Controlling diastereoselectivity in the reactions of enantiomerically pure α-bromoacyl-imidazolidinones with nitrogen nucleophiles: substitution reactions with retention or inversion of configuration†‡

N. R. Treweeke,[a] P. B. Hitchcock,[a] D. A. Pardoe[b] and S. Caddick*[c]

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Diastereoselective substitution reactions of α-bromoacyl-imidazolidinones with nitrogen nucleophiles can be promoted with either retention or inversion of configuration by carrying out reactions under epimerising or non-epimerising conditions.

The preparation of enantiomerically pure α-amino acid derivatives has always been a challenge for the organic chemist and a number of different catalytic and stoichiometric strategies have been employed.[1] Over a number of years we[2] and others[3] have been interested in the development of dynamic kinetic resolution (DKR), particularly for the synthesis of α-amino-acids. Dynamic kinetic resolution is a conceptually appealing approach as it involves the conversion of a mixture of stereoisomers into a single product isomer.[4,5]

In previous studies we have investigated substitution reactions of α-haloacyl-imidazolidinones with amines and other nucleophiles under DKR conditions. These reactions provide access to diastereomerically enriched products by employing a chiral auxiliary to control the stereochemical outcome of the substitution reaction. Molecular modelling by Santos *et al.*[6] indicates that the selective reaction of one epimer can be attributed to the ease with which the halide can depart without suffering an undesirable steric interaction with the stereocontrolling group on the chiral auxiliary (Fig. 1 A *versus* B). This is in contrast to the majority of chiral auxiliary controlled reactions using acyl-imidazolidinones and oxazolidinones in which the key interaction is between the incoming group and the stereodirecting group.[7]

From a synthetic perspective there are still limitations to the aforementioned DKR method for making α-substituted carboxylic acid derivatives. The most obvious is that if access to both diastereoisomers of a substitution product is required then, in general, access to both enantiomers of the chiral auxiliary is required. In this paper we describe a method which avoids this limitation, providing a simple route to either diastereomer (and hence enantiomer) of an amine-substituted carboxylic acid derivative. This solution is a result of the differing, (and stereocomplementary) effects of the auxiliary on an incoming halide when enolate chemistry is used, and on an outgoing halide when nucleophilic substitution is used. We demonstrate this concept by application to the synthesis of aromatic containing α-amino acids.

We had previously described a stereocomplementary approach to α-amino acids using a crystallisation induced dynamic resolution (CIDR)/DKR approach.[8] However reliance on the CIDR method is limited, principally because of the lack of certainty associated with such a crystallisation approach. It is never clear which epimer will selectively crystallise from the rapidly epimerising mixture.[9] Thus an alternative general strategy was sought (Fig. 2). We envisaged that substitution of the (2′*R*)-bromide **1** with a nucleophile under epimerising conditions should lead to a product **2** with overall retention of configuration *via* DKR in which the (2′*S*)-isomer would be most reactive. This would be complemented by classical inversion providing access to **3** under non-epimerising conditions (Fig. 2).

In order to test this hypothesis we needed to prepare a variety of 2-bromo-derivatives (**4a–4e**). In our hands, and after considerable experimentation, we identified bromination conditions utilising LHMDS for enolate generation, using bromine as an electrophile.

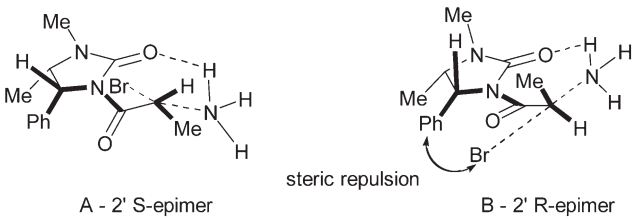


Fig. 1 Transition state assemblies for substitution reactions of α-bromoacyl-imidazolidinones.

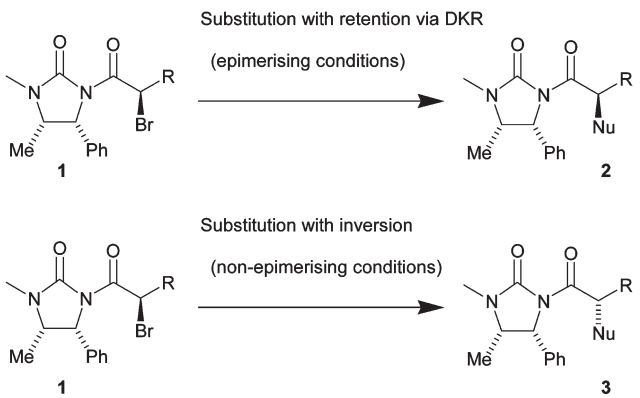


Fig. 2 Strategy for complementary stereochemical approach to α-amino acid derivatives from a single bromide.

