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Tetrahedron
Tetrahedron 63 (2007) 11965–11972

Stereoselective construction of the 1,1,1-trifluoroisopropyl moiety by asymmetric hydrogenation of 2-(trifluoromethyl)allylic alcohols and its application to the synthesis of a trifluoromethylated amino diol

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Received 8 August 2007; revised 5 September 2007; accepted 6 September 2007
Available online 9 September 2007

Abstract—The asymmetric hydrogenation of a series of 2-(trifluoromethyl)allylic alcohols **1a**–**g** catalyzed by a BINAP–Ru(II) diacetate complex gave the corresponding products **2a**–**g** in high yield (>90% yield) and high diastereoselectivity (>95% de). The asymmetric hydrogenation of 2-(trifluoromethyl)allylic alcohols provided an efficient stereoselective method to construct the 1,1,1-trifluoroisopropyl moiety. Based on the asymmetric hydrogenation of the 2-(trifluoromethyl)allylic alcohol **5a** prepared by the reaction of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde with 3,3,3-trifluoroisopropenyllithium, (2*R*,3*S*,4*R*)-4-trifluoromethyl-1-aminopentane-2,3-diol **9** was synthesized in 36% overall yield over five steps.

1. Introduction

The stereoselective synthesis of fluorinated molecules is one of the most fascinating aspects of organofluorine chemistry.[1] Trifluoromethylated compounds exhibit specific biological and physical properties and thus have been widely used as biologically active agents and liquid crystalline materials. This explains the continuing interest in developing methods and reagents for the asymmetric construction of stereogenic centers bearing a CF_3 group.[1d–g,2] The 1,1,1-trifluoroisopropyl moiety ($CF_3CH(CH_3)$–) was used as an important trifluoromethylated group for the modification of amino acids (such as 4,4,4-trifluorovaline and 5,5,5-trifluoroleucine, Fig. 1)[3] and biologically active compounds (such as fluorinated quassinoid, Fig. 1).[4] It must be emphasized, however, that the racemic 1,1,1-trifluoroisopropyl moieties are incorporated into most of these molecules,[4] which is probably due to the shortcomings of existing methods for stereoselective construction of the 1,1,1-trifluoroisopropyl moiety. To the best of our knowledge, the chiral 1,1,1-trifluoroisopropyl moiety was successfully constructed by few research groups. Iseki and Kobayashi had reported that diastereoselective

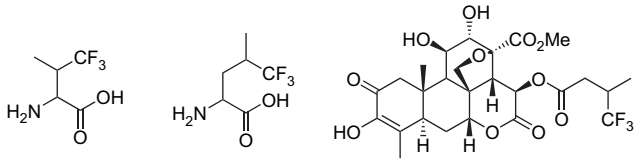

Figure 1. Examples of biologically interesting molecules with a 2-(trifluoromethyl)propyl moiety.

trifluoromethylation of chiral imide enolates with iodotrifluoromethane mediated by triethylborane constructed this moiety in 62% de in 86% yield[5] and hydrogenation of 2-(trifluoromethyl)acrylic acid in the presence of 1 mol % of $Ru_2Cl_4((R)\text{-BINAP})_2N(C_2H_5)_3$ provided optically active 2-(trifluoromethyl)propionic acid in 80% ee.[6] Yamazaki et al. noted that the Michael addition of methyl copper toward (*S*)-3-[(*E*)-4,4,4-trifluorobut-2-enoyl]-4-phenyloxazolidin-2-one provided a chiral 1,1,1-trifluoroisopropyl-containing compound in good yield and high diastereoselectivity.[7] Koenig et al. described that the asymmetric hydrogenation of 1,1,1-trifluoro-2-(acetyloxy)-2-propene produced 1,1,1-trifluoro-2-(acetyloxy)-2-propane with up to 77% ee[8] and the enantioselectivity was improved by using novel C_2 symmetric chiral bidentate ligand developed by Burk.[9] Therefore,

Keywords: Asymmetric hydrogenation; Trifluoromethylated compounds; Amino diols.
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0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.09.013

more efficient methods to construct the chiral 1,1,1-trifluoroisopropyl moiety were highly desired. We now describe an efficient route to chiral 2-(trifluoromethyl)propyl alcohols by the asymmetric hydrogenation of 2-(trifluoromethyl) allylic alcohols.

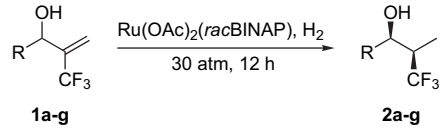
2. Results and discussion

Directed asymmetric hydrogenation of substituted chiral allylic alcohols is a particularly simple route to diverse types of structures with high and predictable diastereoselectivity.[10] In 1988, Noyori reported that the two enantiomers of racemic allylic alcohols were hydrogenated by optically pure BINAP–Ru(II) diacetate complexes at different rates so that they could be resolved efficiently. Furthermore, the hydrogenation of chiral allylic alcohols with either antipodal BINAP–Ru(II) catalyst led to the products with equally high *threo* selectivity.[11] We were interested in extending Noyori's reaction to 2-(trifluoromethyl)allylic alcohols for the construction of the chiral 2-(trifluoromethyl)propyl moiety, although the reactivities and enantioselectivities of fluorine-containing olefins often differ from those of the non-fluorinated substrates.[1e–g]

