Highly enantioselective propargylic monofluorination established by carbon-13 and fluorine-19 NMR in chiral liquid crystals

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Carbon-13 and fluorine-19 NMR experiments in a chiral polypeptide liquid crystalline solvent (PBLG) are used to establish enantioselective propargylic monofluorination.

Fluorine strongly modifies the physical, chemical and biological properties of organic molecules, giving access to new drugs or pharmacological tools and useful agrochemicals.[1] Monofluorination remains a challenging problem in terms of regio- and stereo-control,[2] especially in positions vicinal to unsaturated systems, even if some transition metal complexes can control the dehydroxyfluorination.[3] An alternative is to prepare small, chiral, fluorinated building blocks which can be elaborated into the target molecules.[4] Since acetylenic derivatives have high potentialities for stereoselective synthesis,[5] propargylic fluorides should be versatile intermediates.[6] In this strategy, control of the absolute configuration at the stereogenic center is important, therefore the preparation of optically active propargylic fluorides becomes a central question.[7,8]

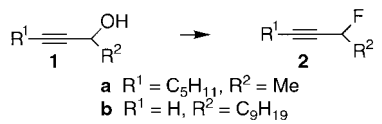
Here we report the first study of enantioselectivity in dehydroxyfluorination using alcohols **1a** and **1b** as models. Furthermore, we demonstrate NMR in chiral liquid crystals as a powerful method for the analysis of the enantiomeric purity of these propargylic fluorides.

The reaction of (±)-**1a** with diethylaminosulfur trifluoride (DAST) at −50 °C is regiocontrolled,[9] giving exclusively (55% yield) the propargylic fluoride (±)-**2a** (Scheme 1).[10] Such chiral propargylic fluorides appear rather difficult to discriminate, and until now, none of the usual tools in the field of enantiomeric analysis (chiral GC or HPLC, chiral shift reagents *etc.* have allowed the differentiation of the enantiomers of (±)-**2a** for instance. It was therefore of interest to explore other analytical approaches such as NMR in chiral liquid crystalline solvents.[11–13] Indeed, it has been demonstrated that ^{2}H, ^{13}C or ^{19}F NMR in organic solutions of poly(γ-benzyl L-glutamate) (PBLG) can provide a competitive alternative when normal methods fail. In proton-decoupled natural abundance ^{13}C NMR (^{13}C{^{1}H}), enantiomeric discrimination is observed through a difference in the ^{13}C chemical shift anisotropies (CSA), leading to two separated peaks for each discriminated carbon of the molecule. This allows the measurement of ees with an accuracy of about ±5%.[12] As the parameters governing the strength of the ^{13}C CSA mainly increases with the electronegativity of the substituents and the hybridization state of the carbons [$\Delta\sigma$ (sp) > $\Delta\sigma$ (sp^2) > $\Delta\sigma$ (sp^3)], we could expect to obtain a measurable chiral discrimination on the acetylenic carbons of the fluorinated propargylic compounds.[12]

Fig. 1(*a*) presents the 100.62 MHz ^{13}C{^{1}H} spectrum associated with the ethynyl carbons of (±)-**2a** recorded in the PBLG/$CHCl_3$ phase.†‡ Analysis of the spectrum shows two doublets centred at different chemical shifts for the C-1 and the C-2 carbons. The splittings, noted T_{CF}, arise from the ^{13}C–^{19}F scalar (J_{CF}) and dipolar (D_{CF}) couplings, the latter being also order sensitive ($T_{CF} = J_{CF} + 2D_{CF}$).[12] However, as indicated in Fig. 1(*a*), it appears that the two enantiomers are mainly discriminated through a difference of CSA. The chemical shift differences ($\delta_R - \delta_S$) for C-1 and C-2 are of 0.07 and 0.06 ppm, respectively. Note also that a small chiral discrimination was also observed on the sp^3 chiral carbon of (±)-**2a**.

