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A Novel Method for Stereoselective Synthesis of β-Trifluoromethylated Homoallylic Alcohols in Water

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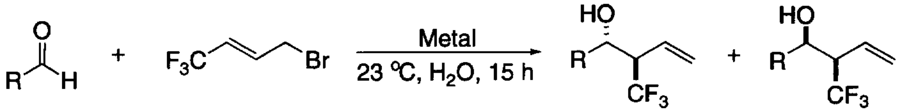
Abstract: The indium-mediated allylation reaction of aldehydes with 1,1,1-trifluoro-4-bromo-2-butene in water afforded an important trifluoromethylated building block β-trifluoromethylated homoallylic alcohol with high yield and excellent diastereoselectivity.

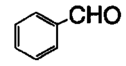
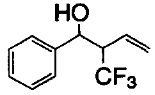
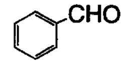
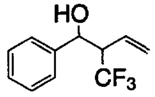
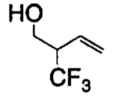
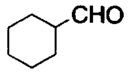
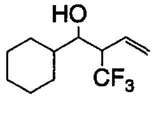
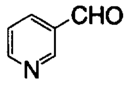
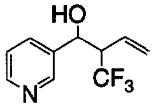
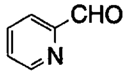
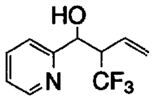
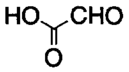
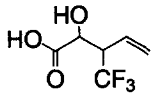
Trifluoromethylated compounds with their unique physiological and physical properties have been widely applied in various fields.[1] The synthesis of these compounds has thus become of considerable importance in all aspects of organic chemistry. However, the methodology for the preparation of trifluoromethylated compounds is very limited because of the low reactivity of various trifluoromethylating reagents and the requirement for mild reaction conditions.[2] One such way is through the use of organometallic trifluoromethylating reagent. However, the reported examples of introducing trifluoromethyl group into carbonyl compounds through organometallic reagents of zinc, calcium, manganese, magnesium, silver and lithium[3] suffered from the drawback of eliminating metal fluoride as side reaction. Therefore, the search for new organometallic trifluoromethylating reagents and their further utilization in synthesis is a new challenge to organic chemists. In connection with our interest to develop a practical method for the synthesis of organofluorine compounds in aqueous media,[4] the allylmetal trifluoromethylating reagents were investigated. A novel trifluoromethylating allylic reagent, 1,1,1-trifluoro-4-bromo-2-butene was prepared from 4,4,4-trifluorocrotonate and used in the allylation reaction of aldehydes in aqueous solution (Scheme 1).



Scheme 1

It was found that organometallic zinc insertion with 1,1,1-trifluoro-4-bromo-2-butene in allylation reaction with benzaldehyde, in saturated ammonium chloride solution, resulted in complicated mixture of fluorine compounds. The desirable product β-trifluoromethylated homoallylic alcohol was not detected in both zinc and tin mediated reaction. However, the indium-mediated allylation[5] gave the corresponding product in good yield. When various other aliphatic and aromatic aldehydes were used to react with the allylindium reagent in water, high yields and excellent diastereoselectivities were also obtained (Table 1). The reaction procedure was as follows. To the mixture of indium (1 mmol) and 1,1,1-trifluoro-4-bromo-2-butene (1.5 mmol) in H_2O (5 ml) was added aldehyde (0.5 mmol). The resulting suspension was stirred at room temperature for 15 h. The product was extracted with ethyl acetate, dried with anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuum. The product was purified by column chromatography over silica gel. The results are shown in Table 1.

