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An Efficient Entry to Optically Active *anti*- and *syn*-β-Amino-α-trifluoromethyl Alcohols

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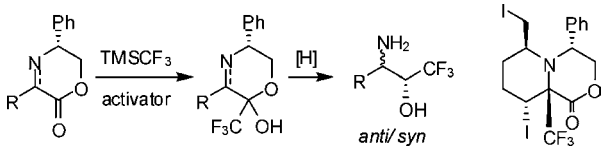
ABSTRACT



The reaction of chiral 5,6-dihydro-2*H*-1,4-oxazin-2-ones with $TMSCF_3$ in the presence of a suitable activator leads to trifluoromethyl lactols, which can be selectively reduced to *anti*-β-amino-α-trifluoromethyl alcohols. The corresponding syn diastereoisomers are obtained when the starting imines are reduced and the nitrogen atom is conveniently protected. In addition, a novel rearrangement of the CF_3 group in the lactol intermediates has been observed. This represents a formal CF_3 addition to the imine function in the starting substrates.

Nucleophilic trifluoromethylation reactions[1] constitute one of the simplest ways of introducing the valuable trifluoromethyl group into organic molecules.[2] The most common method for achieving this involves the use of the Ruppert−Prakash reagent ($TMSCF_3$)[3] in combination with a variety of activators/catalysts to facilitate the addition of CF_3 groups to electrophilic substrates such as aldehydes, ketones, esters, and imines. Fluoride sources such as TBAF or CsF are commonly employed as activators in this process, although other reagents such as Lewis bases[4] and acids[5] can also be used in catalytic amounts. The reaction can even work in the absence of a catalyst with DMSO as solvent.[6] Although asymmetric trifluoromethylations with chiral activators have been reported,[7] they more often entail the diastereoselective addition of $TMSCF_3$ to chiral substrates.

In connection with our interest in the preparation of enantiopure fluorine-containing synthons of biologically interesting molecules,[8] we have now developed an efficient method for preparing both *anti*- and *syn*-β-amino-α-trifluo-

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(7) (a) Kuroki, Y.; Iseki, K. *Tetrahedron Lett.* **1999**, *40*, 8231−8234. (b) Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2007**, *36*, 666−667. (c) Zhao, H.; Qin, B.; Liu, X.; Feng, X. *Tetrahedron* **2007**, *63*, 6822−6826.

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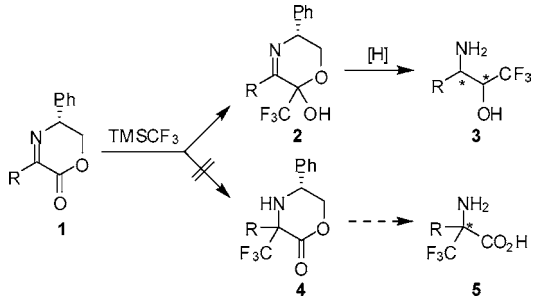
romethyl alcohols. These fluorinated amino alcohols are a useful class of compounds because they serve as precursors of more elaborate molecules such as peptidyl fluoroalkyl ketones, which are thought to act as protease inhibitors.[9] In addition, fluorinated amino alcohols have been used as chiral ligands/auxiliaries in asymmetric processes in much the same way as their nonfluorinated counterparts.[10] Several synthetic approaches to these compounds have been reported,[11] but the direct addition of $TMSCF_3$ to chiral α-amino aldehydes usually affords only low to moderate diastereoselectivities.[11e,12] In contrast, our method involves the addition of $TMSCF_3$ to optically pure 5,6-dihydro-2*H*-1,4-oxazin-2-ones **1** (Scheme 1). Since the lactone moiety should be more reactive[13] than

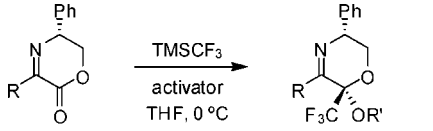
Scheme 1. Synthetic Plan



the imino functionality,[14] this reaction should afford the corresponding trifluoromethyl lactols **2** rather than α-trifluoromethyl amines **4**. Stereoselective reduction of both the lactol and imino functionalities in **2** and subsequent removal of the chiral auxiliary should then yield the target compounds **3**. Because we have found that suitably substituted compounds **2** can undergo a migration of the CF_3 group toward the imino carbon, this particular procedure may also provide an indirect access to trifluoromethyl amino acids **5**.[15]

