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Visible-Light-Promoted Direct C3-H Cyanomethylation of 2*H*-Indazoles

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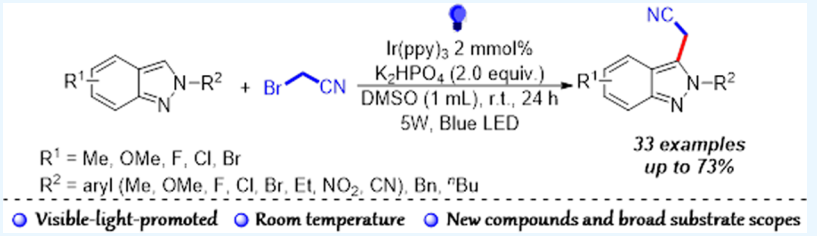

ABSTRACT: The efficient visible-light-promoted cyanomethylation of 2*H*-indazoles in the presence of $Ir(ppy)_3$ as the photocatalyst and bromoacetonitrile as the cyanomethyl radical source was achieved under mild conditions, providing a series of C3-cyanomethylated derivatives in good yields.

INTRODUCTION

The cyanomethylation of (hetero)aromatic rings is of great research interest to organic and medicinal chemists due to the prevalence of cyano groups in biologically active molecules.[1] Moreover, the cyano group can easily be converted to many other functional groups, such as primary amines, amides, carboxylic acids, esters, aldehydes, and heterocycles.[2] Commonly, (hetero)arylacetonitriles are prepared through the cyanation of benzyl halides,[3] the dehydration of arylacetaldoximes or amides,[4] or the metal-catalyzed cross-coupling of aryl halides with functionalized acetonitriles.[5] The radical cross-dehydrogenative coupling reaction of acetonitrile with a heterocycle developed in recent years also provides an alternative strategy for heteroarylacetonitrile synthesis.[6] However, these strategies usually require the prefunctionalization of substrates, highly toxic cyanidation reagents, excess oxidants, or a high reaction temperature. Consequently, the exploration of highly efficient methods to access (hetero)arylacetonitriles is still highly desirable.

In the past years, visible-light photocatalysis has provided another suitable approach to installing the cyanomethyl group into the molecules of interest, benefiting from the advantages of its high efficiency, mild reaction conditions, energy-saving ability, and operation simplicity.[7] Bromoacetonitrile is a cheap and commercially available compound that can be activated by visible-light catalyst to form the acetonitrile radical. It has been used as a cyanomethyl radical source for the cyanomethylation of activated alkenes, alkynes, and aldehydes via a radical pathway.[8] However, few studies have focused on the dehydrogenative C_{sp^2}−H cyanomethylation of heterocycles with bromoacetonitrile through visible-light catalysis.[9] On the other hand, indazoles, an important class of N-heterocycles, play an important role in organic synthesis and medical chemistry exhibiting a wide range of biological activities such as antitumor, antimicrobial, anti-inflammatory, antiplatelet, and anticontraceptive activity while being also applied in HIV protease inhibition.[10] Many strategies have been developed to synthesize such important molecules.[11] For example, the direct C3−H phosphonylation, amination, arylation, alkylation, and alkoxylation of 2*H*-indazole by visible-light photoredox have been reported previously.[12] However, efficient protocols for various functionalizations of 2*H*-indazole are still urgently needed. With our continuous study on the sustainable modification of heterocycles,[13] we herein present the efficient visible-light-promoted cyanomethylation of 2*H*-indazoles in the presence of $Ir(ppy)_3$ as the photocatalyst and bromoacetonitrile as an inexpensive and readily available cyanomethyl radical source under mild conditions.

RESULTS AND DISCUSSION

Initially, 2-phenyl-2*H*-indazoles (**1a**) with bromoacetonitrile (**2**) were selected as the model substrates. The reaction proceeded with 2 mol % $Ir(ppy)_3$ as the photocatalyst and 2 equiv of K_2HPO_4 as the base in MeCN with 5 W blue LED irradiation at room temperature under argon atmosphere and provided the C3-cyanomethylated 2*H*-indazole **3a** in 67% yield (Table 1, entry 1). Then, a series of photocatalysts were

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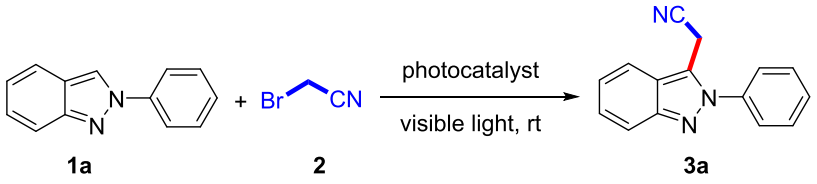
Table 1. Optimization of Reaction Conditions[a]



1a 2 3a

entry	catalyst	base	solvent	yield[b] (%)
1	$Ir(ppy)_3$	K_2HPO_4	MeCN	67
2	$Ru(bpy)_2Cl_2$	K_2HPO_4	MeCN	trace
3	$[Ir(dtbbpy)(ppy)_2]PF_6$	K_2HPO_4	MeCN	trace
4	Rhodamine 6G[h]	K_2HPO_4	MeCN	N.R.
5	Rose Bengal[h]	K_2HPO_4	MeCN	N.R.
6	Methylene blue[i]	K_2HPO_4	MeCN	N.R.
7	$Ir(ppy)_3$	K_2CO_3	MeCN	trace
8	$Ir(ppy)_3$	Na_2CO_3	MeCN	48
9	$Ir(ppy)_3$	$NaHCO_3$	MeCN	11
10	$Ir(ppy)_3$	K_3PO_4	MeCN	19
11	$Ir(ppy)_3$	2,6-lutidine	MeCN	35
12	$Ir(ppy)_3$	DIPEA	MeCN	trace
13	$Ir(ppy)_3$	K_2HPO_4	DMF	N.R.
14	$Ir(ppy)_3$	K_2HPO_4	DCE	45
15	$Ir(ppy)_3$	K_2HPO_4	DCM	28
16	$Ir(ppy)_3$	K_2HPO_4	MeOH	N.R.
17	$Ir(ppy)_3$	K_2HPO_4	DMSO	73
18	$Ir(ppy)_3$	K_2HPO_4	acetone	61
19	$Ir(ppy)_3$		DMSO	N.R.
20	$Ir(ppy)_3$	K_2HPO_4	DMSO	73[c]
21	$Ir(ppy)_3$	K_2HPO_4	DMSO	63[d]
22	$Ir(ppy)_3$	K_2HPO_4	DMSO	N.R.[e]
23	$Ir(ppy)_3$	K_2HPO_4	DMSO	N.R.[f]
24	-	K_2HPO_4	DMSO	N.R.[g]

