Electronic Supplementary Information

Photocatalytic Scale-up Synthesis of 2*H*-Indazoles as Drug Scaffolds in a Multi-Capillary Assembly Microreactor

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Table of contents:

1) General Considerations:

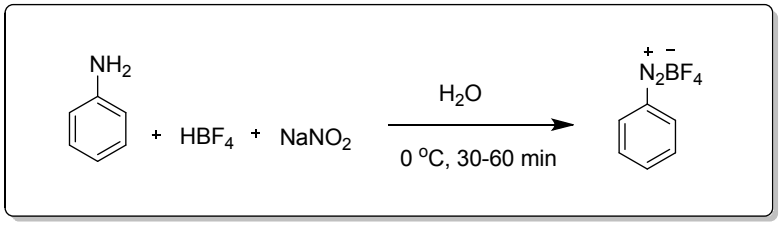
IR spectra were recorded on a Fourier transform infrared spectrophotometer in the wavenumber range of 650–4000 cm^{-1} using a JASCO (Tokyo, Japan) FT/IR-4600 instrument equipped with a universal ZnSe ATR accessory. ^{1}H NMR spectra were recorded on 600 MHz spectrometer at RT in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) (δ_H = 0.00 ppm) or $CHCl_3$ (δ_H = 7.25 ppm). ^{13}C NMR spectra were recorded on 150 MHz spectrometer at RT in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [δ_C = 77.00 ppm (central line of triplet)] using Bruker AVANCE 600 spectrometer. In the ^{1}HNMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet and br s. = broad singlet. The assignment of signals was confirmed by ^{1}H, ^{13}C CPD, and DEPT spectra. All reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel Aluminium plates 60 F_{254}; visualization was accomplished with short wavelength UV light (254 nm).

All small scale reactions were carried out using standard syringe-septum technique. Reactions monitored by TLC on silica gel using a combination of petroleum ether and ethyl acetate as eluents. Generally, reactions were run under nitrogen and oxygen atmosphere wherever necessary. Reagent-grade solvents were used; hexane, ethyl acetate and ether were obtained from commercial suppliers. Acme's silica gel (230-400 mesh) was used for column chromatography (approximately 20 g per one gram of crude material). For all compounds, we have given the ^{1}H and ^{13}C NMR data.

2) General Procedures

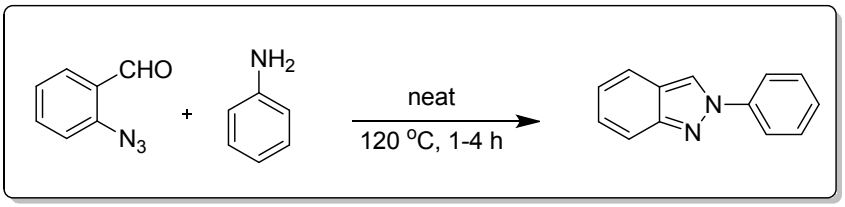
a) Preparation of aryl diazonium tetrafluoroborates[1]

The appropriate aniline (10 mmol) was dissolved in a mixture of 3.4 mL of 50% hydrofluoroboric acid and 4 mL of distilled water. Consequently, cooling the reaction mixture to 0 °C using ice bath and the sodium nitrite in water (0.69 g in 1.5 mL) was added dropwise in 5 min interval of time. The resulting mixture was stirred for 30-60 min depending upon the aniline and the precipitate was collected by filtration and re-dissolved in minimum amount of acetone. Diethyl ether was added until precipitation of diazonium tetrafluoroborate, which was filtered, washed several times with diethyl ether and dried under vacuum. The obtained salts were preserved under dark and cool atmosphere.



b) Preparation of 2*H*-indazoles[2]

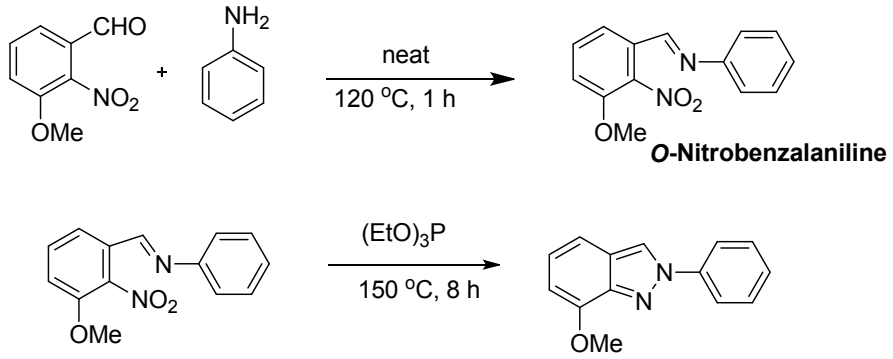
Azidobenzaldehyde (1 mmol), aniline (1 mmol) were taken in a 10 mL oven dried schlenck tube and it was closed with stopcock and placed in external heating oil bath at 120 ˚C for 1-4 h. After complete reaction of the starting material, the mixture was cooled to room temperature and was purified on a silica gel column chromatography (hexane/ethylacetate 90:10) which furnished the respective indazoles.



c) Synthesis of 7-methoxy-2-phenyl-2*H*-indazole[3]

A mixture of (1 mole) of aniline and (1 mole) of o-nitrobenzaldehyde is heated in a 20 mL round-bottomed flask on an oil bath for 1 hour, allowed to cool, and dissolved in 20 mL of ether. The ethereal solution is dried, and the ether is removed by distillation. The residue solidifies on standing and is recrystallized from 10 mL of water-ethanol (1:8) to yield 80% of yellow o-nitrobenzalaniline.

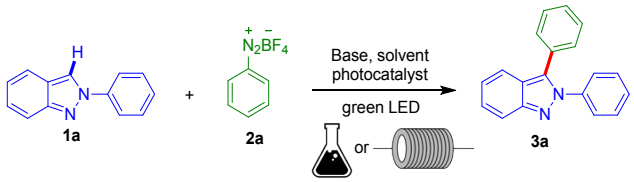
7-methoxy-2-phenyl-2*H*-indazole: 3 mole of triethyl phosphite and 1 mole of *o*-nitrobenzalaniline were taken in a 10 mL oven dried schlenk tube and it was flushed with nitrogen then closed with stopcock and placed in external heating oil bath at 150 ˚C for 8 hours and cooled, and triethyl phosphate, are removed by distillation under reduced pressure. On cooling, the black residue solidifies. The reaction mixture was purified by column chromatography.



d) Reaction of 2*H*-indazole with diazonium tetrafluoroborates in batch (3a-3c):

In a 5 mL snap vial equipped with magnetic stirring bar the Eosin Y (0.03 equiv.), 2*H*-indazole **1** (1 equiv.) and aryl diazonium tetrafluoroborate **2** (1.2 equiv.) were dissolved in 2 mL of DMSO (0.20 M) then slowly added the DIPEA (1 equiv.) to the reaction mixture. The resulting reaction mixture was irradiated with flexible green LED strip at room temperature with cooling by fan. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was transferred to a separating funnel, diluted with diethyl ether and washed with 15 mL of water. The aqueous layer was washed three times with diethyl ether. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum. Purification of the crude product was achieved by column chromatography using petrol ether/ethyl acetate as an eluent.

