

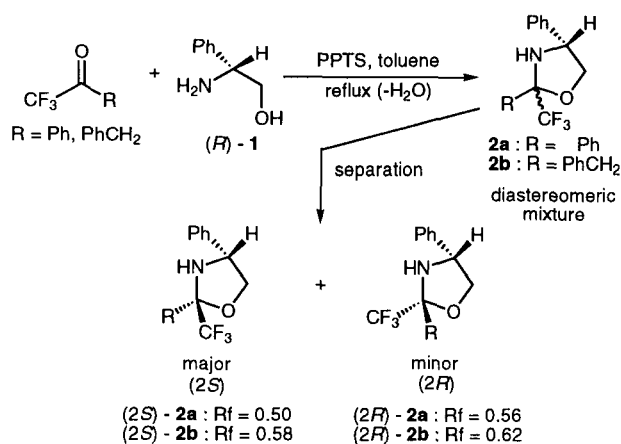
Stereospecific Reduction with Retention of Chiral Fluoral-derived 1,3-Oxazolidines with LiAlH_4 : Asymmetric Synthesis of 1-Substituted 2,2,2-Trifluoroethylamines

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The asymmetric synthesis of 1-substituted 2,2,2-trifluoroethylamines from chiral 1,3-oxazolidines having trifluoromethyl group derived from trifluoromethyl ketones and (*R*)-phenylglycinol is described. The stereospecific reduction of chiral 1,3-oxazolidines with LiAlH_4 proceeds in *retention* fashion.

There is current interest in developing an efficient method for the asymmetric synthesis of organofluorine compounds.² However, the method established for nonfluorine substrates can not be always applied to organofluorine counterparts because of unique electronic and/or steric character of fluorine.³ As a part of a research program directed toward the asymmetric synthesis of organofluorine compounds, we report herein a practical route to the asymmetric synthesis of 1-substituted 2,2,2-trifluoroethylamines by the stereospecific reduction of chiral 1,3-oxazolidines with LiAlH_4 in *retention* fashion. Particularly, 1-phenyl-2,2,2-trifluoroethylamine thus synthesized is useful as a chiral derivatizing agent for the chromatographic separation and ^{19}F -NMR analysis.⁴



Scheme 1.

Table 1. Preparation of 1,3-oxazolidines

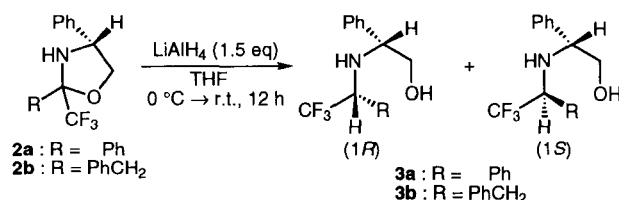
run	oxazolidine: R	2S : 2R ^a	time (h)	yield (%) ^b
1	2a: Ph	1.6 : 1	50	97
2	2b: PhCH ₂	1.9 : 1	16	92

^a Determined by ^1H -NMR analysis. ^b Isolated yield.

The starting chiral 1,3-oxazolidine having trifluoromethyl group at 2-position was prepared as follows. The condensation of trifluoromethyl ketones with (*R*)-phenylglycinol (1) by heating in toluene with azeotropic removal of water gave the chiral 2-trifluoromethyl-1,3-oxazolidines in excellent yields as a diastereomeric mixture (2a (Rf (CH₂Cl₂ : n-hexane = 1 : 2)) ;

major (0.50) : minor (0.56) = 1.6 : 1, 2b (Rf) ; major (0.58) : minor (0.62) = 1.9 : 1 by ^1H -NMR analysis) (Scheme 1, Table 1). The each diastereomer was separated by column chromatography. The absolute configuration of the minor diastereomer (2a) was determined to be 2*R*, 4*R* by X-ray analysis. 2-Benzyl-1,3-oxazolidine (2b) is also deduced to possess the same stereochemistry.

When each diastereomer was treated with LiAlH_4 , the opposite sense of diastereoselectivity was obtained, presumably through direct displacement of the 1,3-oxazolidines (Scheme 2, Table 2, run 1 vs 2, run 3 vs 4), in direct contrast to the nonfluorinated cases which give a single diastereomer by catalytic reduction through an equilibrium mixture with imine.⁵



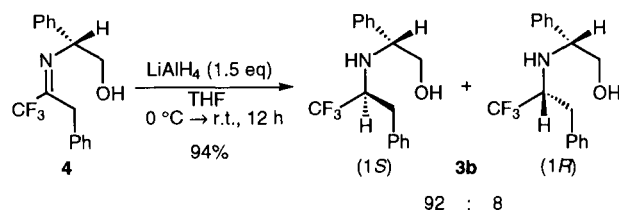
Scheme 2.

Table 2. Asymmetric reduction of 1,3-oxazolidine with LiAlH_4

run	oxazolidine	product	1R : 1S ^a	yield (%) ^b
1	(2S)-2a	(1R)-3a	88 : 12	93
2	(2R)-2a	(1S)-3a	10 : 90	90
3	(2S)-2b	(1R)-3b	94 : 6	94
4	(2R)-2b	(1S)-3b	0 : 100	92

^a Determined by ^1H -NMR analysis. ^b Isolated yield.

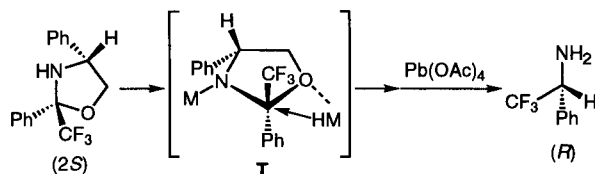
Therefore, asymmetric reduction of imine (4)⁶ having trifluoromethyl and benzyl group was next investigated with LiAlH_4 (Scheme 3). Because (1*S*)-3b was obtained in highly diastereoselective manner, it can be concluded that 1,3-oxazolidine does not react after transformation to the metalloimine⁷ through ring opening with LiAlH_4 .



Scheme 3.

These results suggest that 1,3-oxazolidine having trifluoromethyl group at 2-position directly reacted with LiAlH_4 in *retention* fashion (T) without formation of the imine intermediate.

These phenomenon may be attributed to retardation of ring opening to imine by introduction of highly electron-withdrawing group to destabilize the possible formation of the positive charge at the 2-position.⁸ To the best of our knowledge, this is the first example of stereospecific nucleophilic substitution in *retention* fashion at the carbon α to trifluoromethyl group.⁹ In this asymmetric reduction, both enantiomers of fluorinated amines can be prepared from the single enantiomeric source because the each diastereomer of 1,3-oxazolidines are transformed to the known⁴ chiral 1-substituted 2,2,2-trifluoroethylamines by oxidative cleavage or hydrogenolysis¹⁰ of the reduction products (**3a**, **3b**) without epimerization.



Thus, we achieved the asymmetric synthetic route to 1-substituted 2,2,2-trifluoroethylamines by employing the stereospecific reduction of chiral 1,3-oxazolidines having trifluoromethyl group with LiAlH_4 in *retention* fashion.

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