Synthesis of Functionalised Phenylalanines Using Rhodium Catalysis in Water

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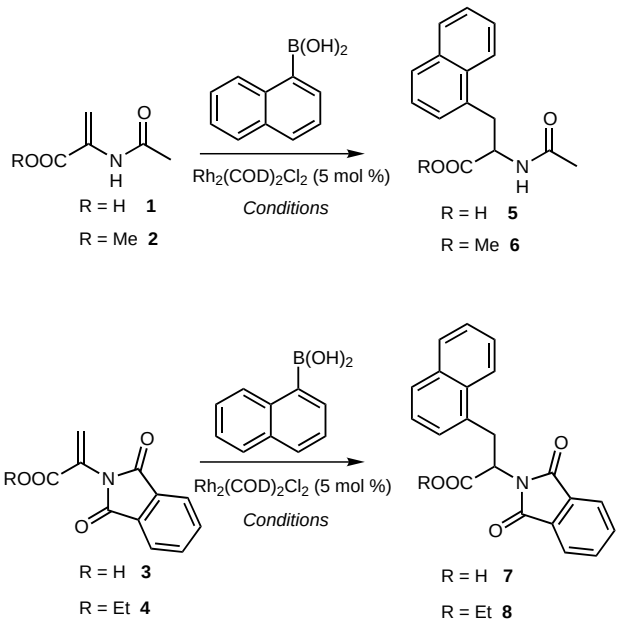
Abstract: The efficient synthesis of substituted phenylalanine-type amino acids using a rhodium-catalysed, conjugate addition of arylboronic acids is described. The reactions are run in water and use a low loading (0.5 mol %) of rhodium catalyst.

Keywords: arylation; boronic acids; C-C coupling; conjugate addition; rhodium

The synthesis of α-amino acids continues to be of significant interest as a consequence of the diverse utility of amino acids in chemistry and biochemistry.[1] Common synthetic approaches include the addition to imines,[2] carbonylation reactions[3] and catalytic hydrogenation reactions.[4] Recently, Li has reported the conjugate addition of carbon nucleophiles (organotin, organobismuth and organosilicon reagents) to α,β-dehydroamino acid derivatives.[5] Here we report the utility of the *boron*/rhodium transmetalation process as a means to promote the conjugate addition of aryl nucleophiles to α,β-dehydroalanine derivatives, allowing rapid access to a wide range of substituted phenylalanine-type α-amino acids. Reetz has performed one example of this type of transformation to prepare the naturally occurring amino acid phenylalanine (Phe).[6] Synthetic analogues of Phe provide a useful way of increasing chemical functionality in proteins or peptides, and have considerable potential in pharmaceutical applications. Examples of Phe-based non-coded amino acids have been successfully utilised in the synthesis of potent bradykinin antagonists and oxytocin analogues.[7] Another such derivative, 4-biphenylalanine is employed as an effective element in a potent, long-acting angiotensin II antagonist.[8] This communication details a clean, catalytic approach to functionalised Phe derivatives.

The rhodium-catalysed addition of boronic acids to organic electrophiles has emerged as fundamental methodology for organic synthesis. An efficient transmetalation between boron and rhodium permits the addition of organoboronic acids to a range of activated olefins.[9] The key steps in the catalytic cycle have recently been elucidated and reported by Hayashi.[10] Further to this the addition of arylboronic acids to aldehydes,[11] imines[12] and anhydrides has also been achieved.[13] Significant advances have also been made by Lautens in the coupling of hetereoaromatic olefins in aqueous media.[14] In these reactions, the catalyst $Rh_2(COD)_2Cl_2$ (COD = cyclooctadiene) was used with the water-soluble ligand triphenylphosphinodisulphonate (TPPDS) and sodium dodecyl sulphate (SDS) as a phase transfer agent. For this study we investigate the coupling of substituted arylboronic acids with amidoacrylate electrophiles (**1**–**4**) using water as the reaction solvent.[15]

Initial experiments examined the addition of 1-naphthaleneboronic acid promoted by $Rh_2(COD)_2Cl_2$ as catalyst, selected results are shown in Table 1. It was clear from the outset that the presence of a free carboxylic acid group was having a detrimental effect



Scheme 1. Conjugate addition to dehydroalanine derivatives.

Table 1. Rhodium-catalysed synthesis of amino acid derivatives.

Entry	Enamide	Conditions	Product	Yield [%][a]
1	**1**	H_2O, 100 °C, 24 hours	**5**	< 5
2	**2**	H_2O, 100 °C, 24 hours	**6**	30
3	**3**	H_2O, 100 °C, 24 hours	**7**	< 5
4	**4**	H_2O, 100 °C, 24 hours	**8**	98
5	**4**	H_2O, SDS, 100 °C, 24 hours	**8**	89
6[b]	**4**	H_2O, 100 °C, 24 hours	**8**	92

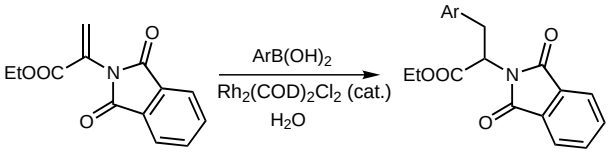
[a] Isolated yield after flash chromatography.
[b] 0.5 mol % $Rh_2(COD)_2Cl_2$.

