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# Construction of fluorinated pyrazole derivatives via a one-pot tandem C–H insertion/electrophilic fluorination reaction

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ABSTRACT

A series of 4-fluoro-pyrazole derivatives were synthesized in moderate to good yields via a one-pot tandem procedure involving an $Rh_2(OAc)_4$-catalyzed C–H insertion and an electrophilic fluorination with *N*-fluorobenzenesulfonimide (NFSI).



## 1. Introduction

Pyrazoles are a type of valuable azaheterocyclic compounds occurring in numerous natural and biologically active compounds with a wide range of pharmaceutical properties.[1] Many of these compounds have been developed as anti-inflammatory, anti-platelet, analgesic, anti-bacterial, and anti-cancer agents in the pharmaceutical industry.[2] Therefore, the development of efficient synthetic methods for the synthesis of this class of azaheterocycles has been an intriguing field in organic chemistry.

On the other hand, the unique properties of the fluorine atom have made the introduction of fluorine to organic molecule almost a routine work in medicinal chemistry and related fields.[3] In this context, numerous electrophilic fluorinating agents with an N–F subunit structure have been developed.[4] Particularly, over the past decades, *N*-fluorobenzenesulfonimide (NFSI) has emerged as a very important electrophilic fluorinating reagent since its appearance in 1987.[5,6] Our group has been interested in the development of tandem processes involving electrophilic fluorination to synthesize a range of fluorinated compounds.[7] Moreover, Zhu's group have recently developed $Rh_2(OAc)_4$-catalyzed C–H insertion reactions of 3-trifluoromethyl-4-diazo pyrazolinone with arenes for the formation of substituted pyrazole derivatives.[8] We then reasoned that if an electrophilic fluorinating agent was added after the C–H insertion, novel fluorinated pyrazole derivatives would be formed (Scheme 1). Herein, we present a tandem $Rh_2(OAc)_4$-catalyzed C–H insertion/electrophilic fluorinating approach to substituted fluorinated pyrazole derivatives.

## 2. Results and discussion

Pyrazole diazo compounds were prepared by diazo-transfer reaction from the corresponding 1-phenyl-2-pyrazolin-5-one.[9] The reaction between 3-trifluoromethyl-4-diazo pyrazolinone **1a** with 1,3-dimethoxybenzene **2b** was selected as the model reaction. Our initial attempts to find a cheaper metal catalyst to replace the expensive $Rh_2(OAc)_4$ to catalyze the C–H insertion step failed: no reaction took place with metal catalyst, such as CuBr, $Cu(OTf)_2$ or $Sc(OTf)_3$ (Table 1, entries 1–3).[10] Under the catalysis of 1 mol % of $Rh_2(OAc)_4$, the insertion step could complete after 3 h with the arene **2b** as the solvent. Several other solvents, such as $PhCF_3$, MeCN, DMSO, and DMF were also investigated with inferior results. For the electrophilic fluorination step, two commercial fluorinating reagents, both Selectfluor and NFSI were tested. When the more reactive Selectfluor was used, the reaction completed within 0.5 h to provide the corresponding fluorinated product in a moderate yield (Table 1, entry 4). In the case of NFSI, a base additive was required for the reaction to proceed, and the use of 1.1 equiv $K_2CO_3$ turn out to be the most suitable condition to give a yield of 67% (Table 1, entries 5–8). Lower temperature for the electrophilic

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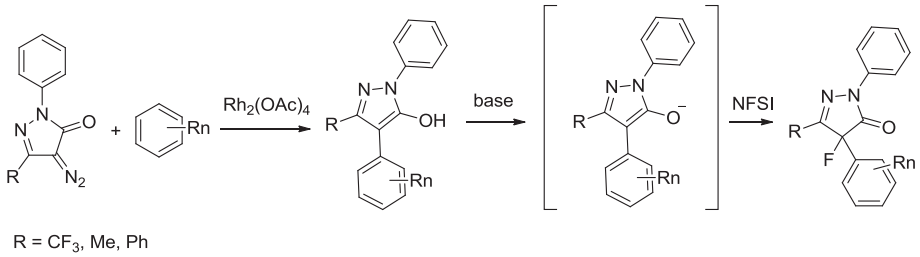
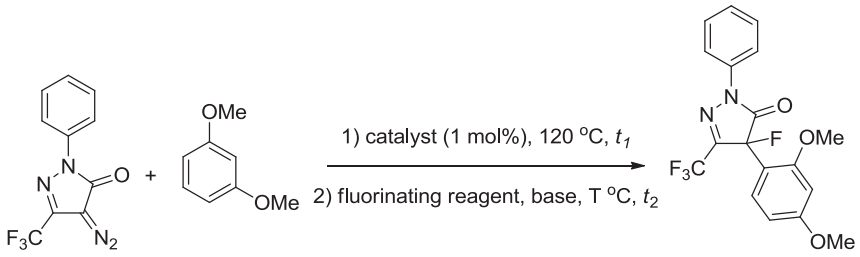



**Scheme 1.** Tandem $Rh_2(OAc)_4$-catalyzed C–H insertion/electrophilic fluorination reaction to give fluorinated pyrazole derivatives.

