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Synthesis of Optically Active α-Trifluoromethylamines by Rearrangement of β-Amino-α-trifluoromethyl Alcohols

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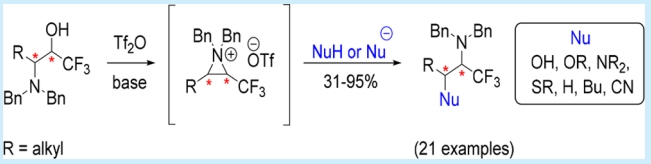
Supporting Information

ABSTRACT: The synthesis of various optically active α-trifluoromethylamines has been realized from β-amino-α-trifluoromethyl alcohols via an aziridinium ion intermediate under kinetic conditions.

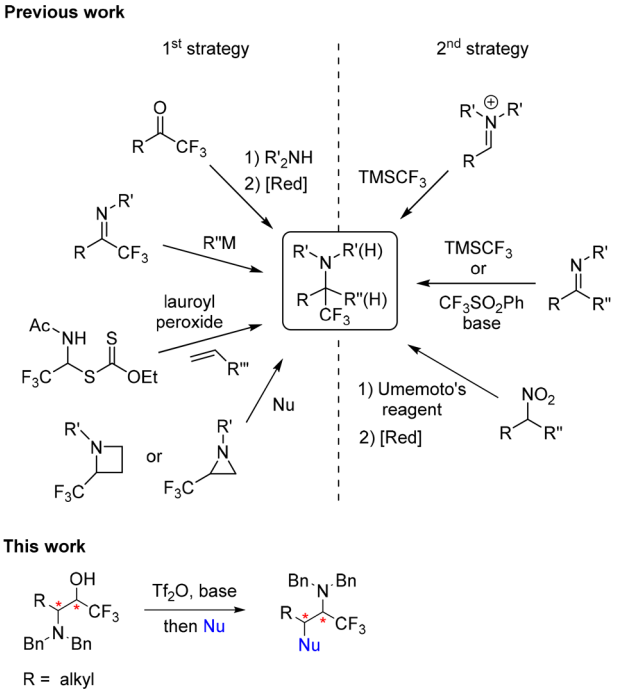


Compounds containing a trifluoromethyl group have received extensive attention as the lipophilicity of this group can increase the bioavailability of the molecules by increasing their ability to cross membranes. Furthermore, as a C−F bond is stronger than a C−H bond, an increase of the metabolic stability of CF_3-containing compounds is observed.[1] To synthesize α-trifluoromethylamines, two main strategies have been developed. One strategy consists of the transformation of trifluoromethylated substrates to α-trifluoromethylamines such as reductive amination of trifluoromethyl ketones,[2] addition of organometallic reagents on α,α,α-trifluoromethylimines,[3] generation of radicals from *N*-acetyl aminotrifluoromethyl dithiocarbonate, and addition of these radicals on alkenes,[4] as well as the ring opening of trifluoromethylaziridines or 2-trifluoromethylazetidines by nucleophiles.[5] The second strategy is the introduction of a CF_3 group on the substrates using trifluoromethylating reagents.[6] In this regard, the Ruppert−Prakash reagent has been added to iminium[7−9] as well as to imines.[10] In addition, trifluoromethylphenyl sulfone was used to access α-trifluoromethylamines from imines,[6b] and Umemoto's reagent was utilized to synthesize α-trifluoromethyl nitrones, which are precursors of amines (Scheme 1).[11] However, it is worth mentioning that there are only a few reports on the synthesis of optically active α-trifluoromethylamines by either diastereo-[3a,b,5a,b,f] or enantioselective[2a,d,3c,d] reactions.

In the context of our studies on ring expansion and ring contraction of heterocycles containing nitrogen[12] and on the rearrangement of β-amino alcohols,[13] via aziridinium ion intermediates,[14] we would like to report here that optically active functionalized α-trifluoromethylamines **A** can be obtained from β-amino-α-trifluoromethyl alcohols **B** with good diastereo- and enantioselectivity by regioselective ring opening of an aziridinium ion intermediate **C** by a variety of nucleophiles under kinetic conditions (Scheme 2).

