Tetrahedron 69 (2013) 6993–7000

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A new and direct route to 3-fluoromethyl substituted pyrazol-4-acrylates via Pd-catalyzed C–H activation

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ARTICLE INFO

Article history:
Received 6 April 2013
Received in revised form 8 June 2013
Accepted 17 June 2013
Available online 24 June 2013

Keywords:
3-Fluoromethyl pyrazoles
Pd-catalyzed C4–H activation
Benzoquinone
Concerted metalation–deprotonation (CMD)

ABSTRACT

Direct C4–H activation of 3-fluoromethyl pyrazoles followed by an oxidative coupling with acrylates, which is perhaps the most direct method for the synthesis of 3-fluoromethyl substituted pyrazol-4-acrylates of biological interest, remains challenging. Here, the first example of the straightforward olefination via Pd-catalyzed C4–H activation of both C3–CF_3 and C3–CF_2H substituted pyrazoles is reported. The reaction of various C3–CF_3 substituted pyrazoles with acrylates proceeds smoothly in the presence of $Pd(OAc)_2$ and Ag_2CO_3, whereas olefination of C3–CF_2H substituted pyrazoles requires the addition of benzoquinone. A further computational study reveals that reactivity of the pyrazolyl substrates employed are strongly impacted by the substituents of different nature on their C1 or C5 position, which is in good agreement with the experimental data.

1. Introduction

1,3,5-Trisubstituted pyrazoles that contain CF_3 and CF_2H functionalities are the core structure of many agrochemical and pharmaceutical products,[1] such as the non-steroidal anti-inflammatory drug Celecoxib,[1] SC-560,[1b,c] which is a COX-1 inhibitor and shows anti-tumor activity, and Deracoxib,[2] a marketed agent for the treatment of inflammation (Fig. 1).

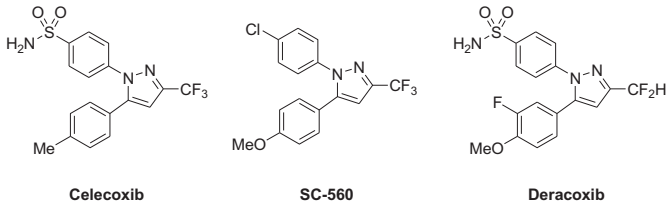

Fig. 1. Bioactive 1,3,5-trisubstituted pyrazoles.

While modification of the C4-position of 1,3,5-trisubstituted pyrazoles may lead to a further diversification of this compound library of biological interest, the conventional C4-functionalization is implemented by generating pyrazol metals, halides, and aldehydes as intermediates,[3] which have drawbacks in terms of atomic economy. Recently, the direct arylation and alkenylation of pyrazoles have been reported independently by Doucet,[4] Sames,[3d] and Chappell.[5] Although direct olefinations could be carried out based on electron-rich arenes and heterocycles,[6,7] reaction of electron-deficient arenes with olefins are still challenging.[8] This is mainly due to the difficulty for electron-deficient arenes to undergo an electrophilic attack of a Pd (II) complex to the reactant and their poor coordination with Pd catalysts.[8a,8d,8f] Previous work in regard to olefination of electron-deficient arenes mainly relies on the activation of the *meta*-position[8a] of arenes substituted with strong electron-withdrawing groups with only an *ortho*-directed[9] alkenylation as an exception.

Herein, we report the first example of $Pd(OAc)_2$ catalyzed direct *ortho*-olefination of electron-deficient CF_3 and CF_2H substituted pyrazoles with a range of substrates in moderate to high yields and high regioselectivities. Moreover, a computational study was performed to investigate the mechanism of action.

2. Results and discussion

2.1. Olefination of CF_3 substituted pyrazoles

Initially, a highly electron-deficient pyrazole **1a** and *n*-butyl acrylate **2a** were chosen as model substrates (Table 1). With

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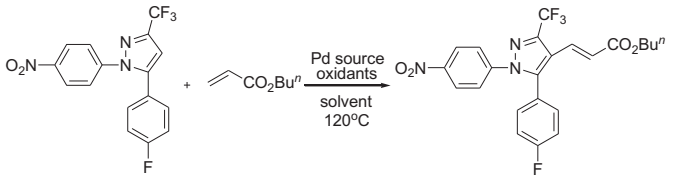
http://dx.doi.org/10.1016/j.tet.2013.06.058

Table 1
Optimization of reaction conditions for the olefination of 3-trifluoro-pyrazole **1a**



1a **2a** **3a**

Entry	Pd source (10%)	Ratio (**1a**:**2a**)	Oxidant (2 equiv)	Solvent	Yield (%)[a]
1	$PdCl_2$	1:2	$Cu(OAc)_2$	DMF	22
2	$PdCl_2(PPh_3)_2$	1:2	$Cu(OAc)_2$	DMF	9
3	$Pd(OAc)_2$	1:2	$Cu(OAc)_2$	DMF	40
4	$Pd(OAc)_2$	1:2	AgOAc	DMF	33
5	$Pd(OAc)_2$	1:2	Ag_2CO_3	DMF	52
6	$Pd(OAc)_2$	1:2	Ag_2CO_3	DMF+ DMSO (5%)	43
7	$Pd(OAc)_2$	1:2	Ag_2CO_3	DMSO	20
8	$Pd(OAc)_2$	1:2	Ag_2CO_3	DMA	35
9	$Pd(OAc)_2$	1:4	Ag_2CO_3	DMF	50
10	$Pd(OAc)_2$	1:1	Ag_2CO_3	DMF	50
11	$Pd(OAc)_2$	2:1	Ag_2CO_3	DMF	69
12	**$Pd(OAc)_2$**	**3:1**	**Ag_2CO_3**	**DMF**	**81**
13	$Pd(OAc)_2$	4:1	Ag_2CO_3	DMF	83

[a] Isolated yield.

10 mol % Pd source as a catalyst and $Cu(OAc)_2$ as an oxidant in *N*,*N*-dimethylformamide (DMF), the reaction was proceeded for 24 h at 120 °C. The desired product **3a** was obtained in yields of 22%, 9%, and 40% while $PdCl_2$, $PdCl_2(PPh_3)_2$, and $Pd(OAc)_2$ were used as the catalyst, respectively. Then we noticed that Ag_2CO_3 (entry 5) was a more efficient oxidant than $Cu(OAc)_2$ (entry 3) and AgOAc (entry 4). A screen of solvent showed that the reaction efficiency was decreased in DMF+DMSO (5%), DMSO and DMA (entries 6–8). Moreover, the ratio of **1a**:**2a** was critical for the reaction efficiency, and the good yield (81%) was obtained while **1a**:**2a** is 3:1 (entry12). The ratio increased to 4:1 did not improve the yield (entry 13). Therefore, the reaction carried out with **1a** (3 equiv), **2a** (1 equiv) and Ag_2CO_3 (2 equiv), which functions as both a base and oxidant in the presence of $Pd(OAc)_2$ (10 mol %) at 120 °C in DMF (entry 12).

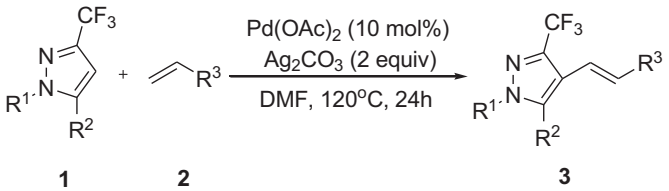
With the optimized conditions in hand, a variety of 3-trifluoromethyl substituted pyrazol-4-acrylates **3** were synthesized to explore the substrates scope and representative results are listed in Table 2. The alkenylation of pyrazoles **1** proceeded well with nearly all electron-deficient olefins bearing esters, cyanogen groups, and moderate to excellent yields were obtained in high regioselectivities (entries 1–14). However, in the cases of **3j** (56%, entry 10) and **3m** (54%, entry 13), the yields are less satisfactory probably because of the presence of their bulky tertiary butyl group. Acrylonitrile-substituted olefin was also tolerated, but an isomeric mixture (*E*/*Z*=1:0.78) of **3o** with a low yield of 38% was provided (entry 15). Regrettably, the reaction of 5-(4-fluorophenyl)-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazole with styrene (entry 16) was unsuccessful and no pure product was obtained.