**Table 1**
Optimization of reaction conditions[a]




**1a** **2b** **3ab**

| Entry | Catalyst | Fluorinating reagent | Base | T | $t_1$[b] | $t_2$[c] | Yield[d] (%) |
|---|---|---|---|---|---|---|---|
| 1 | CuBr | — | — | — | 10 h | — | NR[e] |
| 2 | $Cu(OTf)_2$ | — | — | — | 10 h | — | NR[e] |
| 3 | $Sc(OTf)_3$ | — | — | — | 10 h | — | NR[e] |
| 4 | $Rh_2(OAc)_4$ | Selectfluor | — | rt | 3 h | 0.5 h | 53 |
| 5 | $Rh_2(OAc)_4$ | NFSI | — | rt | 3 h | — | NR[f] |
| 6 | $Rh_2(OAc)_4$ | NFSI | NaOH | rt | 3 h | 10 min | 32 |
| 7 | $Rh_2(OAc)_4$ | NFSI | $K_2CO_3$ | rt | 3 h | 1.5 h | 67 |
| 8 | $Rh_2(OAc)_4$ | NFSI | KOAc | rt | 3 h | 6 h | 61 |
| 9 | $Rh_2(OAc)_4$ | NFSI | $K_2CO_3$ | 0 °C | 3 h | 3 h | 64 |
| 10 | $Rh_2(OAc)_4$ | NFSI | $K_2CO_3$ | −20 °C | 3 h | 5 h | 69 |

[a] The reaction was carried out with **1a** (0.2 mmol), **2b** (3 mL), and catalyst (0.002 mmol) at 120 °C, after completion of the C–H insertion step, the reaction mixture was cooled to room temperature and Selectfluor or NFSI (1.1 equiv), base (1.1 equiv) were added.
[b] The reaction time of the C–H insertion step.
[c] The reaction time of the electrophilic fluorination step.
[d] Isolated yield.
[e] NR: no reaction.
[f] NR: no reaction occurred for the electrophilic fluorination step.

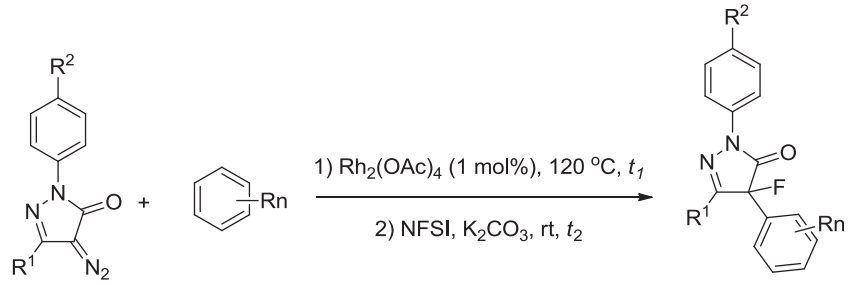
fluorination step contributed no significant improvement to the final yield. Then we conducted the tandem reaction stepwise. It's worth mentioning that with the optimized conditions (Table 1, entry 7), the overall yield of the tandem reaction mainly depended on the yield of the first C–H insertion step in that the isolated yield of insertion step was almost equivalent to the overall yield and independent treatment of the isolated intermediate with NFSI and $K_2CO_3$ gave almost quantitative yield of the final product **3ab**.

With the optimized reaction conditions established, the scope of the reaction was explored (Table 2). Three different 3-substituted diazo compounds **1a**–**1c** and several different electron-rich arenes were investigated in the reaction. Notably, as reported, the C–H insertion step could not take place between the diazo compound and an arene with electron-withdrawing substituents.[8] Except for the bulky mesitylene (Table 2, entries 5, 10, and 15), all the arenes examined participated well in the reaction to furnish the corresponding 4-fluoro-pyrazole derivatives in moderate to good yield. The variation in the structure of diazo **1** also showed little influence in the reaction result as similar yields were observed for the three diazo substrates. The most of the insertion reactions took place in the *ortho*-position of methoxy and methyl except anisole, which we could only obtain a *para*-position insertion product. Notably, when the substrate 4-methylanisole (**2c**), the C–H insertion occurred preferably at the *ortho*-position of the methoxy group (Table 2, entries 3, 8, and 13). It is assumed that the electron-deficient diazo compounds of 3-trifluoromethyl-4-diazopyrazolinones catalyzed by $Rh_2(OAc)_4$ could in situ generate the corresponding reactive metal-carbene intermediate to occur the regioselective C–H insertion on *ortho*-position at electronic-rich benzene ring.

Some other electron-rich arenes or heteroarenes such as naphthalene, indole, and pyrrole were found to be not compatible with this tandem system under the optimized conditions, probably due to the relatively high reactivity of these arenes toward the electrophilic fluorinating reagent NFSI. For example, the reaction between pyrazolinone **1a** and indole could give the C–H insertion product **3ag** uneventfully, while the ensuing electrophilic fluorination step with NFSI gave a complicated system (Scheme 2).

Preliminary studies were also done to probe the possibility of achieving enantiocontrol in this protocol. A screen of several chiral cinchona alkaloids as the base for the electrophilic fluorination step revealed that the use of 1.0 equiv amount of cinchonidine would give a modest ee value of 61% for product **3aa**, and the chiral alkaloid could easily be recovered and reused. To confirm the absolute configuration of product **3** and verify the fluorinating reaction site at 4-methylanisole ulteriorly, we also conduct the reaction of 4-bromophenyl pyrazolinone **1d** with 4-methylanisole **2c** to obtain a modest ee value of 53% using the same chiral base (Scheme 3). After twice recrystallization, an almost optically pure single crystal

