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# The synthesis of 3-aryl-3-azetidinyl acetic acid esters by rhodium(I)-catalysed conjugate addition of organoboron reagents

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ABSTRACT

A practical route to 3-aryl-3-azetidinyl acetic acid esters is developed. The key step involves the rhodium(I)-catalysed conjugate addition of an organoboron reagent to an α,β-unsaturated alkene. Elaboration of one conjugate addition product to give a novel spiroazetidine ring system is also described.



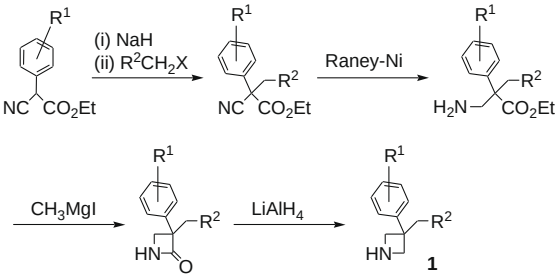
Despite their increasing utility in drug discovery, substituted azetidines have received considerably less attention than their larger ring pyrrolidine and piperidine analogs.[1] This is in large part due to the greater difficulty associated with the synthesis of this strained heterocycle.

As part of a kinase inhibitor programme, we required efficient entry into 3,3-disubstituted azetidines of type **1**. These moieties are traditionally synthesised via reduction of the corresponding azetidine-2-ones, which in turn are prepared from poorly accessible 2-aryl-2-cyanoacetates (Scheme 1).[2,3] The variety of azetidines accessible by this route is clearly limited by the highly reactive reagents used in a number of the steps.

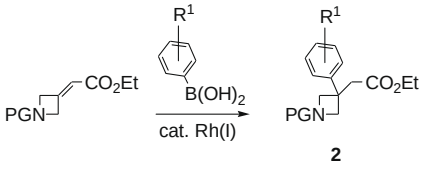
We envisioned a more direct approach into this class of compound that uses the Rh(I)-catalysed boronic acid conjugate addition protocol pioneered by Hayashi and Miyaura.[4,5] This methodology was predicted to be compatible with a wide range of aromatic substituents ($R^1$) and provide 3-aryl-3-azetidinyl acetic acid ester derivatives **2** possessing a valuable ester group for further synthetic manipulation (Scheme 2).

Investigations began with the reaction of phenylboronic acid with α,β-unsaturated ester **3**, easily prepared by Horner–Wadsworth–Emmons reaction from *N*-Boc-3-azetidinone (Scheme 3).[6] Encouragingly, the desired conjugate addition adduct **4**, was obtained in 85% yield after stirring at room temperature for one hour in the presence of chloro(1,5-cyclooctadiene)rhodium(I) dimer.[7]

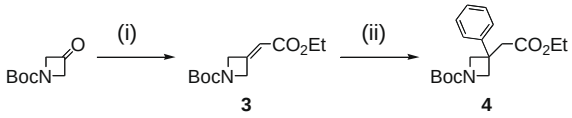
Further similar experiments were used to explore the scope and limitations of the process and the results are summarised in Table 1.[8,9] In general, the reactions were carried out under microwave heating at 100 °C for 5 min.[10] The steric bulk of the N-protecting group in unsaturated ester **3** did not appear to hinder the reaction. Indeed, the reaction was also successful when the larger diphenylmethyl N-protection, a commonly used protecting group for the azetidine ring, was used (Table 1, entry 2).




**Scheme 1.** An established method for 3,3-disubstituted azetidine synthesis.




**Scheme 2.** Proposed synthesis of 3-aryl-3-azetidinyl acetic acid esters.




**Scheme 3.** Reagents and conditions: (i) $EtO_2CCH_2P(O)(OEt)_2$, NaH, THF, rt, 72%; (ii) $PhB(OH)_2$ (2 equiv), $[Rh(cod)Cl]_2$ (0.03 equiv), 1.5 M KOH (2 equiv), 1,4-dioxane, rt, 1 h, 85%.

As expected, the reaction worked well with a range of boronic acids that incorporated both electron-donating and electron-withdrawing groups. Boronic esters are equally competent partners in the coupling reaction (entry 14). We obtained a poor yield of 36% in the coupling reaction with 3-nitrophenylboronic acid under

