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# Asymmetric synthesis of trifluoromethyl substituted dihydropyrans via organocatalytic cascade Michael–hemiketalization reaction

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ABSTRACT

Asymmetric conjugate addition of ethyl 4,4,4-trifluoroacetoacetate and other trifluoromethyl substituted nucleophiles to β,γ-unsaturated α-keto esters has been developed. The reaction efficiently provided dihydropyrans via cascade Michael–hemiketalization pathways. Quinine-derived thiourea was identified to be the best catalyst. A number of trifluoromethyl substituted dihydropyrans with three consecutive chiral centers were obtained in excellent yields, diastereoselectivities, and enantioselectivities. The product was readily transformed to the corresponding tetrahydropyridine without the loss of the optical purity.



## 1. Introduction

Heterocycles with trifluoromethyl group have played a unique and important role in medicinal and agricultural chemistry.[1] Trifluoromethyl substitution usually exerts profound effects on chemical and physical properties of the mother compound.[2] Continuous efforts have been made to develop efficient synthetic methods of these compounds, especially in an enantioselective manner.[3] β,γ-Unsaturated α-keto esters are active Michael acceptors. Chiral metal-based catalysts have been used successfully for their asymmetric conjugate additions with a number of nucleophiles.[4] In recent years asymmetric organocatalysis has emerged as a powerful tool for organic synthesis.[5] Organocatalytic conjugate addition of nucleophiles, such as nitroalkanes, indoles, 2-naphthols, malonates, malononitrile, 1,3-diketones, β-oxo aldehydes to β,γ-unsaturated α-keto esters had been developed.[6] While cyclic 1,3-diketones,[6c,l,n] β-oxo aldehydes,[6f] and α-cyano ketones[6i] were used, cascade Michael–hemiketalization reactions occurred to give dihydropyrans. To the best of our knowledge, the conjugate addition of acetoacetates to β,γ-unsaturated α-keto esters is not successful due to the lower reactivity of acetoacetates. We speculate that the reactivity of acetoacetates can be improved by introducing strong electron-withdrawing trifluoromethyl group. In this paper, we report organocatalytic conjugate addition of ethyl 4,4,4-trifluoroacetoacetate and other trifluoromethyl substituted nucleophiles to β,γ-unsaturated α-keto esters. The reaction provided trifluoromethyl substituted dihydropyrans with three consecutive chiral centers in excellent yields, diastereoselectivities, and enantioselectivities.

## 2. Results and discussion

The reaction of (*E*)-methyl 2-oxo-4-phenylbut-3-enoate **1a** and ethyl 4,4,4-trifluoroacetoacetate **2a** was studied initially. A series of thiourea-tertiary amine catalysts **4a**–**d** were examined and the results are summarized in Table 1. The cyclized product **3a** was obtained in all cases, which is obviously generated via cascade conjugate addition and intramolecular hemiketalization. Takemoto's catalyst **4a** gave **3a** in good yield and enantioselectivity (Table 1, entry 1).[7] Increasing steric hindrance of Takemoto's catalyst led to catalyst **4b**, however it provided **3a** with the same enantioselectivity (Table 1, entry 2). Slight improvement in the enantioselectivity was achieved by using catalyst **4c** derived from (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine (Table 1, entry 3). Quinine-derived thiourea **4d** gave better enantioselectivity and yield (Table 1, entry 4).[8] As expected, cinchonine-derived thiourea catalyst **4e** provided enantiomeric **3a** in excellent enantioselectivity and yield (Table 1, entry 5). Besides in dichloromethane, the reaction proceeded also very well in toluene, THF, and ether (Table 1, entries 6–8). Protonic solvents, such as methanol, led to the significant loss of enantioselectivity and yield (Table 1, entry 9). Decreasing the loading of catalyst **4d** to 5 mol % resulted in small erosion of enantioselectivity (Table 1, entry 10). The reaction at lower reaction temperature did not provide favorable improvement in enantioselectivity and yield (Table 1, entry 11).

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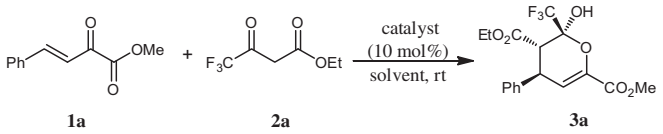
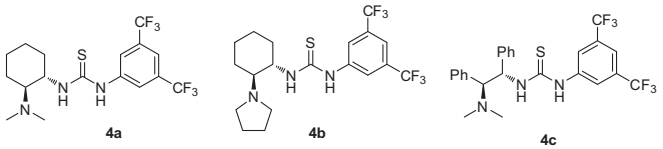
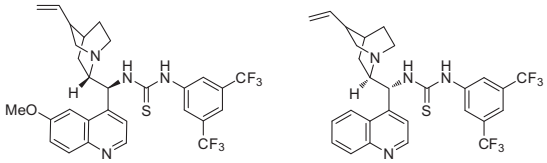
**Table 1**
Catalyst screening and optimization of reaction conditions[a]




1a 2a 3a



4a 4b 4c



4d 4e

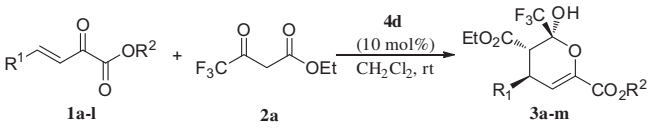
| Entry | Catalyst | Solvent | Time/h | Yield[b]/% | dr[c] | ee[d]/% |
|---|---|---|---|---|---|---|
| 1 | **4a** | $CH_2Cl_2$ | 15 | 92 | >30:1 | 92 |
| 2 | **4b** | $CH_2Cl_2$ | 15 | 89 | >30:1 | 92 |
| 3 | **4c** | $CH_2Cl_2$ | 15 | 89 | >30:1 | 94 |
| 4 | **4d** | $CH_2Cl_2$ | 15 | 93 | >30:1 | 96 |
| 5 | **4e** | $CH_2Cl_2$ | 15 | 91 | >30:1 | 95 |
| 6 | **4d** | Toluene | 15 | 81 | >30:1 | 95 |
| 7 | **4d** | THF | 15 | 86 | >30:1 | 96 |
| 8 | **4d** | Ether | 15 | 91 | >30:1 | 96 |
| 9 | **4d** | MeOH | 15 | 41 | >30:1 | 55 |
| 10[e] | **4d** | $CH_2Cl_2$ | 18 | 91 | >30:1 | 93 |
| 11[f] | **4d** | $CH_2Cl_2$ | 36 | 81 | >30:1 | 96 |

