) in DCE (2 mL) was heated in an oil bath at 100 °C for 14 h. Upon completion of the reaction, the mixture was cooled to room temperature. The residue was purified by flash column chromatography on silica gel (200–300 mesh) with ethyl acetate and petroleum ether (1:6 v/v) as the elution solvent to give the desired products 5.

**Scheme 5. Proposed Reaction Mechanism**
12-Chloro-2-methyl-2,3-dihydro-1H-quinazolino[3,2-f]-phenanthidine-4,14-dione (3g). Yellow solid. 112 mg, 63% yield; mp: 213–215 °C; 1H NMR (300 MHz, CDCl3): δ 9.07 (d, J = 8.1 Hz, 1H), 8.89 (d, J = 7.8 Hz, 1H), 8.23 (s, 1H), 7.89–7.64 (m, 3H), 7.58 (t, J = 7.5 Hz, 1H), 3.47 (dd, J = 18.3, 10.8 Hz, 1H), 3.22 (d, J = 17.1 Hz, 1H), 2.78 (d, J = 16.5 Hz, 1H), 2.49 (d, J = 16.5, 12.9 Hz, 1H), 2.21 (s, 1H), 1.17 (d, J = 6.3 Hz, 3H); 13C NMR (75 MHz, CDCl3): δ 190.0, 161.2, 149.5, 145.1, 135.6, 132.7, 131.8, 129.5, 128.7, 128.4, 126.9, 126.7, 126.4, 126.2, 121.0, 118.5, 47.3, 39.1, 29.9, 20.9; IR (KBr) ν: 2958, 1697, 1670, 1595, 1562, 1444, 1362, 1296, 1064, 837, 771, 690 cm⁻¹; HRMS (ESI) calcld for C₂₃H₂₂ClN₂O₂ [M + H]+, 363.0895; found, 363.0895.

7-Chloro-2-methyl-2,3-dihydro-1H-quinazolino[3,2-f]-phenanthidine-4,14-dione (3h). Yellow solid. 81 mg, 46% yield; mp: 220–222 °C; 1H NMR (300 MHz, CDCl3): δ 9.09–8.74 (m, 2H), 8.27 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 6.3 Hz, 2H), 7.49 (t, J = 6.3 Hz, 1H), 7.37–7.11 (m, 1H), 3.50 (dd, J = 18.3, 10.8 Hz, 1H), 3.26 (d, J = 18.3 Hz, 1H), 2.78 (d, J = 16.8 Hz, 1H), 2.60–2.35 (m, 1H), 2.21 (s, 1H), 1.17 (d, J = 6.3 Hz, 3H); 13C NMR (75 MHz, CDCl3): δ 197.7, 162.1, 152.5, 151.3, 146.3, 135.3, 129.8, 129.7, 127.1, 126.8, 126.3, 119.9, 116.7, 116.4, 112.8, 47.2, 39.2, 29.9, 20.9; IR (KBr) ν: 2964, 1693, 1598, 1550, 1490, 1323, 771 cm⁻¹; HRMS (ESI) calcld for C₂₃H₂₁ClN₂O₂ [M + H]+, 363.0895; found, 363.0900.

8-Hydroxy-2-methyl-2,3-dihydro-1H-quinazolino[3,2-f]-phenanthidine-4,14-dione (3i). Yellow solid. 85 mg, 50% yield; mp: 197–199 °C; 1H NMR (300 MHz, CDCl3): δ 8.81 (s, 1H), 8.51 (d, J = 8.1 Hz, 1H), 8.28 (d, J = 7.8 Hz, 1H), 7.84 (t, J = 7.5 Hz, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.62 (t, J = 8.1 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.11 (d, J = 8.1 Hz, 1H), 3.44 (dd, J = 18.3, 10.8 Hz, 1H), 3.18 (d, J = 17.1 Hz, 1H), 2.78 (d, J = 16.8 Hz, 1H), 2.48 (dd, J = 16.8, 2.6 Hz, 1H), 2.20 (s, 1H), 1.17 (d, J = 6.6 Hz, 3H); 13C NMR (75 MHz, CDCl3): δ 197.5, 161.1, 152.5, 150.0, 148.6, 134.8, 135.6, 134.9, 130.2, 127.3, 126.6, 125.0, 119.8, 114.9, 116.4, 116.5, 47.4, 39.0, 29.8, 20.9; IR (KBr) ν: 3419, 2958, 2708, 1708, 1564, 1548, 1494, 1334, 1269, 810, 758, 696 cm⁻¹; HRMS (ESI) calcld for C₂₃H₂₁NO₃ [M + H]+, 345.1234; found, 345.1233.

