JOC The Journal of Organic Chemistry

Note

Metal-Free Trifluoromethylation of Indazoles

Payel Ghosh, Susmita Mondal, and Alakananda Hajra

J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 15 Oct 2018

ACS Publications

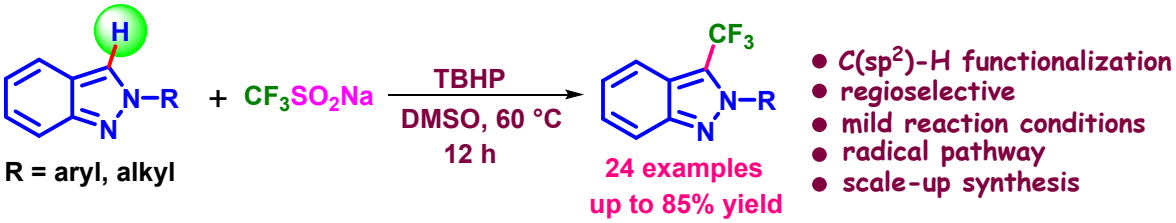
is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Metal-Free Trifluoromethylation of Indazoles

Payel Ghosh, Susmita Mondal, and Alakananda Hajra*

Department of Chemistry, Visva-Bharati (A Central University), Santiniketan 731235, India

Email: alakananda.hajra@visva-bharati.ac.in



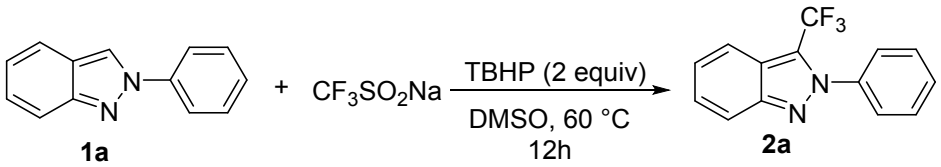
Abstract: A simple and efficient *tert*-butyl hydroperoxide mediated direct trifluoromethylation of indazoles using sodium trifluoromethanesulfinate has been developed under metal-free conditions. A library of trifluoromethylated products with broad functionalities has been synthesized with moderate to good yields. A radical mechanistic pathway has been proposed for the present protocol.

Incorporation of fluorine-containing group into organic molecules has gained much attention to the organic chemists because the presence of fluorine atom or fluorine-containing group often changes the chemical, physical, and biological properties of parent molecules.[1] Fluorinated compounds are widely applicable in pharmaceutical and agrochemical industries as well as in material sciences.[2] Among the different F-containing groups, trifluoromethyl group becomes more interesting in organic synthesis owing to its strong electron-withdrawing power, metabolic stability, and high lipophilicity.[3] Therefore, tremendous efforts have been done for the direct trifluoromethylation of heterocycles via C-H bond functionalization using various radical, nucleophilic, and electrophilic trifluoromethylating agents like Togni's reagent,[4] Umemoto's reagent,[5] Ruppert's reagent,[6] Langlois' reagent[7] etc. Among these, Langlois' reagent is the most

preferable as it is less expensive and easy to handle.[8] In 1991, Langlois first reported trifluoromethylation of aromatic compounds using sodium trifluoromethanesulfinate (Langlois' reagent) as trifluoromethylating agent.[8a] After that several trifluoromethylation reactions have been reported using Langlois' reagent.[9] Recently, Kumar and co-workers reported visible-light-induced trifluoromethylation of 1,6-enynes using Langlois' reagent.[9e] However, most of the reported methods are involved the use of different metal-catalysts like Cu, Ag, Mn, Fe etc.

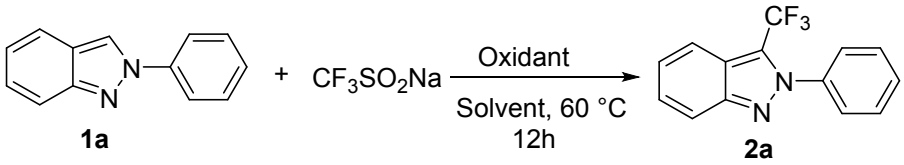
Indazole, a nitrogen-containing fused heterocycle has been gained a lot importance in medicinal chemistry as it shows a number of pharmacological and biological activities like antitumor,[10a] antimicrobial,[10b] anti-inflammatory,[10c] anticancer,[10d] HIV-protease inhibition,[10e] anti-depressant,[10f] anti-platelet[10g] etc. Indazoles are also known as efficient bioisosteres of indoles and benzimidazoles in pharmaceutical chemistry.[10] Several marketed drugs containing this moiety are MK-4827 (anticancer agent),[11a] pazopanib,[11b] bendazac (votrient, tyrosine kinase inhibitor),[11c] and gamendazole.[11d] It is also used as estrogen receptors[12a] and bacterial gyrase β-inhibitors.[12b] Therefore, various approaches have been made for the synthesis of indazole moieties.[13] However, there are only few methods for the functionalization of indazoles.[14] To the best of our knowledge there is no method for the direct trifluoromethylation of indazoles. Considering the importance of both indazole moiety and trifluoromethyl group, herein we report a C-3 trifluoromethylation of indazoles under metal-free conditions using TBHP as an oxidant (Scheme 1).

Scheme 1. Direct Trifluoromethylation of Indazoles



We started our investigation taking 2-phenyl-2*H*-indazole (**1a**) as model substrate and sodium trifluoromethanesulfinate (Langlois' reagent) as trifluoromethylating reagent (Table 1). Initially we performed the reaction using **1a** (0.2 mmol), Langlois' reagent (2 equiv), and 2 equiv *tert*-butyl hydrogen peroxide (TBHP) in CH_3CN solvent at 60 °C. To our delight 2-phenyl-3-(trifluoromethyl)-2*H*-indazole (**2a**) was obtained in 56% yield after 12 h. No further improvement of the yield was obtained after 24 h. Inspired by this initial result we carried out the reaction in different conditions to optimize the reaction conditions. At first we screened the effect of solvents such as 1,2-DCE, THF, 1,4-dioxane, toluene, ethanol, DCB, DMF, DMSO, and DMAc (Table 1, entries 2-10). Better result was achieved in DMSO solvent affording the desired product in 81% yield (Table 1, entry 9). Next, we carried out the reaction using different oxidants like di-*tert*-butyl peroxide (DTBP), *tert*-butyl peroxybenzoate (TBPB), dicumyl peroxide (DCP), and $K_2S_2O_8$ (Table 1, entries 11-14). But these were not suitable like TBHP. Moreover, the reaction was carried out under O_2 atmosphere without TBHP but the desired product was not formed (Table 1, entry 15). The yield was diminished with decreasing the loading of both TBHP and CF_3SO_2Na (Table 1, entry 16). No significant improvement of the yield was obtained at 80 °C but lowering of the yield was observed at room temperature (Table 1, entry 17). Finally, the optimized reaction condition was achieved using 2 equiv CF_3SO_2Na and 2 equiv TBHP in DMSO at 60 °C for 12 h (Table 1, entry 9).

