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Fluorinated Compounds

Intramolecular Cycloaddition Azomethine Ylides and α-(Trifluoromethyl)styrenes Moieties as Dipolarophiles

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Abstract: The synthesis of polycyclic fluorinated tertiary amines has been accomplished by means of an intramolecular azomethine ylide cycloaddition with fluorinated dipolarophiles. Thus, tri- and tetracyclic fused pyrrolidines bearing a quaternary trifluoromethyl group were obtained in moderated yields in a stereoselective manner. This is one of the few examples reported in the literature of intramolecular 1,3-dipolar cycloaddition of azomethine ylides with fluorinated dipolarophiles. Initial attempts of the asymmetric version of the process have been performed, but low levels of diastereoselectivity were achieved.

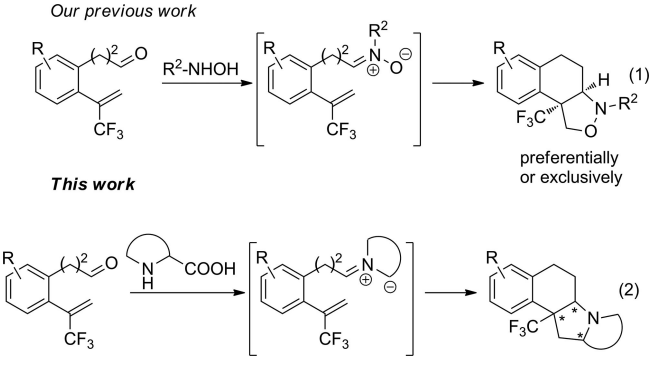
Introduction

1,3-Dipolar cycloadditions are one of the most reliable methodologies for the generation of five membered-ring heterocycles. Among the dipoles used in those transformations, azomethine ylides (AMY) are probably the most popular *N*-centered allyl type dipoles. Their reactions with alkenes enable the synthesis of highly substituted pyrrolidines with the generation of up to four stereocenters.[1] The pyrrolidine ring, either isolated or in a fused manner, is considered a privileged structure in medicinal chemistry that can be found in a great variety of alkaloids and biologically relevant compounds, and therefore, its construction in a stereodefined fashion has attracted high interest from synthetic organic chemists.[2]

Azomethine ylides are mostly generated in situ due to their high reactivity, in the presence of the dipolarophile, undergoing the subsequent cycloaddition, either in an inter- or intramolecular fashion. Several methods have been devised for AMY generation, being one of the most popular the condensation of an aldehyde precursor with a secondary amine, which generates an iminium ion that is deprotonated (in the case of secondary α-amino esters) or decarboxylates (in the case of α-amino acids). This method of preparation is commonly referred to as the iminium route.[3]

The use of azomethine ylide cycloadditions is prevalent in the literature and, therefore, the proficiency reached allows for the creation of a wide variety of pyrrolidines in a diastereoselective fashion. However, the use of fluorinated substrates lagged behind, especially in an intramolecular manner. While several examples of intermolecular reactions have been reported in the literature,[4] the intramolecular AMY cycloaddition reaction (AMYR) incorporating fluorine-containing substrates remained almost unexplored. Only four examples have been described to date; two of them take advantage of the use of difluorocarbene which generates the corresponding dipole by reaction with aryl and alkyl imines of O-acylated salicylaldehydes and then undergo the intramolecular cycloaddition.[5] The third employs a fluorinated dipolarophile, difluorinated allylic alcohol that reacted with the AMY generated from sarcosine.[6]The last one, recently described by our research group, involved the reaction of benzaldehydes bearing a trifluoromethyl alkene in ortho position with an azomethine ylide precursor derived from chiral 2-amino indanol, giving rise to fluorinated proline derivatives with excellent levels of diastereoselectivity.[7]

In previous work from our laboratory, we have introduced the use of triflurometyl styrenes as fluorinated dipolarophiles in intramolecular dipolar cycloadditions with nitrones (Scheme 1, Equation 1). We found that the role of the trifluoromethyl group is crucial in the regioselectivity of the reaction, directing the process to the major or exclusive formation of the fused derivatives.[8] Herein, we report the extension of this protocol to AMY cycloadditions. Thus, α-trifluoromethyl styrenes bearing an aldehyde in the *ortho* position were treated



Scheme 1. Intramolecular dipolar cycloadditions of α-trifluoromethyl styrenes.

