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Difluoroketenimine: Generation from Difluorocarbene and Isocyanide, and Its [3+2] Cycloadditions with Alkenes or Alkynes

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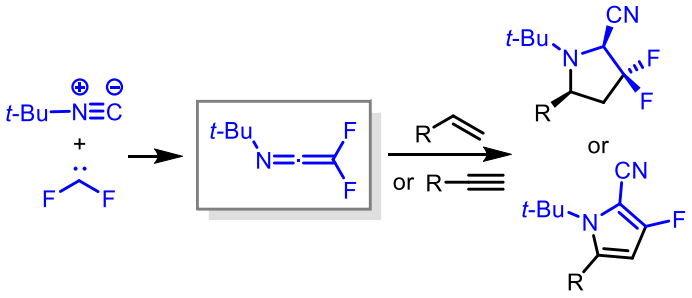


ABSTRACT. Ketenimines have been explored as useful building blocks for the synthesis of heteroatom containing cyclic compounds through the cycloaddition with polar multiple bonds. Herein we report the cycloaddition of difluoroketenimine with non-polar multiple bonds, namely the cycloaddition with alkenes or alkynes. The difluoroketenimine is generated from the coupling of *tert*-butylisocyanide and difluorocarbene, which is formed in situ from (bromodifluoromethyl)trimethylsilane. The difluoroketenimine then reacts in situ with alkenes or alkynes to afford fluorinated pyrrolidines or pyrroles. DFT study suggests that a fluorinated cyclic (alkyl)(amino)carbene is involved as the key intermediate in these reactions.

INTRODUCTION

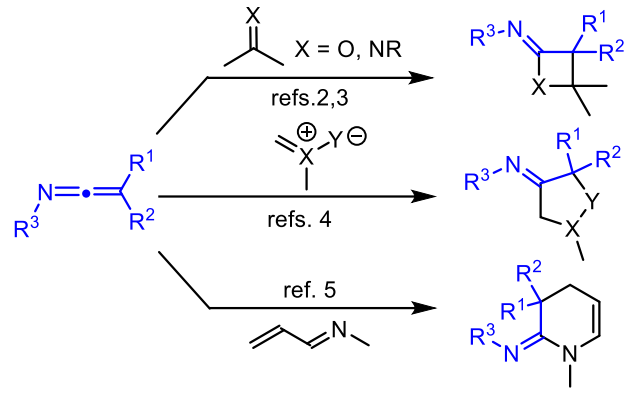
Ketenimines are a type of unique building blocks in organic synthesis, and are generally served as a 2π species in cycloaddition reactions, due to the high reactivity of their cumulated double bonds.[1] For instance, ketenimines can undergo formal [2+2] reactions with imines[2] and ketones,[3] [3+2] reactions with 1,3-dipolars[4] and [4+2] reactions with azadienes[5] (Scheme 1a). Conjugated vinyl/phenyl-substituted ketenimines can also serve as 4π species in various [4+2] reactions.[6] Despite these known reaction modes, the cycloaddition reaction of ketenimines is still limited. In most cases, only the carbon-carbon bond in ketenimines is involved in the cycloaddition process[7] and another reaction component is restricted in polar multiple bonds, such as imines or ketones. So far, the cycloaddition reactions between ketenimines and nonpolar multiple bonds, especially those where both double bonds in ketenimines are involved, still remain challenging and unexplored.

On the other hand, fluorine-containing molecules have attracted significant attention in recent years, due to their importance in life science, drug industry and material science.[8] Consequently, various fluorinated reagents have been developed to introduce fluorine atoms into complex molecules.[9] We have recently reported the in-situ generation of a new fluorinated intermediate, difluoroketenimine, via the reaction between difluorocarbene and isocyanides.[10] Difluoroketenimine can serve as the surrogate of the highly unstable intermediate difluoroketene[11] and undergoes [2+2] reaction with imines to give *α,α*-difluoro-*β*-amino amides and *α,α*-difluoroazetidinimines (Scheme 1b). We also found that the introduction of fluorine atoms would significantly enhance ketenimines' reactivity in [2+2] cycloadditions. To further explore the intriguing chemistry of the newly discovered difluoroketenimine and its application in the synthesis of fluorine-containing molecules, we conceived to develop the [3+2] cycloaddition reaction between difluoroketenimines and nonpolar multiple bonds (Scheme 1c). Herein we report that the reaction leads to one-step synthesis of fluorinated multi-substituted pyrrolidines and pyrroles, which are important backbones in various natural products and pharmaceuticals.[12] Mechanistic

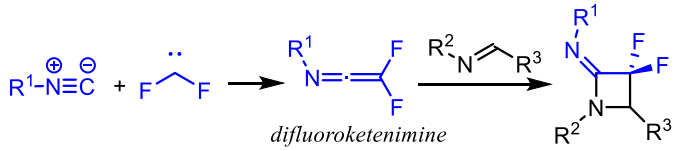
study through DFT calculation reveals that a fluorinated cyclic (alkyl)(amino)carbene (CAAC) species is likely involved as key intermediate.

Scheme 1. Cylcoaddition Reactions of Ketenimines and Difluoroketenimines

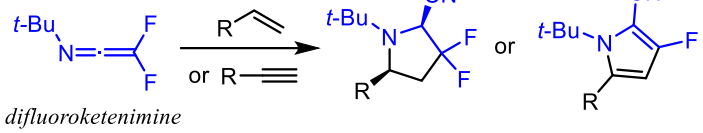
a) Reported cycloaddition reactions with ketenimines



b) Generation of difluoroketenimine and its [2+2] reaction with imines (ref.10).



c) Cycloaddition reaction of ketenimine with alkene or alkyne (this work).

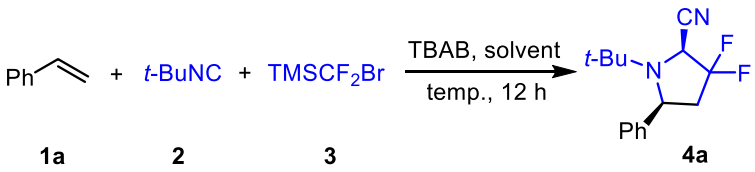


RESULTS AND DISCUSSIONS

To test our hypothesis, styrene **1a** was chosen as the model substrate and reacted with tert-butylisocyanide **2**, (bromodifluoromethyl)trimethylsilane **3** and *tetra-n*-butylammonium bromide (TBAB) under similar conditions which we have reported before. A pyrrolidine derivative **4a** was obtained in 29% ^{1}H NMR yield (Table 1, entry 1), whose structure was determined unambiguously via X-ray diffraction (see Supporting Information for details). Interestingly, the structure features an α-cyano substitution, which indicates the participation of a second equivalent of isocyanide during the [3+2] reaction. Satisfyingly, the reaction demonstrated excellent diastereoselectivity for the phenyl and cyano

substituents, and we could only observe the syn-diastereomer via careful ^{1}H and ^{13}C NMR analysis of the crude mixture. The yield slightly increased with less TBAB and higher temperature (Table 1, entries 2-3). Under 90 °C, **2** and **3** was added dropwise to avoid side reactions of the in situ formed difluoroketenimine and **4a** was obtained in 46% yield (Table1, entry 4). With 3 equivalents of **2**, we further screened a series of solvents. Toluene and diglyme are superior choices to give **4a** in 74% and 75% yield respectively (Table 1, entries 5-8). In consideration of that polar substrates always show better solubility in diglyme, we finally choose diglyme as the solvent. Further increasing the amount of **4a** to 4 equivalents gave the best result and **4a** was isolated in 84% yield (Table 1, entry 9).

Table 1. Optimization of the Reaction Conditions[a]



1a **2** **3** **4a**

entry	ratio of **1a**:**2**:**3**	TBAB (mol%)	solvent	temp. (°C)	yield (%)[b]
1	1:2:2	50	DCE	50	29
2	1:2:2	50	DCE	70	33
3	1:2:2	30	DCE	70	38
4[c]	1:2:2	30	DCE	90	46
5[c]	1:3:2	30	DCE	90	56
6[c]	1:3:2	30	toluene	90	74
7[c]	1:3:2	30	$PhCF_3$	90	70
8[c]	1:3:2	30	diglyme	90	75
9[c]	1:4:2	30	diglyme	90	82(84)[d]

[a]The reactions were run on a 0.2 mmol scale. The concentration of **1a** was 1.33M. [b]The yields were determined by ^{1}H NMR with CH_2Br_2 as the internal standard. The *dr* value was determined by ^{1}H NMR analysis of the crude mixture. Under all circumstances, only the syn diastereomer was identified (*dr* > 20:1). [c]The solution of **2** and **3** in 0.5 mL solvent was added dropwise in 3 h. [d]The reaction was run on 0.4 mmol scale and the isolated yield was given. TBAB: *tetra*-*n*-butylammonium bromide

