Regioselective C3-H trifluoromethylation of 2*H*-indazole under transition-metal-free photoredox catalysis

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Abstract

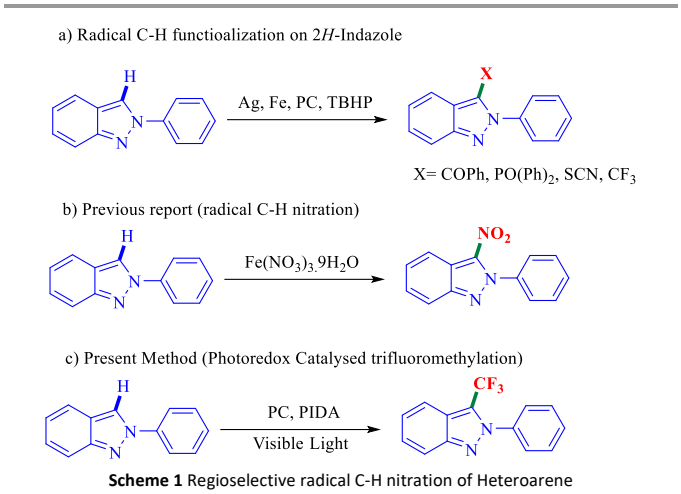
Here we report a visible-light-promoted metal-free regioselective C3-H trifluoromehtylation reaction that proceeds via radical mechanism and which supported by control experiments. The combination of photoredox catalysis and hypervalent iodine reagent provides a practical approach for the present trifluoromethylation reaction and synthesis of a library of trifluoromethylated indazoles.

Introduction

The halo-organic compounds are typically considered as sites of high electron density because of their more electronegativity. In general, the halogen atoms can form attractive interaction due to electron donor sites (*i.e* nucleophiles).[1] Among them, the C-F bond has importance causes of long-standing significance in the development of pharmaceuticals, the prevalent halogen found in drugs. This comes out due to fluorine's similar size to hydrogen but significantly increased electronegativity.[2] In this context, the trifluoromethyl group has very important structural motifs in agrochemical, pharmaceutical, drug candidates and it can enhance their chemical and metabolic stability, increase lipophilicity and bioavailability, and also trifluoromethyl containing organic compounds are commonly applied in material like liquid crystals.[3]

Over the past decade, due to the importance of trifluoromethylation process several methods have been developed by using various radical, nucleophilic, and electrophilic trifluoromethylating agents such as CF_3I,[4] CF_3SO_2Cl,[5] CF_3COOH,[6] Ruppert-Prakash reagent ($TMSCF_3$),[7] Tognis' reagent,[8] Umemotos' reagent[9] and Baran reagent/Langlois' ($(CF_3SO_2)_2Zn$[10] /CF_3SO_2Na,[11]). Among these reagents, Langlois' reagent is a benchtop-stable, cheapest, easy to handle and convenient reagent for trifluoromethylation reaction.[12] Hence there is a wide scope for the development of strategies for the radical trifluoromethylation of heteroarenes.[13]

In recent years, the visible light induced photoredox catalytic activation of organic molecules has been established as a powerful strategy in modern organic synthesis with providing an attractive features, like mild environmentally begin, excellent functional group tolerance, and high reactivity.[14] In photoredox catalysis, metal complexes and organic dyes as photocatalysts have the ability to involve on single-electron-transition (SET) process upon photoexcitation with visible light.[15] Moreover, the usage of organic dyes is inexpensive and easy to handle as photoredox catalysts, and hence this would be a superior substitute to inorganic transition metal photocatalyst.



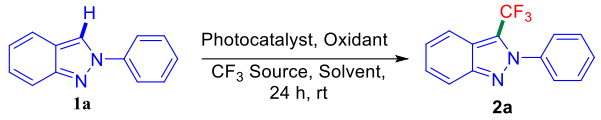
Scheme 1 Regioselective radical C-H nitration of Heteroarene

Nitrogen containing heterocycle compounds are gained significant importance in natural products and have a huge number of biological activities.[16] Among them, indazoles have bioactivities[17] such as antitumor,[18] antimicrobial,[19] anti-inflammatory,[20] anti-HIV,[21] anti-platelet[22] and anti-contraceptive.[23] Considering the immense importance of derivatives of 2*H*-indazole in the field of contemporary medicinal chemistry. In this context, an expensive effort has been devoted for the synthesis and functionalization of 2*H*-indazole.[24] Recently, oh's group have reported the silver catalyzed direct acyl radical addition to 2*H*-indazole[25a] and Hajra *et al* have also realized the construction of carbon-phosphorus (C-P)[25b] and carbon-sulfur (C-S)[25c] bond formations on indazole under mild condition (scheme 1a). Very recently, Hajira and co-workers described a new approach for direct C3-trifluoromethylation of 2*H*-indazole mediated by peroxides (scheme 1a).[25d] The transition-metal catalyst, peroxides and high temperatures were required in these elegant works.

