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# Synthesis of trifluoromethylated pyrazolidines by [3 + 2] cycloaddition†

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A highly efficient [3 + 2] cycloaddition between trifluoromethylated *N*-acylhydrazones and nitroolefins in the presence of potassium hydroxide under phase transfer catalysis is developed to afford potentially bioactive trifluoromethylated pyrazolidines, which can be further transformed into trifluoromethylated pyrazoles in good yields.

## Introduction

Pyrazolidines and their derivatives are valuable compounds because of their widespread natural occurrence,[1] important biological properties,[2] and applications in materials science[3] (Fig. 1). After N–N bond cleavage, pyrazolidines can be easily converted to 1,3-diamines, which are important building blocks for the synthesis of nitrogen-containing bioactive compounds.[4] In addition, the trifluoromethyl group is the most prevalent fluorine-containing group appearing in organofluorine compounds.[5] Incorporation of the trifluoromethyl group into drugs usually dramatically alters their metabolic stability, lipophilicity and bioactivities.[5a,b] However, there were only two reports about the synthesis of trifluoromethylated pyrazolidines from the [3 + 2] cycloaddition of azomethine imines with trifluoromethylated olefins.[6] Therefore, introduction of the $CF_3$ group into pyrazolidines should be very desirable and will result in further advances in pharmacological application. In general, there are two principal ways of introducing the trifluoromethyl group into organic molecules: the direct trifluoromethylation by using trifluoromethylating reagents,[7a] or the trifluoromethylated synthetic building-block strategies.[7b] In our research studies on fluorine chemistry,[8] we found that trifluoromethylated *N*-acylhydrazones could be easily prepared from commercially available aqueous trifluoroacetaldehyde methyl hemiacetal and *N*-acylhydrazines, and were also found to be bench stable. Thus, we tried to develop the trifluoromethylated *N*-acylhydrazones into trifluoromethyl building blocks to access trifluoromethylated nitrogen-containing organic compounds.[8c]

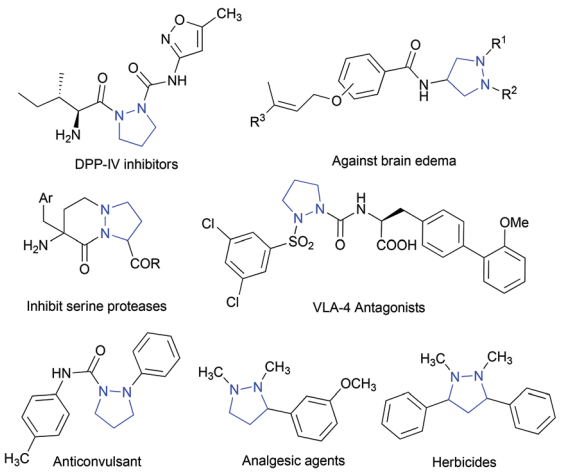


**Fig. 1** Some bioactive molecules containing pyrazolidine units.

Pyrazolidine derivatives are usually constructed by [3 + 2] cycloaddition between azomethine imines and alkenes or alkynes.[9] The [3 + 2] cycloaddition between *N*-acylhydrazones and alkenes represents another convenient access to pyrazolidine derivatives, which are generally achieved under acidic conditions[10] or at high temperature.[11] Recently, it was reported that the base-promoted reaction between 2-aroyl-1-chlorocyclopropanecarboxylates and *N*-acylhydrazones could also afford pyrazolidine derivatives.[12] In our research studies, we found that trifluoromethylated *N*-acylhydrazones could react with β-nitrostyrene derivatives in the presence of potassium hydroxide under phase transfer catalysis to give trifluoromethylated pyrazolidine derivatives in good to excellent yields. Herein, we would like to report the results of [3 + 2] cycloaddition between trifluoromethylated *N*-acylhydrazones and nitroolefins

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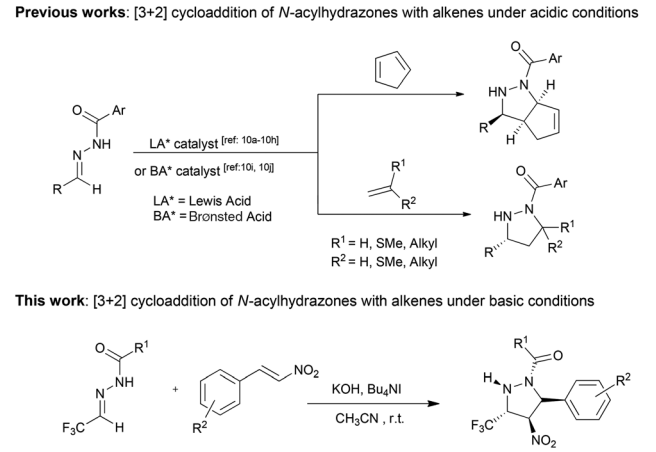
†Electronic supplementary information (ESI) available: General experimental details, X-ray representations and copies of $^1$H and $^{13}$C NMR spectra. CCDC 1537670 and 1537674. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ob01299c




**Scheme 1** Synthesis of trifluoromethylated pyrazolidines.

under basic conditions (Scheme 1). Furthermore, the produced pyrazolidines could be easily transformed into trifluoromethylated pyrazoles.

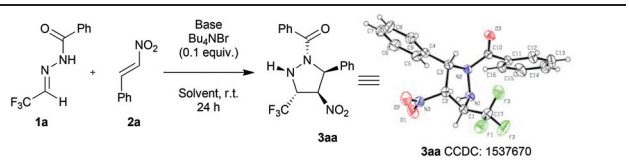
## Results and discussion

To commence the investigation, *N*′-(2,2,2-trifluoroethylidene)-benzohydrazide **1a** (1 equiv.), (*E*)-β-nitrostyrene **2a** (2 equiv.) and DBU (2.5 equiv.) were dissolved in THF and stirred at room temperature, but there was no product formed after 24 hours. The reaction was then carried out again at 50 °C, and it occurred to afford the product **3aa** in 5% yield. After careful examination of reaction conditions, the yield of **3aa** increased to 47% when **1a** reacted with **2a** in the presence of $Cs_2CO_3$ in acetonitrile at room temperature by using $Bu_4NBr$ as the phase transfer catalyst (Table 1, entry 1).

Encouraged by this result, the reaction conditions were optimized in detail. The solvent screening showed that acetonitrile was the suitable solvent (Table 1, entries 1–6). Examination of the mole ratio of the reactants indicated that the suitable ratio of **1a**/**2a**/$Cs_2CO_3$ was 1/3.5/1.5 (Table 1, entry 10), which gave the product **3aa** in 58% yield. The investigation of different bases revealed that potassium hydroxide was the suitable one, which let the yield of product **3aa** to increase to 64% (Table 1, entries 11–17). It was found that the yield of product **3aa** could be further increased to 79% when the potassium hydroxide pellet was ground to fine powder (Table 1, entry 18). Finally, examination of the effects of different quaternary ammonium salts demonstrated that tetrabutyl ammonium iodide was the best phase transfer catalyst, which afforded the product in 86% yield (Table 1, entries 18–21).

In the above reaction, only one isomer of **3aa** was obtained. The $^{19}F$ NMR spectra showed that another isomer maybe existing (see the ESI†), but we never obtained it in our experiments. The relative configuration of **3aa** was determined by single-crystal X-ray diffraction. Its formation could be explained in Scheme 3.

**Table 1** Optimization of reaction conditions



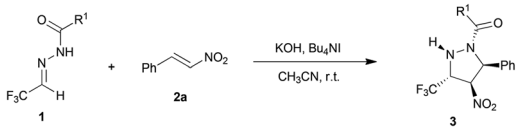

| Entry | Mole ratio of **1a**/**2a**/base | Base | Solvent | Yield **3aa**[a] (%) |
|---|---|---|---|---|
| 1 | 1/2.5/2.5 | $Cs_2CO_3$ | $CH_3CN$ | 47 |
| 2 | 1/2.5/2.5 | $Cs_2CO_3$ | $CH_2Cl_2$ | 38 |
| 3 | 1/2.5/2.5 | $Cs_2CO_3$ | Toluene | 22 |
| 4 | 1/2.5/2.5 | $Cs_2CO_3$ | MeOH | 18 |
| 5 | 1/2.5/2.5 | $Cs_2CO_3$ | THF | 16 |
| 6 | 1/2.5/2.5 | $Cs_2CO_3$ | $CH_3CN/H_2O$ = 9/1 | 32 |
| 7 | 1/2.5/1.5 | $Cs_2CO_3$ | $CH_3CN$ | 48 |
| 8 | 1/2.5/1.0 | $Cs_2CO_3$ | $CH_3CN$ | 32 |
| 9 | 1/2.5/0.5 | $Cs_2CO_3$ | $CH_3CN$ | 22 |
| 10 | 1/3.5/1.5 | $Cs_2CO_3$ | $CH_3CN$ | 58 |
| 11 | 1/3.5/1.5 | $Na_2CO_3$ | $CH_3CN$ | Trace |
| 12 | 1/3.5/1.5 | $CaCO_3$ | $CH_3CN$ | 14 |
| 13 | 1/3.5/1.5 | $K_2CO_3$ | $CH_3CN$ | 48 |
| 14 | 1/3.5/1.5 | $K_3PO_4$ | $CH_3CN$ | 55 |
| 15 | 1/3.5/1.5 | $Na_3PO_4$ | $CH_3CN$ | 48 |
| 16 | 1/3.5/1.5 | NaOH | $CH_3CN$ | 33 |
| 17 | 1/3.5/1.5 | KOH | $CH_3CN$ | 64 |
| 18 | 1/3.5/1.5 | KOH[b] | $CH_3CN$ | 79 |
| 19[c] | 1/3.5/1.5 | KOH[b] | $CH_3CN$ | 67 |
| 20[d] | 1/3.5/1.5 | KOH[b] | $CH_3CN$ | 75 |
| 21[e] | 1/3.5/1.5 | KOH[b] | $CH_3CN$ | 86 |

[a] Isolated yields. [b] Ground to fine powder. [c] In the presence of $Bu_4NF$ (0.1 equiv.). [d] In the presence of $Bu_4NCl$ (0.1 equiv.). [e] In the presence of $Bu_4NI$ (0.1 equiv.).

