

# An Efficient Entry to Optically Active *anti*- and *syn*- $\beta$ -Amino- $\alpha$ -trifluoromethyl Alcohols

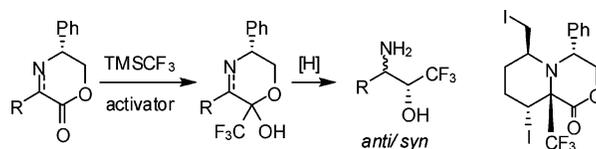
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## ABSTRACT



The reaction of chiral 5,6-dihydro-2H-1,4-oxazin-2-ones with  $\text{TMSCF}_3$  in the presence of a suitable activator leads to trifluoromethyl lactols, which can be selectively reduced to *anti*- $\beta$ -amino- $\alpha$ -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  $\text{CF}_3$  group in the lactol intermediates has been observed. This represents a formal  $\text{CF}_3$  addition to the imine function in the starting substrates.

Nucleophilic trifluoromethylation reactions<sup>1</sup> constitute one of the simplest ways of introducing the valuable trifluoromethyl group into organic molecules.<sup>2</sup> The most common method for achieving this involves the use of the Ruppert–Prakash reagent ( $\text{TMSCF}_3$ )<sup>3</sup> in combination with a variety of activators/catalysts to facilitate the addition of  $\text{CF}_3$  groups to electrophilic substrates such as aldehydes, ketones, esters, and imines. Fluoride sources such as TBAF or  $\text{CsF}$  are commonly employed as activators in this process, although other reagents such as Lewis bases<sup>4</sup> and acids<sup>5</sup> can also be

used in catalytic amounts. The reaction can even work in the absence of a catalyst with DMSO as solvent.<sup>6</sup> Although asymmetric trifluoromethylations with chiral activators have been reported,<sup>7</sup> they more often entail the diastereoselective addition of  $\text{TMSCF}_3$  to chiral substrates.

In connection with our interest in the preparation of enantiopure fluorine-containing synthons of biologically interesting molecules,<sup>8</sup> we have now developed an efficient method for preparing both *anti*- and *syn*- $\beta$ -amino- $\alpha$ -trifluo-

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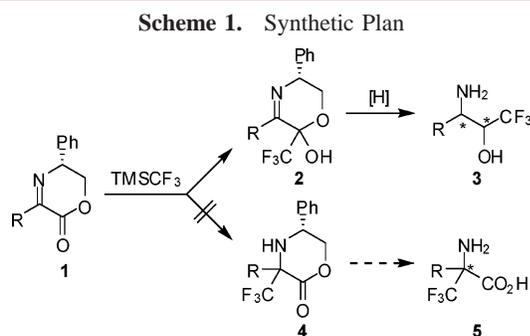
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(b) Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2007**, *36*, 666–667. (c) Zhao, H.; Qin, B.; Liu, X.; Feng, X. *Tetrahedron* **2007**, *63*, 6822–6826.

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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.<sup>9</sup> In addition, fluorinated amino alcohols have been used as chiral ligands/auxiliaries in asymmetric processes in much the same way as their nonfluorinated counterparts.<sup>10</sup> Several synthetic approaches to these compounds have been reported,<sup>11</sup> but the direct addition of  $\text{TMSCF}_3$  to chiral  $\alpha$ -amino aldehydes usually affords only low to moderate diastereoselectivities.<sup>11e,12</sup> In contrast, our method involves the addition of  $\text{TMSCF}_3$  to optically pure 5,6-dihydro-2*H*-1,4-oxazin-2-ones **1** (Scheme 1). Since the lactone moiety should be more reactive<sup>13</sup> than



the imino functionality,<sup>14</sup> this reaction should afford the corresponding trifluoromethyl lactols **2** rather than  $\alpha$ -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  $\text{CF}_3$  group toward the imino carbon, this particular procedure may also provide an indirect access to trifluoromethyl amino acids **5**.<sup>15</sup>

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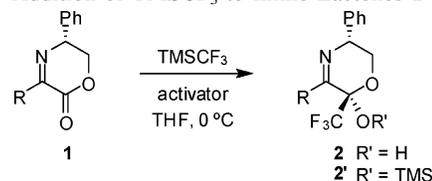
(12) For additional examples of nonselective additions of  $\text{TMSCF}_3$  to Garner's aldehyde, see: (a) Qing, F.-L.; Peng, S.; Hu, C.-M. *J. Fluorine Chem.* **1998**, *88*, 79–81. (b) See also ref 4b.

(13) For examples of additions of  $\text{TMSCF}_3$  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  $\text{TMSCF}_3$  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.