Table 1. Optimization of the Reaction Conditions[a]

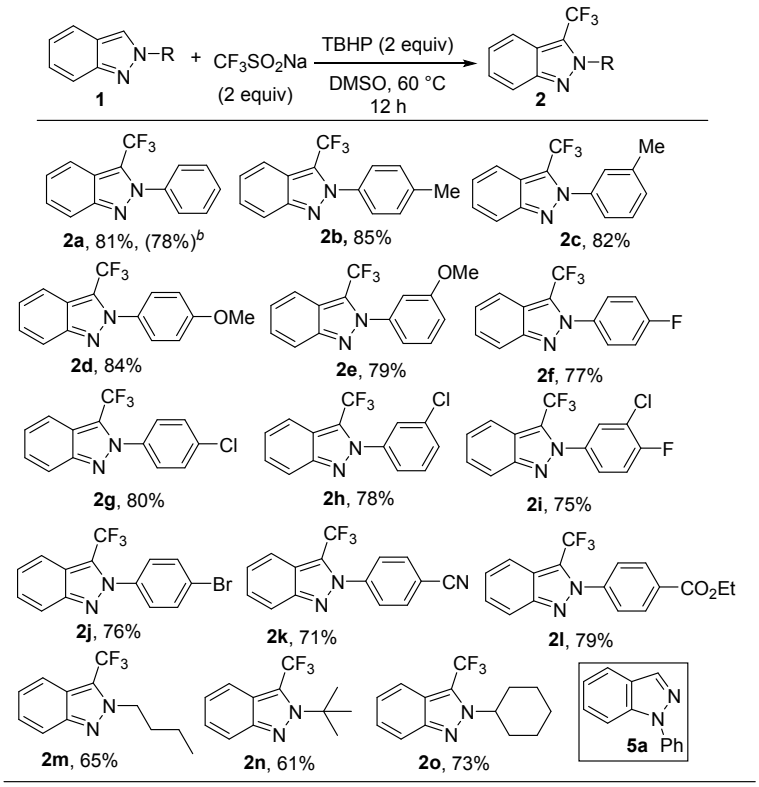


entry	oxidant (equiv)	solvent	Yield (%)
1	TBHP (2)	CH_3CN	56
2	TBHP (2)	1,2- DCE	15
3	TBHP (2)	THF	trace
4	TBHP (2)	1,4-dioxane	no reaction
5	TBHP (2)	toluene	trace
6	TBHP (2)	EtOH	trace
7	TBHP (2)	DCB	no reaction
8	TBHP(2)	DMF	23
9	TBHP (2)	DMSO	81
10	TBHP (2)	DMAc	11
11	DTBP (2)	DMSO	trace
12	TBPB (2)	DMSO	61
13	DCP (2)	DMSO	trace
14	$K_2S_2O_8$ (2)	DMSO	trace
15	O_2	DMSO	no reaction
16	TBHP (1)	DMSO	51, 45[b]
17	TBHP (2)	DMSO	82[c], 63[d]

[a]All reactions were carried out with **1a** (0.2 mmol), CF_3SO_2Na (2 equiv), oxidant (2 equiv), and solvent (2 mL) for 12 h at 60 °C. [b]1 equiv CF_3SO_2Na used. [c]At 80 °C. [d]At room temperature.

With this optimized reaction conditions we explored the substrates scope of the present methodology as shown in Scheme 2. We first examined the effect of the different N-2 substituent of 2*H*-indazoles. 2-Phenyl-2*H*-indazoles containing electron-donating substituents like -Me and -OMe at the different positions of phenyl ring efficiently produced the trifluoromethylated products in good yields (**2b**-**2e**). Halogen substituted 2-phenyl-2*H*-indazoles were also underwent the reaction very smoothly (**2f**-**2j**). Highly electron-withdrawing group (4-CN) substituted 2*H*-indazole was also well tolerable for such transformation (**2k**). Ethyl 4-(2*H*-indazol-2-yl)benzoate (**1l**) effectively reacted with CF_3SO_2Na to provide the desired product (**2l**) in good yield. In addition, 2*H*-indazoles with alkyl (*n*-butyl and *tert*-butyl) and cyclohexyl substitution at N-2 position also afforded the trifluoromethylated products in moderate to good yields (**2m**-**2o**). Ortho substituted 2-phenyl-2*H*-indazoles and 1*H*-indazole (**5a**) were unable to produce the desired products. *p*-Methoxy benzyl substituted indazole produced an inseparable mixture of products under the optimized reaction conditions. The gram-scale reaction of the present method was carried out under the normal laboratory setup taking 2-phenyl-2*H*-indazole (**1a**, 5 mmol) under the optimized reaction conditions. To our delight, the trifluoromethylated product (**2a**) was obtained without a significant decrease in yield (78%) which clearly demonstrates the practical applicability of our proposed method.

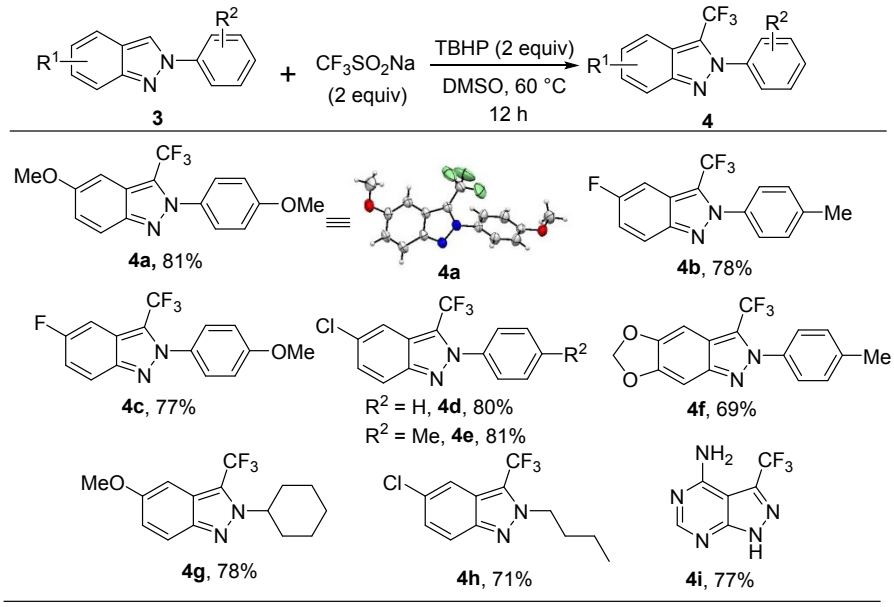
Scheme 2. Substrates Scope of the Present Method[a]



[a]Reaction conditions: **1** (0.2 mmol), CF_3SO_2Na (2 equiv), TBHP (2 equiv), and DMSO (2 mL) for 12 h at 60 °C. [b]On a 5 mmol scale.