2.2. Olefination of CF_2H substituted pyrazoles

Under the optimal conditions obtained for CF_3 substituted pyrazoles, CF_2H substituted pyrazole **4b** was also employed for the Pd-catalyzed oxidative olefination (Table 3). However, the corresponding product **5b** could not be afforded in good yield (10%, entry 1). Considering the different inductive effect between CF_3 and CF_2H group, the pk_a of the reaction system might influence the deprotonation of arenes. However, addition of K_2CO_3 (0.5 equiv) did not increase the yield, but led to the generation of only a trace amount of **5b** (entry 3). Since employment of sole oxidant could not successfully improve the reactivity, we sought to adopt ligand-induced C–H activation with Pd (II). According to Hull's[10] and Boele's[11] reports, benzoquinone (BQ) due to its oxidability, facile coordinative ability and small steric effect, was applied. However, addition of BQ alone even in 2 equiv did not affect the reaction (entry 10); therefore we attempted to mix BQ (0.5 equiv) with AgOAc or Ag_2CO_3 to promote the reaction. Mixture of Ag_2CO_3 with BQ appeared to give more effectively the desired product **5b** (entry 6), and after optimization, we found the optimal condition to be the addition of 1.5 equiv of BQ to a reaction system including $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2 equiv), and **4b** and **2a** in a ratio of 3:1 in DMF (entry 8).

Next, we explored substrate scope of the CF_2H substituted pyrazoles. Series of 3-difluoromethyl substituted pyrazol-4-acrylates **5**

Table 2
Reaction of 1,3,5-trisubstituted pyrazoles (CF_3) with acrylates[a]

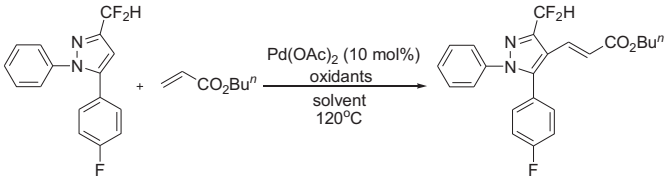


1 **2** **3**

Entry	R^1	R^2	R^3	Product	Yield (%)[b]
1	4-NO_2–C_6H_4	4-F–C_6H_4	$CO_2{}^nBu$	**3a**	81
2	Ph	4-F–C_6H_4	$CO_2{}^nBu$	**3b**	78
3	CH_3	4-F–C_6H_4	$CO_2{}^nBu$	**3c**	77
4	4-OMe-C_6H_4	4-F–C_6H_4	$CO_2{}^nBu$	**3d**	76
5	4-NO_2-C_6H_4	Ph	$CO_2{}^nBu$	**3e**	78
6	Ph	Ph	$CO_2{}^nBu$	**3f**	88
7	CH_3	Ph	$CO_2{}^nBu$	**3g**	75
8	4-OMe-C_6H_4	Ph	$CO_2{}^nBu$	**3h**	77
9	4-NO_2-C_6H_4	4-OMe–C_6H_4	$CO_2{}^nBu$	**3i**	82
10	Ph	4-OMe–C_6H_4	$CO_2{}^tBu$	**3j**	56
11	CH_3	4-OMe–C_6H_4	CO_2Et	**3k**	81
12	4-OMe-C_6H_4	4-OMe–C_6H_4	$CO_2{}^nBu$	**3l**	77
13	Ph	4-F–C_6H_4	$CO_2{}^tBu$	**3m**	54
14	Ph	4-F–C_6H_4	CO_2Et	**3n**	80
15	Ph	4-F–C_6H_4	CN	**3o**	38 (*E*/*Z*=1:0.78)[c]
16	Ph	4-F–C_6H_4	Ph	[d]	

[a] Unless otherwise noted, the reactions were carried out with pyrazoles **1** (0.42 mmol), acrylates **2** (0.14 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.0 equiv) in DMF (1 mL) at 120 °C for 24 h.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis of the crude product.
[d] The reaction was complicated.

Table 3
Optimization of reaction conditions for the olefination of 3-difluoro-pyrazole **4b**



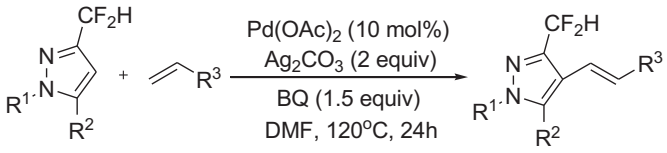
4b **2a** **5b**

Entry	Oxidant (equiv)	Additive (equiv)	Yield (%)[a]
1	Ag_2CO_3 (2)	—	10%
2	AgOAc (2.5)	—	36%
3	Ag_2CO_3 (2)	K_2CO_3 (0.5)	Trace
4	Ag_2CO_3 (2)	COD (0.5)	Trace
5	AgOAc (2.5)	BQ (0.5)	25%
6	Ag_2CO_3 (2)	BQ (0.5)	40%
7	Ag_2CO_3 (2)	BQ (1)	62%
8	**Ag_2CO_3 (2)**	**BQ** (1.5)	**78%**
9	Ag_2CO_3 (2)	BQ (2)	65%
10	—	BQ (2)	Trace

Bold signifies the optimal condition.
[a] Isolated yield.

were examined, shown in Table 4. Despite the different R^1 (4-NO_2–C_6H_4, Ph, CH_3, and 4-OMe–C_6H_4) and R^2 (4-F–C_6H_4, Ph, 4-OMe–C_6H_4 and 4-NO_2–C_6H_4) substituents on 3-CF_2H substituted pyrazoles **4** and the different acrylates **2** employed, the yields of the majority of the reactions are moderate (40–60%). Although in some cases the yields of the reactions could reach up to 70–80% (entries 2, 3, 8, and 14), the reactivity of CF_2H-substituted pyrazoles is weaker than that of CF_3-substituted pyrazoles. Acrylonitrile could proceed with 3-(difluoromethyl)-5-(4-fluorophenyl)-1-phenyl-1*H*-pyrazole, but a ratio of isomers (*E*/*Z*=0.87:1) was obtained in a low yield of 35% (entry 15).

Table 4
Reaction of 1,3,5-trisubstituted pyrazoles (CF_2H) with acrylates[a]



4 **2** **5**

Entry	R^1	R^2	R^3	Product (**5**)	Yield (%)[b]
1	4-NO_2–C_6H_4	4-F–C_6H_4	$CO_2{}^n$Bu	**5a**	55
2	Ph	4-F-C_6H_4	$CO_2{}^n$Bu	**5b**	78
3	CH_3	4-F-C_6H_4	$CO_2{}^n$Bu	**5c**	73
4	4-OMe–C_6H_4	4-F-C_6H_4	$CO_2{}^n$Bu	**5d**	52
5	4-NO_2–C_6H_4	Ph	$CO_2{}^n$Bu	**5e**	61
6	Ph	Ph	$CO_2{}^n$Bu	**5f**	29
7	4-OMe–C_6H_4	Ph	$CO_2{}^n$Bu	**5g**	35
8	4-NO_2–C_6H_4	4-OMe–C_6H_4	$CO_2{}^n$Bu	**5h**	80
9	Ph	4-NO_2–C_6H_4	$CO_2{}^n$Bu	**5i**	48
10	CH_3	4-NO_2–C_6H_4	**$CO_2{}^n$Bu**	**5j**	51
11	4-OMe–C_6H_4	4-NO_2–C_6H_4	$CO_2{}^n$Bu	**5k**	43
12	Ph	4-F–C_6H_4	CO_2Bu^t	**5l**	43
13	Ph	4-F-C_6H_4	CO_2Et	**5m**	46
14	CH_3	4-F-C_6H_4	CO_2Et	**5n**	73
15	Ph	4-F-C_6H_4	CN	**5o**	35 (*E*/*Z*=0.87:1)[c]

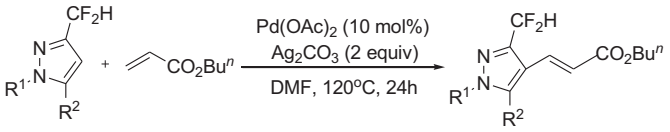
[a] Unless otherwise noted, the reactions were carried out with pyrazoles **4** (0.42 mmol), acrylates **2** (0.14 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.0 equiv), BQ (1.5 equiv) in DMF (1 mL) at 120 °C for 24 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis of the crude product.