We first tested the addition of  $\text{TMSCF}_3$  to the known imino lactone **1a** ( $R = \text{Me}$ ), available from the condensation of methyl pyruvate with (*R*)-2-phenylglycinol.<sup>16</sup> Several activators and reaction conditions were tested (see Table 1). The

**Table 1.** Addition of  $\text{TMSCF}_3$  to Imino Lactones **1**



entry	<b>1</b>	R	activator (equiv)	<b>2</b>	yield (%)
1	<b>1a</b>	Me	TBAF (0.5)	<b>2a</b>	56
2	<b>1a</b>	Me	TBAT (0.5)	<b>2a</b>	54
3	<b>1a</b>	Me	$\text{CsF}$ (1.0)	<b>2a</b>	55
4	<b>1a</b>	Me	$\text{KO}t\text{-Bu}$ (0.5)	<b>2a</b>	38 <sup>a</sup>
5	<b>1a</b>	Me	$\text{K}_2\text{CO}_3$ (0.1) <sup>b</sup>	<b>2a</b>	65
6	<b>1a</b>	Me	TASF (0.5)	<b>2a</b>	72
7	<b>1b</b>	$\text{Ph}(\text{CH}_2)_2$	TASF (0.5)	<b>2b</b>	75
8	<b>1c</b>	$\text{MeO}_2\text{C}(\text{CH}_2)_2$	TASF (0.5)	<b>2c</b>	74
9	<b>1d</b>	<i>t</i> -Bu	TASF (0.5)	<b>2d</b>	65
10	<b>1e</b>	Ph	TASF (0.5)	<b>2e</b>	32
11	<b>1f</b>	$\text{CH}_2=\text{CH}(\text{CH}_2)_3$	TASF (0.5)	<b>2f</b>	69

<sup>a</sup> 12% of silyl ether **2a'** was also isolated. <sup>b</sup> 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  $\text{NH}_4\text{Cl}$ , 3 h) afforded compound **2a** isolated as a single isomer in moderate yield<sup>17</sup> (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).  $\text{CsF}$  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  $\text{TMSCF}_3$  to **1** (entry 6).

Following a procedure reported by Harwood and co-workers,<sup>16,18</sup> we then proceeded to prepare other imino lactones by varying the R groups (Scheme 2). This method

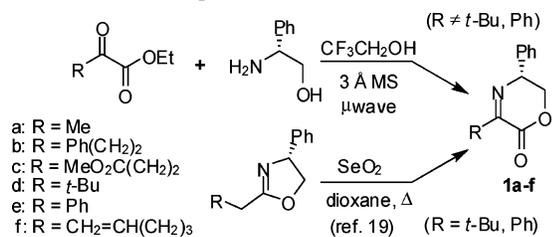
(15) For a review, see: Qiu, X.-L.; Meng, W.-D.; Qing, F.-L. *Tetrahedron* **2004**, *60*, 6711–6745.

(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  $\alpha$ -keto esters with (*R*)-phenylglycinol occurred under microwave irradiation in order to reduce the reaction times.  $\alpha$ -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**

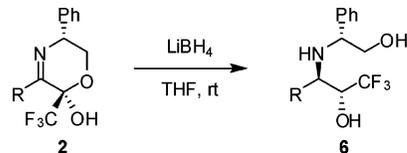


was not suitable in the case of compounds **1d,e**, which contain  $\alpha$ -branched R groups; thus, a SeO<sub>2</sub>-promoted rearrangement of oxazolines as described by Schafer and Molinski<sup>19</sup> was carried out instead.

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<sup>16</sup> (entry 10). In the case of compound **1c** (entry 8), the addition of CF<sub>3</sub> 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.<sup>20</sup> The best results were achieved with LiBH<sub>4</sub>, which produced *anti*-amino diols **6** as the major isomers with good selectivity<sup>21</sup> (Table 2, entries 1, 3, and 6). However,

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



entry	<b>2</b>	R	<b>6</b>	yield <sup>a</sup> (%)	dr <sup>b</sup>
1	<b>2a</b>	Me	<b>6a</b>	74	96:2:2:0
2	<b>2b</b>	Ph(CH <sub>2</sub> ) <sub>2</sub>	<b>6b</b>	88	76:15:5:4
3	<b>2c</b>	MeO <sub>2</sub> C(CH <sub>2</sub> ) <sub>2</sub>	<b>6c</b> <sup>c</sup>	68	91:5:4:0
4	<b>2d</b>	<i>t</i> -Bu	<b>6d</b>	75	73:18:6:3
5	<b>2e</b>	Ph	<b>6e</b>	55	55:34:9:2
6	<b>2f</b>	CH <sub>2</sub> =CH(CH <sub>2</sub> ) <sub>3</sub>	<b>6f</b>	74	89:5:3:3

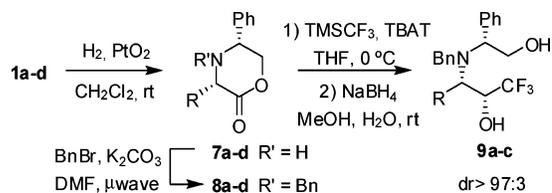
<sup>a</sup> Overall yield of pure products. <sup>b</sup> Determined by integration in the <sup>19</sup>F NMR crude spectra. <sup>c</sup> The ester group was also reduced to the corresponding primary alcohol (R = HO(CH<sub>2</sub>)<sub>3</sub>).

the selectivity decreased somewhat when R = Ph(CH<sub>2</sub>)<sub>2</sub> 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

$\beta$ -amino lactols could reverse the reduction selectivity.<sup>22</sup> Thus, the starting substrates **1a–d** were hydrogenated as described (H<sub>2</sub>, PtO<sub>2</sub>)<sup>23</sup> to afford **7a–d**, after which the amino group was protected with BnBr to yield **8a–d** (Scheme 3).

