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Iodine-Catalyzed Aerobic Oxidation of *o*-Alkylazoarenes to *2H*-Indazoles

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[b]State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China.

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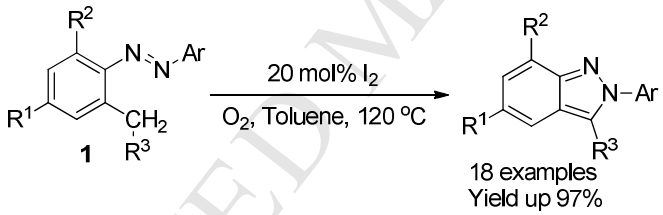

Iodine-Catalyzed Aerobic Oxidation of *o*-Alkylazoarenes to *2H*-Indazoles

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Abstract

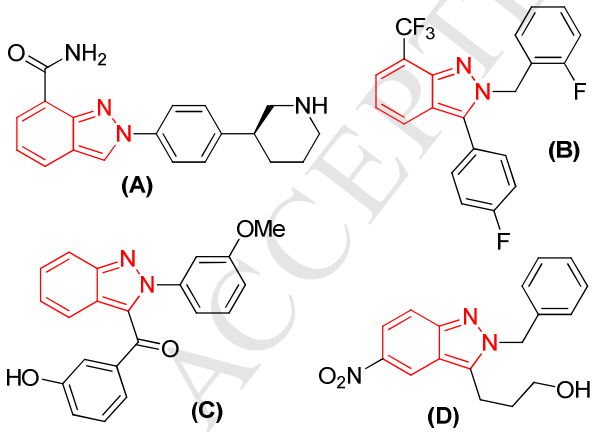
An iodine-catalyzed aerobic-oxidative C-H functionalization of *o*-alkylazoarenes to afford 2*H*-indazoles has been developed. CuI was found to be an effective additive to accelerate the regeneration of iodine in the catalytic cycle. This catalytic system is suitable for both electron-rich and electron-deficient azoarenes and tolerates a variety of functional groups with high yields. A gram-scale reaction was successfully conducted, proving the scalability of this reaction.

Keywords

Iodine catalysis; sp^3 C-H functionalization; Aerobic oxidation; *2H*-Indazole.

Introduction

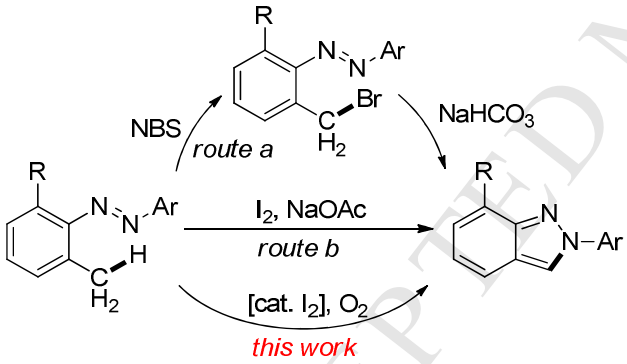
2*H*-Indazole is an important skeleton of nitrogen-containing heterocycle present in many biologically active compounds, including in natural products and pharmaceuticals (Scheme 1).[1] For example, molecule **A** as a poly(ADP-ribose)polymerase inhibitor displays antiproliferation activity against BRCA-deficient cancer cells.[1a] Compound **B** acts as a Liver-X-receptor agonist and thus is a drug for cardiovascular diseases.[1b] Molecule **D** is a kind of antiparasitic drug.[1d] One traditional approach to yield 2*H*-indazoles is reductive cyclization of N-(o-nitrobenzylidene)anilines[2] or N-(2-aminobenzyl)anilines.[3] Another way to prepare 2*H*-indazoles is *via* cross coupling reactions,[4] such as palladium-catalyzed coupling of 2-halophenyl acetylenes with hydrazines,[4c] and reaction of 2-chloromethylarylzinc reagents with aryldiazonium salts.[4e] Among these methods leading to the 2*H*-indazole derivatives, many of them suffer from complicated preparation of substrates or using air sensitive organometallic reagents with poor functional tolerance. Accordingly, development of facile and scalable routes to construct the 2*H*-indazoles is still desirable.



Scheme 1: Several Bioactive 2*H*-Indazoles.

