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Synthesis Design

A Direct, Concise, and Enantioselective Synthesis of 2-Substituted 4,4,4-Trifluorobutane-1,3-diols Based on the Organocatalytic In Situ Generation of Unstable Trifluoroacetaldehyde

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Abstract: A direct, concise, and enantioselective synthesis of 2-substituted 4,4,4-trifluorobutane-1,3-diols based on the organocatalytic asymmetric direct aldol reaction of an ethyl hemiacetal of trifluoroacetaldehyde with various aldehydes was examined. A catalytic amount (30 mol%) of commercially available and inexpensive L-prolinamide is quite effective as an organocatalyst for the catalytic in situ generation of gaseous and unstable trifluoroacetaldehyde from its hemiacetal, and a successive asymmetric direct aldol reaction with various aldehydes in dichloromethane at 0 °C, followed by reduction with sodium borohydride, gives 2-substituted 4,4,4-trifluorobutane-1,3-diols in moderate to good yields (31–84%) with low diastereoselectivities and good to excellent enantioselectivities (64–97% *ee*).

Introduction

Much attention has been devoted to the asymmetric synthesis of 1,3-diols because chiral 1,3-dioxygenated frameworks are found in many naturally occurring organic products, such as polyketide derivatives.[1] Therefore, many attempts, including organocatalytic approaches,[2] have been made to achieve the asymmetric synthesis of various types of 1,3-diols, which are used in the synthesis of natural products.

On the other hand, over 20% of approved pharmaceuticals and 30–40% of commercially available agrochemicals contain fluorine atoms or a trifluoromethyl group.[3] Some reports have appeared in the literature dealing with the importance of fluorine atoms in the design and development of catalysts.[4] Among them, enantiopure 4,4,4-trifluorobutane-1,3-diol is essential for the synthesis of befloxatone, which is a reversible monoamine oxidase A (MAO-A) inhibitor.[5]

Almost 30 years ago, the groups of Kitazume[6] and Seebach[7] independently established the microbial asymmetric synthesis of 4,4,4-trifluorobutane-1,3-diol derivatives through the reduction of ethyl 4,4,4-trifluoro-3-hydroxybutanoate by baker's yeast. Furthermore, 20 years ago, Iseki and co-workers developed an asymmetric chemical synthesis of chiral 2-substituted trifluoromethylated 1,3-diols based on the Evans aldol reaction of gaseous trifluoroacetaldehyde (CF_3CHO).[8] However, this method has intrinsic disadvantages, such as not only the need for multiple synthetic operations, including the introduction and removal of a chiral auxiliary, but also the use of unstable CF_3CHO[9,10] in the gaseous form through the use of an excess amount of dehydrating agents under a high reaction temperature.

However, to the best of our knowledge, only a few catalytic approaches to 4,4,4-trifluorobutane-1,3-diol derivatives have been developed so far. In the first example, Mikami et al. developed a catalytic asymmetric synthesis of 4,4,4-trifluorobutane-1,3-diol by using the asymmetric titanium–BINOL (BINOL = 1,1′-bi-2-naphthol) complex-catalyzed ene reaction of enol silyl ether.[11] Qing and Jiang reported the asymmetric synthesis of 2-substituted 4,4,4-trifluorobutane-1,3-diols based on a catalytic Sharpless asymmetric dihydroxylation of a trifluoromethylated allyl alcohol ether.[12] Recently, Shibatomi and co-workers developed an organocatalytic asymmetric synthesis of 4,4,4-trifluorobutane-1,3-diol based on the organocatalytic asymmetric 1,4-addition of benzaldehyde oxime to 4,4,4-trifluorocrotonaldehyde.[13] Despite these advances, much more direct, concise, and catalytic asymmetric methods for the synthesis of trifluoromethylated 1,3-diol derivatives are still needed because these routes require multiple steps not only for the preparation of the trifluoromethylated starting compounds, but also for derivatization to 4,4,4-trifluorobutane-1,3-diol derivatives.

Previously, we developed an imine/enamine (derived from ketones[14a,b] or aldehydes[14c])-assisted or organocatalytic[15] in situ generation of gaseous and unstable CF_3CHO from its hemiacetal and a successive (asymmetric) carbon–carbon bond-forming reaction under mild conditions without the need for a large amount of acid or base. Herein, we describe in detail the first organocatalytic asymmetric synthesis of 2-substituted 4,4,4-trifluorobutane-1,3-diols based on the organocatalytic in situ generation of gaseous and unstable CF_3CHO from its hem-

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iacetal, and an asymmetric direct aldol reaction with various aldehydes followed by reduction.[16] In this method, some manipulations in a one-pot procedure include multiple steps, such as 1) the ready and exclusive formation of chiral (*E*)-enamines from aldehydes, 2) the enamine-assisted in situ generation of gaseous and unstable CF_3CHO from its hemiacetal, 3) successive asymmetric carbon–carbon bond-formation reactions of in situ generated CF_3CHO with the chiral (*E*)-enamine, and 4) hydrolysis of the intermediates and reduction of 2-substituted 4,4,4-trifluoro-3-hydroxybutanals to give not only 2-substituted 4,4,4-trifluorobutane-1,3-diols (**4**) with low diastereoselectivities and high enantioselectivities, but also regeneration of the organocatalyst. The present method is a convenient and enantioselective route to 2-substituted 4,4,4-trifluorobutane-1,3-diols and offers several advantages, such as removing the need for a step to generate CF_3CHO, the use of only a catalytic amount of inexpensive and commercially available asymmetric organocatalysts, and removing the need for complicated manipulations.

