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Highly Diastereoselective Synthesis of Enantiopure β-Trifluoromethyl β-Amino Alcohols from Chiral Trifluoromethyl Oxazolidines (Fox)

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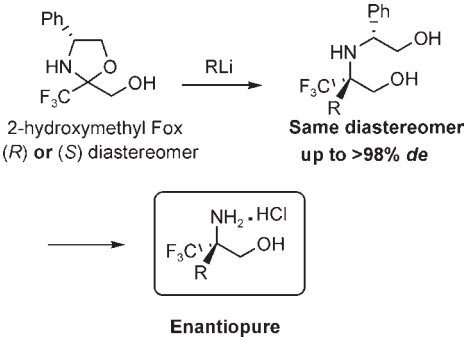
ABSTRACT



The organolithium species addition to 2-hydroxymethyl fluorinated oxazolidines (Fox) provides a highly diastereoselective and straightforward route for the synthesis of enantiopure trifluoromethyl β-amino alcohols quaternarized at the β-position.

Enantiopure β-amino alcohols are very interesting compounds for biological use[1] and for the design of chiral ligands or auxiliaries.[2] Because of the great impact of the incorporation of a trifluoromethyl group on the chemical and the biological properties of molecules,[3] β-trifluoromethyl β-amino alcohols are very attractive compounds mainly as biologically active compounds such as peptidomimetic units.[4] Although several methodologies have been reported for the asymmetric synthesis of β-trifluoromethyl β-amino alcohols monosubstituted in the β-position,[5] to our knowledge very few reports exist on the synthesis of their analogues quaternarized at the β-position.[6] The limitations of these methods are their low diastereoselectivity[6a,b] or the numerous steps required to obtain the enantiopure target compound.[6c]

In order to provide a straight forward and highly stereoselective access to these challenging quaternarized

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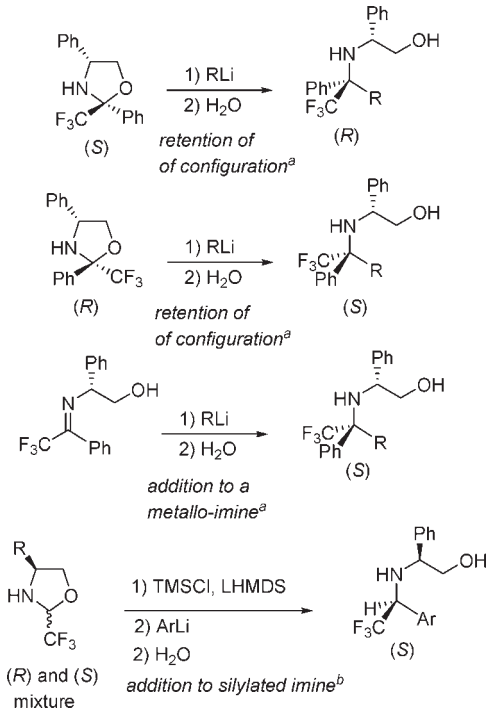
β-trifluoromethyl β-amino alcohols, we decided to investigate the addition reactions of organometallic species to a chiral 2-trifluoromethyl-2-hydroxymethyl-1,3-oxazolidine. The addition of organometallics to unfunctionalized chiral trifluoromethyloxazolidines (Fox) has been reported to provide a convenient access to chiral α-trifluoromethylamines.[7−12] However the stereoselectivity of the organolithium reagent addition to (*R*)-phenylglycinol based fluorinated oxazolidines was reported to proceed with retention of configuration.[8] As a consequence, this strategy requires a tedious separation of the starting oxazolidine diastereomers before the reaction with the organometallics (Scheme 1). Other procedures involve the stereoselective addition of organolithium reagents on a hydroxylated imine which is difficult to isolate or on silylated imine intermediates (Scheme 1).[8,9]

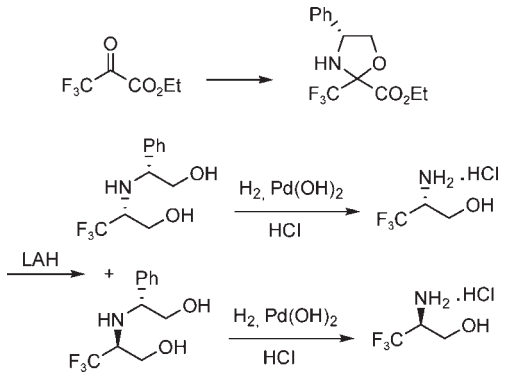
Scheme 1. Stereoselective Synthesis of Chiral Trifluoromethylated Amines from Trifluoromethylated Oxazolidines and Imines



[a] See ref 8. [b] See ref 9.

