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Synthesis of 1*H*-Indazoles via Silver(I)-Mediated Intramolecular Oxidative C−H Bond Amination

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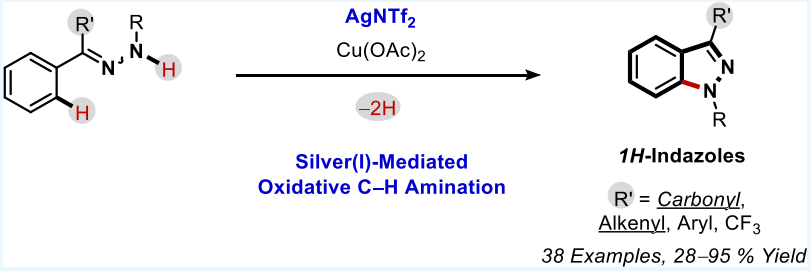

ABSTRACT: We described a silver(I)-mediated intramolecular oxidative C−H amination that enables the construction of assorted 1*H*-indazoles that are widely applicable in medicinal chemistry. The developed amination was found to be efficient for the synthesis of a variety of 3-substituted indazoles that are otherwise difficult to be synthesized by other means of C−H aminations. Preliminary mechanistic studies suggested that the current amination proceeds via single electron transfer (SET) mediated by Ag(I) oxidant.

INTRODUCTION

Indazole and its derivatives are ubiquitously found in a broad spectrum of biological and pharmaceutical applications.[1] In particular, as a surrogate of indole that is a central motif in natural and synthetic pharmacophores,[2] indazole still has extensive space of derivatization to expand a new chemical territory for the acquisition of patents. Indeed, indazole moiety is found in a variety of FDA-approved drugs such as Granisetron (5-HT_3 antagonist) as an antiemetic drug[3a] and Lonidamine (antiglycolytic drug) for brain tumor treatment.[3b] In addition, indazoles are also found as a core structure in tyrosine kinase inhibitors such as Axitinib, Pazopanib, and Entrectinib for renal cell carcinoma treatment[3c,d] or for ROS-1 positive, metastatic nonsmall cell lung cancer.[3f] More recently, poly[ADP-ribose]polymerase inhibitor (PARP inhibitor) Niraparib with indazole core was FDA-approved for recurrent epithelial ovarian cancer[3e] (Scheme 1).

Based on this high demand of indazole derivatives in pharmaceutical chemistry, a wide range of synthetic approaches have been reported in precedent literature (Scheme 2):[4] (a) [3 + 2] cycloaddition of diazomethanes with benzyne,[4a−i] (b) diazotization or nitrosation of *ortho*-alkylanilines,[4j−l] (c) intramolecular amination of *ortho*-haloarylhydrazones,[4m−q] and (d) addition and cyclization of hydrazines with *ortho*-haloarylaldehydes or ketones.[4r−w] More recently, as a straightforward and atom-efficient method, C−H bond functionalization has recently been developed,[5] and C−C- or C−N-bond-forming reactions in both inter-/intramolecular C−H functionalization grant access to synthetic variants of indazole moiety (Scheme 3).[6]

Despite recent advances, a vast majority of current methods still exhibit a limited access to indazoles possessing 3-carbonyl or 3-alkenyl substituents, which have been proven to exhibit an exceptional level of pharmaceutical activity (Scheme 1, upper line). These considerations led us to develop a new C−H amination system that allows us to give an array of 3-substituted 1*H*-indazoles as a promising potential pharmacophore (Scheme 3).

RESULTS AND DISCUSSION

We commenced our study on intramolecular C−H amination via the cross-dehydrogenative coupling (CDC) strategy with α-ketoester-derived hydrazone **1a** under catalytic oxidative conditions (Table 1). The initial effort on the application of well-established Pd- or Cu-mediated systems[4] that are previously employed in C−H amidation/amination was totally ineffective (entries 1 and 2). During the course of investigation employing precedent CDC reaction conditions,[7] we realized that the iridium(III)-based catalyst system[8] successfully afforded the desired product (entry 3). Surprisingly, it was revealed that the amination was high-yielding in the absence of iridium catalyst (entry 4). This result differentiates the current

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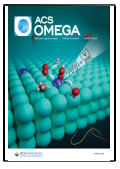

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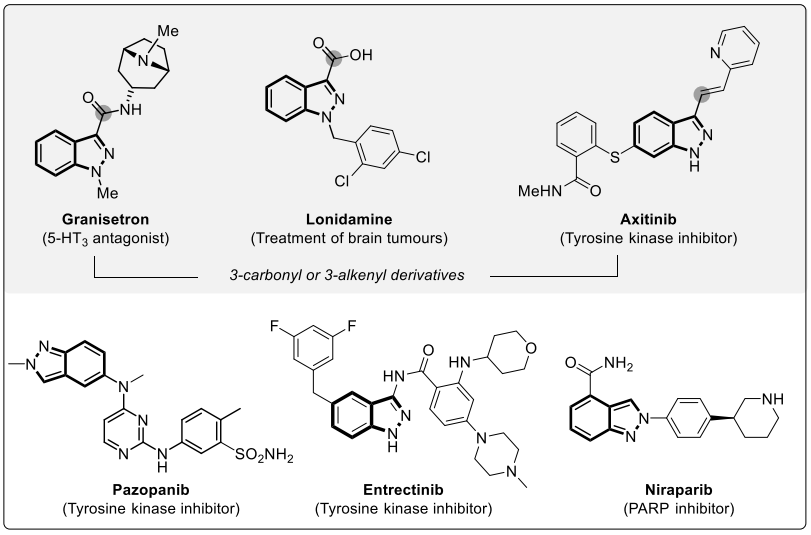
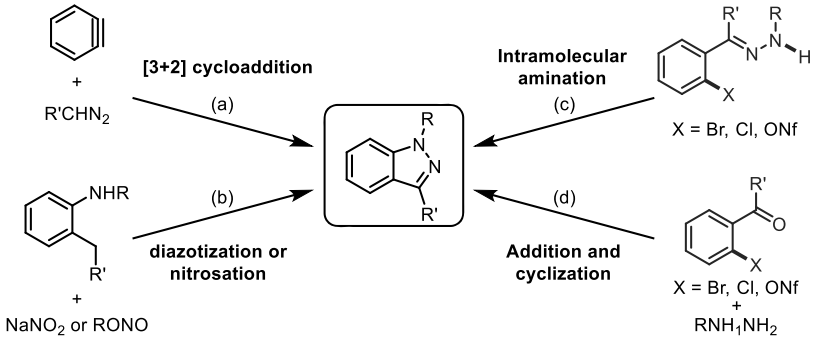
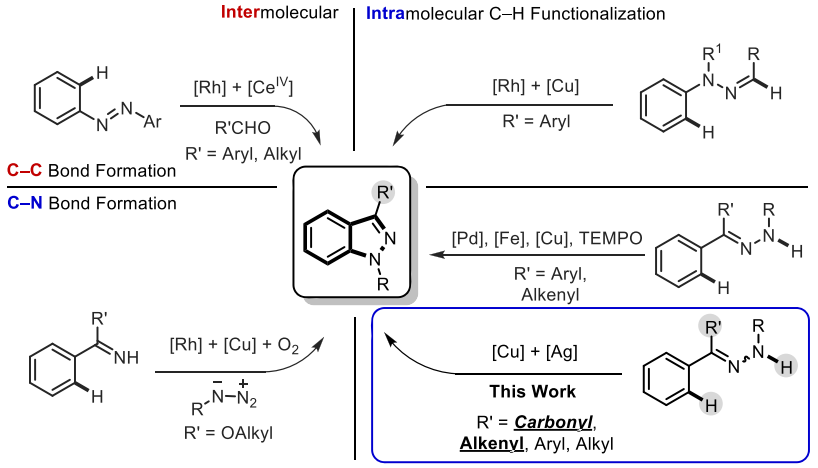
Scheme 1. 1*H*-Indazole Derivatives in Pharmaceutical Use



Scheme 2. Diverse Approaches to 1*H*-Indozoles



Scheme 3. Synthesis of 1*H*-Indozoles via C−H Functionalization



reaction protocol from the previous example. A set of control experiments suggested that the copper species promotes the reaction, but not is not necesary for the amination (entries 5 and 6). These results imply that copper plays a role as a base additive, rather than a chemical oxidant. Not only the amount of silver(I) oxidant (entry 7) but also the choice of the counteranion (entries 8 and 9) was found to be crucial. We were pleased to see that the amination showed an excellent yield under elevated temperatures (entry 10). However, the use of silver as a catalyst by employing terminal oxidants was not efficient, showing a low catalyst turnover at the present stage (entries 11 and 12).

With the optimized reaction conditions in hand, we next investigated the scope of the current amination (Table 2). The arylhydrazones bearing electron-donating substituents at para-position (**1a−1f**) smoothly participated in the present amination in give good to excellent yields. It was notable to see that the substrate with unmasked amine substituent

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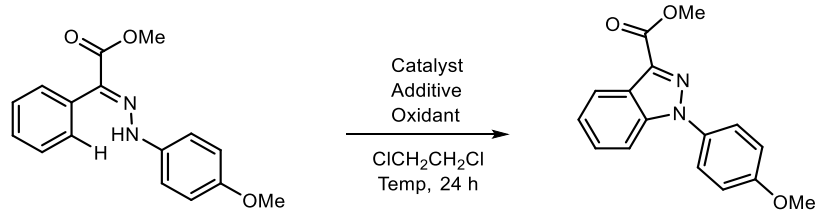
Table 1. Reaction Optimization[a]



1a 2a

entry	catalyst (mol %)	additive (equiv)	oxidant (equiv)	temp (°C)	yield (%)[b]
1	$Pd(OTf)_2$ (5)		$Na_2S_2O_8$ (4.0)	80	n.r.
2	$Cu(OAc)_2$ (100)	Na_2CO_3 (1.0)	O_2 (1 atm)	80	n.r.[c]
3	$[IrCp^*Cl_2]_2$ (5)	$Cu(OAc)_2$ (0.5)	$AgNTf_2$ (3.0)	25	90
4		$Cu(OAc)_2$ (0.5)	$AgNTf_2$ (3.0)	25	92
5			$AgNTf_2$ (3.0)	25	73
6		NaOAc (1.0)	$AgNTf_2$ (3.0)	25	60
7		$Cu(OAc)_2$ (0.5)	$AgNTf_2$ (1.0)	25	50
8		$Cu(OAc)_2$ (0.5)	Ag_2CO_3 (3.0)	25	n.r.
9		$Cu(OAc)_2$ (0.5)	AgOTf (3.0)	25	25
10		$Cu(OAc)_2$ (0.5)	$AgNTf_2$ (3.0)	80	97 (95)
11	$AgNTf_2$ (20)	$Cu(OAc)_2$ (0.5)	$Na_2S_2O_8$ (4.0)	80	21
12	$AgNTf_2$ (20)	$Cu(OAc)_2$ (0.5)	$PhI(OAc)_2$ (2.0)	80	22

[a]**1a** (0.3 mmol), catalyst, additive and oxidant in 1,2-dichloroethane (1.0 mL) for 24 h. [b]Yield based on ^1H NMR analysis of the crude reaction mixture using CH_2Br_2 as the internal standard (isolated yield in parentheses). [c]DMSO (2.0 mL) as a solvent.

successfully converted into desired product (**2f**). It was also revealed that the intramolecular amination of arylhydrazones with electron-withdrawing substituents was successful (**2g**−**2k**), showing a good compatibility with halogen substituents such as F, Cl, and Br (**1i**−**1k**). Biaryl- or naphthyl-derived arylhydrazones (**1l**−**1m**) also showed good yields. The current amination took place to form a more sterically accessible C−H bond when a meta-substituted arylhydrazone was tested (**2n**). Disubstituted arylhydrazones (**1o**−**1p**) were also converted to the desired products in moderate yields. Notably, 1*H*-indazoles including amide, ketone, olefin, aryl, and even CF_3 group as substituents at 3-position could be obtained under the current C−H amination protocol (**2q**−**2u**).

