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Fluorinated Heterocycles

# Straightforward and Highly Stereoselective Synthesis of 3,3,4-Trifluoropyrrolidines Involving 1,3-Dipolar Cycloaddition with 2,3,3-Trifluoroacrylate

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**Abstract:** The reactions of benzyl 2,3,3-trifluoroacrylate with azomethine ylides, generated by the treatment of imino esters with lithium diisopropylamide, took place smoothly to give the corresponding 1,3-dipolar cycloadducts, fluorine-containing pyrrolidines, in good yields and with high diastereoselectivities (>95:<5). When the fluorinated acrylate bore a chiral auxiliary as a substituent, for instance (L)-(–)-menthyl ester, the 1,3-dipolar cycloaddition reaction was found to give the corresponding fluorinated pyrrolidine derivatives in not only a diastereoselective but also an enantioselective manner.

## Introduction

Fluorine- and fluoroalkyl-containing pyrrolidine derivatives have attracted a great deal of attention in the field of medicinal and pharmaceutical chemistry.[1] Such fluorine-containing substituents play important roles in enhancing biological activity and improving the disposition and safety of drugs, as well as their physical and chemical properties.[2] Therefore, much attention has been given to the development of new fluorine-containing biologically active substances.

Our group has been devoted to the discovery of new organofluorine molecules containing hydroxy acid[3] and amino acid scaffolds in recent years.[4] We have successfully developed new synthetic approaches to such fluorine-containing biologically active molecules. In particular, during studies on optically active α-fluoro-α-(trifluoromethyl)-β-amino esters,[4b] we unexpectedly found that a fluorine-substituted pyrrolidine derivative was produced as one of the side-products in the reaction of 2-bromo-2,3,3,3-tetrafluoropropanoic ester with an (*S*)-phenylglycinate-derived imino ester in the presence of zinc dust. After investigation on the reaction in detail, we proposed that the fluorine-containing pyrrolidine could be formed through a cycloaddition reaction of in-situ-generated 2,3,3-trifluoroacrylate (**1A**) with an imino-ester-derived azomethine ylide. This led us to develop a straightforward approach to fluorine-substituted pyrrolidine scaffolds.

In the past decade, we have extensively studied the various C–C-bond-forming reactions of **1A** with nucleophiles and with electron-rich dienes. We have reported that **1A** could be conveniently used to produce various kinds of fluorinated vinyl monomers in a stereoselective fashion,[5] as well as fluorine-containing carbocycles in a regioselective manner.[6] Building on this pioneering work, we turned our attention to expanding the synthetic applications of **1** for the construction of heterocyclic scaffolds, such as pyrrolidine analogues. Although several groups have described the effective formation of fluorine- or fluoroalkyl-substituted pyrrolidine derivatives,[7] to the best of our knowledge, there are no reports on the synthesis of trifluorinated pyrrolidine analogues, except for our pioneering report.

In this article, we disclose a straightforward and stereoselective synthesis of 3,3,4-trifluoropyrrolidines involving 1,3-dipolar cycloaddition reactions of **1** with various imino-ester-based chiral azomethine ylides in detail (Figure 1). We also describe the highly diastereoselective and enantioselective construction of 3,3,4-trifluoropyrrolidine derivatives through 1,3-dipolar cycloaddition reactions using fluorinated acrylates with chiral auxiliaries.

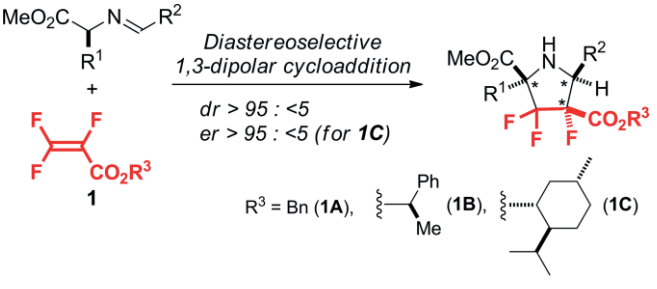


Figure 1. Outline of this work.

## Results and Discussion

We initially attempted the 1,3-dipolar cycloaddition of **1A** with the azomethine ylide generated from methyl (*S*)-phenylglycinate-based imino ester **2a**. This is a classical synthetic route to construct the pyrrolidine motif, and many pyrrolidine derivatives have been accessed in a similar manner.[8] Using the reac-

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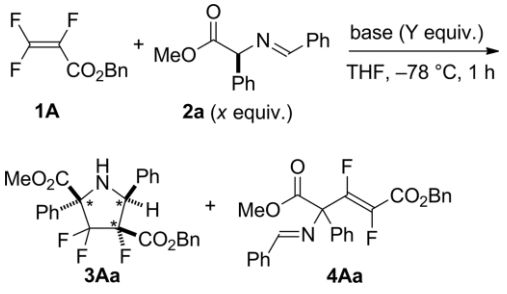
tion conditions mentioned in refs.[8e,8f] the reaction of **1A** with imino ester **2a** in the presence of AgOAc/DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) or LiBr/DBU as a base in THF at room temperature for 2 h did not result in the effective formation of cycloadduct **3Aa**. Instead, a complex mixture or a trace amount of **3Aa** was formed (Table 1, entries 1 and 2). To try to obtain cycloadduct **3Aa** more effectively, we examined the reaction conditions further. The results are shown in Table 1.

Table 1. Optimization of the reaction conditions.




| Entry | Base (*x* equiv.) | Imino ester **2a** [*y* equiv] | Yield[a,b] of **3Aa** [%] | Yield[a] of **4Aa** [%] |
|---|---|---|---|---|
| 1[c] | AgOAc/DBU (1.1) | 1.2 | –[d] | –[d] |
| 2[e] | LiBr/DBU (1.1) | 1.2 | trace | 0 |
| 3 | *n*BuLi (1.1) | 1.2 | 42 | 4 |
| 4 | *n*BuLi (2.0) | 2.2 | 40 | 6 |
| 5 | *t*BuLi (1.1) | 1.2 | 34 | 2 |
| 6 | *t*BuLi (2.0) | 2.2 | 45 | – |
| 7 | LDA (1.1) | 1.2 | 43 | 28 |
| 8 | LDA (2.0) | 2.2 | 59 (35)[f] | 24 |
| 9 | LHMDS (1.1) | 1.2 | 40 | 39 |
| 10 | LHMDS (2.0) | 2.2 | 53 | 23 |

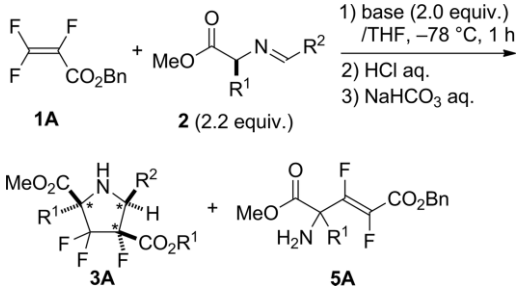
[a] Determined by $^{19}F$ NMR spectroscopy. $CF_3CO_2Et$ was used as an internal reference. Value in parentheses is the isolated yield. [b] Unless otherwise noted, the diastereoselectivity observed was >95:<5. [c] With the reaction conditions given in ref.[8e] [d] A complex mixture was observed in the reaction mixture. [e] With the reaction conditions given in ref.[8f] [f] Isolated yield after acidic hydrolysis of **4Aa**.

The reaction of **1A** with 1.1 equiv. of azomethine ylide, generated from imino ester **2a** and *n*-butyllithium, in THF at –78 °C for 2 h resulted in the formation of the corresponding cycloadduct (i.e., **3Aa**) in 42 % yield, together with a small amount of side-product **4aA**.

To our great delight, $^{19}F$ NMR spectroscopic analysis of the reaction mixture showed the formation of only two products, in a ratio of >95:<5, in spite of the presence of three chiral centres. This means that the 1,3-dipolar cycloaddition of **1A** with the azomethine ylide proceeded in a highly diastereoselective manner. When the reaction was carried out with an increased amount of *n*-butyllithium or with the more basic *tert*-butyllithium, no significant change was observed in the yield of **3Aa** (Table 1, entries 3–6). Under these conditions, we did not recover any of the starting material (i.e., **1A**), which clearly indicates that butyllithium was not suitable as a base due to its high nucleophilicity. To increase the yield of cycloadduct **3Aa** and suppress undesired side reactions, we adopted lithium amides like lithium diisopropylamide (LDA) and lithium hexamethyldisilazide (LHMDS) as bases. These reagents have both a high basicity and a low nucleophilicity. When LDA (1.1 equiv.) was used as a base, the yields of **3Aa** and **4Aa** were 43 and 28 %, respectively (Table 1, entry 7). Increasing the amount of azomethine ylide up to 2.0 equiv. was found to promote the formation of **3Aa**, which was then obtained in 59 % yield (Table 1, entry 8). Owing to the difficulty in the separation of **3Aa** and **4Aa**, the reaction mixture was exposed to acidic conditions in order to convert **4Aa** into the corresponding amino diester (i.e., **5Aa**). After this, **3Aa** was successfully isolated in 35 % yield as the sole product. When LHMDS was used as a base, as shown in Table 1, entries 9 and 10, no great difference in the yields of **3Aa** and **4Aa** was observed, compared with the results shown in Table 1, entries 7 and 8. It is noteworthy that pyrrolidine derivative **3Aa** was formed with a high diastereoselectivity (>95:<5) in all cases.

