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A CONVENIENT SYNTHESIS OF 5-TRIFLUOROMETHYL-5-CYCLOPROPYL-SUBSTITUTED PYRAZOLINES

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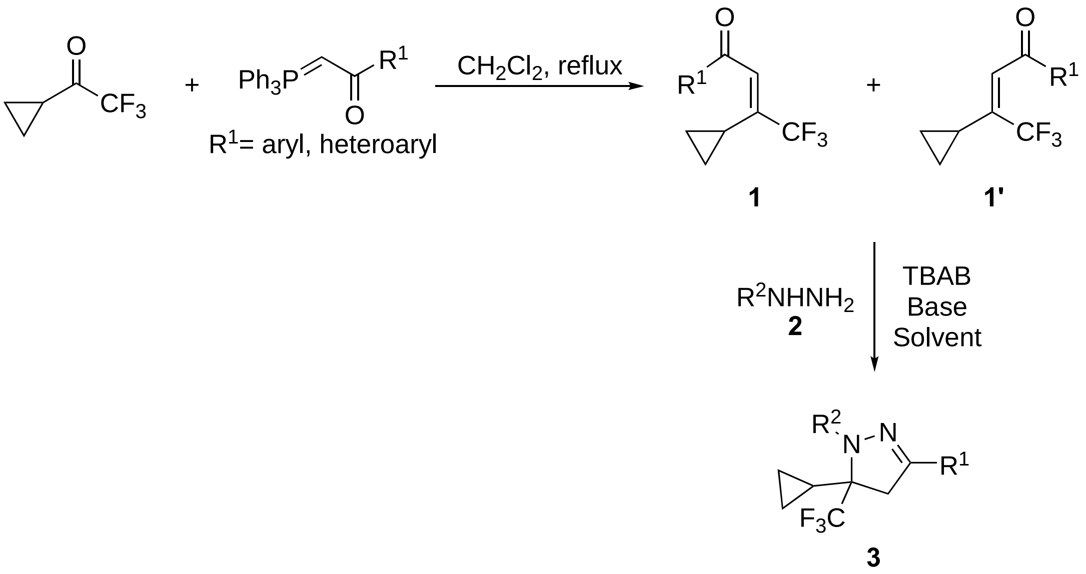
Abstract – A new method for the preparation of 5-trifluoromethyl-5-cyclopropyl-pyrazoline derivatives via cesium hydroxide mediated condensation reaction of β-trifluoromethyl-β-cyclopropyl-substituted unsaturated ketones with hydrazines was reported. The approach featuring mild reaction conditions, broad substrates scope and good functional group tolerance, provided a strategy to synthesize new functionalized pyrazolines bearing both trifluoromethyl and cyclopropyl groups.

Pyrazolines are a very important class of nitrogen-containing heterocyclic compounds and have a wide application in the field of pharmaceuticals, agrochemicals and material sciences.[1] Due to the advantage of trifluoromethyl (CF_3) group in improving the lipophilicity, bioavailability and metabolic stability of organic molecules,[2] trifluoromethyl-substituted pyrazolines have gained particular attentions.[3] The condensation of 1,1,1-trifluoro-α-enones with substituted hydrazines constitutes the most common synthetic method for trifluoromethyl-substituted pyrazolines.[4] Recently, the dipolar cycloaddition of CF_3CHN_2 with electron-deficient alkenes or allenes and formal [4 + 1]-annulation of trifluoroethylidene sulfur ylide with azoalkenes as new strategies to construct 5-(trifluoromethyl)pyrazolines have been developed.[5] Despite of these advances, there is an urge demand to synthesize new trifluoromethyl-substituted pyrazolines with multiple functional groups.[6]