We subsequently investigated the substrate scope with respect to the substituents on the 1-aryl group of indazole (Table 3). A wide range of functional groups on para-position was successfully applied to afford indazole products regardless of the electronic nature of the substituents (**4a**−**4h**). Substrates bearing ortho- (**3i**−**3k**) or meta- (**3l**−**3n**) substituents were also tested, albeit with somewhat diminished reaction efficiency. Besides, reaction with multisubstituted aryl rings were proven to be effective as well (**4o**−**4q**), furnishing the generality of current amination.

To gain mechanistic insight for current amination, we first conducted an initial rate comparison test with deuterium-labeled substrate under standard reaction conditions (Figure 1A). No significant amount of primary kinetic isotope effect (KIE) value was measured (k_H/k_D = 1.04), implying that the C−H bond cleavage step is not involved in the rate-determining stage.

Cyclic voltammetry (CV) data showed that the oxidation of **3e** displayed two irreversible anodic waves with peak potentials of 1.5 and 2.2 V, respectively (Figure 1B, black line). And it was found that the second oxidation is responsible for the corresponding 1*H*-indazole product **4e** (red line). Since the low potential threshold for an outer-sphere electron transfer event (e.g., from anode to **3e**) is typically ca. 500 mV below the thermodynamic potential of the substrate,[9] this results provided a clue that the reaction can go through outer-sphere electron transfer from the employed Ag(I) oxidant (1.05 V vs Ag/AgCl)[10] to afford desired 1*H*-indazole products from direct oxidation of *α*-ketoester-derived hydrazones. In addition, the reaction efficiency was measured to be significantly dropped when (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), butylated hydroxytoluene (BHT), and 1,1-diphenylethylene (DPE) were utilized as radical scavengers, indicating that the current amination presumably proceeds via a radical intermediacy (Figure 1C).

Although additional mechanistic details remained unclear at the present stage, a plausible reaction pathway is depicted on the basis of the above preliminary experiments and precedent literature[6,11] (Figure 1D). First, an equivalent amount of silver induces proton-coupled oxidation via single electron transfer (SET) to give a nitrogen-centered radical (NCR) intermediate (**II**).[12] A rapid intramolecular C−N bond formation is proposed to give a subsequent radical intermediate **III**, which could afford the desired product **IV** by second SET oxidation followed by concomitant base-assisted rearomatization. According to the optimization study (Table 1, entry 2), Cu(II) is more likely involved in deprotonation rather than an oxidation of a substrate.

CONCLUSIONS

In conclusion, we report a new synthetic route to 1*H*-indazoles by intramolecular oxidative C−H amination. This silver(I)-mediated process was found to be particularly efficient for the synthesis of assorted 1*H*-indazoles possessing amide, ketone, ester, olefin, aryl, and even CF_3 groups on 3-position that are widely applicable in medicinal chemistry. Preliminary mechanistic studies suggest that it proceeds via outer-sphere electron transfer mediated by the employed Ag(I) oxidant.

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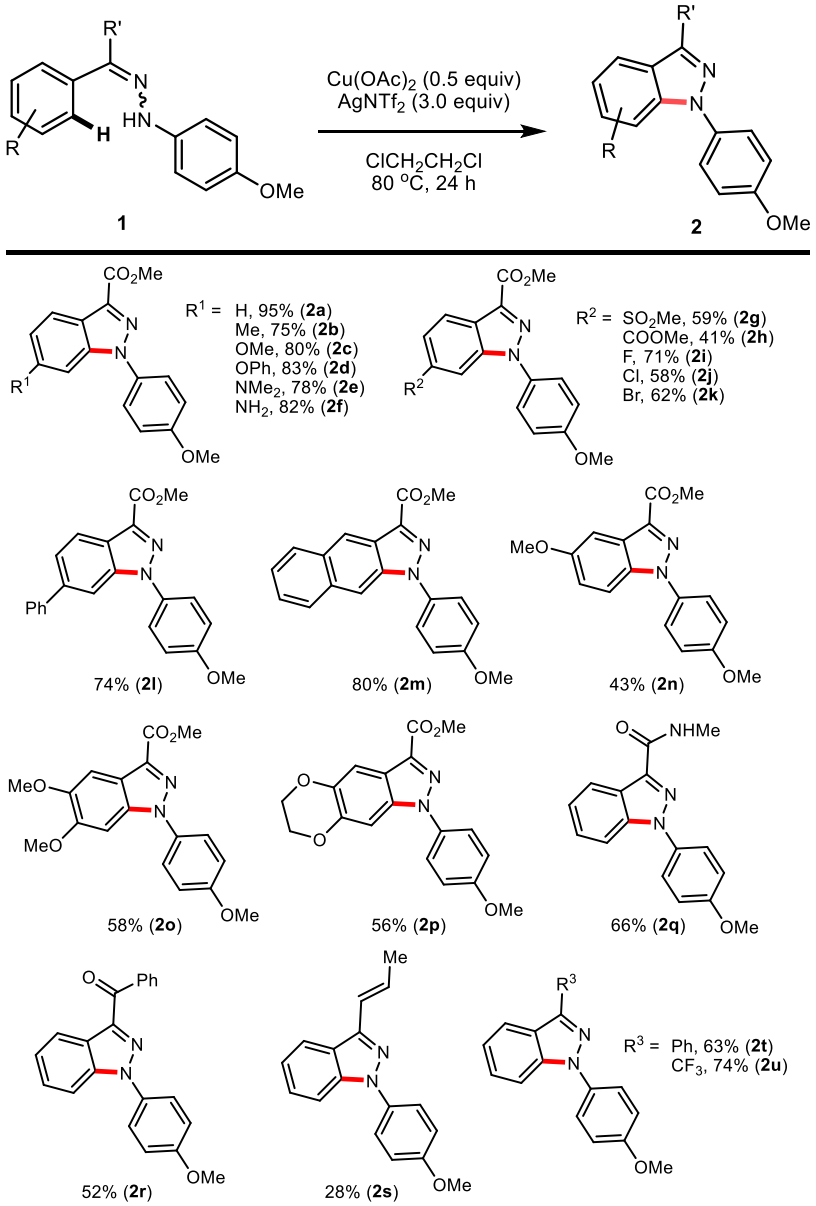
Table 2. Substrate Scope of 1*H*-Indazoles[a]



[a]**1** (0.3 mmol), 0.5 equiv $Cu(OAc)_2$, and 3.0 equiv $AgNTf_2$ in 1,2-dichloromethane (1.0 mL) at 80 °C for 24 h. Isolated yields are reported.

EXPERIMENTAL SECTION

General Methods. All chemicals and solvents were purchased from Sigma-Aldrich, Alfa Aesar, and TCI Chemicals unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using EMD 0.2 mm silica gel 60-F plates. Column chromatography was performed on E. Merck 60 Å silica gel (230−400 mesh). ^{1}H NMR spectra were recorded on Bruker 300 (300 MHz). Chemical shifts were quoted in parts per million (ppm) referenced to the appropriate solvent peak or 0 ppm for TMS. ^{1}H NMR data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, td = triplet of doublet, m = multiplet), integration, and coupling constant (s) J in hertz (Hz). ^{13}C NMR spectra were recorded on a Varian Gemini 500 (125 MHz). Chemical shifts were reported in ppm referenced to the center of a triplet at 77.0 ppm of chloroform-*d*. ^{19}F NMR spectra were recorded on a Bruker Avance NEO 500 (471 MHz). Infrared (IR) spectra were recorded on FR-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on a Varian 1200L quadrupole MS (EI) spectrophotometer. Melting points were obtained on a Mettler Toledo MP40 apparatus.

Preparation of Arylhydrazones. α-Ketoester-derived hydrazones were prepared according to the reference procedure.[13]

General Procedure for the Synthesis of 1*H*-Indazoles via Silver(I)-Mediated Intramolecular Oxidative C−H Amination. To a screw-capped vial with a Spinvane triangular-shaped Teflon spinbar were added arylhydrazones (0.3 mmol), $AgNTf_2$ (0.6 mmol), $Cu(OAc)_2$ (0.15 mmol), and 1,2-dichloroethane (1.0 mL) under atmospheric conditions. The reaction mixture was stirred in a preheated oil bath at 80 °C for 24 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was

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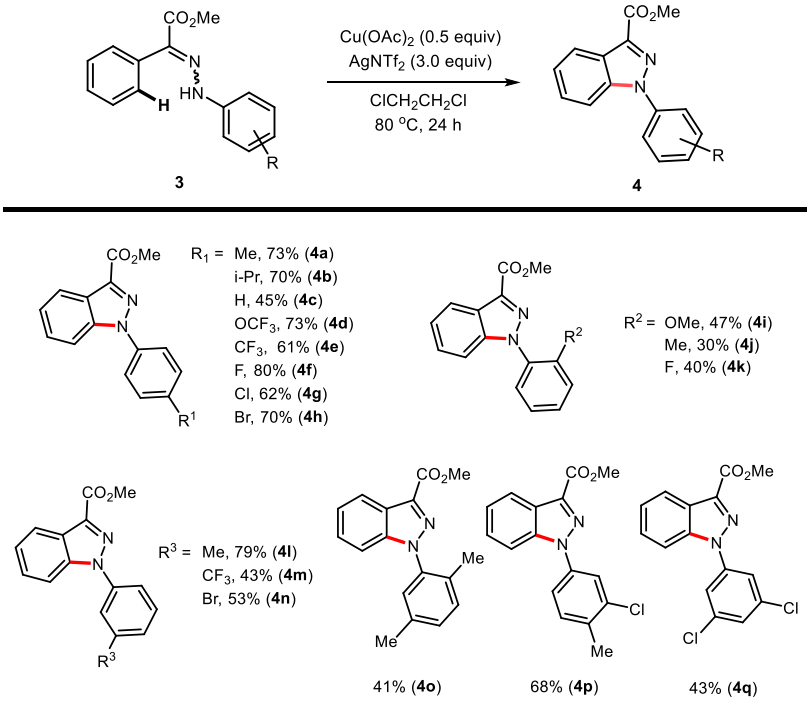
Table 3. Substrate Scope with Respect to 1-Aryl Substituents[a]



[a]**3** (0.3 mmol), 0.5 equiv $Cu(OAc)_2$, and 3.0 equiv $AgNTf_2$ in 1,2-dichloromethane (1.0 mL) at 80 °C for 24 h. Isolated yields are reported.

purified by chromatography on silica gel to give the desired product.

