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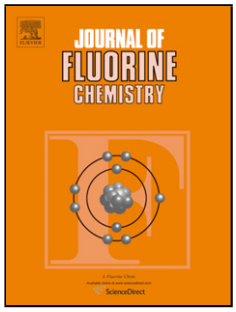

A straightforward access to 3-trifluoromethyl-1*H*-indazoles via (3+2)-cycloaddition of arynes with nitrile imines derived from trifluoroacetonitrile

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A straightforward access to 3-trifluoromethyl-1*H*-indazoles via (3+2)-cycloaddition of arynes with nitrile imines derived from trifluoroacetonitrile

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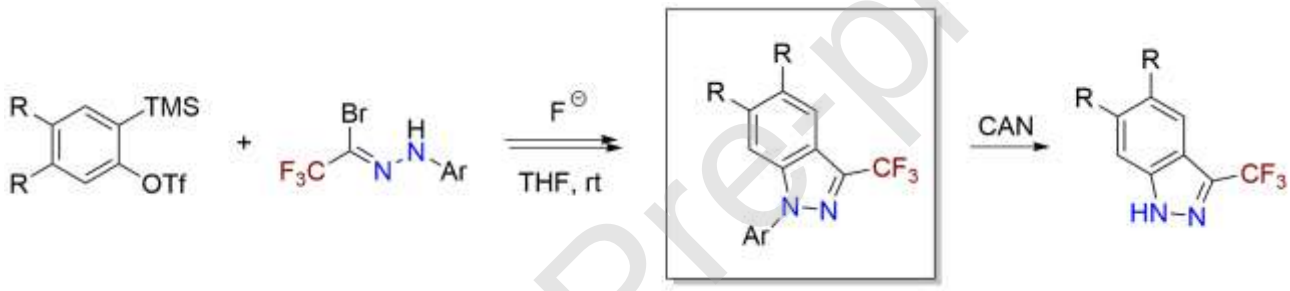
Graphical abstract



Highlights

- The *N*-aryl nitrile imines derived from trifluoroacetonitrile trap the in situ generated arynes
- In these reactions the fluoride anion plays a dual role as a base and desilylating reagent
- Under mild conditions the (3+2)-cycloadditions lead to 3-trifluoromethyl-1*H*-indazoles in high yield
- The CAN mediated dearylation allows the synthesis of *N*-unsubstituted 3-trifluoromethylindazole
- Fluorinated analogue of lonidamine was prepared via *N*-alkylation using 2,4-dichlorobenzyl chloride

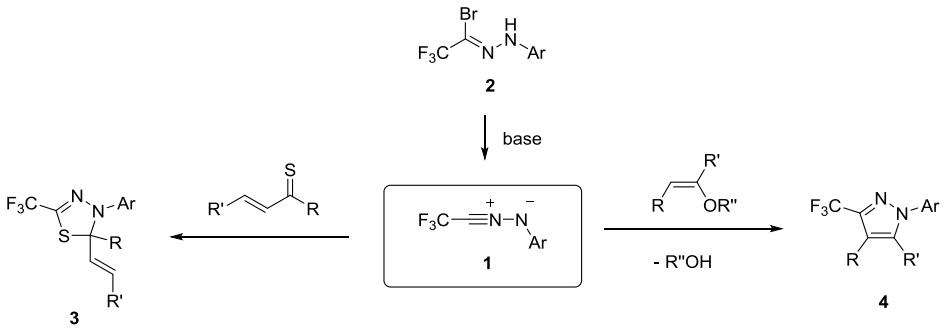
Abstract

In situ generated arynes react with nitrile imines derived from trifluoroacetonitrile at 0 °C in THF solutions yielding 3-trifluoromethyl-1*H*-indazole derivatives as the only intermolecular products. The reaction corresponds the expected (3+2)-cycloadditions which belong to the *Type III* (inverse-electron-demand) of Sustmann's classification. Subsequent CAN-mediated dearylation of the model *N*-(*p*-methoxy)phenyl indazole leads to *N*-unsubstituted analogue, which easily undergoes alkylation and acylation reactions. Presented protocol offers a superior method for preparation of the 3-CF_3 substituted indazole derivatives.

Keywords: nitrile imines, arynes, (3+2)-cycloadditions, indazoles, fluorinated heterocycles

