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Acid-promoted Bicyclization of Diaryl Alkynes: Synthesis of 2*H*-Indazoles with in situ Generated Diazonium Salt as Nitrogen Source

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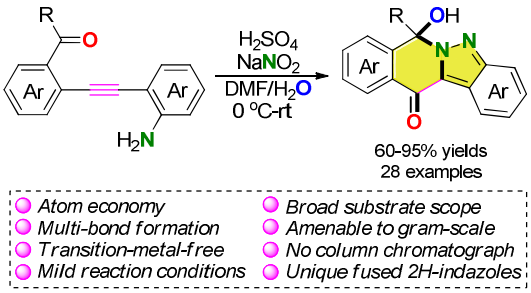


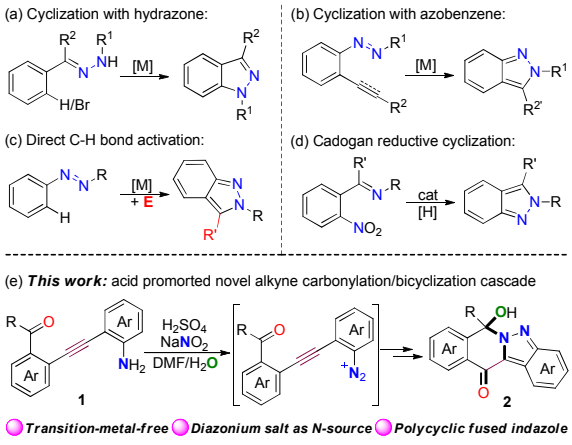
ABSTRACT: An unprecedented transition-metal-free tandem bicyclization of diaryl alkynes has been disclosed, which provides a streamlined access to a range of polycyclic 2*H*-indazoles in high to excellent yields. The salient features of this reaction include readily available starting materials, good functional group compatibility, mild reaction conditions, no column chromatography, high bond-formation efficiency, and ease in further transformations. Notably, this is the first example for the synthesis of 2*H*-indazoles with in situ generated diazonium salt as the nitrogen source, and a mechanistic rationale involving an acid-promoted tandem diazonium salt formation/bicyclization process is discussed.

INTRODUCTION

Indazole motif is widely found in natural products and pharmaceutics[1] as well as common versatile synthons in organic synthesis,[2] and have received considerable

attention in the past decades due to their versatile biological activities, such as for the treatment of respiratory disease,[3] Parkinson's disease,[4] central nervous system (CNS) disorders,[5] diabetes mellitus,[6] cancers,[7] and others.[8] These important and broad activities have inspired the synthetic organic chemists to continue to pursue novel methods for the synthesis of functionalized indazole derivatives for the small molecule screening in drug discovery. However, these reported methods often preferentially generated the thermodynamically more stable 1*H*-indazoles as the major products, such as direct indazole ring modification,[9] and 1,3-dipolar cycloaddition.[10] As an alternative to these two general approaches, considerable effort has been focused on the catalytic cyclization reactions (Scheme 1), Beyond the synthesis of 1*H*-indazoles (Scheme 1a),[11] three general catalytic approaches for selective construction of 2*H*-indazoles are well estabilised,[12-16] including catalytic intramolecular cyclization *via* C-N bond formation (Scheme 1b),[12] formal [4+1] annulation with transition-metal-catalyzed direct C-H activation as the key step (Scheme 1c),[13] and Cadogan reductive cyclization of *ortho*-imino-nitrobenzene (Scheme 1d).[14] Recently, the only example of catalytic Cadogan heterocyclization was successfully realized by Radosevich and coworkers.[14c] Nevertheless, usage of expensive transition metal catalysts, and/or stoichiometric reductant are the two main drawbacks of these methods. Consequently, the development of operationally simple and mild methods to access this privileged pharmacophore starting from readily available materials is highly appealing. Especially, the 2*H*-indazole species, are more difficult to prepare compared to the 1*H*-indazoles,[15] and have in particular begun to attract increased attention due to the promise of drug candidates that contain this motif as the pharmacophore.[16]

Scheme 1. Catalytic Cyclization for the Indazole Synthesis



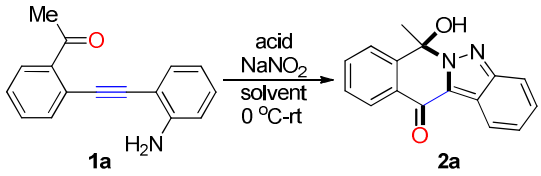
On the other hand, catalytic alkyne transformations, which are reported as efficient tools for the installation of various functional groups,[17] have shown broad applications in synthetic organic chemistry for the preparation of complex organic molecules,[18] including alkyne hydration, which introduces the carbonyl moiety with complete atom economy.[19] Recently, the neighboring carbonyl group assisted alkyne carbonylation strategy,[20] which is pioneered by Stork with Hg catalyst,[20a] is well demonstrated by Jiang,[20b] Baire,[20c] and us[20d] for the regioselective carbonylation of internal alkynes in the presence of Pd, Ag, and Au catalysts, respectively. Inspired by these works and as the continuation of our interests in alkyne bifunctionalization for the heterocycle synthesis,[21] we envisioned that the alkyne carbonylation could be realized with the assistance of appropriate adjacent electrophilic species in the absence of metal catalyst.[22] Herein, we present our recent results in this context, an acid-promoted unprecedented carbonylation/bicyclization cascade reaction of diaryl alkynes **1** for the straightforward synthesis of polycyclic 2*H*-indazoles, and the in situ generated diazonium salt is proposed as the key intermediate in this cascade transformation (Scheme 1e). To our best knowledge, this is the first example of using in situ generated diazonium salt as the nitrogen source for the synthesis of 2*H*-indazoles,[23,24a-b] and the advances of this transition-metal-free strategy is obvious in comparison with disclosed methods with other nitrogen sources in the presence of precious metal catalyst (Scheme 1a-1d).[25]

RESULTS AND DISCUSSION

The evaluation of the initial hypothesis was carried out using diaryl alkyne **1a**, easily synthesized from corresponding terminal alkyne and aryl halide *via* coupling reaction,[26] as the model substrate in the presence of sodium nitrite under acidic conditions (Table 1). To our delight, the fused 2*H*-indazole **2a** was obtained in 90% isolated yield with aqueous sulfuric acid solution (1.7 M, 3.4 equiv) in dimethylsulfoxide (DMSO). It should be noted that longer reaction time was necessary to achieve comparable yields with reduced amount of acid (entries 2 and 3), and no reaction occurred with substoichiometric quantities of acid (entry 4) , thus demonstrating extraordinary robustness of this process. Further screening of solvents indicated that this reaction was compatible with a variety of organic solvents and produced the indazole product in high to excellent yield (entries 5-9). Notably, 80% yield of pure product **2a** was isolated after filtration without column chromatography

when the reaction was carried out in water, although long reaction time (4 days) was needed to ensure the complete conversion due to the lower solubility of the material under these conditions (entry 9). To make the process greener, DMF and H_2O (1:3) mixed solvent was found as the best condition to gave **2a** in 95% yield after filtration without column chromatography (entry 11). Under these conditions, comparable yields could be obtained in presence of aqueous HCl (93% yield), trifluoroacetic acid (TFA, 91% yield), or *p*-toluenesulfonic acid (90% yield). However, acetic acid, due to its lower acidity, could not promote this transformation and the material **1a** remained intact (entry 15). The structure of the generated product **2a** was confirmed by single-crystal X-ray diffraction analysis.[27] In addition, with synchronous formation of the isoquinolinone ring, potential bioactivity could be expected since both isoquinolinone and indazole motifs are prevalently present in natural products or medicinal molecules.[16]

Table 1. Optimization of Reaction Conditions[a]



1a **2a**

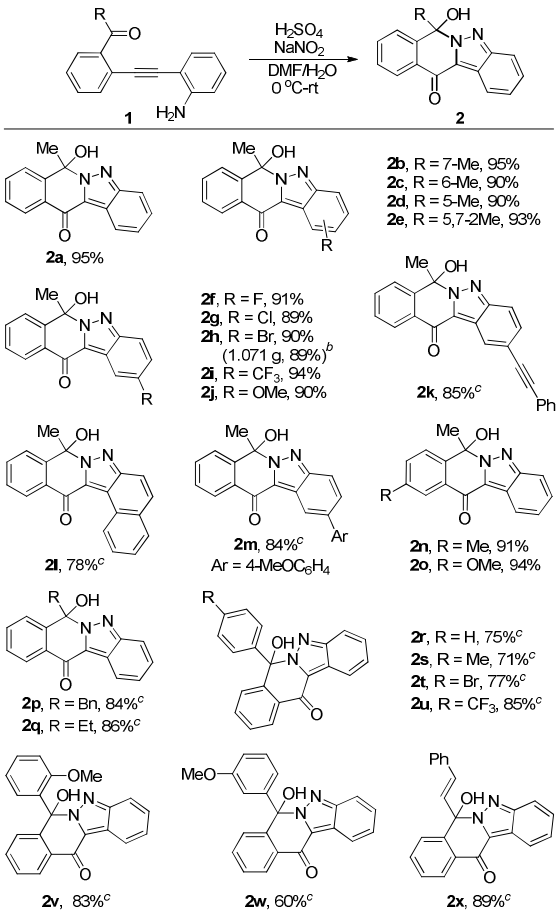
entry	acid	solvent	time	yields (%)[b]
1	H_2SO_4 (3.4 equiv)	DMSO	6 h	90
2	H_2SO_4 (2.0 equiv)	DMSO	18 h	90
3	H_2SO_4 (1.0 equiv)	DMSO	24 h	84
4[c]	H_2SO_4 (0.5 equiv)	DMSO	24 h	NR
5	H_2SO_4 (3.4 equiv)	CH_3CN	0.5 h	96
6	H_2SO_4 (3.4 equiv)	DMF	0.5 h	90
7	H_2SO_4 (3.4 equiv)	Acetone	4 h	89
8	H_2SO_4 (3.4 equiv)	CH_3OH	4 h.	77
9	H_2SO_4 (3.4 equiv)	H_2O	4 day	80[d]
10	H_2SO_4 (3.4 equiv)	DMF:H_2O = 1:5	4 day	83[d]
11	**H_2SO_4 (3.4 equiv)**	**DMF:H_2O = 1:3**	**7 h**	**95[d]**
12	HCl (3.4 equiv)	DMF:H_2O = 1:3	7 h	93[d]
13	TFA (3.4 equiv)	DMF:H_2O = 1:3	7 h	91[d]
14	TsOH·H_2O (3.4 equiv)	DMF:H_2O = 1:3	7 h	90[d]
15[c]	AcOH (3.4 equiv)	DMF:H_2O = 1:3	12 h	NR

[a]Reactions were carried out on a 0.2 mmol scale in 2.0 mL solvent with corresponding acid, and $NaNO_2$ (18 mg, 0.26 mmol, 1.3 equiv) in H_2O (0.3 mL) was added drop wise at 0 °C. Then the reaction mixture was stirred for indicated time and warmed to room temperature slowly. [b]Isolated

yields. [c]Material **1a** was recovered in >90% yield. [d]Yields are given of dried products after filtration without column chromatography, see SI for details. NR = No reaction.