The development of efficient and direct C-H bond functionalization has received a much attractive and reliable for various transformations and became step- and atom-economy advantages.[26] In recent years metal-free radical C-H functionalization has paid much attention by several synthetic chemists.[27] Due to the recent appearance of radical C–H functionalization as a new paradigm in contemporary chemistry and as part of our investigation on C–H functionalization and indazoles chemistry.[28] Herein, we would like to report a novel metal-free organic dye visible light photoredox catalysis for regioselective C3-trifluoromthylation on 2*H*-indazole.

Results and discussion

Table 1 Optimization of Reaction Conditions for the Synthesis of **2a**[a]

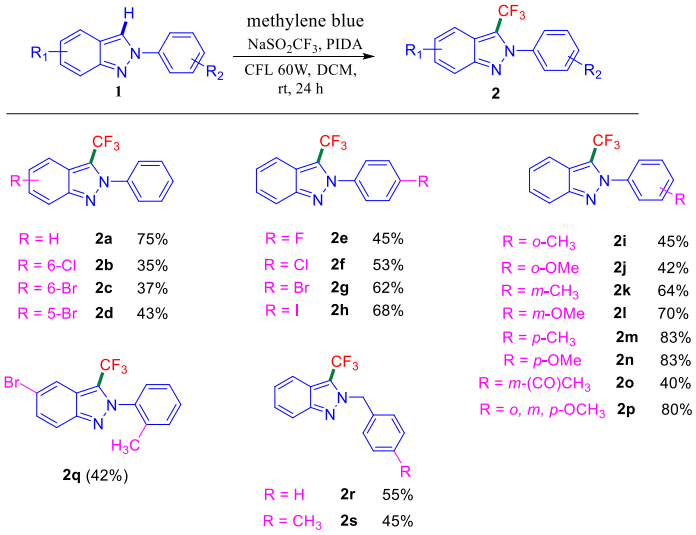


entry	nitro source	oxidants	solvent	time (h)	yield (%)[b]
1	Rosebengal	PIDA	$NaSO_2CF_3$	DCM	60
2	Rosebenga	$K_2S_2O_8$	$NaSO_2CF_3$	DCM	-
3	Rosebenga	TBHP	$NaSO_2CF_3$	DCM	-
4	Rosebenga	IBA-OAc	$NaSO_2CF_3$	DCM	Trace
5	Rosebenga	PhIO	$NaSO_2CF_3$	DCM	Trace
6	Rosebenga	-	$NaSO_2CF_3$	DCM	ND
7	-	PIDA	$NaSO_2CF_3$	DCM	Trace
8	$RuCl_2$	PIDA	$NaSO_2CF_3$	DCM	Trace
9	Eosin-Y	PIDA	$NaSO_2CF_3$	DCM	50
10	RhodamineB	PIDA	$NaSO_2CF_3$	DCM	Trace
11	**Methylene blue**	**PIDA**	$NaSO_2CF_3$	**DCM**	**75**
12	Azure-B	PIDA	$NaSO_2CF_3$	DCM	55
13	Riboflavin	PIDA	$NaSO_2CF_3$	DCM	Trace
14	Methylene blue	PIDA	$NaSO_2CF_3$	CH3CN	30
15	Methylene blue	PIDA	$NaSO_2CF_3$	DCE	50
16	Methylene blue	PIDA	$NaSO_2CF_3$	Acetone	Trace
17	Methylene blue	PIDA	$NaSO_2CF_3$	DMSO	n.d
18	Methylene blue	PIDA	$NaSO_2CF_3$	Toluene	n.d
19	Methylene blue	PIDA	$NaSO_2CF_3$	MeOH	n.d
20	Methylene blue	PIDA	$NaSO_2CF_3$	EtOH	n.d
21	Methylene blue	PIDA	$NaSO_2CF_3$	Dioxane	n.d
22	Methylene blue	PIDA	$NaSO_2CF_3$	DMF	n.d
23	Methylene blue	PIDA	$TMSCF_3$	DCE	n.d
24	Methylene blue	PIDA	ICH_2CF_3	DCE	n.d
25	Methylene blue	PIDA	CF_3SO_2Cl	DCE	n.d