Next, we checked the effect of different substituents at the arene part of 2*H*-indazoles (Scheme 3). 5-Methoxy-substituted 2*H*-indazole gave the desired trifluoromethylated products in good yields (**4a**). The single crystal X-ray analysis of **4a** was performed to confirm the structure of the 5-methoxy-2-(4-methoxyphenyl)-3-(trifluoromethyl)-2*H*-indazole.[15] 2*H*-indazoles bearing halogens like -F and -Cl on C-5 position of arene successfully reacted with Langlois' reagent to produce the desired products (**4b**-**4e**) in moderate to good yields. 2-(*p*-Tolyl)-2*H*-[1,3]dioxolo[4,5-*f*]indazole (**3f**) was also suitable for this trifluoromethylation reaction. Cyclohexyl and *n*-butyl substituted 2*H*-indazoles reacted very well (**4g** and **4h**). It is notable that 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine produced the trifluoromethylated product in good yield (**4i**).

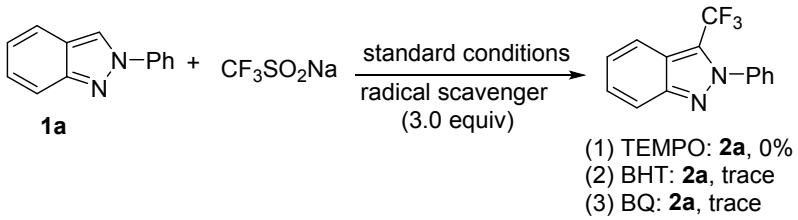
Scheme 3. Substrates Scope[a]



[a]Reaction conditions: **3** (0.2 mmol), CF_3SO_2Na (2 equiv), TBHP (2 equiv), and DMSO (2 mL) for 12 h at 60 °C.

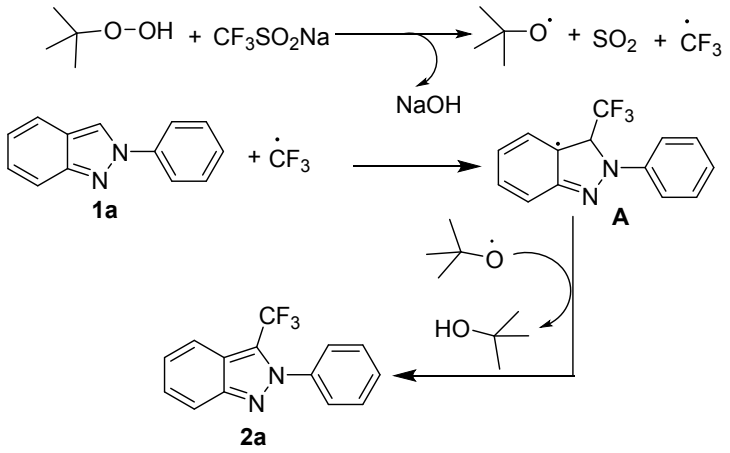
To get the mechanistic pathway of the proposed reaction, few control experiments were carried out (Scheme 4). The reaction did not proceed in the presence of radical scavengers like 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), 2,6-di-*tert*-butyl-4-methyl phenol (BHT), and *p*-benzoquinone (BQ). These observations suggest that the reaction probably proceeds through a radical pathway.

Scheme 4. Control Experiments



Based on the control experiments and previous literature reports,[8d] a plausible mechanistic pathway of the trifluoromethylation reaction has been described in Scheme 5. Initial step involves the formation of CF_3-radical from sodium trifluoromethanesulfinate in presence of TBHP. Next, CF_3 radical reacts at C-3 position of 2*H*-indazole (**1a**) to form the radical intermediate **A**. Then, *tert*-butoxy radical abstracts a hydrogen radical from C-3 position of intermediate **A** to produce the desired product (**2a**).

Scheme 5. Plausible Mechanistic Pathway



In conclusion, we have developed a straightforward method for the regioselective direct trifluoromethylation of 2*H*-indazoles using inexpensive Langlois' reagent as a source of trifluoromethyl group under metal-free conditions. Mild reaction conditions, high functional group tolerance, regioselectivity, and scalability are the important features of our present protocol. To the best of our knowledge this is the first report for the direct trifluoromethylation of 2*H*-indazoles. We believe this strategy will gain much importance in organic synthesis, medicinal chemistry, and as well as in material sciences.

Experimental Section:

General Information: All reagents were purchased from commercial sources and used without further purification. ^{1}H NMR spectra were determined on 400 MHz spectrometer as solutions in $CDCl_3$ and DMSO-d_6. Chemical shifts were expressed in parts per million (δ) and the signals were reported as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet), q (quartet), and coupling constants (J) were given in Hz. $^{13}C\{^1H\}$ NMR spectra were recorded at 100 MHz in $CDCl_3$ and DMSO-d_6 solution. ^{19}F NMR spectra were recorded at 376 MHz in $CDCl_3$ and DMSO-d_6 solution. Chemical shifts as internal standard were referenced to $CDCl_3$ (δ = 7.26 for ^{1}H and δ = 77.16 for $^{13}C\{^1H\}$ NMR) and DMSO-d_6 (δ = 2.50 for ^{1}H and δ = 39.52 for $^{13}C\{^1H\}$ NMR) as internal standard. TLC was done on silica gel coated glass slide. All solvents were dried and distilled before use. Commercially available solvents were freshly distilled before the reaction. All reactions involving moisture sensitive reactants were executed using oven dried glassware. All the 2*H*-indazoles were prepared by reported method.[13b] Commercially available TBHP (70 wt % in water) was used as an oxidant.

Typical experimental procedure for the compound 2-phenyl-3-(trifluoromethyl)-2*H*-indazole (2a):

A mixture of 2-phenyl-2*H*-indazole (**1a**) (0.2 mmol, 38.8 mg), CF_3SO_2Na (2.0 equiv, 0.4 mmol, 62 mg), and TBHP (70 wt % in water, 2.0 equiv, 0.4 mmol, 0.055 mL) was taken in a reaction tube. Then DMSO (2.0 mL) was added to it and stirred at 60°C for 12 h. After completion of the reaction (TLC), the reaction mixture was quenched with water (2.0 mL). The reaction mixture was then extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude residue which was purified by column chromatography on silica gel (60-120 mesh) using petroleum ether:ethyl acetate = 98:02 as an

eluent to afford the pure product 2-phenyl-3-(trifluoromethyl)-2*H*-indazole (**2a**) (42.4 mg, 81%) as a yellow liquid.

2-Phenyl-3-(trifluromethyl)-2H-indazole (2a): Yellow liquid (81%, 42.4 mg); R_f = 0.50 (PE:EA = 98:02); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85-7.82 (m, 2H), 7.60-7.53 (m, 5H), 7.43-7.39 (m, 1H), 7.32-7.28 (m, 1H), $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 148.3, 139.7, 130.1, 129.2, 127.3, 126.2, 125.2, 123.8 (q, J_{C-F} = 40.0 Hz), 121.7, 121.0 (q, J_{C-F} = 269.0 Hz), 119.5, 118.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.5; Anal. Calcd for $C_{14}H_9F_3N_2$: C, 64.12%; H, 3.46; N, 10.68; Found: C, 64.31; H, 3.40; N, 10.79%.

