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Lewis Acid Catalyzed Friedel–Crafts Alkylation of Alkenes with Trifluoropyruvates

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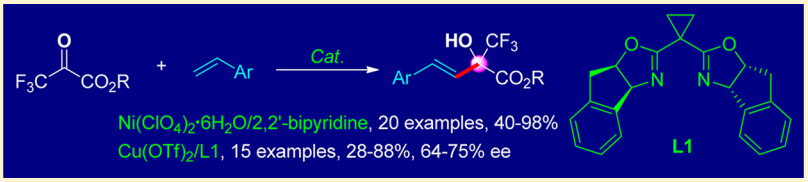
Supporting Information

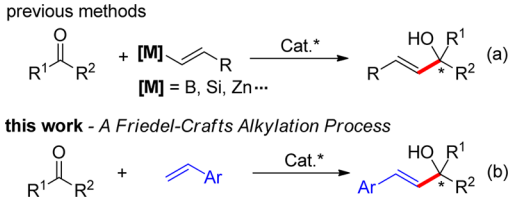


ABSTRACT: A Friedel–Crafts alkylation reaction of styrenes with trifluoropyruvates has been developed, which delivered allylic alcohols in excellent yields (up to 98%) using the $Ni(ClO_4)_2·6H_2O$/bipyridine complex as a catalyst. The asymmetric reaction was catalyzed by the chiral $Cu(OTf)_2$/bisoxazoline complex to afford the corresponding chiral allylic alcohols bearing trifluoromethylated quaternary stereogenic centers in moderate enantioselectivities (up to 75% ee).

In the past decades, asymmetric Friedel–Crafts alkylation reaction of aromatic systems has been extensively developed as an efficient approach to construct chiral benzylic stereocenters.[1] In contrast, Friedel–Crafts alkylation of alkenes that furnishes allylic stereogenic centers has remained largely unexplored. In this context, only a few electron-rich olefins, e.g., silyl enol ethers,[2] enamides,[3] allylidenehydrazine,[4] 4-vinylanlines,[5] and 2-vinylphenols,[6] were documented as nucleophilic substrates in the enantioselective additions to C=O, C=N, or C=C bonds. Simple olefins were rarely involved in this reaction probably due to their lower nucleophilicity, although a few recent examples have disclosed the additions of simple olefins to the C=C bonds of α,β-unsaturated ketones in their racemic versions.[7] Therefore, the development of efficient Friedel–Crafts alkylation of simple olefins, in particular in the asymmetric version, to build allylic stereogenic centers is highly desirable.

Enantioselective alkenylation of carbonyl compounds allows an efficient access to chiral allylic alcohols, which are important building blocks in organic synthesis. Among them, the transition-metal-catalyzed or chiral ligand-promoted enantioselective addition of vinyl organometallic reagents to C=O bonds has being a reliable approach for this purpose (Scheme 1a).[8] In comparison, the direct alkenylation reaction between simple olefins and carbonyl compounds via a Friedel–Crafts alkylation process is more attractive in terms of atom economy and efficiency; however, to the best of our knowledge, it actually remained unexplored.[9] As a continuous interest in the asymmetric Friedel–Crafts reactions,[10] our group has recently developed a $Ni(ClO_4)_2·6H_2O$/(*S*)-BINAP-catalyzed enantioselective addition of styrenes to cyclic *N*-sulfonyl α-iminoesters to access chiral allylic amine derivatives.[11] This encouraged us to explore the Friedel–Crafts alkylation of simple alkenes with ketones (Scheme 1b). We hence report the primary result of a $Ni(ClO_4)_2·6H_2O$/bipyridine-catalyzed Friedel–Crafts reaction between styrenes and trifluoropyruvates in its racemic version and the corresponding asymmetric reaction using chiral $Cu(OTf)_2$/bisoxazoline complex as a catalyst, which delivered allylic alcohols bearing trifluoromethylated quaternary stereogenic centers in excellent yields and moderate enantioselectivities.

Scheme 1. Approaches for Alkenylation of C=O Bonds



At the outset, methyl 3,3,3-trifluoropyruvate (**1a**) and styrene (**2a**) were selected as model substrates to identify the optimal conditions (Table 1). In the presence of a catalytic amount of $Cu(OTf)_2$ (10 mol %) with 2,2′-bipyridine (12 mol %) as a ligand, the desired allylic alcohol **3aa** was obtained in 60% yield in DCM at 100 °C (temperature of oil bath) for 40 h (entry 1). Without the addition of 2,2′-bipyridine ligand, only a trace amount of the product was isolated (entry 2). Other Lewis acids were then tested, and $Ni(ClO_4)_2·6H_2O$ was identified as the best catalyst to deliver **3aa** in 92% yield (entry 6). Subsequent solvent examination indicated that the reaction worked favorably in chlorinated solvents, such as dichloromethane, chloroform, and dichloroethane (entries 6–8), while it was completely suppressed in MeOH (entry 10). An inferior result was obtained for the reactions with 1,10-phenanthroline as a ligand (entry 11). Furthermore, lowering the temperature

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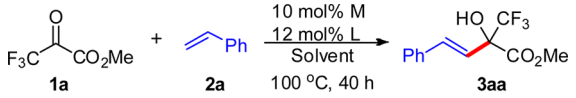
Table 1. Conditions Optimization of Racemic Reaction[a]



entry	M	L	solvent	Y (%)
1	$Cu(OTf)_2$	2,2′-bpy	DCM	60
2	$Cu(OTf)_2$		DCM	7
3	$Zn(OTf)_2$	2,2′-bpy	DCM	31
4	$Cu(ClO_4)_2·6H_2O$	2,2′-bpy	DCM	54
5	$Zn(ClO_4)_2·6H_2O$	2,2′-bpy	DCM	66
6	$Ni(ClO_4)_2·6H_2O$	2,2′-bpy	DCM	92
7	$Ni(ClO_4)_2·6H_2O$	2,2′-bpy	$CHCl_3$	81
8	$Ni(ClO_4)_2·6H_2O$	2,2′-bpy	DCE	85
9	$Ni(ClO_4)_2·6H_2O$	2,2′-bpy	toluene	45
10	$Ni(ClO_4)_2·6H_2O$	2,2′-bpy	MeOH	NR
11	$Ni(ClO_4)_2·6H_2O$	1,10-phen	DCM	68
12[b]	$Ni(ClO_4)_2·6H_2O$	2,2′-bpy	DCM	79
13[c]	$Ni(ClO_4)_2·6H_2O$	2,2′-bpy	DCM	84

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), Lewis acid (10 mol %), and ligand (12 mol %) in solvent (2.0 mL) in an oil bath at 100 °C for 40 h; 2,2′-bpy = 2,2′-bipyridine, 1,10-phen = 1,10-phenanthroline. [b]In an oil bath at 70 °C. [c]Preformed complex of $Ni(ClO_4)_2$/2,2′-bpy (10 mol %) was used.