With the optimized reaction conditions in hand, the substrate scope was investigated. Firstly, a series of substituted trifluoromethylated *N*-acylhydrazones were reacted with **2a** to check the generality of *N*-acylhydrazones. As shown in Table 2, all of the trifluoromethylated aromatic *N*-acylhydrazones with both electron-donating and electron-withdrawing groups reacted with **2a** to give the corresponding products in good to excellent yields. However, the trifluoromethylated *N*-acylhydrazones with electron-withdrawing groups on their phenyl rings usually produced the products in higher yields (Table 2, entries 4–11). For instance, *N*′-(2,2,2-trifluoroethylidene)-4-methylbenzohydrazide gave the product **3da** in 76% yield, but the yield of product **3la** increased to 96% when *N*′-(2,2,2-trifluoroethylidene)-4-nitrobenzohydrazide was used as the substrate. Further observation of the results indicated that the stronger the ability of electron-withdrawing groups on the phenyl rings of *N*-acylhydrazones were, the higher the yields of the corresponding products were (Table 2, entries 7 and 11). The reason was that the acidity of the proton in the N–H bond of *N*-acylhydrazones was influenced by the electronic properties of substituents on the phenyl rings. The stronger the electron-withdrawing ability of the substituents on the phenyl rings was, the more acidic the proton in the N–H bond of *N*-acylhydrazones became. Thus, the *N*-acylhydrazones with stronger electron-withdrawing groups on their phenyl rings would be easier to be deprotonated, and made the reaction

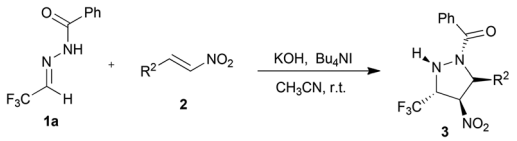
**Table 2** Scope of trifluoromethylated *N*-acylhydrazones[a]




| Entry | $R^1$ | Products | Yield[b] (%) |
|---|---|---|---|
| 1 | *o*-$MeC_6H_4$ | **3ba** | 72 |
| 2 | *m*-$MeC_6H_4$ | **3ca** | 78 |
| 3 | *p*-$MeC_6H_4$ | **3da** | 76 |
| 4 | *p*-$FC_6H_4$ | **3ea** | 85 |
| 5 | *o*-$ClC_6H_4$ | **3fa** | 78 |
| 6 | *m*-$ClC_6H_4$ | **3ga** | 80 |
| 7 | *p*-$ClC_6H_4$ | **3ha** | 83 |
| 8 | *p*-$CF_3C_6H_4$ | **3ia** | 76 |
| 9 | *o*-$O_2NC_6H_4$ | **3ja** | 81 |
| 10 | *m*-$O_2NC_6H_4$ | **3ka** | 85 |
| 11 | *p*-$O_2NC_6H_4$ | **3la** | 96 |
| 12 | 2-Naphthyl | **3ma** | 88 |
| 13 | 2-Furyl | **3na** | 57 |
| 14 | Phenethyl | **3oa** | 88 |
| 15 | Cyclohexyl | **3pa** | 86 |
| 16 | Isopropyl | **3qa** | 83 |
| 17 | *n*-$C_{11}H_{23}$ | **3ra** | 78 |
| 18 | *n*-$C_{17}H_{35}$ | **3sa** | 54 |

[a] Reactions were carried out by using 0.2 mmol of **1**, 3.5 equiv. of **2a**, 0.1 equiv. of $Bu_4NI$, 1.5 equiv. of KOH, 4 mL of $CH_3CN$, at room temperature, 12–24 h. [b] Isolated yields.

**Table 3** Scope of nitroolefins[a]



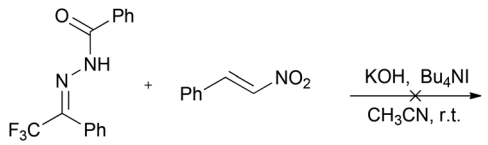

| Entry | $R^2$ | Products | Yield[b] (%) |
|---|---|---|---|
| 1 | *p*-$MeOC_6H_4$ | **3ab** | 68 |
| 2 | *o*-$MeC_6H_4$ | **3ac** | 68 |
| 3 | *m*-$MeC_6H_4$ | **3ad** | 70 |
| 4 | *p*-$MeC_6H_4$ | **3ae** | 76 |
| 5 | *o*-$ClC_6H_4$ | **3af** | 73 |
| 6 | *m*-$ClC_6H_4$ | **3ag** | 79 |
| 7 | *p*-$ClC_6H_4$ | **3ah** | 85 |
| 8 | *o*-$FC_6H_4$ | **3ai** | 86 |
| 9 | *p*-$FC_6H_4$ | **3aj** | 88 |
| 10 | *p*-$CF_3C_6H_4$ | **3ak** | 85 |
| 11 | *p*-$BrC_6H_4$ | **3al** | 95 |
| 12 | 2-Naphthyl | **3am** | 82 |
| 13 | 2-Thienyl | **3an** | 77 |
| 14 | 2-Furyl | **3ao** | 75 |
| 15[c] | $C_6H_5$ | **3aa** | 89 |

[a] Reactions were carried out by using 0.2 mmol of **1a**, 3.5 equiv. of nitroolefins **2**, 0.1 equiv. of $Bu_4NI$, 1.5 equiv. of KOH, 4 mL of $CH_3CN$, at room temperature, 12–24 h. [b] Isolated yields. [c] (*Z*)-β-Nitrostyrene was used.

give the products in higher yields. Aliphatic *N*-acylhydrazones also afforded the corresponding products, but the yields decreased with the aliphatic chains becoming longer (Table 2, entries 16–18).

In order to investigate the reactivity of ketone-derived *N*-acylhydrazones, the reaction of 2,2,2-trifluoroacetophenone derived acylhydrazone and nitrostyrene **2a** was conducted under the standard reaction conditions. The reaction did not occur, and only substrates were recovered (Scheme 2).

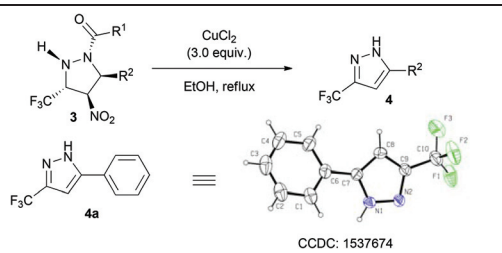
Next, the generality of β-nitrostyrene derivatives **2** was checked by using **1a** as the substrate under the optimized reaction conditions (Table 3). The results revealed that all of the nitroolefins with both electron-donating and electron-withdrawing groups on their phenyl rings smoothly reacted with **1a** to afford the corresponding products in good yields. It was noteworthy that the nitroolefins with *para*-substituents on their phenyl rings usually gave products in higher yields than those with *meta*- or *ortho*-substituents (Table 3, entries 2–4 and 5–7). Heteroaromatic nitroolefins could also be used in the reactions to produce the products in good yields (Table 3, entries 13 and 14). When *cis*-nitrostyrene reacted with trifluoromethylated *N*-acylhydrazones **1a**, the product **3aa** was obtained (yield 89%, Table 3, entry 15).




