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A lactam-derived vinyl boronate as a stable and crystalline reagent for the synthesis of 2-substituted piperidines by Pd-catalyzed coupling reactions

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Abstract—A δ-valerolactam-derived vinyl triflate has been converted into the corresponding vinyl boronate by Pd-catalyzed coupling with bis(pinacolato)diboron, which results in an umpolung. This boronate efficiently couples under Pd catalysis with aryl and heteroaryl bromides to give the corresponding 2-substituted piperidines in excellent yields.

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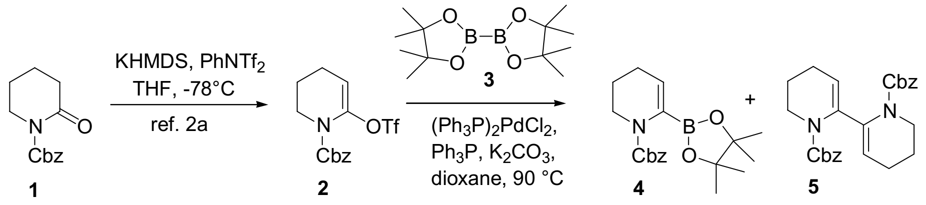
Lactam-derived vinyl triflates[1] have found several applications in the last decade as key intermediates in the synthesis of heterocyclic compounds. Palladium-catalyzed coupling reactions with nucleophiles such as organoboron, organotin, and organozinc derivatives, as well as carbonylations and Sonogashira couplings, in particular, have been used for the preparation of an array of useful α-substituted *N*-heterocycles.[1,2] A further expansion of the synthetic applications of these electrophiles arises from procedures that allow the displacement of the triflate group by a metal such as tin or lithium. This, in practice, results in an umpolung and it has been first reported by Hiemstra and co-workers[3] and successively exploited for the synthesis of fasicularin.[4] We wondered if such an umpolung, followed by metal-catalyzed coupling reactions with various electrophiles, could also be realized by α-borylation of the heterocycle, with the advantage of avoiding the use of toxic tin compounds.[5] The overall procedure should, in principle, be of wide scope due to the availability of the electrophiles (e.g. vinyl and aryl halides and triflates, acyl halides) that are to be used as coupling partners. With this in mind, we first evaluated the feasibility of the transformation of lactam-derived vinyl triflate **2** (Scheme 1) into the corresponding boronate **4**, and then we focused on the Pd-catalyzed coupling of **4** with bromo(hetero)arenes for the synthesis of 2-aryl- and 2-heteroaryl substituted piperidines that are of great interest as intermediates in medicinal chemistry.

Because commercial bis(pinacolato)diboron **3**[6] has successfully been employed for the preparation of air and water stable boronates from diverse vinyl triflates,[7] we attempted the conversion of vinyl triflate **2**[8] into



Scheme 1.

Keywords: Boronates; Lactams; Triflates; Palladium; Coupling; Piperidines.

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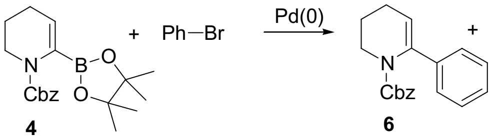
boronate **4** by experimenting all of the reported coupling conditions[7] with **3**. The only suitable protocol was that which uses 1.5 equiv of bis(pinacolato)diboron, in anhydrous dioxane, under $(Ph_3P)_2PdCl_2$ (3%) catalysis, in the presence of Ph_3P and with fine powdered K_2CO_3 as a base at 90 °C.[7a] The reaction was complete in 7 h and vinyl boronate **4** was obtained in 85% yield after chromatographic purification.[9] Under these conditions, in situ coupling of **2** with boronate **4** to give dimer **5**[10] was almost completely suppressed (less than 8% by ^1H NMR analysis of the crude reaction mixture). Boronate **4** is a white solid compound, indefinitely stable at room temperature.[11]

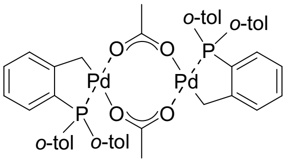
An initial survey of the reaction conditions for the coupling of **4** with bromoarenes was carried out using bromobenzene as the electrophile (Scheme 2 and Table 1).



Scheme 2.

