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Synthesis of optically active partly *gem*-difluorinated allylic alcohols via [2,3]-Wittig rearrangements and lipase-catalyzed reaction

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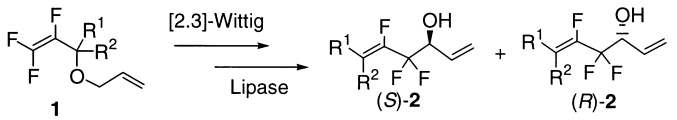
Abstract

[2,3]-Wittig rearrangement of 1,1,2-trifluoroallylic ethers gave five types of novel 4,4,5-trifluoroalk-1,5-dien-3-ols. The rearrangement reaction gave the alcohols with perfect (*E*)*-selection over the newly created olefin bond for two substrates. Lipase-catalyzed optical resolution of 4,4,5-trifluoroalk-1,5-dien-3-ols was successfully performed to afford optically active partly *gem*-difluorinated allylic alcohols for the first time.

Keywords: [2,3]-Wittig rearrangement; partly *gem*-difluorinated allylic alcohols; lipase-catalyzed reaction; asymmmetric synthesis.

The substitution of two fluorine atoms on organic molecules is expected to alter both chemical reactivity and biological activity due to the strong electron-withdrawing nature of fluorine.[1] The synthesis of partly *gem*-difluorinated compounds remains a significant challenge to synthetic organic chemists.[1–3] Herein, we report that [2,3]-Wittig rearrangement of 1,1,2-trifluoroallylic ether **1** gave new types of partly *gem*-difluorinated allylic alcohols: 4,4,5-trifluoroalk-1,5-dien-3-ols (**2**) in a highly stereoselective fashion, and optical resolution of these allylic alcohols was accomplished via lipase-catalyzed reactions (Scheme 1).



Scheme 1.

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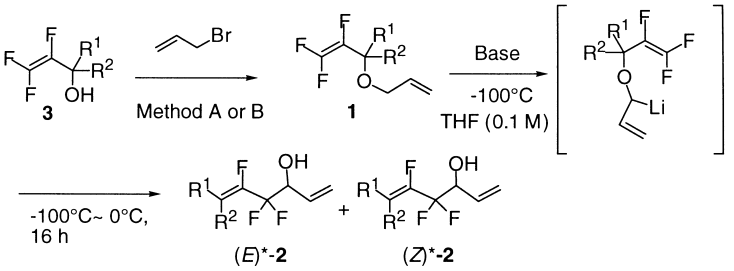
The starting 1,1,2-trifluoroallylic ethers **1** were prepared as follows (Eq. (1)): 1,1,2-Trifluoro-1-alkene-3-ols **3** were synthesized and subsequent conversion to allylic ethers **1** was accomplished by proper choice of the allylation protocol which was developed by Percy et al.[2] Tertiary alcohols **3** were treated with sodium hydride as base and subsequent reaction with allylbromide in a mixed solvent (THF:DMF = 5:1) gave allylic ether **1** in good yield (Method A). In contrast, use of a phase-transfer catalyst-mediated reaction condition (Method B) [4] was essential for allylic ethers derived from secondary alcohols because of the high acidity of the proton at the 3-position of alcohol **3** (Entries 9, 10 and 13, Table 1). Eight types of novel allylic ethers **1** have been synthesized in good or modest yields, except for highly bulky allylic alcohol **3f** (R^1,R^2 = *c*-hexyl) (Entry 12).



(1)

Table 1
Synthesis of fluoroallylic alcohols **2** via [2,3]-Wittig rearrangements

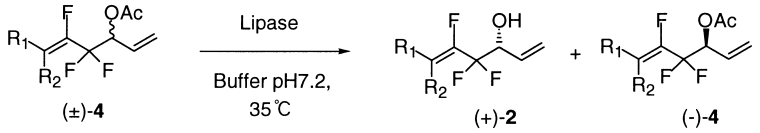
Entry	Starting alcohol	R^1	R^2	Method [a]	Yield of **1**(%)	Base [b]	Yield of **2**(%)	(*E*)*-**2** : (*Z*)*-**2** [c]
1	**3a**	Ph	Me	A	53	BuLi (2 eq.)	25	72:28
2	**3a**	Ph	Me	A	53	LDA (1 eq.)	19	73:27
3	**3a**	Ph	Me	A	53	LDA (2 eq.)	57	70:30
4	**3a**	Ph	Me	A	53	LTMP (2 eq.)	63	63:37
5	**3b**	Me	Me	A	70	LDA (2 eq.)	35	--
6	**3b**	Me	Me	A	70	LTMP (2 eq.)	75	--
7	**3c**	Et	Et	A	79	LDA (2 eq.)	66	--
8	**3c**	Et	Et	A	79	LTMP (2 eq.)	64	--
9	**3d**	$Ph(CH_2)_2$	H	B	66	LDA (2 eq.)	53	>99:<1
10	**3e**	$n\text{-}C_{10}H_{21}$	H	B	59	LDA (2 eq.)	55	>99:<1
11	**3f**	c-Hex	c-Hex	A	0[d]	---	--	--
12	**3g**	$PhCH_2$	$PhCH_2$	A	60	LDA (2 eq.)	0[d]	--
13	**3h**	Ph	H	B	62	LDA (2 eq.)	0[d]	--
14	**3i**	$-(CH_2)_5-$		A	53	LDA (2 eq.)	0[d]	--