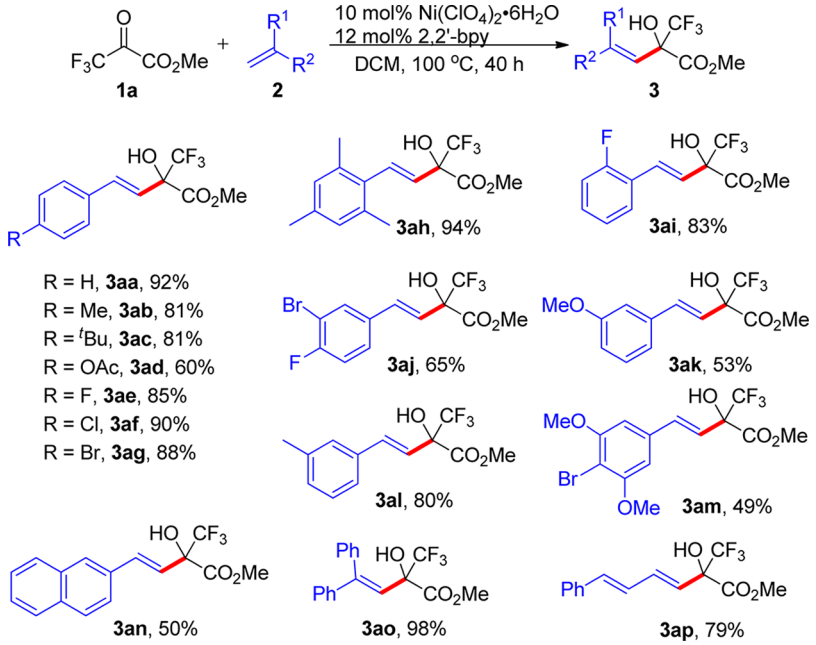
led to a decreased yield (entry 12). As a comparison, a slightly lower yield of product **3aa** was obtained when a preformed complex of $Ni(ClO_4)_2$/2,2′-bipyridine was used as the catalyst (entries 6 vs 13). Noteworthy is that the present reaction could be classified as a Prins reaction, while no other side products through the Prins reaction pathway were isolated.

With the optimal conditions in hand, the scope of alkene was then investigated. As shown in Scheme 2, a wide variety of styrenes bearing either electron-withdrawing or electron-donating substituents on the phenyl ring reacted smoothly with **1a** to produce the corresponding allylic alcohols in moderate to excellent yields. Generally, functionalities in the *para*-position on the benzene ring were well-tolerated, while relatively lower yields of products **3ab**−**3ad** were observed as the corresponding styrenes bearing electron-donating substituents were unstable in the reaction system.[12] Addition of these styrenes to the reaction system in two batches led to improved yields, which are also observed in the cases of **3ah**, **3ak**, and **3al**. In addition, products **3am** and **3an** were obtained in moderate yields. Electron-withdrawing groups were also well-tolerated and led to the products (**3ae**−**3ag** and **3ai**−**3aj**) in satisfactory yields regardless of the steric effect. To our delight, 1,1′-diphenylethene and (*E*)-buta-1,3-dien-1-ylbenzene were also successfully employed in the reactions to afford the corresponding products **3ao** and **3ap** in 98% and 79% yields, respectively. It is noteworthy that no reaction occurred for the reaction of 1,2-diphenylethene and aliphatic terminal alkene (e.g., 1-hexene) failed to deliver any desired product, which implies the limitation of the scope of alkenes.

To further evaluate the scope of this reaction, other ketoesters were examined, and the results are shown in Scheme 3. Different trifluoropyruvates reacted well with styrene **2a** to deliver the corresponding allylic alcohols in moderate yields (74, 60, and 78% for ethyl ester **3ba**, isopropyl ester **3ca**, and *n*-butyl ester **3da**, respectively). In addition, 2-oxomalonate was also applied in the reaction and led to product **3ea** in 40% yield. However, other ketones, such as 2,2,2-trifluoro-1-phenylethanone, acetophenone, and isatine, remained inert in this reaction.

Encouraged by the above success, we then moved our attention to the asymmetric reaction. After systematic investigations of Lewis acids, chiral ligands, and the solvents (see Table S1 in the Supporting Information), the complex of

Scheme 2. Scope of Alkene in the Racemic Reaction[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $Ni(ClO_4)_2·6H_2O$ (0.02 mmol), and 2,2′-bipyridine (0.024 mmol) in DCM (2.0 mL) at 100 °C (temperature of oil bath) for 40 h. Styrenes bearing electron-donating groups (**3ab**−**3ad**, **3ah**, **3ak**, and **3al**) were added to the reaction system in two batches (the second batch of styrenes (0.2 mmol) was added after 24 h).

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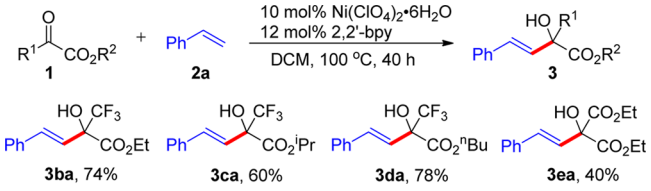
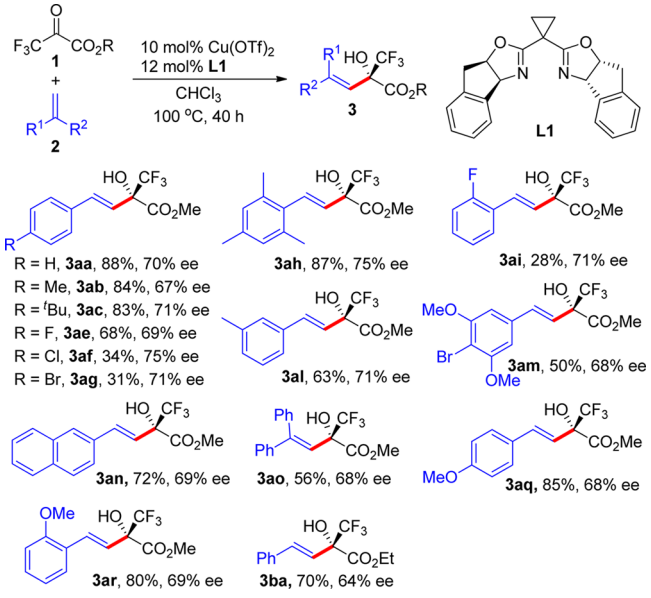
Scheme 3. Scope of Ketoester in the Racemic Reaction[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Ni(ClO_4)_2·6H_2O$ (0.02 mmol), and 2,2′-bipyridine (0.024 mmol) in DCM (2.0 mL) at 100 °C (temperature of oil bath) for 40 h.

