

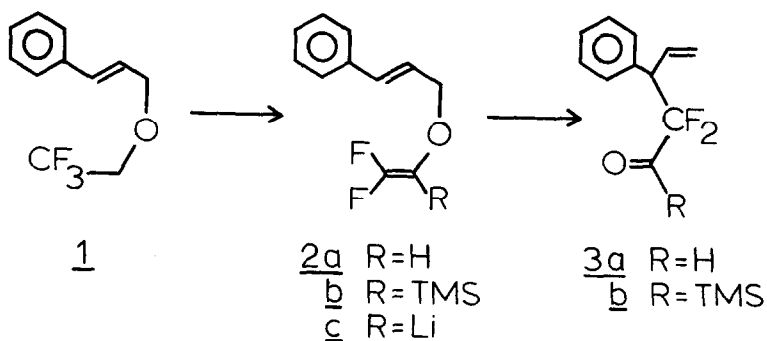
THE SYNTHESIS OF  $\alpha,\alpha$ -DIFLUOROALDEHYDES AND KETONES  
VIA CLAISEN REARRANGEMENTS

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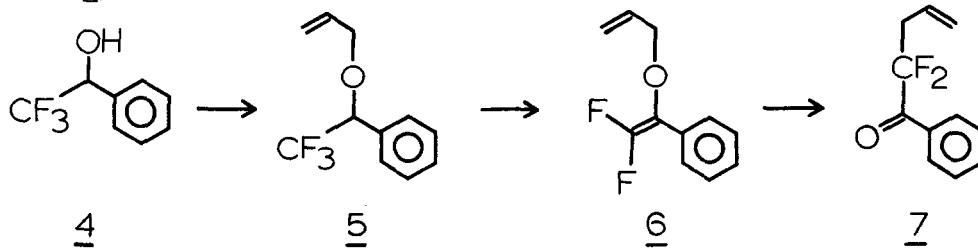
ABSTRACT: The Claisen rearrangements of reactants containing two fluorine atoms in either the allyl or vinyl fragment are described.

The incorporation of fluorine into an organic molecule has often been associated with profound changes in biological profiles of the fluorinated compound when compared to its hydrocarbon counterpart.<sup>1</sup> Such changes are a consequence of the extreme electronegativity of fluorine, as well as its ability to replace hydrogen without notable steric consequences. New methods for the introduction of fluorine are thus of some interest.<sup>2,3,4,5</sup> Except for one case which describes the Claisen rearrangement of trifluorovinyl ethers to afford acylfluorides,<sup>6</sup> the 3,3-sigmatropic rearrangement does not appear to have been explored for this purpose.<sup>7</sup> Some examples of Claisen rearrangements where the fluorine is one atom further removed from the 3,3-framework have been reported.<sup>9</sup> Here we describe the preparations and Claisen rearrangements of some difluorovinyl ethers of allylic alcohols, as well as a complementary procedure where the two fluorine atoms substitute the allylic alcohol component.

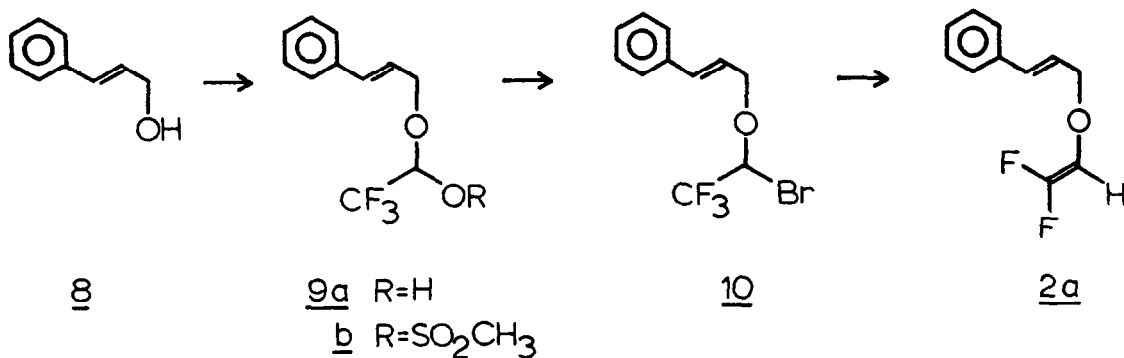


The trifluoroethyl ether 1<sup>10a</sup> can be prepared in 63% yield by treatment of cinnamyl chloride with the alkoxide derived from trifluoroethanol in THF at reflux. Addition of 1 to three equivalents<sup>11</sup> of LDA in THF at -70°C, followed by quenching with water after 10 minutes gave a 2:1 mixture of 2a<sup>10a</sup> and 1. Longer reaction times resulted in decomposition of the intermediate vinyl lithium species 2c. That 2c is indeed an intermediate is demonstrated by the isolation of the vinylsilane 2b<sup>10a,b</sup> in 88% yield when 1 is added to a solution of LDA (3.3 eq.) and TMSCl (3.3 eq.) in THF at -100°C,<sup>12</sup> then allowed to warm to -40°C. Both 2a and 2b readily convert to the products of Claisen rearrangement 3a<sup>10a</sup> and 3b<sup>10b</sup> at 80°C (refluxing CCl<sub>4</sub>).<sup>13</sup> At this temperature 2a is completely rearranged to the  $\alpha,\alpha$ -difluoroketone 3a in 1 hour. The liquid 3a on standing in air converts to a solid material which is presumably the hydrate.

