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Kinetic resolution of fluorinated propargyl alcohols by lipase-catalyzed enantioselective transesterification

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ABSTRACT

In order to obtain optically active fluorinated propargyl alcohols, a lipase-catalyzed kinetic resolution has been carried out. The effect of lipase types, organic solvents, reaction temperature, and acyl donors was examined in the lipase-catalyzed transesterification of 1,1,1-trifluoro-4-phenyl-3-butyn-2-ol. Various enantiomerically pure fluorinated propargyl alcohols have been successfully prepared in good enantiomeric excess (>84%) by Novozym 435-catalyzed transesterification with vinyl butanoate at 60 °C in *n*-hexane. In some cases, the enantiomeric purities were excellent (>99% ee).

1. Introduction

Optically active propargyl alcohols are important building blocks for various natural products and biologically active compounds such as prostaglandins, steroids, and carotenoids.[1] For example, 1-methyl propargyl alcohols are key intermediates for (*R*)-(+)-*N*-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-*N*-hydroxyurea (A-79175), a second generation 5-lipoxygenase inhibitor, which treats inflammatory and allergic disorders.[2] Chiral propargyl alcohols have been prepared by various approaches including asymmetric reduction, asymmetric 1,2-addition, [2,3]-sigmatropic rearrangement, and kinetic resolution.[3] Recently, fluorinated compounds have been attracting attention in various areas, particularly in pharmaceutical research, due to their interesting biological and physical properties. Nowadays, fluoro-organic compounds are routinely synthesized in the pharmaceutical industry.[4] In this respect, a facile and efficient synthesis of chiral fluorinated propargyl alcohols is becoming more important. So far, several methods have been developed for the synthesis of optically active fluorinated propargyl alcohols.[5]

Due to their excellent enantioselectivity, lipases have been widely employed for the synthesis of various chiral compounds including fluorinated alkanols.[6] For example, we succeeded in preparing enantiomerically pure alkyl lactates and halogenated phenyl 2-hydroxypropanones in high yields and enantiopurities by lipase-catalyzed transesterification in organic solvents.[7] Although the lipase-catalyzed kinetic resolution of optically active fluorinated propargyl alcohols has been performed by hydrolysis of the corresponding esters so far, the enantiomeric purity was low (less than 67% ee).[8] Herein, we report on lipase-catalyzed transesterification for the kinetic resolution of various fluoromethyl propargyl alcohols.

2. Results and discussion

First, we screened commercially available lipases for the transesterification of 1,1,1-trifluoro-4-phenyl-3-butyn-2-ol *rac*-**1a** with vinyl butanoate **2a** in *n*-hexane at 30 °C for 12 h. This revealed that the transesterification reaction occurred only for three different lipases. Lipozyme IM (immobilized lipase from *Rhizomucor miehei*) and Lipase AK (free lipase from *Pseudomonas fluorescence*) showed the catalytic activity (yields) but no stereoselectivity. Novozym 435 (immobilized lipase B from *Candida antarctica*), which was successfully used for the kinetic resolution of racemic propargyl alcohols,[3c,d] exhibited the highest reactivity for *rac*-**1a**. From these results, Novozym 435 was chosen as a catalyst for the transesterification of fluorinated propargyl alcohols.

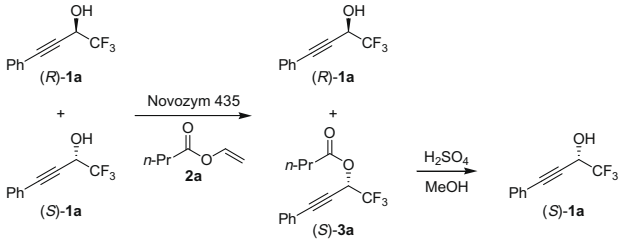

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Table 1
Novozym 435-catalyzed transesterification of *rac*-**1a** in various organic solvents[a]

Entry	Solvent	Time (h)	GC yield (%) of the remaining **1a**		% ee[c] of the isolated **1a**		*E*
			(*R*)-**1a**	(*S*)-**1a**	(*R*)-**1a**	(*S*)-**1a**[d]	
1	*n*-Hexane	35[b]	49	0	>99	98	>200
2	Et_2O	66[b]	49	0	>99	96	194
3	*t*-BuOMe	72[b]	49	0	>99	98	>200
4	THF	72	50	43	8	>99	>200
5	1,4-Dioxane	72	50	37	15	>99	>200
6	CH_2Cl_2	72	50	13	59	>99	>200
7	Toluene	42[b]	49	0	>99	95	146

[a] Reaction conditions: *rac*-**1a** (0.5 mmol), **2a** (1 mmol), and Novozym 435 (25 mg) in various organic solvents (1 mL) were shaken at 30 °C.
[b] The time required for a 50% conversion.
[c] Determined by GC analysis.
[d] Isolated after the hydrolysis of (*S*)-**3a**.

