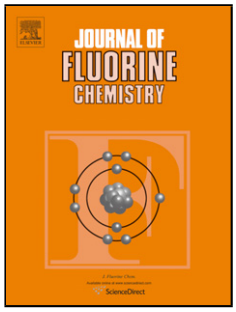


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# Synthesis of fluorovinyl pyrazolyl (thio)ethers by the reaction of *gem*-difluoroalkenes with pyrazolin-5-ones (thiones)

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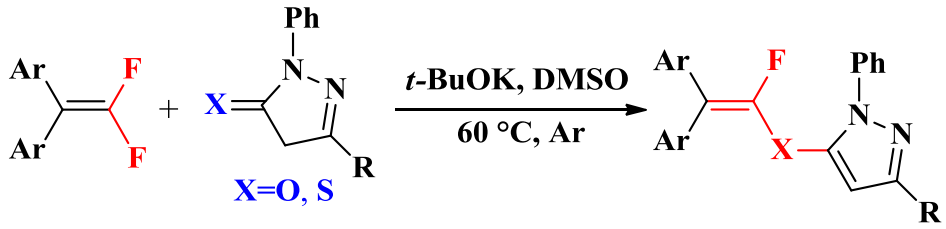
## Graphical abstract

A mild and efficient method for the preparation of fluorovinyl pyrazolyl ethers and thioethers by the reaction of *gem*-difluoroalkenes with pyrazolin-5-ones and pyrazolin-5- thiones, respectively, in the presence of *t*-BuOK is described.



**Highlights**

- An efficient method for the synthesis of fluorovinyl pyrazolyl (thio)ethers is reported.
- The reaction of *gem*-difluoroalkenes with pyrazolin-5-ones (thiones) proceeds efficiently under mild conditions.
- The addition of potassium *tert*-butoxide is essential for efficient conversion.

**Abstract**: A mild and efficient method for the preparation of fluorovinyl pyrazolyl ethers and thioethers by the reaction of *gem*-difluoroalkenes having aryl substituents with pyrazolin-5-ones and pyrazolin-5-thiones, respectively, in the presence of *t*-BuOK is described.

**Keywords**: *gem*-difluoroalkenes; pyrazolone; potassium *tert*-butoxide; fluorovinyl pyrazolyl ethers

## 1. Introduction

Pyrazolone derivatives have found many applications in the fields of dyes, agrochemicals and pharmaceuticals [1]. For example, *O*-pyrazole glucopyranoside (Fig 1, compound **I**) can be used as antidiabetic agent [2] and arene-ruthenium (II) acylpyrazolonato complexe (Fig 1, compound **II**) is particularly active in inducing cell death in all cell lines [3]. Pyrazolones are also used as useful building blocks and intermediates in organic synthesis [4]. Therefore, much effort has been devoted to the exploration of new reaction types of pyrazolones [5]. The current interest is always focused on the Michael addition reaction at activated methylene group of the pyrazolone ring [6] or Michael addition-cyclization reaction occurring at C4 and C5-OH positions [7]. However, example of the

preferential reactivity of the oxygen anion (enol oxygen) over carbon anion has been scarcely reported. More recently, Liu and Zhang reported a novel method for the synthesis of *O*-pyrazole polyfluoroarylated ethers by the $S_NAr$ reaction of pyrazolones with polyfluoroarenes. This transformations involved the use of enol oxygen of pyrazolone as a nucleophile [8].

*gem*-Difluoroalkenes display unusual reactivity toward nucleophiles due to their highly electron-deficient nature of carbon–carbon double bond and the excellent leaving-group ability of the fluoride ion [9]. Therefore, they usually serve as versatile electrophile partner in the fluorovinylation of a variety of nucleophiles [10]. In continuation of our work on the functionalization of the C–F bond of *gem*-difluoroalkenes [11], in this paper, we report an efficient α-fluorovinylation of pyrazolin-5-ones and pyrazolin-5-thiones with *gem*-difluoroalkenes via nucleophilic vinylic substitution reaction ($S_NV$) with the assistance of *t*-BuOK.

## 2. Results and discussion

We used (2,2-difluoroethene-1,1-diyl)dibenzene **1a** and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one **2a** as model reactants for the optimization of the aryloxylation reaction conditions, and the results are shown in Table 1. Initially, the effects of different solvents were evaluated. Generally polar aprotic solvents are effective for the reaction and DMSO proved to be a more suitable solvent for this transformation (entries 1–6). The choice of the base was critical in achieving high efficiency. No reaction took place without the addition of base (entry 7). Among the various bases examined, *t*-BuOK provided the best result (entry 6) and replacement of *t*-BuOK with other bases led to decreased yields (entries 8–12). Two equivalent of *t*-BuOK were essential for achieving high conversion and increasing or decreasing the amount of *t*-BuOK would diminish the yield of **3aa** (entries 6 and 13–14). The influence of the temperature on the reaction was also examined (entries 6 and 15–17). With

increasing the reaction temperature from 25 °C to 60 °C, the conversion of **1a** significantly increased giving highest yield (94 %). Further increase in reaction temperature (at 75 °C) could not improve the conversion. Finally, two equivalents of **2a** was required to obtain satisfactory yield (entry 6) and reducing the amount of **2a** to 1.5 equivalent resulted in lower yield of **3aa** (entry 18).

With the optimal reaction conditions in hand (Table 1, entry 6), the scope of the aryloxylation reaction was extended to various symmetrical *gem*-difluoroalkenes and pyrazolones. The results are summarized in Table 2. As demonstrated in Table 2, most substrates could afford α-fluorovinyl pyrazolyl ethers in moderate to excellent yields. Generally, *gem*-difluoroalkenes bearing electron-withdrawing or neutral groups gave the desired products in higher yields than substrates bearing electron-donating group (for example **3ba** *vs*. **3ga**). Replacing the methyl group with the phenyl group in pyrazolone also afforded the desired products in high yields (**3aa** *vs*. **3ab**). However, the replacement of methyl group with trifluoromethyl group would result in a loss of reactivity of pyrazolones and the yields dropped sharply (**3ac**, **3bc** and **3fc**). Moreover, unsymmetrical *gem*-difluoroalkene (**1i**) could also be served as substrate to give an inseparable mixture of *E*- and *Z*-olefin isomers in excellent yield. The ratio of two isomers was 65/35. However, we were unable to distinguish between two isomers due to the similarity of their $^{1}$H NMR spectra. Interestingly, when the reactions of 9-(difluoromethylene)-9*H*-fluorene **1h** with **2a** or **2b** were performed under the optimized reaction conditions, no desired product was observed and a large amount of byproduct 9-fluorenone was generated due to the thermal and hydrolytical instability of **1h**. Thus, to avoid the decomposition of **1h**, we envisioned that the reaction should be performed in nonoxidizing and less polar solvent at low temperature within a short reaction time. To our delight, the desired products (**3ha**, **3hb**) were obtained in good yields when the reaction was performed in $CH_3CN$ at room temperature for 2 h by using 1.0 equivalent of **2a** or **2b**. Furthermore, when the amount of **2a** or **2b**

was increased to 2.0 equivalents, double aryloxylation products (**3ha'**, **3hb'**) were obtained in moderate yields after 4 hours of stirring at room temperature.

The scope of the aryloxylation reaction was examined with several unsymmetrical *gem*-difluoroalkenes **1j**–**o** (one is hydrogen and the other is aryl group). These unsymmetrical difluoroalkenes reacted smoothly with pyrazolone **2a** producing the expected products in good yields but with low *E*/*Z*-selectivity (Table 3). To our delight, the *Z*- and *E*-isomers of **3ja** and **3ka** could be separated by column chromatography. However, attempts to obtain the pure *E*- or *Z*- isomers of **3la**–**oa** were unsuccessful.

Inspired by the successful aryloxylation of *gem*-difluoroalkenes with pyrazolin-5-ones, we next investigated the reaction of *gem*-difluoroalkenes with some pyrazolin-5-thiones under the above-optimized conditions (Table 4). As expected, pyrazolin-5- thiones behaved similarly as pyrazolin-5-ones in the arylthiolation reaction with different *gem*-difluoroalkenes and afforded the desired products in good yields.

**Conclusions**

In summary, we have developed an efficient and versatile method for the α-fluorovinylation of pyrazolin-5-ones and pyrazolin-5- thiones with *gem*-difluoroalkenes having aryl substituents with the assistance of *t*-BuOK. The reaction is applicable to a variety of *gem*-difluoroalkenes and pyrazolin-5-(thi)ones and provide α-fluorovinyl pyrazolyl (thio)ethers in good to excellent yields under mild conditions.

**4. Experimental**

All reagents were of analytical grade, and obtained from commercial suppliers and used without further purification. THF and other solvents were dried by standard method prior to use. Melting

points were measured in an open capillary using Büchi melting point B-540 apparatus and are uncorrected. $^{1}$H NMR and $^{13}$C NMR spectra were recorded on a 400 spectrometer (400 MHz for $^{1}$H and 100 MHz for $^{13}$C NMR, respectively) using TMS as internal standard, The $^{19}$F NMR spectra were obtained using a 400 spectrometer (376 MHz). $CDCl_3$ was used as the NMR solvent in all cases. High resolution mass spectra (HRMS) were recorded under electron impact conditions using a MicroMass GCT CA 055 instrument and recorded on a MicroMass LCTTM spectrometer. Silica gel (300−400 mesh size) was used for column chromatography. TLC analysis of reaction mixtures was performed using silica gel plates.

