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A new strategy for the synthesis of optically active benzylic fluorides and corresponding five-membered heteroaromatic analogues

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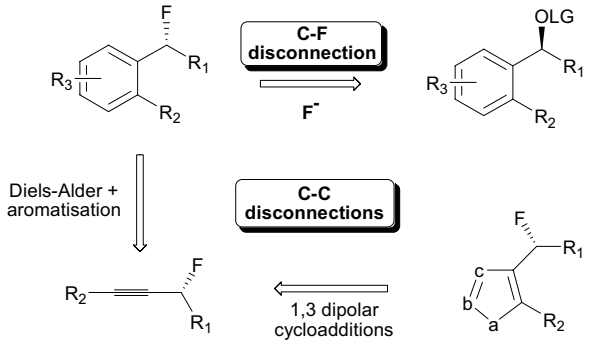
Abstract—Benzylic fluorides, as well as five-membered heterocycles, have been obtained in high ee's through cycloaddition reactions starting from easily accessible optically active propargylic fluorides.

The presence of fluorine atom(s) in organic molecules strongly modifies their physical, chemical and biological properties.[1] The selective replacement of C–H or C–OH bonds by C–F bonds has been already of much use in bioorganic and medicinal chemistry.[2] However, the stereoselective introduction of fluorine is often a key step in the preparation of target molecules, especially if optically active fluorides are required. Many bioactive molecules and/or drugs have an H or an OH in benzylic position. Therefore, their fluorinated analogues appear as potentially useful target molecules, especially in medicinal chemistry. However, due to synthetic problems, only a limited number of representative compounds have been prepared to date.[3] Their synthesis is even more challenging if optically active benzylic fluorides are considered. Only a few synthetic methods have been developed until now, and most of them use a C–F disconnection strategy starting from benzylic precursors.[4] Nucleophilic and dehydroxy-fluorination methods have been studied but they have strong limitations either in scope or in stereoselectivity, or both (Scheme 1). For instance, it has been clearly established that the substitution by F^- is highly stereocontrolled only if there is a strong electron-withdrawing group (R_3) in the para position to the benzylic fluoride chain. For other substituents, the stabilisation of the intermediate carbenium ions induced partial or complete racemisations.[5,6] On the other hand, for electrophilic fluorinations excellent results have been obtained, both under stoichiometric and catalytic reaction conditions, but they require in every case an electron-withdrawing group (R_1) to allow for the use of electrophilic fluorinating reaction conditions.[7]



Scheme 1. Strategy towards the synthesis of optically active benzylic fluorides and five-membered heterocycles.

As part of our programme in asymmetric monofluorination and applications to the synthesis of bioactive molecules analogue,[8] we designed a novel strategy towards such optically active benzylic fluorides, by using completely different disconnections: the basic idea was to start from easily accessible optically active propargylic fluorides[8,9] and to create the C–C bonds during the synthesis by Diels–Alder followed by aromatisation reactions (Scheme 1).

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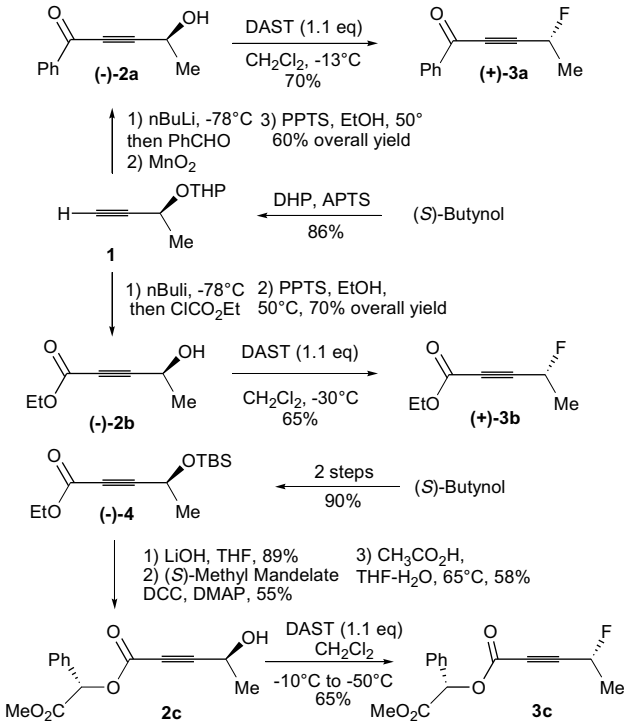
Another key advantage of this new approach is that it could be an easy entry towards heteroaromatic derivatives by using various cycloadditions such as the 1,3 dipolar cycloadditions. Furthermore, these primary adducts appear as versatile intermediates towards the preparation of chemical libraries. The purpose of this communication is to demonstrate, on selected examples, that such strategy has allowed the preparation of these target molecules with high ee's.