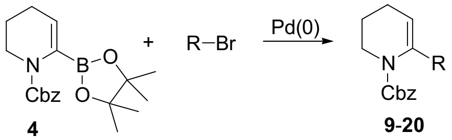
Low yields with aqueous bases (entries 4–5) were mainly due to degradation of the starting material. The $Pd(OAc)_2/Ph_3P$ catalytic system, in the presence of hydrated K_3PO_4 as a base (entry 6), proved superior to $(Ph_3P)_4Pd$ under the same conditions (entry 1). Two were the best protocols: one employs Herrmann catalyst **8**[12] (1 mol%, Fig. 1) in anhydrous toluene at 110 °C (entry 8) with K_2CO_3 as a base (method A);[13] using this procedure, a certain amount of 3,4-dihydro-2*H*-pyridine **7** (16% by ^1H NMR analysis of the crude reaction mixture) was formed; the second procedure employs the $Pd(OAc)_2$ (10 mol%)/Ph_3P (20 mol%) catalytic system in the presence of $K_3PO_4{\cdot}H_2O$ (2 equiv) as a base in dioxane at 100 °C (entry 7, method B).[14] 5 mol% or less of the catalyst can be used with the latter procedure but longer reaction times are required to consume the starting material (entry 6).

Both procedures were applied to a series of commercial electron-rich and electron-deficient aryl bromides and heteroaryl bromides (Scheme 3 and Table 2). Data obtained by using Herrmann catalyst **8** are reported whenever better or comparable yields were obtained under the conditions of method A. Despite the advantage of using a low mol% of catalyst, with this procedure we always observed the formation of the α-unsubstituted *N*-Cbz 3,4-dihydro-2*H*-pyridine **7** as a secondary product, to an extent exclusively depending on the nature of the aryl bromide: for example with 2-bromotoluene as the electrophile the extent of formation of this by-product after 4 h at 110 °C was higher (42% by ^1H NMR analysis of the crude reaction mixture) than with 4-methoxybromobenzene (20%) after 8 h at the same temperature. Moreover, with 2-bromotoluene, changing the catalyst from palladacycle **8** (1%) to $(Ph_3P)_4Pd$ (5%) under the conditions of method A, resulted in a clean, although incomplete after 7 h, reaction to give **9**, suggesting that the H-transfer to the α-position of the heterocycle to give **7** occurs in the presence of catalyst **8** only.[15] Good to excellent yields were obtained with all of the bromoarenes (entries 1–8). Only 2-bromoacetophenone (entry 5) did not react at all either after 2 h under conditions of method B and 7 h by method A, presumably because of steric impediment.



8

Figure 1.



Scheme 3.

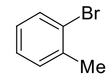
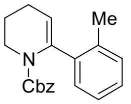
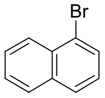
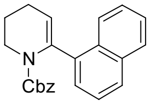
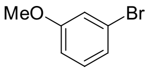
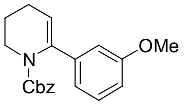
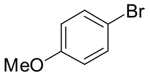
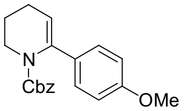
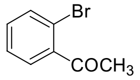
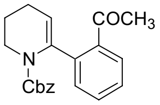
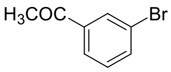
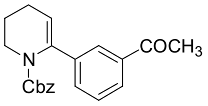
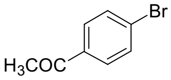
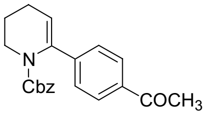
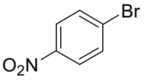
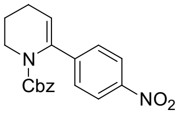
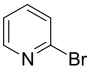
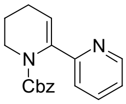
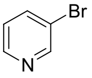
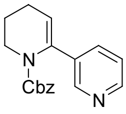
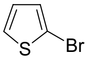
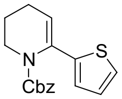
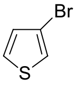
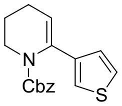
The coupling reactions with heteroaryl bromides (entries 9–12) under conditions B were slower and in some cases did not reach completion even after prolonged heating, as with 2-bromopyridine (entry 9). In one case only,

Table 1. Pd-catalyzed cross-coupling of **4** with bromobenzene[a]