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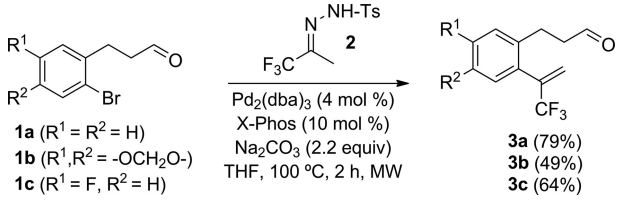
with α-amino acids, following the iminium route for the in situ generation of the AMY, which underwent cycloaddition with the fluorinated alkene in the reaction conditions.

In this manner, fluorinated polycyclic pyrrolidines were obtained with the simultaneous generation of up to three stereocenters (Scheme 1, Equation 2). In those cases, the chiral information of the amino acid is lost, and therefore, initial attempts of the asymmetric version of this process were performed with α-amino esters, specifically with homochiral substituted morpholin-2-ones which allow for the generation of chiral AMY.

Results and Discussion

Following the methodology disclosed by Valdés and co-workers,[9] the preparation of the starting ortho-substituted aldehydes **3a–c** was performed by means of a palladium-catalyzed cross-coupling reaction of 1,1,1-trifluoroacetone tosylhydrazone **2** with several orthobromoaldehydes **1**. Under the optimized reaction conditions, good to excellent yields of conveniently functionalized (trifluoromethyl)styrenes **3** were obtained, as depicted in Scheme 2. It is important to mention that those aldehydes **3** were not stable when stored even at low temperature, and have to be employed freshly prepared.

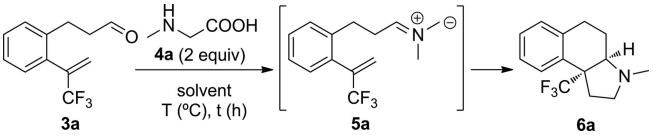


Scheme 2. Preparation of starting aldehydes **3**.

With the starting aldehydes **3** in hand, the next step of our study was the in situ formation of the corresponding AMY **5** by condensation with α-amino acids **4**. The optimization of the reaction conditions was performed with compound **3a** as a model substrate and sarcosine **4a**. In all cases, intermediate AMY **5a** cyclized under the reaction conditions in the 1,3-dipolar mode, hence rendering the corresponding fused pyrrolidine **6a** (Table 1).

An initial attempt was performed in analogous conditions to those described for the nitrone cycloaddition of substrates **3**, in toluene with 2 equiv. of sarcosine **4a** at 120 °C during 4 h. In this manner, tricyclic pyrrolidine **6a** was obtained in 40 % yield (Table 1, entry 1). Reducing the reaction time to 2 h, final adduct **6a** was obtained in 42 % yield (Table 1, entry 2). In both cases, total consumption of the starting material was observed. After 30 min, the reaction afforded only 16 % of the final product, but 60 % of the starting material was recovered unreacted (Table 1, entry 3). On the other hand, longer reaction times were not traduced in increased yields, and after 24 hours no final product was isolated, indicating that compound **6a** decompose in the reaction conditions (Table 1, entries 4, 5). Again, lower temperatures led to uncompleted reactions and the recovery of some starting material unreacted (Table 1, entry 6). The use of polar solvents such as DMF or acetonitrile did not translate into improved yields (Table 1, entries 7, 8). Finally, the

Table 1. Optimization of the reaction conditions.



