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Heck reactions of amino acid building blocks: application to the synthesis of pyrrololine analogues

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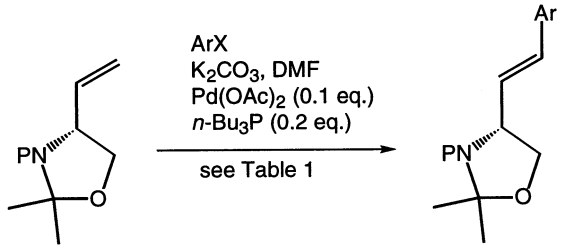
Abstract—Heck reactions of unsaturated amino acid building blocks are described which allow access to homo- and bis-homophenylalanine derivatives and to γ,δ-unsaturated amino acids. Preliminary synthetic studies utilising this chemistry for the preparation of pyrrololine and deoxypyrrololine analogues are also reported.

There has been considerable recent interest in the design of new synthetic routes for the preparation of non-proteinogenic α-amino acids and their derivatives for use in biological studies or as chemical building blocks.[1–4] We have recently described the hydroboration of the amino acid-derived alkenes **1**, **2** and **3** with 9-BBN, and the subsequent Suzuki coupling of the derived triorganoboranes; this chemistry has been used to prepare novel homophenylalanines, bis-homophenylalanines, and related derivatives.[2,3] Herein, we report the utilisation of alkenes **1**, **2** and **3** in Heck coupling reactions. Crisp et al. have also reported Heck coupling reactions of unsaturated amino acids and their derivatives.[4] For example, L-vinylglycine-derivatives **4** and **5** underwent efficient Heck coupling reactions with a number of vinyl triflates, although aromatic halides and triflates gave less predictable results, especially in systems containing additional electron-withdrawing substituents.

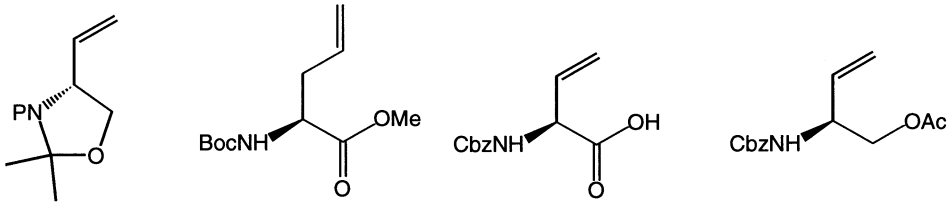
Initial studies were carried out on the Heck coupling reactions of alkenes **1** and **2** with a range of aryl halides, as shown in Scheme 1 and Table 1.[5,6] We discovered that by employing catalytic palladium(II) acetate and tri-*n*-butylphosphine with a slight excess of iodobenzene and potassium carbonate in DMF, the desired Heck coupling product **6** could be obtained from *N*-Boc alkene **1** after 1 h at 100°C in 72% yield {Table 1, entry i: $[\alpha]_D$ −71.5 (*c* 1.9, $CHCl_3$); lit.[7] $[\alpha]_D$ −71.3 (*c* 1.1, $CHCl_3$)}. The regiochemical and stereochemical outcome of the reaction was as expected, giving the terminally-substituted, *E*-alkene **6** (*J* 16.0 Hz). The corresponding *N*-Cbz protected alkene **2**



1, P = Boc
2, P = Cbz

6-10

Scheme 1.



