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HAL Id: hal-02944815

<https://hal.science/hal-02944815v1>

Submitted on 21 Sep 2020

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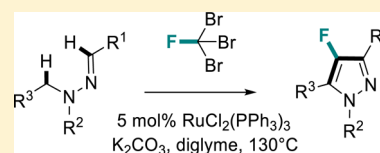
Ruthenium-Catalyzed Tandem C–H Fluoromethylation/Cyclization of *N*-Alkylhydrazones with CBr₃F: Access to 4-Fluoropyrazoles

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Supporting Information

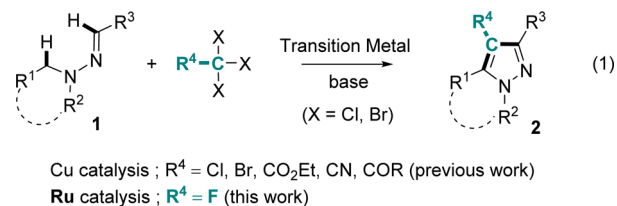
ABSTRACT: 4-Fluoropyrazoles are accessible in a single step from readily available aldehyde-derived *N*-alkylhydrazones through double C–H fluoroalkylation with tribromofluoromethane (CBr₃F). RuCl₂(PPh₃)₃ has been proven to be the most efficient catalyst for this transformation when compared to a range of other Cu-, Pd-, or Fe-based catalyst systems.



The importance of fluorine-containing pyrazoles to the pharmaceutical and agrochemical industries has been increasing steadily in recent years. As a consequence, the development of methods suitable for incorporation of fluorine or fluoroalkyl groups into the pyrazole ring continues to be the subject of intense research.¹ In this area, the number of efficient strategies available for 4-fluoropyrazoles remains fairly limited. The most convenient and reliable methods developed over the past several years toward these valuable compounds are essentially based on a fluorinated building-block approach where the fluorine atom is incorporated early in the synthetic process. These include cyclocondensations of fluorinated carbonyl derivatives, i.e. β -dicarbonyl and α,β -unsaturated compounds, with substituted hydrazines,² as well as cycloaddition reactions of fluoroalkenes or fluoroalkynes with diazocompounds.³ Among limitations that may be associated with these methods are low global yields over several synthetic steps, poor regioselectivities, and the use of dangerous reagents. Unfortunately, alternative approaches based on direct fluorination of the pyrazole ring suffer from rather low reaction efficiency and a narrow substrate scope. Halogen exchange⁴ or Balz–Schiemann⁵ processes are low yielding and require the synthesis of appropriately prefunctionalized pyrazole substrates. On the other hand, direct electrophilic C–H fluorinations are highly substrate dependent and selectivity issues can arise from the use of highly reactive fluorinating species (i.e., F₂, CF₃OF, Selectfluor, NFSI).⁶ Alongside the classical methods, gold-catalyzed tandem cyclization/fluorination reactions of *N*-monosubstituted alkynylhydrazones in the presence of Selectfluor have also been established as an interesting approach toward 4-fluoropyrazoles, although the corresponding nonfluorinated derivatives are also produced as byproducts.⁷

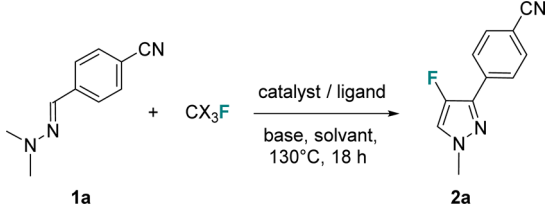
Recently, we developed a new synthetic method for the rapid assembly of pyrazole derivatives based on a copper-chloride-catalyzed double C–H functionalization of aldehyde-derived *N,N*-dialkylhydrazones with trihalomethane derivatives. The process is believed to follow C(sp²)–H haloalkylation/C(sp³)–H cyclization/aromatization cascade reaction sequences.^{8,9} An important feature of the process pertains to the flexible incorporation of functional groups arising from the organic

halides at position C-4 of the pyrazole ring, which include ester, ketone, cyano, and halide (Cl, Br). The method was then envisioned as an attractive opportunity to also access 4-fluoropyrazoles by using a trihalofluoromethane derivative as the alkylating species. The most important advantages of this new approach would be (1) the ready availability of starting materials; (2) the concomitant pyrazole formation and fluorine incorporation avoiding selectivity issues and the necessity for multistep synthesis of fluorinated substrates; (3) the avoidance of highly reactive and often rather expensive fluorinating reagents; and (4) an access to unusual pyrazolo-annulated compounds. Disappointingly, however, our previously established Cu-catalyzed process proved inefficient for this purpose, and this constrained us to re-examine the reaction conditions and possibly identify other metals as viable catalysts for promoting the desired transformation. Herein, we report the successful use of RuCl₂(PPh₃)₃ as an effective, alternative catalyst system in combination with CBr₃F as the fluoromethyl source (eq 1).

