Rhodium-Catalysed 1,4-Additions in Water: Synthesis of Succinic Esters and β²-Amino Acid Derivatives

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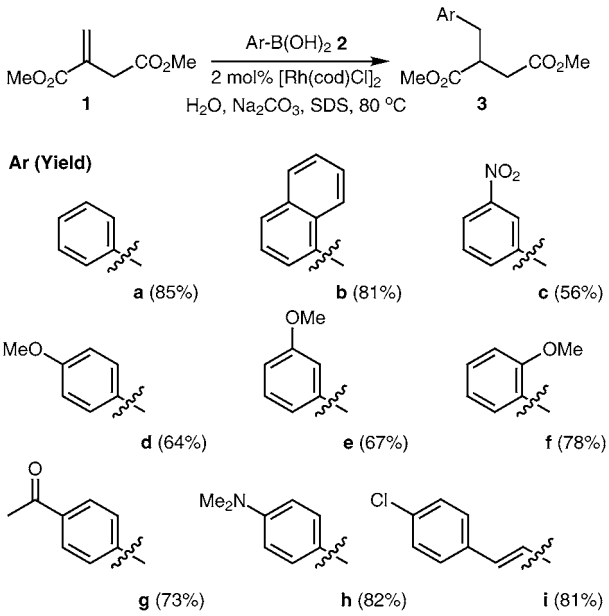
Abstract: The rhodium-catalysed addition of boronic acids to α-substituted activated alkenes proceeds smoothly in water resulting in a unique synthesis of both succinic esters and β²-amino acid derivatives.

Key words: conjugate addition, rhodium, boronic acids, succinic esters, β²-amino acids

Since the first report by Hayashi and Miyaura in 1998, the rhodium-catalysed addition of aryl and alkenyl organometallic reagents to activated alkenes has emerged as important methodology for organic synthesis.[1] Although both Miyaura and Lautens have reported additions to both activated alkenes and heteroaromatic alkenes that proceed with water as solvent, in the majority of reported examples organic solvents are used either alone or as co-solvents.[2] In a previous study we have revealed an efficient rhodium-catalysed conjugate addition of boronic acids to α,β-dehydroamino acid derivatives using water as the only solvent.[3] In an ongoing programme of research we have sought to broaden the scope of this methodology to other α-substituted activated alkenes. In this paper, we wish to present preliminary results in the synthesis of 2-substituted succinic esters and β²-amino acid derivatives. The products from this process are of significant utility as peptidomimetics in the development of pharmaceutical and agrochemical intermediates.[4] The methodology described herein represents a unique alternative to the two-step condensation–hydrogenation approach conventionally employed.[5]

At the outset of this study we chose to investigate the coupling of arylboronic acid (**2b**) with dimethyl itaconate (**1**) using water as the reaction solvent. During preliminary optimisation, the catalyst $[Rh(cod)Cl]_2$ (cod = cycloocta-1,5-diene) was used with sodium dodecylsulfate (SDS) as a phase transfer agent affording a 55% yield of product **3b**. In the absence of SDS the yield fell to less than 10%. The addition of two equivalents of sodium carbonate increased the yield to 81%. Under these optimised conditions a number substituted of substituted aryl and vinylboronic acids (**2a**–**i**) was tested and, pleasingly the reaction proceeded in good isolated yield to provide a useful synthetic approach to 2-substituted succinic esters (Scheme 1).[6] The addition of phosphine ligands did not appear to accelerate the conjugate addition under these conditions. It was useful to note that both electron-rich (**3h**) and electron-deficient aryl boronic acids (**3c**,**g**) could be successfully employed as well as different substitution patterns (**3d**–**f**). The incorporation of functional groups such as -Cl, -COMe, $-NO_2$ and $-NMe_2$ provide pharmacologically interesting products and present opportunities for further modification.