We first tested the addition of $TMSCF_3$ to the known imino lactone **1a** (R = Me), available from the condensation of methyl pyruvate with (*R*)-2-phenylglycinol.[16] Several activators and reaction conditions were tested (see Table 1). The

Table 1. Addition of $TMSCF_3$ to Imino Lactones **1**



entry	1	R	activator (equiv)	2	yield (%)
1	**1a**	Me	TBAF (0.5)	**2a**	56
2	**1a**	Me	TBAT (0.5)	**2a**	54
3	**1a**	Me	CsF (1.0)	**2a**	55
4	**1a**	Me	KO*t*-Bu (0.5)	**2a**	38[a]
5	**1a**	Me	K_2CO_3 (0.1)[b]	**2a**	65
6	**1a**	Me	TASF (0.5)	**2a**	72
7	**1b**	$Ph(CH_2)_2$	TASF (0.5)	**2b**	75
8	**1c**	$MeO_2C(CH_2)_2$	TASF (0.5)	**2c**	74
9	**1d**	*t*-Bu	TASF (0.5)	**2d**	65
10	**1e**	Ph	TASF (0.5)	**2e**	32
11	**1f**	$CH_2{=}CH(CH_2)_3$	TASF (0.5)	**2f**	69

[a] 12% of silyl ether **2a′** was also isolated. [b] The reaction was performed in DMF at rt.

use of a catalytic amount of TBAF produced a mixture of imino lactol **2a** and its silyl ether **2a′** (TLC analysis), which upon aqueous workup (satd NH_4Cl, 3 h) afforded compound **2a** isolated as a single isomer in moderate yield[17] (entry 1). However, since the quality of TBAF severely affected the reproducibility of the reaction, other fluoride sources were evaluated. The non-hygroscopic tetrabutylammonium triphenyldifluorosilicate (TBAT) was found to be effective, but the difficulty in removing TBAT byproducts had a negative effect on the yield of **2a** (entry 2). CsF also led to modest yields, probably due to its low solubility in THF (entry 3). Reagents other than fluorides were also used with similar results (entries 4 and 5). In the end, good yields of **2a** were finally achieved with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF), which, although it is barely soluble in THF, efficiently promoted the addition of $TMSCF_3$ to **1** (entry 6).

Following a procedure reported by Harwood and coworkers,[16,18] we then proceeded to prepare other imino lactones by varying the R groups (Scheme 2). This method

(9) (a) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry* **1985**, *24*, 1813−1817. (b) Veale, C. A.; Damewood, J. R., Jr.; Steelman, G. B.; Bryant, C.; Gomes, B.; Williams, J. *J. Med. Chem.* **1995**, *38*, 86−97.

(10) Katagiri, T.; Iguchi, N.; Kawate, T.; Takahashi, S.; Uneyama, K. *Tetrahedron: Asymmetry* **2006**, *17*, 1157−1160 and references cited therein.

(11) (a) Tomoyasu, T.; Tomooka, K.; Nakai, T. *Synlett* **1998**, 1147−1149. (b) Abouabdellah, A.; Bégué, J.-P.; Bonnet-Delpon, D.; Kornilov, A.; Rodrigues, I.; Richard, C. *J. Org. Chem.* **1998**, *63*, 6529−6534. (c) Prakash, G. K. S.; Mandal, M.; Schweizer, S.; Petasis, N. A.; Olah, G. A. *Org. Lett.* **2000**, *2*, 3173−3176. (d) Jiang, Z.-X.; Qin, Y.-Y.; Qing, F.-L. *J. Org. Chem.* **2003**, *68*, 7544−7547. (e) Andrés, J. M.; Pedrosa, R.; Pérez-Encabo, A. *Eur. J. Org. Chem.* **2004**, 1558−1566. (f) Huguenot, F.; Brigaud, T. *J. Org. Chem.* **2006**, *71*, 7075−7078. (g) Tur, F.; Saá, J. M. *Org. Lett.* **2007**, *9*, 5079−5082.