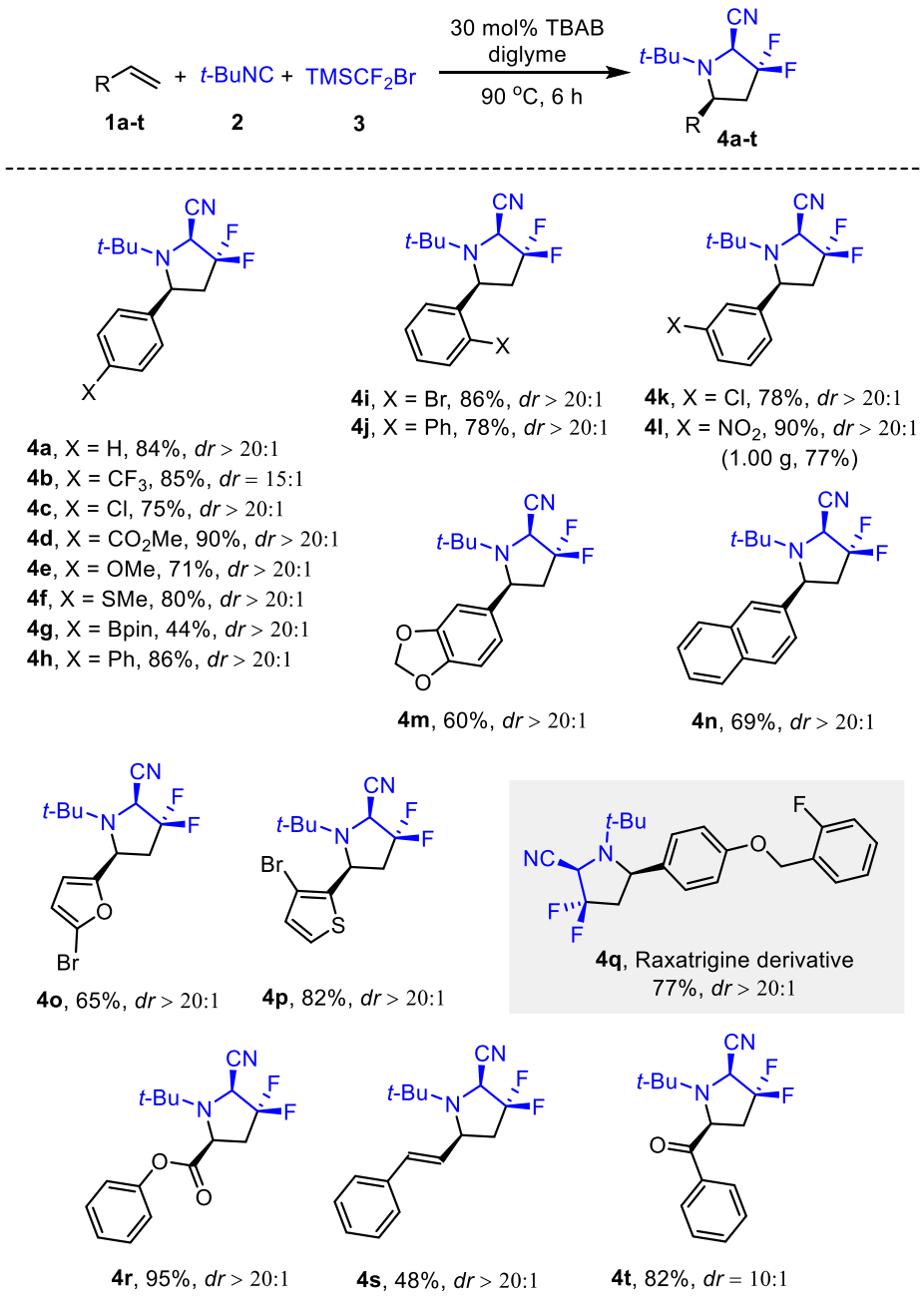
Other isocycnides, including cyclohexyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide, were also examined in the reaction. However, cyclohexyl isocyanide did not give the desired product according to the ^{1}H NMR analysis of the crude product. The reaction with 1,1,3,3-tetramethylbutyl isocyanide gave the corresponding product only in 22% isolated yields. From these results, it is concluded that the secondary alkyl isocynides are not applicable in this reaction, and the efficiency of tertiary isocycnides other than *t*-BuNC is relatively low.

With the optimized conditions in hand, we further evaluated the substrate scope of alkenes. As illustrated in Scheme 2, styrenes with electron-withdrawing groups (**4b**-**d**, **4l**) or electron-donating groups (**4e**, **4f**) are both well tolerated and give the corresponding products in excellent yields. Besides, various functional groups, for instance, ester (**4d**), thioether (**4f**), nitro (**4l**) and boronic ester (**4g**) are compatible under the reaction conditions. The yields for the substrates bearing an *ortho*-substituent (**4i**, **j**) are not affected, indicating that the reaction is not sensitive to steric effects. Substrates with a meta-substituent (**4k**-**m**) also react smoothly to give the products. Notably, the reaction could be scaled up to gram-scale. We could obtain 1.00 g of **4l** without significant loss of the yield.

Other aromatic groups, such as naphthalene (**4n**), furan (**4o**) and thiophene (**4p**), are also compatible in this transformation. The reaction could also be applied in synthesizing the derivative of Raxatrigine (**4q**), a voltage-gated sodium channel inhibitor[13] currently under phase II clinical trials for trigeminal neuralgia and small fiber neuropathy. It is worth noting that the reaction scope is not restricted in alkenes. Acrylate (**4r**), 1,3-dienes (**4s**) and vinyl ketones (**4t**) could give the corresponding products as

well. However, alkenes without conjugated substitutions or multi-substituted alkenes stay inert under the reaction conditions, possibly because of the low activity of double bonds or higher steric hindrance respectively.

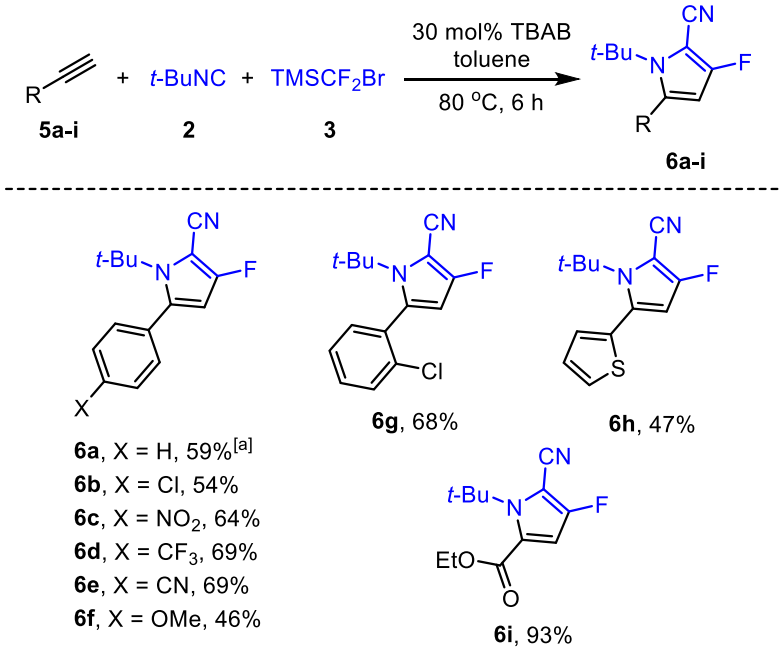
Scheme 2. Scope of Alkenes[a]



[a]Reaction conditions: **1**:**2**:**3**:TBAB = 0.4:1.6:0.8:0.12 (mmol), in 3 mL diglyme at 90 °C for 6 h. The solution of **2** and **3** in 1 mL diglyme was added dropwise in 3 h. All the yields refer to the isolated products after column chromatography on silica gel. The *dr* value was determined by ^{1}H NMR.

We further tested the reaction with alkynes, which are expected to be less reactive toward cycloaddition with difluoroketenimine. Under similar conditions (see Supporting Information for details on reaction condition optimization), the reaction with phenylacetylene proceeded smoothly. After the aforementioned [3+2] cycloaddition reaction, the pyrroline intermediate spontaneously eliminated a hydrogen fluoride to give the mono-fluorinated pyrrole derivative **6a** (Scheme 3). The structure of **6a** was determined unambiguously *via* X-ray diffraction (see Supporting Information for details). Phenylacetylenes with electron-withdrawing groups (**6b**-**e**) gave the corresponding products in moderate to good yields, while the electron-donating methoxy group (**6f**) led to diminished results. Steric hindered (**6g**) or heterocycle (**6h**) substrates were also tolerated. Interestingly, ethyl acetylenecarboxylate gives the product (**6i**) in excellent yields, which indicates that electron deficient multiple bonds are more active in this transformation.

Scheme 3. Scope of Alkynes[a]



[a]Substrate scope of alkynes. Reaction conditions: **5**:**2**:**3**:TBAB = 0.4:2.4:1.2:0.12 (mmol), in 3 mL toluene at 80 °C for 6 h. All the yields refer to the isolated products after column chromatography on silica gel.

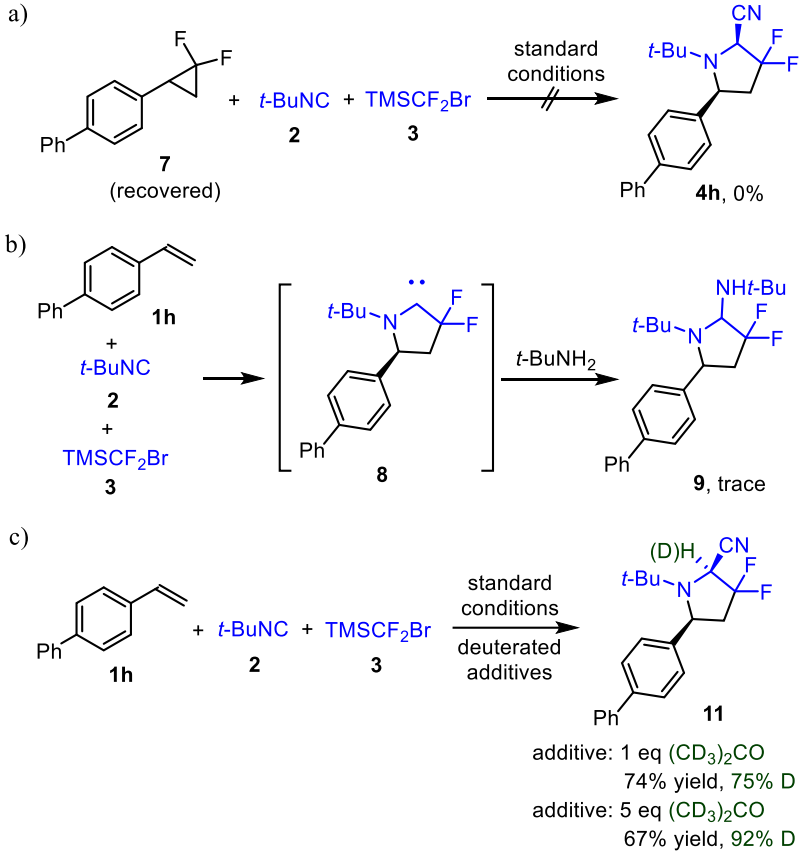
This unique three-component reaction raises intriguing mechanistic questions. In addition to the details of the [3+2] cycloaddition, the origin of cyano group in the product and the high *syn* diastereoselectivity are intriguing. To answer these questions, we conducted the following control experiments. First, to rule out the possible epimerization during the reaction, we have analyzed by ^{1}H NMR the *dr* value of the product (**4a**) under the standard reaction conditions at intervals of 0.5 h, 1 h, 2 h, 4 h and 5 h, after the *tert*-butylisocyanide and $TMSCF_2Br$ were added dropwise to the reaction. The diastereoselectivities of the product **4a** remained almost unchanged (dr > 20:1), which indicated that epimerization did not occur during the time-course of the reaction.