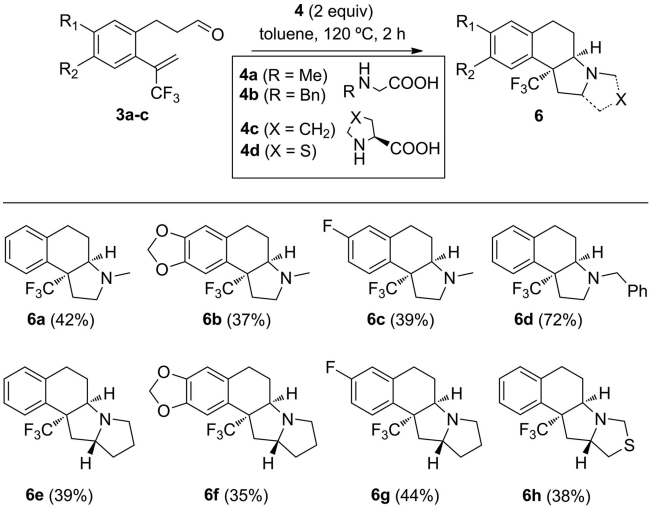
Entry	solvent	Time [h]	Temp. (° C)	Conv. [%]	Yield **6a** [%][a]
1	Toluene	4	120	100	40
2	Toluene	2	120	100	42
3	Toluene	0,5	120	40	18
4	Toluene	12	120	100	20
5	Toluene	24	Rt	100	–
6	Toluene	4	80	51	23
7	DMF	2	120	100	11
8	CH_3CN	2	120	100	30
9[b]	Toluene	2	120	100	18
10[c]	Toluene	2	120	100	44

[a] Isolated yield. [b] 1.2 equiv. of **4a** were used. [c] 4 equiv. of **4a** were used.

use of 1.2 equiv. of sarcosine **4a** produced a clear drop of the final yield (Table 1, entry 9), while the use of 4 equiv. afforded comparable results when compared with the reaction with 2 equiv. (Table 1, entry 10). These data indicate that there is a compromise between the stability of the starting aldehyde **3a** and final product **6a** and the temperature necessary to effect the cyclization. Optimum conditions involved the heating of **3a** with two equivalents of sarcosine **4a** in toluene at 120 °C for 2 h.

Having established the optimized reaction conditions for this transformation, we examined the scope of the reaction on the already synthesized family of starting materials **3a–c** and *N*-alkyl amino acids **4a-d**. The results are summarized in Table 2.

Table 2. Scope of the intramolecular AMY cycloaddition with fluorinated dipolarophiles.



Tricyclic (**6a-d**) and tetracyclic (**6e–h**) pyrrolidines were synthesized in moderate yields either with aromatic rings bearing electron deficient or electron donating properties. In all cases, final products were obtained as single diastereoisomers. In the case of compound **6d**, the reaction was performed in gram-

scale; starting from 850 mg of **3a**, 910 mg of **6d** were obtained (77 % yield), indicating that this process is suitable for scale-up.

The relative stereochemistry of the tri- and tetracyclic cycloaddition products **6** was determined by means of NMR experiments on compound **6h**. Heteronuclear correlation (HOESY) between the fluorine nuclei and proton H^3 allowed us to assign a cis relative stereochemistry between the trifluoromethyl group and this proton. Additional correlations with protons H^2, H^5 and H^7 were also observed (Figure 1). The interaction with H^5 is only possible if the relative relationship between the CF_3 and H^6 in anti; otherwise, with a cis disposition both protons H^5 would point out to the opposite direction avoiding the heteronuclear interaction. The same stereochemistry was assumed for all derivatives **6**.

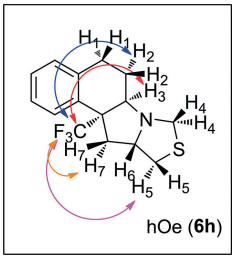
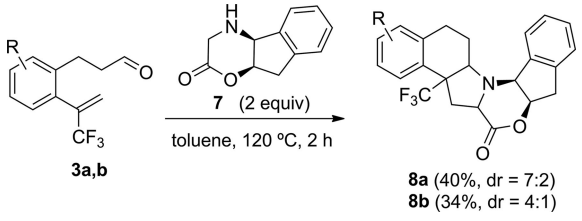


Figure 1. Heteronuclear correlations observed in compound **6g**.