Scheme 1

Given the importance of β-amino acids and their derivatives the development of new synthetic methodology to prepare such compounds is of significant interest.[7] We were therefore driven to extend the described methodology to include the addition of boronic acids to β-amidoacrylates affording β²-amino acid derivatives. The orthogonally protected β-amidoacrylate substrate **4** can be prepared in good yield by the reaction of potassium phthalimide (KNPht) with either of bromomethylacrylate or acetoxymethylacrylate.[7b,8] We were pleased to discover that this was a viable route for the synthesis of functionalised β²-phenylalanine derivatives. As previously the combination of $[Rh(cod)Cl]_2$ and sodium dodecylsulfate (SDS) provided a catalyst system for the addition of a range of substituted boronic acids in water (Scheme 2).[9] The lower reactivity of **4** is evident from the higher

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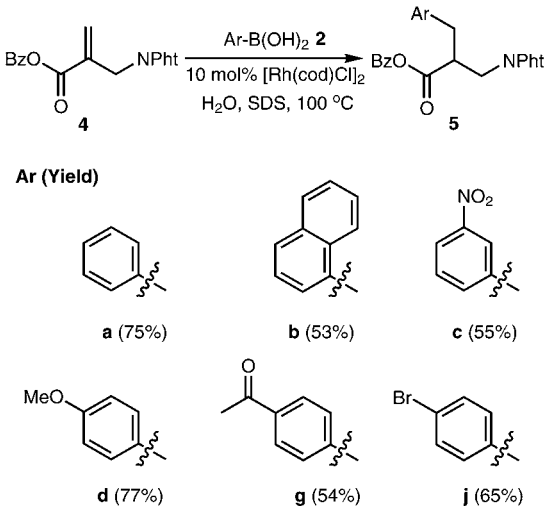
catalyst loading (10 mol%) and higher temperature (100 °C) necessary to afford acceptable isolated yields of product (53–77%). Nevertheless, this represents a new practical method for the synthesis of highly functionalised β²-amino acid derivatives and we are continuing to expand the scope of the transformation. The protecting groups can be cleaved by a two-step route consisting of hydrogenolysis of the benzyl group followed by removal of the phthalyl group with hydrazine.[7b] Alternatively, the simultaneous cleavage of both protecting groups can occur under acidic conditions (6 N HCl–HOAc 4:1) affording the β²-amino acid hydrochloride salts.[3,10]



Scheme 2

The key steps in the catalytic cycle have been elucidated and reported by Hayashi.[11] Assuming the mechanistic observations extend to the presented work, it is likely a rhodium-hydroxide species is the reactive catalyst and the reaction occurs by aryl transfer to rhodium followed by coordination of the substrate (**1**/**4**) and insertion to generate an oxa-π-allyl rhodium species which is hydrolysed to provide the final product (**3**/**5**). The methodology presented here provides a practical route to racemic 2-substituted succinic esters and β²-amino acid derivatives using water as the solvent. We are currently investigating a rhodium-catalysed enantioselective conjugate addition to substrates **1** and **4** employing organoboron reagents and we will report these results in due course.[12]