(12) For additional examples of nonselective additions of $TMSCF_3$ to Garner's aldehyde, see: (a) Qing, F.-L.; Peng, S.; Hu, C.-M. *J. Fluorine Chem.* **1998**, *88*, 79−81. (b) See also ref 4b.

(13) For examples of additions of $TMSCF_3$ to lactones, see: (a) Walter, M. W.; Adlington, R. M.; Baldwin, J. E.; Schofield, C. J. *J. Org. Chem.* **1998**, *63*, 5179−5192. (b) Walter, M. W.; Thaker, N.; Baldwin, J. E.; Müller, M.; Schofield, C. J. *J. Chem. Res., Synop.* **2000**, 310−311. (c) Sydnes, M. O.; Hayashi, Y.; Sharma, V. K.; Hamada, T.; Bacha, U.; Barrila, J.; Freire, E.; Kiso, Y. *Tetrahedron* **2006**, *62*, 8601−8609.

(14) Only a few examples of additions of $TMSCF_3$ to highly activated ketimines have been reported: (a) Félix, C. P.; Khatimi, N.; Laurent, A. J. *Tetrahedron Lett.* **1994**, *35*, 3303−3304. (b) Blazejewski, J.-C.; Anselmi, E.; Wilmshurst, M. P. *Tetrahedron Lett.* **1999**, *40*, 5475−5478. (c) Petrov, V. A. *Tetrahedron Lett.* **2000**, *41*, 6959−6963.

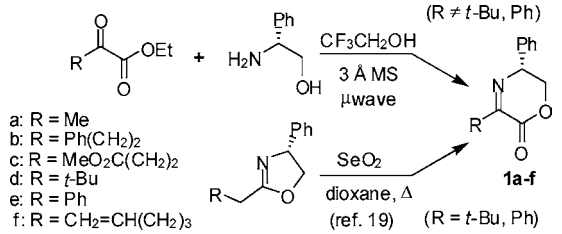
(15) For a review, see: Qiu, X.-L.; Meng, W.-D.; Qing, F.-L. *Tetrahedron* **2004**, *60*, 6711−6745.

(16) Harwood, L. M.; Vines, K. J.; Drew, M. G. B. *Synlett* **1996**, 1051−1053.

(17) The stereochemistry of lactols **2** was deduced as depicted after the further transformations carried out in Scheme 6.

(18) A slight modification was made in that the condensation of α-keto esters with (*R*)-phenylglycinol occurred under microwave irradiation in order to reduce the reaction times. α-Keto esters were commercially available or prepared by Grignard additions to diethyl oxalate; see: Macritchie, J. A.; Silcock, A.; Willis, C. L. *Tetrahedron: Asymmetry* **1997**, *8*, 3895−3902.

Scheme 2. Preparation of Imino Lactones **1a**−**f**

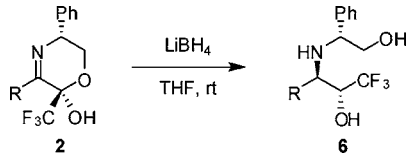


was not suitable in the case of compounds **1d**,**e**, which contain α-branched R groups; thus, a SeO_2-promoted rearrangement of oxazolines as described by Schafer and Molinski[19] was carried out instead.

We then undertook the trifluoromethylation of the different imino lactones and obtained similar results (Table 1, entries 7−11); indeed, the yield was lower solely in the case of **1e**, probably due to undesired imine isomerization[16] (entry 10). In the case of compound **1c** (entry 8), the addition of CF_3 only affected the lactone, leaving the methyl ester moiety unaltered.

The second key step was the stereoselective reduction of imino lactols **2**, which was carried out under a variety of conditions.[20] The best results were achieved with $LiBH_4$, which produced *anti*-amino diols **6** as the major isomers with good selectivity[21] (Table 2, entries 1, 3, and 6). However,