[a]**1a** (0.2 mmol), **2a** (0.4 mmol), photocatalyst (2 mol %), base (0.4 mmol), solvent (1.0 mL), under Ar atmosphere performed in a 25 mL sealed tube with a 5 W blue LED irradiation, r.t., for 24 h. [b]Isolated yield. [c]3 mol % $Ir(ppy)_3$. [d]Bromoacetonitrile (0.8 mmol). [e]Under air. [f]In the dark. [g]Without photocatalyst. [h]With a 5 W green LED irradiation. [i]With a 5 W red LED irradiation.

screened. $Ru(bpy)_3Cl_2$ and $[Ir(dtbbpy)(ppy)_2]PF_6$ only gave trace amounts of the product, while organic photocatalysts, such as rose bengal, methylene blue, and rhodamine 6G, did not show any catalytic activity in this reaction (Table 1, entries 2−6). Using $Ir(ppy)_3$ as the photocatalyst, several commonly used bases such as K_2CO_3, Na_2CO_3, K_3PO_4, 2,6-lutidine, and N,N-diisopropylethylamine (DIPEA), were also studied, with K_2HPO_4 providing the best results this reaction system. (Table 1, entries 7−12). Different solvents (i.e., DMF, DCE, DCM, MeOH, DMSO, and acetone) were then evaluated (Table 1, entries 13−18), with DMSO providing the highest yield of the desired product **3a** (73% yield, entry 17). No reaction happened without base (Table 1, entry 19). Improving the loading of photocatalyst or bromoacetonitrile did not improve the yield (Table 1, entries 20 and 21). The formation of product **3a** was suppressed when the reaction was performed under air instead of argon (Table 1, entry 22). Notably, control experiments conducted in the absence of light or photocatalyst did not generate the target product (entries 23 and 24), indicating that both irradiation and photoredox catalysts are necessary.

With the optimized reaction conditions in hand, we next examined the scope of this protocol with different functionalities in the 2*H*-indazole system (Table 2). 2-Phenyl-2*H*-indazoles bearing an electron-donating group such as Me-, Et-, or MeO- on the 4- or 3-position of the *N*-2-phenyl ring reacted efficiently to produce C3-cyanomethylated 2*H*-indazoles in good yields (**3a−3f**). 2*H*-Indazoles containing an electron-withdrawing group, such as F−, Cl−, Br−, CF_3−, CN−, and NO_2−, also reacted smoothly, providing the respective products in 32−71% yields (**3g−3p**). Among them, 2*H*-indazoles with halogens such as F−, Cl−, and Br− substituted on the 4- or 3-position of the *N*-2-phenyl ring successfully reacted under the present reaction conditions to give the desired products **3g−3l** in good yields. The products **3m−3o**, respectively containing 4-CF_3−, 3-CF_3−, or 3-CN− substituents, were obtained in 55−71% yields. The nitro group was tolerated in the current reaction, and the product (**3p**) was obtained in 32% yield. Substrates with substituents on the *ortho*-position of the phenyl ring had relatively low yields of 34−40% (**3q−3t**), likely due to steric hindrance. In addition, disubstituted 2*H*-indazoles with substituents on the *N*-2-phenyl ring also provided the corresponding products **3u−3x** in moderate yields. 2*H*-Indazoles bearing electron-donating groups (i.e., OMe− and Me−) as well as electron-withdrawing groups (i.e., F−, Cl−, and Br−) on the indazole ring efficiently reacted with **2** to produce the C3-cyanomethylated derivatives **3y−3ae** in 44−65% yields. ^{n}Bu- and Bn- groups at *N*-2 position of 2*H*-indazole afforded provided the desired products **3af−3ag** in relatively low yields. *N*-2-Pyridyl-substituted 2*H*-indazole, 1-Me-1*H*-indazole, and 1-Ph-1*H*-indazole were unreactive under the standard reaction conditions.

