A versatile and practical synthesis of α-trifluoromethylated alcohols from trifluoroacetaldehyde ethyl hemiacetal in water

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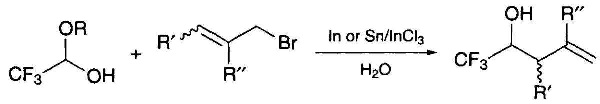
α-Trifluoromethylated alcohols *via* indium-mediated allylation of trifluoroacetaldehyde using a simple and practical preparation in water is described.

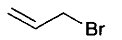
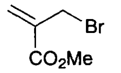
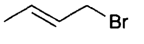
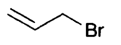
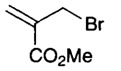
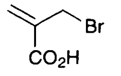
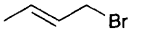
The synthesis of trifluoromethylated alcohols is an important aspect of organofluorine chemistry in relation to analytical and medicinal chemistry and opto-electric substances such as liquid crystals.[1] In principle, nucleophilic addition of trifluoroacetaldehyde to organometallic metals should provide an easy route to various trifluoromethyl alcohol compounds.[2] However, this is hindered by the exceptionally high electrophilicity of the CF_3 functionality in trifluoroacetaldehyde, resulting in a rather unstable and volatile compound that prefers to exist as a more stable hydrate form. Trifluoroacetaldehyde is thus commercially available as the ethyl hemiacetal form which limits its use in most synthetic approaches as most of the organometallic reactions have to be carried out under stringent anhydrous, non-protic conditions and is further complicated by the fact that the corresponding aldehyde which can be generated by dehydration is naturally unstable. Here we overcome some of these problems and describe two easy approaches to various trifluoromethyl homoallylic alcohols by the reaction of the trifluoroacetaldehyde hydrate or commercially available trifluoroacetaldehyde ethyl hemiacetal[3] with allylic indium[4] in water (Scheme 1).



1a R = H
b R = Et
2
3

Scheme 1

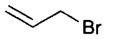
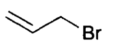
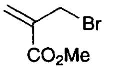
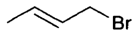
Table 1 Indium-mediated allylation[a]

Entry	R	Halide	Conditions	Yield (%)[b] (dr)[c]
1	H		In, H_2O, 15 h	81
2	H		In, H_2O, 15 h	82
3	H		In, H_2O, 15 h	70 (68:32)
4	Et		In, H_2O, 15 h	95
5	Et		In, H_2O, 15 h	87
6	Et		In, H_2O, 15 h	65
7	Et		In, H_2O, 15 h	80 (65:35)

[a] All reactions were carried out on 0.5–1 mmol scale. [b] Isolated yield. [c] Diastereoisomeric ratio (dr) was determined by ^1H NMR (relative stereochemistry not confirmed).

Commercially available trifluoroacetaldehyde ethyl hemiacetal **1b** reacted with allylic halides in the presence of indium with water as the electrophile. A typical procedure for the preparation of α-trifluoromethyl alcohols is as follows. The trifluoroacetaldehyde hydrate or trifluoroacetaldehyde ethyl hemiacetal (0.5 mmol), allylic halide (1.5 mmol) and indium (1 mmol) in water (5 ml) were stirred at room temperature for 15 h. The product was extracted with ether and purified in the usual manner. The results are summarized in Table 1.

Table 2 Indium trichloride promoted tin-mediated allylation[a]

Entry	R	Halide	Conditions	Yield (%)[b] (dr)[c]
1	Et		Sn, H_2O, 18 h	0
2	Et		Sn, $InCl_3$ (1 equiv.) H_2O, 15 h	85
3	Et		Sn, $InCl_3$ (1 equiv.) H_2O, 15 h	65
4	Et		Sn, $InCl_3$ (1 equiv.) H_2O, 15 h	72 (67:33)

[a] All reactions were carried out on 0.5–1 mmol scale. [b] Isolated yield. [c] Diastereoisomeric ratio (dr) was determined by ^1H NMR (relative stereochemistry not confirmed).

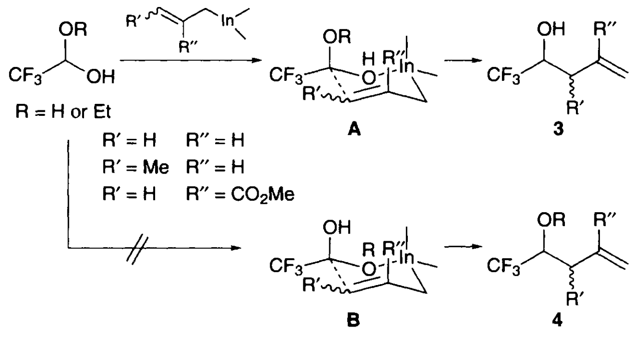
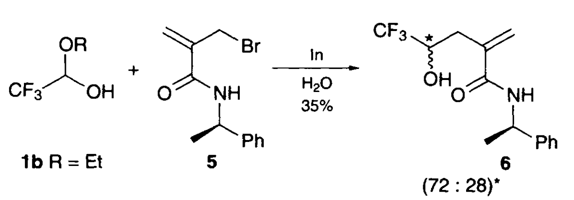


Fig. 1



1b R = Et
5
6

(72 : 28)*
(relative stereochemistry not confirmed)

Scheme 2

Several characteristic features were observed for these reactions. In every case, the reactions proceeded smoothly under extremely mild conditions (almost neutral) to give the corresponding 1-trifluoromethylated homoallylic alcohol in high yields. Generally, the reactions are clean, only the γ-coupled product and unreacted allylic bromide are recovered after the usual work-up. Furthermore, similar results were obtained when trifluoroacetaldehyde hydrate was used as the direct trifluoromethylating agent. The presence of an acid functional group does not affect the reaction, hence negating the use of protecting functionality. In the reaction of trifluoroacetaldehyde ethyl hemiacetal with an allylic metallic reagent in water, the corresponding 1-trifluoromethylated homoallylic alcohol was obtained as the product. In all cases, the possible ethoxy substituted compound was not detected.

Although the analogous carbon–carbon bond formation using trifluoroacetaldehyde ethyl hemiacetal, trifluroacetaldehyde N,O- and N,S-acetals in organic solvent has already been reported,[5] these reactions in water has been little reported in the literature. The allylation reaction of trifluoroacetaldehyde ethyl hemiacetal using tin as the mediated metal was also explored. Unlike those involving indium, this reaction does not proceed due to the lesser reactivity of tin. Recently, our group has found that indium trichloride-promoted tin-mediated allylation reactions of carbonyl compounds in water afforded the corresponding alcohols in high yields. The advantages of this indium trichloride mediated-tin reaction are both the cheapness of tin compared to indium metal and that, in contrast to the indium-mediated reaction which requires 3 equiv. of allylic halide, only 1 equiv. of allylic halide is required. Extending this methodology to trifluoroacetaldehyde ethyl hemiacetal in water provided the corresponding alcohols in good yields (Table 2).[4c]

The strong preference for compound **3** instead of **4** suggests the predominance of the six-membered intermediate **A** transition state over that of **B**, as predicted by HSAB theory, whereby the compatibility of the intermolecular forces between the organo-indium and the CF_3 alcoholic substrate resulted in the preferred complexation of intermediate **A**, hence the sole formation of the homoallylic alcohol.

Preliminary studies on the use of chiral bromide **5** are in progress leading to the production of compound **6** in morderate diastereoselectivity (72:28). Efforts to increase the selectivity are now underway.

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