Pergamon

Tetrahedron Letters 39 (1998) 1199–1202

TETRAHEDRON LETTERS

Stereocontrol at the Quaternary Center in 1-Substituted 1-Phenyl-2,2,2-Trifluoroethylamines: Stereospecific Substitution with *Retention* of a Chiral Cyclic Fluoral N,O-acetal with Organolithium Reagents

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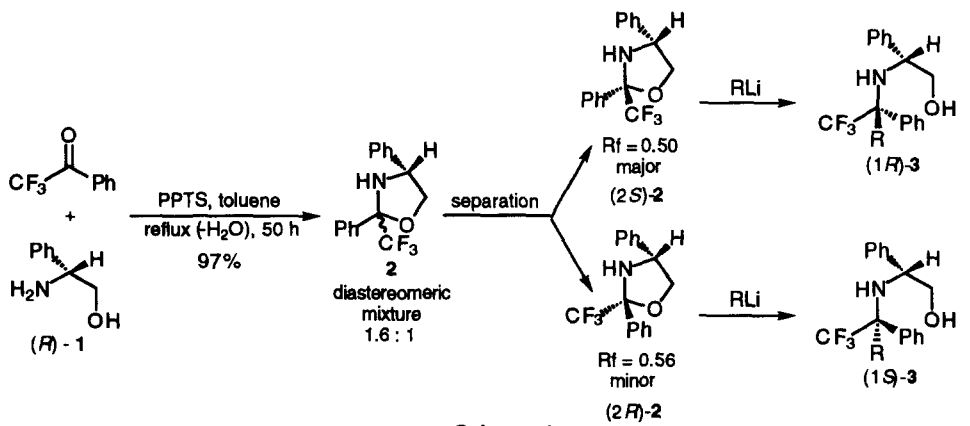
Received 16 October 1997; revised 26 November 1997; accepted 8 December 1997

Abstract: The asymmetric synthesis of 1-substituted 1-phenyl-2,2,2-trifluoroethylamines from chiral 1,3-oxazolidines is described. The stereospecific substitution reaction with organolithium reagents of chiral 1,3-oxazolidines having a trifluoromethyl group proceeds with *retention* to control the newly created quaternary center.

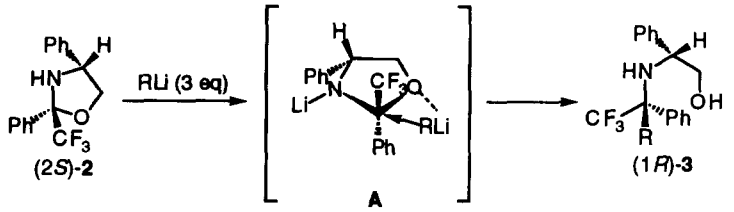
There is current interest in developing efficient methods for the asymmetric synthesis of organofluorine compounds through carbon-carbon bond formation.[2] However, asymmetric synthesis of organofluorine compounds bearing a quaternary carbon has not been well developed.[2b, d] As a part of a research program directed toward the asymmetric synthesis of organofluorine compounds, we report herein a practical route for the asymmetric synthesis of 1-substituted 1-phenyl-2,2,2-trifluoroethylamines having a quaternary carbon, which employs the stereospecific substitution reaction of chiral 1,3-oxazolidines with organolithium reagents, which proceeds with *retention*. The 1-substituted 1-phenyl-2,2,2-trifluoroethylamines thus synthesized are potentially useful candidates for chiral derivatizing agents for chromatographic separation and ^{19}F-NMR analysis.[3]



Scheme 1

The starting chiral 1,3-oxazolidine with a trifluoromethyl group at the 2-position was prepared as follows. Condensation of 2,2,2-trifluoroacetophenone with (*R*)-phenylglycinol (**1**) by heating in toluene with azeotropic removal of water gave the chiral 2-trifluoromethyl-1,3-oxazolidine (**2**) in excellent yield as a diastereomeric mixture (Rf (CH_2Cl_2 : *n*-hexane = 1 : 2) ; major (0.50) : minor (0.56) = 1.6 : 1 by ^{1}H-NMR analysis) (Scheme 1). The diastereomers were separated by column chromatography. The absolute configuration of the minor diastereomer was determined to be 2*R*, 4*R* by X-ray analysis.