Cu catalysis ; R⁴ = Cl, Br, CO₂Et, CN, COR (previous work)Ru catalysis ; R⁴ = F (this work)

In our previous report,⁸ the following conditions [10 mol % CuCl(1,10-phen), Et₃N (4 equiv), 1,4-dioxane, 80 °C, 2 h] had been established as being optimal for the synthesis of 4-functionalized pyrazoles from a series of aromatic aldehyde-derived hydrazones, and various polyhalomethanes, with the notable exception of CCl₃F and CBr₃F. For instance, these conditions proved inefficient in converting 4-cyanobenzaldehyde *N,N*-dimethylhydrazone **1a**, our model substrate for the

Received: January 13, 2017

Table 1. Selected Optimization Experiments toward 4-Fluoropyrazole 2a^a


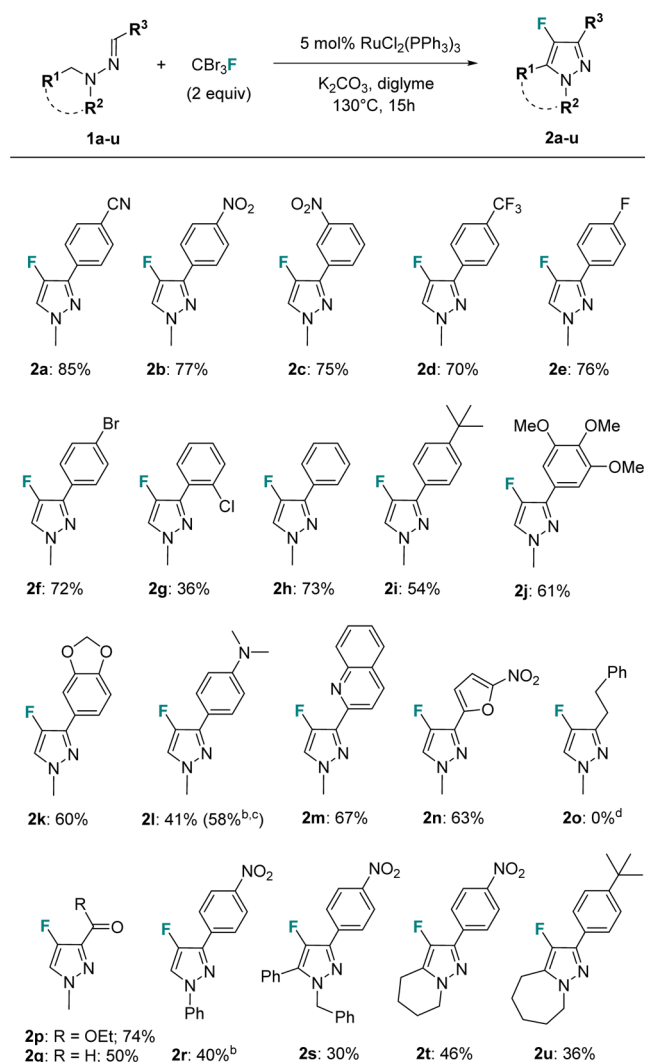
entry	CX ₃ F (equiv)	catalyst (mol %)	base (equiv)	solvent	T (°C)	time (h)	yield (%) ^b
1	CCl ₃ F (5)	CuCl(Phen) (10)	Et ₃ N (4)	dioxane	80	18	trace
2	CBr ₃ F (5)	CuCl(Phen) (10)	Et ₃ N (4)	dioxane	80	18	trace
3	CBr ₃ F (5)	CuCl(Phen) (10)	Et ₃ N (4)	dioxane	130	18	50
4	CBr ₃ F (5)	RuCl ₂ (PPh ₃) ₃ (5)	Et ₃ N (4)	dioxane	130	18	71
5	CBr ₃ F (5)	RuCl ₂ (PPh ₃) ₃ (5)	Et ₃ N (4)	diglyme	130	18	83
6	CBr ₃ F (5)	RuCl ₂ (PPh ₃) ₃ (5)	K ₂ CO ₃ (4)	dioxane	130	18	23
7	CBr ₃ F (5)	RuCl ₂ (PPh ₃) ₃ (5)	K ₂ CO ₃ (4)	diglyme	130	18	99
8	CBr ₃ F (5)	PdCl ₂ (PPh ₃) ₂ (5)	K ₂ CO ₃ (4)	diglyme	130	18	46
9	CBr ₃ F (5)	CuCl(PPh ₃) ₃ (5)	K ₂ CO ₃ (4)	diglyme	130	18	58
10	CBr ₃ F (5)	CuCl(Phen) (10)	K ₂ CO ₃ (4)	diglyme	130	18	89
11	CBr ₃ F (5)	FeCl ₂ (bpy) ₃ (10)	K ₂ CO ₃ (4)	diglyme	130	18	88
12	CBr ₃ F (2)	RuCl ₂ (PPh ₃) ₃ (1)	K ₂ CO ₃ (2)	diglyme	130	18	75
13	CBr ₃ F (2)	RuCl ₂ (PPh ₃) ₃ (5)	K ₂ CO ₃ (2)	diglyme	130	7	99
14	CBr ₃ F (2)	none	K ₂ CO ₃ (2)	diglyme	130	7	16
15	CBr ₃ F (2)	RuCl ₂ (PPh ₃) ₃ (5)	none	diglyme	130	7	trace