*Methyl 1-(4-methoxyphenyl)-1H-indazole-3-carboxylate (**2a**).* White solid; mp 117−119 °C; ^{1}H NMR ($CDCl_3$) δ 8.31 (d, J = 8.2 Hz, 1H), 7.63 (d, J = 8.3 Hz, 3H), 7.46 (t, J = 7.4 Hz, 1H), 7.37 (t, J = 7.2 Hz, 1H), 7.06 (d, J = 8.5 Hz, 2H), 4.07 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 163.1, 159.4, 140.5, 136.2, 132.2, 127.5, 125.6, 124.2, 123.6, 122.3, 114.6, 110.8, 55.6, 52.1; IR (cm^{-1}) 3027, 2957, 2841, 1716, 1517, 1475, 1436, 1408, 1301, 1244, 1193, 1124, 1058, 1020, 970, 835, 819, 790, 771, 743; HRMS (EI) calcd. For $C_{16}H_{14}N_2O_3$ $[M]^+$ 282.1004, found 282.1003.

*Methyl 1-(4-methoxyphenyl)-6-methyl-1H-indazole-3-carboxylate (**2b**).* White solid; mp 137−139 °C; ^{1}H NMR ($CDCl_3$) δ 8.17 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 8.9 Hz, 2H), 7.39 (s, 1H), 7.19 (s, 1H), 7.06 (d, J = 8.9 Hz, 2H), 4.05 (s, 3H), 3.89 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 163.2, 159.3, 141.1, 138.0, 136.1, 132.3, 125.9, 125.6, 122.4, 121.8, 114.6, 110.1, 55.6, 52.1, 22.0; IR (cm^{-1}) 3030, 2962, 2918, 1711, 1517, 1451, 1398, 1302, 1249, 1209, 1160, 1138, 1103, 1059, 1022, 972, 836, 814, 759; HRMS (EI) calcd. For $C_{17}H_{16}N_2O_3$ $[M]^+$ 296.1161, found 296.1158.

*Methyl 6-methoxy-1-(4-methoxyphenyl)-1H-indazole-3-carboxylate (**2c**).* White solid; mp 218−220 °C; ^{1}H NMR ($CDCl_3$) δ 8.14 (d, J = 8.9 Hz, 1H), 7.59 (d, J = 8.9 Hz, 2H), 7.06 (d, J = 8.9 Hz, 2H), 7.01 (dd, J = 9.0, 2.1 Hz, 1H), 6.91 (d, J = 2.1 Hz, 1H), 4.04 (s, 3H), 3.89 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 163.2, 160.2, 159.3, 141.9, 136.2, 132.3, 125.7, 123.0, 118.9, 115.7, 114.7, 91.5, 55.6, 52.1; IR (cm^{-1}) 2958, 2843, 1714, 1624, 1509, 1467, 1432, 1407, 1355, 1273, 1172, 1126, 1084, 1038, 1017, 972, 880, 833, 821, 784; HRMS (EI) calcd. For $C_{17}H_{16}N_2O_4$ $[M]^+$ 312.1110, found 312.1090.

*Methyl 1-(4-methoxyphenyl)-6-phenoxy-1H-indazole-3-carboxylate (**2d**).* Colorless oil; ^{1}H NMR ($CDCl_3$) δ 8.24 (d, J = 8.9 Hz, 1H), 7.55 (d, J = 9.0 Hz, 2H), 7.35 (t, J = 8.0 Hz, 2H), 7.17−7.15 (m, 1H), 7.13−7.08 (m, 2H), 7.05−7.00 (m, 4H), 4.06 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 163.0, 159.3, 157.4, 156.9, 141.3, 136.3, 132.1, 129.9, 125.3, 123.7, 123.5, 120.6, 118.9, 117.2, 114.6, 99.4, 55.6, 52.1; IR (cm^{-1}) 3255, 2953, 1709, 1547, 1482, 1459, 1444, 1317, 1270, 1241, 1197, 1166, 1117, 1059, 932, 886, 805, 766, 715; HRMS (EI) calcd. For $C_{22}H_{18}N_2O_4$ $[M]^+$ 374.1267, found 374.0777.

*Methyl 6-(dimethylamino)-1-(4-methoxyphenyl)-1H-indazole-3-carboxylate (**2e**).* Yellow solid; mp 130−132 °C; ^{1}H NMR ($CDCl_3$) δ 8.08 (d, J = 9.1 Hz, 1H), 7.61 (d, J = 8.9 Hz, 2H), 7.05 (d, J = 8.9 Hz, 2H), 6.95 (dd, J = 9.1, 2.2 Hz, 1H), 6.60 (d, J = 2.1 Hz, 1H), 4.03 (s, 3H), 3.88 (s, 3H), 3.02 (s, 6H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 163.4, 159.0, 150.7, 142.7, 136.1, 132.7, 125.6, 122.3, 116.4, 114.5, 113.1, 90.0, 55.6, 51.9, 40.9; IR (cm^{-1}) 2995, 2947, 2915, 2847, 1703, 1621, 1513, 1440, 1394, 1352, 1298, 1249, 1198, 1141, 1113, 1059, 1026, 958, 849, 806, 791, 776, 746; HRMS (EI) calcd. For $C_{18}H_{19}N_3O_3$ $[M]^+$ 325.1426, found 325.1418.

*Methyl 6-amino-1-(4-methoxyphenyl)-1H-indazole-3-carboxylate (**2f**).* Brown oil; ^{1}H NMR ($CDCl_3$) δ 8.03 (dd, J = 8.5, 0.9 Hz, 1H), 7.57 (d, J = 8.9 Hz, 2H), 7.02 (d, J = 9.0 Hz, 2H), 6.77−6.73 (m, 2H), 4.02 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 163.3, 159.1, 146.7, 142.3, 136.3, 125.5, 123.0, 117.9, 115.3, 114.5, 92.9, 55.6, 52.0; IR (cm^{-1}) 3373, 2953, 2843, 1714, 1627, 1480, 1323, 1196, 1123, 1054, 798, 743; HRMS (EI) calcd. For $C_{16}H_{15}N_3O_3$ $[M]^+$ 297.1113, found 297.1114.

*Methyl 1-(4-methoxyphenyl)-6-(methylsulfonyl)-1H-indazole-3-carboxylate (**2g**).* White solid; mp 206−208 °C; ^{1}H NMR ($CDCl_3$) δ 8.52 (d, J = 8.6 Hz, 1H), 8.27−8.26 (m, 1H), 7.87 (dd, J = 8.6, 1.5 Hz, 1H), 7.61 (d, J = 8.9 Hz, 2H), 7.10 (d, J = 8.9 Hz, 2H), 4.09 (s, 3H), 3.91 (s, 3H), 3.12 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 162.4, 160.1, 139.7, 139.5,

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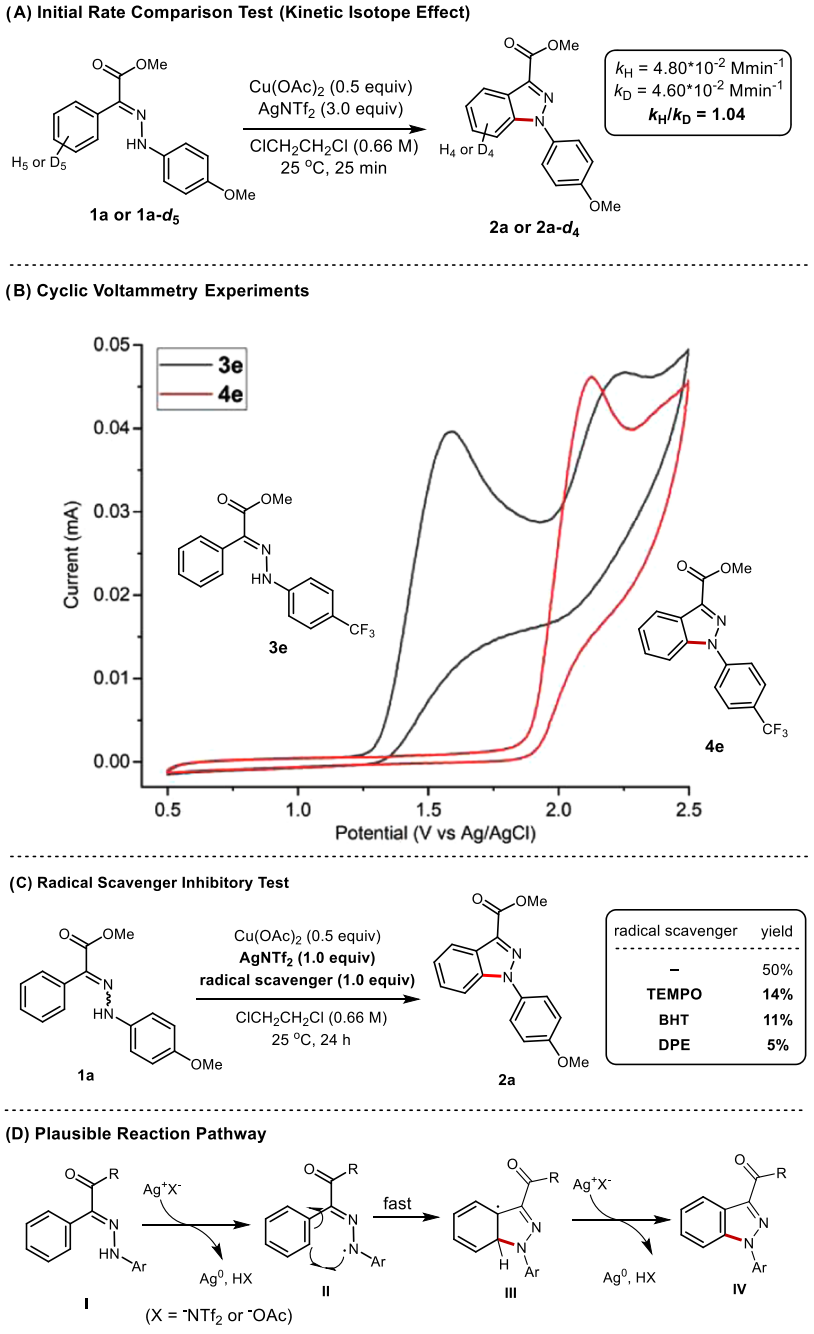

Figure 1. Preliminary mechanistic investigation.