12-Chloro-2-methyl-2,3-dihydro-1H-quinazolino[3,2-f]-phenanthidine-4,14-dione (3j). Yellow solid. 111 mg, 45% yield; mp: 217–219 °C; 1H NMR (300 MHz, CDCl3): δ 9.19 (d, J = 8.4 Hz, 1H), 8.90 (s, 1H), 8.21 (d, J = 7.5 Hz, 1H), 8.08 (d, J = 7.5 Hz, 1H), 7.90–7.73 (m, 1H), 7.64–7.17 (m, 10H), 5.28 (s, 2H), 4.02 (dd, J = 18.0, 11.5 Hz, 2H), 3.70–3.22 (m, 2H), 3.22–2.83 (m, 2H); 13C NMR (125 MHz, CDCl3): δ 197.3, 163.2, 161.9, 149.9, 146.9, 141.9, 136.1, 135.7, 132.0, 129.7, 129.0, 128.7, 127.8, 127.0, 126.7, 119.7, 117.9, 118.86, 109.3, 103.1, 70.4, 47.4, 39.4, 29.9, 20.9; IR (KBr) ν: 2922, 1693, 1674, 1600, 1541, 1498, 1379, 1325, 1242, 1014, 886, 771, 692 cm⁻¹; HRMS (ESI) calcld for C₂₃H₂₁ClN₂O₂ [M + H]+, 345.1703; found, 345.1696.

8-Chloro-2-methyl-2,3-dihydro-1H-quinazolino[3,2-f]-phenanthidine-4,14-dione (3k). Yellow solid. 96 mg, 46% yield; mp: 169–171 °C; 1H NMR (300 MHz, CDCl3): δ 9.06 (d, J = 8.7 Hz, 1H), 8.82 (d, J = 2.1 Hz, 1H), 8.26 (d, J = 7.8 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.83 (t, J = 7.5 Hz, 1H), 7.44 (m, 5H), 7.27 (d, J = 7.5 Hz, 2H), 5.25 (s, 2H), 3.52 (t, J = 5.7 Hz, 2H), 2.90–2.69 (m, 2H), 2.15–1.97 (m, 2H); 13C NMR (125 MHz, CDCl3): δ 198.0, 162.7, 162.0, 151.3, 146.9, 136.2, 135.5, 129.4, 128.7, 128.3, 127.8, 127.1, 126.0, 118.2,
8.45 °C; Yellow solid. 175 mg, 83% yield; mp: 232–234 °C; 1H NMR (500 MHz, CDCl3): δ 8.42 (d, J = 7.7 Hz, 1H), 8.30 (d, J = 7.6 Hz, 1H), 8.28 (d, J = 2.3 Hz, 1H), 7.97–7.87 (m, 2H), 7.70 (d, J = 8.8 Hz, 1H), 7.25–7.22 (m, 1H), 2.87 (s, 2H), 2.49 (s, 2H), 1.12 (s, 6H); 13C NMR (125 MHz, CDCl3): δ 195.7, 158.1, 157.2, 153.7, 153.3, 129.1, 129.0, 128.5, 128.2, 127.1, 124.1, 121.1, 116.9, 52.4, 41.2, 34.1, 28.5; IR (KBr) ν: 2970, 2373, 1596, 1485, 1374, 1343, 1301, 1067, 686 cm⁻¹; HRMS (ESI) calcld for C₂₅H₂₂ClN₂O₃ [M++H]⁺ 393.0991; found, 393.1454.

