CF_3-Containing Enolates

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Highly Diastereoselective Aldol Reaction with α-CF_3-Substituted Enolates**

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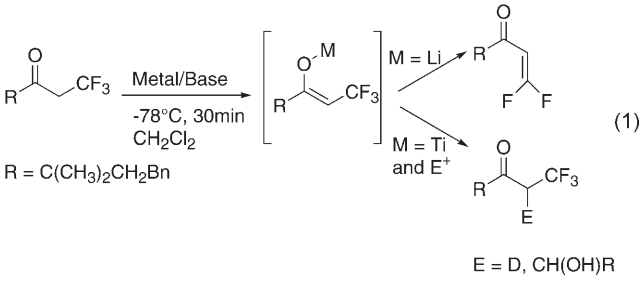
Organofluorine compounds have received much attention lately because of their important applications as pharmacologically active products and their unique physical properties.[1] Of the few organofluorine compounds that occur in nature, those bearing a trifluoromethyl group are of particular interest.[1] Although reactions of α-CF_3-substituted enolates appear to be a most attractive way to prepare CF_3-containing compounds, only one example of the use of a Ti enolate in aldol reactions has been reported thus far.[2,3] Indeed, most of α-CF_3 ketone enolates, such as Li enolates, react by defluorination, affording the corresponding α,β-unsaturated β,β-difluoroketones, whereas their titanium enolate counterparts react with aldehydes at −78 °C [Eq. (1)], because of the

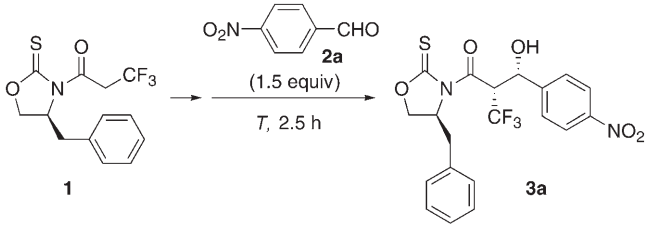


(1)

weaker interaction of titanium with fluorine.[3] These results prompted us to study the reactivity of chiral titanium enolates of α-CF_3 amides, such as (*S*)-*N*-3,3,3-trifluoropropionyl-4-benzyloxazolidine-2-thione (**1**).[4] We report herein that the Ti enolate of a chiral α-CF_3 amide can be generated efficiently, and it reacts with aldehydes in a highly diastereoselective aldol reaction. The CF_3-containing aldols so obtained may then be used as chiral building blocks for the preparation of more elaborate compounds.

The titanium enolates of *N*-propionyl oxazolidine-2-thiones react with achiral aldehydes to provide an alternative and efficient access to Evans or non-Evans *syn* aldols, depending on the type and amount of base used.[5] Thus we first examined the formation of the titanium enolate of the α-CF_3-substituted amide **1**, and its reactivity towards 4-nitrobenzaldehyde (**2a**) (Table 1). The preparation of the required

Table 1: Formation of the titanium enolate from **1** and its reactivity towards 4-nitrobenzaldehyde (**2a**).[a]



Entry	Amine	*T*	Yield [%]	*de* of *syn* product
1	TMEDA	−78 °C to RT	72	>96
2	TMEDA	−40 °C	37	>96
3	TMEDA	0 °C	36	>96
4	DIEA[b]	−78 °C to RT	0	–

[a] Reaction conditions for generation of the Ti enolate: $TiCl_4$ (1 equiv), amine (2.5 equiv), CH_2Cl_2, −78 °C, 20 min. [b] DIEA (1.1 equiv) and $TiCl_4$ (2 equiv).

