Oxy-Cope rearrangements of fluorinated divinylcyclohexanols: a modular method for the construction of selectively fluorinated cyclic ketones

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Oxy-Cope rearrangements of fluorinated divinylcyclohexanols afford access to cyclodecenones containing from two to five fluorine atoms.

The oxy-Cope rearrangement has become a tool of awesome transformative power;^{1,2} ring systems can be constructed and interconverted with ease, opening routes to highly complex and densely functionalised polycyclic molecular architecture. However, oxy-Cope rearrangements of fluorinated substrates have remained uncharted territory.³ The effect of fluorine atom substituents upon the thermodynamic parameters of simple Cope rearrangement systems is well known, thanks to the extensive and rigorous efforts of Dolbier.⁴ Terminal fluorine atom substituents lower the enthalpy of activation, while the entropy of activation usually increases; overall, the rearrangement reaction in which the CF₂ centre rehybridises from sp^2 to sp^3 is favoured.

Cyclic (especially medium to large ring) difluoro ketones have a relatively unexplored chemistry because there are few rational routes for their synthesis. More highly fluorinated cyclic ketones show interesting keto/enol tautomerisation⁵ behaviour that is quite different from that of acylic congeners,⁶ an important class of compounds with well-defined and useful hydration behaviour.⁷ Routes to conformationally-restricted difluoro ketones may therefore be of interest and there is also potential for novel transannular interactions and reactions.⁸ We therefore decided to examine the oxy-Cope rearrangement as a possible novel strategy for the construction of medium to large rings with controllable patterns of selective fluorination.

We chose the divinyl cyclohexanol/cyclodecenone system, studied originally by Marvell and Whalley,⁹ as our starting point and followed their synthetic strategy. Cyclohexene oxide was opened with metallated fluoroalkenes **1a**,^{10*a*} **1b**^{10*b*} and **1c**^{10*c*} to afford alcohols **2a–c** in 69, 64 and 76% isolated yields. Swern oxidation of each followed to afford the corresponding ketones **3a** (83%), **3b** (52%) and **3c** (72%). We were happy to note that these β , γ -unsaturated species, which are presumably destabilised by the vinylic CF₂ centre, did not isomerise and could be purified by column chromatography (Scheme 1).

Next, we added vinylmetals, with the intention of demonstrating that a degree of flexibility was possible in precursor construction. Vinyllithium reacted smoothly with 3a and 3c to afford dienols 4a and 4c in 78 and 68% yields respectively. When the metallated fluoroalkene derived from HFC-134a 1c was added to 3a, a mixture of diastereoisomeric dienols 5a with distinct ¹⁹F NMR spectra were obtained (2.3:1 mixture, 57%). Finally lithiodihydropyran was added to 3a-c to afford 6a-c, completing a preliminary range of representative species. The three latter dienols in particular could not be purified because of decomposition during column chromatography, but crude material could be obtained directly from the addition reaction with satisfactory ¹H and ¹⁹F NMR spectra. In general, we were not able to free any of the preceding dienols completely from trace amounts of hydrocarbon impurities so they were taken on without being characterised fully.



Scheme 1 Reagents and conditions: i, cyclohexene oxide, $BF_3 \cdot OEt_2$, THF, $-78 \,^{\circ}C$; ii, DMSO, (COCl)₂, $-78 \,^{\circ}C$, then Et_3N ; iii, alkenylmetal, THF, $-78 \,^{\circ}C$ (see text).



We chose to investigate the neutral oxy-Cope in anticipation of problems arising from the high nucleophilicity of potassium alkoxides and enolates, the potential for fluoride ion loss, and the known high electrophilicity of perhaloalkenes. The rearrangements were initiated by heating small samples of the dienols in dry xylene in sealed (Ace) tubes at progressively higher temperatures until appropriate ¹⁹F NMR spectral changes were observed, or ¹H NMR changes in the case of **10**. No attempt was made at this stage to measure rate constants or determine activation parameters but we did run a number of substrates at 150 °C to allow some qualitative comparisons to be made (Table 1) with **10**.

Substrates **4a**, **5a** and **6a** all reacted smoothly at 150 °C in short reaction times; however, **10** failed to react at all in one week at that temperature and only underwent a slow conversion at 225 °C in xylene. Of the three series of compounds, the chlorinated congeners appeared to be more reactive than the fluorinated or oxygenated counterparts.¹¹ The relatively low temperatures of the rearrangements are most encouraging and suggest that a rather general method of fluoro ketone synthesis may be available.¹² Structural assignment was made by ¹H

Table 1 Rearangement conditions and outcomes for fluorinated dienols

Dienol	$T^{a/\circ}\mathrm{C}$	t^{b}/h	Product	Yield ^c (%)
4a	125	8	7a	67
4a	150	3	7a	58
4c	125	46	7c	72
5a	150	1.75	8a	73
6a	150	3	9a	65
6b	155	9	9b	62
6c	140	17	9c	84
10	150	168	11	_
10	225	24	11	49

^{*a*} Reactions in sealed tubes in xylene. ^{*b*} Time for complete consumption of starting dienol by NMR. ^{*c*} Isolated yield.



NMR COSY and GOESY experiments.¹³ By ¹⁹F NMR, we were able to detect only products with a single double bond configuration, assumed *trans* with respect to the mutual location of the ring bonds. Unambiguous proof of alkene configuration was then obtained in the case of **9a** when single crystals¹⁴ were grown and subjected to analysis by X-ray diffraction (Fig. 1). Also, the ³*J*_{H-F} couplings across the alkene bond in **7c** (33.7 Hz) and **9c** (32.4 Hz) were entirely consistent with this arrangement.

We have therefore shown that oxy-Cope systems can be assembled rapidly, and that fluorinated cyclodecenones and



Fig. 1 The molecular structure of **9a**. The *cis*-ring junction and *trans*-ring bonds can be seen clearly.

more complex species can be developed from simple fluoroalkene building blocks. Work to define the scope and kinetic parameters of oxy-Cope rearrangement systems that contain fluorinated vinylic components is in progress.

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