JOC*Note*

Convenient Asymmetric Synthesis of β-Trifluoromethyl-β-amino Acid, β-Amino Ketones, and γ-Amino Alcohols via Reformatsky and Mannich-Type Reactions from 2-Trifluoromethyl-1,3-oxazolidines

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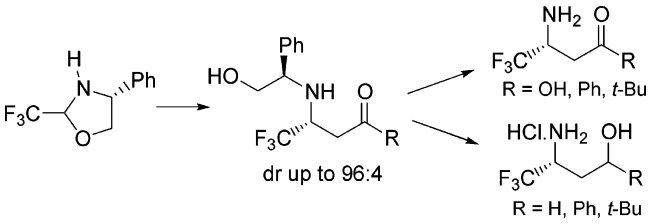

The stereoselective syntheses of β-trifluoromethyl-β-amino ester, β lactams, and β-amino ketones starting from an oxazolidine derived from trifluoroacetaldehyde hemiacetal and (*R*)-phenylglycinol are reported. The Mannich-type reaction involving a chiral fluorinated iminium ion occurred in a good yield and with a higher stereoselectivity (dr up to 96:4) than that of the Reformatsky-type reaction. This straightforward strategy was applied to the short syntheses of (*R*)-3-amino-4,4,4-trifluorobutanoic acid, a series of novel enantiopure unprotected fluorinated β-amino ketones, and their corresponding γ-amino alcohols.

Introduction

In the field of amino acid chemistry, β-amino acids have proven to be of great interest because of their unique biological properties.[1] Likewise, β-amino carbonyl compounds, generally obtained by Mannich-type reactions, are very important compounds as biologically active molecules.[2] The corresponding γ-amino alcohols resulting from their reduction are also very useful molecules for their biological properties and their application as ligands in asymmetric syntheses.[3] Moreover, the introduction of fluorine atoms into a molecule often produces significant changes in its physical, chemical, and biological properties.[4] In particular, fluorinated amino acids and amino alcohols have proven to be of great interest.[5] In this context, the design of new synthetic methodologies for the asymmetric synthesis of fluorinated β-amino acids, β-amino ketones, and γ-amino alcohols is of considerable current interest. Several synthetic approaches of chiral β-trifluoromethyl β-amino acids have been reported in the literature,[6] but the preparation of chiral β-trifluoromethyl-β-amino ketones and γ-amino alcohols is less documented.[7] Among the various methods involving nucleophilic additions on trifluoromethyl imines or related acetals and

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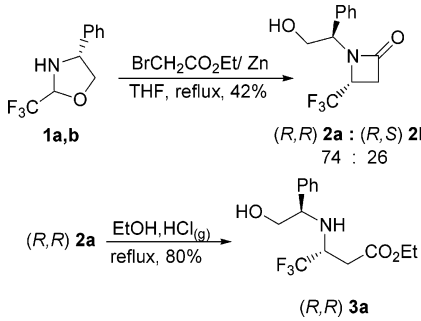
iminium[8] are the Reformatsky[9] and the Mannich-type[10] reactions, which have emerged as powerful approaches for the synthesis of β-trifluoromethylated β-amino carbonyl compounds, mainly in the racemic series. In the course of our studies, we have reported the Lewis-acid promoted ring opening of chiral 2-trifluoromethyl-1,3-oxazolidines into a chiral iminium salt, and its use for the stereoselective C−C bond formation.[11] These 2-trifluoromethyl-1,3-oxazolidines have already been reported as very powerful synthons for the stereoselective synthesis of chiral trifluoromethyl amino compounds.[12−14] We now report our results about the application of the Reformatsky and the Mannich-type reactions to the straightforward stereoselective synthesis of trifluoromethylated β-amino acid, β-amino ketones, and γ-amino alcohols in enantiopure form.