7-Bromo-2,2-dimethyl-2,3-dihydrobenzo[c]phenanthro[2,3-c]quinolino[2,1-b]azaindole (5e). Yellow solid. 154 mg, 82% yield; mp: 218–220 °C; 1H NMR (500 MHz, CDCl3): δ 8.44–8.37 (m, 1H), 8.33–8.27 (m, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.97–7.85 (m, 2H), 7.35–7.27 (m, 1H), 7.12–7.03 (m, 1H), 3.52 (d, J = 18.3 Hz, 1H), 5.24 (d, J = 15.6 Hz, 1H), 2.41 (d, J = 15.6 Hz, 1H), 2.27 (d, J = 18.2 Hz, 1H), 1.17 (s, 3H), 1.07 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 195.7, 157.9 (d, J = 270 Hz), 154.4 (d, J = 26.3 Hz), 152.2, 135.5, 134.4, 129.6 (d, J = 28.8 Hz), 128.9 (d, J = 7.5 Hz), 126.7, 122.4, 121.3 (d, J = 11.3 Hz), 116.4 (d, J = 18.8 Hz), 115.9, 52.3, 40.5, 33.7, 29.8, 27.5; 19F NMR (70 MHz, CDCl3): δ 687 cm⁻¹; HRMS (ESI) calcld for C₂₅H₂₂BrN₂O₃ [M++H]⁺, 415.2016; found, 415.2022.
ACS Omega

2,7-Dimethyl-2,3-dihydrobenzo[c]phthalazino[2,3-al]cinnoline-4,10,15(1H)-trione (5n). Yellow solid. 170 mg, 95% yield; mp: 287–289 °C; 1H NMR (500 MHz, CDCl3); δ 4.82 (d, J = 7.3 Hz, 1H), 8.30 (d, J = 7.7 Hz, 1H), 8.16 (d, J = 8.2 Hz, 1H), 7.94–7.86 (m, 2H), 7.59 (s, 1H), 7.07 (d, J = 8.2, 0.6 Hz, 1H), 2.91 (d, J = 18.1 Hz, 1H), 2.79 (d, J = 18.3 Hz, 1H), 2.69–2.62 (m, 1H), 2.38–2.31 (m, 5H), 1.11 (d, J = 5.2 Hz, 3H); 13C NMR (125 MHz, CDCl3); δ 196.3, 158.2, 157.3, 153.2, 138.8, 134.4, 127.2, 120.2, 120.1, 118.7, 47.2, 35.6, 30.5, 21.8, 21.6; IR (KBr) ν: 2958, 2380, 2346, 1683, 1675, 1318, 1293, 1239, 821, 688 cm⁻¹; HRMS (ESI) calcd for C27H16NiN5O5 [M + H⁺], 539.1390; found, 539.1395.

7-Bromo-2-methyl-2,3-dihydrobenzo[c]phthalazino[2,3-al]cinnoline-4,10,15(1H)-trione (5o). Yellow solid. 171 mg, 81% yield; mp: 267–269 °C; 1H NMR (500 MHz, CDCl3); δ 8.43–8.41 (m, 1H), 8.31 (d, J = 7.6, 1.2 Hz, 1H), 8.18 (d, J = 8.7 Hz, 1H), 7.96–7.88 (m, 3H), 7.38 (d, J = 8.7, 2.0 Hz, 1H), 2.91 (d, J = 18.5 Hz, 1H), 2.78 (d, J = 28.9 Hz, 1H), 2.67 (d, J = 12.2 Hz, 1H), 2.36–2.32 (m, 2H), 1.12 (d, J = 6.1 Hz, 3H); 13C NMR (125 MHz, CDCl3); δ 195.9, 158.0, 157.3, 154.5, 154.6, 135.6, 134.7, 128.5, 128.1, 117.9, 47.1, 35.7, 30.4, 21.6; IR (KBr) ν: 2964, 2368, 1677, 1315, 1296, 1229, 783, 686 cm⁻¹; HRMS (ESI) calcd for C27H15BrN5O5 [M + H⁺], 423.0339; found, 423.0334.