136.5, 131.2, 131.0, 127.9, 126.7, 125.7, 124.1, 121.2, 115.0, 111.7, 55.7, 52.5, 44.7; IR (cm^{-1}) 3012, 2996, 2916, 1706, 1592, 1513, 1404, 1361, 1289, 1243, 1191, 1132, 1057, 1025, 967, 839, 835, 783, 763; HRMS (EI) calcd. For $C_{17}H_{16}N_2O_5S$ $[M]^+$ 360.0780, found 360.0777.

*Dimethyl 1-(4-methoxyphenyl)-1H-indazole-3,6-dicarboxylate (**2h**).* White solid; mp 196−198 °C; ^1H NMR ($CDCl_3$) δ 8.35 (d, J = 7.0 Hz, 1H), 8.34 (s, 1H), 8.03 (d, J = 9.5 Hz, 1H), 7.63 (d, J = 8.9 Hz, 2H), 7.09 (d, J = 8.9 Hz, 2H), 4.08 (s, 3H), 3.96 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 166.8, 162.7, 159.7, 140.1, 136.2, 131.7, 129.3, 126.7, 125.7, 124.0, 122.3, 114.8, 113.2, 55.7, 52.5, 52.3; IR (cm^{-1}) 2955, 2840, 1714, 1518, 1442, 1412, 1294, 1259, 1238, 1196, 1130, 1087, 1063, 1025, 985, 966, 825, 797, 765, 734; HRMS (EI) calcd. For $C_{18}H_{16}N_2O_5$ $[M]^+$ 340.1059, found 340.1059.

*Methyl 6-fluoro-1-(4-methoxyphenyl)-1H-indazole-3-carboxylate (**2i**).* White solid; mp 139−141 °C; ^1H NMR ($CDCl_3$) δ 8.26 (dd, J = 8.9, 5.2 Hz, 1H), 7.58 (d, J = 8.9 Hz, 2H), 7.28−7.24 (m, 2H), 7.14 (td, J = 9.0, 2.2 Hz, 1H), 7.06 (d, J = 8.9 Hz, 2H), 4.06 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 163.7, 162.8, 161.7, 159.5, 140.9 (d, J = 12.7 Hz) 136.4, 131.9, 125.4, 123.9 (d, J = 10.9 Hz), 121.0, 114.8, 113.6 (d, J = 25.7 Hz), 96.6 (d, J = 26.9 Hz), 55.6, 52.2; ^{19}F NMR (471 MHz, $CDC1_3$) δ −112.4; IR (cm^{-1}) 3080, 3051, 2948, 2846, 1715, 1626, 1520, 1502, 1471, 1443, 1408, 1304, 1250, 1199, 1177, 1111, 1062, 1033, 959, 826, 807, 795; HRMS (EI) calcd. For $C_{16}H_{13}FN_2O_3$ $[M]^+$ 300.0910, found 300.0880.

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*Methyl 6-chloro-1-(4-methoxyphenyl)-1H-indazole-3-carboxylate (**2j**).* White solid; mp 156−158 °C; ^{1}H NMR ($CDCl_3$) δ 8.23 (d, J = 8.7 Hz, 1H), 7.61−7.57 (m, 3H), 7.33 (dd, J = 8.7, 1.7 Hz, 1H), 7.07 (d, J = 8.9 Hz, 2H), 4.06 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 162.7, 159.6, 140.9, 136.4, 134.1, 131.7, 125.6, 124.7, 123.3, 122.7, 114.8, 110.6, 55.7, 52.3; IR (cm^{-1}) 3014, 2988, 2954, 2836, 1734, 1706, 1609, 1517, 1484, 1431, 1395, 1306, 1256, 1195, 1178, 1126, 1056, 1022, 975, 938, 824, 809, 799, 789, 735; HRMS (EI) calcd. For $C_{16}H_{13}ClN_2O_3$ $[M]^+$ 316.0615, found 316.0613.

*Methyl 6-bromo-1-(4-methoxyphenyl)-1H-indazole-3-carboxylate (**2k**).* White solid; mp 158−160 °C; ^{1}H NMR ($CDCl_3$) δ 8.17 (d, J = 8.7 Hz, 1H), 7.79 (s, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.7 Hz, 1H), 7.07 (d, J = 8.8 Hz, 2H), 4.06 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 162.7, 159.6, 141.2, 136.4, 131.7, 127.3, 125.6, 123.5, 123.0, 122.1, 114.8, 113.7, 55.7, 52.3; IR (cm^{-1}) 3077, 3015, 2953, 2835, 1735, 1708, 1607, 1517, 1481, 1392, 1306, 1257, 1194, 1177, 1126, 1048, 1021, 826, 808, 798, 785; HRMS (EI) calcd. For $C_{16}H_{13}BrN_2O_3$ $[M]^+$ 360.0110, found 360.0104.

*Methyl 1-(4-methoxyphenyl)-6-phenyl-1H-indazole-3-carboxylate (**2l**).* White solid; mp 131−133 °C; ^{1}H NMR ($CDCl_3$) δ 8.35 (d, J = 8.5 Hz, 1H), 7.75 (s, 1H), 7.67−7.62 (m, 5H), 7.47 (t, J = 8.7 Hz, 1H), 7.41−7.36 (m, 1H), 7.07 (d, J = 8.8 Hz, 2H), 4.08 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ163.1, 159.4, 141.2, 140.8, 136.2, 132.2, 128.9, 127.8, 127.7, 125.7, 123.9, 123.4, 122.5, 114.7, 108.8, 55.6, 52.2; IR (cm^{-1}) 3088, 3026, 2999, 2960, 2843, 1129, 1614, 1516, 1467, 1427, 1403, 1259, 1233, 1186, 1169, 1130, 1061, 1018, 969, 899, 846, 798, 714; HRMS (EI) calcd. For $C_{22}H_{18}N_2O_3$ $[M]^+$ 358.1317, found 358.1317.

*Methyl 1-(4-methoxyphenyl)-1H-benzo[f]indazole-3-carboxylate (**2m**).* White solid; mp 160−162 °C; ^{1}H NMR ($CDCl_3$) δ 8.29 (d, J = 8.9 Hz, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 8.9 Hz, 1H), 7.57−7.49 (m, 4H), 7.37−7.32 (m, 1H), 7.10 (d, J = 8.9 Hz, 2H), 4.07 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 163.3, 160.6, 137.9, 136.4, 134.0, 133.2, 129.1, 128.7, 126.7, 126.4, 125.5, 121.8, 121.6, 120.7, 119.5, 114.7, 55.7, 52.1; IR (cm^{-1}) 3003, 2954, 2903, 2841, 1714, 1605, 1515, 1478, 1460, 1440, 1385, 1326, 1251, 1171, 1119, 1103, 1055, 1028, 980, 835, 822, 788, 692; HRMS (EI) calcd. For $C_{20}H_{16}N_2O_3$ $[M]^+$ 332.1161, found 332.1160.

*Methyl 5-methoxyl-1-(4-methoxyphenyl)-1H-indazole-3-carboxylate (**2n**).* White solid; mp 173−175 °C; ^{1}H NMR ($CDCl_3$) δ 7.64 (d, J = 2.4 Hz, 1H), 7.60 (d, J = 8.9 Hz, 2H), 7.51 (d, J = 9.2 Hz, 1H), 7.11 (dd, J = 9.2, 2.4 Hz, 1H), 7.05 (d, J = 9.0 Hz, 2H), 4.05 (s, 3H), 3.93 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 163.4, 159.3, 156.8, 125.3, 120.0, 114.6, 111.9, 100.8, 55.8, 55.6, 52.0; IR (cm^{-1}) 3018, 2950, 2831, 1701, 1619, 1518, 1498, 1479, 1459, 1442, 1408, 1348, 1309, 1270, 1252, 1193, 1171, 1161, 1141, 1105, 1052, 1019, 975, 884, 877, 833, 797, 697; HRMS (EI) calcd. For $C_{17}H_{16}N_2O_4$ $[M]^+$ 312.1110, found 312.1085.

*Methyl 5,6-dimethoxyl-1-(4-methoxyphenyl)-1H-indazole-3-carboxylate (**2o**).* White solid; mp 177−179 °C; ^{1}H NMR ($CDCl_3$) δ 7.61 (s, 1H), 7.58 (d, J = 8.9 Hz, 2H), 7.06 (d, J = 9.0 Hz, 2H), 6.91 (s, 1H), 4.03 (s, 3H), 4.01 (s, 3H). 3.91 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 163.6, 159.4, 151.4, 148.3, 136.2, 135.4, 132.3, 125.6, 118.1, 114.7, 100.8, 91.7, 56.3, 56.2, 55.6, 52.1, 50.8; IR (cm^{-1}) 2953, 2837, 1722, 1632, 1515, 1494, 1463, 1436, 1427, 1399, 1352, 1284, 1247, 1192, 1159, 1135, 1111, 1056, 1032, 1012, 977, 868, 830, 796, 783, 744, 703; HRMS (EI) calcd. For $C_{18}H_{18}N_2O_5$ $[M]^+$ 342.1216, found 342.1224.

*Methyl 1-(4-methoxyphenyl)-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]indazole-3-carboxylate (**2p**).* White solid; mp 199−201 °C; ^{1}H NMR ($CDCl_3$) δ 7.72 (s, 1H), 7.60 (d, J = 9.0 Hz, 2H), 7.09 (s, 1H), 7.05 (d, J = 9.0 Hz, 2H), 4.34 (s, 4H), 4.05 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 163.2, 159.1, 145.6, 142.3, 136.3, 135.5, 132.5, 125.1, 119.1, 114.6, 107.6, 97.2, 64.6, 64.1, 55.6, 52.0; IR (cm^{-1}) 3072, 2957, 2874, 1172, 1635, 1607, 1589, 1569, 1509, 1483, 1456, 1440, 1420, 1399, 1388, 1334, 1292, 1268, 1245, 1220, 1183, 1157, 1123, 1106, 1069, 1057, 1033, 1022, 969, 936, 909, 874, 862, 832, 796, 783, 726, 707, 692; HRMS (EI) calcd. For $C_{18}H_{16}N_2O_5$ $[M]^+$ 340.1059, found 340.1054.

*1-(4-Methoxyphenyl)-N-methyl-1H-indazole-3-carboxamide (**2q**).* Yellow solid; mp 127−129 °C; ^{1}H NMR ($CDCl_3$) δ 8.47 (d, J = 8.2 Hz, 1H), 7.65−7.55 (m, 3H), 7.50−7.39 (m, 1H), 7.39−7.28 (m, 1H), 7.12−7.03 (m, 2H), 3.90 (s, 3H), 3.07 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 163.2, 159.1, 140.6, 138.9, 132.5, 127.5, 125.0, 123.4, 123.1, 114.7, 110.3, 55.6, 25.7; IR (cm^{-1}) 3348, 3061, 2969, 1734, 1647, 1535, 1508, 1488, 1448, 1434, 1405, 1370, 1297, 1249, 1199, 1173, 1155, 1130, 1106, 1087, 1030, 1009, 996, 944, 851, 827, 806, 797, 789, 772, 742, 690, 670; HRMS (EI) calcd. For $C_{16}H_{15}N_3O_2$ $[M]^+$ 281.1164, found 281.1147.

