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A Facile Stereocontrolled Synthesis of *anti*-α-(Trifluoromethyl)-β-amino Alcohols

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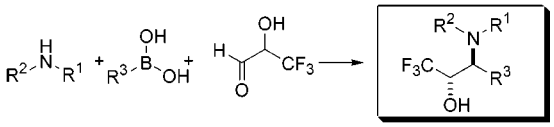
ABSTRACT



A short stereocontrolled preparation of *anti*-α-(trifluoromethyl)-β-amino alcohols is described, involving an initial CF_3 transfer to cinnamaldehyde and a one-step, three-component condensation of 3,3,3-trifluorolactic aldehyde, an alkenyl (aryl) boronic acid, and an amine. Applying this methodology to chiral 3,3,3-trifluorolactic aldehyde allowed us to generate an amino alcohol enantioselectively in 92% ee.

Fluoroalkyl β-amino alcohols, like their nonfluorinated analogues, are the focus of numerous studies.[1] They are used as peptidomimetics and transition state mimics in drug design,[2] as well as novel precursors for the corresponding fluoroalkyl peptidyl ketones.[3] These ketones exist as stable hydrates in aqueous medium because of their exceptionally high electrophilicity. These hydrates serve as an ideal mimic of the tetrahedral transition state of the amide bond, thus inhibiting proteolytic enzymes.[4] Trifluoromethyl-β-amino alcohols can be used as chiral auxiliaries or as ligands in asymmetric synthesis. Reported preparations of these molecules involved reduction of the trifluoromethylated ketone,[5] Henry condensation between nitroalkane[6] and hydrate of fluoral or the opening of epoxy ethers by nitrogen nucleo-

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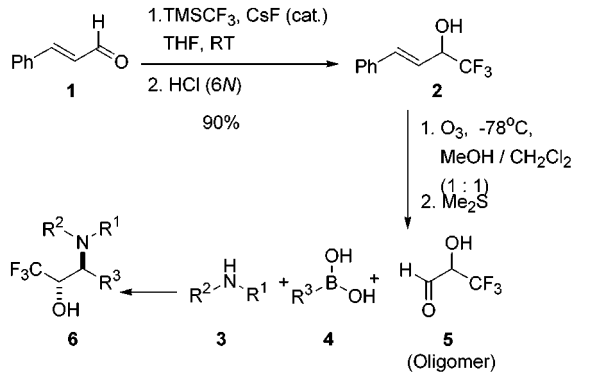
philes,[7] and subsequent reduction. These all require many synthetic steps or suffer from lack of diastereoselectivity.

We report herein an astonishingly short route to α-trifluoromethyl-β-amino alcohols via 3,3,3-trifluorolactic aldehyde. Following the initial report by one of us involving a three-component condensation of boronic acids, amines, and α-hydroxy aldehydes to yield *anti*-β-amino alcohols,[8] we surmised that 3,3,3-trifluorolactic aldehyde under similar conditions would give the corresponding fluorinated *anti*-amino alcohols accordingly.

However, few reports exist on the preparation and properties of trifluorolactic aldehyde[9] or its benzylated derivative.[10] Following our synthetic strategy, cinnamaldehyde was first trifluoromethylated, using $TMSCF_3$ and catalytic amounts of CsF (Scheme 1).[11] After acidic workup (*E*)-1,1,1-trifluoro-

Scheme 1



4-phenyl-3-buten-2-ol (**2**) was obtained in 90% yield. The allylic alcohol **2** was then quantitatively transformed to 3,3,3-trifluorolactic aldehyde (**5**) by ozonolysis, using MeOH/CH_2Cl_2 (1:1). This aldehyde, which exists primarily in its oligomeric form, was reacted with different boronic acids and amines (Table 1). The remarkable feature of this transformation is its diastereoselectivity, providing the *anti*-(trifluoromethyl)-β-amino alcohol **6** in >99% de.[8]

The reactions were carried out under mild conditions using ethanol as a solvent at room temperature.[12] Next we turned our attention to the enantioselective synthesis of α-trifluoromethyl-β-amino alcohols. The preparation of (*E*)- or (*Z*)-

