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The Synthesis of Novel Amino Acids *via* Hydroboration-Suzuki Cross Coupling

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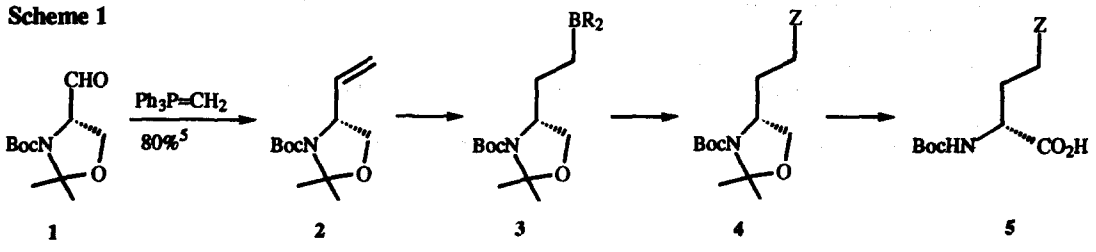
Abstract: *The Garner aldehyde-derived methylene alkene has been hydroborated using 9-BBN and the resulting organoborane employed in palladium-catalysed Suzuki coupling reactions to produce, after hydrolysis-oxidation, a range of novel amino acids as their N-BOC protected derivatives.*

There has been considerable recent interest in the development of synthetic routes to non-proteinogenic amino acids.[1-3] Many of these methods have employed the Garner aldehyde **1** as their cornerstone.[3] During our recent total synthesis of (-)-α-kainic acid,[4] we developed a high yielding and practically facile procedure for the preparation of the Garner aldehyde **1** and the derived alkene **2** (available in 88% and 70% yield, respectively, from L or D-serine).[5] We envisioned a new approach to novel amino acids (Scheme 1) which involved hydroboration of **2** to give an intermediate organoborane **3** which could be further elaborated under mild conditions using palladium catalysed coupling procedures.[6] The resultant products **4** could then be converted into *N*-Boc amino acids **5** in a one pot cleavage-oxidation procedure using Jones' reagent.[7]

Scheme 1



1 **2** **3** **4** **5**

We first sought to establish that alkene **2** did undergo efficient hydroboration in a regioselective manner.[8] Thus (Scheme 2),[9] hydroboration using BH_3.THF followed by oxidative work-up gave a 1.3:1 mixture of the required primary alcohol **6** together with secondary alcohol **7**, obtained as a 6:1 mixture of diastereomers. However, the use of 9-BBN followed by oxidation gave alcohol **6** as a single regioisomer in almost quantitative yield. Alternatively, the 9-BBN-derived organoborane **3** could be iodinated to produce iodide **8**, a potentially useful asymmetric building block {$[\alpha]_D$ -16.2 (c 2.6, $CHCl_3$)}.

We next investigated the palladium catalysed Suzuki coupling reactions of organoborane **3** with vinyl and aryl halides (Table 1).[6] Preliminary studies indicated that the optimum catalyst for these couplings is [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) [$PdCl_2$(dppf)].[6b] We first demonstrated that the

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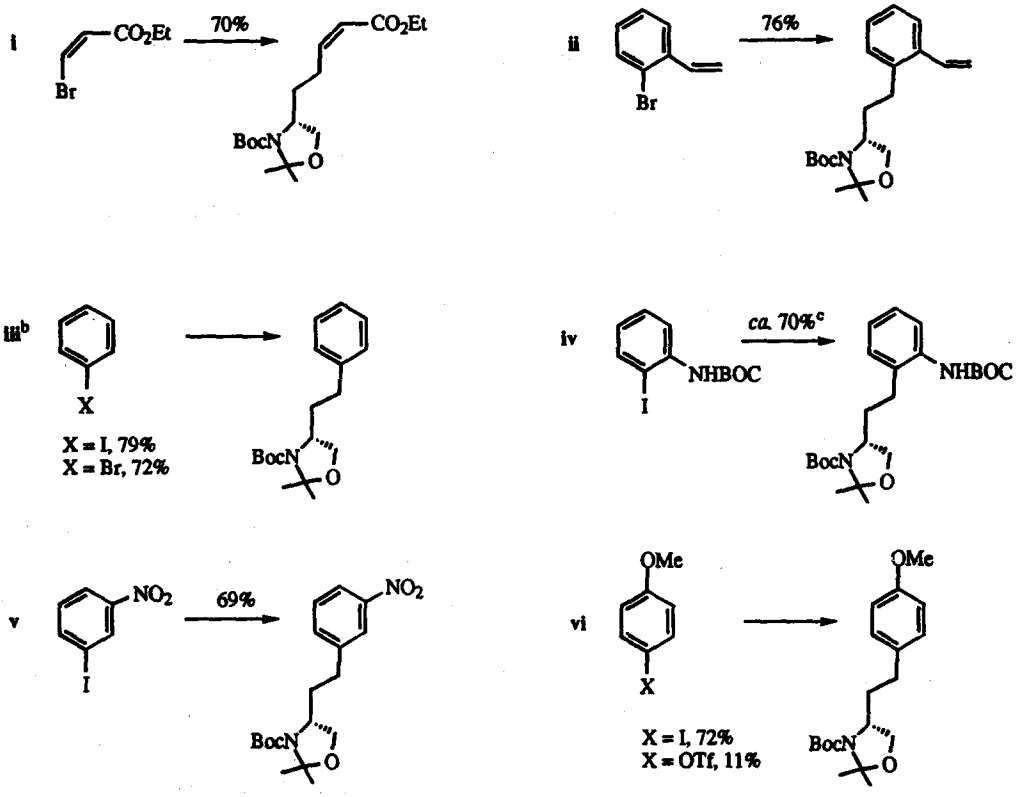
Table 1 Hydroboration-Suzuki cross-coupling with vinyl and aryl halides[a,b]

