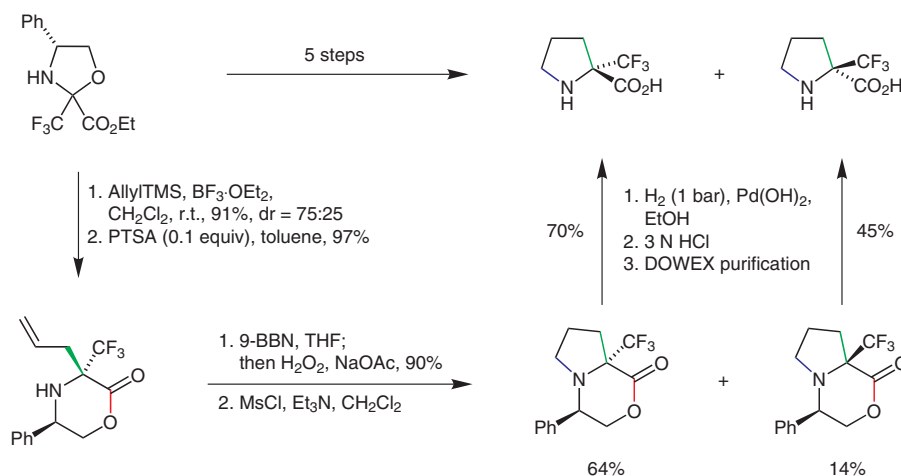


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Straightforward Synthesis of (*S*)- and (*R*)- α -Trifluoromethyl Proline from Chiral Oxazolidinones Derived from Ethyl Trifluoropyruvate

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Synthesis of Enantiopure (*S*)- and (*R*)- α -Trifluoromethyl Proline



Significance: A convenient route to enantiopure α -trifluoromethyl proline is reported. Lewis acid catalyzed allylation of an easily accessible oxazolidinone derived from (*R*)-phenylglycinol generates a morpholin-2-one derivative in 86–92% yields as a diastereomeric mixture (dr = 69:31 to 75:25), independent of the diastereomeric ratio of the educt. Following PTSA-catalyzed lactonization, hydroboration, and mesylation, the pyrrolidine lactone is obtained as a diastereomeric mixture which may be separated by column chromatography. Standard hydrogenolysis affords both enantiomers of trifluoromethyl proline in five steps and up to 36% overall yield.

Comment: The growing interest of fluorinated analogues of proline is based on control of the *cis*–*trans* isomerization of prolyl bonds in oligopeptides (R. Golbik et al. *Biochemistry* **2005**, *44*, 16026-16034) and for the design and synthesis of enzyme inhibitors (L. Chen et al. *J. Org. Chem.* **2006**, *71*, 5468-5473; D. D. Staas et al. *Bioorg. Med. Chem.* **2006**, *14*, 6900-6916). Among the available methods for the synthesis of fluoro-substituted prolines (e.g., J. R. Del Valle, M. Goodman *Angew. Chem. Int. Ed.* **2002**, *41*, 1600-1602), few are known for the introduction of a fluorinated group in the α -position (M. Eckert et al. *Org. Lett.* **2005**, *7*, 3741-3743). The synthesis of racemic ethyl α -difluoromethylproline ester has been recently reported (J. Zhu et al. *Tetrahedron Lett.* **2005**, *46*, 2795-2797). The current method appears to be unique for the synthesis of both enantiopure α -trifluoromethyl prolines and may contribute to further studies of these unnatural amino acids.

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