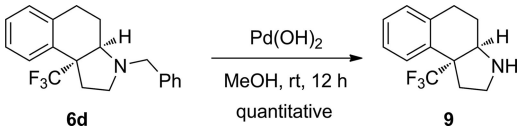
Preliminary attempts of the asymmetric version of the process were carried out. A very common and simple strategy to generate optically active azomethine ylides is the use of homochiral substituted morpholin-2-ones. These amino esters are chiral glycine equivalents which circumvent the unavoidable problem that the original chiral information present in the α-carbon of α-amino acid is necessarily lost in the moment of dipole generation. The group of Fukuyama applied the morpholinone strategy to the asymmetric total synthesis of alkaloid (–)-Lycoposerramine-S. They found that morpholinone 7 derived from (1R, 2S)-cis-1-amino-2-indanol was the best AMY precursor in terms of yield and selectivity.[10] We decided to explore this chiral AMY precursor in our intramolecular AMY cycloaddition. When substrates **3a,b** were treated with morpholinone **7** in the optimized conditions, moderated yields of the corresponding cycloadducts **8a,b** were obtained, as a mixture of two diastereoisomers with moderate levels of diastereoselection (Scheme 3). However, in both cases, it was not possible to separate them.



Scheme 3. Asymmetric approach of the intramolecular AMY cycloaddition.

Efforts to perform the asymmetric version of this protocol are currently underway.

Finally, the deprotection of compound **6d** was performed using $Pd(OH)_2$ as a catalyst in MeOH. The reaction took place at r.t. for 12 h to render deprotected pyrrolidine **9** in excellent yield, which enhances the utility of the methodology (Scheme 4).



Scheme 4. Deprotection of compound **6d**.

Conclusions

In conclusion, an intramolecular AMY cycloaddition with trifluoromethylstyrenes as fluorinated dipolarophiles have been devised. The process takes place in moderate yields and excellent levels of diastereoselectivity, affording tri- and tetracyclic pyrrolidines as single diastereomers in a very simple manner. This protocol constitutes the third example of an intramolecular AMY cycloaddition reaction using fluorinated dipolarophiles. Preliminary attempts of the asymmetric version were also performed, although only moderate levels of diastereoselectivity were achieved.

Experimental Section

Reactions were carried out under a nitrogen atmosphere unless otherwise indicated. Solvents were dried prior to use: THF and toluene were distilled from sodium, and CH_2Cl_2 was distilled from calcium hydride. The reactions were monitored with the aid of TLC on 0.25 mm precoated silica gel plates. Visualisation was carried out with UV light and potassium permanganate stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040–0.063 mm). ^1H, ^{19}F, and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts are given in ppm (δ), referenced to the residual proton resonances of the solvents. Coupling constants (J) are given in Hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet, and quartet, respectively. The designation br indicates that the signal is broad. The abbreviations DCM and THF indicate dichloromethane and tetrahydrofuran, respectively. A QTOF mass analyzer system has been used for the HRMS measurements. Starting materials **3** were previously described. See Supplementary Information for the spectra of all new compounds.

General Procedure for the Intramolecular AMY Cycloaddition of Substrates 3: A solution of aldehyde **3** (0.2 mmol, 1 equiv.) and the corresponding *N*-alkyl amino acid **4** (0.4 mmol, 2 equiv.) in toluene (1 mL, 0.2 M) was heated in a sealed tube at 120 °C for 2 h. The reaction was cooled to r.t., solvents evaporated under reduce pressure and the crude directly purified by flash column chromatography (Hex/ethyl acetate, 20:1).

3-Methyl-9b-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indol (6a): Following the general procedure described above, 29 mg (0.11 mmol) of **6a** were obtained as a pale yellow oil in 42 % yield from 62 mg of **3a** (0.271 mmol) and 48 mg of sarcosine **4a** (0.542 mmol). ^1H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.35 (m, 1H), 7.14–7.21 (m, 2H), 7.10 (m, 1H), 3.08 (t, *J* = 8.4 Hz, 1H), 2.60–2.83 (m, 4H), 2.47 (m, 1H), 2.39 (s, 3H), 2.10–2.21 (m, 2H), 1.70 (m, 1H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 138.7, 129.9 (q, *J* = 241.9 Hz), 129.6, 129.6, 128.5, 127.4, 126.6, 65.4, 55.4, 53.4 (q, *J* =

23.4 Hz), 40.2, 35.2, 25.8, 24.9. ^{19}F-NMR ($CDCl_3$, 282.4 MHz) δ (ppm): –71.2 (s, 3F). IR (cm^{-1}): ν̃ = 2921, 2830, 2792, 1489, 1190, 1156. HRMS (ESI/Q-TOF): *m/z* $[M + H]^+$ calcd. for $C_{14}H_{16}F_3N$: 256,1308, found 256,1318.