To evaluate the scope of this process, a range of diaryl alkynes **1a-1x** were subjected to the optimal reaction conditions (Table 2). Gratifying, various diaryl alkynes **1** bearing both electron-donating and electron-withdrawing groups on the aryl ring worked well to deliver a series of fused indazoles in high to excellent yields (**2a-2o**, 78%-95% yields). It should be noted that the amount of DMF in the mixed solvent was increased to 3:1 in some cases due to the lower solubility of these substrates under standard conditions (see note c). Beyond the methyl ketones, alkyl ketones (**1p** and **1q**) and diaryl ketones (**1r-1w**) were also suitable substrates to produce the corresponding indazoles in high yields (60%-86% yields). It was found that the reaction showed no obvious effect to the steric demand of the arenes (**2b**, **2e**, and **2v**). Various kinds of functional groups, such as alkynyl (**2k**, 85% yield), naphthyl (**2l**, 78% yield), and alkenyl (**2x**, 89% yield) were well tolerated. In addition, this reaction could be carried out on a gram scale with similar yields and efficiency (**2h**, 89% yield, note b). The structure of the generated products **2p** and **2v** were confirmed by single-crystal X-ray diffraction analysis.[27]

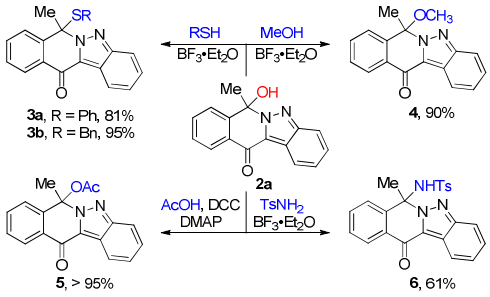
Table 2. Substrate Scope[a]



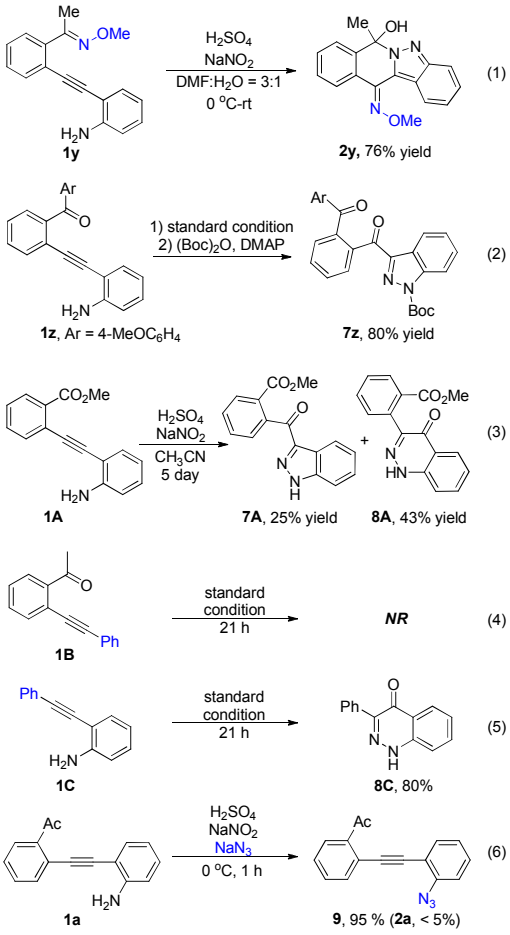
[a]Reactions were carried out on a 0.2 mmol scale in a mixed solvent (2.0 mL, DMF:H_2O = 1:3) with aqueous sulfuric acid solution (0.4 mL, 1.7 M, 3.4 eq), and $NaNO_2$ (18 mg, 0.26 mmol, 1.3 equiv) in H_2O (0.3 mL) was added slowly at 0 °C for 0.5 h, and the reaction mixture was stirred for 7 h and the reaction temperature was allowed to warm up to room temperature slowly. [b]The results in parentheses are the reaction carried out on a 3.5 mmol scale in 10 h. [c]Reactions were carried out in DMF:H_2O = 3:1 (2.0 mL) for 20 hours due to the low solubility of these materials under standard conditions.

To demonstrate the utility of the products, we further investigated transformations of these fused indazoles (Scheme 2). Thiolation and etherification of **2a** occurred smoothly in the presence of $BF_3 \cdot Et_2O$ with thiols and methyl alcohol, respectively.[28] Moreover, esterification of the tertiary alcohol with acetic acid provided **5** in quantitative yield. Notably, corresponding tertiary amino derivative **6** could be generated in 61% yield *via* direct amiamination with *p*-toluenesulfonamide (PTSA). These postsynthetic modifications of the formed 2*H*-indazole **2a** significantly enhance the potential value of current method.

Scheme 2. Postsynthetic Modifications of 2*H*-Indazole

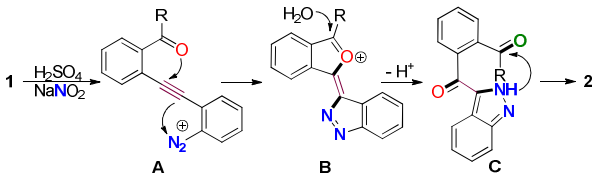


To gain insight into the reaction mechanism, a series of experiments were carried out. First, treatment of oxime (**1y**) under optimized conditions gave rise to the corresponding oxime product (**2y**) in 76% yield (eq 1), and the structure was confirmed by single-crystal X-ray diffraction analysis.[27] These results revealed that the "O" on the carbonyl group of the generated product **2** came from the "O" on carbonyl group of corresponding material **1**, which was also consisted with the previously reported mechanism of alkyne carbonylation under transition-metal catalysis.[20] Considering the possibility of a stepwise cyclization mechanism of this cascade reaction, carbonyl substrates with weaker eletrophilicity (**1z** and **1A**) were applied to the current conditions, and both *exo*- or/and *endo-dig* mono-cyclization products **7** and **8** (eq 2 and eq 3), which might be the intermediate or derivative of the intermediate, were isolated and characterized.[27] In addition, no reaction occurred with substrate **1B** without the amino group under standard conditions (eq 4, and see Figure S1 for details), or with model substrate **1a** in the absence of sodium nitrite (see Figure S2 for details), indicating that the formation of diazonium salt should be the initial step in this reaction. The formation of 6-*endo-dig* cyclization product **8C** from substrate **1C** without the carbonyl group under standard conditions further confirmed that the diazonium salt was likely involved in the catalytic cycle (eq 5, 80% yield),[24] and the longer reaction time (21 h vs 7 h) also supporting the synergistic effect of the neighboring carbonyl group for the acceleration of the cyclization step. The competition reaction between azidation and the designed cyclization process with in situ generated diazonium salt in the presence of NaN_3 was conducted, and the azidation product **9** was isolated in 95% yields after 1 hour (eq 6).[29] These observations implied that the diazonium salt formation was not the rate-determining step in the cascade cyclization reaction.



On the basis of the above investigations and the previous reports,[20,24] a possible mechanism is described in Scheme 3. Initially, the diazonium salt **A** was generated from **1** under acidic condition. Subsequently, a dual 5-*exo*-*dig* cyclization of **A** followed by hydrolysis delivered 2*H*-indazole **C** *via* **B**,[20] and this process was accelerated by the acid (see Figure S3-S7 for details).[26] Moreover, the assistance of the neighboring carbonyl group for the selective 5-*exo*-*dig* cyclization is essential and unique in comparison with reported 6-*endo*-*dig* cyclization process (eq 5),[24] which also ensured to capture the diazonium salt before its decompsotion.[25d,] Finally, nucleophilic addition with the newly installed carbonyl group led to the desired polycyclic product **2**. In the case of R = electron-donating-group (EDG), the nucleophilic addition of the corresponding carbonyl group with weaker eletrophilicity became slow or not favored (eq 2 and eq 3), and 1,5-*H* shift after attack of water would form the thermodynamically more stable 1*H*-indazoles **7**, which would not yield to the cyclized product **2** *via* **C** under these conditions.[24a,b]

Scheme 3. Proposed Reaction Mechanism



In summary, we have developed an acid-promoted tandem bicyclization reaction of diaryl alkynes, which provides a straightforward access to the synthesis of polycyclic 2*H*-indazoles without column chromatography in high to excellent yields. The salient features of this reaction include readily available starting materials, good functional group compatibility, mild and transition-metal-free reaction conditions, ease in further transformations, and high bond-formation efficiency with the formation of two C-N bonds, one C-O bond and one C=O bond in one operation. Notably, this is the only example for the synthesis of 2*H*-indazoles with in situ generated diazonium salt as the nitrogen source. Further investigation of catalytic alkyne bifunctionalization for the diversity synthesis of heterocycles is currently under way in our laboratory.

EXPERIMENTAL SECTION

General. All reactions were carried out under open air. Solvents were dried and degassed by the standard methods. Flash column chromatography was performed using silica gel (300-400 mesh). Analytical thin-layer chromatography was performed using glass plates pre-coated with 200-300 mesh silica gel impregnated with a fluorescent indicator (254 nm and 365 nm). ^{1}H NMR, ^{19}F NMR, and ^{13}C NMR spectra were recorded on 400 or 600 MHz spectrometers in $CDCl_3$ or d^6-DMSO; chemical shifts were reported in ppm with the solvent signals as reference, and coupling constants (*J*) were given in Hertz. The peak information was described as: s = singlet, br = broad, d = doublet, t = triplet, q = quartet, m = multiplet, comp = composite. High-resolution mass spectra (HRMS) were recorded on a commercial apparatus (ESI or CI Source).

General Procedures for the Preparation of Diaryl Alkynes 1. To a 50 mL oven-dried flask containing a magnetic stirring bar, $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol, 1.0 mol %), CuI (1.9 mg, 0.01 mmol, 0.5 mol %), 2-iodoaniline derivative (2.0 mmol), *ortho*-carbonyl phenylacetylene (2.2 mmol), and Et_3N (10 mL) were added in

sequence under argon atmosphere at room temperature. The resulting reaction mixture was stirred for 5 h under these conditions, then the reaction mixture was filtered through a short pad of celite and the solid was washed with EtOAc (10 mL ~~X~~× 2). The combined organic phase was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10:1) to afford pure products **1** in > 80% yields.