Having optimized the reaction conditions, we went on to carry out 1,3-dipolar cycloaddition reactions of **1A** with various azomethine ylides (2.0 equiv.) in THF at –78 °C for 1 h, followed by hydrolysis with an aqueous HCl solution. The results obtained are summarized in Table 2.

Table 2. Diastereoselective 1,3-dipolar cycloaddition reactions of **1A** with various azomethine ylides.




| Entry | Imino ester $R^1$ | $R^2$ | | Yield[a,b] of **3A** [%] | Yield[a,b] of **5A** [%] |
|---|---|---|---|---|---|
| 1 | Ph | Ph | **2a** | 59 (35) | 21 |
| 2 | Ph | 4-$ClC_6H_4$ | **2b** | 77 (47) | 8 |
| 3 | Ph | 4-$CF_3C_6H_4$ | **2c** | 82 (47) | 4 |
| 4 | Ph | 4-$MeOC_6H_4$ | **2d** | 59 (26) | 23 |
| 5 | Ph | 1-Naphthyl | **2e** | 58 (30)[c] | 30 |
| 6 | Ph | *c*Hex | **2f** | 17 (4) | 9 |
| 7 | Ph | *n*Pr | **2g** | –[d] | – |
| 8 | Ph | PhCH=CH | **2h** | 45 | 5 |
| 9 | Me | 4-$ClC_6H_4$ | **2i** | 26 | 24 |
| 10 | $PhCH_2$ | 4-$ClC_6H_4$ | **2j** | 40 (20) | 18 |
| 11 | *i*Pr | 4-$ClC_6H_4$ | **2k** | 23 (21) | 37 |
| 12 | $MeS(CH_2)_2$ | 4-$ClC_6H_4$ | **2l** | 56 (50) | 18 |
| 13 | $MeO_2CCH_2$ | 4-$ClC_6H_4$ | **2m** | 54 (31) | 22 |

[a] Determined by $^{19}F$ NMR spectroscopy. Values in parentheses are isolated yields. [b] Unless otherwise noted, the diastereomeric ratio was >95:<5. [c] The pyrrolidine derivative **3Ae** was obtained as a 45:55 mixture of diastereomers. [d] A complex mixture was obtained.

With the azomethine ylides prepared from imino esters **2b** and **2c**, which have an electron-withdrawing group (Cl or $CF_3$) on the benzene ring of $R^2$, the 1,3-dipolar cycloaddition reactions with **1A** proceeded smoothly to give the corresponding cycloadducts **3Ab** and **3Ac** in 77 and 82 % yields, respectively. NMR spectroscopic analysis of the reaction mixtures showed the highly diastereoselective formation (>95:<5) of the desired products in both cases. Fortunately, the major diastereomer of **3Ab** gave a single crystal, X-ray analysis of which made the

relative configurations of the three chiral centres clear, as shown in Figure 2.

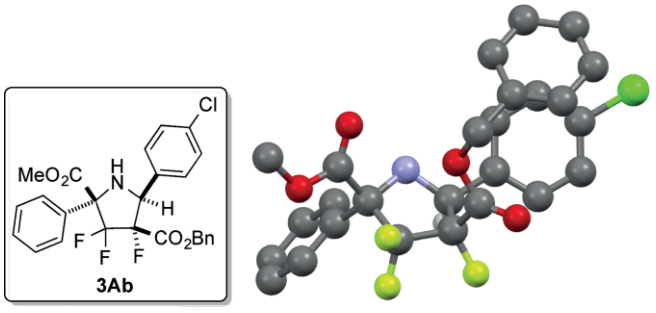


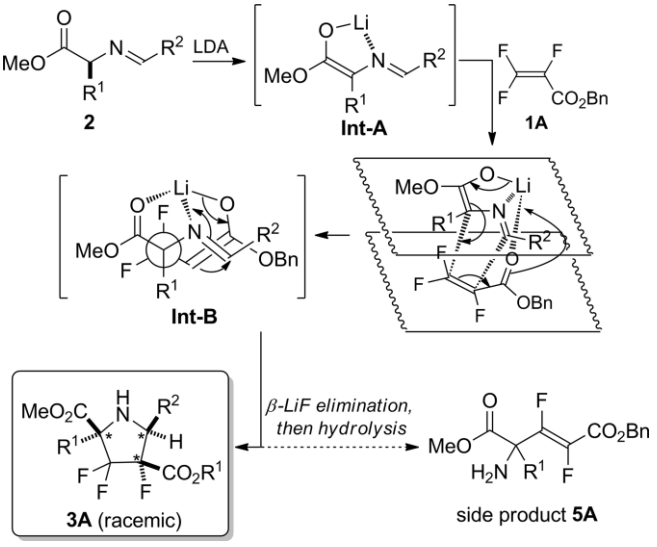

Figure 2. Single-crystal X-ray analysis of pyrrolidine **3Ab**. Hydrogen atoms are omitted for clarity, except for the hydrogen attached to the 5-position of the pyrrolidine backbone.

The azomethine ylide generated from imino ester **2d**, which has an electron-donating group, also participated in the cycloaddition reaction, leading to the corresponding adduct (i.e., **3Ad**) in good yield (59 %; Table 1, entry 4). The cycloaddition reaction using the **2e**-derived azomethine ylide also produced the corresponding pyrrolidine (i.e., **3Ae**) in an acceptable yield. However, the ratio of diastereomers in **3Ae** dropped drastically to 45:55; this might be due to the steric hindrance of the naphthalene moiety (Table 1, entry 5). Azomethine ylides prepared from imino esters **2f** and **2g**, which bear an aliphatic substituent at the $R^2$ position, were not suitable for use in this cycloaddition reaction (Table 2, entries 6 and 7), whereas the ylide derived from **2h**, with an alkenyl substituent, resulted in the formation of cycloadduct **3Ah** in moderate yield (Table 1, entry 8).

Similarly, imino esters **2i**–**2m** derived from various amino esters were used for the cycloaddition reaction as precursors of azomethine ylides. The azomethine ylides formed from alanine- and valine-derived imino esters **2i** and **2k**, respectively, underwent the cycloaddition reaction with **1A**, but the desired products (i.e., **3Ai** and **3Ak**) were obtained in low yields (around 25 %; Table 2, entries 9 and 11). For **2j**, **2l**, and **2m**, on the other hand, the cycloaddition took place well to give the corresponding pyrrolidine derivatives (i.e., **3Aj**, **3Al**, and **3Am**) in moderate yields (up to 56 %; Table 2, entries 10, 12, and 13). It is noteworthy that in these 1,3-dipolar cycloaddition reactions of **1A** with azomethine ylides, we found that the various fluorine-containing pyrrolidine derivatives were obtained diastereoselectively (>95:<5) in most cases.

Considering the relative configuration of the major isomers of **3Ab**, a proposed reaction mechanism is shown in Scheme 1.[9]

The reaction is initiated by abstraction of a proton from imino esters **2** by LDA to generate an azomethine ylide (**Int-A**). This then attacks the electrophilic carbon at the 3-position of **1A** with a *Re*-face selectivity through coordination of the carbonyl oxygen in **1A** to the lithium metal. This gives lithium enolate **Int-B**, with double coordination to both the imine nitrogen and the carbonyl oxygen. The enolate moieties in **Int-B** react with an imine moiety closely located in a *Si*-face selective manner, resulting in the highly diastereoselective formation of the

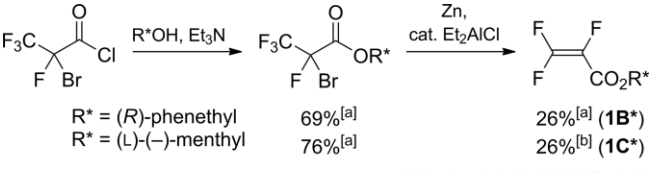



Scheme 1. Possible reaction mechanism for the highly diastereoselective 1,3-dipolar cycloaddition.

desired pyrrolidine derivatives as a racemic adduct. The side-product **5A**, in contrast, can be formed through immediate β-elimination of LiF from **Int-B** taking place instead of the cyclization.

For the next stage of this work on the highly diastereoselective synthesis of pyrrolidines, our efforts were directed towards the asymmetric synthesis of optically active fluorinated pyrrolidine derivatives. Thus, we prepared trifluoroacrylates **1B*** and **1C*** bearing a chiral auxiliary, according to our previously published procedure,[5] and used these chiral dipolarophiles in the 1,3-dipolar cycloaddition reaction.

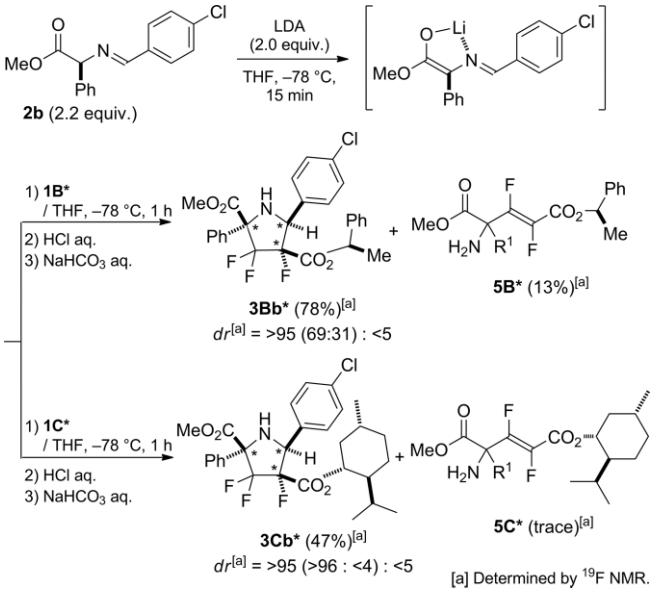
Optically active 2,3,3-trifluoroacrylic esters, **1B*** and **1C*** were successfully synthesized in two steps from commercially available starting acid chloride by using (*R*)-phenethyl alcohol or (L)-(–)-menthol (Scheme 2). The detailed synthetic procedures and spectroscopic data of the products are described in the Supporting Information.