*(1-(4-Methoxyphenyl)-1H-indazole-3-yl)(phenyl)-methanone (**2r**).* Yellow oil; ^{1}H NMR ($CDCl_3$) δ 8.56 (d, J = 7.9 Hz, 1H), 8.42 (d, J = 7.4 Hz, 2H), 7.70−7.66 (m, 3H), 7.59 (d, J = 7.1 Hz, 1H), 7.55−7.47 (m, 3H), 7.42 (t, J = 7.4 Hz, 1H), 7.09 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 188.6, 159.3, 143.1, 140.1, 137.9, 132.5, 130.7, 128.2, 127.6, 125.2, 124.1, 123.4, 114.8, 110.6, 55.7; IR (cm^{-1}) 3055, 2834, 1636, 1596, 1574, 1512, 1465, 1404, 1300, 1279, 1246, 1200, 1177, 1157, 1132, 1106, 1082, 1027, 967, 884, 831, 802, 760, 745, 708, 687; HRMS (EI) calcd. For $C_{21}H_{16}N_2O_2$ $[M]^+$ 328.1212, found 328.1183.

*(E)-1-(4-Methoxyphenyl)-3-(prop-1-en-1-yl)-1H-indazole (**2s**).* Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J = 7.2 Hz, 2H), 7.43−7.37 (m, 4H), 7.32−7.28 (m, 1H), 6.99 (d, J = 8.9 Hz, 2H), 6.50 (s, 1H), 3.86 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 159.1, 151.1, 140.3, 133.4, 128.6, 127.7, 126.6, 125.7, 114.2, 103.8, 55.6, 12.4; IR (cm^{-1}) 3058, 3013, 2912, 2835, 1611, 1551, 1508, 1466, 1453, 1439, 1411, 1365, 1302, 1251, 1175, 1135, 1112, 1082, 1041, 1022, 1003, 972, 951, 840, 826, 798, 764, 735, 716, 693, 658; HRMS (EI) calcd. For $C_{17}H_{163}N_2O$ $[M]^+$ 264.1263, found 264.1282.

*1-(4-Methoxyphenyl)-3-phenyl-1H-indazole (**2t**).* White solid; mp 126−128 °C; ^{1}H NMR ($CDCl_3$) δ 8.09 (d, J = 8.2 Hz, 1H), 8.07−8.01 (m, 2H), 7.72−7.63 (m, 3H), 7.59−7.50 (m, 2H), 7.49−7.40 (m, 2H), 7.34−7.27 (m, 1H), 7.12−7.03 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 158.5, 145.5, 140.6, 133.4, 133.2, 128.8, 128.2, 127.7, 126.9, 124.8, 122.7, 121.7, 121.5, 114.6, 110.5, 55.6; IR (cm^{-1}) 3044, 2837, 1601, 1519, 1508, 1470, 1446, 1419, 1398, 1362, 1348, 1309, 1296, 1251, 1227, 1173, 1126, 1113, 1098, 1072, 1025, 992, 940, 847, 830, 809, 779, 770, 750, 741, 727, 700, 667; HRMS (EI) calcd. For $C_{20}H_{16}N_2O$ $[M]^+$ 300.1263, found 300.1257.

*1-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-indazole (**2u**).* White solid; mp 70−72 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 8.2 Hz, 1H), 7.65 (d, J = 8.6 Hz, 1H), 7.60 (d, J = 9.0 Hz, 2H), 7.49 (t, J = 7.7 Hz, 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.07 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ

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159.3, 140.2, 132.1, 127.9, 125.3, 123.1, 120.3, 114.8, 110.9, 55.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ −60.7; IR (cm^{-1}) 3065, 2850, 1588, 1518, 1497, 1467, 1427, 1409, 1347, 1301, 1282, 1248, 1175, 1151, 1116, 1027, 1007, 946, 828, 772, 756, 739, 681; HRMS (EI) calcd. For $C_{15}H_{11}F_3N_2O$ $[M]^+$ 292.0823, found 292.0822.

*Methyl 1-(p-tolyl)-1H-indazole-3-carboxylate (**4a**).* White solid; mp 119−121 °C; ^{1}H NMR ($CDCl_3$) δ 8.32 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.5 Hz, 1H), 7.61 (d, J = 8.2 Hz, 2H), 7.47 (t, J = 7.6 Hz, 1H), 7.40−7.34 (m, 3H), 4.07 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1, 140.3, 138.1, 136.7, 136.4, 130.1, 127.5, 124.4, 123.8, 123.6, 122.3, 110.9, 52.1, 21.2; IR (cm^{-1}) 2949, 2921, 1708, 1516, 1473, 1439, 1407, 1351, 1249, 1194, 1170, 1118, 1056, 970, 829, 789, 770, 751; HRMS (EI) calcd. For $C_{16}H_{14}N_2O_2$ $[M]^+$ 266.1055, found 266.1048.

*Methyl 1-(4-isopropylphenyl)-1H-indazole-3-carboxylate (**4b**).* White solid; mp 92−94 °C; ^{1}H NMR ($CDCl_3$) δ 8.32 (d, J = 8.1 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.47 (t, J = 7.7 Hz, 1H), 7.42−7.36 (m, 3H), 4.07 (s, 3H), 3.08−2.94 (m, 1H), 1.31 (d, J = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1, 149.0, 140.3, 137.0, 136.4, 127.5, 124.4, 123.9, 123.6, 122.3, 111.0, 52.1, 33.9, 24.0; IR (cm^{-1}) 3059, 2955, 2866, 1718, 1605, 1515, 1474, 1435, 1404, 1360, 1258, 1193, 1170, 1164, 1123, 1052, 854, 835, 787, 770, 754; HRMS (EI) calcd. For $C_{18}H_{18}N_2O_2$ $[M]^+$ 294.1368, found 294.1366.

*Methyl 1-phenyl-1H-indazole-3-carboxylate (**4c**).* White solid; mp 71−73 °C; ^{1}H NMR ($CDCl_3$) δ 8.32 (d, J = 8.1 Hz, 1H), 7.76−7.70 (m, 3H), 7.56 (t, J = 7.8 Hz, 2H), 7.51−7.35 (m, 3H), 4.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1, 140.2, 139.2, 136.7, 129.6, 128.1, 127.7, 124.5, 123.9, 123.8, 122.4, 110.9, 52.2; IR (cm^{-1}) 3006, 2953, 1727, 1597, 1476, 1458, 1409, 1364, 1257, 1169, 1127, 1075, 1058, 969, 863, 755, 722; HRMS (EI) calcd. For $C_{15}H_{12}N_2O_2$ $[M]^+$ 252.0899, found 252.0927.

*Methyl 1-(4-(trifluoromethoxyl)phenyl)-1H-indazole-3-carboxylate (**4d**).* White solid; mp 68−70 °C; ^{1}H NMR ($CDCl_3$) δ 8.34 (d, J = 8.1 Hz, 1H), 7.80 (d, J = 8.9 Hz, 2H), 7.71 (d, J = 8.5 Hz, 1H), 7.52 (t, J = 7.7 Hz, 1H), 7.44−7.39 (m, 3H), 4.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 148.3, 140.1, 137.7, 137.2, 128.0, 125.1, 124.5, 123.9, 122.6, 122.1, 120.4 (q, J = 256.4 Hz), 110.5, 52.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ −58.0; IR (cm^{-1}) 3053, 2954, 1729, 1511, 1478, 1408, 1253, 1222, 1194, 1152, 1123, 1044, 969, 951, 921, 860, 808, 789, 749; HRMS (EI) calcd. For $C_{16}H_{11}F_3N_2O_3$ $[M]^+$ 336.0722, found 336.0727.

*Methyl 1-(4-(trifluoromethyl)phenyl)-1H-indazole-3-carboxylate (**4e**).* White solid; mp 100−102 °C; ^{1}H NMR ($CDCl_3$) δ 8.34 (d, J = 8.1 Hz, 1H), 7.93 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 8.6 Hz, 2H), 7.77 (d, J = 8.5 Hz, 1H), 7.54 (t, J = 7.7 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 4.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 142.1, 140.0, 137.8, 129.7 (q, J = 33.0 Hz), 128.3, 126.8 (q, J = 3.6 Hz), 124.8, 124.2, 123.5, 122.8, 110.6, 52.3; ^{19}F NMR (471 MHz, $CDCl_3$) δ −62.5; IR (cm^{-1}) 2956, 1739, 1611, 1483, 1319, 1248, 1157, 1116, 1104, 1066, 1013, 969, 843, 789, 772, 766; HRMS (EI) calcd. For $C_{16}H_{11}F_3N_2O_2$ $[M]^+$ 320.0773, found 320.0771.

*Methyl 1-(4-fluorophenyl)-1H-indazole-3-carboxylate (**4f**).* White solid; mp 140−142 °C; ^{1}H NMR ($CDCl_3$) δ 8.33 (d, J = 8.1 Hz, 1H), 7.77−7.68 (m, 2H), 7.65 (d, J = 8.5 Hz, 1H), 7.50 (t, J = 7.7 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.26 (t, J = 8.5 Hz, 2H), 4.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 162.0 (d, J = 247.2 Hz), 140.3, 136.8, 135.3 (d, J = 3.5 Hz), 127.8, 125.8 (d, J = 8.9 Hz), 124.4, 123.8, 122.5, 116.5 (d, J = 22.6 Hz), 110.6, 52.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ −112.9; IR (cm^{-1}) 3056, 2967, 1711, 1511, 1474, 1423, 1403, 1252, 1198, 1153, 1123, 1060, 972, 846, 810, 790, 738; HRMS (EI) calcd. For $C_{15}H_{11}FN_2O_2$ $[M]^+$ 270.0805, found 270.0803.

*Methyl 1-(4-chlorophenyl)-1H-indazole-3-carboxylate (**4g**).* White solid; mp 131−133 °C; ^{1}H NMR ($CDCl_3$) δ 8.33 (d, J = 8.1 Hz, 1H), 7.75−7.64 (m, 3H), 7.55−7.48 (m, 3H), 7.40 (t, J = 7.5 Hz, 1H), 4.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 140.1, 137.8, 137.1, 133.7, 129.7, 128.0, 124.9, 124.5, 123.9, 122.6, 110.6, 52.3; IR (cm^{-1}) 2993, 2919, 2850, 1709, 1493, 1474, 1408, 1350, 1248, 1194, 1168, 1119, 1090, 1083, 1009, 968, 835, 791, 744, 735; HRMS (EI) calcd. For $C_{15}H_{11}ClN_2O_2$ $[M]^+$ 286.0509, found 286.0508.

