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Access to Enantio-enriched Substituted α-Trifluoromethyl Azepanes from L-Proline

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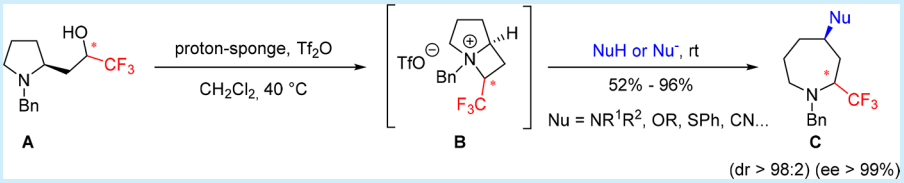
Supporting Information



ABSTRACT: 4-Substituted α-trifluoromethyl azepanes **C** were synthesized via the ring expansion of trifluoromethyl pyrrolidines **A**, which were synthesized from L-proline via a regioselective ring-opening of a bicyclic azetidinium intermediate **B** by various nucleophiles. The regioselectivity of the ring expansion is induced by the presence of a trifluoromethyl group. The chirality of the starting material was transferred to the azepanes with high enantiomeric excess.

Azepanes constitute the core of many natural and bioactive molecules[1,2] (Figure 1) and are one of the 100 most present ring systems in small drug molecules.[3] As a consequence, various methods to access azepanes has been developed.[4] The incorporation of F atoms can influence the biological activity of a molecule by influencing its conformation, metabolic stability, lipophilicity, or p*Ka*.[5] In particular the introduction of a trifluoromethyl group in the α-position of an amino group is very interesting as the presence of a CF_3 in such position is decreasing the basicity of the amine while maintaining its hydrogen bond donor property. Therefore, such α-trifluoromethyl amines can be very good amide isosteres.[6]

Previous syntheses allowing the preparation of α-trifluoromethyl azepanes were reported by using ring-closing metathesis,[7] lactamization of α-trifluoromethyl amines,[8] addition of nucleophiles on trifluoromethyl imines,[9] addition of $TMSCF_3$ on cyclic imines,[10] or intramolecular [2 + 2]-cycloaddition of ω-acetylenic allenes[11] (Scheme 1). However, in most cases, only a few examples were reported, especially for highly enantio-enriched azepanes, which would be important for the discovery of new bioactive compounds. Therefore, here, we report a general method to access highly enantio-enriched α-trifluoromethyl azepanes.

In the context of our ring-expansion program,[12] the synthesis of substituted α-trifluoromethyl azepanes **A** was envisioned from pyrrolidine **D** via an azetidinium intermediate

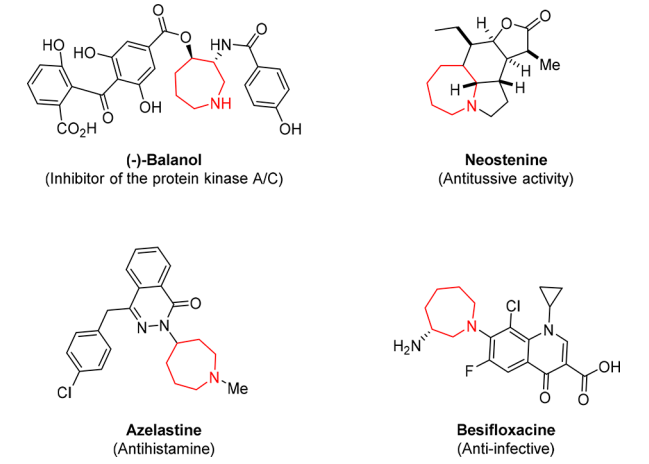
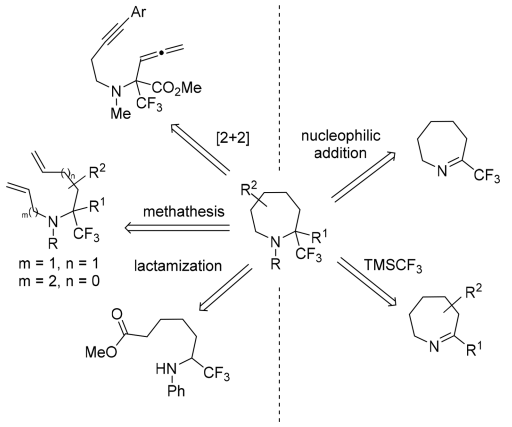


Figure 1. Bioactive molecules containing azepane rings.