Novozym 435-catalyzed transesterification of *rac*-**1a** with **2a** was then conducted in various organic solvents (Eq. 1 and Table 1). In *n*-hexane, diethyl ether, *t*-BuOMe and toluene, enzymatic transesterification of *rac*-**1a** proceeded with excellent yields and ees (entries 1, 2, 3, and 7). However, the time required for 50% conversion in *n*-hexane (35 h) was shorter than in diethyl ether (66 h) in *t*-BuOMe (72 h) and in toluene (42 h). When the other solvents (THF, dioxane, and CH_2Cl_2) were used as a reaction medium, the conversion did not reach 50% within 72 h, and consequently the ee of (*R*)-**1a** was very low (entries 3–6).

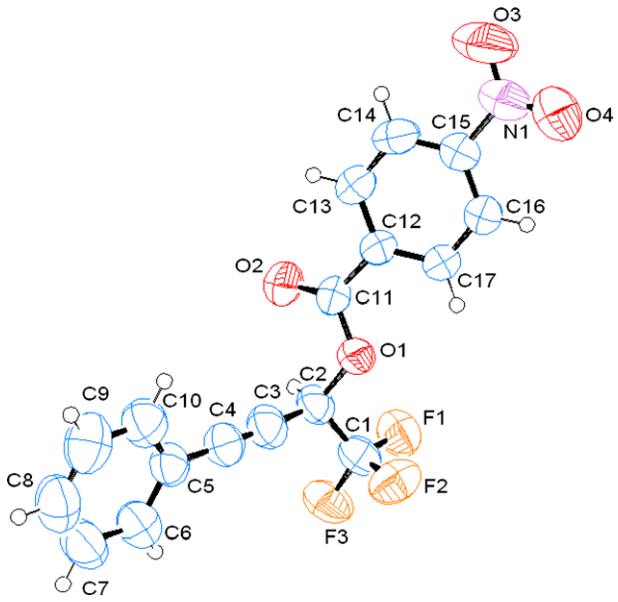
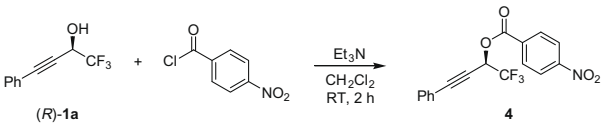


Figure 1. ORTEP depiction of the solid-state molecular structure of **4**.

As shown in Table 1, (*S*)-**1a** was preferably acylated, which followed Kazlauskas's rule.[9] In the case of **1a**, the trifluoromethyl group was considered as a smaller part when compared with the phenylethynyl group. To determine the absolute configuration of **1a**, *p*-nitrobenzoylated **4** was synthesized from *p*-nitrobenzoyl chloride and (*R*)-**1a** (Eq. 2), and characterized by X-ray crystallography (Fig. 1). During the synthesis of **4**, no racemization occurred, which is supported by experimental results of the hydrolysis product of **4** (>99% ee).



(2)

It is known that Novozym 435 can be used at high temperatures for many hours without any significant loss in activity.[10] The reaction temperature effect on the Novozym 435-catalyzed transesterification of *rac*-**1a** with vinyl butanoate in *n*-hexane was examined (Table 2). When the temperature was increased from 30 to 60 °C, the time taken to reach 50% conversion was shortened, indicating that the reaction rate was enhanced. Furthermore, the reaction

Table 3
Novozym 435-catalyzed transesterification of *rac*-**1a** with various vinyl alkanoates[a]

Entry	R	Time[b] (h)	Isolated yield (%)		% ee[d]		*E*
			(*R*)-**1a**	(*S*)-**1a**[c]	(*R*)-**1a**	(*S*)-**1a**	
1	Me **2b**	72	41	31	67	93	94
2	Et **2c**	14	50	42	>99	98	146
3	*n*-Pr **2a**	9	45	49	>99	95	146

[a] Reaction conditions: *rac*-**1a** (0.5 mmol), vinyl alkanoates **2** (1 mmol), and Novozym 435 (25 mg) in *n*-hexane (1 mL) were shaken at 60 °C.
[b] The time required for 50% conversion.
[c] Isolated after the hydrolysis of (*S*)-**3**.
[d] Determined by GC analysis.

Table 2
The temperature effect on the enzymatic transesterification of *rac*-**1a**[a]

Entry	Temp (°C)	Time[b] (h)	Isolated yield (%)			% ee[c]		*E*
			(*R*)-**1a**	(*S*)-**3a**	(*S*)-**1a**[c]	(*R*)-**1a**	(*S*)-**1a**[d]	
1	30	35	49	50	48	>99	98	>200
2	40	23	49	49	48	>99	99	>200
3	50	14	48	47	47	>99	99	>200
4	60	9	45	52	49	>99	95	146

[a] Reaction conditions: *rac*-**1a** (0.5 mmol), **2** (1 mmol), and Novozym 435 (25 mg) in *n*-hexane (1 mL) were shaken at various temperatures.
[b] The time required for 50% conversion.
[c] Determined by GC analysis.
[d] Isolated after the hydrolysis of (*S*)-**3a**.

