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# Preparation of 5-fluoropyrazoles from pyrazoles and NFSI.

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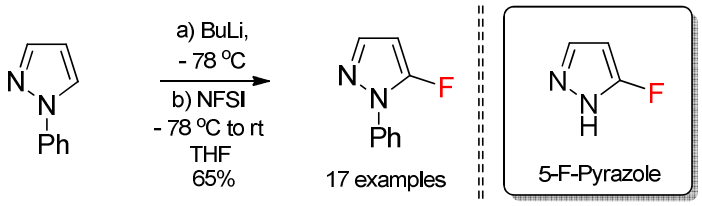



**ABSTRACT:** Facile synthesis of 5-fluoropyrazoles by direct fluorination of pyrazoles with NFSI, was elaborated. This approach was used to prepare the unsubstituted 5-fluoro-1H-pyrazole, the known fungicide *Penflufen* and many functionalized 5-fluoropyrazoles: building blocks for medicinal chemistry and agrochemistry.

## INTRODUCTION

Since the discovery of the anticancer agent 5-fluorouracil by *Heidelberger* in 1957,[1] the stable growth of fluorine-containing drugs was observed. As a fact, in 1970 there were only about 2% of fluorine-containing compounds on the market, while the current number has grown up to about 20%.[2,3] Incorporation of a single fluorine atom into organic molecules affects their metabolic stability, cellular permeability, lipophilicity, and water solubility. Therefore, elaboration of novel methods to prepare the fluorine-containing organic compounds is of high importance.[4]

In 2011, *Bayer CS* launched the novel fungicide with the fragment of 5-fluoropyrazole: *Penflufen*.[5] The single fluorine substitution made the compound more potent and metabolically stable over the non-fluorinated analogue. Since then, the core of 5-fluoropyrazole has been playing an important role in agrochemical projects, as reflected in an ever-increasing number of the corresponding patents.[6] Diverse pharmaceutical and agrochemical companies have actively started to use derivatives of 5-fluoropyrazoles in their research (Figure 1).

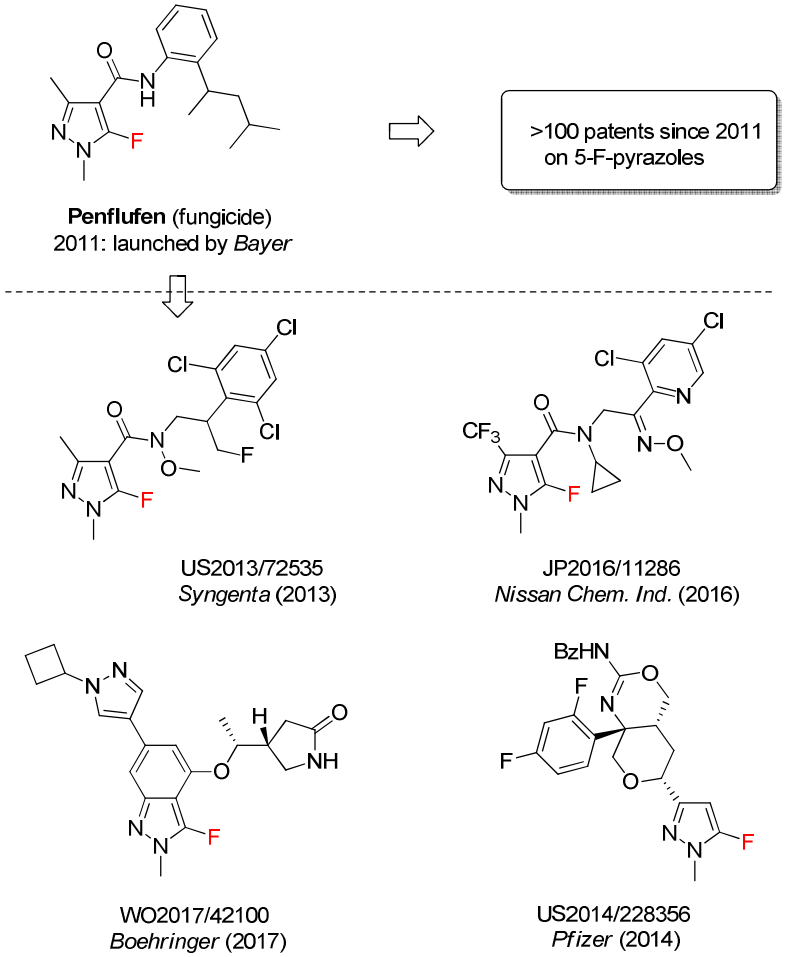



**Figure 1.** Bioactive compounds with the motif of 5-fluoropyrazole.

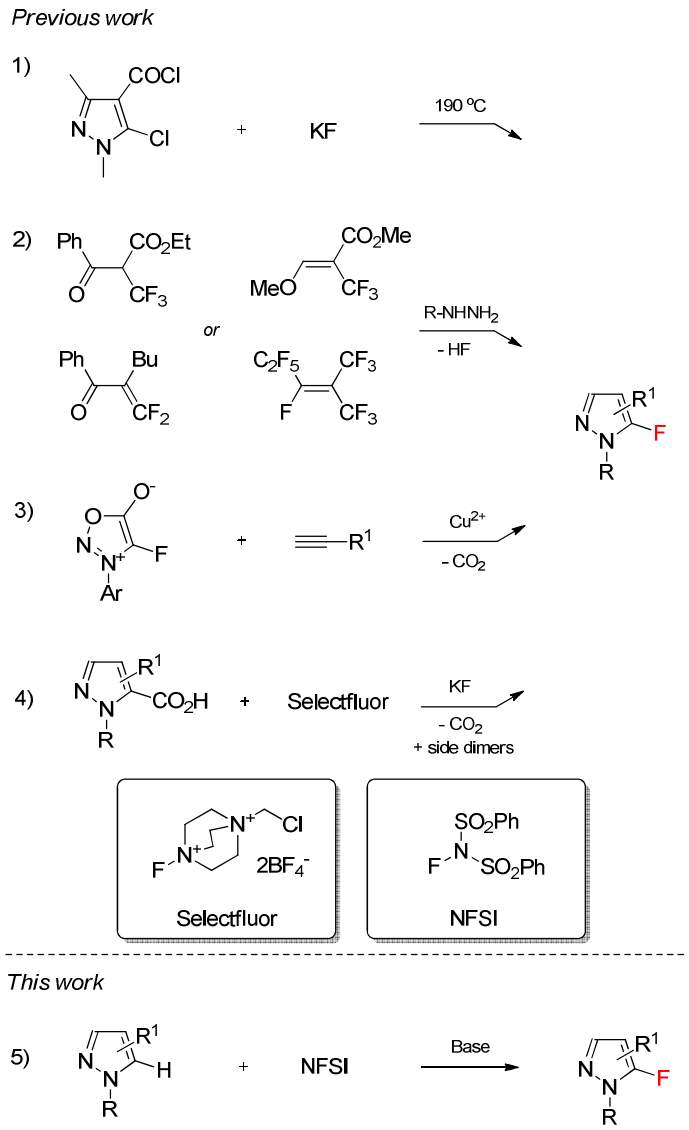
In spite of the huge current interest in fluoropyrazoles,[7,8] the number of the corresponding synthetic approaches to 5-fluoropyrazoles remains still limited.[9] They rely mainly on four approaches. An efficient practical method was developed by *Pazenok* and *Neeff* from *Bayer CS* towards an industrial production of *Penflufen*.[10] At high temperature, 5-chloropyrazoles reacted with KF - propably the cheapest source of a nucleophilic fluorine atom nowadays - to provide 5-fluoropyrazoles (Scheme 1, 1).

The second approach requires the fluorinated synthon for 1,3-dicarbonyl compounds. With hydrazines, the activated $CF_3$/$CF_2$-groups act as a hidden equivalent for the carbonyl group to form 5-fluoropyrazoles accompanied with HF-elimination/heteroaromatization. The groups of *Yamakawa*,[11] *Ichikawa/Minami*,[12] *Schlosser*,[13] and *Chiba*[14] used different starting compounds to synthesize the target products (Scheme 1, 2)). Perfluoro(2-methyl-2-pentene) also reacts with hydrazines to provide polyfluorinated 5-fluoropyrazoles (Scheme 1, 2).[15]

In 2016, *Taran* and colleagues elaborated the "*ultrafast*" copper-catalyzed click-reaction of fluorosydnones with alkynes to give 5-fluoropyrazoles.[16] The high potential of this reaction was demonstrated by the radiolabelling of pyrazoles with $^{18}$F-isotope (Scheme 1, 3).

