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A Simple and Practical Synthesis of α-Trifluoromethylated Alcohols in Water

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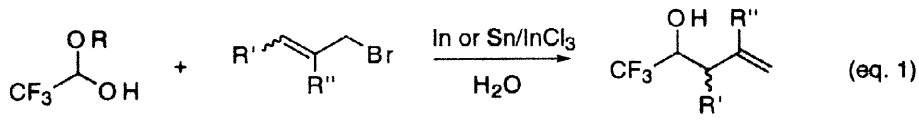
Abstract: A simple and practical preparation of α-trifluoromethylated alcohols in water *via* indium-mediated allylation reaction and tin-mediated indium trichloride-promoted allylation reaction of trifluoroacetaldehyde hydrate and its ethyl hemiacetal is described in this paper.

Keywords: α-Trifluoromethylated alcohols; Allylation; Indium; Water

Introduction

Organofluorine compounds have attracted great interest among organic chemists during the last few decades.[1] Their unique physical, chemical and physiological properties have made them applicable to various fields such as analytical chemistry, medicinal chemistry, agricultural chemistry and biochemistry. The synthesis of trifluoromethylated alcohols is an important aspect of organofluorine chemistry. In principle, nucleophilic addition organometallics to trifluoroacetaldehyde with should provide easy entry into various trifluoromethylated hydroxy 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 the 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 as mentioned unstable in nature. This research overcomes some of these problems and describes 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 (eq. 1).[5]



R = H or R = Et

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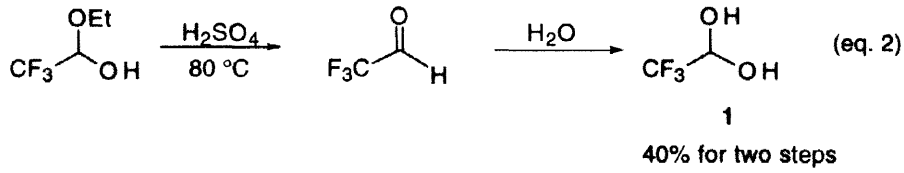
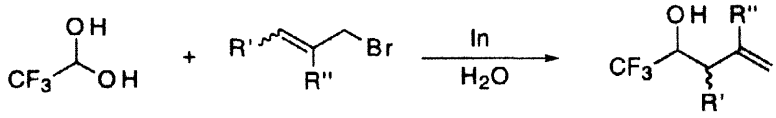
Results and Discussion

Indium-Mediated Allylation Reaction of Trifluoroacetaldehyde Hydrate. As reported before,[6] the hydrate form of aldehydes such as glyoxylic acid can directly undergo tin- or indium-mediated allylation reactions in aqueous media under certain conditions. Furthermore, trifluoroacetaldehyde prefers to exist in its stable hydrate form. In connection with our aim to develop a new method for trifluoromethylation in aqueous media, it is envisaged that trifluoroacetaldehyde hydrate **1** can be used to replace the volatile trifluoroacetaldehyde in the allylation reaction in aqueous media. Therefore, heating the commercially available trifluoroacetaldehyde ethyl hemiacetal in acidic conditions produced the gaseous trifluoroacetaldehyde which was trapped by water to afford the trifluoroacetaldehyde hydrate **1** water solution (eq. 2).



(eq. 2)

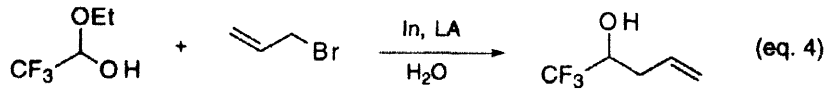
This trifluoroacetaldehyde hydrate water solution was then used directly in the indium-mediated allylation reaction (eq. 3). The results are summarized in Table 1.



(eq. 3)

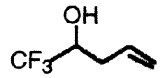
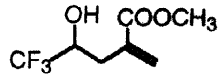
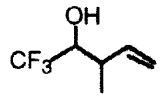
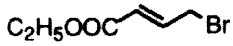
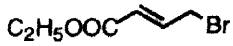
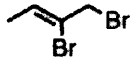
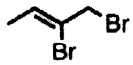
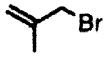
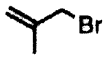
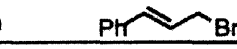
As expected, this hydrate was found to react with allyl bromide smoothly in the presence of indium powder to afford the corresponding product in good yield (Table 1, entry 1). Further investigation showed that other allylic halides such as crotyl bromide and methyl 2-bromomethylacrylate also underwent this indium-mediated allylation reaction. Good yields and moderate diastereoselectivities were obtained (entries 2, 3). However, the indium-mediated reaction between trifluoroacetaldehyde hydrate and the less reactive allylic halides such as ethyl bromocrotonate gave a complex mixture of undesirable products (entry 4). Furthermore, no reaction was observed with 3-bromo-4-bromo-2-butene and 3-bromo-2-methyl-1-butene (entries 6, 8). Addition of ytterbium triflate does not help in any of these cases (entries 5, 7, 9).