**Table 2**
Scope of tandem $Rh_2(OAc)_4$-catalyzed C–H insertion/electrophilic fluorination reaction[a]

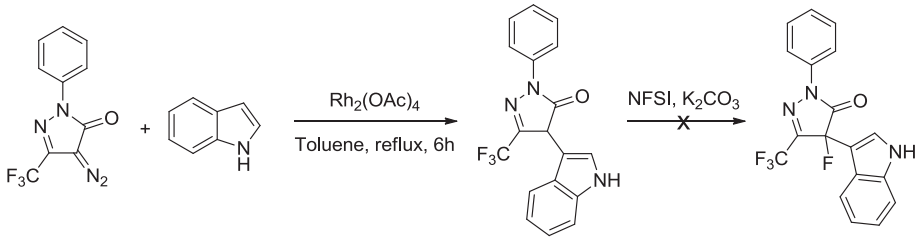



**1** **2(a-e)** **3**

$R^1 = CF_3$, $R^2$ = H **1a**
$R^1$ = Me, $R^2$ = H **1b**
$R^1$ = Ph, $R^2$ = H **1c**
$R^1 = CF_3$, $R^2$ = Br **1d**

| Entry | 1 | 2 | $t_1$[b] (h) | $t_2$[c] (h) | 3 | Yield[d] (%) |
|---|---|---|---|---|---|---|
| 1 | **1a** | Anisole **2a** | 5 | 2 | **3aa** | 59 |
| 2 | **1a** | 1,3-Dimethoxybenzene **2b** | 3 | 1.5 | **3ab** | 67 |
| 3 | **1a** | 4-Methylanisole **2c** | 3 | 1 | **3ac** | 76 |
| 4 | **1a** | *p*-Xylene **2d** | 8 | 3 | **3ad** | 51 |
| 5 | **1a** | Mesitylene **2e** | 12 | 18 | **3ae** | 9 |
| 6 | **1b** | Anisole **2a** | 3 | 2 | **3ba** | 68 |
| 7 | **1b** | 1,3-Dimethoxybenzene **2b** | 1.5 | 2 | **3bb** | 73 |
| 8 | **1b** | 4-Methylanisole **2c** | 2 | 1.5 | **3bc** | 86 |
| 9 | **1b** | *p*-Xylene **2d** | 5 | 6 | **3bd** | 64 |
| 10 | **1b** | Mesitylene **2e** | 6 | — | ND[e] | — |
| 11 | **1c** | Anisole **2a** | 3 | 3 | **3ca** | 65 |
| 12 | **1c** | 1,3-Dimethoxybenzene **2b** | 2 | 3 | **3cb** | 73 |
| 13 | **1c** | 4-Methylanisole **2c** | 2 | 2 | **3cc** | 83 |
| 14 | **1c** | *p*-Xylene **2d** | 7 | 7 | **3cd** | 59 |
| 15 | **1c** | Mesitylene **2e** | 8 | — | NR | — |
| 16 | **1d** | 4-Methylanisole **2c** | 3 | 1 | **3dc** | 83 |

[a] The reaction was carried out with **1** (0.2 mmol), **2** (3 mL) and catalyst (0.002 mmol) at 120 °C, after completion of the C–H insertion step, the reaction mixture was cooled to room temperature and NFSI (69 mg, 0.22 mmol) and $K_2CO_3$ (30 mg, 0.22 mmol) were added.
[b] The reaction time of the C–H insertion step.
[c] The reaction time of the electrophilic fluorination step.
[d] Yield of the isolated product after column chromatography on silica gel.
[e] ND : No desirable product was detected.




**1a** **3ag**

yield: 71%

**Scheme 2.** The reaction of 3-trifluoromethyl-4-diazo pyrazolinone **1c** with indole.

could be obtained and the structure was unambiguously confirmed by X-ray cyrstallographic analysis[11] (Fig 1). The C–Br···F distance is 3.231 Å. This distance is slightly shorter than the sum of the van der waals radii of Br (1.85 Å) and F (1.47 Å),[12] which indicated a weaker intermolecular halogen bond interaction.

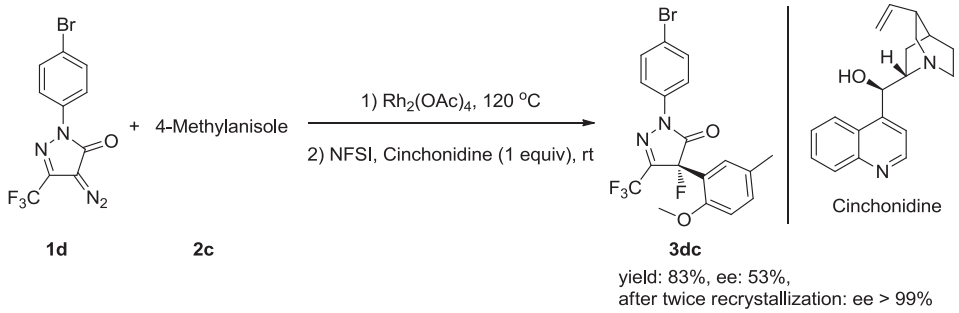
## 3. Conclusion

In summary, we developed a novel one-pot tandem $Rh_2(OAc)_4$-catalyzed C–H insertion/electrophilic fluorination protocol for synthesizing a series of 4-fluoro-pyrazole derivatives. Preliminary study on the asymmetric version of this protocol was also performed to give a modest ee value and efforts toward the improvement of the enantioselectivity are underway in our laboratory.