[a]Reaction conditions: **1a** (1 mmol), nitro source (2 mmol), oxidant (1 mmol), solvent (1 mL), oxygen balloon, 80 ºC, 5 – 12 h. [b]Isolated yield of chromatographically pure products. [c]Starting materials recovered. [d]Reaction carried out in open air.

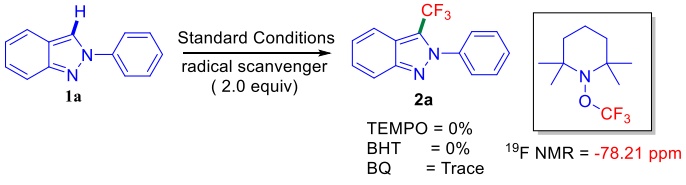
In the initial experiments, we have chosen 2-phenyl-2*H*-indazole as the model substrate, Langlois' reagent as a radical CF_3 source and phenyliodine(III) diacetate (PIDA) as an oxidant with 2mol% rosebengal as a photocatalyst in MeCN solvent irradiated with 60 W Compact Fluorescent Bulb (CFL) blub at room temperature. Delightfully, C3-trifluoromethylated product **2a** was obtained in 60% yield after 24 hrs (table 1, entry 1). Then next the effect of other oxidants such as $K_2S_2O_8$, TBHP, IBA-OAc, and PhIO were examined (table 1, entry 2-5), unfortunately, our attempts went in vain. To improve the reaction efficiency in terms of yields, we have tested the various photocatalysts, and methylene blue (table 1, entry 11) was found to be effective and provided the desired product **2a** with 75% yield. Among solvents screened (table 1, entry 14-22), DCM was found to be most efficient. Further improve the yields eventually a Variety of CF3 sources were tested, and which provided unsatisfactory yields (table 1, entry 23-25).

Table 2 Substrate scope for the C3-trifluoromethylation of 2*H*-indazole[a,b]



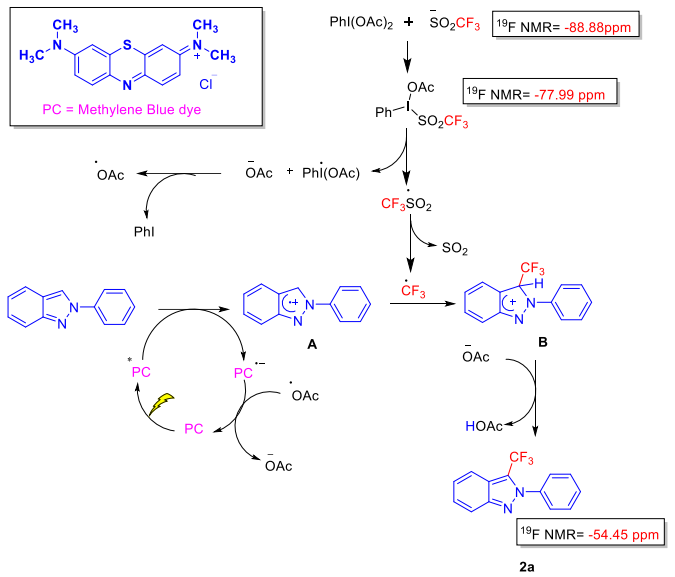
[a]Reaction Condition: **1a** (1 mmol), PIDA (2 mmol), $NaSO_2CF_3$ (2 mmol), DCM (1 mL), 60 W CFL blub, rt, 24h. [b]Isolated yield of chromatographically pure products.