Table S1. **Photocatalytic reaction of 2*H*-indazole with diazonium tetrafluoroborates in batch[a] and in capillary tube[b]**



Entry	Photocatalyst (3 mol%)	Additive	Time	Solvent	Yield (%)[c]
1[a]	Eosin Y		24 h	DMSO	49
2[a]	Eosin Y	DIPEA	18 h	DMSO	65
3[b]	Eosin Y	DIPEA	1 min	DMSO	66

[a]Reaction conditions: **1** (1 equiv.), 1.2 equiv. of **2**, 1 equiv. of DIPEA, 3 mol% of Eosin Y, and 2 mL of DMSO was used. [b]Reaction condition is same with batch but reaction was performed in normal capillary tube without Eosin Y immobilization.(ID: 500 μm, L: 1 m) [c]Yields after chromatographic purification.

3) Fabrication of Eosin Y immobilized capillary tube:

The Eosin Y immobilized capillary tube was prepared by a modified procedure of literatures as following.[4] Briefly, 2 wt% of photoinitiator (Irgacure 369) and 2 wt% of thermal initiator (Dicumyl peroxide) were added to preceramic AHPCS resin as a precursor of silicate glass. The resin kept stirred for 12 h under inert and dark condition to obtain homogeneous resin. For preceramic polymer coating and hydrolysis treatment, the prepared AHPCS resin was injected into HPFA tube (ID: 0.5 mm, OD: 1.59 mm) and partially cured by UV lamp (10,000 $mWcm^{-2}$ @ 365 nm, DTX, Korea) for 3 min. Remaining steps were conducted in a continuous flow manner. Uncured inner resin was removed by air and IPA (isopropyl alcohol) repeatedly. Partially cured outer coating layer was post-cured to consolidate by UV lamp for 5 min and post-heated at 150 ^{o}C for 3 h, resulting in 50 μm thickness coating.

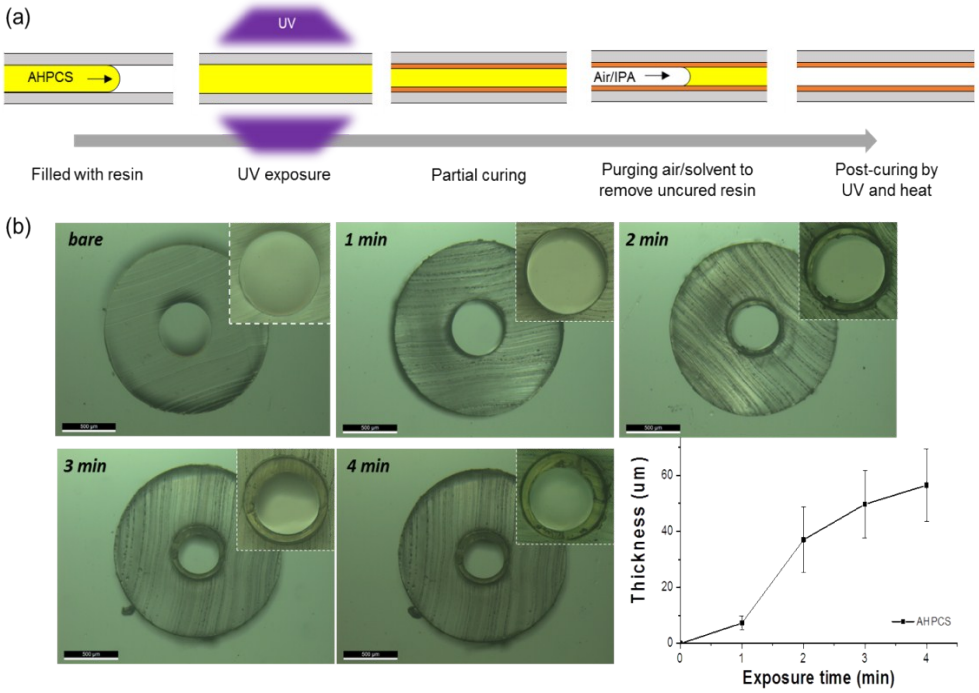


Figure S1. (a) Scheme for AHPCS coating into capillary tube, (b) cross-sectional optical images of AHPCS coated capillary tube, dependence of the coating thickness on UV exposure time.

Subsequently, preceramic polymer-to-silica conversion was carried out by hydrolysis in 0.1 M of NaOH solution at room temperature for 3 h. The silicate surface was functionalized with amine by silanization using 5 vol% of APTES (3-aminopropyltriethoxysilane) ethanol solution at 75 ^{o}C for 6 h. Then, the tubes were thoroughly rinsed with ethanol/DI water and dried 60 ^{o}C. The Eosin Y was immobilized on the amine functionalized silicate surface by injecting a mixture of 8 mM Eosin Y and 32 mM dicyclohexylcarbodiimide (DCC) dissolved in ethanol solution at 60 ^{o}C for overnight and rinsed with ethanol/DI water to remove excess amount of the Eosin Y.

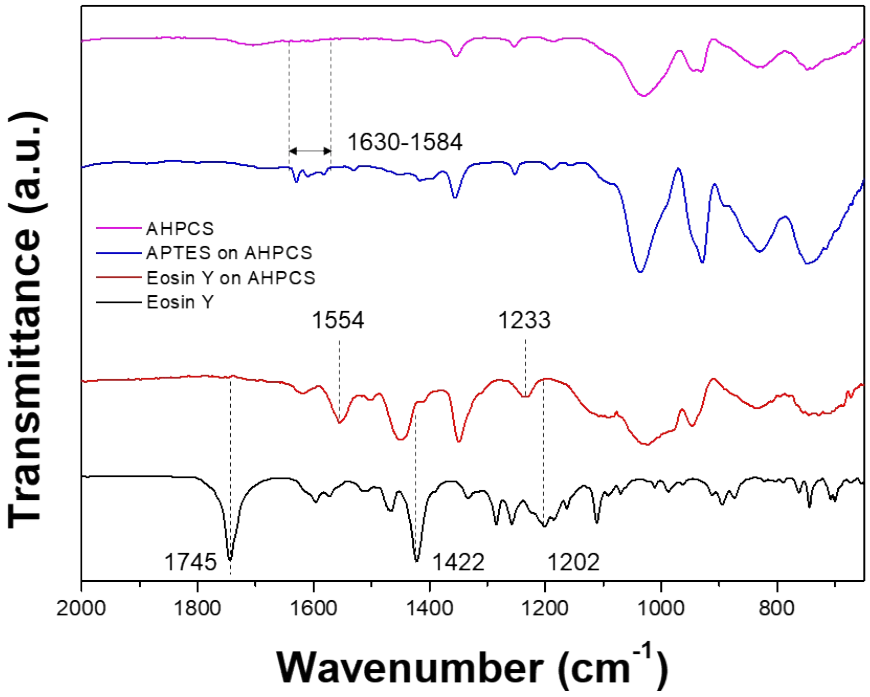


Figure S2. ATR-IR spectrum change by proceeding immobilization step.

