Tin- and Indium-Mediated Allylation Reactions in Water: Highly Stereoselective Synthesis of β-Trifluoromethylated Homoallylic Alcohols[+]

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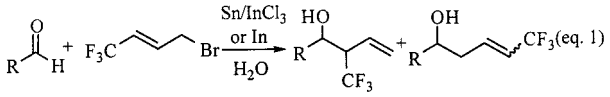
Keywords: Allylation / 1,1,1-Trifluoro-4-bromobut-2-ene / Aldehydes / Tin / Indium / Water

The indium-mediated allylation reaction of aldehydes with 4-bromo-1,1,1-trifluoro-2-butene in water afforded β-trifluoromethylated homoallylic alcohols in high yields. In most cases, high regio- and excellent diastereoselectivities were obtained.

Introduction

Growing interest in trifluoromethylated organic compounds in various fields such as medicine, pharmaceuticals, and fluoropolymers has led to greater impetus in the quest for facile methods allowing the introduction of trifluoromethyl groups so as to give useful intermediates or desired substrates.[1] This is because the trifluoromethyl group, with its strong electronegativity, stability and lipophilicity, often induces considerable changes in the chemical, physical, and physiological properties of the transformed molecule. However, existing methodologies for the preparation of trifluoromethylated compounds are very limited because of the low reactivity of various trifluoromethylating reagents and the need for mild reaction conditions.[2] Thus, the synthesis of intermediates bearing a trifluoromethyl group represents an attractive approach. Although α-trifluoromethylated alcohols have been synthesized using various methods, the synthesis of building blocks bearing a trifluoromethyl group at the β position of an alcohol is generally difficult owing to the limited availability of suitably effective reagents. Here, we describe practical methods for the synthesis of various β-trifluoromethylated homoallylic alcohols employing indium-mediated allylation reactions in aqueous media (Equation 1).



[+] Preliminary results have been published: T.-P. Loh, X.-R. Li, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 980; T.-P. Loh, X.-R. Li, *Tetrahedron Lett.* **1997**, *38*, 869. This research was assisted financially by the National University of Singapore (Research Grant Nos. RP 970615, RP 970616 and 981639).

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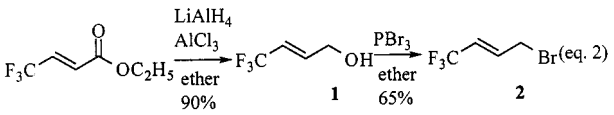
Results and Discussion

Preparation of 1,1,1-Trifluoro-4-bromobut-2-ene

The preparation of 4-bromo-1,1,1-trifluorobut-2-ene (**2**) is essential for the synthesis of β-trifluoromethylated homoallylic alcohols. This novel trifluoromethylating allylic reagent was prepared in two steps from ethyl 4,4,4-trifluorocrotonate[3] (Equation 2). Thus, reduction of ethyl 4,4,4-trifluorocrotonate using $LiAlH_4$ and $AlCl_3$ afforded the corresponding alcohol **1** in 90% yield.[4] The resulting alcohol was then brominated with PBr_3 to afford 4-bromo-1,1,1-trifluorobut-2-ene (**2**), which was purified by fractional distillation of its ethereal extract.



Metal-Mediated Allylation Reactions

The 4-bromo-1,1,1-trifluorobut-2-ene (**2**) obtained as outlined above was then employed in allylation reactions of aldehydes. Among organometallic reagents, allyltin, -zinc, and -indium reagents belong to a unique group which react with aldehydes in aqueous media.[5] Benzaldehyde was chosen as a model substrate for use in reactions with 4-bromo-1,1,1-trifluorobut-2-ene (**2**) in the presence of zinc, tin, and indium metals (Equation 3). The results are shown in Table 1.

It was found that attempted zinc-mediated allylation of benzaldehyde with 4-bromo-1,1,1-trifluorobut-2-ene (**2**) in saturated ammonium chloride solution led to a complicated mixture of fluorinated compounds. The desired β-trifluoromethylated homoallylic alcohol was not detected in either the zinc- or the tin-mediated reactions (Table 1, Entries 1 and 2). In contrast, indium-mediated allylation of benzaldehyde with 4-bromo-1,1,1-trifluorobut-2-ene (**2**) proceeded smoothly in various solvents to give the corresponding homoallylic alcohols in high yields and with high diastereo-

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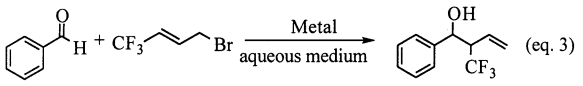
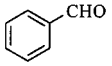
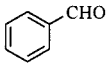
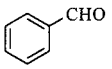
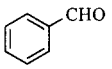
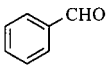


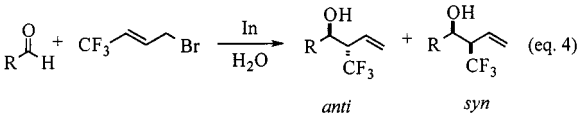
Table 1. The metal-mediated allylation reaction of benzaldehyde[a]

Entry	Aldehyde	Conditions	Diastereomeric ratio[b] (*anti*:*syn*)	Yield(%)[c]
1		Zn, sat. aq. NH_4Cl (15h)	-	0
2		Sn, H_2O (15 h)	-	0
3		In, DMF/H_2O (95:5) (15h)	85:15	82
4		In, EtOH/H_2O (95:5) (15 h)	95:5	90
5		In, H_2O (15 h)	92:8	87

[a] All reactions were carried out on a 0.2−1-mmol scale. − [b] The diastereomeric ratio was determined by ^{1}H-NMR analysis. − [c] Isolated yield.

selectivities. Higher diastereoselectivities were obtained when the reaction was performed in EtOH/H_2O (95:5) or pure H_2O compared to that performed in DMF/H_2O (95:5) (Table 1, Entries 3, 4, 5).