$Cu(OTf)_2$ with a chiral bisoxazoline ligand **L1** was defined as an optimal catalyst for the asymmetric alkenylation of trifluoropyruvates, although only a moderate ee value was obtained. A series of styrenes were then examined to disclose the scope of the asymmetric reactions (Scheme 4). All of the

Scheme 4. Scope of the Asymmetric Reaction[a]

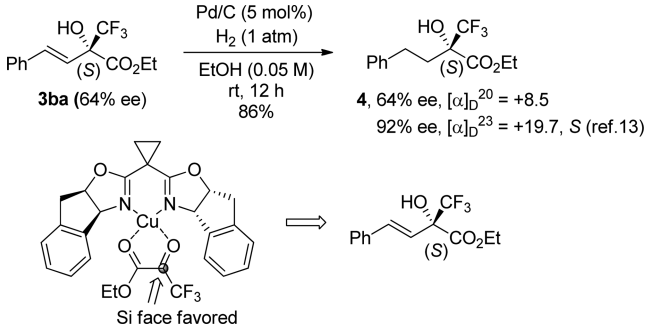


[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Cu(OTf)_2$ (0.02 mmol), and **L1** (0.024 mmol) in $CHCl_3$ (2.0 mL) at 100 °C (temperature of oil bath) for 40 h; ee was determined by chiral HPLC.

reactions afforded the corresponding products in moderate enantioselectivities (64−75% ee). However, the yields were unfavorably influenced by the electron-withdrawing substituents, which resulted in poor to moderate yields for products **3ae**−**3ag** and **3ai**. In contract, styrenes bearing electron-donating groups delivered the products (**3aa**−**3ac**, **3ah**, **3al**, **3aq**, and **3ar**) in relatively higher yield and with the same level of enantioselectivity (around 70% ee). Furthermore, product **3ao** resulting from the reaction of 1,1′-diphenylethene with **1a** was also isolated in 56% yield and 68% ee.

In order to determine the absolute configuration of the product, **3ba** was reduced to compound **4** by the hydrogenation reaction in EtOH for 12 h using Pd/C catalyst (Scheme 5). By comparing the optical rotation with the reported value for compound **4**,[13] the absolute configuration of product **3ba** is conversely determined to be S. A tentative model for asymmetric induction is then proposed, where trifluoropyruvate is activated by the catalyst via a 1,4-chelation of two carbonyl oxygen atoms to Cu(II) and hence facilitates the nucleophilic

Scheme 5. Determination of the Absolute Configuration and Proposed Asymmetric Induction Model



attack of styrene in a favored Si face to result in the S configuration of product **3ba**. As shown in Scheme 6, synthetic transformations of the products were then conducted. Product **3aa** was readily converted to the corresponding amide **5** in 72% yield and 70% ee via a three-step procedure including protection of the hydroxyl group, hydrolysis of the ester, and the condensation of acid chloride with aniline. In addition, a Suzuki-coupling reaction of product **3ag** with $PhB(OH)_2$ was realized in the presence of $Pd(PPh_3)_4$ catalyst, which gave compound **6** bearing a free hydroxyl group in 71% yield and 70% ee.

In summary, a catalytic Friedel−Crafts alkylation of styrenes with trifluoropyruvates has been developed as a straightforward access to allylic alcohols. Moderate to excellent yields of the products were obtained in the racemic reactions catalyzed by the complex of $Ni(ClO_4)_2·6H_2O$ with 2,2′-bypyridine. The asymmetric reactions were established with the chiral Cu-$(OTf)_2$/bisoxazoline complex as a catalyst, which furnished the corresponding chiral allylic alcohols bearing trifluoromethylated quaternary stereogenic centers in moderate enantioselectivities (up to 75% ee).

EXPERIMENTAL SECTION

General Information. Column chromatography was carried out on silica gel (200−300 mesh). ^1H NMR spectra were recorded on 500 MHz in $CDCl_3$; ^{13}C NMR spectra were recorded on 125 MHz in $CDCl_3$. Melting points were determined on a microscopic apparatus and were uncorrected. All new products were further characterized by HRMS obtained on a TOF LC/MS mass spectrometer equipped with an ESI source; copies of their ^1H NMR and ^{13}C NMR spectra are provided. Enantiomeric excesses (ee) were determined by chiral high-performance liquid chromatography (chiral HPLC). Optical rotation values were measured with instruments operating at λ = 589 nm, corresponding to the sodium D line at the temperatures indicated. Anhydrous THF, toluene, and ether were freshly distilled over Na and benzophenone. Anhydrous methanol was freshly distilled over Mg. Anhydrous CH_2Cl_2 and $CHCl_3$ were freshly distilled over calcium hydride.

General Procedure for the Racemic Reaction. To a dried Schlenk tube containing $Ni(ClO_4)_2·6H_2O$ (7.2 mg, 0.02 mmol) and 2,2′-bipyridine (3.7 mg, 0.024 mmol) was added 2.0 mL of anhydrous DCM. The Schlenk tube was sealed with a Teflon cap, and the mixture was stirred at 80 °C for 1 h. After cooling to room temperature, ketoester **1** (0.2 mmol) and styrene **2** (0.4 mmol) were added under a N_2 atmosphere. The Schlenk tube was sealed again, and the mixture was stirred at 100 °C (temperature of oil bath) for 40 h. The solvent was then removed under vacuum, and the residue was purified by chromatography on silica gel, eluting with ethyl/petroleum ether to afford the product **3**. Styrenes bearing electron-donating groups (**2b**−**2d**, **2h**, **2k**, and **2l**) were added in two batches. The second batch of

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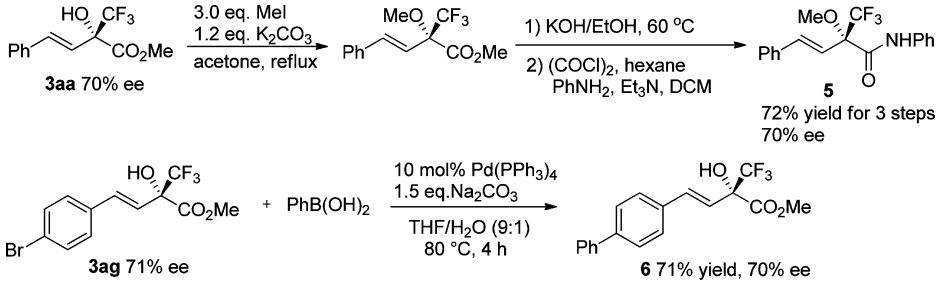
Scheme 6. Synthetic Transformations of the Products



styrene (0.2 mmol) was added to the Schlenk tube after 24 h under a N_2 atmosphere when the tube was cooled to room temperature.

*(E)-Methyl 2-Hydroxy-4-phenyl-2-(trifluoromethyl)but-3-enoate (**3aa**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); white solid, 48.0 mg, 92% yield, mp 55−58 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45−7.47 (m, 2H), 7.35−7.39 (m, 2H), 7.30−7.34 (m, 1H), 7.13 (d, J = 16.0 Hz, 1H), 6.37 (d, J = 15.5 Hz, 1H), 4.12 (s, 1H), 3.97 (s, 3H). ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$): δ 169.5, 135.2, 134.9, 128.8, 128.7, 127.1, 122.8 (q, J = 285.0 Hz), 119.3, 77.2 (q, J = 30.0 Hz), 54.6. ^{19}F{^{1}H}NMR (376 MHz, $CDCl_3$): δ −78.1 (s, 3F); HRMS m/z (ESI+): Calculated for $C_{12}H_{11}F_3NaO_3$ ([M + Na]$^+$): 283.0552, Found 283.0554.