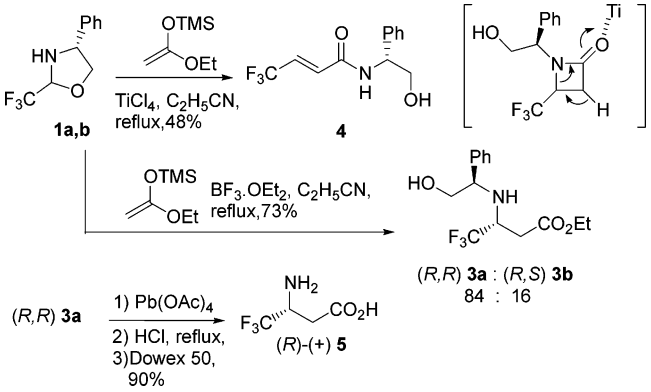
Results and Discussion

The Reformatsky reaction with a diastereomeric mixture of nonfluorinated chiral amino alcohol-based oxazolidines generally occurs with a high diastereoselectivity. This can be explained by the formation of a single chiral imine intermediate resulting from the ring opening of the oxazolidine by the organometallic reagent.[15] The rigidity of this intermediate is due to a chelation of the zinc atom of the alcoholate with the nitrogen atom of the imine.[15,16] We first investigated the Reformatsky-type reaction between chiral 2-trifluoromethyl-1,3-oxazolidines, **1a**,**b**, and ethyl bromoacetate. Oxazolidines, **1a**,**b**, were very conveniently prepared in high yield by the condensation of trifluoroacetaldehyde methyl hemiacetal and (*R*)-phenylglycinol.[12] The reaction of ethyl bromoacetate with **1a**,**b** (62:38 mixture of diastereomers) in the presence of zinc dust at the reflux temperature of THF furnished 4-trifluoromethylazetidin-2-one, **2a**,**b**, in 42% yield as a 74:26 mixture of diastereomers. A pure fraction of **2a** was isolated (Scheme 1). The decrease of the stereoselectivity of this reaction, compared to results reported with nonfluorinated oxazolidines,[15] can be explained by the inhibition of the oxazolidine ring opening into imine as a result of the electron-withdrawing effect of the trifluoromethyl group. In our case, the Reformatsky reagent should directly attack the C-2 carbon of the oxazolidine in a nucleophilic substitution process. Such an unusual behavior of 2-trifluoromethyl-1,3-oxazolidines has already been reported by Mikami et al.[12,13]

SCHEME 1



SCHEME 2



The fact that we were unable to detect the open-chain β-amino esters suggests the efficient cyclization of the intermediate metalloamines into azetidinones **2a**,**b**. This reaction proved to be more selective than previously reported methods in the fluorinated series, affording either the β-amino ester[9b] or a mixture of azetidin-2-one and β-amino ester.[9a] The pure major diastereomer, **2a**, was easily converted into β-amino ester **3a** by ethanolysis under acidic catalysis (Scheme 1). The configuration of **3a** proved to be *R*,*R* (vide infra).

To increase the stereoselectivity of the trifluoromethyl β-amino ester formation, we then considered using the Mannich-type reaction, which would involve a unique iminium intermediate starting from a diastereomeric mixture of oxazolidines **1a**,**b**. We have already reported that the same iminium is formed in situ starting from either **1a** or **1b** under a Lewis-acid activation.[11] Contrary to unfluorinated oxazolidines,[17] the trifluoromethylated oxazolidines, **1a**,**b**, exhibited very poor reactivity toward ethyl (*tert*-butyldimethylsilyl)ketene acetal under Lewis-acid (BF_3·OEt_2, TMSOTf, $GaCl_3$) activation in dichloromethane or propionitrile even at reflux temperature. Only trace amounts of the expected β-amino esters were obtained in these conditions. However, the reaction of oxazolidines **1a**,**b** with ethyl trimethylsilyl ketene acetal[18] occurred in propionitrile at reflux temperature in the presence of a Lewis acid (Scheme 2). With $TiCl_4$ activation, the expected β-amino ester was not detected. The major reaction product was the α,β-unsaturated amide, **4**, which was isolated in 48% yield. Such acrylic trifluoromethyl compounds have already been reported in the literature as a result