*4.1 Preparation of symmetrical gem-difluoroalkenes **1a**–**i** and unymmetrical gem-difluoroalkenes **1j**–**o***

The symmetrical *gem*-difluoroalkenes (**1a**–**i**) were prepared according to the Hu's reported procedure [12]. The unsymmetrical *gem*-difluoroalkenes (**1j**–**o**) were prepared according to the reported procedure [13].

*4.2 Preparation of pyrazolones **2a**–**c** and pyrazol-5-thiones **2d**–**e***

The pyrazolones **2a**–**c** were prepared according to the reported procedure [14]. The pyrazol-5-thiones **2d** and **2e** were prepared according to literature procedures [15].

*4.3 General procedure for the target compounds **3***

To a stirred solution of pyrazolones **2a**–**c** (1.0 mmol) or pyrazol-5-thiones **2d** or **2e** (1.0 mmol) and *t*-BuOK (1.0 mmol, 112 mg) in DMSO (4 mL), *gem*-difluoroalkenes **1a**–**o** (0.5 mmol) were added. The mixture was then stirred at 60 °C for 24 h under an argon atmosphere. The progress of the reaction was monitored by TLC. After the completion of reaction, the mixture was extracted with $H_2O$ (20 mL) and ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine, then dried

over anhydrous $Na_2SO_4$, filtered, and concentrated under vacuum. The crude residue was then purified by column chromatography on silica gel using *n*-hexane/ethyl acetate mixture (40/1 to 10/1) as the eluent to afford pure target compound **3**.

*4.3.1. 5-((1-Fluoro-2,2-diphenylvinyl)oxy)-3-methyl-1-phenyl-1H-pyrazole (**3aa**)*

Light yellow solid, mp: 85.8–86.4 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.38–7.20 (m, 15H), 5.88 (d, $J$ = 2.4 Hz, 1H), 2.28 (s, 3H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.5 (d, $^1J_{CF}$ = 290.7 Hz), 149.0, 137.8, 135.4 (d, $^3J_{CF}$ = 3.7 Hz), 135.2 (d, $^3J_{CF}$ = 4.2 Hz), 129.71, 129.68, 129.65, 129.6, 128.9, 128.4 (d, $^4J_{CF}$ = 4.0 Hz), 127.8, 127.7, 126.9, 122.8, 106.0 (d, $^2J_{CF}$ = 21.6 Hz), 90.3 (d, $^4J_{CF}$ = 1.3 Hz), 14.6 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –91.2 (s, 1F) ; HRMS (EI): calc. for $C_{24}H_{19}FN_2O$ $[M]^+$: 370.1481, found: 370.1483.

*4.3.2. 5-((1-Fluoro-2,2-bis(4-fluorophenyl)vinyl)oxy)-3-methyl-1-phenyl-1H-pyrazole (**3ba**)*

Light yellow solid, mp: 69.5–70.3 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39–7.22 (m, 7H), 7.16–7.13 (m, 2H), 7.06–7.02 (m, 2H), 6.96–6.91 (m, 2H), 5.85 (d, $J$ = 2.0 Hz, 1H), 2.29 (s, 3H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, $^1J_{CF}$ = 246.4 Hz), 162.1 (d, $^1J_{CF}$ = 246.5 Hz), 150.5 (d, $^1J_{CF}$ = 296.8 Hz), 149.0, 148.6 (d, $^3J_{CF}$ = 2.9 Hz), 137.6, 131.3–131.2 (m), 131.0–130.8 (m), 129.6–129.5 (m), 128.9, 128.4 (d, $^3J_{CF}$ = 5.5 Hz), 127.0, 122.8, 115.45 (d, $^2J_{CF}$ = 21.5 Hz), 115.43 (d, $^2J_{CF}$ = 21.5 Hz), 104.1 (d, $^2J_{CF}$ = 22.4 Hz), 90.4 (d, $^4J_{CF}$ = 1.6 Hz), 14.6 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –91.0 (s, 1F), –113.5 to –113.6 (m, 2F) ; HRMS (EI): calc. for $C_{24}H_{17}F_3N_2O$ $[M]^+$: 406.1293, found: 406.1296.

*4.3.3. 5-((1-Fluoro-2,2-bis(3-fluorophenyl)vinyl)oxy)-3-methyl-1-phenyl-1H-pyrazole (**3ca**)*

Oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.40–7.20 (m, 7H), 7.05–6.90 (m, 6H), 5.87 (d, $J$ = 2.8 Hz, 1H ), 2.30 (s, 3H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 162.7 (d, $^1J_{CF}$ = 244.6 Hz), 162.6 (d, $^1J_{CF}$ = 245.1 Hz), 150.9 (d, $^1J_{CF}$ = 292.7 Hz), 149.0, 148.1 (d, $^3J_{CF}$ = 2.4 Hz), 137.5, 136.8 (dd, $^3J_{CF}$ = 8.0 Hz, $^3J_{CF}$

= 3.9 Hz), 136.6 (dd, $^{3}J_{CF}$ = 8.3 Hz, $^{3}J_{CF}$ = 4.6 Hz), 130.0–129.9 (m), 129.0, 127.1, 125.42–125.37 (m), 125.3 (dd, $^{4}J_{CF}$ = 4.4 Hz, $^{4}J_{CF}$ = 3.0 Hz), 122.9, 116.7 (dd, $^{2}J_{CF}$ = 19.3 Hz, $^{4}J_{CF}$ = 3.3 Hz), 116.5 (dd, $^{2}J_{CF}$ = 19.4 Hz, $^{4}J_{CF}$ = 3.0 Hz), 115.0 (d, $^{2}J_{CF}$ = 20.9 Hz), 114.9 (d, $^{2}J_{CF}$ = 20.9 Hz), 104.1–104.0 (m), 103.9–103.8 (m), 90.6 (d, $^{4}J_{CF}$ = 1.7 Hz), 14.5 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –88.6 (s, 1F), –112.4 to –112.5 (m, 1F), –112.6 to –112.7 (m, 1F) ; HRMS (EI): calc. for $C_{24}H_{17}F_3N_2O$ $[M]^+$: 406.1293, found: 406.1295.

*4.3.4. 5-((2,2-Bis(4-chlorophenyl)-1-fluorovinyl)oxy)-3-methyl-1-phenyl-1H-pyrazole (**3da**)*

White solid, mp: 142.5–144.3 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 7H), 7.21–7.18 (m, 4H), 7.10–7.08 (m, 2H), 5.86 (d, *J* = 2.4 Hz, 1H), 2.29 (s, 3H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.7 (d, $^{1}J_{CF}$ = 292.0 Hz), 149.0 148.3 (d, $^{3}J_{CF}$ = 2.6 Hz), 137.5, 133.9, 133.8, 133.3 (d, $^{3}J_{CF}$ = 3.9 Hz), 133.2 (d, $^{3}J_{CF}$ = 4.3 Hz), 130.95 (d, $^{4}J_{CF}$ = 3.1 Hz), 130.93, 130.8, 129.0, 128.7 (d, $^{4}J_{CF}$ = 2.6 Hz), 127.1, 122.8, 103.9 (d, $^{2}J_{CF}$ = 22.4 Hz), 90.6 (d, $^{4}J_{CF}$ = 1.5 Hz), 14.6 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –89.4 (s, 1F) ; HRMS (EI): calc. for $C_{24}H_{17}Cl_2FN_2O$ $[M]^+$: 438.0702, found: 438.0705.

*4.3.5. 5-((2,2-Bis(4-bromophenyl)-1-fluorovinyl)oxy)-3-methyl-1-phenyl-1H-pyrazole (**3ea**)*

Yellow solid, mp: 153.5–155.3 °C ; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.37–7.29 (m, 7H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 5.85 (d, *J* = 2.4 Hz, 1H), 2.29 (s, 3H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.6 (d, $^{1}J_{CF}$ = 292.2 Hz), 149.0, 148.2 (d, $^{3}J_{CF}$ = 2.6 Hz), 137.6, 133.7 (d, $^{3}J_{CF}$ = 3.9 Hz), 133.6 (d, $^{3}J_{CF}$ = 4.3 Hz), 131.7 (d, $^{4}J_{CF}$ = 2.3 Hz), 131.3 (d, $^{4}J_{CF}$ = 3.2 Hz), 131.2, 131.1, 129.0, 127.1, 122.9, 122.1, 122.0, 103.9 (d, $^{2}J_{CF}$ = 22.3 Hz), 90.7 (d, $^{4}J_{CF}$ = 1.5 Hz), 14.6 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –89.0 (s, 1F) ; HRMS (EI): calc. for $C_{24}H_{17}Br_2FN_2O$ $[M]^+$: 527.9671, found: 527.9677.

