First 1,3-Dipolar Cycloaddition of Azomethine Ylides with (*E*)-Ethyl 3-Fluoroacrylate: Regio- and Stereoselective Synthesis of Enantiopure Fluorinated Prolines

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Abstract: Enantiopure fluorinated prolines with four chiral centers were obtained from 1,3-dipolar cycloaddition of azomethine ylides and (*E*)-ethyl 3-fluoroacrylate.

Key words: 1,3-dipolar cycloaddition, fluoroolefins, azomethine ylides, fluorinated prolines

Nitrogen-containing heterocycles have attracted widespread attention in the field of synthetic organic chemistry as well as in medicinal chemistry.[1] In particular, the synthesis of pyrrolidines or prolines has received significant interest due to their known biological activity.[2] The 1,3-dipolar cycloaddition[3] (1,3-DC) of azomethine ylides with π-electronic-deficient olefins has emerged as a popular way for the obtainment of these heterocycles,[4] owing to its high synthetic efficiency and high regio- and stereoselectivity.

It is also well known that the synthesis of organic molecules containing a stereogenic (sp^3-hybridized) carbon atom bearing fluorine has increased greatly in the last decades, since enantiopure fluorine-containing heterocycles have shown great potential as drug candidates.[5]

While there is no doubt that the increasing need of structurally diverse fluorinated enantiopure heterocycles having biological relevancy calls for new synthetic strategies, few general methods to assemble enantiopure fluorinated heterocycles have been reported so far.[5a,b]

The different fluorine substitution in hydroxyprolines has been recently used as probe for stereoelectronic effects in the Xaa position of collagen.[6] Furthermore, it has been demonstrated that both 3-fluoroprolines and pyrrolidines can also be used for the production of recombinant bioadhesive protein analogues.[7a] These moieties have been also claimed as bactericides when incorporated in quinolone carboxylic acid based structures.[7b]

To the best of our knowledge, no methods for the direct formation of fluorinated enantiopure prolines using 1,3-DC have been reported in the literature.

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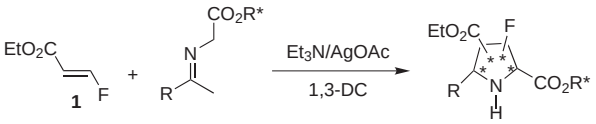


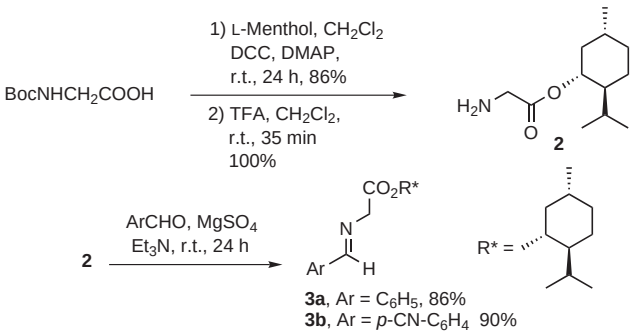
Scheme 1 1,3-DC of **1** with chiral azomethine ylides

Following our interest for the [3+2] cycloaddition of 1,3-dipoles with fluorine-containing dipolarophiles[8] we report herein the 1,3-DC of stabilized chiral N-metalated azomethine ylides with the F-containing π-deficient alkene (*E*)-ethyl 3-fluoroacrylate[9] (**1**) for the synthesis of enantiopure fluorinated prolines (Scheme 1).