[a] Reactions were carried out with **1a** (0.12 mmol), **2a** (0.1 mmol), and catalyst (0.01 mmol) in solvent (0.5 mL) at room temperature.
[b] Isolated yields.
[c] dr was determined by $^{19}F$ NMR analysis.
[d] Determined by HPLC with a Chiralpak IC column.
[e] Compound **4d** (5 mol %) was used.
[f] The reaction was conducted at 0 °C.

With the optimized reaction conditions in hand, we investigated the reaction of a series of β,γ-unsaturated α-keto esters and ethyl 4,4,4-trifluoroacetoacetate **2a**. The results are summarized in Table 2. β,γ-Unsaturated α-keto esters with γ-phenyl or substituted γ-phenyl provided the products in good yields and excellent enantioselectivities. The electronic property of substituents seems to exert small effect on the yields and enantioselectivities (Table 2, entries 1–8). γ-(Thiophen-2-yl)-β,γ-unsaturated α-keto ester gave the product in moderate yield and good enantioselectivity (Table 2, entry 9). Bulk ester groups could be applied and did not exert significant effect on the yield and enantioselectivity (Table 2, entries 10–12). γ-Alkyl substituted β,γ-unsaturated α-keto ester is also a suitable substrate. Excellent yield and good enantioselectivity were achieved (Table 2, entry 13).

A single crystal of **3g** was obtained, however X-ray diffraction analysis indicated it is a mixed crystal of two enantiomers.[9,10] The absolute configuration of **3g** could not be assigned from this analysis, but the relative configuration could be obtained unambiguously (Fig. 1). Other products were proposed to have the same relative configurations. To determine the absolute configuration of the products, compound **3a** was treated with (*R*) and (*S*)-Mosher reagents, respectively. The corresponding Mosher esters were obtained and subjected to $^1H$ NMR analysis. The chemical shifts of 4H and 5H in the ester derived from (*R*)-Mosher reagent moved toward upfield ($\Delta\delta$=−0.42 and −0.27 ppm). On the other hand, the chemical shifts of 4H and 5H in the ester derived from (*S*)-Mosher

**Table 2**
Asymmetric conjugate addition of **2a** to β,γ-unsaturated α-keto esters[a]




1a-l 2a 3a-m

| Entry | $R^1$, $R^2$ | Time/h | yield[b]/% | dr[c] | ee[d]/% |
|---|---|---|---|---|---|
| 1 | Ph, Me | 15 | **3a**, 93 | >30:1 | 96 |
| 2 | 4-Me–Ph, Me | 16 | **3b**, 84 | >30:1 | 94 |
| 3 | 4-OMe–Ph, Me | 17 | **3c**, 82 | >30:1 | 93 |
| 4 | 4-F–Ph, Me | 16 | **3d**, 82 | >30:1 | 97 |
| 5 | 4-Cl–Ph, Me | 15 | **3e**, 85 | >30:1 | 95 |
| 6 | 4-Br–Ph, Me | 14 | **3f**, 91 | 23:1 | 93 |
| 7[e] | 4-Br–Ph, Me | 14 | **3g**, 93 | 28:1 | 92 |
| 8 | 3-Cl–Ph, Me | 15 | **3h**, 90 | >30:1 | 94 |
| 9 | Thiophen-2-yl, Me | 20 | **3i**, 76 | >30:1 | 90 |
| 10 | Ph, Et | 15 | **3j**, 90 | >30:1 | 96 |
| 11 | Ph, $^i$Pr | 18 | **3k**, 85 | 27:1 | 94 |
| 12 | Ph, allyl | 16 | **3l**, 88 | >30:1 | 95 |
| 13 | $^i$Pr, Et | 18 | **3m**, 95 | 18:1 | 87 |

[a] Reactions were carried out with **1a**–**l** (0.12 mmol), **2a** (0.1 mmol), and **4d** (0.01 mmol) in $CH_2Cl_2$ (0.5 mL) at room temperature.
[b] Isolated yields.
[c] dr was determined by $^{19}F$ NMR analysis.
[d] Determined by chiral HPLC.
[e] Methyl 4,4,4-trifluoroacetoacetate **2b** was used instead of **2a** in this reaction.

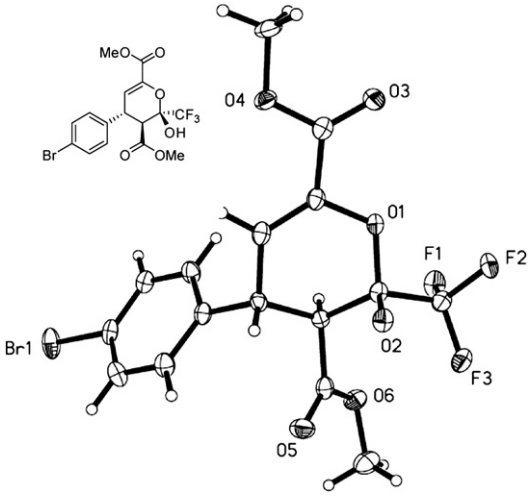


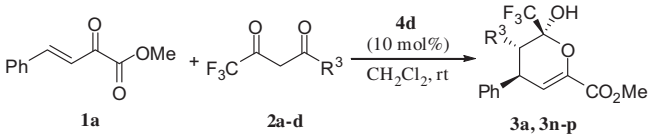

**Fig. 1.** X-ray crystal structure of **3g**.

reagent did not show significant changes, but the chemical shift of 3H moved toward downfield slightly ($\Delta\delta$=+0.10 ppm). Based on the conformational analysis of the Mosher esters, the absolute configuration of **3a** was assigned as (2*S*,3*S*,4*R*) tentatively. The same absolute configurations were suggested for products **3b**–**m**.