Arylation reaction in the Eosin Y immobilized single capillary microreactor (3a):

In an oven-dried glass vial 1 mole of 2*H*-indazole (**1**) and 1.2 mole of aryl diazonium tetrafluoroborate (**2**) were dissolved in 2 mL of DMSO (0.20 M) then slowly added the 1 mole of DIPEA to the reaction mixture. The resulting reaction mixture were transferred into 10 mL NORM-JECT plastic syringes and introduced into the Eosin Y immobilized capillary microreactor in the green LED container through a syringe pump. (**Figure S3**) The flow rate was set to 200 μLmin^{-1}, thus resulting in 0.63 min of residence time. After reaching steady state, a reaction sample was collected in a vial and measured the collected volume. The sample was then diluted with water and extracted with Ether (x 3). The organic layer was washed with brine, dried with Na_2SO_4 and evaporated under reduced pressure. The resulting crude compound was absorbed on silica gel and purified via column chromatography (EtOAc/Hexane, varying ratios). The isolated compound was analysed by NMR. After completion of the reaction the capillary tub was washed with ethanol and water (2 times) and used for next reaction. Likewise this procedure, the stability of immobilized Eosin Y was tested by running for 1 h continuously and determined the yields every 10 min to check the catalyst leaching (**Table 1**).

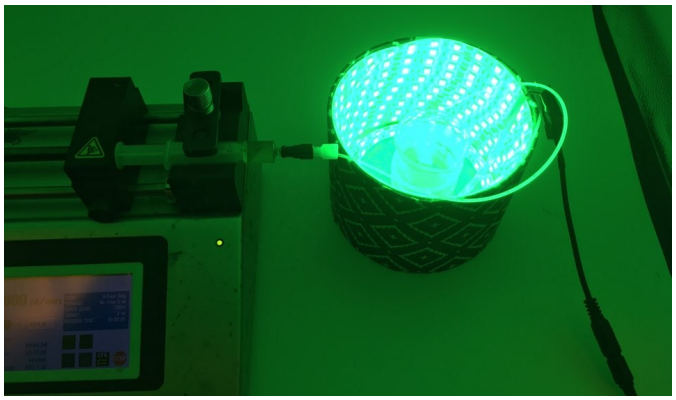


Figure S3. Experimental set-up of photocatalytic continuous-flow reaction in Eosin Y immobilized highly transparent perfluoroalkoxy alkane (HPFA) coil reactor with green LED.

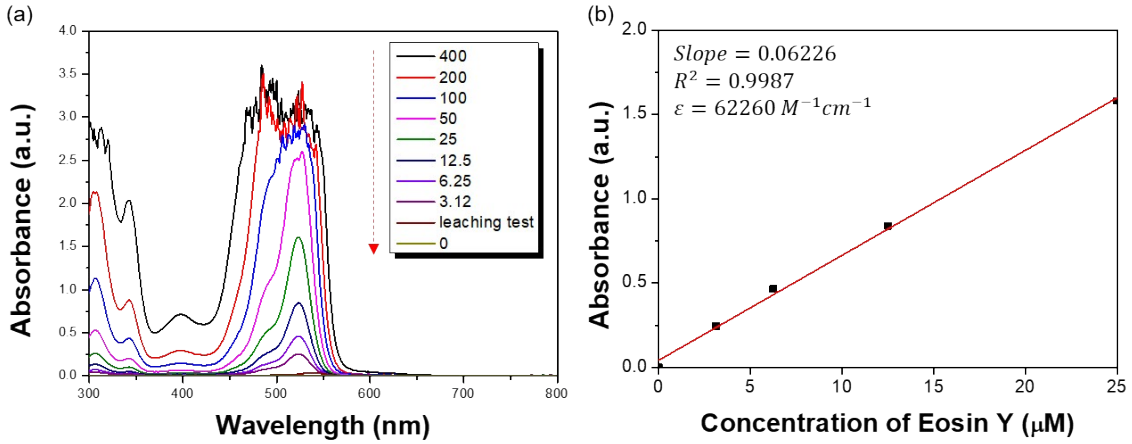
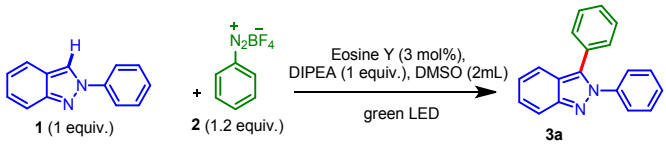


Figure S4. Eosin Y leaching test flowing solvent over a day. (a) UV-vis spectra of various concentration of the known concentration of Eosin Y, (b) calibration curve plot of absorbance at 523 nm versus concentration of Eosin Y.

Table S2. Control reactions for photocatalyzed direct arylation of **1**[a]



Entry	Eosin Y	Light	Yield [%][b]
1	O	O	65
2	X	O	n.d
3	O	X	5

[a]Reaction conditions: **1** (1 equiv.), 1.2 equiv. of **2**, 1 equiv. of DIPEA and 2 mL of DMSO was used. [b]Yields after chromatographic purification.

4) Fabrication of assembly microreactor with Eosin Y immobilization for scale-up synthesis:

The numbered-up capillary microreactor was fabricated by combining three parts (3D printed flow distributor, reaction capillaries, and 3D printed collector) into monolithic compact system (**Figure S5a and b**). A cylinder cone shape of the flow distributor in the scale-up reactor has only a single entrance for delivering a premixed reagent into a chamber of flow distribution by only a single pumping system. Computational fluidic dynamics (CFD) technique simulated that the infused reagent comes through the single entrance and evenly distributed into 10 capillary exits over gravity interference in a co-upstream flow manner. In detail, the fed reagent at bottom center of cylinder cone is equally and radially distributed into 10 exit ports connected with Eosin Y immobilized capillary (ID 0.5 mm, OD 1/16 inch = 1.59 mm) that are located at periphery of flat cylindrical surface with symmetrical arrangement (**Figure S5c and d**).