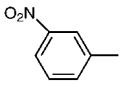
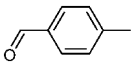
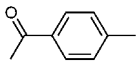
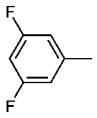
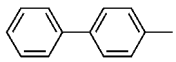
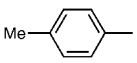
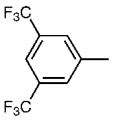
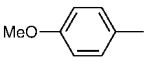
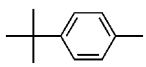
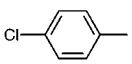
on the course of the reaction (Entries 1 and 3). This can be rationalised by oxidative addition of the acid followed by protolytic cleavage of the rhodium-aryl bond to produce naphthalene which was the observed major product of the reaction.[16] The utilisation of ethyl α-phthalimidoacrylate **4** provided the addition product in excellent isolated yield (Entry 4). The conditions previously described by Lautens either with or without added ligand were also effective. Remarkably, the catalyst loading could be lowered to 0.5 mol % $Rh_2(COD)_2Cl_2$ without any loss of efficiency (Entry 6). The increase in efficiency when using **4** compared to **2** is due to enhanced stability of the phthalyl group in the presence of water as well as electronic effects.

Under the preferred reaction conditions the scope of the process was explored with respect to the boronic acid (Table 2). In all cases the reaction proceeded in good yield to provide a useful synthetic approach to unnatural amino acid derivatives. It was useful to note that both electron-rich and electron-deficient arylboronic acids could be successfully employed. Given that certain rhodium complexes are capable of promoting the addition of arylboronic acids to aldehydes, an interesting result was that arising from the use of 4-formylboronic acid (Table 2, entry 2). It appears that in aqueous media the conjugate addition proceeds cleanly in good yield without the need to protect the aldehyde functionality. The incorporation of functional groups such as CHO, NO_2 and Cl provide pharmacologically interesting products and provide an opportunity for further modification. The protecting groups can be cleaved by a two-step route consisting of ester hydrolysis followed by removal of the phthalyl group with hydrazine. However, a more convenient procedure is the simultaneous cleavage of both protecting groups under acidic conditions (6 N HCl/AcOH, 4:1) which furnishes the amino acid hydrochlorides in excellent overall yield.[17]

In summary, the scope of the rhodium-catalysed addition of boronic acids has been extended to allow the efficient preparation of unnatural α-amino acid derivatives. The reactions can be performed in water at low catalyst loading and without added ligand. Our efforts continue to investigate the scope of this important carbon-carbon bond forming reaction.

Table 2. Synthesis of amino acid derivatives from **4**.[a]



Entry	Ar	Yield [%][b]
1		66
2		59
3		66
4		89
5		85
6		77
7		90
8		88
9		73
10		76

[a] For typical reaction conditions, see Experimental Section.
[b] Isolated yield after flash chromatography.

Experimental Section

General Remarks

All reactions in Table 2 were performed according to the following procedure by using different boronic acids. Experimental data for all new compounds can be found in the supporting information.

3-(4-Acetylphenyl)-2-(1,3-dihydro-1,3-dioxoisoindol-2-yl)-propionic Acid Ethyl Ester (Table 2, Entry 3)

A suspension of ethyl α-phthalimidoacrylate (61 mg, 0.25 mmol), 4-acetylbenzeneboronic acid (82 mg, 0.5 mmol), and chloro-(1,5-cyclooctadiene)rhodium(I) dimer (6 mg, 0.0125 mmol, 5 mol %), in 3 mL of water was refluxed under an air atmosphere. After 24 hours ethyl acetate (10 mL) was added and the phases separated, and the aqueous phase extracted with ethyl acetate (3 × 10 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude material was purified by flash chromatography on silica gel (eluent petroleum ether/ethyl acetate, 4:1) to give the title compound as a white solid; yield: 60 mg (66%); mp 131 – 132 °C; R_f (4:1 petroleum ether:ethyl acetate) 0.20; IR (nujol): $\nu_{max} = 2923$, 2852, 1773, 1739, 1715, 1684, 1606, 1465, 1377, 1271, 1238, 1185, 1106, 1016, 954, 887, 714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.26$ (3H, t, $J = 7.2$ Hz, CH_3), 2.52 (3H, s, $COCH_3$), 3.56 – 3.70 (2H, m, $CHCH_2$), 4.26 (2H, qd, $J = 1.9$, 7.2 Hz, CH_2CH_3), 5.17 (1H, dd, $J = 6.0$, 10.5 Hz, NCH), 7.28 (2H, d, $J = 8.3$ Hz, 2,6-Ar-CH), 7.68 – 7.74 (2H, m, Ar), 7.76 – 7.82 (4H, m, Ar, 3,5-Ar-CH); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 197.7$, 168.5, 167.4, 142.5, 135.8, 134.2, 131.5, 129.1, 128.7, 123.6, 62.2, 52.9, 34.7, 26.6, 14.1; MS (FAB^+): [MH^+]: calcd. for $C_{21}H_{20}NO_5$: *m/z* 366.1341; found: *m/z* 366.1366; anal. calcd. (%) for $C_{21}H_{19}NO_5$: C 69.03, H 5.24, N 3.83; found: C 68.90, H 5.28, N 3.83.

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