0040-4039/98/$19.00
PII: S0040-4039(97)10840-1



a : Me, **b** : *n*-Bu, **c** : vinyl, **d** : *p*-tolyl, **e** : *i*-Pr

Scheme 2

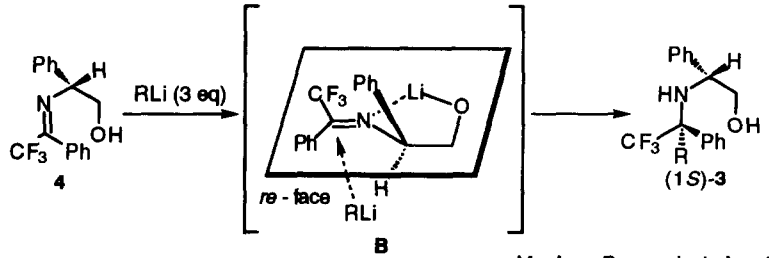
Table I. Asymmetric reaction of 1,3-oxazolidine with RLi.

run	R	solvent	temp. (°C)	time (h)	substrate (2*S*)-2 product[a] (*S* : *R*)	yield (%)[b]	substrate (2*R*)-2 product[a] (*S* : *R*)	yield (%)[b]
1	Me	Et_2O	-40	15	**3a** (1.8 : 98.2)	82	**3a** (96.5 : 3.5)	51
2	Me	Et_2O	-78	15	**3a** (1.8 : 98.2)	84	**3a** (97.8 : 2.2)	27
3	Me	*i*-Pr_2O	-40	15	**3a** (0.9 : 99.1)	87	**3a** (98.2 : 1.8)	34
4	Me	THF	-78	15	**3a** (0.7 : 99.3)	99	**3a** (99.5 : 0.5)	93
5	*n*-Bu	THF	-40	15	**3b** (7.9 : 92.1)	90	**3b** (89.4 : 10.6)	37
6	*n*-Bu	THF	-78	15	**3b** (5.9 : 94.1)	100	**3b** (92.8 : 7.2)	47
7	vinyl	THF	-40	15	**3c** (2.5 : 97.5)	90	**3c** (96.8 : 3.2)	34
8	vinyl	THF	-78	15	**3c** (1.0 : 99.0)	93	**3c** (99.3 : 0.7)	87
9	*p*-tolyl	THF	-78	15	**3d** (99.1 : 0.9)[c]	96	**3d** (2.2 : 97.8)[c]	70
10	*i*-Pr	THF	-78	2	**3e** (18.0 : 82.0)	83	**3e** (94.2 : 5.8)	52

[a] Determined by ^{1}H-NMR analysis. [b] Isolated yield. [c] Because of the priority of substituents.

When each diastereomer of the starting oxazolidine (**2**) was treated with various organolithium reagents, the corresponding diastereomers of the products (**3**) were obtained, presumably through direct displacement of the 1,3-oxazolidines (Scheme 2, Table 1), in sharp contrast to 2-nonfluoroalkyl-1,3-oxazolidines which provide the same diastereomer of product from either diastereomer of starting material via an imine intermediate.[4]

The best results were obtained in THF as a solvent at low temperature (-78 °C) (run 1-8). The diastereoselectivities obtained with *n*-butyllithium and *i*-propyllithium were lower than with methyllithium, vinyllithium and *p*-tolyllithium (run 4, 6, 8-10). In the case of *i*-propyllithium (run 10), the isolated yield fell upon prolonged reaction time because of decomposition of the product (**3e**) by the strongly basic secondary alkyllithium. The reactivity of (2*S*)-**2** was apparently higher than (2*R*)-**2**. The absolute configuration of the major product (**3a**) obtained from the reaction of (2*S*)-**2** with methyllithium was determined to be 1*R* by X-ray analysis of hydrobromic acid salt.