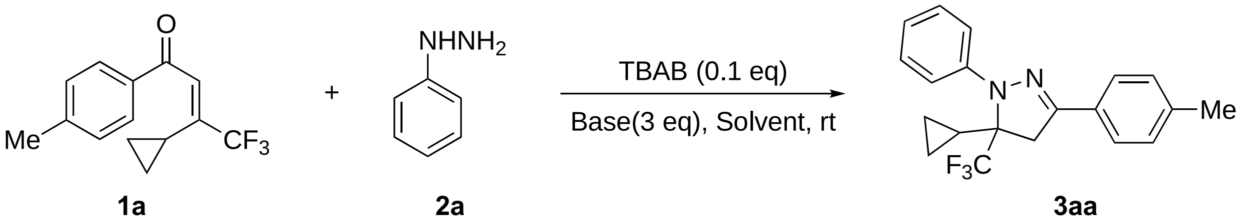
Cyclopropyl group as a structural moiety in many natural products and bioactive molecules, has unique stereospecific, electronic and conformational properties, making it a wide range of applications in organic synthesis, as well as a popular "weapon" in medicinal chemistry.[7] The incorporation of both trifluoromethyl and cyclopropyl groups into various molecules is an appealing challenge.[8] To address this issue, our group utilized the trifluoromethyl cyclopropyl ketone as a new building block, and successfully synthesized trifluoromethyl-/cyclopropyl-substituted 2-isoxazolines.[9] As our continuous research interest, herein, we reported a convenient synthesis of various 5-trifluoromethyl-5-cyclopropyl-substituted pyrazolines. The trifluoromethyl cyclopropyl ketone reacted with various phosphorus ylide reagents to give β-trifluoromethyl-β-cyclopropyl-substituted unsaturated ketone **1** as the major product and *cis*-unsaturated ketone **1'** as the minor product, followed by the condensation with hydrazines (Scheme 1).[10]



Scheme 1 Strategy for the synthesis of the 5-trifluoromethyl-5-cyclopropyl-substituted pyrazolines

We started our investigation by taking *trans*-trifluoromethyl/cyclopropyl-substituted unsaturated ketone **1a** and phenylhydrazine **2a** as the model substrates in *tert*-butyl methyl ether (MTBE) (Table 1). The preliminary studies showed that both base and phase transfer catalyst were essential for the reaction. With tetrabutylammonium bromide (TBAB, 0.1 equiv.) as a phase transfer catalyst, we investigated a variety of bases and the results showed that the base had very crucial effect on this reaction. The weak inorganic bases were not able to trigger the reaction (entries 1-6), in contrast, strong inorganic bases such as NaOH, KOH and $CsOH\cdot H_2O$ could promote this reaction (entries 7-9). With $CsOH\cdot H_2O$ as a base, the desired 5-trifluoromethyl-5-cyclopropyl-substituted pyrazoline **3aa** was obtained in 69% yield within 16 h (entry 9). *t*-BuONa and *t*-BuOK led to the decomposition of **1a** or product **3aa** (entries 10-11). Organic bases like DBU, Et_3N and quinine showed less efficiency to this reaction (entries 12-14). Further solvent screening (entries 15-22) revealed that MTBE was most suitable solvent for the reaction and 72% yield of **3aa** was achieved within 18 h.

Table 1 Screening of bases and solvents for the reaction **1a** with **2a** [a]

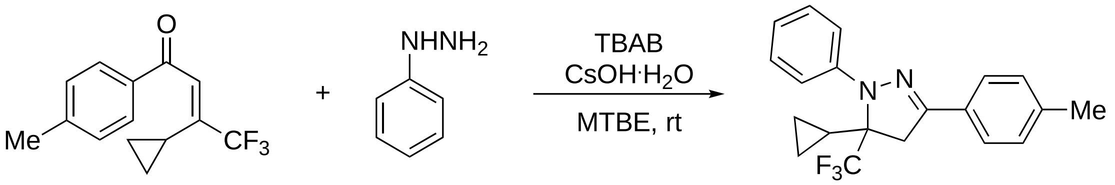


Entry	Base	Solvent	Yield[b](%)	Entry	Base	Solvent	Yield[b](%)
1	Na_2CO_3	MTBE	N.R.	12	DBU	MTBE	12
2	Cs_2CO_3	MTBE	N.R.	13	Et_3N	MTBE	N.R.
3	K_3PO_4	MTBE	N.R.	14	quinine	MTBE	N.R.
4	CsF	MTBE	N.R.	15	$CsOH{\cdot}H_2O$	CH_2Cl_2	8
5	LiOH	MTBE	N.R.	16	$CsOH{\cdot}H_2O$	THF	30
6	NaAc	MTBE	N.R.	17	$CsOH{\cdot}H_2O$	MTBE	72
7	NaOH	MTBE	11	18	$CsOH{\cdot}H_2O$	1,4-dioxane	21
8	KOH	MTBE	57	19	$CsOH{\cdot}H_2O$	MeCN	21
9	$CsOH{\cdot}H_2O$	MTBE	69	20	$CsOH{\cdot}H_2O$	MeOH	56
10	*t*-BuONa	MTBE	decompose	21	$CsOH{\cdot}H_2O$	DMF	5
11	*t*-BuOK	MTBE	decompose	22	$CsOH{\cdot}H_2O$	toluene	54

