Asymmetric Synthesis of Arylalanines via Asymmetric aza-Darzens (ADZ) Reaction

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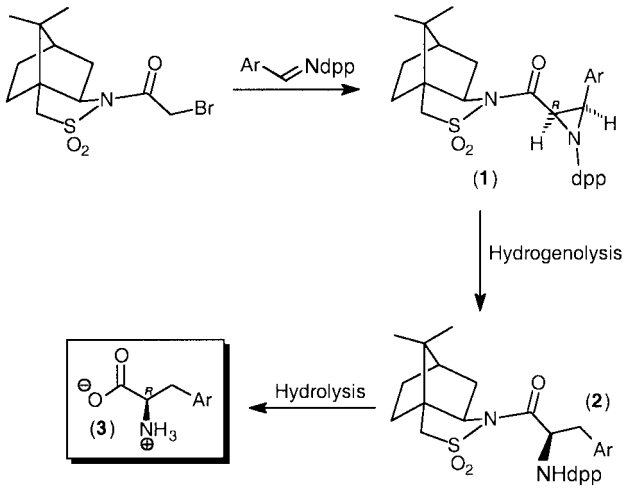
Received 30 June 2003

Abstract: (*R*)-3-Arylalanines may be prepared in high enantiomeric purity from *N*-dpp imines by a four-step reaction sequence involving asymmetric aza-Darzens reaction, dephosphinylation, hydrogenolysis and hydrolysis. The amino acids thus obtained were of >95% enantiomeric purity.

Key words: aziridine, dpp, hydrogenolysis, (*R*)-amino acid

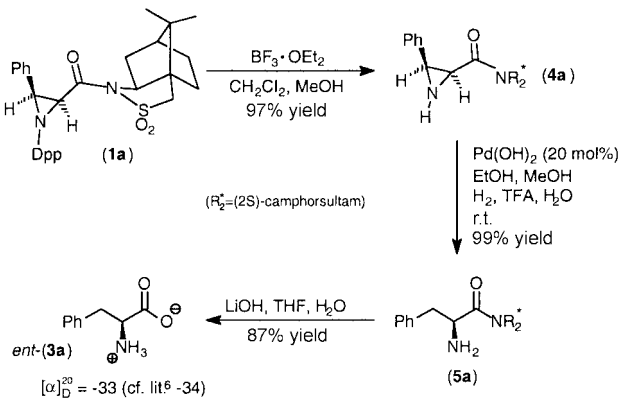
Although the focus of intense activity and experimentation,[1] there is still no single, generally-applicable synthetic method to allow the preparation of a wide range of 2-amino acids (and their derivatives) of high enantiomeric purity from simple precursors. As part of a synthetic programme directed towards the preparation of (2*R*)-configured heterocyclic analogues of phenylalanines (such as azatyrosines), we have recently investigated the hydrogenolysis of *N*-diphenylphosphinyl ('*N*-dpp') aziridines to prepare these compounds and we here report that this methodology does allow efficient entry to a range of non-proteinogenic phenylalanine analogues in good yield and with high levels of enantiomeric purity.



Scheme 1 Proposed arylalanine synthesis via aza-Darzens/hydrogenolysis

The general proposal is shown in Scheme 1: thus, we anticipated that asymmetric aza-Darzens reaction (ADZ) of bromoacyl sultam with a range of *N*-dpp benzaldimines[2] would furnish aziridines **1** which would undergo reductive cleavage in the presence of transition metal catalysts and hydrogen to give the corresponding arylalanine derivatives **2**, which could be hydrolyzed to give the free amino acids **3**. In particular, although it is well known that *N*-tosyl aziridines may be hydrogenolyzed in exactly this manner,[3] prior to our studies, there were no reports that similar dpp-aziridines would undergo an analogous reaction.

