Communications to the Editor

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KINETIC RESOLUTION OF FLUOROALKYL (E)-VINYL CARBINOL DERIVATIVES BY ASYMMETRIC EPOXIDATION WITH TITANIUM-TARTRATE CATALYSTS

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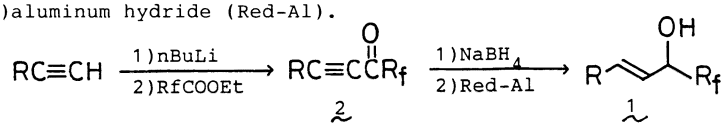
Racemic fluoroalkyl (E)-vinyl carbinols (1a-d) were kinetically resolved by Sharpless epoxidation. The optical purity of the resolved alcohols was excellent (98% ee) in mono- and difluoromethyl derivatives (1b and 1c) and moderate (60% ee) in a trifluoromethyl compound (1a).

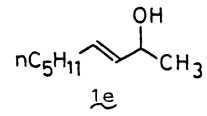
KEYWARDS ——— kinetic resolution; asymmetric epoxidation; fluoroalkyl (E)-vinyl carbinol derivatives; absolute configuration

For many years, we have been investigating the synthesis of the fluoro analogs of bioactive compounds using a functionalized fluorine-containing molecule as a building block.[1] As reported in our recent papers on the synthesis of trifluororetinals,[2] we have prepared a trifluoromethyl (E)-vinyl carbinol derivative (1a) by reducing the trifluoromethyl alkynyl ketone (2a) with sodium borohydride followed by reduction of the triple bond with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al).



2 1

	Rf	R	2		1	
a;	CF_3	nC_6H_{13}	2a	84%	1a	84%
b,	CF_2H	nC_5H_{11}	2b	79	1b	95
c;	CFH_2	nC_5H_{11}	2c	66	1c	66
d;	CF_2Et	nC_5H_{11}	2d	77	1d	78



1e

Chart 1

Compounds 1 and 2 are considered very versatile building blocks for the synthesis of fluoroalkylated carbohydrate(s) and other bioactive compounds, especially when preparing compound 1 in optically active form. Recently, a microbial method for generating optically active 1 has been reported by Kitazume et al.[3] The present paper describes the results of the kinetic resolution of a series of fluoroalkyl (E)-vinyl carbinols (1) by titanium-mediated asymmetric epoxidation.[4] Unless the effects of the fluoroalkyl groups alter the enantiofacial differentiation of asymmetric epoxidation, it should be possible to predict the absolute configurations of the unreacting alcohols (1).[5]

This is one of the advantages of kinetic resolution, compared to resolution by separation of a diastereomeric mixture. It is interesting to know the effects of the fluoroalkyl groups under the asymmetric epoxidation conditions. The starting materials (1a-d) were prepared as shown in Chart 1. The results of the resolution are summarized in Table I.

Table I. Kinetic Resolution of Racemic 1[6] by Asymmetric Epoxidation

1	time[a]	recovered alcohol(%)	config.	% ee[b]	$[\alpha]_D^{25}$ /MeOH	method[c]	epoxide yield (%)	(erythro/threo)[d]
1a	5 d	46	S	60	-1.92 (c=0.31)	A	50	5/1
	3 weeks	51		47	-1.51 (c=0.59)	B	47	4.4/1
1b	4 d	31	S	97	-11.65(c=0.45)	A	59	15/1
	7 d	39		98	-11.76(c=0.68)	B	52	12/1
1c	24 h	43	S	98	-0.39 (c=0.57)	A	56	8/1
	5 d	41		93	-0.35 (c=0.56)	B	46	15/1
1d	4 d	45		14	-2.27 (c=1.32)	A	52	1.7/1
1e	24 h	40	R	98		A		
	5 d	34		97		B		

a) The reaction was followed by GLC (SE-30) analysis of the reaction mixture.
b) Determined by ^{1}H- and ^{19}F-NMR analysis of the (-)-MTPA ester of resolved 1.
c)

	L-(+)-DIPT	$Ti(O\text{-}iPr)_4$	TBHP	Temp.	Sol.
A:	1.2 eq.	1.0 eq.	0.55eq.	-20°C	CH_2Cl_2
B:	0.19	0.13	0.55	-20°C	CH_2Cl_2

d) Determined by integrating the ^{19}F-NMR signals of a mixture of epoxides.[7]

In a typical reaction, compound 1b was resolved as follows: A mixture of L-(+)-DIPT (405 mg, 1.73 mmol) and $Ti(OiPr)_4$ (409 mg, 1.44 mmol) in dry CH_2Cl_2 (10 ml) was stirred at -20°C for 20 min. After the mixture was coolrd at -78° C, 1b (257 mg, 1.44 mmol) was added then stirred for several minutes before adding anhydrous TBHP (0.26 ml of 3M solution in toluene). The reaction mixture was kept at -20°C for 6 d and then worked up by adding a solution of 0.3 ml of H_2O in 17 ml of acetone at -20°C. The resulting precipitate was removed by filtration through a pad of Celite and the solvent was removed in vacuo to give a crude product. The crude oil was purified by column chromatography (SiO_2, Hexane-AcOEt=10 : 1) to give two fractions. Unreacted 1b (78.7 mg, 0.44 mmol) (31%) was recovered in the first fraction. The second fraction yielded a mixture of epoxides (165 mg, 59%).