*Methyl 1-(4-bromophenyl)-1H-indazole-3-carboxylate (**4h**).* White solid; mp 110−112 °C; ^{1}H NMR ($CDCl_3$) δ 8.33 (d, J = 8.1 Hz, 1H), 7.71−7.63 (m, 5H), 7.51 (t, J = 7.7 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 4.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 140.1, 138.3, 137.2, 132.7, 128.0, 125.2, 124.6, 124.0, 122.6, 121.6, 110.6, 52.3; IR (cm^{-1}) 3080, 3051, 2946, 1715, 1586, 1481, 1447, 1418, 1343, 1246, 1199, 1169, 1120, 1069, 1057, 835, 820, 792, 771, 743; HRMS (EI) calcd. For $C_{15}H_{11}BrN_2O_2$ $[M]^+$ 330.0004, found 330.0001.

*Methyl 1-(2-methoxyphenyl)-1H-indazole-3-carboxylate (**4i**).* White solid; mp 166−168 °C; ^{1}H NMR ($CDCl_3$) δ 8.30 (d, J = 7.9 Hz, 1H), 7.51−7.44 (m, 2H), 7.42−7.33 (m, 2H), 7.24 (s, 1H), 7.13−7.09 (m, 2H), 4.05 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 154.6, 142.0, 136.5, 130.6, 129.0, 127.5, 127.1, 123.6, 123.3, 121.9, 120.9, 112.2, 111.4, 55.8, 52.1; IR (cm^{-1}) 3073, 2969, 2841, 1729, 1598, 1507, 1478, 1432, 1405, 1244, 1193, 1163, 1142, 1124, 1115, 1066, 953, 810, 789, 769; HRMS (EI) calcd. For $C_{16}H_{14}N_2O_3$ $[M]^+$ 282.1004, found 282.1003.

*Methyl 1-(o-tolyl)-1H-indazole-3-carboxylate (**4j**).* White solid; mp 77−79 °C; ^{1}H NMR ($CDCl_3$) δ 8.32 (d, J = 7.7 Hz, 1H), 7.46−7.35 (m, 6H), 7.23 (d, J = 8.3 Hz, 1H), 4.06 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 141.7, 137.4, 136.2, 135.9, 131.3, 129.7, 127.7, 127.5, 126.8, 123.5, 123.4, 122.1, 110.6, 52.1, 17.7; IR (cm^{-1}) 3057, 2944, 1706, 1495, 1472, 1441, 1403, 1251, 1210, 1193, 1132, 1115, 1060, 986, 776, 751, 729; HRMS (EI) calcd. For $C_{16}H_{14}N_2O_2$ $[M]^+$ 266.1055, found 266.1046.

*Methyl 1-(2-fluorophenyl)-1H-indazole-3-carboxylate (**4k**).* White solid; mp 95−97 °C; ^{1}H NMR ($CDCl_3$) δ 8.32 (d, J = 8.8 Hz, 1H), 7.69−7.63 (m, 1H), 7.54−7.47 (m, 2H), 7.42−7.30 (m, 4H), 4.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 157.5, 155.5, 141.6, 137.6, 130.6 (d, J = 7.7 Hz), 128.6, 127.8, 126.7 (d, J = 11.9 Hz), 125.0 (d, J = 3.8 Hz), 123.8, 122.2, 117.0 (d, J = 19.3 Hz), 110.9 (d, J = 4.3 Hz), 52.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ −120.2; IR (cm^{-1}) 3010, 2959, 1720, 1509, 1440, 1404, 1250, 1222, 1195, 1177, 1126, 1098, 1060, 1028, 827, 808, 768; HRMS (EI) calcd. For $C_{15}H_{11}FN_2O_2$ $[M]^+$ 270.0805, found 270.0818.

*Methyl 1-(m-tolyl)-1H-indazole-3-carboxylate (**4l**).* Colorless oil; ^{1}H NMR ($CDCl_3$) δ 8.32 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.57−7.35 (m, 5H), 7.23 (s, 1H), 4.07 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1, 140.2, 139.8, 139.1, 136.5, 129.2, 128.8, 127.6, 124.6, 123.7, 122.4, 120.8, 111.0, 52.2, 21.4; IR (cm^{-1}) 3031, 2951, 1713, 1608, 1591, 1477, 1438, 1407, 1348, 1252, 1214, 1166, 1123,

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1062, 1011, 936, 846, 788, 749, 694; HRMS (EI) calcd. For $C_{16}H_{14}N_2O_2$ $[M]^+$ 266.1055, found 266.1048.

*Methyl 1-(3-(trifluoromethyl)phenyl)-1H-indazole-3-carboxylate (**4m**).* White solid; mp 83−85 °C; ^{1}H NMR ($CDCl_3$) δ 8.35 (d, J = 8.1 Hz, 1H), 8.05 (s, 1H), 7.99−7.96 (m, 1H), 7.74−7.70 (m, 3H), 7.57−7.51 (m, 1H), 7.46−7.40 (m, 1H), 4.09 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 162.7, 140.0, 139.7, 137.6, 132.2 (q, J = 32.8 Hz), 130.2, 128.2, 126.6, 124.6, 124.5 (q, J = 3.9 Hz), 124.1, 123.5 (q, J = 271.0 Hz), 122.7, 120.6 (q, J = 3.8 Hz), 110.4, 52.3; ^{19}F NMR (471 MHz, $CDC1_3$) δ −62.7; IR (cm^{-1}) 2956, 1711, 1595, 1484, 1445, 1414, 1318, 1271, 1243, 1199, 1170, 1103, 1061, 933, 886, 828, 792, 756, 696; HRMS (EI) calcd. For $C_{16}H_{11}F_3N_2O_2$ $[M]^+$ 320.0773, found 320.0790.

*Methyl 1-(3-bromophenyl)-1H-indazole-3-carboxylate (**4n**).* White solid; mp 113−115 °C; ^{1}H NMR ($CDCl_3$) δ 8.33 (d, J = 8.1 Hz, 1H), 7.95 (t, J = 2.0 Hz, 1H), 7.77−7.67 (m, 2H), 7.63−7.48 (m, 2H), 7.48−7.38 (m, 2H), 4.08 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 162.8, 140.3, 140.1, 137.3, 131.0, 130.8, 128.1, 126.8, 124.6, 124.0, 123.1, 122.6, 122.1, 110.7, 52.3; IR (cm^{-1}) 3054, 2951, 1724, 1709, 1590, 1486, 1470, 1436, 1409, 1250, 1196, 1185, 1123, 1063, 986, 875, 786, 761, 749, 696; HRMS (EI) calcd. For $C_{15}H_{11}BrN_2O_2$ $[M]^+$ 330.0004, found 329.9999.

*Methyl 1-(2,5-dimethylphenyl)-1H-indazole-3-carboxylate (**4o**).* White solid; mp 108−110 °C; ^{1}H NMR ($CDCl_3$) δ 8.32 (d, J = 7.8 Hz, 1H), 7.46−7.34 (m, 2H), 7.28−7.20 (m, 4H), 4.06 (s, 3H), 2.37 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 163.2, 141.6, 137.2, 136.7, 136.1, 132.4, 131.1, 130.4, 128.3, 127.4, 123.4, 122.1, 110.7, 52.1, 20.7, 17.2; IR (cm^{-1}) 3053, 3004, 2954, 2918, 1714, 1508, 1495, 1476, 1438, 1403, 1250, 1217, 1187, 1172, 1151, 1142, 1122, 1112, 1055, 1002, 933, 828, 796, 772, 752; HRMS (EI) calcd. For $C_{17}H_{16}N_2O_2$ $[M]^+$ 280.1212, found 280.1211.

*Methyl 1-(3-chloro-4-methylphenyl)-1H-indazole-3-carboxylate (**4p**).* White solid; mp 94−96 °C; ^{1}H NMR ($CDCl_3$) δ 8.32 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 2.2 Hz, 1H), 7.72−7.36 (m, 1H), 7.55−7.48 (m, 2H), 7.42−7.37 (m, 2H), 4.08 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 162.9, 140.1, 137.9, 136.9, 136.0, 135.1, 131.5, 127.9, 124.5, 124.3, 123.9, 122.5, 121.8, 110.7, 52.2, 19.8; IR (cm^{-1}) 3058, 2984, 2948, 1711, 1604, 1493, 1476, 1443, 1409, 1247, 1210, 1192, 1119, 1063, 943, 863, 839, 817, 796, 737; HRMS (EI) calcd. For $C_{16}H_{13}ClN_2O_2$ $[M]^+$ 300.0666, found 300.0651.

*Methyl 1-(3,5-dichlorophenyl)-1H-indazole-3-carboxylate (**4q**).* White solid; mp 148−150 °C; ^{1}H NMR ($CDCl_3$) δ 8.33 (d, J = 8.1 Hz, 1H), 7.59−7.47 (m, 4H), 7.41 (t, J = 7.5 Hz, 1H), 7.29 (s, 1H), 4.07 (s, 3H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 162.7, 141.5, 137.7, 137.1, 133.4, 131.5, 130.9, 130.1, 130.0, 127.9, 123.9, 123.5, 122.4, 110.9, 52.3; IR (cm^{-1}) 3077, 2957, 1719, 1588, 1489, 1439, 1341, 1250, 1197, 1143, 1122, 1064, 942, 867, 831, 805, 789, 745, 679; HRMS (EI) calcd. For $C_{15}H_{10}Cl_2N_2O_2$ $[M]^+$ 320.0119, found 320.0093.

■ ASSOCIATED CONTENT

Supporting Information

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Procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Thangadurai, A.; Minu, M.; Wakode, S.; Agrawal, S.; Narasimhan, A. Indazole: a medicinally important heterocyclic moiety. *Med. Chem. Res.* **2012**, *21*, 1509−1523. (b) Gaikwad, D. D.; Chapolikar, A. D.; Devkate, C. G.; Warad, K. D.; Tayade, A. P.; Pawar, R. P.; Domb, A. J. Synthesis of indazole motifs and their medicinal importance: An Overview. *Eur. J. Med. Chem.* **2015**, *90*, 707−731. (c) Dong, J.; Zhang, Q.; Wang, Z.; Huang, G.; Li, S. Recent Advances in the Development of Indazole-based Anticancer Agents. *ChemMedChem* **2018**, *13*, 1490−1507. (d) Zhang, S.-G.; Liang, C.-G.; Zhang, W.-H. Recent advances in indazole-containing derivatives: Synthesis and Biological Perspectives. *Molecules* **2018**, *23*, 2783.

(2) Inman, M.; Moody, C. J. Indole synthesis − something old, something new. *Chem. Sci.* **2013**, *4*, 29−41.