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol, 3 equiv.), TBAB (0.01 mmol, 0.1 equiv.), and base (0.3 mmol, 3 equiv.) in solvent (1 mL), stirred at room temperature for 16 h (entries 1-14) or 18 h (entries 15-22) in a sealed tube; [b] Yields were determined by ^{19}F NMR using 1-fluoronaphthalene as an internal standard.

Next, we further optimized the amounting of $CsOH{\cdot}H_2O$, phenylhydrazine and TBAB in the reaction (Table 2). It was found that the reaction with 2 equivalents of $CsOH{\cdot}H_2O$ gave the product **3aa** in 73% yield, similar to that of 2.5 equivalents of $CsOH{\cdot}H_2O$ (entries 1-2). A further decrease of the amount of $CsOH{\cdot}H_2O$ led to a diminished yield (entries 3-6). The amount of phenylhydrazine **2a** could be reduced to 2.5 equivalents without the loss of yield (entries 7-8), but further reduction of the amount of **2a** would result in a depressed yield (entries 9-11). Furthermore, increasing the amount of TBAB was beneficial for the conversion (entries 12-15). When 0.5 equivalent of TBAB was added, the yield of **3aa** was increased to 83% (entry 14). Nevertheless, further increase of the amount of TBAB did not help to improve the yield (entry 15).

Table 2 Optimization of the amounting of the reactants [a]



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

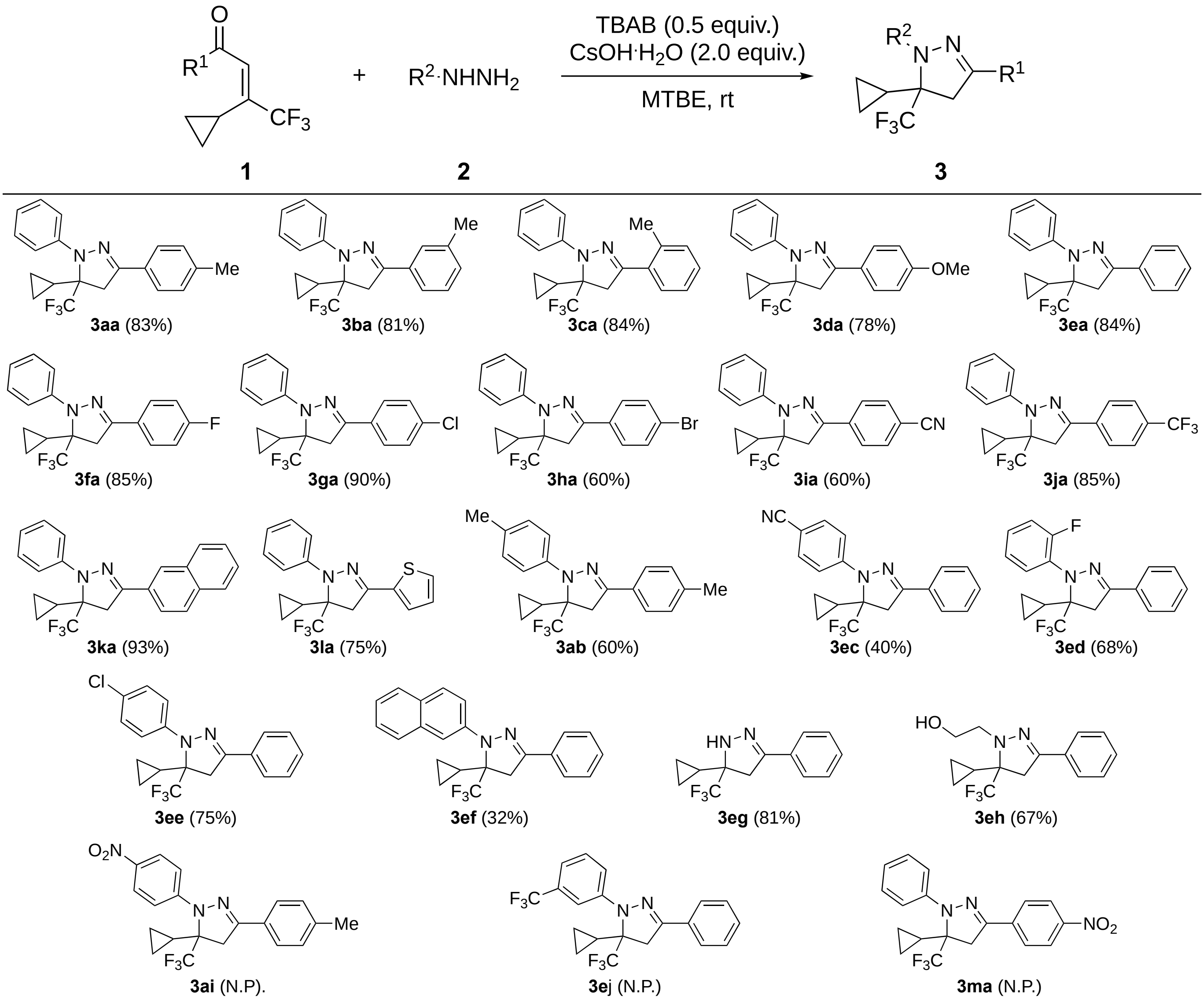
Entry	**2a** (equiv.)	TBAB (equiv.)	CsOH·H_2O (equiv.)	time (h)	Yield[b] (%)
1	3.0	0.1	2.5	20	75
2	3.0	0.1	2.0	20	73
3	3.0	0.1	1.5	20	45
4	3.0	0.1	1.0	20	13
5	3.0	0.1	0.5	20	12
6	3.0	0.1	0.1	20	2
7	3.0	0.1	2.0	24	68
8	2.5	0.1	2.0	24	68
9	2.0	0.1	2.0	24	54
10	1.5	0.1	2.0	24	25
11	1.0	0.1	2.0	24	11
12	2.5	0.1	2.0	20	63
13	2.5	0.25	2.0	20	75
14	2.5	0.50	2.0	20	83
15	2.5	0.75	2.0	20	83

