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Synthesis of Enantiopure α-Alkoxy-α-Trifluoromethyl Aldehydes and Carboxylic Acids from Trifluoromethyl Ketones**

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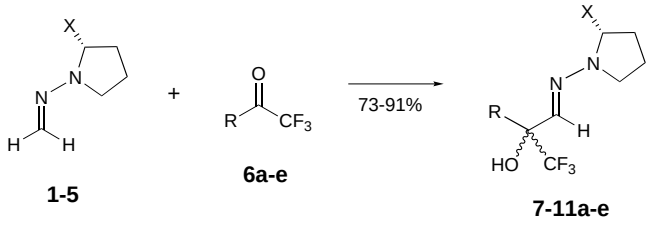
The unique properties conferred to organic compounds by the introduction of one or more fluorine atoms have recently found many applications in a variety of fields including pharmaceuticals, material science, and agrochemistry.[1] This fact, combined with the lack of appropriate fluorinated building blocks from natural sources, has evoked in the last few years the development of new synthetic methods for such compounds; the synthesis of enantiomerically enriched trifluoromethyl-containing building blocks is of particular significance in medicinal chemistry[2] and material science.[3] In this context, easily available trifluoromethyl ketones[4] appear as appropriate starting materials, but their reactions with d^1 reagents for the synthesis of interesting α-hydroxy-α-trifluoromethyl carbonyl compounds have been scarcely investigated.[5]

We have recently reported on the use of formaldehyde dialkylhydrazones as a new class of neutral formyl anion and cyanide equivalents, and this new methodology has been successfully applied to the formylation of several electrophilic substrates, including conjugated nitroalkenes,[6] α,β-unsaturated ketones,[7] and aldehydes.[8] As a natural extension of the method, we now report the nucleophilic 1,2-addition of these compounds to trifluoromethyl ketones, which provides a straightforward, short route to both racemic or enantiomerically pure α-alkoxy-α-trifluoromethyl aldehydes and carboxylic acids.

All tested couples of formaldehyde hydrazones **1**–**5** and a variety of trifluoromethyl ketones (**6a**–**e**) easily reacted in the absence of any catalyst or promoter, giving rise to the expected α-hydroxy-α-trifluoromethylhydrazones **7**–**11** in excellent yields, even when less reactive aromatic trifluoromethyl ketones (**6c**, **e**) were used as substrates (Scheme 1; selected results are collected in Table 1). Racemic adducts were best synthesized with the more reactive pyrrolidine-containing hydrazone **1**,[8] as this reagent led to the corresponding adducts **7a**–**e** in better yields and shorter reaction times than the simple formaldehyde dimethylhydrazone. Concerning the asymmetric version of the reaction, we found that use of the chiral formaldehyde SAMP-hydrazone **2**[6c] (SAMP = (*S*)-1-amino-2-(methoxymethyl)pyrrolidine) resulted in very low inductions under all tested reaction conditions; the selectivity of these additions was only slightly or not at all affected by temperature. Under the assumption that the origin of selectivity should be steric in nature, hydrazones **3**–**5**, in which the modified chiral auxiliaries are more sterically demanding than SAMP units, were synthesized. The influence by the tuned auxiliaries was analyzed from the results of the addition to compound **6b** (Table 1, entries 4 – 7). These experiments indicated a direct correlation between size and selectivity: The benzhydryl-containing reagent **3** gave slightly better results (d.r. 64:36) than **2**, while the asymmetric inductions effected by **4** and **5**, having bigger (quaternary) groups on position 2 of the pyrrolidine ring, were higher (d.r. 71:29 and 81:19, respectively). Nevertheless, crystalline derivative **5** proved to be the reagent of choice for practical



	1,7	2,8	3,9	4,10	5,11
X	H	CH_2OMe	$CHPh_2$	CEt_2OMe	CPh_2OMe

6-15	a	b	c	d	e
R	Me	Bn	Ph	n-C_7H_{15}	

Scheme 1. Synthesis of α-hydroxyhydrazones **7**–**11**.

