Asymmetric Synthesis

DOI: 10.1002/anie.200604802

Asymmetric Nucleophilic Glyoxylation through a Metalated α-Aminonitrile Derivative in Michael Additions to Nitroalkenes**

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Dedicated to Professor Hans-Joachim Gais on the occasion of his 65th birthday

α-Keto acids and their derivatives play an important role in organic synthesis.[1] They have been successfully incorporated into peptidic molecules to generate potent inhibitors of proteolytic enzymes such as serine, cysteine, and aspartyl proteases.[2] They are also effective as inhibitors of leukotriene A4 hydrolase.[3] Furthermore, they are an integral part of many biologically active natural products such as 3-deoxy-D-*manno*-2-octulosonic acid (KDO), 3-deoxy-D-glycero-D-galacto-2-nonulosonic acid (KDN) and *N*-acetylneuraminic acid.[1,4] The introduction of the keto acid structure in these compounds is synthetically challenging and different methodologies to build up this moiety have already been developed, which include ozonolysis of α-methylene esters,[5] oxidation of α-alkoxy esters with MoO_5·Py·HMPA (MoOPH; Py = pyridine, HMPA = hexamethylphosphoramide) using a strong base[6] or through β elimination of a diol cyclic sulfite.[7]

In several methods, the concept of Umpolung[8] has been applied, which allows the nucleophilic introduction of the α-keto acid system. In 1994, Takahashi et al. introduced a protected cyanohydrin as an acyl anion equivalent of alkyl glyoxylate[9a] that was later on used in the synthesis of KDO and KDN.[9b] Schmidt and co-workers were able to successfully synthesize 3-deoxy-D-*arabino*-2-heptulosonic acid (DAH), which plays an important role in the biosynthesis of amino acids in microorganisms and plants, by stereoselectively applying a diethyl thioacetal protected alkyl glyoxylate as the C_2 nucleophile.[10] Furthermore, several alkylation reactions of lithiated 1,3-dithiane-protected alkyl glyoxylates have been reported.[11] To the best of our knowledge, a method for asymmetric nucleophilic glyoxylation has not yet been developed. In addition, the number of methods that offer a direct approach to enantioenriched α-keto esters are also rather limited.[12] This fact encouraged us to develop the first asymmetric method by using a metalated glyoxylate aminonitrile **B** as a chiral equivalent of a nucleophilic glyoxylate d^1 synthon **A** (Figure 1).

Figure 1. Metalated aminonitrile **B** as a chiral equivalent of a nucleophilic glyoxylate d^1 synthon **A**.

The synthetic utility of metalated aminonitriles[13] as equivalents of masked acyl anions [14] is well known. Use of the enantiomerically pure secondary amine (*S*,*S*)-**1** as a chiral auxiliary has already proven to give excellent asymmetric induction in many nucleophilic acylation reactions with different Michael acceptors.[15] In our attempts to synthesize the glyoxylate aminonitrile **2**, we first tried an asymmetric Strecker reaction starting with the glyoxylic acid ester, the pure secondary amine (*S*,*S*)-**1**, and potassium cyanide in water.[16] This attempt failed probably because of formation of the aldehyde hydrate under these conditions.[17]

The best method we found was the reaction of the pure secondary amine (*S*,*S*)-**1** with chloroacetonitrile,[18] and further functionalization through the addition of di-*tert*-butyl dicarbonate (Boc_2O) and subsequent treatment with two equivalents of lithium diisopropylamide (LDA).[19] This two-step conversion led to the corresponding aminonitrile **2** as an epimeric mixture in good yield (73%; Scheme 1).

To determine the best conditions for metalation of the chiral glyoxylate aminonitrile **2**, we first carried out test alkylation reactions with methyl iodide, in which we found that bases such as LDA or *tert*-butyllithium were not suitable and only afforded traces of the methylation product. However, the strong, hindered base potassium diisopropylamide (KDA) allowed an almost quantitative conversion of **2** into its methylated derivative. Next we trapped the metalated aminonitrile with various nitroalkenes **3**, which are excellent Michael acceptors in asymmetric conjugate additions[20] and allow synthetic transformations of the nitro group to many other functionalities.[21] As was recently discovered, for simple aminonitriles derived from aldehydes,[22] the asymmetric 1,4-additions afforded the Michael adducts **4** in high yields (69–84%) and excellent diastereomeric excesses (75–96%), which could be improved to greater than 98% *de* by flash chromatography (Scheme 1, Table 1).