2.3. Mechanism of pyrazole (CF_3 and CF_2H) palladation

Several reaction pathways have been proposed for the Pd-catalyzed C–H activation including oxidative C–H insertion,[12] electrophilic aromatic substitution (S_EAr),[13] Heck-like[14] anionic cross-coupling, and concerted metalation–deprotonation (CMD).[15] Two of which are most prevalent: S_EAr with electron-rich, π-nucleophilic heteroarenes and CMD with simple and electron-deficient benzenes. Fagnou[15b] demonstrated that the CMD pathway predicts not only the reactivity of simple and electron-deficient benzenes but also that of a diverse range of arenes and that have been proposed to react via S_EAr. Recently Ding[15e] reported that the rate- and regio-determining step of C–C coupling is a common CMD C–H activation of arenes featuring a six-membered ring transition state to form a Pd(II)-aryl intermediate. Possible arene/arene or alkene/alkene homocoupling pathways have been shown to be kinetically less competitive compared to the desired cross-coupling pathway. Therefore we performed the CMD pathway to form the Pd (II)-aryl intermediates, exploring why the activity is so different between the CF_3 substituted and CF_2H substituted pyrazoles.

Using the same conditions, which were used in Table 2 (Table 2, entries 5–8), we first probed the reactions compiled in Table 5

Table 5
Reaction of 1,3,5-trisubstituted pyrazoles (CF_2H) with acrylates[a] (No **BQ**)



4 **2a** **5**

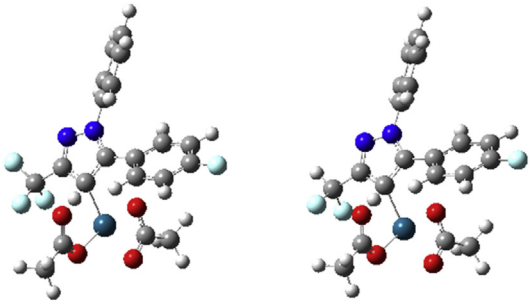
Entry	R^1	R^2	Product (**5**)	Yield[b] (%)
1	4-NO_2–C_6H_4	Ph	**5e**	39
2	Ph	Ph	**5f**	13
3	4-OMe–C_6H_4	Ph	**5g**	Trace
4	CH_3	Ph	**5p**	Trace
5	Ph	4-F–C_6H_4	**5b**	Trace
6	4-NO_2–C_6H_4	4-OMe–C_6H_4	**5h**	30
7	4-OMe–C_6H_4	4-NO_2–C_6H_4	**5k**	35
8	Ph	4-NO_2–C_6H_4	**5i**	56

[a] Unless otherwise noted, the reaction conditions were as follows: pyrazoles **4** (0.42 mmol), *n*-butyl acrylate **2a** (0.14 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.0 equiv), DMF (1 mL), 120 °C 24 h.
[b] Isolated yield.

without BQ (Table 5, entries 1–4). Obviously, CF_3-substituted pyrazoles are superiorly more reactive than the CF_2H-substituted counterparts regardless of the substituents on the pyrazole ring. In addition, the presence of an electron-withdrawing group, 4-NO_2–C_6H_4, may enhance the reactivity to give the olefinated product **5e** in a relatively better yield (entry 1). However, products can be hardly obtained for the reactions in entry 3 and entry 4. The trend of reactivity is mainly oriented by the electron-withdrawing ability of the substituent (CH_3<4-OMe–C_6H_4<Ph<4-NO_2–C_6H_4). Furthermore, when R^1 is remained unchanged, a better yield can be obtained (56%, entry 8) while an electron-withdrawing group (4-NO_2–C_6H_4) is present (vs 13%, entry 2). In contrast, while an electron-donating group (4-OMe–C_6H_4) was introduced into the C5 position of CF_2H substituted pyrazole with unchanged R^2, the yield (35%, entry 7) was decreased (vs 56%, entry 8).

Since generally the coordination ability ($E_{int(TS)}$) of CF_3 is weaker than that of CF_2H, the different reactivity between the two differently substituted pyrazoles could mainly be ascribed to the diverse distortion energy ($E_{dist(TS)}$) of the pyrazolyl core under the participation of $Pd(OAc)_2$.

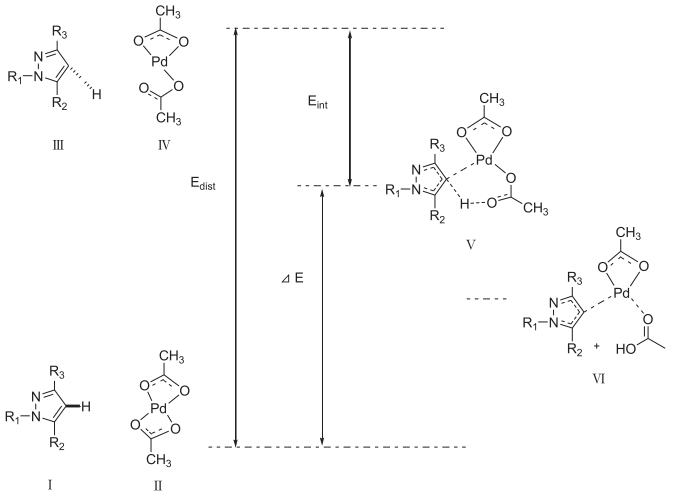
The mechanism of the olefination of CF_3-substituted pyrazoles **1A**–**1Q** and CF_2H-substituted pyrazoles **4A**–**4Q** is further evaluated by density functional theory (DFT) with the B3LYP exchange-correlation functional. [16] In each case, a relevant transition state (TS-**1K** and TS-**4K**) corresponding to the CMD pathway is located (TSs involving two acetate ligands for CF_3–pyrazole **1K** and CF_2H–pyrazole **4K** are shown in Fig. 2). This pathway corresponds to the lowest energy and predicts reactivity for all pyrazoles, regardless of their electronic properties (The blue ball stands for Pd, red balls for O, gray balls for C, white balls for H, and light blue balls for F).



TS-**1K** TS-**4K**

Fig. 2. Transition states TS-**1K** and TS-**4K**.

To explore the factors controlling the oxidative addition, we analyze the energies to distort isolated reactants to the transition state geometry (the distortion energy) and the energy of interaction between these distorted reactants (the interaction energy). This, which is known as an activation strain model, has been applied by Bickelhaupt [17] to Pd (0) oxidative additions, and is also related to the deformation/interaction method developed by Morokuma [18] for other systems. Distortion energies on which we focuse have also been discussed by Guthrie. [19] The decomposition of the activation energy into distortion (ΔE_{dist}) and interaction energies (ΔE_{int}) is shown (Scheme 1).



Scheme 1. Activation strain analysis.

The analysis is carried out with compound **4G** (Fig. 3), and data of other substrates similar to **4G** are summarized in Table 6 and Fig. 4. The $E_{dist(TS)}$ of the heterocycle portion for all the transition structures of oxidative addition are decomposed into their out-of-plane ($E_{dist(out\text{-}of\text{-}plane)}$) and bending components ($E_{dist(stretch)}$). The stretching contribution of the distortion is obtained by freezing the bond length of the C–H bond upon, which the oxidative addition occur, and the geometry is reoptimized at B3LYP/6-31G(d). The out-of-plane component is obtained by substracting bending components from the heterocycle portion (Fig. 3). $E_{dist(out\text{-}of\text{-}plane)}$ of both CF_3 and CF_2H pyrazoles is 3–4 kcal/mol greater than their

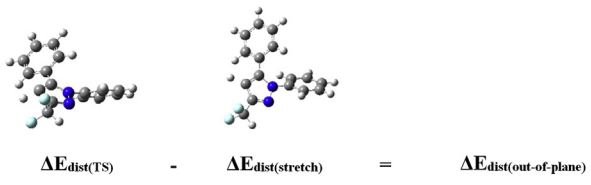
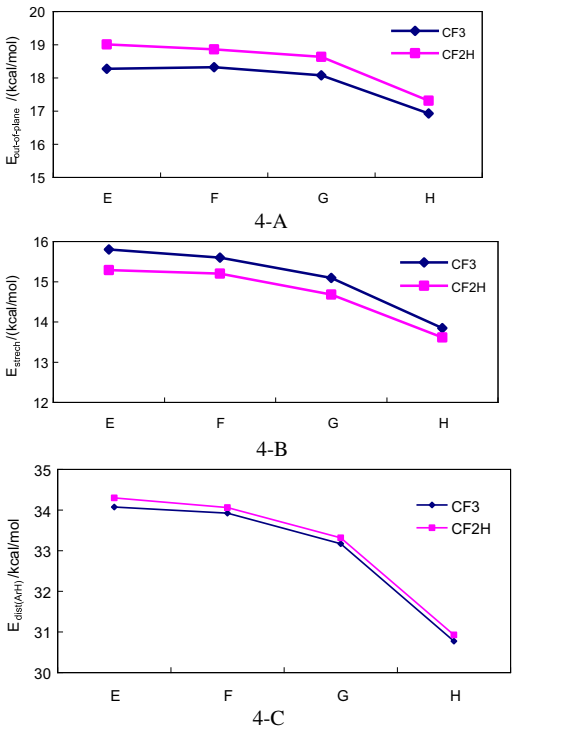


Fig. 3. The out-of-plane component was obtained by substraction.

