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A New Highly Stereoselective Monofluorination in Benzylic Position

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Abstract : *Reaction of DAST with secondary alcohols vicinal to an arene $Cr(CO)_3$ unit gives with very high* exo *stereoselectivity the corresponding fluorides; the stereochemistry of the reaction appears to be exclusively controlled by the organometallic moiety.* Copyright © 1996 Published by Elsevier Science Ltd

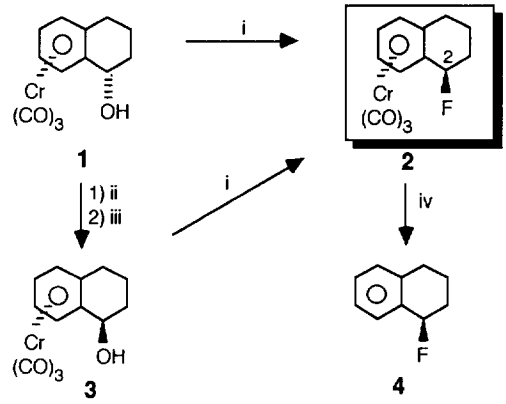
The organic chemistry of fluorine is a very rapidly growing field, especially in bioorganic chemistry since introduction of fluorine can have profound and unexpected effects on the activity of biomolecules.[1] Thus, the stereoselective synthesis of organofluorine molecules has become an important research area.[2]

The monofluorination ***in benzylic position*** could be extremely serviceable to the preparation of analogs of various natural products or medicinal drugs. Several methods have been already reported in this context: electrophilic additions on double bonds,[3] for instance with XeF_2,[4] occur usually with low selectivities. The ring opening of epoxides[5] or aziridines[6] by Olah's reagent is interesting especially for the stereoselective preparation of amino acid analogs; a complementary approach involves reductive amination of pyruvic acid derivatives.[7] An electrochemical method is particularly useful for the preparation of functionalized derivatives.[8] However, very few examples of enantioselective syntheses have been described so far.[9] They rely on selective fluorination of various enolates: chiral non racemic fluorinating agents give moderate enantiomeric excess[10], while diastereoselective fluorination using an enolate based on an optically active oxazolidinone gives both an excellent yield and a good diastereomeric excess.[11]

As part of our program to expand the utilization of transition metal complexes in organic synthesis[12] we have recently developed an efficient asymmetric synthesis of dienes with a fluorine atom in allylic position.[13] The purpose of this note is to describe a new, simple method, based on the same metalloassistance strategy, to effect stereoselective monofluorination in benzylic position.

Arene transition metal complexes[14] and especially the chromium derivatives [15] are useful intermediates in organic synthesis. Due to their planar chirality and their easy access in optically pure form, they are also efficient reagents for asymmetric induction as demonstrated, for instance, with the perfluoroalkylation in benzylic position.[16] Furthermore, these complexes strongly stabilize vicinal carbocations and react with many nucleophiles to form stereoselectively new C-C and C-heteroatom bonds.[17] However, fluorination is a notable exception: reaction of such cations with F^- do not lead to the expected monofluorinated compounds.[18]

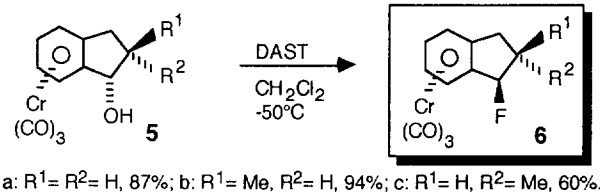
The known[19] *endo* tetralol complex **1** reacts with diethylaminosulfurtrifluoride (DAST) to give the fluorinated derivative **2** in excellent yield with a complete diastereoselectivity (NMR control).[20] The *exo* position of the fluorine atom is easily established by ^1H NMR with H(2) as a dt ($^3J_{ea} \approx {}^3J_{ee} = 4.6$ Hz).[21]



i: DAST (1.25 eq.), CH_2Cl_2, -50°C, 91%; ii: Ph_3P, DIAD (2 eq.), THF, 0°C, $PhCO_2H$ (2 eq.), 56%;
iii: Dibal-H (1.1 eq.), CH_2Cl_2, 95%; iv: Air, visible light, ether, room temp., 42%

The corresponding *exo* alcohol **3** was prepared from **1** *via* the Mitsunobu procedure. The reaction of **3** with DAST gives exclusively the ***same*** *exo* fluoride **2** in good yield. This result proves that the stereochemistry of the fluoration is independent of the stereochemistry at the secondary carbinol center. The decomplexation of **2** under standard conditions (air, light) gives the desired compound **4**.

The indanols **5**[19] displayed identical reactivity: in each case, the reaction gives rise exclusively[20] to the monofluorinated derivatives **6**. The *exo* position of the fluorine is unambiguously established by ^1H NMR: ^3J= 4.6 Hz for **6b** and ^3J= 1.6 Hz for **6c**.[22]



a: R^1= R^2= H, 87%; b: R^1= Me, R^2= H, 94%; c: R^1= H, R^2= Me, 60%.

The comparison between **5b** and **5c** indicates that the stereogenic center vicinal to the alcohol function has also no influence on the reaction diastereoselectivity.

All these results indicate that, with these cyclic models, ***the fluorination is completely stereoselective and that the stereochemistry of the reaction [anti to the $Cr(CO)_3$ unit] is exclusively controlled by the organometallic moiety.*** This appears as a key point for future developments in asymmetric synthesis since these complexes, like many arene chromium tricarbonyl derivatives[15] are easily accessible in optically active form.[19]

In conclusion, we have described a simple and efficient[23] method for the stereoselective monofluorination in benzylic position. Extension of this approach to other derivatives and applications to asymmetric synthesis or to the preparation of natural products analogs are under active investigation in our laboratory.