Scheme 1. Previous Syntheses of α-Trifluoromethyl Azepanes



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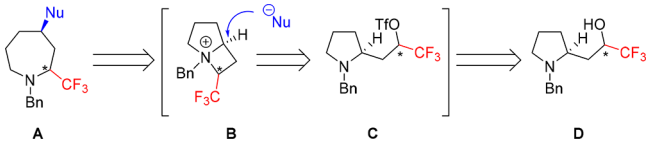
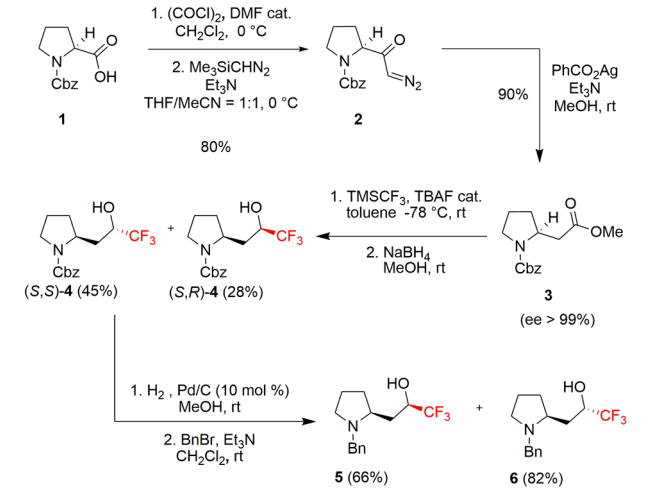
B (Scheme 2). This type of bicyclic azetidinium intermediate as already been employed to access azepanes, but with regioselectivity problems during the ring opening.[4i,13] In our case, the presence of the trifluoromethyl group should render the nucleophilic attack regioselective.[12d,14]

Scheme 2. Strategy To Access α-Trifluoromethyl Azepanes



Pyrrolidines **D** were prepared from L-proline by realizing a one-carbon Arndt−Eistert homologation. Initially, (*S*)-*N*-Cbz-proline **1** was treated with oxalyl chloride to produce the corresponding acid chloride, which was treated with trimethylsilyldiazomethane to form, after 5 h at 0 °C, diazoketone **2** (Et_3N, THF/MeCN = 1:1, 80%). When diazoketone **2** was treated with AgOBz, Et_3N in MeOH, a Wolff rearrangement occurred to produce the desired methyl ester **3** (90%, >99% enantiomeric excess (ee)).[15] The addition of $TMSCF_3$ to **3**, in the presence of a catalytic amount of TBAF (toluene, −78 °C), under Prakash's conditions,[16] led to a ketone intermediate that was not isolated but directly reduced with $NaBH_4$ to produce two separable diastereomers: pyrrolidines (*S*,*S*)-**4** and (*S*,*R*)-**4** in 45% and 28% yields, respectively. Subsequently, the *N*-Cbz protecting group of compounds (*S*,*S*)-**4** and (*S*,*R*)-**4** was replaced by a *N*-benzyl group in order to make the nitrogen lone pair available for the formation of the azetidinium intermediate **B** (Scheme 3).

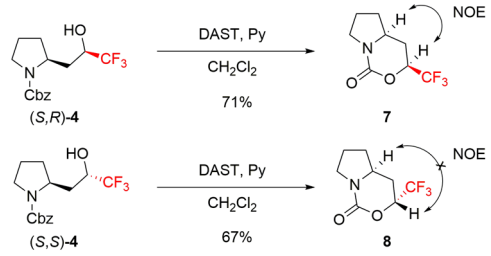
Scheme 3. Synthesis of Trifluoromethyl Pyrrolidines



The relative stereochemistry of compounds **4** was determined by NOE experiments on the bicyclic compounds **7** and **8** which were prepared from (*S*,*R*)-**4** and (*S*,*S*)-**4**, respectively, by treatment with DAST (Scheme 4).