Indium-Mediated Allylation Reaction of Trifluoroacetaldehyde Ethyl Hemiacetal in Water. In spite of the good results obtained using trifluoroacetaldehyde hydrate in the allylation reaction in water, the trifluoroacetaldehyde hydrate has to be prepared from trifluoroacetaldehyde ethyl hemiacetal as described above. Furthermore, trifluoroacetaldehyde hydrate is usually obtained in low yield. Thus, a more convenient and economical method is required. The direct use of trifluoroacetaldehyde ethyl hemiacetal in the indium-mediated allylation reaction was attempted. The indium-mediated allylation reaction of trifluoroacetaldehyde ethyl hemiacetal with allyl bromide was performed at room temperature in water both in the presence and absence of Lewis acid (eq. 4). The results are listed in Table 2.



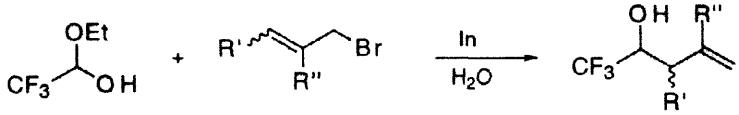
(eq. 4)

Table 1 Indium-Mediated Allylation Reaction of Trifluoroacetaldehyde Hydrate[a]

Entry	Halide	Conditions	Product	Yield, %[b] (ratio)[c]
1		In, H_2O, 15 h	 **2**	81
2		In, H_2O, 15 h	 **3**	82
3		In, H_2O, 15 h	 **4**	70 (68:32)
4		In, H_2O, 15 h	complex mixture	0
5		In, $Yb(OTf)_3$, H_2O, 15 h	complex mixture	0
6		In, H_2O, 15 h	-	no reaction
7		In, $Yb(OTf)_3$, H_2O, 15 h	-	no reaction
8		In, H_2O, 15 h	-	no reaction
9		In, $Yb(OTf)_3$, H_2O, 15 h	-	no reaction
10		In, H_2O, 15 h	-	no reaction

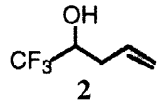
a All reactions were carried out on 0.5-1 mmol scale. b. Isolated yield. c. Diastereomeric ratio was determined by ^1H NMR and ^{19}F NMR spectroscopic analyses (relative stereochemistry not confirmed).

Surprisingly, these Lewis acids which have been reported as good promoters in most of the allylation reactions had a negative effect on the reaction of trifluoroacetaldehyde ethyl hemiacetal (Table 2, entries 2, 3). Next, we carried out the reactions of trifluoroacetaldehyde ethyl hemiacetal with various allylic halides in the presence of indium in water (eq. 5).



(eq. 5)

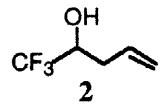
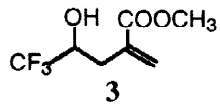
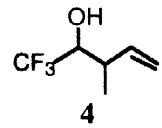
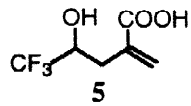
Table 2 Indium-Mediated Allylation Reaction of Trifluoroacetaldehyde Ethyl Hemiacetal with Allyl Bromide[a]

Entry	Halide	Conditions	Product	Yield (%)[b]
1		In, H_2O, 15 h	 **2**	95
2		In, $La(OTf)_3$ (1 eq.), H_2O, 15 h	**2**	54
3		In, $Yb(OTf)_3$ (1 eq.), H_2O, 15 h	**2**	43

a All reactions were carried out on 0.5-1 mmol scale. b. Isolated yield.

As expected, the reactions using crotyl bromide and methyl-(2-bromomethyl) acrylate occurred smoothly and afforded the corresponding products in good yields (Table 3). The diastereoselectivity in the indium-mediated allylation reaction of crotyl bromide is almost the same as with the reaction of trifluoroacetaldehyde hydrate (Table 3, entry 3). Furthermore, bromomethyl acrylic acid can be directly used in this allylation reaction. The acid functionality did not affect the reaction and the product was obtained in moderate yield (entry 4). It is also noteworthy that the possible cyclized γ-lactone product was not observed.