4-benzyloxazolidine-2-thione was straightforward and followed reported procedures.[6] Quantitative N-acylation was achieved by treatment with 3,3,3-trifluoropropanoic acid in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-dimethylaminopyridine (DMAP) in dichloromethane at 0 °C. Upon addition at −78 °C of nitrobenzaldehyde **2a** to the $TiCl_3$ enolate of **1**, which was prepared in situ (1 equiv of $TiCl_4$ and 2.5 equiv of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in CH_2Cl_2 at −78 °C for 20 min), the *syn* aldol product **3a** was obtained in good yield (72 %) and with high diastereoselectivity (>96 % *de*) (entry 1, Table 1. When the aldehyde **2a** was added at −40 °C or 0 °C, the yields were lower (around 36 % in both cases) but the diastereoselectivity was not affected, and no defluorination was observed (entries 2 and 3, Table 1). When diisopropylethyl amine (DIEA) was used, little or no reaction occurred (entry 4, Table 1). In all cases the *de* values were determined from the crude mixtures by the integration of the ^{19}F NMR signals. Indeed, two doublets in a >98:2 ratio were observed at $\delta = -63.69$ and −64.54 ppm, corresponding to the nonseparable diastereomers.

The *syn* relationship of the hydroxy and CF_3 groups in **3a** was determined by ^1H NMR analysis of the corresponding enantiomerically pure acetonide **4a**, which was prepared from aldol **3a** (reduction with $LiBH_4$, followed by treatment with $(CH_3)_2C(OMe)_2$, see Scheme 1) in an unoptimized 50 % overall yield. At this stage, the chiral auxiliary, the (*S*)-5-benzyloxazolidine-2-thione, was easily recovered in 93 % yield. The observed coupling constant between H_a and H_b of

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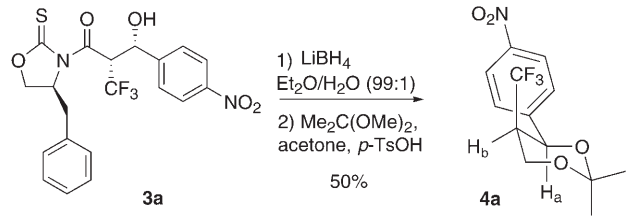
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

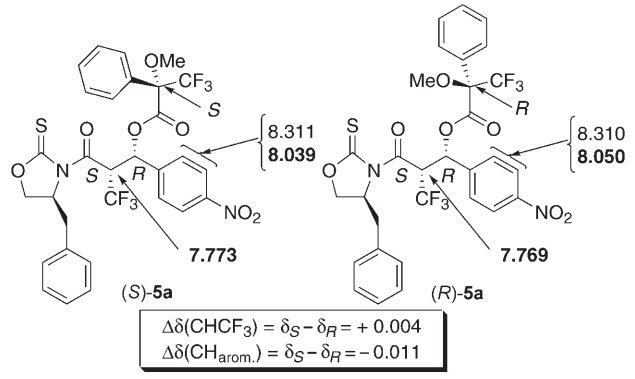


Scheme 1. *p*-TsOH = *p*-toluenesulfonic acid.

the acetonide **4a** was <1 Hz, as expected for an H_{ax},H_{eq} coupling constant in such an acetonide.[7] It is also important to note that the *anti* acetonide with a phenyl group (instead of a 4-nitrophenyl moiety) has already been prepared by a different approach, and showed a different and typical H_{ax},H_{ax} coupling constant of 10 Hz.[8]

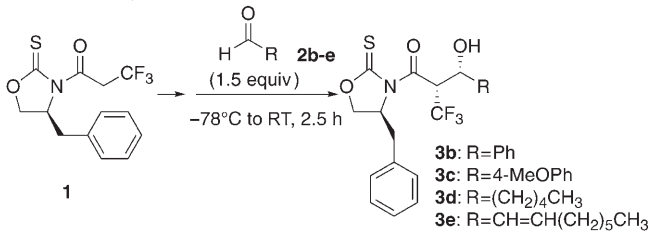
The *syn* diastereoselectivity of the reaction can be rationalized by evoking the formation of the *Z* enolate to give the *syn* aldol via a cyclic transition state, as is usually observed with Ti/amine systems.[9] It is interesting to note that in the case of Ti enolates generated from α-CF_3 ketone, the *anti* aldols are formed as the major products.[3] In our case, we suppose that the affinity of Ti for sulfur is stronger than for fluorine, thus the usual cyclic transition state gives rise to the expected *syn* aldols. At this stage, we may also suppose that the *syn* Evans aldol was produced. In order to confirm this hypothesis, we prepared the Mosher's esters of aldol **3a** directly in an NMR tube.[10] Careful analysis of the differences of the chemical shifts at the positions α and α′ to the carbinol group of esters (*S*)-**5a** and (*R*)-**5a** ($\Delta\delta(CHCF_3)=\delta_S-\delta_R=+0.004$, and $\Delta\delta(CH_{arom})=\delta_S-\delta_R=-0.011$) allowed us to tentatively assign the *R* absolute configuration to the stereogenic center bearing the hydroxy group (because of the rather weak $\Delta\delta(CHCF_3)$ values) (Scheme 2). Then because of the known *syn* relationships, the adjacent stereogenic center bearing the CF_3 group must have the *S* absolute configuration. These 2*S*,3*R* configurations for the newly created stereogenic centers confirm that the *syn* Evans aldol **3a** has been obtained.

