Regiocontrolled Syntheses of 3- or 5-Fluorinated Pyrazoles from 2,2-Difluorovinyl Ketones[1]

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2,2-Difluorovinyl ketones **1** react with monosubstituted hydrazines to afford 5-fluoropyrazoles in a regioselective manner *via* replacement of the fluorine by the substituted nitrogen of the hydrazines and dehydration between the carbonyl group of **1** and the NH_2 end. The reactions are successfully effected for both aliphatic and aromatic hydrazines in aqueous ethanol under neutral conditions and in THF under basic conditions with butyllithium, respectively. A similar ring-forming reaction of **1** with hydrazine monohydrate is induced by the addition of trifluoroacetic acid to give *N*-unsubstituted 3-fluoropyrazoles, which in turn react with alkyl and aryl halides in the presence of sodium hydride, leading to a regiocontrolled synthesis of 3-fluoropyrazoles.

Introduction

Selectively fluorinated heterocyclic compounds have attracted much attention in terms of their biological and physiological activities, which are often dramatically raised or changed by the introduction of fluorine onto the molecules.[2] Among heteroaromatic systems, pyrazoles are important not only as a component of pharmaceuticals, agrochemicals, and dyestuffs[3] but also as a bioisoteric replacement for substituted pyrroles. Therefore, several methods have recently been reported for the synthesis of their fluorinated counterparts. Most of these methods are, however, for pyrazoles with a perfluoroalkyl group;[4] so efficient routes to ring-fluorinated compounds are quite limited.[5,6] Especially, for the synthesis of 3- and 5-fluoropyrazoles there were only two methods: (i) Baltz−Schiemann-type fluorination, which required a multistep sequence with very low yields[6a] and (ii) electrochemical fluorination with less generality and efficiency.[6b] These circumstances prompted us to investigate a regioselective and practical entry to ring-fluorinated pyrazoles.

Recently, we have developed a facile synthetic method for 2,2-difluorovinyl ketones **1**[7] and also revealed their remarkable reactivity toward nucleophilic substitution for the fluorines *via* a 1,4-addition−elimination process, which was due to (i) double activation of the carbon−carbon double bond by the two fluorine atoms as well as the carbonyl group and (ii) leaving-group ability of fluorine as a fluoride ion. Making use of these properties, we have disclosed the synthetic utility of **1** as building blocks for the syntheses of α,β-unsaturated ketones (*via* the reaction with *C*-nucleophiles)[8] and α-oxoketene acetal derivatives (*via* the reaction with *O*-, *S*-, and *N*-nucleophiles).[9,10] We then turned our attention to combining this replacement of fluorine and dehydration at the carbonyl group in **1** by employing nucleophiles with another functional group, the sequence of which might allow construction of a ring system through a two-site reaction. Hydrazines were selected as a kind of bifunctional nucleophile to permit the preparation of pyrazoles bearing a fluorine atom directly on the ring. We wish to report here the regiocontrolled syntheses of both 5- and 3-fluoropyrazoles by the reaction of **1** with monosubstituted hydrazines and the reaction of **1** with unsubstituted hydrazine followed by alkylation on the ring nitrogen, respectively.

Results and Discussion

Synthesis of 5-Fluoropyrazoles. Initially, we investigated the reaction of 2,2-difluorovinyl ketones **1** with

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(1) Presented in part at the 50th Anniversary International Symposium on Organic Synthesis, Tokyo, Japan, August. 3−4, 1992 (PS-55).

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(10) Once the NH_2 group (*N*-2 atom) of the hydrazines attacks **1** at its CF_2 end, formation of a C−N double bond *via* double dehydrofluorination seems to occur more readily than the cyclization, in consideration of the fact that **1** reacted with primary amines to afford α-oxoketenimines in good yields. See: Ichikawa, J.; Yokota, N.; Kobayashi, M.; Amano, K.; Minami, T. *Synlett* **1996**, in press.

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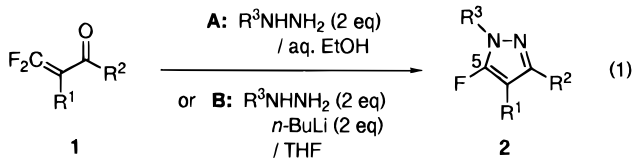
Table 1. Synthesis of 5-Fluoropyrazoles 2 from 2,2-Difluorovinyl Ketones 1

entry	R^1	R^2	R^3	method	conditions	product (**2**)	yield,[a] % (**2**/**3**)[b]
1	*n*-Bu	Ph	Me	A	rt, 0.5 h	**2a**	95 (100/0)
2	*n*-Bu	Ph	*n*-Bu	A	rt, 0.3 h	**2b**	92 (99/1)
3	*n*-Bu	Ph	Bn	A	rt, 0.5 h	**2c**	89 (97/3)
4	*n*-Bu	Ph	allyl	A	rt, 1 h	**2d**	92 (96/4)
5	*n*-Bu	Ph	Ph	B	−78 °C, 1 h	**2e**	92 (100/0)
6	*n*-Bu	Ph	*p*-tol[c]	B	−78−0 °C, 1 h	**2f**	79 (>99/<1)[d]
7	*n*-Bu	*c*-hex	Ph	B	−78 °C−rt, 0.4 h	**2g**	85 (100/0)
8	*sec*-Bu	Ph	Ph	B	−78−0 °C, 1.5 h	**2h**	76 (>99/<1)

[a] Isolated yields. [b] Determined by GLC analysis. [c] Hydrazine hydrochloride was employed. An additional equimolar amount of butyllithium was used to liberate the corresponding free hydrazine. [d] Determined by ^{19}F NMR analysis.

monosubstituted hydrazines, employing 2-butyl-3,3-difluoro-1-phenyl-2-propen-1-one (**1a**, R^1 = *n*-Bu, R^2 = Ph) and methylhydrazine as model compounds. After screening reaction conditions, we found that treatment of **1a** with 1.1 equiv of methylhydrazine in aqueous ethanol afforded *N*-methyl-5-fluoropyrazole **2a** (R^1 = *n*-Bu, R^2 = Ph, R^3 = Me) even at room temperature in 88% yield without its regioisomer, 3-fluoropyrazole **3a** (*vide infra*). Using an excess (2 equiv) of methylhydrazine in this reaction improved the yield of **2a** up to 95% (method A), probably due to the capture of hydrogen fluoride generated through the substitution. In a similar manner, several other monoalkylhydrazines almost exclusively gave 5-fluoropyrazoles **2b**−**d** in excellent yields (eq 1, Table 1, entries 1−4).

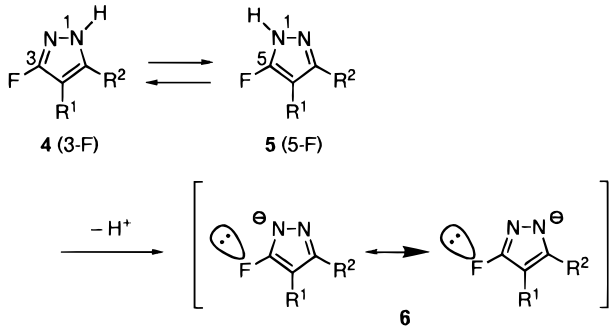
Under the same reaction conditions, phenylhydrazine yielded **2e** (R^1 = *n*-Bu, R^2 = R^3 = Ph) only in a low yield (45%) along with non-fluorinated byproducts. The contrast with alkyl hydrazines is attributable to the fact that the substituted nitrogen (*N*-1) of phenylhydrazine is less nucleophilic than the terminal nitrogen (*N*-2) in neutral medium.[3a,10] We then conducted the reaction under basic conditions in order to raise the reactivity at the *N*-1 atom by abstraction of its proton. On treatment of **1a** with 2 equiv of $PhNLiNH_2$, generated by using butyllithium, the reaction was complete at −78 °C in 1 h to give **2e** as a sole regioisomeric product in 92% yield (method B). These conditions were also effective for other aromatic hydrazines to allow the high-yielding synthesis of *N*-aryl-5-fluoropyrazoles **2f**−**h** as shown in Table 1 (entries 5−8).



