Asymmetric aziridine synthesis *via* aza-Darzens reaction of bromoacylcamphorsultam

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The aza-Darzens reaction of the chiral enolate derived from bromoacetylcamphorsultam 1 with *N*-(diphenylphosphinyl)aryl- and *tert*-butyl-methanimines proceeds in good yield to give *cis*-*N*-(diphenylphosphinyl)aziridinylcarbonyl sultams with high de. Monochiral *cis*-aziridinecarboxylates may be obtained in acceptable yield by hydrolysis of these sultams.

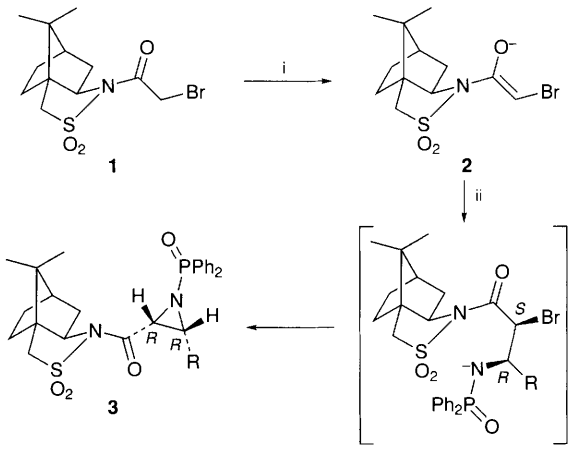
There has been much attention of late focused on the synthesis and uses of chiral aziridines.[1] Despite this burgeoning interest, there are few generally applicable methods for one-step preparation of aziridines of high enantiomeric purity from readily available precursors and, furthermore, the mainly nitrene-based methodology described suffers from the drawback that the substituents present on nitrogen are frequently not compatible with subsequent synthetic manipulation.[2] Since we have investigated the utility of the diphenylphosphinyl (Dpp) group as an activator for aziridine ring-opening reactions,[3] we were naturally curious as to whether we would be able to devise an asymmetric preparation of such *N*-Dpp aziridines, with particular emphasis upon preparation of chiral 2-carboxyaziridines species, usually prepared from naturally occurring (*S*)-amino acids. We were interested in the use of such compounds as precursors through ring-opening to non-proteinogenic 2-amino acids.[4] Our initial idea was to examine the suitability of *N*-Dpp imines as substrates in an aza-Darzens reaction[5] with a chiral α-bromoenolate. We report here the preliminary results of our studies into such an asymmetric reaction which show that the method allows preparation of chiral *N*-Dpp-2-carboxyaziridines with high levels of stereogenic purity.

We chose the Oppolzer sultam[6] as the first chiral auxiliary of our study. Deprotonation of bromoacyl sultam **1** at −78 °C using lithium hexamethyldisilazide (LHMDS) in THF gave bromoenolate **2**, to which was immediately added *N*-(diphenylphosphinyl)phenylmethanimine[7] (R = Ph) as a solution in THF (Scheme 1). After 3 h at −78 °C, aqueous work-up gave the crude product, aziridinyl sultam **3a** as a single diastereoisomer. Chromatographic purification gave **3a** in 71% yield.‡

The diastereoselectivity of the ring-formation was complete and shown to be *cis* by the magnitude of the ^{1}H NMR coupling constants exhibited by the product ($J_{H2'-H3'}$ 6.1 Hz[8]); the face selectivity of the reaction was >95%, as shown by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy. Single crystal X-ray analysis of this compound confirmed our diastereomeric and enantiomeric analysis and revealed the absolute stereochemistry of the newly-created asymmetric centres to be (2′*R*, 3′*R*) (Fig. 1).§ This necessarily implies a *syn*-selective aldol reaction, proceeding *via* nucleophilic attack of the *si*-face of the enolate upon the *si*-face of the imine, followed by ring-closure. We were particularly pleased to observe isolation of aziridine rather than the precursor amino bromide, because previously reported asymmetric Darzens and aza-Darzens reactions using boron-containing asymmetric reagents or catalysts did not proceed directly to the heterocycle, relying instead on a subsequent separate ring-closing step to provide non-racemic epoxides or aziridines.[9] Perhaps the extra nucleophilicity of an amide anion compared with an oxyboron or aminoboron nucleophile explains the phenomenon.

Encouraged by this result, we next turned our attention to an examination of the range of imines which would undergo this asymmetric reaction. The results of our study are collated in Table 1.