We next examined the generalization of this reaction (Table 2). We were pleased to observe that under the same reaction conditions, benzaldehyde (**2b**), and 4-methoxybenzaldehyde (**2c**) gave the expected *syn* aldols **3b** and **3c** in 86 and 85% yields, respectively (entries 2 and 3, Table 2). Again, the diastereoselectivity was excellent and superior to >96% *de*, in both cases. Finally, even aliphatic aldehydes such as pentanal (**2d**) and (*E*)-non-2-en-1-al (**2e**) gave exclusively the *syn* aldols **3d** and **3e** (>96% *de*) in yields of 64 and 63%, respectively (entries 3 and 4, Table 2). The *syn* stereochemistry of the products was secured by NMR analysis of their corresponding enantiomerically pure acetonides. The absolute configuration of aldols **3b–e** is supposed to be 2*S*,3*R* because the same cyclic six-membered transition state may be invoked, and specific rotations of aldols, and of the corresponding acetonides have the same signs (see the Supporting Information).



Scheme 2. Stereochemical assignment based on analysis of the differences of the ^{1}H NMR chemical shifts at the positions α and α′ to the carbinol group of esters (*S*)-**5a** and (*R*)-**5a**.

Table 2: Formation of the titanium enolate from **1** and its reactivity towards aldehydes **2b–e**.[a]



Entry	Aldehyde	Yield [%]	*de* of *syn* product
1	benzaldehyde (**2b**)	86	>96
2	4-methoxybenzaldehyde (**2c**)	85	>96
3	pentanal (**2d**)	63	>96
4	(*E*)-non-2-en-1-al (**2e**)	64	>96

[a] Reaction conditions for generation of the Ti enolate: $TiCl_4$ (1 equiv), TMEDA (2.5 equiv), CH_2Cl_2, −78°C, 20 min.

It is worth noting that under the reaction conditions used we never observed the defluorination reaction leading to the vinylic CF_2 product. This result can be explained by the stability of the $TiCl_3$ enolate of the α-CF_3 amide possessing the oxazolidine-2-thione moiety (vide infra).

We are now studying the scope and limitation of this reaction in our laboratories by varying the type of electrophile that can react with the titanium enolate of **1**. We will also examine reactions with bulkier oxazolidine-2-thiones (such as 5,5-biphenyl-4-benzyloxazolidine-2-thione) in order to study the influence of the steric hindrance of the titanium enolates of the corresponding α-CF_3 amides on the course of the reaction.

In conclusion, the reaction of titanium enolate of the α-CF_3-substituted amide (*S*)-*N*-3,3,3-trifluoropropionyl-4-benzyloxazolidin-2-thione (**1**) with several aldehydes afforded the enantiomerically pure *syn* aldols in good to excellent yields and high diastereoselectivity (>96% *de*). The absolute configuration of aldol **3a** has been determined unambiguously through the Mosher's esters. The absolute configurations of the other aldols have not been determined but are assumed to be identical to those of **3a**. We are currently preparing sugar derivatives to confirm the absolute configuration of the newly created stereogenic centers, especially in the case of aliphatic aldehydes.[11] $LiBH_4$ reduction of the *syn* aldols shoulc provide the corresponding enantiomerically

pure 1,3-diols and thus open a new access to chiral CF_3-containing compounds. These results show the large scope of such an aldol reaction, and will probably find application in the preparation of pharmacologically active products in the near future.

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