Table 2. Anti Reduction of Imino Lactols **2**



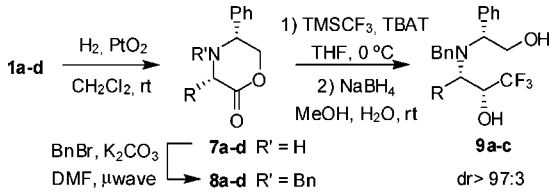
entry	**2**	R	**6**	yield[a] (%)	dr[b]
1	**2a**	Me	**6a**	74	96:2:2:0
2	**2b**	$Ph(CH_2)_2$	**6b**	88	76:15:5:4
3	**2c**	$MeO_2C(CH_2)_2$	**6c**[c]	68	91:5:4:0
4	**2d**	*t*-Bu	**6d**	75	73:18:6:3
5	**2e**	Ph	**6e**	55	55:34:9:2
6	**2f**	CH_2=$CH(CH_2)_3$	**6f**	74	89:5:3:3

[a] Overall yield of pure products. [b] Determined by integration in the ^{19}F NMR crude spectra. [c] The ester group was also reduced to the corresponding primary alcohol (R = $HO(CH_2)_3$).

the selectivity decreased somewhat when R = $Ph(CH_2)_2$ or *t*-Bu (entries 2 and 4), affording only a 55:34:9:2 mixture of unseparable diols when R = Ph (entry 5).

For the preparation of the corresponding syn diastereoisomers, we reasoned that the use of appropriately protected β-amino lactols could reverse the reduction selectivity.[22] Thus, the starting substrates **1a**−**d** were hydrogenated as described (H_2, PtO_2)[23] to afford **7a**−**d**, after which the amino group was protected with BnBr to yield **8a**−**d** (Scheme 3).

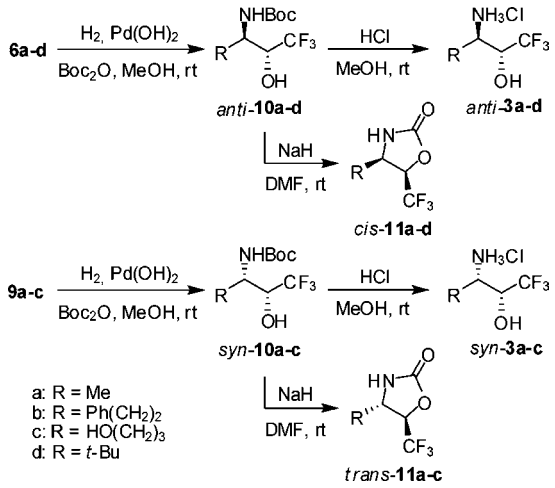
Scheme 3. Syn Reduction of Benzyl-Protected Amino Lactols



The addition of $TMSCF_3$ to these amino lactones was more effective when using TBAT as activator;[24] further reduction with $NaBH_4$ produced *syn*-diols **9a**−**c** with excellent diastereoselectivity (>97:3).[25]

From **6a**−**d**, removal of phenylglycinol through hydrogenation was best carried out in the presence of Boc_2O in order to facilitate the isolation of *N*-Boc-protected amino alcohols *anti*-**10a**−**d**, which were then deprotected to afford the target compounds *anti*-**3a**−**d**, isolated as their hydrochloride salts (Scheme 4). In addition, hydrogenolysis and

Scheme 4. Preparation of Amino Alcohols **3**



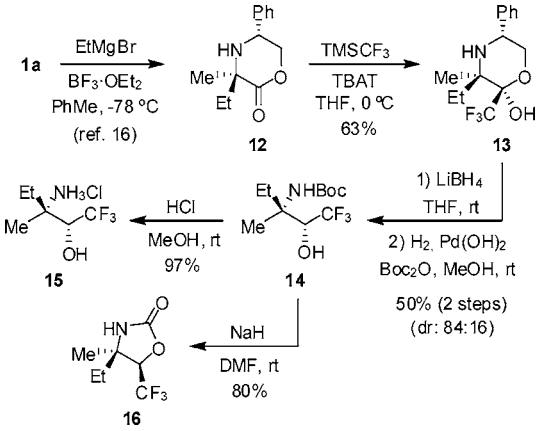
in situ *N*-Boc protection of **9a**−**c** provided *syn*-**10a**−**c**, which were subsequently transformed into *syn*-**3a**−**c**. The relative stereochemistry of these amino alcohols was confirmed through coupling constant analysis in the corresponding *cis*