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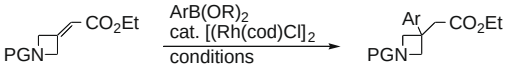
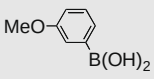
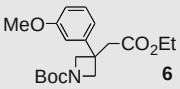
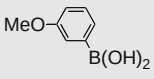
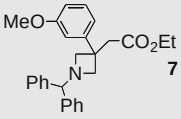
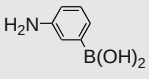
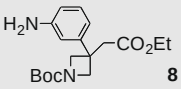
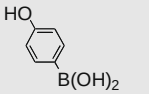
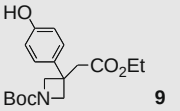
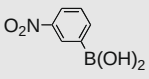
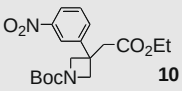
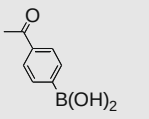
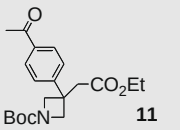
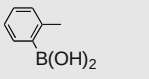
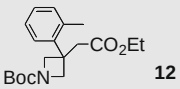
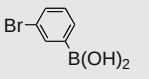
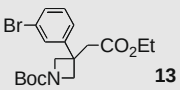
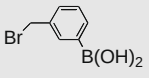
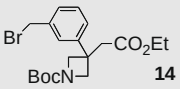
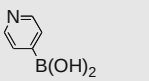
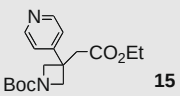
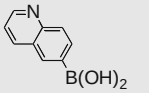
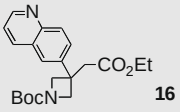
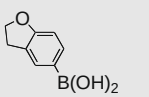
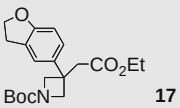
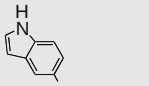
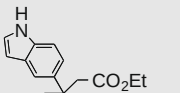
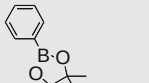
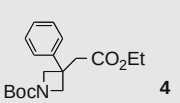
**Table 1**
Rhodium-catalysed coupling of alkene **3** or **5** with aromatic boronic acids/esters




PG = Boc, **3**
PG = $Ph_2CH$, **5**

**4,6-18**

| Entry | Alkene | Boronic acid/ester | Product | Method[a] | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | 3 |  |  **6** | A | 90 |
| 2 | 5 |  |  **7** | A | 73 |
| 3 | 3 |  |  **8** | A | 80 |
| 4 | 3 |  |  **9** | A | 88 |
| 5 | 3 |  |  **10** | B | 73 |
| 6 | 3 |  |  **11** | A | 83 |
| 7 | 3 |  |  **12** | A[c,d] | 73 |
| 8 | 3 |  |  **13** | A | 79 |
| 9 | 3 |  |  **14** | A[c] | 65 |
| 10 | 3 |  |  **15** | A | 7[e] |
| 11 | 3 |  |  **16** | A | 75 |
| 12 | 3 |  |  **17** | A | 83 |
| 13 | 3 |  |  **18** | A | 74 |
| 14 | 3 |  |  **4** | A | 74 |

[a] *Method A*: $ArB(OH)_2$ (2 equiv), $[Rh(cod)Cl]_2$ (0.03 equiv), 1.5 M KOH (2 equiv), 1,4-dioxane, microwave (300 W, CEM Discover), 100 °C, 5 min. *Method B*: $ArB(OH)_2$ (3 equiv), $[Rh(cod)Cl]_2$ (0.03 equiv), $K_2CO_3$ (3 equiv), 2-propanol (3 equiv), THF, 60 °C, conventional heating, 2 h.
[b] Isolated yields based on alkene **3** or **5**.
[c] Carried out at rt, overnight.
[d] 5 equiv of boronic acid used.
[e] % Conversion based on LC–MS (AUC).

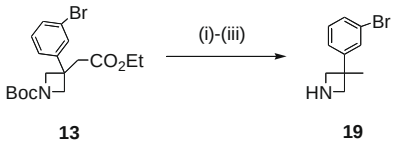
our standard coupling conditions (Table 1, method A). However, it is known that rhodium-catalysed protodeboronation of the boronic acid can be a significant competing side reaction when employing certain electron-deficient boronic acids.[11–14] This yield was improved from 36% to 73% by adopting conditions similar to those reported by Parker (entry 5).[11] Here, the replacement of water with *iso*-propanol, minimizes the water-assisted protodeboronation. In our studies, we found that three equivalents of the boronic acid were still necessary to consume the starting material.

We were pleased to observe smooth coupling with a sterically hindered boronic acid (entry 7) in light of the poorer results reported with *ortho*-substituted boronic acids by Iyer et al. in their related studies.[10] The anhydrous Parker conditions did not provide any advantage in this case with respect to reducing the amount of boronic acid used. The reaction is highly functional group tolerant. Boronic acids containing a bromine atom (entry 8) and unprotected aniline, phenol and ketone functionalities (entries 3, 4 and 6) were all coupled smoothly and in high yield. Remarkably, 3-bromomethylphenylboronic acid (entry 9) was also a suitable coupling partner, furnishing the desired conjugate addition product **14** in 65% isolated yield.