We recently reported that the LAH reduction of (*R*)-phenylglycinol and ethyl trifluoropyruvate based oxazolidines provided a straightforward access to enantiopure (*S*)- and (*R*)-trifluoroalaninols (Scheme 2).[5k]

Scheme 2. LAH Reduction of Chiral Ethyl Trifluoropyruvate-Based CF_3-Oxazolidines Leading to Enantiopure (*S*)- and (*R*)-Trifluoroalaninols[a]



[a] See ref 5k.

In order to extend this approach to the synthesis of chiral β-trifluoromethyl β-amino alcohols quaternarized at the β-position, we report herein the stereoselective addition of various organolithium compounds to fluorinated 2-hydroxymethyl oxazolidines **2**. The oxazolidines **2** were conveniently obtained as a 71:29 diastereomeric mixture through the chemoselective $NaBH_4$ reduction of the trifluoropyruvate-based oxazolidine **1** (Scheme 3).[13] Each diastereomer of oxazolidines **2** could be easily isolated by silica gel chromatography[14] or by precipitation of the major diastereomer in pentane.

Scheme 3. $NaBH_4$ Reduction of the Chiral Ethyl Trifluoropyruvate-Based CF_3-Oxazolidine **1**[a]

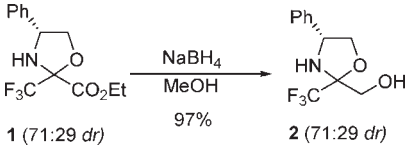


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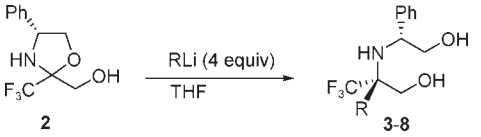
Table 1. Diastereoselective Organolithium Reagents Addition to 2-Hydroxymethyloxazolidines **2**



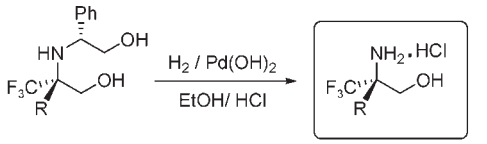
2 **3-8**

entry	oxazolidine	R	*de* (%)[a]	product	yield (%)[b]
1	$\mathbf{2_{maj}}$	Me	>98	(*R*)-**3**	93
2	$\mathbf{2_{min}}$	Me	90	(*R*)-**3**	80
3	**2**[c]	Me	>98	(*R*)-**3**	74
4	$\mathbf{2_{maj}}$	*n*Bu	>98	(*R*)-**4**	77
5[d]	$\mathbf{2_{maj}}$	Ph	>98	(*R*)-**5**	67
6[e]	$\mathbf{2_{maj}}$	≡—TMS	>98	(*R*)-**6**	59
7[e]	$\mathbf{2_{min}}$	≡—TMS	>98	(*R*)-**6**	77
8	$\mathbf{2_{maj}}$	*i*Bu	82	(*R*)-**7**	66
9	$\mathbf{2_{min}}$	*i*Bu	66	(*R*)-**7**	73
10	**2**[c]	*i*Bu	76	(*R*)-**7**	66
11	**2**[f]	CH_2SPh	76	(*R*)-**8**	54

[a] Measured by ^1H and ^{19}F NMR spectroscopy analysis of the crude reaction mixture. >98% means that one single diastereomer was detected. [b] Yields of pure isolated compounds. [c] 71:29 mixture of $\mathbf{2_{maj}/2_{min}}$. [d] Reaction performed at −40 °C. [e] Reaction performed at −20 °C. [f] 88:12 mixture of $\mathbf{2_{maj}/2_{min}}$

The major diastereomer $\mathbf{2_{maj}}$ was treated with an excess amount of methyllithium (4 equiv) at −78 °C in THF to give the amino diol (*R*)-**3** in 93% yield with complete diastereoselectivity (Table 1, entry 1). Intriguingly the addition of methyllithium to the minor diastereomer $\mathbf{2_{min}}$ gave the same amino diol (*R*)-**3** in 80% yield and 90% *de* (Table 1, entry 2). These results strongly contrast with the organolithium reagent additions on diastereomerically pure (*S*) or (*R*) non-hydroxylated oxazolines giving different diastereoisomers (Scheme 1).[8] This result suggests that the same transition state should be involved in the methyllithium addition reaction on both oxazolidines diastereomers $\mathbf{2_{maj}}$ and $\mathbf{2_{min}}$. This was confirmed by the fact that the addition of methyllithium to a 71:29 diastereomeric mixture of oxazolidines **2** also gave the unique (*R*)-**3** diastereomer with an excellent diastereoselectivity (Table 1, entry 3). The addition of *n*-butyllithium and phenyllithium to $\mathbf{2_{maj}}$ occurred also with complete diastereoselectivity (>98% *de*) to give (*R*)-**4** and (*R*)-**5** in 77% and 67% yields respectively (Table 1, entries 4 and 5). The addition of lithium trimethylsilyl acetylide to isolated oxazolidines $\mathbf{2_{maj}}$ and $\mathbf{2_{min}}$ was also completely diastereoselective (>98% *de*) giving the same (*R*)-**6** aminodiol in 59% and 77% yields respectively (Table 1, entries 6 and 7). The addition of *iso*-butyllithium and phenylthiomethyllithium to $\mathbf{2_{maj}}$ and $\mathbf{2_{min}}$ proceeded with lower diastereoselectivity (66% to 82% *de*) although the yields of diastereomerically pure compounds were acceptable after silica gel purification (54% to 73%) (Table 1, entries 8−11). As a preliminary study, the addition of a Grignard reagent (EtMgBr) was investigated but the expected addition product was obtained in a low yield (28%) and an average diastereoselectivity (74% *de*).