2-(p-Tolyl)-3-(trifluoromethyl)-2H-indazole (2b): White soild (85%, 46.9 mg); R_f = 0.55 (PE:EA = 98:02); M.p. 83-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.83 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.42-7.38 (m, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.31-7.27(m, 1H), 2.46 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ* 148.1, 140.2, 137.2, 129.6, 127.1, 125.8, 124.9, 123.5 (q, J_{C-F} = 39.0 Hz), 121.5, 121.0 (q, J_{C-F} = 269.0 Hz), 119.3, 118.4, 21.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$Calcd for $C_{15}H_{12}F_3N_2$: 277.0947; found: 277.0962.

2-(m-Tolyl)-3-(trifluoromethyl)-2H-indazole (2c): Yellow liquid (82%, 45.2 mg); R_f = 0.45 (PE:EA = 97:03); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.83 (d, *J* = 9.2 Hz, 2H), 7.44-7.35 (m, 5H), 7.31-7.27 (m, 1H), 2.45 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ* 148.2, 139.6, 139.4, 130.8, 128.9, 127.3, 126.8, 125.1, 123.7 (q, J_{C-F} = 41.0 Hz), 123.2, 121.6, 121.0 (q, J_{C-F} = 267.0 Hz), 119.5, 118.5, 21.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.5; Anal. Calcd for $C_{15}H_{11}F_3N_2$: C, 65.22; H, 4.01; N, 10.14%; Found: C, 65.00; H, 4.05; N, 10.07%.

2-(4-Methoxyphenyl)-3-(trifluoromethyl)-2H-indazole (2d):[13g] Yellow gummy mass (84%, 49.0 mg); R_f = 0.45 (PE:EA = 98:02); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.83-7.80 (m, 2H), 7.50 (d, *J* =

8.8 Hz, 2H), 7.42-7.38 (m, 1H), 7.30-7.27 (m, 1H), 7.05-7.01 (m, 2H), 3.88 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 160.6, 148.0, 132.4, 127.3, 127.1, 124.9, 123.8 (q, J_{C-F} = 41.0 Hz), 121.4, 121.1 (q, J_{C-F} = 268.0 Hz), 119.3, 118.3, 114.1, 55.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.6.

2-(3-Methoxyphenyl)-3-(trifluoromethyl)-2H-indazole (2e): Yellow liquid (79%, 46.1 mg); R_f = 0.40 (PE:EA = 97:03); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 9.2 Hz, 2H), 7.45-7.39 (m, 2H), 7.31-7.27 (m, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.14-7.08 (m, 2H), 3.86 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 160.0, 148.2, 140.6, 129.9, 127.3, 125.1, 123.7 (q, J_{C-F} = 41.0 Hz), 121.6, 121.04 (q, J_{C-F} = 269.0 Hz), 121.03, 119.5, 118.5, 118.4, 116.2, 55.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.5; Anal. Calcd for $C_{15}H_{11}F_3N_2O$: C, 61.65; H, 3.79; N, 9.59%; Found: C, 61.80; H, 3.73; N, 9.67%.

2-(4-Fluorophenyl)-3-(trifluoromethyl)-2H-indazole (2f): White solid (77%, 43.1 mg); R_f = 0.50 (PE:EA = 98:02); M.p. 68-69 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83-7.80 (m, 2H), 7.58-7.55 (m, 2H), 7.44-7.40 (m, 1H), 7.32-7.29 (m, 1H), 7.26-7.20 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 163.4 (d, J_{C-F} = 249.0 Hz), 148.3, 135.7 (d, J_{C-F} = 2.0 Hz), 128.2 (d, J_{C-F} = 9.0 Hz), 127.5, 125.3, 123.9 (q, J_{C-F} = 40.0 Hz), 121.6, 121.0 (q, J_{C-F} = 268.0 Hz), 119.5, 118.5, 116.3 (d, J_{C-F} = 24.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.5, -110.2; Anal. Calcd for $C_{14}H_8F_4N_2$: C, 60.01; H, 2.88; N, 10.00%; Found: C, 60.17; H, 2.92; N, 9.91%.

2-(4-Chlorophenyl)-3-(trifluoromethyl)-2H-indazole (2g): Yellow solid (80%, 47.3 mg); R_f = 0.55 (PE:EA = 99:01); M.p. 81-82 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83-7.80 (m, 2H), 7.56-7.51 (m, 4H), 7.44-7.40 (m, 1H), 7.33-7.29 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 148.5, 138.1, 136.3, 132.4, 129.5, 127.6, 127.5, 125.4, 122.0 (q, J_{C-F} = 53.0 Hz), 121.0 (q, J_{C-F} = 271.0

Hz), 119.5, 118.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.4; Anal. Calcd for $C_{14}H_8ClF_3N_2$: C, 56.68; H, 2.72; N, 9.44%; Found: C, 56.51; H, 2.78; N, 9.56%.

2-(3-Chlorophenyl)-3-(trifluoromethyl)-2H-indazole (2h): Yellow liquid (78%, 46.1 mg); R_f = 0.45 (PE:EA = 98:02); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83-7.80 (m, 2H), 7.63 (s, 1H), 7.56-7.48 (m, 3H), 7.44-7.40 (m, 1H), 7.31 (t, J = 8.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.5, 140.6, 135.0. 130.3, 130.1, 127.7, 126.7, 125.5, 124.48 (q, $J_{C\text{-}F}$ = 32.0 Hz), 124.43, 121.8, 120.9 (q, $J_{C\text{-}F}$ = 268.0 Hz), 119.5, 118.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.4; Anal. Calcd for $C_{14}H_8ClF_3N_2$: C, 56.68; H, 2.72; N, 9.44%; Found: C, 56.83; H, 2.67; N, 9.54%.

2-(4-Chloro-3-fluorophenyl)-3-(trifluoromethyl)-2H-indazole (2i): White solid (75%, 47.1 mg); R_f = 0.55 (PE:EA = 98:02); M.p. 84-85 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82-7.79 (m, 2H), 7.70 (dd, J = 6.4 Hz, 2.4 Hz, 1H), 7.51-7.47 (m, 1H), 7.44-7.40 (m, 1H), 7.33-7.29 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.0 (d, $J_{C\text{-}F}$ = 252.0 Hz), 148.5, 136.0 (d, $J_{C\text{-}F}$ = 3.0 Hz), 128.9, 127.8, 126.1 (d, $J_{C\text{-}F}$ = 8.0 Hz), 125.6, 132.9 (q, $J_{C\text{-}F}$ = 40.0 Hz), 121.8 (d, $J_{C\text{-}F}$ = 26.0 Hz), 120.8 (q, $J_{C\text{-}F}$ = 271.0 Hz), 119.4, 118.5, 117.1, 116.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.4, -112.1; Anal. Calcd for $C_{14}H_7ClF_4N_2$: C, 53.44; H, 2.24; N, 8.90%; Found: C, 53.21; H, 2.30; N, 8.83%.