Finally, in 2017, *Tang* demonstrated that electron-rich heteroaromatic carboxylic acids reacted with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) to form fluoroheterocycles accompanied with decarboxylation.[17] In many cases, however, formation of the side dimeric products was also observed (Scheme 1, 4).

We were very much surprised since very little was known on the direct incorporation of the electrophilic fluorine atom into pyrazoles. In recent years, this reaction was mentioned in many patents of agrochemical and pharmaceutical companies using diverse fluorination agents: $XeF_2$,[18] *N*-fluorobenzenesulfonimide (NFSI)[19] and Selectfluor[20] with the yields typically below 30%. However, to the best of our knowledge no systematic study in the open literature has been performed so far.[21] In this context, and within our current interest in fluorinated heterocycles,[22,23,24,2526] herein we have elaborated an efficient practical method to 5-fluoropyrazoles from pyrazoles and NFSI. The high potential of this approach was demonstrated by the synthesis of 5-fluoropyrazole and *Penflufen*.

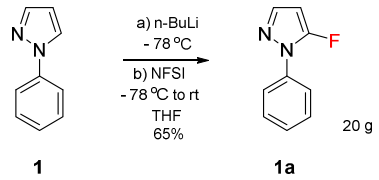



**Scheme 1.** Approaches to 5-fluoropyrazoles.

## RESULTS AND DISCUSSION

***Validation of the hypothesis and scale up.*** First, we tried to perform fluorination of the model none-functional pyrazole **1** with NFSI. Initial attempts to directly introduce fluorine atom in the absence of a strong base were unsuccessful. Therefore, we next treated the starting material with *n*-BuLi at −78 °C followed by a transfer of a pre-cooled solution of NFSI in THF (−78 °C) via a

cannula. After the addition, the reaction mixture was stirred for 2 h under cooling. The crude product contained ca. 85% of product **1a** and 15% of the starting material. Unfortunately, all attempts to improve the conversion of the reaction by increasing the reaction time, amount of NFSI and the reaction temperature did not help. Gratifyingly, however pyrazole **1a** was isolated in 65% yield after the column chromatography (Scheme 2). Importantly, the procedure was still effective on a gram scale, as we easily synthesized 20 g of the product in a single run.



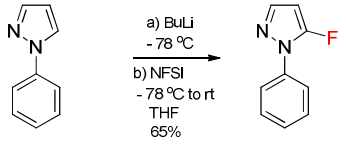

**Scheme 2.** Synthesis of 5-fluoropyrazole **1a**.

***Reaction Scope***. Having a validated procedure in hand, we next studied its scope and limitations. Diverse *N*-aryl substituted pyrazoles **2-9** were tested (Table 1, Entry 2-9). To avoid the bromine-lithium exchange in pyrazoles **6** and **7**, LDA was used instead of BuLi. Under the above described conditions, according to LC-MS data all reaction mixtures contained ca. 80% of the needed fluoropyrazoles, the starting materials and the side products: $PhSO_2$-pyrazoles.[27] For all tested compounds **2-9**, except for **7**, the needed substituted 5-fluoropyrazoles **2a-6a** and **8a**, **9a** were isolated from the reaction mixtures by column chromatography in appropriate yields of 60-65%. Pyrazole **7** gave mainly the side product **7b** and only 5% of the needed fluoropyrazole **7a**, as detected by LC-MS (Scheme 3b).

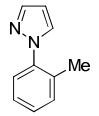
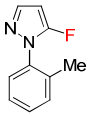
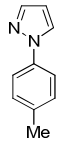
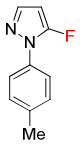
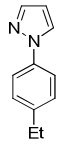
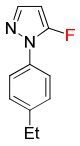
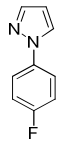
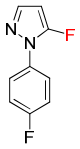
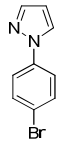
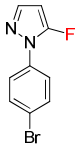
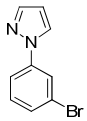
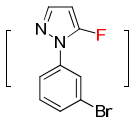
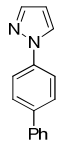
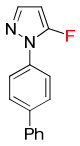
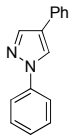
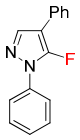
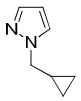
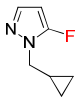
Next, we studied the fluorination of *N*-alkyl substituted pyrazoles (Table 1, Entry 10-18). *N*-Isopropylpyrazole **10** gave a fluorinated product **10a** in a moderate yield of 51%. In case of pyrazole **11** no reaction was observed. Due to a sterically bulky *tert*-butyl substituent, anion **A** did not react with NFSI. The LC-MS and GC-MS analysis of the reaction mixture showed that a major component of the reaction was the starting pyrazole **11** (Scheme 3b). With more active electrophile - carbon dioxide, - the corresponding acid **19** was obtained in 75% yield.

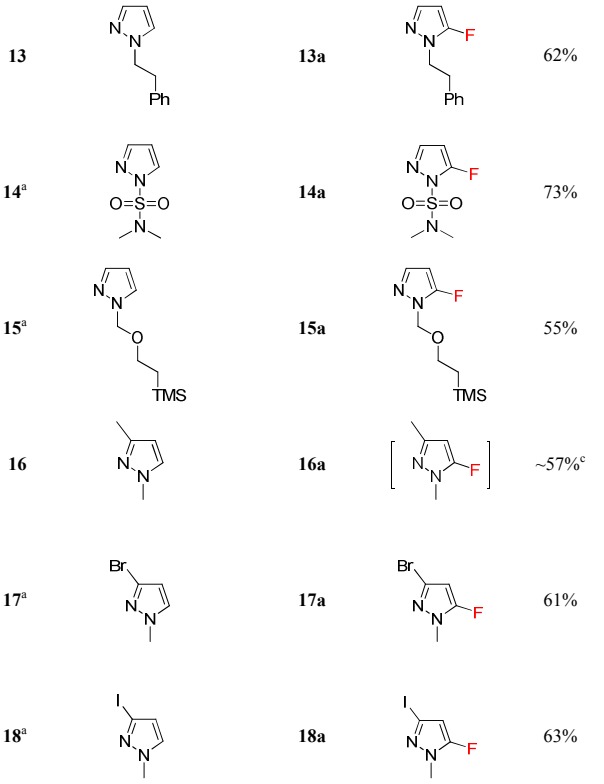
Substrates **12-18** smoothly underwent lithiation/fluorination and gave the desired products **12a-18a** in 50-73% yield. LDA was used instead of BuLi in case of pyrazoles **14**, **15** and also **17**, **18** to avoid the halogen-lithium exchange. All *N*-alkyl fluorinated pyrazoles were volatile. The product **16a** was very volatile, and we did not isolate it in the individual state. Its solution in THF was directly used for subsequent transformations (Scheme 7).

**Table 1**. Scope and limitations of the reaction.

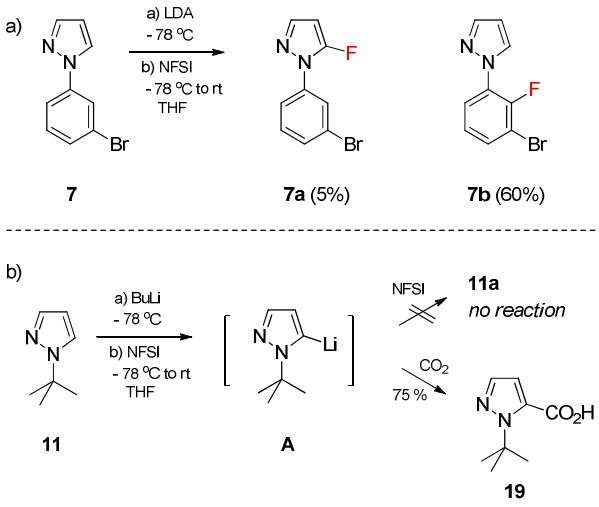



| Pyrazole | Product | Yield |
|---|---|---|
| **1** | **1a** | 65% |

| | | | | |
|---|---|---|---|---|
| **2** |  | **2a** |  | 61% |
| **3** |  | **3a** |  | 60% |
| **4** |  | **4a** |  | 64% |
| **5** |  | **5a** |  | 63% |
| **6**[a] |  | **6a** |  | 65% |
| **7**[a] |  | **7a** |  | ~5%[b] |
| **8** |  | **8a** |  | 63% |
| **9** |  | **9a** |  | 61% |
| **10** |  | **10a** |  | 51% |
| **11** |  | **11a** | *no reaction* | |
| **12** |  | **12a** |  | 68% |




a) LDA was used instead of BuLi. b) Yield by LC-MS. C) Yield by $^1$H NMR. The compound was not isolated due to a high volatility, but was used next as a solution in THF.