Several structurally-related trifluoromethyl substituted nucleophiles were also examined and the results are summarized in Table 3. Methyl 4,4,4-trifluoroacetoacetate **2b** provided similar yield and enantioselectivity with **2a** (Table 3, entries 1 and 2). 1,1,1-Trifluoroacetone is also a suitable nucleophile. Good yield and enantioselectivity were obtained (Table 3, entry 3). 4,4,4-Trifluoro-1-phenylbutane-1,3-dione **2d** showed lower reactivity. Moderate yield and good enantioselectivity were achieved after extended reaction time (Table 3, entry 4).

The product **3n** was treated with ammonium acetate according to the procedure developed by Zhao and co-workers.[6i] Tetrahydropyridine **5** was obtained in acceptable yield and excellent enantioselectivity (Scheme 1). Its absolute configuration was hypothesized to be similar with **3n**.

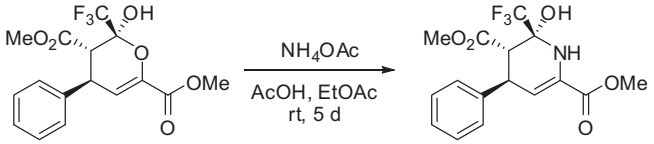
**Table 3**
Conjugate addition of trifluoromethyl substituted nucleophiles **2a–d** to **1a**[a]




1a 2a-d 3a, 3n-p

| Entry | $R^3$ | Time/h | Yield[b]/% | dr[c] | ee[d]/% |
|---|---|---|---|---|---|
| 1 | OEt, **2a** | 15 | **3a**, 93 | >30:1 | 96 |
| 2 | OMe, **2b** | 14 | **3n**, 96 | 22:1 | 97 |
| 3 | Me, **2c** | 24 | **3o**, 77 | >30:1 | 92 |
| 4[e] | Ph, **2d** | 45 | **3p**, 57 | >30:1 | 81 |

[a] Reactions were carried out with **1a** (0.12 mmol), **2a–d** (0.1 mmol), and **4d** (0.01 mmol) in $CH_2Cl_2$ (0.5 mL) at room temperature.
[b] Isolated yields.
[c] Determined by $^{19}F$ NMR analysis.
[d] Determined by chiral HPLC.
[e] Compound **1a** (0.2 mmol) was used in this case.




**3n** 97% ee **5** 62% yield, 95% ee

**Scheme 1.** Transformation of product **3n** to tetrahydropyridine **5**.

## 3. Conclusion

In conclusion, we have developed an efficient cascade Michael–hemiketalization reaction of trifluoromethyl substituted nucleophiles with β,γ-unsaturated α-keto esters. Quinine-derived thiourea was identified to be the best catalyst. A range of β,γ-unsaturated α-keto esters are compatible with this transformation. Trifluoromethyl substituted dihydropyrans with three consecutive chiral centers were prepared in excellent yields, diastereoselectivities, and enantioselectivities. The products could be transformed to the corresponding chiral tetrahydropyridines conveniently.

## 4. Experimental section

### 4.1. General information

$^1H$ NMR, $^{13}C$ NMR, and $^{19}F$ NMR spectra were recorded on Bruker AVANCE 400 spectrometer. Chemical shifts of protons are reported in parts per million (ppm, $\delta$) downfield from tetramethylsilane ($\delta$=0.00 ppm). Chemical shifts of carbons are referenced to the central line of the chloroform signal ($\delta$=77.00 ppm). Peaks are labeled as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Optical rotations were measured on a Perkin–Elmer 341 digital polarimeter. Melting points were measured on a WRS-2A melting point apparatus and are uncorrected. High-resolution mass spectra were obtained with Shimadzu LCMS-IT-TOF spectrometer. Infrared (IR) spectra were recorded on a Bruker Tensor 37 spectrophotometer. Data are represented as follows: frequency of absorption ($cm^{-1}$) and intensity of absorption (s=strong, m=medium, and w=weak). Enantiomeric excesses were determined by HPLC using Daicel Chiralpak IC or AD-H column and eluting with a hexane/$^i$PrOH solution. Flash chromatography was performed over silica gel (230–400 mesh), purchased from Qingdao Haiyang Chemical Co., Ltd.

### 4.2. Typical procedure for asymmetric conjugate addition of ethyl 4,4,4-trifluoroacetoacetate to β,γ-unsaturated α-keto esters

A solution of (*E*)-methyl 2-oxo-4-phenylbut-3-enoate **1a** (0.12 mmol), ethyl 4,4,4-trifluoroacetoacetate **2a** (0.1 mmol), and **4d** (0.01 mmol) in $CH_2Cl_2$ (0.5 mL) was stirred at room temperature for 14 h. After the solvent was evaporated under vacuum, the residue was purified by flash column chromatography over silica gel to afford **3a** as a colorless oil.

### 4.3. Spectral data of products 3a–p

*4.3.1. 3-Ethyl 6-methyl 2-hydroxy-4-phenyl-2-(trifluoromethyl)-3,4-dihydro-2H-pyran-3,6-dicarboxylate (**3a**).* Colorless oil, $[\alpha]_D^{20}$ +131.4 (*c* 1.02, $CH_2Cl_2$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.34–7.31 (m, 3H), 7.18–7.16 (m, 2H), 6.30 (d, *J*=2.4 Hz, 1H), 5.40 (s, 1H), 4.03 (dq, *J*=7.2, 1.6 Hz, 2H), 3.98 (dd, *J*=11.6, 2.4 Hz, 1H), 3.83 (s, 3H), 2.93 (d, *J*=11.6 Hz, 1H), 0.99 (t, *J*=7.2 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 172.4, 161.7, 140.0, 138.3, 129.0, 128.2, 127.9, 121.9 (q, $^1J_{CF3}$=285 Hz), 114.0, 94.1 (q, $^2J_{CF3}$=34 Hz), 62.3, 52.6, 47.3, 40.2, 13.6; $^{19}F$ NMR (376 MHz, $CDCl_3$): $\delta$ −83.92; IR (KBr): 3400 (m), 2959 (w), 1741 (s), 1662 (m), 1496 (m), 1442 (m), 1190 (s), 763 (m), 703 (m); HRMS (ESI) calcd for $C_{17}H_{16}F_3O_6$ $(M-H)^-$: 373.0899, found: 373.0907. The enantiomeric excess was determined by HPLC with a Chiralpak IC column (hexane/2-propanol=95:5, $\lambda$=220 nm, 0.8 mL/min); $t_R$ (major enantiomer)=10.78 min, $t_R$ (minor enantiomer)=18.01 min, 96% ee.