Table 3 Indium-Mediated Allylation Reaction of Trifluoroacetaldehyde Ethyl Hemiacetal[a]

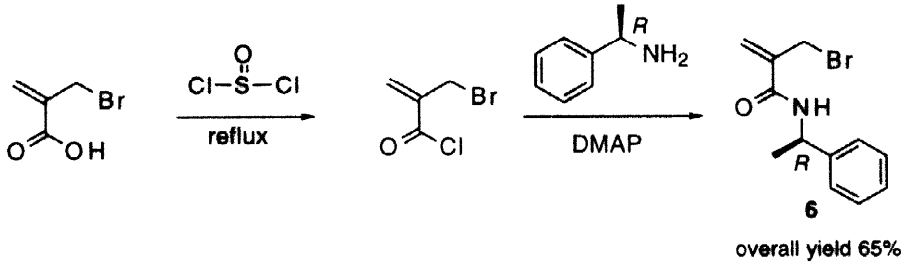
Entry	Halide	Conditions	Product	Yield (%)[b] (ratio)[c]
1		In, H_2O, 15 h	 **2**	95
2		In, H_2O, 15 h	 **3**	87
3		In, H_2O, 15 h	 **4**	80 (65:35)
4		In, H_2O, 15 h	 **5**	65

a All reactions were carried out on 0.5-1 mmol scale. b. Isolated yield. c. Diastereomeric ratio was determined by ^1H NMR spectroscopic analysis (relative stereochemistry not confirmed).

Based on these results, the less reactive allylic halides such as 2-methyl-4-bromo-2-butene, ethyl 4-bromocrotonate, cinnamyl bromide and geranyl bromide were also used in the indium-mediated allylation reaction

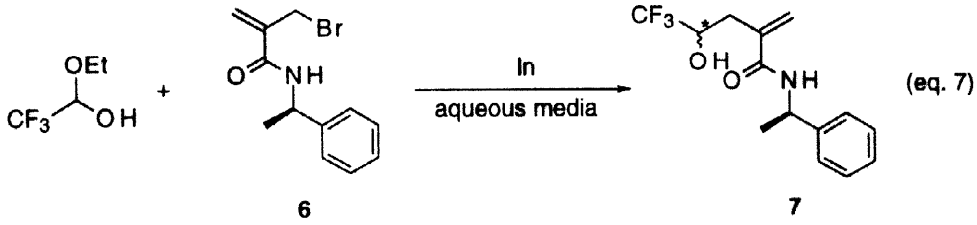
of trifluoroacetaldehyde ethyl hemiacetal in water. Unfortunately, the reactions were generally complex and the desired products were not obtained even in the presence of Lewis acids such as $La(OTf)_3$ and $Yb(OTf)_3$. Besides, the change of solvent from water to a mixture of ethanol/water (1:1) in the indium-mediated allylation reaction of trifluoroacetaldehyde ethyl hemiacetal with unreactive ethyl 4-bromocrotonate also did not afford the desired product.

Following these investigations, we further studied the allylation reaction of trifluoroacetaldehyde ethyl hemiacetal with an allylic bromide bearing a chiral auxiliary. The (α-methylbenzyl)-2-methylene-3-bromo-propanamide **6** was chosen because it can be prepared in optically pure form from commercially available chiral amine and 2-bromomethyl acrylic acid. The 2-bromomethyl acrylic acid was converted to its acyl chloride using thionyl chloride under refluxing conditions. After removing the excess thionyl chloride *in vacuo*, the acyl chloride formed in *situ* was reacted with *R*-(+)-α-methylbenzyl amine catalyzed by DMAP to produce the desired chiral allylic bromide **6** in good yield (eq. 6). Interestingly, if triethylamine was added into the second step to remove the HCl formed in the reaction, the cyclized β-lactam was obtained.



(eq. 6)

The optically pure (α-methylbenzyl)-2-methylene-3-bromo-propanamide **6** obtained was then applied in the allylation reaction in water. However, no reaction was observed in this case. It was found that the solid starting allylic bromide did not dissolve in water at all. This observation implies that the indium species cannot be formed under this condition due to low solubility of the amide in water. Therefore, the reaction was carried out in aqueous media (eq. 7).