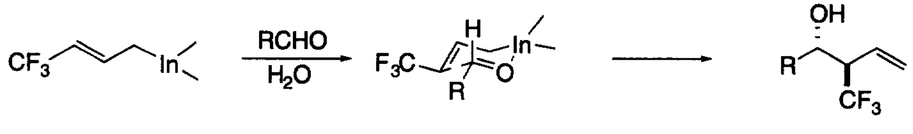
Table 1. Indium-mediated allylation reaction using 1,1,1-trifluoro-4-bromo-2-butene[a]

Entry	Aldehyde	Condition	Product	Yield(%)[b] (*anti:syn*)
1		In, DMF, 15 h		82[6] (85:15)
2		In, H_2O, 15 h		87 (92:8)
3	HCHO	In, H_2O, 15 h		86
4		In, H_2O, 15 h		90 (100:0)
5		In, H_2O, 15 h		95 (100:0)
6		In, H_2O, 15 h		88[6] (0:100)
7		In, H_2O, 15h		80 (4:96)

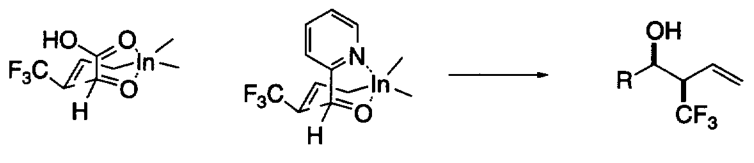
a. All reactions were carried out on 0.5-1 mmol scale. b. Isolated yield. The isomer ratio was determined by ^1H and ^{19}F NMR analysis.

The following points were observed for the indium-mediated allylation reactions. (1) In all cases, the reactions proceeded very smoothly at room temperature in aqueous media. The reactions were clean. After aqueous workup, the excess low boiling starting trifluoromethylated allylic bromide was easily removed. High yields of the coupling products were obtained. (2) The reaction was found to give higher diastereoselectivity in water than in DMF (entries 1 and 2). (3) Water soluble substrates such as formaldehyde and glyoxylic acid could be used directly in these reactions. (4) Only γ-coupling products were obtained in all described cases. (5) The diastereoselectivities in the reactions were excellent. The *anti* products predominate in most allylation reactions. Only when 2-pyridinecarboxylaldehyde and glyoxylic acid were used, the *syn* product was preferred.

The excellent diastereoselectivity obtained in the allylation by trifluoromethylated allylindium reagent in water can be explained by the following mechanism (Figure 1). In the six-membered transition state, the CF_3 and substituent of aldehyde will be in the equatorial position and the reaction afforded mainly the *anti* product. In contrast, when 2-pyridinecarboxaldehyde and glyoxylic acid were used, the 5-membered ring chelation with indium as seen in Figure 1 was probably formed, locking the 2-pyridine and COOH group in the axial position, hence leading to high *syn* -selectivity. It also confirms the finding of both Corey, Kitazume and Yamazaki.[7] showing that trifluoromethyl group to be a highly steric group thereby resulting in the excellent diastereoselectivity obtained.



R = Ph , Cyclohexyl or 3-Pyridine



R = COOH

R = 2-Pyridine

Figure 1

In conclusion, we have described a very efficient method for introducing trifluoromethyl group to carbonyl compounds. In this reaction, the important β-trifluoromethylated homoallylic alcoholic intermediate was synthesized in high yield and selectivity in water. The simplicity of reaction procedures will no doubt serve as a practical method in the synthesis of various biologically active compounds. Further investigations are in progress to synthesize optically pure organofluorine compounds using this methodology.[8]

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Tokyo, **1982**. (d) Banks, R. E. Ed. *Preparation, Properties and Industrial Applications of Organofluorine Compounds*, Ellis Horwood, Chichester, **1982**. (e) Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, 2nd Ed., Ellis Horwood, Chichester, **1976**. (f) Chambers, R. D. *Fluorine in Organic Chemistry*, Wiley-interscience, New York, NY, **1973**. (g) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*, Wiley, New York, NY, **1990**. (h) Ishikawa, N. Ed. *Synthesis and Reactivity of Fluorocompounds*, CMC, Tokyo, **1987**, Vol. 3. (i) Resnati, G. *Tetrahedron* **1993**, *49*, 9385-9445.

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6. The stereochemical configurations were confirmed by chemical manipulations to the corresponding acetonides. The β-trifluoromethylated homoallylic alcohols were ozonolyzed and then reduced to diols. The diols reacted with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-TsOH to furnish the acetonides. The *anti* and *syn* stereochemistry of the β-trifluoromethylated homoallylic alcohols were deduced from the ^{1}H NMR coupling constant of the axial proton adjacent to both the hydroxy and trifluoromethyl group in acetonide respectively.
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