^aReaction conditions: **1a** (0.3 mmol), CX₃F, base, and catalyst system in 2 mL of solvent at 130 °C. Phen = 1,10-phenanthroline; bpy = 2,2'-bipyridine. ^bDetermined by ¹⁹F NMR spectroscopy using hexafluorobenzene as an internal standard.

present study, into the corresponding 4-fluoropyrazole (**2a**), even over a prolonged period of time (18 h) in the presence of 5.0 equiv of the fluoromethylating reagents (Table 1, entries 1–2). Although an increase in reaction temperature (up to 130 °C) using CBr₃F as the fluoromethyl radical source enhanced the reaction efficiency to some extent (Table 1, entry 3), this result was still not satisfying in terms of yield (50% as estimated by ¹⁹F NMR spectroscopy), and small amounts of several other unidentified side products were produced in the process. Other catalysts were thus investigated. Aside from copper salt derivatives, transition metal complexes derived from ruthenium, iron, palladium, or nickel are among the most commonly suggested catalysts for promoting radical reactions of polyhaloalkanes.¹⁰ Gratifyingly, the commercially available and inexpensive ruthenium(II) complex [RuCl₂(PPh₃)₃] has been found to be a very effective alternative catalyst for the desired transformation even at a lower loading level (5 mol %) (Table 1, entry 4).¹¹ Furthermore, the ethereal solvent diglyme having a higher boiling point than 1,4-dioxane proved to be the solvent of choice, particularly when associated with potassium carbonate as a base in place of triethylamine (Table 1, entries 4–6). Pleasingly, these modified reaction conditions allowed clean formation of the desired pyrazole **2a** in quantitative yield (Table 1, entry 7). Notably, the related palladium(II)- and copper(I)-derived catalysts (i.e., PdCl₂(PPh₃)₂; CuCl(PPh₃)₃) were found to be less effective (Table 1, entries 8–9). On the other hand, metal complexes of nitrogen-based bidentate ligands, e.g. CuCl(Phen) and FeCl₂(bpy)₃, gave satisfactory results under the new reaction conditions, but at higher catalyst loadings (Table 1, entries 10–11). Finally, it was found that the amount of both base and CBr₃F could be decreased to 2 equiv without any noticeable effect on yield, while lowering the amount of RuCl₂(PPh₃)₃ to 1 mol % still afforded the pyrazole in a good 75% yield (Table 1, entry 12). However, 5 mol % of the catalyst ensures complete reaction within 7 h (Table 1,

entry 13), and this loading level was thus used in the following experiments. It is of note that the same reaction performed in the absence of catalyst did only proceed to a very limited extent (Table 1, entry 14). The base was also found to be critical to the success of the reaction (Table 1, entry 15).

Next, we investigated the generality of the reaction by using a series of diversely substituted *N*-alkylhydrazones (Scheme 1). Variation of para- and meta-substituents on the aryl moiety of benzaldehyde *N,N*-dimethylhydrazone derivatives was well tolerated (see **2a–l**), with the best yields being generally achieved with electron-withdrawing substituents.¹² For instance, while the *p*-cyano-substituted benzaldehyde derivative furnished the highest isolated yield (**2a**, 85%), the analogous substrate bearing a strongly electron-donating *p*-dimethylamino group participated less efficiently in the reaction affording the desired pyrazole (**2l**) in only 41% yield. However, the yield of **2l** could be increased to 58% by simply raising the reaction temperature to 150 °C and using sodium carbonate as a base, which was found to be superior to potassium carbonate in this case. As illustrated by **2g**, even sterically hindered ortho-substituted aryls were tolerated to some extent. Importantly, heterocyclic hydrazones (e.g., 2-quinoliny (see **2m**), and 2-furyl (see **2n**)) proved suitable substrates for the transformation (**2m–n**). We then attempted to expand the substrate scope to nonaromatic aldehyde hydrazones. Disappointingly, as already observed in our previous work,⁸ aliphatic aldehyde hydrazones were not tolerated in this reaction, as illustrated with **2o**.¹³ On the other hand, we were pleased to discover that hydrazones derived from α -ketoaldehydes, and notably from ethyl glyoxylate (see **2p**) and glyoxal (see **2q**), were suitable substrates for this transformation, which further demonstrates the broad applicability of the method. Overall, the reaction displayed good tolerance toward a variety of functional groups, including cyano, carboxylic ester, formyl, and halide which may serve as useful reaction handles for further elaborations. Finally,

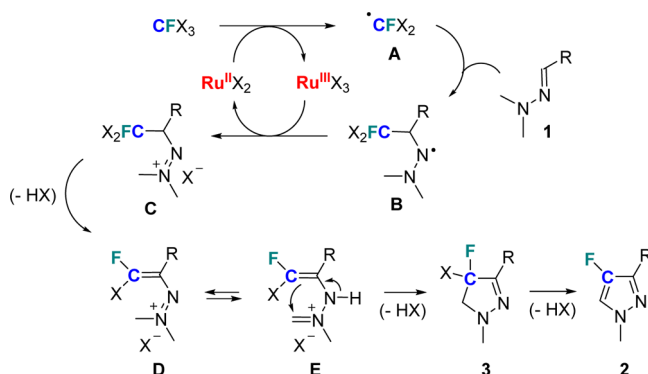
Scheme 1. Scope of the Ru-Catalyzed Synthesis of 4-Fluoropyrazoles^a