The established optimized reaction condition (table 1, entry 11) in our hand, we have examined the substrate scope of this protocol with different substitution on 2*H*-indazole. Initially, we have checked the halogen substitution on 2*H*-indazole (**2b-h**). The presence of halogen at 5th and 6th positions of 2*H*-indazoles (**2b-d**) gave a poor yield. On the other hand, the halogen substitution in *para*-position of the amine partner of 2*H*-indazoles (**2e-h**) gave 45% to 68% yields. Likewise, the amine partner of 2*H*-indazoles bearing electron donating group (-Me, -OMe) resulted the estimated products with very good yield (**2k-n** & **2p**). This may be due to increasing the electron density at C3-position on 2*H*-indazole. However, the electron donating groups (-Me, -OMe) substitution in *ortho*-position (**2i-j**) gave moderate yield, this is due to steric hindrance of the *ortho*-substitution. We have observed poor yield, when electron withdrawing group presence on 2*H*-indazole (**2o**), since it is decreasing the electron density at C3-position. In case of benzylamine partner C3-H trifluoromethylated indazole were obtained in low yield.



Scheme 3 Control Experiments

Few control experiments were performed to insights a better understanding of the possible mechanistic pathway as shown in scheme 3. We have observed that 2-phenyl-2*H*-indazole (**1a**) failed to produce the corresponding trifluoromethylation product (**2a**) in the presence of radical scavengers such as TEMPO, BHT, BQ. These results indicate, the reaction mechanism proceed through a radical pathway.



Scheme 4 Plausible Mechanism

Based on the control experiment result (see SI) and previous literature reports,[28] the plausible reaction mechanism of the present trifluoromethylation on 2-phenyl-2H-indazole depicted in scheme 4. Initially, the CF_3 radical species would generated by the reaction of $NaSO_2CF_3$ with PIDA. Meanwhile, the photocatalyst (**PC**) converted to its excited state **PC*** upon absorption of photons from visible light. The **PC*** produce the indazole radical cation A from the oxidation of indazole along with generation of photocatalytic radical anion **PC** via single electron transfer (SET) process. The regeneration of photocatalyst from photocatalyst radical anion in presence of acetate radical. The generated CF3 radical would attack intermediate B. finally deprotonation of intermediate B affords the trifluoromethylation product **2a**.

Conclusions

We have successfully demonstrated a novel photoredox radical regioselective C-H trifluoromethylation on 2*H*-indazole. This protocol offers transition metal-free photoredox catalyzed C3-H trifluoromethylation with inexpensive and benchtop-stable Langlois' reagent under mild condition. The present protocol will gain much significance in organic chemistry, pharmaceutical chemistry, and material science.

Conflicts of interest

There are no conflicts to declare

Acknowledgements

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General Considerations

IR spectra were recorded on a FTIR spectrophotometer. ^{1}H NMR spectra were recorded on 400 MHz spectrometer at 295 K 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 100 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)]. 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, and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded using Q-TOF multimode source. Melting points were determined on an electro thermal melting point apparatus and are uncorrected. *o*-azidobenzaldehydes prepared by using literature known procedures, 2-aminophenols all were commercial available. Pd-catalysts and all bases were purchased from Sigma Aldrich. All dry solvents were used, toluene were dried over sodium metal and DMSO, CH_3CN and DMF were dried over calcium hydride and which are commercial available.

All small scale dry reactions were carried out using standard syringe-septum technique. Reactions were monitored by TLC on silica gel using a combination of petroleum ether and ethyl acetate as eluents. Reactions were generally run under argon, nitrogen and oxygen atmosphere wherever necessary. Solvents were distilled prior to use; petroleum ether with a boiling range of 40 to 60 ˚C was used. Acme's silica gel (60–120 mesh) was used for column chromatography (approximately 20g per one gram of crude material). All 2-azidobenzaldehydes (**1a-1c and 1e**) except **1d** have been synthesized by using literature known procedures.

General procedure (GP-I) for the synthesis of 2-phenyl-2*H*-indazole

Azidobenzaldehyde **1** (1 mmol), aniline **2** (1 mmol) were taken in a 10 mL oven dried schlenck tube and it was closed with stopcock with argon balloon and placed in external heating oil bath at 120 ˚C for 1-3 hrs (oil bath temperature). After completion 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 products **1a-s.**

General procedure (GP-II) for the synthesis of 2-phenyl-3-(trifluoromethyl)-2*H*-indazole

In oven-dried reaction vessel equipped with a magnetic stir bar. Then 2-phenyl-2*H*-indazole (1 mmol), PIDA (2 mmol), sodium triflate (2mmol) were added and followed by addition of DCM (1 mL). the resulting reaction mixture was irradiated using a 60 W CFL bulb. The progress of the reaction was monitored by TLC until the reaction was completed. The reaction mixture was quenched by addition of aq. NH_4Cl solution and extracted with ethyl acetate (3 ×

10 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuum. Purification of the residue on a silica gel column chromatography using petroleum ether/ethyl acetate as (petroleum ether/ethylacetate 97:3 to 95:5) eluent furnished the product trifluoromethylated indazoles 2a-s.