With **5** and **6** in hand, the formation of the bicyclic azetidinium intermediates **B** as well as their ring opening with different nucleophiles was evaluated. When **5** was treated at room temperature with Tf_2O (1.1 equiv), in the presence of 1,8-bis(dimethylamino)naphthalene (proton-sponge) (2.0 equiv) in CH_2Cl_2, only the triflate intermediate **C** was detected

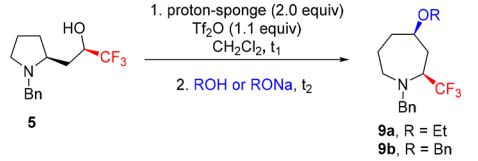
Scheme 4. Determination of the Relative Configuration of (*S*,*R*)-4 and (*S*,*S*)-4 by NOE



by GC-MS and TLC after 5 h. The temperature had to be increased to 40 °C to observe the complete disappearance of the triflate **C** by TLC, after 5 h. This observation allowed us to assume that an azetidinium intermediate was formed. Nucleophiles (2.5 equiv) were then added to the reaction mixture at room temperature.

When ethanol or benzyl alcohol were added to **5**, the corresponding azepanes were not formed (see Table 1, entries 2 and 3), even after heating the reaction mixture at 40 °C (Table 1, entries 4 and 5). However, using the corresponding sodium ethoxide and benzyloxide, which are more nucleophilic than the alcohols, azepanes **9a** and **9b** were formed with an excellent diastereoselectivity and they were isolated in good yields of 86% and 95%, respectively (Table 1, entries 6 and 7).

Table 1. Ring-Expansion Conditions



entry	nucleophile	t_1	t_2	yield (%)
1		rt		
2	EtOH	40 °C	rt[a]	
3	BnOH	40 °C	rt[a]	
4	EtOH	40 °C	40 °C	
5	BnOH	40 °C	40 °C	
6	EtONa	40 °C	rt[a]	86 (dr > 98:2)
7	BnONa	40 °C	rt[a]	95 (dr > 98:2)

[a]Room temperature.

We were pleased to find that the reaction is general, because various nucleophiles can be used. The use of sodium phenoxide and tetrabutylammonium acetate respectively led to **9c** (77%) and **9d** (87%) (Scheme 5). When other nucleophiles such as amines, which are more nucleophilic than alcohols, were utilized the corresponding 2-trifluoromethyl-4-amino azepanes **9e**−**9i** were isolated in good yields (79%−95%). Benzhydrazine and tetrabutylammonium azide were also used as nucleophiles and led to the corresponding substituted azepanes **9j** and **9k**. It is worth mentioning that sodium trifluoromethyl acetimidate allowed the formation of the corresponding azepanes **9l** in 73% yield with an excellent diastereoselectivity and an excellent enantiomeric excess (ee >99%). Since azepane **9l** was crystalline, an X-ray diffraction (XRD) of the compound was realized and the relative and absolute configuration of the stereogenic centers at C2 and C4 was confirmed (Figure 2). Other nucleophiles, such as thiophenol and tetrabutylammonium borohydride also showed

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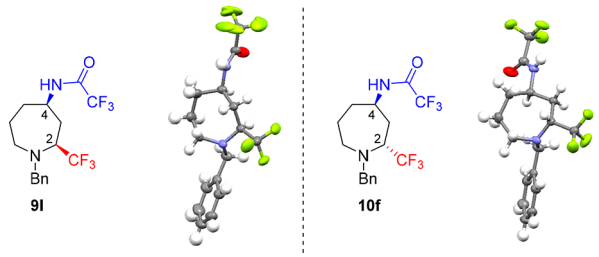
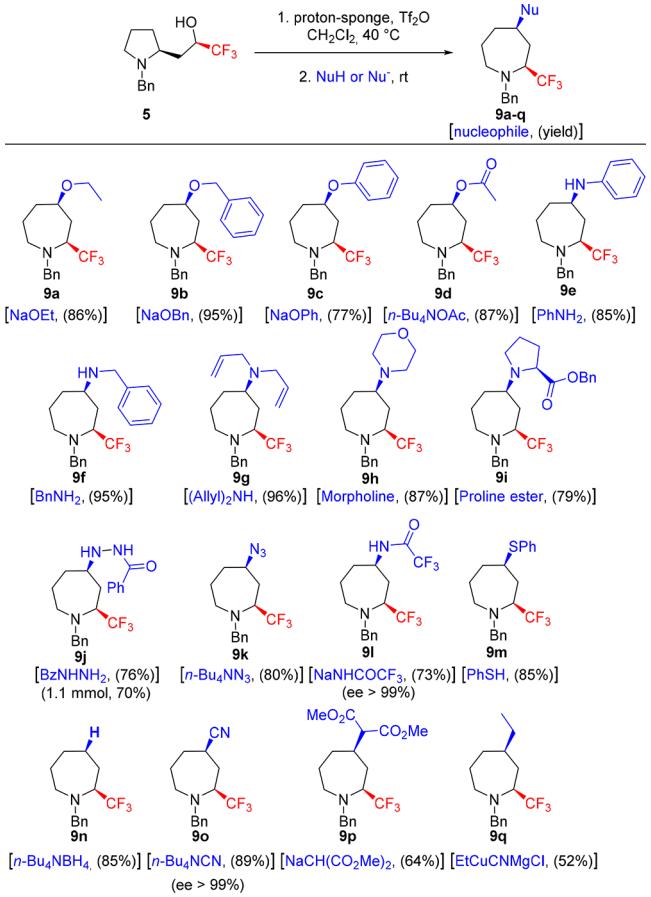