Typical Experimental Procedure: Dimethyl itaconate (**1**, 0.210 g, 1.308 mmol), 1-naphthylboronic acid (**2b**, 0.578 g, 3.36 mmol, 2.5 equiv), SDS (0.189 g, 0.684 mmol, 0.5 equiv) and Na_2CO_3 (0.291 g, 3.648 mmol, 2.0 equiv) were added to a solution of $[Rh(cod)Cl]_2$ (0.012 g, 0.058 mmol, 2 mol%) in water (6.6 mL). The resulting solution was stirred at 80 °C overnight. After cooling to r.t. the product was extracted with Et_2O (3×). The organic extracts were then combined, washed with brine (3×) and dried with $MgSO_4$. Flash chromatography in (4:1) petroleum ether–EtOAc afforded the product **3b** as a colourless crystalline solid (65%). Mp 96–97 °C (lit.[13] 96.7 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.37 (1 H, dd, *J* = 5.1, 17.1 Hz, CH_2), 2.69 (1 H, dd, *J* = 9.3, 17.1 Hz, CH_2), 3.06 (1 H, dd, *J* = 9.3, 13.5 Hz, CH_2), 3.25 (1 H, m, CH_2), 3.52 (2 H, dd, *J* = 5.7, 13.5 Hz, CH_2), 3.54 (3 H, s, CH_3), 3.61 (3 H, s, CH_3), 7.21 (1 H, d, *J* = 8.1 Hz, Ar), 7.32 (1 H, t, *J* = 6.9 Hz, Ar), 7.46 (2 H, m, Ar), 7.69 (1 H, d, *J* = 8.4, Ar), 7.80 (1 H, d, *J* = 9.3, Ar), 8.02 (1 H, d, *J* = 8.7, Ar). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 35.5, 35.6, 42.5, 52.1, 52.4, 123.9, 125.7, 126.1, 126.7, 127.8, 128.1, 129.3, 132.1, 134.3, 134.6, 175.3, 172.6. IR (nujol): 1159 (s), 1377 (s), 1462 (s), 1719 (m), 2724 (m), 2862 (br) cm^{-1}. MS (FAB$^+$): *m/z* (%) = 286 (56) [M$^+$ + H]. HRMS (FAB$^+$): $C_{17}H_{18}O_4$ requires [M]: 286.1205; found: 286.1210 [M$^+$ + H]. Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.30; H, 6.34%.

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(6) All compounds have been satisfactorily characterised by ^{1}H NMR and ^{13}C NMR. ^{1}H NMR data (300 MHz, $CDCl_3$) for **3a**: δ = 2.34 (1 H, dd, *J* = 4.8, 16.8 Hz), 2.66 (2 H, m), 3.03 (2 H, m), 3.57 (3 H, s), 3.60 (3 H, s), 7.16 (5 H, m). Compound **3c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (1 H, dd, *J* = 5.7, 17.1 Hz), 2.65 (1 H, dd, *J* = 8.7, 17.1 Hz), 2.88 (1 H, dd, *J* = 10.5, 16.8 Hz), 3.09 (2 H, m), 3.57 (3 H, s), 3.60 (3 H, s), 7.42 (2 H, m), 8.01 (2 H, m). Compound **3d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (1 H, dd, *J* = 5.1, 16.8 Hz), 2.61 (2 H, m), 2.98 (2 H, m), 3.57 (3 H, s), 3.60 (3 H, s), 3.72 (3 H, s), 6.76 (2 H, d, *J* = 8.7 Hz), 7.00 (1 H, d, *J* = 8.7 Hz). Compound **3e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34 (1 H, dd, *J* = 4.5, 16.5 Hz), 2.62 (2 H, m), 3.02 (2 H, m), 3.57 (3 H, s), 3.62 (3 H, s), 3.72 (3 H, s), 6.67 (3 H, m), 7.15 (1 H, dd, *J* = 9.6, 17.4 Hz). Compound **3f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (1 H, dd, *J* = 4.8, 17.1 Hz), 2.66 (2 H, m), 2.97 (1 H, dd, *J* = 6.3, 13.2 Hz), 3.14 (1 H, m), 3.55

(3 H, s), 3.59 (3 H, s), 3.75 (3 H, s), 6.79 (2 H, m), 7.00 (1 H, d, *J* = 9.0 Hz), 7.15 (2 H, m). Compound **3g**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35 (1 H, dd, *J* = 5.1, 16.8 Hz), 2.63 (2 H, dd, *J* = 8.4, 16.8 Hz), 2.78 (2 H, dd, *J* = 7.5, 12.9 Hz), 3.07 (2 H, m), 3.58 (3 H, s), 3.59 (3 H, s), 7.19 (2 H, d, *J* = 8.4 Hz), 7.83 (2 H, d, *J* = 8.1 Hz). Compound **3h**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (1 H, dd, *J* = 4.8, 16.8 Hz), 2.58 (2 H, m), 2.85 (6 H, s), 2.99 (2 H, m), 3.56 (3 H, s), 3.61 (3 H, s), 6.60 (2 H, d, *J* = 8.7 Hz), 6.95 (2 H, d, *J* = 8.7 Hz). Compound **3i**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (3 H, m), 2.64 (1 H, dd, *J* = 8.7, 16.5 Hz), 2.91 (1 H, m), 3.58 (3 H, s), 3.63 (3 H, s), 6.00 (1 H, m), 6.30 (1 H, d, *J* = 15.6 Hz), 7.19 (4 H, s).