^aReaction conditions: Selected hydrazone (0.6 mmol), CBr₃F (1.2 mmol), K₂CO₃ (1.2 mmol), RuCl₂(PPh₃)₃ (5 mol %) in 3.0 mL of diglyme at 130 °C for 15 h. Isolated yields are given. ^bReaction performed at 150 °C. ^cNa₂CO₃ was used as base. ^dOnly decomposition of the substrate was observed.

the effect of varying the nature of the terminal amino group of hydrazones was investigated. For example, a *N*-methyl-*N*-phenyl hydrazone provided the corresponding *N*-phenyl-substituted pyrazole (2r) but required a higher temperature. A *N,N*-dibenzylhydrazone furnished the corresponding *N*-benzyl derivative (2s) as a group potentially removable from *N*-1, while enabling installation of a phenyl substituent at the C-5 position of the pyrazole ring. Other hydrazones bearing cyclic amino groups, e.g. 1-piperidyl (see 2t) and 1-homopiperidyl (see 2u), also participated in the cyclization process, giving the corresponding pyrazolo-annelated products in fair yields.

The reaction path is assumed to follow a Ru^{II}/Ru^{III} redox mechanism similar to that previously proposed for the related copper-catalyzed process.⁸ Halide abstraction from CBr₃F by the Ru(II) complex would generate haloalkyl radical A with concomitant generation of Ru(III).¹¹ Subsequent trapping of A by the hydrazone would generate aminyl radical B.⁹ Oxidation of this intermediate with Ru(III) would recycle Ru(II) and lead

to diazenium species C. Base-induced elimination of HBr from this cationic intermediate would then give unsaturated species D, which would tautomerize into the corresponding iminium cation E by proton abstraction from the *N*-methyl group.¹⁴ Subsequent intramolecular cyclization of the enamine-type structure would then provide pyrazoline 3.^{14d,15} Finally, another loss of HBr from 3 would lead to the desired aromatized product 2 (Scheme 2). Total inhibition of the standard reaction

Scheme 2. Ru^{II}/Ru^{III} Redox Mechanism Involving a Dihaloalkyl Radical

of 1a in the presence of radical scavenger 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO, 2 equiv) supports such a radical-initiated mechanism.

In summary, we have developed a novel method for preparing 4-fluoropyrazoles from aldehyde-derived hydrazones, tribromofluoromethane, and a ruthenium(II) catalyst. The method has the advantages of ready availability of starting materials, a simple one-step protocol, a broad substrate scope, and excellent functional-group tolerance. Moreover, concomitant pyrazole formation and fluorine incorporation ensure total control over product selectivity.

EXPERIMENTAL SECTION

General Information. All starting aldehyde-derived hydrazones were prepared as described in our previous papers.^{8,9a-d} CCl₃F and CBr₃F are commercially available reagents and were used as purchased. ¹H (300 or 400 MHz) NMR spectra were recorded in CDCl₃ with reference to the residual undeuterated solvent signal (δ 7.26 ppm). ¹³C (101 MHz) NMR spectra were recorded relative to the central CDCl₃ resonance (δ 77.16 ppm). ¹⁹F (282 MHz) NMR spectra with ¹H decoupling were recorded relative to CCl₃F (δ 0.0 ppm). NMR yields were determined by adding hexafluorobenzene (C₆F₆, δ −164.9 ppm) as an internal standard to the crude reaction mixtures and by integration of crude ¹⁹F NMR. Flash chromatographies were performed on silica gel (40–63 μm). Melting points (Mp) are uncorrected. The high resolution mass spectra were recorded by direct introduction in a positive and negative ion mode on a hybrid quadrupole time-of-flight mass spectrometer (MicroTOFQ-II, Bruker Daltonics, Bremen) with an Electrospray Ionization (ESI) ion source. The solutions were infused at 180 μL/h. The mass range of the analysis was 50–1000 *m/z*, and the calibration was done with sodium formate.

General Procedure. Preparation of 4-Fluoropyrazoles (2). In a 10 mL microwave reaction vial equipped with a magnetic stir bar, K₂CO₃ (166 mg, 1.2 mmol), CBr₃F (120 μL, 1.2 mmol), and RuCl₂(PPh₃)₃ (28 mg, 5 mol %) were successively added to a solution of the selected hydrazone (0.6 mmol) in diglyme (3 mL). The vial was flushed with argon and capped, and the reaction mixture was stirred overnight at 130 °C (oil bath). The mixture was cooled to room temperature and filtered through Celite using ethyl acetate as eluent to

remove solid residues. The volatiles were then removed from the filtrate under vacuum to yield a crude residue which was purified by silica gel flash chromatography to afford the corresponding pyrazole.

