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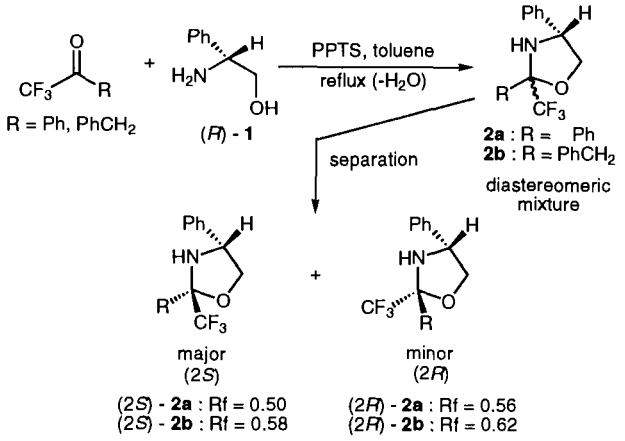
The asymmetric synthesis of 1-substituted 2,2,2-trifluoroethylamines from chiral 1,3-oxazolidines having trifluoromethyl group derived from trifluoromethyl ketones and (*R*)-phenylglycinol is described. The stereospecific reduction of chiral 1,3-oxazolidines with $LiAlH_4$ proceeds in *retention* fashion.

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.

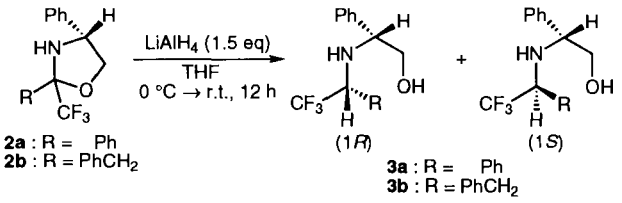
Table 1. Preparation of 1,3-oxazolidines

run	oxazolidine: R	2*S* : 2*R* [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 (CH_2Cl_2 : 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]



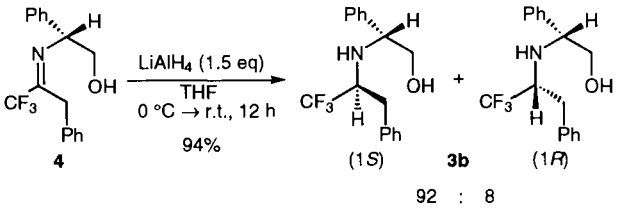
Scheme 2.

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

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

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

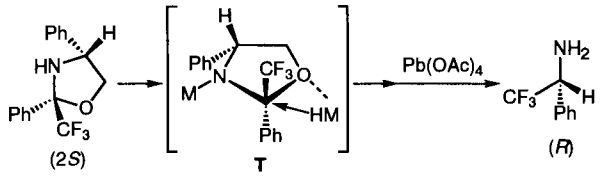
Therefore, asymmetric reduction of imine (**4**)[6] having trifluoromethyl and benzyl group was next investigated with $LiAlH_4$ (Scheme 3). Because (1*S*)-**3b** was obtained in highly diastereoselective manner, it can be concluded that 1,3-oxazolidine does not react after transformation to the metallo-imine[7] 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 known[4] chiral 1-substituted 2,2,2-trifluoroethylamines by oxidative cleavage or hydrogenolysis[10] 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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References and Notes

1 On leave from Chemical Research Center, Central Glass Co. Ltd., Kawagoe, Saitama 350-11

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