Table 4
The transesterification of various fluorinated propargyl alcohols *rac*-**1** with vinyl butanoate catalyzed by Novozym 435[a]

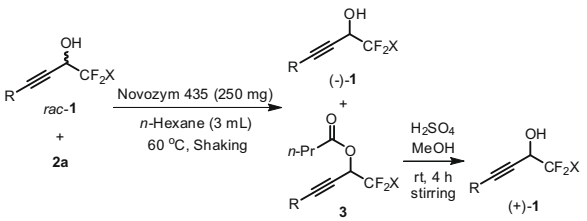
Entry		R	X	Time[b] (h)	GC area (%)		Isolated yield (%)			% ee		$[\alpha]_D$[d]		*E*
					(−)-**1**	**3**	(−)-**1**	**3**	(+)-**1**[c]	(−)-**1**	(+)-**1**[c]	(−)-**1**	(+)-**1**	
1	**1a**[e]	Ph	F	11	39	61	46	49	46	98	91	−6.8[f]	7.2	67
2	**1b**[g,h]	Ph	Cl	48	40	60	49	45	41	98	91	−18.0	14.6	67
3	**1c**[g,h]	Ph	Br	96	45	55	47	45	40	84	96	−15.5	17.3	194
4	**1d**[e]	Cyclohexyl	F	6	42	58	49	49	45	>99	96	−1.9	2.7	194
5	**1e**[e]	*n*-Hexyl	F	5	42	58	46	48	42	>99	96	−2.8	3.6	194
6	**1f**[e]	*n*-Butyl	F	5	37	63	38	46	26	>99	>99	−2.9	2.3	>200
7	**1g**[e]	*n*-Propyl	F	7	43	57	35	48	24	97	98	−2.3	2.2	>200

[a] Reaction conditions: *rac*-**1** (5 mmol), vinyl butanoate (10 mmol), and Novozym 435 (250 mg) in *n*-hexane (3 mL) were shaken at 60 °C.
[b] The time required for 50% conversion.
[c] Isolated after hydrolysis of **3**.
[d] *c* = 0.02, methanol.
[e] Determined by GC analysis (Rt™-βDEXcst column).
[f] $[\alpha]_D$ of (*R*)-**1a** was −6.8 unlike the literature.[5a]
[g] Determined by LC analysis (Chiralcel OJ-H column).
[h] Five hundred milligrams of Novozym 435 were used.

temperature had little effect on the enantioselectivity toward (*R*)-**1a**, as shown in Table 2.

In order to investigate the effects of the chain length of vinyl alkanoates, Novozym 435-catalyzed transesterifications of *rac*-**1a** were carried out with vinyl acetate **2b**, propionate **2c**, or butanoate **2a** at 60 °C in *n*-hexane. Table 3 shows that increasing the chain length of vinyl alkanoate from vinyl acetate to vinyl butanoate improved the reaction rate and ee value of Novozym 435-catalyzed transesterification. The enantioselectivity study of Novozym 435 revealed that the activity of the lipase increased when increasing the acyl chain length from ethyl acetate (C_2) to ethyl caproate (C_6) in the transesterification with butanol in cyclohexane.[11]

Finally, the kinetic resolution of various fluorinated propargyl alcohols (*rac*-**1**) by Novozym 435 was conducted at 60 °C in *n*-hexane (Eq. 3 and Table 4). The acylated products, (*R*)- and (*S*)-**3** were not successfully separated under various GC or HPLC conditions. Therefore, the ee of **3** was determined by using the hydrolysis products of **3**. When the F atom was replaced with the larger Cl and Br atoms, the time required to reach 50% conversion was considerably prolonged (entries 1–3). The substitution of other groups (cyclohexyl, *n*-hexyl, *n*-butyl, and *n*-propyl) for the phenyl group decreased the reaction time from 11 h to 5–7 h and improved the ee of the product from 91% to 96–>99% as shown in Table 4 (entries 1 and 4–7). Thus, we succeeded in obtaining enantiomerically pure fluorinated propargyl alcohols (+)/(-)-**1** in high ee (>91%) except for (−)-**1c**.



(3)

3. Conclusions

The kinetic resolution of various fluorinated propargyl alcohols was performed by a lipase-catalyzed transesterification with vinyl alkanoate in organic solvents. When the reaction was carried out with vinyl butanoate in *n*-hexane at 60 °C using Novozym 435 (immobilized lipase B from *C. antarctica*), racemic fluorinated propargyl alcohols were efficiently resolved in good enantiopurities (>84% ee). In some cases, the enantiomeric purities were excellent (>99% ee).