1, P = Boc
2, P = Cbz

3 **4** **5**

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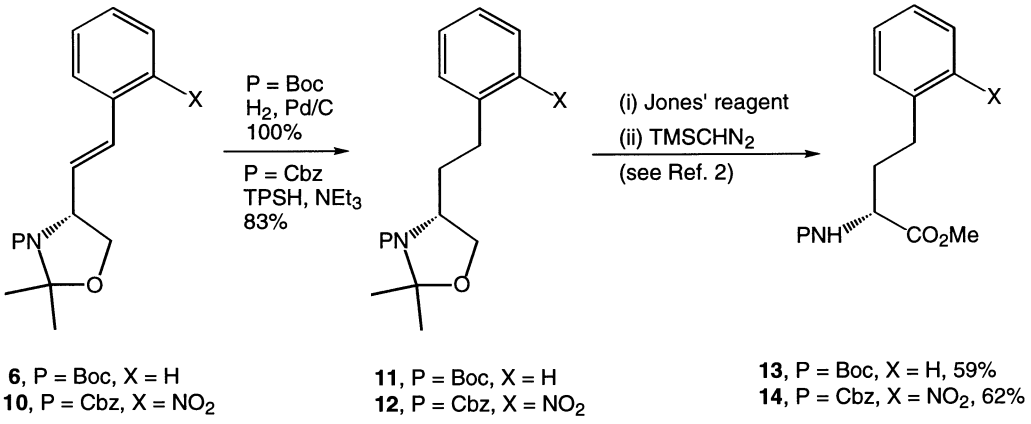
Table 1. Heck coupling reactions of alkenes **1** and **2**

Entry	P	ArX	Product	$[\alpha]_D$ (in $CHCl_3$)	Yield (%)
i	Boc (**1**)	PhI	**6**	−71.5 (*c* 1.9)	72
ii	Cbz (**2**)	PhI	**7**	−94.7 (*c* 2.2)	80
iii	Cbz (**2**)	PhBr	**7**	−94.7 (*c* 2.2)	77
iv	Cbz (**2**)	4-MeO-C_6H_4I	**8**	−95.9 (*c* 0.6)	78
v	Cbz (**2**)	4-MeO_2C-C_6H_4Br	**9**	−123.8 (*c* 1.0)	85
vi	Cbz (**2**)	2-O_2N-C_6H_4I (2 equiv.)	**10**	−109.6 (*c* 2.3)	82

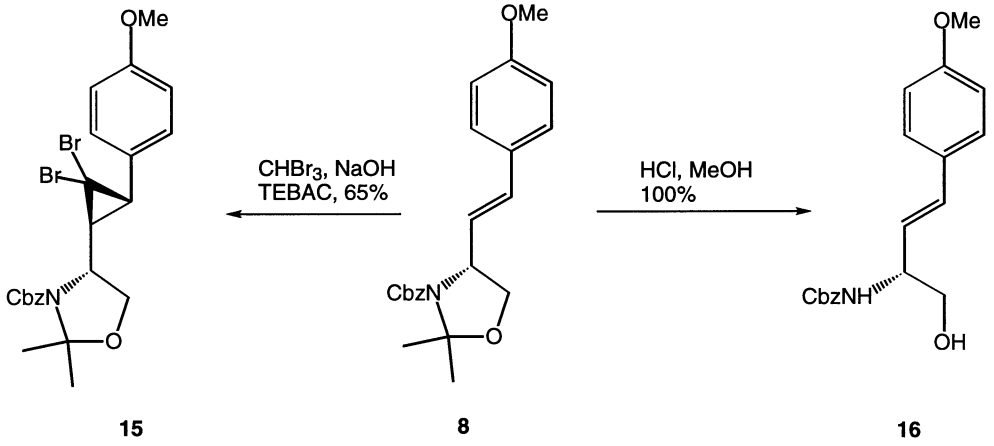
underwent coupling with iodobenzene and bromobenzene giving adduct **7** in even higher yields (Table 1, entries ii and iii, 80 and 77%, respectively), and the remaining reactions were therefore carried out using compound **2**. Heck coupling on this system was shown to be compatible with electron-donating and electron-withdrawing substituents (Table 1, entries iv–vi). The coupling with 2-nitro-iodobenzene required slightly more forcing conditions (110°C, overnight with 2 equiv. of aryl iodide) for the reaction to proceed to completion, but the desired product **10** was obtained in 82% yield (Table 1, entry vi).

The Heck coupling adducts can be easily transformed into homophenylalanine derivatives. Thus, adducts **6** and **10** can be readily converted into protected amino acids **13** and **14**, respectively, by reduction followed by our published[2] hydrolysis–oxidation–methylation sequence (Scheme 2). Reduction of the *N*-Boc-protected oxazolidine **6** was achieved using standard hydrogen–Pd/C conditions to give **11** quantitatively, while reduction of the *N*-Cbz compound **10** was performed in 83% yield using diimide generated from 2,4,6-tri-*iso*-propylbenzenesulfonyl hydrazide (TPSH) by the action of base.