Next, we observed that no corresponding product **4h** was detected in the reaction with difluorocyclopropane **7**[14] as the substrate (Scheme 4a), which was completely recovered under the standard conditions. This result rules out the possibility that the reaction is initiated by cyclopropanation between styrenes and the difluorocarbene. Thus, it is more likely that the *in situ* generated difluorocarbene is captured by the nucleophilic isocyanide to give difluoroketenimine, which afterwards undergoes [3+2] cycloaddition with styrenes.

Furthermore, we envisioned that the [3+2] product **8** would feature a fluorinated cyclic (alkyl)(amino)carbene (CAAC) structure. CAACs are a large group of singlet carbenes stabilized by the adjacent amino group, which have attracted considerable attentions in recent years.[15] We tried several common strategies to trap the CAAC intermediate **8**, for example, quenching the reaction with Se or metal complexation.[16] However, none of the them were proved successful, possibly because the intermediate **8** is less sterically hindered and less nucleophilic comparing to traditional CAACs.[17] The intermediate **8** would be readily captured by the excess isocyanide in the reaction mixture, thus rendering the mechanistic study further difficult. Fortunately, we managed to detect the N-H bond insertion product of the intermediate with amines (Scheme 4b). Finally, to elucidate the origins of cyano group and the α-proton, we conducted deuterium labeling experiments (Scheme 4c). The deuterium in

additives[18] is incorporated in the reaction and the α-proton in the final product is partly deuterated. While these control experiments provide some insights, the mechanistic details still remain elusive.

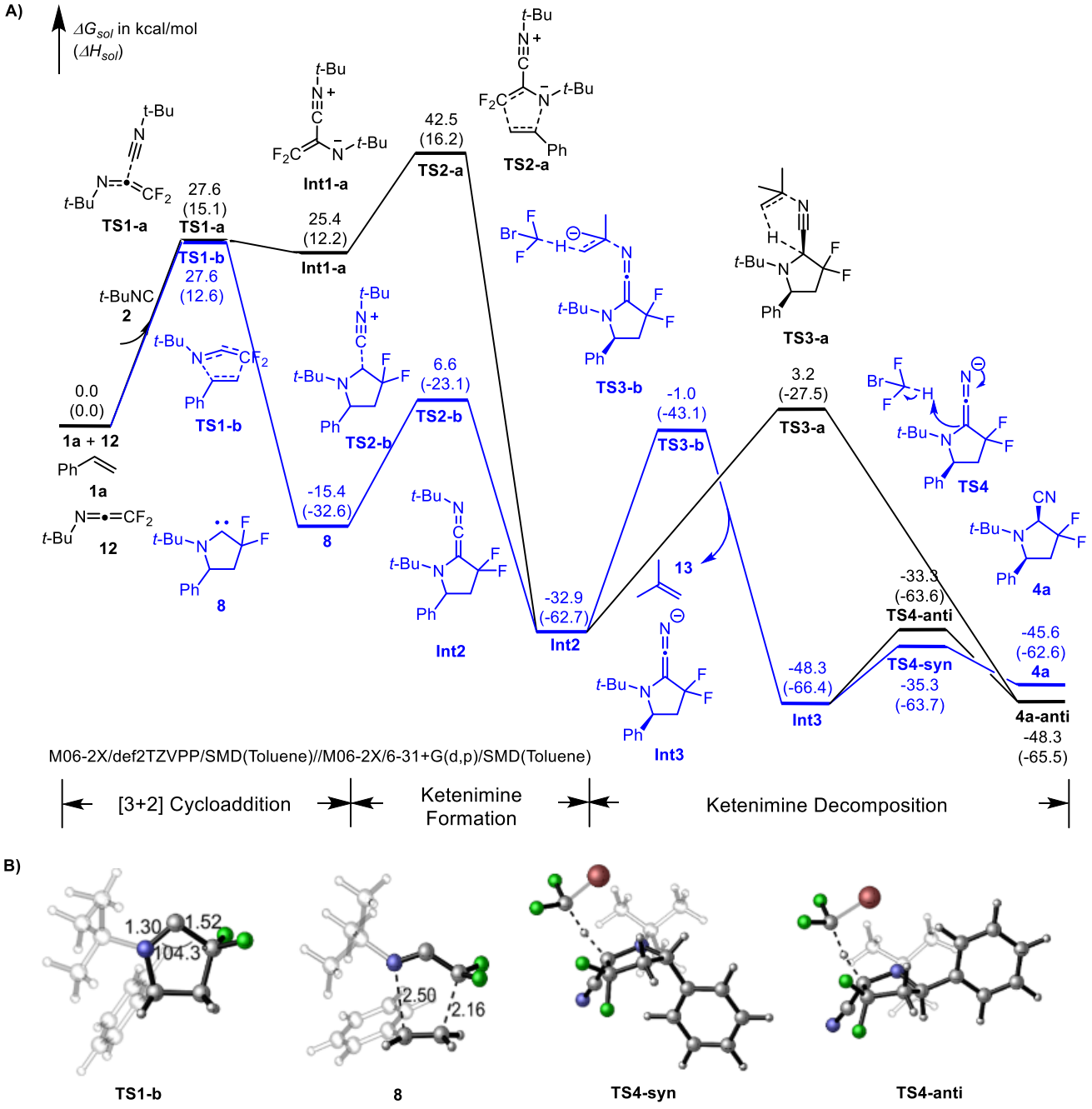
Scheme 4. Control Experiments



To further shed light on the mechanistic details of this transformation, we conducted DFT calculations (Figure 1). All calculations were performed with Gaussian 09.[19] First, the [3+2] cycloaddition step goes through a concerted but asynchronous transition state **TS1-b** with a barrier of 27.6 kcal/mol. Other possible processes, for example, [3+2] reaction with 1,3-dipolar **Int1-a** are also carefully considered and proved unfavored with the activation barrier of 42.5 kcal/mol. The calculation further confirmed the existence of the CAAC-type intermediate **8**, which is then attacked by the nucleophilic isocyanide to give a ketenimine intermediate **Int2**. Ketenimines are known to undergo facile decomposition when heating. Research has shown that *N*-benzyl ketenimines give the 1,3-rearrangement products via homolytic cleavage and radical recombination.[20] However, the

decomposition of *N*-*tert*-butyl ketenimines requires higher temperature and yields nitrile products without alkyl migration, probably through a retro-ene transition state.[21]

Figure 1. A) Energy Profile of the Reaction Pathways. B) Key Optimized Structures with Selected Bond Lengths in Angstroms.

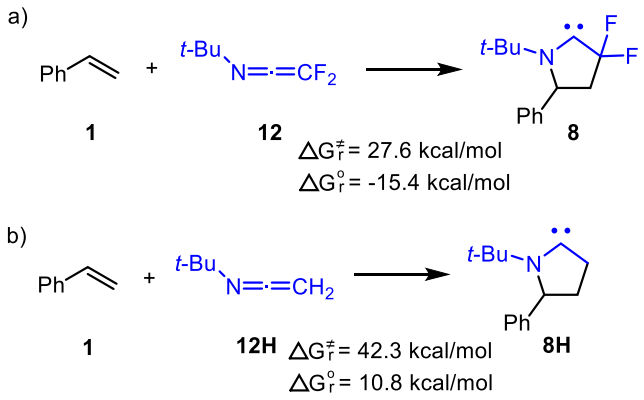


For our ketenimine product **Int2**, the retro-ene mechanism **TS3-a** requires a high activation barrier (36.1 kcal/mol) and shows moderate *anti* selectivity (the *anti* transition state favors by 1.1 kcal/mol),

which is in sharp contrast to the excellent *syn* diastereoselectivity that we observed. Besides, this intramolecular proton transfer mechanism cannot explain the incorporation of deuterium in our mechanistic experiments. Then we speculated that **Int2** could also be cleaved to give **Int3** with the assist of strong base, in our system for example, the anion of bromodifluoromethane generated by decomposition of the difluorocarbene source **3**.[22] The step, with an activation barrier of 31.9 kcal/mol, is responsible for the high temperature required for this transformation. **Int3** is then protonated by proton sources in the reaction mixture. This intermolecular proton transfer mechanism (**TS3-b**) has lower activation barrier than the retro-ene process and the diastereoselectivity is controlled by the protonation step. The sterically hindered proton sources tend to attack opposite to the bulky phenyl group, therefore pushing the cyano and phenyl group to the *syn* position.[23] The structures of *syn* and *anti* transition states in the protonation step are shown in Figure 1B. The calculated 2.0 kcal/mol gap between *anti* and *syn* transition states is consistent with our experimental observation.

The role of fluorine substitution has also been considered by the calculation with ketenimine **12H** (Scheme 5). Without fluorine substitution, the activation barrier of the [3+2] reaction increased to 42.3 kcal/mol, and the Gibbs free energy of the reaction increased to 10.8 kcal/mol (see Supporting Information for details). This result indicates that this [3+2] reaction is unfavored both kinetically and thermodynamically. The fluorine atoms can not only activate the double bonds in ketenimines, but also stabilize the carbene intermediate.