The unreacted alcohol (1a) was determined to have the S-configuration, by converting the resolved alcohol (1a) to compound 3 whose R-isomer has been prepared in high optical purity.[8] The absolute configurations of the difluoro- and monofluoromethyl compounds (1b and 1c) were confirmed by correlation with compounds which have been prepared from D-glyceraldehyde acetonide in an unambiguous way (Chart 2).

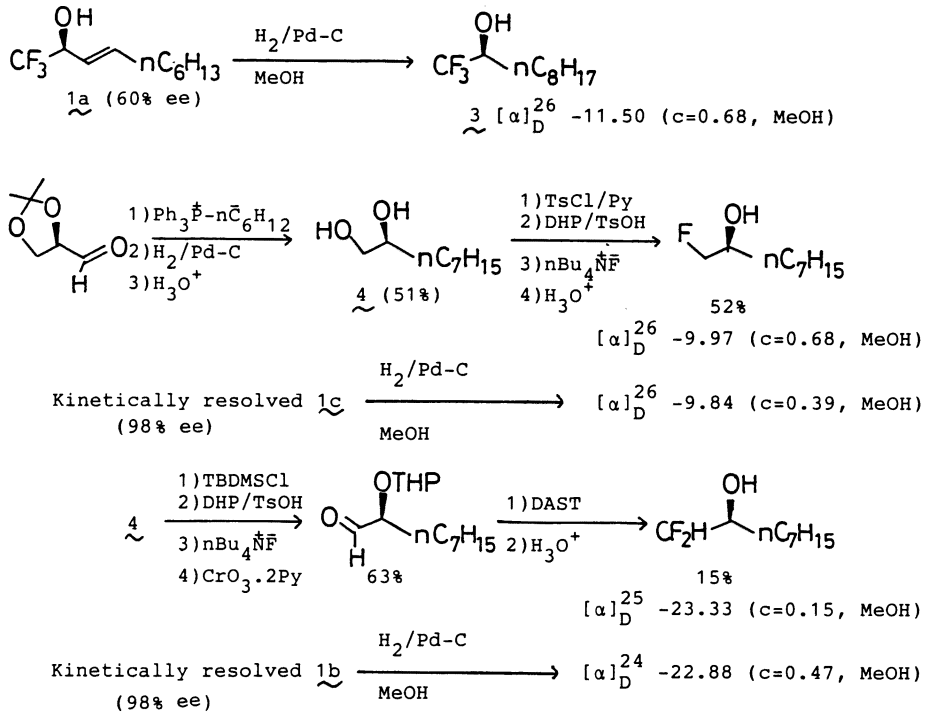


Chart 2

The fact that each resolved alcohol (1a-c) has the S-configuration indicates the kinetic preference in the asymmetric epoxidation of racemic fluoroalkyl compounds (1a-d) to be the same as that of existing examples.[5] It is worth noting that the monofluoromethyl compound (1c) behaves essentially the same as the methyl compound (1e) under the conditions of asymmetric epoxidation, with respect to the rate of epoxidation and optical purity. In difluoro- and trifluoromethyl compounds (1b and 1a), retardation of the rate or lowering of the optical purity of the recovered alcohols was observed. The poor resolution (14% ee) of 1d and moderate resolution (60% ee) of 1a compared to the excellent resolution of 1b and 1c shows that the fluoroalkyl substituents of 1a and 1d tend to be like the tertiary alkyl group in the kinetic resolution. Although the little kinetic resolution of t-butyl vinyl carbinol has been attributed to the steric effect of the large substituent,[5] the electronic effect of fluorine(s) may possibly perform an important function in the kinetic resolution of racemic 1a—1d by asymmetric epoxidation.[9] For further discussion, we should await an accumulation of more experimental results concerning the fluoroalkyl groups.

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References and Notes

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6) The attempt to resolve the Z-isomer of 1 by the asymmetric epoxidation to obtain the optically active Z-isomer of 1 was without success.

7) The structures of the epoxides were estimated by the preference of erythro epoxide in Sharpless epoxidation and by comparing them with epoxides obtained from m-chloroperbenzoic acid (mcpba)-oxidation products (threo-selective) of racemic 1.

8) T. Kitazume, S. Lin and M. Asai, P84 Abstracts of the tenth fluorine symposium at Kanazawa, Japan, 1985.

9) Recently, the pseudo-π charactor of the trifluoromethyl group has been presented to explain the stereochemistry of trifluoromethylated olefin. C. L. Bumgardner, J. E. Bunch and M.-H. Whangbo, Tetrahedron Lett., 27, 1883 (1986) and references cited therein.

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