The flow distributor and collector was fabricated using a digit light processing (DLP) type of 3D printer (MiiCraft Plus, Rays Opticals Inc., Taiwan) with commercially available resin (BV-007, MiiCraft).[5] For computational fluid dynamics (CFD) analysis of the 3D-printed flow distributor, the incompressible Navier-Stokes equations were discretized using Autodesk CFD (Autodesk, USA) using the available commercial packages. The viscosity and density of the working fluid was assumed to be the same as that of dimethyl sulfoxide (DMSO) (1.996 cPs and 1.1004 g/cm^3). No-slip boundary conditions are applied to wall boundaries (**Figure S5e**). The premixed reagent with 2 mLmin^{-1} of flow rate (red) are fed into the 3D printed flow distributor and flow rate was drastically decreased in the 3D printed flow distributor. Then, the reagent come out through 10 exits with 200 μLmin^{-1} of flow rate (sky blue) and go into the Eosin Y immobilized capillary tubes. The actual fluid distribution was experimentally measured by weighing the solution at each outlet to support the uniform fluid distribution calculated by CFD analysis.(**Figure S5f**) We infused the water with 2 mL/min in the scale-up microreactor and collected the samples from the outlets for 10 min. The maldistribution factor (MF) as a measure of flow uniformity was calculated by measuring the weights of the collected 10 samples.

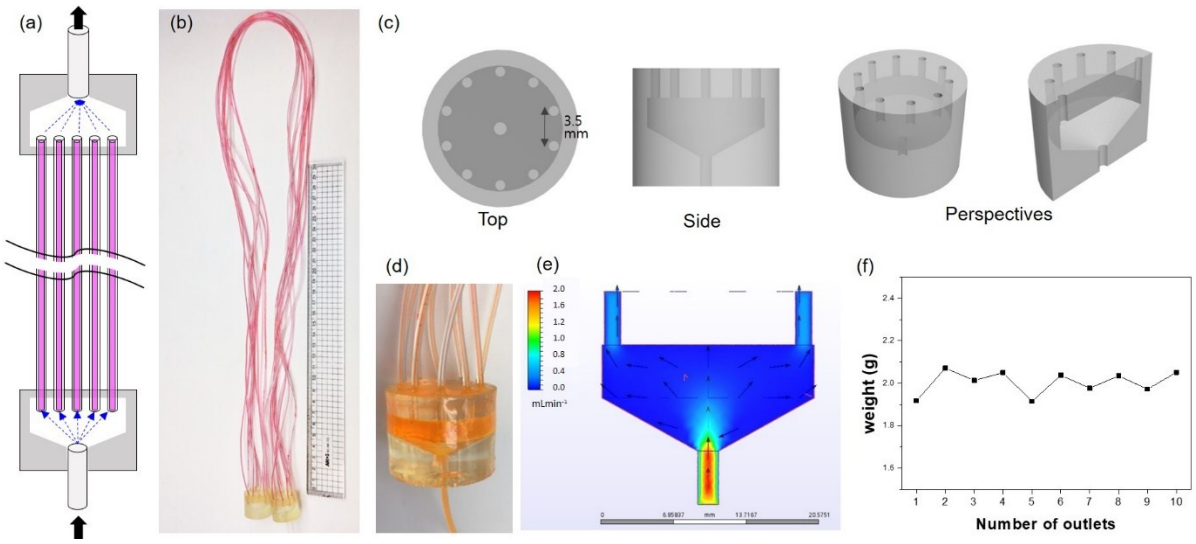
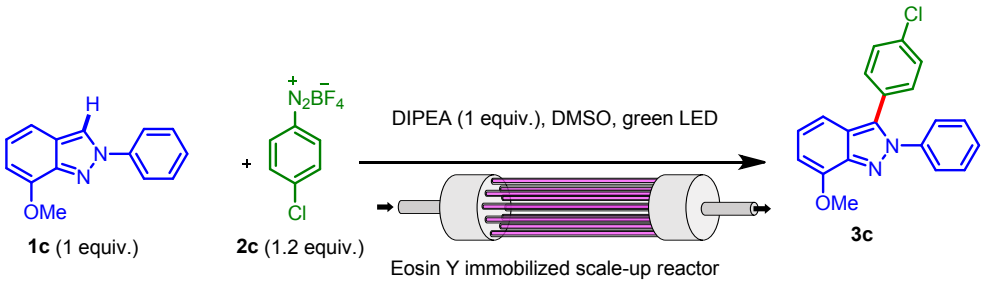


Figure S5. (a) Cross-sectional scheme of scale-up assembly microreactor and its co-upstream flow direction, (b) photographic image of Eosin Y immobilized 10 capillaries with 1 m length that are connected at both ends to 3D printed inlet and outlet fixtures, (c) detailed 3D max design of 3D printed distributor and collector. (d) photographic image of 3D printed distributor filling with orange dye, (e) Cross-sectional CFD analysis of the 3D-printed flow distributor, (f) The actual fluid distribution measured by weighing the collected solution samples from 10 outlets.

General procedure for large-scale synthesis of 3c:



In an oven-dried glass vial, 1 equivalent of 7-methoxy-2-phenyl-2*H*-indazole (4 g) and 1.2 equivalent of 4-chloro-phenyl diazonium tetrafluoroborate (4.84 g) were dissolved in 120 mL of DMSO then slowly added the 1 equivalent of DIPEA (2.26 g) to the reaction mixture. The vial was fitted with a PTFE septum and purged with argon. The solutions were transferred into NORM-JECT plastic syringes and introduced into the photo-microreactor through a syringe pump. The flow rate was set to 2 $mLmin^{-1}$, thus resulting in 0.63 min residence time. After reaching steady state, the photoreaction product was connected to work-up process directly and collected in a vial. The organic layer was dried with Na_2SO_4

and evaporated under reduced pressure. The resulting crude compound was absorbed on silica gel and purified via column chromatography (EtOAc/Hexane, varying ratios) and found the 63% of yield (3.75 gh^{-1}).

5) Experimental set-up of a compact assembly microreactor for autonomous serial process:

The entire photocatalytic reaction set-up was presented in **Figure S6**. Photocatalytic reactor was vertically put in 1 m length of transparent quartz tube (45 mm) and 5 m green LED lamp strip coiled around quartz (**Figure S6a**). To enhance light concentration in the reactor, aluminum foil covered outside of quartz and hand type fan was installed to avoid thermal effect during the long-term reaction (**Figure S6b**). The premixed reagent was fed from the bottom of scale-up photocatalytic reactor using syringe pump. After photocatalytic reaction, the reagent came out from the top of reactor and directly went to cross-junction for continuous generation of alternating DMSO/water droplet and ether droplet with volume < 0.5 μL in the HPFA capillary (1mm diameter) Note that water is well-miscible with DMSO to become a hydrophilic aqueous-like phase, but immiscible with less polar ether medium. At the cross-junction, DMSO/water/diethyl ether were mixed together and generated uniform micro droplets (Volume < 0.5 μL). by individually injecting water and ether at 2 $mLmin^{-1}$ (**Figure S6c)**. The sufficient difference in polarity of DMSO/water and ether accomplished the extraction of product (**3c**) from the DMSO/water phase to the ether phase, followed by decanted separation of the supernatant ether mixture (**Figure S6c**).