Thus, the metalated aminonitrile **2** turned out to be an efficient reagent for asymmetric nucleophilic glyoxylations with high asymmetric induction. Maintaining the reaction temperature at −78°C proved to be very important, as

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[**] This work was supported by the Fonds der Chemischen Industrie. We thank Boehringer Mannheim GmbH, BASF AG, and Bayer AG for the donation of chemicals. The collection of the X-ray data by Dr. C. W. Lehmann, MPI Mülheim, is gratefully acknowledged.

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

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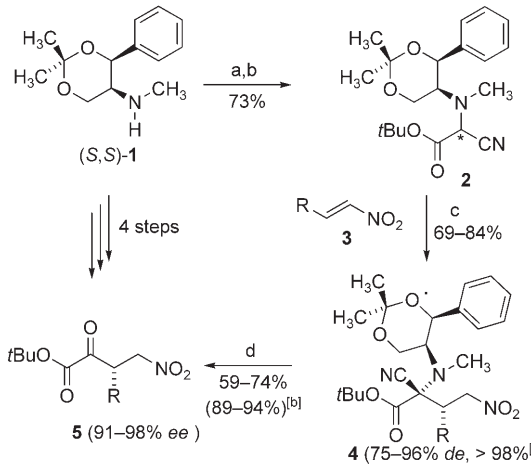

[a] After flash chromatography. [b] Yield of crude product.

Scheme 1. Asymmetric nucleophilic glyoxylation of nitroalkenes. a) $ClCH_2CN$, Et_3N, THF, reflux, 5 h; b) Boc_2O, THF, −78 °C, then LDA, 3 h; c) KDA, THF, −78 °C, then **3**; d) 2.0 N $AgNO_3$, THF/H_2O, RT, 7 days.

Table 1: Synthesis of the Michael adducts **4**.

4	R	Yield [%]	*de* [%][a]	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)
a	Me	84	96 (>98)	+42.3 (1.48)
b	Et	81	96 (>98)	+47.5 (1.00)
c	*i*Pr	69	75 (>98)	+49.1 (1.00)
d	*c*-C_6H_{11}	75	92 (>98)	+32.1 (1.00)
e	$BnOCH_2$	78	96 (>98)	+33.9 (1.38)

[a] Determined by ^1H and ^{13}C NMR spectroscopy; *de* values after flash chromatography are given in brackets.

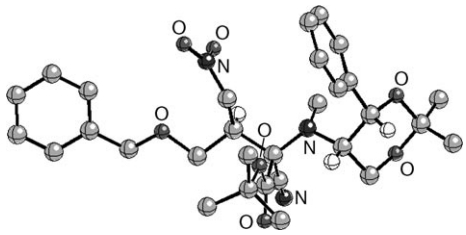

Figure 2. X-ray crystal structure of **4e**.

When the reaction was performed over seven days, an excellent conversion (89–94 %) into the glyoxylated products **5a–e** was achieved, and the products were isolated in moderate yields (59–74 %) by flash chromatography (Scheme 1, Table 2). The slightly lower yield is due to the tendency of the products to eliminate HNO_2 on silica gel to form the β,γ-unsaturated α-keto esters. For that reason, aromatic nitroalkenes were not used. The best results were obtained from a quick purification through a short pad of silica gel (Scheme 1, Table 2).

Table 2: Cleavage of the Michael adducts **4** to give the keto esters **5**.

5	R	Yield [%][a]	*ee* [%][b]	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	Config.
a	Me	70 (92)	91	−54.8 (0.80)	*S*
b	Et	63 (92)	96	−59.4 (0.50)	*S*
c	*i*Pr	74 (90)	94	−65.9 (0.70)	*S*
d	*c*-C_6H_{11}	62 (94)	98	−55.4 (1.00)	*S*
e	$BnOCH_2$	59 (89)	95	+17.7 (0.89)	*R*

[a] Yield after flash chromatography with yield before purification given in brackets. [b] Determined by HPLC on a chiral stationary phase.

warming up the reaction mixture led to a considerable decrease in diastereoselectivity and yield. The occurrence of the retro-Michael addition at higher temperatures seemed to be responsible for this phenomenon. A further interesting observation was the fact that there was a clear limitation in the steric bulkiness of the substituent R: a change from an ethyl to an isopropyl group led to only a small decrease in yield and diastereomeric excess, whereas in the case of R = *t*Bu, no product was detected. Evidently, the metalated aminonitrile **B** is sterically demanding, which conversely permits the high asymmetric induction.