*4.3.6. 5-((1-Fluoro-2,2-bis(3-(trifluoromethyl)phenyl)vinyl)oxy)-3-methyl-1-phenyl-1H-pyrazole (**3fa**)*

Oil (yellow); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.58–7.45 (m, 5 H), 7.41–7.27 (m, 8 H), 5.89 (d, *J* = 1.6 Hz, 1H), 2.29 (s, 3H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 151.3 (d, $^{1}J_{CF}$ = 293.0 Hz), 149.0, 147.7 (d, $^{3}J_{CF}$ = 1.9 Hz), 137.4, 135.4 (d, $^{3}J_{CF}$ = 3.9 Hz), 135.3 (d, $^{3}J_{CF}$ = 4.2 Hz), 133.0 (d, $^{4}J_{CF}$ = 1.5 Hz), 132.8 (d, $^{4}J_{CF}$ = 2.8 Hz), 131.1 (q, $^{2}J_{CF}$ = 32.0 Hz), 131.1 (q, $^{2}J_{CF}$ = 32.2 Hz), 129.2, 129.1, 129.0, 127.2, 126.5–126.3 (m), 126.3–126.1 (m), 125.0–124.9 (m), 124.8–124.7 (m), 123.9 (q, $^{1}J_{CF}$ = 271.3 Hz), 123.8 (q, $^{1}J_{CF}$ = 270.8 Hz), 122.9, 103.4 (d, $^{2}J_{CF}$ = 22.5 Hz), 90.9 (d, $^{4}J_{CF}$ = 1.6 Hz), 14.5 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –62.7 (s, 3F), –62.7 (s, 3F), –88.1 (s, 1F) ; HRMS (EI): calc. for $C_{26}H_{17}F_7N_2O$ $[M]^+$: 506.1229, found: 506.1230.

*4.3.7. 5-((1-Fluoro-2,2-di-p-tolylvinyl)oxy)-3-methyl-1-phenyl-1H-pyrazole (**3ga**)*

Oil (grey); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.31–7.22 (m, 4H), 7.17–6.96 (m, 9H), 5.77 (d, *J* = 2.0 Hz, 1H), 2.27 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.2 (d, $^{1}J_{CF}$ = 289.8 Hz), 149.2 (d, $^{3}J_{CF}$ = 3.1 Hz), 149.0, 137.7, 137.5, 137.4, 132.5 (d, $^{3}J_{CF}$ = 3.7 Hz), 132.4 (d, $^{3}J_{CF}$ = 4.2 Hz), 129.53, 129.50, 129.46, 129.0, 128.8, 126.8, 122.7, 105.8 (d, $^{2}J_{CF}$ = 21.6 Hz), 90.2 (d, $^{4}J_{CF}$ = 1.3 Hz), 21.24, 21.23, 14.6 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –92.1 (s, 1F) ; HRMS (EI): calc. for $C_{26}H_{23}FN_2O$ $[M]^+$: 398.1794, found: 398.1795.

*4.3.8. 5-((1-Fluoro-2,2-diphenylvinyl)oxy)-1,3-diphenyl-1H-pyrazole (**3ab**)*

Yellow solid, mp: 110.2–112.7 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.86–7.84 (m, 2H), 7.47–7.23 (m, 18H), 6.38 (d, *J* = 2.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.9, 150.5 (d, $^{1}J_{CF}$ = 291.2 Hz), 149.6 (d, $^{3}J_{CF}$ = 3.0 Hz), 137.8, 135.3 (d, $^{3}J_{CF}$ = 3.6 Hz), 135.1 (d, $^{3}J_{CF}$ = 4.2 Hz), 132.9, 129.66, 129.70 (d, $^{4}J_{CF}$ = 3.1 Hz), 129.66, 129.0, 128.7, 128.5, 128.4, 127.9, 127.8, 127.2, 125.6, 123.0, 106.2 (d, $^{2}J_{CF}$ = 21.2 Hz), 87.9 (d, $^{4}J_{CF}$ = 1.6 Hz) ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –91.2 (s, 1F) ; HRMS (EI): calc. for $C_{29}H_{21}FN_2O$ $[M]^+$: 432.1638, found: 432.1640.

*4.3.9. 5-((1-Fluoro-2,2-bis(4-fluorophenyl)vinyl)oxy)-1,3-diphenyl-1H-pyrazole (**3bb**)*

Light yellow solid, mp: 120.3–121.2 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.2 Hz, 2H), 7.49–7.23 (m, 10H), 7.18–7.15 (m, 2H), 7.07–7.03 (m, 2H), 6.96–6.91 (m, 2H), 6.37 (d, *J* = 2.4 Hz, 1H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 162.3 (d, $^{1}J_{CF}$ = 246.5 Hz), 162.2 (d, $^{1}J_{CF}$ = 246.9 Hz), 150.9, 150.5 (d, $^{1}J_{CF}$ = 290.4 Hz), 149.3 (d, $^{3}J_{CF}$ = 2.9 Hz), 137.7, 132.7, 131.4–131.3 (m), 131.0–130.9 (m), 130.9–130.8 (m), 129.0, 128.7, 128.5, 127.4, 125.6, 123.0, 115.6 (d, $^{2}J_{CF}$ = 21.5 Hz), 115.5 (d, $^{2}J_{CF}$ = 21.5 Hz), 104.4 (d, $^{2}J_{CF}$ = 22.1 Hz), 88.0 (d, $^{4}J_{CF}$ = 1.2 Hz) ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –91.1 (s, 1F), –113.38 to –113.39 (m, 2F) ; HRMS (EI): calc. for $C_{29}H_{19}F_3N_2O$ $[M]^+$: 468.1449, found: 468.1451.

*4.3.10. 5-((2,2-Bis(4-chlorophenyl)-1-fluorovinyl)oxy)-1,3-diphenyl-1H-pyrazole (**3db**)*

Yellow solid, mp: 82.6–83.3 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.85–7.83 (m, 2H), 7.48–7.29 (m, 10H), 7.22–7.19 (m, 4H), 7.12–7.10 (m, 2H), 6.37 (d, *J* = 2.8 Hz, 1H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 151.0, 150.7 (d, $^{1}J_{CF}$ = 292.3 Hz), 148.9 (d, $^{3}J_{CF}$ = 2.6 Hz), 137.6, 134.0, 133.9, 133.2 (d, $^{3}J_{CF}$ = 3.8 Hz), 133.1 (d, $^{3}J_{CF}$ = 4.4 Hz), 132.7, 131.0 (d, $^{4}J_{CF}$ = 3.2 Hz), 130.9 (d, $^{4}J_{CF}$ = 4.6 Hz), 129.1, 128.81, 128.76, 128.7, 128.6, 127.5, 125.6, 123.1, 104.2 (d, $^{2}J_{CF}$ = 21.9 Hz), 88.3 (d, $^{4}J_{CF}$ = 1.6 Hz) ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –89.4 (s, 1F) ; HRMS (EI): calc. for $C_{29}H_{19}Cl_2FN_2O$ $[M]^+$: 500.0858, found: 500.0857.

*4.3.11. 5-((2,2-Bis(4-bromophenyl)-1-fluorovinyl)oxy)-1,3-diphenyl-1H-pyrazole (**3eb**)*

White solid, mp: 150.5–153.3 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.85–7.82 (m, 2H), 7.48–7.29 (m, 12H), 7.15–7.10 (m, 2H), 7.05–7.03 (m, 2H), 6.36 (d, *J* = 2.8 Hz, 1H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.9, 150.5 (d, $^{1}J_{CF}$ = 292.5 Hz), 148.8 (d, $^{3}J_{CF}$ = 2.6 Hz), 137.5, 133.5 (d, $^{3}J_{CF}$ = 3.8 Hz), 133.4 (d, $^{3}J_{CF}$ = 4.3 Hz), 132.6, 131.7, 131.6, 131.2 (d, $^{4}J_{CF}$ = 3.2 Hz), 131.1 (d, $^{4}J_{CF}$ = 4.5 Hz), 129.0, 128.6, 128.4, 127.4, 125.5, 123.0, 122.2, 122.0, 104.1 (d, $^{2}J_{CF}$ = 22.0 Hz), 88.2 (d, $^{4}J_{CF}$ = 1.7 Hz) ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –89.2 (s, 1F) ; HRMS (EI): calc. for $C_{29}H_{19}Br_2FN_2O$ $[M]^+$: 589.9828,

found: 589.9833.

*4.3.12. 5-((1-Fluoro-2,2-bis(3-(trifluoromethyl)phenyl)vinyl)oxy)-1,3-diphenyl-1H-pyrazole (**3fb**)*

Oil (yellow); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.6 Hz, 2H), 7.61–7.32 (m, 16H), 6.39 (d, *J* =2.4 Hz, 1H ) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 151.2 (d, $^{1}J_{CF}$ = 293.4 Hz), 151.0, 148.3 (d, $^{3}J_{CF}$ = 1.9 Hz), 137.5, 135.3 (d, $^{3}J_{CF}$ = 3.9 Hz), 135.2 (d, $^{3}J_{CF}$ = 4.2 Hz), 133.0 (d, $^{4}J_{CF}$ = 1.4 Hz), 132.9 (d, $^{4}J_{CF}$ = 2.9 Hz), 132.7, 131.23 (q, $^{2}J_{CF}$ = 32.3 Hz), 131.21 (q, $^{2}J_{CF}$ = 32.3 Hz), 129.3, 129.2, 129.1, 128.7, 128.5, 123.9 (q, $^{1}J_{CF}$ = 270.9 Hz), 123.8 (q, $^{1}J_{CF}$ = 270.9 Hz), 127.6, 126.5–126.4 (m), 126.3–126.1 (m), 125.6, 125.2–125.0 (m), 124.9–124.8 (m), 123.1, 103.6 (d, $^{2}J_{CF}$ = 22.2 Hz), 88.5 (d, $^{4}J$ = 1.8 Hz) ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –62.7 (s, 3F), –62.7 (s, 3F), –88.3 (s, 1F) ; HRMS (EI): calc. for $C_{31}H_{19}F_7N_2O$ $[M]^+$: 568.1386, found: 568.1389.