Scheme 4. Removal of the Phenylethanol Side Chain of (*R*)-**3**, (*R*)-**4**, and (*R*)-**5**



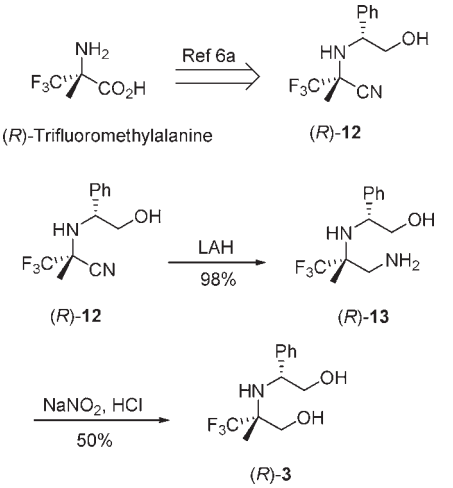
(*R*)-**3** : R = Me (*R*)-**9** : R = Me, 94%

(*R*)-**4** : R = *n*Bu (*R*)-**10** : R = *n*Bu, 89%

(*R*)-**5** : R = Ph (*R*)-**11** : R = Ph, 99%

In order to obtain the enantiopure targeted amino alcohols, the phenylethanol side chains of (*R*)-**3**, (*R*)-**4**, and (*R*)-**5** were cleanly removed by hydrogenolysis. The enantiopure fluorinated amino alcohol hydrochlorides (*R*)-**9**, (*R*)-**10**, and (*R*)-**11** were then obtained in 94%, 89%, and 99% yields respectively (Scheme 4).

Scheme 5. Structure Correlation for the Assignment of (*R*)-**3** Absolute Configuration



The (*R*) configuration of the amino alcohols obtained was assigned by structure correlation with known compounds. We previously reported that the enantiopure (*R*)-trifluoromethylalanine was efficiently obtained in a few steps from the (*R*)-amino nitrile (*R*)-**12** (Scheme 5).[6a] Thus the amino nitrile (*R*)-**12** and its corresponding diamino alcohol (*R*)-**13** were resynthesized according to our reported procedure[6a] and (*R*)-**13** was converted into the

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(14) Although each diastereomer was obtained in enantiopure form, their configurations at the C-2 could not be assigned.

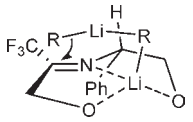

Figure 1. Postulated transition state: *si*-face attack of a chelated *Z* metallo-imine.

corresponding diastereomerically pure amino diol (*R*)-**3** through a diazotization reaction (Scheme 5). The optical rotation and the spectral data of this compound perfectly matched the compound (*R*)-**3** synthesized in this work (Table 1, entry 1). Because of similar postulated reaction mechanisms the configurations of compounds **4** to **8** were also anticipated to be (*R*).

In order to explain these results we suggest that the reaction proceeds through the same *Z*-metallo-imine resulting from the organometallic mediated ring opening of the hydroxymethyloxazolidines $\mathbf{2}_{\mathbf{maj}}$ and $\mathbf{2}_{\mathbf{min}}$. To rationalize the diastereoselectivity of this reaction we propose a transition state inspired by both Iwao's model[15] based on the *N*,*O* (phenylglycinol) metal chelation and Spero's model[16] involving a *N*,*O* (oxymethyl) chelation. The *N*,*O*,*O*-tridentate chelation model we propose is consistent with an *si*-face attack of the chelated *Z* metallo-imine by a dimeric organolithium compound (Figure 1).

In summary, the organolithium species addition on chiral hydroxymethyl trifluoromethyl oxazolidines is highly diastereoselective. This provides a convenient and straightforward access to enantiopure β-trifluoromethyl β-amino alcohols quaternarized at the β-position.

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Supporting Information Available. Complete experimental procedures, and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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