Results and Discussion

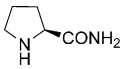
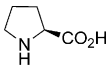
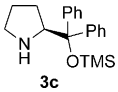
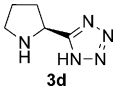
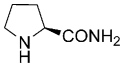
When an ethyl hemiacetal of CF_3CHO (**1a**) was treated with 3 equivalents of 3-phenylpropanal (**2a**) in CH_2Cl_2 at room temperature for 24 h in the presence of a catalytic amount (30 mol%) of commercially available and inexpensive L-prolinamide (**3a**), followed by reduction with $NaBH_4$ in a mixture of CH_2Cl_2 and ethanol at room temperature for 3 h, 2-benzyl-4,4,4-trifluorobutane-1,3-diol (**4aa**) was obtained in 47% yield with low diastereoselectivity (*syn*/*anti* = 41/59) and low enantioselectivities (35% *ee* for the *syn* isomer and 54% *ee* for the *anti* isomer; Table 1, entry 1).

Among the solvents examined, including CH_2Cl_2, ethanol, and hexane, CH_2Cl_2 gave the best yield and enantioselectivity (Table 1, entries 1–3). A decrease in the reaction temperature (0 °C) for a prolonged reaction time significantly improved the enantioselectivities of both diastereomers (Table 1, entry 4). Other commercially available asymmetric organocatalysts, such as L-proline (**3b**), (*S*)-2-{diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidine (**3c**), and (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole (**3d**), provided lower yields (8–42% yield) with higher diastereoselectivities, but lower enantioselectivities (Table 1, entries 5–7). Although the yield of the product **4aa** was low, interestingly, in the case of **3c**, inversion of the absolute configuration of *anti*-**4aa** was observed (Table 1, entry 6). Finally, a change in the molar ratio of **1a**/**2a** from 3/1 to 1/5 gave the best yield with similar enantioselectivity (Table 1, entry 8). Based on screening of the reaction conditions shown in Table 1, other aldehydes, such as 2-phenylacetaldehyde (**2b**), hexanal (**2c**), octanal (**2d**), and 3-methylbutanal (**2e**), were also examined (Scheme 1).

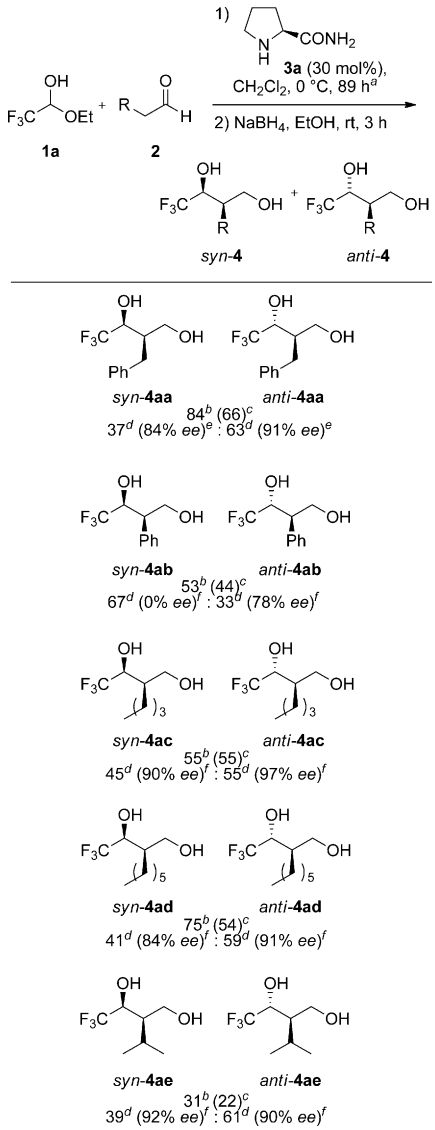
Consequently, compounds **2c** and **2d** could participate in the **3a**-catalyzed in situ generation of CF_3CHO from hemiacetal **1a** and successive asymmetric direct aldol reaction, followed by reduction, to give 2-butyl-4,4,4-trifluorobutane-1,3-diol (**4ac**) and 4,4,4-trifluoro-2-hexylbutane-1,3-diol (**4ad**) in yields of 55 and 75%, as determined by ^{19}F NMR spectroscopy (isolated in yields of 54 and 55%), respectively, with low diastereoselectivities and good to excellent enantioselectivities. The reaction of **2b** gave 4,4,4-trifluoro-2-phenylbutane-1,3-diol (**4ab**) in moderate yield with slight *syn* selectivity with much lower enantioselectivities (0% *ee* for the *syn* isomer and 78% *ee* for the *anti* isomer).

To improve the *ee* values of product **4ab** derived from **2b**, another asymmetric organocatalyst, (*S*)-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]pyrrolidine-2-carboxamide (**3e**), was examined in place of **3a**. Consequently, a significant improvement in enantioselectivities (64% *ee* for the *syn* isomer and 87% *ee* for the *anti* isomer) was achieved (Scheme 2). In all cases, the *syn* and *anti* isomers of **4**, shown in Schemes 1 and 2, could be separated by column chromatography on silica gel.

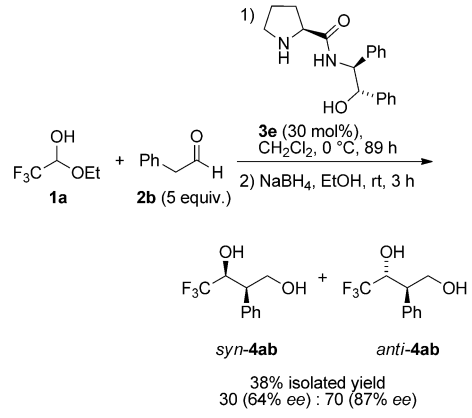
Table 1. Screening of the reaction conditions.