Thus, a range of aromatic imines was found to undergo aza-Darzens reaction in acceptable yield and with virtually complete diastereo- and enantio-control. In all cases, deacylated sultam



Scheme 1 *Reagents and conditions*: i, LHMDS, THF, −78 °C; ii, RCH=NP(O)Ph$_2$, THF, −78 °C

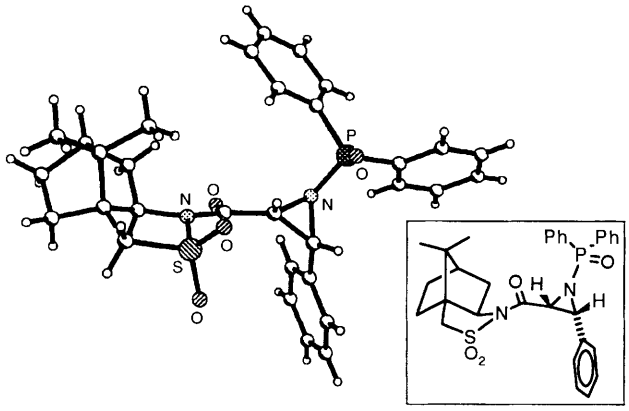


Fig. 1

was isolated in addition to the desired aziridines; presumably this by-product arises by elimination from the initially formed bromoenolate, or by a self-condensation. In any case, the yield of this asymmetric process was always >75% when taking into account returned bromoacyl sultam, with the exception of the reaction of the 2,2-dimethylpropanimine species (R = Bu^t), where aziridine **3i** (40%) and the intermediary compound **4** (13%) were isolated.

Removal of the chiral auxiliary under basic conditions was accomplished by treatment with lithium hydroxide monohydrate (1 equiv.), yielding the corresponding *N*-Dpp aziridinecarboxylates **5** in acceptable yield, with the exception of **3c**, **3g** and **3h**, whose delicate natures have thus far precluded hydrolysis (Scheme 2 and Table 2). Optimization of this hydrolysis protocol is currently under study in our laboratory.

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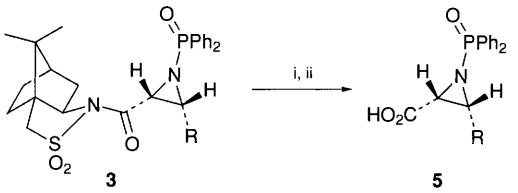
Table 1 Yields and optical rotations of compounds **3a–i**

Compound	R	Isolated yield (%)	$[\alpha]_D$/deg cm^2 g^{-1}
3a	Ph	71	−11.3
3b	4-BrC$_6$H$_4$	65	−16.0
3c	4-MeOC$_6$H$_4$	74	−14.9
3d	2-O$_2$NC$_6$H$_4$	72	−112.4
3e	4-O$_2$NC$_6$H$_4$	77	−28.6
3f	2-naphthyl	73	−16.6
3g	fluoren-2-yl	68	−20.0
3h	2-furyl	71	−18.9
3i	Bu^t	40[a]	+11.9

[a] Compound **5** was also isolated in 13% yield



Scheme 2 *Reagents and conditions*: i, LiOH, THF–H_2O, room temp.; ii, 2 M HCl

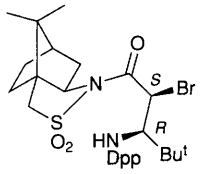


Table 2 Yields and optical rotations for compounds **5a,b,d–f,i**

Compound	R	Isolated yield (%)	$[\alpha]_D$/deg cm^2 g^{-1}
5a	Ph	64	−6.0
5b	4-BrC$_6$H$_4$	61	−6.6
5d	2-O$_2$NC$_6$H$_4$	67	+2.3
5e	4-O$_2$NC$_6$H$_4$	60	−4.4
5f	2-naphthyl	67	−10.0
5i	Bu^t	47	+3.7

Footnotes

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‡ All previously unreported compounds gave satisfactory spectroscopic and microanalytical data.

§ *X-Ray crystallographic data* for **3a**: $C_{31}H_{33}N_2O_4PS$, M = 560.62, orthorhombic, space group $P2_12_12_1$, a = 9.114(2), b = 10.517(2), c = 29.654(8) Å, V = 2842.2 Å^3, Z = 4, D_c = 1.310 g cm^{-3}, $F(000)$ = 1184. Data were collected on a Siemens SMART CCD area-detector 3-circle diffractometer (138 K, Mo-Kα radiation, graphite monochromator, λ = 0.71073 Å). For three settings of ϕ, narrow data 'frames' were collected for 0.3° increments in ω. The data frames were integrated using SAINT.[10] Of the 13605 data collected ($2\theta \leq 50.0°$), 5012 unique data were used for structure solution and refinement. The structure was solved by conventional direct methods procedures and was refined by full-matrix least-squares on all F^2 using Siemens SHELXTL 5.03 program.[10] All non-hydrogen atoms were refined with anisotropic thermal parameters. All other hydrogen atoms were included in calculated positions with isotropic thermal parameters 1.2 × (aromatic or CH_2) or 1.5 × (Me) the equivalent isotropic thermal parameters of their parent carbon atoms. Final full-matrix least-squares refinement led to wR_2 = 0.0872 (based on all F_o^2 data).

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/282.

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