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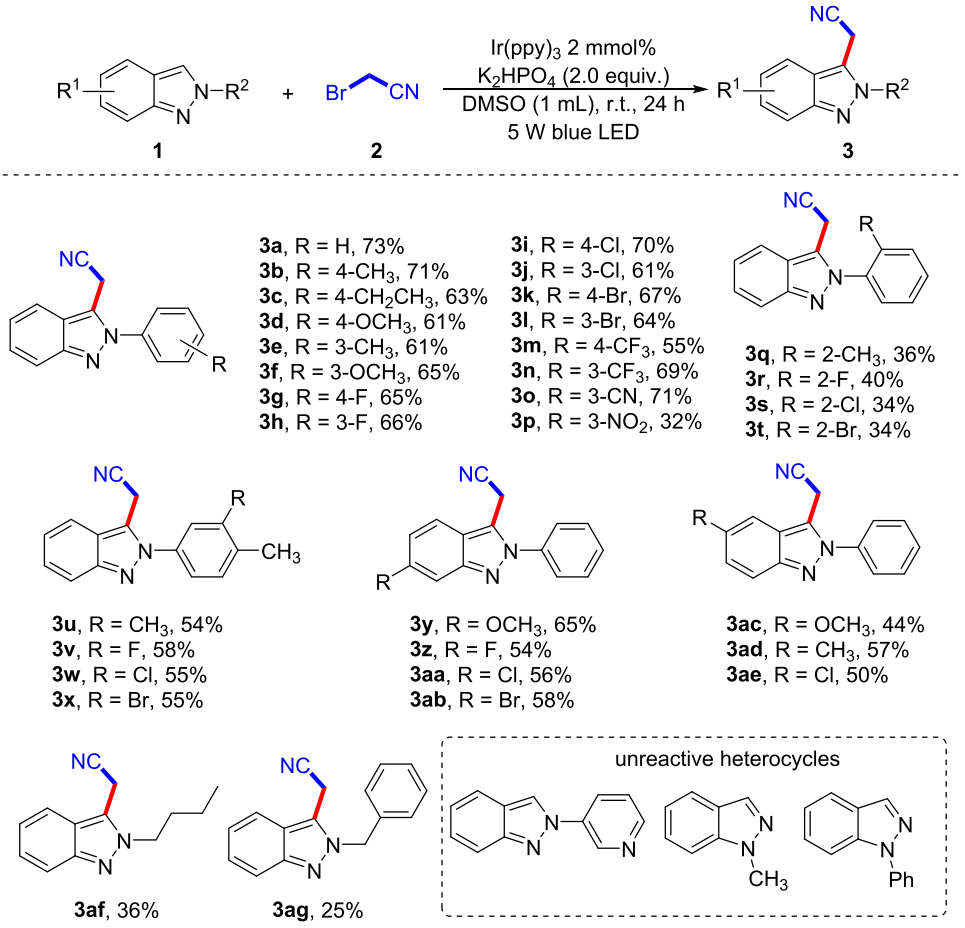
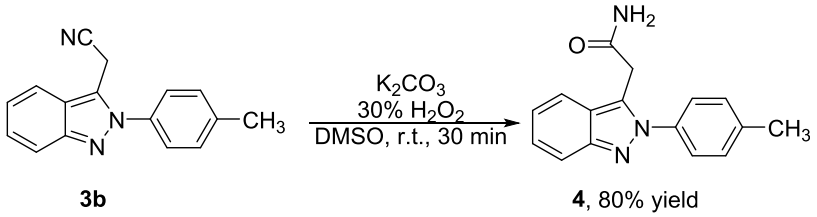
Table 2. Substrate Scope[a,b]

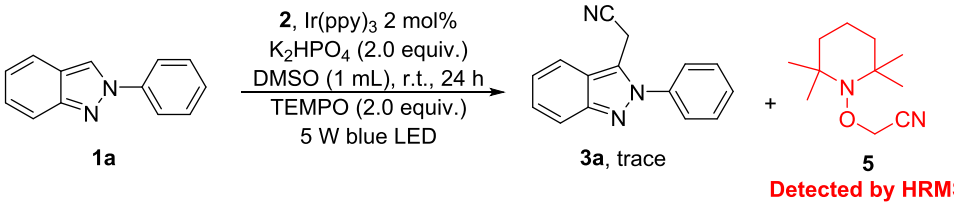


[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), Ir(ppy)$_3$ (2 mol%), K_2HPO_4 (0.4 mmol), DMSO (1 mL) under Ar atmosphere 24 h with 5 W blue LED irradiation. [b]Isolated yields are given.

Scheme 1. Transformation of the C3-Cyanomethylated Compound 3b



Scheme 2. Radical-Trapping Experiments



To further demonstrate the viability of this approach, we transformed the nitrile group into an amide in the presence of K_2CO_3 and H_2O_2, obtaining the target product **4** in 80% yield (Scheme 1).

To gain insight into the mechanism of this transformation, we performed the reaction under standard conditions with the addition of the radical scavenger 2,2,6,6-tetramethylpiperidinooxyl (TEMPO) and obtained trace amounts of product **3a** (Scheme 2). However, the coupling product **5** of TEMPO-CH_2CN was captured by high-resolution mass spectrometry. These results indicated that the radical process may be involved in the cyanomethylation reaction.

The Stern−Volmer fluorescence quenching experiments were conducted by mixing the photocatalyst Ir(ppy)$_3$ with

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$BrCH_2CN$, K_2HPO_4 and **1a**, respectively, and these results are shown in Figure 1 (see the SI for details). We disclosed that

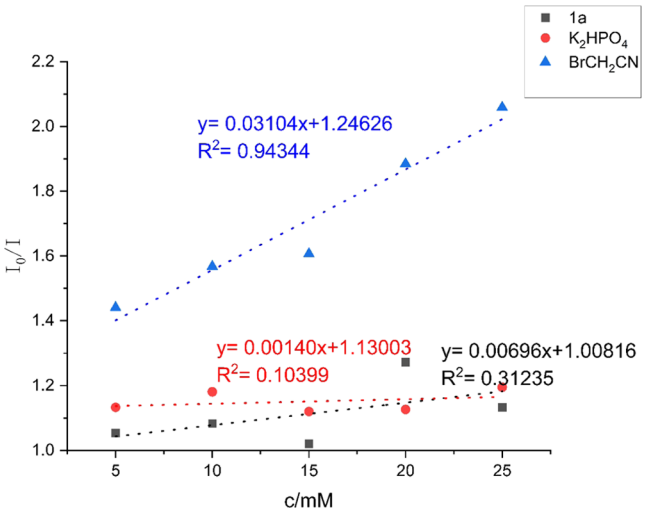


Figure 1. Luminescence quenching studies.

the fluorescence of the excited photocatalyst could be remarkably quenched by $BrCH_2CN$, while being rarely influenced by K_2HPO_4 and **1a**. Moreover, the luminescence intensities exhibited an obvious linear correlation with the concentration of $BrCH_2CN$, which indicated that $BrCH_2CN$ acted as an important quencher in this visible-light-promoted system.