3-Methyl-10b-(trifluoromethyl)-2,3,3a,4,5,10b-hexahydro-1H-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-e]indol (6b): Following the general procedure described above, 21 mg (0.069 mmol) of **6b** were obtained as a pale yellow oil in 37 % yield from 50 mg of **3b** (0.184 mmol) and 33 mg of sarcosine **4a** (0.367 mmol). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.82 (d, *J* = 1.6 Hz, 1H), 6.57 (s, 1H), 5.90 (q, *J* = 1.4 Hz, 2H), 3.07 (t, *J* = 8.3Hz, 1H), 2.75 (dd, *J* = 6.3, 4.7 Hz, 1H), 2.67 (m, 1H), 2.58 (m, 1H), 2.91 (m, 1H), 2.44 (m, 1H), 2.37 (s, 3H), 2.11 (m, 2H), 1.68 (m, 1H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 146.8, 146.4, 132.6, 128.4 (q, *J* = 282.2 Hz), 128.0, 109.3, 108.3, 101.0, 66.2, 55.3, 53.4, 40.2, 35.2, 25.9, 24.8. ^{19}F-NMR ($CDCl_3$, 282.4 MHz) δ (ppm): –71.2 (s, 3F). IR (cm^{-1}): ν̃ = 2922, 2830, 2792, 1490, 1191, 1171. HRMS (ESI/Q-TOF): *m/z* $[M + H]^+$ calcd. for $C_{15}H_{16}F_3NO_2$: 300.1206, found 300.1220.

7-Fluoro-3-methyl-9b-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indol (6c): Following the general procedure described above, 22 mg (0.080 mmol) of **6c** were obtained as a pale yellow oil in 39 % yield from 50 mg of **3c** (0.203 mmol) and 36 mg of sarcosine **4a** (0.406 mmol). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.32 (m, 1H), 6.90 (td, *J* = 8.5, 2.8 Hz, 1H), 6.81 (dd, *J* = 9.3, 2.8 Hz, 1H), 3.07 (t, *J* = 8.4 Hz, 1H), 2.81–2.58 (m, 4H), 2.46 (m, 1H), 2.37 (s, 3H), 2.14 (m, 2H), 1.69 (m, 1H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 163.4, 160.1, 141.1, 131.3, 128.2 (q, *J* = 280.7 Hz), 114.8 (d, *J* = 20.7 Hz), 113.7 (d, *J* = 21.4Hz), 65.1, 55.3, 53.10 (q, *J* = 23.6 Hz), 40.1, 35.2, 25.9, 24.4. ^{19}F-NMR ($CDCl_3$, 282.4 MHz) δ (ppm): –71.3 (s, 3F). IR (cm^{-1}): ν̃ = 2945, 2844, 2789, 1487, 1454, 1142. HRMS (ESI/Q-TOF): *m/z* $[M + H]^+$ calcd. for $C_{14}H_{15}F_4N$: 274.1213, found 274.1212.

3-Benzyl-9b-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indol (6d): Following the general procedure described above, 52 mg (0.16 mmol) of **6d** were obtained as a pale yellow oil in 72 % yield from 50 mg of **3a** (0.219 mmol) and 73 mg of *N*-benzylglycine **4b** (0.438 mmol). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.37–7.06 (m, 9H), 4.04 (d, *J* = 13.0 Hz, 1H), 3.30 (d, *J* = 13.0 Hz, 1H), 3.12 (dd, *J* = 7.3, 4.9 Hz, 1H), 2.92–2.72 (m, 2H), 2.69–2.50 (m, 2H), 2.47–2.31 (m, 1H), 2.18–2.04 (m, 2H), 1.83–1.61 (m, 1H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 139.4, 139.3, 135.5, 129.6, 128.9, 128.5 (q, *J* = 282.1 Hz), 128.4, 128.3, 127.4, 127.1, 126.5, 63.9, 58.3, 53.7 (q, *J* = 23.4 Hz), 52.3, 34.9, 26.3, 26.1. ^{19}F-NMR (282 MHz, $CDCl_3$) δ = –71.31 (s, 3F). IR (cm^{-1}): ν̃ = 2938, 2834, 1493, 1452, 1275, 1115. HRMS (ESI/Q-TOF): *m/z* $[M + H]^+$ calcd. for $C_{20}H_{21}F_3N$: 332.1626, found 332.1620.