(3) (a) Navari, R.; Grandara, D.; Hesketh, P.; Hall, S.; Mailliard, J.; Friedman, H. R.; Fitts, D.; et al. Comparative clinical trial of granisetron and ondansetron in the prophylaxis of cisplatin −induced emesis. The Graninsetron study group. *J. Clin. Oncol.* **1995**, *13*, 1242−1248. (b) Nath, K.; Guo, L.; Nancolas, B.; Nelson, D. S.; Shestov, A. A.; Lee, S.-C.; Roman, J.; Zhou, R.; Leeper, D. B.; Halestrap, A. P.; Blair, I. A.; Glickson, J. D. Mechanism of Antineoplastic Activity of Lonidamine. *Biochim. Biophys. Acta, Rev. Cancer* **2016**, *1866*, 151−162. (c) Grünwald, V.; Merseburger, A. S. Axitinib for the treatment of patients with advanced metastatic renal cell carcinoma (mRCC) after failure of prior systemic treatment. *OncoTargets Ther.* **2012**, *5*, 111−117. (d) Modi, S. J.; Kulkarni, V. M. Vascular Endothelial

Growth Factor Receptor (VEGFR-2)/KDR Inhibitors: Medicinal Chemistry Perspective. *Med. Drug Discovery* **2019**, *2*, No. 100009. (e) Drilon, A.; Siena, S.; Dziadziuszko, R.; Barlesi, F.; Krebs, M. G.; Shaw, A. T.; de Braud, F.; Rolfo, S.; Ahn, M.-J.; Wolf, J.; Seto, T.; Cho, B. C.; patel, M. R.; Chiu, C.-H.; John, T.; Goto, K.; Karapetis, C. S.; Arkenau, H.-T.; K, S.-W.; Ohe, Y.; Li, Y.-C.; Chae, Y. K.; Chung, C. H.; Otterson, G. A.; Murakami, H.; Lin, C.-C.; Tan, D. S. W.; Prenen, H.; Riehl, T.; Chow-Maneval, E.; Simmons, B.; Cui, N.; Johnson, A.; Eng, S.; Wilson, T. R.; Doebele, R. C. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials. *Lancet Oncol.* **2020**, *21*, 261−270. (f) Ison, G.; Howie, L. J.; Amiri-Kordestani, L.; Zhang, L.; Tang, S.; Sridhara, R.; Pierre, V.; Charlab, R.; Ramamoorthy, A.; Song, P.; Li, F.; Yu, J.; Manheng, W.; Palmby, T. R.; Ghosh, S.; Horne, H. N.; Lee, E. Y.; Philip, R.; Dave, K.; Chen, X. H.; Kelly, S. L.; Janoria, K. G.; Banerjee, A.; Eradiri, O.; Dinin, J.; Goldberg, K. B.; Pierce, W. F.; Ibrahim, A.; Kluetz, P. G.; Blumenthal, G. M.; Beaver, J. A.; Pazdur, R. FDA Approval Summary: Niraparib for the Maintenance Treatment of Patients with Recurrent Ovarian Cancer in Response to Platinum-Based Chemotherapy. *Clin. Cancer Res.* **2018**, *24*, 4066−4071.

(4) (a) Jin, T.; Yamamoto, Y. An Efficient, Facile, and General Synthesis of 1*H*-Indazoles by 1,3-Dipolar Cycloaddition of Arynes with Diazomethane Derivatives. *Angew. Chem., Int. Ed.* **2007**, *46*, 3323−3325. (b) Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. Synthesis of Indazoles by the [3+2] Cycloaddition of Diazo Compounds with Arynes and Subsequent Acyl Migration. *J. Org. Chem.* **2008**, *73*, 219−226. (c) Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. Synthesis of indazoles by the [3+2] cycloaddition of diazo compounds with arynes and subsequent acyl migration. *J. Org. Chem.* **2008**, *73*, 219−226. (d) Spiteri, C.; Keeling, S.; Moses, J. E. New Synthesis of 1-Substituted-1*H*-indazoles via 1,3-Dipolar Cycloaddition of in situ Generated Nitrile Imines and Banzyne. *Org. Lett.* **2010**, *12*, 3368−3371. (e) Li, P.; Zhao, J.; Wu, C.; Larock, R. C.; Shi, F. Synthesis of 2-Substituted Indazoles from Arynes and *N*-Tosylhydrazones. *Org. Lett.* **2011**, *13*, 3340−3343. (f) Li, P.; Wu, C.; Zhao, J.; Rogness, D. C.; Shi, F. Synthesis of Substituted 1*H*-Indazoles from Arynes and Hydrazones. *J. Org. Chem.* **2012**, *77*, 3149−3158. (g) Liu, Z.; Wang, L.; Tan, H.; Zhou, S.; Fu, T.; Xia, Y.; Zhang, Y.; Wang, J. Synthesis of 1*H*-indazoles from *N*-tosylhydrazones and nitroaromatic compounds. *Chem. Commun.* **2014**, *50*, 5061−5063. (h) Phatake, R. S.; Mullapudi, V.; Wakchaure, V. C.; Ramana, C. V. Fluoride-Mediated Dephosphonylation of α−Diazo-β-carbonyl Phosphonates. *Org. Lett.* **2017**, *19*, 372−375. (i) Chen, G.; Hu, M.; Peng, Y. Switchable Synthesis of 3-Substituted 1*H*-Indazoles and 3,3-Disubstituted 3*H*-Indazole-3-phosphonates Tuned by Phosphoryl Groups. *J. Org. Chem.* **2018**, *83*, 1591−1597. (j) Stadlbauer, W. Indazoles. In *Science of Synthesis*; Neier, R., Ed.; Georg-Thieme-Verlag Stuttgart: New York, 2002; pp 227−324. (k) Caron, S.; Vazquez, E. A Versatile and Efficient Synthesis of Substituted 1*H*-Indazoles. *Synthesis* **1999**, 588−592. (l) Haag, B.; Peng, Z.; Knochel, P. Preparation of polyfunctional indazoles and heteroarylazo compounds using highly functionalized Zinc reagents. *Org. Lett.* **2009**, *11*, 4270−4273. (m) Song, J. J.; Yee, N. K. Synthesis of 1-aryl-1*H*-indazoles via the palladium-catalyzed cyclization of *N*-aryl-*N*′-(*o*-bromobenzyl)hydrazines and [*N*-aryl-*N*′-(*o*-bromobenzyl)-hydrazinato-*N*′]-triphenylphosphonium bromides. *Tetrahedron Lett.* **2001**, *42*, 2937−2940. (n) Inamoto, K.; Katsuno, M.; Yoshino, T.; Suzuki, I.; Hiroya, K.; Sakamoto, T. Efficient Synthesis of 3-Substituted Indazoles Using Pd-Catalyzed Intramolecular Amination Reaction of *N*-Tosylhydrazones. *Chem. Lett.* **2004**, *33*, 1026−1027. (o) Inamoto, K.; Katsuno, M.; Yoshino, T.; Arai, Y.; Hiroya, K.; Sakamoto, T. Synthesis of 3-substituted indazoles and benzoisoxazoles via Pd-catalyzed cyclization reactions: application to the synthesis of nigellicine. *Tetrahedron* **2007**, *63*, 2695−2711. (p) Thomé, I.; Besson, C.; Kieine, T.; Bolm, C. Base-Catalyzed Synthesis of Substituted Indazoles under Mild, Transition-Metal-Free Conditions. *Angew. Chem., Int. Ed.* **2013**, *52*, 7509−7513. (q) Tang, M.; Kong, Y.; Chu, B.; Feng, D. Copper(I) Oxide-Mediated Cyclization of *o*-Haloaryl *N*-Tosylhydrazones: Efficient Synthesis of Indazoles. *Adv. Synth. Catal.* **2016**, *358*, 926−939. (r) Cho, C. S.; Lim, D. K.; Heo, N. H.; Kim, T.-J.; Shim, S. C. Facile palladium-catalyesd synthesis of 1-aryl-1*H*-indazoles from 2-bromobenzaldehydes and arylhydrazines. *Chem. Commun.* **2004**, 104−105. (s) Lebedev, A. Y.; Khartulyari, A. S.; Voxkoboynikov, A. Z. Synthesis of 1-Aryl-1*H*-indazoles via Palladium-Catalyzed Intramolecular Amination of Aryl Halides. *J. Org. Chem.* **2005**, *70*, 596−602. (t) Lukin, K.; Hsu, M. C.; Femando, D.; Leanna, M. B. New Practical Synthesis of Indazoles via Condensation of *o*-Fluorobenzaldehydes and Their *O*-Methyloximes with Hydrazin. *J. Org. Chem.* **2006**, *71*, 8166−8172. (u) Viña, D.; Olmo, E.; Lópea-Pérez, J. L.; Feliciano, A. S. Regioselective Synthesis of 1-Alkyl- or 1-Aryl-1*H*-indazoles via Copper-Catalyzed Cyclizations of 2-Haloarylcarbonylic Compounds. *Org. Lett.* **2007**, *9*, 525−528. (v) Veerareddy, A.; Gogireddy, S.; Dubey, P. K. Resioselective Synthesis of 1-substituted Indazole-3-carboxylic acid. *J. Heterocycl. Chem.* **2014**, *51*, 1311−1321. (w) Tang, X.; Gao, H.; Yang, J.; Wu, W.; Jiang, H. Efficient access to 1*H*-indazoles via copper-catalyzed cross-coupling/cyclization of 2-bromoaryl oxime acetates and amines. *Org. Chem. Front.* **2014**, *1*, 1295−1298. (x) Conlon, I. L.; Konsein, K.; Morel, Y.; Chan, A.; Fletcher, S. Construction of 1*H*-Indazoles from *ortho*-aminobenzoximes by the Mitsunobu reaction. *Tetrahedron Lett.* **2019**, *60*, No. 150929. (y) Li, X.; Ye, C.; Wei, C.; Shan, C.; Wojtas, L.; Wang, Q.; Shi, X. Diazo Actication with Diazonium Salts: Synthesis of Indazoles and 1,2,4-Triazole. *Org. Lett.* **2020**, *22*, 4151−4155. (z) Zhang, L.; Chen, J.; Chen, X.; Zheng, X.; Zhou, J.; Zhong, T.; Chen, Z.; Yang, Y.-F.; Jiang, X.; She, Y.-B.; Yu, C. Rh(III)-catalyzed, hydrazine-directed C-H functionalization with 1-alkynylcyclobutanols: a new strategy for 1*H*-indazoles. *Chem. Commun.* **2020**, *56*, 7415−7418.