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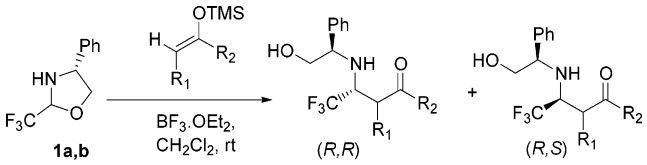
(18) Ethyl (trimethylsilyl)ketene acetal was obtained as a 70:30 inseparable mixture with ethyl 2-trimethylsilyl acetate: Colvin, E. *Silicon Reagents in Organic Synthesis*; Academic Press: London, U.K., 1988. As ethyl 2-trimethylsilyl acetate proved to be completely inert in the Mannich-type reaction conditions, the 70:30 mixture was used for the next reaction.

TABLE 1. Mannich-Type Reactions of Oxazolidines 1a,b with Various Enoxysilanes[a]



entry	R_1, R_2	products	yield[b] (%)	dr[c]
1	H, Ph	**6a** (*R*,*R*), **6b** (*R*,*S*)	66	**6a**:**6b**, 96:4
2	H, *t*-Bu	**7a** (*R*,*R*), **7b** (*R*,*S*)	88	**7a**:**7b**, 94:6
3	$(CH_2)_4$	**8a** (*R*,*R*), **8′a** (*R*,*R*)	60	**8a**:**8′a**, 54:46

[a] Enoxysilane, 2 equiv; Lewis acid, 3 equiv. [b] Isolated yield. [c] Measured by the ^{19}F NMR of the crude reaction mixture.

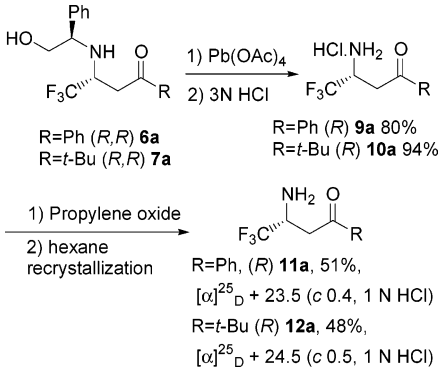
of elimination reactions of β-amino ketones.[10b,c] In our case, the compound **4** should arise from the in situ β elimination of an intermediate azetidin-2-one promoted by $TiCl_4$. When $BF_3{\cdot}OEt_2$ was used as the Lewis acid, the expected β-amino esters **3a** and **3b** were obtained in 73% yield as an 84:16 diastereomeric mixture. The major **3a** diastereomer was obtained in pure form after silica-gel chromatography. The synthesis of the target β-amino acid required the removal of the chiral auxiliary and the hydrolysis of the ester function. This was achieved in 90% yield in a three-step procedure involving the reaction with $Pb(OAc)_4$, HCl (6 N) hydrolysis, and propylene oxide treatment (Scheme 2). The *R* configuration of the β-trifluoromethyl-β-amino acid **5** obtained was assigned by comparison with the optical rotation reported in the literature[6p] ($[\alpha]^{25}_D$ +26.6 (*c* 0.5, 6 N HCl), $[\alpha]^{25}_{D(lit.)}$ −27.6 (*c* 1.4, 6 N HCl) for *S* enantiomer).

As very few examples of stereoselective methods for the synthesis of β-trifluoromethyl-β-amino ketones are reported in the literature, we next designed to investigate the Mannich-type reaction with enoxysilanes. The trimethylsilyl enol ethers derived from acetophenone, *tert*-butyl methyl ketone, and cyclohexanone[19] were submitted to the Mannich-type reaction with the oxazolidines **1a**,**b** in CH_2Cl_2 in the presence of $BF_3{\cdot}Et_2O$. The reaction proceeded very smoothly at room temperature, and the corresponding β-amino ketones **6**, **7**, and **8** were obtained in good yield. The new amino stereogenic center was formed with a high stereoselectivity control (Table 1). It is worthwhile noting that the reaction of the trimethylsilyl enol ether derived from cyclohexanone produced only two of the four possible β-amino ketone diastereomers (Table 1, entry 3). Further stereochemical arguments demonstrated that they were syn/anti diastereomers (vide infra).