Entry	Catalyst	Ratio **1a**/**2a**	Solvent	*T* [°C]/*t* [h]	Yield[a] [%]	*syn*[b] (*ee*)[c]/*anti*[b] (*ee*)[c] [%]
1	 **3a**	3/1	CH_2Cl_2	RT/24	47	41 (35)/16 (54)
2		3/1	EtOH	RT/24	(6)	43 (–)/57 (–)
3		3/1	hexane	RT/24	26	38 (36)/62 (35)
4		3/1	CH_2Cl_2	0/89	50	44 (73)/56 (92)
5	 **3b**	3/1	CH_2Cl_2	0/89	8	27 (5)/73 (93)
6	 **3c**	3/1	CH_2Cl_2	0/89	11	15 (16)/85 (25)[d]
7	 **3d**	3/1	CH_2Cl_2	0/89	42	34 (38)/66 (78)
8[e]	 **3a**	1/5	CH_2Cl_2	0/89	66 (84)	37 (84)/63 (91)

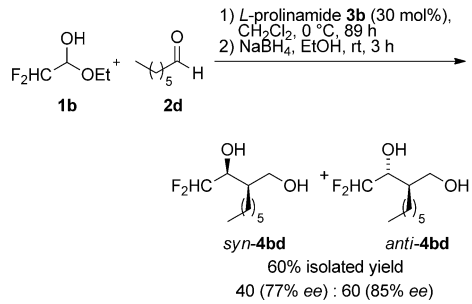
[a] Yields of products **4aa**. Values in parentheses are the yields determined by ^{19}F NMR spectroscopy. [b] Determined by ^{19}F NMR spectroscopy before isolation. [c] Measured by HPLC with a Chiralcel OD column. [d] The absolute configuration is the opposite. [e] A syringe pump was used.



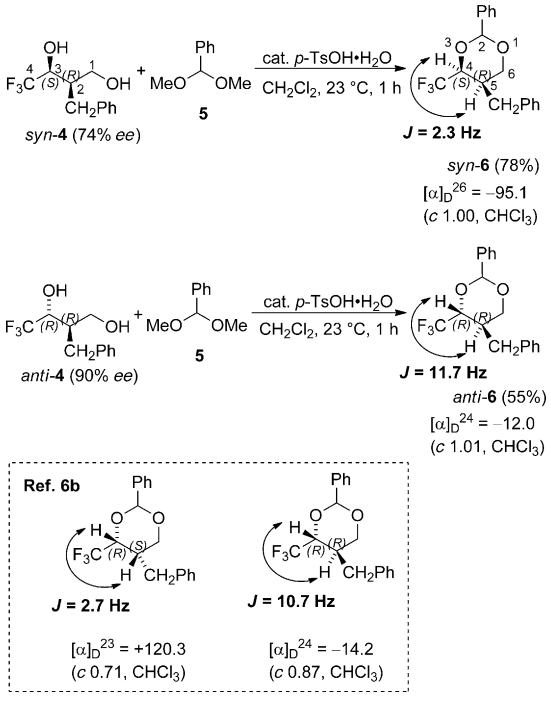
Scheme 1. The **3a**-catalyzed in situ generation of CF_3CHO from **1a** and successive asymmetric direct aldol reactions with aldehydes **2**, followed by reduction, leading to 2-substituted 4,4,4-trifluorobutane-1,3-diols (**4**). [a] Reaction conditions: hemiacetal **1a** (1 mmol) and aldehyde (5 mmol) in CH_2Cl_2 (4 mL) at 0 °C for 89 hours using a syringe pump. [b] ^{19}F NMR yields using benzotrifluoride. [c] Combined yields of both isolated diastereomers. [d] Determined by ^{19}F NMR of the reaction mixture. [e] Measured by HPLC. [f] Measured by GC.



Scheme 2. Use of asymmetric organocatalyst **3e** with aldehyde **2b**.



Scheme 3. Use of an ethyl hemiacetal of **1b**.



Scheme 4. Synthesis of cyclic acetal **6** and determination of the relative stereochemistry and absolute configurations. *p*-TsOH = *p*-toluenesulfonic acid.

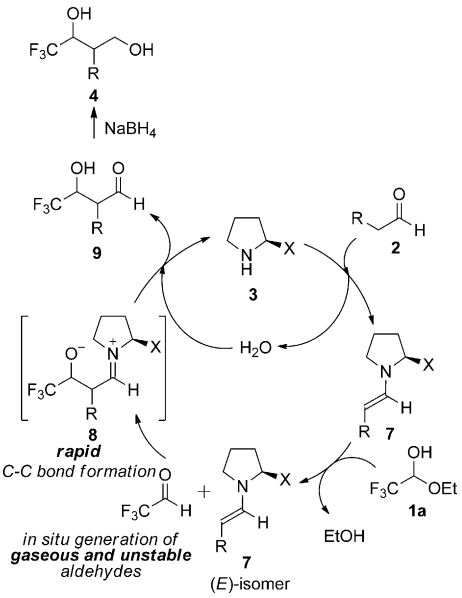
As shown in Scheme 3, an ethyl hemiacetal (**1b**) of difluoroacetaldehyde (CHF_2CHO) also participated well in the organocatalytic in situ generation of CHF_2CHO and successive direct aldol reaction with **2d**, followed by reduction with $NaBH_4$, to give 4,4-difluoro-2-hexylbutane-1,3-diol (**4bd**) in 60% yield with lower diastereo- (*syn*/*anti* = 40/60) and enantioselectivities (77% *ee* for the *syn* isomer and 85% *ee* for the *anti* isomer), compared with trifluoromethylated **4ad** (*syn*/*anti* = 41/59, 84% *ee* for the *syn* isomer and 91% *ee* for the *anti* isomer) owing to steric differences between the tri- and difluoromethyl groups[17] (Scheme 3).