(1)

Moreover, in the case of aliphatic hydrazines, the production of pyrazoles was depressed under the basic conditions of method B, where electrophilic attack would preferably occur at the *N*-2 atom of their conjugate bases, contrary to the *N*-1 atom of those of aromatic hydrazines as mentioned above.[3a,10] The reaction mechanism for this regioselective ring formation has not been completely clarified; but judging from (i) the differences in the outcome depending on the neutral and basic conditions and (ii) the high reactivity of **1** in 1,4-addition,[8,9] we suppose that replacement of the fluorine is initially induced by the *N*-1 atom of hydrazines, followed by dehydration between the carbonyl group of **1** and the NH_2 end to construct a pyrazole framework.[3,11] In this sense,

Scheme 1



the fluorines of **1** play an important role in directing the regiochemistry.

Synthesis of 3-Fluoropyrazoles. An *N*-unsubstituted unsymmetrical pyrazole can exist as a mixture of two tautomers, whereas abstraction of the proton on nitrogen in 3- and 5-fluoropyrazoles **4** and **5** generates the same ambident anion **6**, which could be attacked by electrophilic reagents at either one of the ring nitrogen atoms. Furthermore, the site of electrophilic attack in anion **6** would be governed by the repulsive interaction between the lone pair of the fluorine and the negative charge on the nitrogen closer to the fluorine (Scheme 1)[12,13]. On the basis of these considerations, we explored the fluorine-directed alkylation of *N*-unsubstituted 3(5)-fluoropyrazoles to achieve the selective synthesis of 3-fluoropyrazoles.

For the purpose of preparing *N*-unsubstituted fluoropyrazoles, **1a** was treated with hydrazine under the neutral or basic conditions (method A or B; *vide supra*), both of which resulted in poor yields of the desired product **4a**. Addition of trifluoroacetic acid (3 equiv), however, cleanly promoted the reaction of **1a** with hydrazine monohydrate in tetrahydrofuran (THF) to raise the yield of **4a** up to 95%, where high dilution and adding hydrazine in two portions at some interval brought about better results (eq 2).[14] The *N*-unsubstituted fluoropyrazole **4a** thus obtained was found to exist

(11) Rudorf, W.-D.; Augstin, M. *J. Prakt. Chem.* **1978**, *320*, 585−599.

(12) Fluorine is well known to stabilize β-anions both inductively and by negative hyperconjugation and to destabilize α-anions by I_π repulsion. See: Chambers, R. D. *Fluorine in Organic Chemistry*; Antony Rowe: Chippenham, 1973; pp 1−13. Smart, B. E. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: New York, 1994; pp 57−88. In anion **6**, the pyrazole ring structure might depress the effect of anionic hyperconjugation, while causing the electronic repulsion between the fluorine and the β-nitrogen.

(13) For the regioselective alkylation of *N*-unsubstituted pyrazoles, see: ref 3. Katritzky, A. R.; Lagowski, J. M. In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon Press: Oxford, 1984; Vol. 5, pp 39−110. See also for recent examples: Luo, Y.; Potvin, P. G. *J. Org. Chem.* **1994**, *59*, 1761−1765. Valk, P. v. d.; Potvin, P. G. *J. Org. Chem.* **1994**, *59*, 1766−1770.

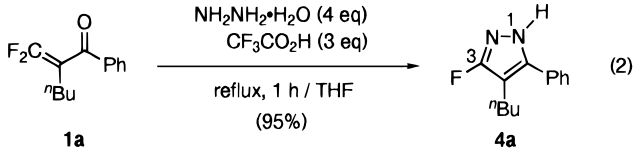
(14) In the absence of CF_3CO_2H, the same reaction mainly gave non-fluorinated products.[10]

Table 2. *Fluorine-Directed* Alkylation of *N*-Unsubstituted Fluoropyrazole 4a

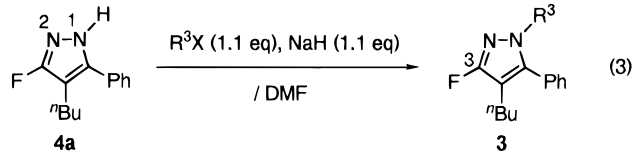
entry	R^3X	conditions	product (**3**)	yield,[a] % (**3**/**2**)[b]
1	MeI	−45 °C, 1.5 h	**3a**	97 (97/3)
2	*n*-BuI	−45 °C, 5.6 d	**3b**	96 (84/16)
3	*n*-BuBr	rt, 2 h	**3b**	quant (74/26)
4	BnBr	−45 °C, 20 h	**3c**	98 (90/10)
5	allyl-Br	−45 °C, 6 h	**3d**	98 (88/12)
6	*i*-PrI	rt, 75 h	**3i**	89 (64/36)
7	*p*-$NO_2C_6H_4F$	rt, 20 h	**3j**	96 (68/32)

[a] Isolated yields. [b] Determined by GLC analysis.

in a "3-fluoro" tautomeric form as evidenced by ^{13}C NMR measurement in $CDCl_3$ (*vide infra*).[15,16]

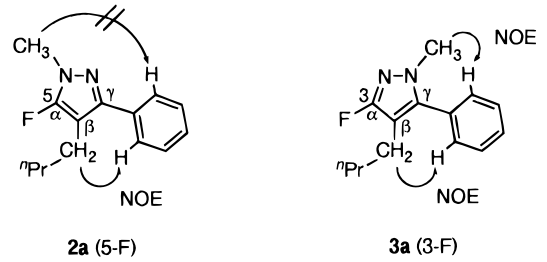


Next, **4a** was successively treated with sodium hydride (1.1 equiv) and methyl iodide (1.1 equiv) in *N*,*N*-dimethylformamide (DMF) at −45 °C for alkylation at the ring nitrogen. The reaction proceeded regioselectively under the control of fluorine as expected, leading to the corresponding *N*-methylated products (97%) in marked preference for the more hindered isomer, 3-fluoropyrazole **3a** (97/3) (eq 3).[3a] Under the same conditions, several

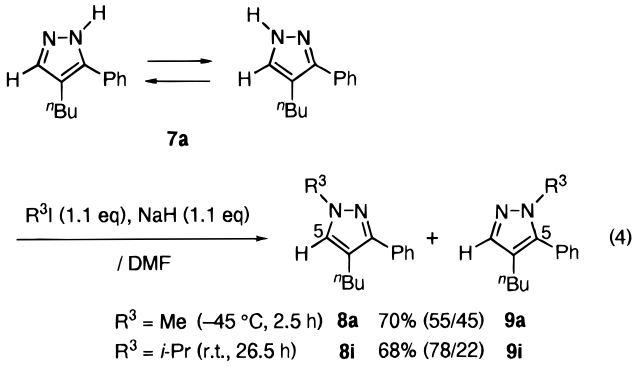


3-fluoropyrazoles **3b**−**d** and **3i** were obtained in excellent yields with good to high regioselectivities in spite of the steric hindrance between R^3 and the phenyl group (eq 3, Table 2, entries 1−6). The alkylation with butyl bromide was further investigated under modified conditions: (i) by employing butyllithium or potassium hydride instead of sodium hydride, (ii) in the presence of 15-crown-5 (2 equiv), or (iii) in THF instead of DMF. All of these attempts gave similar isomer ratios (74/26−76/24), which suggested that the binding of countercation to **6** has little influence on the regioselectivity. In addition to the alkylation, arylation at the nitrogen was also accomplished in 96% yield by the use of 1-fluoro-4-nitrobenzene as an electrophile to afford 3-fluoropyrazole **3j** (R^1 = *n*-Bu, R^2 = Ph, R^3 = *p*-$NO_2C_6H_4$) as a major regioisomer (Table 2, entry 7).[3a] On the other hand, the methylation of neutral **4a** occurred with dimethyl sulfate at 80 °C for 3.5 h without solvent to give the 5-fluorinated isomer **2a** as the sole regioisomeric product in 81% yield.[6a] This result was effected by electrophilic attack at the pyridine-like *N*-2 atom of **4a**, due to its stronger nucleophilicity than that of the *N*-1 atom in neutral medium, followed by proton loss from the *N*-1.