Recently, C-H functionalization strategy has been introduced to the synthesis of 2*H*-indazoles to make the reactions more step- and atom-economical. Several protocols of sp^2 C-H activation of azobenzenes by Pd,[5] Rh,[6] Re[7] and Co[8] with incorporation of carbonyl compounds have been reported to afford the *2H*-indazoles.

Methods of direct sp^3 C-H functionalization of alkylazobenzenes leading to *2H*-indazoles are still limit.[9] A stepwise bromination-cyclization procedure (Scheme 2, *route a*) was reported, which potentially suffers from selectivity problem of bromination in multiaralkyl-containing substrates.[9a] More recently, a stoichiometric iodine-mediated procedure has been reported by our group (Scheme 2, *route b*).[9c] From the point of sustainability and green chemistry, it is highly desired to use more regenerative and abundant oxidant like O_2 to fulfil this conversion.[10] As a part of our ongoing project on the construction of heterocycles,[11] herein, we report an iodine-catalyzed aerobic-oxidative reaction for construction of *2H*-indazoles (Scheme 2, *this work*). Besides the high efficiency and environmentally friendly nature of the reagents, this reaction displays extensive substrate scope, excellent functional tolerance, and good scalability.



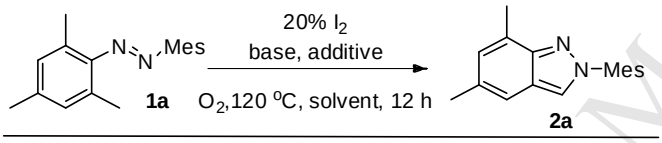
Scheme 2: Cyclization of *ortho*-Alkylazobenzenes to *2H*-Indazoles *via* sp^3 C-H Functionalization.

Results and Discussion

Based on the conditions for stoichiometric I_2-mediated reaction,[9c] we first tried reduced amount of I_2 (20 mol%) and oxygen atmosphere (entry 1, Table 1), and the product **2a** was obtained in 43% yield, with 50% starting material remaining. This result suggests that I_2 can catalyze this conversion, yet the regeneration of I_2 from I^-

might not be fast enough under this condition. Therefore, we tried to add several metal salts, such as CuBr, CuI, $CuCl_2$, $FeBr_2$, $MnCl_2$ (entry 2-6), as additive to facilitate the oxidation of I^-, and we found that addition of 10 mol% CuI led to **2a** in 81% yield. Then, the solvent dichloroethane (DCE) was respectively replaced with $CHCl_3$, CH_3CN, and toluene (entry 7-9), and toluene was found to behave better than DCE for this reaction. During the reaction in toluene, we noticed that the solubility of NaOAc was poor, so organic bases were tried (entry 10-11) and pyridine as base was found to increase the yield to 96%. The amount of CuI could be reduced to 5 mol% (97% yield, entry 12), while reduction of I_2 to 10 mol% led to a lower yield (entry 13). Therefore, the optimized condition is shown in entry 12.

Table 1: Optimization Reaction Conditions[a].



1a O_2,120 °C, solvent, 12 h **2a**

entry	additive	solvent	base	yield[b]/ %
1	_	DCE	NaOAc (40%)	43
2	CuBr (10%)	DCE	NaOAc (40%)	70
3	CuI (10%)	DCE	NaOAc (40%)	81
4	$CuCl_2$ (10%)	DCE	NaOAc (40%)	59
5	$FeBr_2$ (10%)	DCE	NaOAc (40%)	55
6	$MnCl_2$ (10%)	DCE	NaOAc (40%)	47
7	CuI (10%)	$CHCl_3$	NaOAc (40%)	70
8	CuI (10%)	CH_3CN	NaOAc (40%)	60
9	CuI (10%)	toluene	NaOAc (40%)	87
10	CuI (10%)	toluene	NEt_3 (40%)	27
11	CuI (10%)	toluene	pyridine (40%)	96
12	CuI (5%)	toluene	pyridine (40%)	97, 93[c]
13[d]	CuI (10%)	toluene	pyridine (20%)	75

[a]Reaction condition: 0.2 mmol **1a**, 0.04 mmol I_2, 0.08 mmol base, 1 mL solvent, 120 °C under O_2 in sealed tube. [b]NMR yield. [c]Isolated yield. [d]10 mol% I_2 was used.