The configuration of the two newly created stereogenic centers was determined by X-ray analysis on the Michael adduct **4e** and was found to be *S*,*S* (Figure 2).[23] Considering a uniform reaction mechanism for all the prepared compounds **4a–e**, they should all have this configuration. Remarkably, the observed relative topocity is the opposite to that found previously in related cases.[13c,d] Possible explanations could be the relatively small size of the nitro substituent and the high electron-withdrawing ability of the nitroalkenes.[21a]

The isolation of the α-keto esters **5a–e** required the cleavage of the Michael adducts **4a–e**. Initial attempts were made using copper sulfate, which has already been successfully employed in several asymmetric nucleophilic aroylation reactions,[15] but proved to be too mild a reagent. Silver nitrate led to an almost quantitative cleavage to the α-keto ester. Furthermore, it could be shown from HPLC measurements that the cleavage with silver nitrate was almost free of racemization (91–98 % *ee*). Once isolated, the products **5a–e** were found to be configurationally stable for an extended period of time. The absolute configuration of the keto esters **5** was based on the X-ray structure of **4e**, and is *S* in the case of compounds **5a–d** and *R* for **5e**.

In conclusion, we have developed the first asymmetric nucleophilic glyoxylation method, which employs metalated enantiopure aminonitriles. This method opens up a new high-yielding and enantioselective route to chiral γ-nitro α-keto esters, which are synthetically important trifunctional building blocks and possible precursors of γ-amino α-keto esters. The extension of this methodology to different Michael acceptors is currently being investigated.

Experimental Section

(*S*,*S*/*R*)-**2**: A dry three-necked flask was charged with (*S*,*S*)-**1** (442.3 mg, 2.0 mmol, 1.0 equiv), chloroacetonitrile (0.15 mL, 2.4 mmol, 1.2 equiv), and triethylamine in tetrahydrofuran (0.37 mL, 2.6 mmol, 3 M, 1.3 equiv). After heating the reaction mixture to reflux for 5 h, the colorless ammonium chloride precipitate was removed by filtration, and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (silica, pentane/diethyl ether 1:1) and isolated as a colorless solid (426.4 mg, 82 %).

Boc_2O (360.1 mg, 1.65 mmol, 1.1 equiv) was added to a solution of the resulting aminonitrile in tetrahydrofuran (390.0 mg, 1.5 mmol,

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0.1 M, 1.0 equiv). The reaction mixture was cooled to −78 °C and a solution of LDA in tetrahydrofuran (214.3 mg, 3.0 mmol, 1 M, 2.0 equiv) was added slowly. The reaction mixture was stirred for 3 h and then allowed to warm to −50 °C. The reaction mixture was quenched with saturated NH_4Cl solution, extracted three times with diethyl ether and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography (silica, pentane/diethyl ether 4:1) to give **2** as a colorless solid (648.3 mg, 90 %).

4a–e: Potassium *tert*-butoxide (1.2 equiv) was placed in a dry Schlenk flask and carefully heated under vacuum to avoid sublimation. After cooling to room temperature and addition of tetrahydrofuran (5 mL mmol^{-1}) and diisopropylamine (0.17 mL, 1.2 mmol, 1.2 equiv), the reaction mixture was cooled to −78 °C and *n*BuLi (0.48 mL (2.5 M), 1.2 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred for 30 min at −78 °C and then a solution of the aminonitrile **2** (360.2 mg, 1.0 mmol, 1.0 equiv) in tetrahydrofuran (10 mL mmol^{-1}) was added. Deprotonation was complete after 1 h, the nitroalkene **3a–e** (1.3 equiv, 1.3 mmol) in tetrahydrofuran (2 mL mmol^{-1}) was slowly added at −78 °C. The reaction mixture was stirred for 3 h and then quenched at −78 °C with saturated NH_4Cl solution. The reaction mixture was extracted three times with diethyl ether and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The Michael adducts **4a–e** were purified by flash chromatography (silica, pentane/diethyl ether 4:1) and isolated as colorless solids.

5a–e: A one-necked flask, wrapped in aluminum foil, was charged with the Michael adduct **4a–e** (0.5 mmol, 1.0 equiv) in tetrahydrofuran (10 mL mmol^{-1}) and $AgNO_3$ (1 mL, 2.0 N, 2.0 mmol, 4.0 equiv). The reaction mixture was stirred for 7 days, after which time diethyl ether (20 mL mmol^{-1}) was added, and the mixture stirred for an additional 30 min. The silver residues were removed by filtration and the filtrate washed with diethyl ether and water. After partitioning, the aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The α-keto esters were purified by flash chromatography (silica, pentane/diethyl ether 4:1) and isolated as colorless oils.

Received: November 27, 2006
Published online: February 15, 2007

Keywords: aminonitriles · asymmetric synthesis · keto esters · Michael addition · Umpolung

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[23] CCDC-290371 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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