Two propargylic fluorides, (+)-**3a** and (+)-**3b**, have been selected as test molecules. They have been prepared by a diethylaminosulfurtrifluoride (DAST) mediated dehydroxy-fluorination route from the corresponding propargylic alcohols, as indicated in Scheme 2.

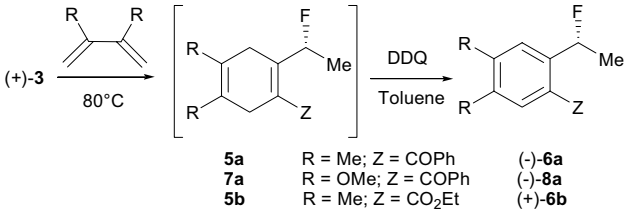
Ketone (−)-**2a** was prepared from (*S*)-butynol following literature procedures.[10] A similar two-step sequence was followed for the preparation of the ester (−)-**2b** in 70% overall yield from **1**. For both propargylic alcohols, NMR in the presence of $Eu(hfc)_3$ established a 96% ee. After optimisation of the reaction conditions, the dehydroxy-fluorination with DAST were performed at −13 °C in the case of (−)-**2a** and −30 °C for (−)-**2b**, affording the corresponding propargylic fluorides in 70% and 65% yields, respectively. On these fluorides, the ee's could not be established clearly, neither by NMR nor by chromatography on chiral columns. However since their cycloadducts demonstrated also ee's of 96%, as shown later, it was concluded that no racemisation has occurred during these fluorinations. As a complementary test the mandelate ester **2c** was also prepared in 28% overall yield and 96% de from (−)-**4**. Under the same conditions as for (−)-**2b** (at −30 °C), the dehydroxy-fluorination was completely stereoselective, affording **3c** in 96% de. The same yields and selectivities were obtained in reactions performed at −10 °C or at −50 °C.[11] These results are in agreement with previous studies on the dehydroxy-fluorination of propargylic alcohols with electron-withdrawing groups in the terminal position.[12]



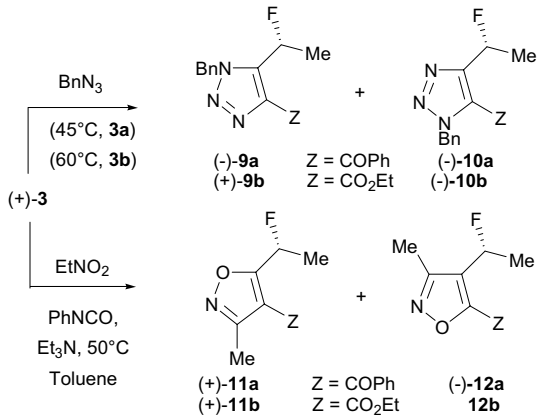
Scheme 2. Synthesis of the optically active propargylic fluorides.