Scheme 5. Difluoroketenimine 12 vs Ketenimine 12H in [3+2] Cycloaddition



CONCLUSION

In summary, we have reported the first example of [3+2] cycloaddition reaction between ketenimine and alkenes or alkynes. The reaction yields fluorinated pyrrolidines or pyrroles in excellent yield and diastereoselectivity. Mechanistic experiments and DFT calculations have suggested the existence of a cyclic (alkyl)(amino)carbene intermediate and further explained the origins of cyano group and the high diastereoselectivity observed in this reaction. This work not only extends the reaction mode of ketenimines, but also provides an efficient one-pot synthesis for fluorinated heterocycles.

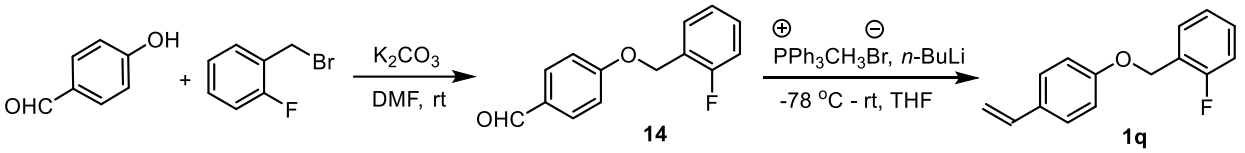
EXPERIMENTAL SECTION

General Methods. All the reactions were performed under nitrogen atmosphere with a flamed-dried reaction tube. Oil bath was used for heating reactions. All solvents were distilled under nitrogen atmosphere prior to use. THF, diethyl ether, toluene and 1,4-dioxane were dried by distillation over sodium/benzophenone. DCE and CH_3CN were distilled over CaH_2. DMF and diglyme were available from commercial sources without further purification. TLCs were performed on silica gel HS-GF 254 plates. For chromatography, 200-300 mesh silica gel was employed. Melting points were measured in open capillary vials. ^1H NMR spectra were recorded on Bruker ARX 400 (400 MHz) or Brucker ARX 500 (500 MHz); ^{13}C NMR spectra were recorded on Bruker ARX 400 (101 MHz). ^{19}F NMR was recorded at 470 MHz with Brucker ARX 500 spectrometer. The data for NMR spectra were reported as follows: chemical shifts (δ) were reported in ppm using tetramethylsilane as internal standard when using $CDCl_3$ as solvent, and coupling constants (J) were in Hertz (Hz). IR spectra were recorded on Nicolet 5MX–S infrared spectrometer and were reported in terms of frequency of absorption (cm^{-1}). HRMS were obtained on Bruker APEX IV FTMS. HRMS was detected through Bruker Solarix XR FTMS by ESI.

PE: petroleum ether; EA: ethyl acetate; DCM: dichloromethane; DCE: 1,2-dichloroethane; DMF: dimethylformamide; diglyme: TBAB: *tetra*-*n*-butylammonium bromide.

Synthesis of the Substrates. The alkene substrates **1a-1c**, **1h**, **1k**, **1n**, **1s** were purchased from commercial sources. **1d-1g**, **1i**, **1j**, **1l**, **1m**, **1o**, **1p** were synthesized by Wittig reaction.

*1-Fluoro-2-((4-vinylphenoxy)methyl)benzene (**1q**).* **1q** was synthesized by the following method:



Under a nitrogen atmosphere, 4-hydroxybenzaldehyde (1.28 g, 10.4 mmol, 1.0 equiv), 1-(bromomethyl)-2-fluorobenzene (2.27 g, 12.0 mmol, 1.15 equiv), K_2CO_3 (3.32 g, 24 mmol, 2.3 equiv) and 25 mL DMF were added to a 50 mL Schlenk flask and stirred at room temperature. The reaction was monitored by TLC. After 4 h, the mixture was extracted by EA (50 mL × 3), washed by water (50 mL × 3) and 50 mL brine. The solvent was removed under reduced pressure and the crude product was purified by column chromatography using PE/EA as solvents to give 2.32 g (96%) alkylation product **14**. White solid; mp 57-58 °C; R_f = 0.20 (PE:EA = 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.89 (s, 1H), 7.90–7.80 (m, 2H), 7.49 (td, 1H, J = 7.5, 1.8 Hz), 7.34 (tdd, 1H, J = 7.5, 5.3, 1.8 Hz), 7.21–7.05 (m, 4H), 5.22 (s, 2H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ 190.8, 163.5, 160.5 (d, J = 247.2 Hz), 132.0, 130.3 (d, J = 7.7 Hz), 130.2, 129.7 (d, J = 3.7 Hz), 124.4 (d, J = 3.7 Hz), 123.2 (d, J = 14.2 Hz), 115.5 (d, J = 21.2 Hz), 115.1, 64.0 (d, J = 4.5 Hz); ^{19}F NMR (377 MHz, $CDCl_3$): δ -118.5 (s, 1F); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{12}FO_2$ 231.0821; Found 231.0816; IR (film): 2917, 2849, 1694, 1602, 1578, 1508, 1495, 1458, 1388, 1313, 1253, 1160, 1110, 1005, 833 cm^{-1}.

Under a nitrogen atmosphere, methyltriphenylphosphonium bromide (2.79 g, 7.8 mmol, 1.3 equiv), 30 mL THF and a stir bar were added to a 100 mL Schlenk flask and cooled to -78 °C. To this solution was slowly added *n*-butyllithium (2.5 M, 2.9 mL, 1.2 equiv). The reaction mixture was then allowed to slowly warm up to room temperature and stir for another 1 h. The flask was again cooled down to -78 °C and **14** (1.38 g, 6.0 mmol, 1.0 equiv) was added. The mixture was slowly warmed up to

room temperature. The reaction was monitored by TLC until **14** was fully consumed. Then, the reaction was filtered through a short silica gel pad and washed with EA. The solvent was removed under reduced pressure and the crude product was purified by column chromatography using PE/EA as solvents to give **1q** (1.36 g, 99%). White solid; mp 58-59 ℃; R_f = 0.35 (PE); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (t, 1H, J = 7.3 Hz), 7.39–7.24 (m, 3H), 7.14 (t, 1H, J = 7.4 Hz), 7.07 (t, 1H, J = 9.2 Hz), 6.93 (d, 2H, J = 8.4 Hz), 6.65 (dd, 1H, J = 17.6, 10.9 Hz), 5.61 (d, 1H, J = 17.6 Hz), 5.17–5.03 (m, 3H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 160.5 (d, J = 246.9 Hz), 158.4, 136.2, 130.9, 129.8 (d, J = 5.2 Hz), 129.7, 127.5, 124.3 (d, J = 3.5 Hz), 124.2 (d, J = 14.3 Hz), 115.4 (d, J = 21.1 Hz), 114.9, 111.9, 63.7 (d, J = 4.5 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ -118.7 (s, 1F); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{14}FO$ 229.1029; Found 229.1024; IR (film): 3047, 1607, 1509, 1493, 1458, 1384, 1306, 1242, 1115, 1013, 990, 902, 834 cm^{-1};

General Procedures for the [3+2] Cycloaddition with Alkene (1a-t). Under a nitrogen atmosphere, the corresponding alkene **1a-t** (0.4 mmol, 1.0 equiv), TBAB (38.6 mg, 0.12 mmol, 0.3 equiv) and diglyme (2 mL) were added to a dry Schlenk tube successively. A solution of 2-isocyano-2-methylpropane **2** (132.8 mg, 184 μL, 1.6 mmol, 4.0 equiv) and (bromodifluoromethyl)trimethylsilane **3** (162.4 mg, 124 μL, 0.8 mmol, 2.0 equiv), in diglyme (1 mL) was added dropwise in 3 h at 90 ℃. The mixture was stirred at 90 ℃ for another 3 h. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel with PE-EA as the eluent to afford the products.

*rac-(2S,5S)-1-(tert-Butyl)-3,3-difluoro-5-phenylpyrrolidine-2-carbonitrile (**4a**).* Yield: 88.5 mg, 84%, *dr* > 20:1; pale yellow oil; R_f = 0.31 (PE:EA = 30:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (d, 2H, J = 7.3 Hz), 7.26 (t, 2H, J = 7.5 Hz), 7.17 (t, 1H, J = 7.3 Hz), 4.30–4.20 (m, 2H), 2.58 (td, 1H, J = 13.8, 6.7 Hz), 2.23 (dddd, 1H, J = 31.3, 14.0, 10.0, 7.0 Hz), 0.95 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 145.0, 128.8, 127.5, 126.1, 124.0 (dd, J = 263.9, 250.2 Hz), 117.5 (d, J = 14.3 Hz), 60.6 (d, J = 7.5 Hz), 57.1 (dd, J = 38.4, 23.3 Hz), 56.3, 44.2 (dd, J = 22.5, 18.9 Hz), 27.2; ^{19}F NMR (377 MHz, $CDCl_3$) δ -101.3 (dddd, 1F, J = 227.2, 31.5, 16.3, 13.7 Hz), -107.2 (dd, 1F, J = 227.3, 7.0 Hz); HRMS(ESI) m/z: [M +

H]$^+$ Calcd for $C_{15}H_{19}F_2N_2$ 265.1516; Found 265.1510; IR (film): 2976, 1493, 1456, 1399, 1373, 1332, 1255, 1220, 1161, 1128, 1087, 1030, 981, 920, 838 cm^{-1}.