*Synthesis of **1n** and **1o**.* To a 50 mL oven-dried flask containing a magnetic stirring bar, $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol, 1.0 mol %), CuI (1.9 mg, 0.01 mmol, 0.5 mol %), 1-(2-iodophenyl)ethanone derivative (2.0 mmol), 2-ethynylaniline (2.2 mmol), and Et_3N (15 mL) were added in sequence under argon atmosphere at room temperature. The resulting reaction mixture was stirred for 5 h under these conditions, then the reaction mixture was filtered through a short pad of celite and the solid was washed with EtOAc (10 mL × 2). The combined organic phase was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10:1) to afford pure products **1** in > 70% yields (**1n** and **1o**).

*Synthesis of **1y**.* To a 50 mL oven-dried flask containing a magnetic stirring bar, 1-(2-ethynylphenyl)ethanone (720 mg, 5.0 mmol), $MeONH_2 \cdot HCl$ (543 mg, 6.5 mmol), NaOAc (533 mg, 6.5 mmol), and MeOH (10 mL) were added in sequence. The reaction mixture reflux at 70 ºC for 7 h. After cooling to the room temperature, the reaction mixture was extracted with ethyl acetate (15 mL × 3). The organic layers were combined, and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum after filtration, and the residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10:1) to afford corresponding *O*-methyl oxime as brown oil in 65% yield. And the compound **1y** was prepared in 73% yield following the general procedures for the preparation of **1** with this obtained *O*-methyl oxime as starting material.

*1-(2-((2-Aminophenyl)ethynyl)phenyl)ethanone (**1a**).* 423 mg, 90% yield; Yellow solid; mp = 118 – 119 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.83 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.51 – 7.47 (m, 1H), 7.39 – 7.35 (m, 2H), 7.15 – 7.13 (m, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 6.69 – 6.66 (m, 1H), 5.05 (br, 2H), 2.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.8, 149.9, 138.0, 134.2, 132.1, 131.9, 130.4, 130.0, 127.5, 122.6, 117.1, 114.2, 107.1, 94.4, 92.0, 28.8; HRMS (ESI-TOF) m/z:

$[M+H]^+$ Calcd for $C_{16}H_{14}NO$ 236.1075; Found 236.1088.

*1-(2-((2-Amino-3-methylphenyl)ethynyl)phenyl)ethanone (**1b**)*. 408 mg, 82% yield; Yellow solid; mp = 106 – 107 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.86 – 7.84 (m, 1H), 7.69 – 7.67 (m, 1H), 7.53 – 7.49 (m, 1H), 7.41 – 7.37 (m, 1H), 7.28 – 7.26 (m, 1H), 7.06 – 7.04 (m, 1H), 6.64 – 6.60 (m, 1H), 5.04 (br, 2H), 2.68 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.8, 148.2, 138.1, 134.3, 132.0, 131.4, 129.97, 129.96, 127.5, 122.8, 121.5, 116.9, 106.8, 94.2, 92.5, 28.8, 17.7; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{16}NO$ 250.1232; Found 250.1235.

*1-(2-((2-Amino-4-methylphenyl)ethynyl)phenyl)ethanone (**1c**)*. 398 mg, 80% yield; Yellow solid; mp = 109 - 110 ºC; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.83 – 7.81 (m, 1H), 7.65 – 7.63 (m, 1H), 7.49 – 7.46 (m, 1H), 7.37 – 7.34 (m, 1H), 7.25 – 7.23 (m, 1H), 6.54 (s, 1H), 6.49 (d, J = 7.8 Hz, 1H), 4.95 (br, 2H), 2.66 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.9, 149.8, 140.9, 138.1, 134.2, 132.0, 131.9, 129.9, 127.4, 122.9, 118.5, 114.9, 104.5, 94.0, 92.5, 28.9, 21.9; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{16}NO$ 250.1232; Found 250.1229.

*1-(2-((2-Amino-5-methylphenyl)ethynyl)phenyl)ethanone (**1d**)*. 398 mg, 80% yield; Yellow solid; mp = 116 – 117 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.83 (d, J = 7.9 Hz, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.52 – 7.48 (m, 1H), 7.40 – 7.36 (m, 1H), 7.18 (s, 1H), 6.97 (d, J = 8.1 Hz, 1H), 6.65 (d, J = 8.2 Hz, 1H), 4.83 (br, 2H), 2.68 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.9, 147.5, 138.3, 134.2, 132.2, 131.9, 131.4, 129.8, 127.6, 126.5, 122.7, 114.5, 107.2, 94.2, 92.3, 28.9, 20.4; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{16}NO$ 250.1232; Found 250.1230.

*1-(2-((2-Amino-3,5-dimethylphenyl)ethynyl)phenyl)ethanone (**1e**)*. 405 mg, 77% yield; Yellow solid; mp = 85 – 86 ºC; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.84 (d, J = 7.9 Hz, 1H), 7.67 – 7.64 (m, 1H), 7.51 – 7.48 (m, 1H), 7.39 – 7.36 (m, 1H), 7.09 (s, 1H), 6.89 (s, 1H), 4.85 (br, 2H), 2.68 (s, 3H), 2.22 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.9, 145.9, 138.2, 134.3, 132.6, 131.9, 129.9, 127.5, 126.1, 122.8, 121.7, 106.9, 94.0, 92.8, 28.9, 20.4, 17.7; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{18}NO$ 264.1388; Found 264.1385.

*1-(2-((2-Amino-5-fluorophenyl)ethynyl)phenyl)ethanone (**1f**)*. 410 mg, 81% yield;

Yellow solid; mp = 166 – 167 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.86 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.54 – 7.50 (m, 1H), 7.43 – 7.39 (m, 1H), 7.08 – 7.05 (m, 1H), 6.91 – 6.86 (m, 1H), 6.67 – 6.64 (m, 1H), 4.90 (s, 2H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.6, 154.92 (d, *J* = 234.8 Hz), 146.4, 138.2, 134.5, 132.1, 130.0, 128.0, 122.2, 117.8 (d, *J* = 6.1 Hz), 117.5 (d, *J* = 6.5 Hz), 115.2 (d, *J* = 8.0 Hz), 107.8 (d, *J* = 9.4 Hz), 95.0, 90.8, 28.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) – 28.17; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{13}NOF$ 254.0981; Found 254.0979.

1-(2-((2-Amino-5-chlorophenyl)ethynyl)phenyl)ethanone ***(1g)***. 495 mg, 92% yield; Yellow solid; mp = 160 – 161 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.87 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.54 – 7.50(m, 1H), 7.43 – 7.39 (m, 1H), 7.32 (d, *J* = 2.1 Hz, 1H), 7.10 – 7.07 (m, 1H), 6.65 (d, *J* = 8.7 Hz, 1H), 5.11 (br, 2H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.6, 148.6, 138.0, 134.4, 132.1, 131.3, 130.4, 130.1, 127.9, 122.3, 121.3, 115.3, 108.5, 95.3, 90.6, 28.7; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{13}NOCl$ 270.0686; Found 270.0683.

1-(2-((2-Amino-5-bromophenyl)ethynyl)phenyl)ethanone ***(1h)***. 501 mg, 80% yield; Yellow solid; mp = 162 – 163 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.86 (d, *J* = 7.9 Hz, 1H), 7.66 – 7.64 (m, 1H), 7.54 – 7.50 (m, 1H), 7.46 (d, *J* = 2.3 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.22 – 7.20 (m, 1H), 6.60 (d, *J* = 8.7 Hz, 1H), 5.13 (br, 2H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.6, 149.0, 137.9, 134.4, 134.1, 133.1, 132.1, 130.1, 127.9, 122.2, 115.7, 109.0, 108.0, 95.4, 90.4, 28.7; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{13}NOBr$ 314.0181; Found 314.0182.

1-(2-((2-Amino-5-(trifluoromethyl)phenyl)ethynyl)phenyl)ethanone ***(1i)***. 515 mg, 85% yield; Yellow solid; mp = 141 – 142 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.89 (d, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.62 (s, 1H), 7.56 – 7.52 (m, 1H), 7.44 – 7.41 (m, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 6.74 (d, *J* = 8.6 Hz, 1H), 5.51 (br, 2H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.5, 152.5, 137.8, 134.5, 132.3, 130.3, 129.6 (q, *J* = 3.9 Hz), 128.0, 127.2 (q, *J* = 3.6 Hz), 124.7 (q, *J* = 270.6 Hz), 122.2, 118.9 (q, *J* = 33.0 Hz), 113.6, 106.7, 95.4, 90.4, 28.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) – 61.34; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{13}NOF_3$ 304.0949;

Found 304.0951.

*1-(2-((2-Amino-5-methoxyphenyl)ethynyl)phenyl)ethanone (**1j**)*. 440 mg, 83% yield; Yellow solid; mp = 81 – 82 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.84 – 7.81 (m, 1H), 7.68 – 7.65 (m, 1H), 7.51 – 7.47 (m, 1H), 7.40 – 7.38 (m, 1H), 6.91 (d, *J* = 2.9 Hz, 1H), 6.81 – 6.78 (m, 1H), 6.68 (d, *J* = 8.8 Hz, 1H), 3.75 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.8, 151.4, 144.2, 138.3, 134.3, 131.9, 129.8, 127.7, 122.4, 118.3, 115.8, 115.6, 107.7, 94.4, 91.9, 56.0, 28.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{16}NO_2$ 266.1181; Found 266.1189.

*1-(2-((2-Amino-5-(phenylethynyl)phenyl)ethynyl)phenyl)ethanone (**1k**)*. 543 mg, 81% yield; Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.82 (d, *J* = 7.9 Hz, 1H), 7.66 (d, *J* = 7.1 Hz, 1H), 7.61 (d, *J* = 1.8 Hz, 1H), 7.55 – 7.53 (m, 2H), 7.49 – 7.46 (m, 1H), 7.36 – 7.30 (comp, 5H), 6.68 (d, *J* = 8.4 Hz, 1H), 5.41 (br, 2H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.5, 150.0, 137.5, 135.4, 134.2, 133.7, 132.0, 131.3, 130.1, 128.3, 127.71, 127.65, 123.8, 122.2, 114.0, 111.1, 107.0, 94.9, 90.9, 89.8, 87.3, 28.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{18}NO$ 336.1388; Found 336.1396..

*1-(2-((2-Aminonaphthalen-1-yl)ethynyl)phenyl)ethanone (**1l**)*. 462 mg, 81% yield; Yellow solid; mp = 152 – 153 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.22 (d, *J* = 8.0 Hz, 1H), 7.91 – 7.89 (m, 1H), 7.84 – 7.82 (m, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.58 – 7.54 (m, 1H), 7.52 – 7.48 (m, 1H), 7.43 – 7.38 (m, 1H), 7.27 – 7.23 (m, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 2.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.6, 149.6, 137.4, 134.8, 134.3, 132.1, 130.8, 130.2, 128.4, 127.4, 127.3, 127.1, 124.3, 123.3, 122.6, 117.1, 99.9, 98.9, 91.0, 28.7; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{16}NO$ 286.1232; Found 286.1234.

