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High Regio-and Stereocontrol in the Dehydroxy - Fluorination of Propargylic Alcohols and the Corresponding Cobalt-Carbonyl Complexes

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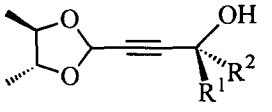
Abstract : *The reaction of DAST with chiral propargylic alcohols 1 and 2 occurs with high stereoselectivities and in a stereodivergent manner; this is the first example for the use of Cobalt-carbonyl complexes in nucleophilic fluorination.* © 1999 Published by Elsevier Science Ltd. All rights reserved.

It is well established that introduction of fluorine atoms, with their small size, very high electronegativity and strong bond energies, induce important modifications in the properties of organic molecules[1] and as a result, interest in fluorine chemistry has developed intensely in many directions. In bioorganic chemistry for instance, it contributed to the discovery of new drugs and useful pharmacological tools as well as novel agrochemicals.[2] Molecules with a single fluorine atom are of particular interest but the control of the selectivity during the monofluorination remains, in many cases, a challenging problem especially when absolute configuration is concerned. Several useful solutions have been proposed recently for asymmetric monofluorination.[3] They include molecular fluorine addition,[4] aldol reactions,[5] rearrangements[6] and asymmetric hydrogenations[7]. Also electrophilic fluorinations,[8] dehydroxy-fluorination,[9] or the use of chiral transition metal complexes in nucleophilic fluorination, a method that we initiated a few years ago,[10] have been utilized. Molecules with a single fluorine in the propargylic position are very attractive building blocks in synthesis, especially with regard to the preparation of fluorinated analogs of biomolecules.[11] Very few compounds of this general type have been described previously [12] and, to the best of our knowledge, there are only two examples reported (in the prostaglandin family) for optically active propargylic fluorides.[13] The purpose of this paper is to report the first detailed study of the diastereoselectivity during propargylic fluorination, using derivatives **1a** and **1b** which have been selected as models. We will furthemore establish for the first time that corresponding cobalt-carbonyl complexes **2** can be used in dehydroxy-fluorination and that the transition metal cluster can modulate the stereoselectivity of the fluorination.



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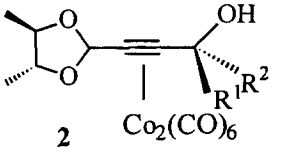

2

a : $R^1 = Me$; $R^2 = H$ **b** : $R^1 = H$; $R^2 = Me$

The synthesis of **1a** and **2a** is show in Scheme 1. A four step sequence starting from commercially available (S)-(-)-3-butyn-2-ol and also utilizing (2R,3R)-(-)-2,3-butanediol provided **1a** in 28% overall yield. Further complexation with $Co_2(CO)_8$ gave **2a** in 90% yield.

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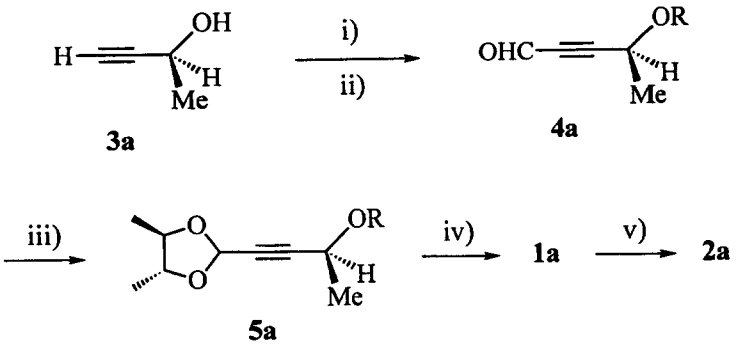
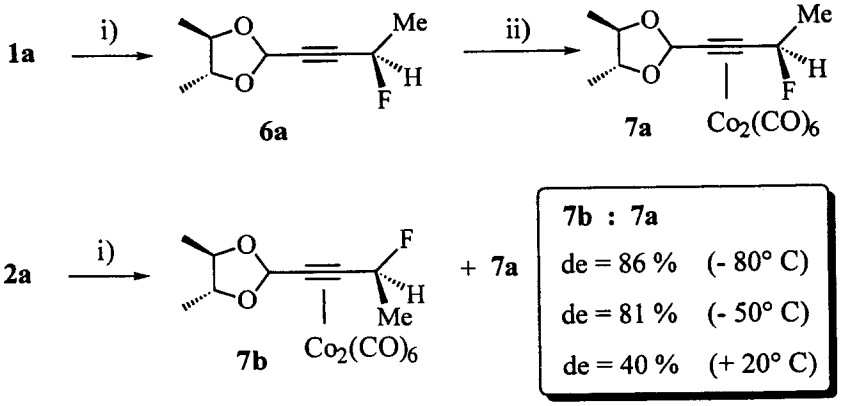