2-(4-Bromophenyl)-3-(trifluoromethyl)-2H-indazole (2j):[13g] Yellow liquid (76%, 51.8 mg); R_f = 0.45 (PE:EA = 98:02); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90-7.80 (m, 2H), 7.70-7.66 (m, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.43-7.39 (m, 1H), 7.34-7.28 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.5, 138.7, 138.4, 132.4, 127.7, 127.6, 125.4, 123.7 (q, $J_{C\text{-}F}$ = 40.0 Hz), 124.3, 120.9 (q, $J_{C\text{-}F}$ = 268.0 Hz), 119.5, 118.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.3.

4-(3-(Trifluoromethyl)-2H-indazol-2-yl)benzonitrile (2k): Yellow gummy mass (71%, 40.7 mg); R_f = 0.50 (PE:EA = 97:03); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88-7.85 (m, 2H), 7.83-7.80

(m, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.46-7.42 (m, 1H), 7.35-7.31 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 148.9, 143.0, 133.2, 128.9, 128.1, 126.9, 125.9, 123.8 (q, $J_{C\text{-}F}$ = 40.0 Hz), 122.1, 120.8 (q, $J_{C\text{-}F}$ = 268.0 Hz), 118.6, 117.7, 114.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.0; Anal.Calcd for $C_{15}H_8F_3N_3$: C, 62.72; H, 2.81; N, 14.63%; Found: C, 62.87; H, 2.85; N, 14.56%.

Ethyl 4-(3-(trifluoromethyl)-2H-indazol-2-yl)benzoate (2l): Yellow liquid (79%, 52.7 mg); R_f = 0.45 (PE:EA = 98:02); ^1H NMR (400 MHz, $CDCl_3$): δ 8.25-8.22 (m, 2H), 7.84-7.81 (m, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.44-7.40 (m, 1H), 7.33-7.29 (m, 1H), 4.43 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.5, 148.6, 143.0, 132.0, 130.6, 127.7, 126.1, 125.5, 121.8 (q, $J_{C\text{-}F}$ = 28.0 Hz), 121.6, 120.9 (q, $J_{C\text{-}F}$ = 269.0 Hz), 119.5, 118.5, 61.6, 14.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.2; Anal. Calcd for $C_{17}H_{13}F_3N_2O_2$: C, 61.08; H, 3.92; N, 8.38%; Found: C, 61.29; H, 3.85; N, 8.49%.

2-Butyl-3-(trifluoromethyl)-2H-indazole (2m): Colourless liquid (65%, 31.4 mg); R_f = 0.45 (PE:EA = 98:02); ^1H NMR (400 MHz, $CDCl_3$): δ 7.75-7.72 (m, 2H), 7.35-7.31 (m, 1H), 7.24-7.20 (m, 1H), 4.52 (t, J = 7.6 Hz, 2H), 2.05-1.98 (m, 2H), 1.46-1.37 (m, 2H), 0.97 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 147.6, 126.5, 124.5, 122.9 (q, $J_{C\text{-}F}$ = 28.0 Hz), 122.3 (q, $J_{C\text{-}F}$ = 265.0 Hz), 120.1, 119.2 (d, $J_{C\text{-}F}$ = 1.0 Hz), 118.1, 52.8, 32.8, 20.0, 13.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.3; Anal. Calcd for $C_{12}H_{13}F_3N_2$: C, 59.50; H, 5.41; N, 11.56%; Found: C, 59.36; H, 5.44; N, 11.61%.

2-(Tert-butyl)-3-(trifluoromethyl)-2H-indazole (2n): Yellow liquid (61%, 29.5 mg); R_f = 0.50 (PE:EA = 98:02); ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.56 (dd, J= 7.2 Hz, 2.0 Hz, 1H), 7.07 (t, J = 8.4 Hz, 1H), 1.76 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 143.5 126.0, 124.8, 123.7 (q, $J_{C\text{-}F}$ = 5.0 Hz), 122.5 (d, $J_{C\text{-}F}$ = 22.0 Hz), 120.2 (q, $J_{C\text{-}F}$ = 266.0

Hz), 119.7, 118.5, 60.9, 30.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.2; Anal. Calcd for $C_{12}H_{13}F_3N_2$: C, 59.50; H, 5.41; N, 11.56%; Found: C, 59.32; H, 5.37; N, 11.50%.

2-Cyclohexyl-3-(trifluoromethyl)-2H-indazole (2o): Yellow liquid (73%, 39.1 mg); R_f = 0.60 (PE:EA = 99:01); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78-7.73 (m, 2H), 7.34-7.30 (m, 1H), 7.21 (t, J = 8.0 Hz, 1H), 4.56-4.48 (m, 1H), 2.23-2.07 (m, 4H), 1.99-1.95 (m, 2H), 1.80-1.76 (m, 1H), 1.53-1.45 (m, 2H), 1.43-1.33 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.5, 126.2, 124.4, 121.72 (q, $J_{C\text{-}F}$ = 39.0 Hz), 121.70 (q, $J_{C\text{-}F}$ = 270.0 Hz), 120.5, 119.2, 118.2, 61.9, 33.6, 25.7, 25.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.2; Anal. Calcd for $C_{14}H_{15}F_3N_2$: C, 62.68; H, 5.64; N, 10.44%; Found: C, 62.45; H, 5.60; N, 10.52%.

5-Methoxy-2-(4-methoxyphenyl)-3-(trifluoromethyl)-2H-indazole (4a): Yellow solid (81%, 52.1 mg); R_f = 0.50 (PE:EA = 97:03); M.P. 117-118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 9.6 Hz, 1H), 7.47 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 9.6 Hz, 2.4 Hz, 1H), 7.02-7.00 (m, 2H), 6.95 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.6, 157.3, 145.0, 132.7, 127.4, 122.9, 122.6, 122.1, 121.3 (q, $J_{C\text{-}F}$ = 267.0 Hz), 119.8, 114.2, 95.3, 55.7, 55.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.5; Anal. Calcd for $C_{16}H_{13}F_3N_2O_2$: C, 59.63; H, 4.07; N, 8.69%; Found: C, 59.84; H, 4.16; N, 8.82%.

5-Fluoro-2-(p-tolyl)-3-(trifluoromethyl)-2H-indazole (4b): Yellow solid (78%, 45.8 mg); R_f = 0.50 (PE:EA = 98:02); M.P. 85-86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81-7.78 (m, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.40-7.38 (m, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.22-7.17 (m, 1H), 2.46 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.1 (d, $J_{C\text{-}F}$ = 243.0 Hz), 145.6, 140.5, 137.1, 129.8, 125.8, 124.1 (d, $J_{C\text{-}F}$ = 48.0 Hz), 121.4 (q, $J_{C\text{-}F}$ = 12.0 Hz), 120.9 (q, $J_{C\text{-}F}$ = 268.0 Hz), 120.8 (d, $J_{C\text{-}F}$ = 10.0 Hz), 119.2 (d, $J_{C\text{-}F}$ = 29.0 Hz), 102.4 (d, $J_{C\text{-}F}$ = 26.0 Hz), 21.4; ^{19}F NMR (376 MHz,

$CDCl_3$) δ -54.7, -114.7; HRMS (ESI-TOF) *m/z*: [M + H]$^+$Calcd for $C_{15}H_{11}F_4N_2$: 295.0853; found: 295.0856.