11a-(Trifluoromethyl)-6,6a,8,9,10,10a,11,11a-octahydro-5H-benzo[e]pyrrolo[1,2-a]indol (6e): Following the general procedure described above, 24 mg (0.085 mmol) of **6e** were obtained as a pale yellow oil in 39 % yield from 50 mg of **3a** (0.219 mmol) and 50 mg of proline **4c** (0.438 mmol). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.46 (m, 1H), 7.20 (m, 2H), 7.15 (m, 1H), 3.32 (m, 1H), 3.26–3.10 (m, 2H), 2.94 (m, 1H), 2.75–2.65 (m, 2H), 2.47 (dd, 1H, *J* = 12.4, 6.5 Hz). 7.32 (m, 1H), 6.90 (td, *J* = 8.5, 2.8 Hz, 1H), 6.81 (dd, *J* = 9.3, 2.8 Hz, 1H), 3.07 (t, *J* = 8.4 Hz, 1H), 2.81–2.58 (m, 4H), 2.46 (m, 1H), 2.37 (s, 3H), 2.14 (m, 2H), 1.69 (m, 1H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 138.7, 127.42 (q, *J* = 281.5 Hz), 129.4, 129.3, 128. 6 (q, *J* = 2.0 Hz), 127.6, 126.1, 125.6, 64.3, 61.9, 54.8 (q, *J* = 23.9 Hz), 53.6, 41.0, 32.3, 25.7, 24.5, 23.6. ^{19}F-NMR ($CDCl_3$, 282.4 MHz) δ (ppm): –70.5 (s, 3F). IR (cm^{-1}): ν̃ = 2939, 2867, 1489, 1452, 1284, 1142. HRMS (ESI/Q-TOF): *m/z* $[M + H]^+$ calcd. for $C_{16}H_{18}F_3N$: 282.1464, found 282.1463.

11a-(Trifluoromethyl)-6,6a,8,9,10,10a,11,11a-octahydro-5H-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-e]pyrrolo [1,2-a]indol (6f): Following the general procedure described above, 19 mg (0.058 mmol) of **6f** were obtained as a pale yellow oil in 35 % yield from 45 mg of **3b** (0.165 mmol) and 38 mg of proline **4c** (0.330 mmol). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.91 (s, 1H), 6.59 (s, 1H), 5.91 (s, 2H), 3.27 (m, 2H), 3.10–2.93 (m, 2H), 2.71–2.67 (m, 1H), 2.58 (ddd, *J* = 16.6, 5.7, 2.1 Hz, 1H), 2.37 (dd, *J* = 12.4, 6.5 Hz, 1H), 2.50–1.95 (m, 1H), 1.95–1.75 (m, 5H), 1.60–1.50 (m, 1H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 147.0, 146.0, 144.0, 132.5, 127.2 (q, *J* = 279.7 Hz) 108.7, 108.0, 100.9, 64.0, 61.8, 54.8, 53.5, 40.9, 32.2, 25.5, 24.5, 23.3. ^{19}F-NMR ($CDCl_3$, 282.4 MHz) δ (ppm): –70.7 (s, 3F). IR (cm^{-1}): ν̃ = 2939, 2868, 1487, 1457, 1286, 1145. HRMS (ESI/Q-TOF): *m/z* $[M + H]^+$ calcd. for $C_{17}H_{18}F_3NO_2$: 326.1362, found 326.1365.