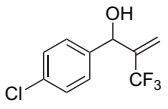
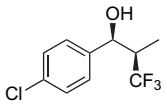
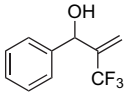
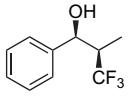
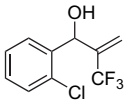
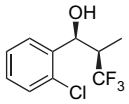
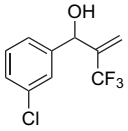
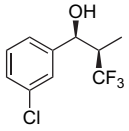
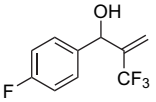
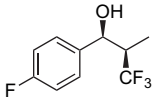
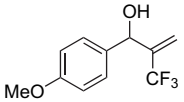
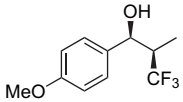
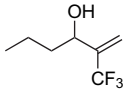
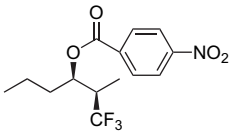
2-(Trifluoromethyl)allylic alcohols **1a**–**g** were prepared by the Barbier-type reaction of 2-bromo-3,3,3-trifluoropropene with aldehydes in the presence of Zn–Ag couple.[12] Firstly, we tested the diastereoselectivity of BINAP–Ru(II)-catalyzed hydrogenation of 2-(trifluoromethyl)allylic alcohols. In view of the enantioface-differentiating ability of BINAP–Ru(II) diacetate complex, racemic BINAP–Ru(II) diacetate complex was used as catalyst. The hydrogenation of compound **1a** was carried out in methanol with a substrate/catalyst mole ratio (S/C) of 200 under an initial hydrogen pressure of 30 atm at room temperature for 12 h. To our delight, ^{19}F NMR analysis showed that a conversion of 100% and a diastereoselectivity of 95% de was achieved (Table 1, entry 1). The hydrogenation product **2a** was isolated in 97% yield. This procedure was then applied to various substrates to clarify the generality of the hydrogenation and the results are shown in Table 1. The hydrogenation of aromatic substrates **1b**–**f** provided corresponding products **2b**–**f** in high yield (>90% yield) and high diastereoselectivity (>95% de) (entries 2–6). Fuchikami had reported the synthesis of **2b** as the major isomer by reduction of 2-(trifluoromethyl)propiophenone with $LiEt_3BH$ and determination of its relative configuration by transformation of **2b** into known 2-hydroxy-3-(trifluoromethyl)butanoate.[13] Therefore, The relative configuration of products **2** was determined by comparison of the spectral data of **2b** with the data published by Fuchikami. The aliphatic substrate **1g** was also suitable for the hydrogenation (entry 7). As the hydrogenation product was volatile, it was converted into *p*-nitrobenzoic ester **2g** in 86% yield over two steps by treatment of the crude hydrogenation product with *p*-nitrobenzoic acid in the presence of DCC and DMAP. The high diastereoselectivity of the asymmetric hydrogenation of 2-(trifluoromethyl)allylic alcohols showed that this reaction constituted an efficient method to construct chiral 1,1,1-trifluoroisopropyl moiety.

Then the hydrogenation of racemic 2-(trifluoromethyl) allylic alcohols catalyzed by optically pure BINAP–Ru(II) was investigated to test the level of kinetic enantiomer selection (k_f/k_s). The optically active (*R*)-BINAP–Ru(II) diacetate complex was used as a catalyst instead of the racemic one for hydrogenation of **1a** under the same reaction conditions shown in Table 1. As we expected, ^{19}F NMR of the reaction mixture showed that only 54% of **1a** was converted. However, the unreacted **1a** and the hydrogenation product could not be separated by column chromatography. Thus it was difficult to evaluate the kinetic enantiomer selection (k_f/k_s)

Table 1. Asymmetric hydrogenation of 2-trifluoromethyl allylic alcohols



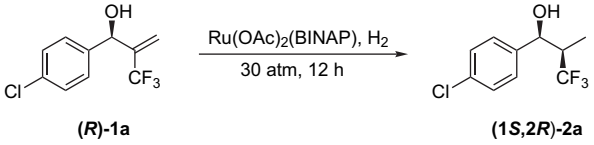
1a-g **2a-g**

Entry	Substrate	Product[a]	de[b] (%)	Yield[c] (%)
1	 **1a**	 **2a**	95	97
2	 **1b**	 **2b**	98	94
3	 **1c**	 **2c**	95	90
4	 **1d**	 **2d**	95	92
5	 **1e**	 **2e**	98	95
6	 **1f**	 **2f**	95	96
7[d]	 **1g**	 **2g**	98	86

[a] Enantiomers.
[b] Determined by ^{19}F NMR.
[c] Isolated yield.
[d] The hydrogenation product of compound **1g** was converted into its *p*-nitrobenzoic ester **2g** without further purification due to its volatility.

of the hydrogenation based on the analysis of the product. To evaluate the kinetic enantiomer selection (k_f/k_s), the optically pure (*R*)-**1a** was prepared by the chemical resolution of **1a**[14] and the hydrogenation of (*R*)-**1a** with (*R*)- and (*S*)-BINAP–Ru(II) diacetate complex as the catalyst was carried out (Table 2). In this way, the level of kinetic enantiomer selection (k_f/k_s) could be measured by the ratio of conversion of (*R*)-**1a** determined by ^{19}F NMR. When (*R*)-**1a** was hydrogenated for 12 h with (*S*)-BINAP–Ru(II) as catalyst, the reaction was complete and gave optically pure product (1*S*,2*R*)-**2a** in 98% de and 94% isolated yield (entry 1). In comparison, the hydrogenation of (*R*)-**1a** in the presence of (*R*)-BINAP–Ru(II) led to very low conversion (9%) and high selectivity (98% de) (entry 2). The difference of conversion indicated a high level of kinetic enantiomer selection (k_f/k_s>100:9) and suggested that racemic 2-(trifluoromethyl)-allylic alcohols could be resolved by BINAP–Ru(II)-catalyzed hydrogenation efficiently.