To determine the relative stereochemistry and absolute configuration of **4aa**, the derivatization of 1,3-diol **4aa** to form a cyclic acetal was carried out (Scheme 4). Separated *syn*- and *anti*-**4aa** react with benzaldehyde dimethylacetal **5** in the pres-

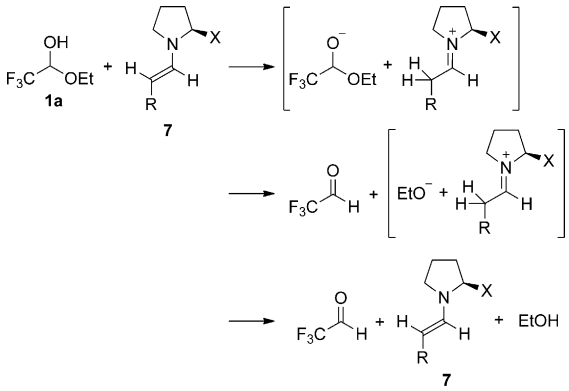
ence of a catalytic amount (20 mol%) of *p*-TsOH monohydrate to give the corresponding *syn*- and *anti*-1,3-dioxane **6**, in yields of 78 and 55%, respectively. The relative stereochemistry of **4aa** could be determined from the vicinal coupling constants of the obtained *syn*- and *anti*-1,3-dioxane **6** in ^{1}H NMR spectroscopy. Thus, *syn*-1,3-dioxolane **6**, which has vicinal protons at C-4 and C-5 in a *syn* arrangement, has a smaller coupling constant ($^3J(H_{ax},H_{eq}) = 2.3$ Hz) than that ($^3J(H_{ax},H_{ax}) = 11.7$ Hz) of *anti*-**6**, according to the reported values ($^3J(H_{ax},H_{eq}) = 2.7$ Hz for the *syn* isomer, $^3J(H_{ax},H_{ax}) = 10.7$ Hz for the *anti* isomer), as shown in Scheme 4.[8b] Stereochemical assignments of the other 1,3-diols **4** were made by comparison of the chemical shifts to those of *syn*- and *anti*-**3c** in ^{19}F NMR spectroscopy. The absolute configurations of the stereogenic centers of C-4 and C-5 of *syn*- and *anti*-**6**, derived from *syn*- and *anti*-**4aa**, were determined to be 4*S*,5*R* in the *syn* isomer and 4*R*,5*R* in the *anti* isomer by comparison to the reported values for the optical rotations of both enantiomers of (4*R*,5*S*)-*syn*-**6** and (4*R*,5*R*)-*anti*-**6**.[8b]

Furthermore, as shown in Scheme 5, the absolute configuration of the stereogenic centers of C-2 and C-3 of **4ac** could also be determined as 2*R*,3*S* in the *syn* isomer and 2*R*,3*R* in the *anti* isomer by comparison to the reported values for the optical rotations of both enantiomers of (2*S*,3*R*)-*syn*-**4ac** and (2*S*,3*S*)-*anti*-**4ac**.[8b] A proposed catalytic reaction mechanism is shown in Scheme 6.

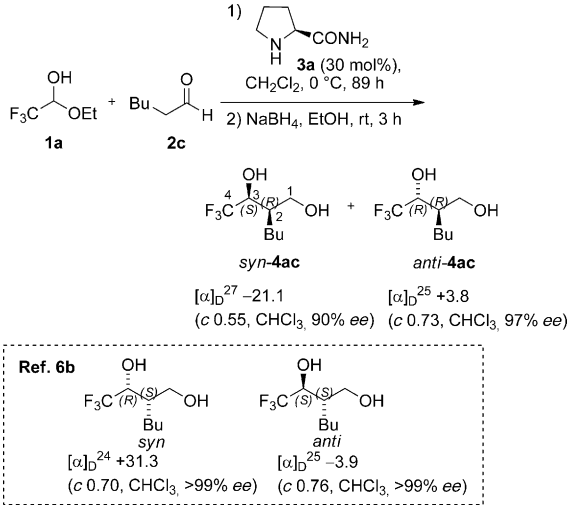
Thus, the chiral pyrrolidine catalyst **3** reacts with aldehyde **2** to give chiral (*E*)-enamine **7**, exclusively.[18] Based on our results of enamine-assisted in situ generation of CF_3CHO from its hemiacetal,[19] as shown in Scheme 7, the reaction of chiral (*E*)-enamine **7** with hemiacetal **1a** gives the ammonium alkoxide, and elimination of the ethoxide leads to the in situ generation of gaseous and unstable CF_3CHO. CF_3CHO reacts rapidly with regenerated chiral (*E*)-enamine through the reaction of an iminium ion with the ethoxide, through successive asymmetric carbon–carbon bond-formation steps, to produce intermediate **8**. Hydrolysis of intermediate **8** gives 2-substituted 4,4,4-trifluoro-3-hydroxybutanal **9** and recovery of asymmetric organocatalyst **3a**, and subsequent reduction with $NaBH_4$ gives 2-substituted 4,4,4-trifluorobutane-1,3-diols **4** with low diastereo- and good to excellent enantioselectivities.



Scheme 6. Proposed catalytic cycle of organocatalysts **3**.



Scheme 7. Proposed reaction mechanism for the generation of CF_3CHO from hemiacetal **1a**.



Scheme 5. Determination of the absolute configurations of *syn*- and *anti*-**4ac**.

Based on the relative and absolute configurations of **4** (Schemes 4 and 5), in situ generated CF_3CHO reacts with chiral (*E*)-enamine **7** through different transition states, such as **TS-1** leading to (2*R*,3*R*)-*syn*-**4** and **TS-2** leading to (2*R*.3*S*)-*anti*-**4**, as depicted in Figure 1. In **TS-1** and **TS-2**, significant points include 1) the chiral (*E*)-enamine **7** is formed exclusively because of steric repulsion between the R and pyrrolidyl groups;[18] 2) there is an antiperiplanar relationship between the trifluoromethyl group and the carbon–carbon double bond of the chiral (*E*)-enamine **7**, owing to electrostatic interactions between the trifluoromethyl group and carbon–carbon double bond;[8b] and 3) chiral (*E*)-enamine **7** attacks CF_3CHO through hydrogen bonding between the oxygen atom of CF_3CHO and the hydrogen atom of the amido group.

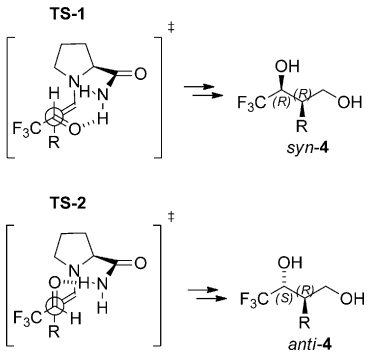


Figure 1. Proposed transition states for the reaction of chiral (*E*)-enamine **7**.