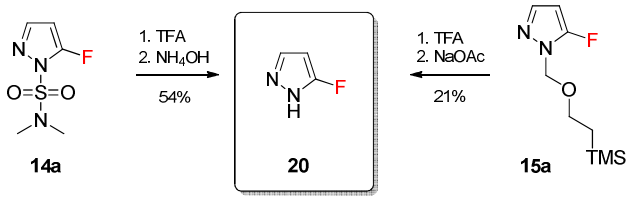



**Scheme 3.** Limitation of the method.

***Synthesis of 5-fluoropyrazole.*** 5-Fluoropyrazole **20** was described in 1996 by *Reimlinger* and *Van Overstraeten*.[28] The authors thermally decomposed pyrazolyl diazonium tetrafluoroborate in the presence of NaF to obtain the product **20** in 0.3% yield. So far, this is the only known method towards compound **20**. It is not surprising therefore, that in spite of huge practical potential, no one used pyrazole **20** in medicinal chemistry, agrochemistry or organic synthesis. Because of the lack of synthetic approaches, pyrazole **1a** is also not commercially available.

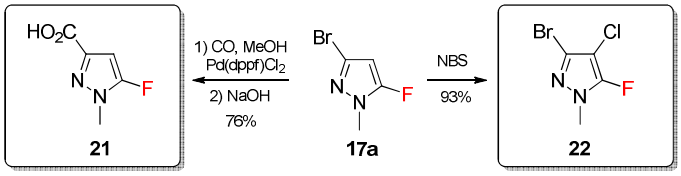
The above results on *N*-protected pyrazoles **14a** and **15a** suggested us a good method to **20** (Scheme 4). Treatment of compound **15a** with TBAF at room temperature during 64 h gave only 65% of conversion. In strict contrast, treatment of compound **15a** with trifluoracetic acid at -10 °C gave the corresponding salt, and a further hydrolysis with sodium acetate in ethanol afforded product **20** in 21% isolated yield. When we treated compound **14a** with trifluoracetic acid, we received the pure pyrazole **20** in 54% isolated yield.

We believe that with this novel synthetic strategy, pyrazole **20** will find soon a wide practical application in organic synthesis as a building block, and also in coordination chemistry as a ligand for transition metals.[29,30]




**Scheme 4.** Synthesis of 5-fluoropyrazole **20**.

***Synthesis of building blocks.*** Next, we transformed several products into the representative functionalized building blocks for organic synthesis. Reaction of bromide **17a** with gaseous carbon monoxide in the presence of cat. $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ in dry methanol in a steel autoclave gave an intermediate ester that after the hydrolysis with 10% aq. NaOH afforded the target acid **21** in 76% yield. Treatment of pyrazole **17a** with NBS in acetonitrile at room temperature gave compound **22** in 93% yield (Scheme 5). The difference in activity of F, Cl and Br atoms in pyrazole **22** makes it an interesting target for further functionalization by sequential metal-catalyzed cross-couplings.

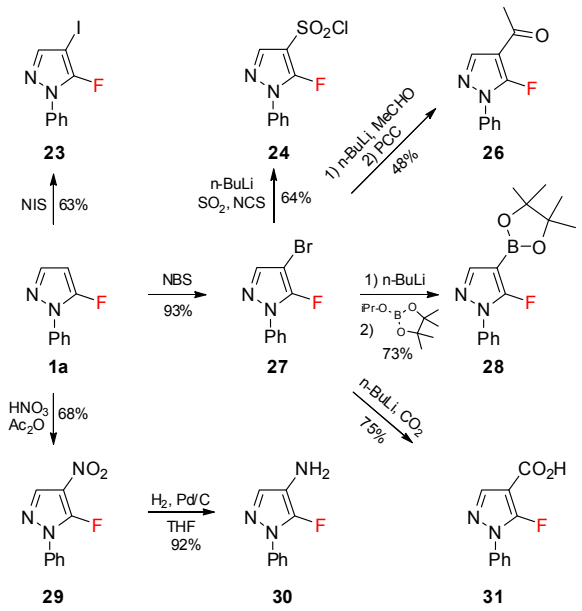



**Scheme 5.** Synthesis of pyrazoles **21** and **22**.

Different classes of organic compounds were next synthesized from pyrazole **1a** (Scheme 6). First, we treated compound **1a** with *N*-iodosuccinimide under heating at reflux in acetonitrile during two days to obtain iodide **23** in 63% yield. Treatment of pyrazole **1a** with a mixture of the fuming nitric acid and acetic anhydride led to a nitro product **29** in good yield of 68%. Further reduction of the nitro group with hydrogen over Pd/C as a catalyst in methanol at room temperature produced a mixture of **30** and the undesired product 5-methoxy-1-phenyl-1*H*-pyrazol-4-amine in 1:1 ratio. When we replaced methanol with THF, the target amine **30** was isolated in 92% yield. Next, we treated pyrazole **1a** with *N*-bromosuccinimide in acetonitrile at room temperature to obtain bromide **27** in 93% yield.

Pyrazole **1a** did not react with acetic anhydride in the presence of Lewis acids even under the heating. Therefore, we treated bromide **27** with *n*-BuLi, followed by an addition of MeCHO. The intermediate crude alcohol **25** was oxidized with pyridinium chlorochromate in an overall yield of 48%. To synthesize sulfonyl chloride **24**, we mixed bromide **28** with *n*-BuLi, followed by an addition of a solution of $SO_2$ and NCS. Compound **27** was also a subject for the reaction with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in the presence of *n*-BuLi to give ester **28** in 73% yield. The structure of compound **28** was confirmed by X-ray

analysis (Figure 2). We also changed bromine atom in pyrazole **27** by a carboxylic acid group with *n*-BuLi and dry ice to get **31** in 75% yield (Scheme 6).




**Scheme 6.** Synthetic utility of pyrazole **1a**.

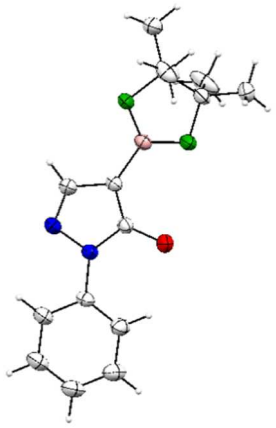
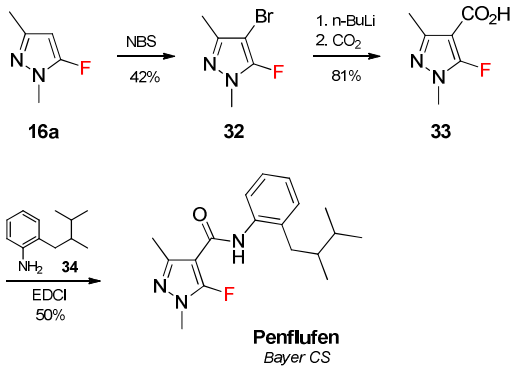


**Figure 2.** X-ray crystal structure of pyrazole **28**.[31]

***Synthesis of Penflufen.*** Finally, we developed an alternative synthesis of the commercialized fungicide *Penflufen* (Figure 1, Scheme 7). Bromination of pyrazole **16a** with NBS in acetonitrile afforded bromide **32** in 42% yield. Treatment of **32** with BuLi, followed by an addition of dry ice gave acid **33** in 81% yield. The last step of the synthesis was an amide coupling between acid **33** and aniline **34** in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI). *Penflufen* was obtained in 50% yield.