Entry	Conditions	Time (h)	Yield (%)[b]
1	6% $(Ph_3P)_4Pd$, $K_3PO_4{\cdot}H_2O$ (2 equiv), dioxane, 90 °C	5	55
2	5% $(Ph_3P)_4Pd$, K_2CO_3 (2 equiv), toluene, 110 °C	5	61
3	5% $(Ph_3P)_4Pd$, $K_3PO_4{\cdot}H_2O$ (2 equiv), toluene, 110 °C	5	66
4	5% $(Ph_3P)_2PdCl_2$, 2 M KOH, dioxane, 80 °C	1	43
5	5% $(Ph_3P)_2PdCl_2$, 2 M KOH, dioxane, 50 °C	2	37
6	5% $Pd(OAc)_2$, 10% Ph_3P, $K_3PO_4{\cdot}H_2O$ (2 equiv), dioxane, 100 °C	5.5	71
7	10% $Pd(OAc)_2$, 20% Ph_3P, $K_3PO_4{\cdot}H_2O$ (2 equiv), dioxane, 100 °C	1.5	88
8	1% **8**, K_2CO_3 (2 equiv), toluene, 110 °C	4	75

[a] Reactions were carried out on 52 mg of **4** (0.15 mmol) with 1.5 equiv of PhBr and stopped after 5 h or when TLC showed complete consumption of **4**.
[b] Isolated yield after chromatography.

Table 2. Pd-catalyzed cross-coupling of **4** with aryl and heteroaryl bromides[a]

Entry	R–Br	Conditions[b]	Time (h)	Product		Yield (%)[c]
1		B	2.5		**9**	87
2		B	2		**10**	91
3		B	2		**11**	93
4		A[d]	8		**12**	73
5		A/B	7/2		**13**	0
6		B	2		**14**	89
7		B	2		**15**	87
8		B	1.5		**16**	83
9		B	5		**17**	45
10		B	4		**18**	77
11		A[d]	7		**19**	81
12		B	2		**20**	62

[a] Reactions were carried out on 52 mg of **4** (0.15 mmol) and stopped when TLC showed complete consumption of **4**.

[b] Conditions A: 1% Herrmann catalyst **8**, K_2CO_3 (2 equiv), RBr (1.5 equiv), toluene, 110 °C. Conditions B: 10% $Pd(OAc)_2$, 20% Ph_3P, RBr (1.5 equiv), $K_3PO_4{\cdot}H_2O$ (2 equiv), dioxane, 100 °C.

[c] Isolated yield after chromatography. All new compounds gave satisfactory NMR and elemental analysis.

[d] 2 mol% catalyst.

conditions A using palladacycle **8** were superior (entry 11) which allowed the synthesis of 2-thienyl derivative **19** in 81% yield.

In conclusion, we have demonstrated that δ-valerolactam-derived vinyl triflate **2** can be converted into the corresponding vinyl boronate **4**, which results in an umpolung. This boronate efficiently couples under Pd catalysis with aryl and heteroaryl bromides to give the corresponding 2-substituted piperidines. The overall methodology is of wide applicability due to the vast range of commercially available aryl and heteroaryl bromides. Ongoing studies aim at expanding the scope of the reaction to different classes of electrophiles.

Acknowledgements

MIUR, University of Florence and COFIN 2002–2004 are acknowledged for financial support.

