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Stereoselective Syntheses of 3,3-difluoro-1-propene Derivatives

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Abstract: A highly regio- and stereo-selective introduction of a difluoromethylene group in allylic position is described. The key step is the treatment of 3-acetoxy-1,1-difluoro-1-propenes with Grignard reagents in the presence of copper and lithium salts.

During the past few years, fluorinated organic molecules have drawn much attention due to their unique biological properties. The replacement of hydrogen atoms by fluorine atoms in biological molecules causes only a small steric perturbation but leads to major changes in hydrophobicity and polarity of the hydrocarbon chain[1]. Some syntheses allowing to prepare products in which a methylene group α to the double bond is replaced by a CF_2 group have been described[2-5].

Herein, we report an efficient method for the incorporation of a difluoromethylene group in an allylic position. We show its application to the synthesis of various alkenes and styrenes.

Table. $R^1R^2C{=}O \xrightarrow[2)\ CH_3COCl]{1)\ CF_2{=}CHLi} R^1R^2C(OAc)\text{-}CH{=}CF_2 \xrightarrow[CuCN,\ LiCl]{R^3MgX} R^1R^2C{=}CH\text{-}CF_2\text{-}R^3$

R^1	R^2	R^3	X	Yield[a] (%)	E/Z[b]	^{19}F NMR-δ(ppm)/$CFCl_3$ E	^{19}F NMR-δ(ppm)/$CFCl_3$ Z	Experimental conditions
n-Hex	H	Me	Br	75[c]	97/3	-87.3	-83.8	24h/20°C
n-Hex	H	n-Bu	Br	95	98/2	-95.1	-91.3	8h/-15°C
n-Hex	H	i-Pr	Br	94[d]	97/3	-103.8	-100.0	2h/-20°C
n-Hex	H	t-Bu	Cl	95	95/5	-109.0	-104.6	3h/-20°C
Thienyl	H	t-Bu	Cl	70	100/0	-108.9	--	1h/-20°C
$(CH_2)_5$		i-Pr	Br	85	--	-97.9		1h/-30°C

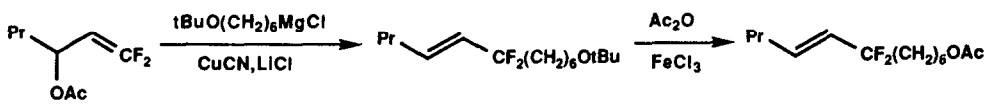
a: yield for the second step; b: E/Z ratio determined by ^{19}F NMR; c: containing also 15% of HexCH(Me)CH=CFMe (Z/E=4/1); d: 80% with only 2 eq. of R^3MgX.

Our procedure is based on two key steps; an initial reaction between difluorovinyl lithium, prepared with 1,1-difluoroethylene and s-BuLi, and various carbonyl compounds leads to the allylic β,β-difluorinated

alcoxides[6], which are acetylated *in situ*. Secondly, the intermediate acetates are attacked by Grignard reagents in the presence of copper and lithium salts *via* an S_N2', substitution reaction of an acetate moiety by an alkyl group, to afford the corresponding allylic difluorinated compounds with high regio- and stereoselectivities (no product of S_N2 is present and if R^2=H, the *E* isomer is major (≥95%)).

Experimental procedure: the treatment of carbonyl derivatives with 2,2-difluorovinyl lithium, prepared *in situ* from 1,1-difluoroethylene and s-BuLi in THF and Et_2O (80/20) at -100°C (15 min), leads to the difluorinated alcoxides which are acetylated *in situ* with AcCl (addition at -50°C, then 30 min at 0°C). In the case where $R^1,R^2=(CH_2)_5$, the alcohol is isolated and acetylated (Ac_2O, 4-DMAP, CH_2Cl_2, +20°C, 2h)[7]. To these intermediate acetates (5.10^{-3} mol,1 eq.), in the presence of CuCN (3 eq.) and LiCl (3 eq.) in THF (40 ml), is added the Grignard reagent (3eq.) (see Table) to afford the allylic difluorinated products which are then purified by flash silica-gel chromatography (pentane).

This methodology is exemplified by the preparation of the difluoromethylene allylic analogue of (E)-5-decenyl acetate, a sex pheromonal component of *Grapholita molesta* (oriental fruit moth). Previously, Fried *et al.* have reported a synthesis of the same difluorinated analogue[4].



The protected Grignard reagent reacts with the adequate acetate to afford the corresponding allylic difluoride ether in 65% yield (steric purity=97%)[8]. The ether function is then deprotected into the acetate with Ac_2O and $FeCl_3$ in Et_2O (80% yield, steric purity=93%)[8].

In conclusion, this route appears to be a general and highly regioselective method for the allylic introduction of a difluoromethylene group into various alkenes and styrenes. This reaction allows us to prepare readily products of high stereoisomeric and chemical purities, in good overall yields and in two steps from available starting materials.

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8. ^{19}F NMR: Ether: -95.2 (E,97%), -91.1 (Z,3%); Acetate: -95.3 (E,93%), -91.2 (Z,7%).

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