*1-(2-((4-Amino-4'-methoxybiphenyl-3-yl)ethynyl)phenyl)ethanone (**1m**)*. 552 mg, 81% yield; Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.85 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.60 (d, *J* = 2.1 Hz, 1H), 7.52 – 7.47 (comp, 3H), 7.40 – 7.36 (m, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 1H), 5.12 (br, 2H), 3.84 (s, 3H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.7, 158.5, 148.8, 138.0, 134.3, 133.3, 132.0, 129.98, 129.95, 128.9, 127.6, 127.4, 122.6, 114.7, 114.2, 107.5, 94.5,

92.0, 55.4, 28.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{20}NO_2$ 342.1494; Found 342.1498.

*1-(2-((2-Aminophenyl)ethynyl)-4-methylphenyl)ethanone (**1n**)*. 378 mg, 76% yield; Yellow solid; mp = 106 – 107 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.78 (d, *J* = 8.1 Hz, 1H), 7.50 (s, 1H), 7.38 – 7.36 (m, 1H), 7.21 – 7.15 (m, 2H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.75 – 6.71 (m, 1H), 2.65 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.2, 149.8, 142.8, 135.4, 134.9, 132.2, 130.3, 128.5, 122.8, 117.3, 114.3, 107.4, 100.1, 94.8, 91.6, 28.6, 21.4; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{16}NO$ 250.1232; Found 250.1237.

*1-(2-((2-Aminophenyl)ethynyl)-4-methoxyphenyl)ethanone (**1o**)*. 387 mg, 73% yield; Yellow solid; mp = 131 – 132 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.82 (d, *J* = 8.8 Hz, 1H), 7.39 – 7.36 (m, 1H), 7.17 – 7.13 (m, 2H), 6.88 – 6.86 (m, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.68 – 6.64 (m, 1H), 3.88 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.8, 162.2, 150.2, 132.6, 132.2, 130.7, 130.5, 125.0, 118.5, 117.0, 114.2, 113.9, 107.0, 94.8, 92.1, 55.7, 28.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{16}NO_2$ 266.1181; Found 266.1188.

*1-(2-((2-Aminophenyl)ethynyl)phenyl)-2-phenylethanone (**1p**)*. 516 mg, 83% yield; Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.83 – 7.81 (m, 1H), 7.68 – 7.66 (m, 1H), 7.49 - 7.45 (m, 1H), 7.39 – 7.27 (comp, 7H), 7.18 – 7.14 (m, 1H), 6.72 – 6.67 (m, 2H), 4.34 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 199.0, 149.7, 138.3, 134.5, 134.1, 132.1, 131.7, 130.4, 129.5, 129.3, 128.7, 127.5, 127.0, 122.8, 117.2, 114.2, 107.1, 94.1, 92.0, 47.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{18}NO$ 312.1388; Found 312.1386.

*1-(2-((2-Aminophenyl)ethynyl)phenyl)propan-1-one (**1q**)*. 398 mg, 80% yield; Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.79 – 7.77 (m, 1H), 7.67 – 7.65 (m, 1H), 7.49 – 7.45 (m, 1H), 7.39 – 7.34 (m, 2H), 7.17 – 7.13 (m, 1H), 6.73 – 6.71 (m, 1H), 6.69 – 6.65 (m, 1H), 4.76 (br, 2H), 3.03 (q, *J* = 7.2 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 202.2, 149.8, 138.7, 134.1, 132.1, 131.5, 130.3, 128.8, 127.6, 122.4, 117.2, 114.2, 107.2, 94.2, 91.6, 34.1, 8.6; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{16}NO$ 250.1232; Found 250.1228 .

*(2-((2-Aminophenyl)ethynyl)phenyl)(phenyl)methanone (**1r**)*. 475 mg, 80% yield; Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.86 (d, *J* = 7.6 Hz, 2H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.54 – 7.45 (comp, 4H), 7.41 – 7.37 (m, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.10 – 7.06 (m, 1H), 6.62 – 6.59 (m, 2H), 4.36 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.8, 149.0, 140.0, 137.5, 133.3, 133.1, 132.1, 130.8, 130.5, 130.2, 129.5, 128.6, 127.4, 122.8, 117.3, 114.2, 107.1, 92.8, 91.8; HRMS (TOF MS ESI$^+$) calculated for $C_{21}H_{16}NO$ $[M+H]^+$: 298.1232, found 298.1231.

*(2-((2-Aminophenyl)ethynyl)phenyl)(p-tolyl)methanone (**1s**)*. 529 mg, 85% yield; Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.78 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.41 – 7.38 (m, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 1H), 7.11 – 7.07 (m, 1H), 6.64 – 6.60 (m, 2H), 4.08 (br, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.5, 149.0, 144.3, 140.4, 134.8, 132.9, 132.1, 130.7, 130.5, 130.1, 129.3, 129.2, 127.4, 122.6, 117.3, 114.2, 107.1, 92.8, 91.6, 21.8; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{18}NO$ 312.1388; Found 312.1389.

*(2-((2-Aminophenyl)ethynyl)phenyl)(4-bromophenyl)methanone (**1t**)*. 608 mg, 81% yield; Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.72 – 7.68 (comp, 3H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.54 – 7.50 (m, 1H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.41 – 7.37 (m, 1H), 7.14 – 7.12 (m, 1H), 7.11 – 7.07 (m, 1H), 6.64 – 6.60 (m, 2H), 4.43 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.7, 149.0, 139.3, 136.2, 133.1, 132.1, 131.87, 131.85, 131.0, 130.3, 129.4, 128.5, 127.5, 122.8, 117.4, 114.2, 106.9, 92.7, 92.1; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{15}NOBr$ 376.0337; Found 376.0325.

*(2-((2-Aminophenyl)ethynyl)phenyl)(4-(trifluoromethyl)phenyl)methanone (**1u**)*. 584 mg, 80% yield; Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.94 (d, *J* = 8.2 Hz, 2H), 7.74 – 7.70 (comp, 3H), 7.57 – 7.54 (m, 1H), 7.50 (d, *J* = 7.1 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.11 – 7.08 (m, 2H), 6.66 – 6.60 (m, 2H), 4.23 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.6, 149.0, 140.6, 138.8, 134.4 (d, *J* = 32.7 Hz), 133.4, 132.1, 131.5, 130.6, 130.4, 129.9, 127.6, 125.6 (q, *J* = 3.8 Hz), 123.7 (d, *J* = 272.8 Hz), 123.2, 117.4, 114.3, 106.8, 92.7, 92.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ – 63.05; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{15}NOF_3$ 366.1106; Found 366.1112.

*(2-((2-Aminophenyl)ethynyl)phenyl)(2-methoxyphenyl)methanone (**1v**)*. 562 mg, 86%

yield; Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.68 – 7.66 (m, 1H), 7.51 – 7.45 (comp, 4H), 7.32 – 7.27 (m, 1H), 7.26 – 7.24 (m, 1H), 7.13 – 7.09 (m, 1H), 7.06 – 7.02 (m, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.67 – 6.62 (m, 2H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.1, 158.1, 149.6, 139.8, 133.5, 132.9, 132.2, 131.3, 131.1, 130.5, 130.2, 129.1, 127.2, 122.7, 120.7, 117.1, 114.1, 111.8, 107.3, 94.0, 91.6, 55.8; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{18}NO_2$ 328.1338; Found 328.1330.

(2-((2-Aminophenyl)ethynyl)phenyl)(3-methoxyphenyl)methanone ***(1w)***. 542 mg, 83% yield; Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.69 – 7.67 (m, 1H), 7.53 – 7.48 (m, 2H), 7.44 – 7.43 (m, 1H), 7.40 – 7.35 (comp, 3H), 7.18 – 7.06 (comp, 3H), 6.64 – 6.59 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.6, 159.8, 149.0, 140.0, 138.8, 133.1, 132.2, 130.8, 130.2, 129.54, 129.49, 127.4, 123.6, 122.8, 119.9, 117.4, 114.31, 114.26, 107.1, 92.8, 91.7, 55.7; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{18}NO_2$ 328.1338; Found 328.1337.

(E)-1-(2-((2-Aminophenyl)ethynyl)phenyl)-3-phenylprop-2-en-1-one ***(1x)***. 549 mg, 85% yield; Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.75 – 7.73 (m, 1H), 7.70 – 7.66 (m, 2H), 7.60 – 7.58 (m, 2H), 7.53 – 7.49 (m, 1H), 7.44 – 7.37 (comp, 5H), 7.30 – 7.28 (m, 1H), 7.13 – 7.09 (m, 1H), 6.68 – 6.66 (m, 1H), 6.64 – 6.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.1, 149.3, 145.6, 140.3, 134.7, 133.5, 132.1, 131.2, 130.8, 130.3, 129.1, 128.9, 128.6, 127.7, 125.3, 122.6, 117.3, 114.2, 107.1, 93.4, 92.1; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{18}NO$ 324.1388; Found 324.1384.

(E)-1-(2-((2-Aminophenyl)ethynyl)phenyl)ethanone O-methyl oxime ***(1y)***. 385 mg, 73% yield; Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.59 – 7.57 (m, 1H), 7.40 – 7.33 (comp, 4H), 7.17 – 7.12(m, 1H), 6.73 – 6.70 (m, 2H), 4.32 (br, 2H), 4.02 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.1, 148.1, 139.7, 132.8, 132.1, 130.0, 128.6, 128.4, 128.3, 121.9, 117.9, 114.4, 107.8, 93.4, 90.2, 61.9, 16.3; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{17}N_2O$ 265.1341; Found 265.1352.

(2-((2-Aminophenyl)ethynyl)phenyl)(4-methoxyphenyl)methanone ***(1z)***. 536 mg, 82% yield; Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.85 (d, *J* = 8.9 Hz, 2H), 7.66

(d, J = 7.7 Hz, 1H), 7.51 – 7.45 (m, 2H), 7.40 – 7.36 (m, 1H), 7.16 – 7.14 (m, 1H), 7.09 – 7.05 (m, 1H), 6.94 (d, J = 8.9 Hz, 2H), 6.64 – 6.59 (comp, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.6, 163.9, 149.0, 140.8, 132.9, 132.8, 132.1, 130.3, 130.2, 130.1, 128.8, 127.4, 122.4, 117.3, 114.2, 113.9, 107.1, 92.8, 91.5, 55.7; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{18}NO_2$ 328.1338; Found 328.1340.

*Methyl 2-((2-aminophenyl)ethynyl)benzoate (**1A**)*.[30a] 477 mg, 95% yield; Yellow solid; mp = 57 - 58 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.03 – 8.01 (m, 1H), 7.68 – 7.66 (m, 1H), 7.53 – 7.48 (m, 1H), 7.40 – 7.33 (m, 2H), 7.17 – 7.13 (m, 1H), 6.73 – 6.66 (m, 2H), 5.04 (br, 2H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.4, 149.8, 133.8, 132.13, 132.10, 130.6, 130.3, 130.2, 127.4, 124.7, 117.1, 114.2, 107.3, 93.7, 92.7, 52.4; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{14}NO_2$ 252.1025; Found 252.1019.