At first, β-amino-α-trifluoromethyl alcohols **B** were synthesized from commercially available optically active *N*,*N*-dibenzylamino alcohols **1** (Scheme 3). These *N*,*N*-dibenzylamino alcohols **1** were transformed to the corresponding *N*,*N*-dibenzylamino aldehydes **2** in good yields by a Swern oxidation.[15] It is worth mentioning that aldehydes **2** were engaged in the next step without any purification to avoid the epimerization of the stereogenic center. Aldehydes **2** were then treated with the Ruppert−Prakash reagent in the presence of tetra-*n*-butylammonium fluoride to produce the optically active β-amino-α-trifluoromethyl alcohols **3**−**6** as a mixture of *anti*/*syn* diastereoisomers, which were separated by

Scheme 1. Main Strategies for α-Trifluoromethylamine Synthesis



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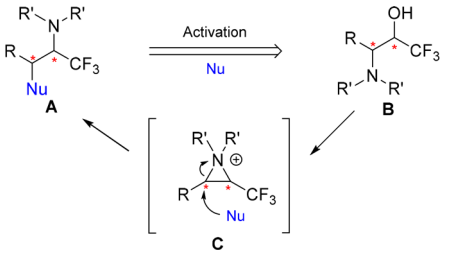
Scheme 2. Synthesis of α-Trifluoromethylamines by Rearrangement of β-Amino-α-trifluoromethyl Alcohols



Scheme 3. Synthesis of β-Amino-α-trifluoromethyl Alcohols

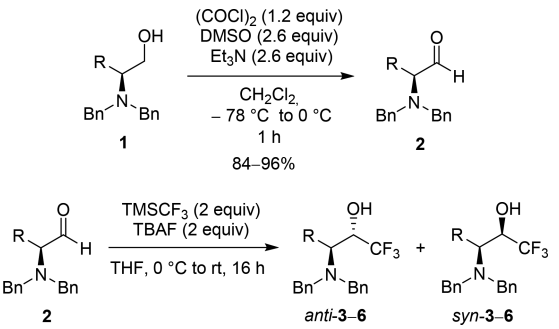
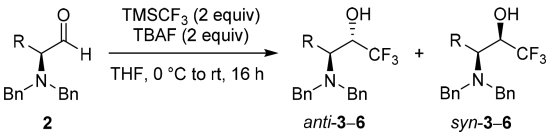
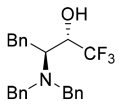
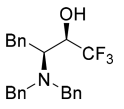
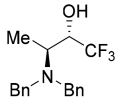
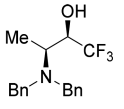
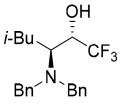
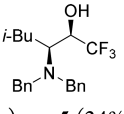
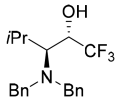
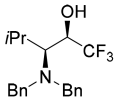


Table 1. Synthesis of β-Amino-α-trifluoromethyl Alcohols by Trifluoromethylation



entry	*anti*/*syn*[a]	*anti*-**3**–**6** (yield)[b]	*syn*-**3**–**6** (yield)[b]
1	79:21	 (+)-*anti*-**3** (52%)	 (+)-*syn*-**3** (20%)
2	79:21	 (+)-*anti*-**4** (67%)	 (+)-*syn*-**4** (18%)
3	72:28	 (−)-*anti*-**5** (51%)	 (+)-*syn*-**5** (24%)
4	84:16	 (+)-*anti*-**6** (56%)	 (+)-*syn*-**6** (10%)

[a]The *anti*/*syn* ratio was determined by analysis of ^{19}F NMR spectra of the crude. [b]Isolated yields.

flash column chromatography on silica gel, with the *anti*-isomer being the major compound (Table 1).[16−18]