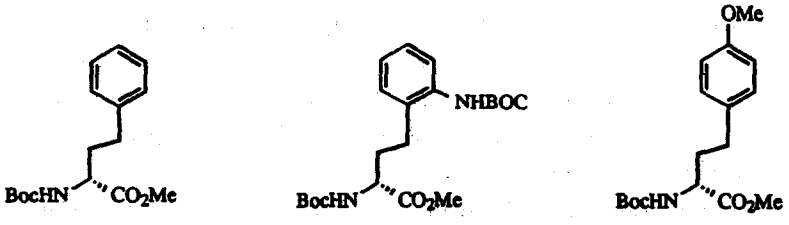


[a]Yields based on alkene 2

[b]Experimental details are given in the references and notes section.[10]

[c]A quantitative yield was obtained but the expected product was accompanied by ca. 30% of an unidentified, inseparable impurity

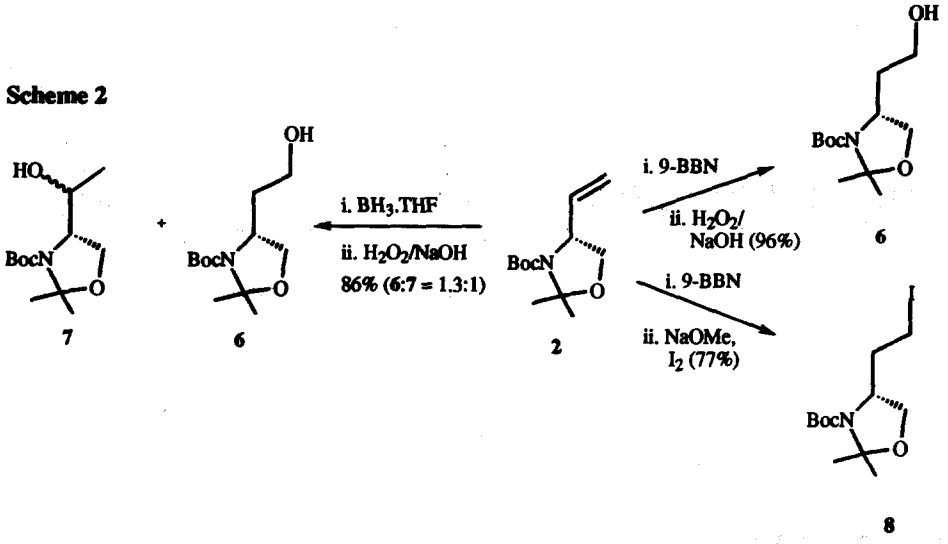
Table 2 Oxazolidine cleavage and oxidation to *N*-BOC amino acids[a]



9, 59% **10**, 30% from alkene 2 **11**, 54%

[a]All compounds were esterified using ethereal diazomethane for the purposes of characterisation

Scheme 2



reaction proceeds in a good yield with a vinyl bromide (entry i), and that the *Z*-stereochemistry was retained throughout the reaction (*J* 11.4 Hz).

Aryl bromides were also found to undergo efficient coupling (entries ii and iii) but aryl triflates were not viable coupling partners (entry vi). The remainder of the studies were carried out on aryl iodides and it was established that the reaction proceeds efficiently on unsubstituted as well as on *ortho-*, *meta-* and *para-*disubstituted systems (entries iii-vi, respectively). In addition, we established that the coupling reaction is compatible with electron donating (entries iv and vi) and electron withdrawing (entry v) groups.[10]

Having confirmed that alkene **2** is an excellent precursor for a range of hydroboration-coupling reactions, we next investigated the conversion of these coupled products into *N*-BOC α-amino acids *via* a one pot cleavage-oxidation procedure using the Jones' oxidant.[7] Three of the above examples were studied and the results are summarised in Table 2. All oxazolidines were cleanly hydrolysed-oxidised under unoptimised conditions and the resulting acids were esterified to aid characterisation. Homophenyl alanine derivative **9** displayed spectroscopic data consistent with those published[11] and corresponded well in terms of polarimetry {$[\alpha]_D$ +14.5 (c 0.8, MeOH); lit.[11] (enantiomer), -14.7 (c 1.2, MeOH)} thus demonstrating the conservation of stereochemical integrity. Hydrolysis of *N*-BOC amino ester **11** with 6 M HCl at 80°C gave the hydrochloride salt of the amino acid in > 90% yield. The optical rotation of homoanisyl alanine was in good agreement with the published[12] value {$[\alpha]_D$ -33.4 (c 0.7, 1 *M* HCl); lit.[12] (enantiomer), +34.6 (c 0.5, 1 *M* HCl)}.