rac-(2S,5S)-1-(tert-Butyl)-3,3-difluoro-5-(4-(trifluoromethyl)phenyl)pyrrolidine-2-carbonitrile ***(4b)***. Yield: 112.1 mg, 85%, *dr* = 15:1; pale yellow oil; R_f = 0.21 (PE:EA = 30:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62–7.58 (m, 4H, *J* = 6.0 Hz), 4.45–4.39 (m, 1H), 4.36 (d, 1H, *J* = 15.7 Hz), 2.76–2.65 (m, 1H), 2.28 (dddd, 1H, *J* = 30.7, 14.0, 9.6, 7.2 Hz), 1.04 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 149.2, 129.8 (q, *J* = 32.4 Hz), 126.5, 125.8 (q, *J* = 3.7 Hz), 127.8–121.1 (m, 1C, observe complexity due to F-C coupling), 124.1 (q, *J* = 271.8 Hz), 117.25 (d, *J* = 13.6 Hz), 60.1 (d, *J* = 7.1 Hz), 57.0 (dd, *J* = 38.1, 23.3 Hz), 56.5, 43.8 (dd, *J* = 22.7, 19.7 Hz), 27.1; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -62.5 (s, 3F), -101.5 (ddt, 1F, *J* = 228.3, 29.7, 14.5 Hz), -106.8 (dd, 1F, *J* = 227.5, 6.0 Hz); HRMS (ESI) *m*/*z*: [M + H]$^+$ Calcd for $C_{16}H_{18}F_5N_2$ 333.1390; Found 333.1385; IR (film): 2971, 1620, 1471, 1374, 1325, 1206, 1161, 1107, 1067, 1018, 983, 920, 841 cm^{-1}.

rac-(2S,5S)-1-(tert-Butyl)-5-(4-chlorophenyl)-3,3-difluoropyrrolidine-2-carbonitrile ***(4c)***. Yield: 79.6 mg, 75%, *dr* > 20:1; pale yellow oil; R_f = 0.24 (PE:EA = 30:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43–7.27 (m, 4H), 4.39–4.25 (m, 2H), 2.66 (td, 1H, *J* = 13.6, 6.9 Hz), 2.37–2.15 (m, 1H), 1.02 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 143.6, 133.1, 128.98, 127.5, 123.9 (dd, *J* = 263.8, 250.5 Hz), 117.4 (d, *J* = 14.1 Hz), 59.9 (d, *J* = 7.3 Hz), 57.0 (dd, *J* = 38.2, 23.3 Hz), 56.4, 44.0 (dd, *J* = 22.6, 19.2 Hz), 27.2; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -101.4 (ddt, 1F, *J* = 227.7, 30.1, 14.8 Hz), -106.9 (dd, 1F, *J* = 228.1, 7.2 Hz); HRMS (ESI) *m*/*z*: [M + H]$^+$ Calcd for $C_{15}H_{18}ClF_2N_2$ 299.1127; Found 299.1121; IR (film): 2974, 1490, 1399, 1373, 1330, 1254, 1220, 1182, 1161, 1130, 1014, 982, 920, 830 cm^{-1}.

rac-Methyl 4-((2S,5S)-1-(tert-Butyl)-5-cyano-4,4-difluoropyrrolidin-2-yl)benzoate ***(4d)***. Yield: 115.8 mg, 90%, *dr* > 20:1; pale yellow oil; R_f = 0.10 (PE:EA = 30:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (d, 2H, *J* = 7.6 Hz), 7.54 (d, 2H, *J* = 7.6 Hz), 4.45–4.30 (m, 2H), 3.92 (s, 3H), 2.70 (td, 1H, *J* = 13.5, 7.0 Hz), 2.30 (ddt, 1H, *J* = 30.8, 15.7, 8.6 Hz), 1.03 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 166.8, 150.2, 130.2, 129.6, 126.1, 126.7–120.3 (m), 117.3 (d, *J* = 14.0 Hz), 60.3 (d, *J* = 7.3 Hz), 57.0 (dd, *J* =

38.3, 23.3 Hz), 56.5, 52.1, 44.3–43.1 (m), 27.1; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -101.4 (ddt, 1F, J = 228.0, 30.2, 14.7 Hz), -106.9 (dt, J = 228.0, 6.8 Hz); HRMS (ESI) m/z: Calcd for $[M + H]^+$ $C_{17}H_{21}F_2N_2O_2$ 323.1571; Found 323.1558; IR (film): 2975, 1722, 1612, 1471, 1437, 1373, 1331, 1280, 1205, 1130, 1116, 1085, 1019, 912 cm^{-1}.

*rac-(2S,5S)-1-(tert-Butyl)-3,3-difluoro-5-(4-methoxyphenyl)pyrrolidine-2-carbonitrile (**4e**).* Yield: 84.0 mg, 71%, *dr* > 20:1; pale yellow oil; R_f = 0.27 (PE:EA = 30:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, 2H, J = 8.3 Hz), 6.87 (d, 2H, J = 8.3 Hz), 4.36–4.23 (m, 2H), 3.80 (s, 3H), 2.63 (td, 1H, J = 14.1, 6.8 Hz), 2.28 (dddd, 1H, J = 31.4, 14.2, 9.8, 7.4 Hz), 1.02 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 158.9, 137.0, 127.2, 124.0 (dd, J = 263.9, 250.3 Hz), 118.0 (d, J = 14.3 Hz), 114.1, 60. 0 (d, J = 7.6 Hz), 57.1 (dd, J = 38.3, 23.2 Hz), 56.3, 55.3, 44.2 (dd, J = 22.3, 18.4 Hz), 27.2; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -100.9 – -101.7 (m, 1F), -107.0 (ddd, 1F, J = 227.3, 11.0, 6.7 Hz); HRMS (ESI) m/z: Calcd for $[M + H]^+$ $C_{16}H_{21}F_2N_2O$ 295.1622; Found 295.1616; IR (film): 2975, 1613, 1513, 1467, 1441, 1373, 1246, 1221, 1182, 1127, 1085, 1036, 982 cm^{-1}.

*rac-(2S,5S)-1-(tert-Butyl)-3,3-difluoro-5-(4-(methylthio)phenyl)pyrrolidine-2-carbonitrile (**4f**).* Yield: 99.9 mg, 80%, *dr* > 20:1; yellow oil; R_f = 0.27 (PE:EA = 30:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36 (d, 2H, J = 7.4 Hz), 7.22 (d, 2H), 4.38–4.24 (m, 2H), 2.65 (td, 1H, J = 13.8, 6.9 Hz), 2.48 (s, 3H), 2.27 (ddt, 1H, J = 31.2, 16.2, 8.5 Hz), 1.02 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 141.9, 137.5, 126.9, 126.7, 126.6–120.8 (m), 117.5 (d, J = 14.2 Hz), 60.1 (d, J = 7.5 Hz), 57.0 (dd, J = 38.3, 23.2 Hz), 56.4, 44.0 (dd, J = 22.5, 18.8 Hz), 27.2, 15.8; ^{19}F NMR ($CDCl_3$, 471 MHz): δ -100.9 – -101.8 (m, 1F), -106.9 (dt, 1F, J = 227.6, 5.6 Hz); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{21}F_2N_2S$ 311.1394; Found 311.1388. IR (film): 2974, 2920, 2880, 1600, 1493, 1438, 1399, 1330, 1253, 1206, 1182, 1129, 1085, 1031, 981 cm^{-1}.

*rac-(2S,5S)-1-(tert-Butyl)-3,3-difluoro-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine-2-carbonitrile (**4g**).* Yield: 68.6 mg, 44%, *dr* > 20:1; yellow oil; R_f = 0.15 (PE:EA = 30:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, 2H, J = 8.0 Hz), 7.45 (d, 2H, J = 8.0 Hz), 4.44–4.22 (m,

2H), 2.65 (td, 1H, *J* = 12.7, 11.8, 6.8 Hz), 2.39–2.20 (m, 1H), 1.34 (s, 12H), 1.02 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 148.1, 135.3, 125.5, 123.9 (dd, *J* = 264.1, 250.2 Hz), 117.39 (d, *J* = 14.4 Hz), 83.8, 60.7 (d, *J* = 7.4 Hz), 57.1 (dd, *J* = 38.4, 23.2 Hz), 56.4, 44.0 (dd, *J* = 22.7, 19.0 Hz), 27.2, 24.9; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -100.8 – -101.5 (m, 1F), -107.1 (dd, 1F, *J* = 227.5, 6.9 Hz); HRMS (ESI) *m*/*z*: calcd $[M + H]^+$ for $C_{21}H_{30}BF_2N_2O_2$ 391.2368; Found 391.2367; IR (film): 2978, 1611, 1470, 1362, 1328, 1273, 1220, 1129, 1087, 1020, 963, 859 cm^{-1}.

*rac-(2S,5S)-5-([1,1'-Biphenyl]-4-yl)-1-(tert-butyl)-3,3-difluoropyrrolidine-2-carbonitrile (**4h**).* Yield: 117.7 mg, 86%, *dr* > 20:1; yellow oil; R_f = 0.43 (PE:EA = 30:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61–7.54 (m, 4H), 7.50 (d, 2H, *J* = 8.2 Hz), 7.43 (t, 2H, *J* = 7.6 Hz), 7.33 (t, 1H, *J* = 7.3 Hz), 4.41–4.28 (m, 2H), 2.68 (td, 1H, *J* = 13.8, 6.8 Hz), 2.34 (dddd, 1H, *J* = 31.3, 14.0, 9.9, 7.1 Hz), 1.05 (s, 2H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 144.1, 140.7, 140.4, 128.8, 127.5, 127.4, 127.1, 126.6, 126.8–121.3 (m), 117.5 (d, *J* = 14.3 Hz), 60.3 (d, *J* = 7.4 Hz), 57.1 (dd, *J* = 38.3, 23.2 Hz), 56.4, 44.1 (dd, *J* = 22.5, 18.9 Hz), 27.3; ^{19}F NMR ($CDCl_3$, 471 MHz,) δ -101.2 (ddt, 1F, *J* = 227.4, 30.8, 14.9 Hz), -106.99 (d, 1F, *J* = 227.4 Hz); HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{21}H_{23}F_2N_2$ 341.1829; Found 341.1823; IR (film): 2975, 1487, 1399, 1373, 1329, 1252, 1220, 1161, 1129, 1084, 982, 911, 838 cm^{-1}.