(19) Shafer, C. M.; Molinski, T. F. *J. Org. Chem.* **1996**, *61*, 2044−2050.
(20) Other reducing agents tested ($LiAlH_4$, $NaBH_4$, $NaCNBH_3$, DIBAL-H, Red-Al) led to lower selectivities and/or partial reductions.
(21) The anti diastereoselectivity could be attributed to the initial reduction of the latent trifluoromethyl ketone prior to the imino group under these conditions.
(22) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121−1162.
(23) Cox, G. C.; Harwood, L. M. *Tetrahedron: Asymmetry* **1994**, *5*, 1669−1672.
(24) The corresponding benzylated lactols were obtained as mixtures of unseparable epimers. Compound **8d** failed to react with $TMSCF_3$ under all conditions tested.
(25) In contrast, $TMSCF_3$ addition to unprotected **7a**, and subsequent reduction with $LiBH_4$ afforded the *anti*-amino alcohol with (2*S*,3*S*) configuration as the major diastereoisomer (dr 80:20).

and *trans* oxazolidinones **11**.[26] Finally, comparison of compounds *cis*-**11a** and *trans*-**11a** with those previously reported by Pedrosa and co-workers confirmed their absolute configuration.[11e]

We next embarked on the synthesis of amino alcohols containing a quaternary center in β-position. Thus, addition of $TMSCF_3$ to the known amino lactone **12**[16] gave lactol **13** (Scheme 5). Further reduction with $LiBH_4$ and hydrogenation

Scheme 5. Synthesis of Quaternary Amino Alcohol **15**

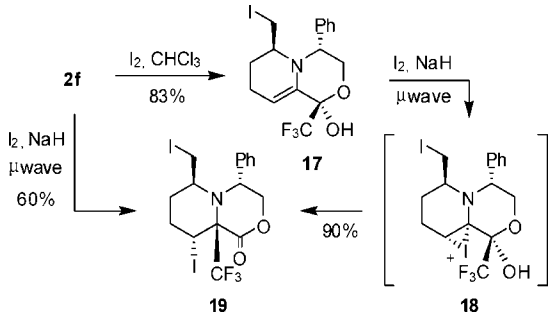


produced a separable mixture of **14** and its epimer (84:16 diastereoselectivity). Finally, Boc removal with HCl afforded amino alcohol **15** as its hydrochloride salt; subsequent cyclization to oxazolidinone **16** again provided the configuration of the newly formed stereocenter with the aid of NOE correlations (see the Supporting Information).

Compound **2f** containing an unsaturated side chain was found to be a substrate suitable for further cyclization reactions. For instance, when treated with I_2 in order to promote an iodoamination reaction, iodide **17** was obtained as a single isomer (Scheme 6). However, under harsher conditions (I_2, NaH, microwave), a second iodine atom was introduced, presumably through a iodonium cation intermediate **18** which evolves to compound **19** by means of the rearrangement of the CF_3 group[27] with concomitant regeneration of the lactone functionality.[28] These conditions were also

(26) The coupling constant between vicinal protons in the oxazolidinone ring was significantly larger in the cis isomers.

Scheme 6. Synthesis of Bicyclic Diiodide **19**



applied to **2f** to yield **19** in a one-pot reaction. Overall, this process constitutes a formal addition of CF_3 to the starting ketimine, which cannot be carried out directly (see Scheme 1).

In summary, we have developed a simple methodology for the preparation of either *anti*- or *syn*-β-amino-α-trifluoromethyl alcohols. Both enantiomeric series can be obtained by simply changing the chiral auxiliary. In addition, we observed a novel rearrangement of the CF_3 group which allowed for the preparation of chiral quaternary α-trifluoromethyl amines. Further investigations are currently underway.

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Supporting Information Available: Experimental procedures and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) To the best of our knowlegde, only two examples of migrations of CF_3 groups have been reported. See: (a) Hein, F.; Burger, K.; Firl, J. *J. Chem. Soc., Chem. Commun.* **1979**, 792−793. (b) Chambers, R. D.; Cheburkov, Y. A.; Tanabe, T.; Vaughan, J. F. S. *J. Fluorine Chem.* **1995**, *74*, 227−228.

(28) The stereochemistry in **19** was assigned with the aid of various 2D NMR experiments (COSY, NOESY, and $^1H-^{19}F$ HOESY); see the Supporting Information.