Table 6
Decomposition of the distortion energy of the pyrazole portion with changes in C–H bond lengths (Δd_{C-H}) and changes in H–C4–C3–N2 dihedrals ($\Delta_{dihedral}$) in terms of the substitution variants

Pyrazoles	$E_{dist\ (TS)}$	$\Delta_{dihedral}$	$E_{dist\ (out\text{-}of\text{-}plane)}$	$\Delta d_{(C-H)}$	$E_{dist\ (stretch)}$
1E	34.074	54.262	18.2737	0.238	15.8003
1F	33.923	52.845	18.3234	0.236	15.5996
1G	33.171	52.069	18.0767	0.232	15.0943
1H	30.774	49.525	16.9292	0.220	13.8448
4E	34.298	55.295	19.0107	0.234	15.2873
4F	34.061	53.524	18.8601	0.233	15.2009
4G	33.315	52.584	18.6343	0.228	14.6807
4H	30.926	49.544	17.3121	0.218	13.6139



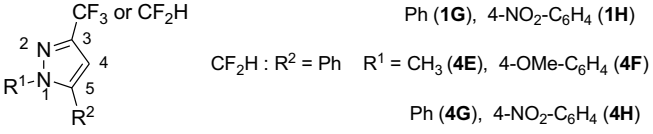


Fig. 4. Relationship between the differently substituted CF_3– or CF_2H–pyrazoles and their corresponding A: $E_{out\text{-}of\text{-}plane}$; B: E_{strech}; C: $E_{dist\ (ArH)}$ via CMD-based transition state.

$E_{dist(stretch)}$ in the same structure (Table 6), indicating its important contribution to $E_{dist(TS)}$. This is in good agreement with the experimental results above (Fig. 4A and Table 5). However, the predicted $E_{dist(stretch)}$ is contrary to that obtained by experimental results (Fig. 4B and Table 5). According to the $E_{dist(out\text{-}of\text{-}plane)}$ values we conclude several points as follows: (1) On a similar structural basis, $E_{dist(out\text{-}of\text{-}plane)}$ of CF_3 pyrazoles is 0.5–0.7 kcal/mol lesser than that of CF_2H pyrazoles with a relatively small bending angle (Table 6). Similar to the calculation results, CF_3 pyrazoles are more reactive in experimental observations (Tables 2 and 5) as expected. (2) For pyrazoles **4E**–**4H**, when electron-donating groups (4-OMe–C_6H_4 and CH_3) are replaced by an electron-withdrawing group (4-NO_2–C_6H_4), values for $E_{dist(out\text{-}of\text{-}plane)}$ and $E_{dist(stretch)}$ decrease. Thus the computational activity (CH_3<4-OMe–C_6H_4 <Ph<4-NO_2–C_6H_4) is in good agreement with experimental results in Table 5. (3) The above two points are also applicable to other substrates (all other values of $E_{dist(TS)}$, $E_{dist(out\text{-}of\text{-}plane)}$ and $E_{dist(stretch)}$ are listed in Supplementary data).

3. Conclusion

In summary, a novel protocol for the synthesis 3-fluoromethyl substituted pyrazol-4-acrylates was developed via a Pd (II)-catalyzed C–H bond activation under mild conditions. The C3–CF_3 substituted pyrazoles reacted with acrylates directly under the action of $Pd(OAc)_2$ and Ag_2CO_3, while BQ was found to be additionally needed for olefination of C3–CF_2H substituted pyrazoles. A computational study suggests the reactivity of both substrate

classes is strongly affected by substitution effects, according well with the experimental data. Further studies to enlarge the substrate scope and to investigate the mechanism of action using calculations are currently underway.

4. Experimental

4.1. General

All chemicals used in this study were obtained from commercial sources and used without further purification. The chromatographic purification of the products was conducted by flash chromatography using Merck silica gel 60 (200–300 mesh). IR spectra were measured on a Nicolet Magna IR-550 spectrometer using potassium bromide pellet. High resolution mass spectra were carried out on a Finnigan GC–MS-4021 spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded on a Brucker AM-400 spectrometer with Me_4Si as the internal standard. ^{19}F NMR spectra were obtained on a Brucker AM-400 (367.5 MHz) spectrometer in $CDCl_3$ with $CFCl_3$ as the external standard, with down-field shifts being designated as negative. All chemical shifts (δ) are expressed in parts per million and coupling constants (J) are given in Hertz.

4.2. General procedure for olefination of CF_3 substituted pyrazoles via C–H bond activation

To a solution of $Pd(OAc)_2$ (10 mol %) in DMF (1 mL) were added Ag_2CO_3 (2.0 equiv), the pyrazoles (3.0 equiv), and the acrylates (1.0 equiv). The mixture was then heated to 120 °C (oil bath) and stirred for 24 h. The resulting mixture was cooled to room temperature, diluted with ethyl acetate, washed with 1 N HCl and brine, dried over Na_2SO_4, filtered, and then concentrated. The resulting residue was purified with silica gel chromatography to provide the pure product.

*4.2.1. (E)-Butyl 3-(5-(4-fluorophenyl)-1-(4-nitrophenyl)-3-(trifluoro methyl)-1H-pyrazol-4-yl) acrylate (**3a**).* IR (KBr): 3087, 2961, 2874, 1707, 1346, 1185, 857, 693 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21 (2H, d, J=7.2 Hz), 7.46–7.42 (3H, m), 7.25–7.18 (4H, m), 6.16 (1H, d, J=13.2 Hz), 4.16 (2H, t, J=5.4 Hz), 1.68–1.62 (2H, m), 1.42–1.37 (2H, m), 0.95 (3H, t, J=6.0 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −61.7 (3F, s), −108.1 (1F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.5, 163.8 (d, J=194.9 Hz), 147.0, 144.0, 143.0, 141.9 (q, J=30.9 Hz), 132.2, 132.1, 130.8, 125.2, 124.7, 124.6, 122.1 (q, J=209.7 Hz), 117.2, 117.0, 64.7, 30.6, 19.1, 13.7. MS (EI): m/z (%): 477 (M^+, 7), 404 (23), 376 (100). HRMS (EI) calcd for $C_{23}H_{19}N_3O_4F_4$: 477.1312, found: 477.1317.

*4.2.2. (E)-Butyl 3-(5-(4-fluorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)acrylate (**3b**).* IR (KBr): 3071, 2962, 2874, 1713, 1332, 1183, 844, 693 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (1H, d, J=12.8 Hz), 7.35–7.34 (3H, m), 7.22–7.19 (4H, m), 7.11 (2H, t, J=6.8 Hz), 6.15 (1H, d, J=12.8 Hz), 4.15 (2H, t, J=5.4 Hz), 1.67–1.64 (2H, m), 1.42–1.37 (2H, m), 0.95 (3H, t, J=6.0 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −61.6 (3F, s), −109.7 (1F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.8, 163.4 (d, J=201.2 Hz), 143.9, 141.1 (q, J=33.5 Hz), 138.3, 132.3, 132.2, 131.8, 129.2, 128.7, 125.4 (q, J=213.5 Hz), 125.3, 121.0, 116.6, 116.4, 64.6, 30.7, 19.2, 13.7. HRMS (ESI) calcd for $C_{23}H_{20}N_2O_2F_4$ $[M+H]^+$: 433.1539, found: 433.1527.

*4.2.3. (E)-Butyl 3-(5-(4-fluorophenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)acrylate (**3c**).* IR (KBr): 3074, 2962, 2875, 1713, 1177, 848, 627 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41 (1H, d, J=12.8 Hz), 7.34 (2H, dd, J=6.6 Hz, J=4.2 Hz), 7.27 (2H, d, J=13.6 Hz), 5.97 (1H, d, J=13.2 Hz), 4.12 (2H, t, J=5.2 Hz), 3.77 (3H, s), 1.65–1.60 (2H, m), 1.40–1.35 (2H, m), 0.93 (3H, t, J=6.0 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −61.3 (3F, s), −109.4 (1F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.9, 163.7 (d, J=201.5 Hz), 144.3, 139.3 (q, J=30.9 Hz), 131.93, 131.87, 131.81, 122.4 (d, J=209.5 Hz), 116.9, 116.7, 114.1, 64.5, 37.7, 30.7, 19.1, 13.7. MS (EI): m/z (%): 370 (M^+, 4), 297 (23), 269 (100), 244 (36). HRMS (EI) calcd for $C_{18}H_{18}N_2O_2F_4$: 370.1304, found: 370.1305.