Scheme 2



In order to confirm the effect of fluorine on the regiochemistry, we conducted the *N*-alkylation of a fluorine-free pyrazole. While **4a** was regioselectively alkylated to afford the more hindered isomer **3** as shown above (Table 2, entries 1 and 6), its non-fluorinated counterpart, 4-butyl-3(5)-phenylpyrazole **7a**,[16] exhibited a poor (R^3 = Me) and a reverse (R^3 = *i*-Pr) selectivity, leading to a mixture of the *N*-alkylated products (**8a**/**9a** = 55/45, **8i**/**9i** = 78/22) (eq 4).[17] Furthermore, the methylation of **7a** with dimethyl sulfate in the absence of a base and a solvent also afforded a regioisomeric mixture (**8a**/**9a** = 69/31), probably due to the rapid equilibrium of **7a**. Thus, without a fluorine substituent, the less hindered isomers were rather favored under both the basic and neutral conditions, which results revealed the ability of fluorine as a controller over the course of reactions.



Structural Assignment of 3- and 5-Fluoropyrazoles. The structure of regioisomeric *N*-methylated fluoropyrazoles **2a** and **3a** was assigned by ^1H NMR measurement on the basis of the observed NOE between the methyl protons on the nitrogen and the *o*-phenyl protons only for the 3-fluorinated isomer **3a**, in contrast to the observed NOE between the methylene protons of the butyl group and the *o*-phenyl protons for both isomers (Scheme 2). Moreover, the EI mass spectrum of **3a** showed a fragment of 118 mass units attributable to $MeN^+{\equiv}CPh$, an observation consistent with the above-assigned regiochemistry.[5c]

Having determined the regioisomeric identity of **2a** and **3a** by NOE experiments and mass spectroscopic analysis, we found comparative ^{13}C and ^{19}F chemical shifts[18] and

(15) For the MNDO and AM1 calculations on 3- and 5-fluoropyrazoles, see: Garcia, J.; Vilarrasa, J. *Heterocycles* **1988**, *27*, 1803−1807. Hammadi, A. E.; Mouhtadi, M. E.; Notario, R.; Abboud, J.-L. M.; Elguero, J. *J. Chem. Res. (M)* **1995**, 1080−1096.

(16) In contrast to **4a**, **7a** existed as a tautomeric mixture, which was indicated by the broad signals of the three ring carbons in the ^{13}C NMR spectrum ($CDCl_3$: δ 118.8, 134.7, and 144.3) at the average values of both tautomers.

(17) Regiochemistry was assigned for **8a** and **9a** by NMR measurement on the basis of (i) the observed NOE between the methyl protons on the nitrogen and the ring proton for **8a** or the *o*-phenyl protons for **9a**, and (ii) the cross peaks between the methyl protons and the C-5 carbon for each isomer in the COLOC spectrum of their mixture. The structure of **8i** and **9i** was assigned by ^1H NMR measurement on the basis of the observed two NOE's between the methyl protons of the isopropyl group and the the ring proton for **8i** and between the methine proton of the isopropyl group and the *o*-phenyl protons for **9i**.

Table 3. ^{13}C and ^{19}F NMR Chemical Shifts and Carbon−Fluorine Coupling Constants of 5- and 3-Fluoropyrazoles 2, 3, and 4[a]

compound	α-C	β-C	γ-C	F
2a (5-F)	152.0 (d) $^1J_{CF}$ = 275 Hz	98.3 (d) $^2J_{CF}$ = 13 Hz	148.5 (d) $^3J_{CF}$ = 10 Hz	23.6
3a (3-F)	161.8 (d) $^1J_{CF}$ = 243 Hz	102.4 (d) $^2J_{CF}$ = 21 Hz	142.5 (s)	26.5
2b (5-F)	151.7 (d) $^1J_{CF}$ = 275 Hz	98.0 (d) $^2J_{CF}$ = 12 Hz	148.3 (d) $^3J_{CF}$ = 10 Hz	23.7
3b (3-F)	161.9 (d) $^1J_{CF}$ = 243 Hz	102.2 (d) $^2J_{CF}$ = 20 Hz	142.5 (s)	26.6
2c (5-F)	151.7 (d) $^1J_{CF}$ = 276 Hz	98.6 (d) $^2J_{CF}$ = 12 Hz	148.7 (d) $^3J_{CF}$ = 10 Hz	24.5
3c (3-F)	162.1 (d) $^1J_{CF}$ = 244 Hz	103.0 (d) $^2J_{CF}$ = 21 Hz	142.9 (s)	27.6
2d (5-F)	151.7 (d) $^1J_{CF}$ = 276 Hz	98.5 (d) $^2J_{CF}$ = 11 Hz	148.7 (d) $^3J_{CF}$ = 9 Hz	24.2
3d (3-F)	162.2 (d) $^1J_{CF}$ = 244 Hz	102.8 (d) $^2J_{CF}$ = 21 Hz	142.7 (s)	27.4
2e (5-F)	151.2 (d) $^1J_{CF}$ = 281 Hz	100.5 (d) $^2J_{CF}$ = 14 Hz	149.9 (d) $^3J_{CF}$ = 10 Hz	28.3
2f (5-F)	151.1 (d) $^1J_{CF}$ = 280 Hz	100.2 (d) $^2J_{CF}$ = 12 Hz	149.5 (d) $^3J_{CF}$ = 11 Hz	28.3
2g (5-F)	150.7 (d) $^1J_{CF}$ = 279 Hz	99.3 (d) $^2J_{CF}$ = 12 Hz	156.0 (d) $^3J_{CF}$ = 9 Hz	27.8
2h (5-F)	150.6 (d) $^1J_{CF}$ = 282 Hz	105.4 (d) $^2J_{CF}$ = 13 Hz	150.3 (d) $^3J_{CF}$ = 11 Hz	31.7
2i (5-F)	151.0 (d) $^1J_{CF}$ = 275 Hz	98.4 (d) $^2J_{CF}$ = 12 Hz	147.9 (d) $^3J_{CF}$ = 9 Hz	24.2
3i (3-F)	162.0 (d) $^1J_{CF}$ = 242 Hz	101.9 (d) $^2J_{CF}$ = 21 Hz	141.6 (s)	27.1
2j (5-F)	151.7 (d) $^1J_{CF}$ = 283 Hz	102.2 (d) $^2J_{CF}$ = 13 Hz	151.8 (d) $^3J_{CF}$ = 10 Hz	31.3
3j (3-F)	164.4 (d) $^1J_{CF}$ = 249 Hz	107.8 (d) $^2J_{CF}$ = 21 Hz	142.2 (s)	31.0
4a (3-F)	163.8 (d) $^1J_{CF}$ = 244 Hz	101.8 (d) $^2J_{CF}$ = 21 Hz	141.6 (s)	28.8

[a] The spectra were obtained in $CDCl_3$ except for ^{19}F NMR spectra of **2a**, **2e** ($CDCl_3$−CCl_4), and **2g** (C_6D_6).

carbon−fluorine coupling constants[19] of the three ring carbon atoms and the fluorine atom, which were diagnostic for regiochemical assignments of 3- and 5-fluoropyrazoles as shown in Table 3. The following consistent differences were observed in the ^{13}C and ^{19}F NMR spectra of the 5-fluorinated isomers, compared to those of the 3-fluorinated isomers: (i) the ring carbon α to the fluorine is upfield (150.6−152.0 *vs* 161.8−164.4 ppm) with a larger carbon−fluorine coupling ($^1J_{CF}$ = 275−283 *vs* 242−249 Hz), (ii) the ring carbon β to the fluorine is upfield (98.0−100.5 *vs* 101.8−103.0 ppm)[20] with a smaller coupling ($^2J_{CF}$ = 11−14 *vs* 20−21 Hz), (iii) the ring carbon γ to the fluorine is downfield (147.9−156.0 *vs* 141.6−142.9 ppm) with a larger coupling ($^3J_{CF}$ = 9−11 *vs* 0 Hz), and (iv) the fluorine is upfield in the case of R^3 = alkyl (23.6−24.5 *vs.* 26.5−27.6 ppm).[21] Based on these spectral criteria, regiochemistry was assigned for fluoropyrazoles **2**, **3**, and **4a** as described above.