a : Me, **b** : *n*-Bu, **c** : vinyl, **d** : *p*-tolyl, **e** : *i*-Pr

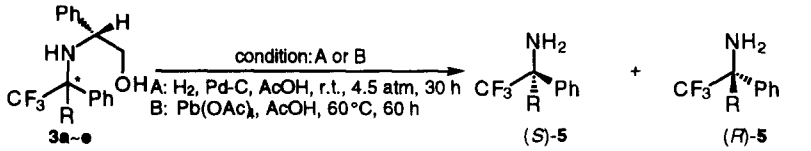
Scheme 3

Table 2. Asymmetric reaction of imine with RLi.

run	R	solvent	temp. (°C)	time (h)	product[a] (*S* : *R*)	yield (%)[b]
1	Me	THF	-40	15	**3a** (98.9 : 1.1)	82
2	Me	THF	-78	15	**3a** (99.5 : 0.5)	100
3	Me	Et_2O	-40	15	**3a** (97.2 : 2.8)	54
4	Me	Et_2O	-78	15	**3a** (98.1 : 1.9)	30
5	Me	*i*-Pr_2O	-40	15	**3a** (97.7 : 2.3)	51
6	*n*-Bu	THF	-40	15	**3b** (71.3 : 28.7)	36
7	*n*-Bu	THF	-78	15	**3b** (73.7 : 26.3)	74
8	vinyl	THF	-40	15	**3c** (93.3 : 6.7)	20
9	vinyl	THF	-78	15	**3c** (98.7 : 1.3)	60
10	*p*-tolyl	THF	-78	15	**3d** (4.8 : 95.2)[c]	67
11	*i*-Pr	THF	-78	2	**3e** (88.0 : 12.0)	49

[a] Determined by ^{1}H-NMR analysis. [b] Isolated yield. [c] Because of the priority of substituents.

In order to clarify the reaction course of the fluoral-derived 1,3-oxazolidines, the reaction of the chiral imine (**4**)[5] with the same organolithium reagents, which proceeds through metallo-imine intermediate[6] (**B**), was investigated (Scheme 3, Table 2). The geometry of the chiral imine (**4**) was determined to be *E* by X-ray analysis. Because (1*S*)-**3a~e** were obtained with lower diastereoselectivity, it can be concluded that 1,3-oxazolidine does not react after transformation to the metallo-imine, as is the case with the nonfluorinated analogues. These results suggest that 1,3-oxazolidines having trifluoromethyl group at the 2-position undergo a direct reaction with organolithium reagents with *retention* (**A**), and do not react through formation of an imine intermediate. This phenomenon may be attributed to the retardation of the ring opening to the imine by the highly electron-withdrawing group which would destabilize the incipient positive charge at the 2-position.[7] To the best of our knowledge, this is the first example of a stereospecific carbon-carbon bond formation with *retention* at the carbon α to trifluoromethyl group.[8]



a : Me, **b** : *n*-Bu, **c** : vinyl, **d** : *p*-tolyl, **e** : *i*-Pr, **f** : Et

Scheme 4

Table 3. Hydrogenolysis or oxidative cleavage of product.

			(1*S*)-**3**		(1*R*)-**3**	
run	**3** : R	condition	product[a]	yield (%)[b]	product[a]	yield (%)[b]
1	**3a** : Me	A	**5a**	86	**5a**	79
2	**3b** : *n*-Bu	A	**5b**	92	**5b**	91
3	**3c** : vinyl	A	**5f**	81	**5f**	82
4	**3d** : *p*-tolyl	A	**5d**	85	**5d**	81
5	**3e** : *i*-Pr	A	**5e**	79	**5e**	86
6	**3c** : vinyl	B	**5c**	42	**5c**	45

[a] Without epimerization. [b] Isolated yield.

The chiral auxiliary can be cleaved from the products (**3a~e**) by hydrogenolysis or oxidative cleavage[9] to give the fluorinated amines (**5a~f**) (Scheme 4, Table 3). The hydrogenolysis of benzylic carbon-nitrogen bond occured regioselectively and no epimerization of the quaternary centers was observed.

Thus, by use of the appropriate diastereomer of the oxazolidine, either enantiomer of the product amine can be obtained from a single enantiomer of the chiral auxiliary.

We thank Emeritus Prof. Hiroshi Takahashi for his encouragement and useful discussion.

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