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A versatile synthesis of 4-aryl tetrahydropyridines via palladium mediated Suzuki cross-coupling with cyclic vinyl boronates

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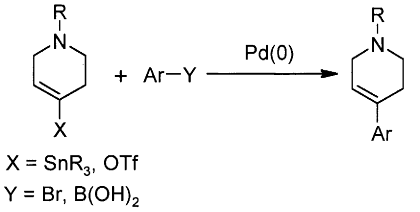
Abstract

A simple preparation of cyclic vinyl boronates derived from the vinyl triflates of *N*-protected tetrahydropyridines is described. Suzuki coupling of the boronates with aryl bromides, iodides and triflates proceeds in good yield to give 4-aryl tetrahydropyridines. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Suzuki reactions; piperidines; palladium.

4-Arylpiperidine-derived skeletons are present in a diverse array of biologically active entities and therapeutic agents[1] and as such represent important synthetic targets. Of the literature methods used to synthesise compounds of this type,[2] among the most useful are those which utilise a palladium-mediated cross-coupling to introduce the aromatic ring (Scheme 1). Examples of efficient coupling partners used include the combinations vinyl tin–aryl bromide[3] and vinyl triflate–aryl boronate.[4] The former method, although wide in scope due to the availability of aryl bromides, involves the use and often difficult removal of toxic tin compounds; the latter method is restricted as the commercial availability of aryl boronates is somewhat limited.



Scheme 1.

As part of ongoing medicinal chemistry programs, we were interested in a convenient synthesis of 4-aryl piperidines and 4-aryl tetrahydropyridines. In particular, we required a simple method of varying the aryl moiety in order to prepare scaffolds for chemical libraries. Herein we describe a method which

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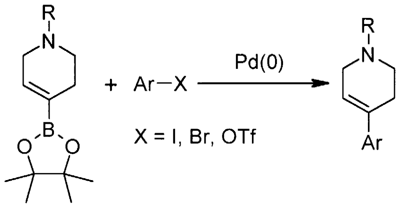
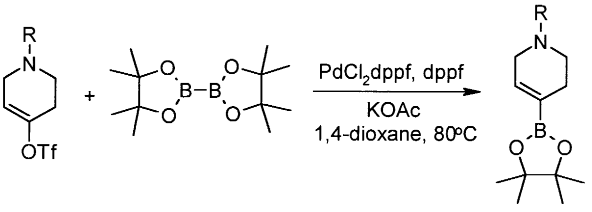
combines the advantages of both of the above methods by the coupling of vinyl boronates with the more abundant aryl halides or triflates (Scheme 2).



Scheme 2.

The desired *N*-protected cyclic boronates were synthesised in high yield from the readily available vinyl triflates[5] via a palladium-mediated cross-coupling with bis(pinacolato)diboron (Scheme 3).[6] The optimal conditions for this reaction were found by running a series of parallel reactions using a 'carousel reaction station'™.[7] An alternative synthesis of similar compounds has been described via a ring closing metathesis (RCM) reaction.[8]

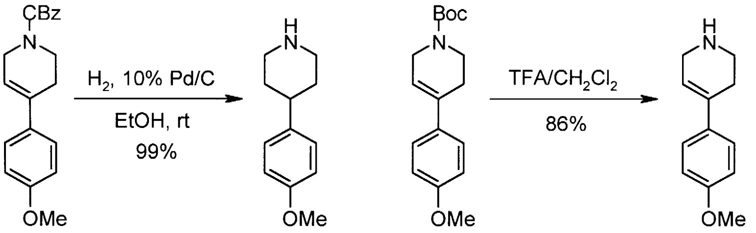


1: R = Boc (87%)
2: R = Cbz (85%)

Scheme 3.

Palladium-mediated reaction of **1** and **2** with a variety of aromatic substrates ($PdCl_2dppf$, K_2CO_3, DMF, 80°C) led to the desired cross-coupled products in good to high yield (Table 1). A range of functionality was tolerated including electron-withdrawing (entries 6–8) and electron-donating groups (entries 4, 5, 10 and 11), heterocycles (entry 9), esters (entry 6) and *o*-substituted compounds (entry 3). Although reaction occurred at room temperature with iodobenzene (entry 2), a higher yield was obtained under the standard conditions at 80°C. The use of an aryl triflate as a substrate (entry 12) also gave a high yield of the desired product. Similar yields are obtained with **1** and **2** (entries 10 and 11). The only case where any significant by-product was observed was in the reaction of 4-cyanobromobenzene (entry 7) which also produced an olefinic isomer.