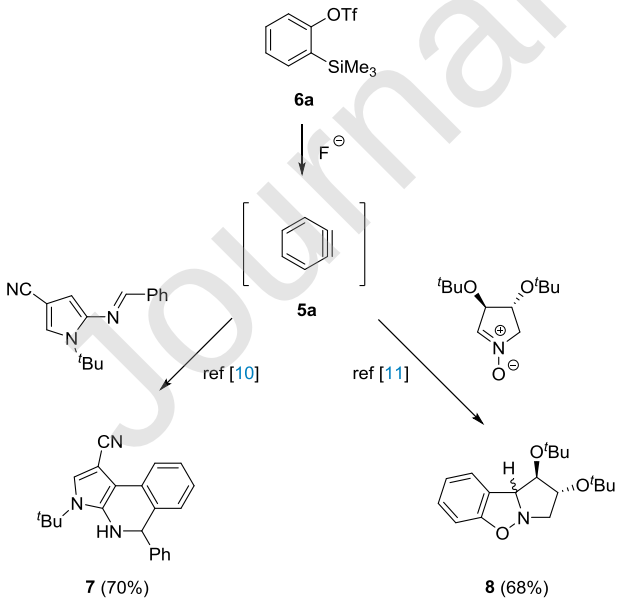
1. Introduction

In the current organic synthesis the (3+2)-cycloadditions (the *Huisgen reaction*) are considered as a powerful and universal tool for the preparation of five-membered heterocycles [1]. Thus, reactions of ethylenic or acetylenic dipolarophiles with 'nitrogen-centered' 1,3-dipoles such as nitrile imines, nitrile oxides, nitrile ylides, nitrones or azomethine ylides open access to variety of *N*-heterocyclic systems i.e. pyrazole, isoxazole, pyrrole, isoxazoline, and pyrroline derivatives, respectively [2a-f]. Moreover, the (3+2)-cycloadditions of organic azides with alkynes, performed in the presence of Cu(I) salts (the *click reactions*) are known as a group of the most widely applied transformations of organic compounds with great importance for interdisciplinary studies [2g]. In a series of our recent publications, trifluoroacetonitrile imines of type **1** generated in situ from the corresponding hydrazonoyl bromides **2** were demonstrated as a useful 1,3-dipoles for the efficient introduction of the CF_3 group into the 5-membered nitrogen heterocycles with diverse number of heteroatoms. For example, trapping of *in situ* generated **1** with thiocarbonyl dipolarophiles such as thioketones, thiochalcones or thioamides led to 1,3,4-thiadiazole derivatives of type **3** in a fully chemo- and regioselective manner [3] (Scheme 1). On the other hand, trifluoroacetonitrile imines **1** were reported to react smoothly with electron-rich C=C dipolarophiles yielding the corresponding pyrazole derivatives **4** also in a completely selective fashion [4]. In contrast, the (3+2)-cycloadditions of **1** with acetylenic dipolarophiles are lesser explored presumably due to low regioselectivity [5]. In these reactions, formation of complex mixtures of products resulting from the competitive additions of acetylide ions derived from some terminal acetylenes is a serious limitation.



Scheme 1. Reactions of trifluoroacetonitrile imines **1** with exemplary C=S and C=C dipolarophiles leading to 2,3-dihydro-1,3,4-thiadiazoles **3** and pyrazoles **4**, respectively.

Notably, there is a growing number of publications dealing with both (3+2)- and (4+2)-cycloadditions of arynes **5** [6]. These highly congested and therefore very reactive intermediates can be used either as dipolarophiles or dienophiles and they are currently easily accessible under mild conditions via fluoride anion-induced elimination from *ortho*-substituted (trialkylsilyl)aryl triflates **6** as commercially available, common precursors (Scheme 2) [7]. In this context, preparation of 1-substituted 1*H*-indazoles via *the Huisgen reaction* from the in situ generated benzynes **5** and *C,N*-di(hetero)aryl-functionalized nitrile imines was described as a promising method to synthesize these type of the fused heterocycles [8]. Prompted by these results reported for the first time by Moses' group, we decided to examine a series of trifluoroacetonitrile imines **1** with selected arynes **5** in order to prepare hitherto little known 3-trifluoromethylated 1*H*-indazoles [9]. Furthermore, the target products seemed to be an interesting class of organic substrates for further functionalization, e.g. *via* dearylation of the N(1) atom followed by alkylation or acylation at this position.



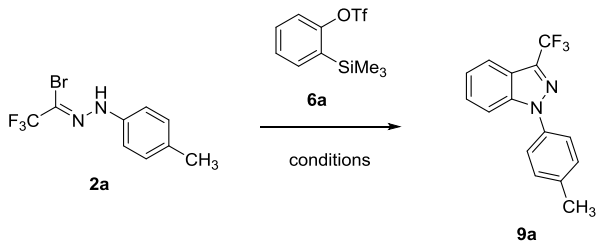
Scheme 2. Generation of benzyne (**5a**) and its cycloaddition reactions with selected heterodienes and 1,3-dipoles leading to the respective benzo-fused systems **7** and **8** as initial products of cycloaddition reactions (for details see, refs. [10] and [11]).

Hence, the goal of the present study was the synthesis and selected transformations of 3-trifluormethyl-1*H*-indazoles via in situ trapping of arynes with the title fluorinated nitrile imines derived from trifluoroacetonitrile.