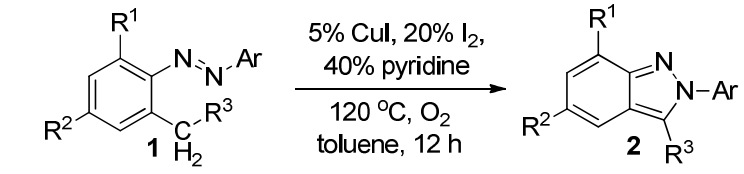
With the optimal conditions in hand, the substrate scope was examined and representative results are showed in Scheme 3. Replacing the bulky mesityl in **1a**

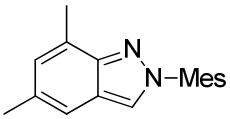
with phenyl furnished 5,7-dimethyl-2-phenyl-2*H*-indazole **2b** in 92% yield. Then, *para*-Substitution on the phenyl ring in **1b** was changed from electron-donating to electron-withdrawing group (OMe, H, Br and CN). The former three substrates (**1c**, **1d**, and **1e**) gave excellent yields (**2c**, 94%; **2d**, 85% and **2e**, 84% respectively), while **1f** required higher I_2 load and longer reaction time to achieve moderate yield (**2f**, 58%). Replacing one *ortho*-methyl in **1b** with phenyl led to product **2g** in 90% yield. Substrates with *ortho*-bromo and -iodo group also afforded products in high yields (**2h**+**2i**, 93%; **2i**, 90%). It is noteworthy that when substrate **1h** was treated, bromo group is partially substituted by iodo group in the product (**2h**: **2i** = 1: 0.13).

Then, the functional group tolerance on the other aryl group of azobenzene was examined. Electron-withdrawing group like CN and CO_2Me resulted in desired products in high yield (**2j**, 95% and **2k**, 83% respectively), while COMe substituent led to product **2l** in only 31% yield. To our delight, the crystal of **2j** was suitable for single crystal analysis, and its structure was fully characterized by X-ray diffraction analysis, which unequivocally confirmed the 2-aryl-2*H*-indazole backbone of the product.

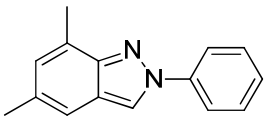
Strong electron-donating group NMe_2 could also be tolerated in this reaction and afforded product **2m** in 43% yield. Moreover, acetyl-protected indole was tolerated and gave the product **2n** in 42% yield. Interestingly, the radical-sensitive phenol moiety didn't show any prohibition and the corresponding product **2o** was obtained in 70% yield. Four substrates with *ortho*-methylene were tested. When 2,6-diethylazobenzene **1p** was used, the product **2p** was also formed in 89% yield. 2-Ethyl-6-methylazobenzene **1q** furnished two separable products (**2q**, 75% yield and **2q'**, 17% yield), while **1r** and **1s** were selectively transformed into 3-substituted products, respectively in 85% (**2r**) and 88% (**2s**) yield. As is consistent with our

former work,[9c] substrates with only one *ortho*-methyl, such as 2,4-dimethylazobenzene (**1t**), are unreactive.

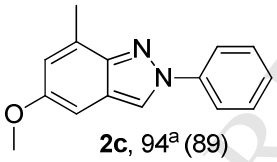




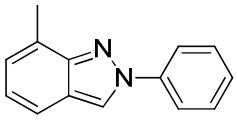
2a, 97 (93)



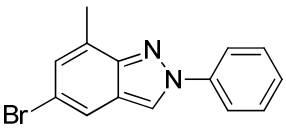
2b, 92 (88)



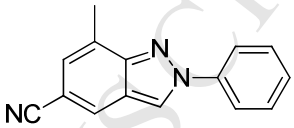
2c, 94[a] (89)



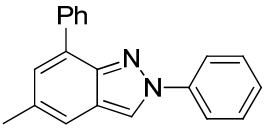
2d, 85[b] (80)



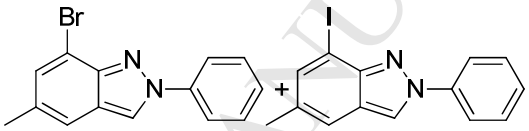
2e, 84 (80)



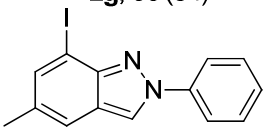
2f, 58[c] (51)



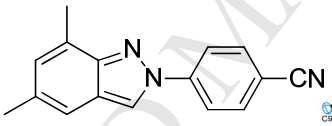
2g, 90 (84)