**Scheme 7.** Synthesis of fungicide *Penflufen*.

## CONCLUSIONS

We elaborated a one-step synthesis of 5-fluoropyrazoles by direct lithiation/fluorination of pyrazoles with NFSI. The procedure was scalable, and 20 g of pyrazole **1a** was synthesized in one run. The obtained products were transformed into the representative acids, amines, sulfonyl chlorides and boronates. Also, novel synthetic approaches towards 5-fluoropyrazole **20**, and the known fungicide *Penflufen* were developed. Given the high efficiency, simplicity, and low costs of our method, we believe that 3/5-fluoropyrazoles will find soon a wide application in agrochemistry and medicinal chemistry as valuable building blocks, while pyrazole **20** - in coordination chemistry as a ligand for transition metals.

## EXPERIMENTAL SECTION

### General methods

All starting materials were taken at Enamine Ltd. Autoclaves were provided by UOSLab (en.uoslab.com). Column chromatography was performed using Kieselgel Merck 60 (230-400 mesh) as the stationary phase. Reverse phase column chromatography was performed using $C_{18}$-modified silica gel as a stationary phase, column: SunFire Waters, 5 µm, 19 mm × 100 mm. $^{1}$H-, $^{19}$F-, $^{13}$C-NMR spectra were recorded on at 500 or 400 MHz, 376 MHz and 125 or 101 MHz respectively. Chemical shifts are reported in ppm downfield from TMS ($^{1}$H, $^{13}$C) or $CFCl_3$ ($^{19}$F) as internal standards. Mass spectra were recorded on an LC-MS instrument with chemical ionization (CI). LC-MS data were acquired on Agilent 1200 HPLC system equipped with DAD/ELSD/LCMS-6120 diodematrix and mass-selective detector, column: Poroshell 120 SBC18, 4.6 mm × 30 mm. Eluent, A, acetonitrile–water with 0.1% of FA (99: 1); B, water with 0.1% of FA.

**General procedure for fluorination with NFSI in the presence of *n*-BuLi or LDA.** A 3-neck round-bottom flask was equipped with a dropping funnel, thermometer, air-bubbles counter, and filled with argon. Then, the appropriate pyrazole (1 equiv), dry THF were loaded to the flask, and the mixture was cooled to -65 °C. To the stirred solution *n*-BuLi or LDA (1.05 equiv) was added dropwise. When addition was finished the mixture was stirred for 45 min at the same temperature. Then, it was cooled to -75 °C, and a solution of NFSI (1.2 equiv) in THF was added dropwise. The mixture was stirred for 2 h at the same temperature. The cooling bath was removed, and the mixture was stirred at rt for 12 h, diluted with a saturated solution of ammonium chloride, and concentrated under reduced pressure. The residue was dissolved in MTBE, washed with a sodium bicarbonate solution (3 times). The organic layer was separated, dried over sodium sulfate and concentrated under reduced pressure.

**General procedure for halogenation with *N*-bromosuccinimide**. A solution of the appropriate compound (1 equiv) in acetonitrile was combined with NBS (1.05 equiv), and the resulting mixture was stirred for 14 h at rt. Then, it was concentrated, and the residue

was dissolved in MTBE. The organic solution was washed with sodium bicarbonate, dried over sodium sulfate and concentrated to get a pure product.

**5-Fluoro-1-phenyl-1*H*-pyrazole (1a)**: *n*-BuLi was used as the base, the compound was purified by column chromatography (gradient, MTBE, 0-35%). Yield 3.3 g (65%), colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.7 Hz, 2H), 7.50 (s, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 5.91 – 5.70 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.4 (d, *J* = 242.2 Hz), 139.6 (d, *J* = 11.0 Hz), 137.3, 129.3, 127.3, 121.4 (d, *J* = 4.1 Hz), 88.2 (d, *J* = 15.4 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$) δ -133.3. Anal. Calcd for $C_9H_7FN_2$: C, 66.66; H, 4.35; N, 17.27. Found: C, 66.52; H, 4.49; N, 17.39.

**5-Fluoro-1-(*o*-tolyl)-1*H*-pyrazole (2a)**: *n*-BuLi was used as the base. Yield 3.1 g (61%), yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 2.1 Hz, 1H), 7.46 – 7.05 (m, 4H), 5.86 (dd, *J* = 5.7, 1.8 Hz, 1H), 2.20 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 153.9 (d, *J* = 276.5 Hz), 139.7 (d, *J* = 10.6 Hz), 135.4 (d, *J* = 7.6 Hz), 131.1, 129.5, 127.3, 126.6, 86.5 (d, *J* = 15.0 Hz), 17.4. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -134.7. Anal. Calcd for $C_{10}H_9FN_2$: C, 68.17; H, 5.15; N, 15.90. Found: C, 68.05; H, 5.40; N, 15.68.

**5-Fluoro-1-(*p*-tolyl)-1*H*-pyrazole (3a)**: *n*-BuLi was used as the base. Yield 4.5 g (60%), yellow oil. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.64 – 7.61 (m, 1H), 7.50 (d, *J* = 7.0 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 6.20 (dd, *J* = 5.3, 1.8 Hz, 1H), 2.35 (s, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 152.6 (d, *J* = 277.8 Hz), 139.6 (d, *J* = 11.3 Hz), 137.1, 134.2, 129.9, 121.5 (d, *J* = 3.6 Hz), 88.3 (d, *J* = 15.3 Hz), 20.5. $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ -134.4. MS (APCI) *m/z* $[M+H]^+$ calculated for $C_{10}H_{10}FN_2$: 177.1; found: 177 (M+H). Anal. calcd. for $C_{10}H_9FN_2$: C, 68.17; H, 5.15; N, 15.90. Found: C, 68.02; H, 5.30; F, N, 15.78.

**1-(4-Ethylphenyl)-5-fluoro-1*H*-pyrazole (4a)**: *n*-BuLi was used as the base. Yield 2.8 g (64%), yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.48 (m, 3H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.89 (dd, *J* = 5.4, 1.7 Hz, 1H), 2.71 (q, *J* = 7.5 Hz, 2H), 1.26 (t, *J* = 7.6 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 142.3 (d, *J* = 283.0 Hz), 139.6, 139.5, 128.6, 121.7 (d, *J* = 3.8 Hz), 119.4, 107.4, 88.1 (d, *J* = 15.4 Hz), 28.5, 15.6. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -133.7. MS (APCI) *m/z* $[M+H]^+$ calculated for $C_{11}H_{12}FN_2$: 191.1; found: 191 (M+H). Anal. calcd. for $C_{11}H_{11}FN_2$: C, 69.46; H, 5.83; N, 14.73. Found: C, 69.63; H, 5.98; N, 14.59.

**5-Fluoro-1-(4-fluorophenyl)-1*H*-pyrazole (5a)**: *n*-BuLi was used as the base, compound was purified by column chromatography (gradient, MTBE, 0-35%). Yield 2.3 g (63%), yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.60 (ddd, *J* = 8.8, 4.6, 1.6 Hz, 2H), 7.51 (dd, *J* = 3.0, 2.0 Hz, 1H), 7.15 (dd, *J* = 9.0, 8.2 Hz, 2H), 5.90 (dd, *J* = 5.4, 2.0 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.6 (d, *J* = 247.3 Hz), 153.4 (d, *J* = 280.0 Hz), 139.8 (d, *J* = 11.0 Hz), 133.5, 123.5 (dd, *J* = 8.5, 4.0 Hz), 116.3 (d, *J* = 23.0 Hz), 88.3 (d, *J* = 15.3 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$) δ -114.6, -133.7. Anal. Calcd for $C_9H_6F_2N_2$: C, 60.00; H, 3.36; N, 15.55. Found: C, 60.25; H, 3.62; N, 15.28.

**1-(4-Bromophenyl)-5-fluoro-1*H*-pyrazole (6a)**: LDA was used as the base, compound was purified by column chromatography (gradient, MTBE, 0-35%). Yield 1.8 g (65%), orange oil. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.73 (d, *J* = 8.6 Hz, 2H), 7.68 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 6.25 (d, *J* = 3.8 Hz, 1H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 152.8 (d, *J* = 279.5 Hz), 140.4 (d, *J* = 11.2 Hz), 135.9, 132.5, 123.1 (d, *J* = 4.3 Hz), 120.1, 88.9 (d, *J* = 15.1 Hz). $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ -133.2. MS (APCI) *m/z* $[M+H]^+$ calculated for $C_9H_7BrFN_2$: 242.1; found: 242 (M+H). Anal. calcd. for $C_9H_6BrFN_2$: C, 44.84; H, 2.51; N, 11.62. Found: C, 44.69; H, 2.71; N, 11.48.