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(9) All compounds have been satisfactorily characterised by ^{1}H NMR and ^{13}C NMR. ^{1}H NMR data (300 MHz, $CDCl_3$) for **5a**: δ = 2.85 (1 H, dd, *J* = 6.6, 14.1 Hz), 3.10 (1 H, dd, *J* = 8.7, 14.1 Hz), 3.35 (1 H, m), 3.85 (1 H, dd, *J* = 6.0, 13.8 Hz), 4.05 (1 H, dd, *J* = 8.4, 13.8 Hz), 5.00 (2 H, s), 7.10–7.25 (10 H, m), 7.67 (2 H, m), 7.78 (2 H, m). Compound **5b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.36 (1 H, m), 3.50 (2 H, m), 3.95 (1 H, dd, *J* = 4.8, 13.8 Hz), 4.15 (1 H, dd, *J* = 7.8, 13.8 Hz), 4.95 (2 H, s), 7.05 (2 H, dd, *J* = 1.7, 7.7 Hz), 7.15 (2 H, m,), 7.30 (3 H, m), 7.45 (2 H, m), 7.60–7.88 (6 H, m), 8.00 (1 H, d, *J* = 8.4 Hz). Compound **5c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.00 (1 H, dd, *J* = 5.9, 14.0 Hz), 3.15 (1 H, dd, *J* = 9.2, 14.0 Hz), 3.35 (1 H, m), 3.90 (1 H, dd, *J* = 6.0, 13.8 Hz), 4.08 (1 H, dd, *J* = 7.8, 13.8 Hz), 5.00 (2 H, s), 7.15 (2 H, m), 7.25 (3 H, m), 7.35 (1 H, m), 7.50 (1 H, d, *J* = 7.8 Hz), 7.70 (2 H, m), 7.85 (2 H, m), 8.00 (1 H, d, *J* = 8.1 Hz), 8.05 (1 H, s). Compound **5d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.80 (1 H, dd, *J* = 6.6, 13.8 Hz), 3.00 (1 H, dd, *J* = 8.6, 14.0 Hz), 3.30 (1 H, m), 3.75 (3 H, s), 3.85 (1 H, dd, *J* = 6.0, 13.8 Hz), 4.05 (1 H, dd, *J* = 8.3, 13.7 Hz), 5.00 (2 H, s), 6.75 (2 H, d, *J* = 8.7 Hz), 7.05 (2 H, d, *J* = 8.7 Hz), 7.15 (2 H, m), 7.23 (3 H, m), 7.68 (2 H, m), 7.78 (2 H, m). Compound **5g**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.55 (3 H, s), 2.95 (1 H, dd, *J* = 6.3, 14.1 Hz), 3.15 (1 H, dd, *J* = 8.7, 14.1 Hz), 3.35 (1 H, m), 3.90 (1 H, dd, *J* = 6.2, 14.0 Hz), 4.05 (1 H, dd, *J* = 8.1, 13.8 Hz), 5.00 (2 H, s), 7.15 (2 H, m), 7.18–7.28 (5 H, m), 7.70 (2 H, m), 7.78 (4 H, m). Compound **5j**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.80 (1 H, dd, *J* = 6.5, 14.0 Hz), 3.00 (1 H, dd, *J* = 9.0, 14.1 Hz), 3.30 (1 H, m), 3.90 (1 H, dd, *J* = 6.3, 13.8 Hz), 4.05 (1 H, dd, *J* = 8.1, 13.8 Hz), 5.00 (2 H, s), 7.05 (2 H, d, *J* = 8.4 Hz), 7.15 (2 H, m), 7.23 (3 H, m), 7.29 (2 H, d, *J* = 8.4 Hz), 7.70 (2 H, m), 7.80 (2 H, m).

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