**Scheme 2** Reaction of 2,2,2-trifluoroacetophenone derived acylhydrazone and nitrostyrene **2a**.

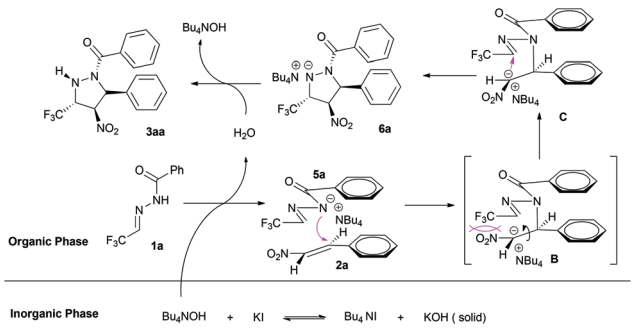
The trifluoromethylated pyrazolidines obtained in the above reactions could be further transformed into trifluoromethylated pyrazole derivatives **4**. As summarized in Table 4, trifluoromethylated pyrazoles were produced in good yields when pyrazolidines **3** were refluxed in ethanol in the presence of copper chloride. In this transformation, the acyl groups and

**Table 4** Further transformation of the products[a]




| Entry | $R^1$ | $R^2$ | Time (h) | Products | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ | $C_6H_5$ | 6 | **4a** | 88 |
| 2 | Isobutyl | $C_6H_5$ | 8 | **4a** | 78 |
| 3 | *m*-$MeC_6H_4$ | $C_6H_5$ | 6 | **4a** | 80 |
| 4 | $C_6H_5$ | *p*-$MeOC_6H_4$ | 8 | **4b** | 68 |
| 5 | $C_6H_5$ | *p*-$ClC_6H_4$ | 6 | **4c** | 87 |
| 6 | $C_6H_5$ | 2-Naphthyl | 8 | **4d** | 87 |

[a] Reactions were carried out by using 0.1 mmol of **3**, 3.0 equiv. of $CuCl_2$, 4 mL of EtOH, reflux, 6–8 h. [b] Isolated yields.




Scheme 3 Plausible mechanism.

nitro group were lost from pyrazolidines, which were aromatized to produce trifluoromethylated pyrazoles.

Finally, the mechanism is proposed in Scheme 3 based on our experiments and literature.[13] In the inorganic phase, anions exchange between $Bu_4NI$ and KOH producing $Bu_4NOH$, which was then transferred into the organic phase. Deprotonation of *N*-acylhydrazone **1a** by $Bu_4NOH$ gave *N*-acylhydrazonyl anion **5a**, which attached to **2a** to give carbon anion **B**. The nitro group rotated around the C–C σ bond in carbon anion **B** to form carbon anion **C** because of the steric hindrance between $CF_3$ and $NO_2$ groups in carbon anion **B**. The carbon anion **C** cyclized to produce intermediate **6a**. After proton extraction of intermediate **6a** from water, product **3aa** was then produced.

## Conclusions

In conclusion, a novel [3 + 2] cycloaddition reaction between trifluoromethylated *N*-acylhydrazones and nitroolefins is developed in the presence of potassium hydroxide under phase transfer catalysis. This method provides an efficient way to access potentially bioactive trifluoromethylated pyrazolidines in good to excellent yields under mild reaction conditions. The trifluoromethylated pyrazolidines can be easily transformed into trifluoromethylated pyrazoles. Further studies to develop the trifluoromethylated *N*-acylhydrazones into trifluoromethyl building blocks to access trifluoromethylated nitrogen-containing compounds are in progress in our laboratory.

## Experimental section

### General experimental procedures for the synthesis of compounds 3aa–3sa and 3ab–3ao

A solution of trifluoromethylated *N*-acylhydrazones **1** (0.2 mmol), nitroolefins **2** (0.7 mmol), KOH (0.3 mmol) and $Bu_4NI$ (0.02 mmol) in $CH_3CN$ (5 mL) was stirred at room temperature for 6–24 h and monitored by thin layer chromatography (TLC) until the starting materials were not detected. $CH_3CN$ was removed from the reaction mixture under vacuum. The saturated $NH_4Cl$ solution (10 mL) was poured into the mixture and stirred for 10 min, and then the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by silica gel column chromatography using petroleum ether : acetone (4 : 1) as the eluent furnished the products **3**.

**((3*R*,4*S*,5*R*)-4-Nitro-5-phenyl-3(trifluoromethyl)pyrazolidin-1-yl)(phenyl)methanone (3aa).** White solid (63 mg, 86% yield); m.p. 198–199 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.75 (d, $J$ = 7.2 Hz, 2H), 7.52–7.50 (m, 1H), 7.44 (t, $J$ = 7.2 Hz, 2H), 7.38–7.34 (m, 3H), 7.32–7.31 (m, 2H), 6.22 (d, $J$ = 7.8 Hz, 1H), 5.90 (d, $J$ = 5.4 Hz, 1H), 5.75 (d, $J$ = 8.4 Hz, 1H), 4.41–4.38 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 172.4, 134.0, 132.8, 131.2, 129.2, 128.9, 128.8, 127.9, 126.3, 122.9 (q, $J$ = 280.0 Hz), 90.1, 65.4, 64.9 (q, $J$ = 32.0 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −73.85 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{17}H_{15}F_3N_3O_3$ $[M + H]^+$ 366.1060, found 366.1055.

**((3*R*,4*S*,5*R*)-4-Nitro-5-phenyl-3-(trifluoromethyl)pyrazolidin-1-yl)(*o*-tolyl)methanone (3ba).** White solid (55 mg, 72% yield); m.p. 193–194 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 7.57 (d, $J$ = 7.2 Hz, 2H), 7.52 (d, $J$ = 6.6 Hz, 1H), 7.36 (t, $J$ = 7.2 Hz, 2H), 7.33–7.31 (m, 2H), 7.27–7.22 (m, 2H), 6.85 (d, $J$ = 6.0 Hz, 1H), 6.27–6.26 (m, 2H), 4.98–4.96 (m, 1H), 2.39 (s, 3H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 173.6, 137.2, 136.5, 135.9, 131.2, 130.1, 129.4, 129.3, 128.9, 128.0, 125.9, 125.0 (q, $J$ = 279.0 Hz), 91.6, 66.2, 65.4 (q, $J$ = 31.5 Hz), 19.7; $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −69.32 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{18}H_{17}F_3N_3O_3$ $[M + H]^+$ 380.1217, found 380.1215.

**((3*R*,4*S*,5*S*)-4-Nitro-5-phenyl-3-(trifluoromethyl)pyrazolidin-1-yl)(*m*-tolyl)methanone (3ca).** White solid (59 mg, 78% yield); m.p. 175–176 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.52 (br, 2H), 7.34–7.25 (m, 7H), 6.19 (d, $J$ = 8.0 Hz, 1H), 5.83 (d, $J$ = 5.6 Hz, 1H), 5.72 (d, $J$ = 8.4 Hz, 1H), 4.35–4.28 (m, 1H), 2.39 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 172.7, 137.6, 134.0, 132.8, 131.9, 129.2, 129.1, 128.9, 127.7, 126.3, 125.8, 122.9 (q, $J$ = 279.0 Hz), 90.1, 65.3, 64.8 (q, $J$ = 31.5 Hz), 21.3; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −73.83 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{18}H_{17}F_3N_3O_3$ $[M + H]^+$ 380.1217, found 380.1214.

**((3*R*,4*S*,5*R*)-4-Nitro-5-phenyl-3-(trifluoromethyl)pyrazolidin-1-yl)(*p*-tolyl)methanone (3da).** White solid (65 mg, 86% yield); m.p. 217–220 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 7.84 (d, $J$ = 8.4 Hz, 2H), 7.55 (d, $J$ = 7.2 Hz, 2H), 7.33 (t, $J$ = 7.2 Hz, 2H), 7.31–7.28 (m, 1H), 7.25 (d, $J$ = 7.8 Hz, 2H), 7.06 (d, $J$ = 6.0 Hz, 1H), 6.34 (d, $J$ = 8.4 Hz, 1H), 6.23 (d, $J$ = 8.4 Hz, 1H), 5.06–5.01 (m, 1H), 2.38 (s, 3H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 173.1, 142.0, 136.1, 133.2, 130.4, 129.3, 129.2, 129.1, 128.0, 125.0 (q, $J$ = 279.0 Hz), 91.4, 66.5, 65.6 (q, $J$ = 31.5 Hz), 21.6; $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −74.74 (d, $J$ = 11.28 Hz); HRMS (ESI): calculated for $C_{18}H_{17}F_3N_3O_3$ $[M + H]^+$ 380.1217, found 380.1213.

**(4-Fluorophenyl)((3*R*,4*S*,5*S*)-4-nitro-5-phenyl-3-(trifluoromethyl) pyrazolidin-1-yl)methanone (3ea).** White solid (65 mg, 85% yield); m.p. 181–182 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.84–7.81 (m, 2H), 7.35–7.34 (m, 3H), 7.30–7.29 (m, 2H), 7.11 (t, $J$ = 9.0 Hz, 2H), 6.21 (d, $J$ = 7.8 Hz, 1H), 5.82 (d, $J$ = 4.8 Hz, 1H), 5.73 (d, $J$ = 8.4 Hz, 1H), 4.39–4.36 (m, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 171.2, 164.4 (d, $J$ = 250.5 Hz), 132.7, 131.4 (d, $J$ = 7.5 Hz), 129.8 (d, $J$ = 3.0 Hz), 129.2, 128.9, 126.3, 122.9 (q, $J$ = 279.0 Hz),

115.0 (d, $J$ = 21.0 Hz), 90.0, 65.6, 64.9 (q, $J$ = 31.5 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −73.85 (d, $J$ = 7.52 Hz), −108.24; HRMS (ESI): calculated for $C_{17}H_{14}F_4N_3O_3$ $[M + H]^+$ 384.0966, found 384.0960.