4-(4-Fluoro-1-methyl-1H-pyrazol-3-yl)benzonitrile (2a). Chromatography using ethyl acetate/cyclohexane (25:75) gave the title compound as a pale yellow solid (103 mg, 85%). Mp = 166–167 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.92 (d, *J* = 8.7 Hz, 2H), 7.66 (d, *J* = 8.7 Hz, 2H), 7.34 (d, *J* = 4.8 Hz, 1H), 3.88 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 147.7 (d, *J* = 251.5 Hz), 135.7 (d, *J* = 4.1 Hz), 134.9 (d, *J* = 5.9 Hz), 132.5, 126.1 (d, *J* = 4.4 Hz), 119.1, 118.1 (d, *J* = 28.4 Hz), 110.9, 40.3. ¹⁹F NMR (282 MHz, CDCl₃) δ −175.6 (s). HRMS (ESI): Calcd for C₁₁H₅FN₃ [M + H⁺]: 202.0775, found 202.0779.

4-Fluoro-1-methyl-3-(4-nitrophenyl)-1H-pyrazole (2b). Chromatography using ethyl acetate/cyclohexane (25:75) gave the title compound as a yellow solid (102 mg, 77%). Mp = 160–162 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.23 (d, *J* = 9.0 Hz, 2H), 7.97 (d, *J* = 9.0 Hz, 2H), 7.36 (d, *J* = 4.8 Hz, 1H), 3.90 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 147.9 (d, *J* = 251.4 Hz), 146.9, 137.6 (d, *J* = 4.1 Hz), 134.7 (d, *J* = 5.9 Hz), 126.2 (d, *J* = 4.6 Hz), 124.1, 118.2 (d, *J* = 28.4 Hz), 40.4. ¹⁹F NMR (282 MHz, CDCl₃) δ −175.2 (s). HRMS (ESI): Calcd for C₁₀H₅FN₃O₂ [M + H⁺]: 222.0673, found 222.0675.

4-Fluoro-1-methyl-3-(3-nitrophenyl)-1H-pyrazole (2c). Chromatography using ethyl acetate/cyclohexane (20:80) gave the title compound as a yellow solid (100 mg, 75%). Mp = 95–97 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.67 (t, *J* = 1.9 Hz, 1H), 8.21–7.99 (m, 2H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 4.8 Hz, 1H), 3.89 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 148.7, 147.4 (d, *J* = 250.9 Hz), 134.6 (d, *J* = 6.0 Hz), 133.0 (d, *J* = 4.1 Hz), 131.5 (d, *J* = 4.3 Hz), 129.7, 122.3, 120.7 (d, *J* = 4.3 Hz), 118.0 (d, *J* = 28.2 Hz), 40.3. ¹⁹F NMR (282 MHz, CDCl₃) δ −176.4 (s). HRMS (ESI): Calcd for C₁₀H₅FN₃O₂ [M + H⁺]: 222.0673, found 222.0671.

4-Fluoro-1-methyl-3-((4-trifluoromethyl)phenyl)-1H-pyrazole (2d). Chromatography using ethyl acetate/cyclohexane (30:70) gave the title compound as a brown oil (102 mg, 70%). ¹H NMR (400 MHz, CDCl₃) δ 7.95 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 4.8 Hz, 1H), 3.84 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 147.9 (d, *J* = 250.5 Hz), 134.7 (d, *J* = 6 Hz), 134.1 (d, *J* = 3.8 Hz), 128.8 (q, *J* = 32.4 Hz), 125.3 (d, *J* = 4.2 Hz), 124.9 (q, *J* = 3.8 Hz), 123.7 (q, *J* = 271.8 Hz), 117.1 (d, *J* = 28.4 Hz), 39.4. ¹⁹F NMR (282 MHz, CDCl₃) δ −65.7 (s), −176.5 (d). HRMS (ESI): Calcd for C₁₁H₅F₄N₂ [M + H⁺]: 245.0702, found 245.0696.

4-Fluoro-3-(4-fluorophenyl)-1-methyl-1H-pyrazole (2e). Chromatography using ethyl acetate/cyclohexane (25:75) gave the title compound as a colorless oil (85 mg, 72%). ¹H NMR (400 MHz, CDCl₃) δ 7.81 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.30 (d, *J* = 4.8 Hz, 1H), 7.10 (t, *J* = 8.8 Hz, 2H), 3.85 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 162.5 (d, *J* = 247.4 Hz), 147.0 (d, *J* = 249.0 Hz), 136.1 (d, *J* = 6.3 Hz), 127.7 (dd, *J* = 8.1, 4.0 Hz), 127.4 (t, *J* = 3.8 Hz), 117.6 (d, *J* = 28.4 Hz), 115.7 (d, *J* = 21.6 Hz), 40.1. ¹⁹F NMR (282 MHz, CDCl₃) δ −117.2 (s), −178.2 (s). HRMS (ESI): Calcd for C₁₀H₅F₂N₂ [M + H⁺]: 195.0728, found 195.0731.