Next, we investigated indium-mediated allylation reactions of various aliphatic and aromatic aldehydes in water (Equation 4). The results are summarized in Table 2.

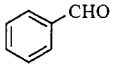
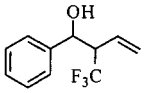
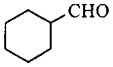
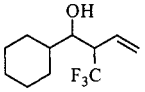
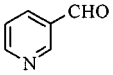
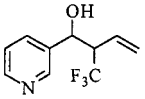
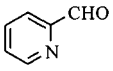
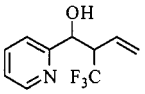
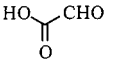
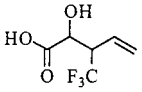


As expected, the novel reagent 4-bromo-1,1,1-trifluorobut-2-ene (**2**) proved to be very reactive towards aldehydes in the presence of indium powder. The following generalizations can be made concerning its reactivity in indium-mediated allylation reactions: 1. In all cases, the reactions proceeded very smoothly at room temperature in water. Generally, these reactions were clean and the products were obtained in high yields. 2. Water-soluble substrates such as formaldehyde and glyoxylic acid could be used directly in the reactions. 3. In all cases examined, only the γ-coupling products were obtained. 4. The diastereoselectivities were excellent. The *anti* products predominated in most of the allylation reactions. In contrast, allylation reactions of 2-pyridinecarboxaldehyde and glyoxylic acid afforded the corresponding *syn* products with excellent diastereoselectivities.

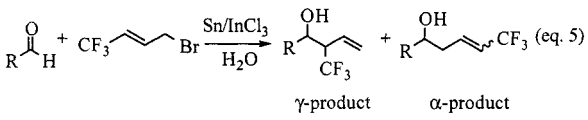
Tin-Mediated Indium Trichloride Promoted Allylation Reactions

As described above (Table 1), attempted direct tin-mediated allylation of benzaldehyde with 4-bromo-1,1,1-trifluorobut-2-ene (**2**) failed to give the corresponding trifluoromethylated homoallylic alcohol. However, indium trichloride promoted tin-mediated allylation reactions of various carbonyl compounds with 4-bromo-1,1,1-trifluorobut-2-ene (**2**) afforded the desired products in water (Equation 5).[6] Under optimized conditions, a wide variety of aldehydes, including aliphatic, aromatic, as well as water-soluble substrates, were subjected to allylation reactions. In all cases, the corresponding trifluoromethylated allylation products were obtained in high yield. The results are summarized in Table 3. The presence of indium trichloride was shown to be essential for the reaction of 4-bromo-1,1,1-trifluorobut-2-ene (Table 3, Entries 1 and 2). The diastereoselectivities were excellent in all cases. Generally, the *anti* diastereomer was obtained as the major product, except again in the reactions of 2-pyridinecarboxaldehyde and glyoxylic acid, where the *syn* diastereomer was obtained as the major product. Unlike in the indium-mediated reaction, a mixture of γ- and α-coupling products was observed in the case of benzaldehyde (Entry 2).

Table 2. Indium-mediated allylation reaction of 4-bromo-1,1,1-trifluorobut-2-ene with various aldehydes[a]

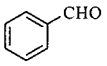
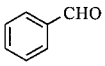
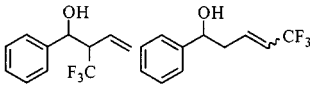
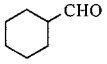
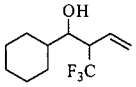
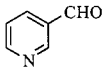
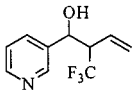
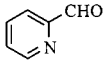
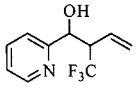
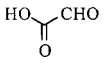
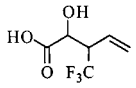
Entry	Aldehyde	Condition	Product	Diastereomeric ratio[b] (*anti* :*syn*)	Yield (%)[c]
1		In, H_2O, 15 h		92:8	87
2	HCHO	In, H_2O, 15 h		-	86
3		In, H_2O, 15 h		>99: <1	90
4		In, H_2O, 15 h		>99: <1	95
5		In, H_2O, 15 h		<1: >99	88
6		In, H_2O, 15h		4:96	80

[a] All reactions were carried out on a 0.2−1-mmol scale. − [b] The diastereomeric ratio was determined by ^{1}H- and ^{19}F-NMR analyses. − [c] Isolated yield.