**(2-Chlorophenyl)((3*R*,4*S*,5*R*)-4-nitro-5-phenyl-3-(trifluoromethyl)pyrazolidin-1-yl)methanone (3fa).** White solid (62 mg, 78% yield); m.p. 216–218 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 7.57 (d, $J$ = 7.8 Hz, 2H), 7.52–7.50 (m, 1H), 7.47–7.45 (m, 2H), 7.43–7.40 (m, 1H), 7.36 (t, $J$ = 7.2 Hz, 2H), 7.32 (t, $J$ = 7.2 Hz, 1H), 6.77 (d, $J$ = 6.0 Hz, 1H), 6.30 (d, $J$ = 8.4 Hz, 1H), 6.24 (d, $J$ = 7.8 Hz, 1H), 5.03–4.98 (m, 1H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 170.3, 137.3, 135.4, 131.8, 131.7, 130.3, 129.9, 129.4, 129.3, 128.0, 127.8, 124.9 (q, $J$ = 279.0 Hz), 91.5, 66.4, 65.0 (q, $J$ = 31.5 Hz); $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −74.44 (d, $J$ = 11.28 Hz); HRMS (ESI): calculated for $C_{17}H_{14}ClF_3N_3O_3$ $[M + H]^+$ 400.0670, found 400.0667.

**(3-Chlorophenyl)((3*R*,4*S*,5*R*)-4-nitro-5-phenyl-3-(trifluoromethyl)pyrazolidin-1-yl)methanone (3ga).** White solid (64 mg, 80% yield); m.p. 189–190 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 8.0 (s, 1H), 7.82 (d, $J$ = 7.8 Hz, 1H), 7.58–7.54 (m, 3H), 7.48 (t, $J$ = 7.8 Hz, 1H), 7.35–7.29 (m, 3H), 7.20 (d, $J$ = 5.4 Hz, 1H), 6.32 (d, $J$ = 7.8 Hz, 1H), 6.25 (d, $J$ = 8.4 Hz, 1H), 5.10–5.05 (m, 1H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 171.8, 138.0, 135.6, 134.0, 131.7, 130.5, 130.0, 129.4, 129.3, 128.5, 128.0, 124.9 (q, $J$ = 279 Hz), 91.3, 66.7, 65.54 (q, $J$ = 30.0 Hz); $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −74.68 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{17}H_{14}ClF_3N_3O_3$ $[M + H]^+$ 400.0670, found 400.0665.

**(4-Chlorophenyl)((3*R*,4*S*,5*S*)-4-nitro-5-phenyl-3-(trifluoromethyl)pyrazolidin-1-yl)methanone (3ha).** White solid (66 mg, 83% yield); m.p. 212–213 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 7.95 (d, $J$ = 8.4 Hz, 2H), 7.56 (d, $J$ = 7.2 Hz, 2H), 7.49 (d, $J$ = 8.4 Hz, 2H), 7.35–7.30 (m, 3H), 7.15 (d, $J$ = 6.0 Hz, 1H), 6.33 (d, $J$ = 8.4 Hz, 1H), 6.25 (d, $J$ = 8.4 Hz, 1H), 5.09–5.04 (m, 1H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 172.2, 137.3, 135.8, 134.7, 132.0, 129.4, 129.3, 128.8, 128.0, 124.9 (q, $J$ = 279.0 Hz), 91.3, 66.7, 65.5 (q, $J$ = 30.0 Hz); $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −69.53 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{17}H_{14}ClF_3N_3O_3$ $[M + H]^+$ 400.0670, found 400.0667.

**((3*R*,4*S*,5*S*)-4-Nitro-5-phenyl-3-(trifluoromethyl)pyrazolidin-1-yl)(4-(trifluoromethyl)phenyl)methanone (3ia).** White solid (66 mg, 76% yield); m.p. 205–206 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 8.10 (d, $J$ = 8.4 Hz, 2H), 7.82 (d, $J$ = 8.4 Hz, 2H), 7.58 (d, $J$ = 7.8 Hz, 2H), 7.37–7.31 (m, 3H), 7.20 (d, $J$ = 6.0 Hz, 1H), 6.34 (d, $J$ = 8.4 Hz, 1H), 6.28 (d, $J$ = 8.4 Hz, 1H), 5.11–5.06 (m, 1H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 172.1, 140.7, 135.6, 131.4 (q, $J$ = 31.5 Hz), 130.6, 129.5, 129.4, 128.0, 125.6 (q, $J$ = 3.0 Hz), 124.9 (q, $J$ = 279.0 Hz), 91.4, 66.7, 65.4 (q, $J$ = 31.5 Hz); $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −63.77, −74.71 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{18}H_{14}F_6N_3O_3$ $[M + H]^+$ 434.0934, found 434.0928.

**((3*R*,4*S*,5*R*)-4-Nitro-5-phenyl-3-(trifluoromethyl)pyrazolidin-1-yl)(2-nitrophenyl)methanone (3ja).** White solid (66 mg, 81% yield); m.p. 169–170 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 8.22 (d, $J$ = 7.8 Hz, 1H), 7.87 (t, $J$ = 7.8 Hz, 1H), 7.74 (t, $J$ = 7.8 Hz, 1H), 7.62 (d, $J$ = 7.8 Hz, 1H), 7.59 (d, $J$ = 7.8 Hz, 2H), 7.37 (t, $J$ = 7.2 Hz, 2H), 7.33 (t, $J$ = 7.2 Hz, 1H), 6.88 (d, $J$ = 6.0 Hz, 1H), 6.30 (d, $J$ = 8.4 Hz, 1H), 6.20 (d, $J$ = 8.4 Hz, 1H), 5.02–4.97 (m, 1H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 168.9, 147.2, 135.2, 134.9, 133.6, 131.4, 130.2, 129.5, 129.3, 128.0, 125.0, 124.9 (q, $J$ = 279.0 Hz), 91.3, 66.7, 64.8 (q, $J$ = 31.5 Hz); $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −69.07 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{17}H_{14}F_3N_4O_5$ $[M + H]^+$ 411.0911, found 411.0915.

**((3*R*,4*S*,5*S*)-4-Nitro-5-phenyl-3-(trifluoromethyl)pyrazolidin-1-yl)(3-nitrophenyl)methanone (3ka).** White solid (70 mg, 85% yield); m.p. 179–180 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 8.80 (s, 1H), 8.40 (d, $J$ = 7.8 Hz, 1H), 8.31 (d, $J$ = 7.8 Hz, 1H), 7.79 (t, $J$ = 7.8 Hz, 1H), 7.61 (d, $J$ = 7.2 Hz, 2H), 7.40 (d, $J$ = 5.4 Hz, 1H), 7.37–7.32 (m, 3H), 6.36 (d, $J$ = 8.4 Hz, 1H), 6.29 (d, $J$ = 8.4 Hz, 1H), 5.15–5.10 (m, 1H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 171.1, 148.8, 137.6, 136.1, 135.5, 130.3, 129.5, 129.3, 128.0, 126.4, 125.0, 124.9 (q, $J$ = 279 Hz), 91.3, 67.0, 64.5 (q, $J$ = 31.5 Hz); $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −69.47 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{17}H_{14}F_3N_4O_5$ $[M + H]^+$ 411.0911, found 411.0916.

**((3*R*,4*S*,5*S*)-4-Nitro-5-phenyl-3-(trifluoromethyl)pyrazolidin-1-yl)(4-nitrophenyl)methanone (3la).** White solid (79 mg, 96% yield); m.p. 209–210 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 8.33 (d, $J$ = 9.0 Hz, 2H), 8.14 (d, $J$ = 8.4 Hz, 2H), 7.59 (d, $J$ = 7.2 Hz, 2H), 7.37–7.31 (m, 3H), 7.24 (d, $J$ = 5.4 Hz, 1H), 6.33 (d, $J$ = 8.4 Hz, 1H), 6.29 (d, $J$ = 8.4 Hz, 1H), 5.13–5.08 (m, 1H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 171.7, 150.1, 142.2, 135.4, 131.1, 129.5, 129.4, 128.0, 124.9 (q, $J$ = 279.0 Hz), 123.8, 91.3, 66.8, 65.3 (q, $J$ = 30.0 Hz); $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −74.67 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{17}H_{14}F_3N_4O_5$ $[M + H]^+$ 411.0911, found 411.0906.