*4.3.13. 5-((1-Fluoro-2,2-diphenylvinyl)oxy)-1-phenyl-3-(trifluoromethyl)-1H-pyrazole (**3ac**)*

Yellow solid, mp: 75.8–77.4 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.35–7.26 (m, 13H), 7.20–7.18 (m, 2H), 6.32 (d, *J* = 2.4 Hz, 1H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.1 (d, $^{1}J_{CF}$ = 291.6 Hz), 149.2 (d, $^{3}J_{CF}$ = 2.8 Hz), 142.2 (q, $^{2}J_{CF}$ = 38.8 Hz), 136.8, 134.9 (d, $^{3}J_{CF}$ = 3.6 Hz), 134.6 (d, $^{3}J_{CF}$ = 4.3 Hz), 129.7 (d, $^{4}J_{CF}$ = 3.1 Hz), 129.6 (d, $^{4}J_{CF}$ = 4.5 Hz), 129.2, 128.6, 128.50, 128.46, 128.1, 128.0, 123.6, 120.8 (q, $^{1}J_{CF}$ = 267.6 Hz), 106.8 (d, $^{2}J_{CF}$ = 20.2 Hz), 89.1–89.0 (m) ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –63.0 (s, 3F), –92.5 (s, 1F) ; HRMS (EI): calc. for $C_{24}H_{16}F_4N_2O$ $[M]^+$: 424.1199, found: 424.1198.

*4.3.14. 5-((1-Fluoro-2,2-bis(4-fluorophenyl)vinyl)oxy)-1-phenyl-3-(trifluoromethyl)-1H-pyrazole (**3bc**)*

Oil (yellow); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.42–7.34 (m, 5H), 7.26–7.22 (m, 2H), 7.14–7.11 (m, 2H), 7.06–7.00 (m, 2H), 6.97–6.92 (m, 2H), 6.31 (d, *J* = 2.4 Hz, 1H ) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 162.4 (d, $^{1}J_{CF}$ = 246.9 Hz), 162.3 (d, $^{1}J_{CF}$ = 246.9 Hz), 150.1 (d, $^{1}J_{CF}$ = 291.5 Hz), 148.8 (d, $^{3}J_{CF}$ = 2.7 Hz), 142.1 (q, $^{2}J_{CF}$ = 38.9 Hz), 136.6, 132.4–132.1 (m), 131.4–131.2 (m), 130.6–130.5 (m), 130.4–

130.3 (m), 129.2, 128.6, 123.5, 120.7 (q, $^{1}J_{CF}$ = 267.6 Hz), 115.65 (d, $^{2}J_{CF}$ = 21.6 Hz), 115.57 (d,$^{2}J_{CF}$ = 21.6 Hz), 104.9 (d, $^{2}J_{CF}$ = 21.1 Hz), 89.21–89.18 (m) ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –63.2 (s, 3F), –92.3 (s, 1F), –113.0 to –113.1 (m, 2F) ; HRMS (EI): calc. for $C_{24}H_{14}F_6N_2O$ $[M]^+$: 460.1010, found: 460.1012.

*4.3.15. 5-((1-Fluoro-2,2-bis(3-(trifluoromethyl)phenyl)vinyl)oxy)-1-phenyl-3-(trifluoromethyl)-1H-pyrazole (**3fc**)*

Oil; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.61–7.57 (m, 2H), 7.52–7.48 (m, 3H), 7.42–7.35 (m, 8H), 8.35 (d, *J* = 2.8 Hz, 1H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.7 (d, $^{1}J_{CF}$ = 293.9 Hz), 147.8 (d, $^{3}J_{CF}$ = 1.6 Hz), 142.2 (q, $^{2}J_{CF}$ = 39.2 Hz), 136.4, 134.9 (d, $^{3}J_{CF}$ = 4.8 Hz), 134.7 (d, $^{3}J_{CF}$ = 4.2 Hz), 132.9 (d, $^{4}J_{CF}$ = 1.5 Hz), 132.73–132.69 (m), 131.3 (q, $^{2}J_{CF}$ = 32.4 Hz), 131.2 (q, $^{2}J_{CF}$ = 32.4 Hz), 129.3, 129.2, 128.8, 123.8 (q, $^{1}J_{CF}$ = 238.4 Hz), 123.7 (q, $^{1}J_{CF}$ = 270.9 Hz), 126.4–126.3 (m), 126.2–126.0 (m), 125.3–125.2 (m), 125.1–125.0 (m), 120.5 (q, $^{1}J_{CF}$ = 267.7 Hz), 104.1 (d, $^{2}J_{CF}$ = 21.2 Hz), 89.7–89.6 (m) ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –62.7 (s, 6F), –63.3 (s, 3F), –89.5 (s, 1F) ; HRMS (EI): calc. for $C_{26}H_{14}F_{10}N_2O$ $[M]^+$: 560.0946, found: 560.0947.

*4.3.16. (E/Z)-5-((1-Fluoro-2-(4-fluorophenyl)-2-phenylvinyl)oxy)-3-methyl-1-phenyl-1H-pyrazole (E/Z-**3ia**)*

Oil; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.40–7.14 (m, 12H), 7.06–7.00 (m, 0.65 × 2H), 6.95–6.90 (m, 0.35 × 2H), 5.87–5.86 (m, 1H), 2.29 (s, 3H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, $^{1}J_{CF}$ = 246.1 Hz), 162.1 (d, $^{1}J_{CF}$ = 246.4 Hz), 151.9, 150.6 (d, $^{1}J_{CF}$ = 290.6 Hz), 150.6 (d, $^{1}J_{CF}$ = 290.9 Hz), 149.11, 149.10, 149.0, 148.8–148.7 (m), 137.7, 135.1 (d, $^{3}J_{CF}$ = 3.6 Hz), 135.0 (d, $^{3}J_{CF}$ = 4.2 Hz), 131.4–131.3 (m), 131.2–131.1 (m), 129.7 (d, $^{4}J_{CF}$ = 3.1 Hz), 129.6, 129.5, 128.93, 128.91, 128.5, 128.4, 127.9, 127.8, 127.0, 126.9, 122.8, 115.4 (d, $^{2}J_{CF}$ = 21.5 Hz), 105.1 (d, $^{2}J_{CF}$ = 21.7 Hz), 105.0 (d, $^{2}J_{CF}$

= 22.4 Hz), 90.4 (d, $^{4}J_{CF}$ = 1.6 Hz), 90.3 (d, $^{4}J_{CF}$ = 1.5 Hz), 14.6 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –90.9 (s, 0.35 × 1F), –91.4 (s, 0.65 × 1F), –113.7 to –113.8 (m, 1F) ; HRMS (EI): calc. for $C_{24}H_{18}F_2N_2O$ $[M]^+$: 388.1387, found: 388.1389.

*4.3.17. 5-((9H-Fluoren-9-ylidene)fluoromethoxy)-3-methyl-1-phenyl-1H-pyrazole (**3ha**)*

Grey solid, mp: 96.9–98.4 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.81–7.74 (m, 5H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.50–7.46 (m, 2H), 7.40–7.31 (m, 4H), 7.20–7.16 (m, 1H), 5.91 (d, *J* = 2.0 Hz, 1H), 2.30 (s, 3H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 151.3 (d, $^{1}J_{CF}$ = 301.5 Hz), 149.3, 147.1, 139.3 (d, $^{3}J_{CF}$ = 5.2 Hz), 139.0, 137.7, 134.6 (d, $^{3}J_{CF}$ = 6.3 Hz), 134.3 (d, $^{3}J_{CF}$ = 7.0 Hz), 129.3, 127.9 (d, $^{5}J_{CF}$ = 1.9 Hz), 127.8 (d, $^{5}J_{CF}$ = 2.1 Hz), 127.44, 127.42, 127.3, 124.4, 124.2, 123.6 (d, $^{4}J_{CF}$ = 1.9 Hz), 123.0, 120.1, 120.0, 102.6 (d, $^{2}J_{CF}$ = 23.1 Hz), 91.8 (d, $^{4}J_{CF}$ = 1.4 Hz), ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –77.7 (s, 1F) ; HRMS (EI): calc. for $C_{24}H_{17}FN_2O$ $[M]^+$: 138.1325, found: 368.1327.

*4.3.18. 5,5'-(((9H-Fluoren-9-ylidene)methylene)bis(oxy))bis(3-methyl-1-phenyl-1H-pyrazole) (**3ha'**)*

White solid, mp: 197.0–198.5 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.69–7.64 (m, 4H), 7.38–7.36 (m, 4H), 7.29–7.23 (m, 6H), 7.19–7.12 (m, 4H), 5.48 (s, 2H), 1.96 (s, 6H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 148.9, 147.8, 147.1, 139.5, 137.5, 134.9, 129.0, 128.1, 127.5, 127.1, 124.3, 122.7, 120.1, 109.5, 92.3, 14.5 ; HRMS (EI): calc. for $C_{34}H_{26}N_4O_2$ $[M]^+$: 522.2056, found: 522.2057.