(eq. 7)

The chiral amide was dissolved in a small amount of DMF followed by the addition of indium powder. The resulting mixture was allowed to stir at room temperature for 15 h and then trifluoroacetaldehyde ethyl hemiacetal and water were added into the reaction mixture. After usual workup, the desired product **7** was obtained in only 35% isolated yield. The reaction does not proceed to completion even when excess trifluoroacetaldehyde ethyl hemiacetal was added. The diastereofacial selectivity is moderate as determined by ^1H NMR and ^{19}F NMR spectroscopic analyses. The absolute configuration of the newly created stereogenic center was not confirmed. In search of a more efficient method for this allylation reaction, THF was used to replace DMF to dissolve the chiral

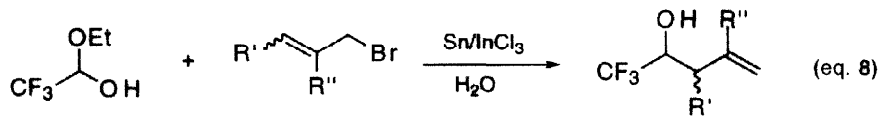
amide. Under the same conditions, the reaction gave only trace amounts of the product. Whereas, a successful reaction was observed with a mixture of ethanol and water (1:1). The chiral amide **6** was found to have completely converted to the corresponding trifluoromethylated product **7** at room temperature. However, no diastereoselectivity was observed (Table 4).

Table 4 Solvent Effect on the Allylation Reaction of Chiral Allylic Bromide[a]

Entry	Solvent	Yield[b] (%)	Diastereofacial selectivity[c] (%)
1	H_2O	0	-
2	THF/H_2O (1:25)	trace	-
3	DMF/H_2O (1:25)	35	70:30
4	ethanol/H_2O (1:1)	70	50:50

a All reactions were carried out on 0.5-1 mmol scale. b. Isolated yield. c. diastereomeric ratio was determined by ^1H NMR and ^{19}F NMR spectroscopic analyses (relative stereochemistry not confirmed).

Tin-Mediated Indium Trichloride-Promoted Allylation Reaction of Trifluoroacetaldehyde Ethyl Hemiacetal in Water. Next, we applied the methodology of indium trichloride-promoted tin-mediated allylation reactions of carbonyl compounds in water[6] for the synthesis of α-trifluoromethylated homoallylic alcohols. Thus, commercially available trifluoroacetaldehyde ethyl hemiacetal was employed in the indium trichloride-promoted tin-mediated allylation reactions (eq. 8). The results are summarized in Table 5.



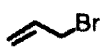
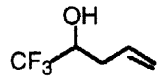
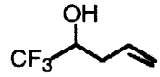
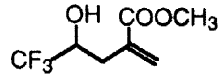
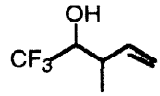
(eq. 8)

Initial allylation reactions of the trifluoroacetaldehyde hemiacetal with allyl bromide were carried out both with indium trichloride and without indium trichloride in water. In contrast to the described allylation reactions of reactive aldehydes, such as benzaldehyde which gave the product under both conditions, the allylation of trifluoroacetaldehyde ethyl hemiacetal did not occur in the absence of indium trichloride (Table 5, entry 2). The addition of 0.1 equivalent of indium trichloride in the presence of tin lead to the corresponding product in only a trace amount (entry 3). The addition of 1 equivalent of indium trichloride in relation to the hemiacetal dramatically promoted the reaction to afford the 4-hydroxyl-5,5,5-trifluoro-1-butene **2** in good yield (entry 4). The result in entry 1 showed that both indium trichloride and tin are necessary for the success of this reaction. These results provided new evidence that the water-stable indium trichloride Lewis acid can promote tin-mediated allylation reactions in water. Next, we replaced the allylic bromide with crotyl bromide. The reaction also occurred smoothly at room temperature in water in the presence of indium trichloride. Moderate diastereoselectivity was observed. These results are shown in Table 5.

Interestingly, in all cases, the indium-mediated and tin-mediated indium trichloride-promoted allylation reactions gave the γ–coupling products without any detection of the α-coupling products. Besides, the possible ethoxy substituted compound **8** (Figure 1) was never detected and only the corresponding 1-trifluoromethylated

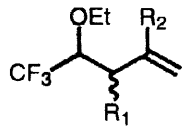
homoallylic alcohol was obtained. It is also noteworthy that the reaction of crotyl bromide with trifluoroacetaldehyde hydrate or ethyl hemiacetal in both indium-mediated allylation and tin-mediated indium trichloride-promoted allylation gave the corresponding product with similar diastereoselectivity. These results

Table 5 Indium Trichloride-Promoted Tin-mediated Allylation of Trifluoroacetaldehyde Ethyl Hemiacetal[a]

Entry	Halide	Conditions	Product	Yield (%)[b] (ratio)[c]
1		$InCl_3$ H_2O, 18 h	-	0
2		Sn, H_2O, 18 h	-	0
3		Sn, $InCl_3$ (0.1 eq.) H_2O, 15 h	 **2**	trace
4		Sn, $InCl_3$ (1 eq.) H_2O, 15 h	 **2**	85
5		Sn, $InCl_3$ (1 eq.) H_2O, 15 h	 **3**	65
6		Sn, $InCl_3$ (1 eq.) H_2O, 15 h	 **4**	72 (67:33)

a All reaction were carried out on 0.5-1 mmol scale. b. Isolated yield. c. Diastereomeric ratio was determined by ^1H NMR (relative stereochemistry not confirmed).

imply that the reactions involving the two different kind of allylic indium species may have the same transition state which is dependent on the substituents of the allylic halide and the aldehyde used, but not on the substituent of the allylic indium.



