Pergamon

Tetrahedron Letters 42 (2001) 5817–5819

TETRAHEDRON LETTERS

Suzuki–Miyaura cross-coupling of lithium *n*-alkylborates

Gang Zou and J. R. Falck*

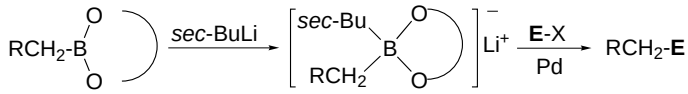
Departments of Biochemistry and Pharmacology, University of Texas Southwestern Medical Center, Dallas, TX 75390-9038, USA

Received 24 May 2001; revised 19 June 2001; accepted 22 June 2001

Abstract—The palladium-catalyzed cross-coupling of lithium *n*-alkylborates, generated in situ via addition of *sec*-butyl lithium to boronate esters, proceeds in moderate to good yields with a wide variety of electrophiles.

The palladium-mediated cross-coupling of boronic acids/esters with organic electrophiles, known as the Suzuki–Miyaura reaction, has gained wide popularity for its tolerance of common functional groups, mild reaction conditions, air-stable components, and innocuous by-products.[1] Extensive optimization[2] of the reaction parameters by numerous investigators has significantly extended its scope to include, inter alia, aryl/alkenyl chlorides and triflates,[3] haloheterocycles,[4] and sulfonium salts[5] as well as sterically demanding substrates.[6] In contrast to aryl and alkenyl boronic acids, however, accounts of *n*-alkylboronic acid/ester participation are sporadic and the yields are normally not synthetically useful.[7] To improve the outcome, stoichiometric heavy metals, e.g. thallium[8] and silver salts,[7a] have been exploited. While not as robust as boronic acids, trialkylboranes[9] and *n*-alkylborinates[10] are often more efficacious in Suzuki–Miyaura couplings and, thus, have helped focus attention on the functional state of the boron as an important determinant. This was elegantly illustrated recently by Molander and Ito[11] who described the cross-coupling of potassium *n*-alkyltrifluoroborates with aryl- and alkenyltriflates. Herein, we report the palladium-catalyzed cross-coupling of readily available lithium *n*-alkylborates with a wide variety of electrophiles (Eq. (1)).[12,13]

According to the widely accepted mechanism proposed by Suzuki,[1] the critical step in the cross-coupling of organoboranes is the transmetalation between the palladium(II) intermediate, generated by oxidative addition to an organic electrophile, and a boron 'ate' complex. Armed with the knowledge that unactivated alkylboronic esters readily form 'ate' complexes with alkyl lithium reagents even at low temperatures,[14] we evaluated a series of in situ generated lithium borate esters and found them to be suitable partners for Suzuki–Miyaura cross-couplings. Pinacol and pinanediol esters, prepared from commercial boronic acids according to literature procedures,[15] were used typically as a consequence of their superior air and moisture stability.[16] These were complexed with *sec*-BuLi or *t*-BuLi (1 equiv.) at −78°C prior to cross-coupling. Reaction parameters were briefly explored utilizing lithium *n*-butylborate **1** and vinyl iodide **2**. The best yields of adduct **3** were obtained with (dppf)$PdCl_2$ in THF at 80°C (Table 1).[17] Comparable results were attained in DMF at room temperature, but required significantly longer reaction times. Even though the lithium borate esters are formally coordinately saturated, added NaOAc or KOH were equally effective in accelerating the reaction rates and improving yields; their role, however, remains obscure, but may involve stabilization of the Pd(II) intermediate.[18] Notably,



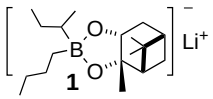
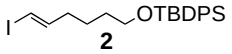
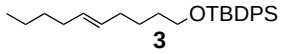
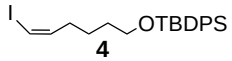
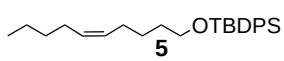
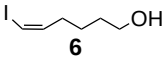
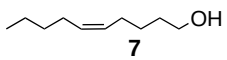
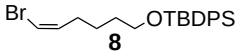
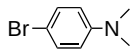
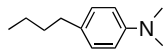
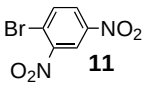
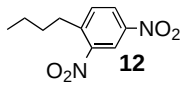
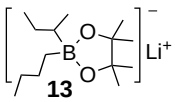
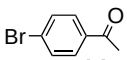
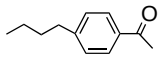
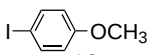
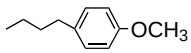
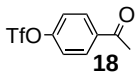
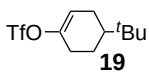
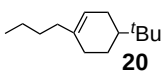
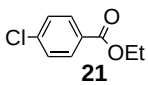
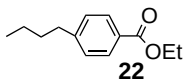
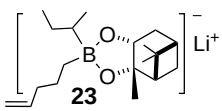
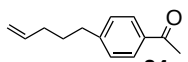
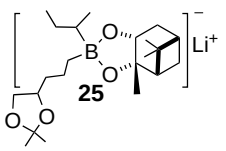
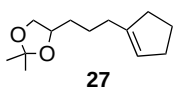
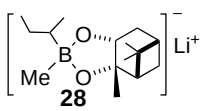
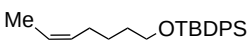
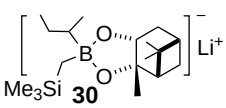
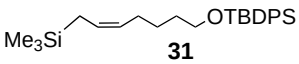
(1)