**1-([1,1'-Biphenyl]-4-yl)-5-fluoro-1*H*-pyrazole (8a)**: *n*-BuLi was used as the base, compound was purified by column chromatography (gradient, MTBE, 0-35%). Yield 1.1 g (63%), yellow solid, mp 59-60 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.77 – 7.62 (m, 5H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 1H), 6.26 (d, *J* = 3.6 Hz, 1H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 152.8 (d, *J* = 278.8 Hz), 140.1 (d, *J* = 11.3 Hz), 139.1, 138.9, 135.9, 129.0, 127.8, 127.7, 126.7, 121.7 (d, *J* = 3.9 Hz), 88.7 (d, *J* = 15.3 Hz). $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ -133.7. MS (APCI) *m/z* $[M+H]^+$ calculated for $C_{15}H_{12}FN_2$: 239.1; found: 239 (M+H). Anal. calcd. for $C_{15}H_{11}FN_2$: C, 75.62; H, 4.65; N, 11.76. Found: C, 75.88; H, 4.90; N, 11.51.

**5-Fluoro-1,4-diphenyl-1H-pyrazole (9a)**: *n*-BuLi was used as the base, compound was purified by column chromatography (gradient, MTBE, 0-35%). Yield 1.2 g (61%), yellow solid, mp 57-58 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 3.0 Hz, 1H),

7.70 (d, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.8 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 149.8 (d, *J* = 283.9 Hz), 138.1 (d, *J* = 9.5 Hz), 137.3, 129.8 (d, *J* = 5.0 Hz), 129.5, 129.1, 127.6, 127.0, 125.9 (d, *J* = 3.4 Hz), 121.6 (d, *J* = 4.1 Hz), 103.9 (d, *J* = 9.6 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$) δ -133.7. MS (APCI) *m/z* $[M+H]^+$ calculated for $C_{15}H_{12}FN_2$: 239.1; found: 239 (M+H). Anal. calcd. for $C_{15}H_{11}FN_2$: C, 75.62; H, 4.65; N, 11.76. Found: C, 75.48; H, 4.76; N, 11.91.

**5-Fluoro-1-isopropyl-1*H*-pyrazole (10a)**: *n*-BuLi was used as the base, compound was purified by distillation (20 mmHg, 57-60 °C). Yield 2.1 g (51%), colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.25 (s, 1H), 5.59 (d, *J* = 1.5 Hz, 1H), 4.41 (m, 1H), 1.40 (d, *J* = 6.7 Hz, 6H), $^{13}$C NMR (101 MHz, $CDCl_3$) δ 152.9 (d, *J* = 273.9 Hz), 137.8 (d, *J* = 11.0 Hz), 86.1 (d, *J* = 15.2 Hz), 49.4, 21.7. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -138.0. Anal. Calcd for $C_6H_9FN_2$: C, 56.24; H, 7.08; N, 21.86. Found: C, 56.34; H, 6.98; N, 21.74.

**1-(Cyclopropylmethyl)-5-fluoro-1*H*-pyrazole (12a)**: *n*-BuLi was used as the base, compound was purified by column chromatography (gradient, MTBE, 0-30%). Yield 2.3 g (68%), colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 5.70 (d, *J* = 4.6 Hz, 1H), 3.87 (d, *J* = 7.0 Hz, 2H), 1.37 – 1.03 (m, 1H), 0.58 (q, *J* = 5.1 Hz, 2H), 0.36 (d, *J* = 4.9 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.5 (d, *J* = 274.3 Hz), 137.9 (d, *J* = 10.9 Hz), 85.9 (d, *J* = 15.1 Hz), 52.0, 10.8, 3.5. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -138.4. Anal. Calcd for $C_7H_9FN_2$: C, 59.99; H, 6.47; N, 19.99. Found: C, 59.82; H, 6.31; N, 20.16.

**5-fluoro-1-phenethyl-1*H*-pyrazole (13a)**: *n*-BuLi was used as the base, compound was purified by column chromatography (gradient, MTBE, 0-30%). Yield 1.4 g (62%), colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 1H), 7.33 – 7.16 (m, 3H), 7.11 (d, *J* = 6.9 Hz, 2H), 5.63 (dd, *J* = 5.6, 1.9 Hz, 1H), 4.21 (t, *J* = 7.4 Hz, 2H), 3.12 (t, *J* = 7.4 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.8 (d, *J* = 274.9 Hz), 138.6 (d, *J* = 10.8 Hz), 137.7, 128.7, 128.6, 126.8, 86.0 (d, *J* = 14.9 Hz), 48.6, 36.0. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -138.2. Anal. Calcd for $C_{11}H_{11}FN_2$: C, 69.46; H, 5.83; N, 14.73. Found: C, C, 69.71; H, 5.69; N, 14.60.

**5-Fluoro-*N*,*N*-dimethyl-1*H*-pyrazole-1-sulfonamide (14a)**: LDA was used as the base, after the general procedure compound was obtained as the mixture of the desired product and the starting pyrazole in the ratio of 7:3 in 4.3 g (73%) yield. It was used in the next step as the spectra data matched the reference (Kurihara, T.; Harusawa, S.; Matsuda, C.; Araki, L. *Synthesis*. **2006**, 793).

**5-Fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (15a)**: LDA was used as the base, compound was purified by column chromatography (gradient, hexane/MTBE, 0-70%). Yield 3.8 g (55%), colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 5.73 (dd, *J* = 5.5, 1.8 Hz, 1H), 5.33 (s, 2H), 3.71 – 3.40 (m, 2H), 0.96 – 0.77 (m, 2H), -0.03 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 154.3 (d, *J* = 277.4 Hz), 139.3 (d, *J* = 10.6 Hz), 86.8 (d, *J* = 14.4 Hz), 75.6, 66.9, 17.7, -1.5. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -137.5. Anal. Calcd for $C_9H_{17}FN_2OSi$: C, 49.97; H, 7.92; N, 12.95. Found: C, 49.81; H, 7.78; N, 13.06.

**3-Bromo-5-fluoro-1-methyl-1*H*-pyrazole (17a)**: LDA was used as the base, compound was purified by column chromatography (gradient, hexane/MTBE 0-35%). Yield 3.4 g (61%), yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 5.69 (d, *J* = 5.9 Hz, 1H), 3.60 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.2 (d, *J* = 280.7 Hz), 124.0 (d, *J* = 13.9 Hz), 89.4 (d, *J* = 15.3 Hz), 34.1. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -131.2. Anal. Calcd for $C_4H_4BrFN_2$: C, 26.84; H, 2.25; N, 15.65. Found: C, 26.72; H, 2.35; N, 15.81.

**5-Fluoro-3-iodo-1-methyl-1*H*-pyrazole (18a)**: LDA was used as the base, compound was purified by column chromatography (gradient, hexane/MTBE 0-50%). Yield 4.6 g (63%), colorless crystals, mp 29-30 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 5.86 (d, *J* = 6.0 Hz, 1H), 3.68 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.6 (d, *J* = 281.4 Hz), 95.1 (d, *J* = 14.3 Hz), 93.0 (d, *J* = 12.4 Hz), 34.4. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -132.9. Anal. Calcd for $C_4H_4IFN_2$: C, 21.26; H, 1.78; N, 12.40. Found: C, 21.01; H, 1.97; N, 12.21.

**1-(3-Bromo-2-fluorophenyl)-1*H*-pyrazole (7b)**: LDA was used as the base, compound was purified by column chromatography (gradient, hexane/MTBE 0-35%). Yield 1.1 g (60%), colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.86 (t, *J* = 7.5 Hz, 1H), 7.74 (s, 1H), 7.47 (t, *J* = 6.8 Hz, 1H), 7.12 (t, *J* = 8.0 Hz, 1H), 6.49 (s, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 149.1, 141.3, 131.2, 130.9, 130.8, 125.6 (d, *J* = 4.6 Hz), 123.6, 110.5 (d, *J* = 20.4 Hz), 108.0. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -133.7. MS (APCI) *m/z* $[M+H]^+$ calculated for $C_9H_7BrFN_2$: 242.1; found: 242 (M+H). Anal. calcd. for $C_9H_6BrFN_2$: C, 44.84; H, 2.51; N, 11.62. Found: C, 44.98; H, 2.68; N, 11.40.