8

Figure 1

Mechanistic Study. In the reported analogous carbon-carbon bond formation reaction using trifluoroacetaldehyde ethyl hemiacetal,[3,7] trifluoroacetaldehyde N,O-acetals[8] and N,S-acetals,[9] the Lewis acids in all cases are essential for the success of the reactions. In addition, these reactions must be carried out under strict anhydrous conditions. The application of trifluoroacetaldehyde ethyl hemiacetal in water as in our studies has

never been reported. To explain the observation that the allylation reactions of trifluoroacetaldehyde ethyl hemiacetal gave only the homoallylic alcohols **10** without the possible ethoxy product **8**, the six-membered ring transition state formed from trifluoroacetaldehyde ethyl hemiacetal and allylic indium species was suggested to be intermediate **9** instead of **11** as predicted by HSAB theory. Generally, the indium species was thought to be a hard acid and preferred to combine with a hard base. The hydroxyl group is a harder base than the ethoxyl group, whereby the compatibility of the intermolecular forces between the organoindium and the CF_3 alcoholic substrate resulted in the predominate complexion of intermediate **9** which lead to the sole formation of the homoallylic alcohol **10** (Figure 2).

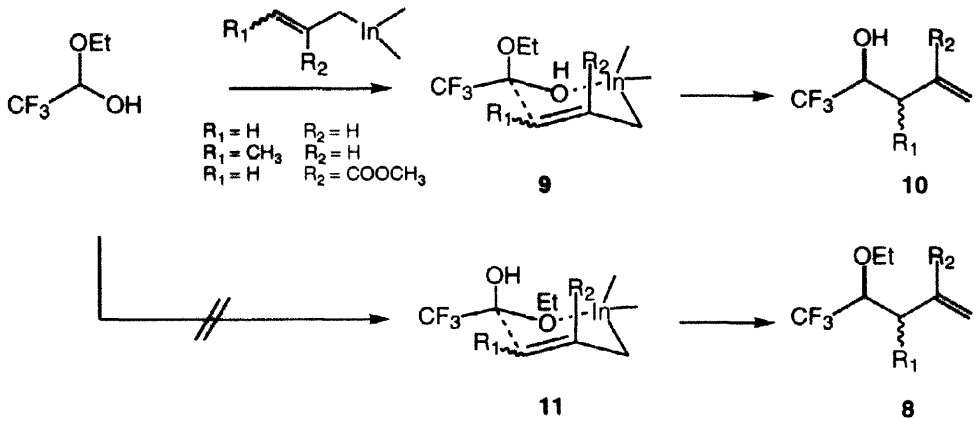


Figure 2 Mechanism of the Allylation of Trifluoroacetaldehyde Ethyl Hemiacetal

On the other hand, the effect of Lewis acid such as $Yb(OTf)_3$ on the allylation reaction of trifluoroacetaldehyde ethyl hemiacetal or hydrate is different from that on the allylation reaction of normal aldehydes. It is possible that the Lewis acid may combine with trifluoroacetaldehyde hydrate or ethyl hemiacetal and hence hinder formation of the six-membered ring transition state **9**.

Conclusion

The tin-mediated indium trichloride-promoted and indium-mediated allylation reactions of trifluoroacetaldehyde ethyl hemiacetal and hydrate with various allylic halides were successfully carried out in water. These reactions have the following characteristic features: (1) The reactions using reactive allylic halides proceeded smoothly under extremely mild conditions (almost neutral) to give the corresponding 1-trifluoromethylated homoallylic alcohols in high yields. (2) Generally, the reactions were clean, only the γ-coupled product and unreacted allylic bromide were recovered after usual workup. (3) The presence of an acid functional group did not affect the reaction, hence removing the need for protecting groups. (4) 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.

Therefore, two of the most practical methods for the synthesis of homoallylic trifluoromethylated alcohols have been developed. The simplicity of the reaction procedures will no doubt serve as a practical method for the synthesis of α-trifluoromethylated alcohols which may be readily transformed into various biologically active

compounds. Further investigation to develop an asymmetric version of these reactions is ongoing in our group.