*4.3.19. 5-((9H-Fluoren-9-ylidene)fluoromethoxy)-1,3-diphenyl-1H-pyrazole (**3hb**)*

Yellow solid, mp: 101.3–103.4 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.87–7.81 (m, 5H), 7.78–7.72 (m, 2H), 7.60–7.58 (m, 1H), 7.53–7.49 (m, 2H), 7.40–2.29 (m, 7H), 7.20–7.15 (m, 1H), 6.41 (d, *J* = 2.0 Hz, 1H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 151.3 (d, $^{1}J_{CF}$ = 301.6 Hz), 151.2, 147.8 (d, $^{4}J_{CF}$ = 2.0 Hz), 139.4 (d, $^{3}J_{CF}$ = 5.2 Hz), 139.1, 137.8, 134.6 (d, $^{3}J_{CF}$ = 6.3 Hz), 134.3 (d, $^{3}J_{CF}$ = 6.9 Hz), 132.7

129.4, 128.7, 128.6, 128.1 (d, $^{5}J_{CF}$ = 2.0 Hz), 128.0 (d, $^{5}J_{CF}$ = 1.9 Hz), 127.8, 127.5, 127.4, 125.6, 124.5, 124.3, 123.7 (d, $^{4}J_{CF}$ = 1.9 Hz), 123.3, 120.2, 103.0 (d, $^{2}J_{CF}$ = 22.9 Hz), 89.5 (d, $^{4}J_{CF3}$ = 1.3 Hz) ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –77.8 (s, 1F) ; HRMS (EI): calc. for $C_{29}H_{19}FN_2O$ $[M]^+$: 430.1481, found: 430.1487.

*4.3.20. 5,5'-(((9H-Fluoren-9-ylidene)methylene)bis(oxy))bis(1,3-diphenyl-1H-pyrazole) (**3hb'**)*

White solid, mp: 177.6–188.5 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.6 Hz, 2H ), 7.78 (d, *J* = 7.6 Hz, 2H ), 7.62–7.60 (m, 4H), 7.53–7.51 (m, 4H), 7.39–7.20 (m, 14H), 7.15–7.12 (m, 2H), 6.14 (s, 2H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.9, 147.8, 147.6, 139.6, 137.4, 134.8, 132.6, 129.1, 128.5, 128.39, 128.36, 127.7, 127.6, 125.6, 124.5, 123.0, 120.2, 110.1, 89.8 ; HRMS (EI): calc. for $C_{44}H_{30}N_4O_2$ $[M]^+$: 646.2369, found: 646.2366.

*4.3.21. (E)-5-((2-(4-Chlorophenyl)-1-fluorovinyl)oxy)-3-methyl-1-phenyl-1H-pyrazole (E-**3ja**)*

Oil (yellow); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.46–7.42 (m, 2H), 7.36–7.32 (m, 1H), 7.22–7.17 (m, 4H), 5.82 (d, *J* = 2.0 Hz, 1H), 5.58 (d, *J* = 5.6 Hz, 1H), 2.28 (s, 3H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 152.3 (d, $^{1}J_{CF}$ = 285.8 Hz), 149.1, 147.4 (d, $^{3}J_{CF}$ = 1.9 Hz), 137.7, 132.9 (d, $^{4}J_{CF}$ = 2.1 Hz), 129.4 (d, $^{3}J_{CF}$ = 7.7 Hz), 129.1, 129.0 (d, $^{4}J_{CF}$ = 3.6 Hz), 128.8, 127.3 123.1, 91.0 (d, $^{4}J_{CF}$ = 2.6 Hz), 90.6 (d, $^{2}J_{CF}$ = 34.9 Hz), 14.5 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –85.3 (dd, *J* = 5.6 Hz, *J* = 2.0 Hz, 1F) ; HRMS (EI): calc. for $C_{18}H_{14}ClFN_2O$ $[M]^+$: 328.0779, found: 328.0782.

*4.3.22. (Z)-5-((2-(4-Chlorophenyl)-1-fluorovinyl)oxy)-3-methyl-1-phenyl-1H-pyrazole (Z-**3ja**)*

Oil; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 2H), 7.47–7.43 (m, 2H), 7.34–7.29 (m, 5H), 5.87 (s, 1H), 5.36 (d, *J* = 28.0 Hz, 1H), 2.31 (s, 3H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 154.5 (d, $^{1}J_{CF}$ = 287.6 Hz), 149.0, 148.1, 137.7 132.9 (d, $^{4}J_{CF}$ = 3.1 Hz), 129.7 (d, $^{3}J_{CF}$ = 6.2 Hz), 129.13, 129.06, 128.9, 127.2, 122.6, 91.7, 88.9 (d, $^{2}J_{CF}$ = 16.5 Hz), 14.5 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –85.1 (d, *J*

= 27.8 Hz, 1F) ; HRMS (EI): calc. for $C_{18}H_{14}ClFN_2O$ $[M]^+$: 328.0779, found: 328.0777.

*4.3.23. (E)-5-((2-(3-Bromophenyl)-1-fluorovinyl)oxy)-3-methyl-1-phenyl-1H-pyrazole (E-**3ka**)*

Oil (yellow); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.6 Hz, 2H), 7.47–7.43 (m, 3H), 7.36–7.31 (m, 2H), 7.22–7.20 (m, 1H), 7.11–7.07 (m, 1H), 5.83 (d, *J* = 2.4 Hz, 1H), 5.56 (d, *J* = 6.0 Hz, 1H), 2.29 (s, 3H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.5 (d, $^1J_{CF}$ = 286.8 Hz), 149.1, 147.2 (d, $^3J_{CF}$ = 1.3 Hz), 137.6, 133.1 (d, $^3J_{CF}$ = 7.9 Hz), 130.6 (d, $^4J_{CF}$ = 3.5 Hz), 130.2 (d, $^5J_{CF}$ = 1.8 Hz), 130.1, 129.2, 127.4, 126.3 (d, $^4J_{CF}$ = 3.5 Hz), 123.2, 122.7, 91.1 (d, $^4J_{CF}$ = 1.8 Hz), 90.2 (d, $^2J_{CF}$ = 25.0 Hz), 14.5 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –84.6 (dd, *J* = 6.0 Hz, *J* = 2.3 Hz, 1F) ; HRMS (EI): calc. for $C_{18}H_{14}BrFN_2O$ $[M]^+$: 374.0253, found: 374.0255.

*4.3.24. (Z)-5-((2-(3-Bromophenyl)-1-fluorovinyl)oxy)-3-methyl-1-phenyl-1H-pyrazole (Z-**3ka**)*

Oil (yellow); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.52–7.52 (m, 1H), 7.47–7.44 (m, 2H), 3.37–7.26 (m, 3H), 7.21–7.17 (m, 1H), 5.88 (s, 1H), 5.33 (d, *J* = 27.6 Hz, 1H), 2.32 (s, 3H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 154.9 (d, $^1J_{CF}$ = 287.7 Hz), 149.1, 147.9, 137.9, 133.3 (d,$^4J_{CF}$ = 6.3 Hz), 130.6 (d, $^3J_{CF}$ = 7.4 Hz), 130.12, 130.09, 129.1, 127.2, 126.4 (d, $^4J_{CF}$ = 6.9 Hz), 122.8, 122.7, 91.9, 88.4 (d, $^2J_{CF}$ = 16.2 Hz), 14.6 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –84.0 (d, *J* = 27.8 Hz, 1F) ; HRMS (EI): calc. for $C_{18}H_{14}BrFN_2O$ $[M]^+$: 374.0253, found: 374.0255.

*4.3.25. (E/Z)-5-((1-Fluoro-2-(4-methoxyphenyl)vinyl)oxy)-3-methyl-1-phenyl-1H-pyrazole (E/Z-**3la**)*

Oil (grey); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.67–7.64 (m, 2H), 7.47–7.42 (m, 2H), 7.34–7.31 (m, 1H + 0.25 × 2H, *Z*-isomer), 7.25–7.21 (m, 0.75 × 2H, *E*-isomer), 6.89–6.86 (m, 0.25 × 2H, *Z*-isomer), 6.78–6.76 (m, 0.75× 2H, *E*-isomer), 5.85 (d, *J* = 1.2 Hz, 0.25 × 1H, *Z*-isomer), 5.81 (d, *J* = 1.6 Hz, 0.75 × 1H, *E*-isomer), 5.61 (d, *J* = 6.0 Hz, 0.75 × 1H, *E*-isomer), 5.40 (d, *J* = 28.0 Hz, 0.25 × 1H, *Z*-isomer), 3.80 (s, 0.25 × 3H, *Z*-isomer), 3.76 (s, 0.75× 3H, *E*-isomer), 2.30 (s, 0.25 × 3H, *Z*-isomer), 2.28 (s, 0.75× 3H, *E*-isomer) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 158.8–158.7 (m), 153.8, 153.3 (d, $^1J_{CF}$

= 287.3 Hz), 151.0, 149.1, 149.0 (d, $^{3}J_{CF}$ = 1.8 Hz), 148.1 (d, $^{3}J_{CF}$ = 2.6 Hz), 137.8, 137.8, 129.2, 129.2, 129.1, 129.5, 127.1, 127.0, 123.5 (d, $^{3}J_{CF}$ = 6.1 Hz), 123.1 (d, $^{3}J_{CF}$ = 7.1 Hz), 122.9, 122.6, 114.2, 114.1, 91.5 (d, $^{2}J_{CF}$ = 34.3 Hz), 91.2, 90.7 (d, $^{4}J_{CF}$ = 1.2 Hz), 90.1 (d, $^{2}J_{CF}$ = 17.2 Hz), 55.3, 55.3, 14.6, 14.5 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –88.1 (d, *J* = 27.8 Hz, 0.25 × 1F, *Z*-isomer), –88.5 (dd, *J* = 5.6 Hz, *J* = 1.5 Hz, 0.75× 1F, *E*-isomer) ; HRMS (EI): calc. for $C_{19}H_{17}FN_2O_2$ $[M]^+$: 324.1274, found: 324.1273.