Although both enantioselectivities of *syn*- and *anti*-**4** are high, the diastereoselectivities of **4** are low owing to similar steric properties between **TS-1** and **TS-2**.

Conclusion

We have developed a commercially available and inexpensive **3a**-catalyzed in situ generation of gaseous and unstable CF_3CHO from its hemiacetal, and the successive asymmetric direct aldol reaction with various aldehydes, followed by reduction with $NaBH_4$, to give 2-substituted 4,4,4-trifluorobutane-1,3-diols in fair to good yields (31–84%) with low diastereoselectivities and good to excellent enantioselectivities (64–97% *ee*). In this method, some manipulations in the one-pot procedure include multiple steps, such as 1) the ready and exclusive formation of chiral (*E*)-enamines from aldehydes; 2) the enamine-assisted in situ generation of unstable CF_3CHO from its hemiacetal; 3) successive asymmetric carbon–carbon bond-formation reactions of in situ generated CF_3CHO with the chiral (*E*)-enamine; and 4) hydrolysis of the intermediates and reduction of 2-substituted 4,4,4-trifluoro-3-hydroxybutanals to give not only 2-substituted 4,4,4-trifluorobutane-1,3-diols (**4**) with low diastereoselectivities and high enantioselectivities, but also the regeneration of **3a**. The present method is a direct, concise, and enantioselective route to 2-substituted 4,4,4-trifluorobutane-1,3-diols and offers several advantages, such as eliminating the need for a step to generate unstable CF_3CHO, the use of only a catalytic amount of inexpensive and commercially available asymmetric organocatalyst, and eliminating the need for complicated manipulations.

Experimental Section

General

^{1}H NMR spectra were measured at 400 MHz in $CDCl_3$ or CD_3OD with Me_4Si as an internal standard. ^{13}C NMR spectra were obtained at 100 MHz in $CDCl_3$ or CD_3OD with Me_4Si as an internal standard. ^{19}F NMR spectra were recorded at 372 MHz in $CDCl_3$ or CD_3OD with trifluoroacetic acid (TFA) as an external standard and converted into the $CFCl_3$ standard by using the following equation: $\delta(CFCl_3) = -[77.0-\delta(TFA)]$. The data are reported as (s = singlet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, coupling constant(s), integration).

Typical Procedure for the Preparation of 1,3-Diols 4

A solution of **2a** (0.671 g, 5 mmol) in CH_2Cl_2 (3 mL) was slowly added by using a syringe pump over 12 h to a solution of **1a** (0.170 g, 1.18 mmol) in the presence of a catalytic amount (30 mol%) of **3a** in CH_2Cl_2 (2 mL). After the mixture was stirred at 0 °C for 89 h, $NaBH_4$ (0.189 g, 5 mmol) and ethanol (4 mL) were added. After the mixture was stirred at room temperature for 3 h, it was then quenched with an aqueous solution of Na_2CO_3 (30 mL), extracted with ether (3×30 mL), dried over Na_2SO_4, and concentrated in vacuo to give a residue. The residue was measured by ^{19}F NMR spectroscopy with benzotrifluoride (84% of **4aa**). Purification by flash chromatography on silica gel (hexane–EtOAc = 4:1) gave **4aa** (0.183 g, 66%).

syn-2-Benzyl-4,4,4-trifluorobutane-1,3-diol (*syn*-4aa)[8b]

R_f 0.52 (hexane/ethyl acetate = 1:1); $[\alpha]_D^{22} = -24.5^\circ$ ($c = 0.46$, $CHCl_3$, 84% *ee*); m.p. 106.5–107.5 °C (84% *ee*); IR (CH_2Cl_2): $\tilde{\nu} = 3358$ cm^{-1} (OH); ^{1}H NMR (CD_3OD): $\delta = 2.16$ (s, 1H), 2.48 (t, $J = 12.92$ Hz, 1H), 3.02 (d, $J = 12.92$ Hz, 1H), 3.48 (s, 2H), 4.33 (q, $J = 7.60$ Hz, 1H), 4.89 (s, 2H), 7.08–7.32 ppm (m, 5H); ^{13}C NMR (CD_3OD): $\delta = 32.1$ (s), 44.6 (s), 60.9 (s), 69.1 (q, $J = 29.8$ Hz), 127.1 (s), 127.6 (q, $J = 282.8$ Hz), 129.4 (s), 130.0 (s), 141.3 ppm (s); ^{19}F NMR (CD_3OD): $\delta = -76.6$ ppm (d, $J = 7.60$ Hz, 3F); HRMS (EI): *m/z* calcd for $C_{11}H_{13}F_3O_2$ $[M]^+$: 234.0868; found: 234.0871.

anti-2-Benzyl-4,4,4-trifluorobutane-1,3-diol (*anti*-4aa)[8b]

R_f 0.68 (hexane–ethyl acetate = 1:1); $[\alpha]_D^{23} = +4.9^\circ$ ($c = 0.94$, $CHCl_3$, 91% *ee*); IR (neat): $\tilde{\nu} = 3347$ cm^{-1} (OH); ^{1}H NMR ($CDCl_3$): $\delta = 2.10$–2.21 (m, 1H), 2.69 (br s, 1H), 2.99 (qd, $J = 15.12$, 7.98 Hz, 2H), 3.73 (d, $J = 11.20$ Hz, 1H), 3.94–4.08 (m, 1H), 4.14 (d, $J = 10.80$ Hz, 1H), 4.61 (d, $J = 7.20$ Hz, 1H), 7.22–7.41 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta = 35.1$ (s), 40.2 (s), 62.7 (s), 72.9 (q, $J = 30.1$ Hz), 125.6 (q, $J = 283.4$ Hz), 126.8 (s), 128.8 (s), 129.3 (s), 138.9 ppm (s); ^{19}F NMR ($CDCl_3$): $\delta = -76.4$ ppm (d, $J = 7.20$ Hz, 3F); HRMS (EI): *m/z* calcd for $C_{11}H_{13}F_3O_2$ $[M]^+$: 234.0868; found: 234.0875.

