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The Synthesis of Optically Pure 2-Trifluoromethyl Lactic Acid by Asymmetric Hydroformylation

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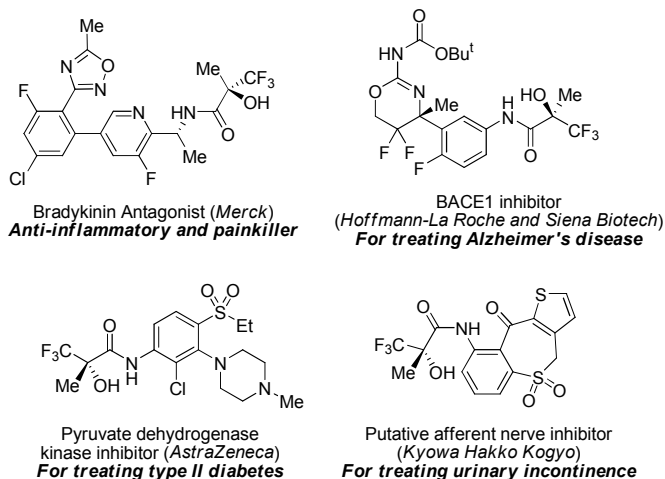
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ABSTRACT: By utilizing Rh catalysts ligated by the *P*-chirogenic ligands QuinoxP* and DuanPhos, 3,3,3-trifluoroprop-1-en-2-yl acetate could be hydroformylated and subsequently oxidized to yield enantiomerically pure 2-trifluoromethyl lactic acid.

Trifluoromethylated compounds, including optically active ones, have received increasing attention in the fields of synthetic and medicinal chemistry.¹ The construction of trifluoromethyl-substituted quaternary stereogenic centers remains a formidable challenge in organic synthesis.² Enantiomerically pure 2-trifluoromethyl lactic acid (TFMLA, **1**), also known as the Soloshonok acid, serves as an important building block for many active pharmaceutical ingredients in different therapeutic areas (Scheme 1).³ It is also used for studying the different physical properties (in particular, sublimation behavior) between enantiomerically pure compounds and their corresponding racemic counterparts.⁴ The large-scale synthesis of **1** normally involves a Zn-mediated asymmetric addition reaction of a methyl Grignard Reagent to 2,2,2-trifluoropyruvate, providing **1** with an enantiomeric excess of 50%. The enantiomerically pure compound is derived from the crude product by resolution.⁵ Shaw has reported a process that employed the addition of cyanide to trifluoroacetone, followed

by an enzymatic resolution of the racemic adduct.⁶ However, an efficient enantioselective synthesis of this valuable molecule is highly desirable.

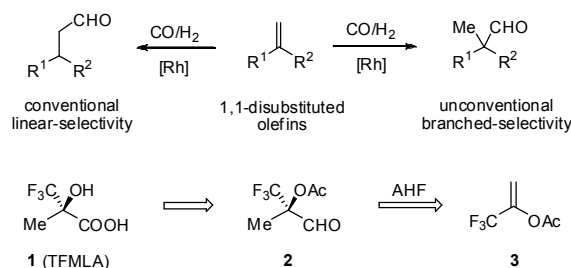
Scheme 1. TFMLA (1) as an important chiral building block of drug candidates.