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Table 1. Synthesis of α-hydroxy-α-trifluoromethylhydrazones **7**–**11**.

Entry	Ketone **6**	Hydrazone	Adducts **7**–**11**, yield [%]	d.r.[a]	Pure adducts **11**,[b] yield [%]	$[\alpha]_D^{22}$ ($c = 1$, $CHCl_3$)
1	**6a**	**5**	*rac*-**7a**, 90			
2	**6a**	**6**	**13a**, 90	70:30	(*S*,*S*)-**11a**, 63	−170.2
					(*R*,*S*)-**11a**, 27	−163.4
3	**6b**	**1**	*rac*-**7b**, 81			
4	**6b**	**2**	**8b**, 84	54:46[c]		
5	**6b**	**3**	**9b**, 70	64:36[c]		
6	**6b**	**4**	**10b**, 70	71:29[c]		
7	**6b**	**5**	**11b**, 91[d]	81:19	(*S*,*S*)-**11b**, 74	−38.6
					(*R*,*S*)-**11b**, 17	−198.3
8	**6c**	**1**	*rac*-**7c**, 87			
9	**6c**	**5**	**11c**, 90	58:42	(*S*,*S*)-**11c**, 52	−152.7
					(*R*,*S*)-**11c**, 37	−154.4
10	**6d**	**1**	*rac*-**7d**, 80			
11	**6d**	**5**	**11d**, 85[d]	62:38	(*S*,*S*)-**11d**, 49	−175.1
					(*R*,*S*)-**11d**, 36	−119.2
12	**6e**	**1**	*rac*-**7e**, 73			
13	**6e**	**5**	**11e**, 82	51:49	(*S*,*S*)-**11e**, 42[e]	−172.1
					(*R*,*S*)-**11e**, 40[e]	−152.8

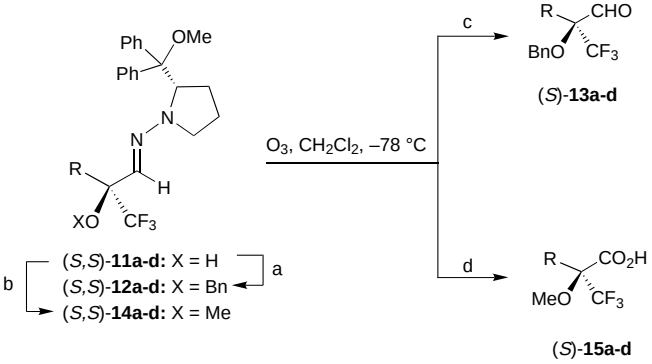
[a] Determined by ^{13}C and ^1H NMR spectroscopy of unpurified reaction mixtures. [b] After flash chromatography, $de \geq 96\%$. [c] Inseparable mixture of diasteromers. [d] 5% of Et_3N was added to the reaction mixture. [e] Configuration assigned tentatively.

The absolute configuration of the newly created quaternary center of the minor isomer (*R*,*S*)-**11a** was unequivocally determined by X-ray diffraction analysis[9] (Figure 1), while that of (*S*)-**15c** was assigned by comparison of its optical rotation with that of commercial Mosher's acid [(*S*)-MPTA]. The absolute configuration of compounds in the series **b** and **d** was assigned by analogy. Of course, use of *ent*-**5** (available from D-proline) would led to products with the opposite configuration.

To summarize, appropriate formaldehyde hydrazones, acting as neutral d^1 synthons, readily add to trifluoromethyl ketones. This reaction, combined with standard hydrazone cleavage, constitutes the first general method for the asymmetric synthesis of enantiomerically pure quaternary trifluoromethyl-substituted α-alkoxy carbonyl compounds.

reasons: With this reagent, both diastereoisomers (*S*,*S*)- and (*R*,*S*)-**11b** could be easily separated by simple flash chromatography. The interesting properties as resolving agent exhibited by the (*S*)-1-amino-2-(methoxydiphenylmethyl)pyrrolidine auxiliary proved to be a general characteristic, and led to the easy chromatographic separation of all diastereomeric mixtures obtained from **5** (see Table 1).