Especially noteworthy is the fact that only 1.5 equivalents of the trifluoromethylated allylic bromide were sufficient to completely convert the aldehydes to the corresponding products. In the indium-mediated allylation reactions, we

Table 3. Tin-mediated indium trichloride promoted allylation reactions[a]

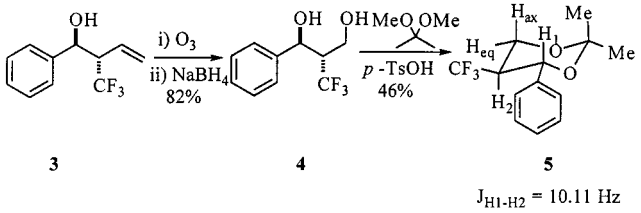
Entry	Aldehyde	Product	Yield(%)[b] *regio-* (γ:α)[c]	*anti:syn*[d] (γ-)
1		-	0[e]	-
2		 (*E*:*Z*[f] 60:40)	87[g] (91:9)	95:5
3	HCHO		90	-
4			92 (100:0)	>99 : <1
5			95 (100:0)	92:8
6			96 (100:0)	<1 : >99
7			83 (100:0)	<1 : >99

[a] All reactions were carried out on a 0.2−1-mmol scale; conditions: 1.5 equiv. Sn, 1.5 equiv. $InCl_3$, 1.5 equiv. 4-bromo-1,1,1-trifluorobut-2-ene, H_2O, 15 h. − [b] Yield of purified product. − [c] The isomer ratio was determined by ^{19}F-NMR analysis. − [d] The isomer ratio was determined by ^1H- and ^{19}F-NMR analyses. − [e] No $InCl_3$ was added in this reaction. − [f] The isomer ratio was determined by ^{19}F-NMR analysis. − [g] The regiostereomer was separated by column chromatography on silica gel.

usually required 3 equivalents of the reagent in order to obtain the products in satisfactory yields.

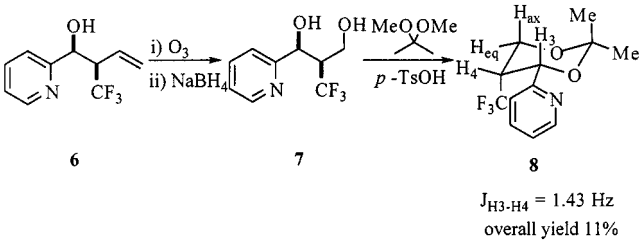
Structure Determination

The *anti* and *syn* stereochemistries of compounds **3** and **6** could be confirmed following their transformation to the corresponding acetonides **5** and **8** (Schemes 1 and 2). Thus, ozonolysis of 2-(trifluoromethyl)-1-phenylbut-3-en-1-ol (**3**), obtained from the reaction of benzaldehyde with 4-bromo-1,1,1-trifluorobut-2-ene, followed by direct reductive cleavage of the ozonide using sodium borohydride,[7] afforded the corresponding diol **4** in 82% yield. It is important to note that ozonolysis of **3**, followed by addition of dimethyl sulfide in the usual manner, gave only a trace amount of the aldehyde. It is known that because of the strong electron-withdrawing property of the trifluoromethyl group, the preparation of such an aldehyde is very difficult due to facile enolization[8] or defluorination.[9] Subsequently, diol **4** was treated with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-TsOH to furnish the acetonide **5** in 46% yield. The *anti* stereochemistry of compound **3** was deduced from the ^1H-NMR coupling constant (J = 10.11 Hz) of the axial proton adjacent to both the hydroxy and trifluoromethyl groups in compound **5**.



Scheme 1. Structural determination of the *anti* configuration of 1-phenyl-2-(trifluoromethyl)but-3-en-1-ol

The homoallylic alcohol **6** obtained from the reaction of 2-pyridinecarboxaldehyde with 4-bromo-1,1,1-trifluorobut-2-ene was converted into the corresponding acetonide in the same manner (Scheme 2). The coupling constant between H^3 and H^4 in compound **8** was found to be very small (J = 1.43 Hz). Therefore, the original homoallylic alcohol must have been in the *syn* configuration. The relative stereochemistries of other homoallylic alcohols were established on the basis of their similar ^1H- and ^{19}F-NMR shifts.



Scheme 2. Structural determination of the *syn* configuration of 1-(2-pyridyl)-2-(trifluoromethyl)but-3-en-1-ol

Mechanistic Study

Transmetallation

Of mechanistic interest is the fact that the tin-mediated allylation reaction does not proceed in the absence of indium trichloride. Formation of the more reactive allylindium species is necessary in order to generate the coupling product. Thus, we have previously proposed that the initially formed allyltin species **9** undergoes transmetallation with indium trichloride to afford the allylindium species **10** (Figure 1).[6] Subsequent 1,3-allylic shift results in the formation of two other possible species, **11** and **12**. The ratio of species **11** and **12** is dependent on their relative thermal stabilities.

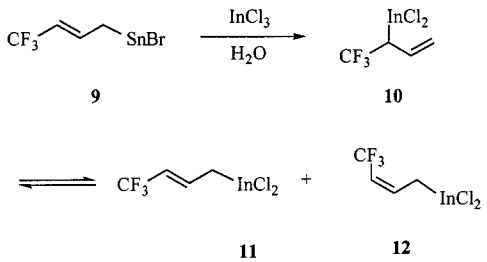


Figure 1. Transmetallation mechanism involved in the tin-mediated indium trichloride promoted allylation reaction

In the indium-mediated allylation reactions (Figure 2), indium species **13** is formed, which exists in equilibrium with its regioisomer **14**.[10] This equilibrium permits isomerization of the double bond in the ally indium species, allowing the possible formation of species **15**. The aldehyde attacks the indium species **13** or **15** yielding the γ-coupling product. Generally, species **14** is the most labile, while species **13** is more stable than its (*Z*) isomer **15** due to the presence of the bulky CF_3 group.

