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A Concise Synthesis of Functionalised *gem*-Difluoroalkenes *via* the Addition of Organolithium Reagents to α-Trifluoromethylstyrene

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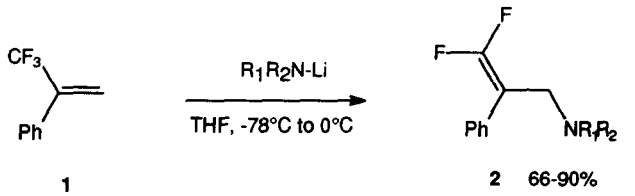
Keywords- *α-Trifluoromethylstyrene, gem-difluoroalkenes, organolithium reagents*

Abstract:- ***The treatment of α-trifluoromethyl styrene with organolithium reagents results in the selective formation of gem-difluoroalkenes in good to excellent yield. This reaction has been applied to the synthesis of a range functionalised gem-difluoroalkenes.***

There is considerable interest in the design of molecules of biological activity, which contain the *gem*-difluoroalkene or difluoromethylene moieties.[1,2] This property of difluoroalkenes coupled with the fact that they are versatile building blocks for the synthesis of compounds containing a difluoromethylene group makes them interesting synthetic targets.[3]

A variety of different synthetic strategies has been reported for the synthesis of *gem*-difluoroalkenes. For example, the addition of difluoromethylene ylides[4] or difluorophosphonate anions[5] to carbonyl groups have afforded alkenes. Other successful approaches have included the trapping of stabilised difluorovinyl anions derived from 1,1,1-trifluoroethanol,[6-9] the Reformastsky reaction of 4-chloro-4,4-difluorocrotonate,[3] and treatment of chlorodifluoromethyl epoxyethers with butyl lithium.[10]

A little utilised approach involves the addition of organolithium reagents to trifluoromethyl alkenes[11-14]. This strategy has only been applied successfully to the reaction of 1,1,1-trifluoropropene with simple organolithium reagents such as butyllithium[11], phenyl dimethyl silyl lithium[12] and more interestingly with lithium ester enolates.[13] The reaction of 2-trifluoromethylacrylic acid with butyllithium has been reported to be uncontrolable, with the formation of products arising from the addition of two molecules of butyllithium.[14] More recently, we have reported a concise synthesis of 3-*gem*-difluoro-2-phenyl allylic amines **2** in which the key step was the addition of N-lithiated amines to α-trifluoromethyl styrene **1** (Scheme 1).[15] The success of this reaction prompted us to investigate the reactivity of **1** towards organolithium reagents.

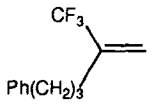


1 2 66-90%

Scheme 1

Our initial objective was to ascertain that the addition of organolithium reagents to α-trifluoromethyl styrene **1** was controllable. We therefore performed our initial investigations with simple commercial organolithium reagents. The addition of **1** to a solution of butyl lithium (1.2 equivalents) in THF at -78°C followed by warming to 0°C resulted in the formation of a mixture of the desired *gem*-difluoroalkene and monofluoroalkenes. These monofluoroalkenes were produced by the the well documented addition of an organolithium reagent to a difluoroalkene.[9] To prevent the occurrence of this process, the order of addition was reversed and the number of equivalents reduced to exactly one. In all cases the reaction of α-trifluoromethyl styrene **1** with commercial reagents (*n*-butyl-, *t*-butyl-, methyl-, phenyl-lithium) gave only the desired difluoroalkenes in excellent yield (Table 1 entries 1, 3, 5, 7) indicating that **1** is more reactive than the difluoroalkene product.

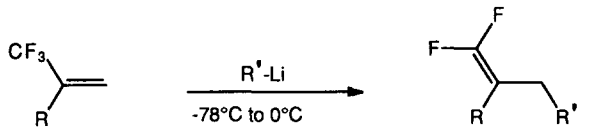
We then investigated the reactivity of functionalised organolithium reagents as a route to functionalised *gem*-difluoroalkenes (Table 1 entries 9-15). For these reagents, products arising from multiple addition were not detected even when **1** was added to a preformed solution of the organolithium reagent. In the light of this result, the order of addition chosen was the more practical addition of **1** to the preformed organolithium at -78 °C.[16] The reaction was successfull with organolithium reagents containing the phosphonate, sulphone, or sulphoxide functions and the desired *gem*-difluoroalkenes were isolated in excellent yields (entries 9, 11, 12 Table 1). A masked aldehyde in the form of a 1,3-dithian and the more readily deprotected diethylaminoacetonitrile were also introduced in high yield (entries 13, 14 Table 1). However unlike 1,1,1-trifluoropropene,[13] α-trifluoromethyl styrene **1** does not react with lithium ester enolates even after prolonged reaction times.