*4.3.2. 3-Ethyl 6-methyl 2-hydroxy-4-p-tolyl-2-(trifluoromethyl)-3,4-dihydro-2H-pyran-3,6-dicarboxylate (**3b**).* Light yellow oil, $[\alpha]_D^{20}$ 93.2 (*c* 0.50, $CH_2Cl_2$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.21 (d, *J*=8.0 Hz, 2H), 7.05 (d, *J*=8.0 Hz, 2H), 6.27 (d, *J*=2.4 Hz, 1H), 5.38 (s, 1H), 4.09–3.99 (m, 2H), 3.94 (dd, *J*=11.6, 2.4 Hz, 1H), 3.83 (s, 3H), 2.91 (d, *J*=12.0 Hz, 1H), 2.34 (s, 3H), 1.01 (t, *J*=7.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 172.6, 161.7, 140.0, 137.9, 135.2, 129.7, 127.7, 121.9 (q, $^1J_{CF3}$=285 Hz), 114.3, 94.1 (q, $^2J_{CF3}$=33 Hz), 62.3, 52.5, 47.3, 39.8, 21.0, 13.6; $^{19}F$ NMR (376 MHz, $CDCl_3$): $\delta$ −83.98; IR (KBr): 3402 (m), 2957 (w), 1173 (s), 1661 (m), 1515 (m), 1441 (m), 1188 (s), 815 (m), 700 (m); HRMS (ESI) calcd for $C_{18}H_{19}F_3NaO_6$ $(M+Na)^+$: 411.1031, found: 411.1012. The enantiomeric excess was determined by HPLC with a Chiralpak IC column (hexane/2-propanol=95:5, $\lambda$=220 nm, 0.8 mL/min); $t_R$ (major enantiomer)=10.98 min, $t_R$ (minor enantiomer)=21.24 min, 94% ee.

*4.3.3. 3-Ethyl 6-methyl 2-hydroxy-4-(4-methoxyphenyl)-2-(trifluoromethyl)-3,4-dihydro-2H-pyran-3,6-dicarboxylate (**3c**).* Yellow oil, $[\alpha]_D^{20}$ +90.9 (*c* 0.58, $CH_2Cl_2$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.09 (d, *J*=8.8 Hz, 2H), 6.86 (d, *J*=8.8 Hz, 2H), 6.26 (d, *J*=2.4 Hz, 1H), 5.42 (s, 1H), 4.09–4.00 (m, 2H), 3.94 (dd, *J*=8.0, 2.4 Hz, 1H), 3.82 (s, 1H), 3.80 (s, 3H), 2.90 (d, *J*=8.0 Hz, 1H), 1.03 (t, *J*=7.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 172.4, 161.8, 159.4, 139.9, 130.2, 129.0, 121.9 (q, $^1J_{CF3}$=285 Hz), 114.5, 114.4, 94.1 (q, $^2J_{CF3}$=34 Hz), 62.2, 55.3, 52.5, 47.5, 39.4, 13.6; $^{19}F$ NMR (376 MHz, $CDCl_3$): $\delta$ −84.00; IR (KBr): 3419 (m), 2958 (w), 1740 (s), 1660 (m), 1612 (m), 1514 (s), 1441 (m), 1185 (s), 829 (m); HRMS (ESI) calcd for $C_{18}H_{19}F_3NaO_7$ $(M+Na)^+$: 427.0981, found: 427.0966. The enantiomeric excess was determined by HPLC with a Chiralpak IC column (hexane/2-propanol=95:5, $\lambda$=220 nm, 0.8 mL/min); $t_R$ (major enantiomer)=17.56 min, $t_R$ (minor enantiomer)=28.47 min, 93% ee.

*4.3.4. 3-Ethyl 6-methyl 4-(4-fluorophenyl)-2-hydroxy-2-(trifluoromethyl)-3,4-dihydro-2H-pyran-3,6-dicarboxylate (**3d**).* Colorless oil, $[\alpha]_D^{20}$ +105.4 (*c* 0.48, $CH_2Cl_2$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.18–7.14 (m, 2H), 7.06–7.01 (m, 2H), 6.25 (d, *J*=2.0 Hz, 1H), 5.34 (s, 1H), 4.06–3.98 (m, 3H), 3.83 (s, 3H), 2.89 (d,

$J$=11.6 Hz, 1H), 1.03 (t, $J$=7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 172.1, 162.5 (d, $J$=246 Hz), 161.6, 140.1, 134.1 (d, $J$=3.0 Hz), 129.6 (d, $J$=8.0 Hz), 121.9 (q, $^1J_{CF3}$=285 Hz), 116.0 (d, $J$=21 Hz), 113.7, 94.1 (q, $^2J_{CF3}$=34 Hz), 62.3, 52.6, 47.4, 39.4, 13.6; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −83.96, −113.60; IR (KBr): 3377 (m), 2926 (w), 1741 (m), 1710 (m), 1652 (m), 1515 (m), 1452 (m), 1194 (s), 836 (m); HRMS (ESI) calcd for $C_{17}H_{16}F_4NaO_6$ $(M+Na)^+$: 415.0781, found: 415.0768. The enantiomeric excess was determined by HPLC with a Chiralpak IC column (hexane/2-propanol=95:5, $\lambda$=220 nm, 0.8 mL/min); $t_R$ (major enantiomer)=10.62 min, $t_R$ (minor enantiomer)=13.52 min, 97% ee.