With this tool in hand, it now becomes possible to study the enantioselectivity of the dehydroxyfluorination reaction on (+)-**1a** and (−)-**1a** at various temperatures. The synthesis of (+)-**1a** or (−)-**1a** (ee ⩾ 95%) is straightforward, starting from commercially available (*R*)- or (*S*)-but-3-yn-2-ol (Scheme 2). Fig. 1(*b*) presents the ^{13}C{^{1}H} NMR signals associated with the C-1 and C-2 carbons of (−)-**2a** prepared at −55 °C from (−)-**1a**. When comparing these data with that of (±)-**2a**, we clearly observe a difference in peak intensity for both sp carbons. The measurement of the ee for the spectrum in Fig. 1(*b*) is, therefore, possible using both the signal of C-1 and C-2, which enhances the confidence interval in the determination of the ee. Thus, at −55 °C, the ee calculated using either peak integration or deconvolution tools is 45 ± 5%, whereas the ee increases to 75 ± 5% when the reaction temperature is lowered to −95 °C. Note that the (*S*)-enantiomer exhibits the most shielded signal for both carbons and all these experimental values were confirmed when (−)-**1a** was replaced by (+)-**1a**.

Thus, the dehydroxyfluorination reaction of (+)-**1a** or (−)-**1a** has a good enantioselectivity (⩾75%) at low temperature. This



Scheme 1

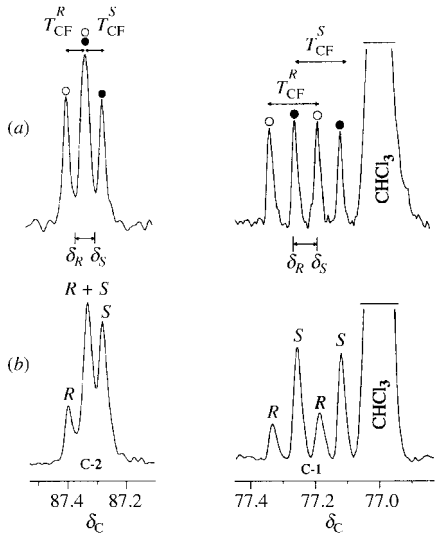
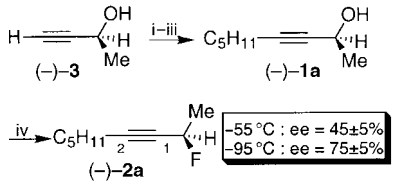
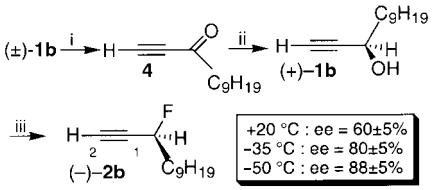


Fig. 1 ^{13}C{^{1}H} spectrum associated with the ethynyl carbons of (*a*) (±)-**2a** and (*b*) (−)-**2a** recorded at 298 K. Gaussian filtering was applied to enhance the spectral appearance. For (±)-**2a**, we measure T^R_{CF} = ± 14.9 Hz, T^S_{CF} = ± 14.4 Hz for the C-1 carbon, and T^R_{CF} = ± 6.9 Hz, for the C-2 carbon.



Scheme 2 *Reagents and conditions*: i, TBDMSCl, imidazole, DMAP, THF (84%); ii, BuLi, $C_5H_{11}Br$, THF–HMPA (3:1), −30 °C (85%); iii, Bu_4NF, THF (93%); iv, DAST, CH_2Cl_2 (55%).



Scheme 3 *Reagents and conditions*: i, PCC, AcONa, CH_2Cl_2 (56%); ii, *R*-Alpine-Borane (89%); iii, DAST, CH_2Cl_2 (51%).

reaction exhibits a strong temperature dependence since the ee is only 45% at *ca.* −55 °C. In agreement with the mechanism generally accepted for DAST fluorination,[14] inversion of configuration is assumed.

A similar sequence was followed by the case of **2b**. Starting from (±) = **1b**[6] the racemic derivative (±)-**2b** is obtained, together with a small amount of the corresponding enyne separated by chromatography. The optically active alcohol (+)-**1b** (ee = 90%) is obtained by asymmetric reduction of **4** (Scheme 3).[15] Once again, ^{13}C NMR in PBLG allowed the study of the enantioselectivity of the fluorination.