*4.2.4. (E)-Butyl 3-(5-(4-fluorophenyl)-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)acrylate (**3d**).* IR (KBr): 2961, 2872, 1701, 1517, 1167, 834, 703 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (1H, d, J=16.0 Hz), 7.21–7.18 (2H, m), 7.13–7.08 (4H, m), 6.82 (2H, d, J=9.2 Hz), 6.12 (1H, d, J=16.4 Hz), 4.14 (2H, t, J=6.8 Hz), 3.79 (3H, s), 1.68–1.61 (2H, m), 1.43–1.34 (2H, m), 0.94 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −61.4 (3F, s), −109.9 (1F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.9, 163.4 (d, J=241.4 Hz), 159.6, 144.0, 140.1 (q, J=30.9 Hz), 132.3, 132.2, 131.8, 131.3, 126.7, 120.7 (d, J=218.6 Hz), 116.6, 116.4, 114.6, 114.3, 64.6, 55.5, 30.7, 19.2, 13.7. MS (EI): m/z (%): 462 (M^+, 29), 389 (22), 361 (100). HRMS (EI) calcd for $C_{24}H_{22}N_2O_3F_4$: 462.1567, found: 462.1570.

*4.2.5. (E)-Butyl 3-(1-(4-nitrophenyl)-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)acrylate (**3e**).* IR (KBr): 3087, 2961, 2874, 1700, 1347, 1195, 856, 706 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21 (2H, d, J=8.8 Hz), 7.53–7.41 (6H, m), 7.25–7.23 (2H, m), 6.16 (1H, d, J=16.4 Hz), 4.14 (2H, t, J=6.8 Hz), 1.67–1.60 (2H, m), 1.43–1.34 (2H, m), 0.93 (3H, t, J=7.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −61.8 (3F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.6, 146.9, 145.1, 143.2, 142.0 (q, J=29.4 Hz), 131.1, 130.6, 130.1, 129.7, 129.0, 127.4, 125.2, 124.5, 121.8 (q, J=219.9 Hz), 116.1, 64.6, 30.6, 19.1, 13.7. HRMS (ESI) calcd for $C_{23}H_{21}N_3O_4F_3$ $[M+H]^+$: 460.1484, found: 460.1459.

*4.2.6. (E)-Butyl 3-(1,5-diphenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)acrylate (**3f**).* IR (KBr): 2964, 2930, 2870, 1712, 1336, 1186, 761, 702 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52 (1H, d, J=16.4 Hz), 7.44–7.38 (3H, m), 7.33–7.29 (3H, m), 7.33–7.20 (4H, m), 6.15 (1H, d, J=16.4 Hz), 4.14 (2H, t, J=6.6 Hz), 1.67–1.60 (2H, m), 1.43–1.34 (2H, m), 0.94 (3H, t, J=7.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −61.4 (3F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.9, 145.0, 140.8, 138.5 (q, J=32.3 Hz), 132.0, 130.2, 129.9, 129.0, 128.6, 127.9, 125.2, 120.7, 120.3 (q, J=218.8 Hz), 114.8, 64.5, 30.7, 19.2, 13.7. MS (EI): m/z (%): 414 (M^+, 5), 341 (11), 313 (100), 293 (12). HRMS (EI) calcd for $C_{23}H_{21}N_2O_2F_3$: 414.1555, found: 414.1561.

*4.2.7. (E)-Butyl 3-(1-methyl-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)acrylate (**3g**).* IR (KBr): 3071, 2961, 2874, 1703, 1120, 974, 707 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56–7.55 (3H, m), 7.43 (1H, d, J=16.4 Hz), 7.35–7.32 (2H, m), 5.97 (1H, d, J=16.0 Hz), 4.11 (2H, t, J=6.8 Hz), 3.77 (3H, s), 1.65–1.58 (2H, m), 1.41–1.32 (2H, m), 0.92 (3H, t, J=7.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −61.2 (3F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 167.0, 145.4, 139.3 (q, J=30.9 Hz), 132.1, 130.2, 129.8, 129.4, 127.9, 120.3 (q, J=211.3 Hz), 119.8, 113.9, 64.4, 37.7, 30.7, 19.1, 13.7. MS (EI): m/z (%): 352 (M^+, 4), 279 (28), 251 (100), 231 (29). HRMS (EI) calcd for $C_{18}H_{19}N_2O_2F_3$: 352.1399, found: 352.1391.

*4.2.8. (E)-Butyl 3-(1-(4-methoxyphenyl)-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)acrylate (**3h**).* IR (KBr): 3066, 2958, 2871, 1704, 1517, 1166, 833, 704 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51 (1H, d, J=16.4 Hz), 7.43–7.38 (3H, m), 7.21–7.19 (2H, m), 7.13 (2H, d, J=9.2 Hz), 6.80 (2H, d, J=9.2 Hz), 6.13 (1H, d, J=16.4 Hz), 4.13 (2H, t, J=6.8 Hz), 3.77 (3H, s), 1.69–1.60 (2H, m), 1.43–1.33 (2H, m), 0.93 (3H, t, J=7.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −61.3 (3F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 167.0, 159.5, 145.0, 140.3 (q, J=37.8 Hz), 132.1, 131.5, 130.3, 129.8, 129.1, 128.0, 126.6, 120.5 (q, J=220.7 Hz), 114.5, 114.1, 64.5, 55.5, 30.7, 19.2, 13.7. MS (EI): m/z (%): 444 (M^+, 24),

371,[17] 343 (100). HRMS (EI) calcd for $C_{24}H_{23}N_2O_3F_3$: 444.1663, found: 444.1661.

*4.2.9. (E)-Butyl 3-(5-(4-methoxyphenyl)-1-(4-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl) acrylate (**3i**).* IR (KBr): 3089, 2962, 2874, 1714, 1341, 1183, 858, 692 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.19 (2H, d, J=8.0 Hz), 7.50–7.43 (3H, m), 7.15 (2H, d, J=7.6 Hz), 6.98 (2H, d, J=7.6 Hz), 6.18 (1H, d, J=16.4 Hz), 4.15 (2H, t, J=6.6 Hz), 3.87 (3H, s), 1.68–1.61 (2H, m), 1.44–1.35 (2H, m), 0.94 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −61.8 (3F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.7, 161.2, 146.8, 145.2, 143.4 (q, J=28.9 Hz), 131.5, 125.2, 124.5, 122.2, 121.4 (q, J=220.1 Hz), 120.0, 119.1, 115.8, 115.1, 114.5, 64.6, 55.4, 30.7, 19.1, 13.7. MS (EI): m/z (%): 489 (M^+, 15), 459 (57), 388 (73), 358 (100), 342.[12] HRMS (EI) calcd for $C_{24}H_{22}N_3O_5F_3$: 489.1512, found: 489.1517.

*4.2.10. (E)-tert-Butyl 3-(5-(4-methoxyphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl) acrylate (**3j**).* IR (KBr): 3086, 2973, 2842, 1712, 1294, 1141, 870, 693 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.43 (1H, d, J=16.4 Hz), 7.32–7.31 (3H, m), 7.24–7.21 (2H, m), 7.12 (2H, d, J=8.8 Hz), 6.91 (2H, d, J=8.8 Hz), 6.12 (1H, d, J=16.4 Hz), 3.83 (3H, s), 1.48 (9H, s). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −61.6 (3F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.3, 160.6, 145.0, 140.3, 138.7 (q, J=30.5 Hz), 131.6, 131.1, 129.0, 128.4, 125.2, 122.5, 122.1, 120.4 (q, J=217.3 Hz), 120.0, 114.6, 80.5, 55.3, 28.2. MS (EI): m/z (%): 444 (M^+, 9), 388 (27), 343 (100), 323.[14] HRMS (EI) calcd for $C_{24}H_{23}N_2O_3F_3$: 444.1661, found: 444.1660.

*4.2.11. (E)-Ethyl 3-(5-(4-methoxyphenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)acrylate (**3k**).* IR (KBr): 2953, 2899, 1700, 1332, 1197, 835, 719 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.43 (1H, d, J=16.4 Hz), 7.25 (2H, d, J=8.8 Hz), 7.06 (2H, d, J=8.8 Hz), 6.00 (1H, d, J=16.4 Hz), 4.17 (2H, q, J=7.2 Hz), 3.90 (3H, s), 3.76 (3H, s), 1.27 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −61.2 (3F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 167.0, 161.0, 145.4, 139.3 (q, J=29.5 Hz), 132.3, 131.2, 121.4 (q, J=215.5 Hz), 119.8, 119.4, 114.9, 113.8, 60.4, 55.4, 37.6, 14.2. MS (EI): m/z (%): 354 (M^+, 19), 309,[19] 281 (100), 261 (29). HRMS (EI) calcd for $C_{17}H_{17}N_2O_3F_3$: 354.1191, found: 354.1192.

