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Optically active propargylic and allylic alcohols with a difluoromethyl group at the terminal carbon

Ling Xiao and Tomoya Kitazume *

Department of Bioengineering, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 226, Japan

Abstract: Enantioselective esterification of α-substituted propargylic alcohols was found to proceed very smoothly in the presence of a catalytic amount of lipase (Nobozym 435) to yield the corresponding (*R*)-alcohols and (*S*)-acetates with high enantiomeric excess. Further, the preparation of optically active propargylic and allylic alcohols with a difluoromethyl group at the terminal carbon is described. © 1997 Elsevier Science Ltd

Optically active difluoromethylated materials have been recognized as a quite important class of materials because of their interesting characteristics[1,2] and potential applicability to optical devices.[3] In particular, the utility of optically active propargylic alcohols and/or allylic alcohols with a CHF_2 group at the terminal carbon as synthetic intermediates for functionalized materials are attractive synthetic targets. Despite their utility, their preparation remains problematic in terms of the starting materials, availability of reagents, and synthetic strategies to obtain non-racemic materials.[4]

Accordingly, we have devoted our attention to the synthesis of optically active propargylic alcohols and allylic alcohols with a CHF_2 group at the terminal carbon. Our synthetic strategy to obtain the target materials is the use of chiral propargylic alcohols as key intermediates. Kinetic resolutions of propargylic alcohols, with a wide range of lipases [lipase PS (*Pseudomonas cepacia*, Amano Pharmaceutical Co. Ltd), lipase MY (*Candida rugosa*, Meito Sangyo Co. Ltd), lipase QL (*Alcaligenes* sp. Meito Sangyo Co. Ltd), Novozym 435 (*Candida antrarctica*, immobilized; Novo Nordisk Co. Ltd)] were examined. After several explorations of reaction conditions using *rac*-**1a**, we found that Novozym 435 in *n*-hexane with vinyl acetate gave acetylates (*S*) alcohol. As shown in Figure 1, by controlling the extent of hydrolysis conversion, either product or unreacted substrate would be obtained with high enantioselectivity.

Thus, this system allowed us to obtain the unreacted 4-heptyn-3-ol **1a** {$[\alpha]_D$ +24.8 (*c* 1.404, Et_2O); lit.[5] $[\alpha]_D^{25}$ +17.4 (*c* 3.0, dioxane), 85% ee}, with the (*R*) alcohol, 1-configuration (>98% ee) with 60% conversion, while 64% conversion of 1-octyn-3-ol **1b** affords (*S*)-**2b** in 54% ee and recovered (*R*)-1-octyn-3-ol **1b** {$[\alpha]_D$ +20.8 (*c* 1.000, Et_2O); lit.[5] $[\alpha]_D$ +20.5 (*c* 2.0, Et_2O)}, >99% ee) as shown in Scheme 1. In this reaction system, (*S*)-**2a** with 89% ee or (*S*)-**2b** with 54% ee was also isolated,

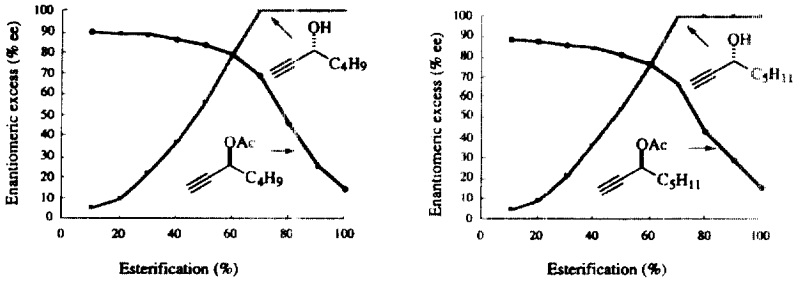
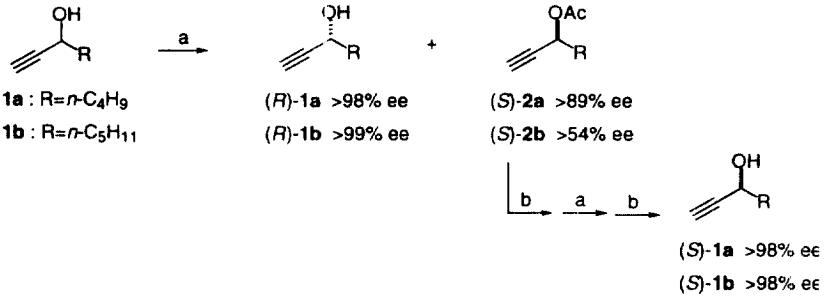


Figure 1. Dependence of enantiomeric excess on the esterification.