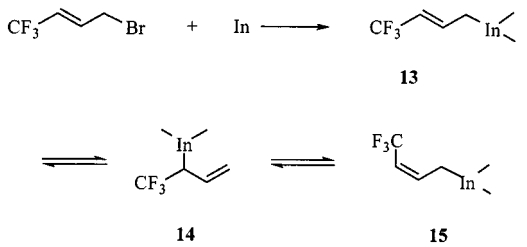


Figure 2. Mechanism of the indium-mediated allylation reaction

Diastereoselectivity

The strong preference for formation of the *anti* adduct in both the indium-mediated and the tin-mediated indium trichloride promoted allylation reactions can be explained in terms of the six-membered ring transition state (Figure 3). The aldehyde attacks the more stable indium species **11** or **13** to give the six-membered ring transition state **16** or **17**. The diastereoselectivity with which the allylation reaction yields the γ-coupling product depends on the steric bulk of the substituents on both the allylic bromide and the aldehyde.[10] If the substituent on the aldehyde has sufficient steric bulk, then the reaction will proceed through transition state **17**, where the R and CF_3 groups preferentially adopt equatorial positions, thereby leading to the *anti* product.

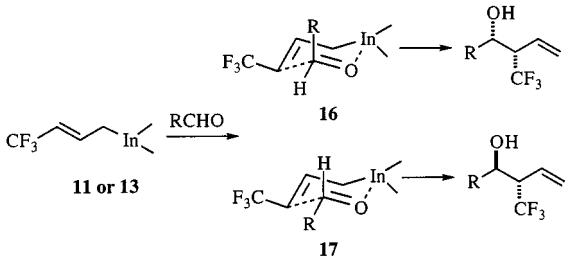


Figure 3. Transition states of the *anti*-diastereoselective reactions

It is noteworthy that in contrast to the reaction using crotyl bromide, which gave the product with no diastereoselectivity,[6][10] excellent diastereoselectivities in the reactions of 4-bromo-1,1,1-trifluorobut-2-ene with carbonyl compounds are observed. These results further indicate that the CF_3 group is indeed a sterically very demanding group. This observation is consistent with the findings of Corey[11] and of Kitazume and Yamazaki.[12]

In contrast, the high *syn* selectivity observed with 2-pyridinecarboxaldehyde and glyoxylic acid indicates that the 2-pyridine and COOH groups preferentially adopt axial positions. This is most probably attributable to 5-membered ring chelation with indium as shown in Figure 4.

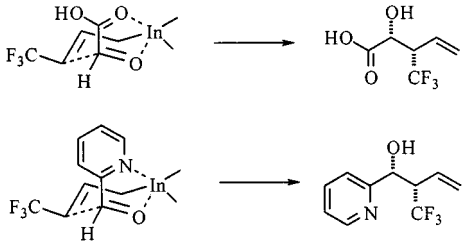


Figure 4. Transition states of the *syn*-diastereoselective reactions

Conclusions

In summary, we have developed versatile methods for the synthesis of β-trifluoromethylated homoallylic alcohols, which represent synthetically useful trifluoromethylated building blocks. The novel reagent 4-bromo-1,1,1-trifluorobut-2-ene, prepared in two steps, has been successfully employed in allylation reactions of various aldehydes in water. Both the indium-mediated and the tin-mediated indium trichloride promoted allylation reactions afforded the β-trifluoromethylated homoallylic alcohols in high yields and with excellent diastereoselectivities. The bulky trifluoromethyl group is responsible for the high diastereoselectivity of the reaction.

Owing to the simplicity and efficiency of these two methodologies, they will no doubt serve as practical methods for the synthesis of various organofluorine compounds. On the other hand, the methodology of trifluoromethylation in water, as a new concept in organofluorine chemistry, should promote the development of both organic synthesis in aqueous media and the synthesis of fluorine-containing drugs. Further investigations are currently in progress aimed at synthesizing optically pure organofluorine compounds using this methodology.

Experimental Section

Materials and Methods: Ethyl 4,4,4-trifluorocrotonate was purchased from Aldrich Chemical Co. and was used directly as obtained. Aldehydes were distilled prior to use. Analytical thin-layer chromatography was performed using Merck 60 F_{254} precoated silica gel plates (0.2 mm thickness). Following elution, UV-active materials were visualized by ultraviolet illumination at 254 nm or by staining with iodine vapor or a solution of potassium permanganate. Flash chromatography was performed on Merck silica gel 60 (40−63 μm particle size) using distilled solvents as eluents. Columns were typically packed as a slurry and equilibrated with the appropriate solvents prior to use. Infrared (IR) spectra were recorded with a Perkin−Elmer 1600 FT-IR spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H NMR) and carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded with a Bruker ACF 300 or 500 spectrometer at the frequency indicated. Mass-spectral analyses were carried out with a VG7035 Micromass mass spectrometer and are reported in units of mass/charge

(*m*/*z*). Electron impact (EI) at an ion current of 70 eV was used for fragmentation of molecules.