Adducts (*S*,*S*)-**11** were transformed in their O-benzyl derivatives (*S*,*S*)-**12** (Scheme 2); subsequent hydrazone cleavage by ozone afforded the corresponding aldehydes



Scheme 2. Synthesis of compounds (*S*,*S*)-**12**/(*S*,*S*)-**14** and (*S*)-**13**/(*S*)-**15**. a) BnBr, NaH, DMF; b) MeI, NaH, THF; c) Me_2S; d) $NaClO_2$, *t*BuOH, isobutene.

(*S*)-**13** in good yields. Alternatively, compounds (*S*,*S*)-**11** were transformed into carboxylic acids (*S*)-**15** by successive methylation [→(*S*,*S*)-**14**], ozonolysis, and in situ oxidation of the crude aldehydes. The (*S*)-2-methoxydiphenylmethyl-1-nitrosopyrrolidine obtained as by-product during the ozonolysis to **13** or **15** was recycled to the reagent **5** by reduction ($LiAlH_4$) and condensation with trioxane (79–86% overall yield). The results for the syntheses of compounds (*S*)-**12**–(*S*)-**15** are summarized in Table 2.

Table 2. Synthesis of compounds (*S*)-**12**–(*S*)-**15**.

Hydrazone (*S*,*S*)-**11**	R	(*S*,*S*)-**12**, yield [%]	(*S*)-**13**, yield [%]	$[\alpha]_D^{22}$[a]	(*S*,*S*)-**14**, yield [%]	(*S*)-**15**, yield [%]	$[\alpha]_D^{22}$[a]
a	Me	87	66	−38.5	85	90	−1.1
b	Bn	89	84	+43.1	87	72	+24.6
c	Ph	82	77	−39.8	73	74	−71.6[b]
d	*n*-C_7H_{15}	72	74	−24.1	83	80	−8.4

[a] $c = 1$, $CHCl_3$. [b] $c = 2$, MeOH; commercially available (*S*)-MPTA (Aldrich) has a $[\alpha]_D^{20}$ value of −73 under these conditions.

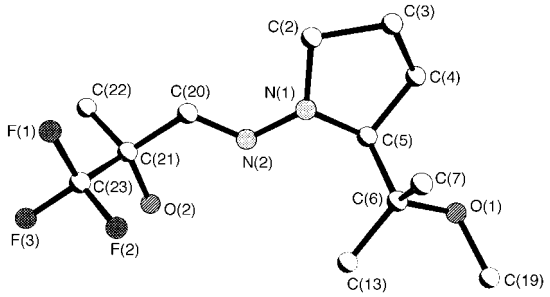


Figure 1. Crystal structure of (*R*,*S*)-**11a**. Phenyl groups have been omitted for clarity.

Experimental Section

Chiral auxiliary: Compound **3** was prepared from (*S*)-[3.3.0]-2-oxo-4,4-diphenyl-1-aza-3-oxa-bicyclooctane[11] by hydrogenolysis (Pd/C, H_2), nitrosation (*t*$BuNO_2$), reduction ($LiAlH_4$, THF), and condensation with trioxane (51% overall yield). Compounds **4** and **5** were prepared from their corresponding hydrazines[12] by reaction with trioxane, and purified by distillation and flash chromatography, respectively.

Adducts **7a**,**b**–**11a**,**b**: To a solution of the hydrazone **1**–**5** (3 mmol) in toluene (**a**, 2 mL) or cyclohexane (**b**, 5 mL) was added the ketone **6a** (6 mmol) or **6b** (12 mmol), and the mixture was stirred until thin-layer chromatography (TLC) indicated total consumption of the starting hydrazone. The mixture was then concentrated and purified by flash chromatography.