*1-(2-(Phenylethynyl)phenyl)ethanone (**1B**)*.[30b] 425 mg, 97% yield; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.77 – 7.75 (m, 1H), 7.64 – 7.62 (m, 1H), 7.57 – 7.54 (m, 2H), 7.50 – 7.46 (m, 1H), 7.42 – 7.40 (m, 1H), 7.38 – 7.35 (m, 3H), 2.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 200.5, 140.9, 134.0, 131.6, 131.4, 128.9, 128.8, 128.6, 128.4, 123.0, 121.8, 95.1, 88.6, 30.1. HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{12}O$ 220.0888; Found 220.0892.

*2-(Phenylethynyl)aniline (**1C**)*.[30c] 374 mg, 97% yield; Pale yellow solid; mp = 87 - 89 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.55 – 7.53 (m, 2H), 7.39 – 7.37 (m, 1H), 7.36 – 7.32 (m, 3H), 7.17 – 7.12 (m, 1H), 6.79 – 6.74 (m, 2H), 4.74 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 147.2, 132.3, 131.6, 129.9, 128.5, 128.4, 123.4, 118.6, 114.9, 108.6, 95.0, 85.9. HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{12}N$ 194.0970; Found 194.0978.

General Procedure for the Acid-promoted Bicyclization. Method A. To a 10 mL oven-dried vial with a magnetic stirring bar, **1** (0.2 mmol), and aqueous sulfuric acid solution (0.4 mL, 1.7 M, 3.4 eq) in DMF:H_2O = 1:3 (2.0 mL), was added an aqueous solution of $NaNO_2$ (18 mg, 1.3 eq, in 0.3 mL H_2O) slowly at 0 °C for 0.5 h. The reaction mixture was stirred for 7 h and the reaction temperature was allowed to warm up to room temperature slowly. When the reaction was completed (monitored by

TLC), water (30 mL) was added to the reaction mixture and the resulting mixture was standing for 1 h. Then solid was precipitated out and filtered by Buchner funnel, washed with water and *n*-hexane in sequence and dried under infrared lamp for 7 h to give the pure product **2** in high yields.

Method B. To a 10 mL oven-dried vial with a magnetic stirring bar, **1** (0.2 mmol), and aqueous sulfuric acid solution (0.4 mL, 1.7 M, 3.4 eq) in DMF:H_2O = 3:1 (2.0 mL), was added an aqueous solution of $NaNO_2$ (18 mg, 1.3 eq, in 0.3 mL H_2O) slowly at 0 °C for 0.5 h. The reaction mixture was stirred for 20 h and the reaction temperature was allowed to warm up to room temperature slowly. When the reaction was completed (monitored by TLC), water (30 mL) was added to the reaction mixture and the resulting mixture was standing for 1 h. Then solid was precipitated out and filtered by Buchner funnel, washed with water and *n*-hexane in sequence and dried under infrared lamp for 20 h to give the pure product **2** in high yields.

*7-Hydroxy-7-methylindazolo[2,3-b]isoquinolin-12(7H)-one (**2a**)*. 50 mg, 95% yield (Method A). Yellow solid; mp = 192 – 193 ºC; ^{1}H NMR (400 MHz, *d*^{6}-DMSO) δ (ppm) 8.28 (d, *J* = 8.1 Hz, 1H), 8.21 (d, *J* = 7.7 Hz, 1H), 8.00 – 7.98 (comp, 3H), 7.89 – 7.85 (m, 1H), 7.71 – 7.67 (m, 1H), 7.54 – 7.44 (m, 2H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, *d*^{6}-DMSO) δ (ppm) 174.3, 147.7, 144.7, 134.2, 129.1, 128.4, 127.7, 127.5, 127.3, 126.2, 125.4, 121.3, 121.2, 118.8, 86.8, 32.1; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{13}N_2O_2$ 265.0977; Found 265.0937.

*7-Hydroxy-4,7-dimethylindazolo[2,3-b]isoquinolin-12(7H)-one (**2b**)*. 53 mg, 95% yield (Method A). Yellow solid; mp = 172 – 173 ºC; ^{1}H NMR (400 MHz, *d*^{6}-DMSO) δ (ppm) 8.21 – 8.19 (m, 1H), 8.00 – 7.96 (m, 2H), 7.96 (s, 1H), 7.89 – 7.84 (m, 1H), 7.70 - 7.66 (m, 1H), 7.36 – 7.32 (m, 1H), 7.27 (d, *J* = 6.8 Hz, 1H), 2.69 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, *d*^{6}-DMSO) δ (ppm) 174.4, 147.9, 144.9, 134.2, 129.1, 128.6, 128.4, 128.0, 127.4, 126.5, 126.4, 125.4, 121.2, 118.6, 86.8, 32.2, 16.9; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{15}N_2O_2$ 279.1134; Found 279.1139.

*7-Hydroxy-3,7-dimethylindazolo[2,3-b]isoquinolin-12(7H)-one (**2c**)*. 50 mg, 90% yield (Method A). Yellow solid; mp = 219 – 220 ºC; ^{1}H NMR (600 MHz, *d*^{6}-DMSO) δ (ppm) 8.20 – 8.18 (m, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.97 (d, *J* = 7.5 Hz, 1H), 7.94 (s, 1H), 7.88 – 7.84 (m, 1H), 7.74 – 7.73 (m, 1H), 7.70 – 7.66 (m, 1H), 7.31 – 7.28 (m,

1H), 2.48 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (150 MHz, d^6-DMSO) δ (ppm) 174.2, 148.3, 144.8, 136.9, 134.1, 129.1, 128.8, 128.4, 127.6, 127.42, 125.4, 120.7, 119.5, 117.2, 86.6, 32.1, 21.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{15}N_2O_2$ 279.1134; Found 279.1131.

*7-Hydroxy-2,7-dimethylindazolo[2,3-b]isoquinolin-12(7H)-one (**2d**).* 50 mg, 90% yield (Method A). Yellow solid; mp = 201 – 202 ºC; ^{1}H NMR (400 MHz, d^6-DMSO) δ (ppm) 8.19 (d, *J* = 7.8 Hz, 1H), 8.04 (s, 1H), 7.97 (d, *J* = 7.9 Hz, 1H), 7.94 (s, 1H), 7.87 – 7.84 (m, 2H), 7.68 – 7.66 (m, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 2.48 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, d^6-DMSO) δ (ppm) 174.3, 146.6, 144.7, 135.9, 134.1, 129.9, 129.1, 128.5, 127.4, 127.1, 125.4, 121.7, 119.6, 118.5, 86.7, 32.2, 21.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{15}N_2O_2$ 279.1134; Found 279.1128.

*7-Hydroxy-2,4,7-trimethylindazolo[2,3-b]isoquinolin-12(7H)-one (**2e**).* 54 mg, 93% yield (Method A). Yellow solid; mp = 194 – 195 ºC; ^{1}H NMR (600 MHz, d^6-DMSO) δ (ppm) 8.18 (d, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 7.9 Hz, 1H), 7.91 (s, 1H), 7.86 – 7.83 (m, 2H), 7.68 – 7.65 (m, 1H), 7.10 (s, 1H), 2.64 (s, 3H), 2.43 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, d^6-DMSO) δ (ppm) 174.3, 146.9, 144.8, 136.2, 134.0, 129.04, 129.02, 128.5, 128.2, 127.4, 127.3, 125.3, 121.7, 117.0, 86.6, 32.2, 21.7, 16.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{17}N_2O_2$ 293.1290; Found 293.1295.

*2-Fluoro-7-hydroxy-7-methylindazolo[2,3-b]isoquinolin-12(7H)-one (**2f**).* 51 mg, 91% yield (Method A). Yellow solid; mp = 214 – 215 ºC; ^{1}H NMR (600 MHz, d^6-DMSO) δ (ppm) 8.18 (d, *J* = 7.6 Hz, 1H), 8.08 – 8.06 (m, 1H), 8.01 (s, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.89 – 7.85 (m, 2H), 7.70 – 7.67 (m, 1H), 7.45 – 7.41 (m, 1H), 2.10 (s, 3H); ^{13}C NMR (150 MHz, d^6-DMSO) δ (ppm) 174.2, 160.5 (d, *J* = 243.5 Hz), 145.0, 144.6, 134.3, 129.1, 128.3, 128.28 (d, *J* = 7.9 Hz), 127.5, 125.4, 121.6 (d, *J* = 10.2 Hz), 121.1 (d, *J* = 12.6 Hz), 118.3 (d, *J* = 28.3 Hz), 104.2 (d, *J* = 25.0 Hz), 87.1, 32.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ – 113.90; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{12}N_2O_2F$ 283.0883; Found 283.0882.

*2-Chloro-7-hydroxy-7-methylindazolo[2,3-b]isoquinolin-12(7H)-one (**2g**).* 53 mg, 89% yield (Method A). Yellow solid; mp = 222 – 223 ºC; ^{1}H NMR (400 MHz, d^6-DMSO) δ (ppm) 8.22 (m, 1H), 8.20 – 8.17 (m, 1H), 8.05 – 8.02 (m, 2H), 7.98 (d, *J*

= 7.8 Hz, 1H), 7.90 – 7.86 (m, 1H), 7.71 – 7.67 (m, 1H), 7.53 – 7.50 (m, 1H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, d^6-DMSO) δ (ppm) 174.3, 146.0, 144.7, 134.5, 130.9, 129.2, 128.2, 128.1, 127.6, 127.5, 125.5, 121.6, 121.0, 119.9, 87.2, 32.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{12}N_2O_2Cl$ 299.0587; Found 299.0592.

2-Bromo-7-hydroxy-7-methylindazolo[2,3-b]isoquinolin-12(7H)-one ***(2h)****.* 62 mg, 90% yield (Method A). Yellow solid; mp = 229 – 230 ºC; ^{1}H NMR (600 MHz, d^6-DMSO) δ (ppm) 8.38 (m, 1H), 8.18 – 8.16 (m, 1H), 8.04 (s, 1H), 7.99 – 7.95 (m, 2H), 7.89 – 7.86 (m, 1H), 7.69 – 7.66 (m, 1H), 7.61 – 7.60 (m, 1H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, d^6-DMSO) δ (ppm) 174.3, 146.1, 144.7, 134.5, 130.6, 129.20, 128.1, 127.5, 127.4, 125.5, 123.2, 122.3, 121.1, 119.2, 87.2, 32.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{12}N_2O_2Br$ 343.0082; Found 343.0070.