Preparation of 4,4,4-Trifluoro-1-hydroxybut-2-ene (1):[4] To a suspension of anhydrous $AlCl_3$ (17 mmol, 2.27 g) in diethyl ether (30 mL) at 0°C was added a solution of $LiAlH_4$ (1.90 g, 50 mmol) in diethyl ether (40 mL). The resulting mixture was stirred at this temperature for 15 min. A solution of ethyl 4,4,4-trifluorocrotonate (2.99 mL, 20 mmol) in diethyl ether (10 mL) was then added at 0°C and stirring was continued for a further 2 h. The reaction mixture was subsequently quenched with saturated Na_2SO_4 solution at 0°C. The resulting suspension was dried with anhydrous $MgSO_4$, filtered, and the solids were washed with diethyl ether. The combined ethereal phases were then concentrated in vacuo, and the residue was purified by distillation to afford pure **1** in 90% yield (2.27 g); b.p. 128−129°C. − R_f = 0.40 (hexane/ethyl acetate, 4:1). − FT-IR (thin film): $\tilde{\nu}$ = 3426.5, 1691.9, 1637.9, 1300.3, 1267.5, 1131.9, 1086.2, 1018.7 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.64 (br., 1 H, OH), 4.10 (m, 2 H, CH_2), 5.95 (m, 1 H), 6.53 (m, 1 H). − ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 61.00, 117.86 (q, *J* = 33.9 Hz), 123.20 (q, *J* = 269.1 Hz), 138.94 (q, *J* = 6.3 Hz). − ^{19}F NMR (84.2 MHz, $CDCl_3$): δ = 11.43 (m, CF_3, TFA). − EI-HRMS: $C_4H_5F_3O$ [M^+]: calcd. 126.02923; found 126.0299.

Preparation of 1,1,1-Trifluoro-4-bromobut-2-ene (2): To a solution of 1,1,1-trifluoro-4-hydroxylbut-2-ene (2.52 g, 20 mmol) in diethyl ether (40 mL) at −10°C was slowly added PBr_3 (2.85 mL, 30 mmol). The reaction mixture was stirred for 1 h at this temperature and then allowed to warm to room temperature. After stirring for a further 2 h, water was slowly added to quench the reaction. The product was extracted with diethyl ether, washed with water and brine, and dried with anhydrous $MgSO_4$. After filtration, the ethereal solution was fractionally distilled to afford 4-bromo-1,1,1-trifluorobut-2-ene (**2**) in 65% yield (2.45 g); b.p. 95−97°C. − R_f = 0.60 (hexane/ethyl acetate, 4:1). − FT-IR (thin film): $\tilde{\nu}$ = 2976.9, 1691.9, 1429.6, 1321.6, 1259.8, 1180.7, 1118.9, 1045.7, 964.6, 621.2 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 3.97 (m, 2 H, CH_2), 5.91 (m, 1 H), 6.52 (m, 1 H). − ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 61.01, 122.02 (q, *J* = 33.9 Hz), 122.27 (q, *J* = 270.4 Hz), 135.06 (q, *J* = 6.3 Hz). − ^{19}F NMR (84.2 MHz, $CDCl_3$): δ = 10.91 (m, CF_3, TFA).

Representative Procedure for the Indium-Mediated Allylation Reactions of Aldehydes with 4-Bromo-1,1,1-trifluorobut-2-ene in Water. − Preparation of 1-Phenyl-2-(trifluoromethyl)but-3-en-1-ol (3): To a suspension of indium powder (45.9 mg, 0.4 mmol) in water (2 mL) at room temperature was added 4-bromo-1,1,1-trifluorobut-2-ene (113.4 mg, 0.6 mmol) followed by benzaldehyde (0.020 mL, 0.2 mmol). The resulting mixture was stirred for 15 h at room temperature and then extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with water and brine, and dried with anhydrous $MgSO_4$. After filtration, the ethyl acetate was removed in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate, 10:1) to afford the pure product **3** in 87% yield (37.6 mg). ^1H-NMR analysis showed the product to be a diastereomeric mixture in a 92:8 (*anti*/*syn*) ratio. R_f = 0.49 (hexane/ethyl acetate, 4:1). − FT-IR (thin film): $\tilde{\nu}$ = 3439.9, 2936.4, 1643.8, 1456.6, 1259.8, 1126.7 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): *anti* diastereomer: δ = 2.12 (d, *J* = 3.0 Hz, 1 H, OH), 2.94−3.03 (m, 1 H, $CHCF_3$), 5.09 (d, *J* = 17.3 Hz, 1 H, CH_2=), 5.21 (br. s, 1 H, CHOH), 5.37 (d, *J* = 10.4 Hz, 1 H, CH_2=), 5.89−5.96 (m, 1 H, CH=), 7.28−7.37 (m, 5 H); *syn* diastereomer: δ = 3.03−3.06 (m, 1 H, $CHCF_3$), 5.40−5.48 (m, 1 H, CH=). − ^{13}C NMR (125.7 MHz, $CDCl_3$): *anti* diastereomer: δ = 55.82 (q, *J* = 24.7 Hz), 71.10, 123.77, 126.08 (q, *J* = 281.1 Hz), 126.09, 126.62, 128.02, 128.37, 141.03. − ^{19}F NMR (84.2 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 9.8 Hz, CF_3, TFA). − EI-HRMS: $C_{11}H_{11}F_3O$ [M^+]: calcd. 216.0762; found 216.0748.