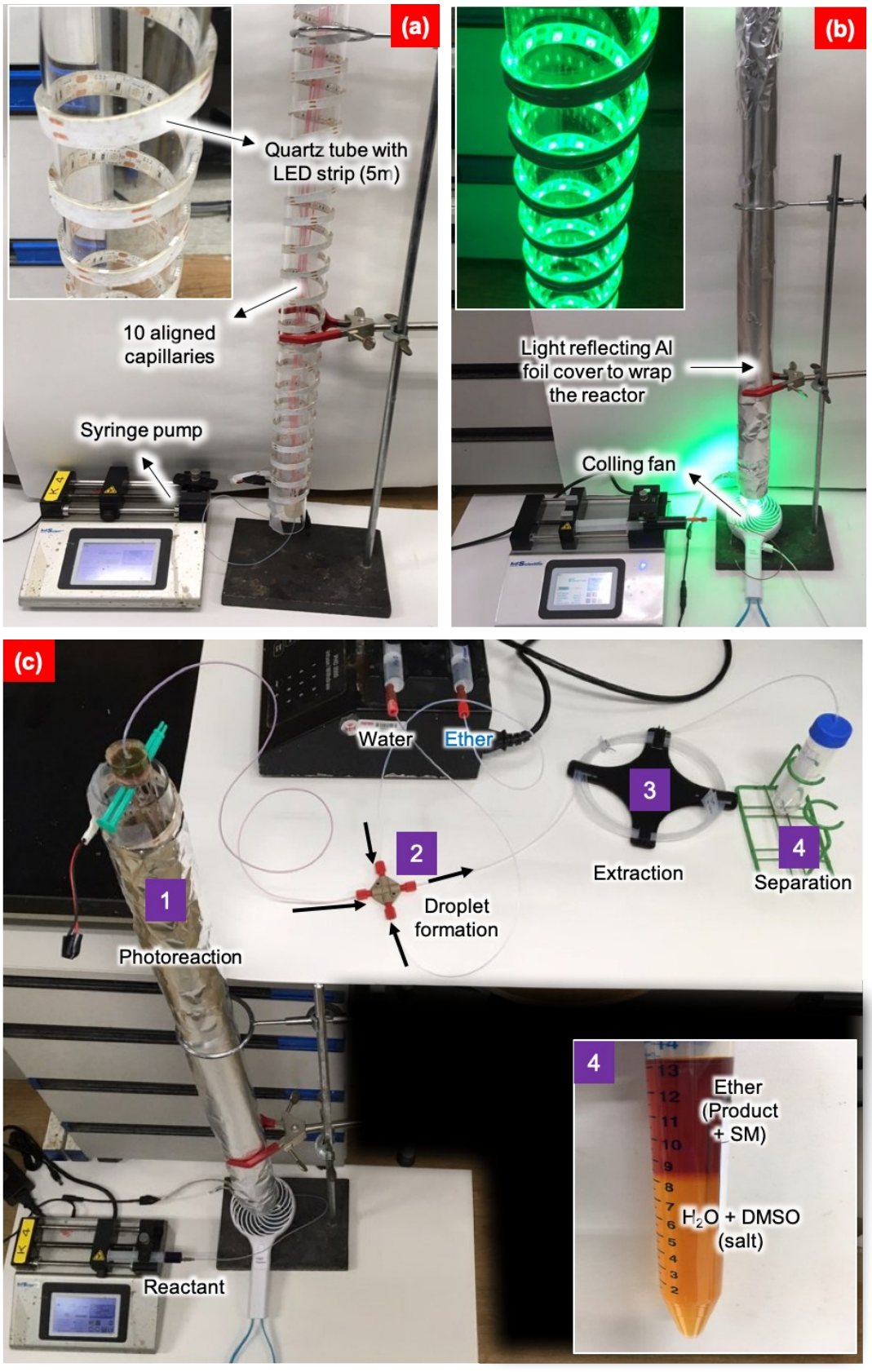

(a)
Quartz tube with LED strip (5m)
10 aligned capillaries
Syringe pump
(b)
Light reflecting Al foil cover to wrap the reactor
Colling fan
(c)
Water
Ether
1
Photoreaction
2
Droplet formation
3
Extraction
4
Separation
Reactant
4
Ether (Product + SM)
H2O + DMSO (salt)

Figure S6. Photographic images of scale-up assembly system and the integrated process. (a) Photocatalytic microfluidic set-up installed into quartz outer tube without illumination, (inset) magnified quartz tube image; (b) turned on green LED lamp. (c) (1) wrapping the entire reactor with light reflecting Al foil cover and cooling fan, (inset) magnified quartz tube image; (2) alternating droplet microfluidic generator by infusing water and ether to cross mixer. (3) Product extraction along HPFA capillary (1~15 m length, ID: 1 mm) from non-volatile DMSO to highly volatile ether. (4) Collected vial with phase separation, product was readily isolated by drying the solvent from the supernatant ether mixture.

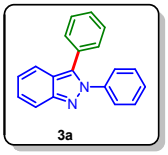
Table S3. Optimization of product (**3c**) isolation via alternating liquid-liquid droplet extraction process at different length of HPFA capillary at fixed flow rate 2 mL/min.

Entry	Capillary length (m)	Extraction time (min)	Yield (%)
1	1	0.16	34
2	3	0.47	43
3	6	0.94	55
4	10	1.57	60
5	15	2.36	63
6[a]	Separatory funnel	-	63

[a]Conventional work-up process result by using separatory funnel

6) Spectral data of all synthesized compounds (3a-3c):

2,3-Diphenyl-2*H*-indazole (3a)[6]



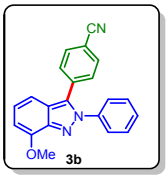
^{1}HNMR (600 MHz, $CDCl_3$):

δ ppm 7.82 (d, 1H, J = 8.7 Hz), 7.74 (d, 1H, J = 8.3 Hz), 7.47-7.45 (m, 2H), 7.42-7.37 (m, 9H), 7.17-7.15 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$):

δ ppm 149.0, 140.2, 135.4, 129.9, 129.7, 129.0, 128.8, 128.3, 128.2, 127.0, 126.0, 122.5, 121.7, 120.5, 117.8.