Based on these observations and literature, a plausible mechanism for the C3-cyanomethylation of 2*H*-indazoles with bromoacetonitrile is proposed (Scheme 3). Initially, the excited state $[Ir(III)(ppy)_3]^*$ was formed under blue LED irradiation. Then, the excited $[Ir(III)(ppy)_3]^*$ undergoes a single-electron transfer (SET) with **2** to generate radical **A** and $[Ir(IV)(ppy)_3]^+$. Subsequently, radical **A** attacks the π electrons at the C3-position of **1a** to construct intermediate **B**, which is converted into intermediate **C** by undergoing single-electron oxidation. Finally, the radical intermediate **C** is deprotonated under the action of a base to produce **3a**, during which $[Ir(III)\ (ppy)_3]$ is regenerated.

CONCLUSIONS

In summary, we successfully achieved the efficient visible-light-induced C3-cyanomethylation of 2*H*-indazoles using bromoacetonitrile as the cyanomethyl radical source and $Ir(ppy)_3$ as the photocatalyst. Various cyanomethylated 2*H*-indazoles derivatives were prepared in moderate yields with a wide range of functional group tolerance at room temperature. This new protocol features a short synthetic route, green chemistry, low cost, and mild reaction conditions, making it an attractive strategy for installing cyanomethyl groups on 2*H*-indazoles.

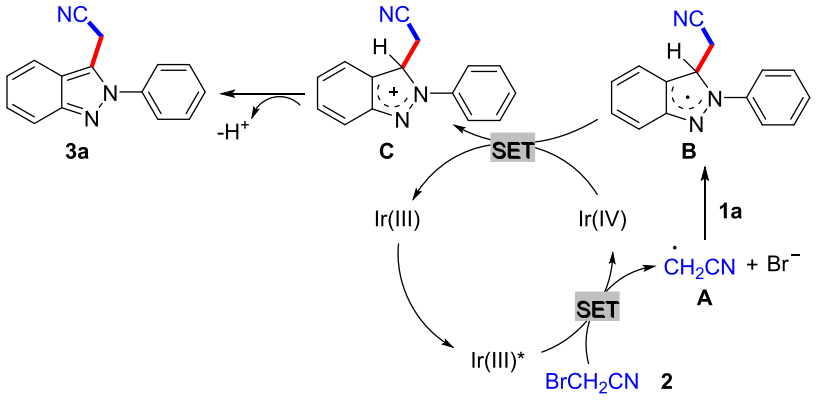
EXPERIMENTAL SECTION

General Information. All catalytic reactions were carried out under argon atmosphere. Unless otherwise stated, all reagents were purchased without further purification. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel GF254 plates. Visualization on TLC was achieved using UV light (254 nm). Column chromatography was undertaken on silica gel (200−300 mesh) using a proper eluent system. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded at 400, 101, and 376 MHz, respectively, with $CDCl_3$ or DMSO-d_6 as solutions. The chemical shifts δ are reported in ppm relative to tetramethylsilane or residual $CHCl_3$ (δ_c = 77.00 ppm). The following abbreviations were used to describe peak splitting patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet) m (multiplet), dd (doublet of doublet), ddd (doublet of doublet of doublet), td (triplet of doublet). Coupling constants, *J*, are reported in hertz (Hz). High-resolution mass spectrometry (HRMS) was performed on a Q-TOF spectrometer with micromass MS software using electrospray ionization (ESI). Emission intensities were recorded using an Edinburgh UK FLS100 photoluminescence spectrometer from 450 to 750 nm. Substituted 2*H*-indazole derivatives were prepared according to the published procedure.[14]

General Catalytic Procedure. Under argon atmosphere, a reaction tube (25 mL) equipped with a magnetic stirrer bar was charged with 2*H*-indazole (**1**, 0.2 mmol), bromoacetonitrile (**2**, 0.4 mmol, 28 uL), $Ir(ppy)_3$ (0.004 mmol, 2 mol %, 2.6 mg), K_2HPO_4 (0.4 mmol, 55.3 mg), and DMSO (1.0 mL). The reaction mixture was stirred with a 5 W blue LED irradiation at room temperature for 24 h, filtered through a pad of celite, and then washed with ethyl acetate (3 × 10 mL). The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (eluent: EA/PE) to give the desired product **3**.

*2-(2-Phenyl-2H-indazol-3-yl)acetonitrile (**3a**).* 34 mg, 73% yield, red oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 8.7, 4.2 Hz, 2H), 7.62−7.48 (m, 5H), 7.37 (dd, *J* = 8.3, 7.0 Hz,

Scheme 3. Proposed Reaction Mechanism



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1H), 7.19 (dd, J = 8.3, 7.0 Hz, 1H), 4.05 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.7, 138.6, 129. 8, 129.7, 127.3, 125.8, 123.0, 122.8, 121.4, 118.9, 118.1, 115.0, 15.0. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{12}N_3$ 234.1026, found 234.1024.

*2-(2-(p-Tolyl)-2H-indazol-3-yl)acetonitrile (**3b**).* 35 mg, 71% yield, pale red solid; mp 69−71 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 8.7, 4.0 Hz, 2H), 7.56−7.28 (m, 5H), 7.19 (dd, J = 8.5, 6.6 Hz, 1H), 4.05 (s, 2H), 2.46 (s, 3H).$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.6, 140.1, 136.1, 130.3, 127.1, 125.6, 122.9, 122.8, 121.3, 118.8, 118.1, 115.1, 21.3, 15.0. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{14}N_3$ 248.1182, found 248.1180.

*2-(2-(4-Ethylphenyl)-2H-indazol-3-yl)acetonitrile (**3c**).* 33 mg, 63% yield; red oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 9.4 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 7.42−7.35 (m, 3H), 7.23−7.15 (m, 1H), 4.08 (s, 2H), 2.77 (q, J = 7.6 Hz, 2H), 1.31 (t, J = 7.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.6, 146.3, 136.2, 129.2, 127.2, 125.8, 122.9, 122.7, 121.3, 118.8, 118.2, 115.1, 28.6, 15.4, 15.1. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{16}N_3$ 262.1339, found 262.1341.