**1-(*tert*-Butyl)-1*H*-pyrazole-5-carboxylic acid (19)**: *n*-BuLi was used as the base. Yield 0.9 g (75%), white solid, mp 140-141 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.41 (d, *J* = 1.9 Hz, 1H), 6.84 (d, *J* = 1.8 Hz, 1H), 1.64 (s, 9H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 161.8, 135.4, 133.5, 113.5, 61.7, 29.3. MS (APCI) *m/z* [M-H]$^-$ calculated for $C_8H_{11}N_2O_2$: 167.1; found: 167 (M-H). Anal. calcd. for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.01; H, 7.06; N, 16.85.

**5-Fluoropyrazole (20). Method A, SEM-protection.** To a solution of **15a** (1.2 g, 5.55 mmol, 1 equiv) in dry dichloromethane (5 mL) trifluoroacetic acid (8.5 mL, 111 mmol, 20 equiv) was added dropwise at -10 °C. The reaction mixture was stirred for 12 h at rt, and then concentrated under reduced pressure. The residue was dissolved in dry ethanol (20 mL) and sodium acetate (2.3 g, 27.7 mmol, 5 equiv) was added. The reaction mixture was stirred for 12 h at rt and then concentrated. The residue was purified by column chromatography (gradient, MTBE/acetonitrile, 0-30%) to get the desired compound in 100 mg (21%) yield. **Method B, DMSA-protection**. To a solution of **14a** (4.6 g, 23.8 mmol, 1 equiv) in dry dichloromethane (100 mL) trifluoroacetic acid (36.5 mL, 476 mmol, 20 equiv) was added dropwise at -10 °C. The reaction mixture was stirred for 12 h at rt, and then concentrated. The residue was dissolved in water (20 mL) and basified with ammonia to pH 9. The compound was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (gradient, MTBE/acetonitrile, 0-30%) to get the desired compound in 1.1 g (54%) yield as yellow liquid. $^1$H NMR (500 MHz, $CDCl_3$) δ 11.77 (s, 1H), 7.42 (t, *J* = 2.1 Hz, 1H), 5.84 (dd, *J* = 5.8, 2.4 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 164.5 (d, *J* = 243.0 Hz), 130.6, 89.1 (d, *J* = 24.1 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$) δ -134.0. Anal. Calcd for $C_3H_3FN_2$: C, 41.87; H, 3.51; N, 32.55. Found: C, 41.70; H, 3.39; N, 32.74.

**5-Fluoro-1-methyl-1*H*-pyrazole-3-carboxylic acid (21).** To a solution of **17a** (1 equiv) in THF, $Et_3N$ (5 equiv) and cat. Pd(dppf)$Cl_2$×$CH_2Cl_2$ (0.1 equiv) were added in a steel autoclave. The resulted mixture was stirred with CO at 10-15 atm pressure at rt for 18 h. The mixture was filtered through $SiO_2$, treated with 10% aq. NaOH (2 equiv) and left stirred at rt overnight. The solution was partially concentrated under reduced pressure and diluted with MTBE. The organic layer was separate, and the aqueous layer was acidified with $H_3PO_4$ to pH 2. The desired acid was extracted with $CH_2Cl_2$, dried over $Na_2SO_4$, and concentrated under reduced pressure to give **21** as a white solid, mp 153-154 °C, 5.6 g, (76% yield). $^1$H NMR (500 MHz, DMSO-$d_6$) δ 12.90 (br s, 1H), 6.38 (d, *J* = 5.8 Hz, 1H), 3.77 (s, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 162.6 (d, *J* = 2.2 Hz), 153.0 (d, *J* = 276.8 Hz), 141.2 (d, *J* = 10.2 Hz), 88.8 (d, *J* = 14.0 Hz), 34.7. $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ -133.6. MS (APCI) *m/z* [M-H]$^-$ calculated for $C_5H_4FN_2O_2$: 143.1; found: 143 (M-H). Anal. calcd. for $C_5H_5FN_2O_2$: C, 41.67; H, 3.50; N, 19.44. Found: C, 41.79; H, 3.63; N, 19.26.

**3-Bromo-4-chloro-5-fluoro-1-methyl-1*H*-pyrazole (22)**. A solution of **17a** (1.05 g, 5.87 mmol, 1 equiv) in acetonitrile (50mL) was combined with NCS (0.82 g, 6.16 mmol, 1.05 equiv), and the resulting mixture was stirred for 14 h at rt. The mixture was concentrated, and the residue was dissolved in $CH_2Cl_2$. The organic solution was washed with sodium bicarbonate (3 × 30 mL), dried over sodium sulfate and concentrated to get a pure product as brown oil. Yield 1.15 g (93%). $^1$H NMR (500 MHz, $CDCl_3$) δ 3.74 (d, *J* = 1.2 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 149.2 (d, *J* = 281.1 Hz), 124.5 (d, *J* = 8.7 Hz), 92.3 (d, *J* = 15.1 Hz), 35.5. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -131.3. MS (APEI) *m/z* [M] calculated for $C_4H_3BrClFN_2$: 213. Found: 213 (M). Anal. calcd. for $C_4H_3BrClFN_2$: C, 22.51; H, 1.42, N, 13.13. Found: C, 22.30; H, 1.26, N, 13.36.

**5-Fluoro-4-iodo-1-phenyl-1*H*-pyrazole (23)**. A solution of **1a** (2 g, 12.33 mmol, 1 equiv) in acetonitrile (75 mL) was combined with NIS (5.85 g, 25.9 mmol, 2.1 equiv), and the resulting mixture was stirred for 48 h at 60 °C. Then it was concentrated, and residue was dissolved in dichloromethane. The organic solution was washed with sodium thiosulfate (3 times), sodium bicarbonate (3 times), dried over sodium sulfate and concentrated. The residue was purified by column chromatography (gradient, hexane/MTBE, 0-35%) to get a pure product. Yield 2.2 g (63%), beige crystals, mp 166-167 °C, $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.61 (d, *J* = 7.6 Hz, 2H), 7.55 (d, *J* = 2.1 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ

153.8 (d, *J* = 278.1 Hz), 143.6 (d, *J* = 7.9 Hz), 137.0, 129.5, 128.0, 121.4 (d, *J* = 3.9 Hz), 38.8 (d, *J* = 21.7 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$) δ -130.0. Anal. Calcd for $C_9H_6FIN_2$: C, 37.53; H, 2.10; N, 9.72. Found: C, 37.30; H, 2.28; N, 9.61.

**5-Fluoro-1-phenyl-1*H*-pyrazole-4-sulfonyl chloride (24)**. To a solution of **27** (4.7 g, 19.5 mmol, 1 equiv) in 200 mL of $Et_2O$ was added *n*-BuLi (8.2 mL, 20.47 mmol, 1.05 equiv) dropwise at -78 °C under argon. The mixture was stirred for 30 min, then was added a fresh prepared solution of $SO_2$ in $Et_2O$ at the same temperature, and left to warm-up to rt overnight. The resulted precipitate was filtered, washed with ether and dried under reduced pressure to give a solid residue (4 g, 17.23 mmol, 1 equiv) which was treated with NCS in dry acetonitrile. The mixture was stirred for 16 h, then it was concentrated under reduced pressure. The resulted residue was dissolved in 100 mL of $CH_2Cl_2$ and washed with water (3 × 30 mL). The organic layer was dried over $Na_2SO_4$, filtered and concentrated. The desired compound was obtained as a yellow solid, mp 63-64 °C, 3.3 g (64%). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 1.6 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.2 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 149.6 (d, *J* = 297.6 Hz), 138.3 (d, *J* = 5.3 Hz), 135.3, 130.0, 129.7, 122.4 (d, *J* = 3.5 Hz), 110.3 (d, *J* = 11.5 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$) δ -119.0. MS (APEI) *m/z* [M] calculated for $C_9H_6ClFN_2O_2S$: 260. found: 260 (M). Anal. calcd. for $C_9H_6ClFN_2O_2S$: C, 41.47; H, 2.32; Cl, 13.60; N, 10.75; S, 12.30. Found: C, 41.59; H, 2.52; Cl, 13.72; N, 10.60; S, 12.11.