Scheme 1 : i) $tBuMe_2SiCl$ (1eq.), DMAP (0.1 eq.), Et_3N (2 eq.), THF, RT, 12h ; ii) BuLi (1 eq.), THF-HMPA (9 : 1) -80°C → -40°C, 0.5h, then DMF (2 eq.), **4a**, (59% overall yied) ; iii) (2R, 3R)-butanediol, APTS (cat), 3 mol.sieves, CH_2Cl_2 reflux, 4h, **5a** (64 %) ; iv) nBu_4NF, THF, RT, 2h, **1a** (80 %) ; v) $Co_2(CO)_8$ (1eq.), THF, RT, 2h, **2a** (88 %).

The high field (^1H and ^{13}C) NMR analysis established a (94 ± 3%) d.e for both compounds. Similar reactions were performed starting from (R)-(+)-3-butyn-2-ol, giving **1b** and **2b** with identical d.e's (94 ± 3%).
The reaction of **1a** with diethylaminosulfur trifluoride (DAST) at -50° C gave, almost instantaneously and in excellent yield, the fluoride **6a** which can be isolated and further transformed into complex **7a** (Scheme 2).The NMR analysis gave a (92 ± 3%) d.e for both compounds **6a** and **7a**, establishing a very high diastereoselectivity (d.s ≥ 98%) for the fluorination step. Furthermore, this reaction shows very little temperature dependence since **6a** is obtained with a 88% d.e at room temperature. In agreement with the mechanism generally accepted for such nucleophilic fluorination,[14] inversion of configuration was assumed in this reaction yielding the (R)-fluoride. It is also interesting to point out that no transposition into allenes was observed during this fluorination. This result is in agreement with the examples already reported in racemic series,[12] with exceptions found in perfluorinated derivatives which lead to some fluorallenes. [15]



Scheme 2 : i) DAST(1.2 eq.), CH_2Cl_2, -50°C, 10 min, then Na_2CO_3, **6a** (87 %), **7b** (80 %). ii) $Co_2(CO)_8$ (1eq.), THF, RT, 2h, **7a** (90 %).

The reaction of complex **2a** with DAST (Scheme 2) is particularly interesting from several points of view :

- These reactions give excellent yields and, to the best of our knowledge, they are the first examples of a dehydroxyfluorination in the presence of cobalt-carbonyl complexes.
- The diastereoselectivity is strongly temperature dependent since the d.e increases from 40% at room temperature to a high 86% at - 80°C. Therefore, this fluorination shows, once more, a very good stereoselectivity (d.s ≥ 90%) but only at low temperature. The major diastereoisomer obtained in this reaction is **7b** and not **7a** ([19] F NMR control). This demonstrates that the cobalt complex can control the stereochemistry leading to the (S) derivative with an overall retention of configuration. This appears as the first extension to fluorination of the well know Nicholas reaction[16] where dicobalthexacarbonyl propargylic cations are usually involved as intermediates. Thus, our results establish also that the diastereoisomerization process[17] of cations derived from **2a** or **2b** is slow at low temperature, at least compared to the rate of fluorination.
- The same reactions have been performed with isomers **1b** and **2b** ; they gave identical results with exactly the same diastereoselectivities.[18] This is also an important result which establishes that, in these models, the stereoselectivity of the fluorination is controled exclusively by the secondary alcohol stereocenter ; there is no influence from the remote stereocenters in the chiral dioxolane. [19]
- The exact nature of the fluorinating agent[20] in these reactions is an intriguing question since it has been established that $F^{\ominus}$ is a efficient reagent for decomplexation of the alkyne-cobalt carbonyl clusters.[21] The very high yields in our reactions indicate that either the fluorination step is facter than the decomplexation or that other reactive intermediates (such as, for instance, $Et_2NSF_2^{\ominus}$)[22] could be involved. It can be anticipated also that the nature of substituents, both on the triple bond and at the propargylic position, should have effects on the stereoselectivity of the fluorination. These aspects are under active study in our group.

In conclusion, we have demonstrated that propargylic fluorination can occur with very high regio - and stereoselectivities. Furthemore, cobalt-carbonyl complexes can be used in this reaction and this lead to an interesting stereodivergent process to give either the (R)-or the (S)-fluoride. Taking into account the good regio- and stereo-control, propargylic fluorides of this type should provide new routes to selectively modified monofluorinated analogs of derivatives with unsaturated or polyunsaturated systems.

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