This methodology can be employed to generate a range of novel amino acids and related compounds. For example (Scheme 3), the aryl-scaffolded "dimeric" amino acid derivative **12** has been prepared by employing sub-stoichiometric amounts of 1,4-di-iodobenzene.

In summary, we have established that readily available organoborane **3** is an excellent homoalanine anion equivalent[11] which can simply be transformed into a range of known and novel non-proteinogenic amino acids under very mild conditions in two straightforward steps.

Acknowledgement

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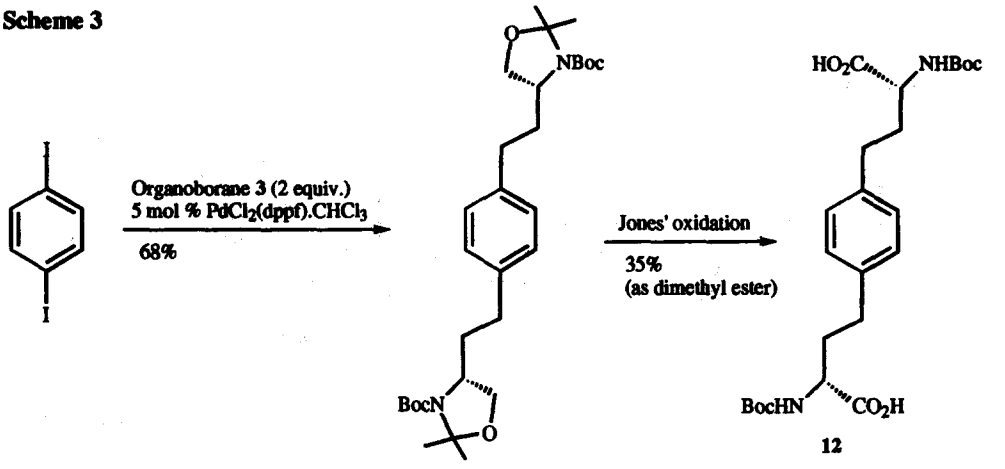
Scheme 3



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9. All new compounds were fully characterised by high field NMR spectroscopy and by HRMS.
10. Representative procedure (Table 1, entry iii): To alkene **2** (50 mg, 0.22 mmol) in dry THF (1 mL) was added 9-BBN-H (0.5 *M* in THF, 0.88 mL, 0.44 mmol) at 0°C with stirring under nitrogen. The mixture was allowed to warm to rt and was stirred for a further 2 h. The flask was covered with silver foil and aq. K_3PO_4 (3 *M*, 0.15 mL, 0.45 mmol) was added, followed immediately by iodobenzene (50 mg, 0.24 mmol) in DMF (2 mL) and $PdCl_2(dppf).CHCl_3$ (9.4 mg, 5 mol %). The reaction was stirred for 16 h and monitored by tlc. The solvent was removed *in vacuo* and Et_2O (20 mL) and sat. sodium bicarbonate (5 mL) added. The organic layer was separated, dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography on silica gel (light petroleum-ethyl acetate) gave the product (53mg, 79%) as a white solid, mp 51-52.5°C, R_f 0.45 (9:1 light petroleum-ethyl acetate); {$[\alpha]_D$ -40.1 (c 2.5)}; υ_{max} (cm^{-1}) 2977, 1695, 1389; δ_H ($C_6D_5CD_3$, 270 MHz, 80°C) 1.59 (9 H, s, ^tBu), 1.68 (3 H, s, CH_3), 1.83 (3H, s, CH_3), 1.95-2.06 (1 H, m, $CHCH_2$), 2.20-2.35 (1 H, m, $CHCH_2$), 2.63-2.71 (2 H, m, CH_2Ph), 3.71 (1 H, dd, *J* 8.8, 1.7 Hz, OCH_2), 3.85 (1 H, dd, *J* 8.8, 5.8 Hz, OCH_2), 3.90-4.00 (1 H, m, NCH), 7.17-7.34 (5 H, m, ArH); δ_C ($C_6D_5CD_3$, 67.9 MHz, 80°C) 25.3, (CH_3) 28.4 (CH_3), 29.6 ($(CH_3)_3C$), 34.0 ($CHCH_2$), 36.5 (CH_2Ph), 58.7 (NCH), 68.2 (OCH_2), 80.2 [$(CH_3)_3C$], 94.9 [$NC(CH_3)_2O$], 127.1, 129.6, 143.0 (Ar), 153.0 (C=O); *m/z* (CI) 306 (MH^+, 15%); HRMS (CI): Found 306.2071, MH^+. $C_{18}H_{28}NO_3$ requires 306.2069 (0.4 ppm error).
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