Synthesis of 7-, 8- and 9-Membered Rings *via endo* Heck Cyclisations of Amino Acid Derived Substrates

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Aryl iodides tethered to dehydroalanine units by two to four methylene groups undergo intramolecular Heck reactions under anhydrous Jeffery conditions to give 7-, 8- and 9-membered rings by the *endo*-mode of cyclisation; under harsher conditions, a palladium intermediate formed by the *exo*-mode of cyclisation is expressed as reduced products.

The palladium-catalysed coupling of haloarenes and haloalkenes with alkenes, the Heck reaction,[1] is now well-established as an important synthetic reaction.[2] Over the last decade the intramolecular version of this reaction has attracted a considerable amount of attention and there are now many elegant and impressive examples of its use in organic synthesis.[3] Examination of the intramolecular Heck literature reveals that i) in the overwhelming majority of cases, products resulting from an *exo*-cyclisation pathway are isolated in preference to products that would result from an *endo*-cyclisation pathway,† and ii) attention to date has focussed almost completely on the formation of five- and six-membered rings. We thus wish to report herein the synthesis of cyclic amino acid derivatives *via* 7-, 8- and 9-*endo* Heck reactions. These reactions provide a rare example of a 7-*endo* Heck cyclisation,‡ a very rare example of an 8-*endo* Heck cyclisation,§ and, to the best of our knowledge, the first example of a 9-*endo* Heck cyclisation.¶

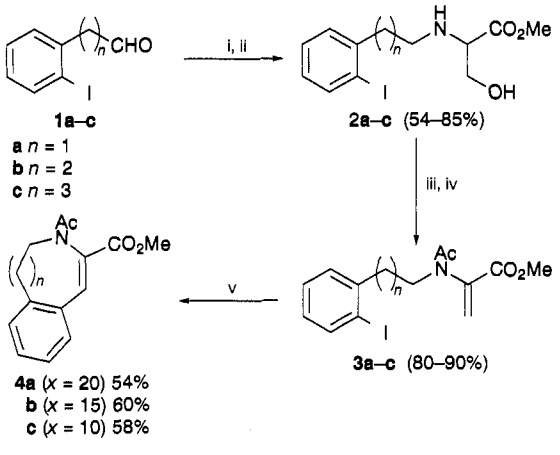
The intermolecular Heck coupling of aryl halides and dehydroalanine derivatives, in which carbon–carbon bond formation occurs at the β-carbon of the dehydroalanine derivative to give (*Z*)-dehydrophenylalanine derivatives, is well established.[12] When combined with rhodium-catalysed asymmetric hydrogenation, this reaction provides efficient access to both the D- and L-forms of natural and unnatural amino acids. For example, an intermolecular Heck reaction between *N*-acetyl dehydroalanine methyl ester and 3,5-dimethyl-4-iodophenyl acetate followed by asymmetric hydrogenation and hydrolysis gave kilogram quantities of the unnatural amino acid 2,6-dimethyl-L-tyrosine.[13] Thus we postulated that if Heck reactions of dehydroalanines tethered to aryl halides would proceed intramolecularly to give medium-sized rings rather than intermolecularly to give dimers and polymers and that if the cyclisation occurred *via* an *endo* rather than an *exo* pathway, then this coupling could ultimately form the key step in a route to both the D- and L- forms of conformationally restricted phenylalanine derivatives, a type of compound which is currently of considerable interest to medicinal chemists.[14]

The cyclisation candidates **3a–c**, in which the dehydroalanine and iodobenzene partners are tethered to each other by two to four methylene groups, were constructed from the iodoaldehydes **1a–c**‖ *via* the serine derived intermediates **2a–c**. In a typical example, formation of the key carbon-nitrogen bond was achieved by reacting 2-(2-iodophenyl)ethanal **1a** with serine methyl ester and sodium cyanoborohydride to give **2a** in 85% yield. Acetylation of the alcohol and amine of **2a** followed by DBU elimination of acetic acid gave **3a** in 90% yield from **2a** and 76% overall yield from the aldehyde **1a**.