a) Method A: NaH, allyl bromide, THF-DMF. Method B: allyl bromide, $(n\text{-}Bu)_4N{\bullet}HSO_4$, 50%NaOH aq. CH_2Cl_2. b) Use of 2 eq. of LDA or LTMP gave better results than n-BuLi or 1eq. of LDA. c) Determined by capillary GC analysis (MS-25M). Because fluorine atom is superior to carbon atom, this nomenclature does not follow the IUPAC rule. We adapted this nomenclature to discuss the stereochemistry of [2,3]-Wittig rearrangements. (*E*)* and (*Z*)* corresond to (*Z*) and (*E*), respectively. d) Neither the desired compound nor the starting material was obtained.

It was found that proper choice of the base was essential for the next [2,3]-Wittig rearrangement (Eq. (1)); lithium diisopropylamide (LDA) or lithium 2,2,6,6-tetramethylpiperazide (LTMP) gave good results and the initial base treatment of allylic ether **1** should be performed at –100°C. Unidentified polymerized products were formed when the base treatment was carried out at an elevated temperature over –80°C. Five types of novel fluorinated alcohols **2** were thus obtained in

satisfactory yield (Entries 1–10), while reactions of three types of allylic ethers were unsuccessful (Entries 12–14) (Table 1). It has been reported that [2,3]-Wittig rearrangement exhibits a high (*E*)-selectivity over the newly created olefin bond.[5] In fact, perfect (*E*)*-selective reaction (>99%) was achieved over the newly created olefin bond of **2d** and **2e** (Entries 9 and 10); no stereoisomer was detected by capillary GC analysis and the stereochemistry was confirmed by ^{1}H and ^{19}F NMR analyses.[6] However, the stereoselectivity was insufficient when allylic ether **1a** (R^1 = Ph, R^2 = Me) was subjected to the reaction and no improvement in the (*E*)*-selectivity was observed by switching the base (Entries 1–4). For three types of allylic ethers, **1g**, **1h** and **1i**, no desired product was obtained and only unidentified polymerized products were produced, though we performed the reactions at various temperature conditions (Entries 12–14).

The synthetic value of lipase has been well-recognized because the reaction proceeds efficiently and selectively under mild conditions,[7] so we decided to use lipase-catalyzed hydrolysis protocol for the preparation of optically active **2**. Initially, we tested lipase-catalyzed *trans*-esterification of (±)-6-ethyl-4,4,5-trifluorooct-1,5-dien-3-ol (**2c**) as a model compound. The reaction, however, was very slow due to lack of nucleophilicity of the hydroxyl group of **2c** by the electron-withdrawing nature of the difluoromethylene group at the 4-position, though the reaction exhibited perfect enantioselectivity. Fortunately, lipase-catalyzed hydrolysis of the corresponding acetate (±)-**4c** proceeded very successfully and optically pure **2c** was obtained in good yield (Eq. (2)).



(2)

Among eight commercially available lipases screened, four enzymes gave excellent results with lipase PS providing the best of these (Table 2, Entry 1).[8] The absolute configuration of **2c** produced was assigned to be (*R*) based on the results of Mosher's modified method proposed by Kusumi et al.[10] (Fig. 1).[11] It was found that all four enzymes preferred to hydrolyze (*R*)-alcohols for **2b**, **2c** and **2d**. Two types of partly difluorinated allylic alcohols **2b** (R^1,R^2 = Me) and **2c**, were thus obtained in optically pure form for the first time (Table 2), although results of the optical resolution of **2d** (R^1 = $PhCH_2CH_2$, R^2 = H) remained at an insufficient level.

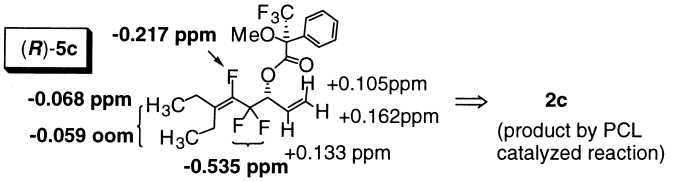


Figure 1. Assignment of the absolute configuration of 6-ethyl-4,4,5-trifluorooct-1,5-dien-3-ol (**2c**) obtained by lipase-catalyzed hydrolysis

In conclusion, new types of partly fluorinated allylic alcohols were synthesized in stereoselective fashion through [2,3]-Wittig rearrangements and successful optical resolution was accomplished by the lipase-catalyzed reaction. The present method affords a valuable means of preparing optically active partly fluorinated allylic alcohols. Further study of the scope and limitations of this reaction will make it even more beneficial.