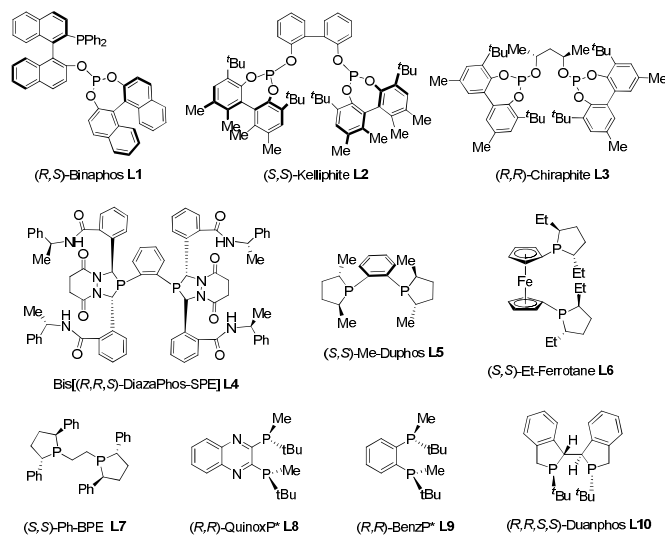
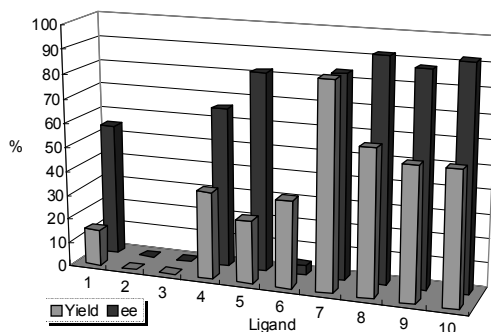
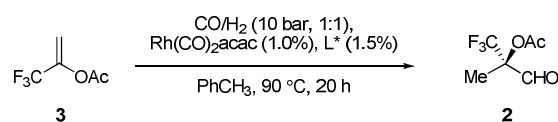
An attractive alternative route to access **1** would be the asymmetric hydroformylation (AHF)^{7,8} of 1-(trifluoromethyl)ethenyl acetate (**3**), a relatively inexpensive precursor. During the course of our study on the AHF of 1,1-disubstituted olefins,⁹ we were surprised to observe that the AHF of **3** was selective for the branched product **2** (disfavored by Keulemans' rule).¹⁰ Compound **2** could be oxidized to afford **1** (Scheme 2). We thus sought to optimize our initial result with the intent of realizing an efficient and industrially-relevant process for the preparation of **1**. While vinyl acetate is one of the most widely examined substrates in previous studies of hydroformylation,^{8c,d} the AHF of **3** has not been disclosed. In fact, to the best of our knowledge, the only AHF of 1,1-disubstituted olefins reported to provide exclusively branched aldehyde products was with α,β -dehydroamino acid esters as substrates, and proceeded with low levels of enantioselectivity.¹¹ Herein we

report the results of a study of the AHF of **3** to provide **2**, which constitutes the first example of an AHF that forms a quaternary stereogenic center with high enantioselectivity.

Scheme 2. Synthesis of TFMLA via an asymmetric quaternary-selective hydroformylation.



We began our work by evaluating a variety of chiral ligands for the AHF of **3**; the representative results are summarized in Scheme 3.¹² Diazaphospholane (**L4**), which was reported to be highly selective in the AHF of a broad range of monosubstituted olefins,^{8c,d} gave the product in 66% ee. Three representative ligands from the DuPhos, FerroTANE and BPE families were also examined (**L5**, **L6** and **L7**). One of these, Ph-BPE (**L7**), was found to provide the best results among all traditional AHF ligands, providing **2** in high yield with an ee of 84%. However, *P*-chirogenic ligands such as QuinoxP* (**L8**), BenzP* (**L9**) and DuanPhos (**L10**) provided the best results, giving the desired product with ee's of 92%, 88% and 92%, respectively. Similar to the AHF of α -alkylacrylates that we recently reported,⁹ we believe that the *P*-chirality is a critical feature for catalysts derived from bidentate phosphorus ligands to achieve high enantioselectivity in the AHF of **3**, since the chiral pocket is more confined and closer to the reaction site as compared to traditional ligands.¹³

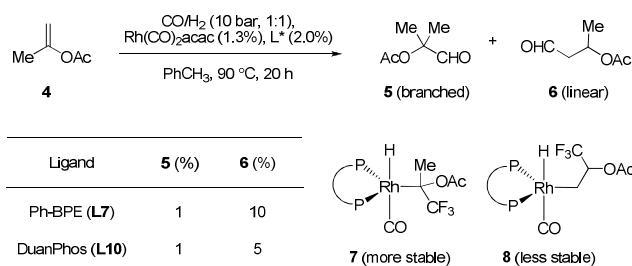
Scheme 3. Ligand evaluation for the AHF of 3,3,3-trifluoroprop-1-en-2-yl acetate (**3**).

^a GC yields are reported. ^b The ee values were determined by chiral GC. The absolute configuration of **2** was determined by converting it to the methyl ester of **1** (see the experimental section).