## 4. Experimental

### 4.1. General information

The starting materials pyrazolinones **1** were prepared according to known procedures.[13] Melting points were measured on Temp-Melt apparatus and uncorrected. $^1H$ and $^{19}F$ NMR spectra




**Scheme 3.** Cinchonidine-promoted asymmetric synthesis of **3dc**.

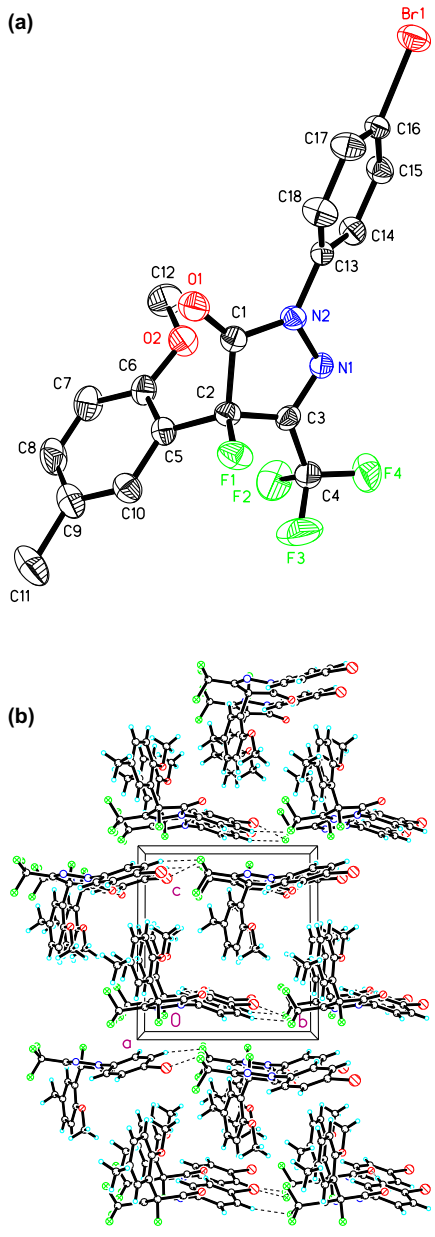


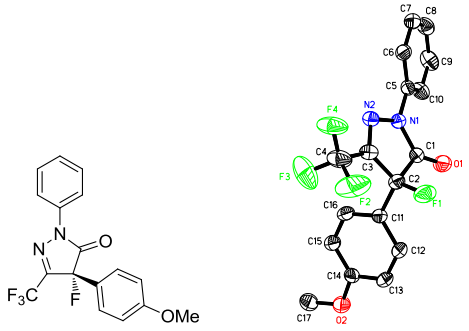

**Fig. 1.** (a) X-ray crystal structure of **3dc**. (b) Packing map of **3dc**. The fluorine atoms are green, and the bromine atoms are red. The intermolecular C–Br···F interaction are shown using dashed lines.

were recorded in $CDCl_3$ on Bruker AM-300 or AM-400 instruments with $Me_4Si$ and $CFCl_3$ (with upfield negative) as the internal and external standards, respectively. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Low-resolution mass spectra or high-resolution mass spectra (HRMS) were recorded on an HP-5989A spectrometer. Analytical high performance liquid chromatography (HPLC) was carried out on SHIMADZU equipment using chiral columns. Optical rotations were measured on a JASCO P-1010 Polarimeter at $\lambda$=589 nm. X-ray diffraction crystal structure analysis was obtained on Bruker P4 instrument. All reactions as well as column chromatography were monitored routinely with the aid of TLC or $^{19}F$ NMR spectroscopy.

## 4.2. Typical experimental procedures

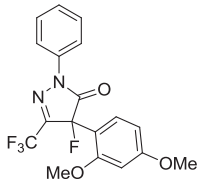
4-Diazo pyrazolinone (0.2 mmol) **1** and $Rh_2(OAc)_4$ (1 mg, 0.002 mmol) were dissolved in arene **2** (3 mL). The reaction mixture was stirred at 120 °C under nitrogen atmosphere until the disappearance of **1** as monitored by TLC. Then the mixture was cooled down to room temperature and NFSI (69 mg, 0.22 mmol), $K_2CO_3$ (30 mg, 0.22 mmol) were added rapidly. When the reaction completed, the solvent was removed in vacuum and the residue was purified on silica gel using petroleum ether/ethyl acetate (20:1) as eluent to afford the corresponding products **3**.

*4.2.1. (R)-4-Fluoro-4-(4-methoxyphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one (**3aa**).*



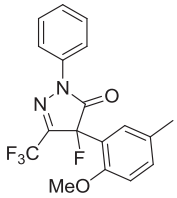

Yield: 59%; yellow solid; $[\alpha]_D^{26}$ 94.9 (*c* 0.25, $CHCl_3$); mp 88–89 °C; IR (neat): $\nu$ 3074, 2936, 2827, 1757, 1610, 1500, 1153, 756 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.84 (d, $J$=7.9 Hz, 2H), 7.47 (t, $J$=8.0 Hz, 2H), 7.36 (d, $J$=8.8 Hz, 2H), 7.32 (t, $J$=7.5 Hz, 1H), 3.84 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 166.81 (d, $^2J_{C-F}$=22.0 Hz), 161.35, 146.51 (qd, $^2J_{C-F}$=38.7 Hz, $^2J_{C-F}$=16.7 Hz), 136.36, 129.26, 126.88, 126.95, 121.54 (d, $^2J_{C-F}$=25.8 Hz), 119.08, 118.48 (q, $^1J_{C-F}$=271.8 Hz), 114.86, 92.10 (d, $^1J_{C-F}$=199.7 Hz), 55.39; $^{19}F$ NMR (282.3 MHz, $CDCl_3$): $\delta$ −64.22 (s, 3F), −166.63 (s, 1F); HRMS (ESI) *m/z* calcd for $C_{17}H_{12}F_4N_2O_2$ $[(M+Na)^+]$: 375.0738; found: 375.0727. Enantiomeric excess: 61%, determined by HPLC (Chiralpak AS-H column, hexane/*i*-PrOH=98:2, $\lambda$=254 nm, flow rate=0.5 mL/min; $t_R$ (minor)=11.4 min; $t_R$ (major)=12.1 min).