4-(7-Methoxy-2-phenyl-2*H*-indazol-3-*yl*)benzonitrile (3b)[7a, 8]



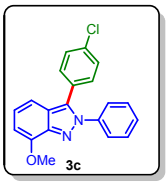
^{1}HNMR (600 MHz, $CDCl_3$):

δ ppm 7.70-7.68 (m, 2H), 7.48 (d, 2H, J = 8.3 Hz), 7.45-7.43 (m, 4H), 7.28-7.27 (m, 2H), 7.15 (t, 1H, J = 7.9 Hz), 6.69 (d, 1H, J =7.2 Hz), 4.09 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$):

δ ppm 150.7, 142.7, 139.7, 134.6, 133.6, 133.2, 132.5, 130.0, 129.2, 128.8, 126.3, 124.5, 123.5, 118.4, 111.7, 111.4, 103.6, 55.6.

3-(4-Chlorophenyl)-7-methoxy-2-phenyl-2*H*-indazole (3c) [7a, 8]



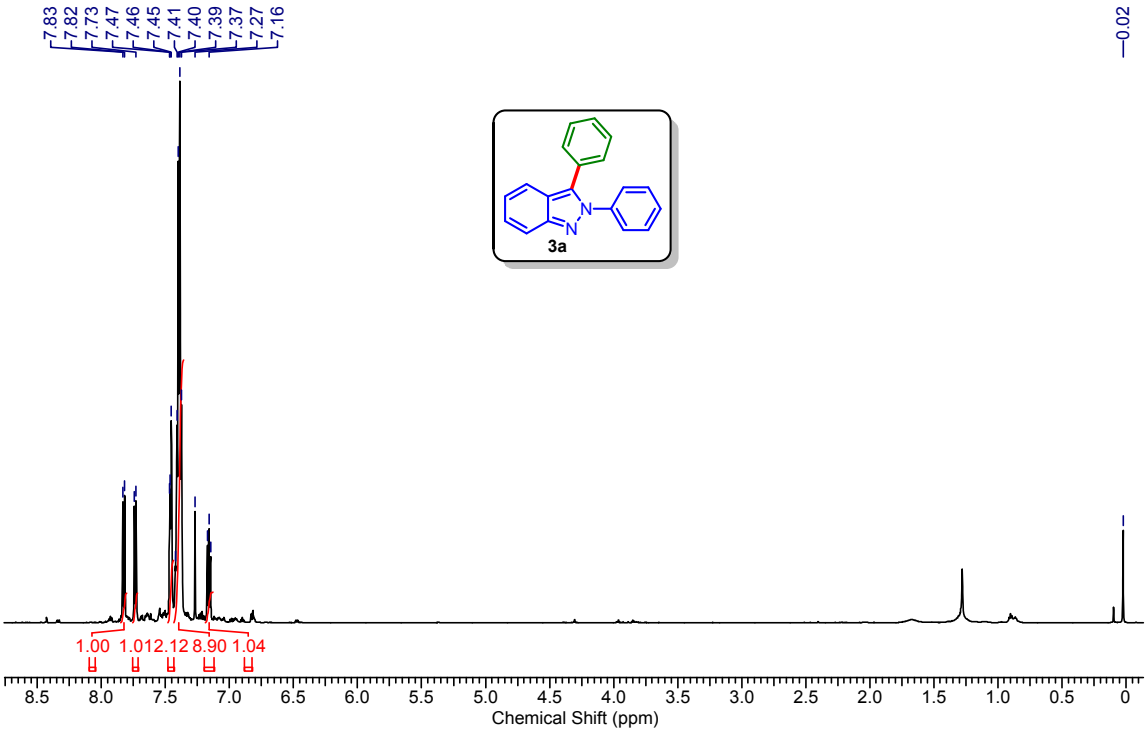
^{1}HNMR (600 MHz, $CDCl_3$):

δ ppm 7.47-7.44 (m, 2H), 7.42-7.37 (m, 5H), 7.31-7.29 (m, 2H), 7.26 (d, 1H, J = 8.5 Hz), 7.1 (t, 1H, J = 7.9 Hz), 6.66 (d, 1H, J = 7.3 Hz), 4.08 (s, 3H).

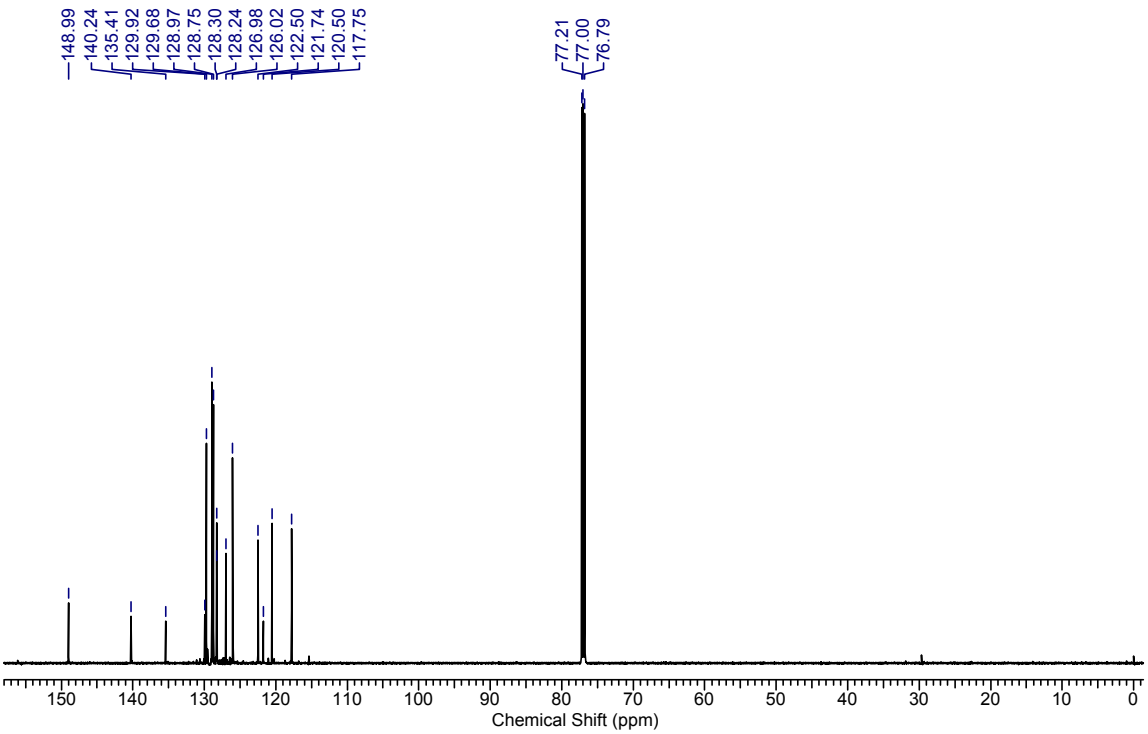
^{13}C NMR (150 MHz, $CDCl_3$):

δ ppm 150.7, 142.7, 140.2, 134.5, 134.4, 131.1, 129.2, 129.1, 128.7, 128.6, 126.4, 123.7, 123.5, 112.1, 103.7, 55.8.

