The Aldol Reaction with Difluoroenolates

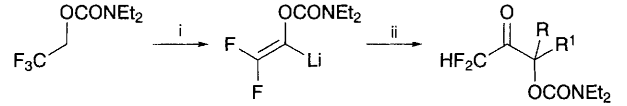
Judith A. Howarth,[a] W. Martin Owton[b] and Jonathan M. Percy*[a]

[a] *School of Chemistry, University of Birmingham, Edgbaston, Birmingham, UK B15 2TT*
[b] *Lilly Research Centre Ltd., Eli Lilly and Co., Erl Wood Manor, Windlesham, Surrey, UK GU20 6PH*

The reaction between lithium enolates of difluoroketones and non-enolisable aldehydes proceeds smoothly to afford difluoroaldol adducts in good yields; structurally complex fluoroketones can be constructed in a facile one-pot procedure from trifluoroethanol.

The aldol reaction is a key method for the synthesis of complex molecules;[1] carbon–carbon bond formation with stereochemical control at relative and absolute levels is now achieved routinely and the factors governing the formation and reactions of simple lithium enolates are well understood. However, the chemistry of difluoroenolates has not been explored extensively. This may be because there are no completely general methods for their generation.

A number of groups have published in the area of fluoroenolate chemistry. Kuroboshi and Ishihara described copper(I)-catalysed reactions of zinc difluoroenolates, generated from the corresponding chlorodifluoromethyl ketones.[2] The precursor ketones were synthesised by the action of Grignard reagents on chlorodifluoroacetic acid, limiting the level of functionality present in the adducts. Simple difluoroenol silyl ethers have been prepared by Brook rearrangement, following the reaction of fluorinated acyl silanes with Grignard reagents.[3] Lewis acid-mediated Mukaiyama-type aldol reactions with a steroidal aldehyde have been reported.[4] However, the chemistry has never been published with experimental details, and has failed in our hands. A recent publication by Portella and coworkers[5] described a concise preparation of difluoroenoxy silanes from acyl silanes *via* a difluorostannate-catalysed addition of Rupperts reagent. A one-pot procedure allowed the silyl enol ethers to be elaborated *via* the aldol reaction. Overall, the Portella chemistry achieved the installation of a difluoromethylene group into a mid-chain position, starting from a trifluoromethyl-containing precursor.



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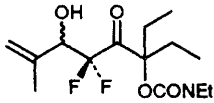
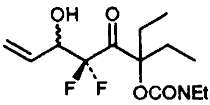
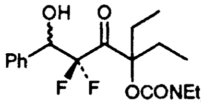
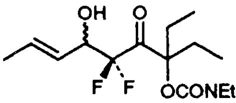
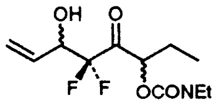
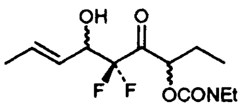
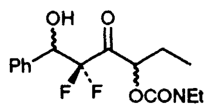
Scheme 1 *Reagents and conditions*: i, 2 LDA, THF, −78 °C; ii, RCOR[1]

Table 1 Difluoroaldol products obtained

Electrophiles used	Product	Yield (%)
Pentan-3-one Methacrolein		55
Pentan-3-one Acrolein		64
Pentan-3-one Benzaldehyde		69
Pentan-3-one Crotonaldehyde		68
Propanal Acrolein		61
Propanal Crotonaldehyde		62
Propanal Benzaldehyde		60

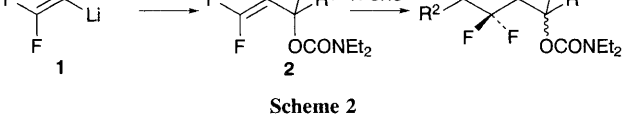
We have also found that difluoroenol silyl ethers bearing a carbamato substituent at the allylic carbon fail to undergo aldol reactions when exposed to aldehydes and Lewis acids. Instead, the products of protodesilylation were isolated. Confronted by this discouraging result, we examined the chemistry of lithium enolates with a more rigorous attitude. In 1992, we described metallated enol carbamate chemistry based upon trifluoroethanol, an inexpensive and readily available starting material.[6] Metallated difluoroenol carbamate **1** added to carbonyl electrophiles afforded difluoromethyl ketones in good yield following aqueous work up. The ketones were formed *via* protonation of the lithium difluoroenolates **2**, released upon transacylation of the first-formed alkoxide.

Early experiments which involved adding an excess of enolisable aldehydes, such as propanal, to the enolate solution failed to yield aldol products. However, we have discovered recently that the addition of a second non-enolisable aldehyde allows the lithium enolate to be trapped (Scheme 1), leading to the formation of aldol products (Table 1) in good yield.

In a typical sequence, the metallated enol carbamate was generated at −78 °C following our published procedure.[6,7] An aldehyde or ketone (1.0 equiv.) was added and the mixture was stirred for 1 h at −78 °C, than allowed to warm to 0 °C. Addition of the second non-enolisable aldehyde (R^2CHO, 1.2 equiv.) and stirring for a further 1 h followed by aqueous work up afforded the aldols, which were purified by flash column chromatography (Scheme 2).

We suspect that the failure of the aldol reaction with enolisable aldehydes arises from the low nucleophilicity of the difluoroenolate. Proton abstraction may then occur more rapidly than carbon–carbon bond formation. We are attempting to confirm this hypothesis with labelling experiments, the results of which will be reported elsewhere.

Our one-pot procedure has a number of distinct advantages. The starting material is inexpensive and easy to handle, and the methodology leads to highly functionalised materials. Potentially, a wide and diverse array of fluorine-containing ketones can be generated rapidly using this chemistry. Any functionality compatible with organolithium reagents may be located in either or both of the electrophiles. Potentially, transmetallation chemistry at either the acyl anion equivalent or enolate level



Scheme 2

could further widen the scope of this procedure. The significant problem of learning how to perform the aldol reaction with stereochemical control remains to be solved; we are actively pursuing this goal. We are also exploring applications of this chemistry in the syntheses of fluorinated carbohydrates and other complex unnatural products.

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