Figure 2. X-ray diffraction (XRD) of **9l** and **10f**

their ability to open the bicyclic azetidiniums, giving the corresponding azepanes **9m** and **9n**, respectively. Carbon nucleophiles such as cyanide, sodium malonate, and cuprate led to the formation of the corresponding substituted azepanes **9o**–**9q** from pyrrolidines **5** in moderate to good yields (see Scheme 5).

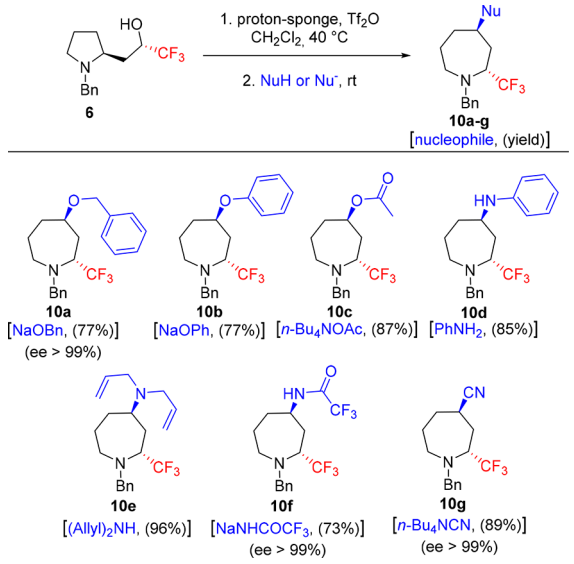
Scheme 5. Ring Expansion of 5 with Various Nucleophiles



The diastereomer **6**, was also treated under the same conditions as **5** and, whatever the nucleophiles, e.g., alcoholate, phenolate, acetate, amines, trifluoromethylacetamide, or cyanide, the corresponding azepanes **10a**–**10g** were obtained in good yields (73%–96%) (Scheme 6). It is worth mentioning that the 2-trifluoromethyl-4-trifluoromethylacetamide azepanes **10f** was crystalline, allowing us to perform an XRD analysis that confirmed the relative and absolute configuration of the stereogenic centers at C2 and C4 (Figure 2).

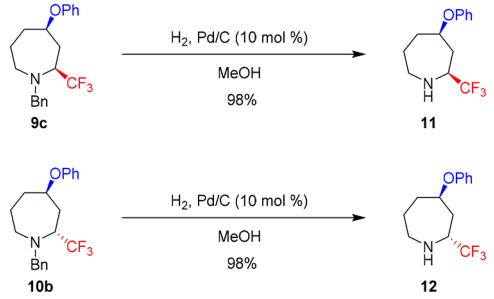
We were able to perform the debenzylation (Pd/C, H_2, MeOH) of the diastereomers **9c** and **10b**, which produced the

Scheme 6. Ring Expansion of 6 with Various Nucleophiles



deprotected azepanes **11** and **12**, respectively, with excellent yields and without any epimerization of the stereogenic centers (Scheme 7).

Scheme 7. Debenzylation of 9c and 10b



In conclusion, the ring expansion of pyrrolidines **D** to azepanes **A** via bicyclic azetidinium intermediates **B** showed an excellent regioselectivity and a complete chirality transfer from the L-proline to the azepanes. This method allows easy access to 2-trifluoromethyl-4-substituted azepanes in highly diastereomeric and enantiomeric excess, and should be of interest to medicinal chemists.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02167.

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

Accession Codes

CCDC 1850085 and CCDC 1850086 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 emailing data_ request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12

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Notes

The authors declare no competing financial interest.

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