3-(4-Bromophenyl)-4-fluoro-1-methyl-1H-pyrazole (2f). Chromatography using ethyl acetate/cyclohexane (25:75) gave the title compound as a pale yellow solid (116 mg, 76%). Mp = 54–56 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 4.8 Hz, 1H), 3.84 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 147.2 (d, *J* = 249.8 Hz), 135.8 (d, *J* = 6.1 Hz), 131.8, 130.2 (d, *J* = 4.1 Hz), 127.5 (d, *J* = 4.1 Hz), 121.7, 117.7 (d, *J* = 28.4 Hz), 40.1. ¹⁹F NMR (282 MHz, CDCl₃) δ −177.2 (s). HRMS (ESI): Calcd for C₁₀H₅BrFN₂ [M + H⁺]: 254.9928, found 254.9934.

3-(2-Chlorophenyl)-4-fluoro-1-methyl-1H-pyrazole (2g). Chromatography using ethyl acetate/cyclohexane (gradient elution 10:90 to 30:70) gave the title compound as a pale yellow oil (45 mg, 36%). ¹H NMR (300 MHz, CDCl₃) δ 7.45–7.35 (m, 2H), 7.25–7.18 (m, 3H), 3.78 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 146.9 (d, *J* = 249.1 Hz), 136.0 (d, *J* = 9.5 Hz), 133.5, 131.6, 130.0 (d, *J* = 3.4 Hz), 129.9, 129.7, 126.8, 116.9 (d, *J* = 28.1 Hz), 40.1. ¹⁹F NMR (282 MHz, CDCl₃) δ −173.6 (s). HRMS (ESI): Calcd for C₁₀H₈ClFN₂Na [M + Na⁺]: 233.0258, found 233.0256.

4-Fluoro-1-methyl-3-phenyl-1H-pyrazole (2h). Chromatography using ethyl acetate/cyclohexane (30:70) gave the title compound as a colorless oil (77 mg, 73%). ¹H NMR (400 MHz, CDCl₃) δ 7.94–7.77 (m, 2H), 7.44–7.39 (m, 2H), 7.35–7.29 (m, 2H), 3.86 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 147.3 (d, *J* = 249.3 Hz), 137.0 (d, *J* = 6.2 Hz), 131.3 (d, *J* = 4.0 Hz), 128.7, 127.8, 126.0 (d, *J* = 3.9 Hz), 117.6 (d, *J* = 28.5 Hz), 40.1. ¹⁹F NMR (282 MHz, CDCl₃) δ −177.8 (s). HRMS (ESI): Calcd for C₁₀H₁₀FN₂ [M + H⁺]: 177.0823, found 177.0823.

3-(4-tert-Butyl)phenyl)-4-fluoro-1-methyl-1H-pyrazole (2i). Chromatography using ethyl acetate/cyclohexane (20:80) gave the title compound as a colorless oil (75 mg, 54%). ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 4.8 Hz, 1H), 3.84 (s, 3H), 1.36 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 150.8, 147.2 (d, *J* = 248.9 Hz), 137.0 (d, *J* = 6.3 Hz), 128.4 (d, *J* = 4.1 Hz), 125.7 (d, *J* = 3.8 Hz), 125.6, 117.4 (d, *J* = 28.5 Hz), 40.0, 34.7, 31.4. ¹⁹F NMR (282 MHz, CDCl₃) δ −178.1 (s). HRMS (ESI): Calcd for C₁₄H₁₈FN₂ [M + H⁺]: 233.1449, found 233.1444.

4-Fluoro-1-methyl-3-(3,4,5-trimethoxyphenyl)-1H-pyrazole (2j). Chromatography using ethyl acetate/cyclohexane (gradient elution 30:70 to 50:50) gave the title compound as a pale yellow solid (97 mg, 61%). Mp = 117–120 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.29 (d, *J* = 4.8 Hz, 1H), 7.07 (s, 2H), 3.91 (s, 6H), 3.86 (s, 3H), 3.84 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 153.5, 147.0 (d, *J* = 248.9 Hz), 137.8, 136.6 (d, *J* = 5.8 Hz), 126.9 (d, *J* = 4.2 Hz), 117.7 (d, *J* = 28.7 Hz), 103.1 (d, *J* = 4.3 Hz), 61.0, 56.2, 40.0. ¹⁹F NMR (282 MHz, CDCl₃) δ −177.6 (s). HRMS (ESI): Calcd for C₁₃H₁₅FN₂NaO₃ [M + Na⁺]: 289.0959, found 289.0950.

3-(Benzo[d][1,3]dioxol-5-yl)-4-fluoro-1-methyl-1H-pyrazole (2k). Chromatography using ethyl acetate/cyclohexane (gradient elution 30:70 to 50:50) gave the title compound as a pale yellow solid (79 mg, 60%). Mp = 82–85 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.31 (m, 2H), 7.27 (d, *J* = 4.8 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 5.97 (s, 2H), 3.83 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 148.0, 147.2, 146.8 (d, *J* = 248.0 Hz), 136.7 (d, *J* = 6.2 Hz), 125.3 (d, *J* = 4.2 Hz), 119.8 (d, *J* = 4.7 Hz), 117.5 (d, *J* = 28.6 Hz), 108.6, 106.6 (d, *J* = 3.7 Hz), 101.1, 40.0 (s). ¹⁹F NMR (282 MHz, CDCl₃) δ −178.2 (s). HRMS (ESI): Calcd for C₁₁H₁₀FN₂O₂ [M + H⁺]: 221.0721, found 221.0728.