4. Experimental

4.1. General

All chemicals were purchased from Sigma, Aldrich, Fluka, and TCI. The lipases screened were as follows: *C. antarctica* lipase B, immobilized (Novozym 435, Novozymes); *R. miehei* lipase, immobilized (Lipozyme IM, Novozymes); *Aspergillus niger* lipase, free (Lipase A, Amano); *Burkholderia cepacia* lipase, free (Lipase PS, Amano); *B. cepacia* lipase, immobilized on ceramic (Lipase PS-C, Amano); *B. cepacia* lipase, immobilized on diatomite (Lipase PS-D, Amano); *Candida rugosa* lipase, free (Lipase AY, Amano); *Mucor javanicus* lipase, free (Lipase M, Amano); *Penicillium camembertii* lipase, free (Lipase G, Amano); *P. fluorescence* lipase, free (Lipase AK, Amano); *Rhizopus oryzae* lipase, free (Lipase F-AP 15, Amano); *C. rugosa* lipase, free (Sigma); wheat germ lipase, free (Sigma); *C. rugosa* lipase, free (Lipase OF, Meito Sangyo). The conversion and ee of the substrates **1** were analyzed by GC or HPLC. GC analysis was conducted with a Young-Lin M600D equipped with a flame ionization detector using Rt™-βDEXcst (30 m × 0.25 mm, Restek) and nitrogen as a column and carrier gas, respectively. The injector and detector temperatures were 210 °C and 230 °C, respectively. HPLC analysis was performed with a Young-Lin M930 pump system connected to a Young-Lin M720 absorbance detector. Separations were carried out over a Chiralcel OJ-H (250 mm × 4.6 mm, Daicel Chemical Industries) using *n*-hexane/isopropyl alcohol (10:1, v/v) at a flow rate of 0.6 mL/min and monitored at 254 nm. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded in ppm (δ) on a Varian Gemini 300 (300 MHz) and a Bruker AM-500 (125 MHz) using $CDCl_3$ as solvent, respectively. IR spectra and Mass spectra were obtained on a Shimadzu IR-435 spectrometer and a Varian GC/MS 1220L, respectively.

4.2. Synthesis of the substrates (fluoromethyl propargyl alcohols)

4.2.1. Typical procedure

The fluoromethyl propargyl alcohols were obtained by reducing fluoroalkyl alkynyl ketones, which were synthesized by the reaction of lithiated alkynes with alkyl fluoroacetate according to the method by Kitazume and Sato.[5c] To a mixture of alkyne (10.0 mmol) and anhydrous THF (30 mL) at −78 °C was added *n*-BuLi (10.0 mmol, 2.5 M solution) for 5 min. After 20 min stirring at −78 °C, ethyl fluoroacetate (10.0 mmol), boron trifluoride diethyl etherate (12.0 mmol), and anhydrous THF (20 mL) were added. After an additional 2 h of stirring, the reaction was

quenched with saturated NaCl solution (50 mL). The reaction medium was extracted with ethyl acetate (3 × 50 mL), dried over $MgSO_4$, and then concentrated under reduced pressure. The resulting ketone was purified by silica gel chromatography (*n*-hexane/ethyl acetate = 9:1). The ketone was dissolved in methanol (10 mL). To the solution was added $NaBH_4$ (10.0 mmol) slowly and the reaction solution was stirred for 30 min at room temperature. The mixture was quenched by adding brine (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Finally, purification by silica gel chromatography (*n*-hexane/ethyl acetate = 9:1) yielded the fluoromethyl propargyl alcohols.

4.2.2. 1,1,1-Trifluoro-4-phenyl-3-butyn-2-ol 1a

A yield of 76% (1.5 g) was obtained from phenyl acetylene (1.07 mL, 10.0 mmol) and ethyl trifluoroacetate (1.19 mL, 10.0 mmol) by using the typical procedure. The baseline separation of *rac*-**1a** was achieved by gas chromatography. The column temperature was maintained at 60 °C for 5 min, raised to 130 °C at 5 °C/min, kept at 130 °C for 30 min, and then increased to 180 °C at 5 °C/min. Under these conditions, the retention times were 52.49 min for (*R*)-**1a** and 52.06 min for (*S*)-**1a**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.50–7.47 (m, 2H), 7.42–7.31 (m, 3H), 4.96–4.87 (m, 1H), 2.48 (d, 1H, J = 8.37 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 132.2, 129.7, 128.6, 123.0 (q, CF_3, J = 279.9 Hz), 121.0, 88.1, 80.5, 63.1 (q, CH, J = 36.0 Hz); IR (neat) ν_{max}: 3370, 1273, 1187, 1077, 981, 838, 757, 690 cm^{-1}; MS (relative intensity) 200 (M^+, 52), 183 (3), 169 (3), 149(4), 131 (100), 103 (50), 77 (48).