**Naphthalen-2-yl((3*R*,4*S*,5*S*)-4-nitro-5-phenyl-3-(trifluoromethyl)pyrazolidin-1-yl)methanone (3ma).** White solid (73 mg, 88% yield); m.p. 217–219 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 8.58 (s, 1H), 8.02 (d, $J$ = 7.8 Hz, 1H), 8.00–7.95 (m, 3H), 7.62–7.57 (m, 4H), 7.35 (t, $J$ = 7.2 Hz, 2H), 7.32 (t, $J$ = 7.2 Hz, 1H), 7.21 (s, 1H), 6.43–6.42 (m, 1H), 6.29–6.28 (m, 1H), 5.09–5.04 (m, 1H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 173.3, 136.0, 135.5, 133.5, 133.4, 130.7, 129.9, 129.4, 129.3, 128.7, 128.5, 128.1, 128.0, 127.5, 126.9, 125.0 (q, $J$ = 279.0 Hz), 91.5, 66.6, 65.5 (q, $J$ = 30.5 Hz); $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −74.71 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{21}H_{17}F_3N_3O_3$ $[M + H]^+$ 416.1217, found 416.1210.

**Furan-2-yl((3*R*,4*S*,5*S*)-4-nitro-5-phenyl-3-(trifluoromethyl)pyrazolidin-1-yl)methanone (3na).** White solid (41 mg, 57% yield); m.p. 167–169 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 7.76–7.75 (m, 1H), 7.69 (d, $J$ = 3.6 Hz, 1H), 7.48–7.46 (m, 2H), 7.33–7.27 (m, 3H), 7.07 (d, $J$ = 5.4 Hz, 1H), 6.65–6.64 (m, 1H), 6.26–6.23 (m, 2H), 5.23–5.18 (m, 1H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 161.2, 147.3, 146.7, 135.8, 129.3, 129.2, 127.9, 125.1 (q, $J$ = 279.0 Hz), 119.8, 112.4, 90.9, 66.9, 65.5 (q, $J$ = 31.5 Hz); $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −74.88 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{15}H_{13}F_3N_3O_4$ $[M + H]^+$ 356.0653, found 356.0650.

**1-((3*R*,4*S*,5*S*)-4-Nitro-5-phenyl-3-(trifluoromethyl)pyrazolidin-1-yl)-2-phenylethan-1-one (3oa).** White solid (67 mg, 88% yield); m.p. 166–167 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 7.36–7.22 (m, 10H), 6.87 (d, $J$ = 5.4 Hz, 1H), 6.23 (d, $J$ =

8.4 Hz, 1H), 6.06–6.05 (m, 1H), 5.15–5.12 (m, 1H), 4.16 (d, $J$ = 15.0 Hz, 1H), 3.94–3.93 (m, 1H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 174.3, 136.7, 135.9, 130.6, 129.9, 129.2, 129.1, 127.8, 127.4, 125.2 (q, $J$ = 279.0 Hz), 91.6, 66.1, 65.4, (q, $J$ = 31.5 Hz), 41.0; $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −69.61 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{18}H_{17}F_3N_3O_3$ $[M + H]^+$ 380.1217, found 380.1214.

**Cyclohexyl((3*R*,4*S*,5*R*)-4-nitro-5-phenyl-3-(trifluoromethyl) pyrazolidin-1-yl)methanone (3pa).** White solid (64 mg, 86% yield); m.p. 206–207 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 7.37 (d, $J$ = 7.2 Hz, 2H), 7.30–7.25 (m, 3H), 6.90 (d, $J$ = 6.0 Hz, 1H), 6.19 (d, $J$ = 8.4 Hz, 1H), 6.00 (d, $J$ = 8.4 Hz, 1H), 5.09–5.04 (m, 1H), 3.24–3.20 (m, 1H), 1.79–1.76 (m, 2H), 1.71–1.66 (m, 2H), 1.46–1.19 (m, 6H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 179.0, 136.2, 129.2, 129.1, 127.8, 125.2 (q, $J$ = 279.0 Hz), 91.5, 65.8, 65.3 (q, $J$ = 30.0 Hz), 42.0, 31.3, 28.6, 26.9, 26.8, 26.2; $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −74.77 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{17}H_{21}F_3N_3O_3$ $[M + H]^+$ 372.1530, found 372.1527.

**2-Methyl-1-((3*R*,4*S*,5*R*)-4-nitro-5-phenyl-3-(trifluoromethyl) pyrazolidin-1-yl)propan-1-one (3qa).** White solid (55 mg, 83% yield); m.p. 197–198 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.33–7.30 (m, 3H), 7.17–7.16 (m, 2H), 5.91 (d, $J$ = 8.4 Hz, 1H), 5.69 (d, $J$ = 8.4 Hz, 1H), 5.62 (d, $J$ = 6.0 Hz, 1H), 4.44–4.40 (m, 1H), 3.40–3.35 (m, 1H), 1.23 (d, $J$ = 7.2 Hz, 3H), 1.11 (d, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 180.0, 133.0, 129.0, 128.8, 126.0, 123.1 (q, $J$ = 279.0 Hz), 90.2, 64.9, 64.8 (q, $J$ = 31.5 Hz), 31.5, 20.4, 17.7; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −73.95 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{14}H_{17}F_3N_3O_3$ $[M + H]^+$ 332.1217, found 332.1214.

**1-((3*R*,4*S*,5*R*)-4-Nitro-5-phenyl-3-(trifluoromethyl)pyrazolidin-1-yl)dodecan-1-one (3ra).** White solid (69 mg, 78% yield); m.p. 115–116 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.32–7.30 (m, 3H), 7.19–7.17 (m, 2H), 5.91 (d, $J$ = 7.8 Hz, 1H), 5.68 (d, $J$ = 8.4 Hz, 1H), 5.60 (d, $J$ = 5.4 Hz, 1H), 4.43–4.38 (m, 1H), 2.71–2.59 (m, 2H), 1.65–1.61 (m, 2H), 1.34–1.26 (m, 16H), 0.88 (t, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 176.5, 133.0, 129.0, 128.8, 126.1, 123.1 (q, $J$ = 279.0 Hz), 90.3, 65.1, 64.8 (q, $J$ = 31.5 Hz), 33.6, 31.9, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 24.6, 22.7, 14.1; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −74.06 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{22}H_{33}F_3N_3O_3$ $[M + H]^+$ 444.2469, found 444.2465.

**1-((3*R*,4*S*,5*R*)-4-Nitro-5-phenyl-3-(trifluoromethyl)pyrazolidin-1-yl)octadecan-1-one (3sa).** White solid (60 mg, 54% yield); m.p. 106–108 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.33–7.28 (m, 3H), 7.19–7.17 (m, 2H), 5.92 (d, $J$ = 8.4 Hz, 1H), 5.69 (d, $J$ = 8.4 Hz, 1H), 5.60 (d, $J$ = 5.4 Hz, 1H), 4.42–4.40 (m, 1H), 2.71–2.65 (m, 1H), 2.65–2.59 (m, 1H), 1.65–1.61 (m, 2H), 1.34–1.25 (m, 28H), 0.88 (t, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 176.5, 133.0, 129.0, 128.8, 126.1, 123.1 (q, $J$ = 279.0 Hz), 90.3, 65.1, 64.7 (q, $J$ = 31.5 Hz), 33.6, 31.9, 29.7, 29.69, 29.67, 29.65, 29.62, 29.5, 29.4, 29.3, 29.2, 24.6, 22.7, 14.1; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −74.06 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{28}H_{45}F_3N_3O_3$ $[M + H]^+$ 528.3408, found 528.3401.

**((3*R*,4*S*,5*R*)-5-(4-Methoxyphenyl)-4-nitro-3-(trifluoromethyl) pyrazolidin-1-yl)(phenyl)methanone (3ab).** White solid (54 mg, 68% yield); m.p. 169–170 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 7.89 (d, $J$ = 7.8 Hz, 2H), 7.51–7.42 (m, 5H), 7.08 (d, $J$ = 6.0 Hz, 1H), 6.89–6.87 (m, 2H), 6.29 (d, $J$ = 8.4 Hz, 1H), 6.17 (d, $J$ = 8.4 Hz, 1H), 5.04–4.99 (m, 1H), 3.77 (s, 3H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 173.1, 160.9, 136.2, 131.6, 130.1, 129.3, 128.5, 127.6, 125.0 (q, $J$ = 279.0 Hz), 114.6, 91.4, 66.1, 65.4 (q, $J$ = 31.5 Hz), 55.7; $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −74.76 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{18}H_{17}F_3N_3O_4$ $[M + H]^+$ 396.1166, found 396.1161.

**((3*R*,4*S*,5*R*)-4-Nitro-5-(*o*-tolyl)-3-(trifluoromethyl)pyrazolidin-1-yl)(phenyl)methanone (3ac).** White solid (52 mg, 68% yield); m.p. 206–207 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 7.92 (d, $J$ = 7.8 Hz, 2H), 7.59 (d, $J$ = 7.8 Hz, 1H), 7.50 (t, $J$ = 7.8 Hz, 1H), 7.43 (t, $J$ = 7.8 Hz, 2H), 7.20 (d, $J$ = 4.2 Hz, 2H), 7.14–7.11 (m, 1H), 7.09 (d, $J$ = 5.4 Hz, 1H), 6.40 (d, $J$ = 8.4 Hz, 1H), 6.29 (d, $J$ = 8.4 Hz, 1H), 5.06–5.02 (m, 1H), 2.56 (s, 3H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 172.9, 137.3, 136.0, 134.3, 131.7, 131.2, 130.1, 129.4, 128.5 127.0, 126.9, 124.7 (q, $J$ = 279.0 Hz), 90.0, 65.5 (q, $J$ = 30.0 Hz), 64.0, 19.9; $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −69.31 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{18}H_{17}F_3N_3O_3$ $[M + H]^+$ 380.1217, found 380.1219.