Experimental Section

Materials and Methods. The trifluoroacetaldehyde ethyl hemiacetal was purchased from Fluka Chemical company and used directly in the reaction. Analytical thin layer chromatography was performed using Merck 60 F_{254} precoated silica gel plates (0.2 mm thickness). Subsequent to elution, ultraviolet illumination at 254 nm was allowed for visualization of UV active material. Staining with iodine vapour or a solution of potassium permanganate was used for further visualization. Flash chromatography was performed using Merck silica gel 60 (40 - 63 μm particle size) and distilled solvents. Columns were typically packed as a slurry and equilibrated with the appropriate solvents prior to use. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. Optical rotations were determined using a Jasco DIP-1000 digital polarimeter. Proton nuclear magnetic resonance spectra (^{1}H NMR) and carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a Bruker ACF 300 or 500 nuclear magnetic resonance spectrometer at the frequency indicated. Mass spectral analyses were carried out on a VG7035 Micromass mass spectrometer and were reported in units of mass to charge (*m/z*). Electron impact (EI) at an ion current of 70 eV was used for fragmentation of molecules.

Preparation of trifluoroacetaldehyde hydrate (1) water solution. To the trifluoroacetaldehyde ethyl hemiacetal (2.32 mL, 90%, 20 mmol) was added concentrated H_2SO_4 (0.109 mL, 98%, 2 mmol). Heating the resulting mixture at 90 °C and collecting the gas with 5 mL of water afforded an aqueous solution of trifluoroactaldehyde hydrate. According to the increased weight (930 mg, 8 mmol, 40% yield), the concentration was adjusted to 1M and directly used for the allylation reactions.

Representive procedure for the indium-mediated allylation reaction of trifluoroacetaldehyde hydrate in water: preparation of methyl 2-(3,3,3-trifluoro-2-hydroxypropyl)prop-2-enoate (3). To a solution of trifluoroacetaldehyde hydrate in water (1 mL, 1M, 1 mmol) was added indium powder (228 mg, 2 mmol) and water (4 mL) followed by methyl 2-(bromomethyl) acrylate (0.36 mL, 3 mmol) at room temperature. After stirring for 15 h, ether (50 mL) was added to extract the product. The solution was then washed with water, brine, dried over $MgSO_4$. After filtration, the solvent was removed in vacuum and the crude product was purified by silica gel column chromatography (hexane: ethyl acetate 8:1) to afford the pure product as colorless oil in 82% yield (163 mg).

Rf 0.46 (hexane: ethyl acetate 4:1); FTIR (thin film): υ 3453.4, 2959.5, 1720.9, 1632.2, 1450.8, 1279.1, 1159.5, 1099.7 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.63 (dd, J = 9.6 Hz and J = 14.4, 1H, CH_2), 2.76 (dd, J = 2.3 Hz and J = 14.4 Hz, 1H, CH_2), 3.81 (s, 3H, OCH_3), 4.10-4.14 (m, 1H, CHOH), 5.82 (s, 1H, CH=), 6.35 (s, 1H, CH=); ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 33.42, 52.49, 69.85 (q, J = 30.9 Hz), 124.83 (q, J = 282.2 Hz), 129.80, 134.89, 168.25; ^{19}F NMR (84.2 MHz, $CDCl_3$): δ -4.08 (d, J = 7.32 Hz, CF_3) (TFA); EIHRMS: Calcd. for. $C_7H_9F_3O_3$: 198.0504 found: 198.0482.

Representive procedure for the indium-mediated allylation reaction of trifluoroacetaldehyde ethyl hemiacetal in water: preparation of 1,1,1-trifluoropent-4-en-2-ol (2).[10] To a suspension of indium powder (5.74 g, 50 mmol) in water (50 mL) was added allyl bromide (6.50 mL, 75 mmol) followed by trifluoroacetaldehyde ethyl hemiacetal (2.90 mL, 25 mmol) at room temperature. The resulting mixture was stirred for 15 h at room temperature and then extracted with minimum ether (50 mL). The ether solution was then washed with water, brine, dried over anhydrous $MgSO_4$. After filtration, the ether was removed by slowly blowing with nitrogen. The crude product was then distilled to afford the pure compound as colorless oil in 95%

yield (3.32 g).