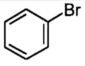
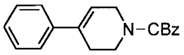
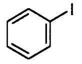
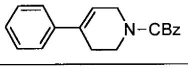
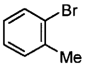
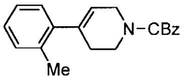
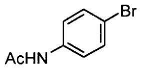
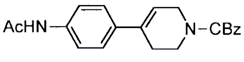
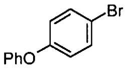
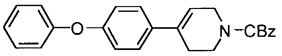
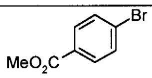
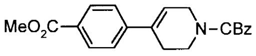
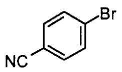
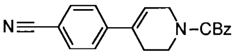
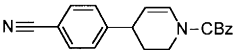
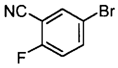
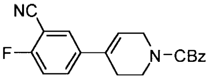
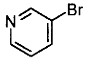
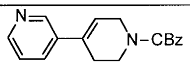
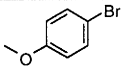
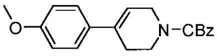
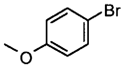
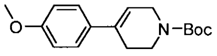
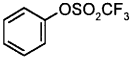
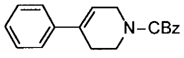
The desired piperidine and tetrahydropyridine templates ready for further functionalisation on nitrogen were easily accessed via standard deprotection methods[10] as illustrated in Scheme 4.



Scheme 4.

In summary, we have described a simple method for the synthesis of cyclic vinyl boronates and their use has been illustrated by the formation of 4-aryltetrahydropyridine and piperidine intermediates.

Table 1
Palladium-mediated cross-coupling of vinyl boronates **1** and **2**

Entry	Boronate	Substrate	Product(s)	Yield(%)[a]
1	**2**			80
2	**2**			90 (55)[b]
3	**2**			74
4	**2**			87
5	**2**			80
6	**2**			75
7	**2**		 	60 29
8	**2**			92[c]
9	**2**			85
10	**2**			73
11	**1**			65
12	**2**			87

[a] Isolated yields.
[b] Reaction carried out at room temperature for 24h.
[c] Reaction performed on 6.5 mmol of Boronate.

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3. See, for example: Bono, F.; Fournier, J.; Herbert, J.-M.; Lamarche, I.; Umberto, G. PCT Patent Appl. WO 9853821.
4. Wustrow, D. J.; Wise, L. D. *Synthesis* **1991**, *11*, 993.
5. Prepared in high yield from the commercially available ketones (LiHDMS, THF, −78°C then $PhNTf_2$ −78°C to 0°C).
6. Representative procedure: To a flask were added bis(pinacolato)diboron (5.75 mmol), KOAc (15.7 mmol), $PdCl_2dppf$ (3 mol%), dppf (3 mol%) and the contents flushed with nitrogen. A solution of the triflate (5.2 mmol) in 1,4-dioxane (30 mL) was added and the mixture was stirred at 80°C overnight. After work-up, flash chromatography (SiO_2, Pentane/EtOAc)

gave the boronates as white solids. Compound **1**: ^{1}H NMR ($CDCl_3$) 1.25 (s, 12H), 1.45 (s, 9H), 2.20 (m, 2H), 3.40 (m, 2H), 3.90 (m, 2H), 6.45 (br s, 1H); MS (MH^+); mp 99–101°C. Compound **2**: ^{1}H NMR ($CDCl_3$) 1.25 (s, 12H), 2.20 (m, 2H), 3.50 (m, 2H), 4.00 (m, 2H), 5.10 (s, 2H), 6.45 (br d, 1H), 7.30–7.40 (m, 5H); MS (MH^+); mp 88–90°C.

7. A single piece of equipment capable of heating and stirring 12 independent reactions under nitrogen. Available from Radleys, Shire Hill, Saffron Walden, Essex, CB11 3AZ, UK, http://www.radleys.co.uk
8. Renaud, J.; Ouellet S. G. *J. Am. Chem. Soc.* **1998**, *120*, 7995.
9. Representative procedure: To a nitrogen flushed flask containing the boronate (0.75 mmol), K_2CO_3 (2.25 mmol) and $PdCl_2$dppf (6 mol%) was added a solution of the bromide (0.79 mmol) in DMF (5 mL). The mixture was heated to 80°C and stirred under N_2 overnight when TLC indicated completion of the reaction. Work-up, followed by flash chromatography (SiO_2, Pentane/EtOAc) gave the coupled products.
10. Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991.