2-phenyl-3-(trifluoromethyl)-2*H*-indazole (2a) Dark yellow Solid (50 mg, 75%), mp 40-42 °C; IR (MIR-ATR, 4000–600 cm^{-1}): υmax = 3736, 3673, 3613, 3565, 3032, 2968, 2381, 1734, 1700, 1650, 1556, 1540, 1521, 1508, 1458, 1420, 1218, 1120, 940, 757, 667, 631; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.79 - 7.87 (m, 2H), 7.52 - 7.63 (m, 5H), 7.39 - 7.45 (m, 1H), 7.28 - 7.34 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 148.2, 139.6, 130.0, 29.1, 127.3, 126.1, 125.1, 123.5 (q), 121.3 (q), 119.4, 118.4; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.5; HR-MS (ESI+) m/z calculated for $[C_{14}H_9F_3N_2]^+$ = $[M+H]^+$: 263.0791; found: 263.0794.

6-chloro-2-phenyl-3-(trifluoromethyl)-2*H*-indazole (2b): Dark orange Solid (29 mg, 35%), mp 44-46 °C; IR (MIR-ATR, 4000–600 cm^{-1}): υmax = 3673, 3613, 3565, 3525, 3068, 2926, 2854, 2355, 1695, 1634, 1596, 1549, 1502, 1470, 1439, 1314, 1290, 1222, 1178, 1126, 1104, 999, 768, 691, 621, 544; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.73 (d, 1H, J = 8.8 Hz), 7.56 - 7.41 (m, 6H), 7.34 (s, 1H), 6.95 - 6.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.4, 139.6, 139.3, 135.5, 129.8 (q), 127.7, 126.0, 121.4 (q), 119.4, 119.3, 105.7; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.7; HR-MS (ESI+) m/z calculated for $[C_{14}H_8ClF_3N_2]^+$ = $[M+H]^+$: 297.0401; found: 297.0408.

6-bromo-2-phenyl-3-(trifluoromethyl)-2*H*-indazole(2c): Yellow Solid (27 mg, 37%), mp 42-44 °C; IR (MIR-ATR, 4000–600 cm^{-1}): υmax = 2116, 2032, 1596, 1540, 1502, 1462, 1432, 1305, 1220, 1179, 1127, 1106, 998, 934, 798, 768, 692, 571, 515; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.04 - 7.98 (m, 1H), 7.71 (dd, 1H, J_a = 1.5 and J_b= 9.8 Hz), 7.62 - 7.51 (m, 5H), 7.38 (dd, 1H, J_a = 1.7 and J_b = 9.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.7, 139.2, 129.8 (q), 128.9, 126.0, 121.9 (q), 120.7, 120.0, 119.2; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.7; HR-MS (ESI+) m/z calculated for $[C_{14}H_8BrF_3N_2]^+$ = $[M+H]^+$: 340.9896; found: 340.9914.

5-bromo-2-phenyl-3-(trifluoromethyl)-2*H*-indazole (2d): Dark yellow Solid (31 mg, 43%), mp 52-54 °C; IR (MIR-ATR, 4000–600 cm^{-1}): υmax = 3648, 3588, 3547, 3070, 2924, 2321, 1735, 1596, 1502, 1420, 1271, 1216, 1169, 1124, 1107, 1043, 996, 861, 804, 768, 692, 634, 596; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 8.01 (s, 1H), 7.70 (d, 1H, J = 9.3 Hz), 7.62 - 7.50 (m, 5H), 7.50 - 7.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 146.6, 139.3, 137.9, 132.5, 129.8 (q), 124.6, 123.0, 122.6, 121.9 (q), 120.1, 118.6, 116.5, 112.7; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.6; HR-MS (ESI+) m/z calculated for $[C_{14}H_8BrF_3N_2]^+$ = $[M+H]^+$: 340.9896; found: 340.9900.