*4.3.5. 3-Ethyl 6-methyl 4-(4-chlorophenyl)-2-hydroxy-2-(trifluoromethyl)-3,4-dihydro-2H-pyran-3,6-dicarboxylate (**3e**).* Colorless oil, $[\alpha]_D^{20}$ +113.1 ($c$ 0.42, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.32 (d, $J$=8.4 Hz, 2H), 7.12 (d, $J$=8.4 Hz, 2H), 6.23 (d, $J$=2.0 Hz, 1H), 5.37 (s, 1H), 4.10–4.02 (m, 2H), 3.99 (dd, $J$=12.0, 2.4 Hz, 1H), 2.89 (d, $J$=12.0 Hz, 1H), 1.04 (t, $J$=7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 171.9, 161.6, 140.2, 136.9, 134.1, 129.3, 129.2, 121.8 (q, $^1J_{CF3}$=285 Hz), 113.5, 94.1(q, $^2J_{CF3}$=34 Hz), 62.4, 52.6, 47.3, 39.5, 13.6; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −83.91; IR (KBr): 3393 (m), 2959 (w), 1740 (s), 1662 (m), 1492 (m), 1441 (m), 1191 (s), 822 (m), 709 (m); HRMS (ESI) calcd for $C_{17}H_{16}ClF_3NaO_6$ $(M+Na)^+$: 431.0485, found: 431.0480. The enantiomeric excess was determined by HPLC with a Chiralpak IC column (hexane/2-propanol=95:5, $\lambda$=220 nm, 0.8 mL/min); $t_R$ (major enantiomer)=11.04 min, $t_R$ (minor enantiomer)=12.99 min, 95% ee.

*4.3.6. 3-Ethyl 6-methyl 4-(4-bromophenyl)-2-hydroxy-2-(trifluoromethyl)-3,4-dihydro-2H-pyran-3,6-dicarboxylate (**3f**).* Colorless oil, $[\alpha]_D^{20}$ +96.7 ($c$ 0.72, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.47 (d, $J$=8.4 Hz, 2H), 7.07 (d, $J$=8.4 Hz, 2H), 6.22 (d, $J$=2.4 Hz, 1H), 5.35 (s, 1H), 4.10–4.01 (m, 2H), 3.98 (dd, $J$=12.0, 2.4 Hz, 1H), 3.83 (s, 3H), 2.89 (d, $J$=12.0 Hz, 1H), 1.04 (t, $J$=7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 171.8, 161.6, 140.2, 137.4, 132.2, 129.6, 122.1, 121.8 (q, $^1J_{CF3}$=285 Hz), 113.4, 94.1 (q, $^2J_{CF3}$=34 Hz), 62.4, 52.6, 47.2, 39.6, 13.6; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −83.87; IR (KBr): 3359 (m), 2982 (w), 1741 (s), 1715 (s), 1668 (m), 1486 (m), 1446 (m), 1196 (s), 824 (m), 706 (m); HRMS (ESI) calcd for $C_{17}H_{16}BrF_3NaO_6$ $(M+Na)^+$: 474.9980, found: 474.9978. The enantiomeric excess was determined by HPLC with a Chiralpak IC column (hexane/2-propanol=95:5, $\lambda$=220 nm, 0.8 mL/min); $t_R$ (major enantiomer)=11.90 min, $t_R$ (minor enantiomer)=13.03 min, 93% ee.

*4.3.7. Dimethyl 4-(4-bromophenyl)-2-hydroxy-2-(trifluoromethyl)-3,4-dihydro-2H-pyran-3,6-dicarboxylate (**3g**).* Colorless oil, $[\alpha]_D^{20}$ 81.3 ($c$ 0.52, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.47 (d, $J$=8.4 Hz, 2H), 7.06 (d, $J$=8.4 Hz, 2H), 6.22 (d, $J$=2.4 Hz, 1H), 5.36 (s, 1H), 4.02 (dd, $J$=12.0, 2.4 Hz, 1H), 3.82 (s, 3H), 3.58 (s, 3H), 2.92 (d, $J$=11.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 171.8, 161.7, 140.1, 137.4, 132.2, 129.5, 122.2, 121.7 (q, $^1J_{CF3}$=285 Hz), 94.1 (q, $^2J_{CF3}$=34 Hz), 52.9, 52.6, 47.4, 39.4; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −83.91; IR (KBr); HRMS (ESI) calcd for $C_{16}H_{14}BrF_3NaO_6$ $(M+Na)^+$: 460.9824, found: 460.9807. The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol=95:5, $\lambda$=220 nm, 0.7 mL/min); $t_R$ (minor enantiomer)=19.4 min, $t_R$ (major enantiomer)=20.9 min, 92% ee.

*4.3.8. 3-Ethyl 6-methyl 4-(3-chlorophenyl)-2-hydroxy-2-(trifluoromethyl)-3,4-dihydro-2H-pyran-3,6-dicarboxylate (**3h**).* Colorless oil, $[\alpha]_D^{20}$ +87.7 ($c$ 0.62, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.30–7.26 (m, 2H), 7.17 (m, 1H), 7.09–7.06 (m, 1H), 6.25 (d, $J$=2.0 Hz, 1H), 5.29 (s, 1H), 4.07 (qd, $J$=7.2, 0.4 Hz, 2H), 3.97 (dd, $J$=12.0, 2.4 Hz, 1H), 3.84 (s, 3H), 2.89 (d, $J$=11.6 Hz, 1H), 1.04 (t, $J$=7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 172.1, 161.5, 140.4, 140.3, 134.9, 130.3, 128.5, 128.1, 126.1, 121.8 (q, $^1J_{CF3}$=285 Hz), 113.0, 94.0 (q, $^2J_{CF3}$=34 Hz), 62.5, 52.6, 47.1, 39.9, 13.6; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −83.92; IR (KBr): 3402 (m), 2966 (w), 1740 (s), 1661 (m), 1587 (w), 1440 (m), 1197 (s), 780 (m), 697 (m); HRMS (ESI) calcd for $C_{17}H_{16}ClF_3NaO_6$ $(M+Na)^+$: 431.0485, found: 431.0478. The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol=98:2, $\lambda$=220 nm, 0.6 mL/min); $t_R$ (major enantiomer)=41.79 min, $t_R$ (minor enantiomer)=45.51 min, 94% ee.