*4.2.2. 4-(2,4-Dimethoxyphenyl)-4-fluoro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one (**3ab**).*



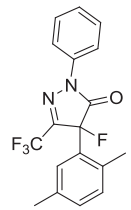
Yield: 67%; yellow solid; mp 81–82 °C; IR (neat): $\nu$ 3017, 2954, 2839, 1766, 1614, 1503, 1152, 756 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.84 (d, $J$=10.4 Hz, 2H), 7.58 (d, $J$=11.4 Hz, 1H), 7.48 (t, $J$=10.5 Hz, 2H), 7.31 (t, $J$=9.88 Hz, 1H), 6.66 (dd, $J$=2.8, 11.6 Hz, 1H), 6.45 (s, 1H), 3.83 (s, 3H), 3.64 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 166.35 (d, $^2J_{C-F}$=19.0 Hz), 162.12, 155.82, 142.30 (qd, $^2J_{C-F}$=37.9 Hz, $^2J_{C-F}$=16.4 Hz), 136.31, 128.68, 126.82 (d, $^1J_{C-F}$=12.0 Hz), 125.98, 118.66, 118.14 (q, $^1J_{C-F}$=271.4 Hz), 111.00, 105.26, 98.30, 89.70 (d, $^1J_{C-F}$=188.7 Hz), 55.34, 54.97; $^{19}F$ NMR (282.3 MHz, $CDCl_3$): $\delta$ −65.75 (s, 3F), −171.64 (s, 1F); HRMS (ESI) $m/z$ calcd for $C_{18}H_{14}F_4N_2O_3$ [$(M+Na)^+$]: 405.0834; found: 405.0833.

*4.2.3. 4-Fluoro-4-(2-methoxy-5-methylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one (**3ac**).*



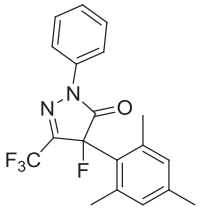
Yield: 76%; white solid; mp 96–97 °C; IR (neat): $\nu$ 3032, 2959, 2850, 1745, 1598, 1503, 1139, 762 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.85 (d, $J$=8.32 Hz, 2H), 7.50–7.48 (m, 3H), 7.32 (t, $J$=14.84 Hz, 1H), 7.23 (dd, $J$=1.32, 8.36 Hz, 1H), 6.80 (d, $J$=8.32 Hz, 1H), 3.63 (s, 3H), 2.39 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 166.76 (d, $^2J_{C-F}$=18.8 Hz), 153.14 (d, $^3J_{C-F}$=6.1 Hz), 143.53 (qd, $^2J_{C-F}$=38.1 Hz, $^2J_{C-F}$=16.0 Hz), 136.83, 131.87, 131.26, 129.22, 126.74 (d, $^2J_{C-F}$=12.0 Hz), 126.56, 119.24, 119.00, 118.67 (q, $^1J_{C-F}$=271.0 Hz), 110.97, 90.20 (d, $^1J_{C-F}$=189.1 Hz), 55.94, 20.68; $^{19}F$ NMR (282.3 MHz, $CDCl_3$): $\delta$ −65.70 (s, 3F), −171.89 (s, 1F); HRMS (ESI) $m/z$ calcd for $C_{18}H_{14}F_4N_2O_2$ [$(M+Na)^+$]: 389.0870; found: 389.0884.

*4.2.4. 4-(2,5-Dimethylphenyl)-4-fluoro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one (**3ad**).*



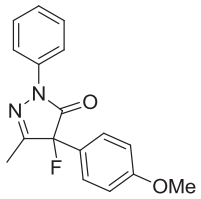
Yield: 51%; white solid; mp 78–79 °C; IR (neat): $\nu$ 3069, 2919, 2867, 1766, 1598, 1500, 1153, 759 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.88 (d, $J$=8.3 Hz, 2H), 7.51–7.48 (m, 3H), 7.35 (t, $J$=7.4 Hz, 1H), 7.19 (d, $J$=7.7 Hz, 1H), 7.11 (d, $J$=7.7 Hz, 1H), 2.40 (s, 3H), 2.13 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 166.21 (d, $^2J_{C-F}$=19.7 Hz), 144.81 (qd, $^2J_{C-F}$=38.3 Hz, $^2J_{C-F}$=16.1 Hz), 136.58, 136.39, 131.94, 131.05, 129.35, 127.74 (d, $^2J_{C-F}$=23.21 Hz), 127.01, 126.01, 125.86, 119.20, 118.46 (q, $^1J_{C-F}$=271.5 Hz), 91.70 (d, $^1J_{C-F}$=189.91 Hz), 21.09, 18.30; $^{19}F$ NMR (282.3 MHz, $CDCl_3$): $\delta$ −65.42 (s, 3F), −164.24 (s, 1F); HRMS (ESI) $m/z$ calcd for $C_{18}H_{14}F_4N_2O$ [$(M+Na)^+$]: 373.0937; found: 373.0934.