4.2.3. 1-Chloro-1,1-difluoro-4-phenyl-3-butyn-2-ol 1b

A yield of 71% (4.6 g) was obtained from phenyl acetylene (3.29 mL, 30.0 mmol) and methyl chlorodifluoroacetate (3.16 mL, 30.0 mmol) by using the typical procedure. The baseline separation was achieved by HPLC analysis. The retention times were 16.92 min for (−)-**1b** and 18.74 min for (+)-**1b**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.51–7.46 (m, 2H), 7.39–7.28 (m, 3H), 4.94 (t, 1H, J = 6.3 Hz), 3.04 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 132.1, 129.5, 128.5, 127.4 (t, CF_2Cl, J = 295.0 Hz), 120.9, 88.2, 81.2, 69.8 (t, CH, J = 31.5 Hz); IR (neat) ν_{max}: 3370, 2238, 1491, 1201, 1177, 1011, 993, 952, 802, 690, 658 cm^{-1}; MS (relative intensity) 216 (M^+, 10), 199 (1), 181 (1), 131 (100), 114 (4), 85 (15), 77 (44).

4.2.4. 1-Bromo-1,1-difluoro-4-phenyl-3-butyn-2-ol 1c

A yield of 94% (3.6 g) was obtained from phenyl acetylene (1.65 mL, 15.0 mmol) and ethyl bromodifluoroacetate (1.90 mL, 15.0 mmol) by using the typical procedure. The baseline separation was achieved by HPLC analysis. The retention times were 22.84 min for (−)-**1c** and 24.39 min for (+)-**1c**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.49–7.46 (m, 2H), 7.39–7.28 (m, 3H), 4.75 (t, 1H, J = 6.5 Hz), 3.03 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 132.1, 129.3, 128.4, 122.1 (t, CF_2Br, J = 309.5 Hz), 120.9, 88.4, 81.5, 69.1 (t, CH, J = 29.5 Hz); IR (neat) ν_{max}: 3368, 2237, 1490, 1194, 1167, 1125, 1077, 1034, 922, 795, 690, 609 cm^{-1}; MS (relative intensity) 260 (M^+, 22), 164 (15), 149 (11), 131(100), 103 (60), 77 (55).

4.2.5. 4-Cyclohexyl-1,1,1-trifluoro-3-butyn-2-ol 1d

A yield of 64% (2.7 g) was obtained from cyclohexyl acetylene (2.58 mL, 20.0 mmol) and ethyl trifluoroacetate (2.38 mL, 20.0 mmol) by using the typical procedure. The baseline separation was achieved by GC analysis. The column temperature was maintained at 60 °C for 5 min, raised to 100 °C at 5 °C/min, kept at 100 °C for 40 min, and then increased to 180 °C at 5 °C/min. Under these conditions, the retention times were 65.33 min for (−)-**1d** and 65.10 min for (+)-**1d**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.67–4.64 (m, 1H), 2.88 (br s, 1H), 2.45–2.43 (m, 1H), 1.82–1.67 (m, 4H), 1.52–1.29 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 123.1 (q, CF_3, J = 279.8 Hz), 93.6, 72.3, 62.7(q, CH, J = 35.9 Hz), 32.0, 29.0, 25.9, 24.8; IR (neat) ν_{max}: 3370, 2933, 2858, 2240, 1450, 1352, 1273, 1163, 1055, 706 cm^{-1}; MS (relative intensity) 205 (M^+,1), 188 (2), 137 (38), 122 (2), 119 (19), 107 (32), 99 (3), 83 (14), 19 (40).

4.2.6. 1,1,1-Trifluoro-3-decyn-2-ol 1e

A yield of 60% (2.5 g) was obtained from 1-octyne (2.95 mL, 20.0 mmol) and ethyl trifluoroacetate (2.38 mL, 20.0 mmol) by using the typical procedure. The baseline separation was achieved by GC analysis. The column temperature was maintained at 60 °C for 5 min, raised to 100 °C at 5 °C/min, kept at 100 °C for 10 min, and then increased to 200 °C at 5 °C/min. Under these conditions, the retention times were 35.19 min for (−)-**1e** and 35.04 min for (+)-**1e**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.69–4.62 (m, 1H), 2.71 (br s, 1H), 2.24 (t, 2H, J = 7.0 Hz), 1.56–1.51 (m, 2H), 1.38–1.27 (m, 6H), 0.89 (t, 3H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 123.1 (q, CF_3, J = 279.9 Hz), 89.9, 72.3, 62.8(q, CH, J = 35.8 Hz), 31.4, 28.6, 28.2, 22.7, 18.7, 14.2; IR (neat) ν_{max}: 3370, 2957, 2934, 2862, 2240, 1468, 1354, 1274, 1053, 699 cm^{-1}; MS (relative intensity) 209 (M^+,1), 139 (8), 109 (18), 99 (4), 85 (1), 69 (68), 41 (100).

