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Generation and reactions of α-trifluoromethyl stabilized aziridinyl anion, a general synthetic precursor for stereospecific construction of α-amino-α-trifluoromethylated quaternary carbon

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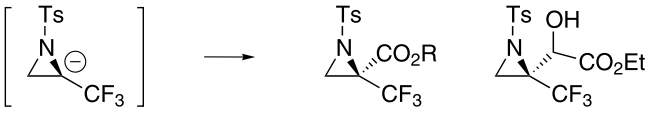
Abstract—Optically pure α-trifluoromethylated aziridinyl anions react with various electrophiles to give the corresponding optically pure 2-trifluoromethyl-2-substituted aziridines, which are general synthetic precursors for optically pure α-amino-α-trifluoromethylated compounds, such as trifluoromethylated α/β-amino acids, in good yields.

Development of new synthetic methodologies for introduction of fluorine atoms into various bioactive compounds,[1] such as amino acids,[2] has been eagerly demanded. Among such demands, construction of a chiral trifluoromethylated quaternary carbon center is a tough problem which remains to be solved. Introduction of a trifluoromethyl group toward the α-carbon of amino acid to construct the trifluoromethylated quaternary carbon sometimes resulted in providing higher chemical stability, strict conformational fixation, and remarkable change in reactivity compared to the parent amino acids. Such quaternary carbons have mainly been prepared from starting materials such as CF_3TMS,[3] CF_3I,[4] 1,1,2-perfluoroalkyl(aryl)ethylenes,[5] trifluoroacetoimidoyl halides,[6] and trifluoropyruvates;[7] thus further resolution of the racemate or individual stereoselective methodology was needed for obtaining a chiral one. Zanda et al. succeeded in construction of optically active quaternary trifluoromethylated α-amino acids via diastereoselective alkylation of chiral sulfimines derived from trifluoropyruvate with Grignard reagents[7b,c] or the reaction of non-chiral imine from the pyruvate with chiral nucleophiles,[7d–f] although individual effort was needed for every amino acid to tune the reaction conditions to attain high diastereoselectivity. Meanwhile, no deprotonation followed by stereospecific alkylation on the α-trifluoromethylated methine carbon (CF_3-CH-RR′) has been realized.



Scheme 1.

We recently reported that the trifluoromethylated three-membered ring system is useful for a stereospecific construction of quaternary trifluoromethylated compounds; generation of a trifluoromethyl-stabilized oxiranyl anion from highly available optically pure 2,3-epoxy-1,1,1-trifluoropropane,[8,9] and stereospecific alkylation.[10] This result clearly demonstrates that the oxiranyl anion does not racemize in the course of the reaction, and is a very efficient precursor for stereospecific construction of tertiary trifluoromethylated alcohols with optically pure quaternary carbon. On this basis, optically pure 2-trifluoromethyl-2-substituted aziridines would be general precursors for β-trifluoroamines[11] with a quaternary stereogenic carbon center and could be prepared by the stereospecific alkylation of the trifluoromethylaziridinyl anion.[8,12] This protocol would be useful for the preparation of optically pure trifluoromethylated quaternary amino acids and β-amino-α-hydroxy-β-trifluoromethyl carboxylic acids; the latter would be a key structure of protease inhibitors (Scheme 1).

The preparation of *N*-substituted-2-trifluoromethyl aziridines is summarized in Scheme 2. The common starting material, optically pure 2,3-epoxy-1,1,1-trifluoropropane **1**, was prepared via hydrolytic kinetic resolution.[10] Preparative methods for *N*-benzyl aziridine **5**, *N*-(*p*-anisyl) aziridine **6** and *N*-(*o*-anisyl)