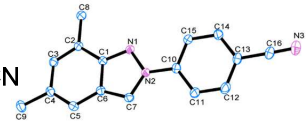
2h+ 2i, 93[c] (90), 1:0.13



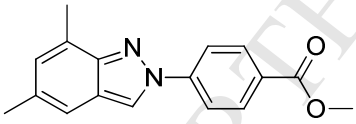
2i, 90[b] (84)



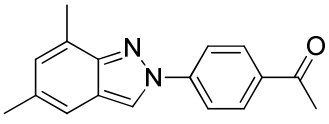
2j, 95 (88)



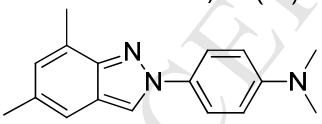
crystal structure of **2j**
(CCDC: 1486855)



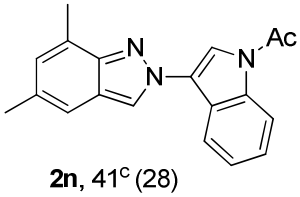
2k, 83 (78)



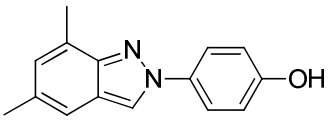
2l, 31[b] (27)



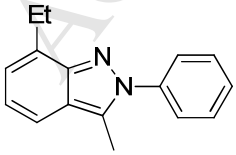
2m, 43[c] (32)



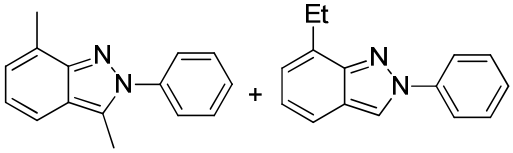
2n, 41[c] (28)



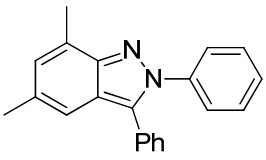
2o, 70[c] (54)



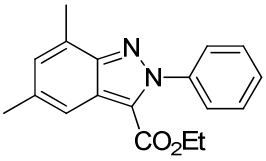
2p, 89 (83)



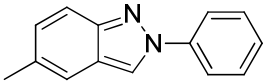
2q, 75 (71) **2q'**, 17 (16)



2r, 85[a] (80)



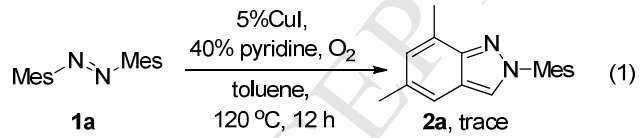
2s, 88[a] (82)

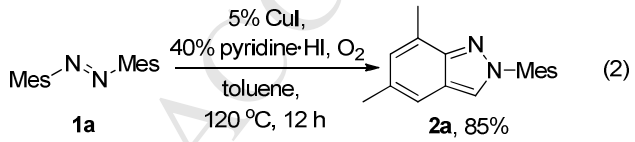


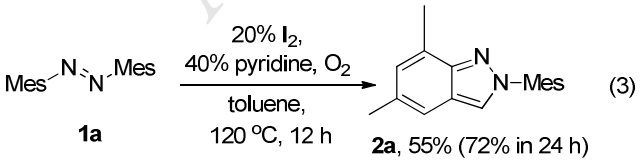
2t, 0

Scheme 3: Scope of Substrates for Synthesis of 2*H*-Indazoles. Reaction condition: 0.2 mmol **1**, 0.04 mmol I_2, 0.01mmol CuI, 0.08 mmol pyridine, 1 mL toluene, 120 ^{o}C under O_2 for 12 h in sealed tube; ^{1}H-NMR yields (%) and isolated yields (%, in bracket) are displayed. [a] Reaction time: 6 h. [b] Reaction time: 24 h. [c] Reaction time: 24 h, 30 mol% I_2, 60 mol% pyridine.

Iodine has been reported to mediate C-H functionalization of benzyl C-H in *o*-alkylazoarenes to form 2*H*-indazoles *via* a radical chain mechanism.[9c] To elucidate the process of this catalytic reaction, several additional experiments were conducted. First, iodine was removed from the conditions (Eq. 1), and the reaction did not proceed, which proves the central role of iodine in mediating the conversion of *o*-alkylazoarenes. Then, pyridine hydroiodide was used in place of I_2 and pyridine, and products **2a** was still obtained in 85% yield (Eq. 2), suggesting that I^- can be oxidized to I_2 to mediate the reaction. When CuI was eliminated from the reaction, the product **2a** was obtained in 55% yield in 12 h and 72% yield in 24 h (Eq. 3), and this observation is consistent with the proposed role of CuI to facilitate the oxidation of I^- to I_2 under oxygen.