4.2.7. 1,1,1-Trifluoro-3-octyn-2-ol 1f

A yield of 50% (3.6 g) was obtained from 1-hexyne (4.60 mL, 40.0 mmol) and ethyl trifluoroacetate (4.76 mL, 40.0 mmol) by using the typical procedure. The baseline separation was achieved by GC analysis. The column temperature was maintained at 60 °C for 5 min, raised to 100 °C at 5 °C/min, kept at 100 °C for 10 min, and then increased to 200 °C at 5 °C/min. Under these conditions, the retention times were 29.90 min for (−)-**1f** and 30.79 min for (+)-**1f**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.70–4.64 (m, 1H), 2.30–2.25 (m, 3H), 1.59–1.39 (m, 4H), 0.94 (t, 3H, J = 7.20 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 122.8 (q, CF_3, J = 279.8 Hz), 89.6, 72.1, 62.5 (q, CH, J = 36.0 Hz), 30.0, 21.8, 18.2, 13.5; IR (neat) ν_{max}: 3370, 2962, 2938, 2876, 2240, 1354, 1274, 1056, 1042, 699 cm^{-1}; MS (relative intensity) 179 (M^+, 2), 165 (2), 147 (19), 111 (100), 93 (46), 81 (36), 71 (47), 55 (45).

4.2.8. 1,1,1-Trifluoro-3-heptyn-2-ol 1g

A yield of 59% (3.9 g) was obtained from 1-pentyne (3.94 mL, 40.0 mmol) and ethyl trifluoroacetate (4.76 mL, 40.0 mmol) by using the typical procedure. The baseline separation was achieved by GC analysis. The column temperature was maintained at 60 °C for 5 min, raised to 100 °C at 5 °C/min, kept at 100 °C for 10 min, and then increased to 200 °C at 5 °C/min. Under these conditions, the retention times were 26.38 min for (−)-**1g** and 25.78 min for (+)-**1g**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.69–4.62 (m, 1H), 2.71 (br s, 1H), 2.24 (t, 2H, J = 7.0 Hz), 1.56–1.51 (m, 2H), 1.38–1.27 (m, 6H), 0.89 (t, 3H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 122.9 (q, CF_3, J = 279.8 Hz), 89.3, 72.2, 62.5 (q, CH, J = 35.4 Hz), 21.5, 20.5, 13.3; IR (neat) ν_{max}: 3370, 2970, 2240, 1356, 1275, 1160, 1056, 700 cm^{-1}; MS (relative intensity) 167 (M^+, 40), 149 (100), 137 (4), 129 (10), 113 (17), 97 (90), 83 (60), 71 (41), 57 (56).

4.3. Synthesis of the products (fluoromethyl propargyl esters)

4.3.1. Typical procedure

A mixture of fluoromethyl propargyl alcohols (1.0 mmol) and triethylamine (1.5 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL) at 0 °C. After 20 min stirring at 0 °C, butanoyl chloride (2.0 mmol) was added in the solution, and the reaction mixture was stirred for 30 min at room temperature. The reaction was quenched with saturated NaCl solution (20 mL) and extracted with ethyl acetate (3 × 50 mL). The extract was dried over $MgSO_4$, concentrated under reduced pressure, and then purified by silica gel chromatography (hexane/ethyl acetate = 9:1).

4.3.2. 1,1,1-Trifluoro-4-phenylbut-3-yn-2-yl butanoate 3a

A yield of 99% (268 mg) was obtained from 1,1,1-trifluoro-4-phenyl-3-butyn-2-ol (200 mg, 1.0 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.51–7.50 (m, 2H), 7.48–7.31 (m, 3H), 6.11 (q, CH, J = 5.85 Hz), 2.45 (t, 2H, J = 7.35 Hz), 1.75 (h, 2H, J = 8.28 Hz), 0.99 (t, 3H, J = 7.38 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.4, 132.4, 129.8, 128.6, 123.2 (q, CF_3, J = 278.8 Hz), 121.0, 88.1, 78.0, 61.8 (q, CH, J = 37.3 Hz), 35.8, 18.5, 13.6; IR (neat) ν_{max}: 2970, 2940, 2240, 1763, 1361, 1274, 1256, 1101, 1053, 757, 690 cm^{-1}; MS (relative intensity) 270 (M^+, 18), 241 (4), 228 (8), 133 (23), 85 (25), 71 (100).

4.3.3. 1-Chloro-1,1-difluoro-4-phenylbut-3-yn-2-yl butanoate 3b

A yield of 36% (61 mg) was obtained from 1-chloro-1,1-difluoro-4-phenyl-3-butyn-2-ol (128 mg, 0.6 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.52–7.48 (m, 2H), 7.39–7.34 (m, 3H), 6.16 (t, 1H, J = 7.0 Hz), 2.46 (t, 2H, J = 7.3 Hz), 1.74 (h, 2H, J = 7.4 Hz), 1.00 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.4, 132.4, 129.8, 128.6, 125.7 (t, CF_2Cl, J = 294.5 Hz), 121.1, 88.3, 78.9, 66.4 (t, CH, J = 32.4 Hz), 35.9, 18.5, 13.6; IR (neat) ν_{max}: 2969, 2939, 2240, 1760, 1207, 1179, 1147, 1101, 1055, 959, 926, 757, 690 cm^{-1}; MS (relative intensity) 286 (M^+, 46), 251 (10), 216 (11), 198 (51), 164 (100), 131 (31), 105 (27), 71 (100).