*2-(2-(4-Methoxyphenyl)-2H-indazol-3-yl)acetonitrile (**3d**).* 32 mg, 61% yield, pale yellow solid; mp 97−99 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 8.7, 3.3 Hz, 2H), 7.51−7.42 (m, 2H), 7.40−7.34 (m, 1H), 7.23−7.17 (m, 1H), 7.11−7.03 (m, 2H), 4.05 (s, 2H), 3.89 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.5, 148.5, 131.4, 127.2, 127.1, 122.9 (2C), 121.2, 118.8, 118.1, 115.1, 114.8, 55.7, 15.0. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{14}N_3O$ 264.1131, found 264.1130.

*2-(2-(m-Tolyl)-2H-indazol-3-yl)acetonitrile (**3e**).* 30 mg, 61% yield, red oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 9.4 Hz, 2H), 7.46 (m, 1H), 7.39−7.35 (m, 3H), 7.31 (d, J = 7.7 Hz, 1H), 7.20 (dd, J = 8.9, 6.7 Hz, 1H), 4.08 (s, 2H), 2.46 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.7, 140.2, 138.6, 130.6, 129.5, 127.3, 126.6, 123.0, 122.8, 122.7, 121.4, 118.9, 118.2, 115.1, 21.4, 15.1. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{14}N_3$ 248.1182, found 248.1179.

*2-(2-(3-Methoxyphenyl)-2H-indazol-3-yl)acetonitrile (**3f**).* 34 mg, 65% yield, yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 8.7, 4.2 Hz, 2H), δ 7.47 (t, J = 8.2 Hz, 1H), 7.41−7.35 (m, 1H), 7.23−7.17 (m, 1H), 7.09 (dd, J = 6.9, 3.7 Hz, 3H), 4.09 (s, 2H), 3.87 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.6, 148.7, 139.6, 130.5, 127.3, 123.1, 122.8, 121.4, 118.9, 118.2, 117.8, 116.1, 115.1, 111.4, 55.7, 15.1. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{14}N_3O$ 264.1131, found 264.1131.

*2-(2-(4-Fluorophenyl)-2H-indazol-3-yl)acetonitrile (**3g**).* 33 mg, 65% yield, pale yellow solid; mp 111−113 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 8.7, 4.2 Hz, 2H), 7.58−7.51 (m, 2H), 7.43−7.36 (m, 1H), 7.32−7.26 (m, 2H), 7.22 (dd, J = 8.4, 6.7 Hz, 1H), 4.06 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.1 (d, J = 251.1 Hz), 148.7, 134.7 (d, J = 3.2 Hz), 127.9 (d, J = 8.9 Hz), 127.5, 123.3, 123.0, 121.4, 118.8, 118.2, 116.9 (d, J = 23.2 Hz), 114.9, 15.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.02. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{11}FN_3$ 252.0932, found 252.0930.

*2-(2-(3-Fluorophenyl)-2H-indazol-3-yl)acetonitrile (**3h**).* 33 mg, 66% yield, pale yellow solid; mp 108−110 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 9.5 Hz, 2H), 7.57 (td, J = 8.3, 6.2 Hz, 1H), 7.42−7.32 (m, 3H), 7.31−7.26 (m, 1H), 7.24−7.17 (m, 1H), 4.11 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.9 (d, J = 250.4 Hz), 148.9, 139.9 (d, J = 9.7 Hz), 131.2 (d, J = 9.0 Hz), 127.7, 123.4, 122.8, 121.6, 121.5 (d, J = 3.4 Hz), 118.9, 118.2, 117.0 (d, J = 21.0 Hz), 114.8, 113.8 (d, J = 24.5 Hz), 15.1. ^9F NMR (376 MHz, $CDCl_3$) δ −109.25. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{11}FN_3$ 252.0932, found 252.0931.

*2-(2-(4-Chlorophenyl)-2H-indazol-3-yl)acetonitrile (**3i**).* 38 mg, 70% yield, pale red solid; mp 143−145 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 8.7, 4.6 Hz, 2H), 7.60−7.47 (m, 4H), 7.42−7.35 (m, 1H), 7.21 (dd, J = 8.6, 6.3 Hz, 1H), 4.07 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.9, 137.1, 136.0, 130.0, 127.6, 127.1, 123.4, 122.9, 121.6, 118.8, 118.2, 114.9, 15.0. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{11}ClN_3$ 268.0636, found 268.0634.

*2-(2-(3-Chlorophenyl)-2H-indazol-3-yl)acetonitrile (**3j**).* 33 mg, 61% yield, yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 9.5 Hz, 2H), 7.63−7.59 (m, 1H), 7.58−7.50 (m, 2H), 7.49−7.44 (m, 1H), 7.42−7.36 (m, 1H), 7.25−7.19 (m, 1H), 4.11 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.9, 139.6, 135.6, 130.7, 130.0, 127.6, 126.4, 123.9, 123.4, 122.8, 121.6, 118.8, 118.2, 114.8, 15.1. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{11}ClN_3$ 268.0636, found 268.0633.

*2-(2-(4-Bromophenyl)-2H-indazol-3-yl)acetonitrile (**3k**).* 42 mg, 67% yield, pale red solid; mp 152−154 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.79−7.68 (m, 4H), 7.48−7.42 (m, 2H), 7.41−7.36 (m, 1H), 7.22 (dd, J = 8.6, 6.4 Hz, 1H), 4.08 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.9, 137.7, 133.0, 127.6, 127.4, 124.0, 123.4, 122.8, 121.6, 118.8, 118.2, 114.9, 15.0. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{11}BrN_3$ 312.0131, found 312.0129.