*4.2.12. (E)-Butyl 3-(1,5-bis(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)acrylate (**3l**).* IR (KBr): 2961, 2874, 2842, 1713, 1517, 1255, 837, 705 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.51 (1H, d, J=16.4 Hz), 7.15–7.10 (4H, m), 6.91 (2H, d, J=8.4 Hz), 6.81 (2H, d, J=9.2 Hz), 6.15 (1H, d, J=16.4 Hz), 4.14 (2H, t, J=6.6 Hz), 3.83 (3H, s), 3.79 (3H, s), 1.68–1.61 (2H, m), 1.42–1.36 (2H, m), 0.94 (3H, t, J=7.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −61.4 (3F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 167.1, 160.5, 159.4, 145.1, 140.2 (q, J=36.8 Hz), 132.4, 131.7, 131.6, 126.6, 122.8 (q, J=219.6 Hz), 120.1, 119.9, 114.6, 114.2, 114.1, 64.5, 55.5, 55.3, 30.7, 19.2, 13.7. MS (EI): m/z (%): 474 (M^+, 28), 401,[11] 373 (100). HRMS (EI) calcd for $C_{25}H_{25}N_2O_4F_3$: 474.1766, found: 474.1770.

*4.2.13. (E)-tert-Butyl 3-(5-(4-fluorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)acrylate (**3m**).* IR (KBr): 3072, 2976, 2936, 1709, 1313, 1123, 872, 693 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.41 (1H, d, J=12.8 Hz), 7.35–7.33 (3H, m), 7.22–7.19 (4H, m), 7.11 (2H, t, J=6.8 Hz), 6.10 (1H, d, J=13.2 Hz), 1.49 (9H, s). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −61.7 (3F, s), −109.8 (1F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.1, 163.4 (d, J=201.2 Hz), 143.9, 140.5 (q, J=31.9 Hz), 138.4, 132.3, 132.2, 130.7, 129.2, 128.7, 126.3, 122.6 (q, J=222.4 Hz), 116.6, 116.4, 116.0, 80.7, 28.1. MS (EI): m/z (%): 432 (M^+, 4), 376,[11] 331 (100). HRMS (EI) calcd for $C_{23}H_{20}N_2O_2F_4$: 432.1461, found: 432.1474.

*4.2.14. (E)-Ethyl 3-(5-(4-fluorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)acrylate (**3n**).* IR (KBr): 3070, 2983, 2904, 1696, 1329, 1127, 834, 694 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.49 (1H, d, J=16 Hz), 7.34–7.32 (3H, m), 7.22–7.19 (4H, m), 7.11 (2H, t, J=8 Hz), 6.15 (1H, d, J=16 Hz), 4.20 (2H, q, J=7.2 Hz), 1.29 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −61.5 (3F, s), −109.7 (1F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.8, 163.4 (d, J=241.4 Hz), 143.9, 140.6 (q, J=32.1 Hz), 138.3, 132.3, 132.2, 131.7, 129.2, 128.7, 126.3, 121.9 (q, J=212.9 Hz), 116.6, 116.4, 114.9, 60.6, 14.2. MS (EI): m/z (%): 404 (M^+, 10), 359,[16] 331 (100). HRMS (EI) calcd for $C_{23}H_{20}N_2O_2F_4$: 404.1148, found: 404.1149.

*4.2.15. 3-(5-(4-Fluorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)acrylonitrile (**3o**) (cis:trans≈0.78:1).* IR (KBr): 3071, 2220, 1630, 1489, 1236, 1059, 1022, 845, 694 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ *cis* 7.38–7.36 (1.4H, m), 7.24–7.14 (2.6H, m), 7.06 (0.44H, d, J=8.8 Hz), 5.52 (0.42H, d, J=9.2 Hz); *trans* 7.38–7.36 (1.9H, m), 7.24–7.14 (3.5H, m), 7.08 (0.62H, d, J=8.8 Hz), 5.58 (0.54H, d, J=13.2 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ *cis* −109.9 (0.44F, s), −61.2 (0.99F, s); *trans* −108.5 (0.57F, s), −61.4 (1.57F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ *cis* 163.3 (d, J=201.1 Hz), 142.76, 140.58 (q, J=30.2 Hz), 138.35, 137.81, 132.20, 132.02, 126.61, 119.97 (q, J=222.1 Hz), 116.78, 116.54, 115.80, 114.98, 113.46, 100.0; *trans* 163.6 (d, J=201.1 Hz), 143.96, 141.02 (q, J=31.1 Hz), 137.97, 137.92, 132.14, 131.95, 125.50, 123.33 (q, J=232.9 Hz), 116.96, 116.37, 115.98, 115.27, 114.25, 98.9. MS (EI): m/z (%): 357 (M^+, 100), 356 (60). HRMS (EI) calcd for $C_{19}H_{11}F_4N_3$: 357.0889, found: 357.0886.

4.3. General procedure for olefination of CF_2H substituted pyrazoles via C–H bond activation

To a solution of $Pd(OAc)_2$ (10 mol %) in DMF (1 mL) were added Ag_2CO_3 (2.0 equiv), BQ (1.5 equiv), the pyrazoles (3.0 equiv), and the acrylates (1.0 equiv). The mixture was then heated to 120 °C (oil bath) and stirred for 24 h. The resulting mixture was cooled to room temperature, diluted with ethyl acetate, washed with 1 N HCl and brine, dried over Na_2SO_4, filtered, and then concentrated. The resulting residue was purified with silica gel chromatography to provide the pure product.

*4.3.1. (E)-Butyl 3-(3-(difluoromethyl)-5-(4-fluorophenyl)-1-(4-nitrophenyl)-1H-pyrazol-4-yl) acrylate (**5a**).* IR (KBr): 3086, 2960, 1716, 1527, 1453, 1345, 1186, 1038, 857, 691 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.21–8.19 (2H, m), 7.44 (1H, d, J=16.5 Hz), 7.41–7.39 (2H, m), 7.24–7.16 (4H, m), 6.87 (1H, t, J=53.6 Hz), 6.38 (1H, d, J=16.3 Hz), 4.16 (2H, t, J=6.7 Hz), 1.69–1.62 (2H, m), 1.44–1.35 (2H, m), 0.94 (3H, t, J=7.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −108.56 (1F, s), −113.20 (2F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.94, 163.70 (d, J=252.5 Hz), 146.70, 145.82 (t, J=29.7 Hz), 144.19, 143.26, 132.20, 131.51, 124.88, 124.65, 123.63, 121.70, 117.00 (d, J=22.1 Hz), 116.65, 111.74 (t, J=235.2 Hz), 64.60, 30.68, 19.17, 13.74. MS (EI): m/z (%): 459,[9] 386 (26), 358 (100), 338 (23). HRMS (EI) calcd for $C_{23}H_{20}F_3N_3O_4$: 459.1406, found: 459.1409.

*4.3.2. (E)-Butyl 3-(3-(difluoromethyl)-5-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)acrylate (**5b**).* IR (KBr): 3074, 2961, 2873, 1708, 1639, 1332, 1191, 1034, 765, 523 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.49 (1H, d, J=16.4 Hz), 7.34–7.33 (3H, m), 7.21–7.18 (4H, m), 7.10 (2H, t, J=8.6 Hz), 6.87 (1H, t, J=53.8 Hz), 6.37 (1H, d, J=16.0 Hz), 4.15 (2H, t, J=6.6 Hz), 1.69–1.62 (2H, m), 1.44–1.35 (2H, m), 0.94 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −110.09 (1F, s), −112.62 (2F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 167.26, 163.34 (d, J=250.50 Hz), 144.63 (t, J=29.6 Hz), 144.15, 138.50, 132.32, 129.17, 128.48, 125.06, 124.18, 120.60, 116.39, 115.23, 112.15 (t, J=234.4 Hz), 64.46, 30.72, 19.19, 13.76. MS (EI): m/z (%): 414,[12] 341 (24), 313 (100), 293 (30). HRMS (EI) calcd for $C_{23}H_{21}F_3N_2O_2$: 414.1555, found: 414.1557.