Table 2. Asymmetric hydrogenation of (*R*)-**1a**



(*R*)-**1a** (1*S*,2*R*)-**2a**

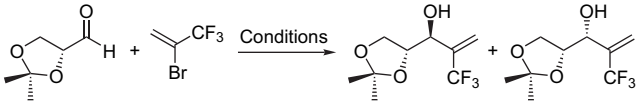
Entry	BINAP	de[a] (%)	Conversion[a] (%)	Yield (%)
1	*S*	98	100	94[b]
2	*R*	98	9	9[a]

[a] Determined by ^{19}F NMR.
[b] Isolated yield.

followed by the asymmetric hydrogenation of the resulting 2-(trifluoromethyl)allylic alcohol (Fig. 2).

Initially, the reaction of 2-bromo-3,3,3-trifluoropropene **4** with (*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde **3** in the presence of Zn–Ag couple for the synthesis of optically active 2-(trifluoromethyl)allylic alcohol was carried out (Table 3).[12] Unfortunately, the allylic alcohols **5a** and **5b** were obtained only in 30% total yield (**5a/5b**=1.5:1) (entry 1). We were pleased to find that whether the yield of allylic alcohols **5a** and **5b** could be increased when the more active 3,3,3-trifluoroisopropenyllithium was used. Treatment of aldehyde **3** with in situ generated 3,3,3-trifluoroisopropenyllithium in Et_2O at −95 °C gave the allylic alcohols **5a** and **5b** in 51% total yield (**5a/5b**=1:1.5) (entry 2).[18] The difference of stereoselectivity could be illustrated with chelation (lithium reagent) or non-chelation control (zinc reagent) in addition reactions.[19]

Table 3. The preparation of allylic alcohols **5a** and **5b**



3 **4** **5a** **5b**

Conditions	Yield[a] (%)	**5a/5b**[b]
3, **4**, Zn–Ag, DMF, 50 °C, 12 h	30%	1.5:1
3, **4**, *n*-BuLi, Et_2O, −95 °C, 2 h	51%	1:1.5

[a] Isolated yield.
[b] Determined by ^{19}F NMR.

Aminodiols are common subunits of many important biologically active compounds, such as renin and HIV-1 protease inhibitor, sphingosine, etc.[15] Fluorinated amino acids and amino alcohols have attracted increasing attention.[16] Fluorinated amino diols **A**, **B**, and **C** (Fig. 2) could be considered as fluorinated analogs of these biologically active molecules and used as building blocks for synthesis of important fluorinated amino acids.[17] We wanted to develop a general stereoselective synthetic strategy for fluorinated amino diols **A**, **B**, and **C** based on the reaction of chiral pool (*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde with 3,3,3-trifluoroisopropenyl metallic (zinc[12] or lithium[18]) reagents,

With compounds **5a** and **5b** in hand, the hydrogenation of **5a** and **5b** catalyzed by BINAP–Ru(II) was investigated (Table 4). When **5a** was hydrogenated with (*S*)-BINAP–Ru(II) diacetate complex at 30 atm for 12 h, the reaction was complete and a diastereoselectivity of 98% was achieved. The single hydrogenation product **6a** was isolated in 90% yield (entry 1). However, the hydrogenation of **5a** with mismatched (*R*)-BINAP–Ru(II) diacetate complex was incomplete (59% conversion) even at 60 atm for 36 h and only a diastereoselectivity of 10% was achieved with compound **6a** as the major product (entry 2). Similarly, the hydrogenation of **5b** with matched (*R*)-BINAP–Ru(II) diacetate

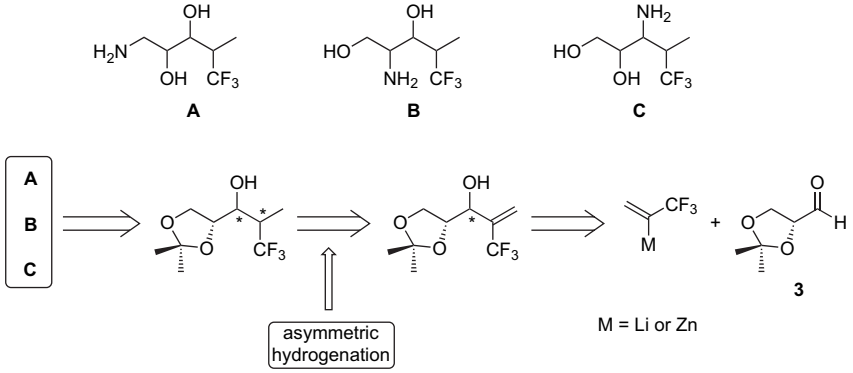
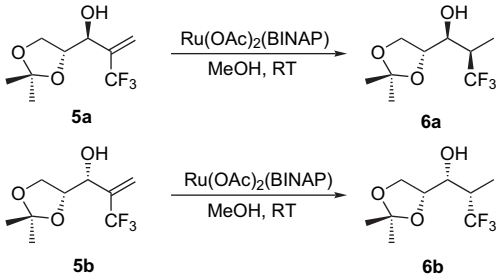


Figure 2. Synthetic strategy to trifluoromethylated aminodiols.

Table 4. Asymmetric hydrogenation of **5a** and **5b**



Entry	Substrate	BINAP	Conditions	Major product	Conversion[a] (%)	de[a] (%)	Yield (%)
1	**5a**	(*S*)	30 atm, 12 h	**6a**	100	98	90[b]
2	**5a**	(*R*)	60 atm, 36 h	**6a**	59	10	32[a]
3	**5b**	(*R*)	30 atm, 12 h	**6b**	100	98	95[b]
4	**5b**	(*S*)	60 atm, 36 h	**6b**	90	54	69[a]

[a] Determined by ^{19}F NMR.
[b] Isolated yield.

complex at 30 atm for 12 h was complete. A diastereoselectivity of 98% was achieved and a single product **6b** was isolated in 95% yield (entry 3), while hydrogenation of **5b** with mismatched (*S*)-BINAP–Ru(II) diacetate complex was incomplete (90% conversion) at 60 atm for 36 h and a diastereoselectivity of 54% was achieved with **6b** as the major product (entry 4). It was noteworthy that the hydrogenation of **5a** and **5b** with the mismatched catalyst (Table 4, entries 2 and 4) led to low diastereoselectivity and higher conversion rate. This result may be explained by the influence of the oxygen atoms. In our opinion, the hydrogenation of **5a–b** was predominantly directed by allylic hydroxyl group in the presence of matched catalyst. When mismatched catalyst was used, the hydrogenation would be influenced by the direction of the other two oxygen atoms of **5a–b**, which made the reaction results complicated.