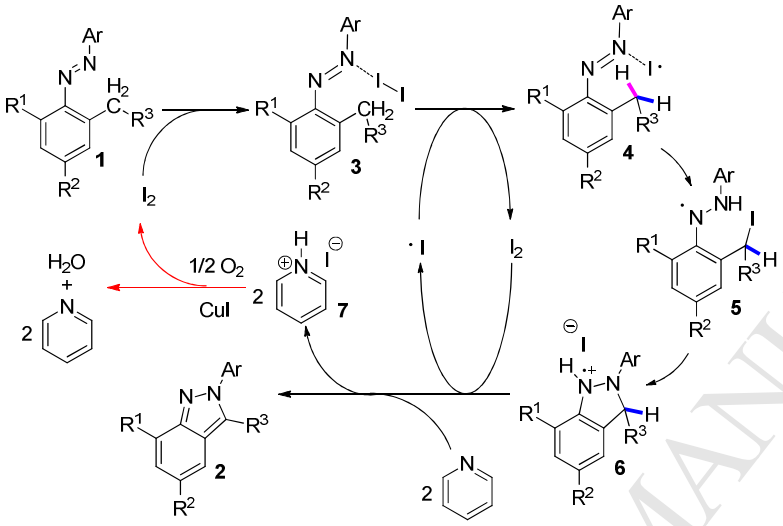






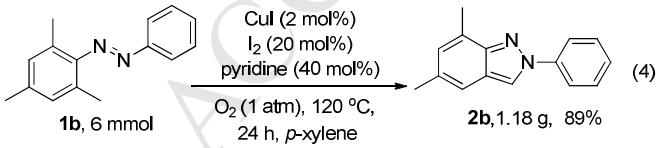
Based on these results and reported literature,[9c] a possible reaction mechanism has been proposed as shown in Scheme 4. First, azo substrate **1** associates with I_2 to form compound **3**. Then, iodine radical mediates homolysis of I–I

bond in the compound **3** to give intermediate **4**, which undergoes hydrogen transfer and cyclization to a□ord intermediate **6** *via* intermediate **5**. Abstraction of a second benzylic hydrogen by I_2 achieves the product **2** with generation of pyridine hydroiodide in the presence of pyridine. Finally, I_2 is regenerated by aerobic oxidation of pyridine hydroiodide with the assistance of CuI.



Scheme 4: Proposed Reaction Mechanism.

To further demonstrate the applicability of this procedure, a gram-scale reaction of **1b** was run in schlenk tube (atmospheric pressure), using *p*-xylene as a solvent and CuI (2 mol%). The product **2b** was obtained in 89% isolated yield (Eq. 4). This trial suggests that this reaction can be easily scaled up for synthesis of substantial amount of 2-aryl-2*H*-indazoles.



Conclusion

An efficient iodine-catalyzed aerobic-oxidative C-H functionalization method has been developed for the synthesis of 2*H*-indazoles from *o*-alkylazoarenes.

Utilization of CuI as oxidation promotor successfully enabled the use of oxygen as terminal oxidant and catalytic amount of iodine, which makes this reaction very environmentally benign. Moreover, this reaction can tolerate a variety of functional groups with high yields and can be easily amplified for gram-scale synthesis of 2*H*-indazoles.

Experimental

General Procedure for Synthesis of Azobenzenes 1 (GP1): 2.2 mmol of aniline and 2.0 mmol nitrosobenzene were added into 20 mL acetic acid. The reaction mixture was shielded form light and stirred at 30 ^{o}C for 2 days. After the reaction completed, the mixture was diluted with 20 mL water and then extracted twice with 20 mL petroleum ether (PE). The organic phase was washed with 20 mL $NaHCO_3$ solution, dried and evaporated. The obtained residual was separated by chromatography (PE-DCM) to give the corresponding products (**1b**-**1i**, **1p**, **1q** and **1t**). Additionally, **1a**, **1r** and **1s** was prepared *via* coupling reactions.[9c] Specific preparation procedures are provided along with the characterization data in ESI.