The unsaturated Heck coupling products could also be transformed into novel amino acid precursors and homochiral synthetic building blocks (Scheme 3). For example, dibromocyclopropanation[8] of alkene **8** gave adduct **15**, while oxazolidine cleavage in **8** under acidic conditions furnished styrenyl amino alcohol **16** {$[\alpha]_D$ −62.5 (*c* 0.2, EtOH)}.



Scheme 2.



Scheme 3.

Next, we investigated the Heck coupling reactions of protected allylglycine **3** with a range of aromatic iodides and bromides (Scheme 4). We were delighted to observe the efficient formation of the corresponding γ,δ-unsaturated amino acid products, in protected form, under the same reaction conditions as before (Table 2). As before, reasonable yields were obtained in coupling with a range of aromatic iodides and bromides, including examples containing electron-donating and electron-withdrawing substituents. Hydrogenation of the alkene double bond in adduct **20** gave the known[3] bis-homophenylalanine derivative **22**, which displayed an optical rotation in good agreement with the reported value {$[\alpha]_D$ +15.7 (*c* 0.7, $CHCl_3$); lit.[3] $[\alpha]_D$ +16.2 (*c* 1.5, $CHCl_3$)}.

We next investigated applications of this Heck methodology. Pyrrololine **23** and deoxypyrrololine **24** are important cross-linking agents in human bone collagen and have become attractive synthetic targets due to their novel structural features and practical applications in the diagnosis of osteoporosis and other bone diseases.[9] We decided to explore the use of our Heck coupling for the introduction of the pyrrole C-3 and C-4 amino acid side chains.

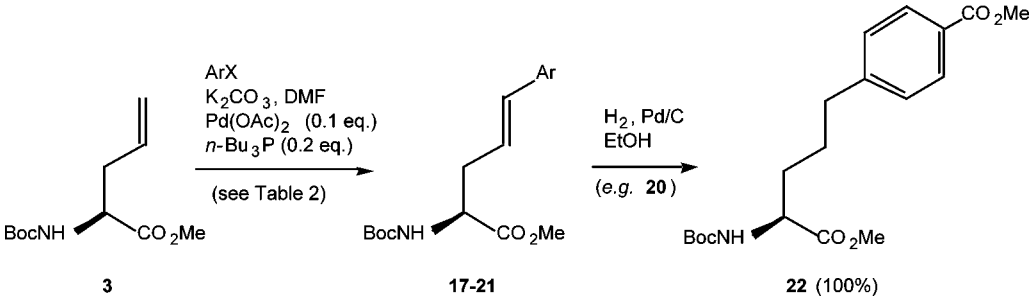
The first approach utilised 3,4-diiodo-*N*-methylpyrrole **26**, readily obtained by iodination of *N*-TIPS pyrrole **25** using the procedure of Muchowski et al.[10] (Scheme 5). The double Heck coupling reaction with alkene **2** proceeded in an unoptimised yield of 20%, giving adduct **27**, an ideal precursor for the preparation of *N*-truncated pyrrololine analogues.

A second double Heck approach was explored which employed the protected vinyl glycinol derivatives **29**[11] and **30** (Scheme 6). Coupling of *N*-SEM diiodopyrrole **32** with vinyl glycinol **29** gave the required double adduct in only 14% yield (22% based on recovered starting material), which underwent diimide reduction to give **33**. With the SEM-protected alkene **30**, the key Heck coupling reaction proceeded in an unoptimised 21% yield (33% based on recovered starting material) giving pyrrole **34** after alkene reduction. Although optimisation is obviously required, compounds **33** and **34** are valuable intermediates for the synthesis of pyrrololine **23** and deoxypyrrololine **24**.