Having succeeded in the stereoselective construction of the 1,1,1-trifluoroisopropyl moiety of **6a** and **6b**, we then explored the concise stereoselective synthetic route to a stereoisomer of fluorinated amino diol **A** from compound **6a** (Scheme 1). Treatment of alcohol **6a** with trifluoromethanesulfonic anhydride and pyridine afforded the crude trifluoromethanesulfonic ester product. Exposure of this crude product to sodium azide in DMF at room temperature gave azide **7** in 48% yield for two steps. Reduction of the azido group of **7** by hydrogenation followed by direct treatment of resultant amine with Boc_2O gave compound **8** in quantitative yield. Finally, removal of isopropylidene ketal of compound **8** with TsOH in methanol proceeded smoothly to afford the fluorinated amino diol **9** in 81% yield. The absolute configuration of compound **9** was determined by X-ray diffraction analysis (Fig. 3).[20] The absolute configuration of compounds **5a** and **6a** was also confirmed by X-ray structure of compound **9**. The formation of **9** indicated that trifluoromethanesulfonic ester of primary alcohol **11** was formed when compound **6a** was treated with trifluoromethanesulfonic anhydride and pyridine. We thought that this was probably due to the migration of isopropylidene ketal (Scheme 1).

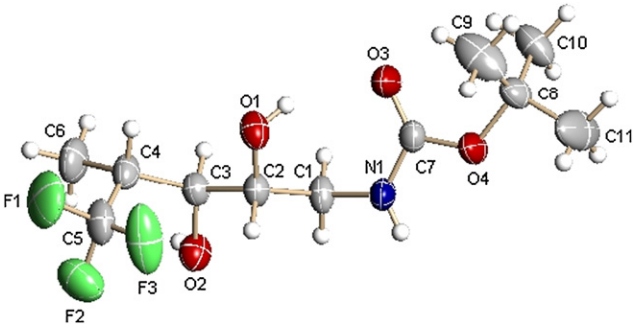
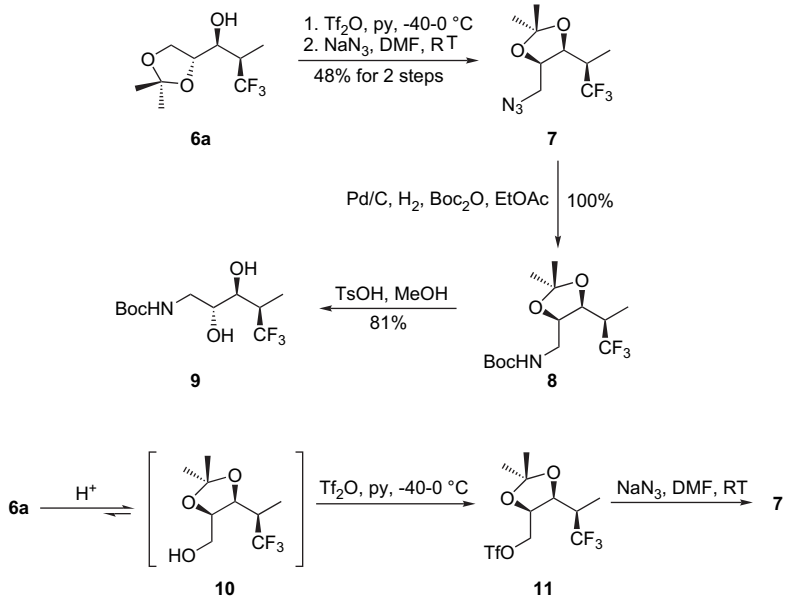


Figure 3. X-ray structure of compound **9**.



Scheme 1.

There was a kinetic equilibrium between **6a** and **10** under the acidic condition.[21] The primary alcohol of **10** was esterified more easily to give **11** as the major product.

In conclusion, the asymmetric hydrogenation of 2-(trifluoromethyl)allylic alcohols catalyzed by BINAP–Ru(II) diacetate complex provided an efficient method for stereoselective construction of 1,1,1-trifluoroisopropyl moiety. Based on the asymmetric hydrogenation of 2-(trifluoromethyl)allylic alcohol **6a** that was prepared by the reaction of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde with in situ generated 3,3,3-trifluoroisopropenyllithium, we developed a stereoselective synthetic strategy to 4-trifluoromethyl-1-aminopentane-2,3-diol **9**.

3. Experimental section

3.1. General procedure for asymmetric hydrogenation

To a mixture of 2-trifluoromethyl allylic alcohols **1** (0.1 mmol) and Ru(BINAP)$(OAc)_2$ (0.005 mmol) was added dry methanol (4 mL) in autoclave and then the reaction mixture was stirred under an hydrogen pressure of 30 atm at room temperature for 12 h. The reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=20:1) to afford **2**.

3.1.1. (1*S,2*R**)-1-(4-Chlorophenyl)-3,3,3-trifluoro-2-methylpropan-1-ol (2a).** Compound **2a**: 97%; clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.28 (m, 4H), 4.83 (d, J=7.8 Hz, 1H), 2.69–2.55 (m, 1H), 2.20 (br, 1H), 0.90 (d, J=7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.57 (d, J=8.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 139.3, 134.2, 128.7, 128.3, 127.5 (q, J=210.5 Hz), 73.1 (q, J=1.6 Hz), 44.7 (q, J=18.3 Hz), 10.2 (q, J=2.1 Hz); IR (thin film) ν_{max} 3415, 2993, 1600, 1494, 1373, 1259, 1172, 1097, 839 cm^{-1}; MS (EI) *m*/*z* 238 (M^+, 1.10), 141 (100); HRMS (EI) calcd for $C_{10}H_{10}ClF_3O$: 238.0372; found: 238.0366.