Scheme 2. Preparation of optically active 2,3,3-trifluoroacrylic esters.

With chiral trifluoroacrylic esters **1B*** and **1C*** in hand, we examined 1,3-dipolar cycloaddition reactions with an azomethine ylide derived from imino ester **2b**. The results are shown in Scheme 3.

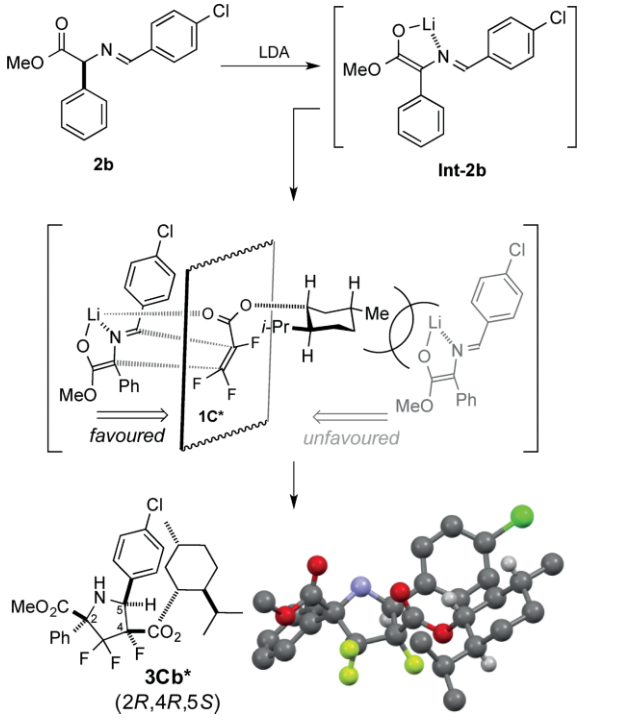
Thus, reaction of in-situ-prepared azomethine ylide (2.0 equiv.) with (*R*)-phenethyl ester **1B*** in THF at –78 °C for 1 h, followed by acidic treatment, proceeded smoothly to give the corresponding cycloadduct (i.e., **3Bb***) in 78 % yield, together with a small amount of side-product **5B***. In this reaction, **3Bb*** was obtained with excellent diastereoselectivity (>95:<5) and moderate enantioselectivity (69:31). In the case of




Scheme 3. Enantio- and diastereoselective 1,3-dipolar cycloaddition using optically active trifluoroacrylic esters **1B*** and **1C***.

(L)-(–)-menthyl ester **1C***, in sharp contrast, the cycloaddition reaction occurred with moderate efficiency (47 % yield), but with excellent diastereoselectivity and enantioselectivity. To our delight, the major isomer of **3Cb*** was successfully crystallized for X-ray crystallographic analysis. This showed that the absolute configuration of **3Cb*** was (2*R*,4*R*,5*S*).

The crystal structure of **3Cb*** and the rational reaction mechanism are shown in Scheme 4. To provide the cycloadduct with the excellent stereoselectivity mentioned above in Scheme 1,




Scheme 4. Rational explanation of the formation of enantiomerically pure pyrrolidine **3Cb**, and the crystal structure. Hydrogen atoms are omitted for clarity, except for the hydrogens attached to tertiary carbon atoms.

the 1,3-dipolar cycloaddition should occur in a facially selective fashion. In chiral **1C***, as shown in Scheme 4, the initial nucleophilic attack of the azomethine ylide favourably occurs from *Si*-face of the ylide because of the hindrance at the opposite face from the sterically bulky (L)-(–)-menthyl group. Subsequent cyclization through *Re*-face attack of the enolate onto the imine moiety then leads to the pyrrolidine derivative with excellent enantioselectivity. In the case of **1B***, on the other hand, the enantiomeric ratio is moderate, due to the lack of the initial facial selectivity; this is because the phenethyl group is much less bulk than a menthyl moiety.

## Conclusions

In this study, we have shown that the synthetic applications of 2,3,3-trifluoroacrylates can be extended to the construction of key substructures of biologically active substances. Thus, 1,3-dipolar cycloaddition reactions of 2,3,3-trifluoroacrylates with azomethine ylides, easily generated from imino esters, took place to produce the corresponding fluorine-substituted pyrrolidine derivatives in good yields, and with excellent diastereoselectivities. By using a chiral fluorinated ester bearing an (L)-(–)-menthyl group, a highly diastereoselective and enantioselective synthesis of trifluorinated pyrrolidine derivatives was successfully accomplished through this 1,3-dipolar cycloaddition reaction with an azomethine ylide. Based from these results with 2,3,3-trifluoroacrylates, these fluorinated alkenes can be seen as promising building blocks that can be used to obtain versatile monomers for the synthesis of fluorine-containing polymers, as well as fluorinated carbocycles and heterocycles that may show biological activity. In the near future, we plan to disclose further synthetic applications, using not only these compounds, but also other fluorinated alkenes.

## Experimental Section

**General Methods:** Infrared spectra (IR) were recorded with a Shimadzu FTIR-8200A (PC) spectrophotometer. $^1$H (500.13 MHz) and $^{13}$C (125.75 MHz) NMR spectra were measured with a Bruker DRX 500 spectrometer in a [D]chloroform ($CDCl_3$) solution with tetramethylsilane ($Me_4Si$, TMS) as an internal reference. A JEOL JNM-EX90A (84.21 MHz, FT) spectrometer was used for determining the yields of the products with internal trifluoromethylbenzene (BTF) or ethyl trifluoroacetate. The JEOL JNM-EX90A (84.21 MHz, FT) spectrometer and a Bruker DPX 300 (282.38 MHz) spectrometer were used for determining the diastereomeric ratio (*dr*) of the products; *de* values were also determined by $^{19}$F NMR spectroscopy in $CDCl_3$ solution containing $CFCl_3$ ($\delta_F$ = 0) as an internal standard. High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-700 mass spectrometer by electron impact (EI) or FAB ($Cs^+$) methods.

**Materials:** Tetrahydrofuran (THF, anhydrous) and diethyl ether ($Et_2O$, anhydrous) were purchased from Wako Pure Chemical Industries, Ltd. Various amino acid ester hydrochlorides were purchased from Aldrich Chemical Company, Inc. All chemicals were of reagent grade, and, if necessary, were purified in the usual manner before use. Thin-layer chromatography (TLC) was carried out with Merck

silica gel 60 $F_{254}$ plates, and column chromatography was carried out with Wako gel C-200. All reactions were carried out under an atmosphere of argon.

**Typical Procedure for the Preparation of Imino Ester 2a:** Phenylglycine methyl ester hydrochloride (2.22 g, 11.0 mmol) was dissolved in distilled water (30.0 mL), and benzaldehyde (1.06 g, 10.0 mmol) and sodium carbonate (3.18 g, 30.0 mmol) were added to the stirred solution. The reaction mixture was stirred for 45 min at 40 °C, then it was cooled to room temperature, where it was stirred for a further 21 h. After this time, the reaction was quenched with satd. aq. ammonium sulfate. The mixture was extracted with diethyl ether (3 ×). The combined organic layers were dried with anhydrous sodium sulfate, filtered, and concentrated. The residue was recrystallized from hexane and diethyl ether to give **2a** in good yield.

**Typical Procedure for the Cycloaddition Reaction of 1A with Imino Ester 2a in the Presence of Lithium Diisopropylamide (LDA):** *n*-Butyllithium (1.6 M hexane solution; 0.63 mL, 1.00 mmol) was added to a stirred solution of diisopropylamine (0.101 g, 1.00 mmol) in dry THF (1 mL) at 0 °C. Then the solution was cooled to –78 °C, and a solution of imino ester **2a** (0.28 g, 1.10 mmol) in dry THF (2 mL) was added to the mixture. The mixture was stirred for 15 min at that temperature, then a solution of **1A** (0.11 g, 0.50 mmol) in dry THF (1 mL) was added dropwise. The mixture was stirred for a further 1 h at –78 °C, then the reaction was quenched with satd. aq. ammonium chloride solution. The mixture was extracted with ethyl acetate (3 ×). The combined organic layers were dried with anhydrous sodium sulfate, filtered, and concentrated. The yield of the product was determined by $^{19}F$ NMR spectroscopy in the presence of ethyl trifluoroacetate (10 μL, 0.084 mmol), and then the crude residue was purified by silica gel column chromatography to give pure product **3Aa** (82 mg, 0.18 mmol, 35 %).