*(E)-Methyl 2-Hydroxy-4-(p-tolyl)-2-(trifluoromethyl)but-3-enoate (**3ab**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); white solid, 44.2 mg, 81% yield, mp 71−73 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 6.5 Hz, 2H), 7.08 (d, J = 15.5 Hz, 1H), 6.31 (d, J = 16.0 Hz, 1H), 4.10 (s, 1H), 3.97 (s, 3H), 2.37 (s, 3H). ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$): δ 169.6, 138.8, 134.8, 132.4, 129.4, 127.1, 122.9 (q, J = 285.0 Hz), 118.2, 77.2 (q, J = 30.0 Hz), 54.6, 21.2. ^{19}F{^{1}H}NMR (376 MHz, $CDCl_3$): δ −78.2 (s, 3F); HRMS m/z (ESI+): Calculated for $C_{13}H_{17}F_3NO_3$ ([M + NH_4]$^+$): 292.1155, Found 292.1152.

*(E)-Methyl 4-(4-(tert-Butyl)phenyl)-2-hydroxy-2-(trifluoromethyl)-but-3-enoate (**3ac**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); yellow oil, 51.4 mg, 81% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (s, 4H), 7.10 (d, J = 16.0 Hz, 1H), 6.33 (d, J = 15.5 Hz, 1H), 4.11 (s, 1H), 3.96 (s, 3H), 1.33 (s, 9H). ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$): δ 169.6, 152.1, 134.6, 132.4, 126.9, 125.6, 122.9 (q, J = 285.0 Hz), 118.4, 77.2 (q, J = 31.3 Hz), 54.5, 34.7, 31.2. ^{19}F{^{1}H}NMR (376 MHz, $CDCl_3$): δ −78.2 (s, 3F); HRMS m/z (ESI+): Calculated for $C_{16}H_{19}F_3NaO_3$ ([M + Na]$^+$): 339.1179, Found 339.1181.

*(E)-Methyl 4-(4-Acetoxyphenyl)-2-hydroxy-2-(trifluoromethyl)-but-3-enoate (**3ad**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:5 (v/v); white solid, 38.0 mg, 60% yield, mp 98−101 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, J = 8.5 Hz, 2H), 7.09−7.12 (m, 3H), 6.33 (d, J = 15.5 Hz, 1H), 4.16 (s, 1H), 3.97 (s, 3H), 2.32 (s, 3H). ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$): δ 169.4, 169.2, 151.0, 134.0, 133.0, 128.1, 122.8 (q, J = 285.0 Hz), 121.9, 119.6, 54.6, 21.0. ^{19}F{^{1}H}NMR (376 MHz, $CDCl_3$): δ −78.1 (s, 3F); HRMS m/z (ESI+): Calculated for $C_{14}H_{17}F_3NO_5$ ([M + NH_4]$^+$): 336.1053, Found 336.1054.

*(E)-Methyl 4-(4-Fluorophenyl)-2-hydroxy-2-(trifluoromethyl)but-3-enoate (**3ae**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); white solid, 47.0 mg, 85% yield, mp 48−51 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (dd, J = 9.0, 5.0 Hz, 2H), 7.09 (d, J = 15.5 Hz, 1H), 7.05 (t, J = 8.5 Hz, 2H), 6.29 (d, J = 15.5 Hz, 1H), 4.11 (s, 1H), 3.97 (s, 3H). ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$): δ 169.4, 163.0 (d, J = 246.3 Hz), 133.8, 131.4 (d, J = 3.8 Hz), 128.8 (d, J = 8.8 Hz), 122.8 (q, J = 285.0 Hz), 119.0, 115.7 (d, J = 22.5 Hz), 54.6. ^{19}F{^{1}H}NMR (376 MHz, $CDCl_3$): δ −78.1 (s, 3F), −112.5 (s, 1F); HRMS m/z (ESI+): Calculated for $C_{12}H_{10}F_4NaO_3$ ([M + Na]$^+$): 301.0458, Found 301.0457.

*(E)-Methyl 4-(4-Chlorophenyl)-2-hydroxy-2-(trifluoromethyl)but-3-enoate (**3af**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); white solid, 53.3 mg, 90% yield, mp 72−74 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 7.08 (d, J = 16.0 Hz, 1H), 6.35 (d, J = 15.5 Hz, 1H), 4.13 (s, 1H), 3.97 (s, 3H). ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$): δ 169.3, 134.6, 133.8, 133.8, 128.9, 128.4, 122.8 (q, J = 285.0 Hz), 120.0, 77.2 (q, J = 31.3 Hz), 54.6. ^{19}F{^{1}H}NMR (376 MHz, $CDCl_3$): δ −78.1 (s, 3F); HRMS m/z (ESI+): Calculated for $C_{12}H_{10}ClF_3NaO_3$ ([M + Na]$^+$): 317.0163, Found 317.0164.

*(E)-Methyl 4-(4-Bromophenyl)-2-hydroxy-2-(trifluoromethyl)but-3-enoate (**3ag**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); white solid, 59.9 mg, 88% yield, mp 80−82 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 15.8 Hz, 1H), 6.36 (d, J = 15.8 Hz, 1H), 4.13 (s, 1H), 3.97 (s, 3H). ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$): δ 169.3, 134.2, 133.8, 131.9, 128.6, 122.8, 122.7 (q, J = 285.0 Hz), 120.1, 77.2 (q, J = 30.0 Hz), 54.6. ^{19}F{^{1}H}NMR (376 MHz, $CDCl_3$): δ −78.1 (s, 3F); HRMS m/z (ESI−): Calculated for $C_{12}H_9BrF_3O_3$ ([M − H]$^-$): 336.9693, Found 336.9684.

*(E)-Methyl 2-Hydroxy-4-mesityl-2-(trifluoromethyl)but-3-enoate (**3ah**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); white solid, 57.0 mg, 94% yield, mp 67−69 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (d, J = 16.0 Hz, 1H), 6.92 (s, 2H), 5.96 (d, J = 16.0 Hz, 1H), 4.18 (s, 1H), 3.99 (s, 3H), 2.32 (s, 3H), 2.28 (s, 6H). ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$): δ 169.7, 137.1, 135.9, 133.3, 132.2, 128.7, 124.5, 122.9 (q, J = 285.0 Hz), 54.4, 20.9, 20.5. ^{19}F{^{1}H}NMR (376 MHz, $CDCl_3$): δ −78.2 (s, 3F); HRMS m/z (ESI+): Calculated for $C_{15}H_{17}F_3NaO_3$ ([M + Na]$^+$): 325.1022, Found 325.1025.