(5) (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. Rhodium-Catalyzed C-C Bond Formation via Heteroatom-Directed C-H Bond Activation. *Chem. Rev.* **2010**, *110*, 624−655. (b) Lyons, T. W.; Sanford, M. S. Palladium-Catalyzed Ligand-Directed C-H Functionalization Reactions. *Chem. Rev.* **2010**, *110*, 1147−1169. (c) Ackermann, L. Carboxylate-Assisted Transition-Metal-Catalyzed C-H Bond Functionalizations: Mechanism and Scope. *Chem. Rev.* **2011**, *111*, 1315−1345. (d) McMurray, L.; O'Hara, F.; Gaunt, M. J. Recent developments in natural product synthesis using metal-catalysed C-H bond functionalization. *Chem. Soc. Rev.* **2011**, *40*, 1885−1898. (e) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. Towards mild metal-catalyzed C-H bond activation. *Chem. Soc. Rev.* **2011**, *40*, 4740−4761. (f) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. Recent advances in the transition metal-catalyzed twofold oxidative C-H bond activation strategy for C-C and C-N bond formation. *Chem. Soc. Rev.* **2011**, *40*, 5068−5083. (g) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. Ruthenium(II)-Catalyzed C-H Bond Activation and Functionalization. *Chem. Rev.* **2012**, *112*, 5879−5918. (h) Song, G.; Wang, F.; Li, X. C-C, C-O and C-N bond formation via rhodium(III)-catalyzed oxidative C-H activation. *Chem. Soc. Rev.* **2012**, *41*, 3651−3678. (i) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. Weak Coordination as a Powerful Means for Developing Broadly Useful C-H Functionalization Reactions. *Acc. Chem. Res.* **2012**, *45*, 788−802. (j) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. Copper-Catalyzed C-H Functionalization Reactions: Efficient Synthesis of Heterocycles. *Chem. Rev.* **2015**, *115*, 1622−1651. (k) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. Oxidative Coupling between Two Hydrocarbons: An Update of Recent C-H Functionalizations. *Chem. Rev.* **2015**, *115*, 12138−12204. (l) Song, G.; Li, X. Substrate Activation Strategies in Rhodium(III)-Catalyzed Selective Functionalization of Arenes. *Acc. Chem. Res.* **2015**, *48*, 1007−1020. (m) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. Mild metal-catalyzed C-H activation: examples and concepts. *Chem. Soc. Rev.* **2016**, *45*, 2900−2936. (n) Qin, Y.; Zhu, L.; Luo, S. Organocatalysis in Inert C-H Bond Functionalization. *Chem. Rev.* **2017**, *117*, 9433−9520. (o) Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. A comprehensive overview of directing groups applied in metal-catalysed C-H functionalization chemistry. *Chem. Soc. Rev.* **2018**,

https://dx.doi.org/10.1021/acsomega.1c00025
ACS Omega 2021, 6, 6498−6508

47, 6603−6743. (p) Rej, S.; Chatani, N. Rhodium-Catalyzed C(sp^2)- or C(sp^3)-H Bond Functionalization Assisted by Removable Directing Groups. *Angew. Chem., Int. Ed.* **2019**, *58*, 8304−8329. (q) Woźniak, Ł.; Tan, J.-F.; Nguyen, Q.-H.; Vigné, A. M.; Smal, V.; Cao, Y.-X.; Cramer, N. Catalytic Enantioselective Functionalizations of C-H Bonds by Chiral Iridium Complexes. *Chem. Rev.* **2020**, *120*, 10516−10543.

(6) (a) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. Palladium-Catalyzed C-H Activation/Intramolecular Amination Reaction: A New Route to 2-Aryl/Alkylindazoles. *Org. Lett.* **2007**, *9*, 2931−2934. (b) Lian, Y.; Bergman, R. G.; Lavis, L. D.; Ellman, J. A. Rhodium(III)-Catalyzed Indazole Synthesis by C-H Bond Functionalization and Cyclative Capture. *J. Am. Chem. Soc.* **2013**, *135*, 7122−7125. (c) Yu, D. G.; Suri, M.; Glorius, F. Rh^{III}/Cu^{II}-Cocatalyzed Synthesis of 1*H*-Indazoles through C-H Amidation and N-N Bond Formation. *J. Am. Chem. Soc.* **2013**, *135*, 8802−8805. (d) Zhang, T.; Bao, W. Synthesis of 1*H*-indazoles and 1*H*-Pyrazoles via $FeBr_3/O_2$ Mediated Intramolecular C-H Amination. *J. Org. Chem.* **2013**, *78*, 1317−1322. (e) Li, X.; He, L.; Chen, H.; Wu, W.; Jiang, H. Copper-Catalyzed Aerobic C(sp^2)-H Functionalization for C-N Bond Formation: Synthesis of Pyrazoles and Indazoles. *J. Org. Chem.* **2013**, *78*, 3636−3646. (f) Kashiwa, M.; Sonoda, M.; Tanimori, S. Facile Access to 1*H*-Indazoles through Iodobenzene-Catalyzed C-H Amination under Mild, Transition-Metal-Free Conditions. *Eur. J. Org. Chem.* **2014**, 4720−4723. (g) Hu, J.; Xu, H.; Nie, P.; Xie, X.; Nie, Z.; Rao, Y. Synthsis of Indazoles and Azaindazoles by Intramolecular Aerobic Oxidative C-N Coupling under Transition-Metal-Free Conditions. *Chem. - Eur. J.* **2014**, *20*, 3932−3938. (h) Yu, J.; Lim, J. W.; Kim, S. Y.; Kim, J.; Kim, J. N. An efficient transition-metal-free synthesis 1*H*-indazoles from arylhydrazones with montmorillonite K-10 under O_2 atmosphere. *Tetrahedron Lett.* **2015**, *56*, 1432−1436. (i) Wang, Q.; Li, Z. Synthesis of 1*H*-Indazoles from Imidates and Nitrosobenzenes via Synergistic Rhodium/Copper Catalysis. *Org. Lett.* **2016**, *18*, 2102−2105. (j) Xu, P.; Wang, G.; Wu, Z.; Li, S.; Zhu, C. Rh(III)-catalyzed double C-H activation of aldehyde hydrazones: a route for functionalized 1*H*-indazole synthesis. *Chem. Sci.* **2017**, *8*, 1303−1308. (k) Zhang, Z.; Huang, Y.; Huang, G.; Zhang, G.; Liu, Q. [Bis-(trifluoroacetoxy)iodo]benzene-Mediated Oxidative Direct Amination C-N Bond Formations: Synthesis of 1*H*-Indazoles. *J. Heterocycl. Chem.* **2017**, *54*, 2426−2433. (l) Wei, W.; Wang, Z.; Yang, X.; Yu, W.; Chang, J. Divergent Synthesis of 1*H*-Indazoles and 1*H*-Pyrazoles from Hydrazones via Iodine-Mediated Intramolecular Aryl and sp^3 C-H Amination. *Adv. Synth. Catal.* **2017**, *359*, 3378−3387. (m) Chopra, R.; Kumar, M.; Bhalla, V. Fabrication of Polythiophene-Supported Ag@Fe3O4 Nanoclusters and Their Utilization as Photocatalyst in Dehydrogenative Coupling Reactions. *ACS Sustainable Chem. Eng.* **2018**, *6*, 7412−7419. (n) Janardhanan, J. C.; Mishra, R. K.; Das, G.; Sini, S.; Jayamurthy, P.; Suresh, C. H.; Praveen, V. K.; Manoj, N.; Babu, B. P. Functionalizable 1*H*-Indazoles by Palladium Catalyzed Aza-Nenitzescu Reaction: Pharmacophores to Donor-Acceptor Type Multi-Luminescent Fluorophores. *Asian J. Org. Chem.* **2018**, *7*, 2094−2104. (o) Zhang, G.; Fan, Q.; Zhao, Y.; Ding, C. Copper-Promoted Oxidative intramolecular C-H Amination of Hydrazones to Synthesize 1*H*-indazoles and 1*H*-Pyrazoles Using a Cleavable Directing Group. *Eur. J. Org. Chem.* **2019**, 5801−5806. (p) Wang, G.; Sun, J.; Wang, K.; Han, J.; Li, H.; Duan, G.; You, G.; Li, F.; Xia, C. Palladium-catalyzed direct C-H nitration and intramolecular C-H functionalization for the synthesis of 3-nitro-1-(phenylsulfonyl)-1*H*-indazole derivatives. *Org. Chem. Front.* **2019**, *6*, 1608−1612.

(7) (a) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. Direct Amination of Azoles via Catalytic C−H, N−H Coupling. *Org. Lett.* **2009**, *11*, 1607−1610. (b) Wang, Q.; Schreiber, S. L. Copper-Mediated Amidation of Heterocyclic and Aromatic C−H Bonds. *Org. Lett.* **2009**, *11*, 5178−5180. (c) Oda, Y.; Hirano, K.; Satoh, T.; Miura, M. Synthesis of N-Azolylindoles by Copper-Catalyzed C−H/N−H Coupling−Annulation Sequence of o-Alkynylanilines. *Org. Lett.* **2012**, *14*, 664−667. (d) Cho, S. H.; Kim, J.; Lee, S. Y.; Chang, S. Silver-Mediated Direct Amination of Benzoxazoles: Tuning the Amino Group Source from Formamides to Parent Amines. *Angew. Chem., Int. Ed.* **2009**, *48*, 9127−9130. (e) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. Beyond Directing Groups: Transition-Metal-Catalyzed C−H Activation of Simple Arenes. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236−10254. (f) Kim, H.; Chang, S. Transition-Metal-Mediated Direct C−H Amination of Hydrocarbons with Amine Reactants: The Most Desirable but Challenging C−N Bond-Formation Approach. *ACS Catal.* **2016**, *6*, 2341−2351.

(8) Kim, H.; Shin, K.; Chang, S. Iridium-Catalyzed C.−H. Amination with Anilines at Room Temperature: Compatibility of Iridacycles with External Oxidants. *J. Am. Chem. Soc.* **2014**, *136*, 5904−5907.

(9) Francke, R.; Little, R. D. Redox Catalysis in Organic Electrosynthesis: Basic Principles and Recent Developments. *Chem. Soc. Rev.* **2014**, *43*, 2492−2521.

(10) Connelly, N. G.; Geiger, W. E. Chemical Redox Agents for Organometallic Chemistry. *Chem. Rev.* **1996**, *96*, 877−910.

(11) (a) Park, Y.; Kim, Y.; Chang, S. Transition Metal-Catalyzed C−H Amination: Scope, Mechanism, and Applications. *Chem. Rev.* **2017**, *117*, 9247−9301. (b) Suzuki, C.; Hirano, K.; Satoh, T.; Miura, M. Direct Synthesis of N−H Carbazoles via Iridium(III)-Catalyzed Intramolecular C−H Amination. *Org. Lett.* **2015**, *17*, 1597−1600. (c) Maity, S.; Zheng, N. A Visible-Light-Mediated Oxidative C−N Bond Formation/Aromatization Cascade: Photocatalytic Preparation of *N*-Arylindoles. *Angew. Chem., Int. Ed.* **2012**, *51*, 9562−9566.

(12) (a) Xiong, T.; Zhang, Q. New amination strategies based on nitrogen-centered radical chemistry. *Chem. Soc. Rev.* **2016**, *45*, 3069−3087. (b) Hioe, J.; Šakić, D.; Vrček, V.; Zipse, H. The stability of nitrogen-centered radicals. *Org. Biomol. Chem.* **2015**, *13*, 157−169.

(13) Zhuang, J.; Wang, C.; Xie, F.; Zhang, W. One-pot efficient synthesis of aryl α−keto esters from aryl-ketones. *Tetrahedron* **2009**, *65*, 9797−9800.

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