4.3.4. 1-Bromo-1,1-difluoro-4-phenylbut-3-yn-2-yl butanoate 3c

A yield of 53% (30 mg) was obtained from 1-bromo-1,1-difluoro-4-phenyl-3-butyn-2-ol (44 mg, 0.17 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.52–7.49 (m, 2H), 7.39–7.32 (m, 3H), 6.14 (t, 1H, J = 7.8 Hz), 2.46 (t, 2H, J = 7.3 Hz), 1.74 (h, 2H, J = 7.4 Hz), 1.00 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.3, 132.4, 129.8, 128.6, 121.1, 119.1 (t, CF_2Br, J = 307.8 Hz), 88.5, 79.3, 67.7 (t, CH, J = 29.9 Hz), 35.9, 18.4, 13.7; IR (neat) ν_{max}: 2968, 2938, 2238, 1760, 1243, 1198, 1102, 1078, 1052, 940, 922, 757, 690 cm^{-1}; MS (relative intensity) 330 (M^+, 4), 262 (6), 251 (43), 242 (9), 180 (20), 164 (71), 129 (12), 114 (18), 71 (100).

4.3.5. 4-Cyclohexyl-1,1,1-trifluorobut-3-yn-2-yl butanoate 3d

A yield of 28% (38 mg) was obtained from 4-cyclohexyl-1,1,1-trifluoro-3-butyn-2-ol (103 mg, 0.5 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.91–5.87 (m, 1H), 2.47 (m, 1H), 2.43 (t, 2H, J = 7.34 Hz), 1.81–1.78 (m, 2H), 1.78–1.69 (m, 2H), 1.51–1.36 (m, 4H), 1.36–1.34 (m, 4H), 1.00 (t, 3H, J = 7.38 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.2, 121.9 (q, CF_3, J = 278.6 Hz), 93.4, 69.4, 61.4 (q, CH, J = 37.3 Hz), 35.6, 31.8, 28.7, 25.7, 24.5, 18.2, 13.4; IR (neat) ν_{max}: 2936, 2858, 1763, 1358, 1274, 1244, 1164, 1142, 1096, 1015, 934 cm^{-1}; MS (relative intensity) 276 (M^+, 3), 192 (3), 107 (3), 71 (100), 69 (6).

4.3.6. 1,1,1-Trifluorodec-3-yn-2-yl butanoate 3e

A yield of 42% (68 mg) was obtained from 1,1,1-trifluoro-3-decyn-2-ol (125 mg, 0.6 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.79–5.75 (m, 1H), 2.33 (t, 2H, J = 7.34 Hz), 2.18–2.15 (m, 2H), 1.63 (h, 2H, J = 7.39 Hz), 1.45 (p, 2H, J = 7.23 Hz), 1.32–1.28 (m, 2H), 1.27–1.19 (m, 4H), 0.90 (t, 3H, J = 7.40 Hz), 0.82 (t, 3H, J = 6.86 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.4, 122.2 (q, CF_3, J = 278.5 Hz), 90.0, 69.6, 61.6 (q, CH, J = 37.3 Hz), 35.8, 31.4, 28.5, 28.1, 22.7, 18.8, 18.5, 14.1, 13.6; IR (neat) ν_{max}: 2960, 2936, 2862, 1763, 1360, 1273, 1140, 1013 cm^{-1}; MS (relative intensity) 278 (M^+, 6), 256 (4), 236 (3), 213 (2), 207 (4), 161 (6), 149 (18), 137 (11), 123 (9), 111 (15), 97 (26), 81 (38), 71 (100).

4.3.7. 1,1,1-Trifluorooct-3-yn-2-yl butanoate 3f

A yield of 91% (137 mg) was obtained from 1,1,1-trifluoro-3-octyn-2-ol (108 mg, 0.6 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.85–5.83 (m, 1H), 2.40 (t, 2H, J = 7.38 Hz), 2.27–2.22 (m, 2H), 1.70 (h, 2H, J = 7.41 Hz), 1.55–1.35 (m, 4H), 0.97 (t, 3H, J = 7.44 Hz), 0.91 (t, 3H, J = 7.41 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.4, 122.2 (q, CF_3, J = 278.6 Hz), 90.0, 69.6, 61.6 (q, CH, J = 36.6 Hz), 35.8, 30.2, 22.0, 18.49, 18.47, 13.7, 13.6; IR (neat) ν_{max}: 2964, 2939, 2877, 1763, 1360, 1274, 1245, 1140, 1102, 1013, 933 cm^{-1}; MS (relative intensity) 250 (M^+, 1), 179 (1), 163 (1), 123 (1), 111 (1), 99 (1), 81 (1), 71 (100), 69 (3), 57 (1).

