



Tetrahedron Letters 44 (2003) 233-235

TETRAHEDRON LETTERS

Synthesis of benzylic boronates via palladium-catalyzed cross-coupling reaction of bis(pinacolato)diboron with benzylic halides

André Giroux*

Department of Medicinal Chemistry, Merck-Frosst Centre for Therapeutic Research, PO Box 1005, Pointe-Claire-Dorval, Québec, Canada H9R 4P8

Received 18 October 2002; revised 8 November 2002; accepted 13 November 2002

Abstract—The palladium cross-coupling reaction of benzyl halides with diboron 1 yielded structurally diverse pinacol benzylic boronates. Under these reaction conditions, sensitive functionalities such as esters and nitriles are tolerated and the benzylic boronates are obtained in good to high yields. © 2002 Published by Elsevier Science Ltd.

The widespread use of organoboronates in various metal catalyzed C-C bond forming reactions has created a substantial demand for these versatile synthetic intermediates.1 The Suzuki coupling offers several advantages, such as mild reaction conditions, comparative stability and low toxicity.² However, their utility is sometimes restricted because the most common methods for boronate preparation are based on anionic³ or hydroboration⁴ processes which are not always compatible with sensitive, functionalized molecules. For example, the most popular method for the synthesis of benzylic boronates relies on the reaction of trialkyl borate with the corresponding Grignard reagent.⁵ Other methods include homologation,⁶ displacement of alphahaloboronates⁷ and cross-coupling of alphametalloboronates8 or alphahaloboronates.9 More recently C-H borylation of alkylbenzenes has been reported using compound 1 and pinacolborane.10 Herein, we report the versatile and facile synthesis of pinacol benzylboronates under Suzuki palladium catalyzed conditions using diboron 1 (Scheme 1).¹¹

Our initial efforts were directed toward finding the optimal condition using 4-methylbenzyl bromide (2) as the model substrate under different reaction conditions (Table 1). The best conditions found for the cross-coupling reaction of the diboron 1 with aryl halides,¹² using $PdCl_2(dppf)$ and KOAc as the base in DMF, provided exclusively the corresponding benzyl acetate

(entry 1). Therefore, the cross-coupling reaction of benzyl bromide **2** with the diboron **1** with different bases was investigated. Using K_2CO_3 as the base gave a 3:1 mixture of the desired product **3** with the presence of a small amount of benzyl alcohol **4** and dimer **5** as side products (entry 2).

Other bases tried, K_3PO_4 and Cs_2CO_3 gave lower conversions to the desired benzyl boronate **3** (entries 3, 4). Similarly, changing the catalyst to $Pd(PPh_3)_4$ (entry 5) also provided after 18 hours the same crude mixture as entry 2. Many other conditions were surveyed using different bases, solvents and catalysts in order to optimize the conditions for the coupling while eliminating the side products. Gratifyingly, an excellent conversion of the benzyl bromide **2** to the desired coupled product **3** was obtained when dioxane was used as the solvent. Running the reaction in dioxane eliminated the formation of the benzyl alcohol **4**, and furthermore reduced the reaction time, formation of the dimer **5**, and catalyst loading to 5 mol% (entry 6).





^{*} Tel.: (514) 428-3451; fax: (514) 428-4900; e-mail: andre_giroux@ merck.com





^a Ratios were determined by ¹H NMR.

^b The corresponding benzyl acetate was obtained.

^c 5% catalyst was used for the reaction.

With these results in hand, we next carried out the Suzuki cross-coupling reaction on a variety of benzyl bromides and the results are summarized in Table 2. Under our optimal conditions *p*-methylbenzyl bromide 2 gave an isolated yield of 83% for the corresponding pinacol boronate 3. Similarly, benzyl bromide (6) and p-fluorobenzyl bromide (8) also undergo the coupling reaction in excellent yields providing the benzylic boronates 7 in 79% yield and the benzylic boronate 9 in 82% yield (entries 2, 3). meta- and ortho-substituted benzyl bromides were also evaluated under these reaction conditions. The cross-coupling of *m*-methoxybenzyl bromide (10) cleanly provided the benzyl boronate 11 in 91% yield (entry 4). Similarly, the coupling reaction of methyl 3-(bromomethyl)benzoate (12) and 3-(bromomethyl)benzonitrile (14) under these mild conditions afforded products 13 and 15 in good yields of 75% (entry 5) and 65% (entry 6), respectively.¹³ Substitution at the ortho position required a longer reaction time in order to achieve complete conversion, as seen for the o-methylbenzyl bromide (16) which required 18 h to go to completion, yet the boronate 17 was efficiently obtained in 74% yield (entry 7).

The cross-coupling reaction of benzyl chlorides with the pinacol diboron 1 was also evaluated (Table 3). High yields of the cross-coupling products were obtained for *para*-substituted benzyl chlorides (entries 1, 2). However, a moderate yield of 68% was obtained for the benzamide 22 (entry 3). In this case, a small amount of the corresponding *N*-benzyl-4-methylbenzamide was detected. Under these reaction conditions, the cross-coupling occurs exclusively at the benzylic site, while an aryl chloride is not affected.¹⁴

For example, *m*-chlorobenzyl chloride (23) was converted to the desired *m*-chlorobenzyl boronate (24) in a high yield of 91% (entry 4). Similarly, the cross-coupling reaction of *ortho*-substituted benzyl chloride 25 and 1-(chloromethyl)naphthalene (27) afforded the coupled products 26 and 28 in high yields of 70% (entry 5) and 80% (entry 6), respectively.

In summary, we have developed a versatile high yielding method for preparing benzyl boronates. This procedure is advantageous when sensitive groups such as esters and nitriles are present. Furthermore, this methodology is applicable to benzylic bromides and chlorides.