2. Results and Discussion

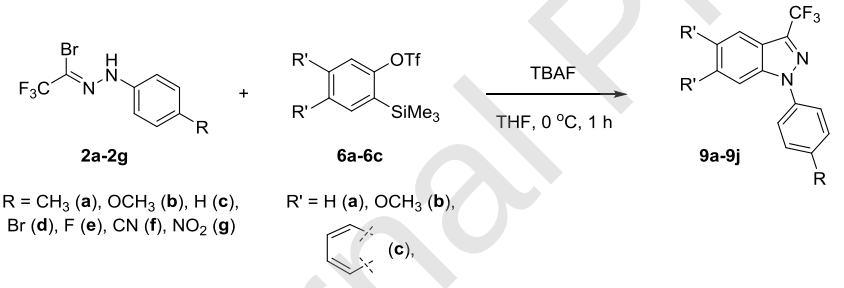
The starting nitrile imines **1** were generated based on a procedure routinely applied in our laboratory for a longer time, i.e. by dehydrobromination of hydrazonoyl bromides **2** with an organic or inorganic base, in anhydrous aprotic solvents [3,4]. In a test experiment, corresponding precursor of the nitrile imine **1a** (0.5 mmol) bearing the NMR-diagnostic *p*-tolyl group, and *o*-trimethylsilyl-phenyl triflate (**6a**, 0.75 mmol) were treated with tetrabutylammonium fluoride (TBAF, 1.3 mmol) in dry THF at room temperature. As expected, the application of the two-fold amount of TBAF assured dual role of the fluoride anion for both, smooth generation of benzyne (**5a**) as well as for dehydrohalogenation of hydrazonoyl bromide **2a**. According to the TLC tests, triflate **6a** was fully consumed after 20 min, and the ^{1}H NMR spectrum registered for crude reaction mixture revealed the presence of the expected (3+2)-cycloadduct **9a** along with unreacted nitrile imine precursor **2a**, which were isolated in 42% and 38% yield, respectively. Optimization of the reaction conditions revealed that the increased amounts of both triflate **6a** (2.0 equiv.) and TBAF (4.0 equiv.) are necessary for complete consumption of the bromide **2a** (Table 1). Neither the change of the solvent (MeCN) nor the decrease of the reaction temperature to –20 °C showed remarkable impact on the reaction outcome. Notably, the replacement of TBAF by CsF as a source of fluoride anion was unsuccessful and the reduced solubility of the latter in THF can be the explanation of that result. Thus, by running the reaction of **2a** with two-fold excess of benzyne precursor **6a** and four-fold excess of TBAF, in THF at 0 °C, the desired (3+2)-cycloadduct **9a** was isolated in satisfactory yield of 74% (Table 1, entry 4; Scheme 3). The pure product was isolated by column chromatography, and its structure was confirmed by spectroscopic methods. For example, in the ^{19}F NMR spectrum the signal of the CF_3 group appeared as a singlet located at –60.8 ppm. Furthermore, in the ^{13}C NMR the characteristic quartets attributed to the CF_3 moiety and the C(3) atom were found at 122.0 ($^{1}J_{C,F}$ = 269.2 Hz) and 135.8 ($^{2}J_{C,F}$ = 38.4 H Hz) ppm, respectively. Finally, high resolution MS measurements for the sample confirmed the molecular formula of 1-(*p*-tolyl)-3-trifluoromethyl-1*H*-indazole (**9a**) as $C_{15}H_{11}F_3N_2$.

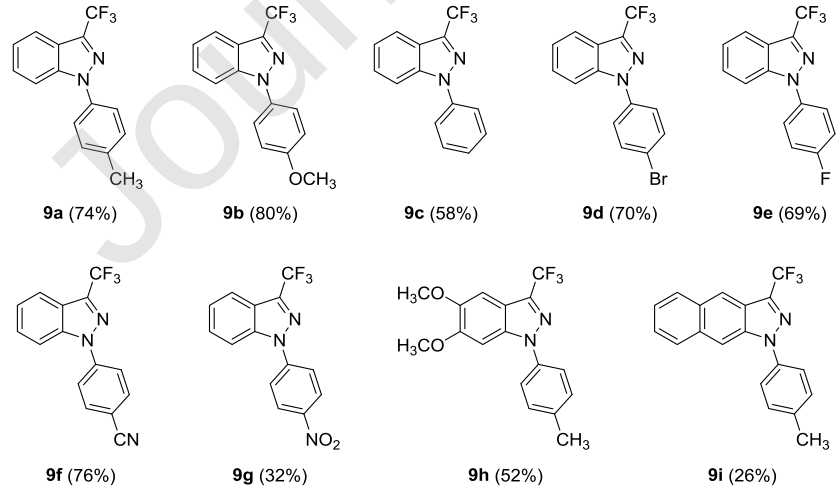
Table 1. Optimisation of the reaction conditions by using **2a** and **6a** as model substrates.



Entry	**6a** (equiv.)[a]	F⁻ source (equiv.)[a]	Solvent	Temp.	Time	**9a** [%] [b]
1	1.5	CsF, 2.5	THF	rt	24 h	NR
2	1.5	TBAF, 2.5	THF	rt	20 min	42 [c]
3	1.5	TBAF, 3.0	THF	rt	20 min	58 [d]
3	2.0	TBAF, 4.0	THF	rt	20 min	72
4	2.0	TBAF, 4.0	THF	0 °C	1 h	74
5	2.0	TBAF, 4.0	THF	–20 °C	1 h	70
6	2.0	TBAF, 4.0	THF	–78 °C	1 h	46
7	2.0	TBAF, 4.0	MeCN	0 °C	1 h	71

[a] with respect to hydrazonoyl bromide **2a**; all experiments were performed in a 0.5 mmol (**2a**) scale.
[b] isolated yield.
[c] unreacted **2a** was recovered in 38% yield.
[d] traces (<5%) of starting **2a** were found in the crude mixture.





Scheme 3. Synthesis of 3-trifluoromethyl-1*H*-indazole derivatives **9a**-**9i** by the (3+2)-cycloaddition of arynes **5a**-**5c** with nitrile imines **1a**-**1g**.

The optimized conditions were applied for a series of experiments performed with diverse *para*-substituted nitrile imines **1b**-**1g** and the model benzyne (**5a**) (Scheme 3). In all the studied cases, the desired indazoles of type **9** were isolated as sole intermolecular products in satisfactory to high yields (58-80%) with one exception of the representative **9g** (32%) functionalized with electron-withdrawing NO_2 group.

