COMMUNICATION

Asymmetric nucleophilic α-amino-acylation with metalated chiral amino nitriles: enantioselective synthesis of 3-substituted 5-amino-4-oxo-esters *via* asymmetric Michael addition

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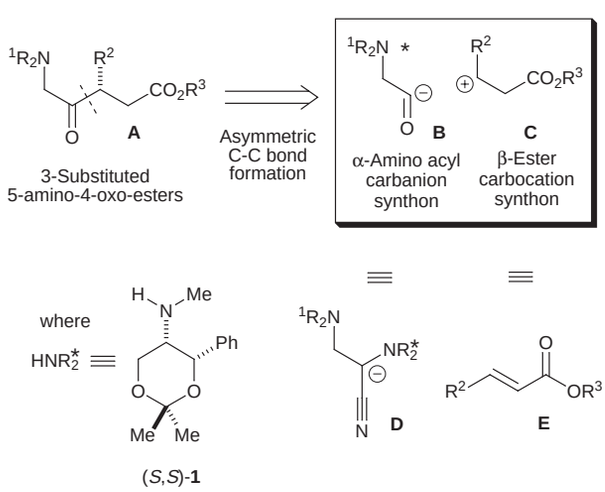
Highly stereoselective conjugate addition of an enantiopure metalated β-amino substituted amino nitrile to α,β-unsaturated esters, with subsequent silver nitrate induced hydrolysis of the amino nitrile adducts affords 3-substituted 5-amino-4-oxo-esters with high enantiomeric purity, thus achieving the overall asymmetric Michael addition of an α-amino-acyl carbanion.

Amino nitriles have historically occupied an important position as versatile intermediates in organic synthesis.[1,2] In addition, since the amino nitrile moiety may be hydrolysed to the corresponding carbonyl compound under extremely mild conditions,[3] their metalation is significant in that it generates polarity-reversed masked acyl carbanion equivalents[4] with non-classical d^1 reactivity.[5] Of particular importance is the use of metalated amino nitriles as nucleophilic acylating agents in carbon–carbon bond forming processes leading to 1,2-[6] and 1,4-difunctionalized materials, with a great deal of attention given to conjugate additions to α,β-unsaturated carbonyl compounds.[7]

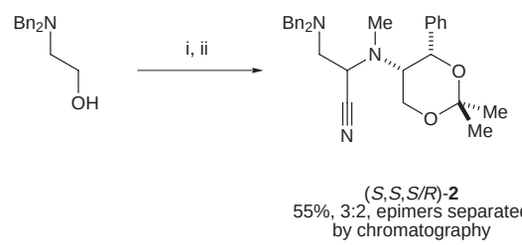
We have recently demonstrated that the incorporation of enantiopure amines, such as (*S*,*S*)-**1**, into amino nitriles as chiral auxiliaries, allows highly stereoselective nucleophilic aroylations of prochiral substrates *via* asymmetric Michael addition to generate, following amino nitrile hydrolysis, chiral 1,4-dicarbonyl compounds with high enantiomeric purity.[8] This methodology has recently been directed towards enantioselective total synthesis of lignans.[9]

We now wish to report our investigations into the extension of this methodology to the asymmetric synthesis of 3-substituted 5-amino-4-oxo-esters **A**, bearing both α-amino ketone and δ-amino ester functionalities (Scheme 1). Since α-amino ketones are precursors to chiral β-amino alcohols[10,11] and chiral amines,[11] their asymmetric synthesis has the potential to provide valuable intermediates for the synthesis of biologically active compounds, including peptidomimetics.[12] Retrosynthetic analysis of **A** leads to α-amino acyl carbanion **B** and β-ester carbocation **C** synthons, synthetic equivalents of which are the amino-acetaldehyde derived metalated amino nitrile **D** with chiral auxiliary (*S*,*S*)-**1** and an α,β-unsaturated ester **E**, respectively. We chose, therefore, to develop a procedure for the overall enantioselective conjugate addition of an α-amino acyl carbanion equivalent **D** to α,β-unsaturated esters in order to access the target 3-substituted 5-amino-4-oxo-esters.



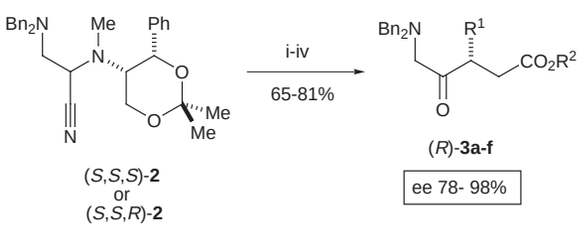
Scheme 1 Retrosynthetic strategy.