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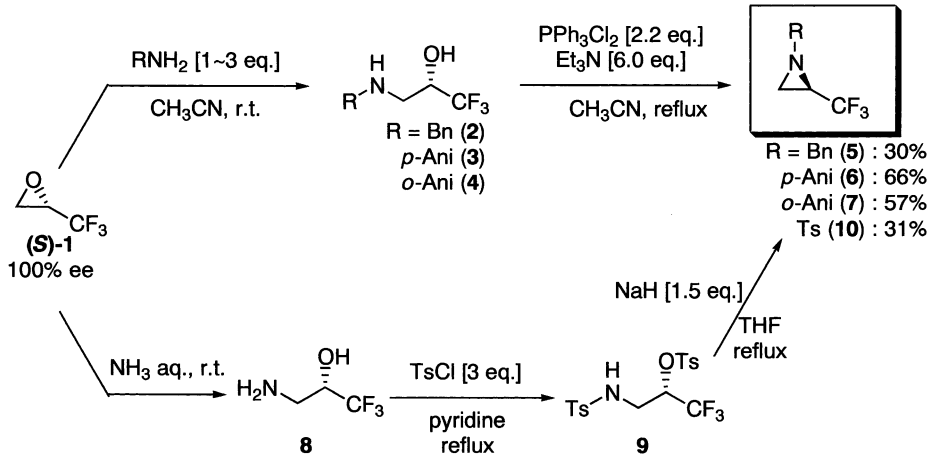
aziridine **7** were already reported.[13] *N*-Tosyl aziridine **10** was prepared via intramolecular S_N2 substitution of tosylate **9** of α-trifluoromethyl amino alcohol **8**.

Generation of aziridinyl anions was confirmed by the reaction with PhCHO. The generation of the anion was markedly affected by the structure of the *N*-substituent, as summarized in Table 1. Detailed experimental conditions are described in the footnote to Table 1. The combination of *N*-(anisyl)-aziridines **6** and **7** with *s*-BuLi and *N*-Ts-aziridine **10** with *n*-BuLi gave the expected aziridinyl alcohols **11a** in 68%, **11b** in 45% and **12a** in 83% yields, respectively (Table 1, entries 3, 5, and 6). The diastereoselectivity of the product **12a** was 75/25. The present results suggested that the electron-withdrawing property of *N*-substituents and the deprotonating ability of the alkyllithium are essential to promote the reaction. Thus, the Ts group would act as the best *N*-substituent among those tested.

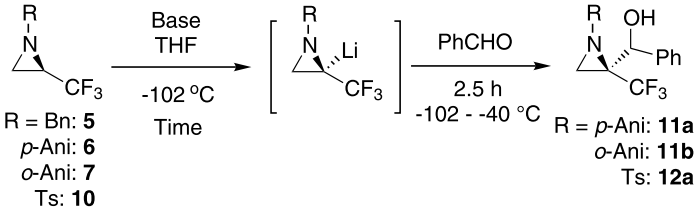
The scope of the electrophiles of the reaction is summarized in Table 2. The aziridinyl anion from *N*-Ts aziridine **10** reacted with aldehydes and ketones smoothly to give the corresponding alcohols in moderate to good yields (entries 1–5). The reaction with glyoxylate gave **12e**,[14] a general α-hydroxy-β-amino acid precursor, predominantly (entry 5). The reactions with acid chloride and halo formate gave the expected products in good yields (entries 6 and 7). The product **12g** is the general precursor for α-trifluoromethyl-α-amino acids.[15] The reaction with benzyl bromide gave alkylated product **12h** in 13% yield (entry 8).

The stereochemistry of the product was confirmed by an X-ray crystallographic analysis of a ring-opened derivative of compound **12g**. Compound **12g** was allowed to react with optically pure phenethyl amine to give compound **13**, 1,1,1-trifluoromethyl-2,3-diamino acid (Scheme 3). The ORTEP view of **13** is shown in Figure 1.[16] Retention of the configuration at the trifluoromethylated quaternary carbon center in the course of the reaction was confirmed.



Scheme 2.