† Electronic supplementary information (ESI) available: representative procedures and characterisation data for all compounds. See http://www.rsc.org/suppdata/cc/b4/b417954d/

‡ This paper is dedicated with admiration and respect to Professor Steven V. Ley on the occasion of his 60th birthday.

*s.caddick@ucl.ac.uk

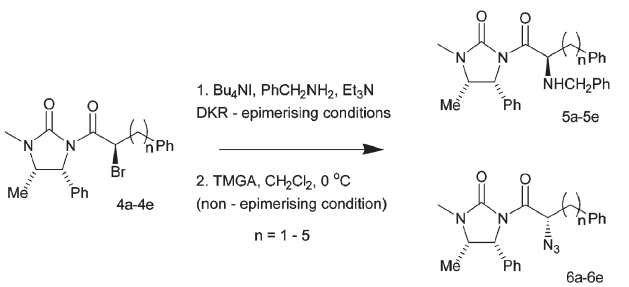
Using this protocol we were able to isolate the (2′*R*)-bromo-derivatives (**4a–4e**) as single diastereomers (>95% by NMR) in isolated yields in excess of 70%. The other by-products observed in the reactions were either dibrominated species (<10%) or, in the cases of **4d** and **4e**, the (2′*S*)-bromide. The relative (and hence) absolute stereochemistry of the bromides was unambiguously established by X-ray analysis of the epimer of **4b**§ (also see ESI†).

Substitution of the diastereomerically pure bromides (**4a–4e**) with benzylamine under DKR conditions (using Bu_4NI as an epimerising reagent) was examined and shown to proceed with a high level of stereocontrol (^{1}H NMR) and with retention of configuration. The sense of diastereoselectivity was confirmed by X-ray analysis of **5b**§ (also see ESI†). This is consistent with a reaction involving initial conversion of the (2′*R*) bromide into a mixture of (2′*S*)/(2′*R*) halides and thence selective reaction of the (2′*S*) product with inversion of configuration. Yields and diastereoselectivities are sufficiently high to be synthetically useful (Table 1).

Substitution of the (2′*R*) bromides (**4a–4e**) with a nitrogen nucleophile under non-epimerising conditions required careful experimentation. Initial work using benzylamine was promising but difficulties in avoiding epimerisation with a concomitant compromise in diastereoselectivity were encountered. However success was achieved using the nucleophile tetramethylguanidinium azide (TMGA).[10] Exposure of the (2′*R*) bromides (**4a–4e**). to TMGA in dichloromethane at 0 °C led to excellent yields and diastereoselectivities of products (**6a–6e**, Table 1). Diastereoselectivities were estimated by careful analysis of ^{1}H NMR spectra and the relative (and hence absolute) stereochemical assignments confirmed by X-ray analysis of **6b**.

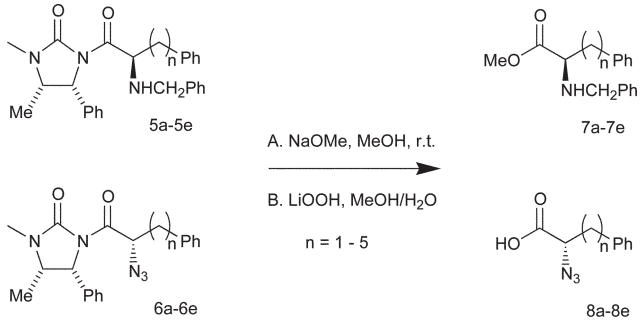
As expected and by analogy with prior reports in the literature auxiliary cleavage could be readily achieved using either sodium methoxide[11] (α-methylbenzylamino-products (**5a–5e**)) or lithium peroxide (α-azido-products) (**6a–6e**).[12] Both procedures proceeded with excellent recovery of the chiral auxiliary (Table 2). The stereochemical integrity of the products derived from auxiliary cleavage could be confirmed at this stage, in the case of **7b**, by correlation with a sample prepared by independent synthesis, starting from *R*-homophenylalanine (see ESI†). Hydrogenolysis of the α-benzylamino group could be achieved in good yields and without significant racemisation (see ESI†) using Pearlman's catalyst (>95% yields). Hydrogenation of the α-azido species was most effective using Pd/C provided the α-amino acids in good yields (>85%). The stereochemical integrity of the α-amino esters or acid derivatives resulting from these procedures were judged to have retained high levels of optical purity (>90%) by comparison with literature data, where available (see ESI for details†).