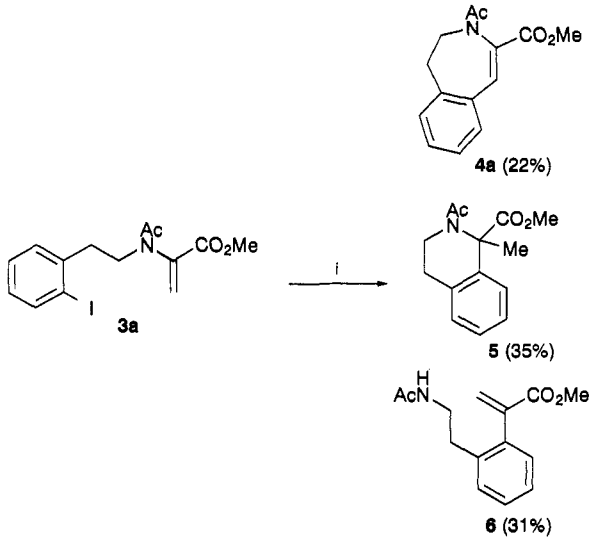
The cyclisation candidates were then reacted with catalytic quantities of $Pd(OAc)_2$, in the presence of $NaHCO_3$ (2.5 equiv.), Bu_4NCl (1.0 equiv.) and 3 Å molecular sieves (anhydrous Jeffery conditions[15]). The reactions were performed in acetonitrile (0.16–0.18 mol dm^{-3}) at 95 °C for 16.5 h under an atmosphere of nitrogen and we were delighted to find that, under these conditions, **3a**, **b** and **c** reacted with 20, 15 and 10 mol% $Pd(OAc)_2$ respectively to give product mixtures from which it was possible to isolate 54, 60 and 58% of **4a**, **b** and **c**** resulting from 7-, 8- and 9-*endo*-cyclisations respectively.

Although only products derived from *endo*-carbopalladation of **3a–c** were observed and isolated in the reactions described above, *exo*-carbopalladation cannot be discounted as a significant competing mode of cyclisation. Of note in this context is the reaction of **3a** (0.16 mol dm^{-3}) with catalytic quantities of $Pd(OAc)_2$ in the presence of Et_3N in acetonitrile at 110 °C for 120 h. These harsher reaction conditions produced not only the 7-*endo* cyclisation product **4a** (22%) but also the reduced products **5** (35%) and **6** (31%) which are derived from the palladium intermediate generated by a 6-*exo*-cyclisation.

To explain the results presented here, we postulate that the ratio of the rate of the *endo*-mode of cyclisation to the rate of the *exo*-mode of cyclisation increases as the length of the tether increases (presumably the rate of *endo*-cyclisation is retarded by



Scheme 1 *Reagents and conditions* i, serine methyl ester; ii, $NaBH_3CN$; iii, Ac_2O, py; iv, DBU; v, *x* mol% $Pd(OAc)_2$, $NaHCO_3$ (2.5 equiv.), Bu_4NCl (1.0 equiv.), 3 Å molecular sieves, MeCN, 95 °C, 16.5 h, N_2



Scheme 2 *Reagents and conditions*: i, $Pd(OAc)_2$ (12 mol%), Et_3N (3.0 equiv.), MeCN, 110 °C, 120 h, N_2

stereoelectronic constraints when the tether is shorter).†† We also postulate that under the relatively mild Jeffery conditions, the palladium intermediate generated by *exo*-cyclisation does not react further; it thus uses up an equivalent of palladium and gradually removes the palladium from the catalytic cycle generating the *endo*-product. Therefore, as the length of the tether increases and the rate of *exo*-cyclisation relative to the rate of *endo*-cyclisation decreases, the rate at which the palladium is 'locked up' also decreases. This explains the experimental observation that the length of the tether bears an inverse relationship to the amount of catalyst required to generate essentially the same yield of *endo*-cyclised product.

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Footnotes

† The authors of a recent report of a noteworthy 6-*endo* Heck reaction have also come to this conclusion.[4]

‡ An intramolecular Heck reaction of 1-(2′-bromobenzenesulfonyl)-1,2,5,6-tetrahydropyridine which gives a 1 : 1 mixture of 6-*exo* and 7-*endo* derived products,[5] and a 5-*exo*, 7-*endo* cascade onto a heterocycle[6] provide earlier examples of 7-*endo* Heck cyclisations. It is also of note, in this context, that an apparent 7-*endo* cyclisation of a 2-iodo-1,7-diene is thought to proceed *via* a 6-*exo* cyclisation followed by a cyclopropylcarbinyl-to-homoallyl rearrangement.[7]

§ A Heck cyclisation of a substituted tryptophan leading to 7-*exo* and 8-*endo* products has been reported.[8]

¶ 7-*Exo* Heck cyclisations are uncommon but known,[5,8–11] 8-*exo* cyclisations are to date very rare,[11] and to the best of our knowledge, a 9-*exo* cyclisation has yet to be reported.

‖ Iodoaldehydes **1a–c** were prepared from 2-iodobenzaldehyde by standard organic procedures. Details of these reactions will be given in the full account of this study.

** The novel compounds **4a–c**, **5** and **6** all gave satisfactory microanalytical and spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, *m/z*) data. In addition, X-ray crystallographic analyses of compounds **4a** and **4b** have been performed (the details of these analyses will be published in the full account of this study).

†† The explanation presented here assumes that carbopalladation is irreversible.

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