Table 1. Preparations and reactions of aziridinyl anion with PhCHO

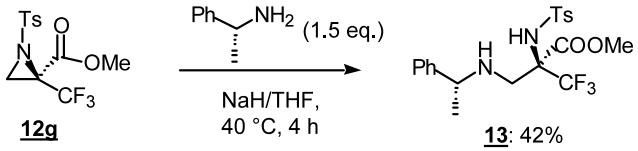


Entry	Aziridine	Base	Time (min)	Isolated yield (%)	
1	**5**	*n*-BuLi	30	No reaction	(Recovery of **5**, 97%)
2	**6**	*n*-BuLi	30	**11a** (11)[a]	(Recovery of **6**, 84%)
3	**6**	*s*-BuLi	30	**11a**, 68	
4	**7**	*n*-BuLi	30	**11b** (8)[a]	(Recovery of **7**, 83%)
5	**7**	*s*-BuLi	30	**11b**, 45	
6	**10**	*n*-BuLi	10	**12a**, 83	

General reaction procedure: To a solution of aziridine (1 mmol) in dry THF (5 ml), cooled to –102°C, base (1.1 equiv.) was added. After 10–30 min, benzaldehyde (1.5 mmol) was added and then stirred for a further 10 min.

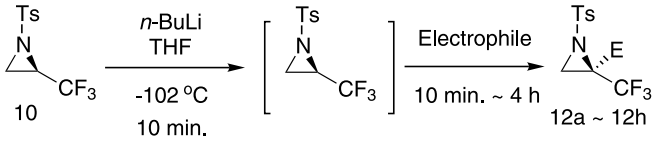
[a] Yield was determined by ^{19}F NMR.

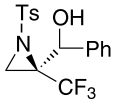
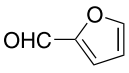
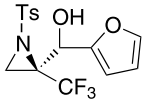
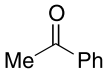
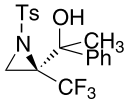
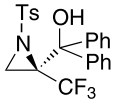
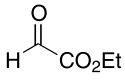
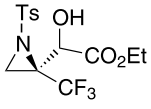
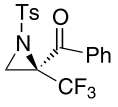
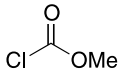
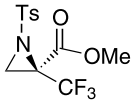
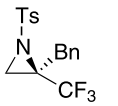
In conclusion, we have succeeded in the generation and the stereospecific alkylation of α-trifluoromethylated aziridinyl anions. The *N*-substituents were found essential for generation of the anion. The aziridinyl anion reacted well with various electrophiles in moderate to good yields. Moreover, the reaction proceeded with retention of the absolute configuration at the trifluoromethylated quaternary carbon center throughout the reactions. The present products, especially **12e** and **12g** can be general precursors for optically pure trifluoromethylated α/β-amino acids. Further optimization of the reaction conditions and synthetic applications are now in progress.



Scheme 3.

Table 2. Scope of the electrophiles



Entry	Electrophile	Product	Isolate yields [%]	Diastereoselectivity[a]
1	PhCHO		**12a**, 91[99]	77/23
2			**12b,** 95	77/23
3			**12c,** 75	No separation[b]
4			**12d,** 45	
5			**12e**, 27	67/33
6			**12f,** 67	
7			**12g,** 85	
8	BnBr		**12h,** 13	

[a]Determined by ^{19}F NMR and GC. [b]Not separated by GC, and no separation of ^{19}F nor ^{1}H NMR.