Scheme 4. Treatment of β-Amino-α-trifluoromethyl Alcohols 3 with DAST

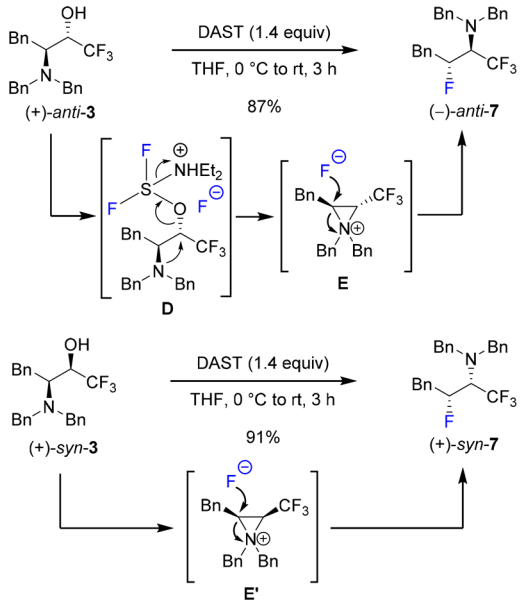
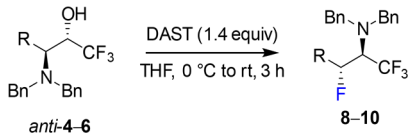
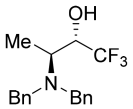
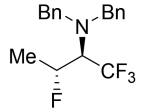
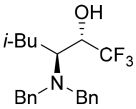
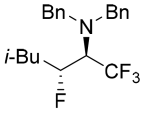
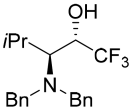
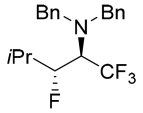


Table 2. Treatment of the β-Amino-α-trifluoromethyl Alcohols with DAST



entry	*anti*-**4**–**6**	**8**–**10** (yield[a])
1	 (+)-*anti*-**4**	 (+)-**8** (77%)
2	 (−)-*anti*-**5**	 (+)-**9** (95%)
3	 (+)-*anti*-**6**	 (+)-**10** (66%)

[a]Isolated yields.

Having compounds *anti*-**3**−**6** and *syn*-**3**−**6** in hand, compounds (+)-*anti*-**3** and (+)-*syn*-**3** were selected as model substrates. As *N*,*N*-diethylaminosulfur trifluoride (DAST)[19] is able to initiate the formation of rearranged products via the participation of neighboring groups, such as amines,[20] compounds (+)-*anti*-**3** and (+)-*syn*-**3** were treated with DAST (Scheme 4). When (+)-*anti*-**3** was treated with 1.4 equiv of DAST, compound (−)-*anti*-**7** was isolated with 87% yield with an excellent diastereoselectivity (better than 99%).[21] Under the same conditions, (+)-*syn*-**7** was obtained from (+)-*syn*-**3** with 91% yield (dr better than to 99%). After

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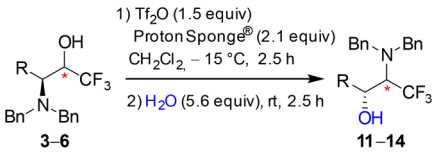
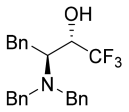
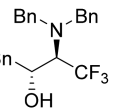
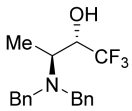
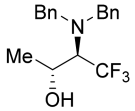
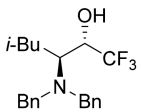
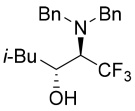
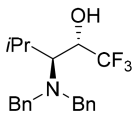
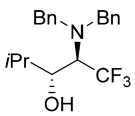
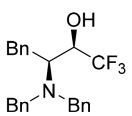
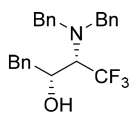
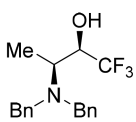
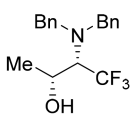
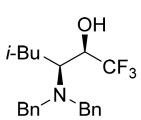
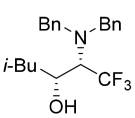
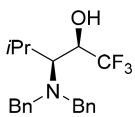
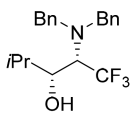
Table 3. Synthesis of β-Trifluoromethyl-β-aminoalcohols