3.1.2. (1*S,2*R**)-3,3,3-Trifluoro-2-methyl-1-phenylpropan-1-ol (2b).** Compound **2b**: 94%; clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.32 (m, 5H), 4.81 (d, J=8.1 Hz, 1H), 2.70–2.57 (m, 1H), 1.98 (br, 1H), 0.86 (d, J=7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.57 (d, J=9.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 140.9, 128.6, 128.5, 127.7 (q, J=210.7 Hz), 126.9, 74.0 (q, J=1.4 Hz), 44.7 (q, J=18.3 Hz), 10.5 (q, J=2.4 Hz); IR (thin film) ν_{max} 3425, 3036, 1496, 1373, 1259, 1173, 1008, 764 cm^{-1}; MS (EI) *m*/*z* 186 (M^+-H_2O, 0.82), 127 (0.85), 107 (100); HRMS (EI) calcd for $C_{10}H_9F_3$: 186.0656; found: 186.0661.

3.1.3. (1*S,2*R**)-1-(2-Chlorophenyl)-3,3,3-trifluoro-2-methylpropan-1-ol (2c).** Compound **2c**: 90%; clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.14 (m, 4H), 5.24 (d, J=8.1 Hz, 1H), 2.70–2.57 (m, 1H), 2.22 (br, 1H), 0.88 (d, J=7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.21 (d, J=8.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.8, 132.6, 129.6, 129.3, 128.3, 127.7 (q, J=210.3 Hz), 127.4, 70.3, 44.4 (q, J=18.4 Hz), 10.6 (q, J=2.3 Hz); IR (thin film) ν_{max} 3416, 3073, 2996, 1746, 1575, 1256, 1176, 1032, 950, 758 cm^{-1}; MS (EI) *m*/*z* 238 (M^+, 0.47), 141 (93.85), 77 (100); HRMS (EI) calcd for $C_{10}H_{10}ClF_3O$: 238.0372; found: 238.0365.

3.1.4. (1*S,2*R**)-1-(3-Chlorophenyl)-3,3,3-trifluoro-2-methylpropan-1-ol (2d).** Compound **2d**: 92%; clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.19 (m, 4H), 4.89 (d, J=8.1 Hz, 1H), 2.67–2.54 (m, 1H), 2.20 (br, 1H), 0.89 (d, J=6.9 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.55 (d, J=8.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 142.8, 134.5, 129.8, 128.6, 127.4 (q, J=210.8 Hz), 127.1, 125.1, 73.2 (q, J=1.2 Hz), 44.7 (q, J=18.4 Hz), 10.3 (q, J=2.0 Hz); IR (thin film) ν_{max} 3416, 2994, 1599, 1467, 1258, 1176, 1081, 887, 700 cm^{-1}; MS (EI) *m*/*z* 238 (M^+, 1.79), 141 (83.19), 77 (100); HRMS (EI) calcd for $C_{10}H_{10}ClF_3O$: 238.0372; found: 238.0376.

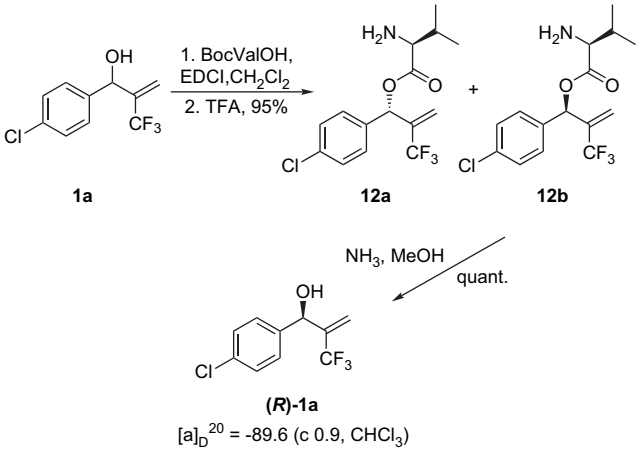
3.1.5. (1*S,2*R**)-3,3,3-Trifluoro-1-(4-fluorophenyl)-2-methylpropan-1-ol (2e).** Compound **2e**: 95%; clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.18 (m, 2H), 7.01–6.94 (m, 2H), 4.72 (d, J=8.1 Hz, 1H), 2.58–2.44 (m, 1H), 2.21 (br, 1H), 0.78 (d, J=6.9 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −69.88 (d, J=9.6 Hz, 3F), −116.74 to −116.85 (m, 1F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 162.6 (d, J=185.3 Hz), 136.7 (d, J=2.3 Hz), 128.6 (d, J=6.8 Hz), 127.6 (q, J=210.5 Hz), 115.5 (d, J=16.1 Hz), 73.1, 44.8 (q, J=18.4 Hz), 10.3 (q, J=2.2 Hz); IR (thin film) ν_{max} 3416, 2928, 1607, 1512, 1259, 1173, 1093, 842, 767 cm^{-1}; MS (EI) *m*/*z* 222 (M^+, 0.37), 125 (100); HRMS (EI) calcd for $C_{10}H_{10}F_4O$: 222.0668; found: 222.0673.