4-(4-Fluoro-1-methyl-3-1H-pyrazol-3-yl)-N,N-dimethylaniline (2l). Chromatography using ethyl acetate/cyclohexane (30:70) gave the title compound as a light brown solid (76 mg, 58%). Mp = 90–91 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 4.8 Hz, 1H), 6.69 (d, *J* = 8.9 Hz, 2H), 3.75 (s, 3H), 2.90 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 150.4, 147.1 (d, *J* = 247.5 Hz), 137.8 (d, *J* = 6.5 Hz), 127.2 (d, *J* = 3.7 Hz), 120.0, 117.6 (d, *J* = 28.6 Hz), 112.9, 40.9, 40.2. ¹⁹F NMR (282 MHz, CDCl₃) δ −179.1 (s). HRMS (ESI): Calcd for C₁₂H₁₅FN₃ [M + H⁺]: 220.1245, found 220.1237.

2-(4-Fluoro-1-methyl-1H-pyrazol-3-yl)quinoline (2m). Chromatography using ethyl acetate/cyclohexane (50:50) gave the title compound as a yellow oil (91 mg, 67%). ¹H NMR (400 MHz, CDCl₃) δ 8.22 (d, *J* = 8.6 Hz, 1H), 8.18 (d, *J* = 8.7 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.78 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.69 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.49 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.38 (d, *J* = 4.8 Hz, 1H), 3.94 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 150.5 (d, *J* = 4.4 Hz), 148.3 (d, *J* = 248.5 Hz), 136.9 (d, *J* = 5.0 Hz), 136.7, 130.0, 129.7, 127.5, 127.5, 126.5, 119.6 (d, *J* = 5.0 Hz), 118.1 (d, *J* = 28.5 Hz), 40.4. ¹⁹F NMR (282 MHz, CDCl₃) δ −174.4 (s). HRMS (ESI): Calcd for C₁₃H₁₀FN₃ [M + H⁺]: 228.0943, found 228.0934.

4-Fluoro-1-methyl-3-(5-nitrofur-2-yl)-1H-pyrazole (2n). Chromatography using ethyl acetate/cyclohexane (gradient elution 30:70 to 50:50) gave the title compound as a yellow solid (80 mg, 63%). Mp = 153–154 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.40 (d, *J* = 3.8 Hz, 1H), 7.36 (d, *J* = 4.7 Hz, 1H), 6.81 (dd, *J* = 3.8, 1.0 Hz, 1H), 3.92 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 151.54 (br s), 148.5, 147.16 (d, *J* = 255.3 Hz), 127.88 (d, *J* = 8.0 Hz), 117.89 (d, *J* = 26.1 Hz), 113.53, 109.61 (d, *J* = 3.5 Hz), 40.61. ¹⁹F NMR (282 MHz, CDCl₃) δ −174.2 (s). HRMS (ESI): Calcd for C₈H₆FN₃NaO₃ [M + Na⁺]: 234.0291, found 234.0286.

Ethyl 4-Fluoro-1-methyl-1H-pyrazole-3-carboxylate (2p). Chromatography using ethyl acetate/cyclohexane (gradient elution 30:70 to

50:50) gave the title compound as a pale yellow solid (77 mg, 74%). Mp = 56–58 °C. ^1H NMR (300 MHz, CDCl_3) δ 7.31 (d, J = 4.8 Hz, 1H), 4.39 (d, J = 7.1 Hz, 2H), 3.89 (s, 1H), 1.37 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 160.68 (d, J = 3.7 Hz), 149.75 (d, J = 258.3 Hz), 129.70 (d, J = 5.9 Hz), 118.11 (d, J = 27.2 Hz), 61.15, 40.82, 14.42. ^{19}F NMR (282 MHz, CDCl_3) δ -169.8 (s). HRMS (ESI): Calcd for $\text{C}_7\text{H}_5\text{FN}_2\text{NaO}_2$ [$\text{M} + \text{Na}^+$]: 195.0540, found 195.0531.

4-Fluoro-1-methyl-1H-pyrazole-3-carbaldehyde (2q). Chromatography using ethyl acetate/cyclohexane (30:70) gave the title compound as a colorless oil showing moderate volatility under rotary evaporation (38 mg, 50%). ^1H NMR (300 MHz, CDCl_3) δ 9.91 (s, 1H), 7.33 (d, J = 4.7 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 184.2, 149.75 (d, J = 261.1 Hz), 137.39 (d, J = 5.7 Hz), 118.42 (d, J = 26.1 Hz), 41.00. ^{19}F NMR (282 MHz, CDCl_3) δ -172.0 (s). HRMS (ESI): Calcd for $\text{C}_5\text{H}_5\text{FN}_2\text{O}$ [$\text{M} + \text{H}^+$]: 128.0380, found 128.0378.