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4. Fenster, M. D. B.; Dake, G. R. *Org. Lett.* **2003**, *5*, 4313.
5. Very recently the nucleophilic addition of lactam-derived vinyl triflates to electrophiles such as aldehydes, mediated by nickel(II) and chromium(II) salts, has been reported: Easton, L. P.; Dake, G. R. *Can. J. Chem.* **2004**, *82*, 139.
6. Bis(pinacolato)diboron **3** can also be prepared according to the procedure reported in: Abu Ali, H. A.; Goldberg, I.; Srebnik, M. *Eur. J. Inorg. Chem.* **2002**, 73.
7. For example see: (a) Ishiyama, T.; Tagaki, J.; Kamon, A.; Miyaura, N. *J. Organomet. Chem.* **2003**, *687*, 284; (b) Takagi, J.; Kamon, A.; Ishiyama, T.; Miyaura, N. *Synlett* **2002**, 1880; (c) Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001–8006; (d) Eastwood, P. R. *Tetrahedron Lett.* **2000**, *41*, 3705; (e) Ishiyama, T.; Itoh, Y.; Takahiro, K.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447.
8. Lactam-derived vinyl triflate **2** is best prepared by treatment of the lactam **1** with KHMDS at −78 °C in THF, followed by the addition of $PhNTf_2$ according to a procedure reported in Ref. 2a.
9. Preparation of **4**: *N*-Cbz triflate **2** (780 mg, 2.14 mmol) was dissolved in anhydrous dioxane (14 mL) in a two-necked flask under nitrogen atmosphere. To the solution were added, in the order, bis(pinacolato)diboron **3** (816 mg, 3.21 mmol), $(Ph_3P)_2PdCl_2$ (46 mg, 0.066 mmol), Ph_3P (34 mg, 0.13 mmol), and anhydrous K_2CO_3 (444 mg, 3.21 mmol). The mixture was heated with an oil bath to 90 °C and left under stirring for 7 h, after which time the reaction was complete (by TLC). After cooling to room temperature the mixture was diluted with Et_2O (60 mL) and washed with water (3 × 40 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The crude oil was chromatographed (SiO_2, EtOAc–petroleum ether, 1:8, R_f 0.20) obtaining pure **4** (623 mg, 85%) as a white solid: mp = 65–66 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35–7.20 (m, 5H), 5.28 (br s, 1H), 5.20 (s, 2H), 3.59–3.50 (m, 2H), 2.09–2.02 (m, 2H), 1.81–1.66 (m, 2H), 1.31 (s, 12H); ^{13}C NMR (50.33 MHz, $CDCl_3$) δ 155.6 (s), 135.5 (s), 133.0 (br), 128.2 (d, 2C), 127.9 (d, 2C), 127.6 (d), 114.5 (d), 82.8 (s, 2C), 68.2 (t), 41.5 (t), 24.6 (q, 4C), 21.7 (t), 21.2 (t); MS *m/z* (%) 343 (M^+, 0.1), 194 (20), 152 (31), 91 (100). Elemental analysis calcd C, 66.49; H, 7.64; N, 4.08. Found C, 66.84; H, 7.74; N, 4.01.
10. ^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **5**: δ 7.35–7.25 (m, 10H), 5.33 (br t, 2H), 5.07 (s, 4H), 3.50–3.10 (br m, 4H), 2.10–1.95 (br m, 4H), 1.75–1.50 (br m, 4H).
11. Attempts at preparing the corresponding vinyl boronate from the *N*-Ts pyrrolidinone-derived vinyl triflate were hampered by the ready decomposition of this intermediate under the coupling conditions.
12. This palladacycle was prepared according to the procedure reported in: Herrmann, W. A.; Brossmer, K. Ö.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844.
13. General procedure A: catalyst **8** (1.4 mg, 1.5 μmol) and boronate **4** (52 mg, 0.15 mmol) were dissolved in anhydrous toluene (2 mL) in a Schlenk flask under nitrogen atmosphere. To the solution was added bromobenzene (24 μL, 0.225 mmol), followed by anhydrous K_2CO_3 (41.4 mg, 0.30 mmol) and the resulting mixture was heated at 110 °C. After 4 h the reaction was complete (by TLC) and the mixture was diluted with Et_2O (15 mL), washed with water (30 mL), and dried over Na_2SO_4. Evaporation of the solvent and chromatography (SiO_2, EtOAc–petroleum ether, 1:8, $R_f = 0.39$) gave pure **6**[2e] (33 mg, 75%) as a colorless oil.
14. General procedure B: $Pd(OAc)_2$ (3.4 mg, 15 μmol), Ph_3P (8 mg, 30 μmol) and boronate **4** (52 mg, 0.15 mmol) were dissolved in anhydrous dioxane (1.5 mL) in a Schlenk flask under nitrogen atmosphere. To the solution was added bromobenzene (24 μL, 0.225 mmol), followed by $K_3PO_4{\cdot}H_2O$ (69 mg, 0.30 mmol) and the resulting mixture was heated at 100 °C. After 1.5 h the reaction was complete (by TLC) and the mixture was diluted with Et_2O (15 mL), washed with water (30 mL), and dried over Na_2SO_4. Evaporation of the solvent and chromatography as above gave pure **6**[2e] (39 mg, 88%) as a colorless oil.
15. The reaction takes also place at lower temperature (90 °C) with the Herrmann catalyst, although it is much slower (15% conversion after 3.5 h) and, in practice, the ratio between **9** and by-product **7** does not change.