* Corresponding author. Email: tkitazum@bio.titech.ac.jp

which was resolved by further enzymatic esterification using the same conditions {(*S*)-**1a**, $[\alpha]_D$ −24.6 (*c* 1.248, Et_2O), >98% ee with 90% conversion; (*S*)-**1b** [$[\alpha]_D$ −20.0 (*c* 1.663 , Et_2O), >98% ee with 80% conversion; lit.[6] $[\alpha]_D$ −21.0 (*c* 1.0, Et_2O)}.



Scheme 1. (a) Novozym 435 (*Candida antarctica*), vinyl acetate, *n*-hexane; (b) K_2CO_3, MeOH.

Optically active propargylic alcohols protected with the *tert*-butyldimethylsilyl group containing a CHF_2 group at the terminal carbon were prepared by the literature method, in which the *O*-protected **1** was treated with a CF_2 carbene generated from CF_2HCl with acetylide (Scheme 2). The obtained propargylic alcohols were transformed into the corresponding 1,1-difluoro-2-alkyn-4-ols **3** by conventional methods (TsOH–MeOH). According to the literature procedure,[7] optically active propargylic alcohols with a difluoromethyl group at the terminal carbon were treated with Red-Al in toluene at −78°C to afford (*E*)-allylic alcohols in 86–92% yield. Further, (*Z*)-isomers were obtained when the reduction of substrate was performed between −30 and −20°C using half the amount of Lindlar catalyst (5 mg/1 mmol of substrate) compared to the literature method.[8] Optically active 1,1-difluoro-4-alkanols **6** were also prepared by the reduction of the propargylic alcohols using Pd–C/H_2 system.

Experimental

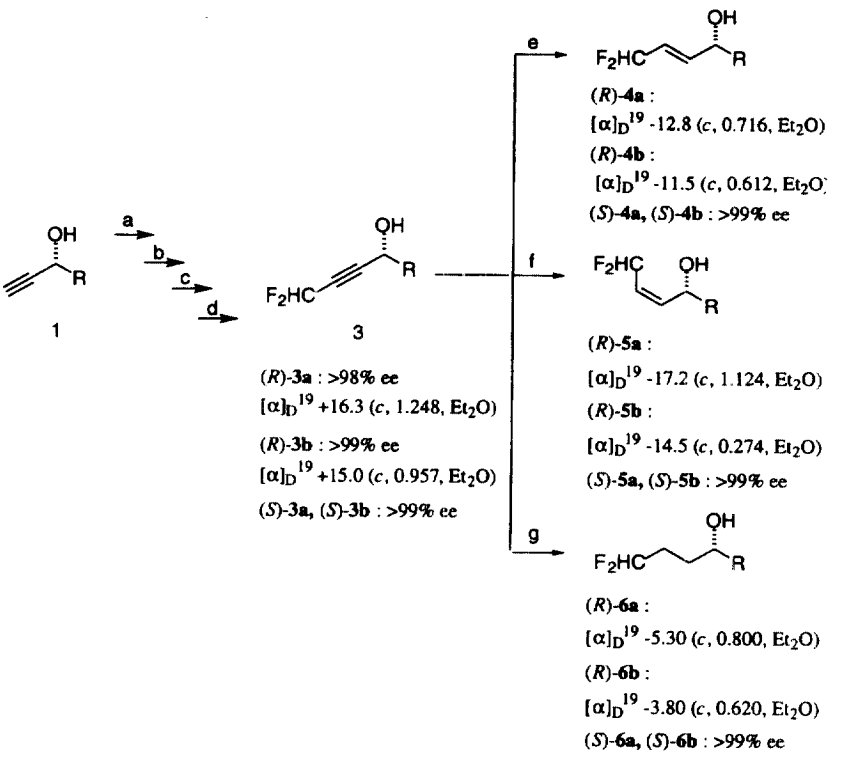
All commercially available reagents were used without further purification. Chemical shifts of ^1H (500 MHz) and ^{13}C (50 MHz) NMR spectra were recorded in ppm (δ) downfield from the following internal standards (Me_4Si, δ 0.00, or $CHCl_3$, δ 7.24). The ^{19}F (470 MHz) NMR spectra were recorded in ppm downfield from int. C_6F_6 in $CDCl_3$ using Varian VXR 500 instument. Coupling constants were reported in Hertz (Hz). Enantiomeric excess was determined by the diastereomeric excess of MTPA ester with NMR and/or GLC (column: URBON HR-20M on Chromosorb W, 30 m×3 mm).