Keywords: Suzuki; alkylation; boron; coupling reactions; palladium.

* Corresponding author. Tel.: 214-648-2406; fax: 214-648-6455; e-mail: j.falck@utsouthwestern.edu

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01128-5

Table 1. Li *n*-alkylboronate cross-couplings

Entry	Borate[a]	Electrophile	Adduct	Yield (%)
1	 **1**	 **2**	 **3**	70
2	**1**	 **4**	 **5**	67
3	**1**	 **6**	 **7**	60
4	**1**	 **8**	**5**	72
5	**1**	 **9**	 **10**	73
6	**1**	 **11**	 **12**	71
7	 **13**	 **14**	 **15**	90
8	**13**	 **16**	 **17**	69
9	**13**	 **18**	**15**	88
10	**13**	 **19**	 **20**	78
11[b]	**13**	 **21**	 **22**	62
12	 **23**	**14**	 **24**	73
13[b]	 **25**	 **26**	 **27**	58
14	 **28**	**4**	 **29**	65
15	 **30**	**4**	 **31**	71

[a]Generated in situ. [b]$Pd_2(dba)_3/(^tBu)_3P/KF$

cross-couplings using the corresponding boronic acids or simple boronate esters gave rise to little, if any, adduct under the same reaction conditions.

As anticipated,[1] cross-couplings of *trans*-vinyl iodide **2** and its *cis*-isomer **4** with borate **1** proceeded with complete retention of configuration furnishing **3**[19] (entry 1) and **5** (entry 2), respectively. Even the unprotected alcohol **6** provided a useful yield of dec-5(*Z*)-en-1-ol (**7**) (entry 3). Bromide **8** was also a suitable substrate and smoothly generated *cis*-olefin **5** (entry 4). Interestingly, both electron rich and deficient aryl bromides were well behaved and provided similar yields of adduct, e.g., the transformation of **9** and **11** into **10** (entry 5) and **12** (entry 6), respectively. A wide variety of electrophiles could be coupled to pinacol ester **13**, inter alia, aryl bromide **14**, aryl iodide **16**, aryl triflate **18**, and vinyl triflate **19** affording methyl ketone **15** (entry 7), methyl ether **17** (entry 8), **15** (entry 9), and cyclohexene **20** (entry 10), respectively. Chlorides dis-

played sluggish reactivity with (dppf)$PdCl_2$ as catalyst even at elevated temperatures and prolonged reaction times, but could be successfully coupled using $(dba)_3Pd_2/{}^tBu_3P$/KF in THF, e.g. **21** to **22** (entry 11).[2a,7a] The conversion of terminal olefin **23** and acetonide **25** to **24** (entry 12) and **27** (entry 13), respectively, demonstrated that a variety of functional groups are well tolerated in the lithium borate moiety. Finally, it is important to note that for the demanding cases of methyl and trimethylsilylmethyl cross-couplings, **28** to **29** (entry 14) and **30** to **31** (entry 15), no transfer of the *sec*-butyl radical was observed.

In summary, we describe a practical two-step, one-pot strategy for the Suzuki–Miyaura cross-coupling of unactivated primary alkyl groups from *n*-alkylboronates under mild conditions.

General procedure: Commercial *sec*-BuLi (0.1 mmol, 1.3 M in cyclohexane) was added dropwise to a −78°C solution of boronate ester (0.11 mmol) in THF (6 mL). The mixture was gradually warmed to ambient over 1.5 h, then cannulated into a stirring suspension of Pd catalyst (0.05 equiv.) and NaOAc (3–5 equiv.) in THF (5 mL) under argon followed after a few minutes by the electrophile (0.1 mmol). The resulting brown solution was heated at 70–80°C for 8–12 h, cooled to room temperature, and quenched with 30% H_2O_2/10% aq. NaOH. The reaction mixture was extracted thrice with Et_2O and the combined ethereal extracts were concentrated in vacuo. Purification of the residue via SiO_2 chromatography provided the adducts in the indicated yields.

Acknowledgements

Supported financially by the USPHS NIH (GM31278, DK38226), the Robert A. Welch Foundation, and an unrestricted grant from Taisho Pharmaceutical.