Entry	Substrate	Time (h)	Product ^b	Yield ^c
1	$p-MeC_6H_4CH_2Br$ (2)	6	$p-\text{MeC}_6\text{H}_4\text{CH}_2\text{Bpin}^d$ (3)	83
2	$C_6H_4CH_2Br$ (6)	6	$C_6H_4CH_2Bpin$ (7)	79
3	p-FC ₆ H ₄ CH ₂ Br (8)	6	p-BrC ₆ H ₄ CH ₂ Bpin (9)	82
4	m-MeOC ₆ H ₄ CH ₂ Br (10)	6	p-ClC ₆ H ₄ CH ₂ Bpin (11)	91
5	m-MeO ₂ CC ₆ H ₄ CH ₂ Br (12)	6	m-MeO ₂ CC ₆ H ₄ CH ₂ Bpin (13)	75
6	m-CNC ₆ H ₄ CH ₂ Br (14)	6	m-CNC ₆ H ₄ CH ₂ Bpin (15)	65
7	$o - MeC_6H_4CH_2Br$ (16)	18	$o-\text{MeC}_6\text{H}_4\text{CH}_2\text{Bpin}$ (17)	74

Table 2. Cross-coupling of benzyl bromides with bis(pinacolato)diboron^a

^a Reactions were carried out in dioxane using 5 mol% of Pd(PPh₃)₄, benzyl bromide (1.0 equiv.), diboron 1 (1.2 equiv.) and K_2CO_3 (3.0 equiv.) as the base at 80°C for 6 h.

^b All new compounds were fully characterized and all analytical and spectral (IR, NMR, MS) data are fully consistent with the assigned structures. All known compounds were characterized by NMR.

^c Isolated yield.

^d The pinB abbreviates 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl group.

Table 3. Cross-coupling of benzyl chlorides with bis(pinacolato)diboron^a

Entry	Substrate	Product ^b	Yield ^c
1			81
2	MeO 19		93
3			68
4			91
5			70
6	CI 27		80

^aReactions were carried out in dioxane at 100 °C for 18 h using 5 mol% of Pd(PPh₃)₄, benzyl chloride (1.0 eq), diboron 1 (1.2 eq) and K_2CO_3 (3.0 eq) as the base. ^bAll new compounds were fully characterized and all analytical and spectral (IR, NMR, MS) data are fully consistent with the assigned structures. All known compounds were characterized by NMR. ^cIsolated yield.

References

- (a) Perlter, A.; Smith, K.; Brown, H. C. Borane Reagents; Academic Press: London, 1998; (b) Yamamoto, Y.; Asao, N. Chem. Rev. 1993, 93, 2207–2293; (c) Ishiyama, T.; Miyaura, N. J. Organomet. Chem. 2000, 611, 392; (d) Charette, A. B.; Giroux, A. J. Org. Chem. 1996, 61, 8718–8719; (e) Ramnauth, J.; Poulin, O.; Bratovanov, S.; Rakhit, S.; Maddaford, S. P. Org. Lett. 2001, 3, 2571–2573.
- (a) Suzuki, A.; Miyaura, N. Chem. Rev. 1995, 2457–2483;
 (b) Mckenna, J. M.; Moliterni, J.; Qiao, Y. Tetrahedron Lett. 2001, 42, 5797–5800; (c) Carbonnelle, A.-C.; Zhu, J. Org. Lett. 2000, 2, 3477–3480; (d) Fizooznia, F.; Gude, C.; Chan, K.; Marcopulos, N.; Satoh, Y. Tetrahedron Lett. 1999, 40, 213–216.
- (a) Wuts, P. G.; Thompson, P. A.; Callen, G. R. J. Org. Chem. 1983, 48, 5398–5400; (b) Watanabe, T.; Miyaura, N.; Suzuki, A. J. Organomet. Chem. 1993, 444, C1–C3.
- (a) Wang, K. K.; Liu, C.; Gu, Y. G.; Burnett, F. N. J. Org. Chem. 1991, 56, 1914–1922; (b) Ishiyama, T.; Yamamoto, M.; Miyaura, N. Chem. Commun. 1996, 2073–2074.
- (a) Thompson, W.; Gaudino, J. J. Org. Chem. 1984, 49, 5237–5243; (b) Crisofoli, W. A.; Keay, B. A. Tetrahedron Lett. 1991, 32, 5881–5884.

- Sadhu, K. M.; Matteson, D. S. Organometallics 1985, 4, 1687–1689.
- 7. Martin, R.; Jones, J. B. Tetrahedron Lett. 1995, 36, 8399–8402.
- Kanai, G.; Miyaura, N.; Suzuki, A. Chem. Lett. 1993, 845–848.
- Falck, J. R.; Muralidhar, B.; Ye, J.; Cho, S.-D. *Tetrahedron* Lett. **1999**, 40, 5647–5650.
- (a) Ishiyama, T.; Ishida, K.; Takagi, J.; Miyaura, N. Chem. Lett. 2001, 1082–1083; (b) Shimada, S.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. Angew. Chem., Int. Ed. 2001, 11, 2168–2171.
- For leading applications of this methodology see: (a) Furstner, A.; Seidel, G. Org. Lett. 2002, 4, 541–543; (b) Giroux, A.; Han, Y.; Prasit, P. Tetrahedron Lett. 1997, 38, 3841–3844; (c) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. Tetrahedron Lett. 1997, 38, 3447–3450.
- Ishiyama, T.; Murata, M.; Miyaura, N. J. Org. Chem. 1995, 60, 7508–7510.
- 13. These isolated yields exclude the small amount of the corresponding acid detected in the crude reaction mixtures.
- 14. Ishiyama, T.; Ishida, K.; Takagi, J.; Miyaura, N. Chem. Lett. 2001, 1082-1083.