In conclusion, convenient synthetic methods have been developed for the selective preparations of pyrazoles fluorinated at a definite position of the ring carbon starting from 2,2-difluorovinyl ketones and hydrazines. These routes are applicable to pyrazoles with a variety of substitution patterns and are complimentary to reported syntheses of 4-fluorinated isomers.[5] The electronic effects and the leaving-group ability of fluorine activate the substrates and control the pathway of the reactions. This work demonstrates the utility of fluorine substituent as a versatile tool in organic synthesis.[22]

Experimental Section

Melting points were measured in open capillary tubes and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at the indicated field strengths. Chemical shift values of ^{19}F NMR were given in ppm relative to internal C_6F_6. 2-Butyl-3,3-difluoro-1-phenyl-2-propen-1-one (**1a**), 2-butyl-1-cyclohexyl-3,3-difluoro-2-propen-1-one (**1b**), and 2-*sec*-butyl-3,3-difluoro-1-phenyl-2-propen-1-one (**1c**) were prepared according to the method established in our laboratory.[7,9] Commercial hydrazines and hydrazine salts were used without further purification.

4-Butyl-5-fluoro-1-methyl-3-phenylpyrazole (2a) (Method A). Methylhydrazine (34 mg, 0.73 mmol) was added to a solution of **1a** (82 mg, 0.36 mmol) in ethanol−H_2O (10:1, 3.5 mL) at room temperature, and the resulting mixture was stirred for 30 min. After phosphate buffer (pH 7) was added, organic materials were extracted with ethyl acetate three times. The combined extracts were washed with brine and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (hexane−ethyl acetate 5:1) to give **2a** (80 mg, 95%) as a pale yellow liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.6 Hz), 1.33 (2H, tq, J = 7.6, 7.6 Hz), 1.52 (2H, tt, J = 7.6, 7.6 Hz), 2.53 (2H, t, J = 7.6 Hz), 3.74 (3H, d, J_{HF} = 0.9 Hz), 7.32 (1H, tt, J = 7.4, 1.5 Hz), 7.39 (2H, t, J = 7.4 Hz) 7.57−7.62 (2H, m). ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.8, 22.0 (d, J_{CF} = 4 Hz), 22.4, 31.9, 34.0, 98.3 (d, J_{CF} = 13 Hz), 127.4, 127.7, 128.5, 134.3, 148.5 (d, J_{CF} = 10 Hz), 152.0 (d, J_{CF} = 275 Hz). ^{19}F NMR (94 MHz, $CDCl_3$−CCl_4) 23.6 (1F, s) ppm. IR (neat) 2900, 1605, 1575, 1530, 1455, 1380, 1300, 1220, 1165, 1075, 1030, 915, 770, 690 cm^{-1}. MS (70 eV) m/z 232 (M^+), 189 (base peak), 77. Anal. Calcd for $C_{14}H_{17}N_2F$: C, 72.39; H, 7.38; N, 12.06. Found: C, 72.60; H, 7.58; N, 11.89.

1,4-Dibutyl-5-fluoro-3-phenylpyrazole (2b). Compound **2b** was prepared by the method described for **2a** using butylhydrazine (80 mg, 0.90 mmol) and **1a** (101 mg, 0.45 mmol) in ethanol−H_2O (10:1, 4 mL). Purification by thin layer chromatography on silica gel (hexane−ethyl acetate 5:1) gave **2b** and **3b** (114 mg, 92%, **2b**/**3b** = 99/1) as a pale yellow liquid. **2b:** ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.3 Hz), 0.95 (3H, t, J = 7.3 Hz), 1.33 (2H, tq, J = 7.3, 7.3 Hz), 1.36 (2H, tq, J = 7.6, 7.6 Hz), 1.53 (2H, tt, J = 7.6, 7.6 Hz), 1.83 (2H, tt, J = 7.3, 7.3 Hz), 2.53 (2H, t, J = 7.6 Hz), 4.03 (2H, t, J = 7.3 Hz), 7.32 (1H, tt, J = 7.4, 1.6 Hz), 7.40 (2H, td, J = 7.4, 1.5 Hz), 7.57−7.62 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.6, 13.8, 19.8, 22.0 (d, J_{CF} = 3 Hz), 22.4, 31.7, 31.9, 47.3, 98.0 (d, J_{CF} = 12 Hz), 127.4, 127.6, 128.4, 134.4, 148.3 (d, J_{CF} = 10 Hz), 151.7 (d, J_{CF} = 275 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) 23.7 (1F, s) ppm. IR (neat) 2975, 2950, 2900, 1610, 1580, 1520, 1460, 1385, 780, 700 cm^{-1}. MS (70 eV) m/z (rel intensity) 274 (M^+; 53), 231 (97), 189 (98), 175 (100), 128 (46), 77 (40). Anal. Calcd for $C_{17}H_{23}N_2F$: C, 74.42; H, 8.45; N, 10.21. Found: C, 74.59; H, 8.63; N, 10.02.

1-Benzyl-4-butyl-5-fluoro-3-phenylpyrazole (2c). Compound **2c** was prepared by the method described for **2a** using benzylhydrazine (118 mg, 0.97 mmol) and **1a** (108 mg, 0.48 mmol) in ethanol−H_2O (10:1, 4 mL). Purification by thin layer chromatography on silica gel (hexane−ethyl acetate 5:1) gave **2c** and **3c** (131 mg, 89%, **2c**/**3c** = 97/3) as a pale yellow liquid.

(18) The ^{13}C chemical shift trends of regioisomeric pyrazoles have been reported for 3- and 5-hydroxypyrazoles and pyrazolecarboxylic esters. See: ref 4h. Sohár, P.; Fehér, O.; Tihanyi, E. *Org. Magn. Reson.* **1979**, *12*, 205−208.

(19) Begtrup, M.; Boyer, G.; Cabildo, P.; Cativiela, C.; Claramunt, R. M.; Elguero, J.; García, J. I.; Toiron, C.; Vedsø, P. *Magn. Reson. Chem.* **1993**, *31*, 107−168.

(20) The chemical shift of the β-carbon in **2h** (105.4 ppm) is an exception due to the downfield shift induced by its *sec*-Bu substituent. In the case of **2j** and **3j**, the signals of their β-carbons appear out of the range described in the text, although they still have a similar tendency ($\delta_{\beta\text{-C(2j)}} < \delta_{\beta\text{-C(3j)}}$).

(21) The fluorines in **2** (R^3 = aryl) are shifted downfield by the anisotropic effect of the aryl group at the *N*-1 atom.

(22) Ichikawa, J.; Miyazaki, S.; Fujiwara, M.; Minami, T. *J. Org Chem.* **1995**, *60*, 2320−2321. Fish, P. V.; Johnson, W. S.; Jones, G. S.; Tham, F. S.; Kullnig, R. K. *J. Org. Chem.* **1994**, *59*, 6150−6152.