Representative Procedure for the Tin-Mediated Indium Trichloride Promoted Allylation Reactions of Aldehydes with 4-Bromo-1,1,1-trifluorobut-2-ene in Water. − Preparation of 1-(3-Pyridyl)-2-(trifluoromethyl)but-3-en-1-ol: To a suspension of tin powder (35.6 mg, 0.3 mmol) and indium trichloride (66.3 mg, 0.3 mmol) in water (2 mL) at room temperature, was added 4-bromo-1,1,1-trifluorobut-2-ene (56.7 mg, 0.3 mmol), followed by 3-pyridinecarboxylaldehyde (0.019 mL, 0.2 mmol). The resulting mixture was stirred for 15 h at room temperature and then extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with water and brine, and dried with anhydrous $MgSO_4$. After filtration, the ethyl acetate was removed in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate, 2:1) to afford the pure product in 95% yield (41.2 mg). ^1H-NMR analysis showed the product to be a diastereomeric mixture in a 92:8 (*anti*/*syn*) ratio. R_f = 0.46 (hexane/ethyl acetate, 1:1). − FT-IR (thin film): $\tilde{\nu}$ = 3434.6, 2932.5, 1645.7, 1431.5, 1263.7, 1185.7, 1105.5 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): *anti* diastereomer: δ = 2.90−2.94 (m, 1 H), 5.07 (d, *J* = 17.2 Hz, 1 H, CH_2=), 5.24 (d, *J* = 3.2 Hz, 1 H, CHOH), 5.37 (d, *J* = 10.4 Hz, 1 H, CH_2=), 5.89−5.96 (m, 1 H, CH=), 7.28 (m, 1 H), 7.70 (m, 1 H), 8.45 (m, 2 H); *syn* diastereomer: δ = 5.42−5.48 (m, 1 H, CH=). − ^{13}C NMR (125.7 MHz, $CDCl_3$): *anti* diastereomer: δ = 55.84 (q, *J* = 24.9 Hz), 68.80, 123.31, 124.26, 126.29, 125.90 (q, *J* = 280.9 Hz), 134.48, 137.22, 147.56, 148.79. − ^{19}F NMR (84.2 MHz, $CDCl_3$): *anti* diastereomer: δ = 8.05 (d, *J* = 7.3 Hz, CF_3, TFA); *syn* diastereomer: δ = 9.19 (d, *J* = 7.3 Hz, CF_3). − EI-HRMS: $C_{10}H_{10}F_3NO$ [M^+]: calcd. 217.07144; found 217.07261.

5,5,5-Trifluoro-1-phenylpent-3-en-1-ol: α product [a mixture of (*E*) and (*Z*) isomers)]: R_f = 0.44 (hexane/ethyl acetate, 4:1). − (*E*) isomer: ^1H NMR (500 MHz, $CDCl_3$): δ = 1.95 (d, *J* = 3.1 Hz, 1 H, OH), 2.58−2.63 (m, 2 H, CH_2), 4.82 (m, 1 H, CHOH), 5.66−5.73 (m, 1 H, CH=), 6.38−6.44 (m, 1 H, CH=), 7.29−7.39 (m, 5 H, aryl). − ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 41.00, 73.15, 121.16 (q, *J* = 33.6 Hz), 121.05 (q, *J* = 276.5 Hz), 125.71, 128.12, 128.72, 136.55 (q, *J* = 6.7 Hz), 143.26. − ^{19}F NMR (84.2 MHz, $CDCl_3$): δ = 11.28−11.43 (m, CF_3, TFA). − (*Z*) isomer: ^1H NMR (500 MHz, $CDCl_3$): δ = 1.92 (d, *J* = 3.3 Hz, 1 H, OH), 2.74−2.80 (m, 2 H, CH_2), 4.82 (m, 1 H, CHOH), 5.66−5.73 (m, 1 H, CH=), 6.08−6.13 (m, 1 H, CH=), 7.29−7.39 (m, 5 H, aryl). − ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 37.58, 73.48, 120.27 (q, *J* = 33.6 Hz), 121.84 (q, *J* = 276.5 Hz), 125.74, 128.07, 128.70, 138.51 (q, *J* = 5.3 Hz), 143.30. − ^{19}F NMR (84.2 MHz, $CDCl_3$): δ = 17.23−17.39 (m, CF_3, TFA).

1-(2-Pyridyl)-2-(trifluoromethyl)but-3-en-1-ol (6): *syn* diastereomer: R_f = 0.64 (hexane/ethyl acetate, 1:1). − FT-IR (thin film): $\tilde{\nu}$ = 3439.9, 2922.9, 1651.5, 1462.4, 1246.3, 1173.0, 1113.2 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 3.25−3.33 (m, 1 H, $CHCF_3$), 4.23 (d, *J* = 7.9 Hz, 1 H, OH), 5.00 (dd, *J* = 7.9 Hz, *J* = 5.7 Hz, 1 H, CHOH), 5.22 (d, *J* = 17.1 Hz, 1 H, CH_2=), 5.27 (d, *J* = 10.2 Hz, 1 H, CH_2=), 5.55−5.63 (m, 1 H, CH=), 7.23−7.26 (m, 2 H), 7.66−7.69 (m, 1 H), 8.58 (dd, *J* = 1.7 Hz, *J* = 5.5 Hz, 1 H). − ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 55.51 (q, *J* = 23.9 Hz), 71.32, 122.26, 122.94, 123.16, 125.90 (q, *J* = 280.5 Hz), 128.12, 136.44, 148.54, 157.83. − ^{19}F NMR (84.2 MHz, $CDCl_3$): δ = 9.99 (d, *J* = 9.8 Hz, CF_3, TFA). − EI-HRMS: $C_{10}H_{10}F_3NO$ [M^+]: calcd. 217.07144; found 217.0701.