*(E)-Methyl 4-(2-Fluorophenyl)-2-hydroxy-2-(trifluoromethyl)but-3-enoate (**3ai**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); white solid, 46.0 mg, 83% yield, mp 33−34 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (td, J = 8.0, 1.5 Hz, 1H), 7.28−7.34 (m, 1H), 7.26 (d, J = 16.0 Hz, 1H), 7.05−7.17 (m, 2H), 6.51 (d, J = 16.0 Hz, 1H), 4.17 (s, 1H), 3.98 (s, 3H). ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$): δ 169.4, 160.7 (d, J = 250.0 Hz), 130.1 (d, J = 7.5 Hz), 128.5 (d, J = 3.8 Hz), 128.0 (d, J = 2.5 Hz), 124.2 (d, J = 3.8 Hz), 123.1 (d, J = 11.3 Hz), 122.8 (q, J = 285.0 Hz), 122.0 (d, J = 6.3 Hz), 116.0 (d, J = 22.5 Hz), 77.3 (q, J = 31.3 Hz), 54.7. ^{19}F{^{1}H}NMR (376 MHz, $CDCl_3$): δ −78.1 (s, 3F), −116.2 (s, 1F); HRMS m/z (ESI+): Calculated for $C_{12}H_{10}F_4NaO_3$ ([M + Na]$^+$): 301.0458, Found 301.0468.

*(E)-Methyl 4-(3-Bromo-4-fluorophenyl)-2-hydroxy-2-(trifluoromethyl)but-3-enoate (**3aj**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); yellow solid, 46.2 mg, 65% yield, mp 86−87 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (dd, J = 6.5, 2.0 Hz, 1H), δ 7.33−7.36 (m, 1H), 7.11 (t, J = 8.5 Hz, 1H), 7.03 (d, J = 15.5 Hz, 1H), 6.31 (d, J = 16.0 Hz, 1H), 4.17 (s, 1H), 3.98 (s, 3H). ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$): δ 169.2, 159.2 (d, J = 236.3 Hz), 133.0 (d, J = 3.75 Hz), 132.7, 131.9, 127.8 (d, J = 7.5 Hz), 122.7 (q, J = 285.0 Hz), 120.6, 116.7 (d, J = 22.5 Hz), 109.5 (d, J = 22.5 Hz), 54.7. ^{19}F{^{1}H}NMR (376 MHz, $CDCl_3$): δ −78.1 (s, 3F), −106.9 (s, 1F); HRMS m/z (ESI+): Calculated for $C_{12}H_9BrF_4NaO_3$ ([M + Na]$^+$): 378.9563, Found 378.9568.

*(E)-Methyl 2-Hydroxy-4-(3-methoxyphenyl)-2-(trifluoromethyl)-but-3-enoate (**3ak**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); yellow oil, 30.2 mg, 53% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27−7.31 (m, 1H), 7.10 (d, J = 15.5 Hz, 1H), 7.06 (d, J = 7.5 Hz, 1H), 6.97−7.01 (m, 1H),

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6.86−6.91 (m, 1H), 6.37 (d, J = 15.5 Hz, 1H), 4.16 (s, 1H), 3.97 (s, 3H), 3.85 (s, 3H). $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 169.4, 160.0, 136.6, 134.9, 129.7, 122.8 (q, J = 285.0 Hz), 119.7, 119.7, 114.5, 112.6, 77.2 (q, J = 30.0 Hz), 55.3, 54.6. $^{19}F\{^1H\}$NMR (376 MHz, $CDCl_3$): δ −78.1 (s, 3F); HRMS m/z (ESI+): Calculated for $C_{13}H_{14}F_3O_4$ ([M + H]$^+$): 291.0839, Found 291.0844.

*(E)-Methyl 2-Hydroxy-4-(m-tolyl)-2-(trifluoromethyl)but-3-enoate (**3al**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); yellow oil, 43.8 mg, 80% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 7.28 (s, 1H), 7.24−7.27 (m, 2H), 7.13−7.19 (m, 1H), 7.10 (d, J = 16.0 Hz, 1H), 6.36 (d, J = 16.0 Hz, 1H), 4.12 (s, 1H), 3.97 (s, 3H), 2.38 (s, 3H). $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 169.5, 138.3, 135.1, 135.0, 129.6, 128.6, 127.7, 124.4, 122.8 (q, J = 285.0 Hz), 119.0, 77.2 (q, J = 30.0 Hz), 54.6, 21.3. $^{19}F\{^1H\}$NMR (376 MHz, $CDCl_3$): δ −78.1 (s, 3F); HRMS m/z (ESI+): Calculated for $C_{13}H_{17}F_3NO_3$ ([M + NH_4]$^+$): 292.1155, Found 292.1163.

*(E)-Methyl 4-(4-Bromo-3,5-dimethoxyphenyl)-2-hydroxy-2-(trifluoromethyl)but-3-enoate (**3am**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); white solid, 39.0 mg, 49% yield, mp 132−134 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.07 (d, J = 16.0 Hz, 1H), 6.64 (s, 2H), 6.35 (d, J = 15.5 Hz, 1H), 4.14 (s, 1H), 3.99 (s, 3H), 3.94 (s, 6H). $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 169.2, 157.3, 135.5, 134.8, 122.7 (q, J = 285.0 Hz), 120.0, 103.7, 101.9, 56.6, 54.7. $^{19}F\{^1H\}$NMR (376 MHz, $CDCl_3$): δ −78.0 (s, 3F); HRMS m/z (ESI+): Calculated for $C_{14}H_{15}BrF_3O_5$ ([M + H]$^+$): 399.0049, Found 399.0052.

*(E)-Methyl 2-Hydroxy-4-(naphthalen-2-yl)-2-(trifluoromethyl)-but-3-enoate (**3an**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); white solid, 30.8 mg, 50% yield, mp 89−91 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.84 (t, J = 8.0 Hz, 4H), 7.64 (d, J = 9.5 Hz, 1H), 7.48−7.53 (m, 2H), 7.29 (d, J = 17.5 Hz, 1H), 6.50 (d, J = 15.5 Hz, 1H), 4.19 (s, 1H), 4.00 (s, 3H). $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 169.5, 135.1, 133.5, 133.5, 132.7, 128.4, 128.2, 127.8, 127.7, 126.5, 126.1, 123.6, 122.9 (q, J = 283.8 Hz), 119.6, 54.6. $^{19}F\{^1H\}$NMR (376 MHz, $CDCl_3$): δ −78.0 (s, 3F); HRMS m/z (ESI+): Calculated for $C_{16}H_{13}F_3NaO_3$ ([M + Na]$^+$): 333.0709, Found 333.0731.