2c: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.5 Hz), 1.32 (2H, tq, J = 7.5, 7.5 Hz), 1.52 (2H, tt, J = 7.5, 7.5 Hz), 2.53 (2H, t, J = 7.5 Hz), 5.23 (2H, s), 7.25−7.36 (6H, m), 7.40 (2H, t, J = 7.5 Hz), 7.59−7.64 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 21.9 (d, J_{CF} = 3 Hz), 22.3, 31.7, 51.4, 98.6 (d, J_{CF} = 12 Hz), 127.4, 127.4, 127.7, 127.8, 128.4, 128.6, 134.1, 136.0, 148.7 (d, J_{CF} = 10 Hz), 151.7 (d, J_{CF} = 276 Hz). ^{19}F NMR (94 MHz, $CDCl_3$) 24.5 (1F, s) ppm. IR (neat) 3050, 2950, 2850, 1605, 1575, 1515, 1455, 1375, 1325, 1075, 1025, 695 cm^{-1}. MS (70 eV) m/z (rel intensity) 308 (M^+; 47), 265 (66), 91 (100). Anal. Calcd for $C_{20}H_{21}N_2F$: C, 77.89; H, 6.86; N, 9.08. Found: C, 77.93; H, 7.06; N, 8.89.

1-Allyl-4-butyl-5-fluoro-3-phenylpyrazole (2d). Compound **2d** was prepared by the method described for **2a** using allylhydrazine (59 mg, 0.82 mmol) and **1a** (92 mg, 0.41 mmol) in ethanol−H_2O (10:1, 6 mL). Purification by thin layer chromatography on silica gel (hexane−ethyl acetate 10:1) gave **2d** and **3d** (97 mg, 92%, **2d**/**3d** = 96/4) as a pale yellow liquid. **2d:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.6 Hz), 1.33 (2H, tq, J = 7.6, 7.6 Hz), 1.53 (2H, tt, J = 7.6, 7.6 Hz), 2.54 (2H, t, J = 7.6 Hz), 4.66 (2H, dd, J = 5.8 Hz, J_{HF} = 0.6 Hz), 5.19 (1H, dd, J = 17.1, 1.2 Hz), 5.24 (1H, ddt, J = 10.4, 1.2, 1.2 Hz), 6.00 (1H, ddt, J = 17.1, 10.4, 5.8 Hz), 7.32 (1H, tt, J = 7.5, 1.6 Hz), 7.40 (2H, td, J = 7.5, 1.4 Hz), 7.58−7.62 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 21.9 (d, J_{CF} = 4 Hz), 22.4, 31.8, 50.0, 98.5 (d, J_{CF} = 11 Hz), 118.0, 127.4, 127.7, 128.4, 132.1, 134.1, 148.7 (d, J_{CF} = 9 Hz), 151.7 (d, J_{CF} = 276 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) 24.2 (1F, s) ppm. IR (neat) 3100, 2975, 2950, 2900, 1610, 1580, 1520, 1460, 1380, 1320, 1250, 995, 935, 920, 780, 700 cm^{-1}. MS (70 eV) m/z (rel intensity) 258 (M^+; 31), 215 (100), 187 (6), 155 (8), 77 (11). Anal. Calcd for $C_{16}H_{19}N_2F$: C, 74.39; H, 7.41; N, 10.84. Found: C, 74.39; H, 7.55; N, 10.63.

4-Butyl-5-fluoro-1,3-diphenylpyrazole (2e) (Method B). Butyllithium (0.83 mL, 1.63 M in hexane, 1.34 mmol) was added to a solution of phenylhydrazine (145 mg, 1.34 mmol) in THF (3 mL) at −78 °C under a nitrogen atmosphere. After the mixture had been stirred for 10 min, a solution of **1a** (150 mg, 0.67 mmol) in THF (2 mL) was added at −78 °C. The reaction mixture was stirred for 1 h at −78 °C, and phosphate buffer (pH 7) was then added to quench the reaction. Organic materials were extracted with ethyl acetate three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (hexane−ethyl acetate 20:1) to give **2e** (182 mg, 92%) as a yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.5 Hz), 1.37 (2H, tq, J = 7.5, 7.5 Hz), 1.59 (2H, tt, J = 7.5, 7.5 Hz), 2.61 (2H, t, J = 7.5 Hz), 7.30 (1H, tt, J = 7.3, 1.1 Hz), 7.37 (1H, tt, J = 7.0, 1.7 Hz), 7.41−7.48 (4H, m), 7.68−7.75 (4H, m). ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.8, 22.0 (d, J_{CF} = 3 Hz), 22.4, 31.7, 100.5 (d, J_{CF} = 14 Hz), 121.0 (d, J_{CF} = 4 Hz), 126.8, 127.6, 128.1, 128.5, 129.2, 133.8, 137.5 (d, J_{CF} = 3 Hz), 149.9 (d, J_{CF} = 10 Hz), 151.2 (d, J_{CF} = 281 Hz). ^{19}F NMR (94 MHz, $CDCl_3$−CCl_4) 28.3 (1F, s) ppm. IR (neat) 2980, 1615, 1600, 1510, 1480, 1455, 1380, 755, 690 cm^{-1}. MS (70 eV) m/z 294(M^+), 251(base peak), 148. Anal. Calcd for $C_{19}H_{19}N_2F$: C, 77.52; H, 6.51; N, 9.52. Found: C, 77.55; H, 6.61; N, 9.29.

4-Butyl-5-fluoro-3-phenyl-1-*p*-tolylpyrazole (2f). Compound **2f** was prepared by the method described for **2e** using butyllithium (1.42 mL, 1.63 M in hexane, 2.31 mmol), *p*-tolylhydrazine hydrochloride (182 mg, 1.15 mmol), and **1a** (124 mg, 0.55 mmol) in THF (5 mL). Purification by column chromatography on silica gel (hexane−ethyl acetate 15:1) gave **2f** (136 mg, 79%) as a yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.6 Hz), 1.36 (2H, tq, J = 7.6, 7.6 Hz), 1.58 (2H, tt, J = 7.6, 7.6 Hz), 2.37 (3H, s), 2.60 (2H, t, J = 7.6 Hz), 7.24 (2H, d, J = 8.2 Hz), 7.35 (1H, tt, J = 7.3, 1.6 Hz), 7.42 (2H, t, J = 7.3 Hz), 7.58 (2H, dd, J = 8.2, 1.7 Hz), 7.69 (2H, dd, J = 8.2, 1.2 Hz). ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.7 (d, J_{CF} = 4 Hz), 20.9 (d, J_{CF} = 4 Hz), 21.9 (d, J_{CF} = 2 Hz), 22.4, 31.7, 100.2 (d, J_{CF} = 12 Hz), 121.0, 127.5, 128.0, 128.4, 129.7 (d, J_{CF} = 4 Hz), 133.9, 135.0 (d, J_{CF} = 2 Hz), 136.6, 149.5 (d, J_{CF} = 11 Hz), 151.1 (d, J_{CF} = 280 Hz). ^{19}F NMR (94 MHz, $CDCl_3$) 28.3(1F, s) ppm. IR (neat) 2900, 1605, 1520, 1480, 1445, 1380, 770, 695 cm^{-1}. MS (70 eV) m/z 308 (M^+), 265, 105 (base peak), 91, 77. Anal. Calcd for $C_{20}H_{21}N_2F$: C, 77.89; H, 6.86; N, 9.08. Found: C, 77.78; H, 6.93; N, 8.98.