2-Hydroxy-3-(trifluoromethyl)pent-4-enoic Acid: *syn* diastereomer: R_f = 0.33 (hexane/ethyl acetate, 1:1). − FT-IR (thin film): $\tilde{\nu}$ =

3453.4, 2585.2, 1724.8, 1630.2, 1246.3, 1145.9, 1099.7 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 3.00 (br. s, 1 H, OH), 3.37 (m, 1 H, $CHCF_3$), 4.42 (s, 1 H, CHOH), 5.46 (d, J = 10.4 Hz, 1 H, CH_2=), 5.49 (d, J = 17.1 Hz, 1 H, CH_2=), 5.91–5.99 (m, 1 H, CH=). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 51.62 (q, J = 26.2 Hz), 69.97, 123.12, 125.34 (q, J = 281.2 Hz), 128.05, 174.99. – ^{19}F NMR (84.2 MHz, $CDCl_3$): δ = 9.70 (d, J = 8.5 Hz, CF_3, TFA). – EI-HRMS: $C_6H_7F_3O_3$ [M^+]: calcd. 184.0347; found 184.0348.

1-Cyclohexyl-2-(trifluoromethyl)but-3-en-1-ol: *anti* diastereomer: R_f = 0.47 (hexane/ethyl acetate, 4:1). – FT-IR (thin film): $\tilde{\nu}$ = 3439.9, 2922.9, 2855.3, 1643.8, 1456.6, 1254.0, 1099.7, 1024.5 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 0.94–1.78 (m, 11 H), 2.90–2.98 (m, 1 H, $CHCF_3$), 3.71 (dd, J = 1.9 Hz, J = 8.7 Hz, 1 H, CHOH), 5.32 (d, J = 17.4 Hz, 1 H, CH_2=), 5.45 (d, J = 10.4 Hz, 1 H, CH_2=), 5.85–5.92 (m, 1 H, CH=). – ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 25.67, 25.84, 26.23, 28.77, 28.89, 40.50, 50.34 (q, J = 24.5 Hz), 72.88, 123.08, 126.74 (q, J = 280.8 Hz), 127.86. – ^{19}F NMR (84.2 MHz, $CDCl_3$): δ = 8.02 (d, J = 9.8 Hz, CF_3, TFA).

2-(Trifluoromethyl)but-3-en-1-ol: R_f = 0.36 (hexane/ethyl acetate, 4:1). – FT-IR (thin film): $\tilde{\nu}$ = 3429.4, 2917.8, 1643.8, 1462.4, 1259.8, 1118.9, 1032.2 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 2.99 (m, 1 H, $CHCF_3$), 3.77 (m, 1 H, CH_2OH), 3.92 (m, 1 H, CH_2OH), 5.40–5.45 (m, 2 H, CH_2=), 5.75 (m, 1 H, CH=). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 53.50 (q, J = 24.6 Hz), 65.34, 123.36, 126.51 (q, J = 280.7 Hz), 128.54. – ^{19}F NMR (84.2 MHz, $CDCl_3$): δ = 6.58 (d, J = 9.7 Hz, CF_3, TFA). – EI-HRMS: $C_5H_7F_3O$ [M^+]: calcd. 140.0449; found 140.0442.

Preparation of 1-Phenyl-2-(trifluoromethyl)propane-1,3-diol (4): Ozone was bubbled through a solution of 1-phenyl-2-trifluoromethylbut-3-en-1-ol (**3**) (21.6 mg, 0.1 mmol) in $CHCl_3$ (2 mL) at −40 °C. The reaction was monitored by TLC and was allowed to proceed until **3** had been completely consumed. A solution of $NaBH_4$ (37.8 mg, 1 mmol) in ethanol (5 mL, 95%) was then added dropwise and the resulting mixture was stirred for 10 min at this temperature. The mixture was warmed to 0 °C, stirred for 1 h, and then allowed to warm to room temperature. H_2O (1 mL) was added and the resulting mixture was stirred for a further 6 h. The ethanol was then removed in vacuo and the product was extracted with ethyl acetate (3 × 10 mL). The combined extracts were washed with water and brine, and dried with anhydrous $MgSO_4$. After filtration, the ethyl acetate was removed in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate, 1:1) to afford the pure product in 82% yield (18 mg). – R_f = 0.51 (hexane/ethyl acetate, 1:2). – FT-IR (thin film): $\tilde{\nu}$ = 3370.0, 2924.7, 1453.0, 1380.4, 1255.2, 1159.5, 1123.4, 1062.5 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 2.48–2.55 (m, 1 H, $CHCF_3$), 2.72 (br. s, 1 H, OH), 3.24 (br. s, 1 H, OH), 3.98 (br. s, 2 H, CH_2OH), 5.28 (s, 1 H, CHOH), 7.30–7.39 (m, 5 H, aryl-H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 51.12 (q, J = 23.2 Hz), 58.03, 71.84, 125.79, 126.61 (q, J = 281.6 Hz), 128.19, 128.74, 141.52. – ^{19}F NMR (84.2 MHz, $CDCl_3$): δ = 9.15 (d, J = 9.6 Hz, CF_3, TFA). – EI-HRMS: $C_{10}H_{11}F_3O_2$ [M^+]: calcd. 220.0711; found 220.0724.