**((3*R*,4*S*,5*S*)-4-Nitro-5-(*m*-tolyl)-3-(trifluoromethyl)pyrazolidin-1-yl)(phenyl)methanone (3ad).** White solid (53 mg, 70% yield); m.p. 206–207 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 7.91 (d, $J$ = 7.2 Hz, 2H), 7.50 (t, $J$ = 7.2 Hz, 1H), 7.44 (t, $J$ = 7.8 Hz, 2H), 7.39 (s, 1H), 7.34 (d, $J$ = 7.8 Hz, 1H), 7.21 (d, $J$ = 7.8 Hz, 1H), 7.11 (d, $J$ = 7.8 Hz, 1H), 7.07 (d, $J$ = 6.0 Hz, 1H), 6.30 (d, $J$ = 7.8 Hz, 1H), 6.22 (d, $J$ = 9.0 Hz, 1H), 5.04–4.99 (m, 1H), 2.30 (s, 3H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 173.2, 138.8, 136.2, 135.9, 131.7, 130.1, 130.0, 129.2, 128.6, 128.5, 125.1, 125.0 (q, $J$ = 279.0 Hz), 91.4, 66.5, 65.4 (q, $J$ = 31.5 Hz), 21.5; $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −69.53 (d, $J$ = 11.2 Hz); HRMS (ESI): calculated for $C_{18}H_{17}F_3N_3O_3$ $[M + H]^+$ 380.1217, found 380.1221.

**((3*R*,4*S*,5*R*)-4-Nitro-5-(*p*-tolyl)-3-(trifluoromethyl)pyrazolidin-1-yl)(phenyl)methanone (3ae).** White solid (58 mg, 76% yield); m.p. 207–208 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 7.90 (d, $J$ = 7.2 Hz, 2H), 7.50 (t, $J$ = 7.2 Hz, 1H), 7.44 (t, $J$ = 7.2 Hz, 4H), 7.14 (d, $J$ = 7.8 Hz, 2H), 7.06 (d, $J$ = 6.0 Hz, 1H), 6.30 (d, $J$ = 8.4 Hz, 1H), 6.20 (d, $J$ = 8.4 Hz, 1H), 5.04–5.00 (m, 1H), 2.29 (s, 3H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 173.1, 139.0, 136.2, 132.9, 131.6, 130.1, 129.9, 128.5, 128.0, 125.2 (q, $J$ = 279.0 Hz), 91.4, 66.3, 65.4 (q, $J$ = 31.5 Hz), 21.3; $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −74.75 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{18}H_{17}F_3N_3O_3$ $[M + H]^+$ 380.1217, found 380.1215.

**((3*R*,4*S*,5*S*)-5-(2-Chlorophenyl)-4-nitro-3-(trifluoromethyl) pyrazolidin-1-yl)(phenyl)methanone (3af).** White solid (58 mg, 73% yield); m.p. 200–201 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 7.96 (s, 2H), 7.75 (d, $J$ = 6.0 Hz, 1H), 7.54–7.45 (m, 4H), 7.37–7.30 (m, 2H), 7.20 (s, 1H), 6.45–6.44 (m, 1H), 6.22–6.19 (m, 1H), 5.12–5.09 (m, 1H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 173.3, 135.7, 134.1, 133.8, 131.9, 131.3, 130.3, 130.2, 129.1, 128.6, 128.3, 124.8 (q, $J$ = 279.0 Hz), 89.8, 65.5 (q, $J$ = 31.5 Hz), 64.6; $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −74.66 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{17}H_{14}ClF_3N_3O_3$ $[M + H]^+$ 400.0670, found 400.0664.

**((3*R*,4*S*,5*R*)-5-(3-Chlorophenyl)-4-nitro-3-(trifluoromethyl) pyrazolidin-1-yl)(phenyl)methanone (3ag).** White solid (63 mg, 79% yield); m.p. 189–190 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 7.95–7.94 (m, 2H), 7.65–7.61 (m, 1H), 7.55–7.50 (m, 2H), 7.46–7.44 (m, 2H), 7.39–7.34 (m, 2H), 7.20 (d, $J$ = 6.0 Hz, 1H), 6.34 (d, $J$ = 7.8 Hz, 1H), 6.27 (d, $J$ = 8.4 Hz, 1H), 5.11–5.06 (m, 1H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 173.4, 138.4, 135.8, 134.8, 131.8, 131.0, 130.2, 129.5, 128.6, 127.9, 126.8, 124.9 (q, $J$ = 279.0 Hz), 91.3, 66.2, 65.5 (q, $J$ = 31.5 Hz); $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −69.54 (d, $J$ = 11.2 Hz); HRMS (ESI): calculated for $C_{17}H_{14}ClF_3N_3O_3$ $[M + H]^+$ 400.0670, found 400.0672.

**((3*R*,4*S*,5*S*)-5-(4-Chlorophenyl)-4-nitro-3-(trifluoromethyl) pyrazolidin-1-yl)(phenyl)methanone (3ah).** White solid (68 mg, 85% yield); m.p. 182–184 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 7.92 (d, $J$ = 7.8 Hz, 2H), 7.61 (d, $J$ = 8.4 Hz, 2H), 7.55–7.50 (m, 1H), 7.45 (t, $J$ = 7.8 Hz, 2H), 7.38 (d, $J$ = 8.4 Hz, 2H), 7.13 (d, $J$ = 6.0 Hz, 1H), 6.33 (d, $J$ = 8.4 Hz, 1H), 6.25 (d, $J$ = 8.4 Hz, 1H), 5.09–5.04 (m, 1H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 173.3, 135.9, 135.0, 134.8, 131.8, 130.1, 129.8, 129.4, 128.6, 124.9 (q, $J$ = 279.0 Hz), 91.4, 66.1, 65.4 (q, $J$ = 31.5 Hz); $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −74.74 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{17}H_{14}ClF_3N_3O_3$ $[M + H]^+$ 400.0670, found 400.0665.

**((3*R*,4*S*,5*S*)-5-(2-Fluorophenyl)-4-nitro-3-(trifluoromethyl) pyrazolidin-1-yl)(phenyl)methanone (3ai).** White solid (66 mg, 86% yield); m.p. 199–201 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 7.93 (d, $J$ = 7.8 Hz, 2H), 7.65 (t, $J$ = 7.8 Hz, 1H), 7.52 (t, $J$ = 7.2 Hz, 1H), 7.45 (t, $J$ = 7.8 Hz, 2H), 7.41–7.38 (m, 1H), 7.17 (t, $J$ = 6.0 Hz, 2H), 7.10 (d, $J$ = 5.4 Hz, 1H), 6.44 (d, $J$ = 7.8 Hz, 1H), 6.22 (d, $J$ = 7.8 Hz, 1H), 5.13–5.08 (m, 1H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 173.2, 164.3 (d, $J$ = 244.5 Hz), 135.7, 131.9, 131.7 (d, $J$ = 7.5 Hz), 130.1, 129.1 (d, $J$ = 3.0 Hz), 128.6, 125.5 (d, $J$ = 4.5 Hz), 124.9 (q, $J$ = 279.0 Hz), 123.1 (d, $J$ = 13.5 Hz), 116.1 (d, $J$ = 21.0 Hz), 90.4, 65.5 (q, $J$ = 31.5 Hz), 61.1; $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −74.62 (d, $J$ = 7.52 Hz), −117.81; HRMS (ESI): calculated for $C_{17}H_{14}F_4N_3O_3$ $[M + H]^+$ 384.0966, found 384.0962.

**((3*R*,4*S*,5*S*)-5-(4-Fluorophenyl)-4-nitro-3-(trifluoromethyl)pyrazolidin-1-yl)(phenyl)methanone (3aj).** White solid (68 mg, 88% yield); m.p. 214–215 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 7.92 (t, $J$ = 6.0 Hz, 2H), 7.64–7.62 (m, 2H), 7.52–7.50 (m, 1H), 7.46–7.43 (m, 2H), 7.13–7.10 (m, 3H), 6.34 (t, $J$ = 7.8 Hz, 1H), 6.24 (dd, $J$ = 8.4, 3.0 Hz, 1H), 5.06–5.04 (m, 1H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 173.4, 163.7 (d, $J$ = 243.0 Hz), 136.0, 132.1, 131.8 (d, $J$ = 3.0 Hz), 130.2 (d, $J$ = 7.5 Hz), 130.1, 128.6 (d, $J$ = 1.5 Hz), 124.9 (q, $J$ = 279.0 Hz), 116.1 (d, $J$ = 22.5 Hz), 91.4, 66.0, 65.5 (q, $J$ = 30.0 Hz); $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −74.74 (d, $J$ = 7.52 Hz), −115.78; HRMS (ESI): calculated for $C_{17}H_{14}F_4N_3O_3$ $[M + H]^+$ 384.0966, found 384.0964.