2,8-Dimethyl-2,3-dihydrobenzo[c]phthalazino[2,3-al]cinnoline-4,10,15(1H)-trione (5p). Yellow solid. 152 mg, 85% yield; mp: 217–219 °C; 1H NMR (500 MHz, CDCl3); δ 8.39–8.36 (m, 1H), 8.30 (d, J = 7.7, 0.8 Hz, 1H), 8.08 (d, J = 18.7, 7.9 Hz, 1H), 7.93–7.91 (m, 1H), 7.88–7.85 (m, 1H), 7.30–7.27 (m, 1H), 7.17 (d, J = 7.4 Hz, 1H), 3.04 (d, J = 17.9, 11.0 Hz, 1H), 2.69–2.60 (m, 2H), 2.40–2.34 (m, 2H), 2.01 (d, J = 7.5 Hz, 3H), 1.11 (d, J = 6.3 Hz, 3H); 13C NMR (125 MHz, CDCl3); δ 196.9, 159.8, 159.3, 157.0, 157.2, 155.5, 155.2, 134.1, 131.9, 130.9, 128.9, 128.0, 124.4, 117.0, 116.7, 47.2, 35.7, 27.8, 21.9, 20.1; IR (KBr) ν: 2958, 2875, 1685, 1672, 1602, 1376, 1321, 1293, 1243, 781, 683 cm⁻¹; HRMS (ESI) calcd for C28H16BrN5O5 [M + H⁺]⁺, 539.1390; found, 539.1397.

2-Phenyl-2,3-dihydrobenzo[c]phthalazino[2,3-al]cinnoline-4,10,15(1H)-trione (5q). Yellow solid. 175 mg, 86% yield; mp: 188–190 °C; 1H NMR (500 MHz, CDCl3); δ 8.48–8.42 (m, 1H), 8.32 (d, J = 7.6, 1.8 Hz, 1H), 8.26 (d, J = 8.1 Hz, 1H), 8.06–7.58 (m, 4H), 7.47–7.31 (m, 3H), 7.30–7.27 (m, 3H), 3.53–3.46 (m, 1H), 3.34–3.29 (m, 1H), 3.12 (d, J = 17.3 Hz, 1H), 2.96–2.86 (m, 2H); 13C NMR (125 MHz, CDCl3); δ 195.5, 158.2, 157.3, 153.8, 142.4, 135.3, 134.4, 129.3, 128.6, 128.5, 127.8, 127.5, 127.1, 126.1, 125.2, 122.8, 119.9, 45.8, 40.8, 35.3; IR (KBr) ν: 3064, 2964, 2373, 2340, 1672, 1652, 1290, 1248, 733, 692 cm⁻¹; HRMS (ESI) calcd for C28H15NiN5O5 [M + H⁺]⁺, 407.1390; found, 407.1390.

6-Chloro-2-methyl-2,3-dihydrobenzo[c]phthalazino[2,3-al]cinnoline-4,10,15(1H)-trione (5r). Yellow solid. 179 mg, 81% yield; mp: 186–188 °C; 1H NMR (500 MHz, CDCl3); δ 8.40 (dd, J = 11.6, 5.0 Hz, 2H), 8.25 (d, J = 7.7 Hz, 1H), 7.95–7.91 (m, 2H), 7.71 (d, J = 8.9 Hz, 1H), 7.36–7.33 (m, 3H), 7.28–7.27 (m, 2H), 7.25 (s, 1H), 3.50–3.45 (m, 1H), 3.33–3.28 (m, 1H), 3.12 (d, J = 19.2 Hz, 1H), 2.90 (d, J = 9.5 Hz, 2H); 13C NMR (125 MHz, CDCl3); δ 195.0, 158.2, 157.2, 154.8, 142.2, 135.4, 134.6, 133.8, 132.7, 130.1, 129.3, 128.9, 128.6, 128.5, 127.9, 127.3, 127.1, 124.3, 117.5, 45.7, 40.7, 35.4; IR (KBr) ν: 3070, 2379, 1694, 1672, 1596, 1374, 1298, 1251, 1184, 1070, 697 cm⁻¹; HRMS (ESI) calcd for C28H15ClNiN5O5 [M + H⁺]⁺, 441.1000; found, 441.1005.

ACS Omega 2018, 3, 14375–14384

14582
DOI: 10.1021/acsomega.8b01930
Ethyl 2-Bromo-6-methyl-8,13-dioxo-8,13-dihydrophthalozino[2,3-aj]cinnoline-5-carboxylate (5x). Yellow solid. 196 mg, 92% yield; mp: 182−183 °C; 1H NMR (500 MHz, CDCl3): δ 8.39 (d, J = 7.4 Hz, 1H), 8.32−8.26 (m, 1H), 8.00 (d, J = 1.7 Hz, 1H), 7.93−7.83 (m, 2H), 7.32 (dd, J = 8.5, 1.7 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 2.39 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H); 13C NMR (125 MHz, CDCl3): δ 165.9, 157.7, 157.5, 142.2, 136.6, 134.9, 134.7, 129.9, 129.9, 129.5, 128.9, 128.4, 126.4, 122.9, 122.8, 121.9, 118.7, 62.1, 18.0, 17.9, 14.6; IR (KBr) ν: 2987, 2360, 2338, 1719, 1671, 1317, 1238, 1053, 804, 690 cm−1; HRMS (ESI) calcld for C20H13BrN2O4 [M + H]+, 427.0288; found, 427.0293.