Enantioselective esterification of propargyl alcohols

A solution of propargyl alcohol **1** (20 mmol), vinyl acetate (30 mmol) and Novozym 435 (*Candida antrarctica*, 1 g, 7000 u/g, Novo Nordisk Co. Ltd) in *n*-hexane (10 ml) was stirred for 3 h at 40°C. The residue was removed by filtration, the solvent was evaporated and then the conversion was determined by NMR integral intensity. The corresponding acetate and recovered alcohol were purified by column chromatography on silica gel, eluting with a mixture of hexane–ethyl acetate (6:1).

(R)-1,1-Difluoro-2-octyn-4-ol 3a

To a solution of *n*-BuLi (1.6 M in hexane, 0.75 ml, 1.2 mmol) in distilled THF (5 ml), 4-(*tert*-butyldimethylsilyl)oxy-1,1-difluoro-2-octyne (1 mmol) in THF (1 ml) was added at −78°C under a nitrogen atmosphere, and then stirred for 30 min at that temperature. A large excess of CHF_2Cl (gas) was bubbled through the above solution at −78°C, which was then stirred for 1.5 h at that temperature. After quenching with saturated NH_4Cl solution, oily materials were extracted with diethyl ether, and the extract was washed with water and brine, and dried over $MgSO_4$. On removal of the solvent, the crude material was purified by column chromatography on silica gel.



Scheme 2. (a) *TBS*-Cl, imidazole, DMF; (b) *n*-BuLi, THF, −78°C; (c) CHF_2Cl, THF, −78°C; (d) TsOH, MeOH; (e) Red-Al, toluene, −78°C; (f) Lindlar catalyst, H_2, *n*-hexane, −30 to −20°C; (g) 5% Pd–C, H_2, EtOH.

A solution of crude material and methanol (5 ml) in the presence of a catalytic amount of TsOH was stirred overnight at room temperature. After quenching with saturated $NaHCO_3$ solution, the solvent was removed. The resultant materials were diluted with diethyl ether (10 ml), and the ethereal solution was washed with saturated NH_4Cl, water and brine, and dried over $MgSO_4$. On removal of the solvent, the residue was purified by column chromatography on silica gel, eluting with hexane–ethyl acetate (4:1) to give compound (*R*)-**3a** in 78% yield {$[\alpha]_D^{19}$ +16.3 (*c* 1.248, Et_2O), >98% ee}.

^1H NMR ($CDCl_3$): δ 0.93 (3 H, t, *J*=7.3 Hz), 1.38 (2 H, m), 1.45 (2 H, m), 1.76 (2 H, m), 1.87 (1 H, d, *J*=5.6 Hz), 4.46 (1 H, m), 6.22 (1 H, dt, *J*=1.0, 54.7 Hz). ^{13}C NMR ($CDCl_3$): δ 13.84, 22.19, 26.96, 36.61, 61.94 (t, *J*=2.1 Hz), 75.86 (t, *J*=34.0 Hz), 89.85 (t, *J*=6.9 Hz), 103.57 (t, *J*=230.9 Hz). ^{19}F NMR ($CDCl_3$): δ 55.7 (dd, *J*=4.6, 53.4 Hz).

(R)-1,1-Difluoro-2-nonyn-4-ol ***3b***

In the above reaction, 4-*tert*-butyldimethylsilyloxy-1,1-difluoro-2-nonyne (1 mmol) was used, and then worked up similarly. (*R*)-1,1-Difluoro-2-nonyn-4-ol **3b** was purified by column chromatography on silica gel, eluting with hexane–diethyl ether (2:1) to give compound (*R*)-**3b** in 70% yield {$[\alpha]_D^{19}$ +15.0 (*c* 0.957, Et_2O), >99% ee}.

^1H NMR ($CDCl_3$): δ 0.90 (3 H, t, *J*=7.0 Hz), 1.20–1.80 (8 H, m), 1.90 (1 H, d, *J*=5.9 Hz), 4.46 (1 H, m), 6.22 (1 H, dt, *J*=1.0, 54.9 Hz). ^{13}C NMR ($CDCl_3$): δ 13.86, 22.41, 24.53, 31.24, 36.85 (t, *J*=1.8 Hz), 61.89 (t, *J*=2.4 Hz), 75.79 (t, *J*=34.1 Hz), 89.85 (t, *J*=7.1 Hz), 103.57 (t, *J*=232.1 Hz). ^{19}F NMR ($CDCl_3$): δ 55.7 (dd, *J*=4.6, 54.9 Hz).