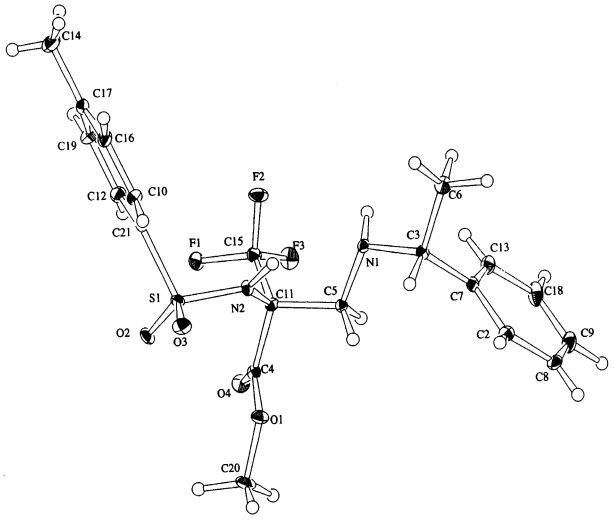


Figure 1. The ORTEP view of **13**.

Acknowledgements

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14. Spectroscopic data for **14e** (a mixture of diastereomers): Overall yield was 27%, ds = 67/33, viscous colorless liquid. IR (neat) 3520, 1750 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, $J=9$ Hz, 2H, minor), 7.87 (d, $J=9$ Hz, 2H, major), 7.35–7.38 (m, 2H, major and minor), 5.04 (d, $J=7$ Hz, 1H, major), 5.02 (br, 1H, minor), 4.22–4.38 (m, 2H, major and minor), 3.61 (d, $J=4$ Hz, 1H, minor), 3.55 (d, $J=7$ Hz, 1H, major), 3.16 (s, 1H, minor), 3.02 (d, $J=2$ Hz, 1H, major), 2.85 (s, 1H, minor), 2.74 (s, 1H, major), 2.46 (s overlap?, 3H, major and minor), 1.33 (t, $J=7$ Hz, 3H, minor), 1.28 (t, $J=7$ Hz, 3H, major) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 91.4 (s, CF_3, minor), 91.1 (s, CF_3, major) ppm; DI/MS m/z (%) 367 (tr, M^+), 294 (7), 212 (5), 195 (4), 155 (47), 138 (27), 91 (100), 65 (30); Anal calcd for $C_{14}H_{16}F_3NO_5S$: C, 45.77; H, 4.39; N, 3.81. Found: C, 45.78; H, 4.58; N, 4.15; $[\alpha]_D^{25} = -0.4$ (diastereo mixture, c 1.06, MeOH).
15. Spectroscopic data for **12g**: Overall yield was 85%, white solid. IR (KBr) 1760 cm^{-1}; mp = 81–82°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82–7.86 (m, 2H), 7.26–7.39 (m, 2H), 3.93 (s, 3H), 3.54 (q, $J=2$ Hz, 1H), 2.79 (s, 1H), 2.47 (s, 3H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 89.0 (s, CF_3) ppm; GC/MS m/z (%) 323 (2: M^+), 292 (2), 168 (20), 155 (56), 91 (100), 65 (23). Anal. calcd for $C_{12}H_{12}F_3NO_4S$: C, 44.58; H, 3.74; N, 4.33. Found: C, 44.63; H, 4.03; N, 4.31; $[\alpha]_D^{25} = -60.7$ (c 1.16, MeOH).
16. Crystal data for **13** at 150 K: $C_{20}H_{23}F_3N_2O_4S$; Mr = 444.47; orthorhombic; $P2_12_12_1$ (#19); $a=7.2660(2)$, $b=13.3922(4)$, $c=21.2120(9)$ Å, $V=2064.1(1)$ Å^3, $Z=4$, $Dx=1.430$ g/cm^3; $\mu=2.13$ cm^{-1} for Mo Kα radiation ($\lambda=0.7107$ Å). The structure was solved by a direct method (SIR92), expanded using Fourier techniques (DIRDIF94), and refined by a full-matrix least-square method. Final R was 0.030 and R_w was 0.033 for 2290 reflections with $I_0 > 3.00\sigma$ (I_0). Reflection/parameter ratio was 6.31, Goodness of fit indicator was 1.73. Max shift/error in final cycle was 0.06.