*4.3.26. (E/Z)-5-((1-Fluoro-2-(4-(methylthio)phenyl)vinyl)oxy)-3-methyl-1-phenyl-1H-pyrazole (E/Z-**3ma**)*

Oil (brown); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.65–7.63 (m, 2H), 7.45–7.40 (m, 2H), 7.32–7.29 (m, 0.62 × 3H, *Z*-isomer), 7.28–7.26 (m, 0.38 × 1H, *E*-isomer), 7.21–7.14 (m, 2H), 7.09–7.07 (m, 0.38 × 2H, *E*-isomer), 5.85 (d, *J* = 0.8 Hz, 0.62 × 1H, *Z*-isomer), 5.81 (d, *J* = 1.0 Hz, 0.38 × 1H, *E*-isomer), 5.58 (d, *J* = 5.6 Hz, 0.38 × 1H, *E*-isomer), 5.37 (d, *J* = 28.4 Hz, 0.62 × 1H, *Z*-isomer), 2.44 (s, 0.62 × 3H, *Z*-isomer), 2.41 (s, 0.38 × 3H, *E*-isomer), 2.29 (s, 0.62 × 3H, *Z*-isomer), 2.27 (s, 0.38 × 3H, *E*-isomer) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 154.1 (d, $^{1}J_{CF}$ = 288.6 Hz), 153.0 (d, $^{1}J_{CF}$ = 284.8 Hz), 149.1, 149.0, 148.6, 147.8 (d, $^{3}J_{CF}$ = 2.3 Hz), 137.8, 137.8, 137.7 (d, $^{5}J_{CF}$ = 2.0 Hz), 137.7 (d, $^{5}J_{CF}$ = 2.5 Hz), 129.1, 128.3 (d, $^{3}J_{CF}$ = 6.9 Hz), 128.2 (d, $^{4}J_{CF}$ = 3.6 Hz), 127.8 (d, $^{4}J_{CF}$ = 6.2 Hz), 127.5 (d, $^{3}J_{CF}$ = 7.3 Hz), 127.2, 127.1, 126.6, 126.5, 122.9, 122.6, 91.5, 91.5, 90.9 (d, $^{4}J_{CF}$ = 1.2 Hz), 89.8 (d, $^{2}J_{CF}$ = 16.6 Hz), 15.6, 15.6, 14.6,14.6 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –85.7 (d, *J* = 27.8 Hz, 0.62 × 1F, *Z*-isomer), –86.4 (dd, *J* = 5.6 Hz, *J* = 1.1 Hz, 0.38 × 1F, *E*-isomer) ; HRMS (EI): calc. for $C_{19}H_{17}FN_2OS$ $[M]^+$: 340.1046, found: 340.1047.

*4.3.27. (E/Z)-5-((1-Fuoro-2-(naphthalen-2-yl)vinyl)oxy)-3-methyl-1-phenyl-1H-pyrazole (E/Z-**3na**)*

Oil (brown); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.93–7.91 (m, 0.36 × 1H, *E*-isomer), 7.80–7.69 (m, 4H), 7.62–7.60 (m, 0.64 × 1H, *Z*-isomer), 7.49–7.40 (m, 5H), 7.32–7.27 (m, 0.64 × 2H, *Z*-isomer),

7.27–7.25 (m, 0.36 × 1H, *E*-isomer), 7.21–7.17 (m, 0.36 × 1H, *E*-isomer), 6.19 (d, *J* = 5.2 Hz, 0.36 × 1H, *E*-isomer), 6.00–5.94 (m, 0.64 × 2H, *Z*-isomer), 5.82 (d, *J* = 2.4 Hz, 0.36 × 1H, *E*-isomer), 2.32 (s, 0.64 × 3H, *Z*-isomer), 2.23 (s, 0.36 × 3H, *E*-isomer) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 154.9 (d, $^1J_{CF}$ = 285.2 Hz), 153.9 (d, $^1J_{CF}$ = 277.1 Hz), 149.2, 149.0, 148.5, 148.1 (d, $^3J_{CF}$ = 1.9 Hz), 138.0, 137.7, 133.7, 133.6, 131.6 (d, $^3J_{CF}$ = 3.4 Hz), 131.4, 129.3, 129.0, 128.8, 128.7, 128.2, 128.1, 127.4 (d, $^3J_{CF}$ = 4.5 Hz), 127.3, 127.2, 127.0, 126.8 (d, $^3J_{CF}$ = 7.3 Hz), 126.5 (d, $^5J_{CF}$ = 2.0 Hz), 126.4 (d, $^4J_{CF}$ = 3.8 Hz) 126.0, 126.0, 125.6, 125.5, 123.9, 123.8, 122.9, 122.8, 91.9, 91.0 (d, $^4J_{CF}$ = 1.3 Hz), 88.4 (d, $^2J_{CF}$ = 33.8 Hz), 86.4 (d, $^2J_{CF}$ = 18.3 Hz), 14.7, 14.6 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –85.4 to –85.4 (m, 0.36 × 1F, *E*-isomer), –88.3 (d, *J* = 26.3 Hz, 0.64 × 1F, *Z*-isomer) ; HRMS (EI): calc. for $C_{22}H_{17}FN_2O$ $[M]^+$: 344.1325, found: 344.1328.

*4.3.28. (E/Z)-5-((2-(3,4-Dimethylphenyl)-1-fluorovinyl)oxy)-3-methyl-1-phenyl-1H-pyrazole (E/Z-**3oa**)*

Oil (grey); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.68–7.64 (m, 2H), 7.46–7.42 (m, 2H), 7.34–7.30 (m, 1H), 7.15–6.98 (m, 3H), 5.85 (d, *J* = 1.2 Hz, 0.25 × 1H, *Z*-isomer), 5.81 (d, *J* = 2.4 Hz, 0.75 × 1H, *E*-isomer), 5.60 (d, *J* = 6.0 Hz, 0.75 × 1H, *E*-isomer), 5.38 (d, *J* = 28.4 Hz, 0.25 × 1H, *Z*-isomer), 2.30 (s, 0.25 × 3H, *Z*-isomer), 2.27 (s, 0.75 × 3H, *E*-isomer), 2.24 (s, 0.25 × 6H, *Z*-isomer), 2.19 (s, 0.75 × 3H, *E*-isomer), 2.10 (s, 0.75 × 3H, *E*-isomer) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.8 (d, $^1J_{CF}$ = 287.8 Hz), 152.8 (d, $^1J_{CF}$ = 283.7 Hz), 149.1, 149.0, 148.9, 148.1 (d, $^3J_{CF}$ = 2.6 Hz), 137.9, 136.9, 136.8, 135.9 (d, $^5J_{CF}$ = 1.8 Hz), 135.9 (d, $^5J_{CF}$ = 2.3 Hz), 130.0, 129.9, 129.2, 129.1, 129.0 (d, $^4J_{CF}$ = 3.4 Hz), 128.6 (d, $^4J_{CF}$ = 6.1 Hz), 128.2 (d, $^3J_{CF}$ = 7.1 Hz), 127.1, 127.0, 125.4 (d, $^3J_{CF}$ = 7.0 Hz), 125.3 (d, $^4J_{CF}$ = 3.5 Hz), 122.9, 122.6, 91.8 (d, $^2J_{CF}$ = 33.8 Hz), 91.3, 90.6 (d, $^4J_{CF}$ = 1.4 Hz), 90.3 (d, $^2J_{CF}$ = 16.8 Hz), 19.8, 19.7, 19.5, 19.5, 14.6, 14.6 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –86.7 (d, *J* = 28.6 Hz, 0.25 × 1F, *Z*-isomer), –87.3 (d, *J* = 6.0 Hz, 0.75 × 1F, *E*-isomer) ; HRMS (EI): calc. for

$C_{20}H_{19}FN_2O$ $[M]^+$: 322.1481, found: 322.1484.

*4.3.29. 5-((1-Fluoro-2,2-diphenylvinyl)thio)-3-methyl-1-phenyl-1H-pyrazole (**3ad**)*

Oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.44–7.42 (m, 2H), 7.39–7.34 (m, 3H), 7.32–7.22 (m, 6H), 7.12–7.10 (m, 2H), 7.06–7.04 (m, 2H), 6.46 (s, 1H), 2.34 (s, 3H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 149.7, 147.8 (d, $^1J_{CF}$ = 304.0 Hz), 139.2, 137.4 (d, $^3J_{CF}$ = 4.1 Hz), 136.5 (d, $^3J_{CF}$ = 2.6 Hz), 130.3 (d, $^4J_{CF}$ = 3.1 Hz), 129.6, 129.5, 128.9, 128.7, 128.3, 128.1, 127.93, 127.86, 127.7, 125.4, 113.9, 13.7 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –91.2 (s, 1F) ; HRMS (EI): calc. for $C_{24}H_{19}FN_2S$ $[M]^+$: 386.1253, found: 386.1257.