General Procedure for I_2-Catalyzed Synthesis of 2*H*-Indazoles 2 (GP2): A seal tube (25 mL) was charged with 0.2 mmol azobenzene and 0.01 mmol CuI (1.9 mg) and then vacuumized and refilled with O_2. Subsequently, 0.04 mmol I_2 (10.8 mg), 0.08 mmol pyridine (6 μL) and 1 mL toluene were added. The reaction vessel was heated at 120 ^{o}C for 12 h. After the reaction completed, 0.5 mL 1 mol/L amonia solution and 3 drops of saturated $Na_2S_2O_3$ solution was added and the mixture was extracted with EA. Column seperation gives the corresponding 2*H*-indazoles.

Characterization data of unkown products are displayed below.

5-Bromo-7-methyl-2-phenyl-2H-indazole **(2e):** synthesized *via* GP2; white solid (46.1 mg, 80% isolated yield); M.p. 139-141 ^{o}C; Rf: 0.45 (PE: EA=10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (s, 1H), 8.25 - 8.21 (m, 2H), 8.03 (dd, *J* = 1.5, 0.6 Hz, 1H), 7.89 - 7.84 (m, 2H), 7.77 - 7.72 (m, 1H), 7.51 - 7.49 (m, 1H), 3.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8, 140.5, 130.5, 129.7, 129.2, 128.2, 123.6, 121.2, 120.1, 119.9, 116.2, 17.0; GC-MS: 286; HRMS (ESI positive mode) calcd for $C_{14}H_{11}BrN_2+H^+$ 287.0178, found 287.0175.

4-(5,7-Dimethyl-2H-indazol-2-yl)benzonitrile **(2j):** synthesized *via* GP2; white crystal (43.4 mg, 88% isolated yield); M.p. 176-177 ^{o}C; Rf: 0.20 (PE: EA=4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H), 8.03 - 7.99 (m, 2H), 7.77 - 7.72 (m, 2H), 7.22 (s, 1H), 6.93 (s, 1H), 2.61 (s, 3H), 2.38 (d, *J* = 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0, 143.6, 133.6, 133.2, 129.8, 127.9, 123.5, 120.6, 119.5, 118.4, 115.8, 110.6, 21.9, 17.0; GC-MS: 247; HRMS (ESI positive mode) calcd for $C_{16}H_{13}N_3+H^+$ 248.1182, found 248.1180.

Methyl 4-(5,7-dimethyl-2H-indazol-2-yl)benzoate **(2k):** synthesized *via* GP2; white solid (43.4 mg, 78% isolated yield); M.p. 150-152 ^{o}C; Rf: 0.26 (PE: EA=4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H), 8.21 - 8.14 (m, 2H), 8.02 - 7.97 (m, 2H), 7.23 (s, 1H), 6.93 (d, *J* = 1.1 Hz, 1H), 3.95 (s, 3H), 2.64 (s, 3H), 2.38 (d, *J* = 0.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 149.8, 144.0, 132.8, 131.2, 129.5, 128.9, 127.9, 123.3, 120.1, 119.7, 115.8, 52.4, 22.0, 17.1; GC-MS: 280; HRMS (ESI positive mode) calcd for $C_{17}H_{16}N_2O_2+H^+$ 281.1285, found 281.1280.

1-(4-(5,7-Dimethyl-2H-indazol-2-yl)phenyl)ethanone **(2l):** synthesized *via* modified GP2 (24 h); white solid (14.1 mg, 27% isolated yield); M.p. 167-169 ^{o}C; Rf: 0.42 (PE: EA = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 0.5 Hz, 1H), 8.09 (d, *J* = 8.1 Hz, 2H), 8.04 - 8.00 (m, 2H), 7.24 (s, 1H), 6.93 (s, 1H), 2.64 (m, 6H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0, 149.9, 144.0, 135.7, 132.9, 130.0, 129.6, 127.9,

123.4, 120.3, 119.8, 115.8, 26.8, 22.0 17.1; GC-MS: 264; HRMS (ESI positive mode) calcd for $C_{17}H_{16}N_2O+H^+$ 265.1335, found 265.1332.