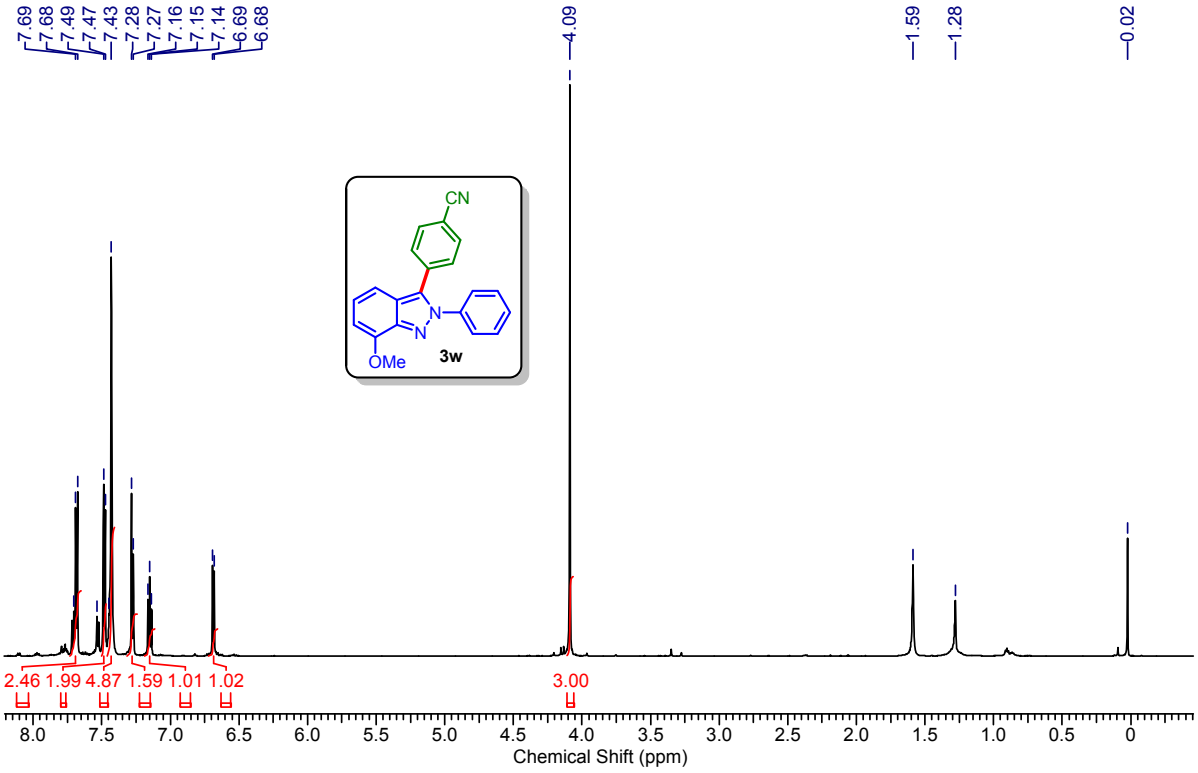
7) NMR copies of all synthesized compounds (3a-3c):



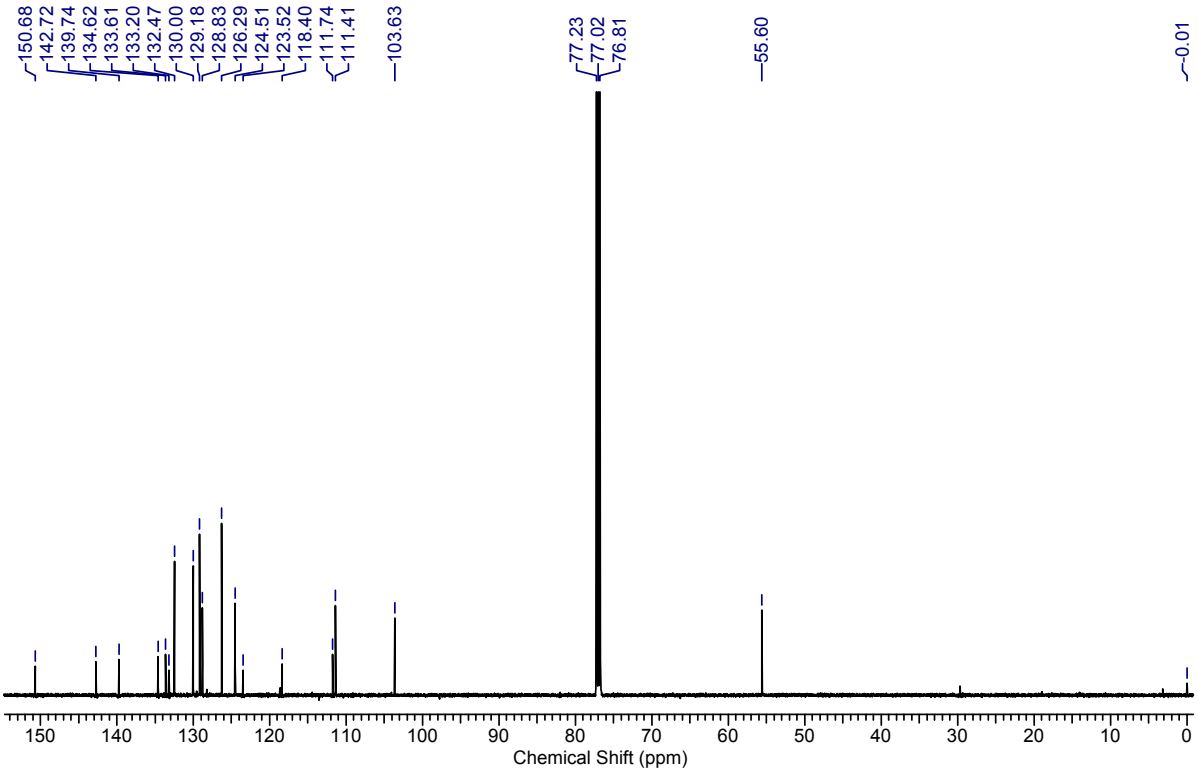
^{1}H NMR spectrum of compound **3a** in $CDCl_3$