To further investigate the cause of the unconventional regioselectivity in the AHF of **3**, the hydroformylation of 2-propenyl acetate (**4**) was conducted under the same conditions as in Scheme 3. Linear aldehyde **6** was found to be the major product (Scheme 4). The most likely reason for the reversal of regioselectivity in the

hydroformylation of **3** is the presence of the strongly electron-withdrawing trifluoromethyl group, which favors the branched intermediate (**7**) relative to the linear isomer (**8**). The well known effect of electron-withdrawing substituents to alter the regiochemical control in e.g., the hydroformylation of vinyl acetate, is in accord with this result.^{8c,d} We also observed that the overall yield of aldehyde products (**5** and **6**) was much lower than that of **2** with the same ligands.¹⁴

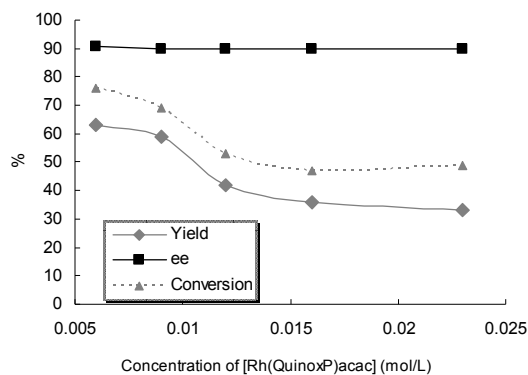
Scheme 4. The hydroformylation of 2-propenyl acetate (4**).**



The influence of reaction conditions on the yield and enantioselectivity of **2** was next explored using **L8**. Using 1 mol% of catalyst, we observed a negative correlation between the concentration of the precatalyst and the yield of **2** as well as the conversion of **3**, over the range of 5–25 mmol/L (Scheme 5), although the ee remained relatively constant over the same concentration range. We reasoned that at higher concentration, the aggregation of the [Rh(QuinoxP*)acac] precatalyst is responsible for its lowered catalytic activity, thus leading to lower conversion and yield.¹⁵ An evaluation of different L/Rh ratios was also performed, since it has been reported by Landis that this ratio is often a crucial factor in the reproducibility of rhodium-catalyzed hydroformylations.^{8d} We found that the L/Rh value had a profound impact on the yield of product although,

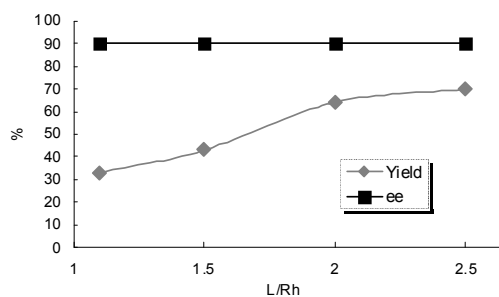
again, the ee remained largely unaffected (Scheme 6). Finally, the temperature dependence of this transformation was examined. The product yield increased up to 90 °C, at which point it decreased dramatically with an increase in the formation of side products, such as the hydrogenation product of **3**. The temperature has only a small effect on the enantioselectivity of the process, diminishing only slightly (3%) on going from 80 to 100 °C.

Scheme 5. Effect of precatalyst concentration.



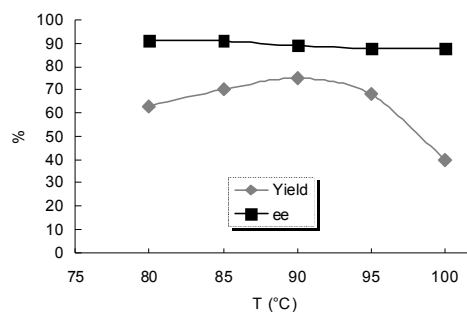
Reaction conditions: CO/H₂ (10 bar, 1:1), Rh(CO)₂acac (1.0 mol%), (*R,R*)-QuinoxP* (1.5 mol%), toluene, 95 °C, 8 h.

Scheme 6. Effect of L/Rh ratio.



Reaction conditions: CO/H₂ (10 bar, 1:1), Rh(CO)₂acac (1.0 mol%), (*R,R*)-QuinoxP* (1.1–2.5 mol%), toluene, 92 °C, 8 h.