5-Fluoro-2-(4-methoxyphenyl)-3-(trifluoromethyl)-2H-indazole (4c): Yellow solid (77%, 47.7 mg); R_f = 0.45 (PE:EA = 98:02); M.p. 91-92°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80-7.76 (m, 1H), 7.47 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 9.2 Hz, 1H), 7.21-7.16 (m, 1H), 7.03-7.01 (m, 2H), 3.88 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.3, 159.9 (d, $J_{C\text{-}F}$ = 196.0 Hz), 145.5, 132.4, 127.3, 124.2 (d, $J_{C\text{-}F}$ = 37.0 Hz), 121.3 (d, $J_{C\text{-}F}$ = 15.0 Hz), 120.9 (q, $J_{C\text{-}F}$ = 267.0 Hz), 120.7 (d, $J_{C\text{-}F}$ = 9.0 Hz), 119.0 (d, $J_{C\text{-}F}$ = 29.0 Hz), 114.3, 102.3 (d, $J_{C\text{-}F}$ = 27.0 Hz), 55.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.9, -114.8; Anal. Calcd for $C_{15}H_{10}F_4N_2O$: C, 58.07; H, 3.25; N, 9.03%; Found: C, 58.24; H, 3.31; N, 8.95%.

5-Chloro-2-phenyl-3-(trifluoromethyl)-2H-indazole (4d): Yellow solid (80%, 47.3 mg); R_f = 0.50 (PE:EA = 99:01); M.P. 90-91 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.77-7.75 (m, 1H), 7.60-7.53 (m, 5H), 7.35 (dd, J = 9.2 Hz, 2.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 146.6, 139.4, 131.2, 130.5, 129.3, 129.0, 126.1, 123.5 (q, $J_{C\text{-}F}$ = 41.0 Hz), 122.0, 120.7 (q, $J_{C\text{-}F}$ = 269.0 Hz), 120.1, 118.3 (d, $J_{C\text{-}F}$ = 18.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.6; Anal. Calcd for $C_{14}H_8ClF_3N_2$: C, 56.68; H, 2.72; N, 9.44%; Found: C, 56.46; H, 2.68; N, 9.51%.

5-Chloro-2-(p-tolyl)-3-(trifluoromethyl)-2H-indazole (4e): Yellow solid (81%, 50.2 mg); R_f = 0.60 (PE:EA = 98:02); M.p. 98-99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.34-7.32 (m, 3H) 2.46 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 146.5, 140.6, 136.9, 131.0, 129.8, 128.8, 125.8 , 123.5 (q, $J_{C\text{-}F}$ = 40.0 Hz), 122.0, 120.7 (q, $J_{C\text{-}F}$ = 268.0 Hz), 120.0, 118.3, 21.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.7; HRMS (ESI-TOF) *m/z*: [M + H]$^+$Calcd for $C_{15}H_{11}ClF_3N_2$: 311.0557; found: 311.0555.

2-(p-Tolyl)-3-(trifluoromethyl)-2H-[1,3]dioxolo[4,5-f]indazole (4f): Off white gummy mass (69%, 44.2 mg); R_f = 0.45 (PE:EA = 98:02); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.02 (s, 1H), 6.99 (s, 1H), 6.02 (s, 2H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 149.9, 148.0, 145.8, 139.9, 137.3, 129.7, 125.8, 121.1 (q, $J_{C\text{-}F}$ = 269.0 Hz), 120.3, 119.7 (q, $J_{C\text{-}F}$ = 6.0 Hz), 101.5, 94.4, 94.3 (d, $J_{C\text{-}F}$ = 3.0 Hz), 21.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.8; Anal. Calcd for $C_{16}H_{11}F_3N_2O_2$: C, 60.00; H, 3.46; N, 8.75%; Found: C, 59.84; H, 3.51; N, 8.84%.

2-Cyclohexyl-5-methoxy-3-(trifluoromethyl)-2H-indazole (4g): Yellow liquid (78%, 46.4 mg); R_f = 0.50 (PE:EA = 99:01); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 8.8 Hz, 1H), 7.01 (dd, J = 9.6 Hz, 2.4 Hz, 1H), 6.9 (s, 1H), 4.49-4.42 (m, 1H), 3.84 (s, 3H), 2.15-2.05 (m, 4H), 1.98-1.93 (m, 2H), 1.78-1.74 (m, 1H), 1.52-131 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 157.0, 144.2, 121.9 (q, $J_{C\text{-}F}$ = 269.0 Hz), 121.3, 120.9, 120.5, 119.6, 95.5, 61.7, 55.5, 33.6, 25.7, 25.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.0; Anal. Calcd for $C_{15}H_{17}F_3N_2O$: C, 60.40; H, 5.74; N, 9.39%; Found: C, 60.59; H, 5.69; N, 9.48%.

2-Butyl-5-chloro-3-(trifluoromethyl)-2H-indazole (4h): Yellow liquid (71%, 40.3 mg); R_f = 0.55 (PE:EA = 98:02); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.67 (d, J = 9.2 Hz, 1H), 7.28-7.25 (m, 1H), 4.50 (t, J = 7.6 Hz, 2H), 2.05-1.96 (m, 2H), 1.46-1.36 (m, 2H), 0.96 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 145.9, 130.5, 128.1, 122.2 (q, $J_{C\text{-}F}$ = 40.0 Hz), 121.4, 121.0 (q, $J_{C\text{-}F}$ = 267.0 Hz), 119.6, 118.0 (d, $J_{C\text{-}F}$ = 2.0 Hz), 53.0, 32.6, 19.9, 13.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.5; Anal. Calcd for $C_{12}H_{12}ClF_3N_2$: C, 62.68; H, 5.64; N, 10.44%; Found: C, 62.45; H, 5.60; N, 10.52%.

3-(Trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (4i): Light yellow gummy mass (77%, 31.3 mg); R_f = 0.50 (PE:EA = 30:70); ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.32 (s, 1H),

8.29 (s, 1H), 7.10 (br s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6): δ 156.8, 156.5, 156.2, 132.3 (q, J_{C-F} = 40.0 Hz), 121.0 (q, J_{C-F} = 267.0 Hz), 95.7; ^{19}F NMR (376 MHz, DMSO-d_6) δ -59.1; Anal. Calcd for $C_6H_4F_3N_5$: C, 35.48; H, 1.98; N, 34.48%; Found: C, 35.61; H, 2.01; N, 34.43%.

Supporting information: Scanned copies of ^{1}H, $^{13}C\{^{1}H\}$, and ^{19}F NMR spectra of the synthesized compounds, CIF file for compound **4a** are available as supporting information. This material is available free of charge via the Internet at http://pubs.acs.org.