*4.3.30. 5-((1-Fluoro-2,2-bis(3-(trifluoromethyl)phenyl)vinyl)thio)-3-methyl-1-phenyl-1H-pyrazole (**3fd**)*

Oil (yellow); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.6 Hz, 1H), 7.51–7.49 (m, 1H), 7.45–7.34 (m, 7H), 7.29–7.27 (m, 2H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 6.45 (s, 1H), 2,33 (s, 3H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.1 (d, $^1J_{CF}$ = 306.2 Hz), 149.8, 139.1, 137.3 (d, $^3J_{CF}$ = 4.4 Hz), 136.4 (d, $^3J_{CF}$ = 2.4 Hz), 133.7, 132.6 (d, $^4J_{CF}$ = 3.3 Hz), 131.0 (q, $^2J_{CF}$ = 32.3 Hz), 130.7 (q, $^2J_{CF}$ = 32.2 Hz), 129.1, 129.0, 128.8, 128.3, 123.84 (q, $^1J_{CF}$ = 272.5 Hz), 123.81 (q, $^1J_{CF}$ = 270.9 Hz), 127.1–127.0 (m), 126.7, 126.2–126.1 (m), 125.4, 125.3–125.2 (m), 124.9–124.8 (m), 124.4 (d, $^2J_{CF}$ = 15.8 Hz), 114.8, 13.7 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –62.5 (s, 3F), –62.7 (s, 3F), –88.0 (s, 1F) ; HRMS (EI): calc. for $C_{26}H_{17}F_7N_2S$ $[M]^+$: 522.1001, found: 522.1002.

*4.3.31. 5-((1-Fluoro-2,2-di-p-tolylvinyl)thio)-3-methyl-1-phenyl-1H-pyrazole (**3gd**)*

Oil (yellow); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.44–7.32 (m, 5H), 7.11–7.00 (m, 6H), 6.95–6.93 (m, 2H), 6.45 (s, 1H), 2.36 (s, 3H), 2.33 (s, 3H), 2.30 (s, 3H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 149.7, 147.1 (d, $^1J_{CF}$ = 303.1 Hz), 139.3, 137.9, 137.7, 134.7 (d, $^3J_{CF}$ = 4.2 Hz), 133.8 (d, $^4J_{CF}$ = 2.7 Hz), 130.2 (d, $^4J_{CF}$ = 3.1 Hz), 129.5 (d, $^3J_{CF}$ = 5.3 Hz), 129.2, 128.9, 128.8, 128.7, 127.8, 125.3, 125.1,

113.7, 21.3, 21.2, 13.7 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –92.0 (s, 1F) ; HRMS (EI): calc. for $C_{26}H_{23}FN_2S$ $[M]^+$: 414.1566, found: 414.1572.

*4.3.32. 5-((1-Fluoro-2,2-bis(3-(trifluoromethyl)phenyl)vinyl)thio)-1,3-diphenyl-1H-pyrazole (**3fe**)*

Oil (yellow); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.86–7.84 (m, 2H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.54–7.30 (m, 13H), 7.22–7.19 (m, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 6.96 (s, 1H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 152.3, 149.9 (d, $^1J_{CF}$ = 306.4 Hz), 139.2, 137.2 (d, $^3J_{CF}$ = 4.4 Hz), 136.4 (d, $^3J_{CF}$ = 2.4 Hz), 133.7, 132.6 (d, $^3J_{CF}$ = 3.4 Hz), 132.3, 131.0 (q, $^2J_{CF}$ = 32.3 Hz), 130.8 (q, $^2J_{CF}$ = 32.2 Hz), 129.1, 129.1, 128.9, 128.8, 128.6, 128.5, 127.9, 127.1–127.0 (m), 126.3–126.1 (m), 125.74, 125.65, 125.5–125.3 (m), 125.0–124.9 (m), 124.6 (d, $^2J_{CF}$ = 15.5 Hz), 123.9 (q, $^1J_{CF}$ = 270.8 Hz), 123.1 (q, $^1J_{CF}$ = 270.9 Hz), 112.3 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –62.5 (s, 3F), –62.6 (s, 3F), –87.9 (s, 1F) ; HRMS (EI): calc. for $C_{31}H_{19}F_7N_2S$ $[M]^+$: 584.1157, found: 584.1161.

*4.3.33. (E/Z)-5-((1-Fluoro-2-(4-methoxyphenyl)vinyl)oxy)-3-methyl-1-phenyl-1H-pyrazole (E/Z-**3jd**)*

Oil (yellow); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.56–7.15 (m, 9H), 6.49 (s, 1H), 6.42 (d, *J* = 16.0 Hz, 0.82 × 1H, *E*-isomer), 5.82 (d, *J* = 32.4 Hz, 0.18 × 1H, *Z*-isomer), 2.33 (s, 3H) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 151.2 (d, $^1J_{CF}$ = 297.4 Hz), 151.1 (d, $^1J_{CF}$ = 308.1 Hz), 149.8, 139.2, 139.0, 133.7 (d, $^4J_{CF}$ = 1.5 Hz), 130.2 (d, $^3J_{CF}$ = 9.0 Hz), 130.0 (d, $^3J_{CF}$ = 3.2 Hz), 129.9, 128.9, 128.8, 128.5, 128.2, 128.1, 127.6, 127.2 (d, $^4J_{CF}$ = 1.5 Hz), 125.7, 125.6, 125.1, 115.2 (d, $^2J_{CF}$ = 30.0 Hz), 114.8 (d, $^2J_{CF}$ = 11.1 Hz), 114.4, 113.7, 110.4, 14.4, 13.7 ; $^{19}$F NMR (376 MHz, $CDCl_3$) δ –82.2 (d, *J* = 16.2 Hz, 0.82 × 1F, *E*-isomer), –87.1 (d, *J* = 32.3 Hz, 0.18 × 1F, *Z*-isomer) ; HRMS (EI): calc. for $C_{18}H_{14}ClFN_2S$ $[M]^+$: 344.0550, found: 344.0551.

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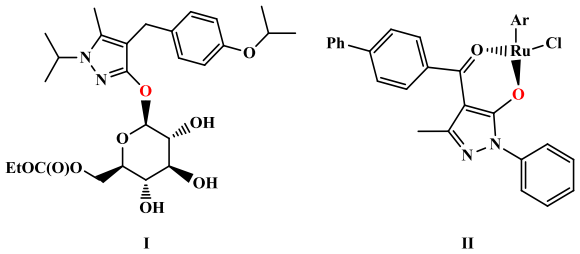
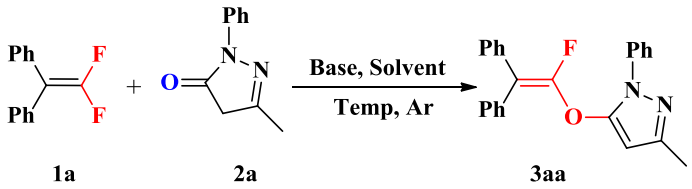