4.3.8. 1,1,1-Trifluorohept-3-yn-2-yl butanoate 3g

A yield of 77% (109 mg) was obtained from 1,1,1-trifluoro-3-heptyn-2-ol (100 mg, 0.6 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.85–5.83 (m, 1H), 2.40 (t, 2H, J = 7.35 Hz), 2.24–2.19 (m, 2H), 1.70 (h, 2H, J = 7.41 Hz), 1.59–1.52 (m, 2H), 0.98 (t, 3H, J = 7.35 Hz), 0.97 (t, 3H, J = 7.38 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.4, 122.2 (q, CF_3, J = 278.3 Hz), 89.8, 69.8, 61.6 (q, CH, J = 37.0 Hz), 35.8, 21.6, 20.7, 18.5, 13.6, 13.4; IR (neat) ν_{max}: 2969, 2941, 2879, 1763, 1361, 1273, 1245, 1140, 1010, 934 cm^{-1}; MS (relative intensity) 236 (M^+, 5), 216 (10), 207 (30), 194 (24), 165 (6), 149 (5), 127 (23), 120 (32), 101 (24), 71 (100).

4.4. Enzymatic transesterification of *rac*-1

To mixture of *rac*-**1** (5 mmol) and vinyl butanoate (10 mmol) in anhydrous *n*-hexane (3 mL) was added Novozym 435 (250 mg). The reaction mixture was shaken at 200 rpm at 60 °C. During the reaction, the samples were taken, and then subjected to GC/HPLC analysis to monitor the reaction. When a 50% conversion was monitored, the reaction mixture was filtered to remove Novozym 435. The filtrate was concentrated in vacuum, and then purified by silica gel chromatography (*n*-hexane/diethyl ether = 9:1) to provide the remaining (−)-**1** and **2**. To **2** in methanol (10 mL) was added H_2SO_4 (10.0 mmol) with stirring at room temperature for 4 h. The reaction mixture was quenched and neutralized with 2 M NaOH solution. The extraction with ethyl acetate, concentration, and purification of the reaction mixture offered (+)-**1**. Using an Auto Digital Polarimeter, the angle of rotation of **1** was measured from which the specific rotation $[\alpha]_D^{25}$ was obtained.

4.5. Synthesis of compound 4

Mixture of (*R*)-**1a** (0.38 mmol) and triethylamine (0.57 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL). After 30 min stirring at rt, *p*-nitrobenzoyl chloride (0.57 mmol) was added slowly into the solution, and the reaction mixture was stirred for 2 h at room temperature. The reaction was quenched with saturated NaCl solution (30 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The extract was washed with saturated $NaHCO_3$ solution and dried over $MgSO_4$, concentrated under reduced pressure, and then purified by silica gel chromatography (hexane/ethyl acetate = 9:1) to give a yellowish solid **4** (103 mg) in a 73% yield. mp 78–79 °C, $[\alpha]_D^{25}$ = +45.9 (*c* 0.01, CH_3OH), ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.34–8.32 (m, 5H), 7.53–7.50 (m, 2H), 6.39–6.32 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.5, 151.2, 133.5, 132.3, 131.4, 129.9, 128.5, 123.8, 121.8 (q, CF_3, J = 278.9 Hz), 120.4, 89.0, 77.3, 63.2 (q, CF_3, J = 37.6 Hz); IR (neat) ν_{max}: 2924, 2853, 2239, 1745, 1608, 1530, 1497, 1349, 1252, 1192, 1143, 1088 cm^{-1}; MS (relative intensity) 348.3 (M^+), 320.3, 282.3, 242.0, 193.2.

4.6. X-ray analysis of compound 4

Molecular formula: $C_{17}H_{10}F_3NO_4$, M_w = 349.26, Rhombohedral, T = 296 K, space group $R3$, Z = 9, a = 30.9135(12) Å, b = 30.9135(12) Å, c = 4.4600(2) Å, V = 3691.1(3) Å^3, d_{calcd} = 1.414 g cm^{-3}, F(0 0 0) = 1602, λ = 0.71073 Å (Mo Kα), μ = 0.123 mm^{-1}, Bruker SMART Apex II CCD diffractometer, θ range 1.32–28.35°,

22659 collected reflections, 4070 unique, full-matrix least-squares on F^2 (SHELXL97), $R_1 = 0.0350$, $wR_2 = 0.0754$, ($R_1 = 0.0955$, $wR_2 = 0.0951$ all data), goodness of fit = 0.971. Further details on the crystal structure are available on request from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK on quoting the depository number CCDC 715765.

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