*(E)-Methyl 2-Hydroxy-4,4-diphenyl-2-(trifluoromethyl)but-3-enoate (**3ao**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); colorless oil, 65.9 mg, 98% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 7.35−7.42 (m, 3H), 7.29−7.34 (m, 3H), 7.24−7.26 (m, 2H), 7.19−7.21 (m, 2H), 6.35 (s, 1H), 3.88 (s, 1H), 3.59 (s, 3H). $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 169.3, 150.0, 141.5, 137.9, 129.8, 128.5, 128.3, 128.2, 127.9, 127.6, 123.4 (q, J = 285.0 Hz), 119.4, 76.5 (q, J = 28.8 Hz), 53.9. $^{19}F\{^1H\}$NMR (376 MHz, $CDCl_3$): δ −78.9 (s, 3F); HRMS m/z (ESI+): Calculated for $C_{18}H_{16}F_3O_3$ ([M + H]$^+$): 337.1046, Found 337.1055.

*(E)-Methyl 2-Hydroxy-6-phenyl-2-(trifluoromethyl)hexa-3,5-dienoate (**3ap**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); yellow solid, 45.5 mg, 79% yield, mp 60−63 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.40−7.45 (m, 2H), 7.35 (t, J = 7.0 Hz, 2H), δ 7.26−7.29 (m, 1H), δ 6.81−6.92 (m, 2H), 6.71 (d, J = 15.0 Hz, 1H), 5.97 (d, J = 14.5 Hz, 1H), 4.06 (s, 1H), 3.96 (s, 3H). $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 169. 5, 136.6, 136.1, 135.0, 128.7, 128.2, 126.7, 126.6, 122.5, 122.8 (q, J = 285.0 Hz), 54.5. $^{19}F\{^1H\}$NMR (376 MHz, $CDCl_3$): δ −78.2 (s, 3F); HRMS m/z (ESI+): Calculated for $C_{14}H_{13}F_3NaO_3$ ([M + Na]$^+$): 309.0709, Found 309.0720.

*(S,E)-Ethyl 2-Hydroxy-4-phenyl-2-(trifluoromethyl)but-3-enoate (**3ba**).*[14] Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); yellow oil, 40.4 mg, 74% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 7.43−7.49 (m, 2H), 7.37 (t, J = 8.0 Hz, 2H), 7.32 (t, J = 7.5 Hz, 1H), 7.13 (d, J = 15.5 Hz, 1H), 6.38 (d, J = 15.5 Hz, 1H), 4.42 (m, 2H), 4.15 (s, 1H), 1.39 (t, J = 7.0 Hz, 3H).

*(E)-Isopropyl 2-Hydroxy-4-phenyl-2-(trifluoromethyl)but-3-enoate (**3ca**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); yellow oil, 40.1 mg, 60% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 7.44−7.47 (m, 2H), 7.37 (t, J = 7.0 Hz, 2H), 7.32 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 16.0 Hz, 1H), 6.37 (d, J = 16.0 Hz, 1H), 5.22 (m, 1H), 4.17 (s, 1H), 1.37 (t, J = 6.5 Hz, 6H). $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 168.4, 135.4, 134.7, 128.7, 128.7, 127.1, 122.9 (q, J = 285.0 Hz), 119.6, 72.9, 21.5, 21.3. $^{19}F\{^1H\}$NMR (376 MHz, $CDCl_3$): δ −78.0 (s, 3F); HRMS m/z (ESI+): Calculated for $C_{14}H_{15}F_3NaO_3$ ([M + Na]$^+$): 311.0866, Found 311.0866.

*(E)-Butyl 2-Hydroxy-4-phenyl-2-(trifluoromethyl)but-3-enoate (**3da**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:20 (v/v); colorless oil, 47.1 mg, 78% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 7.45−7.47 (m, 2H), 7.36−7.39 (m, 2H), 7.32−7.34 (m, 1H), 7.14 (d, J = 16.0 Hz, 1H), 6.39 (d, J = 16.0 Hz, 1H), 4.40−4.45 (m, 1H), 4.29−4.34 (m, 1H), 4.19 (s, 1H), 1.71−1.77 (m, 2H), 1.41−1.47 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H). $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 169.1, 135.3, 134.8, 128.7, 128.7, 127.1, 122.9 (q, J = 285.0 Hz),119.5, 68.1, 30.3, 18.8, 13.5. $^{19}F\{^1H\}$-NMR (376 MHz, $CDCl_3$): δ −78.0 (s, 3F); HRMS m/z (ESI−): Calculated for $C_{15}H_{16}F_3O_3$ ([M − H]$^-$): 301.1057, Found 301.1060.

*(E)-Diethyl 2-Hydroxy-2-styrylmalonate (**3ea**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); yellow oil, 22.0 mg, 40% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, J = 7.5 Hz, 2H), 7.35 (t, J = 7.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 6.98 (d, J = 15.5 Hz, 1H), 6.62 (d, J = 16.0 Hz, 1H), 4.28−4.38 (m, 4H), 4.10 (s, 1H), 1.33 (t, J = 7.0 Hz, 6H). $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 169.6, 136.1, 131.5, 128.6, 128.1, 127.0, 123.9, 78.6, 62.9, 14.0. HRMS m/z (ESI+): Calculated for $C_{15}H_{19}O_5$ ([M + H]$^+$): 279.1227, Found 279.1226.

General Procedure for the Asymmetric Reaction. To a dried Schlenk tube containing $Cu(OTf)_2$ (7.2 mg, 0.02 mmol) and **L1** (8.6 mg, 0.024 mmol) was added 2.0 mL of anhydrous $CHCl_3$, and the mixture was stirred for 1 h at room temperature. Subsequently, trifluoropyruvate **1** (0.2 mmol) and alkene **2** (0.4 mmol) were added and the Schlenk tube was sealed with a Teflon cap. The reaction mixture was stirred at 100 °C (temperature of oil bath) for 40 h. The solvent was then removed under vacuum, and the residue was purified by chromatography on silica gel, eluting with ethyl/petroleum ether to afford the product **3**.

*(E)-Methyl 2-Hydroxy-4-phenyl-2-(trifluoromethyl)but-3-enoate (**3aa**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); 46.0 mg, 88% yield; $[\alpha]_D^{20}$ = +56.0 (c 0.5, CH_2Cl_2), 70% ee [Daicel Chiralpak AD-H column (25 cm × 0.46 cm ID), n-hexane/i-PrOH = 90/10, 0.8 mL/min, 254 nm; t_{major} = 8.9 min, t_{minor} = 17.2 min].

*(E)-Methyl 2-Hydroxy-4-(p-tolyl)-2-(trifluoromethyl)but-3-enoate (**3ab**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); 45.8 mg, 84% yield; $[\alpha]_D^{20}$ = +54.0 (c 0.5, CH_2Cl_2), 67% ee [Daicel Chiralpak AD-H column (25 cm × 0.46 cm ID), n-hexane/i-PrOH = 90/10, 0.8 mL/min, 254 nm; t_{major} = 10.1 min, t_{minor} = 30.8 min].