*4.3.9. 3-Ethyl 6-methyl 2-hydroxy-4-(thiophen-2-yl)-2-(trifluoromethyl)-3,4-dihydro-2H-pyran-3,6-dicarboxylate (**3i**).* Light yellow oil, $[\alpha]_D^{20}$ +62.2 ( $c$ 0.54, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.27–7.25 (m, 1H), 6.96–6.92 (m, 2H), 6.31 (d, $J$=2.4 Hz, 1H), 5.28 (s, 1H), 4.36 (dd, $J$=11.6, 2.4 Hz, 1H), 4.12 (q, $J$=7.2 Hz, 2H), 2.99 (d, $J$=12.0 Hz, 1H), 1.10 (t, $J$=7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 172.0, 161.6, 140.6, 139.6, 127.0, 126.2, 126.1, 121.5 (q, $^1J_{CF3}$=285 Hz), 113.5, 94.1 (q, $^2J_{CF3}$=34 Hz), 62.5, 52.6, 47.8, 35.5, 13.6; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −83.90; IR (KBr): 3422 (m), 2989 (w), 1738 (s), 1658 (m), 1446 (m), 1196 (s), 703 (m); HRMS (ESI) calcd for $C_{15}H_{15}F_3NaO_6S$ $(M+Na)^+$: 403.0439, found: 403.0446. The enantiomeric excess was determined by HPLC with a Chiralpak IC column (hexane/2-propanol=95:5, $\lambda$=220 nm, 0.8 mL/min); $t_R$ (major enantiomer)=11.47 min, $t_R$ (minor enantiomer)=15.74 min, 90% ee.

*4.3.10. Diethyl 2-hydroxy-4-phenyl-2-(trifluoromethyl)-3,4-dihydro-2H-pyran-3,6-dicarboxylate (**3j**).* Colorless oil, $[\alpha]_D^{20}$ 86.7 ($c$ 0.58, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.36–7.31 (m, 3H), 7.19–7.17 (m, 2H), 6.27 (d, $J$=2.4 Hz, 1H), 5.39 (s, 1H), 4.32–4.25 (m, 2H), 4.02 (qd, $J$=7.2, 1.2 Hz, 2H), 3.98 (dd, $J$=12.0, 2.4 Hz, 1H), 2.94 (d, $J$=12.0 Hz, 1H), 1.32 (t, $J$=7.2 Hz, 3H), 0.98 (t, $J$=7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 172.4, 161.2, 140.2, 138.4, 129.0, 128.1, 127.9, 121.9 (q, $^1J_{CF3}$=285 Hz), 113.7, 94.1 (q, $^2J_{CF3}$=34 Hz), 62.2, 61.7, 47.3, 40.2, 14.0, 13.6; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −83.91; IR (KBr): 3432 (m), 2988 (w), 1737 (s), 1658 (m), 1459 (m), 1197 (s), 760 (m), 702 (m); HRMS (ESI) calcd for $C_{18}H_{19}F_3NaO_6$ $(M+Na)^+$: 411.1031, found: 411.1023. The enantiomeric excess was determined by HPLC with a Chiralpak IC column (hexane/2-propanol=95:5, $\lambda$=220 nm, 0.8 mL/min); $t_R$ (major enantiomer)=9.40 min, $t_R$ (minor enantiomer)=13.84 min, 96% ee.

*4.3.11. 3-Ethyl 6-isopropyl 2-hydroxy-4-phenyl-2-(trifluoromethyl)-3,4-dihydro-2H-pyran-3,6-dicarboxylate (**3k**).* Colorless oil, $[\alpha]_D^{20}$ 73.6 ($c$ 0.62, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.36–7.31 (m, 3H), 7.20–7.18 (m, 2H), 6.23 (d, $J$=2.0 Hz, 1H), 5.49 (s, 1H), 5.17–5.09 (m, 1H), 4.04–3.98 (m, 3H), 2.94 (d, $J$=12.0 Hz, 1H), 1.29 (t, $J$=6.0 Hz, 6H), 0.98 (t, $J$=7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 172.1, 160.7, 140.3, 138.5, 128.5, 128.1, 127.9, 121.9 (q, $^1J_{CF3}$=285 Hz), 113.4, 94.0 (q, $^2J_{CF3}$=33 Hz), 69.5, 62.1, 47.4, 40.1, 21.6, 21.5, 13.5; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −83.96; IR (KBr): 3438 (m), 2985 (w), 2930 (w), 1734 (m), 1665 (m), 1502 (w), 1458 (m), 1194 (m), 762 (m), 703 (m); HRMS (ESI) calcd for $C_{19}H_{21}F_3NaO_6$ $(M+Na)^+$: 425.1188, found: 425.1200. The enantiomeric excess was determined by HPLC with a Chiralpak IC column (hexane/2-propanol=95:5, $\lambda$=220 nm, 0.8 mL/min); $t_R$ (major enantiomer)=7.85 min, $t_R$ (minor enantiomer)=11.35 min, 94% ee.