*4.2.5. 4-Fluoro-4-mesityl-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one (**3ae**).*



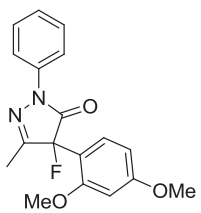
Yield: 9%; white solid; mp 67–68 °C; IR (neat): $\nu$ 2964, 2925, 1763, 1610, 1500, 1400, 1292, 1149, 1106, 758 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.85 (d, $J$=8.0 Hz, 2H), 7.49 (t, $J$=8.0 Hz, 2H), 7.33 (t, $J$=7.4 Hz, 1H), 6.96 (s, 1H), 6.82 (s, 1H), 2.56 (d, $J$=11.2 Hz, 3H), 2.28 (s, 3H), 1.96 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 166.58 (d, $^2J_{C-F}$=19.2 Hz), 144.46 (qd, $^2J_{C-F}$=38.3 Hz, $^2J_{C-F}$=15.3 Hz), 139.30 (d, $^2J_{C-F}$=49.8 Hz), 136.42, 133.97, 132.91, 130.62, 129.26, 126.95, 123.73, 119.18, 118.60 (q, $^1J_{C-F}$=271.1 Hz), 20.70, 19.56; $^{19}F$ NMR (282.3 MHz, $CDCl_3$): $\delta$ −65.73 (s, 3F), −157.62 (dd, $J$=11.3, 22.66 Hz, 1F); HRMS (ESI) $m/z$ calcd for $C_{19}H_{16}F_4N_2O$ [$(M+Na)^+$]: 387.1104, found: 387.1091.

*4.2.6. 4-Fluoro-4-(4-methoxyphenyl)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**3ba**).*



Yield: 68%; yellow solid; mp 58–59 °C; IR (neat): $\nu$ 3057, 2960, 2833, 1731, 1596, 1501, 1179, 756 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.91 (d, $J$=8 Hz, 2H), 7.43 (t, $J$=8 Hz, 2H), 7.33 (d, $J$=8.8 Hz, 2H), 7.22 (t, $J$=7.4 Hz, 1H), 6.98 (d, $J$=8.8 Hz, 2H), 3.82 (s, 3H), 2.17 (d, $J$=1.6 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 167.98 (d, $^2J_{C-F}$=22.8 Hz), 160.87, 158.15 (d, $^2J_{C-F}$=16.7 Hz), 137.49, 128.98, 126.10, 125.52, 123.75 (d, $^2J_{C-F}$=25.8 Hz), 118.60, 114.77, 94.42 (d, $^1J_{C-F}$=193.6 Hz), 55.39, 13.28; $^{19}F$ NMR (282.3 MHz, $CDCl_3$): $\delta$ −169.53 (s, 1F); HRMS (ESI) $m/z$ calcd for $C_{17}H_{15}FN_2O_2$ [$(M+Na)^+$]: 299.1182; found: 299.1190.

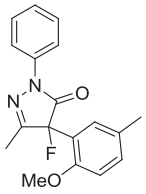
*4.2.7. 4-(2,4-Dimethoxyphenyl)-4-fluoro-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**3bb**).*



Yield: 73%; yellow solid; mp 87–88 °C; IR (neat): $\nu$ 3069, 2971, 2827, 1735, 1596, 1501, 1210, 757 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.90 (d, $J$=11.2 Hz, 2H), 7.55 (d, $J$=11.6 Hz, 1H), 7.43 (t, $J$=10.4 Hz, 2H), 7.21 (t, $J$=9.8 Hz, 1H), 6.63 (dd, $J$=2.0, 11.2 Hz, 1H), 6.43 (s, 1H),

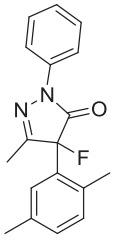
3.82 (s, 3H), 3.61 (s, 3H), 1.98 (d, $J$=2.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 167.88 (d, $^2J_{C-F}$=19.7 Hz), 162.11, 156.38, 155.54 (d, $^2J_{C-F}$=15.9 Hz), 137.851, 128.92, 127.23, 125.13, 118.64, 113.50 (d, $^2J_{C-F}$=25.0 Hz), 105.34, 98.87, 93.17 (d, $^1J_{C-F}$=183.8 Hz), 55.86, 55.49, 12.91; $^{19}$F NMR (282.3 MHz, $CDCl_3$): $\delta$ −173.39 (s, 1F); HRMS (ESI) $m/z$ calcd for $C_{18}H_{17}FN_2O_3$ [(M+H)$^+$]: 329.1299; found: 329.1296.

*4.2.8. 4-Fluoro-4-(2-methoxy-5-methylphenyl)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**3bc**).*



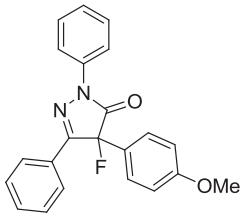
Yield: 86%; white solid; mp 109–110 °C; IR (neat): $\nu$ 3005, 2954, 2833, 1732, 1595, 1501, 1263, 759 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.93 (d, $J$=8.4 Hz, 2H), 7.47–7.42 (m, 3H), 7.22 (t, $J$=7.5 Hz, 1H), 7.19 (dd, $J$=1.6, 8.4 Hz, 1H), 3.59 (s, 3H), 2.38 (s, 3H), 2.00 (d, $J$=2.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 167.36 (d, $^2J_{C-F}$=19.7 Hz), 155.29 (d, $^2J_{C-F}$=15.9 Hz), 153.16, 137.88, 131.22, 130.83, 128.94, 126.75, 125.17, 120.86 (d, $^2J_{C-F}$=25.1 Hz), 118.67, 111.17, 93.20 (d, $^1J_{C-F}$=184.5 Hz), 55.99, 20.73, 13.01; $^{19}$F NMR (282.3 MHz, $CDCl_3$): $\delta$ −169.88 (s, 1F); HRMS (ESI) $m/z$ calcd for $C_{18}H_{17}FN_2O_2$ [(M+H)$^+$]: 313.1349; found: 313.1347.