*2-(2-(3-Bromophenyl)-2H-indazol-3-yl)acetonitrile (**3l**).* 40 mg, 64% yield, pale red solid; mp 115−117 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J = 5.7, 3.7 Hz, 3H), 7.70 (dt, J = 7.6, 1.6 Hz, 1H), 7.54−7.43 (m, 2H), 7.42−7.33 (m, 1H), 7.25−7.17 (m, 1H), 4.11 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.9, 139.7, 133.0, 130.9, 129.2, 127.6, 124.3, 123.4, 123.3, 122.9, 121.6, 118.8, 118.2, 114.8, 15.1. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{11}BrN_3$ 312.0131., found 312.0130.

*2-(2-(4-(Trifluoromethyl)phenyl)-2H-indazol-3-yl)-acetonitrile (**3m**).* 31 mg, 55% yield, pale red solid; mp 115−117 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.4 Hz, 2H), 7.77 (dd, J = 2.7, 1.8 Hz, 1H), 7.76−7.70 (m, 3H), 7.41 (ddd, J = 8.7, 6.6, 0.9 Hz, 1H), 7.26−7.19 (m, 1H), 4.12 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.1, 141.5, 131.8 (q, J = 33.3 Hz), 127.8, 127.1 (q, J = 3.7 Hz), 126.3, 123.6, 123.5 (q, J = 273.7 Hz), 122.9, 121.8, 118.8, 118.3, 114.8, 15.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.67. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{11}F_3N_3$ 302.0900, found 302.0901.

*2-(2-(3-(Trifluoromethyl)phenyl)-2H-indazol-3-yl)-acetonitrile (**3n**).* 42 mg, 69% yield, red oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.83 (d, J = 6.9 Hz, 1H), 7.80−7.72 (m, 4H), 7.40 (ddd, J = 8.7, 6.6, 0.8 Hz, 1H), 7.23 (dd, J = 8.6, 6.5 Hz, 1H), 4.10 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.1, 139.2, 132.6 (q, J = 33.5 Hz), 130.5, 129.0 (d, J = 0.7 Hz), 127.8, 126.6 (q, J = 3.6 Hz), 123.6, 123.2 (q, J = 273.7 Hz), 123.2 (q, J = 3.8 Hz), 123.0, 121.7, 118.8, 118.2, 114.7, 15.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.72. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{11}F_3N_3$ 302.0900, found 302.0904.

*2-(3-(Cyanomethyl)-2H-indazol-2-yl)benzonitrile (**3o**).* 37 mg, 71% yield, pale red solid; mp 136−138 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (t, J = 1.6 Hz, 1H), 7.87−7.82 (m, 2H),

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7.75 (dd, J = 12.9, 5.1 Hz, 3H), 7.43−7.38 (m, 1H), 7.26−7.21 (m, 1H), 4.13 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.2, 139.6, 133.2, 130.9, 130.0, 129.4, 128.0, 123.8, 123.1, 121.8, 118.9, 118.2, 117.2, 114.6, 114.3, 15.1. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{11}N_4$ 259.0978, found 259.0975.

2-(2-(3-Nitrophenyl)-2H-indazol-3-yl)acetonitrile (***3p***). 18 mg, 32% yield, pale yellow solid; mp 174−176 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.55 (t, J = 2.1 Hz, 1H), 8.46 (ddd, J = 8.3, 2.2, 0.9 Hz, 1H), 8.19 (ddd, J = 8.0, 2.0, 0.9 Hz, 1H), 8.01−7.91 (m, 2H), 7.74 (d, J = 8.8 Hz, 1H), 7.41 (ddd, J = 8.8, 6.6, 1.0 Hz, 1H), 7.23 (dd, J = 8.5, 6.6 Hz, 1H), 4.75 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 148.8, 148.7, 140.0, 132.5, 131.7, 128.0, 125.9, 124.6, 123.0, 121.7, 121.2, 120.5, 118.1, 116.9, 14.9.

2-(2-(o-Tolyl)-2H-indazol-3-yl)acetonitrile (***3q***). 18 mg, 36% yield, yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.83−7.74 (m, 2H), 7.50 (t, J = 7.5 Hz, 1H), 7.46−7.37 (m, 3H), 7.33 (d, J = 7.7 Hz, 1H), 7.25−7.19 (m, 1H), 3.92 (s, 2H), 2.05 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.7, 137.3, 135.9, 131.6, 130.6, 127.3, 127.1, 127.1, 123.5, 123.0, 120.5, 118.8, 118.3, 114.6, 17.1, 14.6. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{14}N_3$ 248.1182, found 248.1180.

2-(2-(2-Fluorophenyl)-2H-indazol-3-yl)acetonitrile (***3r***). 20 mg, 40% yield, pale red solid; mp 133−135 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.6 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.64 (td, J = 7.7, 1.7 Hz, 1H), 7.58 (tdd, J = 6.9, 5.0, 1.7 Hz, 1H), 7.43−7.31 (m, 3H), 7.22 (dd, J = 8.5, 6.7 Hz, 1H), 4.06 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.3 (d, J = 252.3 Hz), 149.3, 132.0 (d, J = 7.9 Hz), 129.3, 127.5, 126.5 (d, J = 12.0 Hz), 125.5 (d, J = 3.9 Hz), 124.5, 123.2, 120.9, 118.9, 118.2, 116.9 (d, J = 19.5 Hz), 114.5, 14.7 (d, J = 4.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.24. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{11}FN_3$ 252.0932, found 252.0930.

2-(2-(2-Chlorophenyl)-2H-indazol-3-yl)acetonitrile (***3s***). 18 mg, 34% yield, red oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.6 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.63 (m, 1H), 7.60−7.48 (m, 3H), 7.40 (m, 1H), 7.25−7.21 (m, 1H), 3.99 (dd, J = 83.7, 18.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.1, 136.2, 131.9, 131.6, 130.6, 129.7, 128.2, 127.5, 124.4, 123.2, 120.6, 119.0, 118.4, 114.5, 14.8. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{11}ClN_3$ 268.0636 found 268.0636.