**((3*R*,4*S*,5*S*)-4-Nitro-3-(trifluoromethyl)-5-(4-(trifluoromethyl) phenyl)pyrazolidin-1-yl)(phenyl)methanone (3ak).** White solid (74 mg, 85% yield); m.p. 203–204 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 7.95–7.93 (m, 2H), 7.83 (d, $J$ = 7.8 Hz, 2H), 7.72 (d, $J$ = 8.4 Hz, 2H), 7.53 (t, $J$ = 7.2 Hz, 1H), 7.47–7.45 (m, 2H), 7.20 (d, $J$ = 4.8 Hz, 1H), 6.43–6.40 (m, 1H), 6.34 (dd, $J$ = 8.4, 2.4 Hz, 1H), 5.11–5.09 (m, 1H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 173.4, 140.7, 135.8, 131.9, 131.0 (q, $J$ = 31.5 Hz), 130.2, 128.9, 128.6, 126.3 (q, $J$ = 4.5 Hz), 125.3 (q, $J$ = 270.0 Hz), 124.9 (q, $J$ = 279.0 Hz), 91.4, 66.3, 65.5 (q, $J$ = 31.5 Hz); $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −63.52, −74.74 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{18}H_{14}F_6N_3O_3$ $[M + H]^+$ 434.0934, found 434.0929.

**((3*R*,4*S*,5*R*)-5-(4-Bromophenyl)-4-nitro-3-(trifluoromethyl) pyrazolidin-1-yl)(phenyl)methanone (3al).** White solid (84 mg, 95% yield); m.p. 175–176 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 7.92 (d, $J$ = 7.8 Hz, 2H), 7.54–7.50 (m, 5H), 7.45 (t, $J$ = 7.2 Hz, 2H), 7.13 (d, $J$ = 5.4 Hz, 1H), 6.31 (d, $J$ = 7.8 Hz, 1H), 6.25 (d, $J$ = 8.4 Hz, 1H), 5.08–5.04 (m, 1H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 173.3, 135.9, 135.5, 132.4, 131.8, 130.1, 128.6, 127.7, 124.9 (q, $J$ = 279.0 Hz), 122.9, 91.3, 66.1, 65.5 (q, $J$ = 31.5 Hz); $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −74.75 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{17}H_{14}BrF_3N_3O_3$ $[M + H]^+$ 444.0165, found 444.0158.

**((3*R*,4*S*,5*R*)-5-(Naphthalen-2-yl)-4-nitro-3-(trifluoromethyl) pyrazolidin-1-yl)(phenyl)methanone (3am).** White solid (68 mg, 82% yield); m.p. 210–211 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 8.59 (d, $J$ = 8.4 Hz, 1H), 7.98–7.97 (m, 2H), 7.94 (d, $J$ = 7.8 Hz, 1H), 7.90–7.87 (m, 2H), 7.64–7.61 (m, 1H), 7.56–7.54 (m, 1H), 7.52–7.50 (m, 1H), 7.46–7.43 (m, 3H), 7.19 (d, $J$ = 4.2 Hz, 1H), 7.08–7.06 (m, 1H), 6.60 (dd, $J$ = 8.4, 4.2 Hz, 1H), 5.11–5.06 (m, 1H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 173.1, 136.1, 134.7, 132.2, 131.8, 131.7, 130.2, 130.1, 129.7, 128.6, 127.6, 127.0, 126.2, 125.3, 125.0 (q, $J$ = 279.0 Hz), 124.5, 90.8, 65.4 (q, $J$ = 31.5 Hz), 64.0; $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −74.38 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{21}H_{17}F_3N_3O_3$ $[M + H]^+$ 416.1217, found 416.1214.

**((3*R*,4*S*,5*R*)-4-Nitro-5-(thiophen-2-yl)-3-(trifluoromethyl)pyrazolidin-1-yl)(phenyl)methanone (3an).** White solid (57 mg, 77% yield); m.p. 182–183 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 7.87–7.86 (m, 2H), 7.53–7.50 (m, 1H), 7.46–7.43 (m, 2H), 7.41 (dd, $J$ = 4.8, 1.8 Hz, 1H), 7.25–7.24 (m, 1H), 7.08 (d, $J$ = 6.6 Hz, 1H), 7.00 (dd, $J$ = 4.8, 1.2 Hz, 1H), 6.62 (d, $J$ = 7.8 Hz, 1H), 6.23 (dd, $J$ = 7.8, 1.2 Hz, 1H), 5.13–5.07 (m, 1H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 173.2, 138.2, 135.7, 131.9, 130.1, 128.6, 128.0, 127.5, 126.6, 125.0 (q, $J$ = 279.0 Hz), 90.9, 65.4 (q, $J$ = 31.5 Hz), 62.2; $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −74.44 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{15}H_{12}F_3N_3O_3SNa$ $[M + Na]^+$ 394.0444, found 394.0440.

**((3*R*,4*S*,5*R*)-5-(Furan-2-yl)-4-nitro-3-(trifluoromethyl)pyrazolidin-1-yl)(phenyl)methanone (3ao).** White solid (53 mg, 75% yield); m.p. 165–167 °C; $^1$H NMR (600 MHz, $(CD_3)_2CO$) $\delta$ 7.83 (d, $J$ = 7.2 Hz, 2H), 7.53–7.49 (m, 2H), 7.43 (t, $J$ = 7.8 Hz, 2H), 6.96 (d, $J$ = 6.6 Hz, 1H), 6.60 (d, $J$ = 3.6 Hz, 1H), 6.52 (d, $J$ = 7.8 Hz, 1H), 6.42 (dd, $J$ = 3.0, 1.8 Hz, 1H), 6.18 (dd, $J$ = 8.4, 3.0 Hz, 1H), 5.18–5.12 (m, 1H); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$) $\delta$ 172.5, 149.1, 144.5, 135.3, 131.9, 130.2, 128.6, 125.4 (q, $J$ = 279.0 Hz), 111.7, 110.5, 88.8, 65.7 (q, $J$ = 31.5 Hz), 59.6; $^{19}$F NMR (376 MHz, $(CD_3)_2CO$) $\delta$ −75.21 (d, $J$ = 7.52 Hz); HRMS (ESI): calculated for $C_{15}H_{13}F_3N_3O_3$ $[M + H]^+$ 356.0853, found 356.0849.

**General experimental procedures for the synthesis of compounds 4**

A solution of trifluoromethylated pyrazolidine **3** (0.1 mmol) and 3.0 equiv. of $CuCl_2$ in EtOH (4 mL) was stirred at reflux for 6–8 h and monitored by thin layer chromatography (TLC) until the starting material was not detected, and the reaction mixture was cooled to room temperature. The solid was filtered from the reaction mixture. The filtrate was concentrated under vacuum. Purification of the residue by silica gel column chromatography using petroleum ether : acetone (4 : 1) as the eluent furnished the products **4**.

**5-Phenyl-3-(trifluoromethyl)-1*H*-pyrazole (4a).** White solid; ($R^1$ = phenyl, 37 mg, 88% yield; $R^1$ = isobutyl, 32 mg, 78% yield; $R^1$ = *m*-tolyl, 34 mg, 80% yield); m.p. 118–119 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 12.6 (s, 1H), 7.56–7.55 (m, 2H), 7.45–7.39 (m, 3H), 6.70 (s, 1H); $^{13}$C NMR (150 MHz, CDC) $\delta$ 145.1, 129.4, 129.2, 127.9, 125.6, 120.5 (q, $J$ = 267.0 Hz), 101.0; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −62.55; HRMS (ESI): calculated for $C_{10}H_8F_3N_2$ $[M + H]^+$ 213.0634, found 213.0632.

**5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazole (4b).** White solid (33 mg, 68% yield); m.p. 145–146 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 11.7 (s, 1H), 7.49 (d, $J$ = 8.4 Hz, 2H), 6.97–6.96 (m, 2H), 6.6 (s, 1H), 3.8 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 160.5, 144.9, 127.0, 121.2 (q, $J$ = 267.0 Hz), 120.6, 114.6, 100.3, 55.4; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −62.60; HRMS (ESI): calculated for $C_{11}H_{10}F_3N_2O$ $[M + H]^+$ 243.0740, found 243.0742.

**5-(4-Chlorophenyl)-3-(trifluoromethyl)-1*H*-pyrazole (4c).** White solid (43 mg, 87% yield); m.p. 149–150 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 12.74 (s, 1H), 7.47 (d, $J$ = 8.4 Hz, 2H), 7.40 (d, $J$ = 8.4 Hz, 2H), 6.69 (s, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 144.2, 135.5, 129.5, 126.8, 126.3, 121.9 (q, $J$ = 267.0 Hz), 101.3; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −62.55; HRMS (ESI): calculated for $C_{10}H_7ClF_3N_2$ $[M + H]^+$ 247.0244, found 247.0247.