3.1.6. (1*S,2*R**)-3,3,3-Trifluoro-1-(4-methoxyphenyl)-2-methylpropan-1-ol (2f).** Compound **2f**: 96%; clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J=8.7 Hz, 2H), 6.91 (d, J=9.0 Hz, 2H), 4.75 (d, J=8.7 Hz, 1H), 3.82 (s, 3H), 2.67–2.54 (m, 1H), 2.29 (br, 1H), 0.87 (d, J=7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.59 (d, J=8.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.6, 133.1, 128.1, 127.6 (q, J=210.5 Hz), 113.9, 73.4, 55.2, 44.7 (q, J=18.4 Hz), 10.4; IR (thin film) ν_{max} 3439, 3003, 2953, 2842, 1614, 1515, 1253, 1175, 837, 767 cm^{-1}; MS (EI) *m*/*z* 234 (M^+, 5.89), 137 (100); HRMS (EI) calcd for $C_{11}H_{13}F_3O_2$: 234.0868; found: 234.0866.

3.1.7. (2*R,3*R**)-1,1,1-Trifluoro-2-methylhexan-3-yl 4-nitrobenzoate (2g).** To a stirred solution of the crude hydrogenation product of compound **1g** were added *p*-nitrobenzoic acid, DCC, and DMAP subsequently. The resulting mixture was stirred at room temperature overnight. The reaction was quenched with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=10:1) to give **2g** (86% for two steps) as a clear oil. Compound **2g**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24–8.13 (m, 4H), 5.37–5.31 (m, 1H), 2.69–2.55 (m, 1H), 1.79–1.59 (m, 2H), 1.39–1.26 (m, 2H), 1.15 (d, J=6.9 Hz, 3H), 0.88 (t, J=7.5 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.67 (d, J=7,9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.9, 150.7, 135.3, 130.8, 127.0 (q, J=280.6 Hz), 123.6, 73.3, 41.32 (q, J=26.2 Hz), 33.0, 18.5, 13.7, 9.7 (q, J=2.3 Hz); IR (thin film) ν_{max} 3115,

2966, 1729, 1531, 1280, 1181, 837 cm^{-1}; MS (ESI) *m/z* 340 (M^++Na); HRMS (ESI) calcd for $C_{14}H_{16}F_3NO_4Na$: 342.0924; found: 342.0922.

3.1.8. Preparation of (*R*)-1a by chemical resolution of 1a.



To a stirred solution of L-BocValOH (516 mg, 2.38 mmol) in methylene chloride (6 mL) was added at 0 °C a solution of **1a** (576 mg, 2.44 mmol), DMAP (48 mg, 0.39 mmol), and EDCI (672 mg, 3.46 mmol) in methylene chloride (6 mL). The resulting mixture was stirred at room temperature for 4 h and then quenched with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford a crude product. To a solution of this crude product in methylene chloride (20 mL) was added TFA (3.36 mL) at room temperature, and the resulting mixture was stirred overnight. The solvent was removed in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=5:1) to give **12a** (345 mg, 47%) and **12b** (351 mg, 48%). Compound **12a**: clear oil; $[\alpha]_D^{20}$ 80.2 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.27 (m, 4H), 6.50 (s, 1H), 6.00 (s, 1H), 5.61 (s,1H), 3.35 (d, *J*=7.8 Hz, 1H), 2.17–2.06 (m, 1H), 1.46 (br, 2H), 0.99 (d, *J*=6.9 Hz, 3H), 0.88 (d, *J*=6.6 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.21 (s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.9, 173.7 (q, *J*=17.7 Hz), 135.0, 134.8, 128.9, 128.7, 122.6 (q, *J*=167.1 Hz), 122.5, 71.3, 60.1, 31.7, 19.4, 16.5; IR (thin film) ν_{max} 3396, 2967, 1744, 1599, 1490, 1175, 1093, 834 cm^{-1}; MS (EI) *m/z* 336 (M+H); HRMS (EI) calcd for $C_{15}H_{18}ClF_3NO_2$: 336.0973; found: 336.0977. Compound **12b**: $[\alpha]_D^{20}$ −60.4 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.21 (m, 4H), 6.42 (s, 1H), 5.91 (s, 1H), 5.59 (s,1H), 3.31 (d, *J*=7.8 Hz, 1H), 2.01–1.90 (m, 1H), 1.72 (br, 2H), 0.84 (d, *J*=6.6 Hz, 3H), 0.69 (d, *J*=6.9 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.20 (s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.6, 137.4 (q, *J*=22.2 Hz), 134.9 (q, *J*=5.7 Hz), 134.8, 128.8, 128.7, 122.5 (q, *J*=205.7 Hz), 121.9 (q, *J*=3.9 Hz), 71.3, 59.7, 31.8, 19.2, 16.7; IR (thin film) ν_{max} 3392, 2966, 1745, 1599, 1494, 1175, 1092, 965 cm^{-1}; MS (EI) *m/z* 336 (M+H); HRMS (EI) calcd for $C_{15}H_{18}ClF_3NO_2$: 336.0973; found: 336.0972.

A solution of **12b** (351 mg, 1.05 mmol) in NH_3/MeOH (5 mL) was stirred at room temperature overnight. The solvent was removed in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=5:1) to give (*R*)-**1a** (247 mg, 100%). Compound (*R*)-**1a**: clear oil; $[\alpha]_D^{20}$ −89.6 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.29 (m, 4H), 5.94 (d, *J*=1.2 Hz, 1H), 5.80 (t, *J*=1.2 Hz, 1H), 5.42 (s,1H), 2.05 (s, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.18 (s).

3.1.9. (1*S*,2*R*)-1-(4-Chlorophenyl)-3,3,3-trifluoro-2-methylpropan-1-ol ((1*S*,2*R*)-2a). The hydrogenation of (*R*)-**1a** catalyzed with (*S*)-BINAP–Ru(II) dicarboxylate complex gave (1*S*,2*R*)-**2a** (94%) as a clear oil. Compound (1*S*,2*R*)-**2b**: $[\alpha]_D^{20}$ −24.0 (*c* 0.65, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.28 (m, 4H), 4.83 (d, *J*=7.8 Hz, 1H), 2.69–2.55 (m, 1H), 2.20 (br, 1H), 0.90 (d, *J*=7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.57 (d, *J*=8.7 Hz).