I II

**Fig. 1.** Examples of bioactive *O*-pyrazole derivatives.

**Table 1.** Optimization of reaction conditions.[a, b]




1a 2a 3aa

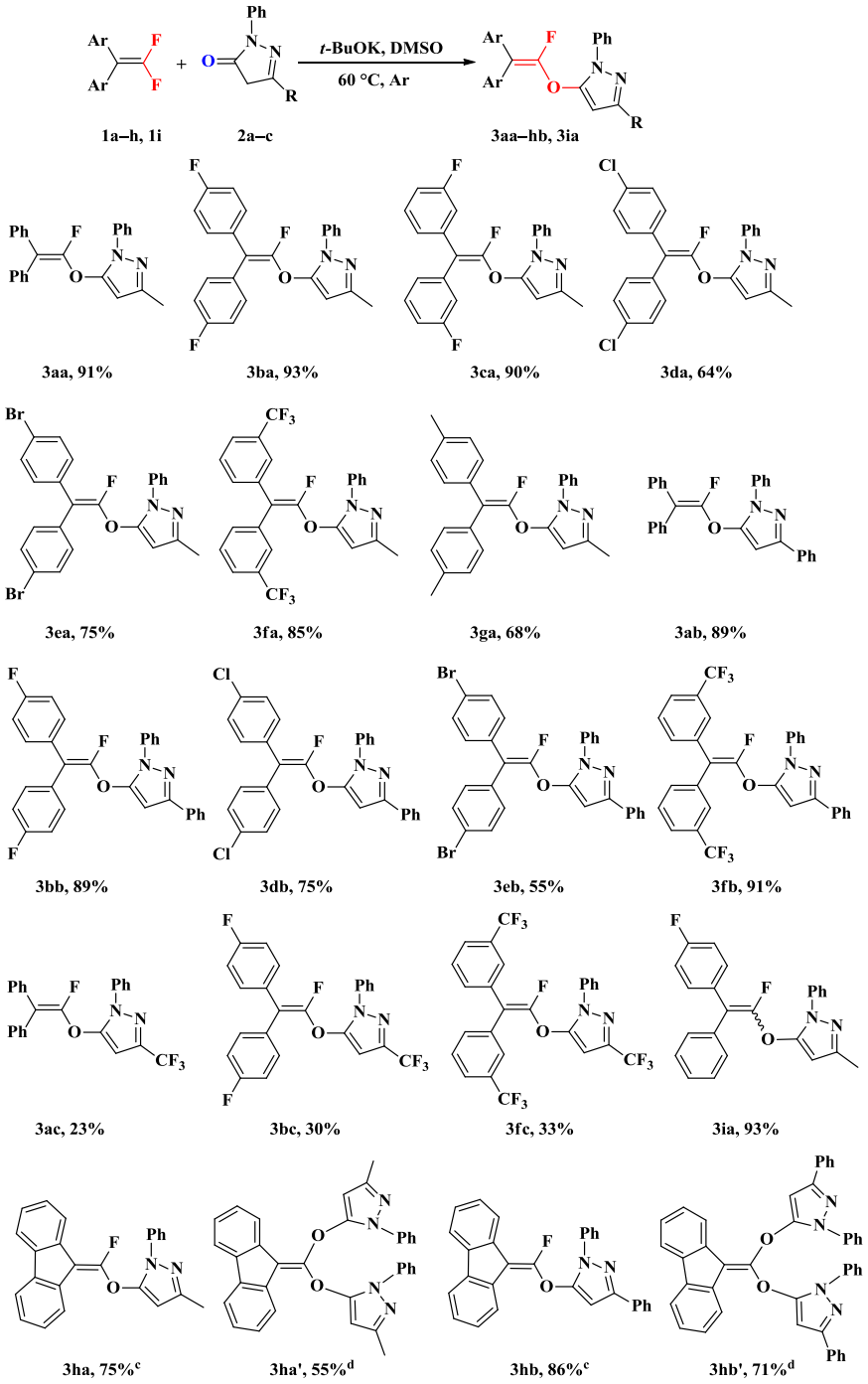
| Entry | **2a** (equiv) | Base (equiv) | Temp. (°C) | Solvent | Yield of **3aa** (%)[b] |
|---|---|---|---|---|---|
| 1 | 2.0 | *t*-BuOK (2.0) | 60 | 1,4-Dioxane | 0 |
| 2 | 2.0 | *t*-BuOK (2.0) | 60 | THF | 0 |
| 3 | 2.0 | *t*-BuOK (2.0) | 60 | $CH_3CN$ | 23 |
| 4 | 2.0 | *t*-BuOK (2.0) | 60 | NMP | 30 |
| 5 | 2.0 | *t*-BuOK (2.0) | 60 | DMF | 61 |
| 6 | 2.0 | *t*-BuOK (2.0) | 60 | DMSO | 94 |
| 7 | 2.0 | None | 60 | DMSO | 0 |
| 8 | 2.0 | *t*-BuOLi (2.0) | 60 | DMSO | 47 |
| 9 | 2.0 | $K_3PO_4$ (2.0) | 60 | DMSO | 50 |
| 10 | 2.0 | $Cs_2CO_3$ (2.0) | 60 | DMSO | 56 |
| 11 | 2.0 | NaOH (2.0) | 60 | DMSO | 83 |
| 12 | 2.0 | KOH (2.0) | 60 | DMSO | 80 |
| 13 | 2.0 | *t*-BuOK (2.5) | 60 | DMSO | 90 |

| | | | | | |
|---|---|---|---|---|---|
| 14 | 2.0 | *t*-BuOK (1.5) | 60 | DMSO | 75 |
| 15 | 2.0 | *t*-BuOK (2.0) | 25 | DMSO | 71 |
| 16 | 2.0 | *t*-BuOK (2.0) | 45 | DMSO | 89 |
| 17 | 2.0 | *t*-BuOK (2.0) | 75 | DMSO | 92 |
| 18 | 1.5 | *t*-BuOK (2.0) | 60 | DMSO | 67 |

[a] Reaction conditions: **1a** (0.25 mmol), solvent (2 mL), 24 h.

[b] Yields were determined by GC-MS analysis and based on **1a**.

**Table 2.** Reaction of various symmetrical *gem*-difluoroalkenes with pyrazolones.[a, b]



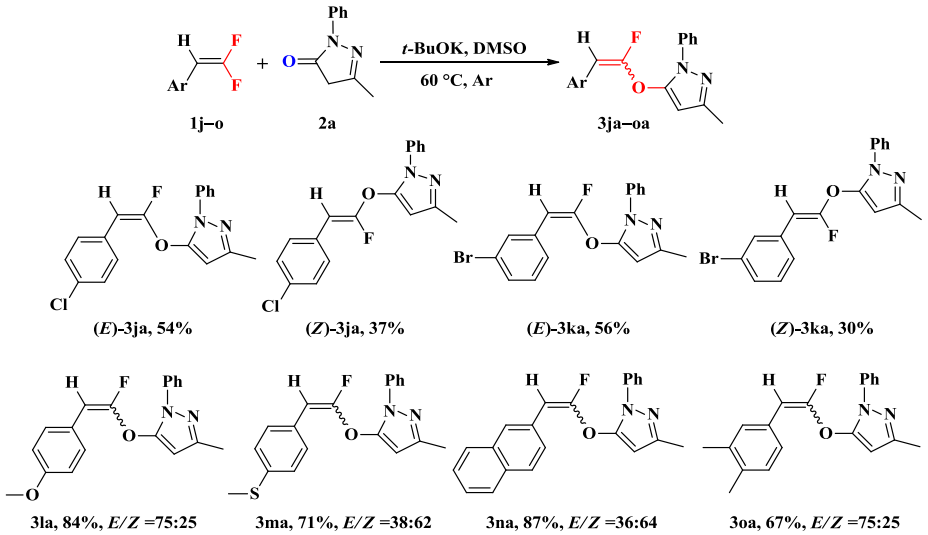

[a] Reaction conditions: **1a**–**g**, **1i** (0.5 mmol), **2a**–**c** (1.0 mmol), *t*-BuOK (1.0 mmol), DMSO (4 mL), 60 °C, 24 h.

[b] Isolated yields.

[c] Reaction conditions: **1h** (0.5 mmol); **2a**, **2b** (0.5 mmol), MeCN (4 mL), RT, 2 h.

[d] Reaction conditions: **1h** (0.5 mmol); **2a**, **2b** (1.0 mmol), MeCN (4 mL), RT, 4 h.

**Table 3.** Reaction of various umsymmetrical *gem*-difluoroalkenes with pyrazolones.[a,b,c]

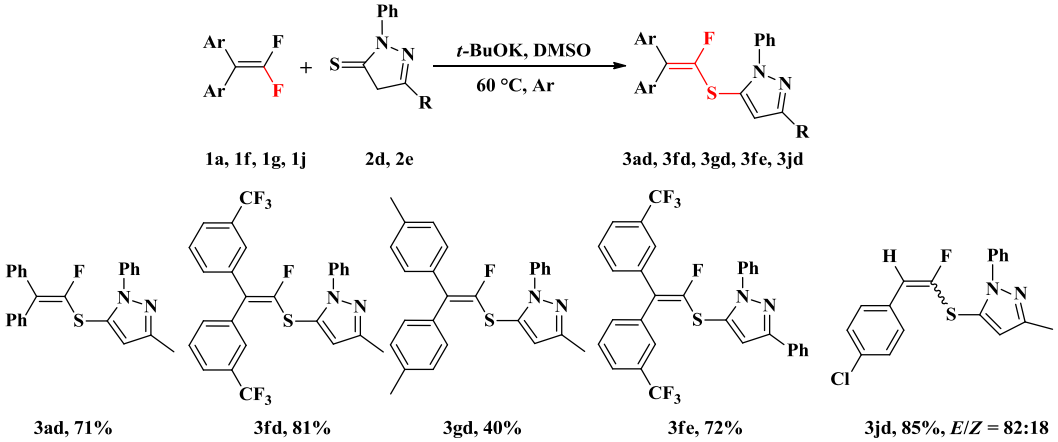



[a] Reaction conditions: **1j**–**o** (0.5 mmol), **2a** (1.0 mmol), *t*-BuOK (1.0 mmol), DMSO (4 mL), 60 °C, 24 h.

[b] Isolated yields of pure isomer or inseparable *E*/*Z* mixture of the products.

[c] *E*/*Z* selectivity was determined by $^{19}$F NMR spectra. The configurations of *E*- and *Z*-isomers were determined by their $^{3}J_{HF}$ coupling constants in $^{1}$H NMR spectra.

**Table 4.** Reaction of various *gem*-difluoroalkenes with pyrazol-5-thiones.[a, b, c]




[a] Reaction conditions: **1a**, **1f**, **1g**, **1j** (0.5 mmol), **2d**, **2e** (1.0 mmol), *t*-BuOK (1.0 mmol), DMSO (4 mL), 60 °C, 24 h.

[b] Isolated yields.

[c] *E/Z* selectivity was determined by $^{19}$F NMR spectra. The configurations of *E*- and *Z*-isomers were determined by their $^{3}J_{HF}$ coupling constants in $^{1}$H NMR spectra.