Table 1. Synthesis of *anti*-α-(Trifluoromethyl)-β-amino Alcohols

Amine	Boronic Acid	Product	Yield (%)	de (%)
3a	**4a**	**6a**	85	>99
3b	**4b**	**6b**	67	>99
3b	**4c**	**6c**	73	>99
3a	**4d**	**6d**	80	>99
3a	**4e**	**6e**	75	>99
3b	**4f**	**6f**	70	>99
3a	**4g**	**6g**	75	>99

1,1,1-trifluoro-4-phenyl-3-buten-2-ol enantioselectively has been accomplished by means of a microbial reduction of the corresponding ketone with *Geotrichum candidum* in 94% ee, but the saturated alcohol was obtained along with the desired allylic alcohol.[13] Other synthetic approaches gave a lower enantioselectivity.[14] Starting from (*E*)-1,1,1-trifluoro-4-phenyl-3-buten-2-one (**7**), which was obtained from the alcohol **2** by Swern oxidation, a variety of reagents are generally

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(8) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798−11799.

(9) Coinciding with our studies, Fessner et al. reported a similar approach to trifluorolactic aldehyde: Fessner, W.-D.; Goâe, C.; Jaeschke, G.; Eyrisch, O. *Eur. J. Org. Chem.* **2000**, 125−132.

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(11) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393−395.

(12) **Typical Reaction Procedure.** To a solution of the aldehyde **5** in EtOH was added the amine **3a** and 2-furylboronic acid (**4a**) successively. The reaction mixture was sealed and stirred at room temperature for 24 h. After concentration under vacuum, the residue was purified by chromatography with hexanes/ethyl acetate (9:1) to yield **6a** as colorless oil (560 mg, 85% yield, >99% de).

(13) Arnone, A.; Bernardi, R.; Blasco, F.; Cardillo, R.; Resnati, G.; Gerus, I. I.; Kukhar, V. P. *Tetrahedron* **1998**, *54*, 2809−2818.

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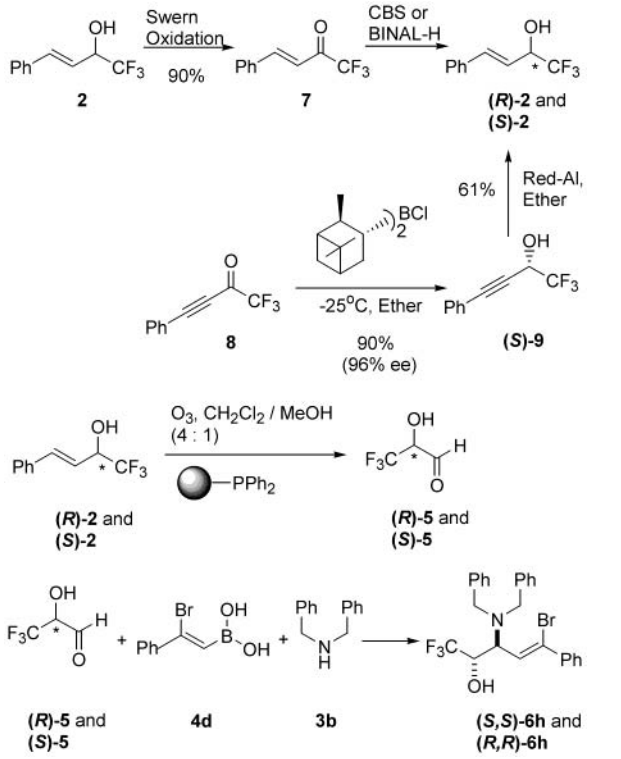
suitable for the enantioselective reduction.[15] (*S*)-BINAL-H[16] was selected first and applied to the reduction of ketone **7**, but it afforded (*S*)-1,1,1-trifluoro-4-phenyl-3-buten-2-ol [**(*S*)-2**] in only 71% ee (Scheme 2).[17]Chiral oxazaborolidines

Scheme 2



represent an alternative catalyst system.[18] The most commonly used reducing systems comprise the CBS-oxazaborolidine catalyst, bearing a methyl- or *n*-butyl-group attached to the boron, and BH_3 or catecholborane as stoichiometric reducing agent. The less reactive catecholborane allows the reaction to be carried out at a lower temperature and is more compatible with olefinic ketones. The combination of *(S)-B-*^{n}Bu-CBS and catecholborane allowed us to obtain the (*R*)-carbinol **(*R*)-2** in 85% yield and 85% ee (Table 2).[19]