2-(2-(2-Bromophenyl)-2H-indazol-3-yl)acetonitrile (***3t***). 21 mg, 34% yield, yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.83-7.76 (m, 3H), 7.57-7.55 (m, 2H), 7.53−7.46 (m, 1H), 7.44−7.37 (m, 1H), 7.25-7.21 (m, 1H), 3.98 (dd, J = 90.4, 18.5 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.0, 137.7, 133.7, 132.1, 129.8, 128.8, 127.5, 124.2, 123.3, 121.4, 120.6, 119.0, 118.3, 114.5, 14.9. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{11}BrN_3$ 312.0131, found 312.0131.

2-(2-(3,4-Dimethylphenyl)-2H-indazol-3-yl)acetonitrile (***3u***). 28 mg, 54% yield, pale yellow solid; mp 89−91 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 9.1 Hz, 2H), 7.40−7.34 (m, 1H), 7.32 (d, J = 7.9 Hz, 2H), 7.24 (dd, J = 8.0, 2.0 Hz, 1H), 7.20 (dd, J = 8.6, 6.4 Hz, 1H), 4.08 (s, 2H), 2.36 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.6, 138.8, 138.6, 136.3, 130.6, 127.1, 126.9, 122.9, 122.9, 122.7, 121.3, 118.8, 118.2, 115.2, 19.9, 19.6, 15.1. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{16}N_3$ 262.1339, found 262.1338.

2-(2-(3-Fluoro-4-methylphenyl)-2H-indazol-3-yl)-acetonitrile (***3v***). 31 mg, 58% yield, pale red solid; mp 82−84 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, J = 8.5 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.60-7.55 (m, 2H), 7.46 (dd, J = 8.1, 2.1 Hz, 1H), 7.38 (m, 1H), 7.19 (dd, J = 9.2, 6.6 Hz, 1H), 4.68 (s, 2H), 2.37 (d, J = 1.6 Hz, 3H).$^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 160.8 (d, J = 245.0 Hz), 148.4, 138.2 (d, J = 10.2 Hz), 132.8 (d, J = 6.0 Hz), 127.6, 126.3 (d, J = 17.0 Hz), 125.2, 122.7, 122.0 (d, J = 3.4 Hz), 121.5, 120.4, 118.0, 116.9, 113.3 (d, J = 25.7 Hz), 14.8, 14.5 (d, J = 2.9 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ −114.77. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{13}FN_3$ 266.1088, found 266.1089.

2-(2-(3-Chloro-4-methylphenyl)-2H-indazol-3-yl)-acetonitrile (***3w***). 31 mg, 55% yield, red oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 9.5 Hz, 2H), 7.58 (d, J = 2.1 Hz, 1H), 7.47−7.32 (m, 3H), 7.24−7.17 (m, 1H), 4.09 (s, 2H), 2.48 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.8, 138.3, 137.2, 135.5, 131.7, 127.5, 126.6, 123.8, 123.3, 122.8, 121.5, 118.8, 118.2, 114.9, 20.0, 15.1. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{13}ClN_3$ 282.0793, found 282.0789.

2-(2-(3-Bromo-4-methylphenyl)-2H-indazol-3-yl)-acetonitrile (***3x***). 36 mg, 55% yield, pale red solid; mp 102−104 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (t, J = 5.7 Hz, 3H), 7.47−7.34 (m, 3H), 7.24−7.18 (m, 1H), 4.09 (s, 2H), 2.51 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.8, 140.2, 137.2, 131.5, 129.7, 127.5, 125.5, 124.4, 123.3, 122.9, 121.5, 118.8, 118.2, 114.9, 22.8, 15.1. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{13}BrN_3$ 326.0287, found 326.0285.

2-(6-Methoxy-2-phenyl-2H-indazol-3-yl)acetonitrile (***3y***). 34 mg, 65% yield, pale red solid; mp 141−143 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 9.3 Hz, 1H), 7.58 (dt, J = 7.7, 2.0 Hz, 2H), 7.56−7.51 (m, 3H), 7.08 (dd, J = 9.3, 2.3 Hz, 1H), 6.90 (d, J = 2.2 Hz, 1H), 4.05 (s, 2H), 3.89 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.0, 145.6, 138.8, 129.8, 129.6, 125.8, 122.6, 121.5, 121.3, 119.6, 115.2, 94.6, 55.5, 15.1. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{14}N_3O$ 264.1131, found 264.1129.

(6-Fluoro-2-phenyl-2H-indazol-3-yl)acetonitrile (***3z***). 27 mg, 54% yield, pale red solid; mp 124−126 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 9.4, 4.6 Hz, 1H), 7.64−7.56 (m, 3H), 7.56−7.52 (m, 2H), 7.35 (dd, J = 8.8, 2.3 Hz, 1H), 7.18 (td, J = 9.2, 2.4 Hz, 1H), 4.05 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.8 (d, J = 243.0 Hz), 146.1, 138.5, 130.0, 129.9, 125.8, 122.9 (d, J = 8.8 Hz), 120.8 (d, J = 11.5 Hz), 120.5 (d, J = 9.8 Hz), 119.1 (d, J = 29.1 Hz), 114.8, 101.5 (d, J = 24.9 Hz), 15.1.^{19}F NMR (376 MHz, $CDCl_3$) δ −117.02. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{11}FN_3$ 252.0932, found 252.0927.

2-(6-Chloro-2-phenyl-2H-indazol-3-yl)acetonitrile (***3aa***). 30 mg, 56% yield, pale yellow solid; mp 133−135 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.77−7.69 (m, 2H), 7.65−7.57 (m, 3H), 7.54 (dd, J = 7.7, 2.0 Hz, 2H), 7.31 (dd, J = 9.2, 1.9 Hz, 1H), 4.06 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 147.1, 138.3, 130.1, 129.9, 128.9, 128.8, 125.8, 122.6, 121.8, 119.8, 117.6, 114.7, 15.1. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{11}ClN_3$ 268.0636, found 268.0635.