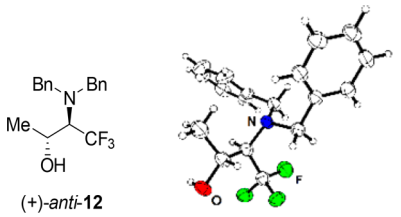


3–6 11–14

entry	3–6	8–11 (yield[a])
1	 (+)-*anti*-**3**	 (−)-*anti*-**11** (81%)
2	 (+)-*anti*-**4**	 (+)-*anti*-**12** (89%)
3	 (−)-*anti*-**5**	 (+)-*anti*-**13** (82%)
4	 (+)-*anti*-**6**	 (+)-*anti*-**14** (52%)
5	 (+)-*syn*-**3**	 (+)-*syn*-**11** (91%)
6	 (+)-*syn*-**4**	 (−)-*syn*-**12** (91%)
7	 (+)-*syn*-**5**	 (−)-*syn*-**13** (63%)
8	 (+)-*syn*-**6**	 (−)-*syn*-**14** (31%)

[a]Isolated yields.

activation of the hydroxy group of (+)-*anti*-**3** by DAST, intermediate **D** is formed, producing the aziridinium ion **E**. Due to electrostatic repulsion of the CF_3 group toward nucleophiles, the regioselective nucleophilic attack by the fluoride on the nontrifluoromethylated carbon of the aziridinium ion gives (−)-*anti*-**7**. Similarly, (+)-*syn*-**3** is transformed into (+)-*syn*-**7** via the aziridinium ion **E′**.



(+)-*anti*-**12**

Figure 1. Structure of (+)-*anti*-**12** by X-ray diffraction.

Treatment of *anti*-β-amino-α-trifluoromethyl alcohols **4**–**6** with DAST was performed (Table 2). The corresponding fluorinated compounds **8**–**10** were obtained with good yields. Compounds (+)-**8** and (+)-**9** were isolated with 77 and 95% yields, respectively (Table 2, entries 1 and 2). However, compound (+)-*anti*-**6** led to the corresponding product (+)-**10** with a modest yield of 66%, probably due to the steric hindrance of the isopropyl group (Table 2, entry 3).

To access β-amino-β-trifluoromethyl alcohols, which can be important to produce biologically active compounds,[1,2] treatment of *anti*-**3**–**6** and *syn*-**3**–**6** with a stoichiometric amount of triflic anhydride (Tf_2O) and 1,8-bis-(dimethylamino)naphthalene (Proton Sponge) in dichloromethane (− 15 °C, 2.5 h), followed by the addition of H_2O as the nucleophile (5.6 equiv, rt, 2.5 h), has been realized.[12g,h] Under these conditions, optically active *anti*-**3**–**6** were diastereoselectively converted to the corresponding optically active β-amino-β-trifluoromethyl alcohols *anti*-**11**–**14** in good to excellent yields. Likewise, treatment of optically active *syn*-**3**–**6**, under the same conditions, led to the corresponding products *syn*-**11**–**14**.[22] The results are summarized in Table 3. An X-ray diffraction of (+)-*anti*-**12** was possible and allowed us to determine the relative and absolute configuration of the stereocenters of the rearranged products (Figure 1).

In addition to H_2O, other nucleophiles can be used to transform amino alcohols **B** to trifluoromethyl amines **A**. As a model substrate, β-amino-α-trifluoromethyl alcohol (+)-*anti*-**3** was transformed into a variety of α-trifluoromethylamines **15** (Table 4). Using alcohols, alcoholates (Table 4, entries 1–3), amines (Table 4, entries 4–6), sodium pyrazolide (Table 4, entry 7), thiols (Table 4, entry 8), bromide (Table 4, entry 9), hydride (Table 4, entry 10), and carbanion (Table 4, entries 11 and 12), compounds **15a**–**l** were isolated in good yields and excellent diastereoselectivity.