7-Hydroxy-7-methyl-2-(trifluoromethyl)indazolo[2,3-b]isoquinolin-12(7H)-one ***(2i)****.* 62 mg, 94% yield (Method A). Yellow solid; mp = 233 – 234 ºC; ^{1}H NMR (600 MHz, d^6-DMSO) δ (ppm) 8.57 (s, 1H), 8.21 – 8.18 (m, 2H), 8.13 (s, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.91 – 7.88 (m, 1H), 7.73 (d, J = 9.0 Hz, 1H), 7.71 – 7.68 (m, 1H), 2.14 (s, 3H); ^{13}C NMR (150 MHz, d^6-DMSO) δ (ppm) 174.4, 148.1, 144.8, 134.6, 129.2 128.0, 127.5, 127.2, 126.2 (q, J = 31.5 Hz), 125.4, 124.5 (q, J = 272.0 Hz), 122.9, 120.5, 119.63, 119.62 (q, J = 4.8 Hz), 87.5, 31.9; ^{19}F NMR (376 MHz, d^6-DMSO) δ – 60.57; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{12}N_2O_2F_3$ 333.0851; Found 333.0841.

7-Hydroxy-2-methoxy-7-methylindazolo[2,3-b]isoquinolin-12(7H)-one ***(2j)****.* 53 mg, 90% yield (Method A). Yellow solid; mp = 235 – 236 ºC; ^{1}H NMR (400 MHz, d^6-DMSO) δ (ppm) 8.18 (d, J = 7.6 Hz, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.90 – 7.84 (comp, 3H), 7.70 – 7.66 (m, 1H), 7.54 (d, J = 2.1 Hz, 1H), 7.18 – 7.15 (m, 1H), 3.90 (s, 1H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, d^6-DMSO) δ (ppm) 174.1, 158.3, 144.6, 144.1, 134.0, 129.0, 128.4, 127.4, 127.2, 125.2, 122.3, 121.4, 120.3, 98.0, 86.5, 55.5, 32.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{15}N_2O_3$295.1083; Found 295.1094.

7-Hydroxy-7-methyl-2-(phenylethynyl)indazolo[2,3-b]isoquinolin-12(7H)-one ***(2k)****.* 62 mg, 85% yield (Method B). Yellow solid; mp = 218 – 219 ºC; ^{1}H NMR (400 MHz, d^6-DMSO) δ (ppm) 8.45 – 8.44 (m, 1H), 8.22 – 8.20 (m, 1H), 8.04 – 7.98 (comp, 3H),

7.90 – 7.86 (m, 1H), 7.71 – 7.67 (m, 1H), 7.65 – 7.60 (m, 3H), 7.47 – 7.44 (m, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, *d*^{6}-DMSO) δ (ppm) 174.3, 146.8, 144.7, 134.4, 131.5, 129.9, 129.2, 128.9, 128.8, 128.2, 127.9, 127.5, 125.5, 124.7, 122.3, 121.0, 119.8, 119.4, 90.2, 89.8, 87.1, 31.9; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{17}N_2O_2$ 365.1290; Found 365.1301.

*9-Hydroxy-9-methylbenzo[4,5]indazolo[2,3-b]isoquinolin-14(9H)-one (**2l**)*. 49 mg, 78% yield (Method B). Yellow solid; mp = 218 – 219 ºC; ^{1}H NMR (400 MHz, *d*^{6}-DMSO) δ (ppm) 9.93 – 9.91 (m, 1H), 8.34 – 8.32 (m, 1H), 8.04 – 7.99 (comp, 3H), 7.93 – 7.87 (comp, 3H), 7.76 – 7.64 (comp, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, *d*^{6}-DMSO) δ (ppm) 174.8, 146.9, 144.1, 134.3, 131.9, 130.5, 129.7, 129.2, 128.9, 128.7, 127.6, 127.04, 127.03, 126.96, 126.95, 126.3, 118.7, 117.8, 86.9, 32.2; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{14}N_2O_2Na$ 337.0953; Found 337.0940.

*7-Hydroxy-2-(4-methoxyphenyl)-7-methylindazolo[2,3-b]isoquinolin-12(7H)-one (**2m**)*. 62 mg, 84% yield (Method B). Yellow solid; mp = 240 – 241 ºC; ^{1}H NMR (400 MHz, *d*^{6}-DMSO) δ (ppm) 8.41 (m, 1H), 8.22 – 8.20 (m, 1H), 8.04 (d, *J* = 8.9 Hz, 1H), 8.00 – 7.98 (m, 2H), 7.90 – 7.85 (m, 1H), 7.82 – 7.79 (m, 1H), 7.73 – 7.68 (m, 3H), 7.09 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, *d*^{6}-DMSO) δ (ppm) 174.2, 159.1, 146.9, 144.7, 138.0, 134.2, 132.4, 129.1, 128.4, 128.2, 127.9, 127.4, 127.2, 125.4, 122.0, 119.3, 117.3, 114.6, 86.8, 55.2, 32.1; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{19}N_2O_3$ 371.1396; Found 371.1383.

*7-Hydroxy-7,10-dimethylindazolo[2,3-b]isoquinolin-12(7H)-one (**2n**)*. 51 mg, 91% yield (Method A). Yellow solid; mp = 189 – 190 ºC; ^{1}H NMR (400 MHz, *d*^{6}-DMSO) δ (ppm) 8.28 – 8.26 (m, 1H), 7.99 – 7.96 (m, 2H), 7.91 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.68 – 7.66 (m, 1H), 7.53 – 7.43 (m, 2H), 2.46 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, *d*^{6}-DMSO) δ (ppm) 174.4, 147.6, 142.1, 138.7, 135.0, 128.2, 127.8, 127.4, 127.2, 126.1, 125.3, 121.2, 118.7, 86.7, 32.1, 20.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{15}N_2O_2$ 279.1134; Found 279.1146.

*7-Hydroxy-10-methoxy-7-methylindazolo[2,3-b]isoquinolin-12(7H)-one (**2o**)*. 55 mg, 94% yield (Method A). Yellow solid; mp = 207 – 208 ºC; ^{1}H NMR (400 MHz, *d*^{6}-DMSO) δ (ppm) 8.27 – 8.25 (m, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.7 Hz,

1H), 7.87 (s, 1H), 7.63 (d, *J* = 2.8 Hz, 1H), 7.53 – 7.42 (comp, 3H), 3.91 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, *d*^{6}-DMSO) δ (ppm) 174.1, 159.5, 147.7, 137.2, 129.7, 129.1, 127.8, 127.3, 126.2, 121.3, 121.2, 118.8, 108.0, 86.7, 55.6, 32.1; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{15}N_2O_3$ 295.1083; Found 295.1089.

7-Benzyl-7-hydroxyindazolo[2,3-b]isoquinolin-12(7H)-one (***2p***). 57 mg, 84% yield (Method B). Yellow solid; mp = 120 – 124 ºC; ^{1}H NMR (400 MHz, *d*^{6}-DMSO) δ (ppm) 8.42 (s, 1H), 8.13 – 8.06 (comp, 3H), 7.97 – 7.95 (m, 1H), 7.93 – 7.89 (m, 1H), 7.66 – 7.62 (m, 1H), 7.56 – 7.52 (m, 1H), 7.45 – 7.41 (m, 1H), 6.92 – 6.88 (m, 1H), 6.74 – 6.70 (m, 2H), 5.94 (d, *J* = 7.2 Hz, 2H), 3.94 (d, *J* = 12.9 Hz, 1H), 3.68 (d, *J* = 12.9 Hz); ^{13}C NMR (100 MHz, *d*^{6}-DMSO) δ (ppm) 173.9, 147.7, 142.6, 134.0, 133.5, 129.6, 129.28, 129.26, 128.8, 127.8, 127.6, 127.5, 127.0, 126.2, 124.9, 121.2, 120.8, 118.7, 90.0, 51.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{17}N_2O_2$ 341.1290; Found 341.1294.

Ethyl-7-hydroxyindazolo[2,3-b]isoquinolin-12(7H)-one (***2q***). 48 mg, 86% yield (Method B). Yellow solid; mp = 157 – 158 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (d, *J* = 8.3 Hz, 1H), 8.13 – 8.11 (m, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.71 – 7.67 (m, 1H), 7.47 – 7.42 (m, 2H), 7.38 – 7.35 (m, 1H), 7.02 (s, 1H), 2.83 (m, 1H), 2.45 (m, 1H), 0.15 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.1, 148.4, 141.6, 134.2, 130.1, 129.7, 129.3, 128.0, 126.7, 126.4, 126.1, 122.1, 121.5, 118.1, 90.7, 39.6, 8.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{15}N_2O_2$ 279.1134; Found 279.1129.

7-Hydroxy-7-phenylindazolo[2,3-b]isoquinolin-12(7H)-one (***2r***). 49 mg, 75% yield (Method B). Yellow solid; mp = 171 – 172 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.34 – 8.31 (m, 1H), 8.22 – 8.20 (m, 1H), 7.77 – 7.74 (m, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.47 – 7.43 (m, 1H), 7.42 – 7.37 (m, 2H), 7.26 – 7.22 (m, 5H), 5.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.1, 148.9, 143.3, 142.9, 134.3, 129.6, 129.4, 129.0, 128.6, 128.04, 127.98, 126.8, 126.4, 124.8, 122.0, 121.9, 118.9, 89.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{15}N_2O_2$ 327.1134; Found 327.1136.

7-Hydroxy-7-p-tolylindazolo[2,3-b]isoquinolin-12(7H)-one (***2s***). 48 mg, 71% yield

(Method B). Yellow solid; mp = 220 – 221 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.21 – 8.19 (m, 1H), 8.03 (d, *J* = 7.5 Hz, 1H), 7.69 – 7.65 (m, 2H), 7.52 – 7.50 (m, 1H), 7.35 – 7.30 (m, 3H), 7.10 (d, *J* = 8.2 Hz, 2H), 7.01 (d, *J* = 8.2 Hz, 2H), 6.21 (s, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.2, 148.7, 143.5, 140.3, 138.7, 134.3, 129.5, 129.0, 128.4, 128.1, 127.8, 126.6, 126.1, 124.8, 121.9, 121.8, 118.8, 89.0, 21.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{17}N_2O_2$ 341.1290; Found 341.1295.

7-(4-Bromophenyl)-7-hydroxyindazolo[2,3-b]isoquinolin-12(7H)-one (***2t***). 62 mg, 77% yield (Method B). Yellow solid; mp = 203 – 204 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.11 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 7.7 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.37 – 7.29 (comp, 5H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.18 (s, 1H); ^{13}C NMR (100 MHz, *d*^{6}-DMSO) δ (ppm) 174.3, 148.0, 144.3, 142.7, 134.4, 131.3, 129.3, 129.0, 128.8, 128.4, 128.0, 127.6, 126.6, 125.5, 121.7, 121.2, 121.1, 118.9, 88.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{14}N_2O_2Br$ 405.0239; Found 405.0230.