According to the Scheme 1 this approach should allow a general entry to fluorinated pyrrolidines/prolines having up to four chiral centers giving a satisfactory control of the regio- and stereochemistry of the final heteroycles. We decided to use a chiral auxiliary incorporated into the α-imino esters in order to obtain in situ the chiral enantiopure azomethine ylides.[3a]

Thus, a solution of the NHBoc glycine was esterificated with L-menthol under mild conditions with DCC, DMAP in CH_2Cl_2 to give the ester in 86% yield and the removal of the Boc with TFA gave the free amine **2** in quantitative yield (Scheme 2).[10] We next prepared the α-imino esters **3a**,**b** which were obtained after condensation of **2**, with yields ranging between 86% and 90%, with two aromatic aldehydes (Scheme 2).[11]

Then we examined the conditions required for the cycloaddition of **1** with the azomethine ylides derived from α-iminoesters **3a**,**b**.[4c,d] The cycloaddition was carried out



Scheme 2 Synthesis of the chiral imines **3a**,**b**

in dry toluene using 1.5 equivalents of dry AgOAc and Et_3N at –40 °C for 6 hours since at room temperature we obtained lower yields in the cycloadducts. Analysis of the crude mixtures using ^{19}F NMR showed for each reaction only two new signals for the CH–F in a 9:1 ratio thus indicating the formation of two stereoisomers for each dipolar cycloaddition. After purification with column chromatography on silica gel of the two crudes we were able to obtain (Scheme 3) two diastereoisomeric mixtures containing the couple of the diastereoisomers **4a**,**a′** starting from **3a** (75% overall yield) and **5a**,**a′** starting from **3b** (82% yield).[12]

Semi-preparative HPLC allowed the separation of the enantiopure cycloadducts **4a**, **4a′**, **5a** and **5a′**. The regiochemistry of the adducts was easily demonstrated by the ^{13}C NMR spectra showing that no CH_2 signals were present in the adducts (Figure 1). To investigate the stereochemistry of the adducts, the first step was the assignment of the proton signals by standard 2D-NMR spectra (gCOSY, gHSQC and gHMBC), and then the determination of the relative configuration of the four stereogenic centers (2*R**,3*S**,4*S**,5*R**) by means of DPFGSE-NOE spectra,[13] obtained by selective saturation of the H_2,H_3,H_4, and H_5 signals.[14]

Absolute structure could be satisfactorily suggested by the analysis of the same NOE spectra, looking at the effects on the signals of the enantiopure (–)-menthol. In the case of **4a** and **5a**, selective saturation of H_3 shows additional NOE effects also on two menthol hydrogens, namely the α-CH–O and on the CH of the isopropyl group. NOE ratios show that the distances H_3–H_{R*CH} and H_3–H_4 are very similar, and that the distances H_3–H_{R*iPr} and H_3–H_4 are similar too. By inspecting the MM computed structure,[15] only the (–)-menthol-2*S*,3*R*,4*R*,5*S* structure could match the experimental NOE data. The same approach used for **4a′** and **5a′** suggests that in this case [i.e, the (–)-menthol-2*R*,3*S*,4*S*,5*R* structure], all the menthol hydrogens are too far from any pyrrolidine hydrogen, so only negligible NOE effect should be observed. Indeed, no NOE effects on the menthol hydrogen were experimentally observed, and the structure 2*R*,3*S*,4*S*,5*R* could be satisfactorily assigned.