**4-Benzyl-2-methyl (2*R**,4*R**,5*S**)-3,3,4-Trifluoro-2,5-diphenylpyrrolidine-2,4-dicarboxylate (3Aa):** $^1H$ NMR (500.13 MHz, $CDCl_3$, TMS): $\delta$ = 3.76 (s, 3 H), 4.20 (br. d, *J* = 12.5 Hz, 1 H), 4.53–4.60 (m, 1 H), 4.87 (d, *J* = 12.0 Hz, 1 H), 4.95 (d, *J* = 12.0 Hz, 1 H), 7.01 (d, *J* = 7.7 Hz, 2 H), 7.24–7.40 (m, 11 H), 7.92–7.94 (m, 2 H) ppm. $^{13}C$ NMR (125.75 MHz, $CDCl_3$, TMS): $\delta$ = 53.5, 63.3 (dd, *J* = 4.5, 22.6 Hz), 67.8, 72.8 (t, *J* = 23.2 Hz), 72.9 (d, *J* = 23.2 Hz), 98.7 (ddd, *J* = 20.8, 27.6, 221.9 Hz), 124.1 (ddd, *J* = 18.9, 271.2, 290.1 Hz), 125.9, 128.1, 128.2, 128.4, 128.46, 128.48, 128.66, 128.72, 133.6, 133.9, 134.0, 163.9 (d, *J* = 27.8 Hz), 168.2 ppm; one carbon peak was not detected because of overlap with another carbon peak. $^{19}F$ NMR (84.10 MHz, $CDCl_3$, $CFCl_3$): $\delta$ = –100.20 (d, *J* = 239.6 Hz, 1 F), –108.15 (dd, *J* = 4.5, 239.6 Hz, 1 F), –167.31 (dd, *J* = 4.5, 13.6 Hz, 1 F) ppm. IR (neat): $\tilde{\nu}$ = 3229, 3036, 2957, 1747, 1499, 1456, 1435, 1385, 1331, 1271, 1217, 1097, 1072, 1013, 988, 908, 737, 698 $cm^{-1}$. HRMS (FAB): calcd. for $C_{26}H_{23}F_3NO_4$ [M + H] 470.1579; found 470.1581. $C_{26}H_{22}F_3NO_4$ (469.46): calcd. C 66.52, H 4.72, N 2.98; found C 66.19, H 4.77, N 2.92.

**4-Benzyl-2-methyl (2*R**,4*R**,5*S**)-5-(4-Chlorophenyl)-3,3,4-trifluoro-2-phenylpyrrolidine-2,4-dicarboxylate (3Ab):** M.p. 110–112 °C. $^1H$ NMR (500.13 MHz, $CDCl_3$, TMS): $\delta$ = 3.78 (s, 3 H), 4.08–4.23 (m, 1 H), 4.45–4.55 (m, 1 H), 4.95 (d, *J* = 12.0 Hz, 1 H), 5.00 (d, *J* = 12.0 Hz, 1 H), 7.00–7.05 (m, 2 H), 7.16–7.21 (m, 2 H), 7.24–7.41 (m, 8 H), 7.88–7.92 (m, 2 H) ppm. $^{13}C$ NMR (125.75 MHz, $CDCl_3$, TMS): $\delta$ = 53.7, 62.7 (dd, *J* = 4.5, 22.9 Hz), 68.0, 72.9 (t, *J* = 22.1 Hz), 98.5 (ddd, *J* = 21.0, 28.3, 222.2 Hz), 124.1 (ddd, *J* = 18.9, 271.2, 281.8 Hz), 127.2, 128.13, 128.15, 128.18, 128.5, 128.69, 128.72, 128.8, 132.5, 133.4, 133.8, 134.4, 163.7 (d, *J* = 27.7 Hz), 168.1 ppm. $^{19}F$ NMR (84.10 MHz, $CDCl_3$, $CFCl_3$): $\delta$ = –100.20 (d, *J* = 240.0 Hz, 1 F), –107.41 (dd, *J* = 5.6, 240.0 Hz, 1 F), –167.03 (dd, *J* = 16.9 Hz, 1 F) ppm. IR (KBr): $\tilde{\nu}$ = 3315, 2972, 2955, 2343, 1744, 1599, 1499, 1437, 1379, 1271, 1184, 1134, 1078, 1018, 976, 932, 905, 881, 820, 729, 700, 638, 617 $cm^{-1}$. HRMS (FAB): calcd. for $C_{26}H_{22}{}^{35}ClF_3NO_4$ [M + H] 504.1189; found 504.1197.

**X-ray Structural Analysis:** A crystal of **3Ab** (colourless prism) with approximate dimensions of 0.35 × 0.35 × 0.29 mm was mounted on a glass fibre. All measurements were made with a Rigaku AFC7R diffractometer using filtered Cu-$K_\alpha$ radiation and a rotating anode generator. Compound **3Ab**: triclinic, *a* = 11.632(6) Å, *b* = 13.209(4) Å, *c* = 8.877(4) Å, $\alpha$ = 109.01(3)°, $\beta$ = 105.86(4)°, $\gamma$ = 102.45(3)°, *V* = 1168.8(1) $Å^3$, *T* = 198.1 K, space group $P\bar{1}$ (No. 2), *Z* = 2, $\mu$(Cu-$K_\alpha$) = 1.5418 $mm^{-1}$, 11436 reflections measured, 4146 unique ($R_{int}$ = 0.131), which were used in all calculations. The final $R_1$ and $wR_2$ were 0.077 and 0.221 [$I > 2\sigma(I)$].

All calculations were carried out using the CrystalStructure crystallographic software package [Rigaku and Rigaku/MSC (2000–2003)] except for refinement, which was carried out using SHELXL-97. The structure was solved by direct methods (SIR2002) and expanded using Fourier techniques (DIRDIF99). The goodness-of-fit indicator was 1.089.

**4-Benzyl-2-methyl (2*R**,4*R**,5*S**)-3,3,4-Trifluoro-2-phenyl-5-(4-trifluoromethylphenyl)pyrrolidine-2,4-dicarboxylate (3Ac):** M.p. 84–86 °C. $^1H$ NMR (500.13 MHz, $CDCl_3$, TMS): $\delta$ = 3.83 (s, 3 H), 4.16–4.26 (m, 1 H), 4.53–4.65 (m, 1 H), 4.98 (d, *J* = 11.5 Hz, 1 H), 5.01 (d, *J* = 11.5 Hz, 1 H), 7.03–7.08 (m, 2 H), 7.24–7.53 (m, 10 H), 7.92–7.97 (m, 2 H) ppm. $^{13}C$ NMR (125.75 MHz, $CDCl_3$, TMS): $\delta$ = 53.7, 62.8 (dd, *J* = 4.3, 22.6 Hz), 68.1, 72.9 (t, *J* = 22.6 Hz), 98.4 (ddd, *J* = 20.8, 28.3, 223.4 Hz), 123.8 (q, *J* = 272.2 Hz), 124.1 (ddd, *J* = 20.1, 271.9, 281.6 Hz), 125.5 (q, *J* = 3.6 Hz), 126.2, 128.17 (d, *J* = 3.5 Hz), 128.23, 128.5, 128.78, 128.85, 128.91, 131.5 (q, *J* = 32.4 Hz), 133.1, 133.7, 138.1, 163.6 (d, *J* = 27.0 Hz), 168.0 ppm. $^{19}F$ NMR (84.10 MHz, $CDCl_3$, $CFCl_3$): $\delta$ = –63.04 (s, 3 F), –99.58 (d, *J* = 239.8 Hz, 1 F), –107.05 (dd, *J* = 6.6, 239.8 Hz, 1 F), –166.29 (dd, *J* = 4.4, 13.2 Hz, 1 F) ppm. IR (KBr): $\tilde{\nu}$ = 3325, 3065, 3034, 2962, 2899, 1742, 1622, 1427, 1410, 1381, 1256, 1175, 1036, 986, 876, 735, 669, 642 $cm^{-1}$. HRMS (FAB): calcd. for $C_{27}H_{22}F_6NO_4$ [M + H] 538.1453; found 538.1448.

**4-Benzyl-2-methyl (2*R**,4*R**,5*S**)-3,3,4-Trifluoro-5-(4-methoxyphenyl)-2-phenylpyrrolidine-2,4-dicarboxylate (3Ad):** $^1H$ NMR (500.13 MHz, $CDCl_3$, TMS): $\delta$ = 3.79 (s, 3 H), 3.81 (s, 3 H), 4.10–4.16 (m, 1 H), 4.50–4.56 (d, *J* = 15.9 Hz, 1 H), 4.93 (d, *J* = 12.0 Hz, 1 H), 5.02 (d, *J* = 12.0 Hz, 1 H), 6.78–6.85 (m, 2 H), 7.02–7.08 (m, 2 H), 7.25–7.42 (m, 8 H), 7.92–7.95 (m, 2 H) ppm. $^{13}C$ NMR (125.75 MHz, $CDCl_3$, TMS): $\delta$ = 53.6, 55.2, 63.1 (dd, *J* = 4.6, 23.0 Hz), 67.8, 72.8 (t, *J* = 22.9 Hz), 98.8 (ddd, *J* = 20.9, 27.3, 221.1 Hz), 114.0, 124.1 (ddd, *J* = 18.7, 272.0, 279.9 Hz), 125.9, 127.2, 128.1, 128.2, 128.41, 128.48, 128.51, 128.7, 133.9, 134.1, 159.6, 164.0 (d, *J* = 27.5 Hz), 168.4 ppm. $^{19}F$ NMR (84.10 MHz, $CDCl_3$, $CFCl_3$): $\delta$ = –100.64 (d, *J* = 239.8 Hz, 1 F), –108.71 (dd, *J* = 6.6, 239.8 Hz, 1 F), –168.13 (dd, *J* = 6.6, 15.9 Hz, 1 F) ppm. IR (neat): $\tilde{\nu}$ = 2957, 2936, 2839, 1746, 1614, 1518, 1454, 1437, 1331, 1256, 1219, 1180, 1094, 1036, 1013, 762, 698 $cm^{-1}$. HRMS (FAB): calcd. for $C_{27}H_{25}F_3NO_5$ [M + H] 500.1685; found 500.1694.