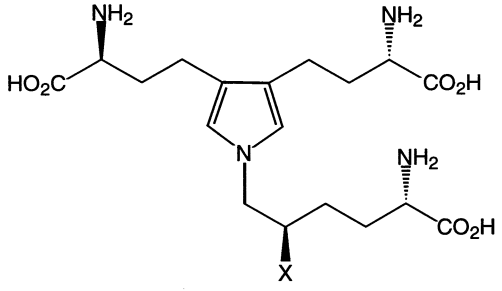
Table 2. Heck coupling reactions of alkene **3**

Entry	ArX	Product	$[\alpha]_D$ (in $CHCl_3$)	Yield (%)
i	PhI	**17**	+32.7 (*c* 2.1)	79
ii	1-Br-Naphthalene	**18**	+28.5 (*c* 0.8)	67
iii	4-MeO-C_6H_4I	**19**	+38.1 (*c* 1.3)	74
iv	4-MeO_2C-C_6H_4Br	**20**	+32.7 (*c* 0.7)	66
v	3-O_2N-C_6H_4I	**21**	+34.4 (*c* 0.9)	70

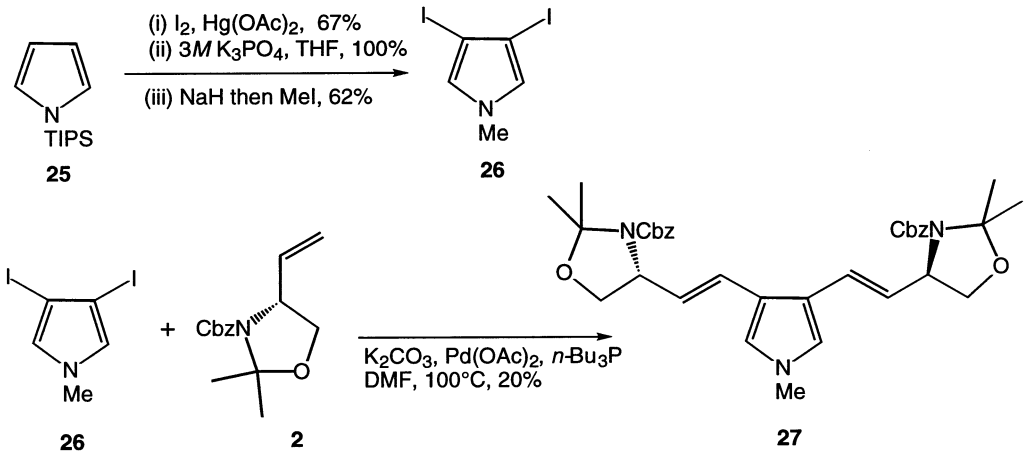
In conclusion, a range of Heck coupling reactions have been successfully accomplished using amino acid-derived alkenes **1**, **2**, **3**, **29** and **30**. The majority of these processes proceed in good yields, even with electron-deficient systems (thereby complementing existing[4] procedures), and provide a route to a range of non-proteinogenic amino acids and related compounds. Work is in progress to optimise the double Heck coupling with diiodopyrroles and to apply it to the total synthesis of pyrrololine **23** and deoxypyrrololine **24**.



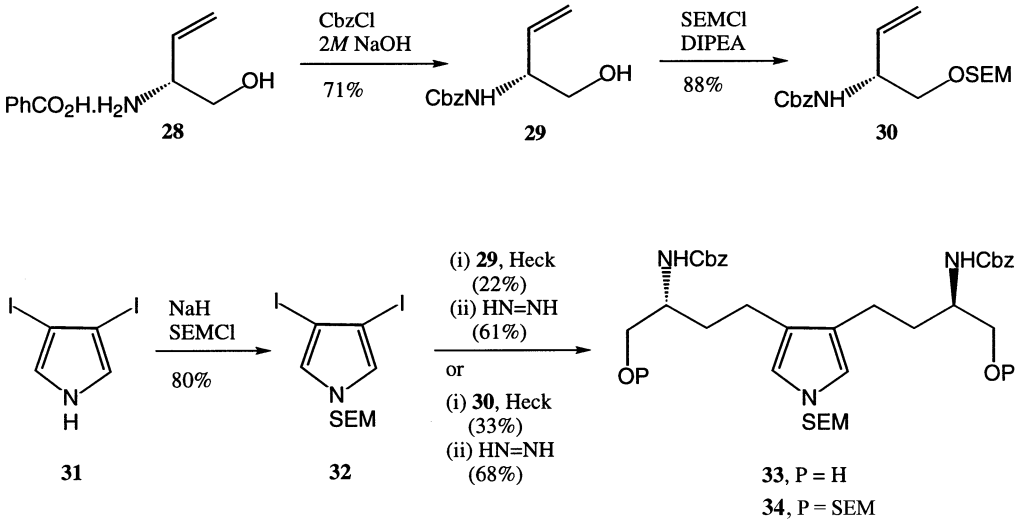
Scheme 4.