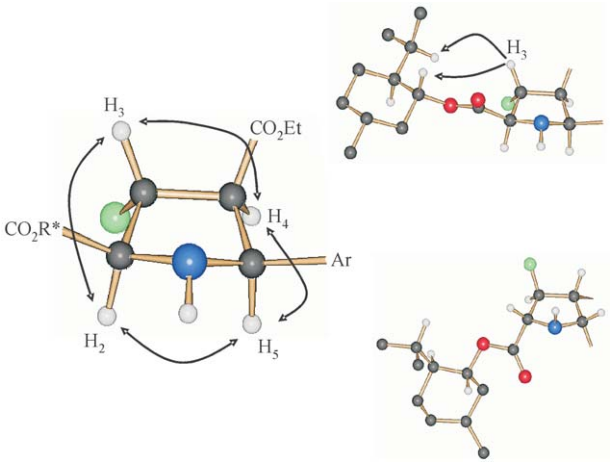
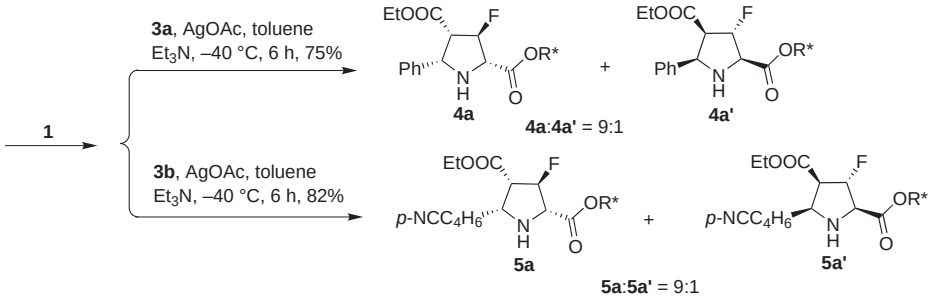
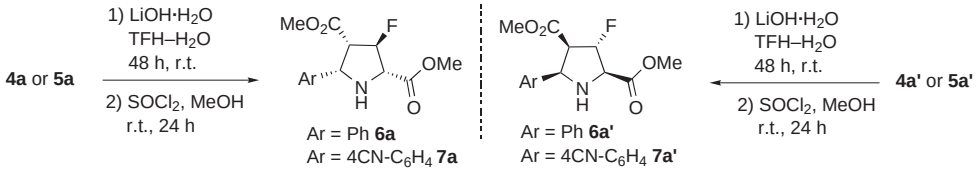


Figure 1 Left: experimentally observed NOE constraints (double ended arrows) for **4** and **5**. Right: calculated structures for **4a**, **5a** (upper) and **4a′**, **5a′** (lower). NOE effects on the (–)-menthol moiety observed for **4a** and **5a** are indicated by the arrows (the aryl groups and the CO_2R moieties are omitted for clarity).

The synthetic scheme was completed by careful hydrolysis of the chiral auxiliary under basic conditions. The removal of the L-menthol moiety took place in 48 hours at room temperature with LiOH in THF–H_2O in high yield for compounds **4a** and **4a′**, the subsequent esterification with $SOCl_2$ in MeOH at room temperature,[16] yielded the diesters **6a** and **6a′** in 50% and 54% yield which proved to be enantiomers by polarimetric measurements thus confirming the attribution of the four stereogenic centers by NMR in the starting cycloadducts (Scheme 4). The same results were obtained starting from **5a**,**a′**, which gave the two enantiomers **7a** and **7a′** in 50% and 52% yield.



Scheme 3 1,3-Dipolar cycloadditions of **1** with **3a**,**b**.



Scheme 4 Removal of the chiral auxiliary

In conclusion, we have developed a mild and general method for the efficient regio- and stereoselective synthesis of enantiopure pharmacologically important 3F-substituted prolines. These fluorinated heterocycles could be used for the creation of new biomaterials for medicinal applications.[6,7]

This approach offers an advantage over the direct nucleophilic fluorination of hydroxyl groups, which often gives side products and requires additional steps of protection–deprotection in the case of polyhydroxylated compounds. Moreover, this protocol overcomes the problems associated[17] with the difficult handling and toxicity of the most commonly used nucleophilic fluorinating reagents. The applications in other target-oriented 1,3-DC with fluorinated olefins calls for other studies in our laboratories and will be reported in due course.