(R)-(E)-1,1-Difluoro-2-octen-4-ol ***4a***

To a solution of Red-Al (3.4 M in toluene, 0.4 ml, 1.6 mmol) in toluene (5 ml), a solution of (*R*)-1,1-difluoro-2-octyn-4-ol **2** (0.5 mmol) in toluene (ml) was added at −78°C under a nitrogen atmosphere, and was then stirred for 5 h at that temperature. After quenching with 1 N HCl, oily materials were extracted with diethyl ether, and the extract was washed with brine and dried over $MgSO_4$. On removal of the solvent, the residue was purified by column chromatography on silica gel, eluting with hexane–ethyl acetate (4:1) to give (*R*)-(*E*)-1,1-difluoro-2-octen-4-ol **4a** in 86% yield {$[\alpha]_D^{19}$ −12.8 (*c* 0.716, Et_2O), >98% ee}.

^{1}H NMR ($CDCl_3$): δ 0.92 (3 H, t, *J*=7.0 Hz), 1.28–1.45 (4 H, m), 1.52–1.62 (3 H, m), 4.21–4.27 (1 H, m), 5.86 (1 H, dddt, *J*=1.5, 5.4, 8.5, 17.3 Hz), 6.11 (1 H, dt, *J*=5.6, 56.4 Hz), 6.12 (1 H, m). ^{13}C NMR ($CDCl_3$): δ 13.91, 22.48, 27.27, 36.40, 70.94, 114.73 (t, *J*=233.0 Hz), 122.41 (t, *J*=23.9 Hz), 141.52 (t, *J*=10.9 Hz). ^{19}F NMR ($CDCl_3$): δ 50.8 (ddq, *J*=3.1, 6.1, 56.5 Hz).

(R)-(E)-1,1-Difluoro-2-nonen-4-ol ***4b***

In the above reaction, (*R*)-1,1-difluoro-nonyn-4-ol **3b** (0.5 mmol) was used, and then worked up similarly. (*R*)-(*E*)-1,1-Difluoro-2-nonen-4-ol **4b** was purified by column chromatography on silica gel, eluting with hexane–diethyl ether (2:1) to give compound **4b** in 92% yield. {$[\alpha]_D^{19}$ −11.5 (*c* 0.612, Et_2O), >99% ee}.

^{1}H NMR ($CDCl_3$): δ 0.89 (3 H, t, *J*=6.8 Hz), 1.20–1.70 (9 H, m), 4.21–4.27 (1 H, m), 5.86 (1 H, dddt, *J*=1.5, 5.4, 8.5, 15.4 Hz), 6.11 (1 H, dt, *J*=5.6, 56.4 Hz), 6.12 (1 H, m). ^{13}C NMR ($CDCl_3$): δ 13.93, 22.49, 24.82, 31.58, 36.65 (t, *J*=1.9 Hz), 70.93, 114.76 (t, *J*=234.1 Hz), 122.40 (t, *J*=24.2 Hz), 141.56 (t, *J*=11.0 Hz). ^{19}F NMR ($CDCl_3$): δ 50.8 (ddq, *J*=3.1, 9.2, 56.5 Hz).

(R)-(Z)-1,1-Difluoro-2-octen-4-ol ***5a***

A solution of (*R*)-1,1-difluoro-2-octyn-4-ol **3a** (0.5 mmol) and a catalytic amount of Lindlar catalyst (*ca* 6 mg) in hexane (5 ml) was stirred between −30 and −20°C under a hydrogen atmosphere. After removing the catalyst by filtration, the residue was purified by column chromatography on silica gel, eluting with hexane–ethyl acetate (4:1) to give (*R*)-(*Z*)-1,1-difluoro-2-octen-4-ol **5a** in 93% yield {$[\alpha]_D^{19}$ −17.2 (*c* 1.124, Et_2O), >98% ee}.

^{1}H NMR ($CDCl_3$): δ 0.92 (3 H, t, *J*=7.2 Hz), 1.25–1.70 (7 H, m), 4.41–4.52 (1 H, m), 5.64 (1 H, m), 5.85 (1 H, m), 6.57 (1 H, ddt, *J*=0.5, 6.5, 56.2 Hz). ^{13}C NMR ($CDCl_3$): δ 13.88, 22.46, 27.12, 36.91, 68.54, 111.69 (t, *J*=230.4 Hz), 123.38 (t, *J*=25.8 Hz), 141.27 (t, *J*=11.1 Hz). ^{19}F NMR ($CDCl_3$) δ 51.4 (ddd, *J*=10.7, 57.2, 313.5 Hz).