**ASSOCIATED CONTENT**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b01930.

Procedures for the preparation of starting materials (CIF)

1H, 13C, and 19F NMR spectra for products (CIF)

X-ray crystallography data for compounds 3a and 5a (PDF)

**AUTHOR INFORMATION**

**Corresponding Authors**

*E-mail: wang_jian989@163.com* (J.W.)

*E-mail: shyyj@mail.ahu.edu.cn* (Y.S.)

**ORCID**

Yongjia Shang: 0000-0001-9783-9150

**Author Contributions**

P.C. and E.Z. contributed equally.

**Notes**

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

This work was supported by the National Natural Science Foundation of China (nos. 21772001, 21702003), Natural Science Foundation of Anhui Province (nos. 1808085MB41, 1808085QB31) and the Start-up Research Fund of Anhui Normal University.

**REFERENCES**

(1) Khan, I.; Ibrar, A.; Ahmed, W.; Saeed, A. Synthetic Approaches, Functionalization and Therapeutic Potential of Quinazoline and Quinazolinone Skeletons: The Advanees Continue. Eur. J. Med. Chem. 2015, 90, 124−169.

(2) Maity, A.; Mondal, S.; Paira, R.; Hazra, A.; Naskar, S.; Sahu, K. B.; Saha, P.; Banerjee, S.; Mondal, N. B. A Novel Approach for the One-pot Synthesis of Linear and Angular Fused Quinazoline. Tetrahedron Lett. 2011, 52, 3033−3037.

(3) Wolfe, J. F.; Rathman, T. L.; Sleevi, M. C.; Campbell, J. A.; Greenwood, T. D. Synthesis and Anticonvulsant Activity of Some New 2-Substituted 3-Aryl-(3H)-quinazolines. J. Med. Chem. 1990, 33, 161−166.

(4) Kornet, M. J.; Varia, T.; Beaver, W. Synthesis and anticonvulsant activity of 3-amino-4H-quinazolines. J. Heterocycl. Chem. 1983, 20, 1553−1555.

(5) Vaidya, N. A.; Panos, C. H.; Kite, A.; Iturrian, W. B.; Blanton, C. D., Jr. Synthesis of 3,4-Dihydro-4-oxoquinazoline Derivatives as Potential Anticonvulsants. J. Med. Chem. 1983, 26, 1422−1425.
(6) Schwender, C. F.; Sunday, B. R.; Herzig, D. J. 11-Oxo-11-H-pyrido[2,1-b]quinoxaline-8-carboxylic Acid, an Orally Active Anti-allergy Agent. J. Med. Chem. 1979, 22, 114.

(7) de Laszlo, S. E.; Quagliato, C. S.; Greenlee, W. J.; Patchett, A. A.; Chang, R. S. L.; Lotti, V. J.; Chen, T. B.; Scheck, S. A.; Faust, K. A. A Potent, Orally Active, Balanced Affinity Angiotensin II AT1 Antagonist and AT2 Binding Inhibitor. J. Med. Chem. 1993, 36, 3207–3210.

(8) Lowe, J. A., III; Archer, R. L.; Chapin, D. S.; Cheng, J. B.; Helweg, D.; Johnson, J. L.; Koe, B. K.; Lebel, L. A.; Moore, P. F. Structure-Activity Relationship of Quinolinolinedione Inhibitors of Calcium-Independent Phosphodiesterase. J. Med. Chem. 1991, 34, 624–628.

(9) Bartroli, J.; Turmo, E.; Alguero, M.; Conompte, E.; Vericat, M. L.; Conte, L.; Ramis, J.; Merlos, M.; Garcia-Rafanell, J.; Forrn, J. New Azole Antifungals. 3. Synthesis and Antifungal Activity of 3-Substituted-4(3H)-quinazolinones \(1^–3\). J. Med. Chem. 1998, 41, 1869–1882.