Adducts **7c–e** and **11c–e**: Hydrazone **1** or **5** was solved in excess (about 5 equiv) of ketone (**6c–e**), and the mixture was stirred until consumption of the former (TLC). Unchanged ketone was recovered (75–85%) by bulb-to-bulb distillation, and the residue was purified by flash chromatography.

Compounds **12** and **14** were synthesized from **11** under standard conditions.

Aldehydes **13**: Ozone was bubbled through a solution of **12** (1 mmol) in dry CH_2Cl_2 (5 mL) at $-78\,^{\circ}C$ until appearance of a permanent blue color (5–10 min). Me_2S (5 mmol) was added. The mixture was allowed to warm to room temperature and concentrated, and the residue purified by column chromatography.

Carboxylic acids **15**: Ozonolysis was carried out from **14** as described above, but only 1 mmol of Me_2S was added. To the resulting solution was added *t*BuOH (12 mL) and isobutene (10 mL). After the mixture was cooled to $0\,^{\circ}C$, a solution of $NaClO_2$ (10 mmol) and KH_2PO_4 (9 mmol) in H_2O (12 mL) was added dropwise and the mixture was stirred for 16 h. The solvent was removed, and the residue was treated with 1M NaOH and extracted with Et_2O (2×10 mL). The aqueous layer was acidified to pH 1 (HCl) and extracted with ethyl acetate (10×5 mL). The combined organic layers were then concentrated and purified by flash chromatography.

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[9] Suitable crystals were obtained from light petroleum ether at room temperature. $C_{22}H_{25}F_3N_2O_2$, $M_r = 406.44$, crystal size $0.1 \times 0.4 \times 0.4$ mm, crystal system orthorombic, space group $P2_12_12_1$, $a = 7.4267(10)$, $b = 14.081(2)$, $c = 20.344(3)$ Å, $V = 2127.5(5)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.269$ g cm^{-3}, $1.76 < \Theta < 23.32^{\circ}$, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), $T = 296(2)$ K; of 4500 reflections collected, 2830 were independent [$I > 2\sigma(I)$]; 362 parameters, $R = 0.0682$ ($wR = 0.1100$). The crystal was coated with resin epoxy and mounted in a CCD diffractometer. The intensities were corrected for Lorentz and polarization effects. No absorption correction. The structure was solved by Patterson and Fourier methods, and a final mixed refinement was undertaken. Hydrogen atoms were located in a difference synthesis, and their coordinates and isotropic thermal parameters refined, except for H2 whose thermal parameter was fixed. Refinement on F^2 for all reflections. Weighted factors (wR) and all GOFs are based on F^2; conventional R factors are based on F. The configuration of C(5) is based on that known for the auxiliary. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-102999. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Detection of Specific Noncovalent Zinc Finger Peptide–Oligodeoxynucleotide Complexes by Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry**

Edda Lehmann and Renato Zenobi*

All retroviruses, including the human immunodeficiency virus type 1 (HIV-1), encode a gag precursor polyprotein which contains zinc binding domains of the type CCHC (CCHC = Cys-X_2-Cys-X_4-His-X_4-Cys, X = variable amino acid).[1] These zinc-coordinated motifs play an important role in the recognition of viral ribonucleic acid and replication of the virus. The interaction between peptides containing such motifs and single-stranded nucleic acids has been extensively studied,[2, 3] mainly in view of developing antiviral agents for the treatment of the acquired immunodeficiency syndrome (AIDS).[4] The methods used for these investigations are rather time-consuming and expensive. Here we report that matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) is suitable for detecting specific noncovalent complexes, and that it is a potential method for rapidly screening antiviral agents. The use of MALDI-MS is now well known for the analysis of high molecular weight biopolymers.[5] However, its ability to detect specific noncovalent complexes is just starting to be explored.[6] Complexes that are stable under physiological conditions in solution may not survive laser desorption and ionization processes. Using carefully designed controls, we were able to establish a correlation between the existence of a specific noncovalent triple complex in solution and in the MALDI mass spectra.

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