Rf 0.42 (hexane: ethyl acetate 4:1); bp: 35-36 °C/ 30 mmHg; FTIR (thin film): υ 3386.7, 2927.3, 1643.7, 1279.1, 1174.0, 1100.2 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.25 (d, J = 5.8 Hz, 1H, OH), 2.37-2.43 (m, 1H, CH_2), 2.50-2.55 (m, 1H, CH_2), 3.98-4.02 (m, 1H, CHOH), 5.22-5.27 (m, 2H, CH_2=), 5.80-5.88 (m, 1H, CH=); ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 34.40, 69.69 (q, J = 30.2 Hz), 119.87, 127.15 (q, J = 282.9 Hz), 131.69; ^{19}F NMR (84.2 MHz, $CDCl_3$): δ -3.880 (d, J = 7.3 Hz, CF_3) (TFA); EIHRMS: Calcd. for.$C_5H_7F_3O$: 140.0449 found: 140.0456.

Representive procedure for the tin-mediated indium trichloride promoted allylation reaction of trifluoroacetaldehyde ethyl hemiacetal: preparation of methyl 2-(3,3,3-trifluoro-2-hydroxypropyl)prop-2-enoate (3). To a mixture of tin powder (119mg, 1mmol), indium trichloride (221 mg, 1 mmol), and methyl 2-(bromomethyl) acrylate (0.12 mL, 1 mmol) in water (5 mL) was added trifluoroacetaldehyde ethyl hemiacetal (0.058 mL, 0.5 mmol) at room temperature. After stirring for 15 h at room temperature, ether (50 mL) was added to extract the product. The solution was then washed with water, brine, dried over $MgSO_4$. After filtration, the solvent was removed in vacuum and the crude product was purified by silica gel column chromatography (hexane: ethyl acetate 8:1) to afford the pure product as as colorless oil in 65% yield (64.5 mg).

1,1,1-Trifluoro-3-methylpent-4-en-2-ol (4).[10] colorless oil; *Rf* 0.45 (hexane: ethyl acetate 4:1); FTIR (thin layer): υ 3386.3, 2940.2, 1642.4, 1276.3, 1162.9, 1151.5 cm^{-1}; major isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (d, J = 0.8 Hz, 3H, CH_3), 2.17 (d, J = 7.2 Hz, 1H, OH), 2.61-2.71 (m, 1H, $CHCH_3$), 3.76-3.86 (m, 1H, CHOH), 5.12-5.26 (m, 2H, CH_2=), 5.75-5.93 (m, 1H, CH=); ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 16.41, 37.98, 73.05 (q, J = 29.8 Hz), 118.19, 126.57 (q, J = 282.3 Hz), 136.72; ^{19}F NMR (84.2 MHz, $CDCl_3$): δ -0.38 (d, J = 7.3 Hz, CF_3) (TFA).

minor isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (d, J = 0.7 Hz, 3H, CH_3), 2.18 (d, J = 6.8 Hz, 1H, OH), 2.61-2.71 (m, 1H, $CHCH_3$), 3.87-3.92 (m, 1H, CHOH), 5.12-5.26 (m, 2H, CH_2=), 5.75-5.93 (m, 1H, CH=); ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 14.17, 38.71, 73.29 (q, J = 30.1 Hz), 116.48, 128.28 (q, J = 282.5 Hz), 138.56. ^{19}F NMR (84.2 MHz, $CDCl_3$): δ 0.20 (d, J = 7.3 Hz, CF_3) (TFA). EIHRMS: Calcd. for $C_6H_9F_3O$: 154.0606 found: 154.0629.

2-(3,3,3-trifluoro-2-Hydroxypropyl)prop-2-enoic acid (5). white solid; *Rf* 0.59 (hexane : ethyl acetate 1:2); FTIR (KBr): υ 3435.5, 1698.7, 1628.3, 1441.2, 1265.6, 1151.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.65 (dd, J = 9.6 Hz and J = 14.4 Hz, 1H, CH_2), 2.77 (dd, J = 2.9 Hz and J = 14.4 Hz, 1H, CH_2), 3.88 (brs, 1H, OH), 4.09-4.23 (m, 1H, CHOH), 5.93 (s, 1H, CH_2=), 6.50 (s, 1H, CH_2=); ^{13}C NMR (75.4 MHz, $CDCl_3$): 32.87, 69.66 (q, J = 31.2 Hz), 124.74 (q, J = 282.0 Hz), 132.18, 134.17, 171.58. ^{19}F NMR (84.2 MHz, $CDCl_3$): δ -4.11 (d, J = 7.3 Hz, CF_3) (TFA); EIHRMS: Calcd. for. $C_6H_7F_3O_3$: 180.0347 found: 180.0349.