3-Fluoro-11a-(trifluoromethyl)-6,6a,8,9,10,10a,11,11a-octahydro-5H-benzo[e]pyrrolo[1,2-a]indol (6g): Following the general procedure described above, 27 mg (0.090 mmol) of **6g** were obtained as a pale yellow oil in 44 % yield from 50 mg of **3c** (0.203 mmol) and 47 mg of proline **4c** (0.406 mmol). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.42 (m, 1H), 6.86 (m, 2H), 3.30 (m, 1H), 3.25–3.10 (m, 2H), 2.93 (m, 1H), 2.70 (m, 2H), 2.42 (m, 1H), 2.05 (dd, *J* = 12.4, 9.4 Hz, 1H), 1.95–1.70 (m, 5H), 1.56 (m, 1H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 163.5, 160.2, 141.2 (d, *J* = 7.5 Hz), 130.3, 127.1 (q, *J* = 282.3 Hz), 115.3 (d, *J* = 20.4 Hz), 113.3 (d, *J* = 20.4 Hz), 63.9, 61.7, 54.3 (q, *J* = 24.3 Hz), 53.4, 40.9, 33.3, 25.6, 24.5, 23.1. ^{19}F-NMR ($CDCl_3$, 282.4 MHz) δ (ppm): –70.8 (s, 3F). IR (cm^{-1}): ν̃ = 2938, 2867, 1497, 1456, 1284, 1145. HRMS (ESI/Q-TOF): *m/z* $[M + H]^+$ calcd. for $C_{16}H_{17}F_4NO$: 300.1370, found 300.1370.

11a-(Trifluoromethyl)-6,6a,10,10a,11,11a-hexahydro-5H,8H-benzo[e]thiazolo[3,4-a]indol (6h): Following the general procedure described above, 25 mg (0.084 mmol) of **6h** were obtained as a pale yellow oil in 38 % yield from 50 mg of **3a** (0.219 mmol) and 58 mg of (4R)-1,3-thiazolincarboxylic acid **4d** (0.438 mmol). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.45 (m, 1H), 7.23–7.20 (m, 2H), 7.16–7.12 (m, 1H), 4.10 (dd, *J* = 10.7 Hz, 2H), 3.51 (m, 1H), 3.42 (t, *J* = 3.0 Hz, 1H), 3.09–3.02 (m, 2H), 2.80–2.67 (m, 2H), 2.56 (dd, *J* = 13.0, 7.2 Hz, 1H), 2.33 (dd, *J* = 13.0, 5.9 Hz, 1H), 2.09–1.98 (m, 1H), 1.95–1.85 (m, 1H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 137.9, 130.9 (q, *J* = 278.4 Hz), 129.4, 129.0, 128.9, 127.8, 126.5, 66.3, 59.6, 57.8, 52.8 (q, *J* = 24.5 Hz), 40.4, 39.0, 24.0, 22.5. ^{19}F-NMR ($CDCl_3$, 282.4 MHz) δ (ppm): –70.1 (s, 3F). IR (cm^{-1}): ν̃ = 2938, 2860, 1490, 1452, 1264, 1044. HRMS (ESI/Q-TOF): *m/z* $[M + H]^+$ calcd. for $C_{15}H_{16}F_3NS$: 300.1343, found 300.1372.

(7aR,12bS)-4b-(Trifluoromethyl)-4b,5,5a,7a,12b,13a,14,15-octahydro-6H,8H-benzo[e]indeno[1′,2′:5,6][1,4]oxazino[4,3-a]indol-6-one (8a): Following the general procedure described above, 29 mg (0.074 mmol) of 8a were obtained as a pale yellow oil in 40 % yield from 42 mg of 3a (0.185 mmol) and 70 mg of morpholinone 7 (0.37 mmol). 8a was obtained as a 7:2 inspeparable mixture of diastereoisomers. NMR data correspond to the mixture of both diastereoisomers. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.52–7.12 (m, 10.4H), 5.54 (td, *J* = 4.3, 0.8 Hz, 1H), 5.28 (td, *J* = 5.7, 2.0 Hz, 0.3H), 4.86 (d, *J* = 5.9 Hz, 0.3H), 4.58 (d, *J* = 4.5 Hz, 1H), 4.20 (dd, *J* = 7.8, 4.9 Hz, 0.3H), 3.87–3.79 (m, 2H), 3.70 (t, *J* = 8.3 Hz, 0.3H), 3.33–2.95 (m, 4.9H), 2.90–2.60 (m, 2.6H), 2.55–2.40 (m, 0.6H), 2.37–2.22 (m, 1H), 2.10–1.96 (m, 1H), 1.93–1.78 (m, 0.3H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ = –70.90 (s, 3 F), –71.75 (s, 0.9 F).