*rac-(2S,5S)-5-(2-Bromophenyl)-1-(tert-butyl)-3,3-difluoropyrrolidine-2-carbonitrile (**4i**).* Yield: 117.8 mg, 86%, *dr* > 20:1; yellow oil, R_f = 0.40 (PE:EA = 30:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, 1H, *J* = 7.7 Hz), 7.47 (d, 1H, *J* = 7.9 Hz), 7.38 (t, 1H, *J* = 7.5 Hz), 7.12 (t, 1H, *J* = 7.5 Hz), 4.77 (t, 1H, *J* = 8.2 Hz), 4.37 (d, 1H, *J* = 15.1 Hz), 2.99–2.73 (m, 1H), 2.28–2.04 (m, 1H), 1.04 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 143.5, 132.5, 129.0, 128.8, 128.3, 124.3 (dd, *J* = 263.3, 251.6 Hz), 121.4, 117.3 (d, *J* = 12.9 Hz), 59.4 (d, *J* = 6.8 Hz), 57.0 (dd, *J* = 37.8, 23.3 Hz), 56.4, 42.0–41.4 (m), 26.9; ^{19}F NMR (471 MHz, $CDCl_3$) δ -100.8 (ddt, *J* = 229.3, 28.2, 14.3 Hz), -104.8 (ddd, *J* = 229.0, 8.1, 4.8 Hz); HRMS (ESI) *m*/*z*: calcd $[M + H]^+$ for $C_{15}H_{18}BrF_2N_2$ 343.0621; Found 343.0625; IR (film): 2973, 1470, 1399, 1373, 1255, 1220, 1202, 1166, 1085, 1023, 981 cm^{-1}.

*rac-(2S,5S)-5-([1,1'-Biphenyl]-2-yl)-1-(tert-butyl)-3,3-difluoropyrrolidine-2-carbonitrile (**4j**).* Yield: 106.5 mg, 78%, *dr* > 20:1; yellow oil, R_f = 0.30 (PE:EA = 30:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (d, 1H, *J* = 7.9 Hz), 7.48–7.37 (m, 4H), 7.28 (t, 1H, *J* = 7.1 Hz), 7.21 (d, 2H, *J* = 6.7 Hz), 7.12 (d, 1H, *J* = 7.4 Hz), 4.32–4.18 (m, 2H), 2.56 (td, 1H, *J* = 14.0, 6.9 Hz), 2.43–2.22 (m, 1H), 0.88 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 142.3, 140.8, 139.79, 129.6, 128.8, 128.5, 128.4, 127.5, 127.0, 126.9, 124.1 (dd, *J* = 263.7, 250.3 Hz), 117.4 (d, *J* = 14.4 Hz), 57.1 (dd, *J* = 38.4, 23.1 Hz), 56.8 (d, *J* = 7.4 Hz), 56.3, 43.9 (dd, *J* = 22.6, 19.0 Hz), 27.0; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -100.9 (ddt, 1F, *J* = 227.3, 31.0, 15.3 Hz), -106.6 (dd, 1F, *J* = 227.4, 7.3 Hz); HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{21}H_{23}F_2N_2$ 341.1829; Found 341.1831; IR (film): 2971, 1478, 1439, 1373, 1252, 1220, 1197, 1164, 1083, 1026, 981 cm^{-1}.

*rac-(2S,5S)-1-(tert-Butyl)-5-(3-chlorophenyl)-3,3-difluoropyrrolidine-2-carbonitrile (**4k**).* Yield: 92.8 mg, 78%, *dr* > 20:1; pale yellow oil; R_f = 0.24 (PE:EA = 30:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, 2H, *J* = 7.3 Hz), 7.26 (t, 2H, *J* = 7.5 Hz), 7.17 (t, 1H, *J* = 7.3 Hz), 4.29–4.21 (m, 2H), 2.58 (td, 1H, *J* = 13.8, 6.7 Hz), 2.23 (dddd, 1H, *J* = 31.3, 14.0, 10.0, 7.0 Hz), 0.95 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 147.2, 134.6, 130.2, 127.7, 126.2, 124.3, 123.9 (dd, *J* = 263.9, 250.5 Hz), 117.2 (d, *J* = 13.9 Hz), 60.1 (d, *J* = 7.3 Hz), 57.0 (dd, *J* = 38.2, 23.2 Hz), 56.5, 43.9 (dd, *J* = 22.7, 19.4 Hz), 27.15; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -101.2 (ddt, *J* = 228.1, 30.2, 14.7 Hz), -106.9 (dd, *J* = 228.3, 7.2 Hz); HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{15}H_{18}ClF_2N_2$ 299.1127; Found 299.1122; IR (film): 2975, 1598, 1475, 1434, 1373, 1349, 1328, 1220, 1202, 1130, 1035, 983 cm^{-1}.

*rac-(2S,5S)-1-(tert-Butyl)-3,3-difluoro-5-(3-nitrophenyl)pyrrolidine-2-carbonitrile (**4l**).* Yield: 111.2 mg, 90%, *dr* > 20:1; pale yellow oil, R_f = 0.09 (PE:EA = 30:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (s, 1H), 8.14 (d, 1H, *J* = 8.0 Hz), 7.96 (d, 1H, *J* = 7.7 Hz), 7.60 (t, 1H, *J* = 7.9 Hz), 4.52–4.46 (m, 1H), 4.40 (d, 1H, *J* = 15.4 Hz), 2.84–2.71 (m, 1H), 2.41–2.22 (m, 1H), 1.06 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 148.4, 147.3, 132.4, 130.2, 123.8 (dd, *J* = 263.7, 251.0 Hz), 122.8, 121.0, 117.1 (d, *J* = 13.3 Hz), 59.9 (d, *J* = 7.0 Hz), 56.9 (dd, *J* = 37.8, 23.2 Hz), 56.7, 43.7 (t, *J* = 20.3, 19.7 Hz), 27.2; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -101.5 (ddt, 1F, *J* = 228.8, 28.8, 14.3 Hz), -106.4 (ddd, 1F, *J* = 228.9, 7.3, 3.1 Hz);

HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{15}H_{18}F_2N_3O_2$ 310.1367; Found 310.1363. IR (film): 2974, 1531, 1477, 1401, 1374, 1352, 1255, 1219, 1163, 1088, 984 cm^{-1}.

Gram scale synthesis of **4l**:

Under a nitrogen atmosphere, 1-nitro-3-vinylbenzene **1l** (98% purity, 635.0 mg, 4.2 mmol, 1.0 equiv), TBAB (403.1 mg, 1.3 mmol, 0.3 equiv) and diglyme (10 mL) were added to a dry 50 mL Schlenk flask successively. A solution of 2-isocyano-2-methylpropane **2** (1.39 g, 16.7 mmol, 4.0 equiv) and (bromodifluoromethyl)trimethylsilane **3** (1.69 g, 8.3 mmol, 2.0 equiv), in diglyme (22 mL) was added dropwise in 3 h at 90 ℃. The mixture was stirred at 90 ℃ for another 3 h. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel with PE-EA as the eluent to afford the products. Yield: 997.5 mg, 77%. Characterization data match those that were reported in smaller scale synthesis.

*rac-(2S,5S)-5-(Benzo[d][1,3]dioxol-5-yl)-1-(tert-butyl)-3,3-difluoropyrrolidine-2-carbonitrile (**4m**).* Yield: 74.4 mg, 60%, *dr* > 20:1; yellow oil; R_f = 0.30 (PE:EA = 30:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.01 (d, 1H, *J* = 1.5 Hz), 6.84 (dd, 1H, *J* = 8.0, 1.5 Hz), 6.74 (d, 1H, *J* = 7.9 Hz), 5.96 (d, 2H, *J* = 2.5 Hz), 4.34–4.28 (m, 1H), 4.25 (dd, 1H, *J* = 9.9, 6.9 Hz), 2.62 (td, 1H, *J* = 13.8, 6.8 Hz), 2.27 (dddd, 1H, *J* = 31.1, 14.0, 10.0, 7.0 Hz), 1.04 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ 148.1, 146.9, 139.1, 123.9 (dd, *J* = 264.1, 250.2 Hz), 119. 1, 117.4 (d, *J* = 14.3 Hz), 108.2, 106.5, 101.1, 60.3 (d, *J* = 7.6 Hz), 57.0 (dd, *J* = 38.4, 23.2 Hz), 56.4, 44.5 – 43.8 (m), 27.2; ^{19}F NMR ($CDCl_3$, 471 MHz): δ -100.8 – -101.8 (m, 1F), -107.0 (dd, 1F, *J* = 227.5, 6.9 Hz); HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{16}H_{19}F_2N_2O_2$ 309.1415; Found 309.1405; IR (film): 2976, 2915, 1504, 1488, 1372, 1244, 1219, 1181, 1085, 1039, 983 cm^{-1}.

*rac-(2S,5S)-1-(tert-Butyl)-3,3-difluoro-5-(naphthalen-2-yl)pyrrolidine-2-carbonitrile (**4n**).* Yield: 87.2 mg, 69%, *dr* > 20:1; yellow oil; R_f = 0.31 (PE:EA = 30:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90–7.74 (m,

4H), 7.66 (d, 1H, *J* = 8.5 Hz), 7.52–7.41 (m, 2H), 4.55–4.44 (m, 1H), 4.35 (d, 1H, *J* = 16.3 Hz), 2.69 (td, 1H, *J* = 13.7, 6.8 Hz), 2.49–2.25 (m, 1H), 1.03 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 142.4, 133.4, 133.1, 129.0, 127.8, 126.4, 126.0, 124.8, 124.2, 124.0 (dd, *J* = 264.0, 250.1 Hz), 117.6 (d, *J* = 14.4 Hz), 60.8 (d, *J* = 7.5 Hz), 57.2 (dd, *J* = 38.4, 23.2 Hz), 56.5, 44.0 (dd, *J* = 22.6, 18.9 Hz), 27.3; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -101.0 (ddt, 1F, *J* = 227.4, 30.6, 15.0 Hz), -107.0 (ddd, 1F, *J* = 227.5, 30.6, 6.9 Hz); HRMS (ESI): *m*/*z* $[M + H]^+$ Calcd for $C_{19}H_{21}F_2N_2$ 315.1673; Found 315.1666. IR (film): 2974, 1507, 1469, 1399, 1371, 1252, 1219, 1125, 1085, 1037, 986 cm^{-1}.