*4.2.9. 4-(2,5-Dimethylphenyl)-4-fluoro-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**3bd**).*



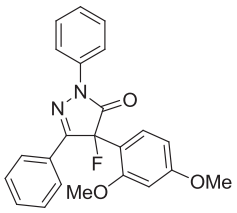
Yield: 64%; yellow solid; mp 82–83 °C; IR (neat): $\nu$ 3040, 2923, 2862, 1735, 1596, 1501, 1363, 756 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.91 (d, $J$=8.0 Hz, 2H), 7.43 (t, $J$=7.9 Hz, 2H), 7.34 (s, 1H), 7.23 (t, $J$=7.5 Hz, 1H), 7.13 (d, $J$=7.8 Hz, 1H), 7.08 (d, $J$=7.8 Hz, 1H), 2.37 (s, 3H), 2.17 (s, 3H), 2.07 (d, $J$=1.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 167.28 (d, $^2J_{C-F}$=20.1 Hz), 156.66 (d, $^2J_{C-F}$=15.8 Hz), 137.47, 136.26, 132.06, 130.38, 129.70 (d, $^2J_{C-F}$=22.9 Hz), 129.02, 125.95, 125.59, 118.68, 94.64 (d, $^1J_{C-F}$=186.0 Hz), 21.10, 18.61, 13.35; $^{19}$F NMR (282.3 MHz, $CDCl_3$): $\delta$ −166.90 (s, 1F); HRMS (ESI) $m/z$ calcd for $C_{18}H_{17}FN_2O$ [(M+Na)$^+$]: 319.1218, found: 319.1217.

*4.2.10. 4-Fluoro-4-(4-methoxyphenyl)-1,3-diphenyl-1H-pyrazol-5(4H)-one (**3ca**).*



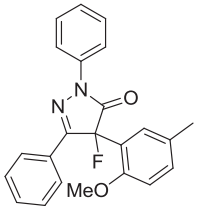
Yield: 65%; yellow solid; mp 106–107 °C; IR (neat): $\nu$ 3062, 2959, 2827, 1740, 1597, 1492, 1162, 755 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.02 (d, $J$=7.8 Hz, 2H), 7.88 (d, $J$=7.8 Hz, 1H), 7.77 (d, $J$=8.0 Hz, 2H), 7.48 (t, $J$=8.0 Hz, 2H), 7.39–7.25 (m, 5H), 7.17 (t, $J$=7.5 Hz, 1H), 6.81 (d, $J$=8.3 Hz, 1H), 3.57 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 167.68 (d, $^2J_{C-F}$=19.7 Hz), 155.22, 152.88 (d, $^2J_{C-F}$=14.4 Hz), 137.81, 130.75, 130.55, 128.63, 126.66, 126.32, 125.48, 122.69 (d, $^2J_{C-F}$=25.0 Hz), 121.41, 118.94, 111.24, 93.20 (d, $^1J_{C-F}$=186.7 Hz), 55.781; $^{19}$F NMR (282.3 MHz, $CDCl_3$): $\delta$ −170.02 (s, 1F); HRMS (ESI) $m/z$ calcd for $C_{22}H_{17}FN_2O_2$ [(M+Na)$^+$]: 383.1181; found: 383.1166.

*4.2.11. 4-(2,4-Dimethoxyphenyl)-4-fluoro-1,3-diphenyl-1H-pyrazol-5(4H)-one (**3cb**).*



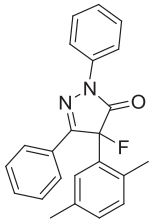
Yield: 73%; yellow solid; mp 152–153 °C; IR (neat): $\nu$ 3074, 2960, 2828, 1736, 1613, 1504, 1185, 758 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.00 (d, $J$=7.8 Hz, 2H), 7.77–7.73 (m, 3H), 7.45 (t, $J$=8.0 Hz, 2H), 7.37–7.29 (m, 3H), 7.24 (t, $J$=7.4 Hz, 1H), 3.79 (s, 3H), 3.51 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 167.90 (d, $^2J_{C-F}$=19.8 Hz), 161.97, 156.36, 153.24 (d, $^2J_{C-F}$=14.4 Hz), 137.85, 130.52, 129.39, 128.97, 128.61, 127.14, 126.68, 125.43, 118.91, 114.97 (d, $^2J_{C-F}$=25.1 Hz), 105.44, 98.99, 93.22 (d, $^1J_{C-F}$=186.1 Hz), 55.76, 55.46; $^{19}$F NMR (282.3 MHz, $CDCl_3$): $\delta$ −169.63 (s, 1F); HRMS (ESI) $m/z$ calcd for $C_{23}H_{19}FN_2O_3$ [(M+H)$^+$]: 391.1463; found: 391.1452.

*4.2.12. 4-Fluoro-4-(2-methoxy-5-methylphenyl)-1,3-diphenyl-1H-pyrazol-5(4H)-one (**3cc**).*



Yield: 83%; yellow solid; mp 116–117 °C; IR (neat): $\nu$ 3069, 2935, 2825, 1735, 1596, 1503, 1128, 756 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.04 (d, $J$=8.2 Hz, 2H), 7.80 (d, $J$=7.7 Hz, 2H), 7.70 (s, 1H), 7.50 (t, $J$=7.9 Hz, 2H), 7.41–7.33 (m, 3H), 7.28 (t, $J$=7.42 Hz, 1H), 7.17 (d, $J$=7.9 Hz, 1H), 6.71 (d, $J$=8.3 Hz, 1H), 3.54 (s, 3H), 2.44 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 167.78 (d, $^2J_{C-F}$=20.5 Hz), 153.23, 153.10 (d, $^2J_{C-F}$=14.4 Hz), 137.84, 131.14, 130.84, 130.55, 129.37, 128.99, 128.65, 126.68, 126.55, 125.48, 122.32 (d, $^2J_{C-F}$=25.1 Hz), 118.96, 111.33, 93.22 (d, $^1J_{C-F}$=186.1 Hz), 55.89, 20.86; $^{19}$F NMR (282.3 MHz, $CDCl_3$): $\delta$ −173.64 (s, 1F); HRMS (ESI) $m/z$ calcd for $C_{23}H_{19}FN_2O_2$ [(M+Na)$^+$]: 397.1321; found: 397.1323.