(7aR,12bS)-4b-(Trifluoromethyl)-4b,5,5a,7a,12b,13a,14,15-octahydro-6H,8H-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-e]indeno[1′,2′:5,6]-[1,4]oxazino [4,3-a]indol-6-one (8b): Following the general procedure described above, 28 mg (0.063 mmol) of 8b were obtained as a pale yellow oil in 34 % yield from 50 mg of 3b (0.185 mmol) and

70 mg of morpholinone 7 (0.37 mmol). 8b was obtained as a 4:1 inspeparable mixture of diastereoisomers. NMR data correspond to the mixture of both diastereoisomers. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.33–7.20 (m, 5H), 6.89 (d, J = 1.3 Hz, 1H), 6.82 (d, J = 1.2 Hz, 0.25H), 6.64 (s, 1H), 6.61 (s, 0.25H), 5.98–5.93 (m, 2.5H), 5.51 (t, J = 3.9 Hz, 1H), 5.33–5.23 (m, 0.25H), 4.83 (d, J = 5.9 Hz, 0.25H), 4.55 (d, J = 4.4 Hz, 1H), 4.12 (dd, J = 7.5, 4.7 Hz, 0.25H), 3.82–3.78 (m, 2H), 3.66 (t, J = 8.3 Hz, 0.25H), 3.32–3.08 (m, 2.5H), 3.06–2.83 (m, 2H), 2.77–2.51 (m, 2.75H), 2.48–2.35 (dd, J = 14.0, 9.3 Hz, 0.5H), 2.31–2.14 (m, 1H), 2.09–1.90 (m, 1H), 1.90–1.76 (m, 0.25H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ = –71.04 (s, 3F), –71.89 (s, 0.75F).

(3aR,9bR)-9b-(Trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole (9): 29 mg (0.087 mmol) of **6d** were dissolved in a round-bottomed flask in MeOH and $Pd(OH)_2$/C (50 mol-% w/w) was added. The flask was put under H_2-atmosphere (balloon) and purged three times. After 16 h, the reaction mixture was filtered through Celite and the solvents evaporated to dryness to afford 21 mg (0.087 mmol) of **9** (quantitative yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.42–7.39 (m, 1H), 7.27–7.19 (m, 2H), 7.18–7.10 (m, 1H), 3.84 (dd, J = 9.6, 5.5 Hz, 1H), 3.49 (br s, 1H), 3.18–2.98 (m, 2H), 2.87–2.58 (m, 3H), 2.31–2.23 (m, 2H), 1.68–1.51 (m, 1H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 139.4, 134.0, 130.1, 128.5 (q, J = 282.2 Hz), 128.4, 127.7, 126.8, 60.2, 55.0 (q, J = 23.3 Hz), 45.7, 37.9, 27.8, 27.2. ^{19}F-NMR (282 MHz, $CDCl_3$) δ = –72.11 (s, 3F). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd. for $C_{13}H_{15}F_3N$:242.1157, found 242.1152.

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Keywords: Azomethine ylides · Cyclization · Cycloaddition · Synthetic methods · Trifluoromethyl group

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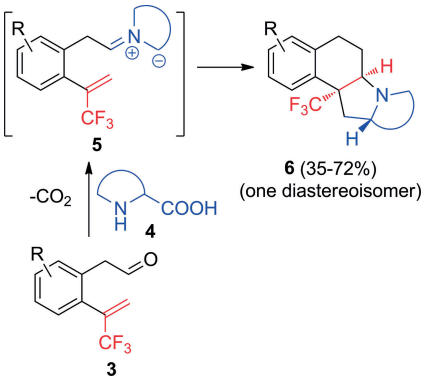
Fluorinated Compounds



The intramolecular azomethine ylide cycloaddition of α-trifluoromethyl styrenes gives rise to the formation of polycyclic fluorinated pyrrolidines. The process takes place in moderate yields and complete diastereoselectivity with the simultaneous generation of up to three stereocenters. Initial attempts of the asymmetric version have been also carried out.

Carlos del Pozo and co-workers (@FacQuimicaUVEG, @UV_EG) report an intramolecular cyclization between azomethine ylides and trifluoromethylstyrenes as dipolarophiles

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