2-(4-fluorophenyl)-3-(trifluoromethyl)-2*H*-indazole(2e): Yellow Solid (50 mg, 45%), mp 52-54 °C; IR (MIR-ATR, 4000–600 cm^{-1}): υmax = 3689, 3620, 3568, 3036, 2938, 2321, 1717, 1540, 1502, 1454, 1252, 1216, 1156, 1118, 1107, 1032, 987, 861, 767, 659, 631; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.86 - 7.75 (m, 2H), 7.62 - 7.53 (m, 2H), 7.45 - 7.39 (m, 1H), 7.31 (dd, 1H, J_a = 6.8 and J_b = 8.3 Hz,), 7.26 - 7.21 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 164.5 (d), 149.7, 148.2, 135.6, 128.1 (d), 127.4, 125.5, 123.6 (q), 121.5, 121.0 (d), 119.4, 118.4, 116.5 (d); ^{19}F NMR ($CDCl_3$, 376 MHz): −54.5, 110.2; HR-MS (ESI+) m/z calculated for $[C_{14}H_8F_4N_2]^+$ = $[M+H]^+$: 281.0696; found: 281.0690.

2-(4-chlorophenyl)-3-(trifluoromethyl)-2*H*-indazole (2f): Dark yellow solid (35 mg, 53%), mp 46-48 °C; IR (MIR-ATR, 4000–600 cm^{-1}): υmax = 3673, 3613, 3547, 3068, 2317, 2089, 1552, 1522, 1498, 1432, 1298, 1220, 1176, 1118, 1089, 1017, 998, 929, 832, 746, 728, 583, 537; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.76 - 7.68 (m, 2H), 7.49 - 7.39 (m, 4H), 7.34 - 7.29 (m, 1H), 7.24 - 7.17 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.4, 138.0, 136.1, 129.8 (q), 127.5, 127.4, 125.7, 123.9, 122.3, 122.2, 121.7, 119.9 (q), 118.4; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.3; HR-MS (ESI+) m/z calculated for $[C_{14}H_8ClF_3N_2]^+$ = $[M+H]^+$: 297.0401; found: 297.0401.

2-(4-bromophenyl)-3-(trifluoromethyl)-2*H*-indazole (2g): Dark yellow (45 mg, 62%), mp 44-46 °C; IR (MIR-ATR, 4000–600 cm^{-1}): υmax = 3673, 3613, 3547, 3068, 1521, 1495, 1432, 1298, 1222, 1176, 1119, 1099, 1068, 1015, 996, 929, 829, 743, 711, 576, 535; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.84 - 7.78 (m, 2H), 7.70 - 7.64 (m, 3H), 7.46 (d, 2H, J = 8.3 Hz), 7.43 - 7.37 (m, 1H), 7.31 - 7.25 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.4, 138.6, 132.8 (q), 127.8, 127.6, 125.3, 124.2, 123.9, 122.5 (q), 119.4, 118.4; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.3; HR-MS (ESI+) m/z calculated for $[C_{14}H_8BrF_3N_2]^+$ = $[M+H]^+$: 340.9896; found: 340.9900.

2-(4-iodophenyl)-3-(trifluoromethyl)-2*H*-indazole(2h): Light yellow (40 mg, 68%), mp 100-102 °C; IR (MIR-ATR, 4000–600 cm^{-1}): υmax = 3736, 3547, 3462, 3032, 2917, 2356, 2154, 1716, 1683, 1556, 1540, 1509, 1362, 1257, 999, 821, 800, 740, 521; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.94 - 7.86 (m, 2H), 7.85 - 7.78 (m, 2H), 7.45 - 7.38 (m, 1H), 7.38 - 7.28 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.4, 139.3, 138.8(q), 127.7, 125.3, 123.8, 122.7, 122.2, 121.7, 119.5 (q), 118.4, 95.8; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.3; HR-MS (ESI+) m/z calculated for $[C_{14}H_8F_3IN_2]^+$ = $[M+H]^+$: 388.9757; found: 388.9756.

2-(o-tolyl)-3-(trifluoromethyl)-2*H*-indazole (2i): Dark yellow Solid (30 mg, 45%), mp 52-54 °C; IR (MIR-ATR, 4000–600 cm^{-1}): υmax =3057, 2927, 1603, 1564, 1501, 1386, 1337, 1306, 1158, 1114, 1039, 969, 957, 863, 810, 751, 716, 663, 605, 573; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.90 - 7.78 (m, 2H), 7.51 - 7.28 (m, 6H), 2.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.1, 139.6, 138.3, 137.1, 135.8, 130.5, 127.3 (q), 125.0, 122.1, 119.4 (q), 116.0, 114.9, 16.8; ^{19}F NMR ($CDCl_3$, 376 MHz): −56.2; HR-MS (ESI+) m/z calculated for $[C_{15}H_{11}F_3N_2]^+$ = $[M+H]^+$: 277.0947; found: 277.0952.