The removal of the (*R*)-phenylglycinol side chain was then very conveniently achieved by the standard $Pb(OAc)_4$ method to give the corresponding novel chiral free β-amino ketones (Scheme 3). Enantiopure β-amino ketones **11a** and **12a** were obtained in a few steps from the corresponding major **6a** and **7a** diastereomers.

We first designed to determine the absolute configuration of the unknown β-amino ketones **6a** and **7a** by means of their conversion into the (*R*,*R*)-β-amino ester **3a** through a Bayer−Villiger oxidation.[20] Unfortunately, the only products obtained after mCPBA oxidation were a result of the nitrogen-atom oxidation. However, the *R* configuration of **11a** and **12a** was

SCHEME 3



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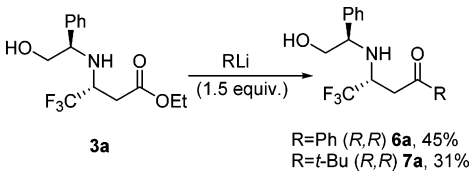

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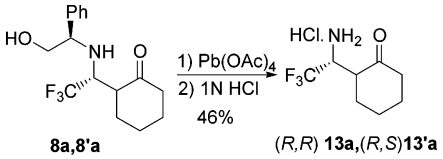

conveniently assigned by correlation with the known configuration of the β-amino esters **3a**. Indeed, the reaction of *(R,R)*-**3a** with PhLi and *t*-BuLi afforded (*R*,*R*)-**6a** and (*R*,*R*)-**7a** (Scheme 4).

As the reaction of the cyclohexanone-derived trimethylsilyl enol ether gave only two of the four diastereomers to be expected, the question was to know whether it was syn−anti, both syn, or both anti diastereomers. To make a decision, the **8a**,**8′a** mixture was submitted to $Pb(OAc)_4$ removal of the phenylglycinol chiral auxiliary. As a result, a mixture of two diastereomers **13a** and **13′a** in the same ratio as that found in the starting mixture was obtained proving that **8a** and **8′a** were syn/anti diastereomers (Scheme 5). By correlation with the *R* configuration of the acyclic analogues **3a**, **6a**, and **7a**, the configuration of the trifluoromethylated amino chiral centers of **8a**, **8′a** and **13a**, **13′a** were anticipated to be *R*. According to the model we previously proposed for the Strecker-type reaction,[11] all these results are consistent with the attack of the intermediate iminium on the less-hindered *re* face (Figure 1).

The LAH reduction of the (*R*,*R*)-β-amino ester **3a** in diethyl ether gave the corresponding (*R*,*R*)-amino diol **14** in 87% yield. The removal of the chiral (*R*)-phenylglycinol side chain of **14** was achieved in 79% yield to give the enantiopure (*R*)-γ-amino alcohol hydrochloride **15** (Scheme 6).

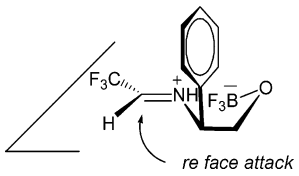

FIGURE 1. Attack (*re* face) of the postulated iminium ion intermediate.

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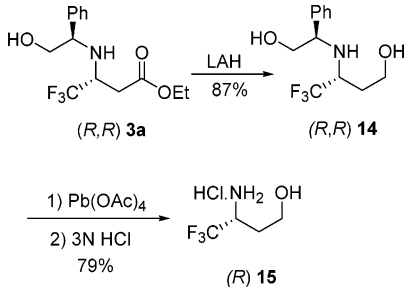
SCHEME 6



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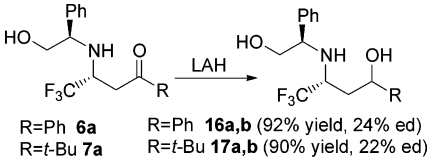