*4.3.12. 6-Allyl 3-ethyl 2-hydroxy-4-phenyl-2-(trifluoromethyl)-3,4-dihydro-2H-pyran-3,6-dicarboxylate (**3l**).* Colorless oil, $[\alpha]_D^{20}$ +75.7 ($c$ 0.70, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.36–7.30 (m, 3H), 7.19–7.17 (m, 2H), 6.30 (d, $J$=2.4 Hz, 1H), 5.96–5.90 (m, 1H), 5.46 (s, 1H), 5.39–5.34 (m, 1H), 5.28–5.25 (m, 1H), 4.77–4.67 (m, 2H), 4.04 (qd, $J$=7.2, 1.6 Hz, 2H), 4.00 (dd, $J$=12.0, 2.4 Hz, 1H), 2.94 (d, $J$=12.0 Hz, 1H), 0.98 (t, $J$=7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 172.2, 160.9, 140.0, 138.3, 131.4, 129.0, 128.1, 127.9, 121.9 (q, $^1J_{CF3}$=285 Hz), 118.8, 114.2, 94.1 (q, $^2J_{CF3}$=34 Hz), 66.1, 62.2, 47.4,

40.2, 13.6; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −83.98; IR (KBr): 3411 (m), 2985 (w), 2937 (w), 1734 (s), 1660 (m), 1495 (m), 1455 (m), 1188 (s), 762 (m), 702 (m); HRMS (ESI) calcd for $C_{19}H_{19}F_3NaO_6$ $(M+Na)^+$: 423.1031, found: 423.1031. The enantiomeric excess was determined by HPLC with a Chiralpak IC column (hexane/2-propanol=95:5, $\lambda$=220 nm, 0.8 mL/min); $t_R$ (major enantiomer)=8.69 min, $t_R$ (minor enantiomer)=11.89 min, 95% ee.

*4.3.13. Diethyl 2-hydroxy-4-isopropyl-2-(trifluoromethyl)-3,4-dihydro-2H-pyran-3,6-dicarboxylate (**3m**).* Colorless oil, $[\alpha]_D^{20}$ +59.3 (*c* 0.56, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.16 (d, *J*=1.2 Hz, 1H), 5.23 (s, 1H), 4.33–4.21 (m, 4H), 2.83–2.76 (m, 2H), 1.81–1.75 (m, 1H), 1.34–1.30 (m, 6H), 1.09 (d, *J*=6.8 Hz, 3H), 0.86 (d, *J*=6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 173.2, 161.2, 140.8, 122.0 (q, $^1J_{CF3}$=285 Hz), 111.1, 93.9 (q, $^2J_{CF3}$=33 Hz), 62.4, 61.5, 42.7, 39.4, 28.3, 20.2, 16.8, 14.0, 13.8; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −83.98; IR (KBr): 3411 (m), 2967 (m), 2932 (m), 1738 (s), 1662 (m), 1468 (m), 1185 (s), 761 (m), 703 (m); HRMS (ESI) calcd for $C_{15}H_{21}F_3NaO_6$ $(M+Na)^+$: 377.1188, found: 377.1179. The enantiomeric excess was determined by HPLC with a Chiralpak IC column (hexane/2-propanol=95:5, $\lambda$=220 nm, 0.8 mL/min); $t_R$ (major enantiomer)=7.33 min, $t_R$ (minor enantiomer)=9.64 min, 87% ee.

*4.3.14. Dimethyl 2-hydroxy-4-phenyl-2-(trifluoromethyl)-3,4-dihydro-2H-pyran-3,6-dicarboxylate (**3n**).* Colorless oil, $[\alpha]_D^{20}$ +98.8 (*c* 0.68, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.36–7.30 (m, 3H), 7.18–7.16 (m, 2H), 6.29 (d, *J*=2.0 Hz, 1H), 6.29 (s, 1H), 4.04 (dd, *J*=12.0, 2.4 Hz, 1H), 3.81 (s, 3H), 3.54 (s, 3H), 2.97 (d, *J*=12.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 172.0, 161.8, 139.8, 138.3, 129.0, 128.1, 127.8, 121.8 (q, $^1J_{CF3}$=285 Hz), 114.4, 94.1 (q, $^2J_{CF3}$=33 Hz), 52.7, 52.4, 47.6, 39.8; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −84.13; IR (KBr): 3369 (m), 2961 (w), 1744 (m), 1713 (m), 1651 (m), 1506 (m), 1196 (m), 760 (m), 707 (m); HRMS (ESI) calcd for $C_{16}H_{15}F_3NaO_6$ $(M+Na)^+$: 383.0718, found: 383.0717. The enantiomeric excess was determined by HPLC with a Chiralpak IC column (hexane/2-propanol=95:5, $\lambda$=220 nm, 0.8 mL/min); $t_R$ (major enantiomer)=10.30 min, $t_R$ (minor enantiomer)=15.10 min, 97% ee.

*4.3.15. Methyl 3-acetyl-2-hydroxy-4-phenyl-2-(trifluoromethyl)-3,4-dihydro-2H-pyran-6-carboxylate (**3o**).* Light yellow oil, $[\alpha]_D^{20}$ 103.3 (*c* 0.18, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.39–7.33 (m, 3H), 7.17–7.15 (m, 2H), 6.26 (d, *J*=2.4 Hz, 1H), 5.63 (s, 1H), 3.87 (dd, *J*=11.6, 2.4 Hz, 1H), 3.83 (s, 3H), 3.21 (d, *J*=11.6 Hz, 1H), 1.81 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 211.4, 161.7, 140.1, 138.3, 129.4, 128.4, 127.8, 122.1 (q, $^1J_{CF3}$=285 Hz), 114.0, 94.4 (q, $^2J_{CF3}$=33 Hz), 52.5, 51.8, 41.3, 32.9; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −83.26; IR (KBr): 3434 (m), 2956 (w), 1736 (s), 1659 (m), 1535 (m), 1497 (m), 1191 (s), 763 (m), 709 (m); HRMS (ESI) calcd for $C_{16}H_{15}F_3NaO_5$ $(M+Na)^+$: 367.0796, found: 367.0764. The enantiomeric excess was determined by HPLC with a Chiralpak IC column (hexane/2-propanol=95:5, $\lambda$=220 nm, 0.8 mL/min); $t_R$ (major enantiomer)=10.91 min, $t_R$ (minor enantiomer)=15.84 min, 92% ee.