X = OH, Pyrrololine **23**
X = H, Deoxypyrrololine **24**



Scheme 5.



Scheme 6.

Acknowledgements

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References

1. (a) Chrystal, E.; Bey, P.; Rando, R. R. *J. Neurochem.* **1979**, *32*, 1501–1507; (b) Walsh, C. *Tetrahedron* **1982**, *38*, 871–909 and references cited therein; (c) Lowe, P. N.; Rowe, A. F. *Comp. Biochem. Physiol., B: Comp. Biochem.* **1987**, *88B*, 223; (d) Angst, C. *Pure Appl. Chem.* **1987**, *59*, 373–380.
2. (a) Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Tetrahedron Lett.* **1999**, *40*, 5263–5266; (b) Collier, P. N.; Patel, I.; Taylor, R. J. K. *Tetrahedron Lett.* **2001**, *42*, 5953–5954; (c) Collier, P. N.; Campbell, A. D.; Patel, I.; Raynham, T. M.; Taylor, R. J. K. *J. Org. Chem.* **2002**, *67*, 1802–1815 and references cited therein.
3. Collier, P. N.; Campbell, A. D.; Patel, I.; Taylor, R. J. K. *Tetrahedron Lett.* **2000**, *41*, 7115–7119.
4. (a) Crisp, G. T.; Glink, P. T. *Tetrahedron* **1992**, *48*, 3541–3556; see also (b) Itaya, T.; Shimomichi, M.; Ozasa, M. *Tetrahedron Lett.* **1988**, *29*, 4129–4132. For related Suzuki approaches see Refs. 2 and 3; for Stille approaches, see: (c) Crisp, G. T.; Glink, P. T. *Tetrahedron* **1994**, *50*, 3213–3234; (d) Kazmaier, U.; Schauß, D.; Raddatz, S.; Pohlman, M. *Chem. Eur. J.* **2001**, *7*, 456–464 and references cited therein. Note added in proof: For Heck reactions of protected allyl glycines, see: Gurjar, M. K.; Talukdar, A. *Synthesis* **2002**, 315–316.
5. All new compounds were fully characterised by NMR spectroscopy and by HRMS etc.
6. Typical procedure: To the alkene (1 equiv., 0.15–0.38 mmol) in anhydrous, degassed DMF (1 mL per 0.1 mmol alkene) was added in rapid succession potassium carbonate (1.1 equiv.), palladium acetate (0.1 equiv.), tri-*n*-butylphosphine (0.2 equiv.) and the aryl halide (1.1 equiv.) at rt under nitrogen. The mixture was covered by aluminium foil, heated (usually to 100°C) and monitored by TLC until complete (usually 1–3 h). The reaction mixture was cooled and saturated aq. NaCl (10 mL per 0.1 mmol alkene) and Et_2O (10 mL per 0.1 mmol alkene) were added. The aqueous layer was re-extracted with

Et_2O (10 mL per 0.1 mmol alkene). The combined organic layers were washed with H_2O (10 mL per 0.1 mmol alkene), dried, filtered and concentrated in vacuo to give the crude product which was purified by flash column chromatography eluting with petroleum ether–EtOAc mixtures to afford the Heck coupling product (yields based on alkenes).

7. Reginato, G.; Mordini, A.; Caracciolo, M. *J. Org. Chem.* **1997**, *62*, 6187–6192.
8. De Frutos, P.; Fernández, D.; Fernández-Alvarez, E.; Bernabé, M. *Tetrahedron* **1992**, *48*, 1123–1130.
9. Adamczyk, M.; Johnson, D. D.; Reddy, R. E. *J. Org. Chem.* **2001**, *66*, 11–19 and references cited therein.
10. Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 6317–6328.
11. Sabat, M.; Johnson, C. R. *Org. Lett.* **2000**, *2*, 1089–1092.