4-Fluoro-3-(4-nitrophenyl)-1-phenyl-1H-pyrazole (2r). Chromatography using ethyl acetate/cyclohexane (5:95) gave the title compound as a yellow solid (68 mg, 40%). Mp = 138–139 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.30 (d, J = 8.9 Hz, 2H), 8.14 (d, J = 8.9 Hz, 2H), 7.93 (d, J = 4.7 Hz, 1H), 7.73–7.70 (m, 2H), 7.53–7.47 (m, 2H), 7.39–7.33 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 149.7 (d, J = 255 Hz), 147.6, 140.0, 137.4 (d, J = 3.9 Hz), 137.0 (d, J = 6.1 Hz), 130.0, 127.7, 126.9 (d, J = 4.4 Hz), 124.4, 119.1, 115.2 (d, J = 29.4 Hz). ^{19}F NMR (282 MHz, CDCl_3) δ -173.1 (s). HRMS (ESI): Calcd for $\text{C}_{15}\text{H}_{11}\text{FN}_3\text{O}_2$ [$\text{M} + \text{H}^+$]: 284.0835, found 284.0828.

1-Benzyl-4-fluoro-3-(4-nitrophenyl)-5-phenyl-1H-pyrazole (2s). Chromatography using ethyl acetate/cyclohexane (5:95) gave the title compound as a yellow gum (67 mg, 30%). ^1H NMR (300 MHz, CDCl_3) δ 8.20 (d, J = 8.9 Hz, 2H), 8.02 (d, J = 8.9 Hz, 2H), 7.41–7.35 (m, 3H), 7.31–7.17 (m, 5H), 7.03–6.98 (m, 2H), 5.25 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 147.1, 145.2 (d, J = 253.7 Hz), 137.7 (d, J = 4.2 Hz), 136.6, 134.8 (d, J = 5.8 Hz), 131.2 (d, J = 23.8 Hz), 129.6, 129.4 (d, J = 1.6 Hz), 129.1, 128.9, 128.1, 127.0, 126.7 (d, J = 3.7 Hz), 126.5 (d, J = 4.5 Hz), 124.2, 54.6. ^{19}F NMR (282 MHz, CDCl_3) δ -174.8 (s). HRMS (ESI): Calcd for $\text{C}_{22}\text{H}_{17}\text{FN}_3\text{O}_2$ [$\text{M} + \text{H}^+$]: 374.1305, found 374.1299.

3-Fluoro-2-(4-nitrophenyl)-4,5,6,7-tetrahydropyrazole[1,5-a]pyridine (2t). Chromatography using ethyl acetate/cyclohexane (20:80) gave the title compound as a yellow solid (72 mg, 46%). Mp = 153–154 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.19 (d, J = 8.9 Hz, 2H), 7.94 (d, J = 8.9 Hz, 2H), 4.11 (t, J = 6.1 Hz, 2H), 2.78 (td, J = 6.1, 1.6 Hz, 2H), 2.08–2.02 (m, 2H), 1.91–1.85 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 147.0, 144.6 (d, J = 247.4 Hz), 138.4 (d, J = 3.9 Hz), 134.0 (d, J = 5.3 Hz), 126.9 (d, J = 28.3 Hz), 126.4 (d, J = 4.6 Hz), 124.3, 49.1, 23.5, 20.3 (d, J = 3 Hz), 19.8. ^{19}F NMR (282 MHz, CDCl_3) δ -178.9 (s). HRMS (ESI): Calcd for $\text{C}_{13}\text{H}_{13}\text{FN}_3\text{O}_2$ [$\text{M} + \text{H}^+$]: 262.0992, found 262.0986.

2-(4-(tert-Butyl)phenyl)-3-fluoro-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a]azepine (2u). Chromatography using ethyl acetate/cyclohexane (30:70) gave the title compound as a pale yellow solid (62 mg, 36%). Mp = 106–108 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.76 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.6 Hz, 2H), 4.36–4.09 (m, 2H), 2.78–2.73 (m, 2H), 1.91–1.77 (m, 4H), 1.77–1.69 (m, 2H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 150.5, 144.0 (d, J = 246.9 Hz), 134.8 (d, J = 6.1 Hz), 130.4 (d, J = 25.6 Hz), 128.8 (d, J = 4.1 Hz), 125.6 (d, J = 2.3 Hz), 54.9, 34.7, 31.4, 31.1, 28.4, 27.1, 23.0 (d, J = 2.9 Hz). ^{19}F NMR (282 MHz, CDCl_3) δ -178.6 (s). HRMS (ESI): Calcd for $\text{C}_{18}\text{H}_{24}\text{FN}_2$ [$\text{M} + \text{H}^+$]: 287.1918, found 287.1925.

■ ASSOCIATED CONTENT

● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00085.

^1H , ^{19}F , and ^{13}C NMR spectra for all new products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was assisted financially by a grant to A.P. from the French Ministry of Higher Education and Research (MESR).

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