Acknowledgment: A.H. acknowledges the financial support from SERB-DST, (Grant no. EMR/2016/001643). P.G. thanks UGC-New Delhi (UGC-JRF) and S.M. thanks CSIR-New Delhi (CSIR-SRF) for their fellowship.

References:

1. (a) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: Chichester, 2009. (b) Truong, T.; Klimovica, K.; Daugulis, O. Copper-Catalyzed, Directing Group-Assisted Fluorination of Arene and Heteroarene C–H Bonds. *J. Am. Chem. Soc.* **2013**, *135*, 9342-9345. (c) Shirai, T.; Kanai, M.; Kuninobu, Y. 2-Position-Selective C–H Perfluoroalkylation of Quinoline Derivatives. *Org. Lett.* **2018**, *20*, 1593-1596.

2. (a) Langlois, B. R.; Billard, T.; Roussel, S. Nucleophilic Trifluoromethylation: Some Recent Reagents and Their Stereoselective Aspects. *J. Fluorine Chem*. **2005**, *126*, 173-179. (b) Muller, K.; Faeh, C.; Diederich, F. Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science* **2007**, *317*, 1881-1886. (c) Zhu, W.; Wang, J.; Wang, S.; Gu, Z.; Acen, J. L.; Izawa, K.; Liu, H.; Soloshonok, V. A.

Recent Advances in the Trifluoromethylation Methodology and New CF_3-containing Drugs. *J. Fluorine Chem*. **2014**, *167*, 37-54.

3. (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in Medicinal Chemistry. *Chem. Soc. Rev*. **2008**, *37*, 320-330. (b) Furuya, T.; Kamlet, A. S.; Ritter, T. Catalysis for Fluorination and Trifluoromethylation. *Nature* **2011**, *473*, 470-477. (c) Kirsch, P. Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications; Wiley-VCH: Weinheim, 2004.

4. Charpentier, J.; Früh, N.; Togni, A. Electrophilic Trifluoromethylation by Use of Hypervalent Iodine Reagents. *Chem*. *Rev*. **2015**, *115*, 650-682.

5. (a) Wilger, D. J.; Gesmundo, N. J.; Nicewicz, D. A. Catalytic Hydrotrifluoromethylation of Styrenes and Unactivated Aliphatic Alkenes via an Organic Photoredox System. *Chem. Sci*. **2013**, *4*, 3160-3165. (b) Jana, S.; Ashokan, A.; Kumar, S.; Verma, A.; Kumar, S. Copper-Catalyzed Trifluoromethylation of Alkenes: Synthesis of Trifluoromethylated Benzoxazines. *Org. Biomol. Chem*. **2015**, *13*, 8411–8415.

6. (a) Chu, L. L.; Qing, F. L. Copper-Catalyzed Direct C–H Oxidative Trifluoromethylation of Heteroarenes**.** *J. Am. Chem. Soc*. **2012**, *134*, 1298-1304. (b) Shang, M.; Sun, S.-Z.; Wang, H.-L.; Laforteza, B. N.; Dai, H.-X.; Yu, J.-Q. Exceedingly Fast Copper(II)-Promoted *ortho* C-H Trifluoromethylation of Arenes Using $TMSCF_3$, *Angew. Chem., Int. Ed*. **2014**, *53*, 10439-10442.

7. Ji, Y. N.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. Innate C-H Trifluoromethylation of Heterocycles. *Proc. Natl. Acad. Sci*. **2011**, *108*, 14411-14415.

8. (a) Langlois, B. R.; Laurent, E.; Roidot, N. Trifluoromethylation of Aromatic Compounds with Sodium Trifluoromethanesulfinate under Oxidative Conditions. *Tetrahedron Lett*. **1991**, *32,* 7525-7528. (b) Langlois, B. R.; Laurent, E.; Roidot, N. "Pseudo-cationic" Trifluoromethylation of Enol Esters with Sodium Trifluoromethanesulfinate. *Tetrahedron Lett*. **1992**, *33*, 1291-1294. (c) Billard, T.; Roques, N.; Langlois, B. R. Synthetic Uses of Thio- and Selenoesters of Trifluoromethylated Acids. 1. Preparation of Trifluoromethyl Sulfides and Selenides. *J. Org. Chem*. **1999**, *64*, 3813-3820. (d) Monir, K.; Bagdi, A. K.; Ghosh, M.; Hajra, A. Regioselective Oxidative Trifluoromethylation of Imidazoheterocycles via C(sp^2)–H Bond Functionalization. *J. Org. Chem*. **2015**, *80*, 1332-1337.

9. (a) Zhang, C. Application of Langlois Reagent in Trifluoromethylation Reactions. *Adv. Synth. Catal*. **2014**, *356*, 2895-2906. (b) Guyon, H.; Chachignon, H.; Cahard, D. CF_3SO_2X (X = Na, Cl) as Reagents for Trifluoromethylation, Trifluoromethylsulfenyl-, -Sulfinyl- and -Sulfonylation. Part 1: Use of CF_3SO_2Na. *Beilstein J. Org. Chem*. **2017**, *13*, 2764-2799. (c) Langlois, B. R. Once Upon a Time Was the Langlois' Reagent: A "Sleeping Beauty". In *Modern Synthesis Processes and Reactivity of Fluorinated Compounds;* Groult, H.; Leroux, F.; Tressaud, A., Eds. Elsevier, 2017, pp 125–140. (d) Deb, A.; Manna, S.; Modak, A.; Patra, T.; Maity, S.; Maiti, D. Oxidative Trifluoromethylation of Unactivated Olefins: An Efficient and Practical Synthesis of α-Trifluoromethyl-Substituted Ketones. *Angew. Chem., Int. Ed.* **2013**, *52*, 9747-9750. (e) Jana, S.; Verma, A.; Kadu, R.; Kumar, S. Visible-Light-Induced Oxidant and Metal-Free Dehydrogenative Cascade Trifluoromethylation and Oxidation of 1,6-Enynes with Water. *Chem. Sci*. **2017**, *8*, 6633-6644. (f) Maji, A.; Hazra, A.; Maiti, D. Direct Synthesis of

α‑Trifluoromethyl Ketone from (Hetero)arylacetylene: Design, Intermediate Trapping, and Mechanistic Investigations. *Org. Lett*. **2014**, *16*, 4524−4527.