(10) Ager, I. R.; Harrison, D. R., P. D.; Taylor, J. B. Synthesis and Central Nervous System Activity of Quinazolines Related to 2-Methyl-3-(o-toly)-4(3H)-quinazoline (Methaqualone). J. Med. Chem. 1977, 20, 379.

(11) Mayakrishnan, S.; Arun, Y.; Balachandran, C.; Emi, N.; Muralidharan, D.; Perumal, P. T. Synthesis of Cinnolines via Rh(III)-catalysed Dehydrogenative C–H/N–H Functionalization: Aggregation Induced Emission and Cell Imaging. Org. Biomol. Chem. 2016, 14, 1958–1968.

(12) Rajkumar, S.; Savarimuthu, S. A.; Kumaran, R. S.; Nagaraja, C. M.; Gandhi, T. Expedition synthesis of new cinnolines diones by Ru-catalyzed Regioselective Unexpected Deoxygenation-oxidative annulation of Propargyl Alcohols with Phthalazinones and Pyridazinones. Chem. Commun. 2016, 52, 2509–2512.

(13) Liu, J.; Zou, J.; Yao, J.; Chen, G. Copper-Mediated Tandem C(sp2)-H Amination and Annulation of Arenes with 2-Aminopyridines: Synthesis of Pyrido-fused Quinazoline Derivatives. Adv. Synth. Catal. 2017, 360, 659–663.

(14) Feng, Y.; Tian, N.; Li, Y.; Jia, C.; Li, X.; Wang, L.; Cui, X. Construction of Fused Polyheterocycles through Sequential \([4+2]\) and \([3+2]\) Cycloaditions. Org. Lett. 2017, 19, 1658–1661.

(15) Lu, H.; Yang, Q.; Zhou, Y.; Guo, Y.; Deng, Z.; Ding, Q.; Peng, Y. Cross-Coupling/Annulations of Quinazolines with Alkynes for Access to Fused Polycyclic Heteroaromatics under Mild Conditions. Org. Biomol. Chem. 2014, 12, 758–764.

(16) Mayakrishnan, S.; Arun, Y.; Balachandran, C.; Emi, N.; Muralidharan, D.; Perumal, P. T. Synthesis of cinnolines via Rh(III)-catalysed Dehydrogenative C–H/N–H Functionalization: Aggregation Induced Emission and Cell imaging. Org. Biomol. Chem. 2016, 14, 1958–1968.

(17) Rajkumar, S.; Savarimuthu, S. A.; Kumaran, R. S.; Nagaraja, C. M.; Gandhi, T. Expedition Synthesis of New Cinnolinediones by Ru-Catalyzed Regioselective Unexpected Deoxygenation-Oxidative Annulation of Propargyl Alcohols with Phthalazinones and Pyridazinones. Chem. Commun. 2016, 52, 2509–2512.

(18) Arochiam, P. B.; Bruneau, C.; Dixneuf, P. H. Ruthenium(II)-Catalyzed C–H Bond Activation and Functionalization. Chem. Rev. 2012, 112, 5879–5918.

(19) Ritleng, V.; Sirlin, C.; Pfeffer, M. Ru-, Rh-, and Pd-Catalyzed C–C Bond Formation Involving C–H Activation and Addition on Unsatuated Substrates: Reactions and Mechanistic Aspects. Chem. Rev. 2002, 102, 1731–1770.

(20) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. Modern Organic Synthesis with \(\sigma\)-Diazocarbonyl Compounds. Rev. Chem. 2015, 115, 9981–10020.

(21) Xia, Y.; Qiu, D.; Wang, T. Transition-Metal-Catalyzed Cross-Couplings through Carbene Migratory Insertion. Chem. Rev. 2017, 117, 13810–13889.

(22) Li, S.-S.; Xia, Y.-Q.; Hu, F.-Z.; Liu, C.-F.; Su, F.; Dong, L. Ir(III)-Catalyzed One-Pot Cascade Synthesis of Pentacyclic-Fused Carbazoles from Indoles and Diazoles. Chem.—Asian J. 2016, 11, 3165–3168.