4-Butyl-3-cyclohexyl-5-fluoro-1-phenylpyrazole (2g). Compound **2g** was prepared by the method described for **2e** using butyllithium (0.55 mL, 1.69 M in hexane, 0.93 mmol), phenylhydrazine (101 mg, 0.93 mmol), and **1b** (107 mg, 0.47 mmol) in THF (7 mL). Purification by thin layer chromatography on silica gel (hexane−ethyl acetate 20:1) gave **2g** (119 mg, 85%) as a pale yellow solid. Mp 42−44 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.3 Hz), 1.24−1.43 (5H, m), 1.55 (2H, tt, J = 7.6, 7.6 Hz), 1.62 (2H, dddd, J = 12.5, 12.5, 12.5, 2.8 Hz), 1.73 (1H, br d, J = 12.1 Hz), 1.81−1.93 (4H, m), 2.40 (2H, t, J = 7.6 Hz), 2.57, (1H, tt, J = 11.9, 3.4 Hz), 7.24 (1H, t, J = 7.6 Hz), 7.41 (2H, t, J = 7.6 Hz), 7.61 (2H, d, J = 7.6 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 21.3 (d, J_{CF} = 3 Hz), 22.5, 26.1, 26.7, 32.1, 32.2, 37.4, 99.3 (d, J_{CF} = 12 Hz), 120.9 (d, J_{CF} = 4 Hz), 126.2, 129.1, 137.8 (d, J_{CF} = 3 Hz), 150.7 (d, J_{CF} = 279 Hz), 156.0 (d, J_{CF} = 9 Hz). ^{19}F NMR (94 MHz, $CDCl_3$) 27.8 (1F, s) ppm. IR (neat) 2930, 1620, 1600, 1515, 1480, 1455, 1400, 1360, 1300, 1115, 995, 755, 690 cm^{-1}. MS (70 eV) m/z 300 (M^+), 271, 257, 251, 245 (base peak), 77, 55. Anal. Calcd for $C_{19}H_{25}N_2F$: C, 75.96; H, 8.39; N, 9.32. Found: C, 75.99; H, 8.38; N, 9.19.

4-*sec*-Butyl-5-fluoro-1,3-diphenylpyrazole (2h). Compound **2h** was prepared by the method described for **2e** using butyllithium (0.63 mL, 1.63 M in hexane, 1.02 mmol), phenylhydrazine (110 mg, 1.02 mmol), and **1c** (115 mg, 0.51 mmol) in THF (5 mL). Purification by thin layer chromatography on silica gel (hexane−ethyl acetate 15:1) gave **2h** (115 mg, 76%) as a yellow liquid. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.4 Hz), 1.30 (3H, d, J = 7.3 Hz), 1.51−1.85 (2H, m), 2.80 (1H, tq, J = 7.3, 7.3 Hz), 7.20−7.53 (6H, m), 7.61 (2H, dd, J = 7.9, 1.3 Hz), 7.72 (2H, d, J = 7.9 Hz). ^{13}C NMR (68 MHz, $CDCl_3$) δ 12.3, 20.2, 29.4, 30.5 (d, J_{CF} = 4 Hz), 105.4 (d, J_{CF} = 10 Hz), 121.1 (d, J_{CF} = 4 Hz), 126.7, 128.1, 128.4, 128.4, 129.1, 133.8, 137.4 (d, J_{CF} = 3 Hz), 150.3 (d, J_{CF} = 11 Hz), 150.6 (d, J_{CF} = 282 Hz). ^{19}F NMR (94 MHz, $CDCl_3$) 31.7 (1F, s) ppm. IR (neat) 2975, 1605, 1515, 1460, 1385, 1130, 985, 765, 700 cm^{-1}. MS (70 eV) m/z (rel intensity) 294 (M^+; 27), 265 (100), 245 (22), 77 (39). Anal. Calcd for $C_{19}H_{19}N_2F$: C, 77.52; H, 6.51; N, 9.52. Found: C, 77.68; H, 6.56; N, 9.52.

4-Butyl-3-fluoro-5-phenylpyrazole (4a). To a solution of **1a** (85 mg, 0.38 mmol) and trifluoroacetic acid (128 mg, 1.13 mmol) in THF (30 mL) was added hydrazine monohydrate (58 mg, 1.15 mmol) at room temperature. After the mixture was stirred for 0.5 h at reflux, an additional hydrazine monohydrate (19 mg, 0.38 mmol) was added. The resulting mixture was refluxed for 0.5 h, and phosphate buffer (pH 7) was then added to quench the reaction. Organic materials were extracted with ethyl acetate three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane−ethyl acetate 5:1) to give **4a** (79 mg, 95%) as colorless crystals. Mp 93−95 °C (hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.6 Hz), 1.33 (2H, tq, J = 7.6, 7.6 Hz), 1.54 (2H, tt, J = 7.6, 7.6 Hz), 2.52 (2H, t, J = 7.6 Hz), 7.40−7.50 (5H, m), 9.96 (1H, br s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 21.3 (d, J_{CF} = 3 Hz), 22.4, 32.1, 101.8 (d, J_{CF} = 21 Hz), 127.3, 128.9, 129.1, 130.0, 141.6, 163.8 (d, J_{CF} = 244 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) 28.8 (1F, s) ppm. IR (KBr disk) 3150, 2975, 2900, 1535, 1510, 1485, 1310, 1280, 1160, 980, 760, 700 cm^{-1}. MS (70 eV) m/z (rel intensity) 218 (M^+; 28), 175 (100), 155 (14), 77 (14). Anal. Calcd for $C_{13}H_{15}N_2F$: C, 71.54; H, 6.93; N, 12.83. Found: C, 71.35; H, 6.95; N, 12.83.

4-Butyl-3-fluoro-1-methyl-5-phenylpyrazole (3a). Sodium hydride (16 mg, 60.4% dispersion in mineral oil, 0.40 mmol) was added to a solution of **4a** (80 mg, 0.37 mmol) in DMF (2.0 mL) at 0 °C under a nitrogen atmosphere. After the reaction mixture was stirred for 10 min, methyl iodide (57 mg, 0.40 mmol) was added at −45 °C. The resulting mixture was stirred for 1.5 h at −45 °C, and phosphate buffer (pH 7) was then added to quench the reaction. Organic materials were extracted with ethyl acetate three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue

was purified by thin layer chromatography on silica gel (hexane−ethyl acetate 5:1) to give **3a** and **2a** (82 mg, 97%, **3a**/**2a** = 97/3) as a pale yellow liquid. **3a:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (3H, t, J = 7.6 Hz), 1.24 (2H, tq, J = 7.6, 7.6 Hz), 1.42 (2H, tt, J = 7.6, 7.6 Hz), 2.30 (2H, t, J = 7.6 Hz), 3.59 (3H, d, J_{HF} = 0.6 Hz), 7.28−7.32 (2H, m), 7.42−7.50 (3H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 21.4 (d, J_{CF} = 3 Hz), 22.2, 32.2, 36.8, 102.4 (d, J_{CF} = 21 Hz), 128.7, 128.9, 129.7, 129.9, 142.5, 161.8 (d, J_{CF} = 243 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) 26.5 (1F, s) ppm. IR (neat) 2950, 2925, 2875, 1495, 1385, 1220, 1075, 1005, 770, 705 cm^{-1}. MS (70 eV) m/z (rel intensity) 232 (M^+; 32), 189 (100), 169 (9). Anal. Calcd for $C_{14}H_{17}N_2F$: C, 72.39; H, 7.38; N, 12.06. Found: C, 72.71; H, 7.37; N, 11.90.

1,4-Dibutyl-3-fluoro-5-phenylpyrazole (3b). Compound **3b** was prepared by the method described for **3a** using sodium hydride (17 mg, 60.4% dispersion in mineral oil, 0.44 mmol), **4a** (84 mg, 0.39 mmol), and butyl iodide (49 μL, 0.43 mmol) in DMF (3 mL). Purification by thin layer chromatography on silica gel (hexane−ethyl acetate 3:1) gave **3b** and **2b** (102 mg, 96%, **3b**/**2b** = 84/16) as a pale yellow liquid. **3b:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (3H, t, J = 7.4 Hz), 0.80 (3H, t, J = 7.4 Hz), 1.17 (2H, tq, J = 7.4, 7.4 Hz), 1.23 (2H, tq, J = 7.4, 7.4 Hz), 1.41 (2H, tt, J = 7.4, 7.4 Hz), 1.68 (2H, tt, J = 7.4, 7.4 Hz), 2.28 (2H, t, J = 7.4 Hz), 3.81 (2H, t, J = 7.4 Hz), 7.26−7.30 (2H, m), 7.41−7.49 (3H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.6, 13.7, 19.7, 21.3 (d, J_{CF} = 4 Hz), 22.2, 32.2, 32.3, 48.9, 102.2 (d, J_{CF} = 20 Hz), 128.7, 128.9, 129.8, 130.1, 142.5, 161.9 (d, J_{CF} = 243 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) 26.6 (1F, s) ppm. IR (neat) 2975, 2950, 2900, 1575, 1500, 1470, 1405, 1390, 1220, 770, 710 cm^{-1}. MS (70 eV) m/z 274 (M^+), 231 (base peak), 189, 175, 128, 77. Anal. Calcd for $C_{17}H_{23}N_2F$: C, 74.42; H, 8.45; N, 10.21. Found: C, 74.59; H, 8.63; N, 10.02.