Table 2. Asymmetric Reduction of (*E*)-1,1,1-Trifluoro-4-phenyl-3-buten-2-one (**7**)

reagent	configuration of **2**	yield (%)	ee (%)
(*S*)-BINAL-H (3 equiv)	*S*	94	71
(*R*)-*B*-Me-CBS (cat.) catecholborane	*S*	90	75
(*S*)-*B*-^{n}Bu-CBS (cat.) catecholborane	*R*	85	85

In the subsequent ozonolysis of the double bond, the solvent system employed turned out to have a major impact on the outcome of the reaction. The 1:1 solvent mixture of methanol and CH_2Cl_2, which is compatible with the racemic allylic alcohol, results in a racemisation of the product (Table 3). In pure methanol, the outcome was even worse. However,

Table 3. Ozonolysis and Enantioselective Synthesis of the Amino Alcohol **6h**

configuration of **2**	ee of **2** (%)	ratio of MeOH/CH_2Cl_2	chrom. sep. after ozonolysis	ee of **6h** (%)
R	82	1:1	yes	55
R	77	MeOH	yes	8
R	77	MeOH	no	30
R	85	1:4	no	85
S	96	1:4	no	92

a reduced amount of methanol (4:1 mixture of CH_2Cl_2/MeOH) proved to be superior, and after treatment of the crude aldehyde **5** (as oligomer) with bromostyrylboronic acid **4d** and dibenzylamine **3b** the expected β-amino alcohol **(*R,R*)-6h** was obtained in 85% ee and 71% yield.[17] It should be mentioned that column chromatographic purification of the hydroxy aldehyde **5** after ozonolysis also caused racemization due to the highly acidic α proton adjacent to the CF_3 group.

A detailed literature survey revealed that the reduction of the corresponding alkynyl ketone with (−)-DIP-chloride was reported in 98% ee.[20] Following this procedure, the 1,1,1-trifluoro-4-phenyl-3-butyn-2-one (**8**), which results from a coupling of ethyl phenylpropiolate and $TMSCF_3$,[21] was treated with (−)-DIP-chloride to yield (*S*)-1,1,1-trifluoro-4-phenyl-3-butyn-2-ol [**(*S*)-9**] in 96% ee. **(*S*)-9** was then reduced to the alkenyl alcohol **(*S*)-2**, using Red-Al without any stereochemical loss. Ozonolysis (CH_2Cl_2/MeOH, 4:1),

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(17) The % ee was established by HPLC and the ^{19}F NMR of the Mosher ester: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519.

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(19) The absolute configuration was established by comparing the ^{1}H NMR spectra of the *O*-methylmandelate esters of the two enantiomers: Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370−2374. This result is in agreement with Corey's mechanistic and structural analysis of the reduction of trifluoromethyl ketones by CBS, in which he attributes the product configuration to a greater effective bulk of CF_3 as compared to groups such as *tert*-butyl or 9-anthryl.[18b] Ramachandran and Brown come to the same conclusion, claiming that each fluorine atom exerts a steric influence similar to those of the CH_3 group: Ramachandran, P. V.; Teodoroviæ, A. V.; Brown, H. C. *Tetrahedron* **1993**, *49*, 1725−1738.

(20) Ramachandran, P. V.; Gong, B.; Teodorovic, A. V.; Brown, H. C. *Tetrahedron*: *Asymmetry* **1994**, *5*, 1061−1074.

(21) Singh, R. P.; Cao, G.; Kirchmeier, R. L.; Shreeve, J. M. *J. Org. Chem.* **1999**, *64*, 2873−2876.

and immediate reaction of the crude product with boronic acid **4d** and amine **3b** resulted in the formation of **(*S*,*S*)-6h** in 79% yield and 92% ee.[17]

In conclusion, we have reported a facile multicomponent synthesis of *anti*-α-(trifluoromethyl)-*β*-amino alcohols in high diastereoselectivity. The method was extended to the preparation of (*S*,*S*)-4-bromo-2-(*N*,*N*-dibenzylamino)-4-phenyl-1-trifluoromethyl-3-(*Z*)-butenol in 92% ee. The (*R*,*R*)-isomer was also prepared in 85% ee. The evaluation of the properties of this novel class of molecules is currently under way.

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Supporting Information Available: Full characterization data for compounds **6a**−**h** and some experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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