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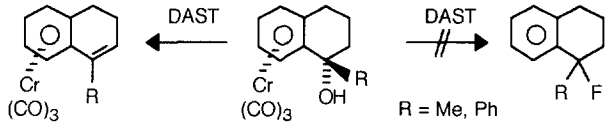
20 - In each case, the diastereoselectivity of the fluorination reaction was established by high field (Bruker ARX 400) NMR analysis (^1H, ^{13}C and ^{19}F) of the crude reaction mixtures. These complexes have been used in racemic form; however, for clarity only one enantiomer is shown on the schemes. All new compounds have been fully characterized by spectroscopical, analytical, and/or high resolution mass spectra data.

21 - **2**: IR (nujol) (cm^{-1}) : 2850, 2830, 2727, 2369, 1968, 1905, 1715; ^1H NMR (400 MHz, C_6D_6): δ 5.06 (dt, J = 51.4 Hz, J = 4.6 Hz, 1H); 5.05 (dd, J = 6.4 Hz, J = 1 Hz, 1H); 4.54 (td, J = 6.4 Hz,J = 1 Hz, 1H); 4.32 (td, J = 6.4 Hz, J = 1 Hz, 1H); 4.27 (d, J = 6.5 Hz, 1H); 2.25-2.16 (m, 1H); 1.97-1.90 (m, 1H); 1.72-1.61 (m, 2H); 1.54-1.42 (m, 1H); 1.31-1.21 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ 232.6; 109.8; 102.1 ($J_{C,F}$= 26.9 Hz); 94.7 ($J_{C,F}$= 3.0 Hz); 93.4, 90.9, 90.0, 86.9 ($J_{C,F}$= 169.4 Hz); 28.0 ($J_{C,F}$= 20.5 Hz); 26.8, 16.9; ^{19}F NMR (376 MHz, C_6D_6): δ -154.58.

22 - **6a**: IR (nujol) (cm^{-1}) : 2950, 2930, 2850, 2726, 2361, 1978, 1909, 1715; ^1H NMR (400 MHz, C_6D_6): δ 5.26 (dd, J = 56.5 Hz, J= 5.2 Hz, 1H); 4.98 (d, J = 6.4 Hz, 1H); 4.56 (t, J = 6.3 Hz, 1H); 4.47 (d, J = 6.4 Hz, 1H); 4.25 (t, J = 6.2 Hz, 1H); 2.57-2.51 (m, 1H); 2.21-2.15 (m, 1H); 2.05-1.75 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6): δ 232.9, 232.26, 232.25, 115.79 ($J_{C,F}$= 1 Hz); 105.11 ($J_{C,F}$= 26.9 Hz); 95.15 ($J_{C,F}$= 173.5 Hz); 94.06, 91.97, 89.42, 87.72, 31.06 ($J_{C,F}$= 23.5 Hz); 28.88 ($J_{C,F}$= 1.4 Hz); ^{19}F NMR (376 MHz, C_6D_6): δ -155.34. **6b**: IR (nujol) (cm^{-1}) : 2950, 2925, 2854, 2361, 1978, 1909, 1730; ^1H NMR (400 MHz, C_6D_6): δ 4.99 (dd, J = 56.9 Hz, J = 4.6 Hz, 1H); 4.95 (d, J = 6.4 Hz, 1H); 4.54 (t, J = 6.2 Hz, 1H); 4.44 (d, J = 6.4 Hz, 1H); 4.23 (t, J = 6.2 Hz, 1H); 2.36-2.23 (m, 2H); 2.22-2.16 (m, 1H); 0.99 (dd, J = 6.6 Hz, J = 2 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 232.34, 232.33, 115.86 ($J_{C,F}$= 1.5 Hz); 105.32 ($J_{C,F}$= 27.2 Hz); 96.07 ($J_{C,F}$= 178.9 Hz); 93.96, 92.01, 89.41, 87.56, 37.33 ($J_{C,F}$= 21.9 Hz); 36.40 ($J_{C,F}$= 1.4 Hz); 12.36 ($J_{C,F}$= 8.9 Hz); ^{19}F NMR (376 MHz, C_6D_6): δ -173.95. **6c**: IR (nujol) (cm^{-1}) : 2970, 2917, 2850, 2727, 2369, 1975, 1915, 1707; ^1H NMR (400 MHz, C_6D_6): δ 5.23 (dd, J = 56.7 Hz, J = 1.6 Hz, 1H); 4.99 (d, J = 6.5 Hz, 1H); 4.49 (t, J = 6.1 Hz, 1H); 4.45 (d, J = 6.1 Hz, 1H); 4.30 (t, J = 6.1 Hz, 1H); 2.64 (ddd, J = 16.5 Hz, J = 8.7 Hz, J = 2 Hz, 1H); 2.31-2.18 (m, 1H); 2.00 (dt, J = 16.6 Hz, J = 3.5 Hz, 1H); 1.12 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 232.41; 113.93; 105.46 ($J_{C,F}$= 28.7 Hz); 101.77 ($J_{C,F}$= 176.8 Hz); 93.15; 90.52; 90.43; 87.66; 38.81 ($J_{C,F}$= 21.7 Hz); 36.69; 19.60 ($J_{C,F}$= 6.9 Hz); ^{19}F NMR (376 MHz, C_6D_6) : δ -150.02.

23 - One of the, actual, limitations appear to be the synthesis of tertiary fluorides: reactions with DAST give the elimination products instead of the desired fluorinated derivatives.



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