For the initial investigations into this transformation, it was decided to employ amino nitrile **2** with the *N*,*N*-dibenzyl protected β-amino group. This was prepared by Swern oxidation of 2-(*N*,*N*-dibenzylamino)ethanol,[13] followed by generation of the intermediate iminium species by treatment of the crude *N*,*N*-dibenzylamino acetaldehyde with a slight excess of the enantiopure amine auxiliary (*S*,*S*)-**1** in dichloromethane containing 4 Å molecular sieves (Scheme 2). Subsequent addition of hydrogen cyanide at 0 °C resulted in the formation of a 3:2 diastereomeric mixture of amino nitriles (*S*,*S*,*S*/*R*)-**2** in 55% yield. It was necessary to purify the diastereoisomers by chromatography and subsequent metalations were performed using single diastereoisomers, although no attempt was made to determine the configuration at the α-centre of either material.



Scheme 2 *Reagents and conditions*: i, $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N; ii, (*S*,*S*)-**1**, 4 Å molecular sieves, CH_2Cl_2, rt, then hydrogen cyanide, 0 °C.

Lithiation of either amino nitrile (*S*,*S*,*S*)-**2** or (*S*,*S*,*R*)-**2** was most effectively achieved using LDA in THF or diethyl ether at 0 °C with subsequent cooling to low temperature before the addition of the requisite (*E*)-α,β-unsaturated ester (Scheme 3).



Scheme 3 *Reagents and conditions*: i, LDA, THF or Et_2O, 0 °C; ii, (*E*)-$R^1CH{=}CHCO_2R^2$, −78 °C or −100 °C; iii, NH_4Cl (aq); iv, $AgNO_3$, THF–H_2O.

Table 1

Entry	R^1	R^2	Conditions[a]	Yield (%)[b]	$[\alpha]_D^{23}$[c]	ee (%)[d]
(*R*)-**3a**	Me	Me	$LiClO_4$, Et_2O, −100 °C	69		78 (≥98)
			Et_2O, −100 °C	81		86 (≥98)
			THF, −40 °C	74		91 (≥98)
			THF, −78 °C	72		93 (≥98)
			THF, −100 °C	75	+12.9	91 (≥98)
(*R*)-**3b**	Et	Me	THF, −78 °C	77	+26.7	94 (≥98)
(*S*)-**3b**[e]	Et	Me	THF, −100 °C	76	−27.9	91 (≥98)
(*R*)-**3c**	^{n}Pr	Me	THF, −100 °C	75	+17.7	93 (≥98)
(*R*)-**3d**	^{n}Bu	Me	THF, −100 °C	72	+24.9	94 (≥96)
(*R*)-**3e**	^{i}Bu	Et	THF, −100 °C	65	+14.2	88
(*R*)-**3f**	Bn	Me	THF, −100 °C	77	+62.8	95

[a] Conditions used for the conjugate addition step. [b] Overall yield of material after chromatography. [c] Measured for materials at the highest given enantiomeric excess, (*c* 1.0, $CHCl_3$). [d] Determined by HPLC on chiral stationary phase, values in parenthesis refer to enantiomeric excesses of recrystallized materials. [e] The amino nitrile with chiral auxiliary (*R*,*R*)-**1** was employed.

After conjugate addition was complete, the reaction mixture was quenched by the addition of ammonium chloride solution, and standard aqueous work-up afforded the crude Michael adducts, which were generally unstable to chromatography on silica. Treatment of these crude adducts, therefore, with silver nitrate in THF–water mixtures effected the rapid hydrolysis of the amino nitrile moiety to generate the desired α-amino-keto-esters **3**.