In the next step, the Diels–Alder reaction was performed on (+)-**3a** with excess dimethylbutadiene under reflux, affording cyclohexadiene **5a**, characterized only by NMR and directly submitted to aromatisation by using DDQ in toluene. The benzylic fluoride (−)-**6a** was obtained in 65% overall yield from (+)-**3a** (Scheme 3). Its optical purity (96% ee) was easily established by ^1H and ^{19}F NMR in the presence of $Eu(hfc)_3$ and by comparison with the data obtained from a racemic sample prepared from (±)-**3a** by the same route. The same series of reactions were performed starting from (+)-**3a** and using 2,3-dimethoxybutadiene, affording (−)-**8a** in 51% overall yield. In the same way, (+)-**6b** was obtained in 46% overall yield from the reaction of (+)-**3b** with dimethylbutadiene followed by aromatisation. We also established by using the same NMR experiments as for (−)-**6a**, that these two benzylic fluorides, as well as intermediate **7a**, have 96% ee's. These results demonstrated unambiguously that no racemisation had occurred at any stage of this synthetic scheme.[13]

Then, extension to five-membered heteroaromatic systems was studied. The reaction of benzyl azide with (+)-**3a** afforded in 75% overall yield a 2:1 mixture of triazoles (−)-**9a** and (−)-**10a,** while the reaction of (+)-**3b** yielded in 80% overall yield a 55:45 mixture of (+)-**9b** and (−)-**10b** (Scheme 4). All these triazoles have been isolated by chromatography on SiO_2 and by using the same NMR experiments as previously described, they have demonstrated 96% ee's. Similar cycloaddition reactions were performed using nitrile oxides as 1,3 dipoles. They were prepared from nitroethane by Mukaiyama's procedure.[14] Addition on (+)-**3a** afforded in 83% overall yield a 91:9 mixture of regioisomers (+)-**11a** and (−)-**12a**, separated by chromatography on SiO_2. Starting from (+)-**3b**, the same reaction afforded in 71% overall yield a 92:8 mixture of (+)-**11b** and **12b**. The major isoxazole (+)-**11b** was isolated by chromatography on SiO_2. Here also, the ee's were established as 96% by NMR on the three pure previous isoxazoles, as well as on mixtures of (−)-**11b** and **12b** for the latter derivative.[15]



Scheme 3. Diels–Alder reactions on optically active propargylic fluorides, followed by aromatisation.



Scheme 4. Azide and nitrile oxide cycloadditions on optically active propargylic fluorides.

In conclusion, these preliminary results clearly established that benzylic fluorides, as well as the corresponding five-membered heterocycles, are accessible in high ee's by using this new route since very little, if any, racemisation occurred under such reaction conditions. This strategy will be used for the preparation of fluorinated analogues of bioactive molecules. Furthermore, the extension to other propargylic fluorides and to other cycloadditions and cyclo-condensations are under active study in our group.