**4-Benzyl-2-methyl (2*R**,4*R**,5*S**)-3,3,4-Trifluoro-5-(1-naphthyl)-2-phenylpyrrolidine-2,4-dicarboxylate (3Ae):** M.p. 138–140 °C. $^1H$ NMR (500.13 MHz, $CDCl_3$, TMS): $\delta$ = 3.85 (s, 3 H), 4.15–4.35 (m, 1 H), 4.66 (d, *J* = 12.0 Hz, 1 H), 4.71 (d, *J* = 12.0 Hz, 1 H), 5.45–5.51 (m, 1 H), 6.74–6.78 (m, 2 H), 7.12–7.25 (m, 3 H), 7.36–7.51 (m, 6 H), 7.63–7.64 (m, 1 H), 7.78–7.88 (m, 2 H), 7.92–7.99 (m, 3 H) ppm. $^{13}C$ NMR (125.75 MHz, $CDCl_3$, TMS): $\delta$ = 53.6, 60.7 (dd, *J* = 2.0, 24.5 Hz), 67.6, 72.5 (t, *J* = 22.2 Hz), 98.8 (ddd, *J* = 20.6, 26.6, 219.8 Hz), 123.06,

123.10, 123.5 (ddd, $J$ = 20.6, 269.7, 278.9 Hz), 123.6, 125.0, 126.0, 126.7, 127.8, 127.9, 128.1, 128.3, 128.4, 128.8 (d, $J$ = 1.5 Hz), 129.4, 130.0 (d, $J$ = 1.2 Hz), 131.4, 133.7, 133.8, 133.9, 163.5 (d, $J$ = 26.5 Hz), 168.7 ppm. $^{19}$F NMR (84.10 MHz, $CDCl_3$, $CFCl_3$): $\delta$ = –105.87 (dd, $J$ = 4.4, 239.9 Hz, 1 F), –110.29 (dd, $J$ = 4.4, 239.9 Hz, 1 F), –163.56 (dt, $J$ = 4.4, 15.4 Hz, 1 F) ppm. IR (KBr): $\tilde{\nu}$ = 3200, 1744, 1726, 1458, 1067, 945, 905, 799, 737, 698 cm$^{-1}$. HRMS (FAB): calcd. for $C_{30}H_{25}F_3NO_4$ [M + H] 520.1736; found 520.1730.

**4-Benzyl-2-methyl 3,3,4-Trifluoro-5-(1-naphthyl)-2-phenylpyrrolidine-2,4-dicarboxylate (3Ae):** An isomer other than (2*R**,4*R**,5*S**); the relative stereochemistry was not determined. $^1$H NMR (500.13 MHz, $CDCl_3$, TMS): $\delta$ = 3.82 (s, 3 H), 4.15–4.55 (m, 1 H), 4.70–4.76 (m, 1 H), 4.83 (d, $J$ = 12.0 Hz, 1 H), 4.90 (d, $J$ = 12.0 Hz, 1 H), 6.78–6.82 (m, 2 H), 6.96–7.01 (m, 2 H), 7.09–7.14 (m, 1 H), 7.35–7.45 (m, 4 H), 7.50–7.54 (m, 2 H), 7.72–7.76 (m, 1 H), 7.78–7.84 (m, 2 H), 7.89 (s, 1 H), 7.95–7.99 (m, 2 H) ppm. $^{13}$C NMR (125.75 MHz, $CDCl_3$, TMS): $\delta$ = 53.6, 63.4 (dd, $J$ = 4.5, 22.4 Hz), 67.9, 73.0 (t, $J$ = 23.3 Hz), 98.8 (ddd, $J$ = 20.7, 27.5, 221.6 Hz), 123.4, 124.3 (ddd, $J$ = 19.1, 271.1, 289.5 Hz), 125.1, 126.4, 126.5, 127.7, 128.20, 128.23, 128.26, 128.32, 128.4, 128.6, 128.8, 131.6, 133.09, 133.12, 133.57, 133.58, 133.7, 163.9 (d, $J$ = 28.0 Hz), 168.2 ppm. $^{19}$F NMR (282.38 MHz, $CDCl_3$, $CFCl_3$): $\delta$ = –100.12 (d, $J$ = 240.0 Hz, 1 F), –107.17 (d, $J$ = 240.0 Hz, 1 F), –166.20 to –166.30 (m, 1 F) ppm.

**4-Benzyl-2-methyl (2*R**,4*R**,5*S**)-5-Cyclohexyl-3,3,4-trifluoro-2-phenylpyrrolidine-2,4-dicarboxylate (3Af):** $^1$H NMR (500.13 MHz, $CDCl_3$, TMS): $\delta$ = 0.82–1.83 (m, 11 H), 2.23–2.27 (m, 1 H), 2.92 (dd, $J$ = 10.5, 13.0 Hz, 1 H), 3.73 (s, 3 H), 5.30 (d, $J$ = 12.0 Hz, 1 H), 5.34 (d, $J$ = 12.0 Hz, 1 H), 7.24–7.45 (m, 8 H), 7.82–7.86 (m, 2 H) ppm. $^{13}$C NMR (125.75 MHz, $CDCl_3$, TMS): $\delta$ = 25.2, 25.4, 26.1, 29.2, 30.7, 38.1, 53.5, 65.4 (dd, $J$ = 4.1, 20.5 Hz), 68.0, 72.5 (t, $J$ = 22.8 Hz), 98.0 (ddd, $J$ = 21.5, 27.7, 224.0 Hz), 124.6 (ddd, $J$ = 18.4, 272.1, 281.2 Hz), 128.0, 128.3 (d, $J$ = 3.4 Hz), 128.5, 128.7, 128.9, 129.2, 134.1, 134.4, 165.0 (d, $J$ = 27.4 Hz), 168.3 ppm. $^{19}$F NMR (84.10 MHz, $CDCl_3$, $CFCl_3$): $\delta$ = –98.61 (d, $J$ = 237.7 Hz, 1 F), –107.89 (dd, $J$ = 6.6, 237.7 Hz, 1 F), –168.20 to –168.60 (m, 1 F) ppm. IR (KBr): $\tilde{\nu}$ = 3348, 2926, 2855, 1763, 1738, 1487, 1454, 1267, 1217, 1180, 1146, 1113, 1092, 1078, 1061, 1009, 737, 698 cm$^{-1}$. HRMS (FAB): calcd. for $C_{26}H_{29}F_3NO_4$ [M + H] 476.2049; found 476.2039.

**4-Benzyl-2-methyl (2*R**,4*R**,5*S**)-3,3,4-Trifluoro-2-phenyl-5-(2-phenylethenyl)pyrrolidine-2,4-dicarboxylate (3Ah):** M.p. 74–76 °C. $^1$H NMR (500.13 MHz, $CDCl_3$, TMS): $\delta$ = 3.50–4.00 (m, 4 H), 4.08 (dd, $J$ = 7.0, 16.5 Hz, 1 H), 5.25 (s, 2 H), 6.03 (dd, $J$ = 7.0, 16.0 Hz, 1 H), 6.71 (d, $J$ = 16.0 Hz, 1 H), 7.20–7.43 (m, 13 H), 7.89–7.93 (m, 2 H) ppm. $^{13}$C NMR (125.75 MHz, $CDCl_3$, TMS): $\delta$ = 53.6, 63.2 (dd, $J$ = 4.1, 24.6 Hz), 67.0, 72.7 (t, $J$ = 22.8 Hz), 97.6 (ddd, $J$ = 20.9, 27.4, 219.7 Hz), 121.4, 123.7 (ddd, $J$ = 19.5, 269.6, 280.5 Hz), 126.8, 128.00, 128.02, 128.1, 128.4, 128.59, 128.65, 128.71, 128.72, 133.9, 134.3, 135.56, 135.59, 164.0 (d, $J$ = 27.5 Hz), 168.4 ppm. $^{19}$F NMR (84.10 MHz, $CDCl_3$, $CFCl_3$): $\delta$ = –104.28 (dd, $J$ = 4.4, 239.8 Hz, 1 F), –109.81 (dd, $J$ = 6.6, 239.8 Hz, 1 F), –169.06 (ddd, $J$ = 4.5, 6.6, 15.4 Hz, 1 F) ppm. IR (KBr): $\tilde{\nu}$ = 3333, 3061, 2962, 1770, 1732, 1495, 1450, 1379, 1335, 1269, 1240, 1192, 1119, 1090, 1011, 970, 908, 802, 735, 698 cm$^{-1}$. HRMS (FAB): calcd. for $C_{28}H_{25}F_3NO_4$ [M + H] 496.1736; found 496.1747.