To the best of our knowledge, reaction conditions that inhibit the fast competing protodeboronation observed when employing pyridine boronic acids have yet to be developed.[15] Therefore the low yield for entry 10 (Table 1) was expected. Despite this problem with pyridines, certain 3-heteroaryl-3-alkyl azetidines can be prepared in good yield from heteroaromatic boronic acids possessing heteroatoms further removed from the boron atom (entries 11–13).

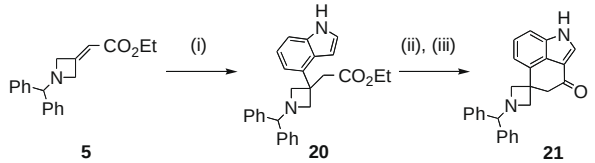
The conjugate addition adducts can be easily converted into simple 3-aryl-3-alkyl azetidines. For example, treatment of the aldehyde derived from ester **13** with Wilkinson's catalyst gave 3-(3-bromophenyl)-3-methylazetidine **19** after *N*-Boc deprotection (Scheme 4).

The conjugate addition adducts could also be of interest in the area of Diversity Oriented Synthesis.[16,17] For example, cyclisation of the acid derivative of adduct **20** gave the previously unreported spiroazetidine **21** in protected form (Scheme 5).




13 19

**Scheme 4.** Reagents and conditions: (i) DIBAL-H, DCM, −78 °C, 1 h, 81%; (ii) $ClRh(PPh_3)_3$, toluene, 4 h, reflux; (iii) TFA, $Et_3SiH$, DCM, 44% (two steps).




5 20 21

**Scheme 5.** Reagents and conditions: (i) indole-4-boronic acid, cat. $[Rh(cod)Cl]_2$, aq KOH, dioxane, 100 °C, microwave, 84%; (ii) 5 M KOH, 1,4-dioxane, reflux; (iii) polyphosphoric acid, 100 °C, 47% (two steps).

In summary, we have developed a practical and efficient route to 3-aryl-3-azetidinyl acetic acid esters by rhodium-catalysed conjugate addition of organoboron reagents to α,β-unsaturated esters derived from N-protected-3-azetidinone. The wide scope of the procedure allowed for the preparation of a range of 3,3-disubstituted azetidines for biological testing in our research programmes.

## Acknowledgements

I would like to thank Drs. J. Golec, S. Young and J.-M. Jimenez for helpful discussions.