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11. Main spectroscopical data for propargylic fluorides. Compound (+)-**3a**: ^{1}H NMR (300 MHz, $CDCl_3$) 8.20–8.13 (m, 2H); 7.69–7.49 (m, 3H); 5.50 (dq, 1H, $J_{HF} = 47.8$, $J = 6.6$); 1.76 (dd, 3H, $J_{HF} = 22.6$, $J = 6.6$). ^{13}C NMR (75 MHz, $CDCl_3$) 177.1 (d, $J = 2.6$); 136.1, 134.6, 129.6, 128.7, 89.9 (d, $J = 26.0$); 84.2 (d, $J = 9.7$); 78.5 (d, $J = 168.8$); 21.7 (d, $J = 24.2$). ^{19}F NMR (282 MHz, $CDCl_3$) −170.35 (dq, $J = 47.8$, $J = 22.6$). $[\alpha]_D^{21}$ +4.2 (*c* 0.54, $CHCl_3$). Compound (+)-**3b**: ^{1}H NMR (300 MHz, $CDCl_3$) 5.33 (dq, 1H, $J_{HF} = 47.7$, $J = 6.7$); 4.27 (q, 2H, $J = 7.2$); 1.66 (dd, 3H, $J_{HF} = 22.7$, $J = 6.7$); 1.33 (t, 3H, $J = 7.2$). ^{13}C NMR (75 MHz, $CDCl_3$) 152.8 (d, $J = 3.0$); 83.2 (d, $J = 26.2$); 78.6 (d, $J = 9.7$); 78.2 (d, $J = 169.3$); 62.4; 21.5 (d, $J = 24.2$); 13.9. ^{19}F NMR (282 MHz, $CDCl_3$) −172.02 (dq, $J = 47.9$, $J = 22.7$). $[\alpha]_D^{21}$ +17.9 (*c* 0.54, $CHCl_3$). Compound **3c**: ^{1}H NMR (300 MHz, C_6D_6) 7.39–7.02 (m, 5H); 6.02 (s, 1H); 4.56 (dq, 1H, $J_{HF} = 47.7$, $J = 6.7$); 3.17 (s, 3H); 0.95 (dd, 3H, $J_{HF} = 22.5$, $J = 6.7$). ^{13}C NMR (75 MHz, C_6D_6) 168.0; 152.0 (d, $J = 2.9$); 133.1; 129.4; 128.8; 128.1; 85.1 (d, $J = 26.4$); 78.5 (d, $J = 9.7$); 78.1 (d, $J = 170.1$); 52.1; 20.7 (d, $J = 24.0$). ^{19}F NMR (282 MHz, $CDCl_3$) −172.18 (the signal for the other diastereoisomer is at −172.16).
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13. Main spectroscopical data for benzylic fluorides: Compound (−)-**6a**: ^{1}H NMR (300 MHz, $CDCl_3$) 8.00–7.45 (m, 5H); 7.48 (s, 1H); 7.16 (s, 1H); 5.90 (dq, 1H, $J_{HF} = 47.6$; $J = 6.3$); 2.39 (s, 3H); 2.29 (s, 3H); 1.69 (dd, 3H, $J_{HF} = 24.0$, $J = 6.3$). ^{13}C NMR (75 MHz, $CDCl_3$) 197.6; 140.4; 139.8 (d, $J = 19.3$); 138.0; 135.6 (d, $J = 1.7$); 133.5 (d, $J = 4.8$); 133.0; 130.5; 130.2; 128.4; 127.0 (d, $J = 9.0$); 88.5 (d, $J = 165.4$); 23.8 (d, $J = 25.6$); 20.0; 19.4. ^{19}F NMR (282 MHz, $CDCl_3$) −167.26 (dq, $J = 47.8$, $J = 23.9$). $[\alpha]_D^{21}$ −87.8 (*c* 0.64, $CHCl_3$). Compound (−)-**8a**: ^{1}H NMR (300 MHz, $CDCl_3$) 7.82–7.40 (m, 5H); 7.22 (s, 1H); 6.90 (s, 1H); 5.95 (dq, 1H; $J_{HF} = 47.5$, $J = 6.2$); 4.02 (s, 3H); 3.81 (s, 3H); 1.69 (dd, 3H, $J_{HF} = 24.0$, $J = 6.2$). ^{13}C NMR (75 MHz, $CDCl_3$) 196.5; 151.6; 147.3 (d, $J = 1.7$); 138.1; 136.8 (d, $J = 19.5$); 133.0; 130.2; 128.5; 127.9 (d, $J = 4.8$); 