*rac-(2S,5S)-5-(5-Bromofuran-2-yl)-1-(tert-butyl)-3,3-difluoropyrrolidine-2-carbonitrile (**4o**).* Yield: 86.2 mg, 65%, *dr* > 20:1; yellow oil; R_f = 0.27 (PE:EA = 30:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.35 (d, 1H, *J* = 3.2 Hz), 6.25 (d, 1H, *J* = 3.3 Hz), 4.39 (t, 1H, *J* = 7.4 Hz), 4.26 (dd, 1H, *J* = 14.3, 2.8 Hz), 2.71–2.47 (m, 2H), 1.11 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 158.3, 124.5 (dd, *J* = 261.9, 252.2 Hz), 120.5, 116.8 (d, *J* = 9.8 Hz), 112.3, 109.5, 56.3 (dd, *J* = 36.5, 23.5 Hz), 56.1, 53.6 (dd, *J* = 5.7, 2.6 Hz), 40.6 (t, *J* = 22.7, 21.0 Hz), 26.8; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -100.1 (ddt, 1F, *J* = 229.3, 21.6, 13.9 Hz), -102.7 (dtd, 1F, *J* = 229.4, 9.3, 3.5 Hz); HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{13}H_{16}BrF_2N_2O$ 333.0414; Found 333.0418; IR (film): 2976, 1504, 1437, 1335, 1250, 1202, 1164, 1084, 1039, 1009, 985 cm^{-1}.

*rac-(2S,5S)-5-(3-Bromothiophen-2-yl)-1-(tert-butyl)-3,3-difluoropyrrolidine-2-carbonitrile (**4p**).* Yield: 114.0 mg, 82%, *dr* > 20:1; yellow oil; R_f = 0.33 (PE:EA = 30:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.23 (d, 1H, *J* = 5.3 Hz), 6.86 (d, 1H, *J* = 5.3 Hz), 4.67 (t, 1H, *J* = 8.0 Hz), 4.30 (d, 1H, *J* = 14.9 Hz), 2.88–2.72 (m, 2H), 2.40 (ddt, 1H, *J* = 27.5, 14.1, 8.3 Hz), 1.11 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 145.6, 129.8, 125.3, 124.1 (dd, *J* = 263.4, 251.7 Hz), 116.7 (d, *J* = 12.2 Hz), 105.9, 56.7, 56.9–56.0 (m), 55.4 (d, *J* = 7.8 Hz), 42.1 (dd, *J* = 22.6, 20.2 Hz), 26.8; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -100.8 (ddt, *J* = 229.4, 27.9, 14.1 Hz), -104.8 (ddd, *J* = 229.0, 8.2, 4.8 Hz); HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{13}H_{16}BrF_2N_2S$ 349.0186; Found 349.0189; IR (film): 2973, 1525, 1469, 1438, 1374, 1271, 1253, 1195, 1160, 1085, 1026, 970 cm^{-1}.

rac-(2R,5R)-1-(tert-Butyl)-3,3-difluoro-5-(4-((2-fluorobenzyl)oxy)phenyl)pyrrolidine-2-carbonitrile

(4q). Yield: 119.4 mg, 77%, *dr* > 20:1; yellow solid; mp 90-92 °C; R_f = 0.30 (PE:EA = 30:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (t, 1H, *J* = 7.5 Hz), 7.36 (d, 2H, *J* = 8.6 Hz), 7.32–7.27 (m, 1H), 7.16 (t, 1H, *J* = 7.5 Hz), 7.08 (t, 1H, *J* = 9.2 Hz), 6.95 (d, 2H, *J* = 8.7 Hz), 5.11 (s, 2H), 4.35–4.22 (m, 2H), 2.62 (td, 1H, *J* = 13.8, 6.8 Hz), 2.27 (dddd, 1H, *J* = 31.3, 14.0, 10.0, 7.0 Hz), 1.02 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 160.5 (d, *J* = 247.0 Hz), 158.0, 137.6, 129.8 (d, *J* = 1.3 Hz), 129.8 (d, *J* = 5.7 Hz), 127.3, 129.0–121.4 (m), 124.3 (d, *J* = 3.6 Hz), 124.1 (d, *J* = 14.2 Hz), 117.6 (d, *J* = 14.3 Hz), 115.4 (d, *J* = 21.2 Hz), 115.0, 63.8 (d, *J* = 4.4 Hz), 60.0 (d, *J* = 7.6 Hz), 57.1 (dd, *J* = 38.3, 23.2 Hz), 56.3, 44.2 (dd, *J* = 22.3, 18.5 Hz), 27.2; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -101.3 (ddt, 1F, *J* = 227.2, 30.9, 15.0 Hz), -107.0 (d, 1F, *J* = 227.2 Hz), -118.7 (s, 1F); HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{22}H_{24}F_3N_2O$ 389.1841; Found 389.1835; IR (film): 2974, 2877, 1611, 1510, 1494, 1457, 1373, 1235, 1172, 1128, 1084, 1022, 982 cm^{-1}.

*rac-Phenyl (2S,5S)-1-(tert-butyl)-5-cyano-4,4-difluoropyrrolidine-2-carboxylate (**4r**).* Yield: 117.1 mg, 95%, *dr* > 20:1; yellow oil; R_f = 0.10 (PE:EA = 30:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (t, 2H, *J* = 7.9 Hz), 7.25 (t, 1H, *J* = 7.4 Hz), 7.10 (d, 2H, *J* = 7.7 Hz), 4.30 (d, 1H, *J* = 15.2 Hz), 4.09 (t, 1H, *J* = 8.1 Hz), 2.87–2.61 (m, 2H), 1.21 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 171.6, 150.5, 129.6, 126.2, 124.2 (dd, *J* = 262.7, 251.3 Hz), 121.0, 116.3 (d, *J* = 12.0 Hz), 58.2 (d, *J* = 5.9 Hz), 56.2 (dd, *J* = 38.0, 23.8 Hz), 56.0, 37.9 (dd, *J* = 24.7, 23.0 Hz), 26.5; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -99.7 – -100.5 (m, 1F), -105.0 (ddd, 1F, *J* = 229.0, 7.7, 5.0 Hz); HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{16}H_{19}F_2N_2O_2$ 309.1415; Found 309.1409; IR (film): 2957, 2928, 1778, 1593, 1459, 1374, 1258, 1223, 1163, 1135, 1088, 1025, 994 cm^{-1}.

*rac-(2S,5S)-1-(tert-Butyl)-3,3-difluoro-5-((E)-styryl)pyrrolidine-2-carbonitrile (**4s**).* Yield: 55.4 mg, 48%, *dr* > 20:1; yellow oil; R_f = 0.27 (PE:EA = 30:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41–7.29 (m, 4H), 7.28–7.21 (m, 1H), 6.49 (d, 1H, *J* = 16.0 Hz), 6.23 (dd, 1H, *J* = 15.9, 7.7 Hz), 4.20 (d, 1H, *J* = 15.9 Hz), 3.98 (q, 1H, *J* = 7.8 Hz), 2.56–2.43 (m, 1H), 2.32 (ddt, 1H, *J* = 27.8, 13.8, 8.6 Hz), 1.16 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 136.4, 133.6, 129.9, 128.7, 127.8, 126.4, 124.1 (dd, *J* = 262.5, 250.7 Hz),

117.5 (d, J = 12.5 Hz), 58.7 (d, J = 6.9 Hz), 56.7 (dd, J = 37.7, 23.3 Hz), 56.1, 41.0 (dd, J = 22.5, 19.2 Hz), 27.5; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -99.6 (ddt, 1F, J = 227.4, 28.1, 14.6 Hz), -104.8 (ddd, 1F, J = 227.4, 8.2, 4.3 Hz); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{21}F_2N_2$ 291.1673; Found 291.1671; IR (film): 2973, 2942, 1598, 1494, 1450, 1399, 1372, 1250, 1185, 1126, 1110, 1086, 1023, 965 cm^{-1}.

*rac-(2S,5S)-5-Benzoyl-1-(tert-butyl)-3,3-difluoropyrrolidine-2-carbonitrile (**4t**).* Yield: 95.4 mg, 82%, *dr* = 10:1; yellow solid; R_f = 0.10 (PE:EA = 30:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, J = 8.2 Hz, 2H), 7.62 (t, 1H, J = 7.4 Hz), 7.52 (t, 2H, J = 7.7 Hz), 4.63 (dd, 1H, J = 10.5, 7.0 Hz), 4.36 (d, 1H, J = 16.7 Hz), 2.71 (td, 1H, J = 13.8, 6.9 Hz), 2.52 (dddd, 1H, J = 30.3, 13.7, 10.7, 7.1 Hz), 1.12 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 198.5, 134.5, 133.8, 129.0, 128.7, 123.9 (dd, J = 264.3, 250.0 Hz), 116.4 (d, J = 14.0 Hz), 62.4–61.7 (m), 56.5 (dd, J = 38.6, 23.7 Hz), 56.1, 38.5 (dd, J = 24.6, 22.0 Hz), 26.5; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -98.8 (dddd, 1F, J = 228.0, 30.2, 16.7, 14.0 Hz), -105.8 (dd, 1F, J = 228.0, 6.9 Hz); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}F_2N_2O$ 293.1465; Found 293.1462. IR (film): 2974, 1702, 1597, 1449, 1400, 1372, 1332, 1254, 1192, 1177, 1136, 1085, 1004, 966 cm^{-1}.