Other  $\alpha,\alpha$ -difluoroketones can be prepared by the alkylation of substituted trifluoroethanols with allyl bromides followed by dehydrofluorination (1 eq. of *n*-BuLi at -70°C) and rearrangement (80°C), as demonstrated for the conversions 4  $\rightarrow$  5<sup>10a,b</sup> (85%)  $\rightarrow$  6<sup>10a,b</sup>  $\rightarrow$  7<sup>10a,b</sup> (41% from 5).<sup>14</sup>

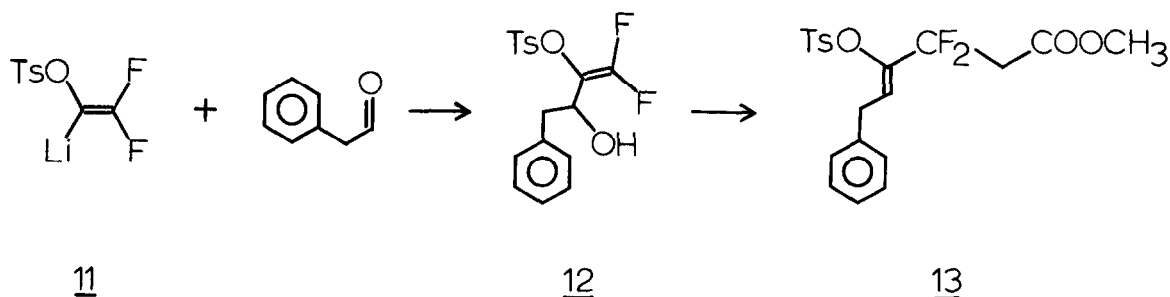


This general procedure of the alkylation of the alkoxide of trifluoroethanol derivatives with allyl halides presumably proceeds with inversion of configuration at the allylic carbon atom. An alternate approach is shown in the conversion of 8 to 2a. This approach should retain the stereochemistry at the allylic center. The examples here provide no test of these stereochemical consequences.

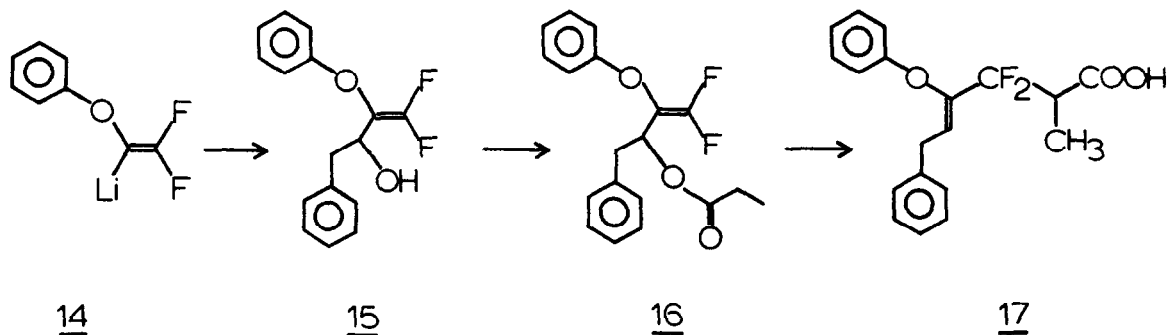


Treatment of the allylic alcohol 8 with anhydrous trifluoroacetaldehyde in ether at 0°C gave the crude hemiacetal 9a which was converted to the mesylate 9b<sup>10a</sup> (MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0°C) then to the bromide 10<sup>10a</sup> (n-Et<sub>4</sub>NBr, acetone, reflux, 3 h) in 59% overall yield. The bromide 10 underwent reductive elimination to afford 2a on treatment with t-butyllithium (2 eq., THF, -70°C) in 41% yield. A related procedure has been used to generate dichloro-vinyl ethers.<sup>6</sup>

The complementary approach, where the allylic component of the Claisen rearrangement substrate is difluoro-substituted, relies on the reaction of 2,2-difluoro-1-tosyloxyvinyl-lithium 11 with aldehydes to generate allylic alcohols<sup>15</sup>. Thus treatment of phenylacetaldehyde with 11 (generated at -70°C with 2.5 eq. of LDA)<sup>15</sup> afforded 12<sup>10a</sup> in 71% yield. Alcohol 12 underwent an orthoacetate Claisen rearrangement (triethyl orthoacetate, propionic acid, 120°C, 1.5 h)<sup>16</sup> to give 13<sup>10a,b</sup> in 84% yield as an oil after chromatography of the residue from distillation of the reaction mixture. From the <sup>19</sup>F n.m.r. spectrum 13 was estimated to consist of a 94:6 mixture of isomers.



In a similar manner, the reaction of 2,2-difluoro-1-phenyloxyvinyl-lithium 14<sup>11</sup> and phenylacetaldehyde afforded 15<sup>10a</sup> in 47% yield. The propionate ester 16, readily obtained from 15, underwent the Ireland enolate Claisen reaction<sup>8,17</sup> to give after silyl ester hydrolysis the acid 17<sup>10a,b</sup> in 57% yield.



The Claisen rearrangement of fluorinated alkyl vinyl ethers thus offers considerable flexibility in the synthesis of fluorinated molecules. The reactions described here are

facile and probably faster than the non-fluorinated cases.<sup>13,14</sup> In principle there should be a significant thermodynamic advantage for fluorine to be bound to  $sp^3$  orbitals.<sup>18</sup>

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