Preparation of 2,2-Dimethyl-4-phenyl-5-(trifluoromethyl)-1,3-dioxane (5): To a solution of 1-phenyl-2-trifluoromethyl-1,3-propanediol (**4**) (11 mg, 0.05 mmol) in THF (3 mL) was added 2,2-dimethoxypropane (0.062 mL, 0.5 mmol) and a catalytic amount of *p*-TsOH (1 mg, 0.005 mmol). The resulting solution was refluxed for 5 h and then the solvent was removed in vacuo. The product was taken up in ethyl acetate and this solution was washed with water and brine and dried with anhydrous $MgSO_4$. After filtration, the filtrate was concentrated in vacuo and purified by column chromatography on silica gel (hexane/ethyl acetate, 8:1) to give pure 2,2-dimethyl-4-phenyl-5-trifluoromethyl-1,3-dioxane in 46% yield (6 mg). – R_f = 0.79 (hexane/ethyl acetate, 4:1). – ^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 3 H, CH_3), 1.57 (s, 3 H, CH_3), 2.76 (m, 1 H, $CHCF_3$), 4.09 (d, J = 5.3 Hz, 1 H, CH_2OH), 4.10 (d, J = 2.7 Hz, 1 H, CH_2OH), 4.92 (d, J = 10.1 Hz, 1 H, CHOH), 7.25–7.40 (m, 5 H, aryl-H). – ^{19}F NMR (84.2 MHz, $CDCl_3$): δ = 8.64 (d, J = 7.3 Hz, CF_3, TFA).

Preparation of 2,2-Dimethyl-4-(2-pyridyl)-5-(trifluoromethyl)-1,3-dioxane (8): Ozone was bubbled through a solution of 1-(2-pyridyl)-2-trifluoromethylbut-3-en-1-ol (**6**) (21.7 mg, 0.1 mmol) in $CHCl_3$ (2 mL) at −40 °C for 5 min. A solution of $NaBH_4$ (37.8 mg, 1 mmol) in ethanol (5 mL, 95%) and water (0.5 mL) was added dropwise and the resulting mixture was stirred for 10 min at this temperature. The reaction mixture was then warmed to 0 °C, stirred for 1 h, allowed to warm to room temperature, and finally stirred for a further 15 h. The ethanol was then removed in vacuo and the product was extracted with ethyl acetate (3 × 10 mL). The combined extracts were washed with water and brine, and dried with anhydrous $MgSO_4$. After filtration, the ethyl acetate was removed in vacuo. The obtained residue **7** was used directly in the next step. – R_f = 0.28 (hexane/ethyl acetate, 1:2). – FT-IR (thin film): $\tilde{\nu}$ = 3425.8, 1441.2, 1259.1, 1181.1, 1041.7 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 2.88–2.93 (m, 1 H, $CHCF_3$), 3.85–3.90 (dd, J = 4.8 Hz, J = 11.8 Hz, 1 H, CH_2OH), 3.97–4.03 (dd, J = 6.1 Hz, J = 11.8 Hz, 1 H, CH_2OH), 5.22 (d, J = 3.5 Hz, 1 H, CHOH), 7.26 (dd, J = 4.8 Hz, J = 7.0 Hz, 1 H), 7.41 (d, J = 7.5 Hz, 1 H), 7.74–7.79 (dd, J = 7.5 Hz, J = 7.0 Hz, 1 H), 8.57 (d, J = 4.8 Hz, 1 H). – ^{19}F NMR (84.2 MHz, $CDCl_3$): δ = 11.29 (d, J = 9.8 Hz, CF_3, TFA). – To a solution of the aforementioned **7** in THF (3 mL) was added 2,2-dimethoxypropane (0.062 mL, 0.5 mmol) and a catalytic amount of *p*-TsOH (0.005 mmol, 1 mg). The resulting mixture was refluxed for 15 h and then the solvent was removed in vacuo. The product was extracted with ethyl acetate, and this solution was washed with water and brine, and dried with anhydrous $MgSO_4$. After filtration, the filtrate was concentrated in vacuo and the residue was purified by preparative TLC on silica gel (hexane/ethyl acetate, 6:1) to afford pure 2,2-dimethyl-4-(2-pyridyl)-5-trifluoromethyl-1,3-dioxane (**8**) (2.8 mg; overall yield 11%). – R_f = 0.19 (hexane/ethyl acetate, 4:1). – ^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 3 H, CH_3), 1.57 (s, 3 H, CH_3), 2.79 (m, 1 H, $CHCF_3$), 4.29 (d, J = 2.4 Hz, 2 H, CH_2OH), 5.35 (d, J = 1.4 Hz, 1 H, CHOH), 7.21 (dd, J = 1.7 Hz, J = 4.0 Hz, 1 H), 7.58 (d, J = 7.7 Hz, 1 H), 7.73 (dd, J = 7.7 Hz, J = 1.7 Hz, 1 H), 8.52 (d, J = 4.0 Hz, 1 H). – ^{19}F NMR (84.2 MHz, $CDCl_3$): δ = 13.14 (d, J = 9.8 Hz, CF_3, TFA).

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