4-(5,7-Dimethyl-2H-indazol-2-yl)-N,N-dimethylaniline **(2m):** synthesized *via* modified GP2 (30% I_2, 24 h); yellowish solid (17.0 mg, 32% isolated yield); M.p. 164-165 ^oC; Rf: 0.40 (PE: EA=4:1); ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.72 (d, *J* = 9.0 Hz, 2H), 7.26 (s, 1H), 6.91 (s, 1H), 6.82 (d, *J* = 6.7 Hz, 2H), 3.02 (s, 6H), 2.65 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9, 131.6, 128.3, 127.5, 122.8, 122.4, 119.6, 115.7, 112.9, 40.9, 21.9, 17.3; GC-MS: 265; HRMS (ESI positive mode) calcd for $C_{17}H_{19}N_3+H^+$ 266.1652, found 266.1655.

1-(3-(5,7-Dimethyl-2H-indazol-2-yl)-1H-indol-1-yl)ethanone **(2n):** synthesized *via* modified GP2 (30% I_2, 24 h); yellowish solid (16.9 mg, 28% isolated yield); M.p. 158-159^oC; Rf: 0.27 (PE: EA = 4:1); ^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, *J* = 8.2 Hz, 1H), 8.30 (s, 1H), 8.00 (d, *J* = 7.6 Hz, 1H), 7.91 (s, 1H), 7.51 - 7.44 (m, 1H), 7.41 (td, *J* = 7.9, 1.0 Hz, 1H), 7.30 (s, 1H), 6.98 (s, 1H), 2.71 (s, 3H), 2.67 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 148.9, 135.1, 132.5, 129.2, 127.4, 126.7, 125.2, 124.7, 123.9, 122.6, 122.0, 119.4, 117.4, 117.1, 115.7, 24.2, 22.0, 17.3; HRMS (ESI positive mode) calcd for $C_{19}H_{17}N_3O+H^+$ 304.1444, found 304.1446.

4-(5,7-Dimethyl-2H-indazol-2-yl)phenol **(2o):** synthesized *via* modified GP2 (30% I_2, 24 h); yellowish solid (25.7 mg, 54% isolated yield); M.p. 196-198 ^oC; Rf: 0.16 (PE: EA=4:1); ^1H NMR (400 MHz, ACETONE-D6): δ 8.76 (s, 1H), 8.53 (d, *J* = 5.6 Hz, 1H), 7.88 (dd, *J* = 8.8, 1.4 Hz, 2H), 7.27 (s, 1H), 7.01 (d, *J* = 8.9 Hz, 2H), 6.88 (s, 1H), 2.56 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, ACETONE-D6): δ 157.9, 149.6, 134.5, 132.1, 128.9, 128.0, 123.9, 122.7, 120.4, 116.9, 116.8, 21.9, 17.2; HRMS (ESI positive mode) calcd for $C_{15}H_{14}N_2O+H^+$ 239.1179, found 239.1178.

7-Ethyl-3-methyl-2-phenyl-2H-indazole **(2p):** synthesized *via* GP2; colorless oil (39.3 mg, 83% isolated yield); Rf: 0.32 (PE: EA=10:1); ^1H NMR (400 MHz, $CDCl_3$): δ

7.60 - 7.51 (m, 4H), 7.51 - 7.46 (m, 2H), 7.13 (dd, *J* = 6.7, 0.8 Hz, 1H), 7.05 (dd, *J* = 8.3, 6.7 Hz, 1H), 3.11 (q, *J* = 7.5 Hz, 2H), 2.63 (s, 3H), 1.44 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 140.2, 133.8, 132.2, 129.3, 128.7, 126.1, 123.7, 121.6, 121.4, 117.5, 24.4, 14.0, 11.3; GC-MS: 236; HRMS (ESI positive mode) calcd for $C_{16}H_{16}N_2$+H^+ 237.1386, found 237.1385.

Gram scale procedure: 6.0 mmol **1b** (1.34 g) and 0.12 mmol CuI (22.8 mg) was added to a 50 mL schlenk tube. Then, 1.2 mmol I_2 (0.30 g), 2.4 mmol pyridine (193 μL) and 10 mL *p*-xylene were in turn added to the tube. The reaction was conducted under oxygen atmosphere at 120 ^{o}C for 24 h. 2 mL 1 mol/L amonia solution and 0.5 mL saturated $Na_2S_2O_3$ solution was added to the reaction mixture after cooling down. Column seperation afforded 1.18 g **2b** (89% isolated yield).

Supporting Information

Supporting information text: Containing detailed experimental procedures, characterization data of known products and some substrates, ^{1}H- and ^{13}C- NMR spectra of all products.

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