The transformation was carried out using a number of (*E*)-α,β-unsaturated esters with alkyl substituents, and the desired (3*R*)-5-amino-1,4-dicarbonyl compounds were obtained in good overall yields (65–81%) with around 85% recovery of the chiral auxiliary (*S*,*S*)-**1** (Table 1). Initial optimization studies of the asymmetric induction for the overall transformation were carried out for conjugate additions to (*E*)-methyl crotonate. It was observed that the use of diethyl ether as solvent at −100 °C resulted in the formation of the 5-amino-4-oxo-ester (*R*)-**3a** in good enantiomeric excess (ee 86%), although this level of induction was somewhat reduced by the use of lithium salt additives such as lithium perchlorate (ee 78%).† Performing the reaction in THF at low temperature (−40 °C to −100 °C), however, resulted in significantly improved levels of asymmetric induction (ee 91–93%). Accordingly, subsequent conjugate additions were carried out in THF at −78 °C or −100 °C, and the resulting 5-amino-4-oxo-esters (*R*)-**3a**–**f** were obtained in excellent enantiomeric excesses (ee 88–95%) after amino nitrile hydrolysis. Identical results were obtained by employing either amino nitrile (*S*,*S*,*S*)-**2** or (*S*,*S*,*R*)-**2**. The high enantiomeric purity of crystalline materials (*R*)-**3a**–**d** could be further improved by simple recrystallization to afford the virtually enantiopure materials (ee ≥96–≥98%). The assignment of the absolute configuration of the newly formed stereogenic centres was possible based on X-ray crystal structure analysis of the amino nitrile (*S*,*S*,*R*,*R*)-**4** with the chiral auxiliary (*S*,*S*)-**1** (Fig. 1), the intermediate Michael adduct in the synthesis of (*R*)-**3b** (R^1 = Et, R^2 = Me).‡ Inspection of the structure revealed the (*R*,*R*)-configuration of the two new stereogenic centres. This is consistent with the asymmetric induction previously observed for the conjugate addition of metalated α-amino nitriles to α,β-unsaturated carbonyl compounds involving (*S*,*S*)-**1** as a chiral auxiliary. We have recently proposed a transition state model for this reaction.[1] Since silver nitrate induced hydrolysis of the intermediate amino nitrile Michael adducts proceeds without affecting the configuration of the remaining stereogenic centre, and assuming uniform reaction pathways, compounds **3a**–**f** were correspondingly assigned as having a (3*R*)-configuration. Furthermore, it was demonstrated that (*S*)-**3b** could be accessed by using the enantiomeric auxiliary (*R*,*R*)-**1**, (76% yield, ee 91%, ≥98% after recrystallization).§

In conclusion, we have developed a method for the highly enantioselective installation of a stereogenic centre at the α′-position of an α-amino ketone *via* asymmetric Michael addition of a metalated β-amino substituted chiral amino nitrile as an α-amino acyl carbanion equivalent to enoates. Further investigations into the elaboration of this methodology and potential applications of the title 5-amino-3-alkyl-4-oxo-esters as enantiopure building blocks in synthesis are currently in progress.

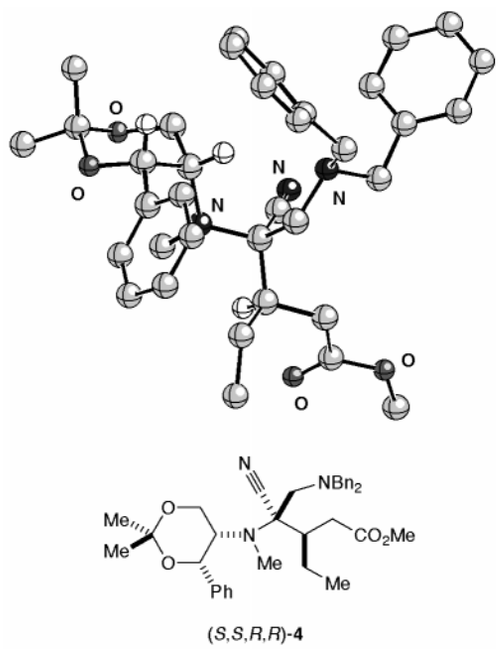


Fig. 1 X-Ray crystal structure of (*R*,*R*,*S*,*S*)-**4**.

Acknowledgements

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Notes and references

† Enantiomeric excesses were determined using HPLC on a chiral stationary phase by correlation with a racemic standard (stationary phase: J. T. Baker, Chiralcel OD2 (4.6 × 250 mm), flow: 0.5 mL min^{-1}, eluants: cyclohexane–propan-2-ol; 9 : 1–99 : 1). The racemic materials *rac*-**3a**–**f** were prepared in an analogous manner to that outlined above, employing the corresponding amino nitrile with a piperidine substituent in place of the chiral auxiliary. Swern oxidation of 2-(*N*,*N*-dibenzylamino)ethanol, treatment with piperidine followed by addition of hydrogen cyanide similarly afforded this amino nitrile in yields of 45–60%.

‡ Crystal data for (*S*,*S*,*R*,*R*)-**4**, $C_{36}H_{45}O_4N_3$ M = 583.76, orthorhombic, a = 9.758(2), b = 17.425(1), c = 19.072(1) Å, V = 3242.9 $Å^3$,

$P2_12_12_1$, $Z = 4$, $\mu = 5.83$ cm^{-1}, no absorption correction, $T = 150$ K, 6428 independent and 5648 observed ($I > 2\sigma(I)$) reflections, 388 parameters in final least squares full-matrix refinement on F, terminating at $R = 0.072$ ($R_w = 0.075$, $w = 1/(\sigma^2(F) + 0.0004F^2)$), goodness of fit 1.472, residual electron density of $-0.42/+0.61$ eÅ^{-3}. CCDC reference number 207/330. See http://www.rsc.org/suppdata/p1/1999/1617 for crystallographic files in .cif format.

§ All new compounds gave satisfactory spectral and analytical data. Experimental details will be reported elsewhere in a full paper.

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