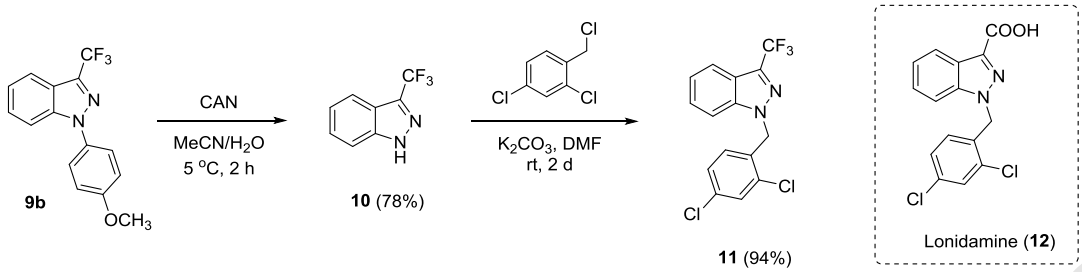
In extension of the study, two further arynes, namely 4,5-dimethoxybenzyne (**5b**) and naphtyne (**5c**), were also examined in reactions with a model N-(*p*-tolyl)trifluoroacetohydrazonoyl bromide (**2a**). Remarkably, introduction of two electron-donating OMe groups in **5b** did not affect the course of the (3+2)-cycloaddition, and the product **9h** was isolated in satisfactory yield of 52%, comparable with other studied reactions (see Table 1). However, the reaction performed with in situ generated naphtyne (**5c**) led to a complex mixture and the expected product was isolated as a colorless solid in 26% yield only.

The mechanism of the studied reaction requires a brief comment. Very likely, formation of the fused indazole system **9** occurs via concerted but rather asynchronous (3+2)-cycloaddition. Taking into account that the presented reactions occur with participation of electron-deficient 1,3-dipoles **1** and electron-rich arynes **5**, they can be classified to *Type 3* (inverse-electron-demand) according to Sustmann's classification of the 1,3-dipolar cycloadditions [12].

In the second part of the study, selected indazole derivative **9b** bearing electron-rich *p*-methoxyphenyl group was used for further transformations aimed at the preparation of new analogues of some indazole-derived biologically active compounds which are of current interest [13]. The initial conversion of a multi-step transformation of **9b** was dearylation using ceric ammonium nitrate (CAN) and this process is depicted in Scheme 4. The reaction was performed in a $MeCN/H_2O$ mixture, at 5 °C. After standard aqueous workup followed by column chromatography, the expected indazole **10** lacking a substituent at N(1) was obtained in satisfactory 78% yield. Its structure was confirmed spectroscopically, and the ^{13}C NMR spectrum showed again the diagnostic signal of the C(3) atom as a quartet located at 135.9 ($^2J_{C,F}$ = 38.2 Hz) ppm, along with the signal of the CF_3 group found at 122.0 ($^1J_{C,F}$ = 268.9 Hz), indicating the presence of a single tautomeric form under the measurement conditions (rt, $CDCl_3$) within the NMR accuracy of >0.1%.

Next, the obtained NH-indazole derivative **10** was checked as a nucleophilic reagent in alkylation and acylation at the N(1) atom using selected electrophiles. For example, treatment of **10** with an excess of 2,4-dichlorobenzyl chloride under mild conditions (room temperature, K_2CO_3, in

DMF) afforded after 2d the desired *N*-benzylated derivative **11** in excellent yield (94%). This is worth of mentioning that this product constitutes a new structural analogue of lonidamine (**12**); the latter is a well-known medicine used for the cancer treatment [14].



Scheme 4. Synthesis of *N*-unsubstituted indazole **10** by CAN-mediated dearylation of **9b** and subsequent alkylation leading to lonidamine analogue **11**.

Two more functionalization of indazole **10** were also performed via alkylation using (*S*)-citronellyl bromide and acylation with cholestanyl-functionalized succinyl monochloride. In both cases, the expected enantiopure products **13** and **14** were obtained in good yields of 87% and 80%, respectively. These results demonstrate that indazole **10** can be explored as a useful building block for the preparation of new terpene- and steroid-containing conjugates. Compounds of this type are of interest e.g. in the context of their antiviral activity [15].

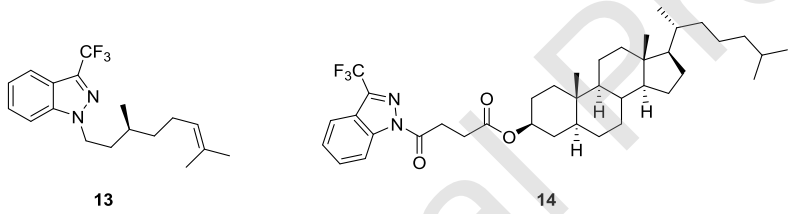


Figure 1. Structures of chiral 3-trifluoromethylindazole-conjugates **13** and **14** obtained by alkylation or acylation of **10** with (*S*)-(+)-citronellyl bromide (**15**) or cholestan-3-yloxycarbonylpropionyl chloride (**16**).

3. Conclusions

The presented method of the synthesis of 3-trifluoromethylated 1*H*-indazoles via the (3+2)-cycloaddition of the in situ generated both trifluoroacetonitrile imines and arynes offers a convenient access to these heterocycles which are of interest as versatile building blocks for preparation of potentially biologically active, fluoromethylated *N*-heterocycles. The importance of fluorinated indazoles is demonstrated by numerous original and review publications [16]. Due to synthetic limitations in preparation of trifluoroacetonitrile imines, only *N*-arylated indazoles can be directly accessed by the presented method. However, a straightforward CAN-mediated dearylation opens a

highly efficient access to known N(1)H-indazole in high yield. It is worth of mentioning that in comparison to other reported methods the procedure described herein can be considered as a method of choice for preparation of this relevant, fluorinated building block [17]. As demonstrated in the present study, the latter indazole displays the expected nucleophilic behavior in alkylation and acylation reactions. On the other side, described results show once more high utility of the in situ generated arynes as highly reactive dipolarophiles for the synthesis of fused, functionalized nitrogen heterocycles.