**1-(5-Fluoro-1-phenyl-1*H*-pyrazol-4-yl)ethanol (25).** A 3-neck round-bottom flask was equipped with a dropping funnel, thermometer, air-bubbles counter, and filled with argon. Then a starting bromide (9.66 mmol, 1 equiv) with dry THF (100 mL) was loaded to the flask, and cooled to -75 °C. To the stirred solution *n*-BuLi (2.5 M in hexane, 4.1 mL, 10.1 mmol, 1.05 equiv) was added dropwise. After 45 min at the same temperature acetaldehyde (2.2 mL, 38.6 mmol, 4 equiv) was added dropwise. Then the cooling bath was removed, and mixture was stirred at rt for 12 h, diluted with a saturated solution of ammonium chloride, and concentrated under reduced pressure. The residue was dissolved in water, and washed with MTBE (3 × 50 mL). The organic solution was washed with water (3 × 30 mL), dried over sodium sulfate, and concentrated. The residue was purified by column chromatography (gradient, hexane/MTBE, 0-100%) to get a pure product. Yield 1.1 g (64%), yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.57 (m, 2H), 7.55 (d, *J* = 3.1 Hz, 1H), 7.45 (t, *J* = 7.9 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 4.91 (d, *J* = 6.4 Hz, 1H), 2.25 (s, 1H), 1.55 (d, *J* = 6.5 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 149.8 (d, $J_{C\text{-}F}$ = 281.8 Hz), 138.1 (d, *J* = 9.9 Hz), 137.2 (d, *J* = 2.8 Hz), 129.4, 127.5, 121.5 (d, *J* = 4.0 Hz), 107.0 (d, *J* = 11.6 Hz), 60.9 (d, *J* = 3.4 Hz), 23.6. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -134.1. Anal. Calcd for $C_{11}H_{11}FN_2O$: C, 64.07; H, 5.38; N, 13.58. Found: C, 64.21; H, 5.53; N, 13.31.

**1-(5-Fluoro-1-phenyl-1*H*-pyrazol-4-yl)ethanone (26)**. To a solution of the corresponding alcohol (5.82 mmol, 1 equiv) in dry dichloromethane (75 mL) was added pyridinium chlorochromate (2 g, 8.73 mmol, 1.5 equiv). The resulting mixture was stirred for 16 h at rt, and then putted onto silica gel. The silica gel was washed with MTBE, and combined organic layers were concentrated. The residue was purified by column chromatography (gradient, hexane/ MTBE, 0-100%) to get a pure product. Yield 0.9 g, (75%), yellow crystals, mp 62-63 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 2.6 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 1H), 2.46 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 189.8 (d, *J* = 4.8 Hz), 152.6 (d, *J* = 292.6 Hz), 140.5 (d, *J* = 8.2 Hz), 136.2, 129.6, 128.6, 122.1 (d, *J* = 3.9 Hz), 106.3 (d, *J* = 9.4 Hz), 28.7. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -123.9. Anal. Calcd for $C_{11}H_9FN_2O$: C, 64.70; H, 4.44; N, 13.72. Found: C, 64.60; H, 4.25; N, 13.89.

**4-Bromo-5-fluoro-1-phenyl-1H-pyrazole (27)**. Yield 9.7 g (93%), brown oil, $^1$H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.54 (m, 2H), 7.50 (t, *J* = 7.0 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.4 (d, *J* = 279.4 Hz), 139.8 (d, *J* = 6.9 Hz), 136.9 (d, *J* = 2.7 Hz), 129.4, 127.8, 121.2 (d, *J* = 3.9 Hz), 75.5 (d, *J* = 18.3 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$) δ -132.9 (d, *J* = 1.8 Hz). Anal. Calcd for $C_9H_6BrFN_2$: C, 44.84; H, 2.51; N, 11.62. Found: C, 44.71; H, 2.62; N, 11.50.

**5-Fluoro-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (28)**. A 3-neck round-bottom flask was equipped with a dropping funnel, thermometer, air-bubbles counter, and filled with argon. Then a starting bromide (9.66 mmol, 1 equiv) in dry THF (50 mL) was loaded to the flask, and cooled to -75 °C. To the stirred solution *n*-BuLi (2.5M in hexane, 4.1 mL, 10.1 mmol, 1.05 equiv) was added dropwise. After 45 min at the same temperature 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-

dioxaborolane (2 g, 11.6 mmol, 2.0 equiv) was added dropwise under stirring, and when addition was finished the mixture was stirred for 20 min more at the same temperature. The cooling bath was removed, and mixture was stirred at rt for 12 h, diluted with a saturated solution of ammonium chloride, and concentrated. The residue was dissolved in MTBE (100 mL), and washed with water (3 × 50 mL), dried over sodium sulfate, and concentrated. The residue was re-crystallized from hexane to get the pure product. Yield 2.1 g (73%), white crystals, mp 76-77 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, $J$ = 2.1 Hz, 1H), 7.60 (d, $J$ = 7.4 Hz, 2H), 7.40 (t, $J$ = 7.5 Hz, 2H), 7.27 (t, $J$ = 7.1 Hz, 1H), 1.28 (s, 12H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 157.9 (d, $J$ = 287.4 Hz), 145.2 (d, $J$ = 12.1 Hz), 136.9, 129.3, 127.5, 121.6 (d, $J$ = 4.2 Hz), 83.6, 24.8. $^{19}$F NMR (376 MHz, CDCl3) δ -124.6. Anal. Calcd for $C_{15}H_{18}BrFN_2O_2$: C, 62.53; H, 6.30; N, 9.72. Found: C, 62.71; H, 6.19; N, 9.56.

**5-Fluoro-4-nitro-1-phenyl-1*H*-pyrazole (29)**. A 3-neck round-bottom flask was equipped with a dropping funnel, thermometer, and air-bubbles counter. Then it was loaded with acetic anhydride (15 mL), cooled to -15 °C, and fuming nitric acid (5.4 mL, 129.5 mmol, 2.1 equiv) was added dropwise. The resulting mixture was stirred for 20 min under cooling, and a solution of **1a** (9.9 g, 61.7 mmol, 1 equiv) in acetic anhydride (10 mL) was added dropwise. The mixture was stirred for 4 h at -10 °C, 12 h at rt, and poured onto the ice. The formed precipitate was collected by filtration and purified by column chromatography (silica gel, hexane, MTBE, gradient, 0-50%). Yield 8.7 g (68%), yellow powder, mp 108-109 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, $J$ = 1.6 Hz, 1H), 7.69 – 7.60 (m, 2H), 7.56 (t, $J$ = 7.6 Hz, 2H), 7.49 (t, $J$ = 7.3 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 147.5 (d, $J$ = 298.7 Hz), 136.0 (d, $J$ = 3.6 Hz), 135.6, 129.9, 129.6, 124.0, 122.3 (d, $J$ = 3.6 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$) δ -121.4. Anal. Calcd for $C_9H_6FN_3O_2$: C, 52.18; H, 2.92; N, 20.28. Found: C, 52.35; H, 2.78; N, 20.15.

**5-Fluoro-1-phenyl-1*H*-pyrazol-4-amine hydrochloride (30)**. To a solution of **29** (2 g, 9.65 mmol, 1 equiv) in THF (50 mL) was added hydrochloric acid (1.2 mL, 9.65 mmol, 1 equiv), and Pd/C (5%, 1 g, 0.05 equiv). The resulting mixture was hydrogenated at 50 atm and monitored by TLC. The mixture was filtered, and filtrate was concentrated to get the desired compound in 1.9 g yield (8.89 mmol, 92%), white crystals, mp 173-174 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.63 (s, 3H), 7.85 (s, 1H), 7.63 (d, $J$ = 7.9 Hz, 2H), 7.57 (t, $J$ = 7.7 Hz, 2H), 7.46 (t, $J$ = 7.3 Hz, 1H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 146.0 (d, $J$ = 281.9 Hz), 136.1, 135.1 (d, $J$ = 7.1 Hz), 129.7, 128.3, 121.6 (d, $J$ = 3.3 Hz), 96.7 (d, $J$ = 12.0 Hz). $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ -134.7. Anal. Calcd for $C_9H_9ClFN_3$: C, 50.60; H, 4.25; N, 19.67. Found: C, 50.49; H, 4.41; N, 19.45.