2-(2-methoxyphenyl)-3-(trifluoromethyl)-2*H*-indazole(2j): Yellow Solid (27 mg, 42%), mp 40-42 °C; IR (MIR-ATR, 4000–600 cm^{-1}): υmax = 3673, 3614, 3525, 2930, 2846, 2316, 1603, 1510, 1437, 1335, 1283, 1202, 1120, 1093, 1021, 966, 804, 753, 653,

603; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.03 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 6.8 Hz, 1H), 7.53 (dt, J_a = 1.7 and J_b = 7.9 Hz, 1H), 7.44 (dd, J_a = 1.5 and J_b = 7.8 Hz, 1H), 7.38 - 7.32 (m, 1H), 7.13 - 7.04 (m, 2H), 3.74 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ =154.8, 143.5, 132.0, 128.7, 127.9 (q), 125.3, 124.8, 123.9, 123.2, 121.8 (q), 119.0, 112.0, 55.7; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.4; HR-MS (ESI+) m/z calculated for $[C_{15}H_{11}F_3N_2O]^+$ = $[M+H]^+$: 293.0896; found: 293.0936.

2-(m-tolyl)-3-(trifluoromethyl)-2*H*-indazole (2k): Brown oil (43 mg, 64%). IR (MIR-ATR, 4000–600 cm^{-1}): υmax = 3648, 3565, 3525, 3065, 2924, 2322, 1611, 1592, 1495, 1476, 1431, 1302, 1221, 1202, 1169, 1118, 1016, 880, 787, 745, 693, 693, 627, 605, 521; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.74 (d, 2H J = 8.8 Hz), 7.39 - 7.24 (m, 5H), 7.20 (dd, 1H, J_a = 7.8 and J_b = 15.2 Hz), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.2, 139.3, 130.7, 129.5, 128.8, 127.1, 126.7, 125.3, 123.1 (q), 119.6 (q), 118.3, 21.2; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.2; HR-MS (ESI+) m/z calculated for $[C_{15}H_{11}F_3N_2]^+$ = $[M+H]^+$: 277.0947; found: 277.0960.

2-(3-methoxyphenyl)-3-(trifluoromethyl)-2*H*-indazole(2l): Brownish yellow Solid (53 mg, 80%), mp 74-76 °C; IR (MIR-ATR, 4000–600 cm^{-1}): υmax = 3614, 3547, 2925, 2846, 2323, 2134, 1734, 1593, 1498, 1468, 1288, 1250, 1201, 1163, 1122, 1044, 976, 885, 755, 688, 521; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.04 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 6.8 Hz, 1H), 7.45 (t, J = 8.3 Hz, 1H), 7.40 - 7.32 (m, 1H), 7.19 (d, J = 7.3 Hz, 1H), 7.15 - 7.08 (m, 2H), 3.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.0, 143.4, 140.0, 129.9, 125.6 (q), 123.7, 122.4, 122.1 (q), 118.5, 116.4, 112.0, 55.6; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.8; HR-MS (ESI+) m/z calculated for $[C_{15}H_{11}F_3N_2O]^+$ = $[M+H]^+$: 293.0896; found: 293.0921.

2-(p-tolyl)-3-(trifluoromethyl)-2*H*-indazole (2m): Yellow Solid (50 mg, 83%), mp 42-44 °C; IR (MIR-ATR, 4000–600 cm^{-1}): υmax = 3673, 3614, 3043, 2925, 2324,1553, 1515, 1471, 1431, 1383, 1298, 1219, 1174, 1117, 1100, 999, 930, 820, 745, 610, 547; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.86 - 7.78 (m, 2H), 7.50 - 7.42 (m, 2H), 7.42 - 7.36 (m, 1H), 7.36 - 7.25 (m, 3H), 2.48 - 2.44 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.1, 140.2, 137.2, 130.2, 128.2, 127.1, 125.9 (q), 123.8, 122.3, 121.5 (q), 119.6, 118.4, 21.3; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.5; HR-MS (ESI+) m/z calculated for $[C_{15}H_{11}F_3N_2]^+$ = $[M+H]^+$: 277.0947; found: 277.0948.