4. Experimental Part

4.1. General information

If not stated otherwise, reactions were carried out under inert atmosphere (argon) in a flame-dried flasks with addition of the reactants by using syringes; subsequent manipulations were conducted in air. Products were purified by standard column chromatography (CC) on silica gel (230–400 mesh), deactivated prior to use with 2% Et_3N in petroleum ether, by using freshly distilled solvents (petroleum ether, CH_2Cl_2, EtOAc). THF was dried over sodium–benzophenone and freshly distilled before usage; anhydrous DMF is available commercialy and was used as received. NMR spectra were measured on a Bruker AVIII instrument (^{1}H at 600 MHz, ^{13}C at 151 MHz, and ^{19}F at 565 MHz). Chemical shifts are reported relative to solvent ($CDCl_3$) residual peaks (^{1}H NMR: δ = 7.26 ppm, ^{13}C NMR: δ = 77.0 ppm) or to $CFCl_3$ (^{19}F NMR: δ = 0.00 ppm) used as external standard. Multiplicity of the signals in ^{13}C NMR spectra were assigned based on supplementary 2D measurements (COSY, HMQC, HMBC). MS (ESI) were performed with a Varian 500-MS LC Ion Trap; high resolution MS (ESI-TOF) measurements were measured with a Synapt G2-Si mass spectrometer (Waters). IR spectra were measured with an Agilent Cary 630 FTIR spectrometer, in neat. Elemental analyses were obtained with a Vario EL III (Elementar Analysensysteme GmbH) instrument. Melting points were determined in capillaries with a MEL-TEMP apparatus (Aldrich) or with a polarizing optical microscope (Opta-Tech), and are uncorrected. Hydrazonoyl bromides **2a**-**2g** were prepared by treatment of the respective trifluoroacetaldehyde arylhydrazones [18] with *N*-bromosuccinimide in dry DMF as described [3a]. Cholestan-3-yloxycarbonylpropionyl chloride (**16**) was prepared following the literature procedure [19].

*4.2. General procedure for the synthesis of 3-trifluoromethyl-1H-indazoles **9***

To a mixture of the respective hydrazonoyl bromide of type **2** (0.5 mmol) and benzyne precursor **5** (1.0 mmol) in dry THF (5 mL) at 0 °C was added dropwise TBAF (1M in THF, 2.0 mL, 2.0 mmol) and the resulting was stirred for 1 h. After solvent was removed under reduced pressure, the resulting mixture was purified by standard column chromatography (CC) on SiO_2 (washed with 2%

Et_3N in petroleum ether) using petroleum ether – dichloromethane mixtures as an eluent to give product **9** as spectroscopically pure samples.

*4.2.1. 1-(p-Tolyl)-3-trifluoromethyl-1H-indazole (**9a**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 4:1), 102 mg (74%), pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.46 (s, 3 H, Me), 7.34-7.36 (m, 1 H), 7.36 (d_{br}, $J \approx 8.2$ Hz, 2 H, Tol), 7.47-7.51 (m, 1 H), 7.59 (d_{br}, $J \approx 8.2$ Hz, 2 H, Tol), 7.71 (d_{br}, $J \approx 8.6$ Hz, 1 H), 7.91-7.93 (m, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 21.1 (Me), 111.0, 120.3 (2 CH), 121.2 (*i*-C), 122.0 (q, $^1J_{C,F} = 269.2$ Hz, CF_3), 123.2, 123.5, 127.9, 130.1 (CH, 2 CH, CH, 2 CH), 135.8 (q, $^2J_{C,F} = 38.4$ Hz, C-3), 136.7, 138.0, 140.0 (3 *i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –60.8 (s, CF_3) ppm; IR (neat): *ν* 2925, 1612, 1502, 1433, 1352, 1173, 1128, 1030, 821, 746 cm^{-1}; EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_{15}H_{11}F_3N_2$: 276.0874; found: 276.0878.

*4.2.2. 1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-indazole (**9b**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 3:1), 117 mg (80%), colourless solid, mp 65–66 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.89 (s, 3 H, Me) 7.07 (d, $J = 8.9$ Hz, 2 H), 7.32-7.36, 7.46-7.50 (2 m, 1 H each), 7.36 (d, $J = 8.9$ Hz, 2 H), 7.64 (d_{br}, $J \approx 8.6$ Hz, 1 H), 7.91 (d_{br}, $J = 8.2$ Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 55.6 (OMe), 110.9, 114.8, 120.2 (CH, 2 CH, CH), 121.0 (*i*-C), 122.0 (q, $^1J_{C,F} = 269.0$ Hz, CF_3), 123.1, 125.3, 127.9, (CH, 2 CH, CH), 132.1 (*i*-C), 135.6 (q, $^2J_{C,F} = 38.3$ Hz, C-3), 140.2, 159.3 (2 *i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –60.7 (s, CF_3) ppm; IR (neat): *ν* 2926, 1526, 1502, 1431, 1253, 1188, 1154, 1132, 1030, 828, 741 cm^{-1}; EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_{15}H_{11}F_3N_2O$: 292.0823; found: 292.0828.

*4.2.3. 1-Phenyl-3-trifluoromethyl-1H-indazole (**9c**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 4:1), 76 mg (58%), yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35-7.38, 7.44-7.46, 7.51-7.53 (3 m, 1 H each), 7.56-7.59 (m, 2 H), 7.72-7.74 (m, 2 H), 7.75 (d, $J = 8.6$ Hz, 1 H), 7.92-7.94 (m, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 111.3, 120.4 (2 CH), 121.3 (*i*-C), 121.9 (q, $^1J_{C,F} = 269.3$ Hz, CF_3), 123.3, 123.6, 128.0, 128.1, 129.6 (CH, 2 CH, CH, CH, 2 CH), 136.2 (q, $^2J_{C,F} = 38.4$ Hz, C-3), 139.2, 140.0 (2 *i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –60.9 (s, CF_3) ppm; IR (neat): *ν* 3064, 1660, 1599, 1497, 1433, 1352, 1298, 1259, 1128, 949, 748 cm^{-1}; EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_{14}H_9F_3N_2$: 262.0718; found: 262.0725.