Preparation of *N*-((*1R*)-1-phenylethyl)-2-(bromomethyl)prop-2-enamide (6). To the 2-(bromomethyl)acrylic acid (825 mg, 5 mmol) was added fresh distilled thionyl chloride (1.094 mL, 15 mmol). The resulting solution was refluxed for 2 h then the excess thionyl chloride was removed *in vacuo*. The formed acyl chloride was dissolved in CH_2Cl_2 (10 mL). To the acyl chloride was added the solution of DMAP (61 mg, 0.5 mmol) and (*R*)-(+)-α-methylbenzylamine (0.58 mL, 4.5 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The reaction mixture was stirred at that temperature for 2h, warmed to room temperature, and stirred for another 15 h. The product was extracted with ethyl acetate (2x50 mL), washed with water, 5% $NaHCO_3$ solution, and brine, and

dried over anhydrous $MgSO_4$. After filtration, the solvent was removed *in vacuo* to afford the crude product which was purified by column chromatography on silica gel (hexane: ethyl acetate 1:1) (783.9 mg, 65% yield). yellow solid; *Rf* 0.59 (hexane:ethyl acetate 1:1); $[\alpha]_D^{33}$ +53 (c = 1, $CHCl_3$); FTIR (KBr): υ 3301.1, 1708.5, 1619.2, 1538.3 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.56 (d, J = 6.9 Hz, 3H, CH_3), 4.30 (d, J = 12.4 Hz, 1H, CH_2Br), 4.34 (d, J = 12.4 Hz, 1H, CH_2Br), 5.17-5.23 (m, 1H, CHNH), 5.69 (s, 1H, CH_2=), 5.85 (s, 1H, CH_2=), 6.24 (brs, 1H, NH), 7.28-7.37 (m, 5H, aryl H); ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 21.70, 43.57, 49.16, 121.91, 126.14, 127.51, 128.76, 141.24, 142.80, 165.50. EIHRMS: Calcd. for $C_{12}H_{14}NO$ (M^+-Br^{79})$^+$: 188.1075 found 188.1101.

Procedure of indium-mediated allylation reaction of trifluoroacetaldehyde ethyl hemiacetal with *N*-((*1R*)-1-phenylethyl)-2-(bromomethyl)prop-2-enamide 6 in aqueous medium: To a solution of *N*-((*1R*)-1-phenylethyl)-2-(bromomethyl)prop-2-enamide (**6**) (134 mg, 0.5 mmol) in DMF (0.2 mL) was added indium powder (114.8 mg, 1 mmol). The resulting mixture was allowed to stir at room temperature for 15 h and then trifluoroacetaldehyde ethyl hemiacetal (0.116 mL, 1 mmol) and water (5 mL) were added into the reaction mixture.After stirring for 40 h at room temperature, the product was extracted with ethyl acetate (3x20 mL). The combined organic extracts were washed with 0.5 MHCl (5 mL), water (5 mL), and brine (5 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed *in vacuo* to afford the crude product which was purified by column chromatography on silica gel (hexane: ethyl acetate 1:1) (50 mg, 35% yield). The diastereoselectioity is 70:30 as determined by ^1H NMR and ^{19}F NMR spectroscopic analyses.

***N*-((*1R*)-1-phenylethyl)-2-(3,3,3-trifluoro-2-hydroxypropyl)prop-2-enamide (7).** colorless oil; *Rf* 0.53 (hexane : ethyl acetate 1:1); FTIR (thin film): υ 3426.4, 2930.6, 1651.5, 1610.9, 1450.8, 1279.1, 1165.3, 1132.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ *major* 1.55 (d, J = 6.9 Hz, 3H, CH_3), 2.59-2.64 (m, 2H, CH_2), 4.00 (m, 1H, CHOH), 5.11-5.16 (m, 1H, CHNH), 5.55 (s, 1H, CH=), 5.69 (s, 1H, CH=), 5.99 (brs, 1H, OH), 6.36 (brs, 1H, NH), 7.27-7.39 (m, 5H, aryl H); *minor:* 5.55 (s, 1H, CH=), 5.71 (s, 1H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ *major* 21.35, 33.92, 49.44, 70.89 (q, J = 30.5 Hz), 121.92, 124.81 (q, J = 281.5 Hz), 126.04, 127.65, 128.77, 140.35, 142.21, 169.15. *minor:* 49.39, 71.02 (q, J = 30.5 Hz), 125.99, 142.13. ^{19}F NMR (282.2 MHz, $CDCl_3$): δ *major* -3.77 (d, J = 3.27 Hz, CF_3) (TFA), *minor:* -3.85 (d, J = 3.27 Hz, CF_3) (TFA); EIHRMS: Calcd. for. $C_{14}H_{16}NF_3O_2$: 287.1133 found: 287.1132.

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