1-Benzyl-4-butyl-3-fluoro-5-phenylpyrazole (3c). Compound **3c** was prepared by the method described for **3a** using sodium hydride (16 mg, 60.4% dispersion in mineral oil, 0.40 mmol), **4a** (80 mg, 0.37 mmol), and benzyl bromide (64 mg, 0.41 mmol) in DMF (2 mL). Purification by thin layer chromatography on silica gel (hexane−ethyl acetate 5:1) gave **3c** and **2c** (110 mg, 98%, **3c**/**2c** = 90/10) as a pale yellow liquid. **3c:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (3H, t, J = 7.4 Hz), 1.24 (2H, tq, J = 7.4 , 7.4 Hz), 1.43 (2H, tt, J = 7.4, 7.4 Hz), 2.30 (2H, t, J = 7.4 Hz), 5.03 (2H, s), 7.01 (2H, d, J = 7.5 Hz), 7.20−7.27 (5H, m), 7.39−7.43 (3H, m). ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.6, 21.3 (d, J_{CF} = 4 Hz), 22.1, 32.1, 52.8, 103.0 (d, J_{CF} = 21 Hz), 127.0, 127.4, 128.4, 128.6, 128.9, 129.7, 129.8, 137.2, 142.9, 162.1 (d, J_{CF} = 244 Hz). ^{19}F NMR (94 MHz, $CDCl_3$) 27.6 (1F, s) ppm. IR (neat) 2950, 2850, 1605, 1555, 1490, 1215, 1155, 1070, 765, 700 cm^{-1}. MS (70 eV) m/z (rel intensity) 308 (M^+; 32), 265 (73), 91 (100). Anal. Calcd for $C_{20}H_{21}N_2F$: C, 77.89; H, 6.86; N, 9.08. Found: C, 77.93; H, 7.06; N, 8.89.

1-Allyl-4-butyl-3-fluoro-5-phenylpyrazole (3d). Compound **3d** was prepared by the method described for **3a** using sodium hydride (15 mg, 60.4% dispersion in mineral oil, 0.37 mmol), **4a** (74 mg, 0.34 mmol), and allyl bromide (45 mg, 0.37 mmol) in DMF (2 mL). Purification by thin layer chromatography on silica gel (hexane−ethyl acetate 3:1) gave **3d** and **2d** (86 mg, 98%, **3d**/**2d** = 88/12) as a pale yellow liquid. **3d:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (3H, t, J = 7.5 Hz), 1.24 (2H, tq, J = 7.5, 7.5 Hz), 1.43 (2H, tt, J = 7.5, 7.5 Hz), 2.30 (2H, t, J = 7.5 Hz), 4.44 (2H, dddd, J = 5.3, 1.4, 1.4 Hz, J_{HF} = 1.4 Hz), 4.99 (1H, ddt, J = 17.1, 1.4, 1.4 Hz), 5.15 (1H, ddt, J = 10.2, 1.4, 1.4 Hz), 5.89 (1H, ddt, J = 17.1, 10.2, 5.3 Hz), 7.28−7.32 (2H, m), 7.42−7.48 (3H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 21.3 (d, J_{CF} = 3 Hz), 22.2, 32.2, 51.7, 102.8 (d, J_{CF} = 21 Hz), 117.5, 128.7, 129.0, 129.8, 129.8, 133.5, 142.7, 162.2 (d, J_{CF} = 244 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) 27.4 (1F, s) ppm. IR (neat) 2975, 2950, 2875, 1500, 1470, 1220, 995, 925, 770, 705, 670 cm^{-1}. MS (70 eV) m/z (rel intensity) 258 (M^+; 56), 215 (100), 184 (4), 155 (3), 77 (3). Anal. Calcd for $C_{16}H_{19}N_2F$: C, 74.39; H, 7.41; N, 10.84. Found: C, 74.39; H, 7.55; N, 10.63.

4-Butyl-3-fluoro-1-isopropyl-5-phenylpyrazole (3i). Compound **3i** was prepared by the method described for **3a** using sodium hydride (18 mg, 62.0% dispersion in mineral oil, 0.47 mmol), **4a** (91 mg, 0.42 mmol), and isopropyl iodide (46 μL, 0.46 mmol) in DMF (3 mL). Purification by thin layer chromatography on silica gel (hexane−ethyl acetate 5:1) gave **3i** and 4-butyl-5-fluoro-1-isopropyl-3-phenylpyrazole **2i** (97 mg, 89%, **3i**/**2i** = 64/36) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$, for 3/2 **3i**/**2i** mixture) δ 0.81 (1.8H, t, J = 7.4 Hz), 0.89 (1.2H, t, J = 7.6 Hz), 1.22 (1.2H, tq, J = 7.4, 7.4 Hz), 1.33 (0.8H, tq, J = 7.6, 7.6 Hz), 1.35 (3.6H, d, J = 6.7 Hz), 1.41 (1.2H, tt, J = 7.4, 7.4 Hz), 1.51 (2.4H, d, J = 6.7 Hz), 1.53 (0.8H, tt, J = 7.6, 7.6 Hz), 2.26 (1.2H, t, J = 7.4 Hz), 2.52 (0.8H, t, J = 7.6 Hz), 4.23 (0.6H, septd, J = 6.7 Hz, J_{HF} = 2.8 Hz), 4.51 (0.4H, sept, J = 6.7 Hz), 7.25−7.32 (1.6H, m), 7.38 (0.6H, t, J = 7.6 Hz), 7.41−7.49 (2.0H, m), 7.61 (0.8H, dd, J = 8.2, 1.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) **3i**: δ 13.7, 21.3 (d, J_{CF} = 3 Hz), 21.8, 22.5, 32.3, 49.9, 101.9 (d, J_{CF} = 21 Hz), 127.5, 128.7, 129.8, 130.2, 141.6, 162.0 (d, J_{CF} = 242 Hz); **2i**: δ 13.8, 22.1 (d, J_{CF} = 3 Hz), 22.2, 22.5, 32.0, 50.1, 98.4 (d, J_{CF} = 12 Hz), 127.5, 128.4, 128.9, 134.6, 147.9 (d, J_{CF} = 9 Hz), 151.0 (d, J_{CF} = 275 Hz). IR (neat) 3280, 2940, 1725, 1670, 1600, 1495, 1220, 1050, 960, 850, 760, 700 cm^{-1}. MS (70 eV) m/z (rel intensity) **3i**: 260 (M^+; 42), 245 (14), 217 (100), 175 (93), 155 (14), 128 (10); **2i**: 260 (M^+; 46), 245 (36), 217 (83), 175 (100), 155 (13), 128 (10). HRMS **3i**: Calcd for $C_{16}H_{21}N_2F$ 260.1689 (M^+); found 260.1685; **2i**: Calcd for $C_{16}H_{21}N_2F$ 260.1689 (M^+); found 260.1648. Anal. Calcd for $C_{16}H_{21}N_2F$: C, 73.81; H, 8.13; N, 10.76. Found: C, 73.76; H, 7.87; N, 10.48.