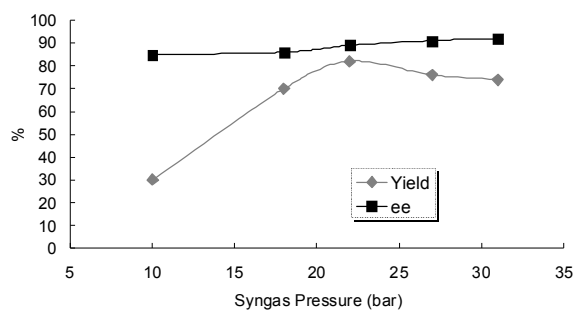
Scheme 7. Effect of reaction temperature.



Reaction conditions: CO/H₂ (10 bar, 1:1), Rh(CO)₂acac (1.0 mol%), (*R,R*)-QuinoxP* (2.0 mol%), toluene, 8 h.

On a larger scale (10 mmol), a considerable pressure drop was observed during the course of the reaction. Thus, it was necessary to use a higher initial pressure than when the reaction was performed on a 1 mmol scale. Unfortunately, the **L8**-derived catalyst lost activity at the elevated pressure. For most rhodium catalysts, a higher CO partial pressure leads to a lower overall reaction rate.¹⁶ In order to overcome this, we examined other catalysts and found that the [Rh(DuanPhos)] catalyst worked well at higher pressures. The influence of the syngas pressure was further explored, and we found that ee of the product increased slightly with increasing pressure, while the yield was maximum at approximately 23 bar (Scheme 8).

Scheme 8. Effect of syngas pressure.



Reaction conditions: CO/H₂ (1:1), Rh(CO)₂acac (0.4 mol%), (*R,R,S,S*)-DuanPhos (0.6 mol%), toluene, 110 °C, 18 h.

Having identified ligands and the corresponding reaction conditions for the AHF, we sought to develop a concise two-step sequence to prepare 2-trifluoromethyl lactic acid (**1**) (Table 1). On a small scale (1 mmol), the reaction of **3** with CO and H₂ (10 bar) in the presence of 1.0 mol% Rh(CO)₂acac and 2.5 mol% QuinoxP* (**L8**) at 85 °C in toluene provided aldehyde **2** with 91% ee, which was immediately oxidized by NaClO₂ and saponified with NaOH to yield **1**, after acidification and crystallization (46% yield (two steps), >99% ee). For a larger scale reaction (10 mmol), DuanPhos (**L10**, 0.6 mol%) was employed with a reduced amount of Rh(CO)₂acac (0.4 mol%), and the AHF was carried out at 110 °C and 31 bar to give **1** after oxidation and purification (52% overall yield, >99% ee).

Table 1. A concise one-pot synthesis of chiral acid **1**.

	Scale	Rh	L	P	T	time	ee	Yield	ee
L	(mmol)	%	%	(bar) ^a	(°C)	(hr)	[2]	[1] ^b	[1] ^c
L8	1	1.0	2.5	10	85	8	91	46	>99
L10	10	0.4	0.6	31	110	18	92	52	>99

^a The pressure before the reaction. ^b Two-step isolated yield (average of two runs). ^c Determined by chiral GC.

In conclusion, we have developed the first example of a highly enantioselective, quaternary-selective hydroformylation process. By utilizing Rh catalysts ligated by the *P*-chirogenic ligands QuinoxP* and DuanPhos, 1,1-disubstituted alkenyl ester **3** could be converted to the corresponding branched aldehyde **2** with high enantioselectivity. Notably, the aldehyde product could be subsequently subjected to a series of transformations, which yield optically pure 2-trifluoromethyl lactic acid **1** in a one-pot fashion on large scale.

EXPERIMENTAL SECTION

General Information. Hydroformylation reactions were set up in a CAT24 autoclave from HEL Inc., or a Parr reactor (model# 4564), and were stirred with a teflon-coated magnetic stir bar. **Caution: Reactions**