7-Hydroxy-7-(4-(trifluoromethyl)phenyl)indazolo[2,3-b]isoquinolin-12(7H)-one (***2u***). 67 mg, 85% yield (Method B). Yellow solid; mp = 218 – 219 ºC; ^{1}H NMR (400 MHz, *d*^{6}-DMSO) δ (ppm) 8.87 (s, 1H), 8.35 – 8.34 (m, 1H), 8.28 (d, *J* = 7.5 Hz, 1H), 7.87 – 7.85 (m, 1H), 7.78 – 7.66 (comp, 4H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.53 – 7.48 (comp, 3H); ^{13}C NMR (100 MHz, *d*^{6}-DMSO) δ (ppm) 174.3, 148.2, 147.5, 144.0, 134.5, 129.5, 129.2, 128.9, 128.6 (d, *J* = 32.0 Hz), 128.5, 127.7, 126.71, 126.68, 125.6, 125.5 (d, *J* = 3.7 Hz), 124.0 (q, *J* = 272.2 Hz), 121.3, 121.1, 118.9, 88.0; ^{19}F NMR (376 MHz, *d*^{6}-DMSO) δ – 61.18; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{14}N_2O_2F_3$ 395.1007; Found 395.1013.

7-Hydroxy-7-(2-methoxyphenyl)indazolo[2,3-b]isoquinolin-12(7H)-one (***2v***). 59 mg, 83% yield (Method B). Yellow solid; mp = 213 – 214 ºC; ^{1}H NMR (400 MHz, *d*^{6}-DMSO) δ (ppm) 8.36 (m, 1H), 8.33 – 8.31 (m, 1H), 8.29 – 8.27 (m, 1H), 8.24 – 8.22 (m, 1H), 7.82 – 7.80 (m, 1H), 7.66 – 7.60 (m, 2H), 7.45 – 7.41 (m, 2H), 7.39 – 7.34 (m, 1H), 7.31 – 7.29 (m, 1H), 7.21 – 7.17 (m, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 2.92 (s, 3H); ^{13}C NMR (100 MHz, *d*^{6}-DMSO) δ (ppm) 175.1, 155.6, 147.4, 144.7, 133.6,

130.9, 130.4, 129.2, 128.9, 128.6, 127.5, 127.1, 127.0, 126.0, 124.8, 121.2, 120.8, 120.2, 118.8, 112.5, 86.1, 55.3; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{17}N_2O_3$ 357.1239; Found 357.1241.

*7-Hydroxy-7-(3-methoxyphenyl)indazolo[2,3-b]isoquinolin-12(7H)-one (**2w**).* 43 mg, 60% yield (Method B). Yellow solid; mp = 68 – 69 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.20 (d, *J* = 7.5 Hz, 1H), 8.04 (d, *J* = 7.7 Hz, 1H), 7.72 – 7.66 (m, 2H), 7.53 – 7.51 (m, 1H), 7.37 – 7.29 (m, 3H), 7.11 – 7.01 (m, 1H), 6.93 (s, 1H), 8.20 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 6.14 (s, 1H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.2, 159.8, 148.8, 144.6, 143.2, 134.3, 129.9, 129.5, 129.2, 128.3, 128.1, 127.9, 126.7, 126.1, 121.9, 121.8, 118.8, 117.3, 113.9, 111.1, 88.8, 55.3; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{17}N_2O_3$ 357.1239; Found 357.1239.

*(E)-7-Hydroxy-7-styrylindazolo[2,3-b]isoquinolin-12(7H)-one (**2x**).* 63 mg, 89% yield (Method B). Yellow solid; mp = 202 – 203 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.26 (d, *J* = 8.2 Hz, 1H), 8.17 (d, *J* = 7.7 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.69 – 7.66 (m, 1H), 7.50 – 7.46 (m, 1H), 7.44 – 7.35 (m, 2H), 7.17 (s, 5H), 6.59 (d, *J* = 15.8 Hz, 1H), 6.55 (s, 1H), 6.48 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.9, 148.6, 141.2, 134.9, 134.1, 131.34, 131.25, 129.6, 129.2, 128.69, 128.66, 128.0, 127.2, 126.7, 126.5, 122.04, 121.99, 118.5, 88.2; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{17}N_2O_2$ 353.1290; Found 353.1296.

*(Z)-7-Hydroxy-7-methylindazolo[2,3-b]isoquinolin-12(7H)-one O-methyl oxime (**2y**).* 45 mg, 76% yield (Method B). Pale pink solid; mp = 175 – 176 ºC; ^{1}H NMR (400 MHz, *d*^{6}-DMSO) δ (ppm) 8.19 (d, *J* = 8.7 Hz, 1H), 8.11 (d, *J* = 7.2 Hz, 1H), 7.96 (s, 1H), 7.88 – 7.82 (m, 2H), 7.61 – 7.57 (m, 1H), 7.52 – 7.48 (m, 1H), 7.41 – 7.37 (m, 1H), 7.25 – 7.21 (m, 1H), 4.23 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, *d*^{6}-DMSO) δ (ppm) 147.9, 139.2, 139.1, 129.9, 128.6, 127.1, 126.2, 125.9, 124.7, 123.8, 122.8, 122.3, 121.2, 118.0, 87.1, 62.7, 40.2, 32.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{16}N_3O_2$ 294.1243; Found 294.1257.

Preparation of 3a and 3b. To a 10 mL oven-dried vial with a magnetic stirring bar, **2a** (53 mg, 0.2 mmol), RSH (0.3 mmol, 1.5 eq), $BF_3{\cdot}Et_2O$ (0.2 mmol, 1.0 eq), and anhydrous CH_3CN (1.0 mL) were added in sequence at room temperature, and the

reaction mixture was stirred for 12 h under these conditions. When the reaction was completed (monitored by TLC), the crude reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 20:1) to give the pure product **3** in high yields.

*7-Methyl-7-(phenylthio)indazolo[2,3-b]isoquinolin-12(7H)-one (**3a**).* 58 mg, 81% yield. Yellow solid; mp = 70 – 71 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.22 (d, *J* = 8.3 Hz, 1H), 8.01 – 7.98 (comp, 3H), 7.78 – 7.74 (m, 1H), 7.51 – 7.44 (m, 2H), 7.39 – 7.35 (m, 1H), 7.14 – 7.10 (m, 1H), 6.81 – 6.77 (m, 2H), 6.24 – 6.22 (m, 2H), 2.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.9, 148.5, 142.9, 136.0, 133.6, 130.8, 130.4, 130.1, 129.0, 128.52, 128.51, 127.9, 127.2, 126.2, 125.5, 121.8, 121.3, 118.6, 74.3, 28.6; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{17}N_2OS$ 357.1062; Found 357.1065.

*7-(Benzylthio)-7-methylindazolo[2,3-b]isoquinolin-12(7H)-one (**3b**).* 70 mg, 95 % yield. Yellow solid; mp = 64 – 65 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.35 – 8.33 (m, 1H), 8.27 (d, *J* = 8.3 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.6 Hz, 1H), 7.78 – 7.74 (m, 1H), 7.60 – 7.56 (m, 1H), 7.46 – 7.42 (m, 1H), 7.38 – 7.34 (m, 1H), 6.86 – 6.84 (comp, 3H), 6.71 – 6.69 (m, 2H), 3.26 (d, *J* = 13.4 Hz, 1H), 3.10 (d, *J* = 13.4 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.2, 148.4, 143.0, 134.9, 134.1, 130.1, 129.8, 128.9, 128.4, 128.0, 127.9, 127.7, 126.9, 126.2, 126.1, 121.8, 121.6, 118.6, 72.4, 35.7, 32.3; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{19}N_2OS$ 371.1218; Found 371.1212.

Preparation of 4. To a 10 mL oven-dried vial with a magnetic stirring bar, **2a** (53 mg, 0.2 mmol), $BF_3{\cdot}Et_2O$ (0.2 mmol, 1.0 eq), and CH_3OH (1.0 mL) were added in sequence at room temperature, and the reaction mixture was stirred for 12 h under these conditions. When the reaction was completed (monitored by TLC), the crude reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 20:1) to the pure product **4** (50 mg) as pale yellow solid in 90% yield. mp = 127 – 128 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.41 – 8.36 (m, 1H), 7.98 – 7.96

(m, 1H), 7.82 – 7.76 (m, 2H), 7.66 – 7.62 (m, 1H), 7.49 – 7.40 (m, 2H), 2.80 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.5, 149.0, 140.8, 134.3, 131.0, 130.3, 129.7, 127.8, 126.8, 126.7, 126.6, 122.00, 121.95, 119.1, 91.4, 52.0, 32.8; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{15}N_2O_2$ 279.1134; Found 279.1138.

Preparation of 5. To a 10 mL oven-dried vial with a magnetic stirring bar, compound **2a** (53 mg, 0.2 mmol), and DMAP (2.5 mg, 0.02 mmol, 10 mol%) in DCM (1.0 mL), was added DCC (61.8 mg, 0.3 mmol, 1.5 eq) slowly at 0 ºC, and the mixture was stirred for 5 h and the reaction temperature was allowed to warm up to room temperature slowly. When the reaction was completed (monitored by TLC), the crude reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 20:1) to give the pure product **5** (59 mg) as white solid in >95 % yield. mp = 143 – 144 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.42 – 8.36 (m, 2H), 7.90 – 7.88 (m, 1H), 7.75 – 7.67 (m, 2H), 7.63 – 7.59 (m, 1H), 7.48 – 7.36 (m, 2H), 2.23 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.0, 167.6, 148.3, 140.9, 133.5, 129.2, 129.1, 128.9, 127.3, 126.27, 126.0, 123.9, 121.6, 121.3, 118.2, 87.4, 32.0, 20.9; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{15}N_2O_3$ 307.1083; Found 307.1082.

Preparation of 6. To a 10 mL oven-dried vial with a magnetic stirring bar, **2a** (53 mg, 0.2 mmol), $TsNH_2$ (34.2 mg, 0.2 mmol, 1.0 eq), $BF_3{\cdot}Et_2O$ (0.2 mmol, 1.0 eq) and anhydrous CH_3CN (1.0 mL) were added in sequence, and the reaction mixture was stirred at 40 ºC for 12 hours. When the reaction was completed (monitored by TLC), the crude reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10:1) to give the pure product **6** (50 mg) as pale yellow solid in 61% yield. mp = 233 – 234 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.40 – 8.38 (m, 1H), 8.22 – 8.20 (m, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.73 – 7.69 (m, 1H), 7.67 – 7.63 (m, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.41 – 7.37 (m, 1H), 7.35 – 7.32 (m, 1H), 6.95 (d, J = 8.3 Hz, 2H), 6.62 (d, J = 8.0 Hz, 2H), 6.35 (s, 1H), 2.21 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.2, 148.1, 143.8, 138.8, 135.4, 133.6, 129.9, 129.7, 129.0, 128.7, 128.6, 127.6, 126.9, 126.6, 126.3, 122.0, 121.3, 118.3, 74.8, 35.3,

21.4; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{20}N_3O_3S$ 418.1225; Found 418.1217.