4-Butyl-3-fluoro-1-*p*-nitrophenyl-5-phenylpyrazole (3j). Compound **3j** was prepared by the method described for **3a** using sodium hydride (20 mg, 62.0% dispersion in mineral oil, 0.51 mmol), **4a** (101 mg, 0.46 mmol), and *p*-fluoronitrobenzene (54 μL, 0.51 mmol) in DMF (3 mL). Purification by thin layer chromatography on silica gel (hexane−ethyl acetate 20:1) gave **3j** and 4-butyl-5-fluoro-1-(*p*-nitrophenyl)-3-phenylpyrazole (**2j**) (151 mg, 96%, **3j**/**2j** = 68/32) as a pale yellow liquid. **3j:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (3H, t, J = 7.5 Hz), 1.29 (2H, tq, J = 7.5, 7.5 Hz), 1.50 (2H, tt, J = 7.5, 7.5 Hz), 2.40 (2H, t, J = 7.5 Hz), 7.21−7.24 (2H, m), 7.29−7.33 (2H, m), 7.41−7.49 (3H, m), 8.07−8.11 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 21.3 (d, J_{CF} = 3 Hz), 22.3, 31.9, 107.8 (d, J_{CF} = 21 Hz), 123.4, 124.4, 129.2, 129.6, 129.7, 142.2, 144.4, 145.3, 164.4 (d, J_{CF} = 249 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) 31.0 (1F, s) ppm. IR (neat) 2925, 1595, 1495, 1335, 1110, 960, 855, 750, 700 cm^{-1}. MS (70 eV) m/z (rel intensity) 339 (M^+; 25), 296 (100), 250 (21), 77 (8). Anal. Calcd for $C_{19}H_{18}N_3O_2F$: C, 67.25; H, 5.35; N, 12.38. Found: C, 67.53; H, 5.58; N, 12.05. **2j:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 7.5 Hz), 1.38 (2H, tq, J = 7.5, 7.5 Hz), 1.59 (2H, tt, J = 7.5, 7.5 Hz), 2.63 (2H, t, J = 7.5 Hz), 7.40−7.50 (3H, m), 7.68−7.72 (2H, m), 7.95−8.00 (2H, m), 8.32−8.36 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 21.9 (d, J_{CF} = 3 Hz), 22.4, 31.5, 102.2 (d, J_{CF} = 13 Hz), 119.9 (d, J_{CF} = 6 Hz), 125.1, 127.6, 128.7, 128.8, 133.0, 142.4 (d, J_{CF} = 3 Hz), 145.4, 151.7 (d, J_{CF} = 283 Hz), 151.8 (d, J_{CF} = 10 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) 31.3 (1F, s) ppm. IR (neat) 2925, 1665, 1595, 1510, 1340, 1110, 855, 750 cm^{-1}. MS (70 eV) m/z (rel intensity) 339 (M^+; 78), 296 (100), 249 (72), 149 (25), 77 (50). HRMS calcd for $C_{19}H_{18}N_3O_2F$ 339.1383 (M^+); found 339.1394.

Methylation of 4-Butyl-3(5)-phenylpyrazole (7a). 4-Butyl-1-methyl-3-phenylpyrazole (**8a**) and 4-butyl-1-methyl-5-phenylpyrazole (**9a**) were prepared by the method described for **3a** using sodium hydride (18 mg, 62.0% dispersion in mineral oil, 0.46 mmol), **7a** (81 mg, 0.41 mmol), and methyl iodide (28 μL, 0.45 mmol) in DMF (3 mL). Purification by thin layer chromatography on silica gel (hexane−ethyl acetate 3:1) gave **8a** and **9a** (61 mg, 70%, **8a**/**9a** = 55/45) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$, for 6/4 **8a**/**9a** mixture) δ 0.83 (1.2H, t, J = 7.4 Hz), 0.90 (1.8H, t, J = 7.4 Hz), 1.27 (0.8H, tq, J = 7.4, 7.4 Hz), 1.37 (1.2H, tq, J = 7.4, 7.4 Hz), 1.46 (0.8H, tt, J = 7.4, 7.4 Hz), 1.55 (1.2H, tt, J = 7.4, 7.4 Hz), 2.36 (0.8H, t, J = 7.4 Hz), 2.60 (1.2H, t, J = 7.4 Hz), 3.72 (1.2H, s), 3.88 (1.8H, s), 7.19 (0.6H, s), 7.27−7.32 (1.4H, m), 7.36−7.42 (2.0H, m), 7.45 (0.8H, tt, J = 7.3, 1.8 Hz), 7.62 (1.2H, dd, J = 8.2, 1.2 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) **8a**: δ 13.9, 22.5, 24.2, 32.8, 38.8, 119.6, 127.1, 127.7, 128.3, 129.7, 134.4, 149.6; **9a**: δ 13.8, 22.3, 23.6, 33.1, 37.1, 120.1, 128.3, 128.6, 129.8, 130.7, 138.1, 140.5 IR (neat) 2920, 2850, 1730, 1605, 1450, 1175, 1025, 990, 780, 700 cm^{-1}. MS (70 eV) m/z (rel intensity) **8a**: 214 (M^+;

28), 171 (100), 130 (15), 103 (8), 77 (17); **9a**: 214 (M^+; 21), 171 (100), 144 (11), 115 (18), 103 (12), 77 (16). HRMS **8a**: Calcd for $C_{14}H_{18}N_2$ 214.1470 (M^+); found 214.1493; **9a**: Calcd for $C_{14}H_{18}N_2$ 214.1470 (M^+); found 214.1471.

Isopropylation of 7a. 4-Butyl-1-isopropyl-3-phenylpyrazole (**8i**) and 4-butyl-1-isopropyl-5-phenylpyrazole (**9i**) were prepared by the method described for **3a** using sodium hydride (14 mg, 62.0% dispersion in mineral oil, 0.35 mmol), **7a** (64 mg, 0.32 mmol), and isopropyl iodide (35 μL, 0.35 mmol) in DMF (3 mL). Purification by thin layer chromatography on silica gel (hexane−ethyl acetate 3:1) gave **8i** and **9i** (53 mg, 68%, **8i**/**9i** = 78/22) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$, for 8/2 **8i**/**9i** mixture) δ 0.82 (0.6H, t, J = 7.4 Hz), 0.91 (2.4H, t, J = 7.4 Hz), 1.26 (0.4H, tq, J = 7.4, 7.4 Hz), 1.37 (1.6H, tq, J = 7.4, 7.4 Hz), 1.41 (1.2H, d, J = 6.4 Hz), 1.45 (0.4H, tt, J = 7.4, 7.4 Hz), 1.52 (4.8H, d, J = 6.7 Hz), 1.56 (1.6H, tt, J = 7.4, 7.4 Hz), 2.32 (0.4H, t, J = 7.4 Hz), 2.61 (1.6H, t, J = 7.4 Hz), 4.32 (0.2H, sept, J = 6.4 Hz), 4.49 (0.8H, sept, J = 6.7 Hz), 7.25−7.31 (1.2H, m), 7.39 (0.8H, s), 7.36−7.47 (2.4H, m), 7.64 (1.6H, dd, J = 8.1, 1.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) **8i**: δ 13.9, 22.6, 23.0, 24.4, 32.7, 53.5, 118.9, 125.5, 126.9, 127.7, 128.2, 134.6, 148.6; **9i**: δ 13.8, 22.3, 22.8, 23.4, 33.1, 49.8, 119.5, 128.2, 128.5, 129.9, 131.0, 138.0, 139.5 IR (neat) 2930, 2860, 1730, 1605, 1450, 1370, 1350, 1265, 1180, 1020, 1005, 770, 700 cm^{-1}. MS (70 eV) m/z (rel intensity) **8i**: 242 (M^+; 42), 199 (100), 157 (94), 130 (19), 77 (11); **9i**: 242 (M^+; 21), 199 (100), 157 (77), 130 (17), 77 (11). HRMS **8i**: Calcd for $C_{16}H_{22}N_2$ 242.1783 (M^+); found 242.1744; **9i**: Calcd for $C_{16}H_{22}N_2$ 242.1783 (M^+); found 242.1819.

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