Table 2
Lipase-catalyzed optical resolution of fluoroallylic alcohols[a]

Entry	R^1	R^2	Lipase [b]	Time	%conv.	%ee of **2** (%yield)	%ee of **4** (%yield)	E [9]
1	Et	Et	PCL	8	49	>99 [c] (38)	94 (42)	>750
2	Et	Et	CAL	1	37	>99 [c] (37)	59 (57)	>363
3	Et	Et	OF	3	28	>99 [c] (22)	39 (48)	>290
4	Et	Et	QL	15	45	>99 [c] (36)	81 (40)	>500
5	Me	Me	PCL	7.5	48	>99 [c] (36)	91 (54)	>645
6	Me	Me	CAL	0.5	42	>99 [c] (23)	73 (21)	>437
7	$PhCH_2CH_2$	H	PCL	8	64	21 (47)	38 (48)	2

a) The reaction was carried out in 0.1 M potassium phosphate buffer at pH 7.2 and enantiomeric excess was determined by capillary GC analysis using Chiraldex-GTa (ϕ 0.25 mm x 20 M, He, 70 °C). b) PCL: *Pseudomonas cepacia* (Amano); CAL: *Candida antractica* (Novo), OF: *Candida rugosa* (Meito), QL: *Alcaligenes* sp. (Meito). c) No isomer was detected by the capillary GC analysis.

Acknowledgements

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6. Synthesis of 6-ethyl-4,4,5-trifluorooct-1,5-dien-3-ol (**2c**): To a THF (150 ml) solution of LDA (44.0 mmol) was added a THF (50 ml) solution of **1c** (4.16 g, 20.0 mmol) at –100°C dropwise for 40 min. The mixture was then allowed to warm to rt with stirring for 12 h. The reaction was quenched by the addition of a saturated NH_4Cl aqueous solution and extracted with ether. The organic layers were dried ($MgSO_4$), evaporated, and chromatographed on silica gel flash column to afford **2c** (2.83 g, 13.6 mmol) in 68% yield: bp 90°C/10 torr (Kugelrohr); R_f 0.4 (hexane:ethyl acetate, 7:1); ^1H NMR (200 MHz, $CDCl_3$, d) 1.03 (6H, t, J = 7.5 Hz), 2.10–2.23 (4H, m), 2.38 (1H, br s), 4.40–4.55 (1H, m), 5.39 (1H, d, J = 10.4 Hz), 5.49 (1H, st, J = 17.3, 1.5 Hz), 5.84–6.01 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) 12.4, 13.3, 21.0 (q, J_{C-F} = 4.4 Hz), 21.9 (d, J_{C-F} = 8.5 Hz), 73.3 (t, J_{C-F} = 28.4 Hz), 117.5 (dt, J_{C-F} = 247.6, 40.4 Hz), 119.8, 130.0 (d, J_{C-F} = 10.8 Hz), 131.8 (t, J_{C-F} = 2.8 Hz), 144.6 (dt, J_{C-F} = 241.8, 31.2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6) 32.20 (1F, br s), 51.54 (2F, ddd, J = 23.1, 20.7, 12.2 Hz); IR (neat, cm^{-1}) 3401, 2975, 1691 and 1462.

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8. The asymmetric hydrolysis of (±)-**4c** was typically carried out as follows: A mixture of **4c** (1.0 mmol) and lipase PS (50 wt% towards the substrate) in a phosphate buffer solution (10 ml, 0.1 M at pH 7.2) was stirred at 35°C (Eq. (2)). The alcohol **2c** produced was extracted with ethyl acetate and purified by silica gel flash column chromatography (hexane:ethyl acetate, 5:1 to 2:1). Compounds **2c** and **4c** were obtained in 38 and 43%, respectively. Enantiomeric excess of alcohol (+)-**2c** ($[\alpha]_D^{23}$ +14.63 (*c* 0.75, $CHCl_3$)) produced was determined by capillary GC analysis using the chiral phase column (Chiraldex G-Ta) as >99% ee because no signal of the enantiomer was observed using chiral column (Chiraldex G-Ta). Acetate (–)-**4c** ($[\alpha]_D^{23}$ –5.8 (*c* 1.23, $CHCl_3$)) unreacted was determined as 94% ee. Retention times on GC analyses of **2c** and **4c** are summarized as follows: Chiraldex G-Ta, ϕ 0.25 mm×20 m, carrier gas: He 40 ml/min. Temp: 70°C, inlet pressure: 1.35 Kg/cm^2, amount 400 ng, detection: FID; compound **2c**: $Rt_{(R)}=33.0$ min, $Rt_{(S)}=36.5$ min; compound **4c**: $Rt_{(S)}=19.0$ min, $R_{(R)}=20.6$ min.
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11. (*R*)- and (*S*)-α-Methoxy-α-(trifluoromethyl)phenylacetic (MTPA) esters (*R*)-**5c** and (*S*)-**5c** showed positive chemical shift differences ($\Delta\delta=\delta S-\delta R$) for protons on C-1 and C-2, while negative chemical shift differences ($\Delta\delta=\delta S-\delta R$) for fluorine atoms on C-4 and C-5, and for protons on C-8 were observed (Fig. 1). The same chemical shift change tendency was observed for all three compounds **2b**, **2c** and **2d**.