Table 1 Complementary DKR and substitution approach to α-azido/amino carboxylic acid derivatives



Entry	Nucleophile	Product	Yield (de)
1	$BnNH_2$	**5a**, *n* = 1	77% (80%)
2	TMGA	**6a**, *n* = 1	94% (95%)
3	$BnNH_2$	**5b**, *n* = 2	98% (80%)
4	TMGA	**6b**, *n* = 2	92% (95%)
5	$BnNH_2$	**5c**, *n* = 3	93% (80%)
6	TMGA	**6c**, *n* = 3	93% (95%)
7	$BnNH_2$	**5d**, *n* = 4	97% (86%)
8	TMGA	**6d**, *n* = 4	91% (95%)
9	$BnNH_2$	**5e**, *n* = 5	90% (81%)
10	TMGA	**6e**, *n* = 5	89% (95%)

Table 2 Auxiliary cleavage protocols



Entry	Nu	Method	Product	Yield (Auxiliary)
1	NaOMe	A	**7a**, *n* = 1	78% (77%)
2	LiOOH	B	**8a**, *n* = 1	96% (90%)
3	NaOMe	A	**7b**, *n* = 2	92% (85%)
4	LiOOH	B	**8b**, *n* = 2	95% (96%)
5	NaOMe	A	**7c**, *n* = 3	86% (90%)
6	LiOOH	B	**8c**, *n* = 3	91% (93%)
7	NaOMe	A	**7d**, *n* = 4	97% (90%)
8	LiOOH	B	**8d**, *n* = 4	75% (92%)
9	NaOMe	A	**7e**, *n* = 5	85% (100%)
10	LiOOH	B	**8e**, *n* = 5	99% (64%)

In summary we have shown that α-amino-substituted carboxylic acid derivatives can be prepared using substitution reactions of α-bromoacyl-imidazolidinones. The stereodirecting group on the auxiliary controls the facial selectivity in the reaction of an enolate with an electrophile to give a single diastereomeric bromide. The resulting (2′*R*) bromides can be converted into the desired substitution product with inversion of configuration (under non-epimerising conditions). Substitution of the (2′*R*) bromides can also be achieved with retention of configuration *via* a DKR pathway. The latter results are consistent with the model involving stereochemical control by the interaction of the bromide as it departs with the stereodirecting group on the auxiliary. The ability to prepare either diastereomer (and hence enantiomer, after auxiliary cleavage) of a substitution product from the same substrate using a single chiral auxiliary offers a complementary approach to the majority of other auxiliary based protocols for the asymmetric synthesis of α-amino acid derivatives.

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N. R. Treweeke,[a] P. B. Hitchcock,[a] D. A. Pardoe[b] and S. Caddick*[c]
[a]*Department of Chemistry, University of Sussex, Brighton, UK BN1 9QJ*
[b]*GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex, UK CM19 5AW*
[c]*Department of Chemistry, University College London, 20 Gordon Street, London, UK WC1H OAJ. E-mail: s.caddick@ucl.ac.uk*

Notes and references

§ Structure corroboration for the epimer of **4b**, for **5b** and **6b** were obtained and full details are available in the ESI.† Summarised data are provided below.

Epimer of **4b** (2′*S*)-isomer, $C_{21}H_{23}BrN_2O_2$: M = 415.3, monoclinic, $P2_1$ (no. 4), a = 10.3839(12), b = 6.2094(4), c = 15.9554(18) Å, β = 108.513(4)°, V = 975.5(2) Å^3, Z = 2, μ(Mo–Kα) = 2.12 mm^{-1}. 3198 Unique reflections, 2534 with $I > 2\sigma(I)$. R_1 = 0.050 for $I > 2\sigma(I)$, wR_2 = 0.104 for all data. CCDC 261877.

5b, $C_{27}H_{39}N_3O_2$: M = 441.6, orthorhombic, $P2_12_12_1$ (no. 19), a = 9.5902(3), b = 10.3216(4), c = 24.9928(10)Å, V = 2473.9(2) Å^3, Z = 4, μ(Mo–Kα) = 0.08 mm^{-1}. 4434 Unique reflections, 3264 with $I > 2\sigma(I)$. R_1 = 0.046 for $I > 2\sigma(I)$, wR_2 = 0.112 for all data. CCDC 261878.

6b, $C_{21}H_{23}N_5O_2$: M = 377.4, monoclinic, $C2$ (no. 5), a = 19.2790(16), b = 6.0518(8), c = 17.189(2) Å, β = 99.200(8)°, V = 1979.7(4) Å^3, Z = 4, μ(Mo–Kα) = 0.08 mm^{-1}. 2477 Unique reflections, 2118 with $I > 2\sigma(I)$. R_1 = 0.086 for $I > 2\sigma(I)$, wR_2 = 0.254 for all data. CCDC 261879. See http://www.rsc.org/suppdata/cc/b4/b417954d/ for crystallographic data in .cif or other electronic format.

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