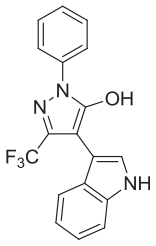
*4.2.13. 4-(2,5-Dimethylphenyl)-4-fluoro-1,3-diphenyl-1H-pyrazol-5(4H)-one (**3cd**).*



Yield: 59%; yellow solid; mp 47–48 °C; IR (neat): $\nu$ 3069, 2913, 2850, 1737, 1597, 1496, 1126, 755 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$):

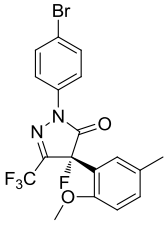
$\delta$ 8.00 (d, $J$=8.0 Hz, 2H), 7.77 (d, $J$=8.4 Hz, 2H), 7.46–7.24 (m, 6H), 7.17 (t, $J$=7.6 Hz, 1H), 7.01 (d, $J$=7.7 Hz, 1H), 6.94 (d, $J$=7.7 Hz, 1H), 2.26 (s, 3H), 2.16 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 167.21 (d, $^2J_{C-F}$=22.0 Hz), 154.51 (d, $^2J_{C-F}$=14.4 Hz), 137.46, 136.24, 132.25, 131.13, 130.92, 130.39, 129.07, 128.84, 128.76, 128.42, 126.93, 125.99 (d, $^2J_{C-F}$=25.1 Hz), 125.85, 118.92, 94.67 (d, $^1J_{C-F}$=187.2 Hz), 21.20, 18.82; $^{19}$F NMR (282.3 MHz, $CDCl_3$): $\delta$ −162.55 (s, 1F); HRMS (ESI) $m/z$ calcd for $C_{23}H_{19}FN_2O$ [(M+Na)$^+$]: 381.1384; found: 381.1374.

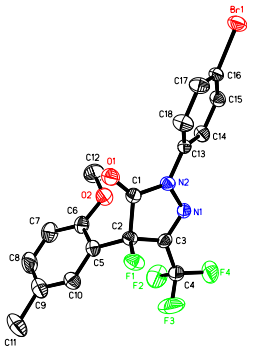
*4.2.14. 4-(1H-Indol-3-yl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-ol (**3ag**).*




Yield: 71%; lavender solid; mp 167–169 °C; IR (neat): $\nu$ 3416, 3284, 3061, 2963, 2926, 1703, 1599, 1520, 1481, 1456, 949, 743 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.44 (s, 1H), 7.80 (d, $J$=7.8 Hz, 2H), 7.55 (d, $J$=7.7 Hz, 1H), 7.51–7.64 (m, 3H), 7.37 (t, $J$=7.3 Hz, 1H), 7.31–7.26 (m, 2H), 7.21 (t, $J$=7.4 Hz, 1H), 6.10 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 149.17, 137.76, 136.08, 129.11, 127.11, 127.58, 126.48, 124.60, 122.92, 122.68 (q, $J_{C-F}$=267.3 Hz), 122.59, 120.76, 118.94, 111.72, 103.11, 95.30; $^{19}$F NMR (282.3 MHz, $CDCl_3$): $\delta$ −61.84 (s, 3F); HRMS (ESI) $m/z$ calcd for $C_{18}H_{12}F_3N_3O$ [(M+H)$^+$]: 344.1004; found: 344.1005.

*4.2.15. (R)-1-(4-Bromophenyl)-4-fluoro-4-(2-methoxy-5-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one (**3dc**).*




Yield: 85%; Yellow solid; $[\alpha]_D^{26}$ 67.8 ($c$ 0.25, $CHCl_3$); mp 99–101 °C; IR (neat): $\nu$ 3093, 2932, 1765, 1608, 1505, 1494, 1142, 1404, 1297, 1142, 1061, 932, 831, 754 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.76 (d, $J$=8.80 Hz, 2H), 7.59 (d, $J$=9.20 Hz, 2H), 7.46 (s, 1H), 7.23 (d, $J$=7.20 Hz, 1H), 6.79 (d, $J$=8.00 Hz, 1H), 3.61 (s, 3H), 2.38 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 166.60 (d, $^2J_{C-F}$=19.0 Hz), 153.03 (d, $^3J_{C-F}$=6.0 Hz), 143.87 (qd, $^2J_{C-F}$=22.0 Hz, $^2J_{C-F}$=16.0 Hz), 135.88, 132.30, 131.97, 131.35, 126.77 (d, $^2J_{C-F}$=12.0 Hz), 120.41, 119.85, 118.71, 118.48 (q, $^1J_{C-F}$=271.0 Hz), 110.95, 90.13 (d, $^1J_{C-F}$=190.0 Hz), 55.97, 20.70; $^{19}$F NMR (282.3 MHz, $CDCl_3$): $\delta$ −65.79 (s, 3F), −171.92 (s, 1F); HRMS (ESI) $m/z$ calcd for $C_{18}H_{13}BrF_4N_2O_2$ [(M+H)$^+$]: 445.0223; found: 445.0231. Enantiomeric excess: 53%, determined by HPLC (Chiralpak AS-H column, hexane/$i$-PrOH=95:5, $\lambda$=254 nm, flow rate=0.5 mL/min; $t_R$ (major)=8.4 min; $t_R$ (minor)=10.4 min).

## Acknowledgements

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