*4.2.4. 1-(4-Bromophenyl)-3-trifluoromethyl-1H-indazole (**9d**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 4:1), 119 mg (70%), yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37-7.39, 7.52-7.55 (2 m, 1 H each), 7.61-7.64 (m, 2 H), 7.68-7.73 (m, 3 H), 7.93 (dd, $J =$ 0.8, 8.2 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 110.8, 120.6 (2 CH), 121.4, 121.5 (2 *i*-C), 121.8 (q, $^1J_{C,F} = 269.4$ Hz, CF_3), 123.6, 124.9, 128.4, 132.8 (CH, 2 CH, CH, 2 CH), 136.7 (q, $^2J_{C,F} =$

38.5 Hz, C-3), 138.2, 139.8 (2 *i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –61.0 (s, CF_3) ppm; IR (neat): *v* 2926, 1516, 1489, 1433, 1257, 1182, 1130, 1026, 949, 829, 746 cm^{-1}; EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_{14}H_8BrF_3N_2$: 339.9823; found: 339.9829.

*4.2.5. 1-(4-Fluorophenyl)-3-trifluoromethyl-1H-indazole (**9e**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 4:1), 97 mg (69%), yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24-7.30 (m, 2 H), 7.35-7.39, 7.49-7.54 (2 m, 1 H each), 7.65-7.70 (m, 3 H), 7.93 (d_{br}, $J \approx$ 8.2 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 110.7 (CH), 116.6 (d, $^2J_{C,F}$ = 23.1 Hz, 2 CH), 120.4 (CH), 121.2 (*i*-C), 121.8 (q, $^1J_{C,F}$ = 269.3 Hz, CF_3), 123.4 (CH), 125.4 (d, $^3J_{C,F}$ = 8.6 Hz, 2 CH), 128.3 (CH), 135.2 (d, $^4J_{C,F}$ = 3.1 Hz, *i*-C), 136.2 (q, $^2J_{C,F}$ = 38.4 Hz, C-3), 140.0 (*i*-C), 161.9 (d, $^1J_{C,F}$ = 248.4 Hz, *i*-CF) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –60.9 (s, CF_3), –113.0 (m_c, Ar-F) ppm; IR (neat): *v* 2929, 1606, 1523, 1501, 1433, 1259, 1236, 1177, 1154, 1127, 1026, 840, 746 cm^{-1}; EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_{14}H_8F_4N_2$: 280.0624; found: 280.0630.

*4.2.6. 4-(3-Trifluoromethyl-1H-indazol-1-yl)benzonitrile (**9f**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 1:1), 109 mg (76%), yellow solid, mp 127–128 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42-7.44, 7.58-7.61 (2 m, 1 H each), 7.82 (d_{br}, $J \approx$ 8.6 Hz, 1 H), 7.86-7.89, 7.92-7.97 (2 m, 2 H, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 110.9 (CH), 111.1 (CN), 118.0 (*i*-C), 120.9 (CH), 121.5 (q, $^1J_{C,F}$ = 269.7 Hz, CF_3), 121.9 (*i*-C), 123.0, 124.1, 129.0, 133.7 (2 CH, CH, CH, 2 CH), 137.9 (q, $^2J_{C,F}$ = 38.7 Hz, C-3), 139.7, 142.7 (2 *i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –61.3 (s, CF_3) ppm; IR (neat): *v* 3310, 2225 (CN), 1605, 1506, 1287, 1159, 938, 748 cm^{-1}; EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_{15}H_8F_3N_3$: 287.0670; found: 287.0674.

*4.2.7. 1-(4-Nitrophenyl)-3-trifluoromethyl-1H-indazole (**9g**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 1:1), 49 mg (32%), yellow solid, mp 140–141 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42-7.46, 7.61-7.64 (2 m, 1 H each), 7.86 (d_{br}, $J \approx$ 8.6 Hz, 1 H), 7.97 (dd, J = 0.7, 8.2 Hz, 1 H), 8.00, 8.46 (2 d_{br}, $J \approx$ 9.1 Hz, 2 H each) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 110.9, 121.0 (2 CH), 121.5 (q, $^1J_{C,F}$ = 269.7 Hz, CF_3), 122.0 (*i*-C), 122.7, 124.3, 125.4, 129.2 (2 CH, CH, 2 CH, CH), 138.2 (q, $^2J_{C,F}$ = 38.8 Hz, C-3), 144.2, 146.3 (2 *i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –61.4 (s, CF_3) ppm; IR (neat): *v* 3090, 1522, 1496, 1344, 1174, 1121, 948, 773 cm^{-1}; EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_{14}H_8F_3N_3O_2$: 307.0569; found: 307.0572.

*4.2.8. 5,6-Dimethoxy-1-(p-tolyl)-3-trifluoromethyl-1H-indazole (**9h**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 3:1), 87 mg (52%), orange solid, mp 112–144 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.46 (s, 3 H, Me), 3.93, 3.98 (2 s, 3 H each, OMe), 7.00, 7.14 (2 s, 1 H each), 7.35, 7.54 (2 d_{br}, $J \approx$ 8.2 Hz, 2 H each, Tol) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 21.1 (Me), 56.1, 56.2 (OMe), 91.9, 98.8 (2 CH), 114.5 (*i*-C), 122.1 (q, $^1J_{C,F}$ = 269.0 Hz, CF_3), 123.4, 130.2 (2 CH each),

135.0 (q, $^{2}J_{C,F}$ = 38.0 Hz, C-3), 135.8, 136.7, 137.9, 147.9, 151.8 (5 *i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –60.7 (s, CF_3) ppm; IR (neat): *v* 2927, 1614, 1510, 1475, 1432, 1290, 1214, 1150, 1007, 826, 734 cm^{-1}; EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_{17}H_{15}F_3N_2O_2$: 336.1086; found: 336.1088.