References

1. Review: Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168.
2. For example, see: (a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028; (b) Lobregat, V.; Alcaraz, G.; Bienayme, H.; Vaultier, M. *Chem. Commun.* **2001**, 817–818; (c) Kabalka, G. W.; Namboodiri, V.; Wang, L. *Chem. Commun.* **2001**, 775.
3. Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.
4. Cooke, G.; Augier de Cremiers, H.; Rotello, V. M.; Tarbit, B.; Vanderstraeten, P. E. *Tetrahedron* **2001**, *57*, 2787–2789.
5. Srogl, J.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 12376–12377.
6. Chaumeil, H.; Signorella, S.; Le Drian, C. *Tetrahedron* **2000**, *56*, 9655–9662.
7. (a) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095–6097; (b) Mu, Y.; Gibbs, R. A. *Tetrahedron Lett.* **1995**, *36*, 5669–5672; (c) Zhou, X.; Tse, M. K.; Wan, T. S. M.; Chan, K. S. *J. Org. Chem.* **1996**, *61*, 3590–3593.
8. Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405–1408.
9. Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321.
10. Soderquist, J. A.; Santiago, B. *Tetrahedron Lett.* **1990**, *31*, 5541–5542.
11. Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393–396.
12. For the application of hypervalent tin reagents to cross-couplings, see: Martinez, A. G.; Barcina, J. O.; del Rosario Colorado Heras, M.; de Fresno Cerezo, A. *Organometallics* **2001**, *20*, 1020–1023.
13. For the cross-coupling of lithium alkenylborates mediated by nickel catalysis, see: Usmani, S. B.; Takahisa, E.; Koyayashi, Y. *Tetrahedron Lett.* **1998**, *39*, 601–604.
14. Pelter, A.; Singaram, B.; Williams, L.; Wilson, J. W. *Tetrahedron Lett.* **1983**, *24*, 623–626.
15. Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447–3450.
16. No significant differences in reactivities of the esters were observed, so we favored the less expensive pinacol for large scale experiments.
17. $Pd(PPh_3)_4$ and $(PPh_3)_2PdCl_2$, for example, were inferior.
18. ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636–1639.
19. Spectral data for **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.69 (m, 4H), 7.34–7.44 (m, 6H), 5.29–5.40 (m, 2H), 3.66 (t, $J=6.4$ Hz, 2H), 1.99–2.08 (m, 4H), 1.54–1.63 (m, 2H), 1.40–1.48 (m, 2H), 1.27–1.36 (m, 4H), 1.05 (s, 9H), 0.89 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 134.4, 130.8, 129.9, 129.7, 127.8, 64.1, 32.4, 32.2, 27.2, 27.1, 26.2, 22.6, 19.4, 14.2. Adduct **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.70 (m, 4H), 7.33–7.45 (m, 6H), 5.34–5.40 (m, 2H), 3.65 (t, $J=6.4$ Hz, 2H), 1.92–2.01 (m, 4H), 1.50–1.62 (m, 2H), 1.37–1.46 (m, 2H), 1.24–1.36 (m, 4H), 1.04 (s, 9H), 0.88 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8, 134.4, 130.8, 130.3, 129.7, 127.8, 64.1, 32.5, 32.3, 32.0, 27.1, 26.0, 22.4, 19.4, 14.2. Adduct **27**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32–5.36 (m, 1H), 4.02–4.14 (m, 2H), 3.51 (t, $J=7.2$ Hz, 1H), 2.26–2.33 (m, 2H), 2.22 (apparent t, 2H), 2.10 (apparent t, 2H), 1.81–1.89 (m, 2H), 1.43–1.69 (complex m, 4H), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 123.9, 108.8, 76.3, 69.7, 35.2, 33.6, 32.6, 31.3, 27.2, 26.0, 24.1, 23.6. Adduct **29**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.70 (m, 4H), 7.34–7.44 (m, 6H), 5.32–5.48 (m, 2H), 3.66 (t, $J=6.4$ Hz, 2H), 2.02 (apparent q, $J=7.2$ Hz, 2H), 1.55–1.64 (m, 5H), 1.40–1.48 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 134.4, 130.8, 129.7, 127.8, 124.1, 64.0, 32.4, 27.1, 26.8, 26.0, 19.5, 13.0. Adduct **31**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.70 (m, 4H), 7.35–7.44 (m, 6H), 5.25–5.44 (m, 2H), 3.68 (t, $J=6.4$ Hz, 2H), 2.00 (apparent q, $J=6.8$ Hz, 2H), 1.58–1.62 (m, 3H), 1.40–1.45 (m, 3H), 1.06 (s, 9H), 0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 134.4, 129.7, 127.8, 127.7, 125.7, 64.1, 32.6, 27.1, 27.0, 26.2, 19.5, 18.6, −1.5.