*(E)-Methyl 4-(4-(tert-Butyl)phenyl)-2-hydroxy-2-(trifluoromethyl)-but-3-enoate (**3ac**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); 52.4 mg, 83% yield; $[\alpha]_D^{20}$ = +60.8 (c 0.5, CH_2Cl_2), 71% ee [Daicel Chiralpak AD-H column (25 cm × 0.46 cm ID), n-hexane/i-PrOH = 90/10, 0.8 mL/min, 254 nm; t_{major} = 9.4 min, t_{minor} = 19.2 min].

*(E)-Methyl 4-(4-Fluorophenyl)-2-hydroxy-2-(trifluoromethyl)but-3-enoate (**3ae**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); 38.5 mg, 68% yield; $[\alpha]_D^{20}$ = +62.0 (c 0.5, CH_2Cl_2), 69% ee [Daicel Chiralpak AD-H column (25 cm × 0.46 cm ID), n-hexane/i-PrOH = 90/10, 0.8 mL/min, 254 nm; t_{major} = 10.3 min, t_{minor} = 28.8 min].

*(E)-Methyl 4-(4-Chlorophenyl)-2-hydroxy-2-(trifluoromethyl)but-3-enoate (**3af**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); 20.1 mg, 34% yield; $[\alpha]_D^{20}$ = +63.6 (c 0.5, CH_2Cl_2), 75% ee [Daicel Chiralcel AS-H column (25 cm × 0.46 cm ID), n-hexane/i-PrOH = 90/10, 0.8 mL/min, 254 nm; t_{minor} = 9.1 min, t_{major} = 10.3 min].

*(E)-Methyl 4-(4-Bromophenyl)-2-hydroxy-2-(trifluoromethyl)but-3-enoate (**3ag**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); white solid, 21.0 mg, 31% yield; $[\alpha]_D^{20}$ = +43.6 (c 0.5, CH_2Cl_2), 71% ee [Daicel Chiralcel AS-H

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column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 90/10, 0.8 mL/min, 254 nm; t_{minor} = 9.4 min, t_{major} = 10.8 min].

*(E)-Methyl 2-Hydroxy-4-mesityl-2-(trifluoromethyl)but-3-enoate (**3ah**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); 52.4 mg, 87% yield; $[\alpha]_D^{20}$ = +16.2 (*c* 0.5, CH_2Cl_2), 75% ee [Daicel Chiralcel AS-H column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 95/5, 0.8 mL/min, 254 nm; t_{minor} = 6.3 min, t_{major} = 7.5 min].

*(E)-Methyl 4-(2-Fluorophenyl)-2-hydroxy-2-(trifluoromethyl)but-3-enoate (**3ai**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); 15.6 mg, 28% yield; $[\alpha]_D^{20}$ = +56.0 (*c* 0.5, CH_2Cl_2), 71% ee [Daicel Chiralpak AD-H column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 90/10, 0.8 mL/min, 254 nm; t_{major} = 8.4 min, t_{minor} = 9.7 min].

*(E)-Methyl 2-Hydroxy-4-(m-tolyl)-2-(trifluoromethyl)but-3-enoate (**3al**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); 34.8 mg, 63% yield; $[\alpha]_D^{20}$ = +70.4 (*c* 0.5, CH_2Cl_2), 71% ee [Daicel Chiralpak AD-H column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 90/10, 0.8 mL/min, 254 nm; t_{major} = 7.4 min, t_{minor} = 8.3 min].

*(E)-Methyl 4-(4-Bromo-3,5-dimethoxyphenyl)-2-hydroxy-2-(trifluoromethyl)but-3-enoate (**3am**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); 39.6 mg, 50% yield; $[\alpha]_D^{20}$ = +41.4 (*c* 0.5, CH_2Cl_2), 68% ee [Daicel Chiralpak AD-H column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 90/10, 0.8 mL/min, 254 nm; t_{major} = 17.0 min, t_{minor} = 23.9 min].

*(E)-Methyl 2-Hydroxy-4-(naphthalen-2-yl)-2-(trifluoromethyl)-but-3-enoate (**3an**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); 44.6 mg, 72% yield; $[\alpha]_D^{20}$ = +31.0 (*c* 0.5, CH_2Cl_2), 69% ee [Daicel Chiralpak AD-H column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 90/10, 0.8 mL/min, 254 nm; t_{major} = 12.4 min, t_{minor} = 23.9 min].

*(S)-Methyl 2-Hydroxy-4,4-diphenyl-2-(trifluoromethyl)but-3-enoate (**3ao**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); 37.6 mg, 56% yield; $[\alpha]_D^{20}$ = +58.0 (*c* 0.5, CH_2Cl_2), 68% ee [Daicel Chiralpak AD-H column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 90/10, 0.8 mL/min, 254 nm; t_{minor} = 8.0 min, t_{major} = 9.1 min].

*(E)-Methyl 2-Hydroxy-4-(4-methoxyphenyl)-2-(trifluoromethyl)-but-3-enoate (**3aq**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); white solid, 49.3 mg, 85% yield, mp 77−79 °C; $[\alpha]_D^{20}$ = +54.4 (*c* 0.5, CH_2Cl_2), 68% ee [Lux 5μ Cellulose-3 column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 90/10, 0.8 mL/min, 254 nm; t_{major} = 21.5 min, t_{minor} = 23.4 min]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 15.5 Hz, 1H), 6.89 (d, *J* = 9.0 Hz, 2H), 6.22 (d, *J* = 16.0 Hz, 1H), 4.10 (s, 1H), 3.96 (s, 3H), 3.84 (s, 3H). ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$): δ 169.7, 160.1, 134.3, 128.5, 127.9, 122.9 (q, *J* = 285.0 Hz), 116.8, 114.1, 55.3, 54.6. ^{19}F{^{1}H}NMR (376 MHz, $CDCl_3$): δ −78.2 (s, 3F); HRMS *m*/*z* (ESI+): Calculated for $C_{13}H_{14}F_3O_4$ ([M + H]$^+$): 291.0839, Found 291.0837.

*(E)-Methyl 2-Hydroxy-4-(2-methoxyphenyl)-2-(trifluoromethyl)-but-3-enoate (**3ar**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); yellow oil, 46.5 mg, 80% yield; $[\alpha]_D^{20}$ = +31.0 (*c* 0.5, CH_2Cl_2), 69% ee [Lux 5μ Cellulose-1 column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 90/10, 0.8 mL/min, 254 nm; t_{major} = 13.2 min, t_{minor} = 16.6 min]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.42 (d, *J* = 16.0 Hz, 1H), 7.30 (t, *J* = 8.5 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.45 (d, *J* = 16.0 Hz, 1H), 4.12 (s, 1H), 3.96 (s, 3H), 3.88 (s, 3H). ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$): δ 169.7, 157.3, 130.0, 129.9, 127.8, 124.1, 122.9 (q, *J* = 285.0 Hz), 120.6, 119.7, 111.0, 77.4 (q, *J* = 30.0 Hz), 55.4, 54.5. ^{19}F{^{1}H}NMR (376 MHz, $CDCl_3$): δ −78.1 (s, 3F); HRMS *m*/*z* (ESI+): Calculated for $C_{13}H_{14}F_3O_4$ ([M + H]$^+$): 291.0839, Found 291.0842.