It is worth noting that a selective deprotection of the *N*,*N*-dibenzylamines can be performed as compound (−)-**16**, prepared by rearrangement of (−)-*anti*-**5** using sodium phenoxide as the nucleophile, was hydrogenolized (1 atm) in the presence of a catalytic amount of Pd/C in methanol. The corresponding free amine (+)-**17** was obtained in 61% yield and was engaged in a peptidic coupling with a natural *N*-protected L-amino acid, *N*-Cbz-L-alanine (Scheme 5). The reaction was performed by generating *in situ* a mixed anhydride from the free carboxylic acid of *N*-Cbz-L-alanine using isobutyl chloroformate,[23] which produced the desired dipeptide (−)-**18** in 58% yield.

In summary, the rearrangement of β-amino-α-trifluoromethyl alcohols by activation of the hydroxy group, followed by the addition of nucleophiles, led to various β-amino-β-trifluoromethyl alcohols and diversely functionalized α-trifluoromethylamines in high yields. The reaction is regio- and diastereoselective. In addition, we demonstrated that the

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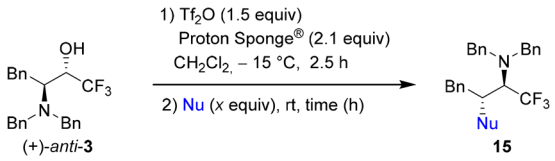
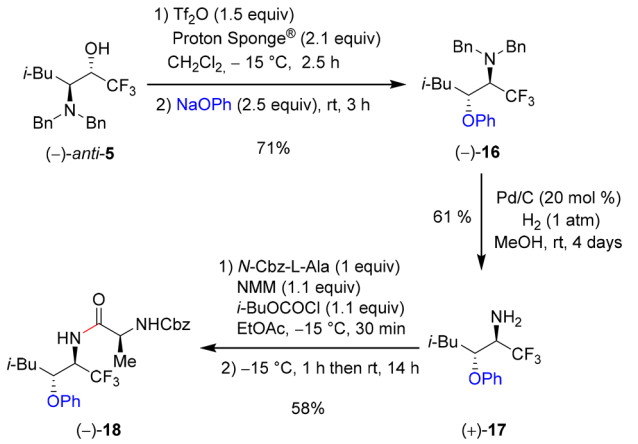
Table 4. Synthesis of α-Trifluoromethylamines



entry	Nu (x equiv)	time (h)	12 (yield[a])
1	MeOH (5)	2.5	(−)-**15a** (84%)
2	 (5)	3	(−)-**15b** (70%)
3	NaOPh (2.5)	4	(−)-**15c** (75%)
4	 (2.5)	3.5	(−)-**15d** (68%)
5	 (2.8)	4	(−)-**15e** (80%)
6	$PhNH_2$ (2.7)	3	(+)-**15f** (95%)
7	 (0.5 M/ THF) (3)	3.5	(+)-**15g** (95%)
8	EtSH (2.5)	4	(−)-**15h** (75%)
9	*n*-Bu_4NBr (3)	3	(−)-**15i** (80%)
10	*n*-Bu_4NBH_4 (2.5)	5	(−)-**15j** (90%)
11	*n*-BuCu(CN)Li (0.15 M/ Et_2O) (3.7)	3	(−)-**15k** (60%)
12	*n*-Bu_4NCN (2.8)	3	(−)-**15l** (60%)

[a]Isolated yields.

Scheme 5. Application of α-Trifluoromethylamines



N-deprotected α-trifluoromethylamines can be involved in a peptidic coupling. The synthesized optically active β-amino-β-trifluoromethyl alcohols and substituted α-trifluoromethylamines can be useful building blocks in medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02353.

Experimental procedures, characterization, ^{1}H, ^{13}C, and ^{19}F NMR spectra of isolated compounds, supercritical fluid chromatography chromatograms of the products (PDF)

Accession Codes

CCDC 1848221 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by sending an e-mail to data_request@ccdc.cam.uk, or by contacting The Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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