112.7; 108.4 (d, $J = 10.3$); 88.5 (d, $J = 165.7$); 56.1 (2C); 24.0 (d, $J = 25.8$). ^{19}F NMR (282 MHz, $CDCl_3$) −166.46 (dq, $J = 47.5$, $J = 24.0$). $[\alpha]_D^{21}$ −60.8 (*c* 0.74, $CHCl_3$). Compound (+)-**6b**: ^{1}H NMR (300 MHz, $CDCl_3$): 7.75 (s, 1H); 7.46 (s, 1H); 6.43 (dq, 1H, $J_{HF} = 48.6$, $J = 6.2$); 4.36 (q, 2H, $J = 7.1$); 2.35 (s, 3H); 2.31 (s, 3H); 1.65 (dd, 3H, $J_{HF} = 24.3$, $J = 6.2$); 1.41 (t, 3H, $J = 7.1$). ^{13}C NMR (75 MHz, $CDCl_3$) 166.7 (d, $J = 0.7$); 142.1 (d, $J = 19.2$); 142.0 (d, $J = 1.0$); 135.8 (d, $J = 1.4$); 131.4; 126.5 (d, $J = 13.0$); 124.4 (d, $J = 4.5$); 88.7 (d, $J = 165.1$); 60.8; 23.7 (d, $J = 25.4$); 20.0; 19.3; 14.3. ^{19}F NMR (282 MHz, $CDCl_3$) −170.95 (dq, $J = 48.6$, $J = 24.3$). $[\alpha]_D^{21}$ +22.4 (*c* 0.32, $CHCl_3$).
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15. Main spectroscopical data for 1,3 dipolar cycloadducts: Compound (−)-**9a**: ^{1}H NMR (300 MHz, $CDCl_3$) 8.41–8.35 (m, 2H); 7.65–7.30 (m, 8H); 6.51 (dq, 1H, $J_{HF} = 46.6$, $J = 6.7$); 5.91 (d, 1H, $J = 14.9$); 5.86 (d, 1H, $J = 14.9$); 1.49 (dd, 3H, $J_{HF} = 23.6$, $J = 6.7$). ^{13}C NMR (75 MHz, $CDCl_3$) 186.9; 143.0 (d, $J = 2.3$); 141.3 (d, $J = 19.2$); 136.7; 134.9; 133.3; 130.7; 128.9; 128.6; 128.3; 128.0; 84.6 (d, $J = 169.6$); 53.9 (d, $J = 7.9$); 20.5 (d, $J = 23.7$). ^{19}F NMR (282 MHz, $CDCl_3$) −182.14 (dq, $J = 46.6$, $J = 23.6$). $[\alpha]_D^{21}$ −49.1 (*c* 0.36, $CHCl_3$). Compound (−)-**10a**: ^{1}H NMR (300 MHz, $CDCl_3$): 7.64–7.17 (m, 10H); 5.73 (d, 1H, $J = 14.6$); 5.68 (d, 1H, $J = 14.6$); 5.43 (dq, 1H, $J_{HF} = 47.7$, $J = 6.5$); 1.72 (dd, 3H, $J_{HF} = 23.7$, $J = 6.5$). ^{13}C NMR (75 MHz, $CDCl_3$): 186.8; 136.7; 134.5; 134.4; 129.4; 128.8 (2C); 128.6; 128.2; 82.7 (d, $J = 165.8$); 53.4; 19.9 (d, $J = 24.5$). ^{19}F NMR (282 MHz, $CDCl_3$) −162.83 (dq, $J = 47.7$, $J = 23.7$). $[\alpha]_D^{21}$ −20.0 (*c* 0.18, $CHCl_3$). Compound (+)-**9b**: ^{1}H NMR (300 MHz, $CDCl_3$) 7.34–7.20 (m, 5H); 6.45 (dq, 1H, $J_{HF} = 46.2$, $J = 6.7$); 5.82 (d, 1H, $J = 15.0$); 5.63 (d, 1H, $J = 15.0$); 4.40 (q, 2H, $J = 7.1$); 1.40 (t, 3H, $J = 7.1$); 1.35 (dd, 3H, $J_{HF} = 23.6$, $J = 6.7$). ^{13}C NMR (75 MHz, $CDCl_3$) 161.0; 140.1 (d, $J = 20.2$); 135.9 (d, $J = 2.9$); 134.9; 128.8; 128.6; 127.7; 83.9 (d, $J = 170.0$); 61.4; 53.9 (d, $J = 7.5$); 20.5 (d, $J = 23.9$); 14.2. ^{19}F NMR (282 MHz, $CDCl_3$) −183.65 (dq, $J = 46.2$, $J = 23.6$). $[\alpha]_D^{21}$ +15.1 (*c* 