*4.3.16. Methyl 3-benzoyl-2-hydroxy-4-phenyl-2-(trifluoromethyl)-3,4-dihydro-2H-pyran-6-carboxylate (**3p**).* Colorless oil, $[\alpha]_D^{20}$ 101.8 (*c* 0.34, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.48–7.43 (m, 3H), 7.27–7.23 (m, 2H), 7.17–7.08 (m, 5H), 6.38 (d, *J*=2.0 Hz, 1H), 6.14 (s, 1H), 4.11–4.03 (m, 2H), 3.84 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 203.3, 161.7, 140.4, 138.1, 136.0, 134.5, 129.0, 128.5, 128.2, 128.0, 127.8, 122.1 (q, $^1J_{CF3}$=285 Hz), 114.2, 95.0 (q, $^2J_{CF3}$=33 Hz), 52.5, 46.2, 42.4; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −83.04; IR (KBr): 3324 (m), 2955 (w), 1715 (m), 1685 (m), 1497 (w), 1450 (m), 1200 (m), 765 (m), 699 (m); HRMS (ESI) calcd for $C_{21}H_{17}F_3NaO_5$ $(M+Na)^+$: 429.0926, found: 429.0914. The enantiomeric excess was determined by HPLC with a Chiralpak IC column (hexane/2-propanol=95:5, $\lambda$=254 nm, 0.8 mL/min); $t_R$ (major enantiomer)=14.95 min, $t_R$ (minor enantiomer)=47.41 min, 81% ee.

### 4.4. Preparation of dimethyl 6-hydroxy-4-phenyl-6-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-2,5-dicarboxylate (5)

Compound **3n** (36.0 mg, 0.1 mmol) was dissolved in ethyl acetate/acetic acid (v/v=1:1, 2.5 mL) and stirred at room temperature for 15 min. After ammonium acetate (92.4 mg, 1.2 mmol) was added in portions, the reaction solution was stirred at room temperature for 5 days. Water (2.0 mL) was added and the aqueous layer was extracted with ethyl acetate (3.0 mL×2). The combined organic layer was washed with brine (2.0 mL) and dried over anhydrous $Na_2SO_4$. After the evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography over silica gel to afford **5** as a light yellow oil, $[\alpha]_D^{20}$ 35.0 (*c* 0.08, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.33–7.29 (m, 3H), 7.19–7.17 (m, 2H), 5.86 (d, *J*=2.0 Hz, 1H), 5.14 (s, 1H), 4.98 (s, 1H), 3.99 (dd, *J*=12.0, 2.4 Hz, 1H), 3.82 (s, 3H), 3.48 (s, 3H), 2.98 (d, *J*=12.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 174.6, 163.4, 139.8, 129.9, 128.9, 127.9, 123.5 (q, $^1J_{CF3}$=285 Hz), 110.0, 80.5 (q, $^2J_{CF3}$=31 Hz), 52.6, 52.5, 48.3, 41.8; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −83.36; IR (KBr): 3396 (m), 2957 (w), 1731 (s), 1663 (m), 1492 (m), 1438 (s), 762 (m), 703 (m); HRMS (ESI) calcd for $C_{16}H_{15}F_3NO_5$ $(M-H)^-$: 358.0902, found: 358.0899. The enantiomeric excess was determined by HPLC with a Chiralpak IC column (hexane/2-propanol=95:5, $\lambda$=254 nm, 0.8 mL/min); $t_R$ (major enantiomer)=7.61 min, $t_R$ (minor enantiomer)=9.59 min, 95% ee.

### 4.5. Preparation of the single crystal of product 3g

To a solution of enantiorich product **3g** (0.27g, 92% ee) in ethyl acetate (5 mL), was added petroleum ether (15 mL). The resulted solution was placed in a small bottle. The mouth of the bottle was covered with a layer of Parafilm™. The film was punctured with several small holes to allow the slow evaporation of the solvent. The solution was kept for a couple of days. Several small crystals were formed and one of them was taken for the X-ray diffraction analysis. The enantiomeric excess of the crystal was 25% as determined by chiral HPLC.

### 4.6. Preparation of the Mosher esters of product 3a

To a solution of **3a** (10 mg, 27 μmol) and 4-dimethylaminopyridine (0.33 mg, 2.6 μmol) in $CH_2Cl_2$ (0.8 mL) were added $Et_3N$ (15 μL, 0.11 mmol) and (*S*)-MTPA-Cl (11.2 μL, 60 μmol) at room temperature. The mixture was stirred for 12 h and diluted with $Et_2O$ (2.0 mL). The organic layer was washed with saturated aqueous $NH_4Cl$ and brine and then dried over anhydrous $Na_2SO_4$. After the solvent was evaporated, the crude product was purified by column chromatography over silica gel (petroleum ether/EtOAc=20:1) to give the corresponding Mosher ester as an oil (8 mg, 51% yield). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.58–7.57 (m, 2H), 7.45–7.44 (m, 3H), 7.31–7.30 (m, 3H), 7.12–7.10 (m, 2H), 6.34 (d, *J*=2.0 Hz, 1H), 4.00–3.89 (m, 2H), 3.87 (s, 3H), 3.84 (dd, *J*=12.0, 2.4 Hz, 1H), 3.53 (d, *J*=0.8 Hz, 3H), 3.02 (d, *J*=12.0 Hz, 1H), 0.97 (t, *J*=7.2 Hz, 3H); $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −70.87, −78.77.

The Mosher ester derived from (*R*)-MTPA-Cl was obtained analogously (10 mg, 62% yield). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.61–7.59 (m, 2H), 7.40–7.38 (m, 3H), 7.28–7.26 (m, 3H), 7.01–7.99 (m, 2H), 6.02 (d, *J*=2.0 Hz, 1H), 3.98–3.89 (m, 2H), 3.87 (s, 3H), 3.69 (d, *J*=1.2 Hz, 3H), 3.47 (dd, *J*=12.0, 2.4 Hz, 1H), 2.94 (d,

$J$=12.0 Hz, 1H), 0.98 (t, $J$=7.2 Hz, 3H); $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −71.53, −77.07.

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