2-(6-Bromo-2-phenyl-2H-indazol-3-yl)acetonitrile (***3ab***). 36 mg, 58% yield, pale red solid; mp 137−139 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 1.5 Hz, 1H), 7.65 (d, J = 9.2 Hz, 1H), 7.61-7.58 (m, 3H), 7.55-7.53 (m, 2H), 7.43 (dd, J = 9.2, 1.7 Hz, 1H), 4.05 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 147.2, 138.3, 131.1, 130.1, 129.9, 125.8, 122.6, 122.4, 121.1, 120.0, 116.7, 114.7, 15.1. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{11}BrN_3$ 312.0131, found 312.0127.

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*2-(5-Methoxy-2-phenyl-2H-indazol-3-yl)acetonitrile (**3ac**).* 23 mg, 44% yield, pale yellow solid; mp 125−127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 9.2 Hz, 1H), 7.56 (dt, J = 11.0, 7.6 Hz, 5H), 6.98 (d, J = 1.7 Hz, 1H), 6.90 (dd, J = 9.1, 1.9 Hz, 1H), 4.05 (s, 2H), 3.89 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.7, 149.9, 138.7, 129.8, 129.6, 125.8, 122.9, 119.7, 118.5, 117.3, 115.0, 94.7, 55.4, 15.1. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{14}N_3O$ 264.1131, found 264.1129.

*2-(5-Methyl-2-phenyl-2H-indazol-3-yl)acetonitrile (**3ad**).* 28 mg, 57% yield, pale red solid; mp 118−120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.7 Hz, 1H), 7.61−7.56 (m, 2H), 7.53 (dt, J = 7.4, 2.3 Hz, 4H), 7.05 (dd, J = 8.7, 1.1 Hz, 1H), 4.06 (s, 2H), 2.48 (s, 3H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.3, 138.7, 137.4, 129.7, 129.7, 126.1, 125.9, 122.6, 119.9, 118.3, 116.3, 115.1, 22.2, 15.1. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{14}N_3$ 248.1182, found 248.1181.

*2-(5-Chloro-2-phenyl-2H-indazol-3-yl)acetonitrile (**3ae**).* 27 mg, 50% yield, pale yellow solid; mp 129−131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78−7.74 (m, 1H), 7.73 (d, J = 9.0 Hz, 1H), 7.64−7.56 (m, 3H), 7.53 (dd, J = 7.7, 1.9 Hz, 2H), 7.16 (dd, J = 9.0, 1.7 Hz, 1H), 4.08 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.9, 138.3, 133.3, 130.1, 129.9, 125.8, 124.7, 123.5, 120.2, 119.9, 117.2, 114.8, 15.2. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{11}ClN_3$ 268.0636, found 268.0634.

*2-(2-Butyl-2H-indazol-3-yl)acetonitrile (**3af**).* 15 mg, 36% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.8 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.37−7.27 (m, 1H), 7.18−7.11 (m, 1H), 4.46−4.38 (m, 2H), 4.12 (s, 2H), 2.05−1.95 (m, 2H), 1.47−1.38 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 147.9, 126.4, 122.4, 121.3, 120.9, 118.3, 117.8, 114.8, 50.9, 32.5, 20.0, 14.1, 13.6. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{13}H_{15}N_3Na$ 236.1158, found 236.1158.

*2-(2-Benzyl-2H-indazol-3-yl)acetonitrile (**3ag**).* 12 mg, 25% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.38−7.31 (m, 4H), 7.20−7.12 (m, 3H), 5.74 (s, 2H), 3.92 (s, 2H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 147.8, 134.8, 129.3, 128.6, 127.0, 126.7, 122.7, 121.9, 121.6, 118.4, 118.0, 114.5, 55.5, 14.3. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{16}H_{13}N_3Na$ 270.1002, found 270.1005.

Procedure for the Derivatization Reaction. Compound **4** was synthesized according to the procedure reported.[15] K_2CO_3 (0.1 mmol, 13.8 mg) and 1 mL of DMSO were added to a tube with substrate **3b** (0.2 mmol). Then, 1.2 mL of aq. H_2O_2 (1.2 mmol, 30%) was dropped at room temperature. The mixture was stirred for 30 min and then the reaction mixture was added to 1 mL of saturated $Na_2S_2O_3$ and 10 mL of saturated $NaHCO_3$ at 0 °C. The resulting mixture was subjected to extraction with ethyl acetate (2 × 15 mL). The combined organic phase was washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and the residue was subjected to flash chromatography (ethyl acetate/petroleum ether 1:2) to give amide **4**.

*2-(2-(p-Tolyl)-2H-indazol-3-yl)acetamide (**4**).* 41 mg, 80% yield, pale white solid; mp 219−221 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.8 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.39−7.30 (m, 3H), 7.17 (dd, J = 8.1, 6.9 Hz, 1H), 5.59 (s, 1H), 5.52 (s, 1H), 3.97 (s, 2H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 148.7, 139.6, 136.7, 130.1, 128.7, 127.1, 125.6, 122.6, 121.7, 119.2, 118.1, 33.0, 21.3. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{16}H_{15}N_3ONa$ 288.1107, found 288.1111.

Procedure for the Radical-Trapping Experiment. Two equivalents of radical scavenger (2,2,6,6-tetramethylpiperidinoxy, TEMPO) were added to the reaction of **1a** with **2** in the standard conditions. After 1 h, the reaction mixture was stopped. Then, the crude reaction mixture was detected by HRMS.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c08094.

^{1}H, ^{19}F, and ^{13}C NMR spectra of compounds **3** and **4** (PDF)

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Notes

The authors declare no competing financial interest.

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