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4 employing elevated pressure should be carried out in suitable equipment behind a blast shield and with
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6 all appropriate precautions. Rh(CO)₂acac and ligands were purchased from Strem Chemical Co.
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9 3,3,3-Trifluoroprop-1-en-2-yl acetate (**3**) was purchased from Alfa Aesar. The syngas (1:1 mixture of CO/H₂)
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11 was purchased from Airgas. **Caution: Syngas is flammable. Carbon monoxide is toxic and all**
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13 **hydroformylation reactions should be carried out in a well ventilated fume hood.** All reagents from
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15 commercial sources were used as received. Flash chromatography was performed with silica gel from
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17 American International Chemical, Inc. (40-63 Micron). New compounds (**2** and the synthetic **1**) were
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19 characterized by ¹H, ¹³C, and ¹⁹F NMR, IR spectroscopy and high resolution mass spectroscopy (see the
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21 Supporting Information for copies of NMR spectra).
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29 **(S)-1,1,1-trifluoro-2-methyl-3-oxopropan-2-yl acetate (2).** In a 2 mL reaction vial (from HEL Inc., made
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31 for the CAT24 reactor), 3,3,3-trifluoroprop-1-en-2-yl acetate (**3**) (77 mg, 0.50 mmol), Rh(CO)₂acac (1.3 mg,
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33 0.0050 mmol) and (*R,R*)-QuinoxP* (2.5 mg, 0.0075 mmol) were dissolved in anhydrous toluene (0.10 mL).
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35 The reaction vial was placed in a HEL-CAT24 reactor, which was pressurized with 10 bar of CO and H₂ (1:1),
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37 and heated to 90 °C while stirring at 700 rpm. The reaction was stopped after 20 h by cooling the reactor in an
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39 ice bath for 15 min followed by slowly venting the system. The mixture was analyzed by chiral GC. The
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41 product was purified by flash chromatography (pentane/Et₂O, 100:1 to 4:1 gradient elution) to afford the title
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43 compound (31 mg, 34%; material loss due to volatility) as a colorless oil. Enantiomeric excess (92%) was
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45 determined by chiral GC analysis [CP Chirasil-Dex CD, 25 m × 0.25 mm × 0.25 mm, flow rate 3.5 mL/min,
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47 method: ramp from 50 °C to 130 °C at 2.0 °C/min, 130 °C for 5 min: (*S*) *t*_r = 4.0 min, (*R*) *t*_r = 4.3 min)]; [α]_D²⁵
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49 +62 (c 0.42, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 9.51 (quasi-d, *J* = 1.0 Hz, 1H), 2.23 (s, 3H), 1.68 (s, 3H);
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¹³C NMR (150 MHz, CDCl₃) δ 190.5 (d, *J* = 6.0 Hz), 169.3 (s), 122.5 (q, *J* = 283.5 Hz), 82.2 (q, *J* = 28.5 Hz), 20.6 (s), 13.8 (t, *J* = 31.5 Hz); ¹⁹F NMR (282 MHz, CDCl₃) δ -77.1 (s, 3F); IR (thin film) 2965, 1762, 1734, 1653, 1457, 1387, 1303, 1237, 728, 668 cm⁻¹; HRMS (DART, TOF) *m/z* [M + H]⁺ calcd for C₆H₈F₃O₃: 185.0426, found 185.0428.

(*S*)-2-Trifluoromethyl lactic acid (1). *Small scale synthesis:* In a 2 mL reaction vial (from HEL Inc., made for the CAT24 reactor), 3,3,3-trifluoroprop-1-en-2-yl acetate (**3**) (154 mg, 1.0 mmol), Rh(CO)₂acac (2.6 mg, 0.010 mmol) and (*R,R*)-QuinoxP* (8.4 mg, 0.025 mmol) were dissolved in anhydrous toluene (1.5 mL). The reaction vial was placed in a HEL-CAT24 reactor, which was pressurized with 10 bar of CO and H₂ (1:1), and heated to 85 °C while stirring at 700 rpm. The reaction was stopped after 8 h by cooling the reactor in an ice bath for 15 min followed by careful venting of the system. The mixture was analyzed by chiral GC. A solution of sodium chlorite (141 mg of commercial 80 w%, 1.25 mmol) in pH 3.5 buffer (2.0 mL) was added dropwise to the combined solution of the crude AHF reaction mixture and 2-methyl-2-butene (2.0 M in THF, 5.0 mL, 10.0 mmol) in *tert*-butyl alcohol (5.0 mL) at room temperature. The reaction progress was monitored by TLC. After 10 h, NaOH (0.40 g) was added and the mixture was stirred for 3 h. At this time, aqueous HCl (3 M) was added dropwise to the mixture until pH = 1. The layers were separated and the aqueous layer was extracted with EtOAc (20 mL × 5). The combined organic layers were concentrated and the crude product was isolated by flash chromatography (hexanes/EtOAc, 4:1 to 0:100 gradient elution) as a yellowish crystal. Rinsing the crude product with cold pentane (0 °C, 2.0 mL × 2, removed by decanting) afforded **1** (73 mg, 46%, two steps) as white crystals: The absolute configuration was later confirmed as (*S*) by converting it to its methyl ester; mp = 101–104 °C; [α]_D²⁵ -687 (c 0.47, MeOH); ¹H NMR (600 MHz, MeOD-*d*₄) δ 1.54 (quasi-q, *J* = 0.6 Hz, 3H);