We first sought to prepare a proteinogenic amino acid, to establish the levels of stereocontrol in the proposed reaction sequence. Thus, using our previously-reported asymmetric aza-Darzens methodology, we prepared *cis*-(2′*S*,3′*S*)-phenyl *N*-dpp-aziridine (**1a**)[2] and exposed this compound to a range of hydrogenolytic procedures: none were successful, with the starting material being recovered in >90% yield under a range of conditions. Given the known utility of phosphinamides as ligands for asymmetric catalysis,[4] we concluded that catalyst poisoning must be involved and we were encouraged to witness that the hydrogenolysis of dephosphinylated aziridine **4a** proceeded in virtually quantitative yield in the presence of Pearlman's catalyst, to give sultam **5a** as a single diastereoisomer. Hydrolytic removal of the auxiliary[5] gave (*S*)-phenylalanine (**3a**) in excellent yield (60% from 2*S*-bromoacylcamphorsultam) and in >95% ee (as judged from specific rotation values, Scheme 2).[6]



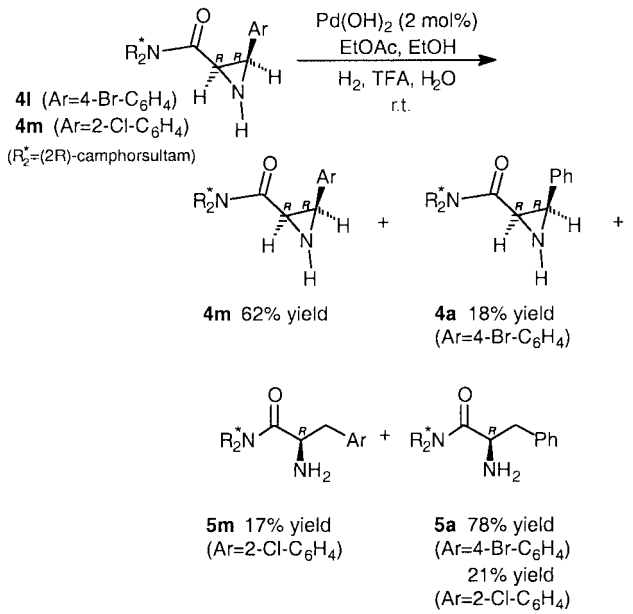
Scheme 2 Phenylalanine via aza-Darzens/hydrogenolysis

Synlett 2003, No. 12, Print: 29 09 2003. Web: 19 09 2003.
Art Id.1437-2096,E;2003,0,12,1898,1900,ftx,en;G15203ST.pdf.
DOI: 10.1055/s-2003-41470

Having demonstrated that the proposed synthetic route was viable, we next examined the scope of the hydrogenolysis reaction in the preparation of the antipodal series of amino acids. Thus, a range of *cis*- and *trans*-aziridinyl (2*R*)-sultams were hydrogenolyzed to give *R*-configured arylalanine derivatives, **5**, in good yield (Table 1). The most general experimental condition involved reaction with H_2 in alcoholic solvent in the presence of 5 mol% $Pd(OH)_2$ at room temperature and atmospheric pressure. Slower reactions (entries 6–9) required the use of elevated hydrogen pressure (5 atm) for best yields.

In most of the reactions examined, the only significant product was that of C-3 ring opening, resulting from cleavage of the benzylic C-N bond. In the case of aziridines bearing an *ortho*-substituted aryl group, the product was contaminated with significant amounts of deaminated products **6**. We presume that these compounds arise via C-2 ring-opening, followed by cleavage of the benzylic C-N bond; in the case of the *ortho*-fluorophenyl substrate (entries 3 and 4), the regioselectivity was improved by utilizing an EtOH–MeOH solvent system for the reaction though this adaptation did not improve the regiocontrol of other reactions.