syn-4,4,4-Trifluoro-2-phenylbutane-1,3-diol (*syn*-4ab)

R_f 0.14 (hexane/ethyl acetate = 3:1); $[\alpha]_D^{24} = +1.2^\circ$ ($c = 0.14$, $CHCl_3$, 64% *ee*); m.p. 93.0–94.5 °C (64% *ee*); IR (KBr): $\tilde{\nu} = 3318$ cm^{-1} (OH); ^{1}H NMR (CD_3OD): $\delta = 3.01$–3.12 (m, 1H), 3.67 (dd, $J = 10.40$, 5.40 Hz, 1H), 3.96 (t, $J = 10.40$ Hz, 1H), 4.49 (qd, $J = 7.95$, 3.38 Hz, 1H), 4.91 (s, 2H), 7.18–7.34 ppm (m, 5H); ^{13}C NMR (CD_3OD): $\delta = 49.0$ (s), 63.6 (s), 69.7 (q, $J = 29.4$ Hz), 127.2 (q, $J = 282.5$ Hz), 128.0 (s), 128.9 (s), 130.7 (s), 139.0 ppm (s); ^{19}F NMR (CD_3OD): $\delta = -76.6$ ppm (d, $J = 7.95$ Hz, 3F); HRMS (EI): *m/z* calcd for $C_{10}H_{11}F_3O_2$ $[M]^+$: 220.0711; found: 220.0713.

anti-4,4,4-Trifluoro-2-phenylbutane-1,3-diol (*anti*-4ab)

R_f 0.14 (hexane–ethyl acetate = 3:1); $[\alpha]_D^{24} = -3.3^\circ$ ($c = 0.28$, $CHCl_3$, 87% *ee*); m.p. 86.5–88.0 °C (87% *ee*); IR (KBr): $\tilde{\nu} = 3325$ cm^{-1} (OH); ^{1}H NMR (CD_3OD): $\delta = 2.98$–3.08 (m, 1H), 3.89–4.07 (m, 2H), 4.23 (sext, $J = 7.46$ Hz, 1H), 4.83 (d, $J = 8.00$ Hz, 2H), 7.17–7.33 ppm (m, 5H); ^{13}C NMR (CD_3OD): $\delta = 49.0$ (s), 64.1 (s), 73.1 (q, $J = 28.8$ Hz), 126.7 (q, $J = 283.4$ Hz), 128.0 (s), 129.4 (s), 129.7 (s), 141.1 ppm (s); ^{19}F NMR (CD_3OD): $\delta = -77.3$ ppm (d, $J = 7.46$ Hz, 3F); HRMS (EI): *m/z* calcd for $C_{10}H_{11}F_3O_2$ $[M]^+$: 220.0711; found: 220.0713.

***syn*-2-Butyl-4,4,4-trifluorobutane-1,3-diol (*syn*-4 ac)**[8b]

R_f 0.18 (hexane–ethyl acetate = 4:1); $[\alpha]_D^{27} = -21.1^\circ$ ($c = 0.55$, $CHCl_3$, 90% *ee*); IR (KBr): $\tilde{\nu} = 3356\ cm^{-1}$ (OH); ^1H NMR ($CDCl_3$): $\delta = 0.90$ (t, $J = 6.51$ Hz, 4H), 1.19–1.45 (m, 6H), 1.48–1.61 (m, 1H), 1.98 (br s, 1H), 3.82 (d, $J = 5.00$ Hz, 2H), 4.25 ppm (qd, $J = 7.93$, 2.48 Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 14.0$ (s), 22.9 (s), 24.4 (s), 29.9 (s), 40.8 (s), 63.7 (s), 72.0 (q, $J = 29.8$ Hz), 125.6 ppm (q, $J = 283.1$ Hz); ^{19}F NMR ($CDCl_3$): $\delta = -75.0$ ppm (d, $J = 7.93$ Hz, 3F); HRMS (CI): *m/z* calcd for $C_8H_{16}F_3O_2$ $[M+H]^+$: 201.1102; found: 201.1108.

***anti*-2-Butyl-4,4,4-trifluorobutane-1,3-diol (*anti*-4 ac)**[8b]

R_f 0.25 (hexane–ethyl acetate = 4:1); $[\alpha]_D^{27} = +3.8^\circ$ ($c = 0.73$, $CHCl_3$, 97% *ee*); IR (KBr): $\tilde{\nu} = 3318\ cm^{-1}$ (OH); ^1H NMR ($CDCl_3$): $\delta = 0.92$ (t, $J = 7.18$ Hz, 3H), 1.28–1.44 (m, 4H), 1.56–1.72 (m, 2H), 1.82 (oct, $J = 3.41$, 1H), 2.60 (br s, 1H), 3.77 (dd, $J = 10.80$, 3.60 Hz, 1H), 4.01 (dd, $J = 7.70$, 3.60 Hz, 1H), 4.11 (d, $J = 11.20$ Hz, 1H), 4.48 ppm (br s, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 14.0$ (s), 22.8 (s), 28.5 (s), 29.3 (s), 38.3 (s), 63.4 (s), 73.7 (q, $J = 30.1$ Hz), 125.6 ppm (q, $J = 283.1$ Hz); ^{19}F NMR ($CDCl_3$): $\delta = -76.8$ ppm (d, $J = 7.70$ Hz, 3F); HRMS (EI): *m/z* calcd for $C_8H_{15}F_3O_2$ $[M]^+$: 200.1024; found: 200.1027.