*4.3.3. (E)-Butyl 3-(3-(difluoromethyl)-5-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)acrylate (**5c**).* IR (KBr): 3069, 2960, 1699, 1639,

1471, 1323, 1201, 1032, 809, 608 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40 (1H, d, J=16.8 Hz), 7.35–7.31 (2H, m), 7.25–7.22 (2H, m), 6.77 (1H, t, J=54.0 Hz), 6.18 (1H, d, J=16.0 Hz), 4.12 (2H, t, J=6.6 Hz), 3.74 (3H, s), 1.66–1.59 (2H, m), 1.42–1.33 (2H, m), 0.93 (3H, t, J=7.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −109.88 (1F, s), −112.39 (2F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 167.31, 163.59 (d, J=251.5 Hz), 144.66, 143.30 (t, J=29.0 Hz), 132.68, 131.97, 124.08, 119.49, 116.62 (d, J=22.0 Hz), 114.19, 111.93 (t, J=234.2 Hz), 64.36, 37.47, 30.70, 19.16, 13.74. MS (EI): m/z (%): 352,[10] 279 (53), 251 (100), 231 (55). HRMS (EI) calcd for $C_{18}H_{19}F_3N_2O_2$: 352.1399, found: 352.1398.

*4.3.4. (E)-Butyl 3-(3-(difluoromethyl)-5-(4-fluorophenyl)-1-(4-methoxyphenyl)-1H-pyrazol-4-yl) acrylate (**5d**).* IR (KBr): 3058, 2959, 1712, 1645, 1517, 1257, 1193, 1021, 840, 710 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.49 (1H, d, J=16.2 Hz), 7.20–7.17 (2H, m), 7.12–7.07 (4H, m), 6.85 (1H, t, J=53.9 Hz), 6.83 (2H, d, J=8.8 Hz), 6.35 (1H, d, J=16.2 Hz), 4.15 (2H, t, J=6.8 Hz), 3.79 (3H, s), 1.68–1.61 (2H, m), 1.44–1.35 (2H, m), 0.94 (3H, t, J=7.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −110.27 (1F, s), −112.50 (2F,s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 167.30, 163.23 (d, J=250.5 Hz), 159.43, 144.31 (t, J=29.6 Hz), 144.16, 132.55, 132.28, 131.54, 126.48, 124.25, 120.37, 116.32 (d, J=21.9 Hz), 114.86, 114.26, 112.19 (t, J=234.4 Hz), 64.42, 55.50, 30.72, 19.18, 13.75. MS (EI): m/z (%): 444 (31), 371,[17] 343 (100), 323 (21). HRMS (EI) calcd for $C_{24}H_{23}F_3N_2O_3$: 444.1661, found: 444.1658.

*4.3.5. (E)-Butyl 3-(3-(difluoromethyl)-1-(4-nitrophenyl)-5-phenyl-1H-pyrazol-4-yl)acrylate (**5e**).* IR (KBr): 3119, 2962, 1711, 1641, 1528, 1346, 1191, 1039, 857, 692 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.18–8.16 (2H, m), 7.52–7.45 (3H, m), 7.48 (1H, d, J=16.4 Hz), 7.42–7.38 (2H, m), 7.25–7.23 (2H, m), 6.88 (1H, t, J=53.7 Hz), 6.38 (1H, d, J=16.3 Hz), 4.15 (2H, t, J=6.7 Hz), 1.68–1.61 (2H, m), 1.44–1.34 (2H, m), 0.93 (3H, t, J=7.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −113.17 (2F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 167.02, 146.59, 145.78 (t, J=29.8 Hz), 145.32, 143.44, 131.82, 130.41, 130.12, 129.55, 129.03, 127.63, 124.81, 124.53, 121.41, 116.49, 111.80 (t, J=235.2 Hz), 64.51, 30.69, 19.16, 13.73. MS (EI): m/z (%): 441,[5] 368,[17] 340 (100), 320.[17] HRMS (EI) calcd for $C_{23}H_{21}F_2N_3O_4$: 441.1500, found: 441.1496.

*4.3.6. (E)-Butyl 3-(3-(difluoromethyl)-1,5-diphenyl-1H-pyrazol-4-yl) acrylate (**5f**).* IR (KBr): 3447, 2965, 1702, 1638, 1385, 1194, 1035, 843, 761, 694 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.53 (1H, d, J=16.3 Hz), 7.42–7.37 (3H, m), 7.32–7.28 (3H, m), 7.22–7.19 (4H, m), 6.87 (1H, t, J=53.9 Hz), 6.37 (1H, d, J=16.3 Hz), 4.14 (2H, t, J=6.7 Hz), 1.68–1.61 (2H, m), 1.44–1.34 (2H, m), 0.93 (3H, t, J=7.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −112.58 (2F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 167.32, 145.23, 144.61 (t, J=29.7 Hz), 138.70, 132.72, 130.28, 129.66, 129.03, 129.01, 128.29, 128.16, 125.03, 120.35, 115.14, 112.22 (t, J=234.4 Hz), 64.36, 30.72, 19.18, 13.75. MS (EI): m/z (%): 396,[8] 323,[14] 295 (100), 275 (25). HRMS (EI) calcd for $C_{23}H_{22}F_2N_2O_2$: 396.1649, found: 396.1656.

*4.3.7. (E)-Butyl 3-(3-(difluoromethyl)-1-(4-methoxyphenyl)-5-phenyl-1H-pyrazol-4-yl)acrylate (**5g**).* IR (KBr): 3128, 2964, 1699, 1518, 1259, 1199, 1025, 841, 697 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.52 (1H, d, J=16.3 Hz), 7.42–7.37 (3H, m), 7.21–7.18 (2H, m), 7.13–7.10 (2H, m), 6.86 (1H, t, J=53.9 Hz), 6.81–6.79 (2H, m), 6.35 (1H, d, J=16.2 Hz), 4.14 (2H, t, J=6.6 Hz), 3.78 (3H, s), 1.67–1.60 (2H, m), 1.43–1.34 (2H, m), 0.93 (3H, t, J=7.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −112.48 (2F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.34, 158.29, 144.19, 143.25 (t, J=29.4 Hz), 131.82, 130.76, 129.27, 128.52, 127.92, 127.20, 125.39, 119.09, 113.75, 113.13, 111.22 (t, J=234.4 Hz), 63.30, 54.45, 29.70, 18.15, 12.72. MS (EI): m/z (%): 426 (31), 353,[17] 325 (100), 305 (21). HRMS (EI) calcd for $C_{24}H_{24}F_2N_2O_3$: 426.1755, found: 426.1754.

*4.3.8. (E)-Butyl 3-(3-(difluoromethyl)-5-(4-methoxyphenyl)-1-(4-nitrophenyl)-1H-pyrazol-4-yl) acrylate (**5h**).* IR (KBr): 3115, 2959, 1715, 1612, 1525, 1348, 1257, 1031, 859, 692 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.19–8.17 (2H, m), 7.48 (1H, d, J=16.2 Hz), 7.43–7.41 (2H, m), 7.15 (2H, d, J=8.6 Hz), 6.99–6.97 (2H, m), 6.86 (1H, t, J=53.8 Hz), 6.38 (1H, d, J=16.3 Hz), 4.15 (2H, t, J=6.7 Hz), 3.87 (3H, s), 1.69–1.62 (2H, m), 1.44–1.35 (2H, m), 0.94 (3H, t, J=7.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −113.17 (2F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 167.13, 161.03, 146.49, 146.01 (t, J=28.2 Hz), 145.72, 145.41, 143.59, 132.11, 131.50, 124.80, 124.52, 120.99, 119.40, 116.23, 115.02, 114.49, 111.86 (t, J=235.1 Hz), 64.49, 55.42, 30.70, 19.17, 13.75. MS (EI): m/z (%): 471 (22), 398,[13] 370 (100), 324.[8] HRMS (EI) calcd for $C_{24}H_{23}F_2N_3O_5$: 471.1606, found: 471.1605.