[a] Reaction conditions: **1a** (0.1 mmol), **2a**, TBAB, and CsOH·H_2O in MTBE (1 mL), stirred at room temperature in a sealed tube; [b]Yields were determined by ^{19}F NMR using 1-fluoronaphthalene as an internal standard.

With the optimized conditions in hand, we turned to examine the substrate scope of this method and the results were summarized in Table 3. Various β-trifluoromethyl-β-cyclopropyl-substituted unsaturated ketones reacted with aromatic hydrazines smoothly to give the corresponding 5-trifluoromethyl-5-cyclopropyl-substituted pyrazolines in moderate to excellent yields (**3aa-3ka**). Different functional groups, such as alkyl, halides (F, Cl, Br), trifluoromethyl, cyano, methyl, and methoxy, were well tolerated the reaction conditions. Moreover, 2-naphthyl-substituted unsaturated ketones turned to a good substrate and gave the product in 93% yield (Table 3, **3ka**). Aromatic heterocyclic unsaturated ketone could also be applied to this reaction (Table 3, **3la**). However, the strong electron-withdrawing group nitro on the benzene of unsaturated ketones prevented the reaction (Table 3, **3ma**). As for the scope of aromatic hydrazines, phenylhydrazine with methyl, F, Cl group served as good substrates (Table 3, **3ab**, **3ed**-**3ee**). 2-

Naphthylhydrazine gave the product in a lower yield (Table 3, **3ef**). The phenylhydrazine bearing strong electron-withdrawing group showed lower reaction activities in this reaction. For instance, 4-cyanophenylhydrazine afforded the target product in 40% yield (Table 3, **3ec**), while 4-nitrophenylhydrazine and 3-(trifluoromethyl)phenylhydrazine gave no product (Table 3, **3ai**, **3ej**). Besides, hydrazine and aliphatic hydrazine also reacted smoothly to deliver the corresponding products in good yields (Table 3, **3eg**, **3eh**).