Preparation of 7z and 7z'. To a 10 mL round-bottom flask with a magnetic stirring bar, **1z** (0.2 mmol, 65.4 mg), aqueous sulfuric acid solution (0.4 mL, 1.7 M, 3.4 eq) in DMF:H_2O = 3:1 (2.0 mL), was added an aqueous solution of $NaNO_2$ (18 mg, 1.3 eq, in 0.3 mL H_2O) slowly at 0 ^oC for 0.5 h, The reaction mixture was stirred for 20 h and the reaction temperature was allowed to warm up to room temperature slowly. When the reaction was completed (monitored by TLC), water (30 mL) was added to the reaction mixture and the resulting mixture was standing for 1 h. Then solid was precipitated out and filtered by Buchner funnel, washed with water and *n*-hexane in sequence, and dried under infrared lamp for 12 h to give the pure product **7z'** (58 mg) in 82% yield. The crystal sample is crystallized out from the solution of mixture solvents (isopropanol, DCM, and Hexanes), and is good enough for the single-crystal X-ray diffraction analysis. However, this sample shows very low solubility in $CDCl_3$, and isomerization occurs when carried out the NMR analysis in d^6-DMSO. Then further transformation by protecting the NH group with Boc-group was conducted. To a 10 mL round-bottom flask with a magnetic stirring bar, **7z'** (58 mg, 0.16 mmol), $(Boc)_2O$ (39 mg, 0.18 mmol), DMAP (1.2 mg, 0.01 mmol, 5 mol %), and THF (1.0 mL) were added in sequence at room temperature and stirred for 10 h. When the reaction was completed (monitored by TLC), the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 20:1) to give the 70 mg pure product **7z** as pale yellow solid (> 95% yield). mp = 148 – 149 ºC; ^1H NMR (400 MHz,$CDCl_3$) δ (ppm) 8.34 (d, J = 8.0 Hz, 1H), 8.10 – 8.08 (m, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.80 – 7.77 (m, 2H), 7.67 – 7.48 (m, 4H), 7.39 – 7.36 (m, 1H), 6.87 – 6.84 (m, 2H), 3.80 (s, 3H), 1.64 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.7, 190.8, 163.3, 148.4, 146.7, 141.4, 140.6, 139.1, 132.4, 130.90, 130.85, 130.7, 130.3, 129.40, 129.35, 125.3, 124.7, 123.2, 114.3, 113.6, 85.8, 55.5, 28.1. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{27}H_{24}N_2O_5Na$ 479.1583; Found 479.1576.

Preparation of 7A and 8A. To a 10 mL round-bottom flask with a magnetic stirring

bar, **1A** (50.2 mg, 0.2 mmol), and aqueous sulfuric acid solution (0.4 mL, 1.7 M, 3.4 eq) in CH_3CN (2.0 mL), was added an aqueous solution of $NaNO_2$ (18 mg, 1.3 eq, in 0.3 mL H_2O) slowly at 0 ^oC for 0.5 h, The reaction mixture was allowed to warm up to room temperature slowly and stirred for 5 day. When the reaction was completed (monitored by TLC), the reaction mixture was extracted with ethyl acetate (10 mL × 3). The organic layers were combined, and dried with anhydrous Na_2SO_4. The solvent was evaporated under vacuum after filtration, and the residue was purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 5:1) to afford compound **7A** as yellow solid (14 mg, 25% yield) and compound **8A** as yellow solid (24 mg, 43% yield).

*Methyl 2-(1H-indazole-3-carbonyl)benzoate (**7A**).* Yellow solid; mp = 56 – 57 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 11.33 (s, 1H), 9.10 (d, J = 8.1 Hz, 1H), 8.66 (d, J = 7.9 Hz, 1H), 8.31 – 8.20 (m, 3H), 8.14 – 8.07 (m, 2H), 8.02 – 7.98 (m, 1H), 4.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 191.8, 167.5, 144.4, 141.5, 141.2, 132.4, 130.3, 130.1, 129.8, 128.4, 127.8, 124.1, 122.8, 122.3, 110.2, 52.4; HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{13}N_2O_3$ 281.0926; Found 281.0915.

*Methyl 2-(4-oxo-1,4-dihydrocinnolin-3-yl)benzoate (**8A**).* Yellow solid; mp = 71 – 72 ºC; ^1H NMR (400 MHz, d^6-DMSO) 13.59 (s, 1H), 8.09 – 8.07 (d, 1H), 7.84 – 7.79 (m, 2H), 7.70 – 7.66 (m, 1H), 7.65 – 7.63 (m,1H), 7.59 – 7.53 (m, 2H), 7.45 – 7.41 (m, 1H), 3.57 (s, 3H); ^{13}C NMR (100 MHz, d^6-DMSO) δ (ppm) 169.0, 167.4, 148.9, 141.2, 134.8, 133.8, 131.8, 131.6, 130.8, 128.8, 128.6, 124.7, 124.6, 122.3, 116.4, 51.8. HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{13}N_2O_3$ 281.0926; Found 281.0931.

Control Experiment with 1B. To a 10 mL round-bottom flask with a magnetic stirring bar, **1B** (44 mg, 0.2 mmol), and aqueous sulfuric acid solution (0.4 mL, 1.7 M, 3.4 eq) in DMF:H_2O = 1:3 (2.0 mL), was added an aqueous solution of $NaNO_2$ (18 mg, 1.3 eq, in 0.3 mL H_2O) slowly at 0 ^oC for 0.5 h, The reaction mixture was stirred for 21 h and the reaction temperature was allowed to warm up to room temperature slowly. Proton NMR of the crude reaction mixture have shown that no reaction occurred (see Figure S1), and >90% of **1B** was recovered.

Control Experiment in the absence of $NaNO_2$. To a 10 mL round-bottom flask with a magnetic stirring bar, **1a** (47 mg, 0.2 mmol), and aqueous sulfuric acid solution (0.4 mL, 1.7 M, 3.4 eq), and DMF:H_2O = 1:3 (2.0 mL) were added insequence at 0 ^oC. The reaction mixture was stirred for 12 h and the reaction temperature was allowed to warm up to room temperature slowly. Proton NMR of the crude reaction mixture have shown that no reaction occurred (see Figure S2), and >90% of **1a** was recovered.

Control Experiment with 1C. To a 10 mL round-bottom flask with a magnetic stirring bar, **1C** (38.6 mg, 0.2 mmol), and aqueous sulfuric acid solution (0.4 mL, 1.7 M, 3.4 eq) in DMF:H_2O = 1:3 (2.0 mL), was added an aqueous solution of $NaNO_2$ (18 mg, 1.3 eq, in 0.3 mL H_2O) slowly at 0 ^oC for 0.5 h. The reaction mixture was stirred for 21 h and the reaction temperature was allowed to warm up to room temperature slowly. When the reaction was completed (monitored by TLC), the reaction mixture was extracted with EtOAc (10 mL × 3). The organic layers were combined, and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum after filtration, and the residue was purified by flash column chromatography on silica gel (eluent: petroleum ether/acetone = 2:1) to afford **8C** (36 mg) as pale yellow solid in 80% yield. mp = 274 – 275 ºC; ^1H NMR (400 MHz, d^6-DMSO) δ (ppm) 13.70 (s, 1H), 8.17 – 8.15 (d, 1H), 8.11 – 8.09 (d, 2H), 7.81 – 7.77 (m, 1H), 7.65 – 7.6 (d, 1H), 7.47 – 7.38 (m, 4H); ^{13}C NMR (100 MHz, d^6-DMSO) δ (ppm) 169.2, 145.4, 140.7, 135.0, 133.6, 128.4, 128.3, 127.8, 124.8, 124.6, 123.5, 116.5. HRMS (CI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{11}N_2O$ 223.0871; Found 223.0868.

Control Experiment in the presence of NaN_3. To a 10 mL round-bottom flask with a magnetic stirring bar, **1a** (47 mg, 0.2 mmol), and aqueous sulfuric acid solution (0.4 mL, 1.7 M, 3.4 eq) in DMF:H_2O = 3:1 (2.0 mL), was added an aqueous solution of $NaNO_2$ (18 mg, 1.3 eq, in 0.3 mL H_2O) and an aqueous solution of NaN_3 (17 mg, 1.3 eq, in 0.2 mL H_2O) in sequence at 0 ^oC, and the reaction mixture was stirred for 1 h under these conditions, When the reaction was completed (monitored by TLC), the reaction mixture was extracted with ethyl acetate (10 mL × 3). The organic layers were combined, and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum after filtration, and the residue was purified by flash column chromatography

on silica gel (eluent: petroleum ether/ethyl acetate = 40:1) to afford pure **9** (50 mg) as orange solid in 95% yield. mp = 71 – 72 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.76 – 7.74 (m, 1H), 7.67 – 7.65 (m, 1H), 7.53 – 7.51 (m, 1H), 7.48 – 7.44 (m, 1H), 7.41 – 7.33 (m, 2H), 7.14 – 7.10 (m, 1H), 2.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 200.3, 141.2, 140.6, 134.1, 133.7, 131.4, 130.1, 128.8, 128.6, 124.8, 121.5, 118.8, 115.1, 94.1, 90.8, 30.10; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{11}N_3ONa$ 284.0800; Found 284.0773.

Reaction Monitoring by Proton NMR in *d*^{6}-DMSO. To a NMR tube, **1a** (24 mg, 0.1 mmol), and $NaNO_2$ (10 mg, 1.4 mmol) in *d*^{6}-DMSO (0.5 mL), was added aqueous sulfuric acid solution (***as indicated amount***) at room temperature. The reaction mixtures were monitored by proton NMR at indicated reaction times, and an obvious acid-promoted acceleration was observed (Figure S3-S7).

Procedure for Scale up. To a 50 mL round-bottom flask with a magnetic stirring bar, **1h** (1.099 g, 3.5 mmol), and aqueous sulfuric acid solution (7.0 mL, 1.7 M, 3.4 eq) in DMF:H_2O = 3:1 (25 mL), was added an aqueous solution of $NaNO_2$ (314 mg, 1.3 eq, in 1.0 mL H_2O) slowly at 0 ^{o}C for 0.5 h, The reaction mixture was stirred for 10 h and the reaction temperature was allowed to warm up to room temperature slowly. When the reaction was completed (monitored by TLC), water (100 mL) was added to the reaction mixture and the resulting mixture was standing for 1 h. Then solid was precipitated out and filtered by Buchner funnel, washed with water and *n*-hexane in sequence, and dried under infrared lamp for 12 h to give the pure product **2h** in 89% yield (1.071g).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.

X-ray crystal data for **2a** (CIF)

X-ray crystal data for **2p** (CIF)

X-ray crystal data for **2v** (CIF)

X-ray crystal data for **2y** (CIF)

X-ray crystal data for **7z'** (CIF)

X-ray crystal data for **7A** (CIF)

^{1}H, ^{19}F and ^{13}C NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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