*(S,E)-Ethyl 2-Hydroxy-4-phenyl-2-(trifluoromethyl)but-3-enoate (**3ba**).* Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v); 38.3 mg, colorless oil, 70% yield; $[\alpha]_D^{20}$ = +62.4 (*c* 0.5, CH_2Cl_2), 64% ee [Daicel Chiralpak AD-H column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 90/10, 0.8 mL/min, 254 nm; t_{major} = 9.0 min, t_{minor} = 17.0 min].

Transformation of 3ba to (*S*)-Ethyl 2-Hydroxy-4-phenyl-2-(trifluoromethyl)butanoate 4.[13] The mixture of **3ba** (25.8 mg, 0.1 mmol, 1.0 equiv) and Pd/C (2.6 mg, 0.0025 mmol, 10 mol %) in 2.0 mL of EtOH was stirred at room temperature for 12 h under a hydrogen balloon. The resulting mixture was filtered off and washed with EtOH. The crude mixture was purified by flash silica gel column chromatography, eluting with ethyl acetate/petroleum ether 1:10 (v/v), to give compound **4** as a colorless oil. 23.6 mg, 86% yield; $[\alpha]_D^{20}$ = +8.5 (*c* 1.0, $CHCl_3$), 64% ee [Daicel Chiralcel AS-H column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 98/2, 0.75 mL/min, 254 nm; t_{minor} = 7.5 min, t_{major} = 9.4 min]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30−7.33 (m, 2H), 7.19−7.24 (m, 3H), 4.21−4.37 (m, 2H), 3.98 (s, 1H), 2.85−2.90 (ddd, *J* = 5.0 Hz, 11.5 Hz, 14.0 Hz, 1H), 2.44−2.50 (ddd, *J* = 5.5 Hz, 11.0 Hz, 13.5 Hz, 1H), 2.32−2.38 (m,1H), 2.21−2.27 (ddd, *J* = 5.0 Hz, 11.5 Hz, 14.0 Hz, 1H), 1.34 (t, *J* = 7.5 Hz, 3H).

Transformation of 3aa to (*S*,*E*)-2-Methoxy-*N*,4-diphenyl-2-(trifluoromethyl)but-3-enamide 5. Step 1: To a solution of **3aa** (52 mg, 0.2 mmol) in acetone (2.0 mL) were added MeI (37.5 μL, 0.6 mmol) and K_2CO_3 (33.1 mg, 0.24 mmol). The resulting mixture was refluxed for 30 h. After cooling to room temperature, the mixture was then filtered and the solvent was removed under vacuum; the obtained residue was used for the next step without purification. Step 2: The residue was dissolved in an ethanolic solution of KOH (5%, 3.0 mL), and the resulting mixture was stirred at 60 °C for 3 h. After removing the solvent, the mixture was treated with cold 2 N HCl and extracted by ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After filtration and concentration under vacuum, the crude intermediate was obtained and used for the next step without purification. Step 3: To a solution of the crude intermediate obtained in step 2 in dry hexane (2.0 mL) were added oxalyl chloride (23.7 μL, 0.28 mmol) dropwise and DMF (15.4 μL, 0.2 mmol) in 10 min at 0 °C under N_2, after which the mixture was stirred at room temperature for 2 h and then evaporated under vacuum to give the acid chloride as a yellow solid. The resulting acid chloride was dissolved in CH_2Cl_2 (2.0 mL), and to the solution were added NEt_3 (44.3 μL, 0.32 mmol) and aniline (18.2 μL, 0.2 mmol). The mixture was stirred at room temperature for 1 h. After diluting with CH_2Cl_2, the mixture was washed subsequently with 1 N HCl, saturated $NaHCO_3$, and brine, and then dried over Na_2SO_4. The solvent was evaporated under vacuum after filtration to afford the crude product, which was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1:5 (v/v)) to give compound **5** as a yellow solid. 48.2 mg, 72% yield for 3 steps, mp 97−99 °C; $[\alpha]_D^{20}$ = −16.6 (*c* 0.5, CH_2Cl_2), 70% ee [Daicel Chiralpak OD-H column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 90/10, 0.8 mL/min, 254 nm; t_{minor} = 14.0 min, t_{major} = 18.8 min]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.52 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 7.5 Hz, 2H), 7.35−7.41 (m, 5H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 16.5 Hz, 1H), 6.51 (d, *J* = 16.5 Hz, 1H), 3.62 (s, 3H). ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$): δ 163.5, 137.8, 136.7, 135.1, 129.1, 129.1, 128.7, 127.1, 125.1, 123.4 (q, *J* = 287.5 Hz), 119.9, 118.0, 82.6 (q, *J* = 27.5 Hz), 54.4. ^{19}F{^{1}H}NMR: (376 MHz, $CDCl_3$): δ −73.8 (s, 3F); HRMS *m*/*z* (ESI−): Calculated for $C_{18}H_{15}F_3NO_2$ ([M − H]$^-$): 334.1060, Found 334.1048.

Transformation of 3ag to (*S*,*E*)-Methyl 4-([1,1′-Biphenyl]-4-yl)-2-hydroxy-2-(trifluoromethyl)but-3-enoate 6. To a solution of **3ag** (33.9 mg, 0.1 mmol) in THF/H_2O (1.0 mL, 9:1) were added $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol), phenylboronic acid (36.6 mg, 0.3 mmol), and Na_2CO_3 (15.9 mg, 0.15 mmol). The resulting mixture was stirred at 80 °C for 4 h under N_2. After dilution with water and extraction by CH_2Cl_2, the combined organic solvent was dried over Na_2SO_4 and concentrated under vacuum. The residue was then purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v), to give compound **6** as a white solid. 23.9 mg, 71% yield, mp 187−189 °C; $[\alpha]_D^{20}$ = +56.8 (*c* 0.5, CH_2Cl_2), 70% ee [Daicel Chiralpak AD-H column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 80/20, 0.8 mL/min, 254 nm; t_{major} = 14.1 min, t_{minor} = 40.8 min]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61−7.63 (m, 4H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 16.0 Hz, 1H), 6.42 (d, *J* = 16.0 Hz, 1H), 4.16 (s, 1H), 3.99 (s, 3H). ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$): δ 169.5,

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141.6, 140.4, 134.5, 134.2, 128.8, 127.6, 127.6, 127.4, 127.0, 122.8 (q, J = 285.0 Hz), 119.2, 77.2 (q, J = 30.0 Hz), 54.7. $^{19}F\{^{1}H\}$NMR (376 MHz, $CDCl_3$): δ −78.1 (s, 3F); HRMS m/z (ESI−): Calculated for $C_{18}H_{14}F_3O_3$ ($[M - H]^-$): 335.0901, Found 335.0898.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00358.

Characterization data, including ^{1}H, ^{13}C, and ^{19}F NMR for all the new compounds and chiral HPLC spectra for the chiral products (PDF)

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Notes

The authors declare no competing financial interest.

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