**4-Benzyl-2-methyl (2*R**,4*R**,5*S**)-5-(4-Chlorophenyl)-3,3,4-trifluoro-2-methylpyrrolidine-2,4-dicarboxylate (3Ai):** $^1$H NMR (500.13 MHz, $CDCl_3$, TMS): $\delta$ = 1.60–1.63 (m, 3 H), 3.60–4.20 (m, 4 H), 4.58 (m, 1 H), 4.95 (d, $J$ = 2.0 Hz, 2 H), 7.00–7.04 (m, 2 H), 7.12–7.21 (m, 4 H), 7.25–7.35 (m, 3 H) ppm. $^{13}$C NMR (125.75 MHz, $CDCl_3$, TMS): $\delta$ = 19.8 (dd, $J$ = 1.9, 7.7 Hz), 53.3, 62.7 (dd, $J$ = 5.2, 22.0 Hz), 67.9, 68.6 (dt, $J$ = 1.3, 23.6 Hz), 98.3 (ddd, $J$ = 20.0, 29.3, 221.7 Hz), 125.0 (ddd, $J$ = 18.5, 268.2, 283.1 Hz), 127.0, 128.5, 128.68, 128.73, 128.8, 132.5, 133.8, 134.2, 163.6 (d, $J$ = 27.7 Hz), 169.2 (d, $J$ = 2.8 Hz) ppm. $^{19}$F NMR (84.10 MHz, $CDCl_3$, $CFCl_3$): $\delta$ = –104.10 (dd, $J$ = 4.4, 243.1 Hz, 1 F), –109.65 (dd, $J$ = 4.4, 243.1 Hz, 1 F), –165.07 (dd, $J$ = 4.4, 13.2 Hz, 1 F) ppm. IR (KBr): $\tilde{\nu}$ = 3308, 3028, 2964, 2926, 1767, 1746, 1497, 1458, 1437, 1288, 1207, 1184, 1074, 955, 899, 826, 754, 696, 621 cm$^{-1}$. HRMS (FAB): calcd. for $C_{21}H_{20}{}^{35}ClF_3NO_4$ [M + H] 442.1033; found 442.1037.

**4-Benzyl-2-methyl (2*R**,4*R**,5*S**)-2-Benzyl-5-(4-chlorophenyl)-3,3,4-trifluoropyrrolidine-2,4-dicarboxylate (3Aj):** $^1$H NMR (500.13 MHz, $CDCl_3$, TMS): $\delta$ = 3.10–3.14 (m, 1 H), 3.41 (dd, $J$ = 2.1, 14.0 Hz, 1 H), 3.55–3.70 (m, 1 H), 3.74 (s, 3 H), 4.68–4.76 (m, 1 H), 4.94 (s, 2 H), 7.00–7.03 (m, 2 H), 7.15–7.20 (m, 2 H), 7.21–7.41 (m, 10 H) ppm. $^{13}$C NMR (125.75 MHz, $CDCl_3$, TMS): $\delta$ = 36.6 (dd, $J$ = 2.7, 6.8 Hz), 52.9, 62.5 (dd, $J$ = 3.8, 22.4 Hz), 67.9, 72.6 (t, $J$ = 22.2 Hz), 98.4 (ddd, $J$ = 21.0, 28.2, 220.0 Hz), 124.8 (ddd, $J$ = 19.4, 272.1, 281.4 Hz), 127.1, 127.2, 128.1, 128.4, 128.6, 128.7, 128.8, 130.5, 132.6, 133.8, 134.2, 134.4, 163.4 (d, $J$ = 27.4 Hz), 167.7 ppm. $^{19}$F NMR (282.38 MHz, $CDCl_3$, $CFCl_3$): $\delta$ = –106.80 (d, $J$ = 242.8 Hz, 1 F), –107.86 (dd, $J$ = 5.6, 242.8 Hz, 1 F), –165.28 (d, $J$ = 19.8 Hz, 1 F) ppm. IR (KBr): $\tilde{\nu}$ = 3317, 3036, 2953, 1736, 1495, 1458, 1439, 1379, 1319, 1258, 1213, 1070, 1040, 1013, 932, 908, 826, 750, 719, 698, 604 cm$^{-1}$. HRMS (FAB): calcd. for $C_{27}H_{24}{}^{35}ClF_3NO_4$ [M + H] 518.1346; found 518.1339.

**4-Benzyl-2-methyl (2*R**,4*R**,5*S**)-5-(4-Chlorophenyl)-3,3,4-trifluoro-2-(2-propyl)pyrrolidine-2,4-dicarboxylate (3Ak):** $^1$H NMR (500.13 MHz, $CDCl_3$, TMS): $\delta$ = 1.04 (d, $J$ = 6.56 Hz, 3 H), 1.09 (d, $J$ = 6.69 Hz, 3 H), 2.46–2.54 (m, 1 H), 3.70–3.81 (m, 4 H), 4.53–4.62 (m, 1 H), 4.91 (s, 2 H), 6.97–7.03 (m, 2 H), 7.13–7.21 (m, 4 H), 7.23–7.36 (m, 3 H) ppm. $^{19}$F NMR (282.38 MHz, $CDCl_3$, $CFCl_3$): $\delta$ = –105.92 (dd, $J$ = 8.5, 249.9 Hz, 1 F), –106.86 (d, $J$ = 249.9 Hz, 1 F), –170.30 to –170.50 (m, 1 F) ppm. IR (neat): $\tilde{\nu}$ = 2957, 2885, 1747, 1705, 1597, 1576, 1497, 1456, 1437, 1387, 1271, 1219, 1188, 1159, 1092, 1061, 1014, 947, 910, 824, 754, 731, 698 cm$^{-1}$. HRMS (FAB): calcd. for $C_{23}H_{24}{}^{35}ClF_3NO_4$ [M + H] 470.1346; found 470.1344.

**4-Benzyl-2-methyl (2*R**,4*R**,5*S**)-5-(4-Chlorophenyl)-3,3,4-trifluoro-2-(2-thiomethoxyethyl)pyrrolidine-2,4-dicarboxylate (3Al):** $^1$H NMR (500.13 MHz, $CDCl_3$, TMS): $\delta$ = 2.02–2.18 (m, 4 H), 2.30–2.38 (m, 1 H), 2.44–2.52 (m, 1 H), 2.66–2.73 (m, 1 H), 3.68–3.89 (m, 4 H), 4.46–4.53 (m, 1 H), 4.94 (s, 2 H), 6.96–7.38 (m, 9 H) ppm. $^{13}$C NMR (125.75 MHz, $CDCl_3$, TMS): $\delta$ = 15.5, 28.3, 30.6 (d, $J$ = 5.4 Hz), 53.3, 62.6 (dd, $J$ = 4.8, 22.1 Hz), 68.0, 71.4 (t, $J$ = 22.4 Hz), 98.3 (ddd, $J$ = 20.2, 29.2, 221.7 Hz), 125.1 (ddd, $J$ = 18.5, 268.7, 282.7 Hz), 126.9, 128.5, 128.69, 128.74, 128.8, 132.4, 133.8, 134.2, 163.5 (d, $J$ = 28.3 Hz), 168.1 (d, $J$ = 2.6 Hz) ppm. $^{19}$F NMR (84.10 MHz, $CDCl_3$, $CFCl_3$): $\delta$ = –105.45 (d, $J$ = 244.3 Hz, 1 F), –108.75 (dd, $J$ = 4.4, 244.3 Hz, 1 F), –165.26 (dd, $J$ = 4.4, 15.4 Hz, 1 F) ppm. IR (neat): $\tilde{\nu}$ = 3314, 2955, 2918, 2851, 1751, 1601, 1497, 1437, 1406, 1381, 1346, 1271, 1213, 1092, 1036, 1016, 911, 908, 827, 752 cm$^{-1}$. HRMS (FAB): calcd. for $C_{23}H_{24}{}^{35}ClF_3NO_4S$ [M + H] 502.1067; found 502.1064.

**4-Benzyl-2-methyl (2*R**,4*R**,5*S**)-5-(4-Chlorophenyl)-3,3,4-trifluoro-2-(2-methoxycarbonylmethyl)pyrrolidine-2,4-dicarboxylate (3Am):** $^1$H NMR (500.13 MHz, $CDCl_3$, TMS): $\delta$ = 2.88–2.94 (m, 1 H), 3.30 (dd, $J$ = 2.2, 16.5 Hz, 1 H), 3.68 (s, 3 H), 3.84–4.03 (m, 4 H), 4.53–4.58 (m, 1 H), 4.92 (d, $J$ = 11.5 Hz, 1 H), 4.97 (d, $J$ = 11.5 Hz, 1 H), 7.01–7.35 (m, 9 H) ppm. $^{13}$C NMR (125.75 MHz, $CDCl_3$, TMS): $\delta$ = 36.8 (dd, $J$ = 2.1, 6.7 Hz), 52.0, 53.5, 63.0 (dd, $J$ = 4.8, 22.5 Hz), 68.0, 69.7 (t, $J$ = 20.3 Hz), 98.1 (ddd, $J$ = 19.4, 29.4, 219.3 Hz), 124.7 (ddd, $J$ = 19.4, 269.1, 283.1 Hz), 127.1, 128.5, 128.7, 128.8, 128.9, 132.1, 133.7, 134.2, 163.0 (d, $J$ = 27.9 Hz), 167.4 (d, $J$ = 3.0 Hz), 169.4 (d, $J$ = 4.1 Hz) ppm. $^{19}$F NMR (84.10 MHz, $CDCl_3$, $CFCl_3$): $\delta$ = –104.73 (d, $J$ = 246.4 Hz, 1 F), –109.35 (dd, $J$ = 4.4, 246.4 Hz, 1 F), –164.35

(dd, $J$ = 4.4, 15.4 Hz, 1 F) ppm. IR (neat): $\tilde{\nu}$ = 3314, 3034, 2955, 1744, 1703, 1597, 1497, 1456, 1439, 1364, 1335, 1286, 1213, 1092, 1059, 1014, 952, 827, 752, 737, 698 $cm^{-1}$. HRMS (FAB): calcd. for $C_{23}H_{22}{}^{35}ClF_3NO_6$ [M + H] 500.1088; found 500.1095.