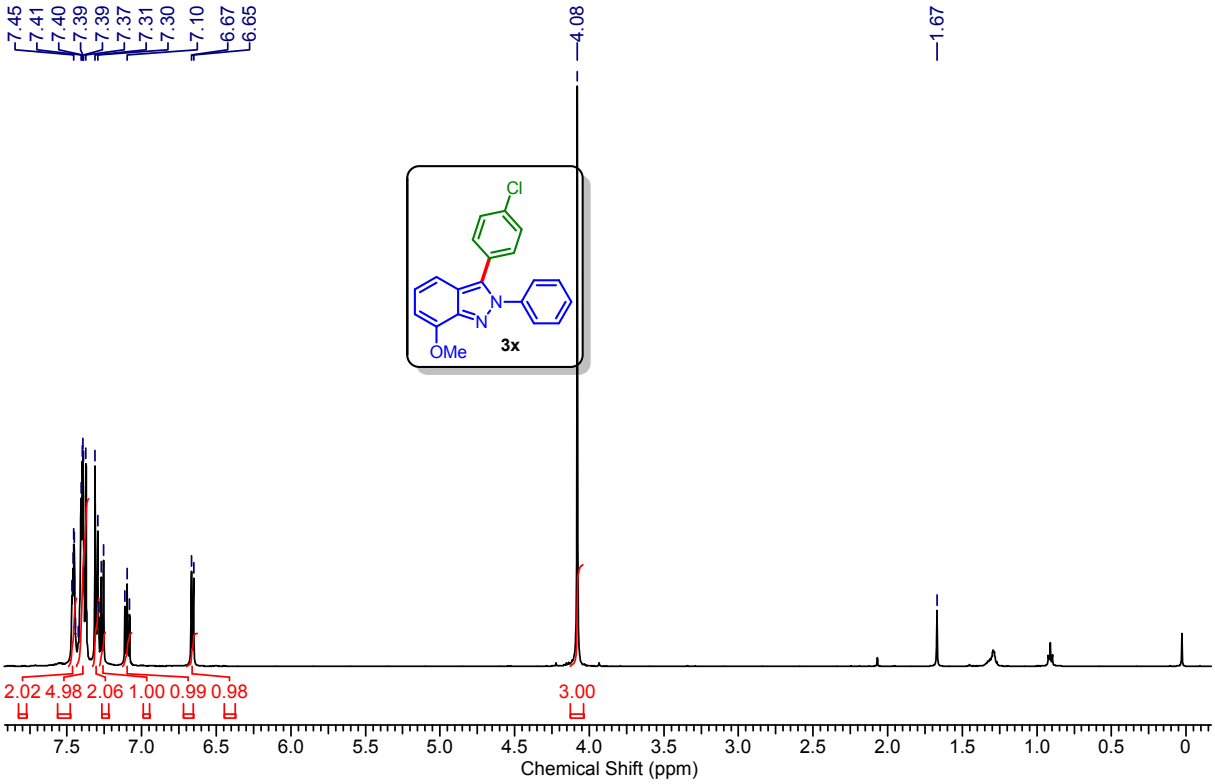
^{13}C NMR spectrum of compound **3a** in $CDCl_3$



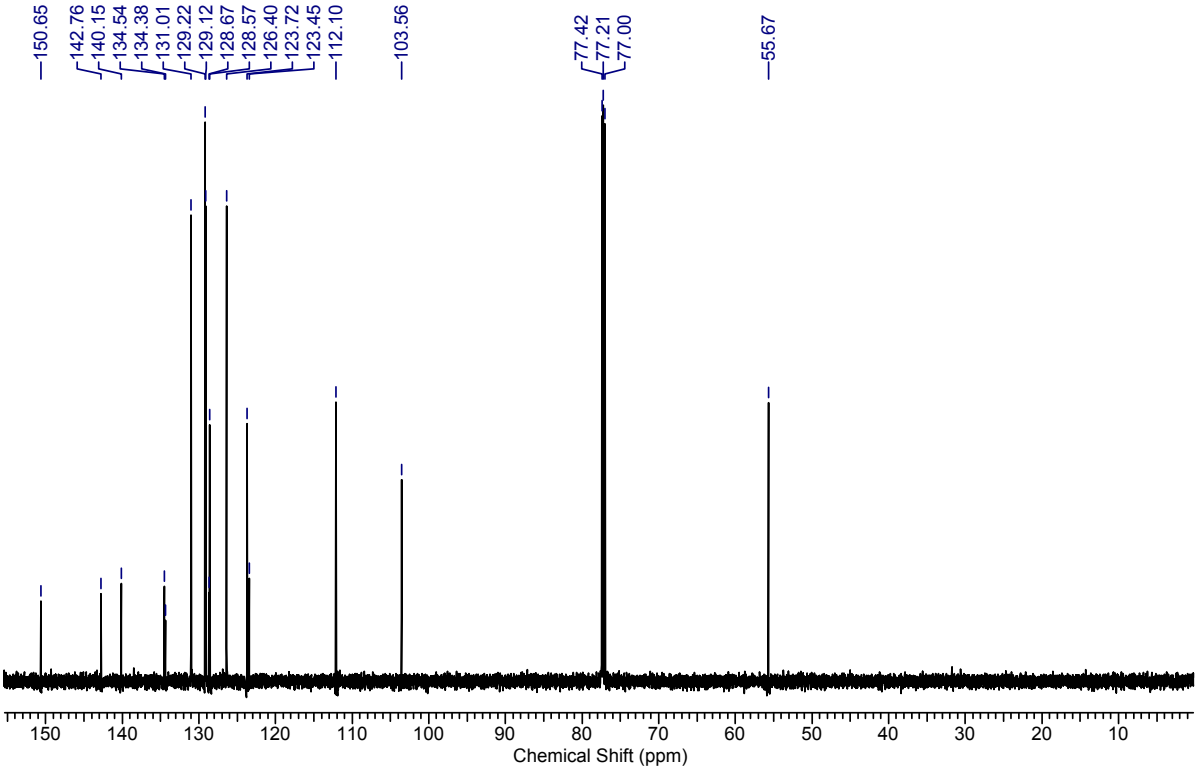
^{1}H NMR spectrum of compound **3b** in $CDCl_3$



^{13}C NMR spectrum of compound **3b** in $CDCl_3$



^{1}H NMR spectrum of compound **3c** in $CDCl_3$



^{13}C NMR spectrum of compound **3c** in $CDCl_3$

8) References:

1. (a) J. Zoller, D. C. Fabry, M. Rueping, *ACS Catal*., **2015**, *5*, 3900−3904. (b) D. P. Hari, P. Schroll, B. König, *J. Am. Chem. Soc*., **2012**, *134*, 2958−2961. (c) H. D. Kim, J. Lee, A. Lee, *Org. Lett*., **2018**, *20*, 764.
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