*4.2.9. 1-(p-Tolyl)-3-trifluoromethyl-1H-benzo[f]indazole (**9i**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 9:1), 42 mg (26%), yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.48 (s, 3 H, Me), 7.42 (d_{br}, *J* ≈ 8.2 Hz, 2 H, Tol), 7.44-7.47, 7.49-7.53 (2 m, 1 H each), 7.71 (d_{br}, *J* ≈ 8.2 Hz, 2 H, Tol), 7.92 (d_{br}, *J* ≈ 8.3 Hz, 1 H), 8.04 (d_{br}, *J* ≈ 8.3 Hz, 1 H), 8.18, 8.48 (2 s, 1 H each) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 21.2 (Me), 106.7, 119.2 (2 CH), 121.4 (*i*-C), 122.0 (q, $^{1}J_{C,F}$ = 269.2 Hz, CF_3), 123.2 (2 CH) 124.8, 126.9, 128.0, 129.1 (4 CH), 129.9 (*i*-C), 130.2 (2 CH), 133.1 (*i*-C), 135.8 (q, $^{2}J_{C,F}$ = 38.5 Hz, C-3), 137.0, 137.6, 138.3 (3 *i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –60.9 (s, CF_3) ppm; IR (neat): *v* 2922, 1608, 1524, 1510, 1489, 1358, 1105, 1010, 818, 744 cm^{-1}; HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{14}F_3N_2$: 327.1109; found: 327.1111.

*4.3. Synthesis of 3-trifluoromethyl-1H-indazole (**10**)* [17]

To a magnetically stirred solution of 1-(4-Methoxyphenyl)-3-trifluoromethyl-1*H*-indazole (**9b**, 146 mg, 0.5 mmol) in MeCN (20 mL) at 5 °C a solution of ceric ammonium nitrate (1.37 g, 2.4 mmol) in H_2O (12 mL) was added. The resulting mixture was stirred for 2 h at this temperature, then neutralized to pH = 7 with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were dried over $MgSO_4$, filtered and the solvents were removed in vacuo. The residue was purified by flash column chromatography (SiO_2, petroleum ether/CH_2Cl_2 4:1) to give *N*-unsubstituted indazole **10** (73 mg, 78%) as colourless solid.

Mp 96–97 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31-7.35, 7.50-7.54 (2 m, 1 H each), 7.62 (d_{br}, *J* ≈ 8.5 Hz, 1 H), 7.89 (dd_{br}, *J* ≈ 0.7, 8.3 Hz, 1 H), 11.57 (s_{br}, 1 H, NH) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 110.5 (CH), 119.5 (*i*-C), 119.9 (CH), 122.0 (q, $^{1}J_{C,F}$ = 268.9 Hz, CF_3), 123.1, 128.1 (2 CH), 135.9 (q, $^{2}J_{C,F}$ = 38.2 Hz, C-3), 141.0 (*i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –60.8 (s, CF_3) ppm; IR (neat): *v* 3184, 3161, 2936, 1475, 1432, 1230, 1186, 1153, 1115, 1028, 911, 743 cm^{-1}; (–)-ESI-MS (*m*/*z*): 184.9 (100, $[M-H]^-$); elemental analysis calcd (%) for $C_8H_5F_3N_2$ (186.1): C 51.62, H 2.71, N 15.05; found: C 51.65, H 3.01, N 14.97.

*4.4. Synthesis of 1-(2,4-dichlorobenzyl)-3-trifluoromethyl-1H-indazole (**11**)*

To a solution of 3-trifluoromethyl-1*H*-indazole (**10**, 93 mg, 0.5 mmol) and K_2CO_3 (207 mg, 1.5 mmol) in DMF (5 mL), 2,4-dichlorobenzyl chloride (117 mg, 0.6 mmol) in DMF (1 mL) was added at room temperature. The reaction mixture was stirred for 48 h, then diluted with water (20 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4

and the solvents were removed under reduced pressure. The residue was purified by column chromatography (SiO_2, petroleum ether/CH_2Cl_2 4:1) to afford **11** (162 mg, 94%) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.73 (s, 2 H, CH_2), 6.76 (d_{br}, $J \approx 8.4$ Hz, 1 H), 7.13 (dd, J = 2.0, 8.4 Hz, 1 H), 7.29-7.33 (m, 1 H), 7.40-7.48 (m, 3 H), 7.87-789 (m, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 50.1 (CH_2), 109.8, 120.3 (2 CH), 120.6 (*i*-C), 121.8 (q, $^1J_{C,F}$ = 269.0 Hz, CF_3), 123.0, 127.7, 127.8, 129.5, 129.6 (5 CH), 132.0, 133.1, 134.6 (3 *i*-C), 134.9 (q, $^2J_{C,F}$ = 38.4 Hz, C-3), 140.6 (*i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –60.7 (s, CF_3) ppm; IR (neat): *v* 2926, 1502, 1431, 1382, 1237, 1115, 1088, 987, 749 cm^{-1}; HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{10}F_3N_2Cl_2$: 345.0173; found: 345.0174.