General Procedures for the [3+2] Cycloaddition with Alkyne (5a-i). Under a nitrogen atmosphere, the corresponding alkyne **5a-i** (0.4 mmol, 1.0 equiv), 2-isocyano-2-methylpropane **2** (199.2 mg, 276 μL, 2.4 mmol, 6.0 equiv) and (bromodifluoromethyl)trimethylsilane **3** (243.6 mg, 186 μL, 1.2 mmol, 3.0 equiv), TBAB (38.6 mg, 0.12 mmol, 0.3 equiv) and toluene (3 mL) were added to a dry Schlenk tube successively. The mixture was stirred at 80 ℃ for 6 h. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel with PE-EA as the eluent to afford the products **6a-i**.

*1-(tert-Butyl)-3-fluoro-5-phenyl-1H-pyrrole-2-carbonitrile (**6a**).* Yield: 57.2 mg, 59%; white solid; R_f = 0.56 (PE:EA = 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43–7.25 (m, 5H), 5.71 (s, 1H), 1.55 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 159.6 (d, J = 259.8 Hz), 137.9 (d, J = 5.9 Hz), 135.1, 130.3, 128.8, 127.9, 113.6 (d, J = 4.2 Hz), 99.8 (d, J = 12.5 Hz), 89.8 (d, J = 22.8 Hz), 62.0, 32.3; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -148.3 (s, 1F); HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{16}FN_2$ 243.1298; Found 243.1290; IR (film): 2973, 2960, 2212, 1561, 1480, 1451, 1372, 1358, 1330, 1212, 1034 cm^{-1}.

*1-(tert-Butyl)-5-(4-chlorophenyl)-3-fluoro-1H-pyrrole-2-carbonitrile (**6b**).* Yield: 62.1 mg, 54%; white solid; R_f = 0.52 (PE:EA = 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 (d, 2H, J = 8.4 Hz), 7.24 (d, 2H, J = 8.4 Hz), 5.72 (s, 1H), 1.55 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ 159.5 (d, J = 260.2 Hz), 136.3 (d, J = 6.0 Hz), 135.1, 133.5 (d, J = 1.5 Hz), 131.6, 128.2, 113.3 (d, J = 4.3 Hz), 100.1 (d, J = 12.7 Hz), 90.3 (d, J = 22.6 Hz), 62.2, 32.4; ^{19}F NMR ($CDCl_3$, 471 MHz): δ -148.0 (s, 1F); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{15}ClFN_2$ 277.0908; Found 277.0901; IR (film): 2962, 2930, 2207, 1654, 1560, 1478, 1397, 1326, 1214, 1087, 1017, 836 cm^{-1}.

*1-(tert-Butyl)-3-fluoro-5-(4-nitrophenyl)-1H-pyrrole-2-carbonitrile (**6c**).* Yield: 73.1 mg, 64%; white solid; R_f = 0.31 (PE:EA = 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (d, 2H, J = 8.6 Hz), 7.54 (d, 2H, J = 8.6 Hz), 5.79 (s, 1H), 1.58 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 159.3 (d, J = 260.9 Hz), 148.0, 141.7, 134.8 (d, J = 6.0 Hz), 131.2, 123.2, 112.8, 100.6 (d, J = 13.2 Hz), 91.4 (d, J = 22.5 Hz), 62.5, 32.4; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -147.5 (s, 1F); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{15}FN_3O_2$ 288.1148; Found 288.1142; IR (film): 3001, 2961, 2208, 1601, 1561, 1479, 1376, 1286, 1103, 1017, 864 cm^{-1}.

1-(*tert*-Butyl)-3-fluoro-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrrole-2-carbonitrile (**6d**). Yield: 86.2 mg, 69%; white solid; R_f = 0.52 (PE:EA = 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, 2H, J = 8.1 Hz), 7.46 (d, 2H, J = 8.0 Hz), 5.75 (s, 1H), 1.56 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 159.4 (d, J = 260.4 Hz), 138.8, 135.9 (d, J = 6.0 Hz), 131.0 (q, J = 32.8 Hz), 130.7, 124.9 (q, J = 3.7 Hz), 123.8 (q, J = 272.4 Hz), 113.1 (d, J = 4.3 Hz), 100.3 (d, J = 13.0 Hz), 90.7 (d, J = 22.6 Hz), 62.3, 32.4; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -62.8 (s, 3F), -147.9 (s, 1F); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{15}F_4N_2$ 311.1171; Found 311.1164; IR (film): 2988, 2215, 1621, 1567, 1481, 1364, 1215, 1169, 1167, 850 cm^{-1}.

*1-(tert-Butyl)-5-(4-cyanophenyl)-3-fluoro-1H-pyrrole-2-carbonitrile (**6e**).* Yield: 74.0 mg, 69%; pale yellow solid; R_f = 0.17 (PE:EA = 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (d, 2H, J = 8.2 Hz), 7.47 (d, 2H, J = 8.2 Hz), 5.76 (s, 1H), 1.56 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 159.4 (d, J = 260.7 Hz), 139.8, 135.3 (d, J = 5.9 Hz), 131.7, 131.0, 118.1, 112.9 (d, J = 4.3 Hz), 112.8, 100.4 (d, J = 13.2 Hz), 91.1 (d, J = 22.5 Hz), 62.4, 32.4; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -147.6 (s, 1F); HRMS (ESI) m/z: [M +

H]$^+$ Calcd for $C_{16}H_{15}FN_3$ 268.1250; Found 268.1243; IR (film): 2962, 2215, 1610, 1481, 1376, 1325, 1215, 1168, 1108, 850 cm^{-1}.

*1-(tert-Butyl)-3-fluoro-5-(4-methoxyphenyl)-1H-pyrrole-2-carbonitrile (**6f**).* Yield: 50.3 mg, 46%; yellow oil; R_f = 0.33 (PE:EA = 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20 (d, 2H, J = 8.7 Hz), 6.88 (d, 2H, J = 8.7 Hz), 5.70 (s, 1H), 3.84 (s, 3H), 1.54 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 159.9, 159.6 (d, J = 259.8 Hz), 137.7 (d, J = 6.1 Hz), 131.5, 127.1, 113.7 (d, J = 4.2 Hz), 113.3, 99.9 (d, J = 12.2 Hz), 89.6 (d, J = 22.6 Hz), 61.9, 55.3, 32.3; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -148.4 (s, 1F); HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{16}H_{18}FN_2O$ 273.1403; Found 273.1393; IR (film): 2956, 2838, 1613, 1529, 1481, 1441, 1324, 1249, 1216, 1109, 839 cm^{-1}.

*1-(tert-Butyl)-5-(2-chlorophenyl)-3-fluoro-1H-pyrrole-2-carbonitrile (**6g**).* Yield: 75.1 mg, 68%; pale yellow solid; R_f = 0.43 (PE:EA = 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45–7.25 (m, 4H), 5.69 (s, 1H), 1.55 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 159.5 (d, J = 259.9 Hz), 135.1, 134.4, 133.6 (d, J = 6.3 Hz), 132.2, 130.6, 129.4, 126.4, 113.3, 99.4 (d, J = 12.8 Hz), 90.2 (d, J = 22.7 Hz), 62.1, 31.3; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -147.7 (s, 1F); HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{15}H_{15}ClFN_2$ 277.0908; Found 277.0899; IR (film): 2991, 2214, 1566, 1479, 1444, 1374, 1327, 1216, 1061, 1032, 798 cm^{-1}.

*1-(tert-Butyl)-3-fluoro-5-(thiophen-2-yl)-1H-pyrrole-2-carbonitrile (**6h**).* Yield: 46.4 mg, 47%; yellow solid; R_f = 0.48 (PE:EA = 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (dd, 2H, J = 5.1, 1.2 Hz), 7.06–6.99 (m, 4H), 5.89 (s, 1H), 1.62 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 159.0 (d, J = 259.8 Hz), 134.4, 130.6, 129.0 (d, J = 6.8 Hz), 127.6, 126.6, 113.1, 102.2 (d, J = 12.3 Hz), 91.2 (d, J = 22.4 Hz), 62.4, 31.8; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -148.3 (s, 1F); HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{13}H_{14}FN_2S$ 249.0862; Found 249.0858; IR (film): 2975, 2214, 1706, 1653, 1547, 1480, 1372, 1205, 1092, 848 cm^{-1}.

*Ethyl 1-(tert-butyl)-5-cyano-4-fluoro-1H-pyrrole-2-carboxylate (**6i**).* Yield: 88.8 mg, 93%; red oil; R_f = 0.45 (PE:EA = 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.41 (s, 1H), 4.32 (q, 2H, J = 7.1 Hz), 1.81 (s, 9H), 1.37 (t, 3H, J = 7.1 Hz); ^{13}C{1H} NMR ($CDCl_3$, 101 MHz) δ 161.4 (d, J = 2.6 Hz), 157.8 (d, J = 259.9 Hz), 127.3 (d, J = 5.0 Hz), 111.9 (d, J = 4.5 Hz), 103.4 (d, J = 13.7 Hz), 94.3 (d, J = 23.1 Hz), 62.8, 62.0, 30.9, 14.0; ^{19}F NMR ($CDCl_3$, 471 MHz) δ -148.5 (s, 1F); HRMS (ESI) m/z: [M + H]$^+$ Calcd

for $C_{12}H_{16}FN_2O_2$ 239.1196; Found 239.1191; IR (film): 2990, 2220, 1729, 1559, 1467, 1342, 1210, 1153, 822 cm^{-1}.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

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Supporting Information

The Supporting Information is available free of charge at http://pubs.acs.org.

Optimization of reaction conditions for alkyne substrates; mechanistic experimental details; X-ray crystallographic data for **4a** and **6a;** DFT calculation; and copies of ^{1}H and ^{13}C spectra for all products.

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