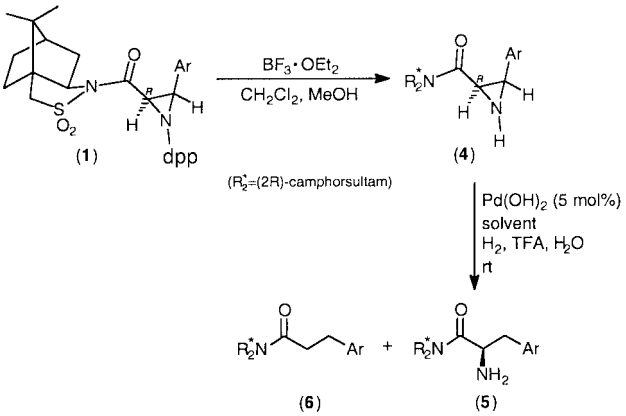
Hydrogenolyses of bromo- and chlorophenyl aziridines **4l** and **4m** gave mixtures of products arising from ring opening and/or dehalogenation (Scheme 3). To ascertain the likely course of the reactions in these cases, each reaction was stopped after 6 hours and the products were isolated and analyzed by ^{1}H NMR. In the case of the chlorophenyl aziridine, the major product was unreacted aziridine with chlorophenylalanine derivative **5m** and the corresponding dehalogenated compound **5a** present in smaller, roughly equal amounts. The bromophenyl aziridine **4l** proved more reactive: the main product in this case was **5a**, i.e., both ring opening and dehalogenation had occurred.



Scheme 3 Hydrogenolyses of haloaryl aziridines

Finally, we have examined the hydrolytic removal of the chiral auxiliary in a representative cross-section of these amino acid derivatives. Thus, reaction of *N*-(2′-amino)acylsultams with lithium hydroxide in THF–water proceeded smoothly to give (after lyophilisation and ion-exchange chromatography) arylalanines **3a**, **3c, 3f**, **3k**, in excellent yield and with high levels of enantiomeric purity (>95% ee, Table 2).

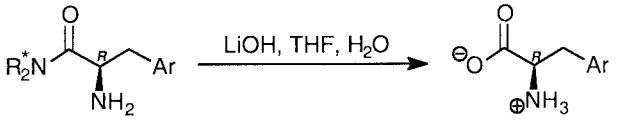
Table 1 Preparation of Arylalanines from Aziridinyl Sultams[7]



Entry[a]	Aryl aziridine (**4**)	Yield **4** /%	Hydrogenolysis yield/%	Ratio **5**:**6**
1	*cis*-Ph (**4b**)	99	99	>99:<1
2[b]	*cis*-Ph (**4b**)	99	99	>99:<1
3	*cis*-2-F-C_6H_4 (**4c**)	82	51	83:17
4[b]	*cis*-2-F-C_6H_4 (**4c**)	82	78	97:3
5[c]	*trans*-2-F-C_6H_4 (**4d**)	96	92	85:15
6[b,c]	*cis*-4-F-C_6H_4 (**4e**)	96	46	>99:<1
7[c]	*cis*-4-F-C_6H_4 (**4e**)	96	67	>99:<1
8[b,c]	*trans*-2-F_3C-C_6H_4 (**4f**)	92	94	71:29
9[c]	*trans*-2-F_3C-C_6H_4 (**4f**)	92	92	76:24
10[b]	*cis*-4-Et-C_6H_4 (**4g**)	90	42	>99:<1
11	*cis*-4-Et-C_6H_4 (**4g**)	90	60	>99:<1
12	*cis*-2-Et-C_6H_4 (**4h**)	87	60	>99:<1
13	*trans*-2-Et-C_6H_4 (**4i**)	88	56	>99:<1
14[d]	*cis*-3-pyridyl (**4j**)	80	45	>99:<1
15[d]	*cis*-3-(2′-MeO) pyridyl **4k**)	79	65	>99:<1

[a] General procedure: aziridines were mixed with Pearlman's catalyst (5 mol%), TFA (1 drop) and H_2O (1 drop) in EtOH and hydrogenated at atmospheric pressure for 14 h.
[b] EtOAc/MeOH (1/1, v/v) used as solvent.
[c] Reaction carried out under 5 atm H_2 for 72 h.
[d] MeOH used as solvent.