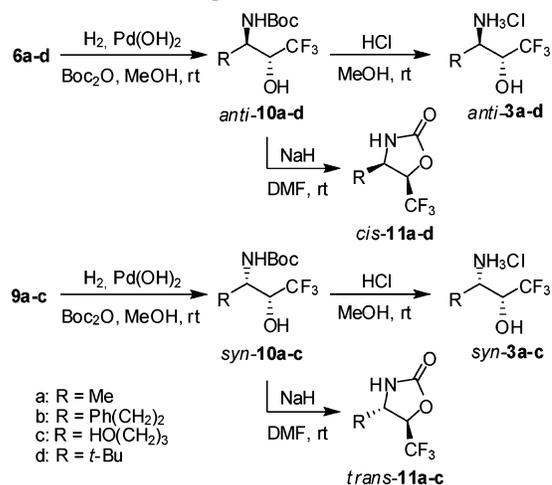
### Scheme 3. Syn Reduction of Benzyl-Protected Amino Lactols



The addition of TMSCF<sub>3</sub> to these amino lactones was more effective when using TBAT as activator;<sup>24</sup> further reduction with NaBH<sub>4</sub> produced *syn*-diols **9a–c** with excellent diastereoselectivity (>97:3).<sup>25</sup>

From **6a–d**, removal of phenylglycinol through hydrogenation was best carried out in the presence of Boc<sub>2</sub>O 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*

(22) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121–1162.

(23) Cox, G. C.; Harwood, L. M. *Tetrahedron: Asymmetry* **1994**, *5*, 1669–1672.

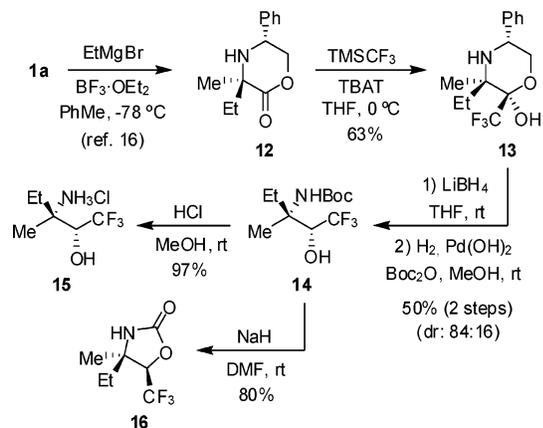
(24) The corresponding benzylated lactols were obtained as mixtures of unseparable epimers. Compound **8d** failed to react with TMSCF<sub>3</sub> under all conditions tested.

(25) In contrast, TMSCF<sub>3</sub> addition to unprotected **7a**, and subsequent reduction with LiBH<sub>4</sub> afforded the *anti*-amino alcohol with (2*S*,3*S*) configuration as the major diastereoisomer (dr 80:20).

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

We next embarked on the synthesis of amino alcohols containing a quaternary center in  $\beta$ -position. Thus, addition of TMSCF<sub>3</sub> to the known amino lactone **12**<sup>16</sup> gave lactol **13** (Scheme 5). Further reduction with LiBH<sub>4</sub> and hydrogenation

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

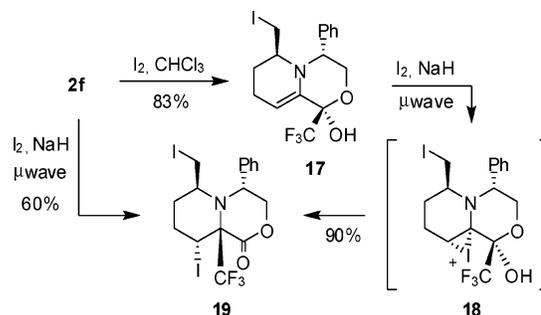


produced a separable mixture of **14** and its epimer (84:16 diastereoselectivity). Finally, Boc removal with HCl afforded amino alcohol **15** as its hydrochloride salt; subsequent cyclization to oxazolidinone **16** again provided the configuration of the newly formed stereocenter with the aid of NOE 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<sub>2</sub> in order to promote an iodoamination reaction, iodide **17** was obtained as a single isomer (Scheme 6). However, under harsher conditions (I<sub>2</sub>, 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<sub>3</sub> group<sup>27</sup> with concomitant regeneration of the lactone functionality.<sup>28</sup> 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<sub>3</sub> 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*- $\beta$ -amino- $\alpha$ -trifluoromethyl alcohols. Both enantiomeric series can be obtained by simply changing the chiral auxiliary. In addition, we observed a novel rearrangement of the CF<sub>3</sub> group which allowed for the preparation of chiral quaternary  $\alpha$ -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 knowledge, only two examples of migrations of CF<sub>3</sub> 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 <sup>1</sup>H–<sup>19</sup>F HOESY); see the Supporting Information.