**Benzyl (*E*)-4-Amino-2,3-difluoro-5-methoxycarbonyl-4-phenyl-2-pentenoate (5Aa):** $^1$H NMR (500.13 MHz, $CDCl_3$, TMS): $\delta$ = 2.10–2.60 (m, 2 H), 3.77 (s, 3 H), 5.32 (s, 2 H), 7.33–7.42 (m, 8 H), 7.56–7.60 (m, 2 H) ppm. $^{13}$C NMR (125.75 MHz, $CDCl_3$, TMS): $\delta$ = 53.6, 65.8 (dd, $J$ = 2.9, 24.3 Hz), 67.6, 127.0, 128.36, 128.40, 128.59, 128.62, 128.8, 134.7, 136.5, 139.2 (dd, $J$ = 42.1, 242.2 Hz), 159.0 (dd, $J$ = 6.2, 31.2 Hz), 159.5 (dd, $J$ = 43.9, 274.1 Hz), 170.4 (d, $J$ = 4.4 Hz) ppm. $^{19}$F NMR (84.10 MHz, $CDCl_3$, $CFCl_3$): $\delta$ = –130.69 (d, $J$ = 134.2 Hz, 1 F), –159.86 (d, $J$ = 134.2 Hz, 1 F) ppm. IR (KBr): $\tilde{\nu}$ = 3385, 3312, 2960, 1718, 1684, 1655, 1456, 1398, 1350, 1261, 1234, 1186, 1080, 1032, 798, 710, 696 $cm^{-1}$. HRMS (FAB): calcd. for $C_{19}H_{18}F_2NO_4$ [M + H] 362.1204; found 362.1206.

**Benzyl (*E*)-4-Amino-4-benzyl-2,3-difluoro-5-methoxycarbonyl-2-pentenoate (5Aj):** $^1$H NMR (500.13 MHz, $CDCl_3$, TMS): $\delta$ = 1.90–2.30 (m, 2 H), 3.26 (d, $J$ = 13.6 Hz, 1 H), 3.36 (d, $J$ = 13.6 Hz, 1 H), 3.78 (s, 3 H), 5.32 (s, 2 H), 7.16–7.21 (m, 2 H), 7.27–7.42 (m, 8 H) ppm. $^{13}$C NMR (125.75 MHz, $CDCl_3$, TMS): $\delta$ = 40.4 (dd, $J$ = 2.1, 5.3 Hz), 53.2, 63.3 (dd, $J$ = 3.2, 22.2 Hz), 67.5, 127.7, 128.3, 128.57, 128.63, 128.66, 130.3, 133.6, 134.7, 139.7 (dd, $J$ = 42.1, 241.4 Hz), 158.9 (dd, $J$ = 6.0, 30.8 Hz), 159.5 (dd, $J$ = 42.0, 279.3 Hz), 171.0 ppm. $^{19}$F NMR (282.38 MHz, $CDCl_3$, $CFCl_3$): $\delta$ = –131.56 (d, $J$ = 132.7 Hz, 1 F), –161.70 (d, $J$ = 132.7 Hz, 1 F) ppm. IR (neat): $\tilde{\nu}$ = 3034, 2955, 1734, 1684, 1653, 1608, 1497, 1456, 1437, 1387, 1323, 1184, 1082, 1014, 912, 818, 735, 700 $cm^{-1}$. HRMS (FAB): calcd. for $C_{20}H_{20}F_2NO_4$ [M + H] 376.1360; found 376.1357.

**Benzyl (*E*)-4-Amino-2,3-difluoro-5-methoxycarbonyl-4-(2-propyl)-2-pentenoate (5Ak):** $^1$H NMR (500.13 MHz, $CDCl_3$, TMS): $\delta$ = 0.97 (d, $J$ = 7.0 Hz, 3 H), 1.02 (d, $J$ = 6.5 Hz, 3 H), 1.82–2.05 (m, 2 H), 2.45–2.55 (m, 1 H), 3.77 (s, 3 H), 5.30 (s, 2 H), 7.28–7.41 (m, 5 H) ppm. $^{13}$C NMR (125.75 MHz, $CDCl_3$, TMS): $\delta$ = 17.1, 17.2, 32.6 (t, $J$ = 1.9 Hz), 53.0, 66.2 (dd, $J$ = 3.5, 21.2 Hz), 67.4, 128.3, 128.5, 128.6, 134.8, 140.1 (dd, $J$ = 42.6, 242.3 Hz), 159.1 (dd, $J$ = 6.0, 31.1 Hz), 160.1 (dd, $J$ = 41.5, 277.9 Hz), 171.2 ppm. $^{19}$F NMR (282.38 MHz, $CDCl_3$, $CFCl_3$): $\delta$ = –131.34 (d, $J$ = 132.7 Hz, 1 F), –161.10 (d, $J$ = 132.7 Hz, 1 F) ppm. IR (neat): $\tilde{\nu}$ = 3342, 3034, 2970, 2881, 1736, 1670, 1608, 1558, 1541, 1499, 1456, 1437, 1389, 1329, 1184, 1126, 995, 914, 826, 737, 698 $cm^{-1}$. HRMS (FAB): calcd. for $C_{16}H_{20}F_2NO_4$ [M + H] 328.1360; found 328.1356.

**Typical Procedure for the Preparation of (*R*)-1-Phenylethyl 2,3,3-Trifluoroacrylate (1B*):** (*R*)-1-Phenylethyl 2-bromo-2,3,3,3-tetrafluoropropionate (2.31 g, 7.01 mmol) was dissolved in dry $Et_2O$ (5 mL), and this solution was added to a stirred suspension of zinc (0.50 g, 7.71 mmol) and diethylaluminium chloride (0.92 M hexane solution; 0.76 mL, 0.70 mmol) in dry $Et_2O$ (10 mL) at room temperature. After 30 min, the reaction mixture was quenched with satd. aq. ammonium chloride solution. Then, the unreacted zinc powder was removed by filtration. The mixture was extracted with ethyl acetate (3 ×). The combined organic layers were dried with anhydrous sodium sulfate, filtered, and concentrated. The yield of product was determined by $^{19}$F NMR spectroscopy in the presence of ethyl trifluoroacetate (10 µL, 0.084 mmol), and then the crude mixture was purified by silica gel column chromatography to give pure (*R*)-1-phenylethyl 2,3,3-trifluoroacrylate (**1B***).

**(*R*)-1-Phenylethyl 2,3,3-Trifluoroacrylate (1B*):** $^1$H NMR (500.13 MHz, $CDCl_3$, TMS): $\delta$ = 1.61 (d, $J$ = 6.8 Hz, 3 H), 6.06 (q, $J$ = 6.8 Hz, 1 H), 7.28–7.38 (m, 5 H) ppm. $^{13}$C NMR (125.75 MHz, $CDCl_3$, TMS): $\delta$ = 22.1, 74.6, 122.1 (ddd, $J$ = 19.0, 19.1, 238.3 Hz), 126.1, 128.3, 128.6, 140.3, 158.06 (dt, $J$ = 41.6, 300.4 Hz), 158.12 (td, $J$ = 7.8, 26.5 Hz) ppm. $^{19}$F NMR (84.10 MHz, $CDCl_3$, $CFCl_3$): $\delta$ = –84.41 (dd, $J$ = 20.9, 35.2 Hz, 1 F), –95.60 (dd, $J$ = 20.9, 113.4 Hz, 1 F), –183.75 (dd, $J$ = 35.2, 113.4 Hz, 1 F) ppm. IR (neat): $\tilde{\nu}$ = 2986, 2903, 1767, 1744, 1717, 1684, 1497, 1456, 1375, 1238, 1194, 1117, 1061, 1030, 1011, 995, 964, 932, 856, 762, 700 $cm^{-1}$. HRMS (FAB): calcd. for $C_{11}H_9F_3O_2$ $[M]^+$ 230.0555; found 230.0554.

**(L)-(–)-Menthyl 2,3,3-Trifluoroacrylate (1C*):** $^1$H NMR (500.13 MHz, $CDCl_3$, TMS): $\delta$ = 0.76 (d, $J$ = 7.0 Hz, 3 H), 0.87–0.95 (m, 7 H), 1.02–1.12 (m, 2 H), 1.42–1.56 (br. m, 2 H), 1.66–1.75 (br. m, 2 H), 1.81–1.88 (m, 1 H), 2.02–2.08 (br. m, 1 H), 4.84–4.92 (m, 1 H) ppm. $^{13}$C NMR (125.75 MHz, $CDCl_3$, TMS): $\delta$ = 16.2, 20.6, 21.9, 23.4, 26.2, 31.4, 34.0, 40.6, 46.8, 76.8, 122.0 (ddd, $J$ = 18.4, 38.4, 238.4 Hz), 158.0 (dt, $J$ = 42.1, 300.4 Hz), 158.6 (td, $J$ = 7.5, 26.0 Hz) ppm. $^{19}$F NMR (282.38 MHz, $CDCl_3$, $CFCl_3$): $\delta$ = –84.68 (dd, $J$ = 22.5, 35.5 Hz, 1 F), –95.98 (dd, $J$ = 22.5, 115.1 Hz, 1 F), –183.50 (dd, $J$ = 35.5, 115.1 Hz, 1 F) ppm.