Acknowledgment

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(10) A solution of BocNHglycine (3.5 g, 20.2 mmol) in 50 mL of CH_2Cl_2 was cooled to 0 °C. *N*,*N*-dicyclohexylcarbodiimide (4.18 g, 20.2 mmol) was added in several portions and a white precipitate formed quickly. After 10 min, L-menthol was added (3.78 g, 24.2 mmol) in 60 mL of CH_2Cl_2 and DMAP (110 g, 0.9 mmol). The mixture was stirred at r.t. for 24 h. After addition of H_2O (15 mL), the organic phase was extracted with Et_2O and dried over $MgSO_4$. The residue was purified on column chromatography on silica gel (PE–Et_2O, 2:1) to afford the L-menthol ester (5.4 g, 86%) as a yellow oil. $[\alpha]_D^{20}$ –46.5 (*c* 0.99, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.06 (s, 1 H), 4.70 (dt, 1 H, *J* = 12.3, 6.1 Hz), 3.83 (d, 2 H, *J* = 4.2 Hz), 1.98–1.90 (m, 1 H), 1.85–1.73 (m, 1 H), 1.67–1.59 (m, 2 H), 1.40 (s, 9 H), 1.37–1.29 (m, 1 H), 1.07–0.76 (m, 4 H), 0.85 (d, 3 H, *J* = 7.3 Hz), 0.84 (d, 3 H, *J* = 7.3 Hz), 0.70 (d, 3 H, *J* = 6.6 Hz). ^{13}C NMR (75.3 MHz, $CDCl_3$): δ = 169.7, 155.4, 79.2, 75.4, 46.8, 42.5, 40.7, 34.0, 31.3, 28.2, 26.1, 23.3, 21.9, 20.6, 16.2. MS (EI): *m/e* = 313 [M^+]. Standard procedures for the removal of the Boc were followed giving (1*R*,2*S*,5*S*)-**2** as a yellow oil. $[\alpha]_D^{20}$ –77.3 (*c* 0.50, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.60 (dt, 1 H, *J* = 12.2, 6.1 Hz), 3.32 (s, 2 H), 2.28 (s, 2 H), 1.92–0.60 (18H). ^{13}C NMR (75.3 MHz, $CDCl_3$): δ = 173.1, 74.3, 46.6, 43.3, 40.4, 33.8, 30.9, 25.8, 23.0, 21.5, 20.3, 15.9. MS (EI): *m/e* = 213 [M^+].

(11) For the condensation see ref. 4c and 4d. Starting from (1*R*,2*S*,5*S*)-**2** (860 mg, 4.0 mmol), Na_2SO_4 (3.2 g, 22.8 mmol) and PhCHO (0.4 mL, 4.0 mmol), 1.03 g (86%) of (1*R*,2*S*,5*S*)-**3a** as a yellow oil were obtained. $[\alpha]_D^{20}$ –54.0 (*c* 0.16, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.67–7.63 (m, 2 H), 7.32–7.26 (m, 3 H), 4.66 (dt, 1 H, *J* = 4.0, 11.3 Hz), 4.26 (s, 2 H), 1.93 (d, 1 H, *J* = 11.8 Hz), 1.84–1.73 (m, 1 H), 1.61–1.50 (m, 2 H), 1.44–1.24 (m, 2 H), 1.00–0.81 (m, 3 H), 0.77 (d, 6 H, *J* = 5.5 Hz), 0.64 (d, 3 H, *J* = 7.3 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 169.4, 164.9, 136.4, 128.7, 128.6, 128.5, 74.6, 62.4, 47.3, 41.2, 34.4, 31.4, 26.6, 23.8, 22.1, 20.8, 16.6. MS (ESI): *m/z* = 324 [M^+ + Na]. Starting from (1*R*,2*S*,5*S*)-**2** (1.67 g, 7.8 mmol), Na_2SO_4 (6.34 g, 44.6 mmol) and 4-CNC_6H_4CHO (1.03g, 7.8 mmol), 2.28 g (90%) of (1*R*,2*S*,5*S*)-**3b** as a yellow oil were obtained. $[\alpha]_D^{20}$ –42.4 (*c* 0.50, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.33 (s, 1 H), 7.89 (d, 2 H, *J* = 8.6 Hz), 7.72 (d, 2 H, *J* = 8.6 Hz), 4.87 (dt, 1 H, *J* = 11.0, 4.3 Hz), 4.43 (s, 2 H), 2.09–0.70 (m, 18 H). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 168.9, 163.1, 139.5, 132.5, 132.2, 129.4, 128.7, 118.4, 114.5, 75.0, 62.2, 47.3, 41.2, 34.3, 31.4, 26.7, 23.8, 22.1, 20.8, 16.6. MS (ESI): *m/z* = 349 [M^+ + Na].