*4.5. Synthesis of (S)-1-(3,7-dimethyloct-6-en-1-yl)-3-trifluoromethyl-1H-indazole (**13**)*

To a solution of *N*-unsubstituted indazole **10** (93 mg, 0.5 mmol) and K_2CO_3 (207 mg, 1.5 mmol) in DMF (5 mL), (*S*)-(+)-citronellyl bromide (131 mg, 0.6 mmol) in DMF (1 mL) was added at room temperature. The reaction mixture was stirred for 24h, then diluted with water (20 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and solvents were removed under reduced pressure. The residue was purified by column chromatography (SiO_2, petroleum ether/CH_2Cl_2 4:1) to yield product **13** (141 mg, 87%) as a colourless oil.

$[\alpha]_D^{20}$ = –1.73 (*c* = 0.11, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.00 (d, J = 6.6 Hz, 3 H, Me), 1.19-1.28, 1.37-1.45, 1.45-1.53 (3 m, 1 H each), 1.58, 1.66 (2 s, 3 H each, 2 Me), 1.72-1.81 (m, 1 H), 1.90-2.05 (m, 3 H), 4.36-4.53 (m, 2 H, NCH_2), 5.02-5.07 (m, 1 H), 7.28 (ddd, J = 2.5, 5.2, 8.0 Hz, 1 H), 7.44-7.48 (m, 2 H), 7.84 (d_{br}, J = 8.0 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 17.6, 19.4 (2 Me), 25.3 (CH_2), 25.6 (Me), 30.1 (CH), 36.5, 36.7, 47.8 (3 CH_2), 109.6, 120.2 (2 CH), 120.4 (*i*-C), 122.0 (q, $^1J_{C,F}$ = 268.6 Hz, CF_3), 122.4 (CH), 124.2 (=CH), 127.0 (CH), 131.6 (*i*-C), 133.6 (q, $^2J_{C,F}$ = 38.1 Hz, C-3), 140.1 (*i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –60.4 (s, CF_3) ppm; IR (neat): *v* 2932, 1718, 1506, 1433, 1228, 1157, 1120, 1075, 978, 745 cm^{-1}; HRMS (ESI-TOF): *m*/*z* $[M–H]^–$ calcd for $C_{18}H_{22}F_3N_2$: 323.1735; found: 323.1740.

*4.6. Cholestan-3-yl 4-(3-trifluoromethyl-1H-indazol-1-yl)-4-oxobutanoate (**14**)*

To a solution of indazole **10** (186 mg, 1.0 mmol) and 4-dimethylaminopyridine (DMAP, 366 mg, 2.44 mmol) in dry DCM (10 mL), cholestan-3-yloxycarbonylpropionyl chloride (558 mg, 1.1 mmol) in dry DCM (10 mL) was added dropwise. The mixture was stirred under argon at room temperature until the starting indazole was fully consumed (TLC monitoring, 1 h). The mixture was quenched with water (20 mL) and diluted with CH_2Cl_2 (10 mL). The organic layer was separated and washed with 2% HCl (10 mL), then with 5% $NaHCO_3$ (10 mL) and water (3 × 25 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product

was purified by standard column chromatography (SiO_2, petroleum ether/AcOEt 8:1) to give **14** (525 mg, 80%) as a light yellow solid.

Mp 126–128 °C. $[\alpha]_D^{20}$ = +11.96 (*c* = 0.27, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.58-0.63 (m, 1H), 0.64, 0.78 (2 s, 3 H each, 2 Me), 0.80-0.85 (m, 1 H), 0.85, 0.86 (2 d, *J* = 2.7 Hz, 3 H each, 2 Me), 0.89 (d, *J* = 6.5 Hz, 3 H, Me), 0.92-1.04 (m, 4 H), 1.04-1.17, 1.17-1.28, 1.28-1.38 (3 m, 5 H each), 1.42-1.49, 1.49-1.56 (2 m, 2 H each), 1.56-1.61, 1.61-1.66 (2 m, 1 H each), 1.71 (dt, *J* = 3.5, 13.3 Hz, 1 H), 1.76-1.84 (m, 2 H), 1.95 (dt, *J* = 3.1, 12.5 Hz, 1 H), 2.82, 3.56 (2 t, *J* = 6.6 Hz, 2 H each, 2 CH_2), 4.70-4.76 (m, 1 H, OCH), 7.43-7.49, 7.60-7.66, 7.82-7.87, 8.46-8.48 (4 m, 1 H each) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 12.0, 12.2, 18.6 (3 Me), 21.2 (CH_2), 22.5, 22.8 (2 Me), 23.8, 24.2, 27.4 (3 CH_2), 28.0 (CH), 28.2, 28.5, 28.8, 30.1, 32.0, 33.9 (6 CH_2), 35.4 (*i*-C), 35.4, 35.8 (2 CH), 36.1, 36.7, 39.5, 39.9 (4 CH_2), 42.6 (*i*-C), 44.6, 54.2, 56.2, 56.4 (4 CH), 74.4 (OCH), 115.8, 120.1 (2 CH), 120.8 (q, $^1J_{C,F}$ = 270.6 Hz, CF_3), 121.8 (*i*-C), 125.7, 130.5 (2 CH), 140.1 (q, $^2J_{C,F}$ = 38.7 Hz, C-3), 140.1 (*i*-C), 171.6, 172.5 (2 C=O) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –62.5 (s, CF_3) ppm; IR (neat): *v* 2930, 2855, 1730 (C=O), 1520, 1374, 1206, 1150, 1109, 1006, 913, 772 cm^{-1}; ESI-MS (*m*/*z*): 679.8 (100, $[M+Na]^+$); elemental analysis calcd (%) for $C_{39}H_{55}F_3N_2O_3$ (656.9): C 71.31, H 8.44, N 4.26; found: C 71.22, H 8.44, N 4.27.

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