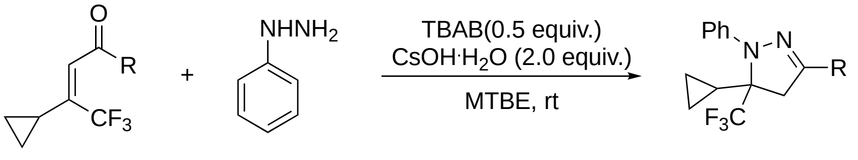
Table 3 Scope of the reaction of unsaturated ketones with hydrazine[a, b]



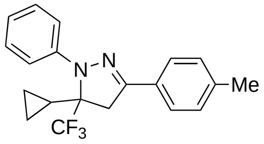
[a] Reaction conditions: **1** (1.0 mmol), **2a** (2.5 mmol), TBAB (0.5 mmol), $CsOH \cdot H_2O$ (2.0 mmol) in MTBE (10 mL), stirred at room temperature in a sealed tube; [b]All yields listed in the table were isolated yields.

Furthermore, *cis*-unsaturated ketone **1’** could also react with phenylhydrazine **2a** to deliver the corresponding products under the optimal reaction condition (Table 4, **3aa**, **3ea**), which structures were consistent with the products of *trans*-unsaturated ketone **1** and phenylhydrazine **2a**. Strong electron-withdrawing group substituent on aromatic ring of *cis*-unsaturated ketone could not be applied to this reaction (Table 4, **3ma**). The results indicated that *cis*-unsaturated ketone **1'** and *trans*-unsaturated ketone **1** had similar reaction activities towards this reaction.

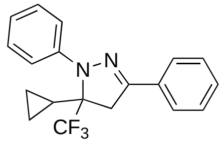
Table 4 *cis*-unsaturated ketone **1'** react with phenylhydrazine **2a** [a,b]



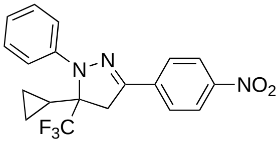
1' **2a** **3**



3aa (81%)



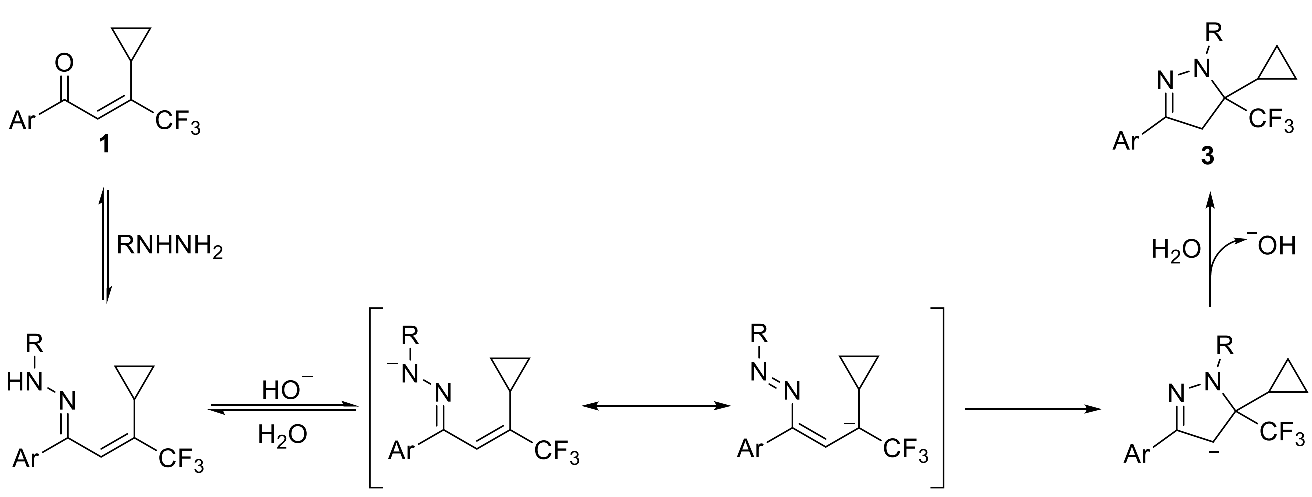
3ea (78%)



3ma (N.P.)

[a] Reaction conditions: **1'** (1.0 mmol), **2a** (2.5 mmol), TBAB (0.5 mmol), $CsOH{\cdot}H_2O$ (2.0 mmol) in MTBE (10 mL), stirred at room temperature in a sealed tube; [b] All yields listed in the table were isolated yields.