In this example, the results were also confirmed through 376.49 MHz $^{19}F\{^1H\}$ NMR. Fig. 2(*a*) presents the $^{19}F\{^1H\}$ spectrum and $^{13}C\{^1H\}$ NMR signal associated with the C-2 carbon of (±)-**2b**. As before, the analysis of the ^{13}C signal shows two doublets centred at two different chemical shifts ($\delta_S - \delta_R$ = 0.14 ppm). Note that the C-1 carbon was also significantly discriminated through a chemical shift difference ($\delta_S - \delta_R$ = 0.20 ppm). Unlike the compound (±)-**2a**, which showed no chiral discrimination *via* $^{19}F\{^1H\}$ NMR, the derivative (±)-**2b** exhibits specific ^{19}F CSAs for each enantiomer ($\delta_S - \delta_R$ = 0.03 ppm). This example is the first case of chiral discrimination through $^{19}F\{^1H\}$ NMR on a monofluorinated compound using a chiral liquid crystal.

Fig. 2(*b*) reports the $^{19}F\{^1H\}$ and $^{13}C\{^1H\}$ NMR signal of (−)-**2b** synthesised at −35 °C starting from (+)-**1b**. We can observe unambiguously the strong difference in intensity of the doublets of each enantiomer compared with (±)-**2b**, thus showing the high enantioselectivity of this reaction. For this example, the ee calculated through peak integration or deconvolution processes is 80 ± 5% at −35 °C. It is noteworthy that the synthesis of (+)-**2b** at −50 °C enable us to further enhance the ee to 88 ± 5%. Therefore, the dehydroxyfluorination of (+)-**1b** has a very high stereoselectivity (≥97%) at −50 °C. As for **1a**, the reaction shows a temperature dependence, since the ee is 80% at −35 °C and only 60% at room temperature. Note here that the (*R*)-enantiomer exhibits the most shielded signals for C-1 and C-2. These results were confirmed using (−)-**1b** as starting material.

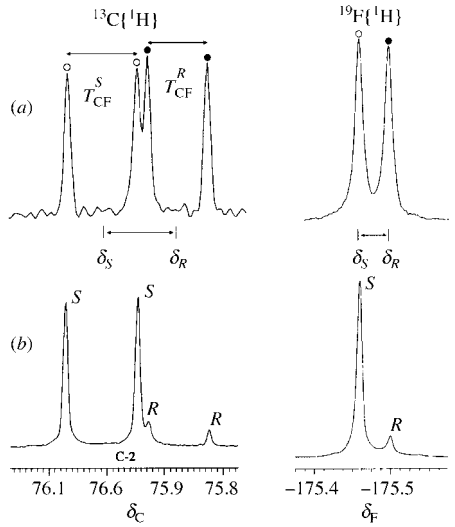


Fig. 2 $^{19}F\{^1H\}$ spectrum and $^{13}C\{^1H\}$ NMR signal associated to the C-2 carbon of (*a*) (±)-**2b** and (*b*) (−)-**2b** recorded at 294 K by adding 64 and 1500 scans, respectively. Gaussian filtering was applied to enhance the spectral appearance. For (±)-**2b**, we measure T_{CF}^S = ± 12.8 Hz, T_{CF}^R = ±11.1 Hz for the C-2 carbon.

These data appear to indicate a competition between S_N2 and S_N1 type processes. In the case of **1a**, the pentyl group can provide better stabilization for the carbocationic intermediate, leading to lower selectivities and a stronger temperature dependence compared to the hydrogen in **1b**. In addition, this study highlights the noteworthy potential of NMR in PBLG as an analytical method. Finally, these results, especially in the case of **2b**,[6] are of interest with regard to the preparation of fluorinated analogues of natural products.

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Notes and references

† *Sample composition*: The liquid crystalline NMR samples were made from 100 mg of PBLG (DP = 534), 100 mg of a chiral material and 350 mg of $CHCl_3$. Sample preparation, see refs. 11–13.

‡ *NMR experiments*: NMR experiments were performed on Bruker DRX-400 (5 mm BBI probe) and ARX-400 (5 mm QNP probe) spectrometers. Broad-band proton decoupling was applied using the WALTZ-16 sequence. The interferograms were acquired using a pulse angle of ~60°, a recycle delay of ~1.5 s and 8 or 16 K of data points. Zero filling to 16 or 32 K was applied to increase the digital resolution.

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