Table 2 Hydrolytic Cleavage of Camphorsultam Auxiliary



(**5**) (**3**)

Entry[a]	Ar	Yield (%)	$[\alpha]_D^{20}$	Ee (%)
1	Ph (*ent*-**3a**)	87 (60)[b]	–33.4[c]	98[d]
2	Ph (**3a**)	87 (59)	+33.2[6]	98
3	4-F-C_6H_4 (**3c**)	92 (50)	+24.9[8]	99
4	2-F_3C-C_6H_4 (**3f**)	94 (45)	+ 9.1	>95
5	3-(2′-MeO)C_5H_4N (**3k**)	76 (20)	+53.2	>95

[a] General procedure: sultams were dissolved in a THF/H_2O solution (1:1, v/v, 5 mL), LiOH monohydrate (2 equiv) added and the solution stirred at r.t. overnight.
[b] Overall yield from imine.
[c] 2′*S*-phenylalanine utilized, giving 2*S*-phenylalanine.
[d] Assessed from specific rotation values and chiral HPLC.

Thus, we have demonstrated that an aza-Darzens–hydrogenolysis–hydrolysis procedure can provide a useful entry into a range of phenylalanine analogues, with high levels of enantiocontrol. We are currently engaged in determining the scope of this process and extrapolating our preliminary data to allow the preparation of a range of biologically significant amino acids.

Acknowledgment

We thank the University of Reading and EPSRC for financial support, the helpful comments of Drs. H. M. I. Osborn and A. T. Russell and we acknowledge the guidance and advice of Mr. G. Buchman and Mr. E. Blair.

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(7) **Representative Experimental Procedure:** To *cis*-2*S*,2′*S*,3′*S*-*N*-[(3-(phenyl)-2-aziridinyl)carbonyl]bornane-10,2-sultam (**4a**) in a EtOAc:MeOH (1:1) mixture (5 mL) was added a substoichiometric amount of H_2O, TFA and $Pd(OH)_2$ (42 mg, 0.06 mmol). The flask was then pump filled with hydrogen and stirred at atmospheric pressure and r.t. overnight. After this time the solution was filtered through a pad of Celite®, the pad washed with further MeOH. The solvent was removed in vacuo to afford *S*-(**5a**) as a colourless solid (110 mg, 0.3 mmol, 99%); R_f = 0.46 (EtOAc); $[\alpha]_D^{20}$ +66.7 (*c* 1, $CHCl_3$). IR (CCl_4): ν_{max} = 3019, 2951 (CH), 1672 (C=O), 1334, 1170 (SO_2), 756, 721, 702 (Ar) cm^{-1}. ^1H NMR (250 MHz, CD_3OD): δ = 1.05 and 1.20 (6 H, 2 × s), 1.28–1.50 and 1.88–2.15 (7 H, m), 2.89 (1 H, dd, *J* = 10.6 Hz, 14.5 Hz), 3.65 (1 H, dd, *J* = 2.8 Hz, 14.5 Hz), 3.76 and 3.87 (2 H, 2 × d, *J* = 14.2 Hz), 4.05 (1 H, dd, *J* = 5.0 Hz, 7.9 Hz), 4.61 (1 H, dd, *J* = 2.8 Hz, 10.6 Hz), 7.32–7.47 (5 H, m). ^{13}C NMR (60 MHz, CD_3OD): δ = 20.53, 21.60, 27.59, 33.95, 39.43, 37.90, 46.50, 49.70, 51.08, 53.72, 56.10, 67.26, 129.49, 130.70, 130.92, 135.92, 168.55. MS (CI): *m/z* (%) = 363 (33) $[MH]^+$, 271 (22), 120 (100), 91 (13), 58 (4). Found: $[MH]^+$, 363.1732, $C_{19}H_{27}N_2O_3S$ requires $[MH]^+$, 363.1743.

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