(12) According to ref. 4c and 4d. Starting from **1** (212 mg, 1.8 mmol) and **3a** (541 mg, 1.8 mmol), 565 mg (75%) of **4a**,**a′** were obtained as mixture after column chromatography on silica with CH_2Cl_2–EtOAc 200:1. After column chromatography the two cycloadducts were subjected to semi-preparative HPLC separation. HPLC (hexane–*i*-PrOH gradient starting from 0.5% *i*-PrOH, to 11 min, then 1.05% *i*-PrOH to 25 min, then 2.25% *i*-PrOH).
Selected data for **4a**,**a′**.

L-Menthol-(2*S*,3*R*,4*R*,5*S*)-**4a**: elution time 9.00 min; yellow oil; $[\alpha]_D^{20}$ –60.5 (*c* 0.55, MeOH). ^{1}H NMR (600 MHz, C_6D_6): δ = 7.22–7.19 (m, 1 H), 7.02–6.95 (m, 4 H), 5.77 (ddd, 1 H, J_{HF} = 53.1 Hz, *J* = 3.1, 1.6 Hz), 4.99 (dt, 1 H, *J* = 11.1, 4.6 Hz), 4.62 (d, 1 H, *J* = 7.4 Hz), 4.21 (dd, 1 H, J_{HF} = 28.6 Hz, *J* = 3.1 Hz), 3.46 (dd, 1 H, *J* = 10.5, 7.3 Hz), 3.44 (dd, 1 H, *J* = 10.5, 7.3 Hz), 3.27 (ddd, 1 H, J_{HF} = 20.1 Hz, *J* = 7.2, 1.6 Hz), 3.11 (s, 1 H), 2.16–2.06 (m, 1 H), 1.47–1.34 (m, 3 H), 1.21–1.08 (m, 1 H), 0.99–0.60 (m, 3 H), 0.90 (d, 3 H, *J* = 7.6 Hz), 0.87 (d, 3 H, *J* = 7.6 Hz), 0.75 (d, 3 H, *J* = 7.1 Hz), 0.48 (t, 3 H, *J* = 7.6 Hz). ^{13}C NMR (150 MHz, C_6D_6): δ = 169.7 (d, J_{CF} = 9.6 Hz), 169.4 (d, J_{CF} = 14.0 Hz), 137.9, 128.0–127.4, 126.9, 98.3 (d, J_{CF} = 187.6 Hz), 75.5, 68.1 (d, J_{CF} = 24.6 Hz), 64.5, 60.0, 56.1 (d, J_{CF} = 22.2 Hz), 46.9, 40.6, 34.0, 31.1, 26.2, 23.1, 21.8, 20.7, 16.0, 13.2. ^{19}F NMR (376 MHz, C_6D_6): δ = –173.77 (ddd, J_{FH} = 51.9, 28.9, 21.0 Hz). MS (ESI): *m/z* = 419 [M$^+$].

L-Menthol-(2*R*,3*S*,4*S*,5*R*)-**4a′**: elution time 9.30 min; yellow oil; $[\alpha]_D^{20}$ –27.1 (*c* 0.75, MeOH). ^{1}H NMR (600 MHz, C_6D_6): δ = 7.23–7.21 (m, 1 H), 7.04–6.95 (m, 4 H), 5.71 (ddd, 1 H, J_{HF} = 52.8 Hz, *J* = 2.7, 1.6 Hz), 5.02 (dt, 1 H, *J* = 10.9, 4.8 Hz), 4.63 (d, 1 H, *J* = 6.8 Hz), 4.20 (dd, 1 H, J_{HF} = 28.7 Hz, *J* = 2.7 Hz), 3.45 (q, 2 H, *J* = 7.3 Hz), 3.27 (ddd, 1 H, J_{HF} = 20.1 Hz, *J* = 7.1, 1.5 Hz), 3.08 (s, 1 H), 2.18–2.13 (m, 1 H), 2.06–2.00 (m, 1 H), 1.48–0.58 (m, 7 H), 0.85 (d, 6 H, *J* = 7.0 Hz), 0.74 (d, 3 H, *J* = 6.5 Hz), 0.47 (t, 3 H, *J* = 7.6 Hz). ^{13}C NMR (150 MHz, C_6D_6): δ = 169.9 (d, J_{CF} = 9.3 Hz), 169.4 (d, J_{CF} = 12.3 Hz), 137.9, 128.0–127.4, 126.8, 98.4 (d, J_{CF} = 186.5 Hz), 75.3, 67.8 (d, J_{CF} = 25.9 Hz), 64.5, 60.0, 56.5 (d, J_{CF} = 24.2 Hz), 47.0, 40.7, 34.1, 31.2, 26.4, 23.4, 21.8, 20.6, 16.4, 13.2. ^{19}F NMR (376 MHz, C_6D_6): δ = –173.95 (ddd, J_{FH} = 48.9, 28.9, 19.9 Hz). MS (ESI): *m/z* = 419 [M$^+$].