3.1.10. (*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(trifluoromethyl)prop-2-en-1-ol (5a) and (*R*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(trifluoromethyl)prop-2-en-1-ol (5b).

3.1.10.1. Preparation from trifluoropropenyl zinc reagent. A mixture of (*R*)-glyceraldehyde **3** (1 g, 7.6 mmol), 2-bromo-3,3,3-trifluoropropene **4** (1.98 g, 11.3 mmol), Zn–Ag (0.98 g, 15.2 mmol), and anhydrous DMF (30 mL) in a Schlenck tube was stirred at room temperature for 2 h. Then the reaction mixture was stirred for 12 h at 50 °C. The reaction was quenched with 1 N aqueous HCl (30 mL) and then extracted with ethyl acetate (30 mL×3). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=10:1) to give **5a** (310 mg, 18%) and **5b** (210 mg, 12%) as clear oil. Compound **5a**: $[\alpha]_D^{20}$ −6.2 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.93 (s, 2H), 4.59 (s, 1H), 4.37–4.32 (m, 1H), 3.91–3.88 (m, 2H), 2.67 (d, *J*=1.8 Hz ,1H), 1.48 (s, 3H), 1.39 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.94 (s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.7 (q, *J*=28.6 Hz), 122.9 (q, *J*=273.3 Hz), 121.3 (q, *J*=5.6 Hz), 109.9, 76.0, 67.2, 63.5, 26.3, 24.9; IR (thin film) ν_{max} 3460, 2992, 1750, 1459, 1384, 1256, 1176 cm^{-1}; MS (EI) *m/z* 211 (M^+-CH_3, 36), 131 (100), 101 (4). Anal. Calcd for $C_9H_{13}O_3F_3$: C, 47.79; H, 5.79. Found: C, 47.62; H, 5.80. Compound **5b**: $[\alpha]_D^{20}$ −13.3 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.97 (d, *J*=5.4 Hz, 1H), 5.84 (d, *J*=4.8 Hz, 1H), 4.31–4.23 (m, 2H), 4.07 (dd, *J*=6.3, 8.4 Hz, 1H), 3.86 (dd, *J*=6.0, 9.0 Hz, 1H), 2.73 (d, *J*=5.4 Hz, 1H), 1.48 (s, 3H), 1.39 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.09 (s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.1 (q, *J*=28.8 Hz), 125.0 (q, *J*=272.8 Hz), 122.0 (q, *J*=5.4 Hz), 110.1, 77.2, 69.3, 66.1, 26.4, 25.0; IR (thin film) ν_{max} 3460, 2992, 1458, 1384, 1258, 1174, 1128 cm^{-1}; MS (EI) *m/z* 227 (M^++1, <1), 211 (M^+-CH_3, 44), 131 (18), 101 (53). Anal. Calcd for $C_9H_{13}O_3F_3$: C, 47.79; H, 5.79. Found: C, 48.08; H, 6.03.

3.1.10.2. Preparation from trifluoropropenyl lithium reagent. 2-Bromo-3,3,3-trifluoropropene **4** (780 mg, 4.48 mmol) in dry ether (15 mL) was cooled to −95 °C under dry nitrogen. *n*-Butyllithium (4.5 mmol) in a mixed solvent (hexane/ether) (4 mL) was added dropwise. The reaction mixture was stirred for 45 min. A solution of (*R*)-glyceraldehyde **3** (390 mg, 3.0 mmol) in ether (2 mL) was

added dropwise. After the addition was finished, the temperature was kept between −90 and −95 °C for 2 h and then the reaction was allowed to warm very slowly to room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate three times. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=10:1) to give **5a** (139 mg, 20%) and **5b** (208 mg, 31%) as clear oil.

3.1.11. (1*S*,2*R*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3,3,3-trifluoro-2-methylpropan-1-ol (6a) and (1*R*,2*S*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,3,3-trifluoro-2-methylpropan-1-ol (6b). The hydrogenation of **5a** in the presence of (*S*)-BINAP–Ru(II) diacetate complex gave **6a** as a clear oil. Compound **6a**: $[\alpha]_D^{20}$ +20.8 (*c* 0.86, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.20 (dd, *J*=5.7, 11.4 Hz, 1H), 4.03 (dd, *J*=6.0, 7.5 Hz, 1H), 3.98–3.87 (m, 2H), 2.60–2.41 (m, 1H), 2.31 (d, *J*=4.2 Hz, 1H), 1.43 (s, 3H), 1.37 (s, 3H), 1.18 (d, *J*=6.9 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.38 (d, *J*=6.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 127.4 (q, *J*=281.0 Hz), 109.1, 76.4, 71.0 (q, *J*=2.1 Hz), 65.2, 40.4 (q, *J*=25.0 Hz), 26.5, 25.1, 10.3 (q, *J*=4.1 Hz); IR (thin film) ν_{max} 3476, 2992, 2940, 1467, 1375, 1253, 1217, 1178, 1134, 1070 cm^{-1}; MS (EI) *m*/*z* 213 (M^+-CH_3, 18), 131 (2), 101 (37). Anal. Calcd for $C_9H_{15}O_3F_3$: C, 47.37; H, 6.63. Found: C, 47.54; H, 6.80. The hydrogenation of **5b** in the presence of (*R*)-BINAP–Ru(II) dicarboxylate complex gave **6b** (95%) as a clear oil. Compound **6b**: $[\alpha]_D^{20}$ −5.5 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.29–4.23 (m, 1H), 4.06 (dd, *J*=6.3, 8.1 Hz, 1H), 3.88 (dd, *J*=6.6, 8.4 Hz, 1H), 3.70–3.64 (m, 1H), 3.52–3.43 (m, 1H), 2.40 (d, *J*=7.2 Hz, 1H), 1.45 (s, 3H), 1.83 (s, 3H), 1.19 (d, *J*=6.9 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.47 (d, *J*=9.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 128.1 (q, *J*=279.3 Hz), 109.6, 74.9, 69.4 (q, *J*=2.9 Hz), 66.9, 39.1 (q, *J*=24.9 Hz), 26.7, 25.0, 5.9 (q, *J*=2.6 Hz); IR (thin film) ν_{max} 3476, 2993, 1468, 1375, 1255, 1174 cm^{-1}; MS (EI) *m*/*z* 213 (M^+-CH_3, 10), 131 (4), 101 (40). Anal. Calcd for $C_9H_{15}O_3F_3$: C, 47.37; H, 6.63. Found: C, 47.47; H, 6.93.