*4.3.9. (E)-Butyl 3-(3-(difluoromethyl)-5-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)acrylate (**5i**).* IR (KBr): 3084, 2960, 1708, 1647, 1516, 1349, 1195, 1038, 857, 763, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.27–8.25 (2H, m), 7.46 (1H, d, J=16.2 Hz), 7.42–7.34 (m, 5H), 7.20–7.18 (2H, m), 6.88 (1H, t, J=53.7 Hz), 6.40 (1H, d, J=16.3 Hz), 4.16 (2H, t, J=6.7 Hz), 1.69–1.62 (2H, m), 1.44–1.35 (2H, m), 0.94 (3H, t, J=7.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −112.69 (2F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.93, 148.27, 144.94 (t, J=29.9 Hz), 142.40, 138.09, 134.59, 131.46, 131.36, 129.46, 129.01, 125.15, 124.21, 121.92, 115.96, 111.91 (t, J=234.8 Hz), 64.64, 30.69, 19.17, 13.75. MS (EI): m/z (%): 441,[12] 368 (43), 340 (100), 320 (58), 294 (28). HRMS (EI) calcd for $C_{23}H_{21}F_2N_3O_4$: 441.1500, found: 444.1499.

*4.3.10. (E)-Butyl 3-(3-(difluoromethyl)-1-methyl-5-(4-nitrophenyl)-1H-pyrazol-4-yl)acrylate (**5j**).* IR (KBr): 3087, 2960, 1704, 1526, 1384, 1270, 1180, 1026, 858, 734 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.44–8.42 (2H, m), 7.58–7.56 (2H, m), 7.37 (1H, d, J=16.2 Hz), 6.78 (1H, t, J=53.9 Hz), 6.21 (1H, d, J=16.2 Hz), 4.13 (2H, t, J=6.7 Hz), 3.80 (3H, s), 1.66–1.59 (2H, m), 1.43–1.31 (2H, m), 0.92 (3H, t, J=7.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −112.50 (2F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.99, 148.65, 143.61 (t, J=29.3 Hz), 142.99, 134.50, 131.77, 131.17, 124.50, 120.76, 114.83, 111.70 (t, J=234.4 Hz), 64.55, 37.81, 30.66, 19.14, 13.73. MS (EI): m/z (%): 379,[11] 306 (100), 278 (65), 258 (88), 232 (29). HRMS (EI) calcd for $C_{18}H_{19}F_2N_3O_4$: 379.1344, found: 379.1350.

*4.3.11. (E)-Butyl 3-(3-(difluoromethyl)-1-(4-methoxyphenyl)-5-(4-nitrophenyl)-1H-pyrazol-4-yl) acrylate (**5k**).* IR (KBr): 3089, 2963, 1703, 1643, 1517, 1350, 1197, 1025, 835, 713 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.27–8.25 (2H, m), 7.46 (1H, d, J=16.2 Hz), 7.41–7.39 (2H, m), 7.11–7.09 (2H, m), 6.86–6.83 (2H, m), 6.86 (1H, t, J=54.0 Hz), 6.38 (1H, d, J=16.3 Hz), 4.16 (2H, t, J=6.7 Hz), 3.80 (3H, s), 1.69–1.61 (2H, m), 1.44–1.35 (2H, m), 0.94 (3H, t, J=7.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −112.58 (2F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.97, 159.81, 148.19, 144.61 (t, J=29.5 Hz), 142.43, 134.69, 131.61, 131.37, 131.04, 130.69, 126.57, 124.16, 121.67, 115.55, 114.53, 111.94 (t, J=234.8 Hz), 64.61, 55.55, 30.68, 19.17, 13.74. MS (EI): m/z (%): 471 (89), 398 (39), 370 (100), 350 (46), 324 (29). HRMS (EI) calcd for $C_{24}H_{23}F_2N_3O_5$: 471.1606, found: 471.1593.

*4.3.12. (E)-tert-Butyl 3-(3-(difluoromethyl)-5-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl) acrylate (**5l**).* IR (KBr): 3074, 2926, 1707, 1608, 1490, 1281, 1162, 1022, 766, 524 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.41 (1H, d, J=16.2 Hz), 7.34–7.31 (3H, m), 7.21–7.18 (4H, m), 7.12–7.07 (2H, m), 6.87 (1H, t, J=53.8 Hz), 6.32 (1H, d, J=16.2 Hz), 1.49 (9H, s). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −110.26 (1F, s), −112.81 (2F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.56, 163.30 (d, J=251.5 Hz), 144.53 (t, J=29.4 Hz), 144.07, 138.55, 132.28, 131.33, 129.13, 128.42, 125.06, 124.26, 122.33, 116.35 (d, J=22.0 Hz), 115.35, 112.15 (t, J=234.4 Hz), 80.51, 28.18. MS (EI): m/z (%): 414,[9] 358,[16] 341,[17] 313 (100), 293 (36). HRMS (EI) calcd for $C_{23}H_{21}F_3N_2O_2$: 414.1555, found: 414.1557.

*4.3.13. (E)-Ethyl 3-(3-(difluoromethyl)-5-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)acrylate (**5m**).* IR (KBr): 3078, 2954, 1703, 1639,

1464, 1332, 1197, 1030, 767, 523 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.50 (1H, d, J=16.4 Hz), 7.35–7.31 (3H, m), 7.21–7.18 (4H, m), 7.10 (2H, t, J=8.4 Hz), 6.87(1H, t, J=53.6 Hz), 6.38 (1H, d, J=16.3 Hz), 4.21 (2H, q, J=7.1 Hz), 1.30 (3H, t, J=7.1 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −110.05 (1F, s), −112.58 (2F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 167.20, 163.34 (d, J=251.5 Hz), 144.64 (t, J=29.8 Hz), 144.16, 138.49, 132.42, 132.28, 129.17, 128.49, 125.07, 124.17, 120.59, 116.42 (d, J=22.0 Hz), 115.22, 112.17 (t, J=234.5 Hz), 60.53, 14.31. MS (EI): m/z (%): 386,[12] 341,[19] 313 (100), 293 (34). HRMS (EI) calcd for $C_{21}F_{17}H_3N_2O_2$: 386.1242, found: 352.1241.

*4.3.14. (E)-Ethyl 3-(3-(difluoromethyl)-5-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)acrylate (**5n**).* IR (KBr): 3064, 2993, 1691, 1473, 1324, 1198, 1028, 866, 608 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40 (1H, d, J=16.3 Hz), 7.36–7.31 (m, 2H), 7.28–7.23 (m, 2H), 6.77 (1H, t, J=53.9 Hz), 6.18 (1H, d, J=16.3 Hz), 4.18 (2H, q, J=7.1 Hz), 3.74 (s, 3H), 1.27 (3H, t, J=7.1 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −109.89 (1F, s), −112.36 (2F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 167.21, 163.59 (d, J=250.5 Hz), 144.63, 143.29 (t, J=29.1 Hz), 132.68, 131.96, 124.09, 119.45, 116.62 (d, J=22.0 Hz), 114.15, 111.95 (t, J=234.1 Hz), 60.41, 37.45, 14.26. MS (EI): m/z (%): 324,[12] 279 (46), 251 (100), 231 (74). HRMS (EI) calcd for $C_{16}H_{15}F_3N_2O_2$: 324.1086, found: 324.1084.

*4.3.15. 3-(3-(Difluoromethyl)-5-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)acrylonitrile (**5o**) (cis:trans≈1:0.87).* IR (KBr): 3072, 2218, 1628, 1489, 1230, 1071, 1026, 839, 692 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ *cis* 7.36–7.33 (1.6H, m), 7.23–7.11 (2.2H, m), 7.15 (0.54H, d, J=8.4 Hz), 7.08–7.04 (1H, m), 6.90 (0.54H, t, J=54.4 Hz), 5.46 (0.54H, d, J=11.7 Hz); *trans* 7.36–7.33 (1.4H, m), 7.23–7.11 (2.8H, m), 7.21 (0.46H, d, J=13.6 Hz), 6.84 (0.46H, t, J=54.0 Hz), 5.85 (0.46H, d, J=16.9 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ *cis* −110.22 (1F, s), -112.76 (2F, s); *trans* −109.06 (1F, s), −112.76 (2F, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ *cis* 163.20 (d, J=250.5 Hz), 145.01 (t, J=28.5 Hz), 142.78, 138.86, 138.54, 131.96, 129.22, 125.50, 124.30, 116.51, 116.29, 115.92, 113.51, 111.62 (t, J=234.0 Hz), 101.51; *trans* 163.54 (d, J=252.5 Hz), 144.38 (t, J=30.0 Hz), 144.22, 138.52, 138.17, 132.21, 128.72, 124.99, 123.58, 118.41, 116.80, 116.58, 114.70, 112.22 (t, J=232.2 Hz), 98.43. MS (EI): m/z (%): 339 (100), 338 (48), 318 (22), 288 (29). HRMS (EI) calcd for $C_{19}H_{12}F_3N_3$: 339.0983, found: 339.0975.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Nos. 21172148, 21202044) and Science and Technology Commission of Shanghai Municipality (No. 10540501300).

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.06.058.

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