2-(4-methoxyphenyl)-3-(trifluoromethyl)-2*H*-indazole (2n): Yellow Solid (53 mg, 83%), mp 74-76 °C; IR (MIR-ATR, 4000–600 cm^{-1}): υmax = 2969, 2887, 2839, 2303, 2043, 1608, 1513, 1433, 1299, 1252, 1175, 11148, 1030, 1015, 998, 928, 834, 736, 703, 611, 557, 536; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.85 - 7.79 (m, 2H), 7.53 - 7.47 (m, 2H), 7.43 - 7.37 (m, 1H), 7.32 - 7.24 (m, 1H), 7.07 - 6.99 (m, 2H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.6, 148.0, 132.5, 127.4 (q), 124.9, 123.5, 122.7, 122.3, 121.4, 119.6 (q), 114.8 (q), 55.6; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.6; HR-MS (ESI+) m/z calculated for $[C_{15}H_{11}F_3N_2O]^+$ = $[M+H]^+$: 293.0896; found: 293.0891.

1-(3-(3-(trifluoromethyl)-2*H*-indazol-2-yl)phenyl)ethanone (2o): Light brown Solid (25 mg, 40%), mp 74-76 °C; IR (MIR-ATR, 4000–600 cm^{-1}): υmax = 3648, 3589, 3504, 3074, 2925, 2323, 1716, 1690, 1589, 1522, 1493, 1430, 1359, 1302, 1256, 1222, 1178, 1149, 1012, 748, 691, 587, 562; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.23 - 8.12 (m, 2H), 7.88 - 7.76 (m, 3H), 7.72 - 7.64 (m, 1H), 7.47 - 7.40 (m, 1H), 7.36 - 7.29 (m, 1H), 2.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 196.4, 148.4, 140.0, 138.0, 130.3, 129.5, 128.2, 127.6, 126.1, 125.4, 123.6 (q), 120.5, 119.5 (q), 118.4, 26.7; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.2; HR-MS (ESI+) m/z calculated for $[C_{16}H_{11}F_3N_2O]^+$ = $[M+H]^+$: 305.0896; found: 305.0914.

3-(trifluoromethyl)-2-(3,4,5-trimethoxyphenyl)-2*H*-indazole (2p): Yellow Solid (48 mg, 78%), mp 126-128 °C; IR (MIR-ATR, 4000–600 cm^{-1}): υmax = 3673, 3648, 3565, 2971, 2881, 2835, 1596, 1556, 1505, 1462, 1415, 1307, 1265, 1233, 1170, 1125, 1106, 1016, 945, 897, 837, 794, 733, 702, 613; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.87 - 7.78 (m, 2H), 7.46 - 7.38 (m, 1H), 7.31 (dd, 1H, J_a = 6.8 and Jb = 8.3 Hz,), 6.83 (s, 2 H), 3.93 (s, 3H), 3.90 (s, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_H = 153.2, 148.0, 139.3, 134.9, 127.3, 125.1 (q), 121.5, 119.6 (q), 03.8, 61.0, 56.3; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.5; HR-MS (ESI+) m/z calculated for $[C_{17}H_{15}F_3N_2O_3]^+$ = $[M+H]^+$: 353.1108; found: 353.1104.

6-bromo-2-(o-tolyl)-3-(trifluoromethyl)-2*H*-indazole (2p): Pale yellow Solid (48 mg, 78%), mp 82-84 °C; IR (MIR-ATR, 4000–600 cm^{-1}): υmax = 2116, 2032, 1596, 1540, 1502, 1462, 1432, 1305, 1220, 1179, 1127, 1106, 998, 934, 798, 768, 692, 571, 515; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.00 (d, 1H, J = 1.0 Hz), 7.88 - 7.79 (m, 1H), 7.77 - 7.70 (m, 1H), 7.67 (d, 1H, J = 7.8 Hz), 7.40 - 7.27 (m, 3H), 2.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 158.3, 150.9, 148.8, 138.9, 129.1, 124.8 (q), 122.1, 121.7 (q), 120.9, 119.4, 115.6, 23.9; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.5; HR-MS (ESI+) m/z calculated for $[C_{15}H_{10}BrF_3N_2]^+$ = $[M+H]^+$: 355.0052; found: 355.0063.

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