3.1.12. (4*R*,5*S*)-4-(Azidomethyl)-2,2-dimethyl-5-((*R*)-1,1,1-trifluoropropan-2-yl)-1,3-dioxolane (7). To a stirred solution of **6a** (110 mg, 0.5 mmol) and pyridine (82 μL) in methylene chloride (4 mL) at −40 °C was added dropwise trifluoromethanesulfonic anhydride (155 mg, 0.55 mmol), the reaction temperature was warmed to 0 °C slowly and then was maintained for 1 h. The reaction mixture was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to afford the crude product of trifluoromethanesulfonic ester. A solution of the crude product and sodium azide (71 mg, 1.0 mmol) in DMF (2 mL) was stirred for 4 h at room temperature. The resulting suspension was diluted with ethyl acetate (10 mL) and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=5:1) to give **7** (58 mg, 48% for two steps) as a clear oil. Compound **7**: clear oil, $[\alpha]_D^{20}$ +46.0 (*c* 1.190, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.26–4.20 (m, 1H), 4.12 (dd, *J*=5.7, 8.4 Hz, 1H), 3.30 (dd, *J*=7.5, 12.9 Hz, 1H), 3.17 (dd, *J*=3.9, 13.2 Hz, 1H), 2.48–2.30 (m, 1H), 1.44 (s, 3H), 1.31 (s, 3H), 1.19 (d, *J*=6.6 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −70.84 (d, *J*=8.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 127.0 (q, *J*=262.5 Hz), 108.5, 76.6, 74.2, 50.9, 37.9 (q, *J*=25.8 Hz), 27.6, 25.2, 10.5; IR (thin film) ν_{max} 2993, 2955, 2105, 1462, 1385, 1258, 1184 cm^{-1}; MS (EI) *m*/*z* 238 (M^+-CH_3, 43); HRMS (EI) calcd for $C_8H_{11}N_3O_2F_3$: 238.0823; found: 238.0813.

3.1.13. *tert*-Butyl ((4*R*,5*S*)-2,2-dimethyl-5-((*R*)-1,1,1-trifluoropropan-2-yl)-1,3-dioxolan-4-yl)methylcarbamate (8). A mixture of 10% palladium on charcoal (20 mg), di-*tert*-butyl dicarbonate (59 mg, 0.27 mmol), and **7** (47 mg, 0.18 mmol) in ethyl acetate (2 mL) was stirred under hydrogen for 4 h at room temperature. After removal of the solvent, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=5:1) to give **8** (61 mg, 100%) as a white solid. Compound **8**: clear oil, $[\alpha]_D^{20}$ +41.4 (*c* 0.915, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.82 (br, 1H), 4.13–4.11 (m, 2H), 3.47–3.41 (m, 1H), 2.96–2.88 (m, 1H), 2.45–2.33 (m, 1H), 1.39 (s, 3H), 1.37 (9H), 1.28 (s, 3H), 1.16 (s, *J*=8.4 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.06 (d, *J*=6.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.8, 127.0 (q, *J*=277.5 Hz), 108.1, 79.5, 76.5, 74.5, 40.7, 37.8 (q, *J*=25.5 Hz), 28.2, 27.6, 25.4, 10.3; IR (thin film) ν_{max} 3460, 3359, 2986, 1718, 1509, 1459, 1384, 1253, 1177 cm^{-1}; MS (ESI) *m*/*z* 350 (M^++Na); HRMS (ESI) calcd for $C_{14}H_{24}NO_4F_3Na$: 350.1550; found: 350.1561.

3.1.14. *tert*-Butyl (2*R*,3*S*,4*R*)-5,5,5-trifluoro-2,3-dihydroxy-4-methylpentylcarbamate (9). A mixture of **8** (46 mg, 0.14 mmol) and *p*-toluenesulfonic acid monohydrate (27 mg, 0.14 mmol) in methanol (2 mL) was stirred overnight. The reaction was quenched with water and extracted with ethyl acetate (3×5 mL). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=2:1) to give **9** (33 mg, 81%) as a white solid. Compound **9**: mp: 93 °C; $[\alpha]_D^{20}$ −28.8 (*c* 1.205, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.10 (br, 1H), 3.83 (br, 1H), 3.55–3.52 (br m, 2H), 3.38 (m, 2H), 3.04 (br, 1H), 2.73 (m, 1H), 1.45 (s, 9H), 1.16 (d, 3H, *J*=6.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −70.79 (d, *J*=9.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.5, 128.3 (q, *J*=277.5 Hz), 80.7, 71.1, 68.4, 43.5, 38.3 (q, *J*=26.2 Hz), 28.2, 5.7; IR (thin film) ν_{max} 3446, 3381, 2996, 1652, 1537, 1444, 1396, 1258 cm^{-1}; MS (ESI) *m*/*z* 310 (M^++Na); HRMS (ESI) calcd for $C_{11}H_{20}NO_4F_3Na$: 310.1237; found: 310.1249.

Acknowledgements

We thank the National Natural Science Foundation of China (No. 20325210, 20472105), Ministry of Education of China and Shanghai Municipal Scientific Committee for funding this work.

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