10. (a) Qian, S.; Cao, J.; Yan, Y.; Sun, M.; Zhu, H.; Hu, Y.; He, Q.; Yang, B. SMT-A07, A 3-(Indol-2-yl) Indazole Derivative, Induces Apoptosis of Leukemia Cells in Vitro. *Mol. Cell. Biochem*. **2010**, *345*, 13-21. (b) Li, X.; Chu, S.; Feher, V. A.; Khalili, M.; Nie, Z.; Margosiak, S.; Nikulin, V.; Levin, J.; Sprankle, K. G.; Tedder, M. E.; Almassy, R.; Appelt, K.; Yager, K. M. Structure-Based Design, Synthesis, and Antimicrobial Activity of Indazole-Derived SAH/MTA Nucleosidase Inhibitors. *J. Med. Chem.* **2003**, *46,* 5663-5673. (c) Runti, C.; Baiocchi, L. The Chemistry of Benzydamine. *Int J Tissue React.* **1985**, *7*, 175-186. (d) Lena, M. D.; Lorusso, V; Latorre, A.; Paclitaxel, Cisplatin and Lonidamine in Advanced Ovarian Cancer. A phase II Study. *Eur J Cancer*. **2001**, *37*, 364-368. (e) Han, W.; Pelletier, J. C.; Hodge, C. N. Tricyclic ureas: A New Class of HIV-1 Protease Inhibitors. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 3615-3620. (f) Ikeda, Y.; Takano, N.; Matsushita, H.; Shiraki, Y.; Koide, T.; Nagashima, R.; Fujimura, Y.; Shindo, M.; Suzuki, S.; Iwasaki, T. Pharmacological Studies on a New Thymoleptic Antidepressant, 1-[3-(Dimethylamino)propyl]-5-methyl-3-phenyl-1*H*-indazole (FS-32). *Arzneim. Forsch*. **1979**, *29*, 511-520. (g) Lee, F.-Y.; Lien, J.-C.; Huang, L.-J.; Huang, T.-M.; Tsai, S.-C.; Teng, C.-M.; Wu, C.-C.; Cheng, F.-C.; Kuo, S.-C. Synthesis of 1-Benzyl-3-(5'-hydroxymethyl-2'-furyl)indazole Analogues as Novel Antiplatelet Agents. *J. Med. Chem.* **2001**, *44,* 3746-3749.

11. (a) Chung, C. K.; Bulger, P. G.; Kosjek, B.; Belyk, K. M.; Rivera, N.; Scott, M. E.; Humphrey, G. R.; Limanto, J.; Bachert, D. C.; Emerson, K. M. Process Development of C–N Cross-Coupling and Enantioselective Biocatalytic Reactions for the Asymmetric

Synthesis of Niraparib. *Org. Process Res. Dev*. **2014**, *18*, 215-227. (b) Jia, Y.; Zhang, J.; Feng, J.; Xu, F.; Pan, H.; Xu, W. Design, Synthesis and Biological Evaluation of Pazopanib Derivatives as Antitumor Agents. *Chem. Biol. Drug Des*. **2014**, *83*, 306-316. (c) Shen, H.; Gou, S.; Shen, J.; Zhu, Y.; Zhang, Y.; Chen, X. Synthesis and Biological Evaluations of Novel Bendazac Lysine Analogues as Potent Anticataract Agents. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2115-2118. (d) Veerareddy, A.; Surendrareddy, G.; Dubey, P. K. Total Syntheses of AF-2785 and Gamendazole-Experimental Male Oral Contraceptives. *Synth. Commun.* **2013**, *43*, 2236-2241.

12. (a) Angelis, M. D.; Stossi, F.; Carlson, K. A.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. Indazole Estrogens: Highly Selective Ligands for the Estrogen Receptor β. *J. Med. Chem*. **2005**, *48*, 1132-1144. (b) Cross, J. B.; Zhang, J.; Yang, Q.; Mesleh, M. F.; Romero, J. A. C.; Wang, B.; Bevan, D.; Poutsiaka, K. M.; Epie, F.; Moy, T.; Daniel, A.; Shotwell, J.; Chamberlain, B.; Carter, N.; Andersen, O.; Barker, J.; Ryan, M. D.; Metcalf, C. A.; Silverman, J.; Nguyen, K.; Lippa, B.; Dolle, R. E. Discovery of Pyrazolopyridones as a Novel Class of Gyrase β Inhibitors Using Structure Guided Design. *ACS Med. Chem. Lett*. **2016**, *7*, 374-378.

13. (a) Hu, J.; Cheng, Y.; Yang, Y.; Rao, Y. A General and Efficient Approach to 2*H*-Indazoles and 1*H*-Pyrazoles Through Copper-Catalyzed Intramolecular N–N Bond Formation Under Mild Conditions. *Chem. Commun.* **2011**, *47*, 10133-10135. (b) Kumar, M. R.; Park, A.; Park, N.; Lee, S. Consecutive Condensation, C–N and N–N Bond Formations: A Copper- Catalyzed One-Pot Three-Component Synthesis of 2*H*-Indazole. *Org. Lett*. **2011**, *13*, 3542-3545. (c) Vidyacharan, S.; Murugan, A.; Sharada, D. S. C(sp^2)–H Functionalization of 2*H*-Indazoles at C3-Position via Palladium(II)-Catalyzed

Isocyanide Insertion Strategy Leading to Diverse Heterocycles. *J. Org. Chem*. **2016**, *81*, 2837-2848. (d) Lian, Y.; Bergman, R.G.; Lavis, L.D.; Ellman, J.A.; Rhodium(III)-Catalyzed Indazole Synthesis by C–H Bond Functionalization and Cyclative Capture. *J. Am. Chem. Soc*. **2013**, *135*, 7122-7125. (e) Wu, C. Fang, Y.; Larock, R. C.; Shi, F. Synthesis of 2*H*-Indazoles by the [3 + 2] Cycloaddition of Arynes and Sydnones. *Org. Lett*. **2010**, *12*, 2234-2237. (f) Yang, W.; Yang, Z.; Xu, L.; Zhang, L.; Xu, X.; Miao, M.; Ren, H. Surfactant-Type Brønsted Acid Catalyzed Stereoselective Synthesis of *trans*-3-Alkenyl Indazoles from Triazenylaryl Allylic Alcohols in Water. *Angew. Chem., Int. Ed*. **2013**, *52*, 14135-14139. (g) Abed, H. B.; Weißing, N.; Schoene, J.; Paulus, J.; Sewald, N.; Nazaré, M. Novel Strategy for the Preparation of 3-Perfluoroalkylated-2*H*-Indazole Derivatives. *Tetrahedron Lett*. **2018**, *59*, 1813–1815.

14. (a) Basu, K.; Poirier, M.; Ruck, R. T.; Solution to the C3−Arylation of Indazoles: Development of a Scalable Method. *Org. Lett*. **2016**, *18*, 3218-3221. (b) Bogonda, G.; Kim, H. Y.; Oh, K. Direct Acyl Radical Addition to 2*H*-Indazoles Using Ag-Catalyzed Decarboxylative Cross-Coupling of α-Keto Acids. *Org. Lett.* **2018**, *20*, 2711-2715. (c) Murugan, A.; Gorantla, K. R.; Mallik, B. S.; Sharada, D. S. Iron Promoted C3–H Nitration of 2*H*-Indazole: Direct Access to 3-Nitro-2*H*-indazoles. *Org. Biomol. Chem.* **2018**, *16*, 5113-5118.
15. Further information can be found in the CIF file. This crystal was deposited in the Cambridge Crystallographic Data Centre and assigned as CCDC **1872608**.