0.57, $CHCl_3$). Compound (−)-**10b**: ^{1}H NMR (300 MHz, $CDCl_3$) 7.32–7.30 (m, 5H); 6.11 (dq, 1H, $J_{HF} = 47.2$, $J = 6.6$); 5.91 (s, 2H); 4.38 (q, 2H, $J = 7.1$); 1.86 (dd, 3H, $J_{HF} = 23.6$, $J = 6.6$). ^{13}C NMR (75 MHz, $CDCl_3$) 158.2 (d, $J = 1.3$); 149.4 (d, $J = 21.5$); 134.9; 128.8; 128.4; 127.9; 125.1 (d, $J = 3.2$); 82.8 (d, $J = 165.6$); 62.2; 53.9; 19.6 (d, $J = 24.7$); 14.0. ^{19}F NMR (282 MHz, $CDCl_3$) −166.33 (dq, $J = 47.2$, $J = 23.6$). $[\alpha]_D^{21}$ −5.9 (*c* 0.98, $CHCl_3$). Compound (+)-**11a**: ^{1}H NMR (300 MHz, $CDCl_3$) 7.82–7.50 (m, 5H); 5.58 (dq, 1H, $J_{HF} = 46.3$, $J = 6.6$); 2.30 (s, 3H); 1.71 (dd, 3H, $J_{HF} = 23.6$, $J = 6.6$). ^{13}C NMR (75 MHz, $CDCl_3$) 189.2 (d, $J = 0.9$); 169.8 (d, $J = 20.8$); 159.2 (d, $J = 1.8$); 137.7; 134.0; 129.2; 128.9; 117.2 (d, $J = 3.4$); 81.4 (d, $J = 171.1$); 19.1 (d, $J = 24.7$); 11.1. ^{19}F NMR (282 MHz, $CDCl_3$) −171.38 (dq, $J = 46.3$, $J = 23.6$). $[\alpha]_D^{21}$ +29.0 (*c* 0.59, $CHCl_3$). Compound (−)-**12a**: ^{1}H NMR (300 MHz, $CDCl_3$) 8.17–8.12 (m, 2H); 7.69–7.50 (m, 3H); 6.22 (dq, 1H, $J_{HF} = 46.7$; $J = 6.6$); 2.52 (d, 3H, $J_{HF} = 1.6$); 1.73 (dd, 3H, $J_{HF} = 23.5$, $J = 6.6$). ^{13}C NMR (75 MHz, $CDCl_3$) 182.7; 161.0 (d, $J = 7.1$); 159.5; 135.5; 134.2; 130.2; 128.7; 125.3; (d, $J = 24.9$); 83.3 (d, $J = 163.5$); 21.3 (d, $J = 24.9$); 11.4 (d, $J = 4.0$). ^{19}F NMR (282 MHz, $CDCl_3$) −176.7 (dqq, $J = 48.3$, $J = 23.5$, $J = 1.6$). $[\alpha]_D^{21}$ −20.2 (*c* 0.47, $CHCl_3$). Compound (+)-**11b**: ^{1}H NMR (300 MHz, $CDCl_3$) 6.23 (dq, 1H, $J_{HF} = 46.2$, $J = 6.6$); 4.35 (q, 2H, $J = 7.1$); 2.48 (s, 3H); 1.75 (dd, 3H, $J_{HF} = 23.6$, $J = 6.6$); 1.39 (t, 3H, $J = 7.1$). ^{13}C NMR (75 MHz, $CDCl_3$) 173.0 (d, $J = 19.2$); 161.3 (d, $J = 1.4$); 159.8 (d, $J = 1.4$); 109.5 (d, $J = 3.2$); 82.0 (d, $J = 171.2$); 61.1; 19.0 (d, $J = 24.8$); 14.1; 11.6. ^{19}F NMR (282 MHz, $CDCl_3$) −176.70 (dq, $J = 47.1$, $J = 23.6$). $[\alpha]_D^{21}$ +32.5 (*c* 0.46, $CHCl_3$). Compound **12b**: ^{1}H NMR (300 MHz, $CDCl_3$) 6.24 (dq, 1H, $J_{HF} = 46.6$, $J = 6.6$); 4.44 (q, 3H, $J = 7.1$); 2.45 (d, 3H, $J_{HF} = 1.6$); 1.64 (dd, 3H, $J_{HF} = 23.4$, $J = 6.6$); 1.42 (t, 3H, $J = 7.1$). ^{13}C NMR (75 MHz, $CDCl_3$) 159.6; 157.1 (d, $J = 1.2$); 154.3 (d, $J = 7.7$); 124.4 (d, $J = 25.4$); 84.4 (d, $J = 163.7$); 62.3; 21.3 (d, $J = 25.1$); 14.1; 11.4 (d, $J = 3.8$). ^{19}F NMR (282 MHz, $CDCl_3$) −177.98 (dqq, $J = 46.6$, $J = 23.4$, $J = 1.6$).