3

The generality of this reaction was investigated by studying the reactivity of a variety of organolithium reagents towards the α-trifluoromethyl-α-alkyl alkene **3** which is readily accessible by the Wittig olefination of the corresponding ketone.[17] The reaction of compound **3** with organolithium reagents such as butyl- or methyllithium were successful but when the reaction was extended to the less reactive phenyllithium or functionalised organolithium reagents, no reaction was observed.

In summary, we have demonstrated that the addition of organolithium reagents to substituted trifluoromethyl alkenes is a viable route to *gem*-difluoroalkenes and we have applied this synthetic strategy for the synthesis of a series of functionalised 1-*gem*-difluoro-2-phenyl alkenes from α-trifluoromethyl styrene **1.**



1 R=Ph
3 R=Ph$(CH_2)_3$

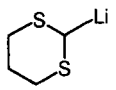
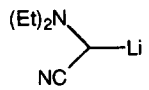
Entry	R	R'-Li	Solvent	Yield%[a,18]
1	Ph	CH_3Li	THF	90[b]
2	$Ph(CH_2)_3$	CH_3Li	THF	85[b]
3	Ph	*n*-C_4H_9Li	THF	93[b]
4	$Ph(CH_2)_3$	*n*-C_4H_9Li	THF	87[b]
5	Ph	*t*-C_4H_9Li	THF	92[b]
6	$Ph(CH_2)_3$	*t*-C_4H_9Li	THF	90[b]
7	Ph	C_6H_5Li	Et_2O	90[b]
8	$Ph(CH_2)_3$	C_6H_5Li	Et_2O	0[b]
9	Ph	$(EtO)_2P(O)CH_2Li$	Et_2O	85[c]
10	$Ph(CH_2)_3$	$(EtO)_2P(O)CH_2Li$	Et_2O	0[c]
11	Ph	$PhS(O)CH_2Li$	THF	83[c]
12	Ph	$PhS(O_2)CH_2Li$	THF	80[c]
13	Ph		THF	90[c]
14	Ph		Et_2O	86[c]
15	Ph	CH_2=CHLi	Et_2O	65[c]

Table 1

[a] Yields refer to chromatographically pure compounds; [b] Organolithium reagent added to a solution of **1** or **3**; [c] **1** or **3** to added to a solution of preformed organolithium reagent.

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(16) Diethylaminonitrile (0.45g, 0.004mol) was added at -78°C over 2 minutes to LDA prepared from n-butyl lithium (1.8mL of a 2.5M solution in hexanes) and diisopropylamine (0.73mL, 45.5mol) in diethylether (20mL). To this was added N,N,N',N'-tetramethylethylenediamine (0.67mL, 0.0045mol) and after a further 10min at -78°C α-trifluoromethylstyrene 1^{19} (0.7g, 0.004mol) was added. The reaction mixture was matained at -78°C for 30 minutes and then allowed to warm to 0°C over 1 hour. The brown solution was poured into saturated ammonium chloride solution, the layers separated and the aqueous phase extracted with diethyl ether (3 x 50mL). The combined organics were dried and evaporated to afford a brown oil which was purified by short-path distillation to give the desired 2-N,N,diethylamino-5,5-difluoro-4-phenyl-but-4-en nitrile as a clear oil (0.9g, 86%) Bp= 60°C at 0.5mm Hg. I.R neat 1730cm^{-1}($\upsilon_{C=C}$), ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -89.6 (br. d($W_{1/2}$= 2HZ.), J_{FF}=37.5Hz) -90.0 (td, J_{FF}=37.5Hz, J_{HF}= 2.3Hz); ^{1}H NMR δ 0.95 (t, J=7.1Hz, 6H), 2.32 (dq, J=13Hz, J=6.9Hz, 2H), 2.6 (dq, J=13Hz, J=6.9Hz, 2H), 2.8 (td J= 7.9Hz, J= 2.3Hz, 2H), 3.5 (t, J= 7.9Hz, 1H), 7.15-7.3 (m, 5H); ^{13}C NMR δ 12.95, 30.7, 45.1, 52.1(t, $^{3}J_{CF}$=2.3Hz), 88.7(dd $^{2}J_{CF}$=17Hz) 117.5, 128.4, 128.6, 131.9, 154.5 (dd $^{1}J_{CF}$= 288.7, 289.4Hz) Anal. Calc. for $C_{15}H_{18}N_2F_2$: C 68.2, H 6.8, N 10.6 found; C 68.5, H, 6.95, N, 11.0%.

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