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(14) In the case of **5a**, on selective saturation of the H_3 signal NOE effects were observed only on H_2 and H_4 (relative distance from H_3: 1.07:1.00), while saturation of H_4 showed NOE effects on H_5 and H_3 (relative distance from H_4: 1.00:1.14). Saturation of H_5 revealed strong NOE effects on H_2 and H_4 and a very small effect on H_3 (relative distance from H_5: 1.00:1.13:ca. 1.8); finally, saturation of H_2 revealed strong NOE effects on H_3 and H_5 and a not negligible effect on H_4 (relative distance from H_2: 1.09:1.00:1.33). These data imply a *trans* relationship between H_2 and H_3, a *trans* relationship between H_3 and H_4, and a *cis* relationship between H_4 and H_5. This concatenation (*trans*-*trans*-*cis*) corresponds to the 2*R**,3*S**,4*S**,5*R** configuration. Analogous data were obtained for **5a′**, **4a** and **4a′**.

(15) MMFF force field as implemented in Titan 1.0.5, Wavefunction, Inc. The standard conformational search was applied to **5a** and **5a′**, and the structures within 3 kcal/mol above the global minima were analyzed for the determination of the distances between the pyrrolidine hydrogens and the menthol hydrogens. In Figure 1 are reported the two global energy minima.

(16) (a) According to: Nyerges, M.; Bendell, D.; Arany, A.; Hibbs, D. E.; Coles, S. J.; Hursthouse, M. B.; Groundwater, P. W.; Meth-Cohn, O. *Synlett* **2003**, 947. (b) Selected data for **7a**,**a′**. Starting from **5a** (130 mg, 0.29 mmol) 44.3 mg (50%) of (2*S*,3*R*,4*R*,5*S*)-**7a** were obtained as a colorless oil; $[\alpha]_D^{20}$ 17.3 (*c* 0.2, MeOH). ^{1}H NMR (600 MHz, C_6D_6): δ = 7.32–7.28 (m, 2 H), 7.12–7.06 (m, 2 H), 5.71 (dd, 1 H, *J* = 52.0, 3.5 Hz), 4.50 (d, 1 H, *J* = 7.1 Hz), 4.15 (dd, 1 H, *J* = 27.9, 3.6 Hz), 3.45 and 3.40 (2 s, 6 H), 3.30 (dd, 1 H, *J* = 20.5, 7.0 Hz), 2.90 (s, 1 H, NH). ^{13}C NMR (150 MHz, C_6D_6): δ = 171.4 (d, *J* = 9.6 Hz), 170.6 (d, *J* = 11.5 Hz), 138.8, 128.7, 128.6, 127.1, 127.0, 117.2, 98.8 (d, *J* = 187.4 Hz), 67.5 (d, *J* = 26.2 Hz), 65.0, 64.6, 56.3 (d, *J* = 22.4 Hz), 52.6. ^{19}F NMR (376 MHz, C_6D_6): δ = –174.00 (ddd, J_{FH} = 51.0, 28.0, 20.7 Hz). MS (ESI): *m/z* = 306 [M$^+$]. Starting from **5a′** the same procedure gave (2*R*,3*S*,4*S*,5*R*)-**7a′** in 52% yield; $[\alpha]_D$ –17.8 (*c* 0.2, MeOH).

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