***syn*-4,4,4-Trifluoro-2-hexylbutane-1,3-diol (*syn*-4 ad)**

R_f 0.13 (hexane–ethyl acetate = 4:1); $[\alpha]_D^{27} = -15.7^\circ$ ($c = 0.36$, $CHCl_3$, 84% *ee*); IR (KBr): $\tilde{\nu} = 3333\ cm^{-1}$ (OH); ^1H NMR ($CDCl_3$): $\delta = 0.88$ (t, $J = 6.73$ Hz, 3H), 1.18–1.33 (m, 10H), 1.34–1.42 (m, 2H), 1.48–1.57 (m, 1H), 1.99 (br s, 1H), 3.83 (d, $J = 5.80$ Hz, 1H), 4.25 ppm (qd, $J = 8.03$, 2.15 Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 14.2$ (s), 22.7 (s), 24.7 (s), 27.7 (s), 29.5 (s), 31.8 (s), 40.8 (s), 63.8 (s), 72.2 (q, $J = 30.1$ Hz), 125.6 ppm (q, $J = 283.1$ Hz); ^{19}F NMR ($CDCl_3$): $\delta = -75.0$ ppm (d, $J = 8.03$ Hz, 3F); HRMS (CI): *m/z* calcd for $C_{10}H_{20}F_3O_2$ $[M+H]^+$: 229.1415; found: 229.1411.

***anti*-4,4,4-Trifluoro-2-hexylbutane-1,3-diol (*anti*-4 ad)**

R_f 0.25 (hexane–ethyl acetate = 4:1); $[\alpha]_D^{27} = +4.0^\circ$ ($c = 0.81$, $CHCl_3$, 91% *ee*); IR (KBr): $\tilde{\nu} = 3337\ cm^{-1}$ (OH); ^1H NMR ($CDCl_3$): $\delta = 0.88$ (t, $J = 6.73$ Hz, 3H), 1.22–1.43 (m, 8H), 1.53–1.68 (m, 2H), 1.82 (oct, $J = 3.41$, 1H), 2.64 (s, 1H), 3.76 (dd, $J = 11.25$, 3.15 Hz, 1H), 4.01 (s, 1H), 4.11 (d, $J = 10.80$ Hz, 1H), 4.50 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 14.2$ (s), 22.7 (s), 27.1 (s), 28.8 (s), 29.4 (s), 31.8 (s), 38.4 (s), 63.5 (s), 73.7 (q, $J = 30.1$ Hz), 125.6 ppm (q, $J = 283.4$ Hz); ^{19}F NMR ($CDCl_3$): $\delta = -76.7$ ppm (d, $J = 7.60$ Hz, 3F); HRMS (CI): *m/z* calcd for $C_{10}H_{20}F_3O_2$ $[M+H]^+$: 229.1415; found: 229.1425.

***syn*-4,4,4-Trifluoro-2-isopropylbutane-1,3-diol (*syn*-4 ae)**

R_f 0.15 (hexane–ethyl acetate = 4:1); $[\alpha]_D^{25} = -6.8^\circ$ ($c = 0.26$, $CHCl_3$, 92% *ee*); m.p. 81.5–83.0 °C (92% *ee*); IR (KBr): $\tilde{\nu} = 3341\ cm^{-1}$ (OH); ^1H NMR ($CDCl_3$): $\delta = 0.97$ (d, $J = 6.51$ Hz, 3H), 1.03 (d, $J = 6.51$ Hz, 3H), 1.82–1.99 (m, 3H), 3.77–3.94 (m, 2H), 3.95–4.07 (m, 1H), 4.31 ppm (qd, $J = 8.10$, 3.20 Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 20.7$ (s), 22.3 (s), 26.0 (s), 47.5 (s), 61.9 (s), 71.3 (q, $J = 29.8$ Hz), 126.0 ppm (q, $J = 284.7$ Hz); ^{19}F NMR ($CDCl_3$): $\delta = -74.1$ ppm (d, $J = 8.10$ Hz, 3F); HRMS (EI): *m/z* calcd for $C_7H_{13}F_3O_2$ $[M]^+$: 186.0868; found: 186.0863.

***anti*-4,4,4-Trifluoro-2-isopropylbutane-1,3-diol (*anti*-4 ae)**

R_f 0.35 (hexane–ethyl acetate = 4:1); $[\alpha]_D^{25} = +1.5^\circ$ ($c = 0.16$, $CHCl_3$, 90% *ee*); IR (KBr): $\tilde{\nu} = 3314\ cm^{-1}$ (OH); ^1H NMR ($CDCl_3$): $\delta = 1.02$ (dd, $J = 11.44$, 6.96 Hz, 6H), 1.52 (q, $J = 3.14$, 1H), 2.07 (oct, $J = 6.73$ Hz, 1H), 2.75 (br s, 1H), 3.93 (d, $J = 9.45$ Hz, 1H), 4.06 (d, $J = 9.45$, 1H), 4.11–4.26 (m, 1H), 4.68 ppm (d, $J = 7.70$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 20.1$ (s), 20.9 (s), 26.3 (s), 44.4 (s), 61.2 (s), 72.1 (q, $J = 29.8$ Hz), 125.7 ppm (q, $J = 283.5$ Hz); ^{19}F NMR ($CDCl_3$): $\delta = -77.0$ ppm (d, $J = 8.50$ Hz, 3F); HRMS (EI): *m/z* calcd for $C_7H_{13}F_3O_2$ $[M]^+$: 186.0868; found: 186.0875.

***syn*-4,4-Difluoro-2-hexylbutane-1,3-diol (*syn*-4 bd)**

R_f 0.13 (CH_2Cl_2–ethyl acetate = 10:1); $[\alpha]_D^{25} = -17.5^\circ$ ($c = 0.72$, $CHCl_3$, 77% *ee*); IR (KBr): $\tilde{\nu} = 3356\ cm^{-1}$ (OH); ^1H NMR ($CDCl_3$): $\delta = 0.87$ (t, $J = 6.51$ Hz, 3H), 1.25–1.33 (m, 8H), 1.37–1.40 (m, 2H), 1.84 (br s, 1H), 2.70 (br s, 1H), 3.54 (br s, 1H), 3.72–3.83 (m, 2H), 3.92–4.03 (m, 1H), 5.80 ppm (td, $J = 55.98$, 5.23 Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 14.2$ (s), 22.7 (s), 24.9 (s), 27.6 (s), 29.6 (s), 31.8 (s), 40.7 (s), 63.6 (s), 73.1 (dd, $J = 24.5$, 21.6 Hz), 115.9 ppm (t, $J = 242.9$ Hz); ^{19}F NMR ($CDCl_3$): $\delta = -129.1$ (ddd, $J = 290.02$, 55.98, 14.95 Hz, 1F), -127.0 ppm (ddd, $J = 290.02$, 55.98, 7.13 Hz, 1F); HRMS (CI): *m/z* calcd for $C_{10}H_{21}F_2O_2$ $[M+H]^+$: 211.1510; found: 210.1509.