**5-(Naphthalen-2-yl)-3-(trifluoromethyl)-1*H*-pyrazole (4d).** White solid (45 mg, 87% yield); m.p. 101–102 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 10.75 (s, 1H), 7.99–7.93 (m, 3H), 7.57–7.54 (m, 4H), 6.83 (s, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 143.2, 133.7, 131.1, 130.2, 128.7, 127.5, 127.4, 126.6, 126.1, 125.2, 124.5, 121.2 (q, $J$ = 267.0 Hz), 104.7; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −62.50; HRMS (ESI): calculated for $C_{14}H_{10}F_3N_2$ $[M + H]^+$ 263.00791, found 263.0794.

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## Notes and references

1 (*a*) L. C. Behr, R. Fusco and C. H. Jarboe, Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings, in *The Chemistry of Heterocyclic Compounds*, ed. R. H. Wiley, Interscience Publishers, New York, 1967, vol. 22; (*b*) C. Kadouri-Puchot and C. Agami, in *Asymmetric Synthesis of Nitrogen Heterocycles*, ed. J. Royer, Wiley-VCH, Weinheim, Germany, 2009, ch. 6.

2 (*a*) H. Berenson, *United States Patent* 3931406, 1976; (*b*) B. Cross, C. P. Grasso and B. L. Walworth, *United States Patent* 3948936, 1976; (*c*) C. Nishino, T. Otake, K. Adachi and R. Inada, *United States Patent* 5849930, 1998; (*d*) M. J. Kornet and R. J. Garrett, *J. Pharm. Sci.*, 1979, **68**, 377; (*e*) P. D. Boatman, C. O. Ogbu, M. Eguchi, H.-O. Kim, H. Nakanishi, B. Cao, J. P. Shea and M. Kahn, *J. Med. Chem.*, 1999, **42**, 1367; (*f*) J. H. Ahn, J. A. Kim, H.-M. Kim, H.-M. Kwon, S.-C. Huh, S. D. Rhee, K. R. Kim, S.-D. Yang, S.-D. Park, J. M. Lee, S. S. Kim and H. G. Cheon, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1337; (*g*) J. H. Ahn, S. H. Jung, J. A. Kim, S. B. Song, S. J. Kwon, K. R. Kim, S. D. Rhee, S.-D. Park, J. M. Lee, S. S. Kim and H. G. Cheon, *Chem. Pharm. Bull.*, 2005, **53**, 1048; (*h*) M. J. Kornet and P. A. Thio, *J. Pharm. Sci.*, 1969, **58**, 724.

3 (*a*) X.-C. Gao, H. Cao, L.-Q. Zhang, B.-W. Zhang, Y. Cao and C.-H. Huang, *J. Mater. Chem.*, 1999, **9**, 1077; (*b*) H.-B. Fu and J.-N. Yao, *J. Am. Chem. Soc.*, 2001, **123**, 1434; (*c*) S. W. Oh, D. R. Zhang and Y. S. Kang, *Mater. Sci. Eng., C*, 2004, **24**, 131.

4 (*a*) W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc.*, 1970, 1597; (*b*) J. E. Shurig, W. T. Brandner, J. B. Huflutalen, G. J. Doyle and J. A. Gylys, *Toxic side effects of platinum analogs. Cisplatin: current status and new developments*, Academic Press, New York, 1980, vol. 227.

5 (*a*) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (*b*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (*c*) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359.

6 (*a*) S. Ogawa, T. Nishimine, E. Tokunaga and N. Shibata, *Synthesis*, 2010, 3274; (*b*) D. Wang, H.-P. Deng, Y. Wei, Q. Xu and M. Shi, *Eur. J. Org. Chem.*, 2013, 401.

7 (*a*) J. Hu, W. Zhang and F. Wang, *Chem. Commun.*, 2009, 7465; (*b*) J. Nie, H.-C. Guo, D. Cahard and J.-A. Ma, *Chem. Rev.*, 2011, **111**, 455.

8 (*a*) S. Ji, A. E. Alkhalil, Y. Su, X. Xia, S. Chong, K.-H. Wang, D. Huang, Y. Fu and Y. Hu, *Synlett*, 2015, 1725; (*b*) W. Zhang, Y. Su, S. Chong, L. Wu, G. Cao, D. Huang, K.-H. Wang and Y. Hu, *Org. Biomol. Chem.*, 2016, **14**, 11162; (*c*) W. Zhang, Y. Su, K.-H. Wang, L. Wu, B. Chang, Y. Shi, D. Huang and Y. Hu, *Org. Lett.*, 2017, **19**, 376; (*d*) G. Du, D. Huang, K.-H. Wang, X. Chen, Y. Xu, J. Ma, Y. Su, Y. Fu and Y. Hu, *Org. Biomol. Chem.*, 2016, **14**, 1492.

9 (*a*) L. M. Stanley and M. P. Sibi, *Chem. Rev.*, 2008, **108**, 2887; (*b*) R. Na, C. Jing, Q. Xu, H. Jiang, X. Wu, J. Shi, J. Zhong, M. Wang, D. Benitez, E. Tkatchouk, W. A. Goddard, H. Guo and O. Kwon, *J. Am. Chem. Soc.*, 2011, **133**, 13337; (*c*) T. Hashimoto, M. Omote and K. Maruoka, *Angew. Chem., Int. Ed.*, 2011, **50**, 3489; (*d*) T. Imaizumi, Y. Yamashita and S. Kobayashi, *J. Am. Chem. Soc.*, 2012, **134**, 20049; (*e*) M. Hori, A. Sakakura and

 

K. Ishihara, *J. Am. Chem. Soc.*, 2014, **136**, 13198; (*f*) X. Liu, Y. Wang, D. Yang, J. Zhang, D. Liu and W. Su, *Angew. Chem., Int. Ed.*, 2016, **55**, 8100; (*g*) H.-W. Zhao, B. Li, H.-L. Pang, T. Tian, X.-Q. Chen, X.-Q. Song, W. Meng, Z. Yang, Y.-D. Zhao and Y.-Y. Liu, *Org. Lett.*, 2016, **18**, 848.

10 (*a*) S. Kobayashi, H. Shimizu, Y. Yamashita, H. Ishitani and J. Kobayashi, *J. Am. Chem. Soc.*, 2002, **124**, 13678; (*b*) S. Kobayashi, R. Hirabayashi, H. Shimizu, H. Ishitani and Y. Yamashita, *Tetrahedron Lett.*, 2003, **44**, 3351; (*c*) Y. Yamashita and S. Kobayashi, *J. Am. Chem. Soc.*, 2004, **126**, 11279; (*d*) S. Shirakawa, P. J. Lombardi and J. L. Leighton, *J. Am. Chem. Soc.*, 2005, **127**, 9974; (*e*) K. Tran, P. J. Lombardi and J. L. Leighton, *Org. Lett.*, 2008, **10**, 3165; (*f*) A. Zamfir and S. B. Tsogoeva, *Synthesis*, 2011, 1988; (*g*) A. Zamfir, S. Schenker, W. Bauer, T. Clark and S. B. Tsogoeva, *Eur. J. Org. Chem.*, 2011, 3706; (*h*) O. V. Serdyuk, A. Zamfir, F. Hampel and S. B. Tsogoeva, *Adv. Synth. Catal.*, 2012, **354**, 3115; (*i*) M. Rueping, M. S. Maji, H. B. Küçük and I. Atodiresei, *Angew. Chem., Int. Ed.*, 2012, **51**, 12864; (*j*) X. Hong, H. B. Küçük, M. S. Maji, Y.-F. Yang, M. Rueping and K. N. Houk, *J. Am. Chem. Soc.*, 2014, **136**, 13769; (*k*) T. Hashimoto, Y. Maeda, M. Omote, H. Nakatsu and K. Maruoka, *J. Am. Chem. Soc.*, 2010, **132**, 4076.

11 For thermal condition induced [3 + 2] cycloadditions of acylhydrazones with olefins, see: (*a*) M. A. Badawy, S. A. El-Bahaie, A. M. Kadry and Y. A. Ibrahim, *Heterocycles*, 1988, **27**, 7; (*b*) V. V. Khau and M. J. Martinelli, *Tetrahedron Lett.*, 1996, **37**, 4323.

12 (*a*) Z. Huang, J. Hu and Y. Gong, *Org. Biomol. Chem.*, 2015, **13**, 8561; (*b*) Z. Huang and Y. Gong, *RSC Adv.*, 2016, **6**, 22357.

13 (*a*) G.-L. Zhao and M. Shi, *Tetrahedron*, 2005, **61**, 7277; (*b*) Z.-L. Yuan, Y. Wei and M. Shi, *Eur. J. Org. Chem.*, 2010, 4088.