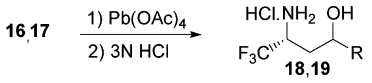

Starting compd	Product	yield (%)
R=Ph **16a**	**18a**	86
R=Ph **16b**	**18b**	86
R=*t*-Bu **17a**	**19a**	71
R=*t*-Bu **17b**	**19b**	70

In a similar manner, enantiopure β-amino ketones **6a** and **7a** were converted into the corresponding γ-amino alcohols **16** and **17** in high yield (90 to 92%) but with a low diastereoselectivity (22 to 24% de; Scheme 7). Fortunately, each diastereomer **16a** (major) and **16b** (minor) could easily be separated by chromatography on silica gel, and the two diastereomers **17a** (major) and **17b** (minor) were efficiently separated by recrystallization. The relative configuration of the 1,3-amino alcohol sequence of each diastereomer could not be assigned. Nevertheless, each isolated amino diol, **16a**, **16b**, **17a**, and **17b**, was treated with $Pb(OAc)_4$ to furnish the four corresponding trifluoromethylated γ-amino alcohol hydrochlorides, **18a**, **18b**, **19a**, and **19b**, in enantiopure form and in good yield (70−86%).

Conclusion

In conclusion, we have developed an efficient straightforward synthetic route for the synthesis of β-trifluoromethylated β-amino acid, β-amino ketones, and γ-amino alcohols from a trifluoacetaldehyde and an (*R*)-phenylglycinol-based oxazolidine. The diastereoselectivity of the reported Reformatsky and Mannich-type reactions was varied (dr up to 96:4). However, the separation of the diastereomers was very efficient due to the phenylglycinol side chain, and the novel target compounds were very conveniently obtained in enantiopure form.

Experimental Section

General Procedure for the Mannich-Type Reaction. (3*R*)-4,4,4-Trifluoro-3-((1*R*)-2-hydroxy-1-phenylethylamino)-1-phenylbutanone (6a). To a solution of oxazolidines **1a**,**b** (62:38 mixture, 1.0 g, 4.6 mmol) in dichloromethane (20 mL) under argon was added acetophenone trimethylsilyl enol ether (1.3 g, 6.9 mmol). The temperature was cooled to −78 °C, and BF_3OEt_2 (0.9 mL, 6.9 mmol) was added. The reaction mixture was warmed to room temperature overnight. The mixture was then poured into a saturated aqueous solution of $NaHCO_3$ (20 mL). The aqueous layer was extracted with dichloromethane (3 × 20 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (4:1 petroleum ether/ethyl acetate) gave pure **6a** (1.03 g, 66%) as a colorless oil. $[\alpha]^{20}_D$ −27.0 (*c* 1.1, $CHCl_3$); IR (neat) 3349, 3030, 2928, 2932, 1686, 1266 cm^{-1}; ^1H NMR δ 1.78 (m, 2H), 3.24 (dd, J_{AB} = 12.5, J = 2.0 Hz, 1H), 3.33 (d, J_{AB} = 12.5 Hz, 1H), 3.58 (dd, J_{AB} = 11.3, J = 7.9 Hz, 1H), 3.79 (dd, J_{AB} = 11.3, J = 3.8 Hz, 1H), 4.04 (qd, J = 7.2, 2.0 Hz, 1H), 4.07 (dd, J = 7.9, 3.8 Hz, 1H), 7.2−7.4 (m, 5H), 7.49 (dd, J = 7.3, 5.2 Hz, 2H), 7.62 (tt, J = 5.2, 1.2 Hz, 1H), 7.95 (td, J = 7.3, 1.2 Hz, 2H); ^{13}C NMR δ 38.6, 54.0 (q, J = 28.6 Hz), 62.4, 67.0, 126.5 (q, J = 274.7 Hz), 127.3, 127.7, 128.2, 128.6, 128.8, 133.9, 136.2, 140.4, 196.9; ^{19}F NMR δ −74.9 (d, J = 7.2 Hz); MS (EI 70 eV) *m*/*z* 338 ($M^+ + 1$), 320, 306, 225, 218, 200, 186. Anal. Calcd for $C_{18}H_{18}F_3NO_2$: C, 64.09; H, 5.38; N, 4.15. Found: C, 64.13; H, 5.59; N, 3.90.