(R)-(Z)-1,1-Difluoro-2-nonen-4-ol ***5b***

In the above reaction, (*R*)-1,1-difluoro-nonyn-4-ol **3b** (0.5 mmol) was used, and then worked up similarly. (*Z*)-1,1-Difluoro-2-nonen-4-ol **5b** was purified by column chromatography on silica gel, eluting with hexane–diethyl ether (2:1) to yield 90% {$[\alpha]_D^{19}$ −14.5 (*c* 0.274, Et_2O), >99% ee}.

^{1}H NMR ($CDCl_3$): δ 0.89 (3 H, t, *J*=6.8 Hz), 1.20–1.70 (9 H, m), 4.40–4.50 (1 H, m), 5.64 (1 H, m), 5.85 (1 H, ddq, *J*=1.0, 7.8, 11.7 Hz), 6.57 (1 H, ddt, *J*=0.7, 6.6, 55.9 Hz). ^{13}C NMR ($CDCl_3$): δ 13.88, 22.46, 24.64, 31.53, 37.13 (t, *J*=1.7 Hz), 68.41, 111.67 (t, *J*=230.4 Hz), 123.30 (t, *J*=25.8 Hz), 141.30 (t, *J*=11.3 Hz). ^{19}F NMR ($CDCl_3$): δ 51.3 (ddd, *J*=10.7, 56.5, 314.3 Hz) ppm from ext. C_6F_6.

(R)-1,1-Difluoro-2-octan-4-ol ***6a***

A solution of (*R*)-1,1-difluoro-2-octyn-4-ol **3a** (0.5 mmol) and a catalytic amount of 5% Pd–C (*ca* 20 mg) in ethanol (5 ml) was stirred at room temperature under a hydrogen atmosphere. After removing the catalyst by filtration, the residue was purified by column chromatography on silica gel, eluting with hexane–ethyl acetate (4:1) to give (*R*)-1,1-difluoro-2-octan-4-ol **6a** in 95% yield {$[\alpha]_D^{19}$ −5.3 (*c* 0.800, Et_2O), >98% ee}.

^{1}H NMR ($CDCl_3$): δ 0.92 (3 H, t, *J*=7.2 Hz), 1.25–1.70 (9 H, m), 1.84–2.20 (2 H, m), 3.64 (1 H, m), 5.88 (1 H, tt, *J*=4.5, 57.0 Hz). ^{13}C NMR ($CDCl_3$): δ 13.99, 22.63, 27.72, 29.41 (t, *J*=5.2 Hz),

30.44 (t, J=21.0 Hz), 37.30, 71.09, 117.40 (t, J=237.6 Hz). ^{19}F NMR ($CDCl_3$): δ 45.3 (1 F, ddt, J=18.3, 55.7, 280.5 Hz), 46.3 (1 F, ddt, J=17.6, 55.8, 280.5 Hz).

(R)-1,1-Difluoro-2-nonan-4-ol ***6b***

In the above reaction, (*R*)-1,1-difluoro-nonyn-4-ol **3b** (0.5 mmol) was used, and then worked up similarly. (*R*)-1,1-Difluoro-2-nonen-4-ol **6b** was purified by column chromatography on silica gel, eluting with hexane–diethyl ether (2:1) to yield 90% {$[\alpha]_D^{19}$ −3.8 (*c* 0.620, Et_2O), >99% ee}.

^{1}H NMR ($CDCl_3$): δ 0.90 (3 H, t, J=7.0 Hz), 1.25–1.70 (11 H, m), 1.84–2.20 (2 H, m), 3.61–3.68 (1 H, m), 5.88 (1 H, tt, J=4.4, 57.0 Hz). ^{13}C NMR ($CDCl_3$): δ 13.98, 22.56, 25.21, 29.29 (t, J=5.1 Hz), 30.38 (t, J=21.2 Hz), 31.72, 37.43, 71.41, 117.33 (t, J=237.5 Hz). ^{19}F NMR ($CDCl_3$): δ 45.3 (1 F, ddt, J=18.3, 56.5, 279.2 Hz), 46.3 (1 F, ddt, J=18.3, 56.5, 279.2 Hz).

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