According to the experimental results, we proposed a possible mechanism (Scheme 2). The 5-trifluoromethyl-5-cyclopropyl-substituted unsaturated ketones **1** reacted with hydrazine reagents **2** to give the hydrazone **A**. Subsequently, $CsOH{\cdot}H_2O$ abstracted proton from the NH group of **A** upon the promotion of phase transfer catalyst TBAB, to afford intermediate **B** or **C**. Due to the fast tautomerization of **B** and **C**, *cis* and *trans* unsaturated ketones **1** gave similar results in the reaction. Finally, intermediate **B** or **C** further underwent intramolecular Michael addition and protonation to offer 5-trifluoromethyl-5-cyclopropylpyrazoline **3**.



Scheme 2 Proposed reaction mechanism

In summary, we have developed a practical method for the preparation of trifluoromethyl and cyclopropyl-substituted pyrazoline derivatives. The β-trifluoromethyl-β-cyclopropyl-substituted unsaturated ketones, derived from the reaction of trifluoromethyl cyclopropyl ketone with phosphorus ylides, underwent the condensation with hydrazines to give a wide range of 5-trifluoromethyl-5-cyclopropylpyrazolines in good to excellent yields. Due to the mild conditions, various common functional groups were well tolerated in the transformation. The approach provided a strategy to synthesize new functionalized pyrazolines bearing both trifluoromethyl and cyclopropyl groups.

EXPERIMENTAL

^{1}H NMR and ^{19}F NMR spectra were obtained with an Agilent AM-400 instrument with Me_4Si as the internal standard. ^{13}C NMR spectra were recorded on a Bruker AV400 instrument with TMS as the internal standard. Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are in Hertz (Hz). FT-IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Mass spectra were obtained on an Agilent 5973 Network or a Waters Micromass GCT Premier instrument. α,β-Unsaturated ketones **1** were prepared according to the literature procedure.[9] All other chemicals were purchased from commercial sources and used directly. All reactions were monitored by TLC or ^{19}F NMR. Flash column chromatograph was carried out using 300-400 mesh silica gel at medium pressure.

Typical Procedure for the Synthesis of 5-Trifluoromethyl-5-cyclopropyl-substituted Pyrazolines.

5-Cyclopropyl-1-phenyl-3-(*p*-tolyl)-5-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazole (3aa). α,β-Unsaturated ketone **1a** (1.0 mmol, 1.0 equiv), phenylhydrazine **2a** (2.5 mmol, 2.5 equiv), TBAB (0.5 mmol, 0.5 equiv), $CsOH\cdot H_2O$ (2.0 mmol, 2.0 equiv) and MTBE (10 mL) were added to a sealed Schlenk tube equipped with a stir bar. The reaction mixture was stirred at room temperature for 20 h. The completion of the reaction was monitored by ^{19}F NMR. When the reaction was completed, the reaction mixture was purified by column chromatography on silica gel to afford desire product **3aa** as a yellow oil; yield: 83%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.37-7.32 (m, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.17-7.13 (m, 1H), 3.23 (d, *J* = 17.7 Hz, 1H), 2.71 (d, *J* = 17.7 Hz, 1H), 2.40 (s, 3H), 1.26-1.19 (m, 1H), 0.72-0.63 (m, 1H), 0.52-0.45 (m, 1H), 0.38-0.25 (m, 2H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.43 (s, 3F) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.45 (s), 144.60 (s), 139.37 (s), 129.40 (s), 129.02 (s), 128.52 (s), 126.43 (q, *J* = 284.4 Hz), 125.81 (s), 124.42 (s), 123.53 (s), 74.27 (q, *J* = 26.5 Hz), 36.01 (s), 21.44 (s), 9.91 (s), 2.62 (s), -0.18 (s) ppm. IR (KBr): 3032, 2923, 1685, 1597, 1516, 1494, 1452, 1431, 1413, 1372, 1308, 1231, 1167, 1085, 1064, 1043, 1020, 910, 880, 815, 764, 731, 713, 698, 634, 536, 480 cm^{-1}. MS (EI): *m/z* (%) 344 (M^+, 27.91), 275 (100), 276, 119, 91, 77, 65, 51. HRMS (EI): Mass calculated for $C_{20}H_{19}N_2F_3$: 344.1500; Found: 344.1498.

SUPPORTING INFORMATION

Supplementary (synthesis of the starting azides, HPLC chromatograms, IR, 1H and 13C NMR, MS spectra, etc.) data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27867/106/4.

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