¹³C NMR (150 MHz, MeOD-*d*4) δ 172.4 (s), 125.9 (q, *J* = 283.5 Hz), 76.1 (q, *J* = 28.5 Hz), 20.4 (q, *J* = 1.5 Hz); ¹⁹F NMR (282 MHz, MeOD-*d*4) δ -81.4 (s, 3F); IR (thin film) 3412, 1735, 1458, 1291, 1169, 1102 cm⁻¹; HRMS (ESI, TOF) *m/z* [M - H]⁺ calcd for C₄H₄F₃O₃: 157.0113, found 157.0116.

Larger scale synthesis of 1: In a Parr reactor (model# 4564), 3,3,3-trifluoroprop-1-en-2-yl acetate (**3**) (1.54 g, 10.0 mmol), Rh(CO)₂acac (10.6 mg, 0.041 mmol) and (*R,R,S,S*)-DuanPhos (22.1 mg, 0.058 mmol) were dissolved in anhydrous toluene (3.0 mL). The reactor was pressurized with 26 bar of CO and H₂ (1:1), and heated to 110 °C (the pressure increased to 31 bar) while stirring at 700 rpm. The reaction was stopped after 18 h (the pressure had decreased to 23 bar) by cooling the reactor in an ice bath for 15 min followed by slowly venting the system. The mixture was analyzed by chiral GC. A solution of sodium chlorite (1.41 g of commercial 80 w%, 12.5 mmol) in pH 3.5 buffer (20 mL) was added dropwise to the combined solution of the crude AHF reaction mixture and 2-methyl-2-butene (2.0 M in THF, 50 mL, 100 mmol) in *tert*-butyl alcohol (50 mL) at room temperature. The reaction progress was monitored by TLC. After 10 h, NaOH (4.0 g) was added and the mixture was stirred for 3 h. At this time, aqueous HCl (3 M) was added dropwise to the mixture until pH = 1. The layers were separated and the aqueous layer was extracted with EtOAc (200 mL × 5). The combined organic layers were concentrated and the crude product was isolated by flash chromatography eluting with hexanes/EtOAc (2:1) as a yellowish crystal. Rinsing the crude product with cold 4:1 pentane/CH₂Cl₂ mixture (0 °C, 10 mL × 2, removed by decanting) afforded **1** (0.82 g, 52%, two steps) as white crystals.

Determination of the absolute configuration of the aldehyde product. A combination of methanol (13 μL, 0.32 mmol), DMAP (1.0 mg, 0.0082 mmol) and EDCI (15 mg, 0.078 mmol) was added to the solutions of

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4 racemic, (*R*)- and synthetic 2-trifluoromethyl lactic acid (**1**) (10 mg each, 0.063 mmol) in CH₂Cl₂ (2.0 mL
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6 each). The solutions were stirred for 2 h at room temperature and monitored by TLC and GC. Each reaction
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8 mixture was filtered through a thin layer of silica gel, and the filtrate was analyzed by chiral GC [CP
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10 Chirasil-Dex CD, 25 m × 0.25 mm × 0.25 mm, flow rate 3.5 mL/min, method: ramp from 50 °C to 130 °C at
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12 4.0 °C/min, 130 °C for 25 min: (*S*) *t_r* = 10.7 min, (*R*) *t_r* = 10.9 min)]; the absolute configuration of the synthetic
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14 sample of **1** was determined as (*S*) with an enantiomeric excess of >99%.
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24 AUTHOR INFORMATION

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33 Notes

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36 The authors declare no competing financial interest.
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48 manuscript.
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53 ASSOCIATED CONTENT

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4 **Supporting Information.** Copies of ^1H and ^{13}C NMR spectra, and chiral GC traces. This material is available free
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7 of charge via the Internet at <http://pubs.acs.org>.
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