**Typical Procedure for the Cycloaddition Reaction of 1B* with Imino Ester 2b:** *n*-Butyllithium (1.6 M hexane solution; 0.63 mL, 1.00 mmol) was added to a stirred solution of diisopropylamine (0.101 g, 1.00 mmol) in dry THF (1 mL) at 0 °C. Then the solution was cooled to –78 °C, and a solution of imino ester **2b** (0.32 g, 1.10 mmol) in dry THF (2 mL) was added. The mixture was stirred for 15 min at that temperature, then a solution of **1B*** (0.12 g, 0.50 mmol) in dry THF (1 mL) was added dropwise. The mixture was then stirred for a further 1 h at –78 °C, then the reaction mixture was quenched with satd. aq. ammonium chloride solution. The mixture was extracted with ethyl acetate (3 ×). The combined organic layers were dried with anhydrous sodium sulfate, filtered, and concentrated. The yield of product was determined by $^{19}$F NMR spectroscopy in the presence of ethyl trifluoroacetate (10 µL, 0.084 mmol), and then the crude mixture was purified by silica gel column chromatography to give pure cycloadduct **3Bb***.

**4-[(*R*)-1-Phenylethyl]-2-methyl (2*R*,4*R*,5*S*)- or (2*S*,4*R*,5*R*)-5-(4-Chlorophenyl)-3,3,4-trifluoro-2-phenylpyrrolidine-2,4-dicarboxylate (3Bb*):** Diastereomeric mixture. $^1$H NMR (500.13 MHz, $CDCl_3$, TMS): $\delta$ = 1.35 and 1.38 (d, $J$ = 6.7 Hz, 3 H, minor isomer, and d, $J$ = 6.6 Hz, 3 H, major isomer), 3.78 and 3.85 (s, 3 H, minor isomer, and s, 3 H, major isomer), 4.05–4.35 (m, 1 H), 4.44–4.57 (m, 1 H), 5.78 (m, 1 H), 7.05–7.44 (m, 12 H), 7.91–7.96 (m, 2 H) ppm. $^{13}$C NMR (125.75 MHz, $CDCl_3$, TMS): $\delta$ = 20.8 and 21.0 (major and minor isomers), 53.6 and 53.7 (minor and major isomers), 62.3 and 62.6 (dd, $J$ = 4.8, 22.6 Hz, major isomer, and dd, $J$ = 4.6, 22.7 Hz, minor isomer), 72.9 and 73.1 (t, $J$ = 23.2 Hz, minor isomer, and t, $J$ = 22.6 Hz, major isomer), 75.1 and 75.3 (minor and major isomers), 98.3 (ddd, $J$ = 20.4, 28.6, 220.8 Hz, major isomer), 121.8–124.5 (m, 1 C, major and minor isomers), 126.2, 126.4, 127.0, 127.3, 128.1, 128.26, 128.32, 128.4, 128.5, 128.72, 128.77, 128.79, 128.84, 132.6, 132.7, 133.1, 133.2, 133.4, 134.1, 134.3, 139.1, 139.3, 162.9 and 163.2 (d, $J$ = 28.4 Hz, major isomer, and d, $J$ = 26.9 Hz, minor isomer), 168.0 and 168.1 (minor and major isomers) ppm. $^{19}$F NMR (84.10 MHz, $CDCl_3$, $CFCl_3$): $\delta$ = –98.54 and –99.60 (d, $J$ = 239.8 Hz, 1 F, major isomer, and d, $J$ = 238.8 Hz, 1 F, minor isomer), –106.26 and –107.45 (dd, $J$ = 4.4, 239.8 Hz, 1 F, major isomer, and dd, $J$ = 6.6, 238.8 Hz, 1 F, minor isomer), –165.22 and –166.50 to –167.00 (dd, $J$ = 4.4, 13.2 Hz, 1 F, major isomer, and m, 1 F, minor isomer) ppm. IR (KBr): $\tilde{\nu}$ = 3325, 3036, 2955, 1747, 1686, 1655, 1599, 1497, 1456, 1435, 1404, 1377, 1352, 1325, 1271, 1182, 1092, 1053, 1014, 980, 930, 887, 850, 814, 746, 723, 698, 664, 638, 617 $cm^{-1}$. HRMS (FAB): calcd. for $C_{27}H_{24}{}^{35}ClF_3NO_4$ [M + H] 518.1346; found 518.1356.

**4-(L)-(–)-Menthyl-2-methyl (2*R*,4*R*,5*S*)-5-(4-Chlorophenyl)-3,3,4-trifluoro-2-phenylpyrrolidine-2,4-dicarboxylate (3Cb*):** $[\alpha]_D^{29}$ =

–49.5 ($c$ = 0.16, $CHCl_3$); *ee* ≥ 99 % *ee*, m.p. 160–162 °C. $^1$H NMR (500.13 MHz, $CDCl_3$, TMS): $\delta$ = 0.51 (d, $J$ = 6.9 Hz, 3 H), 0.64 (q, $J$ = 11.6 Hz, 1 H), 0.75 (d, $J$ = 7.0 Hz, 3 H), 0.83 (d, $J$ = 6.5 Hz, 3 H), 0.70–0.96 (m, 2 H), 1.07–1.18 (m, 1 H), 1.22–1.37 (m, 2 H), 1.38–1.46 (m, 1 H), 1.48–1.70 (m, 2 H), 3.83 (s, 3 H), 4.05–4.30 (m, 1 H), 4.43–4.57 (m, 1 H), 4.64 (dt, $J$ = 4.4, 11.0 Hz, 1 H), 7.32–7.50 (m, 7 H), 7.87–7.98 (m, 2 H) ppm. $^{13}$C NMR (125.75 MHz, $CDCl_3$, TMS): $\delta$ = 15.5, 20.7, 21.8, 22.9, 25.6, 31.2, 33.8, 39.7, 46.2, 53.7, 62.1 (dd, $J$ = 5.2, 22.3 Hz), 72.9 (t, $J$ = 23.5 Hz), 98.5 (ddd, $J$ = 20.2, 28.4, 222.8 Hz), 124.2 (ddd, $J$ = 18.5, 272.6, 281.2 Hz), 127.4, 128.16, 128.2 (d, $J$ = 3.3 Hz), 128.8, 129.0, 133.2, 133.6, 134.4, 163.6 (d, $J$ = 27.0 Hz), 168.3 ppm. $^{19}$F NMR (84.10 MHz, $CDCl_3$, $CFCl_3$): $\delta$ = –98.93 (d, $J$ = 239.5 Hz, 1 F), –107.64 (dd, $J$ = 5.6, 239.5 Hz, 1 F), –167.29 (dd, $J$ = 5.6, 16.9 Hz, 1 F) ppm. IR (KBr): $\tilde{\nu}$ = 3307, 2960, 2924, 2870, 1744, 1495, 1454, 1437, 1369, 1254, 1227, 1182, 1086, 1014, 982, 951, 895, 824, 795, 748, 733, 700 cm$^{-1}$. HRMS (FAB): calcd. for $C_{29}H_{32}{}^{35}ClF_3NO_4$ [M – H] 550.1972; found 550.1978.

**X-ray Structural Analysis:** A crystal of **3Cb*** (colourless prism) with approximate dimensions of 0.46 × 0.21 × 0.09 mm was mounted on a glass fibre. All measurements were made with a Rigaku AFC7R diffractometer using filtered Cu-$K_\alpha$ radiation and a rotating anode generator. Compound **3Cb***: monoclinic, $a$ = 18.970(4) Å, $b$ = 6.940(2) Å, $c$ = 11.090(2) Å, $\alpha$ = 90°, $\beta$ = 106.67(1)°, $\gamma$ = 90°, $V$ = 1398.7(5) Å$^3$, $T$ = 223.1 K, space group $P2_1$ (No. 4), $Z$ = 2, $\mu$(Cu-$K_\alpha$) = 1.5418 mm$^{-1}$, 3706 reflections measured, 3702 unique ($R_{int}$ = 0.057), which were used in all calculations. The final $R_1$ and $wR_2$ were 0.063 and 0.178 [$I > 2\sigma(I)$]. All calculations were carried out using the CrystalStructure crystallographic software package [Rigaku and Rigaku/MSC (2000–2003)] except for refinement, which was carried out using SHELXL-97. The structure was solved by direct methods (SIR2002) and expanded using Fourier techniques (DIRDIF99). The goodness of fit indicator was 1.093.

CCDC 1475841 (for **3Ab**) and 1475842 (for **3Cb***) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

**Keywords:** Fluorine · Cycloaddition · Cyclization · Diastereoselectivity · Nitrogen heterocycles

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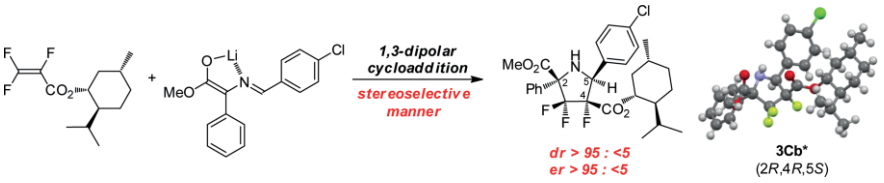
**Fluorinated Heterocycles**






New 3,3,4-trifluoropyrrolidines were easily obtained by 1,3-dipolar cycloaddition reactions of 2,3,3-trifluoroacrylate with imino esters derived from various phenylglycinates. The 1,3-dipolar cycloaddition was found to take place diastereoselectively. With the aid of a chiral auxiliary, the highly enantio- and diastereoselective synthesis of fluorinated pyrrolidine derivatives was achieved.

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