***anti*-4,4-Difluoro-2-hexylbutane-1,3-diol (*anti*-4 bd)**

R_f 0.19 (CH_2Cl_2–ethyl acetate = 10:1); $[\alpha]_D^{24} = -3.7^\circ$ ($c = 0.79$, $CHCl_3$, 85% *ee*); IR (KBr): $\tilde{\nu} = 3356\ cm^{-1}$ (OH); ^1H NMR ($CDCl_3$): $\delta = 0.87$ (t, $J = 6.74$ Hz, 3H), 1.21–1.38 (m, 8H), 1.42–1.54 (m, 2H), 1.78 (br s, 1H), 2.91 (br s, 1H), 3.68–3.98 (m, 4H), 5.86 ppm (td, $J = 56.10$, 4.50 Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 14.1$ (s), 22.7 (s), 27.1 (s), 28.3 (s), 29.4 (s), 31.8 (s), 39.4 (s), 63.1 (s), 73.9 (t, $J = 23.0$ Hz), 116.2 ppm (t, $J = 243.4$ Hz); ^{19}F NMR ($CDCl_3$): $\delta = -128.49$ (ddd, $J = 287.17$, 56.10, 12.45 Hz, 1F), -128.32 ppm (ddd, $J = 287.17$, 56.10, 9.58 Hz, 1F); HRMS (CI): *m/z* calcd for $C_{10}H_{21}F_2O_2$ $[M+H]^+$: 211.1510; found: 211.1514.

Typical Procedure for the Preparation of 1,3-Dioxane 6

Benzaldehyde dimethyl acetal (52.5 mg, 0.345 mmol) and *p*-TsOH monohydrate (9 mg, 0.051 mmol) were added to a solution of ***syn*-4 aa** (55.7 mg, 0.23 mmol) in CH_2Cl_2 (2.4 mL) at 0 °C. After the mixture was stirred for 1 h at room temperature, it was quenched by the addition of a saturated aqueous solution of Na_2HCO_3 (50 mL). The organic materials were extracted with ethyl acetate (3× 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by preparative TLC (ethyl acetate–hexane = 1:7) gave acetal **6** (58.5 mg, 78%).

***(4S,5R)*-5-Benzyl-2-phenyl-4-(trifluoromethyl)-1,3-dioxane (*syn*-6)**

R_f 0.65 (hexane–ethyl acetate = 7:1); $[\alpha]_D^{26} = -95.1^\circ$ ($c = 1.00$, $CHCl_3$); m.p. 53.4–54.9 °C; ^1H NMR ($CDCl_3$): $\delta = 2.00$–2.07 (m, 1H), 3.01 (d, $J = 13.03$ Hz, 1H), 3.21 (t, $J = 13.03$ Hz, 1H), 3.82 (d, $J = 11.85$ Hz, 1H), 4.02 (d, $J = 11.85$ Hz, 1H), 4.54 (qd, $J = 7.18$, 2.25 Hz, 1H), 5.63 (s, 1H), 7.21–7.34 (m, 5H), 7.38–7.59 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta = 30.6$ (s), 35.5 (s), 68.3 (s), 78.1 (q, $J = 31.9$ Hz), 102.7 (s), 123.5 (q, $J = 282.5$ Hz), 126.4 (s), 126.6 (s), 128.6 (s), 128.7 (s), 129.6 (s), 129.7 (s), 137.3 (s), 139.2 ppm (s); ^{19}F NMR ($CDCl_3$): $\delta = -74.0$ ppm (d, $J = 7.18$ Hz, 3F); HRMS (EI): *m/z* calcd for $C_{18}H_{17}F_3O_2$ $[M]^+$: 322.1181; found: 322.1181.

***(4R,5R)*-5-Benzyl-2-phenyl-4-(trifluoromethyl)-1,3-dioxane (*anti*-6)**

R_f 0.65 (hexane–ethyl acetate = 7:1); $[\alpha]_D^{24} = -12.0^\circ$ ($c = 1.00$, $CHCl_3$); m.p. 76.5–78.8 °C; ^1H NMR ($CDCl_3$): $\delta = 2.26$ (dd, $J = 13.65$, 10.77 Hz, 1H), 2.38–2.51 (m, 1H), 3.04 (d, $J = 13.65$ Hz, 1H), 3.51 (t, $J =$

11.58 Hz, 1H), 3.95 (dd, $J=11.58$, 4.75 Hz, 1H), 4.04 (dq, $J=11.20$, 5.64 Hz, 1H), 5.42 (s, 1H), 7.07–7.43 ppm (m, 10H); ^{13}C NMR ($CDCl_3$): $\delta=33.6$ (s), 35.0 (s), 70.3 (s), 78.7 (q, $J=31.0$ Hz), 101.2 (s), 124.0 (q, $J=280.9$ Hz), 126.2 (s), 126.9 (s), 128.4 (s), 128.8 (s), 129.0 (s), 129.4 (s), 137.1 ppm (s, 2C); ^{19}F NMR ($CDCl_3$): $\delta=-73.9$ ppm (d, $J=5.64$ Hz, 3F); HRMS (CI): *m/z* calcd for $C_{18}H_{17}F_3O_2$ $[M]^+$: 322.1181; found: 322.1197.

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Keywords: aldol reaction · asymmetric synthesis · fluorine · organocatalysis · synthesis design

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