Removal of the (*R*)-Phenylglycinol Side Chain of β-Amino Ketones with $Pb(OAc)_4$. (*R*)-3-Amino-4,4,4-trifluoro-1-phenylbutanone Hydrochloride (9a). To a solution of **6a** (338 mg, 1 mmol) in 10 mL of a mixture of $MeOH/CH_2Cl_2$ (2:1) was added $Pb(OAc)_4$ (620 mg, 1.4 mmol) at 0 °C. After 20 min of stirring at 0 °C, the reaction mixture was poured into a buffer aqueous solution (pH = 7, 10 mL) at room temperature and then filtered on Celite. The aqueous layer was extracted with dichloromethane (4 × 10 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. To the crude product was then added 5 mL of 5 N HCl, and the mixture was stirred for 24 h at room temperature. The organic layer was extracted with diethyl ether (3 × 5 mL), and the combined aqueous extracts were concentrated under reduced pressure to afford hydrochloride **9a** (202 mg, 80%) as a pale yellow powder. $[\alpha]^{25}_D$ +23.4 (*c* 0.80, HCl 1 N); IR (KBr) 3382, 2950, 2920, 1694, 1685, 1596, 1205 cm^{-1}; ^1H NMR (D_2O) δ 3.53 (dd, J_{AB} = 19.1, J = 9.5 Hz, 1H), 3.72 (dd, J_{AB} = 19.1, J = 2.3 Hz, 1H), 4.6 (dqd, J = 9.5, 7.7, 2.3 Hz, 1H), 7.3 (m, 2H), 7.5 (m, 1H), 7.8 (m, 2H); ^{13}C NMR (D_2O) δ 37.6, 51.3 (q, J = 32.5 Hz), 126.1 (q, J = 279.6 Hz), 130.8, 131.5, 137.1, 137.4, 199.5; ^{19}F NMR (D_2O) δ −71.8 (d, J = 7.7 Hz).

(3*R*)-3-Amino-1-phenyl-4,4,4-trifluorobutanone (11a). Hydrochloride **9a** (202 mg, 0.8 mmol) was dissolved in propylene oxide (10 mL) and stirred for 1 h at room temperature. The crude mixture was concentrated under reduced pressure. Purification by flash chromatography (17:3 petroleum ether/ethyl acetate) followed by recrystallization in hexane gave **11a** (88 mg, 51%) as a yellow solid. Mp 30 °C; $[\alpha]^{25}_D$ +23.5 (*c* 0.4, HCl 1 N); IR (KBr) 3382, 2950, 2920, 1694, 1685, 1596, 1205 cm^{-1}; ^1H NMR δ 1.56 (m, 2H), 3.09 (dd J_{AB} = 17.5, J = 9.5 Hz, 1H), 3.24 (dd, J_{AB} = 17.5, J = 3.0 Hz, 1H), 3.93 (dqd, J = 9.5, 7.8, 3.0 Hz, 1H), 7.40 (dd, J = 8.8, 6.3 Hz, 2H), 7.52 (dd, J = 6.3, 1.3, 1H), 7.87 (dd, J = 8.8, 1.3, 2H); ^{13}C NMR δ 38.2, 51.3 (q, J = 24.7 Hz), 125.4 (q, J = 280.3 Hz), 127.1, 127.8, 132.7, 135.3, 195.2; ^{19}F NMR δ −78.6 (d, J = 7.8 Hz). Anal. Calcd for $C_{10}H_{10}F_3NO$: C, 55.84; H, 4.64; N, 6.45. Found: C, 55.47; H, 4.55; N, 6.34.

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Supporting Information Available: General experimental methods, complete experimental procedures, and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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