**5-Fluoro-1-phenyl-1*H*-pyrazole-4-carboxylic acid (31)**. A 3-neck round-bottom flask was equipped with a dropping funnel, thermometer, air-bubbles counter, and filled with argon. Compound **27** (13 g, 54.1 mmol, 1 equiv) with dry THF (150 mL) was loaded to the flask, and cooled to -75 °C. To the stirred solution *n*-BuLi (2.5 M in hexane, 23 mL, 56.8 mmol, 1.05 equiv) was added dropwise. The mixture was stirred for 45 min at the same temperature, and crashed dry ice was added. The cooling bath was removed, and mixture was stirred at rt for 12 h, then diluted with a saturated solution of ammonium chloride, and concentrated. The residue was dissolved in water, and washed with MTBE (3 × 50 mL). The separated water layer was acidified with citric acid to pH 4, and the formed precipitate was collected by filtration. Yield 8.7 g (75%), yellow powder, mp 166-167 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 12.96 (s, 1H), 8.02 (d, $J$ = 2.2 Hz, 1H), 7.67 (d, $J$ = 7.9 Hz, 2H), 7.57 (t, $J$ = 7.8 Hz, 2H), 7.48 (d, $J$ = 7.4 Hz, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 162.1 (d, $J$ = 5.0 Hz), 152.7 (d, $J$ = 291.1 Hz), 141.6 (d, $J$ = 7.1 Hz), 136.3, 130.1, 129.0, 122.8 (d, $J$ = 3.3 Hz), 98.2 (d, $J$ = 8.4 Hz). $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ -124.3. Anal. Calcd for $C_{10}H_7FN_2O_2$: C, 58.26; H, 3.42; N, 13.59. Found: C, 58.01; H, 3.54 N, 13.83.

**4-Bromo-5-fluoro-1,3-dimethyl-1*H*-pyrazole (32)**. A 3-neck round-bottom flask was equipped with a dropping funnel, thermometer, air-bubbles counter, and filled with argon. Compound **16** (10 g, 104 mmol, 1 equiv) with dry THF (200 mL) was loaded to the flask, and cooled to -75 °C. To the stirred solution *n*-BuLi (2.5 M in hexane, 44 mL, 109.2 mmol, 1.05 equiv) was added dropwise. The mixture was stirred for 30 min at the same temperature, and a solution of NFSI (39.4 g, 124.8 mmol, 1.2 equiv) in dry THF (50 mL) was added. The mixture was stirred at -75 °C for 2 h, and then left overnight at rt. The mixture was diluted with dry $CH_3CN$ (200 mL) and NBS (20.4 g, 114.4 mmol, 1.1 equiv) was added at rt. The solution was stirred for 12 h at rt.

Solvents were removed under reduced pressure. The residue was dissolved in $CH_2Cl_2$ and washed with sodium bicarbonate (3 × 75 mL), dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (gradient, hexane/$CH_2Cl_2$, 0-50%) to give the desired product as yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 3H), 2.10 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 151.0 (d, *J* = 274.6 Hz), 146.0 (d, *J* = 6.2 Hz), 73.3 (d, *J* = 16.8 Hz), 33.5, 13.0. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -134.6. Anal. Calcd for $C_5H_6BrFN_2$: C, 31.11; H, 3.13; N, 14.51. Found: C, C, 31.21; H, 3.30; N, 14.26.

**5-Fluoro-1,3-dimethyl-1*H*-pyrazole-4-carboxylic acid (33)**. The reaction mixture after hydrolysis was acidified with phosphoric acid to pH 2. Yield 6.9 g (81%), white solid, mp 211-212 °C. The spectra data matched the literature data (Ohtsuka, Y.; Uraguchi, D.; Yamamoto, K.; Tokuhisa, K.; Yamakawa, T. *Tetrahedron*. **2012**, *68*, 2636).

**2-(4-Methylpentan-2-yl)aniline (34)**. Step 1: A flask was charged with 1-(2-aminophenyl)ethan-1-one (26 g, 192.3 mmol, 1 equiv) in THF (750 mL), and to the resulting mixture isobutyl magnesium bromide (355 mL, 2 M in diethyl ether, 3.7 equiv) was added dropwise at -30 °C. When addition was finished, the mixture was stirred for 1 h at the same temperature. Then the cooling bath was removed, and the mixture was stirred at rt for 12 h, diluted with a saturated solution of ammonium chloride and filtered. The filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (250 mL). The solution was washed with water (3 × 50 mL), dried over sodium sulfate, and concentrated to get 2-(1-hydroxy-1,3-dimethylbutyl)aniline in 30.1 g. 81%, yield. Step 2: The above compound (10 g, 51.74 mmol, 1 equiv) was dissolved in toluene (250 mL), and pTSA (0.45 g, 0.05 equiv) was added. The resulting solution was refluxed with Dean-Stark trap till water evaluation finished, then it was cooled and washed with a sodium bicarbonate solution (50 mL), dried over sodium sulfate, and concentrated to get a mixture of 2-(2-Aminophenyl)-4-methylpent-2-en and 2-(4-methylpent-1-en-2-yl)aniline (4:1) in 8.9 g (98%) yield. Step 3: To a solution of above mixture (7 g, 40 mmol) in methanol (100 mL) Pd/C (5%, 4.25 g, 2 mmol) was added, and the mixture was hydrogenated for 24 h. The reaction was controlled by TLC. The mixture was filtered, and the filtrate was concentrated to give the desired product in 6.9 g (97%) yield, brown liquid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 6.86 (t, *J* = 7.4 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 3.67 (s, 2H), 2.90 (dd, *J* = 13.8, 6.9 Hz, 1H), 1.73 – 1.57 (m, 2H), 1.48 (dt, *J* = 13.5, 6.7 Hz, 1H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.00 (dd, *J* = 12.1, 6.2 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 143.5, 132.0, 126.4, 126.2, 119.1, 116.1, 46.3, 30.4, 25.7, 23.1, 22.6, 20.8. Anal. Calcd for $C_{12}H_{19}N$: C, 81.30; H, 10.80; N, 7.90. Found: C, 81.52; H, 10.69; N, 7.77.

**5-Fluoro-1,3-dimethyl-*N*-(2-(4-methylpentan-2-yl)phenyl)-1*H*-pyrazole-4-carboxamide**, **Penflufen™**. To a solution of **33** (300 mg, 1.9 mmol, 1 equiv) in dry DMF (20 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (380 mg, 2.0 mmol, 1.05 equiv) and hydroxybenzotriazole (280 mg, 2.1 mmol, 1.1 equiv). The resulting mixture was stirred for 30 min at rt, and **34** (336 mg, 1.9 mmol, 1 equiv) was added. The resulting mixture was stirred for 1 d at rt, and then diluted with water (200 mL). The formed precipitate was collected by filtration and purified by column chromatography (gradient, hexane with MTBE, 20-100%) to get the desired compound in 300 mg (50%) yield, beige crystals, mp 109-110 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.3 Hz, 1H), 7.28 (s, 1H), 7.19 (d, *J* = 3.8 Hz, 1H), 7.12 (s, 2H), 3.67 (s, 3H), 2.91 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.41 (s, 3H), 1.46 (s, 2H), 1.35 (s, 1H), 1.15 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.0 Hz, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 159.6, 151.4 (d, *J* = 291.1 Hz), 144.8, 139.7, 134.1, 126.4 (d, *J* = 14.3 Hz), 126.1, 125.0, 96.1 (d, *J* = 9.7 Hz), 46.8, 34.1, 31.0, 25.7, 22.9, 22.6, 21.7, 14.9. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -128.3. Anal. Calcd for $C_{18}H_{24}FN_3O$: C, 68.11; H, 7.62; N, 13.24. Found: C, 68.00; H, 7.48; N, 13.10.

**Supporting Information**

Experimental copies of NMR spectra and X-ray crystallography data. This material is available free of charge via the Internet at http://pubs.acs.org.

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**Notes**

The authors declare no competing financial interest.

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