## References and notes

1. Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988–4035, and references therein.
2. Bishop, D. C.; Cavalla, J. F.; Lockhart, L. M.; Wright, M.; Winder, C. V.; Wong, A.; Stephens, M. *J. Med. Chem.* **1968**, *11*, 466–470.
3. Yang, H.; Kazmierski, M. W.; Aquino J. C.; (Smithkline Beecham Corp., US). Application: WO2004055016, 2003-US039618 2003. *Chem. Abstr.* **2004**, *141*, 89006.
4. Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844.
5. Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169–196.
6. *N*-Boc-3-azetidinone is commercially available from a number of suppliers.
7. One example of rhodium-catalysed conjugate addition of a boronic acid to the corresponding oxetane has been reported, see: Wuitschik, G.; Rogers-Evans, M.; Muller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7736–7739.
8. *General procedure, method A* (*for compound* **6**): To a solution of $[Rh(cod)Cl]_2$ (6.1 mg, 0.012 mmol) in 1,4-dioxane (1 mL) was added aqueous KOH (1.5 M, 0.553 mmol, 0.829 mmol). After stirring for 5 min, 3-methoxyphenylboronic acid (126 mg, 0.829 mmol) and then alkene **3** (100 mg, 0.414 mmol) in THF (1.5 mL) were added in rapid succession. The reaction mixture was irradiated with microwaves (300 W) at 100 °C for 5 min, then diluted with water and extracted with EtOAc (2 × 20 mL). The combined organics were dried (magnesium sulfate), filtered and concentrated. Purification by column chromatography (3:1, petroleum ether/EtOAc) gave adduct **6** (130 mg, 90%) as a colourless oil. *General procedure, method B* (*for compound* **10**): To a solution of alkene **3** (100 mg, 0.414 mmol), 3-nitrophenylboronic acid (207 mg, 1.24 mmol) and $K_2CO_3$ (172 mg, 1.24 mmol) in THF (4 mL) and 2-propanol (75 mg, 1.24 mmol) was added a solution of $[Rh(cod)Cl]_2$ (10.1 mg, 0.021 mmol) in THF (1.5 mL) under nitrogen. The reaction was heated at 60 °C for 2 h and then worked-up as in method A. Purification by column chromatography (3:1, petroleum ether/EtOAc) gave adduct **10** (110 mg, 73%) as a colourless oil.
9. *NMR data of some representative compounds*: *compound* **3**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.30 (3H, t, $J$ = 9.2 Hz), 1.48 (9H, s), 4.20 (2H, q, $J$ = 9.2 Hz), 4.60–4.63 (2H, m), 4.82–4.86 (2H, m), 5.77–5.79 (1H, m); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 14.7, 28.7 (3C), 58.3 (2C), 60.8, 80.6, 114.1, 152.9, 156.7, 165.7; *Compound* **6**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.15 (3H, t, $J$ = 7.0 Hz), 1.46 (9H, s), 2.96 (2H, s), 3.82 (3H, s), 4.03 (2H, q, $J$ = 7.0 Hz), 4.21 (2H, d, $J$ = 9.0 Hz), 4.27 (2H, d, $J$ = 9.0 Hz), 6.74 (1H, s), 6.78–6.81 (2H, m), 7.25–7.29 (1H, m); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 14.5, 28.8 (3C), 40.1, 46.1, 55.6, 60.0 (2C, br s), 60.8, 80.0, 112.3, 112.7, 118.7, 129.9, 146.0, 156.8, 160.0, 170.8; *Compound* **10**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.08 (3H, t, $J$ = 7.2 Hz), 1.39 (9H, s), 2.97 (2H, s), 3.95 (2H, q, $J$ = 7.2 Hz), 4.16 (2H, d, $J$ = 8.8 Hz), 4.21 (2H, d, $J$ = 8.8 Hz), 7.44–7.53 (2H, m), 8.00–8.06 (2H, m); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 14.4, 28.7 (3C), 39.9, 45.6, 60.5 (2C, br s), 61.2, 80.5, 121.8, 122.4, 130.0, 133.0, 146.5, 148.7, 156.6, 170.3; *Compound* **12**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.10 (3H, t, $J$ = 7.2 Hz), 1.46 (9H, s), 2.22 (3H, s), 2.97 (2H, s), 3.98 (2H, q, $J$ = 7.2 Hz), 4.23–4.25 (2H, m), 4.33 (2H, d, $J$ = 8.4 Hz), 7.04–7.07 (1H, m), 7.14–7.18 (3H, m); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 14.4, 20.0, 28.8 (3C), 41.1, 44.2, 59.9 (2C, br s), 60.8, 80.1, 126.2, 127.6, 128.0, 131.8, 135.3, 141.1, 157.1, 170.9; *Compound* **19**: $^1$H NMR (400 MHz, DMSO): $\delta$ 1.51 (3H, br s), 3.21–3.85 (4H, br m), 7.23 (1H, d, $J$ = 7.5 Hz), 7.29 (1H, t, $J$ = 7.5 Hz), 7.38–7.41 (2H, m); $^{13}$C NMR (100 MHz, DMSO): $\delta$ 16.9, 28.9, 59.4 (2C, br s), 122.2, 124.7, 127.7, 128.4, 129.0, 130.9; *Compound* **21**: $^1$H NMR (400 MHz, DMSO): $\delta$ 3.21 (2H, d, $J$ = 7.2 Hz), 3.30 (2H, d, $J$ = 7.2 Hz), 3.39 (2H, s), 4.61 (1H, s), 7.17 (2H, t, $J$ = 7.2 Hz), 7.24–7.40 (6H, m), 7.49 (4H, d, $J$ = 7.2 Hz), 7.59 (1H, d, $J$ = 6.4 Hz), 7.92 (1H, s), 12.13 (1H, br s); $^{13}$C NMR (100 MHz, DMSO): $\delta$ 39.7, 51.9, 65.1, 76.5, 110.7, 113.4, 116.5, 124.2, 125.5, 127.3, 127.5, 128.5, 128.8, 134.0 (2C), 142.8, 191.4.
10. Iyer, P. S.; O'Malley, M. M.; Lucas, M. C. *Tetrahedron Lett.* **2007**, *48*, 4413–4418.
11. Brock, S.; Hose, D. R. J.; Moseley, J. D.; Parker, A. J.; Patel, I.; Williams, A. J. *Org. Process Res. Dev.* **2008**, *12*, 496–502.
12. Williams, A.; Patel, I.; Oldfield, J.; (AstraZeneca Ltd, UK). Application: WO2007057643, 2006-GB004205 2006. *Chem. Abstr.* **2007**, *147*, 9654.
13. Boiteau, J.-G.; Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 681–684.
14. Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852–6856.
15. Abarca, B.; Ballesteros, R.; Blanco, F.; Bouillon, A.; Collot, V.; Dominguez, J.-R.; Lancelot, J.-C.; Rault, S. *Tetrahedron* **2004**, *60*, 4887–4893.
16. Schreiber, S. L. *Science* **2000**, *287*, 1964–1969.
17. Spandl, R. J.; Bender, A.; Spring, D. R. *Org. Biomol. Chem.* **2008**, *6*, 1149–1158.